In presenting the dissertation as a partial fulfillment of the requirements for an advanced degree from the Georgia Institute of Technology, I agree that the Library of the Institute shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to copy from, or to publish from, this dissertation may be granted by the professor under whose direction it was written, or, in his absence, by the Dean of the Graduate Division when such copying or publication is solely for scholarly purposes and does not involve potential financial gain. It is understood that any copying from, or publication of, this dissertation which involves potential financial gain will not be allowed without written permission.

7/25/68

STUDIES ON THE EPOXIDATION OF METHYL MALEOPIMARATE, TRIMETHYL MALEOPIMARATE AND TRIMETHYL FUMAROPIMARATE

A THESIS

Presented to

The Faculty of the Division of Graduate

Studies and Research

by

Emanuel Stamatakis

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

Georgia Institute of Technology

February, 1970

STUDIES ON THE EPOXIDATION OF METHYL MALEOPIMARATE,

TRIMETHYL MALEOPIMARATE AND TRIMETHYL FUMAROPIMARATE

Approved:

Chairman

Date approved by Chairman: 2/19/70

ACKNOWLEDGMENTS

I wish to express my sincere appreciation to Dr. Leon H. Zalkow for his inspiration during my undergraduate years of study and for his suggestion of the thesis topic and invaluable guidance and counsel during the course of my graduate work and in the preparation of this thesis.

I would also like to thank Dr. Drury S. Caine, III and Dr. Charles L. Liotta for serving as members of the reading committee.

Partial financial support of this work by the National Institute of Health is gratefully acknowledged.

Finally I wish to thank my parents, Mr. and Mrs. James Stamatakis, for their guidance, encouragement, and unselfish sacrifice in helping me pursue my education.

TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS ii

LIST OF TABLES iv

LIST OF SCHEMES v

GLOSSARY OF ABBREVIATIONS vi

SUMMARY viii

Chapter

I. INTRODUCTION 1

II. INSTRUMENTATION AND EQUIPMENT 9

III. EXPERIMENTAL 11

Preparation of Epoxide 4 11
Preparation of Epoxide 7 13
Preparation of Ketone 8 16
Preparation of Hydroxy Lactone 14 17
Preparation of Epoxide 15 20

IV. DISCUSSION OF RESULTS 23

V. CONCLUSIONS 38

VI. RECOMMENDATIONS 39

APPENDIX 40

BIBLIOGRAPHY 43

LIST OF TABLES

Table | Page

1. Chemical Shifts of the Protons of Epoxides 4, 7 and 15 30

LIST OF SCHEMES

Scheme Page

1. 31

2. 33

3. 34

4. 37

5. 41

6. 42

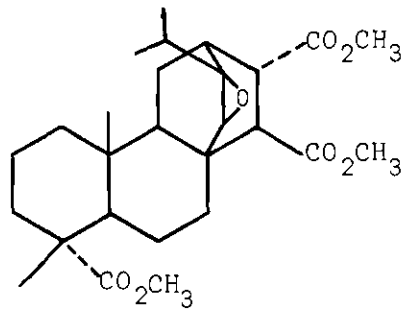
GLOSSARY OF ABBREVIATIONS

C	centigrade
CD	circular dichroism
cm^{-1}	wave numbers (infrared)
cps	cycles per second
C.T.	column temperature
d	doublet (NMR)
dm	decimeter(s)
g	gram(s)
GCQ	gas-chrom-Q
GLC	gas-liquid chromatography
H.F.R.	helium flow rate (GLC)
IR	infrared spectrum
J	coupling constant
lit	literature
M^+	molecular ion in mass spectrum
Mc	megacycles
m/e	mass to charge ratio
mg	milligram(s)
min	minute(s)
ml	milliliters
mol. wt.	molecular weight
m.p.	melting point

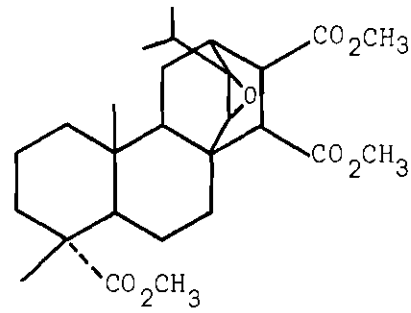
mμ	millimicron
N	normality
NMR	nuclear magnetic resonance
ORD	optical rotary dispersion
R_t	retention time (GLC)
s	singlet (NMR)
t	triplet (NMR)

SUMMARY

This study was undertaken in order to clarify the uncertainties existing in the literature[1,2,3] regarding the structures and stereochemistry of the products formed in the reactions of various Diels-Alder adducts of levopimaric acid with peroxyacids. The epoxides 7 and 15 were unequivocally prepared and correlated with the products

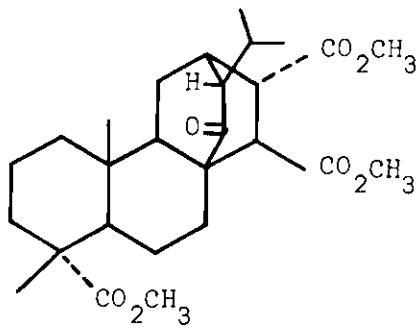


7

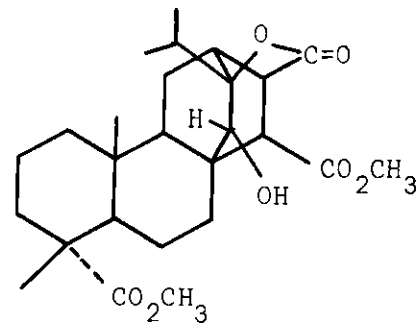


15

obtained directly by treatment of trimethyl fumaropimarate (6) and trimethyl maleopimarate (5) with trifluoroperacetic acid, respectively. In addition, 15 was converted into 14, and 7 was converted into 8, thus verifying these previously proposed[2,3] structures and providing evidence for the intermediacy of 7 and 15 in the formation of 8 and 14 directly from 6 and 5, respectively.



8



14

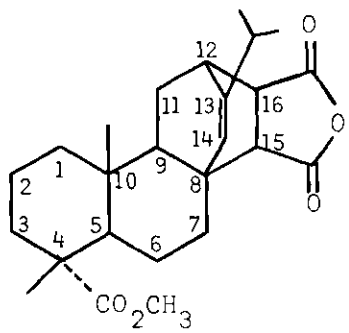
CHAPTER I

INTRODUCTION

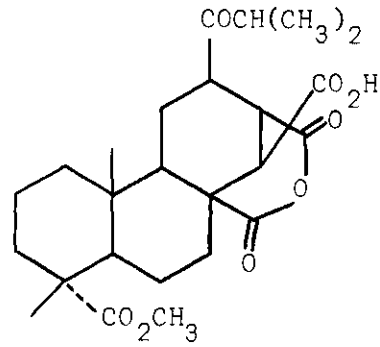
This study is concerned with the reinvestigation of some of the discrepancies in the literature[1,2,3] of the structures reported for the epoxidation of certain Diels-Alder adducts of levopimaric acid.

The first work in this area was the investigation of the ozonolysis of methyl maleopimarate (1) by Wienhaus and Sandermann[4] in 1936. These workers found that the ozonolysis of methyl maleopimarate, the Diels-Alder adduct of levopimaric acid methyl ester and maleic anhydride, gave a methyl ester, $C_{25}H_{34}O_8$ 2,[1,5] m.p. 250°. Several years later, Ruzicka and LaLande[6] reinvestigated the reaction and found in addition to the previous product, two other isomeric monomethyl esters of molecular formular $C_{25}H_{34}O_6$, m.p. 226-227° and m.p. 289-290°.[7] With the help of NMR and additional chemical evidence, Zalkow and coworkers assigned structure 3[8,9] for the product of m.p. 226-227° and structure 4[1] for the product of m.p. 289-290°.

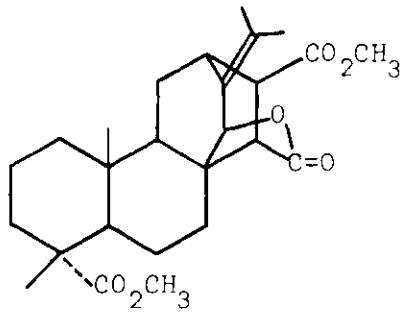
The structure elucidation of 4 proved to be interesting. In the elucidation, it was observed that 4 could be prepared from 1 by treatment with trifluoroperacetic acid,[10] but other peracids such as monoperphthatic or m-chloroperbenzoic were ineffective under the conditions then used.[1] In this study, the reaction of 1 with m-chloroperbenzoic acid was found to proceed very slowly. Treatment of the related



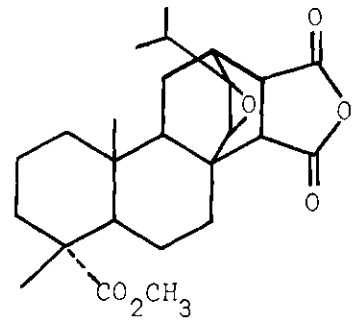
1



2



3

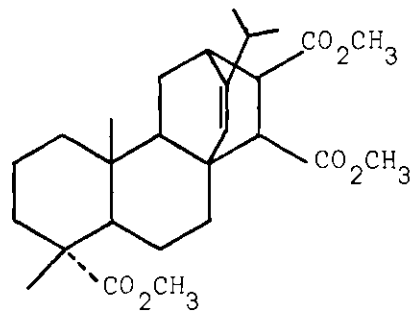


4

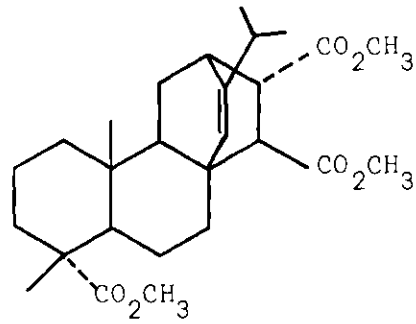
compounds, trimethyl maleopimarate (5) and trimethyl fumaropimarate (6) with trifluoroperacetic acid did not give epoxides as expected, but an "epoxide 7"[1] (actually a ketone 8)[3*] and a hydroxy lactone[1] were obtained. To establish the correct stereochemistry of these two products and a

---

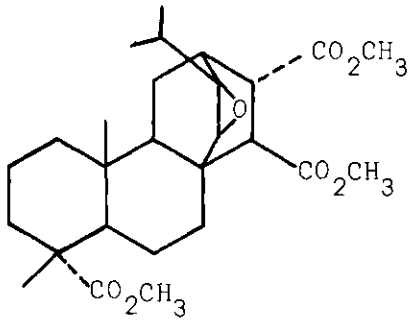
*The identification of the product as an epoxide was simultaneously carried out in our laboratory and by Herz and Blackstone.[3]



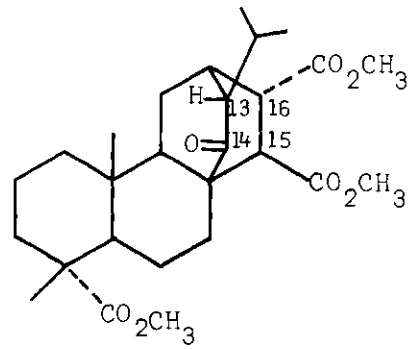
5



6



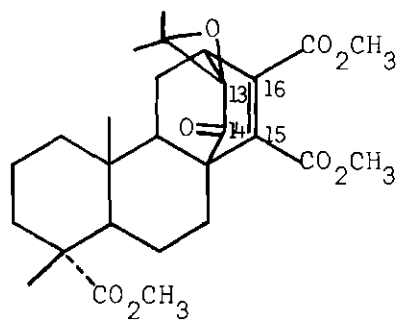
7



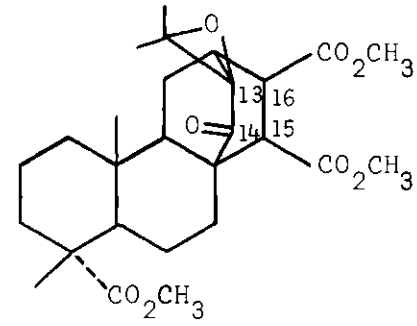
8

strengthening of the stereochemical assignment of 4 were some of the purposes of this research.

The treatment of trimethyl fumaropimarate (6) with trifluoroperacetic acid was reported[1] to yield epoxide 7. According to work in our laboratory and by Herz, *et al.*,[3] the presumed "epoxide 7" showed properties of a ketone (weak positive Cotton effect in the ORD curve) and therefore based on this and other evidence (presented below) the structure 8 was proposed. Herz reasoned that the misidentification of 8 as an epoxide was due to the NMR signal at δ 3.13 which was assigned to the proton at C-14, but which was actually due to the proton at C-15 or C-16. The above conclusion was suggested after comparison of



9



10

the NMR spectrum of compound 9, with that of its dihydro derivative 10.[3] In the NMR spectrum of 9, the signal at δ 3.30 was assigned to the allylic proton at C-12, while in compound 10 a two proton signal at δ 3.10 was assigned to protons at C-15 and C-16, and a one proton signal at δ 2.70 was assigned to the C-12 proton.[3]

The reaction of trimethyl fumaropimarate (6) with m-chloroperbenzoic acid was slow, but a product in harmony (IR and NMR) to the previously postulated structure 7 was obtained.* The most convincing evidence for structure 7, came from the observation that epoxide 4[1,2] could be converted into epoxide 7 and treatment of epoxide 7 with trifluoroacetic acid resulted in the formation of ketone 8.** With trifluoroperacetic acid the first step proposed[3] is the formation of

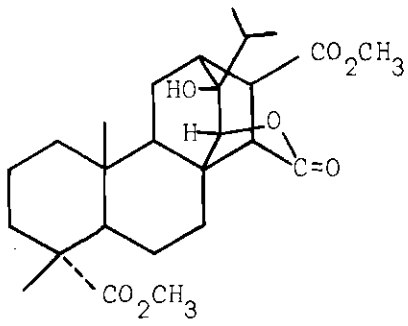
---

*Epoxide 7 was prepared independently in our laboratory and by Herz and Blackstone.[3]

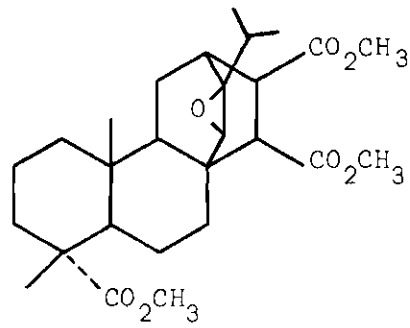
**This reaction was observed independently in our laboratory and by Herz and Blackstone.[3]

the epoxide 7 which in the presence of the Lewis acid, trifluoroacetic acid, rearranges by a pinacol rearrangement to the ketone 8. The preference of a pinacol rearrangement over rearside attack by an external nucleophile was believed due to the severe hindrance for the displacement of the epoxide function once it has coordinated with the acidic reagent. The stereochemistry of ketone 8 at C-13 was suggested by the inversion at C-13 due to the intramolecular rearside attack by the hydride ion, an arrangement which from inspection of the models should be favored thermodynamically.

Treatment of 5 with trifluoroperacetic acid in methylene chloride did not give either an epoxide or a ketone, but rather a hydroxy lactone.[1] The suggested structure 11[1] was postulated to have arisen *via* the intermediate epoxide 12 which in the presence of trifluoroacetic acid undergoes rearside attack by the β-oriented C-15 carbomethoxy nucleophile.

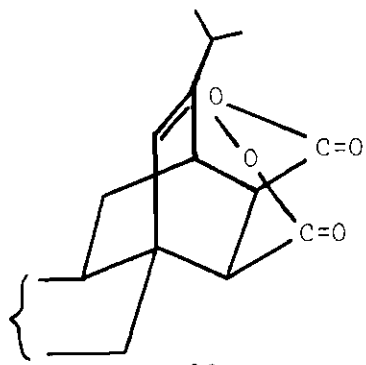


11



12

The apparent stereospecificity observed in the epoxidation of 5 and 6 was explained[1] in the following manner. Looking at a model of 6, the face of the double bond *anti* to the angular C-10 methyl group appeared less hindered than the *syn* side. In 5, however, the *syn* face appeared less hindered. To explain the epoxidation of 1 from the *anti* face, it was postulated that the anhydride ring was converted by trifluoroperacetic acid or ozone in acetic acid, into an intermediate peroxide, such as 13, which then reacted by an intramolecular rearrangement to give 4.

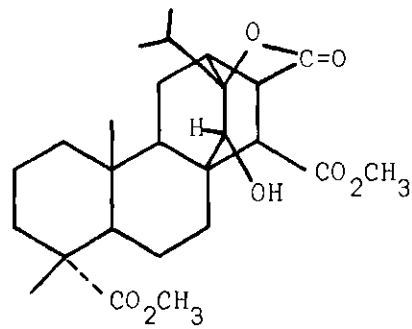


13

However, recent work carried out on bicyclic systems by Zalkow and Gabriel,[11] indicate that steric factors, rather than anhydride participation, first postulated by Henbest[12] are involved in epoxidations of bicyclic anhydrides.

Langlois and Gastambide,[2] in 1965, investigated a product obtained both by the action of methanol-sulfuric acid upon 4 and by the action of p-nitroperbenzoic acid upon 5, that had similar properties

to the hydroxy lactone reported by Zalkow, *et al.*,[1] but their work did not support the previously assigned structure. These workers maintained that the hydroxyl group was both *endo* and secondary and proposed structure 14[2] for this product. The hydroxyl group was assigned the *endo*

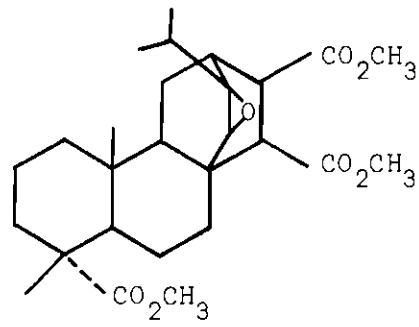


14

configuration on the basis of an infrared band at 3460 cm^{-1} which indicated intramolecular hydrogen bonding and secondary and hindered by the observation that the hydroxyl function could not be oxidized in good yield except under strenuous conditions.

Langlois and Gastambide[2] rationalized that 14 arose *via* the intermediate 15, which undergoes an unusual *cis* opening of the epoxide ring, rather than the classical[13,14] backside opening to give trans diaxial products.

Evidence obtained in our laboratory supports the rationalization of Langlois and Gastambide[2] for the formation of hydroxy lactone 14. It was found that epoxide 15, obtained by the treatment of 5 with m-chloroperbenzoic acid, on treatment with trifluoroacetic acid gave a hydroxy lactone identical to the hydroxy lactone prepared by the



15

procedure of Zalkow *et al.*,[1] and by the procedure of Langois *et al.*,[2] involving conversion of 4 into 14 by treatment with methanolic sulfuric acid.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mulheim, West Germany.

Infrared spectra were recorded using a Perkin-Elmer 237B spectrophotometer. The infrared spectra of liquids were taken as a thin film between two sodium chloride plates, and with solids in the form of potassium bromide pellets. The band at 1601 cm^{-1} of a polystyrene film (0.05 mm) was used as a reference point.

Nuclear magnetic resonance (NMR) spectra were obtained using a Varian Associates Model A-60 spectrometer (60 Mc spectra), or a JEOL Company Model 4H-100 spectrometer (100 Mc spectra*). Chemical shifts are reported in ppm downfield from the internal standard, tetramethylsilane.

Mass spectral data were obtained using a Varian Associates Model M-66 mass spectrometer.*

The optical rotary dispersion and circular dichroism spectra were obtained with a Jasco Model ORD/UV-5 spectrophotometer.**

Gas-liquid chromatography (GLC) was performed using a F&M Model 400 Biomedical gas chromatograph with a glass column and a hydrogen

---

*These spectra were run by Mr. George Turner.

**These spectra were run by Mr. Kenneth French.

flame detector. All GLC analyses were performed on a glass column (6 ft. x 1/8 in. inside diameter) bent in a U shape and packed with 10 per cent SE-30 on 100-120 mesh Gas-Chrom Q unless otherwise stated. The relative peak areas were measured using a Gelman Instruments Company planimeter or by accurately cutting out the peaks and weighing them on an analytical balance. The column substrates and solid supports used in the GLC analyses were obtained from Applied Science Laboratories or from Hewlett Packard Analytical Instruments. GLC analyses were performed on all products of reactions and for the compounds being compared a mixed injection was also carried out.

CHAPTER III

EXPERIMENTAL

Preparation of Epoxide 4

Procedure I--Reaction of Methyl Maleopimarate (1) with Trifluoroperacetic Acid[1,10]

Methyl maleopimarate[8] (1) (2.5g) was dissolved in methylene chloride (30 ml), containing a suspension of anhydrous disodium hydrogen phosphate (4 g). To this was added with stirring a solution of trifluoroperacetic acid over an interval of 20 minutes. The trifluoroperacetic acid was prepared by the dropwise addition at 0°C of 90 per cent hydrogen peroxide (1 ml) to a suspension of trifluoroacetic anhydride (3 ml) in 10 ml of methylene chloride.[10] After the addition was complete, the solution was refluxed for 45 minutes and then stirred an additional 48 hours at room temperature. The solution was washed with 10 per cent aqueous sodium sulfite (100 ml), followed by 10 per cent aqueous sodium bicarbonate (150 ml) and then the solution was filtered (very little material remained on the filter paper and this was discarded). The organic filtrate was washed with water (200 ml), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator to yield 2.2 g of crude crystalline product. Fast recrystallization of the product from hot acetone gave 4 as well formed rhombic shaped crystals, m.p. 291-294°C (lit.[1] m.p. 289-290°C); ν_{max}^{KBr} 2950, 1775 and 1720 cm^{-1}. The NMR spectrum (60 Mc Instrument, $CDCl_3$) showed

signals δ 0.71 (3H, d, isopropyl, J=7 cps), 0.83 (3H, s, C-10 methyl group, 1.05 (3H, d, isopropyl, J=7 cps), 1.17 (3H, s, C-4 methyl group), 3.20 (1H, s, H-14) and 3.67 (3H, s, ester, O-$\underline{CH_3}$). Using a 100 Mc instrument the following signals were observed: δ 0.70 (d, isopropyl, J=7 cps) 0.83 (s, C-10 methyl group), 1.02 (d, isopropyl, J=7 cps), 1.18 (s, C-4 methyl group), 3.19 (s, H-14) and 3.66 (s, ester, O-$\underline{CH_3}$). This material was identical (GLC,* IR, and NMR) to a sample prepared by Kulkarni and Girotra.**

Procedure II--Reaction of Methyl Maleopimarate (1) with m-Chloroperbenzoic Acid

m-Chloroperbenzoic acid (0.721 g, 85%, Aldrich Company) was added to a stirred solution of methyl maleopimarate (1) (1.5 g) in methylene chloride (30 ml). GLC analysis (C.T. 250°C, H.F.R. 67 ml/min.)*** five days after the reaction was started, showed the presence of starting material, R_t 4.2 min (65%) and one compound with R_t 8.8 min (35%) which was identical by mixed injections with epoxide 4 prepared from methyl maleopimarate and trifluoroperacetic acid (Procedure I). Since the reaction was progressing slowly, 15 days after the reaction was started additional m-chloroperbenzoic acid (0.480 g) was added. After 17 days,

---

*As stated in the Instrumentation and Equipment Section, all GLC analyses were done on the compounds alone and by mixed injections with the compound being compared.

**The author is grateful to M. V. Kulkarni and N. N. Girotra for a sample of compound 4.

***Unless otherwise stated, all GLC analyses as explained in the Instrumentation and Equipment section are performed on a glass column packed with 10 per cent SE-30 on 100-120 mesh Gas Chrom Q.

a GLC analysis (3% OV-1 on 100/120 mesh GCQ column, C.T. 260°C, H.F.R. 73 ml/min) showed five components. Mixed injections showed that the compound with R_t 4.2 min (5.4%) was starting material, methyl maleopimarate and the major component with R_t 9.2 min (69%) was epoxide 4. Approximately three-fourths (3/4) of the solution was removed and filtered. The filtrate was washed with 10 per cent aqueous sodium sulfite (70 ml), followed by 10 per cent aqueous sodium bicarbonate (100 ml) and finally with cold water (120 ml). The methylene chloride was dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator to yield 0.78 g of semicrystalline material. Slow recrystallization from hot acetone gave pure compound 4 as well formed rhombic shaped crystals, m.p. 273-279°C. The product was identical by IR and in mixed injections on the GLC to product 4 prepared by Procedure I.

The solution that was not worked up at first was later worked up in the same manner as was described above and an additional 0.142 g of product was obtained.

Preparation of Epoxide 7

Procedure I--Reaction of Trimethyl Fumaropimarate (6) with m-Chloroperbenzoic Acid

m-Chloroperbenzoic acid (0.644 g, 85%, Aldrich Company) was added to a stirred solution of trimethyl fumaropimarate (6) (1.5 g) in methylene chloride (30 ml). Additional m-chloroperbenzoic acid (0.644 g) was added 24 hours after the reaction was started. The reaction was followed by GLC and after 24 days, stirring at room temperature, a GLC

analysis (C.T. 255°C, H.F.R. 80 ml/min) showed one peak, R_t 5.2 min (100%). During this period of time a large amount of the solvent had evaporated and this gave rise to a large precipitate of m-chlorobenzoic acid. The solution was filtered to remove the precipitated m-chlorobenzoic acid and the resulting filtrate was washed with 10 per cent aqueous sodium sulfite (80 ml). The solution was filtered again (nothing was removed) and the filtrate was further washed with 10 per cent aqueous sodium bicarbonate (100 ml) and water (70 ml). The methylene chloride. was dried over anhydrous magnesium sulfate and concentrated to dryness to yield 1.36 g of a clear oily product. A number of different solvents were tried, but the product could not be crystallized from them. However, crystals were obtained by the following procedure: the product was dissolved in hot hexane and the solution was allowed to stand until a turbid solution was obtained. The turbid solution was filtered slowly and the filtrate was allowed to stand for several days allowing a slow evaporation of solvent. Compound 8, identical (IR and NMR) with the non-crystalline material, was obtained as a crystalline solid, m.p. 130.5-132.5°C;* ν_{max}^{KBr} 2950, 1750, 1738 and 1727 cm^{-1}. The NMR spectrum (60 Mc, $CDCl_3$) showed signals at δ 0.77 (3H, d, isopropyl, J=6.5 cps), 0.82 (3H, s, C-10 methyl group), 1.10 (3H, d, isopropyl, J=6.5 cps), 1.17 (3H, s, C-4 methyl group) 3.13 (1H, s, H-14), 3.64 (3H, s, ester, O-$\underline{CH_3}$), 3.67 (3H, s, ester, O-$\underline{CH_3}$), 3.74 (3H, s, ester,

---

*Epoxide 7 was prepared independently in our laboratory and by Herz and Blackstone.[3] The material reported by the latter workers was noncrystalline, and therefore a comparison of melting points was not possible.

O-$\underline{CH_3}$); 100 Mc: δ 0.77 (d, isopropyl, J=6.0 cps), 0.79 (s, C-10 methyl group), 1.08 (3H, d, isopropyl, J=6.0 cps), 1.16 (s, C-4 methyl group), 3.13 (s, H-14), 3.60 (s, ester, O-$\underline{CH_3}$), 3.70 (s, ester, O-$\underline{CH_3}$), 3.73 (s, ester, O-$\underline{CH_3}$). The compound did not show a Cotton effect in its CD and ORD curves.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.12; H, 8.47

Found: C, 67.96; H, 8.28.

Procedure II--Treatment of Anhydride Epoxide 4 with Sodium Hydroxide and Methanol

The anhydride epoxide 4 (440 mg) was added to a stirred solution of 25 per cent aqueous sodium hydroxide (12.5 ml) in methanol (12.5 ml). After the solution had been refluxed on a steam bath for 48 hours, it was diluted with water (100 ml) and filtered. The filtrate was acidified with dilute hydrochloric acid until a pH of 2 was obtained (pH paper) and extracted with ether. The organic layer, after drying with magnesium sulfate, was evaporated to give 315 mg of a clear glassy material. This material (315 mg) was dissolved in ether and to this solution, diazomethane in ether was added until a yellow color persisted. The excess diazomethane and ether were allowed to evaporate very slowly during which time a semicrystalline material was formed which could not be recrystallized from ether. Recrystallization from hexane, by the method described in the preparation of 7 with m-chloroperbenzoic acid (Procedure I above), gave 100 mg of pure compound 7 as a crystalline solid, m.p. 134-136°C. The material was identical in melting point, IR and NMR spectra with epoxide 7 obtained by the action of m-chloroperbenzoic acid on trimethyl fumaropimarate.

Preparation of Ketone 8

Procedure I--Reaction of Trimethyl Fumaropimarate (6) with Trifluoroperacetic Acid[1]

Trimethyl fumaropimarate (6)[9] (1.08 g) was dissolved in methylene chloride (30 ml), containing a suspension of anhydrous disodium hydrogen phosphate (4 g). To this was added with stirring a solution of trifluoroperacetic acid* over an interval of 20 minutes. After the addition was complete, the solution was refluxed for 45 minutes and then stirred at room temperature an additional 48 hours. The solution was washed with 10 per cent aqueous sodium sulfite (100 ml) and then filtered (nothing was removed by the filtration). The filtrate was further washed with 10 per cent aqueous sodium bicarbonate (200 ml) and finally with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated to yield a colorless glassy solid (0.67 g). This solid on recrystallization from ether gave 8 as a crystalline product, m.p. 183-184°C (lit. m.p.[1] 179-181°C); ν_{max}^{KBr} 2945, 1728, and 1705 cm^{-1}. The NMR spectrum (60 Mc, $CDCl_3$) showed signals at δ 0.72 (3H, s, C-10 methyl group), 0.99 (3H, d, isopropyl, J=6 cps), 1.11 (3H, s, C-4 methyl group), 1.31 (3H, d, isopropyl, J=6 cps), 3.62 (3H, s, ester, O-$\underline{CH_3}$), 3.66 (3H, s, ester, O-$\underline{CH_3}$), 3.75 (3H, s, ester, O-$\underline{CH_3}$); 100 Mc: δ 0.70 (s, C-10 methyl group), 0.86 (d, isopropyl, J=6 cps), 1.11 (s, C-4 methyl group), 1.30 (d, isopropyl, J=6 cps), 3.61 (s, ester, O-$\underline{CH_3}$), 3.65 (s, ester, O-$\underline{CH_3}$), 3.75 (s, ester, O-$\underline{CH_3}$);

---

*Trifluoroperacetic acid was prepared as in Procedure I, preparation of epoxide 4.

ORD (c, 0.19745, CH_3OH): $[\Phi]_{589}$ - 120.4, $[\Phi]_{336}$ - 615, $[\Phi]_{326.5}$ - 386, $[\Phi]_{314}$ - 940, $[\Phi]_{296}$ - 1568, $[\Phi]_{280}$ - 1373, a = +11.8.

Procedure II--Reaction of Epoxide 7 with Trifluoroacetic Acid

The epoxide 7 (97.5 mg) was dissolved in methylene chloride (10 ml) and to this stirred solution was added two drops of trifluoroacetic acid. The reaction was followed by GLC analysis and was shown to yield the following percent product in the indicated time: 6 hours, 3%; 1 day 11%; 11 days 64%. GLC analysis (C.T. 250°, H.F.R. 92 ml/min) of the reaction mixture of 11 days showed the presence of four components with R_t 3.8, 5.2, 5.3, 7.3 min (9:64:10:17). Mixed injections showed that the compound with R_t 5.2 min was ketone 8 and the compound with R_t 5.3 min was starting material, epoxide 7. The organic layer was washed with a small amount of 10 per cent aqueous sodium bicarbonate, followed by water. The solution was dried over anhydrous magnesium sulfate and concentrated to give 101.7 mg of semicrystalline product. Recrystallization from ether gave 25.9 mg of compound 8 as well formed crystals, m.p. 184.5-186°C (lit. m.p.[1] 179-181°C); ν_{max}^{KBr} 2945, 1730 and 1707 cm^{-1}. This product showed no depression in a mixed melting point determination with the material from Procedure I above.

Preparation of Hydroxy Lactone 14

Procedure I--Reaction of Trimethyl Maleopimarate (5) with Trifluoroperacetic Acid[1]

Trimethyl maleopimarate (5) (2.5 g) was dissolved in methylene chloride (30 ml), containing a suspension of anhydrous disodium hydrogen phosphate (4 g). To this was added with stirring a trifluoroperacetic

acid* solution over an interval of 20 minutes at room temperature. After the addition was complete, the solution was refluxed for 45 minutes and then stirred an additional 48 hours at room temperature. The solution was washed with 10 per cent sodium sulfite (220 ml), filtered (nothing was removed by the filtration), and the filtrate was washed with 10 per cent aqueous sodium bicarbonate (130 ml) and finally with water (350 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator to yield 2.55 g of a clear glassy product. Crystallization from methanol gave pure compound 14 as well-formed, needle-shaped crystals, m.p. 146-147.5°C (lit. m.p.[1] 146-148°C); ν_{max}^{KBr} 2940, 1778 and 1715 cm^{-1}. The NMR spectrum (60 Mc, $CDCl_3$) showed signals at δ 0.99 (3H, s, C-10 methyl group), 1.00 (3H, d, isopropyl, J=6.5 cps), 1.16 (3H, s, C-4 methyl group), 1.21 (3H, d, isopropyl J=6.5 cps), 3.66 (3H, s, ester, O-$\underline{CH_3}$), 3.71 (3H, s, ester, O-$\underline{CH_3}$), 3.96 (1H, d, H-14, J=13 cps), (changed to a singlet, 3.98 upon addition of D_2O), 4.31 (1H, d, OH-14, J=13 cps) (disappeared on an addition of D_2O); 100 Mc: δ 0.96 (d, isopropyl, J=6.0 cps), 0.97 (s, C-10 methyl group), 1.15 (s, C-4 methyl group), 1.19 (d, isopropyl, J=6.0 cps), 3.65 (s, ester, O-$\underline{CH_3}$), 3.70 (s, ester, O-$\underline{CH_3}$), 3.95 (d, H-14, J=12.5 cps) and 4.29 (d, OH-14, J=12.5 cps).

---

*Trifluoroperacetic acid was prepared as in Procedure I, preparation of epoxide 4.

Procedure II--Treatment of Anhydride Epoxide 4 with Sulfuric Acid and Methanol[2]

The anhydride epoxide 4 (400 mg) was dissolved in methanol (8 ml) and concentrated sulfuric acid (0.08 ml) was added. The solution was refluxed in an oil bath for 17 hours. After cooling, the solution was diluted with water (100 ml) and then extracted twice with chloroform (200 ml, total). The chloroform layer was washed three times with 0.25 N potassium hydroxide (100 ml, total) and finally with water (50 ml). The chloroform solution was evaporated with a rotary evaporator to yield 0.61 mg of a light yellow liquid. Repeated recrystallizations from methanol gave material with m.p. 119-138°C; ν_{max}^{KBr} 2940, 1775 and 1715 cm^{-1}. GLC analysis (C.T. 255°C, H.F.R. 83 ml/min) of this material (m.p. 119-138°C) showed the presence of four components with R_t 3.7, 5.9, 7.4, 11.9 min (11:14:65:10). Mixed injections showed that the compound with R_t 7.4 min (65%) was hydroxy lactone 14.

Procedure III--Reaction of Epoxide 15 with Trifluoroacetic Acid

Trifluoroacetic acid (5 drops) was added dropwise with stirring to a solution of epoxide 15* (100 mg) in methylene chloride (10 ml). The solution was then allowed to stir at room temperature for three days. The organic layer was washed with a small amount of 10 per cent aqueous sodium bicarbonate, and with cold water, then dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator to give 47.5 mg of a clear oily material, which on standing became a clear glassy solid. GLC analysis (C.T. 255°C, H.F.R. 60 ml/min) showed the

*Preparation of this is described in the next section.

clear glassy solid to be a mixture containing three components with R_t 4.5, 6.9, 10.0 min (15:12:73). Mixed injections showed that the compound with R_t 10.0 min (73%) was hydroxy lactone 14, identical with hydroxy lactone prepared in Procedure I above. Recrystallization from methanol a number of times gave pure compound 14 as crystals, m.p. 144-146.5°C (lit. m.p.[1] 146-148°C); ν_{max}^{KBr} 2940, 1780 and 1715 cm^{-1}. The product showed no appreciable depression in a mixed melting point determination with the material from Procedure I above.

Preparation of Epoxide 15

Reaction of Trimethyl Maleopimarate (5) with m-Chloroperbenzoic Acid

First Run. Methyl maleopimarate (5) (1.5 g) was dissolved in methylene chloride (30 ml), and to this solution m-chloroperbenzoic acid (0.644 g, 85%, Aldrich Company) was added with stirring. From GLC the reaction was shown to be progressing slowly. After 11 days an additional 0.214 g of m-chloroperbenzoic acid was added and after 14 days GLC analysis indicated the presence of only 44% 15. After 19 days 57% 15 was present and an additional 0.214 g of m-chloroperbenzoic acid was added. After 25 days 62% 15 was present and again 0.214 g of peracid was added; finally, after 44 days, GLC analysis indicated the presence of 87% 15. The organic layer was washed with 10 per cent aqueous sodium sulfite (90 ml) and then filtered (nothing was removed by the filtration). The filtrate was further washed with 10 per cent aqueous sodium bicarbonate (320 ml), then water (300 ml) and finally dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator to yield a light yellow syrup (1.05 g). A GLC analysis

(C.T. 250°C, H.F.R. 87 ml/min) after work-up showed the light yellow syrup to be a complex mixture containing five components with R_t 6.4, 7.6, 10.0, 11.0, 13.0 min (9:5:16:62:8). The major component with R_t 11.0 min (62%) was the desired epoxide 15. As can be seen from the GLC analysis of the product, the desired product was obtained but a number of additional products were introduced during the work-up. The product resisted all attempts at crystallization and because of this a new reaction was set up in which the product would be isolated in a different manner.

Second Run. m-Chloroperbenzoic acid (0.644 g, 85%, Aldrich Company) was added to a stirred solution of trimethyl maleopimarate (5) (1.5 g) in methylene chloride (30 ml). Additional m-chloroperbenzoic acid was added one day after the reaction was started to help speed up the reaction as had been previously done. The progress of the reaction was followed by GLC and at the end of 28 days, stirring at room temperature, a GLC analysis (C.T. 250°C, H.F.R. 87 ml/min) showed the solution to be a mixture containing five components with R_t 7.5, 9.8, 10.8, 13.2, 15.0 min (6:6:83:3:3). The major component with R_t 10.8 min was the desired epoxide 15. Evaporation of part of the solvent and then filtration, removed a large amount of the m-chlorobenzoic acid. With a large amount of the m-chlorobenzoic acid removed, crystallization of the product from a number of different solvents was tried, but with no success. An analytical sample was obtained by chromatographing the mixture over silica gel (40 g) (made up in benzene) and eluting with chloroform-benzene solvent. Concentration of the

chloroform-benzene (30:70) fraction gave epoxide 15, as a clear viscous substance, ν_{max}^{KBr} 2945, 1740 and 1717 cm^{-1}. The NMR spectrum (60 Mc, $CDCl_3$) showed signals at δ 0.76 (3H, d, isopropyl, J=6.5 cps), 0.82 (3H, s, C-10 methyl group), 1.09 (3H, d, isopropyl, J=6.5 cps), 1.17 (3H, s, C-4 methyl group, 3.10 (1H, s, H-14), 3.64 (3H, s, ester, O-$\underline{CH_3}$), 3.65 (3H, s, ester, O-$\underline{CH_3}$), 3.67 (3H, s, ester, O-$\underline{CH_3}$); 100 Mc: δ 0.72 (d, isopropyl, J=6.0 cps), 0.80 (s, C-10 methyl group), 1.07 (d, isopropyl, J=6.0cps), 1.15 (s, C-4 methyl group), 3.08 (1H, s, H-14), 3.62 (s, ester, O-$\underline{CH_3}$), 3.63 (s, ester, O-$\underline{CH_3}$), 3.66 (s, ester, O-$\underline{CH_3}$). The mass spectrum gave a parent ion at M^+ = 476 (7.2%, base peak at m/e 156) (calcd. for $C_{27}H_{40}O_7$; M^+ = 476). This material could not be crystallized.

CHAPTER IV

DISCUSSION OF RESULTS

As previously stated, the goal of this work was to firmly establish the structures and stereochemistry of the products from the reaction of trifluoroperacetic acid with trimethyl maleopimarate (5) and trimethyl fumaropimarate (6). Since the epoxides derived from trimethyl maleopimarate, 15, and from trimethyl fumaropimarate, 7, were suggested[2,3] as intermediates which could lead to the products obtained by the action of trifluoroperacetic acid on 5 and 6, respectively, it was decided to unequivocally synthesis these epoxides and determine if in fact they could be converted into the above mentioned products. Further, if it was possible to convert the epoxides into the products obtained with trifluoroperacetic acid the proposed mechanisms would be strongly supported.

Four major steps were visualized as being necessary to solve the problem. First, preparation and characterization of authentic samples of the products obtained from the reaction of trifluoroperacetic acid with trimethyl maleopimarate and trimethyl fumaropimarate. Second, preparation of the hydroxy lactone of Langlois and Gastambide[2] by the treatment of anhydride epoxide 4 with methanolic sulfuric acid as previously described by them and comparison of the lactone so obtained with the one reported by Zalkow *et al.*[1] Third, the preparation and structure elucidation of the epoxides of trimethyl maleopimarate and

trimethyl fumaropimarate. Fourth, conversion of the epoxides obtained above in an unambiguous manner into the products obtained with trifluoroperacetic acid.

Epoxidation of methyl maleopimarate (1) with trifluoroperacetic acid* in methylene chloride gave 4 as rhombic shaped crystals, m.p. 291-294°C (lit.[1] m.p. 289-290°C). The infrared spectrum of 4 showed bands at 1775 (anhydride) and 1720 (double bond) cm^{-1}. The NMR** spectrum showed a singlet at δ 0.83 assigned to the C-10 methyl group, a pair of doublets (J=7 cps) centered at δ 0.71 and δ 1.05 assigned to the isopropyl methyl groups, and a sharp singlet at δ 3.20 assigned to the proton at C-14.

It was previously reported[1] that no reaction of 1 was observed with m-chloroperbenzoic acid. However, in this study the reaction was found to occur very slowly. Thus, even in the presence of excess m-chloroperbenzoic acid the reaction proceeded to 69 per cent completion at room temperature only after 17 days. The epoxide obtained was identical in all respects (m.p., IR, and GLC)*** with the epoxide obtained with trifluoroperacetic acid.

The treatment of trimethyl maleopimarate (5) with trifluoroperacetic acid in methylene chloride[1] gave a hydroxy lactone 14[2] in the

---

*The method of preparation of trifluoroperacetic acid is given in the experimental section.

**All NMR data given are for samples run in $CDCl_3$ and on the 60 Mc NMR instrument unless otherwise stated.

***As stated in the Instrumentation and Equipment section, all GLC analyses were done both on the compound alone and as a mixed injection with the compound being compared.

the form of needle shaped crystals, m.p. 146-147.5°C (lit.[1] m.p. 146-148°C). The infrared spectrum of 14 showed bands at 3460 (intramolecular hydrogen bonding),[2] 1778 (γ-lactone) and 1715 (ester) cm^{-1}. The NMR spectrum showed a singlet at δ 0.99 (C-10 methyl group), a pair of doublets (J=6.5 cps) centered at δ 1.00 and δ 1.21 (isopropyl methyl groups), a doublet (J=13 cps) at δ 3.96 (H-14) which upon addition of D_2O changed to a singlet, centered at δ 3.98 and a doublet at δ 4.31 (OH-14) which disappeared on addition of D_2O.

The treatment of trimethyl fumaropimarate (6) with trifluoroperacetic acid in methylene chloride yielded 8[3] as a crystalline product, m.p. 183-184°C (lit.[1] m.p. 179-181°C). Product 8 showed bands in its infrared spectrum at 1728 (ester) and 1705 (ketone) cm^{-1}. The NMR spectrum exhibited a singlet at δ 0.72 (C-10 methyl group), and a pair of doublets (J=6 cps) centered at δ 0.99 and δ 1.31 (isopropyl methyl group).

With the preparation of authentic samples being complete, the second step of comparing the hydroxy lactones was initiated. The reaction of epoxide 4 prepared in our laboratory, with methanol-sulfuric acid *via* the route described by Langlois and Gastambide[2] gave a crude crystalline product containing predominantly (65%) hydroxy lactone 14. The hydroxy lactone thus obtained was identical with the product obtained from trimethyl maleopimarate and trifluoroperacetic acid *via* the route described by Zalkow, *et al.*[1]

The reaction of trimethyl fumaropimarate with m-chloroperbenzoic acid in methylene chloride gave initially epoxide 7 as a noncrystalline

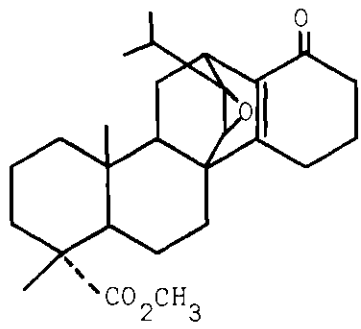
material. Crystallization of this product from hexane by the method described in the experimental section gave crystalline 7 (m.p. 130-132.5°C)* identical in spectral (IR, NMR) properties with the non-crystalline material. It was found that the use of excess m-chloroperbenzoic acid gave an increase in the rate of reaction with no noticeable side effects. The infrared spectrum of 7 showed the three ester absorptions at 1750, 1738, and 1727 cm^{-1}. The NMR spectrum showed a sharp singlet at δ 0.82 (C-10 methyl group) a pair of doublets (J=6.5 cps) centered at δ 0.77 and δ 1.10 (isopropyl methyl groups) and a singlet at δ 3.13 (proton at C-14). Compound 7 did not show a Cotton effect (ORD and CD) as would be expected for an epoxide. The assigned molecular formular, $C_{27}H_{40}O_7$, was further supported by combustion analysis.

Evidence from NMR for the presence of an epoxide ring on the C-13, C-14 bridge in these bicyclic compounds (4, 7, 15) comes from the expected upfield shift of the proton at C-14 from approximately δ 5.5 in the olefinic precursors to approximately δ 3.1,[3] the downfield shift of the angular C-10 methyl group[15,16] signal and the pronounced non-equivalence of the methyl signals of the isopropyl groups. In the Diels-Alder adducts of levopimaric acid and other compounds containing unsaturation in the C-13, C-14 bridge, the signal due to the angular C-10 methyl group is observed at δ 0.6-0.7, because of strong shielding

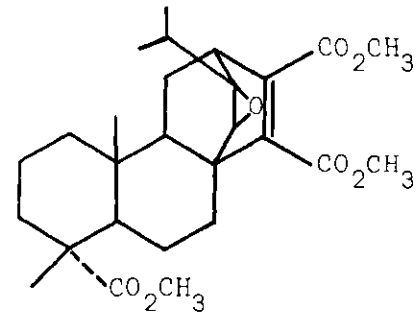
---

*Epoxide 7 was prepared independently by Herz and Blackstone[3] in non-crystalline form and they did not succeed in obtaining crystalline 7.

by the double bond.[15,16] In epoxides like 4,[1,2] 16[3] and 17,[3] the angular C-10 methyl group signal is found 12-15 cycles farther

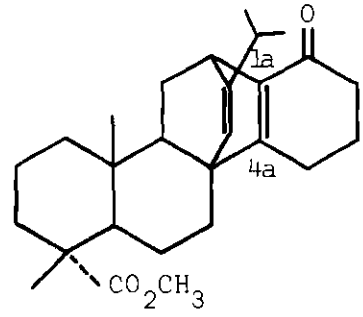


16



17

downfield.[3] In the NMR spectrum of all Diels-Alder adducts and compounds, such as 18,[3] the signals arising from the isopropyl methyl

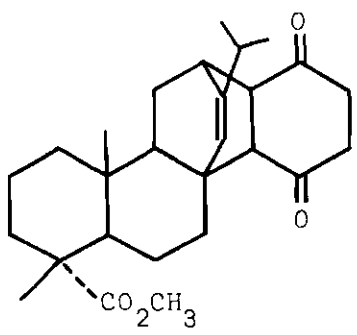


18

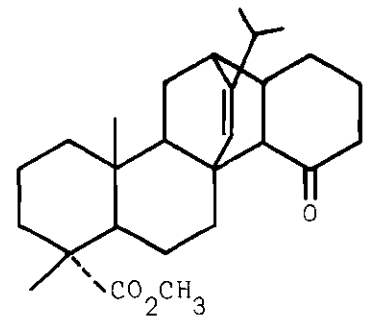
groups appear as identical doublets or doublets of almost identical chemical shifts near δ 1.[16,17,18,19] In epoxides like 4, 16 and 17, the isopropyl methyl group signals appear as two non-equivalent doublets

near δ 1.05 and δ 0.7, respectively, the latter representing the methyl group being shielded more effectively by the epoxide ring.[3]

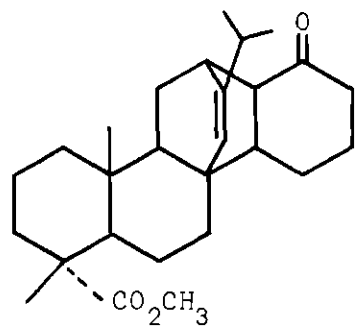
The stereochemical assignment of the epoxide ring in 16 and 17 (and that of epoxides 4 and 7) is based on the severe steric interference, indicated in models, for approach of oxidizing agents from the side of ring (A), and on the non-displaced chemical shift of the angular C-10 methyl groups.[3] It was argued that if the epoxide ring was on the alternate side, a considerable degree of shielding for the angular C-10 methyl group would be expected.[1,3] Further support for the stereochemistry of the epoxide ring was obtained from work with the compounds 19,[17] 20[17] and 21.[17,19] It was observed that none of these



19

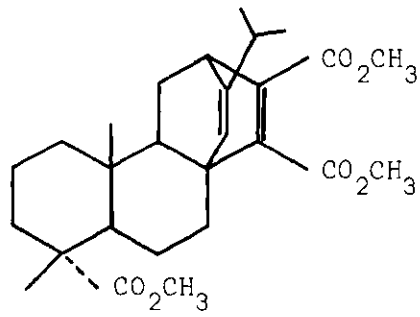


20



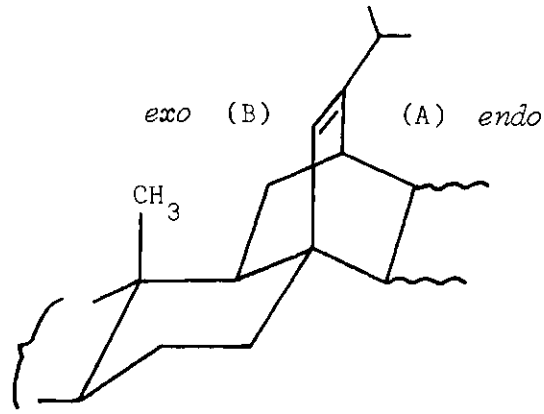
21

compounds were attacked by ozone or by potassium permanganate, whereas compounds like 6 under the same conditions were smoothly oxidized.[9,17] Furthermore, treatment of 19 with m-chloroperbenzoic acid did not effect the double bond, but resulted in a Baeyer-Villiger oxidation of the less hindered carbonyl group.[2,17] It was suggested that the lack of reactivity of 19, 20 and 21 toward oxidizing agents was due to steric hindrance around the double bond as indicated by Dreiding models. Introduction of a 1a-4a double bond as in 18, it was reasoned, should restore normal accessibility. This was substantiated in the epoxidation of 18, which occurred rapidly and preferentially at the bridge double bond to give 16. Similarly the epoxidation of 22[3] with m-chloroperbenzoic acid proceeded smoothly to give 17. From the



22

observation above, it appears that face B of the C-13, C-14 double bond (see below) in all of the compounds discussed is severely hindered to attack by oxidizing agents, presumably by the C-10 methyl group. Therefore, epoxidation of 1, 5 and 6 in the presence of



m-chloroperbenzoic acid would be expected to take place from side A (*endo* side) to give epoxides 4, 15 and 7, respectively.

The similarities in the NMR spectra of epoxide 4, 7 and 15 (Table 1), and in addition the similarities of these spectra with those

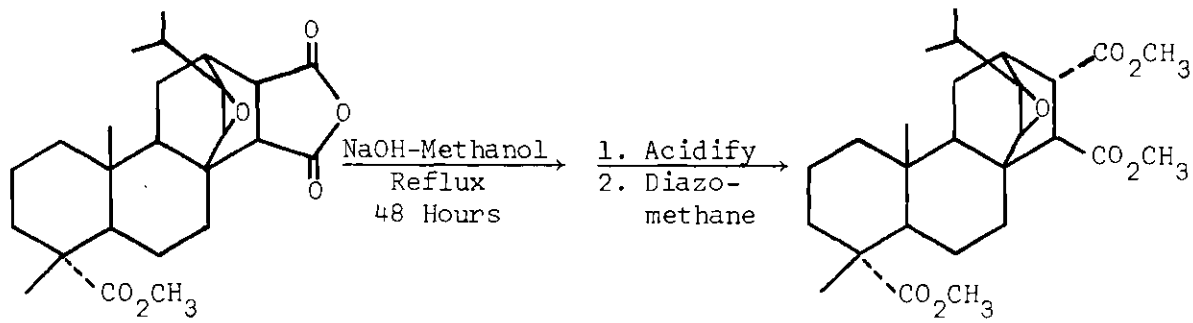
Table 1. Chemical Shifts of the Protons of Epoxides 4, 7 and 15

Compound	Solvent	δ in ppm			
		C-14 Proton	C-10 Methyl	Isopropyl Methyl Groups	
4	$CDCl_3$	3.20	0.83	0.71	1.05
7	$CDCl_3$	3.13	0.81	0.77	1.10
15	$CDCl_3$	3.10	0.82	0.76	1.09

of 16 and 17 reported by Herz *et al.*,[3] strongly suggest that all of these epoxides possess the same absolute configuration at C-13 and C-14. Second, and most important, the epoxide 4 was converted into epoxide 7.

This conversion was carried out by refluxing epoxide 4 with NaOH-methanol for 48 hours, acidifying the reaction and then esterifying with diazomethane (scheme 1). This gave in good yield the epoxide 7, identical in all respects (m.p., IR and NMR) with an authentic sample of 7.

Scheme 1



4 7

Reaction of trimethyl maleopimarate with m-chloroperbenzoic acid in methylene chloride gave epoxide 15, as a clear viscous material which resisted all crystallization attempts. Since the reaction was slow, again it was found useful to use excess m-chloroperbenzoic acid (see experimental section). The infrared absorption for the three ester groups (1740-1717 cm^{-1}) could not be resolved.* The NMR spectrum of 15 shows a sharp singlet at δ 0.82 (C-10 methyl group), a pair of doublets (J=6.5 cps) centered at δ 0.76 and δ 1.09 (isopropyl methyl groups) and a singlet at δ 3.10 for the proton at C-14. The mass

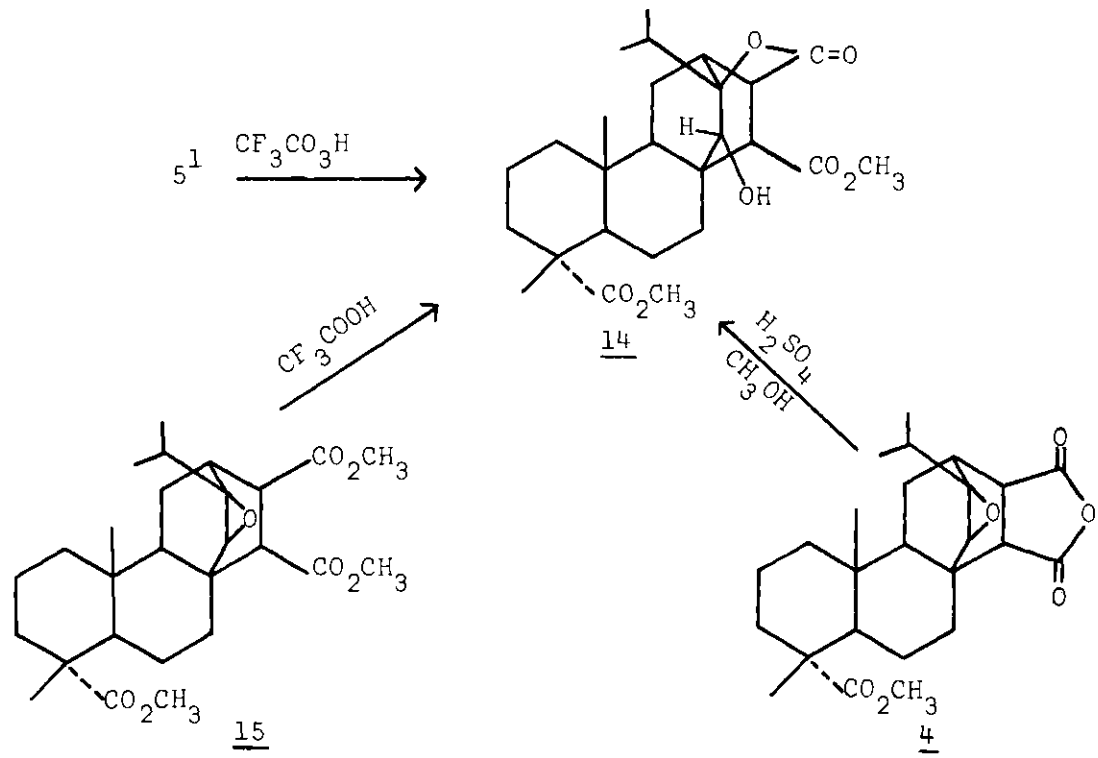
*The infrared was taken on the clear viscous material.

spectrum gave the parent ion at M^+ = 476 (calcd. for $C_{27}H_{40}O_7$; M^+ = 476).

It is interesting to note that 4 could not be converted into 15 with methanolic-diazomethane (no reaction occurred), conditions which suffice for the conversion of 1 into 5.[1] The lack of reactivity of the anhydride moiety in 4 with methanolic diazomethane may arise from the decreased electrophilicity of the anhydride carbonyl groups in 4 as a result of electron donation from the *syn* epoxide oxygen.

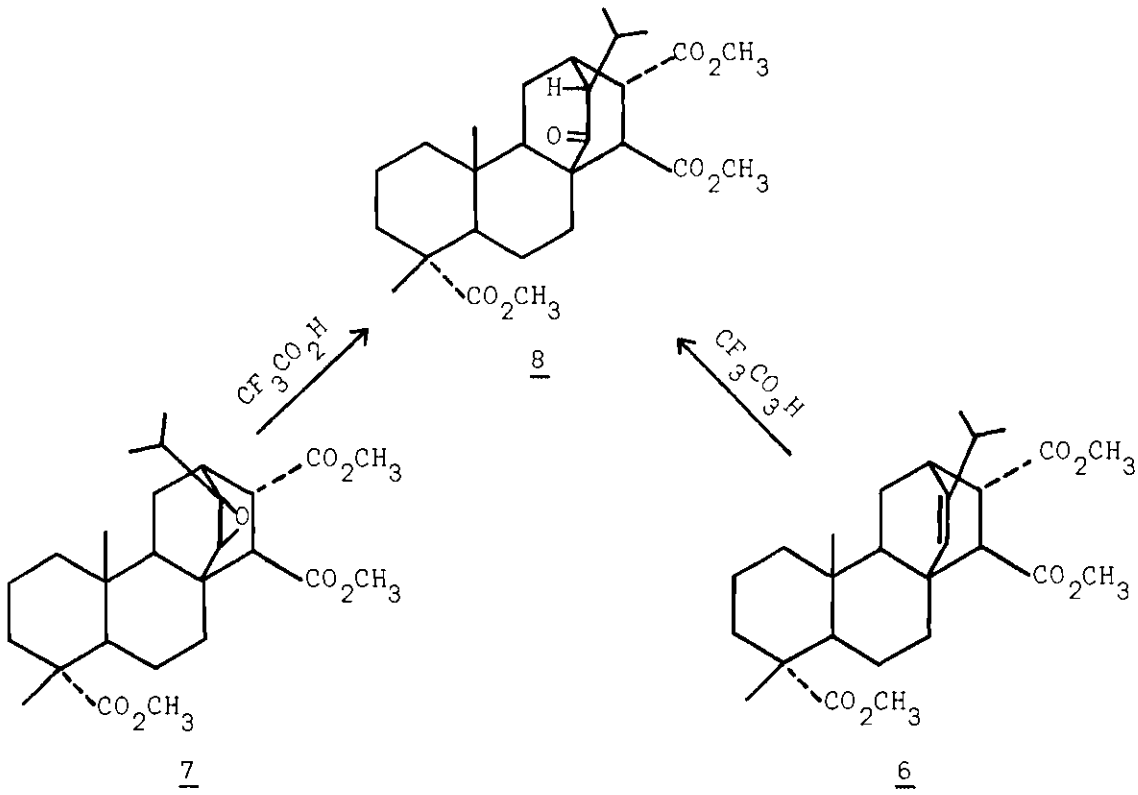
The assignment of structure 15 to the product obtained as described above was based on NMR data and on the important conversion of 15 to the hydroxy lactone 14. Thus the expected upfield shift of the proton at C-14, the downfield shift of the C-10 methyl group, the pronounced non-equivalence of the signals of the methyls of the isopropyl group all are indicative of an *endo* epoxide ring in 15. The conversion of epoxide 15 into the hydroxy lactone 14 (scheme 2), by treatment of 15 with a trace of trifluoroacetic acid, further substantiated the stereochemistry of the epoxide ring. It was shown earlier that the hydroxy lactone 14 could be prepared from epoxide 4,[1,2] by using methanol-sulfuric acid as the reagent.[2] Since both 4 and 15 gave the same hydroxy lactone 14, in unambiguous one step reactions, it can only mean that the stereochemistry of the epoxide ring in both epoxides is the same.

Scheme 2

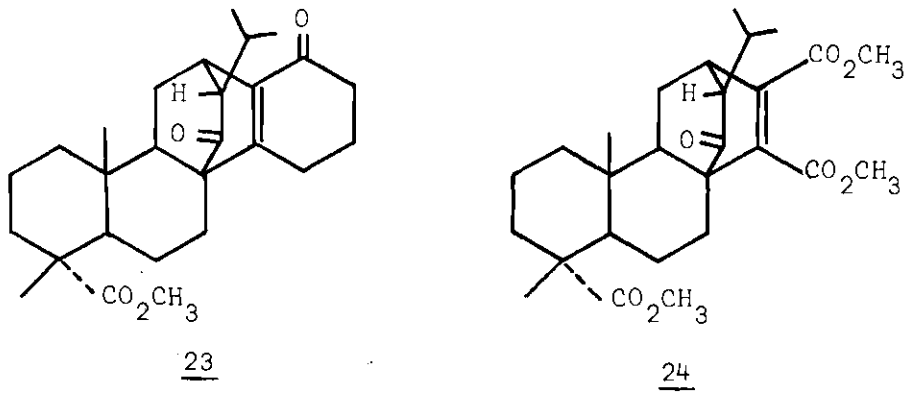


Treatment of epoxide 7 at room temperature with a trace of trifluoroacetic acid resulted in the formation of a ketone, identical in all respects (m.p., IR and GLC) to the ketone 8 obtained by the action of trifluoroperacetic acid on 6 as discussed earlier (scheme 3). The proposed mechanism for the formation of ketone 8 is given in the introduction. In the proposed mechanism, epoxide 7 is considered the intermediate (supported by the above reaction), which in the presence of acid, rearranges by a pinacol rearrangement to the ketone 8.[3] The structure and stereochemistry of ketone 8 follows from its method of preparation from epoxide 7, the stereochemistry of the epoxide ring in the latter having been established as discussed above.

Scheme 3



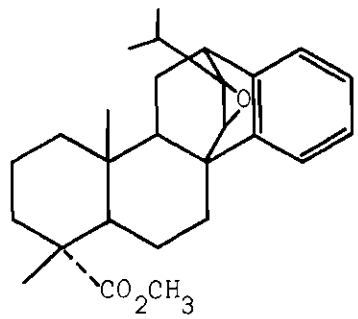
Further support for the stereochemistry of ketone 8 comes from a comparison with the reported NMR spectra of 23 and 24.[3] The assigned



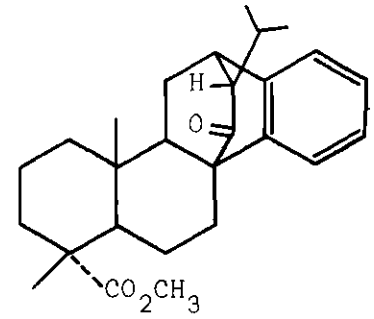
stereochemistry of the isopropyl groups in 23 and 24 is based on the NMR signals for the isopropyl methyl groups. According to Herz,[3]

> . . . the NMR spectra of precursors 16 and 17 show that the methyl doublet at lower field (at 1.07 and 1.04 ppm) has not been affected significantly by the pinacol rearrangement, whereas the more shielded methyl doublet, formerly at 0.80 and 0.76 ppm, has experienced a further upfield shift to 0.67 and 0.63 ppm, respectively. This is consistent with that orientation, that is, 23 and 24, in which one of the methyl groups experiences greater shielding by the conjugated double bond and perhaps the carbonyl and which, from inspection of the models, should interpose a very considerable amount of steric hindrance to the potential reactions of the carbonyl group.[3]

This was actually found to be the case. "24 and 8[1] were not only unreactive toward the usual carbonyl reagents and toward sodium borohydride, but did not undergo the Baeyer-Villiger oxidation."[3] According to Herz, the stereochemical assignment for the isopropyl group is particularly clear in the conversion of 25[3] into the ketone 26.[3] This is based on the expected large diamagnetic shift in the methyl signals



25



26

of the isopropyl group in going from 25 to 26[3] (isopropyl methyl signals appear at δ 0.35).

The above observations on the stereochemistry of ketones 23, 24 and 26, along with the chemical evidence that the ketone 8 and 24 are unreactive toward the usual carbonyl reagents give additional proof for the stereochemistry indicated in ketone 8.

It should be noted that the *endo* epoxides are converted into ketones in the presence of Lewis acids, only in those cases in which C-16 (C-1a) is sp^2 hybridized (16, 17, 25) or the substitutent at C-16 is α oriented (7). That is, in those cases in which the resulting *exo* isopropyl group is sterically unhindered. By contrast, when the epoxide contains a β oriented substituent at C-16 (15), it rearranges in the presence of a Lewis acid to give a lactone containing an *endo* isopropyl group (14) by an unusual front side opening of the epoxide ring.

The conversion of epoxide 15 into the hydroxy lactone 14 was accomplished as reported earlier by the addition of a trace amount of trifluoroacetic acid to the epoxide 15. The hydroxy lactone obtained was identical in all respects (m.p., IR, and mixed injections on GLC) to an authentic sample prepared from trimethyl maleopimarate by trifluoroperacetic acid and from epoxide 4 by methanol-sulfuric acid.

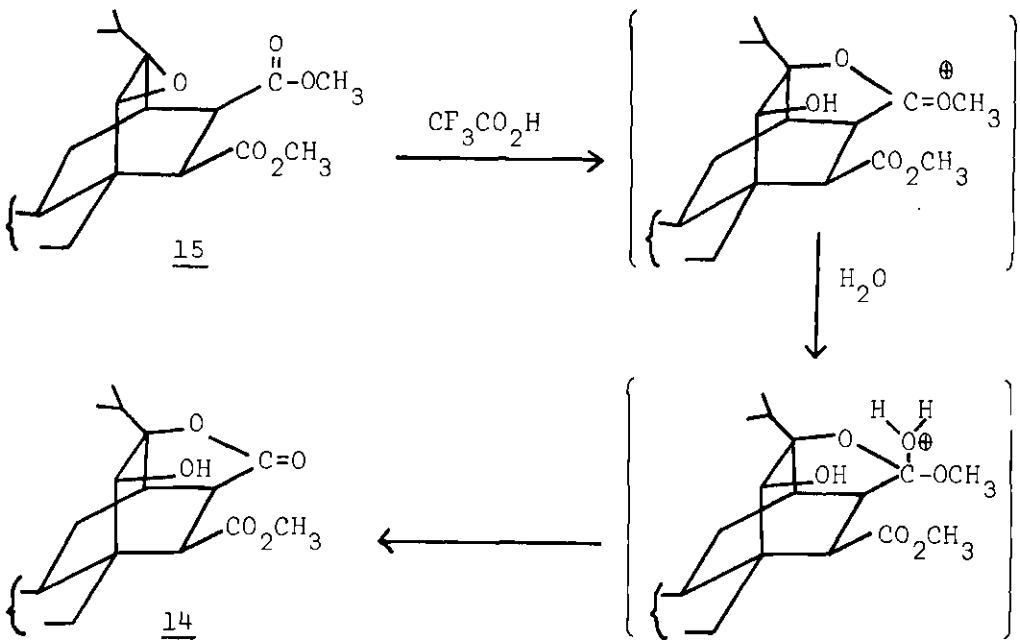
Langlois and Gastambide, as previously reported,[2] assigned the *endo* configuration to the hydroxyl group in the hydroxy lactone 14 on the basis of the infrared band at 3460 cm^{-1} (intramolecular hydrogen bonding), and they assumed the hydroxyl group was secondary and hindered on the basis of chemical evidence. Further, as was reported

earlier, these workers observed that 14 could be prepared from epoxide 4.

Based on the above observations, these workers assigned structure 14, to the hydroxy lactone prepared from trimethyl maleopimarate with peracids, and postulated that the hydroxy lactone 14 arose *via* the intermediate 15, by an unusual cis opening of the epoxide ring, rather than the classical backside opening observed up to that time. (In 1968, another observation of cis opening of an epoxide was reported.[20])

The transformation of epoxide 15 as noted above, in one step into the hydroxy lactone 14 supports the rationalization of *cis* epoxide opening and the mechanism for the formation of the hydroxy lactone 14 (scheme 4).

Scheme 4



CHAPTER V

CONCLUSIONS

Epoxides 7 and 15 prepared from trimethyl fumaropimarate and trimethyl maleopimarate, respectively, have been prepared and their structures elucidated. These epoxides 7 and 15 have been transformed in an unambiguous manner into compounds 8 and 14, respectively, and these conversions provide further verification for structures 8 and 14. Further, these transformations provided evidence that epoxides 7 and 15 were indeed intermediates in the direct formation of 8 and 14 from trimethyl fumaropimarate (6) and trimethyl maleopimarate (5), respectively, by treatment with trifluoroperacetic acid. Lastly, epoxides 4, 7 and 15 were shown to have the same stereochemistry for their epoxide rings, by chemical interconversion and comparison of their NMR spectra.

CHAPTER VI

RECOMMENDATIONS

The structure analysis by X-ray of any one of the epoxides, 4, 7 or 15, would provide exact information regarding the steric environment around the C-13, C-14 bond. This work has provided chemical and NMR evidence which is suggestive of this steric environment.

APPENDIX

The reported quantities for the ORD measurements[21] were calculated as shown in Equations 1-4, where α_{314} is the rotation at 314 mμ, $[\alpha]_{314}$ is the specific rotation at 314, and $[\Phi]_{314}$ is the molecular rotation at 314 mμ.

$$\alpha_{314} = \text{(instrument scale in degrees) x (chart measurement)} \quad (1)$$

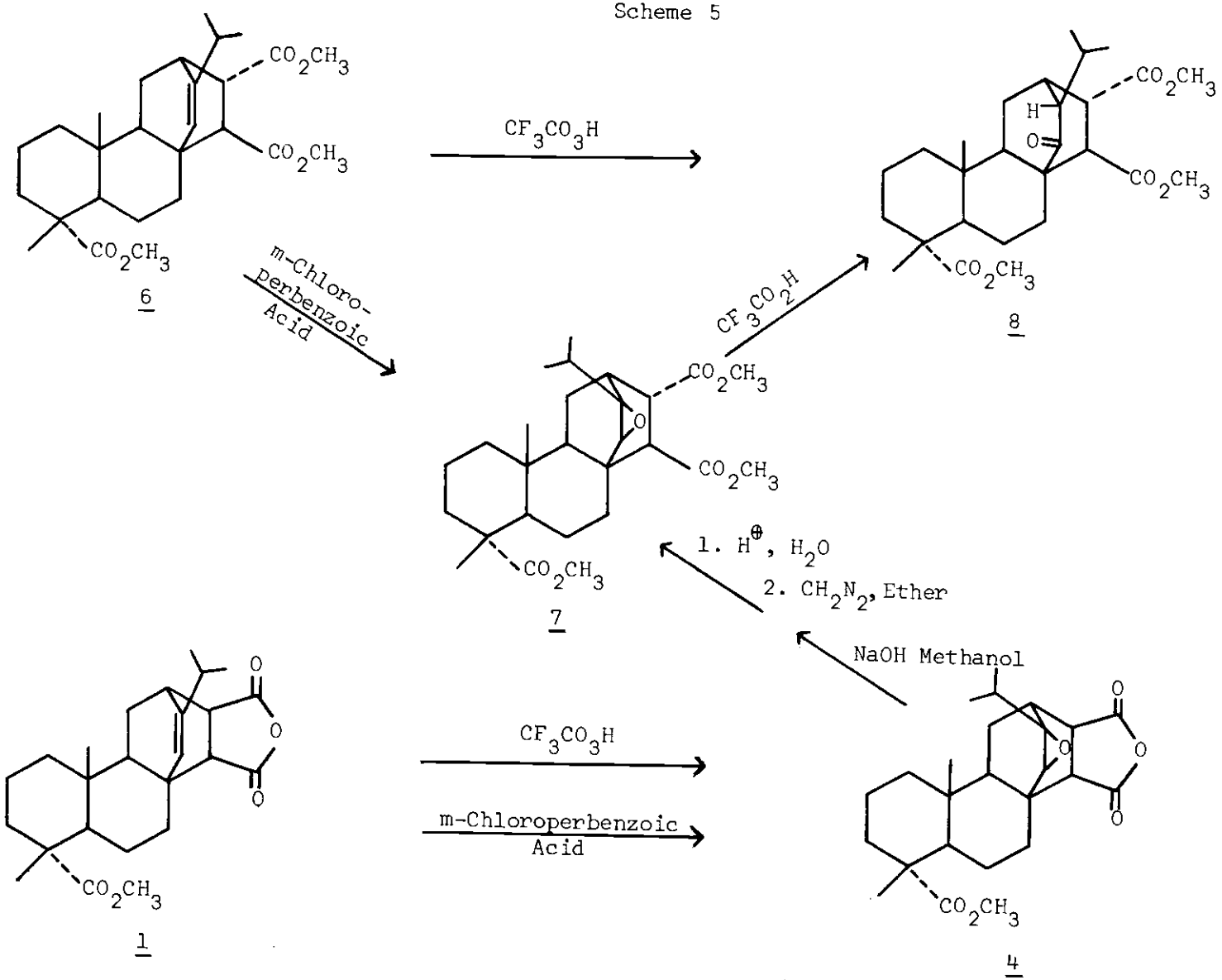
$$[\alpha]_{314} = \frac{100 \times \alpha_{314}}{\text{(Conc. in gm/100 ml)} \times \left\{\begin{array}{c}\text{Path length of transmitted} \\ \text{light in dm}\end{array}\right.} \quad (2)$$

$$[\Phi]_{314} = \frac{[\alpha]_{314} \times \text{(mol. wt.)}}{100} \quad (3)$$

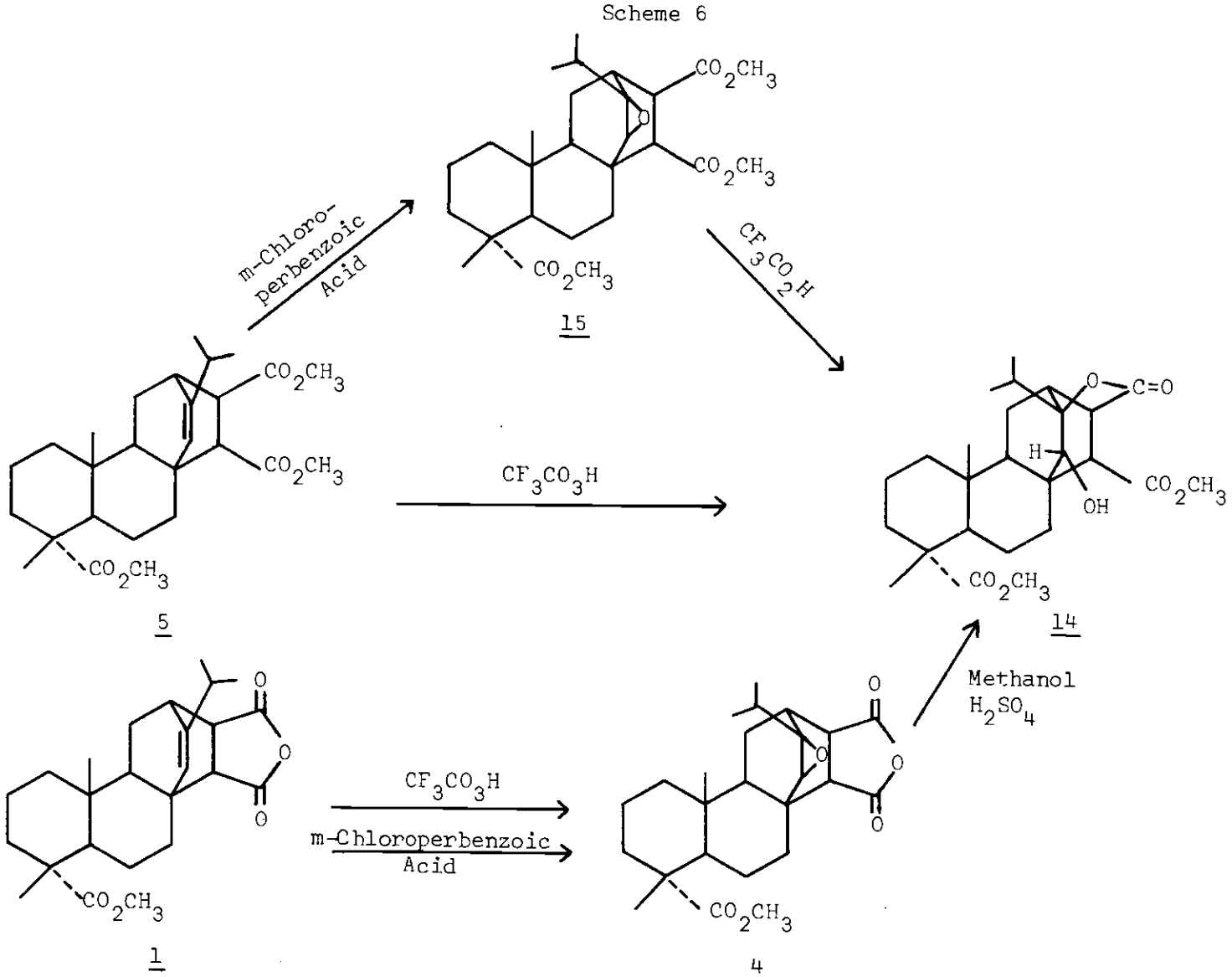
$$a = \frac{[\Phi]_1 - [\Phi]_2}{100} \quad (4)$$

The molecular amplitude, a, is defined as the difference between the molecular rotation at the extremum (peak or trough) of the longer wavelength $[\Phi]_1$, and the molecular rotation at the extremum of shorter wavelength $[\Phi]_2$, divided by 100.

Scheme 5


CO_2CH_3
CO_2CH_3
CO_2CH_3
6
CF_3CO_3H
m-Chloro-
perbenzoic
Acid
CF_3CO_2H
H
O
CO_2CH_3
CO_2CH_3
8
CO_2CH_3
O
CO_2CH_3
CO_2CH_3
7
1. $H^{\oplus}$, H_2O
2. CH_2N_2, Ether
NaOH Methanol
O
O
O
CO_2CH_3
1
CF_3CO_3H
m-Chloroperbenzoic
Acid
O
O
O
O
CO_2CH_3
4

Scheme 6


m-Chloro-perbenzoic Acid
CF3CO2H
CF3CO3H
CF3CO3H
m-Chloroperbenzoic Acid
Methanol
H2SO4
CO2CH3
O
C=O
H
OH

BIBLIOGRAPHY*

1. L. H. Zalkow, M. V. Kulkarni, and N. N. Girotra, *J. Org. Chem. 30,* 1679 (1965).

2. N. Langlois and B. Gastambide, *Bull. Soc. Chim. Fr.,* 2966 (1965).

3. W. Herz and R. C. Blackstone, *J. Org. Chem., 34,* 1257 (1969).

4. H. Wienhaus and W. Sandermann, *Ber., 69,* 2202 (1936).

5. L. Ruzicka, A. G. R. Bacon, R. Lukes, and J. D. Rose, *Helv. Chim. Acta., 21,* 583 (1938).

6. L. Ruzicka, and W. A. LaLande, *Helv. Chim. Acta., 23,* 1357 (1940).

7. The earlier work is described in J. Simonsen, "The Terpenes," Vol. 3, Cambridge University Press, Cambridge, England, 1952, p. 440.

8. L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem., 27,* 3535 (1962).

9. L. H. Zalkow and D. R. Brannon, *J. Org. Chem., 29,* 1296 (1964).

10. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.,* 77, 89 (1955).

11. S. K. Gabriel, Ph.D. Thesis, Georgia Institute of Technology, 1969, p. 37.

12. H. B. Henbest, *Proc. Chem. Soc.,* 159 (1963).

13. D. H. R. Barton, *J. Chem. Soc.,* 1027 (1953).

14. R. E. Parker and N. S. Isaacs, *Chem. Rev.,* 59, 737 (1959).

15. W. L. Meyer and R. W. Hoffman, *Tetrahedron Lett.,* 691 (1962).

16. W. A. Ayer, C. E. MacDonald, and J. B. Stothers, *Can. J. Chem., 41,* 1113 (1963).

---

*Abbreviations used herein follow the form used by *Chemical Abstracts,* Vol. 15, 1, J(1961).

17. W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, 32, 2992 (1967).

18. N. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone, and W. Herz, *J. Org. Chem.*, 29, 1017 (1964).

19. W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, 31, 1800 (1966).

20. N. G. Bisset, *Tetrahedron Lett.*, 3107 (1968).

21. P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, 1965, p. 73.