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THE UNIVERSITY OF ALBERTA

TOWARDS THE SYNTHESIS OF STERPURIC ACID

BY

VICENTE SAMANO

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN

PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled TOWARDS THE SYNTHESIS OF STERPURIC ACID submitted by VICENTE SAMANO in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

W. A. Ayer (Supervisor)

R. Daniel Little

Date: August 4, 1987.

TO MIRNA AND MY FAMILY

ABSTRACT

Sterpuric acid (1) is a novel sesquiterpene isolated from the fungus Stereum purpureum when grown under laboratory conditions. This fungus is the causative agent of the so-called "silver leaf" disease, a serious disease of fruit trees and a variety of shrubs.

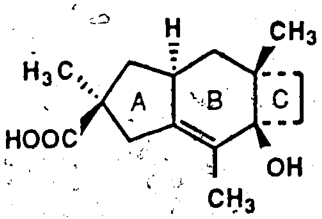
This thesis describes efforts directed towards the total synthesis of sterpuric acid (1) and analogs. The ABC ring system intermediates, compounds 24 and 25, were prepared stereoselectively from readily available starting materials.

Ring B was constructed *via* a Diels-Alder reaction between diene 18 and maleic anhydride. The resulting adduct, compound 19, was transformed to the AB ring system intermediate, compound 20, after some modifications followed by a cycloalkylation reaction utilizing dimethyl malonate.

The construction of ring C was achieved by conversion of compound 20 to carbonate 22, which in turn afforded compound 24 by means of a novel intramolecular [2+2] photocycloaddition reaction.

The α-oriented methyl ester group in compound 20 was reduced to the required methyl group in a number of steps to provide compound 21. Similarly, compound 21 was converted to carbonate 23. The intramolecular [2+2] photocycloaddition of 23 afforded the ABC ring system intermediate, compound 25.

The tetracyclic compound 25 possesses the desired stereochemistry about the ring junctions as well as functional groups which should facilitate its conversion into sterpuric acid and analogs.



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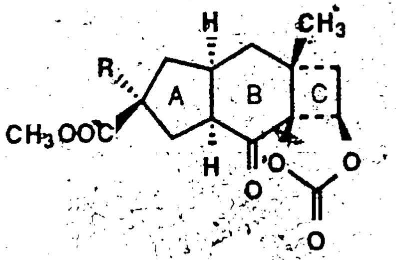
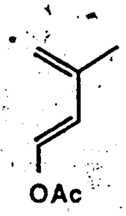


24 , R= COOCH$_3$

25 , R= CH$_3$



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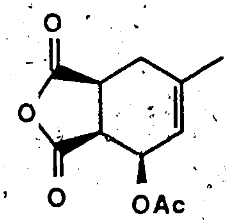

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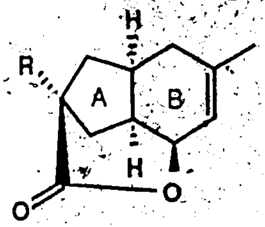
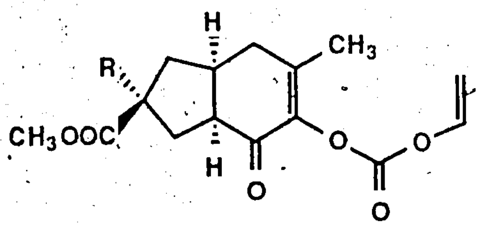


20 , R= COOCH$_3$

21 , R= CH$_3$



22 , R= COOCH$_3$

23 , R= CH$_3$

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ABBREVIATIONS

Ac_2O	acetic anhydride
Ar	aryl
b.p.	boiling point
cims	chemical ionization mass spectrum
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equivalent
Et_3N	triethylamine
Et_2O	ethyl ether
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
ir	infrared spectrum
J	coupling constant
lrm	low resolution mass spectrum
M	molar
MCPBA	*m*-chloroperbenzoic acid
m p.	melting point
MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
nOeds	nuclear Overhauser enhancement difference spectroscopy
nmr	nuclear magnetic resonance
p-TsCl	*p*-toluenesulfonyl chloride

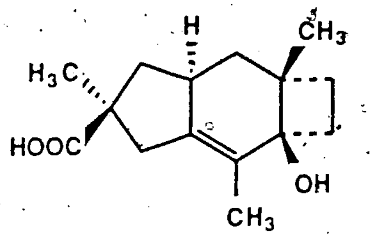
py	pyridine
R_f	retardation factor
S_N2	substitution nucleophilic bimolecular
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
uv	ultraviolet spectrum
W	watt

I. INTRODUCTION

The fungus Stereum purpureum (class Basidiomycetes) is responsible for the so-called silver leaf disease that attacks plum, apple, and other fruit trees[1]. In Alberta it is also found on mountain ash, cotoneaster, and aspen[2]. In 1902, Percival[3] was the first to apply the name "silver leaf" to the disease whose common symptom is silvering of the foliage. Some years later Brooks carried out extensive inoculation experiments on plum and apple trees and showed that the action of S. purpureum was causing the effect[4]. According to his studies the fungus enters through wounds, grows first in the heartwood, then kills the sapwood and bark.

The silvering of the leaves is a secondary symptom primarily due to partial separation of the mesophyl cells from one another and from the epidermis. Owing to the presence of abnormal air spaces thus induced, the light reflecting qualities of the leaf are altered, and the leaves appear silvery.

In 1981, Ayer and co-workers described the isolation and structure elucidation of a group of metabolites produced when S. purpureum is grown in liquid culture[5]. Extraction of the culture broth with ethyl acetate provided crude metabolites which caused silvering in mountain ash seedlings. Furthermore, this extract showed ~~good~~ activity against the pathogens Staphylococcus aureus and Candida albicans[6]. The crude metabolites were separated into neutral and acidic fractions and the crystalline acid, for which they proposed the name sterpuric acid (1).



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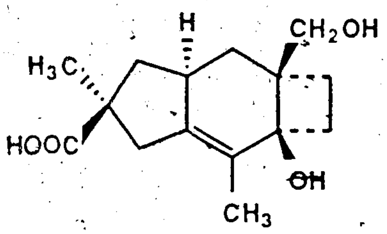

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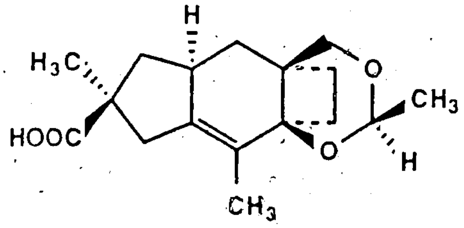

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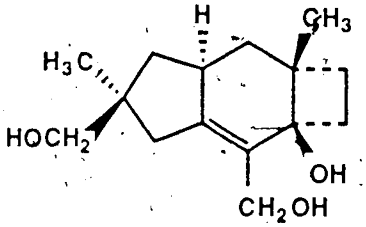

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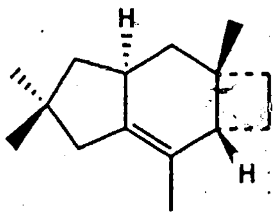
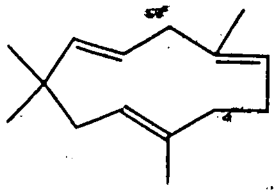


5

Esterification (diazomethane) of the remaining fractions followed by metabolites [illegible] sterpuric acid (2), and hydroxysterpuric acid ethyledene acetal (3) in the form of their methyl esters. Sterpurene-3,12,14-triol (4) and the parent hydrocarbon sterpurene (5) were isolated from the neutral fraction and the mycelium, respectively[7].

The structure of sterpuric acid was deduced from a combination of chemical transformations and spectroscopic analyses and was unequivocally confirmed by X-ray crystallographic studies. The absolute configuration has not been determined.

Sterpuric acid and related sterpurenes represent a type of sesquiterpenoid not previously found in nature[8]. Biosynthetic studies indicate that the sterpurenes are derived from farnesyl pyrophosphate <u>via</u> humulene (6) and the protoilludanyl cation 7[9].



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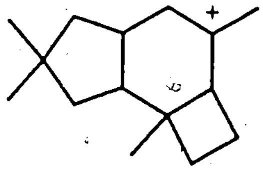

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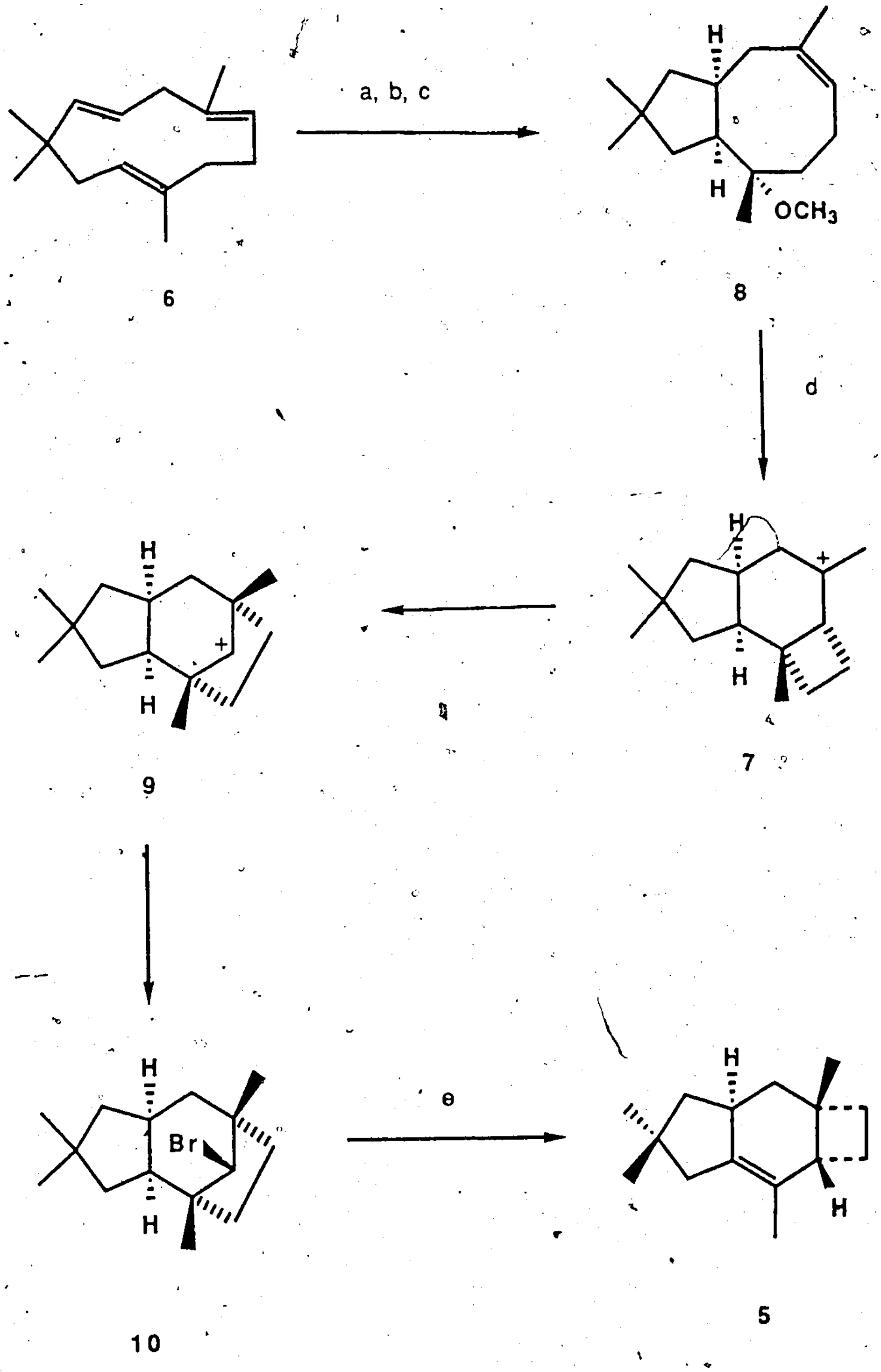
Synthetic efforts towards this class of compounds are limited to two reports on the synthesis of the parent hydrocarbon sterpurene (5).* Murata, Ohtsuka, Shirahama, and Matsumoto[10] described the conversion of humulene (6) to sterpurene (5) <u>via</u> the protoilludanyl cation 7, under conditions that are believed to be analogous to those involved in its biosynthesis (Scheme 1). Methyl ether 8, prepared from 6, was treated with boron tribromide to give bromide 10. Formation of bromide 10 may be interpreted as follows:[11] the methyl ether 8 furnished first the protoilludanyl cation 7 which rearranged to cation 9 leading in a concerted fashion to bromide 10. Treatment of bromide 10 with silver acetate afforded racemic sterpurene (5).

A different approach to sterpurene (5) was recently described by Little and co-workers[12] (Scheme 2). A key feature in this synthesis was the intramolecular electrochemically induced cyclization of bisenoate 11 leading to the cyclopentane diester 12. Acyloin condensation of 12 and deprotection of the initally formed bis(silyl enol) ether afforded α-hydroxyketone 13. Mesylation of 13 followed by elimination provided enone 14 which was then converted to enone 15 by treatment with methyllithium and subsequent oxidation-transposition of the resulting tertiary allylic alcohol using pyridinium chlorochromate. Construction of the cyclobutane ring was achieved <u>via</u> a [2+2] photocycloaddition between enone 15 and ethylene. Finally, the resulting tricyclic ketone 16 was converted to sterpurene (5) by treatment with methyl lithium followed by elimination.

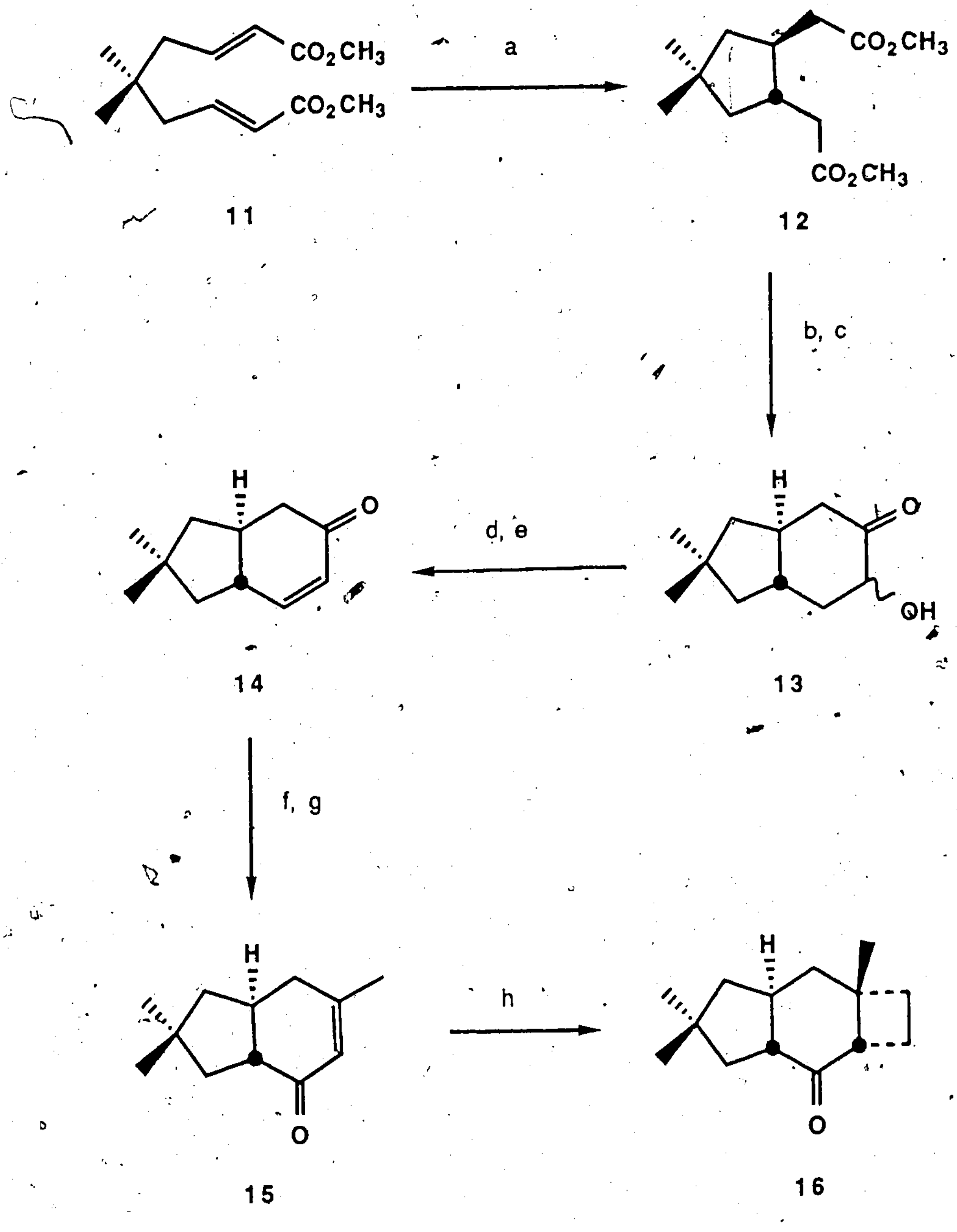
Because of the novel skeleton possessed by the sterpurenes, we became interested in the investigation of their laboratory synthesis. In particular, our efforts were directed towards the development of a stereoselective synthesis of sterpuric acid (1). This will enable us to study in more detail the biological properties of this compound, and will allow us to produce analogs, if required.

SCHEME 1. Formation of sterpurene (5) from humulene (6).[10]



a) $Hg(NO_3)_2$; b) Li-$EtNH_2$; c) NaH, MeI; d) BBr_3; e) AcOAg

SCHEME 2. Little's synthesis of sterpurene (5).[12]



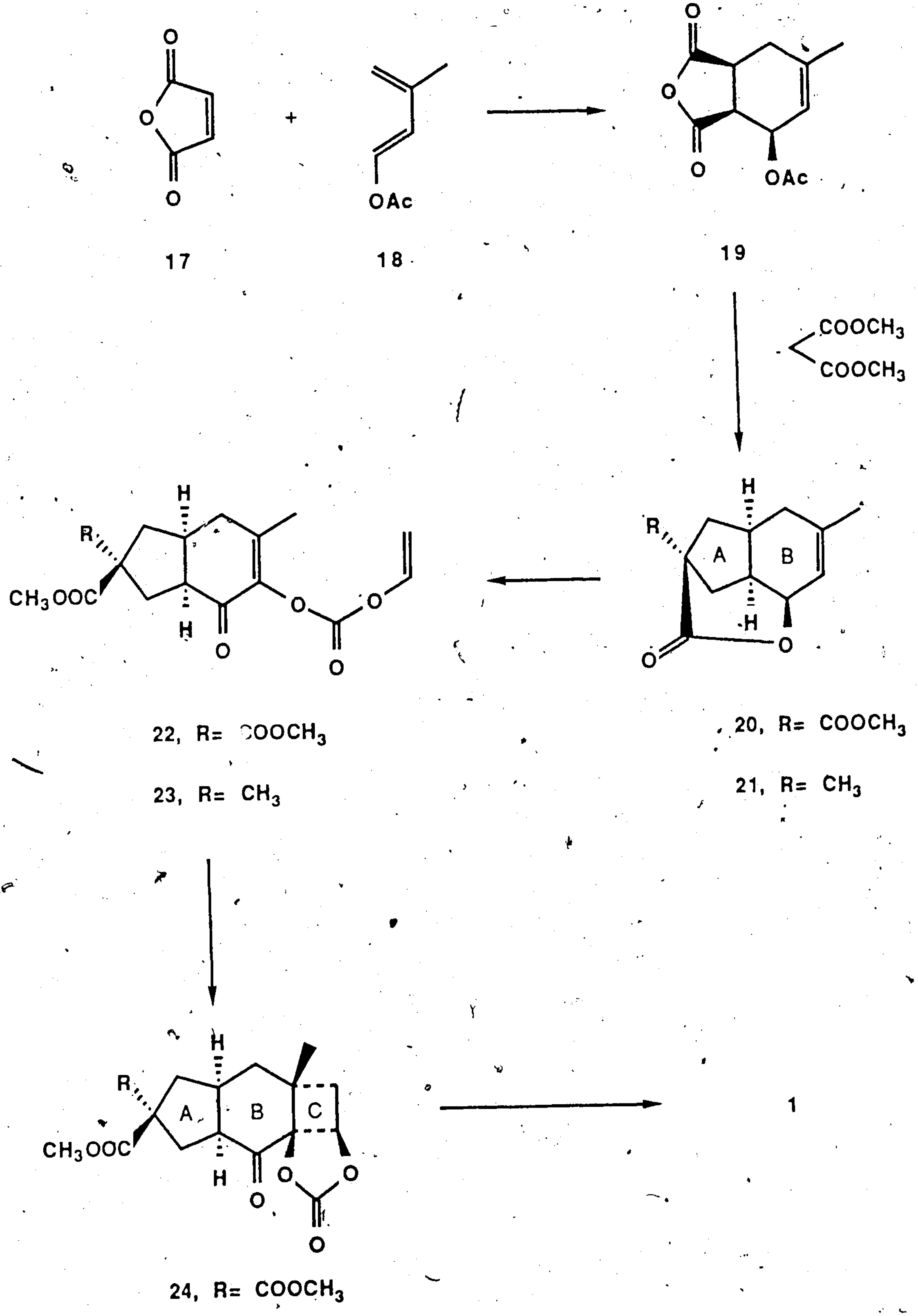
a) +e⁻; b) Na, Me_3SiCl; c) $THF/AcOH/H_2O$;

d) MsCl, Et_3N; e) LiBr, Li_2CO_3, DMF, reflux;

f) MeLi, Et_2O, g) PCC, CH_2Cl_2;

h) hv , ethylene; i) MeLi, Et_2O; $SOCl_2$, pyridine.

SCHEME 3. Synthetic approach to sterpuric acid (1).

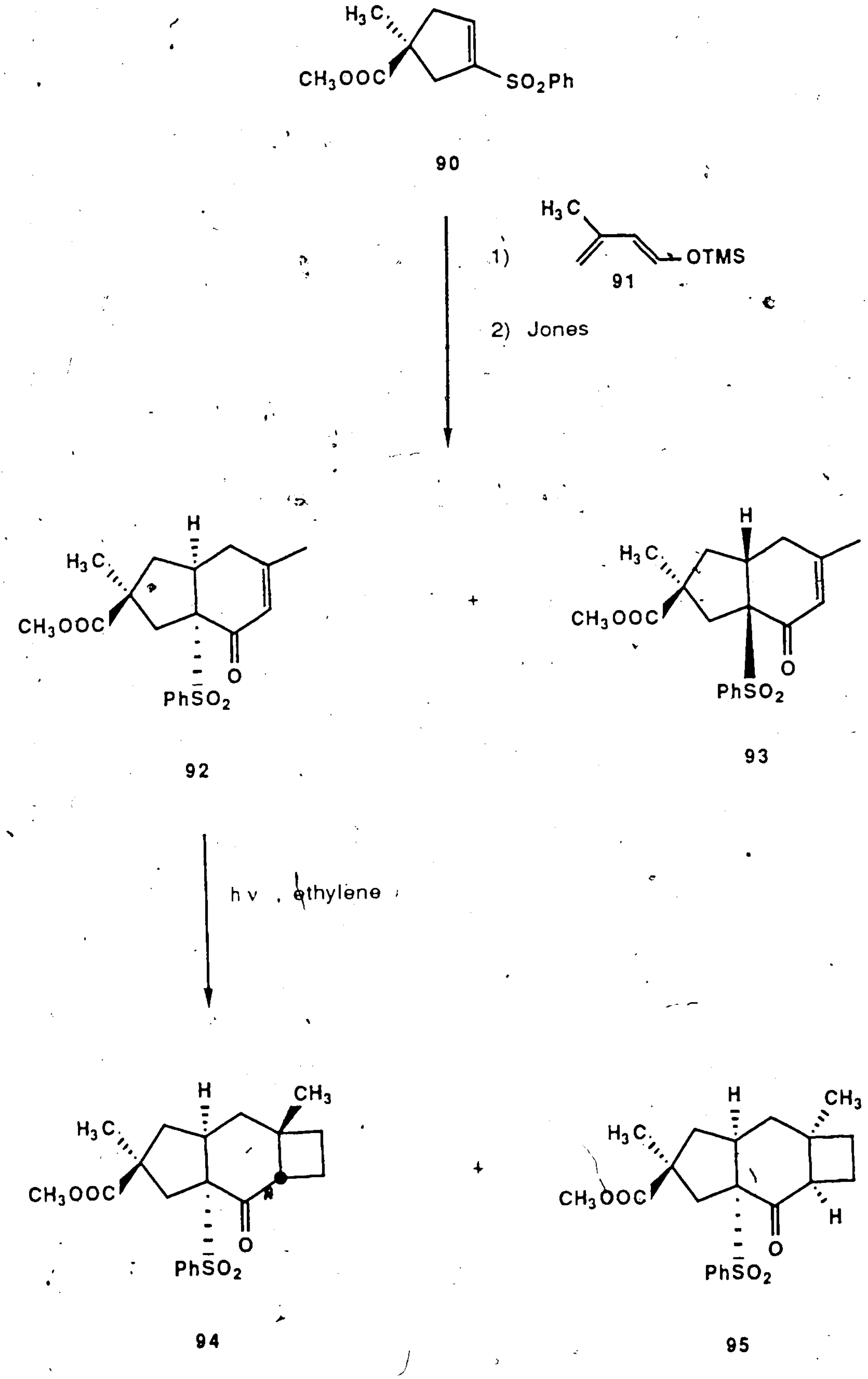


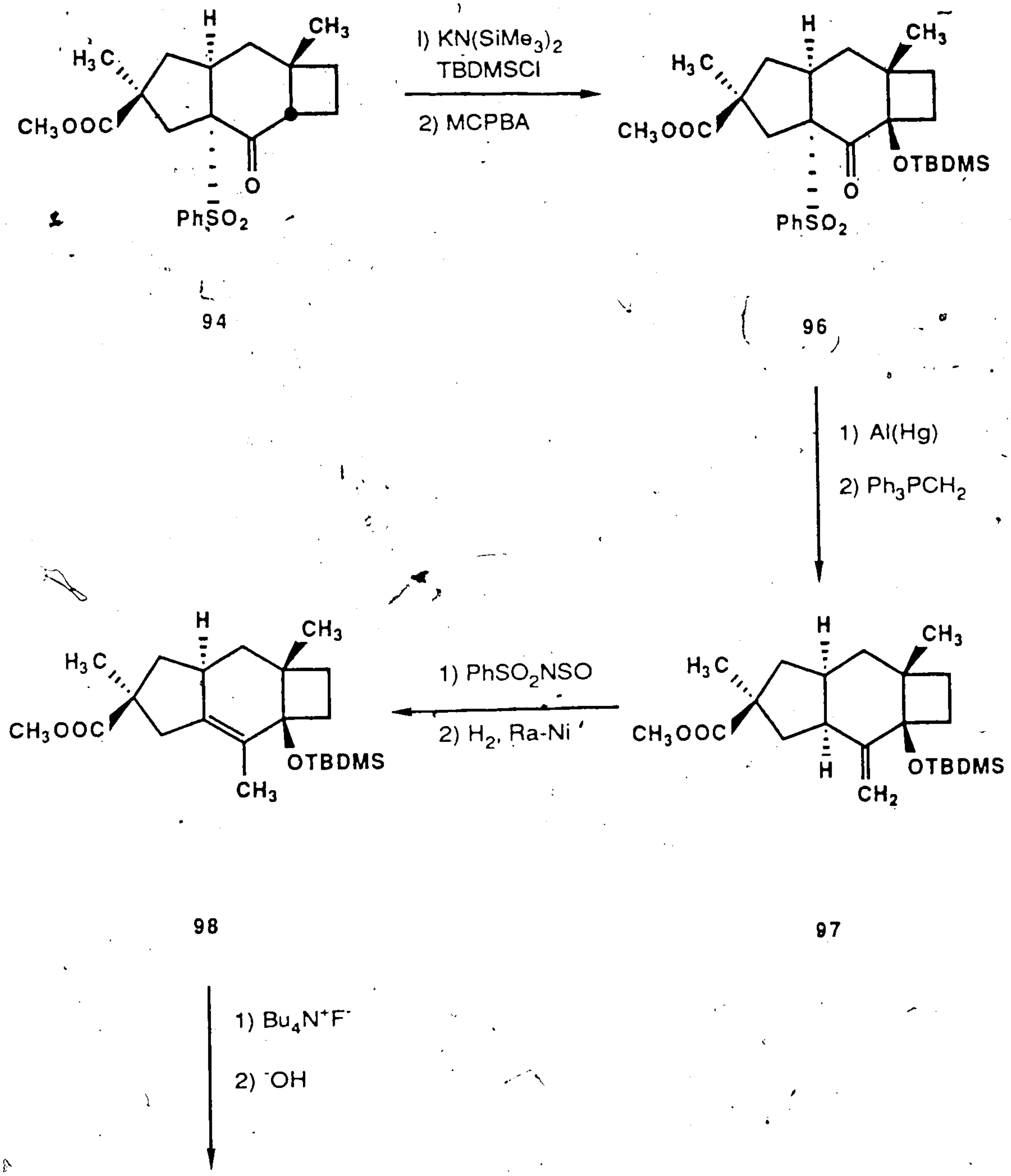
formation of an AB ring system intermediate, to which ring C would be attached following a procedure previously investigated in our laboratories.[13] The general features of the synthetic strategy are outlined in Scheme 3. We envisaged the B ring of sterpuric acid to arise via a Diels-Alder reaction between maleic anhydride (17) and diene 18. The resulting adduct 19 would be converted, after some modifications, to the AB ring system intermediate lactone 20, by cycloalkylation using malonate anion. Formation of the lactone moiety could facilitate the selective transformation of (methyl ester) lactone 20 to the required methyl lactone 21. Of crucial importance in the construction of ring C of sterpuric acid is the generation of the correct cis relationship between the methyl and hydroxyl groups at the ring junction. We felt that the desired stereochemical result could be achieved via a novel [2+2] intramolecular photocycloaddition of carbonate 23, which may be derived from 21. Further modifications of the functional groups of the resulting tetracyclic compound 25 would provide sterpuric acid (1).

In order to facilitate the discussion of these synthetic studies, the results are presented under the following four headings:

1. Synthesis of lactone 20, a precursor of the AB ring system.
2. Tranformation of lactone 20 into the ABC ring intermediate, carbonate 24.
3. Reduction of the (methyl ester) lactone 20 to the required methyl lactone 21.
4. Synthesis of the ABC ring system of sterpuric acid, carbonate 25.

After this introduction was written, the first total synthesis of (±)-sterpuric acid was reported by Paquette and co-workers[78]. The general features of the synthesis are outlined below. Diels-Alder reaction of sulfone 90 with diene 91 followed by Jones oxidation provided 92 and 93 (66%) in a ratio of 2.1:1. Irradiation of the major enone 92 in the presence of ethylene afforded 94 and 95 in 71 and 23% yield, respectively (irradiation was interrupted when 92 was approximately half-consumed). Ketone 94 was converted to its silyl enol ether and this was treated with MCPBA to provide keto sulfone 96 as the major product (66%). Reductive cleavage of the α-sulfonyl substituent (93%) and subsequent Wittig olefination (78%) afforded compound 97. This intermediate proved to be unreactive towards double bond isomerization. The desired compound 98 was obtained by first subjecting 97 to an ene reaction with N-sulfinylbenzenesulfonamide and then carrying out reductive desulfurization (81% yield for the two steps). The synthesis of 1 was completed by sequential deprotection and saponification of 98 (90%). The synthetic sample of racemic 1 was identical with the natural product as determined by comparison with ir and ^{1}H nmr spectra of sterpuric acid.

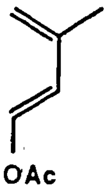

H₃C
CH₃OOC
SO₂Ph
90
1)
H₃C
OTMS
91
2) Jones
H
H₃C
CH₃OOC
O
PhSO₂
92
+
H
H₃C
CH₃OOC
O
PhSO₂
93
h v , ethylene
H
CH₃
H₃C
CH₃OOC
O
PhSO₂
94
+
H
CH₃
H₃C
CH₃OOC
H
O
PhSO₂
95


1) KN(SiMe$_3$)$_2$
TBDMSCl
2) MCPBA
94
96
1) Al(Hg)
2) Ph$_3$PCH$_2$
97
1) PhSO$_2$NSO
2) H$_2$, Ra-Ni
98
1) Bu$_4$N$^+$F$^-$
2) $^-$OH
H
CH$_3$
H$_3$C
CH$_3$OOC
O
PhSO$_2$
OTBDMS
CH$_2$

II. RESULTS AND DISCUSSION

1. Synthesis of lactone 20, a precursor of the AB ring system.

The diene required for the construction of ring B via the Diels-Alder (D.A.) reaction[illegible] should contain a methyl group and an oxygenated functionality arranged as in 18. The oxygenated functionality would ultimately be converted into the vinylic methyl group present in sterpuric acid. Keana and co-workers[15] prepared diene 18 in 71% yield by treatment of 3-methylcrotonaldehyde with potassium acetate (KOAc)in refluxing acetic anhydride (Ac_2O). We decided to utilize a newer procedure described by Cookson[16] in which diene 18 is reported to be obtained in 91% yield, (7:1, trans:cis ratio) via the isomerization of acetate 27 in refluxing benzene in the presence of silver trifluoroacetate. Acetate 27 was readily obtained by acetylation of the commercially available alcohol 26. When 27 was subjected to the



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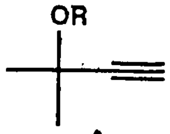
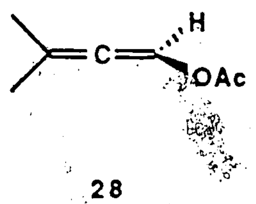


26, R= H

27, R= Ac

conditions described by Cookson, allene 28 was the only isolated product. The observation of allene as an intermediate in this type of reactions is well documented[17,18].

A longer reaction time provided diene 18 in 60% yield along with dimeric products. In order to avoid side reactions, the isomerization



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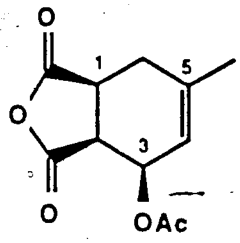
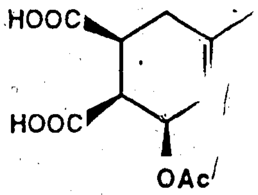


19

was carried out in the presence of maleic anhydride; in this way adduct 19 was obtained as a single stereoisomer. The <u>cis</u> relationship between the anhydride ring and the acetoxyl group in compound 19 was inferred from the well known <u>endo</u> preference in the D.A. reaction of butadiene and maleic anhydride[19]. This is supported by the ^{1}H nuclear magnetic resonance (^{1}H nmr) spectrum of 19 which shows a triplet of quartets at δ 5.43 (J=5.5, 1 Hz) for the hydrogen <u>geminal</u> to the acetoxyl group, a complex multiplet at δ 3.48 for the hydrogens at the ring junction, and signals at δ 2.69 (br d, J=18 Hz) and 2.38 (d d, J=18, 8 Hz) for the methylene hydrogens. Additional evidence will be presented in the discussion of a subsequent intermediate.

Compound 19 was easily hydrolyzed (buffer pH 7.4) to give diacid 29, which shows broad OH (3200-2500 cm^{-1}) and strong carbonyl (1737 cm^{-1}) absorptions in the infrared (ir) spectrum. The next step called for the selective reduction of a carboxylic acid in the presence of an ester. Such a method when applied to 29 would give diol 30, which in turn could be converted to the corresponding ditosylate and then



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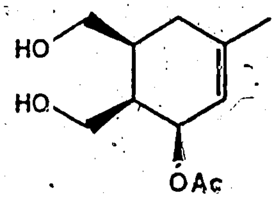
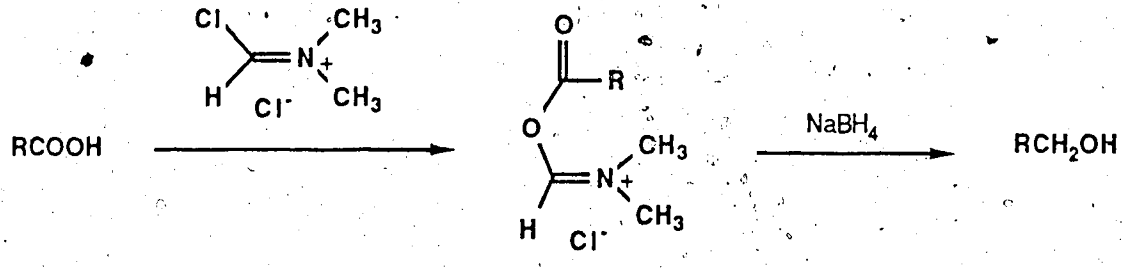


30

Several attempts to carry out the selective reduction failed to give 30. When diacid 29 was treated with two equivalents of borane-tetrahydrofuran complex (BH_3-THF)[20] at -18°C, a complex mixture of products was obtained, probably arising from a competitive reaction of borane with the double bond of 29. A procedure[21] in which a carboxylic acid is converted to its carboxymethyleniminium salt 31 and then reduced with sodium borohydride ($NaBH_4$) to the corresponding alcohol

SCHEME 4 . A mild method for the reduction of carboxylic acids[21].



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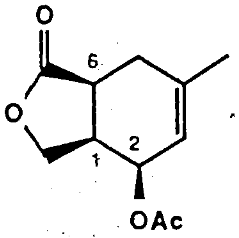
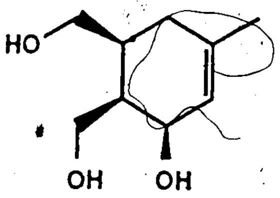
was also investigated (Scheme 4). Under these conditions 29 gave



32

lactone 32. The ^{1}H nmr spectrum of 32 shows a broad triplet at δ 5.26 (J=5 Hz) for the hydrogen <u>geminal</u> to the acetoxyl group (H-2) and doublets of doublets at δ 4.05 (J=9, 3 Hz) and 3.81 (J=9, 7 Hz) for the methylene hydrogens of the lactone ring. The hydrogens at the ring junction appear at δ 2.42 (td, J=9, 3 Hz, H-6) and 2.31 (dddd, J=9, 7, 5, 3 Hz, H-1). Decoupling experiments show that the signal at δ 2.31 (H-1) is coupled to the signals at δ 5.26 (H-2), δ 4.05, δ 3.81, and δ 2.42 (H-6) confirming the proposed structure.

The crude D.A. adduct 19 was reduced with lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) to give triol 33 in 60% overall yield from 27. When we tried to selectively tosylate[22] the two primary hydroxyl groups of 33 with p-toluenesulfonyl chloride and triethylamine at 0°C (p-TsCl, Et_3N, 0°C), ethers 34 and 35 were obtained. Tetrahydrofuran derivatives have been obtained under similar conditions[23]. The chemical ionization mass spectra (cims) of 34 and 35 show a M^+ (molecular ion) +18 ion at m/z 326 (100) and 172 (100)



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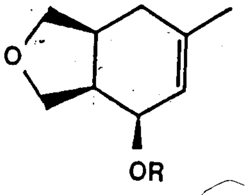
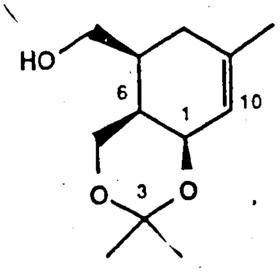
respectively, consistent with the assigned structures.



34, R= Ts

35, R= H

Triol 33 was treated with dimethoxypropane and trifluoroacetic acid [24] to provide a separable mixture of acetonides 36, 37, and 38 in 60, 15, and 5% yield, respectively. Different reaction conditions[25], for example benzaldehyde dimethyl acetal and p-toluenesulfonic acid, gave similar results. Compounds 36 and 37 were easily differentiated by observing the change in their ^1H nmr spectra upon acetylation (Ac_2O, Et_3N). In compound 36, the signals for the hydroxymethyl group at δ 4.04 (dd, J=11.5, 9 Hz) and 3.60 (dd, J=11.5, 4 Hz) are shifted to δ



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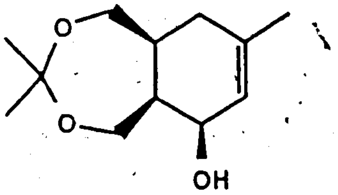

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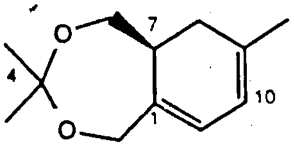

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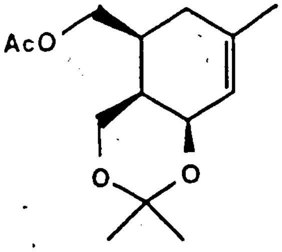

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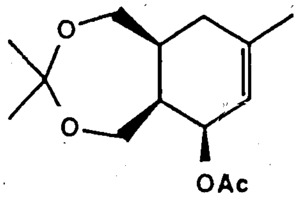
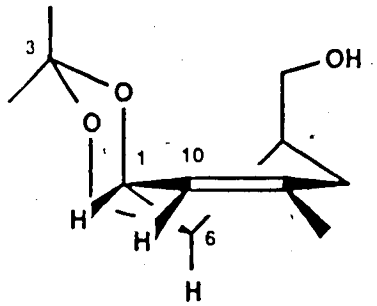


40

4.60 (dd, J=11, 4.5 Hz) and 4.16 (dd, J=11, 9 Hz) in the corresponding acetate 39. The downfield shift of 0.5 ppm is characteristic of primary alcohols [26]. On the other hand, in compound 37, the hydrogen geminal to the hydroxyl group is shifted 1 ppm downfield, from δ 4.50 (br m) to 5.56 (br m) in acetate 40 as expected for a secondary alcohol.

Nuclear Overhauser enhancement difference spectroscopy (nOeds) is a method for determining the relative stereochemistry of substituents in a molecule[27]. An nOe study on compound 36 provided additional evidence for the endo preference in the D.A. reaction mentioned earlier (Figure I). Presaturation of the signal at δ 4.43 (H-1) gives enhancements of 13% at δ 5.41 (H-10), 13% at δ 1.68 (H-6), and 10% at δ 1.55 (C-3 CH_3).

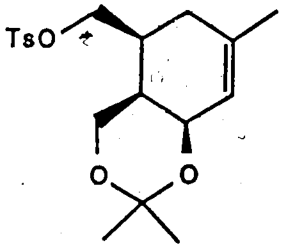
FIGURE I. Conformation of alcohol 36.



The ^1H nmr spectrum of 38 displays signals for the vinylic hydrogens at δ 6.97 (br dd, J=7, 1.5 Hz, H-10) and 6.94 (d, J=7 Hz, H-11).

Compound 36 was converted in 90% yield to tosylate 41 (p-TsCl, Et_3N). The ir spectrum of this compound shows absorptions at 1358 and 1175 cm^{-1}, typical of sulfonate groups[28]. The hydrogens of the aromatic ring appear as an AA'BB' system at δ 7.80 and 7.33 with a coupling constant of 8 Hz and the aromatic methyl group appears as a singlet at δ 2.44.

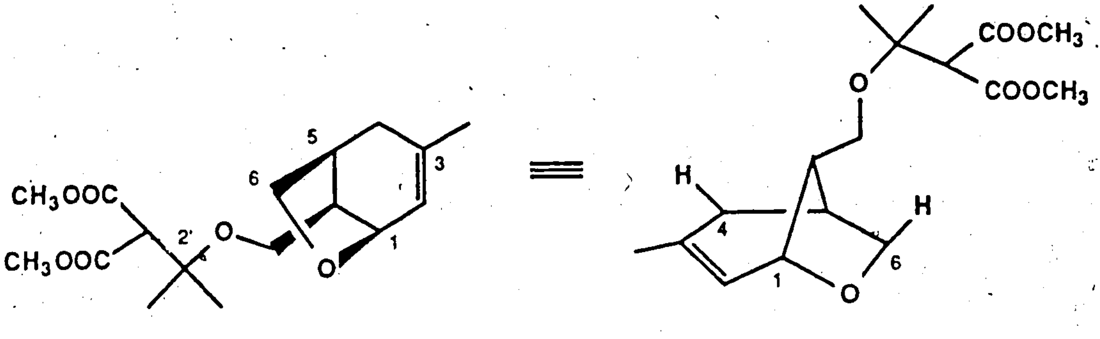
With tosylate 41 in hand we were ready to study the alkylation with malonate anion[29]. Treatment of 41 with the anion of dimethylmalonate ($CH_2(COOCH_3)_2$, NaH) in refluxing THF afforded 42 (23% yield) and recovered starting material. The ir spectrum of 42 shows strong absorptions at 1754, 1739, and 1240 cm^{-1} suggesting the presence of ester groups. A doublet for the gem-dimethyl at 1375 cm^{-1} was also observed. The ^{1}H nmr spectrum of 42



41

displays three new singlets at δ 3.74 (2 OCH_3), 3.75 (H-3'), and 1.44 (gem-dimethyl). The hydrogens at the 6-position appear as a doublet of doublet of doublets at δ 3.92 (J=9, 6, 2 Hz) and a doublet at δ 3.60 (J=9 Hz); those at the 4-position appeared as broad doublets at δ 2.42 and 2.02 (J=17 Hz). Irradiation of the signal at δ 3.92 (6 exo) causes sharpening of the doublet at δ 2.42 (4 exo). This is an indication of a long-range "W" coupling[30a] (J=2 Hz) between those hydrogens, which is typical of bicyclic structures such as 42 (Figure II). The endo-exo assignments are based on the general tendency for the endo-hydrogens to resonate upfield from the corresponding exo-hydrogens in norbornanes[30b]. The cims of 42 shows a peak at m/z 344 (M$^+$+18, 100)

FIGURE II. Structure of compound 42.



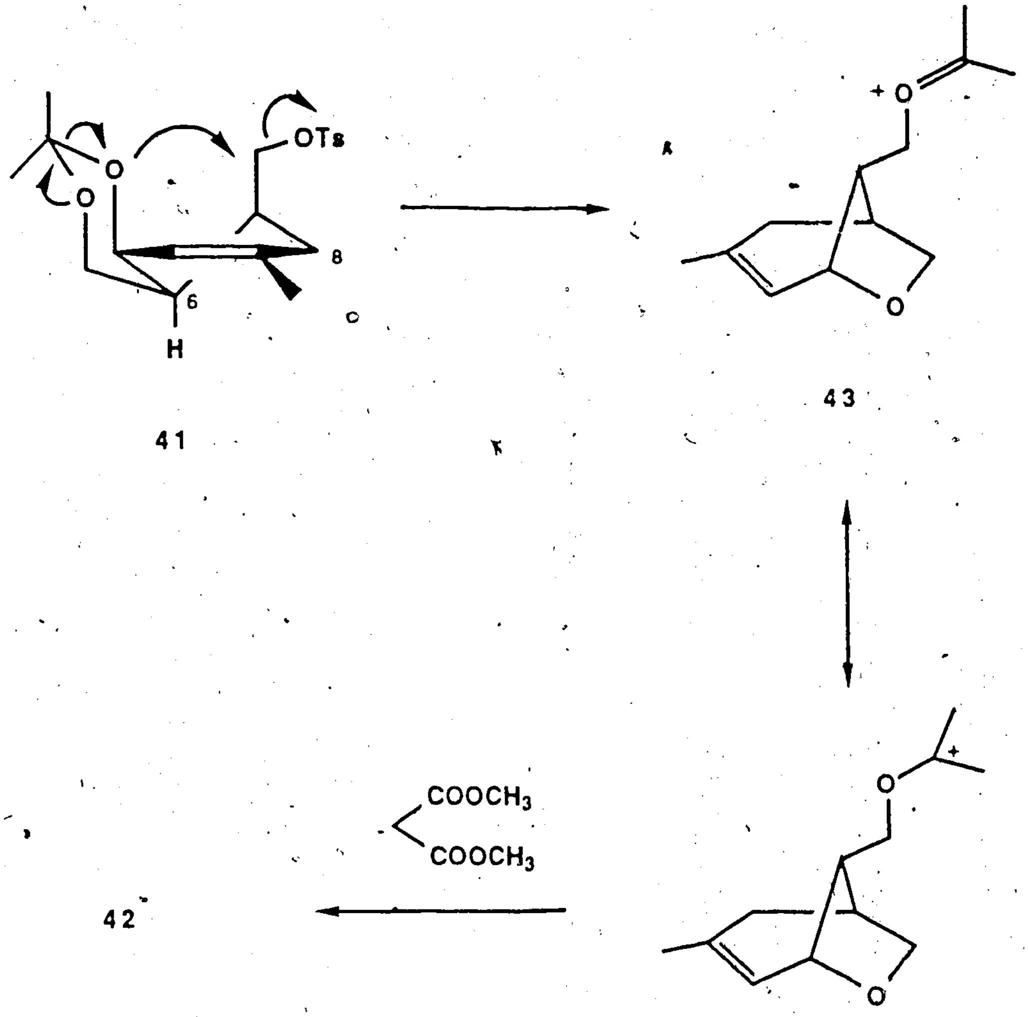
42

corroborating its molecular formula. Formation of compound 42 can be explained as follows. On close examination of the ^{1}H nmr spectrum of the substrate, compound 41, the methylene hydrogens of the 1,3-dioxane ring appear at δ 4.18 and 3.71 as doublets of doublets (J_{gem}=12.5 Hz) showing a coupling of 4.5 and 1.5 Hz, respectively, to the hydrogen at the 6-position (δ 1.60). In addition, only one of the hydrogens at C-8 (δ 2.05) shows a significant coupling (4 Hz) to the methine hydrogen at δ 2.23 (H-7). The observation of small coupling constants suggests that the preferred conformation for compound 41 is that shown in Scheme 5.

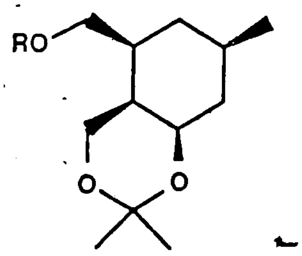
Molecular models of compound 41 show that the approach of the malonate anion to the carbon bearing the leaving group is highly hindered by the acetonide moiety. Alternatively, the departure of the tosylate could be promoted by a 1,3-pseudodiaxial interaction with one of the oxygens of the acetonide as indicated, generating an oxonium ion intermediate 43. Reaction of 43 with malonate anion provides 42.

There are precedents for the reaction between 1,3-diaxial substituents in six-membered ring systems[31].

SCHEME 5. Formation of 42 from tosylate 41.



Saturation of the double bond of 41 should lead to a change in conformation. The saturated tosylate 45 was prepared from alcohol 44 (p-TsCl, Et$_3$,N), which in turn was obtained by catalytic hydrogenation (H_2, platinum oxide) of 36. The ^1H nmr spectrum of 45 displays doublets of doublets at δ 3.76 (J=11, 9.5 Hz) and 3.65 (J=11, 5.5 Hz) for the methylene hydrogens of the 1,3-dioxane ring. The hydrogen at the 6-position appeared as a doublet of quartets at δ 2.35 (J=9.5, 5.5 Hz). The large coupling of 9.5 Hz between the hydrogen at δ 3.76 and

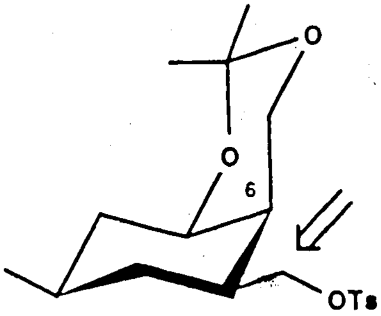


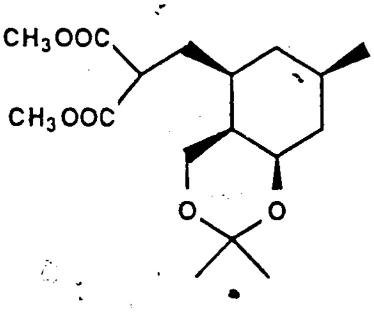
44, R= H

45, R= Ts

the methine hydrogen at δ 2.35 suggests a trans-diaxial relationship so that the preferred conformation for compound 45 is believed to be the one shown in Figure III. In this conformation it can be clearly seen that approach of the nucleophile to the electrophilic center is no longer hindered. Accordingly, treatment of tosylate 45 with the anion of dimethyl malonate (NaH, THF) provided the desired diester 46. The ^{1}H nmr spectrum of 46 shows singlets at δ 3.76 and 3.75 for the methoxyl groups, and a triplet at δ 3.48 (J=7.5 Hz) for the methine bearing the two ester functionalities.

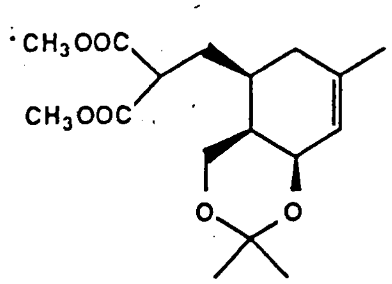
FIGURE III. Conformation of tosylate 45.





46

However, we wished to retain the unsaturation in 41 to serve as latent functionality in a later stage of the synthesis for the introduction of both the hydroxyl group at the ring junction and the four-membered ring C of sterpuric acid. With this in mind we sought an alternative procedure for alkylation of dimethyl malonate with tosylate 41. The utility of polar aprotic solvents in organic synthesis has been widely recognized[32,33]. In particular, hexamethylphosphoramide (HMPA) has proved to be a useful solvent for reactions involving nucleophilic displacement at sterically hindered centers[34]. It has been proposed that the role of the solvent in these reactions is to strongly solvate the cation so that the anion acts as a free nucleophile unencumbered by ion pairing, thereby causing a minimum of steric hindrance to S_N2 (bimolecular nucleophilic substitution) attack. In fact, the alkylation of dimethyl malonate with tosylate 41 proceeded smoothly when HMPA (NaH, 55°C) was used in place of THF as the reaction solvent. Diester 47 and alcohol 48 were obtained in 65 and 20% yield, respectively, after chromatographic separation. The ir spectrum of 47 shows strong carbonyl absorptions at 1740 and 1735 cm^{-1} and its ^{13}C nmr



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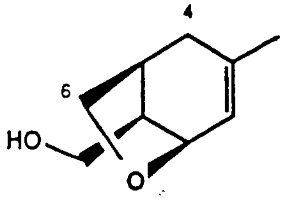
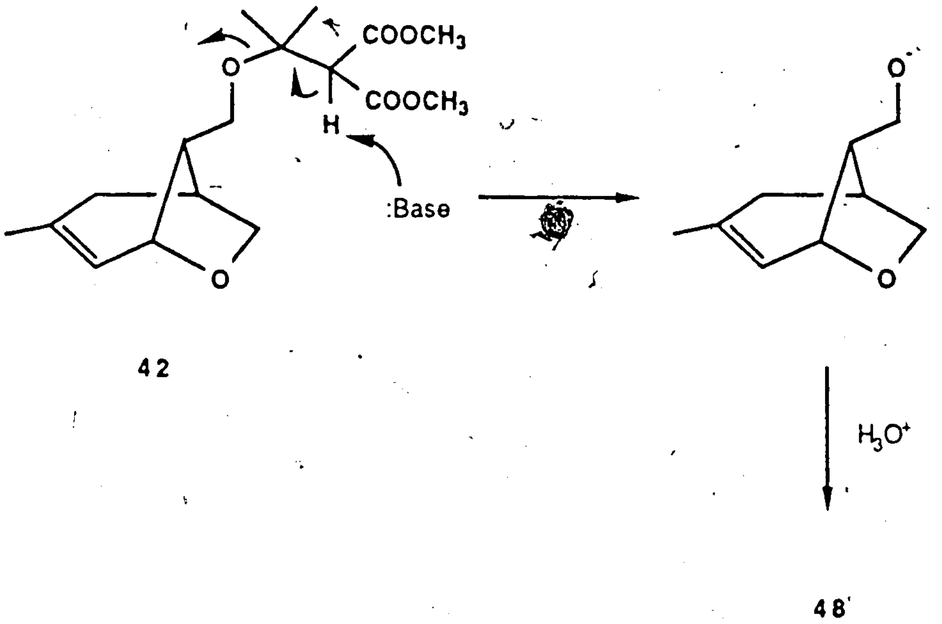


48

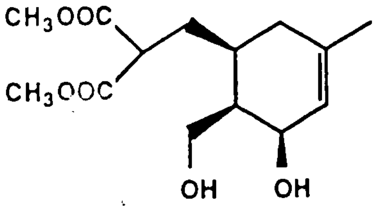
displays signals at δ 170.30 and 170.14 for the ester carbonyls as well as at δ 50.41 for the two methoxyl groups. This compound was easily distinguished from its structural isomer 42 by ^{1}H nmr spectroscopy. Thus in compound 42 the hydrogen of the methine bearing the two ester groups appears as a singlet at δ 3.75, whereas in 47 the same hydrogen appears as a doublet of doublets at δ 3.53 (J=8.5, 7 Hz). The molecular formula of 47 was confirmed by the presence of a peak at m/z 344 (M^++18, 100) in the cims. The ir spectrum of 48 shows hydroxyl absorption at 3400 cm^{-1} and the ^{13}C nmr spectrum displays signals for nine different carbons. The ^{1}H nmr spectrum of this compound shows the same features previously discussed for compound 42, that is, a characteristic "W" coupling of 2 Hz between the H-6 <u>exo</u> (δ 3.94 in 48 and δ 3.92 in 42) and H-4 <u>exo</u> (δ 2.42 in both 48 and 42) hydrogens. The high resolution mass spectrum (hrms) of 48 is consistent with the molecular formula $C_{19}H_{14}O_2$. This compound may arise from 42 via a base-catalyzed β-elimination as shown in Scheme 6.

Deprotection of compound 47 under mild acidic conditions (80% aqueous acetic acid, CH_2Cl_2)^{35} afforded diol 49 in quantitative yield. The use of stronger acids (p-toluenesulfonic acid or dilute HCl)

SCHEME 6 . Formation of alcohol 48 from diester 42 .



brought about elimination of the allylic alcohol function providing diene 50 as a by-product. The ir spectrum of 49 shows strong OH (3400



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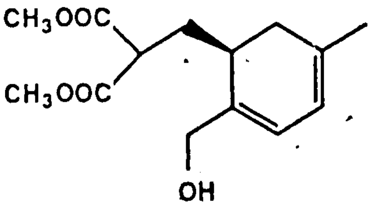
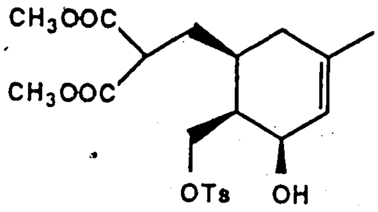


50

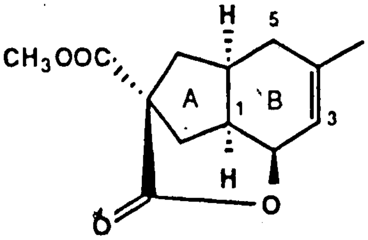
cm^{-1}) and carbonyl (1750 and 1734 cm^{-1}) absorptions and the ^{1}H nmr displays two D_2O exchangeable hydrogens at δ 2.50 as a broad singlet. The cims shows a peak at m/z 304 (M^++18, 100) which supports the proposed molecular formula.

Selective tosylation (p-TsCl, Et_3N) of the primary hydroxyl group of diol 49 provided compound 51 in 82% yield. This compound shows a



51

weak OH (3500 cm^{-1}) absorption in the ir spectrum. Its ^1H nmr spectrum shows an AA'BB' system for the hydrogens of the aromatic ring at δ 7.82 and 7.36 with J_{AB}= 8 Hz, the aromatic methyl appears as a singlet at δ 2.46. The signals for the hydrogens of the methylene bearing the hydroxyl group in diol 49 are shifted downfield from δ 3.87 (dd, J=11, 8.5 Hz) and 3.73 (dd, J=11, 4 Hz) to δ 4.39 (dd, J=10.5, 6.5 Hz) and 4.10 (dd, J=10.5, 6.5 Hz) in tosylate 51, this proving the location of



20

the tosylate group. The hydrogen <u>geminal</u> to the hydroxyl group appears at δ 4.32 as a broad multiplet.

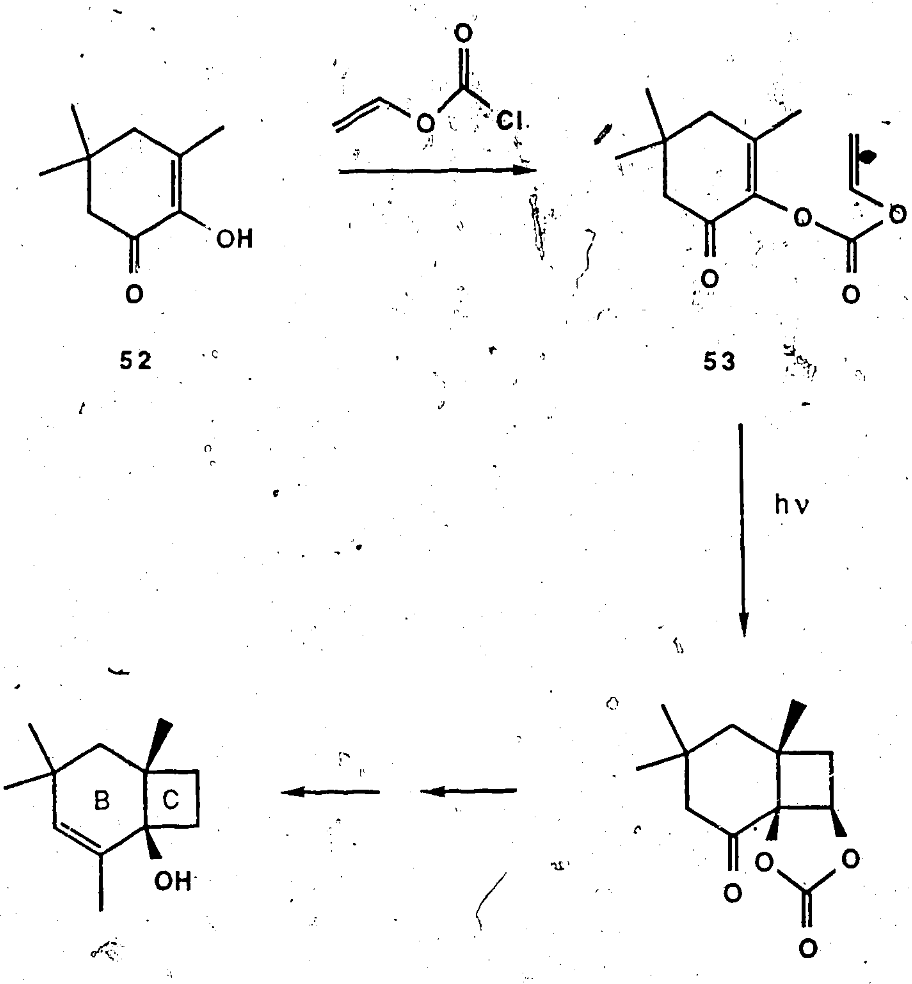
Treatment of tosylate 51 with NaH in THF (room temperature, 1 h) brought about not only cycloalkylation, but also lactonization, providing crystalline 20 in 82% yield. The ir spectrum of 20 displays strong carbonyl absorptions at 1742 and 1727 cm^{-1}, typical of ester and 6-membered lactone[36]. Its ^{1}H nmr spectrum shows that the hydrogen geminal to the oxygen in ring B has been shifted to δ 4.84 (br t, J=5.5 Hz) as compared to 51, in which it appears at δ 4.32. In addition there is only one methoxyl singlet at δ 3.80. These observations are in agreement with the proposed lactonization. The ^{13}C nmr spectrum of 20 shows signals at δ 171.22 and 170.82 for the ester carbonyls, at δ 138.81 (C-4) and 118.68 (C-3) for the two olefinic carbons, and at δ 52.44 for a methoxyl carbon. The hrms of 20 shows a molecular ion at m/z 236 corresponding to the molecular formula $C_{13}H_{16}O_4$. Lactone 20 contains the AB ring system of our target molecule and was used as a model compound for the introduction of ring C.

2. Transformation of lactone 20 into the ABC ring intermediate, carbonate 24.

Earlier studies[13] in our laboratories have shown that the BC ring intermediate 54 can be formed by an intramolecular [2+2] photocycloaddition[37] of enone 53 (Scheme 7). Enone 53 was prepared by treatment of enol 52 with vinyl chloroformate. Carbonate 54 was further elaborated to provide compound 55, a model of the BC ring system of sterpuric acid. These studies showed the efficiency of the intramolecular [2+2] photocycloaddition relative to the intermolecular case where enone 56 proved to be unreactive when irradiated in the presence of various alkenes.

In addition, the regiochemistry of intramolecular [2+2] photocycloadditions, in which the olefinic double bond and the enone

SCHEME 7. Synthesis of the BC ring system intermediate 55.[13]

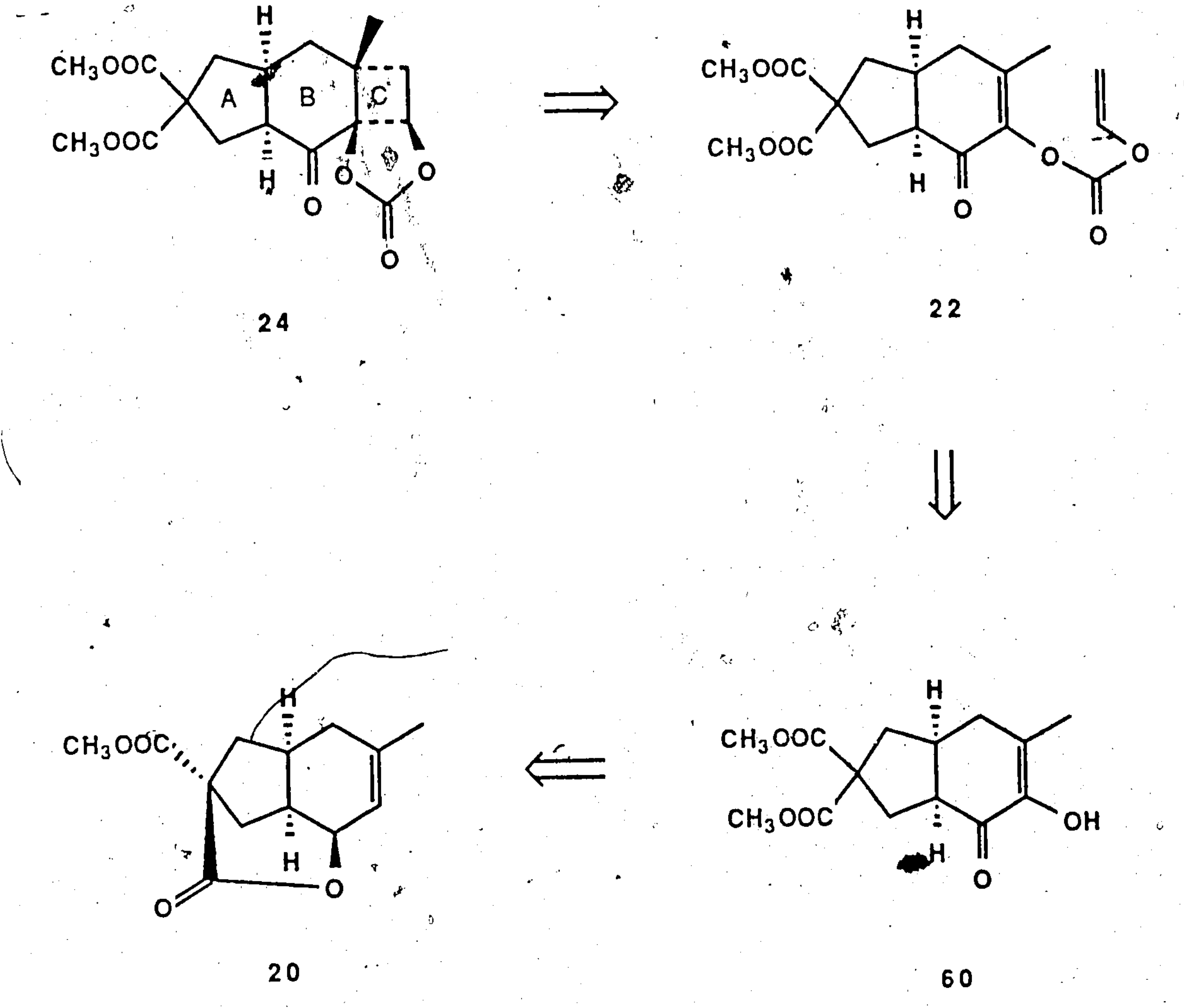


55

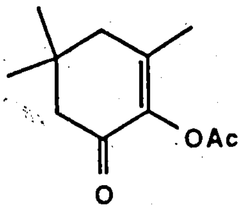
54

are connected by a chain of two to four atoms, can usually be predicted by the empirical "rule of five."[38] This rule states that the major regioisomeric product is that formed by closure of the biradical intermediate to give initially a five-membered ring, in this case

SCHEME 8. Retrosynthesis of the ABC ring intermediate **24**.



suggested that the ABC ring intermediate 24 should be formed by an intramolecular [2+2] photocycloaddition of enone 22 (Scheme 8). The required cis-anti-cis stereochemistry should be favored since it is known that in relatively rigid cyclic enones, where the two faces of the double bond are nonequivalent, the major product of photoaddition to an alkene is usually cis and that which arises by approach from the least hindered side[39]. As a result the ring junction oxygen substituent will be introduced with the correct stereochemistry, that is, cis to the methyl group and cis to the cyclopentane ring. This prediction is in accordance with the Wiesner model for photocycloaddition[40], which combines principles of conformational analysis with the assumption that the β-carbon of the excited state of the enone is pyramidal and can select the more stable configuration. In this way two configurations, 22a and 22b, can be drawn for the excited state of enone 22 (Figure IV). Clearly 22a, wherein there is no 1,3-pseudodiaxial interaction between the orbital on the β-carbon and the five-membered ring, is the more stable configuration. Thus, overlap between the alkene and the orbital on the β-carbon will lead to the product with the required stereochemistry. Enone 22 may be



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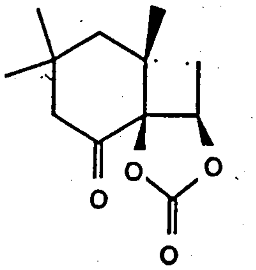

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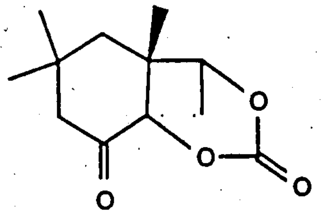

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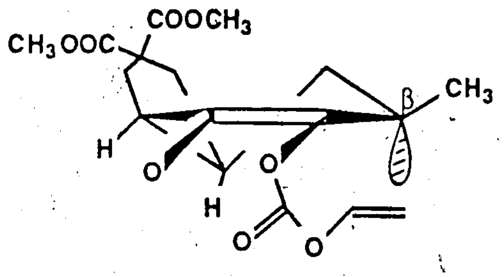
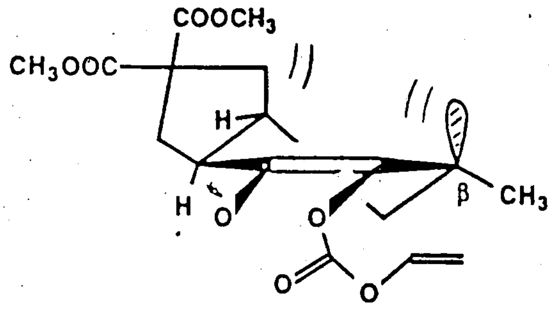
FIGURE IV. Configurations of the excited state of enone 22.

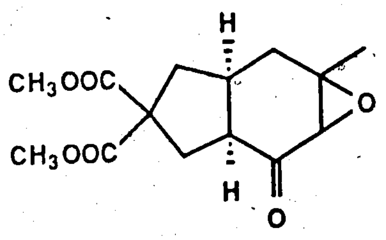


22a



22b

rearrangement[41] of epoxyketone 59. This epoxyketone is potentially available from 20 by opening of the lactone ring, oxidation to the corresponding α,β-unsaturated ketone, and subsequent epoxidation. However, it was not surprising to find that treatment of lactone 20 with methanolic KOH provided an equilibrium mixture of 20 and 61 in which 20 is the major component. Thus, neutralization of the equilibrium mixture with AcOH afforded 20 and 61 in 88% and 10% yield,



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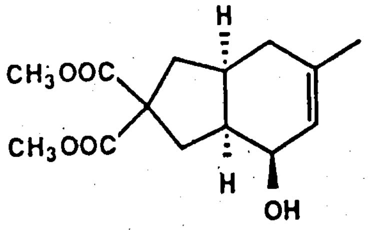
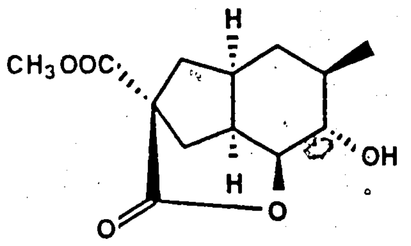


61

cm^{-1}) and carbonyl (1732 cm^{-1}) absorptions and its ^1H nmr spectrum shows methoxyl singlets at δ 3.68 and 3.67. Treatment of lactone 20 under more vigorous conditions provided similar results and it was necessary to investigate a different approach for the preparation of α-diketone 60.

Lactone 20 was subjected to a hydroboration-oxidation sequence (BH_3-THF, -5°C; H_2O_2, NaOH)[42] providing a complex mixture of products from which alcohol 62 was isolated in 30% yield. The structure of compound 62 was assigned on the basis of its spectroscopic properties. Compound 62 shows hydroxyl (3470 cm^{-1}) and carbonyl (1742 cm^{-1}) absorptions in the ir spectrum and its ^1H nmr spectrum displays signals at δ 3.52 (dd, J=8, 4.5 Hz) for the methine hydrogen geminal to the hydroxyl group, at δ 1.89 (d, J=4.5 Hz, D_2O exchangeable) for the hydroxyl hydrogen, at δ 1.42 (dddq, J=13.5, 3, 8, 8 Hz) for the methine hydrogen geminal to the methyl group, at δ 1.03 (d, J=7 Hz) for the methyl group, and at δ 1.91 (ddd, J=13.5, 8.5, 3 Hz) and 1.02 (td, J=13.5, 9 Hz) for the methylene group in the six-membered ring. The



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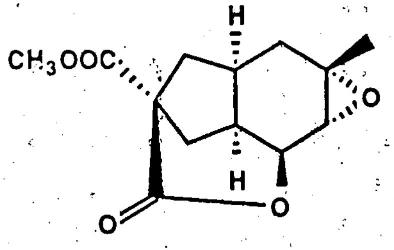
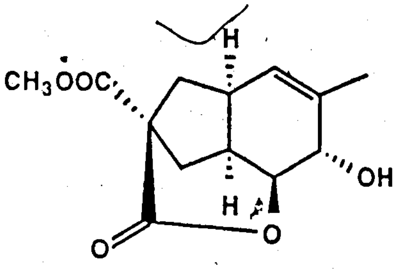


63

groups in compound 62 is in agreement with reported observations in which the hydroboration-oxidation sequence has been found to occur in a cis manner from the less hindered side of the double bond[43].

Alternatively, compound 62 was prepared in excellent yield by a two step procedure involving epoxidation of lactone 20 followed by



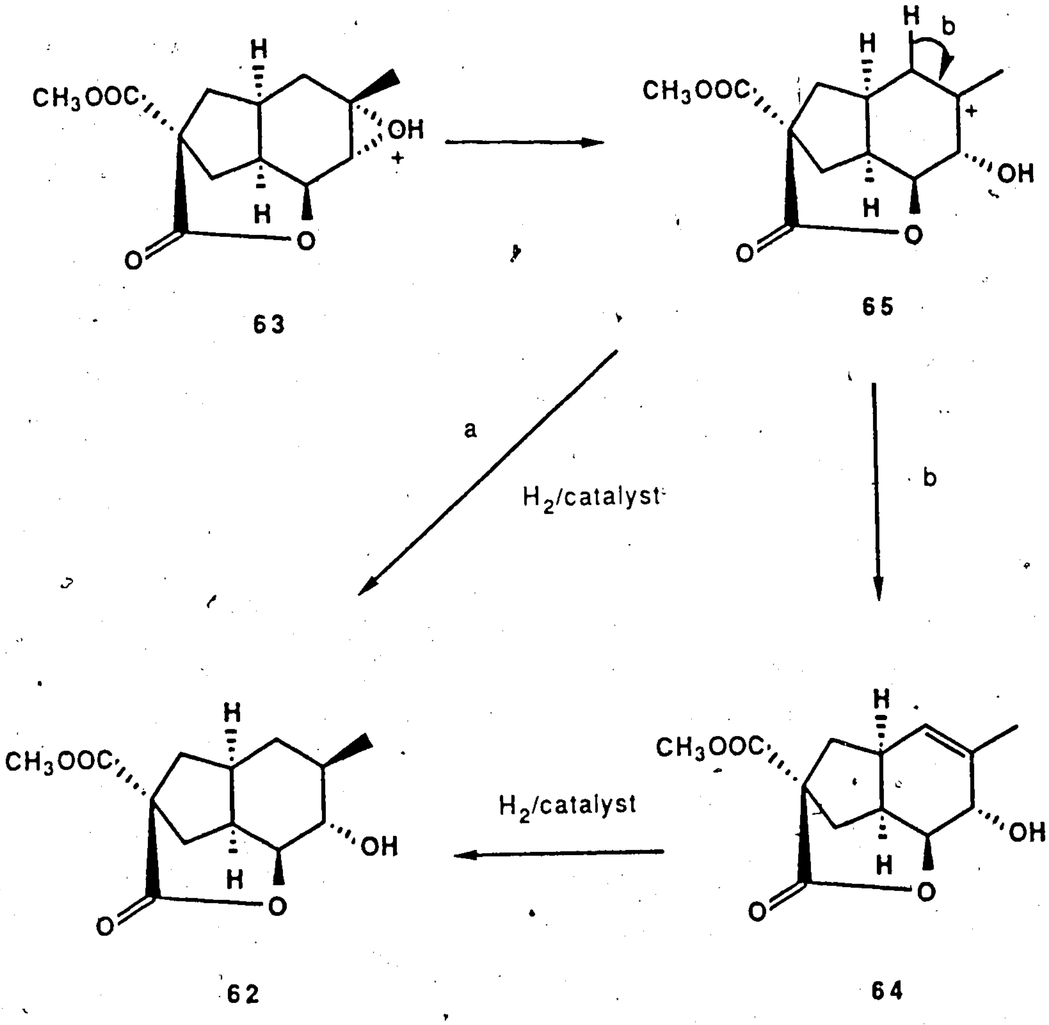
64

hydrogenolysis of the resulting epoxide 63. The epoxidation of 20 was carried out using m-chloroperbenzoic acid (MCPBA, CH_2Cl_2, room temperature)[44] to afford epoxide 63 as a single stereoisomer in 99% yield. The ^1H nmr spectrum of this compound displays a signal at δ 4.94 (dd, J=5, 3 Hz) for the methine hydrogen geminal to the oxygen of the lactone ring. This is coupled to a doublet at δ 3.27 (J=3 Hz) which may be assigned to the methine hydrogen of the epoxide ring. The methyl group appears as a singlet at δ 1.39 and the methylene in the six-membered ring appears at δ 2.26 (dd, J=15, 8.5 Hz) and 1.88 (br d, J=15 Hz). The α-orientation of the epoxide is proposed on the assumption that attack of the peracid is on the less hindered α-face of the double bond of lactone 20[45]. This observation is supported by the of alcohols 62 and 64 in a ratio of 4:1 (^{1}H nmr), respectively. This mixture was converted quantitatively to 62 by in situ hydrogenation brought about by addition of a catalytic amount of platinum oxide. The compound thus obtained proved to be identical in all respects with alcohol 62, previously prepared by hydroboration-oxidation of lactone 20. Allylic alcohol 64 was also obtained in 80% yield when epoxide 63 was recrystallized using a Skellysolve B/EtOAc mixture. Compound 64 shows hydroxyl (3450 cm^{-1}) and carbonyl (1747 cm^{-1}) absorptions in the ir. Its ^{1}H nmr spectrum displays a vinylic hydrogen at δ 5.72 (dm, J=5 Hz), a broad singlet at δ 3.98 for the methine hydrogen on the carbinol carbon, a triplet for the vinylic methyl group at δ 1.83 (J=1.5 Hz), and a D_2O exchangeable broad singlet at δ 1.70 assigned to the hydroxyl hydrogen. Further evidence for the presence and position of the carbon-carbon double bond in compound 64 was given by its ^{13}C nmr spectrum, which shows a singlet at δ 130.53 and a doublet at δ 127.57. The hrms of 64 gives a peak for the molecular ion at m/z 252, consistent with the molecular formula $C_{13}H_{16}O_5$.

These results can be rationalized as follows: it has been suggested that the acid-catalyzed hydrogenolysis of epoxides proceeds via a cationic intermediate[47], as illustrated in Scheme 9 for compound 63. Acid-catalyzed opening of the epoxide ring provides the cation intermediate 65. Hydrogen transfer from the catalyst to the less hindered α-face of 65 affords alcohol 62(a). Compound 64 may be formed from 65 by elimination of the α-proton as shown (b). It is possible that compound 62 is formed exclusively via olefin 64.

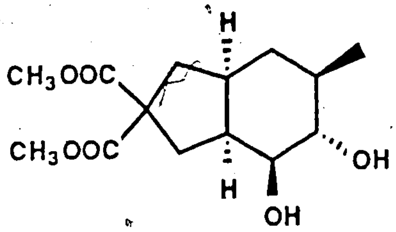
Treatment of alcohol 62 with methanolic KOH afforded diol 66 in

SCHEME 9. Mechanism of formation of alcohols 62 and 64.



91% yield. The ^1H nmr spectrum of diol 66 displays methoxyl singlets at δ 3.74 and 3.72, the hydrogens α to the hydroxyl groups appear at δ

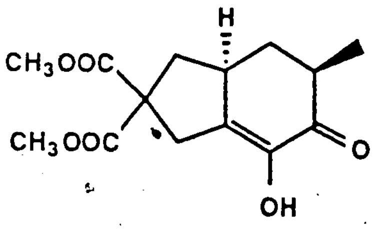
(J=4 Hz), both D_2O exchangeable. The ^{13}C nmr spectrum shows a singlet at δ 173.41 for the ester carbonyls and a quartet at δ 52.83 for the methoxyl groups. The cims of compound 66 shows a (M^+ + 18) ion at m/z 304 consistent with the molecular formula.



66

Several methods for the oxidation of alcohols to carbonyls using dimethylsulfoxide (DMSO) activated by electrophiles have been developed[48]. Among them Swern's procedure[49] using oxalyl chloride as activator provides carbonyl compounds in high yields under mild conditions. We were encouraged to apply this procedure to diol 66 by a report which describes the conversion of 1,12-dodecanediol to the corresponding dialdehyde in 98% yield[50].

Swern oxidation (2.4 eq. oxalyl chloride, 5 eq. DMSO, -60°C; 10 eq. Et_3N) of diol 66 provided α-diketone 60 and α-hydroxyketones 67 and 68 in 45, 37, and 10% yield, respectively. The ir spectrum of compound 60 displays absorptions at 3400 cm^{-1} (medium) characteristic of hydroxyl groups, at 1733 cm^{-1} (strong) for the carbonyl of the ester, and at 1700 (weak) and 1655 cm^{-1} (strong), both characteristic of the enolic form of α-diketones.[51] The ^1H and ^{13}C nmr spectra of this



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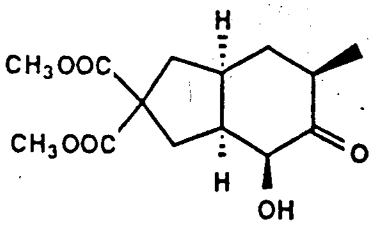

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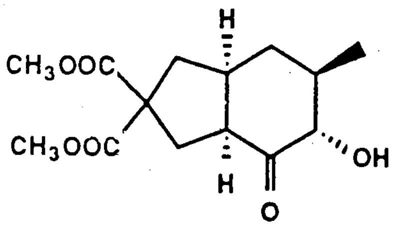

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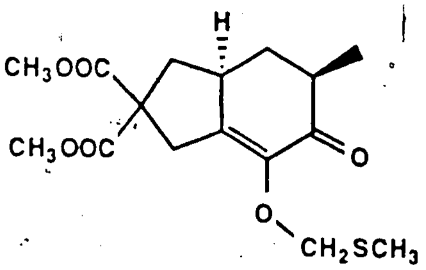
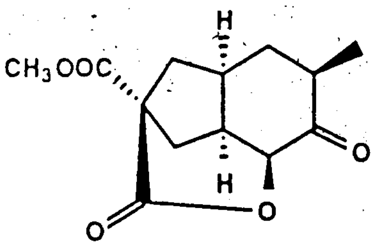


69

for the enolic hydroxyl hydrogen, at δ 3.28 (dt, J=20, 1.5 Hz) and 3.19 (dd, J=20, 3 Hz) for the allylic methylene hydrogens, at δ 2.44 (dqd, J=13, 7, 4 Hz) for the methine hydrogen <u>geminal</u> to methyl group, and at δ 1.18 (d, J=7 Hz) for the methyl group. The ^{13}C nmr spectrum of compound 60 displays typical peaks at δ 196.68 (s) for the ketone carbonyl and at δ 140.90 (s) and 135.29 (s) for the olefinic carbons. α-Hydroxyketones 67 and 68 show very similar ir and hrms spectra, but they were easily differentiated by ^{1}H nmr decoupling experiments. In the case of compound 67 these experiments show that the signal at δ 4.43 (ddd, J=7.5, 3.5, 1 Hz), assigned to the methine hydrogen <u>geminal</u> to the hydroxyl group, is coupled to the methine hydrogen at the ring junction (δ 2.90, dd, J=14, 6.5 Hz), which in turn is coupled to the

J=14, 6.5, 1.5 Hz, and 1.77, t, J=14 Hz). In compound 68 the signal assigned to the methine hydrogen geminal to the hydroxyl group (δ 3.90, dd, J=11.5, 3.5 Hz) is coupled to a methine hydrogen at δ 1.68 (m), which in turn is coupled to the methyl group (δ 1.13, d, J=6 Hz). These observations are in agreement with structures 67 and 68. Methylthiomethyl ether 69 was also isolated as a by-product during the Swern oxidation of diol 66. The formation of methylthiomethyl ethers during Swern oxidation of alcohols is not uncommon.[49]

α-Diketone 60 was prepared more efficiently via an stepwise oxidation route as follows: alcohol 62 was oxidized to provide ketone 70 which upon hydrolysis gave α-hydroxyketone [illegible], in turn was oxidized to afford α-diketone 60 in good yield.



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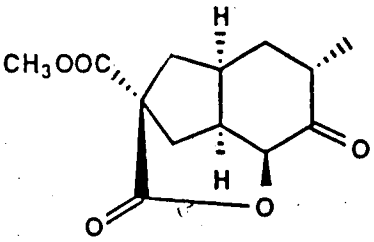
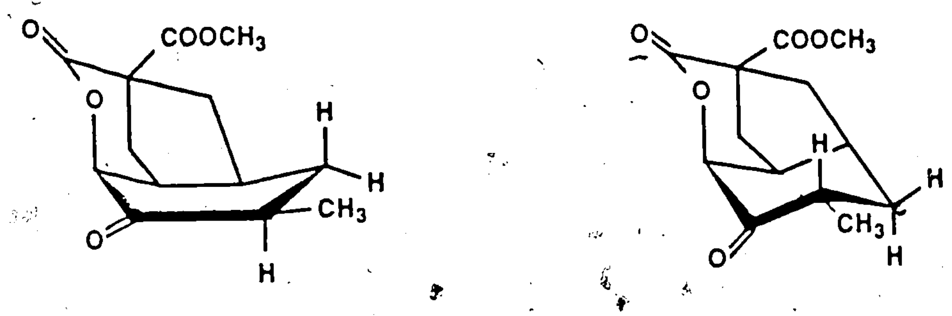


71

Swern oxidation of alcohol 62 provided an epimeric mixture of ketones 70 and 71 in 86 and 8% yield, respectively. This epimerization, which may have occurred because of excess Et_3N present during the oxidation, was not important since the epimerized center had to be converted to an sp^2 carbon in a later stage of the synthesis.

equatorial position (Figure V). Therefore similar couplings between the methine hydrogen geminal to the methyl group and the adjacent

FIGURE V. Conformation of ketones 70 and 71.

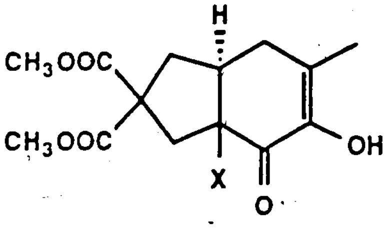


70

71

methylene hydrogens would be expected in the ^{1}H nmr spectrum of each compound. In fact, this is the case and they cannot be distinguished by this method. The tentative assignment of structure 70 to the major isomer was confirmed by basic hydrolysis (methanolic KOH) of this to give an α-hydroxyketone (98% yield) which proved to be identical with compound 67, previously prepared by Swern oxidation of diol 66. Swern oxidation of α-hydroxyketone 67 provided α-diketone 60 in 91% yield.

According to our synthetic scheme the next step involves the conversion of α-diketone 60 to vinyl carbonate 22. Since α-diketone 60 exists in the enol form shown, we had to find a way to transform this to the required enol 72. We thought this could be achieved by introducing some functionality X at the ring junction as shown in 72. This functionality would be removed at a later stage of the synthesis. Treatment of enol 60 with pyridinium bromide perbromide[52] (1.2 eq.



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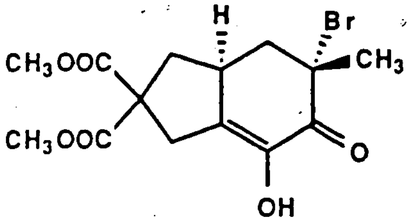

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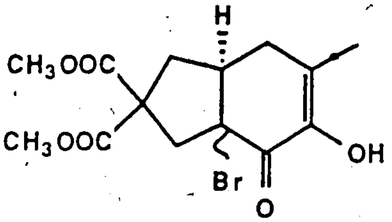
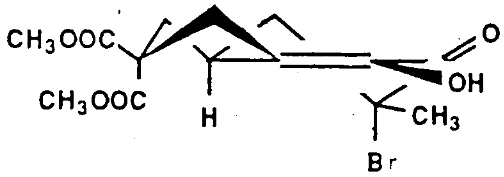


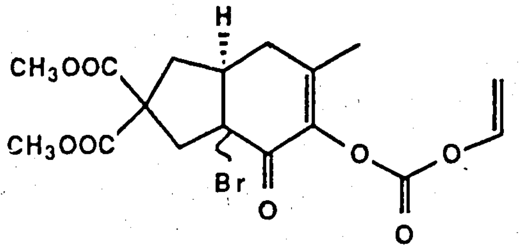
74

single stereoisomer in 66% yield. Presumably, the kinetic product of this reaction is the expected bromodiketone 74 and this is isomerized to the thermodynamically more stable bromodiketone 73 by the hydrogen bromide present in the reaction mixture[53]. The ^{1}H nmr spectrum of compound 73 is very similar to that of enol 60 except for the signals corresponding to the methyl group and the methylene hydrogens in the six-membered ring which in the case of 73 appear as a singlet at δ 1.92 and doublets of doublets at δ 2.57 (J=14.5, 4.5 Hz) and 1.78 (J=14.5, 10 Hz), respectively. The relative stereochemistry of the carbon bearing the bromine is proposed to be that shown based on the which in enol 60 appears at δ 2.95 and in 73 appears shifted to δ 3.14. A 1,3-pseudodiaxial relationship between that hydrogen and the bromine as shown in Figure VI accounts for the observed downfield shift by analogy with data reported in the steroid field[54]. The kinetic bromination of enol 60 was carried out using N-bromosuccinimide (1.1 eq. NBS, THF, -20°C)[55]. Bromodiketone 74 was obtained in 84% yield as an approximately 12:1 mixture of epimers at the carbon bearing the bromine, as indicated by ^1H nmr spectroscopy. The ^1H nmr spectrum of 74 displays signals for the major epimer as follows: a D_2O exchangeable singlet at δ 5.92 for the enolic hydroxyl hydrogen, an AB system at δ 3.62 and 2.89 with J_{AB} 14.5 Hz for the methylene hydrogens next to the carbon bearing the bromine, and a singlet at δ 1.93 for the vinylic methyl group. The hrms of 74 shows peaks of equal intensity at m/z 360 and 362 corresponding to M^+ and M^++2, characteristic of bromine containing compounds[56]. The spectral characteristics (ir, hrms, and ^1H nmr) of compound 74 do not allow an unequivocal assignment of the relative stereochemistry at the carbon bearing the bromine in the major

FIGURE VI. Conformation of bromoketone 73.



Bromodiketone 74 reacted with vinyl chloroformate (1.1 eq., pyridine, CH_2Cl_2) to afford bromocarbonate 75 in 90% yield. The ^{1}H nmr spectrum of compound 75 displays characteristic doublets of doublets at δ 7.06 (J=14, 6 Hz), 4.96 (J=14, 2 Hz), and 4.64 (J=6, 2 Hz) for the vinylic hydrogens. The rest of the spectrum is consistent with the proposed structure.



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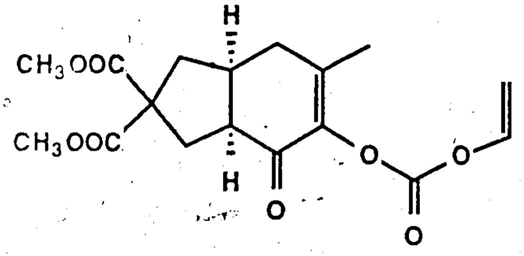
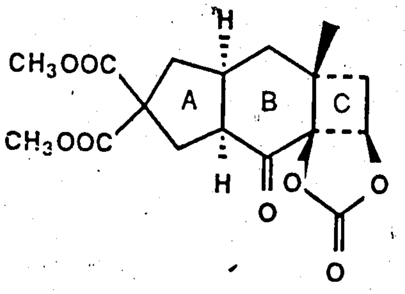


22

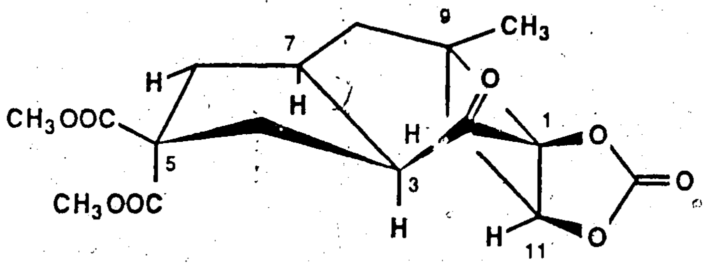
Irradiation of a dega[illegible]ution of bromocarbonate 75 in acetone (250-W mercury lamp, Pyrex or quartz immersion well and filters) led to extensive decomposition. The use of other solvents such as benzene or cyclohexane gave similar results. Decomposition may arise from dissociation of the carbon-bromine bond upon absorption of ultraviolet light[57]. We thus decided to remove the bromine from bromocarbonate 75 prior to irradiation. Debromination of compound 75 occurred smoothly with zinc dust in acetic acid[58] providing carbonate 22, bromocarbonate 75, and enol 60 in 70, 10, and 15% yield, respectively. The ultraviolet (uv) spectrum of carbonate 22 shows a maximum absorption at unsaturated system[59]. The ^1H nmr spectrum of 22 displays signals for the hydrogens at the ring junction at δ 2.87 (dt, J=7.5, 6 Hz) and 2.72 (m). The signal at δ 2.87 was assigned to the hydrogen α to the ketone on the basis of decoupling experiments. The hrms of 22 is consistent with the molecular formula $C_{17}H_{20}O_8$. The stereochemistry at the ring junction was assigned by assuming that under the thermodynamically controlled conditions of debromination, the more stable cis-1-hydrindanone system would be obtained[60]. This assumption is supported by nOe experiments performed on a subsequent intermediate..



24

The intramolecular photocycloaddition was achieved by irradiation of a degassed solution of compound 22 in acetone (250-W mercury lamp, Pyrex immersion well and filter) affording the tetracyclic compound 24 in 56% yield (based on starting material consumed). By analogy with a previous study[13] of the photocycloaddition of the model enone 53 the best yield (56%) of 24 was obtained using acetone as a solvent and when the irradiation was interrupted before 80% of the starting material has been consumed. Apparently compound 24 is photoreactive under the complex mixture of products was obtained. Compound 22 proved to be unreactive when the irradiation was carried out in benzene or cyclohexane. The ir spectrum of compound 24 shows strong carbonyl absorptions at 1812 and 1730 cm^{-1} and its ^1H nmr spectrum displays a doublet of doublets at δ 5.03 (J=7, 3.5 Hz) for the four-membered ring methine hydrogen, a triplet of doublets at δ 3.19 (J=10.5, 8 Hz) for the hydrogen at the ring junction α to the ketone, a multiplet at δ 2.99 for the hydrogen at the other ring junction, and doublets of doublets at δ 2.69 (J=15, 7 Hz) and 2.24 (J=15, 3.5 Hz) for the four-membered ring methylene hydrogens; these assignments are based on decoupling experiments. The _cis-anti-cis_ stereochemistry was inferred from nOe studies on compound 24. Presaturation of H-11 (δ 5.03, see Figure VII) gave a 16% enhancement at δ 3.19 (H-3) and 6% at δ 2.69 (H-10 α); presaturation of H-3 (δ 3.19) gave a 10% enhancement at δ 5.03 (H-11); presaturation of H-7 (δ 2.99) gave a 4% enhancement at δ 5.03 (H-11) and 3% at δ 2.69 (H-10 α). These results indicate that H-3, H-7, H-10α, and H-11 may be close to each other as shown.

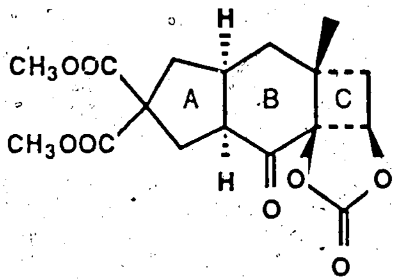
FIGURE VII. Configuration of compound 24.



Compound 24 contains the ABC ring system of sterpuric acid with present in 24 is required in order to pursue the synthesis of the target molecule.

3. Reduction of (methyl ester) lactone 20 to the required methyl lactone 21.

The transformation of compound 24 into our target molecule requires the conversion of the α-oriented methyl ester functionality in ring A to a methyl group. Since compound 24 has been successfully prepared from lactone 20, this compound (20) was chosen as a suitable intermediate to effect such conversion. Furthermore, we could take advantage of the difference in reactivity between the lactone and ester functionalities present in compound 20. Most of the methods reported for the conversion of an ester functionality to a methyl group involve reduction of the ester to the corresponding alcohol or aldehyde, which after derivatization is further reduced under a wide variety of conditions.



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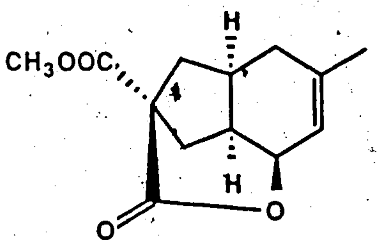

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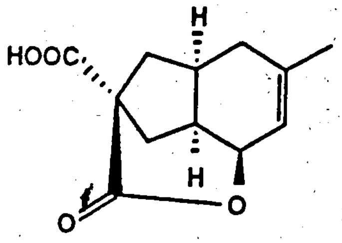
The lactone and methyl ester groups in compound 20 were easily differentiated by basic hydrolysis (aqueous KOH, THF, 0°C; 6N hydrochloric acid) providing acid 76 in 86% yield. The spectroscopic



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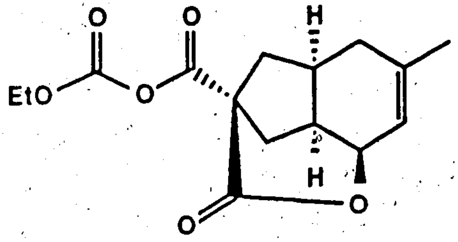
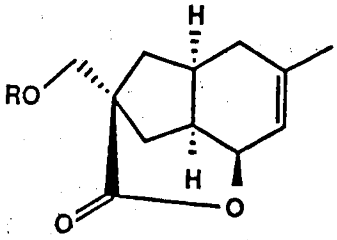


77

The procedures described for the selective reduction of a carboxylic acid to the corresponding alcohol in the presence of an ester group involve the formation of a reactive intermediate (acid chloride, mixed anhydride, etc.) followed by reduction with a mild reagent such as NaBH$_4$[61]. Treatment of compound 76 with oxalyl chloride (oxalyl chloride, benzene, room temperature)[62] did not provide the acid chloride derivative but instead extensive decomposition occurred. In a similar approach[63,64] acid 76 was treated with ethyl chloroformate (ClCOOEt, Et$_3$N, THF, 0°C) to form the intermediate mixed anhydride 77, subsequent reduction with NaBH$_4$ provided alcohol 78 in 60% yield along with recovered acid 76 (21% yield). Several attempts to improve the yield of this transformation failed, including the use of NaH as base which is reported to give better results[65]. The ir spectrum of 78 displays hydroxyl (3443 cm^{-1}) and carbonyl (1723 cm^{-1}) absorptions and its ^{1}H nmr spectrum shows signals for the hydroxymethyl group hydrogens as follows: doublets of doublets at δ 3.84(J=11.5, 7.5 Hz) and 3.75(J=11.5, 6.5 Hz), and a D$_2$O exchangeable apparent triplet at δ 2.84(J=7 Hz). The ^{13}C nmr spectrum shows signals for the ester carbonyl and hydroxymethyl carbons at δ 176.96 and 65.79, respectively.

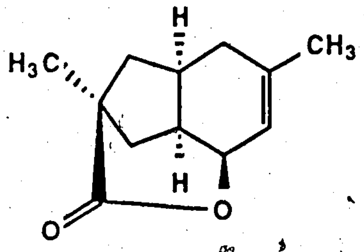
Conventional methods[66] for the deoxygenation of alcohols involve the reduction of a suitable hydroxyl derivative (tosylate, mesylate, etc.) or the nucleophilic replacement of the hydroxyl group by halogen or thiolate with subsequent reductive dehalogenation or desulfurization. These methods have been applied successfully to the deoxygenation of relatively unhindered alcohols. A useful alternative is offered by radical processes as illustrated in a recent review[67]. The conditions required for the deoxygenation of alcohol 78 should be compatible with the presence of the double bond and lactone functionalities. Hutchins[68] reported that $NaBH_4$ in polar aprotic solvents (HMPA, DMSO, sulfolane) furnishes an effective source of nucleophilic hydride which may be utilized for the reductive displacement of primary and secondary alkyl halides and sulfonate



78, R= H

79, R= Ms

esters. The mildness of borohydride allows a number of chemoselective transformations. In order to apply this method, alcohol 78 was converted to mesylate 79 (methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C)[69] in 99% yield. The ir spectrum of 79 shows carbonyl (1729 cm^{-1}) and sulfonate (1354, 1172 cm^{-1}) absorptions. Its ^1H nmr spectrum displays an AB system for the hydrogens of the methylene bearing the sulfonate at δ 4.59 and 4.23 with a coupling constant (J_{AB}) of 10 Hz. The methyl group of the sulfonate appears as a sharp singlet at δ 3.07. The hrms of 79 shows a peak for the molecular ion at m/z 286 consistent with the molecular formula $C_{13}H_{18}O_5S$. Treatment of mesylate 79 with excess $NaBH_4$ in HMPA (45°C, 4 days) provided compound 21 in 60% yield. Lower yields were obtained when DMSO was used as solvent. The ir spectrum of 21 shows a carbonyl (1737 cm^{-1}) absorption and its ^1H nmr spectrum displays a θ methyl singlet at δ 1.32 indicating that deoxygenation has occurred without affecting the lactone moiety. The cims of compound 21 shows a $M^+ + 18$ peak at m/z 210 in agreement with the proposed molecular formula. With compound 21 in hand we proceeded with the formation of ring C.

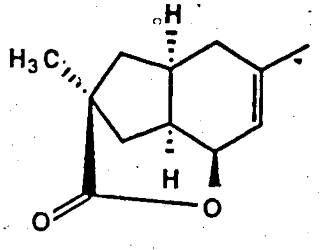


21

4. Synthesis of the ABC ring system of sterpuric acid, carbonate 25.

The addition of ring C to the AB ring system intermediate 21 was achieved following an approach similar to that described in Part 2 for the transformation of lactone 20 into the ABC ring intermediate, carbonate 24. Compound 21 was treated with m-chloroperbenzoic acid

(CH_2Cl_2, room temperature) providing epoxide 80 in 99% yield. The stereochemistry of the epoxide ring was proposed assuming that the epoxidation occurred from the less hindered α-face of the molecule.



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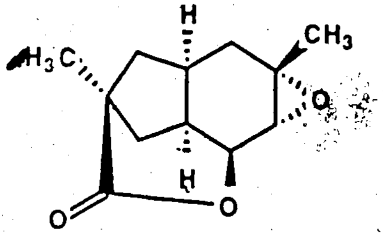
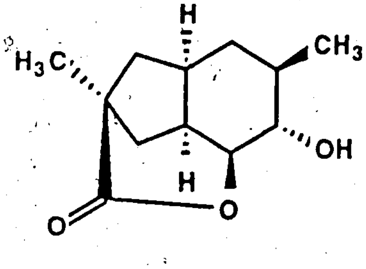


80

The ^1H nmr spectrum of 80 shows a doublet at δ 3.28 (J=3 Hz) for the methine hydrogen of the epoxide and methyl singlets at δ 1.34 and 1.31. Its hrms shows a peak for the molecular ion at m/z 208 corresponding to the molecular formula $C_{12}H_{16}O_3$.



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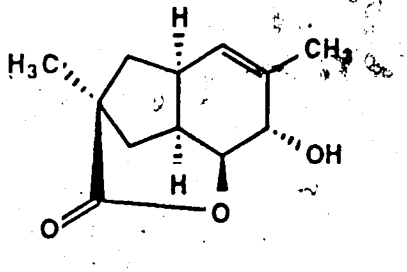
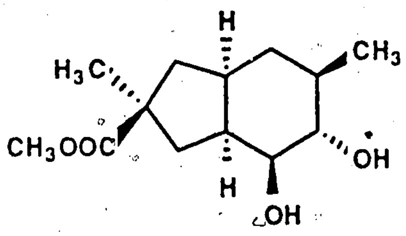


82

Acid-catalyzed hydrogenolysis (H_2, 10% Pd/C, EtOAc, AcOH, 48 hr; platinum oxide, 24 hr) of 80 afforded alcohol 81 and recovered 80 in 85 and 15% yield, respectively. As was observed in the hydrogenolysis of epoxide 63 (Part 2), alcohol 82 was detected by ^1H nmr when the reaction was interrupted after treatment with the palladium catalyst. Therefore <u>in situ</u> hydrogenation with platinum oxide was also necessary. The ir spectrum of 81 displays absorption bands for the hydroxyl (3400 cm^{-1}) and carbonyl (1737 cm^{-1}) groups and its ^1H nmr spectrum shows a large coupling (J=8 Hz) between the <u>vicinal</u> hydrogens of the carbons bearing the hydroxyl and methyl groups, suggesting a diaxial relationship[70]. The methyl group in the six-membered ring appears as a doublet at δ 1.06 (J=7 Hz). The ^{13}C nmr and hrms spectra of 81 are in agreement with the proposed structure.

Basic hydrolysis (methanolic KOH, 0°C) of alcohol 81 gave diol 83 in 88% yield. The ir spectrum of this compound shows typical hydroxyl (3400 cm^{-1}) and carbonyl (1730 cm^{-1}) absorption bands. The ^1H nmr spectrum of 83 displays a methoxyl singlet at δ 3.68 and D_2O exchangeable doublets at δ 2.46 (J=3 Hz) and 2.24 (J=4 Hz) for the



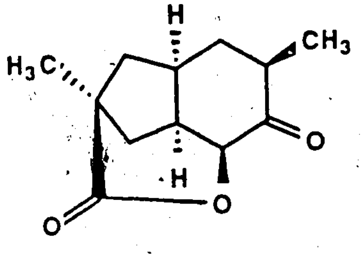
83

hydroxyl hydrogens. The hrms is consistent with the molecular formula $C_{13}H_{22}O_4$.

A modification of Moffatt conditions[71] for the oxidation of alcohols to the corresponding aldehydes or ketones was described by Corey[72] and recently this method has been applied to the oxidation of a 1,2-diol to the corresponding 1,2-diketone[73]. Encouraged by this report we subjected diol 83 to the reaction sequence described which consists of treatment of the diol with diisopropylcarbodiimide (4 eq.) and dichloroacetic acid (1 eq.) in 1:1 benzene-dimethylsulfoxide at room temperature. However in our case a complex mixture of products was obtained.

We next turned our attention to alcohol 81, which after Swern oxidation (oxalyl chloride, DMSO, CH_2Cl_2, -60°C; Et_3N) afforded a 14:1 (by ^1H nmr) mixture of epimers 84 and 85, respectively, in 97% yield. The ir spectrum of the mixture shows ketone and lactone carbonyl absorption bands at 1744 and 1722 cm^{-1}, respectively, and the ^1H nmr spectrum displays signals corresponding to 84 at δ 2.40 (dqd, J=13.5, 6.5, 5 Hz) for the methine hydrogen <u>geminal</u> to the methyl group and at δ 2.32 (ddd, J=13.5, 9, 5 Hz) and 1.50 (td, J=13.5, 9 Hz) for the methylene hydrogens in the six-membered ring. The ^{13}C nmr spectrum shows peaks at δ 205.25 and 175.43 assigned to the ketone and lactone carbonyls, respectively. The hrms gives a peak for the molecular ion at m/z 208 consistent with the molecular formula $C_{12}H_{16}O_3$.

Treatment of the mixture of epimeric ketones 84 and 85 with methanolic KOH (0°C) provided alcohol 86 in 96% yield. The ir spectrum of 86 displays hydroxyl (3480 cm^{-1}) and carbonyl (1726 cm^{-1}) absorptions. Its ^1H nmr spectrum shows a methoxyl singlet at δ 3.78, the β-oriented hydrogen (δ 1.48) of the methylene in the six-membered ring shows a coupling of 13 Hz to both adjacent methine hydrogens, thus



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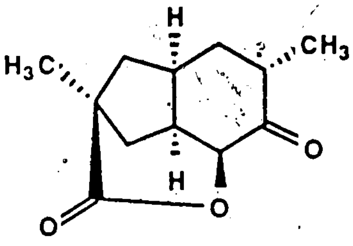
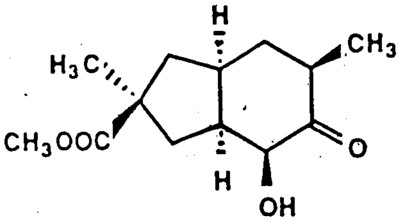


85

indicating their diaxial relationship. The ^{13}C nmr spectrum of alcohol 86 displays a peak for the methoxyl group at δ 52.19 and its hrms is consistent with the proposed structure.

Swern oxidation of alcohol 86 gave α-diketone 87 in 97%



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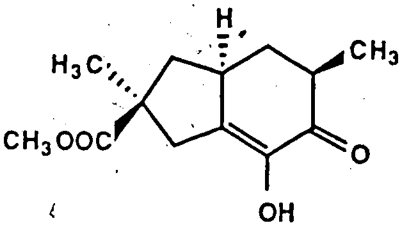
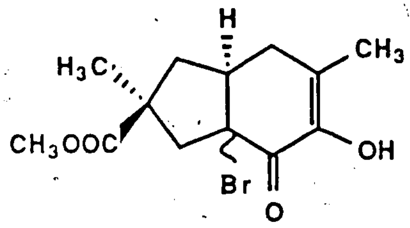


87

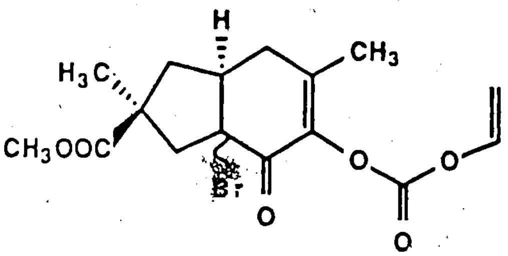
yield. The ir spectrum of 87 displays typical hydroxyl (3400 cm^{-1}) and carbonyl (1729 and 1651 cm^{-1}) absorptions and its ^{1}H nmr spectrum shows a D_2O exchangeable singlet at δ 5.96 for the hydroxyl hydrogen and a doublet at δ 1.19(J=6.5 Hz) for the methyl group α to the ketone, indicating that this α-diketone exists in the enolic form as shown.

Further evidence was provided by the ^{13}C nmr spectrum of 87 which shows peaks at δ 196.98 (α, β-unsaturated ketone carbonyl), 177.50 (ester carbonyl), and 141.02, 137.65 (olefinic carbons). The hrms of 87 shows a peak for the molecular ion at m/z 238, corresponding to the molecular formula $C_{13}H_{18}O_4$.

Treatment of compound 87 with N-bromosuccinimide (1 eq, THF, -20°C) afforded α-bromoketone 88 in 88% yield. The ir spectrum of this compound shows hydroxyl (3440 cm^{-1}), carbonyl (1730, 1677 cm^{-1}), and carbon-carbon double bond (1645 cm^{-1}) absorption bands. Its ^1H nmr spectrum displays a D_2O exchangeable singlet at δ 5.92 and a vinylic methyl singlet at δ 1.92. The hrms of 88 shows characteristic peaks of equal intensity for M^+(m/z 318) and M^+-2(m/z 316), indicating the presence of bromine. From these data we were unable to assign the relative stereochemistry at the carbon bearing the bromine. Molecular models of 87 show that both faces of the double bond are approximately equivalent making it difficult to predict the stereochemistry of the bromination. In keeping with our synthetic plan, the necessary vinyl appendage was attached to α-bromoketone 88 by reaction with vinyl chloroformate (pyridine, CH_2Cl_2), affording bromocarbonate 89 in 95% yield. The ir spectrum of this compound shows carbonate, ester, and

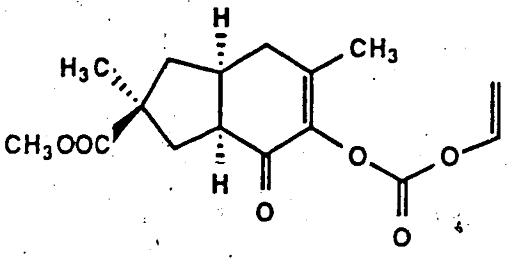


88



89

ketone carbonyl absorption bands at 1777, 1725, and 1690 cm^{-1}, respectively. The

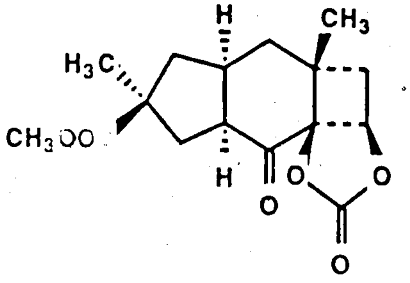


23

vinylic hydrogens appear as doublets of doublets in the ^1H nmr spectrum at δ 7.07(J=13.5, 6 Hz), 5.00(J=13.5, 2 Hz), and 4.64(J=6, 2 Hz). The ^{13}C nmr spectrum of 89 shows signals for the vinylic carbons at δ 142.73 (d) and 98.73 (t) and its hrms displays a peak at m/z 307 corresponding to the M^+-Br fragment.

Removal of the bromine from compound 89 was ~~accomplished by~~ treatment with zinc dust in acetic acid (room temperature), providing carbonate 23 in 87% yield. The ^1H nmr spectrum of 23 displays an apparent quartet at δ 2.87 (J=7 Hz, H-1) for the hydrogen at the ring junction α to the ketone, an apparent sextet at δ 2.75 (J=6.5 Hz, H-6) for the hydrogen at the other ring junction, and a singlet at δ 1.31 for the m group on the five-membered ring. The stereochemistry at the ring junction was inferred from a nOeds study of 23 as follows: presaturation of the signal at δ 2.87 (H-1) gives a 5% enhancement to the signal at δ2.75 (H-6) and a 4% enhancement to the signal at δ 1.31 (C-8 CH_3), presaturation of the methyl singlet at δ 1.31 (C-8 CH_3) gives 2% enhancement to each of the signals at δ 2.87 (H-1) and 2.75

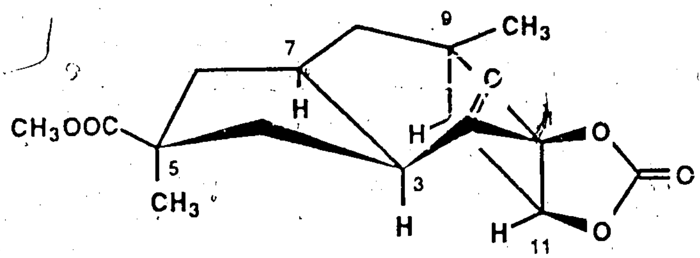
(H-6). These results suggest that H-1, H-6, and the methyl group at position 8 are cis to one another as shown in 23. The ^{13}C nmr and hrms spectra of 23 are consistent with the proposed structure.



25

With carbonate 23 in hand, we were ready to attempt the photocycloaddition reaction to introduce the four-membered ring. A degassed solution of 23 in acetone was irradiated (250-W mercury lamp, Pyrex immersion well and filter) to give starting carbonate 23 (40%) and the tetracyclic compound 25 (40%). By analogy with the irradiation of compound 22, the reaction was interrupted after approximately 50% of the starting material had been consumed, otherwise extensive decomposition occurred lowering the yield of 25. The ir spectrum of this compound shows carbonyl absorptions at 1812 and 1726 cm^{-1} and its ^1H nmr spectrum is similar to that of compound 24, showing signals at δ 5.05 (dd, J=6.5, 3.5 Hz, H-11) for the four-membered ring methine hydrogen geminal to the oxygen, at δ 3.15(td, J=10.5, 8 Hz, H-3) for the hydrogen at the ring junction α to the ketone, at δ 2.98 (ddtd, J=12, 10.5, 7.5, 4.5 Hz, H-7) for the hydrogen at the other ring junction, and at δ 2.69 (dd, J=14.5, 6.5 Hz, H-10α) and 2.24 (dd, J=14.5, 3.5 Hz, H-10β) for the four-membered ring methylene hydrogens.

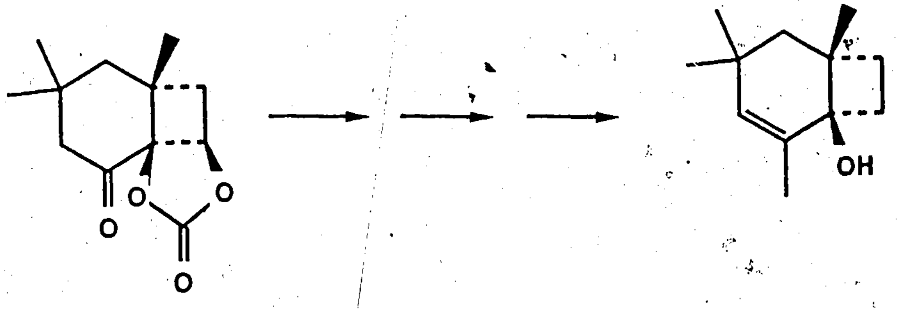
FIGURE VIII. Configuration of compound 25.



The cis-anti-cis stereochemistry was assigned on the basis of a nOeds study of 25. Presaturation of the signal at δ 5.05 (H-11, see Figure VIII) gives 6.5, 2, and 3% enhancements to the signals at δ 3.15 (H-3), 2.98 (H-7), and 2.69 (H-10α), respectively; presaturation of the signal at δ 3.15 (H-3) gives 10 and 5% enhancements to the signals at δ 5.05 (H-11) and 2.98 (H-7), respectively; presaturation of the signal at δ 2.98 (H-7) gives 4 and 7% enhancements to the signals at δ 5.05 (H-11) and 2.69 (H-10α), respectively; presaturation of the signal at δ 2.69 (H-10α) gives a 5% enhancement to each of the signals at δ 5.05 (H-11) and 2.98 (H-7). These results suggest that H-3, H-7, H-10, and H-11 are arranged as shown. Clearly the intramolecular photocycloaddition occurred with approach of the vinyl double bond from the less hindered side of the enone moiety in compound 23.

The ^{13}C nmr spectrum of compound 25 shows characteristic carbonyl peaks at δ 203.02 (ketone), 176.95 (ester), and 154.43 (carbonate) and its hrms displays a peak for the molecular ion at m/z 308 corresponding to the molecular formula $C_{16}H_{20}O_6$.

Compound 25 contains the ABC ring system of the target molecule with the correct stereochemistry of the substituents. Two major transformations are required in order to complete the synthesis of sterpuric acid, namely, the introduction of a double bond and a methyl group in ring B, and the deoxygenation of C-11 in ring C. These transformations were investigated in a previous study in which model compound 54 was converted to 55 in several steps[13]. The conversion of compound 25 to sterpuric acid using a similar procedure is currently being investigated.



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III. EXPERIMENTAL

Unless otherwise stated the following particulars apply. All reactions were done under a positive pressure of dry nitrogen. Reactions requiring anhydrous conditions were performed in oven dry glassware (115 °C, 2 h), cooled in a dessicator, assembled, and sealed with a rubber septa (when applicable) and purged with an inert gas. After work-up, all the organic solutions were dried using Na_2SO_4. The term in vacuo refers to solvent removal via Buchi rotoevaporator at water aspirator pressure. Solvents were distilled before use for chromatography or extraction. Anhydrous solvents were distilled from appropriate drying agents: tetrahydrofuran (THF) by distillation from a blue solution of potassium benzophenone ketyl; dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), dimethylformamide (DMF), triethylamine (Et_3N), pyridine, dimethyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) by distillation from calcium hydride (the latter two under reduced pressure and stored over 3 A molecular sieves under nitrogen); acetone by distillation from $CaSO_4$; Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62-70 °C. Oxalyl chloride, ethyl chloroformate, vinyl chloroformate, and methanesulfonyl chloride (MsCl) were freshly distilled when used. Silver trifluoroacetate was prepared following a reported procedure[75]. A commercial solution (Aldrich) of borane in THF was used as received.

Flash column chromatography was performed by using E. Merk silica gel 60 (230-400 ASTM mesh) according to the procedure of Still[76]. Analytical thin layer chromatography (tlc) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (245 or 350 nm). For tlc, the visualization of the chromatograms was completed by spraying with a solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%, w/v) in sulfuric acid (3%, v/v), followed by careful charring on a hot plate.

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Fourier transform infrared (ir) spectra were recorded on a Nicolet 7199 FT interferometer. Ultraviolet (uv) spectra were recorded on a Hewlett Packard HP8450A diode array spectrometer coupled to a 7470A plotter.

Hydrogen nuclear magnetic resonance (^{1}H nmr) spectra were recorded on Bruker WP-80 (at 80 MHz), Bruker WH-200 (at 200 MHz), Bruker WM-360 (at 360 MHz), Bruker WH-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard and measurements are reported in ppm downfield from TMS (δ). ^{13}C nuclear magnetic resonance (^{13}C nmr) spectra were measured on Bruker AM-300 (at 100.60 MHz) or Bruker WH-400 (at 100.60 MHz) spectrometers. For ^{13}C nmr, deuterochloroform ($CDCl_3$) was employed as the internal standard (assigned as 77.0 ppm downfield from TMS) and measurements are reported in ppm downfield from TMS (δ).

Carbon-13 multiplicities were derived from gated decoupled spin echo experiments[77]. Nuclear Overhauser enhancements (nOe) were determined by making all data points of the control (undecoupled) spectrum negative and computer-adding it to the free induction decay (FID) of the decoupled spectrum before Fourier transformation.

Positive enhancements are defined as multiplets possessing an antiphase with respect to the decoupled signal. Samples for nOe measurements were deoxygenated with nitrogen or argon for 10 min prior to use. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; δ, chemical shift.

High resolution electron impact mass spectra (hrms) were recorded on an A.E.I. MS-50 mass spectrometer coupled to a DS50 computer. Chemical ionization mass spectra (cims, ammonia as reagent gas) and low resolution electron impact mass spectra (lrms) were obtained using an A.E.I. MS-g mass spectrometer. Data are reported as m/z (relative intensity). Combustion elemental analyses were performed by the Microanalytical Laboratory of the University of Alberta.

2-Methyl-3-butyn-2-yl acetate (27).

A mixture of 2-methyl-3-butyn-2-ol (100 mL, 1.03 mol), acetic anhydride (118 mL, 1.25 mol), triethylamine (175 mL, 1.25 mol) and 4-N,N-dimethylaminopyridine (DMAP, 0.1 g) was refluxed for 3 h. The resulting dark solution was diluted with ethyl ether (300 mL), washed successively with 5% hydrochloric acid, water and brine, dried, and concentrated *in vacuo*. Distillation of the residue afforded 27 (103.2 g, 80%) as a colorless liquid; b.p. 124-126°C (lit.[74], 131°C/745 mm); tlc: R_f 0.32 (benzene/ethyl acetate, 96:4); ir (neat): 3280 (m), 2990 (m), 2130 (w), 1746 (s), 1360 (s), 1250 (s), 1137 (s) cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$); δ 2.5 (1H, s), 2.0 (3H, s), 1.67 (6H, s); hrms: m/z calcd for $C_7H_{10}O_2$ (M^+): 126.0681, found: 126.0683 (14), 111 (23), 98 (15), 84 (77), 83 (60), 67 (59), 60 (100).

rel-(1S,2S,3R)-3-Acetoxy-5-methyl-4-cyclohexene-1,2-dicarboxylic anhydride (19).

A solution of acetate 27 (100 g, 0.79 mol), maleic anhydride (77.5 g, 0.79 mol) and freshly prepared silver trifluoroacetate[75] (17.45 g, 0.079 mol) in benzene (1.5 L) was refluxed for 48 h. The solvent was removed *in vacuo* and then ether (600 mL) was added to precipitate the salts. The mixture was filtered and the solvent removed to provide crude 19 (185 g) as a greenish oil. Flash chromatography (toluene/acetone/acetic acid, 94:6:1) of the crude gave an analytical sample of 19 as a colorless viscous oil; tlc: R_f 0.41 (toluene/acetone/acetic acid, 94:6:1); ir ($CHCl_3$, cast): 1783, 1740, 1712 (br s), 1360, 1236 (br s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.83 (1H, dq, J=5.5, 1.5 Hz, H-4), 5.43 (1H, "tq", J=5.5, 1 Hz, H-3), 3.48 (2H, m, H-1, H-2), 2.69 (1H, dm, J=18 Hz, H-6α), 2.38 (1H, br dd, J=18, 8 Hz, H-6β), 2.02 (3H, s, CH_3), 1.83 (3H, m, CH_3); lrms: m/z calcd for $C_{11}H_{12}O_5$ (M^+): 224, found: 224 (1.3), 181 (24), 154 (11), 136 (63), 109 (43), 93 (19), 92 (16), 91 (16), 43 (100).

rel-(1S,2S,3R)-3-Acetoxy-5-methyl-4-cyclohexene-1,2-dicarboxylic acid (29).

Crude 19 (1 g) was dissolved in a mixture of ethyl ether (15 mL) and buffer (30 mL, pH 7.4; 2.16 g of Na_2HPO_4 and 0.60 g of $NaH_2PO_4 \cdot H_2O$ in 0.5 L of water). After stirring for 24 h the aqueous layer was separated, acidified to pH 1 (50% aqueous H_2SO_4) and extracted with ethyl acetate (3 x 40 mL). Removal of the solvent *in vacuo* provided crude 29 (0.80 g) as a yellow foam. An analytical sample was obtained by recrystallization from dichloromethane; m.p. 136-137.5°C; tlc: R_f

0.30 (ethyl acetate/methanol/acetic acid, 75:25:1); ir ($CHCl_3$ cast): 3200-2500 (br s), 1737 (s), 1374 (m), 1239 (s) cm^{-1}; ^{1}H nmr (200 MHz, acetone-d_6): δ 5.51 (1H, dsextet, J=4.5, 2.5 Hz, H-4), 5.26 (1H, br d, J=4 Hz, H-3), 3.54 (1H, dd, J=6, 3.5 Hz, H-2), 3.08 (1H, ddd, J=9, 6, 3.5 Hz, H-1), 2.76 (1H, br dd, J=18, 9 Hz, H-6β), 2.23 (1H, br dd, J=18, 6 Hz, H-6α), 1.97 (3H, s, CH_3COO), 1.74 (3H, br s, C-5 CH_3); hrms: m/z calcd for $C_{11}H_{12}O_5$ (M^+-H_2O): 224.0684, found: 224.0686 (0.83), 138 (27), 109 (23), 93 (100); cims (NH_3): 260 (M^+ + 18, 0.3), 242 (M^+-H_2O + 18, 18), 200 (100); Analysis calcd for $C_{11}H_{14}O_6$: C 54.54, H 5.83; found: C 54.49, H 5.80.

rel-(1R,2R,6S)-2-Acetoxy-4-methyl-7-oxo-8-oxabicyclo [4.3.0]non-3-ene (32).

Oxalyl chloride (0.10 mL, 1.2 mmol) was added to a solution of dimethylformamide (DMF, 31 µL, 0.4 mmol) in dichloromethane (1 mL) at 0°C. After the solution was stirred for 1 h, the solvent was removed in vacuo. The residual white powder was dissolved in acetonitrile (1 mL) and tetrahydrofuran (2 mL). A solution of acid 29 (0.048 g, 0.2 mmol) in tetrahydrofuran (2 mL) was added at -30°C and the mixture was stirred for 1 h at the same temperature. A solution of $NaBH_4$ (1 mL of a 2 M solution in DMF, 2 mmol) was added to the reaction mixture at -78°C, then the temperature was slowly raised to -20°C over 2 h. The reaction was quenched with 2 N hydrochloric acid, extracted with ethyl acetate (3 x 10 mL), washed with satd $NaHCO_3$, brine, and dried. The solvent was removed and the resulting oil purified by flash chromatography (ethyl acetate/Skellysolve B, 70: 30) to give 32 as a colorless oil (0.018 g, 42% yield); tlc: R_f 0.35 (ethyl acetate/Skellysolve B, 55: 45); ir ($CHCl_3$ cast): 1773 (s), 1735 (s), 1670 (w), 1370 (s), 1235 (s) cm^{-1}; ^1H nmr (360 MHz, benzene $-d_6$): δ 5.56 (1H, dq, J=5, 1.5 Hz, H-3), 5.26 (1H, br "t", J=5 Hz, H-2), 4.05 (1H, dd, J=9, 3 Hz, H-9), 3.81 (1H, dd, J=9, 7 Hz, H-9), 2.75 (1H, br d, J=18 Hz, H-5 α), 2.42 (1H, td, J=9, 3 Hz, H-6), 2.31 (1H, dddd, J=9, 7, 5, 3 Hz, H-1), 2.10 (1H, ddm, J=18, 10 Hz, H-5 β), 2.03 (3H, s, CH_3), 1.81 (3H, br s, CH_3); hrms: m/z calcd for $C_{11}H_{14}O_4$ (M^+): 210.0892, found: 210.0892 (7), 168 (38), 152 (60), 123 (100), 91 (70).

<u>rel-(1R,2R,3S)-2,3-Bis(hydroxymethyl)-5-methyl-5-cyclohexen-1-ol (33).</u>

A solution of crude 19 (14.60 g) in tetrahydrofuran (50 mL) was added dropwise over a period of 40 min to a suspension of $LiAlH_4$ (4.90 g) in tetrahydrofuran (70 mL) at 0°C. This mixture was refluxed for 48 h and then water (40 mL) was slowly added. The copious precipitate was filtered and thoroughly washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried and the solvent evaporated <u>in vacuo</u> to afford a yellow oil. The crude was purified by flash chromatography (acetone/dichloromethane, 85:15) to give 33 (6.55 g, 60% yield from 27) as a white gum; tlc: R_f 0.4 (acetone/dichloromethane, 85:15); ir ($CHCl_3$, cast): 3400-3200 (br, s), 1660 (w), 1440 (s), 1047 (s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 5.44 (1H, m, H-6), 4.43 (1H, m, H-1), 3.93 (1H, dd, J=11, 6.5 Hz, CH_2-O), 3.77 (1H, dd, J=11, 5.5 Hz, CH_2-O), 3.73-3.64 (2H, m, CH_2-O), 3.20 (3H, br, D_2O exchangeable, OH), 2.12 (1H, m, CH), 2.06 (1H, br d, J=18 Hz, H-4), 2.02 (1H, m, CH), 1.85 (1H, br d, J=18 Hz, H-4), 1.67 (3H, br s, CH_3);hrms: m/z calcd for $C_9H_{14}O_2$ (M^+-H_2O):

154.0994, found: 154.0998 (18), 123 (74), 106 (30), 93 (100): Analysis calcd for $C_9H_{16}O_3$: C 62.76, H 9.36; found: C 63.08, H 9. 34.

Tosylation of triol 33.

p-Toluenesulfonyl chloride (0.123 g, 0.60 mmol) was added in portions to a solution containing triol 33 (0.052 g, 0.30 mmol), triethylamine (1 mL) and a catalytic amount of DMAP in dichloromethane (3 mL) at 0°C. After stirring at the same temperature for 3 h the mixture was poured into ice-water (4 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with 5% hydrochloric acid, satd $NaHCO_3$, and brine, dried, and concentrated in vacuo to give a yellow oil (0.060 g). The crude was purified by flash chromatography to give compounds 34 (0.009 g, 20% yield, eluting with Skellysolve B/ethyl acetate, 3:1) and 35 (0.018 g, 20% yield, eluting with ethyl acetate/methanol, 97:3) as colorless oils. Starting material (0.02 g, 40%) was recovered. Compound 34, tlc: R_f 0.33 (Skellysolve B/ethylacetate, 3:1); ir ($CHCl_3$ cast): 1650 (w), 1362 (s), 1175 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.79 (2H, d, J=8 Hz, Ar-H), 7.35 (2H, d, J=18 Hz, Ar-H), 5.67 (1H, dq, J=5.5, 1.5 Hz, H-3), 4.07 (1H, d, J=5.5 Hz, H-2), 3.96 (1H, dd, J=9.5, 8 Hz, H-9), 3.86 (1H, dd, J=9.5, 8 Hz, H-9), 3.77 (1H, ddd, J=8, 5.5, 2.5 Hz, H-7), 3.55 (1H, br d, J=8 Hz, H-7), 2.45 (3H, s, Ar-CH_3), 2.43-2.35 (2H, m), 2.29 (1H, t, J=8 Hz, H-1), 2.0 (1H, br dd, J=18, 2.5 Hz, H-5), 1.64 (3H, s, C-4 CH_3); cims (NH_3): 326 (M^+ +18, 100).

Compound 35, tlc: R_f 0.50 (ethyl acetate/methanol, 95:5); ir ($CHCl_3$ cast): 3400 (br s), 1650 (w), 1060 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.44 (1H, brm, H-3), 4.58 (1H, ddd, J=8, 4, 2 Hz, H-2), 3.99

(1H, t, J=8 Hz, H-9), 3.94 (1H, dd, J=8, 5 Hz, H-7), 3.79 (1H, t, J=8 Hz, H-9), 3.58 (1H, dd, J=8, 4 Hz, H-7), 2.74 (1H, quintet, J=8 Hz, H-1), 2.54 (1H, m, H-6), 2.12 (1H, br dd, J=18, 8 Hz, H-5), 1.93 (1H, br dd, J=18, 6 Hz, H-5), 1.76 (3H, s, CH_3), 1.70 (1H, br s, D_2O exchangeable, OH); cims (NH_3): 172 (M^+ + 18, 100).

rel-(1R,6R,7S)-7-Hydroxymethyl-3,3,9-trimethyl-2,4-dioxabicyclo[4.4.0]dec-9-ene (36).

A solution of triol 33 (2.64 g), dimethoxypropane (10 mL) and trifluoroacetic acid (0.2 mL) in dichloromethane (50 mL) was stirred at room temperature for 10 h. The resulting mixture was washed with satd $NaHCO_3$ and brine, dried, and concentrated in vacuo to give a yellowish oil. The crude was purified by flash chromatography (ethyl acetate/Skellysove B, 55:45) to give crystalline 36 (1.95 g, 60%), 37 (0.48 g, 15%) and 38 (0.14 g, 5%). Compound 36, m.p. 79-80°C; tlc: R_f 0.30 (ethyl acetate/Skellysolve B, 3:2), 0.40 (chloroform/acetone, 85:15); ir ($CHCl_3$ cast): 3450 (s), 1680 (w), 1378 (s), 1029 (s) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 5.41 (1H, br m, H-10), 4.43 (1H, br t, J=4 Hz, H-1), 4.28 (1H, dd, J=12, 4.5 Hz, H-5), 4.04 (1H, dd, J=11.5, 9 Hz, CH_2-O), 4.02 (1H, br s, D_2O exchangeable, OH), 3.91 (1H, br d, J=12 Hz, H-5), 3.60 (1H, dd, J=11.5, 4 Hz, CH_2-O), 2.24 (1H, br dd, J=18, 6.5 Hz, H-8), 2.07 (1H, m, H-7), 1.94 (1H, br d, J=18 Hz, H-8), 1.72 (3H, br s, C-9 CH_3) 1.68 (1H, q, J=4 Hz, H-6), 1.55 (3H, s, C-3 CH_3), 1.41 (3H, s, C-3 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 138.98 (s, C-9), 119.49 (d, C-10), 98.48 (s, C-3), 64.61 (d, C-1), 64.40 (t), 63.18 (t), 38.39 (d), 34.21 (t, C-8), 33.85 (d), 29.37 (q, C-9 CH_3), 23.73 (q), 19.15 (q); hrms: m/z calcd for $C_{12}H_{20}O_3$ (M^+): 212.1413, found: 212.1421

(0.67), 194 (1.05), 154 (18), 136 (54), 123 (73), 107 (100), 93 (83); Analysis calcd for $C_{12}H_{20}O_3$: C 67.89, H 9.49; found: C 67.94, H 9.38.

Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of H-1 (δ 4.43) gave 13% enhancement at δ 5.41 (H-10), 13% at δ 1.68 (H-6), and 10% at δ 1.55 (C-3 CH_3).

Compound 37, colorless oil; tlc: R_f 0.34 (ethyl acetate/Skellysolve B, 3:2), 0.26 (chloroform/acetone, 85:15); ir ($CHCl_3$ cast): 3430 (s), 1670 (w), 1370 (m), 1220 (s) 1071 (s) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 5.36 (1H, br s, H-9), 4.50 (1H, br m, H-8), 3.86 (1H, dd, J=12, 3Hz, CH_2-O), 3.80 (1H, dd, J=13, 1.5 Hz, CH_2-O), 3.76 (1H, dd, J=13, 3 Hz, CH_2-O), 3.68 (1H, dd, J=12, 5 Hz, CH_2-O), 2.35 (1H, m, H-11), 2.10-2.00 (3H, m), 1.98 (1H, br dd, J=18, 6 Hz, H-11), 1.74 (3H, br s, C-10 CH_3), 1.37 (3H, s, C-4 CH_3), 1.35 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{12}H_{20}O_3$ (M^+): 212.1413, found: 212.1412 (1.91), 195 (5), 154 (15), 153 (34), 122 (63), 109 (67), 93 (56), 79 (100).

Compound 38, white gum; tlc: R_f 0.36 (ethyl acetate/Skellysolve B, 1:9); ir ($CHCl_3$ cast): 2990 (m), 1358 ([illegible]), 1230 (s), 1061 (s), 1040 (s), 844 (s), 827 (s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 6.97 (1H, br dd, J=7, 1.5 Hz, H-10), 6.94 (1H, d, J=7 Hz, H-11), 4.44 (1H, br d, J=13.5 Hz, H-2), 3.87 (1H, d, J=13.5 Hz, H-2), 3,67 (1H, dd, J=12, 10.5 Hz, H-6), 3.57 (1H, dd, J=12, 5 Hz, H-6), 2.34 (1H, m, H-7), 2.25 (3H, brs, C-9 CH_3), 1.94 (1H,dd, J=17.5, 9 Hz, H-8), 1.87 (1H, br d, J=17.5 Hz, H-8), 1.44 (6H, s, $2xCH_3$); hrms: m/z calcd for $C_{12}H_{18}O_2$ (M^+): 194.1307, found: 194.1312 (3.6), 192 (39), 177 (63), 135 (42), 134 (74), 133 (88), 106 (65), 91 (100).

Acetylation of 36.

Alcohol 36 (0.005 g) was dissolved in acetic anhydride (0.1 mL) and triethylamine (0.1 mL). After stirring for 5 h the mixture was evaporated in vacuo and the crude purified by flash chromatography (ethyl acetate/Skellysolve B, 1:1) to give 39 (0.005 g) as a colorless oil tlc: R_f 0.53 (ethyl acetate/Skellysolve B, 6:4); ^{1}H nmr (200 MHz, $CDCl_3$): δ 5.54 (1H, dq, J=4, 1.5 Hz, H-10), 4.6 (1H, dd, J=11, 4.5 Hz, CH_2OAc), 4.40 (1H, m, H-1), 4.16 (1H, dd, J=11, 9 Hz, CH_2OAc), 4.13 (1H, dd, J=12, 4.5 Hz, H-5), 3.88 (1H, dd, J=12, 3 Hz, H-5), 2.2 (1H, m, H-7), 2.12 (1H, m, H-8), 2.10 (3H, s, CH_3COO), 1.80 (1H, q, J=4.5 Hz, H-6), 1.75 (3H, br s, C-9 CH_3), 1.60 (1H, m, H-8), 1.47 (3H, s, C-3 CH_3), 1.40 (3H, s, C-3 CH_3).

Acetylation of 37.

A mixture of alcohol 37 (0.005 g), acetic anhydride (0.1 mL), triethylamine (0.1 mL) and a catalytic amount of DMAP was stirred for 5 h. The mixture was evaporated <u>in vacuo</u> and the crude purified by flash chromatography (ethyl acetate/Skellysolve B, 6:4) to give 40 (0.005 g) as a colorless oil; tlc: R_f 0.59 (ethyl acetate/Skellysolve B, 6:4); ^{1}H nmr (200 MHz, $CDCl_3$): δ 5.56 (1H, br m, H-8), 5.2 (1H, br m, H-9), [illegible]9 (1H, dd, J=12, 1.5 Hz, CH_2-O), 3.62-3.58 (2H, m, ~~CH_2-O), 3.50~~ (1H, dd, J=12, 3 Hz, CH_2-O), 2.60 (1H, m), 2.30 (1H, m), 2.08 (3H, s, CH_3COO), 2.06 (1H, m), 1.87 (1H, br dd, J=18, 6 Hz, H-11), 1.72 (3H, br s, C-10 CH_3), 1.36 (3H, s, CH_3), 1.34 (3H, s, CH_3).

rel-(1R,6R,7S)-3,3,9-Trimethyl-7-p-tolylsulfonyloxymethyl-2,4-dioxabicyclo[4.4.0]dec-9-ene (41).

p-Toluenesulfonyl chloride (16.15 g, 82 mmol) was added in small portions during 1 h to a solution of alcohol 36 (8.70 g, 41 mmol), triethylamine (60 mL, 410 mmol), and DMAP (0.25 g, 2 mmol) in dichloromethane (250 mL) at 0°C. The reaction mixture was stirred for 24 h at room temperature, filtered, and then poured into ice-water (200 mL). The organic layer was separated, washed with satd $NaHCO_3$ and brine, dried, and concentrated *in vacuo*. The resulting dark oil (17.0 g) was purified by flash chromatography (ethyl acetate/Skellysolve B, 3:7) to give 41 (14.00 g, 90% yield) as a viscous orange oil: tlc: R_f 0.35 (ethyl acetate/Skellysolve B, 3:7), 0.36 (chloroform/acetone, 98:2); ir ($CHCl_3$ cast): 2995 (w), 1600 (w), 1358 (w), 1175 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.80 (2H, d, J=8 Hz, Ar-H), 7.33 (2H, d, J-8 Hz, Ar-H), 5.40 (1H, br m, H-10), 4.61 (1H, ddd, J=10.5, 3.5, 1.5 Hz, CH_2OTs, 4.28 (1H, br m, H-1), 4.22 (1H, dd, J=10.5, 9.5 Hz, CH_2OTs), 4.18 (1H, dd, J=12.5, 4.5 Hz, H-5), 3.71 (1H, dd, J=12.5, 1.5 Hz, H-5), 2.44 (3H, s, Ar-CH_3), 2.23 (1H, m), 2.20 (1H, br d, J=17 Hz, H-8), 2.05 (1H, br dd, J=17, 4 Hz, H-8), 1.65 (3H, s, C-9 CH_3), 1.60 (1H, qd, J=4.5, 1.5 Hz, H-6), 1.45 (3H, s, C-3 CH_3), 1.23 (3H, s, C-3 CH_3); cims (NH_3): 384 (M^+ +18, 85), 366 (M^+, 1), 326 (71), 308 (100).

rel-(1R,5S,8R)-3-Methyl-8-[3,3-bis (methoxycarbonyl)-2-methyl-propyl-2-oxy]-methyl-7-oxabicyclo[3.2.1]oct-2-ene (42).

Sodium hydride (0.41 g of a 60% mineral oil suspension, 1.05 mmol) was placed in a dry flask, washed twice with Skellysolve B and then suspended in dry tetrahydrofuran (3 mL). Dimethylmalonate (0.20 mL, 1.75 mmol) was added slowly and the mixture was stirred for 40 min at room temperature. A solution of tosylate 41 (0.127 g, 0.35 mmol) in dry tetrahydrofuran (2 mL) was then added followed by a catalytic amount of NaI. The resulting mixture was refluxed for 5 days. Water (10 mL) was added, and the aqueous phase was extracted with ethyl ether (3 x 15 mL). The organic extracts were combined, washed with brine, dried, and concentrated. The crude was purified by flash chromatography (ethyl acetate/Skellysolve B, 1:9) to give recovered starting material (23%) and compound 42 (0.011 g, 10%) as a colorless oil; tlc: R_f 0.61 (ethyl acetate/Skellysolve B, 6:4), 0.23 (chloroform/acetone, 98:2); ir ($CHCl_3$ cast): 2980 (m), 1754 (s), 1739 (s), 1660 (w), 1430 (m), 1360 (w), 1240 (s), 1130 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCL_3$): δ 5.74 (1H, dq, J=6, 1.5 Hz, H-2), 4.10 (1H, d, J=6 Hz, H-1), 3.92 (1H, ddd, J=9, 6, 2 Hz, H-6 exo), 3.75 (1H, s, H-3'), 3.74 (6H, s, $2xOCH_3$), 3.60 (1H, d, J=9 Hz, H-6 endo), 3.34 (1H, t, J=8 Hz, C-8 CH_2-O), 3.24 (1H, dd, J=8, 7 Hz, C-8 CH_2-O), 2.42 (1H, br d, J=17 Hz, H-4 exo), 2.38 (1H, m, H-5), 2.08 (1H, t, J=7 Hz, H-8), 2.02 (1H, br d, J=17 Hz, H-4 endo), 1.66 (3H, s, C-3 CH_3), 1.44 (6H, s); hrms: m/z calcd for $C_{12}H_{19}O_2$ [M^+-$CH(COOCH_3)_2$]: 195.1385, found: 195.1387 (6), 173 (20), 136 (100), 107 (50), 93 (30); cims (NH_3): 344 (M^++18, 100), 327 (M^++1, 86), 311 (55).

rel-(1R,6R,7S,9R)-7-Hydroxymethyl-3,3,9-trimethyl-2,4-dioxabicyclo[4.4.0]decane (44).

Alcohol 36 (0.072 g), platinum oxide (0.003 g), and ethyl ether (3 mL) were mixed in a round-bottom flask. A balloon filled with hydrogen was fitted to the flask and the system was purged three times. This

mixture was stirred vigorously for 72 h. Removal of the catalyst by filtration, concentration in vacuo and purification by flash chromatography (chloroform/acetone, 85:15) afforded 44 (0.058 g, 80% yield) as a colorless oil; tlc: R_f 0.23 (chloroform/acetone, 85:15); ir ($CHCl_3$ cast): 3420 (m), 2950 (m),, 1375 (m), 1235 (s), 1072 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 3.99 (1H, dt, J=10, 5 Hz, H-1), 3.88 (2H, d, J=6.5 Hz, CH_2-OH), 3.63 (1H, br d, J=11 Hz, H-5), 3.53 (1H, dd, J=11, 5 Hz, H-5), 2.31 (1H, m), 2.08 (1H, m), 1.94-1.80 (2H, m), 1.68-1.54 (3H, m), 1.46 (6H, s, C-3 $2xCH_3$), 1.00 (3H, d, J=6 Hz, C-9 CH_3), 0.84 (1H, q, J=11 Hz); hrms: m/z calcd for $C_{12}H_{22}O_3$ (M^+): 214.1570, found: 214.1571 (1), 215 (M^++1, 1.5), 199 (83), 169 (12), 139 (100), 109 (36), 95 (57), 93 (71), 79 (35).

rel-(1R,6R,7S,9R)-3,3,9-Trimethyl-7-p-tolylsulfonyloxymethyl-2,4-dioxabicyclo[4.4.0]decane (45).

Compound 45 was obtained from 44 as a yellow oil (80% yield) utilizing the procedure described previously for the preparation of 41; tlc: R_f 0.46 (ethyl acetate/Skellysolve B, 1:3); ^1H nmr (400 MHz, $CDCl_3$): δ 7.80 (2H, d, J=8 Hz, Ar-H), 7.32 (2H, d, J=8 Hz, Ar-H), 3.92 (2H, d, J=7 Hz, CH_2-OTs), 3.86 (1H, dt, J=10.5, 5 Hz, H-1), 3.76 (1H, dd, J=11, 9.5 Hz, H-5), 3.65 (1H, dd, J=11, 5.5 Hz, H-5), 2.46 (3H, s, Ar-CH_3), 2.35 (1H, dq, J=9.5, 5.5 Hz, H-6), 1.96 (1H, m), 1.86 (1H, br dt, J=12, 4 Hz), 1.64-1.54 (2H,m), 1.46 (1H, br d, J=12 Hz), 1.43 (3H, s, C-3 CH_3), 1.41 (3H, s, C-3 CH_3), 1.00 (3H, d, J=6 Hz, C-9 CH_3), 0.84 (1H, q, J=12 Hz).

rel-(1R,6R,7R,9R)-7-[2,2-Bis(methoxycarbonyl)ethyl]-3,3,9-trimethyl-2,4-dioxabicyclo[4.4.0]decane (46).

Compound 46 was obtained from 45 as a colorless oil (40% yield, 20% recovered starting material) by the procedure described for the preparation of compound 42. tlc: R_f 0.37 (chloroform/acetone, 95:5); ir ($CHCl_3$ cast): 1753 (m), 1736 (s), 1440 (w), 1360 (w), 1234 (m), 1153 (m) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ3.98-3.78 (3H, m, H-1, CH_2-O), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.48 (1H, t, J=7.5 Hz, H-2'), 2.36 (1H, dq, J=11, 5 Hz, H-6), 1.89-1.79 (3H, m), 1.62 (1H, q, J=12 Hz), 1.50-1.35 (3H, m), 1.40 (3H, s, C-3 CH_3), 1.38 (3H, s, C-3 CH_3), 0.98 (3H, d, J=6 Hz, C-9 CH_3), 0.82 (1H, td, J=13, 11 Hz); hrms: m/z calcd for $C_{16}H_{25}O_6$ (M^+-CH_3):313.1651, found: 313.1651(80), 253(11), 193(13), 189 (22), 161(15), 121(100), 93(15), 79(13).

rel-(1R,6R,7S)-7-[2,2-Bis(methoxycarbonyl)ethyl]-3,3,9-trimethyl-2,4-dioxabicyclo[4.4.0]dec-9-ene (47).

Sodium hydride (1.00 g of a 50% mineral oil suspension, 21 mmol) was placed in a dry flask, washed twice with Skellysolve B and then suspended in dry hexamethylphosphoramide (HMPA, 40 mL). Dimethylmalonate (3.20 mL, 28 mmol) was added dropwise to the suspension at 0°C and the mixture stirred for 40 min at room temperature. A solution of tosylate 41 (2.55 g, 7 mmol) in dry HMPA (40 mL) was added followed by a catalytic amount of NaI. The resulting mixture was warmed to 55°C (oil bath) with stirring for 7 days. The cooled mixture (ice bath) was neutralized (pH ~7) with acetic acid and then partitioned between ice-water (100 mL) and ethyl ether/Skellysolve B, 1:1 (100 mL). The aqueous phase was extracted with ethyl ether/Skellysolve B, 1:1 (5 x 200 mL) and the combined organic extracts were washed with brine, dried, and concentrated in vacuo. The crude material was purified by flash-chromatography (dichloromethane/acetone, 97:3) to afford **47** (1.51 g, 67% yield) as a slightly yellow oil. The aqueous phase was further extracted with ethyl ether (3 x 200 mL) and the organic extracts washed with brine, dried and evaporated. Purification by flash chromatography afforded **48** (0.11 g, 10%) as a crystalline compound.

Compound **47**, tlc: R_f 0.28 (ethyl acetate/Skellysolve B, 3:7), 0.41 (dichloromethane/acetone, 96:4); ir ($CHCl_3$ cast): 1740(s), 1735 (s), 1450(m), 1200(m), 1240(m) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.50 (1H, dq, J=3.5, 1.5 Hz, H-10), 4.43 (1H, br m, H-1), 3.96 (1H, dd, J=12, 5 Hz, H-5), 3.84 (1H, dd, J=12, 6.5 Hz, H-5), 3.76 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.53 (1H, dd, J=8.5, 7 Hz, H-2'), 2.36 (1H, ddd, J=14, 8.5, 5 Hz, H-1'), 2.00-1.90 (2H, m), 1.96 (1H, ddd, J=14, 8, 7Hz, H-1'), 1.82-1.74 (2H, m), 1.72 (3H, s, C-9 CH_3), 1.42 (3H, s, C-3 CH_3), 1.40 (3H, s, C-3 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 170.30 (s, CO), 170.14 (s, CO), 135.56 (s, C-9), 123.66 (d, C-10), 98.36 (s, C-3), 67.95 (d, C-1), 60.00 (t, C-5), 52.86 (d, C-2'), 50.41 (q, $2xOCH_3$), 34.68 (d), 34.23 (t), 33.88 (d), 30.99 (t), 26.60 (q, C-9 CH_3), 23.94 (q, $2xCH_3$); hrms: m/z calcd for $C_{16}H_{23}O_6$ (M^+ - CH_3): 311.1495, found: 311.1497(8), 219(22), 187(100), 159(27), 136(25), 119(54), 91(28); cims(NH_3): 344 (M^+ + 18, 100).

Compound **48**, m.p. 61-62°C; tlc: R_f 0.26 (dichloromethane/acetone, 3:1); ir ($CHCl_3$ cast): 3400(s), 1660(w), 1450(m), 1070(s), 1020(s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 5.72 (1H, dq, J=5.5, 1.5 Hz, H-2), 4.21 (1H, d, J=5.5 Hz, H-1), 3.94 (1H, ddd, J=8.5, 5.5, 2 Hz, H-6 exo), 3.60 (1H, br d, J=8.5 Hz, H-6 endo), 3.56 (1H, dd, J=10.5, 8 Hz, CH_2-OH), 3.51 (1H, dd, J=10.5, 7 Hz, CH_2-OH), 2.60 (1H, br s D_2O exchangeable, OH), 2.42 (1H, br dm, J=17 Hz, H-4 exo), 2.36 (1H, br m, H-5), 2.12 (1H, dd, J=8, 7 Hz, H-8), 2.02 (1H, br d, J=17 Hz, H-4 endo), 1.66 (3H, s, C-3 CH3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 137.47 (s, C-3), 124.71 (d, C-2), 72.65 (d, C-1), 71.34 (t), 62.96 (t), 48.48 (d), 41.11 (t, C-4), 35.66 (d), 22.09 (q, CH_3); hrms: m/z calcd for $C_9H_{14}O_2$ (M^+): 154.0994, found: 154.0993 (21), 136 (17), 106 (35), 93 (84), 84 (100), 79 (17),

rel-(1R,2R,3S)-2-Hydroxymethyl-3-[2,2-bis(methoxycarbonyl)ethyl]-5-methylcyclohex-5-en-1-ol (49).

A solution of acetonide 47 (5.75 g) in dichloromethane (40 mL) and 80% aqueous acetic acid (40 mL) was stirred at room temperature for 4 h. The solvent was removed in the rotavap first at water aspirator pressure and then using the vacuum pump (2 mm Hg). The residue was dissolved in dichloromethane (100 mL) and washed carefully with satd $NaHCO_3$ and brine, dried, and evaporated to afford diol 49 (5.0 g, quantitative yield) as a colorless oil. An analytical sample was obtained by flash chromatography (dichloromethane/acetone, 7:3); tlc: Rf 0.23 (dichloromethane/acetone, 7:3); ir ($CHCl_3$ cast): 3400(s), 1750(s), 1734(s), 1670(w), 1436(s), 1270-1200(s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.40 (1H, br s, H-6), 4.48 (1H, br m, H-1), 3.87 (1H, dd, J=11, 8.5 Hz, CH_2-OH), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.75 (1H, dd, J=11, 4 Hz, CH_2-OH), 3.50 (1H, dd, J=8, 7 Hz, H-2'), 2.50 (2H, br s D_2O exchangeable, 2xOH), 2.13 (1H, br m), 2.09(1H, ddd, J=14, 8, 6.5 Hz, H-1'), 1.90 (1H, dd, J=14, 7 Hz, H-1'), 1.87 (1H, m), 1.70 (1H, m), 1.67 (3H, s, C-5 CH_3), 1.60 (1H, br dd, J=17, 9 Hz, H-4); hrms; m/z calcd for $C_{14}H_{20}O_5$ (M^+-H_2O): 268.1311, found: 268.1302(4), 187(24), 136(79), 106(100), 96(97), 77(27); cims (NH_3): 304 (M^++18, 100).

rel-(1R,2R,3S)-2-p-Tolylsulfonyloxymethyl-3-[2,2-bis(methoxycarbonyl)ethyl]-5-methylcyclohex-5-en-1-ol (51).

p-Toluenesulfonyl chloride (6.91 g, 36.4 mmol) was added in small portions during 1 h to a solution of diol 49 (5.20 g, 18.2 mmol), triethylamine (20 mL), and DMAP (0.040g, 0.32 mmol) in dichloromethane (250 mL) at 0°C. The mixture was stirred at room temperature for 24 h. Ice water (100 mL) was added. The aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic extracts were washed with brine, dried, and concentrated in vacuo. The resulting dark oil was purified by flash chromatography (dichloromethane/acetone, 95:5) to give 51 (6.50, 82% yield) as a yellow oil; tlc: R_f 0.25 (dichloromethane/acetone, 96:4); ir ($CHCl_3$ cast): 3500(w), 1749(s), 1733(s), 1600(w), 1430(m), 1350(m), 1175(s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.82 (2H, d, J=8 Hz, Ar-H), 7.36 (2H, d, J=8 Hz, Ar-H), 5.40 (1H, br s, H-6), 4.39 (1H, dd, J=10.5, 6.5 Hz, CH_2OTs), 4.32 (1H, br m, H-1), 4.10 (1H, dd, J=10.5, 6.5 Hz, CH_2OTs), 3.75 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.43 (1H, dd, J=8.5, 6.5 Hz, H-2'), 2.46 (3H, s, Ar-CH_3), 2.22 (1H, ddd, J=11, 6, 2 Hz, H-3), 2.05 (1H, ddd, J=13, 8.5, 5 Hz, H-1'), 2.00 (1H, m), 1.97 (1H, ddd, J=13, 9, 6.5 Hz, H-1'), 1.78 (1H, m), 1.76 (1H, br s D_2O exchangeable, OH), 1.75 (1H, m), 1.66 (3H, s, C-5 CH_3); hrms: m/z calcd for $C_{14}H_{19}O_4$ (M^+-$C_7H_9SO_4$): 251.1283, found: 251.1264(2), 250(7), 172(88), 118(33), 107(35), 91(100), 77(15).

<u>rel-(1S,2S,6R,8S)-8-Methoxycarbonyl-4-methylbicyclo[4.3.0]non-3-ene-8,2-carbolactone (20).</u>

Sodium hydride (1.64g of a 60% mineral oil suspension, 41 mmol) was washed twice with Skellysolve B and then added to a solution of tosylate 51 (6.0g, 13.6 mmol) in dry tetrahydrofuran (100 mL). The mixture was stirred at room temperature for 1h and then acetic acid (1.70 mL) was added at 0°C. The mixture was filtered through a sintered glass funnel and the precipitate was washed thoroughly with ethyl ether. Evaporation of the solvent gave crystalline **20** (2.79g, 87% yield). An analytical sample was obtained by recrystallization from Skellysolve B/dichloromethane; white prisms, m.p. 149-151°C; tlc: R_f 0.58 (dichloromethane/acetone, 96:4); ir ($CHCl_3$ cast): 1742(s), 1727(s), 1670(w), 1141(m), 1070(m) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.70 (1H, dm, J=5.5 Hz, H-3), 4.84 (1H, br t, J=5.5 Hz, H-2), 3.80 (3H, s, OCH_3), 2.72 (1H, ddd, J=14.5, 11, 1.5 Hz, H-7), 2.43 (1H, m), 2.43 (1H, br d, J=12 Hz, H-9β), 2.38 (1H, m), 2.36 (1H, br ddm, J=19, 6.5, 1 Hz, H-5), 2.08 (1H, dd, J=12, 4 Hz, H-9α), 2.05 (1H, br d, J=19 Hz, H-5), 1.79 (3H, s, C-4 CH_3), 1.60 (1H, dd, J=14.5, 8.5 Hz, H-7); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 171.22 (s, CO), 170.82 (s, CO), 138.81 (s, C-4), 118.68 (d, C-3), 74.87 (d, C-2), 56.89 (s, C-8), 52.44 (q, OCH_3), 36.47(t), 36.05(d), 35.45(t), 33.48(d), 31.43(t), 23.56(q CH_3); hrms: m/z calcd for $C_{13}H_{16}O_4$ (M^+): 236.1048, found: 236.1046(1), 192(8), 131(11), 100(97), 93(100), 91(30), 77(19); <u>Analysis</u> calcd for $C_{13}H_{16}O_4$: C 66.09, H 6.82; found: C 66.12, H 6.67.

<u>rel-(1S,2S,6R)-8,8-Bis(methoxycarbonyl)-4-methylbicyclo[4.3.0]non-3-en-2-ol (61).</u>

A solution of lactone 20 (0.016 g, 0.066 mmol) in methanol (2 mL) containing 1M methanolic KOH (0.4 mL, 0.4 mmol) was stirred at room temperature for 24 h. The mixture was neutralized with acetic acid and concentrated in vacuo. The residue was redissolved in dichloromethane 5 mL), filtered and the filtrate evaporated. Purification by flash chromatography (dichloromethane/acetone, 95:5) afforded recovered 20 (0.014 g, 88%) and 61 (0.002g, 10% yield) as a colorless oil; tlc: R_f 0.20 (dichloromethane/acetone, 96:4); ir ($CHCl_3$ cast): 3400 (m), 1732 (s), 1680 (w), 1203 (s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 5.37 (1H, br m, H-3), 4.35 (1H, br m, H-2), 3.68 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.44-2.36 (3H, m), 2.16 (1H, dd, J=15, 7 Hz), 2.09 (1H, dd, J=11, 7 Hz), 1.96 (1H, br dd, J=18.5, 6.5 Hz, H-5), 1.73 (1H, br dd, J=18.5, 6 Hz, H-5), 1.65 (3H, s, C-4 CH_3), 1.40 (1H, d, J=6 Hz, D_2O exchangeable OH); hrms: m/z calcd for $C_{14}H_{18}O_4$ (M^+-H_2O): 250.1205, found: 250.1205 (1.5), 219 (5), 190 (13), 145 (100), 131 (28), 113 (28), 109 (39), 93 (21), 77 (11), cims (NH_3): 286 (M^++18, 8), 268 (30), 251 (100).

Hydroboration-oxidation of lactone 20.

A solution of lactone 20 (0.010 g, 0.042 mmol) in dry tetrahydrofuran (1.5 mL) was placed in a dry flask. The flask was immersed in an ice-bath and then a solution of borane-tetrahydrofuran complex (70 µL of a [illegible]tion, 0.07 mmol) was added. The mixture was stirred for 1h at -5 [illegible] 1h at room temperature. Water (0.1 mL) was added and the mixture was stirred for 5 min. The flask was immersed in an ice-bath and 5% aqueous NaOH (0.1 mL) was added followed by 30% H_2O_2 (0.1 mL). The mixture was stirred overnight at room tempe[illegible] and then diluted with ethyl ether (5 mL). The aqueous phase was extracted with ethyl ether (3 x 5 mL) and the combined organic extracts were dried and evaporated in vacuo. A tlc of the crude showed the presence of six major components. The crude was purified by flash chromatography (dichloromethane/acetone, 85:15) to give alcohol **62** (0.003g, 30% yield) as a colorless oil; tlc: R_f 0.31 (ethyl acetate/Skellysolve B, 4:1); ir ($CHCl_3$ cast): 3470(m), 1742(s), 1072(s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 4.44 (1H, d, J=2.5 Hz, H-2), 3.74 (3H, s, OCH_3), 3.52 (1H, dd, J=8, 4.5 Hz, H-3), 2.62 (1H, br td, J=5.5, 2 Hz, H-1), 2.55 (1H, br qd, J=9, 5 Hz, H-6), 2.46 (1H, dd, J=13, 11 Hz, H-7α), 2.35 (1H, dd, J=12, 2 Hz, H-9β), 2.04 (1H, dd, J=12, 5.5 Hz, H-9α), 1.91 (1H, ddd, J=13.5, 8.5, 3 Hz, H-5α), 1.89 (1H, d, J=4.5 Hz, D_2O exchangeable OH), 1.79 (1H, dt, J=13, 2 Hz, H-7β), 1.42 (1H, dddq, J=13.5, 3, 8, 8 Hz, H-4), 1.03 (3H, d, J=7 Hz, C-4 CH_3), 1.02 (1H, td, J=13.5, 9 Hz, H-5β); hrms; m/z calcd for $C_{13}H_{18}O_5$ (M^+): 254.1154, found: 254.1153(4), 220(13), 192(18), 178(35), 156(38), 133(87), 109(53), 93(47), 79(100), 69(41).

rel-(1S,2S,3R,4S,6S,8S)-8-Methoxycarbonyl-4-methyl-3,4-epoxybicyclo[4.3.0]nonano-8,2-carbolactone (63).

m-Chloroperbenzoic acid (0.276 g, 1.6 mmol) was added in portions to a solution of methyl ester **20** (0.19 g, 0.8 mmol) in dichloromethane (20 mL) at 0°C. The mixture was stirred at room temperature for 24 h and then washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$, and brine, dried, and concentrated in vacuo to give **63** (0.20 g, 99% yield) as colorless needles; m.p. 103-105°C; tlc: R_f 0.41 (dichloromethane/acetone, 94:6); ir ($CHCl_3$ cast): 1745(s), 1739(s), 1370(w), 1170(m), 1077(m) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 4.94 (1H, dd, J=5, 3 Hz, H-2), 3.80 (3H, s, OCH_3), 3.27 (1H, d, J=3 Hz, H-3), 2.75 (1H, ddd, J=14, 11, 1 Hz, H-7), 2.44 (1H, br q, J=4.5 Hz, H-1), 2.39 (1H, d, J=12.5 Hz, H-9β), 2.26 (1H, dd, J=15, 8.5 Hz, H-5), 2.21 (1H, m, H-6), 2.08 (1H, dd, J=12.5, 4.5 Hz, H-9α), 1.88 (1H, br d, J=15 Hz, H-5), 1.65 (1H, dd, J=14, 7.5 Hz, H-7), 1.39 (3H, s, C-4 CH_3); hrms: m/z calcd for $C_{13}H_{16}O_5$ (M^{+}): 252.0997, found: 252.0988(1), 224(28), 195(72), 181(100), 166(46), 149(17), 135(61), 107(38), 91(45), 79(73).

rel-(1S,2S,3S,4R,6R,8S)-3-Hydroxy-8-methoxycarbonyl-4-methylbicyclo[4.3.0]nonano-8,2-carbolactone (62).

Epoxide 63 (0.187 g), 10% Pd/C (0.037 g), ethyl acetate (20 mL), and acetic acid (1 mL) were mixed in a round-bottom flask. A balloon filled with hydrogen was fitted to the flask and the system was purged three times. This mixture was vigorously stirred for 12 h. Platinum oxide (0.010g) was added and the mixture stirred under a hydrogen atmosphere for 5h. The catalyst was removed by filtration and the filtrate washed with 5% $NaHCO_3$, brine, and dried. Evaporation of the solvent afforded crystalline 62 (0.188 g, 99% yield); m.p. 130-132°C. This compound has identical spectroscopic properties to the alcohol previously prepared by hydroboration-oxidation of lactone 20.

rel-(1S,2S,3S,6S,8S)-8-Methoxycarbonyl-4-methylbicyclo[4.3.0]non-4-ene-8,2-carbolactone (64).

A solution of crude epoxide 63 (0.050g) in Skellysolve B/ethyl acetate (5 mL, 9:1) was concentrated to half its volume on a steam bath. The resulting solution was cooled to 0°C to give 64 (0.040g) as white prisms; m.p. 185-187°C; tlc: R_f 0.2 (dichloromethane/acetone, 94:6); ir ($CHCl_3$ cast): 3450(m), 1747(s), 1270(m), 1073(s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 5.72 (1H, dm, J=5 Hz, H-5), 4.61 (1H, t, J=3 Hz, H-2), 3.98 (1H, br s, H-3), 3.79 (3H, s, OCH_3), 2.79 (1H, m, H-6), 2.69 (1H, td, J=5.5, 3 Hz, H-1), 2.55 (1H, d, J=12 Hz, H-7), 2.51 (1H, d, J=12 Hz, H-7), 2.44 (1H, br d, J=12 Hz, H-9β), 2.19 (1H, dd, J=12, 5.5 Hz, H-9α), 1.83 (3H, t, J=1.5 Hz, C-4- CH_3), 1.70 (1H, br s, D_2O exchangeable OH); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 170.11(s, CO), 164.04(s, CO), 130.53(s, C-4), 127.57(d, C-5), 81.76(d, C-2), 68.62(d, C-3), 52.73(q, OCH_3), 51.06(s, C-8), 38.21(t), 35.82(t), 33.32(d), 31.36(d), 21.11(q, CH_3); hrms: m/z calcd for $C_{13}H_{16}O_5$ (M^+): 252.0997, found: 252.0994(25), 220(31), 164(15), 155(100), 124(21), 97(30), 77(20).

<u>rel-(1S,2S,3S,4R,6R)-8,8-Bis(methoxycarbonyl)-4-methylbicyclo[4.3.0]nonan-2,3-diol (66).</u>

A *1M* solution of KOH in methanol (1.2 mL, 1.2 mmol) was added to a solution of alcohol **62** (0.190 g, 0.75 mmol) in methanol (20 mL) at 0°C. After 10 min the ice-bath was removed and the mixture stirred for 1h at room temperature. The mixture was neutralized with acetic acid, the solvent evaporated, and the residue redissolved in dichloromethane. The precipitate was filtered and the filtrate concentrated *in vacuo*. The crude was purified by flash chromatography (ethyl acetate/Skellysolve B, 95:5) to give crystalline **66** (0.190 g, 91% yield); m.p. 143-144 °C; tlc: R_f 0.40 (ethyl acetate); ir ($CHCl_3$ cast): 3500-3300(m), 1731(s), 1262(s), 1050(m) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 3.74 (3H, s, OCH_3), 3.72(3H, s, OCH_3), 3.70(1H, ddd, J=9.5, 6, 3 Hz, H-2), 3.25 (1H, td, J=9.5, 4 Hz, H-3), 2.53(1H, m, H-1), 2.50-2.40(2H, m, CH_2), 2.27 (1H, d, J=3 Hz, D_2O exchangeable OH), 2.22 (1H, d, J=14 Hz), 2.17 (1H, m, H-6), 2.06 (1H, d, J=14 Hz), 2.02 (1H, d, J=4 Hz, D_2O exchangeable OH), 1.47 (1H, dt, J=13.5, 4 Hz, H-5), 1.40 (1H, m, H-4), 1.02 (1H, m, H-5), 1.02 (3H, d, J=6 Hz, C-4 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 173.41 (s, 2 x CO), 76.29 (d, C-2 or C-3), 74.96 (d, C-2 or C-3), 58.16 (s, C-8), 52.83 (q, 2 x OCH_3), 45.53(d), 39.54(t), 38.43(d), 36.81(d), 35.79(t), 33.24(t), 17.76(q, C-4 CH_3); hrms: m/z calcd for $C_{14}H_{20}O_5$ (M^+-H_2O): 268.1311, found: 268.1313(37), 254(38), 208(32), 190(37), 145(100), 113(28), 79(33); cims (NH_3): 304 (M^++18, 100); Analysis calcd for $C_{14}H_{22}O_6$: C 58.73, H 7.75; found: C 58.46, H 7.57.

Swern oxidation of diol 66.

Dimethyl sulfoxide (23.5 μL, 0.33 mmol) was added to a stirred solution of oxalyl chloride (14.8 μL, 0.168 mmol) in dichloromethane (1.5 mL) at -60°C. After 10 min a solution of diol 66 0.020g, 0.07 mmol) in dichloromethane (1 mL) was added to the mixture. After 20 min the reaction mixture was treated with triethylamine (0.10 mL, 0.73 mmol) and stirred for 5 min, allowed to warm to room temperature and then treated with half saturated brine (6 mL). The resulting mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried and concentrated in vacuo. Purification by flash chromatography (dichloromethane/acetone, 98:2) afforded compounds 60 (0.009 g, 45%), 67 (0.007 g, 37%), and 68 (0.002 g, 10%). Compound 60, amorphous white solid; tlc: R_f 0.30 (dichloromethane/acetone, 98:2); ir ($CHCl_3$ cast): 3400(m), 1733(s), 1700(w), 1655(s), 1278(s) cm^{-1}; ^1H nmr

(360 MHz, $CDCl_3$): δ 5.93 (1H, s, D_2O exchangeable OH), 3.76 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.28 (1H, dt, J=20, 1.5 Hz, H-9), 3.19 (1H, dd, J=20, 3 Hz, H-9), 2.95 (1H, m, H-6), 2.63 (1H, ddd, J=13, 7, 1 Hz, H-7), 2.44 (1H, dqd, J=13, 7, 4 Hz, H-4), 2.22 (1H, dt, J=13, 4 Hz, H-5α), 1.83 (1H, t, J=13 Hz, H-7), 1.48 (1H, td, J=13, 11 Hz, H-5β), 1.18 (3H, d, J=7 Hz, C-4 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 196.68 (s, C-3), 171.97 (s, CO), 171.49 (s, CO), 140.90 (s, C-2), 135.29 (s, C-1), 59.36 (s, C-8), 52.87 (q, OCH_3), 52.79 (q, OCH_3), 41.19 (d), 40.08(d), 39.73(d), 38.38(t), 35.85(t), 15.33(s, C-4 CH_3); hrms: m/z calcd for $C_{14}H_{18}O_6$ (M^+): 282.1103, found: 282.1101(64), 222(59), 193(30), 163(100), 93(15), 77(12), 59(25).

Compound 67, colorless oil; tlc: R_f 0.16 (dichloromethane/acetone, 98:2), 0.30 (ethyl acetate/Skellysolve B, 1:1); ir ($CHCl_3$ cast): 3440(m), 1732(s), 1490(m), 1267(s), 1171(m) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 4.43(1H, ddd, J=7.5, 3.5, 1 Hz, H-2), 3.70 (6H, s, 2 x OCH_3), 3.56(1H, d, J=3.5 Hz, D_2O exchangeable OH), 2.99 (1H, dq, J=14, 6.5 Hz, H-1), 2.60 (1H, m), 2.55 (1H, m), 2.51 (1H, d, J=14 Hz, H-7), 2.49 (1H, ddd, J=14, 6.5, 1.5 Hz, H-9), 2.17 (1H, d, J=14 Hz, H-7), 1.92 (1H, dtd, J=13.5, 5.5, 1 Hz, H-5), 1.77 (1H, t, J=14 Hz, H-9), 1.36 (1H, q, J=13.5 Hz, H-5), 1.04 (3H, d, J=6.5 Hz, C-4 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 212.82 (s, C-3), 173.02 (s, CO), 172.90 (s, CO), 74.63 (d, C-2), 57.89 (s, C-8), 52.96 (q, 2 x OCH_3). 49.83 (d, C-4), 41.26 (d), 39.08 (t), 38.40 (t), 37.55 (d), 33.40 (t), 13.62 (q, C-4 CH_3); hrms: m/z cald for $C_{14}H_{20}O_6$ (M^+): 284.1260, found: 284.1252 (1.5), 253 (11), 196 (17), 145 (100), 113 (18), 97 (16), 79 (14), 59 (16).

Compound 68, colorless oil; tlc: R_f 0.15 (dichloromethane/acetone, 98:2), ir ($CHCl_3$ cast): 3450(w), 1732(s), 1440(w), 1288(m) cm^{-1}; ^1H nmr

(360 MHz, $CDCl_3$): δ 3.90 (1H, dd, J=11.5, 3.5 Hz, H-3), 3.74 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.56 (1H, J=3.5 Hz, D_2O exchangeable OH), 3.20 (1H, m, H-1), 2.90 (1H, m, H-6), 2.56 (1H, m), 2.51 (1H, d, J=13.5 Hz), 2.17 (1H, d, J=13.5 Hz), 2.09 (1H, d, J=8.5 Hz), 1.70 (1H, m), 1.68 (1H, m, H-4), 1.40 (1H, q, J=13 Hz, H-5), 1.13 (d, J=6 Hz, C-4 CH_3); hrms: m/z calcd for $C_{14}H_{20}O_6$ (M^+): 284.1260, found: 284.1260 (31), 252 (43), 224 (30), 196 (13), 163 (15), 145 (100), ~~125~~ (33), 97 (20), 79 (44), 59 (56).

<u>rel-(1S,2S,4R,6R,8S)-8-Methoxycarbonyl-4-methyl-3-oxo bicyclo[4.3.0]nonano-8,2-carbolactone (70).</u>

A solution of dimethyl sulfoxide (0.15 mL, 2.11 mmol) in dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (77 μL, 0.88 mmol) in dichloromethane (2 mL) at -60°C. After 6 min, a solution of alcohol 62 (0.188g, 0.74 mmol) in dichloromethane (2.5 mL) was added to the mixture. After 17 min at -60°C, the mixture was treated with triethylamine (0.6 mL, 4.4 mmol) and stirred for 5 min. The mixture was allowed to warm to room temperature and then stirred with water (4 mL) for 5 min. The aqueous layer was separated and extracted with ethyl ether (3 x 10 mL). The combined extracts were washed with brine, dried, and concentrated <u>in vacuo</u>. The crude was purified by flash chromatography (ethyl acetate/Skellysolve B, 6:4) to give ketones 70 (0.160 g, 86% yield) and 71 (0.015 g, 8%) as amorphous solids. Compound 70; tlc: R_f 0.42 (dichloromethane/acetone, 96:4), 0.33 (ethyl acetate/Skellysolve B, 7:3); ir ($CHCl_3$ cast): 1740(s), 1732(s), 1280(m), 1080(m) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 4.47 (1H, d, J=3 Hz, H-2), 3.76 (3H, s, OCH_3), 2.81 (1H, m, H-1), 2.75 (1H, m, H-6), 2.59 (1H, dd, J=13.5, 11 Hz, H-7), 2.42 (1H, dd, J=12.5, 1.5 Hz, H-9), 2.40 (1H, m, H-4), 2.38 (1H, ddd, J=13, 9, 4.5 Hz, H-5), 2.13 (1H, dd, J=12.5, 5.5 Hz, H-9), 1.87 (1H, dt, J=13.5, 2.5 Hz, H-7), 1.46 (1H, td, J=13, 9 Hz, H-5), 1.10 (3H, d, J=6.5 Hz, C-4 CH_3); hrms: m/z calcd for $C_{13}H_{16}O_5$ (M^+): 252.0997, found: 252.0993 (26), 121 (8), 113 (9), 97 (32), 94 (40), 81 (100), 79 (25), 59 (13).

Compound 71; tlc: R_f 0.50 (dichloromethane/acetone, 96:4), 0.45 (ethyl acetate/Skellysolve B, 7:3); ^{1}H nmr (360 MHz, $CDCl_3$): δ 4.56 (1H, d, J=4.5 Hz, H-2), 3.82 (3H, s OCH_3), 3.04 (1H, d quintets, J=14, 6 Hz, H-4), 2.75 (1H, dd, J=14, 12 Hz, H-7), 2.70 (1H, br q, J=4.5 Hz, H-1), 2.50 (1H, br d quintets, J=12, 5 Hz, H-6), 2.39 (1H, br d, J=12 Hz, H-9), 2.20 (1H, dd, J=12, 5 Hz, H-9), 2.12 (1H, ddd, J=14, 6, 1.5 Hz), 2.11 (1H, ddd, J=14, 6, 1.5 Hz), 1.71 (1H, td, J=14, 5 Hz, H-5), 1.03 (3H, d, J=6.5 Hz, C-4 CH_3).

rel-(1S,2S,4R,6R)-2-Hydroxy-8,8-bis(methoxycarbonyl)-4-methylbicyclo[4.3.0]nonan-3-one (67).

A 1M solution of KOH in methanol (0.8 mL, 0.8 mmol) was added to a solution of ketone 70 (0.151 g, 0.6 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 30 min then neutralized with acetic acid. The solvent was evaporated and the residue redissolved in dichloromethane. The precipitate was filtered and the filtrate concentrated *in vacuo* to afford 67 (0.166g, 98% yield) as a colorless oil. An analytical sample (flash chromatography, ethyl acetate/Skellysolve B, 1:1) proved to be identical to compound **67**, previously obtained by Swern oxidation of diol **66**.

rel-(4R,6R)-2-Hydroxy-8,8-bis(methoxycarbonyl)-4-methylbicyclo[4.3.0]non-1(12)-en-3-one (60).

A solu[illegible] of dimethyl sulfoxide (0.1 mL, 1.4 mmol) in dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (65 μL, 0.7 mmol) in dichloromethane (2 mL) at -60°C. After 6 min a solution of hydroxyketone 67 (0.166 g, 0.58 mmol) in dichloromethane (2 mL) was added to the reaction mixture. After 17 min the mixture was treated with triethylamine (0.38 mL, 2.9 mmol), stirred for 5 min, and then allowed to warm to room temperature. Water (4 mL) was added and the mixture was stirred for 5 min. The aqueous layer was separated and extracted with ethyl ether (3 x 10 mL). The combined extracts were washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography gave 60 (0.148 g, 91% yeild) as an amorphous white solid. For physical properties of this compound see Swern oxidation of diol 66.

rel-(4S,6S)-4-Bromo-2-hydroxy-8,8-bis(methoxycarbonyl)-4-methyl bicyclo [4.3.0] non-1 (2)-en-3-one (73).

Pyridinium bromide perbromide (0.006 g, 0.018 mmol) was added to a solution of diketone 60 (0.005 g, 0.017 mmol) in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 30 min and then concentrated in vacuo. The crude was purified by flash chromatography (dichloromethane/acetone, 98:2) to give 73 (0.005 g, 66% yield) as a white solid; tlc: R_f 0.33 (dichloromethane/acetone, 98:2); ir ($CHCl_3$ cast): 3420 (m), 1733 (s), 1690 (w), 1650 (m), 1290 (m) cm^{-1}; ^{1}H nmr (360 MHz, $CDCl_3$): δ 5.98 (1H, s, D_2O exchangeable OH), 3,79 (3H, s, OCH_3), 3.76(3H, s, OCH_3), 3.35 (1H, dt, J=20, 2 Hz, H-9), 3.25 (1H, dd, J=20, 3 Hz, H-9), 3.14 (1H, m, H-6), 2.72 (1H, ddd, J=12.5, 7, 1 Hz, H-7), 2.57 (1H, dd, J=14.5, 4.5, H-5α), 1.93 (1H, t, J=12.5 Hz, H-7), 1.92 (3H, s, C-4 CH_3), 1.78 (1H, dd, J=14.5, 10 Hz, H-5β); hrms: m/z calcd for $C_{14}H_{17}O_6$ (M^+-Br): 281.1025, found: 281.1022 (49), 249 (43), 221 (100), 161 (58), 91 (12), 77 (10); cims (NH_3): 380 (M^++18, 10), 378 (M^++18, 9), 298 (70), 164 (100).

rel-(6R)-1-Bromo-3-hydroxy-8,8-bis(methoxycarbonyl)-4-methylbicyclo [4.3.0] non-3-en-2-one (74).

N-Bromosuccinimide (0.10 g, 0.56 mmol) was added to a solution of diketone 60 (0.14 g, 0.5 mmol) in dry tetrahydrofuran (15 mL) at -20°C. The mixture was stirred at the same temperature for 50 min and then concentrated *in vacuo*. The crude material was purified by flash chromatography (dichloromethane/acetone, 98:2) to give 74 (0.151 g, 84% yield) as a yellow oil; tlc: R_f 0.37 (dichloromethane/acetone, 98:2); ir ($CHCl_3$ cast): 3420 (m), 1734 (s), 1675 (m), 1640 (m), 1430 (m), 1268 (s) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.92 (1H, s, D_2O exchangeable OH), 3.76 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.62 (1H, d, J=14.5 Hz, H-9β), 2.89 (1H, d, J=14.5 Hz, H-9α), 2.85-2.80 (2H, m, H-5 and H-6), 2.39 (1H, dd, J=14,7 Hz, H-7), 2.27 (1H, dd, J=14, 12 Hz, H-7), 2.24 (1H, br d, J=18 Hz, H-5), 1.93 (3H, s, C-4 CH_3), signals for the minor epimer (6%) are also observed; hrms: m/z calcd for $C_{14}H_{17}O_6Br$ (M^+): 362.0188, 360.0208, found: 362.0191 (2), 360.0207 (2), 281 (26), 249 (49), 221 (100), 161 (56), 77 (10).

rel-(6R)-1-Bromo-8,8-bis(methoxycarbonyl)-4-methyl-2-oxo bicyclo [4.3.0] non-3-en-3-yl vinyl carbonate (75).

Vinyl chloroformate (39 µL, 0.45 mmol) was added to a solution of bromoketone 74 (0.139 g, 0.38 mmol) and pyridine (62 µL, 0.76 mmol) in dry dichloromethane (5 mL) at 0°C. The mixture was stirred at room temperature for 45 min and then washed with cold 5% hydrochloric acid, satd $NaHCO_3$, and brine. The aqueous layers were extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried and concentrated in vacuo to give 75 (0.147 g, 90% yield) as a slightly yellow oil. An analytical sample was obtained by flash chromatography (dichloromethane/acetone, 99:1); tlc: R_f 0.37 (dichloromethane/acetone, 98:2), 0.29 (ethyl acetate/Skellysolve B, 2:3); ^1H nmr (360 MHz, $CDCl_3$): δ 7.06 (1H, dd, J=14, 6 Hz, $C\underline{H}=CH_2$), 4.96 (1H, dd, J=14, 2 Hz, $CH=C\underline{H}_2$), 4.64 (1H, dd, J=6, 2 Hz, $CH=C\underline{H}_2$), 3.76 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.68 (1H, d, J=15 Hz, H-9), 2.99 (1H, br ddd, J=19, 5.5, 1 Hz, H-5), 2.83 (1H, m, H-6), 2.82 (1H, d, J=15 Hz, H-9), 2.41 (1H, dd, J=14, 7 Hz, H-7), 2.39 (1H, br d, J=19 Hz, H-5), 2.27 (1H, dd, J=14, 13 Hz, $\underline{H}$-$\underline{7}$), 1.97 (3H, s, C-4 $C\underline{H}_3$).

rel-(1S,6R)-8,8-Bis(methoxycarbonyl)-4-methyl-2-oxobicyclo[4.3.0] non-3-en-3-yl vinyl carbonate (22).

Zinc dust (0.015 g) was added to a solution of bromocarbonate 75 (0.05 g, 0.11 mmol) in acetic acid (2 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, the solid washed with ethyl ether (10 mL), and the solvent evaporated. The residue was redissolved in dichloromethane, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (ethyl acetate/Skellysolve B, 35:65) to provide 22 (0.028 g, 70% yield) as a colorless oil. Starting material 75 (0.005 g, 10%) was recovered as well as diketone 60 (0.005 g, 15%)

Compound 22, tlc: R$_f$ 0.28 (ethyl acetate/Skellysolve B, 2:3); ir (CHCl$_3$ cast): 1775 (s), 1733 (s), 1680 (m), 1650(m), 1243 (s), 1100 (m) cm^{-1}; uv (CH$_3$OH) λ_{max}: 239 nm; ^{1}H nmr (360 MHz, CDCl$_3$): δ 7.06 (1H, dd, J=13.5, 6.5 Hz, CH=CH$_2$), 4.99 (1H, dd, J=13.5, 2 Hz, CH=CH$_2$), 4.64 (1H, dd, J=6.5, 2 Hz, CH=CH$_2$), 3.74 (3H, s, OCH$_3$), 3.72 (3H, s, OCH$_3$), 2.87 (1H, dt, J=7.5, 6 Hz, H-1), 2.81 (1H, dd, J=14, 5.5 Hz, H-9), 2.74 (1H, br d, J=15 Hz, H-5), 2.72 (1H, m, H-6), 2.65 (1H, dd, J=14, 8 Hz, H-9), 2.45 (1H, br d, J=15 Hz, H-5), 2.39 (1H, dd, J=13.5, 6 Hz, H-7), 2.26 (1H, dd, J=13.5, 9 Hz, H-7), 1.92 (3H, s, C-4 CH$_3$); hrms: m/z calcd for C$_{17}$H$_{20}$O$_8$ (M$^+$): 352.1158, found: 352.1161 (30), 205 (29), 190 (50), 177 (16), 145 (100), 113 (26), 79 (13).

rel-(1S,3S,7R,9R,11R)-1,11-Carbonyldioxyy-5,5-bis(methoxycarbonyl)-9-methyltricyclo[7.2.0.0^{3,7}]undecan-2-one (24).

A degassed solution of carbonate 22 (0.011 g) in dry acetone (100mL) was irradiated with a 250-W medium pressure mercury lamp through a Pyrex filter contained in a Pyrex immersion well for 4.5 h. The reaction was monitored by tlc and irradiation was discontinued after the disappearance of *ca.* 80% of 22. The solvent was removed *in vacuo* and the residue purified by flash chromatography (dichloromethane/acetone, 97:3) to give unreacted 22 (0.002 g, 18%) and compound 24 (0.005 g, 45% yield) as a colorless oil; tlc: R$_f$ 0.34 (dichloromethane/acetone, 96:4); ir (CHCl$_3$ cast): 1812 (s), 1730 (s), 1430 (w), 1280 (m) cm^{-1}; ^{1}H nmr (360 MHz, CDCl$_3$): δ 5.03 (1H, dd, J=7, 3.5 Hz, H-11), 3.76 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 3.19 (1H, td, J=10.5, 8 Hz, H-3), 2.99 (1H, m, H-7), 2.73 (1H, ddd, J=13, 7.5, 2 Hz, H-6), 2.69 (1H, dd, J=15, 7 Hz, H-10α), 2.62 (1H, ddd, J=14, 8, 2 Hz, H-4), 2.42 (1H, dd, J=14, 10.5 Hz, H-4), 2.24 (1H, dd, J=15, 3.5 Hz, H-10β), 1.87 (1H, dd, J=13, 4.5 Hz, H-6), 1.86 (1H, br d, J=14 Hz, H-8α), 1.30 (1H, dd, J=14, 13 Hz, H-8β), 1.27 (3H, s, C-9 CH_3); hrms: m/z calcd for $C_{17}H_{20}O_8$ (M^+): 352.1158, found: 352.1160 (10), 292 (19), 274 (38), 248 (37), 216 (53), 161 (19), 145 (100), 124 (27), 113 (25), 96 (20), 91 (58), 79 (37), 77 (27), 59 (45). Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of H-11 (δ 5.03) gave a 16% enhancement at δ 3.19 (H-3), and 6% at δ 2.69 (H-10α); presaturation of H-3 (δ 3.19) gave a 10% enhancement at each δ 5.03 (H-11) and 2.62 (H-4); presaturation of H-7 (δ 2.99) gave a 4% enhancement at δ 5.03 (H-11), 3% at δ 2.73 (H-6α), 3% at δ 2.69 (H-10α), and 5% at δ 1.86 (H-8α).

rel-(1S,2S,6R,8S)-8-Carboxy-4-methylbicyclo[4.3.0]non-3-ene-8,2-carbolactone (76).

A solution of 2% KOH in water (15 mL) was added dropwise to a solution of methyl ester 20 (0.62 g, 2.6 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was stirred for 2 h at the same temperature and then acidified (pH 1) with 6N hydrochloric acid. The mixture was saturated with NaCl and extracted with dichloromethane (3 x 30 mL). The organic extracts were washed with brine, dried, and evaporated to give 76 (0.49 g, 86% yield) as a colorless foam. An analytical sample was obtained by flash chromatography (benzene/acetone/acetic acid, 60:40:1); tlc: R_f 0.29 (benzene/acetone/acetic acid, 60:40:1), 0.37 (dichloromethane/acetone/acetic acid, 50:50:1), ir ($CHCl_3$ cast): 3500-3000 (br m), 1731 (s), 1670 (w), 1144 (m) cm^{-1}; ^1H nmr (400 MHz,

$CDCl_3$): δ 5.72 (1H, d m, J=5 Hz, H-3), 4.95 (1H, br t, J=5 Hz, H-2), 2.63 (1H, m), 2.61 (1H, ddd, J=18, 10, 1.5 Hz, H-7), 2.52-2.46 (2H, m), 2.40 (1H, ddm, J=19, 5, 1 Hz, H-5), 2.30 (1H, br dd, J=13, 2 Hz), 2.10 (1H, br d, J=19 Hz, H-5), 1.81 (3H, s, C-4 CH_3), 1.68 (1H, dd, J=18, 13 Hz, H-7); hrms: m/z calcd for $C_{11}H_{14}O_2$ (M^+-CO_2): 178.0994, found: 178.0995 (20), 131 (19), 117 (29), 106 (51), 91 (100), 77 (31); cims (NH_3): 240 (M^++18, 100).

rel-(1S,2S,6R,8S)-8-Hydroxymethyl-4-methylbicyclo[4.3.0]non-3-ene-8,2-carbolactone (78).

Ethyl chloroformate (162 µL, 1.70 mmol) was added to a solution of acid (0.34 g, 1.53 mmol) and triethylamine (245 µL, 1.85 mmol) in dry tetrahydrofuran (30 mL) at 0°C. The mixture was stirred at the same temperature for 1.5 h. The copious precipitate ($Et_3N.HCl$) was filtered and washed with dry tetrahydrofuran (15 mL). The combined filtrate and washings were added over 10 min to a solution of $NaBH_4$ (0.174 g, 4.59 mmol) in water (6 mL) at 0°C. Evolution of gas accompanied the addition. The mixture was stirred for 30 min at 0°C then 45 min at room temperature. Water (6 mL) was added and the mixture was saturated with NaCl. The organic phase was separated and the aqueous phase extracted with ethyl ether (2 x 20 mL) and dichloromethane (2 x 20 mL). The organic extracts were washed with brine, dried, and evaporated. Purification by flash chromatography (dichloromethane/acetone, 9:1) gave 78 (0.186 g, 60% yield) as a colorless oil that crystallizes on standing. The aqueous phase was acidified with 6 N hydrochloric acid, extracted with dichloromethane (3 x 20 mL) and evaporated to provide recovered 76 (0.070 g, 21% yield).

Compound 78, m.p. 71-73°C (recrystallized from Skellysolve B/dichloromethane); tlc: R_f 0.23 (dichloromethane/acetone, 92:8); ir ($CHCl_3$ cast): 3443 (m), 1723 (s), 1676 (w), 1171 (m), 1138 (m), 1033 (m) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 5.72 (1H, dm, J=5.5, 1 Hz, H-3), 4.82 (1H, td, J=5.5, 1 Hz, H-2), 3.84 (1H, dd, J=11.5, 7.5 Hz, CH_2OH), 3.75 (1H, dd, J=11.5, 6.5 Hz, CH_2OH), 2.84 (1H, t, J=7 Hz, D_2O exchangeable, OH), 2.42-2.30 (2H, m, H-1, H-6), 2.32 (1H, br d[illegible], J=18, 6.5, 1 Hz, H-5), 2.13 (1H, br d, J=12 Hz, H-9β), 2.05 (1H, br d, J=18 Hz, H-5), 2.04 (1H, ddd, J=14, 10.5, 1.5 Hz, H-7), 1.80 (3H, s, C-4 CH_3), 1.75 (1H, dd, J=12, 3.5 Hz, H-9α), 1.46 (1H, dd, J=14, 8 Hz, H-7); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 176.96 (s, CO), 138.31 (s, C-4), 118.14 (d, C-3), 74.32 (d, C-2), 65.79 (t, CH_2-O), 51.01 (s, C-8), 35.91 (d), 35.35 (t), 35.14 (t), 33.13 (d), 1.06 (t), 23.23 (q, CH_3); hrms: m/z calcd for $C_{12}H_{16}O_3$ (M^+): 208.1100, found: 208.1104 (0.26), 164 (16), 131 (17), 108 (14), 93 (100), 77 (18); cims (NH_3): 226 (M^++18, 100); <u>Analysis</u> calcd for $C_{12}H_{16}O_3$: C 69.20, H 7.74; found: C 68.55, H 7.60.

<u>rel-1(1S,2S,6R,8S)-8-Methanesulfonyloxymethyl-4-methylbicyclo[4.3.0]non-3-ene-8,2-carbolactone (79).</u>

Methanesulfonyl chloride (0.1 mL, 1.3 mmol) was added to a solution of alcohol 78 (0.18 g, 0.86 mmol) and triethylamine (0.40 mL, 2.84 mmol) in dichloromethane (15 mL) at 0°C. Stirring for 40 min completed the reaction. The mixture was extracted with ice-water (10 mL) followed by cold 5% hydrochloric acid, satd $NaHCO_3$, and brine. Drying of the dichloromethane solution followed by solvent removal gave 79 (0.24 g, 99% yield) as a white oil that crystallizes on standing;

m.p. 103-105°C; tlc: R_f 0.21 (dichloromethane/acetone, 98:2); ir (CHCl$_3$ cast): 1729 (s), 1670 (w), 1354 (s), 1172 (s), 962 (s) cm^{-1}; ^{1}H nmr (360 MHz, CDCl$_3$): δ 5.68 (1H, br d, J=5 Hz, H-3), 4.79 (1H, br t, J=5 Hz, H-2), 4.59 (1H, d, J=10 Hz, CH$_2$-O), 4.25 (1H, d, J=10 Hz, CH$_2$-O), 3.07 (3H, s, SO$_2$CH$_3$), 2.42 (1H, m, H-6), 2.35 (1H, m, H-1), 2.32 (1H, br ddm, J=19.5, 6.5, 1.5 Hz, H-5), 2.14 (1H, br d, J=14 Hz, H-9β), 2.00 (1H, ddd, J=14, 10.5, 1.5 Hz, H-7), 1.99 (1H, br. d, J=19.5 Hz, H-5), 1.91 (1H, dd, J=14, 4 Hz, H-9α), 1.75 (3H, br s, C-4 CH$_3$), 1.40 (1H, dd, J=14, 8 Hz, H-7); hrms: m/z calcd. for $C_{13}H_{18}O_5S$ (M$^+$): 286.0875, found: 286.0874 (5), 242 (10), 190 (15), 150 (29), 145 (39), 131 (78), 105 (64), 93 (100), 77 (27), 71 (51), 54 (40).

rel-(1S,2S,6R,8S)-4,8-Dimethylbicyclo[4.3.0]non-ene-8,2-carbolatone (21).

A solution of sulfonate 79 (0.148 g, 0.52 mmol) and NaBH$_4$ (0.086 g, 2.3 mmol) in dry HMPA (14 mL) was warmed to 45°C (oil bath) and stirred under a nitrogen atmosphere. After 48 h an additional amount of NaBH$_4$ (0.086 g, 2.3 mmol) was added and stirring was continued at the same temperature for 48 h. The mixture was cooled to 0°C, then quenched with acetic acid (1 mL), diluted with water (15 mL), and extracted with Skellysolve B (8 x 25 mL). The organic extracts were washed with brine, dried, and evaporated. The crude was purified by flash chromatography (dichloromethane/acetone, 98:2) to provide 21 (0.059, 60% yield) as white crystals; m.p. 68-69°C; tlc: R_f 0.29 (dichloromethane/acetone, 98:2); ir (CHCl$_3$ cast): 2964 (s), 1737 (s), 1670 (w), 1449 (m), 1172 (m), 1140 (m) cm^{-1}; ^{1}H nmr (360 MHz, CDCl$_3$): δ 5.66 (1H, br dm, J=5.5 Hz, H-3), 4.72 (1H, br t, J=5.5 Hz, H-2), 2.40

(1H, dddd, J=11, 8.5, 7, 5 Hz, H-6), 2.28 (1H, br dd, J=18, 7 Hz, H-5), 2.25 (1H, br q, J=5 Hz, H-1), 2.00 (1H, br d, J=12 Hz, H-9β), 1.95 (1H, d, J=18 Hz, H-5), 1.84 (1H, ddd, J=15, 11, 1.5 Hz, H-7), 1.73 (3H, s, C-4 CH_3), 1.70 (1H, dd, J=12, 3.5 Hz, H-9α) 1.49 (1H, dd, J=15, 8.5 Hz, H-7), 1.32 (3H, s, C-8 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 178.67 (s, CO), 139.22 (s, C-4), 126.05 (d, C-3), 79.43 (d, C-2), 46.58 (s, C-8), 41.56 (t), 40.97 (t), 38.04 (d), 35.23 (d), 32.59 (t), 24.71 (q), 22.48 (q); hrms: m/z calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150, found: 192.1149 (1), 148 (18), 93 (100), 77 (1[illegible]), cims (NH_3): 210 (M^++18, 100), Analysis calcd for $C_{12}H_{16}O_2$: C 74.96, H 8.38; found: C 74.68, H 8.48.

rel-(1S,2S,3R,4S,6S,8S)-4,8-Dimethyl-3,4-epoxybicyclo[4.3.0]nonano-8,2-carbolactone (80).

m-Chloroperbenzoic acid (0.28 g, 1.64 mmol) was added in portions to a solution of lactone 21 (0.16 g, 0.82 mmol) in dichloromethane (16 mL) at 0°C. The mixture was stirred at room temperature for 18 h and then washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$, and brine. The organic layer was dried and concentrated *in vacuo* to give 80 (0.173 g. 99% yield) as white needles; m.p. 78-80°C; tlc: R_f 0.28 (dichloromethane/acetone, 98:2) ir ($CHCl_3$ cast): 2940 (m), 1742 (s), 1450 (m), 1180 (s), 1105 (s) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 4.85 (1H, dd, J=5, 3 Hz, H-2), 3.23 (1H, d, J=3 Hz, H-3), 2.31 (1H, d, J=4.5 Hz, H-1), 2.27 (1H, dd, J=14, 9.5 Hz, H-5), 2.22 (1H, m, H-6), 1.98 (1H, d, J=11.5 Hz, H-9), 1.96 (1H, dd, J=14, 10 Hz, H-7), 1.79 (1H, d, J=14 Hz, H-5), 1.72 (1H, dd, J=11.5, 4.5 Hz, H-9), 1.53 (1H, dd, J=14, 7 Hz, H-7), 1.34 (3H, s, CH_3), 1.31 (3H, s, CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 176.72 (s, CO), 77.26 (d, C-2), 59.40 (d, C-3), 56.02 (s, C-4), 44.89

(s, C-8), 44.38 (t), 39.15 (t), 34.64 (d), 31.73 (d), 30.82 (t), 24.00 (q, CH$_3$), 21.021 (q, CH$_3$); hrms: m/z calcd for C$_{12}$H$_{16}$O$_3$ (M$^+$): 208.1100, found: 208.1107 (2), 180 (32), 152 (26), 151 (84), 137 (72), 122 (34), 107 (28), 93 (100), 81 (58), 79 (48).

rel-(1S,2S,3S,4R,6R,8S)-3-Hydroxy-4,8-dimethylbicyclo[4.3.0]nonano-8,2-carbolactone (81).

Epoxide 80 (0.12 g), 10% Pd/C (0.050 g), ethyl acetate (20 mL), and acetic acid (1 mL) were mixed in a round bottom flask. A balloon filled with hydrogen was fitted to the flask and the system was purged three times. The mixture was vigorously stirred for 48 h, then platinum oxide (0.020 g) was added and stirring was continued for 24 h, under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate washed with 5% NaHCO$_3$, brine, and dried. Evaporation of the solvent followed by purification by flash chromatography (ethyl acetate/Skellysolve B, 65:35) provided recovered 80 (0.018 g, 15%) and alcohol 81 (0.102 g, 85% yield) as a colorless oil; tlc: R$_f$ 0.24 (ethyl acetate/Skellysolve B, 65:35); ir (CHCl$_3$ cast): 3400 (m), 2940 (m), 1737 (s), 1460 (w), 1106 (s) cm^{-1}; ^{1}H nmr (360 MHZ, CDCl$_3$): δ 4.38 (1H, br s, H-2), 3.53 (1H, dd, J=8, 4 Hz, H-3), 2.53 (1H, td, J=6, 2.5 Hz, H-1), 2.51 (1H, br q, J=9 Hz, H-6), 1.97 (1H, dd, J=12, 2 Hz, H-9), 1.88 (1H, ddd, J=13.5, 8.5, 3 Hz, [illegible] 1.85 (1H, dd, J=13, 11 Hz, H-7), 1.83 (1H, d, J=4 Hz, D$_2$O exc[illegible]able OH), 1.76 (1H, dd, J=12, 5.5 Hz, H-9), 1.57 (1H, dt, J=13, 2 Hz, H-7), 1.45 (1H, dquintetd, J=13.5, 8, 3 Hz, H-4), 1.30 (3H, s, C-8 CH$_3$), 1.06 (3H, d, J=7 Hz, C-4 CH$_3$), 1.02 (1H, td, J=13.5, 9 Hz, H-5α); ^{13}C nmr (100.57 MHz, CDCl$_3$): δ 176.72 (s, CO), 87.12 (d, C-2), 76.95 (d, C-3), 46.50 (s, C-8), 45.85

(t), 39.27 (t), 34.96 (d), 34.76 (d), 34.33 (t), 33.65 (d), 20.48 (q, CH_3), 19.45 (q, CH_3); hrms: m/z calcd for $C_{12}H_{18}O_3$ (M^+): 210.1256, found: 210.1258 (68), 164 (31), 148 (61), 133 (70), 124 (39), 109 (38), 106 (82), 95 (60), 93 (100), 81 (98), 77 (24), 55 (29).

rel-(1S,2S,3S,4R,6R,8S)-8-Methoxycarbonyl-4,8-dimethylbicyclo[4.3.0]nonan-2,3-diol (83).

A 1M solution of KOH in methanol (0.1 mL, 0.1 mmol) was added to a solution of alcohol **81** (0.015g, 0.07 mmol) in methanol (2 mL) at 0°C. After 1h the mixture was neutralized with acetic acid, the solvent evaporated, and the residue redissolved in dichloromethane. The precipitate was filtered and the filtrate concentrated *in vacuo*. The crude was purified by flash chromatography (ethyl acetate) to give **83** (0.015g, 88% yield) as a colorless oil; tlc: R_f 0.28 (ethyl acetate); ir ($CHCl_3$ cast): 3400(m), 2970(m), 1730(s), 1460(w), 1200(m), 1050(m), cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 3.69 (1H, ddd, J=9, 5.5, 3 Hz, H-2), 3.68 (3H, s, OCH_3), 3.25 (1H, td, J=9.5, 4 Hz, H-3), 2.55 (1H, d q, J=13, 6 Hz, H-1), 2.46 (1H, d, J=3 Hz, D_2O exchangeable, C-2 OH), 2.24 (1H, d, J=4 Hz, D_2O exchangeable, C-3 OH), 2.20 (1H, t, J=13 Hz, H-9), 2.12 (1H, d q, J=13, 6 Hz, H-6), 2.03 (1H, d, J=14 Hz, H-7), 1.70 (1H, dd, J=13, 7 Hz, H-9), 1.66 (1H, dd, J=14, 7 Hz, H-7), 1.40 (1H, dt, J=15, 4 Hz, H-5α), 1.38 (1H, m, H-4), 1.27 (3H, s, C-8 CH_3), 1.10 (1H, dt, J=15, 13 Hz, H-5β), 0.99 (3H, d, J=6.5 Hz, C-4 CH_3); hrms: m/z calcd for $C_{13}H_{22}O_4$ (M^+): 242.1518, found: 242.1519(2), 224(100), 210(82), 192(21), 164(93), 147(30), 124(47), 109(36), 95(74), 93(50), 81(53), 79(24).

rel-(1S,2S,4R,6R,8S)-4,8-Dimethyl-3-oxobicyclo[4.3.0]nonano-8,2-carbolactone (84).

A solution of dimethyl sulfoxide (0.1 mL, 1.41 mmol) in dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (61 µL, 0.70 mmol) in dichloromethane (3 mL) at -60°C. After 6 min a solution of alcohol 81 (0.136 g, 0.65 mmol) in dichloromethane (2 mL) was added to the reaction mixture. After 17 min at -60°C, the mixture was treated with triethylamine (0.54 mL, 3.9 mmol), and stirred for 5 min, allowed to warm to room temperature and then treated with water (5 mL). The mixture was separated and the aqueous phase extracted with ethyl ether (3 x 10 mL) and dichloromethane (2 x 10 mL). The combined extracts were washed with brine, dried, and concentrated *in vacuo*. The crude was purified by flash chromatography (ethyl acetate/Skellysolve B, 1:1) to give an amorphous white solid (0.130 g, 97% yield) that proved to be a 14:1 epimeric mixture of ketones 84 and 85, respectively. The physical properties given below correspond to the major epimer, ketone 84; tlc: Rf 0.35 (ethyl acetate/Skellysolve B, 1:1); ir. (CHCl$_3$ cast): 1744(s), 1722(s), 1490(w), 1160(w), 1108(w) cm^{-1}; ^{1}H nmr (400 MHz, CDCl$_3$): δ 4.42 (1H, dd, J=2.5, 1 Hz, H-2), 2.74 (2H, m, H-1 and H-6), 2.40 (1H, dqd, J=13.5, 6.5, 5 Hz, H-4), 2.32 (1H, ddd, J=13.5, 9, 5 Hz, H-5), 2.05 (1H, dd, J=12, 2.5 Hz, H-9), 1.99 (1H, dd, J=13, 11 Hz, H-7), 1.85 (1H, dd, J=12, 5 Hz, H-9), 1.68 (1H, dt, J=13, 2.5 Hz, H-7), 1.50 (1H, td, J=13.5, 9 Hz, H-5), 1.36 (3H, s, C-8 CH$_3$), 1.12 (3H, d, J=6.5 Hz, C-4 CH$_3$); ^{13}C nmr (100.57 MHz, CDCl$_3$): δ 205.25 (s, C-3), 175.32 (s, COO), 82.40 (d, C-2), 46.67 (s, C-8), 46.32 (t), 40.67 (d), 38.63 (t), 37.25 (d), 35.34 (t), 32.49 (d), 20.49 (q, C-8 CH$_3$), 14.48 (q, C-4 CH$_3$); hrms: m/z calcd for $C_{12}H_{16}O_3$ (M$^+$):

208.1100, found: 208.1110 (49), 123 (10), 109 (16), 97 (17), 94 (50), 93 (80), 81 (100), 79 (22).

rel-(1S,2S,4R,6R,8S)-2-Hydroxy-8-methoxycarbonyl-4,8-dimethylbicyclo[4.3.0]nonan-3-one (86).

A 1M solution of KOH in methanol (0.7 mL, 0.7 mmol) was added to a solution of ketones 84 and 85 (0.12 g, 0.57 mmol) in methanol (8 mL) at 0°C. The mixture was stirred for 15 min at 0°C and then neutralized with acetic acid. The solvent was removed and the residue redissolved in dichloromethane. The resulting mixture was filtered and the filtrate concentrated in vacuo to give 86 (0.132g, 96%) as a colorless oil. An analytical sample was obtained by flash chromatography (dichloromethane/acetone, 96:4) as a colorless oil; tlc: R_f 0.27 (dichloromethane/acetone, 96:4); ir (CHCl$_3$ cast): 3480(w), 1726(s), 1460(w), 1214(m), 1122(m) cm^{-1}; ^{1}H nmr (400 MHz, CDCl$_3$): δ 4.45 (1H, ddd, J=7, 3.5, 1.5 Hz, H-2), 3.78 (3H, s, OCH$_3$), 3.56 (1H, d, J=3.5 Hz, D$_2$O exchangeable OH), 3.01 (1H, m, H-1), 2.56 (1H, d quintet, J=13, 5.5 Hz, H-4), 2.55 (1H, m, H-6), 2.14 (1H, d, J=13.5 Hz, H-7), 1.87 (1H, dtd, J=13.5, 5.5, 1.5 Hz, H-5α), 1.74 (2H, d, J=10 Hz, H-9α and H-9β), 1.71 (1H, dd, J=13.5, 7 Hz, H-7), 1.48 (1H, dt, J=13.5, 13 Hz, H-5β), 1.28 (3H, s, C-8 CH$_3$), 1.05 (3H, s, C-4 CH$_3$); ^{13}C nmr (100.57 MHz, CDCl$_3$): 213.20 (s, C-3), 179.00 (s, COO), 74.85 (d, C-2), 52.19 (q, OCH$_3$), 49.31 (d, C-4), 47.02 (s, C-8), 43.11 (t), 41.38 (d), 38.55 (t), 38.30 (d), 36.30 (t), 27.64 (q, C-8 CH$_3$), 13.68 (q, C-4 CH$_3$); hrms: m/z calcd for C$_{13}$H$_{20}$O$_4$ (M$^+$): 240.1362, found: 240.1364 (2), 212 (51), 194 (23), 180 (35), 162 (52), 152 (54), 134 (29), 101 (100), 94 (37), 81 (91), 79 (26).

rel-(4R,6R,8S)-2-Hydroxy-8-methoxycarbonyl-4,8-dimethylbicyclo[4.3.0]non-1(2)-en-3-one (87).

A solution of dimethyl sulfoxide (71 µL, 1.0 mmol) in dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (4 µL, 0.5 mmol) in dichloromethane (2mL) at -60°C. After 6 min, a solution of alcohol 86 (0.11 g, 0.46 mmol) in dichloromethane (2 mL) was added to the reaction mixture. After 17 min, the mixture was treated with triethylamine (0.38 mL, 2.9 mmol), stirred for 5 min, and then allowed to warm to room temperature. Water (4 mL) was added and the mixture was stirred for 5 min. The aqueous layer was separated and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with brine, dried, and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane/acetone, 98:2) gave 87 (0.106, 97% yield) as a white solid. Recrystallization from ethyl ether/Skellysolve B provided colorless plates, m.p. 92-93°C; tlc: R$_f$ 0.28(dichloromethane/acetone, 98:2); ir (CHCl$_3$ cast): 3400 (m), 1729 (s), 1651 (s), 1440 (m), 1381 (m), 1269 (m), 1193 (m) cm^{-1}; ^{1}H nmr (400 MHz, CDCl$_3$): δ 5.96 (1H, s, D$_2$O exchangeable OH), 3.72 (3H, s, OCH$_3$), 3.14 (1H, dd, J=20, 3 Hz, H-9), 3.02 (1H, m, H-6), 2.49 (1H, dt, J=20, 1.5 Hz, H-9), 2.47 (1H, dqd, J=13, 6.5, 4 Hz, H-4), 2.20 1H, dt, J=13, 4 Hz, H-5α), 1.96 (1H, ddd, J=12, 7, 1.5 Hz, H-7), 1.79 (1H, t, 12 Hz, H-7), 1.49 (1H, td, J=13, 11 Hz, H-5β), 1.36 (3H, s, C-8 CH$_3$), 1.19 (3H, d, J=6.5 Hz, C-4 CH$_3$); ^{13}C nmr (100.57 MHz, CDCl$_3$): δ 196.98 (s, C-3), 177.50 (s, COO), 141.02 (s, C-2), 137.65 (s, C-1), 52.16 (q, OCH$_3$), 48.25 (s, C-8), 43.62 (t), 40.37 (d), 39.41 (d), 39.30 (t), 38.68 (t), 24.77 (q, C-8 CH$_3$), 15.52 (q, C-4 CH$_3$); hrms: m/z calcd for

$C_{13}H_{18}O_4$ (M^+): 238.1205, found: 238.1206 (46), 179 (50), 178 (100), 163 (24), 149 (19), 79 (14).

rel-(6R,8S)-1-Bromo-3-hydroxy-8-methoxycarbonyl-4,8-dimethylbicyclo[4.3.0]non-3-en-2-one (88).

N-Bromosuccinimide (0.074 g, 0.42 mmol) was added to a solution of diketone 87 (0.10g, 0.42 mmol) in dry tetrahydrofuran (12 mL) at -20°C. The mixture was stirred at the same temperature for 50 min and then concentrated *in vacuo*. The crude material was purified by flash chromatography (dichloromethane/acetone, 98:2) to give 88 (0.115 g, 88% yield) as a yellow oil tlc: R_f 0.38 (dichloromethane/acetone, 98:2); ir ($CHCl_3$ cast): 3440 (m), 2926 (m), 1730 (s), 1677 (w), 1645 (m), 1435 (w), 1273 (m), 1190 (m) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$)): δ 5.92 (1H, s, D_2O exchangeable OH), 3.62 (3H, s, OCH_3), 3.55 (1H, d, J=14.5 Hz, H-9β), 2.90-2.80 (2H, m, H-5 and H-6), 2.29 (1H, dd, J=13.5, 12 Hz, H-7), 2.19 (1H, br d, J=17 Hz, H-5), 2.10 (1H, d, J=14.5 Hz, H-9α), 1.92 (3H, s, C-4 CH_3), 1.70 (1H, dd, J=13.5, 7 Hz, H-7), 1.40 (3H, s, C-8 CH_3), signals for the minor epimer are also observed; hrms: m/z calcd for $C_{13}H_{17}O_4Br$ (M^+): 318.0290, 316.0310, found: 318.0270(2), 316.0311(3), 237(17), 207(9), 177(100), 159(17), 147(21), 107(11), 79(18), 69(12).

rel-(1R,6R,8S)-1-Bromo-8-methoxycarbonyl-4,8-dimethyl-2-oxobicyclo[4.3.0]non-3-en-3-yl vinyl carbonate (89).

Vinyl chloroformate (36 μL, 0.42 mmol) was added to a solution of bromoketone 88 (0.10 g, 0.32 mmol) and pyridine (62 μL, 0.76 mmol) in dry dichloromethane (5 mL) at 0°C. The mixture was stirred at room temperature for 1h and then washed with cold 5% hydrochloric acid, satd

$NaHCO_3$, and the brine. The aqueous layers were extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were dried and concentrated in vacuo to afford 89 (0.116 g, 95% yield) as a yellowish oil. An analytical sample was obtained by flash chromatography (dichloromethane/acetone, 99:1); tlc: R_f 0.43 (dichloromethane/acetone, 98:2); ir ($CHCl_3$ cast): 1777 (s), 1725 (s), 1690 (m), 1650 (w), 1490 (w), 1240 (s), 1120 (m) cm^{-1}; ^1H nmr (360 MHz, $CDCl_3$): δ 7.07 (1H, dd, J=13.5, 6 Hz, $C\underline{H}=CH_2$), 5.00 (1H, dd, J=13.5, 2 Hz, $CH=C\underline{H}_2$), 4.64 (1H, dd, J=6, 2 Hz, $CH=C\underline{H}_2$), 3.63 (3H, s, OCH_3), 3.61 (1H, d, J=14 Hz, H-9β), 3.01 (1H, ddq, J=19, 5.5, 1 Hz, H-5), 2.88 (1H, dddd, J=13.5, 7.5, 5.5, 1.5 Hz, H-6), 2.36 (1H, br d, J=19 Hz, H-5), 2.32 (1H, t, J=13.5 Hz, H-7β), 2.05 (1H, d, J=14 Hz, H-9α), 1.96 (3H, s, C-4 CH_3), 1.71 (1H, dd, J=13.5, 7.5 Hz, H-7α), 1.40 (3H, s, C-8 CH_3); ^{13}C nmr (100.57, $CDCl_3$): δ 183.47 (s, C-2), 176.77 (s, COO), 150.05 (s, CO carbonate), 144.16 (s, C-3), 142.73 (d, $\underline{C}H=CH_2$), 138.28 (s, C-4), 98.73 (t, $CH=\underline{C}H_2$), 61.59 (s, C-1), 52.48 (q, OCH_3), 48.83 (s, C-8), 46.05 (t), 45.88 (d, C-6), 39.14 (t), 29.86 (t), 28.01 (q, C-8 CH_3), 18.11 (q, C-4 CH_3); hrms: m/z calcd for $C_{16}H_{19}O_6$ (M^+-Br): 307.1181, found: 307.1177 (3), 247 (100), 203 (8), 177 (39), 159 (50), 131 (20), 91 (15), 79 (15), 69 (17).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of H-7α (δ 1.71) gave a 7.5% enhancement at δ 2.88 (H-6); presaturation of C-8 CH_3 (δ 1.40) gave a 3% enhancement on each of the following signals δ 2.88 (H-6), 2.05 (H-9α), and 1.71 (H-7α).

rel-(1S,6R,8S)-8-Methoxycarbonyl-4,8-dimethyl-2-oxobicyclo[4.3.0]non-3-en-3-yl vinyl carbonate (23).

Zinc dust (0.010 g) was added to a solution of bromocarbonate 89 (0.040 g, 0.10 mmol) in acetic acid (2 mL) and the resulting mixture was stirred at room temperature for 1h. Excess zinc was removed by filtration and washed with ethyl ether. The combined organic solvent was evaporated and the residue redissolved in dichloromethane, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (dichloromethane/acetone, 99:1) to afford 23 (0.027 g, 87% yield) as a colorless oil; tlc: R_f 0.40(dichloromethane/acetone, 96:4); ir ($CHCl_3$ cast): 1774 (s), 1728 (s), 1680 (w), 1650 (w), 1490 (w), 1245 (s), 1113 (m) cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.07 (1H, dd, J=13.5, 6 Hz, $C\underline{H}=CH_2$), 5.02 (1H, dd, J=13.5, 2 Hz, $CH=C\underline{H}_2$), 4.64 (1H, dd, J=6, 2 Hz, $CH=C\underline{H}_2$), 3.67 (3H, s, OCH_3), 2.87 (1H, "q", J=7 Hz, H-1), 2.75 (1H, "sextet", J=6.5 Hz, H-6), 2.70 (1H, dd, J=13.5, 7 Hz, H-9β), 2.65 (1H, dd, J=18.5, 6.5 Hz, H-5), 2.51 (1H, ddd, J=18.5, 6, 1 Hz, H-5), 2.24 (1H, dd, J=13, 7 Hz, H-7β), 1.92 (3H, s, C-4 CH_3), 1.86 (1H, dd, J=13.5, 8 Hz, H-9α), 1.69 (1H, dd, J=13, 6.5 Hz, H-7α), 1.31 (3H, s, C-8 CH_3); ^{13}C nmr (100.57 MHz, $CDCl_3$): δ 190.84 (s, C-2), 178.22 (s, COO), 150.39 (s, CO carbonate), 145.11 (s, C-3), 142.79 (d, $\underline{C}H=CH_2$), 140.67 (s, C-4), 98.60 (t, $CH=\underline{C}H_2$), 52.29 (q, OCH_3), 49.30 (d), 47.77 (s, C-8), 42.91 (t), 40.08 (t), 37.04 (d), 32.70 (t), 26.99 (q, C-8 CH_3), 17.94 (q, C-4 CH_3); hrms: m/z calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260, found: 308.1257 (62), 248(23), 233(32), 221(12), 204(17), 178(73), 163(17), 161(100), 133(43), 105(21), 91(31), 77(26).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of H-1 (δ 2.87) gave a 5%

enhancement at δ 2.75 (H-6), 8% at δ 1.86 (H-9α), and 4% at δ 1.31 (C-8 CH$_3$); presaturation of H-7β (δ 2.24) gave a 5% enhancement at δ 2.70 (H-9β); presaturation of C-8 CH$_3$ (δ 1.31) gave a 2% enhancement on each of the following signals: δ 2.87 (H-1), 2.75 (H-6), 1.86 (H-9α), and 1.69 (H-7α).

rel-(1S,3S,5S,7R,9R,11R)-1,11-carbonyldioxy-5-methoxycarbonyl-5,9-dimethyltricyclo[7.2.0.0^{3,7}]undecan-2-one (25).

A degassed solution of carbonate 23 (0.01 g) in dry acetone (100 mL) was irradiated with a 250-W medium pressure mercury lamp through a Pyrex filter held in a Pyrex immersion well for 12 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (dichloromethane/aceton, 97:3) to give starting carbonate 23 (0.004g, 40%) and 25 (0.004g, 40%) as a colorless oil; tlc: R$_f$ 0.34 (dichloromethane/acetone, 96:4); ir (CHCl$_3$ cast): 1812(s), 1726(s), 1490(w), 1200(m) cm^{-1}; ^{1}H nmr (360 MHz, CDCl$_3$): δ 5.05 (1H, dd, J=6.5, 3.5 Hz, H-11), 3.68 (3H, s, O CH$_3$), 3.15 (1H, td, J=10.5, 8 Hz, H-3), 2.98 (1H, ddtd, J=12, 10.5, 7.5, 4.5 Hz, H-7), 2.69 (1H, dd, J=14.5, 6.5 Hz, H-10α), 2.42 (1H, dd, J=13.5, 10.5 Hz, H-4β), 2.24 (1H, dd, J=14.5, 3.5 Hz, H-10β), 2.07 (1H, ddd, J=13, 8, 2 Hz, H-6), 1.96 (1H, ddd, J=13.5, 8, 2 Hz, H-4α), 1.86 (1H, dd, J=13, 7.5 Hz, H-6), 1.82 (1H, dd, J=14, 4.5 Hz, H-8α), 1.33 (1H, dd, J=14, 12 Hz, H-8β), 1.28 (3H, s, CH$_3$), 1.26 (3H, s, CH$_3$); ^{13}C nmr (100.57 MHz, CDCl$_3$): 203.02 (s, C-2), 176.95 (s, COO), 154.43 (s, CO carbonate), 88.44 (s, C-1), 72.78 (d, C-11), 52.51 (q, OCH$_3$), 48.96 (d, C-3), 48.38 (s), 47.40 (s), 44.37 (t), 41.62 (t), 37.44 (t), 36.84 (t), 35.55 (d, C-7), 23.69 (q), 23.36 (q); hrms: m/z calcd for C$_{16}$H$_{20}$O$_6$ (M$^+$): 308.1260 found: 308.1252

(16), 276 (6), 249 (12), 205 (22), 204 (43), 186 (39), 175 (15), 161 (30), 149 (26), 133 (24), 124 (46), 109 (27), 97 (51), 96 (82), 81 (100), 79 (66), 73 (78), 71 (25).

Nuclear Overhauser enhancement difference spectroscopy (nOeds) gave the following results: presaturation of H-11 (δ 5.05) gave 6.5, 2, and 3% enhancements at δ 3.15 (H-3), 2.98 (H-7), and 2.69 (H-10α), respectively; presaturation of H-3 (δ 3.15) gave 10, 5, 6, and 4% enhancements at δ 5.05 (H-11), 2.98 (H-7), 1.96 (H-4α), and 1.28 (CH_3) respectively; presaturation at H-7 (δ 2.98) gave 4, 7, and 7% enhancements at δ 5.05 (H-11), 2.69 (H-10α), and 2.07 (H-6α), respectively; presaturation at H-10α (δ 2.69) gave a 5% enhancement to each of the signals at δ 5.05 (H-11) and 2.98 (H-7).

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