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NEW METHODS FOR STEREOCONTROL AND REDUCTIVE CLEAVAGE OF α,β-EPOXY KETONES AND SYNTHETIC STUDIES ON TEUCVIN

by

RENATA JANKOWSKA ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Renata Jankowska

Renata Jankowska

Edmonton, Alberta,
Canada

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled NEW METHODS FOR STEREOCONTROL AND REDUCTIVE CLEAVAGE OF α,β-EPOXY KETONES AND SYNTHETIC STUDIES ON TEUCVIN submitted by RENATA JANKOWSKA in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

H.J. Liu
Supervisor

D. L. J. Clive
D.L.J. Clive

J.M. Stryker

W. Jaeger

E. E. Knaus
E.E. Knaus

M. Majewski
External Examiner

Date: September 3, 1998

Abstract

The extent and type of influence of the C-4 ester substituent on the stereochemical outcome of reactions involving 4,4-disubstituted 2-cyclohexenones were investigated. The results are described in the first chapter of this thesis. Three different types of reactions were studied, namely, hydrogenation, conjugate addition and epoxidation. High preference for hydrogen addition from the side opposite to the ester group (10-12:1 stereoselectivity) was observed for catalytic hydrogenation of cyclohexenones **15** and **31**. The C-4 ester group was also found to effect the stereoselective formation of epoxide from enones **38** and **48** (27:1 and 10:1 selectivity respectively).

The second chapter of this thesis details an efficient procedure for the reductive cleavage of α,β-epoxy ketones to the corresponding β-hydroxy ketones using lithium naphthalenide as a reducing agent. The generality of this method was demonstrated as a number of β-hydroxy ketones was obtained in synthetically useful yields (Table 2-1). The possible use of this method in the preparation of α-substituted and α,α-disubstituted β-hydroxy ketones via reductive alkylation of α,β-epoxy ketones was also investigated.

The third chapter presents the synthesis of several advanced intermediates towards teucvin **5**, a furanoid nor-diterpene. The first key operation involved the face-selective Diels-Alder reaction of dienone aldehyde **22** and pentadienol **29**. The adduct **32**, containing the decaline nucleus with the desired stereochemistry at two adjacent chiral centers C-9 and C-10 (clerodane numbering), was obtained in high yield. The C-8 methyl group in **36** was

introduced *via* stereoselective conjugate addition of lithium dimethylcuprate to enone **35**. Concomitant deacetylation and deformylation of **35**, followed by reduction of the resulting ketone **42** gave diols **52** and **53**. Subsequent steps included protection of each diol as cyclic silyl ether, selective reduction of the less hindered ester group with Red-Al and oxidation of the resulting alcohol with PDC to give aldehydes **58** and **59**. The installation of the furan moiety was accomplished by addition of 3-lithiofuran to aldehydes **58** and **59**. Treatment of the resulting alcohols with sodium hydride led to the formation of spiro-lactones **60-63**. Compounds **62** and **63** were further converted to keto acids **67** and **68** by sequential treatment with tetra-*n*-butylammonium fluoride and Jones reagent, enroute to the target molecule **5**.

Dedicated to Maciek and Anna

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a	anti-phase
Ac	Acetyl
APT	Attached Proton Test
9-BBN	9-Borabicyclo[3.3.1]nonane
br	broad
Bu	Butyl
CSA	Camphorsulfonic Acid
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
equiv.	equivalent
Eq.	equation
Et	Ethyl
FT-ir	Fourier Transform infrared spectroscopy
hreims	high resolution electron impact mass spectrometry
Hz	Hertz
i	iso
ir	Infrared Spectroscopy
J	coupling constant
LDA	Lithium Diisopropylamide
m	multiplet

M	Molar
M^+	Molecular ion
Me	Methyl
MHz	Megahertz
mmol	millimole
mol	mole
MVK	Methyl Vinyl Ketone
m/z	mass to charge ratio
n	normal
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p	para
p	phase
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
PP	Pyrophosphate
p-TsOH	*p*-Toluenesulfonic Acid
Ph	Phenyl
pyr	pyridine
q	quartet
R	generalized alkyl group or substituent
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
s	singlet
SET	Single Electron Transfer
t	tertiary
t	triplet
tlc	thin-layer chromatography

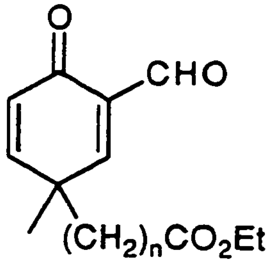
TBAF	Tetrabutylammonium Fluoride
TBDPS	*t*-Butyldiphenylsilyl
TBDPSCl	*t*-Butyldiphenylsilyl Chloride
THF	Tetrahydrofuran

Chapter 1

Facial Selectivity in Selected Reactions of 4-Alkyl-4-carbalkoxy-2-cyclohexenones

Introduction

The Diels-Alder addition of 4,4-disubstituted 2,5-cyclohexadienones **1** - **3** to a suitably substituted 1,3-diene presents itself as an excellent general route for the construction of *cis*-clerodane diterpenes.[1] In a single step, the stereochemistry of three contiguous chiral centers (C-5, C-9 and C-10) featured in the majority of the members of the *cis*-clerodane family, as shown in solidagoic acid A (Figure 1-1),[2] could be induced. The π-facial diastereoselectivity of Diels-Alder addition, however, would be a crucial factor for the success of this approach. This stereochemical feature, which arises when the addends possess two different reactive faces, has attracted considerable attention. Many asymmetric Diels-Alder reactions[3-5] involving optically active dienophiles[6,7] or dienes,[8,9] which carry a removable chiral auxiliary group, have been reported. Whereas the facial selectivities of many dienes have been extensively studied,[10-14] little is known about cycloadditions of cyclohexenone dienophiles possessing nonequivalent substituents at C-4.[15] The Diels-Alder additions of that type of compounds have been a subject of investigation in our laboratories.[16,17]



1 n = 0
2 n = 1
3 n = 2

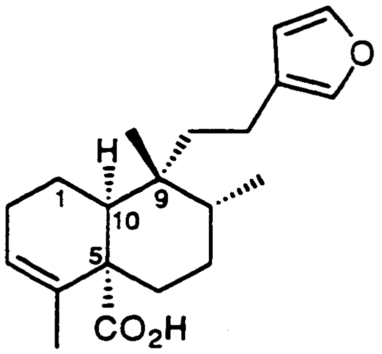
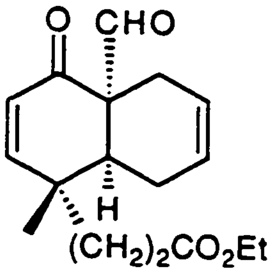


Figure 1-1 Solidagoic acid A

Based on steric grounds, it was expected that the addition of a diene to cyclohexadienones **1**, **2** and **3** should occur preferentially, in each case, from the less hindered methyl face.[3] The results obtained for cycloadditions of compounds **2** and **3** with different dienes were consistent with the prediction. For example, when dienone aldehyde **3** was reacted with 1,3-butadiene in dichloromethane in the presence of zinc chloride as a catalyst, two isomers **4** and **5** were obtained in 5:1 ratio respectively and 91% combined yield.



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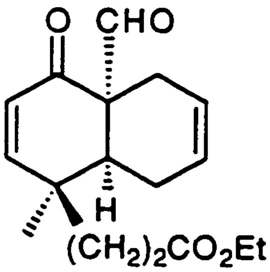

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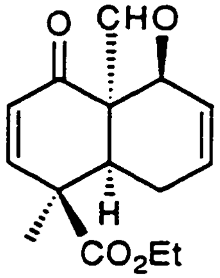

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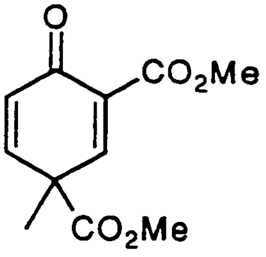
However, an intriguing π-facial selectivity was observed for reactions of cyclohexadienone **1**. Its zinc chloride catalyzed addition to *trans*-piperylene gave virtually a single stereoisomer **6** in 95% yield as a result of the addition from the ester side. This selectivity, although totally unexpected in light of the relative van der Waals sizes estimated for the carbomethoxy group (n = 12.1) and the methyl group (n = 8.5),[18] was found to be consistent in several other reactions examined for the dienophile **1** with a variety of substituted 1,3-butadienes.[16] Essentially the same facial selectivity was observed for cycloadditions involving ester dienone **7**.



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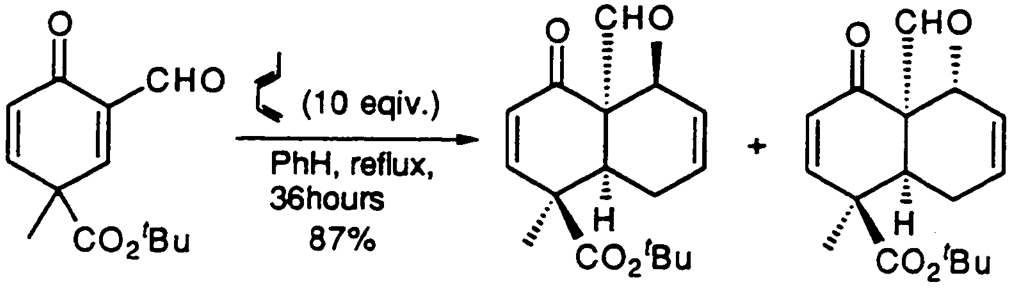
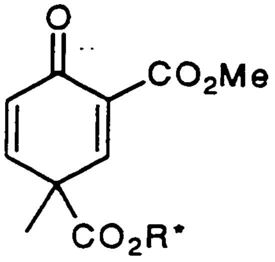
It therefore appeared that the π-facial selectivity was controlled by electronic factors rather than by steric ones. To prove or disprove that the steric interactions with the geminal substituents were the dominating factor in the course of the addition, two other dienone esters **8** and **9** were prepared and their reactions with 1,3-butadiene and *trans*-piperylene were studied.[17,19]



(Eq. 1-1)

8 **8a** **8b**

It was assumed that if the facial selectivity was sterically induced, a bulkier ester group would change the reaction course, giving rise to a different product distribution. The thermal Diels-Alder reaction of **8** with *trans*-piperylene, however, provided mainly (87% yield) diastereomers **8a** and **8b** in *ca.* 3.4:1 ratio (Equation 1-1), proving that the bulk of the C-4 ester group did not affect significantly the mechanistics of the addition. The minor product resulting from the addition from the methyl side was isolated only in 8% yield. Further observation, that even in case of dienone **9** addition of 1,3-butadiene occurred



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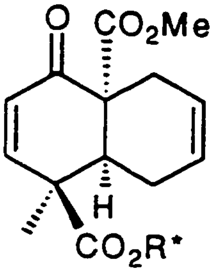
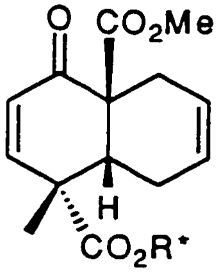
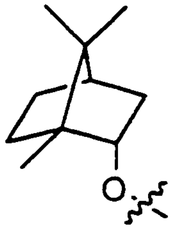


9a



9b

R* =



exclusively from the ester face to furnish products **9a** and **9b** in a ratio of 1:1 in 94% yield, led to the conclusion that steric interactions did not play a major role in the Diels-Alder reaction of these dienone esters.

A delicate balance of many different factors could have influenced the facial selectivity of these cycloadditions. Among them three seem to contribute the most, namely enone conformer population, secondary orbital interactions and electrostatic interactions of dienophile (for example cyclohexadienone **1**) and diene.[17]

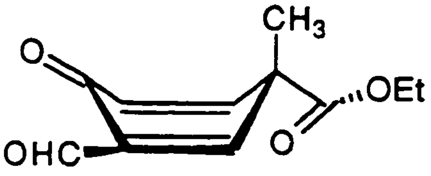


Figure 1-2 A shallow boat conformation of cyclohexadienone 1

Dienone aldehyde **1** exists provably in a shallow boat conformation with the ester group in a quasi-equatorial position (Figure 1-2) as opposed to fully planar conformation due to two reasons: (i) in sacrificing the conjugation, the shallow boat conformation can avoid excessive ring strain experienced in a completely planar form; (ii) the proposed conformation can avoid unfavorable electronic interactions.[17] Figures 1-3 and 1-4 show possible hyperconjugation of σ_{C-C} bond with the LUMO of the enone moiety. The shallow boat conformation should be stabilized with a methyl group in quasi-axial position,

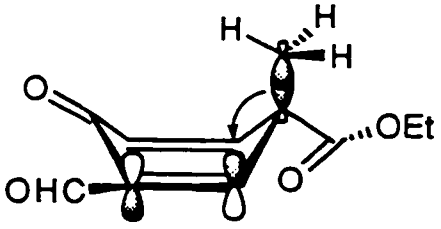


Figure 1-3
Hyperconjugative interactions of σ_{C-C} of the methyl with LUMO of the enone

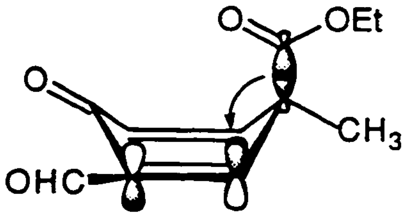


Figure 1-4
Hyperconjugative interactions of σ_{C-C} of the ester with LUMO of the enone

because of its electron-donating nature (Figure 1-3) and destabilized when it is in quasi-equatorial position due to the electron-withdrawing ability of the ester group (Figure 1-4). The resulting energy barrier between the two possible conformations is probably larger than expected. The enone conformer population ratio might then influence the facial selectivity of the reaction.

The second factor that could play a major role in the stereochemical outcome of the additions discussed here is the secondary orbital interaction between the HOMO of the approaching diene with the anti-symmetric π^* of the ester carbonyl group (Figure 1-5). For this interaction to happen, it is necessary that the dienophile exists in a shallow boat conformation with the ester substituent in a quasi-equatorial position, so that its carbonyl group can be coplanar or near coplanar with the cyclohexadienone ring. As depicted, the *endo*-to-ketone transition state is then stabilized and the observed predominating attack from the ester face could be explained.

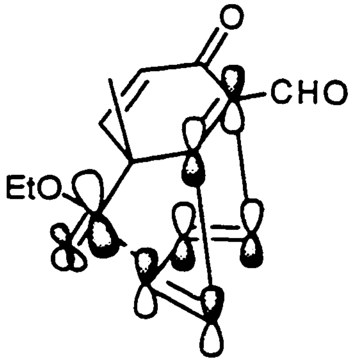
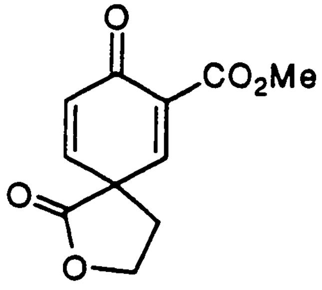


Figure 1-5 The secondary orbital interaction between the HOMO of the diene and the anti-symmetric π* of the ester carbonyl group

This possibility was also supported by a study of the addition to spiro compound **10**.[17] It was assumed that in this dienone, the carbonyl group of the lactone moiety would be sterically confined to be perpendicular instead of being coplanar to the cyclohexadienone ring. Consequently, the proposed secondary orbital interactions would be ruled out. When the lactone **10** was reacted with 1,3-butadiene, two adducts **10a** and **10b** were formed in a 45:55 ratio in a combined yield of 85%, suggesting that steric interactions are not the dominant factors in the studied Diels-Alder reactions. The spiro lactone model also



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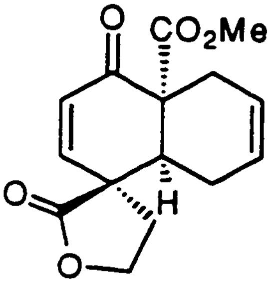
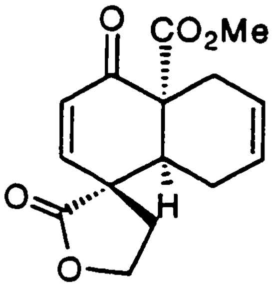


10a



10b

demonstrated the importance of coplanarity of the ester carbonyl group with the dienone ring in order to obtain a high facial selectivity.

The third factor which might have influenced the observed facial selectivity of Diels-Alder reaction of dienone ester **1** is the electrostatic interaction between **1** and the approaching diene. The simple electrostatic interaction model was

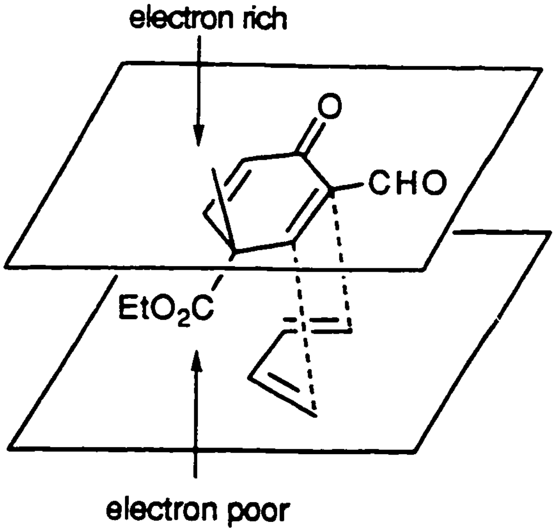


Figure 1-6 The approach of the diene onto the more electrophilic face of cyclohexadienone**1**

originally proposed by Kahn and Hehre and then used to explain the facial selectivities of numerous allylic heterosubstituted dienes and dienophiles.[20] It was concluded that electron poor dienophiles should add preferentially onto the more nucleophilic diene face and electron rich dienes onto the dienophile which exhibits the greater electrophilicity. In the case of cyclohexadienone **1**, more electrophilic is the ester face as shown in Figure 1-6. As a result, the approach of diene from that side is favored.

This model can also be used to discuss the results of the addition to spiro lactone **10**. The lone electron pair of the carbonyl oxygen shields the electron deficient carbon of the lactone carbonyl, causing the bottom face in Figure 1-7 to be more electron rich. The addition of electron rich diene studied occurs therefore preferentially from the top face.

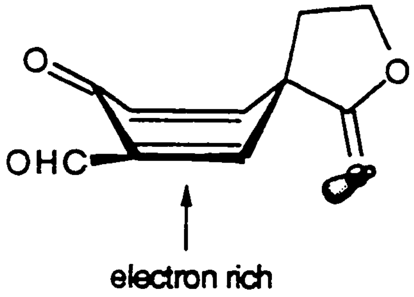
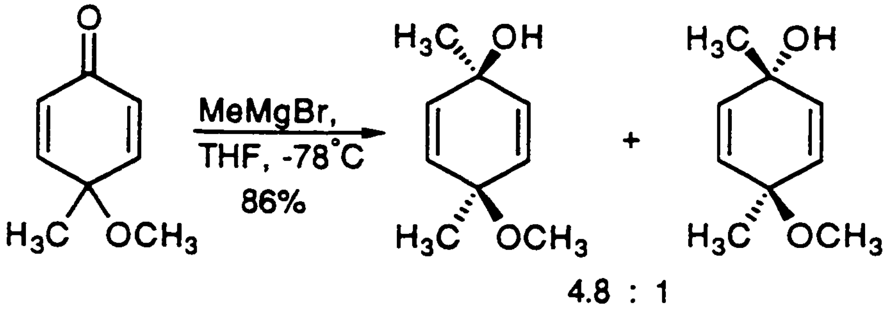


Figure 1-7 The electron rich face of the spiro lactone **10**

In recent years, the influence of coulombic interactions in π-facial stereoselection has been stressed in different types of reactions[21-23] and the first quantitative model for the prediction of the ratio of α- vs. β-facial 1,2-attack in nucleophilic additions to 4,4-disubstituted dienones was proposed by Wipf and coworkers.[24,25] In their study an intriguing variation of selectivity in addition of organometallic reagents to cyclohexadienones **11** - **13** (Figure 1-8) was observed.[24] The addition of methylmagnesium bromide to compound **11**, for example, yielded a 4.8:1 mixture of two diastereomers with the major one resulting from the attack *anti* to the methoxy group (Equation 1-2). Whereas the

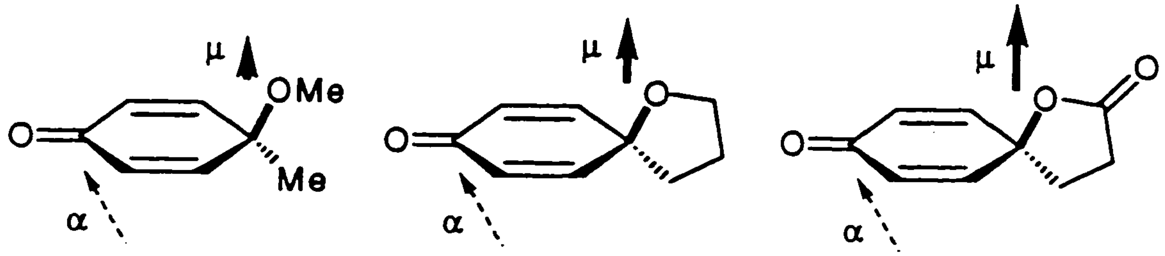


(Eq. 1-2)

11

conversion of **12** under the same conditions, led to a considerable increase in the α/β selectivity and isolation of products in a 8.6:1 ratio. Even greater increase was observed in case of spiro lactone **13** (32:1 ratio of α/β selectivity).

Although the general increase in selectivity from 4-alkoxy- to 4-acyloxydienone can be explained by Ahn-Eisenstein argumentation[26] of transition state stabilization by interaction of the newly forming σ-bond with the σ* of the electronegative substituent in the antiperiplanar position, this theory does not account for differences between the monocyclic and spirocyclic systems studied. Similar problems arose when the Cieplak effect was considered[27] and the application of the principle of frontier orbital distortion proposed by Liotta and Burgess[28] would lead to an experimentally incorrect prediction for β-selectivity.



11 **12** **13**

Figure 1-8 The dipole moments μ of dienones 11 - 13

The possibility of an electrostatic control mechanism in these dienone additions was then considered, as there appeared to be a reasonable correlation of the observed α-selectivity with the expected dipole moment μ of dienones **11** - **13** (Figure 1-8). To test the role of the electrostatic control, pentafluoroethyl dienone with an inverted dipole moment opposite to the carbon-oxygen bond (Figure 1-9) was synthesized.[24] As predicted by the electrostatic effect, the

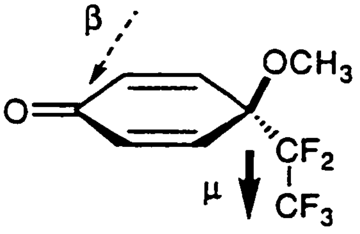


Figure 1-9 The dipole moment μ of pentafluoroethyl dienone

β-face addition product was isolated as the major one when that dienone was reacted with methyllithium in THF. The results presented in that study illustrated also the high sensitivity of the stereoselectivity of 1,2-addition process toward the solvent medium, the electronic structure and the state of aggregation of the nucleophile.

It is clear that a number of different factors, which are still not fully understood, influence the course and the outcome of the reactions. The high degree of π-facial selectivity shown for compounds **1** and **7** in their cycloadditions has strong synthetic implications. These results suggest that the ester group at C-4 could serve as a directing group for facial selectivity in Diels-Alder reactions. The strong preference for the ester group to adapt an equatorial position to avoid unfavorable electronic interactions ($\sigma_{C\text{-}C}$-π^*, Figure 4) could be extrapolated to 2-cyclohexenone derivatives possessing a C-4 carbonyl substituent. If that is true, then the ester moiety can be used as a directing group to achieve high degree of selectivity in reactions such as hydrogenation, conjugated addition and epoxidation. The validity of this statement was tested and the results of the reactions carried out will be discussed in the following section.

Results and Discussion

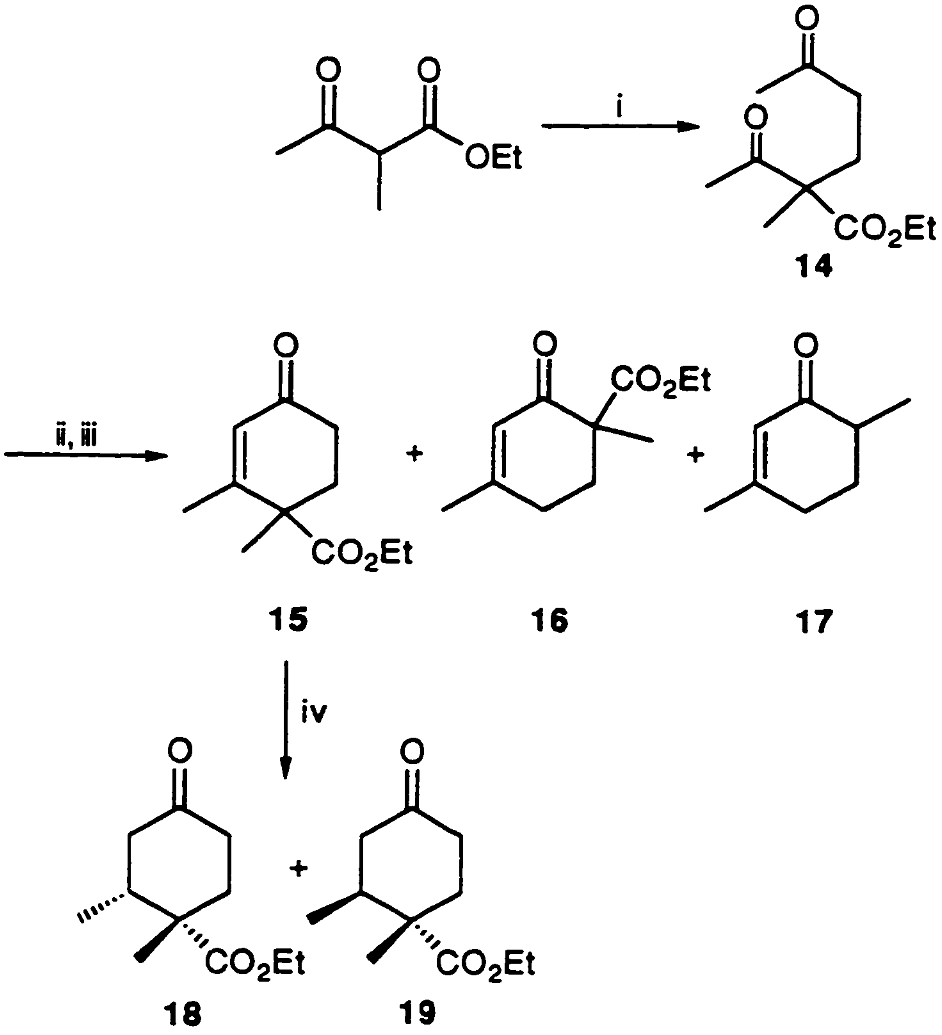
Our study, to test the extent and type of influence the C-4 ester moiety may have on the stereochemical outcome of reactions involving 4,4-disubstituted 2-cyclohexenones, was divided into three parts, as three different types of reactions were investigated, namely: hydrogenation, conjugate addition and epoxidation. In each part, designed enone esters were synthesized and their targeted transformations were explored. The reactions carried out and obtained results on the use of an ester as a directing group are discussed bellow.

A. Hydrogenation

First, known cyclohexenone **15**[17,29] was prepared. The methyl group at C-3 should facilitate the determination of stereochemistry of hydrogenation products of this compound. Its synthesis started with Michael addition of ethyl 2-methylacetoacetate to methyl vinyl ketone using DABCO as a base to afford heptadione **14** in 92% yield (Scheme 1-1). The ir spectrum showed the carbonyl absorptions for both ketones and ester at 1712 cm^{-1}. In the ^{13}C APT nmr spectrum, a total of 11 lines was observed. The ketone carbonyl groups resonated at δ 207.2 and 205.3, and the ester carbonyl at δ 172.5. In the ^{1}H nmr spectrum, two sharp singlets at δ 2.09 and 2.07 were attributed to the two methyl ketone moieties. The mass spectrum displayed a molecular ion peak at m/z 214.1205 corresponding to the formula $C_{11}H_{18}O_4$.

Intramolecular aldol condensation employing LDA as a base was then carried out, followed by dehydration with *p*-TsOH in refluxing benzene. The desired enone ester **15** was obtained as the major product in 51% yield. Two minor products **16** and **17** were produced in less then 15% combined yield and their identities assigned by comparison of the ^{1}H nmr spectrum of the mixture to the data reported.[17] Carbonyl absorptions at 1727 cm^{-1} (ester) and 1676 cm^{-1} (enone) were shown in the ir spectrum of **15**. The mass spectra displayed a molecular ion peak at m/z 196.1101 in agreement with the formula $C_{11}H_{16}O_3$. In ^{13}C APT nmr spectrum, signals at δ 161.5 and 128.1 indicated the presence of a double bond. The ^{1}H nmr spectrum displayed a pair of mutually coupled

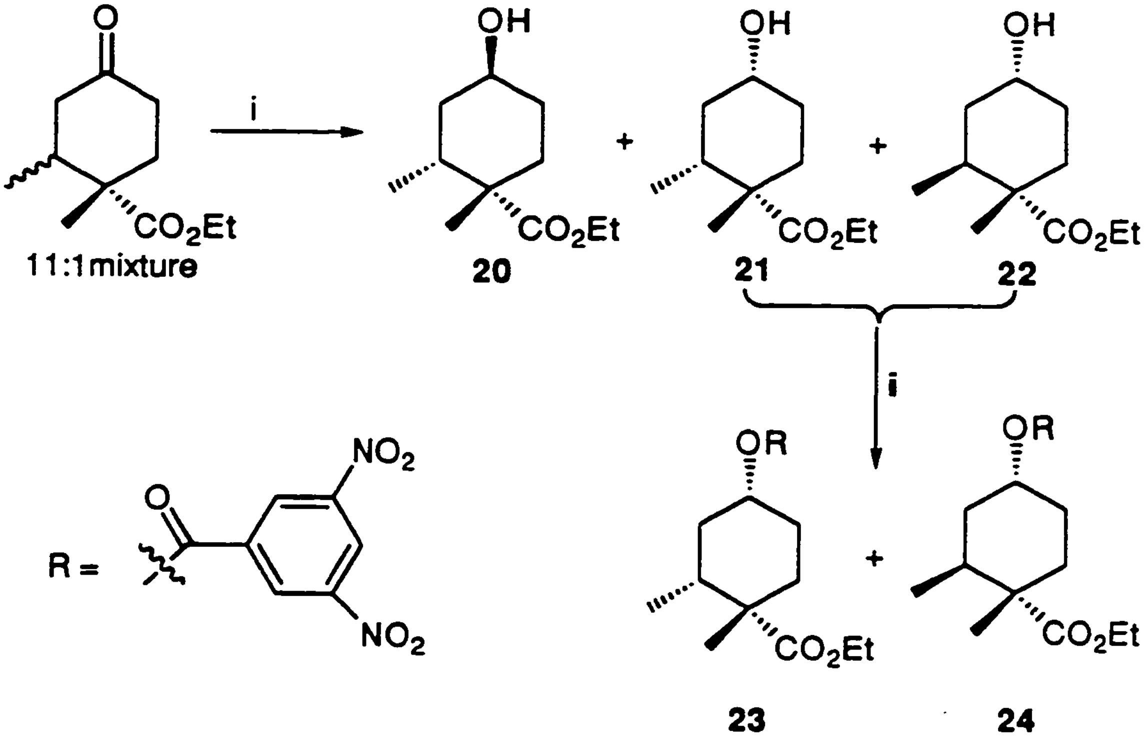
Scheme 1-1



i. DABCO, MVK, DME; ii. LDA, THF; iii. *p* -TsOH, PhH; iv. H_2, 5% Pd/C, EtOAc signals (J = 1.5 Hz): a quartet at δ 5.89 for vinylic proton and a doublet at δ 1.94 for the vinylic methyl group. The elemental analysis also supported the molecular composition.

With cyclohexenone **15** in hand, the hydrogenation reaction was tested. Palladium on carbon (5%) was used as a catalyst and ethyl acetate was chosen as a solvent. In each trial, reaction was completed within three hours, when hydrogen pressure close to 2 atmospheres and vigorous shaking were applied. An inseparable mixture of two isomers **18** and **19** was always obtained in a ratio of 10-12:1 and in a combined yield of 85-89%. The ir spectrum of the resulting mixture showed one intense carbonyl band at 1715 cm^{-1}. A molecular ion peak at m/z 198.1254 was observed in the mass spectrum, corresponding to the formula $C_{11}H_{18}O_3$. In the ^{1}H nmr spectrum, the C-4 methyl group of the major isomer appeared at δ 1.34. The C-3 methyl groups appeared as doublets (J = 7 Hz) at δ 1.02 and δ 0.90 for the major and minor compound, respectively. The ^{13}C APT nmr spectrum confirmed the presence of both isomers and a total of 11 lines was observed for the major product. Attempts to determine stereochemistry were first made through a series of nOe experiments, however they were inconclusive. For example, the lack of enhancement of the C-4 methyl signal, when the C-3 methyl was irradiated, could have indicated that the two methyl groups of the major isomer are on the opposite faces. This could not be confirmed, however, as the signal of the C-4 methyl group for the minor compound could not be assigned, making similar nOe studies for that isomer impossible. To confirm unequivocally the stereochemistry of the hydrogenation products **18** and **19**, a solid derivative of the major isomer was prepared according to Scheme 1-2. The mixture of ketones, in a ratio of 11:1, was reduced using sodium borohydride in ethanol. After 10 minutes, the substrates were completely consumed, and two alcohols **20** and **21** were isolated in 8% and 71% yield respectively.

Scheme 1-2



i. $NaBH_4$, EtOH; $(NO_2)_2C_6H_3COCl$, pyr, PhH

The ir spectrum of the minor product **20** showed a characteristic absorption of hydroxyl group at 3421 cm^{-1} and an intense ester carbonyl band at 1724 cm^{-1}. In the ^1H nmr spectrum, a signal at δ 3.98 was attributed to the C-1 proton. Subsequently, oxidation of that alcohol with PCC in dichloromethane was carried out. The spectral data of the resulting ketone was identical with the data of the major hydrogenation product, proving that both isolated alcohols **20** and **21** were derived from the same ketone. In the ir spectrum of the major alcohol **21**, a hydroxyl absorption at 3364 cm^{-1} and a carbonyl absorption at 1724 cm^{-1}

were observed. A molecular ion peak at m/z 200.1409, corresponding to the formula $C_{11}H_{20}O_3$, was shown in the mass spectrum of **21**. The ^1H nmr spectrum displayed a signal at δ 3.61 for C-1 proton. The presence of a small doublet (*J* = 7 Hz) at δ 0.93 indicated that this alcohol was contaminated by an impurity, possibly **22** derived from the minor ketone of the starting mixture. The desired benzoate **23** was obtained in 81% yield when alcohol **21** was reacted with 3,5-dinitrobenzoyl chloride in benzene in the presence of pyridine. Flash chromatography, followed by recrystallization from ethanol gave needle like crystals of **23**. Characteristic absorptions were observed in the ir spectrum: weak absorption at 3103 cm^{-1} for aromatic C-H stretching, a carbonyl band at 1725 cm^{-1} for both esters and two intense absorptions at 1546 and 1378 cm^{-1} for nitro groups. In the ^{13}C APT nmr spectrum, a total of 16 lines was displayed. The ester groups resonated at δ 175.3 and 162.0, and the signals for benzene ring appeared at δ 148.7, 134.5, 129.4 and 122.3. The mass spectrum showed a molecular ion peak at m/z 394.1368 in agreement with the formula $C_{18}H_{22}O_8N_2$. The ^1H nmr spectrum supported the structural assignment showing two signals for aromatic protons at δ 9.20 and 9.13 and the C-1 proton signal at δ 5.08. Compound **24** was not detected in the ^1H and ^{13}C nmr spectra of the purified benzoate **23**. The sterochemistry of **23** was established by the single crystal X-ray crystallography. The results are shown in Figure 1-10. It was revealed that the two methyl groups at C-3 and C-4 are on the opposite faces, which could explain the lack of enhancements previously observed in the nOe studies of the major hydrogenation product. Based on the X-ray data for **23**, the major ketone was unmistakably assigned the structure **18** and the minor isomer was assigned to structure **19** (Scheme 1-1).

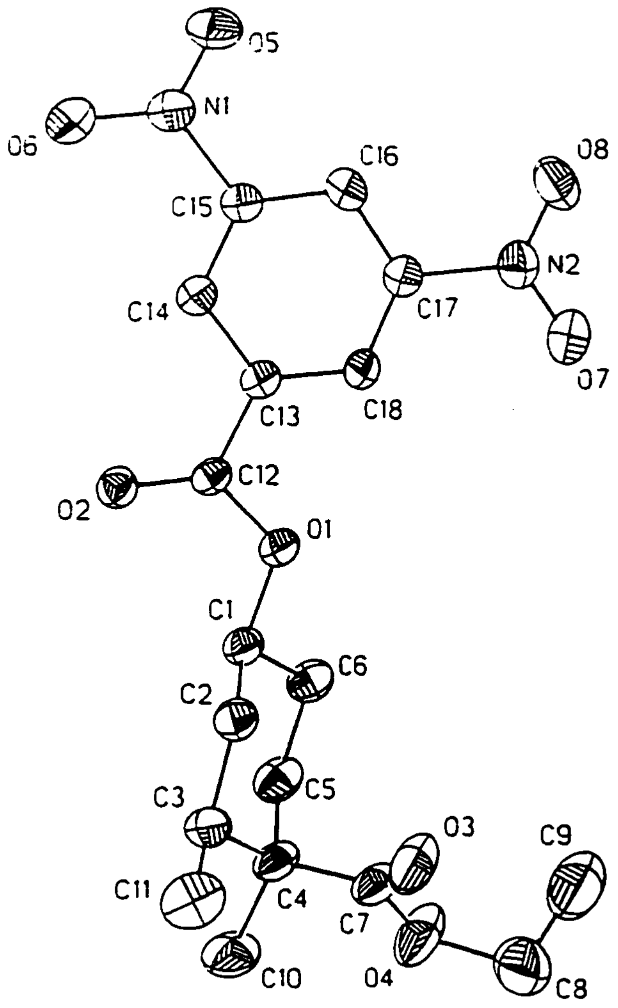
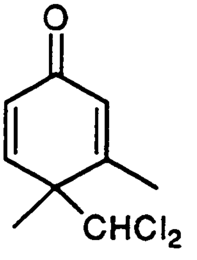


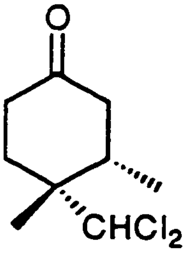
Figure 1-10 X-ray structure of compound **23**

The observation that, in the hydrogenation reaction of the 2-cyclohexenone **15,** hydrogen transfer occurred with a high degree of selectivity (10-12:1) from the C-4 methyl group face was quite intriguing. Based on the reaction outcome one could conclude that the only or the major factor playing an important role in the observed stereoselectivity of the reaction is the steric factor and that the bulk of the ester moiety would prevent binding of the molecule to the surface of the catalyst from that side. As a result, coordination of the double bond in compound **15** would be possible mainly from the side opposite to the ester.

Many cases, in which the steric factor is the controlling one in hydrogenation reaction, have been reported.[30-32] This concept, however, applies best to systems where rigid geometry or substituents present severe steric hindrance. In other compounds only moderate selectivities have been observed. Hydrogenation of the dienone **25**, for example, using 10% Pd/C as a catalyst



25



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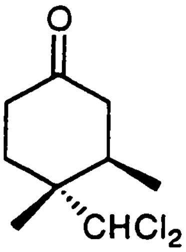
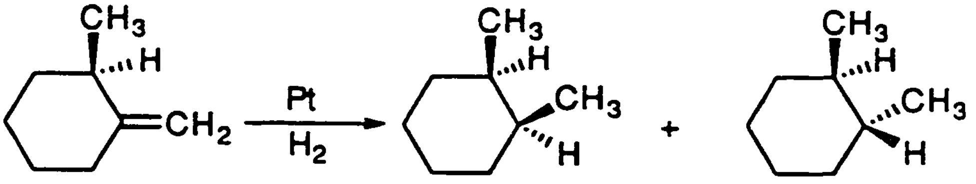


27

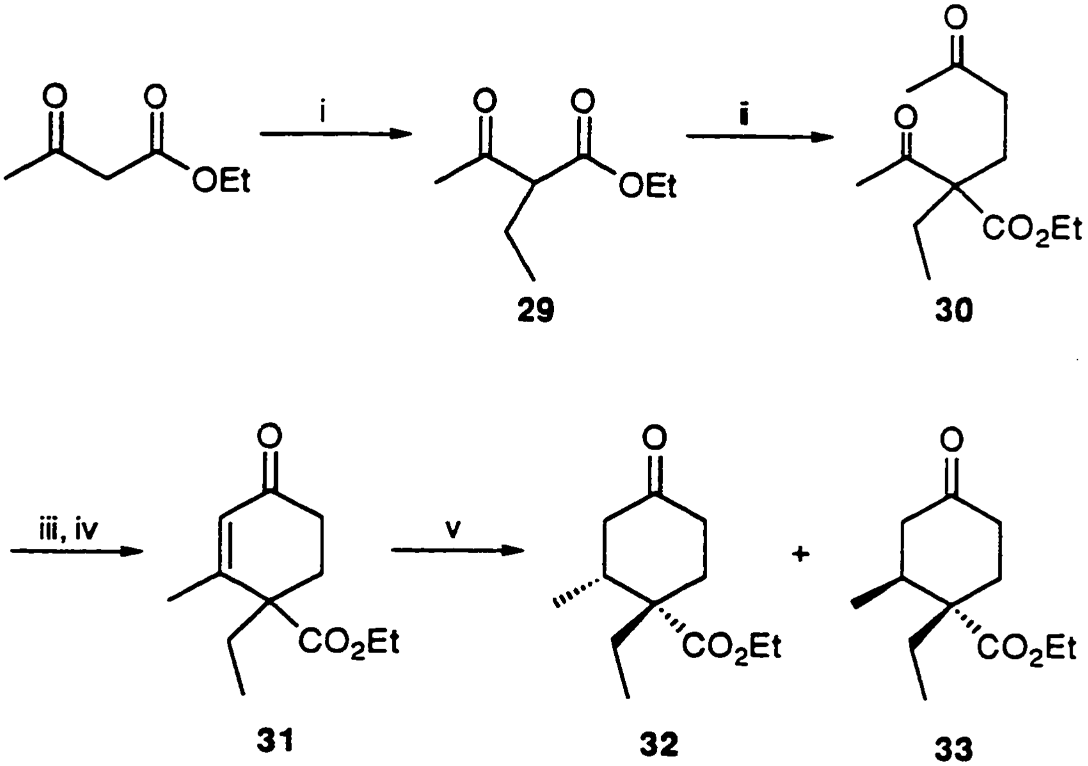
catalyst provided a mixture of **26** and **27** in a 4:1 ratio.[33] The preference for addition from less congested side was shown in hydrogenation of compound **28** and resulted in ~2:1 selectivity (Equation 1-3).[34]



28 70% 30% (Eq. 1-3)

When compared to examples found in the literature, the facial selectivity observed in hydrogenation of cyclohexenone **15** appeared to be quite high. To test to what extent the steric interactions controlled the outcome of the reaction, second cyclohexenone ester **31** was synthesized (Scheme 1-3) and then hydrogenated under the same conditions. It was assumed that if the stereoselectivity was mainly sterically induced, then replacement of the methyl at C-4 by the larger ethyl group would result in more hydrogen addition from the ester side and a decrease in selectivity would be observed.

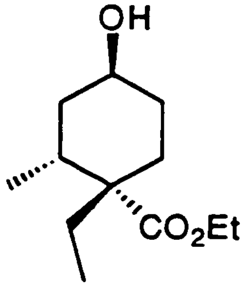
Scheme 1-3



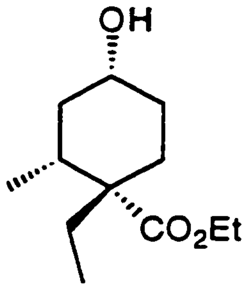
i. EtBr, NaH, DME; ii. MVK, DABCO, DME; iii. LDA, THF; iv. *p*-TsOH, PhH;
v. H_2, 5% Pd/C, EtOAc;

Synthesis of **31** started with alkylation of ethyl acetoacetate using ethyl bromide and sodium hydride, to afford compound **29** in 73% yield. The ir spectrum showed two carbonyl absorptions at 1724 and 1716 cm^{-1} for the ester and ketone, respectively. In the ^1H nmr spectrum, the formation of **29** was confirmed by the presence of a triplet (J = 7.5 Hz) at δ 3.32 for the C-2 proton and two doublets of quartets (J = 7.5, 7.5 Hz) at δ 1.88 and 1.86, together with a triplet (J = 7.5 Hz) at δ 0.92 for protons of the C-2 ethyl group. The mass spectrum displayed a molecular ion peak at m/z 158.0941 corresponding to the formula $C_8H_{14}O_3$. Michael addition of **29** to methyl vinyl ketone was carried out as before for **14** and provided heptadione **30** in good yield of 84%. In the ir spectrum of **30**, intense carbonyl absorptions were observed at 1737 and 1712 cm^{-1}. The ^1H nmr spectrum showed two methyl singlets at δ 2.09 and 2.08. The structure was confirmed by the mass spectrum displaying a molecular ion peak at m/z 228.1337 in agreement with the formula $C_{12}H_{20}O_4$. Conversion of **30** into enone **31** was achieved by an intramolecular aldol process under basic conditions (LDA), followed by dehydration of the condensation product using *p*-TsOH. The compound **31** was obtained in 50% yield and its spectral data were consistent with the structure assigned. It showed ir absorptions at 1725 cm^{-1} for the ester and at 1678 cm^{-1} for the enone. The ^{13}C APT nmr spectrum displayed signals at δ 160.9 and 129.3 indicating the presence of a double bond. In the ^1H nmr spectrum, a quartet ($J = 1$ Hz) at δ 5.91 for the vinylic proton and a doublet at δ 1.97 with a coupling constant of 1 Hz, for the vinylic methyl group was observed. A molecular ion peak was detected at m/z 210.1257 in the mass spectrum, which confirmed the formula $C_{12}H_{18}O_3$.

Having enone **31** prepared, hydrogenation was carried out using 5% Pd/C as a catalyst and ethyl acetate as a solvent. The reaction proceeded smoothly and after 3 hours no starting material was detected by tlc analysis. A mixture of two inseparable isomers was isolated in a 12 : 1 ratio. The ir spectrum of that mixture showed an intense carbonyl absorption at 1728 cm^{-1} for ketone and ester. In the mass spectrum, a molecular ion peak was observed at m/z 212.1409 in agreement with the formula $C_{12}H_{20}O_3$. The ^{13}C APT nmr spectrum displayed a total of 12 lines for the major product and another set of signals confirming the presence of the other isomer. In the ^1H nmr spectrum, the C-3 methyl group of the major isomer resonated at δ 0.95, whereas the methyl group of the C-4 ethyl moiety appeared as a triplet at δ 0.85 for the major product and at δ 0.82 for the minor one. A doublet at δ 0.87, atrributed to the C-3 methyl group of the minor ketone could not be unequivocally assigned as it was overlapped with another signal. This assignment was shown to be correct, however, by the later studies of conjugate addition (discussed later in this section), where a 2:1 mixture of these two ketones was obtained. The ^{1}H nmr spectrum resembled closely that of compounds **18** and **19**. For example, in both cases the C-3 methyl group of the major product resonated at a somewhat lower field (δ 1.02 and 0.95) than the corresponding methyl group of the minor product (δ 0.92 and 0.87). By direct comparison of the chemical shifts of characteristic signals in both spectra, the major ketone was assigned structure **32** and the minor one structure **33**. Further attempts to confirm the stereochemistry of these hydrogenation products by nOe experiments were not successful. To assure the correctness of the assignment, a mixture of **32** and **33** (12:1 ratio) was treated with sodium borohydride in ethanol. After 10 minutes, the reduction was completed. Chromatographic purification of the crude product gave two alcohols **34** and **35** in 8% and 73% respective yields.



34



35

The ir spectrum of **35** showed a strong hydroxyl absorption at 3363 cm^{-1} and a carbonyl ester absorption at 1722 cm^{-1}. The mass spectrum displayed a molecular ion peak at m/z 214.1571 corresponding to the formula $C_{12}H_{22}O_3$. In the ^1H nmr spectrum, the C-1 proton resonated at δ 3.61 and a doublet for the C-3 methyl group was observed at δ 1.06. These chemical shifts were nearly identical with the ones observed for the compound **21** (also δ 3.61 for the C-1 proton and δ 1.04 for the C-3 methyl). The ^1H nmr spectra of the alcohols **20** and **34** also displayed close similarity. It was then concluded that the structures assigned to the major ketone **32** and the minor one **33** were correct.

The same stereoselectivity was observed for catalytic hydrogenation of cyclohexenones **15** and **31**. Equally high preference for hydrogen addition from the side opposite to the ester group indicated that the moderate change in size of C-4 substituent (as going from methyl to ethyl group) did not affect the course of the reaction. Because of the high facial selectivity displayed by both cyclohexenone systems, it was suspected that other then steric factors may have contributed to the outcome of the reactions

One possible factor that could induce the observed selectivity is some type of attraction, which would bind the ester group to the surface of the catalyst in a specific way as to prevent the addition of hydrogen from the same side. Some known interactions between metal catalyst and other molecules include: (a) chemisorption,[35] binding of mulitiply bonded functional groups to the catalyst surface immediately prior to and during transferral of hydrogen to them; (b) poisoning,[36] strong and often irreversible interaction between various transition metal catalysts and certain species containing unshared electron pairs, for example divalent sulfur, mercury and its salts; (c) haptophilic interaction,[37-39] weak and reversible version of catalyst poisoning shown by some functional groups, *e.g.* alcohols and amines. A number of cases has been shown in which a hydroxy group near a reducible double bond has been responsible for introduction of hydrogen *cis* in relation to the alcohol, despite the existing steric hindrance.[38,40] An extensive study on haptophilicities of different functional groups, and the factors that could affect them, was reported by Thompson and coworkers.[39]

In case of the cyclohexenone systems possesing an ester group at C-4 (**15** and **31**), one could imagine the following scenario to account for the observed stereoselectivity. As the molecule approaches the catalyst surface with the ester group in an equatorial position, a reversible adsorption can take place through the lone pairs of carbonyl oxygen (Figure 1-11a). In that arrangement the plane of the double bond to be reduced is not parallel to the catalyst surface and that makes it difficult for the interaction to occur. It can be also envisioned, that if a conformational inversion takes place, right before binding or when a molecule is adsorbed, then although the double bond is positioned parallel to the catalyst surface, the spread of the ester moiety will prevent necessary interaction and addition of hydrogen from that side (Figure 1-11b). Because the ester group is not a strong binder, the molecule leaves the catalyst before the hydrogenation could occur. As a result, the methyl group face of the double

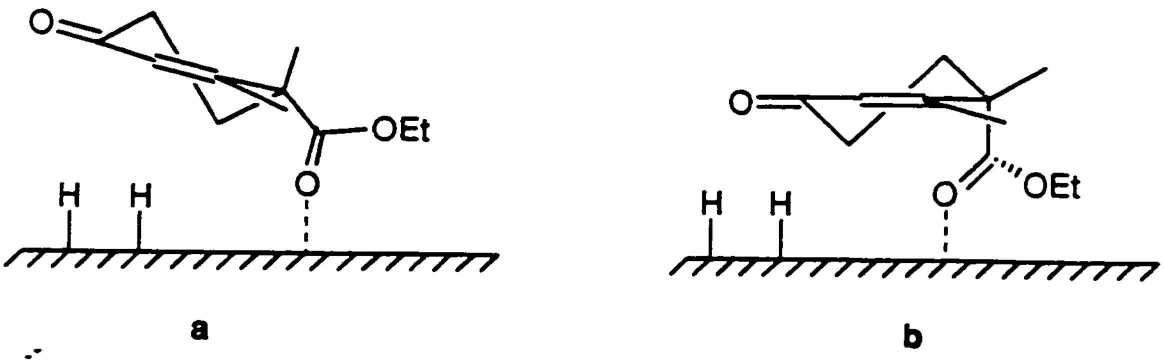


Figure 1-11 Hydrogenation of cyclohexenone **15**

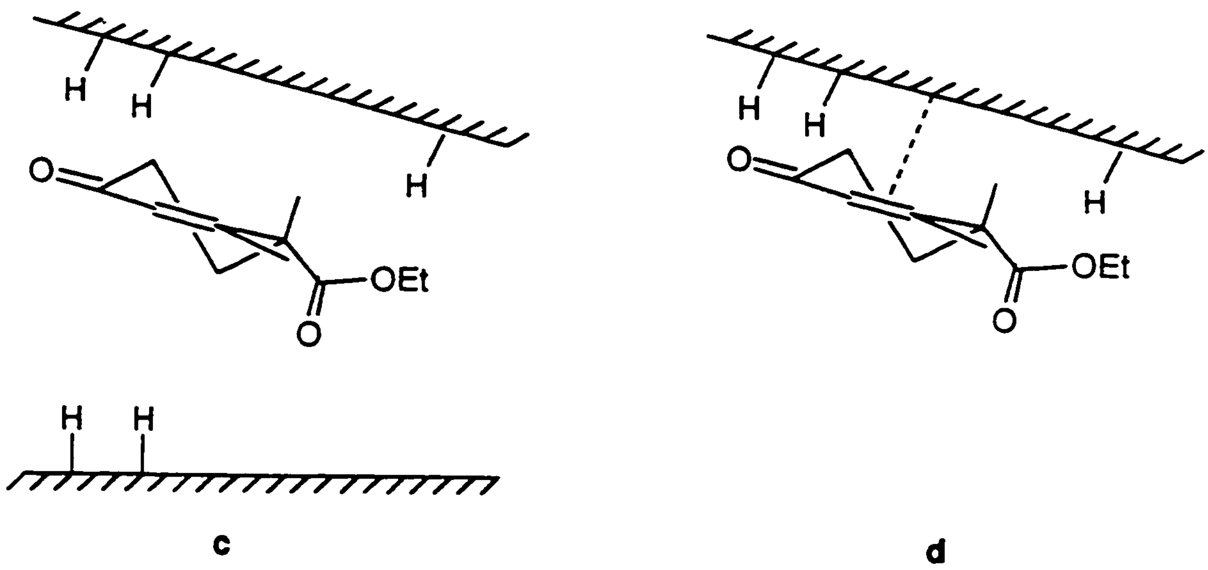


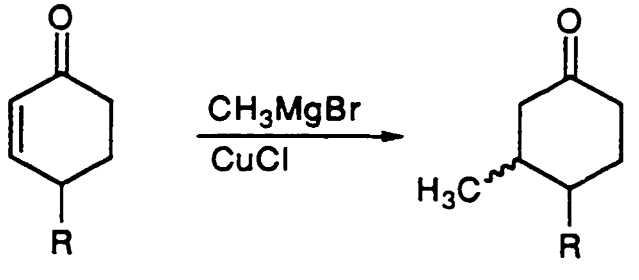
Figure 1-11 (continued)

bond becomes more accessible for the constructive interaction with the surface of another catalyst (Figure 1-11c). Adsorption and hydrogen addition then take place, leading to the observed major products (Figure 1-11d).

In summary, reversible binding of the ester group to the surface of catalyst used in hydrogenation may be an important contributing factor in inducing the observed high stereoselectivity. Although the exact cause of the stereocontrol remains to be understood, the use of an ester group to effect stereoselective formation of cyclohexanone derivatives (possibly derivatives of other cyclic ketones as well) *via* hydrogenation is unprecedented and promises broad synthetic utility.

B. Conjugate addition.

Conjugate additions of carbon- and heteroatom-based ligands (R_3Si- or R_3Sn-) from stoichiometric copper reagents to unsaturated systems are frequently used in structure elaboration in organic synthesis.[41,42] Because of their coupling efficiency and lower basicity, when compared to Grignard reagents, Gilman lithio cuprates (R_2CuLi) are the reagents of choice and in our study, lithium dimethylcopper reagent was employed. The stereochemistry of the conjugate addition has been studied in many systems and the steric factor is often used to explain the observed outcome of the reaction. In the cyclohexenone system **36** (Equation 1-4) the effect of varying the 4-alkyl group on the stereochemistry of copper-catalyzed addition of methyl Grignard reagent was investigated.[43] From each substrate (**36**, R = CH_3, C_2H_5, *i*-C_3H_7), two isomers of the 1,4-adduct **37** were formed, the *trans* always predominating over the *cis*. As the bulk of the 4-alkyl group was increased from methyl to ethyl to isopropyl, the *trans* : *cis* ratio also increased from 72:28 to 77:23 to 89:11. In others studies, the explanation for the preferred anti-periplanar addition, relative to the polar allylic substituent, was offered based on a Felkin-type transition state.[44-46] It was also shown that



36 **37**

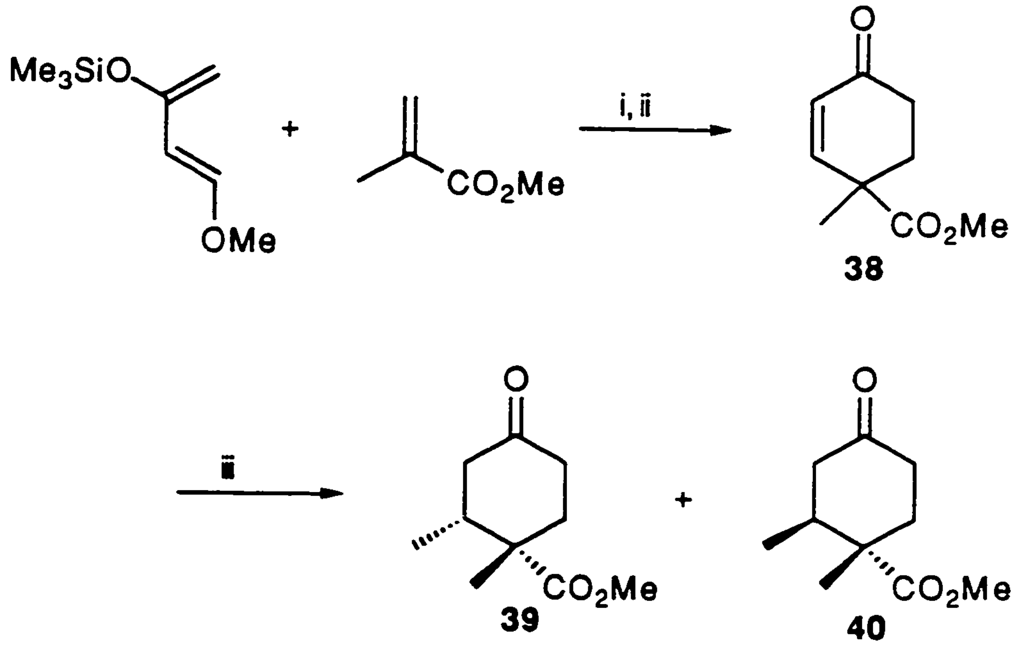
(Eq. 1-4)

product yields and stereochemistry often depends on the nature of the reagent used.[47] No study showing the influence of an ester group on the stereoselectivity in 1,4-addition to 2-cyclohexenone system has been reported.

Enone ester **38** was chosen for our study as the stereochemistry of its addition products could be explicitly determined by direct comparison of their spectral data with those of the known compounds **18** and **19** (*vide supra*). Cyclohexenone **38** was readily prepared by a variation of the known method[48] using Danishefsky diene and methyl methacrylate according to Scheme 1-4. Compound **38** was obtained in 92% yield when a four-fold excess of methyl methacrylate was used for the Diels-Alder reaction followed by acid treatment of the adduct. Its spectral data was identical with an authentic sample. The ir spectrum showed strong carbonyl absorptions at 1732 cm^{-1} (ester) and 1684 cm^{-1} (enone). A molecular ion peak was observed at m/z 168.0790 in the mass spectrum corresponding to the formula $C_9H_{12}O_3$. In the ^{13}C APT nmr spectrum, a total of 9 lines was displayed. The ^1H nmr spectrum showed two doublets (J = 10.5 Hz) at δ 6.87 and 5.96 for the C-3 and C-2 protons, respectively.

When enone ester **38** was reacted with 3 equivalents of lithium dimethylcuprate (Me_2CuLi) in ether at 0° C for one hour, an inseparable mixture of two isomers in a ratio 1.7:1 was obtained. In the ^1H nmr spectrum of the mixture, the C-3 methyl group of the major product resonated at δ 1.01 and its C-4 methyl at δ 1.36, whereas the signals of the respective groups of the minor product appeared at δ 0.90 and 1.27. A comparison of these chemical shifts with those observed for compound **18** and **19** led to the assignment of structure **39** to the major isomer and structure **40** to the minor isomer.

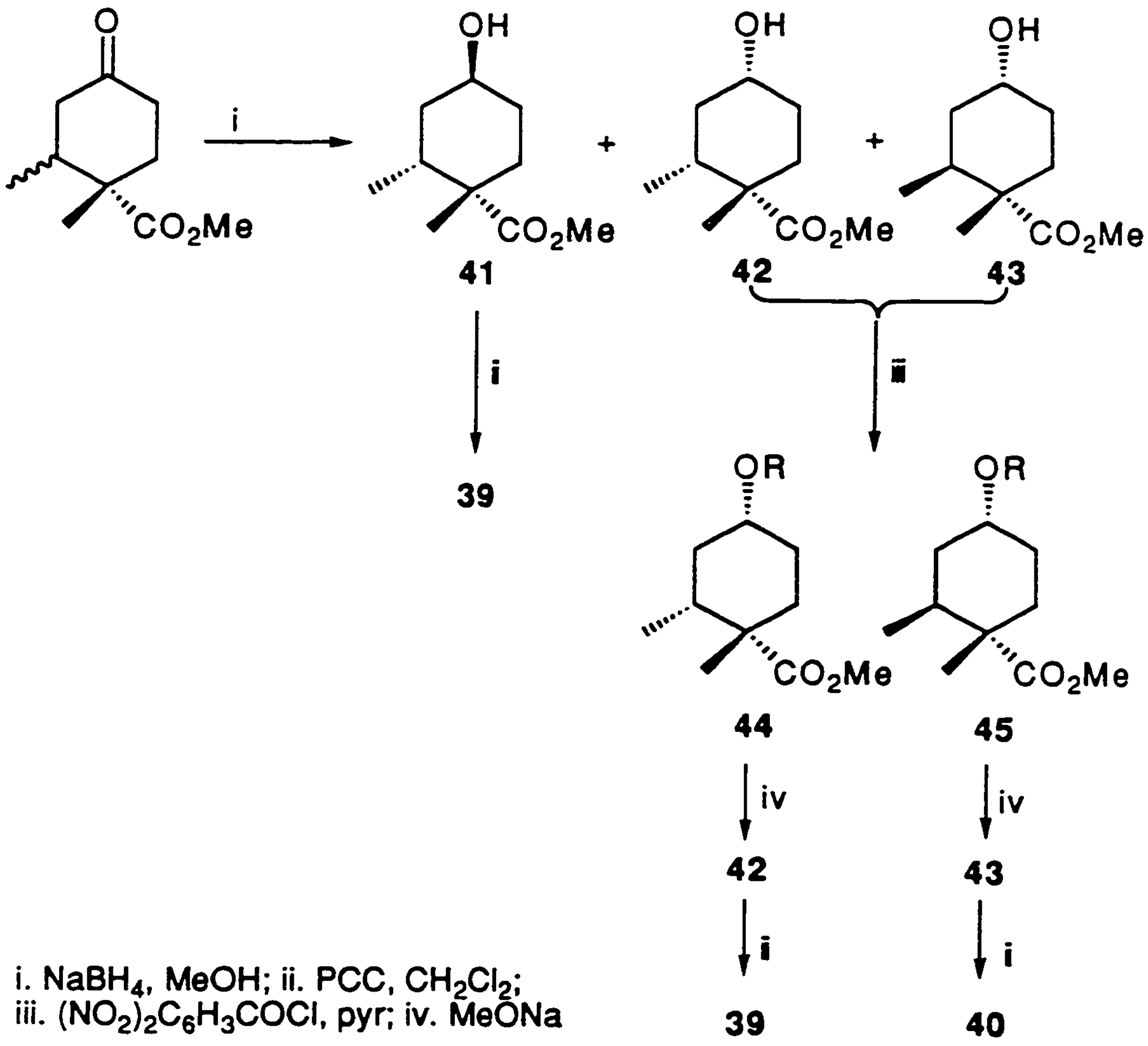
Scheme 1-4



i. toluene, reflux; ii. H_3O^+; iii. Me_2CuLi, Et_2O;

These two diastereomers were separated through a series of functional group transformations (Scheme 1-5) during which the stereochemistry of C-3 and C-4 remained intact. When the 1.7:1 mixture of **39** and **40** was treated with sodium borohydride in methanol, three alcohols were obtained. Pure alcohol **41** was isolated in 7.5% yield. Its ir spectrum showed a typical hydroxyl absorption at 3420 cm^{-1} and a carbonyl absorption at 1729 cm^{-1} the ester. In the mass spectrum, a molecular ion peak was observed at m/z 168.1149. The ^1H nmr spectrum displayed a signal at δ 3.98 (dddd, $J = 7, 7, 4, 4$ Hz) attributed to the C-1 proton. Oxidation of **41** using PCC in dichloromethane yielded ketone **39**, proving that this alcohol was the minor product resulting from the reduction of **39**. Two other alcohols **42** and **43** were isolated as an inseparable mixture

Scheme 1-5



i. $NaBH_4$, MeOH; ii. PCC, CH_2Cl_2;
iii. $(NO_2)_2C_6H_3COCl$, pyr; iv. MeONa

(1.6:1 ratio) in 78% combined yield. These alcohols were converted th the corresponding benzoates **44** and **45** with 3,5-dinitrobenzoyl chloride and pyridine and separated by flash chromatography. Both benzoates showed typical absorptions in the ir spectra, namely, aromatic C-H streching at ~3100 cm^{-1} , ester carbonyl absorbtions at ~1725 cm^{-1} and absorptions for nitro group at ~1550 and 1345 cm^{-1}. In the mass spectra, molecular ion peaks were observed at m/z 380.1217 for benzoate **44** and at m/z 380.1226 for **45**, both in agreement with formula $C_{17}H_{20}O_8N_2$. The ^{13}C APT nmr spectrum of **44** displayed a total of 15 lines; the ester groups resonated at δ 175.8 and 162.1; the aromatic ring signals appeared at δ 148.7, 134.5, 129.5 and 122.3. The ^1H nmr spectrum of **44** resembled very closely that of **45**. The most noticeable difference in chemical shift was displayed by the C-3 methyl groups, which appeared as doublets ($J = 7$ Hz) at δ 1.10 and 0.86, for **44** and **45** respectively. Smaller difference was observed for the C-4 methyl groups. Compound **44** showed a methyl singlet at δ 1.26, whereas in **45** the methyl group resonated at δ 1.20.

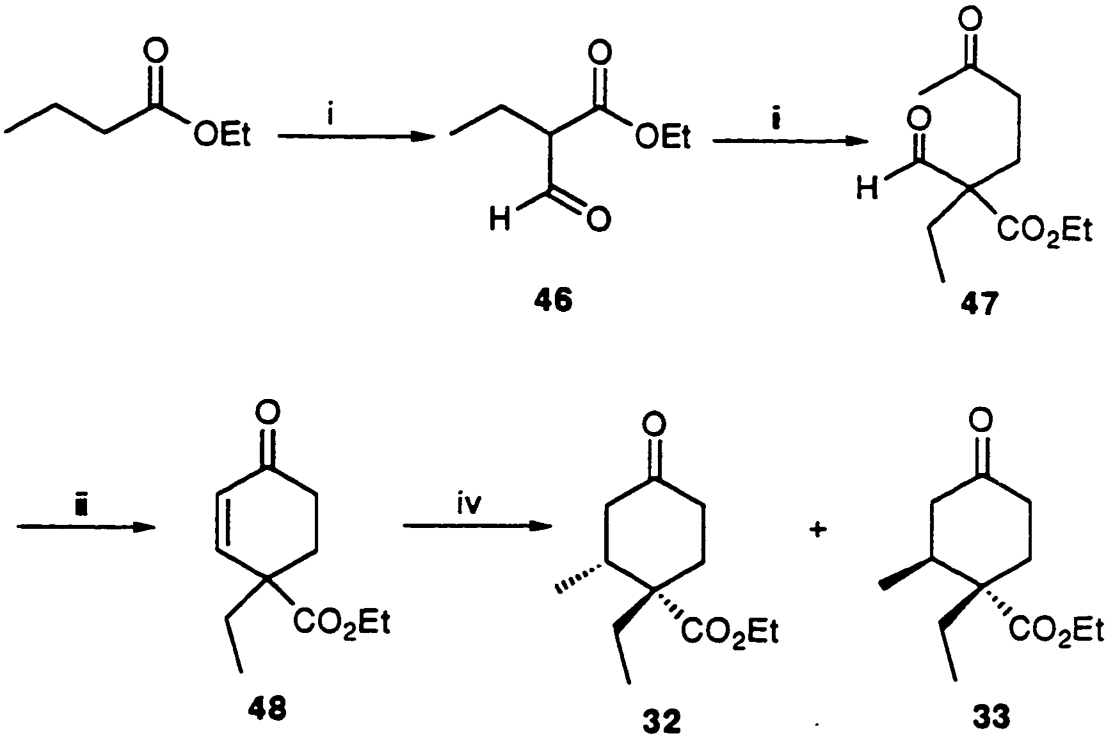
The alcohols **42** and **43** in pure form were produced in very good yields (96% and 91%, respectively) when benzoates **44** and **45** were individually treated with sodium methoxide. Oxidation with PCC in dichloromethane converted alcohol **42** to ketone **39**, whereas alcohol **43** was converted to ketone **40** upon oxidation. Careful analysis of the spectral data of the pure compounds proved that the initial assignment of structures **39** and **40** was correct.

Conjugate addition of lithium dimethylcuprate to enone **38**, under the conditions described, did not show very good stereoselectivity; the isomers were obtained only in a ratio of 1.7:1. However, the fact that the major product was fofmed as a result of addition from the ester side, suggested that the ester group played an important role in stereocontrol. Attempts were made to increase the *cis/trans* selectivity (relative to an ester) by lowering the temperature of reaction. Unfortunately no enhancement in selectivity was observed even when the reaction was carried out at -60°C.

Enone ester **48** was then synthesized as outlined in Scheme 1-6 and its conjugate addition reaction was carried out to check if any change in stereoselectivity would be induced by replacing the methyl group in **38** with an ethyl group. The preparation of cyclohexenone **48** started with a formylation reaction[49]. When ethyl butyrate was reacted with ethyl formate and sodium hydride, compound **46** was obtained in 70% yield. In the ir spectrum, an intense absorption was observed at 1722 cm^{-1} for both the ester and the keto form of the aldehyde. Absorption for the enol form was shown at 1666 cm^{-1}. In the mass spectrum, a molecular ion peak was displayed at m/z 144.0780 corresponding to the formula $C_7H_{12}O_3$. In the ^{13}C APT nmr spectrum, the aldehyde carbonyl resonated at δ 197.5. The ^1H nmr spectrum showed the presence of enol (δ 6.98) and keto forms (δ 9.70) in a ratio of 2:1. Michael addition of **46** to methyl vinyl ketone, using DABCO as a base, afforded heptanone **47**. In its ir spectrum, a strong absorption appeared at 1718 cm^{-1} for all carbonyl groups. The ^1H nmr spectrum showed a singlet at δ 9.72 for the aldehydic proton and a methyl singlet at δ 2.08 atrributed to the acetyl moiety. The mass spectrum displayed a molecular ion peak at m/z 214.1213 in agreement with the formula $C_{11}H_{18}O_4$. Intramolecular aldol condensation under acidic conditions with azeotropic removal of water gave cyclohexenone **48** in 81 % yield. In the ir spectrum, strong carbonyl absorptions were observed at 1729 cm^{-1} and at 1690 cm^{-1} for the ester and enone groups, respectively.

The ^1H nmr spectrum showed a pair of mutually coupled doublets (J = 10 Hz) at δ 6.94 and 6.01, proving formation of the double bond. In the ^{13}C APT nmr spectrum, the ketone appeared at δ 198.5 and the ester resonated at δ 173.1. Between δ 151.1 and 8.8, a total of 9 lines was observed. The molecular composition of $C_{11}H_{16}O_3$ was confirmed by the mass spectrum showing a molecular ion peak at m/z 196.1097.

Scheme 1-6



i. HCO_2Et, NaH, THF; ii. MVK, DABCO, THF; iii. *p*-TsOH; iv. Me_2CuLi, Et_2O;

Reaction of enone ester **48** with lithium dimethylcuprate in ether at 0°C gave an inseparable mixture of two diastereomeric keto esters **32** and **33** in 2:1 ratio in 78% combined yield. These compounds were previously obtained from the catalytic hydrogenation of enone ester **31** and fully characterized (*vide supra).* An analysis of the ^1H and ^{13}C nmr spectra of the mixture with the assistance of the available spectral data of **32** and **33**, led to the conclusion that the major isomer was **32** and the minor isomer **33**.

When the experimental results obtained for the conjugate addition of lithium dimethylcuprate to enones **38** and **48** are compared, only very small increase in selectivity , from 1.7:1 to 2:1, is observed as the C-4 subtituent is changed from methyl to ethyl group. In both cases, the major product results from the addition from the ester side. These results suggest that steric factor alone does not control the course of the addition and probably a number of different factors, in delicate balance, influences the stereoselectivity.

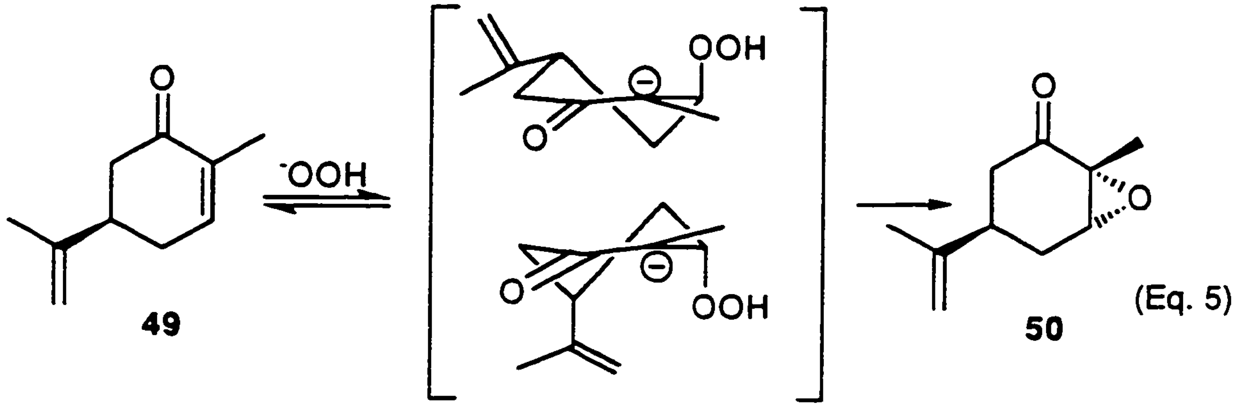
One factor that could account for the preferential attack from the ester side, is electrostatic attraction. The cuprate-enone complex may be preferentially produced from the "electron poor" ester side of the double bond. This is then followed by transfer of a methyl group from the same side to give the observed major product in each reaction.

The observed selectivity may also be a reflection of the strong preference for the ester group to adapt an equatorial position. As the initial cuprate-enone association is said to be reversible,[42] once the complex is formed from the ester side, then the binding to copper species and axial delivery of the methyl is facilitated. However, when the complex forms from the axially positioned methyl side, then binding and the ensuing delivery of a methyl to the equatorial position are unfavorable and slower.

Based on the above results, it can be concluded that the ester moiety can indeed induce the selectivity in conjugate addition. However, the use of an ester as a directing group for the addition has little synthetic value as the observed selectivity is rather poor.

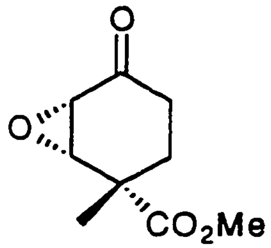
C. Epoxidation

Nucleophilic epoxidation of conjugated enones is a general reaction usually accomplished with hydrogen peroxide, *t*-butyl hydroperoxide or hypochlorite salts such as NaOCl or KOCl.[50] In our study, selectivity of the base induced epoxidation with H_2O_2 was tested. The mechanism of this reaction is well-established.[51] It was shown that, in some cases the alkaline H_2O_2 epoxidation of an enone with the endocyclic double bond, can be entirely stereoselective.[52,53] Thus, carvone **49** gives only epoxide **50** (Equation 1-5). This is in accordance with the fact that the hydroperoxy group must be as close to axial as possible for the cyclization step to occur. Of the two "axial" conformations, the one with the equatorial isopropenyl group will be the predominating one and will lead to the formation of **50**. As no examples have been found that would show the influence of an ester group on the sterochemical outcome of alkaline epoxidation, the following study was carried out to address this issue.



(Eq. 5)

Three cyclohexenones, **15**, **38** and **48** prepared previously (*vide supra*), were chosen for the study. When enone ester **38** was treated with 30% aqueous hydrogen peroxide and lithium hydroxide at room temperature, two diastereomeric epoxides were obtained in a 10:1 ratio and 80% yield. The reaction was very fast, as after 5 minutes no starting material was detected by tlc. Attempts were made to improve the reaction by lowering the reaction temperature. At -10°C, products were isolated in 84% combined yield and with a much improved selectivity of 27:1. In another trial, potassium carbonate was used as a base. In that case the reaction was much slower, and when finally completed at room temperature, the products were isolated in 7:1 ratio. Based on these results, lithium hydroxide was used for subsequent epoxidation reactions . The major epoxide obtained from the reaction of enone **38** showed a carbonyl absorption band at 1716 cm^{-1} for both the ester and ketone groups. In the ^{13}C APT nmr spectrum, a total of 9 lines was observed. The presence of a ketone carbonyl and an ester group was evident from the signals at δ 204.5 and 174.9. The ^{1}H nmr spectrum showed a doublet of doublets (J = 4, 1.5 Hz) at δ 3.71 for the C-3 proton and a doublet (J = 4 Hz) at δ 3.28 for the C-2 proton. The epoxide formation was also confirmed by the mass spectrum displaying a molecular ion peak at m/z 184.0738, corresponding to the formula $C_9H_{12}O_4$. To assign the stereochemistry of the major epoxide, nOe experiments were carried out. Irradiation of the C-4 methyl group at δ 1.35 resulted in 9% enhancement of the C-3 proton signal at δ 3.71. Based on that, the major compound was first assigned structure **51** and the minor product structure **52**. However, this assignment was soon in doubt, when the spectral data of the minor epoxide was collected. Its characteristic protons for the epoxide ring were observed in the ^{1}H nmr spectrum at δ 3.59 (d, J = 4 Hz, C3-H) and 3.35 (d,



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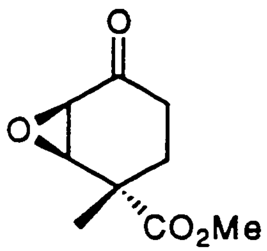
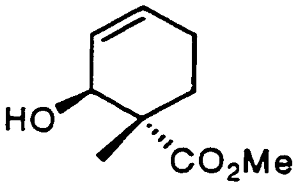


52

J = 4 Hz, C2-**H**). When the nOe experiment was carried out, a large enhancement (11%) of the C-3 proton signal at δ 3.59 was also observed upon irradiation of the methyl group at δ 1.47.

To ensure correct structural assignment, a series of functional group transformations was carried out to obtain a solid derivative of **51**. Wharton reaction[54] was chosen for the transformation of epoxy ketones **51** and **52** into the corresponding allylic alcohols, as it would preserve the stereochemistry at C-3. When the minor epoxide **52** was treated with hydrazine in the presence of acetic acid, alcohol **53** was formed in 54 % yield. In the ir spectrum, a typical hydroxyl absorption was observed at 3492 cm^{-1}. The ^1H nmr spectrum indicated the presence of the allylic alcohol moiety, showing characteristic signals at δ 5.72, 5.61 and 4.55. In an nOe experiment, irradiation of the methyl group at δ 1.20 resulted in no enhancement of the C-1 proton signal, in agreement with the assigned structure. Allylic alcohol **54** was furnished by Wharton reaction of epoxy ketone **51** in a moderate yield of 52%. A broad singlet atrributed to the C-1 proton was displayed at δ 3.87 in the ^1H nmr spectrum. A molecular ion peak shown at m/z 170.0943 in the mass spectrum confirmed the required formula $C_9H_{14}O_3$. To deduce the stereochemistry, nOe experiments were performed. Irradiation of the methyl signal at δ 1.23 gave an 11% enhancement of the C-1 proton signal at δ 3.87.



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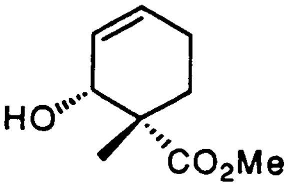

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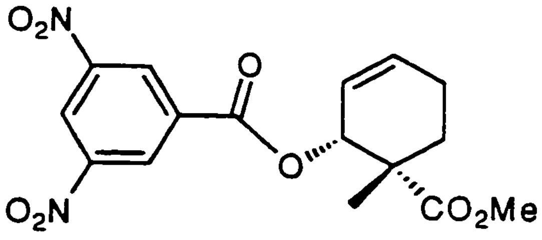


55

Reaction of alcohol **54** with 3,5-dinitrobenzoyl chloride and pyridine in benzene gave crystalline benzoate **55** in 96% yield. The ir spectrum of **55** displayed characteristic absorptions at 3100 cm^{-1} for aromatic C-H streching, 1730 cm^{-1} for ester carbonyls, 1545 and 1345 cm^{-1} for nitro groups. The ^1H and ^{13}C APT nmr spectra clearly indicated the presence of the aromatic ring. In the mass spectrum, a molecular ion peak was observed at m/z 364.0899 in agreement with the formula $C_{16}H_{16}O_8N_2$. A single crystal X-ray crystallographic analysis of benzoate **55** (Figure 1-12) provided final proof for its stereochemical assignment. As a result, the stereochemistry of its precursor **51** was also confirmed.

For the alkaline epoxidation of enone **38**, unusually high selectivity was observed (27:1 ratio of two diasteromers) with the major product resulting from the attack of ^-OOH from the ester side of the carbon-carbon π bond. To test if that strong facial preference was general, enone **48** was treated with hydrogen peroxide and lithium hydroxide in ethanol. The reaction was completed after 2 hours of stirring at 0°C. With lower temperatures, *e.g.* -10°C, the process was very slow. From the reaction carried out at 0°C, two diastereomeric epoxides were isolated in 10:1 ratio and 86% combined yield. The minor product **56** showed an absorption at 1720 cm^{-1} for both the ester and ketone carbonyls.

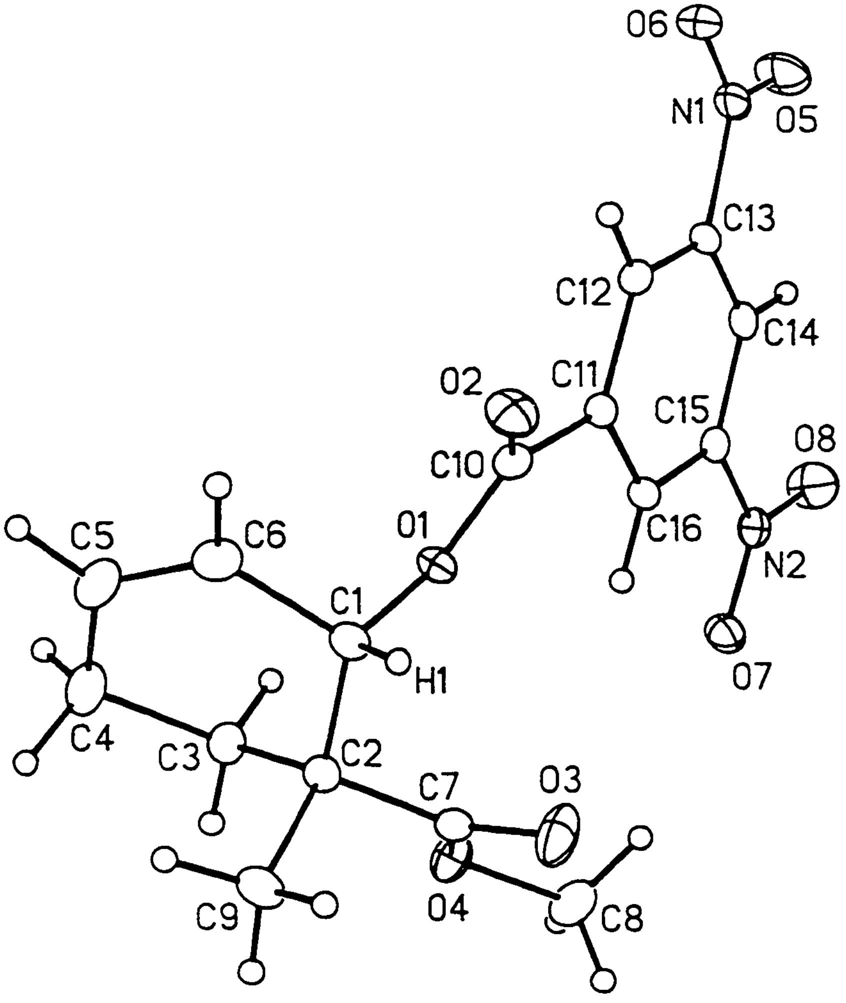
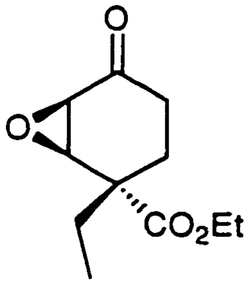
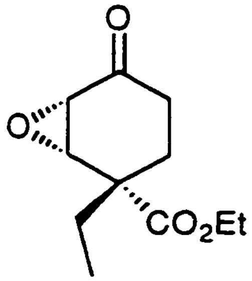


Figure 1-12 X-ray structure of compound **55**

In the ^{1}H nmr spectrum, the C-3 proton resonated at δ 3.69 and the C-2 proton appeared at δ 3.34. The ir spectrum of the major epoxide **57** also showed a single absorption band (1724 cm^{-1}) for both the ester and ketone groups. In the



56



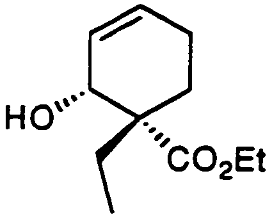
57

^{1}H nmr spectrum, the C-3 and C-2 protons were found at δ 3.75 and 3.27, respectively. In each of the ^{13}C APT nmr spectra of **56** and **57**, a total of 11 lines was observed. In the mass spectra, molecular ion peaks were displayed at m/z 212.1033 for **56** and at m/z 212.1048 for **57** both corresponding to the formula $C_{11}H_{16}O_4$. The ^{1}H nmr spectrum of **56** was found to resemble closely that of epoxide **52** (Table 1-1). The same kind of similarities was also observed when the ^{1}H nmr spectra of epoxides **51** and **57** were compared. Consequently, the structures of epoxides **56** and **57** were assigned. Wharton reaction was also carried out with the major epoxy ketone **57**, giving allylic alcohol **58** in 62 % yield. As expected, the ^{1}H nmr spectrum of **58** was shown to be similar to that of alcohol **54** derived from epoxide **51**. The structure of **58**

Table 1-1. ^{1}H nmr data for epoxides **51**, **52**, **56** and **57**.

proton	**51** δ (in ppm)	**52** δ (in ppm)	**56** δ (in ppm)	**57** δ (in ppm)
C3-**H**	3.71	3.59	3.69	3.75
C2-**H**	3.28	3.35	3.34	3.27

was also supported by the nOe experiment. Irradiation of the methyl group of the ethyl substituent at δ 0.86 resulted in an enhancement (6%) of the C-1 proton signal at δ 4.03.



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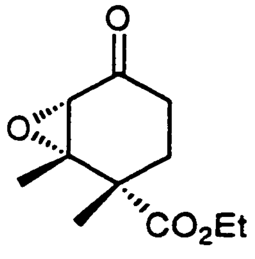
As in the case of enone **38**, good stereoselectivity was observed for the epoxidation of cyclohexenone **48**. The reaction again occured predominantly from the ester side of the molecule.

Epoxidation of enone **15** proved to be more difficult. At room temperature, virtually no reaction took place. Only after the temperature was raised to 35-40°C, the reaction was found to proceed at a resonable rate. Two epoxides were obtained in 79% combined yield after 2 hours. A dramatic decrease in selecitvity occurred and the two isomers were isolated in a 1.5:1 ratio.

The major epoxide was assigned structure **59** and the minor one structure **60** on the basis of the following spectroscopic evidence. The molecular composition of each compound was confirmed by mass spectroscopy. Molecular ion peaks were observed at m/z 212.1045 and 212.1042 for **59** and **60**, respectively. In each of the ^{13}C APT nmr spectra of **59** and **60**, a total of 11



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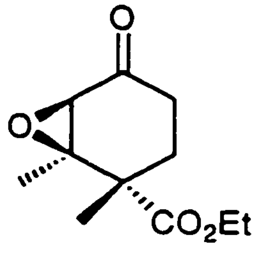


60

lines was observed. The ^1H nmr spectrum of **59** showed a singlet at δ 3.19 for the C-2 proton, whereas the corresponding proton in **60** appeared at δ 3.05. To assign the stereochemistry, an nOe experiment for **60** was carried out. The lack of enhancement of the C-4 methyl signal, when the C-3 methyl signal at δ 1.39 was irradiated, indicated that the two methyl groups of **60** were on the opposite faces. In case of **59**, however, both the C-3 and C-4 methyl groups appeared at δ 1.38, making similar nOe studies impossible. No further effort was made to confirm the stereochemistry of **59** and **60**.

Excellent stereoselectivity was observed for epoxidation of enones **38** and **48**. Because, in each case, the steric effect is relatively small, other factors must have influenced the stereochemical outcome of the epoxidation. One rationale is as follows. As postulated by Cieplak,[27] transition state in nucleophilic addition is stabilized by interaction of antibonding orbitals of the incipient bond σ^* with the vicinal occupied orbitals σ in the periplanar position. This postulation offers a good explanation for the observed preference of attack from the ester side. Having better electron-donating ability, the methyl (ethyl) group in the anti-periplanar position relative to the approaching $^-$OOH stabilizes the highly conceivable transition state shown in Figure 1-13. On the other hand, the

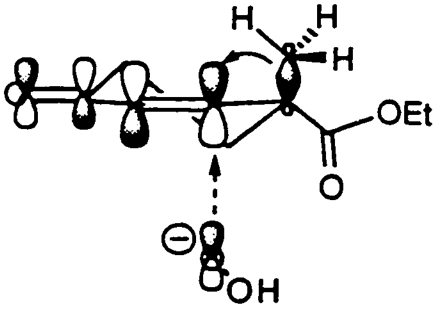


Figure 1-13 Stabilization of the transition state by the methyl group in the anti-periplanar position

anti-periplanarity of the incoming $^{-}$OOH and the ester moiety would destabilize the transition state. As a result, the addition of hydroperoxide ion to **38** and **48** occurs, in each case, mainly from the ester side leading eventually to the observed major product.

As for epoxidation of enone **15**, the reduced selectivity is apparently due, at least in part, to the higher temperature required for the reaction.

In summary, two types of reactions discussed in this section, namely, hydrogenation and epoxidation of 2-cyclohexenones possessing an ester substituent at C-4, were shown to proceed with high stereoselectivity. Although, several factors might have influenced the stereochemical outcome of these reactions, the ester group at C-4 apparently plays an important role. The use of a C-4 ester substituent to control the stereochemistry of alkaline epoxidation and catalytic hydrogenation of 2-cyclohexenones (and possibly other 2-cycloalkenones) is expected to have broad synthetic utility. This new means of stereocontrol may also find application in other types of addition processes, although, the effect on conjugate addition of lithium dimethylcuprate does not appear to be profound.

Experimental

General

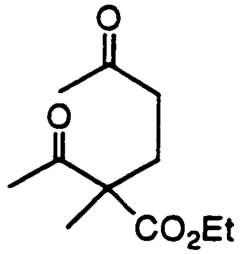
Elemental analyses were carried out using a Perkin Elmer 240-B for C and H detection. Infrared spectra (ir) were obtained on a Nicolet 7199 FTIR spectrophotometer. Electron impact mass spectra (eims) were determined using a AEI Kratos MS-50 high resolution mass spectrometer. Proton nuclear magnetic resonance spectra (^{1}H nmr) were obtained using one of the following spectrometers: Bruker WH-200 (200 MHz), Bruker WH-300 (300 MHz), Bruker AM-400 (400 MHz) or Varian Unity-500 (500 MHz). Coupling constants are reported within ± 0.5 Hz. The following abbreviations are used: s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet and br for broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C nmr) were obtained on a Bruker WH-300 (75.5 MHz) or Varian Unity-500 (125.7 MHz). Carbon-13 multiplicities were determined using spin echo J-modulated experiments (APT, Attached Proton Test).[55] Methyl and methine groups are shown as signals in antiphase (a) with respect to the deuteriochloroform signal, whereas methylene and quaternary carbons appear in phase (p). Nuclear Overhauser Enhancement (nOe)[56] experiments were determined in the difference mode in which a control (unsaturated) spectrum was computer-subtracted from the irradiated spectrum after Fourier Transformation. Positive enhancements appear as signals possessing opposite phase with respect to the irradiated signal. Samples for nOe measurements were deoxygenated by passing argon gas through the solutions for 10-15 minutes prior to the experiments.

Concentrations of solvents used in column chromatography are given by volumes, e.g. 20% ethyl acetate in hexanes means 20 parts of ethyl acetate by volume to 80 parts of hexanes by volume.

Materials

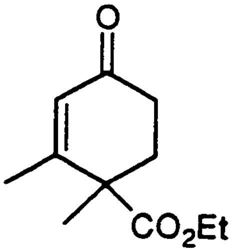
Products were purified by flash chromatography, developed by Still,[57] using silica gel 60 (Merck, 230-400 mesh) or by distillation using a bulb-to-bulb Kugelrohr apparatus. Reactions were monitored by thin layer chromatography performed on Merck aluminum-backed plates precoated with silica gel 60 GF_{254}, 0.2 mm thickness. The chromatograms were examined under UV-light at 254 nm when applicable, and/or visualization was completed using a vanillin acid solution (6 g of vanillin and 4 mL of concentrated sulfuric acid in 230 mL of 95% ethanol). Solvents and reagents were purified prior to use as follows: absolute ethanol and methanol were obtained from 98% or higher purity commercially available reagents by distillation from the corresponding magnesium alkoxide; diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium-benzophenone; toluene was freshly distilled from sodium; dichloromethane, benzene, pyridine and diisopropylamine were distilled from calcium hydride and 1,2-dimethoxyethane (DME) was distilled from lithium aluminum hydride. Purified argon (99.8%) was passed through 4 Å molecular sieves. Solvents used for chromatography were distilled at atmospheric pressure prior to their use.

3-Carbethoxy-3-methyl-2,6-heptadione (14)



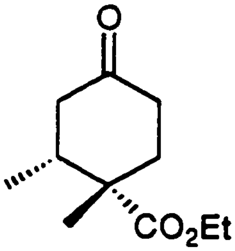
To a solution of DABCO (6.73 g, 60 mmol) in dry DME (50 mL), ethyl 2-methylacetoacetate (5.66 mL, 40 mmol) was introduced slowly, followed by addition of MVK (6.66 mL, 80 mmol). The reaction mixture was stirred at room temperature under an atmosphere of argon for 2.5 days and then cooled down to 0°C. Ice-cold 2N HCl (~30 mL) was added and the resulting solution was extracted with ether (3 x 50 mL). The extracts were combined, washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was distilled at 65°C/0.7 torr on a Kugelrohr apparatus to give the product (7.87 g, 92% yield) as a colorless oil: FT-ir ($CHCl_3$, cast) 1712 cm^{-1} (C=O, ketones and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.13 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 2.31-2.40 (m, 2H), 2.09 (s, 3H, $-CO-CH_3$), 2.07 (s, 3H, $-CO-CH_3$), 1.91-2.13 (m, 2H), 1.27 (s, 3H, $-CH_3$) and 1.21 (t, J = 7 Hz, 3H, $-OCH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 207.2 (p), 205.3 (p), 172.5 (p), 61.3 (p), 58.6 (p), 38.5 (p), 29.8 (a), 28.3 (p), 26.1 (a), 19.2 (a) and 13.9 (a); hreims M^+ 214.1202 (calculated for $C_{11}H_{18}O_4$: 214.1205). Elemental analysis for $C_{11}H_{18}O_4$: calculated %C 61.66, %H 8.47; found: %C 61.45, %H 8.69.

4-Carbethoxy-3,4-dimethyl-2-cyclohexenone (15)



A mixture of diisopropylamine (2.31 mL, 16 mmol) in dry THF (25 mL) was cooled down to 0°C under argon. Then *n*-BuLi (8.33 mL, 1.6M in hexane) was added dropwise. The resulting mixture was stirred at 0°C for 15 minutes and then cooled down to -78°C. 3-Carbethoxy-3-methyl-2,6-heptadione **14** (2.78 g, 13 mmol) in THF (25 mL) was then introduced slowly to the above LDA solution over a period of 15 min. The reaction mixture was then stirred at -78°C for 3 hours and warmed up to 0°C. Saturated ammonium chloride (25 mL) was added and the solution was extracted with ether (3 x 50 mL). The extracts were combined, washed with water and brine and dried over magnesium sulfate. Filtration and concentration afforded the crude product (2.3 g) which was dehydrated directly as follow. A solution of crude product (2.3 g) and *p*-TsOH (0.20 g, 1.1 mmol) in benzene (35 mL) was heated to reflux with azeotropic removal of water for 7 hours. After being cooled down to room temperature, the mixture was washed with half saturated sodium bicarbonate (10 mL) and water, and dried over magnesium sulfate. Filtration and evaporation, followed by flash chromatography (elution with 5% ethyl acetate in hexane) provided a mixture of enones **16** and **17** in less then 16% yield. Further elution gave **15** (1.29 g, 51% yield) as a yellowish oil: FT-ir (CH_2Cl_2, cast) 1727 cm^{-1} (C=O, ester) and 1676 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.89 (q, J = 1.5 Hz, 1H, C2-H), 4.17 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 2.32-2.53 (m, 3H), 1.94 (d, J = 1.5 Hz, 3H, C3-CH_3), 1.86-1.97 (m, 1H), 1.41 (s, 3H, C4-CH_3) and 1.25 (t, *J* =7 Hz, 3H, -OCH_2CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 198.2 (p), 174.1 (p), 161.5 (p), 128.1 (a), 61.4 (p), 47.3 (p), 34.3 (p), 34.2 (p), 22.3 (a), 21.0 (a) and 14.1 (a); hreims M^+ 196.1101 (calculated for $C_{11}H_{16}O_3$: 196.1099). Elemental analysis: calculated for $C_{11}H_{16}O_3$: %C 67.32, %H 8.22; found: %C 67.16, %H 8.39.

(3R*,4S*)-4-Carbethoxy-3,4-dimethylcyclohexanone (18) and (3S*, 4S*)-4-carbethoxy-3,4-dimethylcyclohexanone (19)



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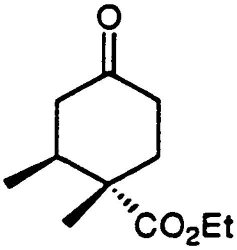

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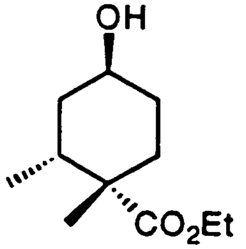
A mixture of enone ester **15** (0.74 g, 3.8 mmol) and 5% Pd/C (148 mg) in ethyl acetate (30 mL) was purged twice with hydrogen gas and then shaken under 30 p.s.i. of hydrogen for 2 hours. Filtration through celite and concentration under reduced pressure provided the crude product. Purification by flash chromatography, using 10% ethyl acetate in hexanes as an eluant, gave an inseparable mixture of two isomers **18** and **19**, (in a ratio of 11:1 respectively), as a colorless oil (0.65 g, 86% yield): FT-ir (film) 1715 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7 Hz, 2H, -OCH_2CH_3), 2.42-2.60 (m, 2H), 2.22-2.42 (m, 3H), 1.98 (m, 1H), 1.70 (m, 1H), 1.34 (s, 3H, C4-CH_3), 1.27 (t, *J* = 7 Hz, 3H, -OCH_2CH_3), 1.02 (d, *J* = 7 Hz, 2.75 H, C3-CH_3 of the major isomer **18**) and 0.90 (d, *J* = 7 Hz, 0.25 H, C3-CH_3 of the minor isomer **19**); ^{13}C nmr (75.5 MHz, $CDCl_3$) for the major isomer **18**: δ 211.2 (p), 175.4 (p), 60.5 (p), 45.6 (p), 44.7 (p), 40.4 (a), 38.3 (p), 34.3 (p), 23.8 (a), 17.2 (a) and 14.3 (a); hreims M+ 198.1254 (calculated for $C_{11}H_{18}O_3$: 198.1256).

(1S*,3R*,4S*)-4-Carbethoxy-3,4-dimethylcyclohexanol (20) and (1R*,3R*,4S*)-4-carbethoxy-3,4-dimethylcyclohexanol (21)



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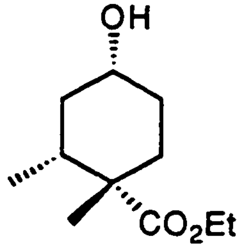
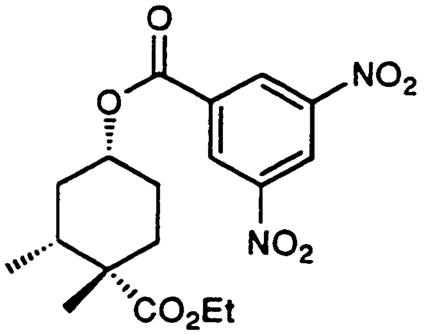


21

A mixture of ketones **18** and **19** (169 mg, 0.86 mmol, 11:1 ratio respectively) was dissolved in dry ethanol (10 mL) and cooled to 0°C under an argon atmosphere. Then, sodium borohydride (33 mg, 0.86 mmol) was added. After 10 minutes, all of the starting material was consumed and the reaction was quenched with saturated ammonium chloride and diluted with water (5 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were washed with water and brine, and dried over magnesium sulfate. Filtration and concentration under reduced pressure gave the crude product, which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes provided alcohol **20** (13 mg, 8% yield): FT-ir ($CHCl_3$, cast) 3421 cm^{-1} (OH) and 1724 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.12 (q, $J = 7$ Hz, 2H, $-OCH_2CH_3$), 3.98 (dddd, $J = 7.5, 7.5, 4, 4$ Hz, 1H, -CHOH), 1.73-2.01 (m, 5H), 1.45-1.67 (m, 3H), 1.25 (s, 3H, C4-CH_3), 1.24 (t, $J = 7$ Hz, 3H, $-OCH_2CH_3$) and 0.96 (d, $J = 7$ Hz, 3H, C3-CH_3).

Further elution afforded alcohol **21** (122 mg, 71% yield): FT-ir ($CHCl_3$, cast) 3364 cm^{-1} (OH) and 1724 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7 Hz, 2H, -OCH_2CH_3), 3.61 (dddd, J = 9, 9, 5, 5 Hz, 1H, -CHOH), 2.25 (br s, 1H, OH), 2.03 (ddd, J = 14, 4, 3.5 Hz, 1H), 1.70-1.88 (m, 2H), 1.32-1.68 (m, 3H), 1.20-1.29 (m, 1H), 1.24 (t, J = 7 Hz, 3H, -OCH_2CH_3), 1.16 (s, 3H, C4-CH_3) and 1.04 (d, J = 7 Hz, 3H, C3-CH_3); hreims M^+ 200.1409 (calculated for $C_{11}H_{20}O_3$: 200.1413).

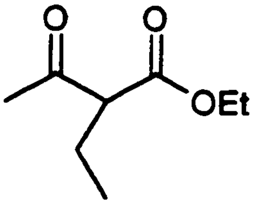
(1R*,3R*,4S*)-4-Carbethoxy-3,4-dimethylcyclohexyl 3,5-dinitrobenzoate (23)



To a solution of alcohol **21** (64 mg, 0.32 mmol) in benzene (4 mL), dry pyridine (0.5 mL) was introduced, followed by addition of 3,5-nitrobenzoyl chloride (147 mg, 0.64 mmol). The resulting mixture was stirred at room temperature and under an atmosphere of argon for 4 hours. The reaction mixture was then diluted with ether (5 mL) and quenched with water (3 mL). After separation, the organic layer was washed with small volumes of 1N hydrochloric acid, saturated sodium bicarbonate and water, and dried over magnesium sulfate. Filtration and concentration gave the crude product, which was subjected to flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to afford the desired benzoate **23** (102 mg, 0.26 mmol) as a white solid in 81%

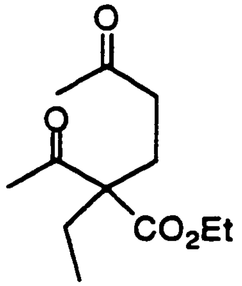
yield: FT-ir (CH_2Cl_2, cast) 3103 cm^{-1} (ArH), 1725 cm^{-1} (C=O, esters), 1546 cm^{-1} and 1378 cm^{-1} (NO_2); ^1H nmr (300 MHz, $CDCl_3$) δ 9.20 (t, J = 2 Hz, 1H, Ar**H**), 9.13 (d, J = 2 Hz, 2H, Ar**H**), 5.08 (m, 1H, C1-**H**), 4.18 (q, J = 7 Hz, 2H, -O**CH$_2$**CH$_3$), 2.15 (ddd, J = 14, 4, 4 Hz, 1H), 1.78-2.05 (m, 4H), 1.49-1.63 (m, 1H), 1.39 (ddd, J =14, 14, 4 Hz, 1H), 1.29 (t, J = 7 Hz, 3H, -OCH$_2$**CH$_3$**), 1.23 (s, 3H, C4-**CH$_3$**) and 1.10 (d, J = 7 Hz, 3H, C3-**CH$_3$**); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 175.3 (p), 162.0 (p), 148.7 (p), 134.5 (p), 129.4 (a), 122.3 (a), 76.0 (a), 60.2 (p), 44.9 (p), 39.5 (a), 36.0 (p), 35.7 (p), 28.6 (p), 25.1 (a), 16.9 (a) and 14.4 (a); hreims M+ 394.1368 (calculated for $C_{18}H_{22}O_8N_2$: 394.1376).

Ethyl 2-ethylacetoacetate (29)



Sodium hydride (1.52 g of 60% suspension in oil, 38 mmol) was placed in a flame-dried flask, DME (20 mL) was added and the resulting mixture was cooled down to 0°C under argon. Bromoethane (4.56 g, 41.8 mmol) was then introduced, followed by dropwise addition of ethyl acetoacetate (4.94 g, 38 mmol) in 15 mL of DME over 10 minutes period. Few drops of ethanol were carefully added and the solution was stirred first for 1 hour at 0°C and then for 24 hours at room temperature. The reaction was quenched with saturated ammonium chloride and the product extracted into ether (3 x 25 mL). The ethereal extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration provided the crude product, which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes afforded compound **29** (4.38 g, 27.7 mmol) in 73% yield as a colorless oil: FT-ir (CHCl$_3$, cast) 1742 cm^{-1} (C=O, ester) and 1716 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 4.19 (q, *J* = 7 Hz, 2H, -OC**H**$_2$CH$_3$), 3.32 (t, *J* = 7.5 Hz, 1H, C2-**H**), 2.21 (s, 3H, (CO)CH$_3$), 1.88 (dq, *J* = 7.5, 7.5 Hz, 1H, -CH-C**H**$_2$CH$_3$), 1.86 (dq, *J* = 7.5, 7.5 Hz, 1H, -CH-C**H**$_2$CH$_3$), 1.26 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 0.92 (t, *J* = 7.5 Hz, 3H, -CH-CH$_2$C**H**$_3$); hreims M$^+$ 158.0941 (calculated for $C_8H_{14}O_3$: 158.0943).

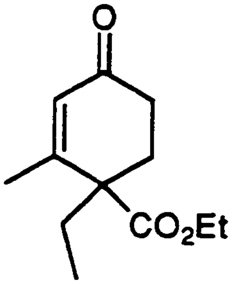
3-Carbethoxy-3-ethyl-2,6-heptadione (30)



MVK (1.48 g, 21 mmol) was added to a stirred solution of DABCO (1.78 g, 15.9 mmol) and ethyl 2-ethylacetoacetate **29** (1.67 g, 10.6 mmol) in dry DME (15 mL). The reaction mixture was stirred for 3 days at room temperature and under an argon atmosphere, and then cooled down to 0°C. Ice-cold 1N HCl (~20 mL) was added and the resulting solution was extracted with ether (3 x 20 mL). The extracts were washed with water and brine, dried over magnesium sulfate and filtered. After concentration, the residue was subjected to flash chromatography, using 15% ethyl acetate in hexanes as an eluant, to afford heptadione **30** (2.03 g, 84% yield) as a yellowish oil: FT-ir (CHCl$_3$, cast) 1737 cm^{-1} (C=O, ester) and 1712 cm^{-1} (C=O, ketones); ^{1}H nmr (300 MHz, CDCl$_3$) δ 4.16 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.15 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 2.21-

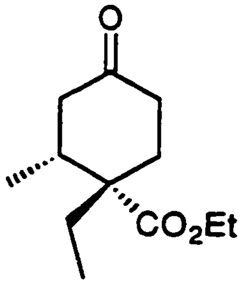
2.34 (m, 2H), 2.09 (s, 3H, (CO)CH_3), 2.08 (s, 3H, (CO)CH_3), 1.98-2.15 (m, 2H), 1.78-1.93 (m, 2H), 1.23 (t, *J* = 7 Hz, 3H, -OCH_2CH_3) and 0.75 (t, *J* = 7.5 Hz, 3H, -CH_2CH_3); hreims M^+ 228.1337 (calculated for $C_{12}H_{20}O_4$: 228.1362).

4-Carbethoxy-4-ethyl-3-methyl-2-cyclohexenone (31)

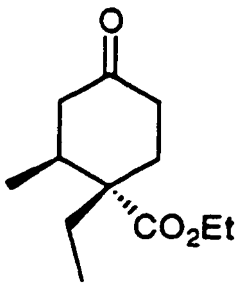


n-BuLi (5.18 mL, 1.6M in hexane, 8.29 mmol) was added dropwise to a solution of diisopropylamine (1.43 mL, 9.95 mmol) in dry THF (15 mL). The resulting mixture was stirred at 0°C for 15 minutes and then cooled down to -78°C. Heptadione **29** (1.89 g, 8.29 mmol) in 10 mL of THF was then introduced slowly to the above LDA solution over 10 minutes period. The reaction mixture was stirred at -78°C for 3 hours and warmed up to 0°C. Saturated ammonium chloride (15 mL) was added and the solution extracted with ether (3 x 30 mL). The combined extracts were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation gave the crude product (1.46 g), which was dehydrated directly as follow. A solution of crude product (1.46 g) and *p*-TsOH (122 mg, 0.64 mmol) in benzene (35 mL) was heated to reflux with azeotropic removal of water for 8 hours. After being cooled down to room temperature, the mixture was washed with half saturated sodium bicarbonate and water, and dried over magnesium sulfate. Filtration and concentration, followed by flash chromatography (elution with 15% ethyl acetate in hexanes) provided enone ester **31** (0.87 g, 50% yield) as a yellowish oil: FT-ir ($CHCl_3$, cast) 1725 cm^{-1} (C=O, ester) and 1678 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.91 (q, J = 1 Hz, 1H, C2-**H**), 4.16 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.15 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 2.46-2.60 (m, 1H), 2.28-2.41 (m, 2H), 1.97 (d, J = 1 Hz, 3H, C3-CH_3), 1.91-2.07 (m, 2H), 1.75 (q, J = 7 Hz, 1H, $-CH_2CH_3$), 1.70 (q, J = 7 Hz, 1H, $-CH_2CH_3$), 1.23 (t, J = 7 Hz, 3H, $-OCH_2CH_3$) and 0.89 (t, J = 7 Hz, 3H, $-CH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 198.5 (p), 173.2 (p), 160.9 (p), 129.3 (a), 61.2 (p), 50.9 (p), 34.4 (p), 29.5 (p), 28.4 (p), 21.2 (a), 14.1 (a) and 8.9 (a); hreims M^+ 210.1257 (calculated for $C_{12}H_{18}O_3$: 210.1256).

(3R*,4S*)-4-Carbethoxy-4-ethyl-3-methylcyclohexanone (32) and (3S*,4S*)-4-Carbethoxy-4-ethyl-3-methylcyclohexanone (33)



32



33

A. Hydrogenation of enone 31

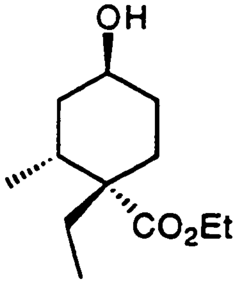
To a solution of enone ester **31** (0.84 g, 3.9 mmol) in 30 mL of ethyl acetate, 5% Pd/C (167 mg) was added. The mixture was flashed twice with hydrogen gas and then shaken under 25 p.s.i. of hydrogen for 3 hours. After filtration through celite and concentration, the crude product produced was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes gave a mixture of two inseparable isomers **32** and **33** (in a ratio of 12:1 respectively) as a colorless oil (0.79 g, 77% yield): FT-ir (neat film) 1718 cm^{-1} (C=O, ketone and ester); ^{1}H nmr (300 MHz, $CDCl_3$) for major isomer **32**: δ 4.15 (q, *J* = 7 Hz, 2H, -OCH_2CH_3), 2.41-2.51 (m, 2H), 2.24-2.32 (dddd, *J* = 15, 9, 6, 1.5 Hz, 1H), 2.15-2.23 (m, 3H), 1.92 (dq, *J* = 15, 7 Hz, 1H), 1.71-1.84 (m, 2H), 1.23 (t, *J* = 7 Hz, 3H, -OCH_2CH_3), 0.95 (d, *J* = 7 Hz, 3H, C3-CH_3) and 0.85 (t, *J* = 7 Hz, 3H, -CH_2CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) for major isomer **32**: δ 210.5 (p), 174.8 (p), 60.1 (p), 48.5 (p), 44.9 (p), 38.5 (a), 37.3 (p), 28.0 (p), 27.1 (p), 17.0 (a), 14.0 (a) and 8.6 (a); hreims M+ 212.1409 (calculated for $C_{12}H_{20}O_3$: 212.1413).

B. Conjugate addition reaction with enone 48

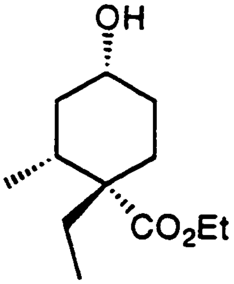
At 0°C, methyllithium (8.13 mL, 1.4M in ether, 11.39 mmol) was added dropwise to a suspension of cuprous iodide (CuI) (1.08 g, 5.69 mmol) in dry ether (15 mL) with vigorous stirring. The resulting clear solution was stirred for 1 hour under argon and then enone **48** (0.37 g, 1.89 mmol) in 5 mL of ether was introduced slowly. The reaction mixture was stirred for another hour at 0°C, then quenched with saturated ammonium chloride and extracted with ether (3 x 25 mL). The combined extracts were washed with water and brine, and dried over magnesium sulfate. After filtration and concentration, the crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes gave an inseparable mixture of cyclohexanones **32** and **33** (2:1; 314 mg, 1.48 mmol) in 78% yield: FT-ir (neat film) 1720 cm^{-1} (C=O, ketone and ester); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7 Hz, 0.7H, -OCH_2CH_3), 4.13 (q, *J* = 7 Hz, 1.3H, -OCH_2CH_3), 2.36-2.51 (m, 2H), 2.04-2.35 (m, 4H), 1.42-1.98 (m, 3H), 1.25 (t, *J* = 7 Hz, 1H, -OCH_2CH_3), 1.23 (t, *J* = 7 Hz, 2H, -OCH_2CH_3), 0.95 (d, *J* = 6.5 Hz, 2H, C3-CH_3), 0.87 (d, *J* = 6.5 Hz, 1H, C3-CH_3), 0.85 (t, *J* = 7 Hz, 2H, -CH_2CH_3) and

0.82 (t, *J* = 7 Hz, 1H, -CH_2CH_3);^{13}C nmr (75.5 MHz, $CDCl_3$) δ for major isomer **32**: 210.6 (p), 174.9 (p), 60.2 (p), 48.7 (p), 45.0 (p), 38.6 (a), 37.4 (p), 28.0 (p), 27.2 (p), 17.0 (a), 14.1 (a) and 8.7 (a); for minor isomer **33**: 211.0 (p), 175.4 (p), 60.5 (p), 49.2 (p), 46.2 (p), 38.2 (p), 35.6 (a), 28.7 (p), 28.1 (p), 17.0 (a), 14.8 (a) and 8.5 (a); hreims M^+ 212.1408 (calculated for $C_{12}H_{20}O_3$: 212.1413).

(1S*,3R*,4S*)-4-Carbethoxy-4-ethyl-3-methylcyclohexanol (34) and (1R*,3R*,4S*)-4-carbethoxy-4-ethyl-3-methylcyclohexanol (35)



34



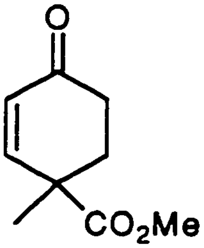
35

A mixture of ketones **32** and **33** (117 mg, 0.55 mmol, 12:1 ratio) was dissolved in ethanol (5 mL) and cooled down to 0°C. Sodium borohydride (21 mg, 0.55 mmol) was then added and the solution was stirred for 10 minutes. The reaction was quenched with saturated ammonium chloride and diluted with water (3 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined extracts were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation under reduced pressure gave the crude product, which was purified by flash chromatography (elution with 10% ethyl acetate in hexanes) to afford alcohol **34** (9 mg, 8% yield): ^1H nmr (300 Hz, $CDCl_3$) δ 4.14 (q, *J* = 7 Hz, 2H, -OCH_2CH_3), 3.90 (m, 1H, C1-**H**), 1.95-2.15 (m, 1H), 1.64-1.89 (m, 4H), 1.59 (br s, 1H), 1.13-1.49 (m, 4H), 1.26 (t, *J* = 7

Hz, 3H, $-OCH_2CH_3$), 0.96 (d, *J* = 7 Hz, 3H, C3-CH_3) and 0.81 (t, *J* = 7 Hz, 3H, C4-CH_2CH_3).

Further elution gave alcohol **35** (87 mg, 73% yield) as a colorless oil: FT-ir ($CHCl_3$, cast) 3363 cm^{-1} (OH) and 1722 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 3.61 (dddd, *J* = 10.5, 10.5, 5, 5 Hz, 1H, C1-**H**), 2.10 (ddd, *J* = 13.5, 4, 4 Hz, 1H), 1.71-1.99 (m, 4H), 1.43-1.69 (m, 2H), 1.12-1.42 (m, 3H), 1.25 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.06 (d, *J* = 7 Hz, 3H, C3-CH_3) and 0.82 (t, *J* = 7 Hz, 3H, $-CH_2CH_3$); hreims M^+ 214.1571 (calculated for $C_{12}H_{22}O_3$: 214.1569).

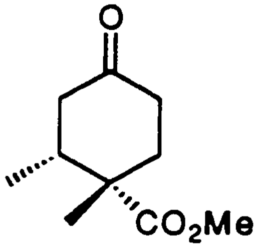
4-Carbomethoxy-4-methyl-2-cyclohexenone (38)



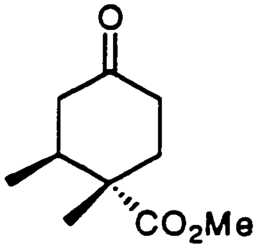
trans-1-Methoxy-3-(trimethylsilyoxy)-1,3-butadiene (1.36 g, 7.8 mmol) was dissolved in dry toluene (15 mL). Methyl methacrylate (3.4 mL, 31.4 mmol) and a few crystals of *m*-dinitrobenzene (*m*-DNB) were then added and the resulting mixture was heated to reflux under an argon atmosphere for 44 hours. After being cooled down to room temperature, the volatiles were removed by bulb-to-bulb distillation. The residue was dissolved in THF-0.005N HCl (4:1, 20 mL) and the mixture was stirred at room temperature for 1.5 hour. Most of the THF was removed under reduced pressure and the remaining solution was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were combined, washed with water and dried over magnesium sulfate.

Filtration and concentration gave the crude product which was purified by flash column chromatography. Elution with 15 % ethyl acetate in hexanes provided enone ester **38** (1.14 g, 92% yield from diene) as a colorless oil: FT-ir (CDCl$_3$, cast) 1732 cm^{-1} (C=O, ester) and 1684 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 6.87 (d, J = 10.5 Hz, 1H, C3-**H**), 5.96 (d, J = 10.5 Hz, 1H, C2-**H**), 3.73 (s, 3H, -OC**H**$_3$), 2.40-2.58 (m, 3H), 1.90-2.03 (m, 1H) and 1.43 (s, 3H, C4-C**H**$_3$); ^{13}C nmr (125.7 MHz, CDCl$_3$) δ 198.3 (p), 174.5 (p), 151.6 (a), 128.7 (a), 52.6 (a), 43.8 (p), 34.5 (p), 32.1 (p) and 24.8 (a); hreims M$^+$ 168.0790 (calculated for $C_9H_{12}O_3$: 168.0786).

(3R*,4S*)-4-Carbomethoxy-3,4-dimethyl-cyclohexanone (39) and (3S*,4S*)-4-carbomethoxy-3,4-dimethyl-cyclohexanone (40)



39



40

A. Conjugate addition reaction with enone ester 38

A suspension of CuI (1.12 g, 5.9 mmol) in ether (8 mL) in a flame-dried flask was cooled down to 0°C and kept under an argon atmosphere. Methyllithium (8.4 mL, 1.4M in ether) was introduced dropwise (a bright yellow precipitate formed first and then redissolved), and the resulting clear solution was stirred at 0°C for 1 hour. Enone ester **38** (0.33 g, 1.96 mmol) in 5 mL of ether was added slowly (a yellow precipitate appeared) and the mixture was stirred for another hour. The reaction was quenched with saturated ammonium chloride and products extracted with ether (3 x 20 mL). The combined extracts were washed with water and brine and dried over magnesium sulfate. The crude product, obtained after filtration and concentration under reduced pressure, was then purified by flash column chromatography. Elution with 10% ethyl acetate in hexanes gave an inseparable mixture of two isomers **39** and **40** (ratio 1.7:1 respectively) as a colorless oil (0.25 g, 70% yield): FT-ir ($CHCl_3$, cast) 1725 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) for mixture: δ 3.72 (s, 1.1H, $-OCH_3$), 3.71 (s, 1.9H, $-OCH_3$), 2.10-2.60 (m, 5H), 1.60-2.05 (m, 2H), 1.36 (s, 1.9H, C4-CH_3), 1.27 (s, 1.1H, C4-CH_3), 1.01 (d, J = 7 Hz, 1.9H, C3-CH_3) and 0.90 (d, J = 7 Hz, 1.1H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) for mixture: δ 211.1 (p), 210.3 (p), 177.3 (p), 175.9 (p), 52.1 (a), 51.7 (a). 45.7 (p), 45.5 (p), 44.9 (p), 40.4 (a), 38.2 (p), 37.5 (p), 37.4 (a), 34.3 (p), 33.5 (p), 23.7 (a), 17.3 (a), 17.2 (a) and 16.4 (a).

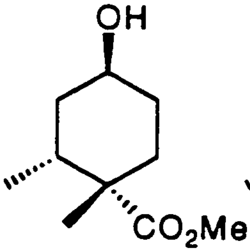
B. Oxidation of alcohols 42 and 43

A solution of alcohol **42** (39.5 mg, 0.21 mmol) in dry dichloromethane (3 mL) was stirred at room temperature and under an argon atmosphere. PCC (0.229 g, 1.1 mmol) was added in one portion and stirring was continued for 6 hours. The reaction mixture was then filtered through celite and solvent removed under reduced pressure. The crude product was purified by flash chromatography, using 10% ethyl acetate in hexanes as an eluant, to give keto ester **39** (32.5 mg, 84% yield) as an colorless oil: FT-ir ($CHCl_3$, cast) 1719 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.71 (s, 3H, $-OCH_3$), 2.23-2.59 (m, 5H), 1.93-2.05 (m, 1H), 1.66-1.78 (m, 1H), 1.36 (s, 3H, C4-CH_3), 1.01 (d, J = 7 Hz, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 211.1 (p), 175.9 (p), 51.7 (a), 45.5

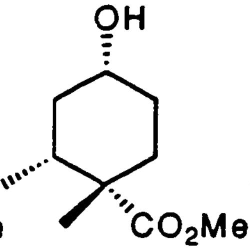
(p), 44.9 (p), 40.5 (a), 38.2 (p), 34.3 (p), 23.7 (a) and 17.2 (a); hreims M+ 184.1100 (calculated for $C_{10}H_{16}O_3$: 184.1099).

Similarly, alcohol **43** (23 mg, 0.12 mmol), dissolved in dry dichloromethane (2 mL), was oxidized using PCC (134 mg, 0.62 mmol). The reaction mixture was stirred for 45 minutes at room temperature and under argon. After filtration through celite and concentration, the product was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes gave ketone **40** (19.4 mg, colorless oil) in 88% yield: FT-ir ($CHCl_3$, cast) 1726 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.72 (s, 3H, $-OCH_3$), 2.48-2.61 (m, 1H), 2.07-2.47 (m, 5H), 1.78-1.89 (ddd, $J = 13, 6.5, 5$ Hz, 1H), 1.27 (s, 3H, C4-CH_3) and 0.91 (d, $J = 7$ Hz, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 210.3 (p), 177.3 (p), 52.2 (a), 45.7 (p, 2 x C). 37.5 (p), 37.4 (a), 33.5 (p), 17.3 (a) and 16.4 (a); hreims M+ 184.1098 (calculated for $C_{10}H_{16}O_3$: 184.1099).

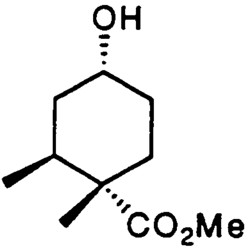
(1S*,3R*,4S*)-4-Carbomethoxy-3,4-dimethylcyclohexanol (41), (1R*,3R*,4S*)-4-carbomethoxy-3,4-dimethylcyclohexanol (42) and (1R*,3S*,4S*)-4-carbomethoxy-3,4-dimethylcyclohexanol (43)



41



42



43

A. Reduction of keto esters 39 and 40

A solution of keto esters **39** and **40** (1.7:1, 0.171 g, 0.93 mmol) in methanol (4 mL) was cooled down to 0°C and sodium borohydride (35.2 mg, 0.93 mmol) was added in one portion. The reaction mixture was stirred for 0.5 hour at 0°C and then quenched with saturated ammonium chloride. Water was added to dissolve the white precipitate formed and the aqueous solution was extracted with ether (3 x 5 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude product, which was subjected to flash chromatography using 15% ethyl acetate in hexanes as the eluant to afford alcohol **41** (12.4 mg, 0.07 mmol) in 7.5% yield: FT-ir ($CHCl_3$, cast) 3420 cm^{-1} (OH) and 1729 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.98 (dddd, *J* = 7, 7, 4, 4 Hz, 1H, C1-**H**), 3.65 (s, 3H, -OCH_3), 1.73-2.01 (m, 3H), 1.46-1.68 (m, 5H), 1.26 (s, 3H, C4-CH_3) and 0.95 (d, *J* = 7 Hz, 3H, C3-$C\mathbf{H}_3$); hreims M^+-H_2O 168.1149 (calculated for $C_{10}H_{18}O_3$: 168.1150).

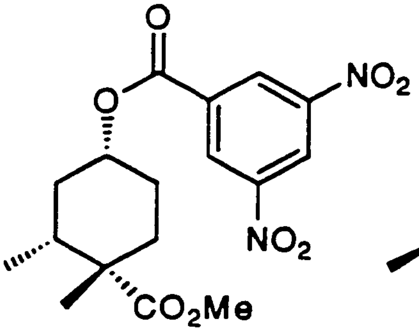
Further elution with 20% ethyl acetate in hexanes gave an inseparable mixture of two alcohols **42** and **43** (0.136 g, 0.73 mmol) in a ratio of 1.6:1 respectively and a combined yield of 79% : FT-ir ($CHCl_3$, cast) 3387 cm^{-1} (OH) and 1728 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.66 (s, 1.2H. -$OC\mathbf{H}_3$), 3.65 (s, 1.8H. -$OC\mathbf{H}_3$), 3.55-3.72 (m, 1H, C1-**H**), 1.98 (m, 1H), 1.72-1.89 (m, 2H), 1.18-1.67 (m, 5H), 1.18 (s, 1.8H, C4-$C\mathbf{H}_3$), 1.09 (s, 1.2H, C4-$C\mathbf{H}_3$), 1.03 (d, *J* = 7 Hz, 1.8H, C3-$C\mathbf{H}_3$) and 0.78 (d, *J* = 7 Hz, 1.2H, C3-$C\mathbf{H}_3$).

B. Alcohols 42 and 43 from benzoates 44 and 45

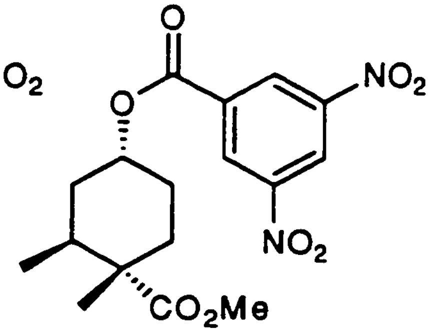
To a solution of benzoate **44** (0.121 g, 0.32 mmol) in dry methanol (2 mL) sodium methoxide (34 mg, 0.64 mmol) in methanol (1 mL) was added dropwise. The resulting mixture was stirred under argon at room temperature for 15 minutes and then quenched with saturated ammonium chloride. The organic product was extracted into ether (3 x 5 mL). The combined extracts were washed with water and brine, and dried over magnesium sulfate. Filtration and concentration provided the crude product, which was subjected to flash chromatography. Elution with 15% ethyl acetate in hexanes gave alcohol **42** (57 mg, 0.31 mmol) as a colorless oil: FT-ir ($CHCl_3$, cast) 3363 cm^{-1} (OH) and 1728 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.65 (s, 3H, $-OCH_3$), 3.55-3.67 (m, 1H, C1-H), 2.04 (ddd, J = 13.5, 3.5, 3.5 Hz, 1H), 1.72-1.89 (m, 2H), 1.32-1.66 (m, 4H), 1.24 (ddd, J = 13.5, 13.5, 3.5 Hz, 1H), 1.17 (s, 3H, C4-CH_3) and 1.03 (d, J = 7 Hz, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 176.1 (p), 70.6 (a), 51.2 (a), 45.1 (p), 40.5 (p), 39.7 (a), 36.4 (p), 32.6 (p), 25.3 (a) and 17.0 (a); hreims M^+ 186.1248 (calculated for $C_{10}H_{18}O_3$: 186.1256).

In the same way, the benzoate **45** (80 mg, 0.21 mmol) was treated with sodium methoxide (23 mg, 0.42 mmol) in dry methanol (3 mL). The resulting mixture was stirred at room temperature and under argon for 15 minutes. The reaction was then quenched with saturated ammonium chloride and extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate and filtered. After concentration, the residue was subjected to flash chromatography (elution with 15% ethyl acetate in hexanes) to afford pure alcohol **43** (35.5 mg, 0.19 mmol) in 91 % yield: FT-ir (CH_2Cl_2, cast) 3373 cm^{-1} (OH) and 1728 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.86 (s, 3H, $-OCH_3$), 3.61-3.73 (m, 1H, C1-H), 2.09 (dddd, J = 19, 7, 7, 3.5 Hz, 1H), 1.70-1.88 (m, 3H), 1.55-1.67 (m, 3H), 1.33-1.46 (m, 1H), 1.12-1.26 (m, 1H), 1.09 (s, 3H, C4-CH_3) and 0.79 (d, *J* = 7 Hz, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 178.6 (p), 70.3 (a), 51.8 (a), 45.8 (p), 39.0 (p), 35.4 (a), 34.9 (p), 30.4 (p), 17.4 (a) and 13.6 (a); hreims M^+ 186.1248 (calculated for $C_{10}H_{18}O_3$: 186.1256).

(1R*,3R*,4S*)-4-Carbomethoxy-3,4-dimethylcyclohexyl 3,5-dinitrobenzoate (44) and (1R*,3S*,4S*)-4-carbomethoxy-3,4-dimethylcyclohexyl 3,5-dinitrobenzoate (45)



44



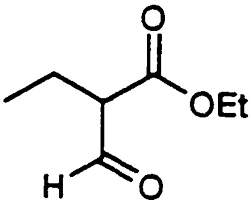
45

A mixture of alcohols **42** and **43** (0.13 g, 0.7 mmol, 1.6:1 ratio), dissolved in dry benzene (5 mL), was stirred at room temperature and under an argon atmosphere. Dry pyridine (1 mL) was added, followed by addition of 3,5-dinitrobenzoyl chloride (0.322 g, 1.4 mmol). The resulting solution was stirred for 8 hours. The reaction was then quenched with water and diluted with ether (10 mL). The separated organic layer was washed with small portions of 1N HCl, half-saturated sodium bicarbonate and water, and dried over magnesium sulfate. After filtration and concentration, the crude product was separated by flash chromatography (elution with 5% ethyl acetate in hexanes) to afford benzoate **44** (0.127 g, 0.33 mmol) as a white solid in 48% yield: FT-ir (CH_2Cl_2, cast) 3103 cm^{-1} (ArH), 1726 cm^{-1} (C=O, esters), 1546 cm^{-1} and 1345 cm^{-1}

(NO_2); ^{1}H nmr (300 MHz, $CDCl_3$) δ 9.21 (t, *J* = 2 Hz, 1H, Ar**H**), 9.14 (d, *J* = 2 Hz, 2H, Ar**H**), 5.03-5.16 (m, 1H, C1-**H**), 3.71 (s, 3H, -OC**H**$_3$), 2.16 (ddd, *J* = 14, 4, 4 Hz, 1H), 1.78-2.07 (m, 4H), 1.51-1.62 (m, 2H), 1.41 (ddd, *J* = 13, 13, 4 Hz, 1H), 1.26 (s, 3H, C4-C**H**$_3$) and 1.10 (d, *J* = 7 Hz, 3H, C3-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 175.8 (p), 162.1 (p), 148.7 (p), 134.5 (p), 129.5 (a), 122.3 (a), 76.0 (a), 51.5 (a), 45.1 (p), 39.6 (a), 36.0 (p), 35.8 (p), 28.6 (p), 25.1 (a) and 17.0 (a); hreims M+ 380.1217 (calculated for $C_{17}H_{20}O_8N_2$: 380.1219).

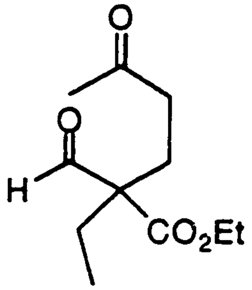
Further elution gave compound **45** (84 mg, 31% yield) as a white solid: FT-ir (CH_2Cl_2, cast) 3102 cm^{-1} (ArH), 1727 cm^{-1} (C=O, esters), 1547 cm^{-1} and 1345 cm^{-1} (NO_2); ^{1}H nmr (300 MHz, $CDCl_3$) δ 9.22 (t, *J* = 2 Hz, 1H, Ar**H**), 9.15 (d, *J* = 2 Hz, 2H, Ar**H**), 5.06-5.18 (m, 1H), 3.7 (s, 3H, -OC**H**$_3$), 2.27 (dddd, *J* = 19, 7, 7, 3 Hz, 1H), 1.82-2.09 (m, 3H), 1.63-1.81 (m, 2H), 1.43-1.6 (m, 1H), 1.20 (s, 3H, C4-C**H**$_3$) and 0.86 (d, *J* = 7 Hz, C3-C**H**$_3$); hreims M+ 380.1226 (calculated for $C_{17}H_{20}O_8N_2$: 380.1219).

Ethyl 2-formylbutyrate (46)



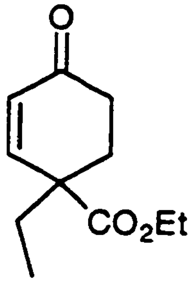
To a suspension of sodium hydride (4.54 g, 60% dispersion in oil, 0.11 mol) in dry THF (60 mL), freshly distilled ethyl formate (12.2 mL, 0.15 mol) was added and the resulting mixture was stirred at 0°C for 1 hour under an argon atmosphere. Ethyl butyrate (8.78 g, 75.6 mmol) in THF (20 mL) was then introduced, followed by careful addition of few drops of dry ethanol. The resulting solution was first stirred at 0°C for 2 hours and then at room temperature for 12 hours. The reaction was quenched with saturated ammonium chloride and the product extracted with ether (3 x 25 mL). The extracts were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash chromatography of the residue, using 10% ethyl acetate in hexanes as an eluant, gave aldehyde **46** (7.63 g, 52.9 mmol) in 70% yield as a colorless oil: FT-ir ($CDCl_3$, cast) 3420 cm^{-1} (OH, enol form), 2725 cm^{-1} (C-H, aldehyde), 1722 cm^{-1} (C=O, ester and aldehyde, keto form) and 1666 cm^{-1} (C=O, ester, enol form); ^1H nmr (300 MHz, $CDCl_3$) δ 11.38 (d, J = 12.5 Hz, 0.66H, =CH-O**H**), 9.70 (d, J = 3 Hz, 0.33H, (CO)-**H**), 6.98 (d, J = 12.5 Hz, 0.66H, =C**H**-OH), 4.13-4.29 (m, 2H, -OC**H**$_2$CH$_3$), 3.17 (td, J = 7.5, 3 Hz, 0.33H, -**C**HCOH), 1.82-2.13 (m, 2H), 1.19-1.36 (m, 3H) and 0.90-1.04 (m, 3H); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 197.5 (a), 172.5 (p), 169.5 (p), 160.2 (a), 106.6 (p), 61.4 (p), 60.3 (p), 59.9 (a), 20.7 (p), 20.0 (p), 14.6 (a), 14.2 (a) (2 x C) and 11.6 (a); hreims M+ 144.0780 (calculated for $C_7H_{12}O_3$: 144.0786).

5-Carbethoxy-5-formyl-2-heptanone (47)



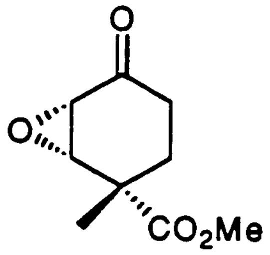
Freshly distilled MVK (7.38 mL, 88.7 mmol) was added dropwise to a solution of aldehyde **46** (6.39 g, 44.3 mmol) and DABCO (7.45 g, 66.5 mmol) in dry DME (50 mL). The resulting solution was stirred at room temperature for 17 hours under an atmosphere of argon and then cooled down to 0°C. The reaction mixture was acidified (pH ~5) with 2N HCl and extracted with ether (3 x 50 mL). The extracts were washed with water and brine, and dried over magnesium sulfate. After filtration and concentration, the residue was subjected to flash chromatography (elution with 15% ethyl acetate in hexanes) to give keto aldehyde **47** (6.84 g, 31.9 mmol) in 72% yield: FT-ir (neat film) 2840 and 2710 cm^{-1} (C-H, aldehyde), 1718 cm^{-1} (C=O, ester, ketone and aldehyde); ^1H nmr (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, -(CO)**H**), 4.23 (q, *J* = 7 Hz, 2H, -$OC\mathbf{H_2}CH_3$), 2.43 (ddd, *J* = 17.5, 10, 6 Hz, 1H), 2.08 (s, 3H, -(CO)$\mathbf{CH_3}$), 1.92-2.07 (m, 2H), 1.70-1.88 (m, 2H), 1.25 (t, *J* = 7 Hz, 3H, -$OCH_2\mathbf{CH_3}$) and 0.83 (t, *J* = 7 Hz, 3H, -$CH_2\mathbf{CH_3}$); hreims M^+ 214.1213 (calculated for $C_{11}H_{18}O_4$: 214.1205).

4-Carbethoxy-4-ethyl-2-cyclohexenone (48)

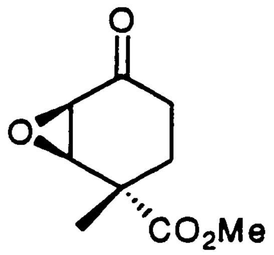


A round bottom flask equipped with a magnetic stirrer, a Dean-Stark apparatus and a condenser was charged with keto aldehyde **47** (5.04 g, 23.6 mmol), *p*-TsOH (0.45 g, 2.4 mmol) and dry benzene (50 mL). The mixture was heated to reflux under argon for 18 hours with azeotropic removal of water. After being cooled down to room temperature and diluted with benzene, the solution was washed with half saturated sodium bicarbonate (50 mL) and water (50 mL) and dried over magnesium sulfate. Filtration and concentration gave the crude product, which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes afforded cyclohexenone **48** (3.74 g, 81% yield) as a yellowish oil: FT-ir (neat film) 1729 cm^{-1} (C=O, ester) and 1690 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 6.94 (d, *J* = 10 Hz, 1H, C3-**H**), 6.01 (d, *J* = 10 Hz, 1H, C2-**H**), 4.21 (q, *J* = 7Hz, 1H, $-OC\mathbf{H}_2CH_3$), 4.2 (q, *J* = 7Hz, 1H, $-OC\mathbf{H}_2CH_3$), 2.38-2.54 (m, 3H), 1.71-2.07 (m, 3H), 1.28 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$) and 0.95 (t, *J* = 7 Hz, 3H, $-CH_2C\mathbf{H}_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 198.5 (p), 173.1 (p), 151.1 (a), 128.9 (a), 61.2 (p), 47.8 (p), 34.5 (p), 31.6 (p), 29.8 (p), 14.1 (a) and 8.8 (a); hreims M^+ 196.1097 (calculated for $C_{11}H_{16}O_3$: 196.1099).

(2S*,3S*,4S*)-4-Carbomethoxy-2,3-epoxy-4-methyl-cyclohexanone (51) and (2R*,3R*,4S*)-4-carbomethoxy-2,3-epoxy-4-methyl-cyclohexanone (52)



51

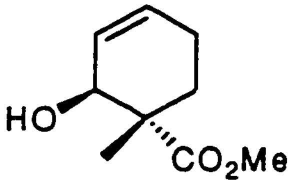


52

A solution of enone **38** (0.25 g, 1.49 mmol) in methanol (5 mL) was cooled down to -10°C. A 30% aqueous solution of hydrogen peroxide (1.64 mmol, 0.15 mL) was introduced dropwise, followed by addition of 1N lithium hydroxide (0.74 mL). The reaction mixture was stirred at -10° for 1 hour, diluted with water (3 mL) and warmed up to room temperature. The resulting solution was then acidified (pH ~7) with 1N HCl and extracted with ether (3 x 10 mL). The combined ethereal extracts were washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product, which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes afforded epoxide **52** (8.4 mg, 3% yield) as a colorless oil: FT-ir ($CHCl_3$, cast) 1723 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, -OCH_3), 3.59 (d, $J = 4$ Hz, 1H, C3-**H**), 3.35 (d, $J = 4$ Hz, 1H, C2-**H**), 2.39 (ddd, $J = 19, 4.5, 4.5$ Hz, 1H, C6-**H**), 2.15 (ddd, $J = 19, 11, 9$ Hz, 1H, C6-**H**), 1.89-1.96 (m, 2H) and 1.47 (s, 3H, C4-CH_3); hreims M^+ 184.0736 (calculated for $C_9H_{12}O_4$: 184.0736).

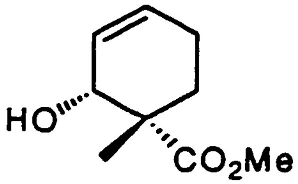
Further elution provided the major epoxy ketone **51** (0.22 g, 1.21 mmol) in 81 % yield as a colorless oil: FT-ir ($CHCl_3$, cast) 1716 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 3.71 (dd, $J = 4, 1.5$ Hz, 1H, C3-**H**), 3.28 (d, $J = 4$ Hz, 1H, C2-**H**), 2.52 (ddd, $J = 17.5, 9.5, 6$ Hz, 1H, C6-**H**), 2.15-2.42 (m, 2H), 1.72 (dddd, $J = 14, 6.5, 4, 1.5$ Hz, 1H, C5-**H**) and 1.35 (s, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 204.5 (p), 174.9 (p), 60.6 (a), 55.0 (a), 52.5 (a), 42.3 (p), 32.3 (p), 25.8 (p) and 19.6 (a); hreims M^+ 184.0738 (calculated for $C_9H_{12}O_4$: 184.0736).

(1S*,6S*)-6-Carbomethoxy-6-methyl-2-cyclohexenol (53)



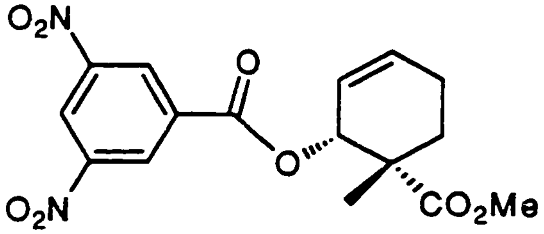
To a solution of epoxy ketone **52** (23 mg, 0.13 mmol) in methanol (2 mL), hydrazine hydrate (15.6 mg, 0.31 mmol) was introduced, followed by addition of acetic acid (1.5 mg, 0.03 mmol). The colorless solution turned immediately deep yellow and gas evolution started. The resulting mixture was stirred at room temperature for 18 hours. Then water (2 mL) was added and the mixture extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate and filtered. After concentration, the residue was subjected to flash chromatography. Elution with 10% ethyl acetate gave allylic alcohol **53** (12 mg, 54% yield) as a colorless oil: FT-ir ($CHCl_3$, cast) 3492 cm^{-1} (OH) and 1735 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 5.67-5.78 (m, 1H, =CH-), 5.61 (dddd, *J* = 10, 2, 2, 2 Hz, 1H, =CH-), 4.55 (dddd, *J* = 2, 2, 2, 2 Hz, 1H, C1-**H**), 3.73 (s, 3H, -OC**H**$_3$), 2.45 (br s, OH), 2.03-2.15 (m, 2H), 1.73-2.88 (m, 2H) and 1.20 (s, 3H, C6-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 178.2 (p), 128.6 (a), 128.1 (a), 69.6 (a), 52.1 (a), 45.7 (p), 28.7 (p), 22.3 (p) and 16.0 (a); hreims M^+ 170.0944 (calculated for $C_9H_{14}O_3$: 170.0943).

(1R*,6S*)-6-Carbomethoxy-6-methyl-2-cyclohexenol (54)



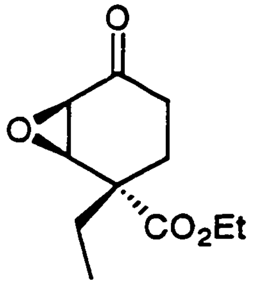
Epoxy ketone **51** (118 mg, 0.64 mmol) was dissolved in methanol (3 mL) and stirred at room temperature. Hydrazine hydrate (80 mg, 1.6 mmol) was added dropwise, followed by introduction of acetic acid (8 mg, 0.13 mmol). The resulting solution turned bright yellow and gas evolution persisted for 10 min. The reaction mixture was stirred overnight at room temperature, then diluted with water (3 mL) and extracted with ether (3 x 5 mL). Extracts were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation followed by purification of the crude product by flash chromatography (using 10% ethyl acetate in hexanes as an eluant) afforded alcohol **54** (56 mg, 52% yield): FT-ir ($CHCl_3$, cast) 3491 cm^{-1} (OH) and 1734 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 5.76 (d, J = 12 Hz, 1H, =CH-), 5.70 (d, J = 12 Hz, 1H, =CH-), 3.87 (br s, 1H, C1-**H**), 3.70 (s, 3H, $-OCH_3$), 3.04 (br s, 1H, O**H**), 1.95-2.12 (m, 3H), 1.56-1.70 (m, 1H) and 1.23 (s, 3H, C6-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 177.7 (p), 129.0 (a) (2 xC), 71.6 (a), 51.9 (a), 46.4 (p), 28.1 (p), 22.9 (p) and 21.5 (a); hreims M^+ 170.0943 (calculated for $C_9H_{14}O_3$: 170.0943).

(1R*,6S*)-6-Carbomethoxy-6-methyl-2-cyclohexenyl 3,5-dinitrobenzoate (55)



A solution of alcohol **54** (31 mg, 0.18 mmol) in dry benzene (3 mL) was stirred at room temperature and under an atmosphere of argon. Dry pyridine (0.5 mL) was first added, followed by addition of 3,5-dinitrobenzoyl chloride (78.6 mg, 0.36 mmol) in one portion. Stirring was continued for 6 hours. The reaction mixture was then diluted with water (3 mL) and extracted with ether (3 x 5 mL). The ethereal extracts were combined, washed with water and brine and dried over magnesium sulfate. After filtration and evaporation, the crude product was purified by flash chromatography on silica gel. Elution with 5% ethyl acetate in hexanes gave benzoate **55** (63 mg, 0,17 mmol) in 96% yield as a white crystalline solid: FT-ir ($CHCl_3$, cast) 3100 cm^{-1} (ArH), 1730 cm^{-1} (C=O, ester), 1545 cm^{-1} and 1345 cm^{-1} (NO_2); ^1H nmr (300 MHz, $CDCl_3$) δ 9.21 (t, J = 2.5 Hz, 1H, Ar**H**), 9.03 (d, *J* = 2.5 Hz, 2H, Ar**H**), 6.06-6.13 (m, 1H), 5.94 (dddd, *J* = 10, 5, 2, 2 Hz, 1H), 5.47 (d, *J* = 5 Hz, C1-**H**), 3.64 (s, 3H, -OCH$_3$), 2.12-2.37 (m, 3H), 1.90-1.98 (m, 1H) and 1.29 (s, 3H, C6-CH$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 175.5 (p), 161.6 (p), 148.7 (p), 134.3 (a), 134.2 (p), 129.3 (a) (2 x **C**), 122.4 (a), 121.4 (a), 74.1 (a), 52.1 (a), 44.6 (p), 24.7 (p), 22.4 (p) and 19.4 (a); hreims M$^+$ 364.0899 (calculated for $C_{16}H_{16}O_8N_2$: 364.0907).

(2R*,3R*,4S*)-4-Carbethoxy-4-ethyl-2,3-epoxycyclohexanone (56) and (2S*,3S*,4S*)-4-carbethoxy-4-ethyl-2,3-epoxycyclo-hexanone (57)



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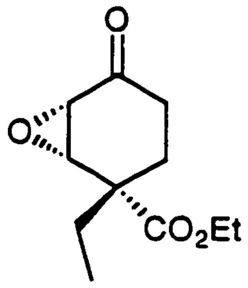

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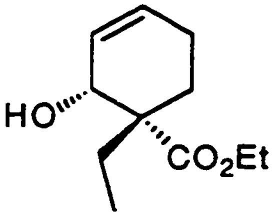
A solution of enone **48** (375 mg, 1.91 mmol) in ethanol (5 mL) was cooled down to 0°C. Hydrogen peroxide (0.25 mL, 2.87 mmol) was introduced dropwise, followed by addition of 1N lithium hydroxide (0.96 mL). The reaction mixture was stirred at 0°C for 2 hours, then diluted with water (3 mL) and acidified (pH ~6) with 1N HCl. Products were extracted into ether (3 x 15 mL) and the combined extracts were washed with brine and dried over magnesium sulfate. After filtration and concentration, the residue was subjected to flash chromatography. Elution with 5% ethyl acetate in hexanes gave epoxy ketone **56** (29 mg, 7% yield) as a colorless oil: FT-ir (CHCl$_3$, cast) 1720 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.5 Hz, 2H, $-OCH_2CH_3$), 3.69 (dd, *J* = 4, 1 Hz, 1H, C3-**H**), 3.34 (d, *J* = 4 Hz, 1H, C2-**H**), 2.41 (ddd, *J* = 19, 5.5, 3.5 Hz, 1H, C6-**H**), 2.14 (ddd, *J* = 19, 12, 7.5 Hz, 1H), 1.84-1.96 (m, 4H), 1.27 (t, *J* = 7.5 Hz, 3H, $-OCH_2C\mathbf{H}_3$) and 1.02 (t, *J* = 7.5 Hz, 3H, $-CH_2C\mathbf{H}_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 204.4 (p), 173.3 (p), 61.3 (p), 57.9 (a), 55.7 (a), 47.2 (p), 33.9 (p), 30.4 (p), 24.7 (p), 14.3 (a) and 8.8 (a); hreims M^+ 212.1033 (calculated for $C_{11}H_{16}O_4$: 212.1049).

Further elution afforded the major epoxide **57** (319 mg, 1.5 mmol) in 79% yield as a colorless oil: FT-ir ($CHCl_3$, cast) 1724 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.25 (q, *J* = 7.5 Hz, 2H, $-OCH_2CH_3$), 3.75 (dd, *J* = 4, 1 Hz, 1H, C3-**H**), 3.27 (d, *J* = 4 Hz, 1H, C2-**H**), 2.54 (ddd, *J* = 17.5, 6.5, 5.5 Hz, 1H, C6-**H**), 2.34 (ddd, *J* = 16, 10, 6.5 Hz, 1H, C5-**H**), 2.16 (ddd, *J* = 17.5, 10, 6 Hz, 1H, C6-**H**), 1.55-1.91 (m, 3H), 1.31 (t, *J* = 7.5 Hz, 3H, $-OCH_2CH_3$) and 0.92 (, *J* = 7.5 Hz, 3H, $-CH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.3 (p), 173.6 (p), 61.3 (p), 61.2 (a), 55.3 (a), 46.5 (p), 32.5 (p), 27.3 (p), 24.2 (p), 14.3 (a) and 8.8 (a); hreims M^+ 212.1048 (calculated for $C_{11}H_{16}O_4$: 212.1049).

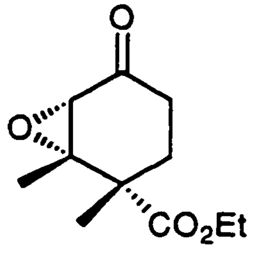
(1R*,6S*)-6-Carbethoxy-6-ethyl-2-cyclohexenol (58)



Hydrazine hydrate (61 mg, 1.23 mmol) was added dropwise to a well stirred solution of epoxy ketone **57** (104 mg, 0.49 mmol) in ethanol (3 mL). Then acetic acid (5.9 mg, 0.1 mmol) was introduced. The resulting mixture, which turned immediately bright yellow, was stirred at room temperature for 12 hours.

Water was then added (3 mL) and the solution extracted with ether (3 x 10 mL). The extracts were washed with water and brine, dried over magnesium sulfate and filtered. Evaporation under reduced pressure provided the crude product, which was purified by flash chromatography using 10% ethyl acetate in hexanes as an eluant. Allylic alcohol **58** (60.2 mg, 0.3 mmol) was obtained in 62% yield as a colorless oil: FT-ir ($CHCl_3$, cast) 3487 cm^{-1} (OH) and 1733 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 5.76 (d, *J* = 10.5 Hz, 1H, =CH-), 5.71 (d, *J* = 10.5 Hz, 1H, =CH-), 4.17 (q, *J* = 7 Hz, 1H, -OCH_2CH_3), 4.16 (q, *J* = 7 Hz, 1H, -OCH_2CH_3), 4.03 (m, 1H, C1-**H**), 2.90 (br s, 1H, -O**H**), 1.88-2.16 (m, 3H), 1.49-1.76 (m, 3H), 1.25 (t, *J* = 7 Hz, 3H, -OCH_2CH_3) and 0.86 (t, *J* = 7.5 Hz, 3H, -CH_2CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 176.4 (p), 129.3 (a), 128.9 (a), 70.3 (a), 60.4 (p), 50.3 (p), 26.9 (p), 23.8 (p), 22.7 (p), 14.2 (a) and 9.0 (a); hreims M^+ 198.1256 (calculated for $C_{11}H_{18}O_3$: 198.1256).

(2R*,3S*,4S*)-4-Carbethoxy-2,3-epoxy-3,4-dimethylcyclohexanone (59) and (2S*,3R*,4S*)-4-carbethoxy-2,3-epoxy-3,4-dimethylcyclohexanone (60)



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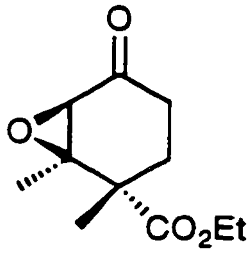

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30% aqueous hydrogen peroxide (3 mmol, 0.26 mL) was added dropwise to a stirred solution of cyclohexenone **15** (0.29g, 1.48 mmol) in ethanol (3 mL). Then, 1N sodium hydroxide (0.74 mL) was introduced rapidly, the temperature of the reaction was raised to 35°-40°C and stirring continued for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water, acidified (pH ~7) with 1N HCl and the organic product extracted into ether (3 x 5 mL). The combined ethereal extracts were washed with water and brine, and dried over magnesium sulfate. After concentration under reduced pressure, the crude product was purified by flash chromatography using 10% ethyl acetate in hexanes as the eluting solvent to afford epoxide **59** (144 mg, 0.68 mmol) as a colorless oil in 46% yield: FT-ir ($CDCl_3$, cast) 1722 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.14 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 3.19 (s, 1H, C2-**H**), 2.35 (m, 1H), 2.00-2.25 (m, 2H), 1.69 (m, 1H), 1.38 (s, 6H, 2 x $-CH_3$) and 1.21 (t, J = 7 Hz, 3H, $-OCH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.2 (p), 173.9 (p), 64.5 (p), 64.1 (a), 61.3 (p), 46.3 (p), 33.6 (p), 29.1 (p), 20.4 (a), 18.5 (a) and 14.1 (a); hreims M^+ 212.1045 (calculated for $C_{11}H_{16}O_4$: 212.1049). Further elution afforded epoxide **60** (103.5 mg, 0.49 mmol) as a colorless oil in 33% yield: FT-ir ($CDCl_3$, cast) 1729 cm^{-1} (C=O, ketone and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.13 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 3.05 (s, 1H, C2-**H**), 2.45-2.6 (m, 2H), 2.16-2.30 (m, 1H), 1.47-1.61 (m, 1H), 1.39 (s, 3H, C3-CH_3), 1.30 (t, J = 7 Hz, 3H, $-OCH_2CH_3$) and 1.29 (s, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.7 (p), 174.2 (p), 66.5 (p), 61.9 (a), 61.3 (p), 46.5 (p), 32.4 (p), 28.1 (p), 19.1 (a), 18.5 (a) and 14.3 (a); hreims M^+ 212.1042 (calculated for $C_{11}H_{16}O_4$: 212.1049).

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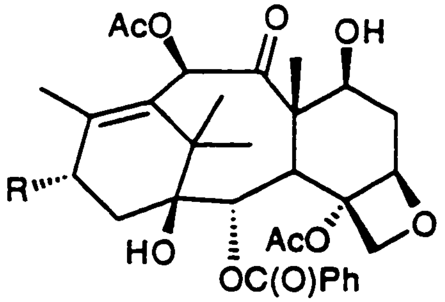
Chapter 2

Lithium Naphthalenide Induced Reductive Cleavage of α,β-Epoxy Ketones to the Corresponding β-Hydroxy Ketones

Introduction

β-Hydroxy ketone and the closely related 1,3-diol group are important functionalities found in prostaglandins,[1] taxol **1** and congeners,[2] and many other interesting natural products. Often, they are shown to be key intermediates in construction of a variety of biologically active compounds.[3-5] β-Hydroxy ketones are commonly prepared by aldol addition[6,7] or reductive cleavage of α,β-epoxy ketones.

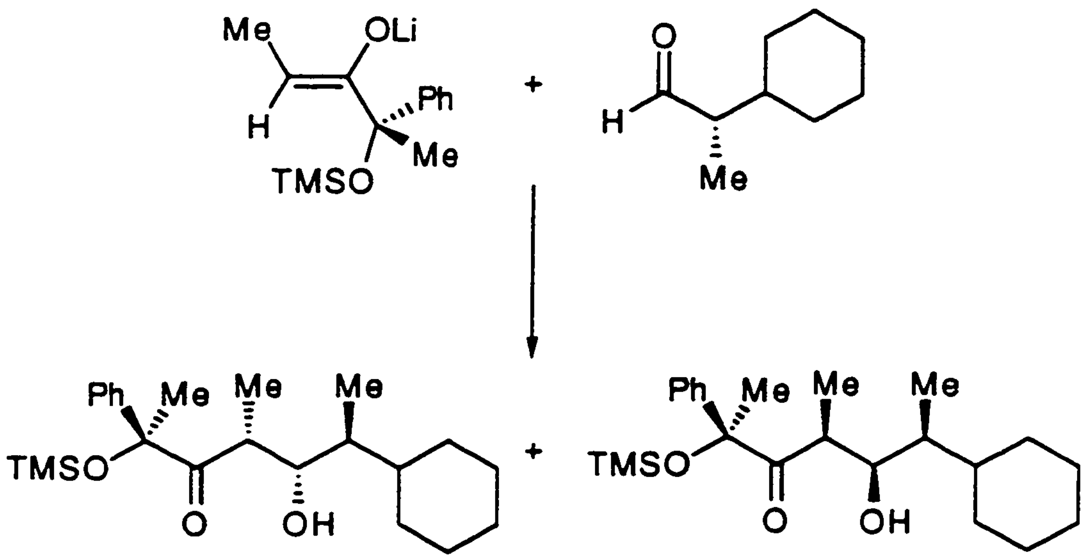


1 R = OC(O)CH(OH)CH(Ph)NHC(O)Ph

The aldol process proved to be especially useful for the preparation of "acyclic" β-hydroxy ketones. Many procedures for directed aldol addition (for example, formation of boron enolates, use of silyl enol ethers or oxazolidinones as chiral auxiliaries) have been developed to achieve high regio- and stereocontrol. The enhanced stereoselectivity resulting from interactions in chiral aldehydes and chiral enolates (double stereodifferentiation) has been used for the construction of systems with several contiguous chiral centers (Scheme 2-1).[8]

For cyclic β-hydroxy ketones, however, application of this method is limited due to generally low regio- and stereoselectivity and side reactions such as

Scheme 2-1



major

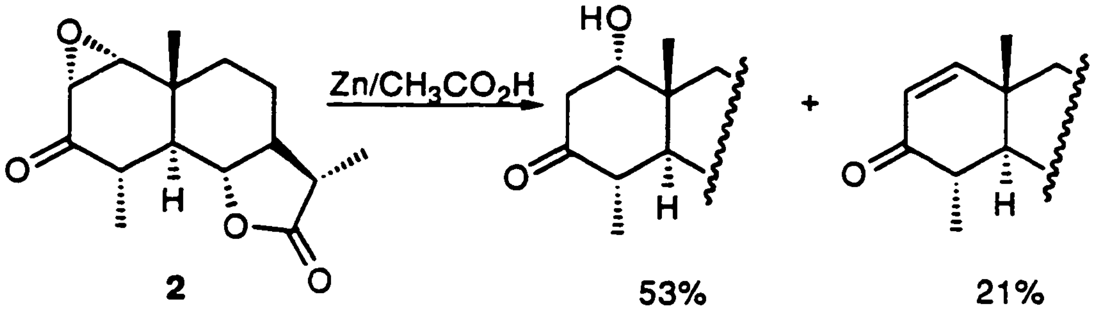
minor

complementary selectivity ratio = 9 : 1

intermolecular aldol addition. Dehydration of the desired product frequently occurs.

Reductive cleavage of epoxy ketones becomes an important choice in many cases since it allows access to not only acyclic but also a variety of cyclic aldols. General interest in the use of epoxides as intermediates in organic synthesis has intensified as a direct result of the development of the Sharpless asymmetric epoxidation reaction.[9] Generation of chiral nonracemic α,β-epoxy alcohols, their straightforward conversion to α,β-epoxy ketones, followed by reductive ring opening has became an important tool in asymmetric synthesis of aldols.

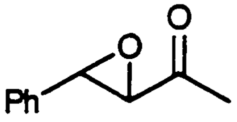
Several reagents such as alkali metal in liquid ammonia[3,5,10,11], zinc with acetic acid[12] and chromous salts in alcohol[13,14] have been reported for reductive cleavage of epoxy ketones. However, use of these methods often results in overreduction and substantial formation of enone, along with inconsistency and decrease in yield of the desired β-hydroxy ketone. For instance, treatment of **2** with activated zinc dust in ethanol in the presence of a small amount of acetic acid afforded (+)-arsantin together with the corresponding enone as a byproduct in 53% and 21% yield, respectively (Equation 2-1).[12]



(Eq. 2-1)

Shapiro and Gentles have utilized electrochemical reduction of epoxy ketone systems.[15] These controlled-potential electrolyses, however, resulted in invariably low yields (26-36%) of the hydroxy ketones. Although aluminum amalgam[4,16,17] and sodium iodide in conjunction with sodium acetate[18] have been successfully applied for this transformation, examples are rather few. Torii and coworkers have employed a combination of palladium catalyst, such as palladium acetate, and triethylammonium formate for reduction of epoxy ketones.[19] This simple procedure proved to be useful but sensitive to steric congestion of the substrate. Whereas reduction of compounds **3** and **4** proceeded smoothly to give the expected aldols in high yields, the sterically congested epoxy ketone **5** was recovered intact under these conditions.

Sodium hydrogentelluride[20] and samarium diiodide[21] have been also shown to be effective reagents for the conversion of epoxy ketones to the corresponding primary, secondary and tertiary hydroxy ketones.



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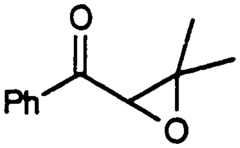

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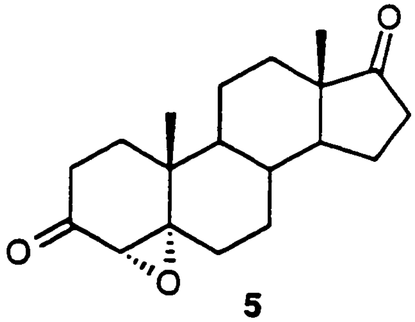

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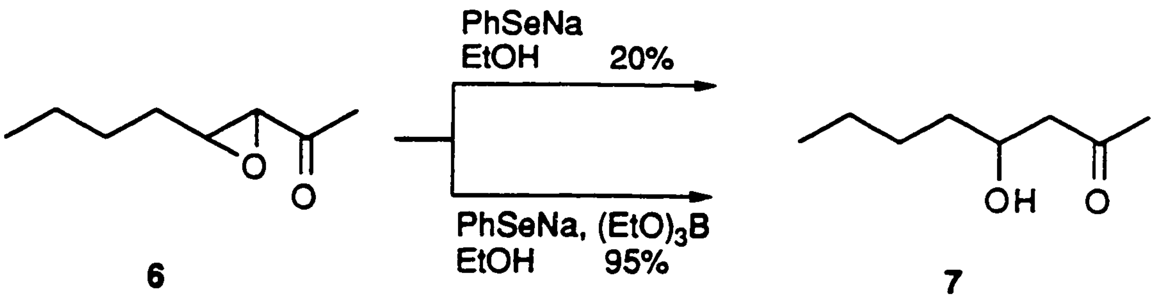
Miyashita and coworkers have reported the organoselenium-mediated reduction of α,β-epoxy ketones and α,β-epoxy esters (glycidic esters) to β-hydroxy carbonyl compounds.[22,23] Reagents like sodium phenylseleno-(triethyl)borate complex Na[PhSeB(OEt)$_3$] prepared by reduction of (PhSe)$_2$ with NaBH$_4$ in ethanol have been demonstrated to serve as good reducing agents, compatible with various functional groups in the substrate. It has been also shown that (EtO)$_3$B plays a crucial role as a scavenger of ethoxide ion generated *in situ* (Scheme 2-2). Upon treatment of acyclic epoxy ketone **6** with the borate complex Na[PhSeB(OEt)$_3$], ketone **7** was exclusively formed in 95% yield, whereas the use of uncomplexed PhSeNa alone resulted in a poor yield of the desired aldol (20%) and formation of many other products resulting from side reactions like dehydration, retro-aldol and Michael reaction, etc.[23]

Many other methods for the preparation of β-hydroxy ketones have been reported.[25] None of them, however, has been as widely used as directed aldol condensation reaction or reductive cleavage of epoxy ketones. Yamamoto, Tsuchihashi and coworkers developed a method for the stereoselective

Scheme 2-2



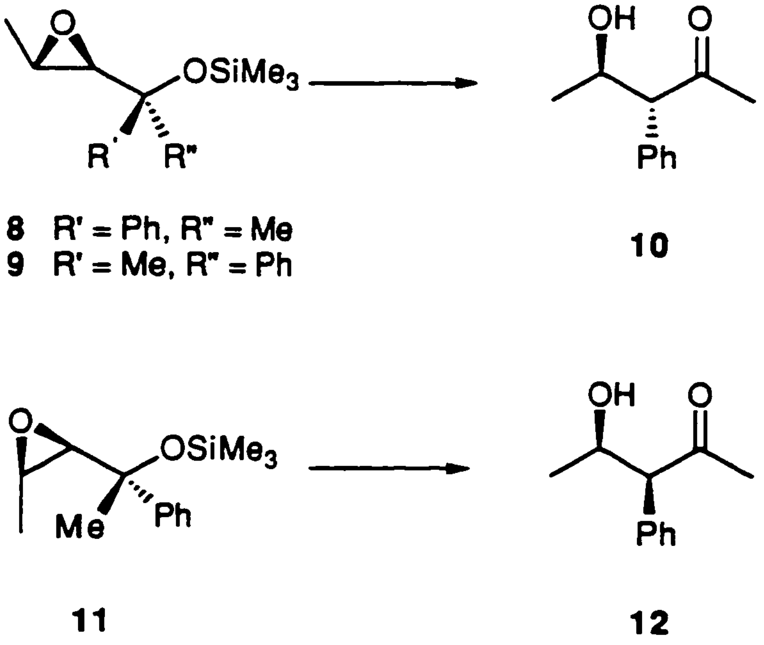
6

7

synthesis of aldols based on 1,2-rearrangement of epoxy silyl ethers.[25,26] The reactions leading to the desired products were effected by the use of $TiCl_4$ or $BF_3{\cdot}OEt_2$. The observed stereoselectivity showed the rigorous anti migration of the phenyl or alkenyl group to the epoxide moiety (Scheme 2-3). Both trans isomers **8** and **9** gave the same aldol **10** (in 95% and 79% yield, respectively), whereas the aldol **12** was obtained exclusively from cis isomer **11** (81% yield). The closely related epoxy alcohol-aldol rearrangement has been also reported by the same research group.[27] Practical utility of these methods, however, is limited by migratory aptitudes of some groups and steric interactions in complex compounds, which can prevent the molecule from adapting the conformation required for the rearrangement.

As reductive cleavage of α,β-epoxy ketones still remains the most direct approach to cyclic β-hydroxy ketones, it was envisioned that lithium naphthalenide could be a mild and yet efficient reducing agent for the

Scheme 2-3



8 R' = Ph, R" = Me
9 R' = Me, R" = Ph

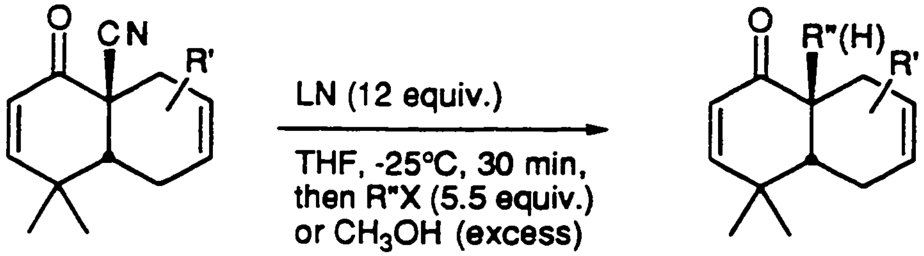
10

11

12

transformation. Recently in our laboratories, lithium naphtalenide was successfully employed in reduction of N,N,N',N'-tetramethylphosphorodiamidates (TMPDA) to the corresponding alkanes[28] and in reductive decyanation and reductive alkylation of α-cyano ketones (Scheme 2-4).[29]

Scheme 2-4



A high-yielding and highly chemoselective procedure for the conversion of benzyl ethers to the corresponding alcohols using this reagent has been also developed.[30] The results of these studies showed that the use of lithium naphthalenide as a reducing agent has the great advantage of operational simplicity and high efficiency and can provide a good alternative to dissolving metal reduction.

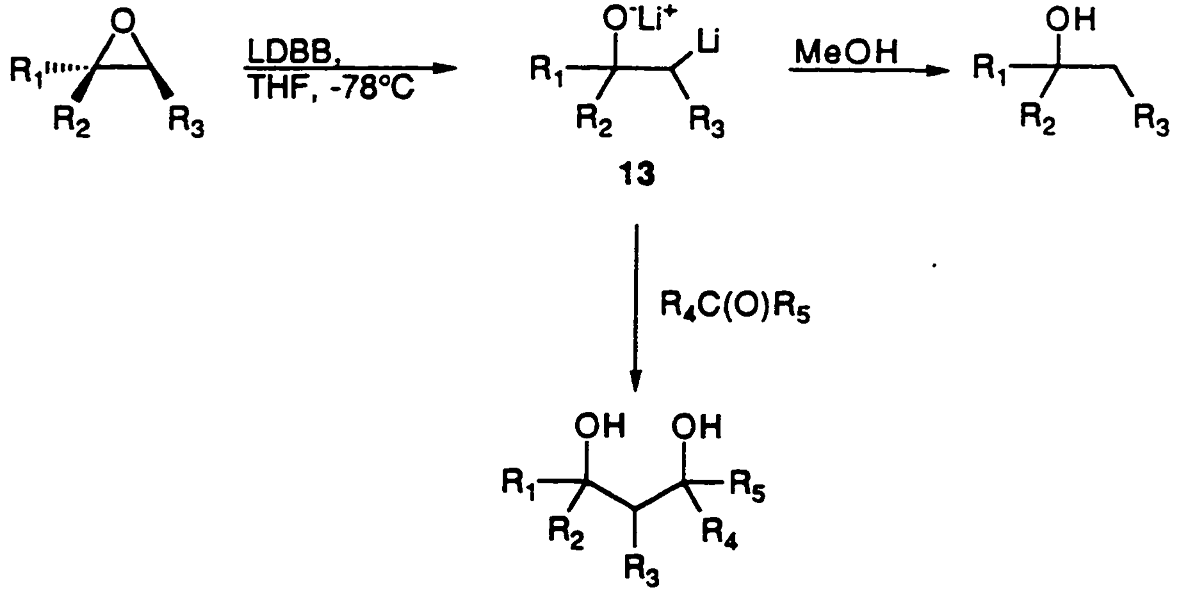
Lithium naphtalenide and many other radical anions generated from aromatic hydrocarbons and alkali metals[31-33] have found wide applications in organic synthesis and organometallic chemistry. Although sodium and lithium are the most commonly used metals, others like potassium and cesium have also been tested. In addition to naphthalene, various aromatic hydrocarbons and their derivatives, such as biphenyl, 4,4'-di-*tert*-butylbiphenyl, α-(N,N-dimethylamino)naphthalene, anthracene, phenanthrene, tetracene *etc.* have been employed. As reducing agents, the radical anions of biphenyl and naphthalene are almost as powerful as the corresponding metals themselve. This makes them the first choice among those tested. Ethers like THF and DME do not react with lithium naphthalenide. This is why the reagent can be prepared and then stored in these solvents for weeks, when kept at ~0°C.[30] At elevated temperatures, ethers are reduced to give alcohols.[34]

The chemical reactions of these radical anions can be divided into two general classes: proton abstraction reaction, due to the high basicity of the radical anion, and single electron transfer (SET) reaction. Some examples of proton abstraction from aldehydes and ketones[35], carboxylic acids[36] and esters[37] are known in the literature. It was estimated that these radical anions were effective in abstracting protons from compounds having a pK_a less than 33. The vast majority of the radical anion reactions, which have been reported, are SET reactions.[38,39] The most commonly seen examples of lithium naphthalenide induced SET reactions are probably the reduction of alkyl, silyl, vinyl and aryl halides,[40-42] dihalides,[43] and pseudo halides.[44] As these reactions can proceed *via* different pathways, they result in a variety of products.[45-47]

The reduction of epoxides by means of these radical anions is quite straightforward and has been reported.[48,49] Bartmann's study[48] involved conversion of epoxides to β-metalloalkoxides by metal (lithium, potassium and magnesium) naphthalenide and biphenylide, whereas Cohen and coworkers[49] employed lithium 4,4'-di-*tert* -butylbiphenylide for the epoxide cleavage. The dianions **13** resulting from the C-O bond cleavage were either quenched with water or methanol to afford alcohols as major products, or captured by alkylation, sulfenylation, and carbonation.[48] Many of the investigated dianions were treated with aldehydes and ketones (Scheme 2-5) to give 1,3-diols.[49] Only moderate yields of the desired products were obtained and significant amounts of olefins were invariably formed.

So far, no application of lithium naphthalenide nor any other arene radical anion in reductive cleavage of α,β-epoxy ketones has been reported. Only one isolated case of reductive cleavage of α,β-epoxy ester has been cited.[48] As greater stability of dianions from epoxy ketones, when compared to those from isolated epoxides, is expected (similar effect was observed in case of allylic radical intermediates from vinyloxiranes and styrene oxides[48,49]), regio-

Scheme 2-5



selective reductive cleavage of epoxy ketones should be facilitated leading to good yields of β-hydroxy ketones. This procedure should also prove useful for completely regioselective alkylation of ketones, as it allows regiocontrol for enolate formation. The use of lithium naphthalenide in reductive cleavage of α,β-epoxy ketones and possibility of direct alkylation of the resulting enolates was investigated. The findings of this study are discussed in the following section.

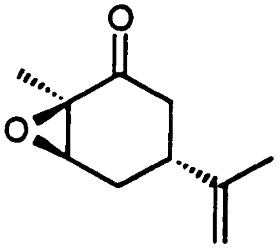
Results and Discussion

To explore the use of lithium naphthalenide as a reducing agent for the cleavage of α,β-epoxy ketones, a number of enones with diverse functionalities were converted to the corresponding epoxides. The enones used were either commercially available or previously synthesized in our laboratories. Alkaline epoxidation, employing 30% aqueous hydrogen peroxide with a catalytic amount of lithium hydroxide in methanol,[50] was chosen for the preparation of epoxides from enones. The general procedure is described in detail in the Experimental section of this chapter.

Lithium naphthalenide was easily prepared as a stable stock solution by mixing stoichiometric amounts of lithium metal and naphthalene in dry tetrahydrofuran at room temperature and under an argon atmosphere.[30] It took about four hours for the lithium metal to completely dissolve. The resulting dark green solution was used right after preparation or stored in the freezer at about -4°C. No apparent change of reactivity was observed after several weeks of storage. The lithium naphthalenide (LN) solutions used were usually 0.5-0.7M in concentration.

A. Determination of the optimum conditions for the reductive cleavage of α,β-epoxy ketones with lithium naphthalenide.

In order to find the best reaction conditions, reduction of *l*-carvone epoxide[51] **14** was studied. This particular epoxy ketone was chosen for the initial investigation because its reductive cleavage to β-hydroxy ketone **15** induced by different reagents has been already reported.[10,21,23] Comparison of the experimental results with those found in the literature would enable us to evaluate the efficiency of the current method using lithium naphthalenide. Reduction using lithium in liquid ammonia at -33°C afforded only a 35% yield of the desired product **15**.[10] When samarium diiodide was employed as a reducing agent, no detectable amount of **15** was produced.[21] Phenylselenium borate complex, on the other hand, proved to be a more efficient reducing agent, and the formation of a 82% yield of hydroxy ketone **15** was reported.[23] That yield however was determined by ^{1}H nmr analysis alone, as high susceptibility of the product to silica gel was claimed. Carvone was also detected in 15% in the products mixture, apparently resulting from dehydration of **15**.



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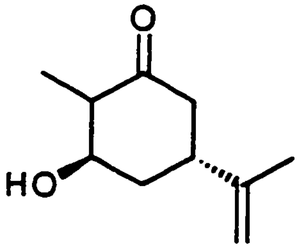


15

l-Carvone epoxide **14** was readily prepared in 93% yield by treatment of the commercially available *l*-carvone with 30% hydrogen peroxide and 1N lithium hydroxide in methanol at 0°C for 1 hour.[10]

In choosing reaction conditions for the lithium naphthalenide (LN) induced cleavage, the following parameters were considered: the reagent/substrate ratio, the reaction temperature and the order of addition. Although, in theory, only two equivalents of LN are required for reductive cleavage, it was found that a minimum of three equivalents was essential to effect complete reduction of **14** at -25°C. The color of the reaction mixture was an indication of the presence of an excess of lithium naphthalenide. In general, the persistent dark green to blue color of the solution indicates the presence of an excess of the reducing agent. When two equivalents of LN were used, the color of the mixture changed rapidly within 2 minutes to yellow, upon addition of the epoxide. In this case, even after prolonged treatment, some of the starting material was still present. Using three equivalents of LN, on the other hand, the mixture stayed in green for 10-15 minutes, and after 0.5 hour the reaction was complete. The yields of the isolated hydroxy ketone **15**, however, were pretty low ranging from 34% to 40% even when the silica gel used for chromatographic purification was preconditioned with triethylamine to aviod dehydration of the product. The use of a larger excess of lithium naphthalenide (6 equivalents) did not improve the yields and it made the work-up procedure more difficult due to the formation of a larger amount of naphtalene. The change in the order of addition, i.e. the addition of a THF solution of LN to a pre-cooled solution of epoxide in THF, did not alter the reaction outcome either. Consequently, the effect of reaction temperature was investigated. By lowering the temperature to -40°C, only slightly higher yields were realized (42-45%). However, when the reductive cleavage of **14** was carried out at -78°C, using three equivalents of LN, the desired product **15** was isolated in 62% yield along with small amount (<5% yield) of *l*-carvone. The change of temperature did not affect the rate of the reaction, which was also finished within 25-30 minutes. It was observed that the reaction needed to be quenched at low temperature before it was warmed up for work-up. The use of water, methanol or ammonium chloride as a proton source during the work-up was also studied, but no apparent effect was detected.

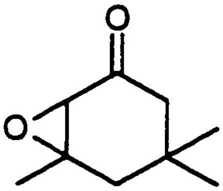
The yield of the reduction could not be further improved and the above conditions were assumed to be optimal for the reductive cleavage of epoxy ketones involving lithium naphthalenide. The general procedure is described in detail in the Experimental section. Considering the fact, that with other reducing agents carvone epoxide cleavage proved to be troublesome[10,21] and its product isolation somewhat problematic[23] , obtained moderate yield (62%) of pure **15** was very promising. It showed that use of lithium naphtalenide should be an efficient method for the synthesis of β-hydroxy ketones.

The spectroscopic properties of the purified hydroxy ketone **15** were identical with those reported.[10,23] The ^1H nmr spectrum showed two vinylic proton signals at δ 4.77 and δ 4.73 and a multiplet at δ 4.29 attributed to the proton adjacent to the hydroxyl group. An analysis of the spectrum revealed the presence of two isomers in a ratio of 10:1, as two doublets (J = 7 Hz) were observed for the methyl group α to the ketone carbonyl, the minor at δ 1.16 and the major at δ 1.10. No attempts were made to identify the stereochemistry of the C-2 center. In the mass spectrum, a molecular ion peak was displayed at m/z 168.1148 corresponding to the formula $C_{10}H_{16}O_2$.

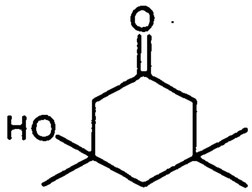
B. Preparation and reductive cleavage of α,β-epoxy ketones.

Several α,β-epoxy ketones were prepared and their reductive cleavage induced by lithium naphthalenide was studied. Alkaline epoxidation proved to be very straightforward in all cases studied. Formation of the desired epoxide in each case was easily detected by ^1H nmr spectroscopy where the disappearance of vinylic proton signal(s) was observed. In the ^{13}C nmr spectrum, the disappearance of two alkene carbon signals accompanied by the appearance of two signals at δ 55-75, attributed to carbons bearing the oxygen atom, indicated clearly the epoxide ring formation. β-Hydroxy ketones, on the other hand, were easily characterized by ir spectrosopy. In the typical case, the ir spectrum displayed a hydroxyl absorption and a carbonyl band for saturated ketone.

Isophorone epoxide **16** was obtained in 94% yield when the parent enone was treated with hydrogen peroxide and lithium hydroxide in methanol. The ir spectrum showed a carbonyl absorption at 1719 cm^{-1}. In the ^{13}C APT nmr spectrum, a total of 9 lines was observed. In the ^1H nmr spectrum, the C-2 proton resonated at δ 3.06 and three methyl singlets appeared at δ 1.41, 1.05 and δ 0.90. A molecular ion peak was observed at m/z 154.0994 in the mass spectrum corresponding to the formula $C_9H_{14}O_2$. The elementary analysis also supported the molecular composition.



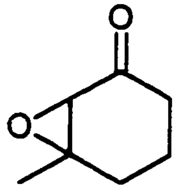
16



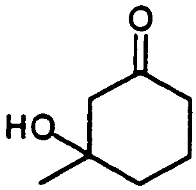
17

Reductive cleavage of epoxy ketone **16** with lithium naphthalenide proved to be very fast (10 min) and gave hydroxy ketone **17** in 78% yield. In the ir spectrum, a hydroxyl absorption was observed at 3376 cm^{-1} and a carbonyl absorption at 1715 cm^{-1}. The mass spectrum displayed a molecular ion peak at m/z 156.1149 in agreement with formula $C_9H_{16}O_2$. This example illustrated the efficiency of lithium naphthalenide to be superior to that of palladium acetate with triethylammonium formate,[19] which afforded **17** in 41% yield, and to be comparable to that of sodium hydrogentelluride,[20] which gave the same aldol in 83% yield.

Epoxidation of 3-methyl-2-cyclohexenone under standard conditions gave epoxy ketone **18** as a colorless oil in 86% yield. In its ir spectrum, a carbonyl absorption was observed at 1708 cm^{-1}. The ^1H nmr spectrum displayed a singlet at δ 3.05 attributed to the C-2 proton and another singlet at δ 1.43 for the methyl group. In the ^{13}C APT nmr spectrum, the carbonyl carbon resonated at δ 206.6 and the carbons of the epoxide ring appeared at δ 62.3 (C-3) and δ 61.9 (C-2). A molecular ion peak was observed at m/z 126.0680 in the mass spectrum, corresponding to the formula $C_7H_{10}O_2$.



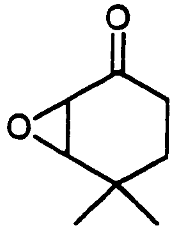
18



19

When compound **18** was subjected to lithium naphthalenide reduction, tertiary alcohol **19** was produced within 15 minutes and in 78% yield. In the ir spectrum, a hydroxyl absorption was displayed at 3426 cm^{-1} and a carbonyl band found at 1704 cm^{-1}. In the ^{13}C APT nmr spectrum, the carbonyl carbon appeared at δ 210.6 and the C-3 carbon resonated at δ 74.0. The mass spectum showed a molecular ion peak at m/z 128.0836 as expected.

4,4-Dimethylcyclohexenone was prepared earlier according to the literature procedure.[52] Epoxidation with aqueous hydrogen peroxide and lithium hydroxide afforded epoxy ketone **20** as a colorless oil in 80% yield. The ir spectrum showed a carbonyl absorption at 1713 cm^{-1}. The ^1H nmr spectrum displayed a doublet (J = 4 Hz) at δ 3.20 and a doublet of doublets (J = 4, 1.5 Hz) at δ 3.15 for the C-2 and C-3 protons. The methyl groups resonated at δ 1.19 and δ 1.04, each as a singlet. A molecular ion peak was shown at m/z 140.0837 in the mass spectrum, in agreement with the formula $C_8H_{12}O_2$.



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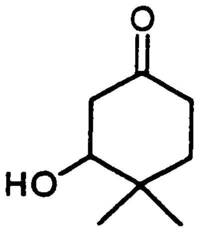
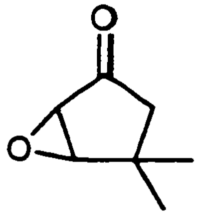


21

Reductive cleavage of epoxide **20** with lithium naphthalenide gave hydroxy cyclohexanone **21** in 71% yield. The ir spectrum showed a hydroxyl absorption at 3450 cm^{-1} and a carbonyl absorption at 1714 cm^{-1}. In ^1H nmr spectrum, a doublet of doublets (J = 8, 4.5 Hz) at δ 3.70 for the C-3 proton and two singlets at δ 1.35 and 1.08 for the methyl gruops were observed. The mass spectrum displayed a molecular ion peak at m/z 142.0993 corresponding to the formula $C_8H_{14}O_2$.

Lithium naphthalenide proved to be an effective reducing agent for epoxy cyclohexanones. In all cases, the corresponding β-hydroxy ketones were produced in good yields and none or very little of side products were detected. To examine its application to other ring systems, epoxy cyclopentanone **22** was prepared.

4,4-Dimethyl-2-cyclopentenone was previously synthesized in our laboratories according to Holder's procedure.[53] Alkaline epoxidation furnished epoxy ketone **22** in 89% yield. The ir spectrum showed a carbonyl absorption at 1752 cm^{-1}. In the ^{1}H nmr spectrum, two mutually coupled doublets ($J = 2.5$ Hz) at δ 3.51 and δ 3.32 for the C-2 and C-3 protons were observed. The ^{13}C APT nmr spectrum displayed 7 lines, three were in-phase and four were anti-phase with respect to the $CDCl_3$ signal. In the mass spectrum, a molecular ion peak was found at m/z 126.0683 corresponding to the formula $C_7H_{10}O_2$.



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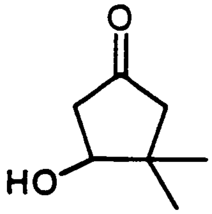
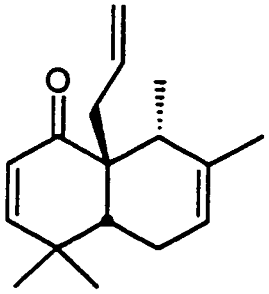


23

Lithium naphthalenide reduction of **22** provided hydroxy pentanone **23** in 68% yield. In the ir spectrum, characteristic absorption bands for alcohol and ketone were displayed at 3443 cm^{-1} and 1738 cm^{-1}, respectively. The C-3 proton resonated at δ 4.03 and two methyl singlets appeared at δ 1.12 and 1.05 in the ^{1}H nmr spectrum. In the ^{13}C APT nmr spectum, the carbonyl carbon appeared at δ 217.0 and the carbon bearing the hydroxy group was found at δ 76.8. The mass spectrum displayed a molecular ion peak at m/z 128.0836 in agreement with the formula $C_7H_{12}O_2$. In addition to the desired product, a small amount (3-6% yield) of the parent enone was also observed. Conversion of epoxy cyclopentanones to β-hydroxy ketones was reported to be problematic when lithium in liquid ammonia and chromous salts were used.[11,14] The outcome of the reduction of **22** suggested, that lithium naphthalenide would be a reagent of choice for that type of transformation.

Compound **24**, which was available from a previous synthetic study in our laboratories,[29] presented itself as an interesting candidate for our investigation. When compound **24** was treated with hydrogen peroxide in the presence of lithium hydroxide, epoxide **25** was produced in 96% yield.



24

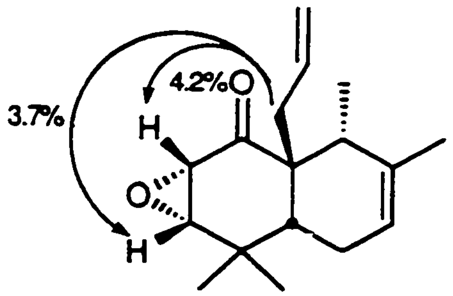
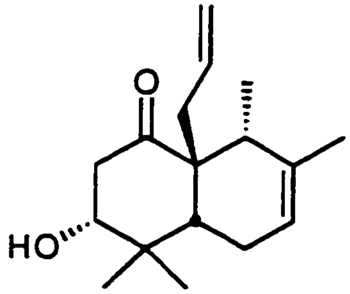


Figure 2-1 The nOe experiment of compound **25**

The ir spectrum showed an alkene absorption at 3074 cm^{-1} (C-H stretching) and a carbonyl absorption at 1696 cm^{-1}. In the ^{1}H nmr spectrum, four vinylic protons resonated at δ 5.51, 5.43, 5.01 and δ 4.94. The hydrogens of the epoxy ring appeared as a pair of mutually coupled doublets (J = 4 Hz) at δ 3.36 (C5-H) and 3.28 (C3-H). The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 209.3 and two carbons from the of the epoxy ring at δ 67.5 and 56.5. A molecular ion peak was observed at m/z 260.1776 in the mass spectrum, in agreement with the formula $C_{17}H_{24}O_2$. Both ^{1}H and ^{13}C nmr spectra indicated that only one isomer was present. The stereochemistry of epoxide **25** was determined by nOe experiments. Irradiation of the methylene protons of the allyl group resulted in enhancement of both C-3 (4.2%) and C-5 proton (3.7%) signals (Figure 2-1).

When epoxide **25** was exposed to lithium naphthalenide, it was converted into β-hydroxy ketone **26** cleanly. The desired product was isolated in good yield (88%) along with a small amount of enone **24** (<4% yield) as the only side product. The ir spectrum of **26** showed a typical hydroxyl absorption at 3476 cm^{-1} and a ketone carbonyl band at 1698 cm^{-1}.

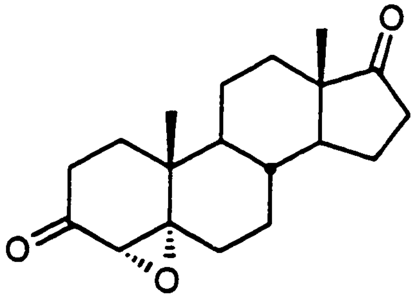


26

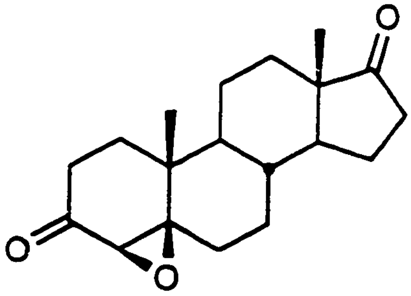
In the ^1H nmr spectrum, the proton attached to the hydroxyl-bearing carbon (C-4) resonated at δ 3.83. In the ^{13}C APT nmr spectrum, a total of 17 lines was displayed. The mass spectrum showed a molecular ion peak at m/z 262.1933 corresponding to the formula $C_{17}H_{26}O_2$.

Previous attempts to cleave reductively steroidal α,β-epoxy ketones often met with low yields of the desired β-hydroxy ketones.[11-14,54] To further test the efficiency of lithium naphthalenide, several steroidal epoxides were prepared and their reductive cleavage reaction examined.

Alkaline epoxidation of androst-4-en-3,17-dione in methanol using hydrogen peroxide and lithium hydroxide gave two epoxides **27** and **28** in 1 : 2 ratio, respectively. The separation of these isomers was found to be difficult. Their stereochemistry was assigned by comparison of the spectral data obtained for the mixture with those reported in the literature.[55] The C-4 proton of 4α,5α-epoxide and that of 4β,5β-epoxide showed distinctive difference in chemical shift. Accordingly, these isomeric epoxides could be readily distinguished.

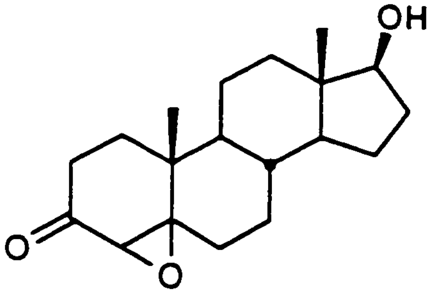


27

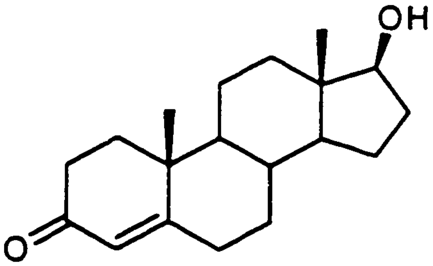


28

When reduction of the mixture of epoxides **27** and **28** was carried out under standard conditions, complex mixture was obtained containing ~50% of the starting compounds. Very little of the desired products was produced. The reduction was repeated with a large excess of lithium naphthalenide (6-8 equivalents), but no improvement was observed. The results were equally disappointing, when the reaction was carried out at higher temperature and/or over longer reaction period. Presumably, the five-membered ketone carbonyl, which was susceptible to reduction, reductive coupling and addition reactions,[35] was complicating the reaction. Similar problems were encountered previously.[30] The problem could, in principle, be circumvented by protection of the ketone moiety in question or by its transformation to a functional group stable to the reaction conditions.



29

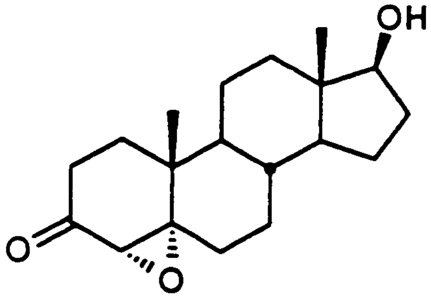


30

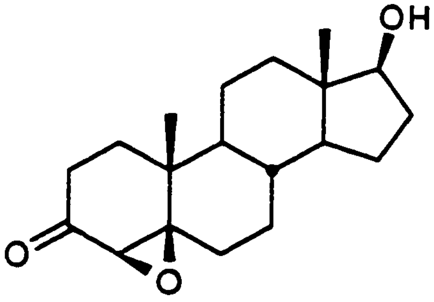
Testosterone epoxide **29** then was envisioned as a suitable starting material, as the hydroxy group should be compatible to the reaction conditions. Although testosterone **30** is commercially available, it was easily prepared from androst-4-ene-3,17-dione, which we had on the shelf, according to the literature procedure.[56]

Reduction of androstenedione with lithium aluminum hydride in dry THF gave a mixture of diols, which without purification, was selectively oxidized with active manganese dioxide to provide testosterone **30** in 89% yield.

Epoxidation of testosterone **30** with aqueous hydrogen peroxide afforded two isomeric epoxides **31** and **32** in 27% and 57% yield respectively. The structures of these compounds were established by comparing their spectral data to those reported reported.[55]



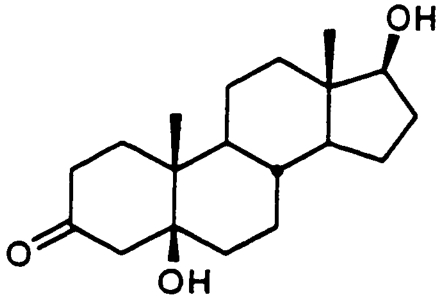
31



32

The ir spectra of both epoxides displayed a strong hydroxyl absorption at ~3340 cm^{-1} and a carbonyl absorption at ~1710 cm^{-1}. In the ^1H nmr spectra, the C-4 proton of **31** resonated at δ 3.03 and the corresponding proton in **32** resonated δ 2.94. The two methyl groups of **31** appeared at δ 1.07 and 0.78, whereas the epoxide **32** showed methyl singlets at δ 1.13 and 0.74. The ^{13}C APT nmr spectra showed 19 lines for each epoxy ketone. The mass spectra supported the formula $C_{19}H_{28}O_3$ for both compounds displaying molecular ions in each case as expected.

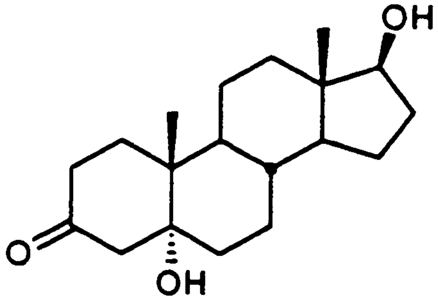
Epoxy ketone **32** was subjected to lithium naphthalenide reduction. As the hydroxy group would first be converted to the alkoxide, one extra equivalent of the reagent was required. When four equivalents of lithium naphthalenide were employed, keto diol **33** was furnished in 77% yield. An 11% yield of testosterone was also isolated. The yield of the desired compound **33** was virtually unchanged when a larger amount of the reducing agent was used.



33

The ir spectrum of the keto alcohol **33** displayed a hydroxyl absorption at 3414 cm^{-1} and a carbonyl band at 1705 cm^{-1}. In the ^1H nmr spectrum, a doublet of doublets (J = 8.5, 8.5 Hz) at δ 3.66 was attributed to the C-17 proton. Two methyl singlets were shown at δ 1.00 and 0.76. In the ^{13}C APT nmr spectrum, the C-17 carbon resonated at δ 82.4 and the ring junction carbon bearing a hydroxyl group appeared at δ 79.3. A molecular ion peak appeared at m/z 306.2197 in the mass spectrum, in agreement with formula $C_{19}H_{30}O_3$.

Reductive cleavage of epoxy ketone **31** using four equivalents of lithium naphthalenide gave hydroxy ketone **34** in 87% yield. A small amount of testosterone **30** (8% yield) was also obtained. The ir spectrum showed characteristic absorption bands for alcohol and ketone at 3460 cm^{-1} and 1716 cm^{-1}, respectively. The C-17 proton resonated at δ 3.65 in the ^1H nmr spectrum, which also showed two methyl singlets at δ 1.18 and 0.76. In the ^{13}C APT nmr spectrum, signals at δ 214.4, 82.5 and 78.1 were attributed to the carbonyl carbon, the C-17 and the C-5 carbon, respectively. The mass spectrum showed a molecular ion peak at m/z 306.2195 corresponding to the formula $C_{19}H_{30}O_3$.



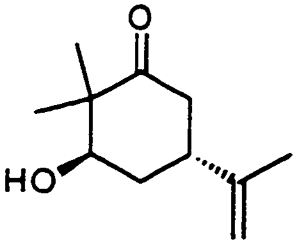
34

The last two examples indicate that lithium naphthalenide is also an effective reagent for reductive cleavage of α,β-epoxy ketones derived from steroids.

C. Reductive alkylation of α,β-epoxy ketones using lithium naphthalenide.

Many successful trapping experiments carried out on the carbanions generated by various arene radical anions have been reported. In a typical experiment, the reduction generating the carbanion was usually carried out at low temperature (~-78°C). Once the reduction was complete, the electrophile was added and trapping was performed at the same temperature. In cases where trapping was slow, the reaction mixture was allowed to warm up, sometimes to room temperature. In order to be captured, the carbanion must be sufficiently stable under the reaction conditions. Lithium naphthalenide induced reductive cleavage of α,β-epoxy ketones generates dianions (alkoxide enolates), which could, in principle, be trapped by alkylating agents to give α-substituted β-hydroxy ketones. When an α-subsituent is already present in the starting compound, then an α,α-disubstituted β-hydroxy ketone should be produced. A brief study on reductive alkylation of α-epoxy ketones using lithium in liquid ammonia has been reported.[57]

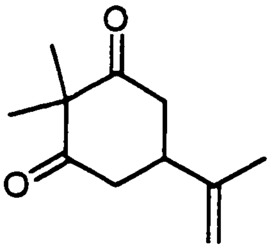
The suitability of lithium naphthalenide as a reagent for reductive alkylation was examined. Carvone epoxide **14** was treated with 3.5 equivalents of lithium naphthalenide in dry THF for 30 minutes at -78°C. Then 5 equivalents of methyl iodide was introduced. When the reaction was kept at low temperature, mostly reduction product and very little of alkylation product were formed. When the reaction mixture, with methyl iodide added, was allowed to warm up slowly to room temperature prior to work-up, the desired reductive alkylation product **35** was furnished in 70% yield. A small amount of the reductive cleavage product **15** was also isolated (~4% yield) together with some carvone (<8% yield).



35

The ir spectrum of **35** showed a hydroxyl absorption at 3473 cm^{-1} and a carbonyl band at 1703 cm^{-1}. In the ^{1}H nmr spectrum, the C-3 proton resonated at δ 3.90 and the germinal methyl groups resonated at δ 1.17 and 1.13. The ^{13}C APT nmr spectrum displayed a total of 11 lines and the mass spectrum showed a molecular ion peak at m/z 182.1307, both in agreement with the assigned structure.

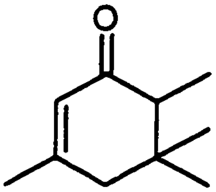
The success of the above reductive alkylation reaction illustrates a potentially useful procedure for the preparation of α,α-disubstituted β-hydroxy ketones. It also provides an opportunity for the preparation of 2,2-disubstituted 1,3-diketones by further oxidation. The latter class of compounds is of considerable synthetic utility, but can not be easily prepared by direct dialkylation of 1,3-diones due to competing O-alkylation.



36

The preparation of diketone **36** was experimentally realized as follows. Treatment of **35** with pyridinium chlorochromate in dichloromethane gave diketone **36** in 78% yield. The ir spectrum showed a carbonyl absorption at 1728 cm^{-1}. In the ^1H nmr spectrum, two vinylic protons resonated at δ 4.86 and 4.74 and two methyl singlets appeared at δ 1.33 and 1.28. The vinylic methyl group was observed at δ 1.76 as a doublet (J = 1 Hz). The mass spectra displayed a molecular ion peak at m/z 180.1154 corresponding to the formula $C_{11}H_{16}O_2$.

The reductive alkylation of epoxy ketone **16** was also attempted. When reductive alkylation was carried out under the previously described conditions with methyl iodide as the alkylating agent, no methylation product was obtained. Hydroxy ketone **17** was isolated in 62% yield together with a *ca.* 25% yield of isophorone. Prolonged treatment (5 hours) at room temperature gave mainly isophorone (51% yield). Interestingly, a totally unexpected product **37** was produced in 31% yield, presumably *via* proton exchange.



37

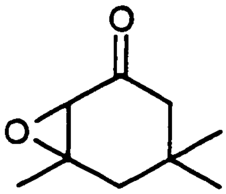
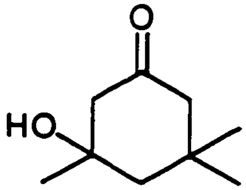
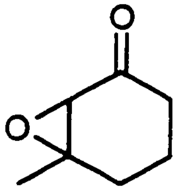
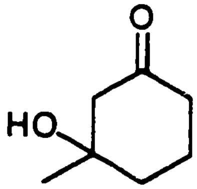
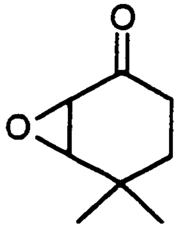
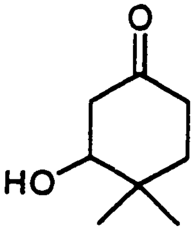
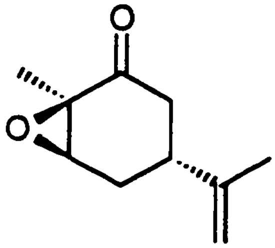
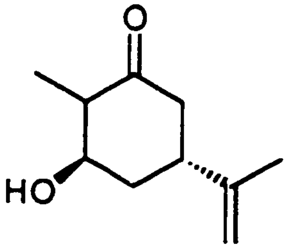
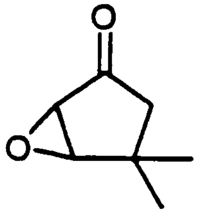
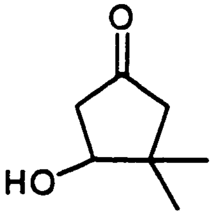
The ir spectrum of **37** showed an enone absorption at 1669 cm^{-1}. In the ^1H nmr spectrum, a vinylic proton appeared at δ 5.80 and a methyl doublet (J = 7 Hz) was displayed at δ 1.01. The ^{13}C APT nmr spectrum showed 10 lines and the mass spectrum displayed a molecular ion peak at m/z 152.1199, in support of the structural assignment.

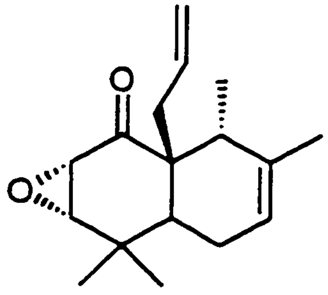
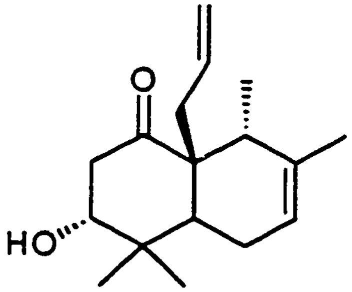
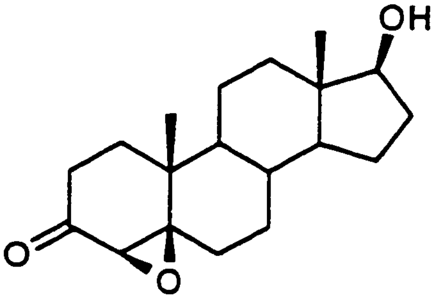
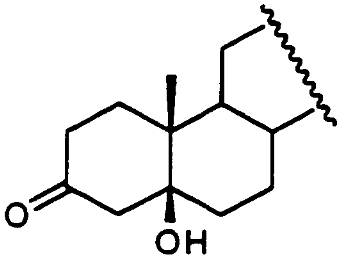
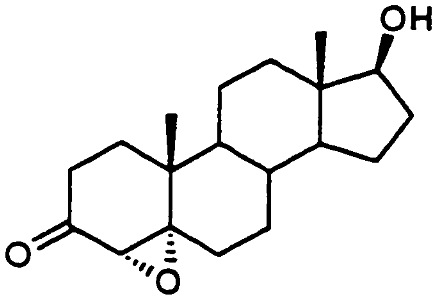
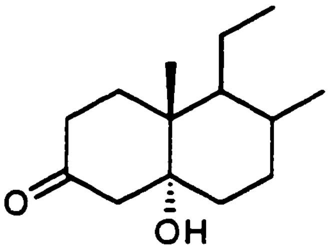
The above results indicated that the enolate generated from epoxy ketone **16** by lithium naphthalenide could not be successfully trapped with methyl iodide under the reaction conditions. Thus, at the present, the reductive alkylation of α,β-epoxy ketones using lithium naphthalenide is not considered a general process for the formation of α-substituted or α,α-disubstituted β-hydroxy ketones. Its successful application depends on the nature of the starting substrate and has to be examined on case-by-case basis.

C. Conclusions.

An efficient and apparently general procedure for reductive cleavage of α,β-epoxy ketones to the corresponding β-hydroxy ketones has been developed. This operationally simple procedure makes use of lithium naphthalenide as a reducing agent. The reaction conditions are sufficiently mild to minimize the side reactions. The desired products were obtained in synthetically useful yields. In several cases, the yields were found to be considerably better than those obtained using other methods. The generality of this method is evident from the results obtained for a number of α,β-epoxy ketones examined (Table 2-1). Although not general, this method is potentially useful for the preparation of α-substituted and α,α-disubstituted β-hydroxy ketones *via* alkylation of the enolate generated from reductive cleavage of the epoxy ring, and also for the preparation of 2,2-disubstituted 1,3-diones by subsequent oxidation.

Table 2-1. Reductive cleavage of α,β-epoxy ketones with lihtium naphthalenide to the corresponding β-hydroxy ketones.

Entry	α,β-Epoxy ketone	Time (min)	Product	Yield (%)
1		10		78
2		15		78
3		15		71
4		30		62
5		25		68

6		20		88
7		30		77
8		30		87

Experimental

General and materials

For detailed experimental remarks, see the Experimental Section of Chapter 1 of this thesis.

The conjugated enones, used for the preparation of α,β-epoxy ketones, were either synthesized previously in our laboratories[29,52,53] or obtained from commercial sources. No purification of these compounds was carried out prior to use. Active manganese dioxide was prepared from manganese sulfate and potassium permanganate, as described in the literature.[58]

General procedure for epoxidation of α,β-unsaturated ketones

A stirred solution of a conjugated enone (2.5 mmol, 1 equivalent) in methanol (5 mL) was cooled down to 0°C. A 30% aqueous solution of hydrogen peroxide (2.75 mmol, 0.24 mL, 1.1 equivalent) was then introduced dropwise, followed by addition of 1N lithium hydroxide (0.75 mmol, 0.3 equivalent). The reaction was monitored by tlc. For slow reactions, the solution was warmed up to room temperature. Upon completion, the reaction mixture was diluted with water (5 mL), acidified with 1N HCl (to pH ~6) and the products were extracted into ether (3 x 10 mL). The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation provided the crude product, which was purified by flash chromatography.

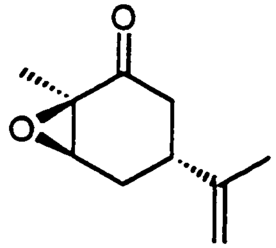
Preparation of lithium naphtalenide stock solution

Lithium was scraped under hexane to remove any oxide and nitride from its surface. Several small pieces of the lithium metal (42 mg, 6.1 mmol) were added to a solution of naphthalene (0.85 g, 6.66 mmol) in dry THF (10 mL). The resulting mixture was vigorously stirred at room temperature and under an atmosphere of argon. Within 3-5 minutes, the dark green color of the radical anion solution appeared and after 3-4 hours the lithium metal was completely dissolved. The 0.61M solution of lithium naphthalenide thus obtained was used immediately for reactions with epoxides or stored in a fridge at *ca.* -4°C under argon atmosphere for future use. The stock solution was found to retain virtually the same reactivity for more than a month.

General procedure for reductive cleavage of α,β-epoxy ketones

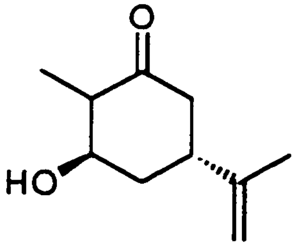
A solution of epoxy ketone (0.32 mmol, 1 equivalent) in dry tetrahydrofuran (2 mL) was added dropwise to a vigorously stirred 0.34M solution of lithium naphthalenide in THF (2.8 mL, 3 equivalents) at -78°C. The resulting mixture was kept at -78°C and under an atmosphere of argon till all of the starting material was consumed (tlc analysis). Then water was added (1 mL) to quench the reaction and the solution was allowed to warm up to room temperature, diluted with water (4 mL) and extracted with ether (3 x 5 mL). The combined organic extracts were washed successively with water and brine, dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to flash chromatography on silica gel which was prewashed with a 1% solution of triethylamine in hexanes. Solutions of ethyl acetate in hexanes containing a small amount of triethylamine (5 drops in 100 mL of solution) were used as eluants.

l-Carvone epoxide (14)



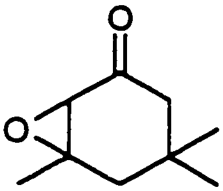
l-Carvone (0.50 g, 3.3 mmol), dissolved in 5 mL of methanol, was treated with 30% hydrogen peroxide (0.32 mL, 3.6 mmol) and 0.99 mL of 1N LiOH. The reaction mixture was stirred for 1 hour at 0°C. The usual work-up and purification provided epoxide **14** (0.51 g, 3.1 mmol) in 93% yield: FT-ir (neat film) 3082 cm^{-1} (alkene C-H stretching) and 1709 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 4.78 (m, 1H, C=CH_2), 4.70 (br s, 1H, C=CH_2), 3.43 (dd, *J* = 3.5, 1.5 Hz, 1H, C3-**H**), 2.72 (dddd, *J* = 11.5, 11.5, 5, 3.5 Hz, 1H, C5-**H**), 2.58 (ddd, *J* = 17.5, 5, 1.5 Hz, 1H, C6-**H**), 2.36 (dddd, *J* = 15, 3.5, 3.5, 1.5 Hz, 1H, C4-**H**), 2.02 (dd, *J* = 17.5, 11.5 Hz, 1H, C6-**H**), 1.88 (ddd, *J* = 15, 11.5, 1.5 Hz, 1H, C4-**H**), 1.7 (s, 3H, =C-CH_3) and 1.4 (s, 3H, C2-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.5 (p), 146.4 (p), 110.5 (p), 61.4 (a), 58.9 (p), 41.8 (p), 35.1 (a), 28.8 (p), 20.6 (a) and 15.3 (a); hreims M^+ 166.0993 (calculated for $C_{10}H_{14}O_2$: 166.0994). Elemental analysis: calculated for $C_{10}H_{14}O_2$: %C 72.26, %H 8.49; found: %C 72.05, %H 8.71.

(3R,5R)-3-Hydroxy-5-isopropenyl-2-methylcyclohexanone (15)



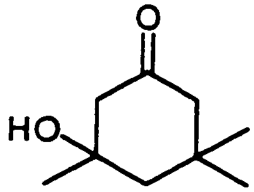
The reaction (-78°C, 0.5 hour) of carvone epoxide **14** (177 mg, 1.07 mmol) with 0.57 M lithium naphthalenide in THF (6.5 mL, 3.73 mmol) afforded hydroxy ketone **15** (111 mg, 62% yield) as a white solid: FT-ir ($CHCl_3$, cast) 3464 cm^{-1} (OH), 1707 cm^{-1} (C=O, ketone) and 1644 cm^{-1} (alkene C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 4.77 (m, 1H, C=C**H**), 4.73 (br s, 1H, C=C**H**), 4.26-4.32 (m, 1H, C3-**H**), 2.85 (dddd, J = 13, 13, 4, 4 Hz, 1H, C5-**H**), 2.56 (qdd, J = 7, 3, 1 Hz, 1H, C2-**H**), 2.46 (ddd, J = 13, 4, 2 Hz, 1H, C6-**H**), 2.26 (ddd, J = 13, 13, 1 Hz, 1H, C6-**H**), 2.12 (dddd, J = 14, 4, 2, 2 Hz, 1H, C4-**H**), 1.89 (br s, 1H, O**H**), 1.83 (ddd, J = 14, 13, 2 Hz, 1H, C4-**H**), 1.75 (br s, 3H, =C-C**H**$_3$) 1.16 (d, J = 7 Hz, 0.27H, C2-C**H**$_3$) and 1.10 (d, J = 7 Hz, 2.73H, C2-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 210.9 (p), 147.2 (p), 110.0 (p), 73.6 (a), 49.3 (a), 46.6 (p), 39.9 (a), 37.7 (p), 20.6 (a) and 10.7 (a); hreims M+ 168.1148 (calculated for $C_{10}H_{16}O_2$: 168.1150). Elemental analysis: calculated for $C_{10}H_{16}O_2$: %C 71.39, %H 9.59; found: %C 71.45, %H 9.90.

2,3-Epoxy-3,5,5-trimethylcyclohexanone (16)



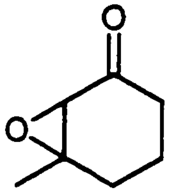
A solution of isophorone (0.54 mL, 3.61 mmol), hydrogen peroxide (30%, 0.37 mL) and 1N LiOH (1.08 mL) in methanol (5 mL) was stirred at room temperature for 6 hours. After work-up, the residue was subjected to flash chromatography (elution with 10% ethyl acetate in hexanes). The desired epoxide **16** was obtained (0.52 g, 3.39 mmol) in 94% yield as a colorless oil: FT-ir (neat film) 2958 cm^{-1} (alkane C-H stretching) and 1719 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.06 (s, 1H, C2-**H**), 2.61 (dd, J = 13.5, 1 Hz, 1H), 2.07 (d, J = 15 Hz, 1H), 1.79 (ddd, J = 13.5, 2, 1 Hz, 1H), 1.68 (dd, J = 15, 2 Hz, 1H), 1.41 (s, 3H, C3-CH_3), 1.05 (s, 3H, C5-CH_3) and 0.9 (s, 3H, C5-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 208.0 (p), 64.3 (p), 61.5 (a), 48.0 (p), 42.8 (p), 36.2 (p), 30.9 (a), 27.9 (a) and 24.1 (a); hreims M^+ 154.0994 (calculated for $C_9H_{14}O_2$: 154.0994). Elemental analysis: calculated for $C_9H_{14}O_2$: %C 70.10, %H 9.15; found: %C 69.86, %H 9.05.

3-Hydroxy-3,5,5-trimethylcyclohexanone (17)



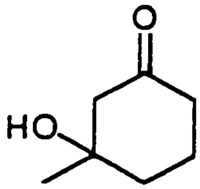
Treatment of isophorone epoxide **16** (49 mg, 0.32 mmol) with 1.15 M lithium naphthalenide in THF (0.82 mL, 0.95 mmol) at -78°C for 10 minutes provided hydroxy ketone **17** (39 mg, 78% yield) as a white solid: FT-ir ($CDCl_3$, cast) 3376 cm^{-1} (OH) and 1715 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 2.44 (d, J = 14 Hz, 1H), 2.38 (d, J = 14 Hz, 1H), 2.21 (s, 2H), 1.80 (d, J = 14 Hz, 1H), 1.73 (d, J = 14 Hz, 1H), 1.35 (s, 3H, C3-CH_3), 1.13 (s, 3H, C5-CH_3) and 1.05 (s, 3H, C5-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 210.4 (p), 74.9 (p), 54.0 (p) (2 x C), 50.2 (p), 35.6 (p), 33.1 (a), 32.6 (a) and 28.5 (a); hreims M^+ 156.1149 (calculated for $C_9H_{16}O_2$: 156.1150). Elemental analysis: calculated for $C_9H_{16}O_2$: %C 69.19, %H 10.32; found: %C 69.12, %H 10.37.

2,3-Epoxy-3-methylcyclohexanone (18)



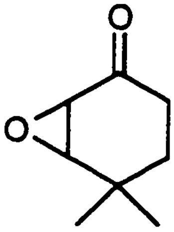
To a solution of 3-methyl-2-cyclohexenone (0.51 mL, 4.54 mmol) in methanol (5 mL), a solution of 30% hydrogen peroxide (0.47 mL, 5.45 mmol) was added, followed by addition of lithium hydroxide (1.36 mL, 1N). After stirring for 4 hours at room temperature, the reaction was stopped. The crude product was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes afforded epoxide **18** (0.49 g, 86% yield) as a colorless oil: FT-ir ($CDCl_3$, cast) 2945 cm^{-1} (alkane C-H stretching) and 1708 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.05 (s, 1H, C2-**H**), 2.41-2.52 (m, 1H), 1.79-2.15 (m, 4H), 1.57-1.66 (m, 1H) and 1.43 (s, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 206.6 (p), 62.3 (p), 61.9 (a), 35.6 (p), 28.3 (p), 22.2 (a) and 17.1 (p); hreims M^+ 126.0680 (calculated for $C_7H_{10}O_2$: 126.0681).

3-Hydroxy-3-methylcyclohexanone (19)



A solution of epoxide **18** (64 mg, 0.51 mmol) in 2 mL of dry THF was introduced dropwise to lithium naphthalenide in THF (2.8 mL, 0.53M) at -78°C. After 15 minutes, tlc showed the absence of starting material. The reaction was worked up in the usual manner and the residue was subjected to flash chromatography, giving compound **19** (51 mg, 0.39 mmol) in 78% yield as a colorless oil: FT-ir ($CHCl_3$, cast) 3426 cm^{-1} (OH) and 1704 cm^{-1} (C=O, ketone); ^1H nmr (360 MHz, $CDCl_3$) δ 2.43 (br s, 2H), 2.31-2.40 (m, 1H), 2.20-2.30 (m, 1H), 1.99-2.12 (m, 1H), 1.72-1.90 (m, 3H) and 1.32 (s, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 210.6 (p), 74.0 (p), 55.1 (p), 40.5 (p), 37.7 (p), 30.2 (a) and 21.4 (p); hreims M^+ 128.0836 (calculated for $C_7H_{12}O_2$: 128.0837).

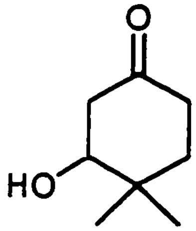
2,3-Epoxy-4,4-dimethylcyclohexanone (20)



4,4-Dimethyl-2-cyclohexenone (0.31 g, 2.52 mmol) in methanol (3 mL) was treated with hydrogen peroxide (0.24 mL of 30% solution) and 1N lithium hydroxide (0.75 mL) at room temperature. After 3 hours, the reaction was complete and usual work-up followed. Purification of the crude product by flash chromatography, eluting with 10% ethyl acetate in hexanes gave epoxide **20**

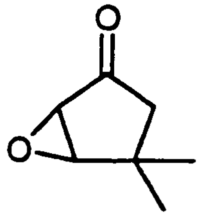
(0.28 g, 80% yield) as a colorless oil: FT-ir ($CDCl_3$, cast) 3011 cm^{-1} (epoxide C-H stretching) and 1713 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.20 (d, *J* = 4 Hz, 1H, C2-**H**), 3.15 (dd, *J* = 4, 1.5 Hz, 1H, C3-**H**), 2.37 (ddd, *J* = 19, 6.5, 3 Hz, 1H, C6-**H**), 2.16 (ddd, *J* = 19, 12, 7 Hz, 1H, C6-**H**), 1.87 (ddd, *J* = 18.5, 12, 6.5 Hz, 1H, C5-**H**), 1.31 (dddd,*J* = 18.5, 7, 3, 1.5 Hz, 1H, C5-**H**), 1.19 (s, 3H, C4-CH_3) and 1.04 (s, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.9 (p), 64.1 (a), 55.9 (a), 33.1 (p), 30.7 (p), 29.8 (p), 27.4 (a) and 22.9 (a); hreims M^+ 140.0835 (calculated for $C_8H_{12}O_2$: 140.0837). Elemental analysis: calculated for $C_8H_{12}O_2$: %C 68.55, %H 8.63; found: %C 68.39, %H 8.82.

3-Hydroxy-4,4-dimethylcyclohexanone (21)



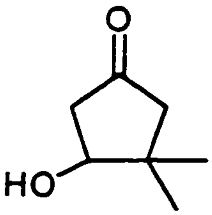
To a 0.68M lithium naphthalenide solution (3 mL), epoxide **20** (87 mg, 0.62 mmol) dissolved in THF (2 mL) was introduced. The reaction mixture was stirred for 15 minutes at -78°C and then quenched with water. After usual work-up and chromatographic purification, hydroxy hexanone **21** (62.5 mg, 0.44 mmol) was obtained in 71% yield as a white solid: FT-ir (C_6D_6, cast) 3450 cm^{-1} (OH) and 1714 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 8, 4.5 Hz, 1H, C3-**H**), 2.65 (ddd, *J* = 14, 4.5, 1.5 Hz, 1H, C2-**H**), 2.31-2.46 (m, 3H), 1.88 (ddd, *J* = 13.5, 6.5, 6.5 Hz, 2H), 1.44-1.54 (m, 1H), 1.35 (s, 3H, C4-CH_3) and 1.08 (s, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, C_6D_6) δ 208.2 (p), 76.3 (a), 46.7 (p), 37.8 (p), 34.5 (p), 34.2 (p), 26.0 (a) and 21.3 (a); hreims M^+ 142.0993 (calculated for $C_8H_{14}O_2$: 142.0994). Elemental analysis: calculated for $C_8H_{14}O_2$: %C 67.57, %H 9.92; found: %C 67.72, %H 10.19.

2,3-Epoxy-4,4-dimethylcyclopentanone (22)



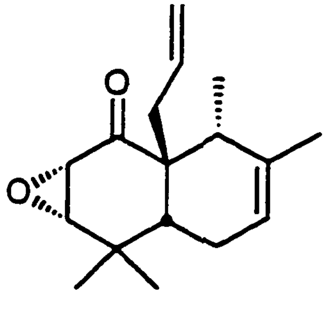
The reaction of 4,4-dimethyl-2-cyclopenten-1-one (0.5 g, 4.5 mmol) with hydrogen peroxide (0.6 mL of 30% solution) and 1N LiOH (1.4 mL) in methanol at 0°C was completed within 3 hours and afforded epoxy ketone **22** (504 mg, 89% yield) as a colorless oil: FT-ir ($CDCl_3$, cast) 3013 cm^{-1} (epoxide C-H stretching) and 1752 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.51 (d, *J* = 2.5 Hz, 1H, C3-**H** or C2-**H**), 3.32 (d, *J* = 2.5 Hz, 1H, C2-**H** or C3-**H**), 2.16 (d, *J* = 17.5 Hz, 1H, C5-**H**), 1.76 (d, *J* = 17.5 Hz, 1H, C5-**H**), 1.25 (s, 3H, C4-CH_3) and 1.05 (s, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 209.6 (p), 65.3 (a), 56.0 (a), 45.4 (p), 35.5 (p), 25.1 (a) and 23.9 (a); hreims M^+ 126.0683 (calculated for $C_7H_{10}O_2$: 126.0681).

4-Hydroxy-3,3-dimethylcyclopentanone (23)



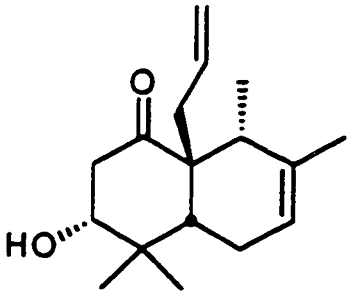
Epoxy ketone **22** (140 mg, 1.1 mmol) in 2 mL of dry THF was added slowly to a solution of lithium naphthalenide in THF (0.7M, 4.7 mL) at -78°C and the resulting mixture was stirred for 25 minutes. After work-up and purification, hydroxy ketone **23** (96 mg, 0.75 mmol, 68% yield) was obtained: FT-ir ($CDCl_3$, cast) 3443 cm^{-1} (OH) and 1738 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 4.03 (dd, J = 6, 4 Hz, 1H, C4-**H**), 2.60 (ddd, J = 19, 6, 1.5 Hz, 1H, C5-**H**), 2.19-2.43 (m, 3H), 2.00 (dd, J = 18, 1 Hz, 1H, C2-**H**), 1.12 (s, 3H, C3-CH_3) and 1.05 (s, 3H, C3-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 217.0 (p), 76.8 (a), 50.7 (p), 46.0 (p), 40.5 (p), 26.6 (a) and 21.8 (a); hreims M^+ 128.0836 (calculated for $C_7H_{12}O_2$: 128.0837).

(1R*,3S*,5S*,7R*,11R*)-1-Allyl-6,6,10,11-tetramethyl-4-oxatricyclo[5.4.0.0^{3,5}]undec-9-en-2-one (25)



Treatment of enone **24** (100 mg, 0.41 mmol) with 30% hydrogen peroxide (0.05 mL, 0.61mmol) and 1N LiOH (0.12 mL) in methanol at 0°C for 2 hours afforded epoxy ketone **25** (102 mg, 0.39 mmol) in 96% yield: FT-ir ($CDCl_3$, cast) 3074 cm^{-1} (alkene C-H stretching), 1696 cm^{-1} (C=O, ketone) and 1637 cm^{-1} (alkene C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 5.51 (ddddd, J = 17, 10, 7, 7, 1 Hz, 1H, C**H**=CH_2), 5.40-5.45 (m, 1H, C9-**H**), 5.01 (dddd, J = 10, 2, 2, 1 Hz, 1H, CH=C**H**$_2$), 4.93 (dddd, J = 17, 2, 2, 1 Hz, 1H, CH=C**H**$_2$), 3.36 (dd, J = 4, 1 Hz, 1H, C5-**H**), 3.28 (dd, *J* = 4, 1 Hz, 1H, C3-**H**), 2.48 (dd, *J* = 7, 1 Hz, 2H, C1-CH_2), 2.35 (q, *J* = 7 Hz, 1H, C11-**H**), 1.88-2.17 (m, 3H), 1.69 (br s, 3H, C10-CH_3), 1.21 (s, 3H, C6-CH_3), 0.95 (s, 3H, C6-CH_3) and 0.87 (dd, *J* = 7, 1 Hz, 3H, C11-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 209.3 (p), 140.0 (p), 134.5 (a), 118.3 (a), 117.9 (p), 67.5 (a), 56.5 (a), 53.6 (p), 45.6 (p), 43.4 (a), 37.2 (a), 35.1 (p), 27.2 (a), 22.5 (a), 22.3 (p), 20.8 (a) and 14.7 (a); hreims M^+ 260.1776 (calcuiated for $C_{17}H_{24}O_2$: 260.1776).

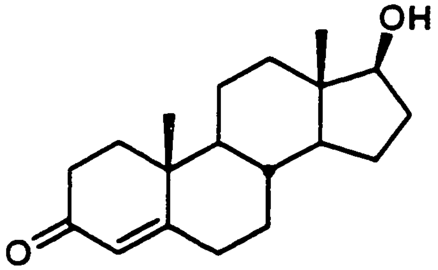
(1R*,4S*,6R*,10R*)-1-Allyl-4-hydroxy-5,5,9,10-tetramethylbicyclo-[4.4.0]dec-8-en-2-one (26)



The epoxide **25** (52 mg, 0.2 mmol) was reacted with lithium naphthalenide (1.1 mL, 0.55M solution) in THF at -78°C. After 20 minutes, all starting material was consumed. Purification of the crude product afforded hydroxy ketone **26** (46 mg, 88% yield) as a white solid: FT-ir ($CHCl_3$, cast) 3476 cm^{-1} (OH), 3074 cm^{-1} (alkene C-H stretching) and 1698 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.58 (dddd, *J* = 17, 10, 7, 7 Hz, 1H, C**H**=CH_2), 5.50 (dddd, *J* = 4.5, 3.5, 3.5, 1.5 Hz, 1H, C8-**H**), 4.99 (ddd, *J* = 10, 2.5, 1 Hz, 1H, CH=CH_2), 4.95 (ddd, *J* = 17, 2.5, 1.5 Hz, 1H, CH=CH_2), 3.83 (dd, *J* = 7, 3 Hz, 1H, C4-**H**), 2.72 (ddd, *J* = 18, 7, 1 Hz, 1H, C1-CH_2), 2.37-2.51 (m, 3H), 2.32 (q, *J* = 7 Hz, 1H, C10-**H**), 2.17 (dd, *J* = 10, 7 Hz, 1H), 1.96-2.13 (m, 2H), 1.88 (br s, 1H, O**H**), 1.71 (br s, 3H, C9-

CH_3), 1.01 (s, 3H, C5-CH_3), 0.91 (d, J = 7 Hz, 3H, C10-CH_3) and 0.87 (s, 3H, C5-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 216.9 (p), 141.1 (p), 136.3 (a), 121.1 (a), 117.7 (p), 75.3 (a), 56.5 (p), 47.2 (p), 46.9 (p), 44.5 (a), 40.4 (a), 38.6 (p), 26.0 (a), 24.1 (p), 22.8 (a), 22.1 (a) and 14.9 (a); hreims M+ 262.1933 (calculated for $C_{17}H_{26}O_2$: 262.1933).

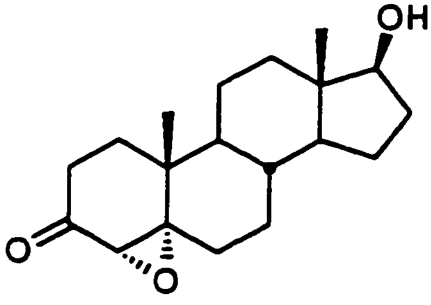
Testosterone (30)



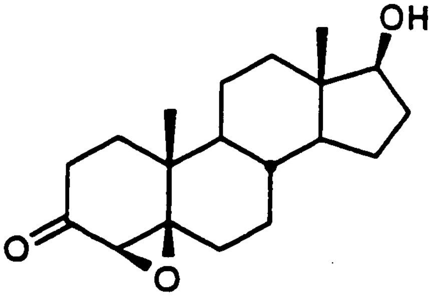
A solution of androst-4-ene-3,17-dione (0.8 g, 2.79 mmol) in dry THF (5 mL) was introduced slowly to a suspension of lithium aluminum hydride (157 mg, 4.2 mmol) in THF (25 mL). The resulting mixture was stirred under an argon atmosphere at 0°C for 1 hour and then at room temperature for additional 3 hours. The excess reagent was decomposed by careful addition of ethyl acetate followed by addition of saturated aqueous sodium sulfate. Then solid sodium sulfate was added, salts were removed by filtration and washed with THF. Evaporation of the solvent gave a mixture of diols, which was without purification suspended in chloroform (20 mL). Active manganese dioxide (4 g) was added and the mixture stirred for 10 hours at room temperature. The precipitate was then removed by filtration and washed with chloroform. The combined organic solutions were concentrated and the residue was subjected to flash chromatography. Elution with 20% ethyl acetate in hexanes gave 0.71 g of testosterone **30** (89% yield): FT-ir ($CHCl_3$, cast) 3424 cm^{-1} (OH), 1661 cm^{-1}

(C=O, enone) and 1614 cm^{-1} (alkene C=C stretching); ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.73 (d, *J* = 1.5 Hz, 1H, C4-**H**), 3.65 (dd, *J* = 8.5, 8.5 Hz, 1H, C17-**H**), 2.21-2.47 (m, 3H), 1.98-2.12 (m, 2H),1.79-1.90 (m, 2H), 1.25-1.76 (m, 9H), 1.19 (s, 3H, C**H**$_3$), 0.95-1.15 (m, 4H) and 0.79 (s, 3H, C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 199.6 (p), 171.3 (p), 123.9 (a), 81.6 (a), 54.0 (a), 50.5 (a), 42.9 (p), 38.7 (p), 36.5 (p), 35.8 (p), 35.7 (a), 34.0 (p), 32.8 (p), 31.6 (p), 30.5 (p), 23.4 (p), 20.7 (p), 17.5 (a) and 11.1 (a); hreims M$^+$ 288.2086 (calculated for $C_{19}H_{28}O_2$: 288.2089).

4α,5α-Epoxy-17β-hydroxyandrostan-3-one (31) and 4β,5β-epoxy-17β-hydroxyandrostan-3-one (32)



31



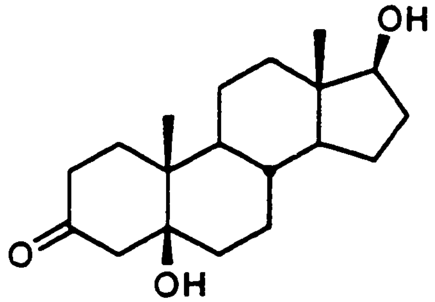
32

A mixture of testosterone (0.4 g, 1.4 mmol), 30% hydrogen peroxide (0.24 mL, 2.78 mmol) and 1N lithium hydroxide (0.69 mL) in methanol (10 mL) was stirred at room temperature for 7 hours. Usual work-up, followed by purification of the crude product by flash chromatography (elution with 20% ethyl acetate in hexanes) gave compound **31** (114 mg, 0.37 mmol) in 27% yield: FT-ir ($CHCl_3$, cast) 3440 cm^{-1} (OH), 2938 cm^{-1} (alkane C-H stretching) and 1708 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 8.5, 8.5 Hz, 1H, C17-**H**), 3.03 (s, 1H, C4-**H**), 2.40 (ddd, *J* = 19, 7.5, 2 Hz,1H, C2-**H**), 2.01-2.31 (m, 3H), 1.08-

1.90 (m, 16H), 1.07 (s, 3H, CH_3) and 0.78 (s, 3H, CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 207.0 (p), 81.8 (a), 70.2 (p), 62.9 (a), 50.9 (a), 50.3 (a), 43.0 (p), 36.9 (p), 36.5 (p), 35.6 (a), 33.1 (p), 30.5 (p), 29.7 (p), 29.2 (p), 28.5 (p), 23.4 (p), 21.1 (p), 16.6 (a) and 11.1 (a); hreims M^+ 304.2046 (calculated for $C_{19}H_{28}O_3$: 304.2039).

Further elution afforded epoxide **32** (241 mg, 0.79 mmol) in 57% yield: FT-ir ($CHCl_3$, cast) 3438 cm^{-1} (OH), 2943 cm^{-1} (alkane C-H stretching) and 1709 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.61 (dd, *J* = 8.5, 8.5 Hz, 1H, C17-H), 2.94 (s, 1H, C4-H), 2.27 (ddd, *J* = 19, 8.5, 2.5 Hz, 1H, C2-H), 1.97-2.21 (m, 3H), 1.73-1.89 (m, 4H), 1.18-1.63 (m, 7H), 1.13 (s, 3H, CH_3), 0.91-1.12 (m, 5H) and 0.74 (s, 3H, CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 206.8 (p), 81.5 (a), 70.3 (p), 62.6 (a), 50.5 (a), 46.6 (a), 43.0 (p), 37.3 (p), 36.2 (p), 35.1 (a), 32.5 (p), 30.3 (p), 29.9 (p), 29.7 (p), 26.1 (p), 23.3 (p), 21.2.(p), 19.0 (a) and 11.1 (a); hreims M^+ 304.2043 (calculated for $C_{19}H_{28}O_3$: 304.2039).

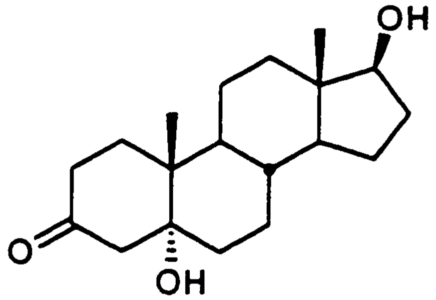
5β,17β-Dihydroxyandrostan-3-one (33)



Epoxy alcohol **32** (98 mg, 0.32 mmol) in dry THF was treated with lithium naphthalenide (2.1 mL of 0.62 M solution, 1.29 mmol) at -78°C for 30 minutes. After work-up and flash chromatography (elution with 30% ethyl acetate in hexane) of the crude product, diol **33** (76 mg, 0.25 mmol) was obtained in 77%

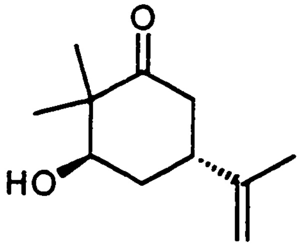
yield: FT-ir (CHCl$_3$, cast) 3414 cm^{-1} (OH) and 1705 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 3.66 (dd, *J* = 8.5, 8.5 Hz, 1H, C17-**H**), 3.02 (d, *J* = 15 Hz, 1H, C4-**H**), 2.28 (ddd, *J* = 14.5, 14.5, 5 Hz, 1H, C2-**H**), 2.19 (dddd, *J* = 14.5, 4.5, 2.5, 2.5 Hz, 1H, C2-**H**), 1.10-2.14 (m, 20H), 1.00 (s, 3H, CH$_3$) and 0.76 (s, 3H, CH$_3$); ^{13}C nmr (75.5 MHz, CD$_3$OD) δ 214.8 (p), 82.4 (a), 79.3 (p), 52.2 (a), 50.2 (p), 44.8 (a), 44.1 (p), 41.4 (p), 38.1 (p), 37.9 (p), 36.6 (p), 36.3 (a), 32.3 (p), 30.7 (p), 29.5 (p), 24.3 (p), 22.4 (p), 16.7 (a) and 11.6 (a); hreims M+ 306.2197 (calculated for $C_{19}H_{30}O_3$: 306.2195).

5α,17β-Dihydroxyandrostan-3-one (34)



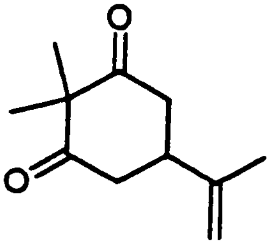
The reaction of epoxy ketone **31** (59 mg, 0.19 mmol) with 0.62M lithium naphthalenide in THF (1.26 mL, 0.78 mmol) at -78°C for 30 minutes provided dihydroxy ketone **34** (51 mg, 0.17 mmol) in 87% yield: FT-ir (uscope) 3460 cm^{-1} (OH) and 1716 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 3.65 (dd, *J* = 8.5, 8.5 Hz, 1H, C17-**H**), 2.68 (d, *J* = 15 Hz, 1H, C4-**H**), 2.32-2.41 (m, 2H), 1.05-2.14 (m, 20H), 1.18 (s, 3H, CH$_3$) and 0.76 (s, 3H, CH$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 214.4 (p), 82.5 (a), 78.1 (p), 52.5 (p), 52.0 (a), 47.1 (a), 44.2 (p), 40.3 (p), 38.7 (p), 38.1 (p), 36.3 (a), 34.8 (p), 33.8 (p), 30.8 (p), 26.8 (p), 24.3 (p), 22.2 (p), 16.0 (a) and 11.7 (a); hreims M+ 306.2206 (calculated for $C_{19}H_{30}O_3$: 306.2195).

(3R,5R)-3-Hydroxy-5-isopropenyl-2,2-dimethylcyclohexanone (35)



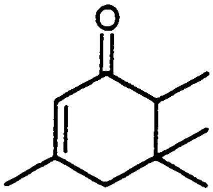
At -78°C, *l*-carvone epoxide **14** (126 mg, 0.76 mmol) in dry THF (2 mL) was added dropwise to a solution of lithium naphthalenide in THF (4.9 mL of 0.54M solution, 2.66 mmol). The resulting mixture was stirred vigorously for 30 minutes at -78°C. Methyl iodide (0.24 mL, 3.79 mmol) was then introduced. The color of the solution changed immediately from deep green to brownish yellow. The reaction mixture was allowed to warm up to room temperature. Saturated ammonium chloride was added and the resulting mixture was extracted with ether (3 x 5 mL). The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. Filtration and concentration yielded the crude product which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes gave compound **35** (96.7 mg, 70% yield) as a colorless oil: FT-ir (CDCl$_3$, cast) 3473 cm^{-1} (OH), 3082 cm^{-1} (alkene C-H stretching) and 1703 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 4.78 (br s, 1H, C=CH$_2$), 4.74 (d, *J* = 1.5 Hz, 1H, C=CH$_2$), 3.90 (dd, *J* = 4.5, 3 Hz, 1H, C3-**H**), 2.84 (dddd, *J* = 12, 12, 4.5, 4.5 Hz, 1H, C5-**H**), 2.53 (dd, *J* = 14, 12 Hz, 1H, C6-**H**), 2.36 (ddd, *J* = 14, 4.5, 2 Hz, 1H, C6-**H**), 2.12 (br s, 1H, O**H**), 2.07 (ddd, *J* = 14, 12, 3 Hz, 1H, C4-**H**), 1.92 (dddd, *J* = 14, 4.5, 4.5, 2 Hz, 1H, C4-H), 1.74 (d, *J* = 1 Hz, 3H, =C-CH_3), 1.17 (s, 3H, C2-CH_3) and 1.13 (s, 3H, C2-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 214.7 (p), 147.2 (p), 110.1 (p), 77.4 (a), 49.7 (p), 42.3 (p), 39.2 (a), 33.1 (p), 24.5 (a), 20.7 (a) and 20.3 (a); hreims M+ 182.1309 (calculated for $C_{11}H_{18}O_2$: 182.1307). Elemental analysis: calculated for $C_{11}H_{18}O_2$: %C 72.49, %H 9.95; found: %C 72.46, %H 9.72.

5-Isopropenyl-2,2-dimethylcyclohexane-1,3-dione (36)



A solution of hydroxy ketone **35** (48 mg, 0.26 mmol) in dry dichloromethane (3 mL) was stirred at room temperature and under an argon atmosphere. Pyridinium chlorochromate (285 mg, 1.32 mmol) was introduced in one portion. After 8 hours of stirring, the reaction mixture was filtered through celite and solvent was removed under reduced pressure. Purification of the crude product by flash chromatography, using 5% ethyl acetate in hexanes as an eluant, gave diketone **36** (37 mg, 0.21 mmol) in 78% yield: FT-ir ($CHCl_3$, cast) 1728 cm^{-1} (C=O, ketone) and 1646 cm^{-1} (alkene C=C stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 4.86 (br s, 1H, C=CH_2), 4.74 (d, *J* = 1 Hz, 1H, C=CH_2), 2.78 (d, *J* = 7 Hz, 4H, -CH_2-CO), 2.60 (q, *J* = 7 Hz, 1H, C5-H), 1.76 (d, *J* = 1 Hz, 3H, =C-CH_3), 1.33 (s, 3H, C2-CH_3) and 1.28 (s, 3H, C2-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 210.1 (p) (2 x C), 145.1 (p), 111.8 (p), 60.8 (p), 42.4 (p) (2 x C), 36.8 (a), 23.5 (a), 21.3 (a) and 20.6 (a); hreims M+ 180.1154 (calculated for $C_{11}H_{16}O_2$: 180.1150).

3,5,5,6-Tetramethyl-2-cyclohexenone (37)



Isophorone epoxide **16** (130 mg, 0.84 mmol) in 2 mL of dry THF was introduced slowly to lithium naphthalenide (4.4 mL of 0.57M solution in THF) at -78°C under an atmosphere of argon. After 15 minutes of vigorous stirring, methyl iodide (0.26 mL, 4.2 mmol) was then added and the reaction mixture was warmed up to room temperature. After 5 hours, the reaction was worked up in the usual manner. Purification of the crude product by flash chromatography (5% ethyl acetate in hexanes was used for elution) afforded enone **37** (40 mg, 0.26 mmol) in 31% yield: FT-ir ($CDCl_3$, cast) 1669 cm^{-1} (C=O, enone) 1641 cm^{-1} (C=C stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 5.80 (s, 1H, C2-**H**), 2.05-2.24 (m, 3H), 1.89 (s, 3H, C3-**CH_3**), 1.02 (s, 3H, C5-**CH_3**), 1.01 (d, $J = 7$ Hz, 3H, C6-**CH_3**) and 0.85 (s, 3H, C5-**CH_3**); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 202.6 (p), 158.5 (p), 125.0 (a), 51.2 (a), 45.3 (p), 36.1 (p), 28.8 (a), 24.3 (a), 22.4 (a) and 9.6 (a); hreims M^+ 152.1199 (calculated for $C_{10}H_{16}O$: 152.1201).

Further elution gave isophorone (59 mg, 0.43 mmol) in 51% yield.

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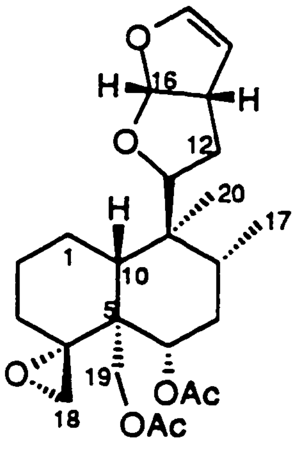
Chapter 3

Synthetic Studies Towards Teucvin

Introduction

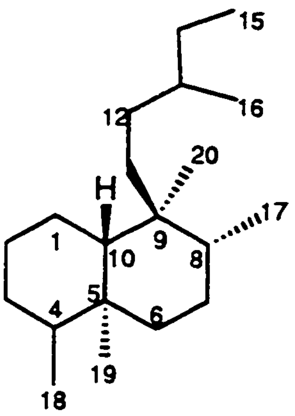
A large number of clerodanes and 19-nor-clerodanes have been isolated from plants over the past thirty years.[1] The name and chirality of this growing subgroup of diterpenes were given by its first member, clerodin 1, isolated in 1961.[2] Since then, interest in these compounds has been stimulated by their biological activity as insect antifeedants and as antitumor, antimicrobial, and antifungal agents.



1

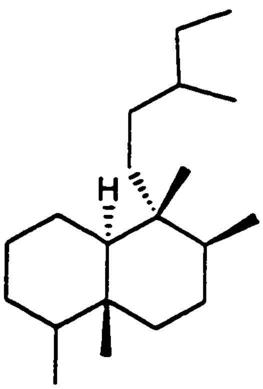
Clerodanes are divided into two series: *neo*-clerodanes and *ent-neo*-clerodanes.[3] The vast majority of compounds known possess the same absolute stereochemistry as clerodin and is named *neo*-clerodanes (Figure 3-1a). Those compounds enantiomeric to clerodin are termed *ent-neo*-clerodanes (Figure 3-1b). Members of this family can be further classified as *cis* or*trans* compounds, depending on the stereochemistry of the decalin ring junction.

Biosynthetically, the clerodanes appear to be related to the labdanes, *via* a series of methyl and hydride shifts.[4] The simplified biogenetic route for *neo*-clerodanes is shown in Scheme 3-1. Starting from geranylgeranyl pyro-



neo-clerodane

Figure 3-1a



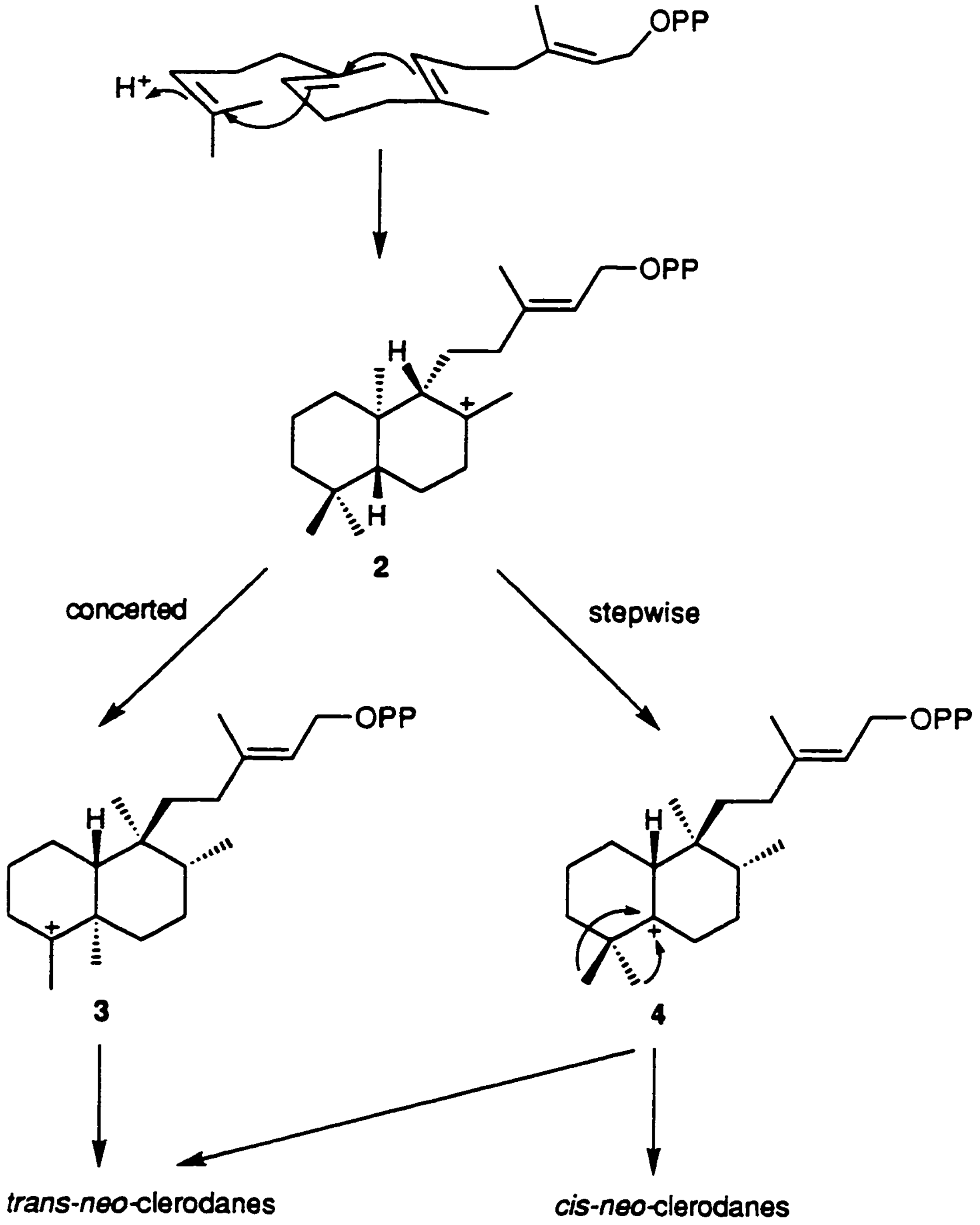
ent-neo-clerodane

Figure 3-1b

phosphate, the labdane skeleton **2** is formed, which through a concerted migration process leads to intermediate **3**, precursor of *trans-neo*-clerodanes. The formation of *cis*-clerodanes, on the other hand, requries a stepwise process to intermediate **4**. Then, depending on which of the C-4 methyl groups migrates, either *cis-* or *trans-neo*-clerodanes can be derived. Alternative cyclization of geranylgeranyl pyrophosphate would produce the enantimeric labdane nucleus, which would lead to the formation of *ent-neo*-clerodanes.

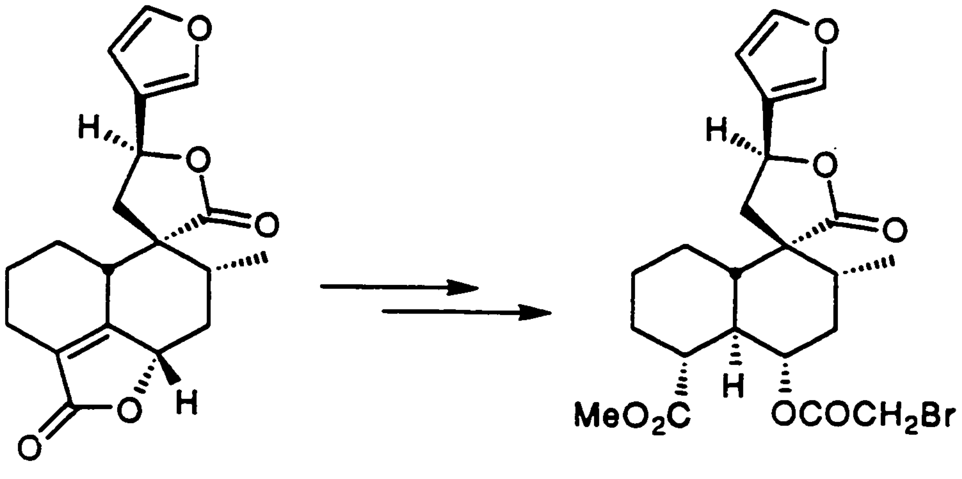
Up to date, the most abundant source of *neo*-clerodane and 19-nor-*neo*-clerodane diterpenoids are the plants belonging to the genus *Teucrium* (family Labiatae), from which over 150 *neo*-clerodanes have been isolated.[5] This apparent productivity may, in part, be due to the extremely extensive investigation of this genus by the groups of Piozzi, Rodriguez, Savona, Malakov and Papanov.[1,6] The *Teucrium* genera shows strong tendency to give compounds with a furan ring, β-substituted with the remainig part of the terpene.

Scheme 3-1



Additional heterocyclic features, occurring in the structures are γ-spirolactone at the C-9 position, α,β-unsaturated γ-lactone, five-membered lactol, pyran ring and epoxide. Almost all diterpenoids from the *Teucrium* species are *trans* compounds or compounds with *sp*^{2} hybridization at C-5 position (19-nor-clerodanes).

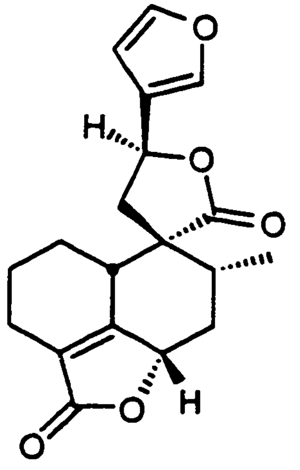
The first *Teucrium* diterpenoid, whose structure was fully elucidated was teucvin **5**. Teucvin was first isolated from the neutral extract of *Teucrium viscidum* Blume *var. Miquelianum* (Maxim.) Hara (Labiatae) by Fuijta and co-workers in 1973.[7] It comprised about 0.07% of the dry weight of the plant material. The structure and absolute configuration of teucvin were established by a combination of spectroscopic and X-ray crystallographic studies of the bromoacetate derivative **6** (Equation 3-1).[8] Subsequently, teucvin was also isolated from other *Teucirium* species: *T. cubanse, T.chamaedrys, T. japonicum* and from *Mallotus repanus*, a specie of the family Euphorbiaceae.[9-11]



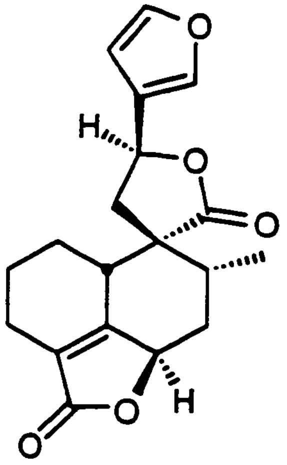
5 **6** (Eq. 3-1)

Teucvin is also known as teuchamaedryn A, eugarzasadine and mallotucin A.[1] Along with teucvin, many structurally very similar clerodanes have been isolated. Some of them are depicted in Figure 3-2.[6,12-17]

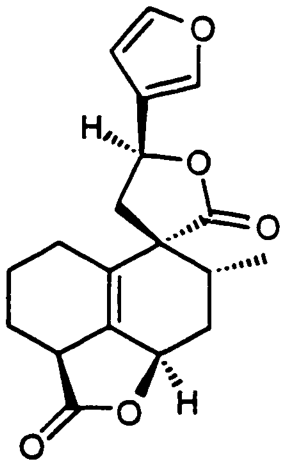
Teucvin has been shown to be amoebicidal and to act as a root development inhibitor.[18] However, it shows no antitumour potential as is the case with teucvidin 7,[19] possesing opposite stereochemistry at C-6 and C-10.



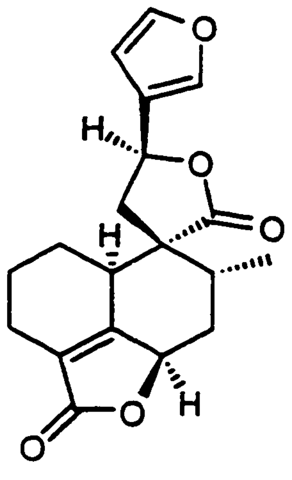
5 Teucvin



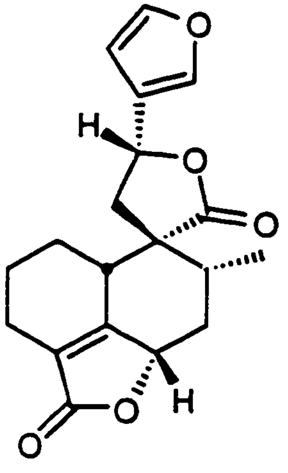
Teuflin



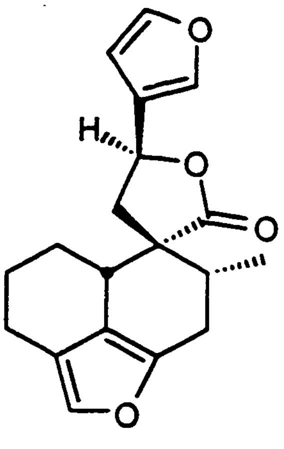
Isoteuflin



7 Teucvidin

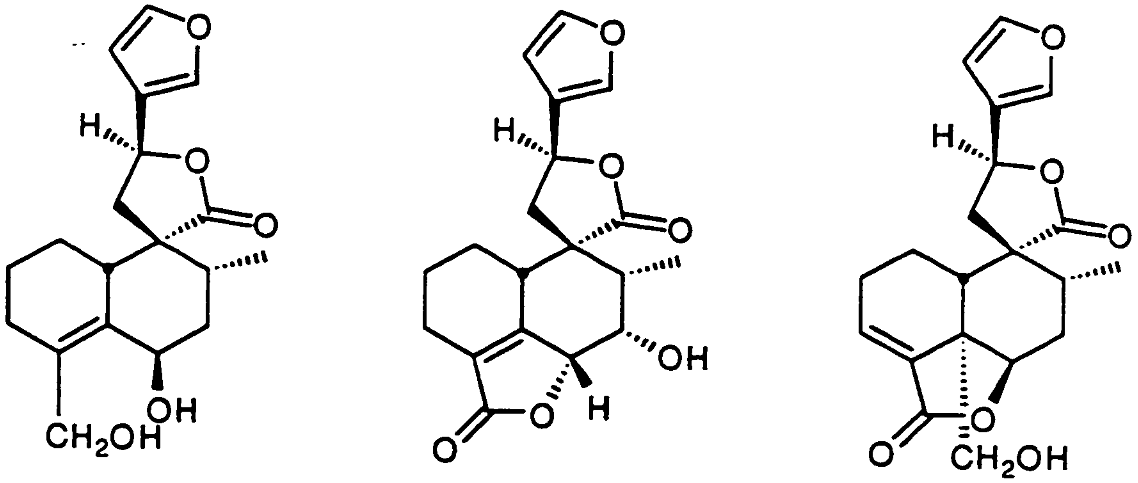


12-*epi*-Teucvin



8 Montanin A

Figure 3-2 Teucvin and structurally similar clerodanes



Montanin B Teucrin A 12-epi-Teuscordonin

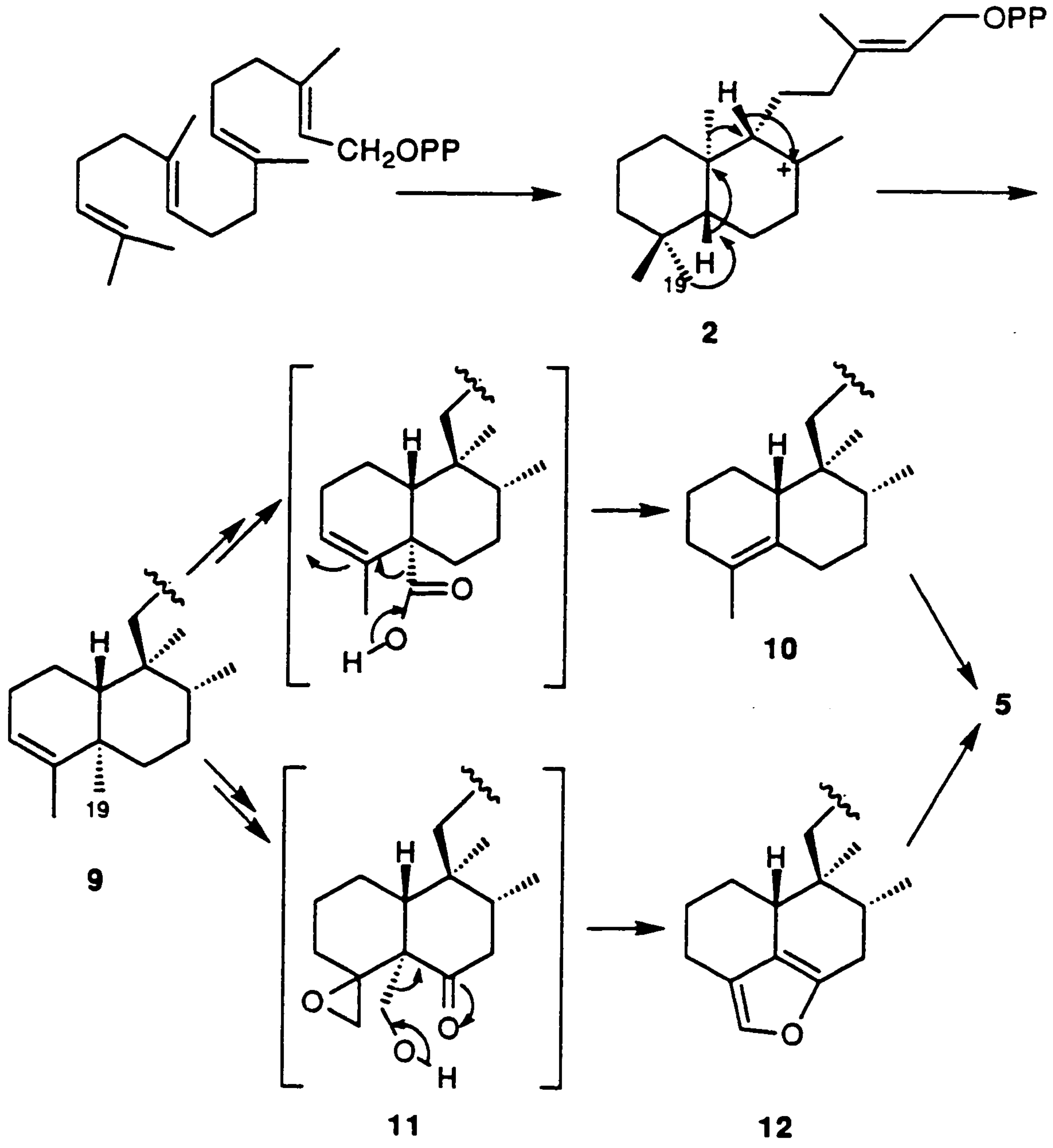
Figure 3-2 (continued)

No experimental work has been done so far on the biogenesis of teucvin or any similar furanoid clerodanes. On the basis of the well accepted theory,[6] however, the plausible route might be as outlined in Scheme 3-2. A labdane type intermediate **2**, arising from geranylgeranyl pyrophosphate, is converted into the *neo*-clerodane type compound **9**. Oxidative elimination of C-19 may occur *via* oxidation to carboxy group followed by decarboxylation into **10**. Then, oxidation of C-6 and C-18 and subsequent formation of α,β-unsaturated γ-lactone may take place.[8] The elimination of C-19 may also occur on structures like **11** by retroaldol splitting of formaldehyde. This may be followed by a cyclization-dehydration pathway to furnish intermediate **12**.[6] The formation of another γ-lactone and a furan ring must occur in some steps between **9** and **5**.

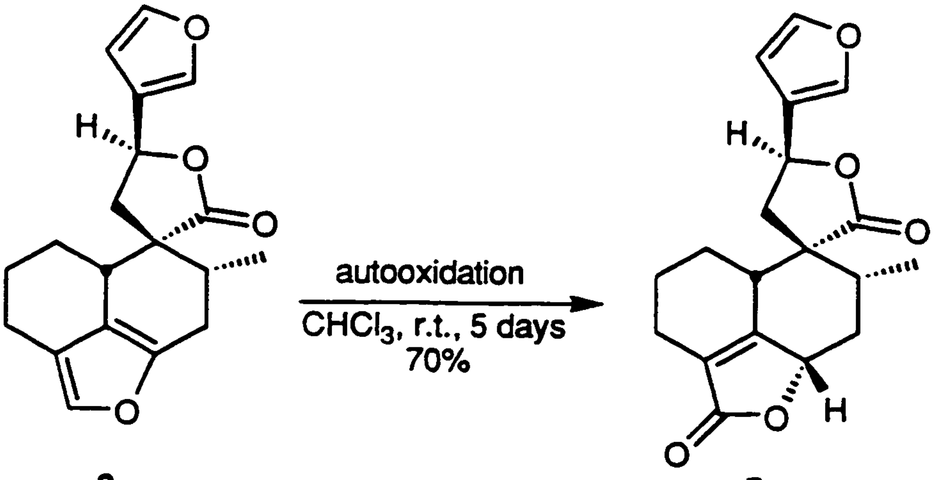
Although approximately eight hundred clerodane diterpenoids have been isolated and identified, less then thirty total syntheses have been reported.[20-39]

In most cases, a linear approach towards the target clerodane compound has been developed.

Scheme 3-2



To date, no total synthesis of teucvin **5** has been reported. Mollov and co-workers obtained teucvin from montanin A **8** (Equation 3-2).[13] When a solution of **8** in chloroform was exposed to daylight for five days at room temperature, autooxidation with high stereoselectivity occurred to give teucvin in 70% yield.



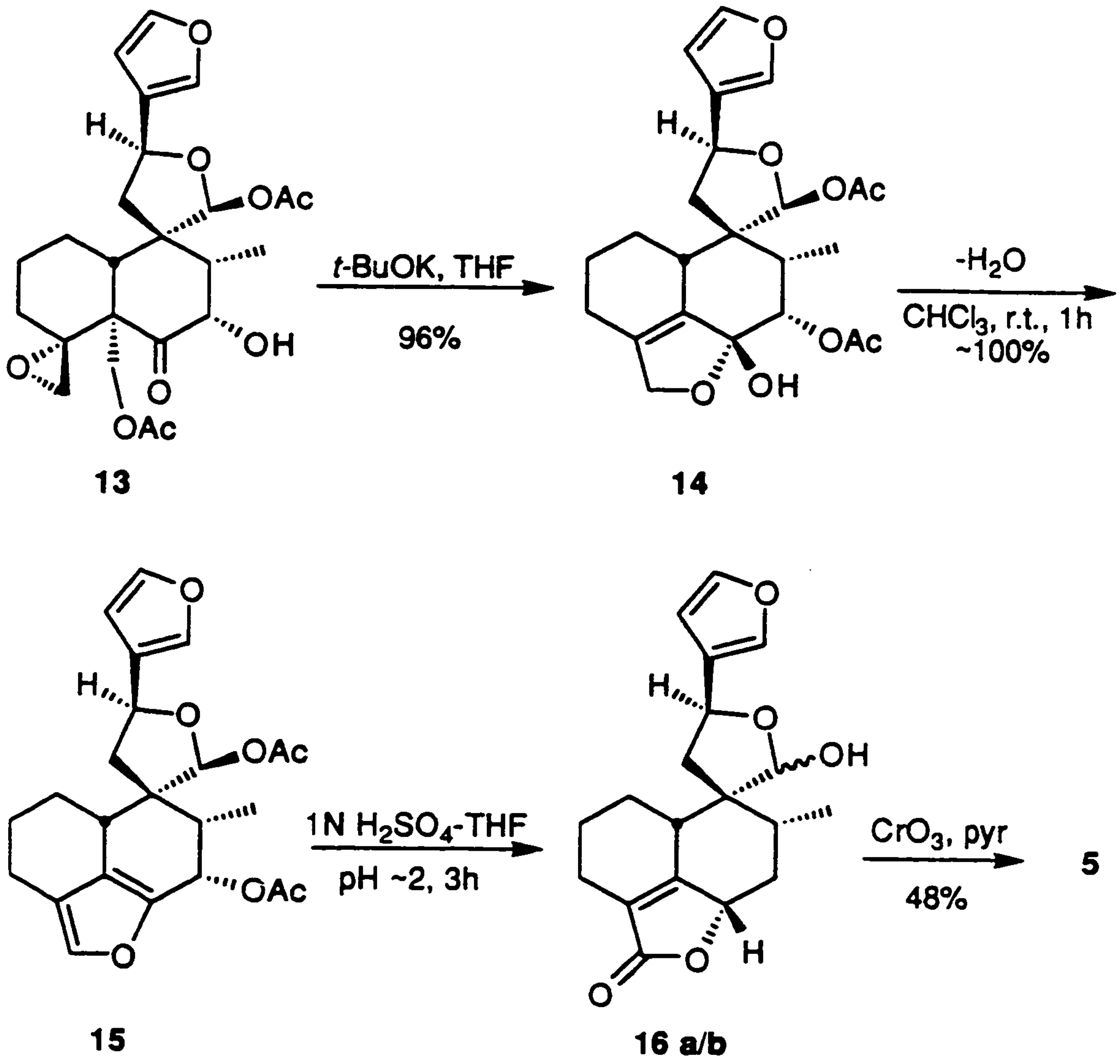
8 **5**

(Eq. 3-2)

Rodriguez and co-workers reported partial synthesis of teucvin from the naturally occurring compound eriocephalin **13** (Scheme 3-3).[40] When diterpenoid **13** was reacted with *tert*-butoxide in dry THF, it was almost quantitatively tranformed into the highly unstable compound **14**, which in turn underwent a dehydration reaction yielding **15** under very mild conditions. Treatment of **15** with sulfuric acid in THF resulted in the hydrolysis of the C-20 acetate group, with epimerization at this center. At the same time, the acid catalyst also caused a rearrangement of the furfuryl alcohol acetate moiety to give an inseparable mixture of lactols **16a** and **16b**. Finally, chromium trioxide-pyridine oxidation of that mixture gave teucvin **5** in 48% yield.

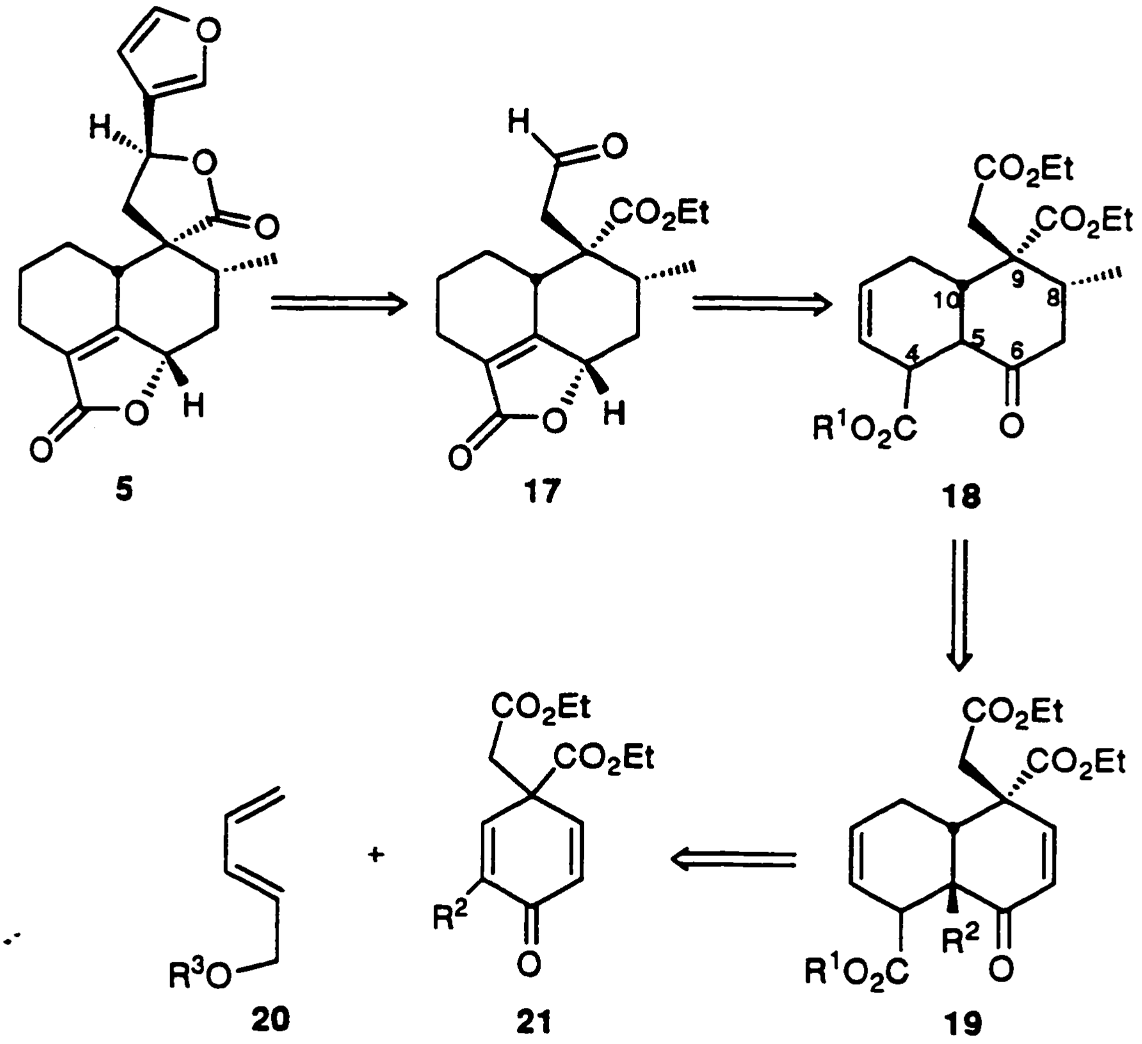
In recent years, the Diels-Alder reactions of several 4,4-disubstituted-2,5-cyclohexadienones have been studied extensively in our laboratories.[41-45] On the basis of these studies, a general synthethic approach facilitating the rapid assembly of a variety of *cis*-clerodanes has been conceived and experimentally realized in two total syntheses.[38,39] It can be envisioned that the Diels-Alder approach can be also employed in construction of the decalin nucleus of teucvin and other nor-clerodane diterpenoids.

Scheme 3-3



A retrosynthetic analysis, outlined in Scheme 3-4, shows that the relative stereochemistry of the two centers at C-9 and C-10 (clerodane numbering) in the key intermediate **19** is expected to be arranged in the same manner as in the natural product *via* a face-selective Diels-Alder reaction of diene **20** and a dienophile of type **21** with two substituents at C-4 of different steric bulk. The addition of the diene should occur preferentially from the less hindered face of the dienophile. The R^2 substituent of **21** must be an activating group, which makes the dienophile more reactive towards cycloaddition reaction to give **19**. This group must also be easily removed afterwards. A formyl group is an

Scheme 3-4



excellent candidate. The enone functionality in **19** can facilitate the installation of the C-8 methyl group *via* 1,4-addition to give **18**. The formyl group (R^2) can be removed either before or after this step. The α,β-unsaturated lactone in **17** can be derived from an alcohol at C-6 and an acid or ester at C-4, after double bond migration to the conjugated position is achieved. The aldehyde group in **17** can be obtained by selective transformation of the sterically less hindered ester group of **18** (for example by hydrolysis to an acid followed by a reduction-oxidation process). A furan moiety can then be installed through addition of 3-lithiofuran to the aldehyde group. From the resulting alcohol and the carbethoxy group at C-9, the spiro-lactone can be formed to complete the synthesis of teucvin **5**.

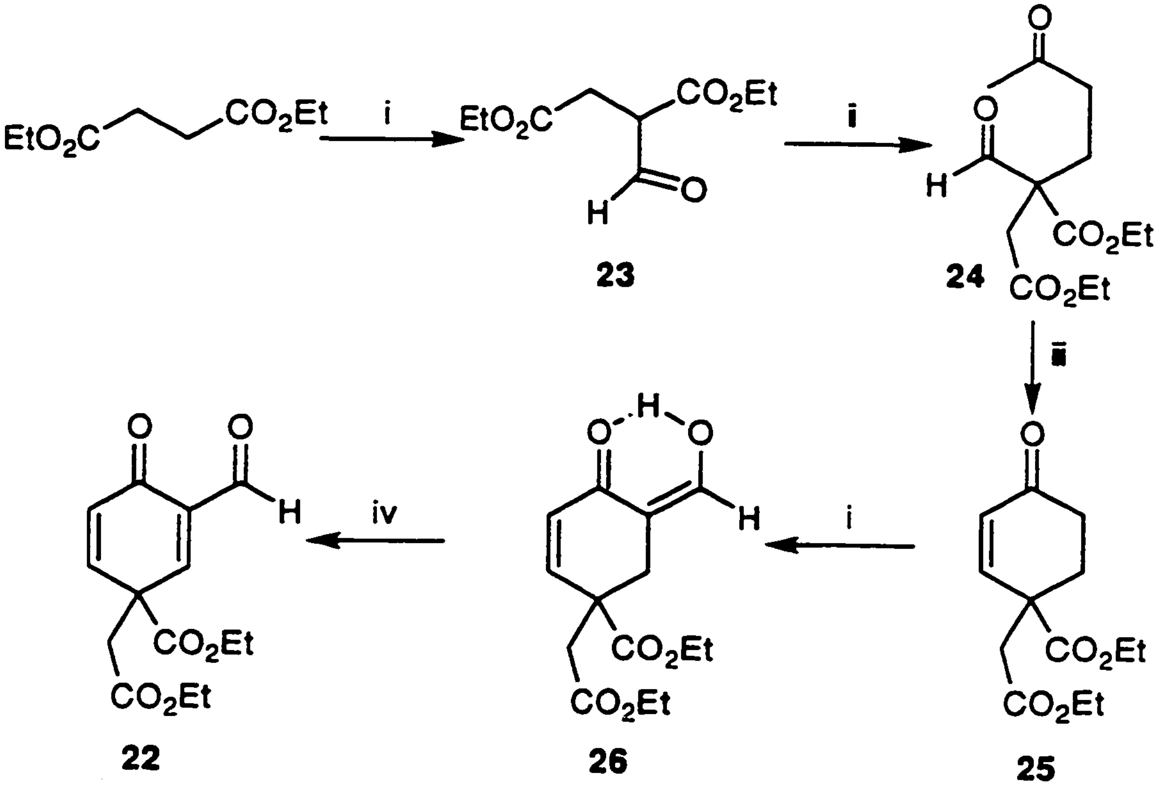
The above synthetic approach can serve as a common route leading to many furaniod clerodanes structurally similar to teucvin (Figure 3-2). The synthetic studies towards teucvin along this scheme are discussed in detail in the following section of this chapter.

Results and Discussion

As outlined in the retrosynthetic analysis (Scheme 3-4), the first key operation in our approach towards teucvin **5** is the construction of the decalin system *via* a Diels-Alder reaction. The facial selectivity of this cycloaddition is crucial to successful arrangement of the desired relative stereochemistry of the two adjacent chiral centers at C-9 and C-10 (clerodane numbering) in the intermediate **19**. It was envisioned that utilizing a dienophile of type **21** would be an efficient way to build up the decalin system and to set up the stage for later functional group transformations. 2-Formyl substituted cyclohexadienones have been previously shown to be reactive species for the Diels-Alder addition.[46] Deformylation of the adduct should be easily achieved and the two ester groups should facilitate the formation of the required γ–substituted spiro-lactone at C-9.

Consequently, dienophile **22** was prepared according to Scheme 3-5. Formylation[47] of diethyl succinate with ethyl formate and sodium hydride in the presence of a catalytic amount of absolute ethanol afforded formyl succinate **23** in 90% yield. Michael addition of **23** to methyl vinyl ketone using DABCO as the base[48] gave heptanoate **24** (86% yield) after two days of stirring at room temperature. Intramolecular aldol condensation under acidic conditions[49] (*p*-TsOH) with azeotropic removal of water furnished cyclohexenone **25** in 89% yield. The ir spectrum of **25** showed two strong carbonyl absorptions, one at 1733 cm^{-1} for the ester groups and the other at 1685 cm^{-1} for the enone system. The molecular ion peak was found at m/z 254.1141 corresponding to the formula $C_{13}H_{18}O_5$. In the ^1H nmr spectrum, the presence of the double bond was revealed by the appearance of the mutually coupled doublets ($J = 10$ Hz) at δ 6.96 for the C-3 proton and at δ 5.98 for the C-2 proton. The presence of two ester groups was confirmed by the quartets ($J = 7$ Hz each) at δ 4.15 and δ 4.08. In the ^{13}C APT nmr spectrum, a total of 13 lines was observed.

Scheme 3-5



i. NaH, HCO$_2$Et, THF; ii. MVK, DABCO, THF; iii. *p*-TsOH, benzene;
iv. DDQ, benzene

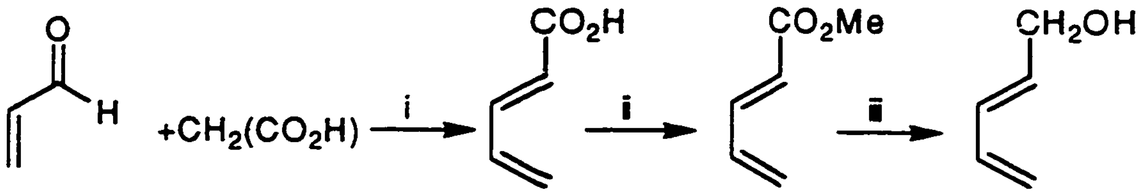
Subsequent formylation of **25** yielded hydroxymethylene enone **26** as the only product (88% yield). In the ^{1}H nmr spectrum, the presence of a broad singlet at δ 13.68 for the chelated hydroxy proton and a vinylic singlet at δ 7.60, each corresponding to one proton, along with the lack of any aldehydic signal indicated that the compound **26** was exclusively in its enol form. In the ^{13}C APT nmr spectrum, the carbonyl carbons of the ketone and two esters resonated at δ

186.6, 173.1 and 170.2, respectively. The enol form of the aldehyde group displayed two signals, one at δ 169.2 for the hydroxyl-bearing carbon and the second at δ 104.9 for the C-6 carbon. A molecular ion peak was observed in the mass spectrum at m/z 282.1104 confirming the molecular composition as $C_{14}H_{18}O_6$.

Treatment of the keto aldehyde **26** with phenylselenenyl chloride and pyridine followed by oxidative work-up using hydrogen peroxide[50] afforded the desired dienone **22**, albeit in low yield (45-50%). The low yield of the product and the high toxicity of the selenene reagent prompted the search for a different method for introducing the double bond. One possibility was to carry out bromination of **26** using N-bromosuccinimide[51] to form the corresponding α-bromo ketone, followed by dehydrobromination[51] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. When this method was employed, however, the desired dienone **22** was not obtained. Quinones, like 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranil, can be used for direct dehydrogenation of ketones.[52] Reaction of **26** with a slight excess of DDQ in dry benzene gave the dienone **22** in a considerably improved yield of 78%. The ir spectrum of **22** displayed three carbonyl absorption bands at 1735 (ester groups), 1708 and 1669 cm^{-1} (conjugated ketone and aldehyde). In the ^1H nmr spectrum, the aldehydic proton was observed at δ 10.20, and three vinylic protons resonated at δ 7.81, 7.12 and 6.45. The two mutually coupled doublets ($J = 17$ Hz) at δ 2.98 and 2.89 were attributed to the methylene protons adjacent to the ester group. In the mass spectrum, a molecular ion peak was not observed. The $[M^+-45]$ peak at m/z 235.0607 corresponding to the formula $C_{12}H_{11}O_5$ was due to the loss of one ethoxy unit (typical for ethyl esters).

Having dienone **22** prepared, different dienes were considered for the Diels-Alder process. Pentadienoic acid **27** and pentadienoate **28**, which can be easily prepared by the established procedures (Scheme 3-6),[53,54] were viewed as excellent candidates since a carboxyl or an ester group could be used directly (no functional group transformation required) in the formation of the α,β-unsaturated γ-lactone. Although pentadienol **29** could serve as well for the construction of the decaline system, it seemed less attractive as it would have to be later converted to the corresponding acid or ester.

Scheme 3-6

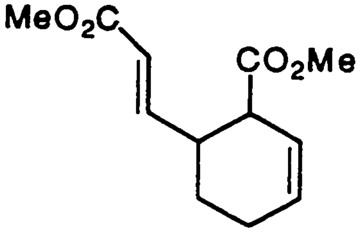


27 **28** **29**

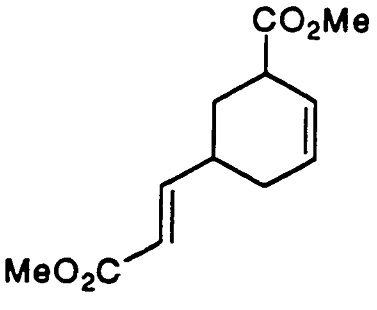
i. pyr; ii.MeOH, H_2SO_4 (cat); iii. $LiAlH_4$, Et_2O.

trans-Pentadienoic acid **27** was readily obtained by condensation of acrolein with malonic acid in pyridine at 35°C. The modest yield (42%) was not much of a concern as the reagents were not expensive and the procedure was fairly easy. After recrystalization from hexane, the white, long, needle-like crystals were used for the subsequent reactions. The spectral data of **27** were identical with the data reported in the literature.[53] When dienone **22** was reacted with acid **27** in refluxing benzene even for a long time (up to 3 days), no Diels-Alder adduct was isolated. Most of the intact dienophile was recovered after each trial. When the reaction was carried out in refluxing xylene, on the other hand, yellowish precipitate formed after 16 hours. No spectral data of that product were obtained as it was insoluble in most of the organic solvents. It was suspected that the precipitate resulted from polymerization of the diene **27**. Attempts to effect the cycloaddition under Lewis acid conditions (using zinc chloride) also failed.

Our attention was turned to methyl pentadienoate **28**,[54] which was obtained in 87% yield from acid catalyzed esterification of **27** in methanol. The ir spectrum showed an ester carbonyl absorption at 1723 cm^{-1} and a carbon-carbon double bond stretching band at 1645 cm^{-1}. Formation of the methyl ester was evident from the ^{1}H nmr spectrum, where a singlet at δ 3.71 attributed to the methoxy protons was observed. A molecular ion peak was displayed in the mass spectrum at m/z 112.0527. When the dienophile **22** was reacted with the ester diene **28** under thermal conditions (refluxing xylene, 2 days), most of the dienone **22** was recovered intact. An inseparable mixture of two new compounds was however isolated. The ^{1}H nmr spectrum of the mixture suggested that these compounds were adducts (**30a** and/or **30b**) resulting from cycloaddition of two molecules of diene **28**. No further attempts were made to determine the structure and stereochemistry of these products. When a mixture of dienone **22**, ester diene **28** and zinc chloride in dichloromethane

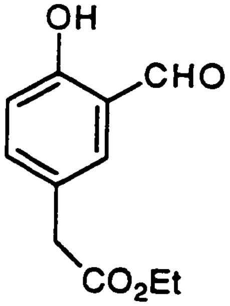


30a



30b

was stirred for two days, phenol **31** was formed in 10% yield. Aromatization of dienophile **22** to give **31** was even faster (2 hours) when ferric chloride or stannic chloride was used to catalyze the cycloaddition.



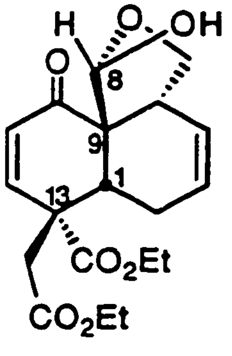
31

The ir spectrum of **31** showed a broad hydroxyl absorption at 2800-3400 cm^{-1} for the hydrogen bonded phenol and two carbonyl absorptions at 1734 and 1657 cm^{-1} for the ester group and the aromatic aldehyde, respectively. The structure was substantiated by the ^1H nmr spectrum which displayed a singlet at δ 10.97 for the phenolic proton and three aromatic proton signals at δ 7.49, 7.46 and 6.98. The presence of a methylene singlet at δ 3.60 clearly indicated that the ester group attached to the ring was the one which was cleaved. The structure was further confirmed by the mass spectum, where a molecular ion peak was observed at m/z 208.0735 corresponding to the formula $C_{11}H_{12}O_4$.

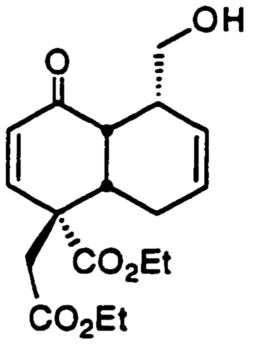
As the dienophile **22** failed to undergo cycloaddition reaction with dienes **27** and **28**, the Diels-Alder process using alcohol **29** was investigated. Lithium aluminum hydride reduction of ester **28** in ether at -25°C furnished alcohol **29** as a colorless liquid in 75% yield. Pentadienoic acid could be directly reduced to provide alcohol **29**, however the yields were much lower and inconsistent. The ir spectrum of **29** showed a strong hydroxyl absorption at 3334 cm^{-1}. In the

^1H nmr spectrum, the methylene protons adjacent to the hydroxy group resonated at δ 4.17. The molecular ion peak was observed in the mass spectrum at m/z 84.0579 in agreement with the formula C_5H_8O.

When dienone **22** was reacted with pentadienol **29** in dichloromethane for 0.5 hour at 0°C using zinc chloride as a catalyst, adducts **32** and **33** were isolated in 82% and 7% yield, respectively. The products were easily separated by flash chromatography. When the same reaction was carried out at room temperature and for a longer period of 5 hours the two products were formed in a ~1 : 1 ratio. Similar results were obtained when the reaction was carried out in ether.



32

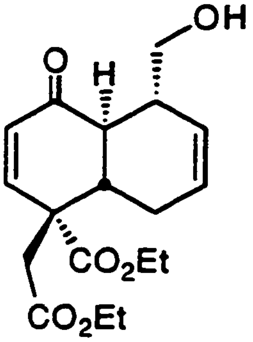


33

The ir spectrum of the main product **32** displayed a strong hydroxyl absorption at 3445 cm^{-1} and two carbonyl absorption bands at 1734 cm^{-1} for esters and at 1687 cm^{-1} for enone. In the ^1H nmr spectrum, the aldehydic proton was not observed. As expected, four vinylic proton signals were observed at δ 7.15, 5.95, 5.84 and 5.42. Two mutually coupled doublets (J = 2.5 Hz) were displayed at δ 5.34 and 3.50. The presence of these two signals together with the lack of aldehyde proton signal indicated the formation of the hemiacetal in the adduct **32**. Acetal formation was further confirmed by the ^{13}C APT nmr spectrum where an anti-phase signal was observed at δ 97.8 due to the acetal carbon. The ^{13}C nmr spectrum also showed three carbonyl signals at δ 197.2 (ketone), 172.6 and 170.8 (esters). The presence of two double bonds was evident from the four signals between δ 146.6 and 124.1. A molecular ion peak was found at m/z 364.1522 corresponding to the formula $C_{19}H_{24}O_7$. It was expected that the addition of the diene should occur from the less hindered face of the dienophile **22** and in an endo-to-ketone fashion. Based on these considerations and the information gathered from the spectral data, the main adduct was tentatively assigned the structure **32** . To prove the relative stereochemistry of the adduct, extensive decoupling and nOe experiments were carried out. Irradiation of the C-8 proton signal resulted in an enhancement of 2.3% of the C-11 vinylic proton at δ 5.95 and 12.4% enhancement of the signal at δ 2.93. Unfortunately, at the latter chemical shift two signals were found to overlap, the C-1 ring junction proton and one of the methylene protons α to the ester. Thus, the nOe results could only be used to deduce the stereochemistry at C-8 (*cis* to C11-H). This together with the *cis*-principle governing the Diels-Alder addition led to the assignment, with certainty, of the stereochemistry of three chiral centers, C-1, C-8 and C-9. The remaining centers C-5 and C-13 were ascertained later (*vide infra*).

The ir spectrum of the minor adduct **33** showed a strong hydroxyl absorption at 3433 cm^{-1} and two carbonyl bands at 1734 cm^{-1} (esters) and 1685 cm^{-1} (enone). In the ^1H nmr spectrum, four vinylic proton signals were observed, as expected, at δ 7.17, 5.97, 5.69 and 5.56. Neither aldehydic proton nor hemiacetal proton was displayed. The absence of the formyl group was also indicated by the ^{13}C APT nmr spectrum, showing a total of 17 signals (both methyl groups resonated at δ 14.2) of which 8 were found to be anti-phase to the chloroform signal and only three at δ 200.0, 172.5 and 170.2 could be attributed to carbonyl groups. Further evidence as to the molecular composition was provided by the mass spectrum, in which a molecular ion peak was found at m/z 336.1574 in agreement with the formula $C_{18}H_{24}O_6$. Decoupling experiments were carried out in an attempt to determine the stereochemistry of the minor product, resulting apparently *via* a deformylation process. Based on these experiments, the broad pseudo-triplet (J = 4.5 Hz) at δ 3.04 was attributed to the C-1 ring junction proton. The small coupling constants (all <4.5 Hz) observed for this proton strongly implied an all-*cis* relationship for C-1, C-6 and C-10. The stereochemistry of C-5, however, could only be tentatively assigned at this stage.

A chemical correlation of compounds **32** and **33** was carried out as follows. Hemiacetal **32** was treated with sodium ethoxide in ethanol at room temperature for 16 hours to give compound **34** as the only product in 91% yield. The ir spectrum showed absorptions at 3440 cm^{-1} (hydroxyl), 1730 cm^{-1} (esters) and 1679 cm^{-1} (ketone).

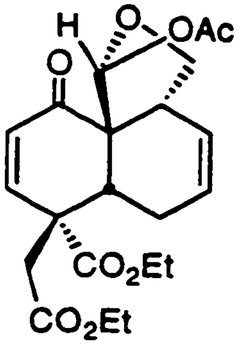


34

The removal of the formyl group was evident from the ^1H nmr spectrum which showed the absence of the aldehydic (hemiacetal) proton. Although the complexity of the ^1H nmr spectrum made accurate stereochemical assignment difficult, the *trans* ring junction could be assigned on the basis of its greater thermodynamic stability than the *cis* one. Similar treatment of compound **33** with sodium ethoxide for 6 hours also afforded compound **34** in 75% yield. These experiments indicated clearly that compound **33** was originated from the Diels-Alder addition product **32**.

The next phase towards the *neo*-clerodane system was to introduce a methyl group to the C-8 position (clerodane numbering). The methyl group could, in principle, be installed simply by a conjugate addition process involving compounds **32** or **34**, both of which were easily obtained in pure form in good yield. Both compounds were examined.

Prior to the addition, the labile hemiacetal group in **32** was first protected. Treatment of **32** with acetic anhydride in pyridine in the presence of a trace amount of DMAP afforded compound **35** in 86% yield.



35

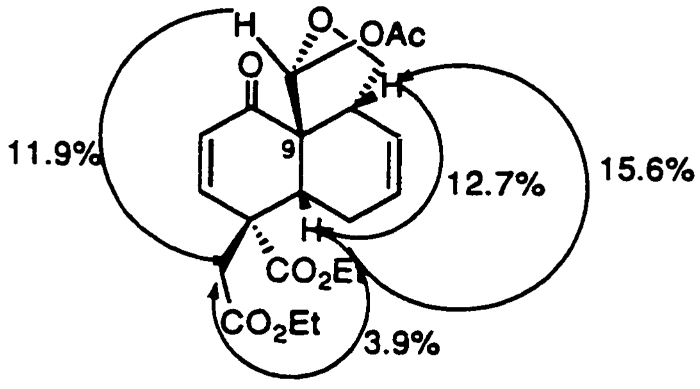
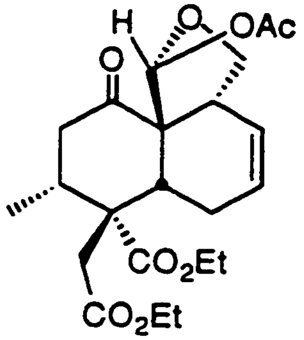


Figure 3-3 The nOe experiment of compound **35**

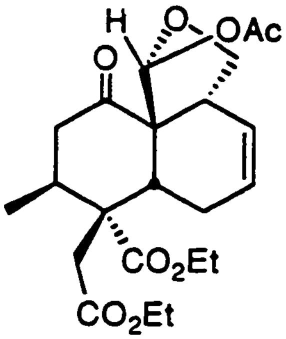
The formation of acetate was indicated by the disappearance of the hydroxyl absorption in the ir spectrum. In the ^1H nmr spectrum, the singlet at δ 6.17 was attributed to the C-8 proton of the acetal. The acetyl group resonated at δ 2.14.

The ^{13}C APT nmr spectrum displayed four carbonyl carbons at δ 195.4, δ 172.4, δ 170.0 and δ 169.81. Extensive decoupling experiments were carried out, followed by nOe studies to assign the stereochemistry of **35**. Some of the nOe results are shown in Figure 3-3. Irradiation of the C-5 proton at δ 3.14 resulted in 12.7% enhancement of the ring junction C-1 proton signal at δ 2.85, proving their *cis* relationship. Conversely, when the C-1 proton was irradiated, a 15.6% enhancement on the C-5 proton was found, together with a 3.9% enhancement of the doublet at δ 3.00, attributed to the methylene proton α to the ester. When the C-8 acetal proton was irradiated, an enhancement of 11.9% on the other methylene proton α to the ester at δ 2.25 was observed, which indicated the proximity of the protons in question. Based on these results the stereochemistry of compound **35** was deduced.

Having acetate **35** in hand, the conjugate addition was carried out. Treatment of **35** with 3 equivalents of lithium dimethylcuprate in ether at 0°C for 20 minutes resulted in a 95% combined yield of the addition products **36** and **37** in 7:1 ratio. The ir spectrum of the major product **36** showed an intense carbonyl absorption at 1721 cm^{-1}. Although the molecular ion peak was not observed in the mass spectrum, a peak at m/z 362.1725 ($C_{20}H_{26}O_6$) due to loss of the



36



37

acetic acid fragment was displayed. In the ^1H nmr spectrum, the signals corresponding to the vinylic protons of the enone moiety present in the starting material disappeared. This along with the appearance of a doublet ($J = 6.5$ Hz) at δ 0.96 indicated that the 1,4-addition had occurred. The ^{13}C APT nmr spectrum further proved the adduct formation, as only two vinylic carbons were displayed. Extensive nOe experiments were carried out in order to assign the stereochemistry. Irradiation of the C-8 proton signal at δ 6.35 resulted in a

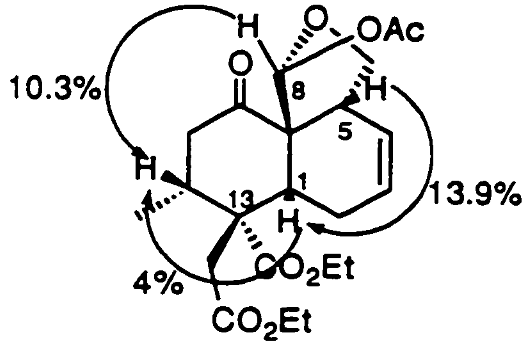


Figure 3-4 The nOe experiment of compound **36**

10.3% enhancement for the C-12 proton signal at δ 2.48 (Figure 3-4). Irradiation of the ring junction C-1 proton at δ 3.38 also resulted in a 4% enhancement of the C-12 proton multiplet, further proving the stereochemistry of the C-12 center. When the C-5 proton was irradiated, an enhancement of 13.9% of the C-1 proton signal was found. Accordingly, the stereochemistry of compound **36** was assigned. The assignment was confirmed by X-ray crystallographic analysis (Figure 3-5).

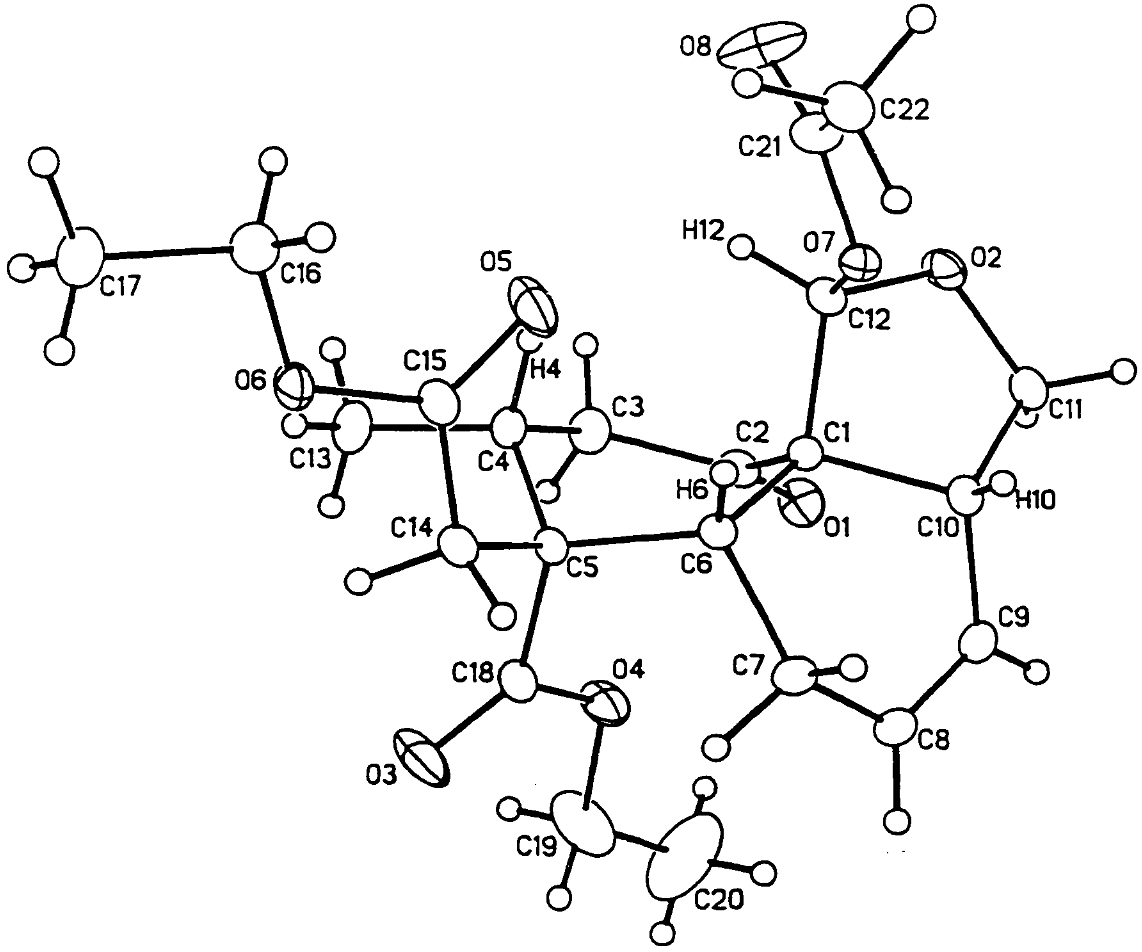


Figure 3-5 X-ray structure of compound **36**

The minor product obtained from the conjugate addition was then assigned the structure **37**, with the opposite stereochemistry at the C-12 center. The ir spectrum of that compound also showed a strong carbonyl absorption at 1742 cm^{-1}. In the ^{1}H nmr spectrum, the C-8 proton appeared at δ 6.42 and the C-12 methyl group resonated at δ 1.00 as a doublet (J = 7 Hz). A total of 21 lines (two carbons at δ 14.06) was observed in the ^{13}C APT nmr spectrum, including four carbonyl carbons at δ 205.0, 171.8, 171.1 and δ 169.9. Attempts to improve the stereoselectivity by adjusting the reaction temperature were unsuccessful.

Conjugate addition was also carried out with keto alcohol **34**, although an examination of its conformation (Figure 3-6) suggested that the addition should occur mainly from the sterically less hindered side as indicated leading to the undesired isomer. Indeed, when compound **34** was treated with lithium dimethylcuprate in ether at 0°C for 1 hour, compound **38** was isolated in 72% yield as the only product. The ir spectrum displayed a hydroxyl absorption at 3452 cm^{-1} and two carbonyl bands at 1731 cm^{-1} (esters) and 1710 cm^{-1} (ketone). In the ^1H nmr spectrum, the signals previously observed for the

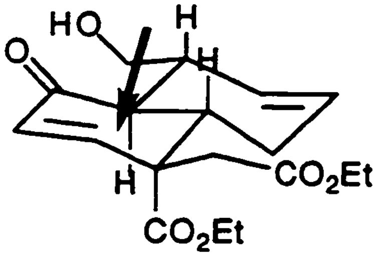
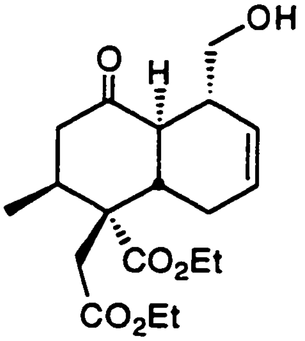


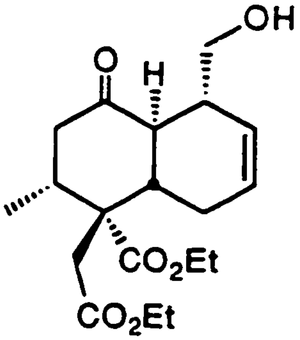
Figure 3-6



38

vinylic protons of the enone moiety in **34** were replaced by a methyl doublet (*J* = 7 Hz) at δ 0.96. The ^{13}C APT nmr spectrum showed a total of 19 lines, of which 10 were in phase with the chloroform signal.

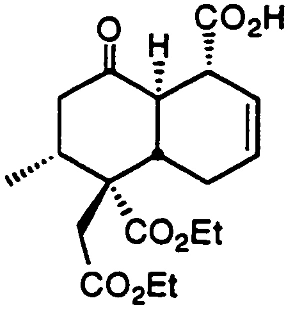
To assign unambiguously the stereochemistry of **38** the following transformations were carried out. Acetate **36** was treated with sodium ethoxide at room temperature for 12 hours to give keto alcohol **39** in 93 % yield. This compound was found to be distinctly different from compound **38**. Its ir spectrum displayed a hydroxyl absorption at 3467 cm^{-1} and a carbonyl absorption at 1712 cm^{-1}. The ^1H nmr spectrum showed a doublet of doublets at δ 3.20 (*J* = 12.5, 9.5 Hz) for the C-1 proton. The magnitude of the coupling constants indicated clearly that this proton was *trans* to both the C-6 and C-10 protons. In the ^{13}C APT nmr spectrum, a total of 19 lines was observed, consistent with the assigned structure of **39**. Similar treatment of compound **37** with sodium ethoxide gave in 75% yield, a single product, which was shown to be identical in all respects with **38**. Thus, the stereochemistry of the addition product obtained from compound **34** was fully established.



39

With keto alcohol **39** in hand, the formation of the α,β-unsaturated γ-lactone present in teucvin **5** was investigated. A conceivable approach involves: (1) oxidation of the alcohol to an acid, (2) migration of the double bond to the conjugated position (C1-C10), (3) reduction of the ketone carbonyl to an alcohol followed by lactone formation.

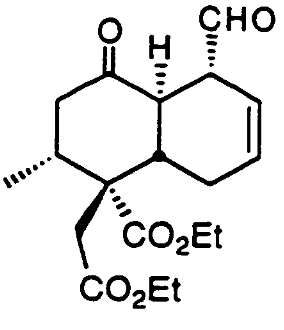
Oxidation of **39**, using Jones reagent,[55] afforded acid **40** in a poor yield of 23% yield. Attempts to improve yield by adjusting the reaction temperature and amount of the reagent failed.



40

The ir spectrum of acid **40** showed a very broad absorption at 2500-3400 cm^{-1} typical for a carboxylic acid and a carbonyl absorption band at 1712 cm^{-1}. In the ^1H nmr spectrum, a doublet of multiplets ($J = 10$ Hz) at δ 3.43 was attributed to the C-10 proton. The acid carbonyl resonated at δ 178.1 in the ^{13}C APT nmr spectrum. The structure was also supported by the mass spectrum showing a molecular ion peak at m/z 366.1693 in agreement with the formula $C_{19}H_{26}O_7$.

Non-allylic alcohols can be oxidized to the corresponding acids by use of pyridinium dichromate in wet DMF.[56] When that method was used, only aldehyde **41** was isolated in 41% yield. Since the direct transformation of alcohol **39** to acid **40** could not be effectively achieved, a stepwise process was explored. Several methods were examined to oxidize alcohol **39** to aldehyde



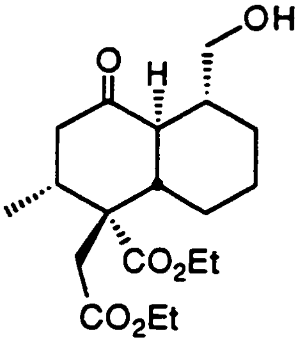
41

41. Use of chromium-based reagents (PCC, PDC) gave invariably low yields of the desired product (10-40%). The best yield (52%) was obtained by Swern oxidation.[57] The ir spectrum of **41** showed a strong carbonyl absorption at 1722 cm^{-1}. Formation of the aldehyde was revealed by the doublet (J = 1 Hz) at δ 9.73 in the ^1H nmr spectrum.

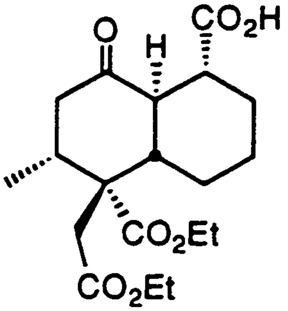
At this stage, the required isomerization of the double bond was attempted with both acid **40** and aldehyde **41** . Application of either basic (NaOEt) or acidic (CSA in benzene) conditions did not bring about the double bond migration. Attempts were also made to isomerize the double bond in alcohol **39**, using rhodium trichloride in ethanol[58] and iodine in refluxing benzene.[59] These attempts were equally unsuccessful.

The above discouraging results, prompted a revision of our synthetic scheme. It was envisioned, that the construction of the α,β-unsaturated γ-lactone could be accomplished by following sequence: (1) hydrogenation of the double bond, (2) oxidation of the alcohol to a carboxylic acid and then (3) lactone formation *via* the enol of the ketone.

Hydrogenation of keto alcohol **39** using 5% palladium on carbon as a catalyst proceeded smoothly to afford saturated alcohol **42** in 89% yield. The ir spectrum showed a hydroxyl absorption at 3446 cm^{-1} and a carbonyl absorption at 1723 cm^{-1}. The saturation of the double bond was evident from the ^{1}H nmr spectrum, as no vinylic proton signal appeared. The structure was verified also by the ^{13}C APT nmr spectrum, which indicated the absence of carbon-carbon double bond. A molecular ion peak was observed in the mass spectrum at m/z 354.2043, corresponding to the formula $C_{19}H_{30}O_6$.



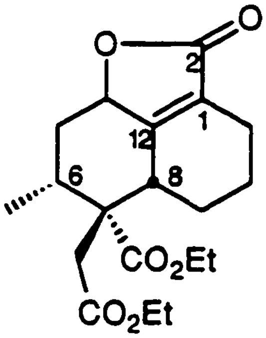
42



43

Oxidation of the alcohol **42** was performed using Jones reagent. The desired acid **43** was obtained in 68% yield without complications. The ir spectrum of the acid **43** displayed a very broad band at 2500-3500 cm^{-1} for the carboxyl group and an intense absorption at 1725 cm^{-1} for all the carbonyl groups. In the ^{1}H nmr spectrum, the doublet of doublets (J = 12, 12 Hz) at δ 3.24 was attributed to the C-1 proton and the multiplet at δ 2.91 to the C-10 proton. The *sp*^{2} carbon of the carboxy group resonated δ 180.7 in the ^{13}C APT nmr spectrum. In the mass spectrum, a molecular ion peak was observed at m/z 368.1846 in agreement with the formula $C_{19}H_{28}O_7$.

The formation of an α,β-unsaturated γ-lactone from a 1,3-keto acid could be effected under acidic conditions. When keto acid **43** was treated with *p*-TsOH in refluxing benzene for 16 hours lactone **44** was formed in 92% yield. The lactone formation was evident from the ir spectrum which showed a characteristic absorption 1755 cm^{-1}.



44

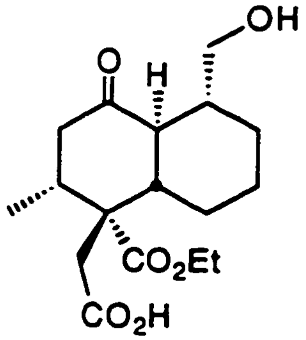
In the ^1H nmr spectrum, a multiplet at δ 4.76 was attributed to the C-4 proton. The ^{13}C APT nmr spectrum did not show any signal corresponding to a ketone carbonyl. The carbonyl carbons of the lactone and esters resonated at δ 173.4, 171.5 and 171.3. The two in-phase signals at δ 164.5 and 125.0 were attributed to the C-12 and C-1 carbons, respectively. The structure was further verified by the mass spectrum, which showed a molecular ion peak at m/z 350.1724 corresponding to the formula $C_{19}H_{26}O_6$. The stereochemistry of the newly introduced chiral center (C-4) could not be deduced on the basis of the available spectral data and remains to be determined.

The next stage in our approach towards teucvin **5** involves: (1) selective conversion of the sterically less hindered ester to an aldehyde, (2) introduction of the 3-furan moiety and (3) formation of the γ-spiro lactone to complete the synthesis.

The ester could be converted to an aldehyde by direct reduction or by reduction to an alcohol first, followed by oxidation. Both processes were considered to be inadequate in the present case due to the presence of the γ-lactone. The required transformation could also be effected, in principle, by hydrolyzing the ester group to an acid first, followed by selective reduction of the acid to an aldehyde either directly or indirectly (reduction then oxidation). This approach was thought to be a reasonable alternative. Although the lactone moiety might also undergo hydrolysis, it could be reinstalled afterwards using the previously described conditions. A frequently used reagent for selective reduction of acids is diborane.[60] Reagents like lithium 9-boratabicyclo[3.3.1]nonane (Li 9-BBNH) in combination with 9-BBN[61] have been reported to selectively reduce acids to the corresponding aldehydes. However, carbon-carbon double bonds are also reactive towards these reducing agents. Thus, the double bond present in the molecule may have to be reintroduced after the reduction step.

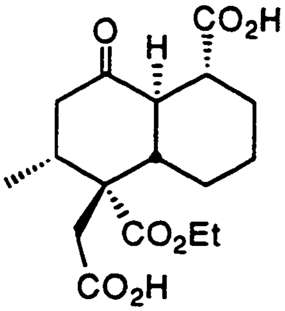
Surprisingly, when a mixture of **44** and potassium carbonate in aqueous THF was heated to reflux for 5 hours, only the starting material was recovered after acidic work-up. Even after prolonged heating with aqueous lithium hydroxide in THF, compound **44** was recovered unchanged. These negative results led us to reevaluate the synthetic scheme. It was decided to carry out the selective hydrolysis on keto alcohol **42** first and to perform the oxidation and lactone formation subsequently.

When a mixture of **42** and LiOH in aqueous THF was heated to reflux for 5 hours, the desired acid **45** was obtained in 91% yield. The ir spectrum showed a very broad absorption band at 3300 cm^{-1} for the alcohol and acid and an intense carbonyl absorption band at 1712 cm^{-1} for the ketone, acid and ester. In the ^{1}H nmr spectrum, two quartets (J = 7 Hz, each for one proton) at δ 4.26 and 4.25 and a triplet (J =7 Hz) at δ 1.34 indicated the presence of a carbethoxy group. The presence of the hydroxymethylene moiety was indicated by a pair of mutually coupled doublet of doublets (J = 10.5 Hz) at δ 3.58 and 3.45.



45

A solution of acid **45** in acetone was subsequently treated with Jones reagent for 1.5 hours to furnish diacid **46** in 53% yield. The ir spectrum displayed absorption bands at 2500-3550 cm^{-1} and 1717 cm^{-1}, consistent with the presence of acids, ketone and ester. In the ^{1}H nmr spectrum, only one carbethoxy group was displayed with two quartets (J = 7 Hz, each for one proton) at δ 4.23 and 4.22 and a triplet (J = 7 Hz) at δ 1.28. Oxidation of the



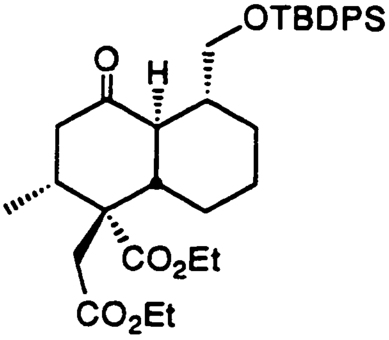
46

alcohol to an acid was evident from the disappearance of the signals corresponding to the methylene protons of hydroxymethyl moiety present in the starting material.

Attempts to construct the α,β-unsaturated γ-lactone system by treatment of **46** with *p*-TsOH in refluxing benzene failed. As a result, a different route leading to teucvin **5** from intermediate **42** was envisioned. The proposed approach was to proceed *via* the following sequence: (1) protection of both the ketone and alcohol groups, (2) conversion of the ester into an aldehyde, (3) addition of a furan moiety followed by spiro-lactone formation, (4) deprotection of the ketone and alcohol functionalities, oxidation of the alcohol to an acid followed by formation of the γ-lactone.

While considering suitable protecting groups for ketone and alcohol, which would survive the above transformations, another possibility was realized. Assuming that the aldehyde should be much more reactive than the ketone towards 3-lithiofuran addition, only the alcohol group needed to be protected for the proposed steps (2) and (3). *tert*-Butyldiphenyl silyl ether seemed to be a good candidate for protection, as it is known to be one of the most stable silyl ethers in a wide range of solution pH's.[62]

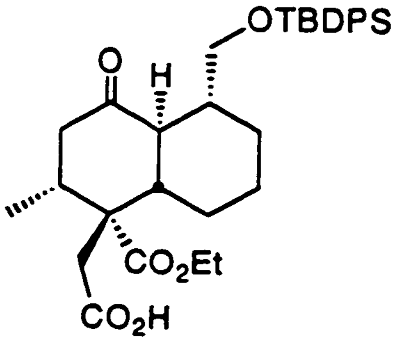
Protection of the hydroxyl in **42** proved to be very straightforward. Treatment of **42** with *t*-butyldiphenylsilyl chloride in THF in the presence of three equivalents of imidazole for 18 hours at room temperature afforded silyl ether **47** in 87% yield. The ir spectrum showed two strong absorption bands at 1723 cm^{-1} and 1712 cm^{-1}, indicative of the esters and the ketone, respectively. In the ^1H nmr spectrum, the appearance of two multiplets at δ 7.65 and 7.40 for a total of 10 protons and a singlet at δ1.08 for 9 protons was in agreement with the silyl ether



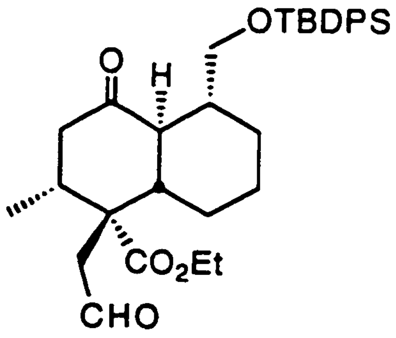
47

formation. The ^{13}C APT nmr spectrum revealed the presence of the aromatic rings, as 6 lines (out of possible 8) were observed between δ 135.7 and δ 127.6. A molecular ion peak was not found in the mass spectrum. However, a [M^+-57] peak, resulting from the loss of a *t*-butyl group, was displayed at m/z 535.2505 ($C_{31}H_{39}O_6Si$).

Selective hydrolysis of the sterically less hindered ester, was accomplished by treatment of **47** with 1N LiOH in THF at room temperature for 25 hours. The desired acid **48** was obtained in 77% yield. In the ir spectrum, a typical absorption for carboxylic acid was observed at 2500-3450 cm^{-1}, together with a strong band at 1712 cm^{-1} for all the carbonyl groups. In the ^{13}C APT nmr spectrum, the acid carbonyl carbon resonated at δ 176.0. The ^{1}H nmr spectrum confirmed the presence of one ester group showing a pair of quartets (*J* = 7 Hz, one proton each) at δ 4.27 and 4.24 and a triplet (*J* = 7Hz, 3 protons) at 1.29. The methylene protons α to the carboxy group were shown as mutually coupled doublets (*J* = 15 Hz) at δ 3.00 and 2.83.



48

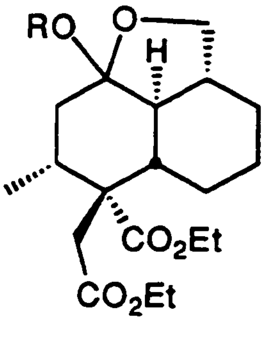


49

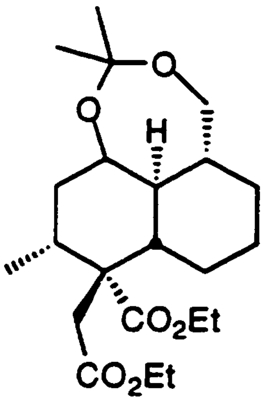
Treatment of acid **48** with borane-THF complex for 2 hours at room temperature, followed by oxidation of the resulting trialkoxyboroxine (without isolation) with PCC in dichloromethane afforded aldehyde **49** in 78% yield. The ir spectrum showed a carbonyl absorption band at 1712 cm^{-1}. The ^{1}H nmr spectrum displayed a triplet (*J* = 3 Hz) at δ 9.79 for an aldehydic proton. In the ^{13}C APT nmr spectrum, carbonyl carbons were observed: at δ 211.6 (ketone), 201.0 (aldehyde) and at δ 172.0 (ester).

Installation of the furan moiety could, in principle, be accomplished by addition of 3-lithiofuran,[63,64] prepared by treatment of 3-bromofuran with *n*-butyllithium in ether or THF at -78°C. When aldehyde **49** was reacted with this reagent, however, a complex mixture was invariably produced. The ^{1}H nmr spectra of the crude products suggested that the lithiofuran failed to serve as a nucleophile. Instead, it might have acted as a base to introduce various aldol related side reactions. This route had to be abandoned.

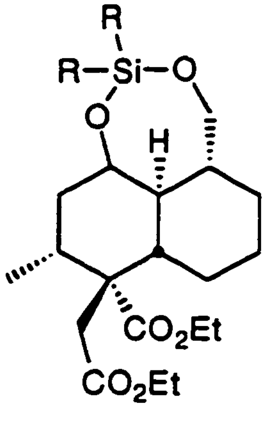
The complications encountered during the introduction of the required furan unit to **49** led to the conclusion that both the ketone and alcohol groups present in keto alcohol **42** had to be protected. To make the synthesis more efficient, the possibilities of protecting both functionalities with one group or in one step were considered. The best option was to form an acetal of type **50a** with the participation of the hydroxy group. Another option was to reduce the ketone to the alcohol level and then to protect the resulting diol in the form of an acetal like acetonide **50b** or a cyclic silyl ether of type **50c**.



50a

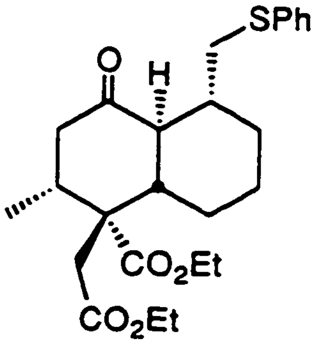


50b



50c

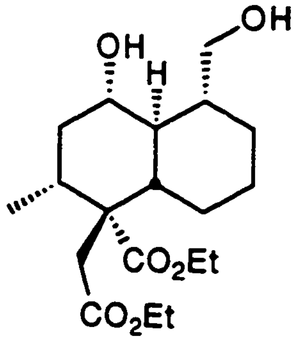
Attempts to make an acetal of type **50a** using *p*-TsOH and triethyl orthoacetate or formate in ethanol or *n*-propyl alcohol were unsuccessful. The use of thiophenol and $BF_3 \cdot OEt_2$ in dichloromethane in an attempt to prepare the sulfur analog was also explored. Interestingly, the reaction gave thioether **51** as the only product in 93% yield. The ir spectrum showed carbonyl absorptions at 1723 cm^{-1} for the esters and at 1711 cm^{-1} for the ketone. In the ^1H nmr spectrum, aromatic protons were observed at δ 7.42, 7.27 and 7.13. The methylene protons adjacent to the sulfur atom were displayed as two doublets of doublets, one at δ 3.36 ($J = 13, 3$ Hz) and the other at δ 2.78 ($J = 13, 8$ Hz). In the ^{13}C APT nmr spectrum, a total of 23 lines was observed.



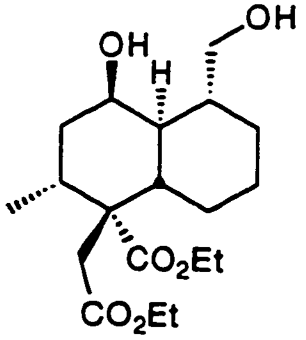
51

The structure was further verified by the mass spectrum. A molecular ion peak was found at m/z 446.2122 corresponding to the formula $C_{25}H_{34}O_5S$.

To examine the feasibility of acetonide or cyclic silyl ether formation, ketone **42** was reduced with sodium borohydride in ethanol to give two diols **52** and **53** in a ratio of 1 : 1 and a combined yield of 82%. When the reduction was carried out with tri-*t*-butoxyaluminohydride in THF, the diols were obtained in a similar ratio with a slightly higher yield of 89%.



52



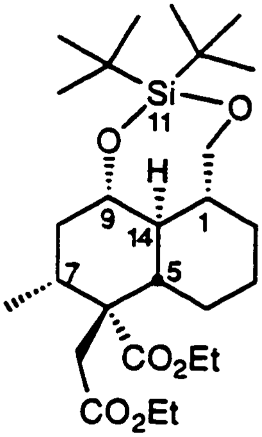
53

The ir spectrum of compound **52**, obtained in 43% yield, showed a strong hydroxyl absorption at 3279 cm^{-1} and a carbonyl absorption at 1723 cm^{-1}. In the ^1H nmr spectrum, a doublet of doublet of doublets (J = 10, 10, 5 Hz) at δ 3.48 was attributed to the C-2 proton with an axial orientation. The two large coupling constants of 10 Hz each, indicated a *trans*-diaxial relationship with the C-1 proton. The ^{13}C APT nmr spectrum supported the diol formation, as only two ester carbonyls were displayed at δ 172.9 and 171.6. The C-2 carbon resonated at δ 72.8 and that of hydroxymethyl group at δ 68.1. A molecular ion peak was observed at m/z 356.2197 in the mass spectrum, corresponding to the formula $C_{19}H_{32}O_6$.

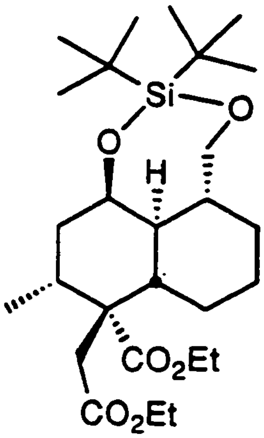
The second diol **53** was isolated in 46% yield. Its ir spectrum displayed a hydroxyl absorption at 3423 cm^{-1} and a carbonyl absorption at 1720 cm^{-1}. The ^1H nmr spectrum was found to be similar to that of **52**, except for the C-2 proton signal, which was shifted downfield to *ca.* δ 4.13 indicating an equatorial orientation.[65] In the ^{13}C nmr spectrum, the carbons bearing hydroxy groups resonated at δ 66.7 for the primary alcohol and at δ 65.9 for the secondary one. A molecular ion peak was observed at m/z 356.2191 in the mass spectrum, in agreement with the formula $C_{19}H_{32}O_6$.

With the diols **52** and **53** in hand, the preparation of acetonide of type **50b** was attempted. However, it proved to be troublesome. When either of the two diols **52** or **53**, was treated with 2,2-diethoxypropane in acetone under acidic conditions (*p*-TsOH) or in neat form with CSA as a catalyst, only the starting material was recovered.

Our attention was then turned to the formation of cyclic silyl ethers of type **50c**. Use of diisopropylsilyl and di-*tert*-butylsilyl ditriflates as effective reagents for the protection of 1,2-, 1,3-, and 1,4-diols under mild conditions has been reported.[67,68] When diol **52** was reacted with di-*tert*-butylsilyl ditriflate in the presence of pyridine, the corresponding di-*tert*-butylsilylene **54** was formed in 89% yield. The ir spectrum showed an ester carbonyl absorption band at 1720 cm^{-1}. In the ^1H nmr spectrum, the doublet of doublet of doublets (J = 10.5, 10.5, 5 Hz) at δ 3.73 was attributed to the C-9 proton. The C-13 methylene protons resonated at δ 3.84 (dd, J = 12, 9 Hz) and δ 3.59 (dd, J = 12, 1.5 Hz). The ^{13}C APT nmr spectrum displayed a total of 22 lines, including carbonyl carbons at δ 173.0 and δ 171.7, as well as alcohol carbons at δ 75.5 (C-9) and δ 71.4 (C-13).



54



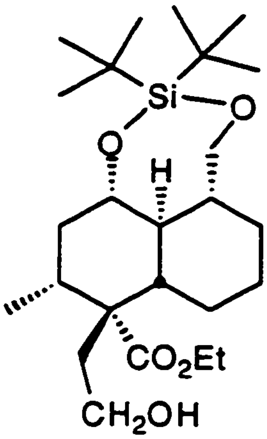
55

Similarly, treatment of diol **53** with di-*tert*-butylsilyl ditriflate and pyridine in THF at 0°C for 25 minutes furnished silylene **55** in 87% yield. The ir spectrum showed a carbonyl absorption at 1723 cm^{-1} for both esters. In the ^1H nmr spectrum, the C-9 proton was observed at δ 4.49 (ddd, J = 3.5, 3, 3 Hz) and the C-13 methylene protons were displayed as two mutually coupled signals (J =

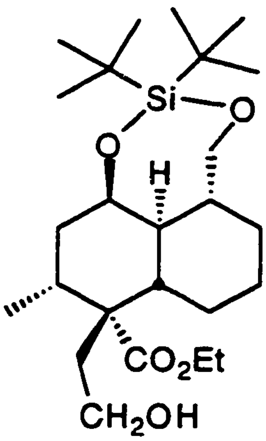
11.5 Hz) at δ 3.99 and 3.74. A total of 23 lines was observed in the ^{13}C APT nmr spectrum, of which 13 were in phase with the chloroform signal.

The next stage involved conversion of the ester group of the acetate unit in each compound into an aldehyde. That transformation was accomplished by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), followed by oxidation of the alcohol thus formed with PDC in dichloromethane. The hydrolysis of ester to an acid, as was done in previous cases, was not investigated since the stability of the cyclic silyl ether under the required conditions was questionable.

Treatment of esters **54** and **55** individually with 1.2 equivalents of Red-Al in dry benzene at 10°C for 4-6 hours resulted in the formation of the corresponding alcohols **56** and **57** in 91% and 88% yield, respectively. The ir spectra showed hydroxyl absorptions at 3424 cm^{-1} for **56** and at 3463 cm^{-1} for **57**. In the ^1H nmr spectrum of **56**, the methylene protons adjacent to hydroxy group appeared as multiplets between δ 3.59-3.69. The counterparts in **57** were found at δ 3.62-3.79 also as multiplets. In each of the ^{13}C APT nmr spectra,



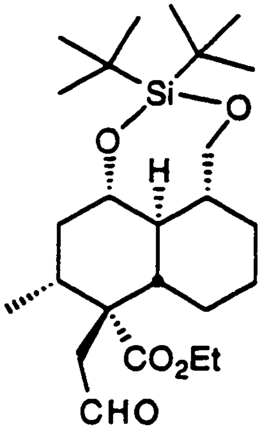
56



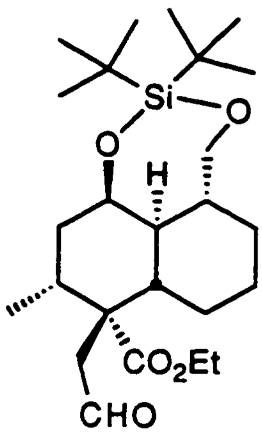
57

only one carbonyl signal was displayed (δ 174.3 for both compounds).

Oxidation of alcohol **56** using PDC in dichloromethane afforded aldehyde **58** in 79% yield. The ir spectrum showed a carbonyl absorption at 1712 cm^{-1} for both the ester and aldehyde groups. Formation of the aldehyde was evident from the ^{1}H nmr spectrum, in which an aldehydic proton was observed at δ 9.88 as a triplet (*J* = 2.5 Hz). The ^{13}C APT nmr spectrum displayed two carbonyl signals at δ 202.2 and 172.6, consistent with the presence of an aldehyde and ester, respectively.



58

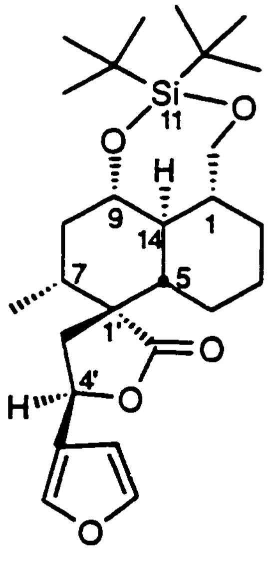


59

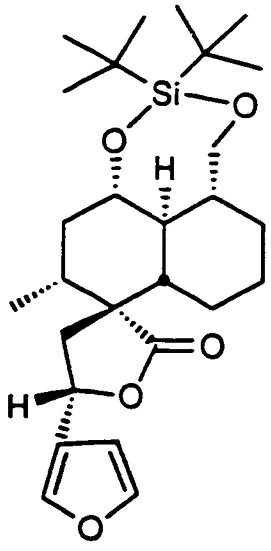
Similarly, oxidation of alcohol **57** was performed to furnish the corresponding aldehyde **59**. A carbonyl absorption band at 1715 cm^{-1} was observed in the ir spectrum. In the ^{1}H nmr spectrum, a triplet (*J* = 3 Hz) at δ 9.89 was attributed to the aldehydic proton. The aldehyde carbon resonated at δ 202.5 and the ester carbonyl carbon at δ 172.7 in the ^{13}C APT nmr spectrum.

Aldehydes **58** and **59** proved to be very unstable compounds. Upon standing at room temperature for a day in neat or for few hours in chloroform, autooxidation to the corresponding acids was observed. Even at *ca.* -5°C and under an argon atmosphere (apparently some oxygen was present) partial oxidation took place after two days. Thus, these compounds should be used immediately after rapid purification by flash chromatography using a short column.

The installation of the furan moiety was accomplished by addition of 3-lithiofuran to the aldehyde. When aldehyde **58** was treated with 1.1 equivalents of 3-lithiofuran in ether at -78°C for 15 minutes, the expected addition products, were formed. Under the reaction conditions, a small portion of the epimeric addition products was shown to undergo cyclization to give the desired spiro-lactone ring. Unfortunately, when the reaction temperature was raised to room temperature after the initial addition was complete, the reaction mixture became quite messy and the product isolation was quite difficult. The following steps were then taken to facilitate the lactone formation. After the initial addition was finished, the reaction was quenched with water at -78°C. The crude product, without purification, was redissolved in THF and treated with excess sodium hydride. After 8 hours of stirring at room temperature, two spiro-lactones **60** and **61** were formed in 86% combined yield and approximately 1:1 ratio. The ir spectrum of **60** showed the characteristic carbonyl absorption for a γ-lactone at 1755 cm^{-1}. In the ^1H nmr spectrum, three furan protons were displayed at δ 7.44 (2 protons) and δ 6.40. A triplet ($J = 9$ Hz) at δ 5.38 was attributed to the C-4' proton. The C-5' protons were found at δ 2.38 and 2.37 as a pair of "doublets" ($J = 9$ Hz each).



60

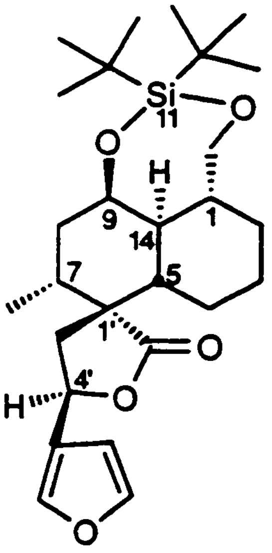


61

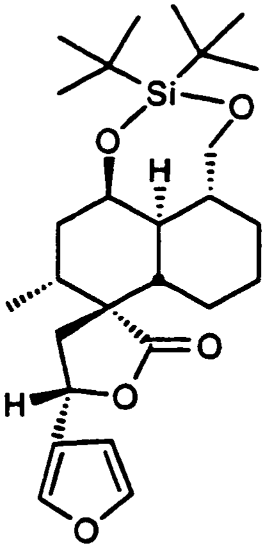
The ir spectrum of the second spiro-lactone **61** showed a carbonyl absorption band at 1760 cm^{-1}. In the ^1H nmr spectrum, two furan protons appeared at δ 7.44 and the third one at δ 6.41. A triplet (J = 8.5 Hz) at δ 5.36 corresponded to the C-4' proton and two doublets of doublets at δ 2.41 and 2.31 (J = 14, 8.5 Hz each) were attributed to the C-5' protons.

The stereochemistry of the newly formed chiral center C-4' in each compound was tentatively assigned as depicted. These assignments were made after a comparison of the coupling patterns observed for their C-5' protons with those reported for the corresponding protons of teucvin **5** and epimer (at C-4') 12-*epi*-teucvin (Figure 3-2). In case of teucvin **5**, the C-5' protons were observed as one "doublet" (J = 8.5 Hz) at δ 2.54,[8] whereas, in the ^1H nmr spectrum of 12-*epi*-teucvin, two doublets of doublets at δ 2.64 (J = 14, 8 Hz) and δ 2.44 (J = 14, 9 Hz) were displayed for the C-5' protons.[16]

In a similar fashion aldehyde **59** was reacted with 3-lithiofuran, followed by treatment of the resulting alcohols with sodium hydride to produce spiro-lactones **62** and **63**. The spiro-lactone **62** was isolated in 39% yield. In the ^{1}H nmr spectrum, the furan protons resonated at δ 7.43 and 6.40. The C-4' proton signal appeared as a triplet (*J* = 9 Hz) at δ 5.37 and the C-5' protons were displayed as two "doublets" at δ 2.44 and 2.42 (*J* = 9 Hz each).



62



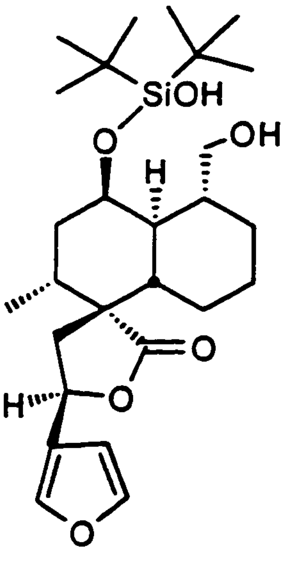
63

The second lactone **63** was formed in 46% yield. The C-4' proton appeared at δ 5.37 as a triplet (*J* = 9 Hz). Two doublets of doublets at δ 2.47 (dd, *J* = 14, 9 Hz) and δ 2.36 (dd, *J* = 14, 9 Hz) were attributed to the C-5' protons. Again, the stereochemistry at the C-4' center in **62** and **63** was assigned after a careful comparison of the splitting patterns of the C-5' protons with those reported for the corresponding protons in teucvin **5** and 12-*epi*-tecvin.

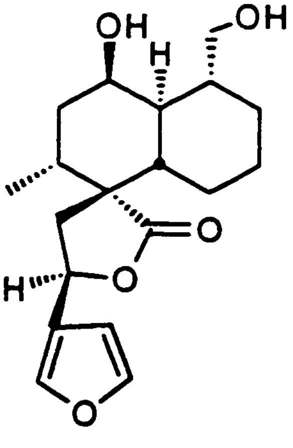
Spiro-lactones **60** and **62** are potential synthetic precursors of teucvin **5**. Their convertion to the natural product requires the following few operations: (1)

deprotection of the diol, (2) oxidation of the secondary alcohol to a ketone and the primary alcohol to a carboxylic acid, (3) formation of the unsaturated lactone to finish the synthesis. Following the same synthetic sequence, the total synthesis of the naturally occurring 12-*epi*-teucvin in racemic form could, in principle, also be achieved from the isomeric spiro-lactones **61** and **63**. It is noteworthy that each epimer of the spiro-lactone pair (**60/61** or **62/63**) may be obtained as a single product, since interconversion of the immediate alcohol precursors of each pair is highly conceivable using Mitsunobu reaction.[66] Thus, the above projected synthetic sequence could also be directed specifically towards either of the natural compounds.

Due to limited availability of spiro-lactones **60 - 63**, the first two operations of the above synthetic sequence were briefly examined. Preliminary results are promising. Deprotection of dialkylsilylene derivatives can be accomplished satisfactorily with aqueous hydrofluoric acid in acetonitrile[67] or tributylamine hydrofluoride (TBAHF) in THF.[68] The use of tetrabutylammonium fluoride (TBAF) in THF has also been reported for this transformation.[68] However, in case of di-*tert*-butylsilanediyl group (DTBS), longer reaction time and large excess of reagent are generally necessary. When cyclic ether **62** was treated with TBAF (20 equivalents) in THF at room temperature for 16 hours, compound **64** was isolated as the product. The structure of **64** was deduced from its ^{1}H nmr spectrum. The methylene protons of adjacent to the hydroxy group appeared at somewhat higher field (δ 3.79 and 3.52) when compared to the corresponding protons (δ 4.00 and 3.75) of the parent compound **62** . Two singlets at δ 1.04 and 1.03 were displayed, indicating that the *tert*-butyl groups

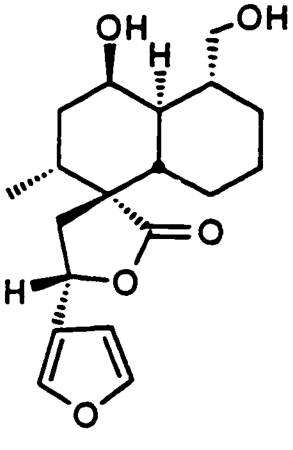


64



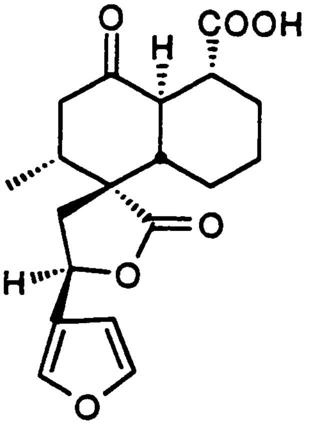
65

were still present. To effect a complete removal of the DTBS group, compound **62** was dissolved in a 1M solution of TBAF in THF and the resulting solution heated under reflux for 2 hours. In the ^{1}H nmr spectrum of the crude product **65**, *t*-butyl singlets were absent in the δ 1.00-1.10 region. The signals at δ 7.43, 6.40 and 5.38 indicated both the furan ring and the γ-lactone moiety remained intact. Similar cleavage of cyclic silyl ether **63** gave diol **66**.

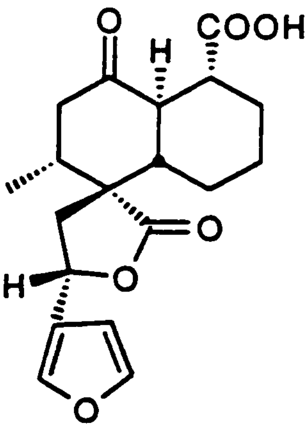


66

With small amount of diols **65** and **66** in hand, their direct oxidation to keto acids **67** and **68**, respectively, was examined. Oxidation of **66** using Jones reagent in acetone at 10°C proceeded smoothly and after 15 minutes only acid **68** was detected in the reaction mixture (tlc analysis). The ir spectrum of the crude product showed a typical acid absorption band at 2500-3350 cm^{-1}. Two carbonyl absorptions were displayed at 1755 and 1710 cm^{-1}, consistent with the presence of a γ-lactone and acid, respectively. Oxidation of diol **65** was also effected with Jones reagent. Similar results were obtained.



67



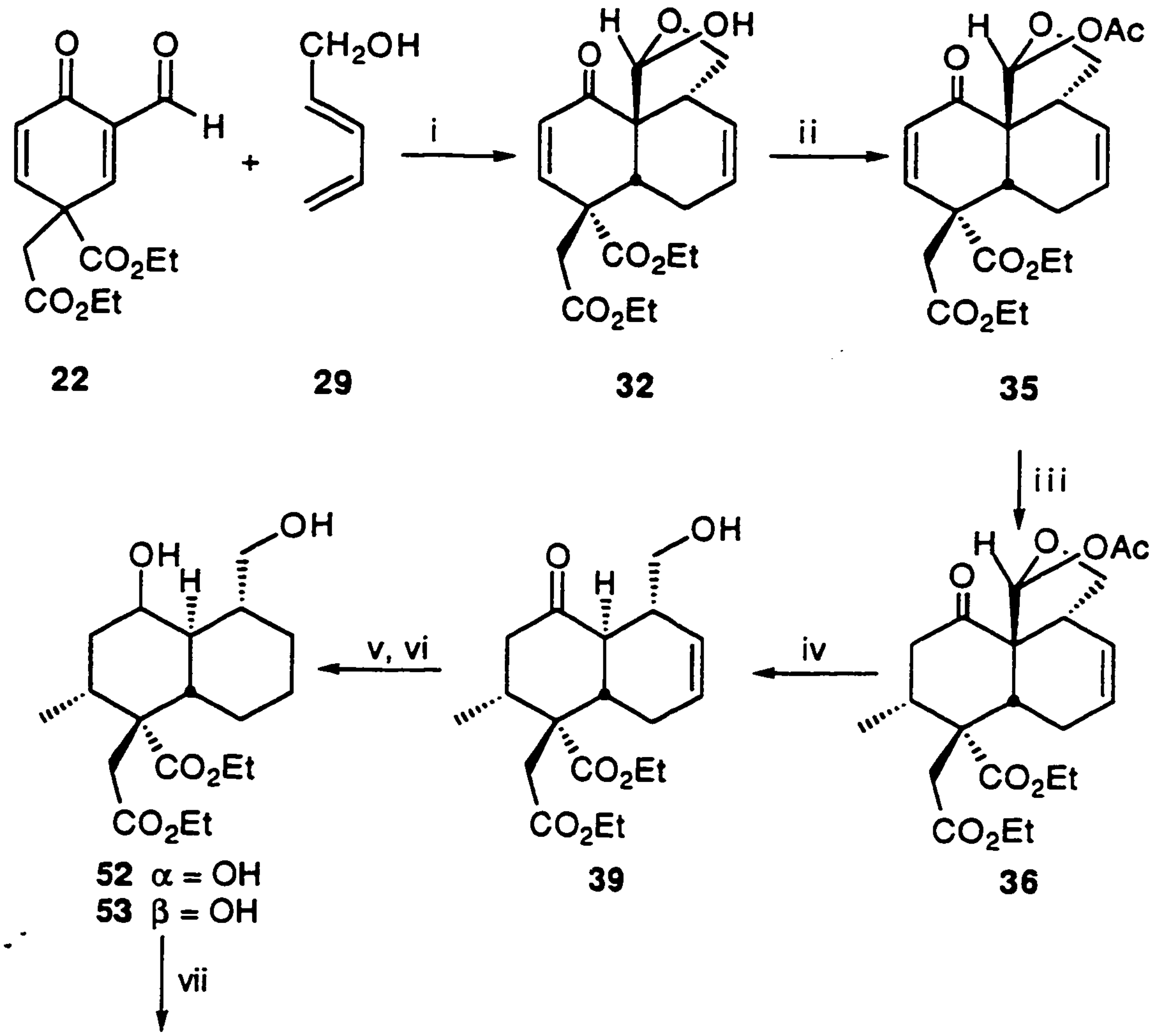
68

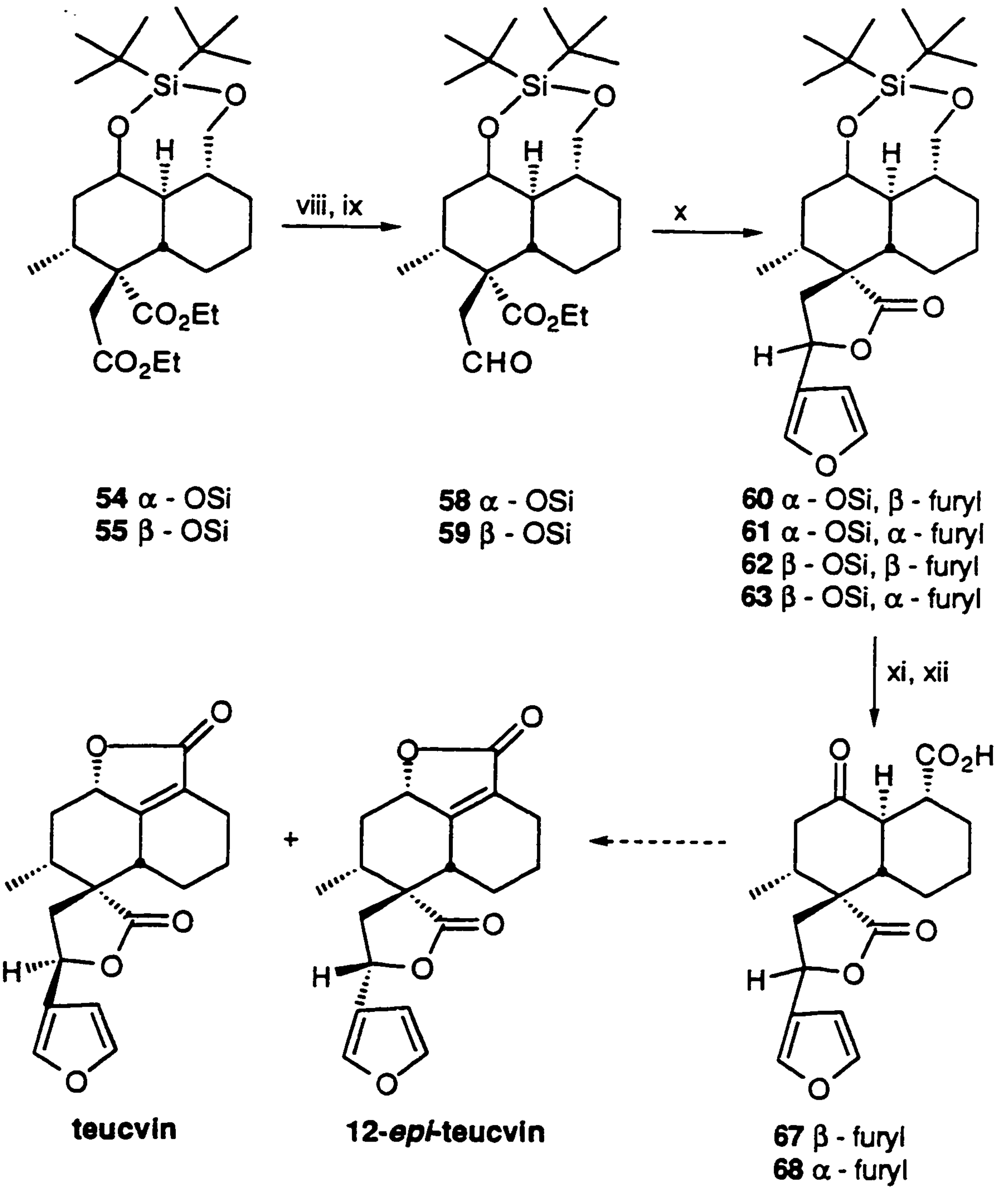
Conclusion

Although the completion of the synthesis of teucvin **5** and 12-*epi*-teucvin was only one step away in each case, the formation of an α,β-unsaturated γ-lactone was not realized due to very little material left. At present, a large scale preparation of keto acids **67** and **68** is being carried out according to the developed synthetic sequence outlined in Scheme 3-7.

In summary, several advanced intermediates towards targeted furanoid nor-diterpenes was synthesized. The spiro-lactones **60-63** were obtained in ten steps and 24% combined yield starting from dienophile **22** and pentadienol **29**. All required transformation were achieved in high yields (80-93%). The synthesis of keto acids **67** and **68** was also examined. Preliminary results were promising. We are fully confident that the total synthesis of teucvin **5** and its C-12 epimer will be accomplished in the near future according to the projected synthetic scheme.

Scheme 3-7





54 α - OSi
55 β - OSi

58 α - OSi
59 β - OSi

60 α - OSi, β - furyl
61 α - OSi, α - furyl
62 β - OSi, β - furyl
63 β - OSi, α - furyl

teucvin

12-*epi*-teucvin

67 β - furyl
68 α - furyl

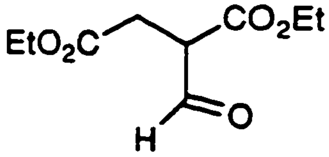
i. $ZnCl_2$, CH_2Cl_2, 82%; ii. Ac_2O, pyr, 86%; iii. Me_2CuLi, Et_2O, 83%; iv. EtONa, EtOH, 93%; v. H_2, Pd/C, EtOAc, 89%; vi. Li(*t*-Bu)$_3$AlH, THF, 89%; vii. (*t*Bu)$_2$Si(OTf)$_2$, pyr, THF, 88%; viii. Red-Al, PhH, 90%; ix. PDC, CH_2Cl_2, 81%; x. 3-lithiofuran, Et_2O, 86%; xi. TBAF, THF; xii. CrO_3, aq. H_2SO_4, acetone.

Experimental

General and materials

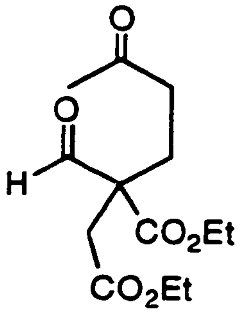
For detailed experimental remarks, see the Experimental Section of Chapter 1 of this thesis.

Diethyl 2-formylsuccinate (23)



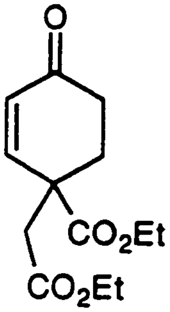
To a suspension of sodium hydride (4.4 g, 60% dispersion in oil, 108 mmol) in dry THF (40 mL), freshly distilled ethyl formate (11.6 mL, 144 mmol) was added and the mixture was stirred at 0°C for 1 hour under an argon atmosphere. Diethyl succinate (12 mL, 72 mmol) in THF (15 mL) was then introduced, followed by careful addition of few drops of dry ethanol. The resulting solution was stirred first at 0°C for 2 hours and then at room temperature for 14 hours. The reaction was quenched with saturated ammonium chloride and the resulting mixture extracted with ether (3 x 25 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was distilled at 66-68°C/0.3 mmHg using a Kugelrohr apparatus to give formyl succinate **23** (13.1 g, 90% yield) as a colorless oil: FT-ir (neat film) 1738 cm^{-1} (C=O, aldehyde and esters); ^{1}H nmr (300 MHz, $CDCl_3$) δ 11.51 (d, *J* = 12.5 Hz, 0.5H, =CH-O**H**, enol form), 9.90 (s, 0.5H, -CHO), 7.07 (dt, J = 12.5, 1.5 Hz, 0.5H, =CH-OH), 4.26 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.21 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.12 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.13 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 3.76 (t, J = 6 Hz, 0.5H, C2-**H**), 3.05 (s, 1H, C3-H_2, enol form), 2.92 (dd, J = 17.5, 6 Hz, 0.5H, C3-H_2, keto form), 2.84 (dd, J = 17.5, 6 Hz, 0.5H, C3-H_2, keto form) and 1.20-1.36 (m, 6H, $-OCH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 195.8 (a), 171.6 (p), 171.5 (p), 171.1 (p), 168.0 (p), 162.7 (a), 99.4 (p), 62.0 (p), 61.1 (p), 60.8 (p), 60.7 (p), 54.1 (a), 33.0 (p), 30.0 (p), 14.2 (a) and 14.1 (a) (3 xC); hreims M^+ 202.0837 (calculated for $C_9H_{14}O_5$: 202.0841).

Ethyl 3-carbethoxy-3-formyl-6-oxoheptanoate (24)



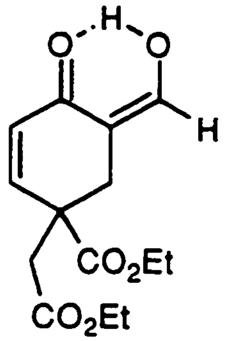
Freshly distilled methyl vinyl ketone (5.08 g, 72.5 mmol) was added dropwise to a mixture of aldehyde **23** (12.2 g, 60.4 mmol) and DABCO (8.13 g, 72.5 mmol) in dry THF (60 mL). The resulting solution was stirred at room temperature for two days under an atmosphere of argon and then cooled down to 0°C. The reaction mixture was acidified (pH ~6) with 2N HCl and extracted with ether (3 x 50 mL). The extracts were washed with water, brine and dried over magnesium sulfate. After filtration and concentration, the residue was subjected to flash chromatography (elution with 10% ethyl acetate in hexanes) to give heptanoate **24** (14.1 g, 52 mmol) as a colorless oil in 86 % yield: FT-ir (CH_2Cl_2, cast) 2984 cm^{-1} (alkane C-H stretching) and 1721 cm^{-1} (C=O, ketone, aldehyde and esters); ^{1}H nmr (300 MHz, CDCl$_3$) δ 10.05 (s, 1H, -CHO), 4.24 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.23 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.09 (q, *J* = 7 Hz, 2H, -OC**H**$_2$CH$_3$), 2.90 (dd, *J* = 17, 1 Hz, 1H, C2-**H**), 2.81 (d, *J* = 17 Hz, 1H, C2-**H**), 2.43 (t, *J* = 7.5 Hz, 2H, C5-**H**), 2.12 (s, 3H, -CO-CH$_3$), 1.93-2.14 (m, 2H, C4-**H**), 1.29 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 1.22 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 206.2 (p), 200.3 (a), 171.4 (p), 170.7 (p), 61.8 (p), 61.2 (p), 57.0 (p), 37.8 (p) (2 x C), 30.0 (a), 27.7 (p) and 14.1 (a) (2 x C); hreims M$^+$ 272.1251 (calculated for $C_{13}H_{20}O_6$: 272.1259). Elemental analysis: calculated for $C_{13}H_{20}O_6$: %C 57.34, %H 7.40; found: %C 57.32, %H 7.41.

4-Carbethoxy-4-(carbethoxymethyl)-2-cyclohexen-1-one (25)



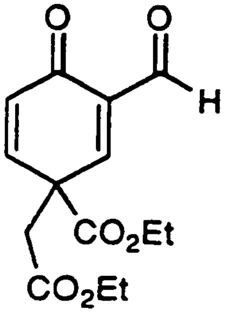
A round bottomed flask equipped with a magnetic stirrer, a Dean-Stark apparatus and a condenser was charged with keto aldehyde **24** (7.9 g, 29 mmol), *p*-TsOH (0.55 g, 2.9 mmol) and dry benzene (60 mL). The mixture was heated to reflux under argon for 8 hours with azeotropic removal of water. The solution was then cooled down to room temperature, diluted with benzene, washed with half saturated sodium bicarbonate (40 mL), water (50 mL) and dried over magnesium sulfate. Filtration and concentration gave the crude product, which was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes afforded cyclohexenone **25** (6.55 g, 26 mmol) in 89% yield: 1685 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 6.96 (d, *J* = 10 Hz, 1H, C3-**H**), 5.98 (d, *J* = 10 Hz, 1H, C2-**H**), 4.15 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 4.08 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 2.84 (d, *J* = 16 Hz, 1H, $-CH_2CO_2Et$), 2.71 (d, *J* = 16 Hz, 1H, $-CH_2CO_2Et$), 2.31-2.58 (m, 3H), 2.01 (m, 1H), 1.22 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$) and 1.19 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 197.6 (p), 172.5 (p), 170.0 (p), 149.2 (a), 129.7 (a), 61.7 (p), 60.9 (p), 45.3 (p), 42.0 (p), 34.0 (p), 31.3 (p), 14.0 (a) and 13.9 (a); hreims M^+ 254.1141 (calculated for $C_{13}H_{18}O_5$: 254.1154).

4-Carbethoxy-4-(carbethoxymethyl)-6-hydroxymethylene-2-cyclohexenone (26)



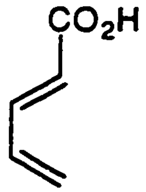
Ethyl formate (10 mL, 135 mmol) was added dropwise to a suspension of sodium hydride (1.3 g of 60% dispersion in oil, 32.4 mmol) in THF (60 mL) at 0°C under an argon atmosphere. The mixture was stirred for 0.5 hour, then cyclohexenone **25** (4.31 g, 16.2 mmol) in 15 mL of THF was introduced slowly over a period of 30 minutes, followed by careful addition of dry ethanol (4 drops). The resulting solution was stirred at 0°C for additional hour and then at room temperature for 8 hours. The reaction was quenched with water (20 mL) and the mixture acidified (pH ~4) with 2N HCl. The product was extracted into ether (3 x 50 mL). The combined organic extracts were washed with water, Purification by flash chromatography (elution with 10% ethyl acetate in hexanes) provided compound **26** (4.2 g, 14.9 mmol, 88% yield) as a pale yellow oil: FT-ir ($CHCl_3$, cast) 1734 cm^{-1} (C=O, esters) and 1649 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 13.68 (br s, 1H, =CH-O**H**, enol form), 7.60 (br s, 1H, =C**H**-OH), 6.98 (dd, *J* = 10, 1.5 Hz, 1H, C3-**H**), 6.14 (d, *J* = 10 Hz, 1H, C2-**H**), 4.21 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 4.11 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 2.91 (dd, *J* = 15, 1.5 Hz, 1H, C5-**H**), 2.85 (d, *J* = 16.5 Hz, 1H, $-CH_2CO_2Et$), 2.73 (d, *J* = 16.5 Hz, 1H, $-CH_2CO_2Et$), 2.53 (d, *J* = 15 Hz, 1H, C5-**H**), 1.27 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$) and 1.23 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 186.6 (p), 173.1 (p), 170.2 (p), 169.2 (a), 147.5 (a), 128.5 (a), 104.9 (p), 61.8 (p), 61.0 (p), 46.0 (p), 41.1 (p), 32.1 (p), 14.13 (a) and 14.07 (a); hreims M^+ 282.1104 (calculated for $C_{14}H_{18}O_6$: 282.1104).

4-Carbethoxy-4-(carbethoxymethyl)-2-formyl-2,5-cyclohexadien-1-one (22)



To a solution of **26** (0.67 g, 2.4 mmol) in dry benzene (5 mL), DDQ (0.65 g, 2.8 mmol) was added. The resulting dark orange solution was stirred at 10°C and under an argon atmosphere. After 30 minutes, tlc analysis showed that no more starting material was present. The reaction mixture was filtered through celite to remove the hydroquinone produced. The filtrate was concentrated and the residue was subjected to flash chromatography. Elution with 15% ethyl acetate in hexanes afforded dienone **22** (519 mg, 1.8 mmol) as a pale yellow solid in 78% yield: FT-ir ($CHCl_3$, cast) 1735 cm^{-1} (C=O, esters), 1708 cm^{-1} (C=O, enone), 1669 cm^{-1} (C=O, enone) and 1630 cm^{-1} (C=C stretching); ^1H nmr (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, -CHO), 7.81 (d, $J = 3$ Hz, 1H, C3-**H**), 7.12 (dd, $J = 10, 3$ Hz, 1H, C5-**H**), 6.45 (d, $J = 10$ Hz, 1H, C6-**H**), 4.24 (q, $J = 7$ Hz, 1H, -OC**H**$_2$CH$_3$), 4.23 (q, $J = 7$ Hz, 1H, -OC**H**$_2$CH$_3$), 4.17 (q, $J = 7$ Hz, 2H, -OC**H**$_2$CH$_3$), 2.98 (d, $J = 17$ Hz, 1H, -C**H**$_2$CO$_2$Et), 2.89 (d, $J = 17$ Hz, 1H, -C**H**$_2$CO$_2$Et), 1.28 (t, $J = 7$ Hz, 3H, -OCH$_2$C**H**$_3$) and 1.26 (t, $J = 7$ Hz, 3H, -OCH$_2$C**H**$_3$); hreims [M^+- 45] 235.0607 (calculated for $C_{12}H_{11}O_5$: 235.0606).

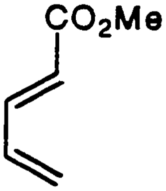
(*E*)-2,4-Pentadienoic acid (27)



Acrolein (15 g, 0.27 mol) was gradually added to a vigorously stirred solution of malonic acid (22.5 g, 0.22 mol) in pyridine (100 mL) at 0°C. After the addition was completed (1 hour), the reaction mixture was heated to 35°C and stirred for 6 hours. After cooling to room temperature and dilution with ether (150 mL), the resulting solution was washed with ice-cold aqueous 10% HCl and water. The organic layer was dried over magnesium sulfate, filtered and concentrated. Recrystalization of the crude product from hexane afforded acid **27** (9 g, 92 mmol, 42% yield) as a white solid: mp 72-73°C; FT-ir ($CHCl_3$, cast) 2400-3300 cm^{-1} (OH, carboxylic acid), 1685 cm^{-1} (C=O) and 1633 cm^{-1} (C=C); ^1H nmr (300

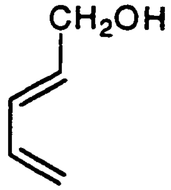
MHz, $CDCl_3$) δ 11.8 (br s, 1H, -CO-O**H**), 7.37 (dddd, *J* = 15.5, 11, 1, 1 Hz, 1H, C3-**H**), 6.5 (dddd, *J* = 17, 11, 10, 1 Hz, 1H, C4-**H**), 5.93 (dddd, *J* = 15.5, 1, 1, 1 Hz, 1H, C2-**H**), 5.68 (dddd, *J* = 17, 1.5, 1, 1 Hz, 1H, C5-**H**) and 5.57 (dddd, *J* = 10, 1.5, 1, 1 Hz, 1H, C5-**H**).

Methyl (*E*)-2,4-pentadienoate (28)



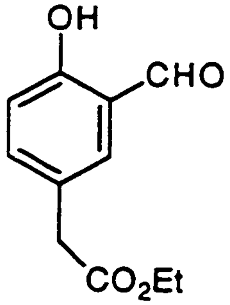
Acid **27** (7g, 71 mmol) was disolved in methanol (100 mL) containing a few drops of concentrated sulfuric acid. The resulting mixture was heated to reflux for 3 hours, then poured into ice-water (100 mL) and extracted with ether. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was distilled at room temperature under reduced pressure (6 torr) to give methyl ester **28** (6.9 g, 62 mmol) as a colorless liquid in 87% yield: FT-ir ($CHCl_3$, cast) 1723 cm^{-1} (C=O, ester) and 1645 cm^{-1} (C=C stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 7.23 (dddd, *J* = 15.5, 11, 1, 1 Hz, 1H, C3-**H**), 6.41 (dddd, *J* = 17, 11, 10, 1 Hz, 1H, C4-**H**), 5.88 (dd, *J* = 15.5, 1 Hz, 1H, C2-**H**), 5.57 (dddd, *J* = 17, 1.5, 1, 1 Hz, 1H, C5-**H**), 5.45 (dddd, *J* = 10, 1.5, 1, 1 Hz, 1H, C5-**H**) and 3.71 (s, 3H, -CO-OC**H**$_3$); hreims M^+ 112.0527 (calculated for $C_6H_8O_2$: 112.0524).

(*E*)-2,4-Pentadien-1-ol (29)



A solution of methyl ester **28** (5 g, 44.6 mmol) in dry ether (25 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.69 g, 44.6 mmol) in ether (40 mL) at -25°C and under an argon atmosphere. After the addition was completed, the reaction mixture was stirred at 0°C for 2 hours and then poured slowly into aqueous 10% sodium hydroxide (50 mL). The aqueous layer was separated and extracted with ether (3 x 50 mL). The organic solutions were combined, washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled at 35°C/3 torr to give alcohol **29** (2.8 g, 33.5 mmol, 75% yield) as a colorless liquid: FT-ir ($CHCl_3$, cast) 3334 cm^{-1} (OH), 3041 cm^{-1} (alkene C-H stretching) and 1640 cm^{-1} (C=C stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 6.19-6.41 (m, 2H, C3-**H** and C4-**H**), 5.83 (dt, *J* = 15, 6 Hz, 1H, C2-**H**), 5.20 (ddd, *J* = 16, 2, 0.5 Hz, 1H, C5-**H**), 5.08 (dd, *J* = 10, 2 Hz, 1H, C5-**H**), 4.17 (br s, 2H, CH_2OH) and 1.87 (br s, -O**H**); hreims M+ 84.0579 (calculated for C_5H_8O: 84.0575).

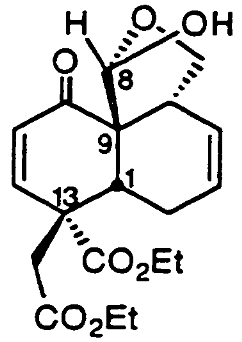
2-Formyl-4-(carbethoxymethyl)phenol (31)



Zinc chloride (27 mg, 0.2 mmol) in a round bottomed flask was fused under argon and then cooled to room temperature. Dry dichloromethane (2 mL) was added and the $ZnCl_2$ was crushed with a spatula to small pieces. The suspension was vigorously stirred for 15 minutes until a fine suspension formed and then cooled to 0°C. Dienone aldehyde **22** (28 mg, 0.1 mmol) in dichloromethane (1 mL) was added dropwise and the resulting mixture was stirred for 10 minutes. Ester **28** (67.1 mg, 0.6 mmol) was then introduced and the solution was stirred for 2 days. The reaction was quenched with water and the mixture was extracted with dichloromethane (3 x 3 mL). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes afforded phenol **31** (2 mg, 10 % yield): FT-ir ($CHCl_3$, cast) 2800-3400 cm^{-1} (broad, OH hydrogen bonded), 1734 cm^{-1} (C=O, ester), 1657 cm^{-1} (C=O, aromatic aldehyde with H-bond) and 1625 cm^{-1} (aromatic C=C streching); ^1H nmr (300 MHz, $CDCl_3$) δ 10.97 (s, 1H, -O**H**), 9.90 (s, 1H, -CHO), 7.49 (d, *J* = 2 Hz, 1H, C3-**H**), 7.46 (dd, *J* = 8, 2 Hz, 1H, C5-**H**), 6.98 (d, *J* = 8 Hz, 1H, C6-**H**), 4.17 (q, *J* = 7 Hz, 2H, $-OC\mathbf{H}_2CH_3$), 3.60 (s, 2H, $-C\mathbf{H}_2CO_2Et$) and 1.27 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$); hreims M^+ 208.0735 (calculated for $C_{11}H_{12}O_4$: 208.0736).

Further elution with the same solvent system gave intact dienophile **22** (24 mg, 86% recovery).

(1R*,5R*,8R*,9S*,13R*)-13-Carbethoxy-13-(carbethoxymethyl)-8-hydroxy-7-oxatricyclo[7.4.0.$0^{5,9}$]trideca-3,11-dien-10-one (32) and (1S*,5R*,6S*,10R*)-5-carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)bicyclo[4.4.0]deca-3,8-dien-2-one (33)



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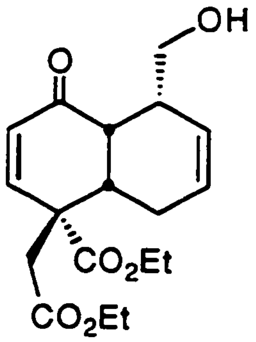
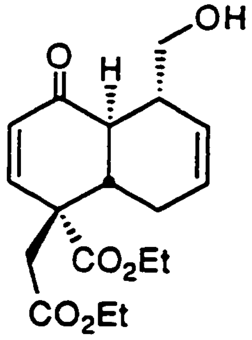


33

Zinc chloride (199 mg, 1.46 mmol) was flame-fuse dried in a round bottomed flask under an argon atmosphere. The flask was cooled to room temperature, dichloromethane (2 mL) was added and the $ZnCl_2$ was crushed into small pieces using a spatula. After 15 minutes of vigorous stirring, the resulting suspension was cooled to 0°C. A solution of dienone **22** (205 mg, 0.73 mmol) and alcohol **29** (92 mg, 1.1 mmol) in dichloromethane (2 mL) was then added and the reaction mixture was stirred at 0°C for 0.5 hour. Upon completion, the reaction was quenched with water and the resulting mixture extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed successively with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was subjected to flash chromatography. Elution with 20% ethyl acetate in hexanes gave adduct **32** (219 mg, 82% yield) as a yellowish oil: FT-ir ($CHCl_3$, cast) 3445 cm^{-1} (OH), 1734 cm^{-1} (C=O, esters) and 1687 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.15 (dd, *J* = 10.5, 2 Hz, 1H, C12-**H**), 5.95 (d, *J* = 10.5 Hz, 1H, C11-**H**), 5.84 (ddd, *J* = 10, 4, 2 Hz, 1H, C4-**H**), 5.42 (ddd, *J* = 10, 6, 3 Hz, 1H, C3-**H**), 5.34 (d, *J* = 2.5 Hz, 1H, C8-**H**), 4.06-4.29 (m, 6H, -OC**H**$_2$CH$_3$ and C4-**H**$_2$), 3.50 (d, *J* = 2.5 Hz, 1H, C8-O**H**), 3.33 (d, *J* =17 Hz, 1H, -C**H**$_2$CO$_2$Et), 3.21 (m, 1H, C5-**H**), 2.93 (m, 1H, C1-**H**), 2.92 (d, *J* = 17 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.04-2.26 (m, 2H, C2-**H**), 1.29 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 1.24 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 197.2 (p), 172.6 (p), 170.8 (p), 146.6 (a), 128.0 (a), 125.1 (a), 124.1 (a), 97.8 (a), 70.1 (p), 61.5 (p), 61.0 (p), 60.9 (p), 50.5 (p), 43.9 (p), 42.6 (a), 41.9 (a), 28.1 (p), 14.2 (a) and 14.1 (a); hreims M$^+$ 364.1522 (calculated for $C_{19}H_{24}O_7$: 364.1515).

Further elution with the same solvent system afforded deformylated adduct **33** (16.4 mg, 0.05 mmol) as a yellowish oil in 7% yield: FT-ir (CHCl$_3$, cast) 3433 cm^{-1} (OH), 1734 cm^{-1} (C=O, esters) and 1685 cm^{-1}(C=O, enone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.17 (dd, *J* = 10.5, 2 Hz, 1H, C4-**H**), 5.97 (d, *J* = 10.5 Hz, 1H, C3-**H**), 5.69 (ddd, *J* = 10, 4, 2 Hz, 1h, C9-**H**), 5.56 (dddd, *J* = 10, 5, 2.5, 2.5 Hz, 1H, C8-**H**), 4.24 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.23 (q, *J* = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.13 (q, *J* = 7 Hz, 2H, -OC**H**$_2$CH$_3$), 3.97 (m, 1H, -C**H**$_2$OH), 3.85 (br d, *J* = 11 Hz, 1H, -C**H**$_2$OH), 3.62 (br s, 1H, -O**H**), 3.19 (d, *J* = 17 Hz, 1H, -C**H**$_2$CO$_2$Et), 3.04 (br t, *J* = 4.5 Hz, 1H, C1-**H**), 3.00 (d, *J* = 17 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.54-2.65 (m, 2H), 2.11 (m, 1H, C7-**H**), 1.85 (br d, *J* = 16.5 Hz, 1H, C7-**H**), 1.30 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 1.24 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 200.0 (p), 172.5 (p), 170.2 (p), 146.9 (a), 128.7 (a), 126.8 (a), 125.0 (a), 64.2 (p), 61.7 (p), 61.2 (p), 49.9 (p), 46.3 (a), 44.3 (a), 41.9 (p), 41.8 (a), 25.1 (p) and 14.1 (a) (2 x C); hreims M$^+$ 336.1574 (calculated for $C_{18}H_{24}O_6$: 336.1573).

(1R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)bicyclo[4.4.0]deca-3,8-dien-2-one (34)



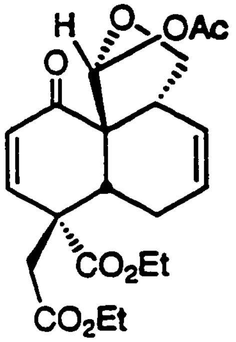
A. Deformylation of hemiacetal 32.

To a solution of hemiacetal **32** (11 mg, 0.03 mmol) in ethanol (1 mL), a trace amount of sodium hydride was added and the resulting mixture was stirred at room temperature overnight. Water (1 mL) was then added and the solution was extracted with ether (2 x 3 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by flash column chromatography (elution with 25% ethyl acetate in hexanes) gave compound **34** (9 mg) in 91% yield: FT-ir ($CHCl_3$, cast) 3440 cm^{-1} (OH), 1730 cm^{-1} (C=O, esters) and 1679 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 7.10 (d, J = 10 Hz, 1H, C4-**H**), 6.18 (d, J = 10 Hz, 1H, C3-**H**), 5.85 (dddd, J = 10, 6.5, 2, 2 Hz, 1H, C9-**H**), 5.55 (ddd, J = 10, 2.5, 2.5 Hz, 1H, C8-**H**), 4.20 (q, J = 7 Hz, 2H, -OCH_2CH_3), 4.15 (q, J = 7 Hz, 2H, -OCH_2CH_3), 3.81 (m, 1H), 3.61 (m, 2H), 3.18 (d, J = 17 Hz, 1H, -CH_2CO_2Et), 2.78-2.88 (m, 1H), 2.70-2.77 (m, 1H), 2.51 (d, J = 17 Hz, 1H, -CH_2CO_2Et), 2.18-2.32 (m, 2H), 1.84-1.92 (m, 1H) and 1.28 (t, J = 7 Hz, 6H, -OCH_2CH_3).

B. Epimerization of adduct 33.

A solution of adduct **33** (8 mg, 0.02 mmol) and a catalytic amount of sodium ethoxide in ethanol (1 mL) was stirred at room temperature for 6 hours. After 1 mL of water was added, the mixture was extracted with ether (2 x 3 mL). The ethereal extracts were then washed with brine, dried over magnesium sulfate and filtered. Evaporation of the solvent, followed by purification of the crude product by flash chromatography (elution with 25% ethyl acetate in hexanes) afforded compound **34** (6 mg) in 75% yield.

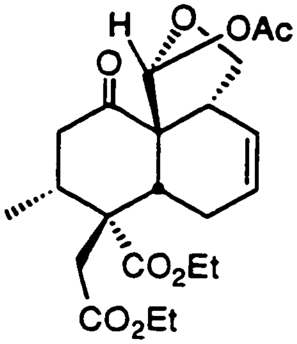
(1R*,5R*,8R*,9S*,13R*)-8-Acetoxy-13-carbethoxy-13-(carbethoxy methyl)-7-oxatricyclo[7.4.0.0^{5,9}]trideca-3,11-dien-10-one (35)



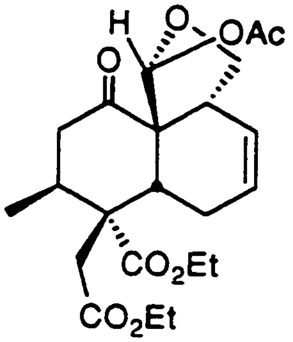
A solution of hemiacetal **32** (332 mg, 0.91 mmol) in dry pyridine (3 mL) was stirred at room temperature and under an atmosphere of argon. Acetic anhydride (0.43 mL, 4.56 mmol) was first added, followed by addition of a trace amount of DMAP. Stirring was continued overnight, while the reaction flask was protected from light. After the reaction was complete, pyridine was evaporated and the residue was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes afforded acetate **35** (317 mg, 0.78 mmol) in 86% yield: FT-ir ($CHCl_3$, cast) 3050 cm^{-1} (alkene C-H stretching), 1739 cm^{-1} (C=O, esters) and

1689 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.16 (dd, J =10.5, 2.5 Hz, 1H, C12-**H**), 6.17 (s, 1H, C8-**H**), 5.97 (d, J = 10.5 Hz, 1H, C11-**H**), 5.84 (dddd, J = 10, 2, 2, 2 Hz, 1H, C4-**H**), 5.43 (dddd, J = 10, 3.5, 3.5, 3.5 Hz, 1H, C3-**H**), 4.03-4.33 (m, 6H, -OC**H**$_2$CH$_3$ and C6-**H**$_2$), 3.14 (m, 1H, C5-**H**), 3.00 (d, J = 17 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.85 (ddd, J = 10, 8, 2.5 Hz, 1H, C1-**H**), 2.45 (d, J = 17 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.06-2.27 (m, 2H, C2-**H**), 2.14 (s, 3H, C**H**$_3$-CO-), 1.29 (t, J = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 1.21 (t, J = 7 Hz, 3H, -OCH$_2$C**H**$_3$); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 195.4 (p), 172.4 (p), 170.0 (p), 169.8 (p), 146.4 (a), 127.8 (a), 125.2 (a), 123.6 (a), 97.0 (a), 70.8 (p), 61.7 (p), 61.2 (p), 59.7 (p), 50.3 (p), 43.5 (p), 43.0 (a), 42.3 (a), 28.0 (p), 21.3 (a) and 14.2 (a) (2 x C).

(1S*,5*R,8R*,9S*,12R*,13R*)-8-Acetoxy-13-carbethoxy-13-(carbethoxymethyl)-12-methyl-7-oxatricyclo[7.4.0.0^{5,9}]tridec-3-en-10-one (36) and (1R*,5*R,8R*,9S*,12S*,13R*)-8-acetoxy-13-carbethoxy-13-(carbethoxymethyl)-12-methyl-7-oxatricyclo [7.4.0.0^{5,9}]tridec-3-en-10-one (37)



36



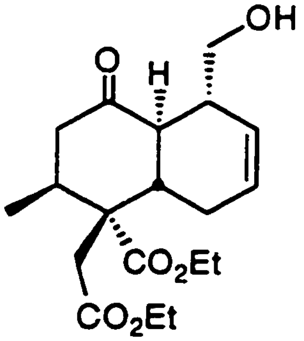
37

A suspension of CuI (209 mg, 1.1 mmol) in ether (10 mL) in a flame dried flask was stirred at 0°C and under an argon atmosphere. Methyllithium (1.6 mL, 1.4M in ether) was introduced dropwise (a bright yellow precipitate formed first and then redissolved), and the resulting clear solution was stirred at 0°C for 1 hour. Enone acetate **35** (149 mg, 0.37 mmol) in 3 mL of ether was added slowly (a yellow precipitate appeared) and the mixture was stirred for 20 minutes. The reaction was quenched with saturated ammonium chloride and the products were extracted with ether (3 x 15 mL). The combined extracts were washed successively with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography. Elution with 15% ethyl acetate in hexanes afforded compound **36** (128 mg, 0.3 mmol) as a white solid in 83% yield: FT-ir ($CHCl_3$, cast) 2978 cm^{-1} (alkane C-H stretching), 1721 cm^{-1} (C=O, esters and ketone) and 1220 cm^{-1} (C-O stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 6.35 (s, 1H, C8-**H**), 6.18 (ddd, *J* = 9.5, 3.5, 3.5 Hz, 1H, C4-**H**), 5.65 (dddd, *J* = 9.5, 6.5, 3, 3 Hz, 1H, C3-**H**), 4.08-4.26 (m, 5H, -OC**H**$_2$CH$_3$ and C6-**H**), 3.98-4.06 (m, 1H, C6-**H**), 3.38 (dd, *J* = 10.5, 2.5 Hz, 1H, C1-**H**), 2.86 (d, *J* = 15 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.78 (m, 1H, C5-**H**), 2.65 (dd, *J* = 18, 7 Hz, 1H, C11-**H**), 2.62 (d, *J* = 15 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.48 (m, 1H, C12-**H**), 2.32 (ddd, *J* = 17, 10.5, 3 Hz, 1H, C2-**H**), 2.16 (s, 3H, C**H**$_3$-CO-), 2.12 (dd, *J* = 18, 10.5 Hz, 1H, C11-**H**), 1.92 (ddd, *J* = 17, 6.5, 2.5 Hz, 1H, C2-**H**), 1.27 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$), 1.23 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$) and 0.96 (d, *J* = 6.5 Hz, 3H, C12-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.5 (p), 172.0 (p), 171.0 (p), 170.3 (p), 126.4 (a) (2 x C), 96.5 (a), 69.6 (p), 64.8 (p), 61.3 (p), 60.6 (p), 52.8 (p), 43.7 (p), 40.9 (a), 39.8 (a), 39.1 (p), 32.1 (a), 28.0 (p), 21.4 (a), 16.9 (a), 14.2 (a) and 13.9 (a); hreims M^+ was not found, $[M-60]^+$ 362.1725 (calculated for $C_{20}H_{26}O_6$: 362.1729) and $[M-45]^+$ 377.1594 (calculated for $C_{20}H_{25}O_7$: 377.16).

Further elution using the same solvent system (15% ethyl acetate in hexanes) gave compound **37** (18 mg, 0.04 mmol) in 12% yield: FT-ir ($CHCl_3$, cast) 2978 cm^{-1} (alkane C-H stretching) and 1742 cm^{-1} (C=O, ketone and esters); ^1H nmr (300 MHz, $CDCl_3$) δ 6.42 (s, 1H, C8-**H**), 5.87 (dddd, *J* = 10, 2, 2, 2 Hz, 1H, C4-

H), 5.47 (dddd, *J* = 10, 3, 3, 3 Hz, 1H, C3-**H**), 4.00-4.30 (m, 6H, -OCH_2CH_3 and C6-$\mathbf{H}_2$), 2.98-3.09 (m, 1H, 2H), 2.78-2.95 (m, 2H), 2.72 (s, 2H, -CH_2CO_2Et), 2.47 (dd, *J* = 15, 13.5 Hz, 1H, C11-**H**), 2.25 (dd, *J* = 15, 5 Hz, 1H, C11-**H**), 2.17 (s, 3H, CH_3-CO-), 1.95-2.20 (m, 2H, C2-**H**), 1.30 (t, *J* = 7 Hz, 3H, -OCH_2CH_3), 1.23 (t, *J* = 7 Hz, 3H, -OCH_2CH_3) and 1.00 (d, *J* = 7 Hz, 3H, C12-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 205.0 (p), 171.8 (p), 171.1 (p), 169.9 (p), 124.4 (a), 123.0 (a), 97.1 (a), 69.4 (p), 61.2 (p), 61.1 (p), 60.9 (p), 50.3 (p), 47.1 (a), 44.3 (p), 41.2 (a), 37.7 (p), 34.3 (a), 26.7 (p), 21.4 (a), 18.7 (a) and 14.1 (a) (2 x C).

(1R*,4S*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]dec-8-en-2-one (38)



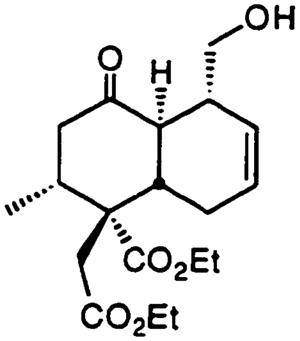
A. Deacetylation-deformylation of 37.

Acetate **37** (14 mg, 0.03 mmol) was treated with sodium ethoxide (10 mg, 0.14 mmol) in ethanol (2 mL). The resulting solution was stirred at room temperature and under an atmosphere of argon for 8 hours. The reaction was then quenched with saturated ammonium chloride and extracted with ether (2 x 3 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate and filtered. After concentration, the crude product was purified by flash chromatography. Elution with 20% ethyl acetate in hexanes afforded alcohol **38** (9 mg) in 75% yield: FT-ir ($CHCl_3$, cast) 3452 cm^{-1} (OH), 2977 cm^{-1} (alkane C-H stretching), 1731 cm^{-1} (C=O, esters) and 1710 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.81 (m, 1H, C9-**H**), 5.55 (br d, *J* = 10 Hz, 1H, C8-**H**), 4.18-4.29 (m, 2H, $-OC\mathbf{H}_2CH_3$), 4.12 (q, *J* = 7 Hz, 2H, $-OC\mathbf{H}_2CH_3$), 3.58 (d, *J* = 5 Hz, 2H, $-C\mathbf{H}_2OH$), 3.20 (dd, *J* = 13.5, 6 Hz, 1H, C1-**H**), 2.77-2.98 (m, 3H), 2.89 (d, *J* = 17 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 2.50 (d, *J* = 17 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 2.38 (m, 1H), 2.20 (dd, *J* = 13.5, 3 Hz, 1H, C3-**H**), 1.95-2.06 (m, 2H), 1.70 (br s, 1H, -O**H**), 1.28 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$), 1.25 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$) and 0.96 (d, *J* = 7 Hz, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 212.2 (p), 173.9 (p), 171.0 (p), 127.4 (a), 127.3 (a), 66.4 (p), 61.1 (p), 60.7 (p), 49.9 (p), 48.2 (a), 46.8 (p), 41.5 (a), 40.1 (p), 38.4 (a), 37.3 (a), 26.9 (p), 16.1 (a), 14.2 (a) and 14.1 (a).

B. Conjugate addition reaction with enone 34.

Methyllithium (0.34 mL of 1.4M solution in ether, 0.48 mmol) was added dropwise to a vigorously stirred suspension of CuI (45.3 mg, 0.24 mmol) in dry ether (3 mL). The resulting clear solution was stirred for 1 hour at 0°C and under an argon atmosphere. Enone **34** (26.6 mg, 0.08 mmol) in 1 mL of ether was then introduced and the reaction mixture was stirred at 0°C for another hour. After the reaction was quenched with saturated ammonium chloride, products were extracted with ether (2 x 5 mL). The combined organic extracts were washed successively with water and brine, dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (elution with 20% ethyl acetate in hexanes) gave alcohol **38** (20.3 mg, 0.06 mmol) in 72% yield.

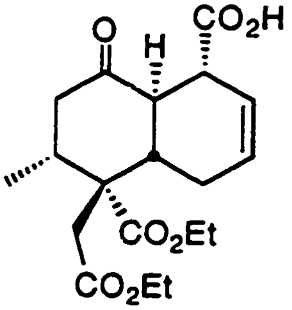
(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]dec-8-en-2-one (39)



To a solution of acetate **36** (126 mg, 0.31 mmol) in ethanol (2 mL), sodium hydride (15 mg, 0.62 mmol) was added. The resulting solution was stirred under an argon atmosphere and at room temperature for 12 hours. The reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with ether (3 x 5 mL). The combined ethereal extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography. Elution with 25% ethyl acetate in hexanes gave alcohol **39** (102 mg, 0.29 mmol) in 93% yield: FT-ir ($CHCl_3$, cast) 3467 cm^{-1} (OH), 1712 cm^{-1} (C=O, ketone and esters) and 1196 cm^{-1} (C-O stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 10, 6, 2, 2 Hz, 1H, C9-**H**), 5.56 (br d, *J* = 10 Hz, 1H, C8-**H**), 4.25 (q, *J* = 7 Hz, 2H, $-OC\mathbf{H}_2CH_3$), 4.11 (q, *J* = 7 Hz, 1H, $-OC\mathbf{H}_2CH_3$), 4.09 (q, *J* = 7 Hz, 1H, $-OC\mathbf{H}_2CH_3$), 3.59 (d, *J* = 5Hz, 2H, $-C\mathbf{H}_2-OH$), 3.20 (dd, *J* = 12.5, 9.5 Hz, 1H, C1-**H**), 2.95 (ddd, *J* = 13, 13, 1 Hz, 1H, C3-**H**), 2.91 (d, *J* = 15 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 2.84 (d, *J* = 15 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 2.81 (m, 1H), 2.33-2.52 (m, 2H), 2.29 (dd, *J* = 13, 4.5 Hz, 1H, C3-**H**), 2.20 (ddd, *J* = 12.5, 12.5, 4.5 Hz, 1H, C6-**H**), 1.90 (br s, 1H, -O**H**), 1.82 (m, 1H, C7-**H**), 1.32 (t, *J* = 7Hz, 3H, $-OCH_2C\mathbf{H}_3$), 1.21 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$) and 1.02 (d, *J* = 6.5 Hz, 3H, C4-$C\mathbf{H}_3$); ^{13}C nmr (75.5 MHz,

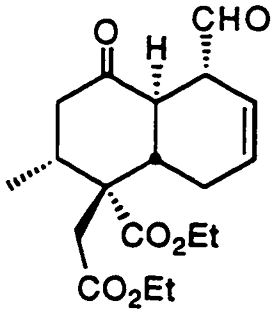
$CDCl_3$) δ 212.1 (p), 172.3 (p), 170.7 (p), 127.8 (a), 126.6 (a), 66.4 (p), 61.2 (p), 60.6 (p), 52.3 (p), 47.8 (a), 46.6 (p), 42.9 (a), 38.4 (a), 37.5 (a), 36.1 (p), 27.5 (p), 17.5 (a), 14.5 (a) and 14.2 (a).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-10-carboxy-5-(carbethoxymethyl)-4-methylbicyclo[4.4.0]dec-8-en-2-one (40)



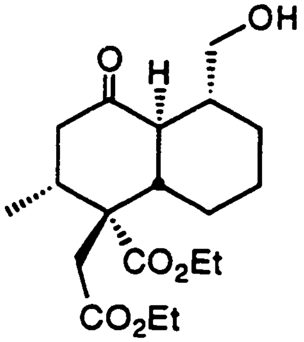
Alcohol **39** (14.3 mg, 0.041 mmol) was dissolved in acetone (2 mL, distilled from $KMnO_4$) and the solution was cooled to 10°C. Jones reagent (0.15 mL, 2.7M) was introduced dropwise and the resulting mixture was stirred for 15 minutes. Water was then added to dissolve all of the green precipitates and the aqueous solution was extracted with dichloromethane (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate and filtered. After concentration, the residue was subjected to flash chromatography. Elution with 40% ethyl acetate in hexanes afforded acid **40** (3.5 mg, 23% yield): FT-ir ($CHCl_3$, cast) 2500-3400 cm^{-1} (OH, carboxylic acid), 1712 cm^{-1} (C=O, acid, esters and ketone), 1197 cm^{-1} (C-O stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 5.74-5.82 (m, 1H, C9-**H**), 5.66 (br d, J = 10 Hz, 1H, C8-**H**), 4.28 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 4.10 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.09 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 3.57 (dd, J = 12.5, 10 Hz, 1H, C1-**H**), 3.43 (dm, J = 10 Hz, 1H, C10-**H**), 2.95 (d, J = 15 Hz, 1H, $-CH_2CO_2Et$), 2.94 (dd, J = 13, 13 Hz, 1H, C3-H), 2.83 (d, $J = 15$ Hz, 1H, $-CH_2CO_2Et$), 2.18-2.50 (m, 4H), 1.89 (m, 1H), 1.32 (t, $J = 7$ Hz, 3H, $-OCH_2CH_3$), 1.22 (t, $J = 7$ Hz, 3H, $-OCH_2CH_3$) and 1.04 (d, $J = 7$ Hz, 3H, $C4-CH_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 209.6 (p), 178.1 (p), 172.1 (p), 170.7 (p), 127.4 (a), 123.5 (a), 61.4 (p), 60.7 (p), 52.0 (p), 47.5 (a), 45.7 (p), 43.1 (a), 41.0 (a), 36.8 (a), 35.9 (p), 27.6 (p), 17.4 (a), 14.4 (a) and 14.2 (a); hreims M^+ 366.1693 (calculated for $C_{19}H_{26}O_7$: 366.1678).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-formyl-4-methylbicyclo[4.4.0]dec-8-en-2-one (41)



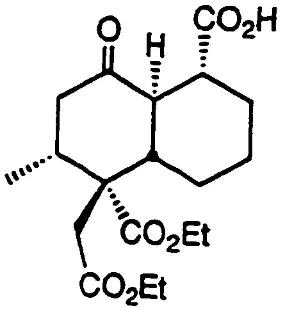
A solution of oxalyl chloride (19.4 mg, 0.08 mmol) in dry dichloromethane (5 mL) was cooled to -55°C under an argon atmosphere. After addition of dimethyl sulfoxide (24 mg, 0.15 mmol), the mixture was stirred for 10 minutes. A solution of alcohol **39** (24.5 mg, 0.07 mmol) in dichloromethane (1.5 mL) was added dropwise and stirring was continued under the same conditions for 15 minutes. Dry triethylamine (0.04 mL, 0.35 mmol) was introduced dropwise. The reaction mixutre was stirred for 5 minutes at -55°C and then allowed to warm up to room temperature with stirring. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed consecutively with 1N HCl, water, 5% sodium bicarbonate and brine. Drying (magnesium sulfate), filtration and evaporation gave the crude product which was subjected to flash chromatography (using 15 % ethyl acetate in hexanes as an eluant) to give aldehyde **41** (12.8 mg, 0.04 mmol) in 52% yield: FT-ir ($CHCl_3$, cast) 2979 cm^{-1} (alkane C-H stretching), 1722 cm^{-1} (C=O, aldehyde, ketone and esters), 1196 cm^{-1} (C-O stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1 Hz, 1H, -CHO), 5.72 (m, 1H, C9-**H**), 5.60 (dm, *J* = 10 Hz, 1H, C8-**H**), 4.20 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 4.06 (q, *J* = 7.5 Hz, 1H, $-OCH_2CH_3$), 4.04 (q, *J* = 7.5 Hz, 1H, $-OCH_2CH_3$), 3.35-3.50 (m, 2H), 2.9 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.88 (dd, *J* = 13.5, 13 Hz, 1H), 2.78 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.18-2.42 (m, 4H), 1.8 (m, 1H), 1.28 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3H, $-OCH_2CH_3$) and 0.98 (d, *J* = 7 Hz, 3H, $C4-CH_3$).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]decan-2-one (42)



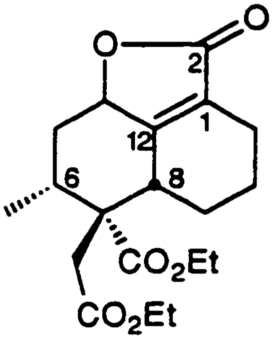
A mixture of alcohol **39** (99.2 mg, 0.28 mmol) and 5% Pd/C (19 mg) in ethyl acetate (20 mL) was purged twice with hydrogen gas and then shaken under 25 p.s.i. of hydrogen for 6 hours. Filtration through celite and concentration under reduced pressure provided the crude product. Purification by flash chromatography, using 15% ethyl acetate in hexanes, gave compound **42** (88.2 mg, 0.25 mmol) as a colorless oil in 89% yield: FT-ir ($CHCl_3$, cast) 3446 cm^{-1} (OH), 2929 cm^{-1} (alkane C-H stretching), 1723 cm^{-1} (C=O, ketone and esters) and 1190 cm^{-1} (C-O streching); ^1H nmr (300 MHz, $CDCl_3$) δ 4.25 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 4.24 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 4.12 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 4.10 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 3.58 (dd, *J* = 11, 4.5 Hz, 1H, $-CH_2-OH$), 3.45 (dd, *J* = 11, 4 Hz, 1H, $-CH_2-OH$), 3.01 (ddd, *J* = 13, 13, 1 Hz, 1H, C1-**H**), 2.88-2.98 (m, 2H), 2.79 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.40 (m, 1H, C4-**H**), 2.23 (dd, *J* = 12.5, 5 Hz, 1H, C3-**H**), 2.05 (br d, *J* = 13 Hz, 1H), 1.73-1.94 (m, 5H), 1.33 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.01-1.30 (m, 3H), 1.23 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$) and 1.01 (d, *J* = 7 Hz, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 213.3 (p), 172.3 (p), 170.8 (p), 67.8 (p), 61.0 (p), 60.6 (p), 52.5 (a), 47.8 (a), 47.3 (p), 39.4 (a), 38.7 (a), 36.2 (p), 29.3 (p), 28.3 (p), 25.2 (p), 17.5 (a), 14.4 (a) and 14.3 (a); hreims M^+ 354.2029 (calculated for $C_{19}H_{30}O_6$: 354.2043).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-4-methyl-2-oxo-10-bicyclo[4.4.0]decanecarboxylic acid (43)



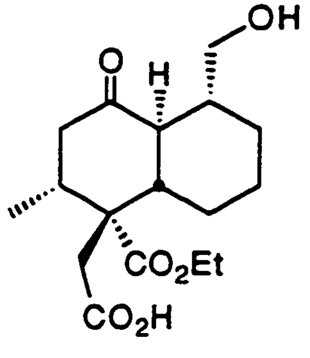
A solution of alcohol **42** (75.6 mg, 0.21 mmol) in acetone (4 mL, distilled from $KMnO_4$) was cooled to 10°C. Jones reagent (0.8 mL, 2.7M solution) was then introduced dropwise and the resulting mixture was stirred for 2 hours. Water (2 mL) was added to dissolve the green precipitate formed during the reaction and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic extracts were combined, washed with brine and dried over magnesium sulfate. Filtration and concentration provided the crude product, which was subjected to purification by flash chromatography. Elution with 50% ethyl acetate in hexanes gave acid **43** (53.4 mg, 0.16 mmol) in 68% yield: FT-ir ($CHCl_3$, cast) 2500-3500 cm^{-1} (OH, carboxylic acid), 2938 cm^{-1} (alkane C-H stretching), 1715 cm^{-1} (C=O, acid, ketone and esters), 1191 cm^{-1} (C-O stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 4.23 (q, *J* = 7 Hz, 1H, $-OCH_2CH_3$), 4.08 (m, 2H, $-OCH_2CH_3$), 3.24 (dd, *J* =12, 12 Hz, 1H, C1-H), 2.85-2.97 (m, 1H, C10-H), 2.9 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.79 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.17-2.42 (m, 3H), 1.98-2.09 (m, 3H), 1.78-1.89 (m, 2H), 1.31 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.16-1.34 (m, 2H), 1.2 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$) and 0.98 (d, *J* = 6.5 Hz, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 209.8 (p), 180.7 (p), 172.1 (p), 170.8 (p), 61.2 (p), 60.6 (p), 52.1 (p), 50.8 (a), 46.0 (p), 45.5 (a), 43.3 (a), 37.6 (a), 36.0 (p), 29.2 (p), 27.9 (p), 25.2 (p), 17.4 (a), 14.5 (a) and 14.3 (a); hreims M^+ 368.1846 (calculated for $C_{19}H_{28}O_7$: 368.1835).

(6R*,7R*,8S*)-7-Carbethoxy-7-(carbethoxymethyl)-6-methyl-3-oxatricyclo[6.3.1.0^{4,12}]dodec-1-en-2-one (44)



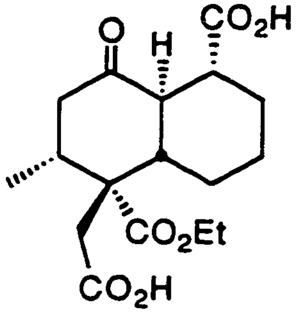
Keto acid **43** (15 mg, 0.041 mmol) was dissolved in dry benzene (15 mL). *p*-TsOH (7.7 mg, 0.04 mmol) was added and the resulting mixture was heated to reflux under an argon atmosphere for 16 hours with azeotropic removal of water. After being cooled to room temperature and diluted with benzene, the solution was washed with half saturated sodium bicarbonate, water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by flash chromatography (using 15% ethyl acetate in hexane as an eluant) to give lactone **44** (13.2 mg, 0.038 mmol) in 92% yield: FT-ir ($CHCl_3$, cast) 2939 cm^{-1} (alkane C-H stretching), 1755 cm^{-1} (C=O, lactone) and 1721 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 4.76 (m, 1H, C4-**H**), 4.17 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 4.09 (q, J = 7 Hz, 2H, $-OCH_2CH_3$), 3.17 (m, 1H, C8-**H**), 3.04 (d, J = 15 Hz, 1H, $-CH_2CO_2Et$), 2.70 (d, J = 15 Hz, 1H, $-CH_2CO_2Et$), 1.79-2.37 (m, 8H), 1.45-1.61 (m, 1H), 1.28 (t, J = 7 Hz, 3H, $-OCH_2CH_3$), 1.20 (t, J = 7 Hz, 3H, $-OCH_2CH_3$) and 0.99 (d, J = 7 Hz, 3H, C6-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 173.4 (p), 171.5 (p), 171.3 (p), 164.5 (p), 125.0 (p), 78.3 (a), 61.1 (p), 60.7 (p), 54.7 (p), 37.0 (a), 36.4 (p), 35.9 (p), 33.1 (a), 24.1 (p), 22.1 (p), 19.7 (p), 16.6 (a), 14.3 (a) and 14.1 (a); hreims M^+ 350.1724 (calculated for $C_{19}H_{26}O_6$: 350.1729).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carboxymethyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]decan-2-one (45)



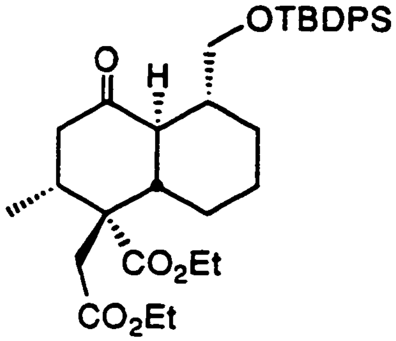
Ester **42** (28.8 mg, 0.081 mmol) was dissolved in THF-1N LiOH (4 : 1, 10 mL) and the solution was heated to reflux for 5 hours. After being cooled to room temperature and diluted with ether (15 mL), the reaction mixture was acidified (pH ~3) with 1N HCl. The organic layer was separated and washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography. Elution with 45% ethyl acetate in hexanes afforded acid **45** (24.1 mg, 91% yield): FT-ir ($CHCl_3$, cast) 3300 cm^{-1} (very broad, OH, carboxylic acid and alcohol), 2928 cm^{-1} (alkane C-H stretching) and 1712 cm^{-1} (C=O, ketone, acid and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.26 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.25 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 3.58 (dd, J = 10.5, 4 Hz, 1H, $-CH_2-OH$), 3.45 (dd, J = 10.5, 4 Hz, 1H, $-CH_2-OH$), 2.91-3.05 (m, 3H), 2.83 (d, J = 15 Hz, 1H, $-CH_2CO_2H$), 2.49 (m, 1H), 2.25 (dd, J = 12.5, 4.5 Hz, 1H, C3-**H**), 1.73-2.11 (m, 6H), 1.34 (t, J = 7 Hz, 3H, $-OCH_2CH_3$), 1.21-1.33 (m, 3H) and 1.02 (d, J = 6.5 Hz, 3H, C4-CH_3).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-10-carboxy-5-(carboxymethyl)-4-methylbicyclo[4.4.0]decan-2-one (46)



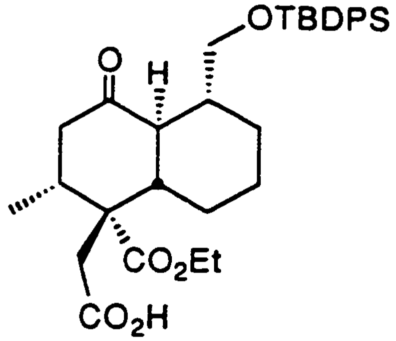
Freshly prepared Jones reagent (0.28 mL, 2.7M solution) was added dropwise to a stirred solution of **45** (24.7 mg, 0.076 mmol) in acetone (5 mL) at 10°C. Stirring was continued for 1.5 hour. Water was then added to dissolve the green precipitate and the resulting mixture was extracted with dichloromethane (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography, using a solution of ethyl acetate, ethanol and hexane (9 : 1 : 10) as the eluant, to give diacid **46** (13.7 mg, 0.04 mmol) in 53% yield: FT-ir ($CHCl_3$, cast) 2500-3550- cm^{-1} (OH, carboxylic acid), 2961 cm^{-1} (alkane C-H stretching) and 1717 cm^{-1} (C=O, ketone, ester and acids); ^1H nmr (300 MHz, $CDCl_3$) δ 4.23 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 4.22 (q, J = 7 Hz, 1H, $-OCH_2CH_3$), 3.21 (dd, J = 11.5, 11.5 Hz, 1H, C1-**H**), 2.90 (d, J = 15 Hz, 1H, $-CH_2CO_2H$), 2.88 (dd, J = 13.5, 13.5 Hz, 1H, C3-**H**), 2.81 (d, J = 15 Hz, 1H, $-CH_2CO_2H$), 2.26-2.44 (m, 2H), 2.20 (dd, J = 13.5, 5 Hz, 1H, C3-**H**), 1.76-2.08 (m, 4H), 1.49-1.68 (m, 1H), 1.18-1.32 (m, 2H), 1.28 (t, J = 7 Hz, 3H, $-OCH_2CH_3$) and 0.97 (d, J = 7 Hz, 3H, C4-CH_3).

(1R*,4R*,5R*,6S*,10R*)-10-(*tert*-Butyldiphenylsiloxymethyl)-5-carbethoxy-5-(carbethoxymethyl)-4-methylbicyclo[4.4.0]decan-2-one (47)



Alcohol **42** (47.9 mg, 0.14 mmol) was dissolved in dry THF (3 mL). Imidazole (27.9 mg, 0.41 mmol) was added and the resulting mixture was stirred at room temperature for 5 minutes under an argon atmosphere. *tert*-Butylchlorodiphenylsilane (148.9 mg, 0.14 mL, 0.54 mmol) was then introduced forming a cloudy white suspension. The reaction mixture was stirred at room temperature for 18 hours, then quenched with water and extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The obtained crude product was purified by flash chromatography on silica gel. Elution with 3% ethyl acetate in hexanes afforded compound **47** (71 mg, 0.12 mmol) in 87% yield: FT-ir ($CHCl_3$, cast) 3071 cm^{-1} (aromatic C-H stretching), 1723 cm^{-1} (C=O, esters), 1712 cm^{-1} (C=O, ketone), 1188 cm^{-1} (C-O stretching) and 1111 cm^{-1} (Si-O-C stretching); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.65 (m, 4H, Ar**H**), 7.40 (m, 6H, Ar**H**), 4.24 (m, 2H, -OC**H**$_2$CH$_3$), 4.10 (m, 2H, -OC**H**$_2$CH$_3$), 3.75 (dd, J = 10, 5 Hz, 1H, -C**H**$_2$-OSiR), 3.68 (dd, J = 10, 2.5 Hz, 1H, -C**H**$_2$-OSiR), 3.17 (dd, J = 12, 11 Hz, 1H, C1-**H**), 2.96 (ddd, J = 12.5, 12.5, 1 Hz, 1H, C3-**H**), 2.95 (d, J = 15 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.77 (d, J = 15 Hz, 1H, -C**H**$_2$CO$_2$Et), 2.37 (m, 1H, C4-**H**), 2.14 (dd, J = 12.5, 5 Hz, 1H, C3-**H**), 2.03-2.11 (m, 1H), 1.78-1.92 (m, 4H), 1.15-1.45 (m, 3H), 1.29 (t, J = 7 Hz, 3H, -OCH$_2$C**H**$_3$), 1.22 (t, J = 7 Hz, 3H, -OCH$_2$C**H**$_3$), 1.08 (s, 9H, -C(C**H**$_3$)$_3$) and 1.04 (d, J = 7 Hz, 3H, C4-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 211.8 (p), 172.3 (p), 170.9 (p), 135.7 (a), 135.6 (a), 134.1 (p), 134.1 (p), 129.5 (a), 127.6 (a), 66.3 (p), 60.9 (p), 60.5 (p), 52.7 (p), 49.1 (a), 47.9 (a), 47.4 (p), 38.1 (a), 38.0 (a), 36.4 (p), 28.6 (p), 28.5 (p), 27.0 (a), 25.2 (p), 19.5 (p), 17.5 (a), 14.5 (a) and 14.3 (a); hreims M$^+$ ion was not observed; [M$^+$-57] 535.2505 (calculated for $C_{31}H_{39}O_6Si$: 535.2516).

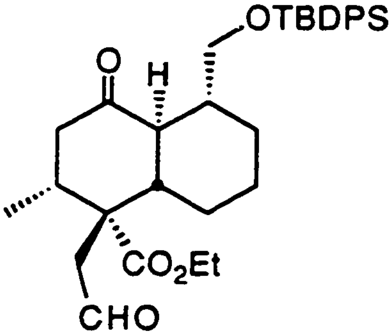
(1R*,4R*,5R*,6S*,10R*)-10-(*tert*-Butyldiphenylsiloxymethyl)-5-carbethoxy-5-(carboxymethyl)-4-methylbicyclo[4.4.0]decan-2-one (48)



Silyl ether **47** (34.6 mg, 0.058 mmol) was dissolved in 2.5 mL of THF. 1N LiOH (0.8 mL) was added and the resulting solution was stirred at room temperature for 25 hours. The reaction mixture was then diluted with water, acidified with 1N HCl and extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography. Elution with 10% ethyl acetate in hexanes gave starting material **47** (5.8 mg, recovery yield). Further elution with 15% ethyl acetate in hexanes afforded the desired acid **48** (20.9 mg, 0.037 mmol) in 77% yield (based on the consumed starting material): FT-ir ($CHCl_3$, cast) 2500-3500 cm^{-1} (OH, carboxylic acid), 3071 cm^{-1} (aromatic C-H stretching), 1712 cm^{-1} (C=O, acid, ester and ketone), 1191 cm^{-1} (C-O stretching) and 1111 cm^{-1} (Si-O-C stretching); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.65 (m, 4H, Ar**H**), 7.43 (m, 6H, Ar**H**), 4.27 (q, J = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 4.24 (q, J = 7 Hz, 1H, -OC**H**$_2$CH$_3$), 3.75 (dd, J = 10, 5 Hz, 1H, -C**H**$_2$-OSiR), 3.67 (dd, J = 10, 2.5 Hz, 1H, -C**H**$_2$-OSiR), 3.18 (dd, J = 11, 11 Hz, 1H, C1-**H**), 3.00 (d, J = 15 Hz, 1H, -C**H**$_2$CO$_2$H), 2.98 (dd, J = 12.5, 12.5 Hz, 1H, C3-**H**), 2.83 (dd, J = 15 Hz, 1H, -C**H**$_2$CO$_2$H), 2.42 (m, 1H, C4-**H**), 2.16 (dd, J = 12.5, 5 Hz, 1H, C3-**H**), 1.77-2.08 (m, 6H), 1.15-1.42 (m, 3H), 1.29 (t, J = 7 Hz, 3H, -OCH$_2$C**H**$_3$), 1.05 (s, 9H, -C(C**H**$_3$)$_3$) and 1.02 (d, J = 7 Hz, 3H, C4-C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 212.1 (p), 176.0 (p), 172.2 (p), 135.7 (a), 135.6 (a), 134.1 (p), 129.5 (a), 127.6

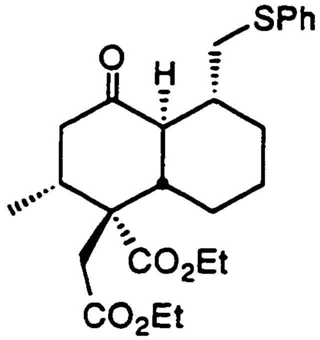
(a), 66.3 (p), 61.1 (p), 52.6 (p), 49.2 (a), 47.8 (a), 47.4 (p), 39.1 (a), 37.9 (a), 36.1 (p), 28.5 (p), 27.0 (a), 25.1 (p), 19.5 (p), 17.5 (a) and 14.4 (a).

(1R*,4R*,5R*,6S*,10R*)-10-(*tert*-Butyldiphenylsiloxymethyl)-5-carbethoxy-4-methyl-5-(2-oxoethyl)bicyclo[4.4.0]decan-2-one (49)



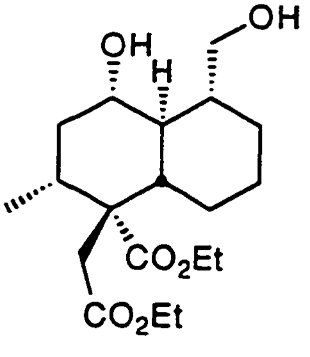
Acid **48** (32.4 mg, 0.057 mmol) was dissolved in dry THF (2 mL). BH_3·THF (0.23 mL, 1M solution in THF, 0.23 mmol) was added dropwise. Evolution of hydrogen gas persisted for 5 minutes and the resulting solution was stirred at room temperature and under an argon atmosphere for additional 2 hours. Solvent was then removed in vacuo and the crude reduction product was redissolved in dichloromethane (3 mL). Pyridinium chlorochromate (PCC) (123.3 mg, 0.57 mmol) was introduced in one portion and the reaction mixture was stirred at room temperature for 6 hours. After filtration through celite, washing with dichloromethane and concentration, the crude product was obtained. Flash chromatography of the crude product, eluting with 10% ethyl acetate in hexanes, gave aldehyde **49** (24.4 mg, 0.044 mmol) as a colorless oil in 78% yield: FT-ir ($CHCl_3$, cast) 3070 cm^{-1} (aromatic C-H stretching), 1712 cm^{-1} (C=O, aldehyde, ketone and ester), 1191 cm^{-1} (C-O stretching) and 1111 cm^{-1} (Si-O-C stretching); ^1H nmr (300 MHz, $CDCl_3$) δ 9.79 (t, J = 3 Hz, 1H, -CHO), 7.62 (m, 4H, ArH), 7.38 (m, 6H, ArH), 4.27 (m, 2H, $-OCH_2CH_3$), 3.76 (dd, J = 10, 4.5 Hz, 1H, -CH_2-OSiR), 3.66 (dd, *J* = 10, 2.5 Hz, 1H, -CH_2-OSiR), 3.20 (dd, *J* = 11.5, 11.5 Hz, 1H, C1-**H**), 2.97 (dd, *J* = 12, 12 Hz, 1H, C3-**H**), 2.91 (dd, *J* = 16.5, 3 Hz, 1H, -CH_2-CHO), 2.81 (dd, *J* = 16.5, 3 Hz, 1H, -CH_2CHO), 2.10-2.28 (m, 2H), 1.56-1.99 (m, 8H), 1.08-1.43 (m, 1H), 1.30 (t, *J* = 7 Hz, 3H, -OCH_2CH_3), 1.05 (s, 9H, -$C(CH_3)_3$) and 1.03 (d, *J* = 7 Hz, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 211.6 (p), 201.0 (a), 172.0 (p), 135.7 (a), 135.6 (a), 134.0 (p), 129.5 (a), 127.6 (a), 66.1 (p), 61.1 (p), 52.9 (p), 49.5 (a), 49.2 (a), 47.4 (p), 46.4 (p), 40.7 (a), 37.9 (a), 28.6 (p), 28.4 (p), 27.0 (a), 25.2 (p), 19.5 (p), 17.7 (a) and 14.5 (a).

(1R*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-4-methyl-10-[(phenylthio)methyl]bicyclo[4.4.0]decan-2-one (51)

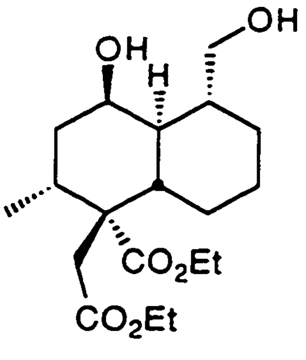


A solution of keto alcohol **42** (39.6 mg, 0.11 mmol) and thiophenol (18.5 mg, 0.17 mmol) in dry dichloromethane (5 mL) was cooled to 0°C under an argon atmosphere. $BF_3 \cdot OEt_2$ (7.95 mg, 0.056 mmol) was added. The mixture was warmed up to room temperature and stirred for 16 hours. Then ice-cold 5% NaOH (5 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The organic layer and the extracts were combined, washed with 5% NaOH, water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product, which was purified by flash chromatography. Elution with 5% ethyl acetate in hexanes afforded thioether **51** (46 mg, 0.1 mmol) in 93% yield: FT-ir ($CHCl_3$, cast) 2929 cm^{-1} (alkane C-H stretching), 1723 (C=O, esters) and 1711 cm^{-1} (C=O, ketone); ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7, 1 Hz, 2H, Ar**H**), 7.27 (t, *J* = 7 Hz, 2H, Ar**H**), 7.13 (t, *J* = 7 Hz, 1H, Ar**H**), 4.26 (m, 2H, -$OC\mathbf{H}_2CH_3$), 4.08 (m, 2H, -$OC\mathbf{H}_2CH_3$), 3.36 (dd, *J* = 13, 3 Hz, 1H, -$C\mathbf{H}_2$-SPh), 3.07 (dd, *J* = 12, 11 Hz, 1H, C1-**H**), 2.91 (d, *J* = 15 Hz, 1H, -$C\mathbf{H}_2CO_2Et$), 2.87 (ddd, *J* = 13, 12, 1 Hz, 1H, C3-**H**), 2.78 (dd, *J* = 13, 8 Hz, 1H, -$C\mathbf{H}_2$-SPh), 2.76 (d, *J* = 15 Hz, 1H, -$C\mathbf{H}_2CO_2Et$), 2.37 (m, 1H, C4-**H**), 2.14 (dd, *J* = 12, 5 Hz, 1H, C3-**H**), 2.02-2.09 (m, 2H), 1.94-2.02 (m, 1H, C10-**H**), 1.85 (ddd, *J* = 12, 12, 3.5 Hz, 1H, C6-**H**), 1.78 (ddd, *J* = 13, 3.5, 3.5 Hz, 1H), 1.32 (t, *J* = 7 Hz, 3H, -$OCH_2C\mathbf{H}_3$), 1.22 (t, *J* = 7 Hz, 3H, -$OCH_2C\mathbf{H}_3$), 0.90-1.30 (m, 3H) and 1.00 (d, *J* = 7 Hz, 3H, C4-$C\mathbf{H}_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 211.7 (p), 172.3 (p), 170.7 (p), 137.5 (p), 128.8 (a), 128.5 (a), 125.3 (a), 61.0 (p), 60.6 (p), 52.5 (p), 52.6 (a), 47.9 (a), 47.3 (p), 39.0 (a), 38.3 (p), 36.2 (p), 35.7 (a), 30.2 (p), 28.4 (p), 25.0 (p), 17.5 (a), 14.5 (a) and 14.2 (a); hreims M^+ 446.2122 (calculated for $C_{25}H_{34}O_5S$: 446.2127).

(1R*,2S*,4R*,5R*,6S*,10R*)-5-Carbethoxy-5-(carbethoxy-methyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]decan-2-ol (52) and (1R*, 2R*,4R*,5R*,6S*,10R*)-5-carbethoxy-5-(carbethoxy-methyl)-10-(hydroxymethyl)-4-methylbicyclo[4.4.0]decan-2-ol (53)



52



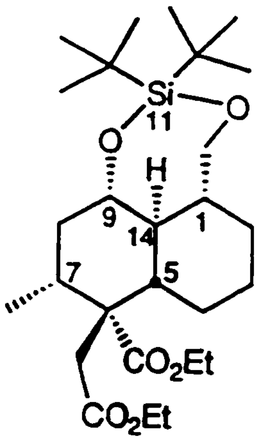
53

A solution of keto alcohol **42** (87.2 mg, 0.25 mmol) in dry THF (3 mL) was cooled to 0°C and stirred under an argon atmosphere. Lithium tri-*tert*-butoxyaluminohydride (0.49 mL, 1M solution in THF, 0.49 mmol) was added dropwise to the above solution and stirring was continued for 0.5 hour. The reaction mixture was then poured into ice-cold 1N HCl (3 mL) and the products were extracted with ether (3 x 10 mL). The combined ethereal extracts were washed with water, saturated bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography, using a solution of 20% ethyl acetate in hexanes as the eluant, to give diol **52** (38.2 mg, 0.11 mmol) as a colorless oil in 43% yield: FT-ir ($CHCl_3$, cast) 3279 cm^{-1} (OH), 2926 cm^{-1} (alkane C-H stretching) and 1723 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 4.16 (q, J = 7 Hz, 2H, -O**CH_2**CH_3), 4.11 (m, 2H, -O**CH_2**CH_3), 3.72 (dd, J = 11.5, 2 Hz, 1H, -**CH_2**-OH), 3.54 (dd, J = 11.5, 6 Hz, 1H, -**CH_2**-OH), 3.48 (ddd, J = 10, 10, 5 Hz, 1H, C2-**H**), 3.18 (br s, 2H, -O**H**), 2.83 (d, J = 15 Hz, 1H, -**CH_2**CO_2Et), 2.77 (d, J = 15 Hz, 1H, -**CH_2**CO_2Et), 1.98-2.12 (m, 1H), 1.68-1.92 (m, 6H), 1.58 (br d, J = 10 Hz, 1H), 1.43 (ddd, J = 12, 12, 3 Hz, 1H), 1.28 (t, J = 7 Hz, 3H, -OCH_2**CH_3**), 1.24 (t, J = 7 Hz, 3H, -OCH_2**CH_3**), 1.12-1.31 (m, 3H) and 0.93 (d, J = 7 Hz, 3H, C4-**CH_3**); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 172.9 (p), 171.6 (p), 72.8 (a), 68.1 (p), 60.5 (p), 60.3

(p), 52.3 (p), 48.6 (a), 47.3 (a), 44.5 (a), 39.5 (p), 36.7 (p), 33.5 (a), 31.4 (p), 28.0 (p), 26.2 (p), 17.2 (a), 14.3 (a) and 14.2 (a); hreims M+ 356.2197 (calculated for $C_{19}H_{32}O_6$: 356.2198).

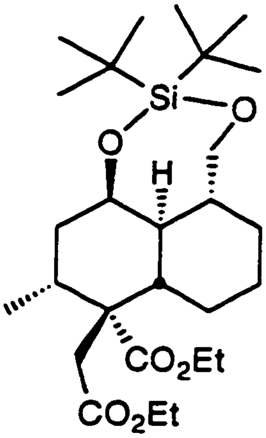
Further elution with the same solvent system afforded diol **53** (40.3 mg, 0.11 mmol) as a colorless oil in 46% yield: FT-ir ($CHCl_3$, cast) 3423 cm^{-1} (OH), 2922 cm^{-1} (alkane C-H stretching), 1720 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 4.07-4.19 (m, 5H, $-OCH_2CH_3$ and C2-**H**), 3.68 (dd, *J* = 10.5, 6 Hz, 1H, $-CH_2$-OH), 3.56 (dd, *J* = 10.5, 3.5 Hz, 1H, $-CH_2$-OH), 2.83 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.77 (d, *J* = 15 Hz, 1H, $-CH_2CO_2Et$), 2.39 (m, 1H), 2.23 (br s, 2H, -O**H**), 1.85-2.02 (m, 2H), 1.63-1.83 (m, 3H), 1.54 (m, 1H), 1.27 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.25 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 1.22-1.33 (m, 1H), 0.96-1.11 (m, 1H), 0.85-0.94 (m, 1H) and 0.88 (d, *J* = 7 Hz, 3H, C4-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 173.2 (p), 171.9 (p), 66.7 (p), 65.9 (a), 60.3 (p), 60.2 (p), 52.4 (p), 45.1 (a), 41.8 (a), 38.5 (a), 37.2 (p), 36.6 (p), 30.1 (p), 28.3 (a), 27.8 (p), 26.1 (p), 17.1 (a), 14.4 (a) and 14.3 (a); hreims M+ 356.2191 (calculated for $C_{19}H_{32}O_6$: 356.2198).

(1R*,5S*,6R*,7R*,9S*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-6-(carbethoxymethyl)-7-methyl-10,12-dioxa-11-silatricyclo-[7.4.1.$0^{5,14}$]tetradecane (54)



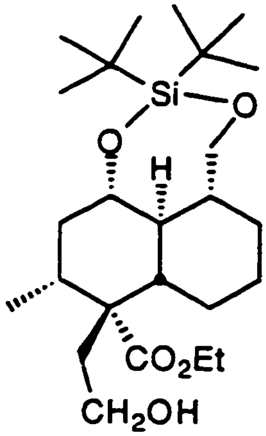
A solution of diol **52** (18 mg, 0.05 mmol) and pyridine (12 mg, 0.15 mmol) in THF (3 mL) was cooled to 0°C and stirred under an argon atmosphere. Di-*tert*-butylsilyl ditriflate (26.7 mg, 0.06 mmol) was added to the above solution and the resulting mixture was stirred for 5 minutes. Then water was added (2 mL), the mixture was warmed up to room temperature and extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography, eluting with 5% ethyl acetate in hexanes, to give compound **54** (22.3 mg, 0.045 mmol) in 89% yield: FT-ir ($CHCl_3$, cast) 2931 cm^{-1} (alkane C-H stretching) and 1725 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 4.12 (m, 4H, $-OC\mathbf{H}_2CH_3$), 3.84 (dd, *J* = 12, 9 Hz, 1H, $-C\mathbf{H}_2$-OSi-), 3.73 (ddd, *J* = 10.5, 10.5, 5 Hz, 1H, C9-**H**), 3.59 (dd, *J* = 12, 1.5 Hz, 1H, $-C\mathbf{H}_2$-OSi-), 2.83 (d, *J* = 15 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 2.76 (d, *J* = 15 Hz, 1H, $-C\mathbf{H}_2CO_2Et$), 1.78-2.10 (m, 3H), 1.61 (m, 3H), 1.53 (m, 2H), 1.16-1.41 (m, 2H), 1.27 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$), 1.23 (t, *J* = 7 Hz, 3H, $-OCH_2C\mathbf{H}_3$), 0.82-1.08 (m, 2H), 1.00 (br s, 18H) and 0.91 (d, *J* = 7 Hz, 3H, C7-$C\mathbf{H}_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 173.0 (p), 171.7 (p), 75.5 (a), 71.4 (p), 60.4 (p), 60.3 (p), 52.4 (p), 50.9 (a), 47.2 (a), 44.3 (a), 39.9 (p), 36.8 (p), 33.9 (a), 30.7 (p), 28.7 (a), 28.3 (a), 27.8 (p), 26.0 (p), 21.2 (p), 21.0 (p), 17.2 (a) and 14.4 (a).

(1R*,5S*,6R*,7R*,9R*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-6-(carbethoxymethyl)-7-methyl-10,12-dioxa-11-silatricyclo [7.4.1.$0^{5,14}$]tetradecane (55)



To a solution of diol **53** (25 mg, 0.07 mmol) in dry THF (3 mL), pyridine (16.6 mg, 0.21 mmol) was introduced, followed by addition of di-*tert*-butylsilyl ditriflate (37.1 mg, 0.08 mmol). The resulting mixture was stirred at 0°C and under an argon atmosphere for 25 minutes. Water was then added (2 mL) and the product was extracted into ether (3 x 5 mL). The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (using 5% ethyl acetate in hexanes as an eluant) to give cyclic silyl ether **55** (30.3 mg, 0.06 mmol) as a colorless oil in 87% yield: FT-ir ($CHCl_3$, cast) 2962 cm^{-1} (alkane C-H stretching) and 1723 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 4.49 (ddd, J = 3.5, 3, 3 Hz, 1H, C9-**H**), 4.14 (m, 4H, -OCH_2CH_3), 3.99 (dd, J = 11.5, 11 Hz, 1H, -CH_2-OSi-), 3.74 (dd, J = 11.5, 1.5 Hz, 1H, -CH_2-OSi-), 2.88 (d, J = 14 Hz, 1H, -CH_2CO_2Et), 2.76 (d, J = 14 Hz, 1H, -CH_2CO_2Et), 2.37 (m, 1H), 1.49-2.09 (m, 11H), 1.29 (t, J = 7 Hz, 3H, -OCH_2CH_3), 1.28 (t, J = 7 Hz, 3H, -OCH_2CH_3), 1.03 (br s, 18H, -C(CH_3)$_3$) and 0.95 (d, *J* = 7 Hz, 3H, C7-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 173.2 (p), 171.5 (p), 70.7 (p), 67.5 (a), 60.3 (p), 60.2 (p), 52.7 (p), 48.2 (a), 45.5 (a), 40.8 (a), 37.1 (p), 36 9 (p), 30.8 (p), 28.7 (a), 28.5 (a), 28.2 (a), 28.0 (p), 26.8 (p), 22.5 (p), 20.6 (p), 17.3 (a), 14.5 (a) and 14.3 (a).

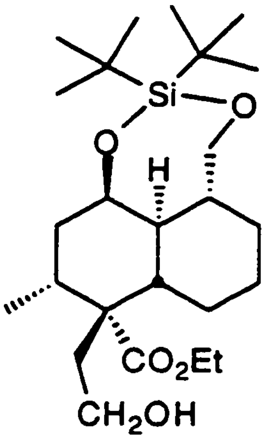
(1R*,5S*,6R*,7R*,9S*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-6-(2-hydroxyethyl)-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.0^{5,14}]-tetradecane (56)



Diester **54** (24.1 mg, 0.049 mmol) was dissolved in dry benzene (2 mL) and stirred at 5-10°C under an argon atmosphere. Sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) (11.7 mg, 0.058 mmol) was then added and the resulting mixture was stirred for 4 hours. The reaction was quenched with saturated ammonium chloride, diluted with 1N HCl to dissolve the white precipitate of aluminum hydroxide formed, and extracted with dichloromethane (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes gave alcohol **56** (18.8 mg, 0.044 mmol) in 91% yield: FT-ir ($CHCl_3$, cast) 3424

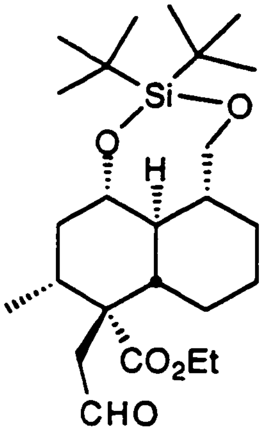
cm^{-1} (OH), 2931 cm^{-1} (alkane C-H stretching) and 1720 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7 Hz, 2H, $-OCH_2CH_3$), 3.87 (dd, *J* = 12, 9 Hz, 1H, C9-**H**), 3.59-3.78 (m, 4H), 2.11 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.66-1.92 (m, 6H), 1.56 (br d, *J* = 12.5 Hz, 1H), 1.15-1.38 (m, 3H), 1.29 (t, *J* = 7 Hz, 3H, $-OCH_2CH_3$), 0.84-1.12 (m, 3H), 1.04 (s, 9H, $-C(CH_3)_3$), 1.02 (s, 9H, $-C(CH_3)_3$) and 0.92 (d, *J* = 6.5 Hz, 3H, C7-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 174.3 (p), 75.8 (a), 71.4 (p), 60.1 (p), 58.8 (p), 51.7 (p), 50.9 (a), 47.3 (a), 44.6 (a), 40.2 (p), 34.4 (p), 34.2 (a), 30.7 (p), 28.7 (a), 28.2 (a), 27.6 (p), 26.1 (p), 21.1 (p), 21.0 (p), 17.4 (a) and 14.4 (a).

(1R*,5S*,6R*,7R*,9R*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-6-(2-hydroxyethyl)-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.0^{5,14}]-tetradecane (57)



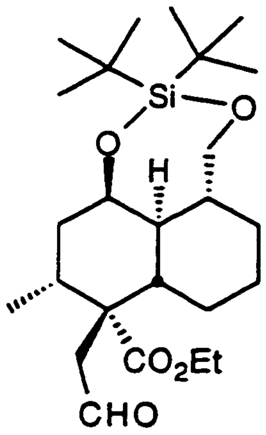
To a solution of **55** (32.1 mg, 0.065 mmol) in dry benzene (2 mL), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (15.6 mg, 0.08 mmol) was added. The resulting solution was stirred at 10°C and under an atmosphere of argon for 6 hours. The reaction was then quenched with saturated ammonium chloride, diluted with 1N HCl and extracted with dichloromethane (3 x 5 mL). The organic extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography, using 10% ethyl acetate in hexanes as an eluant, to give alcohol **57** (25.8 mg, 0.057 mmol) in 88% yield: FT-ir ($CHCl_3$, cast) 3463 cm^{-1} (OH), 2932 cm^{-1} (alkane C-H stretching) and 1718 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.47 (ddd, *J* = 7.5, 3, 3 Hz, 1H, C9-**H**), 4.12 (q, *J* = 7 Hz, 2H, -OC**H**$_2$CH$_3$), 3.97 (dd, *J* = 11.5, 9.5 Hz, 1H, C13-**H**), 3.62-3.79 (m, 3H), 1.90-2.24 (m, 4H), 1.72-1.89 (m, 3H), 1.44-1.68 (m, 5H), 1.2-1.39 (m, 1H), 1.26 (t, *J* = 7 Hz, 3H, -OCH$_2$C**H**$_3$), 1.03 (s, 9H, -C(C**H**$_3$)$_3$), 1.01 (s, 9H, -C(C**H**$_3$)$_3$), 0.83-0.98 (m, 2H) and 0.87 (d, *J* = 6.5 Hz, 3H, -OCH$_2$C**H**$_3$); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 174.3 (p), 70.6 (p), 67.7 (a), 59.9 (p), 58.9 (p), 51.8 (p), 48.3 (a), 45.8 (a), 40.7 (a), 37.0 (p), 34.3 (p), 30.8 (p), 28.6 (a), 28.3 (a), 28.3 (a), 28.1 (p), 26.9 (p), 22.4 (p), 20.7 (p), 17.2 (a) and 14.5 (a).

(1R*,5S*,6R*,7R*,9S*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-7-methyl-10,12-dioxa-6-(2-oxoethyl)-11-silatricyclo[7.4.1.0^{5,14}]-tetradecane (58)



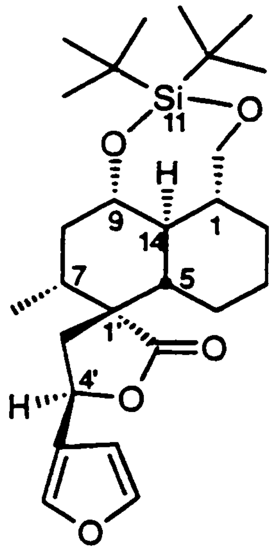
Alcohol **56** (23.4 mg, 0.052 mmol) was dissolved in dichloromethane (2 mL). Pyridinium dichromate (96.9 mg, 0.26 mmol) was added in one portion and the resulting mixture was stirred at room temperature under an argon atmosphere for 10 hours. After dilution with dichloromethane (5 mL), filtration through celite and concentration of the filtrate, the crude product was obtained. Flash chromatography of the crude product, eluting with a solution of 5% ethyl acetate in hexanes, afforded aldehyde **58** (18.4 mg, 0.041 mmol) in 79% yield as a white solid: FT-ir ($CHCl_3$, cast) 2935 cm^{-1} (alkane C-H stretching) and 1712 cm^{-1} (C=O, aldehyde and ester); ^1H nmr (300 MHz, $CDCl_3$) δ 9.88 (t, J = 2.5 Hz, 1H, -CHO), 4.18 (t, J = 7 Hz, 2H, $-OCH_2CH_3$), 3.87 (dd, J = 12, 8.5 Hz, 1H, C13-**H**), 3.72-3.83 (m, 1H, C9-**H**), 3.62 (dd, J = 12, 1.5 Hz, 1H, C13-**H**), 2.86 (dd, J = 15, 2.5 Hz, 1H, $-CH_2$-CHO), 2.80 (dd, J = 15, 2.5 Hz, 1H, $-CH_2$-CHO), 1.66-1.98 (m, 7H), 1.57 (br d, J = 13 Hz, 2H), 1.18-1.38 (m, 3H), 1.31 (t, J = 7 Hz, 3H, $-OCH_2CH_3$), 1.04 (s, 9H, $-C(CH_3)_3$), 1.03 (s, 9H, $-C(CH_3)_3$), 0.96 (d, J = 6.5 Hz, 3H, C7-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 202.2 (a), 172.6 (p), 75.4 (a), 71.3 (p), 60.6 (p), 52.7 (p), 50.9 (a), 47.0 (a), 47.0 (p), 46.1 (a), 40.1 (p), 35.8 (a), 30.6 (p), 28.7 (a), 28.2 (a), 27.9 (p), 26.0 (p), 21.2 (p), 21.0 (p), 17.4 (a) and 14.4 (a).

(1R*,5S*,6R*,7R*,9R*,14R*)-11,11-Di-*tert*-butyl-6-carbethoxy-7-methyl-10,12-dioxa-6-(2-oxaethyl)-11-silatricyclo[7.4.1.0^{5,14}]-tetradecane (59)

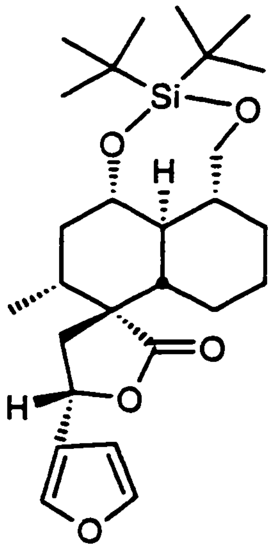


Pyridinium dichromate (73.7 mg, 0.19 mmol) was added to a solution of alcohol **57** (17.8 mg, 0.039 mmol) in dichloromethane (2 mL). The resulting solution was stirred at room temperature and under argon for 6 hours. Then the reaction mixture was diluted with 5 mL of dichloromethane, filtered through celite, dried over magnesium sulfate and concentrated. The residue was subjected to flash chromatography (elution with 10% ethyl acetate in hexanes) to provide aldehyde **59** (14.9 mg, 0.033 mmol) in 84% yield: FT-ir ($CHCl_3$, cast) 2932 cm^{-1} (alkane C-H stretching) and 1715 cm^{-1} (C=O, aldehyde and ester); ^1H nmr (200 MHz, $CDCl_3$) δ 9.89 (t, *J* = 3 Hz, 1H, -CHO), 4.51 (dd, *J* = 8, 3 Hz, 1H, C9-**H**), 4.17 (q, *J* = 7 Hz, 2H, -OCH_2CH_3), 3.99 (dd, *J* = 11.5, 9.5 Hz, 1H, C13-**H**), 3.74 (dd, *J* = 11.5, 2 Hz, 1H, C13-**H**), 2.85 (dd, *J* = 16, 3 Hz, 1H, -CH_2-CHO), 2.74 (dd, *J* = 16, 3 Hz, 1H, -CH_2-CHO), 2.17-2.34 (m, 1H), 2.03 (ddd, *J* = 13, 13, 3 Hz, 1H), 1.49-1.92 (m, 9H), 1.28 (t, *J* = 7 Hz, 3H, -OCH_2CH_3), 1.03 (s, 9H, -$C(CH_3)_3$), 1.02 (s, 9H, -$C(CH_3)_3$) 0.92-1.04 (m, 1H) and 0.93 (d, *J* = 7 Hz, 3H, C7-CH_3); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 202.5 (a). 172.7 (p), 70.5 (p), 67.4 (a), 60.4 (p), 52.4 (p), 48.3 (a), 47.2 (p), 45.5 (a), 42.7 (a), 36.9 (p), 30.6 (p), 30.4 (a), 28.6 (a), 28.3 (a), 28.1 (p), 26.8 (p), 22.5 (p), 20.7 (p), 17.3 (a) and 14.5 (a).

(1R*,4'R*,5S*,6R*,7R*,9S*,14R*)-11,11-Di-*tert*-butyl-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.$0^{5,14}$]tetradecane-6-spiro-1'-[4'-(3-furyl)-3'-oxacyclopentan-2'-one] (60) and (1R*,4'S*,5S*,6R*,7R*,9S*,14R*)-11,11-di-*tert*-butyl-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.$0^{5,14}$]tetradecane-6-spiro-1'-[4'-(3-furyl)-3'-oxacyclopentan-2'-one] (61)



60

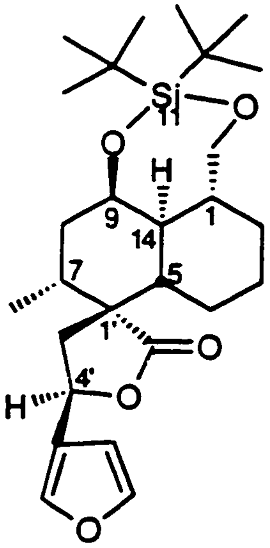


61

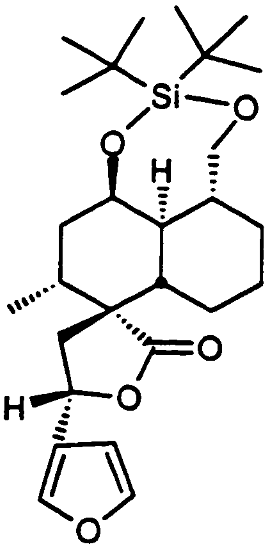
A solution of *n*-butyllithium in hexane (1.2 mmol, 0.75 mL, 1.6M) was added dropwise to a solution 3-bromofuran (1.44 mmol, 0.13 mL) in dry ether (4.1 mL) at -78°C under an argon atmosphere. The resulting solution was stirred for 30 minutes. A portion of this stock solution (0.11 mL, 0.026 mmol of 3-lithiofuran) was transfered to a pre-cooled (-78°C) solution of aldehyde **58** (10.8 mmol, 0.024 mmol) in ether (1 mL). The reaction mixture was stirred under argon for 15 minutes. Water was added and the resulting mixture extracted with ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was redissolved in dry THF (1.5 mL). Sodium hydride (~2 mg, excess) was added and the resulting solution was stirred at room temperature under argon overnight. After dilution with ether (3 mL), water was added (2 mL) and the products were extracted into ether (3 x 5 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate and filtered. Concentration in vacuo provided the crude product, which was subjected to flash column chromatography. Elution with 3% ethyl acetate in hexanes gave lactone **60** (4.7 mg, 41% yield): FT-ir ($CHCl_3$, cast} 2931 cm^{-1} (alkane C-H stretching) and 1755 cm^{-1} (C=O, lactone); ^1H nmr (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 6.40 (dd, J = 1.5, 1 Hz, 1H), 5.38 (t, J = 9 Hz, 1H, C4'-**H**), 3.92 (dd, J = 12, 9 Hz, 1H, C13-**H**), 3.82 (ddd, J = 10, 10, 4.5 Hz, 1H, C9-**H**), 3.63 (dd, J = 12, 2 Hz, 1H, C13-**H**), 2.38 (d, J = 9 Hz, 2H, C5'-**H**), 2.37 (d, J = 9 Hz, 2H, C5'-**H**), 2.02 (m, 1H), 1.64-1.87 (m, 4H), 1.48-1.64 (m, 4H), 1.08-1.36 (m, 3H), 1.14 (d, J = 7 Hz, 3H, C7-CH_3), 1.05 (s, 9H, -$C(CH_3)_3$) and 1.03 (s, 9H, -$C(CH_3)_3$).

Further elution using the same solvent system afforded lactone **61** (5.1 mg, 45% yield): FT-ir ($CHCl_3$, cast) 2928 cm^{-1} (alkane C-H stretching) and 1760 cm^{-1} (C=O, lactone); ^1H nmr (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 6.41 (dd, J = 2, 1 Hz, 1H), 5.36 (t, J = 8.5 Hz, 1H, C4'-**H**), 3.92 (dd, J = 12, 8.5 Hz, 1H, C13-**H**), 3.81 (ddd, J = 11.5, 10, 4.5 Hz, 1H, C9-**H**), 3.63 (dd, J = 12, 1.5 Hz, 1H, C13-**H**), 2.41 (dd, J = 14, 8.5 Hz, 1H, C5'-**H**), 2.31 (dd, J = 14, 8.5 Hz, 1H, C5'-**H**), 2.19 (ddd, J = 13.5, 13.5, 11 Hz, 1H, C14-**H**), 1.81-1.99 (m, 2H), 1.77 (ddd, J = 14, 4, 4 Hz, 1H), 1.51-1.69 (m, 4H), 1.14-1.39 (m, 4H), 1.05 (s, 9H, -$C(CH_3)_3$), 1.03 (s, 9H, -$C(CH_3)_3$) and 1.01 (d, J = 6.5 Hz, 3H, C7-CH_3).

(1R*,4'R*,5S*,6R*,7R*,9R*,14R*)-11,11-Di-*tert*-butyl-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.$0^{5,14}$]tetradecane-6-spiro-1'-[4'-(3-furyl)-3'-oxacyclopentan-2'-one] (62) and (1R*,4'S*,5S*,6R*,7R*,9R*,14R*)-11,11-di-*tert*-butyl-7-methyl-10,12-dioxa-11-silatricyclo[7.4.1.$0^{5,14}$]tetradecane-6-spiro-1'-[4'-(3-furyl)-3'-oxa cyclopentan-2'-one] (63)



62



63

A stock solution of 3-lithiofuran was prepared by addition of *n*-butyllithium (1.07 mL, 1.6M solution in hexane) to a solution of 3-bromofuran (0.18 mL, 0.02 mmol) in ether (3.75 mL), followed by stirring the resulting mixture at -78°C under an argon atmosphere for 30 minutes. A portion of this solution (0.11 mL, 0.037 mmol of 3-lithiofuran) was then added to a pre-cooled (-78°C) solution of aldehyde **59** (15.6 mg, 0.034 mmol) in ether (2 mL). The reaction mixture was stirred for 15 minutes. Water was added and the resulting mixture extracted with ether (3 x 5 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was dissolved in THF (2 mL). Sodium hydride (~2 mg, excess) was introduced. The reaction mixture was stirred at room temperature under argon for 8 hours, then diluted with ether (3 mL) and treated with water. The resulting mixture was extracted with ether (3 x 5 mL). The extracts were washed with brine, dried over magnesium sulfate and filtered. Concentration in vacuo gave the crude product, which was purified by flash chromatography. Elution with 3% ethyl acetate in hexanes afforded lactone **62** (6.7 mg, 39% yield): ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.43 (m, 2H), 6.40 (dd, J = 1.5, 1 Hz, 1H), 5.37 (t, J = 9 Hz, 1H, C4'-**H**), 4.58 (ddd, J = 7, 3, 3 Hz, 1H, C9-**H**), 4.00 (dd, J = 11.5, 10 Hz, 1H, C13-**H**), 3.75 (dd, J = 11.5, 1.5 Hz, 1H, C13-**H**), 2.44 (d, J = 9 Hz, 1H, C5'-**H**), 2.42 (d, J = 9 Hz, 1H, C5'-**H**), 2,31 (ddd, J = 16, 13, 3.5 Hz, 1H), 1.76-2.09 (m, 4H), 1.7 (ddd, J = 14, 3, 3 Hz, 1H), 1.11-1.64 (m, 6H), 1.04 (s, 9H, -C(C**H**$_3$)$_3$), 1.02 (s, 9H, -C(C**H**$_3$)$_3$) and 0.97 (d, J = 6.5 Hz, 3H, C7-C**H**$_3$).

Further elution with the same solvent system gave lactone **63** (8.2 mg, 0.017 mmol) in 46% yield: ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.4 (br s, 1H), 7.43 (dd, J = 1.5, 1.5 Hz, 1H), 6.40 (dd, J =1.5, 1 Hz, 1H), 5.37 (t, J = 9 Hz, 1H, C4'-**H**), 4.54 (dd, J = 7, 2.5 Hz, 1H, C9-**H**), 4.00 (dd, J = 11.5, 9 Hz, 1H, C13-**H**), 3.75 (dd, J = 11.5, 1.5 Hz, 1H, C13-**H**), 2.47 (dd, J = 14, 9 Hz, 1H, C5'-**H**), 2.36 (dd, J = 14, 9 Hz, 1H, C5'-**H**), 2.25-2.37 (m, 1H), 2.03-2.22 (m, 3H), 1.79-1.91 (m, 3H), 1.4-1.78 (m, 4H), 1.23-1.39 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H, C7-C**H**$_3$), 1.03 (s, 9H, -C(C**H**$_3$)$_3$) and 1.02 (s, 9H, -C(C**H**$_3$)$_3$).

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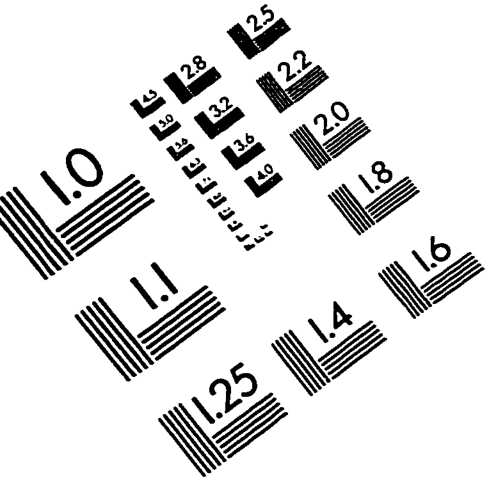

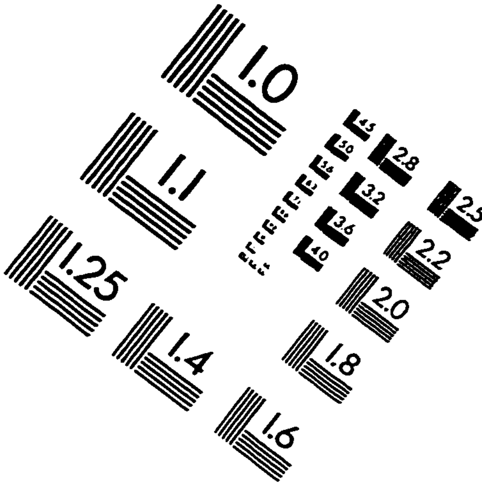

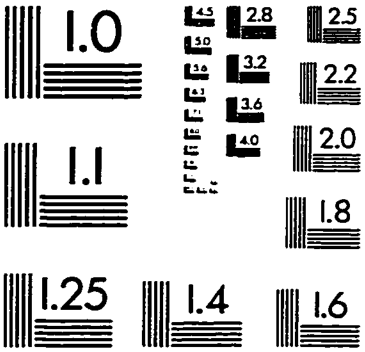

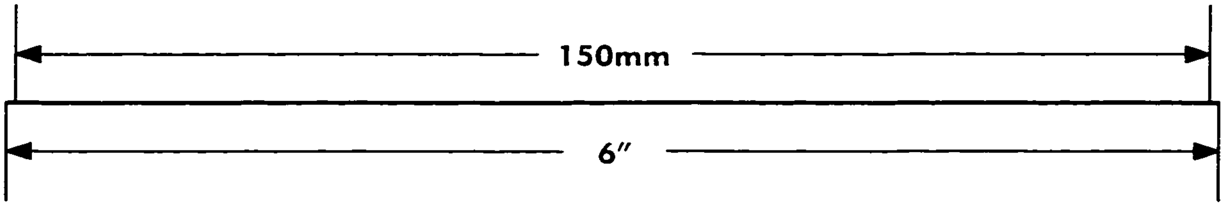

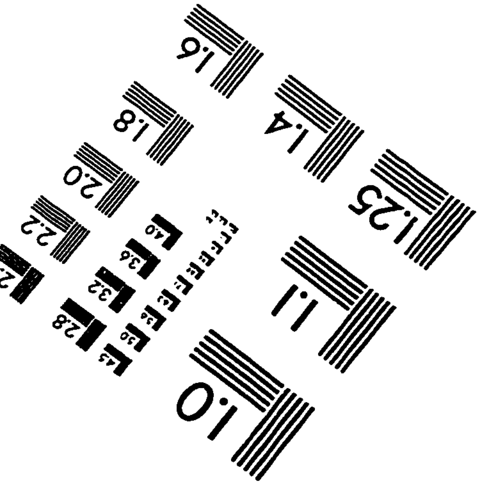

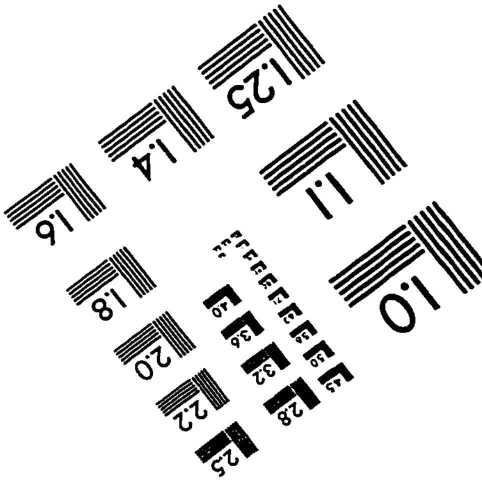

APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989