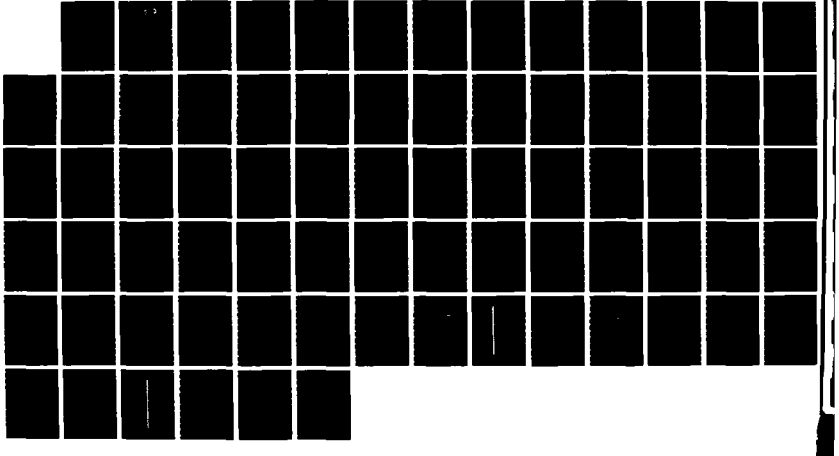
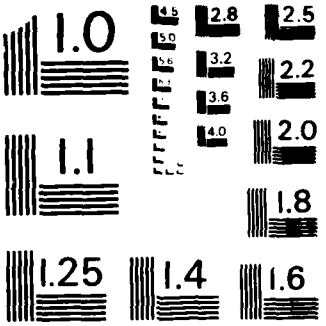
AD-A176 547 AN ENANTIOSELECTIVE SYNTHESIS OF BETA-EUDESMOL(U) AIR FORCE INST OF TECH WRIGHT-PATTERSON AFB OH J A FRYLING 1986 AFIT/CI/NR/87-12T 1/1

UNCLASSIFIED F/G 7/3 NL





AN ENANTIOSELECTIVE SYNTHESIS OF β-EUDESMOL

by

James Allen Fryling

A Thesis Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

1 9 8 6

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER AFIT/CI/NR 87-12T	2. GOVT ACCESSION NO. ADA176547	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) An Enantioselective Synthesis of β-Eudesmol		5. TYPE OF REPORT & PERIOD COVERED THESIS/~~DISSERTATION~~
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) James Allen Fryling		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS AFIT STUDENT AT: Univ of Arizona		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS AFIT/NR WPAFB OH 45433-6583		12. REPORT DATE 1986
		13. NUMBER OF PAGES 66
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

APPROVED FOR PUBLIC RELEASE; DISTRIBUTION UNLIMITED

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

APPROVED FOR PUBLIC RELEASE: IAW AFR 190-1

Lynn Wolaver 14JAN87

LYNN E. WOLAVER
Dean for Research and
Professional Development
AFIT/NR

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

ATTACHED

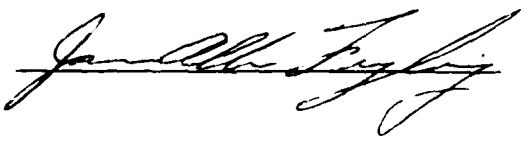
DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

STATEMENT BY AUTHOR

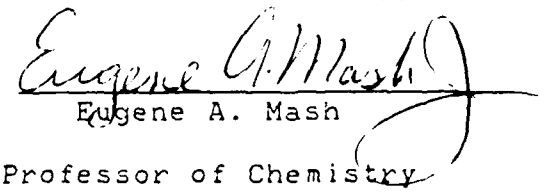
This thesis has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgement the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: 

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:



Eugene A. Mash

Professor of Chemistry

12-12-86

Date

TABLE OF CONTENTS

LIST OF TABLES

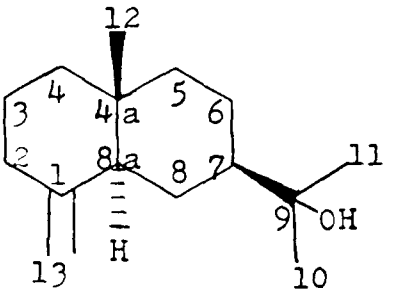
LIST OF ILLUSTRATIONS

ABSTRACT

β-Eudesmol is a bicyclic sesquiterpene which is commonly found in nature. It has been a synthetic target for many researchers, most of whom used approaches based on a Robinson ring annulation reaction to generate the required decalone nucleus with a 4a-methyl substituent. Their syntheses are all of racemic β-eudesmol. We have developed an enantioselective synthesis of (+)-β-eudesmol using diastereoselective cyclopropanation to install the 4a-methyl group in the natural configuration. The method involves cyclopropanation of a chiral ene ketal so that one face of the double bond reacts preferentially. By this route (+)-β-eudesmol was prepared in 7% yield over 12 steps as a 7 to 1 ratio of enantiomers.

INTRODUCTION

(+)-β-Eudesmol is a bicyclic sesquiterpene alcohol having the structure (1) shown. It is a widespread natural product that has been investigated by many organic chemists not only because it is an interesting synthetic target but also because it plays an important role in the stereochemical correlation of terpenes and steroids (Riniker et al., 1954). β-Eudesmol's structure is deceptively simple in appearance; any enantioselective synthesis must take into account the difficulty in establishing the R-configurations of the axial methyl at C-4a and of the isopropyl appendage at C-7. (The naphthalene numbering system will be used throughout this thesis.) A belief that these stereochemical challenges could be conquered using diastereoselective cyclopropanation led to my choice

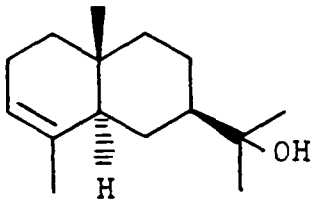


(1)

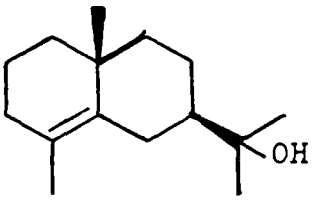
Figure 1-- Structure and Naphthalene Numbering of (+)-β-Eudesmol

of the synthesis of (+)-β-eudesmol as the goal of my masters research.

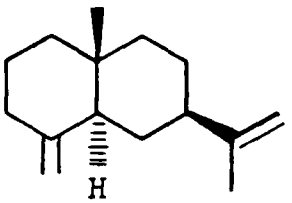
β-Eudesmol is a member of the eudesmane class of sesquiterpenes. The class as a whole is very widespread in nature and has been a most popular target of synthetic organic research. As of 1972, 28 naturally occurring members of this class had been prepared by total syntheses (ApSimon, 1973). In almost every case the 4a-methyldecalin nucleus was constructed by a Robinson ring annulation which, unfortunately, results in racemic products. Members of the eudesmane class which are most similar to β-eudesmol include α-eudesmol (2) and γ-eudesmol (3) which are double bond isomers, and β-selinene (4), costol (5), costal (6), and costic acid (7) which vary on the C-7 appendage as shown. The method of diastereoselective cyclopropanation discussed in this thesis might be used to enantioselectively synthesize these related natural products also.



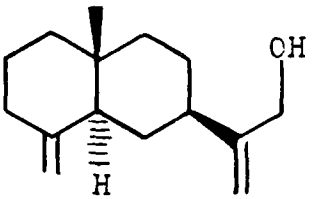
(2)



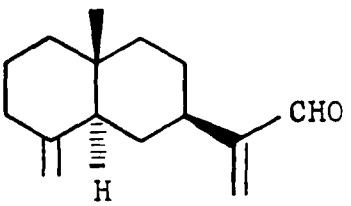
(3)



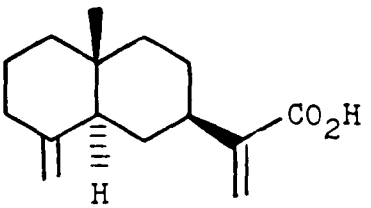
(4)



(5)



(6)



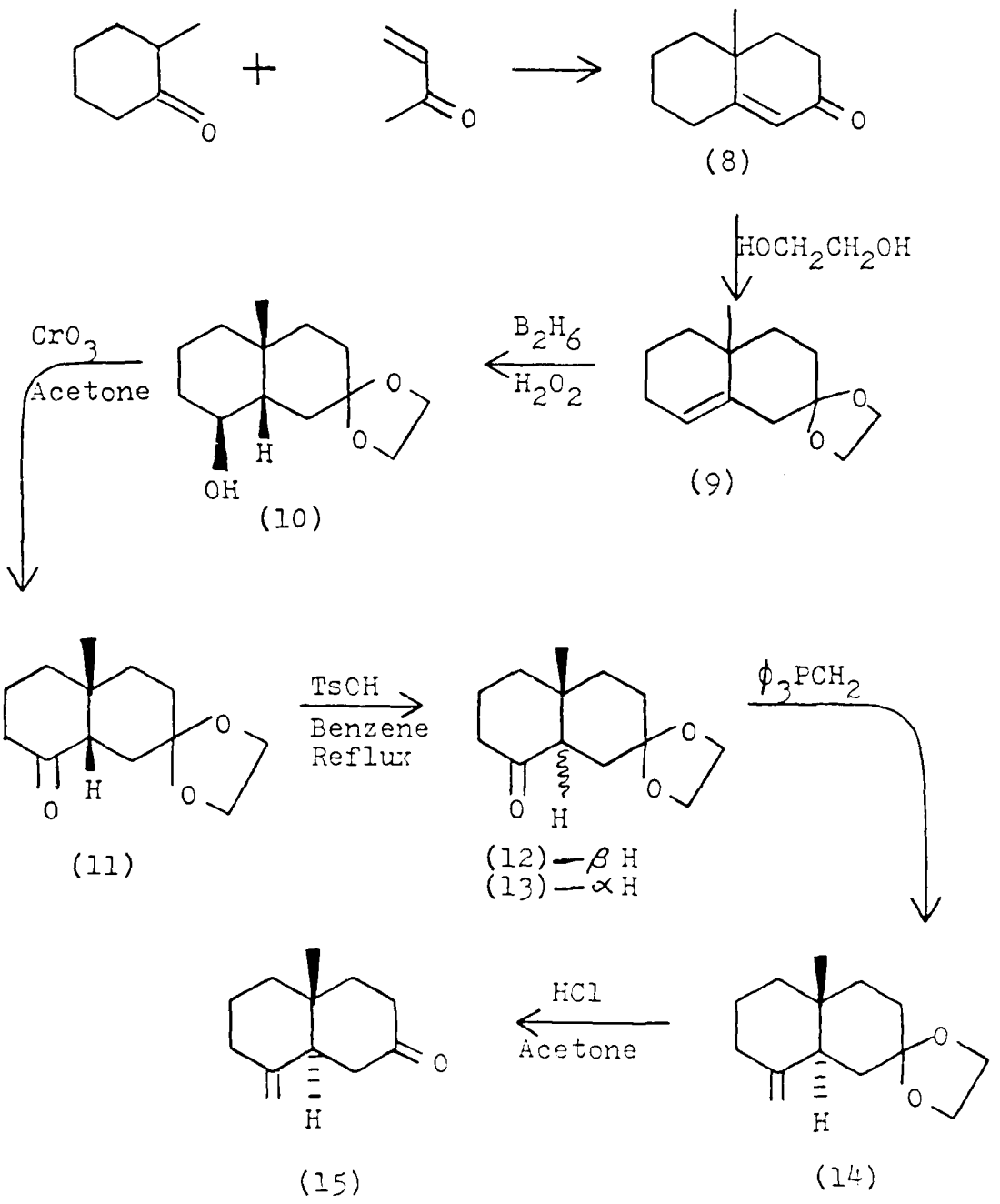
(7)

Figure 2-- Related Eudesmanes

PREVIOUS SYNTHESES OF β-EUDESMOL

Marshall's Approach

Because of the relative simplicity of the molecule and the role it plays in the stereochemical correlation of terpenes and steroids, β-eudesmol has been a popular synthetic target for a number of years, and a large number of total syntheses of β-eudesmol have been reported. One of the first syntheses, and one upon which many subsequent syntheses are based, is a synthesis by Marshall (Marshall, et al., 1966). The key intermediate in his synthesis is decalone (15), which he prepared from octalone (8) by the 6-step sequence outlined in Scheme 1. Octalone (8) was readily obtained by the Robinson ring annulation reaction between 2-methylcyclohexanone and methyl vinyl ketone or its equivalent. The octalone (8) was then ketalized with ethylene glycol using toluene azeotrope (so as to promote double bond migration) to form ketal (9). Hydroboration of the ketal (9) followed by oxidation with alkaline hydrogen peroxide yielded the hydroxy ketal (10) as the major product. The hydroxy ketal could then be oxidized with chromic acid in acetone at 0 °C to give the cis-decalone ketal (11), which was then equilibrated using a catalytic amount of p-toluenesulfonic acid in refluxing



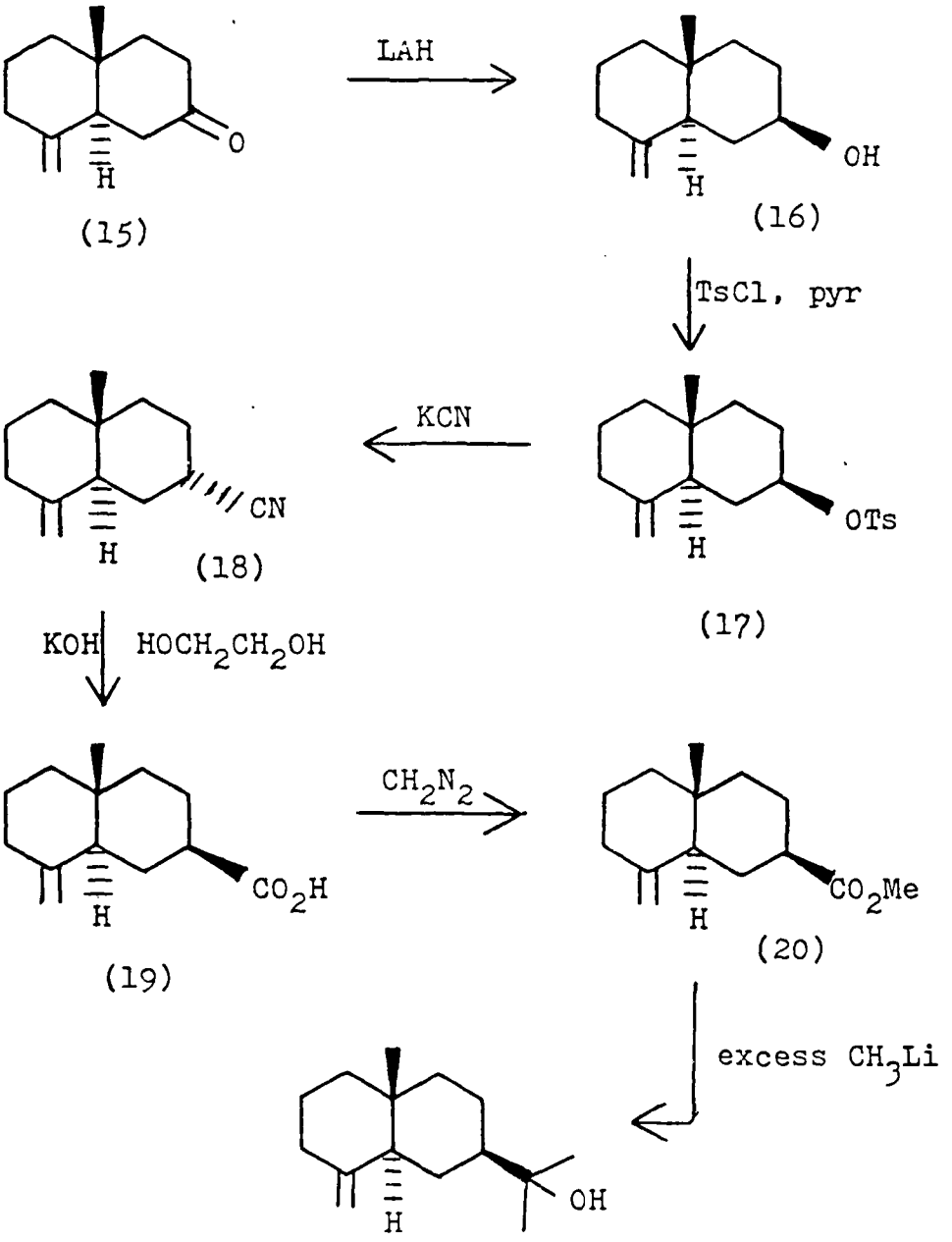
Scheme 1-- Marshall's Approach to Decalone (15)

benzene to afford a 1:4 ratio of the cis- and trans-decalone ketals (12) and (13). Upon treatment with methylene triphenylphosphorane the mixture of 12 and 13 gave the corresponding methylene derivative (14), which when heated with aqueous hydrochloric acid in acetone yielded the decalone (15) as a highly crystalline solid. The yield of decalone (15) was 7.7% from octalone (8).

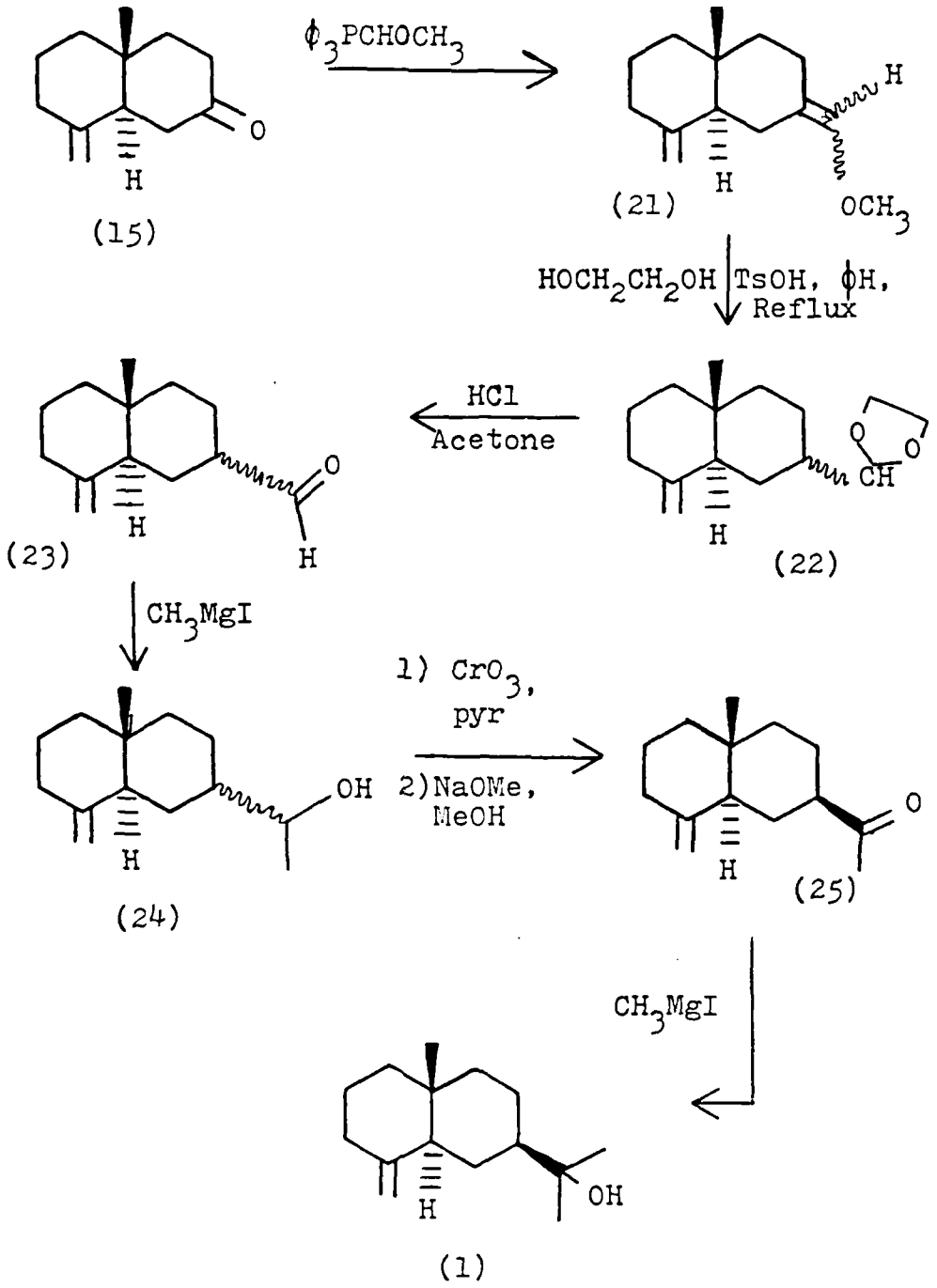
The decalone (15) was converted to β-eudesmol by the process outlined in Scheme 2. Reduction of the ketone with LAH yielded the equatorial alcohol (16) which was tosylated with p-toluenesulfonyl chloride giving (17). Treatment of the tosylate with sodium cyanide in N-methylpyrrolidone afforded the nitrile (18) which yielded the carboxylic acid (19) upon saponification with KOH in ethylene glycol at 160 ^{o}C. Acid 19 was converted to the corresponding ester (20) using ethereal diazomethane. The ester was then converted to β-eudesmol by treatment with excess methyllithium followed by hydrolysis of the lithium salt. The overall yield of racemic β-eudesmol was 1.3% over 12 steps from the octalone 8.

Vig's Approach

Marshall's original approach was modified by Vig (Vig et al., 1968) who provided an alternative method for introducing the isopropanol side chain. Vig's approach, as outlined in Scheme 3, begins with Marshall's decalone



Scheme 2-- Marshall's Approach to β-Eudesmol

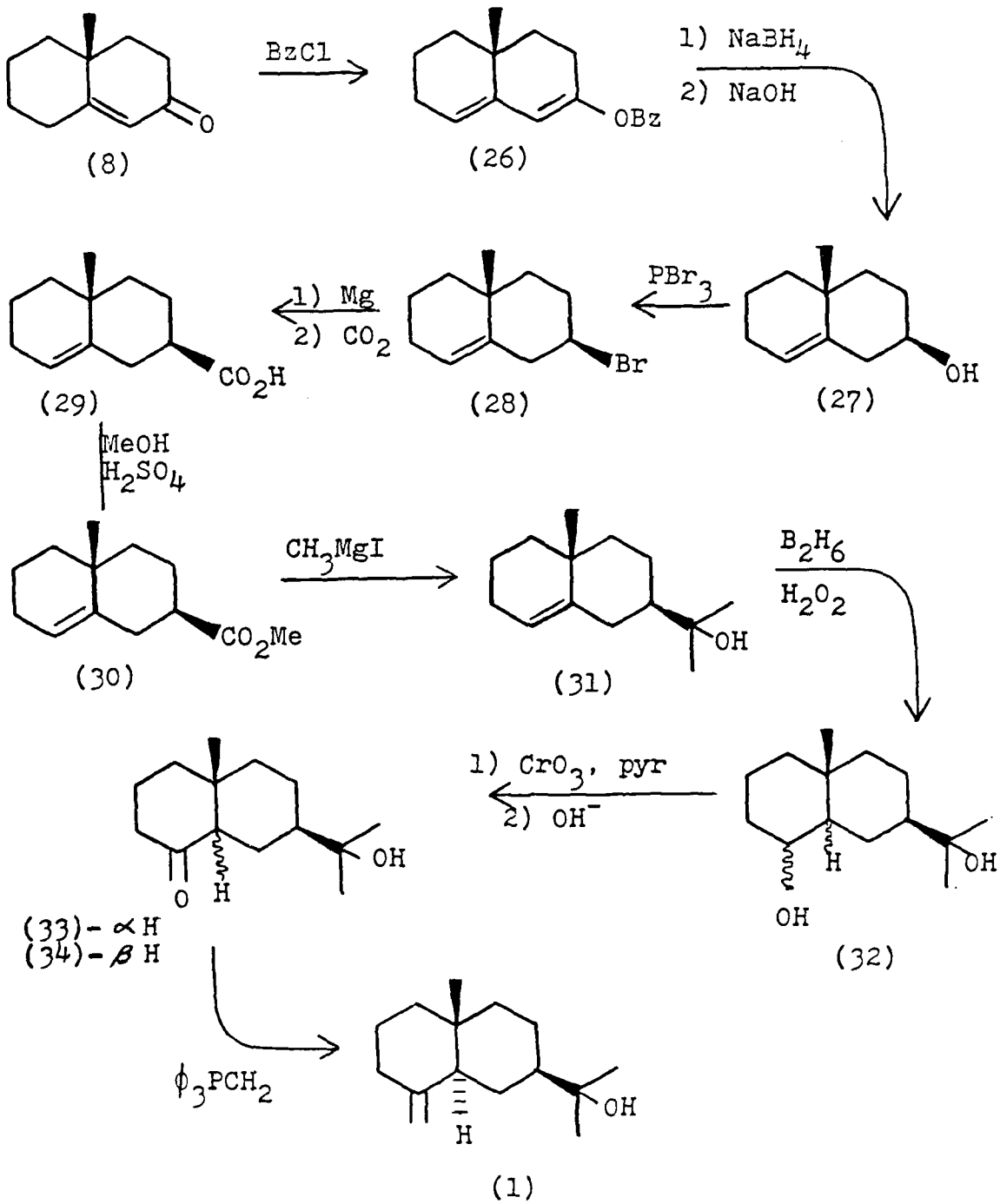


Scheme 3-- Vig's Modification to Marshall's Approach

(15). Treatment of (15) with methoxymethylene triphenylphosphorane gave the enol ether (21). Ether (21) yielded the ethylene ketal (22) upon reflux with ethylene glycol in benzene with tosic acid catalyst. Hydrolysis of the ketal with 10 % HCl in acetone provided the aldehyde (23) which gave the secondary carbinol (24) on treatment with methylmagnesium iodide. Oxidation with Jones reagent followed by epimerization with sodium methoxide furnished the ketone (25) with the correct relative stereochemistry at C-7. Finally, Grignard reaction of the ketone with methylmagnesium iodide yielded racemic β-eudesmol. The overall yield for this reaction sequence to racemic β-eudesmol was 3.4% over 13 steps from the octalone 8.

Heathcock and Kelly's Approach

The next synthesis of β-eudesmol is due to Heathcock and Kelly (Heathcock and Kelly, 1968) and also begins with the octalone (8). Reaction of (8) with benzoyl chloride gave the enol benzoate (26) (Scheme 4). The crude benzoate was reduced with sodium borchydride and the resulting benzyl ester hydrolyzed with NaOH to yield the unsaturated alcohol (27). The alcohol was converted to the Grignard reagent via the bromide (28), which was then quenched with carbon dioxide to produce the unsaturated acid (29). Note that the alcohol, bromine, and carboxylic acid in 27, 28, and 29 all occupy the equatorial

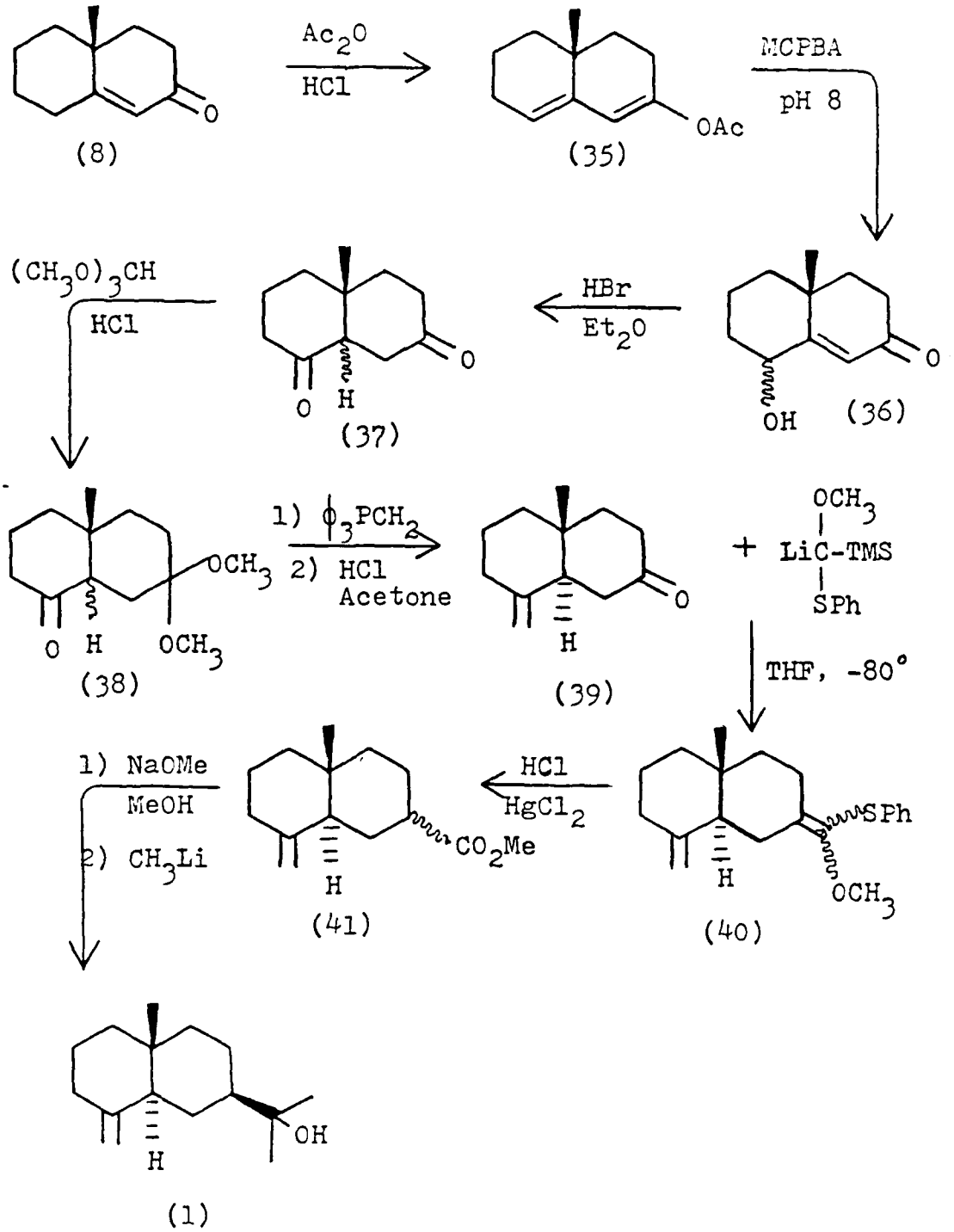


Scheme 4-- Heathcock and Kelly's Approach

position at C-7. Esterification of 29 with ethereal diazomethane or methanolic sulfuric acid produced the ester (30), which gave the alcohol (31) on treatment with methylmagnesium iodide. Hydroboration of 31 (followed by hydrogen peroxide oxidation) gave a mixture of epimeric diols (32) which could be directly oxidized with Jones reagent to give a mixture of ketols (33 and 34). Equilibration with sodium methoxide in methanol gave 34 in good yield. β-eudesmol is then formed on reaction of 34 with methylene triphenylphosphorane in DMSO. The overall yield of racemic β-eudesmol by this route is 7.4% over 12 steps from octalone (8).

Wijnberg, Vader, and deGroot's Approach

The last synthesis of β-eudesmol starting from octalone 8 to be discussed was done by Wijnberg, et al (Winjberg, Vader, and deGroot, 1983). As outlined in Scheme 5, octalone (8) was treated with acetic anhydride with acid catalyst to yield the dienol acetate (35), which was then oxidized with MCPBA to give the enone alcohol (36) as a mixture of epimers. The mixture 36 underwent an acid-catalyzed isomerization to the diketone (37) on treatment with HBr in ether. The ketone at C-7 of diketone 37 was selectively protected by reaction with trimethyl orthoformate in the presence of tosic acid catalyst to give the acetal (38) as an inseparable mixture

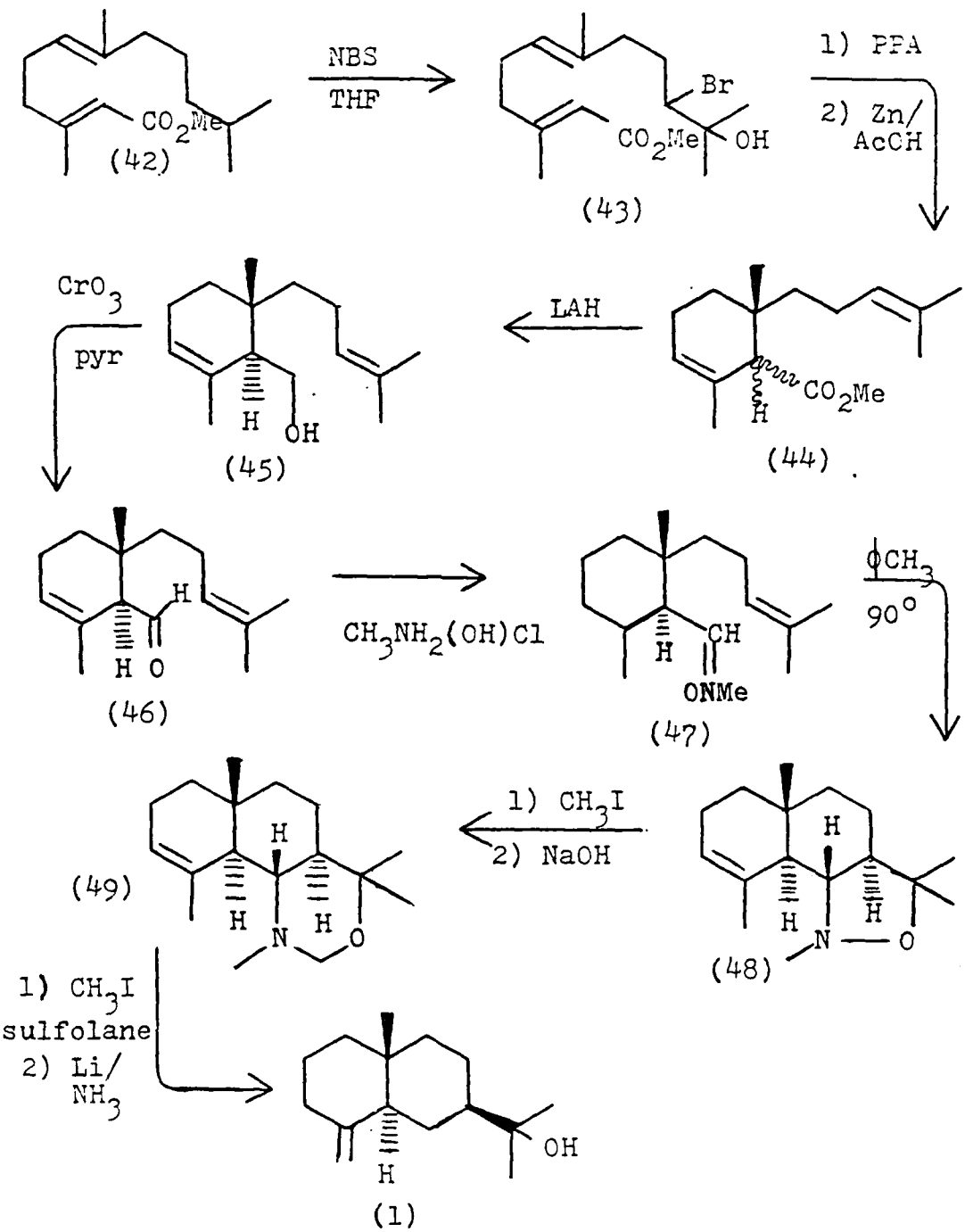


Scheme 5-- Wijnberg, Vader, and deGroot's Approach

of cis- and trans-fused ring isomers. This acetal mixture was then treated with methylene triphenylphosphorane in DMSO followed by HCl in acetone (to hydrolyze the acetal) to give the methylene ketone (39). Reaction of 39 with methoxy(phenylthio)(trimethylsilyl)methyllithium produced the ketene O,S-acetal (40) which was hydrolyzed with HCl in methanol in the presence of mercury (II) chloride to yield the ester (41). Equilibration with sodium methoxide in methanol followed by methylation with methyllithium provided racemic β-eudesmol which was contaminated by a small amount of its C-7 epimer (7:1 ratio of products). The overall yield was 21% of racemic β-eudesmol over 10 steps from octalone (8).

Schwartz and Willbrand's Approach

A biomimetic approach to β-eudesmol was reported by Schwartz and Willbrand (Schwartz and Willbrand, 1984) starting from methyl farnesate (42) as outlined in Scheme 6. Oxidation of (42) with N-bromosuccinimide in aqueous THF produced the 10,11-bromohydrin (43) which was cyclized with phosphoric acid and reduced with zinc and acetic acid to give the methyl monocyclofarnesate (44). LAH reduction of ester (44) gave alcohol (45) as the major product. The alcohol was then oxidized with chromium trioxide in pyridine to yield the aldehyde (46). Treatment of 46 with N-methylhydroxylamine in ethanol afforded the nitrone (47)

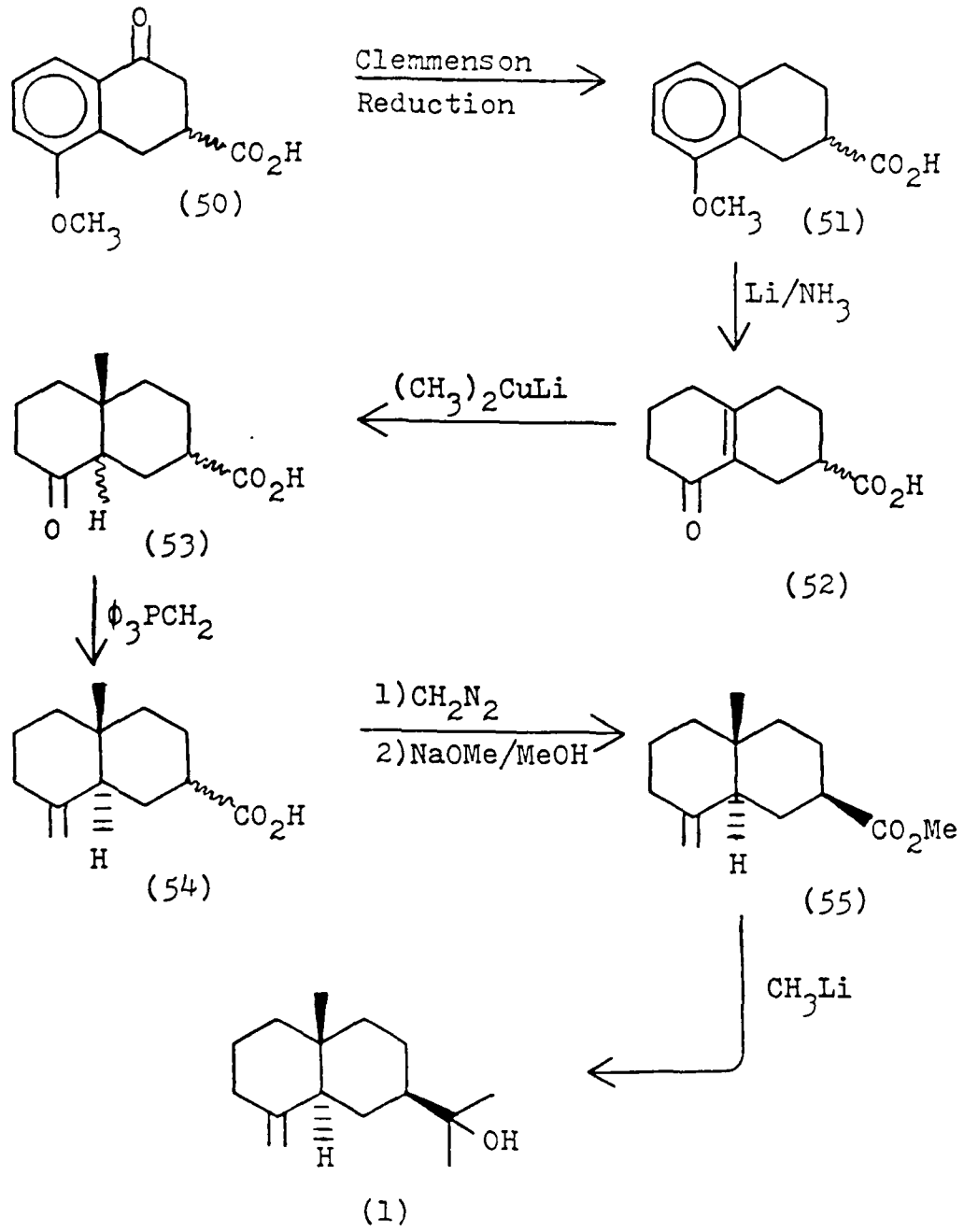


Scheme 6-- Schwartz and Willbrand's Approach

which cyclized upon heating in toluene for several days to form the tricyclic trans-anti-trans isoxazolidine (48) as the major product. 48 reacted smoothly with methyl iodide to form the methiodide which underwent ring expansion to the oxazine (49) on refluxing with aqueous sodium hydroxide in a two-phase medium containing hexane. Alkylation of 49 was accomplished by heating with methyl iodide in technical grade sulfolane (tetrahydrothiophene 1,1-dioxide) with sodium carbonate in a sealed tube at 80-90 °C for several days. Subsequent hydrogenolysis with lithium in liquid ammonia provided β-eudesmol. The overall yield of racemic β-eudesmol for this reaction sequence was 2.9% over 9 steps from methyl farnesate.

Huffman and Mole's Approach

This synthesis (Huffman and Mole, 1972) was an attempt to develop a stereoselective synthesis of -eudesmol which was not based on a Robinson annulation reaction. As shown in Scheme 7 the starting material, 5-methoxytetralone-3-carboxylic acid (50), underwent Clemmensen reduction affording 8-methoxytetralin-2-carboxylic acid (51), which on Birch reduction and acid hydrolysis gave the unsaturated keto acid (52) as the major product. Conjugate addition to 52 using lithium dimethylcuprate produced a mixture of 3 keto acids (53) which, in a subsequent reaction with methylene triphenylphosphorane, produced a

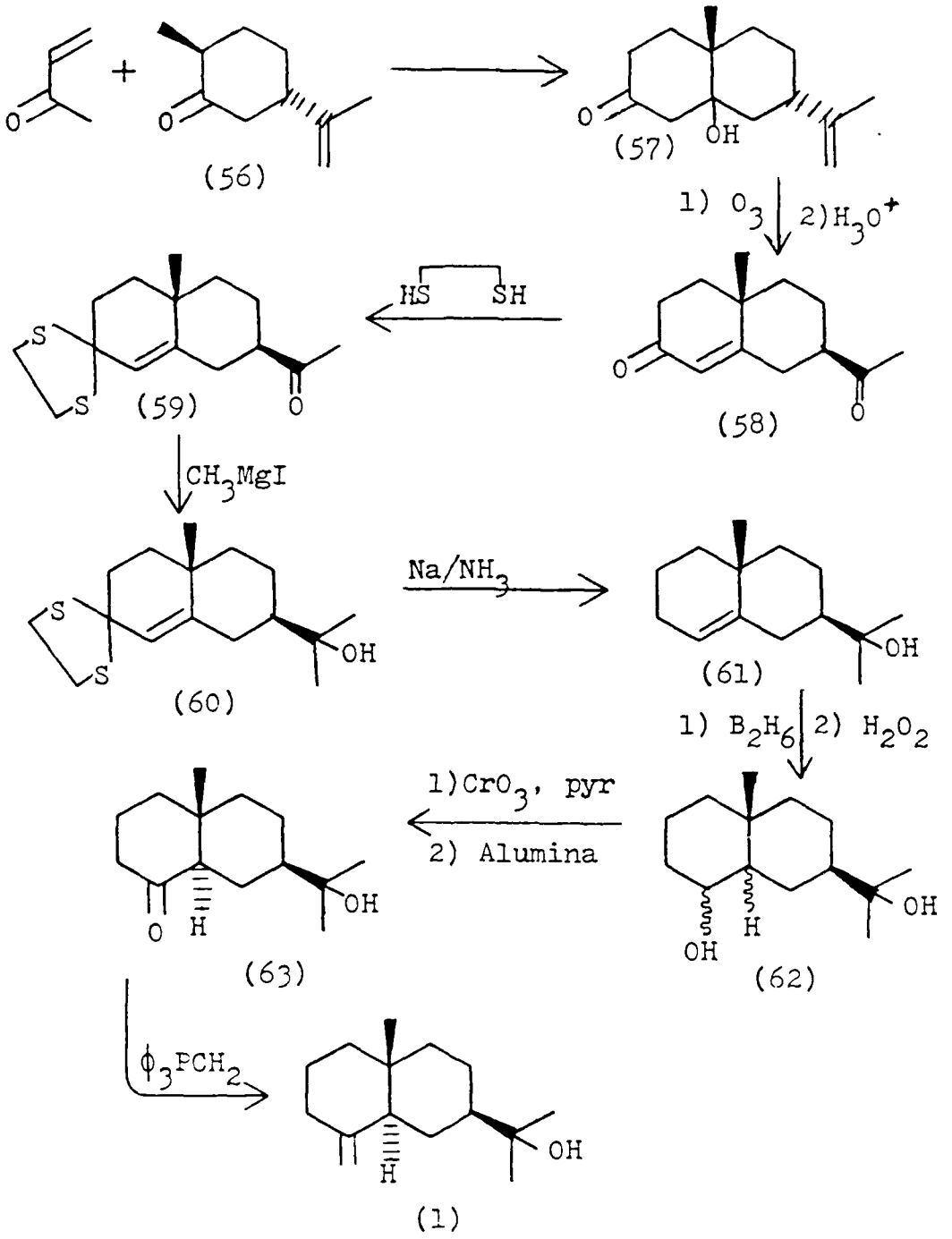


Scheme 7--Huffman and Mole's Approach

mixture of 3 methylene acids (54). After esterification with ethereal diazomethane the mixed esters could be equilibrated by sodium methoxide in methanol to yield the methylene ester (55). Methylation of 55 with methyllithium or methyl Grignard gave β-eudesmol. The yield of racemic -eudesmol is thus 24% over 7 steps from 50. Since 50 was produced by Huffman and Mole from o-anisaldehyde and diethyl succinate in 16% yield over 4 steps the total synthesis of racemic β-eudesmol proceeded in 4% yield over 11 steps.

Humber, Pinder, and William's Approach

The only reported enantioselective approach to (+)-β-eudesmol was by a Robinson-Mannich reaction of (-)-dihydrocarvone (56) as shown in Scheme 8 (Humber, Pinder, and Williams, 1967). Reaction with methyl vinyl ketone afforded the cis-ketol (57) which, upon ozonolysis and acid-catalyzed dehydration with concomitant epimerization, yielded the octalone (58). Condensation of octalone (58) with one equivalent of ethanedithiol gave the thioketal (59) by selective attack on the conjugated carbonyl. Treatment of 59 with methylmagnesium iodide afforded the alcohol (60) which, on desulfurization with sodium and liquid ammonia, produced the unsaturated alcohol (61). Hydroboration with diborane, followed by oxidation with hydrogen peroxide, gave a mixture of diols (62) which gave

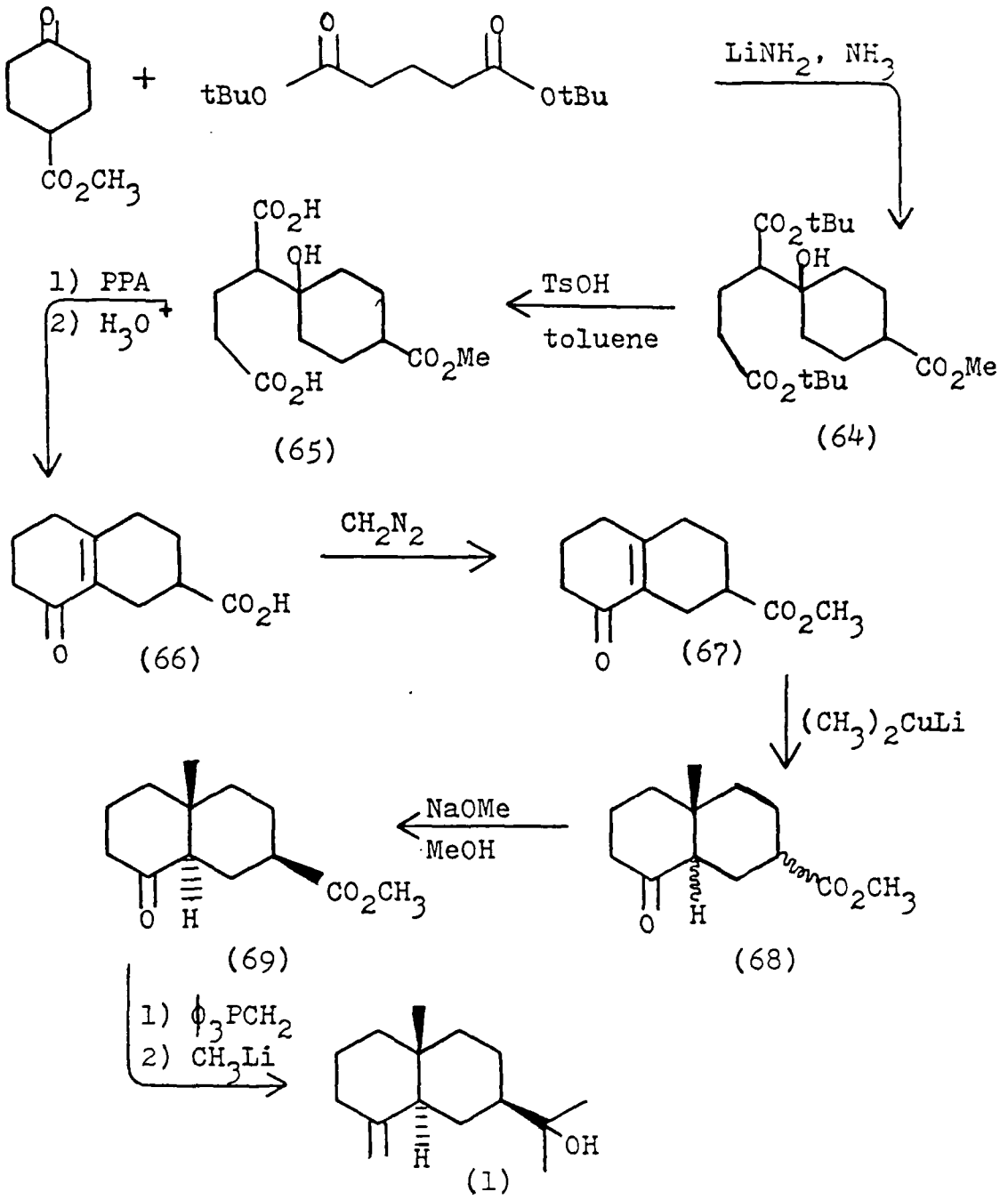


Scheme 8-- Pinder's Approach

the keto alcohol (63) after oxidation with Jones reagent and equilibration on basic alumina. Wittig olefination of ketone (63) with methylene triphenylphosphorane yielded (+)-eudesmol with an optical rotation of +56.6 . The optical rotation of natural (+)-β-eudesmol is +58.0 (Varma and Bhattacharyya, 1964). The overall yield of (+)-eudesmol was 1.5% over 11 steps from (-)-dihydrocarvone (56).

Carlson and Zey's Approach

The final synthesis to be discuss here is outlined in Scheme 9 and is based on the Puterbaugh extension of the Stobbe condensation (Carlson and Zey, 1972). Condensation of di-t-butyl glutarate with 4-carbomethoxycyclohexanone using lithium amide in liquid ammonia resulted in an oily hydroxy triester (64). Treatment of triester (64) with tosic acid in toluene at reflux yielded an unsaturated diacid (65); this diacid was treated with polyphosphoric acid at 55-65 $^{\circ}$C followed by decarboxylation in refluxing aqueous phosphoric acid to give the unsaturated keto acid (66). Esterification with ethereal diazomethane gave an unsaturated keto ester (67). The overall yield to this point in the reaction scheme was 33% over 5 steps. Conjugate addition of lithium dimethylcuprate gave a mixture of 8 diastereomers (4 pairs of enantiomers) of keto ester (68), which on treatment with sodium methoxide in methanol yielded racemic keto ester (69) as the major

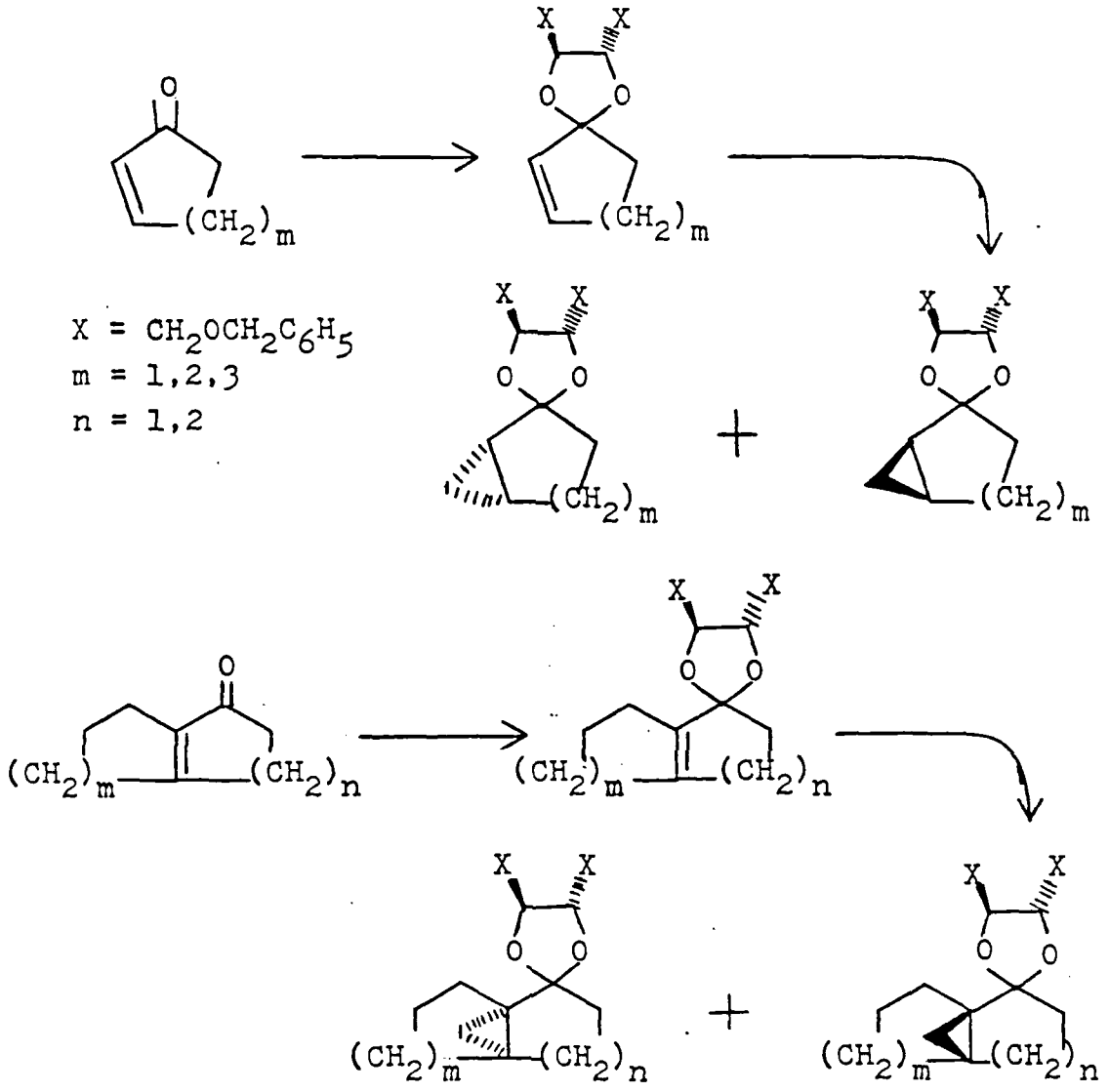


Scheme 9-- Carlson and Zey's Approach

product. Reaction of keto ester (69) with methylene triphenylphosphorane followed by methylation with methyl Grignard or methyllithium would have provided racemic β-eudesmol. The overall yield for this sequence would have been 6% over 9 steps from 4-carbomethoxycyclohexanone.

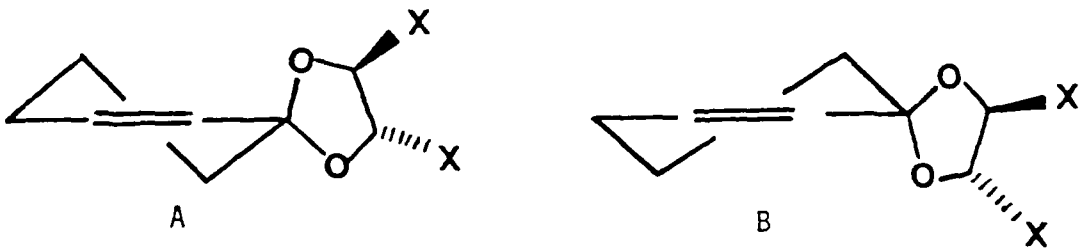
DIASTEREOSELECTIVE CYCLOPROPANATION

Before discussing the approach to (+)-β-eudesmol described herein it is appropriate to briefly review the technique of diastereoselective cyclopropanation. As discussed by Mash and Nelson (Mash and Nelson, 1985) the technique involves ketalization of an enone with a chiral diol to form a homochiral ketal as shown in Scheme 10. Normally, the ketalizations were carried out by refluxing the enone with 1,4-di-O-benzyl-L-threitol in benzene with pyridinium p-toluenesulfonate catalyst using a Dean-Stark trap to azeotropically remove the water formed and drive the reaction to completion. As described in a later paper (Mash and Nelson, 1986), the ketalization reaction required as long as 6 days for bicyclic enones and proceeded in low to moderate yield (21 to 66 percent). The yield for 3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one, which most closely resembles the β-eudesmol ring system, was 58% after 120 hours. Simmons-Smith cyclopropanation of these ene-ketals resulted in stereoselective delivery of the reagent to one face of the double bond. The yield of the cyclopropanation and the diastereoselectivity were found to be functions of the structure of the enone (Mash and Nelson, 1985, and Mash and Nelson, 1986) and of the struc-



Scheme 10-- Diastereoselective Cyclopropanation

ture of the appendages on the ketal (Mash, Nelson, and Heidt, submitted for publication). They determined that apart from appendage oxygen (which could reduce diastereoselectivity) the facial selectivity was a function of the chirality of the dioxolane and was largely independent of the nature of the appendages. Tables 1 (Mash and Nelson, 1986) and 2 (Mash, Nelson, and Heidt, submitted) illustrate the effects of changing the structures on the yields and the diastereoselectivity of the cyclopropanation reactions. They propose that the dioxolane appendages either sterically or conformationally bias the ring system so that conformer A in Figure 1 must be either more reactive or present in higher concentration than conformer B, assuming that reagent delivery is mediated by the pseudoeqatorial dioxolane oxygen atom. Once the cyclopropane has

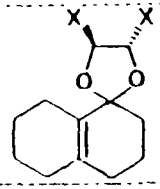
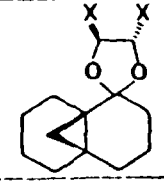
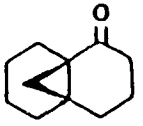
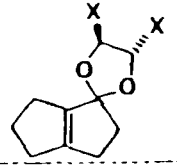
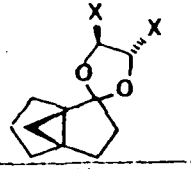
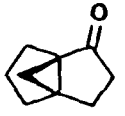
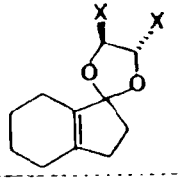
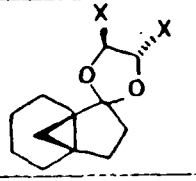
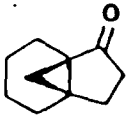
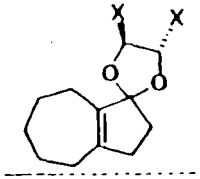
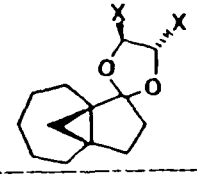
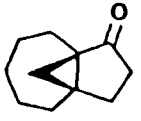


X = $CH_2OCH_2C_6H_5$

Figure 3--Cyclohexanone Ketal Conformers

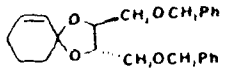
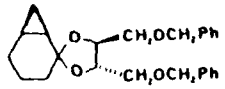
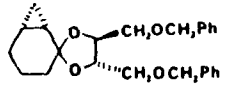
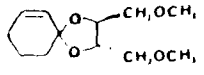
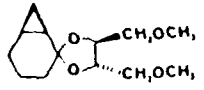
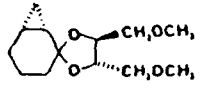
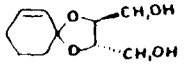
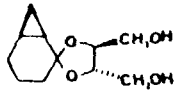
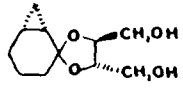
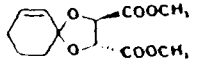
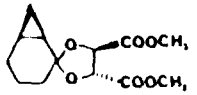
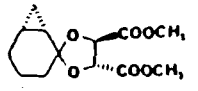
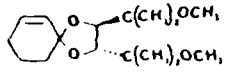
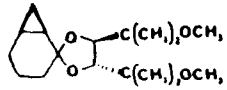
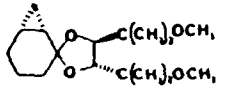
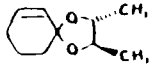
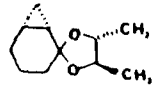
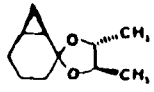
Taken from Mash and Nelson, 1986

TABLE I. Enantioselective Preparation of [m.n.1]Propellanones.

Entry	Ene-Ketal[a,b]	Yield,[c,d] %	$[\alpha]_D^{25}$, deg(c)[e]	Propellanone Ketal	Yield,[c] %	Diastereomer Ratio[f]	Propellanone	Yield,[c] %	$[\alpha]_D^{25}$, deg(c)[e]
1		58 (97)	+25.3 (1.18)		80	7:1		92	+15.0 (2.01)
2		21 (88)	+2.3 (0.65)		78	9:1		77	+15.2 (1.06)[g]
3		66 (100)	+4.3 (3.00)		72	7:1		90	+55.4 (2.80)
4		59 (76)	+2.3 (1.71)		72	9:1		84	-25.9 (2.58)

[a]Prepared by direct ketalization of the corresponding bicyclic enones. [b]X = $CH_2OCH_2C_6H_5$. [c]All yields refer to isolated and purified compounds. Satisfactory IR, NMR, and HRMS data were obtained for all compounds. [d]Yield based on unrecovered diol in parentheses. [e]In $CHCl_3$. [f]Determined by 62.9 MHz ^{13}C NMR spectroscopy. [g]In ether.

Table 2--Appendage Effects On Cyclopropanation From Mash, Nelson, and Heidt, submitted

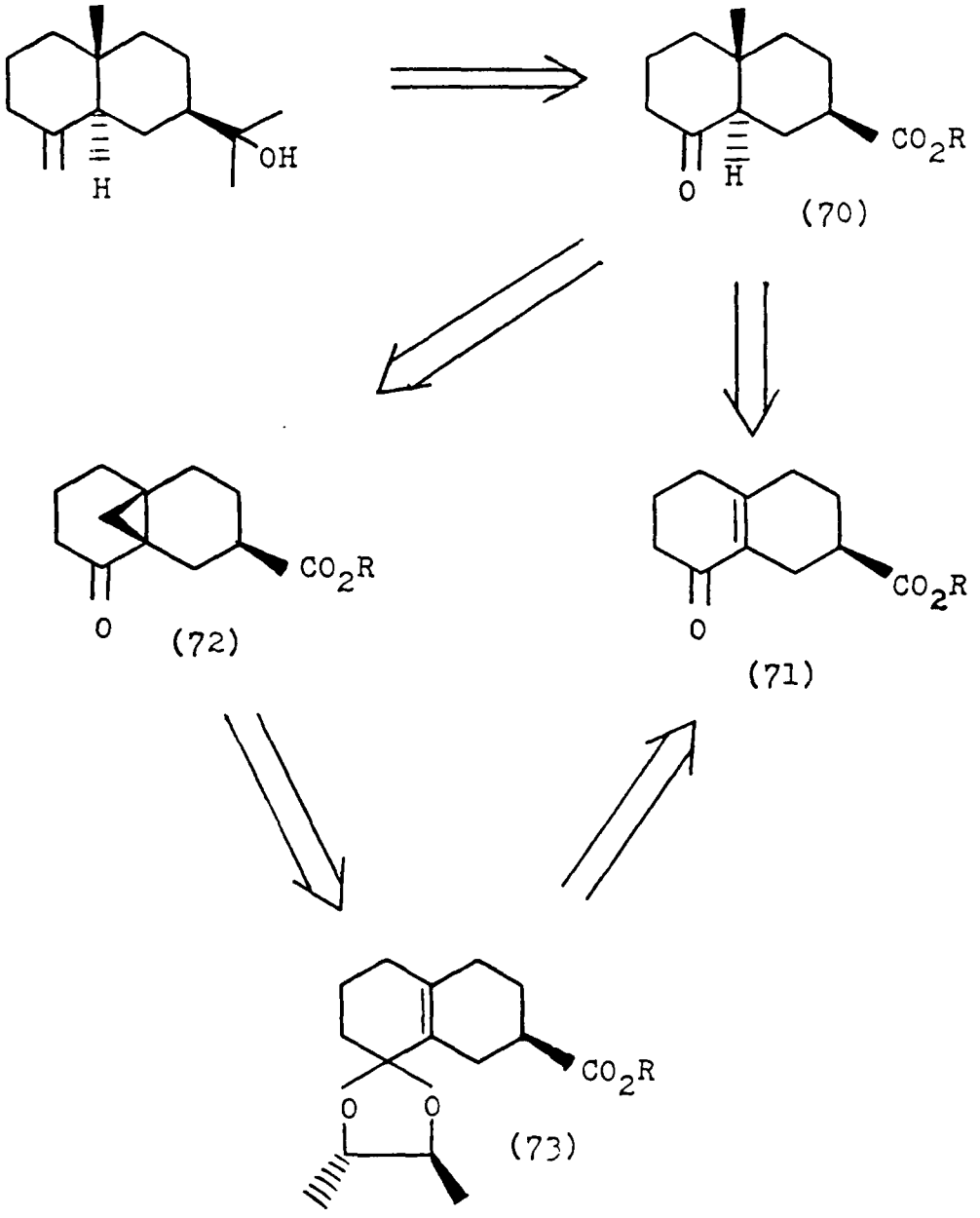
Entry	Alkene	Yield, %	Cyclopropanes		Yield, %	Diastereomer Ratio
1		93			90-98	9:1
2		63			86	5:1
3		70			50(40)	1:2(1:1.5)
4		83			37(42)	1.5:1(3:1)
5		73			91	4:1
6		84			86	9:1

been generated hydrolysis of the ketal yields the cyclopropyl ketones in good yield. This method of diastereoselectively generating the cyclopropane ring was employed to introduce the methyl at C-4a of (+)-β-eudesmol as described below.

AN ENANTIOSELECTIVE SYNTHESIS OF (+)-β-EUDESMOL

A retrosynthetic analysis of (+)-β-eudesmol (Scheme 11) illustrates why the diastereoselective cyclopropanation method was chosen for the synthesis. Retrosynthetically, the exocyclic methylene at C-1 might come from a Wittig reaction on the corresponding ketone and the appendage at C-7 can be derived from methylation of an ester so that ester (70) is a reasonable precursor for synthesis. The required 4a-methyl substituent can be introduced with control of the absolute stereochemistry via the technique of diastereoselective cyclopropanation. Cyclopropyl ketone (72) might be generated diastereoselectively by cyclopropanation of the ene-ketal (73), which could come from enone (71). Since Carlson and Zey have provided an efficient route to this intermediate, our approach to (+)-β-eudesmol commences from the enone (71).

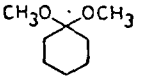
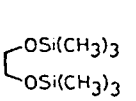
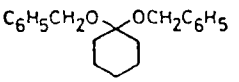
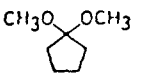
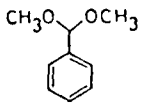
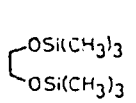
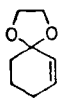
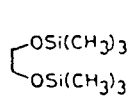
The questions which remain to be answered are threefold. First, which chiral diol should be used to form the ketal to give a good yield of the correct diastereomer? Second, is there any way around the long reaction times and low yields of the ketalization reaction? Finally, what effect, if any, will the appendage at C-7 have on the course of the cyclopropanation? The



Scheme 11-- Retrosynthetic Analysis of β-Eudesmol

answer to the first question can be determined by examining Table 2 in the preceeding section. From the yields and diastereomer ratios shown it is obvious that the di-*O*-benzyl-L-threitol (Entry 1) would give the best overall yield and the best diastereoselectivity. The next best choice would be the (*S*,*S*)-butanediol (enantiomer of the one shown as entry 6). As for the answer to the second question, Tsunoda, Suzuki, and Noyori have developed a process for effecting ketalization in high yield in a short period of time using a trimethylsilyl triflate catalyst (Tsunoda, Suzuki, and Noyori, 1980). As can be seen in Table 3, ketalization of cyclohexenone (Entry 6) can be effected in over 90 % yield within 20 hours at -78 ^{o}C. The ketalization requires the bis-trimethylsilyl ether of the diol, and the reaction is performed in methylene chloride at -78 ^{o}C in most cases. The driving force for the reaction is the formation of the highly stable hexamethylsiloxane so that the equilibrium is shifted to the products. Use of this technique could allow the ketalization in the synthesis of β-eudesmol to be a rapid, high-yield step. The last question is one which cannot be answered without experiment, since none of the ene ketals cyclopropanated by Mash and Nelson bore appendages. One might speculate, however, that the appendage should not have an effect on the course of the reaction since the

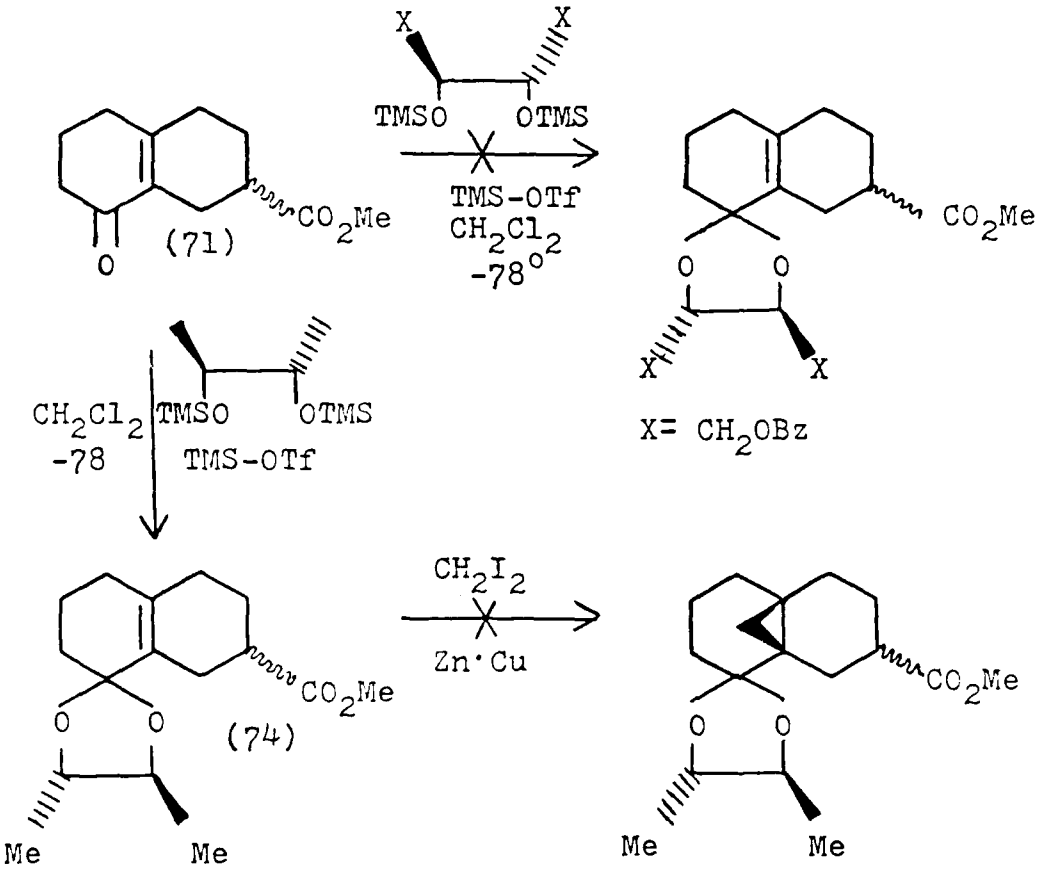
Table 3--Ketalization With TMS-OTf Catalyst[d]

entry	substrate	alkoxysilane	conditions temp, °C	time, h	product (% yield[b])
1		$CH_3OSi(CH_3)_3$	-78	3	 (89)
2			-78	4	 (96)
3		$C_6H_5CH_2OSi(CH_3)_3$	-78	20	 (99)
4		$CH_3OSi(CH_3)_3$	-78	3	 (79, 90[c])
5		$CH_3OSi(CH_3)_3$	-78	3	 (94)
6			-78	20	 (92)
7			-78 then -20	3 0.2	 (99)

[a] Reaction was carried out under argon atmosphere using 1 mol % of TMSOTf in dichloromethane. All new compounds gave consistent NMR and IR characteristics and correct elemental analysis and/or mass spectral data. [b] Isolated yield. [c] Obtained by NMR analysis. [d] Taken from Tsunoda, et al., 1980.

distance between the appendage and the double bond is comparatively large.

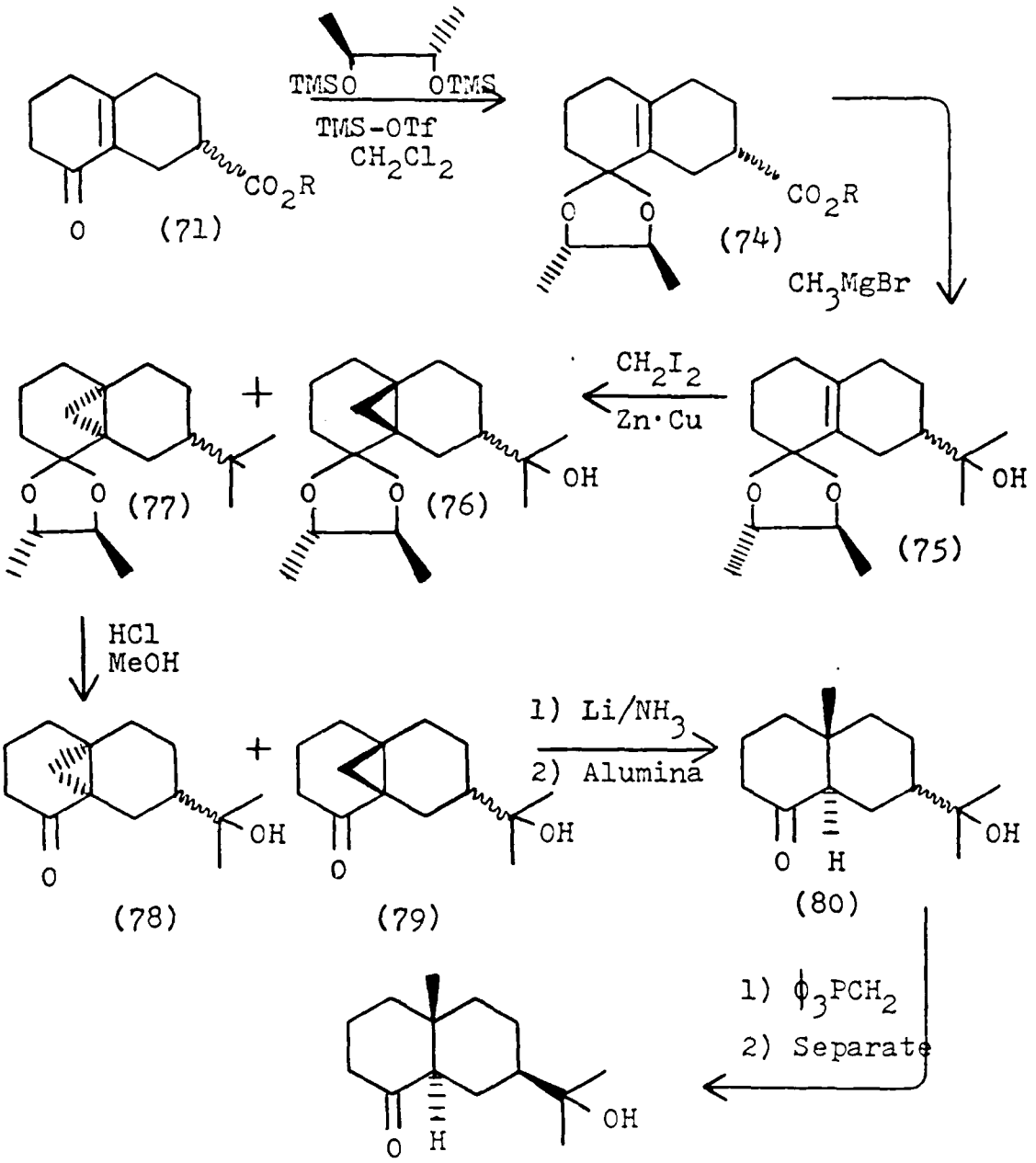
Our synthetic approach to β-eudesmol begins as is shown in Scheme 12. Starting with Carlson and Zey's intermediate enone (71) ketalization with the bis-trimethylsilyl ether of di-O-benzyl-L-threitol might provide the useful ene ketal. Unfortunately, synthesis and purification of the bis-trimethylsilyl ether could not readily be accomplished. Distillation of the bis-trimethylsilyl ether seemed the best way to purify it, but the bis-trimethylsilyl ether of 1,4-di-O-benzyl-L-threitol would have had too high a boiling point to make it easy to distill. For that reason (S,S)-2,3-butanediol was employed for the ketalization, since its bis-trimethylsilyl ether could be distillable from likely impurities. The bis-trimethylsilyl ether of (S,S)-2,3-butanediol was prepared and was distilled at 26 torr at 97-98 ^{o}C. The overall yield for the generation of the bis-ether was 90%. With the ether in hand the ketalization with TMS-OTf catalyst could be attempted. The reaction proceeded very slowly at -78 ^{o}C, and was still slow at -30 ^{o}C, so the reaction was allowed to warm to room temperature overnight. After 21 hours, the reaction was quenched with pyridine, and following workup (see Experimental section), chromatographic purification of the product gave the ketal (74) in 85% yield. Repeated at-



Scheme 12-- Synthesis of Ene Ketal (74)

tempts at cyclopropanation of (74) gave low yields in every case. The presence of the ester group might be the cause of the observed low yields. Note that in Table 2, the dioxolane bearing ester appendages gave very low yields for the cyclopropanation. This problem was circumvented by reordering the steps of the synthesis as outlined in Scheme 13.

The intermediate keto ester (74) was methylated with methyl magnesium bromide, which provided tertiary alcohol (75) in 90% yield. Alcohol (75) was diastereoselectively cyclopropanated using Simmons-Smith reagent (diiodomethane and zinc-copper couple at ether reflux, iodine catalyst), which produced a 7 to 1 mixture of (4a R, 8a R)-propellane (76) and the (4a S, 8a S) diastereomer (77) in 70% yield. These diastereomers were not seperable by chromatography. Hydrolysis of the mixture with 10% HCl in methanol removed the ketals and provided the ketones (78) and (79) in 88% yield. It was at this point that I hoped to separate the diastereomers due to the isopropanol appendage at C-7 but no solvent combination was found which was able to separate them by conventional column chromatography. The cyclopropane rings were then opened using lithium in liquid ammonia, and the resulting crude product was placed on basic alumina in benzene to effect equilibration of the chiral center adjacent to the carbonyl and



Scheme 13-- Synthesis of (+)-β-Eudesmol via Diastereoselective Cyclopropanation

give the ketone (80) as a mixture of diastereomers. Numerous attempts were made at this point to separate the diastereomers using both conventional and flash column chromatography but no separation was obtained. Finally, the ketone was subjected to Wittig olefination to provide β-eudesmol which was purified by preparative GLC to give the (+)-β-eudesmol without the C-7 epimer. The overall yield for the three steps (ring opening, epimerization, and olefination) was approximately 75%. The estimated percentage of (+)-β-eudesmol in the product before separation is 60%, so that the overall yield of (+)-β-eudesmol is estimated to be 21% from the keto ester (71). Since Carlson and Zey prepared 71 in 33% yield over 5 steps the overall synthesis of (+)-β-eudesmol using diastereoselective cyclopropanation proceeds in approximately 7% yield over 12 steps. Since the product is a 7 to 1 mixture of enantiomers the optical activity is 43.39^{o} (natural (+)-β-eudesmol optical rotation is 58.0^{o} (Varma and Battacharyya, 1964)). A comparison of the ^{1}H and ^{13}C NMR spectra of natural β-eudesmol and β-eudesmol prepared by this route provides proof of the synthesis (Figures 4 and 5).

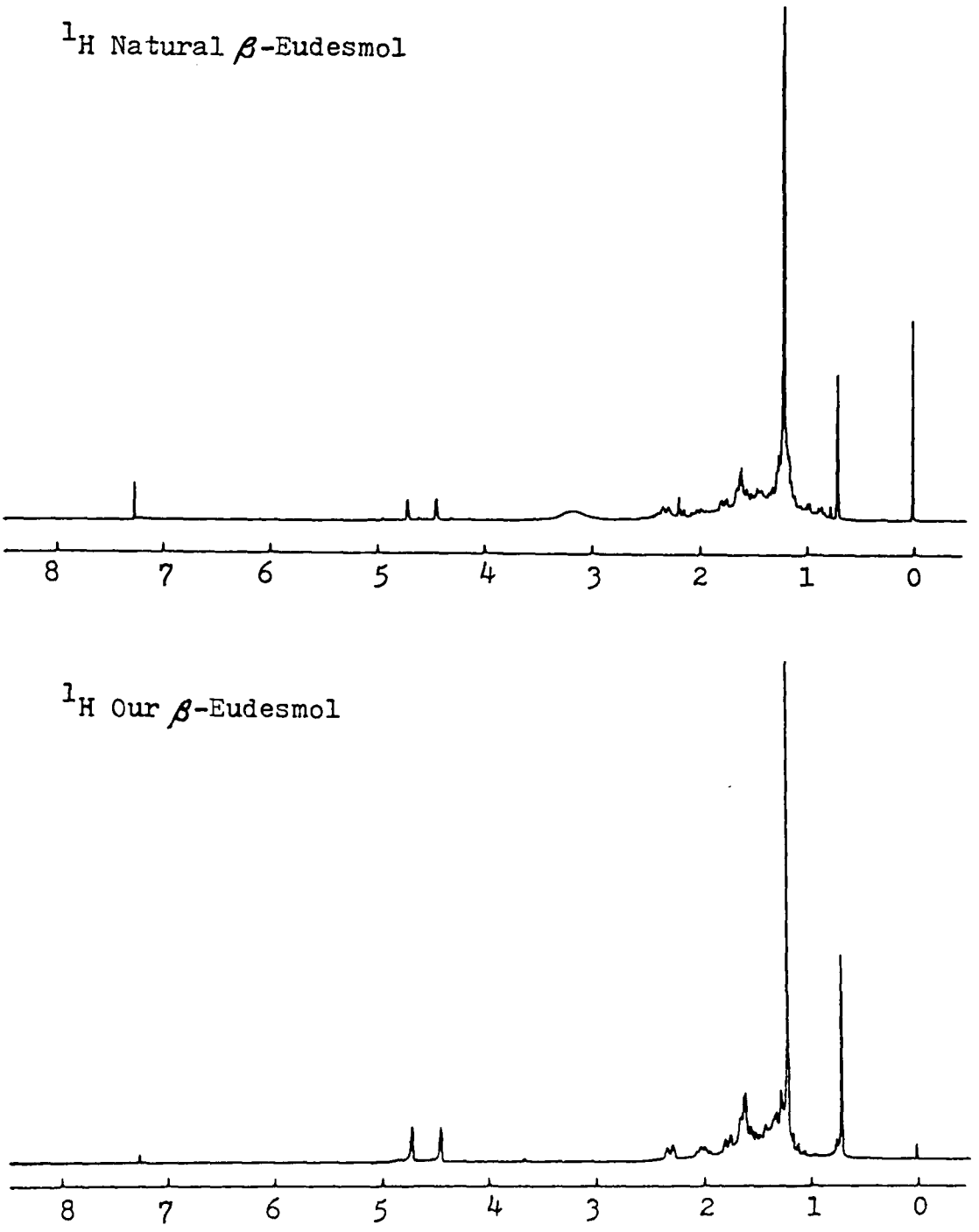


Figure 4-- ^{1}H Comparison of Our β-Eudesmol With Natural β-Eudesmol

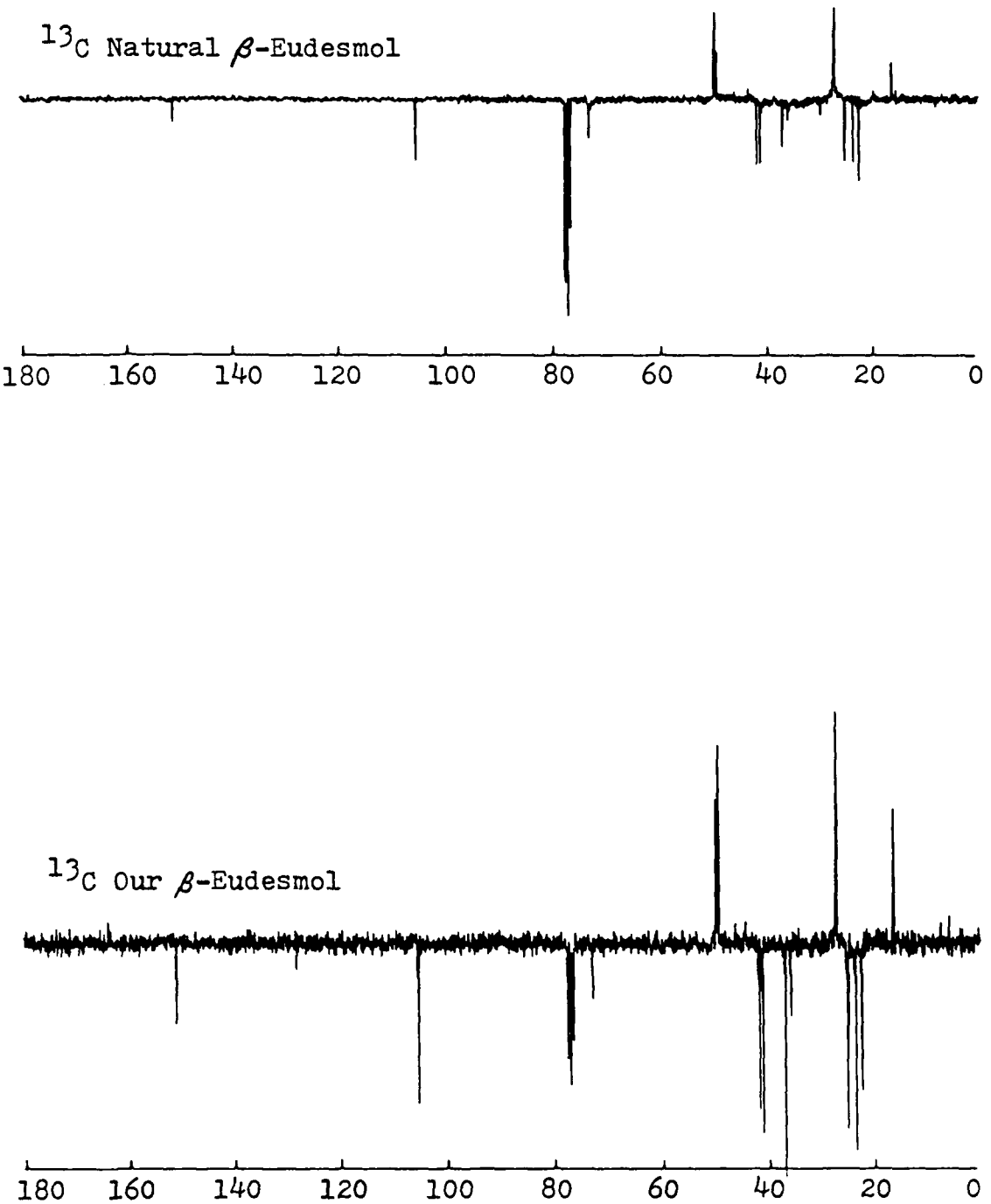


Figure 5-- ^{13}C Comparison of Our β-Eudesmol With Natural β-Eudesmol

CONCLUSIONS

A number of important conclusions can be drawn from this synthesis which may have implications in future work. First, the general method of diastereoselective cyclopropanation is an exceedingly useful tool for conducting enantioselective syntheses. Ketals are often used as protecting groups for ketones and aldehydes and can now be used to control stereochemistry as well. Second, the use of a chiral butanediol to do the ketalization not only gives a good yield but also allows the use of Noyori's ketalization method. Use of this method will circumvent the long reaction times and poor yields of the traditional ketalization reaction. Third, it appears that remote appendages may not affect the diastereoselection of the cyclopropanation reaction, but may interfere with the reaction in a more general way. Esters in general seem to lower yields in the cyclopropanation reaction, while the tertiary alcohol did not appear to play a role in directing the course of the cyclopropanation even though the Simmons-Smith reagent could coordinate to it. Finally, in this synthesis it is readily apparent that the major problem is not the chemical reactions, but the separation of the unwanted diastereomers from the desired product.

Preparative GLC at the end of a synthesis is an effective, but somewhat limiting option and alternatives ought to be investigated. Three other possible methods of separating the (+)-β-eudesmol from its C-7 epimer are: 1) Recrystallization, 2) sublimation, and 3) kinetic separation based on the rates of reketalization of the cyclopropyl ketones with diols. Preliminary indications are that the rate of the reketalization reaction is much faster for one of the diastereomers (78) or (79) than for the other. The possibility of using this rate difference to effect a kinetic separation should be examined.

In summary, (+)-β-eudesmol was synthesized enantioselectively in 7% yield over 12 steps from achiral starting materials. The enantiomeric excess achieved using diastereoselective cyclopropanation was 75% demonstrating the usefulness of the technque for natural product synthesis. A comparison of the methods used to synthesize β-eudesmol is presented in Table 4. From this table it is obvious that considering starting materials, number of steps, overall yields, and optical activity we have demonstrated the best synthesis of β-eudesmol to date.

Table 4-- A Comparison of β-Eudesmol Syntheses

Major Author	Starting Material	Steps	% Yield	Optical Activity
Marshall	Octalone (8)	12	4	Racemic
Vig	Octalone (8)	13	3.4	Racemic
Heathcock	Octalone (8)	12	7.4	Racemic
Winjberg	Octalone (8)	10	21	Racemic
Schwartz	Methyl farnesate (42)	9	2.9	Racemic
Huffman	8-methoxytetralone-3-carboxylic acid (50)	7	24	Racemic
Humber	(-)-dihydrocarvone (56)	11	1.5	$+56.6^{o}$
Carlson	4-carbomethoxycyclohexanone	9	6	Racemic
Our Approach	4-carbomethoxycyclohexanone	12	7	$+43^{o}$

EXPERIMENTAL

Benzene was distilled from calcium hydride and diethyl ether was distilled from phosphorus pentoxide or sodium benzophenone ketyl under an inert atmosphere. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 3 Å molecular sieves. Liquid ammonia was distilled from lithium immediately before use. 7-Carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (71) was prepared by the method of Carlson and Zey (Carlson and Zey, 1972). Zinc-copper couple was prepared according to the method of Shank and Shechter (Shank and Shechter, 1959) immediately before use. Proton magnetic resonance spectra were recorded at 250 MHz on a Bruker WM-250 NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) from tetramethylsilane. Carbon-13 magnetic resonance spectra were recorded at 62.9 MHz on a Bruker WM-250 spectrometer; chemical shifts are reported as δ values in parts per million (ppm) from the center line of the chloroform-d triplet (77.0 ppm). Mass spectral determinations were performed at the Midwest Center For Mass Spectrometry at the University of Nebraska. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer.

Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Preparative gas chromatography was performed on a Shimadru GC-8A gas chromatograph with a 2.5 mm i.d. X 3 m. glass column packed with 15% Carbowax 20M on Chromasorb W-HP (60-80 mesh). Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70-230 mesh ASTM). Merck silica gel 60 (70-230 mesh ASTM) was used for column chromatography. Melting points were determined on a Thomas Hoover Unimelt Capillary Melting Point Apparatus and are uncorrected.

(S,S)-2,3-Butanediol-bis-(trimethylsilyl ether). (S,S)-2,3-Butanediol (3 g, 33.3 mmol) and triethylamine (15 ml, 10.9 g, 107.6 mmol) were dissolved in 50 ml of dry methylene chloride and cooled in an ice bath. Trimethylsilyl chloride (8.56 g, 78.8 mmol) was slowly added via syringe to the stirred solution, and triethylammonium chloride precipitated. The reaction mixture was stirred under argon and reaction progress was monitored by TLC (50% ethyl acetate/ hexanes). After 30 minutes the reaction mixture was filtered to remove the salts, and methylene chloride and excess triethylamine were removed on a rotovap. Vacuum distillation gave product, bp_{26} 97-98 ^{o}C, as a colorless oil. Yield: 5.62 g (23.98 mmol, 72%). ^{1}H NMR ($CDCl_3$) 0.11 (18, s), 1.03-1.09 (6, d, J=6 Hz), and

3.59-3.65 (2, m).

7-Carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (S,S)-2,3-Butanediol Ketal (74). (S,S)-2,3-Butanediol-bis-(trimethylsilyl ether) (5.455g, 23.26 mmol) was dissolved in 5 ml of dry methylene chloride and was stirred under argon and cooled to -78 ^{o}C in a dry ice/isopropanol bath. Trimethylsilyl triflate (37.6 mg, 0.17 mmol) was added via syringe, followed by 4.6638 g (22.39 mmol) of 7-carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (71). Reaction progress was monitored by TLC (50% ethyl acetate/hexanes). After 2 hours the reaction appeared to have made very little progress, so additional TMS-OTf (37.6 mg, 0.17 mmol) was added. At 6 hours there still was very little progress in the reaction, so 115 mg (0.52 mmol) of TMS-OTF was added and the reaction was allowed to warm to room temperature overnight. After 21 hours the reaction was quenched with 0.5 ml (0.489 g, 6.2 mmol) of pyridine, the solvent was removed, and the reaction mixture was chromatographed on 350 g of silica gel eluted with 20% ethyl acetate/hexanes. The product, which eluted after 1 liter in a total volume of 1.2 liters, was obtained as a viscous yellow oil homogeneous by TLC (R_f .62). Yield: 5.36 g (19.1 mmol, 85.4%). IR (neat) cm^{-1} 2932, 2868, 1732, 1437, 1377, 1337, 1312, 1275, 1253, 1227, 1189, 1140, and 1095; ^{1}H NMR ($CDCl_3$) 1.20-1.35 (6,

m), 1.5-2.6 (13, m), 3.6-3.8 (5, m); ^{13}C NMR ($CDCl_3$) 15.84, 15.98, 17.51, 17.66, 20.07, 20.26, 24.45, 24.52, 24.95, 25.13, 29.94, 30.04, 30.15, 35.27, 35.68, 39.63, 39.74, 51.48, 77.53, 77.59, 79.68, 79.79, 106.58, 106.67, 127.87, 127.96, 135.93, 136.01, 176.35, 176.39; mass spectrum (70 eV) m/z (rel intensity) 281 (10), 280 (60), 253 (16), 252 (100), 208 (41), 193 (17), 149 (39), 148 (19), 147 (13), 133 (11), 131 (11), 127 (20), 120 (24), 93 (34), 92 (17), 91 (41), 79 (14), 77 (15), 55 (27); exact mass calcd for C16 H24 O4 280.1674, obsd 280.1680.

7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (S,S)-2,3-Butanediol Ketal (75). Methyl magnesium bromide (2M, 16 ml, 5.345 g, 44.8 mmol) was dissolved in 80 ml of THF under argon and cooled in an ice bath. Ketal 74 (5.01 g, 17.87 mmol) was dissolved in THF and added slowly via syringe to the well-stirred reaction mixure. The reaction mixture was stirred under argon for 3.5 hours, with TLC monitoring (50% ethyl acetate/hexanes) of reaction progress. Additional methyl magnesium bromide (6 ml, 2.00 g, 16.8 mmol and 3 ml, 1.00 g, 8.4 mmol) was added to the reaction mixture at 45 minutes and 160 minutes, respectively. After 3.5 hours the reaction was poured into 75 g of crushed ice in a separatory funnel. 20 ml of saturated sodium bicarbonate and 100 ml of diethyl ether were added and the layers were separated.

The water layer was extracted with 3 additional 100 ml portions of ether, the combined ether layers were dried with 20 g of magnesium sulfate, filtered, concentrated on the rotovap, and the residue chromatographed on 300 g of silica gel eluted with 50% ethyl acetate/hexanes. After an initial 450 ml fraction, 200 ml fractions were collected. Fractions 3-8 were combined to yield 4.52 g (16.12 mmol, 90.2%) of the tertiary alcohol product as a white crystalline solid, m.p. 82.5-85 ^{o}C. IR ($CHCl_3$) cm^{-1} 3605, 3461, 3009, 2975, 2931, 2872, 1454, 1439, 1376, 1212, 1091, 939, 773, 668; ^{1}H NMR ($CDCl_3$) 1.15-1.36 (14, m), 1.45-2.3 (12,m), 3.6-3.8 (2, m); ^{13}C NMR ($CDCl_3$) 16.04, 16.16, 17.65, 17.77, 20.24, 20.45, 23.36, 23.45, 26.18, 26.24, 27.37, 29.98, 30.27, 31.48, 31.74, 35.44, 35.89, 45.18, 45.42, 72.76, 77.59, 79.89, 79.97, 107.05, 107.18, 128.66, 128.81, 136.73, 136.79; mass spectrum (70 eV) m/z (rel intensity) 281 (13), 280 (71), 253 (16), 252 (100), 234 (20), 221 (26), 219 (36), 193 (38), 190 (16), 177 (27), 150 (19), 149 (45), 147 (36), 131 (16), 127 (34), 93 (18), 91 (39), 79 (23), 77 (17), 59 (40), 55 (33); exact mass calcd for C17 H28 O3 280.2039, obsd 280.2043.

(4a R, 8a R)-7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydro-4a,8a-methanonaphthalen-1(2H)-one (S,S)-2,3-Butanediol Ketal (76). Zinc-copper couple (8.26 g, 126

mmol), potassium carbonate (3.76 g, 27.2 mmol) and diiodomethane (5 ml, 16.60 g, 62 mmol) were placed in 80 ml of dry ether under argon and the mixture was stirred at reflux for 30 minutes. The ene-ketal (75) (1.96 g, 9.40 mmol) was added as a solution in THF via syringe, and reaction progress was monitored by TLC (50% ethyl acetate/hexanes). After 20 hours the reaction mixture was cooled in an ice bath and quenched with 15 ml of saturated potassium carbonate. The mixture was stirred at room temperature for 45 minutes, filtered, and the couple rinsed well with ether. The filtrate was washed with 30 ml each of saturated ammonium chloride, saturated sodium bicarbonate, and brine, and then dried with 10 g magnesium sulfate, filtered, and concentrated on the rotovap. The crude product was purified by column chromatography on 395 g of silica gel using 20% ethyl acetate/hexanes as the solvent. After an initial 1 liter fraction, 100 ml fractions were collected. Product (76) eluted in fractions 24-31 to yield 1.94 g (6.59 mmol, 70.1%) of a pale yellow oil. IR (neat) cm^{-1} 3455, 3059, 2934, 1651, 1454, 1375, 1284, 1190, 1096, 1032, 967, 936, 916, 842, 755, 666; ^{1}H NMR ($CDCl_3$) .049-.059 (1, t, J=5 Hz), 0.65-0.75 (1, t, J=5 Hz), 1.0-2.5 (26, m), 3.6-3.8 (2, m); ^{13}C NMR ($CDCl_3$) 15.96, 16.29, 17.77, 18.17, 19.25, 19.77, 20.86, 21.31, 21.46, 23.15, 24.03, 24.40, 24.61, 25.56, 27.19, 27.25,

27.50, 27.66, 28.24, 30.24, 30.86, 31.19, 32.13, 32.98, 41.51, 45.94, 72.53, 72.83, 77.87, 79.30, 79.41, 111.37, 111.79; mass spectrum (70 eV), m/z (rel intensity) 294 (6), 235 (5), 207 (4), 145 (3), 141 (3), 128 (9), 127 (100), 114 (3), 105 (4), 93 (4), 91 (7), 79 (5), 77 (3), 73 (3), 67 (3), 59 (14), 57 (3), 55 (23); exact mass calcd for C18 H30 O3 294.2196, obsd 294.2192.

(4a R, 8a R)-7-(1-methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydro-4a,8a-methanonaphthalen-1(2H)-one (78). Ketal (77) (1.94 g, 6.59 mmol) was dissolved in 35 ml of methanol and was placed in a water bath. 2 ml of 10% HCl was added to the stirred solution via syringe and the progress of the hydrolysis was followed by TLC analysis (50% ethyl acetate/hexanes). After 35 minutes, the reaction was quenched with 50 ml of saturated sodium bicarbonate and extracted 7 times with 50 ml portions of diethyl ether. The combined ether extracts were dried with 20 g of magnesium sulfate, filtered, concentrated, and chromatographed on 325 g of silica gel using 50% ethyl acetate/hexanes as solvent. After an initial 200 ml fraction, 100 ml fractions were collected. Fractions 18-34 yielded 1.2924 g (5.81 mmol, 88.2%) of product as a pale yellow oil. IR (neat) cm^{-1} 3455, 3070, 2934, 1736, 1673, 1464, 1450, 1374, 1324, 1275, 1238, 1212, 1148, 1048, 1015, 988, 975, 937, 898, 875, 857; ^1H NMR ($CDCl_3$) 0.8-1.08 (2, d, J=

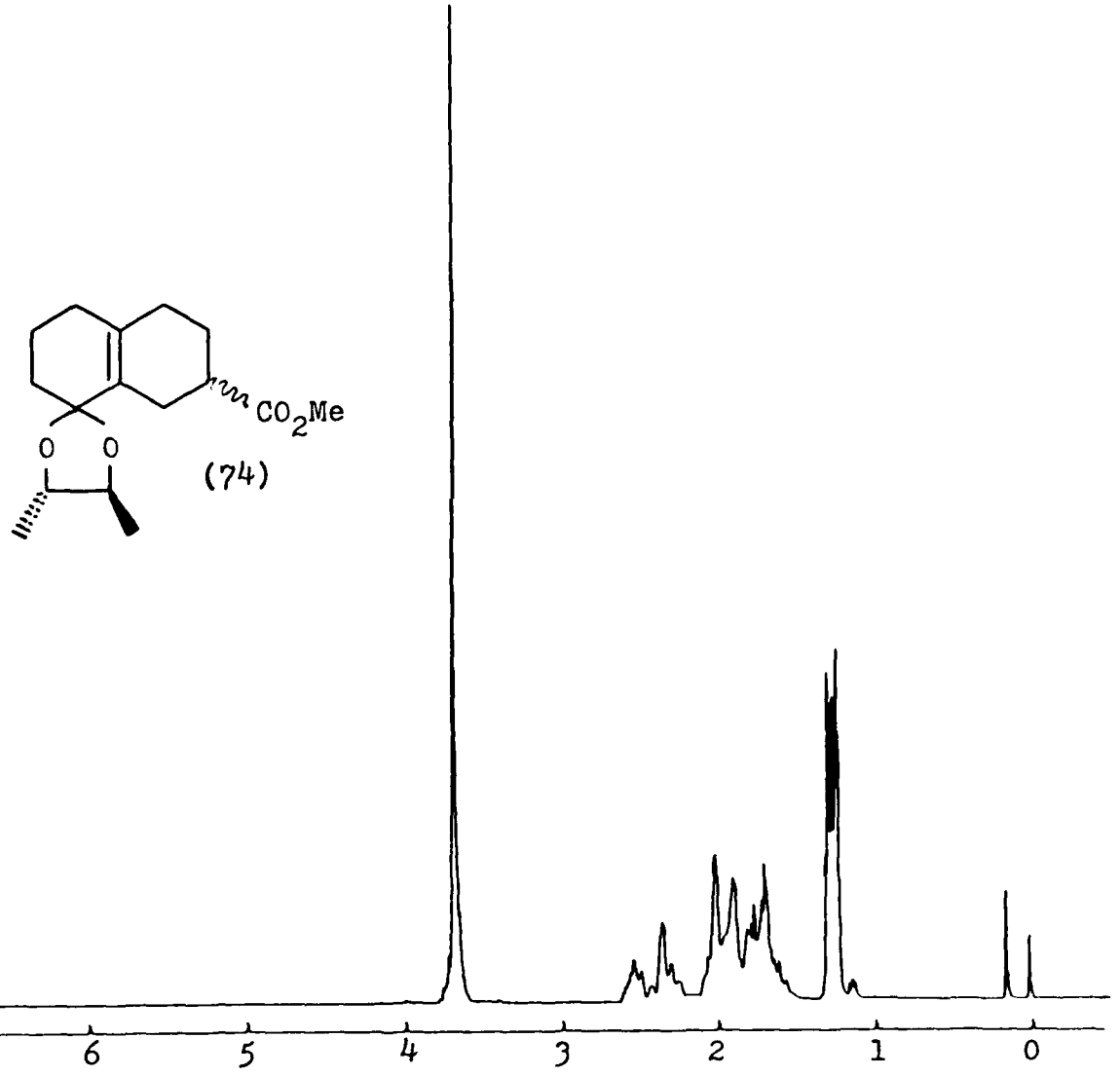
5 Hz), 1.1-1.3 (8, m), 1.5-1.85 (7, m), 1.89-2.17 (3, m), 2.25-2.45 (1, m), 2.85 (1, Q, J= 8 Hz); ^{13}C NMR ($CDCl_3$) 17.92, 18.22, 19.58, 20.63, 21.42, 23.42, 24.98, 25.51, 25.60, 25.80, 27.56, 27.80, 29.42, 29.77, 31.42, 31.93, 35.04, 36.04, 36.18, 36.48, 42.98, 45.68, 72.32, 72.59, 209.45, 210.48; mass spectrum (70 eV) m/z (rel intensity) 222 (1), 204 (21), 189 (12), 164 (26), 161 (27), 160 (11), 149 (22), 148 (15), 146 (13), 143 (33), 135 (20), 133 (19), 131 (18), 123 (20), 122 (13), 119 (11), 108 (32), 107 (14), 105 (24), 93 (25), 91 (31), 79 (24), 77 (14), 67 (13), 59 (100), 55 (16); exact mass calcd for C14 H22 O2 222.1620, obsd 222.1615.

(+)-β-Eudesmol (1). Lithium metal (90 mg, 12.9 mmol) and t-butanol (0.685 ml) were placed in 10 ml of liquid ammonia, and the mixture was stirred under argon. The propellanone (78) (580 mg, 2.61 mmol) was dissolved in 3 ml of dry diethyl ether and was added to the ammonia; the dry ice bath was then removed and the ammonia allowed to reflux. Reaction progress was monitored by TLC (50% ethyl acetate/hexanes), and after 1 hour the reaction mixture was cooled to -78 ^{o}C and the reaction quenched with 1 gram of solid ammonium chloride. 20 ml of diethyl ether was added to the mixture, and the ammonia was allowed to evaporate as the mixture warmed to room temperature. The crude reaction mixture was filtered and concentrated on

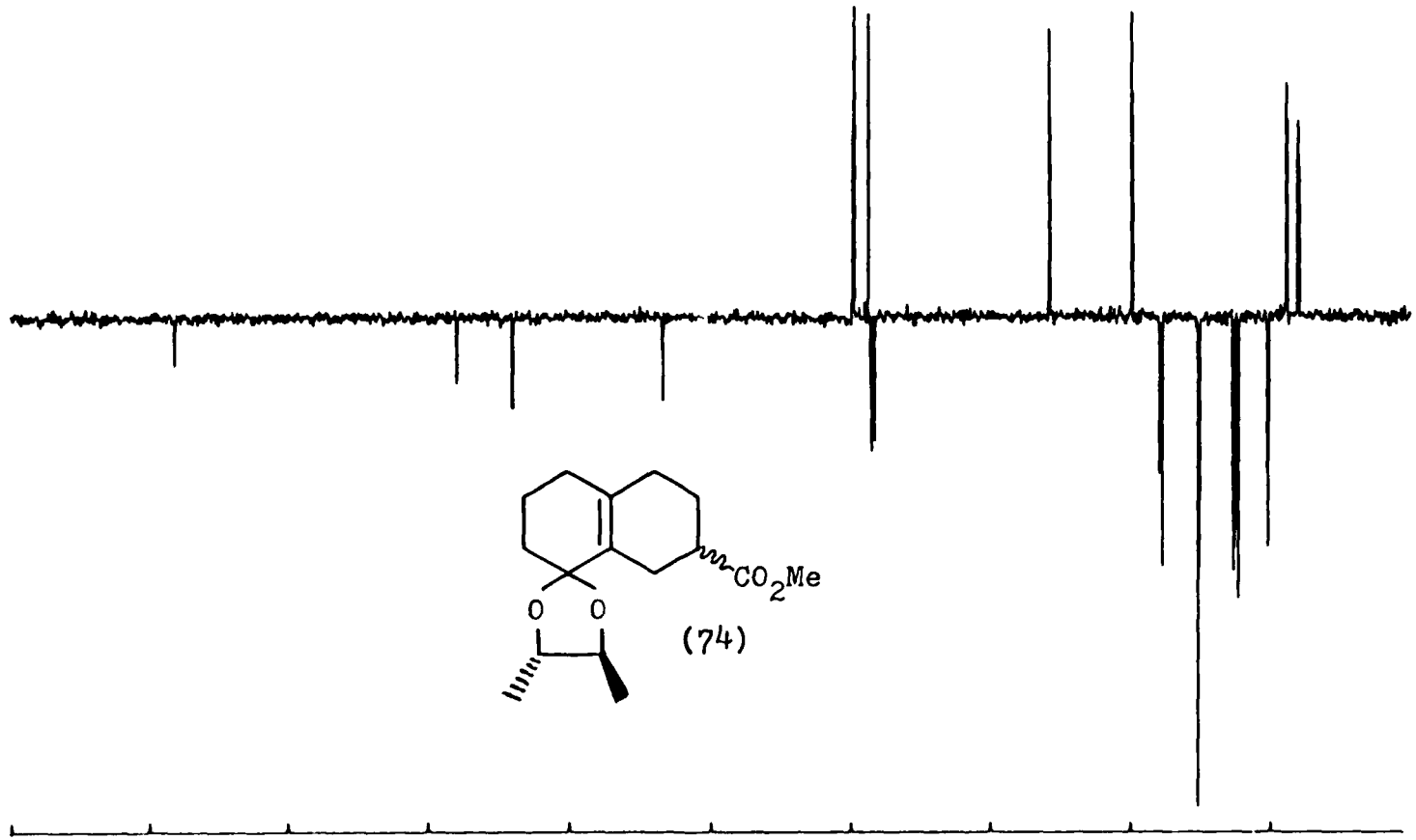
the rotovap and then dissolved in 15 ml of methylene chloride. Pyridinium dichromate (7 g) was added and the mixture stirred for 5 hours. The reaction mixture was then filtered through silica gel to remove the chromium salts, concentrated on the rotovap, and redissolved in benzene. The benzene solution was allowed to equilibrate on 30 g of basic alumina for 2 days. The benzene solution was then washed off the alumina and the solvent removed to give a crude yield of the β-eudesmol ketone of 0.5653 g (96.5%). Dimsyl anion was prepared from NaH (664 mg, 27.6 mmol) and DMSO (13 ml), and 9.5712 g (26.9 mmol) of methyltriphenylphosphonium bromide in 25 ml of DMSO was added to generate the Wittig reagent. The crude β-eudesmol ketone was added to the reaction mixture and the course of the reaction followed by TLC for 52 hours. The reaction was then quenched with ice water and the mixture extracted with two 125 ml portions of diethyl ether. The combined ether extracts were dried with 15 g of magnesium sulfate, filtered, and concentrated. The product was partially purified by column chromatography on 50 g of silica gel using 50% ethyl acetate/hexanes to remove any impurities with retention times which were very different from the desired product. The partially purified product was then further purified by preparative GLC to separate the (+)-β-eudesmol from its C-7 epimer (column temperature= 190 ^{o}C,

injector/detector temperature= 250 ^{o}C, helium flow rate= 60 ml/ min). The retention time of the (+)-β- eudesmol was 11 minutes while the retention time of its C-7 epimer was 8 mirutes. The (+)-β-eudesmol slowly crystallized to give a white solid, m.p. 73-75 ^{o}C, $[\alpha]_D^{24}$ +43.39 (c 0.945, $CHCl_3$) corresponding to 74.8% enantiomeric excess. Literature values: m.p. 80-81 ^{o}C, $[\alpha]_D^{25}$+58.0 (Varma and Bhattacharyya, 1964). IR (CHCl) cm^{-1} 3605, 3455, 3079, 3020, 2975, 2933, 2867, 2844, 1642, 1455, 1439, 1408, 1378, 1188, 1151, 1122, 1091, 1047, 987, 958, 933, 914, 889, 613; ^{1}H NMR ($CDCl_3$) 0.70 (3, s), 1.20 (6, S), 1.1-2.4 (15, M), 4.44 (1, d, J=1.6 Hz), 4.72 (1, d, J=1.6 Hz); ^{13}C NMR ($CDCl_3$) 16.28, 22.35, 23.45, 24.99, 27.11, 35.86, 36.86, 41.10, 41.81, 49.42, 49.76, 72.86, 105.30, 151.11.

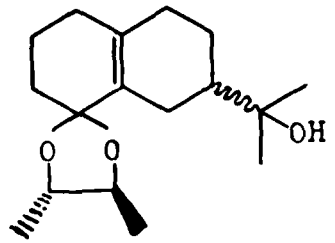
APPENDIX A. NMR SPECTRA OF SELECTED INTERMEDIATES



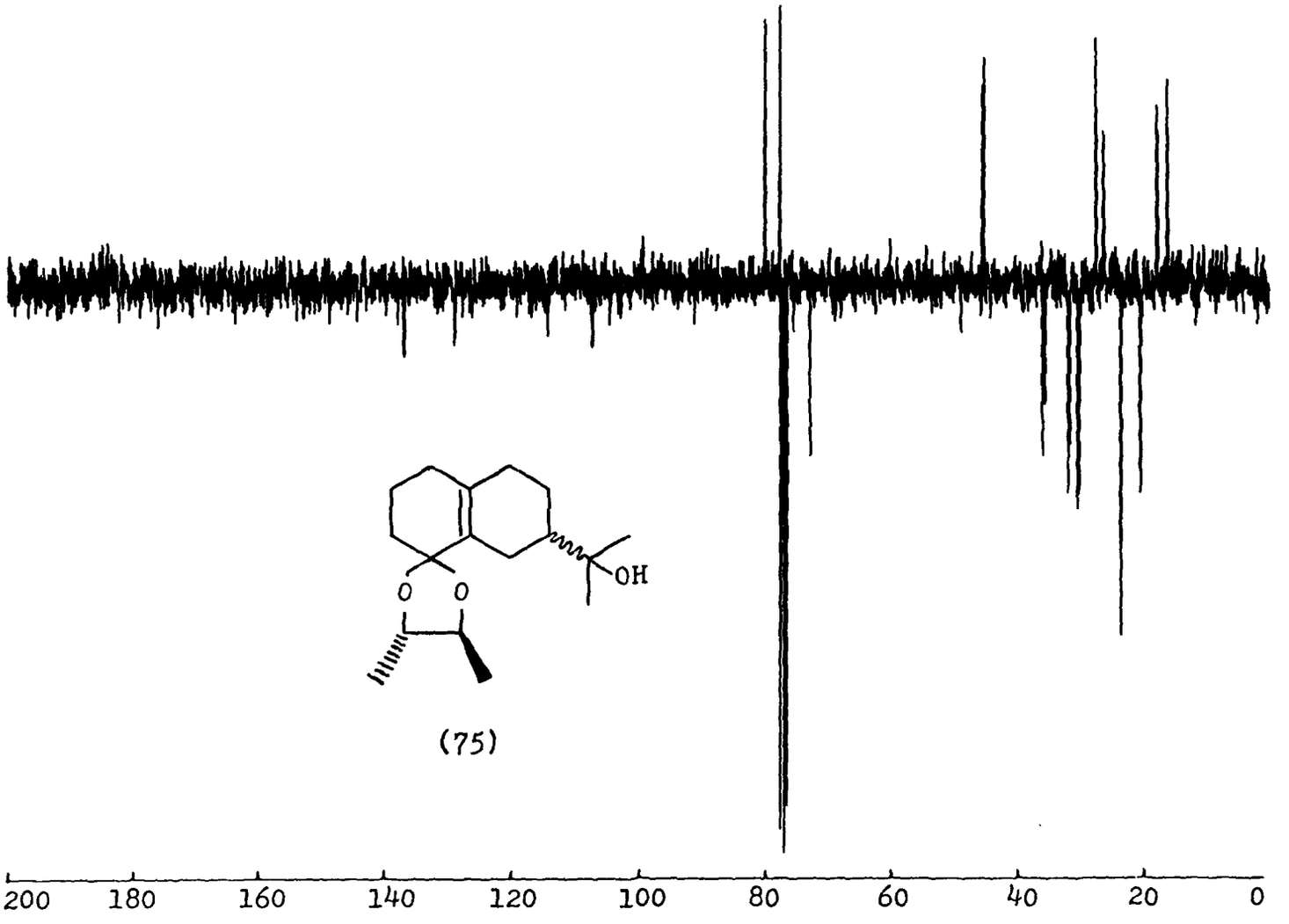
(74)



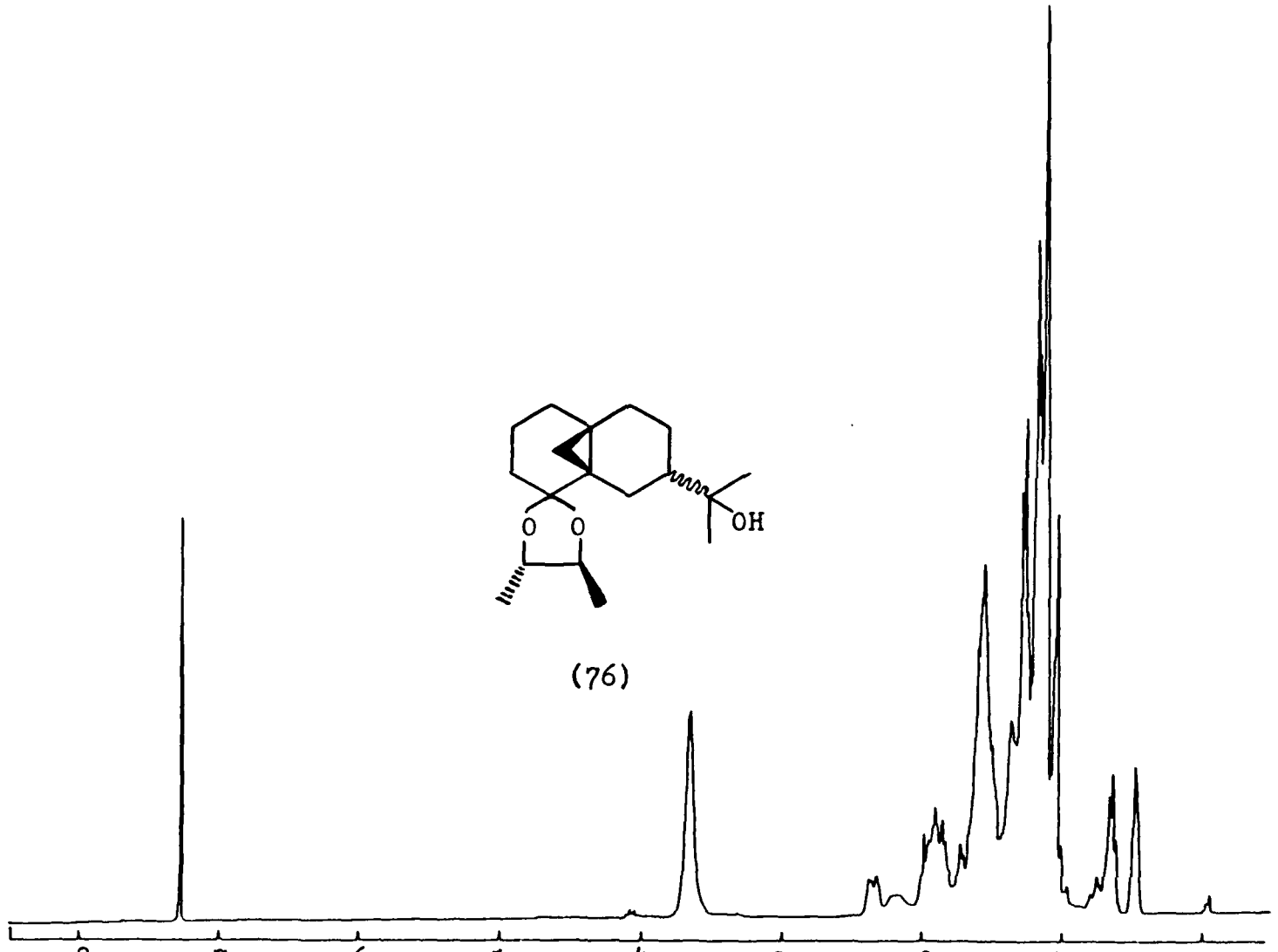
(74)



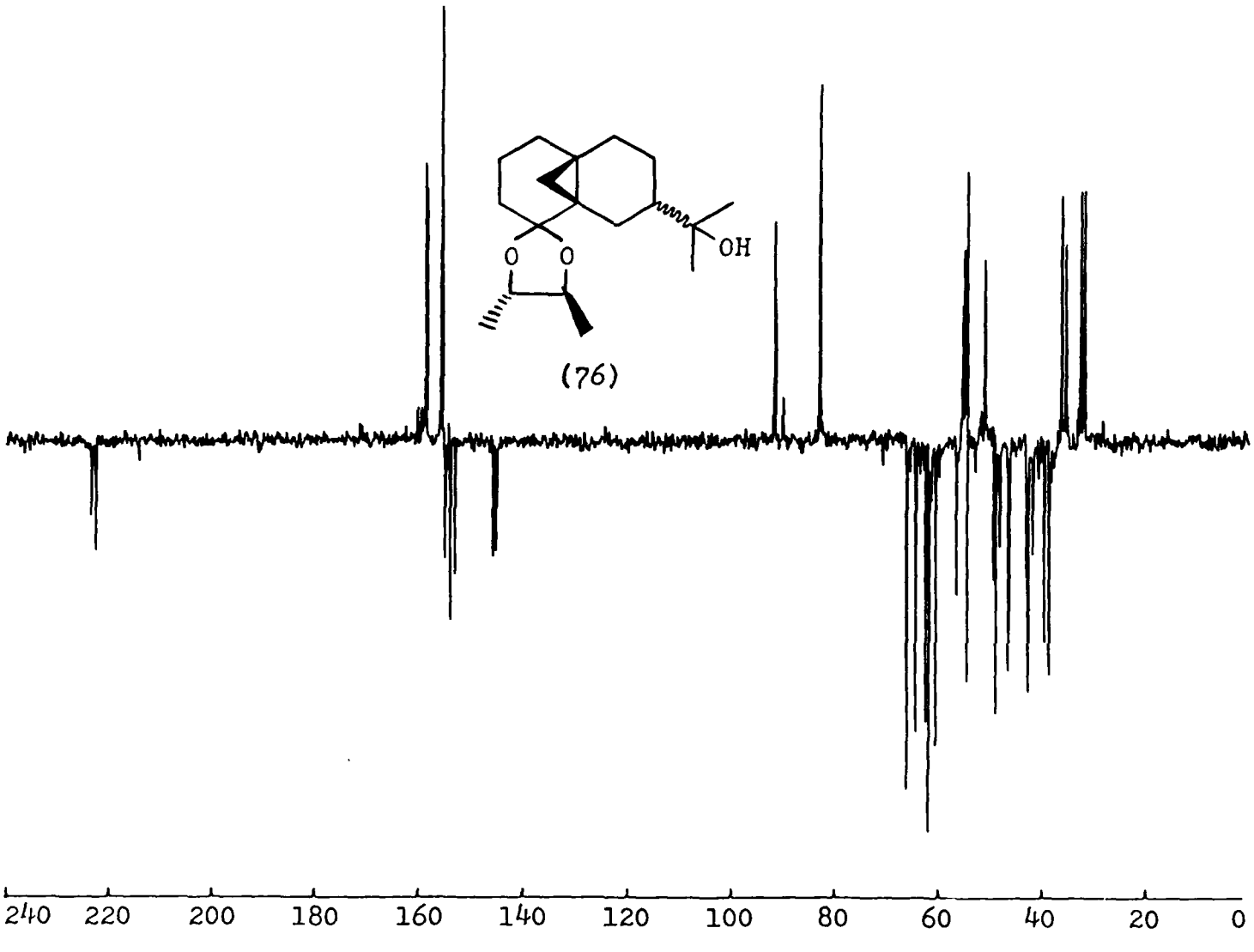
(75)



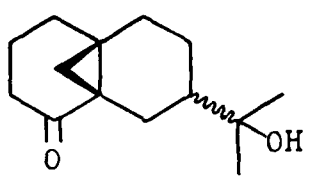
(75)



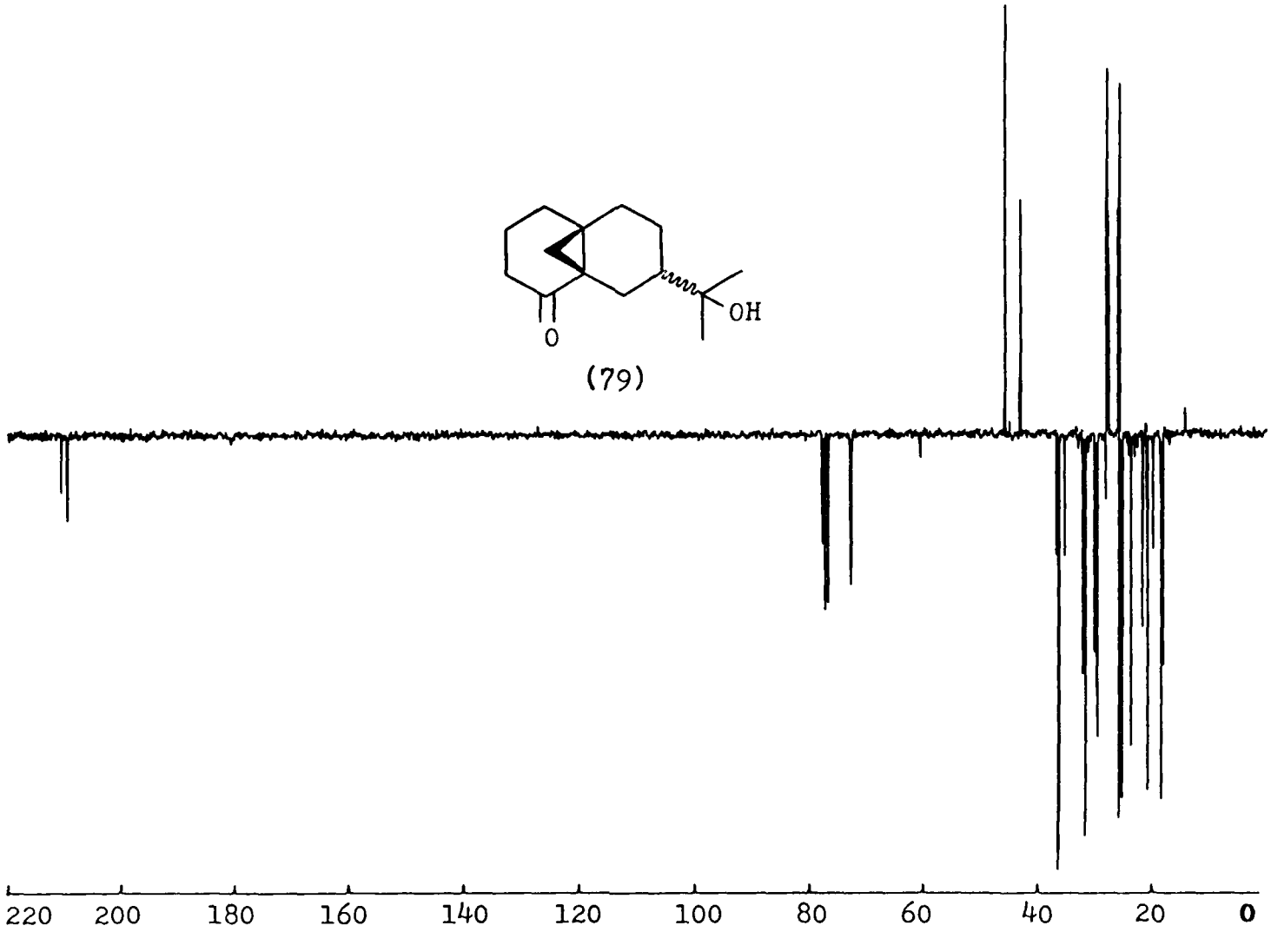
(76)



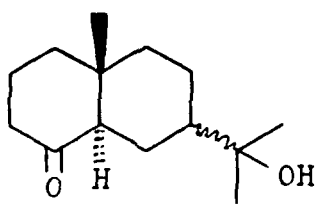
(76)



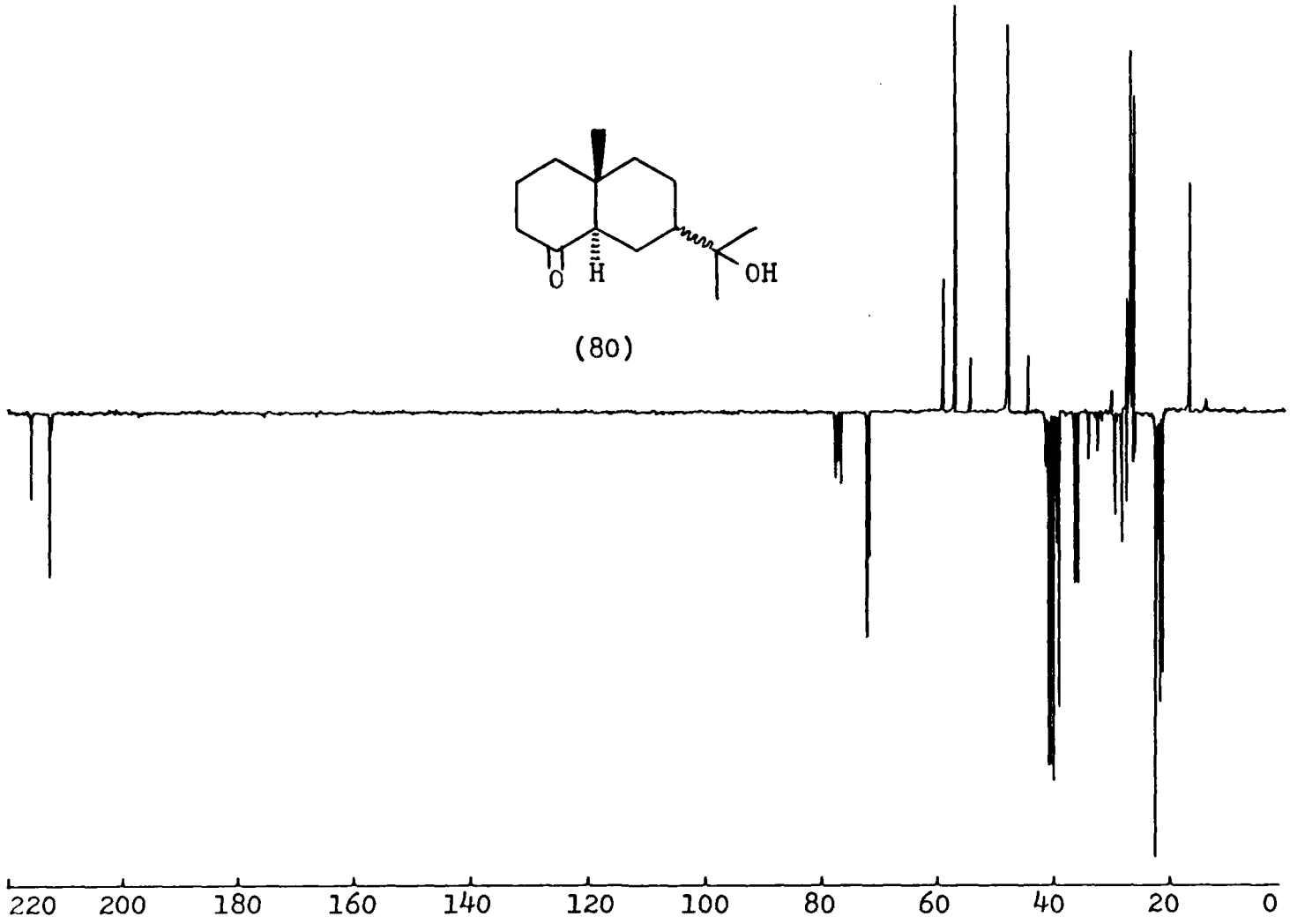
(79)



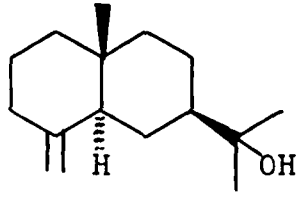
(79)



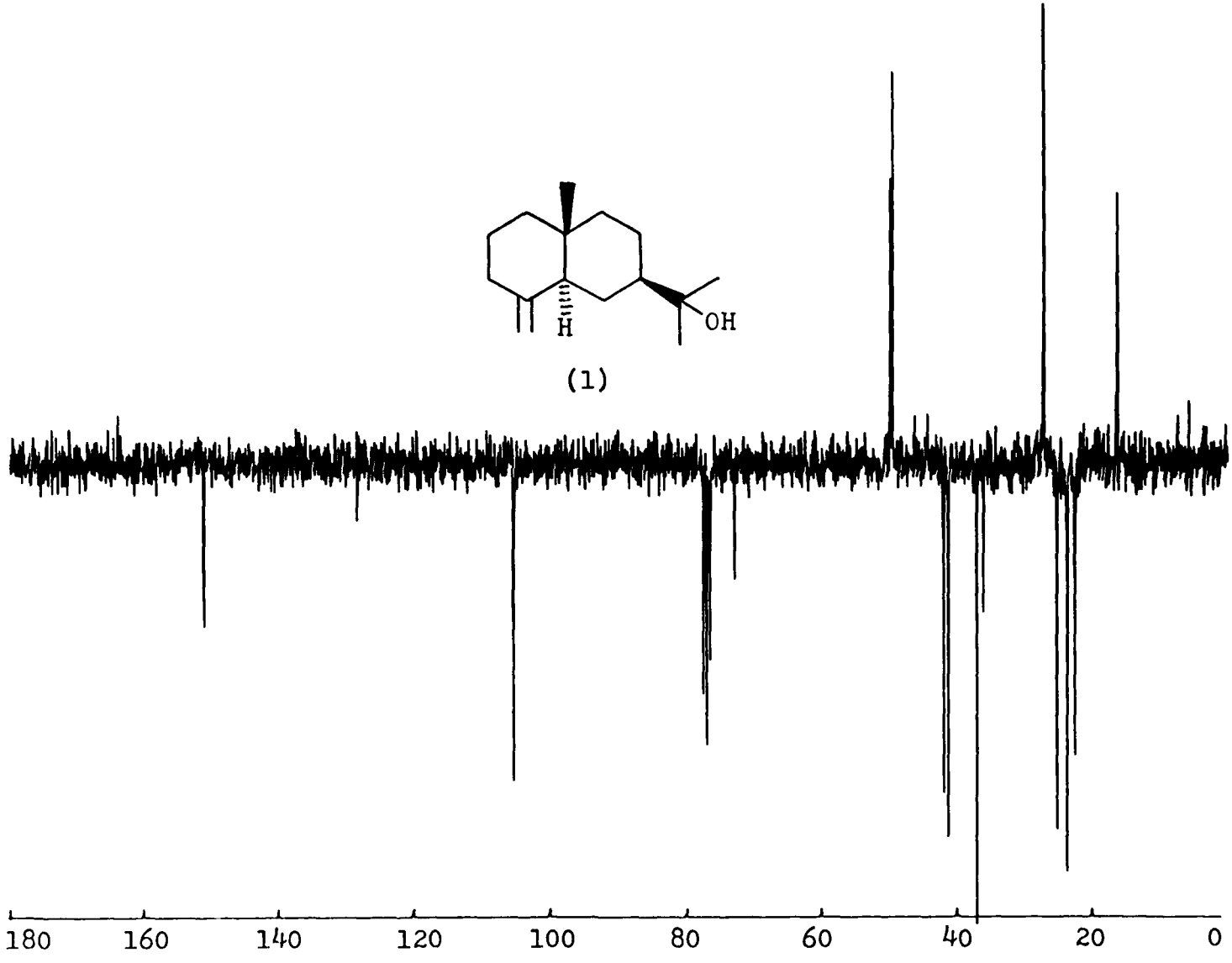
(80)



(80)



(1)



(1)

LIST OF REFERENCES

ApSimon, John. The Total Synthesis of Natural Products. Volume 2. New York: John Wiley and Sons, 1973.

Carlson, Robert G. and Edward G Zey. J. Org. Chem., 37 (15), 2468-2471 (1972).

DeGroot, Aede and Ben J.M. Jansen. Synthetic Communications, 13 (12), 985-990 (1983).

Heathcock, C.H. and T. Ross Kelly. Tetrahedron, 24, 1801-1809 (1968).

Houghton, R.P., D.C. Humber, and A.R. Pinder. Tetrahedron Letters, 3, 353-358 (1966).

Huffman, J.W. and Marvin L. Mole. Tetrahedron Letters, 6, 501-503 (1971).

Huffman, J.W. and Marvin L. Mole. J. Org. Chem., 37 (1), 13-17 (1972).

Humber, D.C., A.R. Pinder, and R.A. Williams. J. Org. Chem., 32, 2335-2340 (1967).

Marshall, James A. and Myron T. Pike. Tetrahedron Letters, 35, 3107-3114 (1965).

Marshall, James A., Myron T. Pike, and Ronnie D. Carroll. J. Org. Chem., 31, 2933-2941 (1966).

Mash, Eugene A. and Kieth A. Nelson. J. Am. Chem. Soc., 107 (26), 8256-8258 (1985).

Mash, Eugene A. and Kieth A. Nelson. Tetrahedron Letters, 27 (13), 1441-1444 (1986).

Mash, Eugene A., Kieth A. Nelson, and Phillip C. Heidt. Submitted for publication.

Riniker, B., J. Kalvoda, D. Arigoni, A. Furst, O. Jeger, A.M. Gold, and R.B. Woodward. J. Am. Chem. Soc., 76, 313-314 (1954).

Schwartz, Martin A. and Ann M. Willbrand. J. Org. Chem., 50 (9), 1359-1365 (1985).

Shank, R.S. and H.J. Shechter. J. Org. Chem., 24, 1825-1826 (1959).

Tsunoda, T., M. Suzuki, and R. Noyori. Tetrahedron Letters, 21, 1357-1358 (1980).

Varma, K.R. and S.C. Bhattacharyya. Tetrahedron, 20, 2927 (1964).

Vig, O.P., R.C. Anand, Baldev Kumar, and S.D. Sharma. J. Indian Chem. Soc., 45 (11), 1033-1036 (1968).

Wijnberg, Johannes B.P.A., Jan Vader, and Aede deGroot. J. Org. Chem., 48 (23), 4380-4387 (1983).

END

3-87

DTIC