I. SYNTHESIS OF JASMONOIDS

II. SYNTHESIS OF CYCLIC KETAL-TYPE INSECT PHEROMONES

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming
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THE UNIVERSITY OF BRITISH COLUMBIA
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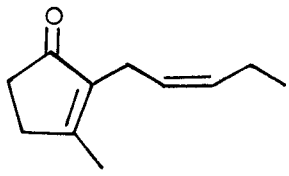
ABSTRACT

This thesis consists of two parts. Part I describes the preparation of cyclopentenones using trimethylsilylpropyne as an acetonyl unit, and its application to the synthesis of cis-jasmone (1) and dihydrojasmone (3). β-Keto ester dianions were alkylated at the γ-carbon with 3-bromo-1-trimethylsilyl-1-propyne. The resulting alkynes were hydrated to give the 1,4-diketo compounds which were then cyclized to the corresponding cyclopentenones, cis-jasmone (1) and dihydrojasmone (3).

Part II describes the synthesis of various cyclic ketal insect pheromones, viz., frontalin (17), endo-brevicomin (16), exo-brevicomin (15), (-)-α-multistriatin (18α) and linealtin (22), which have considerable economic values due to their potential utility in the control of beetle population. The dianion of methyl acetoacetate was alkylated with homoallylic bromides. The resulting alkenes were epoxidized and then cyclized with a Lewis acid to produce esters containing the 6,8-dioxabicyclo[3.2.1]octane skeleton. These esters were hydrolyzed and decarboxylated. This methodology was utilized in a synthesis of frontalin (17) and stereospecific syntheses of endo-brevicomin (16), and exo-brevicomin (15). In addition, one of the intermediates in the synthesis of 15 was partially resolved, leading to optically active exo-brevicomin.

A chiral synthesis of (-)-α-multistriatin (18α) was accomplished using methyl α-D-glucopyranoside (71) as starting material. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-α-D-arabino-hexopyranoside (197) was prepared in six steps from methyl α-D-glucopyranoside (71). The benzylidene 197 was converted into the alkene 207. Then the methyl group at C-4 in the intermediate 201 was generated by a stereoselective hydrogenation of 207 using Wilkinson's catalyst. The dithiane derivative 219 was used to effect both introduction of the ethyl side-chain and the cyclization to form the bicyclic ketal skeleton. The spectral data of the synthetic (-)-α-multistriatin (18α) was found to be identical with those for the natural compound.

A synthesis of lineatin (22) is also described. The cis fused bicyclo[4.2.0] ring system in 22 was constructed via a photocycloaddition reaction involving 3-methyl-5-hydroxy-2-pentenoic acid δ-lactone 119 and allene. A mixture of regioisomers 233 and 234 was obtained in a ratio of 5:3. This mixture was used throughout the subsequent reactions and the final isomeric products lineatin (22) and 23 were separated by column chromatography. The present route to lineatin (22) represents a major improvement over the previous syntheses in terms of efficiency and stereoselectivity.



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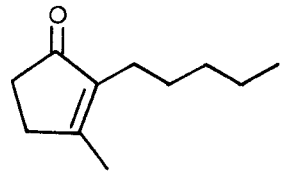

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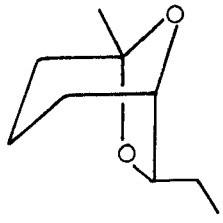

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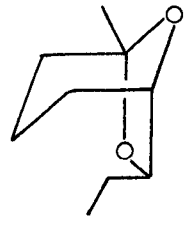

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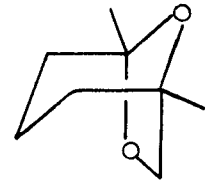

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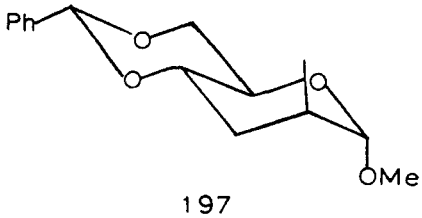

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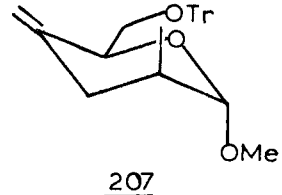

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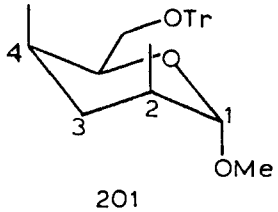

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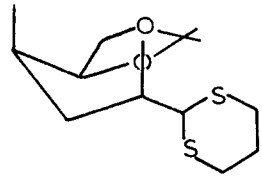

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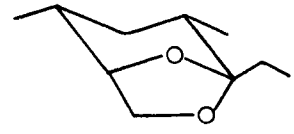
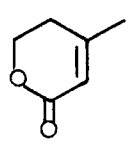


(-)-18α



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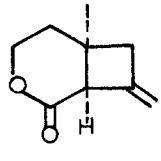

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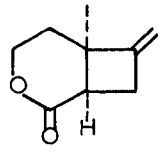

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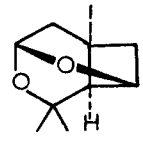

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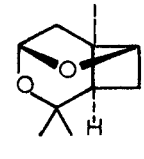

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LIST OF ABBREVIATIONS

AcOH	acetic acid
Ac_2O	acetic anhydride
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
GLC	gas liquid chromatography
HMPA	hexamethylphosphoramide
IR	infrared
LDA	lithium diisopropylamide
MsCl	methanesulfonyl chloride
NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon-13 nuclear magnetic resonance
Pyr	pyridine
L-Selectride	lithium tri-sec-butylborohydride
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TrCl	triphenylchloro methane
TsCl	para-toluenesulfonyl chloride
TsOH	para-toluenesulfonic acid

ACKNOWLEDGMENTS

I wish to express my gratitude to Professor Larry Weiler for his encouragement and guidance throughout the course of this research, and for his help during the preparation of this thesis.

I am indebted to Professor R. E. Pincock and Professor G. S. Bates for reading through the manuscript of this thesis and providing invaluable opinions.

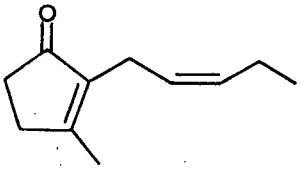
Finally, I wish to thank my husband, Fuk-Wah, whose infinite patience, constant encouragement, and helpful suggestions made this thesis possible.

PART I

SYNTHESIS OF CIS-JASMONE AND DIHYDROJASMONE

INTRODUCTION

cis-Jasmone (1) and methyl jasmonate (2) are constituents of the essential oil of jasmine flowers, Jasminum. Dihydrojasmone (3) is present in bergamot oil and is closely related to cis-jasmone (1) both in structure and in odor. All of these compounds are important substances in the perfume industry.



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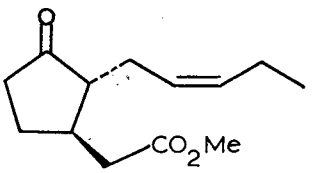

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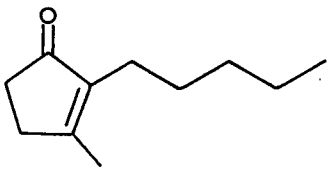

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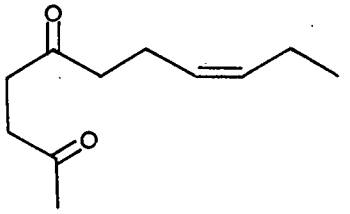
In the past two decades, there has been an increasing interest in the synthesis of these jasmonoids.[1] Two reviews of these syntheses have also been published.[1a,b] The most common strategy among the documented syntheses is via 1,4-diketone intermediates 4 and 5, which upon treatment with base could be cyclized to cis-jasmone (1) and dihydrojasmone (3), respectively. Various methods for the preparation of these 1,4-diketone intermediates 4 and 5 have been reported. Among them, the acid hydrolysis of furan derivatives and the hydration of acetylenes represent two noteworthy approaches to these compounds. One of



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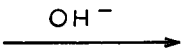

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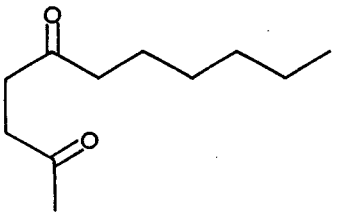

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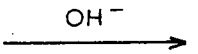

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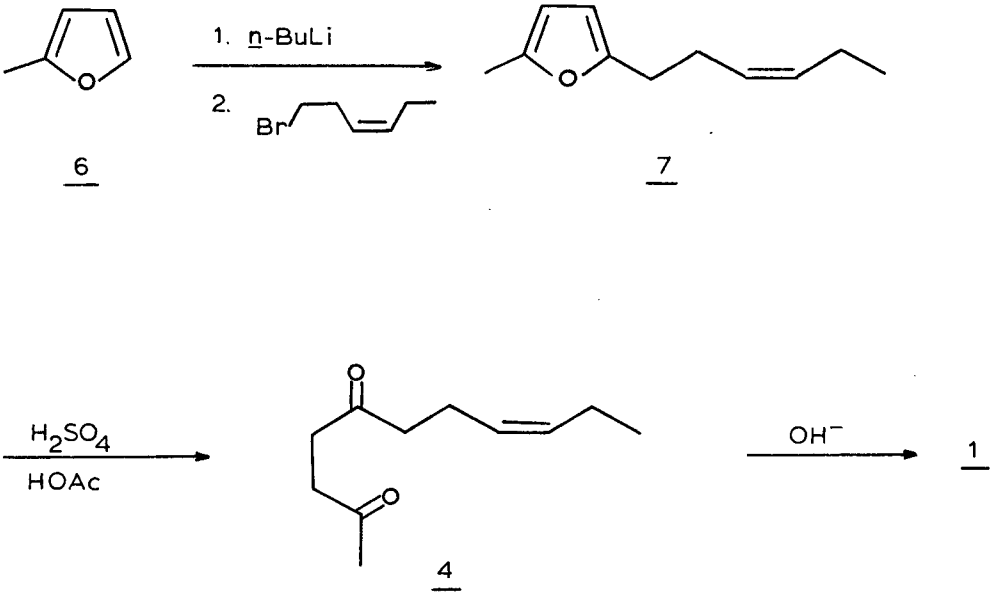
the examples involving the use of furan derivatives is the synthesis reported by Buchi and Wuest[2] (Scheme I). The anion of 2-methylfuran (6) was generated using n-butyllithium and alkylated with 1-bromo-3-hexene to give compound 7. Hydrolysis to the diketone 4 was effected in moderate yield using aqueous sulfuric acid in glacial acetic acid. The resulting diketone was then cyclized in aqueous sodium hydroxide to cis-jasmone (1).

Two examples involving the hydration of an acetylenic compound have been reported. The first synthesis was accom-

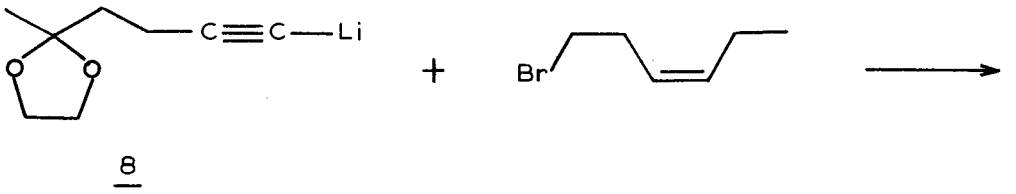
Scheme I. Buchi and Wuest's Synthesis of cis-Jasmone (1)[2]



plished by Stork and Borch[3] (Scheme II). The lithium acetylide 8 was alkylated with 1-bromo-3-hexene to give compound 9 which was hydrolyzed to the corresponding ketone 10. Subsequent hydration of the acetylenic bond in 10, followed by base catalyzed intramolecular condensation of the resulting diketone 4, led to cis-jasmone (1). It was suggested that regioselective hydration of acetylene 10 to give 4 is due to intramolecular participation of the carbonyl group in 10. (1) Another similar

(1) The proposed mechanism is shown in Scheme VII, p. 17.

Scheme II. Stork and Borch's Synthesis of cis-Jasmone (1)[3]



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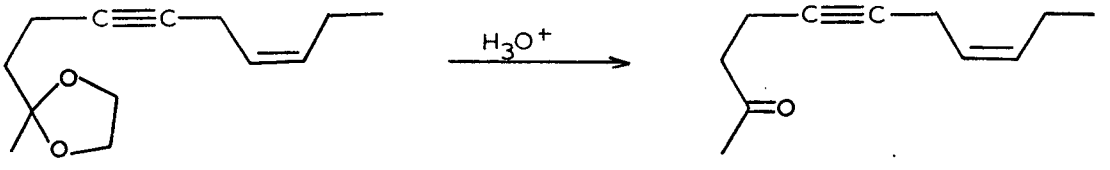
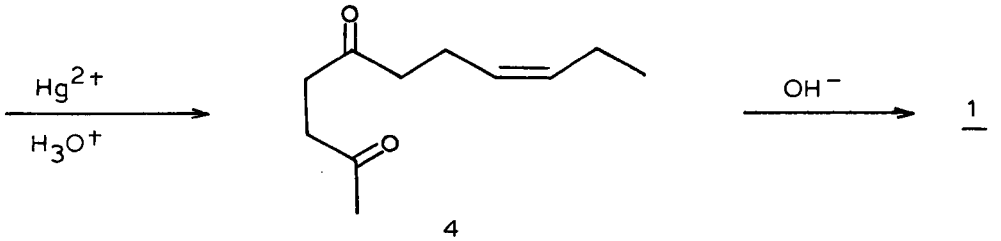


9 10



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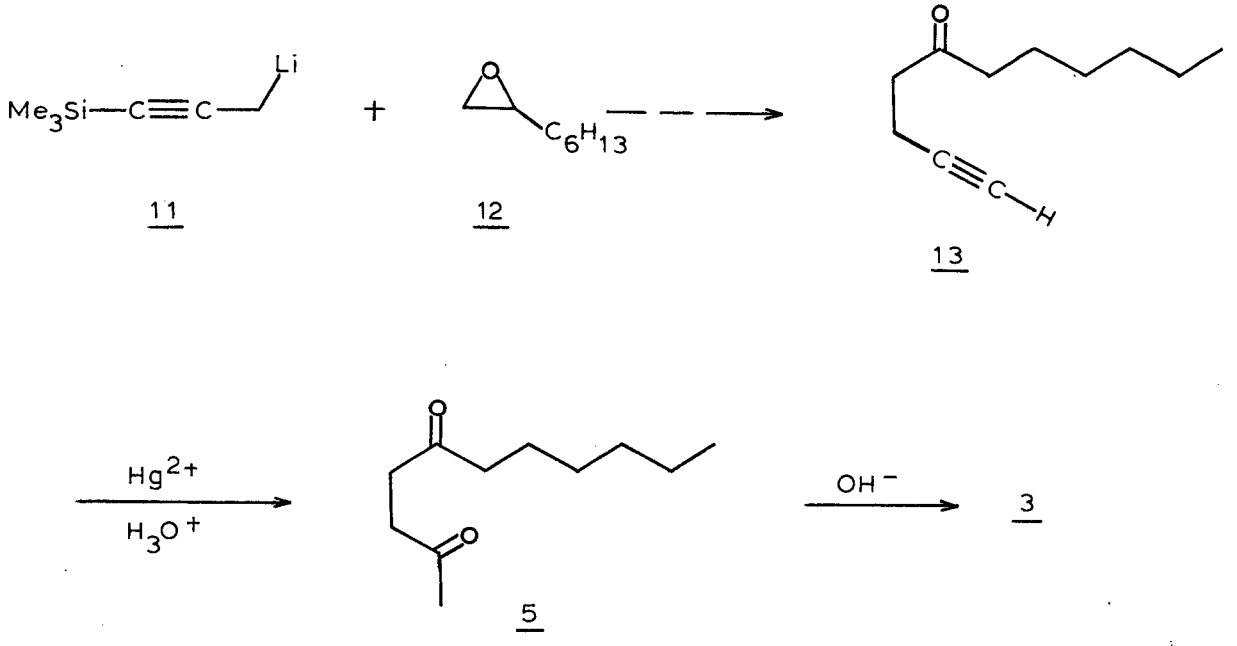
example was reported by Ho[1b] (Scheme III). In this synthesis, the acetylenic ketone intermediate 13 was prepared in three steps, starting with the reaction of lithium compound 11 with epoxide 12. The diketone intermediate 5 was then obtained by hydration of the terminal triple bond in 13. Conversion of 5 into dihydrojasmone (3) was accomplished by the usual base treatment.

Although the jasmonoids have been synthesized by numerous workers, our interest in exploiting the synthetic utility of the dianion chemistry of β-keto esters, developed earlier in

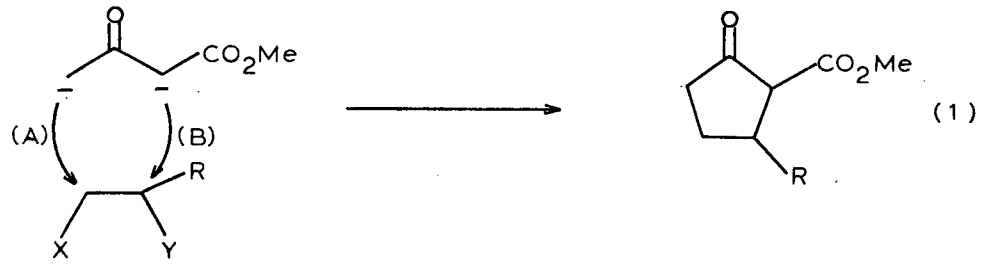
Scheme III. Ho's Synthesis of Dihydrojasmone (3)[1b]



this laboratory,[4] stimulated our interest in developing a new and efficient route to these compounds using β-keto esters as precursors. Our approach is described in the following section.

RESULTS AND DISCUSSION

For several years, we have been interested in utilizing the dianion chemistry of β-keto esters[4] to prepare 2-cyclopentenones which are useful synthetic substrates for many natural products, e.g., jasmonoids, prostaglandins and rethrolones. In principle, this strategy could be accomplished by using methyl acetoacetate as a precursor, which possesses the chemical versatility to undergo alkylation at both the γ- and α-positions (equation 1). Process (A) in equation 1 involving

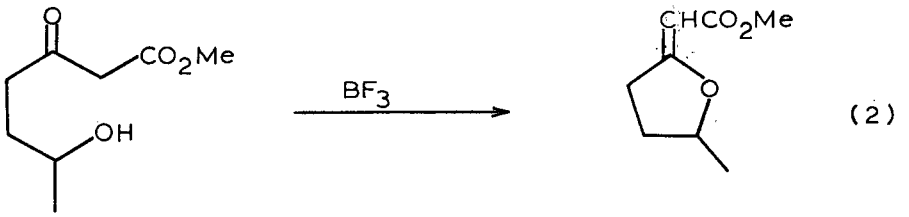


(1)

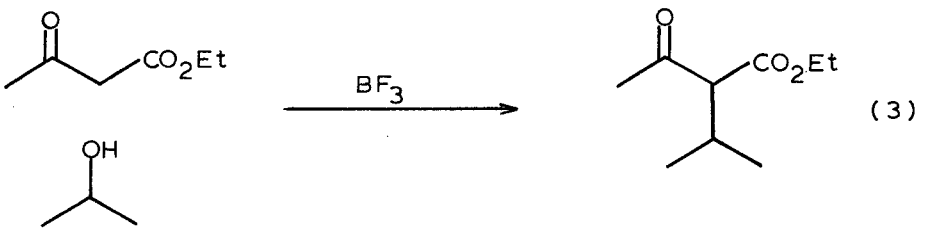
X, Y = leaving groups

the dianion of methyl acetoacetate, has been achieved effectively for a wide range of alkylating agents.[4] It was conceived that, by employing an alkylating agent which would retain (or facilitate after simple transformations) a suitable leaving group Y after the dianion alkylation, formation of a five-membered ring might be effected by intramolecular alkylation at the α-position of the β-keto ester. However, this cycliza-

tion step (B) was unsuccessful under a variety of acid and base catalyzed conditions when the carbon bearing the leaving group was sp^3 hybridized.[5] For example, treatment of 6-hydroxy-3-oxoheptanoate (14) with boron trifluoride gave the 0-cyclized tetrahydrofurylidene 15 in greater than 80% yield (equation 2). No cyclopentanone product was observed.[6] Interestingly, ethyl acetoacetate reacted with 2-propanol to give ethyl α-isopropyl-acetoacetate in 60-70% yield under the same conditions (equation 3).[7] Failure in obtaining the cyclopentanone product in equation 2 is consistent with the rules for ring closure suggested by Baldwin,[8] and could be explained by stereoelectronic



14 15 (2)



(3)

considerations. In theory, the ambident enolate ion 16 may undergo intramolecular alkylation on carbon or oxygen. In the carbon alkylation, approach of the electrophile has to be perpendicular to the plane of the enolate, whereas in the oxygen alkylation, the electrophile may lie in the plane of the enolate (Figure 1). In the formation of a five-membered ring,

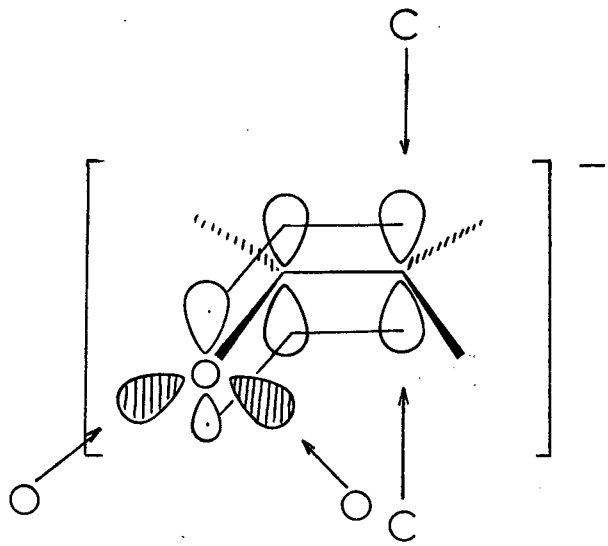
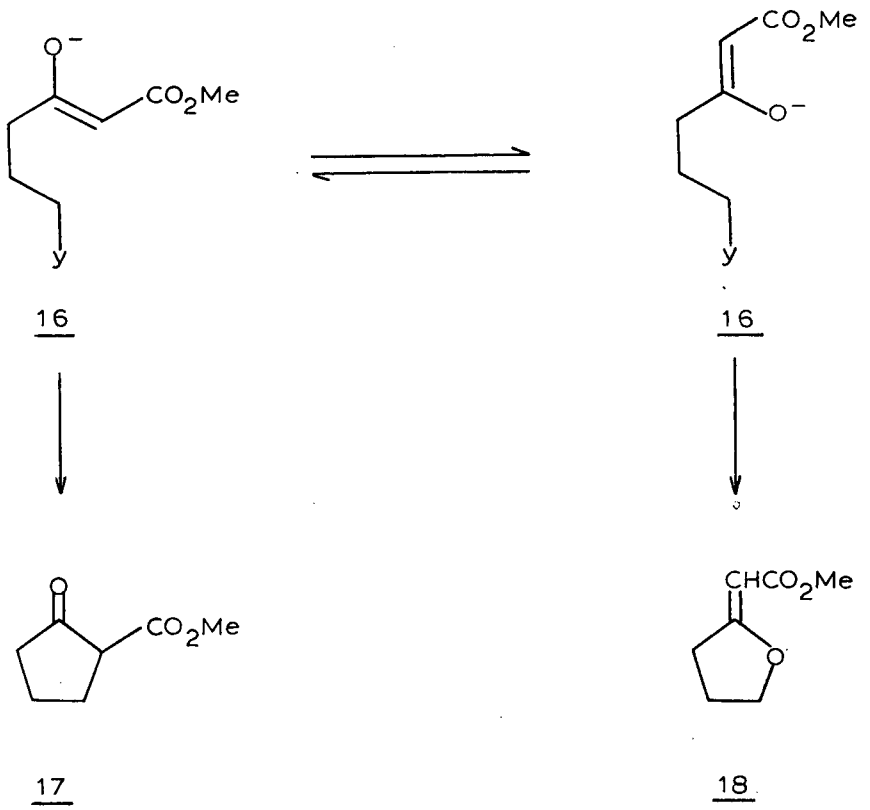


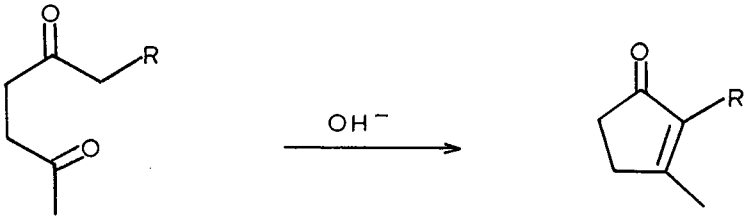
Figure 1. Stereoelectronic Effects for C- and O-Alkylation of Enolates

perpendicular approach of the carbon bearing the leaving group to the carbon site is sterically difficult. On the other hand, the in-plane attack on oxygen to form 18 is sterically facile (Scheme IV).

Scheme IV. Modes of Cyclization of Enolate 16



When the electrophilic carbon in 16 is sp^2 hybridized, cyclization analogous to the transformation of 16 to 17 appeared to be feasible. A typical example is the intramolecular condensation of 19 to give cyclopentenones 20 as shown in equation 4.[1] Since a 1,4-dicarbonyl intermediate would circumvent the difficulties encountered in effecting step (B) in equation 1, we decided to develop an efficient synthesis of 1,4-dicarbonyl derivatives using the dianion of methyl acetoacetate. These



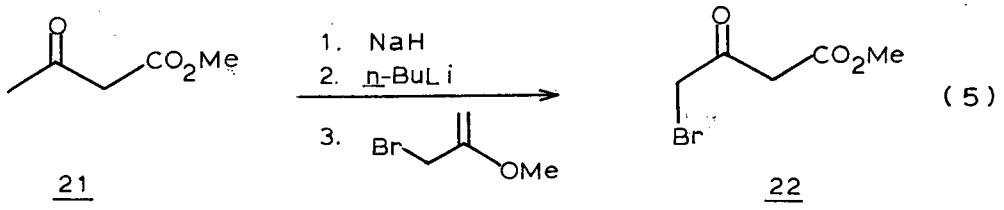
(4)

19 20

1,4-dicarbonyl compounds could then be cyclized to give cyclopentenones. This approach is demonstrated in the synthesis of cis-jasmone (1) and dihydrojasmone (3) described below.

(i) Synthesis of Dihydrojasmone (3)

The reactions of the dianion of methyl acetoacetate with alkylating agents containing a masked carbonyl function adjacent to the leaving group were first investigated for the synthesis of 1,4-diketones. Reaction of the dianion of methyl acetoacetate with α-halo ketones led to a mixture of products which were of no synthetic value. No alkylation product was observed when the dianion of methyl acetoacetate was allowed to react with the α-bromo ketal of acetone. Treatment of the dianion of 21 with 2-methoxyallyl bromide [9] led to formation of the γ-bromo β-keto ester 22 (equation 5). The outcome of this reaction was in agreement with several other examples of bromine transfer in the reaction of β-substituted bromoalkanes with reactive nucleophiles.[10]

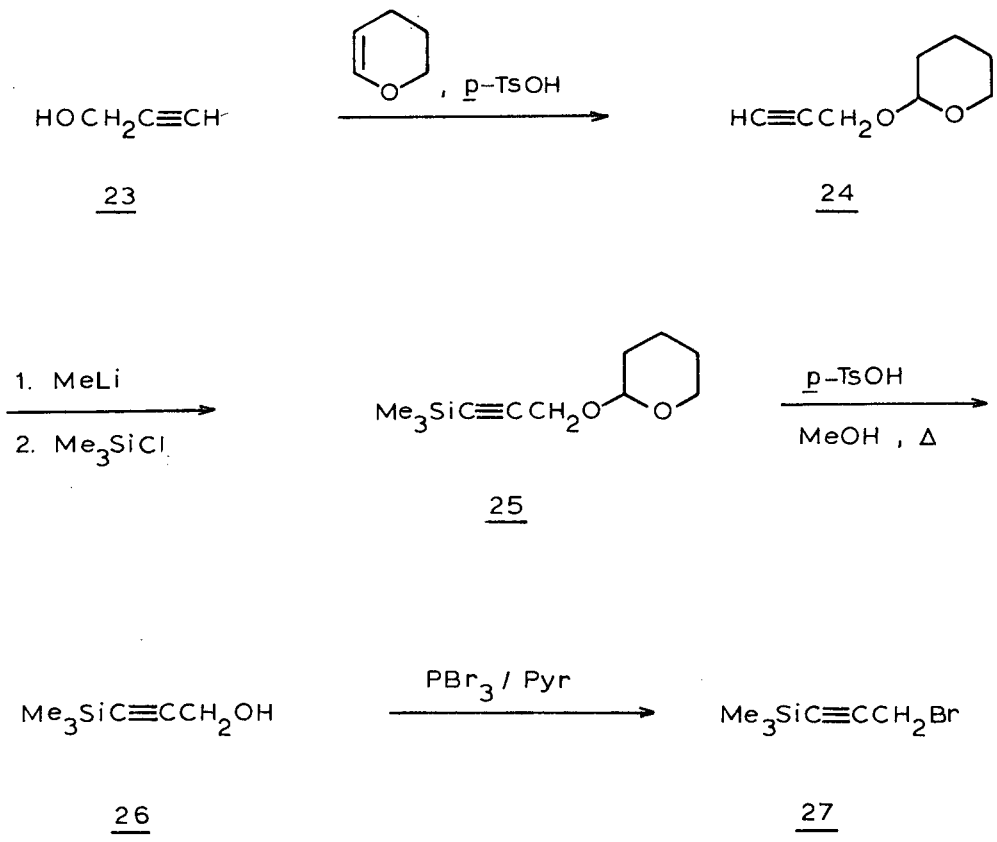


21 22 (5)

A recent report by Miller[11] regarding the successful use of 3-bromo-1-trimethylsilyl-1-propyne (27) as an alkylating agent prompted our interest in utilizing this reagent as a masked acetonyl unit. As shown in Scheme V, compound 27 was prepared in four steps starting from 2-propyn-1-ol (23). The alcohol 23 was first protected as its tetrahydropyranyl derivative 24. The acetylenic anion of 24 was generated with 1.1 equivalents of methyllithium and alkylated with chorotrimethylsilane to give compound 25 in 94% yield. The alcohol 26 obtained after acid-catalyzed hydrolysis of the tetrahydropyranyl group in 25 was treated with phosphorus tribromide and pyridine to give the bromide 27 in 80% yield. The trimethylsilylacetylene moiety in 27 can be easily converted into an acetyl group as illustrated by equation 6.[12b]

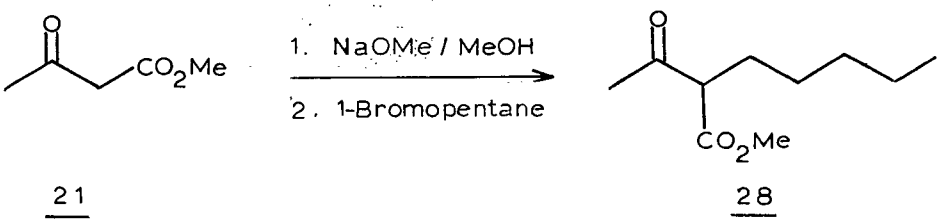
(6)

Scheme V. Synthesis of 3-Bromo-1-trimethylsilylpropyne (27)

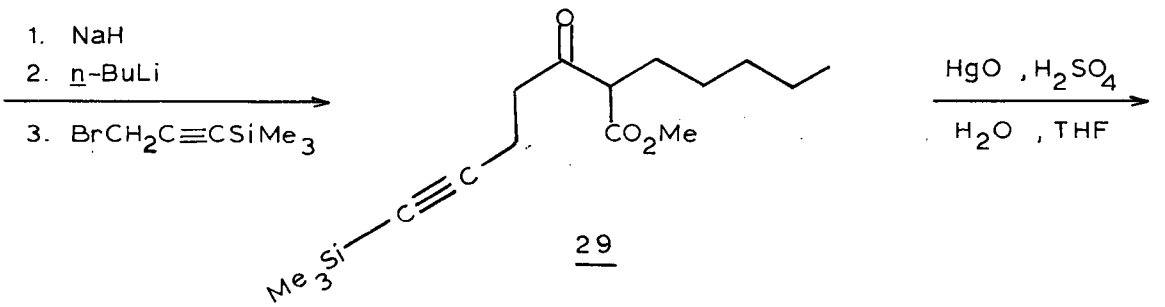


It was envisioned that alkylation of the dianion of a β-keto ester with bromide 27 followed by treatment with Hg^{2+} would provide a convenient route to 1,4-dicarbonyl compounds. Indeed we accomplished this synthetic sequence in a synthesis of dihydrojasmone (3) outlined in Scheme VI.

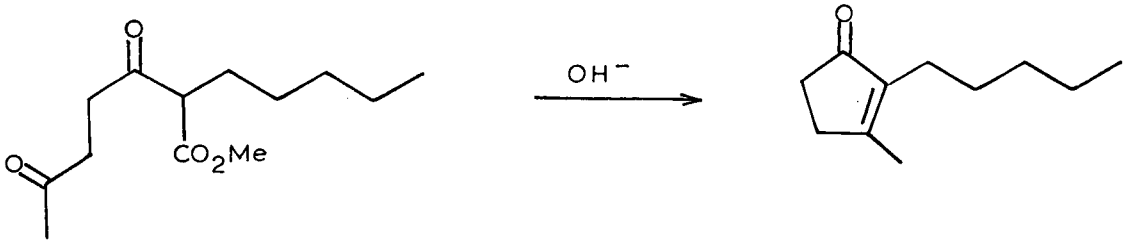
Scheme VI. Synthesis of Dihydrojasmone (3)



21 28



29



30 3

The n-pentyl side chain in the dihydrojasmone (3) was introduced by the alkylation of the monoanion of methyl acetoacetate (21) with 1-bromopentane. Compound 28 was thus obtained in 58% yield. The dianion of β-keto ester 28, prepared by successive treatment with one equivalent of sodium hydride, and one equivalent of n-butylithium, was alkylated with bromide 27 to give the γ-alkylated product 29 in greater than 90% crude yield. Attempts to purify the trimethylsilylalkyne 29 by preparative thin layer chromatography (TLC) were unsuccessful. The proton nuclear magnetic resonance (NMR) spectrum of crude compound 29 showed absorptions at δ 0.25 (s, 9H, $C(CH_3)_3$), 0.8-1.2 (m, 3H, CH_3), 1.2-1.6 (m, 6H, $CH_2CH_2CH_2$), 1.7-2.1 (m, 2H, $-\overset{O}{\overset{\|}{C}}CHCH_2$), 2.5-3.0 (m, 4H, $-\overset{O}{\overset{\|}{C}}-CH_2CH_2C{\equiv}C$), 3.50 (m, 1H, $-\overset{O}{\overset{\|}{C}}CHCO_2CH_3$), and 3.73 (s, 3H, OCH_3), which were consistent with structure 29. The absorption at 2195 cm^{-1} in the infrared (IR) spectrum indicated the presence of the C-C stretching of the triple bond. Compound 29 was further characterized by mass spectra.

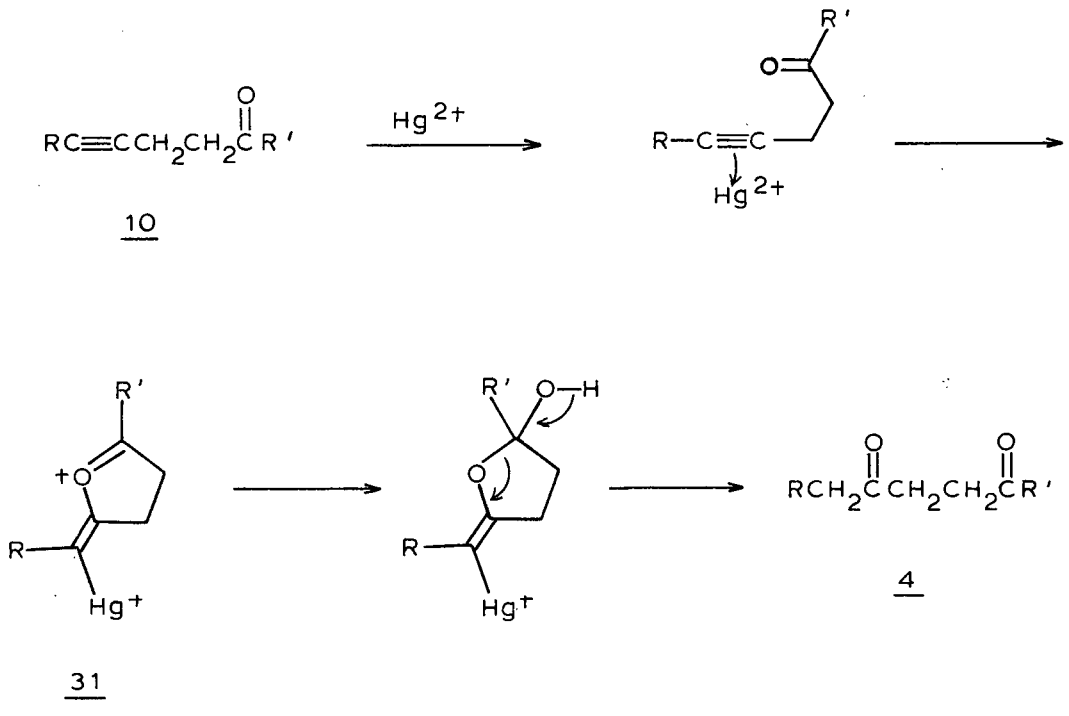
The trimethylsilylacetylene in 29 was hydrolyzed and hydrated by aqueous acid in the presence of a catalytic amount of Hg^{2+} [12] to yield the desired 1,4-diketone 30. The formation of 30 was indicated by the appearance of a sharp three proton singlet at δ 2.15 in the NMR spectrum for the methyl group adjacent to the carbonyl group, and a four proton broad singlet at 2.72 for the methylene protons between the two keto groups. The nine proton singlet at δ 0.25 for the protons on the tri-

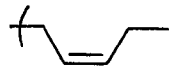
methylsilyl group and the four proton multiplets at 2.5-3.0 for the methylene protons between the triple bond and the keto group observed in compound 29 were absent. The IR spectrum of 30 showed carbonyl absorption at 1715 and 1740 cm^{-1}. The stronger absorption at 1715 cm^{-1} indicated the presence of two ketones whereas the weaker absorption at 1740 was assigned to the ester group.

The exact sequence of occurrence of cleavage of the trimethylsilyl group and hydration of the acetylenic bond during the transformation of 29 to 30 is not clear. In any case, the exclusive formation of the 1,4-diketone 30 could be explained in terms of intramolecular participation of the keto group in 29 during the hydration step. This type of carbonyl assisted regioselective hydration of acetylenes was first reported by Stork and Borch.[3] It was suggested that intramolecular carbonyl participation goes through a kinetically and geometrically favored five-membered ring intermediate 31 as shown in Scheme VII. Apparently, a similar mechanism might be involved for the conversion of 29 into 30 (Scheme VIII).

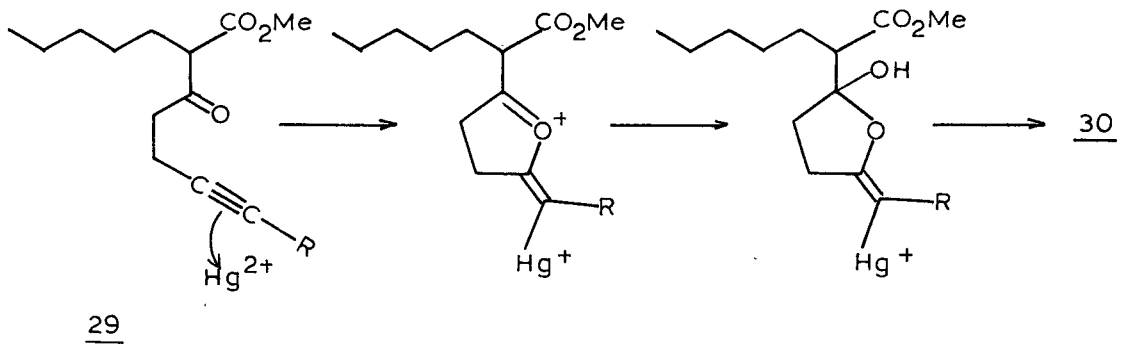
If cleavage of the trimethylsilyl group preceded the hydration step, the usual hydration of terminal acetylenes, following Markovnikov's rule, would also lead to the 1,4-dicarbonyl product 30.

Scheme VII. Proposed Mechanism for the Hydration of Compound 10.[3]



R^1 = Me, R = 

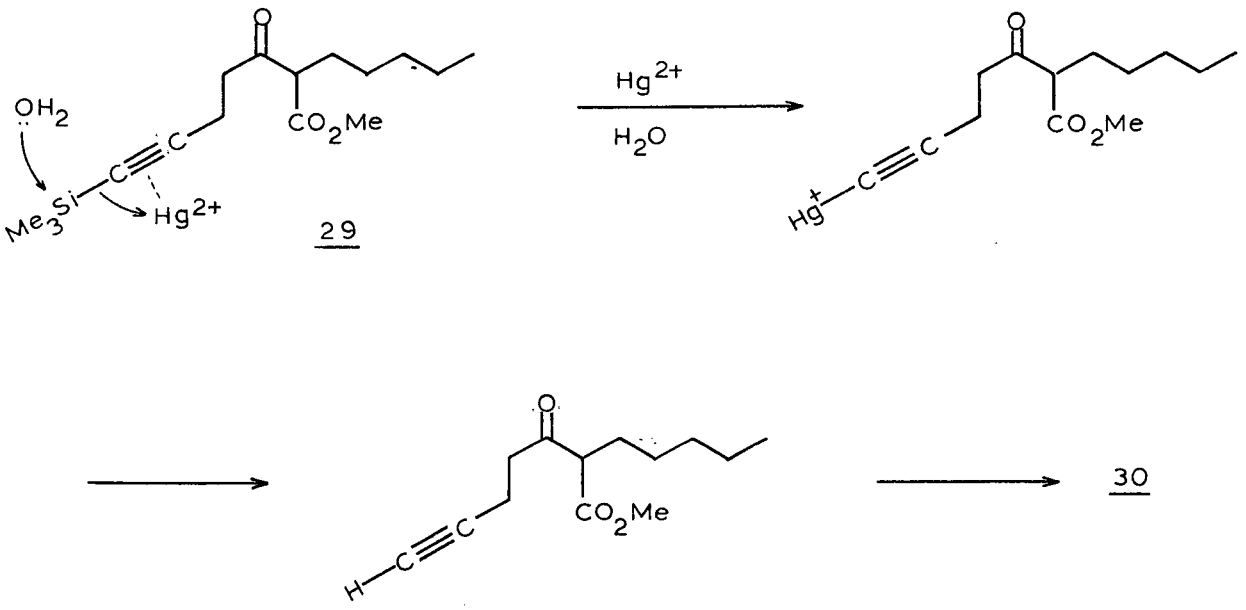
Scheme VIII. Proposed Mechanism for the Hydration of Compound 29



R = $SiMe_3$ or H

Cleavage of the silicon-carbon bond prior to hydration of the acetylene would be assisted by the Hg^{2+} ion as illustrated in Scheme IX. The known Ag^{+} catalyzed cleavage of trimethyl-

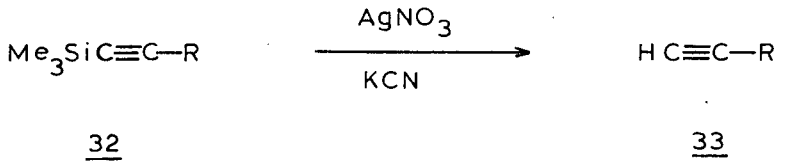
Scheme IX. Proposed Mechanism for the Cleavage of Trimethylsilyl Group of 29.



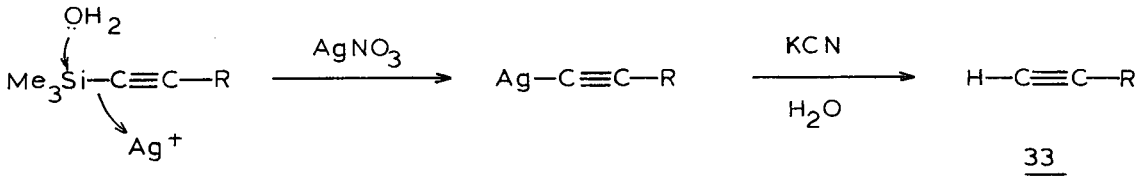
silylacetylenes 32 (Scheme X) supported this mechanism. It was suggested that Ag^{+} formed a complex with the acetylene and thus assisted the displacement at silicon. The cyanide treatment converted the silver acetylide into the acetylene 33.

It is also possible to cleave the trimethylsilyl moiety after

Scheme X. Cleavage of the Trimethylsilyl Group of 32[13]



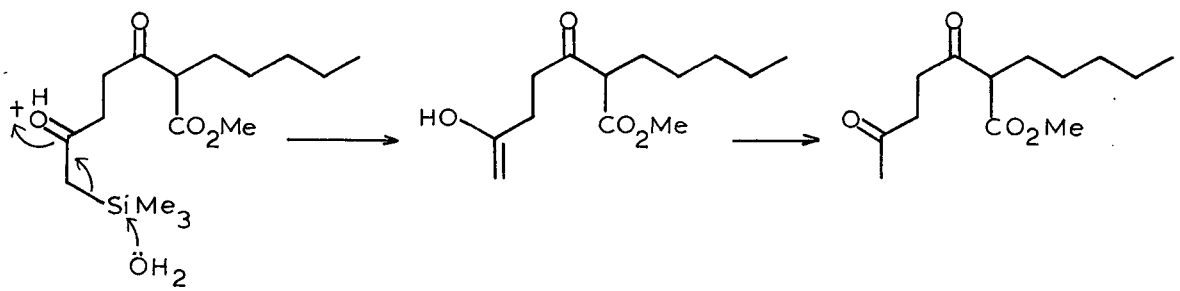
32 33



33

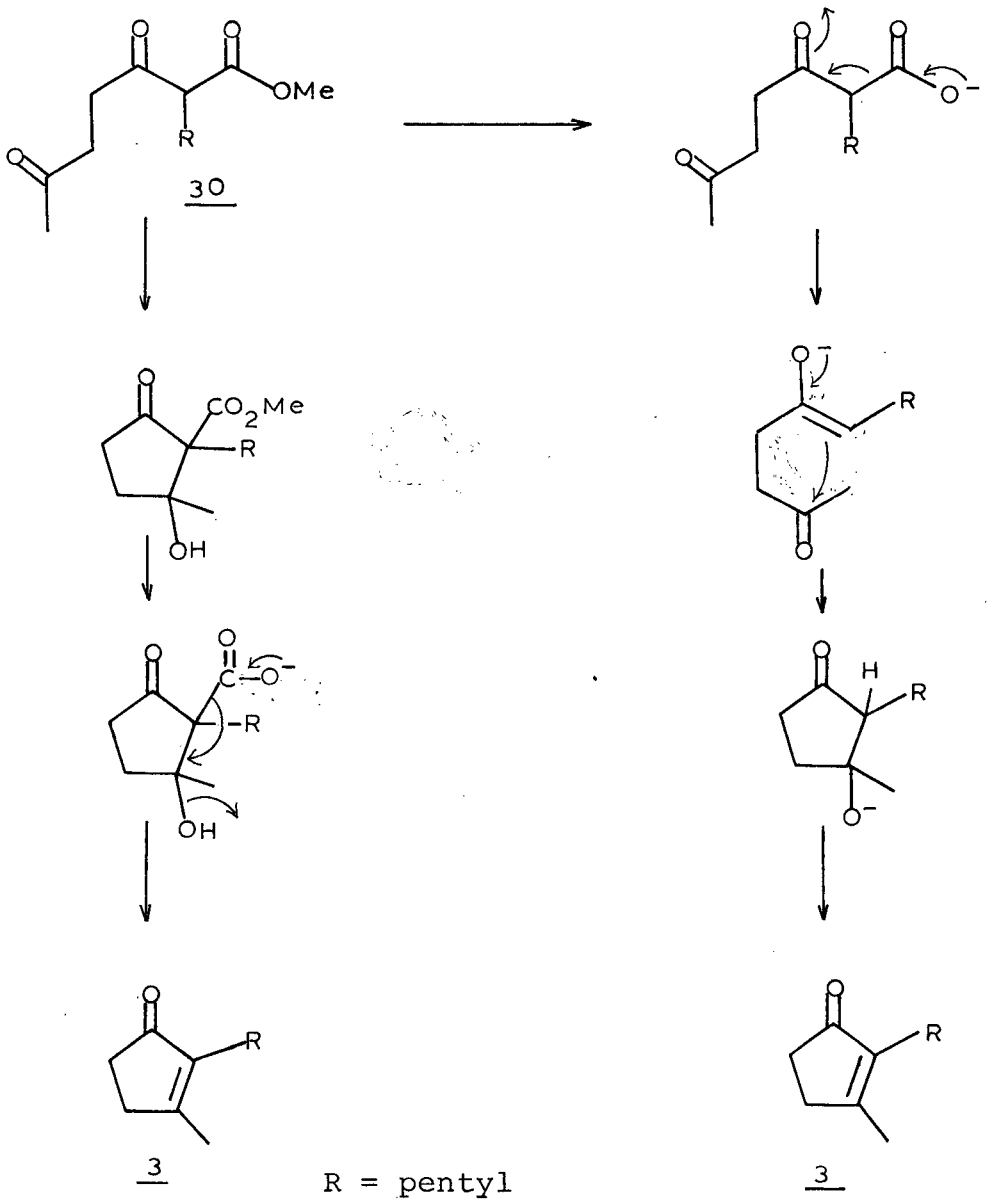
hydration of the acetylene. This process might be facilitated by the α-carbonyl function (Scheme XI).

Scheme XI. Proposed Mechanism for the Cleavage of Trimethylsilyl Group in an α-Trimethylsilyl Ketone



Finally, treatment of the diketone 30 with aqueous base at 70° C effected hydrolysis, decarboxylation, and cyclization in one step to give dihydrojasmone (3) in 75% yield. Scheme XII shows a proposed mechanism for the above conversion.

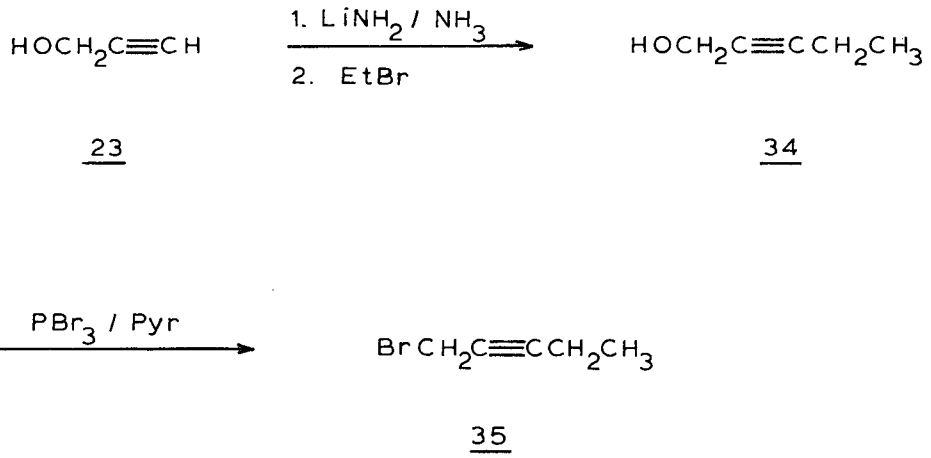
Scheme XII. Proposed Mechanism for the Hydrolysis, Decarboxylation and Cyclization of 30 to 3



(ii) Synthesis of cis-Jasmone (1)

We have also synthesized cis-jasmone (1) using a route similar to that described above. The side chain precursor 35 was prepared as shown in Scheme XIII. The dianion of 2-propyn-1-ol (23) was alkylated with 1-bromoethane to produce 2-pentyn-1-ol (34) in 75% yield. Treatment of alcohol 34 with phosphorus tribromide gave 1-bromo-2-pentyne (35)[14] in 77% yield.

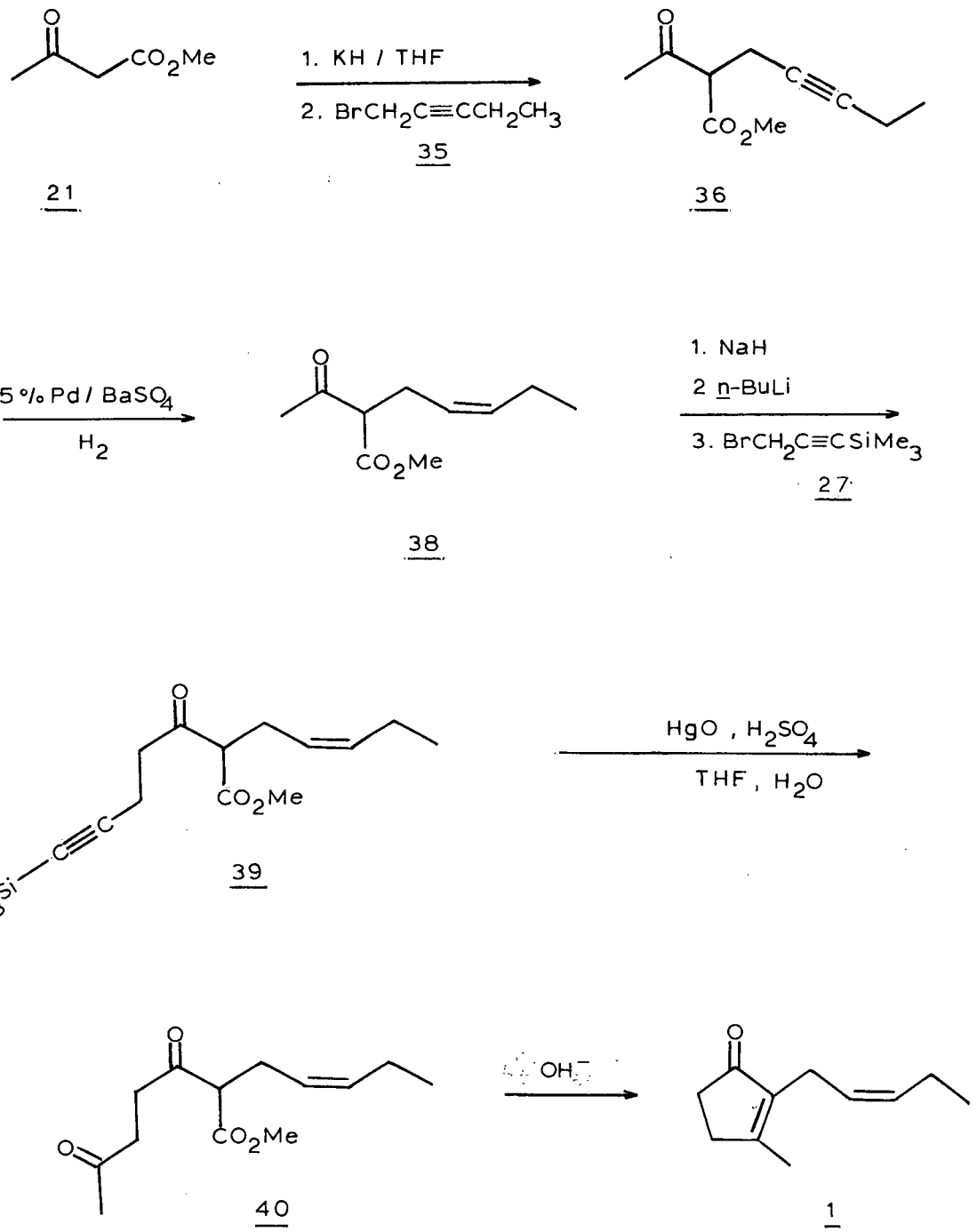
Scheme XIII. Preparation of 1-Bromo-2-pentyne (35)



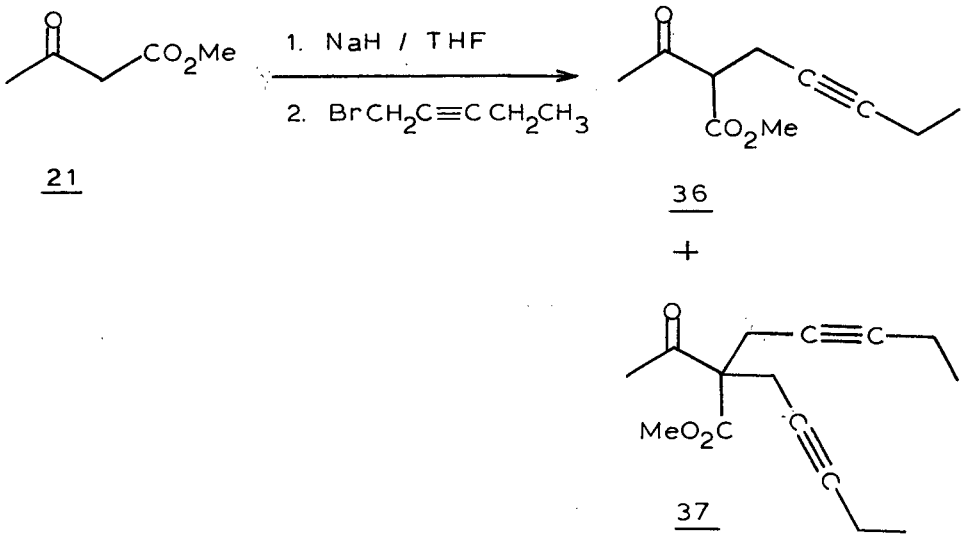
23 34 35

The synthesis of cis-jasmone (1) is illustrated in Scheme XIV. When the monoanion of methyl acetoacetate (21) was generated with sodium hydride in tetrahydrofuran and alkylated with 1-bromo-2-pentyne (35) at room temperature, the desired monoalkylated product 36 was obtained, along with an equal amount of dialkylated product 37 (equation 7). After

Scheme XIV. Synthesis of cis-Jasmone (1).



further investigation, it was found that generation of the monoanion using potassium hydride instead of sodium hydride, improved the yield of the desired monoalkylated product 36 from



21 → 36 + 37 (7)

45 to 70%.

A highly selective monoalkylation of the potassium enolate of 2,4-dimethyl-3-pentanone has been reported previously by Brown.[16] Although the potassium enolates of ketones and 1,3-dicarbonyl compounds are known to be more reactive than the corresponding sodium enolates, it is not clear what the exact reasons are for these observed selective monoalkylations in contrast to the significant dialkylation that occurred with sodium enolates.

The NMR spectrum of methyl 2-acetyl-4-heptynoate (36) was fully consistent with the proposed structure. Signals observed at δ 1.07 (t, J = 7 Hz, 3H), 1.8-2.3 (m, 2H), 2.4-2.8 (m, 2H), 2.27 (s, 3H), 3.60 (t, J = 7 Hz, 1H), and 3.72 (s, 3H) were assigned to the C-7 methyl group, the two methylenes at each end of the triple bond, the methyl group next to the carbonyl, the methine proton and the O-methoxy protons, respectively. Absorptions at 1715 and 1740 cm^{-1} in the IR spectrum indicated the presence of a saturated ketone, and an ester group. In addition, there was a weak band at 2275 cm^{-1} which was ascribable to the C-C stretching of the triple bond. Compound 36 was partially hydrogenated using palladium on barium sulfate[15] as catalyst to give the cis alkene 38 in 89% yield. The NMR spectrum of this hydrogenation product had an absorption at δ 4.9-5.6 (m, 2H) indicating the presence of two vinyl protons. The dianion of the hydrogenated product 38 was generated in the same manner as described above and was alkylated with 3-bromo-1-trimethylsilyl-1-propyne (27). Hydrolysis and hydration of the alkylated product 39 followed by cyclization as before afforded cis-jasmone (1) in greater than 40% overall yield from methyl acetoacetate.

The above syntheses illustrate a facile and efficient route to 1,4-dicarbonyl compounds and cyclopentenones utilizing the trimethylsilylpropyne group as a convenient precursor to the acetonyl unit.

EXPERIMENTAL

General

Unless otherwise stated the following are implied. Melting points (mp) were determined on a Kofler micro heating stage or a Thomas Hoover capillary melting point apparatus and are uncorrected. Gas-liquid chromatography (GLC) was performed on a Hewlett Packard Model 5831A gas chromatograph, using 6' x 1/8" columns and nitrogen as carrier gas. The following columns were employed:

Column	Stationary Phase	Support	Mesh
A	3% OV 17	chromosorb W (HP)	80/100
B	3% OV 101	chromosorb W (HP)	80/100
C	10% DEGS	chromosorb W (HP)	80/100

Carrier gas flow-rate for the column was about 35 mL/min. The 60 MHz nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates Model T-60, the 100 MHz spectra were recorded on Varian Associates Model HA-100 or Model XL-100, and the 270 MHz spectra were recorded on a homebuilt high resolution NMR spectrometer consisting of an Oxford Instruments' 63.4 KG magnet. Chemical shifts in ppm are reported using δ scale with tetramethylsilane (TMS) as internal reference. Signal multiplicity, integrated area and proton assignments are indicated in parenthesis. Infrared spectra (IR) were recorded on

either a Perkin-Elmer model 700 or 710B spectrophotometer. Solution spectra were performed using a sodium chloride solution cell of 0.2 mm thickness. Absorption positions are given in cm^{-1} and are calibrated by means of the 1601 cm^{-1} band of polystyrene. Optical rotations $[\alpha]_D$ were measured with a Perkin-Elmer model 241 MC polarimeter. Low resolution mass spectra were determined on a Varian/Mat model CH4B mass spectrometer. High resolution mass measurements were obtained using Kratos-AEI model MS902 or model MS50 instrument. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver. All solvents used for NMR, IR, and optical rotations were of Spectral grade.

Analytical thin layer chromatography (TLC) plates and preparative TLC plates were prepared from silica gel GF-254 from E. Merck Co. Preparative TLC plates were of about 1 mm in thickness. Column chromatography was carried out in 100-200 mesh ASTM silica gel from Davison Chemical. Plates were visualized under long and short wavelengths ultraviolet radiation and were developed by iodine.

Solvents and reagents used were of either Reagent grade or Certified grade. Solvents were distilled before use. The petroleum ether used was of boiling range ca. 30-60^{o} C. Dry solvents or reagents, where indicated, were prepared as follows:

ethyl ether (ether) and tetrahydrofuran (THF) by refluxing over lithium aluminum hydride followed by distillation; chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2) and carbon tetrachloride (CCl_4) by distillation from phosphorus pentaoxide; hexamethylphosphoramide (HMPA) by distillation from calcium hydride followed by storage over molecular sieve (Type 4A); diisopropylamine and triethylamine by distillation from and storage over potassium hydroxide pellets; pyridine by distillation from barium oxide followed by storage over potassium hydroxide pellets; acetone by distillation from and storage over anhydrous magnesium sulfate; benzene, toluene and n-hexane by distillation from calcium hydride, and methanol by refluxing over magnesium methoxide followed by distillation. Boron trifluoride etherate and phosphorus tribromide were distilled under nitrogen before use.

Methyllithium (in ethyl ether) and n-butyllithium (in hexane) were obtained from Aldrich Chemical Company, Inc. tert-Butyllithium (in pentane) was supplied by Alfa Division, Ventron Corporation. The alkyllithium solutions were standardized by titration against 1.0 M tert-butyl alcohol in benzene using 1,10-phenanthroline as indicator.

Synthesis of Dihydrojasmone

Methyl 2-acetylheptanoate (28)

Approximately 125 mL of anhydrous methanol was added dropwise through an additional funnel to a 3-necked flask containing 1.25 g (54.0 mmol) of sodium (washed oil-free with dry benzene). When all of the sodium had reacted, 5.80 g (50.0 mmol) of methyl acetoacetate was added dropwise. The reaction mixture was heated to a gentle reflux and 8.15 g (54.0 mmol) of 1-bromopentane was added slowly. The reaction mixture was refluxed for an additional 15 h. It was allowed to cool to room temperaure and the methanol was removed under reduced pressure. The residue was diluted with ethyl ether and washed with dilute hydrochloric acid and sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed by evaporation under reduced pressure to give 6.90 g (74%) of crude product. Distillation of the resulting oil gave 5.40 g (58%) of methyl 2-acetylheptanoate (28), bp 60-61° C/0.9 torr;

IR ($CHCl_3$) 1710 and 1740 cm^{-1};

NMR ($CDCl_3$) δ 0.7-1.1 (m, 3H), 1.1-1.5 (m, 6H), 1.6-2.1 (m, 2H), 2.18 (s, 3H), 3.37 (t, J = 7 Hz, 1H), and 3.7 (s, 3H);

mass spectrum: a) high resolution calcd for $C_{10}H_{18}O_3$: 186.1244 amu; found: 186.1241;

b) low resolution m/e (rel intensity)

43(96), 55(28), 87(90), 101(58), 116(100), 117(20), 129(16), 144(64), 155(12), and 186(8).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.38; H, 9.70.

3-(2-Tetrahydropyranyloxy)-1-trimethylsilyl-1-propyne (25)[11]

Under a nitrogen atmosphere, a catalytic amount (ca. 0.40 g) of p-toluenesulfonic acid monohydrate was added to a stirred solution of 8.40 g (150 mmol) of 2-propyn-1-ol and 13.46 g (160 mmol) of dihydropyran in ca. 130 mL of anhydrous dichloromethane at 0° C. The reaction temperature was raised to 25° C and stirring was continued for 2 h. The reaction mixture was then washed with dilute aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Distillation of the crude product gave 19.53 g (93%) of 1-(2-tetrahydropyranyloxy)-2-propyne (24), bp 95-97° C/20 torr [lit.[17] bp 63-65° C/9 torr];

IR ($CHCl_3$) 2150 and 3350 cm^{-1};

NMR ($CDCl_3$) δ 1.2-1.9 (m, 6H), 2.2-2.4 (m, 1H), 3.2-4.0 (m, 2H), 4.18 (d, J = 2.5 Hz, 2H), and 4.75 (br s, 1H).

Under a nitrogen atmosphere, 48.54 mL (100 mmol, 2.06 M in ethyl ether) of methyllithium was added to a stirred solution of 14.0 g (100 mmol) of the tetrahydropyranyl compound 24 in 120 mL of anhydrous ethyl ether at 0° C. A heavy white precipitate was formed and the reaction mixture was stirred for

15 min. Then 10.86 g (100 mmol) of chlorotrimethylsilane was added dropwise, the reaction mixture turned clear and a white precipitate was observed again after the addition of all the chlorotrimethylsilane. The reaction mixture was stirred at 0° C for 15 min, at room temperature for 10 min and then quenched with aqueous sodium bicarbonate, and the mixture diluted with pentane. The organic layer was separated, dried over anhydrous sodium sulfate, and the solvents were removed under reduced pressure to give 21.09 g(99%) of crude product. Kugelrohr distillation (bath temperature 56 -57° C/0.7 torr) gave 19.95 g (94%) of pure compound 25,

IR ($CHCl_3$) 2205 cm^{-1};

NMR ($CDCl_3$) δ 0.24 (s, 3H), 1.4-2.0 (m, 6H), 3.5-4.0 (m, 2H), 4.33 (s, 2H), and 4.8-5.0 (m, 1H);

mass spectrum m/e (rel intensity) 41(31), 43(31), 56 (65), 73(55), 75(35), 83(55), 85(100), 97(22), 101(81), 103(56), 111(69), 113(83), 128(21), 173(22), 197(10), and 212(5).

3-Hydroxy-1-trimethylsilyl-1-propyne (26)[11]

To a solution of 21.2 g (100.0 mmol) of compound 25 in 150 mL of anhydrous methanol was added a catalytic amount of p-toluenesulfonic acid monohydrate (0.10 g). The reaction mixture was refluxed under nitrogen for 2 h. It was then allowed to cool to room temperature and methanol removed under reduced pressure. The yellow oil was diluted with ethyl ether, washed

with dilute aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to give an oil which was purified by distillation (Kugelrohr) to give 11.30 g (88%) of 3-hydroxyl-1-trimethylsilyl-1-propyne (26), bath temperature 48° C/0.6 torr;

IR ($CHCl_3$) 2200, 3300-3800 cm^{-1};

NMR ($CDCl_3$) δ 0.28 (s, 9H), 2.2 (t, J = 6 Hz, 1H), and 4.33 (d, J = 6 Hz, 2H);

mass spectrum m/e (rel intensity) 43(23), 45(31), 61 (31), 75(33), 75(46), 83(23), 85(100), 87(26), 113(99), 114(22), and 128(17).

3-Bromo-1-trimethylsilyl-1-propyne (27)

To a solution of 9.98 g (78.0 mmol) of 3-hydroxy-1-trimethylsilyl-1-propyne, 0.16 g (2.0 mmol) of anhydrous pyridine, and ca. 45 mL of anhydrous ethyl ether was added dropwise 8.66 g (32.0 mmol) of phosphorus tribromide. The reaction mixture was refluxed for 2 h, allowed to cool, and poured onto ice. The ether layer was washed with water, 5% aqueous sodium bicarbonate, and saturated ammonium chloride solution. It was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by distillation to give 11.93 g (80%) of 3-bromo-1-trimethylsilyl-1-propyne (27), bp 75-78° C/20 torr [lit.[11] bp 71-73° C/ ~26 torr] and had the following spectral data;

IR ($CHCl_3$) 2200 cm^{-1};

NMR ($CDCl_3$) δ 0.26 (s, 9H) and 3.92 (s, 2H);

mass spectrum m/e (rel intensity) 43(36), 53(25), 55 (32), 83(37), 85(28), 96(31), 111(47), 113(33), 123(24), 125 (22), 137(49), 139(49), 147(66), 149(67), 175(100), 177(99), 190(20) and 192(19).

6-Carbomethoxy-1-trimethylsilyl-1-undecyn-5-one (29)

A sample of 0.27 g (5.10 mmol) of sodium hydride, as a 50% mineral oil dispersion was weighed into an oven dried flask. It was washed with THF to remove the mineral oil. About 50 mL of dry THF was distilled directly into the flask. The flask was then equipped with a magnetic stirrer, septum cap, flushed with nitrogen, and cooled in ice. Then 0.93 g (5.0 mmol) of methyl 2-acetylheptanoate (28) was added dropwise to the cooled slurry and the reaction was stirred for 10 min, 3.13 mL (5.0 mmol, 1.6 M in hexane) of n-butyllithium was added dropwise to the reaction mixture, and stirred for another 10 min. The resulting dianion was alkylated with 0.98 g (5.2 mmol) of 3-bromo-1-trimethylsilyl-1-propyne (27). After stirring for 2 h at 0° C the reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with ethyl ether, washed with brine, and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to yield 1.6 g of crude 29 which was homogeneous by chromatography and spectro-

scopy. This crude compound 29 was used directly in the next step and the compound was characterized by the following data;

IR ($CHCl_3$) 1715, 1740, and 2195 cm^{-1};

NMR ($CDCl_3$) δ 0.25 (s, 9H), 0.8-1.2 (m, 3H), 1.2-1.6 (m, 6H), 1.7-2.1 (m, 2H), 2.5-3.0 (m, 4H), 3.5 (m, 1H) and 3.73 (s, 3H);

mass spectrum: a) high resolution calcd for $C_{16}H_{28}O_3Si$: 296.1804 amu; found: 296.1803;

b) low resolution m/e (rel intensity) 41(20), 43(28), 55(24), 73(96), 89(42), 139(30), 153(100), 154(15), 169(18), 195(14), 209(10), 211(10), 221(8), 223(7), 225(11), 236(8), 237(11), 249(11), 265(9), 281(68), and 296(3).

6-Carbomethoxy-2,5-undecanedione (30)

A solution of 0.16 g of mercury (II) oxide in 0.26 mL of concentrated sulfuric acid and 6 mL of water was added to 100 mL of THF and warmed to ca. 60° C. A solution of 2.96 g of crude acetylene 29 in 10 mL of tetrahydrofuran was added to this mercuric sulfate solution. The resulting solution was cooled to ca. 40° C and stirred at that temperature for 2 h. The reaction mixture was quenched with water and extracted with ethyl ether. The extracts were dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. The crude oil was distilled at 118° C/0.4 torr (Kugelrohr) to yield 1.91 g (79% from 28) of 6-carbomethoxy-

2,5-undecanedione (30). A small amount of 30 was purified by TLC (using a mixture of CCl_4 and Et_2O, 8:1 v/v), and was characterized by;

IR ($CHCl_3$) 1715 and 1740 cm^{-1};

NMR ($CDCl_3$) δ 0.7-1.0 (m, 3H), 1.1-1.5 (m, 6H), 1.7-2.0 (m, 2H), 2.15 (s, 3H), 2.72 (br s, 4H), 3.45 (t, J = 7 Hz, 1H), and 3.68 (s, 5H);

mass spectrum: a) high resolution calcd for $C_{13}H_{22}O_4$: 242.1503 amu; found: 242.1506;

b) low resolution m/e (rel intensity) 43(50), 55(14), 71(10), 87(10), 99(100), 140(11), 172(20), 211(5), and 242(0.1).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.33; H, 9.25.

Dihydrojasmone (3)

A solution of 0.242 g (1.0 mmol) of diketo ester (30) in 8 mL of 3% aqueous sodium hydroxide was stirred at ca. 70° C for 5½ h. After cooling to room temperature, the reaction was acidified to pH 4 with 25% aqueous sulfuric acid and extracted with ether. The extracts were dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure. The crude yellow oil was distilled (Kugelrohr) at 85° C/0.4 torr [lit.[19] bp 93° C/2.3 torr] to yield 0.12 g (72 %) of dihydrojasmone (3). A TLC (CCl_4:Et_2O 8:1 v/v) purified sample of 3 had spectral data identical to those reported and was characterized by:

IR ($CHCl_3$) 1640 and 1690 cm^{-1};

NMR ($CDCl_3$) δ 0.6-0.9 (m, 3H), 1.0-1.5 (m, 6H), 2.03 (br s, 3H), and 2.0-2.6 (m, 6H);

mass spectrum m/e (rel intensity) 41(25), 67(17), 95 (18), 96(18), 109(21), 110(100), 101(26), 123(23), 137(25), 151(56), and 166(45).

Synthesis of cis-Jasmone

2-Pentyn-1-ol (34)[20]

To 1 L of liquid ammonia in a 2 L three-necked flask fitted with a mechanical stirrer and a dry-ice condenser and a nitrogen outlet, was added a catalytic amount of ferric nitrate and 12.1 g of lithium (washed oil-free with benzene) in small portions. After the disappearance of the dark blue color, 52.5 mL of propargyl alcohol (50.56 g, 887 mmol) in 100 mL of THF was added dropwise over 15 min. Another 150 mL of THF were added over 5 min and the reaction mixture was allowed to reflux (-33° C) for 1 h before a solution of 96.78 g (888 mmol) of 1-bromoethane in 50 mL of THF was added over 10 min. The reaction was allowed to reflux for 30 min and left overnight under a positive N_2 pressure to drive off the ammonia. The residue was poured into a beaker containing some ice and ammonium chloride solution and the aqueous layer was then extracted with (3 x 500 mL) ethyl ether. The ether extracts were combined, washed with saturated brine solution, dried over anhydrous sodium sulfate, and the solvents were removed by evaporation at reduced pressure. The crude product was purified by distillation at reduced pressure to give 56.14 g (75%) of 2-pentyn-1-ol (34), bp 76-77° C/20 torr, [lit.[20] bp 61-62°/15 torr];

IR ($CHCl_3$) 2250 and 3500 cm^{-1};

NMR ($CDCl_3$) δ 1.13 (t, J = 7 Hz, 3H), 1.17-2.5 (m, 3H) and 4.1-4.4 (m, 2H);

mass spectrum m/e (rel intensity) 41(80), 53(29), 55(100), 56(38), 83(61), and 84(28).

1-Bromo-2-pentyne (35)[14]

To a solution of 19.69 g (235 mmol) of 3-pentyn-1-ol (34), 0.48 mL of dry pyridine and 120 mL of anhydrous ethyl ether was added dropwise 9 mL of phosphorus tribromide in 30 mL of anhydrous ethyl ether. The mixture was refluxed for 2 hr and poured onto ice. The ether layer was washed with water, 5% aqueous sodium bicarbonate solution, and saturated ammonium chloride solution. The etheral solution was dried over anhydrous sodium sulfate and the ether was removed under reduced pressure. The crude product was purified by distillation to give 26.253 g (77%) of 1-bromo-2-pentyne (35); bp 60-64° C/20 torr;

IR ($CHCl_3$) 2250 cm^{-1};

NMR ($CDCl_3$) δ 1.15 (t, J = 7 Hz, 3H), 2.0-2.5 (m, 2H), and 3.86 (t, J = 2.5 Hz, 2H);

mass spectrum m/e (rel intensity) 41(47), 50(5), 51 (10), 52(5), 65(10), 67(100), 68(8), 146(27), and 148(23).

Methyl 2-acetyl-4-heptynoate (36)

A sample of 1.80 g (ca. 10.0 mmol) of potassium hydride in mineral oil was washed with dry THF and suspended in 25 mL of dry THF. Then 1.16 g (10.0 mmol) of methyl acetoacetate was added at 0° C and the solution of the monoanion was stirred at 0° for 10 min before it was alkylated with 1.75 g (12 mmol) of

1-bromo-2-pentyne (35). The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl ether, washed with water, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure and the crude product distilled at 75° C/0.1 torr to yield 1.27 (70%) of methyl 2-acetyl-4-heptynoate (36). A small sample of 36 was purified by TLC (using a mixture of CCl_4 and Et_2O, 8:1 v/v) and had the following spectral data;

IR ($CHCl_3$) 1715, 1740 and 2275 cm^{-1};

NMR ($CDCl_3$) δ 1.07 (t, J = 7 Hz, 3H), 1.8-2.3 (m, 2H), 2.27 (s, 3H), 2.4-2.8 (m, 2H), 3.60 (t, J = 7 Hz, 1H), and 3.72 (s, 3H);

mass spectrum: a) high resolution calcd for $C_{14}H_{14}O_3$: 182.0922 amu; found: 182.0918;

b) low resolution m/e (rel intensity) 43(60), 79(22), 106(23), 123(15), 139(100), 140(10), 151(6), 167(2), and 182(4).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92, H, 7.74. Found: C, 66.21; H, 7.87.

Methyl (Z)-2-acetyl-4-heptenoate (38)

A mixture of 3.64 g (20.0 mmol) of methyl 2-acetyl-4-heptynoate (36), 0.12 g of 5% palladium on barium sulfate[66] and 6 drops of distilled quinoline in 125 ml of anhydrous methanol was hydrogenated at atmospheric pressure. After ca. 1 h one equivalent of hydrogen was absorbed, the mixture was filtered,

and the methanol was removed under reduced pressure. The crude product was dissolved in ethyl ether, and washed with dilute aqueous hydrochloric acid and brine. The etheral solution was dried over anhydrous magnesium sulfate and solvent removed under reduced pressure. The crude product was distilled at 75° C/0.1 torr to yield 3.26 g (89%) of methyl (Z)-2-acetyl-4-heptenoate (38). A small sample of 38 was purified by TLC (CCl_4:Et_2O, 8:1 v/v) and was characterized by;

IR ($CHCl_3$) 1710 and 1740 cm^{-1};

NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3H), 1.7-2.2 (m, 2H), 2.22 (s, 3H), 2.57 (m, 2H), 3.43 (t, J = 7 Hz, 1H), 3.70 (s, 3H), and 4.9-5.6 (m, 2H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_3$: 184.1096 amu; found: 184.1095;

b) low resolution m/e (rel intensity) 43(100), 68(45), 81(33), 95(25), 109(30), 123(15), 137(7), 141 (85), 152(10), 166(5), and 184(10).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.37; H, 8.67.

(Z)-6-Carbomethoxy-1-trimethylsilyl-8-undecen-1-yn-5-one (39)

A solution of 1.84 g (10.0 mmol) of the ester 38 in 5 mL of anhydrous THF was added dropwise to a suspension of oil-free sodium hydride (0.55 g) in THF at 0° C under nitrogen. After stirring for 10 min, 4.8 mL of 2.1 M n-butyllithium (10.1 mmol) was added, and after another 10 min, the resulting dianion was alkyla-

ted with 2.28 g (12.0 mmol) of 3-bromo-1-trimethyl-1-propyne (27). The reaction mixture was then stirred at 0° C for 3 h and room temperature for 2 hr. It was quenched with saturated ammonium chloride, extracted with ethyl ether, washed with brine and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to yield 3.0 g (99%) of crude 39 which was used directly in the next step. The alkylation product 39 was homogeneous by chromatography and it was characterized by the following spectral data;

IR ($CHCl_3$) 1720, 1745, and 2200 cm^{-1};

NMR ($CDCl_3$) δ 0.20 (s, 9H), 1.00 (t, J = 7 Hz, 3H), 1.8-2.9 (m, 8H), 3.53 (t, J = 7 Hz, 1H), 3.70 (s, 3H), and 5.1-5.7 (m, 2H);

mass spectrum: a) high resolution calcd for $C_{16}H_{26}O_3Si$: 294.1641 amu; found: 294.1636;

b) low resolution m/e (rel intensity) 41(40), 43(40), 73(100), 89(26), 141(35), 193(11), 235(22), 279(10), and 294(3).

(Z)-6-Carbomethoxy-8-undecen-2,5-dione (40)

The crude trimethylsilylalkyne 39 (1.47 g, 5.0 mmol) was hydrolyzed with 0.076 g of mercuric oxide in sulfuric acid, water and THF under the same conditions as those reported for hydrolysis of 29. The crude product was distilled (Kugelrohr) at 125° C/0.5 torr to give 1.20 g (80%) of dione 40. Further purification was achieved by TLC: 0.1 g of the distilled pro-

duct was chromatographed using carbon tetrachloride and ethyl ether (4:1 v/v) as eluent to yield 0.075 g of pure dione 40 which had the following spectral data;

IR ($CHCl_3$) 1715 and 1745 cm^{-1};

NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H), 1.7-2.2 (m, 2H), 2.17 (s, 3H), 2.57 (m, 2H), 2.73 (br s, 4H), 3.52 (t, J = 7 Hz, 1H), 3.70 (s, 3H), and 5.0-5.7 (m, 2H);

mass spectrum: a) high resolution calcd for $C_{13}H_{20}O_4$: 240.1376 amu; found: 240.1373;

b) low resolution m/e (rel intensity) 41(33), 43(100), 81(25), 99(90), 109(50), 127(29), 129(18), 141(71), 151(21), 172(10), 183(15), 190(13), 208(10), 209(11), 222(18), and 240(10).

Anal. calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.70; H, 8.45.

Cis-Jasmone (1)

A sample of 0.48 g (2.0 mmol) of diketo ester 40 was hydrolyzed and cyclized with 16 mL of 3% aqueous sodium hydroxide using the same procedure as that used in the synthesis of dihydrojasmone (2). The crude product was distilled (Kugelrohr) to yield 0.28 g (85%) of cis-jasmone (1) which was homogeneous by TLC analysis and a TLC purified (CCl_4:Et_2O, 4:1 v/v) sample of 1 had spectral data identical to those reported for cis-jasmone (1);[18]

IR ($CHCl_3$) 1640 and 1690 cm^{-1};

NMR ($CDCl_3$) δ 0.97 (t, J = 7 Hz, 3H), 2.03 (s, 3H), 1.7-2.1 (m, 2H), 2.2-2.6 (m, 4H), 2.9 (m, 2H), and 5.25 (m, 2H),

mass spectrum m/e (rel intensity) 41(38), 43(41), 55(41), 79(35), 109(58), 110(53), 122(44), 135(45), 149(43), and 164(100).

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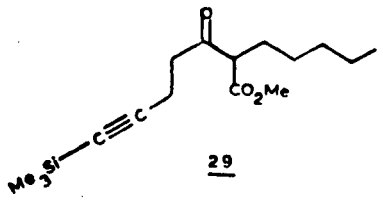
SPECTRAL APPENDIX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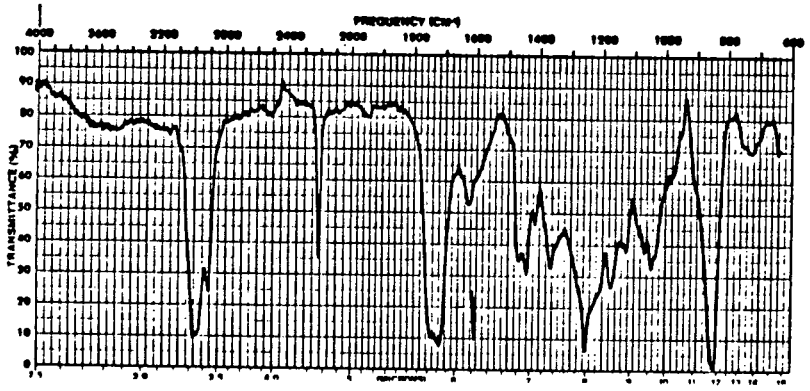
29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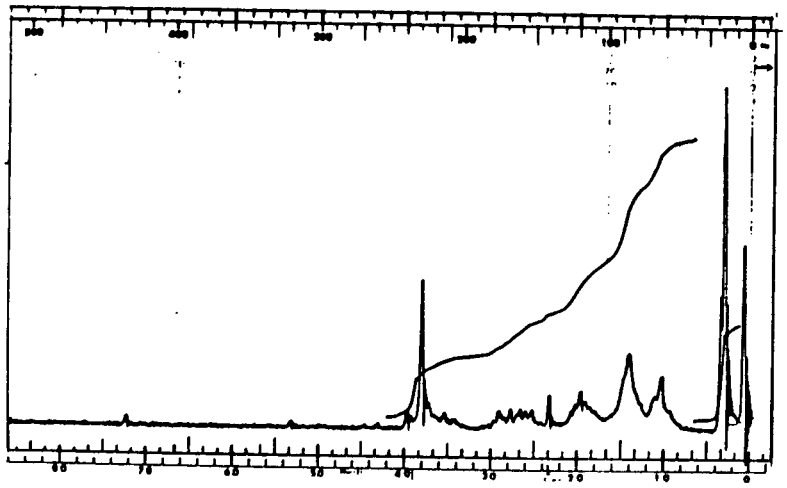

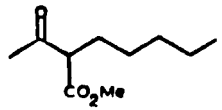
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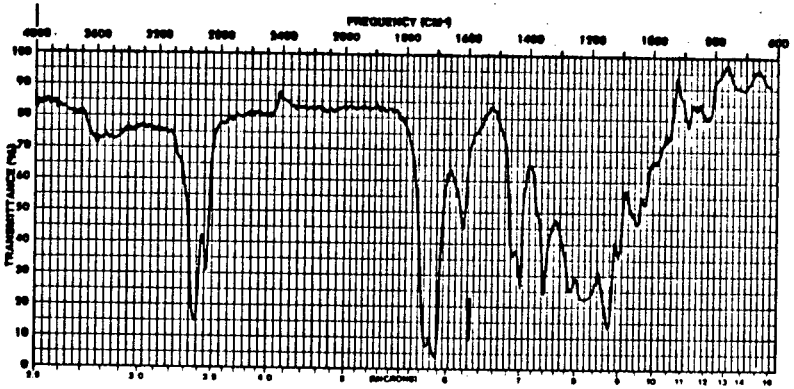
CO2Me

28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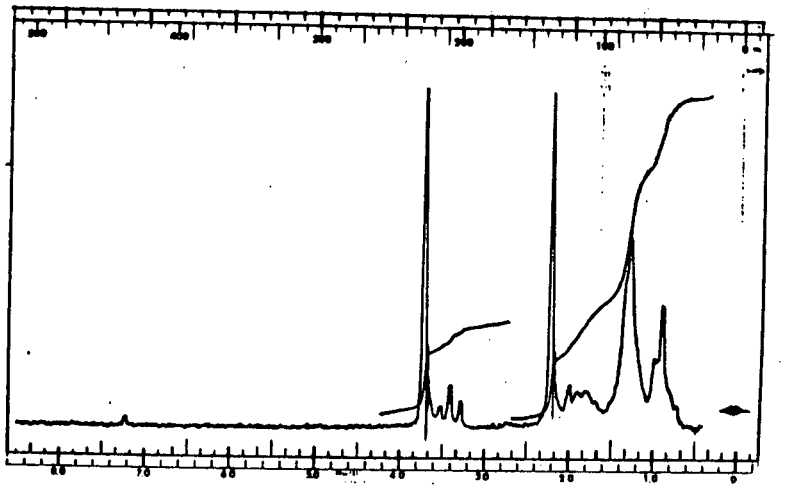

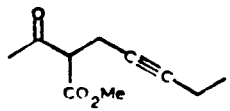
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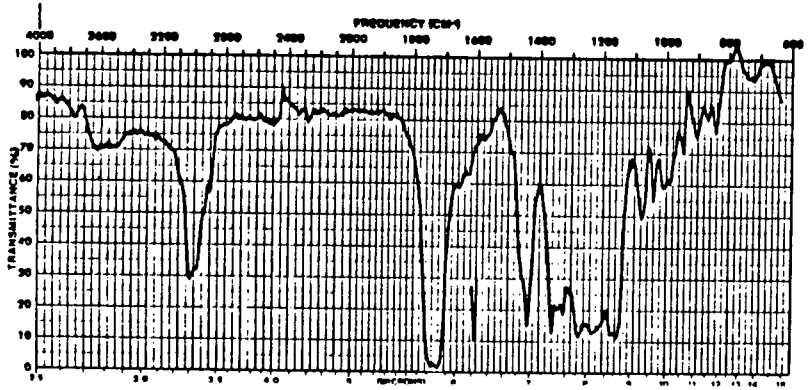
O
CO2Me

36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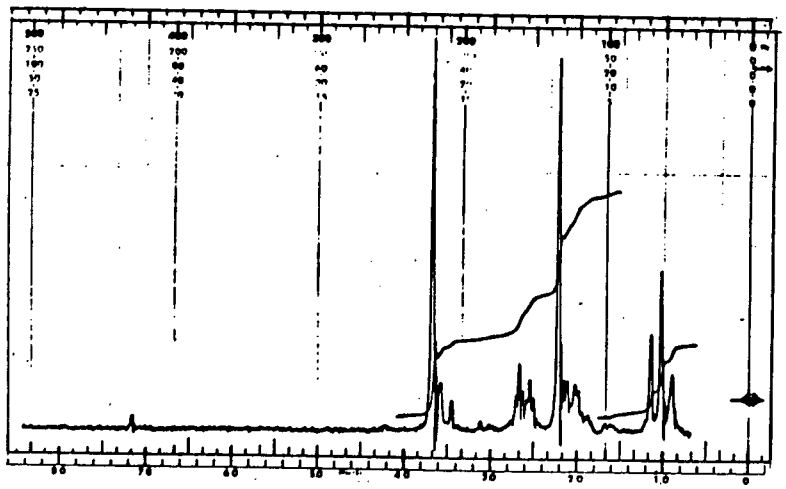

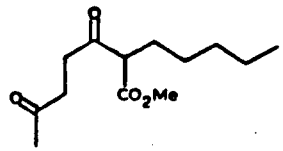
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O
CO2Me

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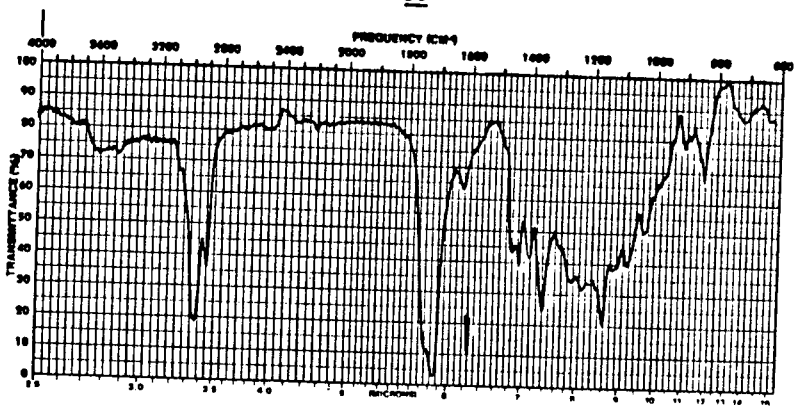
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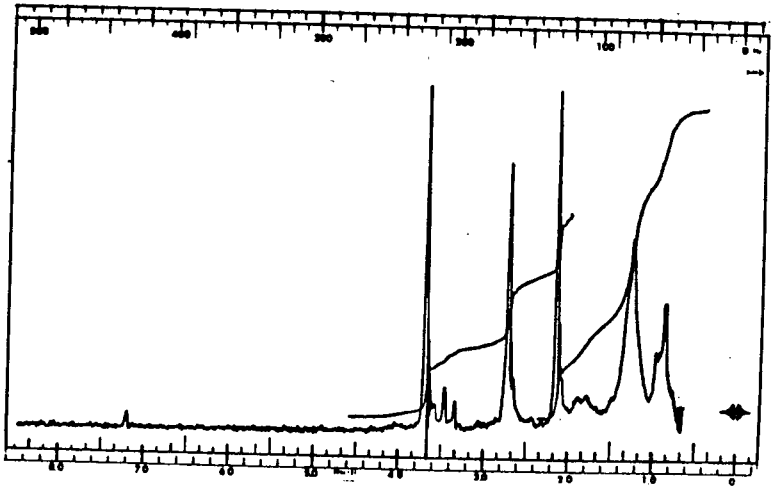

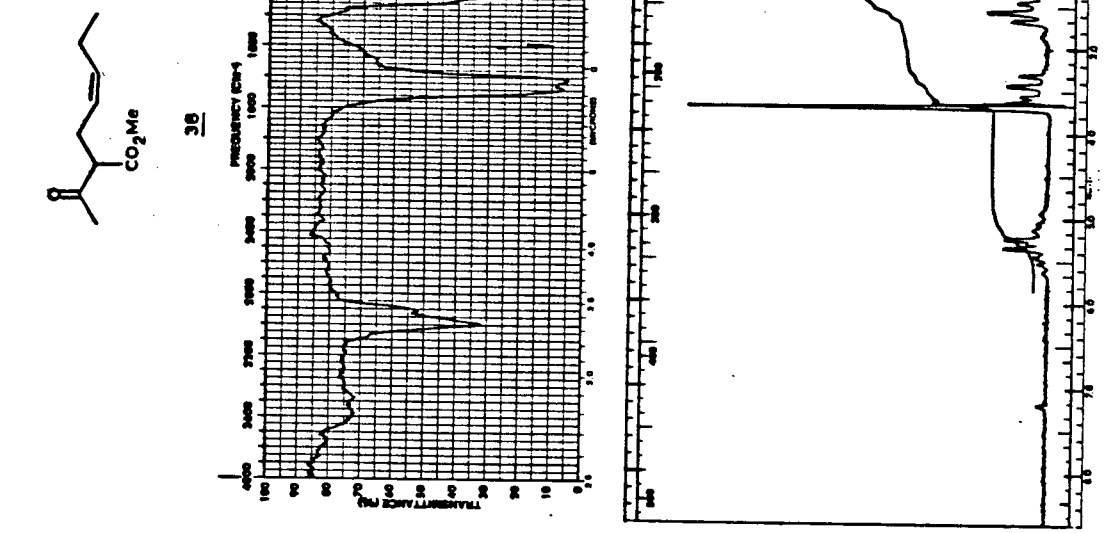
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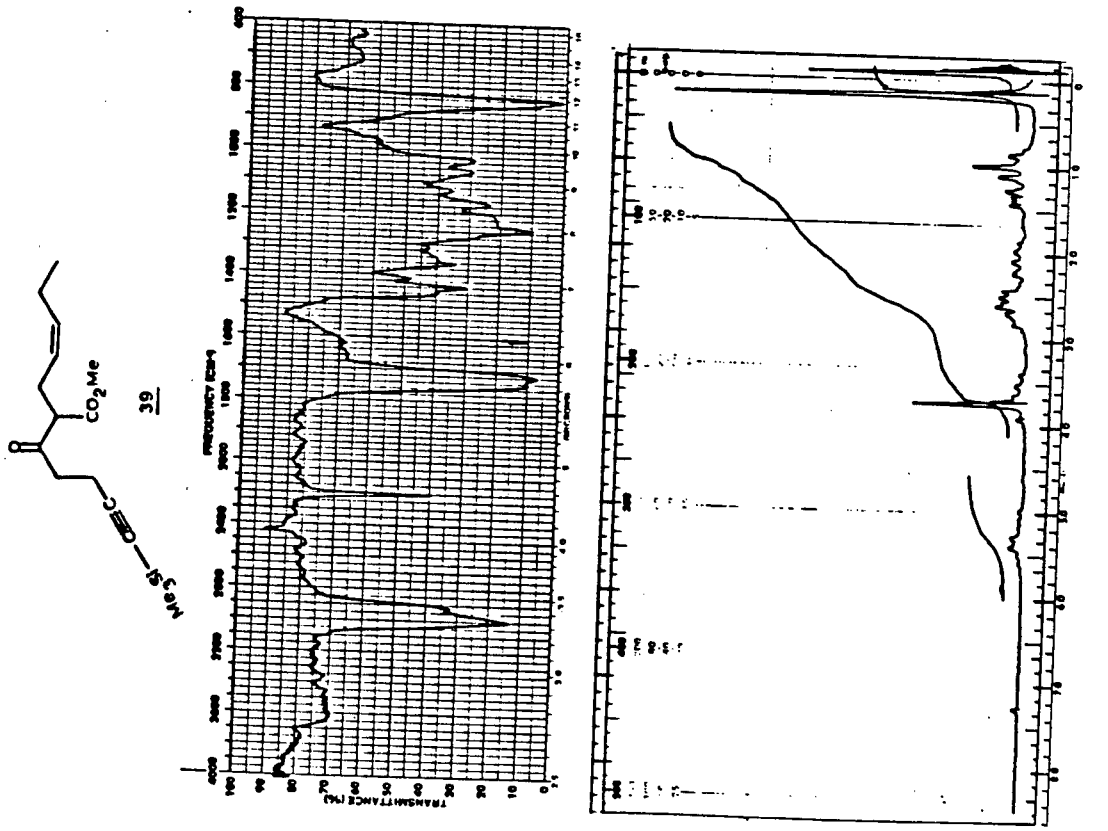
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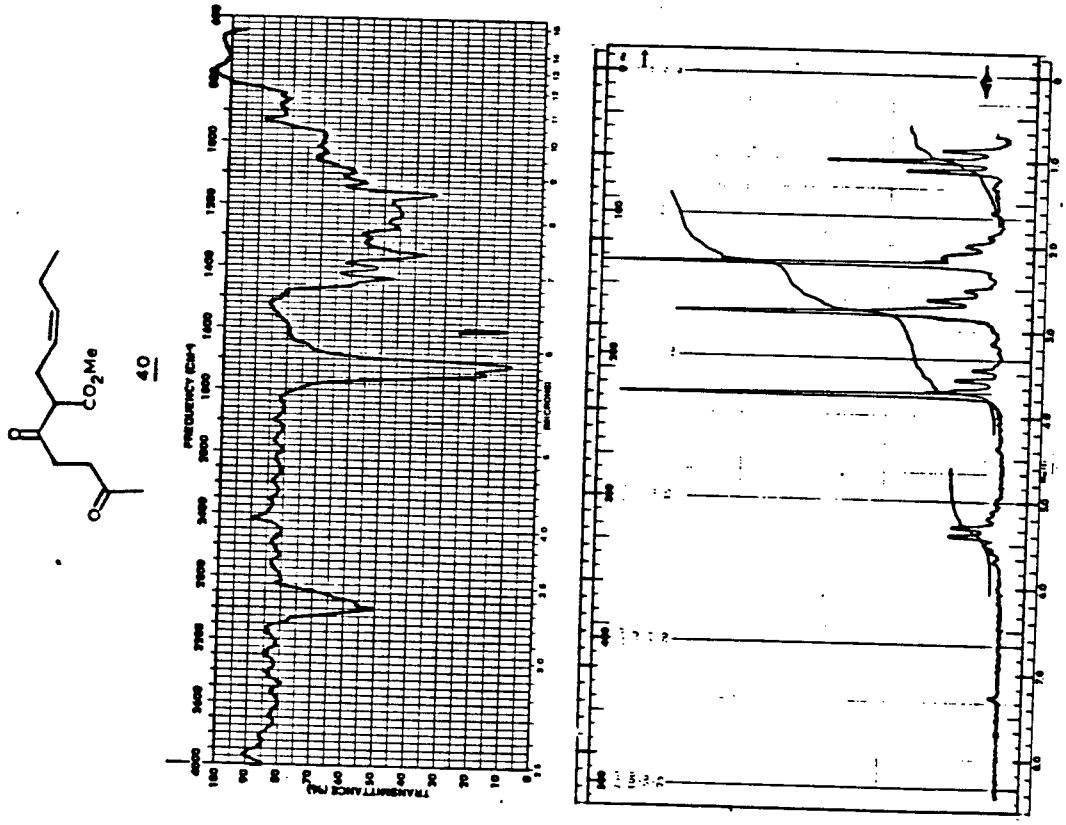
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PART II

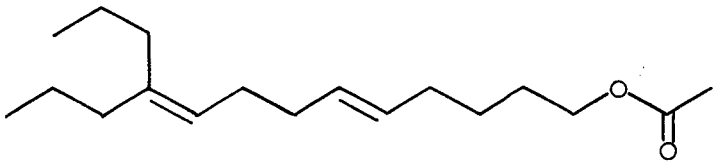
SYNTHESIS OF CYCLIC KETAL-TYPE INSECT PHEROMONES

INTRODUCTION

(i) General

Pheromones are highly active chemical messengers secreted by an insect to influence the behavior of other insects of the same species. The term "Pheromone" is derived from the Greek "pherein" (to carry, transmit) and "hormon" (to excite, stimulate).[1] Compounds which are involved in the internal transport of information in insects, for example, development, metamorphosis and reproduction are called "hormones," while those involved in the external transport of information are called "pheromones." Pheromones include sex attractants, alarm pheromones, and aggregation pheromones whose names are self-explanatory for their functions. Since pheromones are usually transmitted among insects through the atmosphere in very minute quantities, insects can frequently be attracted by an active chemical to a trap for surveying purposes, to a toxic compound that destroys them, or to substances that render them incapable of fertile mating. Pheromones can also be used to interfere with normal insect behavior. Due to the environmental pollution and ecological imbalance caused by insecticides, insect pheromones may serve as an alternate method to control pest insect populations.[2] In recent years, interest in the chemical identification and synthesis of insect pheromones has greatly increased because of their scientific and economic values.

The number of pheromones isolated from various orders of insects has been growing rapidly in the past decade. The structures of many insect pheromones have been found to be simple long-chain, slightly branched olefinic hydrocarbons, or cyclic ethers. Some of these pheromones are chiral compounds. Unsaturated aliphilic alcohols, aldehydes, or acetates are the most commonly occurring features found in the sex pheromones of Lepidoptera (moths and butterflies) species. (E)-10-Propyl-5,9-tridecadienyl acetate (1)[3] has been found to be the sex attractant produced by the virgin female pink bollworm moth. The sex attractant produced by the female gypsy moth was



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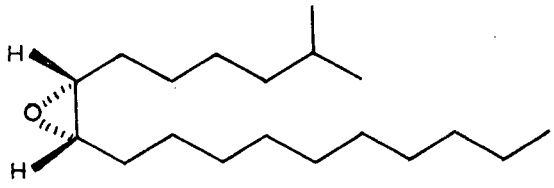
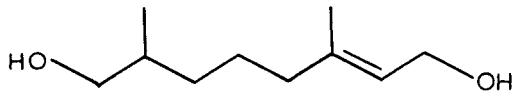
identified as (7R, 8S)-epoxy-2-methyl-octadecane (2). This is also one of the few examples of chiral compounds among the



2

Lepidopterous pheromones.[4,5] Another example is (E)-3,7-dimethyl-2-octen-1,8-diol (3) which is one of the major components secreted by the hairpencils of the African Monarch butterfly, Danaus chrisippus.[6]



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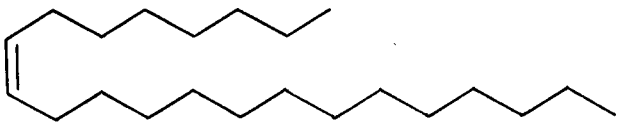
Pheromonal communication has also been found in Dipteran (flies) species, but not many pheromones of this species have been identified. One of the identified compounds is the sex attractant of the common housefly, Musca domestica, which has been characterized as (Z)-9-tricosene (4).[7] Jacobson et al.[8] identified two components of the sex pheromone of the Mediterranean



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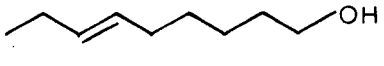
fruit fly, Ceratitis capitata, as (E)-6-nonen-1-ol (5) and methyl (E)-6-nonenoate (6).



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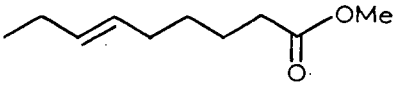
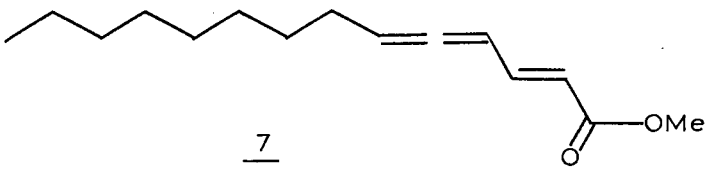


6

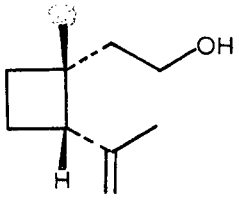
Coleoptera (beetles and weevils) is the largest order of insects and unlike Lepidoptera, the sex pheromones of beetles and weevils are structurally diverse and many of them are chiral compounds. (-)-Methyl (E)-2,4,5-tetradecatrienoate (7) was identified as the pheromone produced by males of the bean weevil,



7

Acanthoscelides obtectus, to attract the virgin female weevils.[9,10] This was also the first known allenic sex pheromone.

The four components (collectively called "grandlure") produced by male boll weevils to attract the female have been identified as (+)-2-(cis-isopropenyl-1-methylcyclobutyl)ethanol (8), (Z)-2-(3,3-dimethylcyclohexylidene)-ethanol (9), (Z)-2-(3,3-dimethylcyclohexylidene)acetaldehyde (10), and (E)-2-(3,3-dimethylcyclohexylidene)acetaldehyde (11).[11-14]



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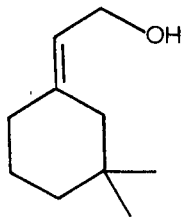

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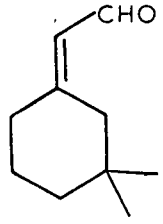

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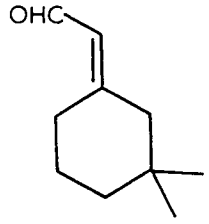
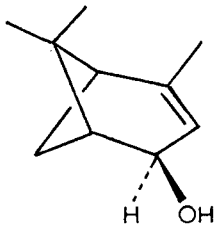


11

Some other interesting pheromones are excreted by bark beetles of the family Scolytidae. (+)-cis-Verbenol (12), (-)-2-methyl-6-methylene-7-octen-4-ol (13) (also named ipsenol), and (-)-2-methyl-6-methylene-2,7-octadien-4-ol (14) (or ipsdienol), are the principal components of the attractant pheromone produced by the bark beetle Ips paraconfusus.[15,16] All of



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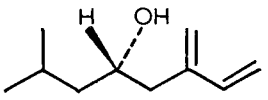

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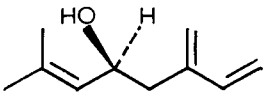


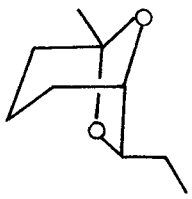
14

these compounds are optically active and none of the individual compounds is attractive to the beetle by itself. However, a mixture of the three compounds attracts the flying beetles in the field.[17-22]

A group of pheromones having an unusual 6,8-dioxabicyclo[3.2.1]octane skeleton have been isolated from bark beetles of the family Scolytidae. The first identified pheromone with this bicyclic ketal skeleton is the attractant pheromone produced by western pine beetles, Dendroctonus brevicomis. It consists of exo- and endo-7-ethyl-5-methyl-6,8-dioxabicyclo [3.2.1]octane (15) and (16), which have been given the trivial

names exo-brevicomin and endo-brevicomin, respectively.[23,24]

1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (17) (frontalin)[25]



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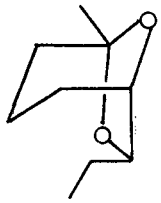

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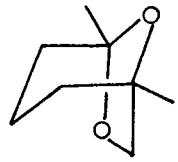
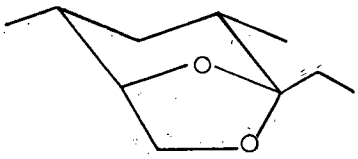


17

is another component of the aggregation pheromone isolated from the hindgut extracts of male western pine beetles and it has also been detected in the southern pine beetle Dendroctonus frontalis.[25] This unusual bicyclic ketal skelton is found in other sex pheromones as well. The aggregation pheromone for the European elm bark beetle, Scolytus multistriatus, has been characterized as a mixture of three components,[26] one of which is 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (18),



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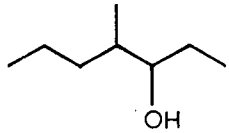

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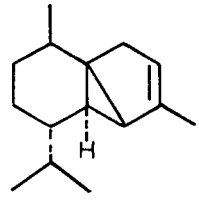
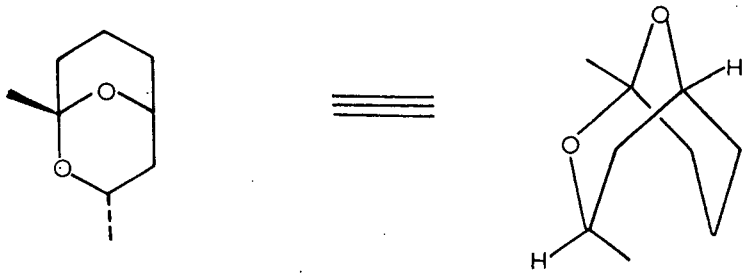


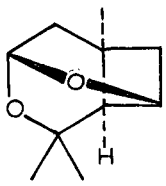
20

named α-multistriatin. The other two components are (-)-4-methyl-3-heptanol (19) and (-)-α-cubebene (20). Compounds 18 and 19 are produced by the beetles while compound 20 is produced by the host elm tree. endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (21),[27,28] a host-specific substance found in Norway spruce infested by Trypodendron lineatum OLIV is another example of the bicyclic ketal-type pheromones.



21

Very recently, a tricyclic ketal-type pheromone was isolated from the frass of Trypodendron lineatum female beetles. The structure of this pheromone was first proposed to be one of the two isomeric compounds 22 or 23 shown below.[29] It was



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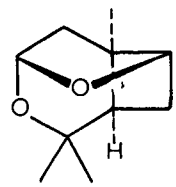


23

later confirmed to be 3,3,7-trimethyl-2,9-dioxatricyclo [3.3.1.$0^{4,7}$]nonane (22) and lineatin is the trivial name given to this pheromone.[30]

Since detailed coverage of a diverse topic such as "Insect Pheromones" is out of the scope of this dissertation, the above description is merely intended to provide a general background for our present work. As can be noted from this brief survey, the cyclic ketal-type pheromones comprise a unique group of compounds, which are structurally and functionally similar and are all excreted by beetles. The economic implication of these pheromones in connection with the timber industry and the synthetic challenge arising from their unusual structures stimulated our interest in tackling the synthesis of these compounds. In the following part of this thesis, brief reviews of the source, structure elucidation, and recorded syntheses of the individual cyclic ketal-type pheromones are presented before a detailed discussion of our syntheses of these compounds (except compound 21).

(ii) Source, Structure Elucidation and Synthesis of Cyclic Ketal-type Beetle Pheromones

(a) exo- and endo- Brevicomin

Source:

The western pine beetle, Dendroctonus brevicomis, is one of the most destructive bark beetle pests. The initial attackers are the female bark beetles. They bore into the ponderosa pine to construct a nuptial chamber, and expel frass - a mixture of wood fragments and fecal pellets. The frass contains the sex attractant which initiates the mass attack that usually kills the tree. Each year, about five billion board-feet of timber are destroyed by these bark beetles, and so far there are no effective methods to control this pest.

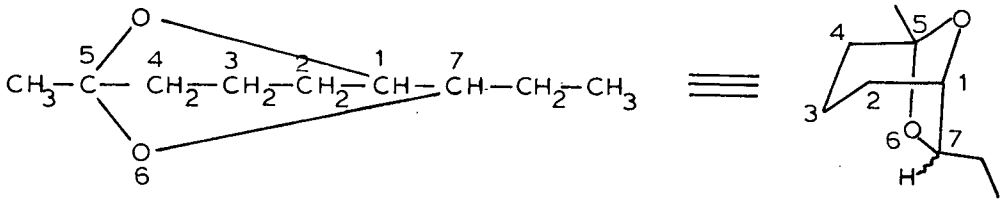
Structure Elucidation:

In 1968, Silverstein et al. isolated about 2 mg of the sex attractant produced by the virgin female D. brevicomis by extracting a total of 1.6 kg of frass.[23] High resolution mass spectrometry established the molecular formula of the pheromone as $C_9H_{16}O_2$. The infrared spectrum showed intense peaks between 1250-900 cm^{-1} (8-11.7 μ) indicating the presence of an ether group. Neither hydroxyl nor carbonyl peaks were observed. The NMR spectrum showed the methyl protons of an ethyl group (δ 0.87, 3H, slightly distorted triplet), a methyl

group on a deshielded quarternary carbon (δ 1.3, 3H, singlet), a multiplet from δ 1.1 to 1.9 (8H), and two single protons at δ 3.78 and 3.98 which must be on carbon atoms adjacent to oxygens.

No reaction was observed when the pheromone was treated with either diborane or lithium aluminum hydride. Since spectral evidence showed the absence of double or triple bonds in the molecule, a bicyclic ether structure was thus suggested.

Catalytic hydrogenation at 250° C gave n-nonane as the major product. This indicated that the ethyl and methyl groups must be at opposite ends of the unfolded molecule. Since NMR showed that the methyl group was attached to a quarternary carbon



15 or 16

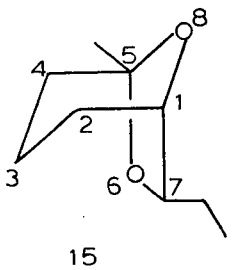
and was deshielded, a bicyclic ketal structure analogous to 15 or 16, was proposed. Assuming that the ethyl group was a side chain on a ring, one oxygen must be joined to C-7, and the other oxygen was attached to C-1 in order to account for the downfield triplet which was attributed to the proton on C-7 (the protons

on C-1 and C-7 have a dihedral angle of 90° in the exo isomer 15, and therefore the coupling constant is close to zero).

Since several bicyclic ketal structures were possible from these data, a synthetic route which would give both exo- and endo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (15 and 16) was designed (Scheme I).[23]

The triphenylphosphonium bromide 24 was treated with phenyllithium and the resulting ylid was allowed to react with propanol to give a mixture of cis and trans olefins 25. After epoxidation, the isomeric epoxides were separated by gas liquid chromatography (GLC). Upon hydrolysis, the cis epoxide 26a cyclized to give the exo compound 15 while the trans epoxide 26b gave the endo compound 16.

The spectral data of the synthetic exo compound 15 matched those of the active isolated compound described above, whereas the spectra of the synthetic endo isomer 16 matched those of an inactive compound isolated also from the frass. Thus, the structure of the active natural compound was assigned as exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (15) and was given the trivial name exo-brevicomin.



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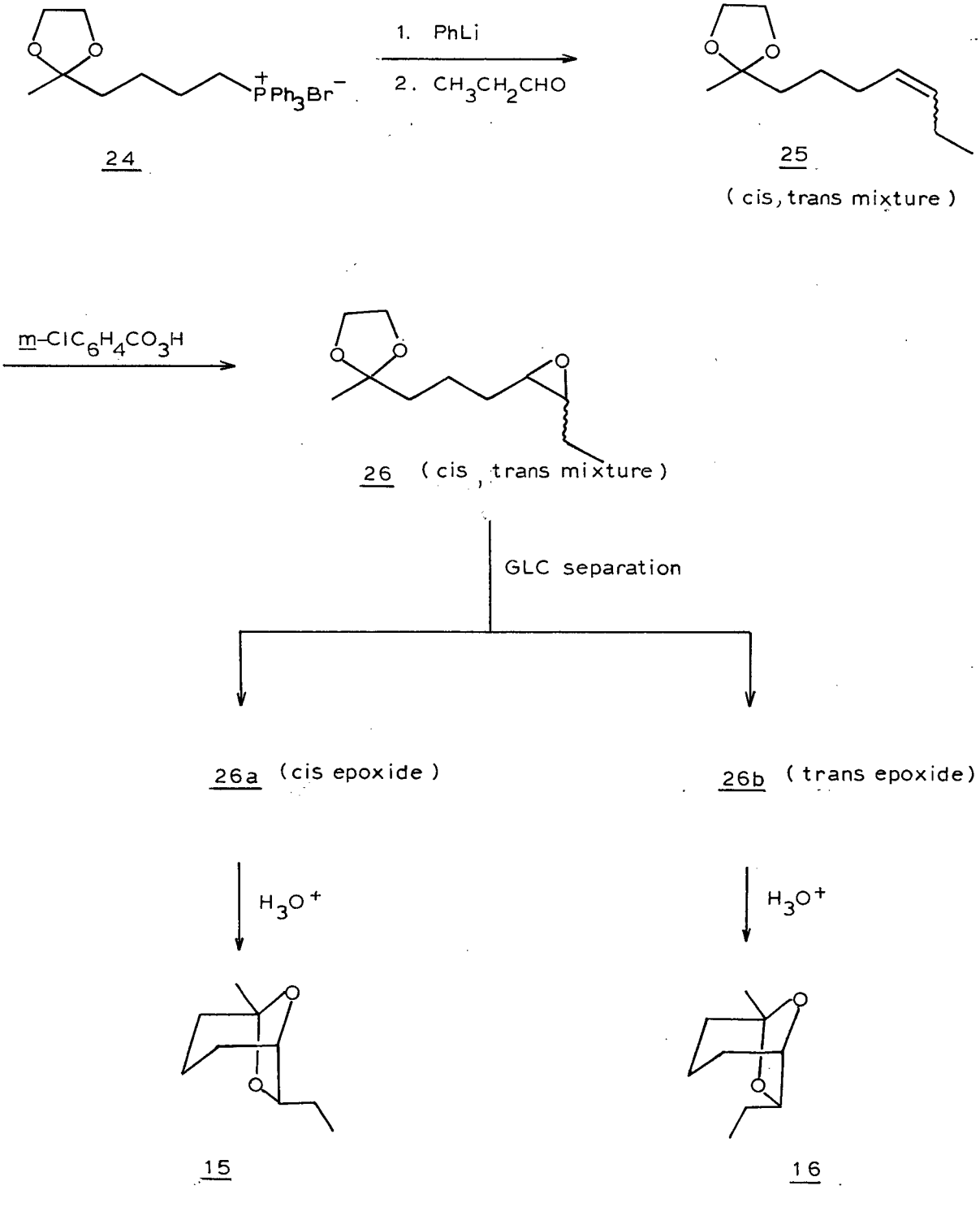
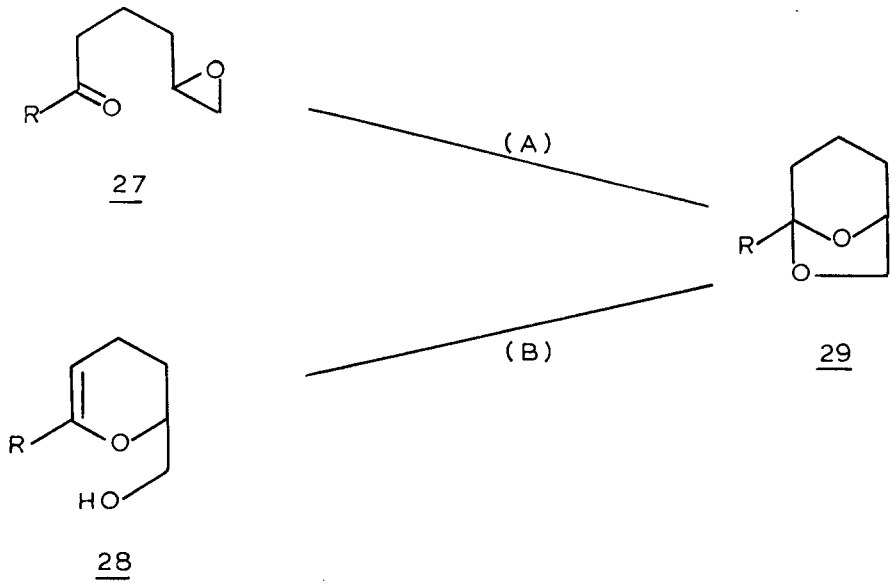
Scheme I. Synthesis of exo- and endo-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (15) and (16)[23]



Synthesis:

Shortly after the report on the structure of brevicomin by Silverstein and coworkers,[23] a number of syntheses of this compound were reported. In these syntheses, the two general methods leading to the formation of the 6,8-dioxabicyclo[3.2.1] octane skeleton were (A) the thermal or acid catalyzed cyclization of keto epoxide 27 to 29, and (B) the cyclization of the dihydropyran 28 to 29.

Figure 1. General Synthetic Pathways to 6,8-Dioxabicyclo[3.2.1]-octane Systems

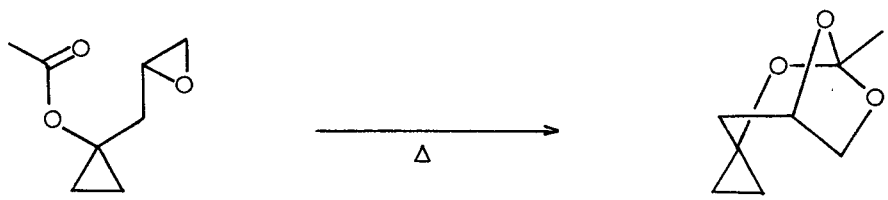


27 29 28

Silverstein and coworkers have developed several synthetic routes to brevicomin utilizing method (A). Besides the aforementioned synthesis which was designed to confirm the

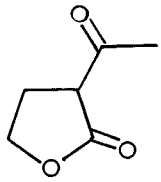
structure of brevicomin (Scheme I),[23] a stereoselective synthesis involving the same intermediate 25a (cis isomer) was also achieved by these workers (Scheme II).[31] The cis alkene 25a was prepared in a stereoselective manner from 2-acetylbutyrolactone (30). Hydrolysis of the lactone in 30 with concomitant decarboxylation and bromination of the resulting hydroxy acid was effected by treatment with 48% hydrobromic acid. The carbonyl group in the bromo ketone thus formed was protected as the ethylene ketal to give 31. Alkylation of sodio 1-butyne with bromide 31 afforded the acetylene 32, which was partially hydrogenated (H_2/Ni(OAc)$_2$-$NaBH_4$) to furnish the cis alkene 25a. exo-Brevicomin was finally obtained by epoxidation of 25a, followed by acid-catalyzed hydrolysis of the ketal group and cyclization of the resultant epoxy ketone.

During a study of the rearrangement of epoxy carbonyl compounds, Wasserman and Barber[32] noted the facile formation of bicyclic compounds, exemplified by the conversion of 33 into 34. This rearrangement was applied to the synthesis of exo-brevicomin.[32] The keto epoxide 35 was synthesized, which upon thermal rearrangement gave the desired product 15 and 16 in the



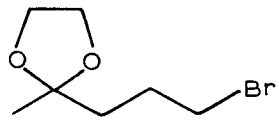
33 34

Scheme II. Stereoselective Synthesis of exo-Brevicomin (15)[31]



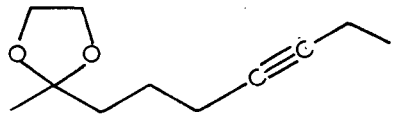
30

1. HBr, H_2O
2. $(HOCH_2)_2$, p-TsOH



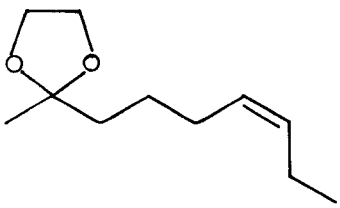
31

Na, $CH_3CH_2C{\equiv}CH$



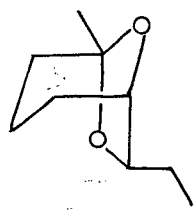
32

H_2 / $Ni(OAc)_2$ – $NaBH_4$



25a

1. m-$ClC_6H_4CO_3H$
2. $HClO_4$



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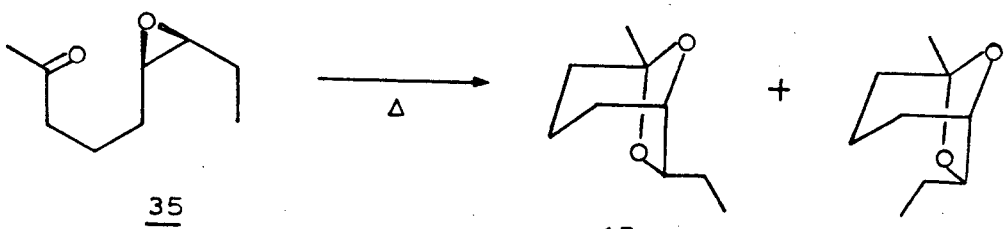


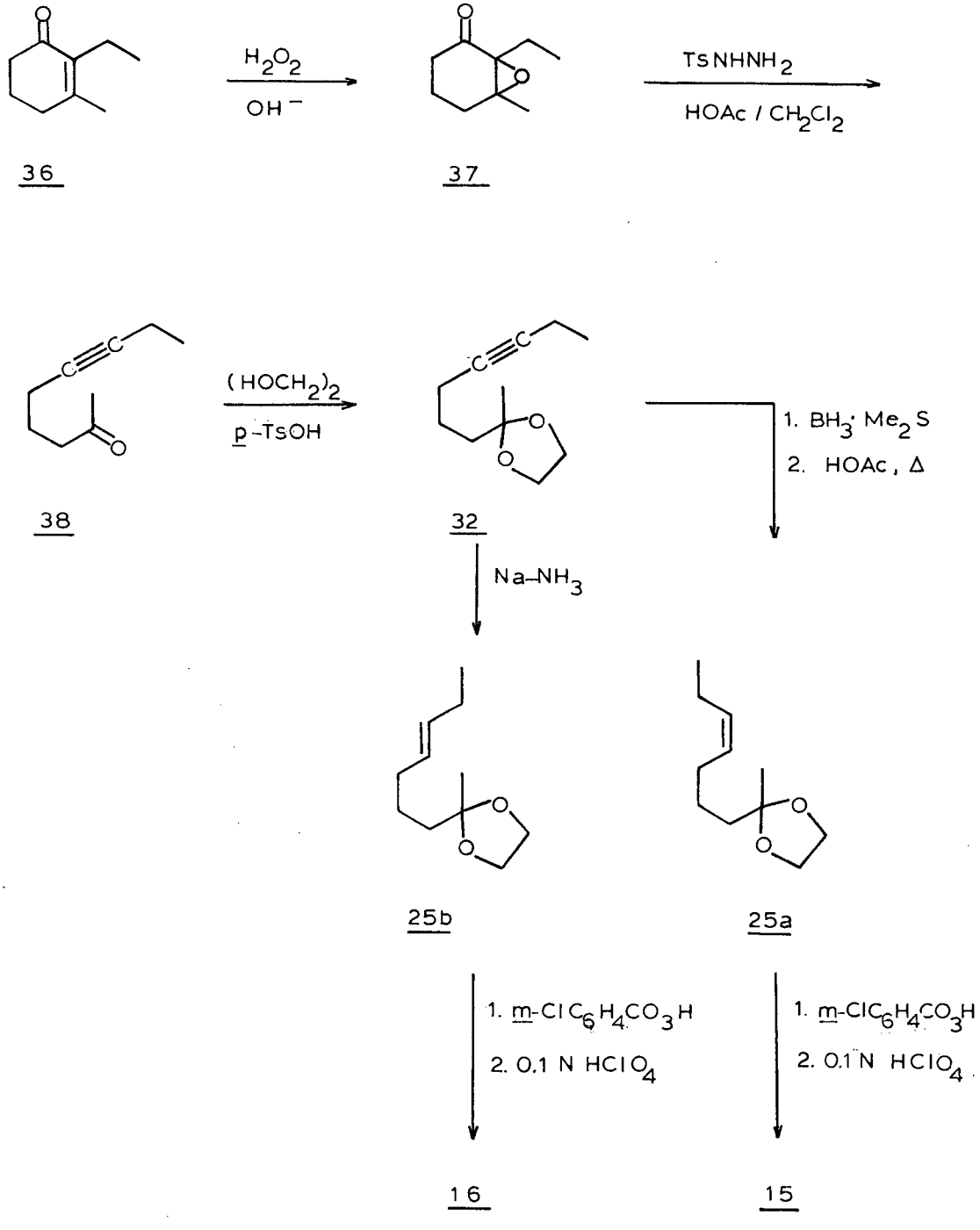
35 → 15 + 16 (9 : 1)

ratio of 9:1.

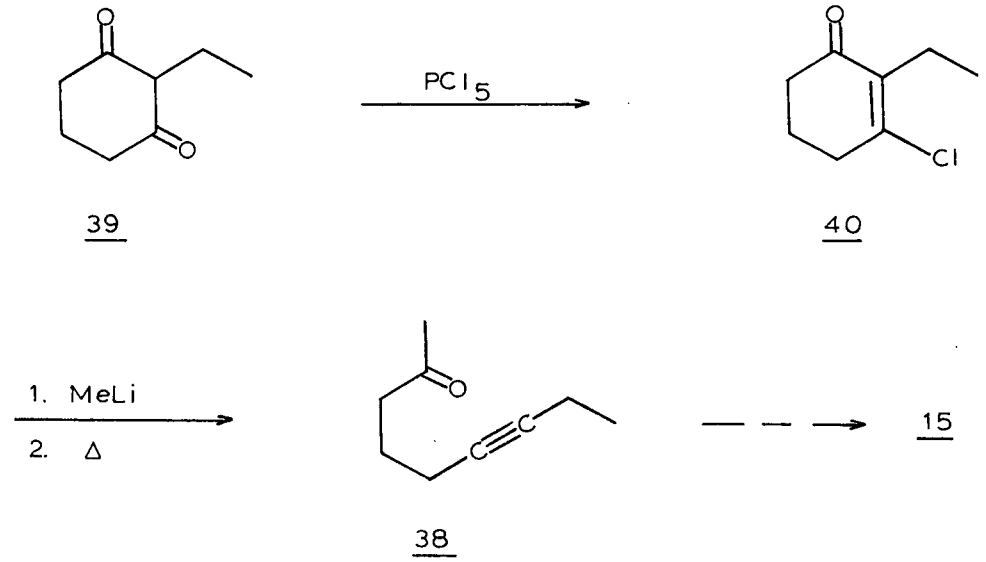
Kocienski and Ostrow[33] reported an interesting synthesis of brevicomin, through an unusual method of generating the acetylenic ketone 38, as shown in Scheme III. The acetylenic ketal 32 was prepared in three steps from the cyclohexenone 36. Eschenmoser fragmentation of the epoxy ketone 37 gave acetylenic ketone 38 which was protected as the corresponding ethylene ketal. Stereoselective reductions of the acetylenic ketal 32 with diborane or sodium in ammonia gave the cis or trans olefins, 25a or 25b, respectively. Epoxidation of 25a followed by acid catalyzed cyclization gave exo-brevicomin (15), while a similar treatment on 25b led to endo-brevicomin (16).

A new synthesis of the acetylenic ketone 38 was reported very recently by Cooke et al.[34] This sequence involved methyllithium addition to the carbonyl group of the β-chloro enone 40 and thermal cleavage of the intermediate alkoxide (Scheme IV). Application to the synthesis of exo-brevicomin (15) was also reported.

Scheme III. Synthesis of Brevicomin from a Cyclohexenone[33]



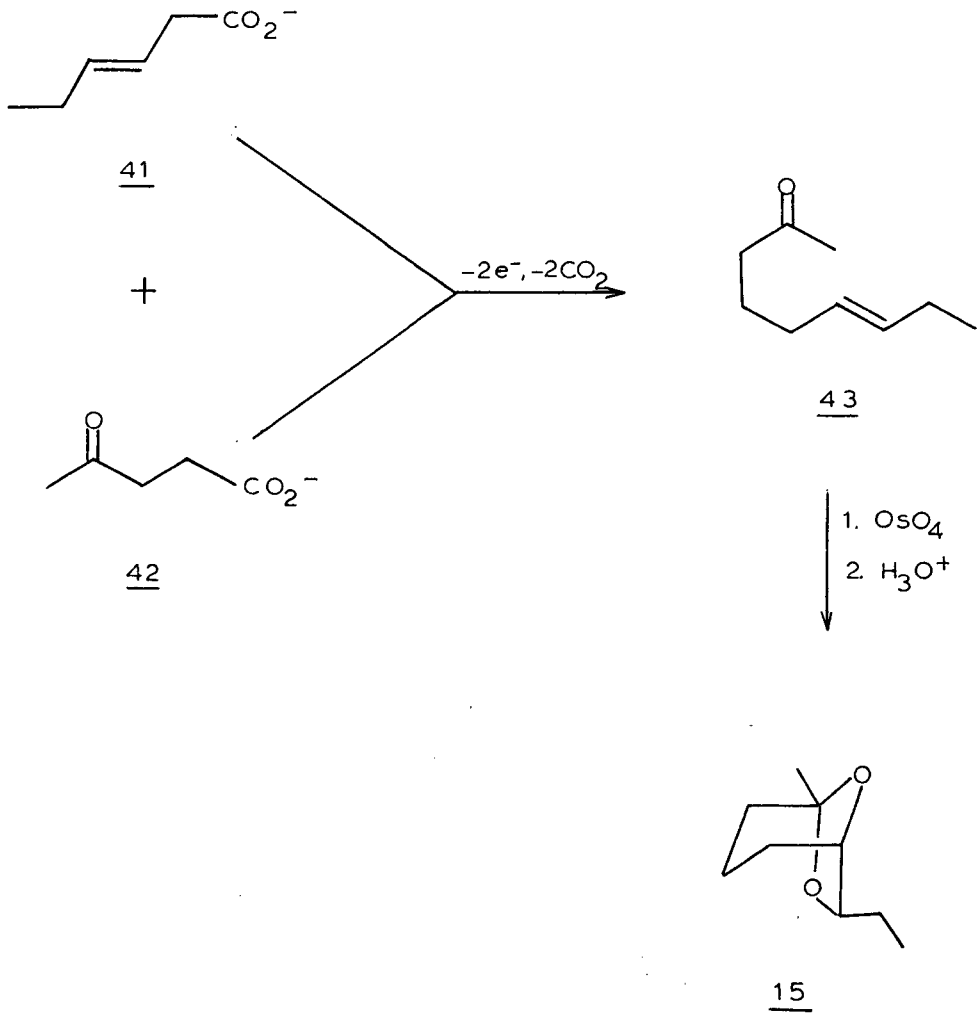
Scheme IV. Synthesis of Acetylenic Ketone 38.[34]



A totally different approach was adopted by Knolle and Schafer.[35] In their synthesis, the olefinic ketone 43 was prepared by a Kolbe electrolysis of trans-3-hexenoic acid (41) and levulinic acid (42). A mixture of dimers and trans-6-nonen-2-one (43) were thus obtained. Compound 43 was then converted into exo-brevicomin (15) by cis hydroxylation with osmium tetraoxide, followed by acid-promoted cyclization (Scheme V).

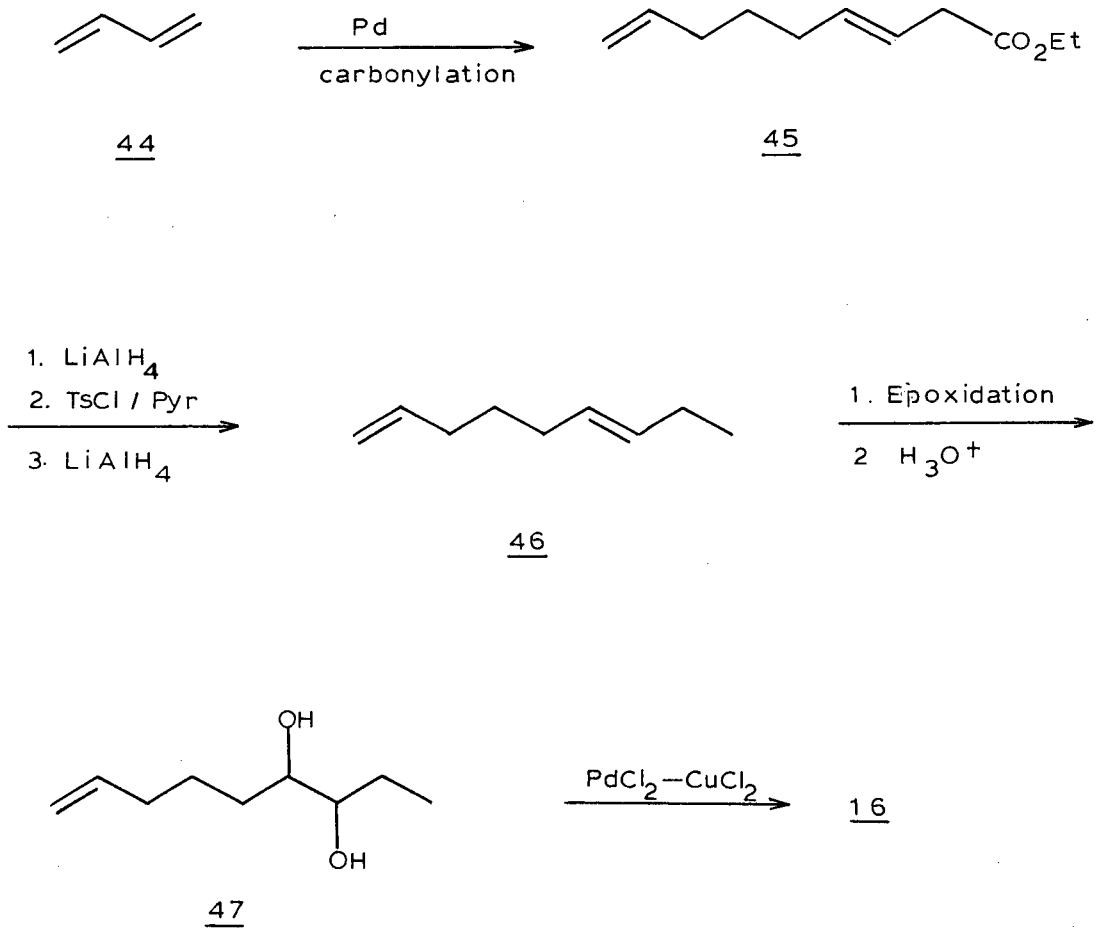
endo-Brevicomin (16) has also been prepared from 1,3-butadiene (44) by a novel approach which may be considered as a variation of method (A) in Figure 1 (Scheme VI).[36] Palladium catalyzed dimerization of 1,3-butadiene (44) with concomitant carbonylation in ethanol gave the nonadienoate 45 which was

Scheme V. Synthesis of exo-Brevicomin via Kolbe Electrolysis [35]



converted by a reduction-tosylation-reduction sequence into the trans-nonadiene 46. Selective epoxidation of 46 followed by hydration gave diol 47 which was cyclized directly to endo-brevicomin (16) using palladium (II) chloride as catalyst in

Scheme VI. Synthesis of endo-Brevicomin from 1,3-Butadiene (44) [36]

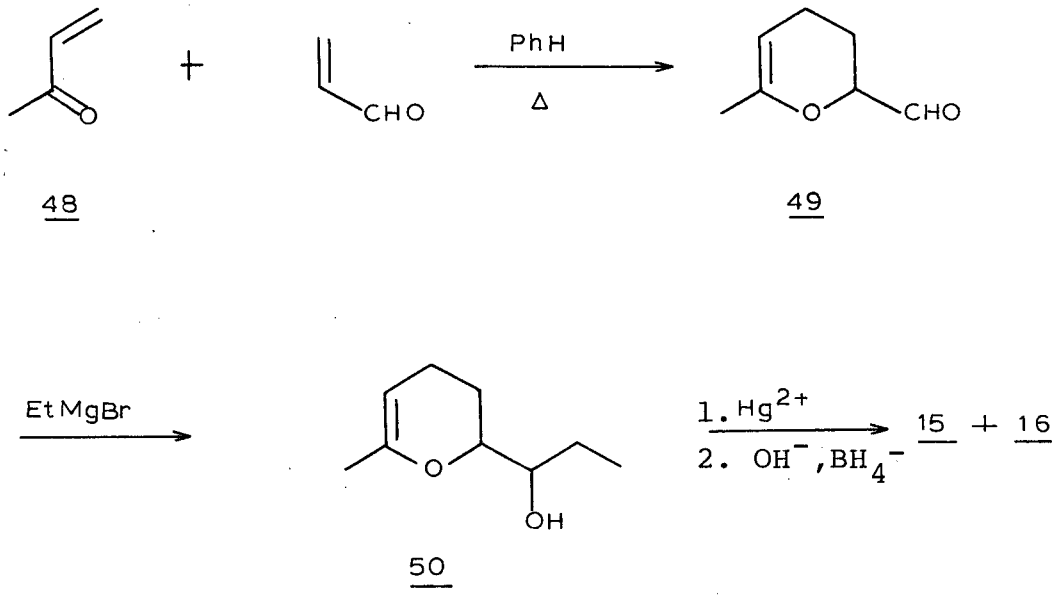


44 45 46 47 16

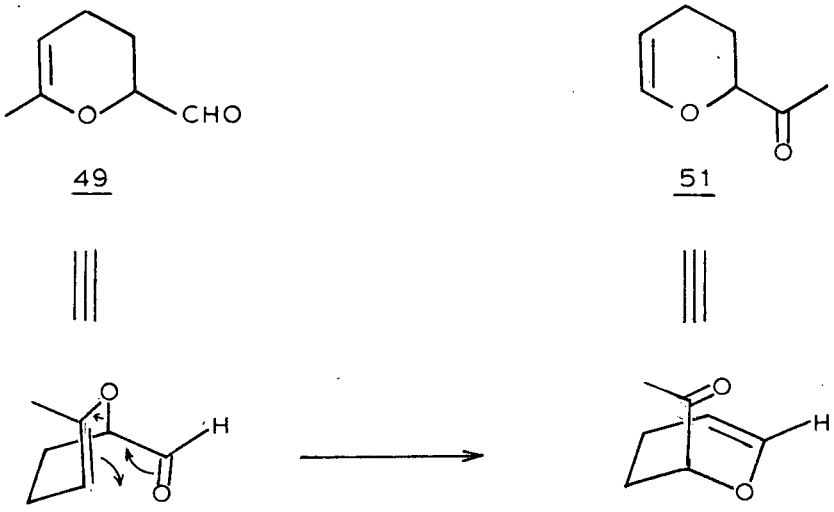
the presence of excess copper (II) chloride.

The use of method (B) (Figure 1) to synthesize brevicomin was first reported by Mundy and coworkers[37] (Scheme VII).

Scheme VII. Diels-Alder Route to exo- and endo-Brevicomin[37]



This synthesis started with the Diels-Alder addition of methyl vinyl ketone (48) to acrolein. The resulting dihydropyran 49 was converted into alcohol 50 with methylmagnesium bromide. Hg^{2+} catalyzed ring closure of 50 gave the desired products 15 and 16. Although the synthesis is short, unfortunately, only a 9% yield of the desired product was obtained.[38-40] This low yield was later rationalized as follows. The Diels-Alder reaction initially led to formation of the desired adduct 49, which could undergo Cope rearrangement to give the more stable and undesired product 51.[41]

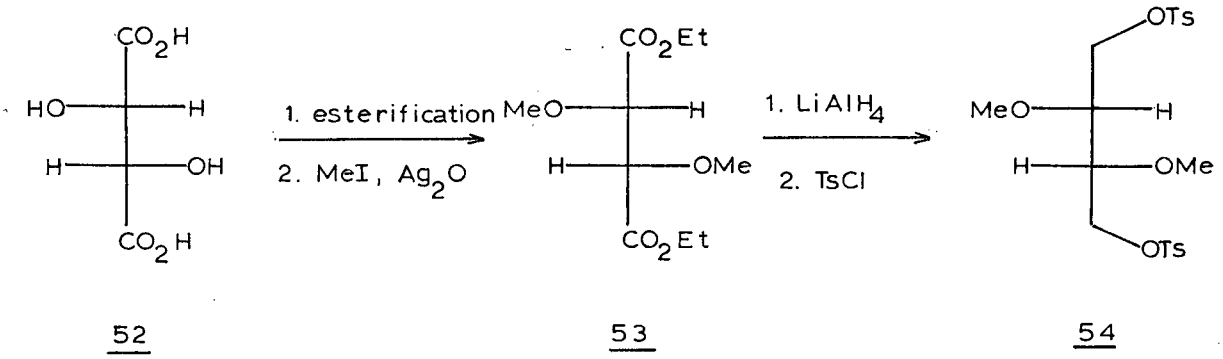


49 51

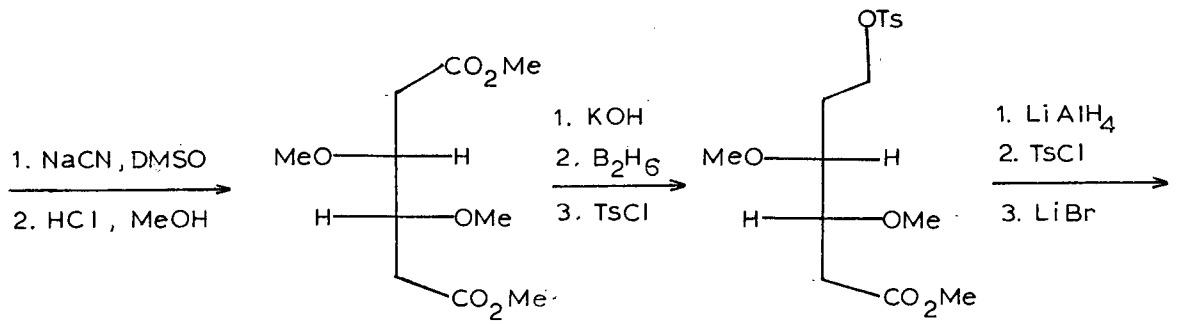
The exo-brevicomin (15) molecule possesses two chiral centres. The fact that a 0.05% hexane solution of the natural compound showed no optical rotation[23] suggested that the pheromone is either racemic or has too small a rotation to be measured in such a dilute solution. In order to establish the absolute configuration of both enantiomers of exo-brevicomin (15) and to clarify the relationship between pheromonal activity and chirality, the synthesis of optically active brevicomin was necessary.

The first synthesis of optically active exo-brevicomin (15) of known absolute configuration was accomplished by Mori in 1974[42] (Scheme VIII). The readily available D-(-)-tartaric acid (52) with known absolute configuration (2S, 3S) was

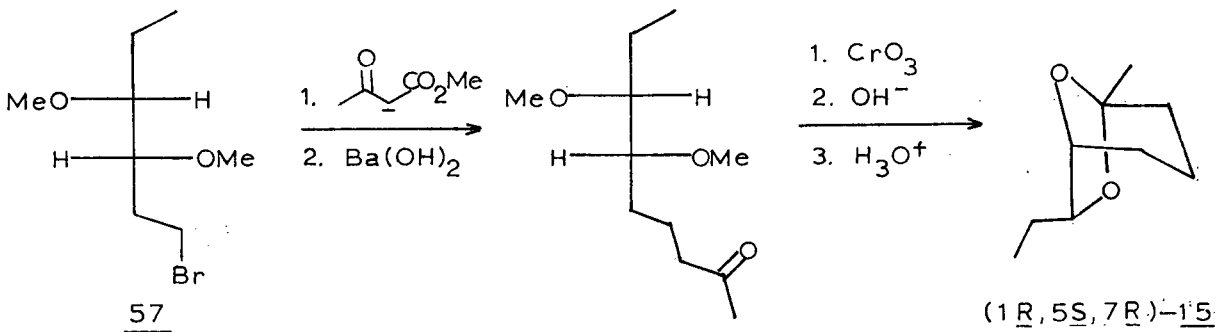
Scheme VIII. Mori's Synthesis of Optically Active exo-Brevicomin (15) from Tartaric Acid[42]



52 53 54



55 56

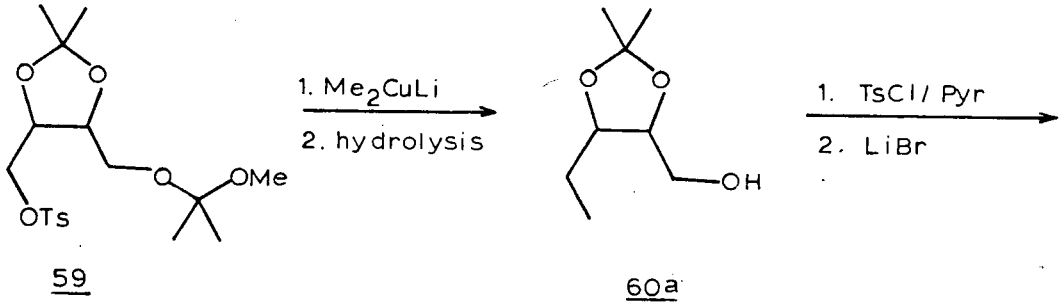


57 58 (1R,5S,7R)-15

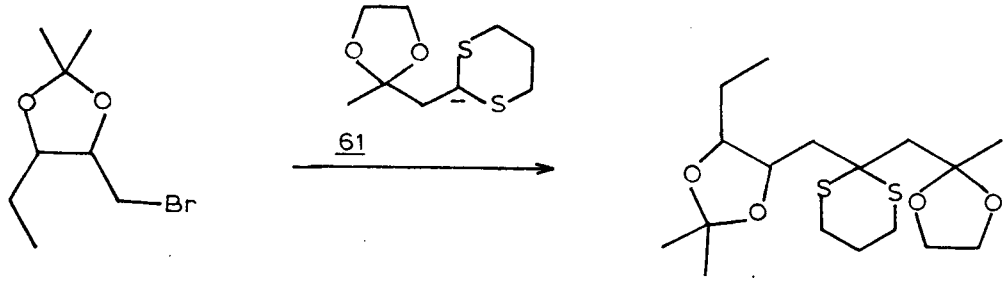
employed to synthesize (1R, 5S, 7R)-exo-brevicomin (15) while its antipode (1S, 5R, 7S)-15 was prepared from (2R, 3R)-L-(+)-tartaric acid. The (3R, 4R)-1-bromo-3,4-dimethoxyhexane (57) prepared in ten steps from diethyl (2S, 3S)-tartrate was used to alkylate the monoanion of ethyl acetoacetate. The resulting product was then hydrolyzed to the (+)-dimethoxy ketone 58. Removal of the methoxy protecting groups was achieved in low yield by chromium trioxide oxidation of the methyl ether to give the corresponding formate ester. Base hydrolysis, followed by acid-catalyzed cyclization gave (1R, 5S, 7R)-15, $[\alpha]_D^{24}$ + 84.1° (ethyl ether). A similar reaction sequence was employed to prepare (1S, 5R, 7S)-15, $[\alpha]_D^{24}$ - 80.0° (ethyl ether), starting from (2S, 3R)-tartaric acid. The entomological study of the synthetic compounds showed that only (1R, 5S, 7R)-15 was biologically active.[43]

Meyer[44] reported another synthesis of exo-brevicomin (15) in its optically active form as shown in Scheme IX. The same starting material, diethyl (+)-(2R, 3R)-tartrate, was used to prepare compound 59 which was allowed to react with lithium dimethylcuprate to give, after hydrolysis, alcohol 60a. The bromide 60b derived from 60a was alkylated with the anion of dithiane 61 to give 62. The thioketal group was cleaved reductively using Raney-Nickel. Subsequent acid-catalyzed cyclization led to the formation of the desired product (1S, 5R, 7S)-15, $[\alpha]_D^{24}$ - 67.5° (ethyl ether).

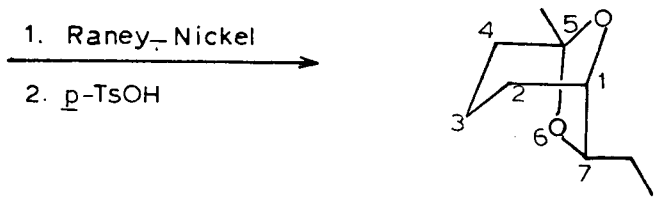
Scheme IX. Meyer's Synthesis of Optically Active exo-Brevicomin from Diethyl (+)-(2R, 3R) Tartrate [44]



59 60a



60b 62



(1S, 5R, 7S)-15

(b) Frontalin

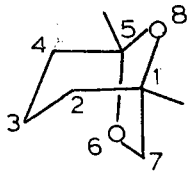
Source:

Frontalin (17) was first detected in the hindguts of females of the southern pine beetle, Dendroctonus frontalis Zimmerman, and was later found in larger amount, in the hindguts of emergent male D. brevicomis,[25] thus providing a better source for isolation and identification.

Structure Elucidation:

About 0.3 mg of the active compound was isolated from approximately 6500 hindguts of male D. brevicomis. The molecular formula as determined by high resolution mass spectrum was $C_8H_{14}O_3$. The infrared spectrum showed no hydroxyl or carbonyl absorptions, while a strong absorption between 1115 and 1025 cm^{-1} indicated the presence of the C-O-C linkage. Two absorption bands of unequal intensities at 1380 and 1390 cm^{-1} were attributable to two different methyl groups. Two sets of three-proton singlets at δ 1.32 and 1.42 in the NMR spectrum were consistent with two methyl groups attached to quaternary carbon atoms. A multiplet at δ 1.63 (6H), and two individual protons at δ 3.93 and 3.42 which must be on carbon atoms adjacent to the oxygens were also observed.

From the above spectral data, the structure of the active compound was concluded to be 1,5-dimethyl-6,8-dioxa-bicyclo[3.2.1]octane (17).[25]

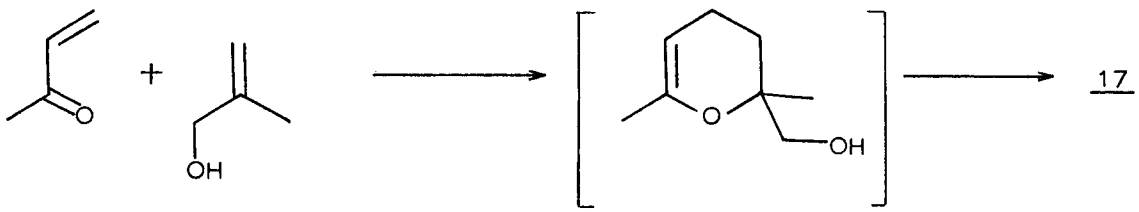


17

Synthesis:

The common strategies adopted in the synthesis of frontalin (17) were similar to those employed in the synthesis of brevicomin (15). Frontalin (17) was first prepared in a one-step synthesis which involved the Diels-Alder reaction of 48 and 63, and the in situ cyclization of 64 as shown in Scheme X.[25,45]

Scheme X. A One-step Synthesis of Frontalin (17) via Diels-Alder Reaction[25,45]

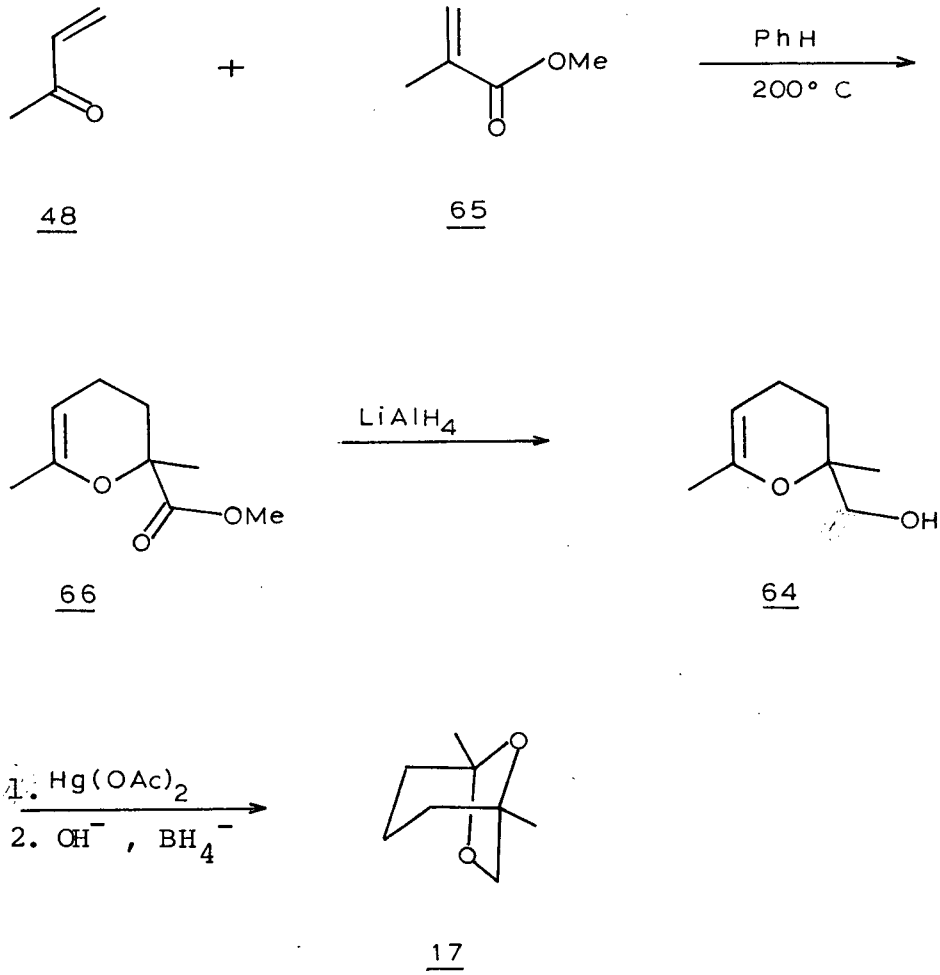


48 63 64

Mundy et al.[37] reported a rather similar synthesis of frontalin (17) from methyl vinyl ketone (48) and methyl methacrylate (65) as illustrated in Scheme XI. Lithium aluminum hydride reduction of the Diels-Alder adduct 66 gave alcohol 64

which was cyclized in the presence of mercuric acetate to 17.

Scheme XI. Mundy's Synthesis of Frontalin (17) via Diels-Alder Reaction [37]



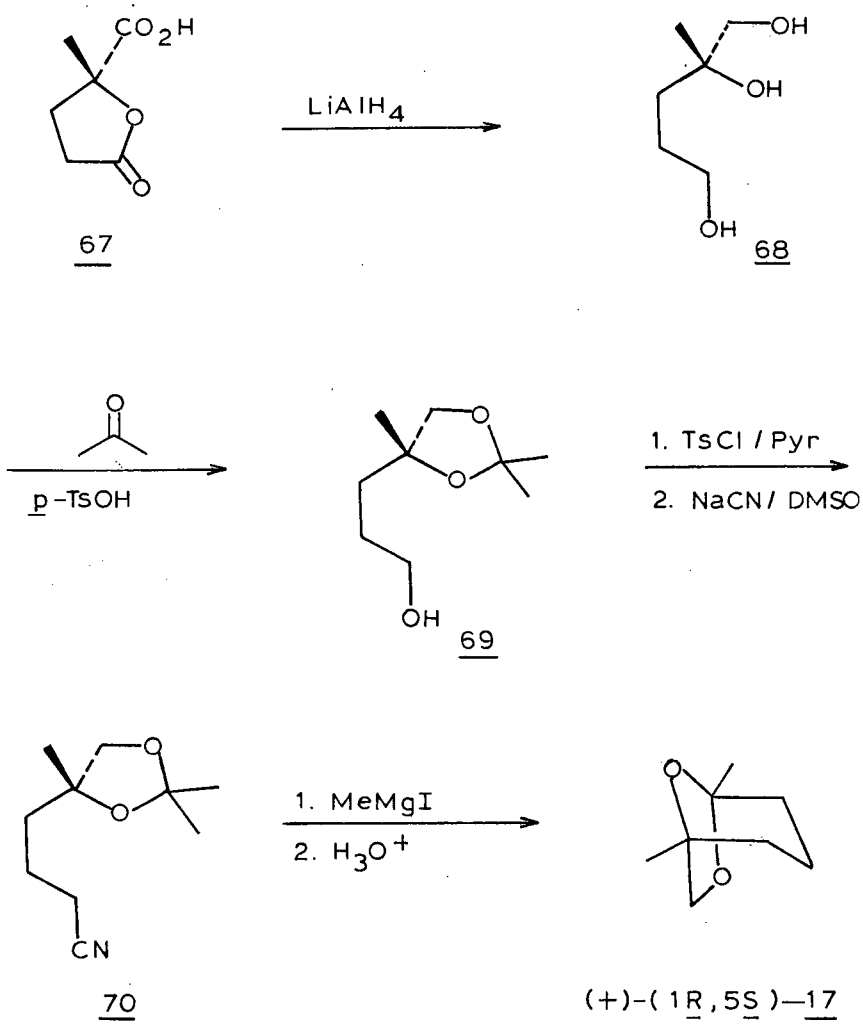
48 65 66 64 17

Due to the scarcity of the pure natural pheromone, it has been impossible so far to establish if naturally occurring frontalin (17) is optically active. However, several

syntheses of optically active frontalin (17) have been reported.

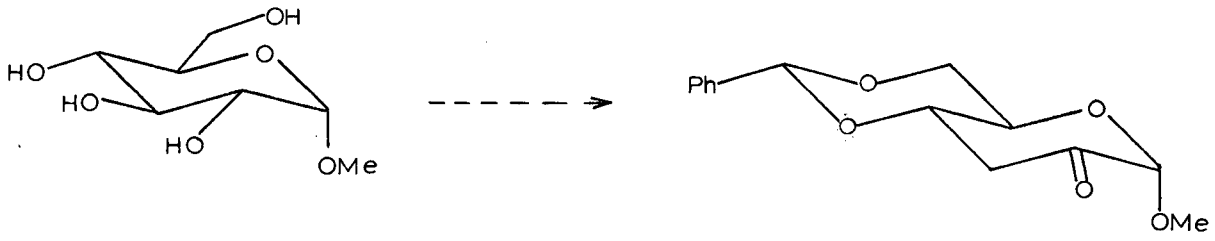
In the synthesis reported by Mori[46] (Scheme XII), the starting material 67 was first resolved and then reduced to the triol 68. The acetonide 69 derived from 68 was tosylated and treated with sodium cyanide to afford compound 70. Subsequent

Scheme XII. Mori's Synthesis of Optically Active Frontalin (17)[46]



reaction of 70 with methylmagnesium iodide, followed by acidification gave (1R, 5S)-frontalin (17), $[\alpha]_D^{23}$ + 53.4 (ethyl ether). An analogous scheme was followed to prepare (1S, 5R)-17, $[\alpha]_D^{23}$ - 52.0 (ethyl ether) from (S)-67.

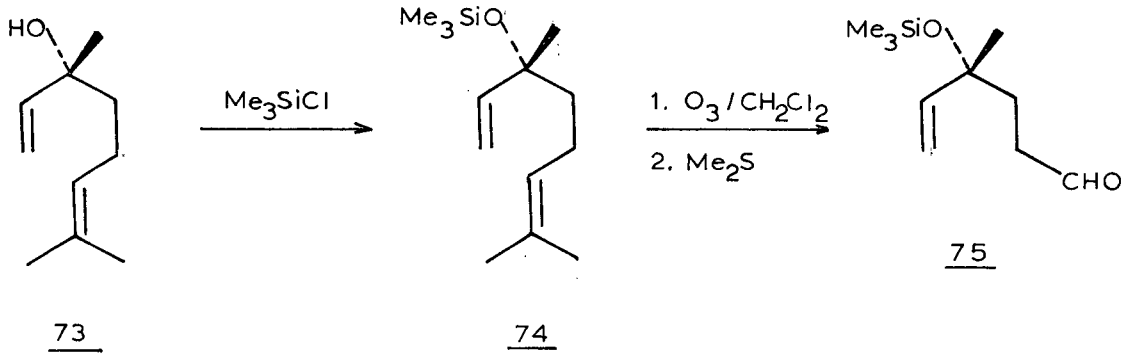
Another synthesis of both enantiomers of frontalin (17) made use of the ketone 72 which was synthesized from methyl α-D-glucopyranoside (71) in four steps.[47] The synthesis was then completed in seven steps from the keto compound 72. This synthesis is rather lengthy and inefficient compared to Mori's.



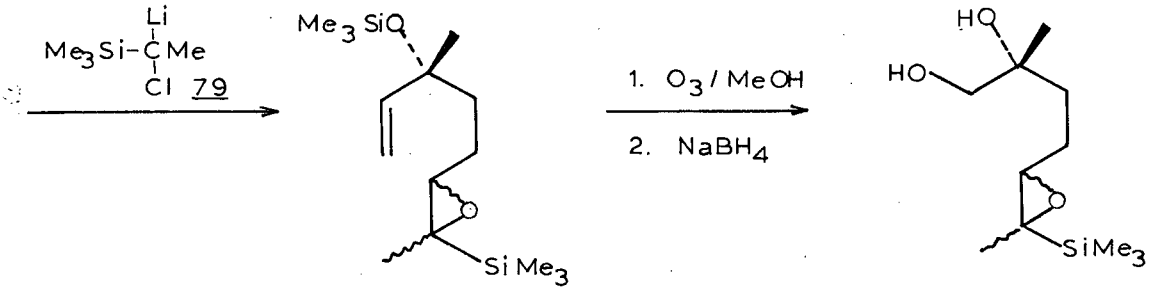
71 72

Very recently, Magnus and Roy[48] reported a synthesis of (+)-(1R, 5S)-frontalin using an α,β-epoxysilane as the key-intermediate (Scheme XIII). In this synthesis, (-)-(3R)-linalool (73), a chiral monoterpene having the crucial asymmetric centre at C-3, was chosen as the starting material. As shown in Scheme XIII, the trimethylsilyl ether 74 prepared from 73

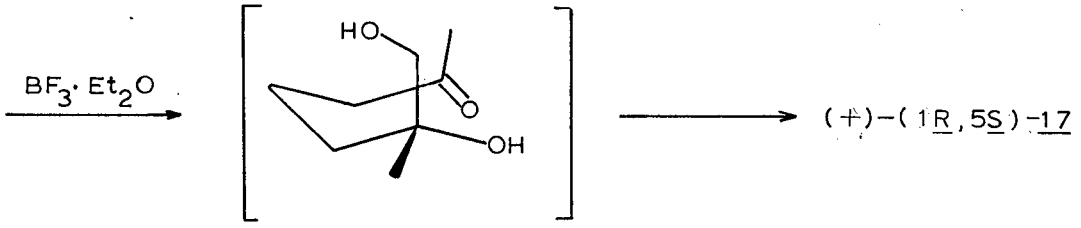
Scheme XIII. Chiral Synthesis of Frontalin via Trimethylsilyl Epoxide[48]



73 74 75



76 77



78

was selectively ozonized to give the aldehyde 75 which was allowed to react with reagent 79 to give the α,β-epoxysilane 76. Crude 76 was ozonized and then reduced with sodium borohydride to give the diol 77. Treatment of the crude diol 77 with boron trifluoride etherate afforded (+)-(1R, 5S)-frontalin (17) in an overall yield of 23-29% from (-)-(3R)-linalool (73).

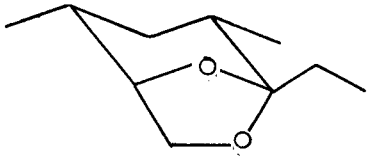
(c) Multistriatin

Source:

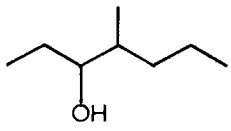
The bicyclic ketal, α-multistriatin (18α), is one of the three components of the aggregation pheromone for the European elm bark beetle, Scolytus multistriatus, which is the prinpal vector of Dutch elm disease in North America.[26]

Structure elucidation:

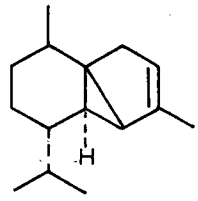
The isolation technique used here was different from that employed in the isolation of other pheromones from Scolytids. The beetle and host-produced volatiles were extracted from the air surrounding virgin female beetles boring in elm logs. Purification of the active fractions confirmed the attractant was a combination of three components, α-2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (18α), 4-methyl-3-heptanol (19), and α-cubebene (20). Compounds 18α and 19 were beetle-produced components, while 20 was a host-produced component. Besides these



18α



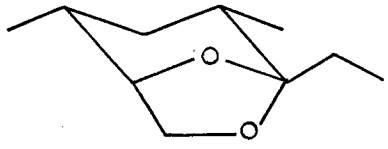
19



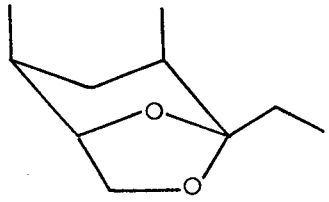
20

active compounds, the β-isomer of compound 18 was also isolated but found to be biologically inactive.[26]

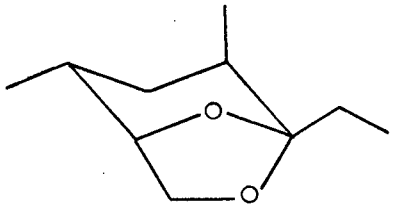
The bicyclic ketal structure of compound 18 was determined on the basis of the spectral data, its hydrogenolysis products, and previous experience with analogous compounds isolated from the Scolytid beetles.[23-26] In addition to the two naturally occurring forms of multistriatin, two other isomers 18γ, and 18δ, are also possible. The α-multistriatin isolated from natural source has been shown to be optically active, $[\alpha]_D^{25}$ - 47° (hexane),[26a] and from now on, this material is referred to as (-)-α-multistriatin or (-)-18α. The absolute configuration of (-)-18α has been established as (1S, 2R, 4S, 5R) by a chiral synthesis,[50] in which the enantiomeric composition of a mixture of (-)- and (+)-18α was determined by ^{13}CNMR analysis, using a chiral shift reagent (see discussion under Synthesis).



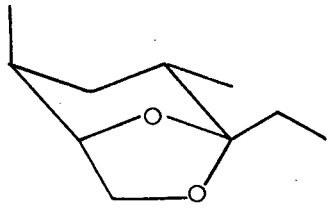
18α



18β



18γ

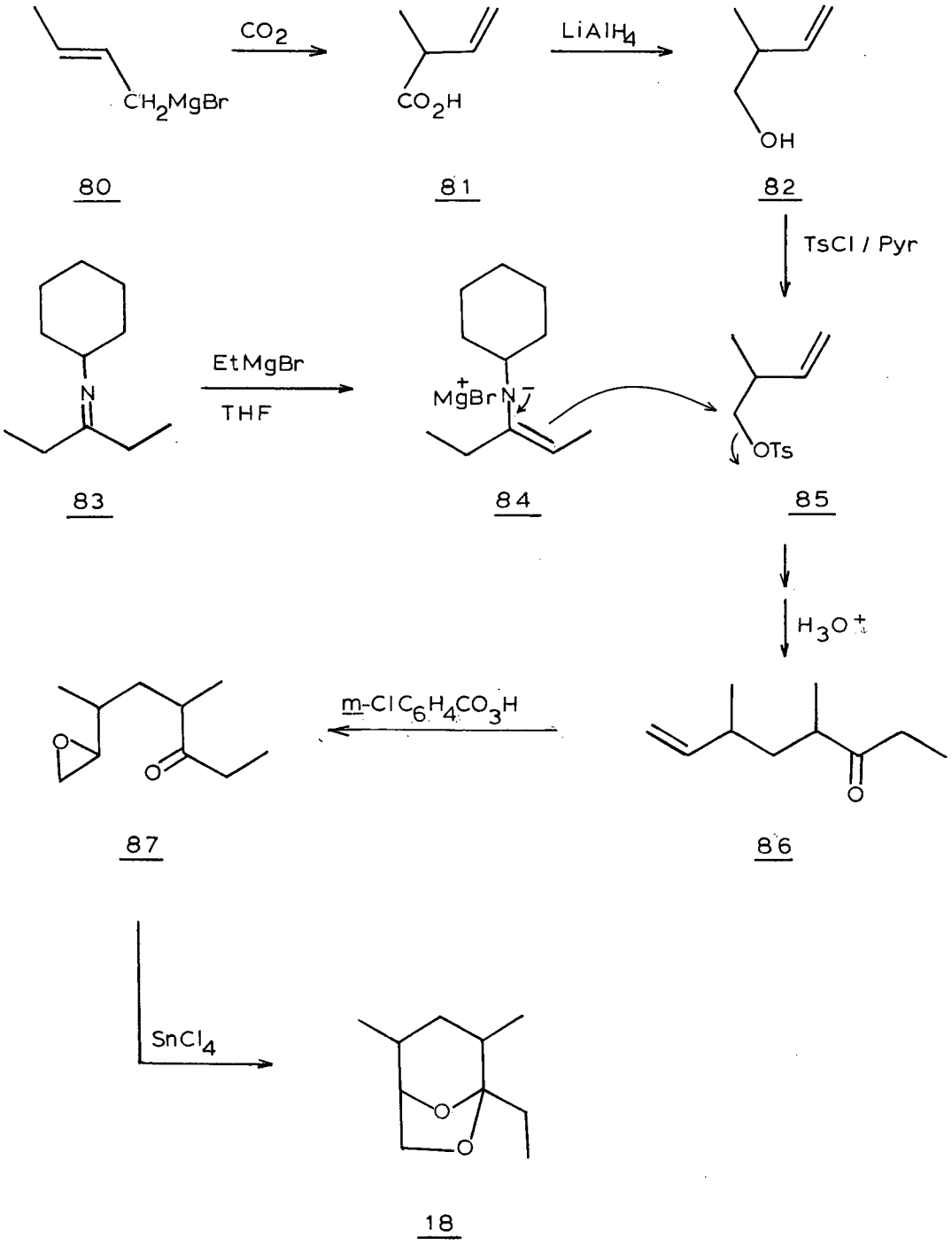


18δ

Synthesis:

The reported approaches to the 6,8-dioxabicyclo[3.2.1]-octane skeleton in multistriatin were similar to those used in the synthesis of frontalin and brevicomin (see above). Pearce and coworkers[26,49] reported a non-stereoselective synthesis of

Scheme XIV. A Non-stereoselective Synthesis of Multistriatin[26,49]



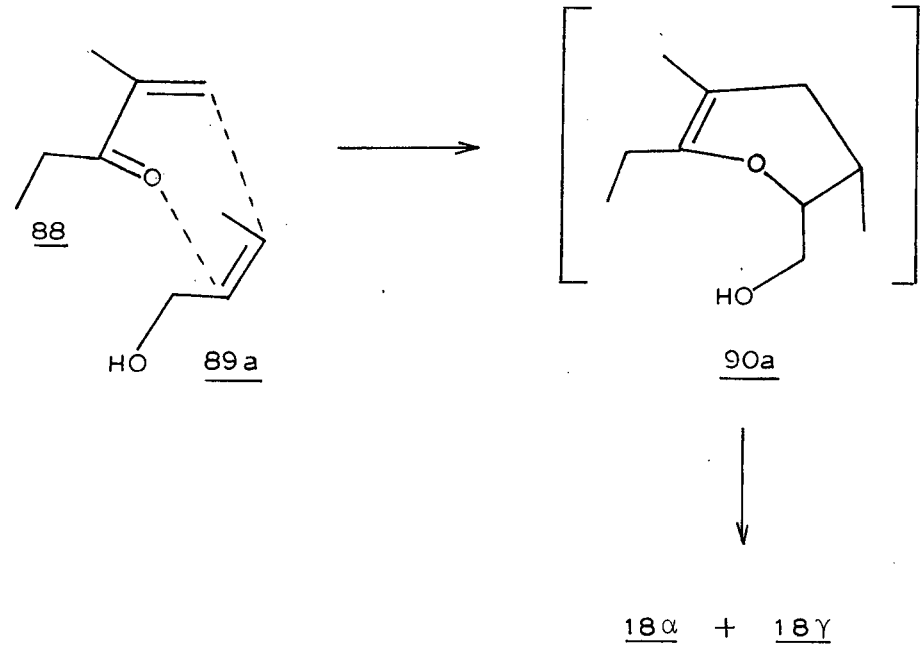
α:β:γ:δ (34:1:7:58)

multistriatin (18) which gave all four isomers (Scheme XIV). The keto olefin 86 was the key-intermediate in this synthesis. The tosylate 85 was prepared in three steps from butenylmagnesium bromide 80. Alkylation of the magnesium bromide derivative 84 of the ketimine 83 with tosylate 85 gave, after acid hydrolysis, compound 86. Epoxidation of alkene 86, followed by Lewis acid-catalyzed cyclization yielded all four bicyclic isomers. Only the α isomer is biologically active.

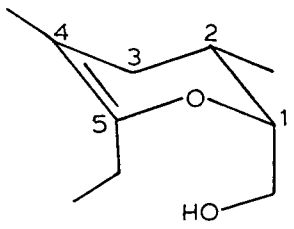
The relative stereochemistry of all four isomers of multistriatin were assigned on the basis of their chemical and spectral data. The following stereospecific synthetic approach (Scheme XV) provided direct chemical evidence for the stereochemistry at C-2 relative to C-1 and C-5.[49] Diels-Alder addition of cis-2-buten-1-ol (89a) to 2-methyl-1-penten-3-one (88) gave 18α and 18γ with the virtual exclusion of the β and δ isomers. However, when 89a was replaced by trans-2-buten-1-ol (89b), 18δ was formed predominantly. Thus the C-2 methyl groups in the α and γ isomers must be in the endo configuration while in the β and δ isomers, they are in the exo configuration.

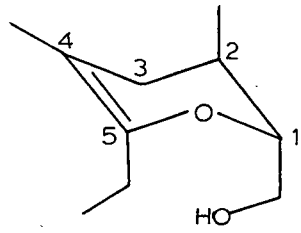
Acid-catalyzed hydrolysis of the multistriatin isomers resulted in interconversion of the isomers with the same configuration at C-2, i.e., $\alpha \rightleftharpoons \gamma, \beta \rightleftharpoons \delta$. Epimerization occurs at

Scheme XV. Stereospecific Synthesis of Multistriatin [49]



C-4 via the dihydropyran intermediates shown below. When the equilibration was effected with trideuteriophosphoric acid,





$\alpha \rightleftharpoons \gamma$ $\beta \rightleftharpoons \delta$

D-H exchange occurred at C-4 and on the methylene group of the ethyl side chain verifying the presence of the above intermediates.

The NMR spectra reported for the four isomers are summarized in Table 1.[49] As shown in Figure 2, the isomer pair 18α and 18γ clearly differs from the 18β and 18δ pair in the patterns observed for the C-7 methylene protons, H_D and H_E. In the 18α and 18γ isomers, these two protons appear as two separate signals at approximately δ 3.7 (H_D) and 3.9 (H_E), respectively, whereas in 18β and 18δ both signals are observed at δ 3.8-3.9.

Figure 2. NMR Spectra of Multistriatin Isomers[49]

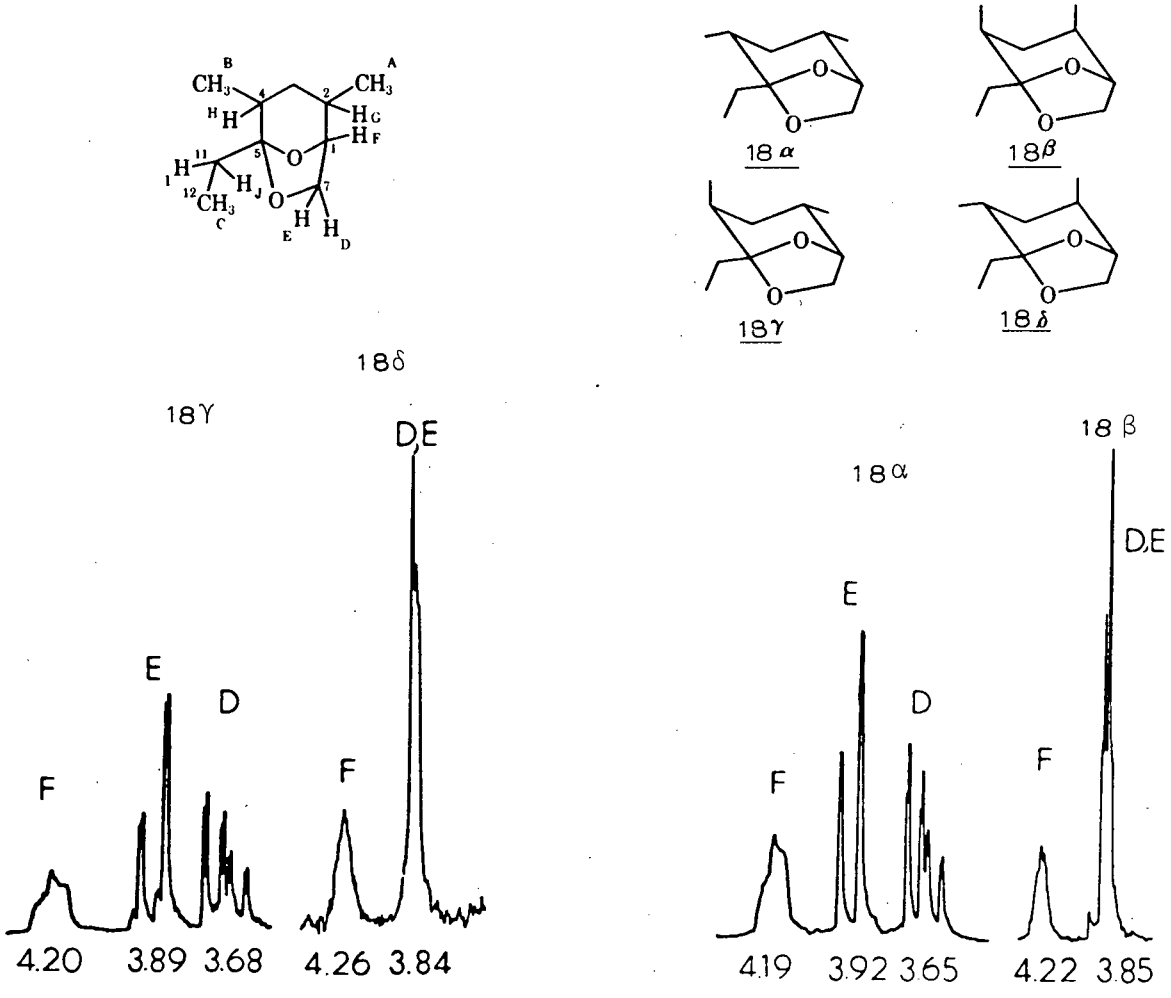


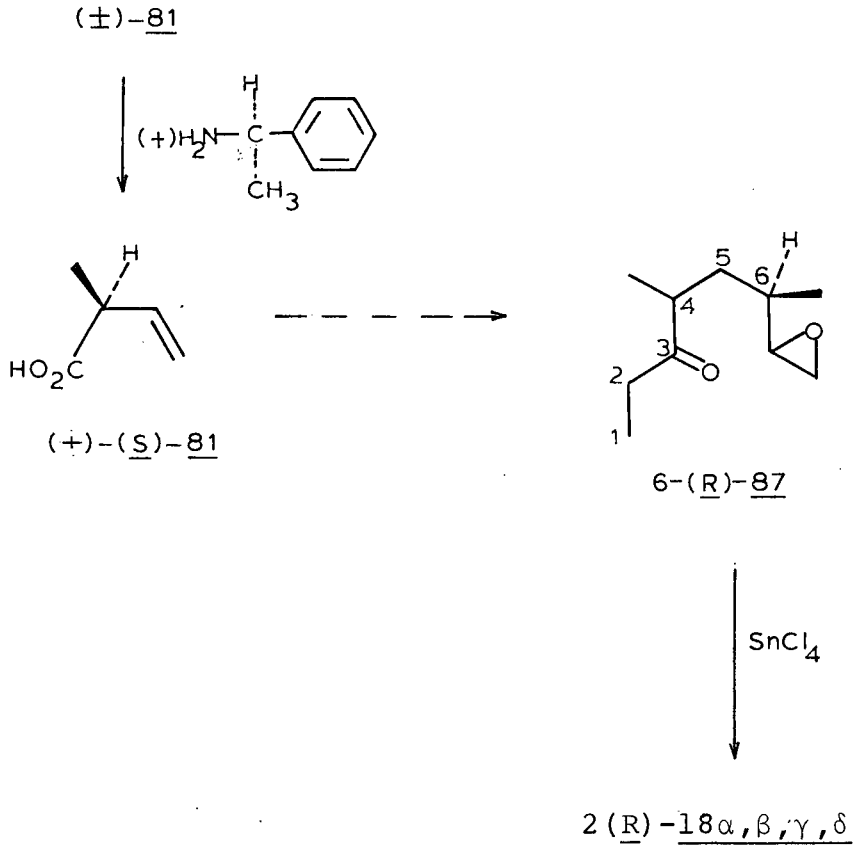
Table 1. NMR Chemical Shifts (δ) for Multistriatin Isomers[49]

Isomer	Multistriatin protons, chemical shifts[a]					
	A	B	C	D	E	F
18α	0.81 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.68 (1 H, ddd)	3.89 (1 H, dd)	4.20 (1 H, m)
18β	1.24 (3 H, d)	1.10 (3 H, d)	0.93 (3 H, t)	3.85 (2 H, m)		4.26 (1 H, m)
18γ	0.80 (3 H, d)	1.01 (3 H, d)	0.92 (3 H, t)	3.65 (1 H, ddd)	3.94 (1 H, d)	4.19 (1 H, m)
18δ	1.15 (3 H, d)	0.81 (3 H, d)	0.94 (3 H, t)	3.85 (2 H, m)		4.22 (1 H, m)

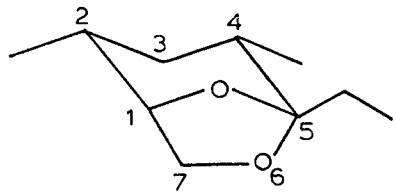
[a] d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, m = multiplet.

Pearce et al.[50] devised a synthesis to establish the absolute configuration of the multistriatin isomers. Racemic 2-methyl-3-butenoic acid (81) used in the previous synthesis (Scheme XIV) was partially resolved with (+)- and (-)-α-methylbenzylamine to give (+)-(S)- and (-)-(R)-81 (70 and 60% optical purities, respectively). Each of these optically enriched acids was used in the synthesis outlined in Scheme XVI. The synthe-

Scheme XVI. Chiral Synthesis of α-Multistriatin (18α)[50]



tic sequence employed was the same as that shown in Scheme XIV for the synthesis of racemic 18. The (+)-(S)-2-methyl-3-butenoic acid (81) gave rise to (-)-(2R)-18α, inferring the absolute configuration (1S, 2R, 4S, 5R) for natural (-)-18α.[50]

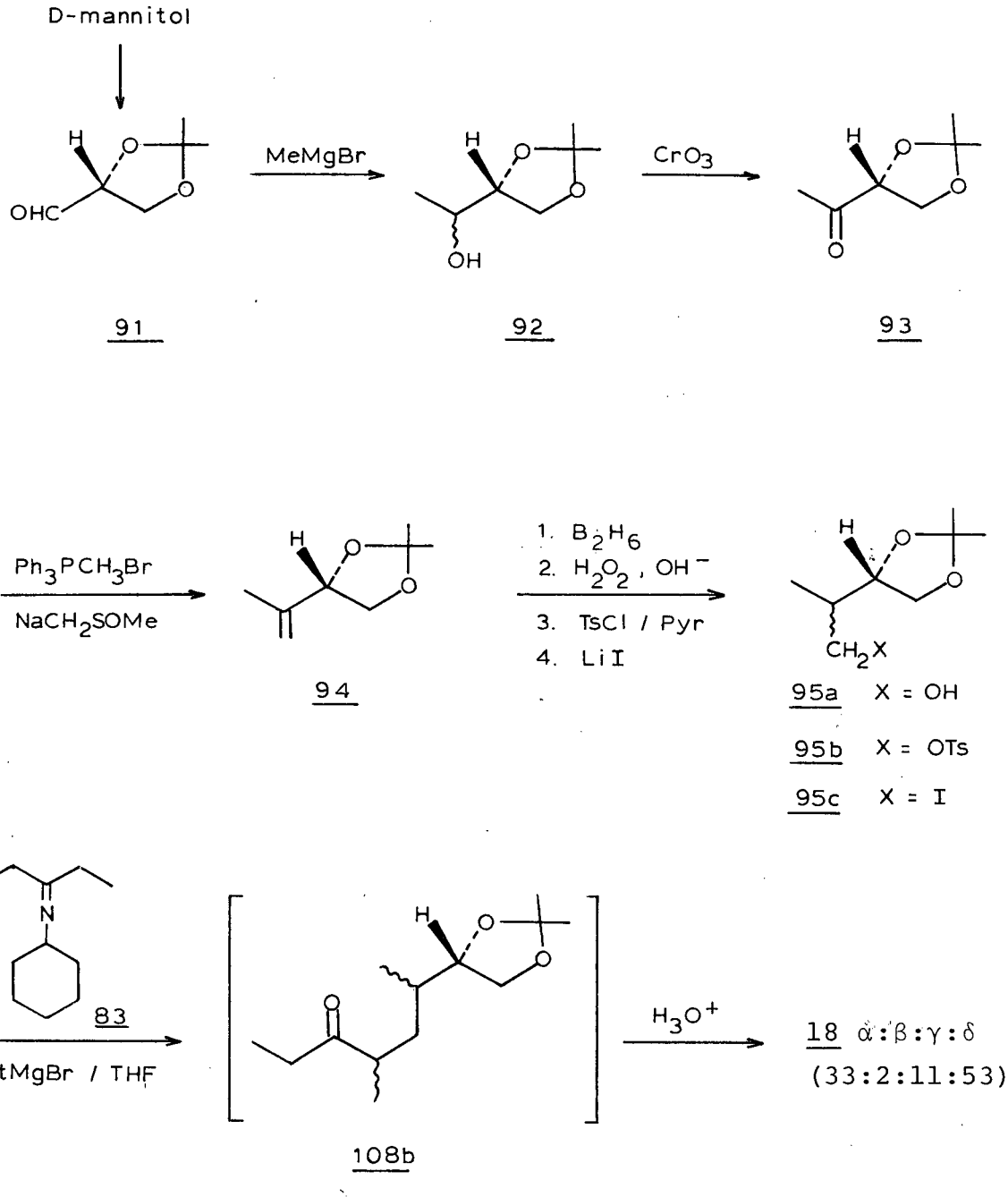


(-)-(1S,2R,4S,5R)-18α

The enantiomeric composition of synthetic (-)- and (+)-18α, determined by ^{13}CNMR with the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III), was 56 and 47% respectively. Comparison of the specific rotation of the isolated (-) enantiomer of 18α (-47^{o}) with the value calculated for the optically pure enantiomers (-47^{o} and $+44^{o}$) indicates that the naturally occurring (-)-α-multistriatin (18) is enantiomerically pure.

Mori reported a chiral synthesis of multistriatin (18) starting from D-mannitol (Scheme XVII).[51] The (+)-(R)-glyceraldehyde acetonide (91) was prepared from D-mannitol and the

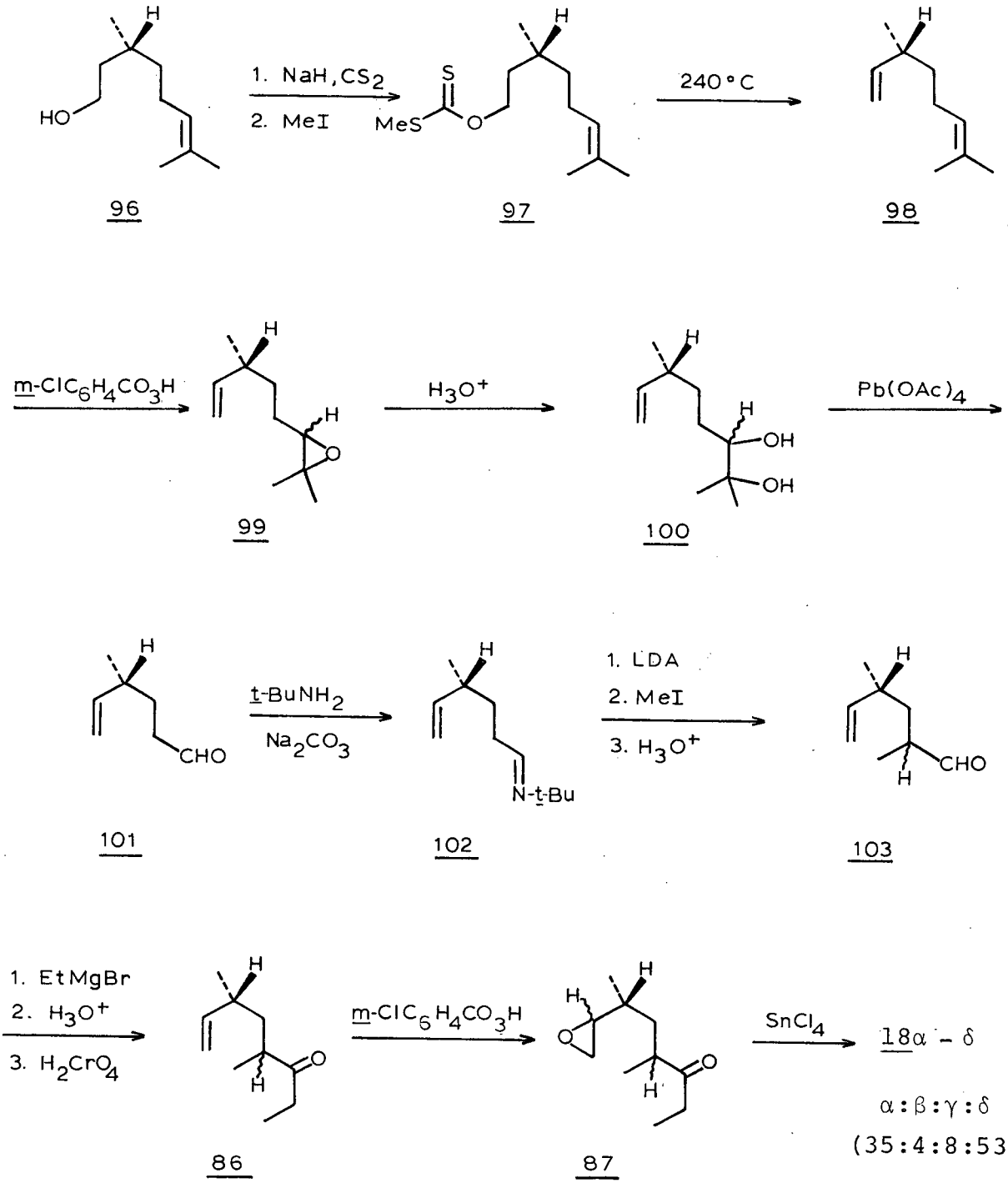
Scheme XVII. Chiral Synthesis of Multistriatin from D-Mannitol[51]



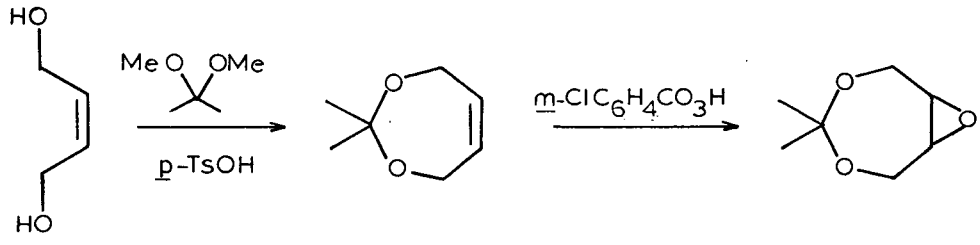
chirality at C-2 in 91 was retained throughout the synthesis to give optically active α-, β-, γ-, and δ-multistriatin (18). Addition of methylmagnesium iodide to 91 gave an epimeric mixture of 92 which was then oxidized to ketone 93. The Wittig reaction of 93 with methylenetriphenylphosphorane gave the alkene 94. Hydroboration-oxidation of 94 afforded the alcohol 95a, which was converted into the iodide 95c via the corresponding tosylate 95b. Iodide 95c was alkylated with the magnesium salt of the cyclohexylimine 83 and the resulting crude product was heated with dilute hydrochloric acid to yield a mixture of the four possible multistriatin stereoisomers. α-Multistriatin, having a specific rotation ($[\alpha]_D^{25}$) of -17° (ether), was isolated from the mixture using preparative GLC.

Very recently, another asymmetric synthesis of multistriatin (18) was accomplished by Cernigliaro and Kocienski[52] (Scheme XVIII). (+)-(3R)-Citronellol, $[\alpha]_D$ + 1.98° (ca. 35% optical purity), was converted into diene 98 by pyrolysis of the corresponding xanthate 97. Epoxidation of the trisubstituted olefin 98 afforded 99 which was hydrated to the diol 100. Subsequent oxidation of 100 with lead tetraacetate gave the aldehyde 101 which was methylated in a three-step sequence via the Schiff base 102 to give the aldehyde 103. Treatment of 103 with ethylmagnesium bromide followed by oxidation afforded 86. The rest of the reaction sequence was the same as those reported by Silverstein and coworkers[26] (see Scheme XIV). The observed specific rotation of -18.7° for the synthetic (-)-18α

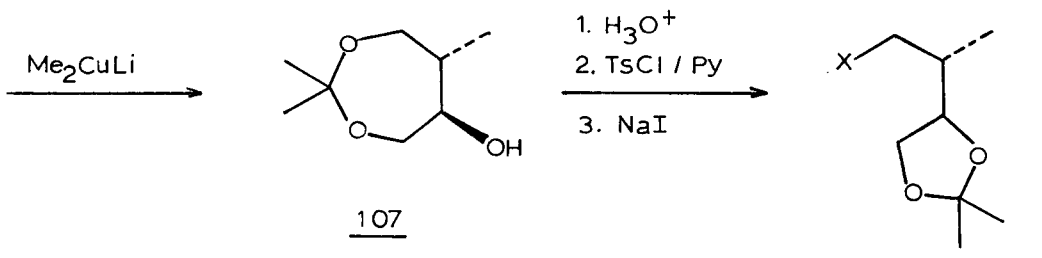
Scheme XVIII. Chiral Synthesis of Multistriatin from (+)-Citronellol[52]



Scheme XIX. Synthesis of α- and γ-Multistriatin from (Z)-2-Buten-1,4-diol[53a]



104 105 106

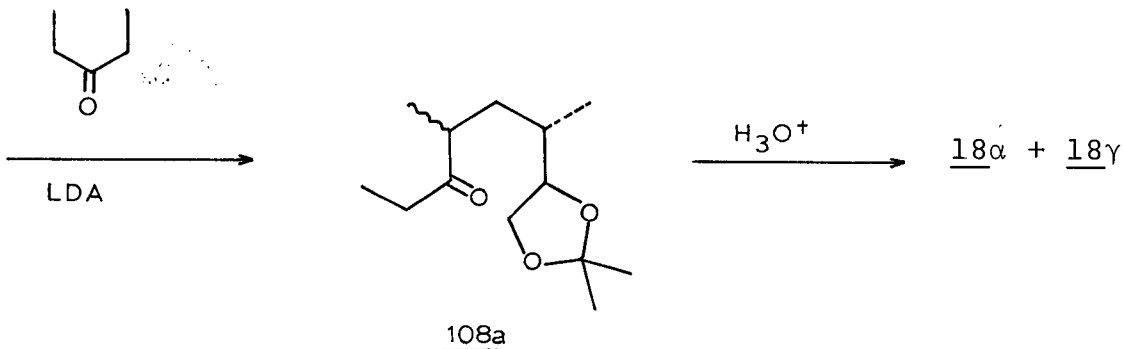


107

95a X = OH

95b X = OTs

95c X = I



108a

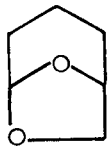
18α + 18γ

obtained after GLC separation, indicates an optical purity of approximately 40%.

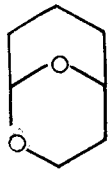
The stereoselective synthesis of an 85:15 equilibrium mixture of α- and γ-multistriatin (18) was reported by Elliot and Fried (Scheme XIX).[53a] The dioxolane 95a, which had been employed in Mori's synthesis,[51] was prepared in a totally different route from (Z)-2-buten-1,4-diol (104). Compound 104 was first protected as its isopropylidene derivative 105. Epoxidation of olefin 105 gave 106 which was treated with lithium dimethylcuprate to afford 107. The crucial alkylation step was effected by treating an excess of the anion of 3-pentanone with the iodo compound 95c. Removal of the acetonide protecting group followed by acid-catalyzed cyclization furnished the racemic multistriatin 18α,γ in 80% yield from 95a. Optically active 95a could also be obtained by resolving 107.[53b]

(d) endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane

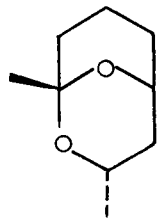
endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (21) is a host-specific substance in Norway spruce infested by Trypodendron lineatum OLIV.[27,28] Unlike the previously described bicyclic ketal pheromones which have the common 6,8-dioxabicyclo [3.2.1]octane (29) skeleton,[23—26] this compound contains the 2,9-dioxabicyclo[3.3.1]nonane structure (109).



29



109

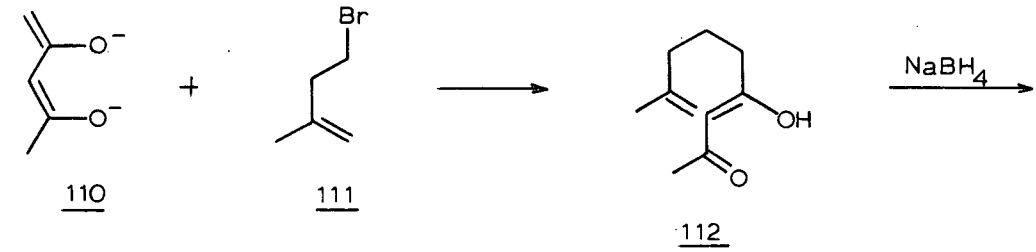


21

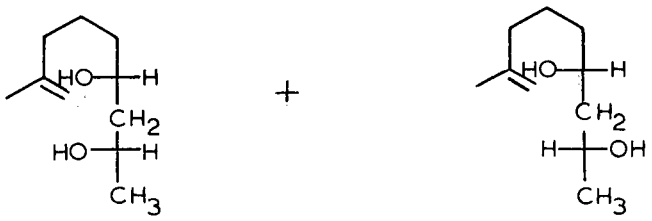
The synthesis of compound 21 was reported by Gerlach and Kunzler in 1977 (Scheme XX).[54] Alkylation of the acetylacetone dianion 110 with 4-bromo-2-methyl-1-butene (111) afforded compound 112. Reduction of 112 with sodium borohydride yielded erythro- and threo-8-methyl-8-nonen-2,4-diol, (113a) and (113b), which were then separated by column chromatography. The configurations of these two diastereomers were established by converting them under equilibrium conditions into their benzal derivatives. Conversion of diol 113a into its benzal derivative gave only 115a, while diol 113b gave rise to both 115b and 115c (the phenyl group assumed an equatorial position in the most stable conformations of these benzal derivatives).

Oxidative cleavage of the terminal double bond in 113a with ozone gave ketone 114a which spontaneously cyclized to endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (21a). The

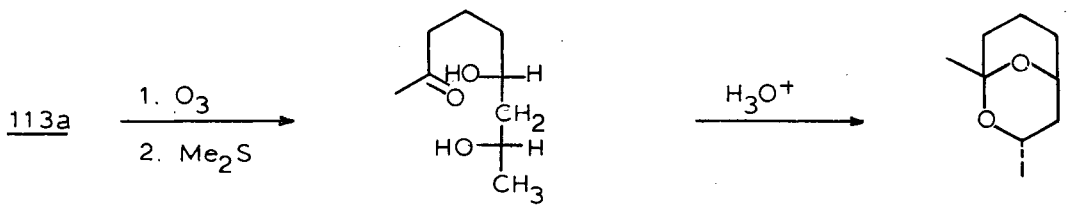
Scheme XX. Synthesis of endo-1,3-Dimethyl-2,9-dioxabicyclo [3.3.1]nonane [54]



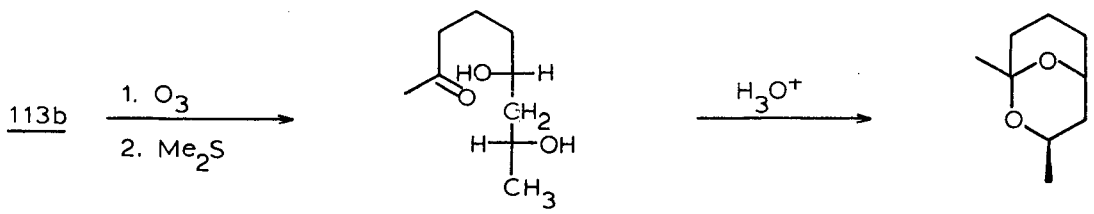
110 111 112



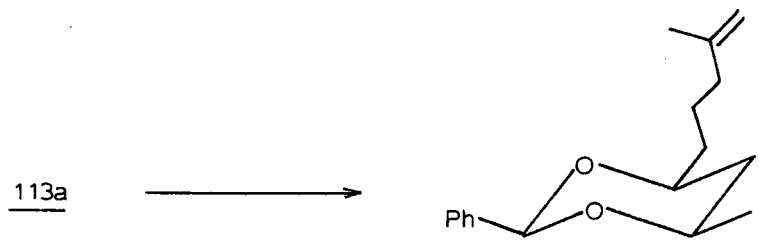
113a (erythro) 113b (threo)



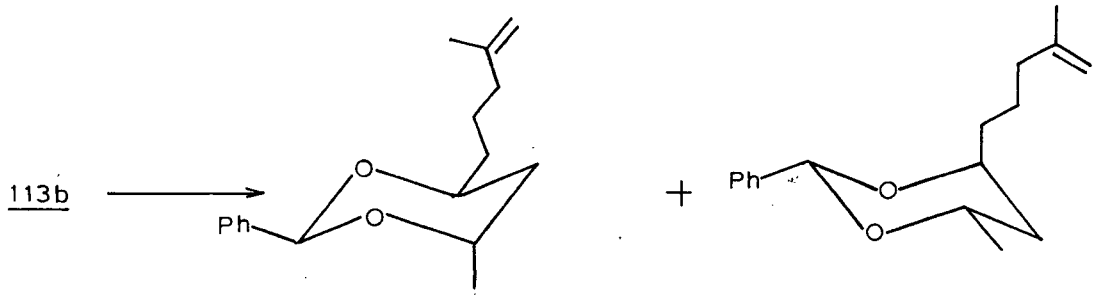
113a 114a endo-21a



113b 114b exo-21b



115a

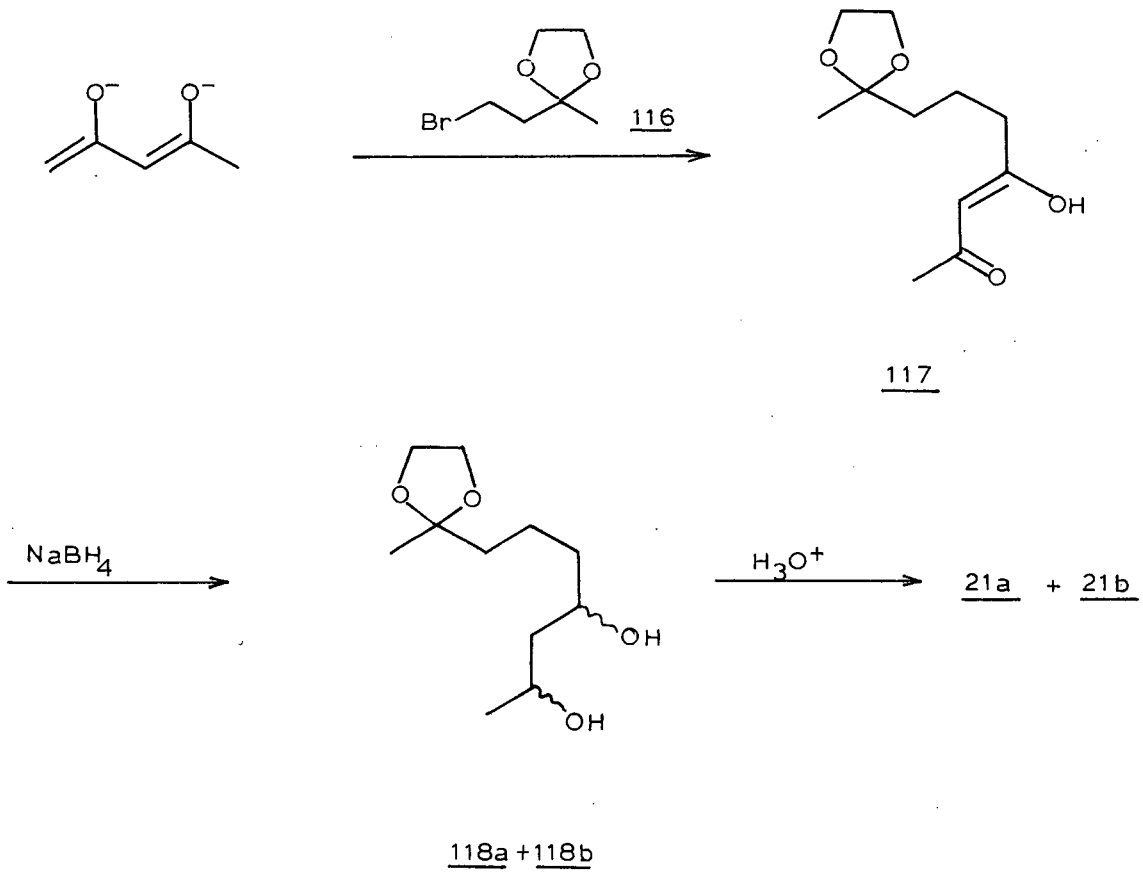


115b 115c

threo diol 113b was converted exclusively into exo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (21b) using the same reaction sequence. Comparison of the NMR data of the two bicyclic acetals, 21a and 21b, with that of the natural compound confirmed the endo configuration of the natural product.

A second, more convenient route starting from the bromo ketal 116 was also reported by Gerlach and Kunzler (Scheme XXI).[54] The bromo ketal 116 was alkylated with the dianion of acetylacetone to give compound 117. Reduction of 117 with sodium

Scheme XXI. Synthesis of 21 from Bromo Ketal 116 [54]



borohydride afforded a mixture of diols 118a and 118b which were cyclized in aqueous acid to yield a mixture of 21a and 21b.

(e) Lineatin

Source:

Female beetles of Trypodendron lineatum produce an attractant compound while boring in fallen Douglas fir logs.[29] About 200 micrograms of the pure attractant, called lineatin, was obtained from 200 grams of frass.

Structure Elucidation:

The high resolution mass spectrum suggested $C_{10}H_{16}O_2$ as the molecular formula and the low resolution mass spectrum (Figure 3) showed the facile loss of 15 mass unit (to m/e 153) which indicated methyl branching. The infrared spectrum (Figure 4) showed no absorptions due to hydroxyl or carbonyl groups and no reactions were observed when the compound was treated with a silylating agent or lithium aluminum hydride. Since all the above data excluded hydroxyl, carbonyl, epoxy and peroxy groups, the ether linkage was obvious. The absorption in the NMR spectrum (Figure 5) at δ 4.35 suggested a H-C-O proton as in exo-brevicomin. Since no olefinic double bond was indicated by infrared spectroscopy, the absorption at δ 4.85 was assigned to a proton deshielded by two oxygen atoms (O-CH-O), and a tricyclic ketal structure was thus suspected. The absorption at δ 1.15 was assigned to two methyl groups, while the one at δ 1.09 represented a third methyl group. The signal at δ 1.05 was considered to be spurious.

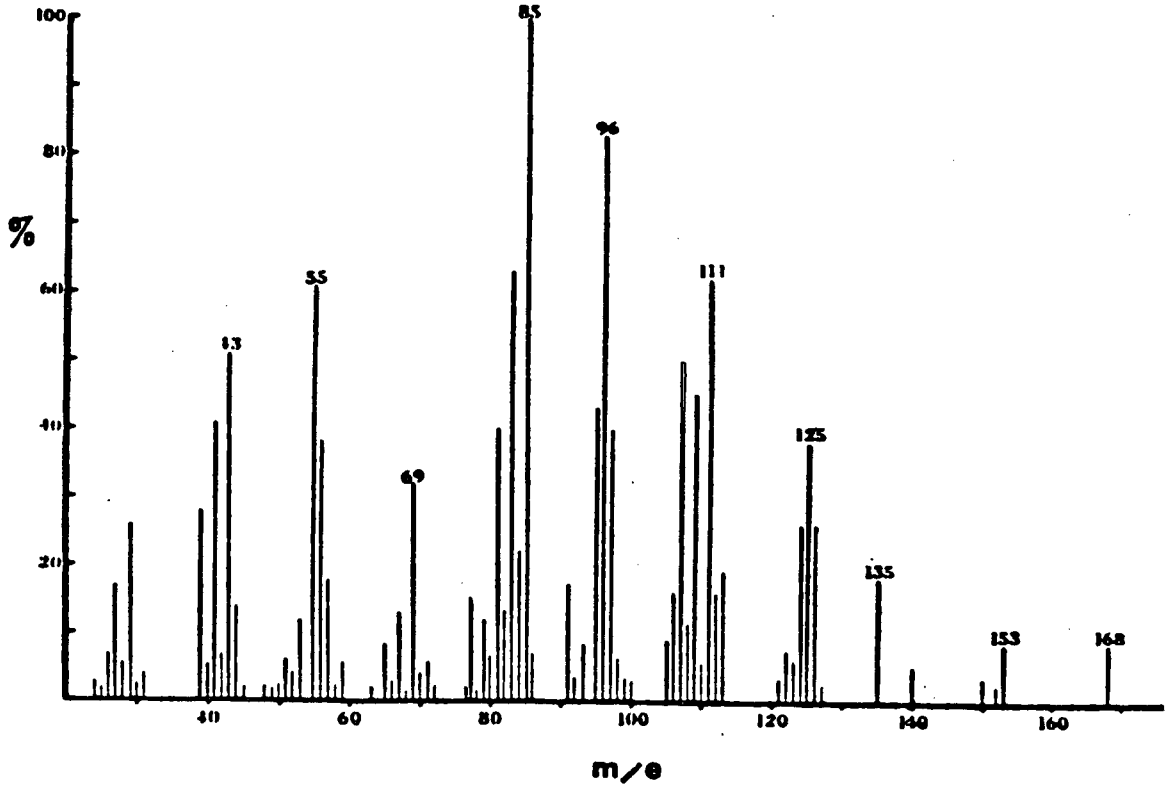


Figure 3. Unit resolution mass spectrum of lineatin.[29]

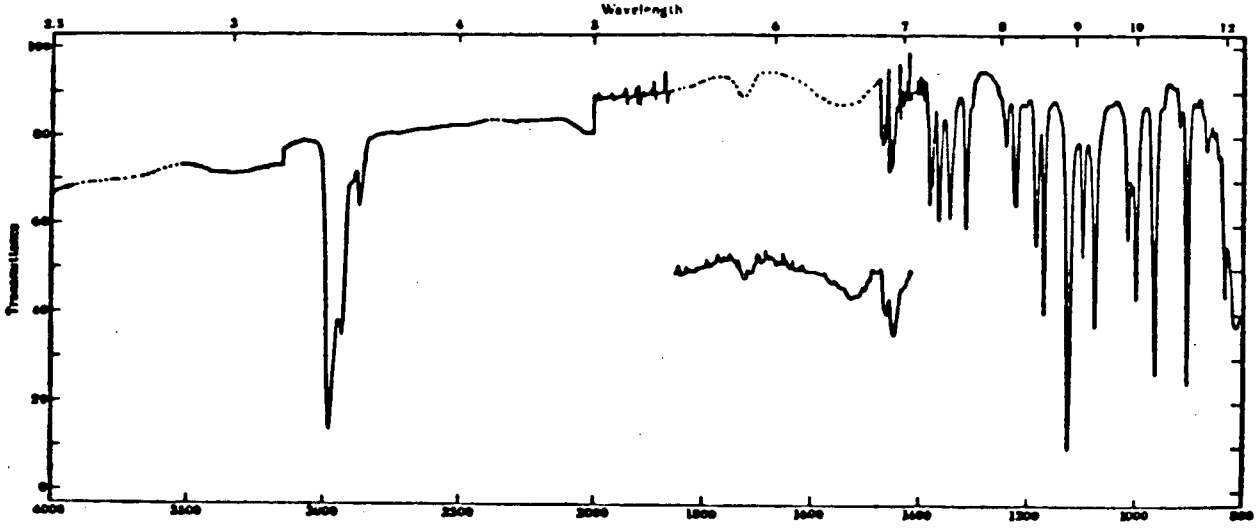


Figure 4. Infrared spectrum, recorded on about 70 μg of pure lineatin in CCl_4.[29]

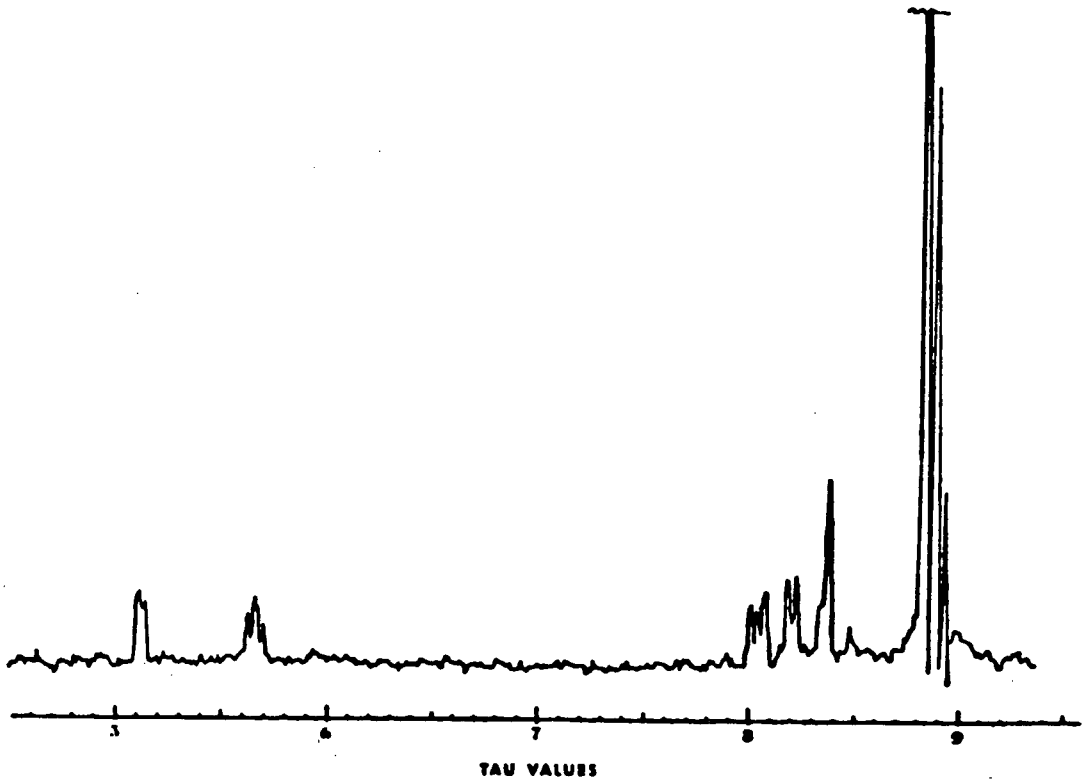


FIG. 5 100-MHz NMR spectrum, recorded on about 200 μg of lineatin in CCl_4.[29]

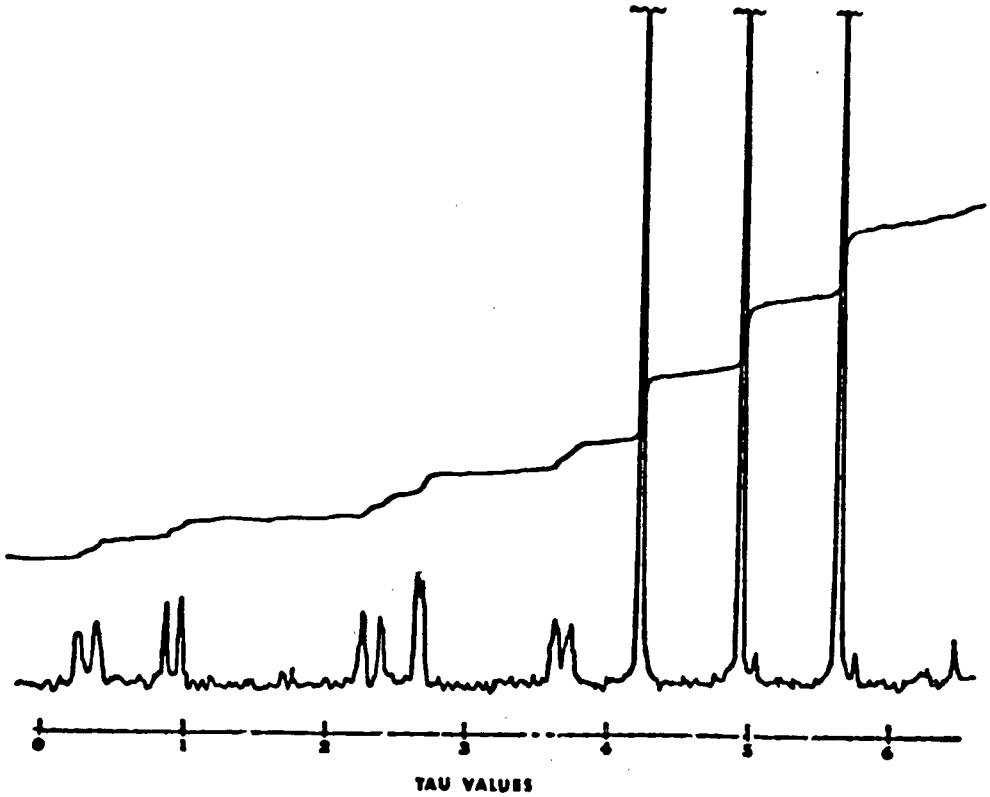
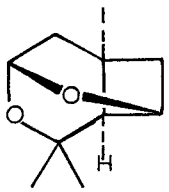
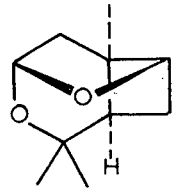


FIG. 6 100-MHz $Eu(fod)_3$-shifted NMR spectrum of lineatin. $Eu(fod)_3$/substrate molar ratio = 1.3, in CCl_4.[29]

One of the hydrogenolysis products of lineatin was 2,6-dimethyloctane. This established the basic carbon skeleton. From the information given by the Eu(fod)$_3$-shifted NMR spectrum of lineatin (Figure 6) and double irradiation experiments on the shifted spectrum, the structure of lineatin was proposed to be one of the two isomeric tricyclic acetals 22 or 23.



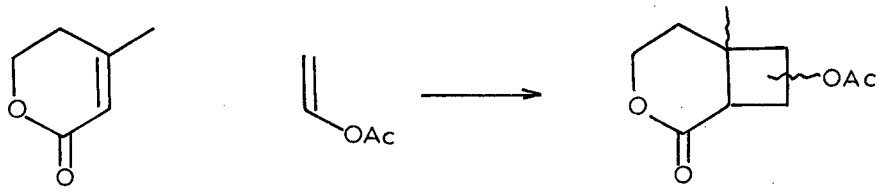
22



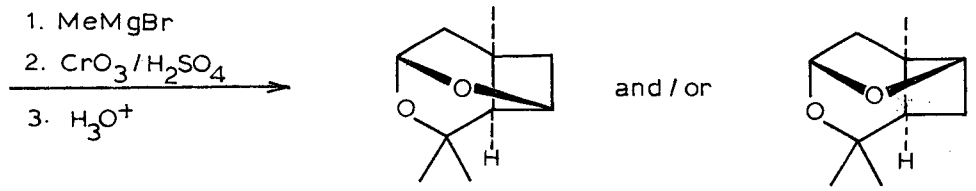
23

An attempt to confirm the structure of lineatin using the synthetic sequence shown in Scheme XXII was reported to be unsuccessful,[29] since the initial photochemical addition gave a mixture of isomers which could not be separated or identified. The reaction sequence was carried through on the crude mixtures of isomers. Although these workers isolated a small amount of product indistinguishable in chromatographic, spectral and biological properties from the natural compound, no definite proof of structure was concluded. The structure of lineatin

Scheme XXII. MacConnell's Synthesis of Lineatin[29]



119 120 121



22 23

was finally established as 22 by an unambiguous synthesis[30a] (see description under Synthesis).

Synthesis:

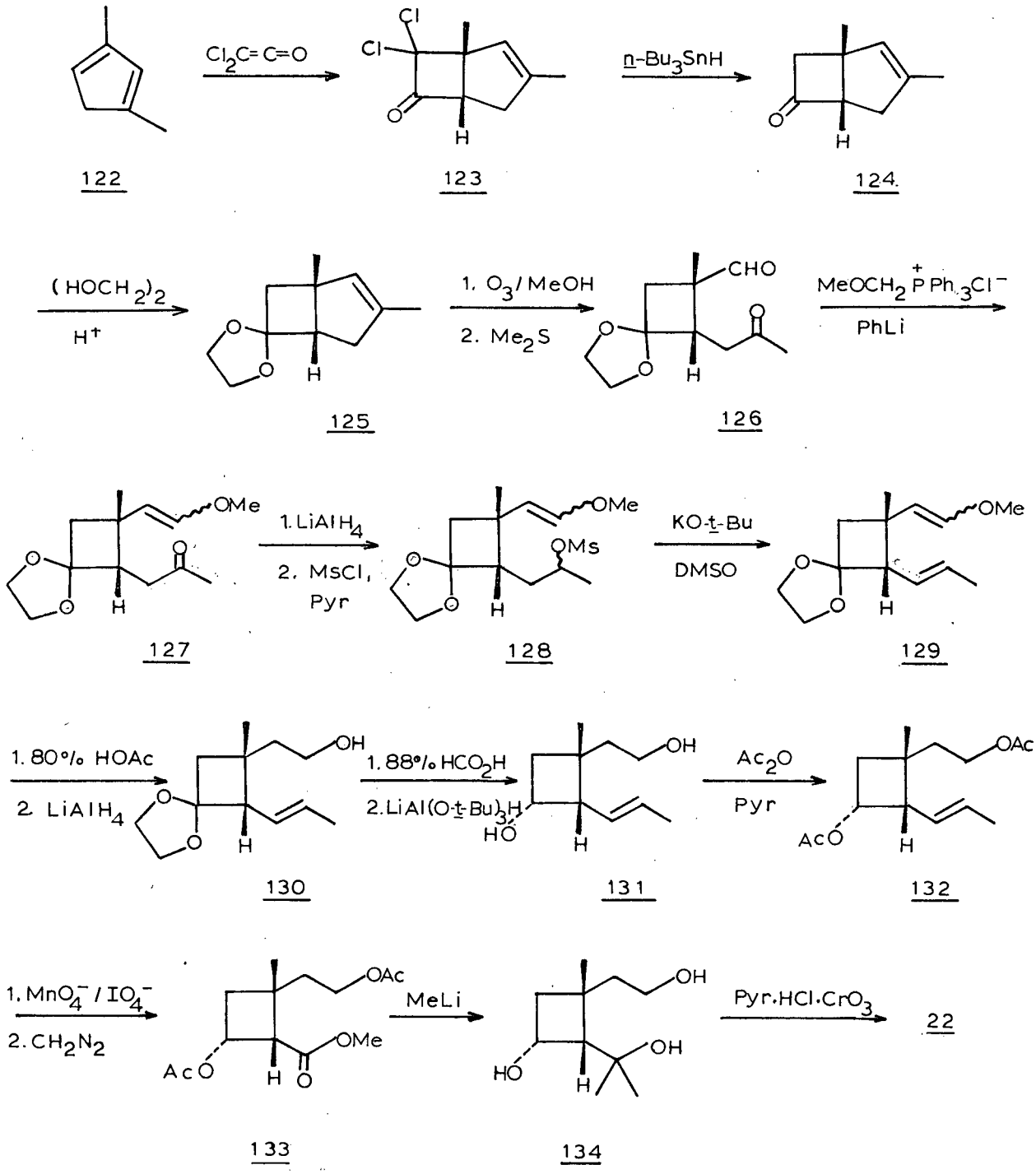
Since the structure of natural lineatin could not be definitely assigned from its spectral data and the chemical

tests, two different syntheses [1] were designed by Borden et al.[30a] to establish the structure of natural lineatin.

Compound 22 was chosen as the initial target compound. Their synthetic route (Scheme XXIII), though lengthy and low yielding, provided an unambigous synthesis of 3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane (22). Cycloaddition of dichloroketene to compound 122 gave adduct 123 which was treated with tri-n-butyltin (IV) hydride to give the dehalogenated compound 124. The keto group in 124 was protected as its ketal. Ozonolysis of the resulting compound 125 gave the keto aldehyde 126. Wittig reaction of the methoxymethyltriphenylphosphorane with the aldehyde 126 gave compound 127 which was then reduced to its alcohol. This alcohol was converted into mesylate 128, which upon treatment with potassium tert-butoxide gave compound 129. Acid hydrolysis followed by lithium aluminum hydride reduction afforded alcohol 130. The ketal in 130 was removed and the resulting ketone was reduced with lithium tri-tert-butoxyaluminum hydride to give 131. The alcohol 131 was then converted into diacetate 132 which was treated with periodate-permanganate, followed by diazomethane to yield compound 133. Reaction of 133 with excess methyllithium gave triol 134 and finally, oxidation of 134 with pyridinium chlorochromate furnished the tricyclic ketal 22.

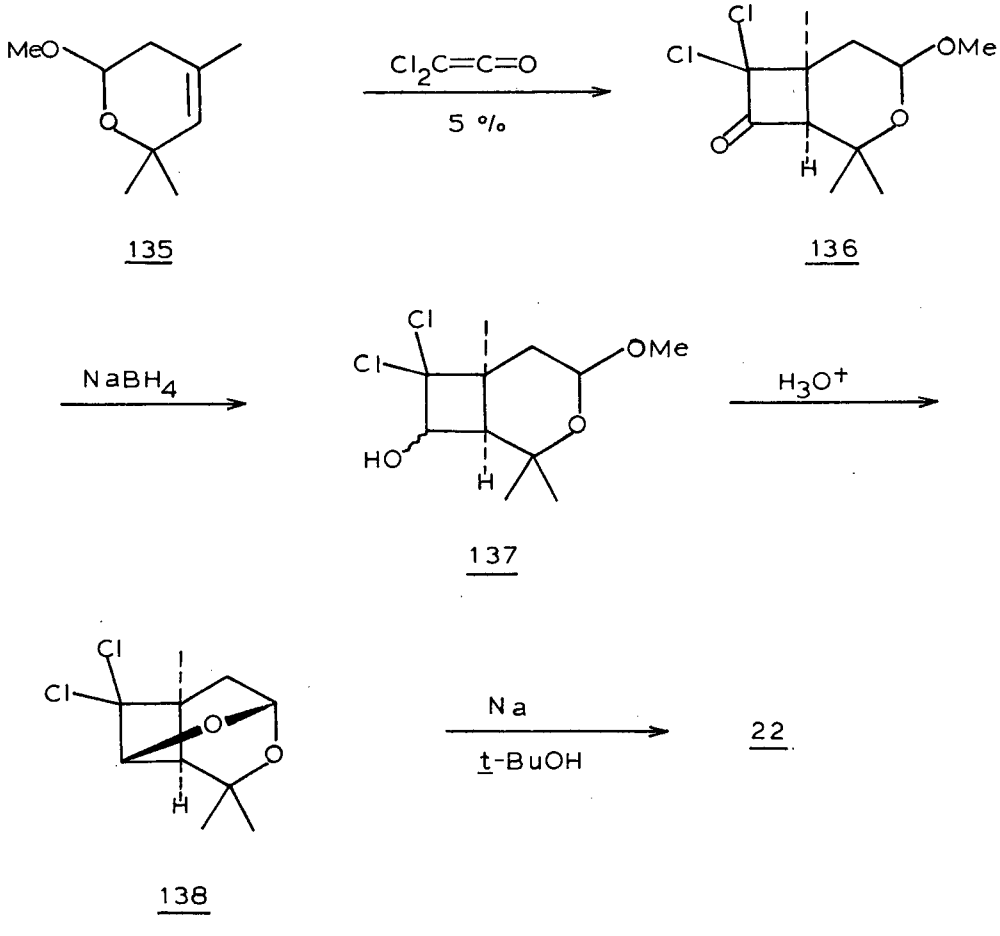
[1] All these syntheses are only briefly stated in reference 30a without experimental details.

Scheme XXIII. Synthesis of Proposed Lineatin Structure 22[30a]



A second synthesis (Scheme XXIV), although shorter (disregarding the preparation of compound 135), suffered from the very low yield (5%) in the cycloaddition of 135 to dichloroketene. The cycloadduct 136 was reduced with sodium borohydride to give the alcohol 137. Acid cyclization of 137 gave compound 138 which on treatment with sodium in tert-butanol gave the tricyclic ketal 22 .

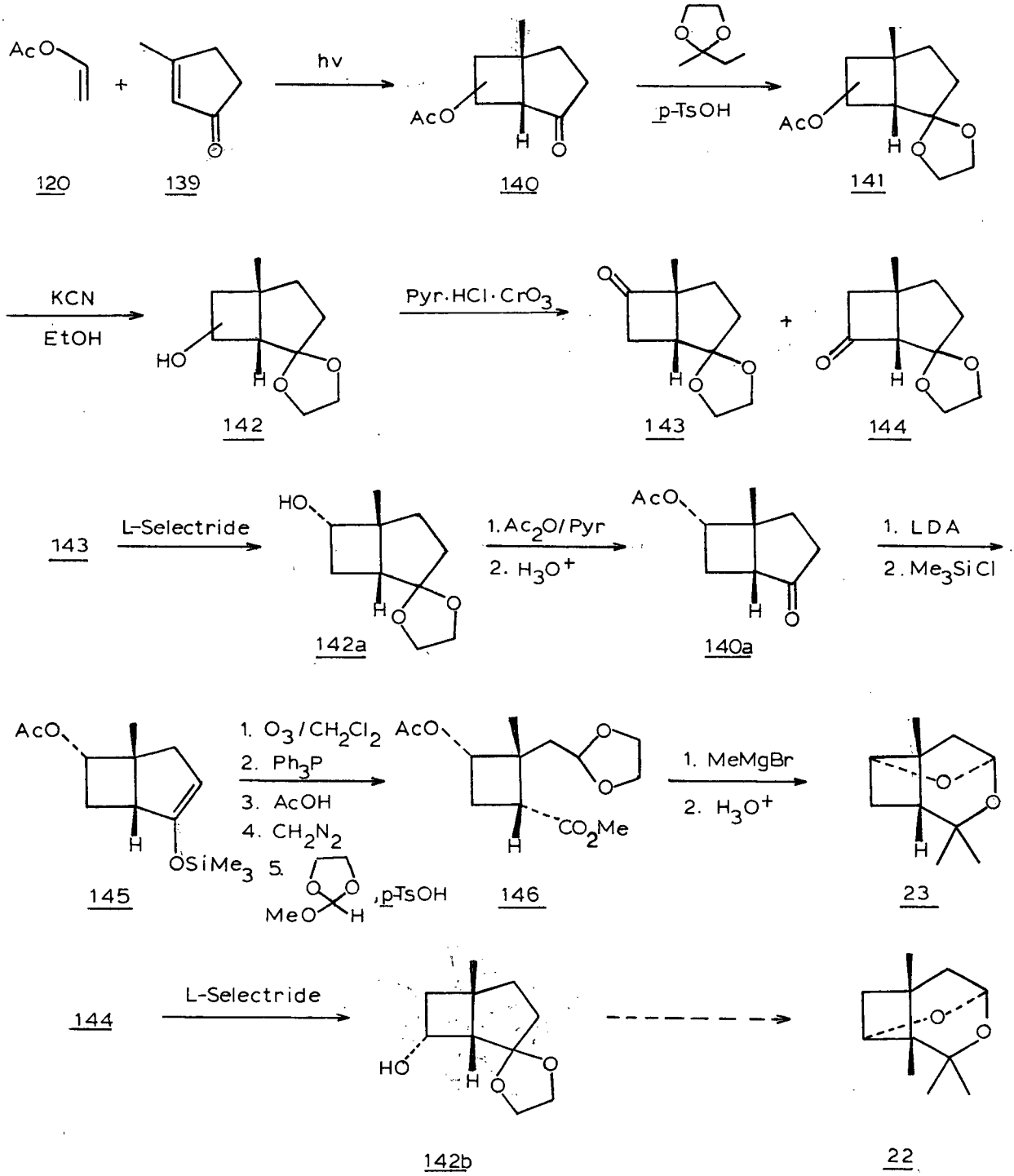
Scheme XXIV. Synthesis of 22 from 135[30a]



Since the spectral, chromatographic and biological properties of the synthetic compound 22 agreed with those of natural lineatin, the structure of the attractant compound was thus identified as 22.

During the preparation of this dissertation, Mori and Sasaki[30b] reported another synthesis of lineatin (22) starting from the photocycloaddition reaction of enol acetate 120 with 3-methyl-2-cyclopentenone (139). Their route which is considerably lengthy, is described in Scheme XXV. It should be pointed out that severely low yielding and low stereoselectivity steps were included in this synthesis. In fact a 60% yield of a mixture of four stereoisomers of 140 was obtained in the first reaction. The mixture of isomers 140 was converted into acetoxy acetals 141 and the acetate moiety was hydrolyzed to give alcohols 142. Oxidation of 142 with pyridinium chlorochromate gave a mixture of two isomeric ketones 143 and 144 in a ratio of 4:1 respectively. The two isomers 143 and 144 were separated by chromatography over silicic acid. It should be noted that only ketone 144, derived from the minor photoadduct, would lead to lineatin (22). The major isomer 143 was reduced with lithium tri-sec-butylborohydride (L-Selectride) to afford alcohol 142a which was protected as its acetate followed by regeneration of the ketone group to yield 140a. This acetoxy ketone was converted into its trimethylsilyl enol ether 145 with lithium diisopropylamide and chlorotrimethylsilane. Ozonolysis of 145 and reductive work-up (triphenylphosphine) of the ozonide gave

Scheme XXV. Mori's Synthesis of Lineatin (22)[30b]



an aldehyde acid. Esterification and acetalization of this compound gave 146 in 11% yield from 145. Finally, reaction of compound 146 with methylmagnesium iodide and subsequent treatment with dilute acid afforded 23 in 28% yield. The synthesis of lineatin (22) was carried out in the same manner as described above, starting from the minor ketone 144. Compound 142b and the corresponding hydroxy ketone were reported to be unstable, suffering from cyclobutane cleavage.

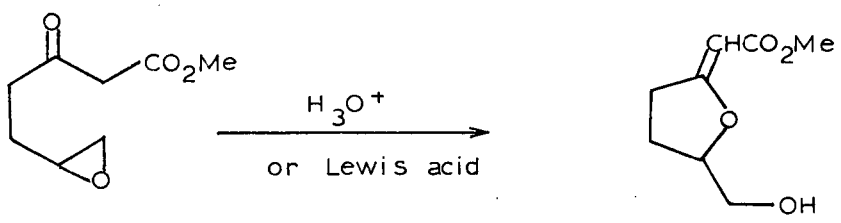
All of the synthetic routes described above proceeded in very low overall yields and often mixtures of isomers were obtained. Consequently, only very small quantities of synthetic lineatin were available for very limited testing.

In the following section of this thesis, we report the results from a study of the cyclization of epoxy β-keto esters which led to efficient syntheses of frontalin, and endo- and exo-brevicomin. A stereoselective synthesis of (-)-α-multistriatin along with an efficient, but nonstereoselective, synthesis of lineatin are also presented.

RESULTS AND DISCUSSION

(i) Synthesis of Frontalin, endo-Brevicomin, and exo-Brevicomin

In continuation of our studies on the cyclization of β-keto esters,[55] the cyclizations of a variety of substituted epoxy β-keto esters were investigated. Results obtained earlier in our laboratory indicated that protic or Lewis acids catalyzed reactions of methyl-6,7-epoxy-3-oxoheptanoate (147), gave only the 0-cyclized product 148.[56]

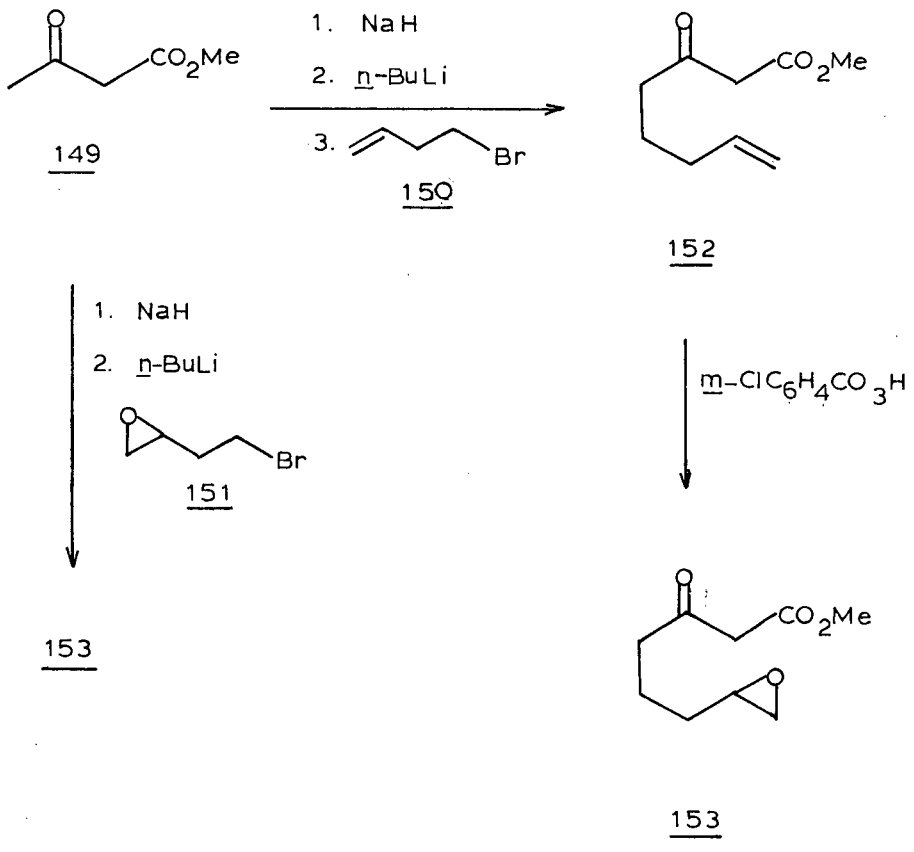


147 148

To test the generality of this type of cyclization, the homologous epoxide 153 and its substituted derivatives were investigated. The epoxide 153 could be prepared in two different ways as shown in Scheme XXVI.

In the first method, the dianion of methyl acetoacetate (149)[57] was alkylated with 4-bromo-1-butene (150) to give the

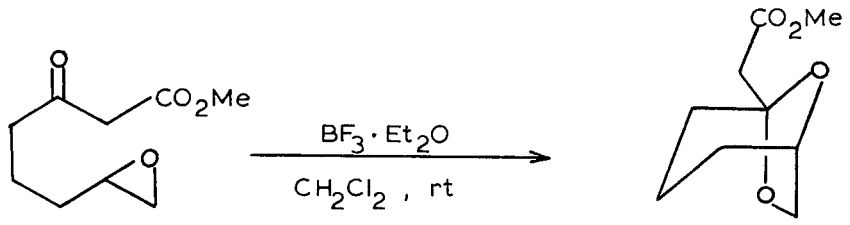
Scheme XXVI. Synthesis of Methyl 7,8-Epoxy-3-oxooctanoate (153)



γ-alkylated product 152. Epoxidation of the resulting alkene gave methyl 7,8-epoxy-3-oxooctanoate (153). In the second method, 4-bromo-1-butene (150) was first converted into its epoxide 151 and then treated with the dianion of methyl acetoacetate. Besides the desired alkylated product 153, TLC analysis also showed several other side products which were not identified.

The complication of this latter reaction could result from attack of the dianion on the epoxide group. We found that the yield of the second method was usually lower than the first method.

Treatment of the epoxide 153 with boron trifluoride etherate in dichloromethane at room temperature for two hours gave a cyclized product in high yield. The structure of this product was readily identified from its spectral data. The salient features were the lack of a saturated ketone absorption and the presence of a single carbonyl band in the infrared at 1740 cm^{-1} which was assigned to an ester function. The NMR of this product showed a three proton singlet at δ 3.68 indicating the methoxy group of an ester, and a multiplet at δ 1.1-2.1 attributable to six methylene protons. The α-methylene of the β-keto ester 153 was replaced by a two proton singlet at δ 2.73. In addition, there were two low field multiplets at δ 3.8 and δ 4.5 ascribable to three protons on carbon atoms adjacent to

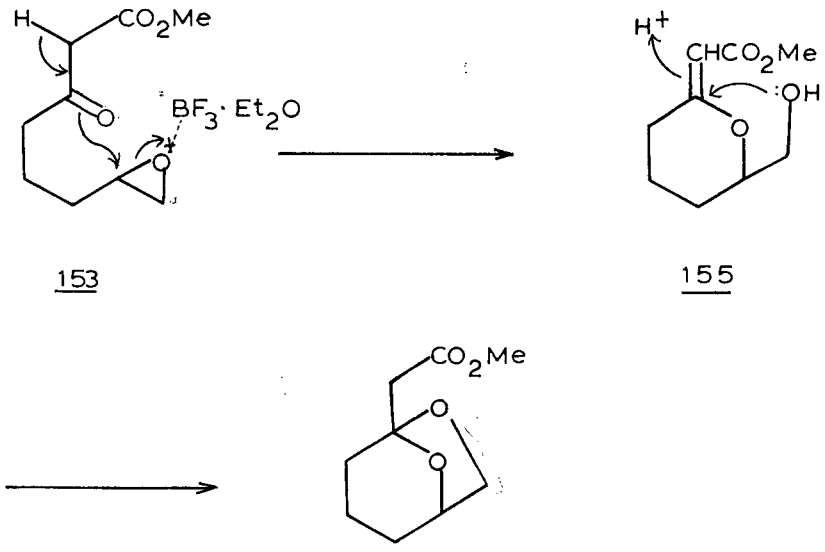


153 154

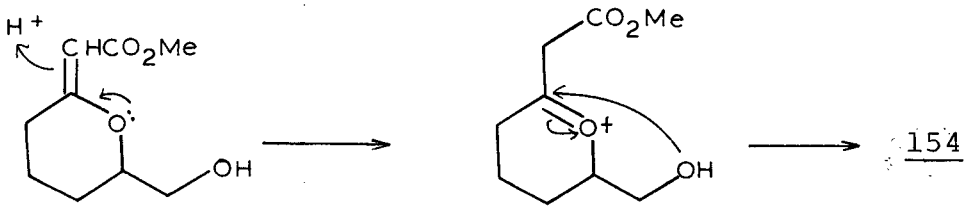
oxygen. The molecular formula of this compound, determined by high resolution mass spectrometry, was $C_9H_{14}O_4$. From these spectral data, the structure of the cyclized product was identified as methyl α-(6,8-dioxabicyclo[3.2.1]octan-5-yl) acetate (154).

The following mechanism (Scheme XXVII) was envisioned for the formation of this bicyclic ketal. Opening of the oxirane ring with intramolecular participation of the keto group would lead to the cyclic enol ether intermediate 155. Further cyclization involving the free hydroxyl group in a Michael type addition to the unsaturated ester then furnished the bicyclic ketal 154. The latter process might also occur via the inter-

Scheme XXVII. Proposed Mechanism for the Cyclization of 153



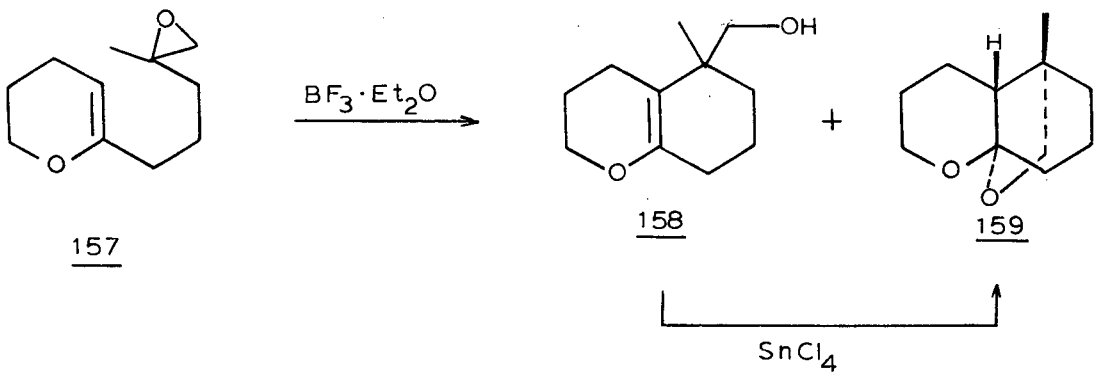
153 155 154



155 156

mediate 156. A similar reaction has been reported recently by Boeckman and coworkers[58] (Scheme XXVIII). The cyclization of epoxide 157 with boron trifluoride etherate in dichloromethane

Scheme XXVIII. Cyclization of Epoxy Dihydropyran 157[58]

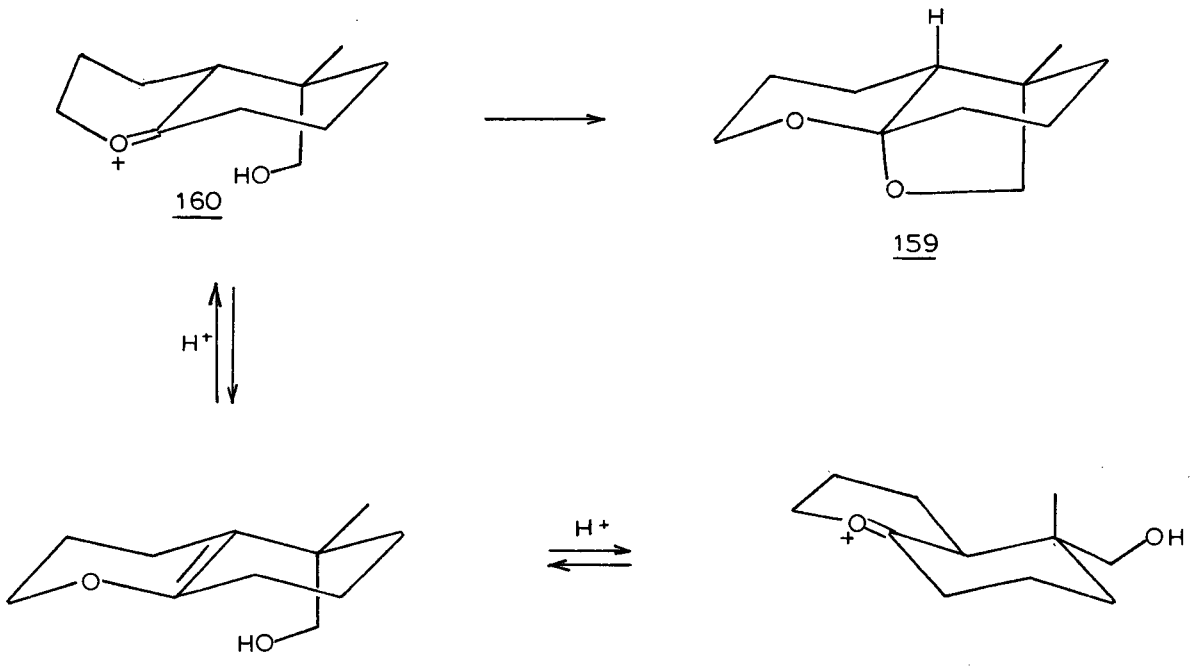


157 158 159

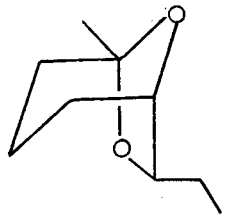
yielded 158 and 159. A mechanism involving the intermediary oxonium ion 160 was proposed for the formation of 159 as shown

in Scheme XXIX.

Scheme XXIX. Proposed Mechanism for the Cyclization of Epoxide 157[58]



Compound 154 has a 6,8-dioxabicyclo[3.2.1]octane skeleton,[59] which is the basic framework of four bark beetle pheromones, exo-brevicomin (15),[23] endo-brevicomin (16),[23] frontalin (17),[25] and α-multistriatin (18α).[26] It is apparent that cyclizations similar to that of 153 should provide a facile and general route to these type of compounds. Because of their potential utility in controlling the population of bark beetles and their unique structural feature, these compounds have been



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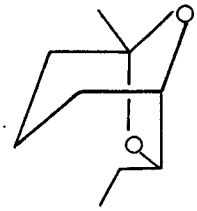

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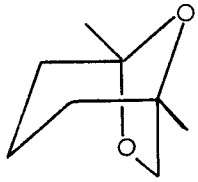
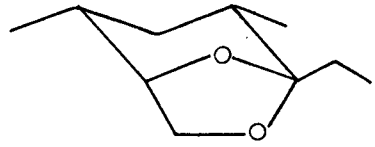


17

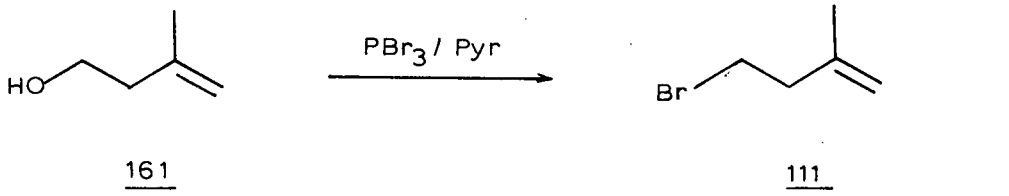


18α

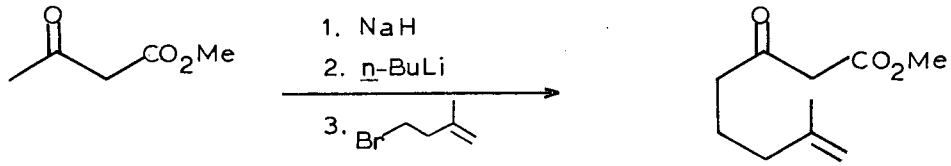
the object of several synthetic (see Introduction) and entomological studies.[28,60] With the same objective, we investigated the preparation of the first three pheromones using the above epoxy β-keto ester cyclization.

The synthesis of frontalin (17) is outlined in Scheme XXX. In this synthesis, 4-bromo-2-methyl-1-butene (111) was prepared in 42% yield from the commercially available 3-methyl-3-buten-1-ol (161) by treating the alcohol 161 with phosphorus tribromide in an ether-pyridine mixture.[61] Alternatively,

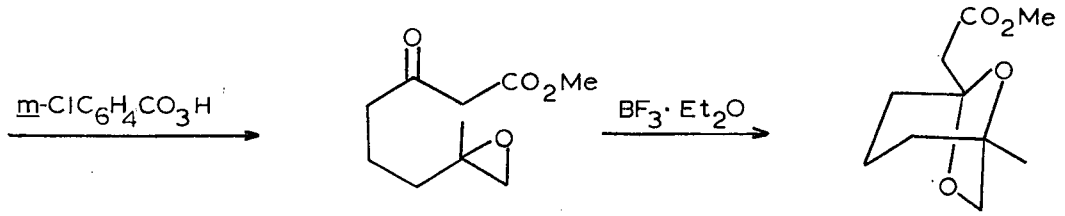
Scheme XXX. Synthesis of Frontalin (17)



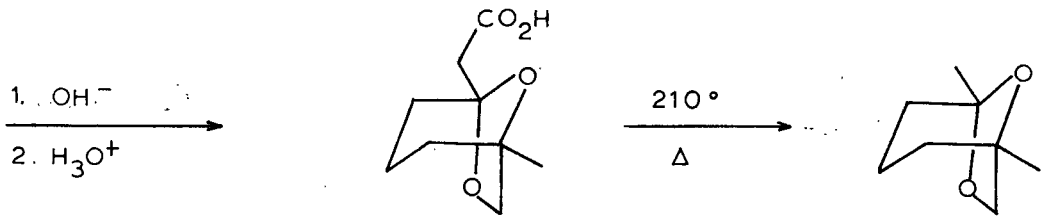
161 111



149 111 162



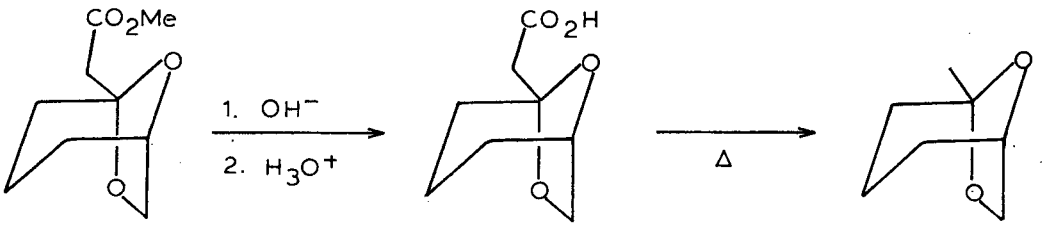
163 164



165 17

bromide 111 could also be prepared by the reaction of 161 with triphenylphosphine and carbon tetrabromide[62] in dichloromethane. Although the alternate method gave high yield (>90%), we found it very difficult to separate the relatively low boiling bromide 111 from the side product tribromomethane formed in the reaction. It was also found that when bromide 111, contaminated with trace amounts of tribromomethane, was used in the subsequent dianion reaction, unsatisfactory results were observed. The dianion of methyl acetoacetate was alkylated with 111 to give the γ-alkylated product 162 in good yield. Compound 162 was epoxidized with m-chloroperbenzoic acid to produce 163 in 73% yield from methyl acetoacetate. Treatment of the epoxy compound 163 with boron trifluoride etherate afforded the bicyclic compound 164 in 95% yield. The IR spectrum showed the characteristic absorption from an ester at 1740 cm^{-1}. The NMR spectrum exhibited absorptions at δ 1.32 (s, 3H) for the bridgehead methyl group, δ 1.5-1.9 (m, 6H) for the methylene protons in the ring, a two proton singlet at δ 2.72 characteristic of the methylene protons adjacent to a carbonyl group, a three proton singlet at δ 3.66 for the methoxy group, and two low field absorptions at δ 3.40 and 3.88 for the methylene protons on the carbon next to oxygen. To convert compound 164 into frontalin (17), it was necessary to develop a convenient method to remove the carbomethoxy group on the side chain at C-5.

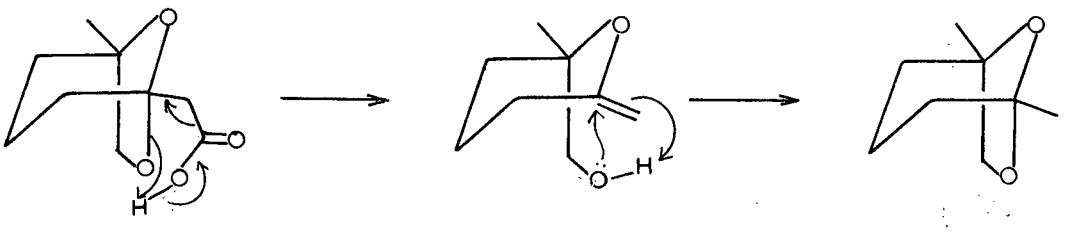
This was first accomplished on the model compound 154. The ester 154 was hydrolyzed by aqueous alkaline to give the corresponding carboxylic acid 166 in good yield. This carboxylic acid underwent a smooth thermal decarboxylation (Kugelrohr oven at 220° C, 5-8 min) to give 167 in 84% yield. A similar reac-



154 166 167

tion sequence was employed to convert ester 164 into frontalin (17) in 85% yield. The NMR, IR and mass spectral data of this product were identical with those reported for frontalin (17).[25]

The rather facile decarboxylation of acid 165 might be due to participation of one of the ketal oxygens as shown in equation 1. A similar mechanism involving the intermediates

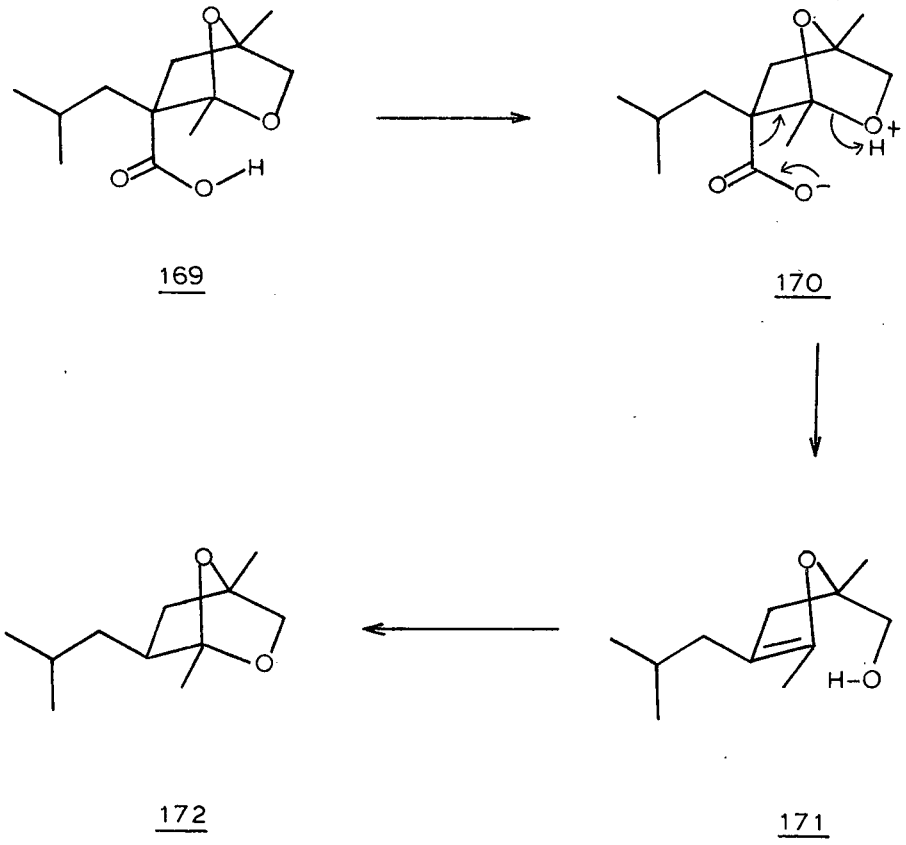


(1)

165 168 17

170 and 171 was proposed by Atkinson and Miller[63] for the decarboxylation of acid 169 to form 172 (Scheme XXXI).

Scheme XXXI. Proposed Mechanism for the Decarboxylation of endo-6-Isobutyl-1,4-dimethyl-2,7-dioxabicyclo [2.2.1]heptane-6-carboxylic acid (169)[63]

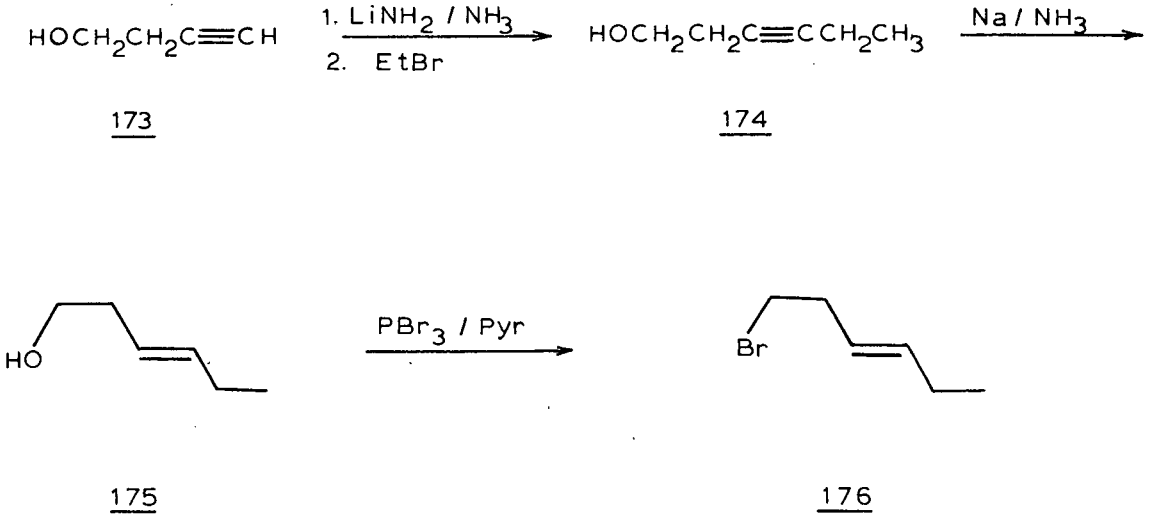


169 170

172 171

The synthesis of endo-brevicomin (16) (Scheme XXXIII) was accomplished using the same methodology. (E)-1-Bromo-3-hexene (176) was prepared from 3-butyn-1-ol (173) as shown in Scheme XXXII. The dianion of 3-butyn-1-ol (173) was generated

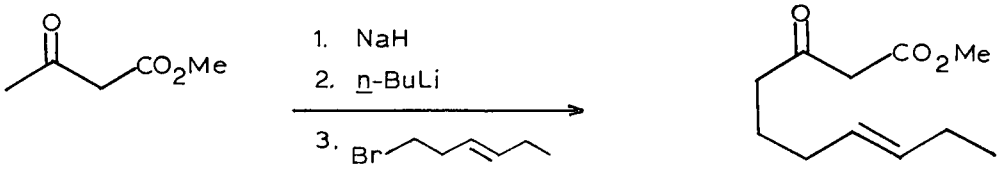
Scheme XXXII. Synthesis of E-1-Bromo-3-hexene (176)



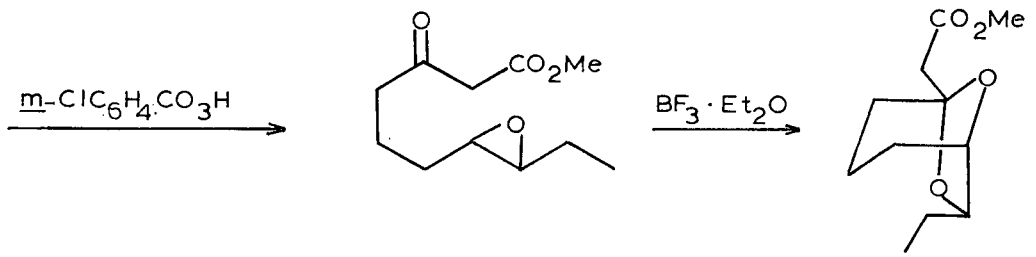
173 174 175 176

with lithium amide in liquid ammonia and then alkylated with 1-bromoethane to give the C-alkylated product 3-hexyn-1-ol (174)[64] in 76% yield. Birch reduction[65] of 174 gave (E)-3-hexen-1-ol (175) in 87% yield, which was converted into (E)-1-bromo-3-hexen (176). The dianion of methyl acetoacetate was alkylated with bromide 176 to give methyl (E)-3-oxo-7-decenoate (177) in 83% yield. Compound 177 was treated with m-chloroperbenzoic acid

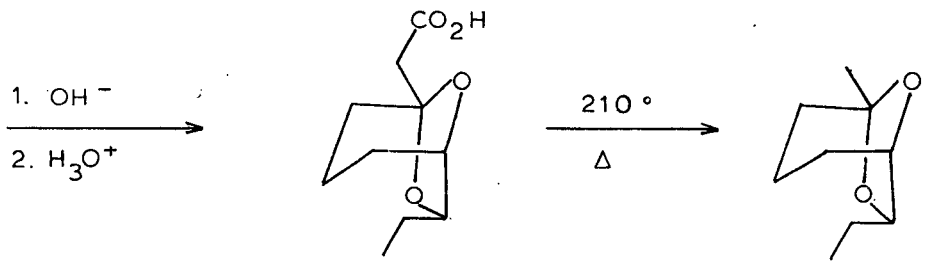
Scheme XXXIII. Synthesis of endo-Brevicomin (16)



149 177



178 179

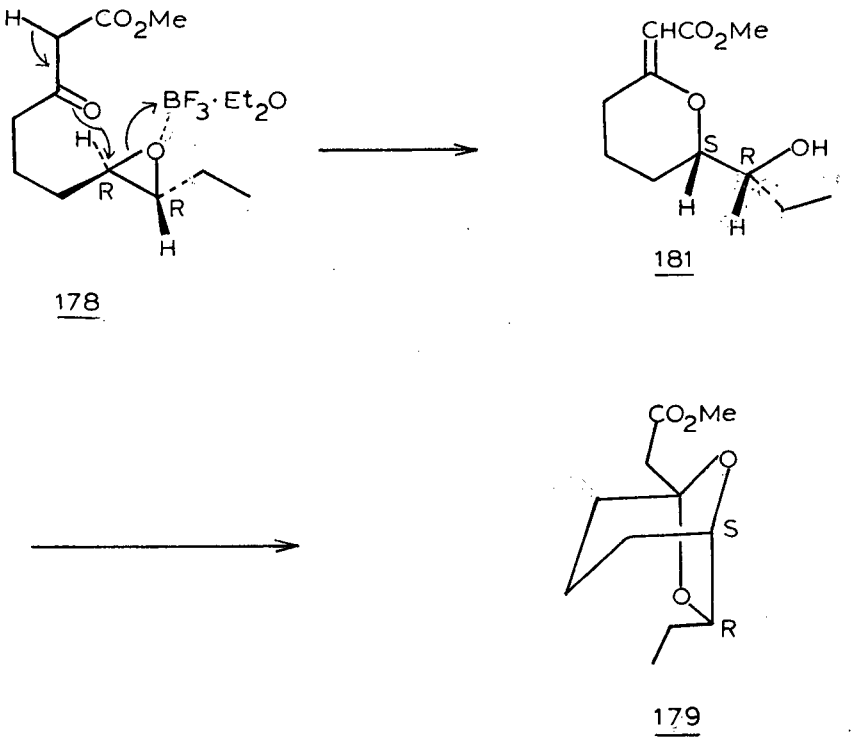


180 16

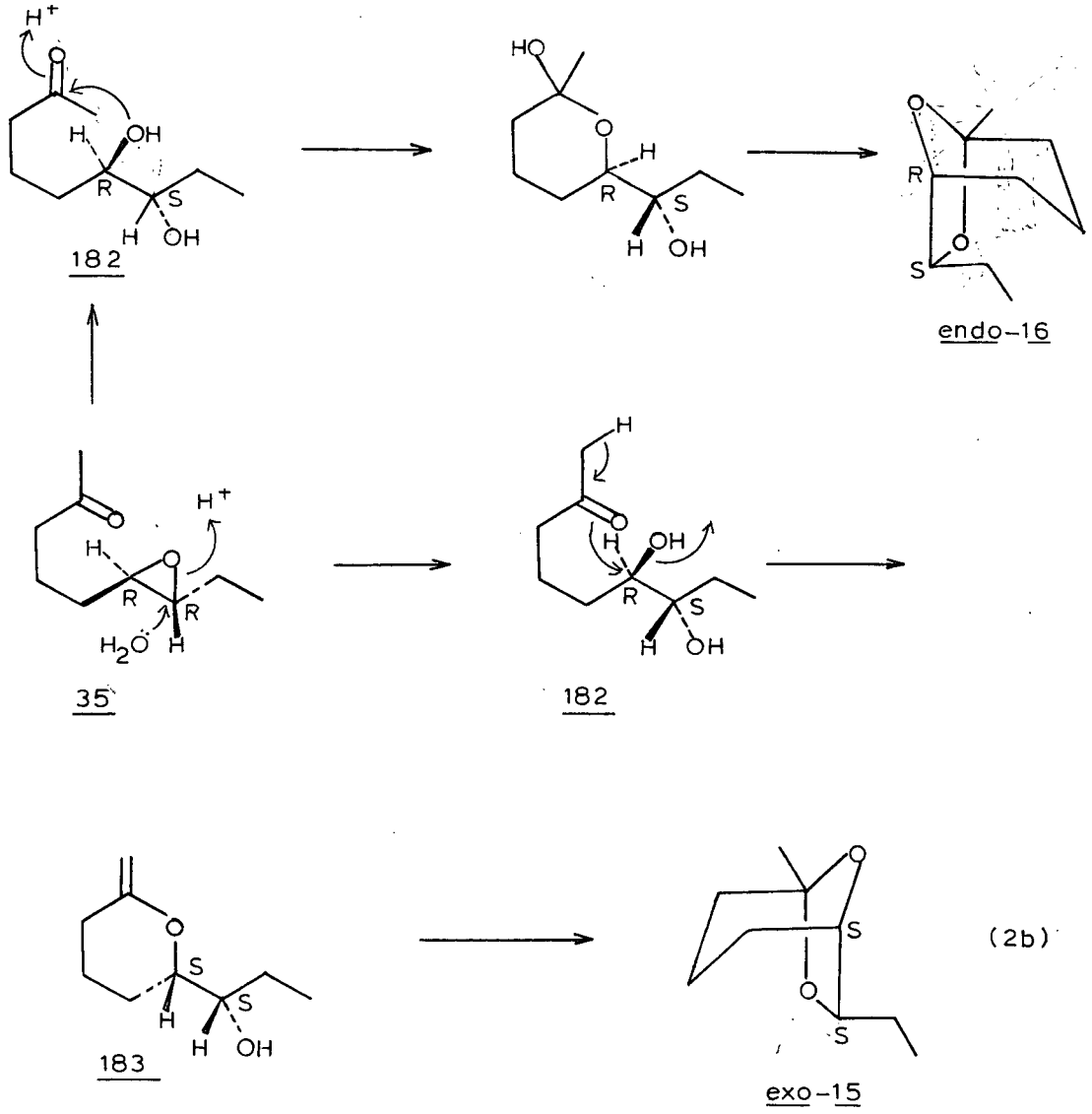
to afford the corresponding epoxide 178 which was cyclized to 179 in 91% yield. We could not detect from the NMR any exo isomer of 179 in this cyclization. GLC analysis of the cyclized product showed that it contained greater than 99% of the endo isomer 179. A number of the earlier syntheses of endo- and exo-brevicomin involved a thermal, Lewis acid or protic acid catalyzed cyclization of keto epoxides to generate the 6,8-dioxabicyclo[3.2.1]octane skeleton[23,31,32,48,50] (see Introduction). Our approach represents the first example of a Lewis acid-catalyzed cyclization of a β-keto ester epoxide.

The high stereospecificity in the cyclization of β-keto ester epoxide 178 is believed to arise from the anhydrous condition of the reaction and the significantly higher enol content of a β-keto ester relative to a simple ketone. It is apparent from the observed results that during the cyclization, the keto group of the β-keto ester attacked the epoxide which underwent oxirane ring opening with inversion of configuration to give 181 as shown in Scheme XXXIV. Most of the reported syntheses based on keto epoxides involved aqueous and catalyzed cyclizations in which two reaction mechanisms were possible. The fact that the trans epoxide 35 gave predominantly the endo isomer 16 indicated that the reaction probably proceeded via a mechanism (equation 2a) which involved initial opening of the epoxide 35

Scheme XXXIV. Mechanism for the Cyclization of Methyl-(E)-7,8-epoxy-3-oxodecanoate (178).



to yield diol 182. Attack of a hydroxy group of the diol on the ketone to form a six-membered ring hemiketal, followed by a second cyclization furnished endo-brevicomin (16). Presence of the exo isomer 15 obviously resulted from the second mechanism (equation 2b). Attack of the ketone on a hydroxy group of the diol in 182 led to the cyclic enol ether 183 which then cyclized to exo-brevicomin (15).

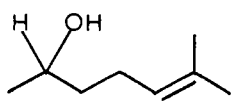


Ester 179 was converted into endo-brevicomin (16) by hydrolysis to the acid 180 (95%) and thermal decarboxylation (85%) as described above. There was no detectable epimerization during the thermal decarboxylation which is consistent with the mechanism proposed in equation 1.

The synthesis of exo-brevicomin (15) was carried out as shown in Scheme XXXV. (Z)-2-hexen-1-ol (184) was prepared by hydrogenation of the acetylene 174 using palladium on barium sulfate as a catalyst and quinoline as a poison.[66] Conversion of the alcohol 184 into the corresponding bromide 185 was effected by phosphorus tribromide and pyridine. Alkylation of the dianion of methyl acetoacetate with bromide 185 gave 186, which was epoxidized to afford 187. This cis epoxide was converted into exo-brevicomin (15) via the ester 188 and the acid 189, employing a similar reaction sequence as described in Scheme XXXIII.

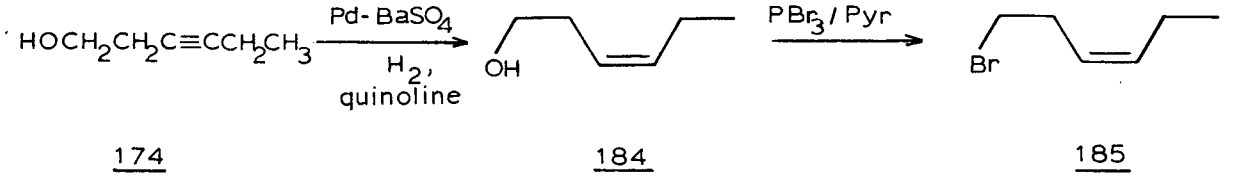
The overall yield of 15 from methyl acetoacetate and (Z)-1-bromo-3-hexene (185) was ca. 85%. In addition to the overall efficiency and high stereospecificity of this route, the carboxylic acid function in compounds 165, 180 and 189 provides a useful handle for the resolution of these intermediates, facilitating the synthesis of both enantiomers of frontalin (17), endo-brevicomin (16) and exo-brevicomin (15).

Comparison of the biological activity of a racemic mixture relative to that of the individual enantiomers can sometimes provide fascinating insight into the insect's receptor site(s).[67,68] For example, it was found that response was greater to racemic sulcatol (190) than to a mixture (65:35) of

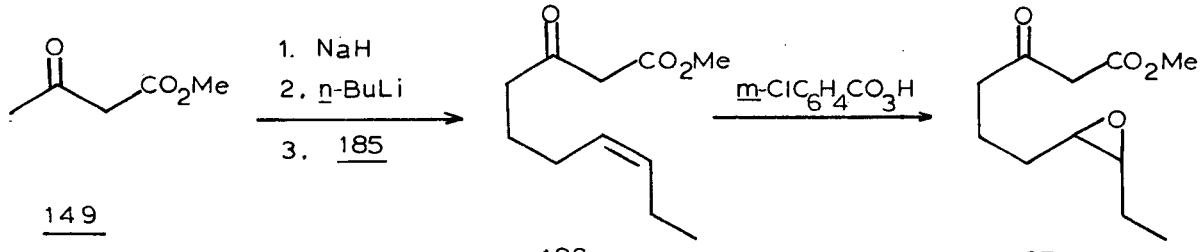


190

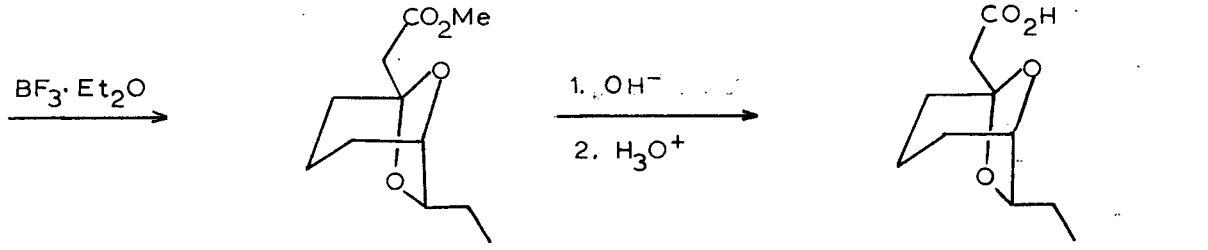
Scheme XXXV. Synthesis of exo-Brevicomin (15)



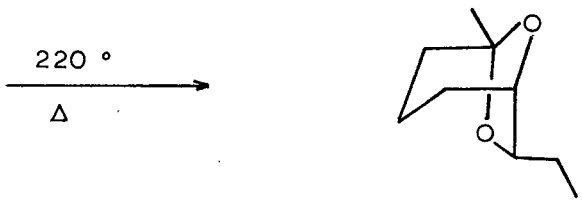
174 184 185



149 186 187



188 189

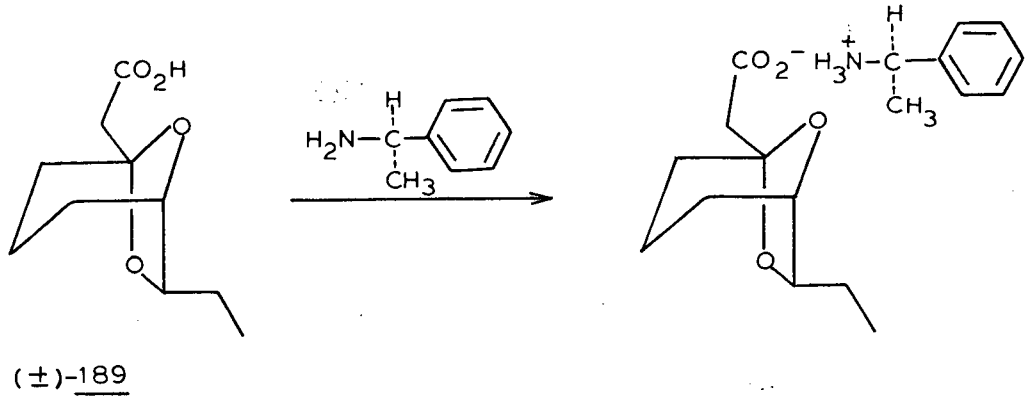


15

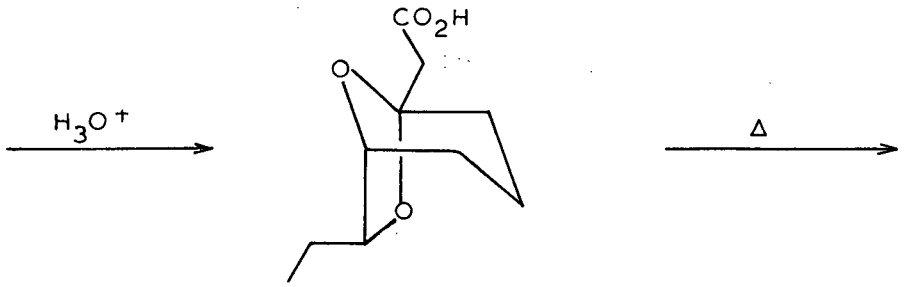
(+)-(S) and (-)-(R) enantiomers, the naturally occurring isomeric ratio.[68]

Since both enantiomers of a pheromone are usually needed for biological testing, a common synthesis leading to both isomers would be most convenient. This can be achieved by resolving a racemic intermediate at a late stage of the synthesis. Although a number of syntheses of optically active exo-brevicomin[42,44] and frontalin[46,47,69] have been reported, the synthesis of these compounds via the resolution approach is so far severely limited by the lack of a useful handle in the common synthetic intermediates that would allow resolution. To our knowledge, the synthesis of (+)-exo-brevicomin (15) by the resolution of an intermediate has not been recorded. Thus we investigated the possibility of resolving the carboxylic acid 189. We chose to resolve 189 via formation of the α-methylbenzylammonium salts (Scheme XXXVI) since both enantiomers of this resolving agent are readily available.[70,71] Two recrystallizations of the (+)-α-methylbenzylammonium salt of 189 gave a 40% yield of a salt (mp 110-115° C). This salt was hydrolyzed in aqueous acid to liberate the free acid which was then thermally decarboxylated to yield an optically active exo-brevicomin (15), $[\alpha]_D^{25}$ + 51.8° (c = 0.12 g/mL, Et_2O). In comparison with the reported $[\alpha]_D^{26}$ + 81.1 °(c = 2.2, Et_2O)[42] for (+)-exo-brevicomin (15), the observed rotation of the resolved material indicated a maximum of 62% resolution of 15.

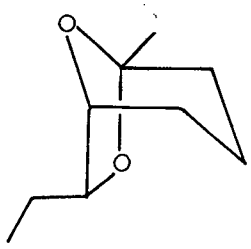
Scheme XXXVI. Resolution of Carboxylic Acid 189.



(±)-189



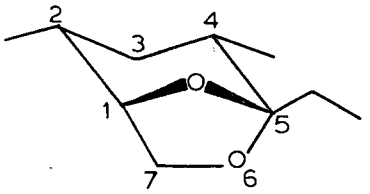
(+)-189



(+)-15

(ii) Synthesis of (-)-α-Multistriatin

Despite the intense studies conducted on multistriatin (18),[26] an efficient and stereoselective route to the pure natural compound has not been achieved. Owing to the biological activity of this compound and the ecological advantages of its use in insect control, a synthesis which would provide convenient access to the natural (-)-α-multistriatin seems necessary. In continuation of our work on exo-brevicomin (15), endo-brevicomin (16) and frontalin (17), we accomplished a stereoselective synthesis of (-)-α-multistriatin (-)-(18α) with the relative and absolute configuration as shown below.

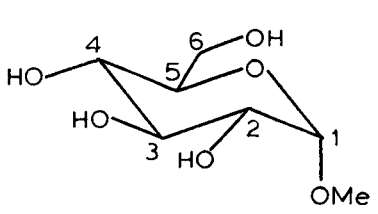


(-)-(1S, 2R, 4S, 5R)-18α

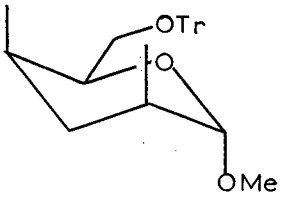
Since chemoreceptors are often capable of distinguishing enantiomeric substrates, the biological activities of pheromones may be affected by the optical purity of these compounds. To study the biological activity of the enantiomers of a pheromone requires access to optically pure forms of such material. The traditional approach to enantiomerically pure compounds by resolving racemic intermediates is not always feasible. Use of an appropriate chiral starting material in an asymmetric synthesis

would avoid the sometimes tedious resolution procedures. For this purpose, carbohydrates that are cheap, readily available, and optically pure provide a useful source of starting materials for the stereospecific synthesis of many optically pure, non-carbobydrate natural products.

A brief examination of the α-multistriatin (18α) molecule reveals that the bicyclic ketal skeleton could be prepared from a sugar moiety. After searching through the readily available sugars, we found methyl α-D-glucopyranoside (71) to be a suitable starting material for two reasons. First, it has the desired absolute configuration at C-5, and secondly, it already contains most of the desired carbon skeleton. In our synthetic plan, the asymmetric centre at C-5 is retained throughout the entire synthesis. Three synthetic objectives are apparent in



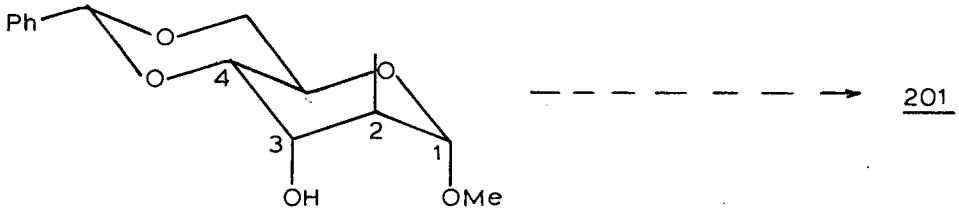
71



201

18α

the transformation of 71 into α-multistriatin (18α), viz., (a) to introduce the two methyl groups at C-2 and C-4 with the correct stereochemistry, (b) to remove the three hydroxyl groups at C-2, C-3, and C-4, and (c) to introduce the ethyl side chain at C-1. To achieve goals (a) and (b) we decided to proceed via the known compound 195 which already had the methyl

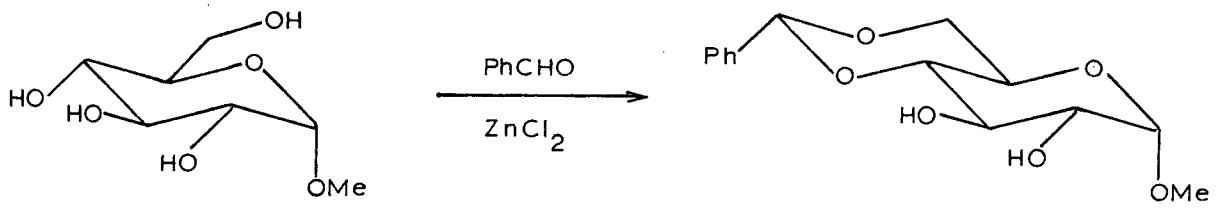


195

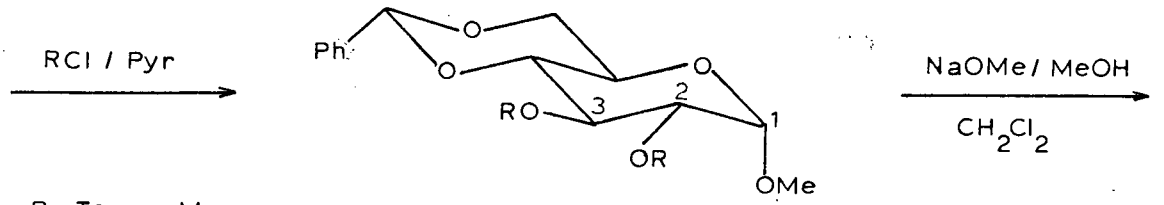
group at C-2 with the desired stereochemistry.

The preparation of compound 195 is shown in Scheme XXXVII. Methyl α-D-glucopyranoside (71) was first protected as its benzylidene derivative 191 which was subsequently converted into the ditosyl compound 192 by treatment with excess p-toluenesulfonyl chloride in anhydrous pyridine for 7 days at room temperature. Treatment of 192 with sodium methoxide in dichloromethane afforded the epoxy compound 194.[73] The mechanism of this reaction has been suggested to involve displacement of the C-3 sulfonyloxy group by backside attack of the adjacent oxide anion, leading to inversion of configuration at C-3.[75] It has also been

Scheme XXXVII. Preparation of Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methyl-α-D-altropyranoside (195)[73,74]

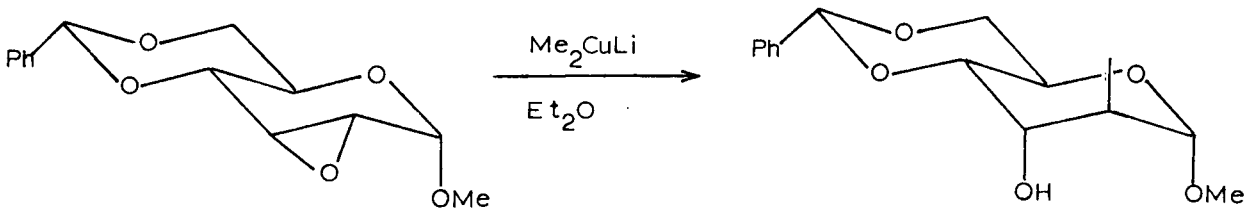


71 191

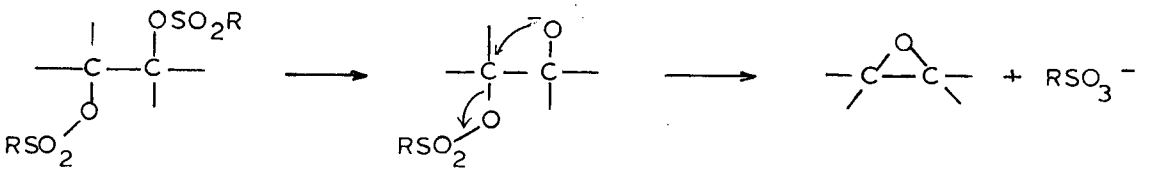


192 R = Ts

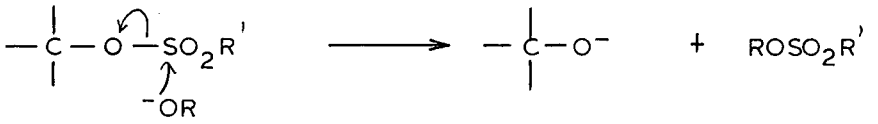
193 R = Ms



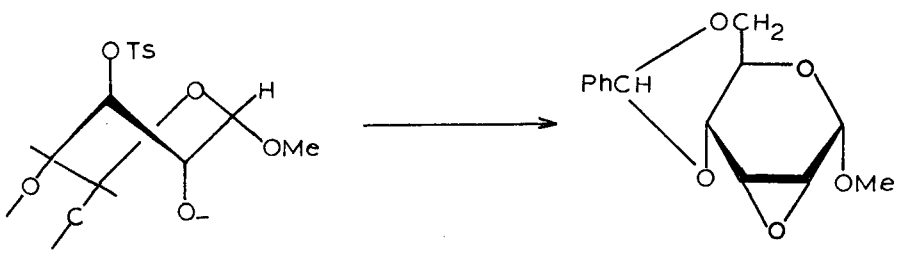
194 195



suggested that the ease of hydrolysis of the C-2 tosylate was due to the inductive effect of the adjacent sulfonyloxy group.[76]



The formation of the epoxy compound 194 is believed to go through a skew conformation in the transition state which would facilitate an S_N2 displacement of the tosylate at C-3 by the adjacent oxide anion.

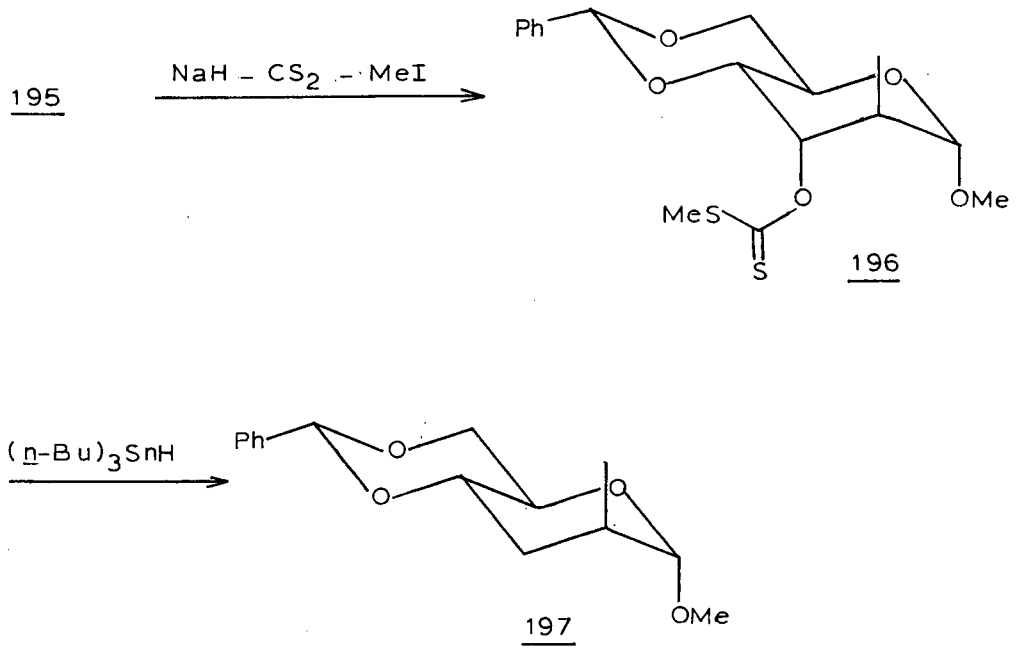


194

An alternate way to synthesize the epoxide 194 via dimesylate 193 was also developed. Treatment of 191 with methanesulfonyl chloride in pyridine for 24 h at room temperature gave the dimesylate 193 in 81% yield. Conversion of the dimesylate 193 into the epoxide 194 was effected in 91% yield by treating 193, with sodium hydroxide in dichloromethane at 0° C for 3 days and then at room temperature for 10 h. The dimesylate route appeared to be more efficient than the ditosylate method described earlier.

Reaction of the epoxide 194 with lithium dimethylcuprate in ether at 0° C, afforded 195[74] in 75% yield. The attack of the lithium dimethylcuprate reagent at C-2 instead of C-3 could be explained by stereoelectronic considerations. Presumably, this reaction involved a trans diaxial opening of the epoxide, which could only be achieved by a nucleophilic attack at C-2. Deoxygenation of the C-3 hydroxyl group in 195 was accomplished using the method reported by Barton and McCombie.[77] As shown in Scheme XXXVIII, the alcohol 195 was first converted into the xanthate ester 196 by treatment with one equivalent of sodium hydride followed by excess amounts of carbon disulfide and iodomethane. The xanthate ester 196 was then heated under reflux with an excess of tri-n-butyltin (IV) hydride[78] in toluene to yield the deoxygenated product 197, the structure of which was corroborated by spectral evidence. It was suggested by Barton and McCombie[77] that the reduction of the thiocarbonate

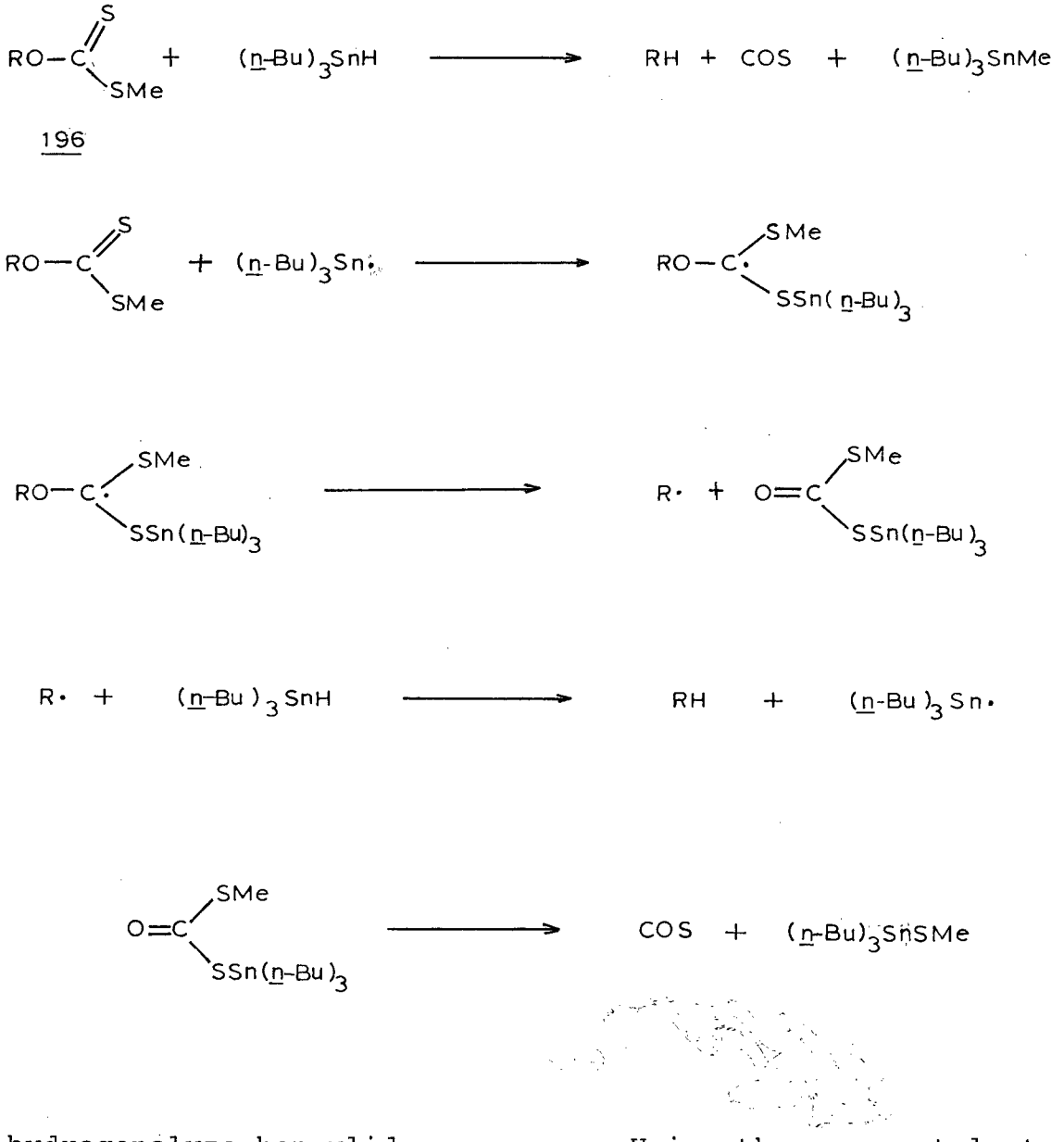
Scheme XXXVIII. Deoxygenation of 195



compound by tri-n-butyltin (IV) hydride involves a free radical mechanism, as described in Scheme XXXIX.

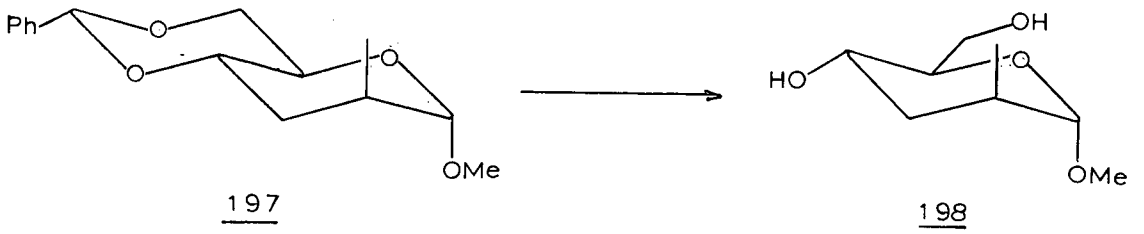
The next step in the synthetic scheme was to remove the benzylidene protecting group and selectively protect the primary alcohol. Subsequent conversion of the hydroxyl group at C-4 into a leaving group and displacement with lithium dimethylcuprate or methylmagnesium halide would lead to the desired intermediate 201 (Scheme XL). Several methods for the removal of the benzylidene group were attempted. Hanessian and Lavallee[79] reported a procedure using hydrogen and a $Pd(OH)_2/C$ catalyst

Scheme XXXIX. Proposed Mechanism for Deoxygenation of 196 with Tri-n-butyltin (IV) hydride[77]

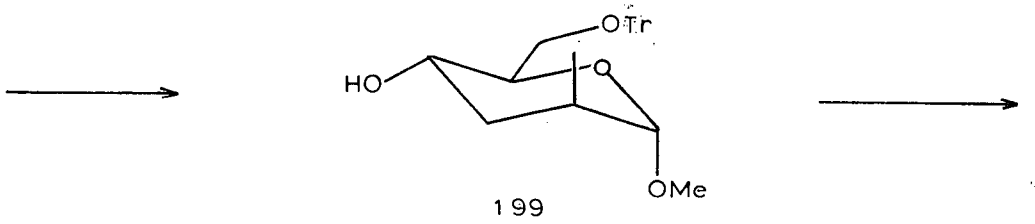


to hydrogenolyze benzylidene groups. Using the same catalyst, we were unable to hydrogenolyze compound 197. Only starting material was recovered. Similarly, no reactions were observed when other catalysts such as Pd/C and Pt/C were used. The

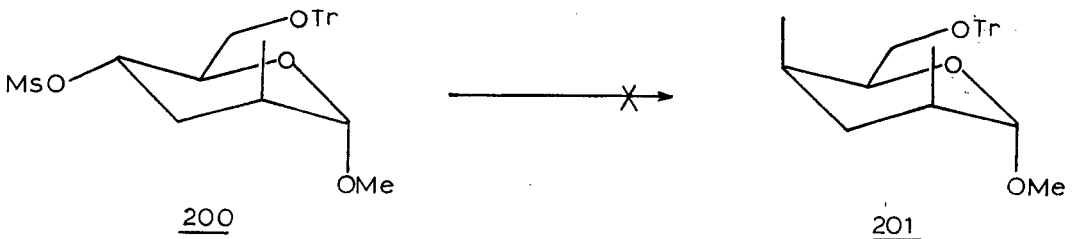
Scheme XL. Attempted Preparation of Compound 201



197 198



199

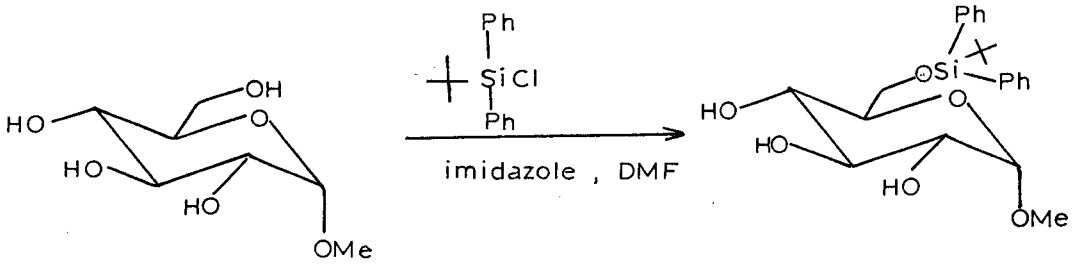


200 201

failure of these reactions could be due to the presence of trace amounts of tin-sulfur by-products derived from the previous stannane reduction. Although purification of compound 197 could be achieved by column chromatography, we found the product isolated from the column was still contaminated with trace amounts of by-products which could be detected easily from the characteristic stench of these by-products. The purified 197 was shown to be homogeneous by spectral and TLC analyses. It was decided at this point to investigate other procedures to cleave the benzylidene group. We found that treatment of compound 197 with a catalytic amount of p-toluenesulfonic acid in methanol at room temperature cleanly gave the desired product 198. If the reaction was worked up carefully as described below, no purification was necessary for 198. The reaction mixture was neutralized with sodium carbonate and the concentrated under reduced pressure. The residue was partitioned between ether and water to get rid of organic impurities. Pure 198 was isolated from the aqueous phase as a colorless syrup in good yield. Compound 198 was readily identified from its spectral data. The IR spectrum showed absorptions for the hydroxyl groups at 3500 and 3650 cm^{-1} and no aromatic protons were observed in the NMR spectrum. The molecular formula was confirmed by mass spectroscopy.

Several reagents are known for the selective protection of the primary hydroxyl group in 198. For example, Hanessian

and Lavallee[80] used tert-butyldiphenylchlorosilane which preferentially silylated primary hydroxyl groups in the presence of secondary ones as indicated by the following example. Treatment of methyl α-D-glucopyranoside (71) with 1.1 equivalents of tert-butyldiphenylchlorosilane in N,N-dimethylformamide containing 2.2 equivalents of imidazole afforded 203 in 70-80% yield. However, we decided to use triphenylchloromethane[81]

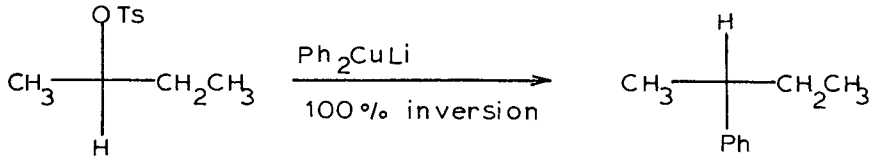


71 203

instead of tert-butyldiphenylchlorosilane for two reasons. First, the former reagent is cheaper and was found to give high yields of 199, and secondly, a leaving group such as a mesylate could be introduced at C-4 without isolating the trityl intermediate 199. This was done in the following manner. The diol 198 was first treated with triphenylchloromethane in anhydrous pyridine at room temperature for 48 h. Without isolating the product 199, more pyridine was added and the mixture was treated with methanesulfonyl chloride to give compound 200 in good yield. Mesylate 200 was identified by its NMR spectrum which showed an absorption at δ 2.8 characteristic of the three

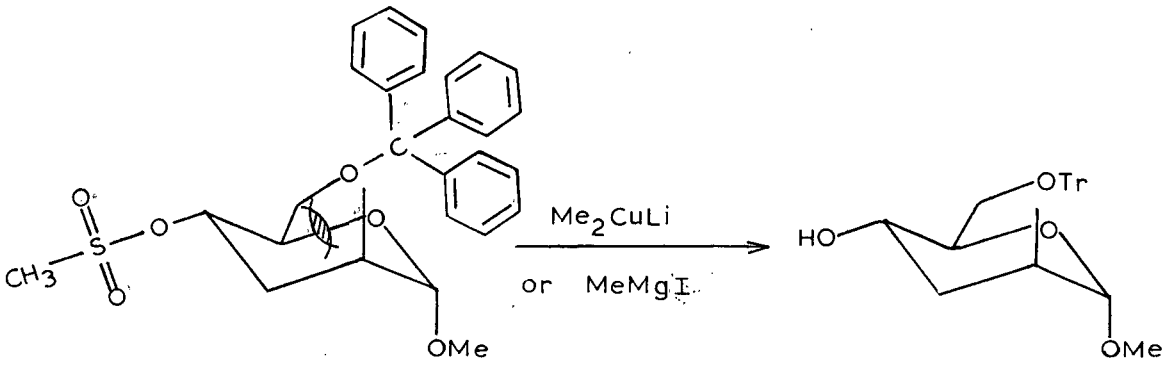
protons on the mesyl group, and low field absorptions at δ 7.0-7.6 attributable to the fifteen protons of the trityl protecting group.

Several attempts were made to displace the 0-mesylate at C-4. Johnson and Dutra[82] developed a procedure in which the alkyl group of a lithium diorganocuprate displaced a tosylate with 100% inversion of configuration. For example, when (+)-2-butyl tosylate (204) was allowed to react with a solution of lithium diphenylcuprate, the product was (-)-2-phenylbutane (205). When compound 200 was treated with lithium dimethyl-

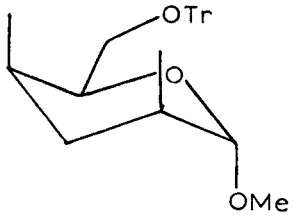


204 205

cuprate, we obtained the alcohol 199 instead of the desired displacement product. A similar result was observed when methylmagnesium iodide was used. Presumably, the 1,3-diaxial interaction arising from the C-2 methyl group and the approaching organometallic reagent prohibited these reagents from approaching the top of the molecule to achieve an S_N2 displacement reaction. Hence, instead of undergoing the desired displacement

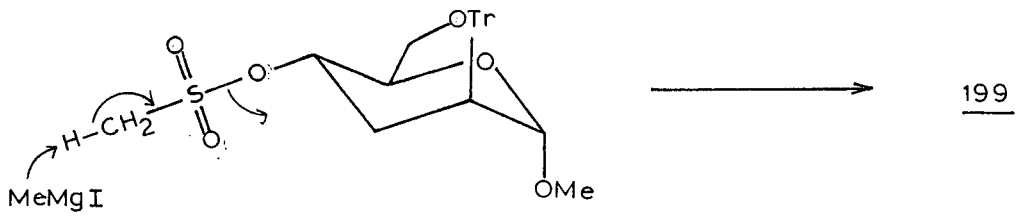


200 199



201

reaction, the cuprate or the methylmagnesium reagent probably abstracted a proton from the mesylate moiety and regenerated alcohol 199 as shown below.



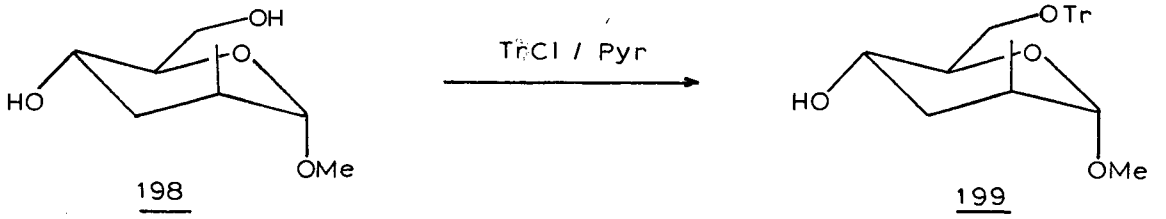
200

Clearly, we had to search for an alternate approach to 201. The preparation of compound 201 was eventually accomplished by the route shown in Scheme XLI. The alcohol 199 was prepared from diol 198 by treatment with 1.5 eq of triphenylchloromethane in anhydrous pyridine.[81] The yield obtained after chromatographic purification was 86%. The IR spectrum of 199 showed an absorption at 3570^{-1} indicating the presence of a hydroxyl group. Presence of the trityl group was shown by absorptions for the aromatic protons at δ 6.7-7.4 (m, 15) in the NMR spectrum.

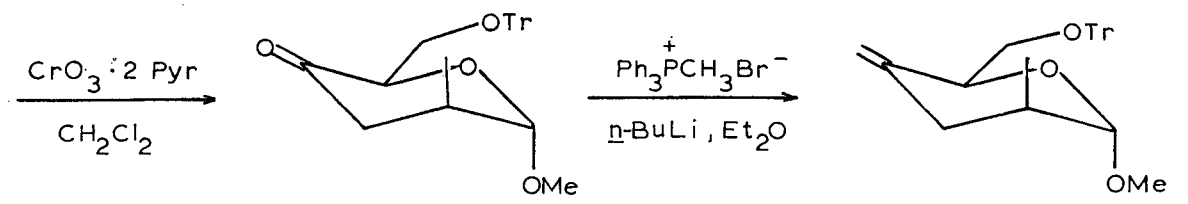
Oxidation of alcohol 199 with chromium trioxide-pyridine complex[83] gave ketone 206 in good yield. A Wittig reaction of ketone 206 with methylenetriphenylphosphorane[84] in etheyl ether afforded 207 in 82% yield. Absence of the carbonyl absorption and appearance of an olefinic absorption at 1660 cm^{-1} in the IR spectrum indicated a successful Wittig reaction. The absorption at δ 4.62 ascribable to terminal vinyl protons in the NMR spectrum of 207 confirmed the presence of the terminal methylene group.

In the next crucial step the axial methyl group at C-4 in 201 was generated by stereoselective hydrogenation of 207 using Wilkinson's catalyst.[85] When this reaction was run at low temperature (0° C or lower) on a 0.065 mmol scale, the stereoselectivity was very high. In fact, we did not detect

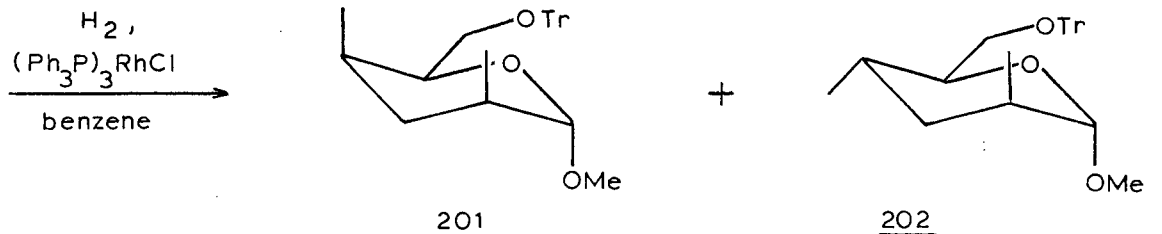
Scheme XLI. Preparation of Compound 201



198 199



206 207

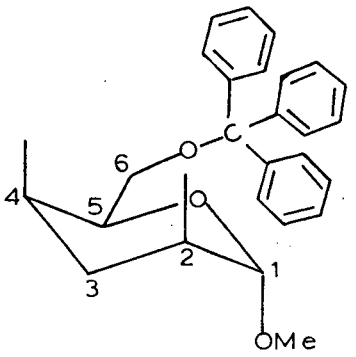


201 202

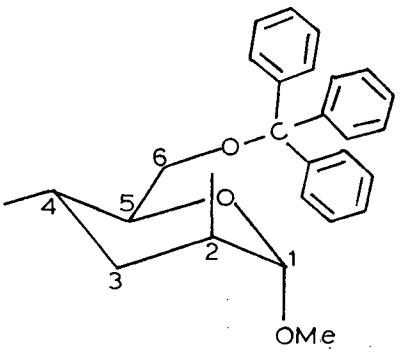
(9 : 1)

any of the C-4 epimer. However, when the same reaction was run at room temperature on larger scales, lower selectivity was observed. Along with the desired compound 201, a small quantity of the C-4 epimer 202 was also obtained. The NMR spectrum of the crude product showed a 9:1 ratio of the two compounds 201 and 202, which could be separated by column chromatography on silica gel. The NMR spectral data of the purified isomers are listed in Table 2. The structure of 201, with an axial methyl group at C-4, was deduced both on mechanistic grounds and from spectroscopic analysis. The one-proton doublet at δ 4.2 assigned to H-1 closely resembled H-1 in 207 both in coupling pattern and chemical shift, indicating retention of the same chair conformation. The lower field absorption (δ 0.70) for the methyl protons at C-4 in 201 than that (δ 0.58) in 202 is probably due to van der Waals deshielding of the 1,3-diaxial methyl groups in 201. The ^{13}C NMR spectrum of 201 also provided evidence for the structural assignments. It has been established that axial methyl groups in cyclohexane rings normally have ^{13}C NMR signals at δ 15-18 whereas the corresponding equatorial methyl groups are usually found at δ 18-25.[86] The ^{13}C NMR spectrum of 201 showed only two signals above δ 30 at 15.93 and 18.30 respectively. This suggested that the methyl groups in 201 are both axial. The predominant formation of 201 is probably due to the steric hindrance caused by the C-2 methyl group and the trityl protecting group on the top face of the molecule

Table 2. NMR Data for Compounds 201 and 202



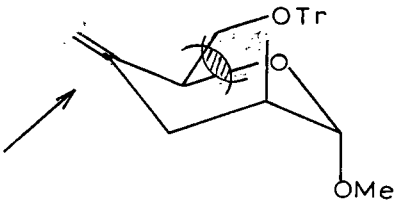
201



202

Compound	201	202
	δ, Chemical shifts in ppm	(TMS, $CDCl_3$)
CH_3 at C-2	0.95 (d, J = 7 Hz, 3H)	1.05 (d, J = 7 Hz, 3H)
CH_3 at C-4	0.70 (d, J = 7 Hz, 3H)	0.58 (d, J = 6 Hz, 3H)
H-1	4.2 (d, J = 5 Hz, 1H)	4.4 (br s, 1H)
OMe at C-1	3.45 (s, 3H)	3.38 (s, 3H)
H-2, H-3, H-4	1.3-2.0 (m, 4H)	1.3-2.0 (m, 4H)
H-5	3.8-4.1 (m, 1H)	2.9-3.6 (m, 3H)
H-6	3.0-3.3 (m, 2H)	
Ph_3	6.9-7.6 (m, 15H)	6.9-7.6 (m, 15H)

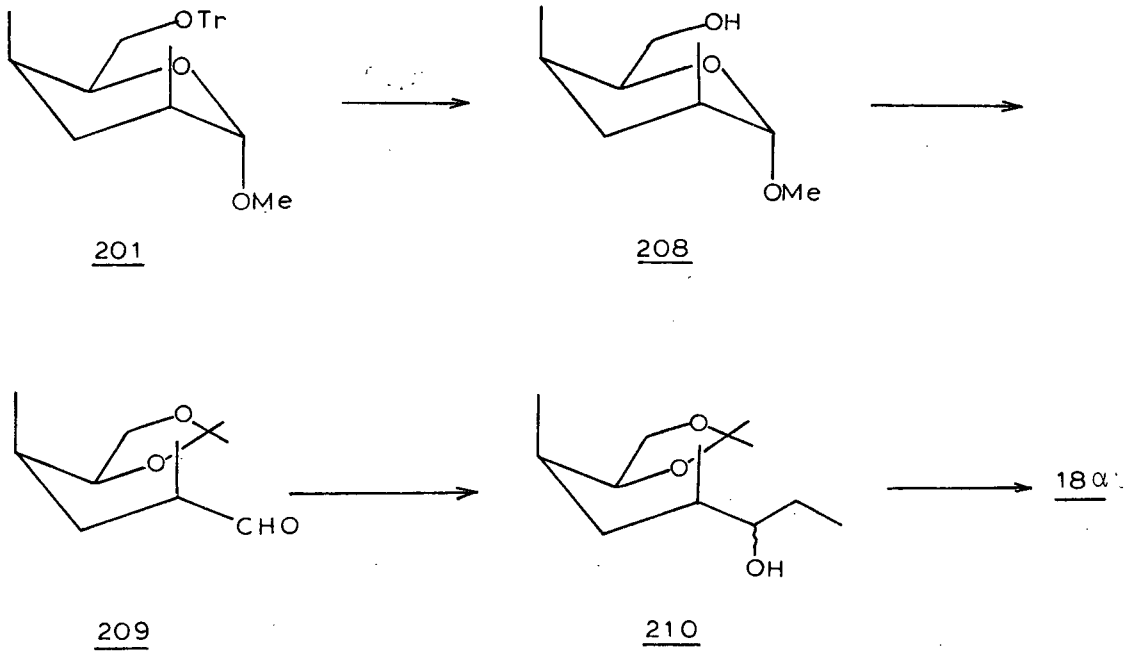
in the favored conformation 207. Hence, hydrogen is preferentially delivered from the bottom face to give the desired 1,3-diaxial compound 201.



207

Introduction of the ethyl side-chain was first planned as shown in Scheme XLII. Hydrolysis of compound 201 would give 208 which could be protected as its isopropylidene derivative 209. The ethyl group could then be introduced via a Grignard reaction affording alcohol 210. Oxidation of 210 to its ketone followed by treatment with acid would lead to the final product 18. However, attempts to hydrolyze the trityl and the methyl ether groups were unsuccessful. When compound 201 was hydrolyzed with a cation exchange resin (Dowex 50 [H^+]), serious difficulties were encountered in the isolation of the water soluble hydrolysis product. Due to this difficulty, we undertook a search for a more efficient route to introduce the ethyl group. We were intrigued by the possibility of applying the method of Corey and Seebach using the alkylation of dithioacetal carbanions to chain extend carbohydrates. In this method,

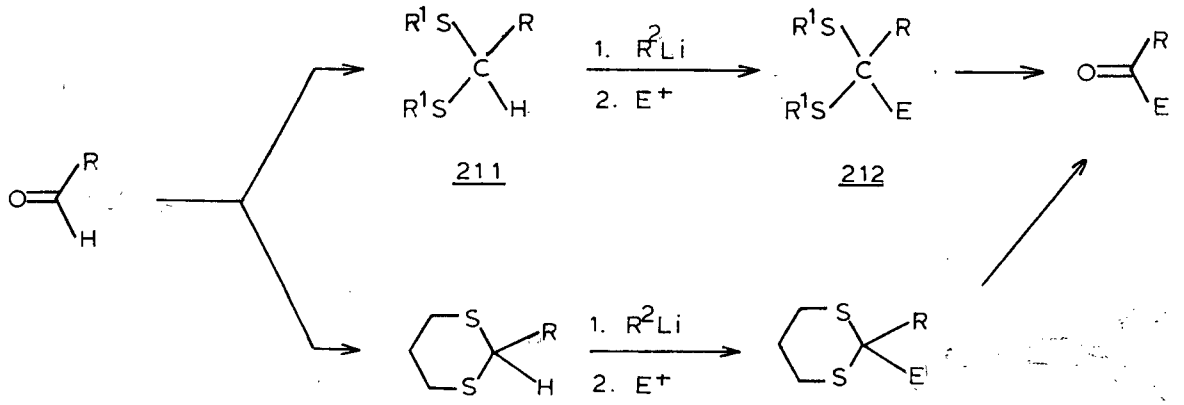
Scheme XLII. A Possible Route to (-)-α-Multistriatin



201 208 209 210

aldehydes were converted into the corresponding thioacetals 211[87,88] or dithiane derivatives 213[88,89] with acid catalysts, (Scheme XLIII). These thioacetals could be deprotonated by

Scheme XLIII. Alkylation of Dithioacetal Carbanions



211 212 213 214

R = alkyl, H

R^1 = CH_3, CH_2CH_3

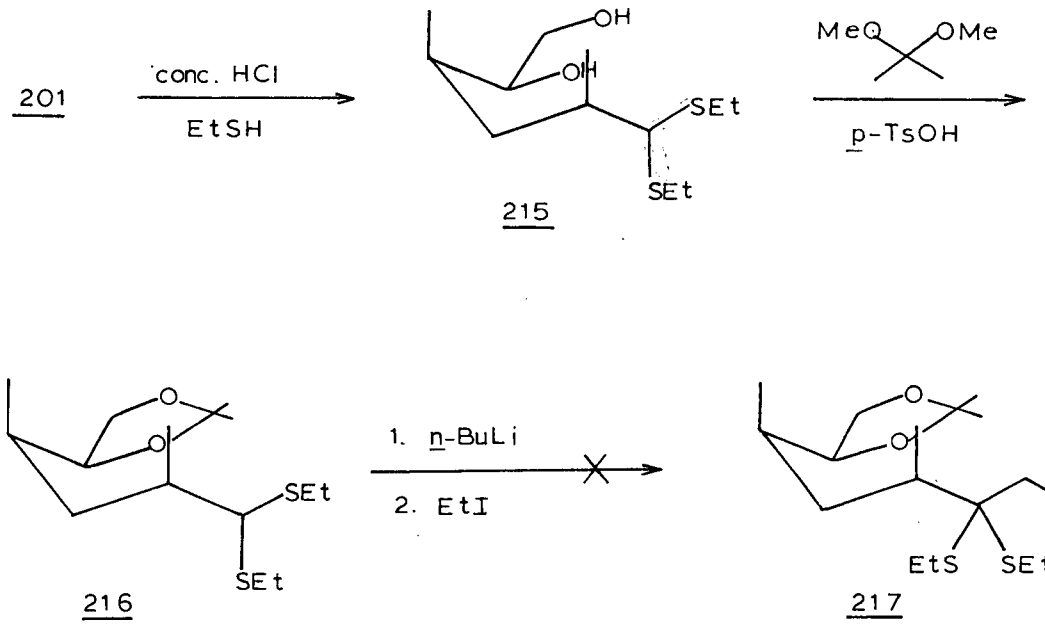
R^2 = alkyl

E = electrophile

alkyllithium reagents to generate the sulfur stabilized carbanions which undergo various reactions with electrophiles to furnish products of type 212 or 214.[90] Since regeneration of the carbonyl function in 212 and 214 can be achieved by mercuric chloride catalyzed hydrolysis, the thioacetal carbanions are equivalent to acyl anions and can be used effectively to reverse the characteristic electrophilicity of a carbonyl carbon. This approach appeared particularly attractive in our synthesis. Two major advantages might arise from adopting the above reactions in our synthetic scheme. First, hydrolysis of the trityl protecting group, liberation of the aldehyde and formation of the thioacetal might all be accomplished in one step. Furthermore, aprotic solvents might be used which would alleviate the water solubility problem encountered before. Secondly, the thioacetal function might facilitate the final cyclization step in our synthetic plan without going through a carbonyl intermediate which could cause epimerization of C-2.

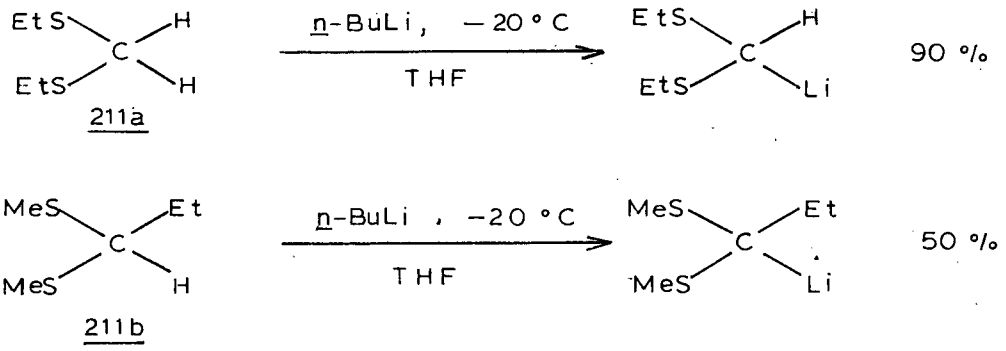
We first investigated the diethyl thioacetal route as shown in Scheme XLIV. Compound 201 was smoothly converted into diethyl thioacetal 215 with concomitant cleavage of the trityl group by treatment with concentrated hydrochloric acid and ethanethiol.[91] The resulting thioacetal diol 215 was then protected as its isopropylidene derivative 216 using a catalytic amount of p-toluenesulfonic acid and 2,2-dimethoxypropane.[92]

Scheme XLIV. Attempted Preparation of Compound 217



Unfortunately, attempts to alkylate the diethyl thioacetal 216 were unsuccessful. The failure of this reaction was found to arise from difficulties in generating the anion of 216. Treatment of 216 with strong bases under various conditions failed to effect carbanion formation. We first investigated the use of n-butyllithium as base. Quenching the mixture with iodoethane gave no detectable amount of the desired product 217. Only starting material was recovered. Different temperatures, reaction times and bases (e.g., tert-butyllithium) were also employed without success. Deuterium oxide quenching experiments invariably showed no significant incorporation of deuterium,

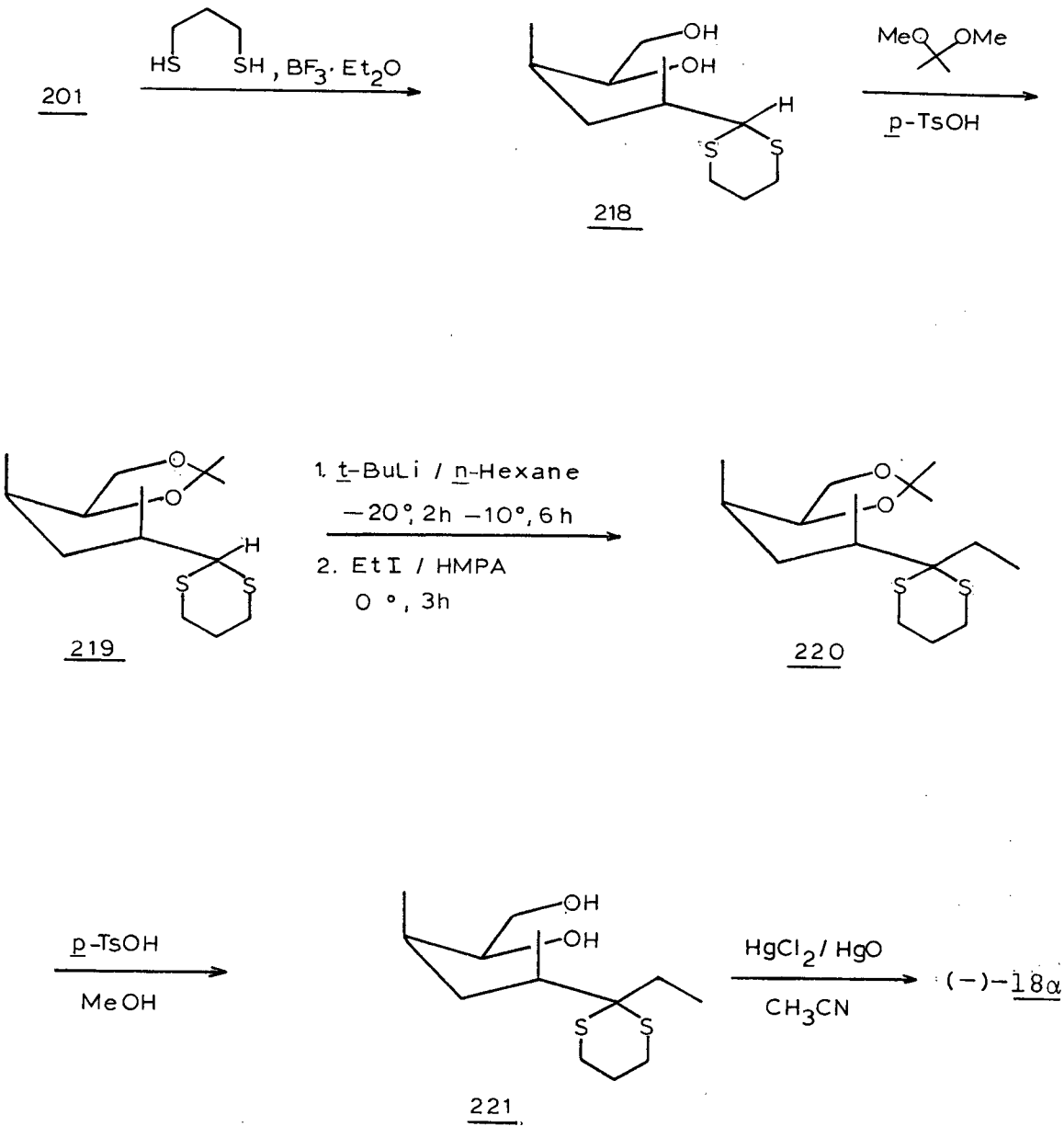
revealing failure in the generation of the sulfur stabilized carbanion. It has been shown that unsubstituted diethyl thioacetal 211a was metallated with n-butyllithium in about 90% yield while under similar conditions the substituted dimethyl thioacetal 211b was only 50% metallated.[88] The reluctance of



216 to form the carbanion was suspected to arise from steric hindrance of the methyl group adjacent to C-2 of the dithioacetal group. In fact, difficulties in alkylating similar α-substituted diethyl thioacetals have also been reported.[88]

Several reports have indicated that the dithiane derivative of aldehydes are less susceptible to the steric effects of an α-substituent in carbanionic alkylation than the corresponding diethyl thioacetals. Indeed, we were able to effect the desired alkylation via the dithiane derivative 219 as shown in Scheme XLV. Compound 201 was treated with 2 equivalents

Scheme XLV. Synthesis of (-)-α-Multistriatin via Alkylation and Cyclization of Dithiane Derivatives



of 1,3-dithiopropane and a catalytic amount of boron trifluoride etherate to give 218 in 80% yield. This diol was then protected as its isopropylidene derivative 219 using the method described above.

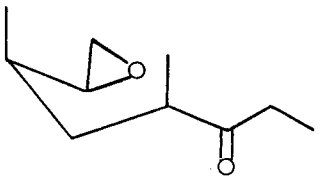
It is known that the ease of metallation of dithiane derivatives varies with the steric and electronic character of the group R in the 2-position of the dithiane compound (Scheme XLIV).[90] For example, metallation of the phenyl derivative - (R = C_6H_5) - occurred within a few minutes, while the tert-butyl derivative - (R = t-Bu) - required about 5 h for complete metallation. An investigation was therefore conducted to develop suitable conditions for the generation of the anion of the dithiane derivative 219. The results obtained were summarized in Table 3. Various bases and solvents were used to deprotonate 219 at different temperatures and for varied periods of time. The extent of anion formation was determined either by D_2O quenching or by iodoethane alkylation. The most satisfactory result was obtained by treating compound 219 with 1.1 equivalents of tert-butyllithium in n-hexane at -20° C for 2 h and then at -10° C for 6 h, followed by the addition of a solution of iodomethane in hexamethylphosphoramide. Progress of the alkylation was monitored by TLC analysis. The occurrence of a white precipitate (presumably lithium iodide) could also be used as an indication of alkylation. The alkylated product 220 was readily

Table 3. Rates of Metallation of Dithiane 219

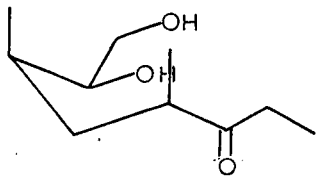
Base-Solvent	Temp °C, Time	% Deuterium incorporated (D.I.) or alkylation (EtI)
n-BuLi-THF	-20 , 10 min; 0 , 1¼ h	0
n-BuLi-THF	-20 , 15 min; 0 , 2 h	45 (D.I.)
n-BuLi-THF	-20 , 15 min; 0 , 4 h	50 (D.I.)
n-BuLi-THF	-20 , 1 h; 0 , 3 3/4 h	40 (alkylated)
tert-BuLi- n-Hexane	-20 , 1 h -10 , 1 h	50 (alkylated)
tert-BuLi- n-Hexane	-20 , 1 h; -10 , 18 h	>90 (alkylated)
tert-BuLi- n-Hexane	-20 , 2 h; -10 , 6 h	>90 (alkylated)

characterized by its NMR spectrum. No absorption corresponding to the methine proton of the dithioacetal was observed. Appearance of a new triplet at δ 0.98 (J = 7 Hz, 3H), ascribable to a primary methyl group confirmed the presence of the ethyl side-chain.

Hydrolysis of 220 with a catalytic amount of p-toluenesulfonic acid in methanol afforded the corresponding diol 221 in 90% yield. Many of the previously reported syntheses of multistriatin (18) involved acid catalyzed cyclization of the epoxy ketone 87 or keto diol 222. These conditions usually result in epimerization of the methyl group adjacent to the carbonyl function. Since hydrolysis of the thioketal 221 to a



87

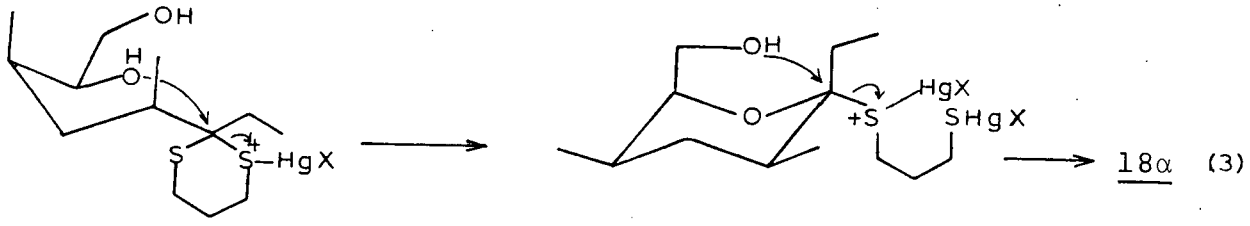


222

ketone under hydrolytic conditions may cause epimerization of the C-2 methyl group, an attempt was made to cleave the thioketal in 221 with concomitant cyclization, without going through the ketone. Mercuric salt catalyzed hydrolysis of thioketal is believed to involve intermediates such as 223.[88] Intra-

223

molecular participation of the diol group during the hydrolysis of 221 should lead directly to α-multistriatin (equation 3).

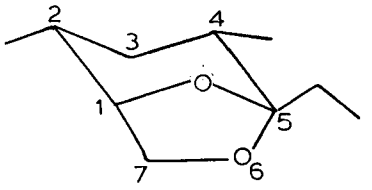


221

Indeed, when 221 was treated with a mixture of mercuric chloride and mercuric oxide in anhydrous acetonitrile,[93,94] the bicyclic ketal 18α was formed in 80% yield. As precautions were taken to exclude water from the reaction mixture, the mechanism shown by equation 3 was presumably involved in this process.

The structure of the final product was confirmed by comparison of its spectral data with those reported for α-multistriatin (18α).[26,95] The NMR spectrum of the synthetic material showed one set of overlapping doublets at δ 0.81 for the methyl groups at C-2 and C-4, identical with that recorded for the α isomer. Absorption patterns of these methyl groups in the diastereomers 18β, 18γ and 18δ are significantly different from the above (see Figure 2). Other NMR signals characteristic of 18α were also present: δ 3.68 (m, 1H) and 3.89 (m, 1H) for the methylene protons on C-7, and δ 4.20 (m, 1H) for the methine proton on C-1. The IR spectrum was identical with that reported

for natural α-multistriatin.[26] That our synthetic product was 18α was further ascertained by a combined GLC analysis with an authentic sample.[(2)] An optical rotation of $[\alpha]_D^{25}$ - 46° (10 mg/mL, hexane) was observed for the synthetic compound, which is in good agreement with the measurement $[\alpha]_D^{25}$ - 47° (1.9 mg/mL, hexane) reported for the natural compound.[26,50]

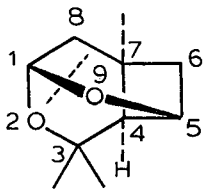


18α

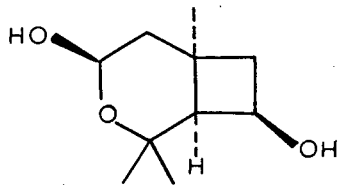
(2) A sample of multistriatin with known composition was obtained from Dr. J. W. Peacock, of the Forest Service, United States Department of Agriculture, Delaware, U.S.A.

(iii) Synthesis of Lineatin (22)

In continuation of our work on the synthesis of cyclic ketal insect pheromones, we also investigated the synthesis of lineatin (22).[29,30] The major synthetic challenge represented



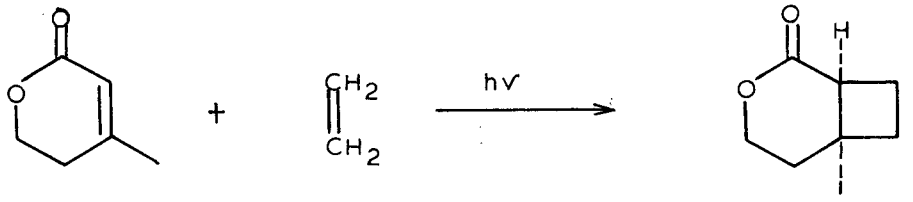
22



224

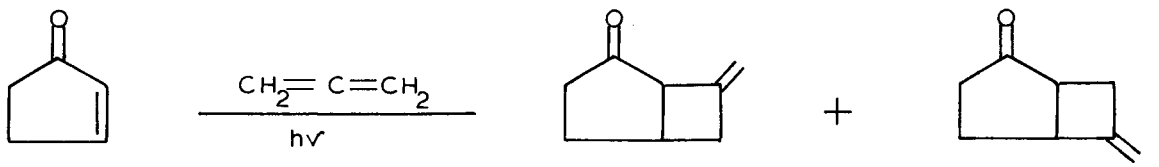
by the lineatin molecule is the construction of the unusual tricyclic acetal skeleton with proper stereochemical control. Antithetic dissection of compound 22 at the C-1, O-9 bond gave the obvious precursor 224. Our approach centred on the synthesis of 224 with reasonable control over stereochemistry.

A convenient way to construct the four-membered ring in 224 is via a [2 + 2] cycloaddition reaction. It has been shown that the photocycloaddition reaction of α,β-unsaturated lactones with olefins gave mainly cis-fused adducts. For example, photocycloaddition of the lactone 119 with ethylene gave the cycloadduct 225.[96] The cycloaddition of α,β-unsaturated ketones or aldehydes with allene has also been reported.[97]

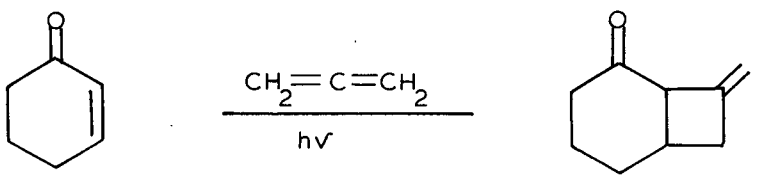


119 225

Addition of 2-cyclopentenone (226) to allene gave a mixture of adducts 227 and 228, with 227 as the major product.[97a] Similarly, irradiation of a mixture of 2-cyclohexenone (229) and allene gave predominantly compound 230.[97b] Ziegler and Kloek[97e]

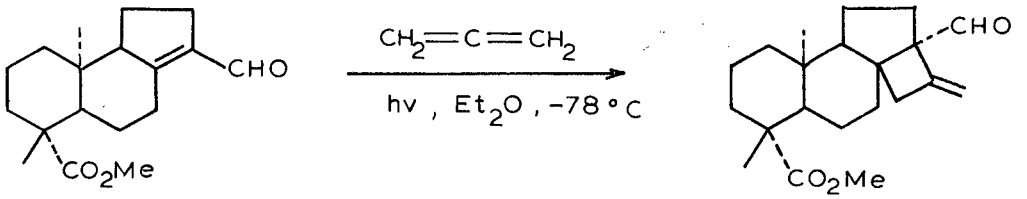


226 227 228



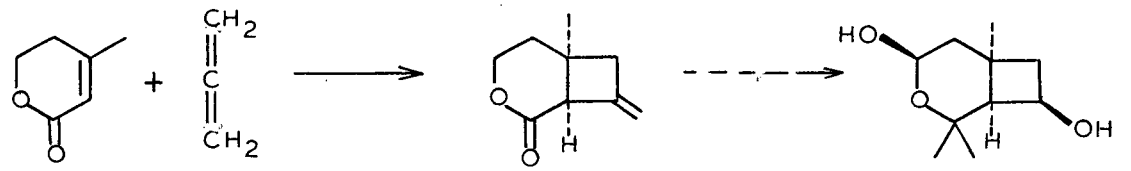
229 230

reported the formation of 232 in 42% yield by irradiating an ether solution of 231 in the presence of allene. Only 3% of an isomer of 232 was isolated. Although both α,β-unsaturated lactones and allenes have been investigated in [2 + 2] cycloaddition reactions,[97] such a reaction of an α,β-unsaturated



231 232

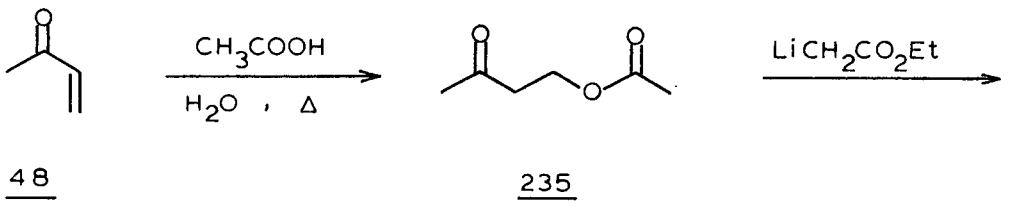
lactone with allene has not been recorded. We chose to adopt this type of photochemical cycloaddition reaction in our synthetic plan because the resulting photoadduct could be readily transformed into the precursor 224.



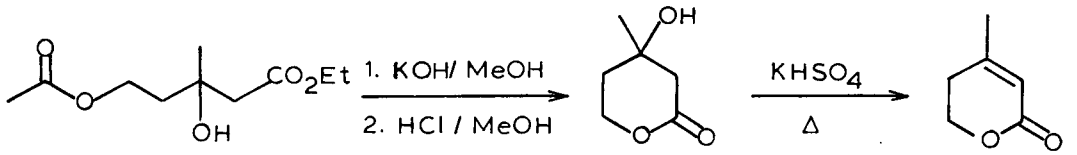
119 224

The preparation of lactone 119 was carried out as shown in Scheme XLVI. 1-Acetoxy-3-butanone (235) was prepared according to the procedure of Cornforth et al.[98] from methyl vinyl ketone 48. Condensation of ethyl lithioacetate with 235 in ether at -78° C afforded 236 in 88% yield.[99] The diester 236 was hydrolyzed in methanolic potassium hydroxide and then cyclized in methanolic hydrochloric acid to give mevalonolactone (237)[98] in good yield. Dehydration of 237 was effected by heating with potassium hydrogen sulfate,[96b] followed by distillation of the product. It was found that the initial distilla-

Scheme XLVI. Synthesis of 3-Methyl-5-hydroxy-2-pentenoic acid δ-lactone (119)

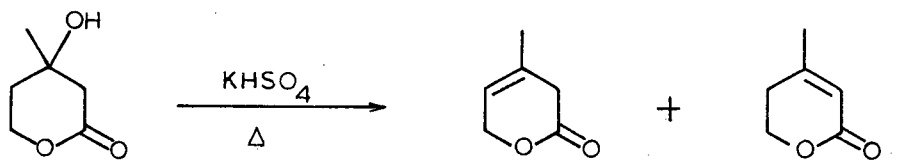


48 235



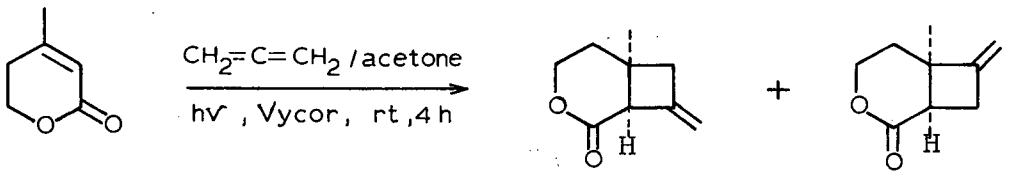
236 237 119

tion product contained a mixture of α,β-unsaturated and β,γ-unsaturated lactones, 119 and 238. By redistillation of this mixture in the presence of potassium hydrogen sulfate at a bath temperature of 190° C, we were able to obtain predominantly the conjugated isomer 119 in 83% yield.



237 238 119

The cycloaddition reaction of lactone 119 with allene was accomplished photochemically. Irradiation of a solution of 119 in acetone at room temperature through a Vycor filter with a moderate rate of introduction of allene gave a mixture of cycloadducts in 80% yield. GLC analysis of the product showed the presence of two barely separable components in a ratio of ca. 5:3. Attempts to separate the mixture were unsuccessful. The IR spectrum of the cycloadduct showed absorptions at 1725 and 1680 cm^{-1}, attributable to the δ-lactone and the terminal double bond respectively. The 270 MHz NMR spectrum had absorptions at δ 4.8-5.2 corresponding to two vinyl protons, and two methyl singlets with different intensities (ca. 5:3) at δ 1.26 and 1.24 respectively. The high resolution mass measurement gave $C_9H_{12}O_2$ as the molecular formula of the product.

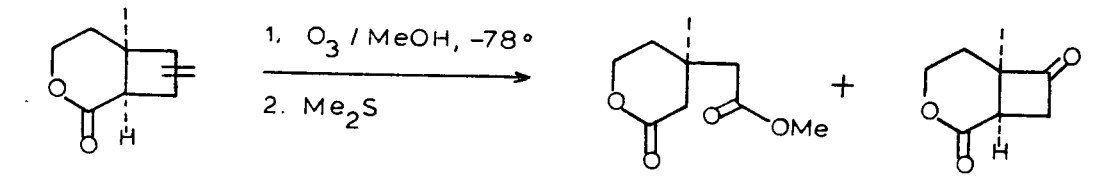


119 233 234

Further evidence for the addition product was obtained from the low resolution mass spectrum and elemental analysis. We were able to assign structures 233 and 234 (5:3) to the two positional isomers in the photoadduct mixture from the results of subsequent

ozonolysis studies described below. The cis ring-fusion in these adducts was ascertained by analogy with the results reported previously on similar photocycloaddition reactions (vide supra). Furthermore, the photoadducts 233 and 234 were not epimerized by base treatment which is in agreement with a cis fused skeleton.

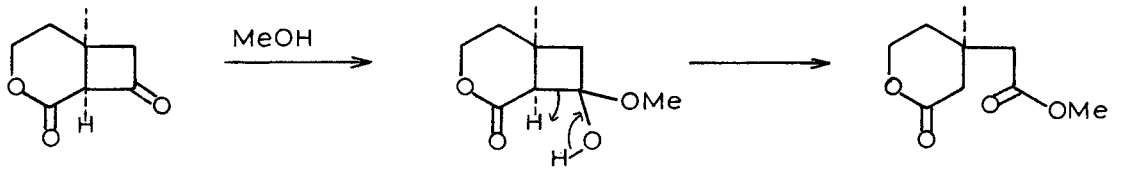
To determine the structures of the photolysis products, we conducted several ozonolysis experiments. When the mixture of photoadducts was ozonized in methanol at -78° C, and worked up with dimethyl sulfide,[100] the NMR spectrum of the crude product showed a mixture of ester 239 and ketone 240 in a ratio of 5:3. Compound 239 was identified by the characteristic absorp-



233 + 234 239 240

tions in its NMR spectrum at δ 3.63 (s, 3H), for the three protons of the methoxy group, and δ 1.18 (s, 3H) for the methyl group. The low resolution mass spectrum showed a parent mass at m/e 186. The IR spectrum had an absorption at 1740 cm^{-1} for the carbonyl group of an ester. The formation of compound 239

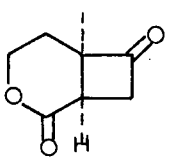
probably arose from nucleophilic attack of methanol on the ketone 241 to give an intermediate 242 which then underwent



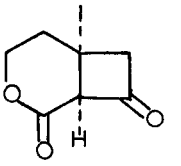
241 242 239

a retro-Dieckmann reaction to produce ester 239. Compound 240 was readily identified by the characteristic IR absorption of the four-membered ring ketone at 1790 cm^{-1}. The structure of 240 was further corroborated by its NMR and mass spectral data. Since 239 was apparently derived from the intermediary ketone 241 which in turn arose from compound 233, and 239 was the major ozonolysis product, the major photoadduct obtained above must be 233.

Ozonolysis of the photoadducts 233 and 234 in dichloromethane containing 1 eq of methanol gave a mixture of 240 and 241 in a ratio of 3:5 according to NMR analysis. Compound 241 was identified by the three proton singlet at δ 1.53 for the angular methyl group in its NMR spectrum and by its IR absorptions at 1720 (δ-lactone) and 1790 cm^{-1} (four-membered ring ketone). The NMR spectrum of compound 240 had a three proton



240

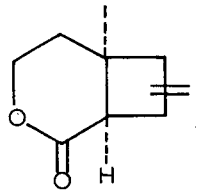
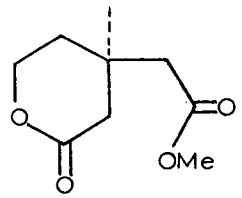
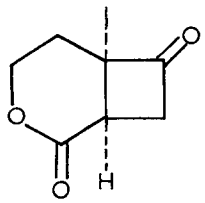
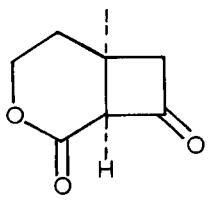


241

singlet at δ 1.33 due to the angular methyl group and the IR spectrum showed the cyclobutanone absorption at 1790 cm^{-1}. Attempts to separate the mixture 240 and 241 by TLC were unsuccessful. Only compound 240 was isolated and compound 241 seemed to decompose upon chromatography. A similar mixture of 240 and 241 was obtained when the ozonolysis was carried out in dichloromethane in the absence of methanol. From the above results, it was clear that the photochemical cycloaddition gave a mixture of adducts 233 and 234 in a ratio of 5:3. The characteristic absorptions in the IR and NMR spectra of compounds 233, 234, 239, 240, and 241 are summarized in Table 4.

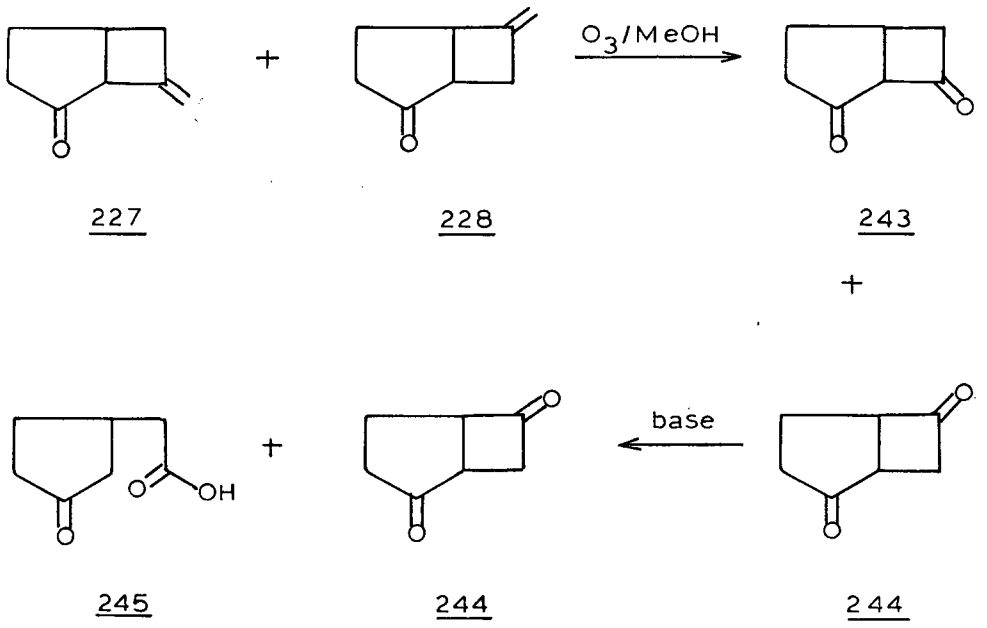
Eaton[97a] has reported an example of cycloaddition reaction of allene with an α,β-unsaturated ketone which led to two regioisomers. The structures of the regioisomers 227 and 228 were also determined by ozonolysis of the photoadducts. Treatment of the ozonolysis products with base produced a mixture of 244 and 245. Of the ozonolysis products 243 and 244, only 243 would be expected to undergo retro-Dieckmann ring opening to

Table 4. Some Characteristic IR and NMR Absorptions for 233+234, 239, 240 and 241.

	NMR (δ)	IR (cm^{-1})
 233 + 234	1.31 (CH_3)	1725 (δ-lactone)
 239	1.18 (CH_3) 3.63 (OCH_3)	1720 (δ-lactone) 1740 (ester)
 240	1.33 (CH_3)	1720 (δ-lactone) 1790 (C=O, cyclobutanone)
 241	1.53 (CH_3)	1720 (δ-lactone) 1790 (C=O, cyclobutanone)

give 245 (Scheme XLVII).

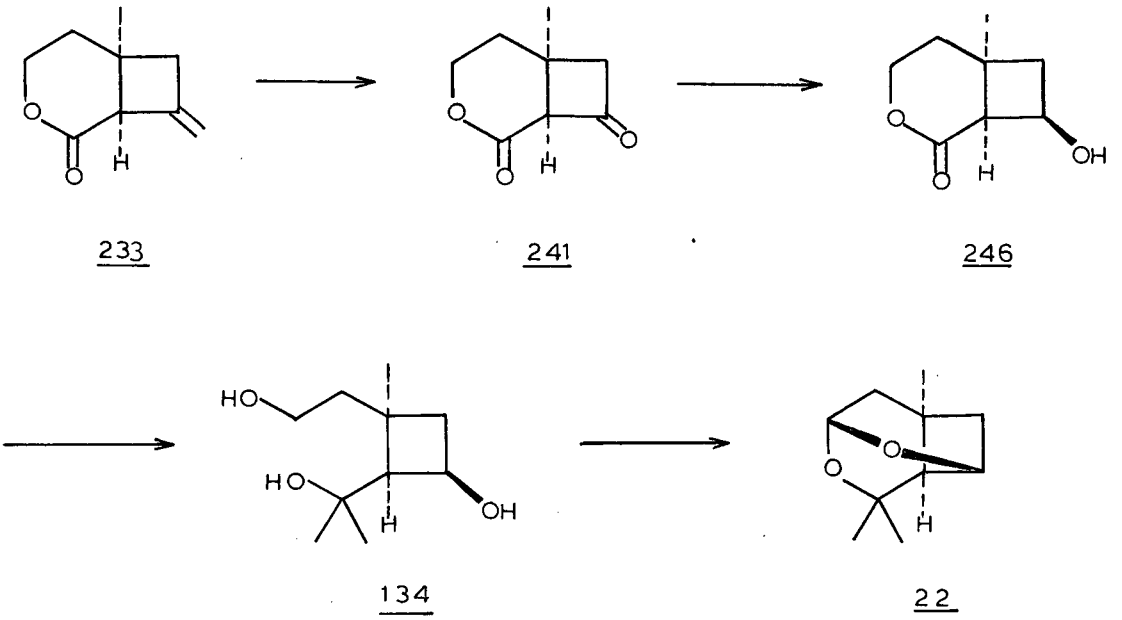
Scheme XLVII. Ozonolysis of Compounds 227 and 228[96a]



227 228 243 + 245 244 244

Our initial synthetic strategy, as depicted in Scheme XLVIII, involved ozonolysis of the photoadduct 233 to give 241 which could be selectively reduced to hydroxy lactone 246. Subsequent reaction of 246 with methyllithium, followed by oxidation of the primary alcohol in the resulting triol 134 with concomitant intramolecular acetal formation would hopefully give the desired tricyclic compound 22. Although this route appeared attractive in terms of number of reaction steps, it was abandoned due to the lability of the β-keto lactone moiety in 241 and the difficulties encountered in the isolation of 241.

Scheme XLVIII. A Possible Route to Lineatin (22) via Ozonolysis of 233



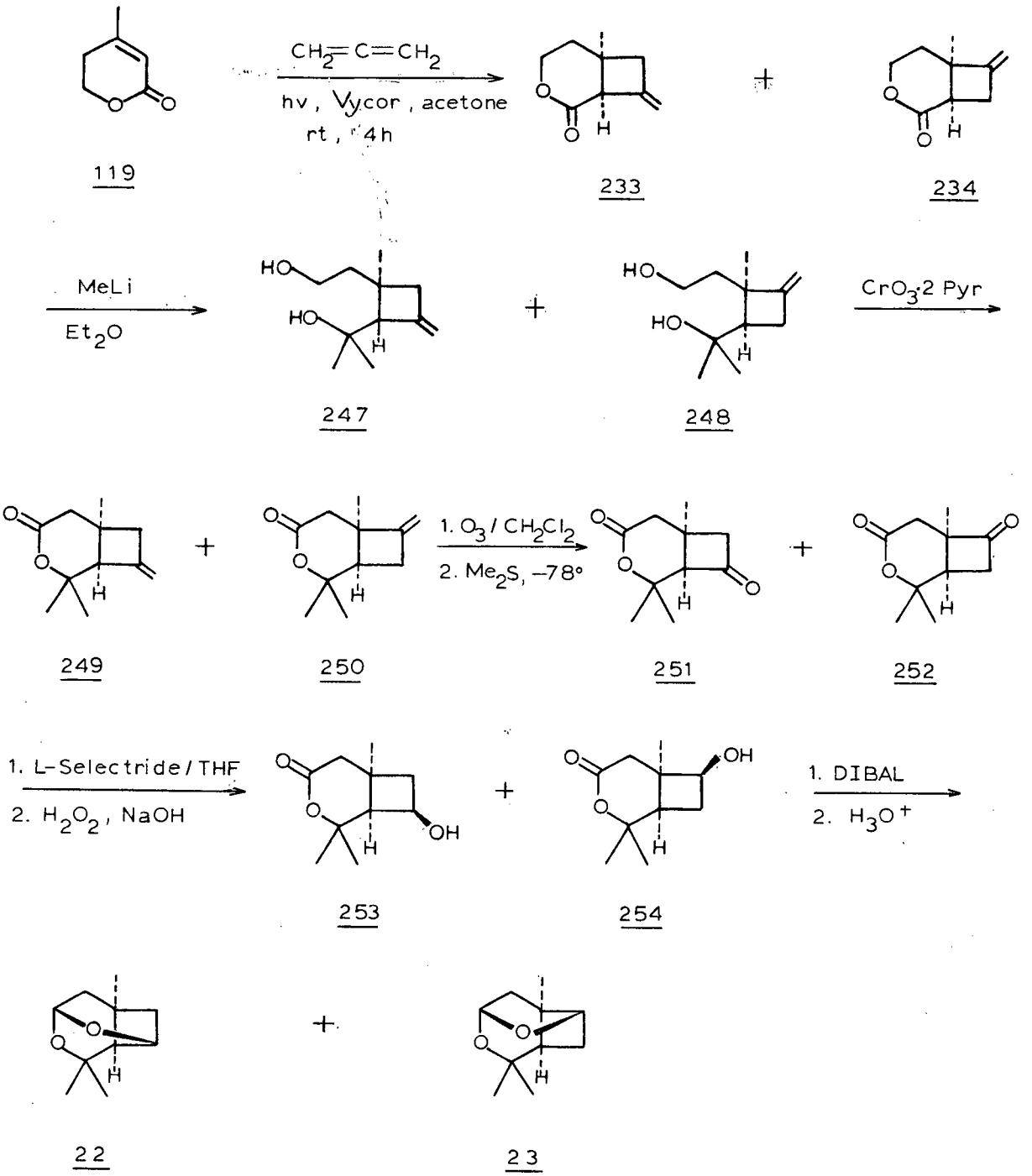
233 241 246

134 22

An alternative approach was then conceived as shown in Scheme XLIX, which consisted of one step more than the original plan. Nevertheless, all the reactions in this sequence were accomplished efficiently to furnish the final product 22. As can be noticed in this modified scheme, the methylidene group was ozonized at a later stage of the synthesis (compounds 249 and 250), where the problem of retro-Dieckmann ring opening was avoided.

Since separation of the two photoadducts was very difficult, we decided to carry through the subsequent steps of the sequence on the isomeric mixture (Scheme XLIX). Addition of the

Scheme XLIX. Synthesis of Lineatin (22)



119 233 234 247 248 249 250 251 252 253 254 22 23

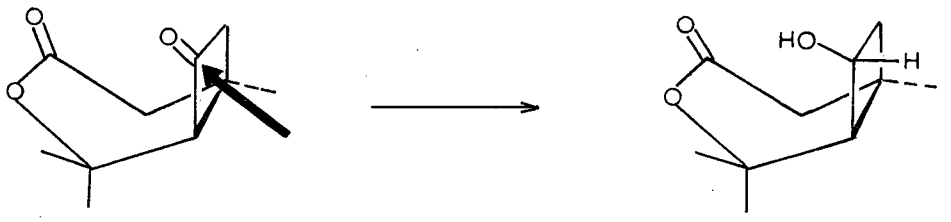
photoadduct mixture 233 and 234 to an excess of methyllithium at 0° C in ethyl ether resulted in the formation of the two diols 247 and 248. The IR spectrum had absorption for the hydroxyl group and no carbonyl absorptions were observed. The NMR spectrum showed several methyl singlets from δ 1.1 to 1.4 for the two isomers, a multiplet at δ 3.5-3.9 for the methylene protons adjacent to a hydroxy group, and a multiplet at δ 4.6-5.0 for the vinyl protons. Again, this mixture of isomers (247 and 248) was homogeneous by TLC analysis. In fact, we have been unable to separate chromatographically the mixtures of isomers for any of the intermediates on a preparative scale until the final stage of the synthesis. The rest of the reaction sequence was therefore conducted on isomeric mixtures. The NMR and IR spectra of all the intermediate mixtures are shown in the spectral index.

Oxidation of the diols 247 and 248 with chromium trioxide-pyridine complex[83] gave a mixture of lactones 249 and 250 in 72% yield. The products were readily recognized from the IR spectrum which exhibited an absorption at 1725 cm^{-1} due to the carbonyl function of the lactone. The NMR showed more than three singlets for the protons of the methyl groups in the region δ 1.2-1.4. A multiplet around δ 1.8-2.0 (total 3H) and a broad singlet at δ 2.37 (total 2H) accounted for the protons on the four-membered ring and the methylene protons next to the carbonyl group, respectively. In addition, there was a multiplet

for the vinyl protons at δ 4.8-5.0. Further evidence for the molecular formula and structure was obtained from mass spectral data and elemental analysis.

The mixture of the lactones 249 and 250 was ozonized in dichloromethane at -78° C, followed by dimethyl sulfide work-up to afford a mixture of keto lactones 251 and 252. Presence of the four-membered ring ketone and the δ-lactone was indicated by the IR absorptions at 1780 and 1730 cm^{-1}, respectively. No vinyl proton signals were observed in the NMR spectrum of this mixture. Selective reduction of the cyclobutanone carbonyl to an alcohol was achieved by treating the mixture of 251 and 252 with 1.2 eq of lithium tri-sec-butylborohydride (L-Selectride).[101]

This reagent was first studied by Brown and Krishnamurthy[102] and was shown to be a highly stereoselective reducing agent for cyclic ketones. It selectively reduces ketones in the presence of esters, and owing to its steric bulk, delivers hydride from the less hindered side of the ketone plane. In the reduction of 251 and 252 with L-Selectride, it is believed that



251 253

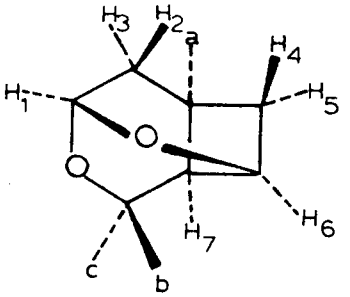
delivery of the hydride from the less hindered, convex face of the cyclobutanone should give predominantly the alcohols 253 and 254 with the stereochemistry as indicated. In fact, the eventual successful transformation of these alcohols into 22 and 23 proved the high stereoselectivity in this reduction. The IR spectrum of these alcohols showed absorptions at 3600 (free -OH) and 3450 cm^{-1} (hydrogen bonded -OH). In addition, an absorption due to the carbonyl of the δ-lactone was observed at 1720 cm^{-1}. The NMR and mass spectral data were consistent with the assigned structures. Finally, the mixture of lactones 253 and 254 was reduced with diisobutylaluminum hydride (DIBAL),[103] followed by treatment of the resulting reaction mixture with aqueous acid to afford the cyclized products 22 and 23. Separation of these two isomers was achieved by column chromatography, giving each compound in 29% yield. Although the isolated yield of 22 and 23 was in a 1:1 ratio, the NMR of the crude mixture showed that the ratio of 22 to 23 was ca. 2:1. The IR, NMR, high and low resolution mass spectra of the synthetic product 22 were identical with those reported by Silverstein and coworkers[29] for natural lineatin. In addition, elemental analysis of compound 22 was consistent with its molecular formula. The IR spectrum of compound 23 showed intense absorptions at 800-1400 cm^{-1} indicating the presence of C-O-C linkages, and neither carbonyl nor hydroxyl groups were present. It is interesting to note that the NMR spectra of the two isomers

22 and 23 showed significant differences. A comparison of the NMR spectral data of these isomers are summarized in Table 5. Assignment of the signals for the protons in 22 and 23 was assisted by the use of spin decoupling experiments.

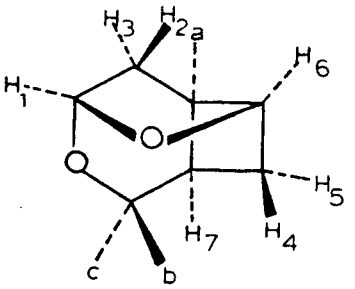
Results from the decoupling experiments conducted on the 270 MHz NMR of lineatin (22) are listed in Table 6. The lowest field signal at δ 4.93 (d, J = 4 Hz) was assigned to the acetal proton H_1. From a molecular model of 22, the dihedral angle between H_1 and H_3 is estimated to be about 90°, therefore we expect the coupling constant $J_{1,3}$ to be small or zero. This explains the observation of a doublet for H_1 instead of a more complex signal. The doublet would be due to the coupling between H_1 and H_2 which have a dihedral angle of about 30°. When H_1 was irradiated, the signal at δ 2.04 (dd, J = 12, 4 Hz) collapsed to a doublet (J = 12 Hz). Hence we assign the signal at δ 2.04 to H_2.

The second low field signal at δ 4.38 (t, J = 4 Hz) is assigned to H_6. Irradiation at δ 4.38 (H_6), showed a change in the signals at δ 1.83 (d, J = 4 Hz) and at δ 1.69 (dt, J = 10.5, 4 Hz). The doublet at δ 1.83 is assigned to the tertiary H_7 which is only coupled to H_6. The fact that $J_{6,7}$ = 4 Hz instead of a normal vicinal cyclobutane coupling of ca. 10 Hz[104] may be due to the electronegative oxygen on the carbon bearing H_6.[105]

Table 5. 270 MHz NMR of Compounds 22 and 23



22



23

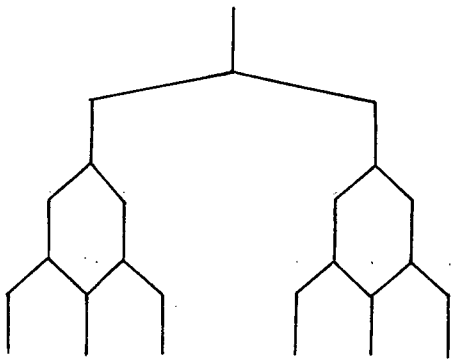
	22		23
	Chemical shift in ppm (δ) from TMS in CCl_4		
H_1	4.93 (d, J = 4 Hz)	H_1	5.32 (d, J = 4 Hz)
H_2	2.04 (dd, J = 12, 4 Hz)	H_2	1.33 (dd, J = 12, 4 Hz)
H_3	1.91 (dd, J = 12, 4 Hz)	H_3	2.09 (d, J = 12 Hz)
H_4	1.61 (d, J = 10.5 Hz)	H_4	2.35 (ddd, J = 13, 9,4 Hz)
H_5	1.69 (dt, J = 10.5, 4 Hz)	H_5	1.9 (m)
H_6	4.38 (t, J = 4 Hz)	H_6	3.93 (t, J = 4 Hz)
H_7	1.83 (d, J = 4 Hz)	H_7	1.9 (m)
Me(a)	1.12 (s)	Me(a)	1.08 (s)
Me(b)	1.17 (s) *	Me(b)	1.39 (s)
Me(c)	1.16 (s) *	Me(c)	1.23 (s)

* These assignments may be reversed.

Table 6. Spin Decoupling on 270 MHz NMR of Compound 22 (see spectral appendix, p. 270)

Irradiated Signal		Decoupled Signal		
δ (multiplicity)	Assigned H	δ (multiplicity) (before decoupling)	δ (multiplicity) (after decoupling)	Assigned H
4.93 (d, J=4 Hz)	H_1	2.04 (dd, J=12, 4 Hz)	(d, J = 12)	H_2
4.38 (t, J=4 Hz)	H_6	1.83 (d, J=4 Hz)	(s)	H_7
		1.69 (ddd, J = 10.5, 4 Hz)	(dd = 10.5, 4 Hz)	H_5
1.83 (d, J=4 Hz)	H_7	4.38 (t, J=4 Hz)	(d, J = 4 Hz)	H_6

The signal at δ 1.69 is a doublet of triplets which would arise from three couplings as shown. We assign this signal to H_5. Irradiation at δ 4.38 (H_6) led to simplification



$J_{ac} = J_{ad}$

of the doublet of triplets at 1.69 to a doublet of doublets (J = 10.5, 4 Hz); thus $J_{5,6}$ = 4 Hz. The geminal hydrogens H_4 and H_5 are coupled with $J_{4,5}$ = 10.5 Hz, and finally H_5 experiences long range coupling with H_3; $J_{3,5}$ = 4 Hz. A study of molecular models indicate that H_3-C_8-C_7-C_6-H_5 can adopt the "W" configuration. The doublet at δ 1.61 (J = 10.5 Hz) then was assigned to H_4. The lack of coupling between H_4 and H_6 may again be due to the electronegative substituent on the cyclobutane ring.

The remaining doublet of doublets at δ 1.91 (J = 12, 4 Hz) is assigned to H_3. This signal was unaltered by irradiation at H_1. Thus the couplings are assigned to $J_{2,3}$ = 12 Hz, a typical value for a geminal coupling, and $J_{3,5}$ = 4 Hz due to the long range coupling described above.

The three methyl singlets at δ 1.12, 1.16 and 1.17 are tentatively assigned as follows. The high field singlet at δ 1.12 is assigned to Me(a) and the two lower field signals to Me(b) and Me(c). The assignment of the signals for the protons in lineatin (22) from the spin decoupling experiments is consistent with the assignment made by Silverstein et al.[29] from the shifted NMR spectrum of natural lineatin (22).

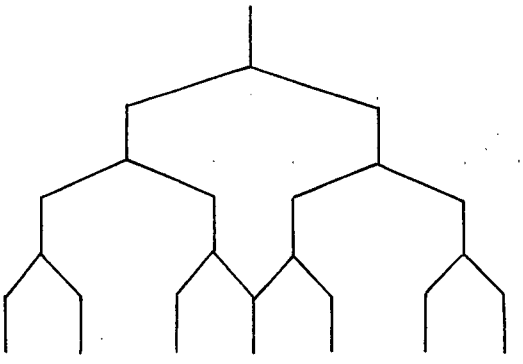
Results from the decoupling experiments performed on the 270 MHz NMR of 23 are given in Table 7. As before, the lowest field signal at δ 5.32 (d, J = 4 Hz) is assigned to the

Table 7. Spin Decoupling on 270 MHz NMR of Compound 23 (see spectral appendix, p. 271)

Irradiated Signal		Decoupled Signal		
δ (multiplicity)	Assigned H	δ (multiplicity) (before decoupling)	δ (multiplicity) (after decoupling)	Assigned H
5.32 (d, J = 4 Hz)	H_1	1.33 (dd, J = 12, 4 Hz)	(d, J = 12 Hz)	H_2
3.93 (t, J = 4 Hz)	H_6	2.35 (ddd, J = 13, 9, 4 Hz)	(dd, J = 13, 9 Hz)	H_4
		1.9 (m)	(simplified)	
1.33 (dd, J = 12, 4 Hz)	H_2	5.32 (d, J = 4 Hz)	(s)	H_1
		2.09 (d, J = 12 Hz)	(s)	
2.09 (d, J = 12 Hz)	H_3	1.33 (dd, J = 12, 4 Hz)	(d, J = 4 Hz)	H_2
2.35 (ddd, J = 13, 9,4 Hz)	H_4	3.93 (t, J = 4 Hz)	(d, J = 4 Hz)	H_6
		1.9 (m)	(simplified)	H_5 and H_7
1.9 (m)	H_5 H_7	3.93 (t, J = 4 Hz)	(d, J = 4 Hz)	H_6
		2.35 (ddd, J = 13, 9, 4 Hz)	(d, J = 4 Hz)	H_4

acetal proton H_1. The dihedral angle between H_1 and H_2 is estimated to be about 30° whereas that between H_1 and H_3 is about 90°. Thus the observed doublet at δ 5.32 is consistent with the lack of coupling between H_1 and H_3. Irradiation of H_1 produced a collapse of the double doublet (J = 12, 4 Hz) at δ 1.33 to a doublet (J = 12 Hz). Hence this double doublet is assigned to H_2 which is expected to show a vicinal coupling, $J_{1,2}$ = 4 Hz, and a geminal coupling, $J_{2,3}$ = 12 Hz. Irradiation of the signal at δ 1.33 led to a collapse of the doublet at δ 2.09 (J = 12 Hz) to a singlet. Hence this doublet is assigned to H_3. Incidently, the irradiation at δ 1.33 also collapsed the doublet at δ 5.32 to a singlet. These assignments were cross-checked by an irradiation at δ 2.09 which collapsed the signal at δ 1.33 to a doublet (J = 4 Hz).

The second lowest field signal at δ 3.93 (t, J = 4 Hz) is assigned to H_6. Irradiation of H_6 produced a simplification of the multiplet at δ 2.35 to a double doublet (J = 13, 9 Hz) and a simplification of the two proton multiplet at δ 1.9. The multiplet at δ 2.35 can arise as shown and the observed



$$J_{ab} = J_{ac} + J_{ad}$$

coupling constants are J_{ab} = 13 Hz, J_{ac} = 9 Hz, and J_{cd} = 4 Hz. Irradiation of the signal at δ 1.9 collapsed the multiplet at δ 2.35 to a doublet (J = 4 Hz). From these decoupling results and the magnitudes of the coupling constants we suggest that the multiplet at δ 2.35 be assigned to H_4. Thus the cis vicinal coupling has the value $J_{4,6}$ = 4 Hz. The geminal coupling, $J_{4,5}$ = 13 Hz, is consistent with lineatin (22) and other cyclobutanes. The trans vicinal coupling $J_{4,7}$ = 9 Hz is typical of value observed in many cyclobutyl compounds.[104,105]

Finally, the multiplet at δ 1.9 is assigned to H_5 and H_7. The low field shift of H_4 relative to the other cyclobutane protons in 22 and 23 is attributed to van der Waals deshielding of H_4 in 23 by Me(b) and O-9. The signal at δ 1.08 is assigned to Me(a) and the remaining two singlets at δ 1.39 and 1.23 are assigned to Me(b) and Me(c) respectively. The low field shift of Me(b) relative to Me(c) might be due to the van der Waals deshielding of Me(b) by H_4.

The previous syntheses of lineatin[29,30] were of very low overall yield and often complex mixtures of isomers were obtained. Hence, only very minute quantities of pure lineatin (22) were available for testing. Our synthesis of lineatin (22) represents a major improvement over the previous methods in terms of both efficiency and stereoselectivity. The intermediate 3-methyl-5-hydroxy-2-pentenoic acid δ-lactone (119) could be

easily synthesized on a large scale. The photochemical cycloaddition reaction of 119 with allene, although not highly regioselective, led to predominant formation of the desired adduct 233. This mixture of regioisomers could be conveniently carried through the subsequent steps to the final product which was readily purified by column chromatography. This sequence has already been utilized to generate gram quantities of 22 and 23, and it should be feasible to synthesize even larger quantities of 22 for extensive biological studies.

EXPERIMENTAL

General: see p. 26.

Synthesis of 5-Methyl-6,8-dioxabicyclo[3.2.1]octane (167)

Methyl 3-oxo-7-octenoate (152)

Sodium hydride, as a 57% mineral oil dispersion, (5.45 g, 100 mmol) was weighed into an oven dried flask. It was washed oil-free with THF and after decantation of the THF, fresh THF (ca. 250 mL) was distilled directly into the flask. The flask was then equipped with a magnetic stirrer, septum cap, cooled in ice and flushed with nitrogen. Methyl acetoacetate (11.60 g, 100 mmol) was added dropwise to the cooled slurry, and after the addition, the reaction mixture was allowed to stir for 10 min. n-Butyllithium, as a 2.1 M solution in hexane (48 mL, 101 mmol) was added dropwise to the reaction mixture and it was allowed to stir for another 10 min. To the resulting dianion was added 14.85 g (110 mmol) of 4-bromo-1-butene. The yellow reaction mixture was stirred for 2 h at 0° C and it was quenched with dilute hydrochloric acid solution until slightly acid. Ethyl ether (2 x 400 mL) was used to extract the reaction mixture. The organic layer was washed with saturated aqueous sodium bicarbonate solution, brine and dried over anhydrous magnesium sulfate. The solvents were removed

under reduced pressure. Purification was achieved by distillation to give 13.43 g (79%) of methyl 3-oxo-7-octenoate (152), bp 62° C/0.1 torr;

IR ($CHCl_3$) 920, 1650, 1720, and 1745 cm^{-1};

NMR ($CDCl_3$) δ 1.5-2.3 (m, 4H), 2.51 (t, J = 7 Hz, 2H), 3.38 (s, 2H), 3.68 (s, 3H), 4.7-5.2 (m, 2H), and 5.3-6.1 (m, 1H);

mass spectrum m/e (rel intensity) 41(57), 43(45), 55(32), 59(37), 69(43), 74(60), 84(32), 97(53), 101(54), 116(100), 129 (13), 138(16), and 170(29).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.51; H, 8.37.

Methyl 7,8-epoxy-3-oxooctanoate (153)

A sample of 1.01 g (5.50 mmol) of 85% m-chloroperbenzoic acid was added to a solution of 0.85 g (5.0 mmol) of methyl 3-oxo-7-octenoate (152) in ca. 20 mL dry dichloromethane at 0° C. The reaction mixture was stirred at 0° C for 0.5 h and at room temperature for an additional 20 h. It was quenched with saturated aqueous sodium bisulfite and the aqueous layer was extracted with 2 x 50 mL ethyl ether. The extracts were combined, washed with aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. The resulting oil was distilled (Kugelrohr, bath temperature 90° C/0.7 torr) to yield 0.70 g (75%) of epoxide 153;

IR ($CHCl_3$) 1720 and 1745 cm^{-1};

NMR ($CDCl_3$) δ 1.1-2.0 (m, 4H), 2.3-3.0 (m, 5H), 3.4 (s, 2H), and 3.68 (s, 3H);

mass spectrum: a) high resolution calcd for $C_9H_{14}O_4$: 186.0892 amu; found: 186.0912;

b) low resolution m/e (rel intensity) 41(71), 43(57), 55(61), 59(57), 69(50), 74(28), 101(100), 113 (25), 116(21), 117(15), 124(15), 155(21), and 186(15).

Methyl α-(6,8-dioxabicyclo[3.2.1]octan-5-yl) acetate (154)

A solution of 0.09 g (0.50 mmol) of epoxy ester 153 in 12 mL of dry dichloromethane was treated with 0.1 mL of distilled boron trifluoride etherate under nitrogen and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched with water and the aqueous layer was extracted several times with ethyl ether. The extracts were combined, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to yield an oil which was distilled (Kugelrohr) at 93° C/0.5 torr to yield 0.08 g (85%) of cyclic ketal 154,

IR ($CHCl_3$) 1740 cm^{-1};

NMR ($CDCl_3$) δ 1.1-2.1 (m, 6H), 2.73 (s, 2H), 3.68 (s, 3H), 3.8 (m, 2H), and 4.5 (m, 1H);

mass spectrum: a) high resolution calcd for $C_9H_{14}O_4$: 189.0908 amu; found: 186.0889;

b) low resolution m/e (rel intensity) 41(11), 57(13), 59(16), 74(15), 87(23), 101(100), 113(13), 155 (23), and 186(32).

α-(6,8-Dioxabicyclo[3.2.1]octan-5-yl)acetic acid (166)

A solution of 0.093 g (0.50 mmol) of ester 154 in 5 mL of methanol and 3 mL of 50% aqueous potassium hydroxide was refluxed for 3 h. The methanol was removed under reduced pressure; the solution was then acidified with dilute hydrochloric acid and extracted several times with ethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, and solvents were removed under reduced pressure to give 0.075 g (87%) of the acid 166. Purification was achieved by TLC (carbon tetrachloride:ethyl ether 2:1 v/v) to give a white solid, mp 77-79° C;

IR ($CHCl_3$) 1715, 1760, and 2700-3300 cm^{-1};

NMR ($CDCl_3$) δ 1.0-2.0 (m, 6H), 2.78 (s, 2H), 3.8-3.95 (m, 2H), 4.35-4.6 (m, 1H), and 9.87 (b s, 1H);

mass spectrum: a) high resolution calcd for $C_8H_{12}O_4$: 172.0736 amu; found: 172.0731;

b) low resolution m/e (rel. intensity) 41(57), 43(62), 55(28), 57(66), 58(43), 67(32), 68(37), 86(100), 87(27), 98(30), and 172(60).

5-Methyl-6,8-dioxabicyclo[3.2.1]octane (167)

A sample of 0.026 g (0.15 mmol) of acid 166 was placed in a small Kugelrohr tube which was then inserted into a preheated (220° C) Kugelrohr oven. The decarboxylated product was distilled within 8 min at that temperature at 1 atm. A total of 0.0192 g (84%) of 5-methyl-6,8-dioxabicyclo[3.2.1]octane (167)

was obtained. Compound 167 was characterized by;

IR ($CHCl_3$) 840, 1015, 1390, and 2990 cm^{-1};

NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.3-2.0 (m, 6H), 3.8 (m, 2H), and 4.5 (m, 1H);

mass spectrum: a) high resolution calcd for $C_7H_{12}O_2$: 128.0837 amu; found: 128.0837;

b) low resolution m/e (rel intensity) 41(16), 43(100), 47(14), 58(18), 68(12), 86(24), 100(15), and 128(30).

Synthesis of Frontalin (17)

4-Bromo-2-methyl-1-butene (111)[61b]

3-Methyl-3-buten-1-ol (161) (1.4 g, 16.0 mmol) was weighed into a 25 mL of R-B flask and 10 mL of anhydrous ethyl ether was added. The flask was then fitted with an additional funnel and a nitrogen outlet. Anhydrous pyridine (0.045 g) was added and the mixture was cooled to -5° C and allowed to stir for 15 min. A solution of 2.07 g of phosphorus tribromide in 5 mL of anhydrous ethyl ether was added dropwise through the additional funnel to the reaction mixture. The reaction mixture was allowed to stir at -5 to 0° C for an additional 4 h. It was then poured onto ice, and the mixture was extracted several times with ethyl ether. The etheral layer was washed with aqueous sodium bicarbonate solution, dried over anhydrous mag-

nesium sulfate and ethyl ether was removed by simple distillation (at 1 atm). Kugelrohr distillation at 105° C/760 torr gave 1.002 g of 4-bromo-2-methyl-1-butene (111), [lit.[61b] bp 105-107° C/760 torr];

NMR ($CDCl_3$) δ 1.76 (br s, 3H), 2.53 (t, J = 7 Hz, 2H), 3.43 (t, J = 7 Hz, 2H), and 4.7-5.0 (m, 2H).

Methyl 7-methyl-3-oxo-7-octenoate (162)

This compound was prepared by the same procedure as that employed in the preparation of methyl 3-oxo-7-octenoate (152). The reagents used were: 0.464 g (4.0 mmol) of methyl acetoacetate, 0.22 g of sodium hydride (as a 57% mineral oil dispersion), 2.5 mL (1.6 M in hexane) of n-butyllithium, and 0.61 g (4.10 mmol) of 4-bromo-2-methyl-1-butene (111). The crude product was distilled at 75° C/0.3 torr to give 1.33 g (80%) of methyl 7-methyl-3-oxo-7-octenoate (162) which had the following spectral data;

IR ($CHCl_3$) 890, 1635, 1650, 1715, and 1745 cm^{-1};

NMR ($CDCl_3$) δ 1.69 (s, 3H), 1.6-2.1 (m, 4H), 2.49 (t, J = 7 Hz, 2H), 3.40 (s, 2H), 3.70 (s, 3H), and 4.65 (m, 2H);

mass spectrum m/e (rel intensity) 41(57), 43(87), 55(77), 59(42), 68(56), 69(58), 74(100), 101(37), 111(35), 116(75), 117 (34), 129(37), 166(18), and 184(24).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.20; H, 8.75.

Methyl 7,8-epoxy-7-methyl-3-oxooctanoate (163)

A solution of 0.184 g (1.0 mmol) of methyl 7-methyl-3-oxo-7-octenoate (162) in 6 mL of anhydrous dichloromethane was cooled to 0° C and treated with 0.24 g (1.30 mmol) of 95% m-chloroperbenzoic acid and 0.21 g (1.50 mmol) of anhydrous sodium monohydrogen phosphate. The reaction mixture was raised to room temperature and stirred for 4 h. It was quenched with saturated aqueous sodium bisulfate, and the aqueous layer was extracted several times with ethyl ether. The extracts were combined, washed with aqueous sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure. Kugelrohr distillation at 95° C/0.7 torr gave 0.172 g (86%) of epoxide 163. A small sample of 163 was purified by TLC (carbon tetrachloride:ethyl ether 8:1 v/v) and was characterized by;

IR ($CHCl_3$) 1720 and 1745 cm^{-1};

NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.5-1.8 (m, 4H), 2.53 (s, 2H), 2.55 (t, J = 7 Hz, 2H), 3.39 (s, 2H), and 3.68 (s, 3H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_4$: 200.1042 amu; found: 200.1035;

b) low resolution m/e (rel intensity) 41(50), 43(100), 55(68), 59(44), 69(40), 72(47), 81(42), 85(49), 101(65), 111(54), 127(30), 129(28), 164(20), 169(25), 170(17), and 200(13).

Methyl α-(1-methyl-6,8-dioxabicyclo[3.2.1]octan-5-yl)acetate (164)

The epoxide 163 was cyclized to the bicyclo ketal 164 by the same procedure as that employed in the preparation of compound 154. The reagents used were 0.08 g (0.4 mmol) of epoxide 163 and 5 drops of distilled boron trifluoride etherate. The crude product was homogeneous for TLC and distilled (Kugelrohr) at 90° C/0.1 torr to yield 0.076 g (95%) of ketal 164. A small sample of 164 was purified by TLC (carbon tetrachloride: ethyl ether 4:1 v/v) and was characterized by;

IR ($CHCl_3$) 1740 cm^{-1};

NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.5-1.9 (m, 6H), 2.72 (s, 2H), 3.66 (s, 3H), 3.40 and 3.88 (dd, J = 7 Hz, 2H);

mass spectrum m/e (rel intensity) 43(59), 72(70), 100 (100), 101(59), 111(15), 169(29), and 200(32).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.86; H, 7.96.

α-(1-Methyl-6,8-dioxabicyclo[3.2.1]octan-5-yl)acetic acid (165)

The ester 164 (0.03 g, 0.15 mmol) was hydrolyzed in the same fashion as that employed in the hydrolysis of compound 154 to yield 0.025 g (88%) of acid 165 which was homogeneous by TLC analysis. A small sample of 165 was purified by TLC (carbon tetrachloride:ethyl ether 2:1 v/v) and had the following data;

IR ($CHCl_3$) 1715, 1755, and 2400-3600 cm^{-1};

NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.5-1.9 (m, 6H), 2.78 (s, 2H), 3.48 and 3.95 (dd, J = 7 Hz, 2H), and 9.52 (br s, 1H);

mass spectrum: a) high resolution calcd for $C_9H_{14}O_4$: 186.0892 amu; found: 186.0895;

b) low resolution m/e (rel intensity) 43(42), 72(79), 87(23), 100(100), 111(24), 156(13), and 186(10).

Frontalin (17)

The crude acid 165 (0.019 g, 0.10 mmol) was decarboxylated by the same procedure as that employed in the preparation of 5-methyl-6,8-dioxabicyclo[3.2.1]octane (167) to yield 0.012 g (85%) of frontalin (17) which had spectral data identical to that reported for natural frontalin (17).[25]

IR ($CHCl_3$) 815, 840, 865, 890, 905, 980, 1020, 1060, 1118, 1170, 1240, 1260, 1285, 1350, 1380, 1390, 1455, 2920, and 2980 cm^{-1};

NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.43 (s, 3H), 1.5-1.8 (m, 6H), 3.40 and 3.88 (dd, J = 7 Hz, 2H);

mass spectrum m/e (rel intensity) 41(15), 43(100), 71(22), 72(77), 100(37), 112(17), 114(13), and 142(40).

Synthesis of Endo-Brevicomin (16)

3-Hexyne-1-ol (174)

To 250 mL of liquid ammonia in a 500 mL 3-necked flask fitted with a mechanical stirrer and dry-ice condenser was added a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ and 2.21 g (320 mmol) of lithium in portions. After the disappearance of the blue color, 10.51 g (150 mmol) of 3-butyn-1-ol (173) in ca. 20 mL of dry THF was added dropwise over 10 min. Another 20 mL of dry THF was added and the reaction mixture was allowed to reflux (-33° C) for 1 h. A solution of 16.88 g (155 mmol) of 1-bromoethane in 10 mL of dry THF was added. The reaction was then continued to reflux for another 1 hr. It was quenched with saturated aqueous ammonium chloride solution and the ammonia was allowed to evaporate. The aqueous layer was extracted several times with ethyl ether, the extracts were combined, dried over anhydrous magnesium sulfate, and solvents were removed under reduced pressure. The crude product was distilled at 80° C/14 torr to yield 11.2 g (76%) of 3-hexyn-1-ol (174), [lit.[64] bp 64° C/7 torr];

IR ($CHCl_3$) 3630 and 3460 cm^{-1};

NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H), 1.8-2.6 (m, 5H), and 3.4-3.9 (m, 2H);

mass spectrum m/e (rel intensity) 40(41), 41(67), 53(66), 67(88), 68(100), and 98(56).

(E)-3-Hexen-1-ol (175)

A solution of 9.80 g (100 mmol) of 3-hexen-1-ol (174), in 50 mL of anhydrous ethyl ether was added dropwise to a solution of 8.81 g of sodium in 500 mL of ammonia. The reaction was stirred at -35° C for 4 hr, quenched with 12 g of ammonia chloride, and the ammonia was allowed to evaporate. The residue was treated with 250 mL of ice-cold water and the aqueous layer was extracted with 4 x 300 mL ethyl ether. The extracts were combined and worked up to yield 8.70 g (87%) of (E)-3-hexen-1-ol (175) which distilled at 72-74° C/20 torr, [lit.[72b] 80-85° C/22 torr], and was characterized by;

IR ($CHCl_3$) 970 and 3200-3600 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.7-2.4 (m, 4H), 3.67 (t, J = 7 Hz, 2H), and 5.0-5.2 (m, 2H);

mass spectrum m/e (rel intensity) 41(100), 42(27), 53(15), 55(41), 57(17), 67(60), 68(15), 69(47), 70(19), 82(47), and 100(15).

(E)-1-Bromo-3-hexene (176)[72c]

This compound was prepared by the same procedure as that employed in the preparation of 4-bromo-2-methyl-1-butene (111). The reagents used were: 6.0 g (60.0 mmol) of (E)-3-hexen-1-ol

(175), 4.34 g (16.0 mmol) of phosphorus tribromide, and 0.30 g of anhydrous pyridine. The crude product was distilled to give 5.40 g (56%) of (E)-1-bromo-3-hexene (176), bp 78-80° C/ 20 torr;

IR ($CHCl_3$) 970, 2925, and 3000 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.7-2.7 (m, 4H), 3.2-3.7 (m, 2H), and 5.0-5.8 (m, 2H);

mass spectrum m/e (rel intensity) 41(100), 55(81), 67 (38), 69(28), 82(38), 83(77), 162(22), and 164(21).

Methyl (E)-3-oxo-7-decenoate (177)

This compound was prepared by the same procedure as that employed in the preparation of methyl 3-oxo-7-octenoate (152). The reagents used were: 2.32 g (20.0 mmol) of methyl acetoacetate, 1.10 g of sodium hydride (as a 57% mineral oil dispersion), 9.6 mL (2.0 M in hexane) of n-butyllithium and 4.05 g (25.0 mmol) of (E)-1-bromo-3-hexene (176). Kugelrohr distillation of the crude product at 81° C/0.1 torr gave 3.27 g (83%) of methyl (E)-3-oxo-7-decenoate (177). Further purification was achieved by preparative TLC (carbon tetrachloride: ethyl ether 8:1 v/v) and redistillation (Kugelrohr) to give pure 177 which was characterized by the following data;

IR ($CHCl_3$) 970, 1630, 1660, 1720, and 1745 cm^{-1};

NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 3H), 1.2-2.1 (m, 6H), 2.48 (t, J = 7 Hz, 2H), 3.39 (s, 2H), 3.70 (s, 3H), and 5.2-5.4 (m, 2H);

mass spectrum m/e (rel intensity) 51(21), 67(55), 82(83), 101(30), 116(100), 117(21), 125(21), 180(32), and 198(32).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.65; H, 9.05.

Methyl (E)-7,8-epoxy-3-oxodecanoate (178)

The procedure used in this reaction was the same as that employed in the preparation of compound 163. The reagents used were: 1.78 g (9.0 mmol) of methyl (E)-3-oxo-7-decenoate, (177), 2.16 g of 90% m-chloroperbenzoic acid, and 1.59 g of anhydrous sodium monohydrogen phosphate; 1.68 g (87%) of crude epoxide 178 was obtained. Purification was achieved by TLC: 0.2 g of the crude product 178 was chromatographed, using a mixture of carbon tetrachloride and ethyl ether (7:3 v/v) as eluent. Pure epoxide (0.165 g, 72%) was isolated and distilled (Kugelrohr) at 96° C/0.1 torr. This epoxide 178 was characterized by the following spectral data;

IR ($CHCl_3$) 1720 and 1745 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.2-2.0 (m, 6H), 2.35-2.7 (m, 4H), 3.43 (s, 2H), and 3.72 (s, 3H);

mass spectrum m/e (rel intensity) 41(66), 43(66), 55(67), 57(51), 59(51), 96(76), 97(68), 101(91), 113(44), 114(45), 116 (59), 124(100), 141(22), 156(56), 184(20), and 214(16).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.38; H, 8.57.

Methyl α-(endo-7-ethyl-6,8-dioxabicyclo[3.2.1]octan-5-yl acetate (179)

In a similar fashion as that employed in the preparation of compound 154, 1.28 g (6.0 mmol) of epoxide 178 was cyclized to give 1.71 g (91%) of bicyclic ketal 179. Purification was achieved by preparative TLC: about 0.15 g of the crude product was chromatographed using carbon tetrachloride and ethyl ether (8:1 v/v) as eluent to give 0.112 g of cyclized ketal 179 which was distilled (Kugelrohr) at 95° C/0.1 torr. This compound was characterized by the following spectral data;

IR ($CHCl_3$) 1740 cm^{-1};

NMR ($CDCl_3$) δ 0.97 (t, J = 7 Hz, 3H), 1.2-2.0 (m, 8H), 2.73 (s, 2H), 3.68 (s, 3H), 3.7-4.1 (m, 1H), and 4.1-4.3 (m, 1H);

mass spectrum m/e (rel intensity) 41(51), 59(54), 68(59), 85(55), 96(61), 101(100), 113(53), 114(61), 124(66), 141(33), 156(75), 184(47), 196(31), and 214(26).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.36; H, 8.29.

α-(endo-7-Ethyl-6,8-dioxabicyclo[3.2.1]octan-5-yl)acetic acid (180)

A sample of 0.107 g (0.5 mmol) of ester 174 was hydrolyzed using the same procedure as that employed in the preparation of compound 166 to give 0.095 g (95%) of acid 180. The

crude material was homogeneous by TLC and had the following data;

IR ($CHCl_3$) 1715, 1765 and 2400-3500 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.2-2.1 (m, 8H), 2.77 (s, 2H), 3.8-4.15 (m, 1H), 4.26 (br s, 1H), and 8.6 (br s, 1H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_4$: 200.1049 amu; found: 200.1045;

b) low resolution m/e (rel intensity) 41(29), 43(100), 44(47), 57(25), 71(26), 98(45), 114(36), 124 (12), 142(14), 149(14), 156(21), 192(14), and 200(3).

endo-Brevicomin (16)

In a similar fashion as that employed in the preparation of 5-methyl-6,8-dioxabicyclo[3.2.1]octane (167), 0.06 g (0.30 mmol) of carboxylic acid 180 was decarboxylated to yield 0.04 g (85%) of endo-brevicomin (16) which had spectral data identical to that reported for natural endo-brevicomin (16).[24]

IR ($CHCl_3$) 840, 865, 900, 962, 995, 1025, 1100, 1170, 1200, 1230, 1260, 1310, 1330, 1350, 1380, 1462, 2905, and 2975 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 2.1 (s, 3H), 1.2-2.0 (m, 8H), 3.7-4.05 (m, 1H), and 4.08 (br s, 1H);

mass spectrum m/e (rel intensity) 41(17), 43(100), 57 (15), 67(13), 68(24), 71(22), 81(16), 86(22), 98(50), 99(17), 113(17), 114(41), and 156(22).

Synthesis of exo-Brevicomin (15)

(Z)-1-Bromo-3-hexene (185)[72a]

A mixture of 4.16 g (41.0 mmol) of 3-hexyn-1-ol, 0.20 g of 5% palladium on barium sulfate, and 3 drops of freshly distilled quinoline in 50 mL of methanol, was hydrogenated at atmospheric pressure. After 2 h, the hydrogenation was stopped and the methanol was removed under reduced pressure. The crude product was dissolved in ethyl ether, washed with dilute aqueous hydrochloric acid, dried over anhydrous magnesium sulfate, and distilled to yield 3.40 g (82%) of (Z)-3-hexen-1-ol (184) by 74° C/20 torr, [lit.[72b] bp 59-61° C/12.5 torr].

A solution of 8.50 g (85.0 mmol) of (Z)-3-hexen-1-ol (184) in 10 mL of anhydrous ethyl ether was added dropwise to a cooled (-30° C) mixture of 7.6 g (28 mmol) of phosphorus tribromide and 0.43 g of anhydrous pyridine in 40 mL of ethyl ether. The reaction mixture was stirred at -30° C for 1 hr, and then at room temperature for 5 h. The reaction was quenched with ice and water, and the aqueous layer was extracted several times with ethyl ether. The extracts were combined, washed with 5% aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The preduct was distilled at 65° C/20 torr to yield 6.30 g (46%) of (Z)-1-bromo-3-hexene (185); [lit.[72a] bp 40-48° C/7 torr];

IR ($CHCl_3$) 1265, 2910, and 3000 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 2.03 (qn, J = 7 Hz, 2H), 2.63 (q, J = 7 Hz, 2H), 3.32 (t, J = 7 Hz, 2H), and 5.0-5.75 (m, 2H);

mass spectrum m/e (rel intensity) 41(89), 55(100), 67 (33), 68(55), 82(31), 83(88), 162(25), and 164(25).

Methyl (Z)-3-oxo-7-decenoate (186)

A solution of the dianion of 3.48 g (30 mmol) of methyl acetoacetate was generated using the same procedure as that employed in the preparation of compound 152. The dianion was alkylated with a solution of 5.82 g (35 mmol) of (Z)-1-bromo-3-hexene (185) in 5 mL of dry THF at 0° C. The reaction mixture was stirred at 0° C for 2 h and at room temperature for an additional 3 h. It was then quenched with dilute hydrochloric acid and extracted several times with ethyl ether. The extracts were combined, washed with sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to give 5.23 g (88%) of crude oil which was distilled as 82-84° C/0.1 torr to give 4.2 g (71%) of pure methyl (Z)-3-oxo-7-decenoate (186);

IR ($CHCl_3$) 1630, 1650, 1715, and 1745 cm^{-1};

NMR ($CDCl_3$) δ 0.96 (t, J = 7 Hz, 3H), 1.4-2.2 (m, 6H), 2.53 (t, J = 7 Hz, 2H), 3.41 (s, 2H), 3.72 (s, 3H), and 4.9-5.5 (m, 2H);

mass spectrum m/e (rel intensity) 41(46), 55(41), 67(68), 82(84), 101(22), 116(100), 117(22), 129(22), 180(25), and 198(10).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.56; H, 9.24.

Methyl (Z)-7,8-epoxy-3-oxodeanoate (187)

A solution of 2.97 g (15 mmol) of methyl (Z)-3-oxo-7-decenoate (186) in 10 mL of dry dichloromethane was cooled to 0° C and treated with 3.147 g (15.5 mmol) of 85% m-chloroperbenzoic acid and 3.179 g (22.3 mmol) of anhydrous sodium monohydrogen phosphate. The reaction mixture was raised to room temperature and stirred for 4 h. It was quenched with saturated sodium bisulfite, and the aqueous layer was extracted several times with ethyl ether. The extracts were combined, washed with aqueous sodium bicarbonate, and worked up to yield 2.88 g (90%) of crude epoxide 187. Purification was achieved by preparative TLC: 0.1 g of the crude product was chromatographed using a mixture of carbon tetrachloride and ethyl ether (8:1, v/v) as eluent. In this way, 0.078 g of pure epoxide 187 was isolated and distilled (Kugelrohr) at 90° C/0.15 torr. Epoxide 187 was characterized by the following spectral data;

IR ($CHCl_3$) 1715 and 1745 cm^{-1};

NMR ($CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 1.3-2.0 (m, 6H), 2.5-3.1 (m, 4H), 3.42 (s, 2H), and 3.70 (s, 3H);

mass spectrum m/e (rel intensity) 41(77), 43(78), 55(72), 57(60), 59(52), 69(52), 83(55), 96(69), 97(71), 101(55), 116 (37), 124(100), 139(41), 141(25), 156(57), 159(21), and 214(15).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.38; H, 8.25.

Methyl α-(exo-7-ethyl-6,8-dioxabicyclo[3.2.1]octan-5-yl)acetate (188)

This compound was prepared by the same procedure as that employed in the preparation of compound 154. The reagents used were: 0.10 mL of distilled boron-trifluoride etherate and 0.30 g (1.40 mmol) of epoxide 187 in 5 mL of anhydrous dichloromethane. The cyclized crude product (0.277 g) was distilled (Kugelrohr) at 90° C/0.15 torr to yield 0.25 g (82%) of product 188. The exo compound 188 thus obtained was contaminated with <1% of the endo isomer 179 by GLC (column A) analysis. Further purification was achieved by TLC (carbon tetrachloride: ethyl ether 8:1, v/v) to give pure 188 which was characterized by the following data;

IR ($CHCl_3$) 1740 cm^{-1};

NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.3-2.0 (m, 8H), 2.71 (s, 2H), 3.67 (s, 3H), 3.91 (t, J = 6 Hz, 1H), and 4.15 (br s, 1H);

mass spectrum m/e (rel intensity) 41(18), 57(15), 59(17), 68(19), 85(50), 101(31), 114(100), 115(10), 124(10), 141(9),

183(15), and 214(10).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.54; H, 8.35.

α-(exo-7-Ethyl-6,8-dioxabicyclo[3.2.1]octan-5-yl)acetic acid (189)

This compound was prepared by the same procedure as that employed in the preparation of compound 166. The reagents used were: 0.214 g (1.0 mmol) of ester 188 in 5 mL of methanol and 6 mL of 50% aqueous potassium hydroxide. The crude acid 189 (0.189 g, 95%) was obtained and used directly in the decarboxylation. Purification was achieved by preparative TLC (carbon tetrachloride:ethyl ether 2:1, v/v) and this acid was characterized by the following data;

IR ($CHCl_3$) 1715, 1750, and 2400-3400 cm^{-1};

NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.3-2.2 (m, 8H), 2.77 (s, 2H), 3.97 (t, J = 6 Hz, 1H), 4.18 (br s, 1H), and 9.72 (br s, 1H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_4$: 200.1049 amu; found: 200.1049;

b) low resolution m/e (rel intensity) 43(25), 57(25), 68(28), 85(82), 87(26), 114(100), 124(11), and 200(3).

exo-Brevicomin (15)

A sample of 0.10 g (0.50 mmol) of the crude acid (189)

was placed in a Kugelrohr tube and inserted into a preheated (200° C) Kugelrohr oven. A colorless oil distilled within 8 min at atm pressure to yield 0.068 g (87%) of exo-brevicomin (15) which had spectral data identical to that reported for natural exo-brevicomin (15).[24]

IR ($CHCl_3$) 840, 875, 925, 965, 1000, 1015, 1030, 1080, 1105, 1140, 1170, 1190, 1200, 1240, 1335, 1355, 1385, 1470, 2900, and 2990 cm^{-1};

NMR ($CDCl_3$) δ 0.9 (t, J = 7 Hz, 3H), 1.4 (s, 3H), 1.3-2.1 (m, 8H), 3.9 (t, J = 7 Hz, 1H), and 4.1 (br s, 1H);

mass spectrum m/e (rel intensity) 41(16), 43(100), 57(16), 67(16), 68(19), 71(16), 85(52), 86(25), 88(36), 89(17), 114(82), 127(15), and 156(30).

Resolution of α-(exo-7-ethyl-6,8-dioxabicyclo[3.2.1]octan-5-yl) acetic acid (189)

A solution of 0.40 g (2.0 mmol) of carboxylic acid 189 in 10 mL of dry dichloromethane was treated with 0.242 g (2.0 mmol) of (+)-α-methyl-benzylamine. The mixture was stirred at room temperature for 2 h and the solvent was removed. The resulting solid was crystallized from ether-hexane. After two such recrystallizations 0.18 g of salt, mp 110-115° C, was obtained. This salt was dissolved in 10% hydrochloric acid and extracted several times with ethyl ether. The extracts were combined and and worked up to yield 0.100 g of partially resolved carboxylic

acid 189, $[\alpha]_D^{25}$ + 39.8° (0.20 g/mL, Et_2O). This acid (0.100 g) was decarboxylated as described before to yield 0.06 g of (+)-exo-brevicomin (15), $[\alpha]_D^{26}$ + 51.8° (0.12 g/mL, Et_2O) [lit.[42] $[\alpha]_D^{24}$ = + 84.1° (ether)].

Synthesis of (-)-α-Multistriatin (18α)

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (191)

A mixture of 120 g (618.5 mmol) of methyl α-D-glucopyranoside (71), 90 g of anhydrous zinc chloride, and 300 mL of benzaldehyde was stirred in a 1 L flask for 18 h. The mixture was poured slowly, with stirring into 2 L of cold water, whereupon the product crystallized readily. The solid was suspended in 150 mL of petroleum ether and this mixture was stirred for 30 min to aid in removing the excess benzaldehyde. The product was filtered, washed twice with 200 mL of cold water, twice with petroleum ether, and again with 200 mL of cold water. The product was dried overnight in air and then in a vacuum oven at 70° C; crude yield of benzylidene compound, satisfactory for the next step, was about 120 g (70%), mp 161-163° C. A small amount of the crude product was purified by recrystallization from chloroform-ethyl ether to give pure methyl 4,6-O-benzylidene-α-D-glucopyranoside (191), mp 162-164° C [lit.[73] mp 163-164° C]. This compound was characterized by;

IR ($CHCl_3$) 3500 and 3630 cm^{-1};

NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.0-4.3 (m, 8H), 4.6 (d, J = 3 Hz, 1H), 5.40 (s, 1H), and 7.1 and 7.65 (m, 5H);

mass spectrum m/e (rel intensity) 45(34), 47(38), 49(41), 105(95), 107(100), 133(48), 162(34), 179(55), and 282(73).

Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-glucopyranoside (192)

To a solution of 60 g (213 mmol) of methyl 4,6-O-benzylidene-α-D-glucopyranoside in 420 mL of pyridine was added 50% excess of p-toluenesulfonyl chloride (120 g) and the mixture was allowed to stand at room temperature for 7 days. The mixture was poured onto cracked ice, whereupon the ditosyl compound crystallized readily. The solution was decanted and extracted with 3 x 300 mL portions of dichloromethane. The dichloromethane extracts were used to dissolve the crude solid and the solution washed several times with dilute hydrochloric acid at 0° C until no trace of pyridine could be detected. It was then washed with water and aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and ethyl ether was added to the resulting thin syrup to effect crystallization. The yield of the material, pure enough for the next step was 100 g (80%). Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-glucopyranoside (192) was recrystallized from chloroform-ethyl ether, needles, mp 148-149° C[lit.[73] mp 147-148° C]. This compound was characterized by;

IR ($CHCl_3$) 1180 and 1605 cm^{-1};

NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.42 (s, 3H), 3.35(2, 3H), 3.5-4.4 (m, 4H), 4.47 (d, J = 3 Hz, 1H), 4.8-5.1 (m, 2H), 5.23 (br s, 1H), and 6.6-7.8 (m, 13H);

mass spectrum m/e (rel intensity) 69(13), 91(70), 105 (21), 121(18), 139(17), 149(15), 155(100), 156(14), 157(30), 203(8), 261(9), 269(10), 375(37), 381(25), 435(26), and 590(8).

Methyl 4,6-O-benzylidene-2,3-di-O-methanesulfonyl-α-D-glucopyranoside (193)

Benzylidene diol 191 (20.0 g, 70.90 mmole) was dissolved in ca. 125 mL of dry pyridine. The solution was cooled in ice and 19.95 g (175 mmol) of methanesulfonyl chloride was added. White heavy precipitation was observed. The reaction was stirred at room temperature for 24 h. The mixture was then poured onto ice and extracted several times with dichloromethane. The combined extracts were washed several times with dilute hydrochloric acid until no trace of pyridine could be detected. It was then washed once with water, once with sodium bicarbonate and water, dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to ca. 150 mL and ethyl ether was added to induce crystallization. The yield of the recrystallized methyl 4,6-O-benzylidene-2,3-di-O-methanesulfonyl-α-D-glucopyranoside (193) was 25.0 g (81%); mp 186-188° C. This compound was characterized by;

IR ($CHCl_3$) 1100, 1130, 1180 and 1420 cm^{-1};

NMR ($CDCl_3$) δ 2.87 (s, 3H), 3.17 (s, 3H), 3.48 (s, 3H), 3.6-4.8 (m, 5H), 4.8-5.2 (m, 2H), 5.51 (s, 1H), and 7.1-7.6 (m, 5H);

mass spectrum: a) high resolution calcd for $C_{16}H_{22}O_{10}S_2$: 438.0655 amu; found: 438.0655;

b) low resolution m/e (rel intensity) 47(13), 49(100), 69(4), 79(4), 107(8), 116(6), 121(4), 149(3), 157(4), 185(4), 193(7), 229(3), 289(3), 299(8), 359(3), 437(11), and 438(7).

Methyl 2,3-anhydro-4,6-0-benzylidene-α-D-allopyranoside (194)

A solution of 100 g (169 mmol) of the ditosyl compound 192 in 1.5 L of anhydrous dichloromethane was cooled in ice and a cold solution containing 19.60 g (852 mmol) sodium in 450 mL of anhydrous methanol was added. The mixture was kept in the refrigerator for 4 days with occasional shaking and then at room temperature for 2 days. The reaction mixture was diluted with water and the dichloromethane layer separated. The aqueous layer was extracted several times with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and solvents were removed under reduced pressure. The product crystallized readily, and was filtered and washed with ether. The crude product was recrystallized from chloroform-ethyl ether to yield 38.25 g (85%) of pure methyl 2,3-anhydro-4,6-0-benzylidene-α-D-allopyranoside (194), needle, mp 198-200° C [lit.[73] mp 200° C]. This compound was characterized by;

IR ($CHCl_3$) 900, 970, 1060, 1090, 1105, 1140, 1390, 2900, and 2950 cm^{-1};

NMR ($CDCl_3$) δ 3.43 (s, 3H), 3.5-4.4 (m, 6H), 4.8 (d, J = 2 Hz, 1H), 5.48 (br s, 1H), and 7.1-7.6 (m, 5H);

mass spectrum m/e (rel intensity) 45(17), 58(19), 59 (18), 77(17), 91(16), 105(31), 115(100), 127(33), 221(35), and 264(72).

Methyl 2,3-anhydro-4,6-0-benzylidene-α-D-allopyranoside (194) was also prepared from dimesylate 193. A solution of sodium methoxide was prepared using 12.7 g (552 mmol) of sodium and 188 mL of dry methanol. Methyl 4,6-0-benzylidene-2,3-di-0-methanesulfonyl-α-D-glucopyranoside (193) (48.18 g, 110 mmol) in 780 mL of dichloromethane was added to the sodium methoxide solution at 0° C. The reaction mixture was kept at 0° C for 3 days and stirred at room temperature for 10 h. Work-up procedure was the same as above. The crude product was recrystallized from a mixture of dichloromethane and ethyl ether to give 26.40 g (91%) of pure epoxide 194. The spectral data were the same as listed above.

Methyl 4,6-0-benzylidene-2-deoxy-2-C-methyl-α-D-altropyranoside (195)

Cuprous iodide (15.2 g, 80.0 mmol) in 90 mL of anhydrous ethyl ether was stirred under nitrogen at 0° C. Then 120 mL (1.7 M) of methyllithium was added to the suspension and a light clear yellow solution was formed. Epoxy compound 194 (10.56 g, 40 mmol) was added to the resulting lithium dimethyl-

cuprate reagent and the reaction was stirred at 0° C for 4 h. The reaction mixture was diluted with ethyl ether, washed with dilute ammonium chloride and saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the crude product recrystallized from ethyl ether-n-hexane to yield 8.44 g (75%) of methyl 4,6-0-benzylidene-2-deoxy-2-C-methyl-α-D-altropyranoside (195), chunky prisms, mp 112-113° C (lit.[74] mp 110-111° C). This compound was characterized by;

IR ($CHCl_3$) 3450-3750 cm^{-1};

NMR ($CDCl_3$) δ 1.09 (d, J = 7 Hz, 3H), 2.0-2.6 (m, 1H), 3.0 (d, J = 7 Hz, 1H), 3.33 (s, 3H), 3.4-4.5 (m, 6H), 5.53 (br s, 1H), and 7.0-7.6 (m, 5H);

mass spectrum m/e (rel intensity) 45(41), 71(43), 72(38), 91(47), 105(100), 106(38), 107(94), 113(66), 131(70), 162(27), 179(97), and 280(88).

Methyl 4,6-0-benzylidene-2-deoxy-2-C-methyl-3-0-[(thiomethyl)-thiocarbonyl]-α-D-altropyranoside (196)

Sodium hydride 1.52 g (31.80 mmol), as a 50% mineral oil dispersion (washed oil-free with ethyl ether), was placed in a 250 mL dry round bottom flask fitted with a magnetic stirrer, reflux condenser, and drying tube. Thirty mL of anhydrous ethyl ether was added to the sodium hydride, then 7.20 g (25.70 mmol) of methyl 4,6-0-benzylidene-2-deoxy-2-C-methyl-

α-D-altropyranoside (195) was dissolved in ca. 150 mL of ethyl ether and added dropwise to the sodium hydride suspension. The reaction mixture was refluxed for 3 h, then 3.18 mL of carbon disulfide and 3.24 mL of iodomethane were added to the solution after 3 hr and 6 h respectively. The reaction was refluxed for another 3 h and water was added to destroy the excess sodium hydride. The reaction mixture was diluted with ethyl ether, washed twice with water, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to give 9.18 g (96%) of crude product which was used directly in the next step. A small amount of compound 196 was purified by preparative TLC (CCl_4:Et_2O, 4:1 v/v) and characterized by the following spectral data, all of which were the same as those reported;[74]

IR ($CHCl_3$) 950, 1005, 1040, 1060, 1100, 1140, and 2950 cm^{-1};

NMR ($CDCl_3$) δ 1.18 (d, J = 7 Hz, 3H), 2.55 (s, 3H), 2.4-2.8 (m, 1H), 3.33 (s, 3H), 3.5-4.5 (m, 5H), 5.55 (br s, 1H), 5.75 (m, 1H), and 7.1-7.6 (m, 5H);

mass spectrum m/e (rel intensity) 41(29), 43(30), 55(21), 57(29), 69(23), 85(44), 91(38), 105(56), 113(44), 121(32), 125 (25), 131(29), 149(100), 150(14), 231(20), 262(47), 263(24), and 370(11).

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-α-D-arabino hexopyranoside (197)

A solution of 22.2 g (60.0 mmol) of the S-methyl dithiocarbonate compound 196 in 260 mL of dry toluene was added over 1.5 h to 34.92 g (120.0 mmol) of tri-n-butylstannane in 240 mL refluxing dry toluene under dry nitrogen. Refluxing was continued overnight, and the solvent was removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100-200 mesh), and a mixture of petroleum ether and ethyl ether (9.5:1, v/v, then 1:1, v/v) to yield 14.30 g (90%) of pure compound 197, $[\alpha]_D^{28}$ + 82.7° (142 mg/mL, ethyl ether). This compound was characterized by;

IR ($CHCl_3$) 930, 950, 1005, 1050, 1100, 1120, 1140, 1380, and 1460 cm^{-1};

NMR ($CDCl_3$) δ 1.13 (d, J = 7 Hz, 3H), 1.4-2.3 (m, 3H), 3.33 (s, 3H), 3.5-4.3 (m, 4H), 4.33 (s, 1H), 5.50 (s, 1H), and 7.0-7.5 (m, 5H);

mass spectrum: a) high resolution calcd for $C_{15}H_{20}O_4$: 264.1362 amu; found: 264.1374;

b) low resolution m/e (rel intensity) 55(15), 73(12), 83(19), 105(21), 115(100), 116(11), 149(11), 221(10), and 264(22).

Methyl 2,3-dideoxy-2-C-methyl-α-D-arabino-hexopyranoside (198)

To a solution of 12.41 g (47.0 mmol) of compound 197 in ca. 30 mL of methanol was added 0.40 g of p-toluenesulfonic acid monohydrate. The reaction mixture was stirred at room temperature and followed by TLC. After the reaction was complete (2.5 h), solid sodium carbonate was added to neutralize the acid. The reaction mixture was filtered, and the methanol was removed under reduced pressure. The residue was dissolved in water and ethyl ether, and extracted several times with water. The combined aqueous extracts were concentrated under reduced pressure and the residue dissolved in dichloromethane and dried over anhydrous magnesium sulfate. The dichloromethane was removed under reduced pressure to give a thick oil, 6.81 g (82%) which was pure enough for the next step. Compound 198 was characterized by the following spectral data;

IR ($CHCl_3$) 960, 1050, 1100, 1150, 2975, 3500, and 3650 cm^{-1};

NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3H), 1.5-2.2 (m, 3H), 2.83 (br s, 2H), 3.33 (s, 3H), 3.6-4.2 (m, 4H), and 4.3 (br s, 1H);

mass spectrum: a) high resolution calcd. for $C_8H_{16}O_4$: 176.1049 amu, found: 176.1047;

b) low resolution m/e (rel intensity) 41(24), 43(27), 55(28), 56(29), 57(27), 72(100), 74(55), 83(23), 113(26), 115(27), 145(33), and 176(1).

Methyl 2,3-dideoxy-2-C-methyl-6-O-triphenylmethyl-α-D-arabino-hexopyranoside (199)

Compound 198 (3.168 g, 18 mmol) was treated with 7.5 g (27 mmol) of trityl chloride in 30 mL of anhydrous pyridine. The reaction mixture was stirred at room temperature for 3 days. It was then poured onto ice cold water, acidified and extracted several times with dichloromethane. The combined extracts were washed with dilute sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and solvents removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100-200 mesh) and a mixture of carbon tetrachloride and ethyl ether (4:1, v/v) as eluent. The yield of compound 199 was 6.465 g (86%) and it had mp 147-149° C, $[\alpha]_D^{26}$ + 26° (200 mg/mL, chloroform). This compound was characterized by;

IR ($CHCl_3$) 1600 and 3570 cm^{-1};

NMR ($CDCl_3$) δ 0.99 (d, J = 7 Hz, 3H), 1.4-2.1 (m, 3H), 2.39 (br s, 1H), 3.31 (s, 3H), 3.0-3.7 (m, 4H), 4.26 (s, 1H), and 6.7-7.4 (m, 15H);

mass spectrum m/e (rel intensity) 43(4), 55(5), 72(4), 77(6), 83(6), 105(13), 113(13), 127(5), 165(27), 175(21), 183 (15), 243(100), 244(27), 258(4), 259(7), 260(5), 309(5), 386(4), and 418(3).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.61; H, 7.21.

Methyl 2,3-Dideoxy-2-C-methyl-6-O-triphenylmethyl-α-D-threo-hexopyranosid-4-ulose (206)

A sample of 6 g (60 mmol) of chromium trioxide was added to a magnetically stirred solution of 9.5 g (120 mmol) of anhydrous pyridine in ca. 150 mL anhydrous dichloromethane. The flask was stopped with a drying tube, and the deep burgundy solution stirred for 15 min at room temperature. At the end of this period, a solution of 4.18 g (10 mmol) of compound 199 in 5 mL of dry dichloromethane was added in one portion. A tarry, black deposit separated immediately. After stirring for 18 h at room temperature, the solution was decanted and the dichloromethane removed under reduced pressure. The residue was dissolved in ethyl ether and the reaction flask was rinsed several times with ethyl ether. The ether layers were combined and filtered through a bed of celite. The slight yellow filtrate was washed with dilute hydrochloric acid and aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to give 3.99 g (96%) of compound 206 which was homogeneous from TLC. The crude product was purified by column chromatography using silica gel (100-200 mesh), and a mixture of carbon tetrachloride and ethyl ether (8:1, v/v) as eluent to give 3.35 g (81%) of compound 206, mp 88-89° C; $[\alpha]_D^{28}$ + 98.8° (200 mg/mL, chloroform), which was characterized by;

IR ($CHCl_3$) 1600, 1730, and 2960 cm^{-1};

NMR ($CDCl_3$) δ 1.14 (d, J = 7 Hz, 3H), 1.9-2.6 (m, 3H), 3.2-3.6 (m, 2H), 3.5 (s, 3H), 3.83 (m, 1H), 4.6 (d, J = 4 Hz, 1H), and 7.0-7.7 (m, 15H);

mass spectrum: a) high resolution calcd for $C_{27}H_{28}O_4$: 416.1988 amu; found: 416.1989;

b) low resolution m/e (rel intensity) 43(4), 45(6), 55(4), 59(7), 71(6), 72(8), 105(7), 157(6), 165 (20), 173(5), 183(5), 243(100), 244(24), 259(6), 339(4), and 416(4).

Methyl 2,3,4-trideoxy-2-C-methyl-4-methylene-6-O-triphenylmethyl-α-D-threo-hexopyranoside (207)

A 250 mL 3-necked round-bottom flask containing ca. 120 mL of anhydrous ethyl ether was fitted with a reflux condenser, an addition funnel, a septum stopper and a nitrogen outlet. n-Butyllithium (8.86 mL of 1.58 M, 14 mmol) was added to the flask and 5.00 g (14 mmol) of triphenylmethylphosphonium bromide was added in portions to the n-butyllithium solution. The orange reaction mixture was refluxed for 4 h and 5.82 g (14 mmol) of keto compound 206 in 30 mL of ethyl ether was added slowly. The orange color discharged and a white precipitate was observed. The reaction mixture was then refluxed for 24 h, cooled, and the precipitate was filtered off. The ether filtrate was washed with water and brine, dried, and the solvents were evaporated under reduced pressure. Purification of the crude product was

achieved by column chromatography using silica gel (100-200 mesh) and a mixture of carbon tetrachloride and ethyl ether (10:1, v/v) as eluent to yield 4.53 g (78%) of compound 207, mp 153-154° C; $[\alpha]_D^{22}$ + 45.4° (74 mg/mL, chloroform) and 0.5 g of compound 206. Thus, the yield was 82% based on recovered starting material 206. This product 207 was characterized by the following spectral data;

IR ($CHCl_3$) 1600, 1660, 2960, 3040, and 3100 cm^{-1};

NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 3H), 1.6-2.8 (m, 3H), 3.30 (d, J = 6 Hz, 2H), 3.43 (s, 3H), 4.2-4.4 (m, 2H), 4.62 (m, 2H), and 6.8-7.6 (m, 15H);

mass spectrum: a) high resolution calcd for $C_{28}H_{30}O_3$: 414.2195 amu; found: 414.2214;

b) low resolution m/e (rel intensity) 41(2), 43(2), 77(2), 81(4), 105(5), 109(14), 139(2), 141(50), 142(5), 165(21), 166(4), 183(2), 215(2), 228(3), 241(3), 243(100), 244(21), and 414(1).

Hydrogenation of compound 207

A 100 mL round bottom flask containing 50 mL of anhydrous benzene, 0.7 g of tris(triphenylphosphine)rhodium chloride[85] and 3.31 g (8.0 mmol) of compound 207, was fitted with a magnetic stirrer and connected to an atmospheric pressure hydrogenation apparatus equipped with a graduated burette to measure the uptake of hydrogen. The system was evacuated and filled with hydrogen.

After 24 h, about 1 eq of hydrogen was absorbed. The solvent was removed under reduced pressure and the product was purified by column chromatography using silica gel (100-200 mesh) and a mixture of ethyl acetate and petroleum ether (10:1, v/v) as eluent. Two components were isolated from this chromatography, and these were, in order of elution: methyl 2,3,4-trideoxy-2,4-di-C-methyl-α-D-arabino-hexopyranoside (202) (0.29 g, 9%), and methyl 2,3,4-trideoxy-2,4-di-C-methyl-α-D-lyxo-hexopyranoside (201) (2.74 g, 80%).

Methyl 2,3,4-trideoxy-2,4-di-C-methyl-α-D-arabino-hexopyranoside (202) was characterized by;

IR ($CHCl_3$) 1600 cm^{-1};

NMR ($CDCl_3$) δ 0.58 (d, J = 6 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 13.-2.0 (m, 4H), 2.9-3.6 (m, 3H), 3.38 (s, 3H), 4.4 (br s, 1H), and 6.9-7.6 (m, 15H);

mass spectrum: a) high resolution calcd for $C_{28}H_{32}O_3$: 416.2351 amu; found: 416.2328;

b) low resolution m/e (rel intensity) 83(10), 85(25), 105(15), 111(17), 141(9), 143(60), 165(40), 173 (48), 243(100), 244(31), 258(8), and 416(5).

Methyl 2,3,4-trideoxy-2,4-di-C-methyl-α-D-lyxo-hexopyranoside (201) had $[\alpha]_D^{24}$ + 27° (66 mg/mL, chloroform) and was characterized by;

IR ($CHCl_3$) 1600 cm^{-1};

NMR ($CDCl_3$) δ 0.70 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H), 1.3-2.0 (m, 4H), 3.0-3.3 (m, 2H), 3.45 (s, 3H), 3.8-4.1 (m, 1H), 4.2 (d, J = 5 Hz, 1H), and 6.9-7.6 (m, 15H);

^{13}C NMR ($CDCl_3$) δ 15.93, 18.3, 30.61, 33.75, 34.73, 55.35, 63.10, 71.96, 104.34, 126.98, 127.77, 128.83, and 144.21;

mass spectrum: low resolution m/e (rel intensity) 55(7), 72(7), 83(8), 85(20), 105(13), 111(16), 115(4), 141(8), 143(65), 144(7), 165(25), 166(6), 173(63), 174(9), 183(7), 229(5), 243 (100), 244(36), 258(3), and 416(1).

Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.73; H, 7.74. Found: C, 80.51; H, 7.55.

(2S, 4S, 4'S)-1,1-Diethylthio-2-methyl-4-(2',2'-dimethyl-1',3'-dioxacyclopent-4'-yl)pentane (217)

To a mixture of 0.83 g of 201 and 1.80 mL of concentrated hydrochloric acid at 0° C was added 1.80 mL of ethanethiol. The reaction mixture was stirred for 24 h at 0° C. Ice and water were added to the reaction mixture and the mixture extracted several times with ethyl acetate. The organic extract was washed with brine and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography, (silica gel 100-200 mesh) using a mixture of petroleum ether and ethyl ether (3:1, v/v); after the side-product had completely eluted, the solvent was changed to ethyl ether. The yield of compound 215 from this chromatography was 0.44 g (83%).

The NMR ($CDCl_3$) of compound 215 had absorptions at δ 0.92 (d, J = 7 Hz, 3H), 1.16 (d, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 6H), 1.4-2.3 (m, 4H), 2.2-3.0 (m, 4H), 3.26 (br s, 2H), 3.4-3.7 (m, 3H), and 3.75 (d, J = 3 Hz, 1H). Compound 215 was characterized as its isopropylidene derivative.

To a solution of compound 215 (0.43 g, 1.60 mmol) in 9 mL of 2,2-dimethoxypropane was added ca. 20 mg of p-toluenesulfonic acid. After stirring at room temperature for 2 h, the reaction mixture was diluted with chloroform, washed with 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and solvents were removed under reduced pressure. The crude product was distilled (Kugelrohr, bath temperature 100° C/0.2 torr) to give 0.40 g (82%) of 217. A small sample was purified by TLC using a mixture of petroleum ether and ethyl ether (4:1, v/v) to give compound 217 and was characterized by;

IR ($CHCl_3$) 860, 1060, 1160, 1260, 1280, 1380, and 1460 cm^{-1};

270 MHz NMR ($CDCl_3$) δ 0.98 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.5-1.7 (m, 3H), 2.0-2.2 (m, 1H), 2.5-2.8 (m, 4H), and 3.6-4.2 (m, 4H);

mass spectrum: a) high resolution calcd for $C_{15}H_{30}O_2O_2$: 306.1687 amu; found: 306.1690;

b) low resolution m/e (rel intensity) 43(38), 55(18), 75(27), 103(19), 107(55), 115(56), 125(29), 135(30), 169(19), 187(100), and 306(30).

(2'S, 4'R, 5'S)-2-(2',4'-Dimethyl-5',6'-dihydroxyhex-2'-yl)-1,3-dithiane (218)

To a solution of 2.08 g (5.0 mmol) of hydrogenated compound 201 in ca. 40 mL of dry dichloromethane was added 1.63 g (15 mmol) of 1,3-dithiolpropane and 1.4 mL of distilled boron trifluoride etherate at 0° C. The reaction was stirred at 0° C for 18 h. It was then diluted with ethyl acetate, washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. Purification of the crude product was achieved by column chromatography using silica gel (100-200 mesh), and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent. After the side product had completely eluted, the eluting solvent was changed to ethyl acetate. The yield of compound 218 from this chromatography was 1.0 g (80%) and this product was characterized by;

IR ($CHCl_3$) 3500 and 3660 cm^{-1};

NMR ($CDCl_3$) δ 0.98 (d, J = 6 Hz, 3H), 1.1 (d, J = 6 Hz, 3H), 1.5-2.5 (m, 8H), 2.7-3.1 (m, 4H), 3.4-3.7 (m, 3H), and 4.12 (d, J = 4 Hz, 1H);

mass spectrum: a) high resolution calcd for $C_{11}H_{22}O_2S_2$: 250.1061 amu; found: 250.1085;

b) low resolution m/e (rel intensity) 41(10), 43(7), 55(6), 73(5), 119(100), 120(8), 121(10), 143(5), 219(5), and 250(16).

(2'S, 4'R, 4"S)-2-[4'-(2",2"-Dimethyl-1",3"-dioxacyclopent-4"-yl)pent-2'-yl]-1,3-dithiane (219)

To a solution of 1.0 g (4.0 mmol) of diol dithiane 218 in 20 mL of 2,2-dimethoxypropane was added a catalytic amount of p-toluenesulfonic acid (0.10 g). The reaction was stirred at room temperature for 1.5 h. It was then diluted with chloroform, washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. The crude product was purified by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent. From this chromatography 1.02 g (88%) of compound 219 was isolated. Kugelrohr distillation (bath temperature 120° C/0.1 torr) of 219 isolated from this column had $[\alpha]_D^{25}$ - 6.2° (150 mg/mL, ethyl ether), and was characterized by;

IR ($CHCl_3$) 920, 1070, 1380, 1390, and 2975 cm^{-1};

270 MHz NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3H), 1.07 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.5-1.9 (m, 4H), 1.95-2.2 (m, 2H), 2.75-3.0 (m, 4H), 3.65 (t, J = 7 Hz, 1H), 3.85 (q, J = 7 Hz, 1H), 4.01 (t, J = 7 Hz, 1H), and 4.16 (d, J = 4 Hz, 1H);

mass spectrum m/e (rel intensity) 41(22), 43(38), 72(21), 119(100), 159(31), 161(18), 232(24), 275(44), and 290(58).

Anal. Calcd for $C_{14}H_{26}O_2S_2$: C, 57.89; H, 9.02. Found: C, 57.70; H, 9.00.

(2'S, 4'R, 4"S)-2-Ethyl-2-[4'-(2",2"-dimethyl-1",3"-dioxacyclopent-4"-yl)pent-2'-yl]-1,3-dithiane (220)

A solution of 0.58 g (2.0 mmol) of compound 219 in ca. 8 mL of dry n-hexane (distilled over calcium hydride) was placed in a 25 mL round bottom flask fitted with a magnetic stirrer and nitrogen outlet. The flask was cooled to ca. -20° C (dry ice and carbon tetrachloride) and 1.5 mL (2.0 M in pentane, 3 mmol) of t-butyllithium was added dropwise. The reaction was stirred at ca. -20° C for 2 h, then kept in the freezer (ca. -10° C) for 16 h. The temperature of the reaction mixture was then raised to 0° C and 0.4 mL (.78 g, 5 mmol) of iodoethane in 1.74 mL (5 eq) of hexamethylphosphoramide was added and a white precipitate formed immediately. The reaction was stirred for 5 hr, diluted with ethyl ether, washed with ice cold dilute hydrochloric acid, sodium bicarbonate solution, and brine, dried over anhydrous sodium sulfate, and the solvents were removed under reduced pressure. The crude product was purified by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent to yield 0.506 g (80%) of compound 220. Kugelrohr distillation (bath temperature 128° C/0.1 torr) of 220 isolated from this column had $[\alpha]_D^{25}$ -28° (50 mg/mL, ethyl ether); and was characterized by:

IR ($CHCl_3$) 860, 1060, 1160, 1380, 1480, and 2970 cm^{-1};

270 MHz NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.01 (d, J = 7 Hz, 3H), 1.1 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.41 (s, 3H),

1.5-2.2 (m, 8H), 2.6-3.0 (m, 2H), 3.7 (t, J = 7 Hz, 3H), and 3.9-4.1 (m, 2H);

mass spectrum m/e (rel intensity) 41(12), 43(16), 134(15), 147(100), 148(13), 149(15), 303(18), and 320(16).

Anal. calcd for $C_{16}H_{30}O_2S_2$: C, 60.30; H, 9.49. Found: C, 60.20; H, 9.53

(2'S, 4'R, 5'S)-2-ethyl-2-(2',4'-dimethyl-5',6'-dihydroxyhex-2-yl)-1,3-dithiane (221)

To a solution of 0.35 g (1.1 mmol) of compound 220 in ca. 15 mL of methanol was added a catalytic amount of p-toluenesulfonic acid monohydrate (0.02 g). The reaction mixture was stirred at room temperature for 24 h. Solid sodium carbonate was added to neutralize the acid. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent to yield 0.20 g (90%) of compound 221, $[\alpha]_D^{24}$ - 42.6° (50 mg/mL, ethyl ether). This compound was characterized by the following spectral data;

IR ($CHCl_3$) 900, 1005, 1050, 1280, 1380, 1460, 2970, 3500, and 3650 cm^{-1};

NMR ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.02 (t, J = 7 Hz, 3H), 1.7-2.3 (m, 8H), 2.38 (br s, 2H),

2.6-3.0 (m, 4H), and 3.4-3.8 (m, 3H);

mass spectrum: a) high resolution calcd for $C_{13}H_{26}O_2S_2$: 278.1374 amu; found: 278.1358;

b) low resolution m/e (rel intensity) 41(8), 47(11), 83(36), 85(23), 147(100), 148(12), 149(13), and 278(12).

α-Multistriatin (18α)

To a stirred solution of 0.43 g (1.6 mmol) of mercuric chloride and 0.17 g (0.80 mmol) of mercuric oxide in ca. 5 mL of dry acetonitrile was added a solution of 0.1974 g (0.71 mmol) of compound 221 in 5 mL of anhydrous acetonitrile under nitrogen. The reaction mixture was refluxed for 4 h with stirring. After cooling, the reaction mixture was filtered and the solid washed with pentane. An equal amount of saturated brine solution was added to the filtrate and this solution was extracted several times with pentane. The organic extracts were washed with aqueous ammonium acetate, dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. Kugelrohr distillation (bath temperature 110° C/20 torr) of the crude produce gave 0.096 g (80%) of α-multistriatin (18α), $[\alpha]_D^{24}$ - 46° (10 mg/mL, hexane); [lit.[26] bp 90° C/20 torr, bath temperature], and all the spectral data were identical to those reported.[26,49] GLC analysis (column C, 100° C) showed a major component (>90%). This was further identified by comparison with a sample of (±)-α-multistriatin kindly provided by Dr. J. W. Peacock; 18α was characterized by;

IR ($CHCl_3$) 895, 920, 1035, 1130, 1180, 1255, 1460, 2925, and 2980 cm^{-1};

NMR ($CDCl_3$) δ 0.81 (d, J = 7 Hz, 3H), 0.81 (d, J = 7 Hz, 3H), 0.93 (t, J = 7 Hz, 3H), 1.4-2.2 (m, 6H), 3.68 (m, 1H), 3.89 (m, 1H), and 4.20 (m, 1H);

mass spectrum: a) high resolution calcd for $C_{10}H_{18}O_2$: 170.1307 amu; found: 170.1298;

b) low resolution m/e (rel intensity) 41(8), 43(6), 54(9), 55(22), 57(100), 71(20), 81(16), 96(25), 99(11), 128(25), and 170(19).

Synthesis of Lineatin or 3,3,7-trimethyl-2,9-dioxatricyclo [3.3.1.$0^{4,7}$]nonane (22)

1-Acetoxybutan-3-one (235)[98]

A mixture of 35 g (500 mmol) of methyl vinyl ketone, 150 mL of glacial acetic acid, and a catalytic amount of water was heated under reflux and under nitrogen for 24 h. Purification of the crude product was achieved by fractional distillation to give 26.0 g (40%) of 1-acetoxybutan-3-one (135), bp 92-95° C/20 torr [lit.[98] bp 78-84° C/14 torr]. This compound was further characterized by;

IR ($CHCl_3$) 1720 and 1735 cm^{-1};

NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.18 (s, 3H), 2.73 (t, J = 7 Hz, 2H), and 4.28 (t, J = 7 Hz, 2H);

mass spectrum m/e (rel intensity) 42(8), 43(100), 55(13), 61(10), 70(10), 71(9), 87(8), 88(17), 115(3), and 130(3).

Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (236)[99]

To a solution of 14.9 g (148 mmol) of diisopropylamine in 250 mL of anhydrous ethyl ether, was added via a syringe a solution of 91.6 mL of 1.6 M (147 mmol) n-butyllithium in hexane at 0° C under nitrogen. After stirring for ½ hr at 0° C, the reaction was cooled to -78° C (dry ice plus acetone) and 12.18 g (138 mmol) of anhydrous ethyl acetate was added slowly. The reaction mixture was stirred for 15 min and 17.32 g (133 mmol)

of 1-acetoxybutan-3-one (235) was added. After 15 min ca. 10 mL of dilute hydrochloric acid was added slowly. The temperature of the reaction mixture was then raised to room temperature. The reaction mixture was diluted with water and extracted several times with ethyl ether. The combined ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to give 25.52 g (88%) of ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (236). Purification was achieved by column chromatography using a mixture of ethyl acetate and petroleum ether (3:7 v/v) as eluent to give 23.6 g (81%) of compound 236 which had spectral data identical to that reported;[99]

IR ($CHCl_3$) 1730 and 3560 cm^{-1};

NMR ($CDCl_3$) δ 1.3 (s, 3H), 1.27 (t, J = 7 Hz, 3H), 1.86 (t, J = 7 Hz, 2H), 2.03 (s, 3H), 2.50 (br s, 2H), 3.52 (br s, 1H), 4.12 (q, J = 7 Hz, 2H), and 4.20 (t, J = 7 Hz, 3H);

mass spectrum: m/e (rel intensity) 43(100), 55(11), 71(36), 85(24), 103(12), 112(9), 113(21), 115(8), 132(88), 143 (25), 173(2), and 218(0.1).

Mevalonolactone (237)[98]

A sample of 28.34 g (130 mmol) of ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (236) was weighed into a 2 L round bottom flask and the flask cooled to ca. -10° C. Then 600 mL of ice cold 1 N methanolic potassium hydroxide was added slowly. The reaction mixture was stirred at room temperature for 24 h.

A 10% solution of concentrated hydrochloric acid in methanol was added until the reaction mixture was acidic. Stirring was continued for another 1 h, and methanol removed under reduced pressure. The residue was diluted with ethyl acetate and the solid filtered off. The solid was washed several times with ethyl acetate and the combined filtrates washed once with saturated brine solution, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 13.10 g (78%) of crude mevalonolactone (237). The crude mevalonolactone (237) was used directly in the next step. A small sample was purified by TLC and Kugelrohr distillation at 130° C/0.9 torr [lit.[98] bp 114° C/0.01 torr]. This compound was characterized by;

IR ($CHCl_3$) 1730 and 3375 cm^{-1};

NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.8-2.1 (m, 2H), 2.5-2.7 (m, 2H), 3.52 (br s, 1H), and 4.1-4.9 (m, 2H);

mass spectrum m/e (rel intensity) 43(100), 53(10), 58(23), 71(77), 85(6), 102(7), 103(8), 112(5), 115(4), and 130(4).

3-Methyl-5-hydroxy-2-pentenoic acid δ-lactone (119)[100]

A mixture of 10.4 g (80 mmol) of mevalonolactone (237) and 13.6 g of potassium hydrogen sulfate was heated under vacuum for 1 h and distilled at 72-78° C/0.9 torr to give 8.0 g of colorless liquid. The NMR of the distilled liquid showed it to be a mixture of compounds 238 and 119. The mixture of products was heated again with 3 g of potassium bisulfate to ca. 190° for 0.5 h, allowed to cool, and redistilled at 72-74° C/0.9 torr

to give 7.4 g (83%) of 3-methyl-5-hydroxy-2-pentenoic acid δ-lactone (119). The spectral data below were the same as those reported for this compound:[100]

IR ($CHCl_3$) 1650 and 1725 cm^{-1};

NMR ($CDCl_3$) δ 2.01 (br s, 3H), 2.37 (t, J = 6 Hz, 2H), 4.33 (t, J = 6 Hz, 2H), and 5.73 (m, 1H);

mass spectrum m/e (rel intensity) 41(10), 53(12), 54(44), 55(11), 82(100), and 112(59).

Photoaddition of 3-methyl-5-hydroxy-2-pentenoic acid δ-lactone (119) to allene

A solution of 1.57 g (14.0 mmol) of 3-methyl-5-hydroxy-2-pentenoic acid δ-lactone (119), in 600 mL of acetone was irradiated with a 450-watt Hanovia high pressure mercury arc at room temperature for 4 h through Vycor filter with continual introduction of allene. At the end of the irradiation the solvent was removed by distillation under reduced pressure to give 2.0 g (90%) of a mixture of photoadducts; 1-methyl-7-methylene-4-oxa-cis-bicyclo[4.2.0]octan-5-one (233) and 1-methyl-8-methylene-4-oxa-cis-bicyclo[4.2.0]octan-5-one (234). The crude product was purified by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl acetate (2:3, v/v) as eluent to give 1.67 g (82%) of a mixture of 233 and 234 which could not be separated by TLC. The material was shown to be a 3:2 mixture of 233 and 234 respectively by 270 MHz

NMR and by GLC (using a 23.2 m x 0.28 mm ID whisker-walled column coated with Carbowax 20 M).[3] Since separation of the individual components of the photoadduct mixture was very difficult, the sequence was carried through on the mixture. The fraction isolated by the above chromatography was further distilled at 120° C/0.8 torr (Kugelrohr) and was characterized by;

IR ($CHCl_3$) 1725 cm^{-1};

NMR ($CDCl_3$) - see spectral appendix p. 267

mass spectrum: a) high resolution calcd for $C_9H_{12}O_2$: 152.0838 amu; found: 152.0845;

b) low resolution m/e (rel intensity) 41(13), 67(10), 77(27), 79(39), 91(20), 93(100), 94(24), 95(10), 107(21), 109(22), 124(15), 137(30), and 152(40).

Anal. calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.77; H, 8.16.

Addition of methyllithium to photoadducts 233 and 234

A solution of 8.0 g (52.60 mmol) of photoadducts 247 and 248 in ca. 20 mL of anhydrous ethyl ether was added dropwise to an ice-cooled flask containing 120 mL (210 mmol) of 1.75 M methyllithium in ethyl ether. The mixture was stirred at 0° C

[3] We wish to thank Dr. H. Pierce, Jr., Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada, for the GLC analysis of this compound.

for 2 h and the excess methyllithium was decomposed with a saturated aqueous solution of ammonium chloride. The ether layer was separated and the aqueous layer extracted several times with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to give 9.35 g (97%) of a mixture of diols 247 and 248 which could not be separated by TLC. The crude mixture was pure enough for the next reaction. A small sample of the mixture of products was chromatographed on a 20 x 20 cm silica gel coated plate, thickness 1 mm, using a mixture of ethyl acetate and petroleum ether (7:1, v/v) as eluent. A thick colorless oil was isolated and characterized by the following data;

IR ($CHCl_3$) 1680, 3420, and 3620 cm^{-1};

NMR ($CDCl_3$) - see spectral appendix p. 267

mass spectrum: a) high resolution calcd for $C_{11}H_{20}O_2$: 184.1463 amu; found: 184.1462;

b) low resolution m/e (rel intensity) 41(45), 43(100), 53(13), 55(33), 59(95), 67(24), 79(27), 83(72), 85(36), 86(32), 105(19), 107(34), 111(59), 121(49), 123(30), 135(60), 151(34), and 166(15) ($P-H_2O$).

Oxidation on mixture of diols 247 and 248

A sample of 31.2 g (312 mmol) of chromium trioxide was added to a stirred solution of 49.32 g (624 mmol) of anhydrous

pyridine[83] in ca. 30 mL of anhydrous dichloromethane. The chromium trioxide-pyridine complex was stirred at room temperature for 25 min. Then a solution of 9.20 g (50 mmol) of the mixture diols 247 and 248 in ca. 5 mL of anhydrous dichlormethane was added in one portion. A tarry, black precipitate separated immediately. After stirring for 4.5 h at room temperature, the solution was decanted from the reaction, and the dichloromethane removed under reduced pressure. The residue was diluted with ethyl ether and the reaction flask rinsed several times with ethyl ether. The combined ether layers were filtered through a bed of celite, washed with ice-cold dilute hydrochloric acid, aqueous sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to give 7.60 g (84%) of a mixture of 2,2,6-trimethyl-8-methylene-3-oxa-cis-bicyclo[4.2.0]octan-4-one (249) and 2,2,6-trimethyl-7-methylene-3-oxa-cis-bicyclo[4.2.0]octan-4-one (250). The crude products were purified by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl acetate (2:3, v/v) as eluent. The fraction isolated from this chromatography was homogeneous by TLC analysis, and shown to be a 3:2 mixture of 249 and 250 by NMR and GLC (using a 23.4 m x 0.28 mm ID whisker-walled column coated with silar -10 C at 180° C) [4] Since separation of the individual components

[4] See foot-note (3) on p. 232.

from the mixture was very difficult, the next sequence of steps was carried through on the mixture. The mixture from the chromatography was further distilled at 100° C/1.0 torr (Kugelrohr) to afford 6.5 g (72%) of a mixture of 249 and 250 which was characterized by;

IR ($CHCl_3$) 1680 and 1725 cm^{-1};

NMR ($CDCl_3$) - see spectral appendix p. 268

mass spectrum: a) high resolution calcd for $C_{11}H_{16}O_2$: 180.1150 amu; found: 180.1158;

b) low resolution m/e (rel intensity) 41(33), 43(69), 79(77). 80(90), 93(32), 109(24), 121(20), 123(31), 125(31), 139(14), 165(10), and 180(17).

Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.10; H, 8.95.

Ozonolysis of alkenes 249 and 250

A stream of ozone and oxygen was bubbled through a solution of 6.93 g (38.50 mmol) of a mixture of compounds 249 and 250 in ca. 250 mL of anhydrous dichloromethane at -78° C until the solution turned blue. Excess dimethylsulfide was added slowly. The reaction mixture was allowed to stir at -78° C for 20 min, warmed slowly to room temperature, washed with water, and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to give 6.27 g (89%) of crude product which was purified by column chromatography using silica

gel (100-200 mesh) and a mixture of petroleum ether and ethyl acetate (1:1, v/v) as eluent. The fraction isolated from this chromatography gave 4.8 g (69%) of a mixture of 2,2,6-trimethyl-3-oxa-cis-bicyclo[4.2.0]octan-4,8-dione (251) and 2,2,6-trimethyl-3-oxa-cis-bicyclo[4.2.0]octan-4,7-dione (252). The mixture of products could not be separated by TLC and was characterized by the following spectral data;

IR ($CHCl_3$) 1730 and 1785 cm^{-1};

NMR ($CDCl_3$) - see spectral appendix p. 268

mass spectrum: a) high resolution calcd for $C_{10}H_{14}O_3$: 182.0943 amu; found: 182.0953;

b) low resolution m/e (rel intensity) 40(27), 41(60), 42(20), 43(78), 44(38), 51(10), 53(32), 54(17), 55(33), 59(10), 67(35), 68(47), 69(30), 70(14), 77(14), 79(30), 81(53), 82(26), 83(28), 95(25), 96(100), 97(79), 98(42), 123(46), 125(89), 126(23), 141(19), 167(8), and 182(6).

Reduction of compounds 251 and 252 with L-Selectride

A solution of 3.19 g (17.5 mmol) of a mixture of 251 and 252 in ca. 20 mL of anhydrous THF was cooled to -78° C and 21 mL (1.0 M in THF, 21 mmol) of L-Selectride[102] was added at -78° C under nitrogen. The reaction was stirred at that temperature for 3 h, and 10 mL of 10% sodium hydroxide and 10 mL of 30% hydrogen peroxide were added slowly. The temperature was then raised to 0° and the reaction was stirred for 1 h. It was

then acidified with dilute hydrochloric acid and the aqueous layer extracted several times with ethyl acetate. The extracts were washed with an equal volume of saturated brine solution, then with saturated aqueous sodium bicarbonate, and finally dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to give 3.01 g (94%) of crude product. A small amount of crude product (140 mg) was chromatographed using a mixture of ethyl acetate and petroleum ether (7:3, v/v) as eluent. The fraction isolated from this chromatography gave 0.102 g (73%) of a mixture of 8-hydroxy-3,2,6-trimethyl-3-oxa-cis-bicyclo[4.2.0]octan-4-one (253) and 7-hydroxy-2,2,6-trimethyl-3-oxa-cis-bicyclo[4.2.0]octan-4-one (254). The mixture of products was homogeneous by TLC analysis and attempts to separate the individual isomers were not successful. The mixture of products was characterized by the following spectral data;

IR ($CHCl_3$) 1720, 3450 and 3600 cm^{-1};

NMR ($CDCl_3$) - see spectral appendix p. 269

mass spectrum: a) high resolution calcd for $C_9H_{13}O_3$: 184.1099 amu; found: 184.1118;

b) low resolution m/e (rel intensity) 41(28), 43(56), 55(23), 56(17), 59(15), 81(17), 83(15), 85(13), 95(51), 96(29), 97(36), 99(41), 107(20), 123(34), 125(100), 127 (14), 141(78), 167(13),and 184(1).

Lineatin (22) and 3,3,7-trimethyl-2,9-dioxatricyclo[4.2.1.$0^{4,7}$] nonane (23)

A solution of 2.355 g (12.8 mmol) of a mixture of 253 and 254 in ca. 20 mL of anhydrous toluene was cooled to -60° C (chloroform and dry ice) and a solution of 32 mL (1.0 M in hexane, 32 mmol) of diisobutylaluminum hydride[103] in hexane was added dropwise under nitrogen. The reaction mixture was stirred at -60° C for 1 h, and saturated ammonium chloride solution was added. The reaction mixture was warmed to 0° C and acidified by dilute hydrochloric acid. Stirring was continued for an additional 1 h and the mixture was extracted several times with ethyl acetate. The extracts were combined, washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and the solvents removed under reduced pressure to give 1.786 g (83%) of crude product. The material was shown to be an 3:2 mixture of 3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$] nonane (22) (lineatin) and 3,3,7-trimethyl-2,9-dioxatricyclo [4.2.1.$0^{4,7}$]nonane (23) by NMR. Purification was achieved by column chromatography using silica gel (100-200 mesh) and a mixture of petroleum ether and ethyl ether (3:2, v/v) as eluent. Two components were isolated from this chromatography, and these were, in order of elution, lineatin (22) (0.619 g, 29%) and 3,3,7-trimethyl-2,9-dioxatricyclo[4.2.1.$0^{4,7}$]nonane (23) (0.616 g, 29%). All the spectral data of compound 22 were the same as those published by Silverstein et al. for lineatin (22).[29]

This synthetic lineatin (22) was distilled at 110° C/20 torr (Kugelrohr) and was characterized by;

IR (CCl_4) 838, 875, 905, 920, 960, 1000, 1020, 1078, 1100, 1125, 1170, 1185, 1210, 1225, 1245, 1318, 1345, 1365, 1380, 1385, 1455, 1470, 2880, 2940, and 2975 cm^{-1};

NMR (100 MHz, CCl_4) δ 1.08 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 1.55-2.1 (m, 5H), 4.34 (t, J = 4 Hz, 1H), and 4.86 (d, J = 3.5 Hz, 1H);

(270 MHz, CCl_4) δ 1.12 (s, 3H), 1.16 (s, 3H), 1.17 (s, 3H), 1.61 (d, J = 10.5 Hz, 1H), 1.69 (dt, J = 10.5, 4 Hz, 1H), 1.83 (d, J = 4 Hz, 1H), 1.91 (dd, J = 12, 4 Hz), 2.04 (dd, J = 12, 4 Hz, 1H), 4.38 (t, J = 4 Hz, 1H), and 4.93 (d, J = 4 Hz, 1H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_2$: 168.1150 amu; found: 168.1148;

b) low resolution m/e (rel intensity) 41(44), 43(43), 55(64), 55(44), 69(34), 83(58), 85(100), 96(84), 97(47), 107(68), 109(51), 111(85), 125(56), 140(12), 153(8), and 168(10).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.76.

3,3,7-Trimethyl-2,9-dioxatricyclo[4.2.1.$0^{4,7}$]nonane (23) was distilled (Kugelrohr) at 110° C/20 torr and was characterized by the following spectral data;

IR (CCl_4) 660, 700, 850, 895, 905, 925, 938, 960, 970,

980, 990, 1000, 1018, 1040, 1050, 1080, 1100, 1115, 1140, 1160, 1178, 1195, 1205, 1220, 1238, 1255, 1295, 1300, 1325, 1345, 1360, 1365, 1382, 1435, 1455, 1470, 2875, 2950, and 2980 cm^{-1};

NMR (100 MHz, CCl_4) δ 1.03 (s, 3H), 1.19 (s, 3H), 1.34 (s, 3H), 1.7-2.45 (m, 5H), 3.86 (t, J = 4 Hz, 1H), and 5.23 (d, J = 4 Hz, 1H);

(270 MHz, CCl_4) δ 1.08 (s, 3H), 1.23 (s, 3H), 1.39 (s, 3H), 1.33 (dd, J = 12, 4 Hz, 1H), 1.9 (m, 2H), 2.09 (d, J = 12 Hz, 1 H), 2.35 (ddd, J = 13, 9, 4 Hz, 1H), 3.93 (t, J = 4 Hz, 1H), and 5.32 (d, J = 4 Hz, 1H);

mass spectrum: a) high resolution calcd for $C_{10}H_{16}O_2$: 168.1150 amu; found: 168.1152;

b) low resolution m/e (rel intensity) 41(37), 43(30), 55(23), 67(13), 69(37), 71(17), 79(14), 81(18), 83(14), 91(45), 92(29), 93(13), 95(22), 97(16), 105(16), 107 (22), 109(100), 120(15), 125(15), 124(60), 125(20), 130(16), 166(6), and 168(1).

Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.59.

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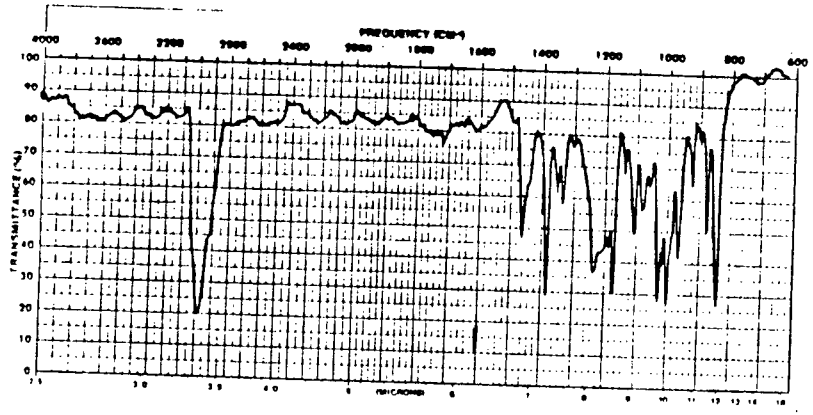
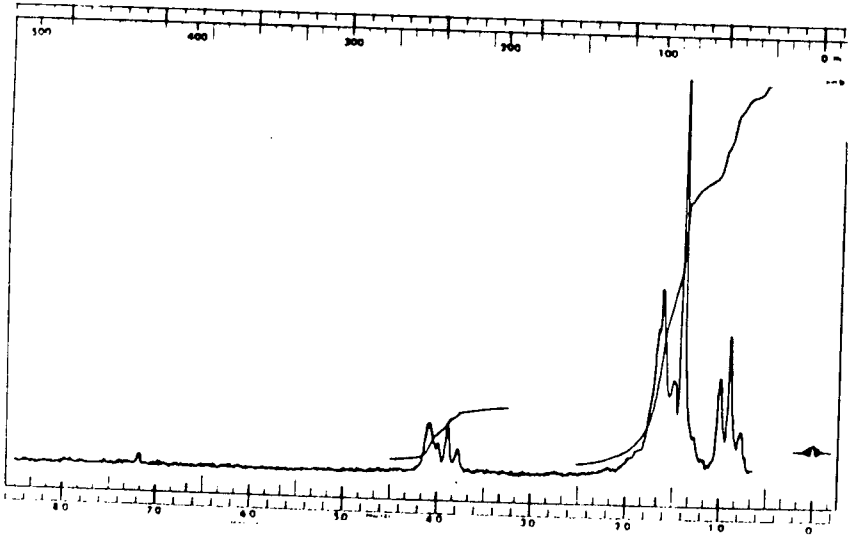
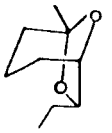
SPECTRAL APPENDIX

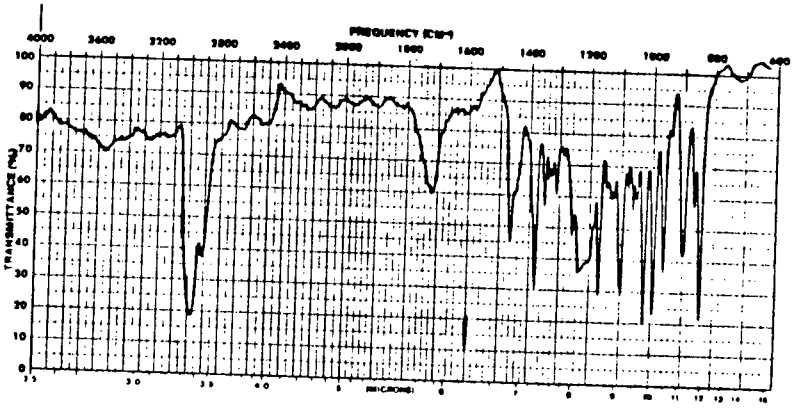
15

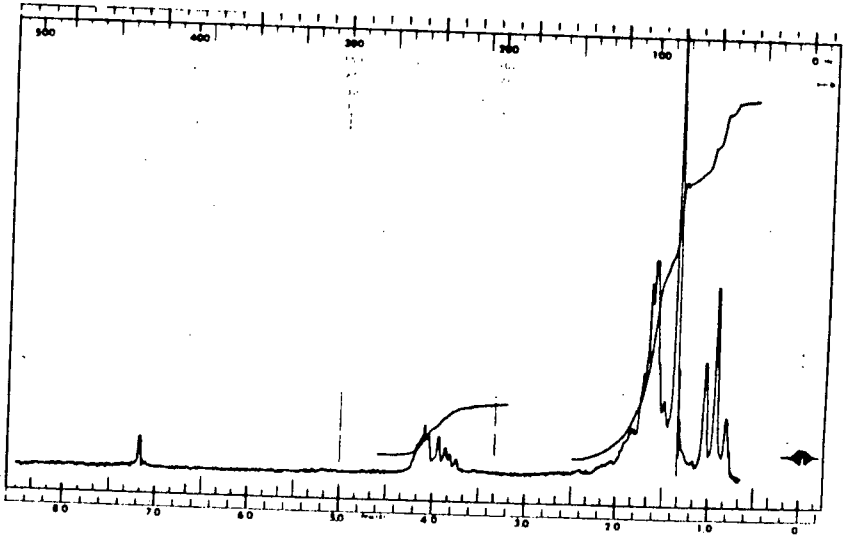


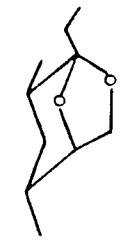




16







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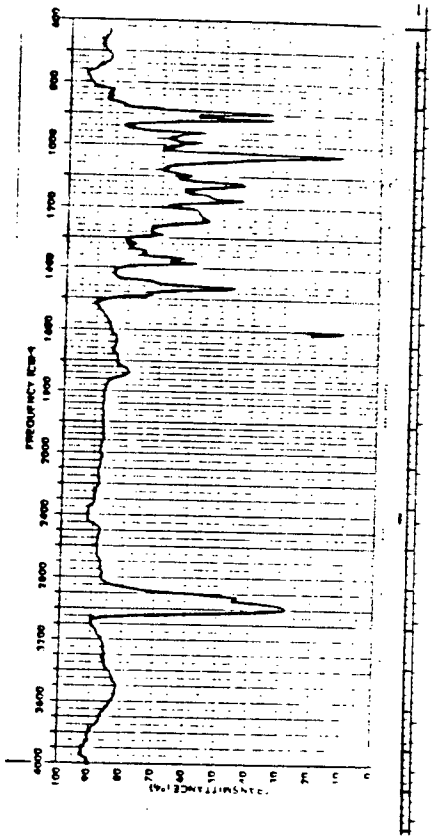

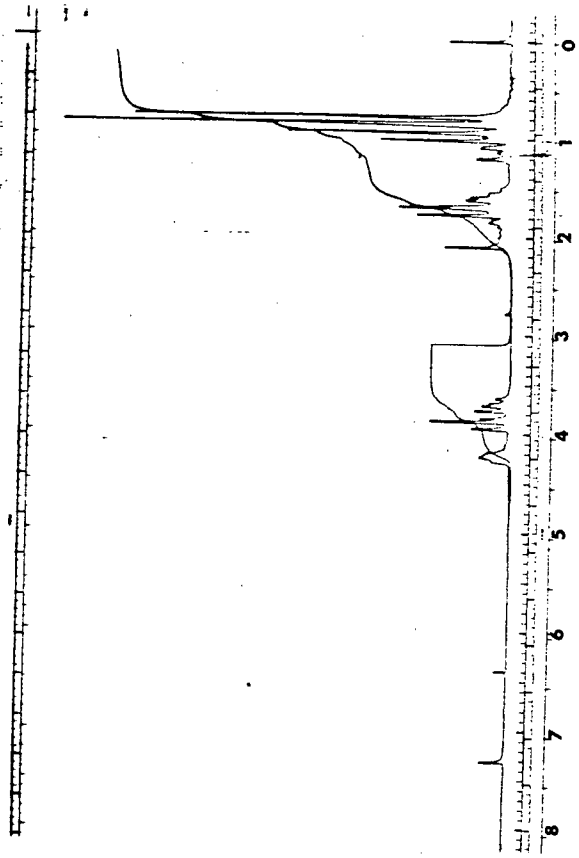

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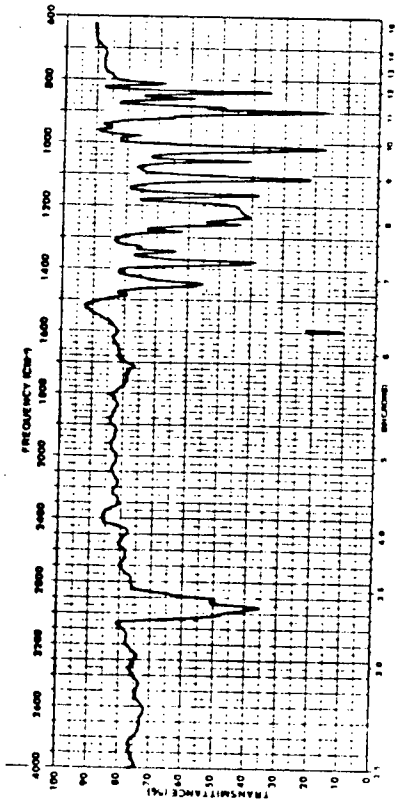
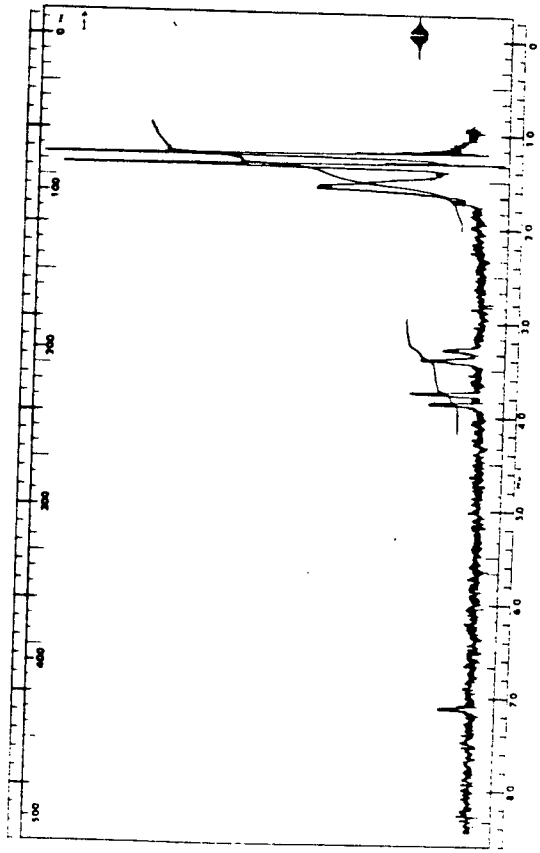
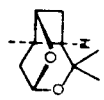
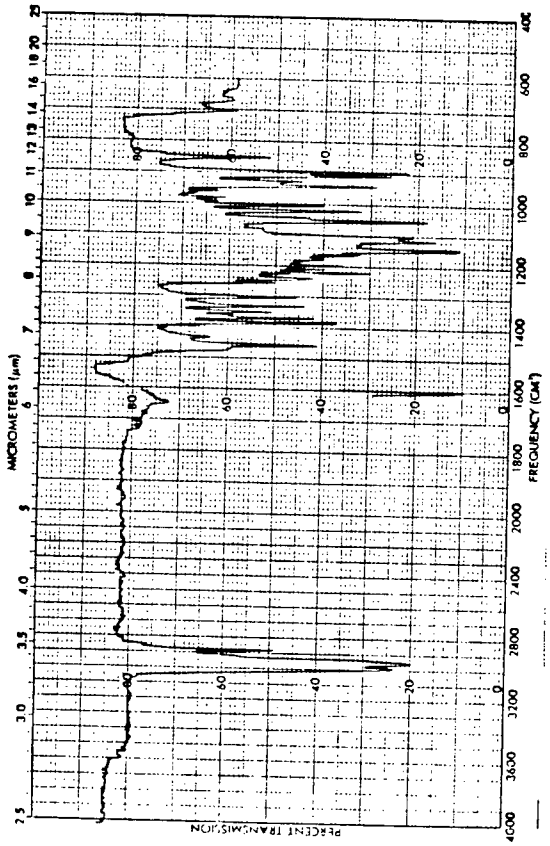
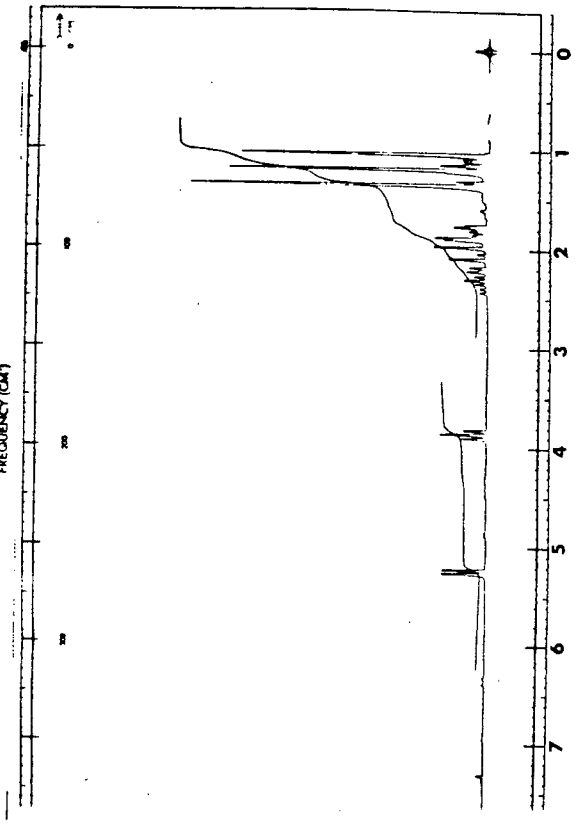


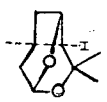




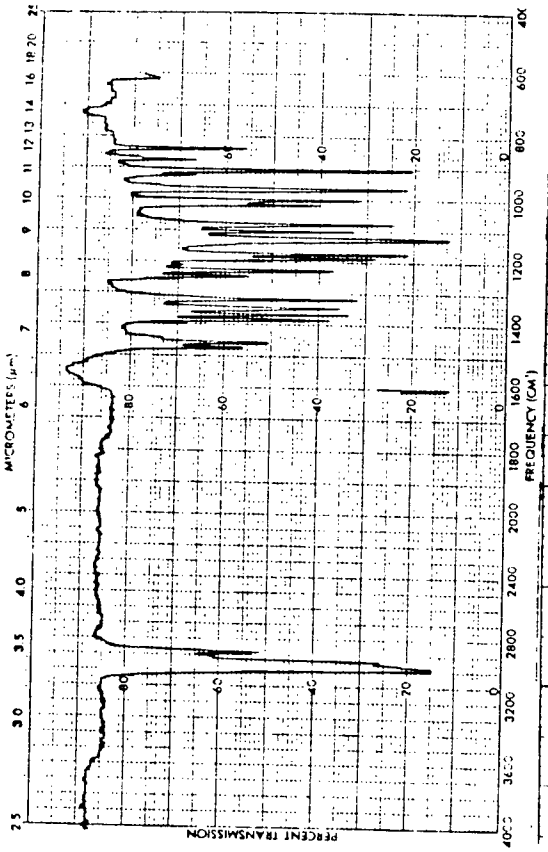
23

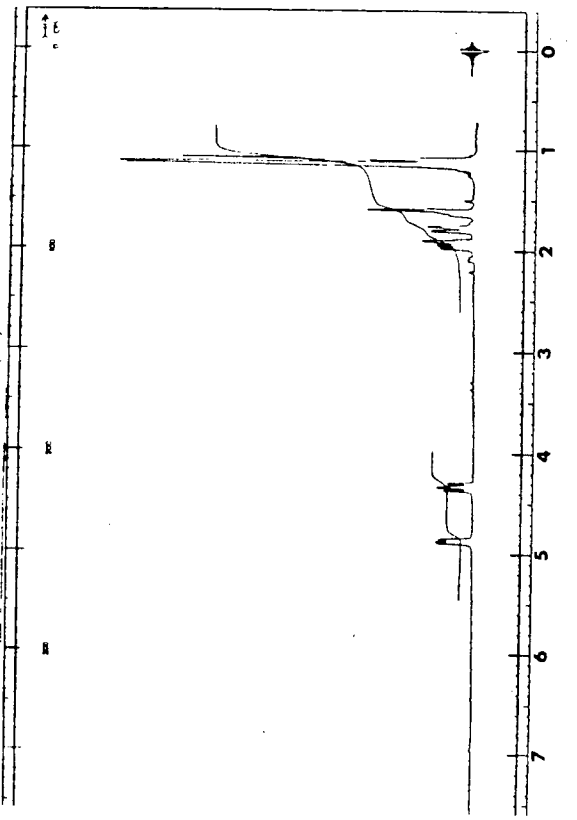

MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION

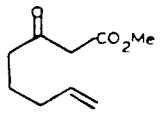




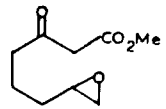
22


MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION

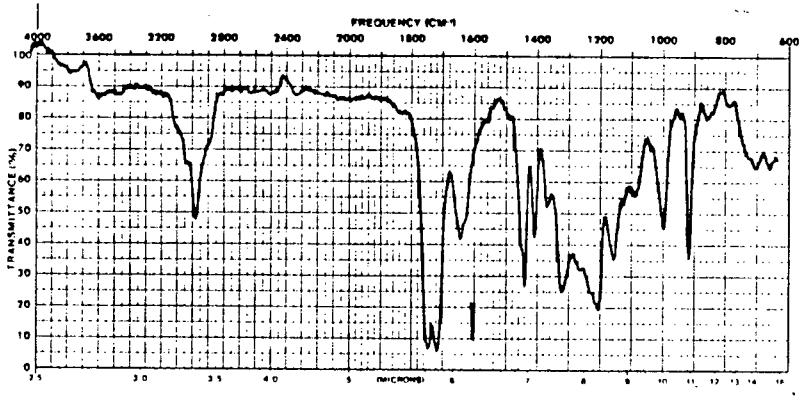


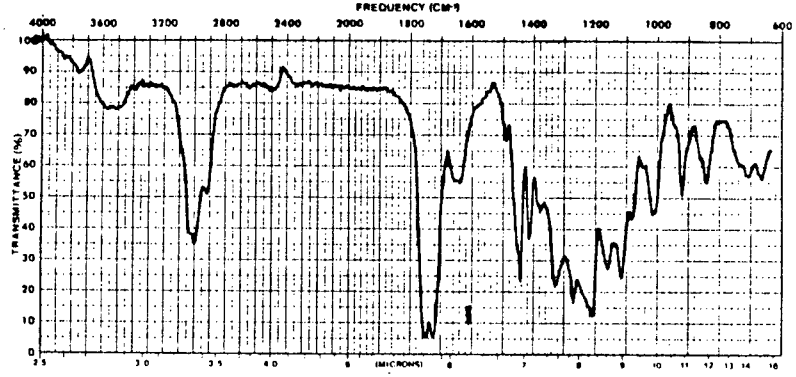

CO2Me

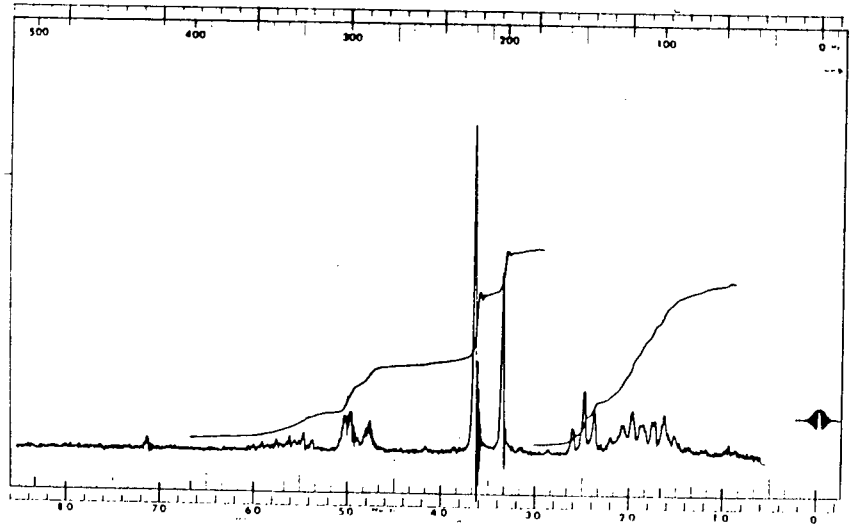
152

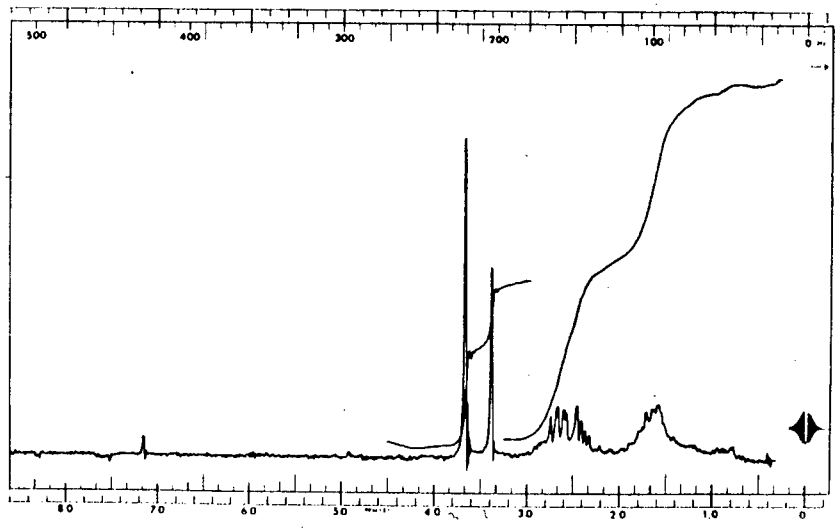

CO2Me

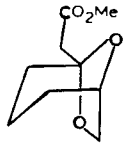
153


FREQUENCY (CM-1)
TRANSMITTANCE (%)
(MICRONS)

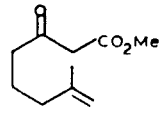

FREQUENCY (CM-1)
TRANSMITTANCE (%)
(MICRONS)



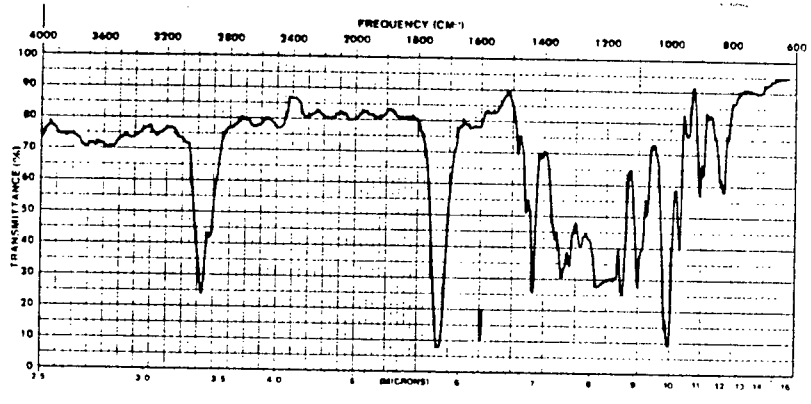


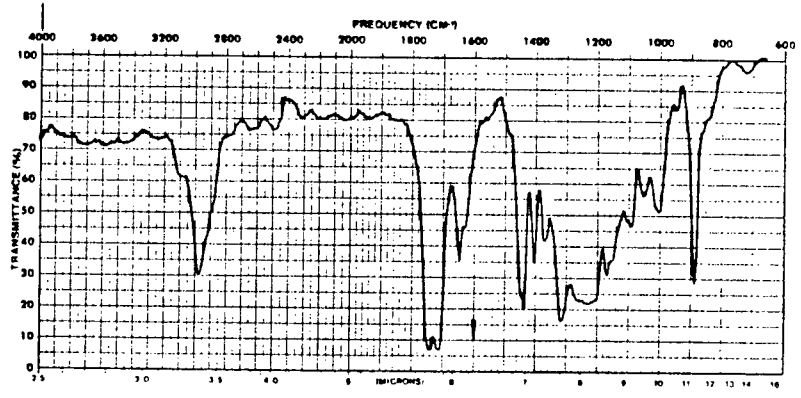

CO2Me

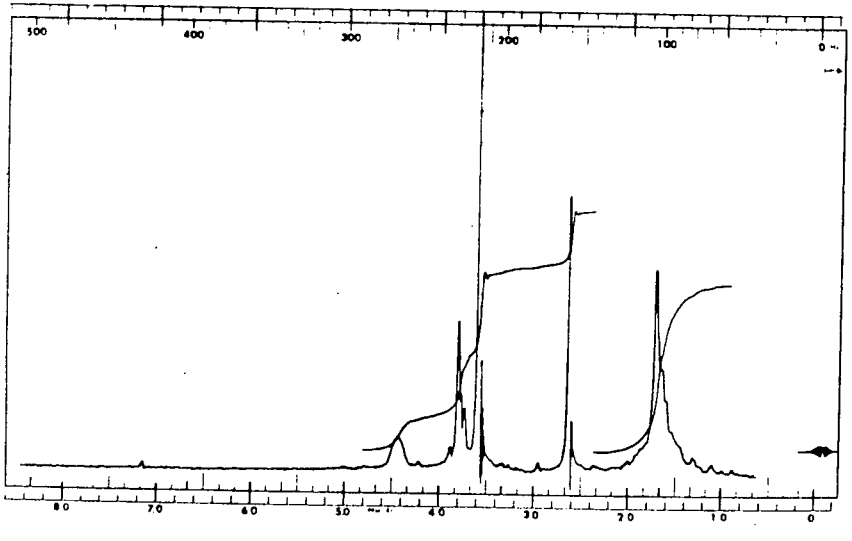
154

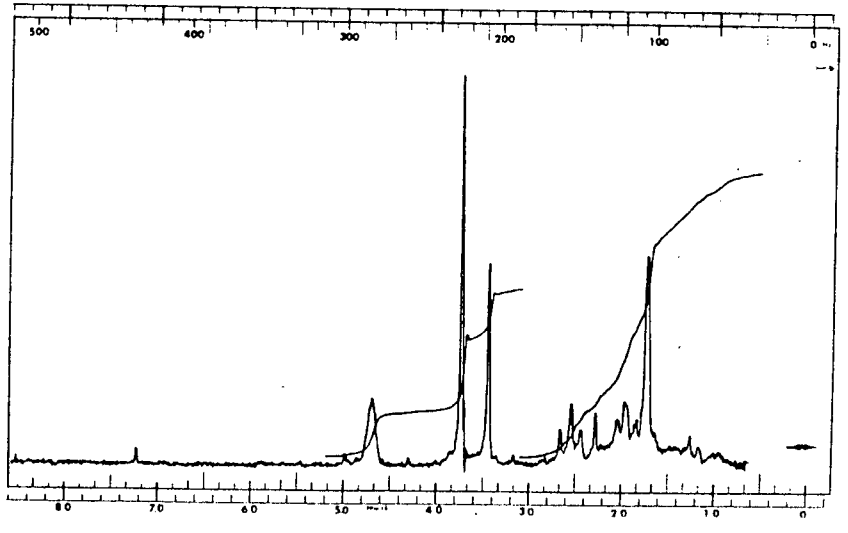

CO2Me

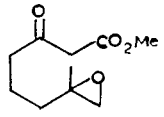
162


FREQUENCY (CM-1)
TRANSMITTANCE (%)
(MICRONS)

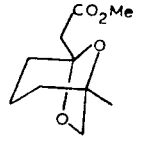

FREQUENCY (CM-1)
TRANSMITTANCE (%)
(MICRONS)






O
CO2Me
O

163


CO2Me
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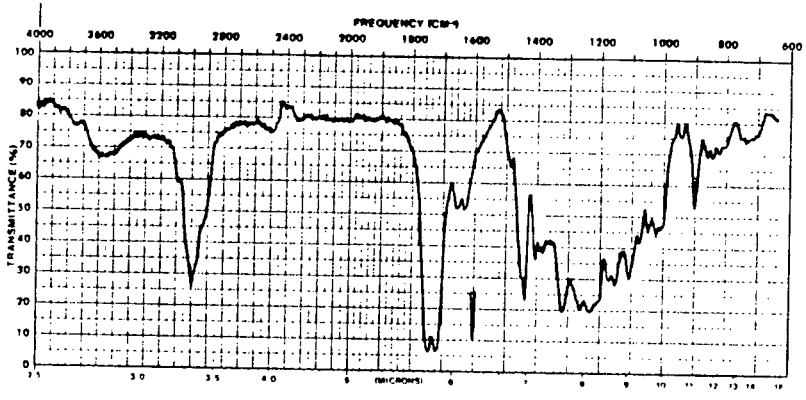
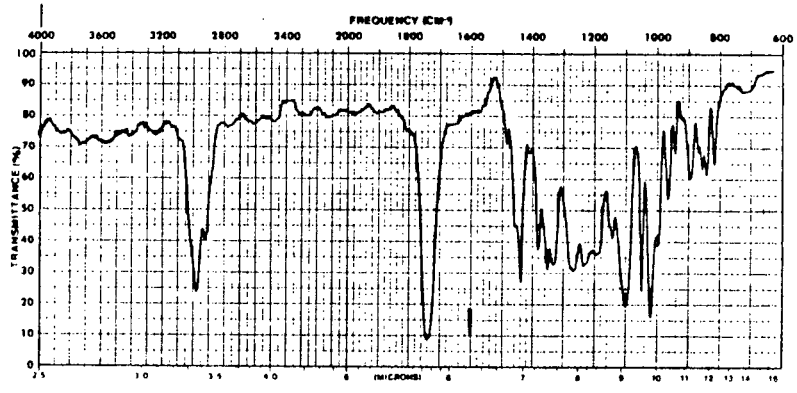
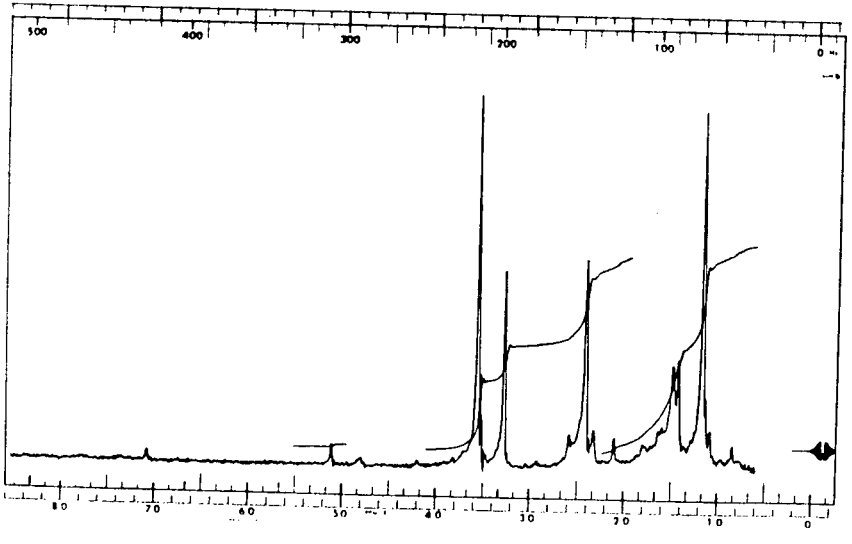
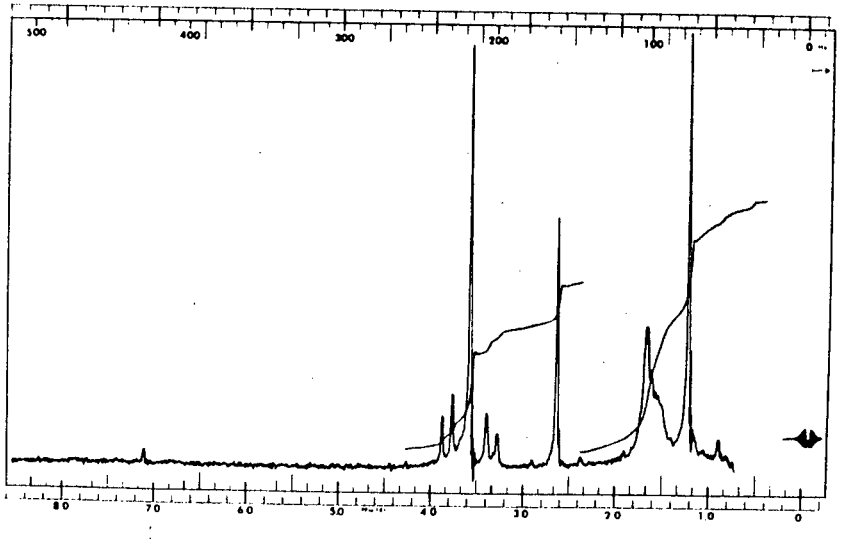
164


FREQUENCY (CM-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 15
(MICRONS)


FREQUENCY (CM-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 15
(MICRONS)


500 400 300 200 100 0
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0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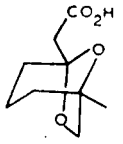
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0


CO2H
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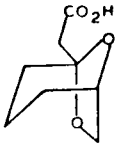
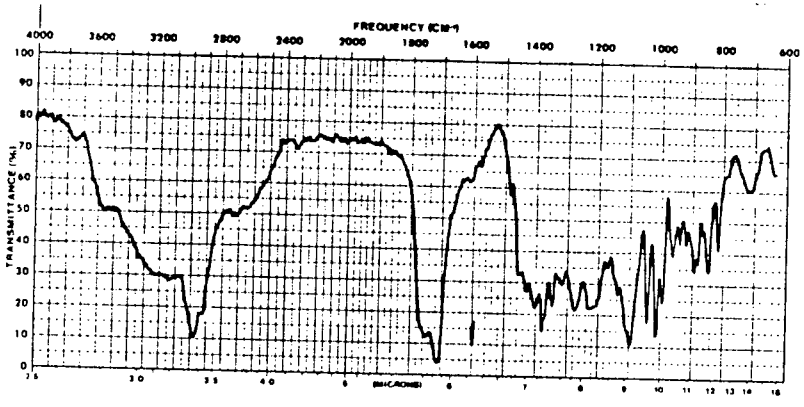
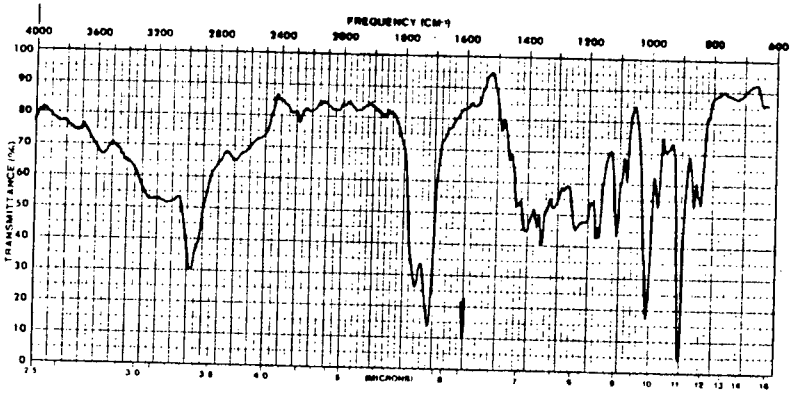
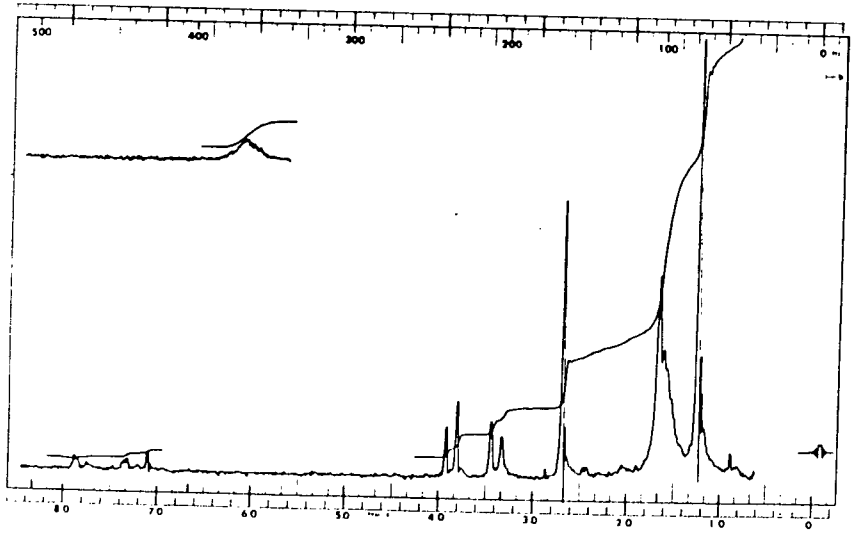
165

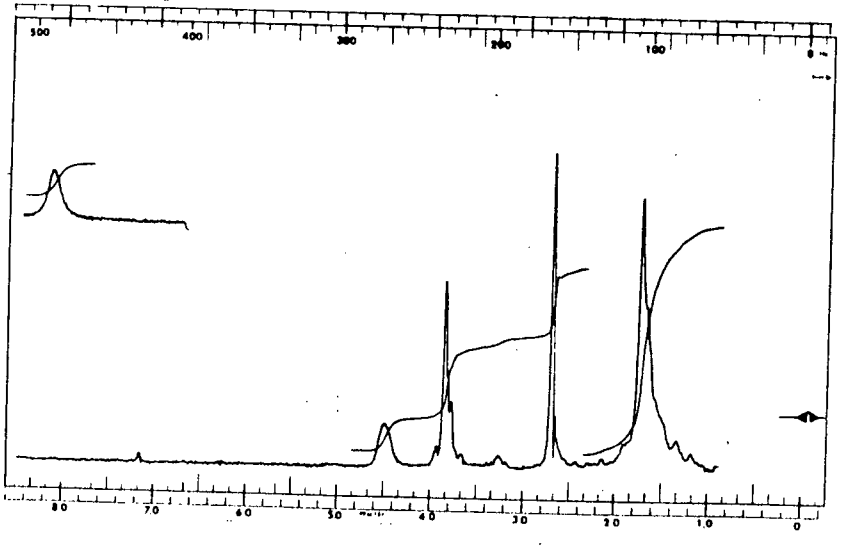

CO2H
O
O

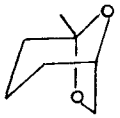
166


FREQUENCY (CM-1)
TRANSMITTANCE (%)


FREQUENCY (CM-1)
TRANSMITTANCE (%)







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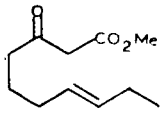
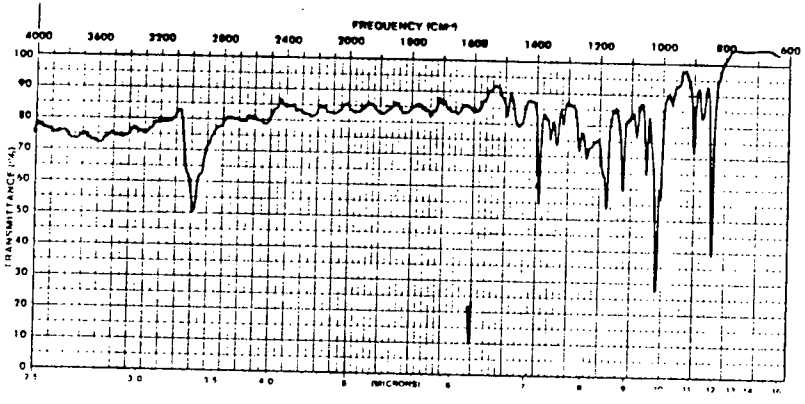
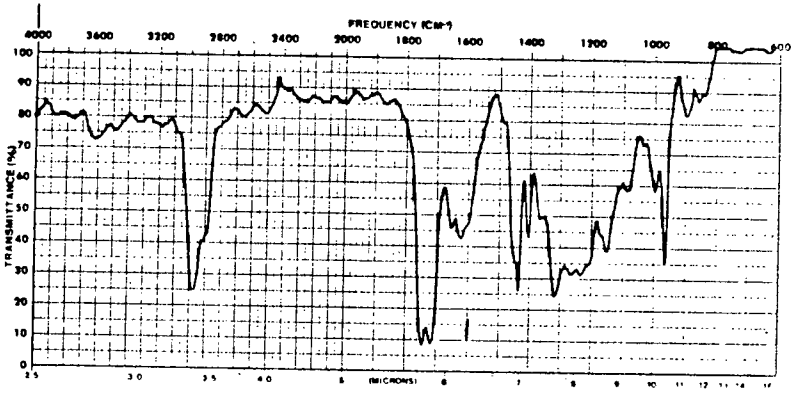
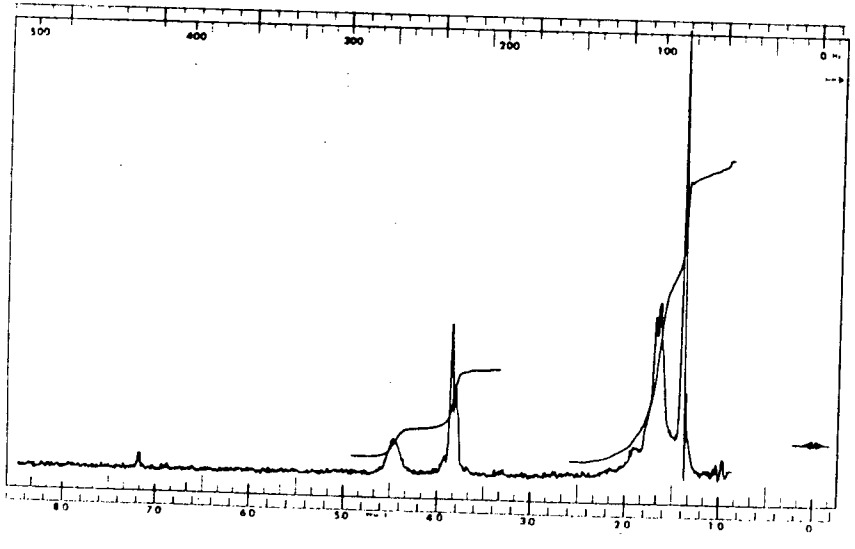
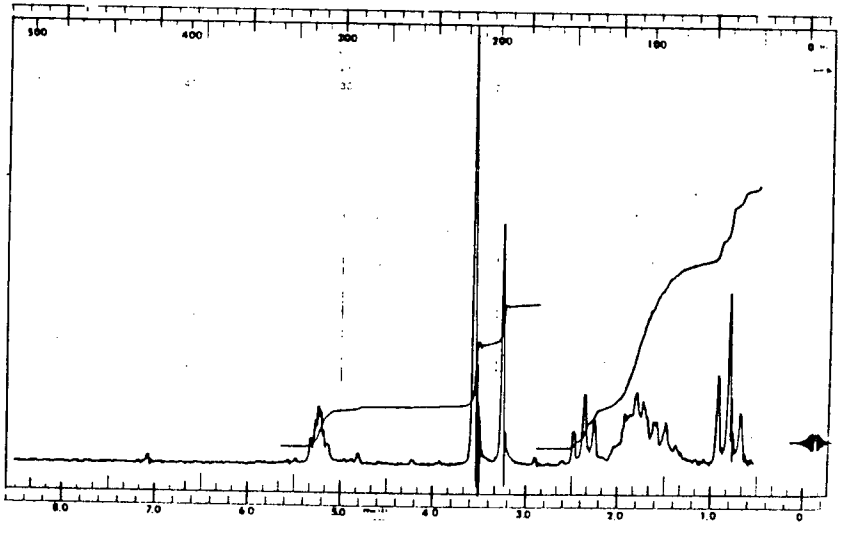

CO_2Me

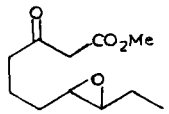
177


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
(MICRONS)


FREQUENCY (Cm-1)
TRANSMITTANCE (%)
(MICRONS)






CO2Me
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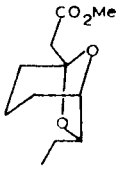
178


CO2Me
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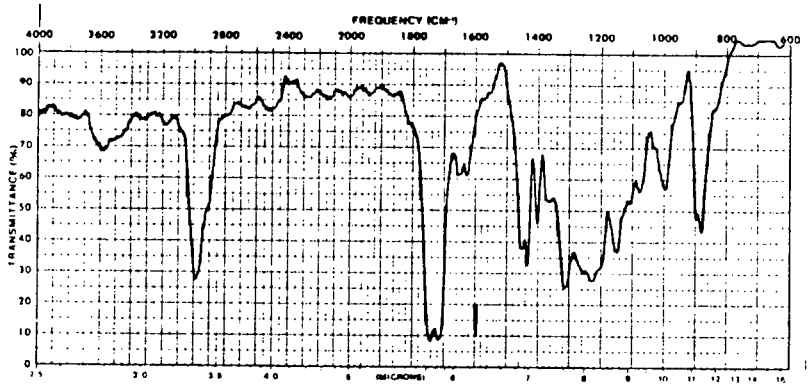
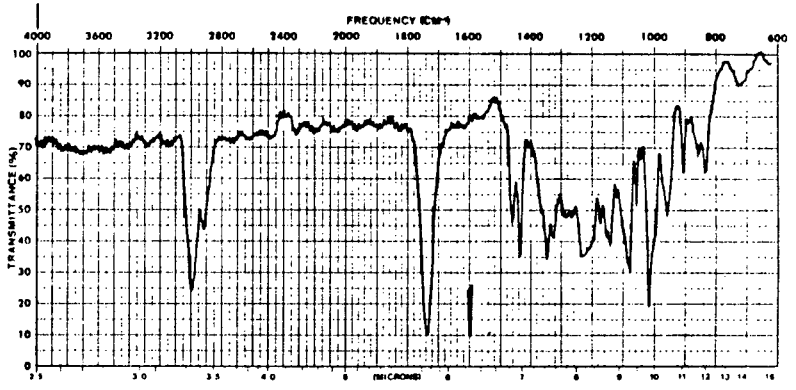
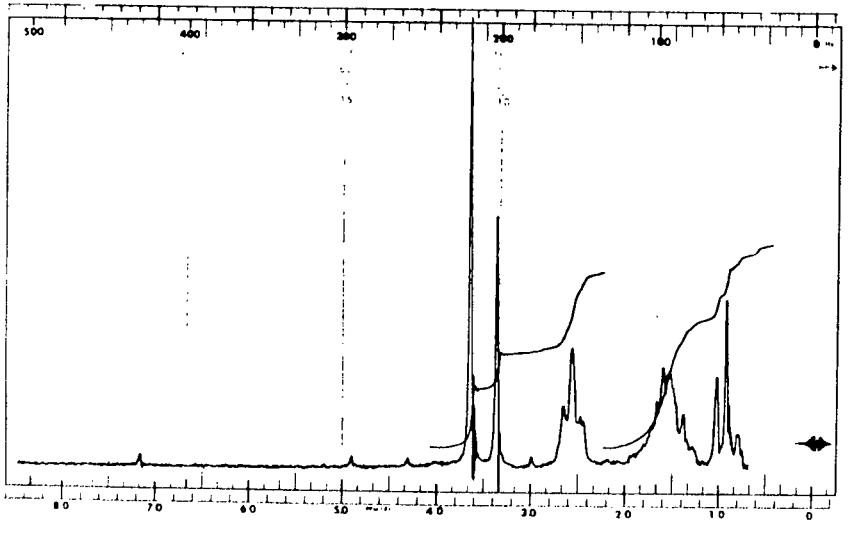
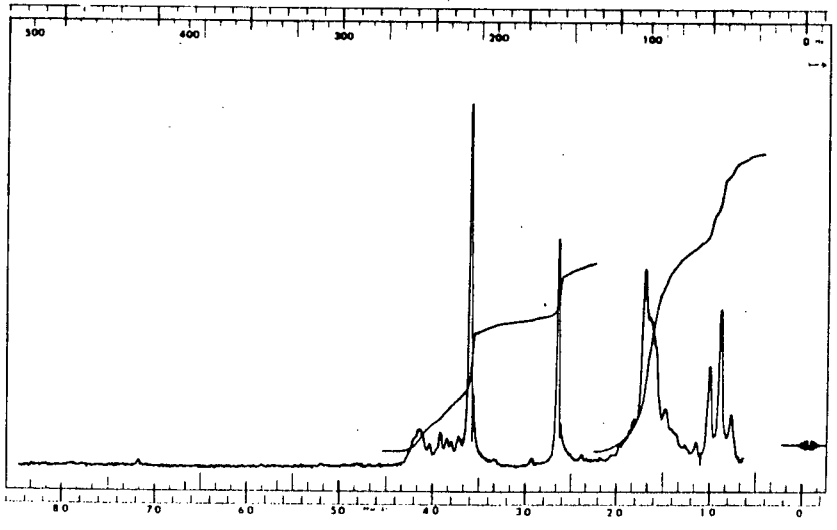
179


FREQUENCY (Cm-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 15
(MICRONS)


FREQUENCY (Cm-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 15
(MICRONS)


500 400 300 200 100 0
80 70 60 50 40 30 20 10 0


500 400 300 200 100 0
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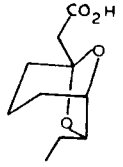
CO2H
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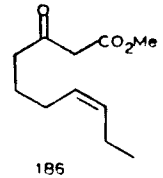
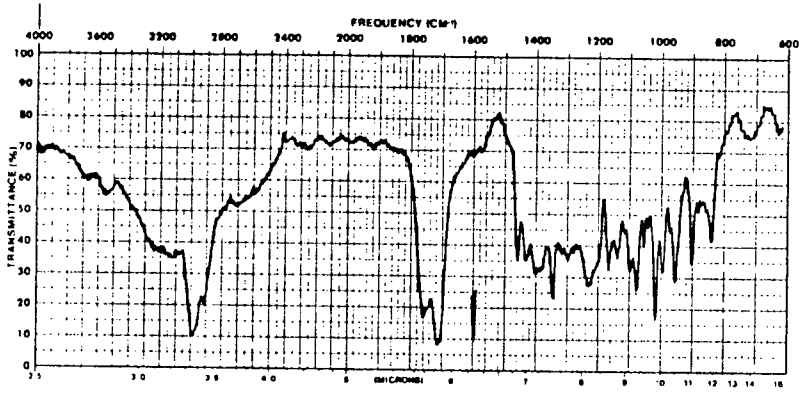
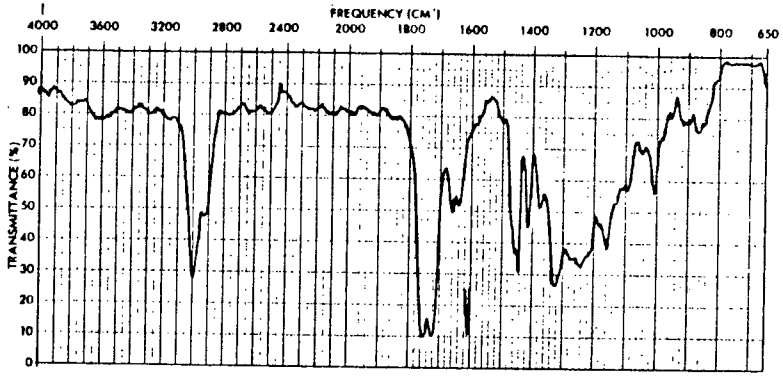
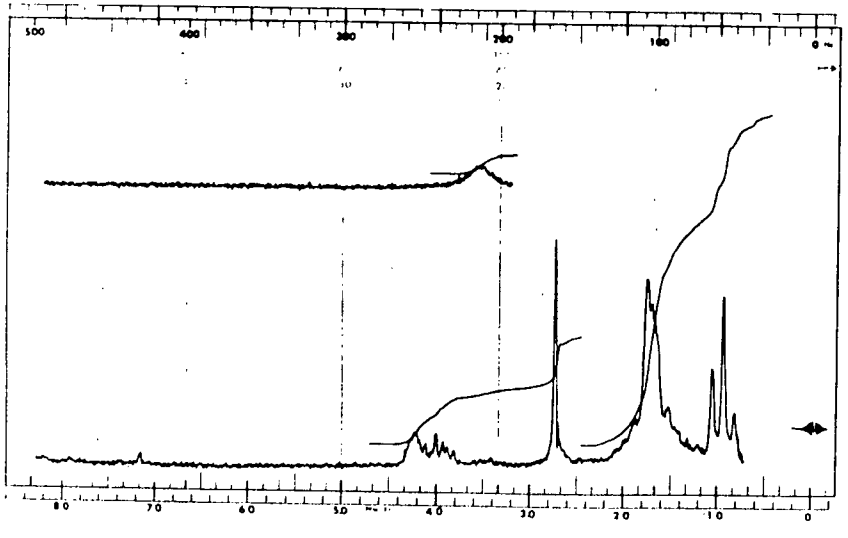
180

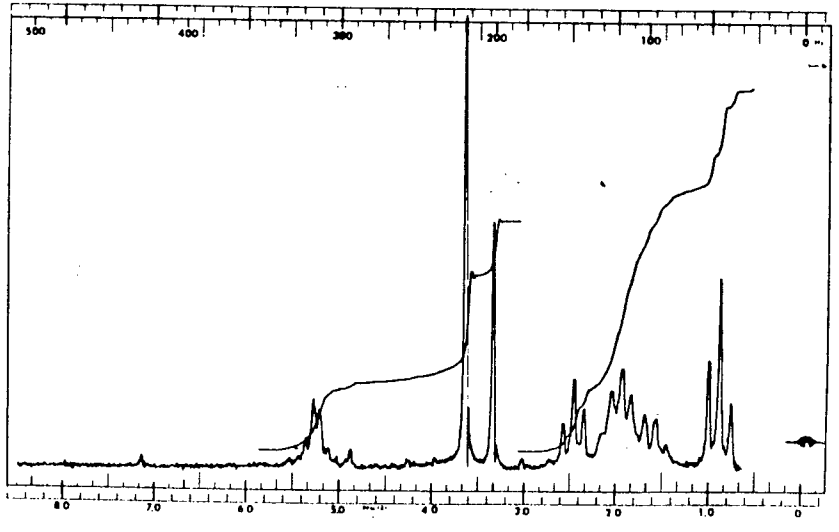

O
CO2Me

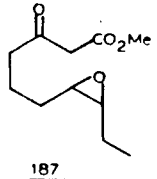
186


FREQUENCY (CM-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0

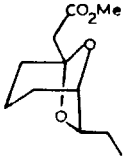

FREQUENCY (CM-1)
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 650
TRANSMITTANCE (%)
100 90 80 70 60 50 40 30 20 10 0


500 400 300 200 100 0
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0

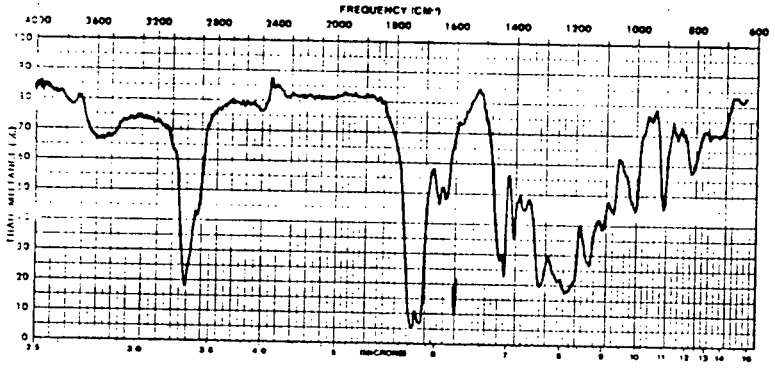

500 400 300 200 100 0
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0

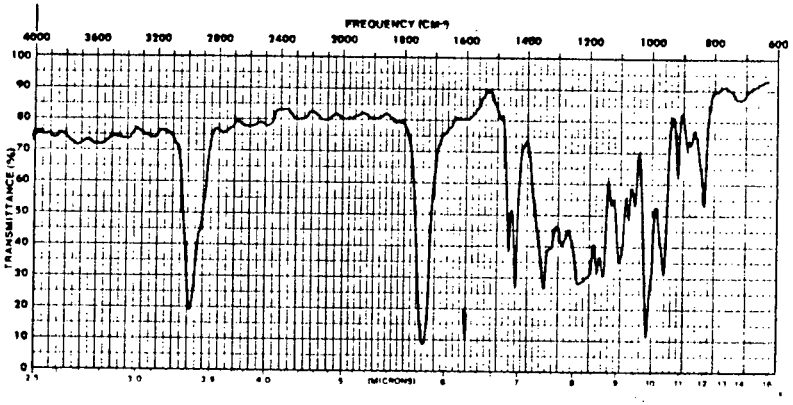

CO2Me

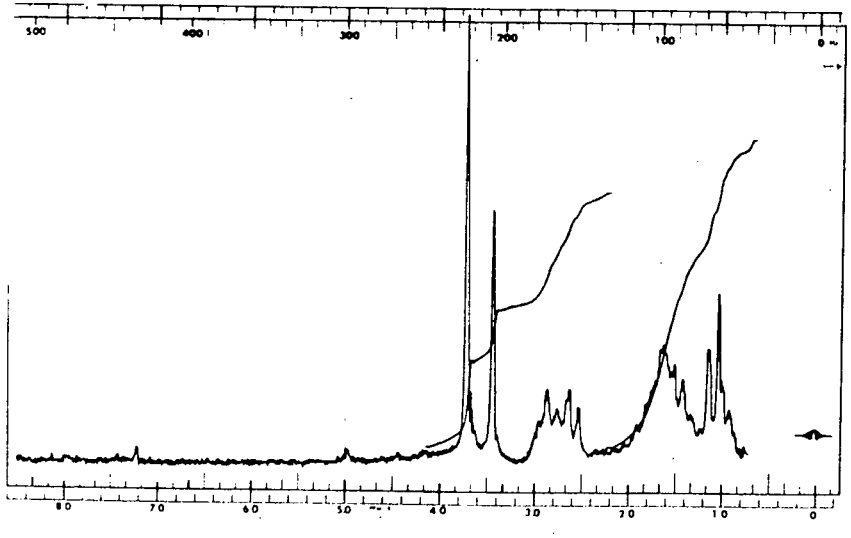
187

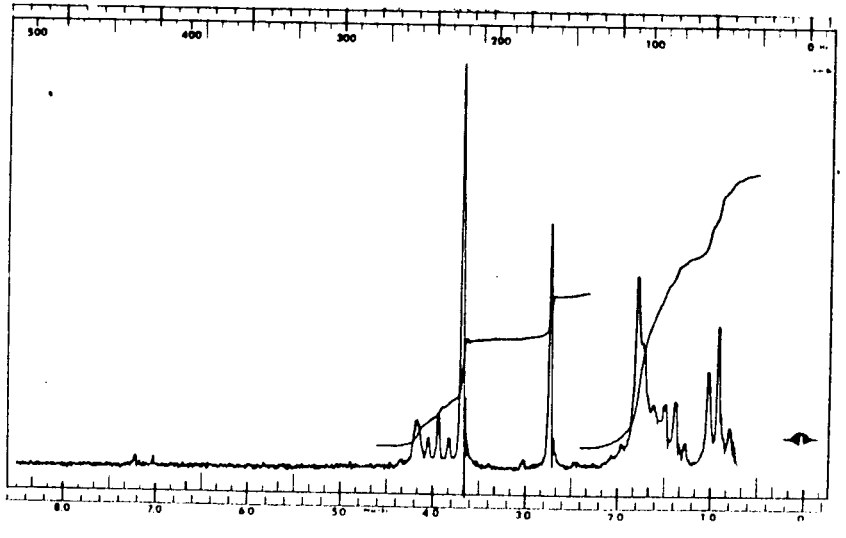

CO2Me

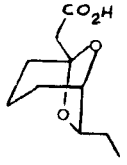
188


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS






CO2H
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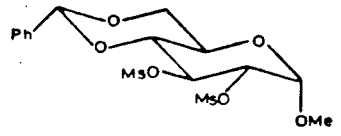
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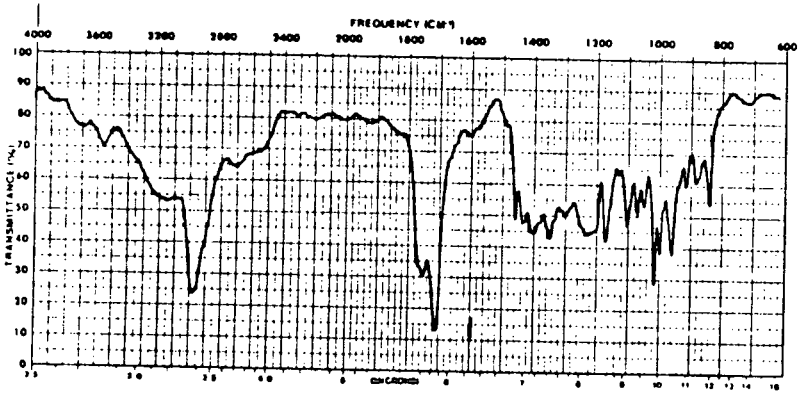
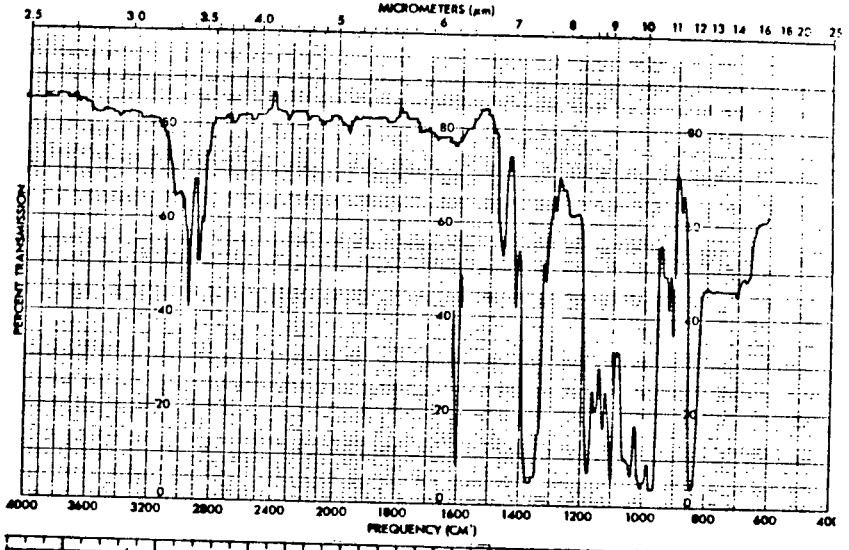
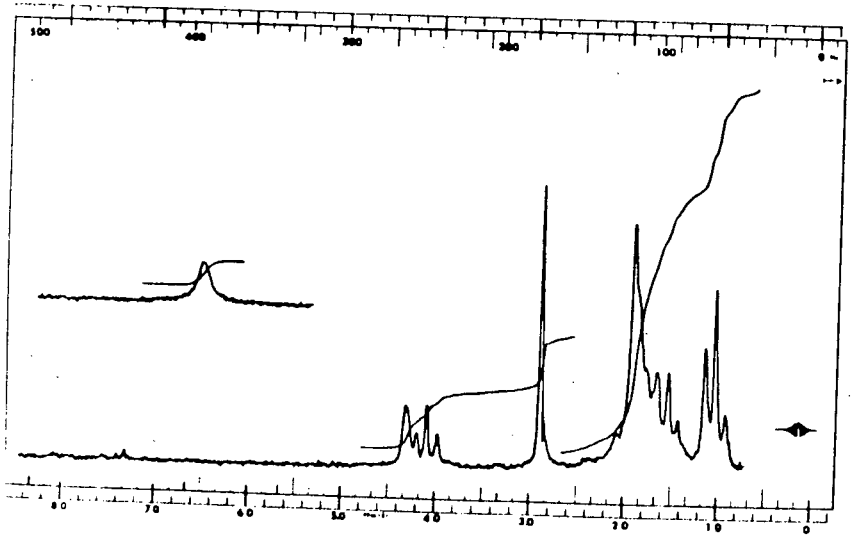
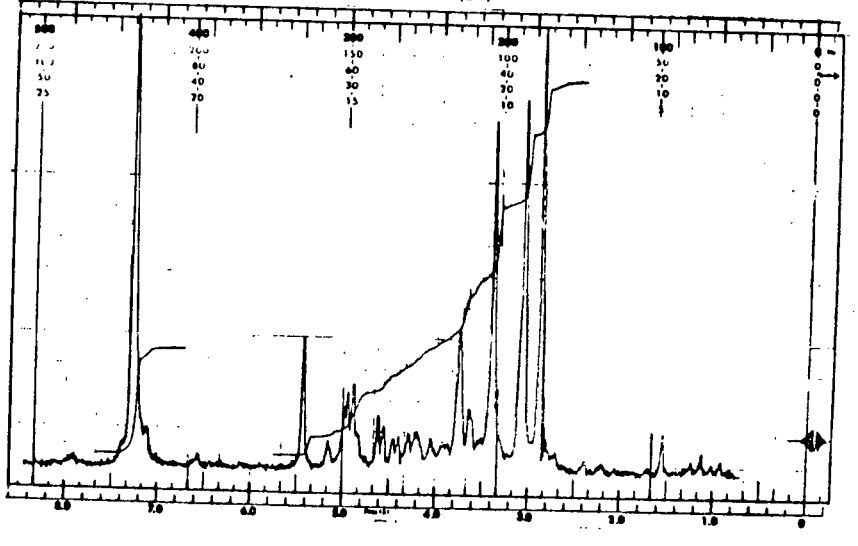
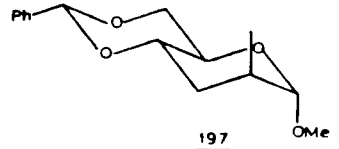

FREQUENCY (CM-1)
TRANSMITTANCE (%)


MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM-1)







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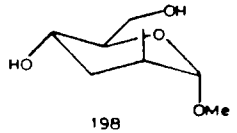

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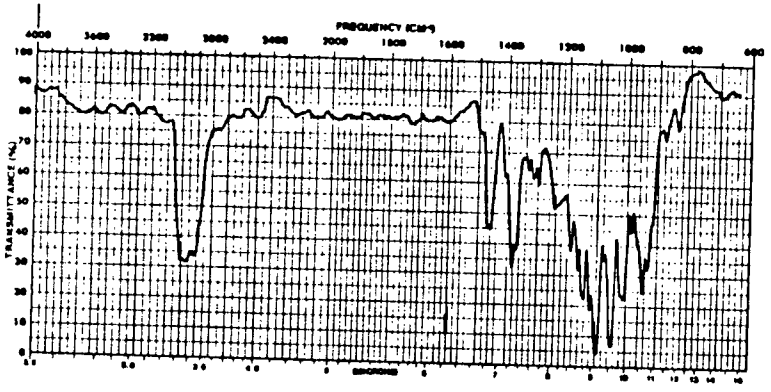

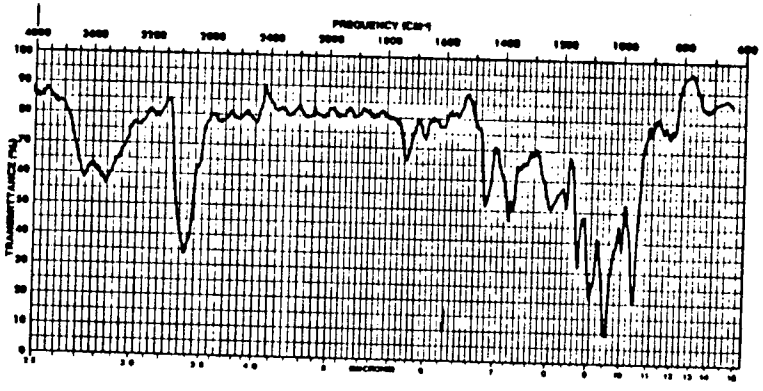

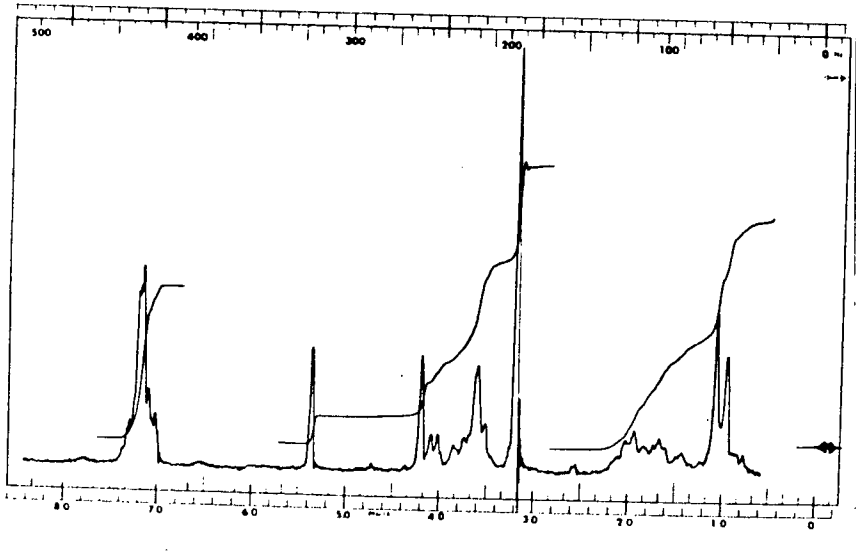

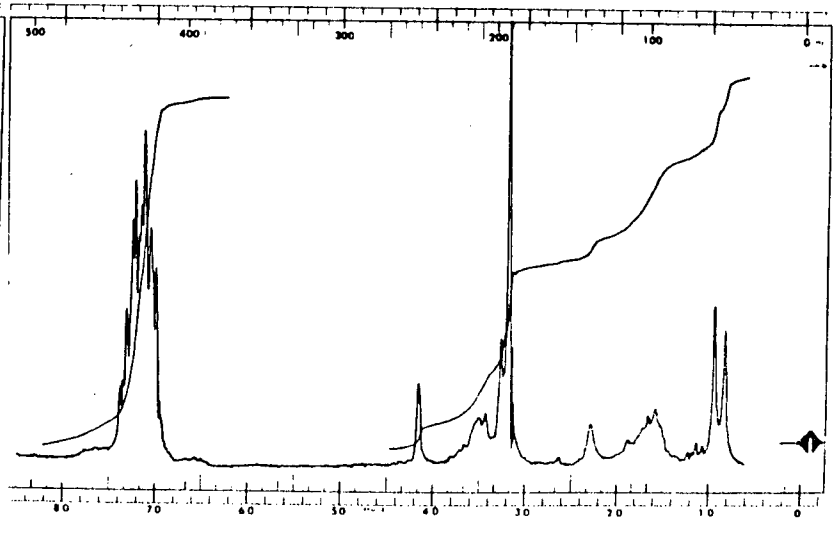

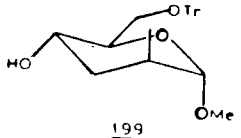

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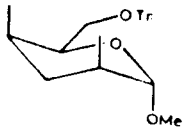

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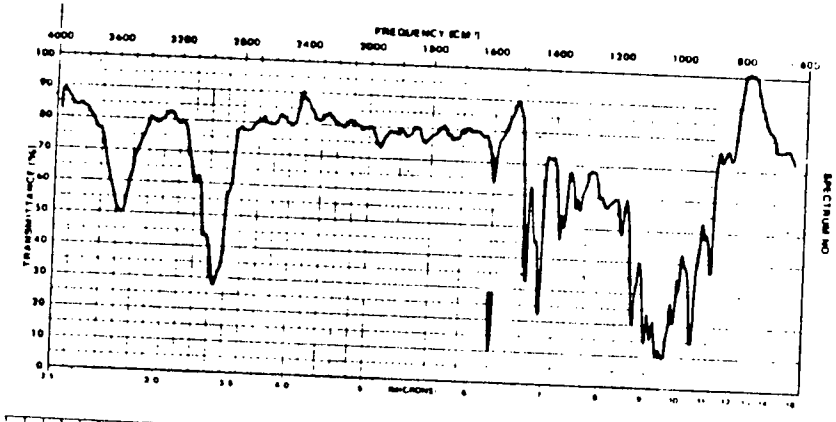

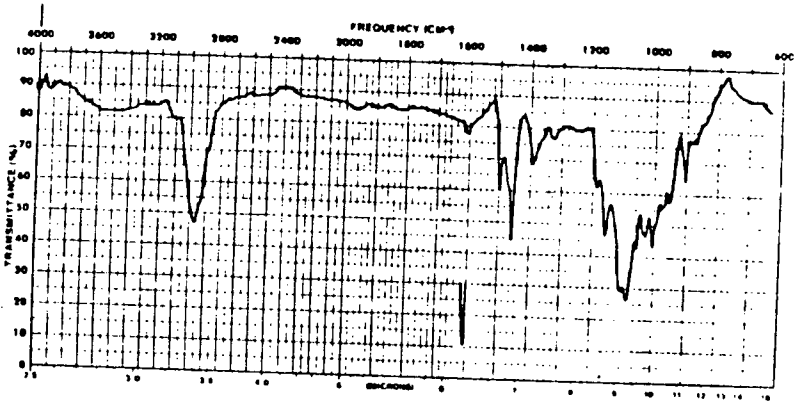

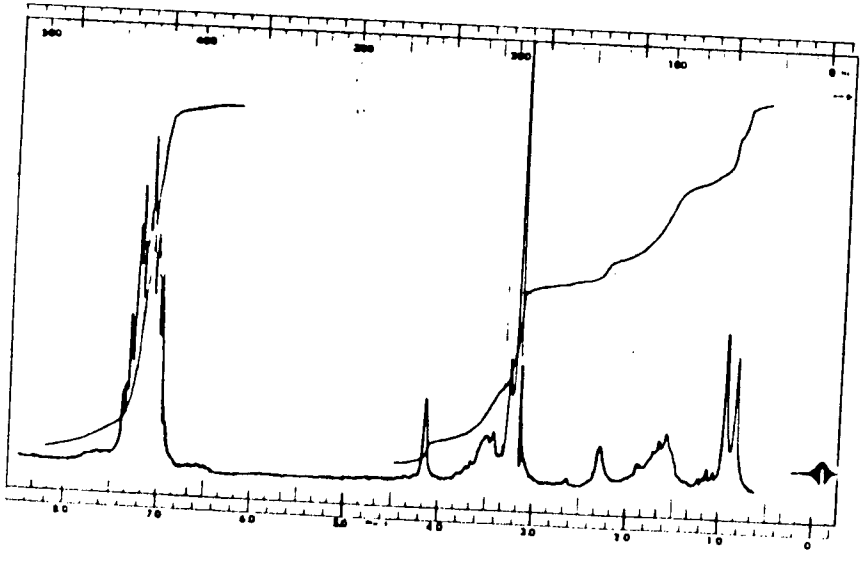

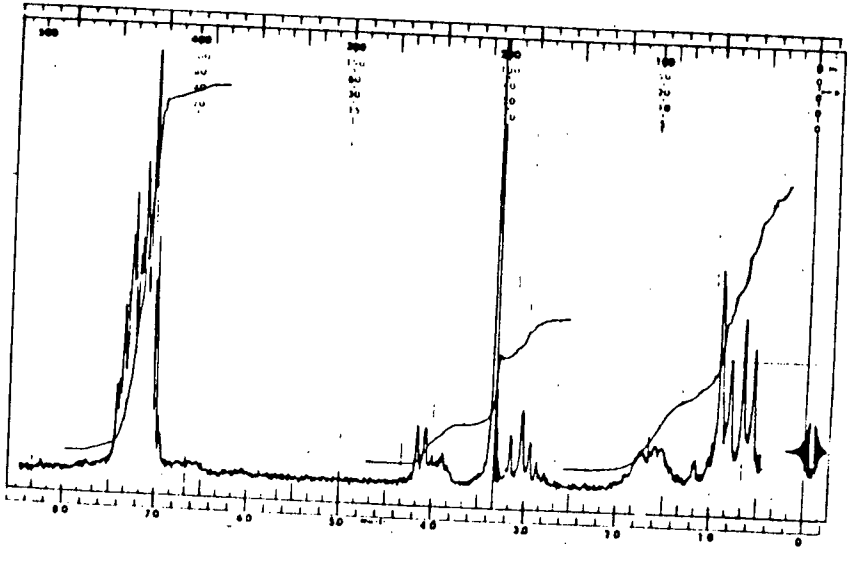

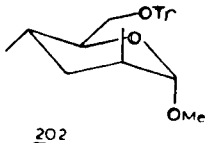
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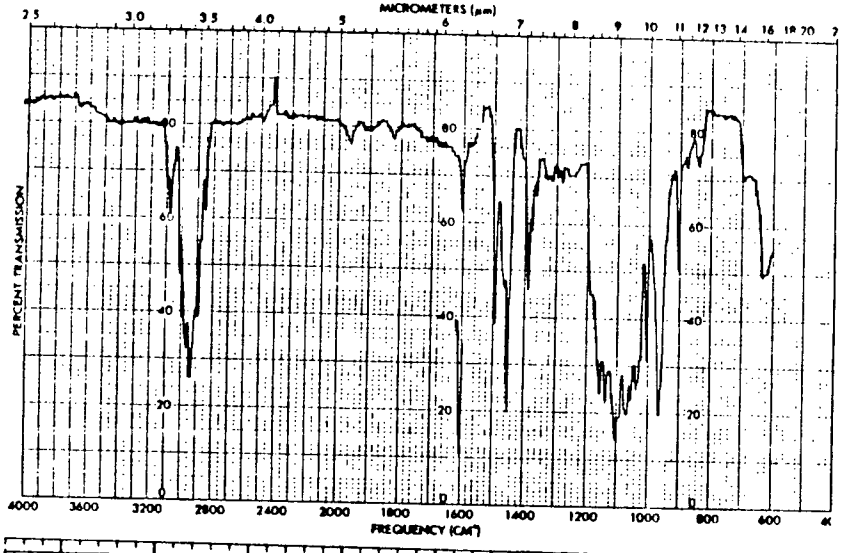
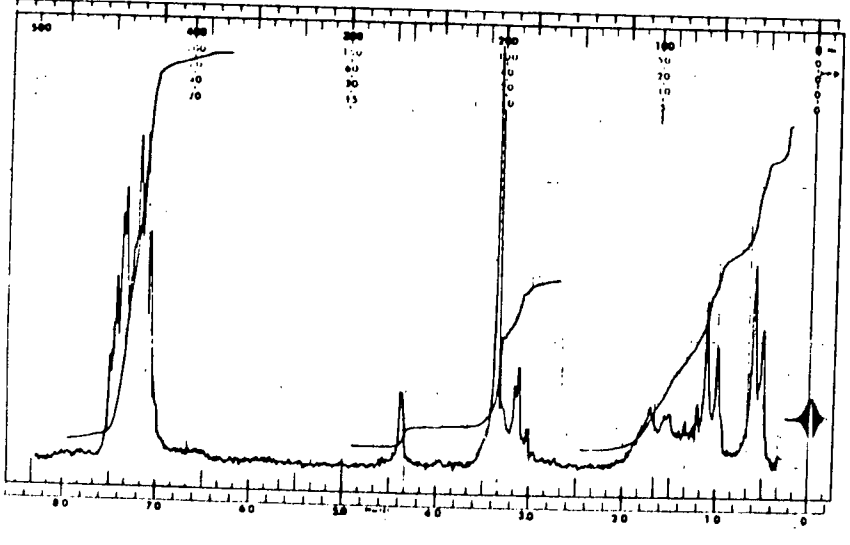
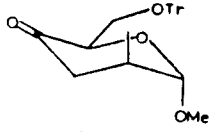

MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)

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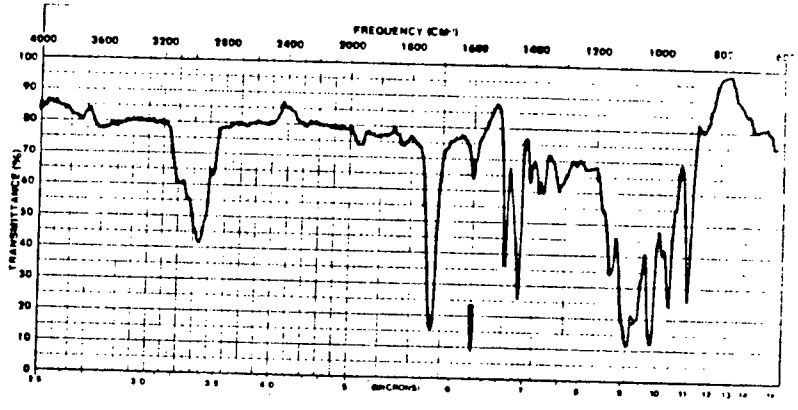
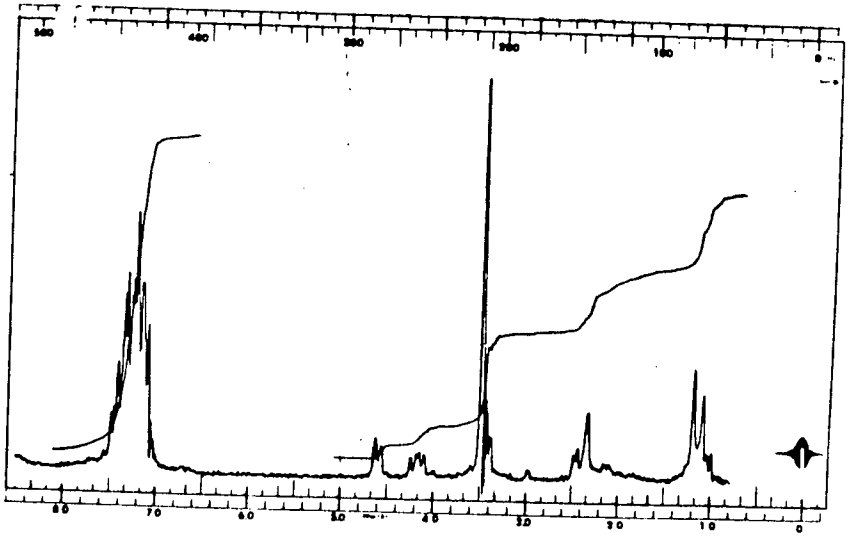
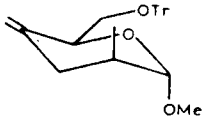

FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)

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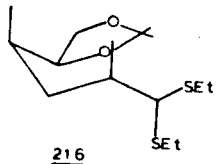
207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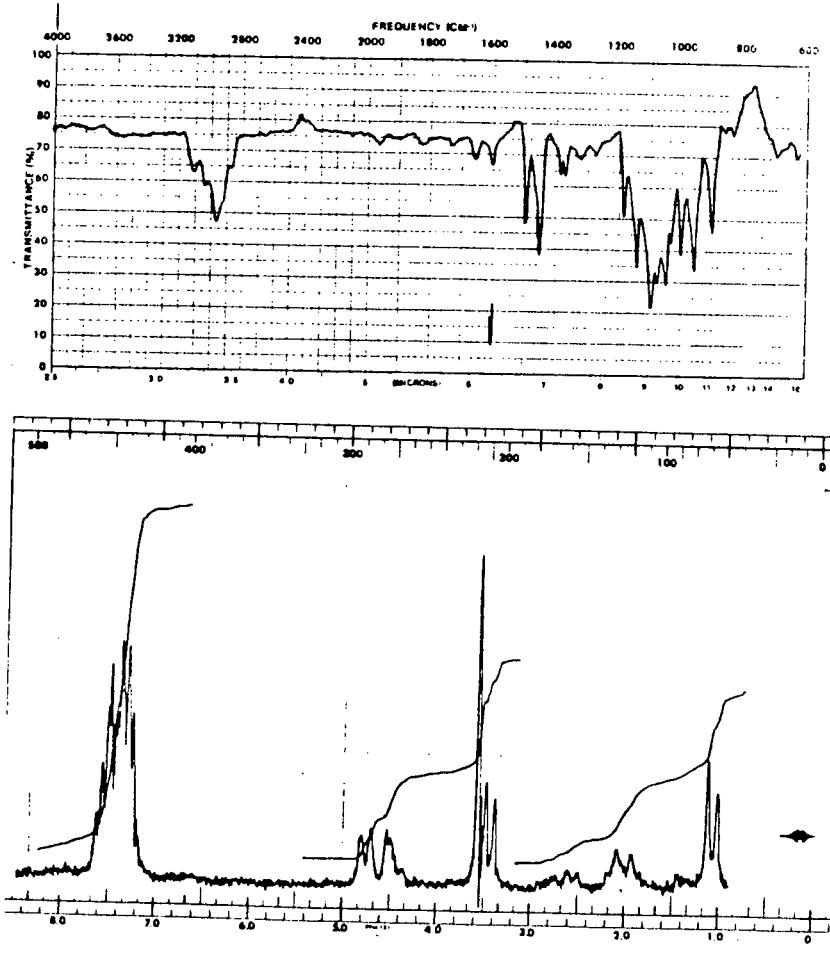
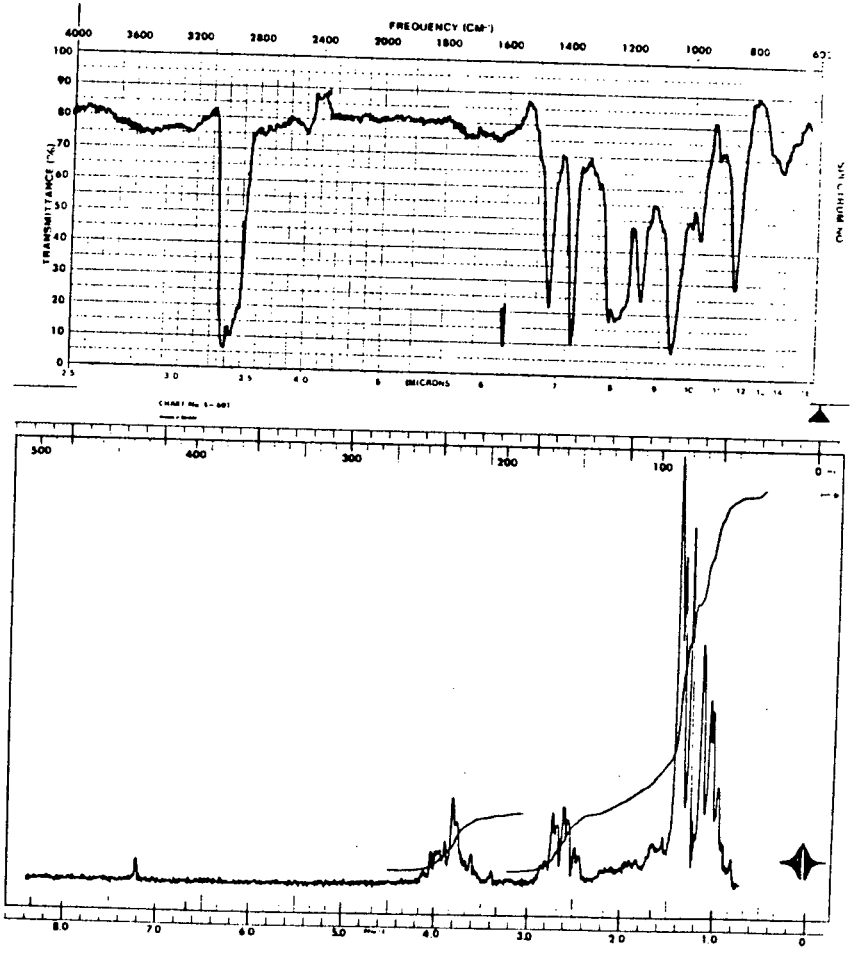
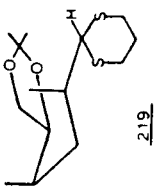
216


FREQUENCY (Cm⁻¹)
TRANSMITTANCE (%)
MICRONS


FREQUENCY (Cm⁻¹)
TRANSMITTANCE (%)
MICRONS



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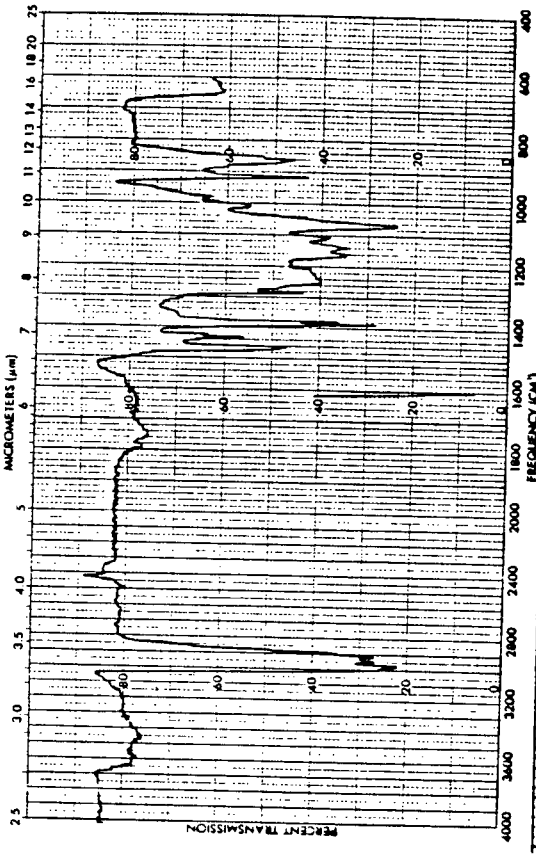
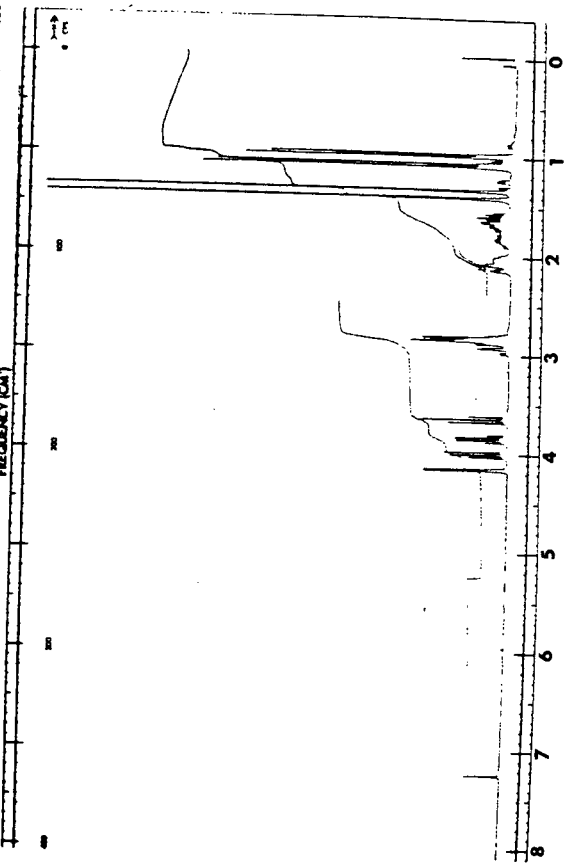
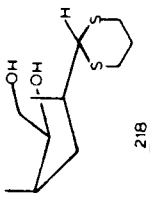

PERCENT TRANSMISSION
MICROMETERS (μm)
FREQUENCY (CM⁻¹)





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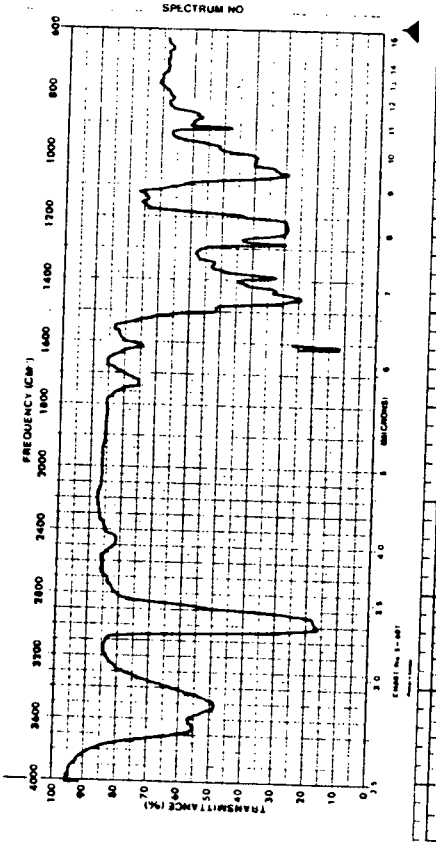
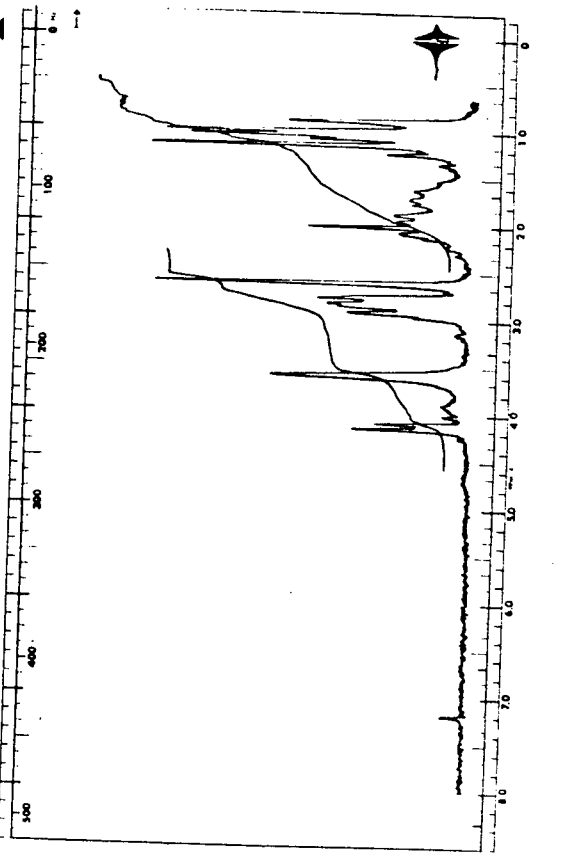
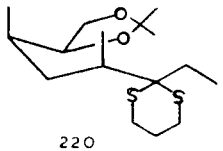

SPECTRUM NO
FREQUENCY (CM⁻¹)
TRANSMITTANCE (%)





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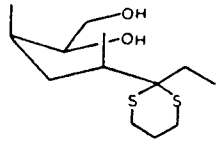

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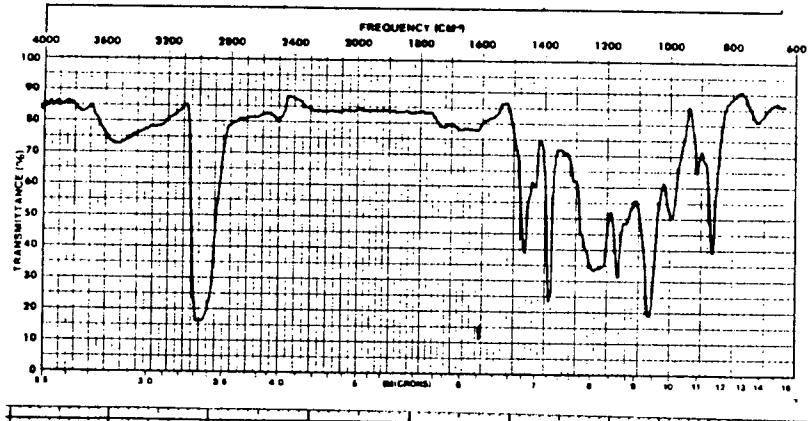
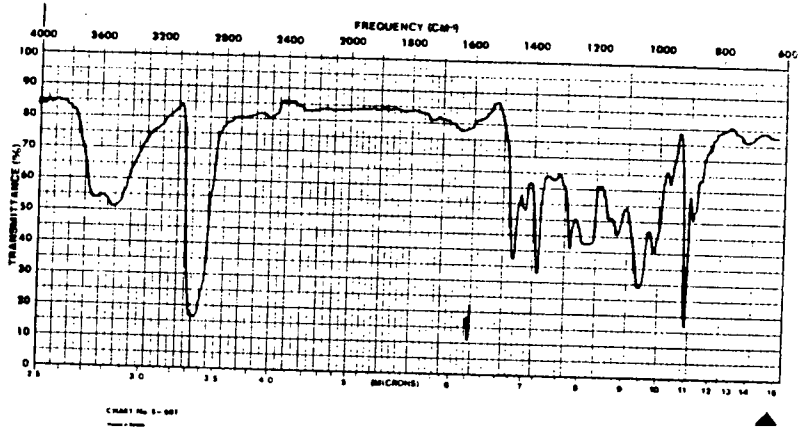
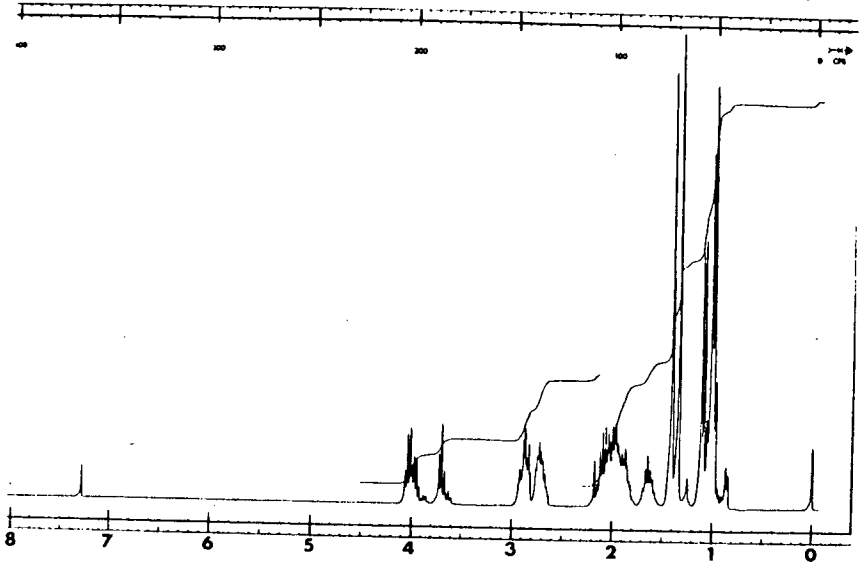

FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS


FREQUENCY (CM-1)
TRANSMITTANCE (%)
MICRONS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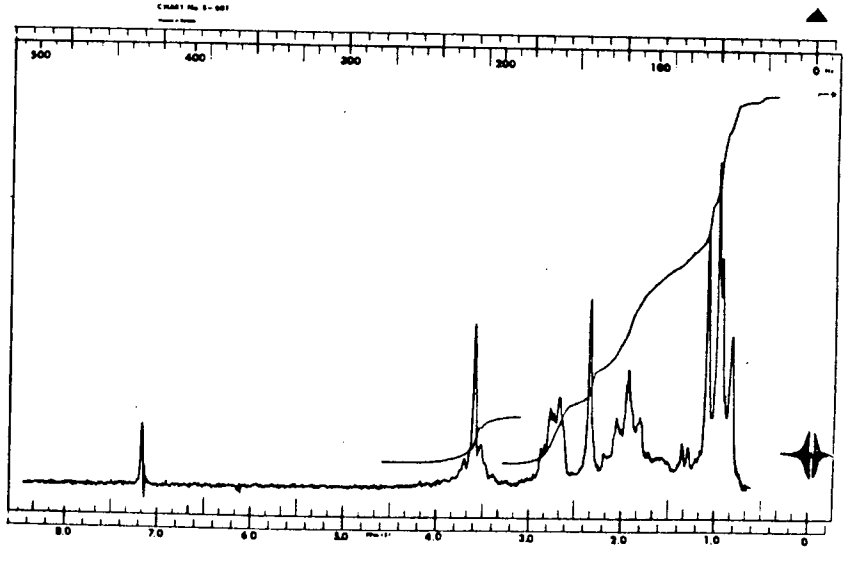
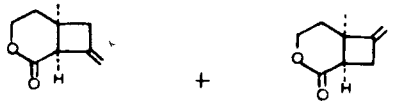
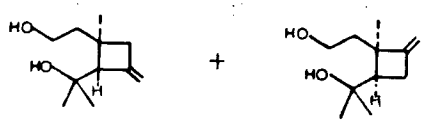
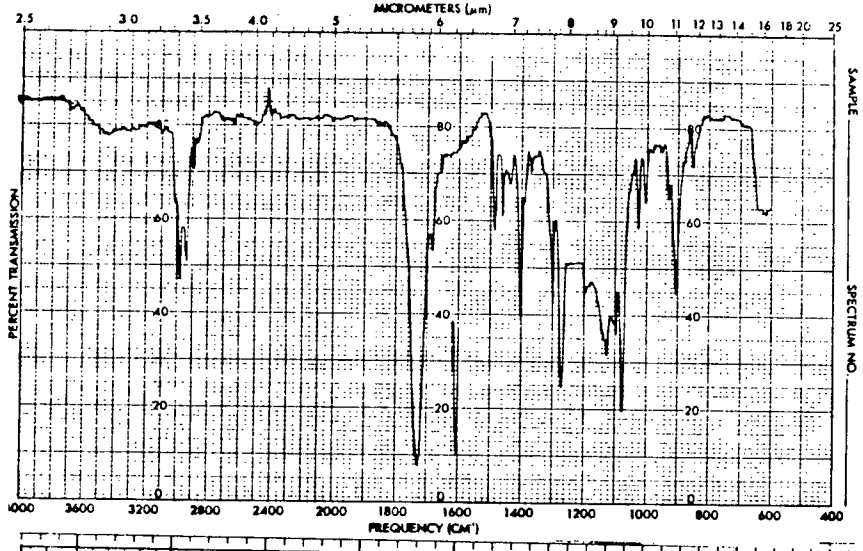


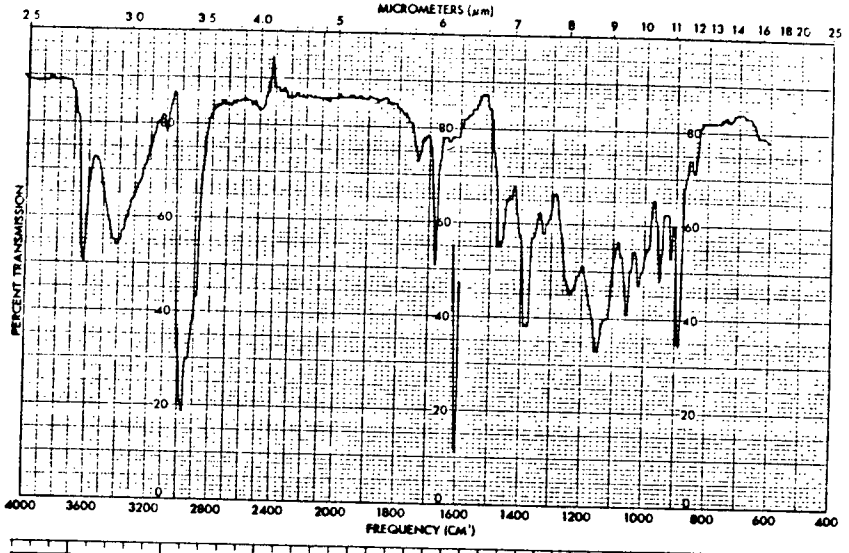


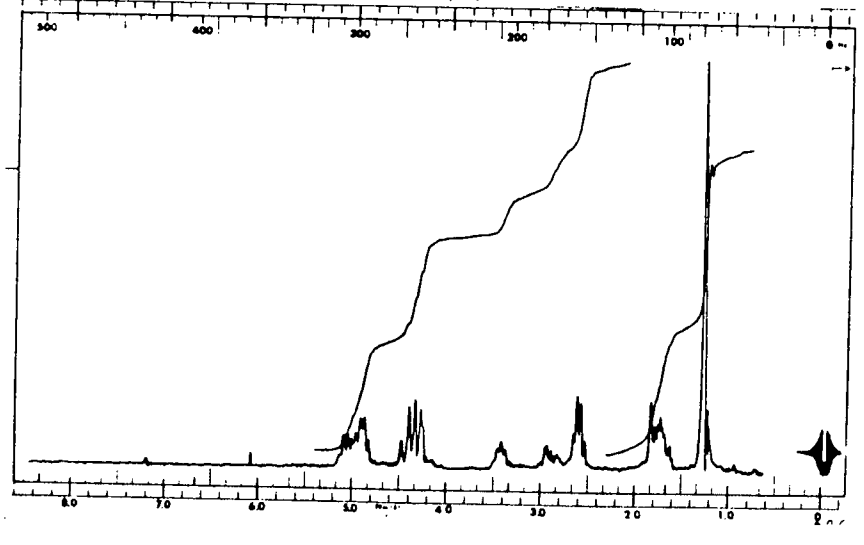
233 + 234

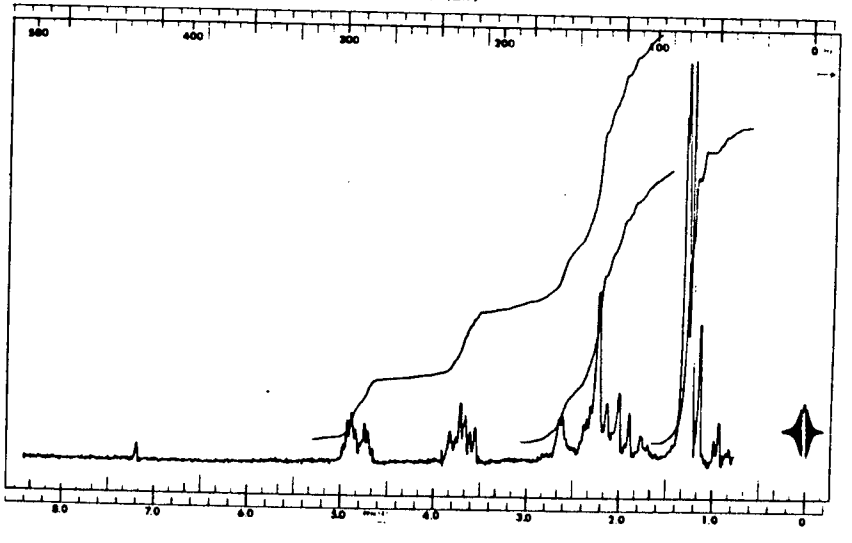


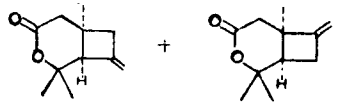
247 + 248



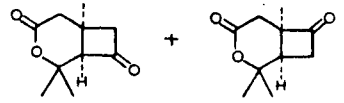




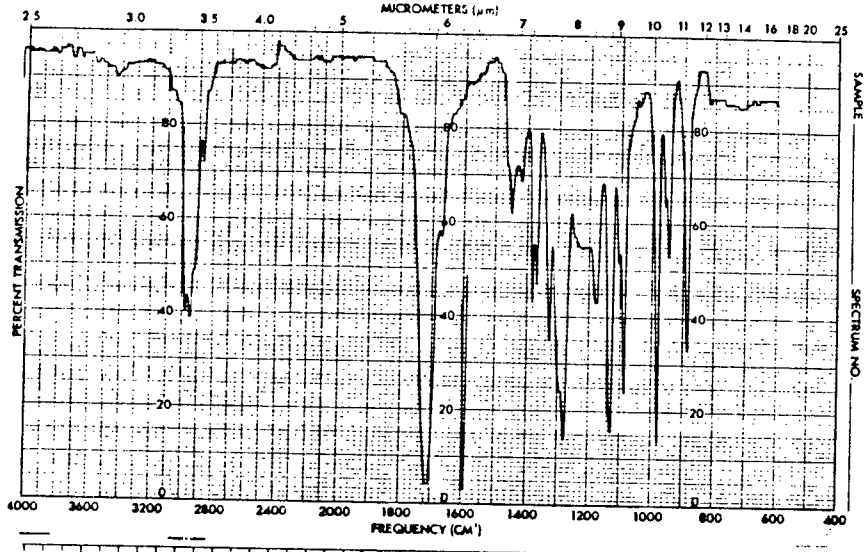


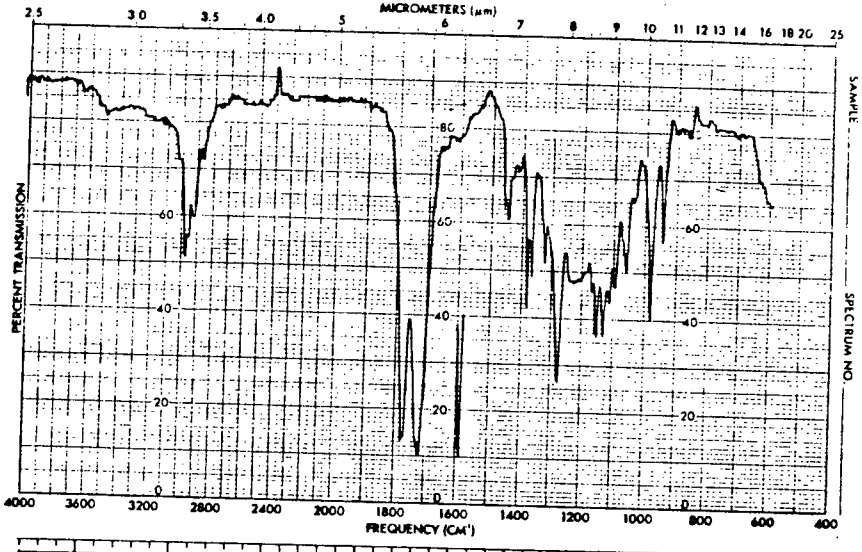


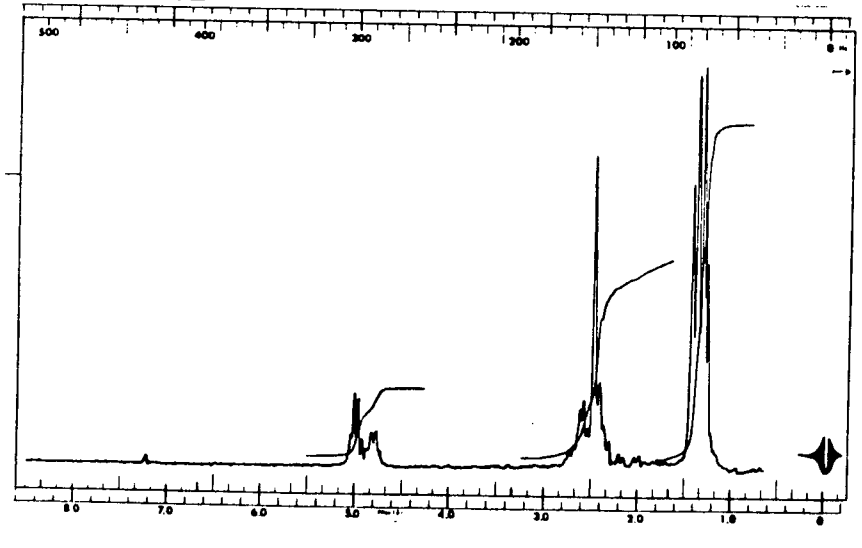
249 + 250

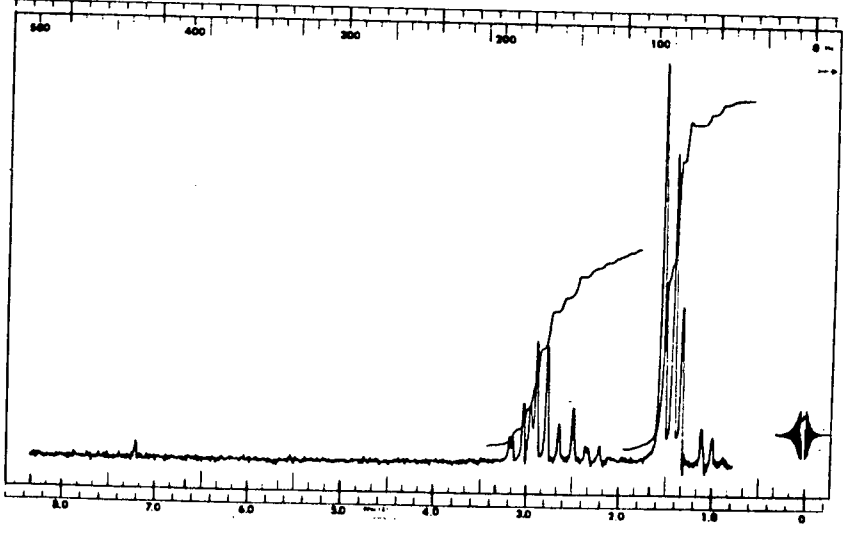


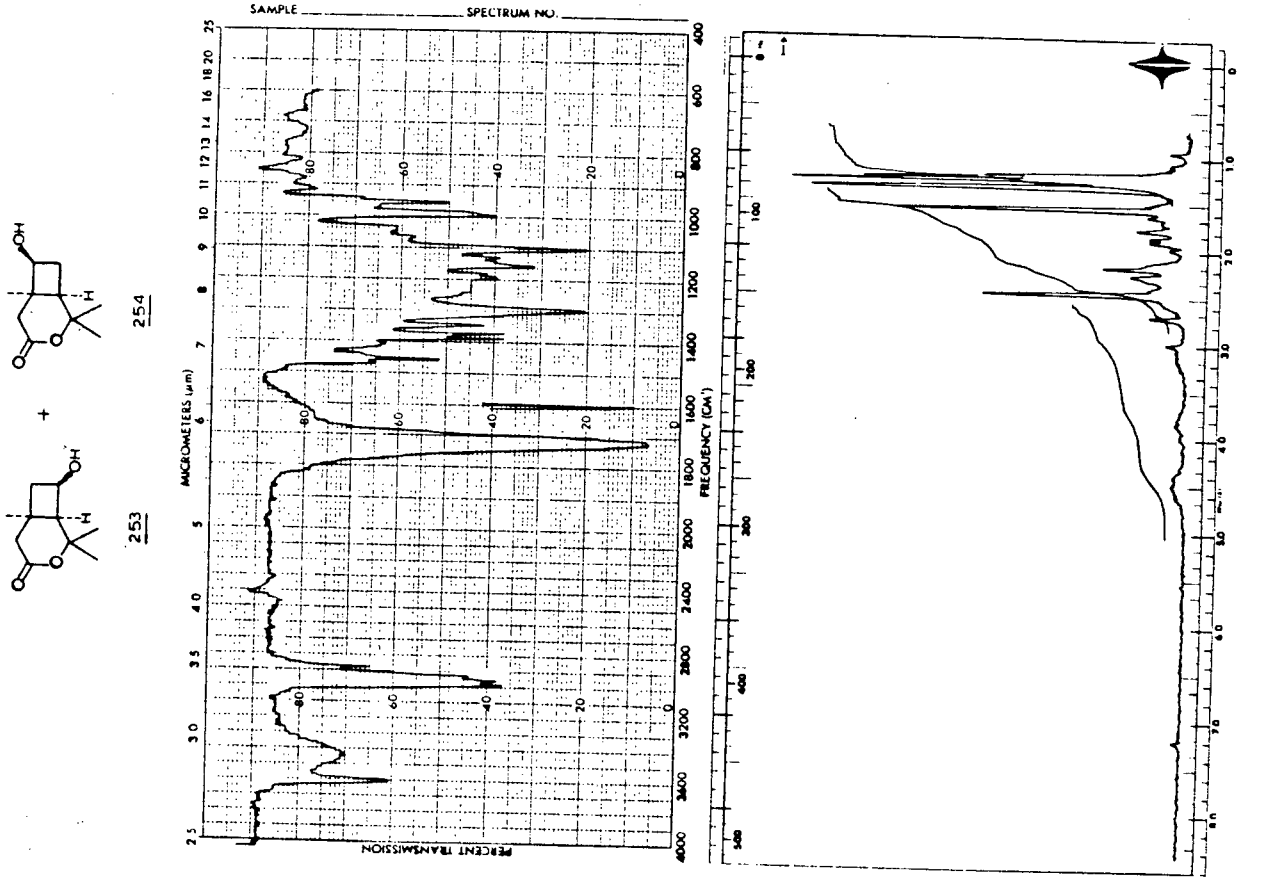
251 + 252





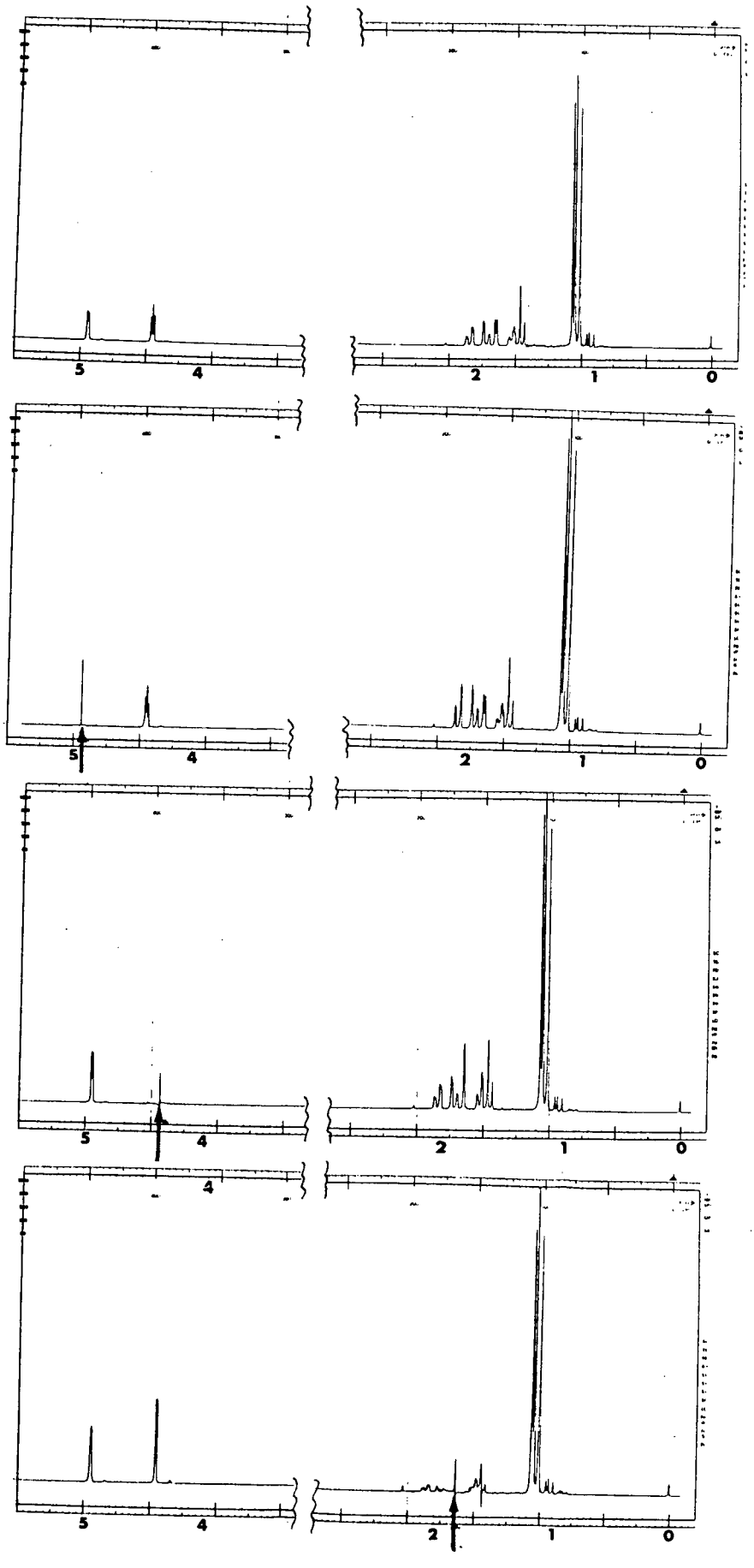




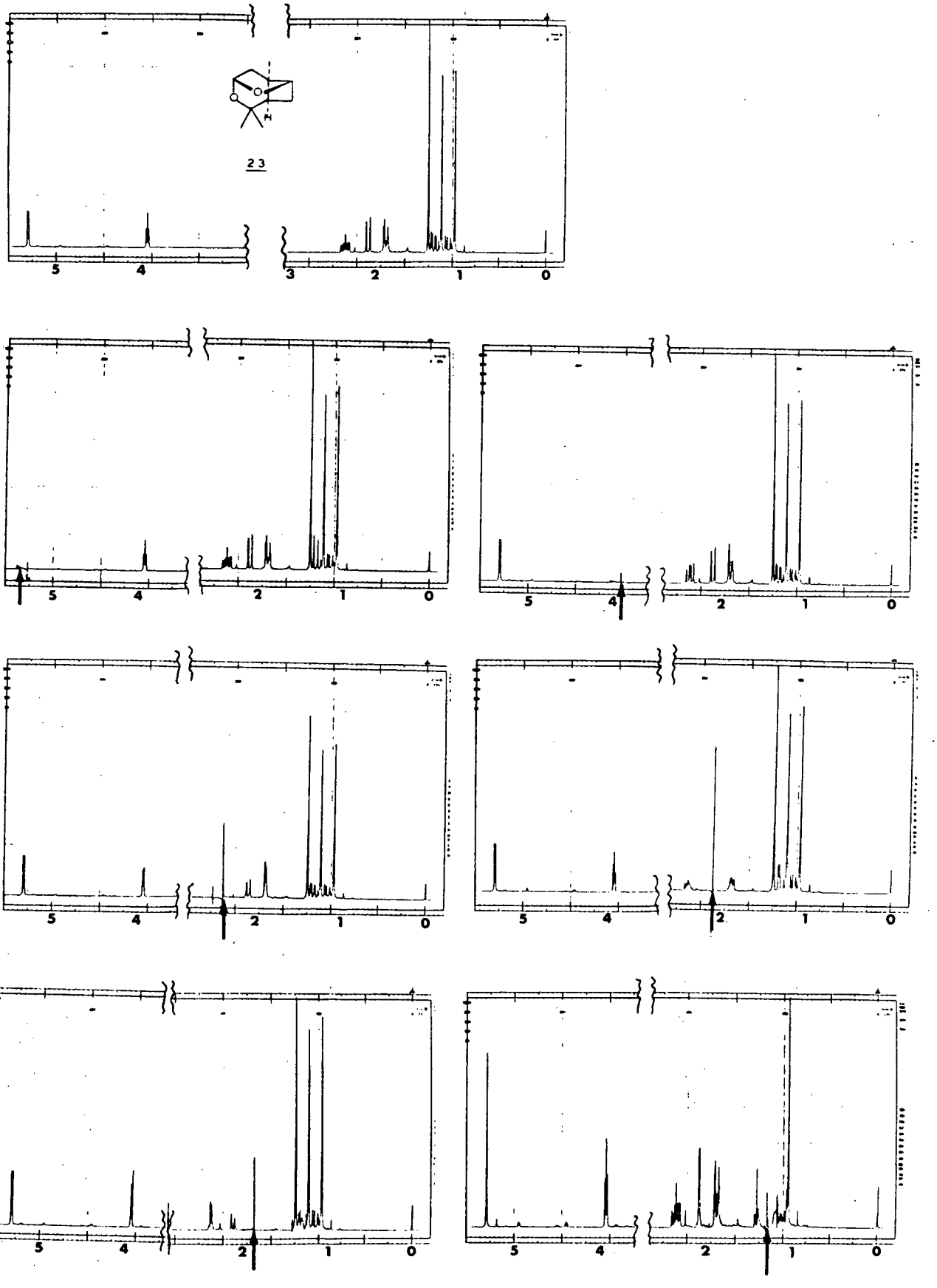

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION

253 + 254

270 MHz NMR of 23 and Decoupling Experiments



270 MHz NMR of 23 and Decoupling Experiments



^{13}C NMR of compound 201