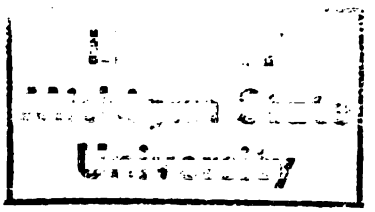


This is to certify that the

dissertation entitled

Epoxide Rearrangement as a possible Approach to Clerodane Diterpenes

presented by

Yousef M. Abdallah

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Major professor

Date 11/18/85

EPOXIDE REARRANGEMENT AS A POSSIBLE APPROACH TO CLERODANE DITERPENES

By

Yousef M. Abdallah

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1985

ABSTRACT

EPOXIDE REARRANGEMENT AS A POSSIBLE APPROACH TO CLERODANE DITERPENES

By

Yousef M. Abdallah

We examined the rearrangement in Equation 1 as a possible approach to clerodanes diterpenes. To demonstrate the viability of such an approach, the Diels-Alder reaction regioselectivity of dienes **100a** and **100b** with acetylenic dienophiles, dimethyl acetylenedicarboxylate, ethyl propiolate and ethyl tetrolate was studied. The regioselectivity of the addition is excellent and the reaction proceeds in high yield (55-95%). The regio-reversed Diels-Alder reaction of dienes **100a,b** with β-nitro-α,β-unsaturated esters **108** was examined and found to be excellent, providing one isomer in good yield (57-78%). An improved synthesis of the diene **100a** via $CuSO_4.5H_2O$ mediated dehydration of vinyl carbinol precursor was discovered.

The epoxidation stereoselectivity of a number of 5,5-dimethyl-3,5,6,7,8,8a-hexahydronaphthalenes **104** with m-chloroperbenzoic acid (MCPBA) and N-bromo-succinimide (NBS) was investigated. Excellent epoxidation stereoselectivity

was observed with substrates containing a methyl at the C-8a-ring junction. Treatment with MCPBA provided the α-epoxides in high yields (82-90%). β-epoxides were obtained as the major stereoisomer with substrates containing an H at the ring junction in excellent yields (MCPBA). Epoxidation of these substrates with NBS, aq. t-BuOH, proceeded with high stereoselectivity providing the α-epoxides as the exclusive, or major, stereoisomer in high yields (60-94%).

Exposure of β-epoxides **110** to $BF_3 \cdot Et_2O$ provided excellent yields (79-92%) of rearranged fused indene oxetanes **117**. Treatment of α-epoxides **109** with $BF_3 \cdot Et_2O$ yielded either the rearranged product **122** or the oxetanes **117** and the related alcohols **123** and **124** in good yields, depending on the ring junction substituent. Treatment of the 6-β-hydroxy-α-epoxide **136** with $BF_3 \cdot Et_2O$ resulted in ring B aromatization while 6-β-hydroxy-β-epoxides **137** provided a gross mixture of product.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

Page

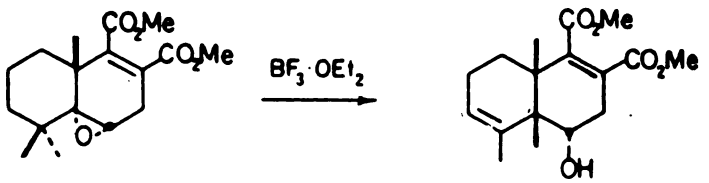
LIST OF EQUATIONS

LIST OF TABLES

INTRODUCTION

INTRODUCTION

Previously, we had investigated the Lewis acid catalyzed rearrangement of the epoxide **1** as shown in Equation 1. Rearranged alcohol **2** was the sole product

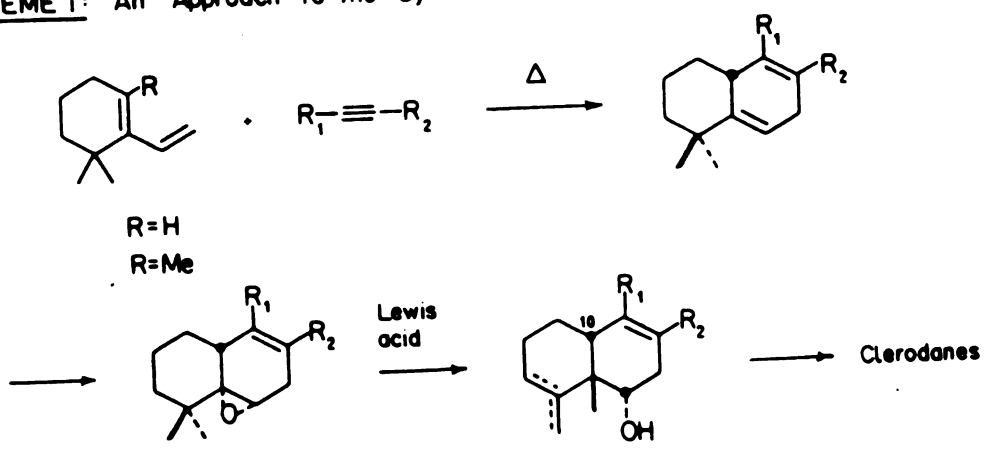


(1)

1 2(76%)

obtained from this reaction, isolated in 76% yield. The close structural relation of the C-3 to C-6 portion of the rearranged product **2** and clerodanes diterpenes suggested the possibility of constructing **3-14** from such a rearrangement. The presence of a C-3, C-4 double bond would allow functionalization at C-3, C-4 and of C-4-CH_3 moiety. However, the ring fusion CH_3 group of **1** must be replaced by an H without effecting the course of the reaction. Such an approach to cis- or trans-, clerodane diterpenes and related compounds (**6-14**) is illustrated in Scheme I. Interest in

SCHEME I: An Approach to the Synthesis of Clerodane Diterpenes



clerodane diterpenes as targets for total synthesis stems mainly from the range of biological activities exhibited by a number of these compounds. For example, the neo-clerodane diterpenes, Ajugarins (I-VI) **3-8**, isolated from the leaves of the East African medicinal plant, *ajuga remota* (Labiatae), exhibit a potent insect antifeedant activity against the desert locust, *sehistocera vega*[2a] and shows, in addition, insecticidal and insect-growth inhibiting activities. Other clerodanes of interest are annonene **9**[2e], **10**[2e], elongatolide-A **11**[2f,g,h] and the sesquiterpenes, Averol **12**[2i], illimaquinone **13**,[2i] which exhibit antibacterial activity, and arenarol **14**.[2i]

Clerodane diterpenoids such as the ajugarins have a rearranged labdane skeleton (**15**) and belong to a novel class of natural products found in nature in ever-increasing

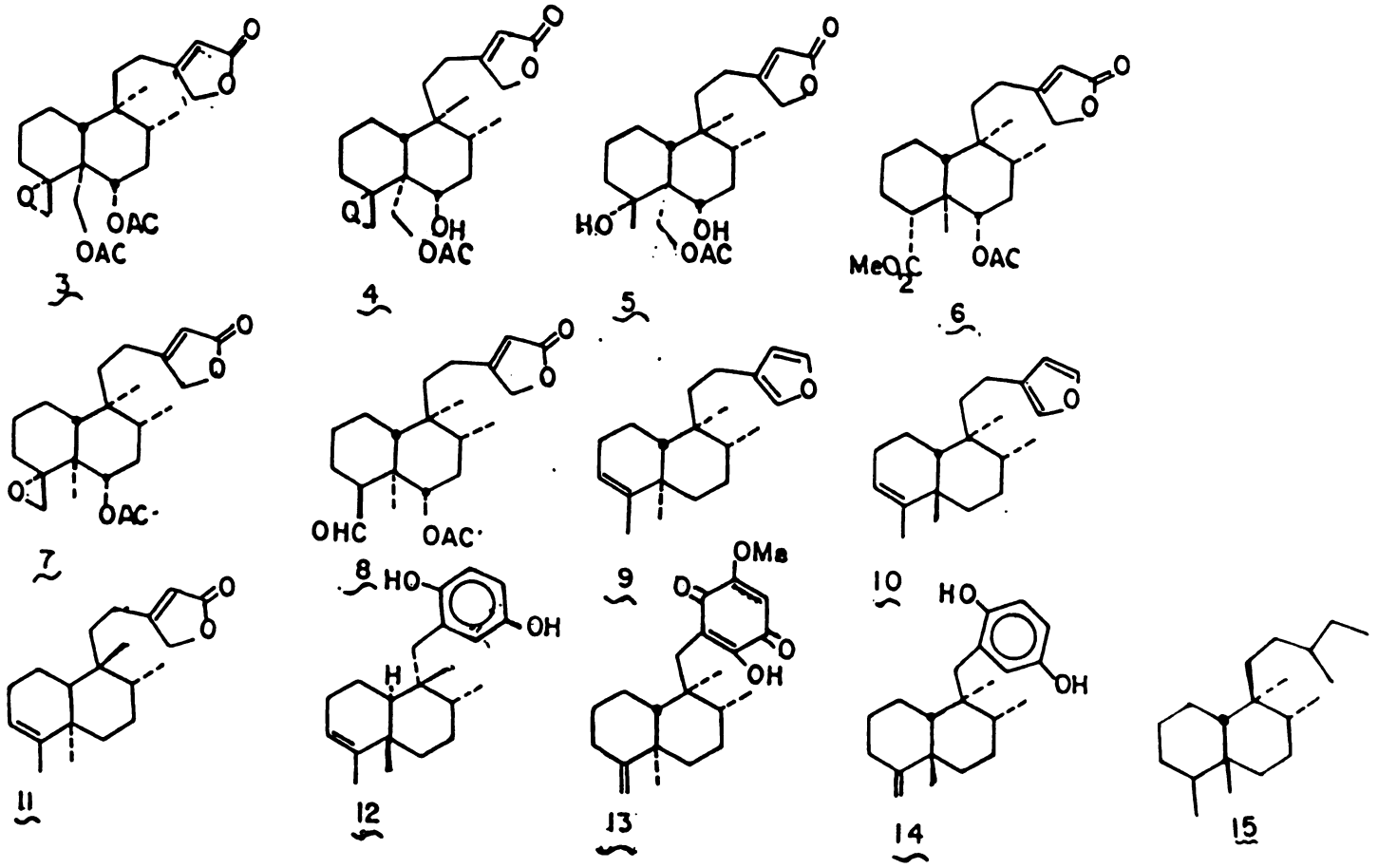


Figure 1 Selected Clerodanes Diterpenes and Relative Compounds

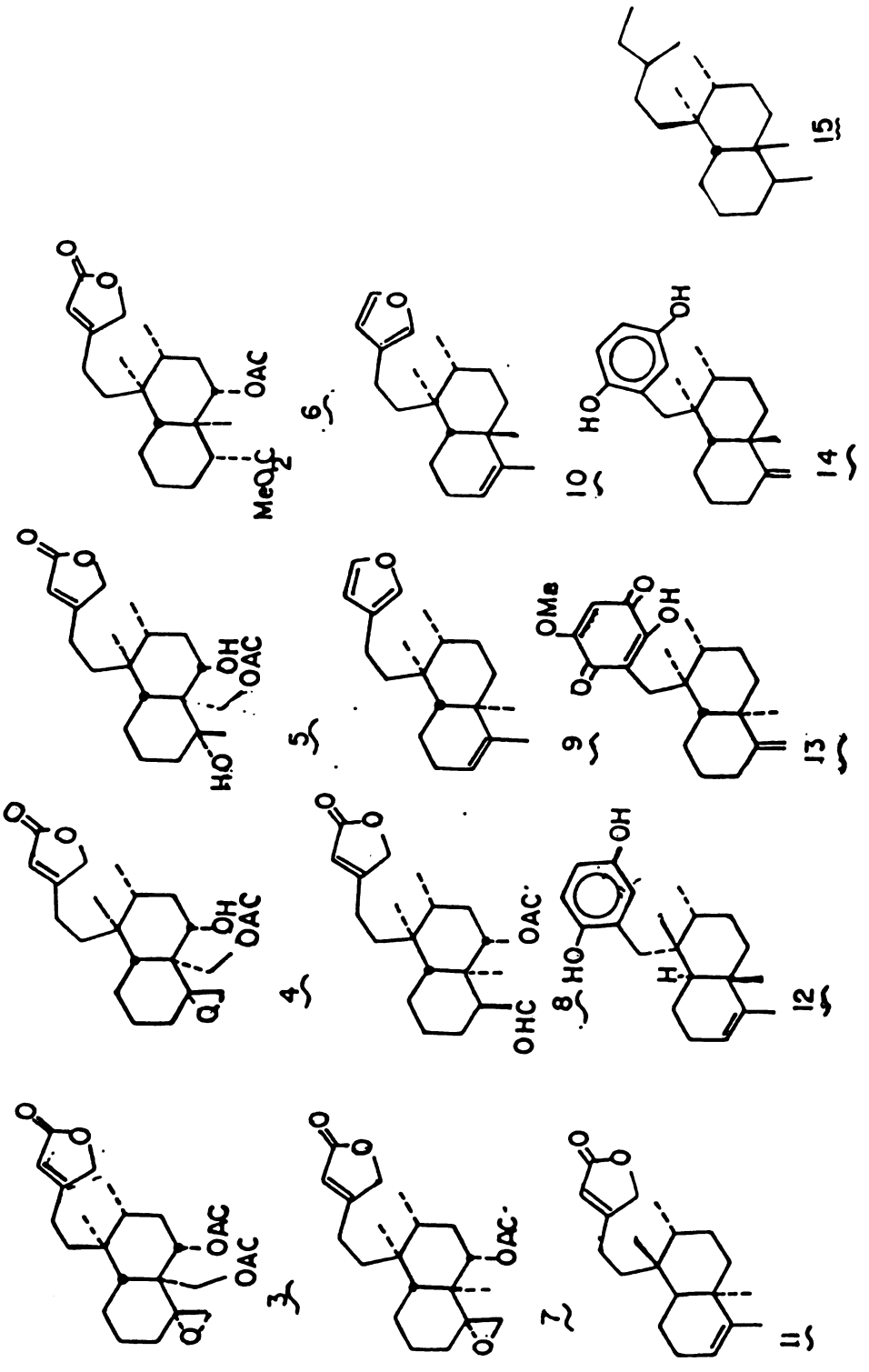


Figure 1 Selected Clerodanes Diterpenes and Relative Compounds

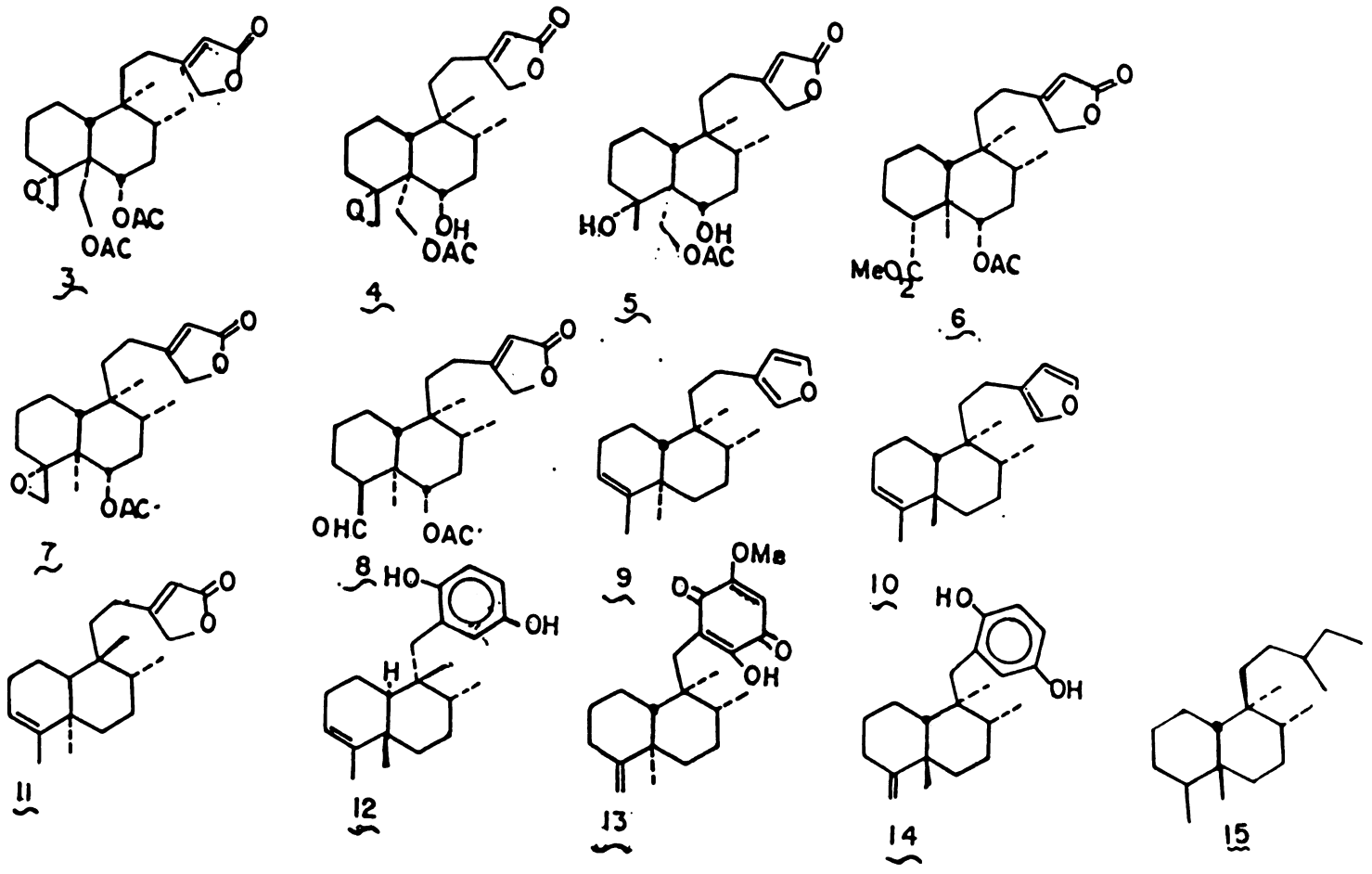
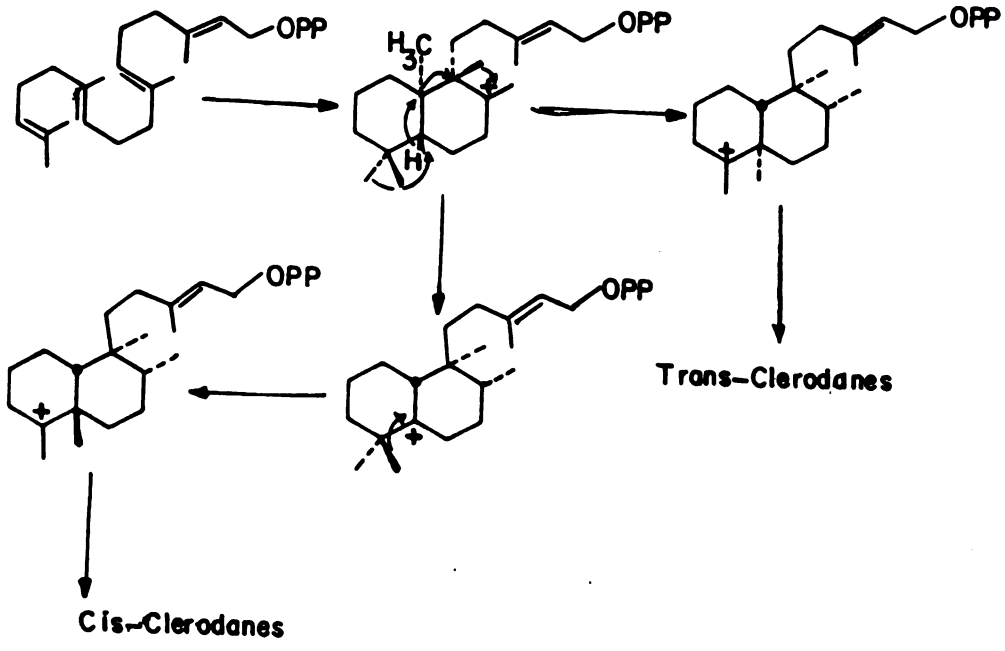


Figure 1 Selected Clerodanes Diterpenes and Relative Compounds

numbers.[3] These compounds, with both cis- and trans-ring fusions, are believed to be formed biogenetically[4] from geranyl geranyl pyrophosphate via a labdane precursor after a series of backbone rearrangements involving hydrides and methyl shifts are catalyzed enzymatically and are thought to proceed these rearrangements as shown in Scheme II. This process could account for both cis- and trans-clerodanes formation.

Scheme II Biogenetic Pathway to Clerodane Synthesis.

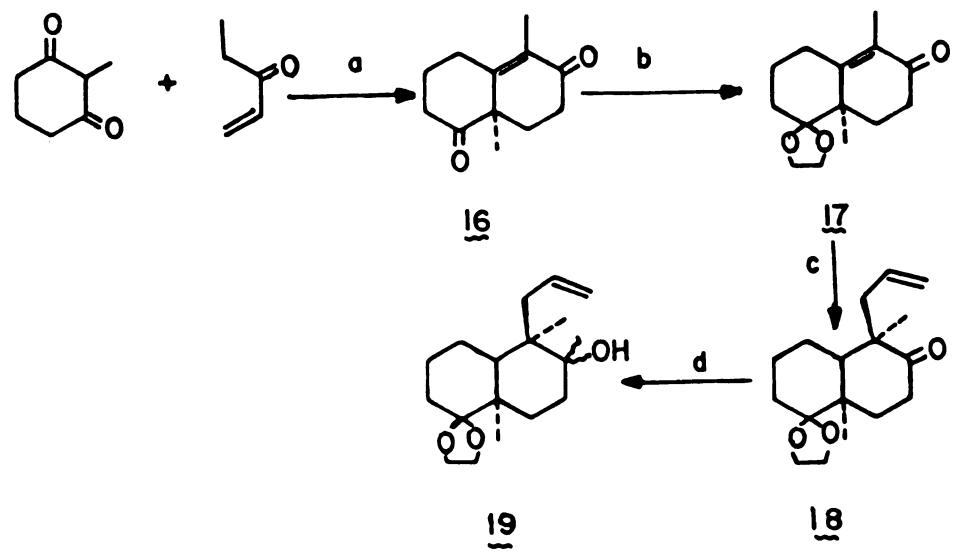


Synthesis and Synthetic Approaches

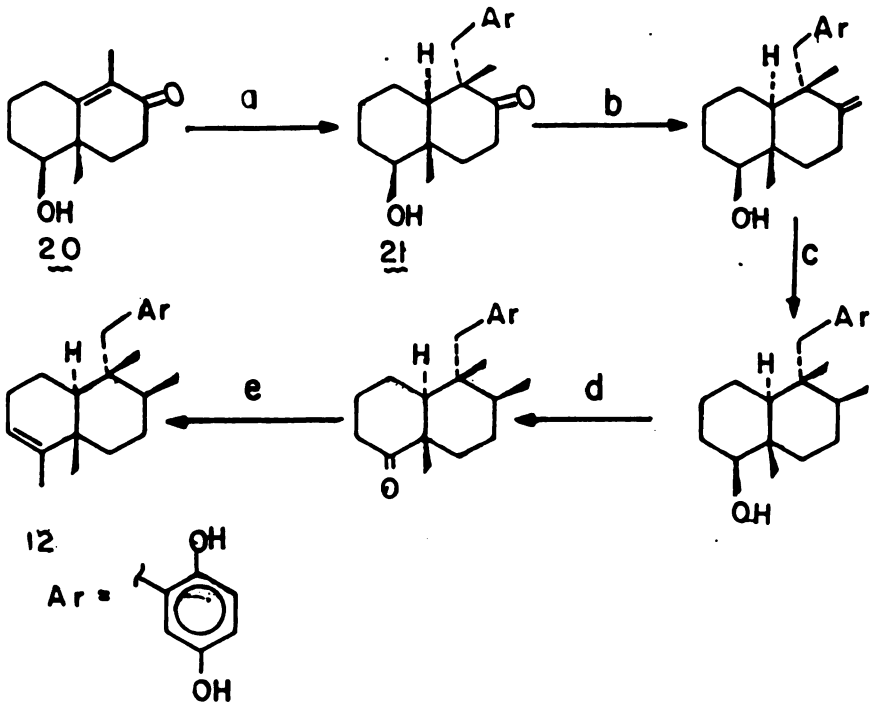
To date, four total syntheses of clerodane diterpenes have been reported; and in addition, a number of approaches to clerodanes were attempted. None of these total syntheses seemed to be sufficiently general or to provide for the preparation of both the cis- and trans-clerodanes. These syntheses or synthetic approaches suffered from being either lengthy, tedious, non-stereospecific, including very low yield steps, or unable to achieve the goal. The major obstacle to be overcome in any syntheses of a clerodane diterpene is the construction of the decalin moiety with the proper chiral centers. Three main pathways have been utilized in the construction of the decalin framework: a) Wieland-Miescher ketones or related compounds, as the basic skeleton, where all the asymmetry has to be introduced; b) conjugate addition to an appropriate precursor enone, followed by cyclizations; and c) a Diels-Alder reaction; [4 + 2] cycloaddition.

In the first synthetic approach by Halsall,[5] the decalin moiety was constructed by a Robinson annulation to form **16** (Scheme III). Selective protection of **16**, followed by reductive alkylation, gave the desired trans-fused compound **18**. The C-8-CH_3 was to be added via a Wittig reaction; however, this sequence failed to methylenate the hindered ketone **18**. Methyl lithium was successfully added

Scheme III Halsall's Approach to the Clerodanes .



a) NaOEt; b) 1,2-ethane diol; c) i) Li/NH_3, ii) allyl bromide; d) CH_3Li



Scheme IV Sarma's Total Synthesis of (±) Averol 12.

a) i) Li/NH_3, ii) $ArCH_2Br$; b) Ph_3PCH_2; c) $H_2/Pd/C$; d) PCC; e) i) CH_3Li, ii) $POCl_3$,pyridine, iii) $RhCl_3$; iv) BuSLi-HMPA

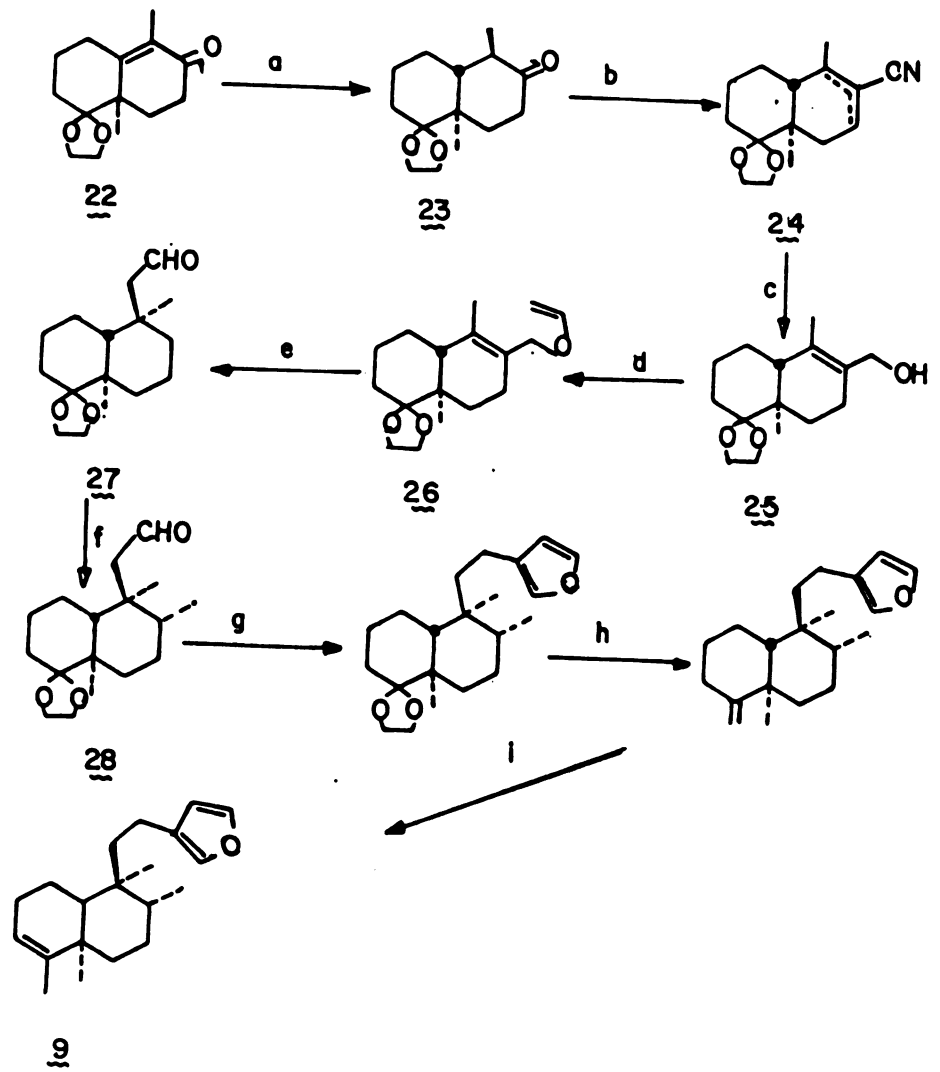
to **18** to provide the alcohol **19**; unfortunately, **19** could not be converted to a clerodane derivative.

A similar Wieland-Miescher ketone-type approach to Averol **12** was reported by Sarma.[6] Reductive alkylation of **20**, Scheme IV, gave the trans-decalol **21** which underwent a Wittig reaction under forcing conditions providing the corresponding exo-methylene compound. Hydrogenation of the hindered exo-methylene compound followed by CH_3Li addition and dehydration afforded (±)Averol **12**.

Kakisawa[7] reported the first non-stereospecific total synthesis of the clerodane diterpenes (±)-Annonene **9**. Their strategy utilized the Wieland-Miescher ketone to construct the bicyclic framework, Scheme V. Dissolving metal reduction of the enone **22** followed by cyano-hydrin formation and dehydration resulted in a mixture (1:1) of the isomers **23**. Separation of the mixture of olefins and reduction of the nitrile <u>via</u> the intermediate aldehyde **24** gave the alcohol **25**. Treatment of **25** with $CH_2{=}CH{-}OCH_2CH_3$ under the exchange conditions gave **26** which underwent the desired Claisen rearrangement upon heating; leading to the aldehyde **27**. This key step in the synthesis was stereoselective and provided an exo-methylene at C-8. Hydrogenation of the C-8 exo-methylene afforded a mixture of **28** and its epimer at C-8; further elaboration converted **28** to (±)annonene **9**.

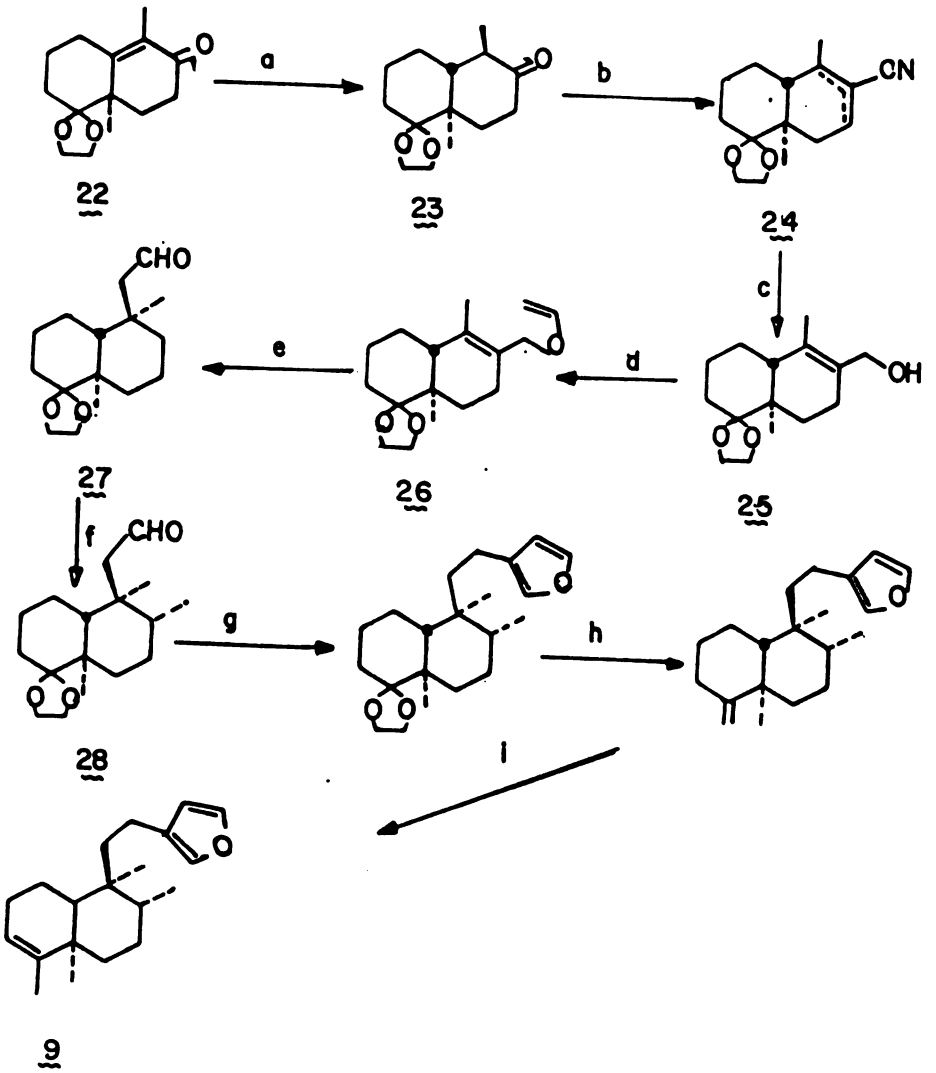
A total synthesis of the clerodane diterpene Ajugarin-IV **6** (Scheme VI) was reported by Kende.[8] These workers also

Scheme V Kakisawa's Total Synthesis of Ammonene 9 .



a) Li/NH_3; b) i) KCN, ii) $SOCl_2$,pyridine; c) i) Dibal, ii) $NaBH_4$; d) ethyl vinyl ether,$Hg(OAc)_2$; e) heat,200°C; f) i) $NaBH_4$, ii) $H_2/pd/C$, iii) PCC; g) i) 3-furyl lithium, ii) Ac_2O, iii) Ca/NH_3; h) i) H^+, ii) Ph_3PCH_2; i) dilithium ethane-1,2-diamine

Scheme V Kakisawa's Total Synthesis of Ammonene 9 .

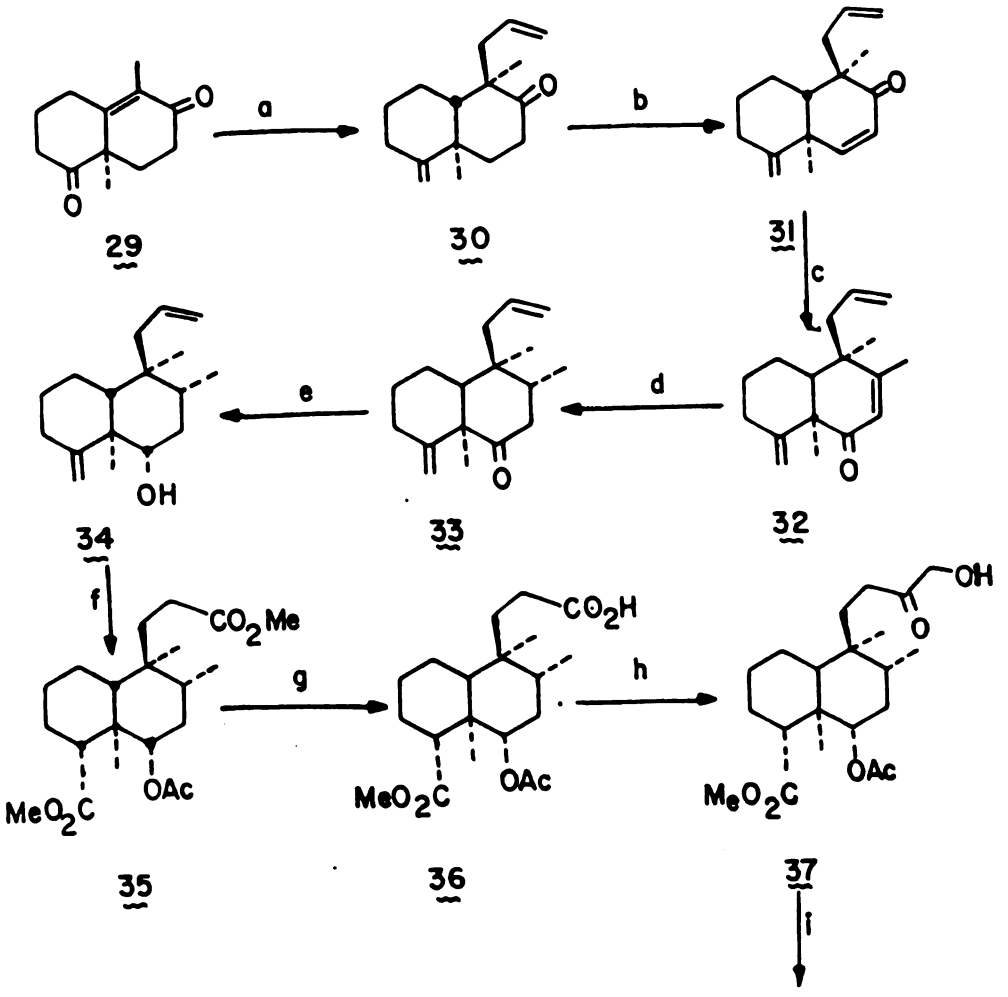


a) Li/NH_3; b) i) KCN, ii) $SOCl_2$,pyridine; c) i) Dibal, ii) $NaBH_4$; d) ethyl vinyl ether,$Hg(OAc)_2$; e) heat,200°C; f) i) $NaBH_4$, ii) $H_2/pd/C$, iii) PCC; g) i) 3-furyl lithium, ii) Ac_2O, iii) Ca/NH_3; h) i) H^+, ii) Ph_3PCH_2; i) dilithium ethane-1,2-diamine

utilized the classical Wieland-Miescher ketone **29** as the basic skeletal building block (Scheme VI). Selective thioketalization, followed by a Wittig reaction, allowed the introduction of the exo-methylene group at C-4 and reductive alkylation then gave **30**. Oxygenation at C-6 was accomplished by bromination-dehydrobromination to provide the enone **31**; CH_3Li addition and 1,3-oxidative transposition ($CrO_3 \cdot pyr_2$) gave the enone **32** in a low yield. Dissolving a metal reduction of **32** in the absence of a proton source resulted in a single isomer **33** with an equatorial methyl at C-8. Lithium aluminum hydride reduction of the C-6 ketone gave the C-6 equatorial alcohol **34**. Hydroboration of **34** under equilibrating conditions with disiamylborane resulted in the conversion of the C-4 exo-methyl to the equatorial C-4,CH_2OH group as well as the conversion of the C_9-allyl group to a proponal chain after oxidation (H_2O_2,^-OH). Oxidation of the resulting diol to the diacid and esterification resulted in **35**. Selective hydrolysis of the diester in **35** allowed the conversion of the least-hindered side chain ester to the acid **36**. The butenolide moiety was introduced by reaction of the derived acid chloride from **36** with tris (trimethyl siloxy) ethylene, followed by heating and acid hydrolysis, to provide the β-hydroxy ketone **37**. A ketenylidene triphenylphosphorane reaction with **37** provided Ajugarin-IV **6**.

Approaches to clerodanes that utilized the Robinson annulation for the construction of the decalin substructure

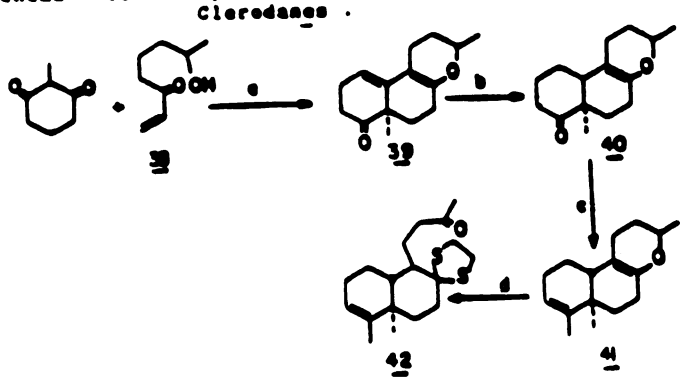
Scheme VI Kende's Total Synthesis of Ajugarin IV 6. .



a) i) 1,2-ethane dithiol,H^+; ii) Ph_3PCH_2; iii) $HgCl_2$-$CdCO_3$; iv) Li/NH_3,allyl bromide; b) i) base,Me_3SiCl; ii) NBS; iii) LiBr-Li_2CO_3,DMF,reflux c) i) CH_3Li; ii) $CrO_3 \cdot 2py$; d) i) Li/NH_3-THF; e) LAH; f) i) Sia_2BH,H_2O_2,OH^-; ii) PDC-DMF; iii) $NaClO_2$; iv) CH_2N_2; g) i) KOH (1.1 equiv),CH_3OH; ii) 6NHCl; iii) Ac_2O,Et_3N,DMAP h) i) $(COCl)_2$; ii) $[(CH_3)_3Si]_2C=CHSi(CH_3)_3$; iii) heat,$H^+$ I) i) $Ph_3P=CH=C=O$

are discussed below. Apsimon[9] reported a route to the trans-clerodane using an acid-catalyzed Michael addition and aldol cyclodehydration of 2-methyl-1,3-cyclohexanedione with enone 38 to give 39, Scheme VII. Monoprotected dione 39 was hydrogenated stereospecifically to 40. Addition of CH_3Li and dehydration gave 41, which after thioketalization and oxidation, gave 42. The conversion of 42 to trans-clerodane has not yet been accomplished.

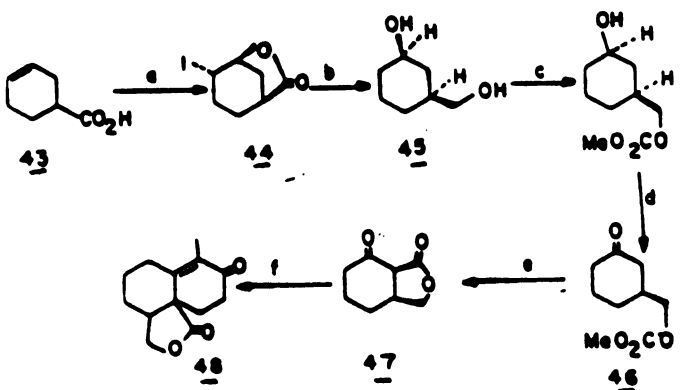
Scheme VII Apsimon's Route to trans-Clerodanes.



a) HOAc; b) H_2/pd-c; c) i) MeMgBr, ii) HCl/MeOH; d) i) 1,2-ethane dithiol,PTSOH, ii) CrO_3.pyr

Goldsmith[10] has reported an approach to Ajugarin-I 3 utilizing the strategy outlined in Scheme VIII.

Scheme VIII Goldsmith's Synthesis of the Intermediate 48.



a) KI_3-$NaHCO_3$; b) LAH; c) methyl chloroformate,pyridine; d) CrO_3; e) NaH; f) P-TSOH,ethyl vinyl ketone

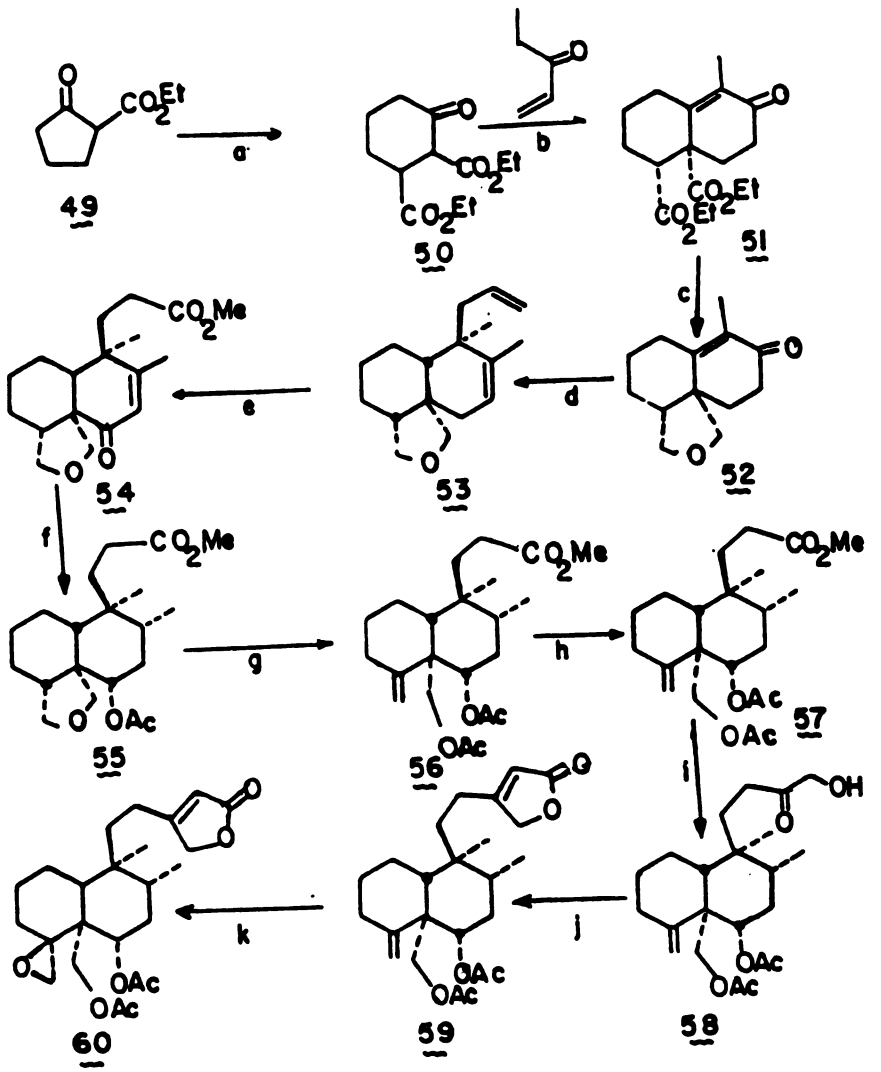
Iodolactonization of 3-cyclohexene-1-carboxylic acid **43** gave the iodolactone **44**, which upon reduction (LAH) provided cis-3-hydroxy methyl cyclohexanol **45**. Selective acylation of the 1°-OH with methyl chloroformate, oxidation to the corresponding ketone **46** and NaH-induced cyclization afforded the lactone **47**. A Robinson-type annulation led to the cis-fused lactone **48**.

deGroot[11] has reported the stereospecific synthesis of the enone ether **52** as intermediates to clerodanes; more recently,[11c] he has reported the conversion of **52** to 4-epi-Ajugarin-I, Scheme IX. The β-ketoester **49** was condensed with α-chloro-ethylacetate, then converted to the keto diester **50**. A Robinson annulation of **50** with ethyl vinyl ketone provided **51** which, after enone protection, (LAH) reduction, dehydration and hydrolysis, provided the key intermediate, enone ether **52**. Dissolving metal reductive allylation of enone **52**, CH_3Li addition and dehydration gave **53**. Hydroboration and conversion of the side chain to the corresponding ester, followed by allylic oxidation of the endocyclic double bond, gave the enone **54**. Stereoselective hydrogenation of the enone **54** resulted in the equatorial C-8-methyl and $Li(t\text{-}BuO)_3AlH$ reduction of C-6-ketone provided the equatorial C-6-OH which, upon acetylation, provided **55**. The tetrahydrofuran ring opening and acetylation gave **56**. The side chain was developed by a procedure analogous to that

discussed in Kende's synthesis via compounds **57**, **58** and **59**. Epoxidation of **59** with MCPBA gave only (±)epi-ajugarin-I **60**.

Ley[12] reported the first total synthesis of Ajugarin-I **3** (Scheme X) utilizing a conjugate addition, annulation protocol. The enone **61**, after protection of the aldehyde, was converted to **63** by conjugate addition. The A ring was generated by hydroboration and oxidation of the butenyl side chain followed by cyclization of the product keto-aldehyde to form the enone **64**. Stereospecific vinyl cuprate addition and trapping of the resulting enolate with formaldehyde allowed the insertion of the hydroxymethyl substituent at C-5 to provide **65**. Selective reduction of the ketone, protection of the diol as the acetonide, and dethioketalization afforded the aldehyde **66**. The introduction of the side chain was accomplished by addition of the lithium anion of phenyl sulfonyl (trimethylsilyl) methane followed by acetylation, and Bu_4NF treatment gave the vinyl sulfone **67** which was reduced with $LiEt_3BH$ to provide **68**. The C-4-vinyl group was converted to the exo-methylene group by ozonolysis, reduction, selenation and β-elimination of the selenoxide to give **70**. To the butenolide precursor **69** was added the anion of **70** yielding **71** after lactonization and desulfurization. Deprotection of the acetonide to the diol epoxidation with m-chloroperbenzoic acid, followed by acetylation, afforded a 1:3 mixture of Ajugarin-I **3** and 4-epi-Ajugarin-I **60** in 82% yield.

Scheme IX deGroot's Synthesis of epi-Ajugarin I 60.



a) i) $ClCH_2CO_2Et$; ii) NaOEt; iii) Na b) Me_3N^+BzOH c) i) $HC(OMe)_3, BF_3 \cdot Et_2O$; ii) LAH; iii) H^+ d) i) Li/NH_3; ii) allyl bromide; iii) CH_3Li; iv) $BF_3 \cdot Et_2O$ e) i) 9-BBN; ii) H_2O_2; iii) Jones; iv) CH_2N_2; v) CrO_3/HOAC f) i) H_2; ii) Li (O-t-Bu)$_3$HAl; iii) Ac_2O g) i) pyridium bromide, Ac_2O h) i) KOH; ii) Ac_2O i) i) oxalyl chloride; ii) CH_2N_2; iii) H_2O, SO_2 j) $Ph_3PC{=}C{=}O$ k) MCPBA

Sc

i)

OMe

omic

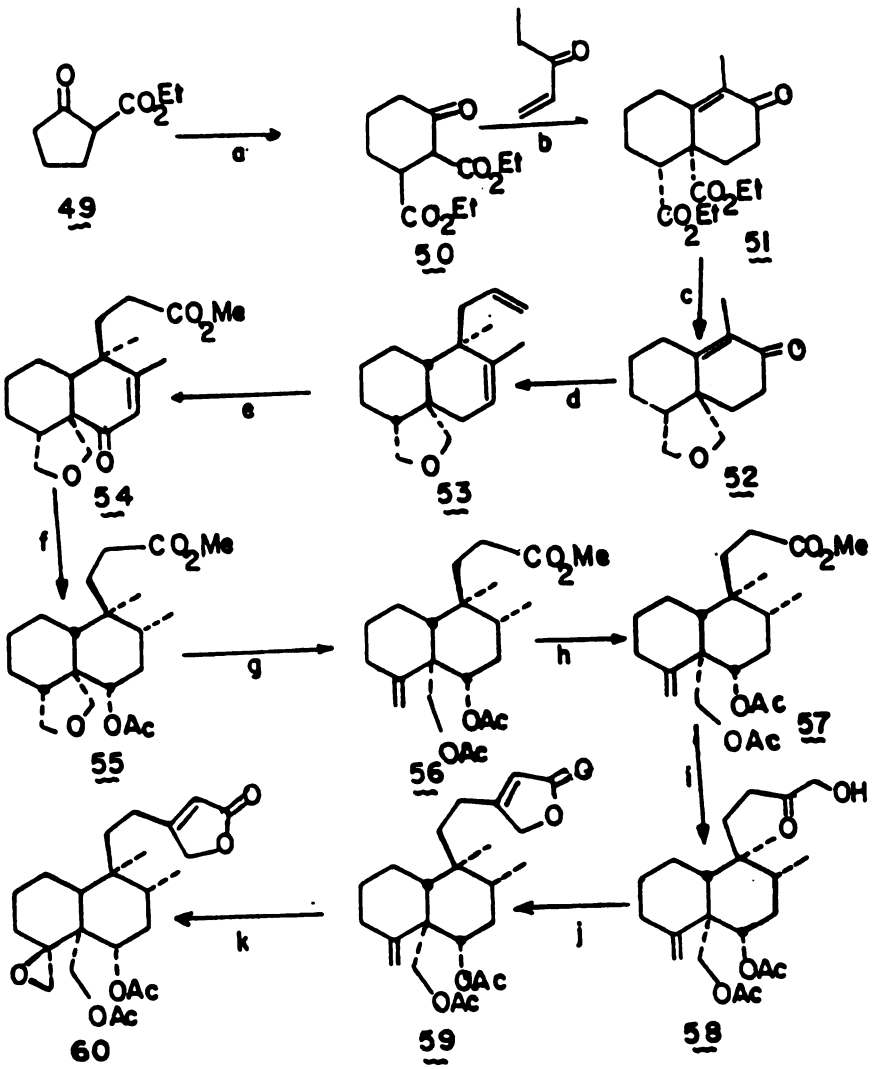
i)

Bu)3

Ac

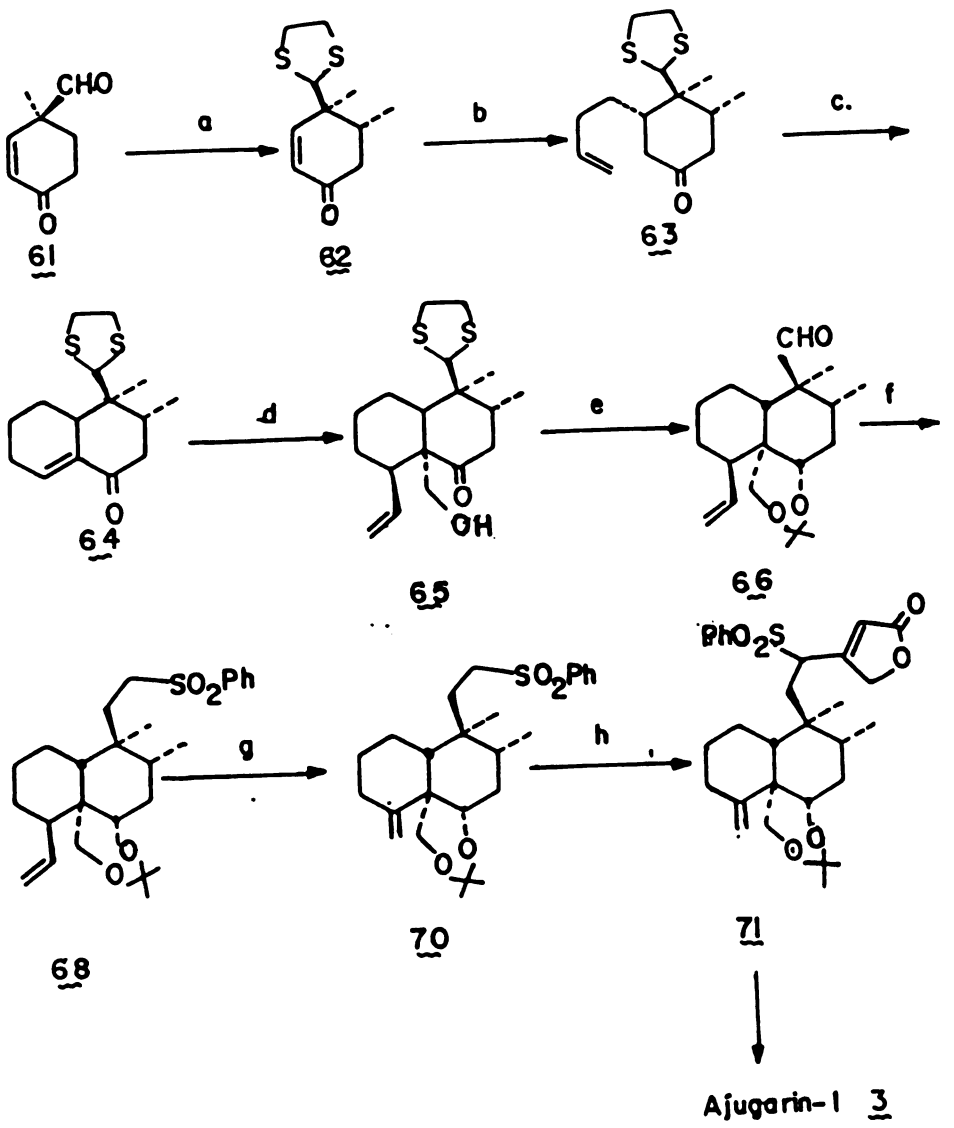
PC=

Scheme IX deGroot's Synthesis of epi-Ajugarin I 60.



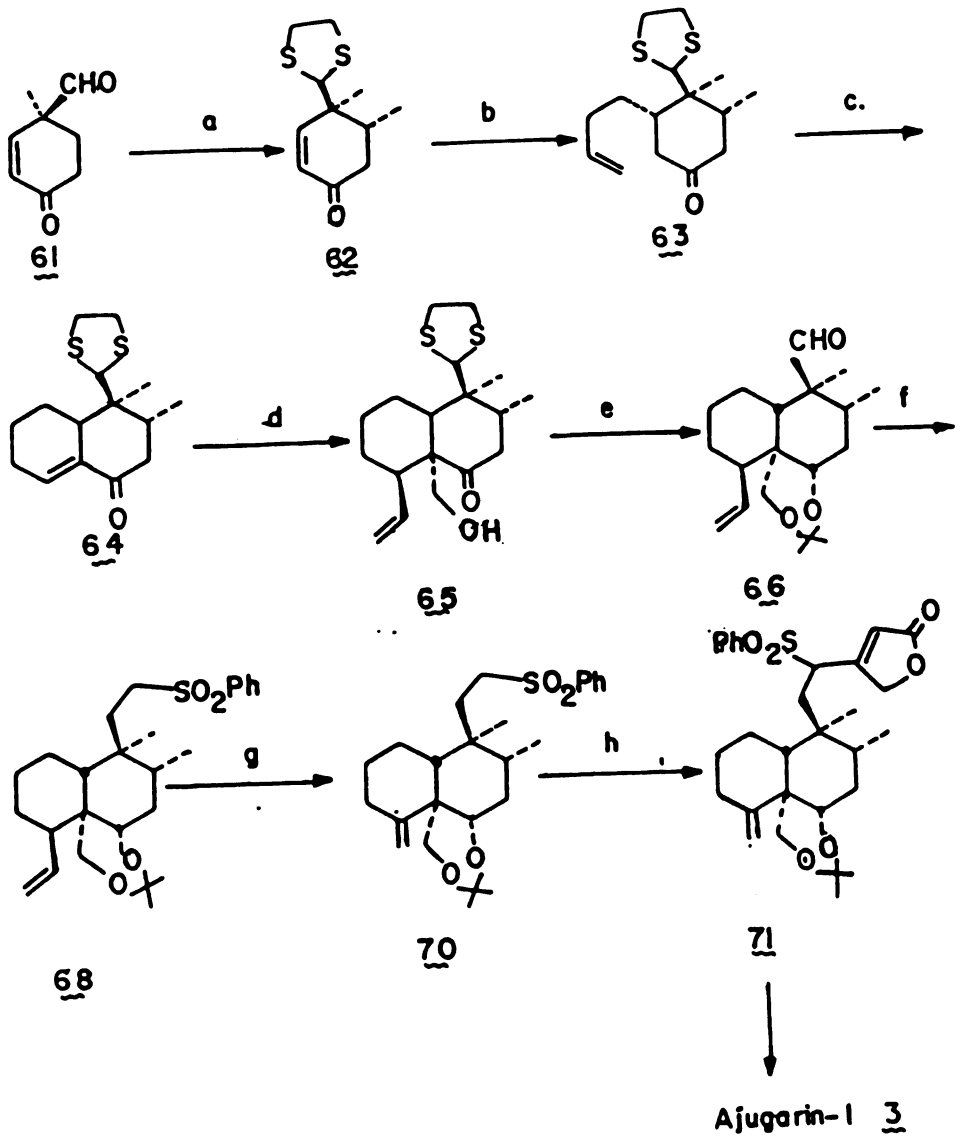
a) i) $ClCH_2CO_2Et$; ii) NaOEt; iii) Na b) Me_3N^+BzOH c) i) $HC(OMe)_3, BF_3 \cdot Et_2O$; ii) LAH; iii) H^+ d) i) Li/NH_3; ii) allyl bromide; iii) CH_3Li; iv) $BF_3 \cdot Et_2O$ e) i) 9-BBN; ii) H_2O_2; iii) Jones; iv) CH_2N_2; v) CrO_3/HOAC f) i) H_2; ii) Li (O-t-Bu)$_3$HAl; iii) Ac_2O g) i) pyridium bromide, Ac_2O h) i) KOH; ii) Ac_2O i) i) oxalyl chloride; ii) CH_2N_2; iii) H_2O, SO_2 j) $Ph_3PC{=}C{=}O$ k) MCPBA

Scheme X Ley's Total Synthesis of Ajugarin I 3. .



a) i) 1,2-ethane dithiol, H^+; ii) $CdCO_3$-HgOAc; b) (5-hexenyl)$_2$CuMgBr; c) i) $BH_3 \cdot (CH_3)_2)S$; ii) NaOH,H_2O_2; iii) py.SO_3 in camphorsulphonic acid; d) i) (vinyl)$_2$CuLi; ii) CH_2O; iii) t-Bu$(CH_3)_2$SiCl, e) LAH; iii) acetone, $CuSO_4$; iv) TI$(OCOCF_3)_3$,THF; f) i) $(Me_3SiCHSO_3Ph)Li^+$, ii) Ac_2O, pyr.DMAP, iii) Bu_4NF, iv) $LiEt_3BH$; g) i) O_3,EtOH; ii) $NaBH_4$; iii) N-phenylselenium phthalimide n-Bu_3P; iv) Et_2NH at reflux; h) i) nBuLi; ii) t-Bu$(Me)_2$Si-O-C≡C-Co_2Et, iii) Bu_4NF; I) i) Na-Hg, ii) TFA, iii) MCPBA, iv) Ac_2O

Scheme X Ley's Total Synthesis of Ajugarin I 3. .



a) i) 1,2-ethane dithiol, H^+; ii) $CdCO_3$-HgOAc; b) $(5\text{-hexenyl})_2CuMgBr$; c) i) $BH_3 \cdot (CH_3)_2S$; ii) $NaOH, H_2O_2$; iii) py.SO_3 in camphorsulphonic acid; d) i) $(vinyl)_2CuLi$; ii) CH_2O; iii) $t\text{-Bu}(CH_3)_2SiCl$, e) LAH; iii) acetone, $CuSO_4$; iv) $TI(OCOCF_3)_3$, THF; f) i) $(Me_3SiCHSO_3Ph)Li^+$, ii) Ac_2O, pyr.DMAP, iii) Bu_4NF, iv) $LiEt_3BH$; g) i) O_3, EtOH; ii) $NaBH_4$; iii) N-phenylselenium phthalimide $n\text{-}Bu_3P$; iv) Et_2NH at reflux; h) i) nBuLi; ii) $t\text{-Bu}(Me)_2Si\text{-}O\text{-}C{\equiv}C\text{-}Co_2Et$, iii) Bu_4NF; I) i) Na-Hg, ii) TFA, iii) MCPBA, iv) Ac_2O

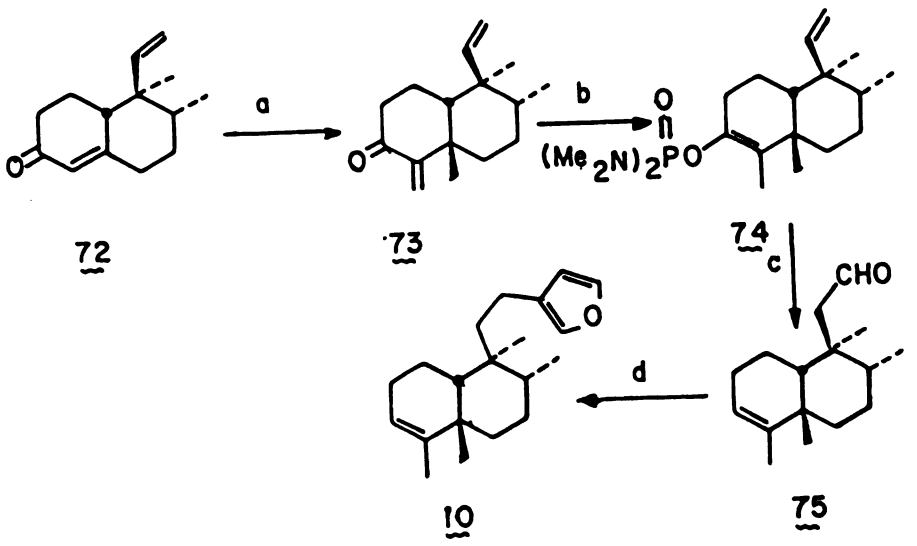
Tokorayama[13] has reported synthesis of both cis- and trans-clerodanes. The synthesis involved the stereoselective conjugate addition reactions to the appropriate enone system. The cis-clerodane synthesis, Scheme XI, started with $(CH_3)_2CuLi$ addition to enone **72** and trapping the resulting enolate with formaldehyde which led to the exo-methylene enone **73** after dehydration. Reduction of **73** with $LiB(CHEtMe)_3H$ in conjugate fashion and trapping of the resulting enolate with $(Me_2N)_2PO$-Cl according to Ireland[14] afford **74**. Removal of the phosphoramide and hydroboration and oxidation of the β-C-9-vinyl moiety gave the aldehyde **75**. The addition of 3-furyl lithium to **75** followed by acetylation and removal of the acetate group provided **10**.

The trans-clerodane annonene **9** was prepared[13] by an anologous pathway, as shown in Scheme XII.

Addition of Nagatta's[15] Et_2AlCN reagent to the enone **76** provided the trans nitrile **77**. Protection of the ketone as the corresponding ethylene ketal and hydroboration-oxidation of the C-9-β-vinyl group gave the aldehyde **78**. Addition of 3-furyl lithium acetylation and acetate removal provided **79**. Ketone reduction and dehydration, followed by nitrile reduction and oxidation to the carboxylic acid **80**, which had previously been converted to annonene **6**.

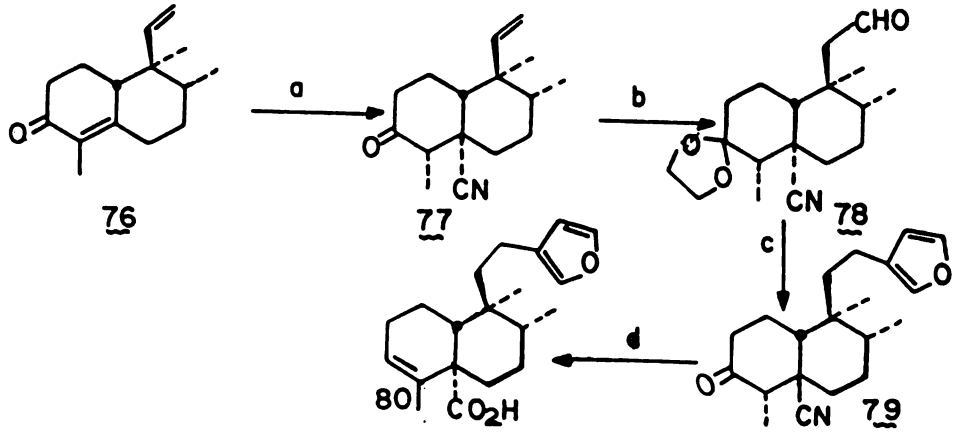
The third strategy employed in clerodane synthesis is the Diels-Alder construction. The first approach reported

Scheme XI Tokorayama's Total Synthesis of the cis-Clerodane 10 .



a) i) $(CH_3)_2CuLi$; ii) CH_2O; iii) CH_3SO_2Cl; iv) DBN b) i) $LiB(CHMeEt)_3H$; ii) $(Me_2N)_2P$-OCl c) i) B_2H_6; ii) H_2O_2,OH; iii) Li/$EtNH_2$,Bu^tOH; iv) $(COCl)_2$,DMSO d) i) 3-furyl lithium; ii) Ac_2O,pyridine; iii) Li/Liq·NH_3

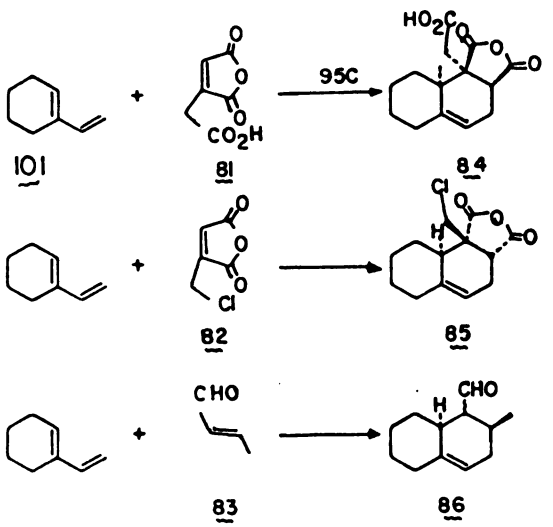
Scheme XII Tokorayama's Total Synthesis of Annonene 9 .



a) i) Et_2AlCN b) 1,2-ethane diol,H^+ c) i) B_2H_6; ii) H_2O_2,OH; iii) DMSO,$(COCl)_2$ d) i) 3-furyl lithium; ii) Ac_2O,pyridine; iii) Li/NH_3; iv) HCl,Acetone; v) Li $B(CHMeEt)_2H$; vi) $POCl_3$,pyridine e) i) Bu_2AlH_2; ii) AcOH; iii) $NaClO_2$,NaH_2PO_4

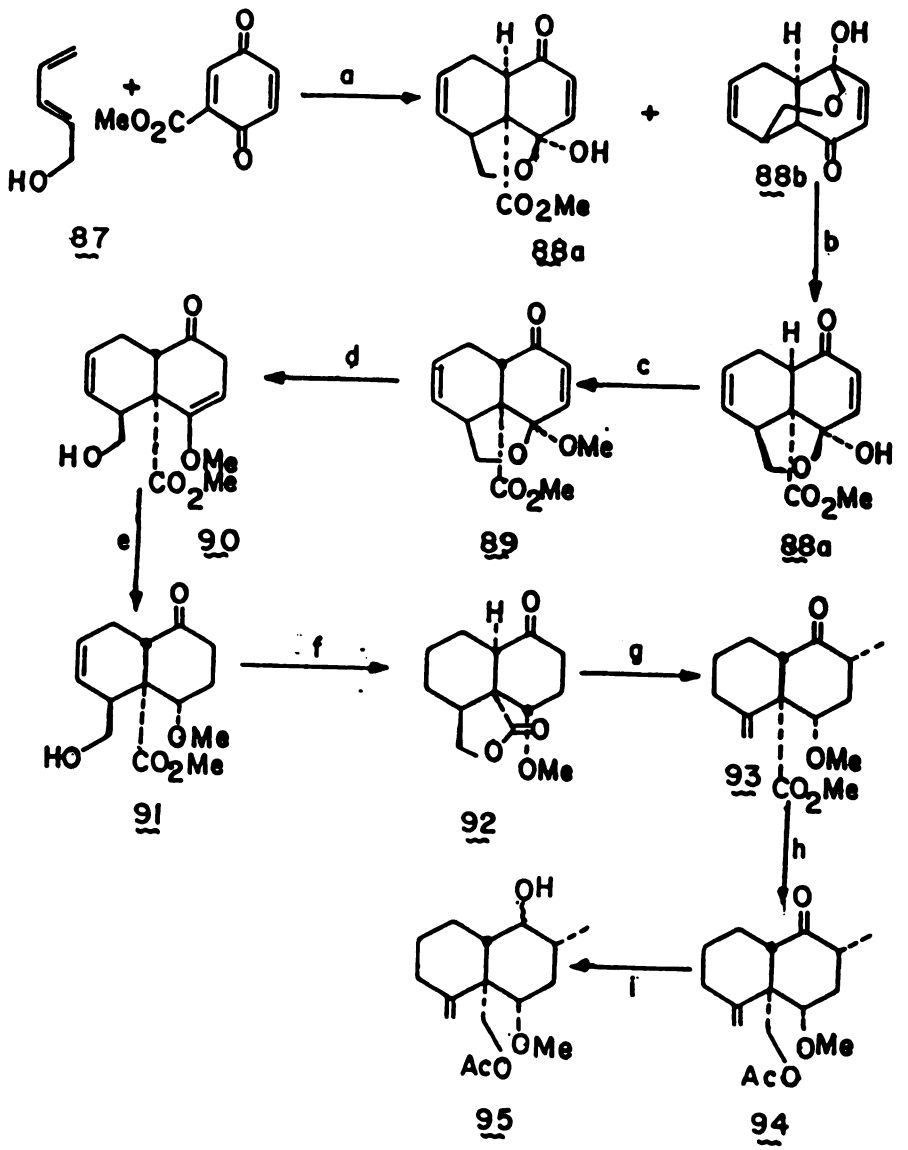
by Tokorayama[16] utilized the [4 + 2] cycloaddition of substituted maleic anhydrides such as Aconitic acid **81** and chloromethyl maleic anhydride **82** and also crotonaldehyde **83** with 1-vinylcyclohexene 101. The addition of aconitic acid **81** to 1-vinyl-cyclohexene 101 afforded the exo-product 84 (Scheme XIII). However, chloromethyl maleic anhydride and crotoraldehyde gave the expected end products **85** and **86**.

Scheme XIII Diels-Alder Reactions of 1-vinyl Cyclohexenes .



Goldsmith[16] used the [4 + 2] cycloaddition protocol in an approach to Ajugarin-I **3** (Scheme XIV). Cycloaddition of 2,4-pentadiene-1-ol **87** with 1-carbomethoxy-P-benzo quinone gave a mixture of hemiketals **88**. Ketalization, ring-junction isomerization **89** and zin-acetic acid reduction of **89** provided **90**. Acetylation, followed by catalytic hydrogenation, resulted in the production of **91**. Alkylation and lactonization of **91** provided **92**; however, during this sequence of reactions, the ring-junction hydrogen epimerized

Scheme XIV Goldsmith's Approach to Ajugarin-I via Diels-Alder Reaction .

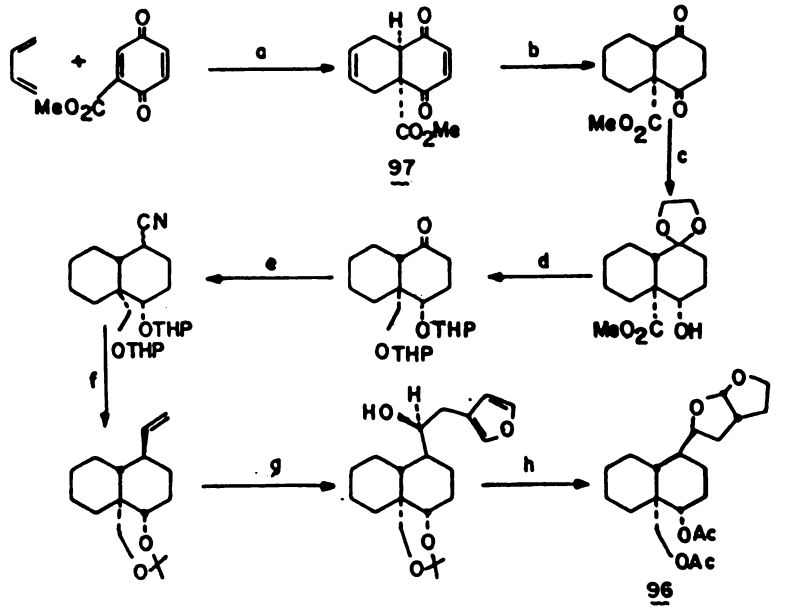


a) Mixing at room temperature in benzene b) DabCO c) H^+/CH_3OH d) Zn/HOAc e) i) Ac_2O; ii) H_2/pt. HOAC f) i) $NaOCH_3, HCO_2Me$; ii) n-BuSH; iii) H_2/Rany nickle g) i) PhSeNa; ii) CH_2N_2; iii) O_3, Et_2NH; h) i) LAH; ii) Ac_2O I) Jones oxidation

resulting in the isolation of the cis-fused **92**. The lactone moiety of **92** was opened (ϕSeNa) and the C-4-methylene group was introduced *via* selnoxide elimination to give **93**. Reduction and selective acetylation, followed by oxidation of the 2°-alcohol **94**, produced the desired intermediate **95**.

Kato and Kojima[117] synthesized a clerodin homolog **96** in 18 steps *via* the Diels-Alder adduct **97**, as shown in Scheme XV. This sequence of reactions is similar to the synthesis

Scheme XV Kato's Synthesis of a Clerodin Homolog **96**.



a) Ag_2O,$SnCl_4$ b) i) Zn,HOAC; ii) NaOMe; iii) H_2/pd/C c) 1,2-ethane diol,H^+ d) i) LAH; ii) DHP,H^+ e) TsMIC,BuOK f) i) Acetone,H^+; ii) Dibal; iii) Ph_3PCH_2 g) i) MCPBA; ii) 3-furyl lithium cuprate h) i) H^+; ii) Ac_2O

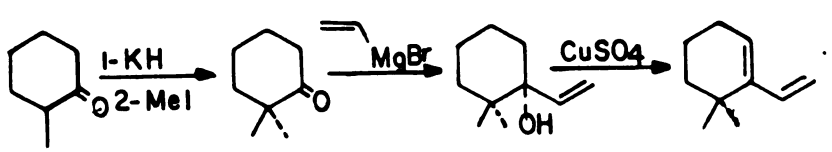
reported previously by Goldsmith and will not be discussed in detail.

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Our synthetic approach to the clerodane diterpene is outlined in Scheme I. The construction of the decalin moiety involves a Diels-Alder reaction of 1-vinyl-6,6-dimethylcyclohexene **100a** with an appropriate acetylenic dienophile, a stereoselective epoxidation of the resulting adducts and a Lewis acid catalyzed rearrangement of such epoxides that should lead to C-5-methyl migration providing substrates containing the required functionality for the decalin portion of the clerodanes.

1-vinyl-6,6-dimethylcyclohexene **100a**[18a] was readily available (Equation 2) by alkylation of 2-methyl

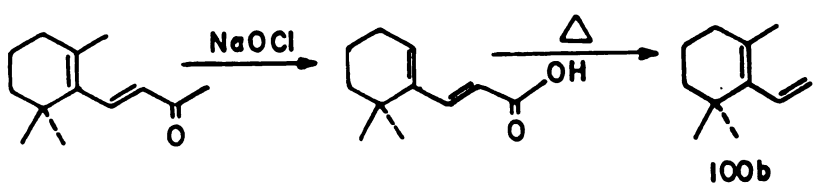


. . . . (2)

cyclohexanone **97** (RH,CH_3I) to provide 2,2-dimethyl cyclohexanone **98** (50-75%) yield after purification by preparative liquid chromatography (prep. HPLC, Waters Prep. 500, ether-hexane, 2:98, 300 mL/min) followed by vinyl magnesium bromide (1.5M) addition to **98** providing 1-vinyl-

2,2-dimethyl-cyclohexanol **99**, 72% yield (BP_{13} 80-85°C). Dehydration was smoothly accomplished with $CuSO_4.5H_2O$[19] (1 equiv.) in refluxing benzene (2 hrs.) with azeotropic removal of water, a modification of the procedure of Ley to provide 1-vinyl-6,6-dimethyl cyclohexene **100a** in 85% yield, (BP_{11} 50-51°C).

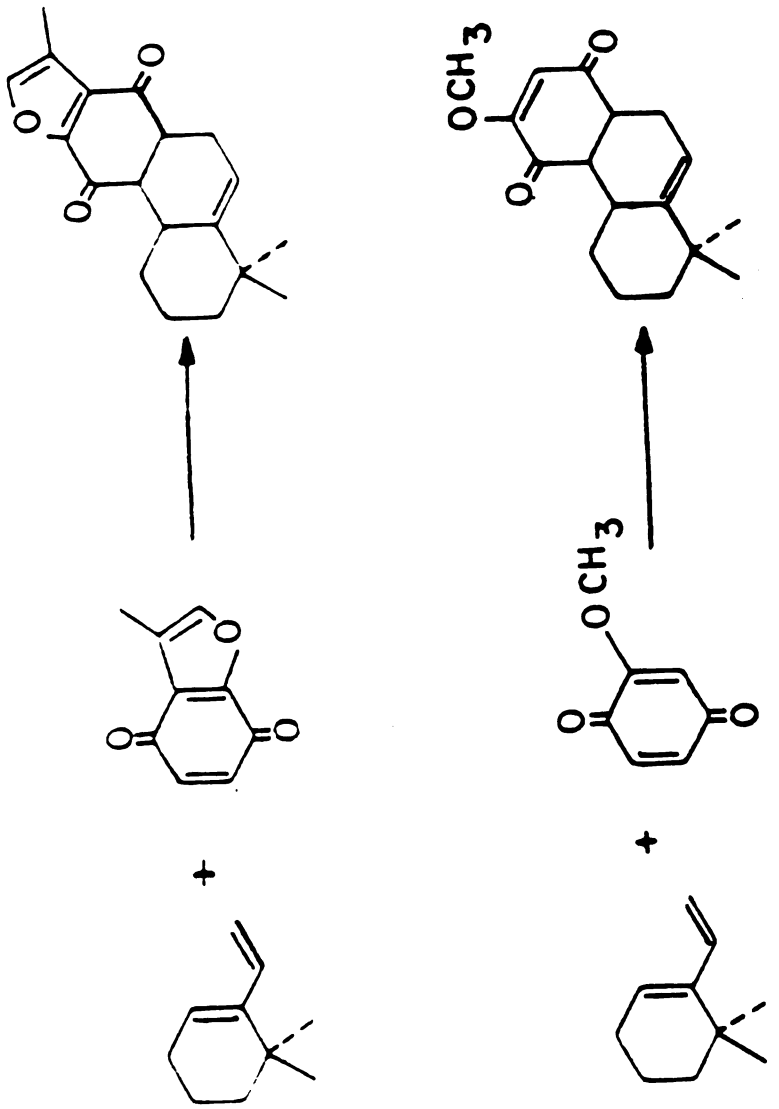
Another diene, 1-vinyl-2,6,6-trimethyl cyclohexene[19] **100b** will be required in order to investigate the generality of the rearrangement protocol and this was available by oxidation of β-ionone with sodium hypochloride 5.5% solution followed by decarboxylation by heating in quinoline as shown in Equation 3.[18b]



(3)

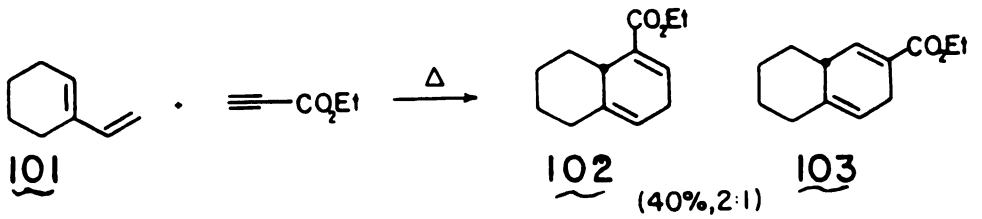
Diels-Alder Reactions.[20]

Inspection of the literature for the Diels-Alder reaction of 1-vinyl-6,6-dimethylcyclohexene **100a** provided only two examples with nonsymmetrical dienophiles,[18] the [4 + 2] cycloaddition with 2-methoxy benzoquinone and 3-methylbenzofuran-4,7-quinone, illustrated in Scheme XVI. These reactions were examined as part of the syntheses of Tanshinone II, Tanshinone III and cryptotanshinone, respectively. Both reaction, with ethylenic dienophiles,



Scheme XVI Diels-Alder Reactions of 6,6-dimethyl-1-vinyl cyclohexenes.

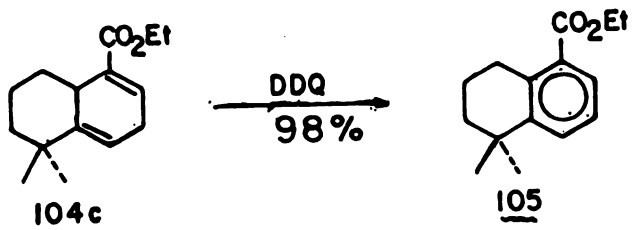
provide excellent regiochemical control (1-isomer), but the low yields obtained (40-50%) were a cause for concern. The related 1-vinylcyclohexene **101** has been studied much more extremely as a partner in the Diels-Alder reaction. We were dismayed to discover a recent report by Markgraf[21] (Equation 4) which indicated that 1-vinylcyclohexene **101** and ethyl



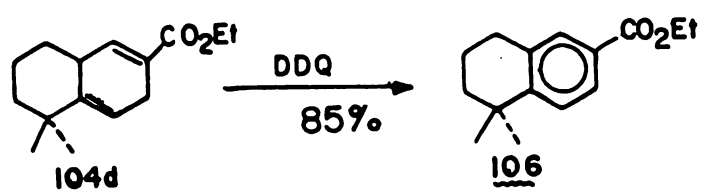
101 **102** (40%, 2:1) **103** (4)

propiolate provided a 2:1 mixture of the ortho:meta products, **102** and **103**, in but 40% yield. This stands in stark contrast to selectivities reported in an earlier report by Anachenko[22] where the reaction of **101** with propiolic acid was claimed to provide a 10:1 ratio of ortho-meta adducts. However, closer inspection of the primary literature suggests that ortho to meta ratios are much closer to those of Markgraf which were obtained as the bulk in the reaction mixture and was reported as a "mixture". Despite the low selectivity observed in the Diels-Alder reaction of 1-vinylcyclohexene with acetylenic dienophiles, we examined the [4 + 2] cycloaddition of the dienes **100a** and **100b** with a group of acetylenic dienophiles or equivalents and studied the regioselectivities.[20] The results are contained in Table I. Diene **100a** reacted exothermally with dimethyl acetylenedicarboxylate and provided **104a** in 95%

yield. The more encumbered diene **100b** reacted sluggishly with dimethyl acetylenedicarboxylate at 120°C to afford the adduct **104b** in 87% yield. Excessive heating (>120°C) causes aromatization of ring B of **104b**. The less reactive unsymmetrical dienophile, ethylpropiolate, reacted with diene **100a** at 110°C to provide the ortho:meta adducts **104c**:**104d** in a 3:1 ratio; the selectivity of this reaction rose to 6:1 (80%) when the reaction temperature was lowered to 50°C. The ratio of the adducts **104c**:104d was determined on the basis of ^{1}H-NMR (250 MHz), high-pressure liquid chromatography (HPLC) and capillary gas chromatographic (GC) analysis. The identity of the adducts **104c** and **104d** was determined by separations on prep. HPLC eluted with ether:hexane, 2:98. The pure regioisomers, **104c** and **104d**, were each separately aromatized by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide **105** and **106**, Equations 5 and 6. Compound **105** exhibited the

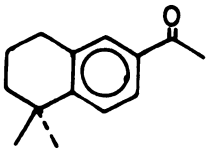


(5)



(6)

following resonances in ^{1}H-NMR (250 MHz) δ = 7.56 (dd, J=7.5,1.25Hz, 1H), 7.49 (dd, J=7.5,1.25Hz, 1H), 7.18 (t, J=7.5Hz, 1H); while **106** exhibited the following signals: δ = 7.83 (d, J=8.3Hz, 1H), 7.73 (br s, 1H), 7.36 (d, J=8.3Hz, 1H). A comparison of these spectral data with the ^{1}H-NMR spectrum of **107**[23], ^{1}H-NMR, δ = 7.56 (br s, 1H), 7.62 (d,

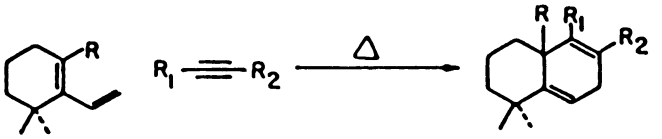


107

complex, J=8Hz, 1H), 7.3 (d, J=8Hz, 1H), indicates that, as expected, the assignment of the regiochemistry is correct.

The reaction of **100b** with ethyl propiolate was slow at 120°C; however, the adducts **104e** and **104f** were obtained in 55% yield and in a 5:1 ratio. Methyl tetrolate reacted slowly at elevated temperature (150°C) in a sealed stainless steel reaction vessel with diene **100a** to provide a 65% yield of the adducts **104g** and **104h** in a 9:1 ratio after 36 hours. Methyl tetrolate failed to react at all with diene **100b**; and increasing the temperature of the reaction above 150°C, resulted in destruction of the starting materials and/or products. Furthermore, attempted Lewis acid catalysis[24] of the reaction of methyltetrolate with diene **100b** was fruitless. Strong Lewis acids like $BF_3 \cdot Et_2O$ resulted in instantaneous diene polymerization even at low temperatures,

Table I Diels - Alder Reactions of 100 a,b With Acetylenic Dienophiles

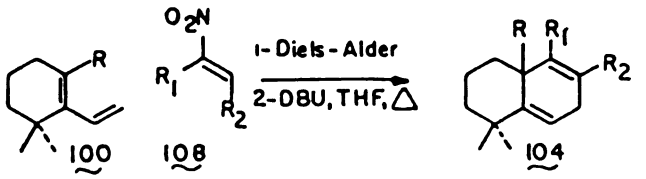


100 a R=H
b R=Me

104

Entry	Diene	R	R_1	R_2	T(C)	Yield	Adduct(ortho/meta)
1	100a	H	CO_2Me	CO_2Me	RT	95%	104a (—)
2	100b	Me	CO_2Me	CO_2Me	120	87%	104b (—)
3	100a	H	CO_2Et	H	50	80%	104c (6/1)
		H	H	CO_2Et			104d
4	100b	Me	CO_2Et	H	120	55%	104e (5/1)
		Me	H	CO_2Et			104f
5	100a	H	CO_2Me	Me	150	65%	104g (9/1)
		H	Me	CO_2Me			104h

Table II. Diels-Alder Reactions of 100a,b with β - Nitro-Esters 108



100 108 104

Entry	Diene	R	R	R	T(C)	Yield	104(Ortho/meta)
1	100a	H	CO_2Et	H	RT	78%	104c/104d(0/100)
2	100b	Me	CO_2Et	H	110	66%	104e/104f(0/100)
3	100a	H	CO_2Et	Me	RT	57%	104g/104i(0/100)

while the more moderate Lewis acids, $EtAlCl_2$ and Et_2AlCl, were ineffective. Other Lewis acids which were reported by Roush to be effective in catalyzing the intramolecular Diels-Alder[24] reaction, $NbCl_5$, WCl_5, $MoC(O)_5$ and ZnI_2, were unsuccessful in this case.

Regio-reversed Diels-Alder Reaction.

Danishefsky[25] has demonstrated that β-nitro conjugated esters can be used in Diels-Alder reactions to provide regio-reversed products,[25] because the nitro group usually predominates over an ester group and directs the cycloaddition. These β-nitro-α,β-unsaturated esters are acetylenic dienophile equivalents providing α,β-unsaturated esters as products after elimination of the elements of nitrous acid. We examined the reactions of β-nitroacrylate **108a** and β-nitrocrotonate **108b** with dienes **100a** and **100b** and the results are tabulated in Table II. These dienophiles were quite reactive, readily providing [4 + 2] adducts in accord with the observations of Danishefsky.

(E)-Ethyl-β-nitroacrylate **108a** was reacted with **100a** at room temperature to provide a mixture of the endo- and exo-adducts in 91% yield. The mixture was treated with 1,8-diazabicyclo[5.4.0]undecane (DBU) in refluxing benzene to provide **104d** in 100% regioselectivity and 78% overall yield. The corresponding (E)-Ethyl-β-nitrocrotonate **108b** reacted with diene **100a** slowly at room temperature (12 hrs.) and provided the Diels-Alder adduct, which, after nitrous acid

elimination, provided **104i** as the sole regioisomer in 57% overall yield.

The less-reactive diene **100b** reacted with β-nitroacrylate **109a** at 110°C (12 hrs.) and provided **104i** after treatment with DBU in 71% overall yield. The more hindered dienophile, (E)-Ethyl-β-nitrocrotonate, did not react with diene **100b** even at high temperature, 150°C; and increasing the temperature above 150°C resulted in destruction of the starting materials and/or products.

The marked increase in yield and regioselectivity observed in the reactions of dienes **100a** and **100b** with acetylenic dienophiles is noteworthy. The presence of the geminal dimethyl substituents at C-6 of **100a** and **100b** is the major deviation from the previous studies of 1-vinyl-cyclohexe **101** with acetylenic dienophiles. As is well known,[26] the barrier for the conformational interconversion in simple dienes is low (<6kcal/mole); and, in the absence of the steric hindrance effects, the s-trans conformer is more stable than the s-cis or s-skew conformer by ca. 2.1 kcal/mole.[26] Reusch[27] has recently examined the UV absorption of diene **100a** and 1-vinylcyclohexane **101** and has concluded that **100a** appears to chiefly assume the s-cis (or s-skew) conformation and 1-vinylcyclohexene **101** exhibits an apparent s-trans-s-cis equilibrium. This factor will likely facilitate the [4 + 2] cycloaddition reaction for **100a,b** relative to the vinyl cyclohexene. Thus, the adducts **104**

are available for a study of the stereoselectivity of the epoxidation sequence and subsequent epoxide rearrangement.

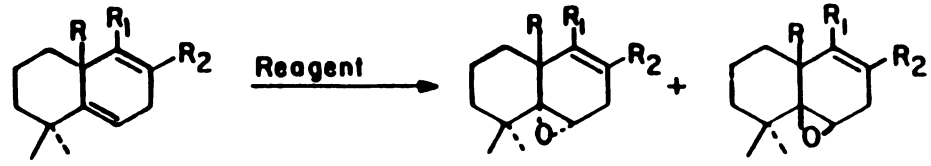
Epoxidation of Hexahydronaphthalenes **104**.

We investigated[28] the epoxidation stereochemistry of the hexahydronaphthalene **104** available from the Diels-Alder reactions (vide supra). The epoxidizing reagents employed were: a) m-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 and b) N-bromosuccinimide (NBS) in aqueous t-butanol (1:2, H_2O:t-BuOH). The epoxidation results, ratios of isomers and yields, are reported in Table III.

Epoxidation of ethyl-5,5-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate **104c** with MCPBA (0°, CH_2Cl_2, 1 hr.) gave a mixture of the α-epoxide **109c** and the β-epoxide **110c**; (**109c**:**110c** = 1:9) in 82% total yield. The ratio of these epoxides was determined by HPLC (10u) silica; ether:hexane; 1:4), gas chromatography (GC, carbowax column), and ^{1}H-NMR (250 MHz). The stereochemistry of these epoxides was determined using ^{1}H-NMR techniques (decoupling and shift reagent studies).

Compound **110c** exhibited the following resonances in ^{1}H-NMR spectrum 6.67 (m, 1H), 3.32 (br s, 1H), 3.22 (d m, J=12.2Hz, 1H), 2.75 (d m, J=20Hz, 1H), 2.59 (d m, J=20Hz), 2.10 (d m, J=12.2Hz). The decoupling results, illustrated in Figure 2b to 2g, are as follows: Irradiation at δ = 6.67 resulted in simplification and collapse of the signals at

Table III Epoxidation of 104 with m-chloroperbenzoic acid (MCPBA) and N-Bromosuccinimide (NBS) in aqueous t-BuOH.



104 109 110

Entry	Compound	R	R	R	Reagent	Yield%	Ratio(109/110)
1	104a	H	CO_2Me	CO_2Me	MCPBA	95	45: 55
2	104b	Me	CO_2Me	CO_2Me	MCPBA	87	95: 5
3	104c	H	CO_2Et	H	MCPBA	82	10: 90
	104c	H	CO_2Et	H	NBS, aq. ^{t}BuOH	94	100: 0
4	104d	H	H	CO_2Et	MCPBA	77	33: 67
	104d	H	H	CO_2Et	NBS, aq. ^{t}BuOH	60	85: 15
5	104e	Me	CO_2Et	H	MCPBA	81	95: 5
6	104f	Me	H	CO_2Et	MCPBA	90	95: 5
7	104g	H	CO_2Me	Me	MCPBA	78	11 : 89
	104g	H	CO_2Me	Me	NBS, aq. ^{t}BuOH	54	100: 0

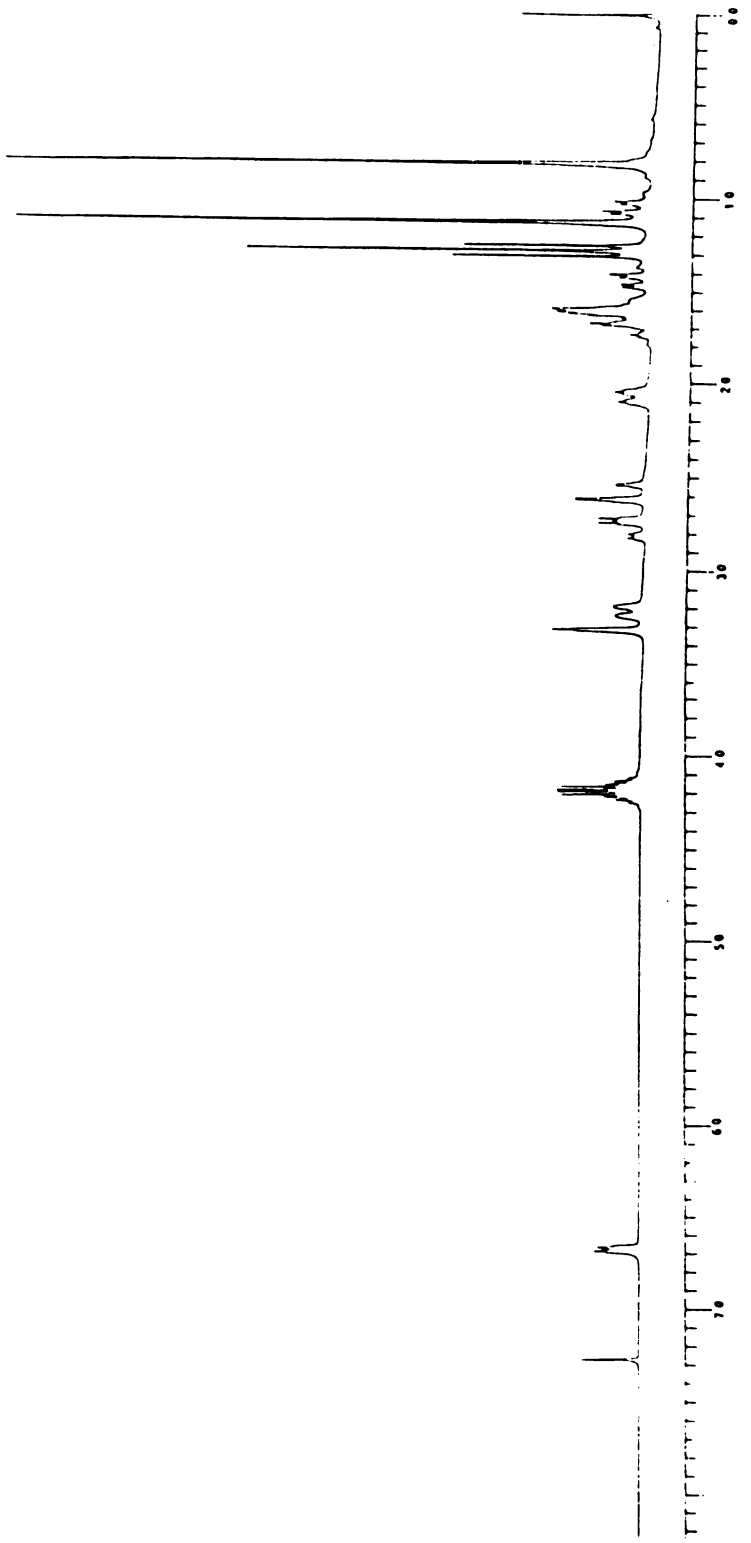


Figure 2a ^{1}H-NMR (250 MHz) Spectrum of 110c

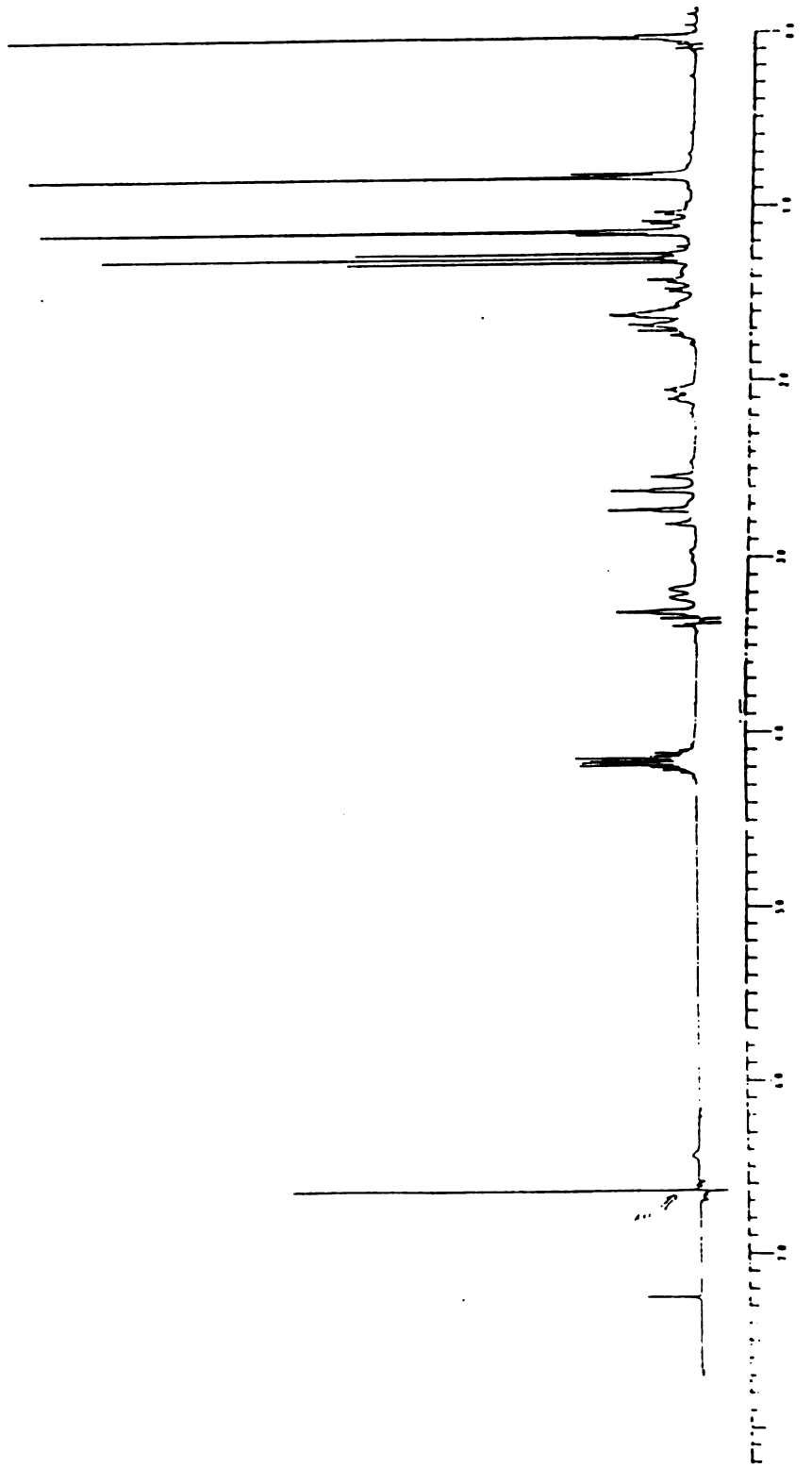


Figure 2b ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 6.67 ppm

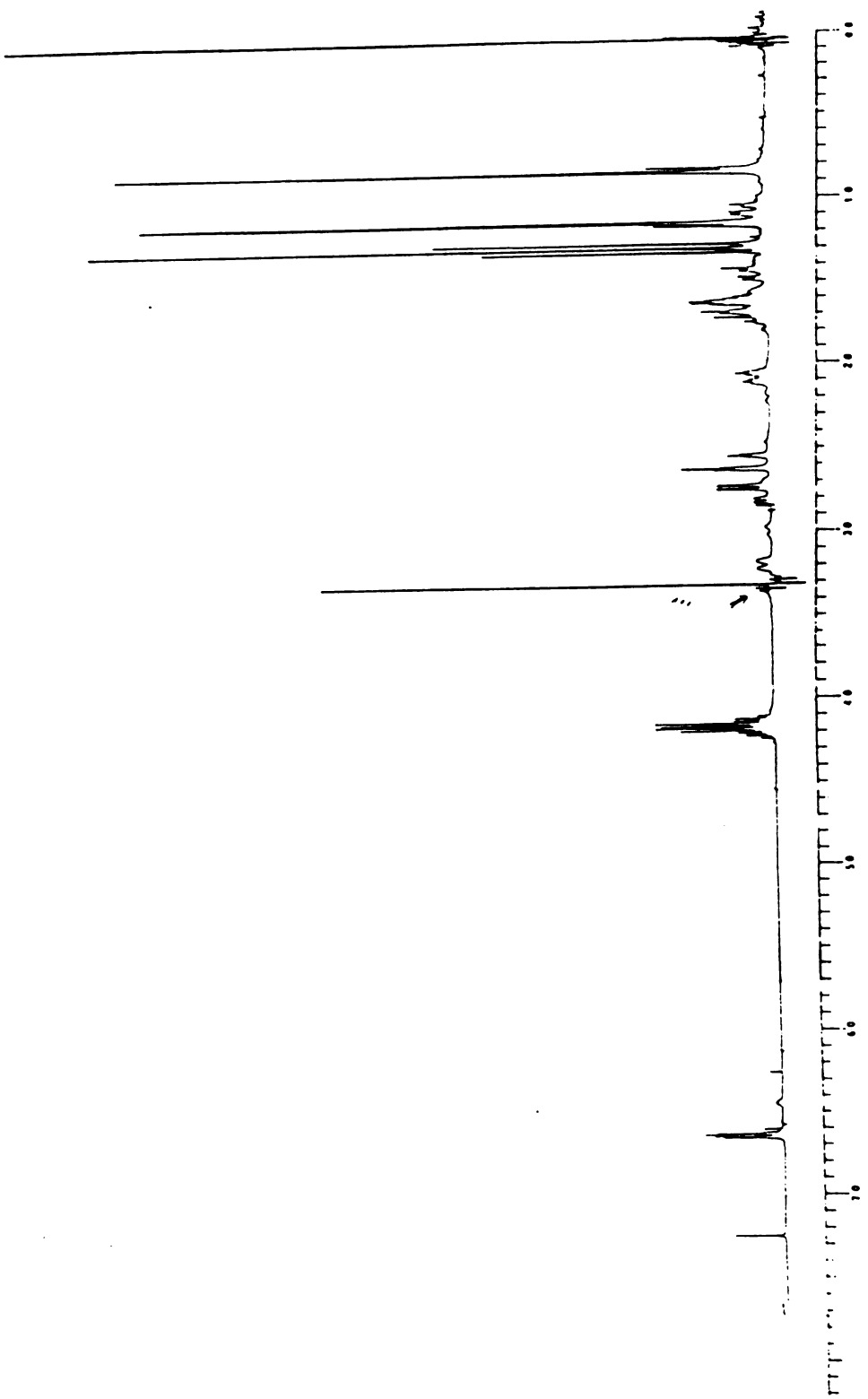


Figure 2c ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 3.32 ppm

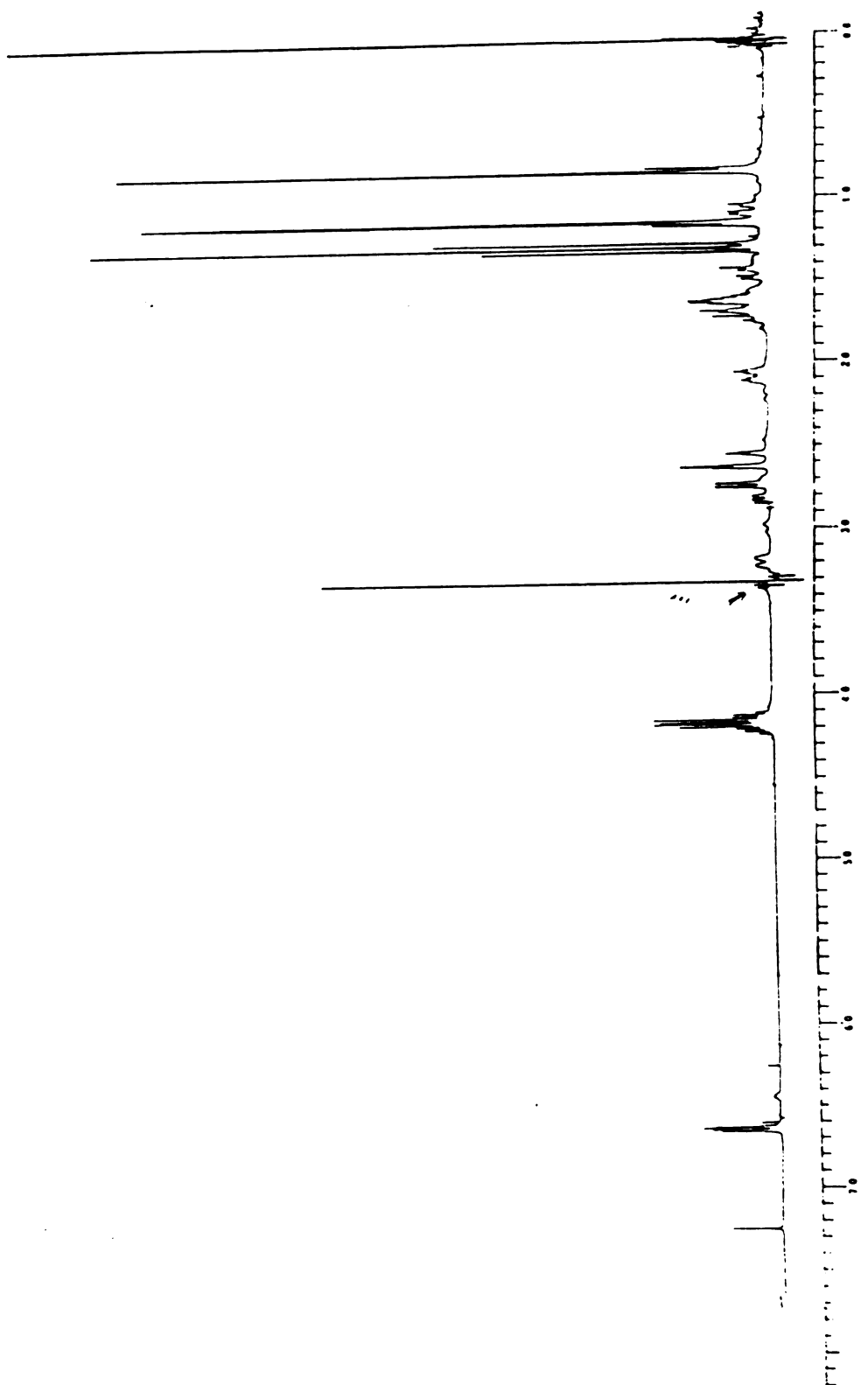


Figure 2c ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 3.32 ppm

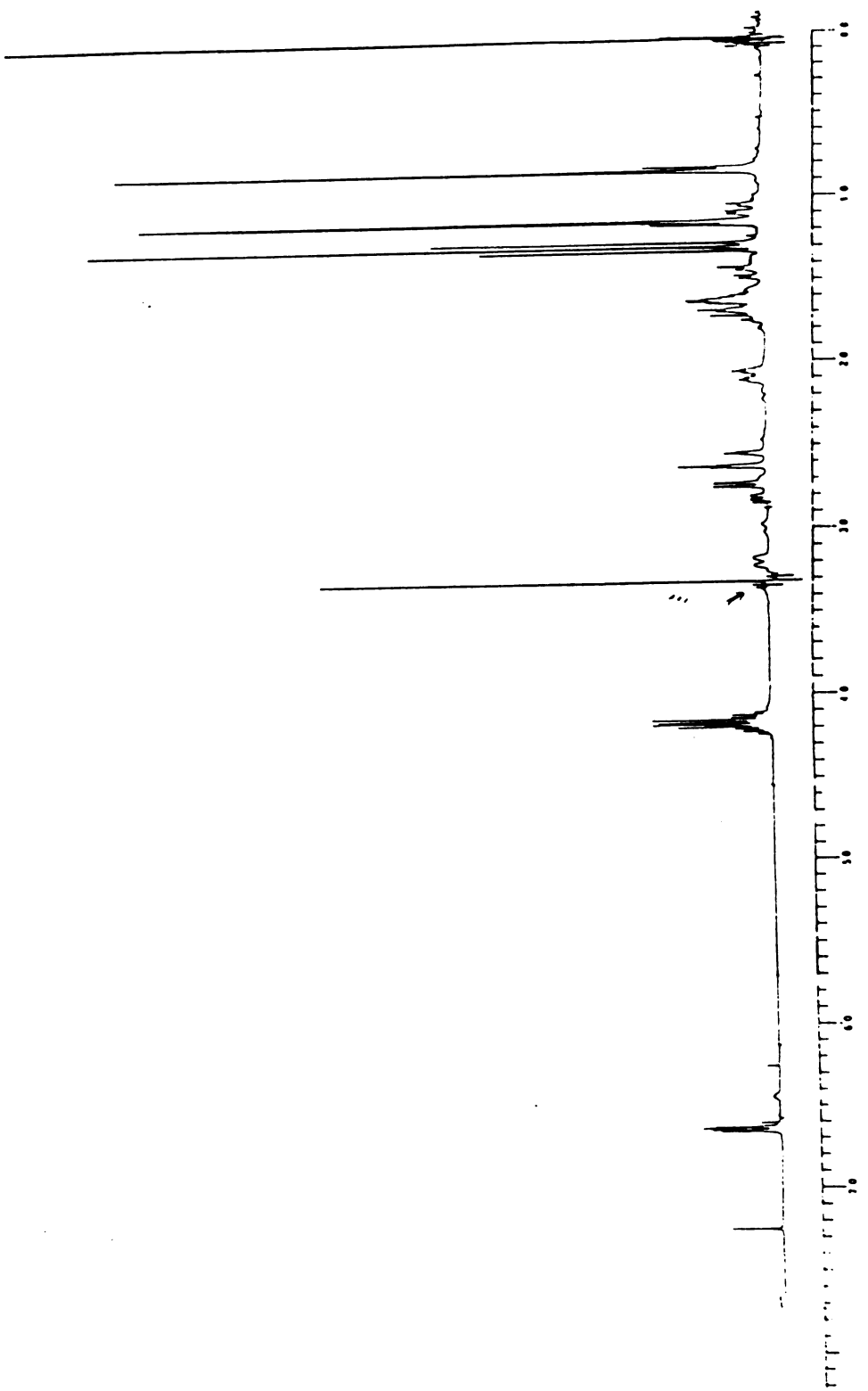


Figure 2c ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 3.32 ppm

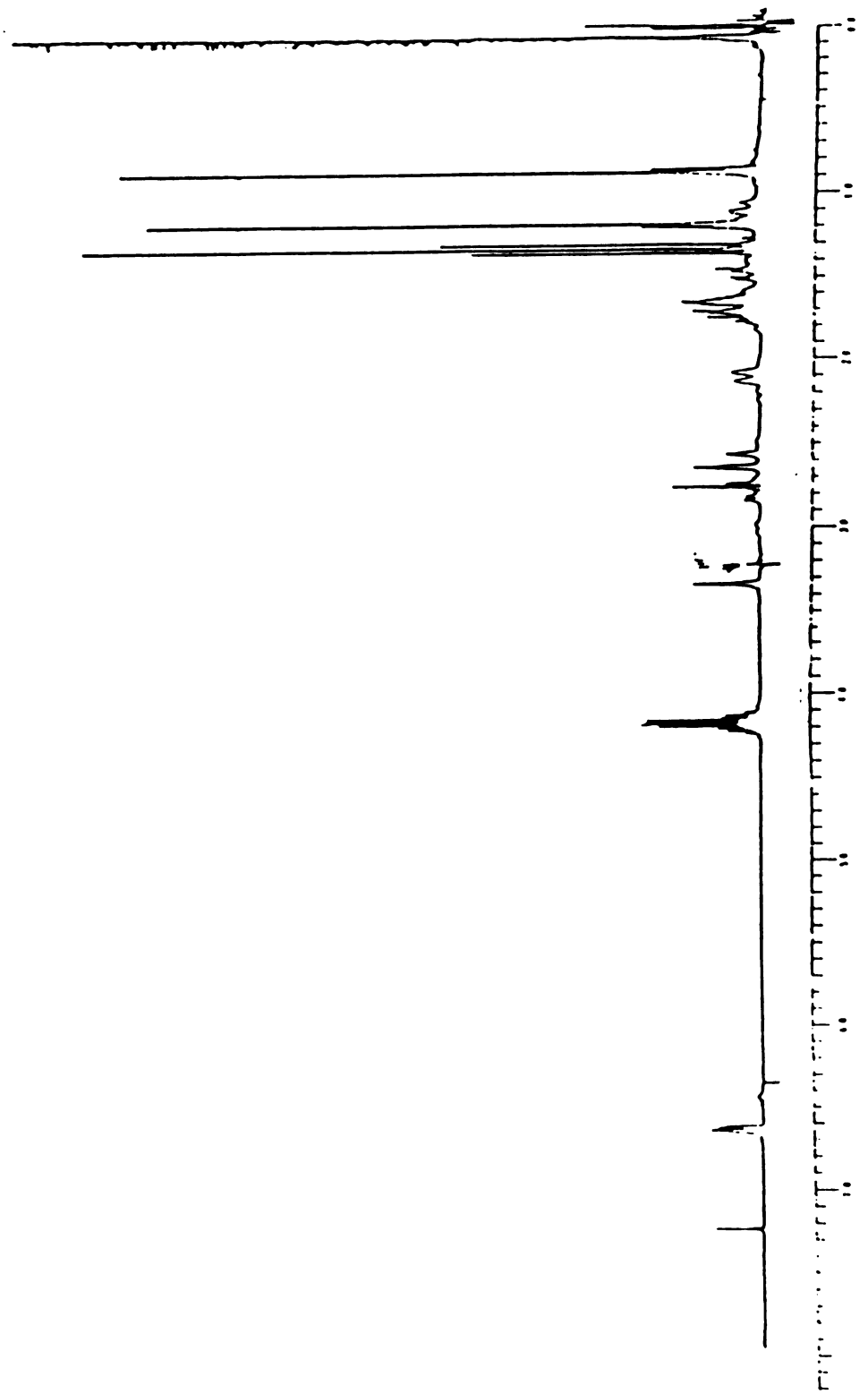


Figure 2d ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 3.22 ppm

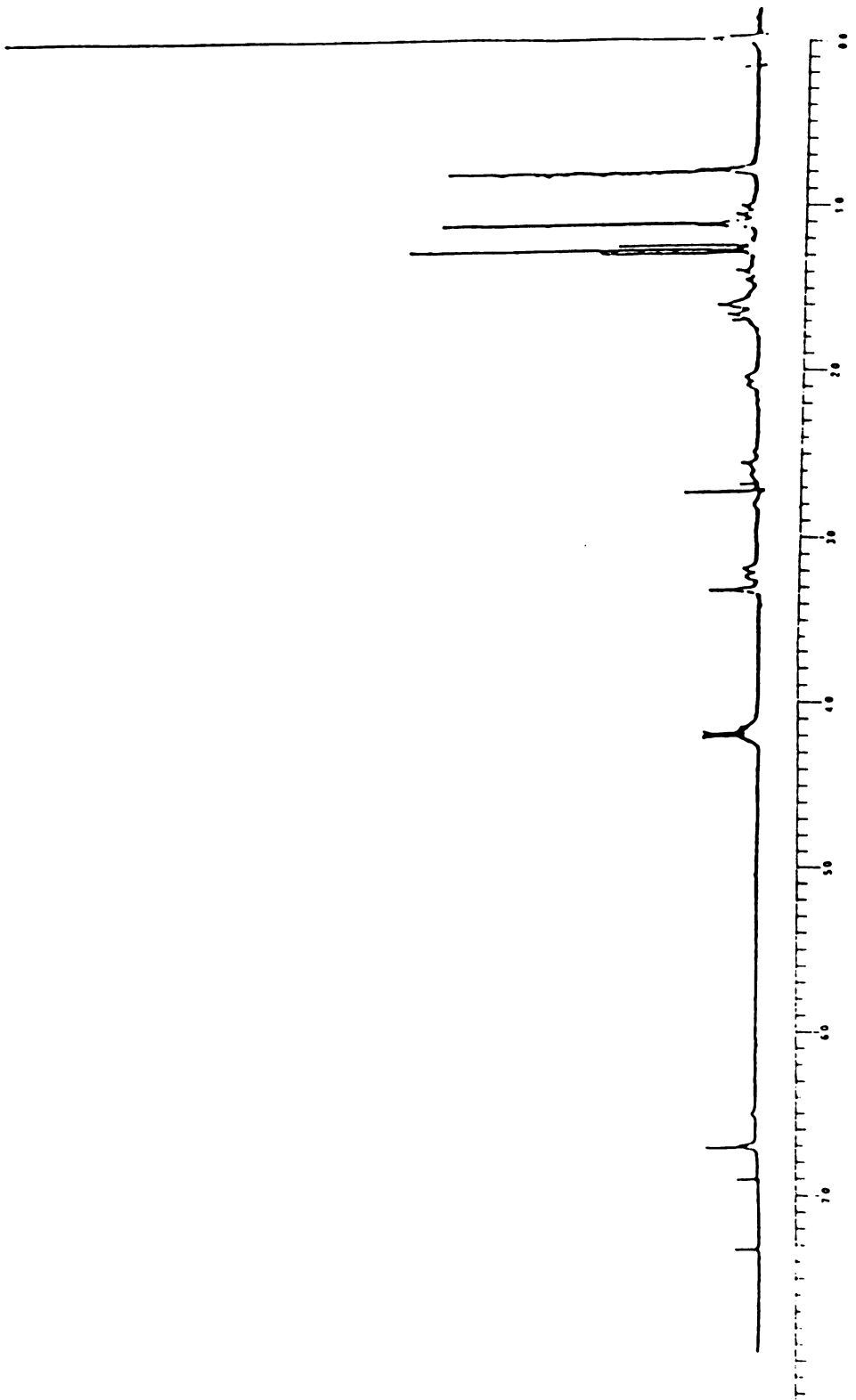


Figure 2e ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 2.76 ppm

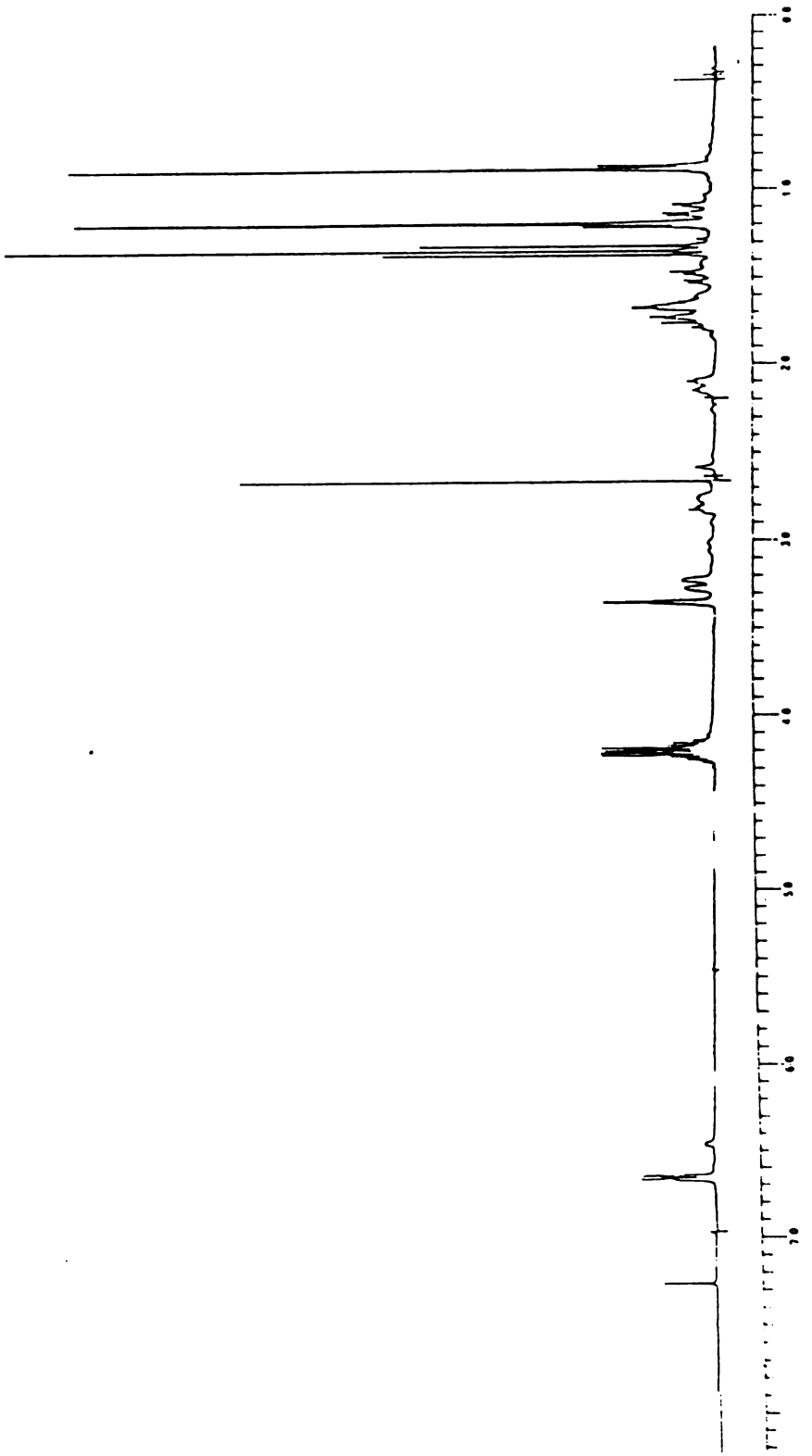


Figure 2f ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 2.59 ppm

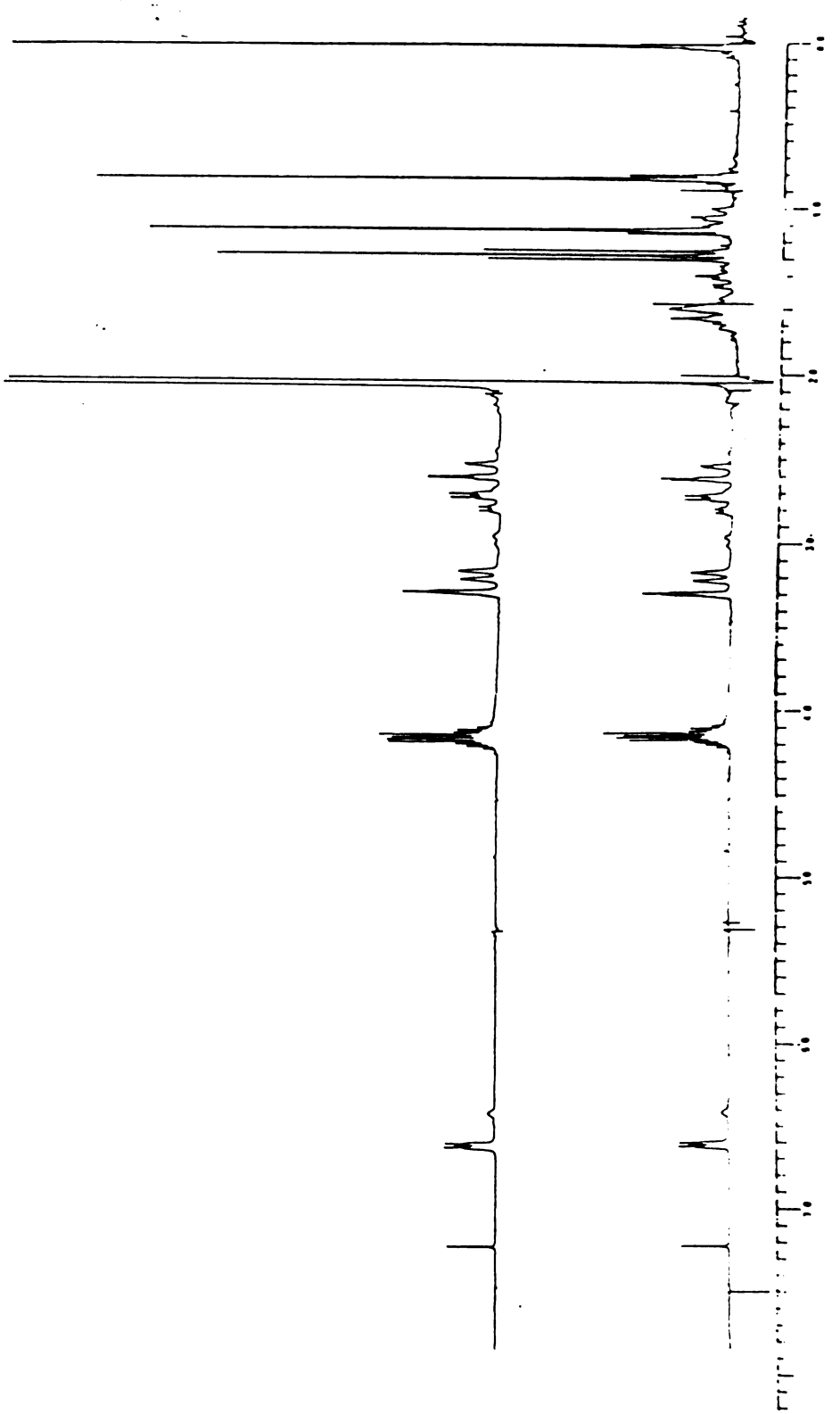


Figure 2g ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 2.10 ppm

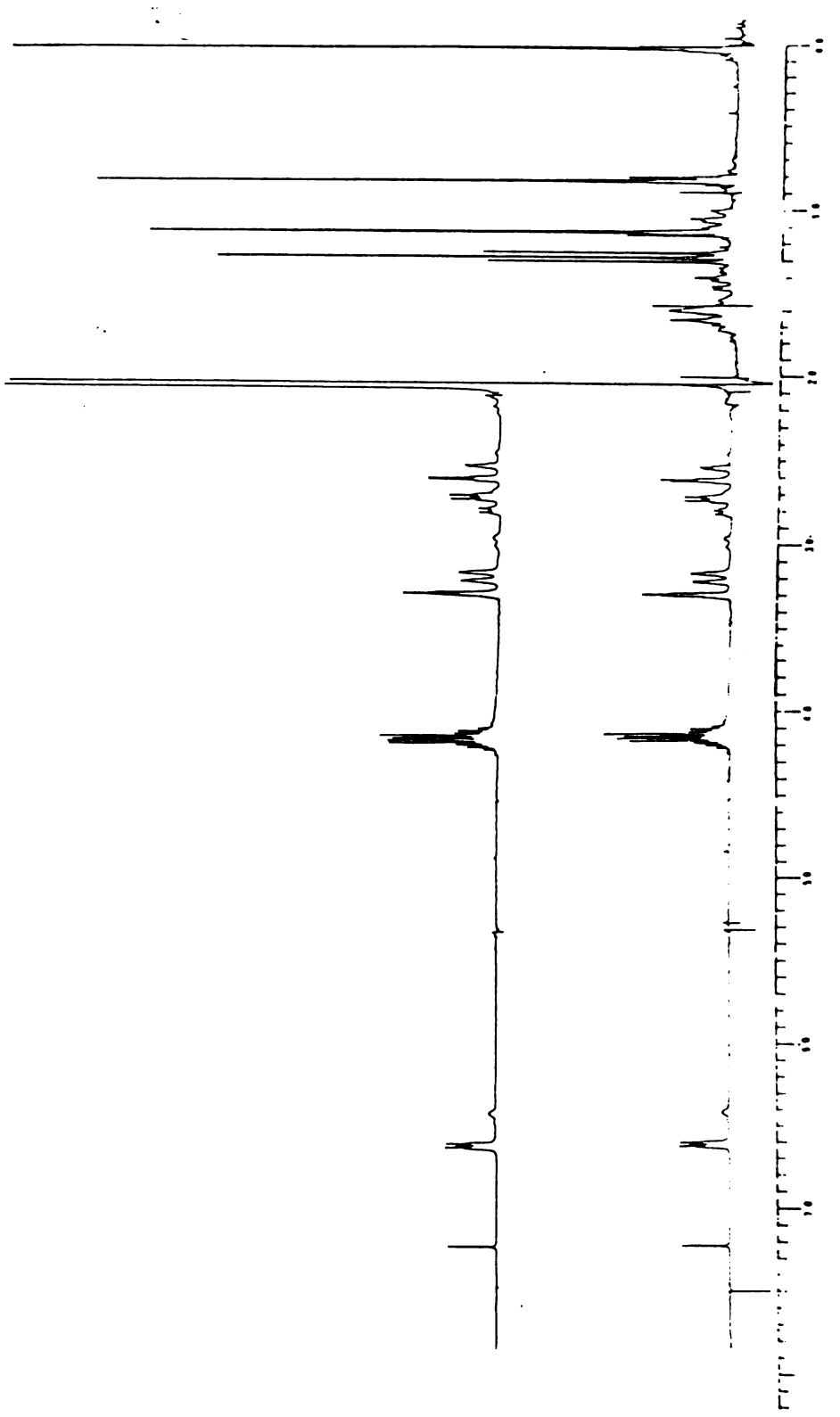


Figure 2g ^{1}H-NMR (250 MHz) Spectrum of 110c with Irradiation at δ = 2.10 ppm

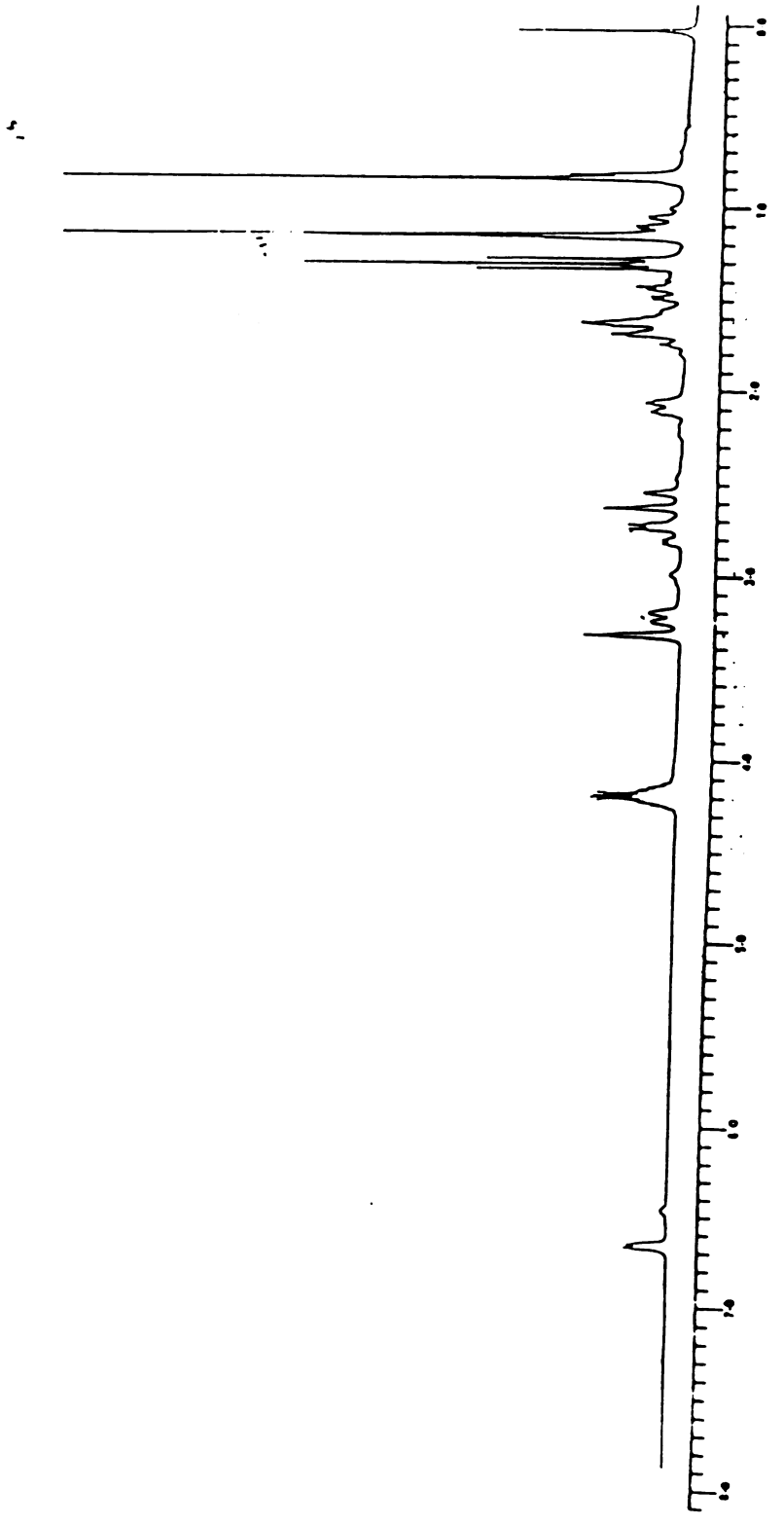


Figure 3a ^{1}H-NMR (250 MHz) Spectrum of 110c with the First Addition of Eu(fod)$_3$.

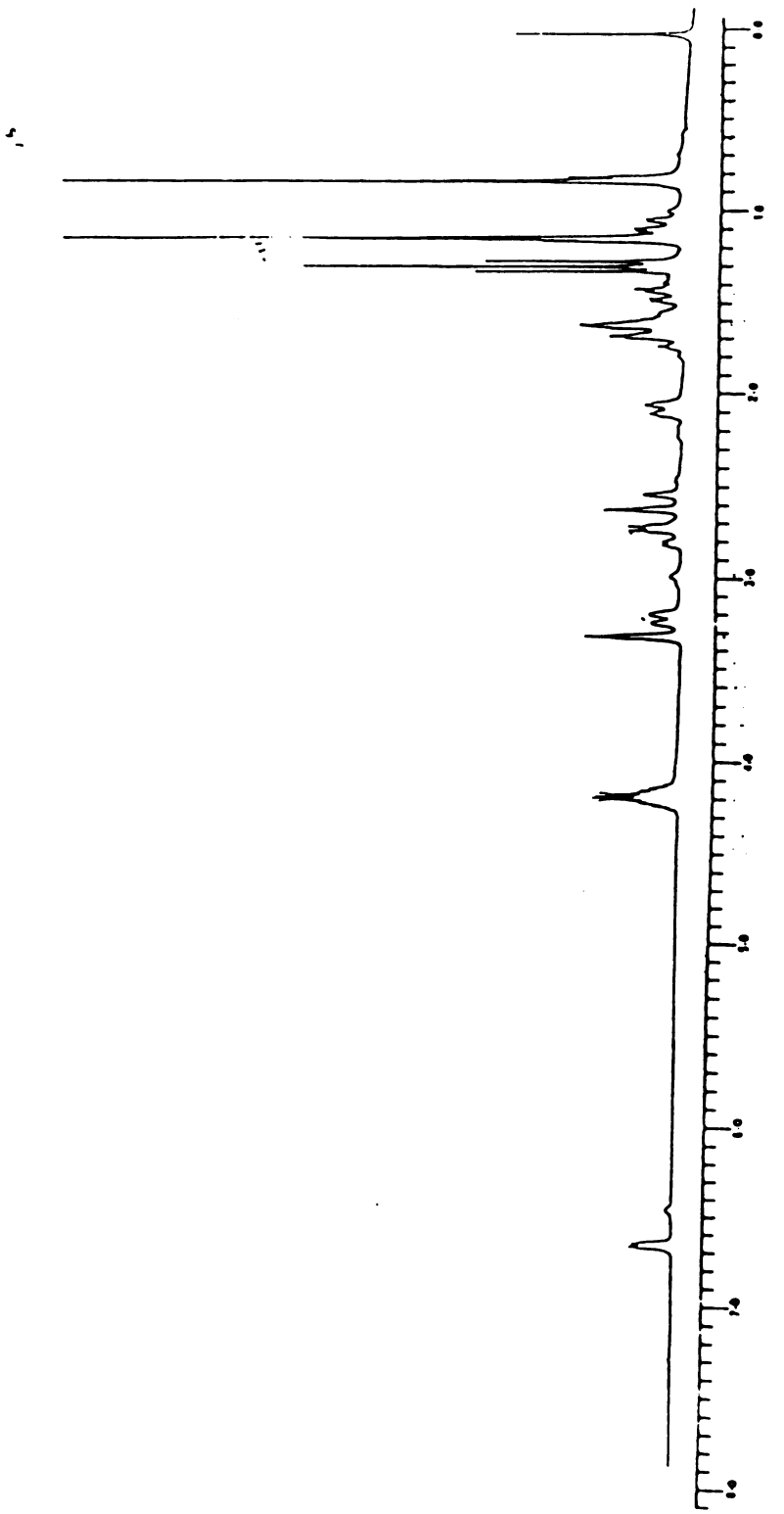


Figure 3a ^{1}H-NMR (250 MHz) Spectrum of 110c with the First Addition of Eu(fod)$_3$.

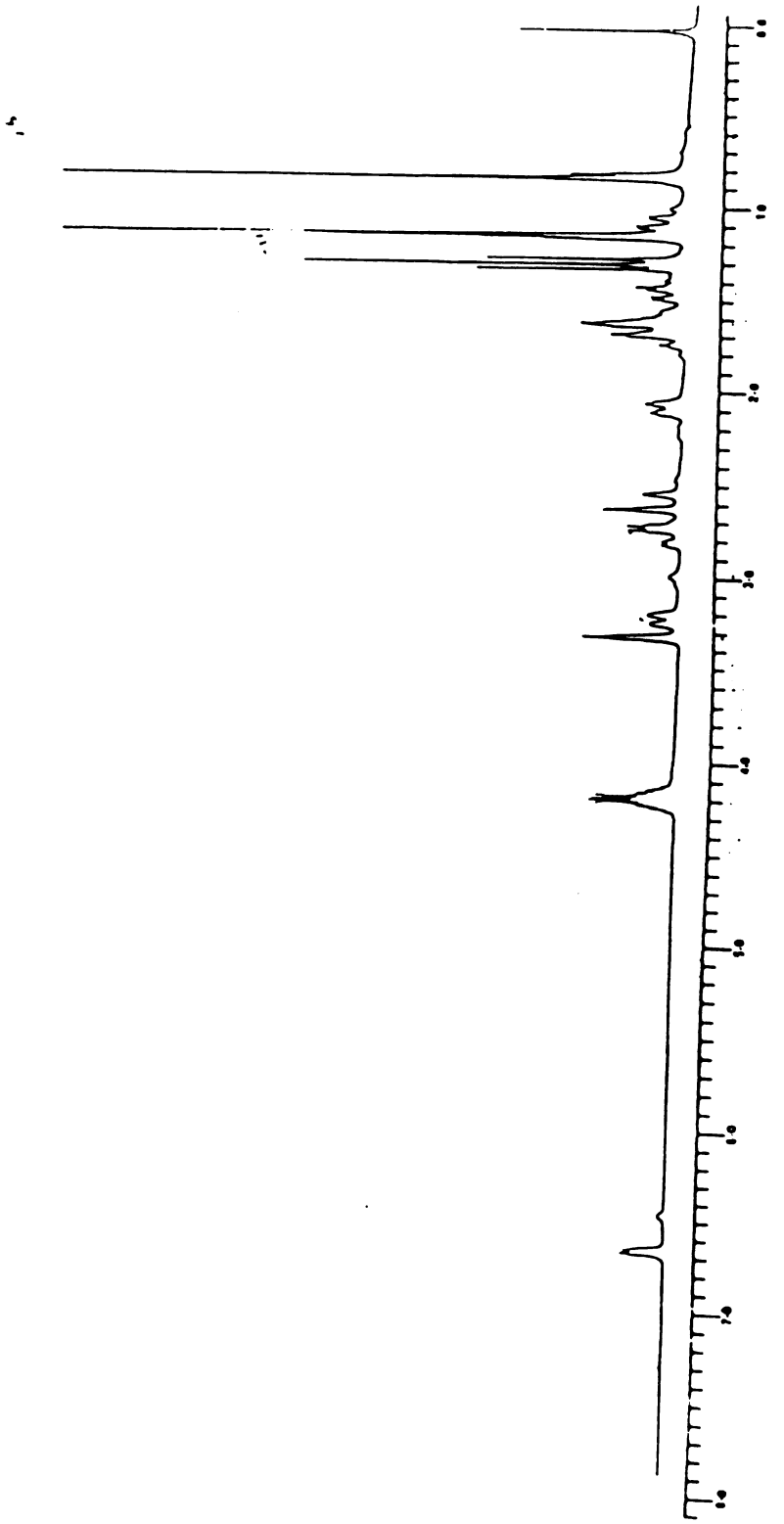


Figure 3a ^{1}H-NMR (250 MHz) Spectrum of 110c with the First Addition of Eu(fod)$_3$.

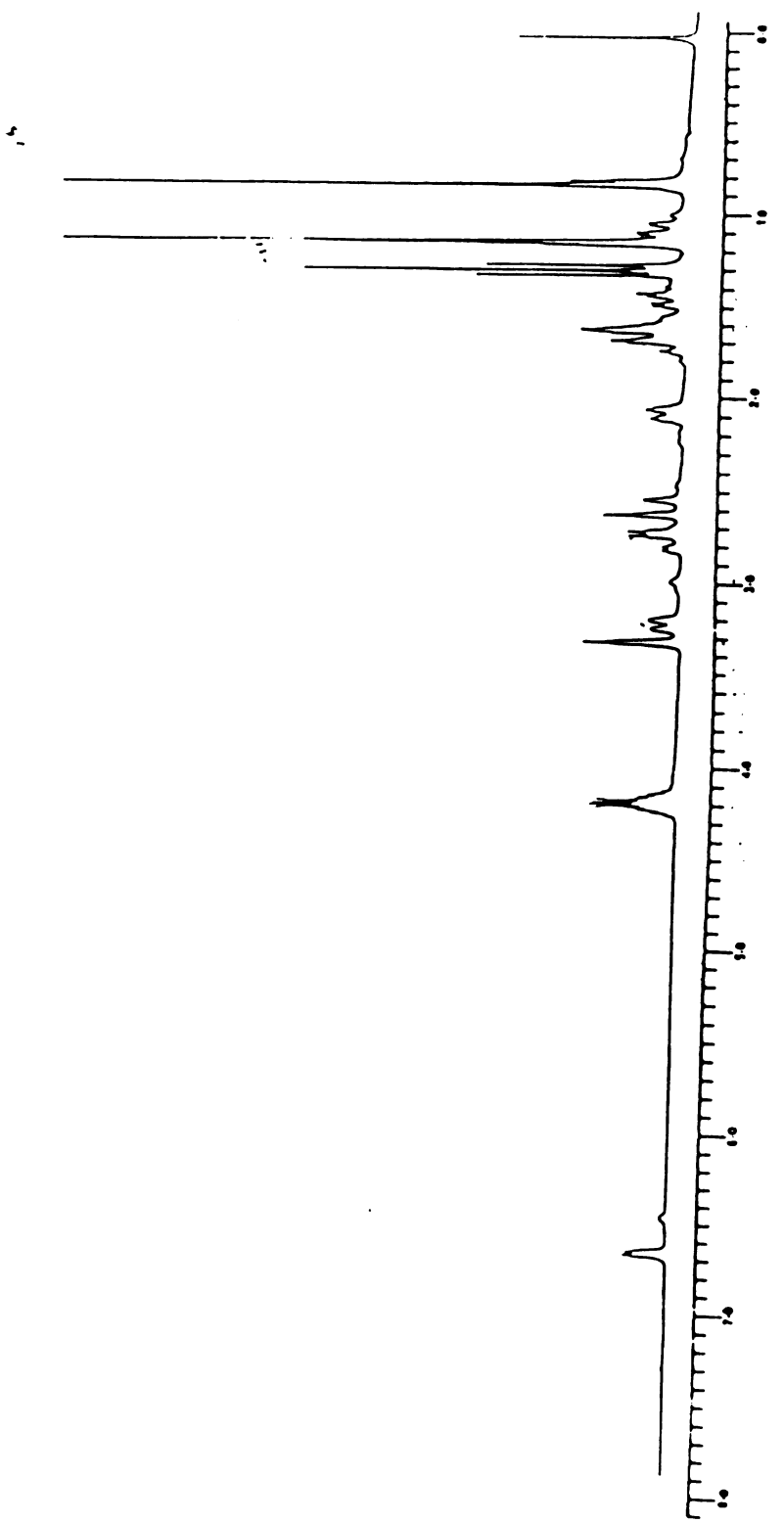


Figure 3a ^{1}H-NMR (250 MHz) Spectrum of 110c with the First Addition of Eu(fod)$_3$.

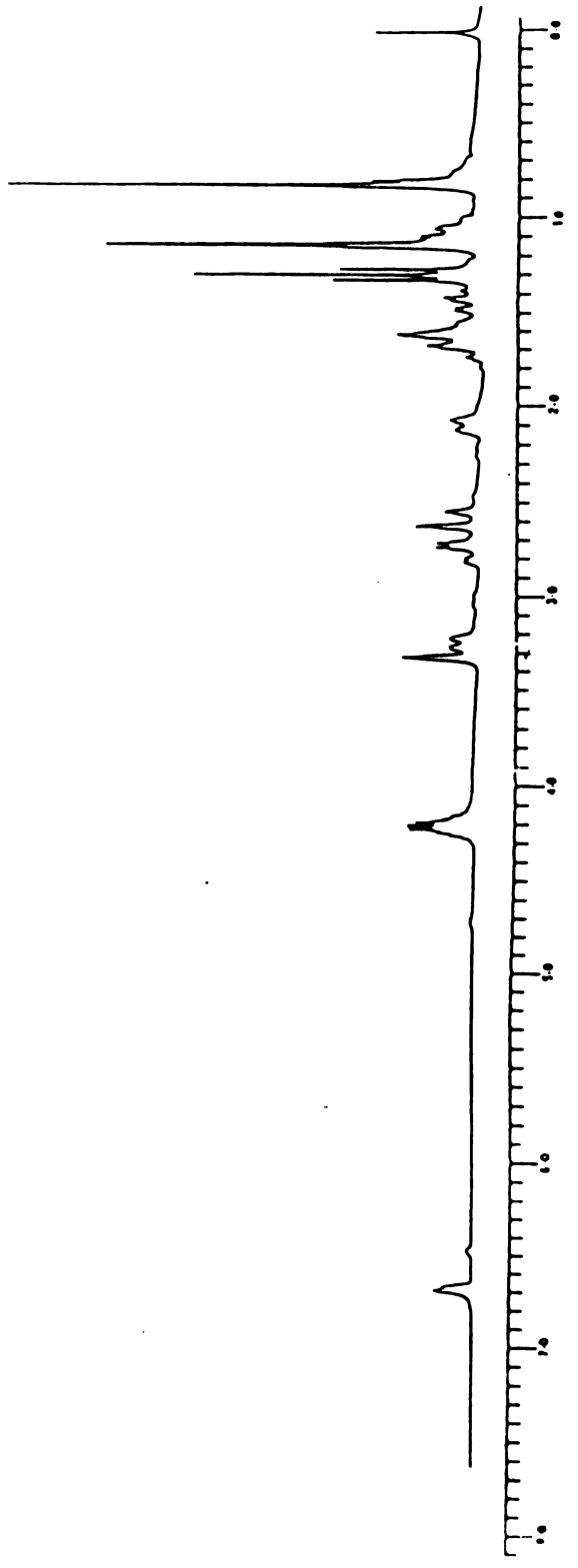


Figure 3b ^{1}H-NMR (250 MHz) Spectrum of 110c with the Second Addition of Eu(fod)$_3$.

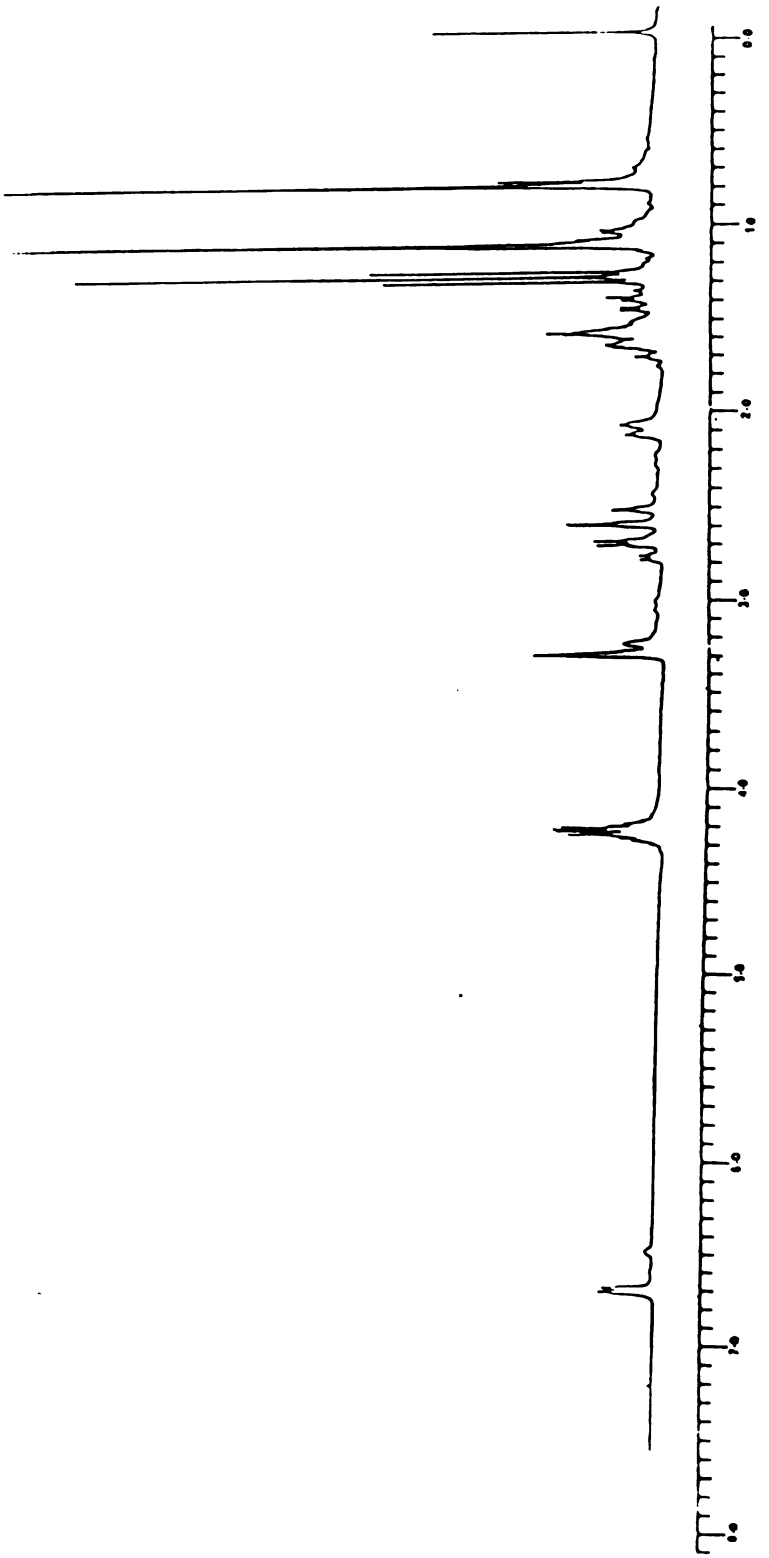


Figure 3c ^{1}H-NMR (250 MHz) Spectrum of 110c with the Third Addition of Eu(fod)$_3$.

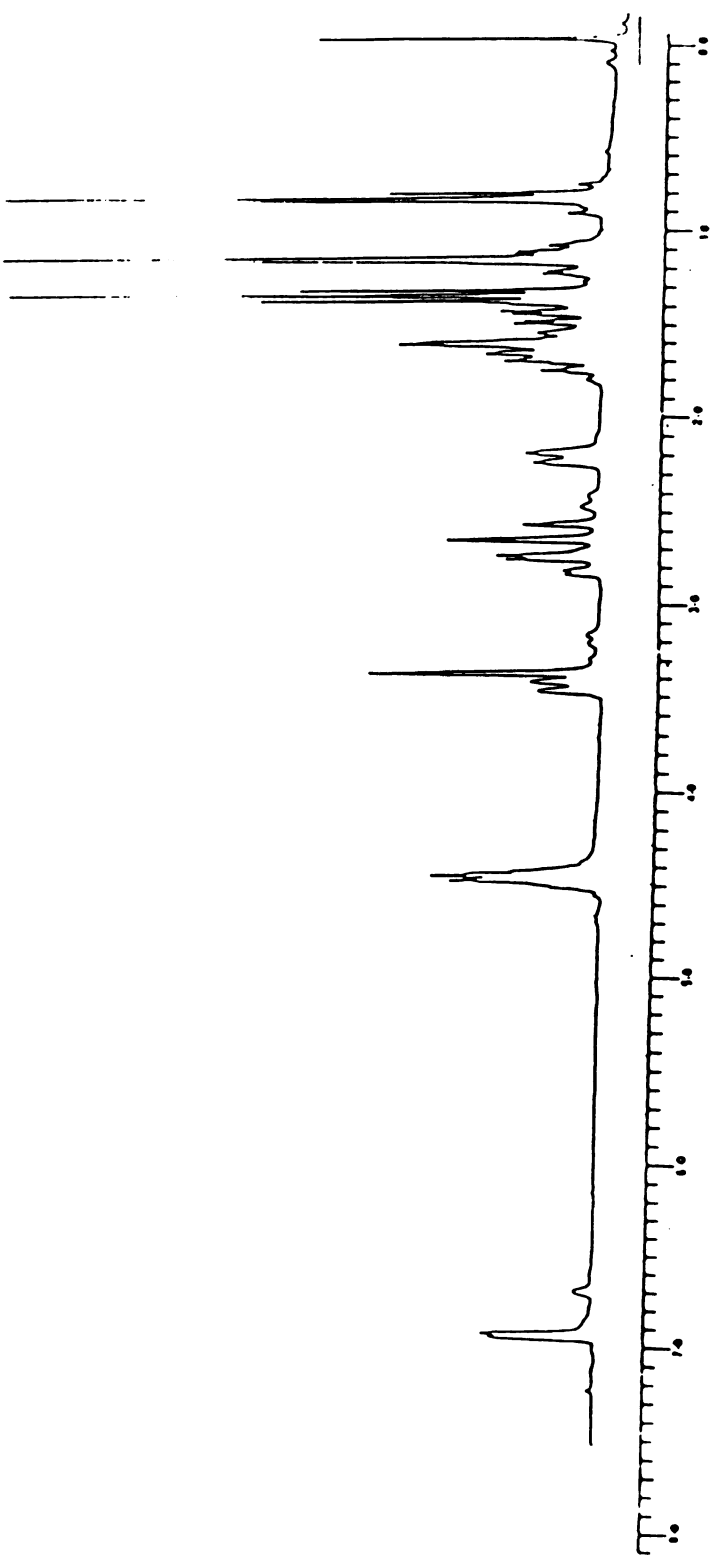


Figure 3d ^{1}H-NMR (250 MHz) Spectrum of 110c with the Fourth Addition of Eu(fod)$_3$.

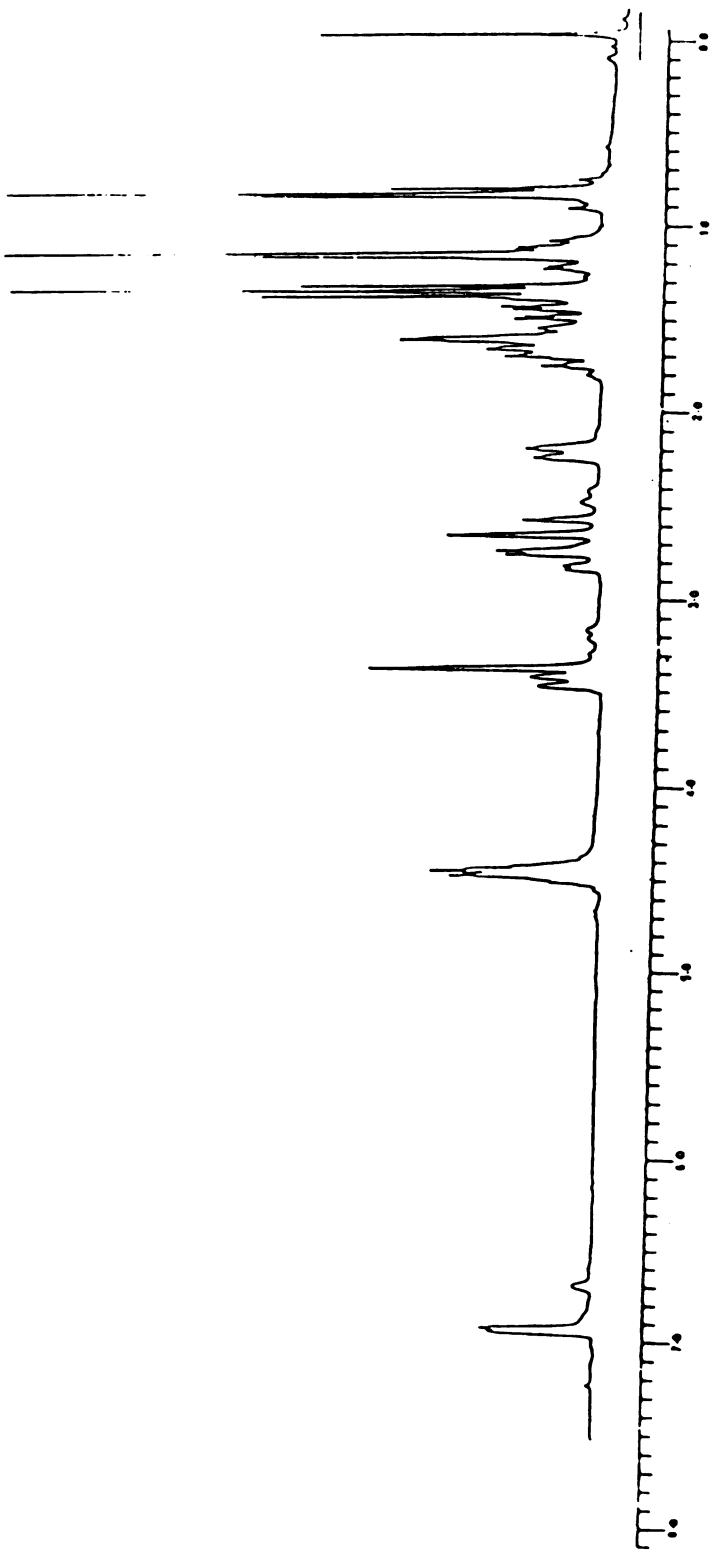
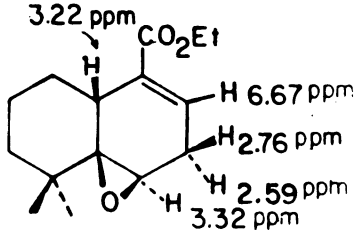


Figure 3d ^{1}H-NMR (250 MHz) Spectrum of 110c with the Fourth Addition of Eu(fod)$_3$.

110c		**109c**	
δ (ppm)	(δ) after Eu(fod)$_3$ addition	δ (ppm)	δ (ppm) after Eu(fod)$_3$ addition
2.10	0.288	2.19	0.864
2.59	0.135	2.52	0.254
2.76	0.102	2.75	0.220
3.22	0.457	3.01	0.644
3.32	0.237	3.33	0.320
6.67	0.490	6.47	0.898



110c.

Figure 4: Chemical shifts changes with Eu(fod)$_3$ addition to **109c** and **110c** and proton chemical shift correlation of **110c**.

3.22, 2.76 and 2.59. Irradiation at δ = 3.32 resulted in sharpening of the signals at 2.76 and 2.59 ppm. Irradiation at δ = 3.22 ppm resulted in simplification of the signals at 6.67, 2.76, 2.59 and 2.10 ppm. Irradiation at δ = 2.76 ppm effected the signals at 6.67, 3.32, 3.22 and 2.59 ppm. Irradiation at δ = 2.59 resulted in sharpening and simplification of the signals at 6.67, 3.32, 3.22 and 2.76 ppm. Irradiation at δ = 2.10 ppm resulted in sharpening the resonance at 3.22 ppm. From these decoupling results and consideration of chemical shifts, the connectivities of the protons of the B-ring was determined to be that shown in Figure 4. The stereochemistry of the epoxide moiety was made on the basis of ($Eu(fod)_3$) studies. In these studies, increments of $Eu(fod)_3$ were added and the chemical shift differences were measured; these results are presented in Figures 5a-e. The resonance at δ 3.22 ppm, which had been attributed to the C-8a-H, shifted the most relative to the other protons, indicating the close spatial proximity of that hydrogen to the basic epoxide oxygen. Therefore, we have concluded that the ring junction hydrogen (3.22 ppm) and the epoxide oxygen are on the same face of the molecule. The structure of **110** as a β-epoxide was secured by single x-ray analysis.

The α-epoxide **109c** was examined in a manner similar to that of the β-epoxide to assign the stereochemistry. Epoxide **109c** exhibited the following signals in the ^1H-NMR spectrum: δ (ppm) = 6.49 (m, 1H), 3.33 (br s, 1H), 3.01 (d

m, J = 12.0Hz), 2.75 (d m, J=20Hz, 1H), and 2.52 (d m, J=20Hz). Decoupling was performed as follows in Figures 6a-e. Irradiation at δ = 6.47 effected the resonances at 3.01, 2.75 and 2.52 ppm. Irradiation at δ = 3.33 sharpened and simplified signals observed at 2.75 and 2.52 ppm. Irradiation at δ = 3.01 simplified those resonances at 6.47, 2.75 and 2.52 ppm. Irradiation at δ = 2.75 simplified the signals at 6.47, 3.33, 3.01 and 2.52 ppm. Irradiation at δ = 2.52 simplified the peaks at 6.47, 3.33, 3.01 and 2.75 ppm. From a consideration of the observed chemical shifts and the couplings relationship of the protons in **109c**, the following assignments can be made, C_2-H at 6.47 ppm, C_4-β-H at 3.33 ppm, C-8a-H at 3.01 ppm, C_2 α-H at 2.75 ppm and C_3 β-H at 2.52 ppm.

The epoxide stereochemistry was suggested to be α- by shift reagent ($Eu(fod)_3$) studies (Figures 6a-6e). The ring junction hydrogen at δ = 3.33 ppm was slightly shifted relative to the other protons of **109c** and in direct contrast to the lanthanide-induced shift of the ring fusion hydrogen of the β-epoxide. These data suggest an α-orientation for the epoxide moiety which is corroborated by single-crystal x-ray crystallography; the ORTEP plot is shown in Figure 7.

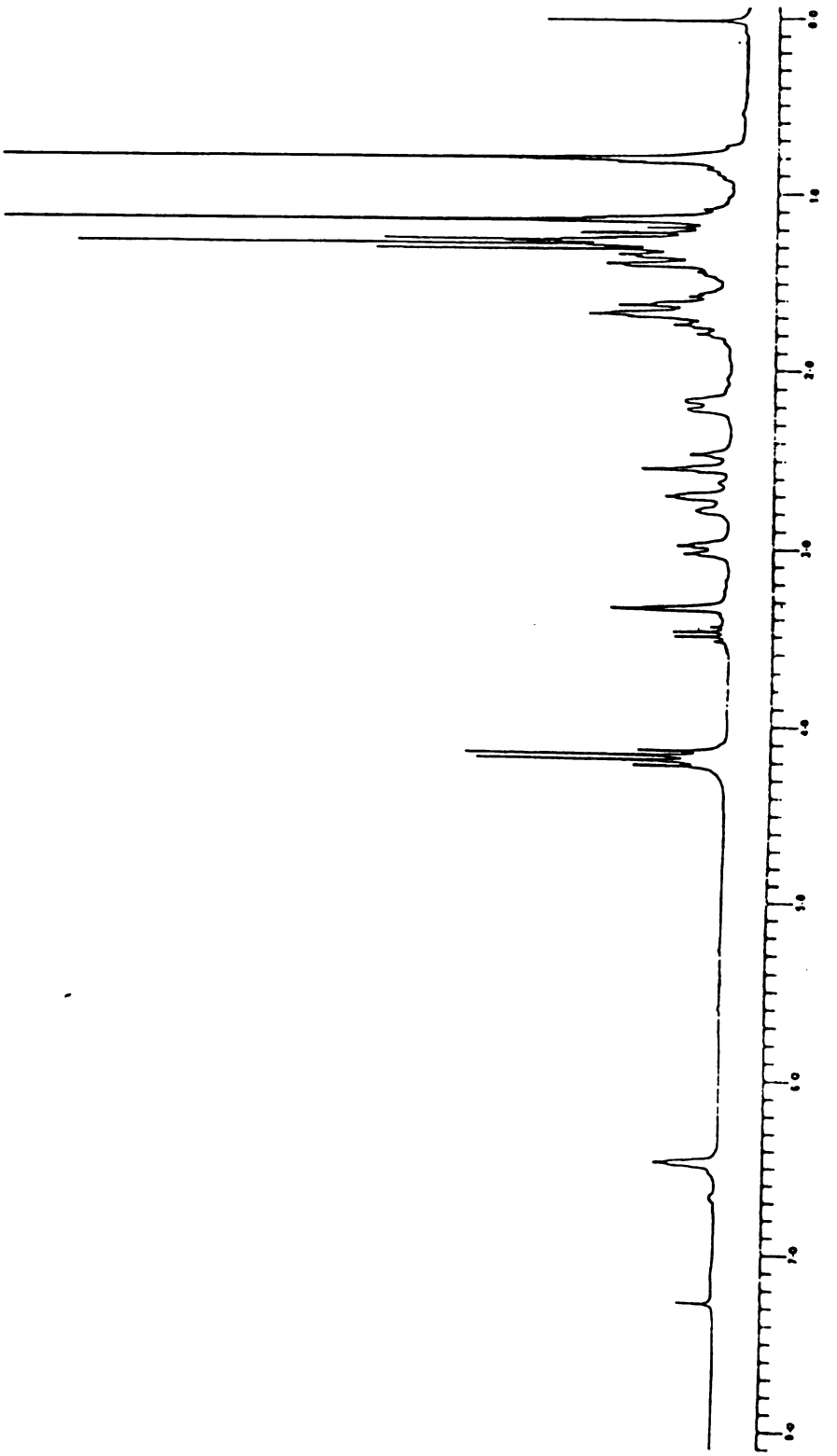


Figure 5a ^{1}H-NMR (250 MHz) Spectrum of 109c .

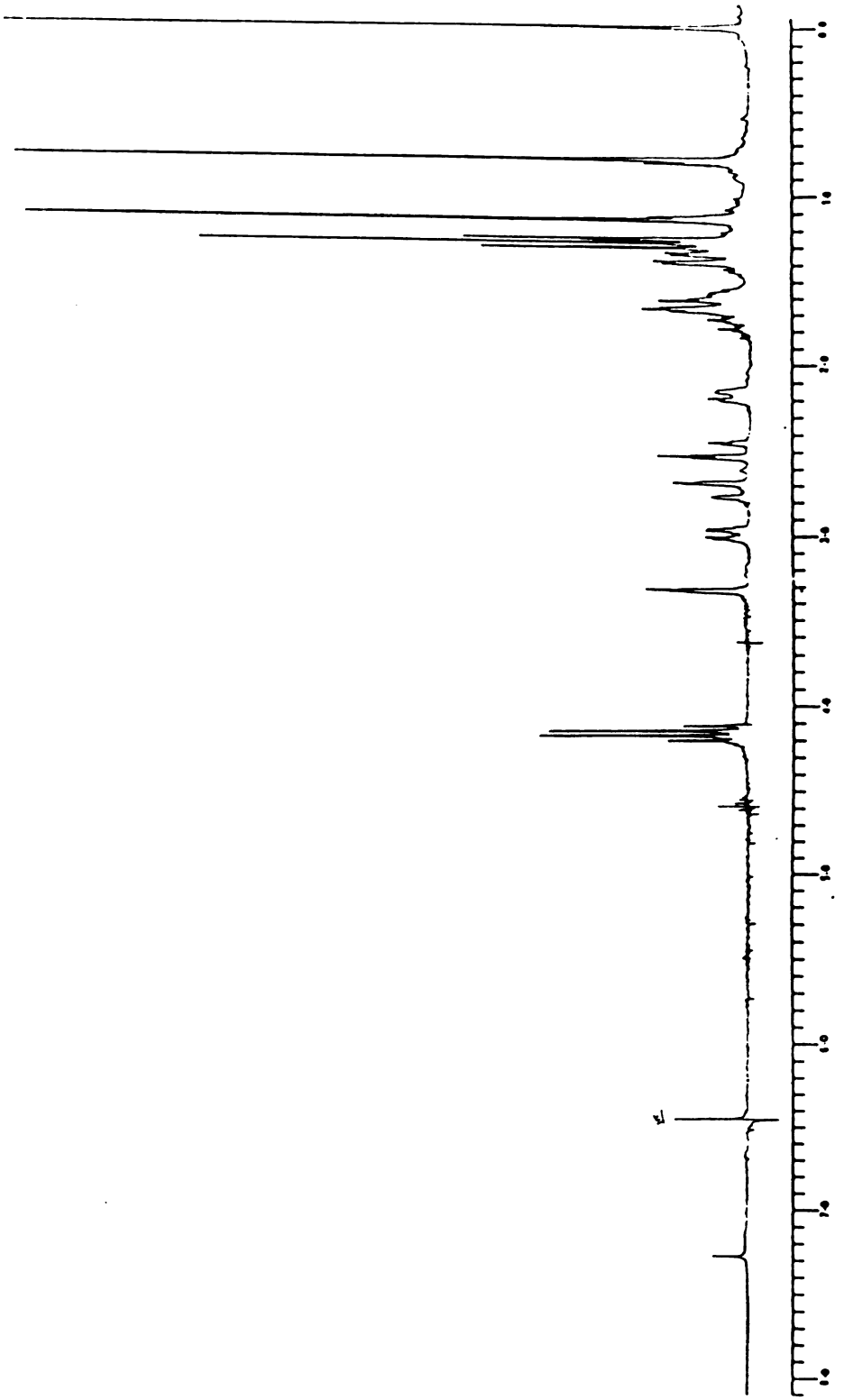


Figure 5b ^{1}H-NMR (250 MHz) Spectrum of 109c with Irradiation at δ = 6.47 ppm .

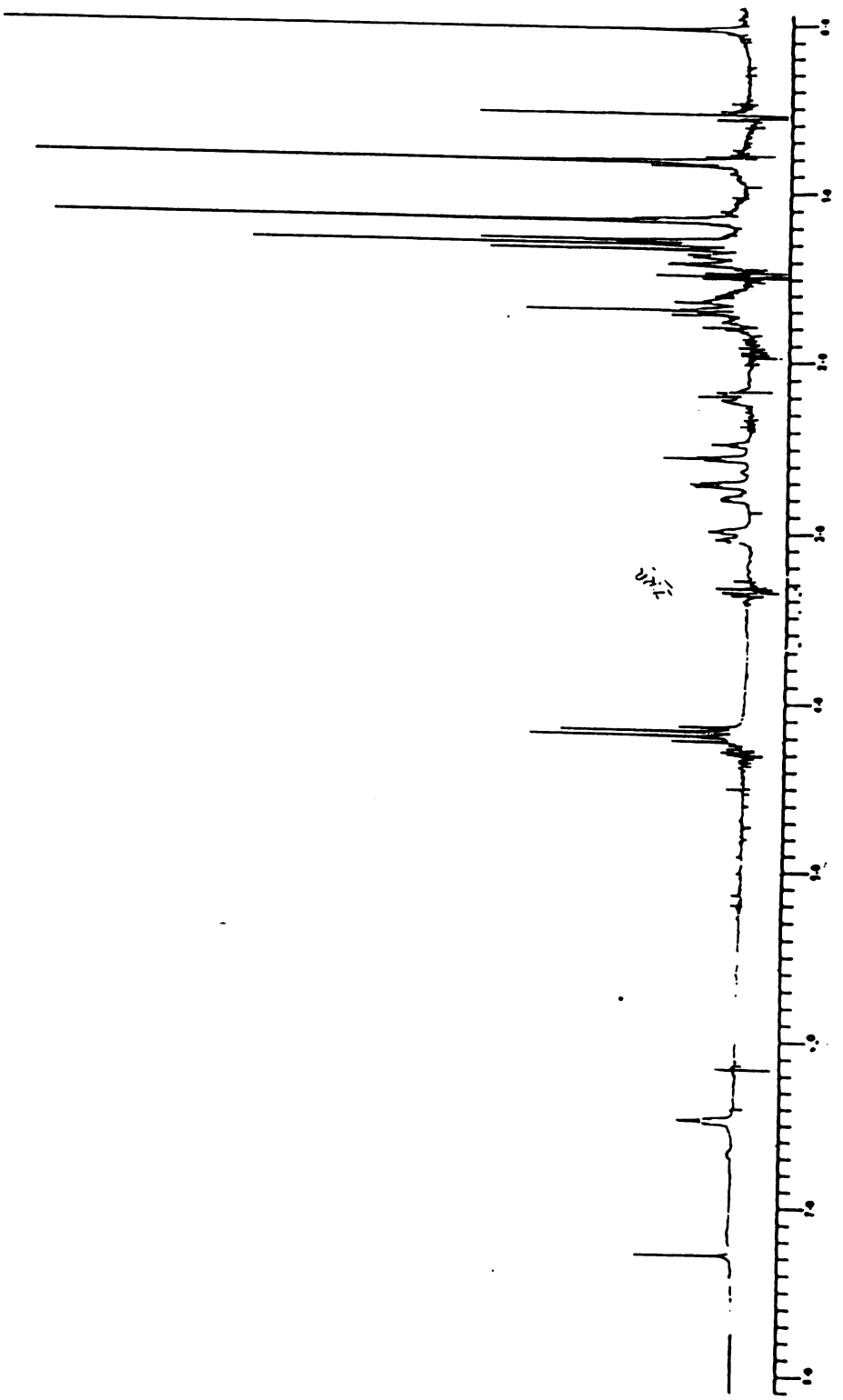


Figure 5c ^{1}H-NMR (250 MHz) Spectrum of 109c with Irradiation at δ = 3.33 ppm .

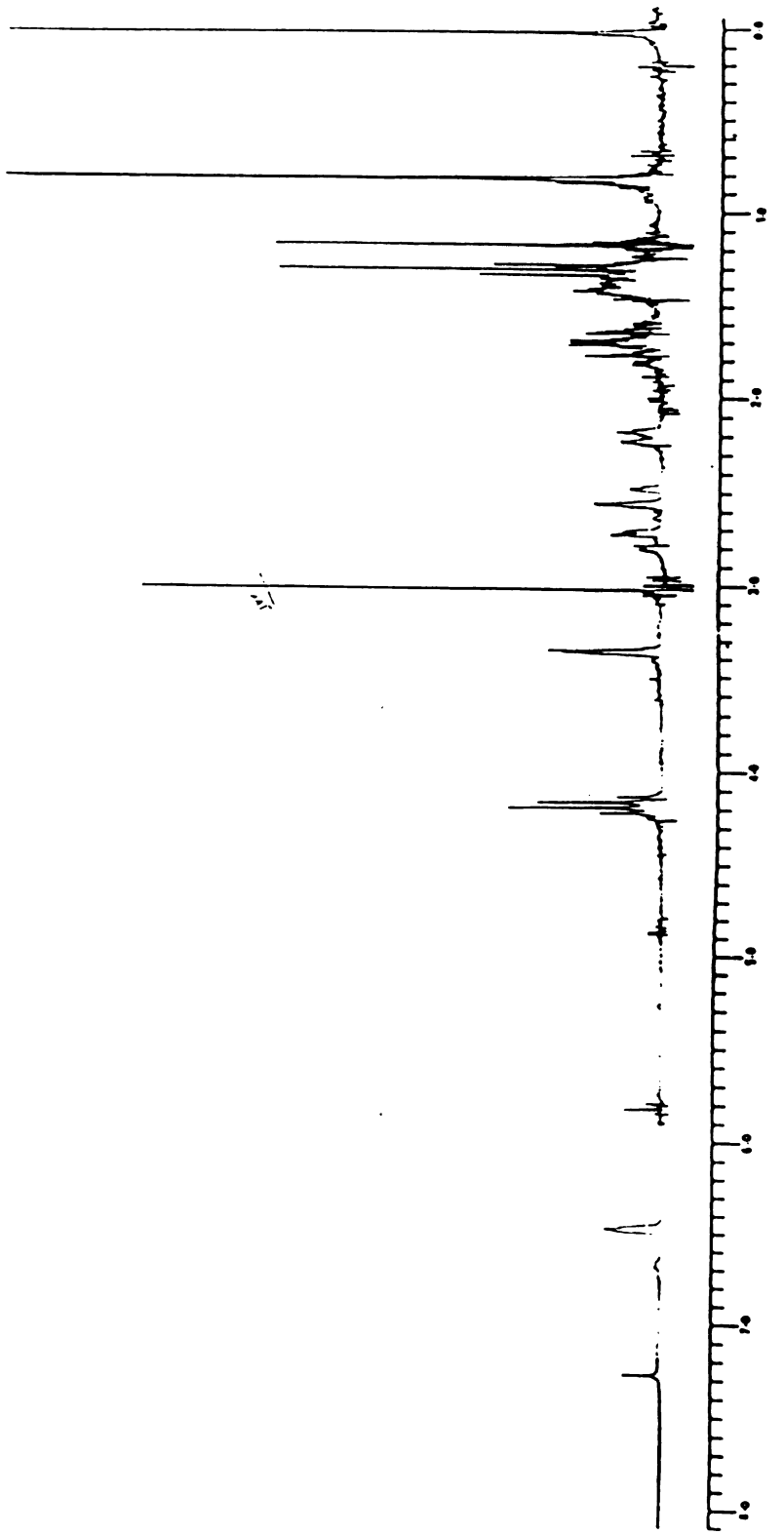


Figure 5d ^{1}H-NMR (250 MHz) Spectrum of 109c with Irradiation at δ = 3.01 ppm .

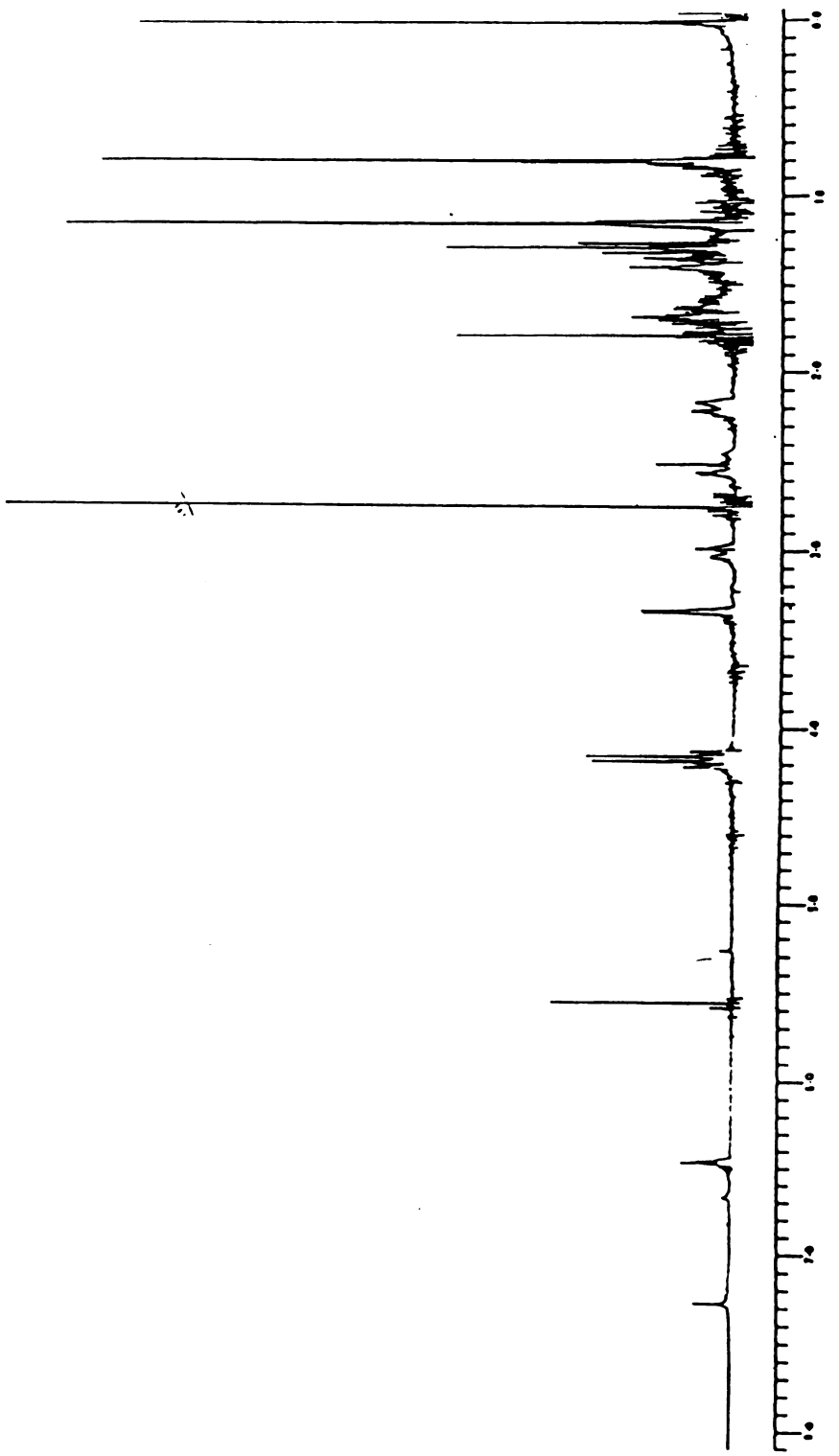


Figure 5e ^{1}H-NMR (250 MHz) Spectrum of 109c with Irradiation at δ = 2.75 ppm .

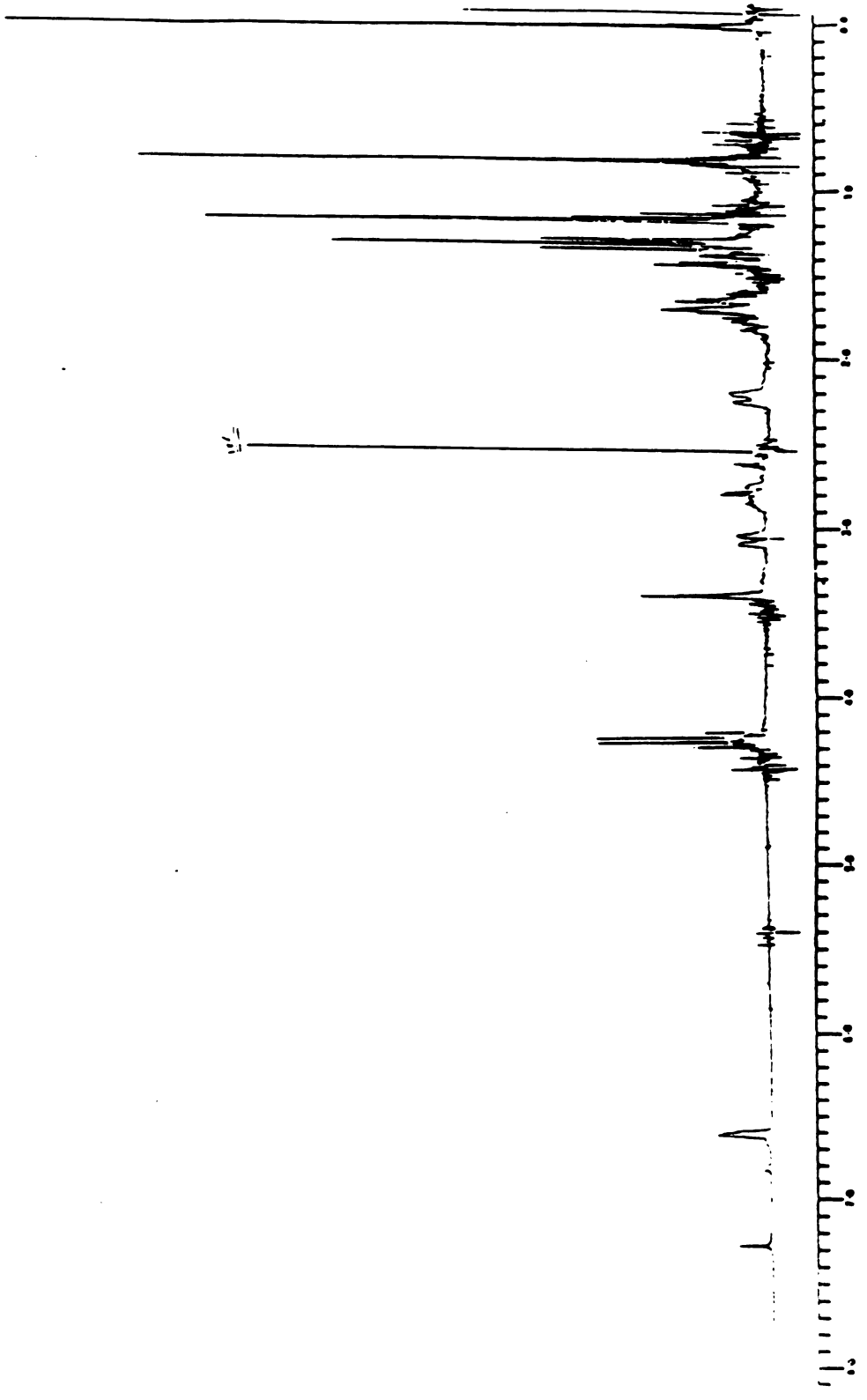


Figure 5f ^{1}H-NMR (250 MHz) Spectrum of 109c with Irradiation at δ = 2.52 ppm .

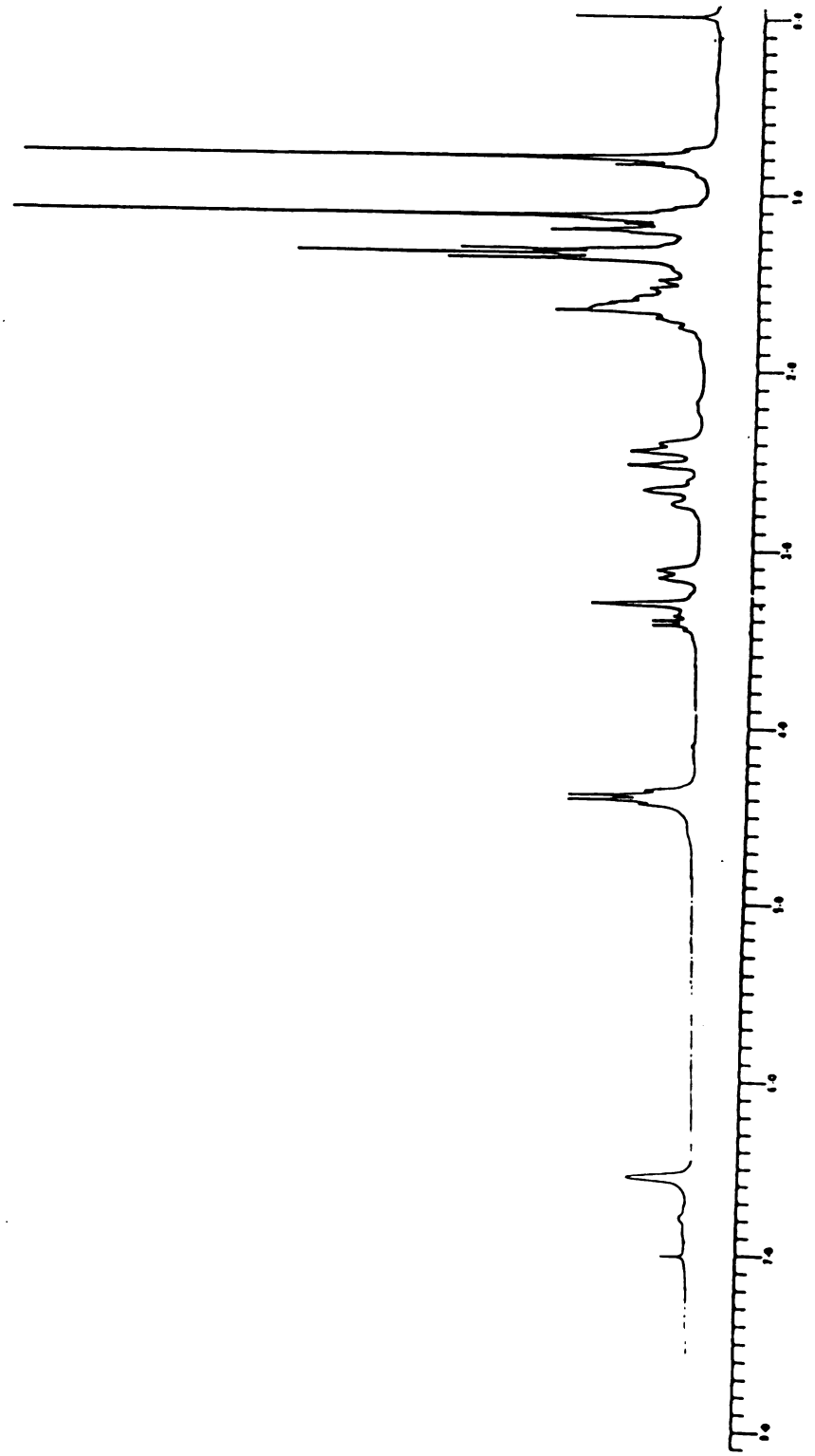


Figure 6a ^{1}H-NMR (250 MHz) Spectrum of 109c with the First Addition of Eu(fod)$_3$.

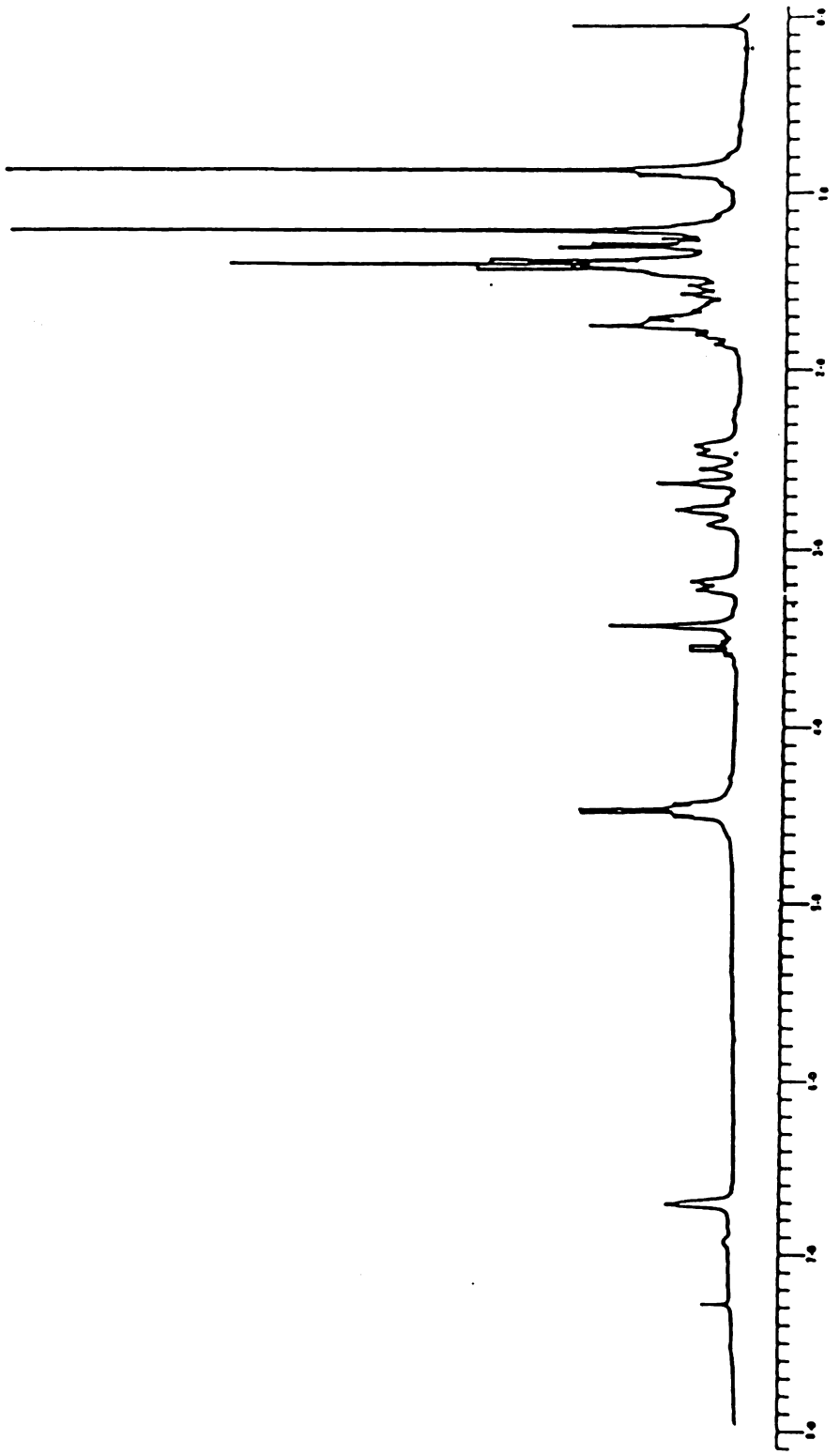


Figure 6b ^{1}H-NMR (250 MHz) Spectrum of 109c with the Second Addition of Eu(fod)$_3$.

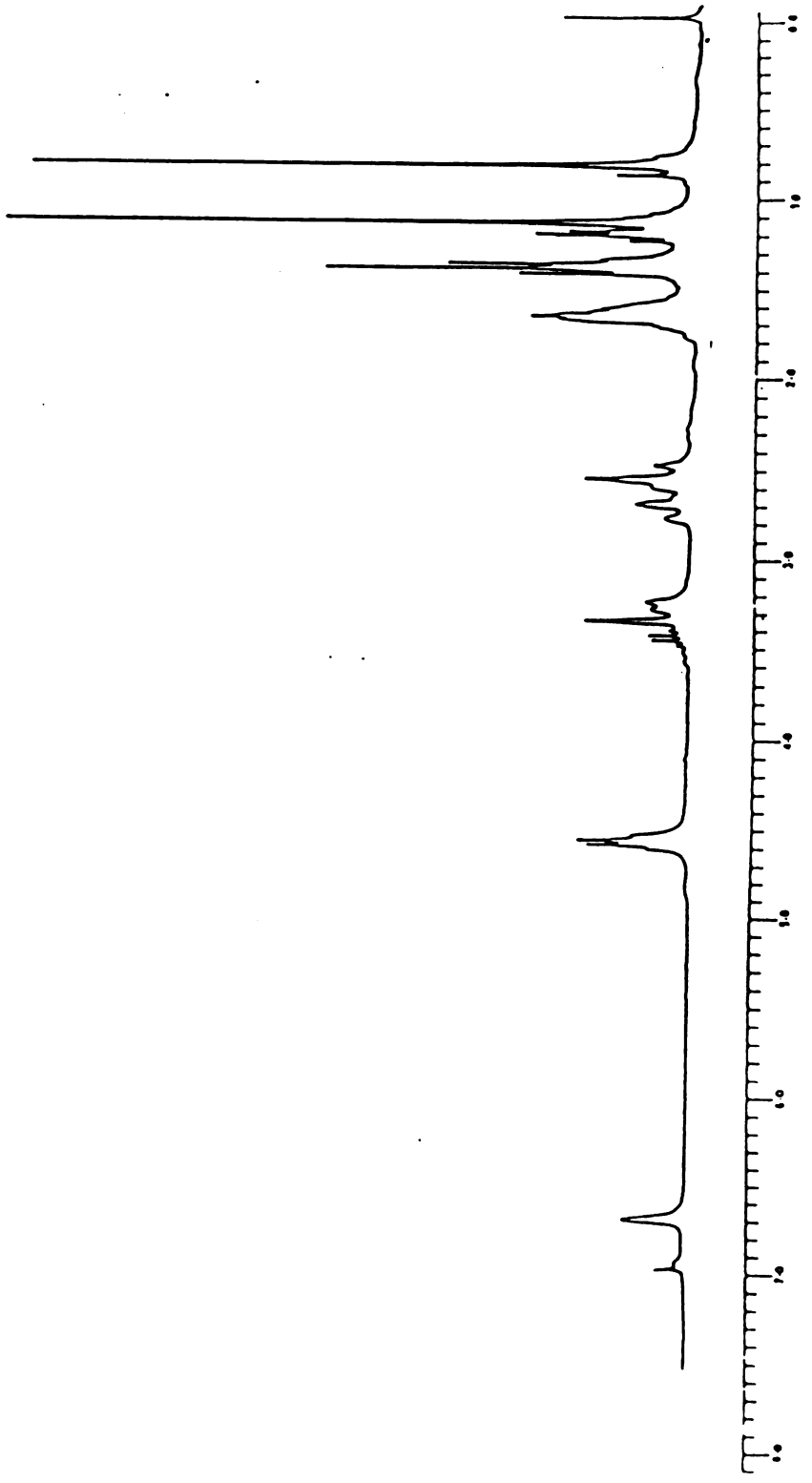


Figure 6c ^{1}H-NMR (250 MHz) Spectrum of 109c with the Third Addition of Eu(fod)$_3$.

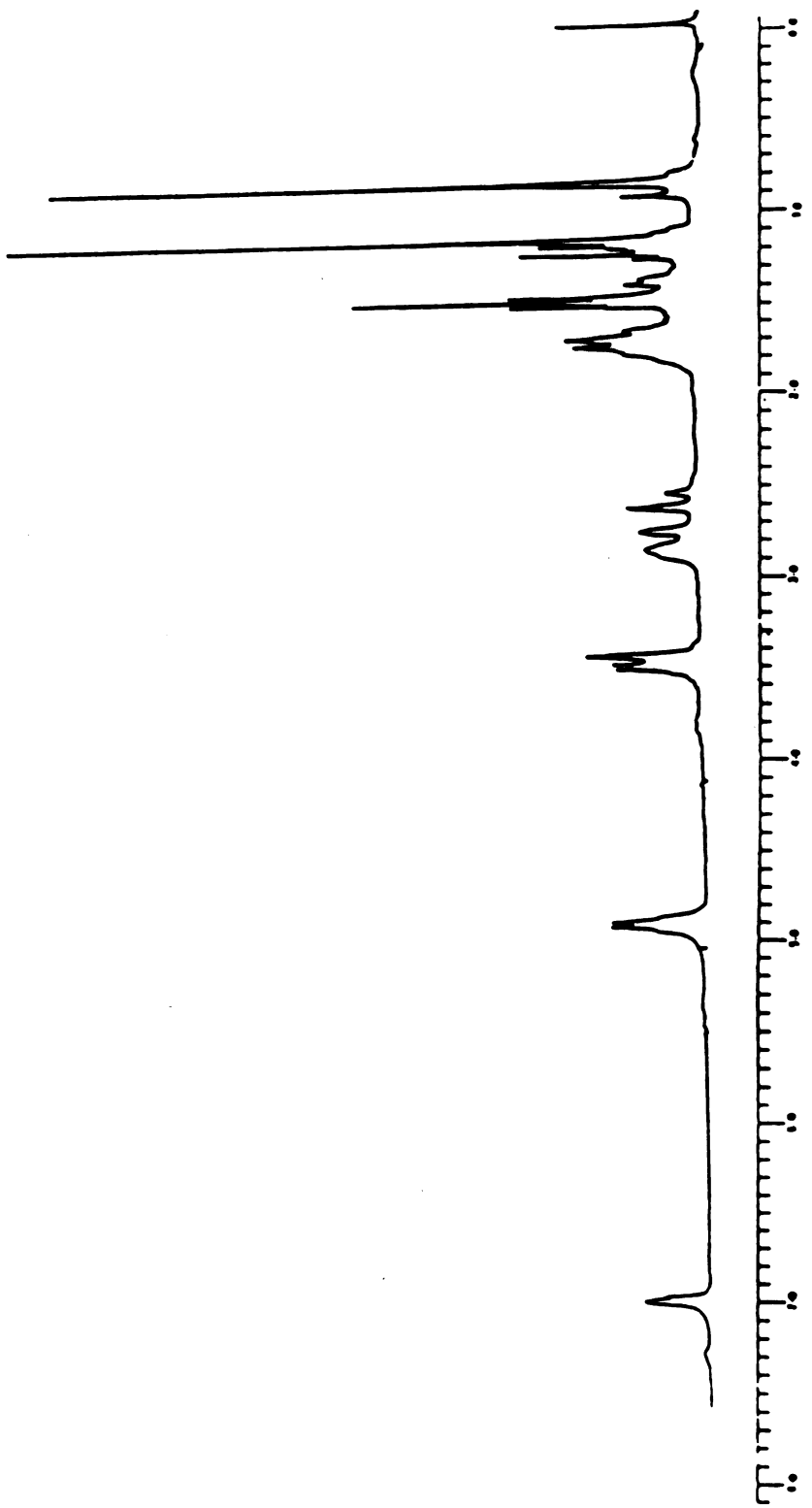


Figure 6d ^{1}H-NMR (250 MHz) Spectrum of 109c with the Fourth Addition of Eu(fod)$_3$.

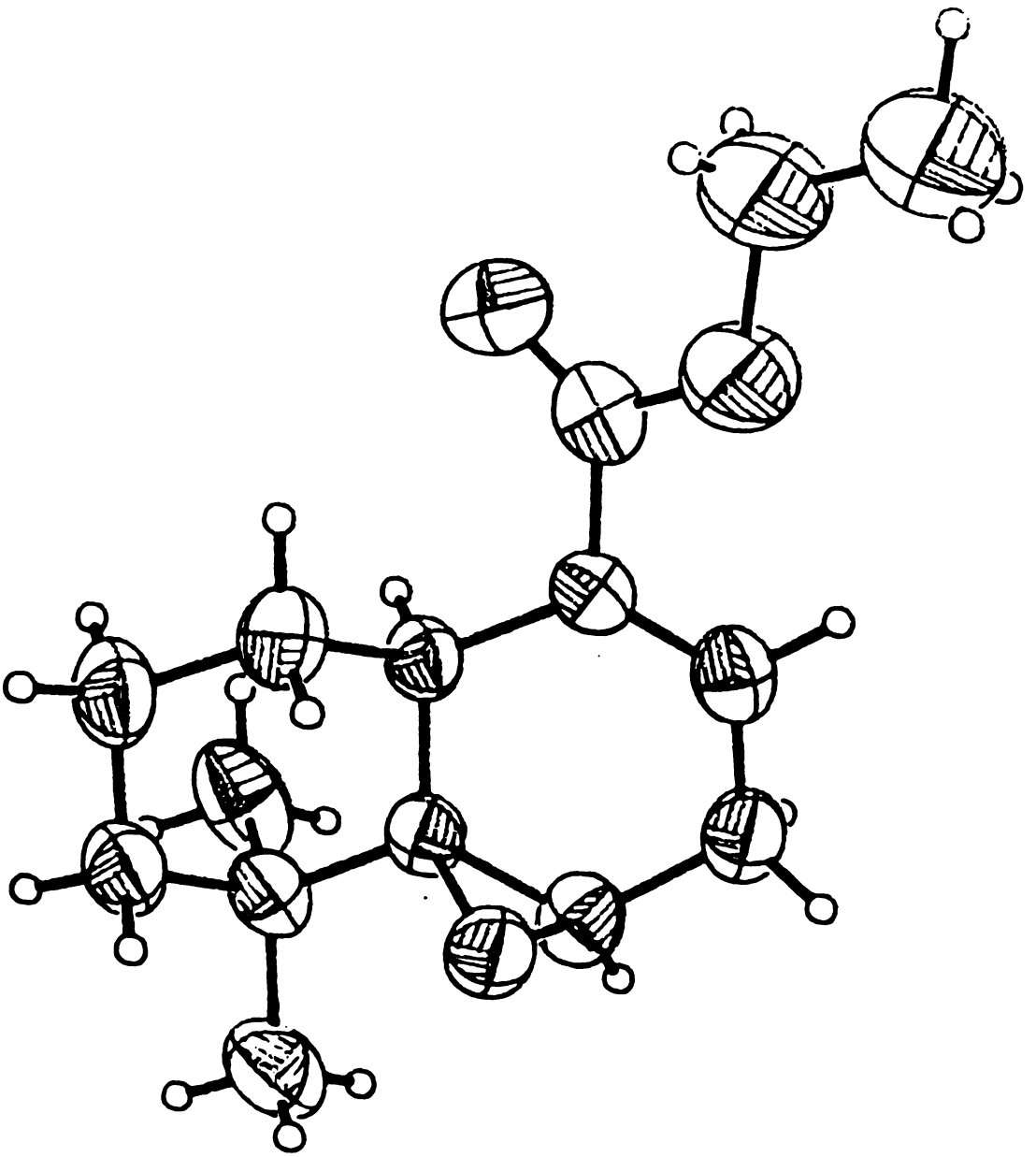


Figure 7 The ORTEP Plot of a Single Crystal X-ray of **109c** .

Using the chemical shift and coupling precedents set in the examination of epoxides **109c** and **110c**, all other remaining epoxide stereochemistries were established. Epoxidation of **104b** with (MCPBA, 0°C) gave a mixture of epoxides 1 and **110b** in 95:5 ratio, 87%. The stereochemistry of the epoxide 1 was determined by ^{1}H-NMR techniques (decoupling and shift reagent studies) and secured by single crystal x-ray crystallography. The ORTEP plot of epoxide 1 is shown in Figure 8.

The stereoselectivity obtained in epoxidation of **104b** is as expected. The α-face selectivity is likely due to steric hindrance in the β-face approach by the axial methyls at C-4 and C-8a. Such selectivity, favoring the α-epoxide formation, is also observed in the epoxidation of **104e** and **104f** providing **109e** and **109f** in 81 and 90% yields, respectively.

Epoxidation (MCPBA) of **104g** provided a mixture of epoxides **109g** and **110g** in 11:89 ratio, respectively and in a 78% overall yield which was separated by chromatography on silica gel.

The stereoselectivity of MCPBA epoxidation dropped in the epoxidation of **104a** and **104d**. In the case of **104a**, a mixture of epoxides, **109a** and **110a**, were obtained in a 45:55, α:β ratio in 95% yield; however, these epoxides were readily separable by fractional crystallization (30:70,

ether:hexane). Epoxidation of **104d** with MCPBA provided a mixture of epoxides **109d** and **110d** in a 33:67 ratio in 77% yield.

The drop in facial selectivity in these last examples was surprising. The only deviation from other substrates is the substitution at C-2 which might cause conformational changes that would expose both the α- and β-face of the 4,4a-double bond.

From these results, we conclude that MCPBA provides mainly the β-epoxides when the group at C_{8a} is a hydrogen, while the selectivity turns around with substrates containing a C-8a-methyl.

Clearly, the desired α-epoxides can be prepared in small quantities at best with MCPBA as the epoxidation reagent. An epoxidation sequence that should provide the less available α-epoxides employs NBS in aqueous t-BuOH. The yields and ratios of products obtained upon treatment of dienes **104c** to **104g** with NBS in aq. t-BuOH as are present in Table III. Treatment of **104c** with 2.0 equivalents of NBS in a 2:1 ratio of t-BuOH:water (2 hours) provided epoxide **109c** directly in 94% yield as the sole product. The obtention of epoxides directly without the observation of an intermediate was a surprising but general event (vide infra). Compound **104g**, when subjected to the NBS-epoxidation conditions, provided only **109g** in 54% yield. Exposure of **104d** to NBS under the standard conditions yielded epoxides **109d** and **110d**

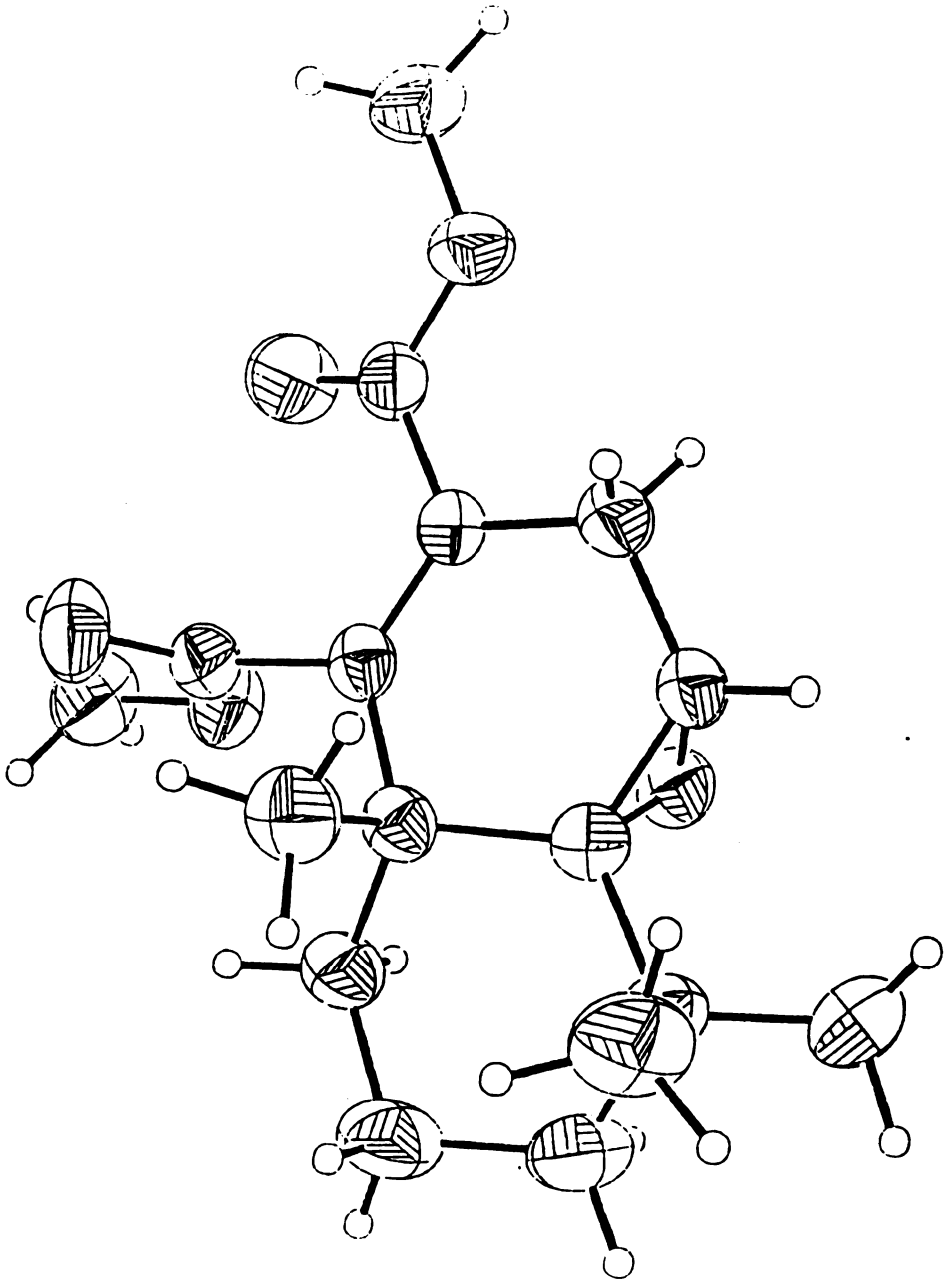


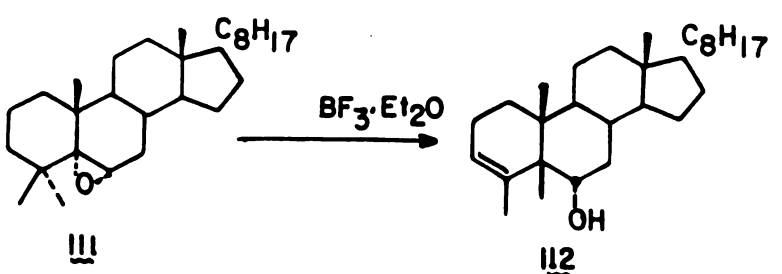
Figure 8 The ORTEP Plot of a Single Crystal X-ray of 1.

(85:15) in 60% yield. The selectivity dropped in this case as it did with MCPBA as the epoxidizing reagent.

Attempts to obtain the β-epoxides **110b**, **110e** and **110f** using the aq. NBS-tBuOH conditions resulted in a mixture of decomposition products including B-ring aromatic materials. Other attempts to convert the α-epoxide **110b** to the α-epoxide **110b** via formation of an intermediate diol (H_3O^+) also failed. With the epoxides **109** and **110** in hand, we proceeded to investigate the rearrangement protomoted by Lewis acids.

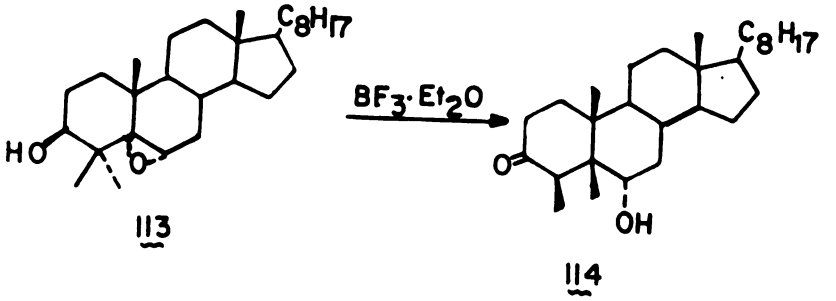
Epoxides **109** and **110**, Rearrangement Catalyzed by $BF_3 \cdot Et_2O$:[28]

Epoxides are well known to rearrange to a variety of products upon Lewis acid treatment.[29] Steroidal epoxides, in which the epoxide moiety is part of a rigid system, have been extensively examined as rearrangement substrates; often with $BF_3 \cdot OEt_2$ serving as the Lewis acid. A number of instructive examples are illustrated in equation 7 to 9. For example, treatment of 4,4-dimethyl-5α,6α-epoxy-cholestane **111** with $BF_3 \cdot Et_2O$ provided alcohol **112** resulting from C_4-CH_3 migration to C-5,[29] Equation 7.



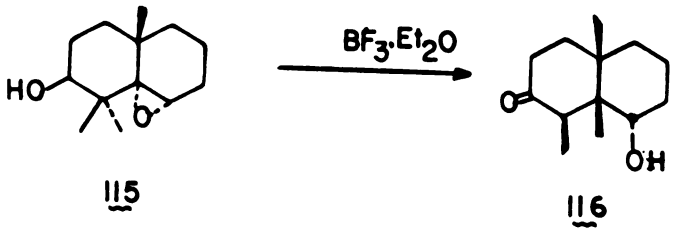
111 **112** (7)

Halsall[29m] studied the 4β-hydroxy-4,4-dimethyl-5α,6α-epoxy-cholestane **113** rearrangement with $BF_3 \cdot Et_2O$ and obtained **114** in 35% yield, a product stemming from synochronous C-5-β-methyl, C-6-α-hydrogen migration (Equation 8). Whitlock[29h] reported a similar rearrangement



113 **114** (8)

of compound **115** to provide **116** in variable yields (21-34%) as shown in Equation 9.



115 **116** (9)

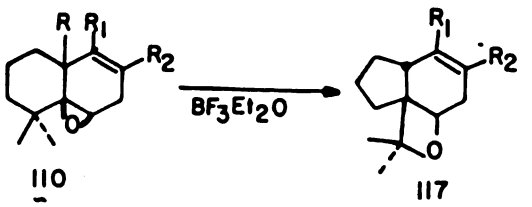
In all of these rearrangements, one might anticipate that a stereoelectronically allowed synchronous C-4 to C-4a methyl migration might energetically favor the release of the 1,3-diaxial interaction between C-4-β-methyl and C-10-angular methyl[29g,h,l] and the release of strain in the three-membered epoxide ring.

With this background in mind and the necessary substrates for the study in hand, we first investigated the rearrangement with $BF_3 \cdot Et_2O$ of the more available β-epoxides **110**. In the steroid series, exposure of related C-4a-C-5 β-epoxides to Lewis acids have generally given a gross mixture of products. The results of β-epoxides **110** are listed in Table IV.

Treatment of the β-epoxide **110a** with $BF_3 \cdot Et_2O$ (1.25 equiv. CH_2Cl_2, 0°C; 10 minutes) provided **117a** in 92% yield. The nature of **117a** was deduced from inspection of the spectral data and subsequent chemical manipulation. The first indications of a novel structure for the product of the rearrangement of **110a** came from ^{1}H-NMR and ^{13}C-NMR data. In the ^{1}H-NMR (250 MHz, $CDCl_3$) compound **117a** exhibited resonances at δ = 4.75 (br m, 1H), 1.80 (br t, J=8.3Hz, 1H), 2.76 (dd, J=18.8,2.3Hz, 1H), 2.2 (dd, J=18.8,4.2Hz, 1H), 1.44 (s, 3) and 1.22 (s, 3). These data are close to what one might expect for the desired, but unexpected in this series, rearrangement products; however, the δ between the observed and expected chemical shift values for an olefinic hydrogen (4.75 ppm vs. ca. 5.25 ppm) and a CH_3- on an sp^2 hybridized carbon (1.44 ppm vs. ca. 1.70 ppm) were cause for concern.

Extensive decoupling (^{1}H-NMR), shift-reagent and nuclear Overhouser difference (NOEDS) studies suggested the C-9 and C-1- through C-4-arrangement with the

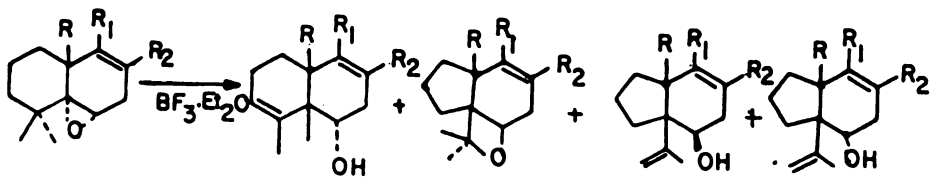
Table. IV. Rearrangement of β-Epoxides 110 with $BF_3 \cdot Et_2O$.



110 117

Epoxide	R	R	R	Yield (%)
110a	H	CO_2Me	CO_2Me	92 %
110c	H	CO_2Et	H	80%
110d	H	H	CO_2Et	87%
110g	H	CO_2Me	Me	79%

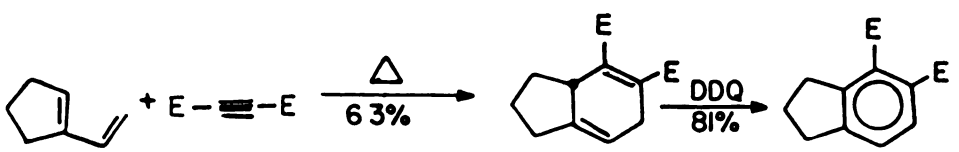
Table V Rearrangement of α-Epoxides 109 with $BF_3 Et_2O$.



109 122 117 123 124

Entry	Epoxide	R	R_1	R_2	Yield % 122	117	123	124
1	109a	H	CO_2Me	CO_2Me	—	53	30	8
2	109c	H	CO_2Et	H	—	60	30	—
3	109d	H	H	CO_2Et	—	52	27	10
4	109e	Me	CO_2Et	H	81	—	—	—
5	109f	Me	H	CO_2Et	87	—	—	—

stereochemistry shown in Table VI for **117a**. The ^{13}C-NMR (68.9 MHz, $CDCl_3$) data for **117a** demonstrated that there was indeed reason for concern, for compound **117a** exhibited but two sp^2 C=C resonances (142.2(s) and 129.0(s)) and two signals (δ = 83.7 and 81.8 ppm) in an unusual chemical shift region. These data, along with the observation of the facile M^+-58(C_3H_6O) loss in EI/MS (70eV), suggested a rearranged oxetane as the structure of compound **117**. Some support for this conclusion was provided by a comparison of the EI/MS fragmentation of **117a** <u>after</u> loss of C_3H_6O with the EI/MS (70eV) fragmentation pattern of dimethyl-2,3,3a,6-tetrahydroindene-4,5-dicarboxylate **120** prepared as described in Equation 10.[31] Additional support for the proposed



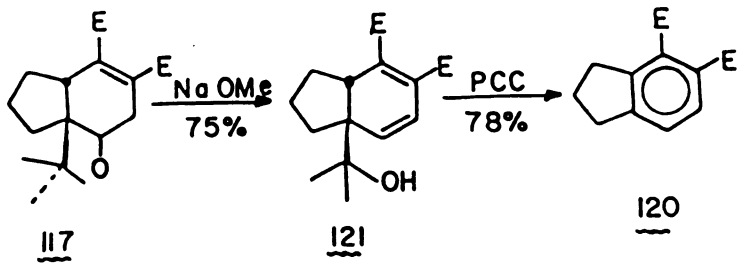
(10)

118 **119** **120**

E = CO_2Me

structure was supplied by a comparison of the ^1H-NMR and ^{13}C-NMR resonances attributed to the oxetane portion of **117a** (^1H-NMR δ = 4.22 ppm, ^{13}C-NMR δ = 83.7,81.8 ppm) with data for oxetanes previously reported.[32]

The nature of the ring system was unequivocally demonstrated by exposure of **117a** to NaOMe,MeOH providing the related 1,3-diene-5-$C(CH_3)_2OH$ ring-opened material **121** (75%, Equation 11). Treatment of the dienol **121** with pyridinium



117 121 120 (11)

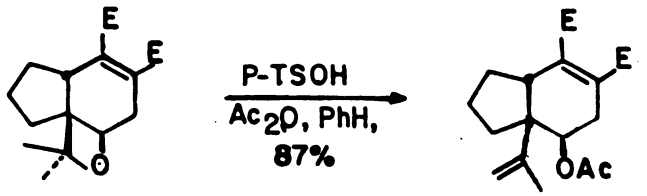
E=CO_2Me

chlorochromate[33] (PCC) afforded the expected dihydroindenediester **120** which was identical in all respects when compared to the literature data[34] and an authentic sample prepared as described in Equation 10. The obtention of oxetanes **117** from the $BF_3 \cdot Et_2O$ treatment of epoxides **110** was unexpected.[29g,h,i,l,m] However, an inspection of molecular models and the x-ray data demonstrates the ideal positioning of the C-3-C-4 ring bond of compounds **110** for migration with respect to the breaking C-5-O-bond giving **117** after ring closure. Similarly, epoxides **110c**, **110d** and **110g** provided oxetanes **117c** (80%), **117d** (87%) and **117g** (79%), respectively.

Rearrangement of α-Epoxides **109** with $BF_3 \cdot OEt_2$

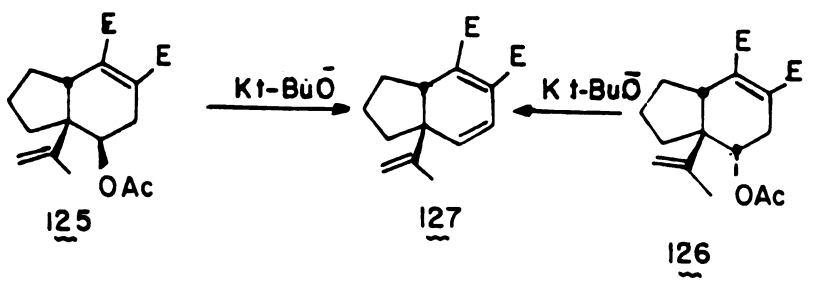
As was mentioned previously, the α-epoxide 1 provided the CH_3-migration product 2 (1.25 equiv. $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°) in 76% yield. Similar treatment of the α-epoxides **109e** and **109f** (Table V) provided **122e** and **122f** in 83% and 81% yields, respectively. Despite this seemingly strong precedent for CH_3-migration, exposure of epoxides **109a**, **109c**, **109d**, and **109g** failed to give even trace quantities of

the desired products **122**, yielding instead, oxetanes **117** (52-60%) and alcohols **123** (27-30%) and **124** (0-10%). The oxetanes **117a**, **117c**, **117d** and **117g** were compared to those isolated from rearrangement of epoxides **110** and were found to be identical in all respects. Alcohols, **123** and **124**, were separated (chromatography) and acetylated (Ac_2O,py,DMAP) to give the acetates **125** and **126**, respectively. These acetates were compared to the 4-OAc,5-isopropenyl compounds derived from oxetanes **117** (P-TsOH,Ac_2O,PhH, reflux, 3 hours),[35] shown in Equation 12.



117 125 (12)

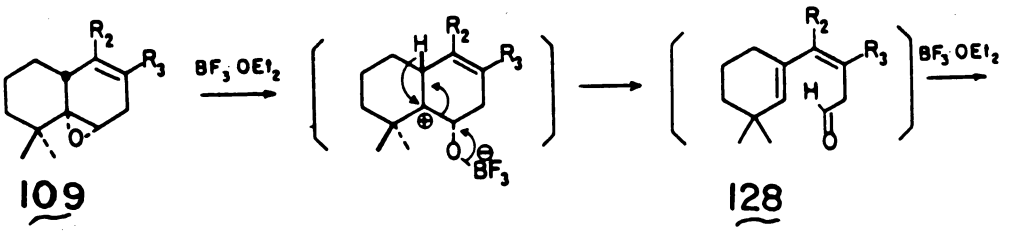
The acetates **125** prepared from the major alcohols **123** were indistinguishable from those derived from the oxetanes **117**. The structures of alcohols **125** were secured after conversion of the acetates **125** and **126** into single trienes **127** ($KOBu^t$,THF, Equation 13); demonstrating that they differed only in stereochemistry at the carbinol center.



125 127 126 13

E = CO_2Me

The conversion of epoxides **109** to oxetanes **117** requires an inversion of configuration at C-4 and C-4a of the parent compounds **109** with respect to the C-8a-H. Such a process might occur as outlined in Equation 14. Rupture of the C-



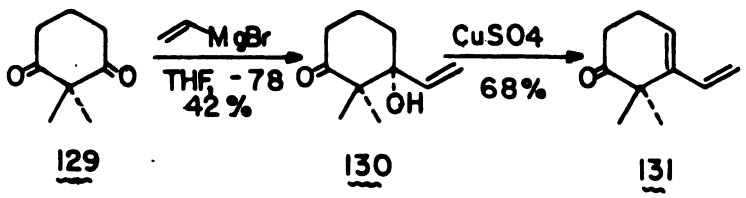
109 **128**

4a-O bond, accompanied by C-8a-H migration and cleavage of the C-4a-C-4-ring bond, could provide the intermediate **128**. Further reaction of **128** with $BF_3 \cdot Et_2O$ could eventually lead to **117**. Some support for the ring cleavage and recombination processes can be found in reports by Whitlock[29h] and Demole[31], respectively.

The processes described above illustrate the importance of remote substituents C-8a-CH_3 and the functional groups (1,2-double bond) in directing the epoxidation of the dienes **104** and the rearrangement of the epoxides **109** and **110**. In order to facilitate the rearrangement of epoxides of the type **109** to clerodane intermediates **122**, the C-8a-H must be replaced with a hydrogen equivalent that will not interfere with the rearrangement process. The group placed at C-8a should be at least as large as a $-CH_3$, must not eliminate, or participate during the rearrangement and must be transformed to the required hydrogen in later stages of the

synthesis. The carboakoxy group is a good candidate for such substituents. An alternative to the introduction of a functional group at the ring fusion might be the placement of a substituent in the A-ring to facilitate CH_3-migration and/or impede oxetane formation. The group of choice might be a 3β-hydroxy group.

The latter of these two possibilities was deemed the simplest to examine and, therefore, was investigated first. The required diene **130** was prepared as outlined in Equation 15 by the addition of vinyl magnesium bromide to 2,2-



129 **130** **131**

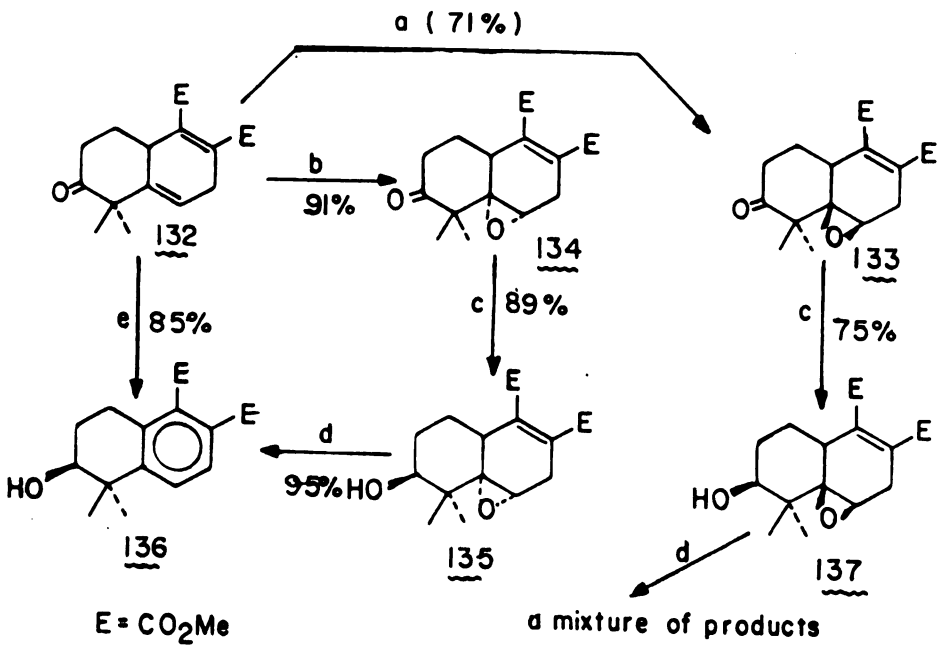
dimethyl-1,3-cyclohexanedione at -78°C followed by dehydration with $CuSO_4 \cdot 5H_2O$ to provide **131**. Although the yield of alcohol **129** was modest (42%), attempts to add vinyl magnesium bromide to the mono-protected diene[36] resulted in the recovery of the starting material unchanged.

The Diels-Alder reaction of **131** with dimethyl acetylenedicarboxylate proceeded slowly at room temperature, providing the adduct **132** in 52% yield (Scheme XVII). Epoxidation of **132** with NBS aqueous, t-butanol provided a 1:6 mixture of epoxides **133** and **134** in 91% yield. Sodium borohydride reduction of the epoxide **134** provided, as expected, the equatorial alcohol **135** in 89% yield.

Rearrangement of **135** with $BF_3 \cdot Et_2O$ resulted in the formation of the related B-ring aromatic diester **136**. The structure of **136** was proved by comparison to an authentic sample, prepared by treatment of **132** with DDQ followed by sodium borohydride reduction; these materials were found to be identical in all respects.

Epoxidation of **132** with MCPBA provided exclusively the epoxide **133** in 71% yield which was reduced with $NaBH_4$ to provide **137**. Treatment of **137** with $BF_3 \cdot Et_2O$ resulted in the formation of a large mixture of product which was unidentified and which concludes that the perturbation in the A ring was not good enough to direct the rearrangement to the required pathway.

Scheme XVII Synthesis of **136** and **137** and Rearrangements .



a) MCPBA, 0°C; b) NBS, aq. t-BuOH, 0°C, **134**:**133** = 6:1; c) $NaBH_4$, CH_3OH; d) $BF_3 \cdot Et_2O$, 0°C; e) i) DDQ; 95%; ii) $NaBH_4$, 89%.

EXPERIMENTAL

EXPERIMENTAL

Experimental Section

General: Tetrahydrofuran (THF) and benzene were dried by distillation, under nitrogen from sodium benzophenone ketyl. Petroleum ether refers to 30-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt, Inc., St. Louis, Missouri, and used as received. All other reagents were used as received unless otherwise stated; all reactions were carried out under a blanket of argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrophotometer with polystyrene as standard. Proton magnetic resonance spectra were recorded on a Varian T-60 at 60MHz or a Bruker WM-250 spectrometer at 250MHz as indicated, as solutions in deuterochloroform unless otherwise indicated. Chemical shifts are reported in parts per million on the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling

constant (Hz), integration]. ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the δ scale. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system.

All chromatography was performed by the flash technique according to the procedure of Still *et al*[37] using the silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters.

6,6-Dimethyl-1-vinyl-cyclohexene **100a**

To 15.4g (0.1 mol) of 2,2-dimethyl-1-vinyl-cyclohexanol in 300 mL of benzene was added 24.9g (0.1 mol) of $CuSO_4 \cdot (H_2O)_5$. The mixture was heated under reflux with azeotropic removal of water for 2 hrs. After cooling to room temperature, the copper sulfate was removed by filtration and the filtrate was concentrated by distillation of the benzene solvent at atmospheric pressure. The residual oil was purified by distillation BP_{11} = 50-52°C, providing 11.6g (87%) of **100a** as a colorless liquid.
^1H-NMR (250 MHz, $CDCl_3$): δ 6.30 (dd, J=17.7,11.6Hz, 1), 5.77 (t, J=3.97Hz, 1), 5.26 (d, J=17.7Hz, 1), 4.91 (d, J=11.6Hz, 1), 1.05 (s, 6), 0.8-2.2 (m, 6). EI/MS (70eV): 136 (M^+, 34.5), 121 (48.9), 107 (24.7), 93 (73.5), 80 (base), 69 (28.5), 55 (32.3), 40 (47.3), 33 (84.8). IR (neat): 2990,

2950, 2915, 2850, 1610, 1450, 1375, 1355, 1260, 1120, 930, 765cm^{-1}.

General Procedure for Diels-Alder Reactions.

Ethyl-5,5-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate 104c and 2-carboxylate 104d

To 2.0g (14.7 mmol) of **100a** was added 3.0g (30.6 mmol) of freshly distilled ethyl propiolate; the mixture was then heated in a 50°C oil bath for 12 hrs. The reaction mixture was cooled to room temperature and the excess ethyl propiolate was removed *in vacuo* to provide a colorless oil. The crude product was purified by preparative LC (Waters Prep 500; 2 columns; ether-hexane, 2:98; 300 mL min^{-1}) providing 2.55g (74.1%) of **104c** as a colorless viscous oil and 0.36g (10.5%) of **104d** as a colorless viscous oil.

104c: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.88 (br t, J=4.0Hz, 1), 5.35 (br t, J=4.0Hz, 1), 4.25 (m, 2), 3.28 (m, 1), 2.77 (m, 2), 1.38 (t, J=8.0Hz, 3), 1.3-2.0 (m, 6), 1.10 (s, 6). EI/MS (70eV): 234 (M^+, 44.3), 219 (7.92), 205 (10.2), 187 (16.0), 173 (9.9), 166 (14.6), 145 (23.3), 135 (20.8), 119 (20.3), 105 (38.6), 91 (base).IR (neat): 2960, 2915, 2880, 1720, 1680, 1650, 1380, 1365, 1255, 1230, 1075, 985cm^{-1}.

104d: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.76 (m, 1), 5.45 (t, J=3.3Hz, 1), 4.20 (q, J=7.02Hz, 2), 2.80-3.10 (m, 3), 1.45-2.8 (m, 6), 1.29 (t, J=7.02Hz, 3), 1.09 (s, 3), 1.04 (s, 3). EI/MS (70eV): 234 (M^+, 39.6), 232 (6.5), 219 (26.6), 205

(9.4), 189 (20.8), 177 (10.5), 163 (13.7), 149 (22.0), 135 (32.7), 119 (26.2), 105 (54.4), 91 (base). IR (neat): 3010, 2960, 2920, 2870, 1716, 1650, 1460, 1380, 1353, 1290, 1253, 1240, 1110, 1090, 1030, 953, 915, 753, 740cm^{-1}.

General Procedure for Regio-Reversed Diels-Alder Reactions

Ethyl-5,5-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-2-carboxylate **104d**

To 0.5g (3.7 mmol) of **100a** in 20 mL of dry benzene was added 1.0g (6.9 mmol) of (Z)-ethyl-β-nitroacrylate[38] **108a** (R_2=H). The resulting yellow-orange solution was allowed to stir for 18 hrs. at room temperature, then the solvent was removed *in vacuo* to give a yellow oil. The crude product was filtered through a short column of silica gel (60-230 mesh, ether-pet. ether, 1:4) to afford the Diels-Alder adducts (0.96g, 91%) as a pale yellow viscous oil.

To 0.6g (2.1 mmol) of the adducts in 20 mL of dry THF was added 0.64g (4.2 mmol) of DBU. The mixture was stirred for 4 hrs. at room temperature, cast into ether (50 mL), washed with 0.1N aq. HCl, saturated aq. $NaHCO_3$ and brine (50 mL each). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide the crude product as a viscous pale yellow oil. The crude **104d** was purified by chromatography on a column of silica gel (20 mm OD; 230-400 mesh; ether-pet. ether, 1:4; 10 mL fractions) using the flash technique[37] to yield **104d** (0.42g, 86%).

Ethyl-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate **105**

To a solution of 0.1g (0.4 mmol) of **104c** in 10 mL of benzene was added 0.17g (0.6 mmol) of DDQ. The mixture was allowed to stir for 12 hours at room temperature; then was filtered through a pad of celite which was rinsed with benzene, and the combined eluate was concentrated *in vacuo* to afford a pale yellow oil. The crude product was purified by chromatography on a column of silica gel (20 mm OD; 60-230 mesh; ether-pet. ether, 1:9; 7 mL fractions) giving 0.097g (98%) of **105** as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$): δ 7.56 (dd, J=7.5,1.25Hz, 1), 7.49 (dd, J=7.5,1.25Hz, 1), 7.18 (t, J=7.5Hz, 1), 4.34 (q, J=7.0Hz, 2), 3.02 (br t, J=6.6Hz, 2), 1.6-1.85 (m, 4), 1.38 (t, J=7.0Hz, 3), 1.28 (s, 6).EI/MS (70eV): 232 (M^+, 68.8), 217 (90.5), 203 (17.3), 187 (48.0), 186 (84.3), 171 (base), 161 (20.1), 143 (39.1), 128 (64.3), 115 (52.9), 105 (11.0), 91 (33.6), 77 (19.5), 51 (16.1), 43 (32.3).IR (neat): 3065, 2960, 2935, 2875, 1720, 1560, 1475, 1450, 1385, 1365, 1275, 1210, 1185, 1150, 1100, 1025, 760, 720cm^{-1}.

Ethyl-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate **106**

In a similar fashion to that described for the preparation of **105**, 0.1g of **104d** yielded 0.084g (85%) of **106** as a viscous colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.78 (br d, J=8.3Hz, 1), 7.73 (br s, 1), 7.36 (d, J=8.3Hz, 1), 4.35 (q, J=7.0Hz, 2), 2.80 (br t, J=6.6Hz, 2), 1.6-1.85 (m, 4), 1.36 (t, J=7.0Hz, 3), 1.28 (s, 6). EI/MS (70eV): 232 (M^+, 18.2), 217 (base), 203 (17.3), 187 (13.9), 171 (8.4), 159 (3.2), 145 (19.1), 128 (16.4), 115 (15.3), 105 (3.9), 91 (11.9), 77 (5.11), 51 (3.6), 43 (6.0), 41 (7.2). IR (neat): 3040, 2960, 2930, 2875, 1720, 1610, 1570, 1460, 1420, 1385, 1365, 1290, 1270, 1235, 1200, 1185, 1170, 1110, 1055, 1020, 915, 770, 730cm^{-1}.

Dimethyl-5,5-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate **104a**

According to the general procedure for Diels-Alder reactions, 1.0g (7.3 mmol) of **100a** was mixed at room temperature with 1.2g (8.5 mmol) of dimethylacetylene dicarboxylate. An instantaneous exothermic reaction occured; the reaction mixture was then stirred for an additional 1 hour. Chromatography of the mixture on a column of silica gel (50g, 60-230 mesh, 40 mm OD; 20 mL fractions). Fractions 5 to 12 gave 1.93g of **104a** as a colorless oil (95%).

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.36 (t, J=3Hz, 1), 3.76 (s, 3), 3.72 (s, 3), 3.0 (m, 3), 1.2-2.0 (m, 6), 1.06 (s, 3), 1.03 (s, 3). EI/MS (70eV): 278 (M^+, 2.5), 263 (2.3), 244 (base), 229 (46.9), 213 (5.05), 203 (11.4), 186 (19.8), 176 (7.4), 159 (12.3), 143 (13.9), 128 (17.9), 111 (61.0), 105

(22.8), 98 (11.6), 91 (37.9), 77 (24.9), 69 (26.2), 59 (61.7), 55 (45.8), 39 (95.6). IR (neat): 3020, 2950, 2930, 2870, 1725, 1430, 1260, 1100, 1040cm^{-1}.

Dimethyl-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate[33b,38] **104b**

According to the general procedure for the Diels-Alder reaction, 5.0g (33.3 mmol) of diene **100b** was heated at 110°C with 5.6g (35 mmol) dimethyl acetylene dicarboxylate for 12 hours. The mixture was cooled to room temperature and filtered through a short column of silica gel (ether:pet. ether; 1:1). Purification of the resulting viscous oil on prep. LC (ether:hexane, 8:92, 250 mL/minute) provided 8.1g of **104b** as a colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.70 (dd, J=3.0,6.0Hz, 1), 3.8 (s, 3), 3.73 (s, 3), 3.20 (dd, J=6.0,23Hz, 1), 2.78 (dd, J=3.0,23Hz, 1), 1.2-1.8 (m, 6), 1.43 (s, 3), 1.18 (s, 3), 1.14 (s, 3). EI/MS (70eV): 292 (M^+, 11.4), 261 (23.3), 260 (51.8), 245 (9.3), 233 (6.3), 217 (28.5), 210 (9.6), 203 (42.4), 189 (20.7), 178 (40.9), 176 (58.8), 163 (24.4), 149 (42.9), 83 (7.5), 69 (8.8), 55 (4.2), 40 (base). IR (neat): 3000, 2960, 2930, 2860, 1735, 1670, 1640, 1440, 1370, 1340cm^{-1}.

Ethyl-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate **104e**

According to the general procedure for Diels-Alder reactions, 1.0g (6.7 mmol) of diene **100b** was mixed with 1.5g (15.3 mmol) ethyl propiolate and heated at 120°C for 24 hours. Chromatography of the mixture on a column of silica gel (70g, 230-400 mesh, ether-hexane, 5:95, 20 mL fractions) afforded 0.77g (45.8%) of **104e** as a colorless oil and 0.15g (9.1%) of **104f**.

104e: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.64 (t, J=4.2Hz, 1), 5.60 (t, J=4.1Hz, 1), 4.16 (q, J=7.0Hz, 2), 2.76 (t, J=4.2Hz, 2), 1.46 (s, 3), 1.28 (t, J=7.0Hz, 3), 1.18 (s, 3), 1.11 (s, 3), 0.9-1.8 (m, 6). EI/MS (70eV): 249 (M^+, 5.97), 233 (47.5), 217 (15.9), 203 (12.1), 187 (40.5), 171 (19.8), 159 (28.9), 145 (41.3), 135 (25.5), 119 (base), 105 (92.4), 91 (78.0), 83 (8.9), 77 (26.8), 69 (15.6). IR (neat): 3060, 2960, 2920, 2870, 2820, 1715, 1670, 1630, 1460, 1385, 1370, 1230, 1180, 1060, 1025, 980cm^{-1}.

104f: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.58 (d, J=3.2Hz, 1), 5.65 (dd, J=5.5,2.5Hz, 1), 4.22 (q, J=7.0Hz, 2), 3.01 (dd, J=5.5,20.8Hz, 1), 2.83 (d t, J=2.5,20.8Hz, 1), 1.3-2.0 (m, 6), 1.31 (t, J=7.0Hz, 3), 1.22 (s, 3), 1.18 (s, 3), 1.13 (s, 3). EI/MS (70eV): 248 (M^+, 6.11), 233 (40.0), 217 (21.3), 203 (12.6), 187 (35.4), 171 (20.6), 159 (27.8), 145 (40.9), 129 (23.9), 119 (base), 105 (95.4), 91 (75.1), 77 (23.9), 69 (15.9). IR (neat): 3060, 2960, 2920, 2870, 2710, 1670,

1625, 1460, 1400, 1380, 1250, 1230, 1180, 1060, 1030, 980cm^{-1}.

Ethyl-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-2-carboxylate **104f**

According to the general procedure for regio-reversed Diels-Alder reactions, 1.5g (10 mmol) of diene **100b** was treated with 1.5g (10.1 mmol) (E)-β-nitroacrylate **108a** at 110°C for 12 hours. The crude product was purified by chromatography on a column of silica gel (50g, 30 mm OD, 60-230 mesh, ether-pet. ether, 5:95) gave 2.28g (78%) yield of a mixture of exo- and endo-adducts. The adducts were treated with 1.7g of (DBU) in 50 mL benzene and the mixture was heated under reflux for 8 hours. Usual workup and chromatography of the residue over silica gel (65g, 40 mm OD, ether-Pet. ether, 2:98) provided 1.75g, 92%, of **104f** as a colorless liquid.

Methyl-2,5,5-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate **104g**

To 0.5g (3.6 mmol) of diene **100a** was added 0.7g (7.1 mmol) methyl tetrolate, and the mixture was heated in a sealed stainless steel cuvette at 150°C for 12 hours. The resulting dark oil was purified by chromatography on a column of silica gel (60g, 40 mm OD, ether-pet. ether, 3:97) to give 0.495g of **104g** (58%) as a colorless oil and 0.055g of **104h** (6.4%).

104g: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.33 (t, J=3.4Hz, 1), 3.67 (s, 3), 2.0-3.2 (m, 3), 1.79 (s, 3), 0.99 (s, 6), 1.0-2.0 (m, 6). EI/MS (70eV): 234 (M^+, 25.7), 219 (34.5), 203 (9), 187 (15.1), 175 (12.7), 159 (26.5), 145 (17.2), 131 (21.2), 119 (34.1), 105 (base), 91 (40.2), 77 (19.1), 59 (21.7). IR (neat): 2950, 2930, 2860, 1720, 1685, 1600, 1435, 1380, 1360, 1325, 1270, 1230, 1150, 1100, 1050, 870cm^{-1}.

Ethyl-1,5,5-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-2-carboxylate **104i**

According to the general procedure for regio-reversed Diels-Alder reactions, 0.6g (4.4 mmol) of **100** and 0.7g (4.9 mmol) of ethyl-β-nitro crotonate reacted with 0.7g (4.9 mmol) **108b** · in 30 mL of benzene at room temperature for 12 hours. The usual workup provided 0.93g (74%) of a yellow liquid of the nitro adducts. To 0.75g of the adducts was added 0.76g of DBU (φH, 1 hr., RT) after the usual workup, and purification of the residue by chromatography on a column of silica gel (30g, 30 mm OD, ether-pet. ether, 3:97) provided 0.57g (90% yield) of **104i**. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.38 (br t, J=3.4Hz, 1), 4.11 (q, J=7.3Hz, 2), 2.7-2.89 (m, 3), 1.95 (br s, 3), 1.21 (t, J=7.3Hz, 3), 1.0 (s, 3), 0.97 (s, 3), 0.9-1.7 (m, 6). EI/MS (70eV): 248 (M^+, 4.3), 175 (82.4), 159 (28.4), 133 (19.9), 119 (37.4), 105 (base), 91 (72.4). IR (neat): 3060, 2960, 2940, 2870, 1735,

1540, 1460, 1385, 1375, 1350, 1220, 1175, 1150, 1100, 1030, 860, 830cm^{-1}.

General Procedure for m-Chloroperbenzoic Acid (MCPBA) Epoxidation

Ethyl-5,5-dimethyl-4-β,4a-β-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **110c** and 4α-4a,α-epoxy **109c**

To a solution of 0.5g (2.1 mmol) of **104c** in 20 mL dry CH_2Cl_2 at 0°C (ice water bath) was added a solution of 6.89g (85%, 4.3 mmol) of m-chloroperbenzoic acid (MCPBA) in 20 mL of dry CH_2Cl_2 over a period of 1 hour. After stirring at 0°C for an additional 1 hour, a white precipitate was formed. The reaction was quenched with 10% aq. $Na_2S_2O_3$ (20 mL), then the mixture was cast into ether - 10% aq., $Na_2S_2O_3$ (100 mL each). The organic layer was separated, washed with saturated aq. $NaHCO_3$, water and brine (100 mL each), and dried (Na_2SO_4). Concentration *in vacuo* provided 0.43g (81%) of a mixture of **109c** and **110c**. Purification of the mixture on a column of silica gel (60g, 40 mm OD, ether-hexane, 5:95) to provide 0.387 (73%) of **110c** as a colorless oil, which solidified upon cooling (colorless crystals), m.p. 52°C. Further elution afforded 0.043g (8.1% yield) of **109c** as a white solid, m.p. 45-47°C. **110c**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.67 (br d, J=20Hz, 1), 4.2 (m, 2), 3.32 (br s, 1), 3.22 (br d, J=12.2Hz, 1), 2.73 (dt, J=6.1,1.5Hz, 1),

2.10 (dt, J=12.2,1.5Hz, 1), 2.59 (dd, J=20,1.5Hz, 1), 1.4-1.8 (m, 6), 1.28 (t, J=7.2Hz, 3), 1.124 (s, 3), 0.81 (s, 3). ^{13}C-NMR (6.9 MHz, $CDCl_3$): δ = 166.4, 132.5, 132.2, 66.3, 60.4, 54.5, 40.4, 34.6, 33.2, 27.1, 25.3, 22.1, 21.5, 14.2. EI/MS (70eV): 250 (M^+, 88.1), 235 (10.1), 222 (35.6), 217 (9.4), 205 (58.5), 189 (24.6), 179 (33.4), 177 (23.5), 171 (17.0), 161 (38.6), 154 (46.5), 149 (61.7), 139 (base). IR (neat): 2980, 2860, 1720, 1660, 1470, 1390, 1372, 1305, 1270, 1250, 1100, 1050, 940, 900, 765cm^{-1}. **109c**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.47 (m, 1), 4.21 (q, J=7.2Hz, 2), 3.33 (br s, 1), 3.01 (dt, J=3,12Hz, 1), 2.75 (dm, J=20Hz, 1), 2.52 (ddd, J=3,1.5,20Hz, 1), 1.3-2.2 (m, 6), 1.25 (t, J=7.2Hz, 3), 1.15 (s, 3), 0.78 (s, 3). ^{13}C-NMR (68.9 MHz, $CDCl_3$): δ = 167.3, 131.84, 131.37, 66.23, 50.24, 53.77, 37.80, 34.66, 32.72, 27.51, 26.98, 24.04, 22.27, 14.21. EI/MS (70eV): 250 (M^+, 55.7), 235 (8.6), 222 (36.1), 217 (15.6), 205 (81.0), 189 (39.6), 179 (51), 171 (21.9), 161 (60.6), 154 (52.9), 69 (34.5), 55 (25.4), 41 (27.8). IR (neat): 2970, 2930, 2870, 1740, 1695, 1440, 1390, 1365, 1280, 1260, 1210, 1120, 1100, 1070, 810cm^{-1}.

A General Procedure for N-Bromosuccinimide Epoxidation in Aqueous t-Butanol

Ethyl-5,5-dimethyl-4-α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **109c**

To 1.5g (6.4 mmol) of **104c** in 30 mL of a mixture of t-butanol-water (2:1) at room temperature was added 1.95g

(11.0 mmol) of N-bromosuccinimide (NBS). The mixture was stirred at room temperature for 1 hour, and then was diluted with water (100 mL). The solution was extracted ether (1x 00 mL); the combined organic phases were washed with saturated aq. $NaHCO_3$ and brine (50 mL each) and dried (Na_2SO_4). Concentration *in vacuo* gave 1.5g (94%) of **109c** as a colorless oil which solidified upon cooling.

Methyl-2,5,5-trimethyl-4β,4aβ-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **110g** and 4α,4aα epoxy **109g**

According to the general procedure for epoxidation with MCPBA, 0.25g (1.06 mmol) of **104g** were treated with a solution of 0.33g (1.5 mmol) MCPBA, 85%. The usual workup and chromatography of the crude product on a column of silica gel provided 0.178g (68%) of **110g** and 0.022g (8.5%) of **109g**.

110g: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.71 (s, 3), 3.28 (d, J=1Hz, 1), 2.6 (br s, 2), 2.48 (m, 2), 1.97 (s, 3), 1.2-2.0 (m, 6), 1.59 (s, 3), 1.15 (s, 3), 0.79 (s, 3). EI/MS (70eV): 250 (M^+, 7.3), 235 (6.7), 219 (8.8), 207 (11.4), 185 (5.3), 176 (16.3), 163 (13.7), 157 (6.0), 91 (66.2), 77 (60.2), 69 (51.2), 55 (57.6), 41 (base). IR (neat): 2960, 2930, 1720, 1700, 1685, 1435, 1390, 1365, 1240, 1070cm^{-1}.

109g: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.73 (s, 3), 3.27 (br s, 1), 2.975 (dm, J=12.3Hz, 1), 2.61 (d, J=19.5Hz, 1), 2.53 (d, J=19.5Hz, 1), 1.22-2.2 (m, 6), 1.70 (br s, 3), 1.11 (s, 3),

0.78 (s, 3). EI/MS (70eV): 250 (M^+, 11.51), 235 (15.0), 232 (6.1), 221 96.24), 219 (18.5), 191 (11.8), 176 (43.6), 163 (28.6), 153 (32.7), 147 (32.0), 133 (21.2), 121 (39.0), 117 (10.8), 103 (31.8), 91 (62.4), 69 (58.7), 41 (base). IR (neat): 2960, 2930, 2860, 1720, 1700, 1685, 1430, 1380, 1365, 1240, 1020cm^{-1}.

Dimethyl-5,5-dimethyl-4β-4aβ-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **109a** and dimethyl-5,5-dimethyl-4α-4aα-epoxy-octahydronaphthalene-1,2-dicarboxylate **110a**

According to the general procedure for epoxidation with MCPBA, 7.0g (23.8 mmol) **104a** was epoxidized with MCPBA (7.0g, 34.5 mmol, 85%) affording 6.73g (95%) of a mixture of epoxides **109a** and **110a** in a ratio of 45:55. Fractional crystallization from ether:hexane (3:7) gave 3.77g (52%) of **110** as white crystals, m.p. 74-76°C, and 3.03g of **109a** (43%) as white crystals, m.p. 112-113°C.

110a: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.74 (s, 3), 3.71 (s, 3), 3.33 (br dd, J=19.0,2.1Hz, 1), 2.12 (dt, J=13.7,2.5Hz, 1), 1.61 (m, 3), 1.1-1.5 (m, 5), 1.08 (s, 3), 0.80 (s, 3). EI/MS (70eV): 294 (M^+, 1.5), 279 (0.7), 263 (26.5), 234 (51.7), 219 (36.4), 202 (23.0), 191 (30.0), 175 (20.8), 165 (base). IR (neat): 1735, 1660, 1290, 1270, 1200, 1090, 1070, 1040, 940, 885, 870, 810, 785, 755cm^{-1}.

109a: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.77 (s, 3), 3.70 (s, 3), 3.35 (t, J=1.5Hz, 1), 3.08 (dm, J=19.2Hz, 1), 3.05 (m, 1),

2.52 (dm, J=19.2Hz, 1), 1.2-1.8 (m, 6), 1.11 (s, 3), 0.8 (s, 3). EI/MS (70eV): 294 (M^+, 4.5), 279 (7.5), 263 (21.7), 247 (13.2), 234 (51.5), 219 (27.9), 202 (17.3), 191 (21.9), 165 (base). IR (neat): 1730, 1720, 1650, 1260, 1090, 1070, 970, 955, 830, 760, 720cm^{-1}.

Ethyl-5,5-dimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **109d** and 4β,4a-β-epoxy **110d**

According to the general procedure for epoxidation with NBS in aq. t-butanol, 0.2g (0.85 mmol) of **104d** was treated with 0.23g (1.28 mmol) of NBS at room temperature to provide 0.11g (52%) of **109d** and 0.0195g, 9%, of **110d** after purification by chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 2:98).
109d: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.66 (dd, J=6.1,3.0Hz, 1), 4.2 (m, 2), 3.34 (br d, J-1.5Hz, 1), 2.93 (dt, J=18.5,1.5Hz, 1), 2.79 (m, 1), 2.46 (ddd, J=18.5,1.5,3.0Hz, 1), 1.92 (m, 1), 1.3-1.7 (m, 6), 1.20 (t, J=7.2Hz, 3), 1.0 (s, 3), 0.74 (s, 3). EI/MS (70eV): 250 (M^+, 26.6), 217 (48.4), 177 (19.5), 161 (80.5), 147 (39.1), 133 (25.0), 119 (46.1), 109 (63.3), 105 (63.3), 105 (64.1), 91 (base). IR (neat): 2960, 2930, 2850, 2840, 1710, 1660, 1460, 1390, 1370, 1300, 1250, 1080, 1010, 895, 780, 740cm^{-1}.
110d: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.45 (t, J=3.3Hz, 1), 4.1 (q, J=7.2Hz, 2), 3.32 (br s, 1), 2.93 (dt, J=18.5,0.5Hz, 1), 2.73 (dm, J=18.5Hz, 1), 2.39 (dm, J=18.5Hz, 1), 1.25-1.8 (m,

1), 1.22 (t, J=7.2Hz, 3), 1.08 (s, 3), 0.78 (s, 3). EI/MS (70eV): 250 (M^+, 10.0), 235 (13.7), 221 (6.6), 204 (52.8), 189 (23.1), 176 (17.2), 161 (57.4), 147 (26.9), 133 (33.3), 123 (20.2), 107 (35.4), 96 (base). IR (CCl_4): 2960, 2930, 2840, 1720, 1660, 1450, 1390, 1370, 1310, 1080, 1000, 895, 780cm^{-1}.

Ethyl-5,5-dimethyl-4β,4a-β-epoxy-3,4,4a,5,6,7,8,8a-oxtahydronaphthalene-2-carboxylate **110d**

According to the general procedure for epoxidation with MCPBA, treatment of 0.2g (0.8 mmol) of **104d** with 0.2g (0.95 mmol, 85%) of MCPBA at 0°C provided, after the usual workup and chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 2:98), 0.11g (51%) of **110d** as a colorless oil and 0.055g (26%) of **109d** as a colorless oil.

Ethyl-5,5,8a-trimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **109e**

According to the general procedure for epoxidation with MCPBA, 0.14g (0.56 mmol) of **104e** was treated with 0.17g (0.84 mmol) of MCPBA at 0°C. After the usual workup, purification by chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 5:95) gave 0.12g (81%) of **109e**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.24 (dt, J=8.3,2.0Hz, 1), 4.22 (q, J=7.0Hz, 2), 3.25 (br s, 1), 2.3-2.8 (m, 3), 1.46 (s,

3), 1.26 (t, J=7.0Hz, 3), 1.21 (s, 3), 0.81 (s, 3). EI/MS (70eV): 264 (M^+, 2.5), 249 (3.7), 235 (10.0), 219 (10.2), 203 (8.1), 191 (8,7), 175 (14.9), 163 (30.8), 147 (205), 133 (15.7), 123 (33.4), 107 (34.4), 91 (45.6), 81 (45.1), 69 (53.3), 55 (57.9), 41 (base). IR (neat): 2980, 2930, 2880, 1715, 1465, 1390, 1375, 1370, 1240, 1230, 1190, 1075, 1065, 1025, 975, 900cm^{-1}.

Ethyl-5,5,8a-trimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **109f**

According to the general procedure for epoxidation with MCPBA, treatment of 0.25g (1 mmol) of **104f** with 0136g (1.5 mmol, 85%) of MCPBA provided, after chromatography on a column of silica gel (35g, 30 mm OD, 230-400 mesh, ether-pet. ether, 20:80) 0.24g (90%) of **109f** as a colorless viscous oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.46 (d, J=3.3Hz, 1), 4.16 (q, J=7.2Hz, 2), 3.37 (m, 1), 3.31 (dd, J=18.7,3.3Hz, 1), 2.45 (dm, J=18.7, 1), 1.27 (t, J=7.2Hz, 3), 1.21 (s, 3), 1.14 (s, 3), 0.8 (s, 3), 1.1-1.8 (m, 6). EI/MS (70eV): 264 (M^+, 4.5), 249 (13.4), 235 (31.8), 218 (22.3), 203 (19.4), 189 (20.7), 175 (24.9), 266 (21.3), 161 (47.9), 147 (28.5), 133 (20.0), 123 (84.4), 107 (37.1), 91 (46.6), 79 (35.3), 69 (50.4), 55 (53.9), 41 (base). IR (neat): 2980, 2930, 2870, 2850, 1710, 1610, 1465, 1390, 1375, 1300, 1250, 1180, 1080, 1005, 975, 780, 740cm^{-1}.

A General Procedure for Epoxide Rearrangement with $BF_3 \cdot Et_2O$

Rearrangement of dimethyl-5,5-dimethyl-4β,4a-β-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **110a** with $BF_3 \cdot Et_2O$

To a solution of 0.1g (0.42 mmol) of **110a** in 20 mL of dry methylene chloride, cooled to 0°C (ice water), was added 0.06g (0.42 mmol) $BF_3 \cdot Et_2O$ in 5 mL CH_2Cl_2. The reaction mixture was allowed to stir for 10 minutes at 0°C under argon then was quenched with 5 mL of saturated aqueous $NaHCO_3$. The reaction mixture was cast into ether, saturated aq. $NaHCO_3$ (50 mL each), and the organic layer was separated and dried (Na_2SO_4). Concentration *in vacuo* and chromatography of the residue on a column of silica gel (30g, 30 mm OD, 60-230 mesh, ether-pet. ether, 1:1) provided 0.092g (92%) of oxetane **117a**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.76 (br t, J=2Hz, 1), 3.82 (s, 3), 3.76 (s, 3), 2.80 (br t, J=8.3Hz, 1), 2.76 (dd, J=18.8, 2.3Hz, 1), 2.26 (dd, J=18.8,4.2Hz, 1), 2.12 (m, 1), 1.90 (t, J=8.3Hz, 2), 1.55 (m, 3), 1.44 (s, 3), 1.22 (s, 3). ^{13}C-NMR (68.9 MHz, $CDCl_3$): δ = 169.4(s), 167.6(s), 142.2(s), 129.0(s), 83.7(s), 81.8(d), 53.1(s), 52.2(q), 52.1(q), 41.7(d), 33.7(t), 32.7(t), 30.3(t), 26.5(q), 24.5(q), 23.9(t). EI/MS (70eV): 295 (M^+1, 0.6), 263 (5.9), 236 (1.4), 204 (m-60,55.4), 176 (base), 145 (32.4), 117 (42.9), 105 (50.8), 91 (31.7). IR (neat): 2945, 2860, 1720(br),

1645, 1430, 1375, 1360, 1260(br), 1190, 1105, 1070, 855, 830, 725cm^{-1}.

Rearrangement of ethyl-5,5-dimethyl-4β,4a-β-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **110c** with $BF_3 \cdot Et_2O$

To 0.5g (2 mmol) of epoxide **110c** was added 0.31g (2.2 mmol) $BF_3 \cdot Et_2O$ at 0°C according to the general procedure for epoxide rearrangement. The usual workup and purification by chromatography on a column of silica gel (60g, 40 mm OD, 230-400 mesh, ether-pet. ether, 3:7) provided 0.41g (82%) of oxetane **117c** as a colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.03 (dm, J=7.2Hz, 1), 4.72 (br s, 1), 4.24 (q, J=6.25Hz, 2), 3.02 (br t, J=9.0Hz, 1), 2.52 (ddd, J=19.5,7.2,1.7Hz, 1), 2.2 (br d, J=19.5Hz, 1), 2.08 (m, 1), 1.43 (s, 3), 1.5-2.0 (5), 1.12 (s, 3). ^{13}C-NMR (68.9 MHz, $CDCl_3$): δ = 166.7, 135.5, 135.3, 83.9, 82.2, 60.4, 53.1, 38.2, 34.2, 38.4, 30.4, 26.7, 24.4, 23.9, 14.2. EI/MS (70eV): 250 (M^+, 2.8), 233 (6.3), 217 (2.6), 205 (8.1), 192 (24.2), 76 (3.4), 163 (20.4), 147 (12.3), 133 (14.22), 119 (93.2), 105 (21.3), 91 (base). IR (neat): 2950, 2850, 1720, 1650, 1460, 1385, 1370, 1260, 1205, 1105, 1080, 950, 915cm^{-1}.

Rearrangement of Methyl-2,5,5-trimethyl-4β,4a-β-epoxy-3,4,5,6,7,8,8a-oxtahydronaphthalene-1-carboxylate **110g** with $BF_3 \cdot Et_2O$

To 0.15g (0.6 mmol) of the β-epoxide **110g** was added 0.128g (0.9 mmol) $BF_3 \cdot Et_2O$ at 0°C according to the general procedure for epoxide rearrangement. The usual workup and purification by chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 1:1) provided 0.122g (81%) of oxetane **117g** as a colorless oil. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.66 (t, J=2.5Hz, 1), 3.78 (s, 3), 2.80 (t, J=9.2Hz, 1), 2.23 (m, 2), 2.14 (s, 3), 1.80 (t, J=7.5Hz, 2), 1.40 (s, 3), 1.17 (t, J=7.5Hz, 2), 1.14 (s, 3), 0.9-1.2 (m, 2). EI/MS (70eV): 250 (M^+, 2.9), 219 (7.5), 192 (39.4), 177 (50.4), 160 (15.2), 133 (89.9), 117 (23.1), 105 (98.4), 91 (40.9), 79 (26.5), 59 (36.6), 43 (base). IR (neat): 2960, 2930, 2860, 1720, 1460, 1390, 1370, 1260, 1200, 1140, 1100, 1030, 975cm^{-1}.

Rearrangement of Ethyl-5,5-dimethyl-4β,4a-β-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **110d** with $BF_3 \cdot Et_2O$

To 0.15g (0.6 mmol) of epoxide **110d** was added 0.11g (0.75 mmol) of $BF_3 \cdot Et_2O$ at 0°C according to the general procedure for epoxide rearrangement. The usual workup and purification by chromatography on a column of silica gel

(30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 1:1) provided 0.13g (87%) of oxetane **117d**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.40 (dd, 7.2,3.0Hz,1), 4.75 (m, 1), 4.18 (q, J=7.2Hz, 2), 2.82 (dd, J=18.75,1.0Hz, 1), 2.65 (dd, J=7.1,1.0Hz, 1), 2.14 (dt, J=18.75,4.0Hz, 1), 1.5-2.1 (m, 6), 1.39 (s, 3), 1.30 (t, J=7.7Hz, 3), 1.125 (s, 3). EI/MS (70eV): 250 (0.7), 217 (0.34), 205 (1.5), 192 (9.3), 163 (10.0), 119 (52.0), 91 (base). IR (neat): 3030, 2960, 2860, 1715, 1450, 1385, 1360, 1250cm^{-1}.

Rearrangement of Dimethyl-5,5-dimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **109a**

To 0.1g (0.34 mmol) of epoxide **109a** was added 0.059g (0.42 mmol) $BF_3 \cdot Et_2O$ according to the general procedure for epoxide rearrangement. The usual workup and purification by chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether-pet. ether, 1:1) gave 0.053g (53%) of oxetane **117a**, 0.030g (30%) of dimethyl-7β-hydroxy-7α,β-isopropenyl-2,3,3a,6,7,7a-hexahydro-indene-4,5-dicarboxylate **123a** and 0.008g (8%) of dimethyl-7α-hydroxy-7a-isopropenyl-2,3,3a,6,7,7a-hexahydroidene-4,5-dicarboxylate **124a**.

123a: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.05 (m, 1), 4.84 (s, 1), 3.77 (s, 3), 3.74 (s, 3), 3.85 (m, 1), 3.06 (t, J=8.2Hz, 1), 2.72 (dd, J=4.0,16.5Hz, 1), 2.29 (ddd, J=2.0,8.2,16.5Hz, 1), 1.84 (br s, 3), 1.4-2.0 (m, 7). EI/MS (70eV): 276 (M^+, H_2O,

2.1), 262 (13.9), 244 (11.8), 234 (43.8), 223 (23.5), 205 (14.9), 159 (13.2), 149 (base). IR (neat): 3600, 3030, 2960, 2930, 2860, 1725, 1600, 1440, 1340, 1250, 1170, 1150, 1100, 1050, 980cm^{-1}.

124a: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.02 (br s, 1), 4.94 (br s, 1), 4.30 (m, 1), 3.80 (s, 3), 3.75 (s, 3), 3.0 (m, 1), 2.63 (ddd, J=18.5,4.0,1.5Hz, 1), 2.45 (ddd, J=18.5,6.0,1.5Hz, 1), 1.80 (s, 3), 1.4-1.8 (m, 7). EI/MS (70eV): 294 (1.7), 276 (5.2), 261 (3.7), 245 (21.4), 237 (10.7), 221 (13.7), 213 (24.9), 201 (9.0), 189 (14.1), 161 (37.3), 145 (13.8), 123 (80.2), 105 (30.8), 91 (43.9), 43 (base). IR (neat): 3600, 2960, 2830, 1735, 1650, 1600, 1460, 1330, 1250, 1200, 1150, 1100, 1035, 980cm^{-1}.

Rearrangement of Ethyl-4,4a-dimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene **109c** with $BF_3 \cdot Et_2O$

To 0.1g (0.40 mmol) of the α-epoxide **109c** was added 0.07g (0.5 mmol) of $BF_3 \cdot Et_2O$ according to the general procedure for epoxide rearrangements. The usual workup and purification by HPLC (Perkin Elmer Series 211 equipped with a Waters Radial Compression Unit, 10u silica gel cartridge, and a Perkin Elmer 7500 Variable Wavelength UV detector, nm, eluted with ether-hexane, 1:4, 4 mL/min) gave 0.060g (60%) of oxetane **117c** and 0.030g (30%) of the β-alcohol **123c**.

117c: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.79 (t, J=4.13Hz, 1), 5.03 (t, J=1.2Hz, 1), 4.83 (br s, 1), 4.21 (m, 2), 3.82 (dd, J=4.9,8.0Hz, 1), 3.09 (t, J=18.3Hz, 1), 2.50 (dt,

J=19.4,4.9Hz, 1), 1.05-1.35 (m, 3), 1.83 (br s, 3), 1.30 (t, J=7.2Hz, 3), 1.4-1.7 (m, 5). EI/MS (70eV): 250 (M^+, 1.5), 232 (10.0), 204 (30.6), 192 (32.7), 176 (19.7), 159 (35.8), 147 (29.4), 133 (60.4), 119 (67.5), 105 (43.5), 91 (79.6), 85 (base). IR (neat): 3450, 2950, 2860, 1710, 1650, 1450, 1375, 1240, 1200, 1100, 1060, 960, 900, 740cm^{-1}.

123c: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.78 (t, J=4.3Hz, 1), 5.03 (t, J=1.2Hz, 1), 4.82 (br s, 1), 4.21 (m, 2), 3.82 (dd, J=4.9,7.9Hz, 1), 3.09 (t, J=8.3Hz, 1), 2.50 (dt, J=19.2,4.9Hz, 1), 1.82 (br s, 3), 1.4-1.75 (m, 5), 1.05-1.35 (m, 3), 1.29 (t, J=7.02Hz, 3). EI/MS (70eV): 250 (M^+, 13.5), 232 (10.0), 204 (30.6), 192 (32.7), 176 (19.7), 159 (35.2), 147 (29.4), 133 (60.4), 119 (67.5), 105 (43.5), 91 (76.6), 85 (base). IR (neat): 3450, 2950, 2850, 1710, 1650, 1450, 1375, 1240, 1200, 1100, 1060, 960, 900, 740cm^{-1}.

Dimethyl-2,3,3a,6-tetrahdro-indene-4,5-dicarboxylate **119**

According to the general procedure for Diels-Alder reactions, 0.5g (5.3 mmol) of 1-vinylcyclopentene **118** was mixed with 1.5g (10.5 mmol) of dimethylacetylene dicarboxylate and heated at 110°C for 24 hours. After cooling to room temperature and purification by chromatography on a column of silica gel (40g, 40 mm OD, 60-230 mesh, ether-pet. ether, 1:4) gave 0.79g (63%) of **119** as a colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.46 (br t, J=2.2Hz, 1), 3.79 (s, 3), 3.75 (s, 3), 3.0 (m, 3), 2.32 (m, 2), 2.01 (m, 2),

1.4-1.7 (2). EI/MS (70eV): 236 (M^+, 0.2), 204 (45.1), 176 (base), 145 (43.8), 117 (70.4), 105 (72.9), 91 (35.9). IR (neat): 3040, 2960, 2870, 1725, 1650, 1590, 1445, 1265, 1040cm^{-1}.

Rearrangement of Methyl-2,5,5-trimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **109g**

To 0.05g (0.2 mmol) of epoxide **109g** was added 0.057g (0.40 mmol) of $BF_3 \cdot Et_2O$ according to the general procedure for epoxide rearrangements. The usual workup and purification by chromatography on HPLC (15:85, ether:hexane, 4 mL/min) provided 0.028g (56%) oxetane **117g**, 0.011g (22%) β-alcohol **123g** and 0.005g (10%) of α-alcohol **124g**.

123g: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.01 (br s, 1), 4.83 (br s, 1), 4.27 (br s, 1), 3.97 (m, 1), 3.74 (s, 3), 3.10 (t, J=8Hz, 1), 2.17 (s, 3), 1.81 (s, 3), 1.1-2.2 (m, 8). EI/MS (70eV): 250 (M^+, 16.0), 232 (12.1), 227 (6.2), 218 (16.5), 207 (25.4), 191 (23.6), 185 (27.3), 173 (27.6), 147 (32.0), 133 (37.7), 119 (31.6), 109 (50.2), 105 (43.8), 79 (42.6), 77 (35.5), 55 (46.8), 41 (base). IR (neat): 3500, 3030, 2980, 2960, 2860, 1720, 1650, 1450, 1320, 1260, 1150cm^{-1}.

α-alcohol 124g: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.96 (br s, 1), 4.94 (br s, 1), 3.80 (s, 3), 3.10 (m, 1), 2.4-2.8 (m, 2), 2.20 (s, 3), 1.82 (s, 3), 1.0-2.0 (m, 8). EI/MS (70eV): 250 (2.9), 232 (1.6), 219 (7.5), 192 (39.4), 177 (50.5), 160 (15.2), 133 (89.9), 117 (23.11), 105 (98.4), 91 (40.9), 79

(26.5), 59 (36.6), 43 (base). IR (neat): 3500, 3030, 2980, 2960, 2860, 1720, 1650, 1450, 1250, 1150, 1070, 980cm^{-1}.

Rearrangement of Ethyl-5,5-dimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **109d** with $BF_3 \cdot Et_2O$

To 0.06g (0.24 mmol) of **109d** was added 0.043g (0.3 mmol) $BF_3 \cdot Et_2O$ according to the general procedure of epoxide rearrangement. The usual workup and purification by chromatography on HPLC (15:85, ether:hexane, 4 mL/min) provided 0.0131g (52%) of oxetane **117d**, 0.017g (27%) of β-alcohol **123d** and 0.005g (8%) of α-alcohol **124d**.

β-alcohol **123d**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.92 (m, 1), 5.09 (br s, 1), 4.80 (br s, 1), 4.21 (q, J=7.2Hz, 2), 3.93 (t, J=4.5Hz, 1), 2.95 (m, 1), 2.4-2.8 (3), 1.83 (s, 3), 1.25 (t, J=7.1Hz, 3), 1.05-2.0 (6). EI/MS (70eV): 250 (M^+, 9.6), 237 (5.1), 219 (8.9), 205 (14.1), 192 (81.7), 177 (50.6), 163 (47.0), 147 (22.3), 133 (76.3), 119 (base). IR (neat): 3500, 3030, 2960, 2930, 2860, 1725, 1650, 1450, 1360, 1280, 1150, 1100, 920, 840cm^{-1}.

α-alcohol **124d**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.22 (m, 1), 5.01 (br s, 1), 4.93 (br s, 1), 4.2 (m, 2), 3.90 (dd, J=6.2,9.0Hz, 1), 3.09 (m, 1), 1.82 (s, 3), 1.29 (t, J=7.0Hz, 3), 1.1-1.75 (m, 7). EI/MS (70eV): 250 (M^+, 5.9), 237 (3.6), 205 (20.4), 192 (45.7), 163 (42.4), 147 (21.2), 135

(15.5), 119 (base). IR (neat): 3500, 3030, 2960, 2860, 1730, 1650, 1430, 1360, 1280, 1100, 920, 840cm^{-1}.

Treatment of Oxetane **117a** with p-Toluenesulfonic acid and Ac_2O

To a solution of 0.05g (0.2 mmol) of oxetane **117a**, in 20 mL benzene, was added 0.5 mL acetic anhydride and 0.1g (0.52 mmol) p-toluene sulfonic acid monohydrate. The mixture was heated under reflux for 4 hours, cooled to room temperature and cast into ether saturated aq. $NaHCO_3$ (100 mL each). The organic phase was separated and washed with water, brine (30 mL each) and dried (Na_2SO_4). Concentration *in vacuo* and chromatography, a column of silica gel (20g, 20 mm OD, 230-400 mesh, ether-pet. ether, 3:7) gave 0.051g (87%) of **127** as a colorless oil.

127: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.97 (dd, J=10,5Hz, 1), 4.86 (br s, 1), 4.70 (br s, 1), 3.71 (s, 3), 3.63 (s, 3), 2.95 (br t, J=8.3Hz, 1), 2.65 (br dd, J=17.5,5Hz, 1), 2.21 (ddd, J=17.5,10,1.67Hz, 1), 1.99 (s, 3), 1.77 (br s, 3), 1.5-2.1 (6). EI/MS (70eV): 302 (M^+-HOAc, 1.5), 276 (2.2), 262 (5.1), 244 (6.2), 216 (6.1), 203 (9.4), 187 (5.0), 176 (7.8), 157 (7.12), 145 (7.4), 131 (6.7), 105 (11), 91 (13.2), 43 (base). IR (CCl_4): 2950, 2880, 1740, 1730, 1650, 1430, 1290, 1270, 1100, 1040, 900cm^{-1}.

(15g, 20 mm OD, 230-400 mesh, ether-pet. ether, 1:4) provided 0.023g (76%) of triene **127**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.15 (d, J=8.4Hz, 1), 5.70 (d, J=8.4Hz, 1), 4.77 (br s, 1), 4.70 (br s, 1), 3.82 (s, 3), 3.80 (s, 3), 2.90 (t, J=8.2Hz, 1), 1.88 (br s, 3), 1.2-2.0 (m, 6). EI/MS (70eV): 276 (M^+, 1.4), 245 (0.88), 234 (1.18), 204 (62.4), 176 (base), 161 (3.4), 145 (26.0), 131 (3.9), 117 (20.5). IR (neat): 3030, 2960, 2930, 2860, 1720, 1640, 1595, 1580, 1400, 1260, 1080, 1030, 960cm^{-1}.

Dimethyl-7a-β-[2-hydroxy-isopropyl]-2,3,3a,7a-tetrahydro indene-4,5-dicarboxylate **121**

To 4.3 mmol of NaOMe, prepared from 0.1g (4.3 mmol) of sodium metal, in methanol (10 mL) was added 0.020g (0.065 mmol) of oxetane **117a** in methanol (5 mL) over five minutes. The resulting solution was stirred at room temperature for 4 hours, then cooled to 0°C; 5 mL of water was added slowly, followed by 10 mL of 1N aq. HCl. The methanol was removed off *in vacuo* and the aqueous layer was extracted with 50 mL of ether. The organic layer was separated and washed with saturated aq. $NaHCO_3$, brine (50 mL each), and dried (Na_2SO_4). Concentration *in vacuo* gave a colorless oil which was purified by chromatography on a column of silica gel (15g, 20 mm OD, 230-400 mesh, ether-pet. ether, 30:70) to provide 0.015g (75%) of **121**.

Dimethyl-7β-acetoxy-7a-β-isopropenyl-2,3,3a,6,7,7a-hexahydroindene-4,5-dicarboxylate **125**

To a solution of 0.02g (0.65 mmol) of the β-alcohol **123a** in 20 mL benzene was added acetic anhydride (1 mL), pyridine (1 mL) and a few crystals of 4-N,N-dimethylaminopyridine (DMAP). The mixture was stirred at room temperature for 8 hours then was quenched with 1N aq. HCl (10 mL). The mixture was cast into ether -1N aq. HCl (50 mL each). The organic layer was separated, washed with water (20 mL), saturated aq. $NaHCO_3$ (50 mL), brine (50 mL) and dried (Na_2SO_4). Concentration *in vacuo* and purification by chromatography on a column of silica gel (15g, 20 mm OD, 230-400 mesh, ether-pet. ether, 1:1) provided 0.019g (84%) of β-acetate **125**.

Dimethyl-7a-β-isopropenyl-2,3,3a,7a-tetrahydro indene-4,5-dicarboxylate **127**

To a solution of 0.037g (0.11 mmol) of a mixture of the α- and β-acetates **125** and **126** in benzene (20 mL) was added 0.020g (0.178 mmol) of KOBut. The resulting mixture was stirred at room temperature for over night; then cast into ether -1N aq. HCl (50 mL each). The organic layer was separated, washed with saturated aq. $NaHCO_3$, brine (30 mL each), and dried (Na_2SO_4). Concentration *in vacuo* and purification by chromatography on a column of silica gel

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.19 (d, J=10.07Hz, 1), 5.71 (d, J=10.07Hz, 1), 3.80 (s, 3), 3.78 (s, 3), 3.00 (br t, J=8.7Hz, 1), 2.27 (m, 2), 1.51 (m, 5), 1.21 (s, 3), 1.15 (s, 3). EI/MS (70eV): 263 (0.7), 236 (3.6), 204 (11.3), 176 (base). IR (neat): 3520(br), 2950, 2870, 1715(br), 1640, 1595, 2580, 1430, 1260(br), 1080, 1030, 950cm^{-1}.

Dimethyl-2,3-dihdry-indene-4,5-dicarboxylate **120**

To a solution of 0.01g (0.037 mmol) of **121** in 15 mL CH_2Cl_2 mixed with 0.3g of celite was added 0.2g (0.9 mmol) of PCC.[33b] The resulting suspension was stirred at room temperature for 3 hours, then the solids were removed by filtration through a pad of celite which was rinsed with CH_2Cl_2 (20 mL). The solvent was removed *in vacuo* to provide a yellow residue which was purified by chromatography on a column of silica gel (10g, 10 mm OD, 230-400 mesh, ether-pet. ether, 30:70) to provide 0.0062g (78%) of **120**. ^{1}H-NMR (250 MHz, C_6D_6): δ = 7.64 (d, J=8.3Hz, 1), 6.69 (d, J=8.3Hz, 1), 3.68 (s, 3), 3.46 (s, 3), 2.82 (t, J=7.3Hz, 2), 2.43 (br t, J=7.3Hz, 2), 1.60 (m, 2). EI/MS (70eV): 234 (M^+, 3.1), 203 (43.8), 202 (base), 201 (20.9), 175 (2.8), 187 (11.1), 144 (9.8), 115 (25.1). IR (neat): 3010, 2960, 2900, 2850, 1730, 1600, 1440, 1250, 1120, 1040, 890, 830, 790, 680cm^{-1}.

Dimethyl-2,3-dihydro-indene-4,5-dicarboxylate **120**

To a solution of 0.015g (0.064 mmol) of **119** in benzene (20 mL) was added 0.1g (0.36 mmol) of DDQ. The resulting mixture was stirred for 10 hours at room temperature, then filtered through a pad of celite, and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by chromatography on a column of silica gel (15g, 20 mm OD, 230-400 mesh, ether-pet. ether, 30:70) to provide 0.012g (81%) of **120**.

Rearrangement of dimethyl-5,5,8a-trimethyl-4α-4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **1**

To 0.5g (1.62 mmol) of **1** in CH_2Cl_2 (30 mL) was added 0.35g (2.48 mmol) of $BF_3 \cdot Et_2O$ according to the general procedure for epoxide rearrangements. The usual workup and purification by chromatography on a column of silica gel (60g, 40 mm OD, 60-230 mesh, ether-pet. ether, 20:80) gave 0.43g (86%) of **2** as a colorless viscous oil. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.76 (m, 1), 3.92 (m, 1), 3.80 (s, 3), 3.75 (s, 3), 2.63 (d, J=4.0Hz, 2), 1.2-2.3 (m, 5), 1.70 (br s, 3), 1.02 (s, 3), 0.95 (s, 3). EI/MS (70eV): 308 (M^+, 8.2), 276 (base), 258 (20.4), 244 (71.3), 230 (13.9), 215 (28.2), 199 (34.8), 189 (20.6), 171 (42.2), 156 (26.3), 91 (70.7). IR (CCl_4): 3570, 2970, 2950, 2880, 1740, 1720, 1620, 1430, 1395, 1390, 1290, 1250, 1200, 1100, 1080, 1060, 1030, 875cm^{-1}.

Rearrangement of Ethyl-5,5,8a-trimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate **109e**

To 0.1g (0.379 mmol) of **109e** was added 0.081g 0.568 mmol) of $BF_3 \cdot Et_2O$, according to the general procedure for epoxide rearrangements. The usual workup and purification by chromatography on a column of silica gel (25g, 20 mm OD, 230-400 mesh, ether-pet. ether, 1:1) gave 0.081g (81%) of alcohol **122e** as a viscous colorless oil. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.73 (t, J=4.0Hz, 1), 5.79 (m, 1), 4.16 (m, 2), 3.84 (m, 1), 2.45 (m, 3), 1.70 (br s, 3), 1.57 (s, 3), 1.29 (t, J=7.0Hz, 3), 1.15 (br s, 3), 0.9-1.3 (m, 4). EI/MS (70eV): 264 (M^+, 13.9), 246 (4.7), 231 (14.6), 218 (26.7), 205 (13.0), 190 (13.6), 185 (63.2), 173 (13.9), 157 (20.0), 135 (7.9), 121 (20.9), 105 (33.0), 91 (47.5), 55 (75.1), 43 (base). IR (neat): 3500, 3030, 2960, 1730, 1430, 1260, 1090, 1060cm^{-1}.

Rearrangement of Ethyl-5,5,8a-trimethyl-4α,4a-α-epoxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate **109f**

To 0.06g (0.227 mmol) of **109f** at 0°C was added 0.048g (0.34 mmol) of $BF_3 \cdot OEt_2$ according to the general procedure for epoxide rearrangements. The usual workup and purification by chromatography on a column of silica gel (15g, 20 mm OD, 230-400 mesh, ether-pet. ether, 1:1) provided 0.05g (83%) of **122f**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.57 (br s, 1), 5.66 (br s, 1), 4.12 (q, J=7.2Hz, 2), 3.89 (t, J=4.3Hz, 1), 2.2-2.5 (m, 2), 1.65 (br s, 3), 1.23 (t, J=7.2Hz, 3), 1.18 (s, 3), 1.04 (s, 3), 1.1-2.0 (m, 5). EI/MS (70eV): 264 (M^+, 17.4), 246 (11.5), 231 (22.7), 218 (23.4), 205 (34.7), 190 (18.6), 185 (base), 173 (42.9), 157 (19.3), 121 (27.6), 91 (53.2). IR (neat): 3600, 3030, 2980, 2960, 2850, 1730, 1650, 1430, 1360, 1250, 1200, 1175, 1100, 1050, 980cm^{-1}.

2,2-Dimethyl-3-hydroxy-3-vinyl-cyclohexanone **130**

To a solution of 2.0g (28.6 mmol) 2,2-dimethyl-1,3-cyclohexane dione in dry THF (50 mL), cooled to -78°C (dry ice-iPrOH), was added 34.32 mL of vinyl magnesium bromide in THF (34.32 mmol) over 1 hour. After the addition was complete, the mixture was stirred for an additional 5 minutes at -78°C then carefully quenched with 30 mL of saturated aq. NH_4Cl. The mixture was diluted with 60 mL of ether, the organic layer was separated, washed with saturated aq. $NaHCO_3$, water, brine (50 mL each), and dried ($MgSO_4$). Concentration *in vacuo* gave a colorless liquid that was purified by chromatography on a column of silica gel (120g, 50 mm OD, 60-230 mesh, ether:pet. ether, 1:1) to provide 1.0g (42%) of **130**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.98 (dd, 11.0,17.0Hz, 1), 5.26 (dd, J=11.0,1.2Hz, 1), 5.14 (dd, J=17.0,1.2Hz, 1), 1.65-2.75 (m, 7), 1.09 (s, 3), 1.02 (s, 3). EI/MS (70eV): 168 (M^+,

17.0), 151 (4.7), 150 (1.8), 140 (1.79), 135 (1.73), 125 (10.3), 107 (4.7), 98 (99.7), 86 (26.8), 83 (82.9), 20 (28.4), 67 (25.4), 55 (base). IR (neat): 3600, 3020, 2985, 2840, 1705, 1460, 1380, 1365, 1315, 1200, 1130, 985, 960, 920, 850, 830, 730cm^{-1}.

6,6-Dimethyl-1-vinyl-5-oxo-cyclohex-1-ene **131**

To a solution of 0.5g (2.97 mmol) of **130** in 60 mL benzene was added 0.74g (2.97 mmol) $CuSO_4 \cdot 5H_2O$. The solution heated under reflux with azeotropic removal of water for 3 hours. The mixture was cooled to room temperature and filtered through a short column of silica gel. The filtrate was washed with water (30 mL) and dried ($MgSO_4$). The solvent was removed by distillation to provide 0.3g (68%) of diene **131** as colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.27 (ddd, J=1.2,10.7,17.1Hz, 1), 5.95 (t, J=4.1Hz, 1), 5.40 (dd, J=1.83,17.1Hz, 1), 5.06 (dd, J=1.83,10.7Hz, 1), 2.54 (m, 2), 2.47 (t, J=4.8Hz, 2), 1.24 (s, 6). EI/MS (70eV): 150 (M^+, 21.8), 135 (3.7), 121 (16.1), 108 (30.1), 93 (base), 85 (7.4), 79 (45.6), 39 (77.0). IR (neat): 3020, 2965, 2925, 2875, 1710, 1468, 1445, 1380, 1360cm^{-1}.

Dimethyl-5,5-dimethyl-6-oxo-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate **132**

To 0.4g (2.6 mmol) of **130** was added 1.0g (7.0 mmol) of dimethyl acetylenedicarboxylate. The mixture was stirred at

room temperature for 2 hours, or could be heated at 110°C for 15 minutes. The reaction mixture was purified by chromatography on a column of silica gel (50g, 40 mm OD, 60-230 mesh, ether-pet. ether, 1:1) to provide 0.4g (52%) of **132** as a white solid, m.p. 76-77°C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.55 (dd, J=3.36,3.66Hz, 1), 3.79 (s, 3), 3.74 (s, 3), 3.59 (m, 1), 3.07 (dm, J=17.0Hz, 2), 2.74 (m, 1), 2.43 (dm, J=17.0Hz, 1), 2.21 (m, 1), 1.51 (m, 1), 1.31 (s, 3), 1.26 (s, 3). EI/MS (70eV): 292 (M^+, 24.9), 260 (44.4), 245 (4.6), 232 (base), 217 (24.2), 205 (89.6), 189 (55.0), 177 (69.6), 163 (20.5), 145 (25.0). IR (neat): 2980, 2945, 2875, 1720, 1680, 1650, 1540, 1435, 1385, 1360, 1260, 1235, 1225, 1105, 1080, 965cm^{-1}.

Dimethyl-5,5-dimethyl-4α,4a-α-epoxy-6-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **133**

To a solution of 0.1g (0.34 mmol) of **132** in 9 mL of mixture of t-BuOH:water (2:1), cooled to 0°C (ice water), was added 0.12g (0.68 mmol) of NBS in one portion. The mixture was stirred for 3 hours at 0°C, then diluted with water (20 mL) and cast into ether (100 mL) and water (30 mL). The organic phase was separated and washed with saturated aq. $NaHCO_3$, water (10 mL each), and dried ($MgSO_4$). Concentration and purification of the residual oil by chromatography on a column of silica gel (25g, 20 mm OD, 230-400 mesh, ether-pet. ether, 7:3) provided 0.014g (13%) of **133** and 0.082g (78%) of **134**.

133: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3), 3.76 (s, 3), 3.62 (br s, 1), 3.46 (dm, J=9.2Hz, 1), 3.10 (br d, J=9.2Hz, 1), 2.85 (t, J=5.0Hz, 2), 2.81, 1.69 (s, 3), 1.34 (s, 3). EI/MS (70eV): 308 (M^+, 1.7), 276 (16.3), 267 (2.0), 248 (3.0), 235 (base), 217 (8.1), 203 (17.6), 189 (10.9), 177 (45.3), 163 (12.4), 145 (15.3), 159 (6.3), 41 (83). IR (CCl_4): 2980, 2960, 2880, 1720, 1660, 1435, 1380, 1360, 1270, 1250, 1160cm^{-1}.

134: ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.31 (m, 1), 4.83 (s, 3), 3.76 (s, 3), 3.36 (dt, J=19.2,3.97Hz, 1), 2.88 (ddd, J=19.2,1.83,1.53Hz, 1), 2.69 (m, 1), 2.55 (dm, J=13.62Hz, 1), 2.15 (br s, 1), 1.93 (m, 2), 1.58 (s, 3), 1.20 (s, 3). EI/MS (70eV): 277 (M^+-OCH_3, 31.9), 259 (17.9), 245 (4.4), 235 (12.3), 217 (18.1), 204 (9.9), 189 (8.0), 177 (9.0), 91 (20.3), 59 (43.0), 43 (base). IR (neat): 2980, 2945, 2875, 1720, 1650, 1550, 1445, 1260, 1105, 1080, 1050, 910cm^{-1}.

Dimethyl-5,5-dimethyl-4β,4a-β-epoxy-6-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate **133**

To a solution of 0.04g (0.136 mmol) of **132** in CH_2Cl_2, cooled to 0°C, was added 0.1g (0.5 mmol) of MCPBA in CH_2Cl_2 (5 mL). The mixture was stirred at 0°C for 1.5 hours, then quenched with saturated aq. $NaHCO_3$ (10 mL) and diluted with 30 mL ether. The organic phase was separated, washed with 10% aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$, water (20 mL each), and dried ($MgSO_4$). Concentration *in vacuo* provided 0.03g (71%) of **133** as a colorless oil.

Dimethyl-5,5-dimethyl-4α,4a-α-epoxy-6β-hydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate 135

To a solution of 0.075g (0.24 mmol) of **134** in methanol (10 mL), cooled to 0°C, was added 0.02g (0.5 mmol) of sodium borohydride in portions over 15 minutes. The mixture was stirred for 1 hour, then quenched by the careful addition of 10 mL of water. The mixture was extracted with CH_2Cl_2 (60 mL), the organic layer was separated and dried ($MgSO_4$). Concentration *in vacuo* and purification of the resulting oil by chromatography on a column of silica gel (20g, 20 mm OD, 230-400 mesh, ether) gave 0.067g (89%) of **135** as a colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3), 3.72 (s, 3), 3.61 (m, 1), 3.37 (br s, 1), 3.06 (dm, J=19.5Hz, 1), 3.05 (br s, 1), 2.55 (dm, J=19.5Hz, 1), 1.91 (m, 1), 1.3-1.7 (m, 4), 1.05 (s, 3), 0.91 (s, 3). EI/MS (70eV): 310 (M^+, 4.9), 292 (0.61), 279 (15.3), 278 (20.0), 260 (12.3), 246 (9.2), 235 (14.9), 217 (14.4), 203 (19.7), 189 (16.5), 179 (22.2), 163 (16.4), 145 (19.6), 119 (21.4), 105 (5.9), 91 (49.5), 77 (40.5), 59 (79.2), 43 (base). IR (CCl_4): 3500, 2940, 1720, 1650, 1430, 1380, 1360, 1260, 1240, 1190, 1060, 940, 890, 870, 825, 805, 760cm^{-1}.

Dimethyl-5,5-dimethyl-4β,4a-β-epoxy-6β-hydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate 137

To 0.02g (0.065 mmol) of 133 in methanol (10 mL) was added 0.05g (0.13 mmol) of $NaBH_4$ according to procedure employed in the preparation of 135 to provide 0.015g (75%) of 137.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.80 (s, 3), 3.73 (s, 3), 3.55 (m, 1), 3.30 (br s, 1), 3.16 (dm, J=9.5Hz, 1), 3.13 (dm, J=17.0Hz, 1), 2.57 (dm, J=17.0Hz, 1), 2.52 (dm, J=9.5Hz, 1), 1.94 (m, 2), 1.58 (m, 2), 1.16 (s, 3), 0.98 (s, 3). EI/MS (70eV): 279 (M^+-OCH_3, 15.6), 278 (13.3), 260 (8.3), 146 (6.4), 232 (13.7), 221 (15.5), 205 (35.5), 191 (30.2), 179 (14.3), 161 (12.9), 145 (17.4), 133 (12.6), 119 (18.3), 105 (25.9), 91 (33.1), 84 (base), 77 (25.6), 67 (19.5), 59 (55.7), 43 (71.3). IR (neat): 3500, 2960, 1720, 1650, 1430, 1380, 1360, 1260, 1190, 1060, 810, 740cm^{-1}.

Rearrangement of 135 with $BF_3 \cdot Et_2O$

To 0.008g (0.026 mmol) of 135 was added 1 drop of $BF_3 \cdot Et_2O$, according to the general procedure for epoxide rearrangements. The usual workup and purification by chromatography on a column of silica gel (30g, 30 mm OD, 230-400 mesh, ether:pet. ether, 7:3) provided 0.0074g (93%) of 136.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, J=8.5Hz, 1), 7.46 (d, J=8.5Hz, 1), 3.96 (s, 3), 3.88 (s, 3), 3.76 (m, 1), 2.86 (m,

2), 2.0 (m, 2), 1.43 (s, 3), 1.39 (s, 3). EI/MS (70eV): 292 (M^+, 4.0), 277 (4.5), 260 (base), 245 (8.9), 227 (17.7), 217 (11.8), 200 (28.3), 185 (9.2), 157 (6.1), 145 (13.8), 129 (15.7), 115 (17.4). IR (neat): 3500, 2980, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **138**

To a solution of 0.01g (0.034 mmol) of **132** in dry benzene (20 mL) was added 0.04g (0.176 mmol) of DDQ. The resulting mixture was heated under reflux for 5 hours then cooled to room temperature and filtered through a plug of silica gel, which was rinsed with benzene. Concentration *in vacuo* provided 0.0095g (95%) of **138**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.91 (d, J=9.1Hz, 1), 7.47 (d, J=8.5, 1), 3.96 (s, 3), 3.90 (s, 3), 3.07 (dd, J=6.4,7.3Hz, 2), 2.68 (dd, J=7.3,6.4Hz, 2), 1.45 (s, 3). EI/MS (70eV): 290 (M^+, 1.6), 258 (base), 243 (4.4), 236 (60.2), 215 (73.5), 199 (30.7), 187 (5.0), 172 (11.4), 158 (7.8), 144 (13.8), 128 (30.0), 115 (27.4). IR (neat): 2980, 2960, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1270, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-β-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **136**

To a solution of 0.005g (0.017 mmol) of **138** in dry methanol (2 mL), cooled to 0°C (ice water), was added 0.005g

2), 2.0 (m, 2), 1.43 (s, 3), 1.39 (s, 3). EI/MS (70eV): 292 (M^+, 4.0), 277 (4.5), 260 (base), 245 (8.9), 227 (17.7), 217 (11.8), 200 (28.3), 185 (9.2), 157 (6.1), 145 (13.8), 129 (15.7), 115 (17.4). IR (neat): 3500, 2980, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **138**

To a solution of 0.01g (0.034 mmol) of **132** in dry benzene (20 mL) was added 0.04g (0.176 mmol) of DDQ. The resulting mixture was heated under reflux for 5 hours then cooled to room temperature and filtered through a plug of silica gel, which was rinsed with benzene. Concentration *in vacuo* provided 0.0095g (95%) of **138**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.91 (d, J=9.1Hz, 1), 7.47 (d, J=8.5, 1), 3.96 (s, 3), 3.90 (s, 3), 3.07 (dd, J=6.4,7.3Hz, 2), 2.68 (dd, J=7.3,6.4Hz, 2), 1.45 (s, 3). EI/MS (70eV): 290 (M^+, 1.6), 258 (base), 243 (4.4), 236 (60.2), 215 (73.5), 199 (30.7), 187 (5.0), 172 (11.4), 158 (7.8), 144 (13.8), 128 (30.0), 115 (27.4). IR (neat): 2980, 2960, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1270, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-β-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **136**

To a solution of 0.005g (0.017 mmol) of **138** in dry methanol (2 mL), cooled to 0°C (ice water), was added 0.005g

2), 2.0 (m, 2), 1.43 (s, 3), 1.39 (s, 3). EI/MS (70eV): 292 (M^+, 4.0), 277 (4.5), 260 (base), 245 (8.9), 227 (17.7), 217 (11.8), 200 (28.3), 185 (9.2), 157 (6.1), 145 (13.8), 129 (15.7), 115 (17.4). IR (neat): 3500, 2980, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **138**

To a solution of 0.01g (0.034 mmol) of **132** in dry benzene (20 mL) was added 0.04g (0.176 mmol) of DDQ. The resulting mixture was heated under reflux for 5 hours then cooled to room temperature and filtered through a plug of silica gel, which was rinsed with benzene. Concentration *in vacuo* provided 0.0095g (95%) of **138**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.91 (d, J=9.1Hz, 1), 7.47 (d, J=8.5, 1), 3.96 (s, 3), 3.90 (s, 3), 3.07 (dd, J=6.4,7.3Hz, 2), 2.68 (dd, J=7.3,6.4Hz, 2), 1.45 (s, 3). EI/MS (70eV): 290 (M^+, 1.6), 258 (base), 243 (4.4), 236 (60.2), 215 (73.5), 199 (30.7), 187 (5.0), 172 (11.4), 158 (7.8), 144 (13.8), 128 (30.0), 115 (27.4). IR (neat): 2980, 2960, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1270, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-β-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **136**

To a solution of 0.005g (0.017 mmol) of **138** in dry methanol (2 mL), cooled to 0°C (ice water), was added 0.005g

2), 2.0 (m, 2), 1.43 (s, 3), 1.39 (s, 3). EI/MS (70eV): 292 (M^+, 4.0), 277 (4.5), 260 (base), 245 (8.9), 227 (17.7), 217 (11.8), 200 (28.3), 185 (9.2), 157 (6.1), 145 (13.8), 129 (15.7), 115 (17.4). IR (neat): 3500, 2980, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **138**

To a solution of 0.01g (0.034 mmol) of **132** in dry benzene (20 mL) was added 0.04g (0.176 mmol) of DDQ. The resulting mixture was heated under reflux for 5 hours then cooled to room temperature and filtered through a plug of silica gel, which was rinsed with benzene. Concentration *in vacuo* provided 0.0095g (95%) of **138**.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.91 (d, J=9.1Hz, 1), 7.47 (d, J=8.5, 1), 3.96 (s, 3), 3.90 (s, 3), 3.07 (dd, J=6.4,7.3Hz, 2), 2.68 (dd, J=7.3,6.4Hz, 2), 1.45 (s, 3). EI/MS (70eV): 290 (M^+, 1.6), 258 (base), 243 (4.4), 236 (60.2), 215 (73.5), 199 (30.7), 187 (5.0), 172 (11.4), 158 (7.8), 144 (13.8), 128 (30.0), 115 (27.4). IR (neat): 2980, 2960, 1740, 1720, 1715, 1600, 1435, 1380, 1360, 1300, 1270, 1150, 970cm^{-1}.

Dimethyl-5,5-dimethyl-6-β-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate **136**

To a solution of 0.005g (0.017 mmol) of **138** in dry methanol (2 mL), cooled to 0°C (ice water), was added 0.005g

(0.13 mmol) of $NaBH_4$. The mixture was stirred for 1 hour at 0°C, then quenched with saturated aq. $NaHCO_3$ (5 mL). The mixture was cast into ether (20 mL), the organic phase was separated, washed with H_2O (5 mL) and dried ($MgSO_4$). Concentration *in vacuo* provided 0.0045g (89%) of **136**.

LIST OF REFERENCES

LIST OF REFERENCES

1. Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398.

2. For isolation and biological activities of some clerodane diterpenes, see:
   a) Kubo, I.; Lee, Y.-W.; Balogh-Nair, I. V.; Nakanishi, K.; Chapya, A. *J. Chem. Soc. Chem. Commun.* **1976**, 949.
   b) Kubo, I.; Klocke, J. A.; Miura, I.; Fukuyama, T. *J. Chem. Soc. Chem. Comm.* **1982**, 618.
   c) Kubo, I.; Fukuyama, Y.; Chapya, A. *Chem. Lett.* **1983**, 223.
   d) Ferrai, M.; Pelizzoni, F.; Ferrari, G. *Phytochemistry* **1971**, *10*, 3267.
   e) Niwa, M.; Yamamura, S. *Tet. Lett.* **1981**, *22*, 2789.
   f) McCrindle, K.; Nakamura, E.; Anderson, A. B. *J. Chem. Soc. Perkin I* **1977**, 1590.
   g) Anderson, T.; McCrindle, R. *Acta, Chem. Scand.* **1969**, *23*, 1066.
   h) Schmitz, F. J.; Lakshmi, V.; Powel, D. R.; Vanderhelm, D. *J. Org. Chem.* **1984**, *49*, 241.
   i) Cartè, B.; Rose, C. B.; Raulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785.

3. Terpenoids and steroids, specialist periodical reports, The Chemical Society, London, Vol. 1, 1971 to Vol. 13, 1983.

4. Misa, R.; Pandey, R. C.; Dev S. *Tetrahedron* **1964**, *49*, 3751.

5. Ardon-Jimenez, A.; Halsall, T. G. *J. Chem. Soc. Perkin I* **1978**, 1461.

6. a) Sarma, A. S.; Chattopadhyay, P. *Tet. Lett.* **1980**, *21*, 3719.
   b) Sarma, A. S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727.

7. Takashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515.

8. Kende, A.; Roth, B.; Kubo, I. *Tet. Lett.* **1982**, *21*, 1751.

9. Apsimon, J. W.; Yamusaki, K. *Chem. Lett.* **1977**, 1453.

10. Goldsmith, D. J.; John, T. R.; Vanmiddlesworth, F. *Synth. Comm.* **1980**, *10* (7), 551.

11. a) Luteijn, J. M.; VanDoorn, M.; deGroot, A. *Tet. Lett.* **1980**, *21*, 4127 and 4129.
    b) Luteijn, J. M.; deGroot, A. *J. Org. Chem.* **1981**, *146*, 3448.
    c) Luteijn, J. M.; deGroot, A. *Tet. Lett.* **1981**, *21*, 789.
    d) Luteijn, J. M.; deGroot, A. *Tet. Lett.* **1982**, *23*, 3421.

12. Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *J. Chem. Soc. Chem. Commun.* **1983**, 503.

13. Tokoroyama, T.; Fujimori, K.; Shimizu, J.; Yamagiwa, Y. *J. Chem. Soc. Chem. Commun.* **1983**, 1516.

14. Ireland, R. E.; Muchmore, D. C.; Hengarter, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

15. Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255.

16. Goldsmith, D. J.; Srouji, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182.

17. Kojima, Y.; Kato, N. *Tet. Lett.* **1980**, *21*, 5033.

18. a) Kakisawa, H.; Ikeda, M. *Nippon Kagaku Zasshi* **1967**, *88*, 476; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Japan* **1969**, *42*, 3318.
    b) Van del Tempel; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293.

19. This method which is a modification of that recently reported by ley: Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc. Perkins I* **1983**, 1579.

20. Tanis, S. P.; Abdallah, Y. M. *Synth. Comm.* **1986**, in press.

21. Markgraf, J. H.; Greeno, E. W.; Miller, M. D.; Zaks, W. J.; Lee, G. A. *Tetrahedron Lett.* **1983**, *24*, 241. For a recent example of the Diels-Alder reaction of **101** with 2-methyl cyclopentanone, see: Ireland, R. E.; Thompson, W. J.; Mandel, N. S. *J. Org. Chem.* **1979**, *44*, 3583.

22. a) For a review, see: Onishchenko, A. S. in "Diene Synthesis", Israil Program for Scientific Translation, Jerusalem, 1964.
b) Nazarov, I. N.; Anachenko, S. N.; Torgov, I. V. *Izv. Akad. Nauk SSSR (Eng. Trans.)* 1959, 84.

23. Julia, M; Malassine, B. *Tetrahedron* 1974, *30*, 695.

24. Roush, W. R.; Gillis, R. H.; Ko, A. I. *J. Am. Chem. Soc.* 1982, *104*, 2669.

25. a) Segal, G. M.; Rybkina, L. P.; Kucherov, V. F. *Izv. Akad. Nauk SSSR (Eng. Trans.)* 1964, 1368.
b) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* 1978, *100*, 2918.
c) Shin, C.; Yamaura, M.; Inui, E.; Ishida, Y.; Yoshimura, J. *Bull. Soc. Chem. Japan* 1978, *51*, 2618.

26. a) Mui, P. W.; Grunwald, E. *J. Am. Chem. Soc.* 1982, *101*, 6562.
b) Squillacote, M. E.; Sheridan, R.; Chapman, O. L.; Anet, F. A. L. *ibid.* 1978, *101*, 3657.
c) Lipnick, R.; Garbish, E. W. *ibid.* 1973, *95*, 6370.

27. Chenera, B.; Reusch, W. *Tetrahedron Lett.* 1984, *25*, 4183.

28. Tanis, S. P.; Abdallah, Y. M.; Williard, P. G. *Tetrahedron Lett.* 1985, *26*, 3651.

29. a) Ramage, R.; Southwell, I. A. *J. Chem. Soc. Perkin Trans. I* 1984, 1323.
b) Bridge, A. W.; Morrison, G. A. *J. Chem. Soc. Perkin Trans. I* 1983, 2933.
c) Selover, S. J.; Crews, P. *J. Org. Chem.* 1980, *45*, 69.
d) Maione, A. M.; torrini, I.; Romeo, A. *J. Chem. Soc. Perkin Trans. I* 1979, 775.
e) Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. *J. Am. Chem. Soc.* 1979, *100*, 1002.
f) Ireland, R. E.; Beslin, P.; Giger, R.; Hengartner, U.; Kirst, H. A.; Maag, H. *J. Org. Chem.I* 1977, *42*, 1267.
g) Guest, I. G.; Marples, B. A. *J. Chem. Soc. Perkin Trans. I* 1973, 900.
h) Whitlock, H. W., Jr.; Olson, A. H. *J. Am. Chem. Soc.* 1970, *93*, 5383.
i) Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* 1969, *25*, 4999.
j) Hikino, H.; Kohama, T.; Takemoto, T. *Tetrahedron* 1969, *25*, 1037.

k) Blunt, J. W.; Hartshorn, M. P.; Kirk, D. N. *Tetrahedron* **1969**, *25*, 149.
l) Blunt, J. W.; Hartshorn, M. P.; Kirk, D. N. *J. Chem. Soc. (C)* **1968**, 635.
m) Halsall, T. G.; Jones, E. R. H.; Tan, E. L.; Chaudhry, G. R. *J. Chem. Soc. (C)* **1966**, 1374.
n) Coxon, J. M.; Hartshorn, M. P.; Rae, W. J. *Tetrahedron* **1970**, *26*, 1091.

30. Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398.

31. Demole, E.; Enggist, P.; Borer, C. *Helv. Chim. Acta* **1971**, *54*, 1845.

32. Similar ^{1}H-NMR and ^{13}C-NMR chemical shifts for oxetane resonances have been previously reported, see, for example:
a) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133.
b) Garcia-Alvarez, M. C.; Lukacs, G.; Neszmelyi, A.; Piozzi, F.; Rodriguez, B.; Savona, G. *J. Org. Chem.* **1983**, *48*, 5123. See also:
c) Welch, S. C.; Prakasa Rao, A. S. C.; Lyon, J. T.; Assercq, J.-M. *J. Am. Chem. Soc.* **1983**, *105*, 252; and references cited therein.

33. a) Burton, L. P. J.; White, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 3226.
b) White, J. D.; Burton, L. P. J. *J. Org. Chem.* **1985**, *50*, 357.

34. Prinzbach, H.; Schmidt, H.-G. *Chem. Ber.* **1974**, *107*, 1988.

35. Stork, G.; Atwal, K. S. *Tet. Lett.* **1983**, *24*, 3819.

36. a) Rajan, N.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1980**, *21*, 1577.
b) Geetha, K. V.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1978**, *34*, 2201.

37. Still, W. C.; Mitra, A.; Khan, M. *J. Org. Chem.* **1978**, *41*, 2923.

38. a) Onezawa, S.; Shonosuke, Z. *Bull. Chem. Soc. Japan* **1963**, 1143.
b) McMurry, J. E.; Musser, J. H. *Org. Synth.* **1977**, *56*, 65.