SPIRO-ANNULATION STRATEGY IN THE TOTAL SYNTHESIS OF TERPENES AND A STEROID

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SPIRO-ANNULATION STRATEGY

IN THE TOTAL SYNTHESIS OF TERPENES AND A STEROID

by

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Abstract

Kuwajima *et al.* reported that the Lewis acid-catalysed reaction of a ketal with 1,2-bis(trimethylsiloxy)cyclobutene (**109**) followed by rearrangement of the resulting cyclobutanone derivative with trifluoroacetic acid (TFA) can provide a 2,2-disubstituted cyclopentane-1,3-dione in a reasonable yield. Our model studies with a variety of ketals revealed that a large excess of $BF_3 \cdot Et_2O$ and a longer reaction time can give cyclopentane-1,3-diones ***directly***, and in better yields. This improved spiro-annulation procedure has been applied to the total synthesis of (±)-isokhusimone (**65**), (±)-3-methoxyestra-1,3,5,8,14-pentaen-17-one (**161**), (±)-*epi*-pentalenene (**279**), and (±)-pentalenene (**230**).

Our synthesis of (±)-isokhusimone (**65**) began with norcamphor. 4,4-Dimethyl-2-oxabicyclo[3.2.1]octan-3-one (**114**) readily available from norcamphor was converted to 3-(1,1-dimethyl-2-oxopropyl)cyclopentanone (**112**) in three steps, and then selectively ketalized. The ketal function underwent Lewis acid-catalysed spiro-annulation with 1,2-bis(trimethylsiloxy)cyclobutene (**109**) affording 7-(1,1-dimethyl-2-oxopropyl)spiro[4.4]nonane-1,4-dione (**106**), and intramolecular titanium-induced ketone-ketone coupling and oxidation provided (±)-isokhusimone in an overall yield of 35% from norcamphor. In an alternative approach, 7-(1-carbomethoxy-1-methylethyl)-1,4-dioxaspiro[4.4]nonane (**149**) was prepared from 4,4-dimethyl-2-oxabicyclo[3.2.1]octan-3-one (**114**) in three steps. Spiro-annulation proceeded in good yield, but subsequent titanium-induced ketone-ester coupling failed to provide the desired tricyclic product, 7,7-dimethyltricyclo[6.2.1.$0^{1,5}$]undecane-2,6-dione (**147**).

Our synthesis of (±)-3-methoxyestra-1,3,5,8,14-pentaen-17-one (**161**) was designed so that the D ring was generated by the Lewis acid-catalysed reaction of

1,2-bis(trimethylsiloxy)cyclobutene (**109**) with a ketal prepared from 6-methoxy-1-tetralone (**220**) *via* an ultrasonically induced Barbier reaction with 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane (**224**).

Our total synthesis of (±)-*epi*-pentalenene and of (±)-pentalenene was started with dimedone (**446**), which was converted to 7-ethyl-9,9-dimethyl-1,4-dioxaspiro[4.5]dec-7-ene (**448**) in three steps. The spiro-annulation of this ketal proceeded smoothly to produce 7-ethyl-9,9-dimethylspiro[4.5]dec-7-en-1,4-dione (**444**). Monoaddition of methyllithium and ozonolysis, followed by intramolecular aldol condensation provided 4,8,8-trimethyl-6-(1-oxopropyl)spiro[4.4]nona-3,6-dien-1-one (**443**). The stereochemical outcome at C-9 depended on the order in which the double bonds of enone **443** were reduced. Catalytic hydrogenation and intramolecular aldol condensation provided a 1 : 5 mixture of *rel*-(4*R*,8*R*,9*R*)- (**439**) and *rel*-(4*R*,8*R*,9*S*)-2,6,6,9-tetramethyltricyclo[6.3.0.$0^{4,8}$]undec-1-en-3-one (**440**) in good yield, but, Birch reduction and catalytic hydrogenation followed by aldol condensation produced a 4 : 1 mixture of **439** and **440**, which were transformed into (±)-pentalenene (**230**) and (±)-*epi*-pentalenene (**279**) in a straightforward fashion.

Two model reactions pertaining to the synthesis of (±)-pentalenolactone (**233**) and some factors affecting geminal acylation reactions were investigated. We discovered that the geminal acylation reactions of ketals with 1,2-bis(trimethylsiloxy)cyclopentene (**543**) proceed in the same fashion as with 1,2-bis(trimethylsiloxy)cyclobutene (**109**) to provide 2,2-disubstituted cyclohexane-1,3-diones in good yields. Our results were at variance with those reported by Pattenden and Teague.

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Glossary of abbreviations

Ac	Acetyl
Am	Amyl = pentyl
APT	Attached proton test
9-BBN	9-Borabicyclo[3.3.1]nonane
BHT	2,6-Di-*tert*-butyl-4-methylphenol
bp	Boiling point
Bu	Butyl
Bzl	Benzyl (=CH_2Ph)
COSY	$^1H-^1H$ Correlation spectrum
CW	Continuous wave
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DIPHOS-4	1,4-Bis(diphenylphosphino)butane
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DME	Dimethoxyethane
en	Ethylenediamine
Et	Ethyl
GC-MS	Gas chromatography-mass spectrometry
HMPA	Hexamethylphosphoric triamide

hυ	Ultraviolet irradiation
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
Me	Methyl
MOM	Methoxymethyl
mp	Melting point
Ms	Mesyl = methanesulphonyl
MS	Mass spectrometry
*m*CPBA	*meta* – Chloroperoxybenzoic acid
NBD	Norbornadiene
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser enhancement
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph.	Phenyl
PPTS	Pyridinum *para* – toluenesulphonate
*p*TSA	*para* – toluenesulphonic acid
TBDMSCl	*tert* – butylchlorodimethylsilane
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMSCl	Chlorotrimethylsilane
Triton B	Benzyltrimethylammonium hydroxide
Ts	Tosyl = *para* – toluenesulphonyl

To my parents

Chapter 1

THE TOTAL SYNTHESIS OF ISOKHUSIMONE

I. Introduction

Vetiver oil is an important raw material for the production of high quality perfumes. It contains several zizaane sesquiterpenes including (+)-zizaene * (**1**),[1,2] (+)-zizanoic acid (**2**),[3,4,5] (+)-epizizanoic acid (**3**),[6] and (-)-khusimone (**4**).[7] It has been postulated that the sesquiterpenes are responsible for retaining a strong woody fragrance.[8] Khusimone (**4**), a minor but olfactively interesting component in the essential oil, has been reported to show repellent activity against some insect pests, such as cockroaches, flies, weevils and mosquitoes.[9] A tricyclo[6.2.1.$0^{1,5}$]undecane skeleton is the basic structural feature of the zizaane-type sesquiterpenes. (-)-Prezizanol (**5**) and (-)-prezizaene (**6**), isolated from the essential oil of *Eremophila georgei*, a kind of sandalwood, were shown to have the same tricyclo[6.2.1.$0^{1,5}$]undecane ring system as in the zizaane-type sesquiterpenes, but they have a slightly different methylation pattern.[10] In addition, (+)-prezizaene (**6**) and (+)-allokhusiol (**7**) were isolated from Indian vetiver oil.[11] It is interesting that all of these tricyclo[6.2.1.$0^{1,5}$]undecane sesquiterpenes have been found only in vetiver oil and sandalwood, and they all possess extremely strong woody fragrances.

The zizaane-type sesquiterpenes have been the subject of considerable synthetic activity not only due to their value to the perfume industry but also due to their unique structural features.[12] The first total synthesis of (±)-zizaene (**1**) was accomplished by

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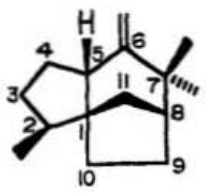
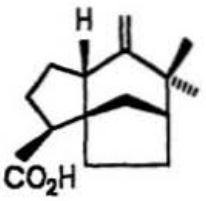
* Alternative names appearing in the literature include tricyclovetivene,[1a] khusinene,[1c] and khusene.[4c]



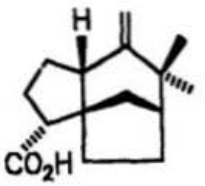
zizaene

1



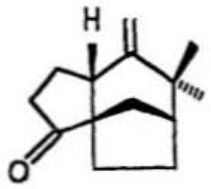
zizanoic acid

2



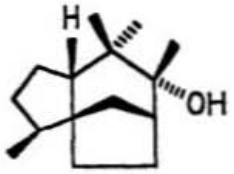
epizizanoic acid

3



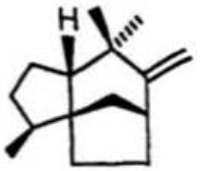
khusimone

4



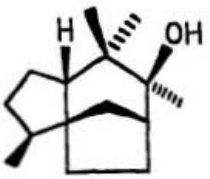
prezizanol

5



prezizaene

6

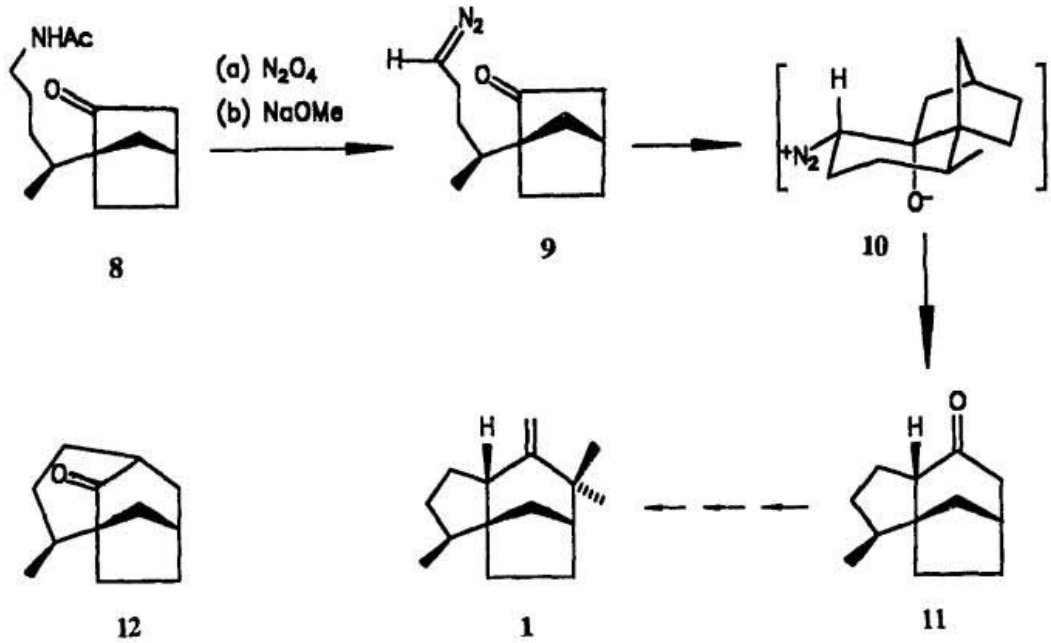


allokhusiol

7

Coates and coworkers[13] *via* an intramolecular diazoalkane–carbonyl ring expansion as the key reaction (Scheme 1). The diazopentylnorcamphor intermediate **9** easily available from **8**, underwent intramolecular ring expansion leading to the tricyclic molecule **11** in 67% yield. The high stereoselectivity of the cyclization **9** →**11** can be explained by an intramolecular *exo* approach to the carbonyl group giving the diazonium alkoxide intermediate **10**. The alternative intermediate resulting from *endo*

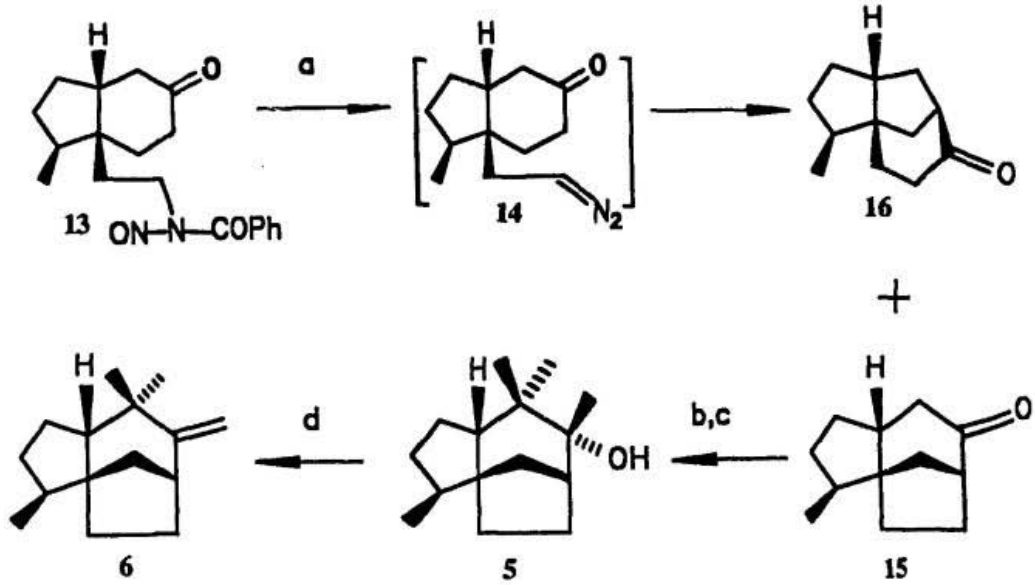
Scheme 1



attack is sterically disfavored relative to **10** by a 1,3 diaxial interaction. If one assumes that the diazo group is in an equatorial position in **10** due to minimization of charge separation, then concerted migration of the carbon–carbon bond antiparallel to the diazo leaving group gives the tricyclic ketone **11** directly. As a result of the rigid norbornyl moiety, there are no conformations of any of the possible diazonium alkoxide stereoisomers in which the alternative methylene carbon has an antiparallel orientation with the diazo group. Therefore, none of the bridged ring ketone **12** was produced. The tricyclic ketone **11** was converted into (±) –zizaene in seven steps.

The same strategy was applied to the total syntheses of (–)–prezizaene (**6**) and (–)–prezizanol (**5**) (Scheme 2).[14] The *N*–nitroso amide **13** was subjected to reaction with potassium *tert*–butoxide in *tert*–amyl alcohol. The diazoethyl ketone **14** thus generated underwent spontaneous cyclization and rearrangement affording 28% of the undesired ketone **16** and 34% of the desired ketone **15**. Ketone **15** was transformed

Scheme 2

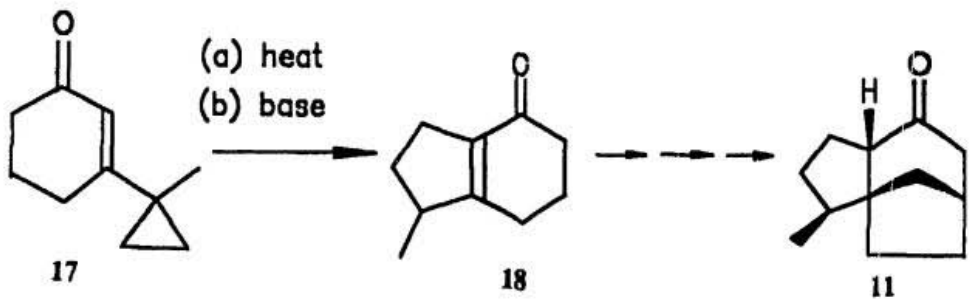


(a) KO–*t*–Bu, *t*–AmOH; (b) KH, MeI; (c) MeLi, Et_2O; (d) MsCl, Et_3N.

into (–)–prezizanol (**5**) and (–)–prezizaene (**6**) in two and three steps, respectively. The low regioselectivity of the cyclization **14** → **15** is the drawback to this approach.

Compound **11**, a key intermediate in the Coates synthesis of (±)–zizaene (**1**), was prepared by Piers and coworkers[15] by thermal rearrangement of a β–cyclopropyl–α,β–unsaturated ketone (Scheme 3). Thermolysis of 3–(1–methyl–

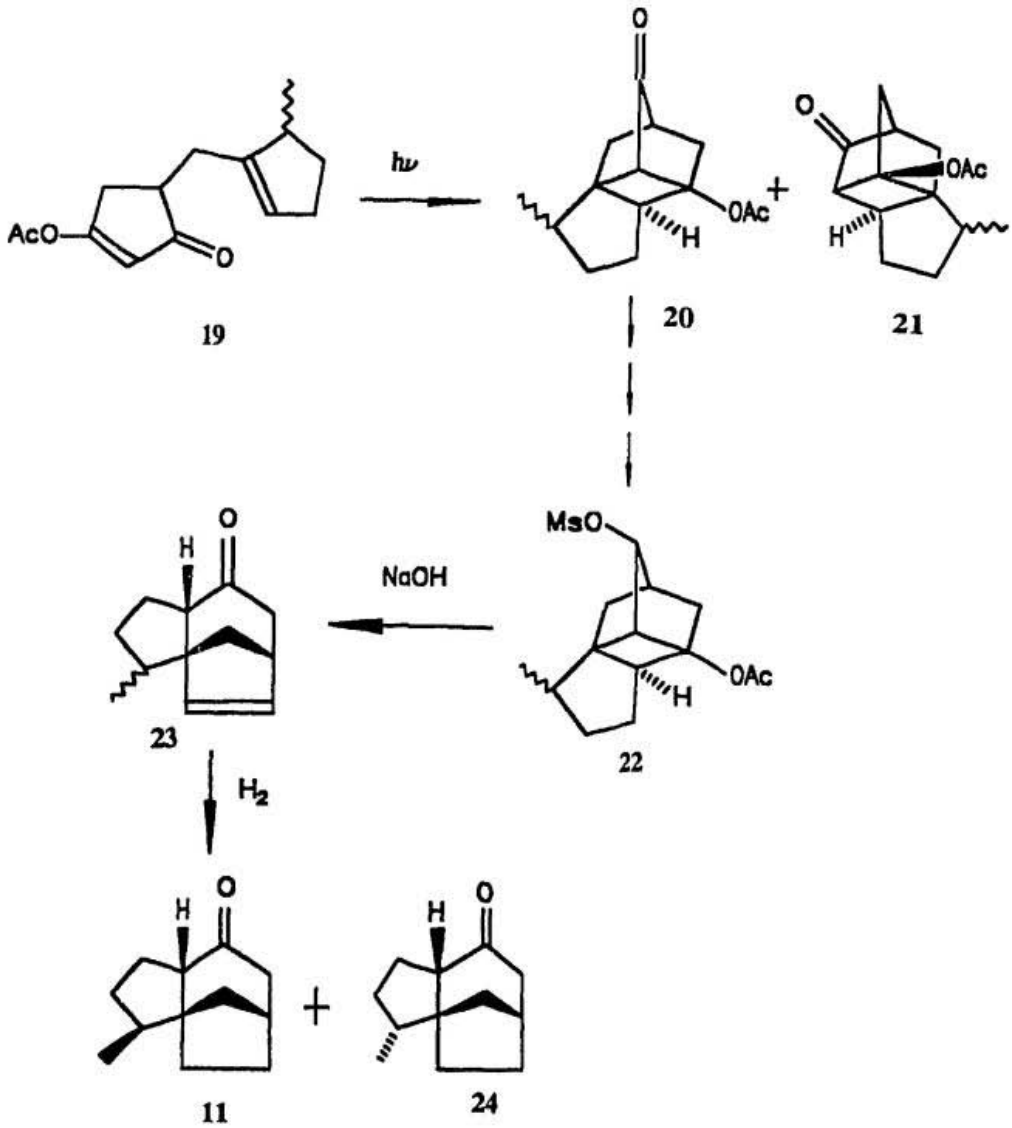
Scheme 3



cyclopropyl)-2-cyclohexenone (**17**) at 450°C, followed by base treatment of the initially formed product, afforded the annulated ketone **18** in 87% yield. Compound 18 was converted, *via* an eleven-step sequence, into the tricyclic ketone **11**.

In Pattenden's[16] approach to the ketone **11**, the tricyclic skeleton was constructed by intramolecular photocycloaddition followed by Grob fragmentation (Scheme 4).

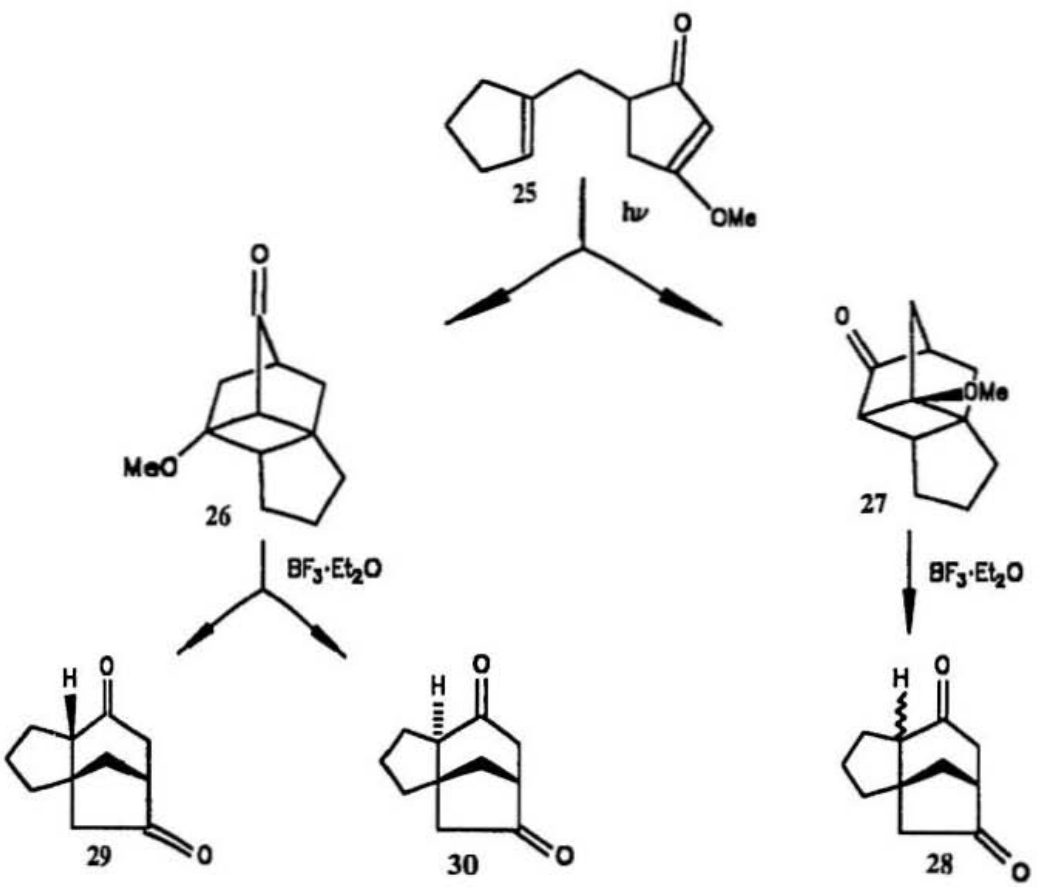
Scheme 4



Irradiation of a 1 : 1 mixture of the enol acetates **19** produced a 7 : 3 mixture of the photoadducts **20** and **21** in 69% yield. The major photoadduct **20** led to the mesylate **22** by reduction followed by mesylation. Treatment of this mesylate with 0.5M NaOH effected simultaneous saponification and Grob fragmentation, with the formation of a mixture of methyl−epimers of the alkene **23**, which was converted into a 1 : 3 mixture of the tricyclic ketones **11** and **24** by hydrogenation. Unfortunately, it was the minor product (**11**) that was the desired tricyclic compound for the synthesis of (±)−zizaene (**1**).

Independently, Oppolzer *et al.*[17] approached the tricyclo[6.2.1.0^{1,5}]undecanedione

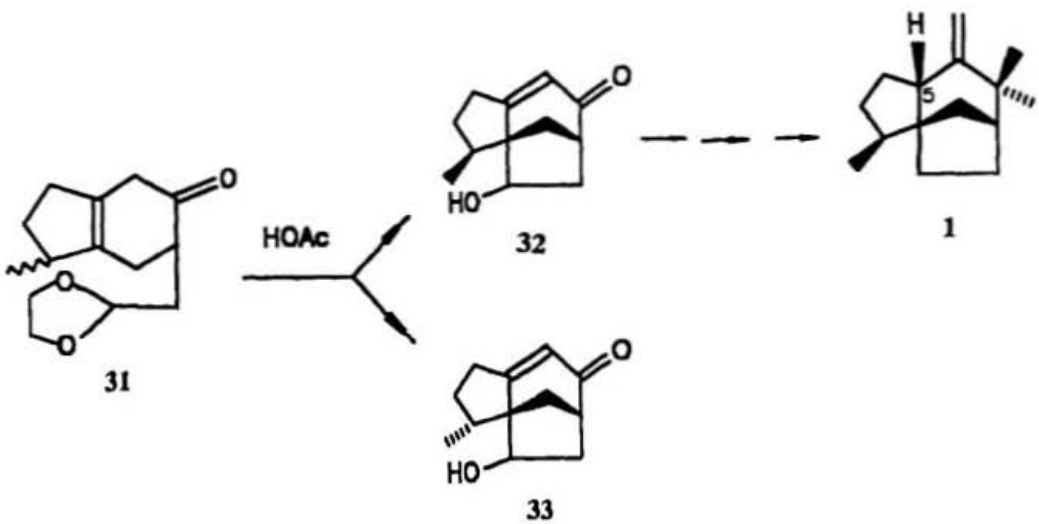
Scheme 5



by an intramolecular photocycloaddition of 3-alkoxy-5-(1-cyclopentenylmethyl)-2-cyclopentenones followed by retro-aldol bond cleavage (Scheme 5). Irradiation of the methoxy dienone **25** furnished two unstable, regioisomeric photoadducts **26** and **27**, which on Lewis acid-catalyzed fragmentation afforded the tricyclic diketone **28** (24% yield from **25**) and the isomers **29** and **30** (31% yield from **25**). The problem associated with this approach is the low regioselectivity of the photocycloaddition of **25**.

In Wiesner's[18] synthesis of (±)-zizaene, cyclization of the β,γ-unsaturated ketone **31** was accomplished by heating it in 80% acetic acid to yield a mixture of tricyclic epimers **32** and **33** in a ratio of 2 : 3 (Scheme 6). The minor compound **32** was transformed into (±)- zizaene in a number of steps. The key cyclization step is elegant but of low yield, and the overall synthesis is quite long due to a stereochemical problem at C-5.

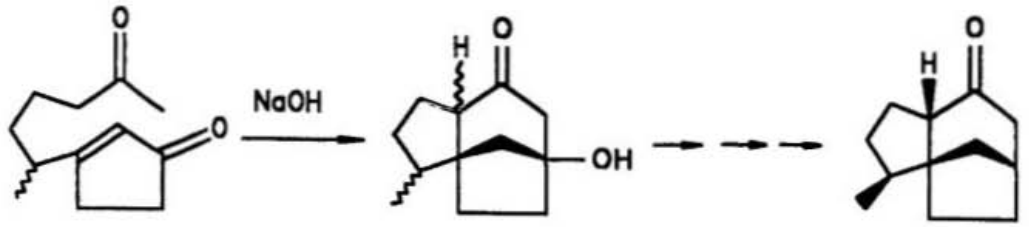
Scheme 6



Posner *et al.*[19] approached the zizaane skeleton from a monocyclic precursor using a double cyclization strategy (Scheme 7). 3-(1-Methyl-5-oxohexyl)-2-cyclopentenone (**34**) underwent a base-promoted intramolecular Michael addition

followed by an internal aldol cyclization to form the tricyclic keto alcohol **35**, which might serve as a precursor to the tricyclic ketone **11**.

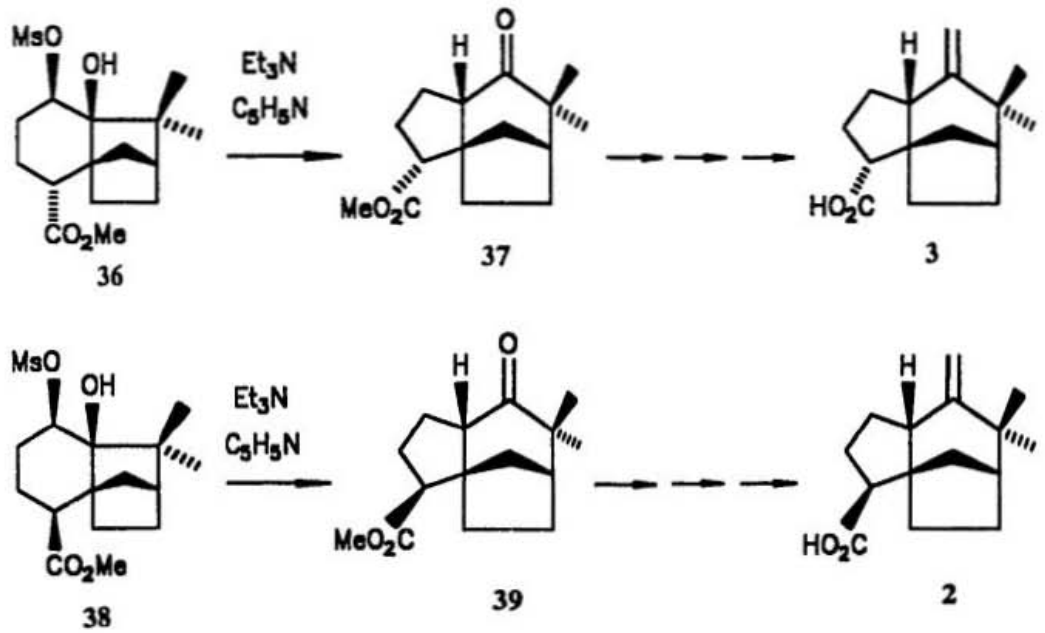
Scheme 7



34 **35** **11**

MacSweeney *et al.*[20] achieved the syntheses of several zizaane sesquiterpenes starting from D−(+)−camphor by utilising a rearrangement of a tricyclo[6.2.1.$0^{1,6}$]−undecane system to form the desired tricyclo[6.2.1.$0^{1,5}$]undecane skeleton (Scheme 8). Compound **36** was subjected to a modified pinacol−type rearrangement in a mixture

Scheme 8



36 **37** **3**

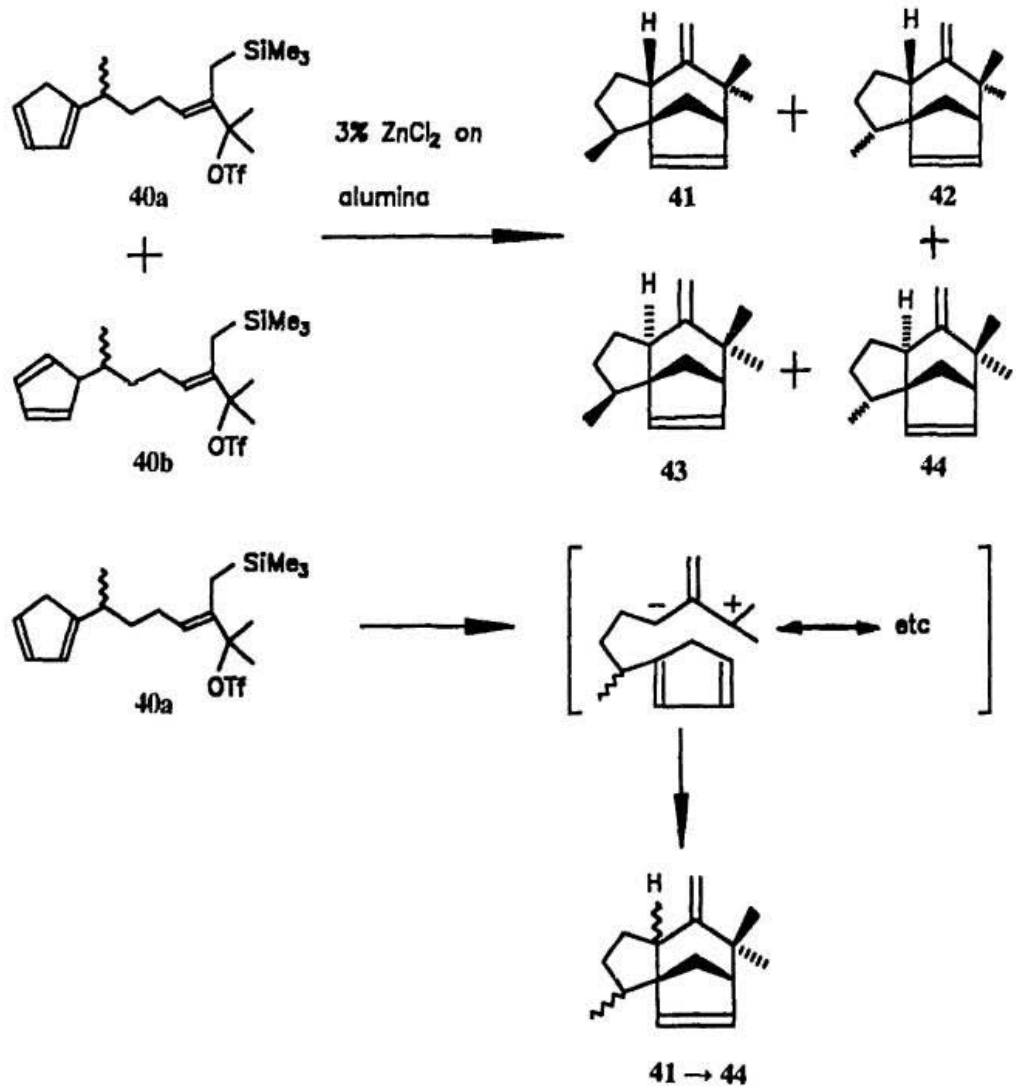
38 **39** **2**

of triethylamine and pyridine to afford **37**, which was transformed into (+)-epizizanoic acid (**3**). Likewise, treatment of **38** produced compound **39**, a key intermediate in the synthesis of (+)-zizanoic acid (**2**).

It is interesting that the same type of key reaction (**36** → **37**) was independently employed by Kido *et al.*[21] to synthesize (+)-epizizanoic acid (**3**).

Hoffmann and coworkers[22] approached the zizaane skeleton *via* carbocation-

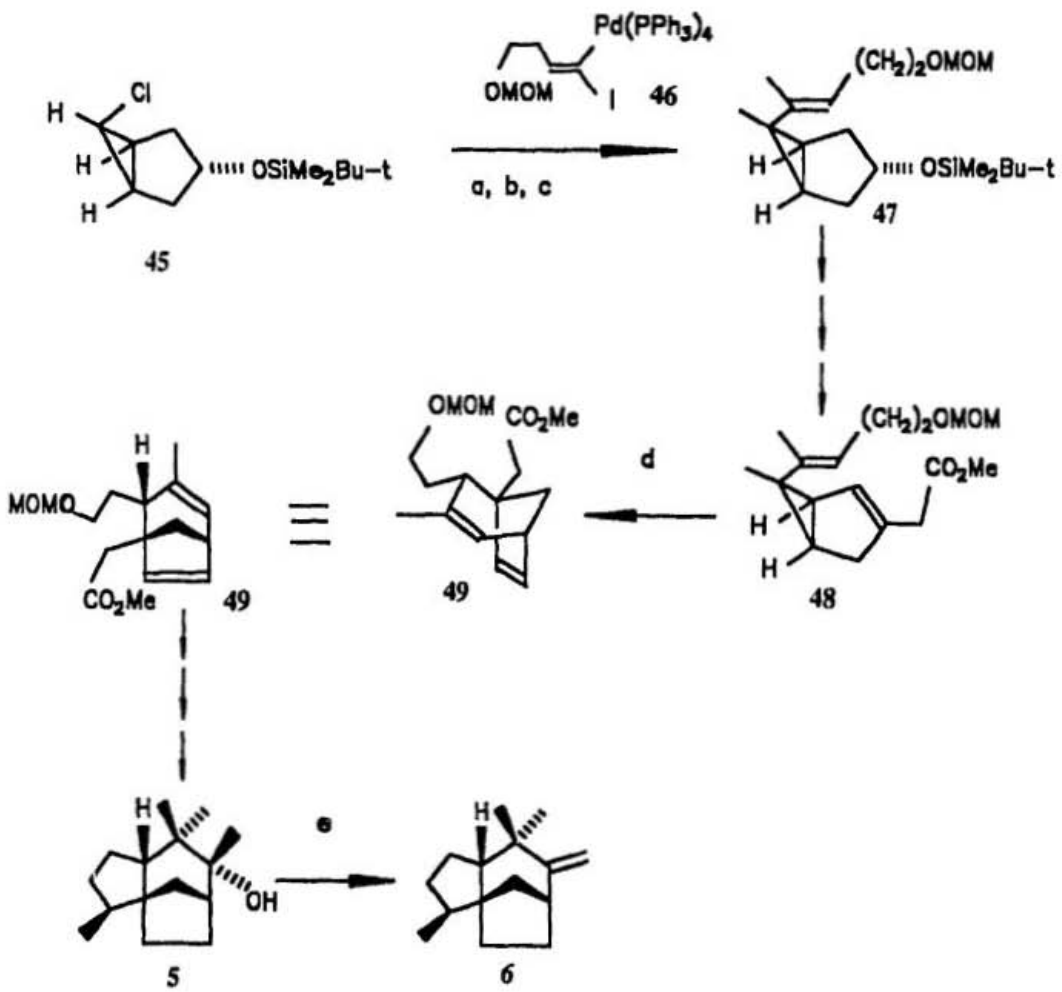
Scheme 9



induced intramolecular cycloaddition (Scheme 9). Compound **40a/b** underwent Lewis acid–initiated tricyclization affording **41**, **42** and **43**, in a ratio of 1: 1.06 : 2.08, as well as a very small amount of **44**. It seemed that the zizaane–type products were derived from **40a**. This novel cyclization approach is relatively short; however, its poor yield and low stereoselectivity limits its practical use in synthesis.

Piers and coworkers[23] synthesized (±)–prezizanol (**5**) and (±)–prezizaene

Scheme 10



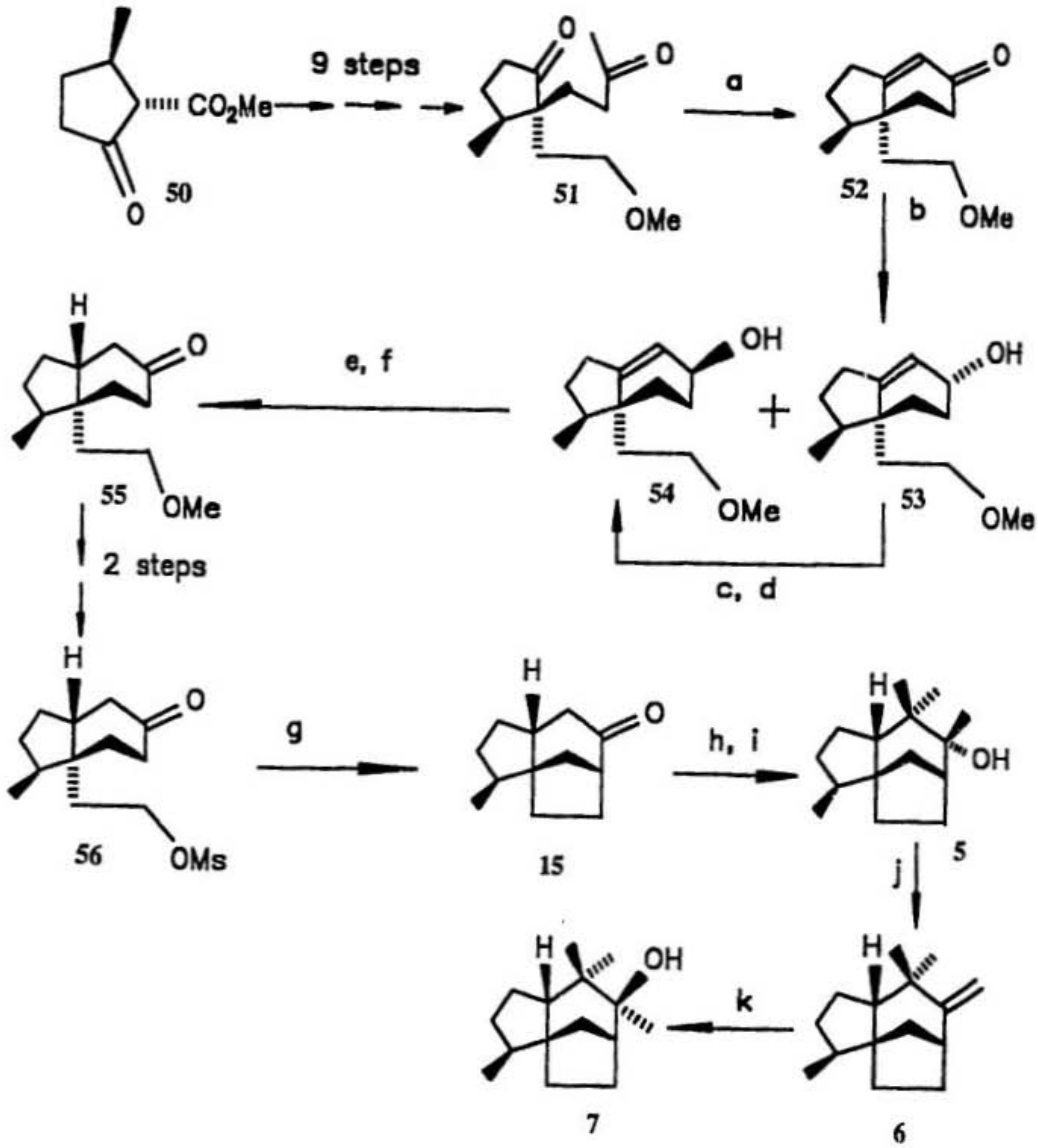
(a) (4,4'–di–*tert*–butylbiphenyl)$^{-}Li^{+}$; (b) $ZnCl_2$, THF; (c) **46**, $Pd(PPh_3)_4$; (d) 110 °C; (e) MsCl, Et_3N.

(6) using a palladium-catalyzed coupling reaction and Cope rearrangement as key reactions (Scheme 10). Treatment of compound **45** with lithium 4,4'-di-*tert*-butyl-biphenylide, conversion of the resulting cyclopropyl-lithium reagent into the corresponding organozinc chloride, followed by $Pd(PPh_3)_4$-catalyzed coupling of the latter species with the iodide **46** gave a 62% yield of **47**, which was converted into the Cope rearrangement precursor **48** in four steps. Compound **48** was distilled at 110°C to afford the bicyclic diene **49** in quantitative yield. Compound **49** was transformed into (±)-prezizanol and (±)-prezizaene in ten and eleven steps, respectively. Although the synthetic sequence is quite long, the key reactions employed are elegant.

Mori and coworkers[24] reported the total synthesis of (-)-prezizanol, (-)-prezizaene and (-)-allokhusiol as shown in Scheme 11. Compound **51**, obtained from **50** in nine steps, underwent base-induced aldol condensation, and the resulting bicyclic ketone was converted into a mixture of **53** and **54** in a ratio of 82 : 18. The major isomer was subjected to the Mitsunobu procedure to give the desired isomer **54**, which, in turn, was hydrogenated followed by Jones' oxidation leading to **55**. Compound **56**, easily prepared from **55** in two steps, cyclised smoothly in the presence of potassium *tert*-butoxide to give the tricyclic ketone **15**, which was the key intermediate in the synthesis of (-)-prezizanol, (-)-prezizaene and (-)-allokhusiol.

As mentioned earlier, the norsesquiterpene (-)-khusimone is not only important to the perfume industry but also has an interesting dimethylmethylene-tricyclo[6.2.1.$0^{1,5}$]undecane skeleton. Therefore, much attention has been paid to its total synthesis. Apart from the degradation of natural zizanoic acid to (-)-khusimone,[25] the first total synthesis of (±)-khusimone was accomplished by Büchi and coworkers[26] as summarised in Scheme 12. The Diels-Alder reaction of α-chloroacrylonitrile and isoprene formed a mixture of two isomers **57** and **58** in a ratio of 7 : 3. The desired diene **59** was obtained by dehydrochlorination of the mixture with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) followed by fractional distillation in 55%

Scheme 11

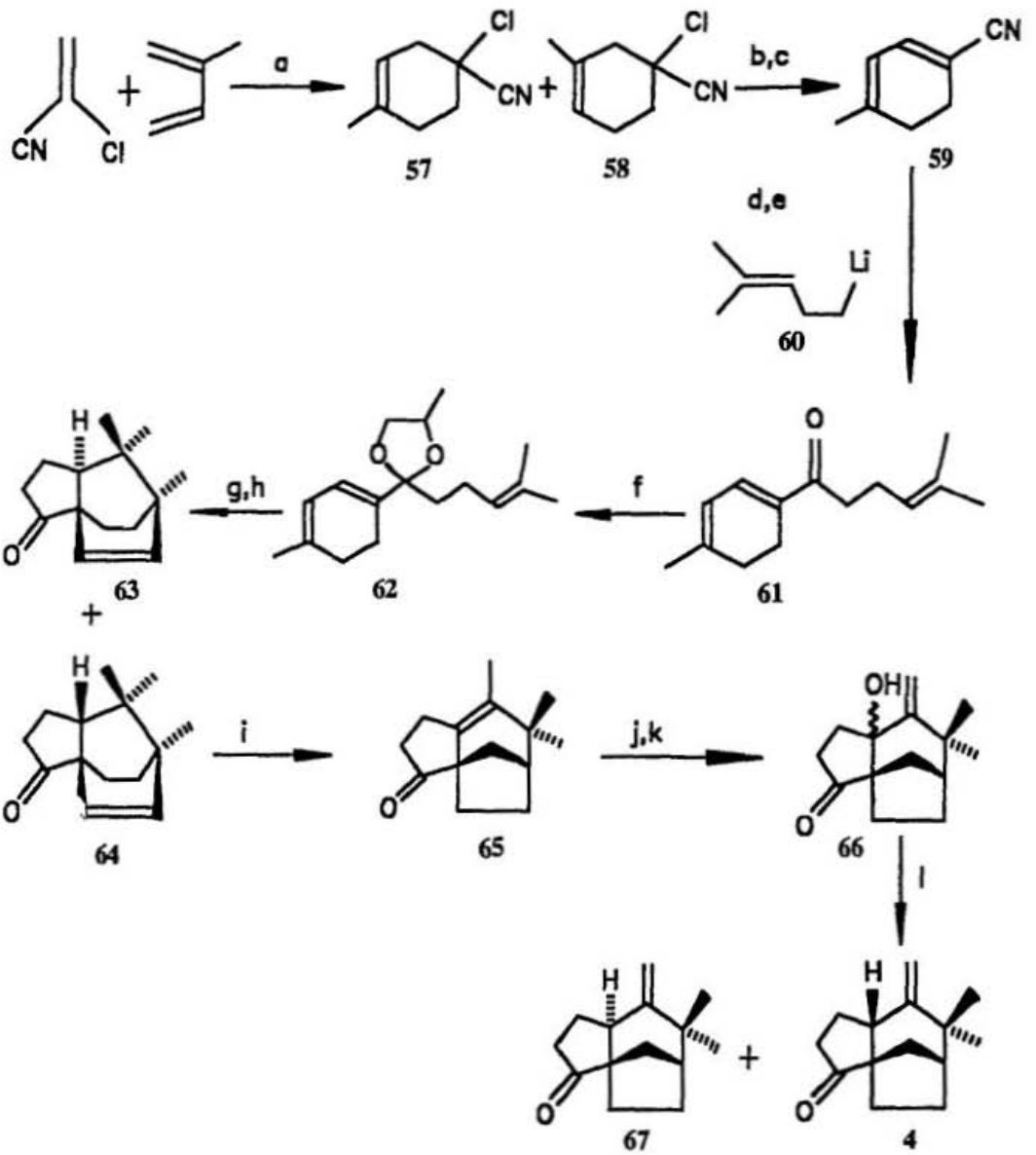


(a) 2% KOH, MeOH; (b) $NaBH_4$, MeOH; (c) Ph_3P, DEAD, $PhCO_2H$; (d) K_2CO_3; (e) H_2, [Rh(NBD)(DIPHOS-4)]ClO_4; (f) Jones' oxidation; (g) *t*-BuOK, THF; (h) KH, MeI; (i) MeLi; (j) MsCl, Et_3N; (k) $Hg(OAc)_2$; $NaBH_4$.

overall yield. Addition of 5-lithio-2-methyl-2-pentene (**60**) resulted in 75% of the trienone **61**, which did not undergo the intramolecular Diels-Alder reaction. Therefore, **61** was ketalised with 1,2-propanediol and the resulting diastereomeric ketals (**62**) were heated at 250°C, and this was followed by acidic hydrolysis to afford a 55% yield of the intramolecular Diels-Alder adducts **63** and **64** in a ratio of 3 : 1. The minor isomer **64** underwent acid-catalyzed skeletal rearrangement to give an 80% yield of isokhusimone (**65**). The contrathermodynamic isomerization of isokhusimone (**65**) to khusimone (**4**) was achieved in two steps. Photosensitized oxygenation (Rose Bengal, EtOH-H_2O) followed by work-up with triethyl phosphite, yielded a mixture of allylic alcohols **66** (77%), which was reduced with zinc and hydrogen chloride in 75% yield to a mixture of 30% epikhusimone (**67**) and 70% (±)-khusimone (**4**). The total synthesis required ten steps, involved two isomer separations, and produced (±)-khusimone **4** in 1.7% overall yield. This approach was quite short, and the low overall yield resulted from the poor stereoselectivity of the intramolecular Diels-Alder reaction of **62**.

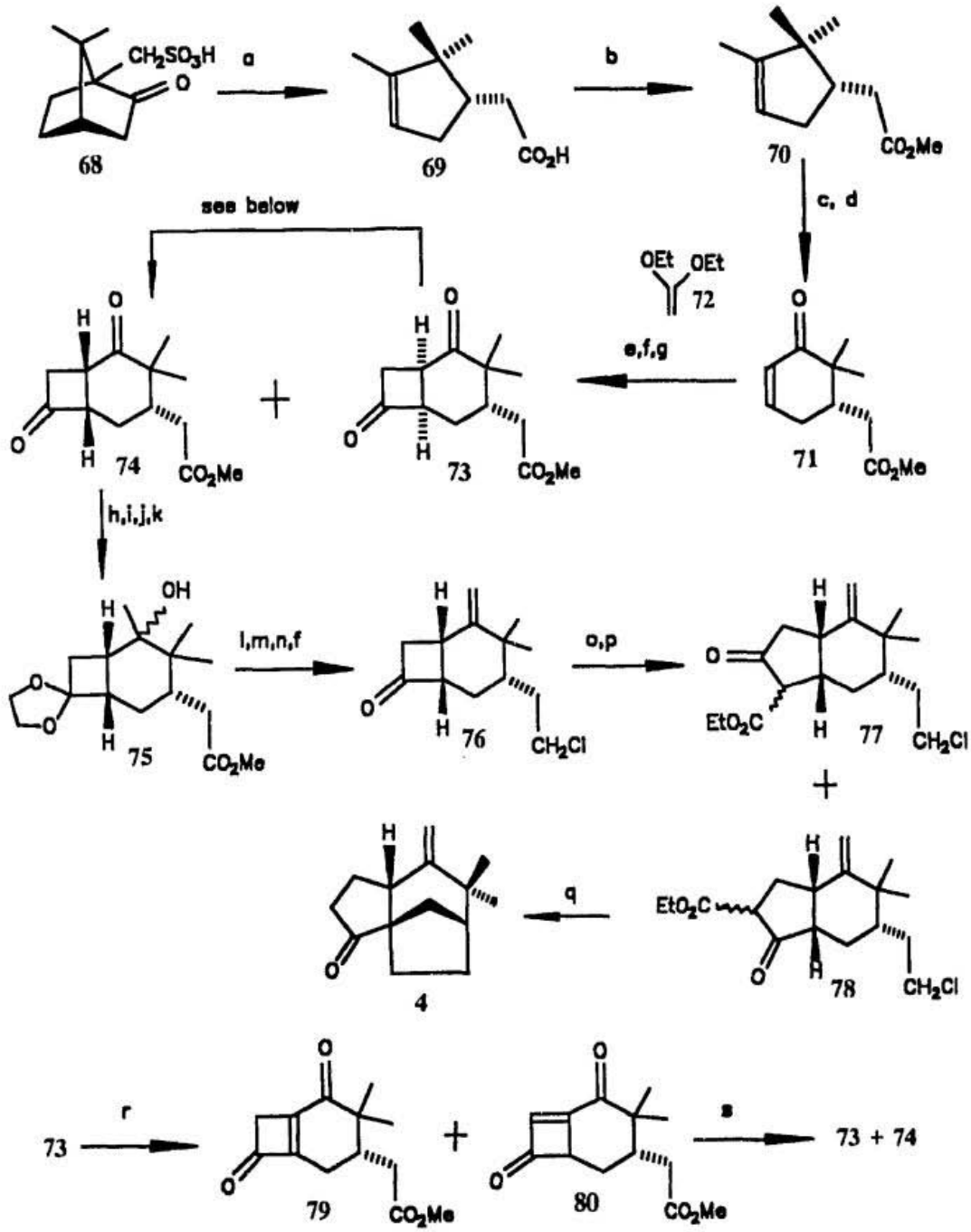
(-)-Khusimone (**4**) was also prepared by Liu and Chan[27] as outlined in Scheme 13. This synthesis began with (-)-camphor-10-sulfonic acid (**68**), which, on fusion with sodium hydroxide, yielded 52% of (-)-α-campholenic acid (**69**). Acid **69** was then esterified and the resulting ester **70** was ozonolysed followed by aldol condensation to yield cyclohexenone **71** in 70% yield. Irradiation of compound **71** with 1,1-diethoxyethene (**72**) and acidic hydrolysis produced two diastereomeric diketones, **73** and **74**, in a ratio of 3 : 5. Of these two diketones, only the former was synthetically useful. Therefore, compound **73** was converted into **74** using a dehydrogenation and hydrogenation sequence. Treatment of compound **73** with pyridinium bromide perbromide in acetic acid induced consecutive bromination and dehyrobromination to yield 66% of **79** and **80** in a ratio of 1 : 7. Reduction of this mixture with zinc dust in acetic acid led to a 3 : 2 ratio of diketones **73** and **74** in 65% yield. Then, the cyclobu-

Scheme 12



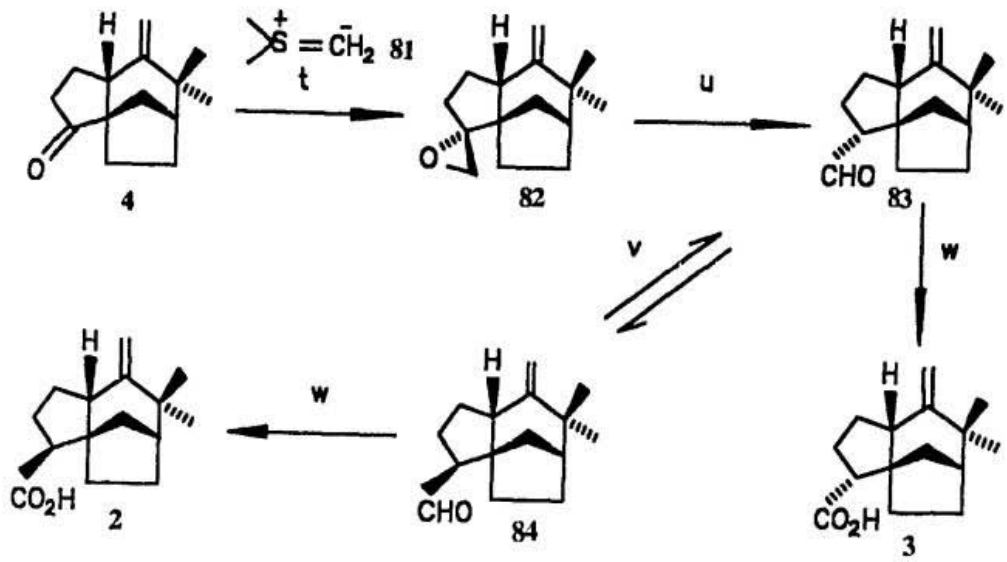
(a) 100 °C; (b) DBN; (c) separate; (d) **60**; (e) H_3O^+; (f) 1,2-propanediol, acid; (g) 250 °C; (h) separate; (i) *p*TSA, C_6H_6 (on **64**); (j) $^1O_2$; (k) $(EtO)_3P$; (l) Zn, HCl.

Scheme 13



(a) NaOH, fusion; (b) K_2CO_3, MeI; (c) O_3, Ph_3P; (d) *p*TSA, C_6H_6; (e) 72, *hν*; (f) H_3O^+; (g) separate; (h) butanone ethylene ketal, acid; (i) NaOH, MeOH; (j) NaH, MeMgBr; (k) CH_2N_2; (l) $SOCl_2$, pyridine; (m) $LiAlH_4$; (n) $POCl_3$; (o) N_2CHCO_2Et, $BF_3{\cdot}Et_2O$; (p) separate; (q) NaOH, MeOH (on 78); (r) pyridinium bromide perbromide, HOAc; (s) Zn, HOAc.

Scheme 13 continued



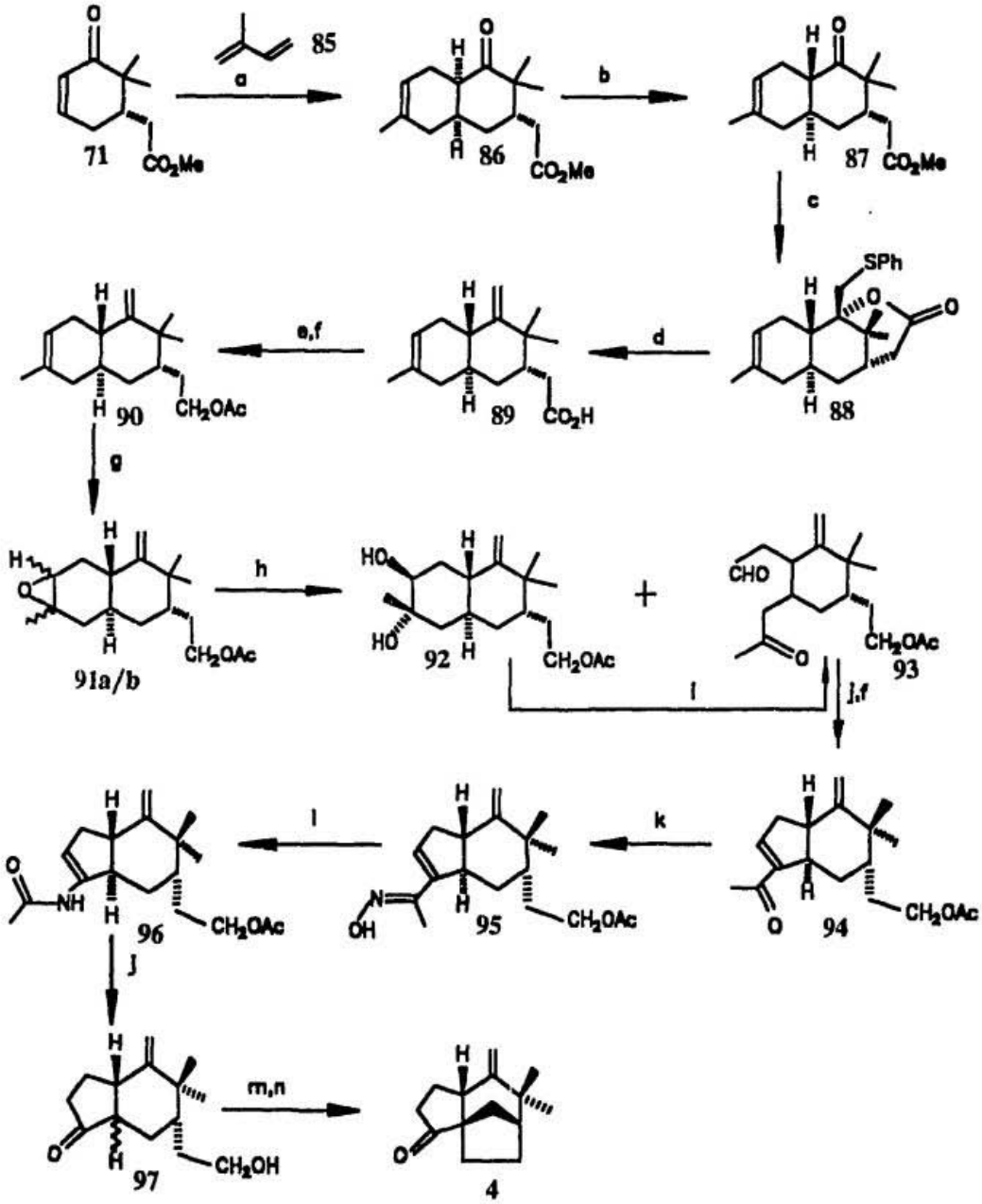
(t) **81**; (u) $BF_3{\cdot}Et_2O$; (v) NaOH; (w) Jones' oxidation.

tanone carbonyl of the diketone **74** was selectively ketalised and the ester was hydrolysed. Addition of methyllithium to the ketone and re-esterification of the acid with diazomethane gave **75**. Dehydration of the tertiary alcohol, reduction of the ester to a primary alcohol, conversion of the alcohol into chloride, and deprotection of the cyclobutanone carbonyl provided ketone **76**. The ketone **76** was ring-expanded by treatment with ethyl diazoacetate and boron trifluoride etherate to afford a 2 : 1 ratio of **77** and **78** in 86% yield. (−)-Khusimone was obtained from **78** *via* concomitant decarboxylation and ring closure. (−)-Khusimone (**4**), upon treatment with an excess of dimethylsulfonium methylide (**81**), produced a single epoxide **82** (52%), which underwent boron trifluoride etherate-induced rearrangement with inversion of stereochemistry to lead to a 100% yield of the aldehyde **83**. This aldehyde was oxidized with Jones' reagent to (−)-epizizanoic acid (**3**) (77%). Likewise, (+)-zizanoic acid (**2**) was prepared from the aldehyde (**84**), which was available from **83** *via*

epimerization on treatment with sodium hydroxide in methanol. The total synthesis of (−)-khusimone required sixteen steps, involved two isomer separations, and the overall yield was 2.7% from **68**. In Liu's synthesis, the photochemical reaction (i.e. **71** → **74**) was not stereoselective. The separation of isomers (e.g. **73** and **74**) can be tedious even if the undesired isomer (**73**) can be converted into the desired one (**74**). In addition, the ring expansion of the ketone **76** was not very regioselective.

Mori's[8] synthesis of (−)-khusimone (**4**) is outlined in Scheme 14. The synthesis began with (*S*)-5-methoxycarbonylmethyl-6,6-dimethyl-2-cyclohexen-1-one (**71**), available in four steps from (−)-camphor-10-sulfonic acid by Liu's process. The tin tetrachloride-catalyzed cycloaddition of isoprene (**85**) to the enone **71** only from the less sterically hindered face gave **86** diastereo- and regioselectively in 35% yield. The *cis*-decalone **86** was converted easily into the *trans*-isomer **87**, which, on treatment with phenylthiomethyllithium followed by lithium-ammonia reductive elimination of the resulting lactone, gave the desired *exo*-methylene acid **89**. The acid was reduced, the primary alcohol was converted into the acetate, and the cyclohexene moiety was epoxidized selectively to yield a mixture of epoxides **91a/b**. The epoxides were allowed to react with periodic acid to give 13.4% of the keto-aldehyde **93**, accompanied by 85.5% of *trans*-diol **92**, which, on reaction with lead tetraacetate, was converted into the desired keto-aldehyde **93**. Compound **93** underwent base-catalyzed cyclization, and acetylation of the resulting alcohol generated the acetate **94**. After reaction with hydroxylamine hydrochloride, the resulting oxime **95** was subjected to Beckmann rearrangement and the enamide **96** formed was hydrolysed. Finally, mesylation of the primary alcohol **97** and cyclization provided (−)-khusimone. In all, the Mori synthesis required fifteen steps from (*S*)-5-methoxycarbonylmethyl-6,6-dimethyl-2-cyclohexenone (**71**), or nineteen steps from (−)-camphor-10-sulfonic acid (**68**). The overall yield was 6.9% from **71**, 2.5% from **68**. Mori's synthesis did avoid isomer separation, but his sequence was three steps longer than Liu's and overall

Scheme 14



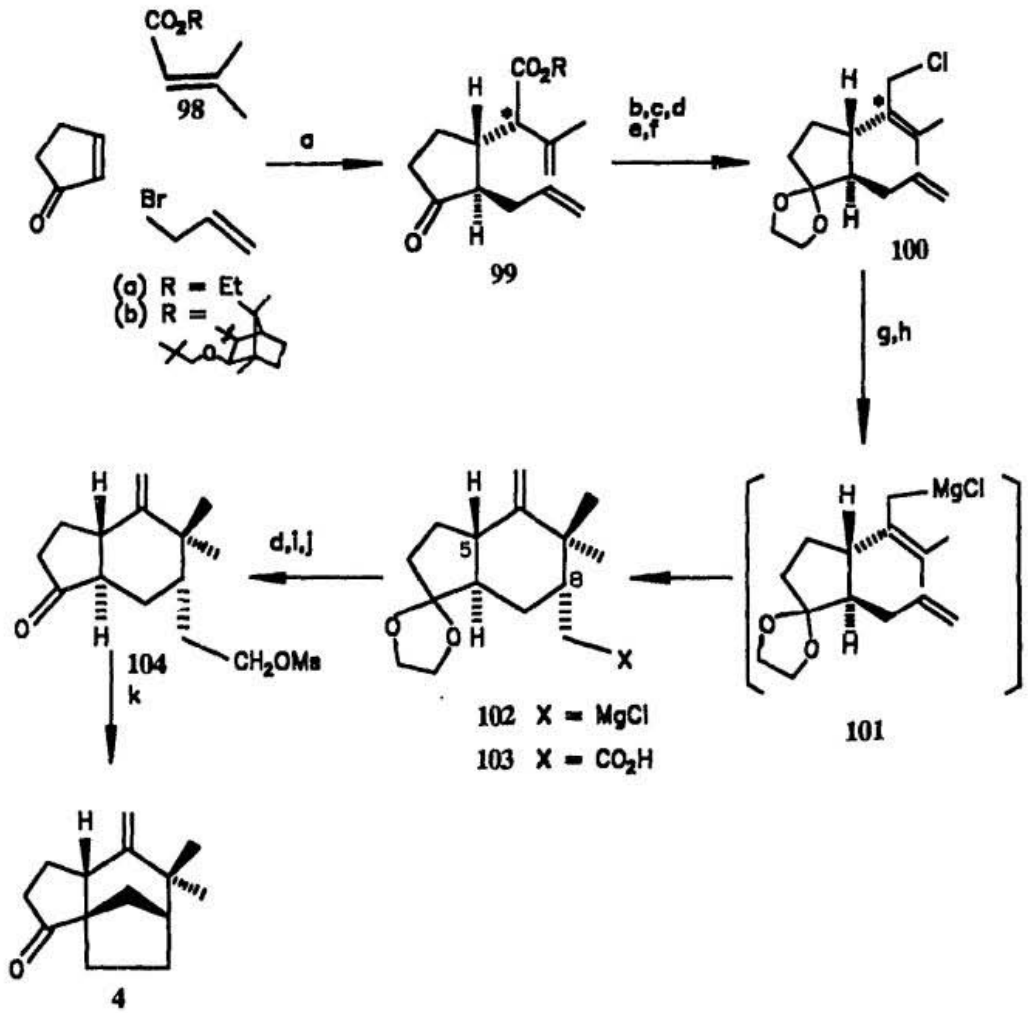
(a) **85**, $SnCl_4$; (b) NaOMe, NaOH; (c) $PhSCH_2Li$; (d) Li, NH_3; (e) $LiAlH_4$; (f) Ac_2O, pyridine; (g) *m*CPBA; (h) HIO_4; (i) $Pb(OAc)_4$; (j) 10 % KOH; (k) $NH_2OH{\cdot}HCl$, pyridine; (l) MsCl, pyridine, DMAP; (m) MsCl, Et_3N; (n) *t*-BuOK.

yield was lower.

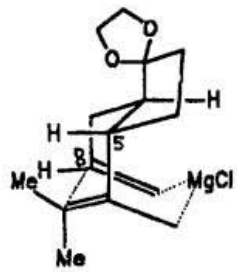
Oppolzer and coworkers[28] developed an interesting route to (±)-khusimone (**4**) that proceeded *via* an intramolecular type-**II** magnesium-ene reaction (Scheme 15). The cyclopentenone conjugate addition of the α-enolate, derived from 3,3-dimethylacrylate (**98a**), coupled with enolate trapping by alkylation with allyl bromide generated directly a mixture of two 2,3-disubstituted cyclopentanones **99a** in 50% yield. Compound **99a** was converted into the key precursor **100** by successive protection of the carbonyl group as an ethylene ketal, base-induced double bond migration, reduction of the ester with $LiAlH_4$, mesylation of the resulting primary alcohol and treatment with LiCl. After slow addition to magnesium powder, the resultant Grignard reagent **101** was heated to furnish the cyclized organomagnesium chloride **102**, which was converted into the acid **103** by trapping with CO_2. The remarkable stereoselectivity of the cyclization was rationalized by examining the alternative transition states **A** and **B**. The boat conformation of the developing cyclohexane in transition state **B** causes a flagpole interaction between one C-7 methyl and the C-1 hydrogen, whereas the evolving chair conformation in **A** is easily attainable. Therefore, **A** is much favored over **B**, which entails the desired *cis* relative stereochemistry of C-5 and C-8 in **102**. The carboxylic acid **103** was reduced, the resulting primary alcohol mesylated, and the ketal cleaved to furnish the ketomesylate **104**. (±)-Khusimone was obtained from **104** via intramolecular alkylation. Oppolzer's synthesis required eleven steps from cyclopentenone and provided (±)-khusimone in 11% overall yield.

Oppolzer's synthesis[29] of (-)-khusimone relied on the π-facially selective aprotic Michael addition of the lithium dienolate derived from the chiral senecioate **98b** to cyclopentenone. The Michael addition followed by *in situ* trapping of the intermediate enolate with allyl bromide proceeded with 53 : 18 facial selectivity to afford a mixture of four diastereomers, of which the predominant isomer (5*S*, 6*S*)-**99b** was isolated in 37% yield.

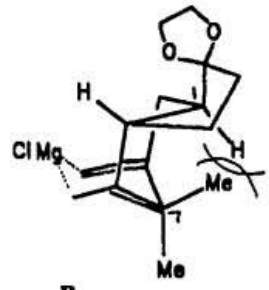
Scheme 15



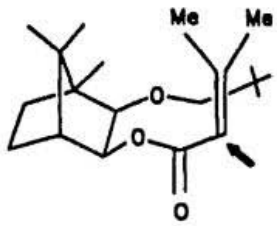
(a) LDA, **98**; cyclopentenone; then allyl bromide; (b) ethylene glycol, *p*TSA; (c) NaOEt, EtOH; (d) $LiAlH_4$; (e) MsCl, pyridine; (f) LiCl; (g) Mg powder; (h) CO_2; (i) MsCl, Et_3N; (j) HCl, H_2O; (k) *t*-BuOK.



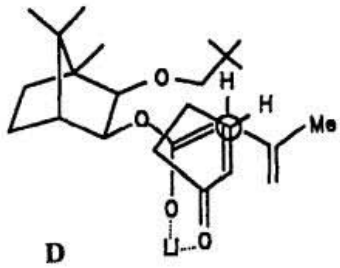
A



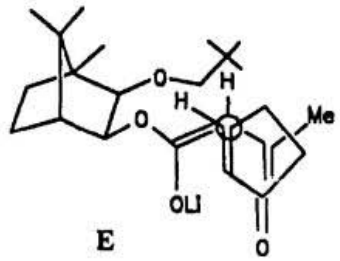
B



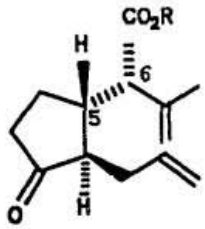
C



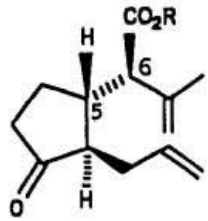
D



E



(5*S*,6*S*) – 99b



(5*S*,6*R*) – 99b

In the Michael addition process, the enone approaches the dienolate from the less sterically hindered face as shown in **C**, thus invoking a staggered approach of the trigonal centers and the operation of electronic factors. Two transition states **D** and **E** can be considered. There is some steric repulsion between a cyclopentenone methylene and the dienolate methyl group in projection **E**. Furthermore, the carbonyl group and the enolate oxygen are too far away to permit chelation. Orientation **D** is

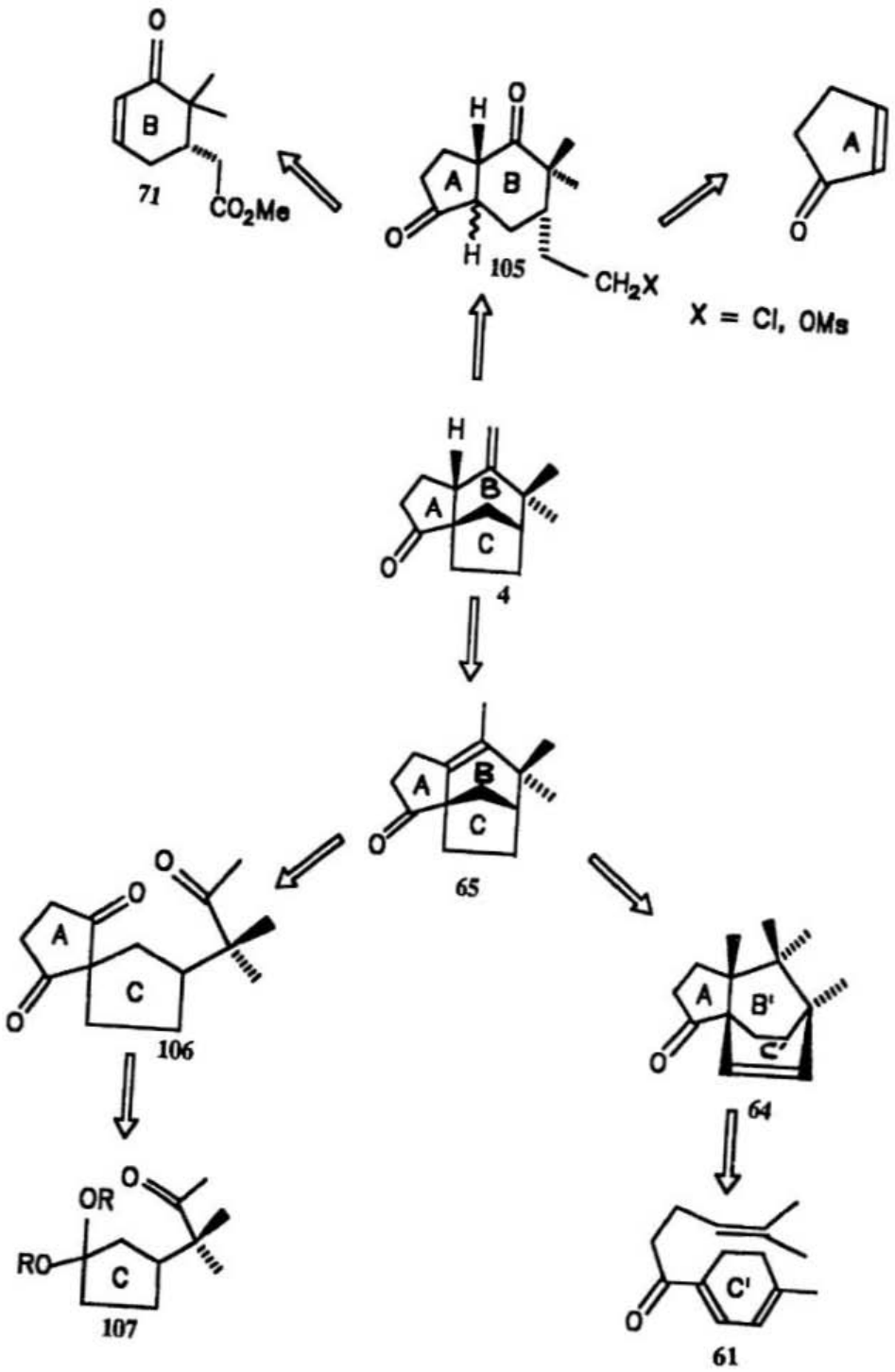
largely free of steric constraints and prone to chelation. Therefore, (5*S*,6*S*)-**99b**, which is formed *via* the more favorable transition state **D**, should predominate. Compound (5*S*, 6*S*)-**99b** was converted into (-)-khusimone (**4**) according to the same reaction sequence as in the synthesis of (±)-khusimone. The Oppolzer synthesis required eleven steps, it involved one isomer separation, and produced (-)-khusimone in 8% overall yield. This approach would be excellent if the facial selectivity in the asymmetric Michael addition were higher.

Although the tricyclo[6.2.1.$0^{1,5}$]undecane ring system has been synthesized by a number of successful approaches, the development of short and selective approaches to specifically functionalized ring systems of this type remains a challenge in modern synthetic organic chemistry. For this purpose, khusimone (**4**) was chosen as one of our synthetic targets because of its considerable importance to the perfume industry and its ready transformation to other members of the zizaane family, such as zizanoic acid (**2**) and epizizanoic acid (**3**).

The retrosynthetic analysis of all known approaches to khusimone (**4**) is shown in Scheme 16. Liu, Mori, and Oppolzer prepared khusimone **4** through a common intermediate **105** *via* a C ring disconnection. Liu's and Mori's syntheses began with **71**, a B ring; while Oppolzer's synthesis started with cyclopentenone, an A ring. In Büchi's synthesis, the A, B' rings in **65** were constructed simultaneously from **61**, a C' ring, *via* Diels-Alder reaction. Modification of the B' and C' rings led to the B and C rings of khusimone.

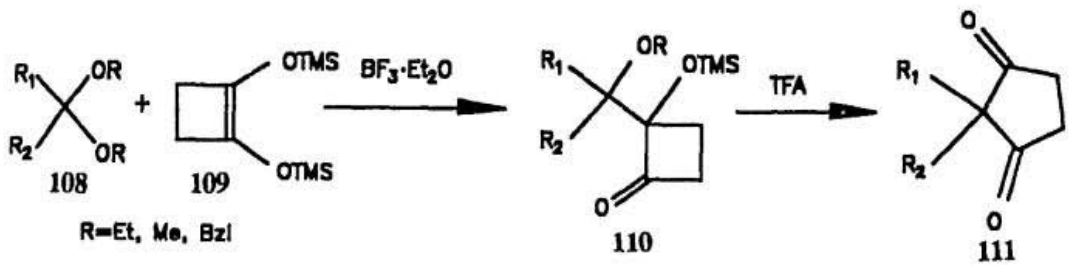
The retrosynthetic scission of the six-membered ring of the zizaane skeleton leads to a system with spiro-linked five-membered rings A and C, of which A can be a symmetrical cyclopentane-1,3-dione moiety (Scheme 16). It is well known that **C**-alkylation of cyclic β-diketones can be a very poor reaction,[30] but Kuwajima *et al.*[31] demonstrated that the Lewis acid-catalyzed reaction of a dimethyl, diethyl or

Scheme 16


O
B
71
CO2Me
H
O
A
B
O
H
105
CH2X
X = Cl, OMs
A
O
H
A
B
C
O
4
A
B
C
O
65
O
O
A
C
O
106
OR
O
RO
C
107
A
B'
C'
O
64
C'
O
61

dibenzyl ketal **108** (but not a ketone) with 1,2-bis(trimethylsiloxy)cyclobutene (**109**) followed by rearrangement of the resulting cyclobutanone **110** with trifluoroacetic acid (TFA) can give a 2,2-disubstituted cyclopentane-1,3-dione **111** in a reasonable yield (Scheme 17).* Thus, our plan was to obtain an appropriately functionalised cyclopentanone ketal **107** on a C ring precursor, to spiro-annulate using **109**, and finally to cyclize the B ring. Indeed, our synthetic proposal was confirmed to be plausible, and the following details this synthetic study.[34]

Scheme 17



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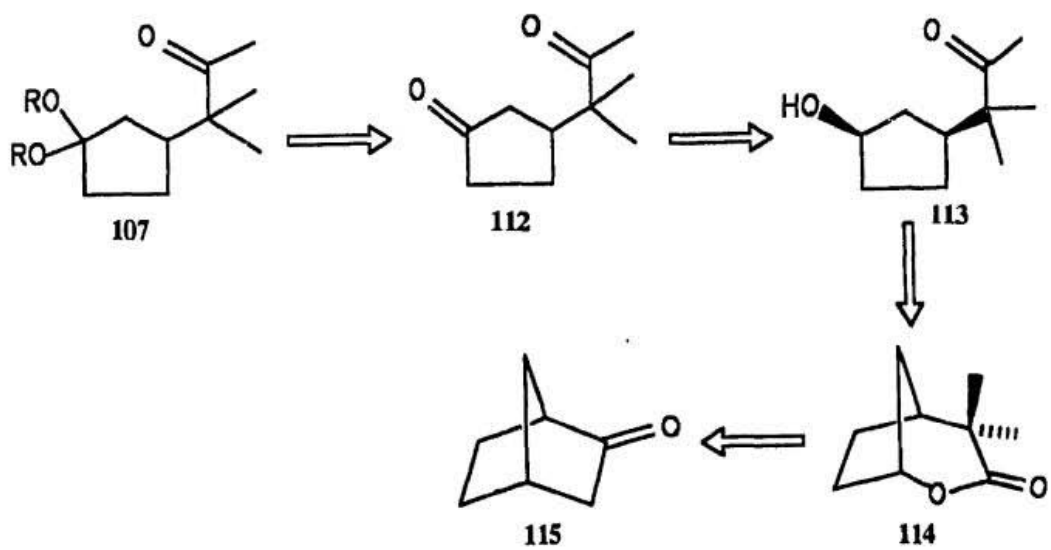
* For other syntheses employing this reaction, see refs. 32 and 33.

II. Results and Discussion

In our retrosynthetic analysis we envisioned that ketal **107**, the key substrate for the spiro-annulation reaction, could be synthesized from the diketone **112**, which in turn might be prepared from compound **113** by oxidation. Addition of an organometallic reagent to the lactone **114** could give hydroxy ketone **113**. We felt that the transformation of norcamphor **115** to the lactone **114** should be readily achieved (Scheme 18).

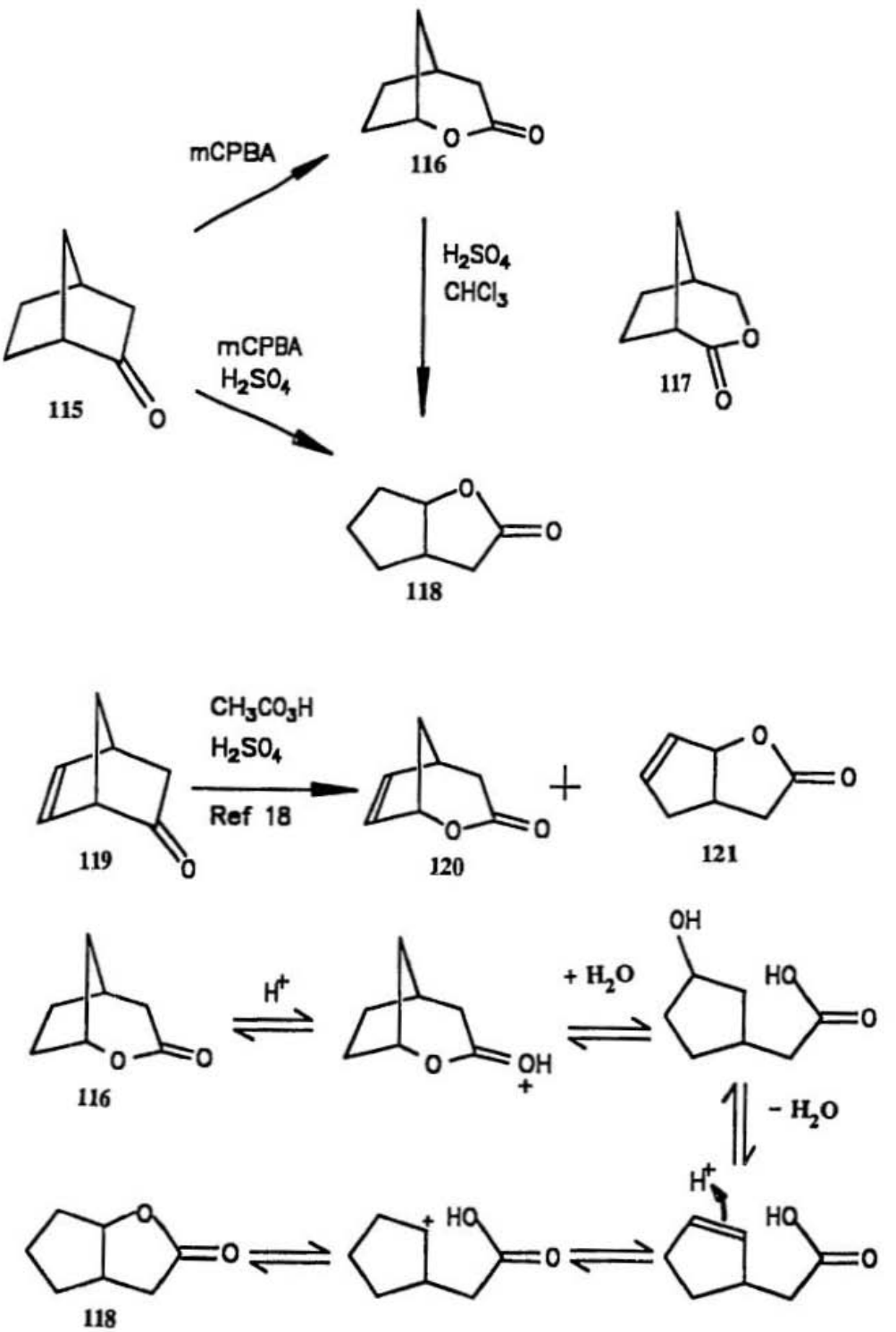
Scheme 18



Meinwald and Frauenglass[35] had reported a number of years ago that norcamphor (**115**) in concentrated sulfuric acid containing peroxyacetic acid led to the expected lactone **116** in 97% crude yield (Scheme 19). In contrast, the oxidation of norbornenone (**119**) under the same conditions gave the unsaturated lactone **120**, but only as a minor product, the major product being an allylically rearranged product **121**.

Baeyer–Villiger reaction under basic conditions ($NaOH-H_2O_2$ in Et_2O-H_2O) also gave **121**. Thus, norcamphor was treated with *m*–chloroperoxybenzoic acid (*m*CPBA) in the presence of concentrated sulfuric acid following a procedure similar to that of Meinwald and Frauenglass. Gas chromatography–mass spectrometric (GC–MS) analysis of the crude product indicated only one compound. Infrared (IR) absorption at 1765 cm^{-1} suggested a five–membered ring lactone, and the ^{13}C NMR showed signals for two methines, at δ 37.7 and 86.2, of which the latter was connected to an oxygen. Furthermore, the $^1H-^1H$ correlation (COSY) spectrum indicated significant coupling between the protons on the two methines, meaning that the two methines were joined. Clearly, this compound could only have been the rearranged product **118**. We believed that **118** was derived from **116** by acid catalysis. Indeed, the Baeyer–Villiger oxidation of norcamphor with *m*CPBA in the absence of concentrated sulfuric acid at room temperature afforded only the desired product **116** in 86% yield after vacuum distillation. The complete regioselectivity of this Baeyer–Villiger oxidation can be rationalised according to the general order of likelihood of migration, or "migratory aptitude", *sec*–alkyl > *pri*–alkyl.[36] In fact, no trace of another isomer **117** was detected by ^1H NMR and GC–MS analysis of the crude product. The structure of compound **116** was derived from the following spectroscopic evidence. A broad singlet at δ 4.866 ppm in the ^1H NMR spectrum indicated a proton on a carbon next to oxygen. The integration of this singlet was only one proton, which precluded the possibility of lactone **117**. Of the two signals for methines in the ^{13}C NMR spectrum (δ 31.1 and 84.1), one (δ 84.1) was consistent with a methine bonded to oxygen. The IR absorption maximum for carbonyl was at 1730 cm^{-1}, which cannot fit structure **118**. Addition of a small amount of concentrated sulfuric acid to lactone **116** in chloroform generated compound **118**. A possible mechanism for this conversion is shown in

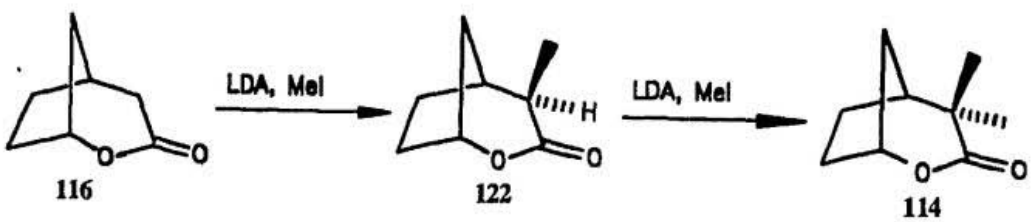
Scheme 19


mCPBA
116
H_2SO_4
$CHCl_3$
mCPBA
H_2SO_4
115
117
118
CH_3CO_3H
H_2SO_4
Ref 18
119
120
121
H^+
$+ H_2O$
OH
HO
116
$- H_2O$
H^+
HO
118

Scheme 19.

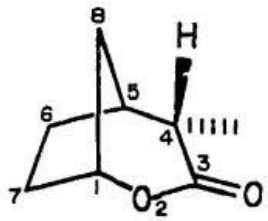
The α-methylation of the lactone **116** was carried out according to procedures derived from those of Posner[37] and Schlessinger.[38] Thus, the lithium enolate of the lactone **116**, which was formed by slowly adding a solution of **116** to a solution of lithium diisopropylamide (LDA) at $-78°C$, was treated with iodomethane in hexamethylphosphoramide (HMPA) at $-40°C$ furnishing a monomethylated product in 85% yield after flash column chromatography. If one assumes that the methyl group is added to the less sterically hindered *exo* face, then the resultant product should be **122** instead of **123**. A methyl doublet in its ^1H NMR spectrum was resolved at δ 1.326 and the proton α to the carbonyl was found as a triple quartet at δ 2.524. Further α-methylation utilizing the same procedure gave a colorless solid **114** in 83% yield. Two methyl singlets were found at δ 1.247 and δ 1.328 in its ^1H NMR spectrum. In practice, crude product **122** could be used for the further α-methylation without any purification, in which case an 82% yield of **114** was obtained from **116** (Scheme 20).

Scheme 20

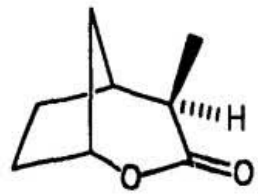


116 **122** **114**

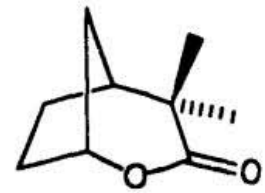
By comparing the ^{13}C NMR chemical shifts of compound **122** with those of **114**, the tentative assignment of the relative stereochemistry at C-4 in compound **122** was confirmed. The C-6 in **114** should be shifted upfield relative to that in **122** because of the γ-gauche effect.[39] In contrast, the C-8 in **114** would be shifted upfield as compared with that in **123**. The assignment of the ^{13}C NMR spectrum was assisted by



123



122

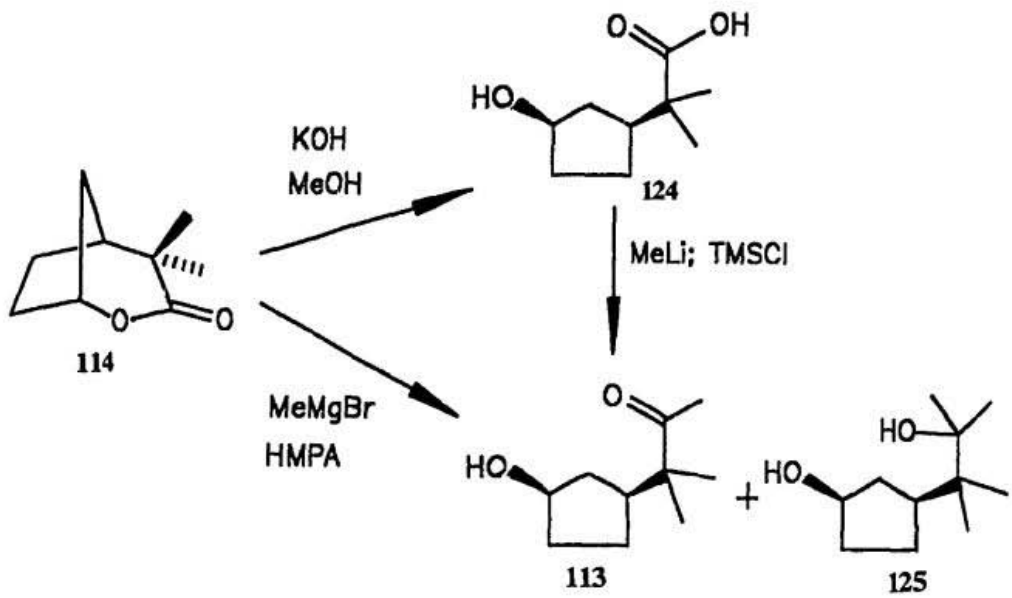


114

$^{13}C-^{1}H$ correlation, attached proton test (APT) and COSY spectra. For example, the APT spectrum of compound **114** can distinguish the two methine resonances in the ^{13}C NMR spectrum, which in turn can locate the corresponding proton signals *via* the $^{13}C-^{1}H$ correlation spectrum. From the COSY spectrum, a proton which is coupled to the protons on both C-1 and C-5 must be attached to C-8. With the assignment of the protons on C-8 possible, then the protons attached to C-6 and C-7 can be located in a straightforward fashion from the COSY and $^{13}C-^{1}H$ correlation spectra. In this way, all the methylene carbons could be assigned from their corresponding protons. We assigned δ 24.0 for C-6, 31.2 for C-7, and 33.5 for C-8 of **114**. The same principle was applied to compound **122**. The chemical shift for C-6 was δ 29.9 and another two methylenes were at δ 32.4 and 32.3. The C-6 upfield shift of 5.9 ppm in **114** is due to the γ-gauch effect. This argument precluded the possibility of the alternative structure **123**.

Initial experiments directed toward the preparation of the methyl ketone **113** were carried out with lactone and methyl magnesium bromide after the method of Huet *et al.*[40] Lactone **114** was allowed to react with 2.2 or 5 equivalents of methyl magnesium bromide in HMPA at 80°C. Chromatography on silica gel did give a very small amount of two products, of which the more abundant one was quite polar as revealed by thin layer chromatography (TLC), and the starting material **114** was recovered to the extent of 83%. Distinctive absorption in the IR spectrum of the less

Scheme 21

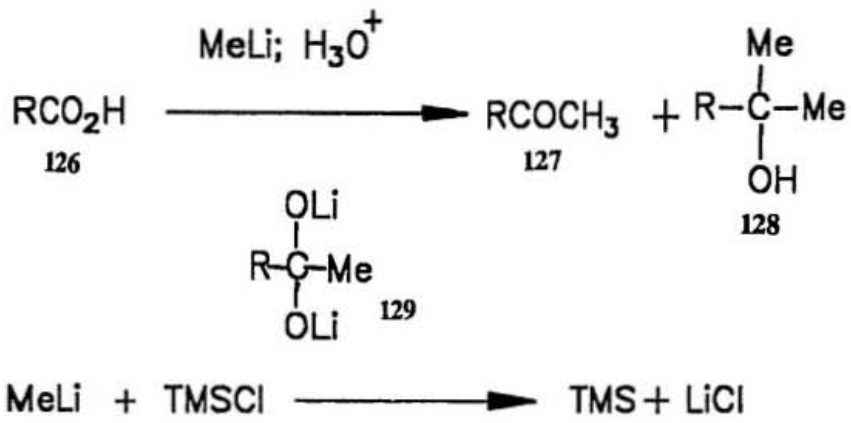


polar minor product appeared at 1710 cm^{-1} and 3420 cm^{-1} (broad), suggesting the presence of a carbonyl group and an hydroxyl. The three-proton singlet at δ 2.131 in its ^1H NMR spectrum might be derived from a methyl ketone moiety. Thus, this minor product appeared to be the desired methyl ketone **113**. The major product was believed to be the diol **125** from the following spectroscopic evidence. Prominent IR absorption came only at 3380 cm^{-1} (broad), thus the product must contain an hydroxyl group, but not a carbonyl group. Four methyl groups were found as four three-proton singlets at δ 0.891, 0.908, 1.202 and 1.203 in the ^1H NMR spectrum. The signals at δ 72.7 and 76.2 in its ^{13}C NMR spectrum indicated two carbons attached to oxygen, one of which, as shown from the APT and $^{13}C-^1H$ correlation spectra, was a methine, the other was a quarternary carbon. Several attempts to optimize the reaction conditions (e.g. temperature, reaction time, amount of the reagents) did not give any improvement. The slow reaction may be attributed to the quarternary carbon adjacent to the

carbonyl group, and the reason for the formation of the major product **125** is that the methyl ketone **113** is more reactive than the lactone **114**, and it would further react with CH_3MgBr once formed (Scheme 21).

An alternative route to methyl ketone **113** started with hydrolysis of the lactone with aqueous sodium hydroxide in ethanol. Acidic work-up gave the acid **124** as a colorless solid in quantitative yield. The IR spectrum showed absorption maxima for the carbonyl, 1700 cm^{-1}, and the O-H's, 2500 cm^{-1}-3600 cm^{-1}. The acidic proton (COO**H**) came at δ 12.01 in the ^1H NMR spectrum in CD_3SOCD_3, the hydroxyl proton of the alcohol at δ 4.45, and both peaks disappeared upon addition of D_2O. Addition of five molar equivalents of methyllithium to the acid following the procedure of House and Bare[41] furnished 22% of the desired ketone **113**, 37% of diol **125**, and 31% of the starting material **124** after flash column chromatography. It was reported that one of the major problems associated with the transformation of carboxylic acids **126** into methyl ketones **127** using methyllithium was the co-production of tertiary alcohols **128** (Scheme 22).[42] If methyllithium is added slowly enough to ensure the complete conversion of the acid into the lithium carboxylate before addition to the

Scheme 22



carbonyl by a second equivalent of methyllithium, then the formation of **128** must be the result of a slow hydrolysis rate of methyllithium relative to the breakdown of **129** into methyl ketone, producing **128** during the work-up* procedure. It was found that quenching the reaction medium by addition of dilute acid with rapid stirring can minimize production of **128**.[42] More recently, Rubottom and Kim[43] developed a procedure which can subvert the production of **128** by using a somewhat different approach, i.e., quenching the reaction mixture with a large excess of chlorotrimethylsilane (Me_3SiCl).** The reaction of Me_3SiCl with excess methyllithium is extremely fast, thereby leaving no organometallic reagent to react with methyl ketone in the subsequent aqueous work-up step. Indeed, treatment of **124** with 10 equivalents of methyllithium following the procedure of Rubottom and Kim gave a 71% yield of **113**, 4% of **125**, and 16% of starting material **124**. The best results in our hands involved a longer term treatment of the hydroxy-acid **124** with 15 molar equivalents of methyllithium at room temperature followed by addition of 20 molar equivalents of chlorotrimethylsilane. In this instance flash chromatography afforded 85% of the methyl ketone **113** and 6% of diol **125**. Addition of a large excess of methyllithium and simple aqueous work-up converted the methyl ketone **113** deliberately into the diol **125** in 76% yield along with 17% of starting material **113** (Scheme 21).

The conversion of the hydroxyketone **113** into the diketone **112** using potassium dichromate in sulfuric acid according to the procedure of Sanborn[44] gave a complex mixture. However, the oxidation with pyridinium chlorochromate (PCC)[45] yielded the diketone **112** in nearly quantitative yield (Scheme 23). The IR spectrum of **112** showed absorption maxima for the five-membered ring ketone at 1740 cm^{-1} and for the methyl ketone at 1700 cm^{-1}. The carbonyl carbons in the ring and side chain were

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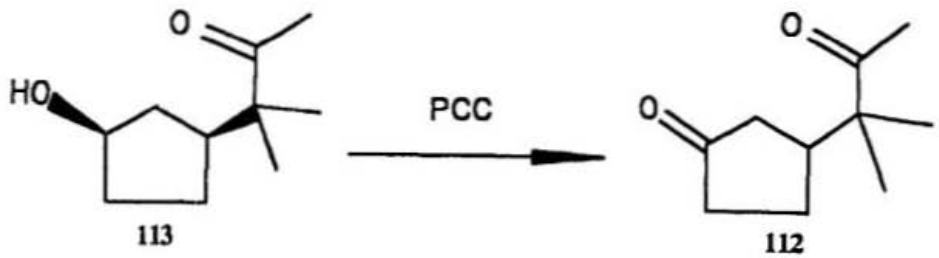
* For the definition of work-up, see **experimental**.

** We thank Dr. A. G. Fallis for bringing ref. 43 to our attention.

Scheme 23

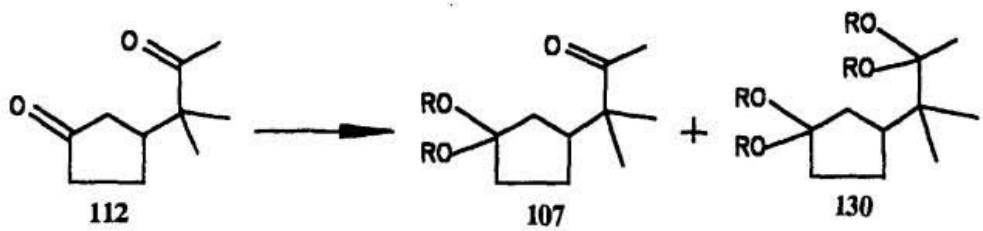


113 **112**

found at δ 218.2 and 212.9, respectively, in the ^{13}C NMR spectrum. The crude product **112** was used for the subsequent ketalization without further purification.

At this stage in our effort, it was hoped that elaboration of the ring ketone of **112** into the symmetrical cyclopentane-1,3-dione moiety of the triketone **106** could be accomplished by the Lewis acid-catalyzed reaction of the monoketal **107** with 1,2-bis(trimethylsiloxy)cyclobutene (**109**) followed by rearrangement of the resulting cyclobutanone derivative **110** with trifluoroacetic acid (TFA) (Scheme 17). Kuwajima and coworkers[31] reported that the geminal acylation reactions of the dimethyl, diethyl or dibenzyl ketals (but not ketones) with **109** gave satisfactory yields of the cyclopentane-1,3-diones. On the other hand, regarding a related reaction leading to a keto-ester, they stated that the (cyclic) trimethylene ketal of 4-methyl-3-cyclohexen-1-one met with considerable difficulties. With this in mind, we decided to prepare the mono- methyl or ethyl ketal, **107a** or **107b**. We thought that monoketalization might be possible because the side chain carbonyl is more sterically hindered than the ring carbonyl. To our disappointment, a mixture of **107a/130a** or **107b/130b** was produced under the following experimental conditions: (1) one molar equivalent of trimethyl or triethyl orthoformate with a catalytic amount of *para*-toluenesulfonic acid (*p*TSA) in refluxing absolute ethanol;[46] (2) one molar equivalent of trimethyl or

Scheme 24



(a) R = Me
(b) R = Et
(c) R, R = CH_2CH_2
(d) R, R = $CH_2C(CH_3)_2CH_2$

triethyl orthoformate with small amount of Amberlyst-15 in dichloromethane at 0°C or at room temperature;[47] (3) one molar equivalent of trimethyl or triethyl orthoformate with small amount of pyridinium *p*-toluene-sulfonate (PPTS) in benzene under reflux.[48] Each reaction was carefully monitored by TLC in which the monoketal **107a** (or **107b**) and the diketal **130a** (or **130b**) could be easily distinguished. If the reaction were stopped before the formation of the diketal, then we obtained a substantial amount of the starting material **112**. On the other hand, if all the starting material were consumed, then the product was composed of both mono-ketal and diketal on the basis of TLC and ^{1}H NMR analysis. The ratio of the monoketal to diketal could be calculated from the ^{1}H NMR spectra.

We were confronted with a failure to prepare the dimethyl or diethyl ketals **107a** and **107b**; therefore, we decided to monoketalize the ring ketone of **112** selectively as a cyclic ketal, and we hoped that a cyclic ketal would behave similarly to a dimethyl or diethyl ketal in the geminal acylation reaction. Once again, the ketalization with ethylene glycol produced both **107c** and **130c** under a variety of conditions such as a catalytic amount of *p*TSA or PPTS in benzene under reflux with a Barrett water-

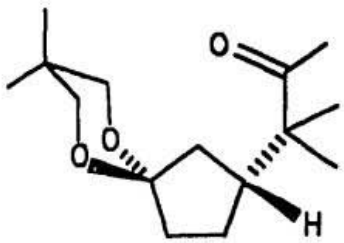
separator; $BF_3 \cdot Et_2O$ in dichloromethane at −9°C after the method of Swenton *et al.*[49]; and a catalytic amount of Amberlyst−15 in dichloromethane at 0°C or at room temperature. As in the reactions with the trimethyl and triethyl orthoformates, if the reaction were stopped before the formation of **130c**, then we were left with a substantial amount of starting material. However, when we stopped the reaction after all the starting material was consumed, the product was a mixture of **107c** and **130c**. For instance, the ketalization with 1.1 equivalents of ethylene glycol in benzene under reflux for 8 hours gave, after flash column chromatography, 49% of the monoketal **107c** along with 40% of the starting material. When a large excess of ethylene glycol was added and the reaction mixture was heated overnight, the product we obtained was a 1 : 2 mixture of **107c** and **130c** as indicated by GC−MS analysis. The ^1H NMR spectrum of **107c** showed a singlet for the methyl ketone at δ 2.128 and a multiplet for the four methylene protons of the 1,3−dioxolane moiety at δ 3.84−3.89. In the ^1H NMR spectrum of the diketal **130c**, the methylene protons of the 1,3−dioxolane moieties appeared as an eight−proton multiplet at δ 3.83−3.97, and signals at δ 114.3 and 117.4 in its ^{13}C NMR spectrum were proof of two ketal carbons. Since **107c** could not be prepared in high yield, we focused our attention on another cyclic ketal, **107d**. To our delight, the ketalization with 1.5 molar equivalents of 2,2−dimethyl−1,3−propanediol catalyzed by PPTS in benzene under reflux for approximately 40 minutes yielded, after column chromatography, 89% of the monoketal **107d** and only 4% of the diketal **130d**. Accordingly, the IR spectrum of the monoketal **107d** showed an absorption maximum only for the methyl ketone at 1710 cm^{-1}, and the ^1H NMR spectrum showed a singlet at δ 2.127 for the side−chain methyl. The signals at δ 108.3 and 213.4 in the ^{13}C NMR spectrum were consistent with the presence of a ketal carbon and a ketone, respectively. In the IR spectrum of the diketal **130d**, no carbonyl absorption was evident, but two ketal carbons appeared at δ 102.4 and 108.7 in its ^{13}C spectrum. It was interesting to examine the methylene signals due to the 1,3−dioxane

Figure 1.

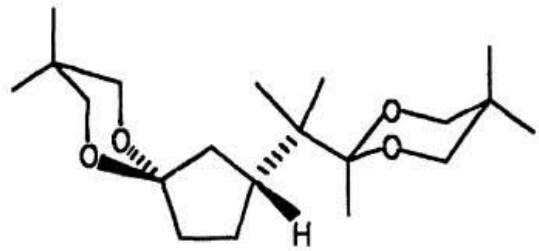
Partial ^{1}H NMR spectrum of **107d**

Figure 2.

Partial ^{1}H NMR spectrum of **130d**



107d



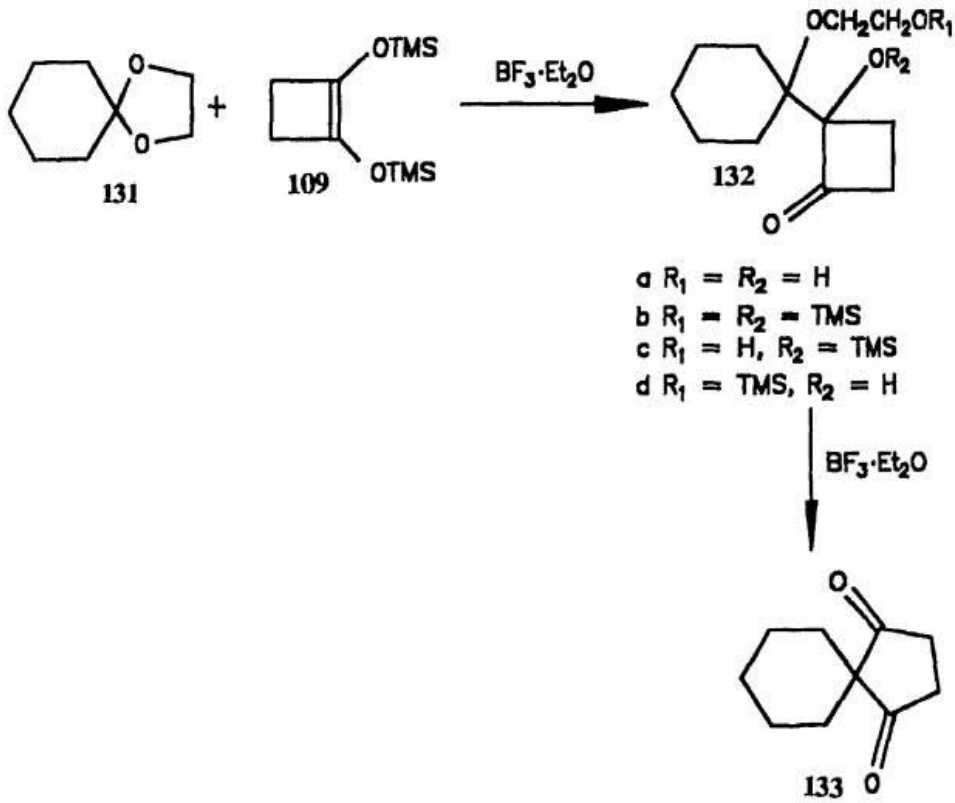
130d

systems of **107d** and **130d** in their 300 MHz ^{1}H NMR spectra (Figures 1 and 2). With respect to the cyclic ketal in **107d**, both substituents attached to the ketal carbon are primary, thus it is expected that this 1,3-dioxane system would be conformationally mobile, and an average signal for both axial and equatorial protons should be observed. Indeed, a four-proton singlet appeared at δ 3.455 in the ^{1}H NMR spectrum

of **107d** (Figure 1). The same argument can be applied to the methylenes due to the 1,3-dioxane system attached to the ring in the diketal **130d**. As shown in Figure 2, a singlet at δ 3.469 was observed for four methylene protons. In contrast, the ketal derived from the methyl ketone is conformationally rigid due to the attachment of one tertiary substituent to the ketal carbon, therefore axial and equatorial protons are distinguishable and form an AB quartet. In agreement with our expectations, the methylene signals of the 1,3-dioxane system in the side chain of **130d** appeared as two doublets on either side of δ 3.469. In general, equatorial protons are deshielded relative to axial protons,[50] thus the two equatorial methylene protons were assigned tentatively to be at δ 3.652, while the axial methylene protons were at δ 3.298. The deliberate preparation of the diketal **130d** involved longer treatment of diketone **112** with a large excess of 2,2-dimethyl-1,3-propanediol and a catalytic amount of PPTS in benzene. Column chromatography provided 71% of the diketal **130d** and 23% of the monoketal **107d**.

With an efficient route to the monoketal **107d**, we were at the threshold of the crucial spiro-annulation reaction. Since the cyclic ketals had never previously been used as substrates in the geminal acylation reactions leading to the 2,2-disubstituted cyclopentane-1,3-diones, we decided to examine first the reactions of some simple cyclic ketals instead of our valuable monoketal **107d** (Scheme 25 and 26). Following the procedure of Kuwajima and coworkers,[31] the cyclohexanone ethylene ketal (**131**) was treated with 1.1 equivalents of **109** and 1.0 equivalent of boron trifluoride etherate in dichloromethane at -78°C for three hours. Aqueous work-up and vacuum distillation provided the cyclobutanone derivative **132**, which underwent pinacol-type rearrangement upon treatment with TFA under reflux. Flash chromatography did give the spiro-diketone **133**, but in only 32% yield. The IR spectrum of **133** showed an absorption maximum for the ring carbonyl at 1716 cm^{-1}, and ^1H NMR spectrum showed a singlet at δ 2.677 for the four protons attached to the carbons next to the carbonyl

Scheme 25

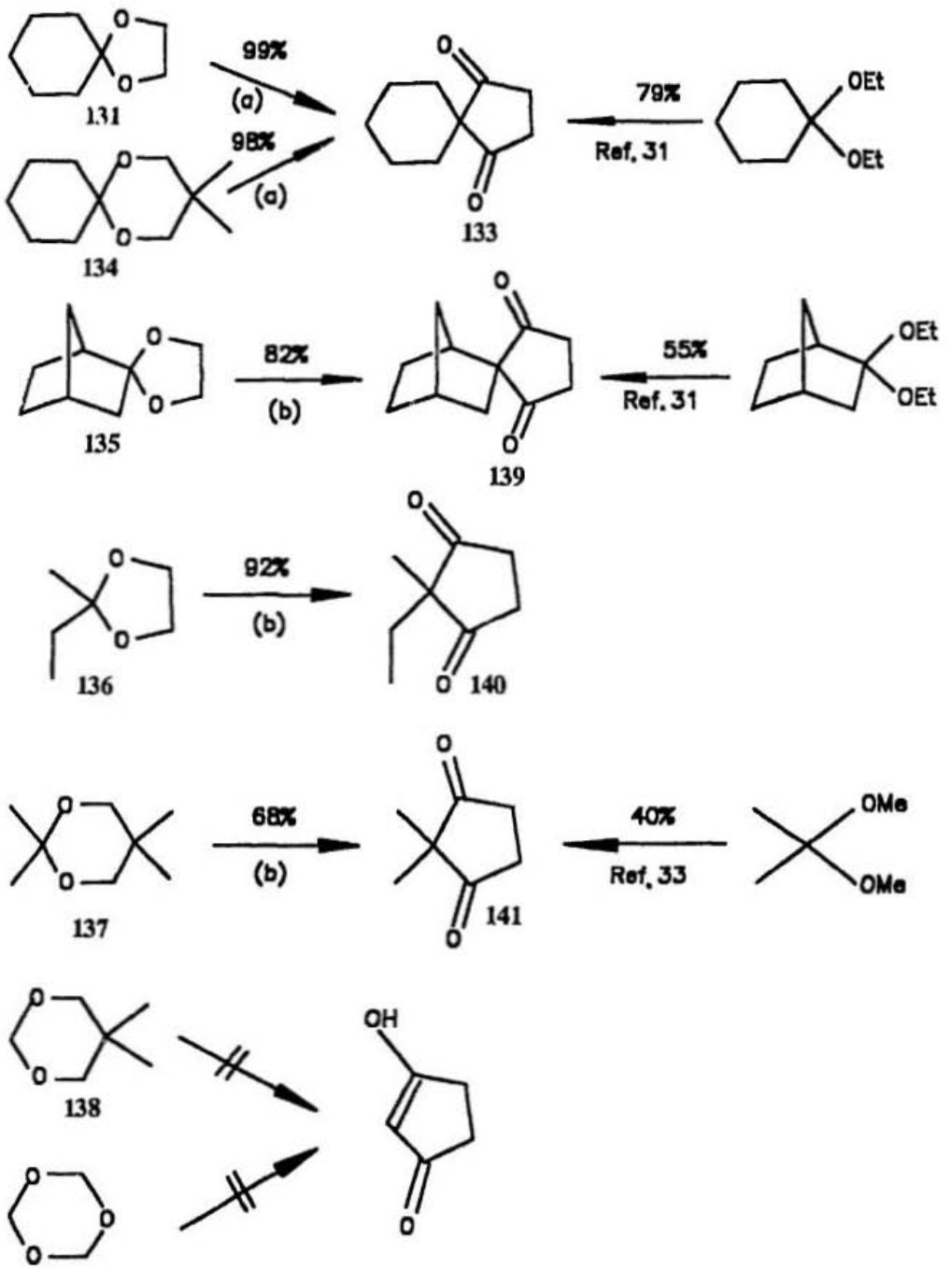


groups. The signal at δ 215.8 in the ^{13}C NMR spectrum clearly indicated the presence of the new carbonyls. Furthermore, all our spectroscopic data and the melting point were in good agreement with those reported by Kuwajima and coworkers. Since the yield was unacceptable for our synthesis, we carried out numerous experiments by varying the Lewis acid, the relative amount of the reagents, the temperature, and the reaction time. Of the three Lewis acids examined ($SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$), $BF_3{\cdot}Et_2O$ was found to be the best. Several small-scale reactions indicated that using an excess of **109** and $BF_3{\cdot}Et_2O$ improved the yield. Furthermore, when **131** was treated with two equivalents of **109** and five equivalents of $BF_3{\cdot}Et_2O$ at $-78°C$ for a longer period, such

as six hours, the resultant crude product was found to contain the cyclobutanone derivative **132** as well as some spiro-diketone **133** as revealed by ^{1}H NMR analysis. Clearly, $BF_3{\cdot}Et_2O$ could catalyze the rearrangement of **132** to **133**. Encouraged by this result, we decided to use more equivalents of $BF_3{\cdot}Et_2O$ and to run the reaction even longer. It was hoped that the spiro-diketone **133** could be obtained from the cyclic ketal **131** in a one-pot operation, without the isolation of the cyclobutanone derivative **132**. Thus, the cyclic ketal **131** was treated with three equivalents of **109** and ten equivalents of $BF_3{\cdot}Et_2O$ in dichloromethane at −78°C for six hours, and the resulting mixture was allowed to attain room temperature while stirring overnight. Aqueous work-up provided colorless crystals of the desired diketone **133** in nearly quantitative yield. This product proved to be pure by GC-MS, ^{1}H NMR as well as ^{13}C NMR. Likewise, compound **133** was obtained in 98% yield from the 1,3-dioxane **134**. The successful results from **131** and **134** prompted us to investigate the generality of this one-pot procedure. Indeed, several other cyclic ketals (**135** → **137**) were treated with **109** and $BF_3{\cdot}Et_2O$ in the same manner as **131** and the resulting crude products were purified by flash chromatography affording the 2,2-disubstituted cyclopentane-1,3-diones (**139** → **141**) in good yields (Scheme 26). Although the crude products were essentially pure by GC-MS analysis, we still applied column chromatography to remove a yellowish color from the products. The spectroscopic data for **139**, **140** and **141** were identical with those reported.[31,33] It should be noted that our one-pot procedure was simpler than the original two-step procedure, and our yields were generally higher than by the original two-step procedure. However, no unsubstituted cyclopentane-1,3-dione was formed when 5,5-dimethyl-1,3-dioxane (**138**) or *s*-trioxane was subjected to the spiro-annulation reaction, even after the addition of TFA.

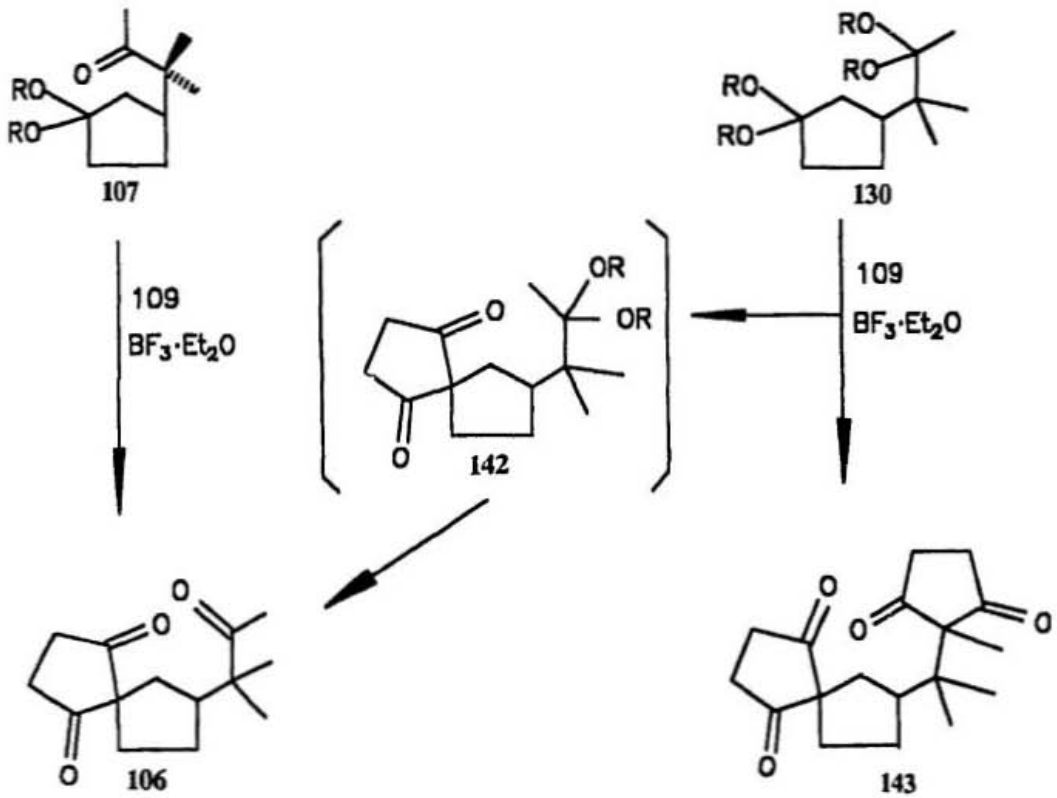
This general procedure for the ***direct*** conversion of the cyclic ketals into the 2,2-disubstituted cyclopentane-1,3-diones led to the examination of the reaction of

Scheme 26



(a) The crude product was confirmed to be pure by GC–MS, ^{1}H and ^{13}C NMR, thus the yield reported was the crude yield. (b) Isolated yield.

Scheme 27



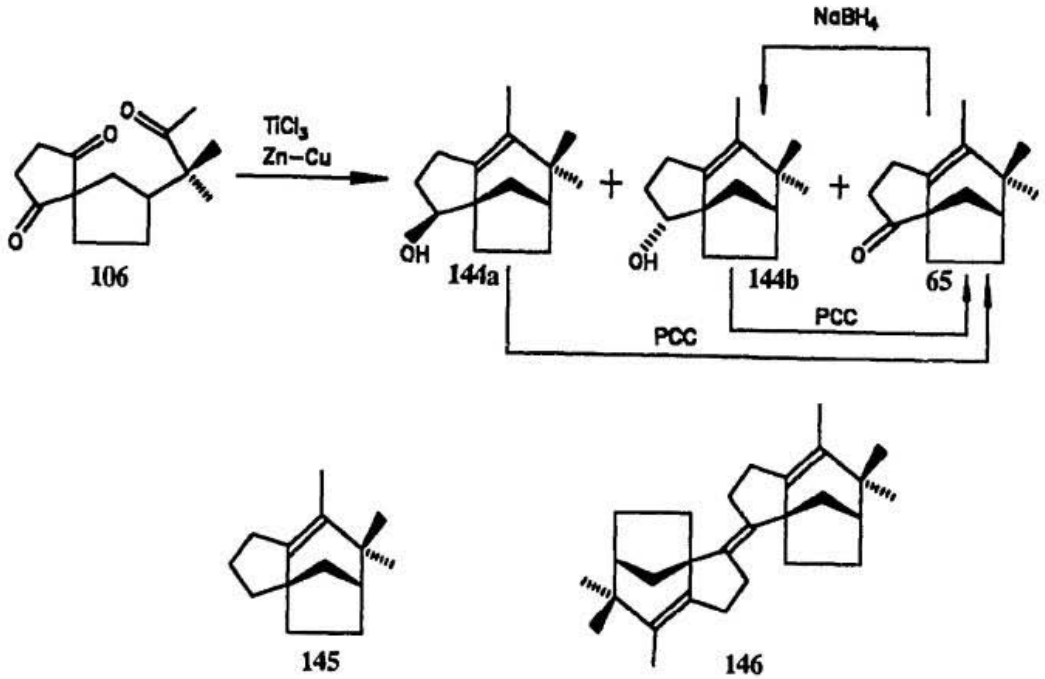
the monoketal **107d** with 1,2-bis(trimethylsiloxy)cyclobutene (**109**). To our delight, exposure of **107d** to three equivalents of **109** and 15 equivalents of $BF_3 \cdot Et_2O$ following our general procedure furnished, after column chromatography, an 86% yield of the triketone **106**. Although the crude product was essentially pure by GC-MS analysis, we still applied column chromatography to get rid of a trace amount of some colored material. The IR spectrum of triketone **106** showed absorption maxima for the ring carbonyls at 1725 cm^{-1} and for the side-chain carbonyl at 1705 cm^{-1}. In the ^1H NMR spectrum, a singlet was evident at δ 2.141 for the methyl ketone (CH_3CO) and a multiplet at δ 2.778 was attributed to the four protons α to the ring carbonyl groups

($COCH_2CH_2CO$). The signals at δ 213.0, 215.0 and 215.7 in the ^{13}C NMR spectrum represented the side-chain carbonyl and two ring carbonyls.

Since the diketals **130c**, **130d** had already been prepared, we were curious about their spiro-annulation products. Due to steric hindrance, we expected **142** and its hydrolyzed form **106** to be the major products. Thus, the diketal **130c** was allowed to react with **109** furnishing, after aqueous work-up, 97% of triketone **106**, 3% of hydrolyzed starting material **112**, and none of **142** or of the tetraketone **143** as revealed by GC-MS analysis. Chromatography of the crude product gave an 86% isolated yield of the desired triketone **106**. However, we obtained a 47% yield of triketone **106** along with 43% recovery of the hydrolyzed starting material **112** when the diketal **130d** was subjected to the spiro-annulation reaction. One small-scale reaction with **130d** generated a small amount of a compound tentatively identified as the tetraketone **143** by its mass spectrum. Although the triketone **106** could be obtained from the diketal **130c** or **130d**, in practice the spiro-annulation reaction of the monoketal **107d** presented the cleanest route (Scheme 27).

Next we turned to the conversion of the triketone **106** into isokhusimone (**65**) *via* an intramolecular titanium-induced dicarbonyl coupling reaction. Since McMurry and coworkers[51] reported a number of intramolecular dicarbonyl coupling reactions involving low-valent titanium, our initial attempts were made following their representive procedure.[52] A dimethoxyethane (DME) solution of the triketone **106** was added *via* syringe pump over a 30 hour period to a refluxing slurry prepared from $TiCl_3$ and Zn-Cu couple. After an additional 14 hour period under reflux, the reaction mixture was passed through a small Florisil pad to remove the black slurry. Flash chromatography of the crude product gave 8% of isokhusimone (**65**), 29% of epimeric alcohols **144a/b**, and a considerable amount of very nonpolar material. The starting material was recovered to the extent of 28%. The IR spectrum of isokhusimone (**65**)

Scheme 28



showed absorption maxima for the ring carbonyl at 1740 cm^{-1} and the double bond at 1675 cm^{-1}. The protons of the methyl group attached to the double bond appeared as a singlet at δ 1.534 in the ^1H NMR spectrum. The signals at δ 130.6, 136.3, and 222.6 in ^{13}C NMR spectrum represented the two olefinic carbons and ring carbonyl, respectively. Our IR and ^1H NMR spectra were identical with those kindly provided by Professor G. Büchi* of the Massachusetts Institute of Technology. The structures of **144a/b** were based on the following findings. The IR spectrum of the mixture of **144a/b** showed a broad absorption maximum for an hydroxyl group at 3370 cm^{-1}. The protons on the carbons bearing the alcohol functions were observed as overlapped

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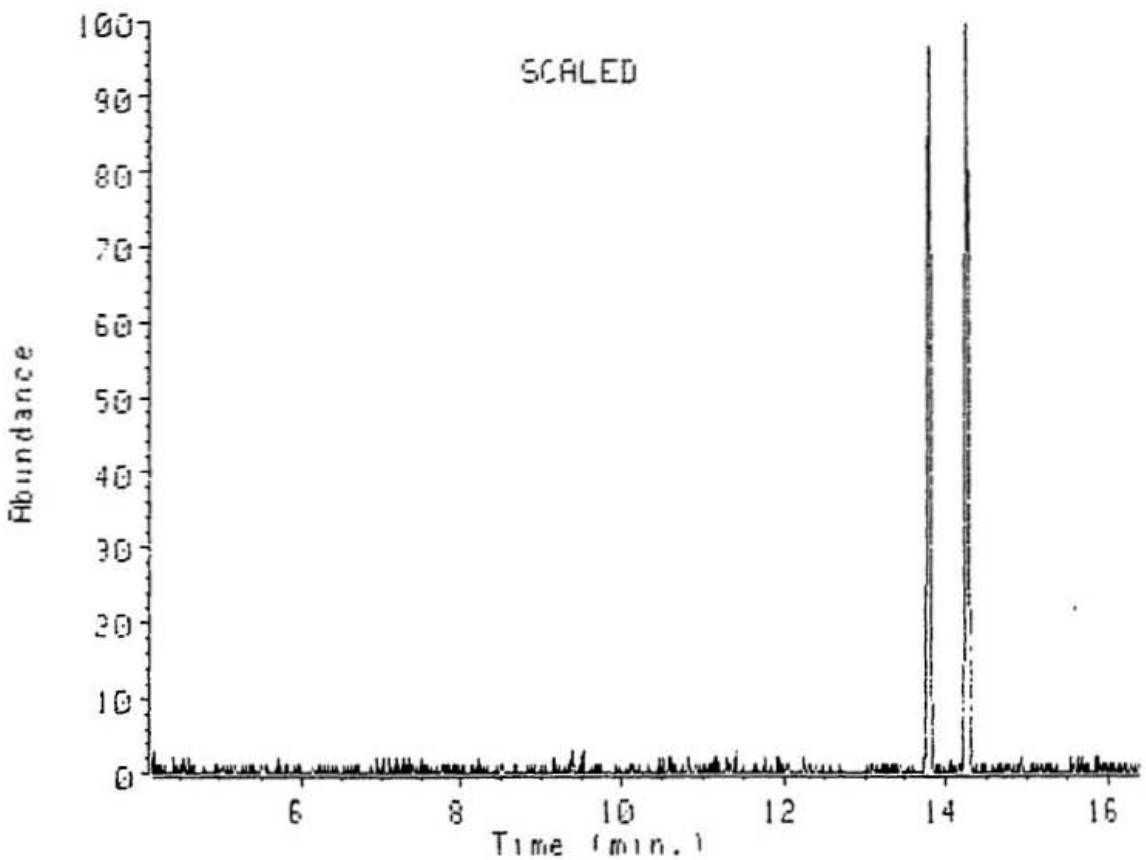
* We are very grateful to Professor G. Büchi for making this comparison possible.

multiplets in the area of 4.0 ppm. In the ^{13}C NMR spectrum, the carbons attached to the oxygens were found at δ 79.7 and 76.3 and the double bond carbons at δ 128.9, 129.7, 138.8, and 139.5. The specific assignment of the ^{1}H and the ^{13}C NMR spectra regarding the relative stereochemistry at C–2 was impossible at this stage. Although the epimeric alcohols **144a/b** could not be separated by flash chromatography on silica gel, GC–MS analysis indicated a 1 : 1 mixture of the two diastereomers as shown in Figure 3. The structures of **144a/b** were confirmed by clean conversion into isokhusimone (**65**) upon treatment with PCC in dichloromethane. With regard to the very

Figure 3. GC–MS chromatogram of the 1 : 1 mixture of **144a** and **144b**



nonpolar side product, the IR and ^{13}C NMR spectra indicated no carbonyl group present, and the many signals around δ 140 ppm in the ^{13}C NMR spectrum implied a mixture of the overreduced and intramolecularly coupled hydrocarbons with gross structures **145** and **146**. Thus, we realized that the overreduction and intramolecular coupling of the remaining ketone had to be suppressed in order to achieve a reasonable yield of the desired dicarbonyl coupling reaction product. Unfortunately, attempts to improve the yield of **65** by varying amounts of $TiCl_3$ and Zn–Cu couple met with little success, producing more **145** and **146** or resulting in more recovered starting material. In addition, our numerous attempts to vary the reducing agents (e.g. $LiAlH_4$,[53] potassium metal,[54] Zn–Ag couple[55]) as well as their relative amounts did not improve the yield.

An alternative approach, to avoid the intramolecular coupling and overreduction, was to use high dilution technology, which might be achieved by adding slowly either the slurry of $TiCl_3$ and Zn–Cu couple or triketone **106** to a relatively dilute DME solution of reagents. Addition of the slurry made from Zn–Cu and $TiCl_3$ to the solution of triketone **106** in many portions over a long period of time was found to be fruitless. Nevertheless, when the triketone **106** was added *via* syringe pump over a fifty–one hour period to the refluxing slurry of $TiCl_3$ and Zn–Cu couple in a relatively large volume of DME (the overall concentration of triketone **106** was 0.02 M) followed by an additional four days at reflux, the product we isolated was 57% of isokhusimone (**65**), 21% of the epimeric alcohols **144a/b**, and 8% of starting triketone **106** (Scheme 28).

Although **144a/b** can be oxidized with PCC in nearly quantitative yield, it was more convenient to oxidize the mixture of reaction products without separation of **65** from **144a/b**. The overall yield of isokhusimone (**65**) from **106** was 78%. Our synthesis required nine steps and produced (±)–isokhusimone (**65**) in a 35% yield from nor-

camphor. Büchi *et al.*[26] had converted isokhusimone (**65**) to khusimone (**4**) in two steps, and Liu and Chan[27] had prepared zizanoic acid and *epi*zizanoic acid from **4** in a straightforward fashion.

It was interesting to note that reduction of isokhusimone (**65**) with sodium borohydride provided only one of the epimeric alcohols, either **144a** or **144b**. If one assumes that the hydride approaches following a trajectory of approximately 120°,*[56] then an examination of molecular models would indicate that the *re*-face of the ketone would be more sterically encumbered than the *si*-face, thereby resulting in the predominant formation of **144b**. Thus, the single product obtained from above reduction was tentatively assigned **144b** (Scheme 28). Its ^{1}H NMR spectrum showed a singlet at δ 1.421 for the vinyl methyl group and a double doublet at δ 4.002 for the proton on the carbon bearing the hydroxyl group. The signals at δ 79.7, 129.7, and 138.8 in the ^{13}C NMR spectrum were due to the carbon attached to the oxygen and two sp^2 carbons. With compound **144b** tentatively assigned, we were able to give a spectroscopic assignment to the signals of its epimer **144a** from the spectrum of the mixture **144a/b** (*vide supra*). In the ^{1}H NMR spectrum, the vinyl methyl was observed as a singlet at δ 1.479 and the proton on the carbon bearing the hydroxyl group as a multiplet at δ 4.031. The carbon attached to the oxygen and the two double bond carbons were found at δ 79.7, 128.9, and 139.5 in the ^{13}C NMR spectrum.

An alternative approach to (±)-khusimone (**4**) was based on the retrosynthetic analysis detailed in Scheme 29. The key steps in this strategy were the spiroannulation reaction (i.e. **149** → **148**) and intramolecular carbonyl coupling of a ketone with an ester (i.e. **148** → **147**).

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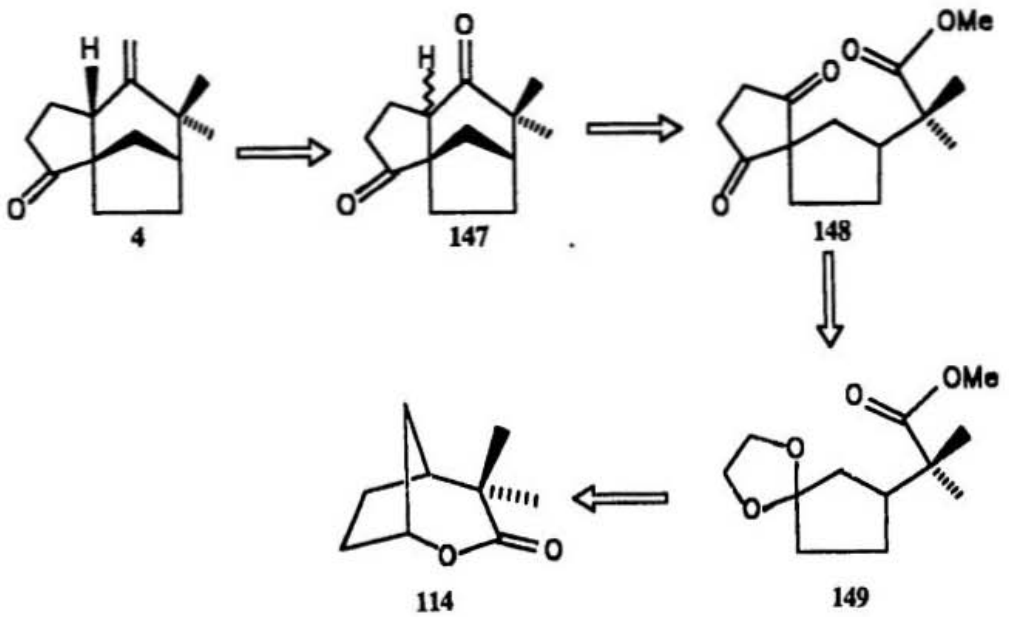
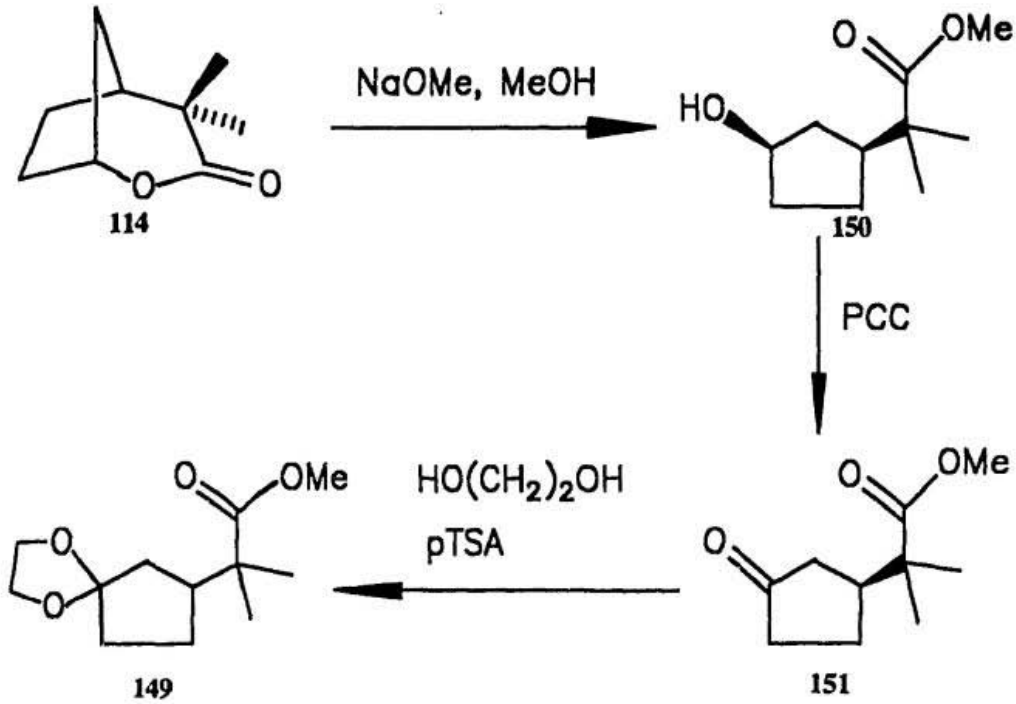
* We thank Dr. Brian Gregory for kindly bringing ref. 56 to our attention.

Scheme 29



With this idea in mind, the lactone **114** was treated with sodium methoxide in methanol under reflux to give the methyl ester **150**. The IR spectrum showed absorption maxima for the hydroxyl group at 3430 cm^{-1} (broad) and the ester carbonyl at 1730 cm^{-1}. A singlet at δ 3.660 in the ^{1}H NMR spectrum clearly arose from the methyl ester. This hydroxy–ester was converted cleanly into the keto–ester **151** upon treatment with PCC. The IR spectrum now showed absorption maxima for both the ring carbonyl at 1740 cm^{-1} and the ester at 1730 cm^{-1}. The signals at δ 177.2 and 218.2 in the ^{13}C NMR were assigned to the ester carbonyl and ring ketone, respectively. Ketalization was easily achieved with ethylene glycol and *p*TSA in benzene under reflux. Thus, we obtained an 83% yield of the ketal–ester **149** from **114**. A multiplet at δ 3.890 in the ^{1}H NMR spectrum represented the four protons of the dioxolane system. The ^{13}C NMR spectrum showed signals at δ 117.2 and 177.5 for the ketal carbon and ester carbonyl, respectively (Scheme 30).

Scheme 30

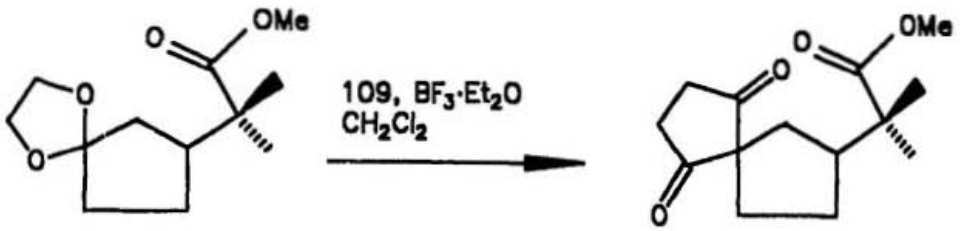


114 150 151 149

Next, our attention turned to the investigation of the spiro-annulation reaction. Addition of **149** to a solution of three equivalents of **109** and fifteen equivalents of $BF_3 \cdot Et_2O$ at −78°C following our general procedure provided the spiro-annulated compound **148** in 80% yield after column chromatography (Scheme 31). Accordingly, the IR spectrum showed a broad absorption maximum for the ring carbonyls and the ester at 1715 cm^{-1}. The four protons α to the ketones were found as a broad singlet at δ 2.777 in the ^1H NMR spectrum. The signals at δ 177.0 and 215.6 in the ^{13}C NMR spectrum represented the ester carbonyl and the two ring carbonyls.

It was hoped that the McMurry coupling reaction of the keto-ester **148** would provide the tricyclic diketone **147** and/or further reduced product **152**. Although McMurry and coworkers[57] published several examples of transformations involving

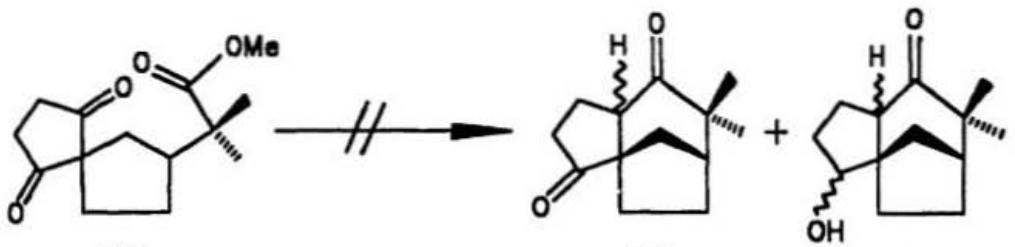
Scheme 31



149 148

titanium–induced coupling of keto–esters, to the best of our knowledge, this reaction has been applied in the syntheses of only two natural products.[51] In our case, several unidentified products were obtained when the keto–ester **148** reacted with $TiCl_3/LiAlH_4$ and Et_3N following McMurry's[57] procedure. Treatment of the crude product with PCC did not give a simpler mixture as revealed from TLC and the ^1H NMR spectrum. Our numerous attempts to modify the reaction conditions (e.g. reducing agents, amounts, concentration) did not meet with success (Scheme 32).

Scheme 32



148 147 152

Although this second approach failed eventually, at least we were pleased to find that the geminal acylation reaction of the ketal ester **149** proceeded smoothly *via* the simple *one*-pot procedure developed in this synthetic study. Compared with some other approaches to the zizaane system in its racemic form, our first route was indeed short and efficient. It should be noted that chiral syntheses of zizaane sesquiterpenoids could be achieved if readily available[58] (+)- or (-)-norcamphor had been used as the starting material instead of (±)-norcamphor.

III. Experimental

General Procedures

All reactions requiring nonaqueous conditions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Solvents and reagents were purified by distillation. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium metal/benzophenone. Dichloromethane, diisopropylamine, toluene, benzene, and diethyl ether were distilled from calcium hydride. Pyridine was dried over anhydrous potassium hydroxide and distilled. Dimethylformamide (DMF) was dried over 4 Å Molecular Sieves, distilled, and stored over 4 Å Molecular Sieves. The phrase "work-up" means extraction of the crude product with diethyl ether or dichloromethane, washing the organic layers with water and with saturated sodium chloride, drying over anhydrous magnesium sulphate, filtration, and concentration by solvent removal with a rotary evaporator, and the term "*in vacuo*" refers to the removal of the solvent with a rotary evaporator followed by evacuation to constant sample weight. All reactions were monitored by gas chromatography-mass spectrometry (GC-MS) or thin-layer chromatography (TLC). The plates were visualized by UV fluorescence, or staining with iodine, or spraying with an aqueous solution of phosphomolybdic acid, ceric sulphate and sulfuric acid followed by heating the plate (125-150 °C). Commercial TLC plates were Merck 60F-254. Flash chromatography was performed according to the method of Still and coworkers[59] on Merck Type 60 silica gel, 230-240 mesh. Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (IR) spectra were recorded on either a Perkin Elmer 283 spectrophotometer (and were corrected by using polystyrene film as calibration standard) or a Mattson FT-IR instrument, and the abbreviation "br" means a broad absorption. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$

solution, unless otherwise noted, on a General Electric GE 300-NB (300 MHz) instrument; chemical shifts were measured relative to internal standards: tetramethylsilane (TMS) for ^1H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Multiplicities are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), tq (triple quartet), mm (multiple multiplets), and so on. The NMR assignments were assisted by attached proton test (APT), and $^1H-^1H$ correlation (COSY) and $^{13}C-^1H$ correlation (HET-CORR) 2-D spectra. In the AB spin systems obtained in 300 MHz NMR spectra, the chemical shifts δ_A and δ_B were calculated according to Equations (1) and (2),[60] respectively,

$$\delta_A = \frac{\nu - \frac{1}{2}\Delta\nu}{300} \tag{1}$$

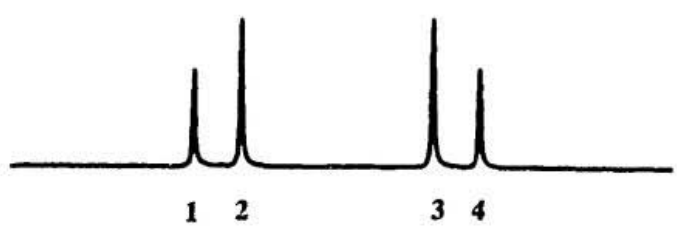
$$\delta_B = \frac{\nu + \frac{1}{2}\Delta\nu}{300} \tag{2}$$

ν and $\Delta\nu$ were derived from Equations (3) and (4), respectively,

$$\nu = \frac{\nu_1 + \nu_4}{2} = \frac{\nu_2 + \nu_3}{2} \tag{3}$$

$$\Delta\nu = [(\nu_1 - \nu_4)(\nu_2 - \nu_3)]^{\frac{1}{2}} \tag{4}$$

Figure 4. ^1H NMR spectrum of AB system



where, as shown in Figure 4, ν_1, ν_2, ν_3, and ν_4 represented the observed frequencies (Hz) of the four peaks in the AB quartet system. ^{1}H NMR nuclear Overhauser enhancement (NOE) data were obtained from sets of interleaved experiments (16K) of 8 transients cycled 12 to 16 times through the list of irradiated frequencies. The decoupler was gated on in continuous wave (CW) mode for 6 seconds with sufficient attenuation to give a 70–90% reduction in intensity of the irradiated peak. Frequency changes were preceded by a 60 second delay. Four scans were used to equilibrate spins before data acquisition, but a relaxation delay was not applied between scans at the same frequency. NOE difference spectra were obtained from zero–filled 32K data tables to which a 1 to 2 Hz exponential line–broadening function had been applied. Except where noted, both the low and the high resolution mass spectral (MS) data were obtained on a V.G. Micromass 7070HS instrument. A Hewlett–Packard system (model 5890 gas chromatograph coupled to a model 5970 mass selective detector) equipped with a Hewlett–Packard 12.5 m fused silica capillary column with cross–linked dimethylsilicone as the liquid phase was used for GC–MS analysis. Microanalyses were accomplished by the Canadian Microanalytical Service Ltd., New Westminster, British Columbia.

2–Oxabicyclo[3.2.1]octan–3–one (116)

Norcamphor (**115**) (6.00 g, 52.5 mmol) and 85% *m*–chloroperoxybenzoic acid (*m*CPBA) (14.10 g, 69.4 mmol) were stirred in chloroform for two days at room temperature. The solution was washed with 10% NaOH (×5) and H_2O (×4), dried over $MgSO_4$, and concentrated. Vacuum distillation of the residue provided pure lactone **116** (5.70 g, 86%). IR (film) ν_{max}: 1730 cm^{-1}; ^{1}H NMR δ: 1.62–2.05 (5H, mm), 2.171 (1H, dt, J = 2.3, 9.5 Hz), 2.491 (1H, dt, J = 1.9, 18.4 Hz), 2.554 (1H, br d, J = 4.6 Hz), 2.727 (1H, ddd, J = 1.8, 5.0, 18.4 Hz), and 4.866 (1H, br s); ^{13}C NMR δ (attached H's): 28.5 (2), 31.1 (1), 31.8 (2), 35.0 (2), 39.9 (2), 80.4 (1), and 170.2 (0); MS (from GC–

MS) *m/z* (%): 126 (5.5, M^+), 98 (14), 97 (11), 83 (39), 82 (66), 69 (42), 67 (99), 55 (48), 54 (51), 42 (54), and 41 (100). *Exact mass* calcd. for $C_7H_{10}O_2$: 126.0680; found: 126.0677.

2-Oxabicyclo[3.3.0]octan-3-one (118)

From norcamphor*

Repeating the above on a small scale, but with the addition of two drops of concentrated sulfuric acid, gave a dark solution that was mainly **118** (95% by GC-MS analysis) with a small amount of **116**. For **118**: IR (film) ν_{max}: 1765 cm^{-1}; ^1H NMR δ: 1.50-2.08 (6H, mm), 2.290 (1H, dd, J = 1.6, 17.1 Hz), 2.78-2.94 (2H, mm), and 5.008 (1H, t, J = 5.1 Hz); ^{13}C NMR δ (attached H's): 23.2 (2), 33.3 (2), 33.4 (2), 35.9 (2), 37.7 (1), 86.2 (1), and 178.6 (0); MS (from GC-MS) *m/z*: 126 (6, M^+), 98 (31), 97 (29), 83 (17), 82 (12), 80 (22), 67 (100), 55 (56), 54 (54), and 41 (79).

From lactone 116

To lactone **116** (30.4 mg, 0.24 mmol) in chloroform was added two drops of concentrated sulfuric acid. After stirring at room temperature overnight, the mixture was washed with 10% NaOH (x3) and the aqueous layer was re-extracted with chloroform (x3). The combined organic extracts were washed with H_2O (x2), saturated NaCl (x2) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* yielded **118** as a colorless oil (31.1 mg, 100%).

4-Methyl-2-oxabicyclo[3.2.1]octan-3-one (122)

Lactone **116** (938 mg, 7.44 mmol) in dry THF was added slowly to 2.0 equivalents of LDA in THF at -78°C. The solution was stirred for one hour before a solution of MeI (3.17 g, 22.3 mmol) and HMPA (2.59 mL, 14.9 mmol) in THF was added over 10

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* We thank Mr. Paul F. Walsh for performing this experiment.

min. The mixture was allowed to warm to −40°C, and was stirred for one hour. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted with diethyl ether (×4). The combined organic layers were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo* to provide the crude monomethyl−lactone **122** along with a small amount of the dimethyl−lactone **114**. This crude product was further α−methylated without further purification. For **122**: IR (film) ν_{max}: 1720 cm^{-1}; ^1H NMR δ: 1.326 (3H, d, J = 7.5 Hz), 1.55 (1H, m), 1.83−2.15 (4H, mm), 2.267 (1H, br t), 2.524 (1H, tq, J = 1.2, 7.5 Hz), and 4.817 (1H, br s); ^{13}C NMR δ: 18.9, 29.5, 31.9, 32.0, 38.3, 45,2, 80.7, and 174.4; MS m/z (%): 140 (4, M^+), 112 (4), 111(3), 97 (50), 96 (21), 83 (26), 81 (56), 68 (30), 67 (67), 56 (33), and 55 (100). *Exact mass* calcd. for $C_8H_{13}O_2$: 140.0836; found: 140.0833.

4,4−Dimethyl−2−oxabicyclo[3.2.1]octan−3−one (114)

Repeatition of the above α−methylation procedure with crude **122** as the starting material gave the crude dimethyl−lactone **114**. Chromatography on silica gel (4% acetone in petroleum ether) yielded pure **114** (936 mg, 82% from **116**): mp 64−65°C; IR (Nujol) ν_{max}: 1740 cm^{-1}; ^1H NMR δ: 1.247 (3H, s), 1.328 (3H, s), 1.55−1.78 (2H, mm), 1.90−2.10 (3H, mm), 2.110 (1H, t, J = 5.5 Hz, methine), 2.269 (1H, br d, J = 13.0 Hz), and 4.772 (1H, br s, methine); ^{13}C NMR δ (attached H's): 24.0 (2), 24.4 (3), 28.4 (3), 31.2 (2), 33.5 (2), 43.1 (0), 43.4 (1), 80.5 (1), and 177.1 (0); MS (from GC−MS) m/z (%): 154 (2, M^+), 111 (14), 110 (16), 95 (20), 69 (100), 67 (68), and 41 (75). *Anal.* calcd. for $C_9H_{14}O_2$: C 70.10, H 9.15; found: C 69.87, H 9.01.

***cis*−2−(3−Hydroxycyclopentyl)−2−methylpropanoic acid (124)**

A solution of the dimethyl−lactone **114** (261 mg, 1.69 mmol) in ethanol, to which 10 mL of 10% NaOH was added, was heated at reflux overnight. Once the solution had cooled, H_2O and 5% HCl were added until pH 4.5. The resulting mixture was

extracted with EtOAc (×5). The combined organic layers were washed with saturated NaCl (×3), dried over $MgSO_4$, and evaporated *in vacuo* to give **124** as a colorless solid (289 mg, 99%): mp 105–106°C; IR (film) ν_{max}: 3600–2500 (very br) and 1700 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ: 1.026 (3H, s), 1.035 (3H, s), 1.16 (1H, m), 1.35–1.48 (3H, m), 1.61 (1H, m), 1.80 (1H, m), 2.03 (1H, m), 4.01 (1H, m), 4.45 (1H, s, OH), and 12.01 (1H, s, CO_2H); ^{13}C NMR (CD_3SOCD_3) δ: 22.4, 22.5, 24.4, 34.9, 36.8, 43.1, 45.3, 71.3, and 178.8; MS *m/z* (%): no M^+, 155 (0.9), 154 (0.8), 128 (2), 111(9), 109 (22), 88 (90), 69 (67), 67 (100), and 41 (68). *Anal.* calcd. for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.30, H 9.24.

***cis*-3-(3-Hydroxycyclopentyl)-3-methyl-2-butanone (113)**

From hydroxy-acid 124

To an ice-bath-cooled solution of **124** (4.661 g, 27.06 mmol) in dry THF was added 1.4 M methyllithium in hexanes (228 mL, 319 mmol). The solution was stirred at room temperature for 47 hours, then at ice-bath temperature TMSCl (75 mL) was added all at once (solution became cloudy), followed by 5% HCl (solution cleared again). After stirring for 30 min, the mixture was extracted with diethyl ether (×3), and the combined organic layers were washed with H_2O (×2), saturated $NaHCO_3$ (×2), and saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography on silica gel (5% acetone in petroleum ether) yielded hydroxy-ketone **113** (3.936 g, 85%) and a very small amount of the diol **125**. For **113**: IR (film) ν_{max}: 3420 cm^{-1} (br) and 1700 cm^{-1}; ^1H NMR δ: 1.111 (3H, s), 1.119 (3H, s), 1.22–2.02 (6H, mm), 2.131 (3H, s), 2.168 (1H, apparent quintet, J = 8.7 Hz, methine), 2.45 (1H, very br, OH), and 4.265 (1H, apparent quintet, J = 4.8 Hz); ^{13}C NMR δ (attached H's): 21.8 (3), 22.0 (3), 24.8 (2), 25.6 (3), 35.4 (2), 36.8 (2), 45.0 (1), 49.3 (0), 73.1 (1), and 214.1 (0); MS *m/z* (%): 170 (0.4, M^+), 152 (3), 127 (14), 109 (100), 86 (44), 67 (78), 55 (35), and 43 (82). *Exact mass* calcd. for $C_{10}H_{18}O_2$: 170.1307;

found: 170.1294; and calcd. $C_{10}H_{16}O$ ($M^+ - H_2O$): 152.1201; found: 152.1213. For **125**: IR (film) ν_{max}: 3380 cm^{-1} (br), 1470 cm^{-1}, and 1380 cm^{-1}; ^1H NMR (OH signals first removed by exchange) δ: 0.880 (3H, s), 0.893 (3H, s), 1.191 (6H, s), 1.383 (1H, m), 1.45 – 1.76 (4H, mm), 1.94 – 2.11 (2H, mm), and 4.220 (1H, m); ^{13}C NMR δ (attached H's): 19.7 (3), 20.4 (3), 26.2 (3), 26.3 (3), 26.5 (2), 34.8 (2), 38.9 (2), 41.3 (0), 43.8 (1), 72.7 (1), and 76.2 (0); MS (from GC – MS) *m/z* (%): no M^+, 153 (2), 150 (4), 135 (9), 110 (20), 109 (24), 84 (60), 83 (91), 69 (78), 67 (77), 59 (59), 55 (93), 43 (55), and 41 (100).

From dimethyl – lactone 114

2.8 M Methyl magnesium bromide in diethyl ether (0.79 mL, 2.2 mmol) was added to HMPA (2.94 mL) and the diethyl ether was removed by vacuum distillation at room temperature for 1.5 hours. A mixture of dimethyl – lactone **114** (154 mg, 1 mmol) and 1.5 mL HMPA was added at room temperature, the resulting solution was heated at 80°C in an oil bath for 20 hours. The cooled mixture was quenched with 20% NH_4Cl and the aqueous layer was extracted with diethyl ether (×4). The combined organic layers were washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. Chromatography on silica gel (4% acetone in petroleum ether) gave **113** (15.0 mg, 9%), **125** (29.8 mg, 16%), and the starting material **114** (98.3 mg, 64%).

***cis* – 3 – (2 – Hydroxy – 1,1,2 – trimethylpropanyl) – 1 – cyclopentanol (125)**

To a solution of dimethyl – lactone **114** (158.8 mg, 1.03 mmol) in diethyl ether (30 mL) was added 1.40 M methyllithium in diethyl ether (4.4 mL, 6.18 mmol), and the resulting mixture was stirred overnight. The reaction was quenched by the cautious addition of H_2O, the aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (4% acetone in petroleum ether) to provide **113** (12.7 mg, 7%) and diol **125** (162.7 mg, 85%).

3-(1,1-Dimethyl-2-oxopropyl)cyclopentanone (112)

A solution of the hydroxy-ketone **113** (3.6642 g, 21.52 mmol) in CH_2Cl_2 (30 mL) was added to PCC (6.97 g, 32.3 mmol) in CH_2Cl_2. The solution was stirred at room temperature for 26 hours. Filtration through a Florisil pad removed a black precipitate. Five volumes of anhydrous diethyl ether were passed through the pad, and concentration of the combined organic solutions provided the diketone **112** (3.5937 g, 99%): IR (film) ν_{max}: 1740 and 1700 cm^{-1}; ^1H NMR δ: 1.144 (3H, s), 1.167 (3H, s), 1.54-2.40 (6H, mm), 2.175 (3H, s), and 2.537 (1H, m, methine); ^{13}C NMR δ (attached H's): 21.2 (3), 21.5 (3), 24.0 (2), 25.5 (3), 38.6 (2), 40.0 (2), 43.4 (1), 48.7 (0), 212.6 (0), and 218.0 (0); MS *m/z* (%): 168 (0.5, M^+), 140 (18), 125 (19), 97 (16), 86 (57), 83 (55), 82 (18), 69 (44), 55 (100), 43 (74), and 41 (47). *Exact mass* calcd. for $C_{10}H_{16}O_2$: 168.1149; found: 168.1149.

7-(1,1-Dimethyl-2-oxopropyl)-1,4-dioxaspiro[4.4]nonane (107c)

A solution of diketone **112** (37.5 mg, 0.223 mmol), ethylene glycol (13.7 μL, 0.25 mmol), and a very small amount of *p*TSA in benzene was heated under reflux for 8 hours with a Barrett water-separator filled with 4 Å Molecular Sieves. The cooled solution was washed with saturated $NaHCO_3$ (×3) and the aqueous layers were extracted with diethyl ether (×2). The combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. Column chromatography on silica gel (4% acetone in petroleum ether) of the residue provided the starting diketone **112** (15.0 mg, 40%) and the monoketal **107c** (22.2 mg, 49%): ^1H NMR δ: 1.072 (3H, s), 1.083 (3H, s), 1.35-1.95 (6H, mm), 2.128 (3H, s), 2.363 (1H, m), and 3.84-3.94 (4H, mm); MS (from GC-MS) *m/z* (%): no M^+, 169 (2, $M^+ - COCH_3$), 141 (6), 127 (100), 99 (31), 86 (17), 83 (19), 55 (38), 43 (40), and 41 (28).

7-(1-Methyl-1-(2-methyl-1,3-dioxa-2-cyclopentyl)ethyl)-1,4-dioxaspiro[4.4]-nonane (130c)

A benzene solution of **112** (61.7 mg, 0.37 mmol) was heated overnight in the presence of a large excess of ethylene glycol (0.4 mL, 7.2 mmol) and a catalytic amount of PPTS. The product consisted of the monoketal **107c** and the diketal **130c** in 1 : 2 ratio as revealed by GC-MS analysis. Chromatography of the crude product provided the monoketal **107c** (17.1 mg, 22%) and the diketal **130c** (57.5 mg, 61%). For **130c**: IR (film) ν_{max}: 2975, 2880, 1475, 1370, and 1330 cm^{-1}; ^1H NMR δ: 0.876 (3H, s), 0.912 (3H, s), 1.235 (3H, s), 1.41-1.56 (1H, m), 1.62-1.94 (5H, mm), 2.09-2.22 (1H, m, methine), and 3.83-3.97 (8H, mm); ^{13}C NMR δ (attached H's): 19.2 (3), 19.4 (3), 20.1 (3), 25.9 (2), 35.8 (2), 38.9 (2), 42.9 (0), 43.3 (1), 64.0 (2), 64.1 (2), 64.5 (2), 64.6 (2), 114.3 (0), and 117.4 (0); MS (from GC-MS) *m/z* (%): no M^+, 241 (3.5), 141 (2), 127 (40), 99 (19), 87 (100), 55 (14), and 43 (32).

2-(1,1-Dimethyl-2-oxopropyl)-8,8-dimethyl-6,10-dioxaspiro[4.5]decane (107d)

A solution of the diketone **112** (435.3 mg, 2.587 mmol), 2,2-dimethyl-1,3-propanediol (700 mg, 6.72 mmol), and PPTS (approximately 120 mg) in benzene was heated under reflux for 40 min. The cooled solution was washed with saturated $NaHCO_3$ (×3) and the aqueous layers were extracted with diethyl ether (×3). The combined organic extracts were washed with H_2O (×2), saturated NaCl (×2), and dried over $MgSO_4$. Evaporation of the solvent under vacuum followed by column chromatography on silica gel (8% acetone in petroleum ether) provided the monoketal **107d** (577.0 mg, 88%) and the diketal **130d** (37.6, 4%). For **107d**: IR (film) ν_{max}: 1710 and 1120 cm^{-1}; ^1H NMR δ: 0.948 (3H, s), 0.965 (3H, s), 1.067 (3H, s), 1.078 (3H, s), 1.30-1.70 (3H, mm), 1.80-2.03 (3H, mm), 2.128 (3H, s), 2.340 (1H, m, methine), and 3.455 (4H, s); ^{13}C NMR δ (attached H's): 21.1 (2C, 3), 22.3 (3), 22.4 (3), 24.5 (2), 25.3 (3), 30.0 (0), 34.8 (2), 36.1 (2), 43.6 (1), 49.1 (0), 71.7 (2), 72.0 (2), 108.3 (0), and

213.4 (0); MS *m/z* (%): no M^+, 239 (0.4, M^+ – Me), 211 (2, $M^+ - COCH_3$), 183 (2), 169 (94), 141 (18), 128 (14), 83 (100), 69 (86), 55 (64), 43 (52), and 41 (56). *Anal.* calcd. for $C_{15}H_{26}O_3$: C 70.83, H 10.30; found: C 70.86, H 10.20. For spectroscopic analysis of the diketal **130d**, see below.

8,8-Dimethyl-2-(1-methyl-1-(2,5,5-trimethyl-1,3-dioxa-2-cyclohexyl)ethyl)-6,10-dioxaspiro[4.5]decane (130d)

A solution of **112** (81.4 mg, 0.484 mmol) and a catalytic amount of PPTS with a large excess of 2,2-dimethyl-1,3-propanediol in benzene was heated under reflux for 19 hours. Chromatography of the crude product yielded the monoketal **107d** (20.1 mg, 16%) and the diketal **130d** (129.4 mg, 79%). For **130d**: IR (film) ν_{max}: 2945, 2865, 1470, and 1120 cm^{-1}; ^1H NMR δ: 0.704 (3H, s), 0.917 (6H, s), 0.937 (3H, s), 0.981 (3H, s), 1.143 (3H, s), 1.314 (3H, s), 1.460 (1H, m), 1.53-1.78 (3H, m), 1.981 (1H, dd, J = 8.9, 10.5 Hz), 2.112 (1H, dd, J = 7.4, 13.4 Hz), 2.273 (1H, m, methine), 3.298 (1H, d, J = 11.5 Hz), 3.469 (4H, s), and 3.652 (2H, d, J = 11.5 Hz); ^{13}C NMR δ (attached H's): 11.8 (3), 18.9 (3), 19.7 (3), 22.38 (2C, 3), 22.42 (3), 23.3 (3), 26.4 (2), 29.7 (0), 30.0 (0), 34.2 (2), 38.8 (2), 42.3 (1), 43.6 (0), 69.9 (2C, 2), 71.6 (2), 71.9 (2), 102.4 (0), and 108.7 (0); MS *m/z* (%): no M^+, 325 (0.6), 205 (3), 169 (10), 141 (5), 129 (7), 115 (18), 88 (10), 86 (63), 84 (100), 69 (24), 56 (46), 47 (22), and 41 (44).

Typical procedure for reaction of 1,2-bis(trimethylsiloxy)cyclobutene (109) with a ketal: 2-ethyl-2-methylcyclopentane-1,3-dione (140)

Compound **109** was prepared by the method of Bloomfield and Nelke.[61] A solution of 2-ethyl-2-methyl-1,3-dioxolane (**136**) (280.5 mg, 2.42 mmol) in CH_2Cl_2 was stirred at −78°C as freshly distilled $BF_3{\cdot}Et_2O$ (2.98 mL, 24.2 mmol) was added, followed over a period of 5 min by a solution of **109** (1.61 mL, 6.05 mmol) in CH_2Cl_2. The mixture was allowed to attain room temperature while stirring overnight. The

solution was washed with H_2O and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with H_2O (×2), saturated $NaHCO_3$ (×3), and saturated NaCl (×3). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow oil that showed as only one component on GC–MS. Chromatography of the oily residue yielded colorless **140** (309.3 mg, 91.5%): IR (film) ν_{max}: 1750 (shoulder) and 1720 cm^{-1}; ^1H NMR δ: 0.808 (3H, t, J = 7.4 Hz), 1.095 (3H, s), 1.668 (2H, q, J = 7.4 Hz), and 2.785 (4H, s); ^{13}C NMR δ (attached H's): 8.7 (3), 17.8 (3), 28.6 (2), 35.0 (2), 56.9 (0), and 216.4 (2C, 0); MS m/z (%): 140 (51, M^+), 125 (92), 97 (31), 84 (12), 83 (13), 69 (100), 56 (36), 55 (29), and 41 (83). *Exact mass* calcd. for $C_8H_{12}O_2$: 140.0837; found: 140.0843.

Spiro[4.5]decane–1,4–dione (133)

From cyclohexanone ethylene ketal (131)

A CH_2Cl_2 solution of the 1,3–dioxolane **131** (263.6 mg, 1.86 mmol) was treated as above with $BF_3{\cdot}Et_2O$ (0.46 mL, 3.72 mmol) and **109** (0.56 mL, 2.23 mmol). After the work–up, the yellow residue was passed through a small pad of Florisil and washed with five volumes of diethyl ether. Evaporation of the solvent *in vacuo* gave pure **133** (295.9 mg, 99%, crystallised from EtOAc): mp 60–61°C (lit.[31] mp 61–62°C); IR ν_{max}: 1755 (weak) and 1720 cm^{-1}; ^1H NMR δ: 1.4–1.7 (10H, mm) and 2.677 (4H, s); ^{13}C NMR δ (attached H's): 20.4 (2C, 2), 24.9 (2), 29.2 (2C, 2), 34.3 (2C, 2), 55.9 (0), and 215.8 (2C, 0); MS m/z (%): 166 (100, M^+), 137 (25), 124 (32), 112 (61), 111 (46), 85 (46), 81 (37), 67 (74), and 56 (44). *Exact mass* calcd. for $C_{10}H_{14}O_2$: 166.0993; found: 166.0985.

From 3,3–dimethyl–1,5–dioxaspiro[5.5]undecane (134)

A CH_2Cl_2 solution of **134** (200.1 mg, 1.09 mmol) was treated as above with $BF_3{\cdot}Et_2O$ (1.34 mL, 10.9 mmol) and **109** (0.58 mL, 2.18 mmol). After the work–up,

the yellow color in the residue was removed by passing it through a small pad of Florisil to provide pure **133** (176.9 mg, 98%).

Spiro(bicyclo[2.2.1]heptane-2,1'-[2,5]cyclopentanedione) (139)

The norcamphor ethylene ketal (**135**) (110.0 mg, 0.72 mmol) in CH_2Cl_2 was treated as above with $BF_3{\cdot}Et_2O$ (0.22 mL, 1.8 mmol) and **109** (0.36 mL, 1.45 mmol). Chromatography of the residue (5% acetone in petroleum ether) provided pure **139** (192.0 mg, 82%, crystallized from diether ether): mp 108-109°C (lit.[31] mp 109.5-110.5°C); IR (film) ν_{max}: 1760 (weak) and 1715 cm^{-1}; ^1H NMR δ: 1.18-1.57 (6H, mm), 1.76-1.89 (2H, mm), 2.372 (1H, br t, bridgehead H), 2.480 (1H, br d, bridgehead H), and 2.51-3.07 (4H, mm); ^{13}C NMR δ (attached H's): 24.5 (2), 28.0 (2), 32.9 (2), 34.4 (2), 35.3 (2), 37.0 (1), 37.2 (2), 48.9 (1), 66.6 (0), and 213.1 (2C, 0); MS *m/z* (%): 178 (19, M^+), 149 (46), 112 (100), 93 (15), 79 (13), 67 (19), 66 (12), and 65 (13). *Exact mass* calcd. for $C_{11}H_{14}O_2$: 178.0993; found: 178.1002.

2,2,5,5-Tetramethyl-1,3-dioxane (137)

A solution of 2,2-dimethyl-1,3-propanediol (15.62 g, 0.15 mmol) and Amberlyst-15 (3 g) in acetone (66 mL, 0.90 mmol) was heated under reflux overnight. Filtration through a Celite pad removed the resin. Two volumes of diethyl ether were passed through the pad, and H_2O was added. The aqueous layer was extracted with diethyl ether (×2), and the combined organic extracts were washed with saturated NaCl (×2) and dried over $MgSO_4$. Simple distillation provided pure ketal **137** (9.05 g, 42%): bp 115-120°C; ^1H NMR (60 MHz) δ: 0.95 (6H, s), 1.40 (6H, s), 3.45 (4H, s).

2,2-Dimethylcyclopentane-1,3-dione (141)

The ketal **137** (209.9 mg, 1.46 mmol) in CH_2Cl_2 was treated as above with $BF_3{\cdot}Et_2O$ (1.80 mL, 14.6 mmol) and **109** (0.97 mL, 3.65 mmol). The crude product

consisted of 92.6% **141** as revealed by GC–MS analysis. Chromatography (5% acetone in petroleum ether) of the crude product gave pure **141** (124.8 mg, 68%): IR (film) ν_{max}: 1725 cm^{-1}; ^1H NMR δ: 1.153 (6H, s) and 2.810 (4H, s); ^{13}C NMR δ (attached H's): 20.2 (2C, 3), 34.5 (2C, 2), 52.6 (0), and 216.3 (2C, 0); MS *m/z* (%): 126 (54, M^+), 111 (19), 83 (18), 70 (100), 56 (23), 55 (21), and 42 (83). Exact mass calcd. for $C_7H_{10}O_2$: 126.0680; found: 126.0678.

5,5–Dimethyl–1,3–dioxane (138)

This procedure was derived from that of Schreiber and coworkers.[62] A solution of 1,3,5–trioxane (5.0 g, 55 mmol), 2,2–dimethyl–1,3–propanediol (26 g, 0.25 mol) and Amberlyst–15 (3 g) in $CHCl_3$ (150 mL) was heated under reflux overnight. The resin was removed by filtration through a Celite pad, and the pad was washed with two volumes of $CHCl_3$. Water was added and the aqueous layer was extracted with $CHCl_3$ (×2). The combined organic solutions were washed with saturated NaCl (×2) and dried over $MgSO_4$. Simple distillation provided pure **138** (15.4 g, 80%): bp 115–119°C; ^1H NMR δ: 0.973 (6H, s), 3.493 (4H, s), and 4.797 (2H, s).

7–(1,1–Dimethyl–2–oxopropyl)spiro[4.4]nonane–1,4–dione (106)

From the monoketal 107d

A solution of **107d** (611.0 mg, 2.402 mmol) in CH_2Cl_2 was cooled to −78°C. Freshly distilled $BF_3{\cdot}Et_2O$ (4.44 mL, 36.1 mmol) was added followed, dropwise, by a solution of **109** (1.60 mL, 6.05 mmol) in CH_2Cl_2. The mixture was stirred overnight, over which time the solution was allowed to attain room temperature. The black solution was washed with H_2O (×2), and the aqueous layers were extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×3) and saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue (5% acetone in petroleum

ether) provided pure **106** (491.2 mg, 87%): IR (film) ν_{max}: 1760 (shoulder), 1725, and 1705 cm^{-1}; ^1H NMR δ: 1.00 (3H, s), 1.136 (3H, s), 1.44 – 1.96 (6H, mm), 2.141 (3H, s), 2.491 (1H, m, methine), and 2.778 (4H, m); ^{13}C NMR δ (attached H's): 21.2 (3), 21.6 (3), 25.3 (3), 27.6 (2), 34.1 (2), 34.7 (2), 34.9 (2), 35.2 (2), 46.7 (1), 48.9 (0), 62.3 (0), 213.0 (0), 215.3 (0), and 215.7 (0); MS (from GC – MS) *m/z* (%): 236 (0.1, M^+), 221 (0.4), 193 (96), 176 (12), 175 (15), 151 (66), 137 (17), 133 (25), 125 (30), 111 (29), 109 (22), 86 (56), 55 (30), 43 (100), and 41 (56). *Exact mass* calcd. for $C_{12}H_{17}O_2$ (M^+ – $COCH_3$): 193.1227; found: 193.1215.

From the diketal 130c

A CH_2Cl_2 solution of the diketal **130c** (129.4 mg, 0.359 mmol) was treated as above with $BF_3{\cdot}Et_2O$ (0.89 mL, 7.2 mmol) and **109** (0.58ml, 2.2 mmol). The GC – MS analysis of the crude product showed **106** as the almost exclusive component along with *ca.* 3% of hydrolysed starting material **112**. Chromatography (5% acetone in petroleum ether) provided pure **106** (72.9 mg, 86%).

From the diketal 130d

A CH_2Cl_2 solution of the diketal **130d** (129.4 mg, 0.380 mmol) was treated as above with $BF_3{\cdot}Et_2O$ (0.94 mL, 7.6 mmol) and **109** (0.61 mL, 2.3 mmol). The GC – MS analysis of the crude product showed a mixture of mainly **106** and the hydrolysed starting material **112** in 1 : 1 ratio. Chromatography on silica gel (5% acetone in petroleum ether) provided pure **106** (42.3 mg, 47%) and recovered **112** (27.6 mg, 43%). The following is the mass spectrum of a compound tentatively identified as **143** from the GC – MS of the crude product of one very small – scale reaction of **130d** with **109**: *m/z* (%): 304 (2, M^+), 239 (5), 221 (2), 219 (2), 207 (24), 153 (25, complete side chain), 137 (23), 123 (100), 81 (33), 79 (24), 73 (15), 69 (18), 55 (18), and 41 (26).

Intramolecular titanium–induced ketone–ketone coupling in 106: isokhusimone (65)

Zn–Cu couple was prepared by the procedure of McMurry *et al.*[52] The couple (556 mg, 8.56 mmol) was added to $TiCl_3$ (516 mg, 3.35 mmol) in 150 mL dry DME, and this was heated under reflux for 4 hours. A solution of the triketone **106** (96.6 mg, 0.409 mmol) in 20 mL DME was added to the hot slurry over a period of 50.5 h using a syringe pump, then the reaction mixture was heated under reflux for another 84 h. The cooled solution was passed through a small pad of Florisil and the black precipitate was washed with three volumes of diethyl ether. After concentration under reduced pressure, the resulting residue was chromatographed (2% acetone in petroleum ether) to give, in order of elution, isokhusimone (**65**) (47.4 mg, 57%), a 1 : 1 mixture of the epimeric alcohols **144a** and **144b** (17.8 mg, 21%), and recovered triketone **106** (8.1 mg, 7%). For isokhusimone (**65**): IR (film) ν_{max}: 1740 and 1675 (weak) cm^{-1}; ^1H NMR δ: 1.020 (3H, s), 1.039 (3H, s), 1.534 (3H, s), 1.64–1.88 (7H, mm), 2.025 (1H, m, methine), and 2.28–2.71 (3H, mm); ^{13}C NMR δ (attached H's): 12.2 (3), 23.1 (2), 24.7 (2), 25.1 (3), 28.2 (3), 35.7 (2), 38.0 (2), 38.3 (2), 40.5 (0), 48.6 (1), 55.9 (0), 130.6 (0), 136.3 (0), and 222.6 (0); MS *m/z* (%): 204 (15, M^+), 189 (36), 161 (23), 133 (30), 119 (100), 105 (12), 91 (22), 77 (15), and 41 (29). *Exact mass* calcd. for $C_{14}H_{20}O$: 204.1513; found: 204.1531. For **144a** (tentative assignment of relative stereochemistry at C–2): ^1C NMR δ: 0.990 (3H, s), 1.037 (3H, s), 1.479 (3H, s), and 4.031 (1H, m);^{13}C NMR (from the spectrum of the epimeric alcohols) δ: 13.4, 25.0, 25.1, 25.8, 32.6, 33.3, 36.6, 40.4, 47.7, 56.3, 79.7, 128.9, and 139.5; MS (from GC–MS) nearly identical with **144b**. For **144b**: see below.

rel*-(1*R*,2*R*,8*R*)-Isokhusimol (144b)

Isokhusimone (**65**) (38.2 mg, 0.187 mmol) was dissolved in methanol (8 mL) and cooled in ice-bath as sodium borohydride was added in small portions. TLC indicated a complete reaction within 30 min. Some water was added and much of the methanol was removed under reduced pressure. The product was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and evaporated *in vacuo*. Although the crude oily residue (39.1 mg, 100%) was homogeneous by TLC and GC-MS, column chramatography (10% acetone in petroleum ether) was used to remove some yellow color. This afforded the alcohol tentatively assigned as epimer **144b** as a colorless powder: mp 102-103°C; IR (film) ν_{max}: 3370 (very br) cm^{-1}; ^1H NMR δ: 0.989 (3H, s), 1.006 (3H, s), 1.20-2.35 (mm), 1.421 (3H, s), and 4.002 (1H, dd, J = 6.0, 11.2 Hz); ^{13}C NMR δ (attached H's): 12.5 (3), 24.1 (2C, 2), 24.9 (3), 28.3 (3), 28.4 (2), 32.1 (2), 36.2 (2), 40.4 (0), 47.2 (1), 53.0 (0), 76.3 (1), 129.7 (0), and 138.8 (0); MS (from GC-MS) m/z (%): 206 (29, M^+), 191 (75), 173 (10), 163 (24), 145 (48), 119 (100), 105 (17), and 91 (25). *Exact mass* calcd. for $C_{13}H_{19}O$ (M^+ - Me): 191.1435; found: 191.1435.

Oxidation of 144a/b and 144b

A solution of the 1 : 1 epimeric alcohols **144a/b** (31.7 mg, 0.15 mmol) in CH_2Cl_2 (20 mL) was added to PCC (49.6 mg, 0.23 mmol) in CH_2Cl_2. The solution was stirred at room temperature overnight. Filtration through a Florisil pad removed a black precipitate. Five volumes of anhydrous diethyl ether were passed through the pad, and evaporation of the solvent *in vacuo* provided pure isokhusimone (**65**) (31.4 mg, 100%). Likewise, a CH_2Cl_2 solution of the alcohol **144b** (27.8 mg, 0.13 mmol) was treated as above with PCC (58.2 mg, 0.26 mmol) to provide pure isokhusimone (**65**) (27.5 mg,

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* IUPAC name: *rel*-(1*R*,2*R*,8*R*)-6,7,7-trimethyltricyclo[6.2.1.$0^{1,5}$]undec-5-en-2-ol.

100%).

Methyl *cis*-2-(3-hydroxycyclopentyl)-2-methylpropanoate (150)

Sodium metal (800 mg) was added to dry methanol (160 mL) followed by the dimethyl-lactone **114** (1.1665 g, 7.564 mmol), and the solution was heated at reflux for 22 h. Much of the solvent was removed by evaporation under reduced pressure, then H_2O was added followed by concentrated HCl to pH 4.5. This was extracted with EtOAc (×4). The combined organic layers were washed with saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated to give a yellow oil (1.5048 g) containing mainly **150** and a small amount of **114**. Only a small portion was purified; for **150**: IR(film) ν_{max}: 3430 (br) and 1730 cm^{-1}; ^1H NMR δ: 1.170 (3H, s), 1.175 (3H, s), 1.376 (1H, m), 1.55-1.77 (3H, mm), 1.95-2.20 (2H, mm), 2.21 (1H, very br, OH), 3.660 (3H, s), and 4.258 (1H, m); ^{13}C NMR δ (attached H's): 23.0 (3), 23.2 (3), 24.9 (2), 35.4 (2), 37.0 (2), 44.1 (0), 46.3 (1), 51.6 (3), 73.1 (1), and 178.3 (0); MS *m/z* (%): no M^+, 169 (0.4), 155 (1.3), 111 (11), 110 (10), 109 (63), 102 (100), 87 (20), 83 (16), 69 (92), 67 (87), 55 (31), and 41 (68).

Methyl 2-methyl-2-(3-oxocyclopentyl)propanoate (151)

A CH_2Cl_2 solution of the crude **150** from the above reaction was stirred overnight in the presence of PCC (2.45 g, 11.37 mmol). The mixture was filtered through a Florisil pad, which was washed with four volumes of diethyl ether, and the combined organic solutions were concentrated *in vacuo* to give a colorless liquid (1.239 g). A small portion was purified; for **151**: IR (film) ν_{max}: 1740 and 1730 cm^{-1}; ^1H NMR δ: 1.205 (3H, s), 1.214 (3H, s), 1.646 (1H, m), 1.98-2.53 (6H, mm), and 3.687 (3H, s); ^{13}C NMR δ (attached H's): 22.5 (3), 22.6 (3), 24.4 (2), 38.8 (2), 40.4 (2), 43.7 (0), 45.0 (1), 51.8 (3), 177.2 (0), and 218.2 (0); MS *m/z* (%): 184 (1, M^+), 156 (3), 125 (17), 102 (100), 87 (14), 83 (57), 82 (19), 70 (13), 69 (28), 55 (65), and 41 (36). *Anal.* calcd. for

$C_{10}H_{16}O_3$: C 65.18, H 8.76; found: C 65.03, H 8.80.

7-(1-Carbomethoxy-1-methylethyl)-1,4-dioxaspiro[4.4]nonane (149)

To a benzene solution of the crude **151** from the above reaction was added ethylene glycol (4.3 mL, 75.8 mmol) and a small amount of *p*TSA. The mixture was heated under reflux with a Barrett water separator for 21 h. The solution was washed with saturated $NaHCO_3$ (×2). The aqueous layers were extracted with diethyl ether (×3) and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo* to give a yellow oil (1.5405 g). Chromatography (2% acetone in petroleum ether) of this material provided pure **149** (1.2429 g, 72% from **114**): IR (film) ν_{max}: 1730 and 1130 cm^{-1}; ^1H NMR δ: 1.141 (3H, s), 1.144 (3H, s), 1.40-1.91 (6H, mm), 2.313 (1H, m, methine), 3.653 (3H, s), and 3.890 (4H, m); ^{13}C NMR δ (attached H's): 22.2 (3), 22.4 (3), 24.7 (2), 35.7 (2), 37.4 (2), 43.7 (0), 45.1 (1), 51.4 (3), 63.9 (2), 64.0 (2), 117.2 (0), and 117.5 (0); MS *m/z* (%): no M^+, 199 (1), 169 (9), 127 (100), 99 (78), 83 (22), 55 (30), and 41 (18). *Anal.* calcd. for $C_{12}H_{20}O_4$: C 63.14, H 8.83; found: C 63.42, H 8.82.

7-(1-Carbomethoxy-1-methylethyl)spiro[4.4]nonane-1,4-dione (148)

A solution of **149** (52.2 mg, 0.229 mmol) in CH_2Cl_2 was cooled to -78°C and $BF_3{\cdot}Et_2O$ (0.43 mL, 3.45 mmol) was added, followed dropwise by a CH_2Cl_2 solution of **109** (0.25 mL, 0.92 mmol). This mixture was stirred for 28 h during which time the reaction was allowed to attain room temperature. The solution was washed with H_2O (×2), and the aqueous layers were extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×3) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed to provide pure **148** (46.1 mg, 80%): mp 32-33°C; IR (film) ν_{max}: 1715 (br) cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.174 (3H, s), 1.182 (3H, s), 1.53-1.95 (6H, mm), 2.435 (1H, m, methine),

2.777 (4H, br s), and 3.668 (3H, s), 2.444 (1H, m), and 3.381 (3H, s); ^{13}C NMR δ ($CDCl_3$) (attached H's): 22.7 (3), 22.9 (3), 27.8 (2), 34.1 (2), 34.6 (2), 34.8 (2), 35.2 (2), 43.5 (0), 48.2 (1), 51.6 (3), 62.4 (0), 177.0 (0), 215.3 (0), and 215.6 (0); ^{13}C NMR δ (C_6D_6): 23.0, 23.4, 28.2, 34.6 (2C), 34.7, 35.4, 43.8, 48.9, 51.3, 62.3, 176.9, 214.3, and 214.5; MS *m/z* (%): 252 (0.4, M^+), 250 (1), 193 (10), 191 (10), 190 (15), 151 (16), 150 (22), 149 (36), 102 (100), 87 (16), 55 (15),and 41 (26). *Anal.* calcd. for $C_{14}H_{20}O_4$: C 66.65, H 7.99; found: C 66.62, H 7.99.

Attempted intramolecular titanium-induced ketone-ester coupling in 148

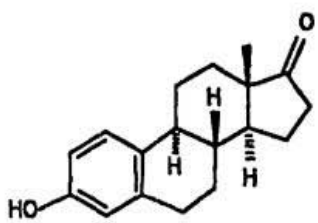
Reaction media based on $TiCl_3/Zn-Cu$, $TiCl_3/Zn-Ag$ couple as well as $TiCl_3/LiAlH_4$ all gave complex mixtures along with significant amounts of recovered starting material **148**. (PCC oxidation of the resulting crude product did not appear to lead to a simpler mixture.)

Chapter 2

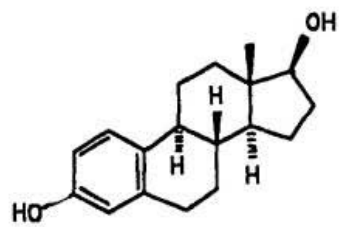
A VERY SHORT SYNTHESIS OF 3-METHOXYESTRA-1,3,5,8,14-PENTAEN-17-ONE

I. Introduction

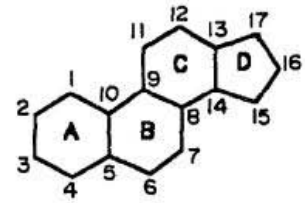
Estrone (**153**) was isolated in 1929 from the urine of pregnant women, and it was the first steroid hormone obtained in pure form. Estrone was originally considered as the main estrogenic hormone, but it has been recognized that estradiol (**154**) is the primary estrogen secreted by the ovary. Both compounds have been interrelated chemically as well as enzymatically with each other and with some structurally similar metabolites. Estrone was also isolated from all the major classes of vertebrates, from higher plants, and from some species of beetles.[63]



153



154



155

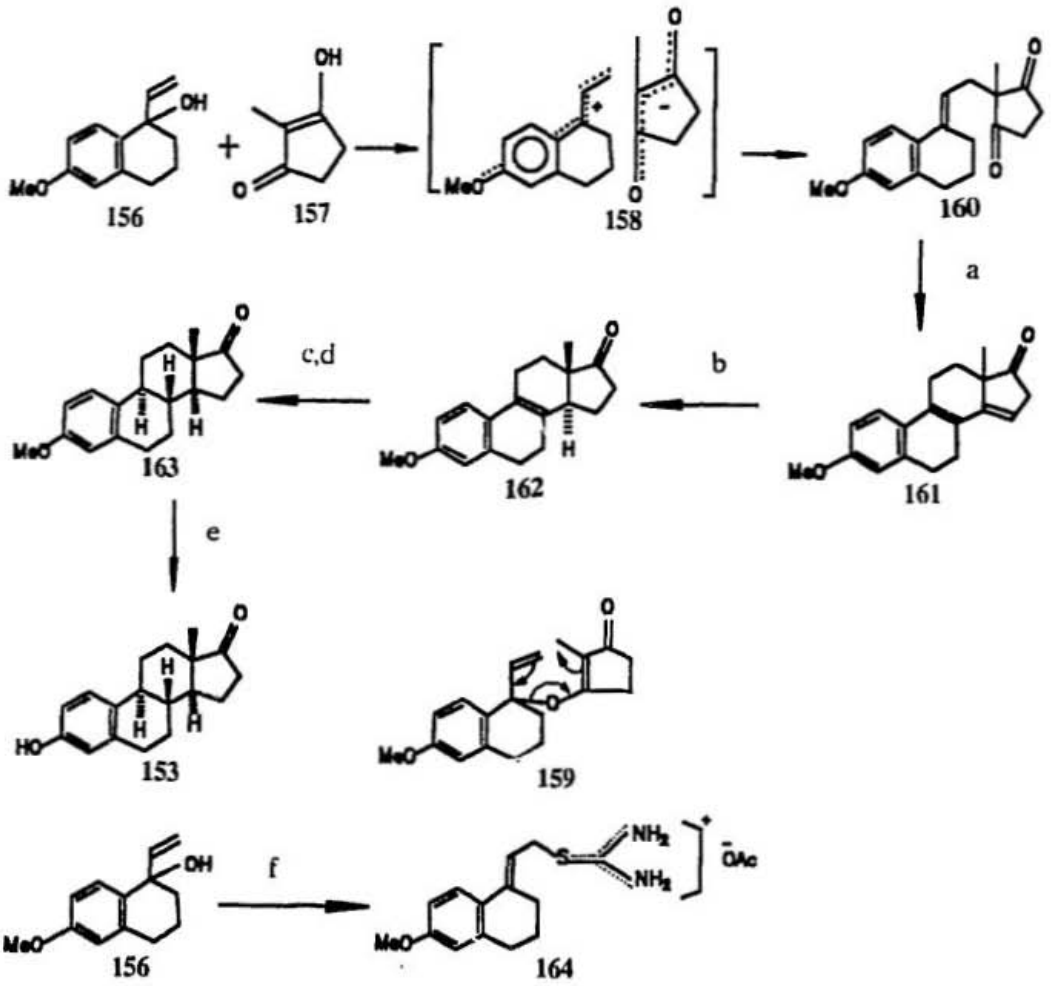
The pronounced physiological activity of estrone and its position as a precursor to commercially important 19-norsteroids has made it the object of numerous, often ingenious, synthetic strategies. In addition, its well defined structure provides an excellent opportunity to test new reactions and to explore their stereochemistry.[64]

In general, the basic framework of steroids **155**, with the four rings designated A, B, C, and D, can be constructed starting with either one or several of the rings containing appropriate functionality for the addition of the remaining rings by aldol condensation, acid-initiated cyclization, Diels-Alder reaction, or other bond-forming reactions. The various synthetic approaches may be conceptualized in an abbreviated form as AB → ABCD, ABD → ABCD, etc., depending on the sequence in which the individual rings are added or formed.[64e] Many successful approaches to estrone have been reported, but only a small selection of typical ones will be briefly discussed here, due to space limitations.

Regarding the early approaches to estrone, particularly noteworthy are the Torgov synthesis[65] (Scheme 33) and the Hughes-Smith synthesis[66] (Scheme 34). The Torgov approach belongs to the ABD → ABCD category. The reaction of vinyl carbinol **156** with 2-methylcyclopentane-1,3-dione (**157**), known as the Torgov reaction, was thought to be base-catalyzed, and at first it was generally achieved in the presence of about 10% of a quaternary ammonium hydroxide, Triton B, in 50-60% yield.[65,66b,67] However, no reaction was observed when a full molar equivalent of base was utilized. In fact, 70% yield of the tricyclic diketone **160** was obtained when the reaction was carried out in the absence of base, thus showing that the reaction is not base-catalyzed: the reaction requires the free β-diketone **157** instead of the corresponding anion, and it may proceed *via* the ion pair **158** and hence to **160**.[68, 69] The enol ether intermediate **159**, which could afford **160** by Cope rearrangement, was found to be impossible by some ^{18}O-labeling studies.[68] Cyclization and dehydration of **160** under strongly acidic conditions led to the tetracyclic estrapentaene **161**, a key intermediate of the Torgov route to estrone (**153**). The introduction of the requisite trans-anti-trans stereochemistry into **161** was accomplished by a two-step reductive sequence. Hydrogenation of the 14,15-double bond occurred mainly from the α-side, resulting in the 8-dehydroestrone methyl ether (**162**), which, in turn, was converted to

the estrone methyl ether (**163**) by Birch reduction and re-oxidation at C-17. Finally, demethylation under strongly acidic conditions led to estrone (**153**) in high yield. The yield of the Torgov reaction was improved when the crystalline isothiuronium acetate **164**, available from the unstable vinyl carbinol **156**, was coupled with **157**. In this way, the tricyclic dione **160** was isolated in 90% yield.[68, 69a]

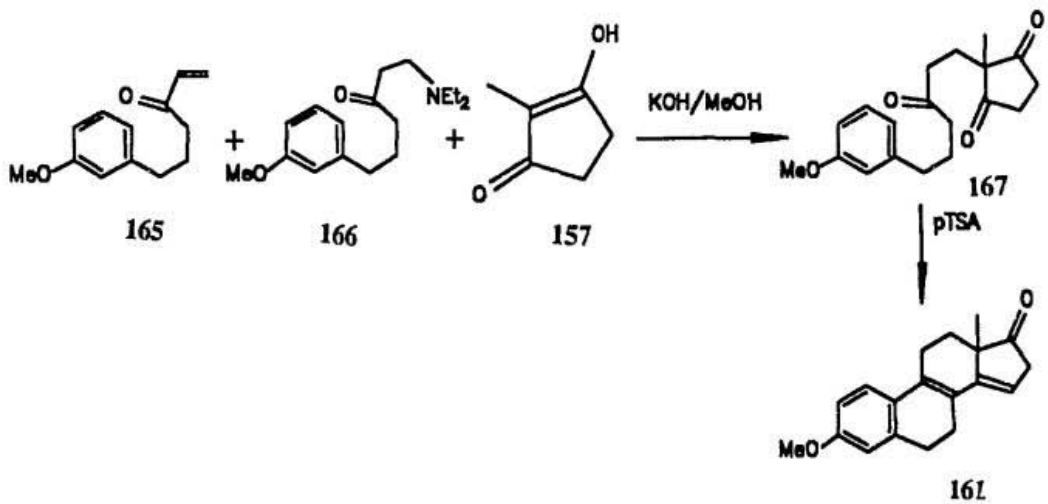
Scheme 33



(a) MeOH, HCl; (b) H_2, Pd-$CaCO_3$; (c) K/NH_3; (d) CrO_3; (e) HOAc, HBr; (f) HOAc, $SC(NH_2)_2$.

The Hughes–Smith synthesis can be classified as an AD → ABCD approach.[66] A mixture of Mannich base **166** and vinyl ketone **165** was condensed with **157** under basic conditions to furnish the bicyclic trione **167**. The closure of the B,C rings was accomplished at the same time with *para*–toluenesulfonic acid (*p*TSA) in refluxing benzene to give the estrapentaene **161** in high yield.

Scheme 34

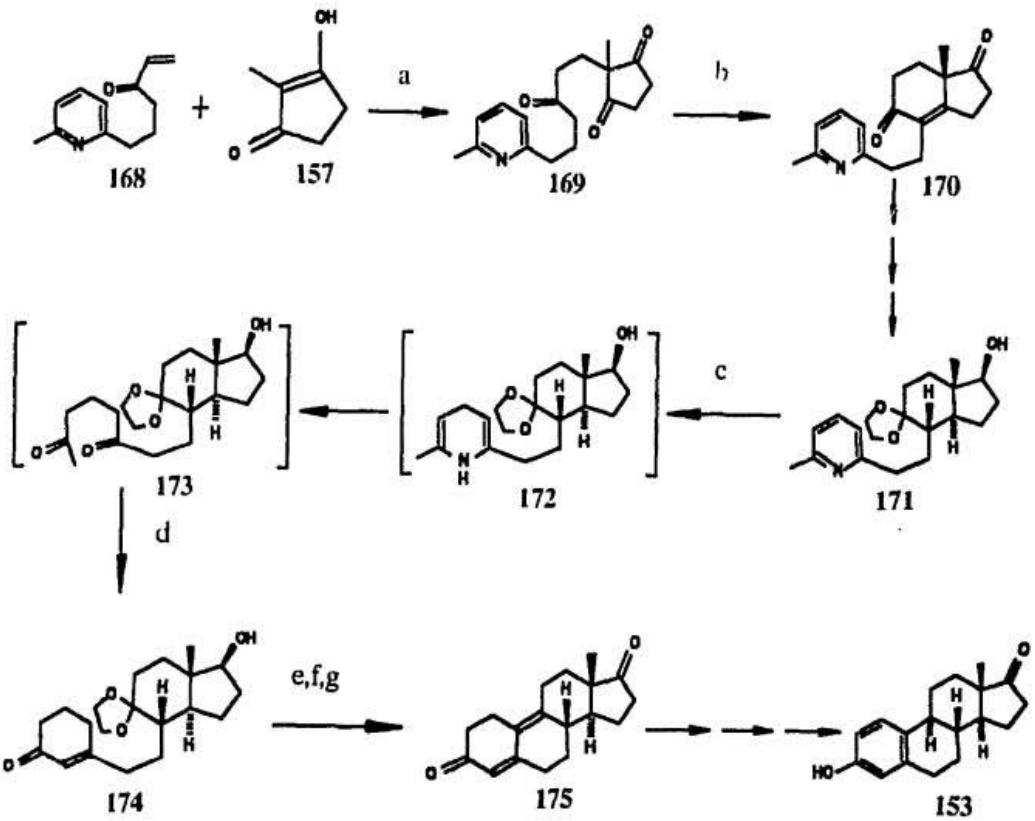


165 **166** **157** **167** **161**

Danishevsky and coworkers[70] developed an ingenious synthesis of (+)–estrone utilizing 6–substituted α–picolines as A ring synthons in a variant of the Robinson annulation process as outlined in Scheme 35. Addition of the enone **168** to **157** gave the prochiral bicyclic trione **169** in quantitative yield. Asymmetric cyclization of **169** with L–phenylalanine and perchloric acid led to (+)–**170** of 86% optical purity in 82% yield. This compound was converted into **171** in 45% yield in three steps. Birch reduction of **171** and hydrolysis of the intermediate bisenamine **172** yielded 1,5–diketone **173**, which cyclized to enone **174** in 90% yield. Deketalization of **174** with aqueous acid and Jones oxidation were followed by acid–catalyzed cyclization of the

resultant triketone. The crude dienedione **175** thus obtained was transformed into (+)−estrone in three steps.

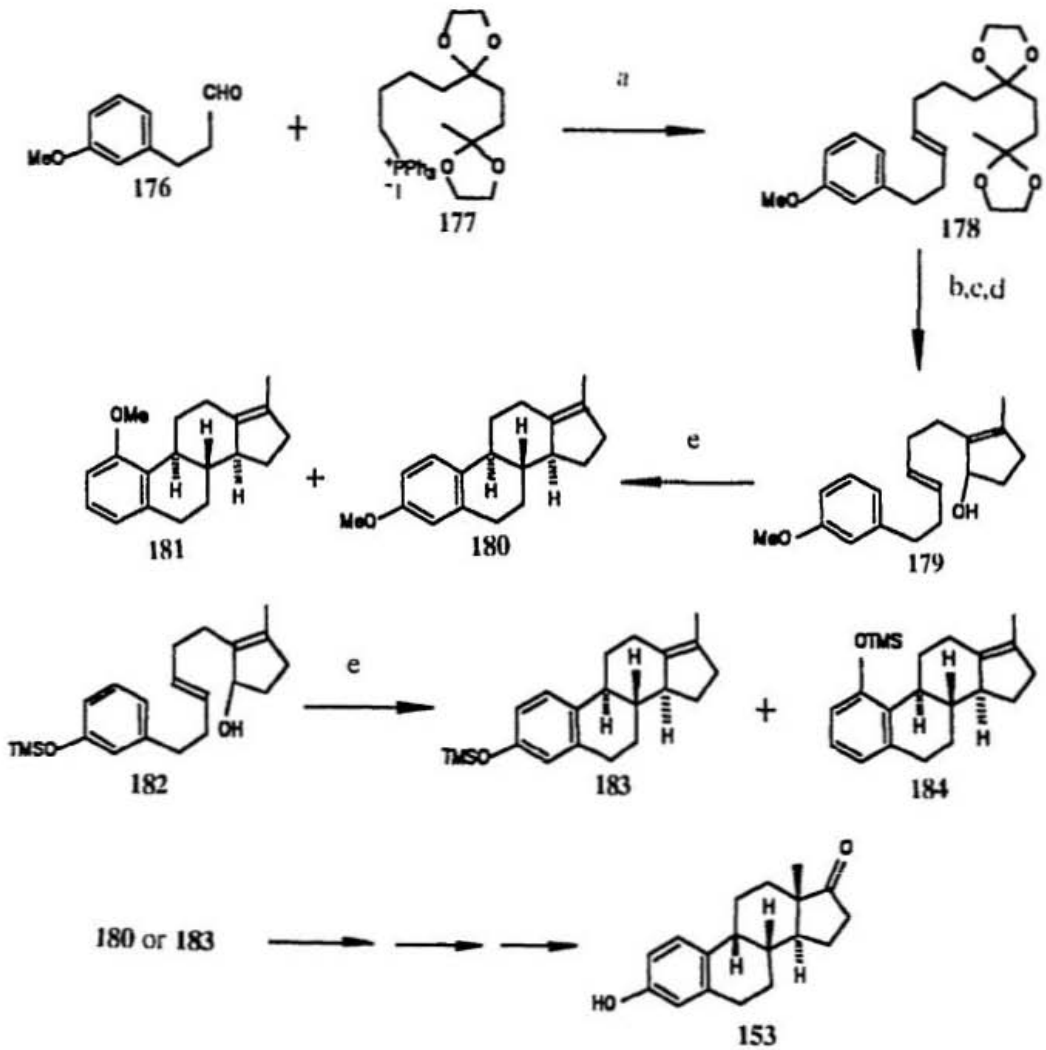
Scheme 35



(a)Et_3N, EtOAc; (b) *L*−phenylalanine, $HClO_4$; (c) Na/NH_3; (d) NaOH, EtOH; (e) H_3O^+; (f) Jones oxidation; (g) *p*TSA, HOAc.

Johnson and coworkers[71] reported a stereoselective synthesis of (±)−estrone based on a biomimetic olefin−cyclization strategy as outlined in Scheme 36. The Wittig reaction of *m*−methoxyphenylpropionaldehyde (**176**) with the phosphonium iodide **177** resulted in a 65% yield of olefin **178**. The key intermediate **179** for the polyene cyclization was obtained from **178** by ketal hydrolysis, cyclization and reduction.

Scheme 36



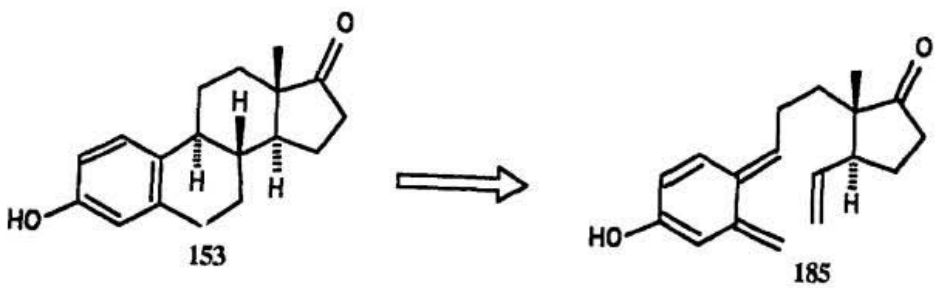
(a) PhLi; (b) HCl, EtOH; (c) NaOH; (d) $NaAlH_2(OCH_2CH_2OCH_3)_2$, THF; (e) $SnCl_4$.

Compound **179** underwent cyclization in the presence of tin(IV) chloride in dichloromethane leading to the isomeric tetracyclic compounds **180** and **181** in the ratio of 4.3 : 1, isolated in 59% and 12% yields, respectively. Fortunately, the cyclization of the 3-trimethylsilyl ether **182** proceeded cleanly to give, after solvolysis with

methanol and benzoylation with benzoyl chloride, tetracycles **183** and **184** in a ratio of 20 : 1. Both **180** and **183** were converted into (±)-estrone in a few steps. The Johnson approach belongs to the A → AD → ABCD category.

An alternative route to estrone was based on the retro-synthetic analysis shown in Scheme 37. The stereospecific construction of the B, C rings could be achieved in one step *via* an intramolecular Diels-Alder reaction of an intermediate like **185**. The *ortho*-xylylene moiety contained in **185** could be generated *via* thermal, photochemical, fluoride-initiated and transition metal-mediated routes.

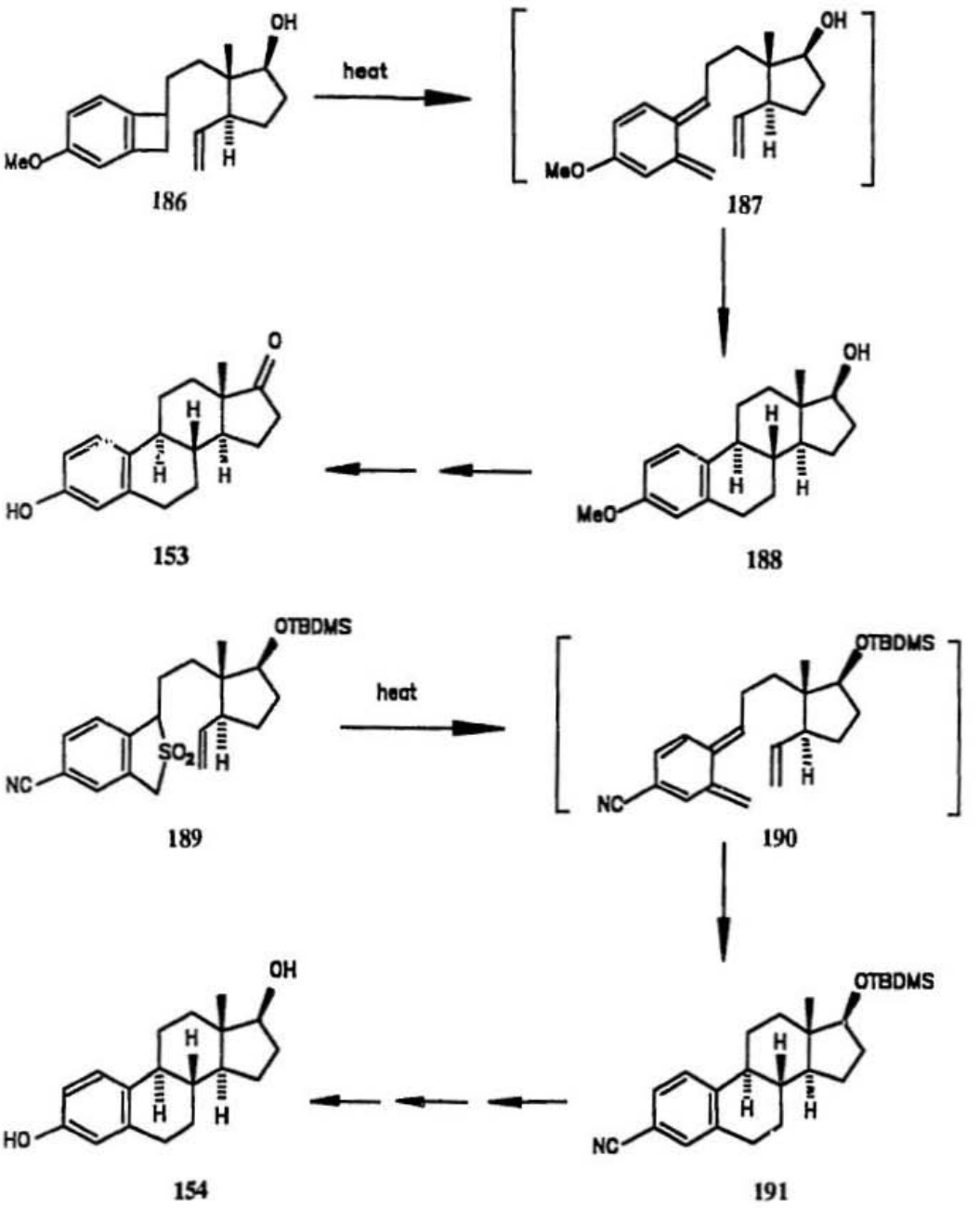
Scheme 37



In Grieco's synthesis[72] of estrone (Scheme 38), thermolysis of benzocyclobutene **186** and trapping of the intermediate *ortho*-xylylene **187** with the internal dienophile generated the trans-anti-trans steroid **188** in high yield. The *ortho*-xylylene can also be derived thermally by means of cheletropic elimination of sulfur dioxide, and this methodology was successfully applied in Oppolzer's[73] synthesis of estradiol (**154**) (Scheme 38). Thus, thermolysis of **189** in refluxing 1,2,4-trichlorobenzene proceeded cleanly *via* **190** to give an 80% yield of *trans-anti-trans* 3-cyanoestratriene **191**.

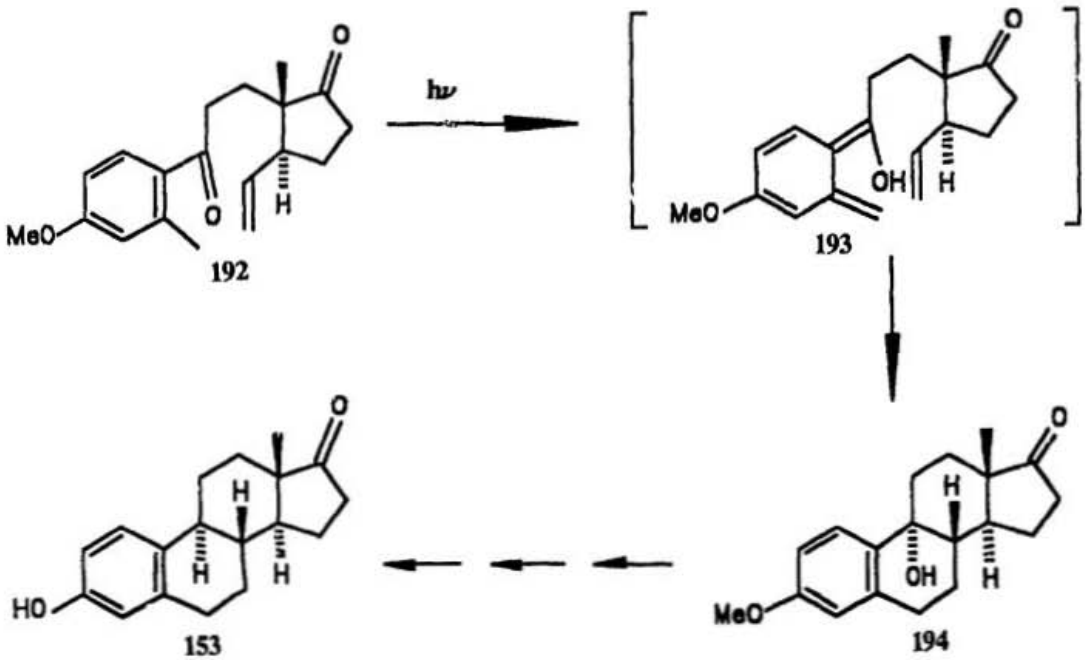
Photolysis of *ortho*-toluyl ketones can result in hydroxy *ortho*-xylylene, which can be trapped with internal dienophiles. Based on this concept, Quinkert and

Scheme 38



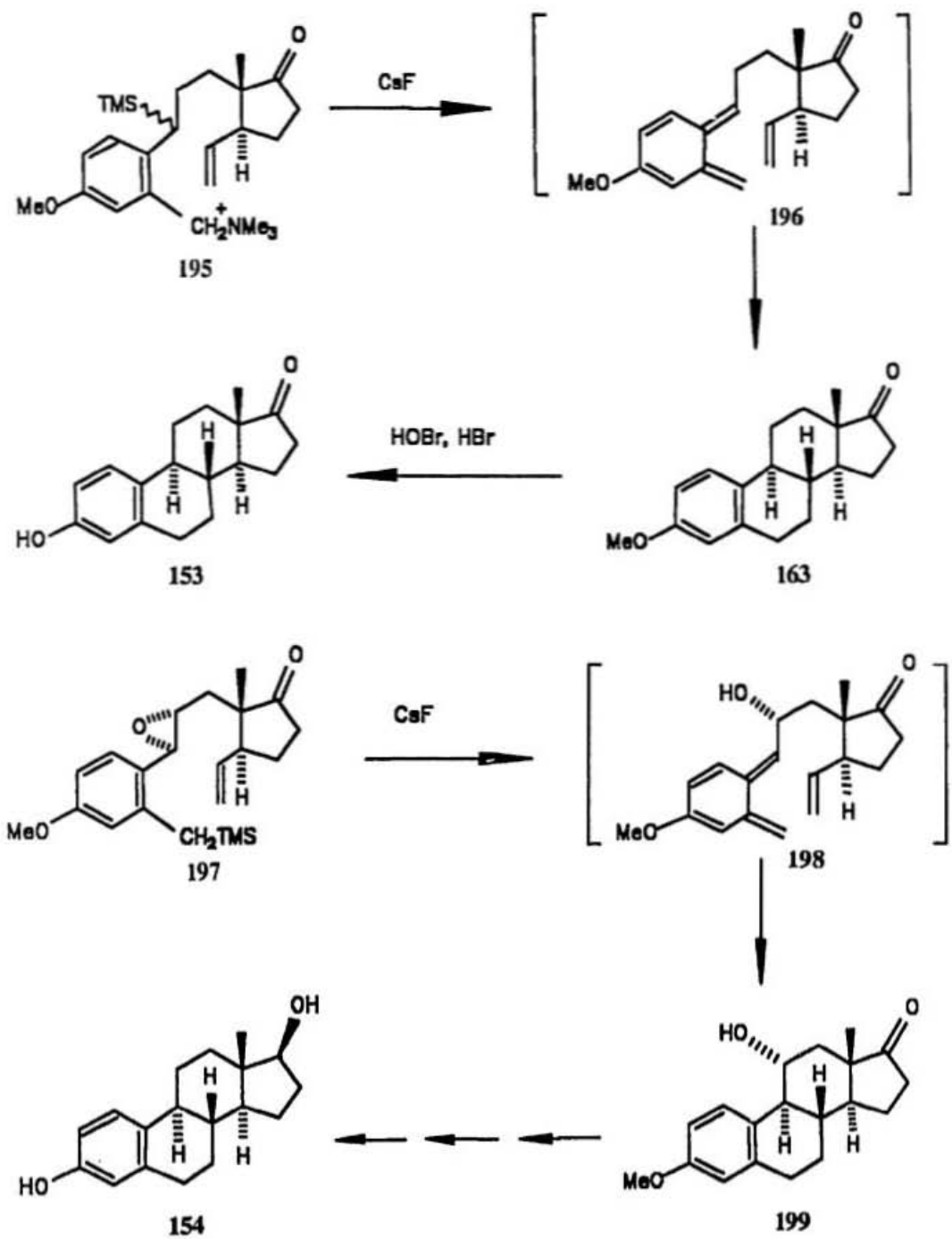
coworkers[74] devised the synthesis of estrone shown in Scheme 39. Thus, compound **192** was exposed to long wavelength UV light at 98°C in methylphenol to furnish **194** and a small amount of the 9β-hydroxy isomer.

Scheme 39



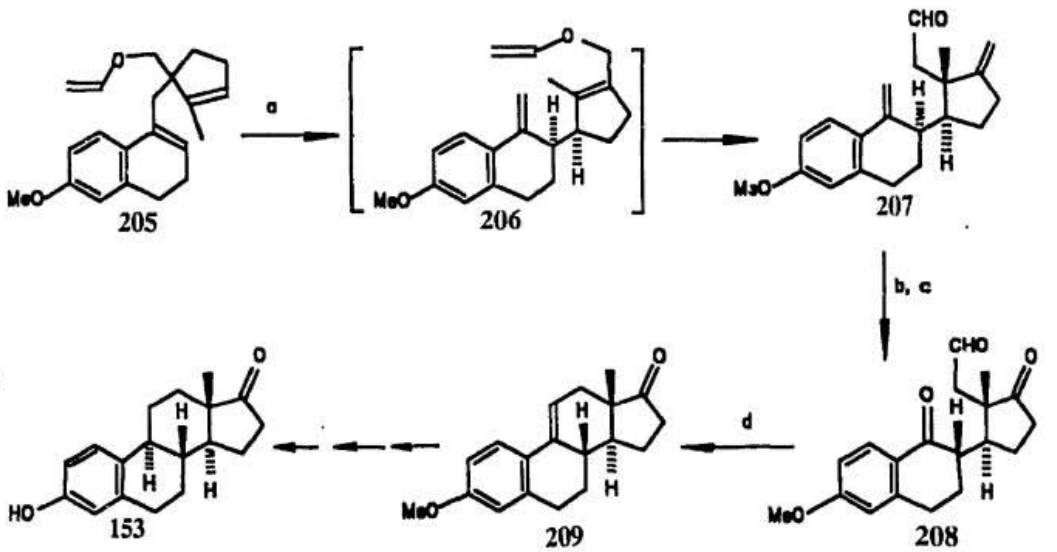
Saegusa and coworkers[75a] developed a synthesis of (±)-estrone involving the *ortho*-xylylene **196**, which was generated by fluoride ion desilylation of *ortho*-(α-trimethylsilylalkyl)benzyltrimethyl ammonium salt **195** (Scheme 40). The reaction was carried out in acetonitrile under reflux for 1.5 hours, and (±)-estrone methyl ether (**163**) (containing 7-8% of the C-9 β-H isomer) was isolated in 86% yield. A similar strategy was employed in Magnus'[75b] approach. Compound **197** was treated with cesium fluoride in diglyme at 27°C for 20 hours leading, *via ortho*-xylylene **198**, to (±)-11α-hydroxyestrone methyl ether (**199**) in 70% yield. The mild conditions

Scheme 40


TMS
MeO
$CH_2NMe_3^+$
195
CsF
MeO
196
HOBr, HBr
HO
153
MeO
163
O
CH_2TMS
197
CsF
HO
MeO
198
HO
MeO
199
OH
HO
154

based on a chair–like transition state, and compound **207** was the major stereoisomer because the bulky dihydronaphthalene group directed the bond formation during the second Claisen rearrangement process. Ozonolysis of aldehyde **207** and epimerization of the resulting tricarbonyl compound with sodium methoxide in methanol furnished a 69% yield of the diketone aldehyde **208**, which was converted into the tetracyclic compound **209** in 56% yield *via* the McMurry coupling reaction.

Scheme 42



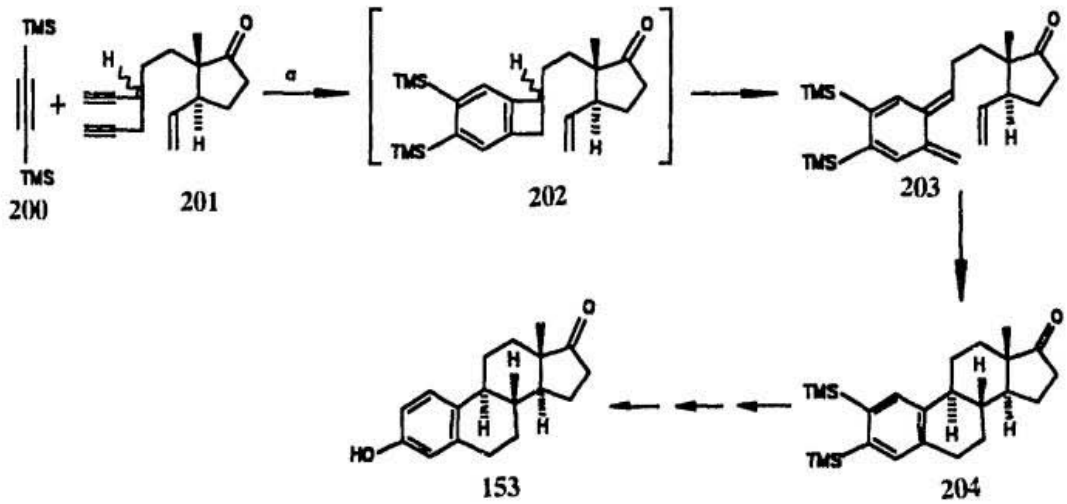
(a) heat; (b) O_3; (c) NaOMe, MeOH; (d) $TiCl_3$, Zn–Ag.

Most recently, Mikami and coworkers[77] designed a novel asymmetric synthesis of (–)–estrone involving tandem Claisen–ene reactions (Scheme 43). Thus, a toluene solution of **211** and cyclic enol ether **210** in the presence of 2,6–dimethylphenol (10% mol) was heated in a sealed tube at 180°C for 60 hours. The reaction proceeded *via* the intermediate **212** to provide, after acidic treatment, **215** in 76% yield. Like in Ziegler's case, the stereochemistry of the first Claisen rearrangement can be inter-

for the cycloadditions in both cases were particularly noteworthy.

Vollhardt *et al.*[76] reported a novel synthesis of estrone based on the co-oligomerization of a α,ω-diacetylene and a monoacetylene in the presence of a cyclopentadienylcobalt dicarbonyl catalyst (Scheme 41). Co-oligomerization of **200** with bistrimethylsilylacetylene (**201**) in the presence of five mol percent of $CpCo(CO)_2$ catalyst proceeded *via* **202** and **203** to yield in a chemo-, regio-, and stereospecific manner the steroid **204** in 71% yield. It was particularly noteworthy that the A, B and C rings were constructed in one operation (i.e. D → ABCD). The bis-silylated estrotrienone **204** was converted into estrone in three steps.

Scheme 41

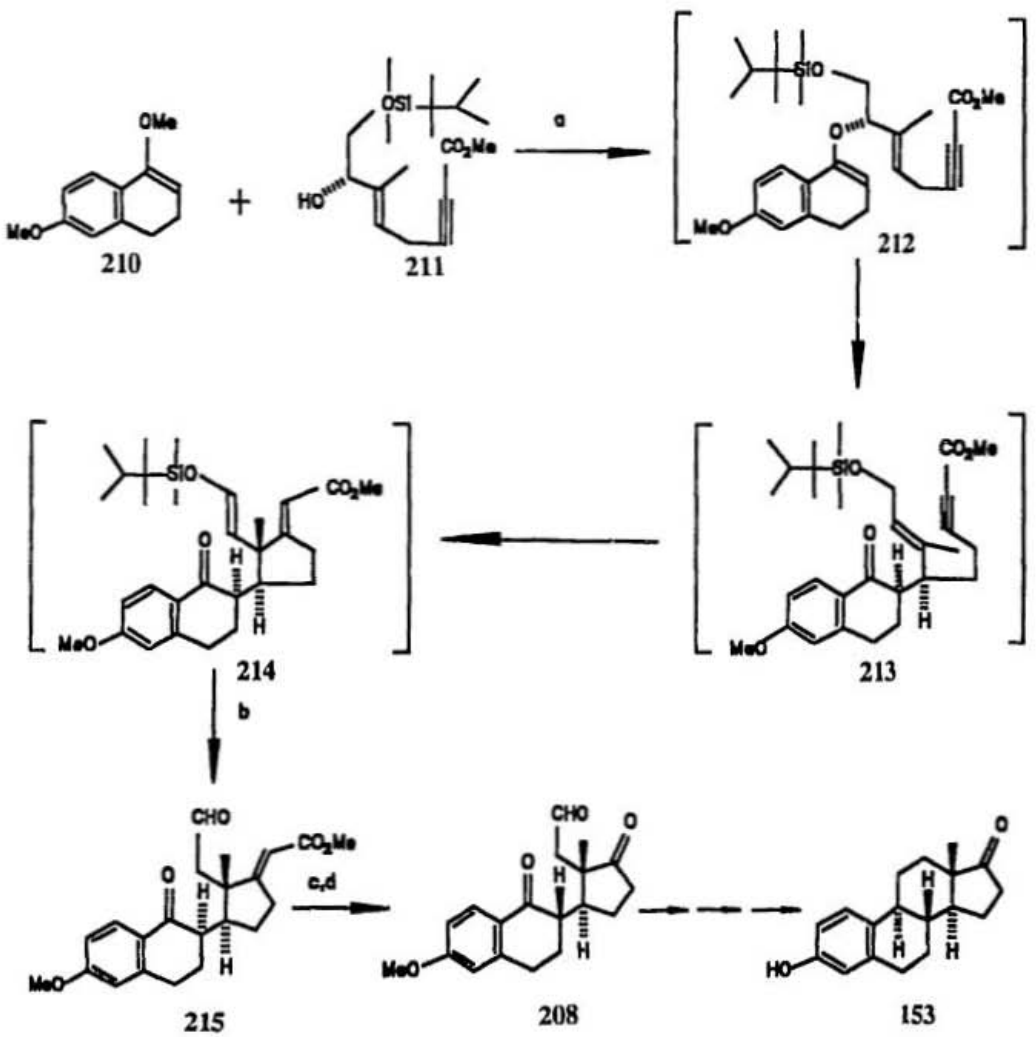


(a) $CpCo(CO)_2$, 140 °C.

Ziegler and Lim[55] applied the tandem Cope-Claisen rearrangements to the synthesis of (±)-estrone (Scheme 42). Compound **205** on thermolysis underwent the tandem rearrangement **205** → **206** → **207** to result in aldehyde **207** in 35% yield. The stereochemical outcome of the first Cope rearrangement can be easily rationalized

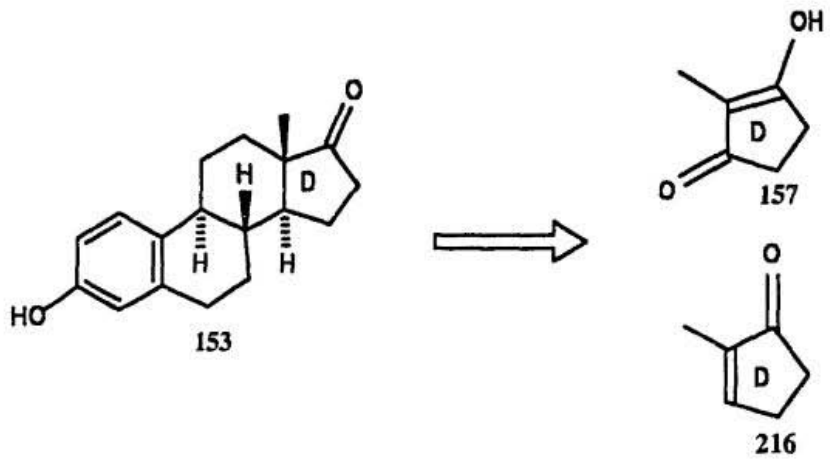
preted by assuming a chair–like transition state, and the formation of compound **214** was attributed to the bulky dihydronaphthalene group, which directed the bond formation during the second ene reaction process. The transformation of the hydrolyzed tandem product **215** to (+)–estrone was accomplished by following Ziegler's procedure.

Scheme 43



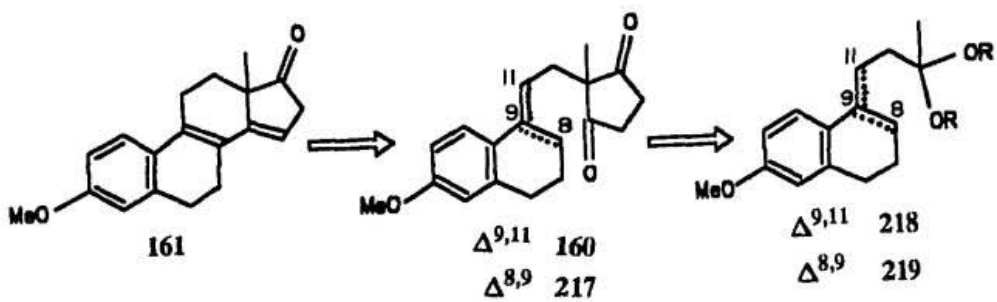
(a) heat; (b) HCl, THF; (c) O_3; (d) NaOMe, MeOH.

Scheme 44



The synthetic approaches described above are only a few among many. After an examination of a number of syntheses of estrone, we realized that the D ring of the steroid was derived in many cases from either 2-methylcyclopentane-1,3-dione (**157**) or 2-methyl-2-cyclopenten-1-one (**216**) (Scheme 44). We felt that the geminal acylation reaction could provide a general approach to the D ring of the steroid. Our synthesis was based on the retrosynthetic analysis as shown in Scheme 45. The estrapentaene **161**, the key intermediate of the Torgov route, could be prepared

Scheme 45

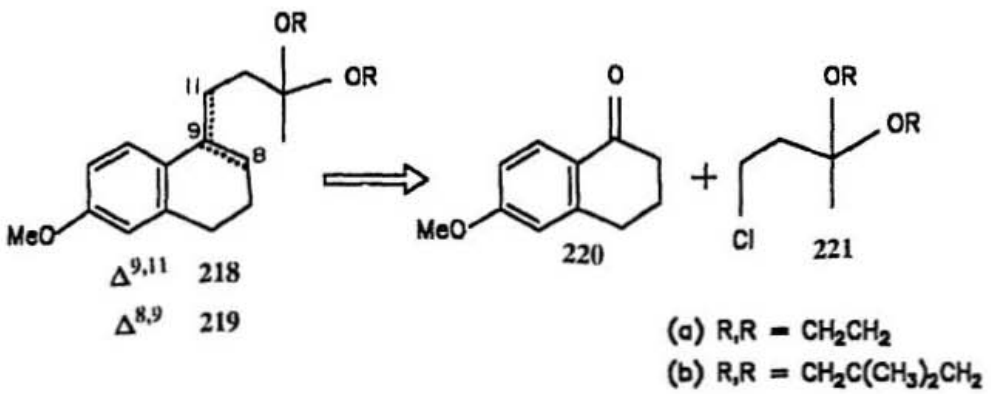


from the tricyclic diketone **160** or **217**. It was hoped that the Lewis acid–catalyzed reaction of either ketal **218** or **219** with **109** following our general one–pot procedure could provide the diketone **160** and/or **217**. The following section describes our detailed study of this synthetic approach.[78]

II. Results and Discussion

We envisioned that the cyclic ketal **218** (or **219**) could be obtained by the addition of chloro-ketal **221a/b** to 6-methoxy-1-tetralone (**220**) (Scheme 46), and we were confident that the chloro-ketal **221a/b** in turn should be available from 4-chlorobutanone.

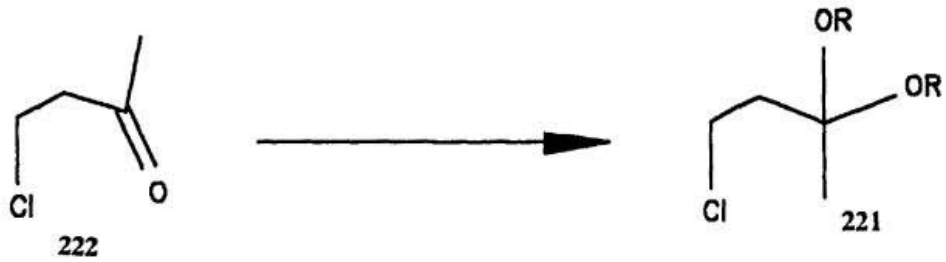
Scheme 46



Indeed, the ketalization of 4-chlorobutanone (**222**) with ethylene glycol in the presence of PPTS in benzene under reflux gave, after vacuum distillation, a mixture of the desired ketal **221a** along with small amount of the starting ketone and a considerable amount of some unidentified material. The ^{1}H NMR spectrum (60 MHz) of **221a** showed a singlet at δ 3.85 for the four methylene protons of the dioxolane system and a singlet at δ 1.25 for the methyl group. The methyl group of the starting material resonated at δ 2.10 ppm. Our attempts to remove the unknown impurities and small amount of starting material by fractional distillation as well as column chromatography were unsuccessful. When 2,2-dimethyl-1,3-propanediol was utilized, a similar result was obtained except that the small amount of starting material was easily

removed during the fractional distillation process.

Scheme 47

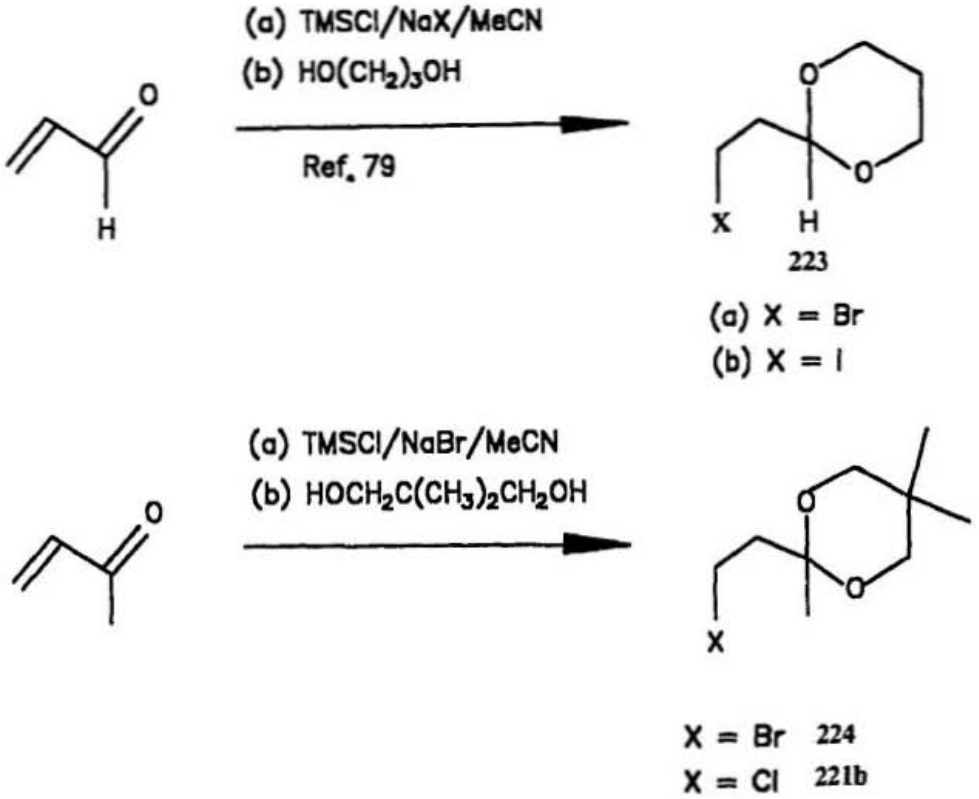


222 221

(a) R,R = CH_2CH_2
(b) R,R = $CH_2C(CH_3)_2CH_2$

Faced with the difficulty of purifying the chloroketal **221a/b**, we turned to an alternative preparation. Larson and coworkers[79] developed a convenient procedure for the synthesis of 2-(2-haloethyl)-1,3-dioxane **223a/b** in a one-pot, two-step reaction as shown in Scheme 48. Considering the fact that the iodo-ketal cannot be stored for as long as the bromo-ketal, and that the ketal derived from 2,2-dimethyl-1,3-propanediol **221b** can be more easily purified than the corresponding ketal derived from ethylene glycol **221a**, we decided to use 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane (**224**) for our synthesis. Thus, following the procedure of Larson *et al.*, a mixture of 3-buten-2-one, sodium bromide and chlorotrimethylsilane in acetonitrile was stirred overnight at room temperature. After addition of 2,2-dimethyl-1,3-propanediol, the mixture was stirred for another five hours. The colorless product was obtained in 58% yield after vacuum distillation. Although the boiling point of this product seemed to be quite constant, GC-MS analysis showed that it was a mixture of two compounds in a ratio of 77 : 23. The major component showed the base peaks at *m/z* 223 and 221 (M^+ – Me), indicating that it was the

Scheme 48



expected bromoketal **224**. The minor component showed the base peaks at *m/z* 179 and 177 (M^+ – Me), which corresponded to the chloro–ketal **221b**. In fact, the mass spectrum of the minor product was identical with that of **221b** prepared from 4–chlorobutanone (see Scheme 47). Accordingly, the two halogen–bearing methylenes of **224** and **221b** were found as multiplets at δ 3.525 and δ 3.685, respectively, in the ^{1}H NMR spectrum of the mixture. In addition, the ^{13}C NMR spectrum showed signals at δ 98.4 and 97.8 for the ketal carbons of the bromo– and chloro–derivatives. It was interesting to note that the 2–(2–bromoethyl)–1,3–dioxane (**223a**), prepared by Larson *et al.*,[79] was also contaminated with 40% of some impurity which they claimed could not be removed by column chromatography on silica gel. We can suggest that their unidentified impurity was also the corresponding chloro–ketal. Clearly, the

chloride was derived from the chlorotrimethylsilane. Since both the chloro- and bromo-ketals could be used for our synthesis, it was unnecessary to attempt to separate those compounds. The mixture of ketals **224/221b** was prepared in multigram quantities, and it could be stored in a freezer for several months without much decomposition.

Next, the addition of the ketals **224/221b** to 6-methoxy-1-tetralone (**220**) was investigated (Scheme 49). Our initial plan was to make an organometallic derivative of the ketals **225** and then to add it to **220**. Thus, the mixture of ketals were allowed to react with magnesium turnings or lithium slices in refluxing tetrahydrofuran. The reactions were found to be extremely slow even with ultrasonic irradiation. We turned to a modified Barbier reaction with ultrasonic irradiation reported by Luche and Damiano.[80] To a tetrahydrofuran solution of a lithium-sodium alloy were added the tetralone **220** and an excess of the ketals **224/221b**, and the mixture was irradiated in the water bath of an ultrasonic laboratory cleaner. The products we obtained after chromatography on silica gel were the desired alcohol-ketal **226** in a yield of 76%, and small amount of the diketal **227** (derived from the Wurtz coupling of **224/221b**), and 19% of the starting material tetralone **220** was recovered. Several attempts to improve the yield of **226** by increasing the proportions of the lithium-sodium alloy and the ketals **224/221b** met with little success. The IR spectrum of the alcohol-ketal **226** showed an absorption maximum for the hydroxyl group at 3460 cm^{-1}. In the ^{13}C NMR spectrum, C-9* appeared at δ 71.4. The structure of the side product **227** was derived mainly from the mass spectrum and the following ^{13}C NMR data. The spectrum showed eight resonances: two quarternary carbons (δ 98.9 and 29.9), of which the former was a ketal carbon, three methyl groups (δ 20.4, 22.5, and 22.7), and three methylenes (37.7, 23.6, and 70.2), of which the last one was attached to oxygen.

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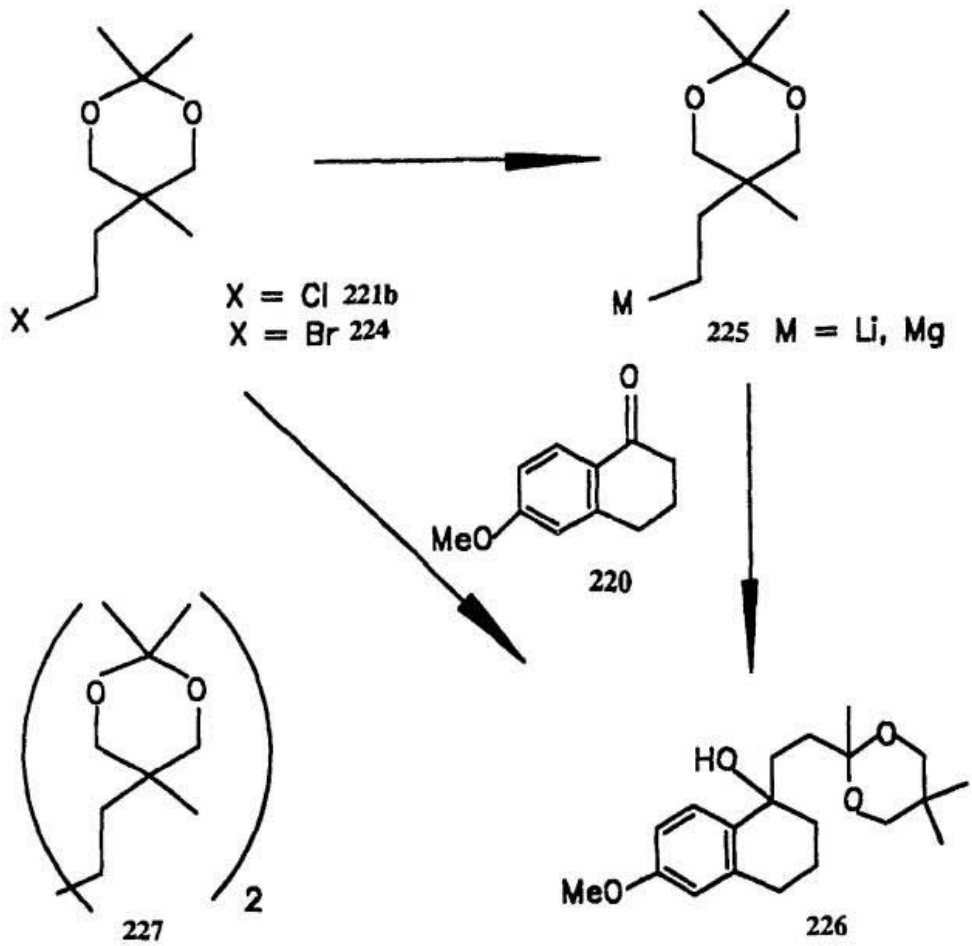
* Carbons are identified by steroid numbering.

Scheme 49



As we had anticipated, the ketal-alcohol **226** underwent dehydration very easily. In fact, when this compound was stored at room temperature for one week, we were left with a mixture that included 30% of the unsaturated compound **219b**, 2% of the unsaturated ketone **228**, along with 64% of the tertiary alcohol **226** (Scheme 50). These were separated by column chromatography on silica gel. Surprisingly, none of the alternative unsaturated ketal **218b** appeared to be formed during the dehydration. The IR spectrum of **219b** showed absorption maxima for the aromatic ring as well as

the 9,10-double bond, at 1610, 1500, and 1255 cm^{-1}. The proton on C-8 was found as a triplet at δ 5.759 in the ^1H NMR spectrum. In addition, the olefinic carbons showed resonances at δ 122.0 and 128.1. The position of the double bond was unambiguously established by a COSY spectrum with the assistance of ^{13}C NMR, APT, and $^{13}C-^1H$ correlation spectra. If the dehydration product were **218b**, then the allylic protons on C-12 should be vicinally coupled only with the olefinic proton on C-11. On the other hand, if the product were **219b**, then the allylic methylene (C-7) should be vicinally coupled to both the olefinic proton and to another methylene (C-6). The COSY spectrum (Figure 5) indicated the latter situation. The IR spectrum of the unsaturated methyl ketone **228** showed an absorption maximum for a carbonyl at 1715 cm^{-1}, and the methyl adjacent to the ketone was observed as a singlet at δ 2.140 in its ^1H NMR spectrum. Compound **219b** was produced in 96% yield by heating a benzene solution of **226** at reflux with 2,2-dimethyl-1,3-propanediol in the presence of small amount of PPTS.

Scheme 50

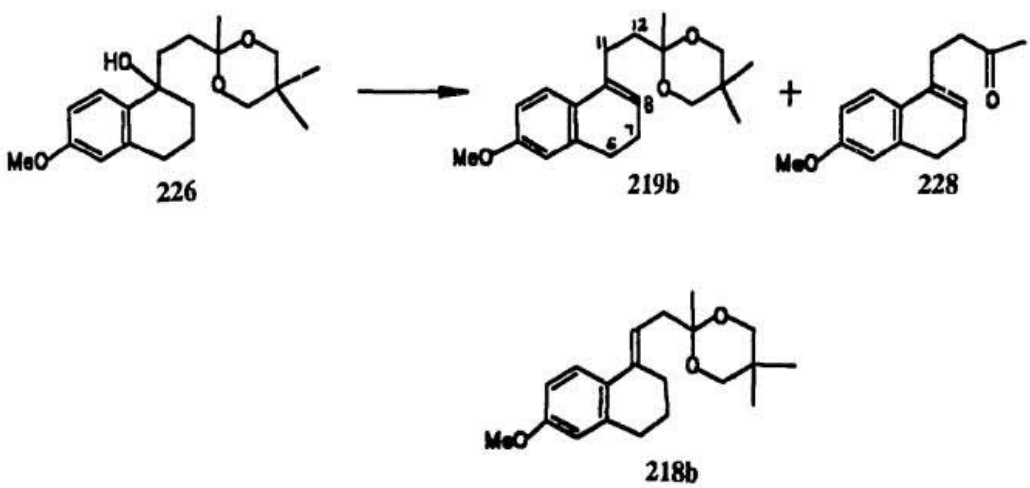
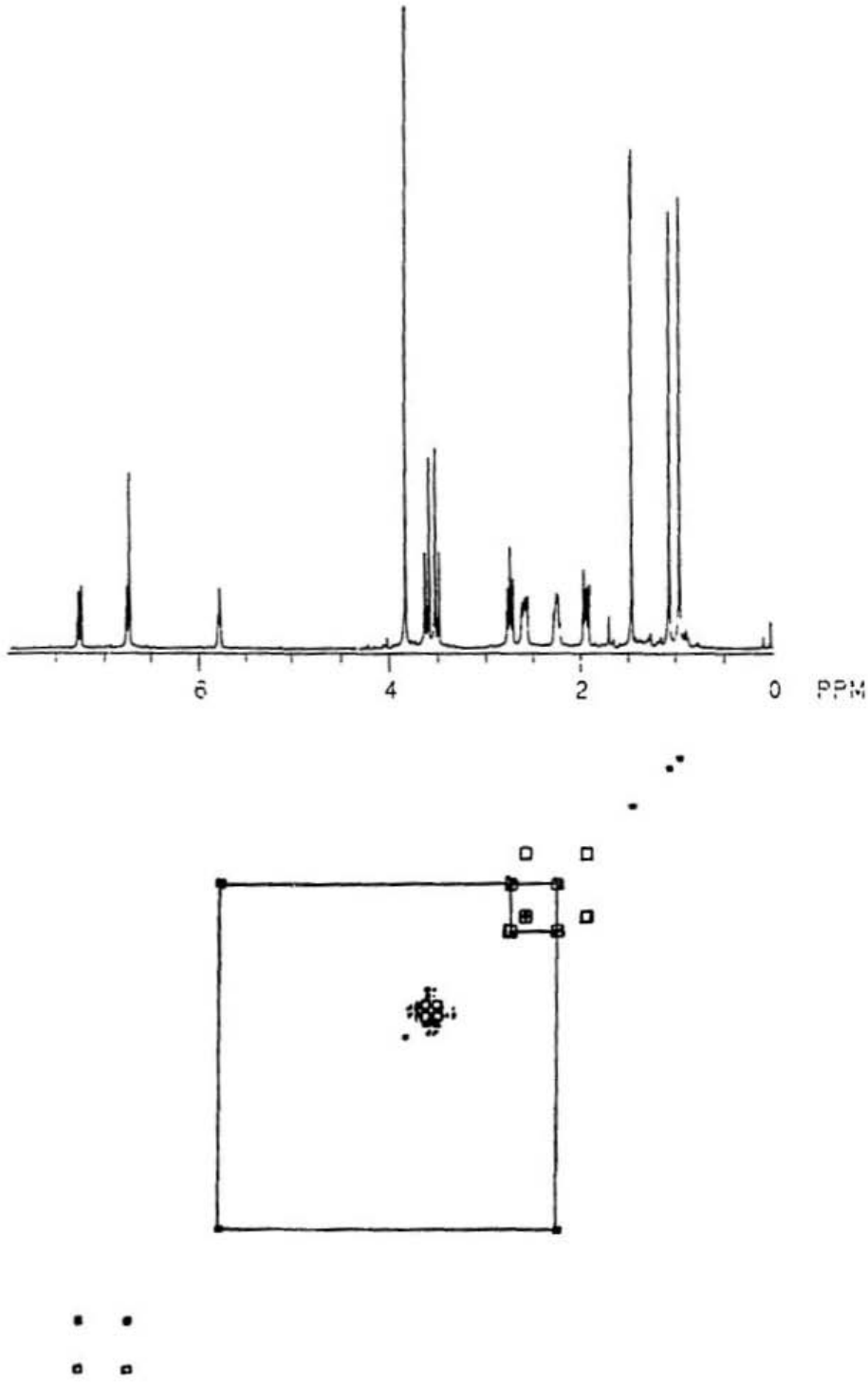


Figure 5. COSY – 90 spectrum of the unsaturated ketal **219b**



With the alcohol–ketal **226** and unsaturated ketal **219b** in hand, the stage was set for the crucial geminal acylation reaction as in Scheme 51. Since the cyclization of the C ring (i.e. **217** → **161**) is normally acid–catalyzed, we expected that the conversion of **226** (or **219b**) to **161** could be achieved in one–pot by treatment with 1,2–bis(trimethylsiloxy)cyclobutene (**109**) and $BF_3{\cdot}Et_2O$, followed by addition of a protic acid. Thus, compound **219b** was exposed to four equivalents of **109** and fifteen equivalents of $BF_3{\cdot}Et_2O$ at -78°C following our general procedure. GC–MS analysis revealed that the crude product consisted of 83% of **217**, whose mass spectrum showed a strong molecular ion at *m/z* 298. By GC–MS and by TLC, not even a trace of estrapentaene **161** was detected in the reaction mixture. The C ring closure was not accomplished by involving an even longer reaction period or by addition of more $BF_3{\cdot}Et_2O$. However, when trifluoroacetic acid (TFA) was added to a solution of crude **217** at room temperature, aqueous work–up provided a 91% yield of crude **161** as a pale brown powder. This crude product was proved to be very nearly pure by GC–MS analysis. Flash chromatography on silica gel gave only a 44% yield of very pure estrapentaene **161** as colorless crystals, whose melting point was 110–110.5°C. The melting point was not changed on admixture with an authentic sample kindly provided by Dr. Ž. Stojanac* of the University of New Brunswick, and our melting point was in good agreement with the literature.[65] The IR spectrum of **161** showed an absorption maximum characteristic of a five–membered ring (D ring) ketone at 1740 cm^{-1}. The C–18 methyl group appeared as singlet at δ 1.132 and the proton on C–15 as a broad triplet at δ 5.833 in the ^1H NMR spectrum. All spectroscopic data of our **161** were in full agreement with those of the authentic sample. The same result was obtained when the alcohol–ketal **226** was directly subjected to the geminal acylation reaction followed by

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* We are very grateful to Dr. Ž. Stojanac for kindly providing the samples of 3-methoxyestra-1,3,5,8,14-pentaen-17-one (**161**) and 3-methoxyestra-1,3,5,8-tetraen-17-one (**162**).

addition of TFA. We feared that the relatively low isolated yield of **161** (44%) arose from the destruction of **161** on silica gel during flash chromatography; the crude yield had been high (91%). This was confirmed in two ways. We repeated the reaction in the presence of an internal reference compound* (anthracene), and we converted the crude product **161** into **162** by catalytic hydrogenation over $Pd-CaCO_3$ before purification (Scheme 51). Column chromatography of the crude hydrogenated material provided a 70% yield of **162**, whose melting point (117–118°C) was identical with that of an authentic sample provided by Dr. Z. Stojanac. (The mixed melting point with an authentic sample was also unchanged.) Furthermore, the spectra of our compound were in full agreement with those of an authentic sample.

In summary, the estrapentaene **161** was prepared from 6-methoxy-1-tetralone (**220**) by an efficient two-pot procedure in which the D ring was derived from the

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* The actual chemical yield of **226** to **161** was calculated based on the internal reference anthracene as follows. Here N_P, N_R, and N_S stand for the number of moles of product, reference, and starting materials, respectively, $(n_P/n_R)_{GC-MS}$ is the GC–MS ratio of the product to reference; and K is the conversion constant which could be used to convert the GC–MS ratio to the actual molar ratio of the product to the reference. For a given reaction, N_R, $(n_P/n_R)_{GC-MS}$ is known. Thus, the actual number of moles of the product (N_P) could be calculated from equation (7) if K is known. The measurement of the conversion constant K was carried out by dissolving measured amounts of authentic product (P) and anthracene (R) in CH_2Cl_2 followed by GC–MS analysis. A simple calculation following equation (6) provided a K value of 0.49. When 0.81 mmol of ketal-alcohol **226** (N_S = 0.81) and 0.52 mmol of anthracene (N_R = 0.52) were utilized, $(n_P/n_R)_{GC-MS}$ was found to be 2.64. According to equation (7), the actual molar number of the product N_P was 0.67. Finally the actual yield (83%) was derived from equation (8).

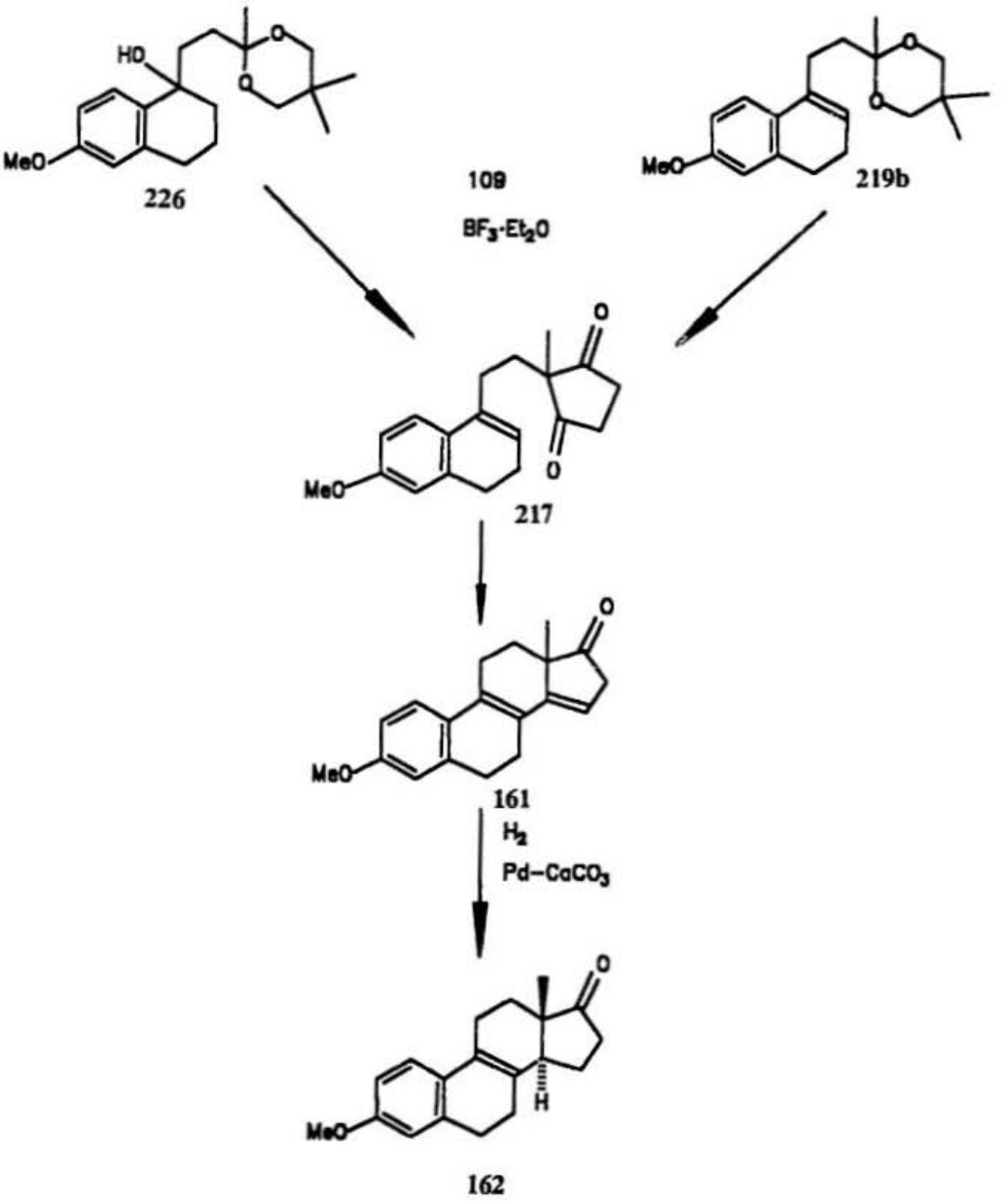
$$\frac{N_P}{N_R} = K\left(\frac{n_P}{n_R}\right)_{GC-MS} \tag{5}$$

$$K = \frac{(N_P/N_R)}{(n_P/n_R)_{GC-MS}} \tag{6}$$

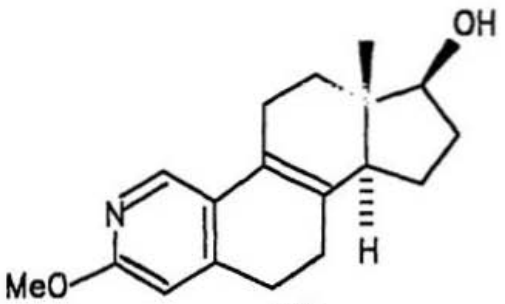
$$N_P = K\left(\frac{n_P}{n_R}\right)_{GC-MS} N_R \tag{7}$$

$$Actual\ Yield = \frac{N_P}{N_S} \times 100\% \tag{8}$$

Scheme 51


HO
MeO
226
109
BF_3·Et_2O
MeO
219b
O
O
MeO
217
O
MeO
161
H_2
Pd–$CaCO_3$
O
H
MeO
162

geminal acylation reaction involving cyclobutene **109**. This strategy may be applicable also to the synthesis of some other steroids such as 2-azaestratriene **229**.[81]



229

III. Experimental*

2-(2-Bromoethyl)-2,5,5-trimethyl-1,3-dioxane (224)

3-Buten-2-one (8.1 mL, 0.10 mol) was added to a stirred suspension of sodium bromide (15.4 g, 0.15 mol) in anhydrous acetonitrile (250 mL) under an atmosphere of dry nitrogen, then chlorotrimethylsilane (19.0 mL, 0.15 mol) was introduced by syringe over a period of 5 min. Stirring was continued at room temperature overnight. 2,2-Dimethyl-1,3-propanediol (15.6 g, 0.15 mol) was added, and the mixture was stirred for a further 4 h. The mixture was poured into a flask containing petroleum ether (300 mL) and 8% aqueous Na_2CO_3 (100 mL) then stirred thoroughly and transferred to a separatory funnel: *three* layers were clearly evident. The lowest (aqueous) layer was removed, and 5% aqueous sodium thiosulfate (100 mL) was added: only two layers were visible. The organic layer was washed with water (×2), saturated NaCl, then dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*, and the residue was distilled under vacuum to provide a mixture of **224** and **221b** (the corresponding chloro compound) (12.2 g, 58%) in a ratio of 77 : 23, respectively (by GC-MS), as a colorless liquid, bp 63-64°C/0.1 Torr: for **224** ^{1}H NMR δ: 0.855 (3H, s) and 1.032 (3H, s) (C-5 methyls), 1.385 (3H, s, C-2 methyl), 2.279 (2H, m, $-CH_2CH_2Br$), 3.406 (2H, d, J = 11.4 Hz, $-CH_2O-$), 3.525 (2H, m, $-CH_2Br$), 3.581 (2H, d, J = 11.4 Hz, $-CH_2O-$); ^{13}C NMR δ: 20.0 (C-2 methyl), 22.4 and 22.8 (C-5 methyls), 27.0 ($-CH_2Br$), 29.8 (C-5), 42.9 ($-CH_2CH_2Br$), 70.4 (2C, C-4 and C-6), 98.4 (C-2); MS (from GC-MS) m/z (%): no M^+, 223 (21, M^+ - Me), 221 (20, M^+ - Me), 153 (11), 151 (10), 137 (11), 135 (10), 129 (71), 107 (10), 69 (44), 56 (43), 55 (15), 43 (100) and 41 (51). For **221b** ^{1}H NMR as for **224** except δ: 1.396 (3H, s, C-2 methyl), 2.190 (2H, m, $-CH_2CH_2Cl$), 3.685 (2H, m, $-CH_2Cl$); ^{13}C NMR as for

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* For General Procedures, see 1.III

224 except δ: 39.5 ($-CH_2Cl$), 42.3 ($-CH_2CH_2Cl$), 97.8 (C-2); MS (from GC-MS) *m/z* (%): no M^+, 179 (10, M^+ - Me), 177 (35, M^+ - Me), 129 (54), 109 (9), 107 (23), 93 (7), 91 (21), 69 (50), 56 (54), 55 (23), 43 (100) and 41 (41).

Alcohol-ketal 226

A flask containing lithium metal (60.5 mg, 8.72 mmol) and sodium metal (4 mg) under vacuum was heated with a heat gun to alloy the metals.* The flask was cooled and an atmosphere of dry nitrogen was introduced. Dry THF (50 mL) was added followed by **220** (227.5 mg, 1.29 mmol) in dry THF (20 mL) and a mixture of **224** and **221b** (1.80 mL, 9.77 mmol). The flask was placed in an ultrasonic cleaning bath (Branson) and irradiated at room temperature for 4 h. After concentration of the mixture *in vacuo*, diethyl ether (30 mL) and saturated aqueous NH_4Cl (30 mL) were added. The aqueous layer was extracted with diethyl ether (×4). The combined organic layers were washed with saturated NaCl (30 mL), dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Flash chromatography of the residue (3% acetone in petroleum ether) provided **226** (326.1 mg, 76%), the recovered **220** (42.0 mg, 19%) and the diketal **227** (30.1 mg). For **226**** IR (film) ν_{max}: 3460 (broad) and 1610 cm^{-1}; ^1H NMR δ: 0.887 (3H, s) and 1.026 (3H, s) (dioxane's C-5 methyls), 1.371 (3H, s, C-18H_3), 1.6-2.05 (8H, br m), 2.20 (1H, s, -OH, disappears with D_2O shake), 2.75 (2H, m, C-6H_2), 3.433 (2H, d, J = 11.5 Hz, $-CH_2O-$), 3.559 (2H, d, J = 11.5 Hz, $-CH_2O-$), 3.780 (3H, s, $-OCH_3$), 6.590 (1H, d, J = 2.5 Hz, C-4H), 6.775 (1H, dd, J = 2.5, 8.7 Hz, C-2H), 7.482 (1H, d, J = 8.7 Hz, C-1H); ^{13}C NMR δ: 19.7 (C-7), 20.4 (C-18), 22.4 and 22.7 (dioxane's C-5 methyls), 29.7 (dioxane's C-5), 30.1 (C-6), 32.4, 35.6 and 35.9 (C-8, C-11 and C-12), 55.0 ($-OCH_3$), 70.1 (2C, $-CH_2O-$),

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* We thank Dr. Gervais Bérubé for showing us the preparation of the Na-Li alloy.

** Carbons are identified by steroid numbering.

71.4 (C−9), 98.8 (C−13), 112.4 (C−2), 112.8 (C−4), 127.6 (C−1), 134.8 and 138.0 (C−5 and C−10), 158.1 (C−3); MS *m/z* (%): no M^+, 316 (5, $M^+ - H_2O$), 175 (13), 174 (68), 172 (17), 129 (14), 85 (65), and 83 (100). For **227**: mp 69−70°C; ^1H NMR δ: 0.906 (6H, s) and 0.999 (6H, s) (dioxanes' C−5 methyls), 1.353 (6H, s, dioxanes' C−2 methyls), 1.422 (4H, m) and 1.711 (4H, m) (methylenes), 3.444 (4H, d, J = 11.3 Hz) and 3.530 (4H, d, J = 11.3 Hz) ($-CH_2O-$ signals); ^{13}C NMR δ: 20.4 (dioxanes' C−2 methyls), 22.5 and 22.7 (dioxanes' C−5 methyls), 23.6 (methylenes β to dioxanes), 29.9 (dioxanes' C−5's), 37.7 (methylenes α to dioxanes), 70.2 ($-CH_2O-$), 98.9 (dioxanes' C−2's); MS *m/z* (%): no M^+, 299 (17, $M^+ - 15$), 213 (7), 129 (100), 125 (27), 84 (16), 81 (29), 71 (19), 69 (77), 56 (31), 43 (100) and 41 (57).

Unsaturated ketal 219b

Approximately 8 mg of PPTS was added to a solution of **226** (105.6 mg, 0.32 mmol) and 2,2−dimethyl−1,3−propanediol (99 mg, 0.95 mmol) in benzene. After heating at reflux with a Barrett water−separator overnight the solvent was evaporated, and the residue was purified by flash chromatography (2% acetone in petroleum ether) to provide pure **219b** (95.4 mg, 96%), which crystallized in the freezer, mp 46−47°C; IR (film) ν_{max}: 1610, 1500 and 1255 cm^{-1}; ^1H NMR δ: 0.920 (3H, s) and 1.029 (3H, s) (dioxane's C−5 methyls), 1.909 (2H, m, C−12H_2), 2.218 (2H, m, C−7H_2), 2.557 (2H, m, C−11H_2), 2.707 (2H, t, J = 7.9 Hz, C−6H_2), 3.473 (2H, d, J = 11.3 Hz, $-CH_2O-$), 3.573 (2H, d, J = 11.3 Hz, $-CH_2O-$), 3.793 (3H, s, $-OCH_3$), 5.759 (1H, t, J = 4.5 Hz, C−8H), 6.708 (1H, apparent s, C−4H), 6.723 (1H, partially overlapped, C−2H), and 7.223 (1H, distorted d, C−1H); ^{13}C NMR δ: 20.7 (C−18), 22.5 and 22.8 (dioxane's C−5 methyls), 23.0 (C−7), 26.5 (C−11), 28.9 (C−6), 29.9 (dioxane's C−5), 36.9 (C−12), 55.2 ($-OCH_3$), 70.4 (2C, $-CH_2O-$), 98.9 (C−13), 110.8 and 113.7 (C−2 and C−4), 122.0 (C−8), 123.8 (C−1), 128.1 (C−9), 136.0 and 138.5 (C−5 and C−10), 158.2 (C−3); MS *m/z* (%): 316 (5, M^+), 301 (3),

230 (5), 199 (5), 187 (17), 174 (82), 172 (29), 129 (81), 83 (20), 69 (55) and 43 (100). When this procedure was carried out for 3 hours in the absence of the diol, flash chromatography provided **219b** (81%) and **228** (6%): IR (film) ν_{max}: 1715, 1610, 1500 and 1255 cm^{-1}; ^1H NMR δ: 2.140 (3H, s, C−18$\mathbf{H_3}$), 2.16−2.25 (2H) and 2.62−2.73 (6H) (methylenes), 3.790 (3H, s, −OC$\mathbf{H_3}$), 5.719 (1H, t, J = 4.5 Hz, C−8H), 6.71 (2H, m, C−2H and C−4H), and 7.129 (1H, apparent d, J = 8.7 Hz, C−1H); ^{13}C NMR δ: 23.0, 26.7, 28.8, 30.1, 42.6, 55.2, 110.8, 113.9, 122.8, 123.5, 127.4, 134.8, 138.6, 158.4, and 208.6; MS m/z (%): 230 (8, M^+), 187 (8), 172 (22), 125 (12), 111 (17), 107 (10), 97 (13), and 43 (100). *Exact Mass*: calcd. for $C_{15}H_{18}O_2$: 230.1306; found: 230.1310.

3−Methoxyestra−1,3,5,8,14−pentaen−17−one (161)

With isolation of pure 161

A solution of **226** (271.2 mg, 0.81 mmol) in anhydrous dichloromethane (30 mL) under an atmosphere of dry nitrogen was cooled to −78°C before $BF_3{\cdot}Et_2O$ (1.50 mL, 12.19 mmol). A solution of **109** (0.86 mL, 3.24 mmol) in dichloromethane (10 mL) was added slowly. The mixture was stirred overnight as it was allowed to reach room temperature. Trifluoroacetic acid (TFA) (3 mL) was added and the mixture was stirred for a further 4 h. Water was added, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic solutions were washed with H_2O (×2), saturated $NaHCO_3$ (×2) and saturated NaCl, then dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **161** (226.8 mg, 91%) as a pale brown powder, mp 106−110°C. Flash chromatography (2% acetone in petroleum ether) provided a very pure fraction (100.4 mg, 44%) as colorless crystals, mp 110−110.5°C (mixed mp 110−110.5°C with similarly purified **161** synthesized by Torgov's method[65]); IR (Nujol) ν_{max}: 1740 and 1610 cm^{-1}; ^1H NMR δ: 1.132 (3H, s, C−18$\mathbf{H_3}$), 1.590 (1H, m) and 2.034 (1H, br dt, J = 3.6, 12.9 Hz) (C−12$\mathbf{H_2}$), 2.300 (1H, m) and 2.55−2.67 (3H, m) (C−7$\mathbf{H_2}$ and C−11$\mathbf{H_2}$), 2.794 (2H, t, J = 7.8 Hz, C−6$\mathbf{H_2}$), 2.926 (1H, dd, J = 2.8, 23.4 Hz) and 3.309

(1H, br d, J = 23.4 Hz) (C−16H_2), 3.804 (3H, s, −OCH_3), 5.853 (1H, br t, $W_{1/2}$ = 6 Hz, C−15H), 6.724 (1H, apparent s, C−4H), 6.739 (1H, partially overlapped, C−2H), and 7.243 (1H, d, J = 8.2 Hz, C−1H); ^{13}C NMR δ: 20.5 (C−18), 22.6 and 22.9 (C−7 and C−11), 27.2 (C−12), 28.3 (C−6), 41.8 (C−16), 48.9 (C−13), 55.1 (−OCH_3), 111.0 and 113.5 (C−2 and C−4), 114.6 (C−15), 124.0 (C−1), 125.2, 128.5, 129.7, 138.0 and 146.8 (olefinic and aromatic), 158.5 (C−3), and 220.0 (C−17); MS m/z (%): 280 (64, M^+), 252 (100), 237 (34), 223 (11), 178 (10), and 165 (16). A chemical yield of 83% was calculated by GC−MS analysis of a reaction involving **226** admixed with anthracene. Reactions starting with **219b** gave **161** in very similar yields. GC−MS analysis of reaction mixtures prior to the addition of TFA showed the mixtures to be composed very predominantly of **217**: MS (from GC−MS) m/z (%): 298 (50, M^+), 280 (8), 241 (18), 240 (17), 228 (100), 227 (52), 171 (23), 165 (22), 153 (23), 141 (22), 128 (26), 115 (30), and 43 (58).

With hydrogenation of crude 161

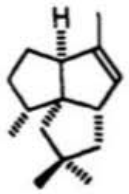
Alcohol−ketal **226** (304.5 mg, 0.9104 mmol) with **109** (0.73 mL) and BF_3·Et_2O (1.68 mL, 13.65 mmol) provided crude **161** after addition of TFA following the procedure above. This was dissolved in toluene (30 mL) and 5% Pd−$CaCO_3$ (90 mg) was added. The reaction was maintained under 1 atmosphere of H_2 until 24 mL of H_2 was taken up. The catalyst was removed and the filtrate was concentrated *in vacuo*. Flash chromatography (2% acetone in petroleum ether) afforded **3−methoxyestra−1,3,5,8−tetraen−17−one (162)** (178.5 mg, 69%) as colorless crystals, mp 117−118°C (lit.[65] 120−121°C), which were identical spectroscopically with material prepared by reduction of the **161** that had been synthesized by Torgov's method,[65] mixed mp 117−118°C.

Chapter 3

THE TOTAL SYNTHESIS OF (±)-PENTALENENE AND (±)-epi-PENTALENENE

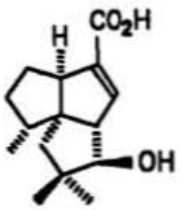
I. Introduction

Pentalenene[82] (**230**), pentalenic acid[83] (**231**), and deoxypentalenic acid glucuron[84] (**232a**) were isolated, together with pentalenolactone[85,86] (**233**), from fermentation broths of several species of *Streptomyces*. This group of angularly fused triquinanes, along with the sesquiterpenes isocomene[87,88] (**234**), silphinene[89,90] (**235**), 5-oxosilphiperfolene[91,92] (**236**), and subergorgic acid[93,94](**237**), the diterpene laurenene[95,96] (**238**) (Nature's only known fenestrane), the unusual sesterterpene retigeranic acid[97,98] (**239**), and crinipellin[99,100] (**240**), contain a tricyclo[6.3.0.$0^{4,8}$]-undecane moiety. Pentalenolactone (**233**) has antibiotic activity against a number of eukaryotic microorganisms as well as antiviral activity.[101,102] Recent studies have revealed that pentalenolactone is a potent and specific inhibitor of glyceraldehyde-3-phosphate dehydrogenase, an important enzyme in the glycolytic pathway.[103] Consistent with the notion that pentalenene (**230**) is the biosynthetic precursor of pentalenic acid (**231**) and pentalenolactone (**233**), labelled pentalenene has been shown to be incorporated into **231** and **233**.[104,105] Pentalenic acid (**231**) was proposed as the potential biosynthetic intermediate between pentalenene (**230**) and pentalenolactone (**233**), but this possibility was ruled out recently by means of other labelling studies.[105] The biosynthesis of **230**, **231** and **233** was put forword by Cane and coworkers[105] based on the extensive investigations outlined in Scheme 52. Thus, farnesyl pyrophosphate (**241**) undergoes initial cyclization leading to humulene (**242**). Reprotonation of **242**



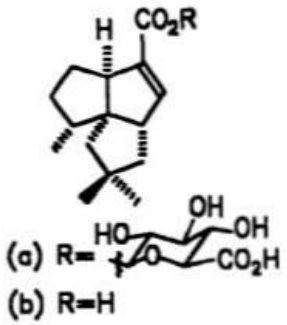
Pentalenene

230



Pentalenic Acid

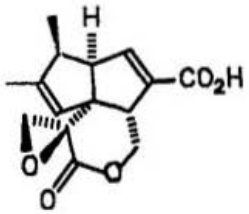
231



(a) R=

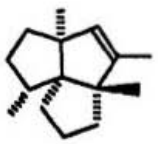
(b) R=H

232



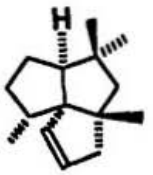
Pentalenolactone

233



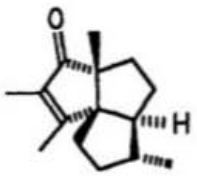
Isocomene

234



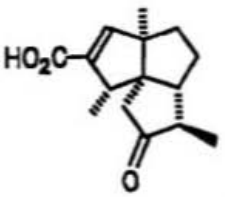
Silphinene

235



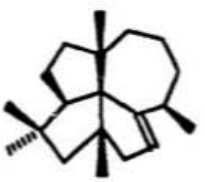
5-Oxosilphiperfolene

236



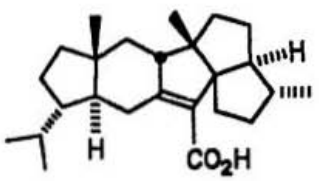
Subergorgic Acid

237



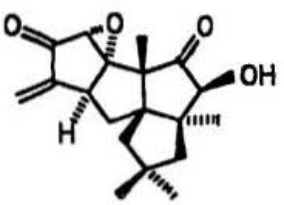
Laurenene

238



Retigeranic Acid

239

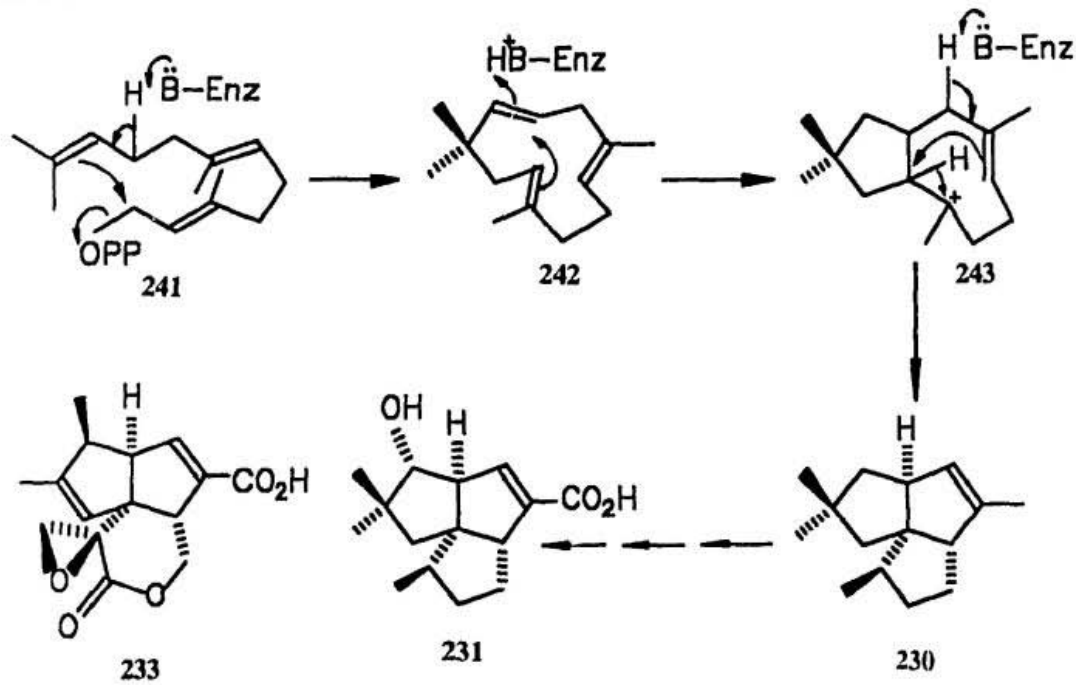


Crinipellin

240

followed by cyclization generates the bicyclic carbocation **243**. The conversion of **243** to pentalenene (**230**) was interpreted in terms of hydride shift, cyclization, and proton loss. Pentalenene (**230**) is biotransformed into **231** and **233** in several oxidative steps.

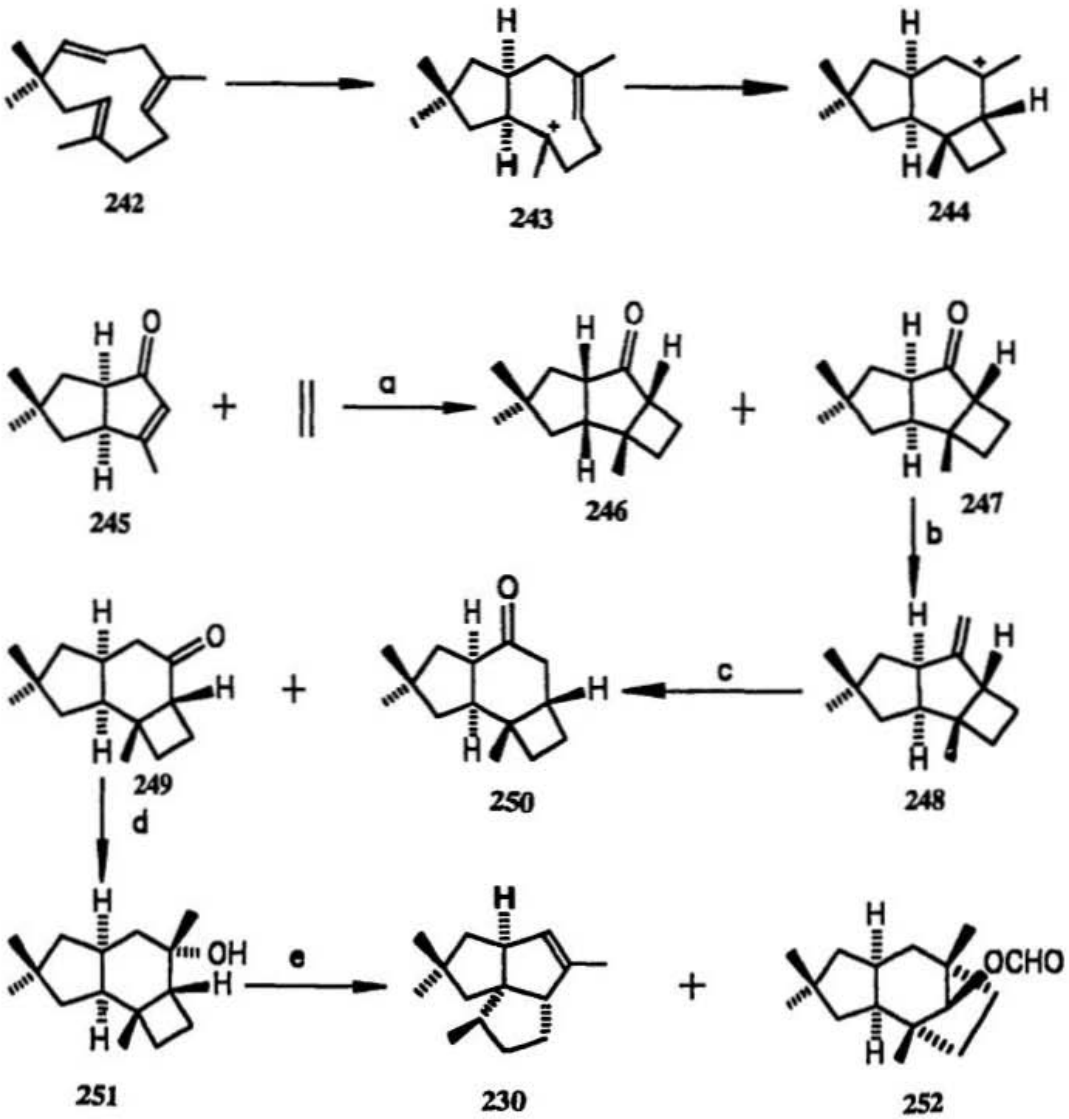
Scheme 52



The total synthesis of these architecturally intriguing molecules has captured the attention of synthetic organic chemists around the world.[106] These molecules are popular targets for the development of new cyclopentane annulation strategies. Additional interest in **230, 231, 232a** has resulted from their interesting biosynthetic origin, the biosynthetic relationship of pentalenene (**230**) to other humulene–derived sesquiterpenes, and the antitumor activity of **232a**.[107]

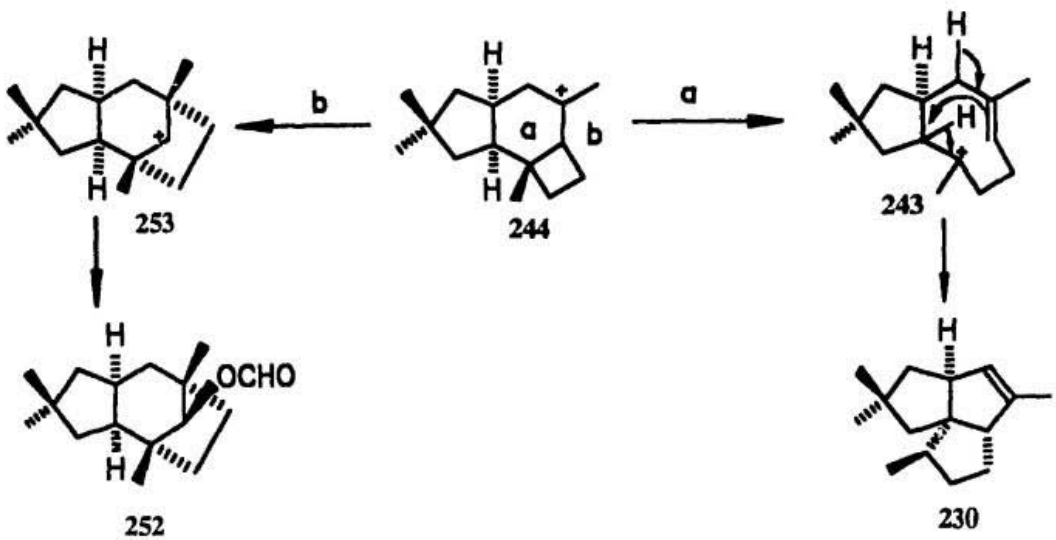
The biosynthetic transformation of humulene (**242**) to the illudoids has long been considered to proceed *via* carbocation **243** to the protoilludyl cation (**244**).[108] In order to mimic this process, Ohfune and coworkers[109] prepared the tertiary alcohol **251**

Scheme 53



(a) hν; (b) $Ph_3P=CH_2$; (c) $Ti(ClO_4)_3$; (d) MeMgBr; (e) HCO_2H.

Scheme 53 continued



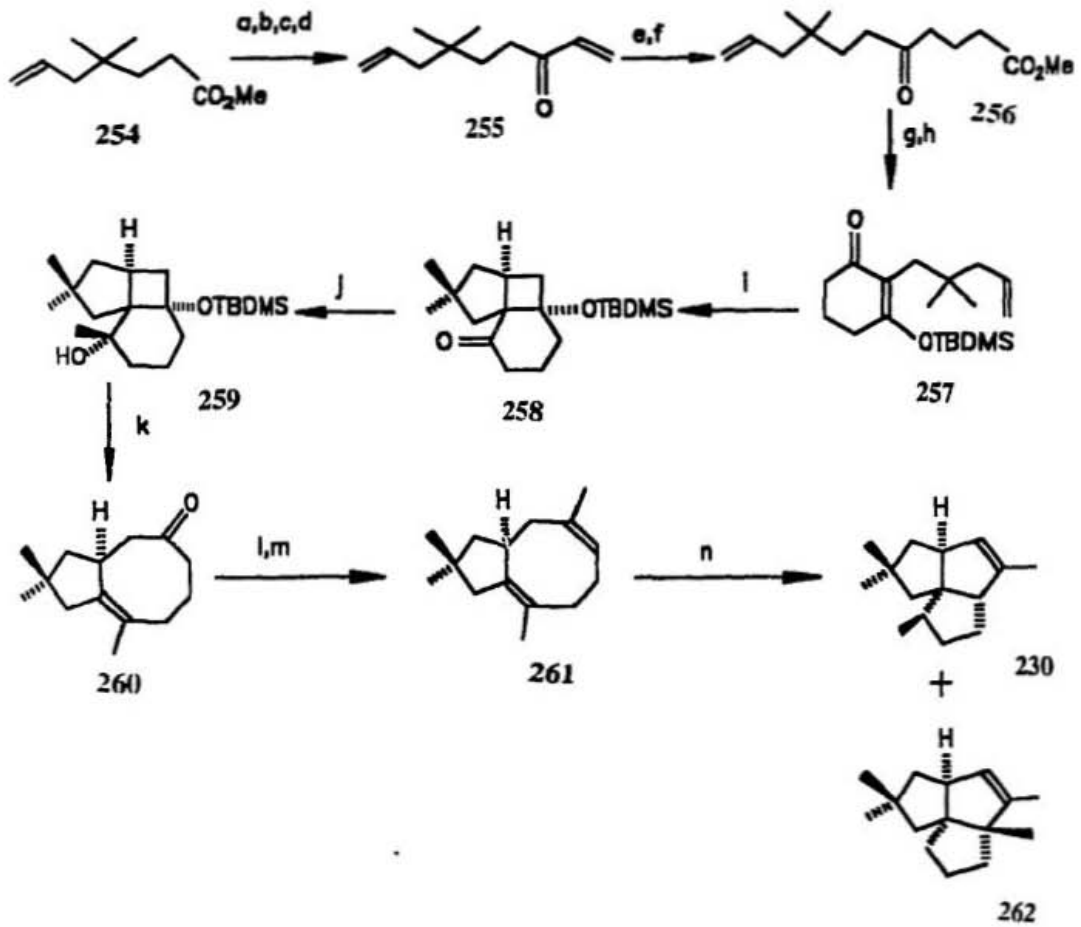
as outlined in Scheme 53. Photochemical cycloaddition of enone **245** with ethylene proceeded stereoselectively to yield the cis-anti-cis cycloadduct **247** (75%) and the cis-syn-cis isomer **246** (8%). After separation, the major isomer **247** was subjected to Wittig reaction to give **248**. Ring enlargement of **248** was achieved by treatment with $Ti(ClO_4)_3$ to provide the desired ketone **249** (57%), accompanied by the isomer **250** (19%). Compound **249** was converted quantitatively into alcohol **251** upon addition of methylmagnesium bromide. The alcohol **251** was heated in formic acid to give a 92% yield of pentalenene (**230**) and the tricyclic bridged formate **252** in a ratio of 3 : 7. This result can be interpreted in terms of the intermediacy of the protoilludyl cation **244**. Wagner-Weerwein shift of **244** (route b) gives cation **253**, which captures formate ion to provide **252**. On the other hand, fragmentation of the central cyclobutane bond in **244** (route a) results in cation **243**, which is converted into pentalenene as described earlier (*vide infra*). It was interesting to note that Ohfune and coworkers achieved the synthesis of pentalenene unintentionally four years before its isolation. This synthesis required five steps from the bicyclic enone **245**; it involved two isomer

separations, and provided pentalenene in 0.11% overall yield. Neither of the key rearrangement reactions (i.e. **248** → **249** and **251** → **230**) was regioselective, thereby impairing greatly the efficiency of the synthesis.

Based on the biosynthetic concept, Pattenden and Mehta independently accomplished the total synthesis of pentalenene and Matsumoto prepared pentalenic acid.

Pattenden's[111] synthesis began with the ester **254**, as outlined in Scheme 54. Reduction of the ester, oxidation of the primary alcohol, and addition of vinylmagnesium bromide to the resulting aldehyde followed by oxidation of the alcohol with manganese(IV) dioxide gave the enone **255** in high yield. Michael addition of malonate anion to **255**, followed by decarboxymethylation of the resulting diester led to the δ-keto-ester **256**. After cyclization under basic conditions, the product, an unstable cyclohexane-1,3-dione, was immediately converted into the corresponding *t*-butyldimethylsilyl enol ether **257**. Compound **257** underwent clean, regioselective photochemical [2 + 2] cycloaddition resulting in **258**, which was converted to the alcohol **259** upon addition with Me_3CuLi_2. The crucial Grob fragmentation was achieved in 73% yield when **259** was treated with hydrofluoric acid. The enone **260** was then converted into the penultimate cycloocta-1,5-diene (**261**), a precursor to pentalenene, following Wittig reaction with methylenetriphenylphosphorane and isomerization of the resulting double bond with rhodium trichloride trihydrate. Finally, treatment of **261** with $BF_3{\cdot}Et_2O$ gave only a 38% yield of pentalenene (**230**), accompanied by a 25-35% yield of the isomeric hydrocarbon **262**. The formation of **230** might proceed through carbocation intermediate **263**, while **262** might arise from the alternative carbocation **264**, which would undergo further rearrangement (i.e. **264** → **265** → **266** → **267**). Pattenden's synthesis required fourteen steps from ester **254**; it involved one isomer separation, and produced pentalenene in 4.66% overall yield. This synthesis could have been better if the co-production of the side product **262** had been

Scheme 54

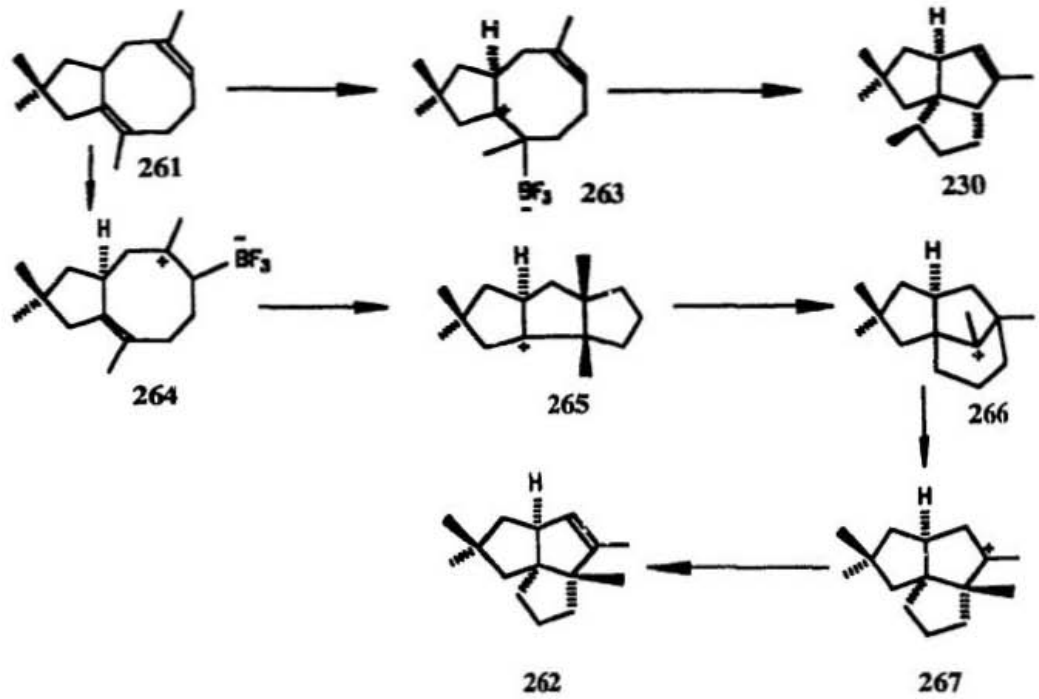


(a) $LiAlH_4$; (b) PCC; (c) vinylmagnesium bromide; (d) MnO_2; (e) $CH_2(COOMe)_2$, *t*-BuOK; (f) NaCl-H_2O-DMSO; (g) *t*-BuOK; (h) TBDMSCl, Et_3N; (i) $h\nu$; (j) Me_3CuLi_2; (k) HF; (l) $Ph_3P{=}CH_2$; (m) $RhCl_3{\cdot}3H_2O$; (n) $BF_3{\cdot}Et_2O$.

suppressed during the final transannular cyclization (i.e. **261** → **230**).

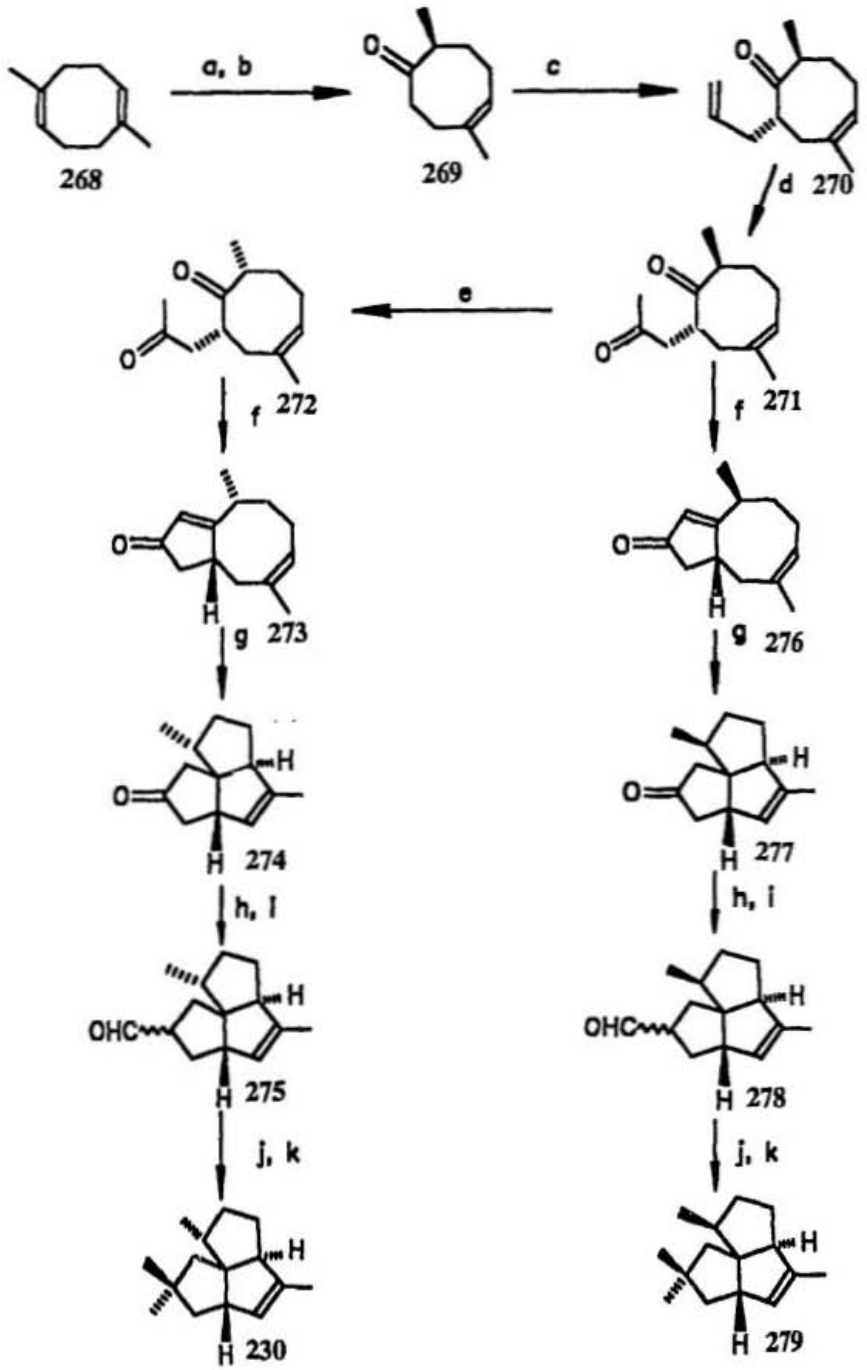
Mehta's[112] synthesis started with the commercially available 1,5-cyclooctadiene (**268**), as summarized in Scheme 55. Selective hydroboration of **268** with 9-BBN and successive oxidation furnished the cyclooctenone **269**. To produce the diketone **271**, **269** was subjected to kinetically controlled allylation with lithium hexamethyldisilazide

Scheme 54 continued



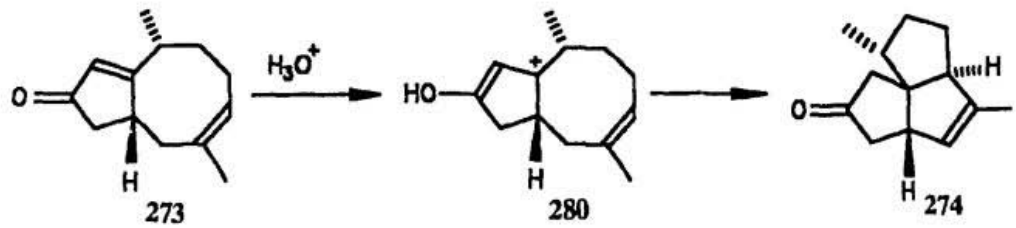
(LiHMDS) and the allyl group was oxidized with $PdCl_2-CuCl$ and molecular oxygen. The stereochemistry of the methyl group next to the carbonyl in **271** was opposite to that of natural pentalenene. Therefore, **271** was equilibrated with methanolic KOH which led to a 1 : 4 mixture of **271** and desired epimer **272**, from which the latter was isolated in 66% yield. When **272** was treated with sodium hydride in THF, a 4 : 1 mixture of **273** and **276** was formed. After column chromatography, the desired epimer **273** was separated in 49% yield. The crucial transannular cyclization of **273** was effected with formic acid in the presence of $BF_3 \cdot Et_2O$ leading to the tricyclic ketone **274**, *via* the carbocation intermediate **280**, in 55% yield. The geminal dimethylation of the C−6 carbonyl group was achieved in three steps. Wittig reaction of **274** with (methoxymethyl)triphenylphosphonium chloride, and the acidic hydrolysis of the product gave aldehyde **275**. After α−methylation followed by Wolff−Kishner reduction,

Scheme 55



For reagents and conditions, see next page.

Scheme 55 continued

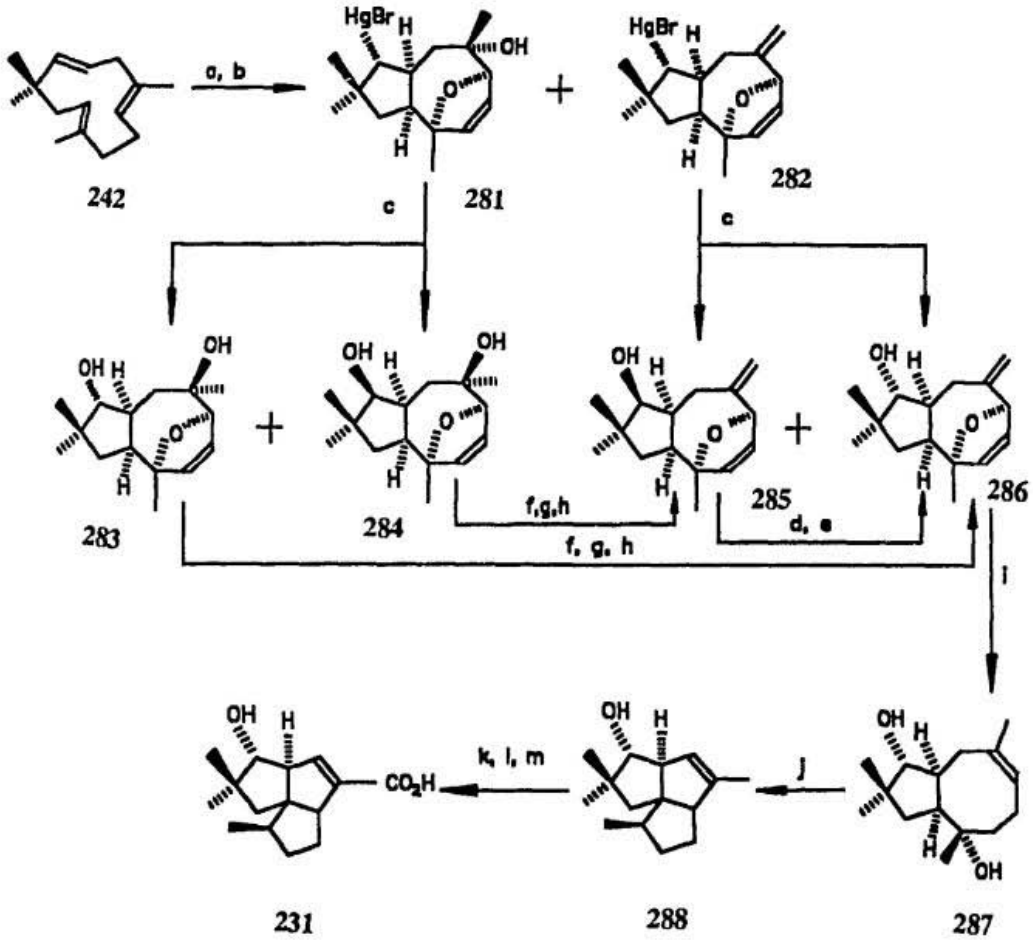


(a) 9-BBN; H_2O_2, NaOH; (b) PCC; (c) LiHMDS, allyl bromide; (d) $PdCl_2$-CuCl-DMF, H_2O, O_2; (e) KOH, MeOH; (f) NaH; (g) $HCO_2H-BF_3{\cdot}Et_2O$; (h) $Ph_3P{=}CHOMe$; (i) $HClO_4$; (j) KH, MeI; (k) NH_2NH_2, Na.

pentalenene was obtained in only 33% yield. *epi*-Pentalenene (**279**) was prepared in exactly the same fashion. Aldol condensation of **271** with sodium hydride in THF produced a 4 : 1 mixture of **276** and **273**, of which the former was isolated and further transformed into *epi*-pentalenene (**279**) in the same way as the latter (i.e. **276** → **277** → **278** → **279**). Mehta's synthesis required ten steps from 1,5-cyclooctadiene (**268**); it involved two isomer separations, and provided pentalenene in 2.03% overall yield. The inefficient, circuitous transformation of the C-6 carbonyl group in **274** into the geminal dimethyls in **230** greatly impaired the brevity of this approach.

Matsumoto's[113] synthesis of pentalenic acid (**231**) started with a biogenetic-like cyclization of humulene (**242**) with $Hg(NO_3)_2$, followed by treatment with aqueous KBr to give two 10α-bromomercuri-3,6-secoprotoilludane derivatives (**281**) (31%) and **282** (21%) (Scheme 56). After separation, the two mercury compounds **281** and **282** were converted to two groups of corresponding 10α- and 10β-hydroxy compounds, **283** (49%) and **284** (33%), **285** (21%) and **286** (66%), respectively, following Whitesides' procedure (O_2, $NaBH_4$, DMF). The transformation of the 7-hydroxy compound **283** (or **284**) into the corresponding exomethylene compound **286** (or **285**)

Scheme 56



(a) $Hg(NO_3)_2$; (b) KBr; (c) $NaBH_4$, O_2, DMF; (d) CrO_3; (e) $NaBH_4$; (f) Ac_2O, pyridine; (g) PBr_3; (h) AmONa, DMSO; (i) $Li/EtNH_2$; (j) $BF_3{\cdot}Et_2O$; (K) SeO_2; (l) MnO_2; (m) KOH – MeOH.

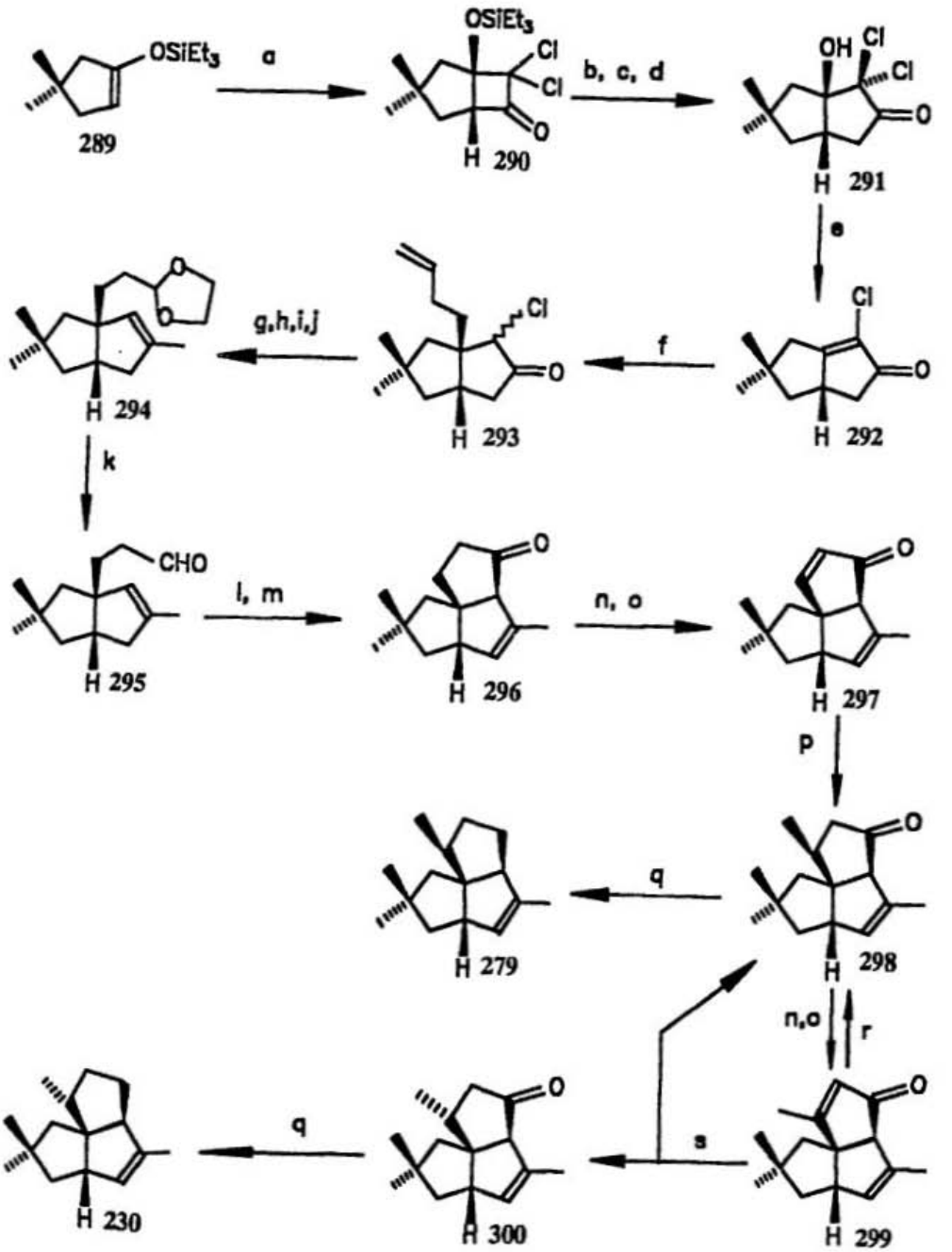
was achieved by acetylation, bromination, and dehydrobromination. Note that the stereochemistry of the 7-hydroxy group in **285** was opposite to that of pentalenic acid. Therefore, compound **285** was converted to **286** by CrO_3 oxidation followed by $NaBH_4$ reduction. Compound **286** was obtained in 34% overall yield from humulene

(**242**). Treatment of **286** with lithium in ethylamine gave the bicyclic ene-diol **287**, which was cyclized in the presence of $BF_3 \cdot Et_2O$ to lead to the tricyclic molecule **288**, but in only 20% yield. After oxidation with selenium dioxide, **288** provided an aldehyde, which was converted to pentalenic acid (**231**) by treatment with MnO_2-KCN and sucessive hydrolysis with KOH-MeOH.

Matsumoto's synthesis required 12 steps from humulene (**242**); it involved three isomer separations, and produced pentalenic acid in 3.0% overall yield. The disadvantages of this approach were the tedious isomer separations and the crucial cyclization of **287**, which was achieved in only 20% yield.

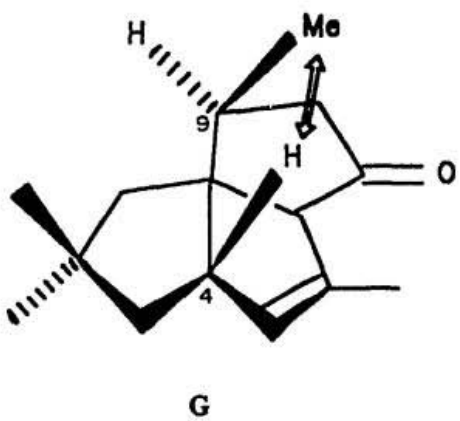
The first published report of a synthetic approach to pentalenene after its isolation came from Paquette and Annis[114] as summarized in Scheme 57. A silyl enol ether **289** underwent smooth [2 + 2] cycloaddition with dichloroketene to furnish cyclobutanone **290** in 83% yield. Then the silicon-oxygen bond was cleaved in acidic methanol, and at the same time a methylhemiketal of the ring carbonyl was formed. This hemiketal was hydrolysed and the four-membered ring was expanded in the presence of diazomethane. The resulting cyclopentanone **291** was exposed to zinc dust in acetic acid to give the α-chloro enone **292**, which, on conjugate addition with lithium bis(3-butenyl)cuprate, provided **293** in 76% yield. At this stage, the ketone **293** was added to methylmagnesium bromide, the double bond was ozonolyzed, the resulting aldehyde was protected as an acetal, and the chlorohydrin moiety was eliminated reductively to give **294** in 59% yield. Deprotection of **294** resulted in the aldehyde **295**. The intramolecular cyclization of **295** with tin(IV) chloride in benzene proceeded efficiently, and the resulting tricyclic alcohol was oxidized cleanly with PCC to yield the ketone **296**. Following the formation of **297** by kinetically controlled selenation of **296** and selenoxide elimination, conjugate addition of lithium dimethylcuprate provided **298** in 87.5% yield. It should be noted that the stereochemistry of the

Scheme 57

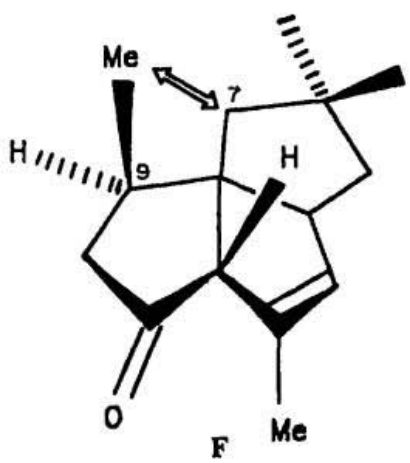


(a) $Cl_2CHCOCl$, Et_3N; (b) MeOH, H_3O^+; (c) *p*TSA, H_2O; (d) CH_2N_2; (e) Zn/HOAc; (f) $(CH_2=CH-CH_2CH_2)_2CuLi$; (g) CH_3MgBr; (h) O_3; Me_2S; (i) ethylene glycol, *p*TSA; (j) Na/NH_3; (k) PPTS, H_2O, acetone; (l) $SnCl_4$; (m) PCC; (n) LDA, PhSeCl; (o) H_2O_2, heat; (p) $(CH_3)_2CuLi$; (q) NH_2NH_2, K_2CO_3; (r) Li/NH_3; (s) Et_3SiH, $(Ph_3P)_3RhCl$.

C–9 methyl group was incorrect in the adduct **298** relative to natural pentalenene (**230**). Indeed, Wolff–Kishner reduction of **298** provided an 83% yield of *epi*–pentalenene (**279**). Then **298** was converted to enone **299**, which was subjected to Birch reduction. Again, **298** was formed exclusively. Since cuprate reactions are generally kinetically controlled and Birch reductions thermodynamically controlled, then it can be concluded that the C–9 methyl group in this tricyclic ketone strongly prefers the β–configuration, a result probably attributed to the strong non–bonded methyl–methylene interaction in **300** (see **F**) relative to the methyl–hydrogen interaction in **298** (see **G**). Nevertheless, reduction of the enone **299** with $(Ph_3P)_3RhCl/(C_2H_5)_3SiH$ provided 66% yield of **298** and **300** in a ratio of 1 : 2.24. Finally this mixture was subjected to Wolff–Kishner reduction to yield a mixture of pentalenene (**230**) and *epi*–pentalenene (**279**), of which the former was unfortunately the minor product. Paquette's synthesis required nineteen steps from 4,4–dimethylcyclopentenone; it involved one isomer separation, and produced pentalenene in 0.44% overall yield. The shortcoming associated with this approach was the poor stereochemical control of the C–9 methyl group.



G

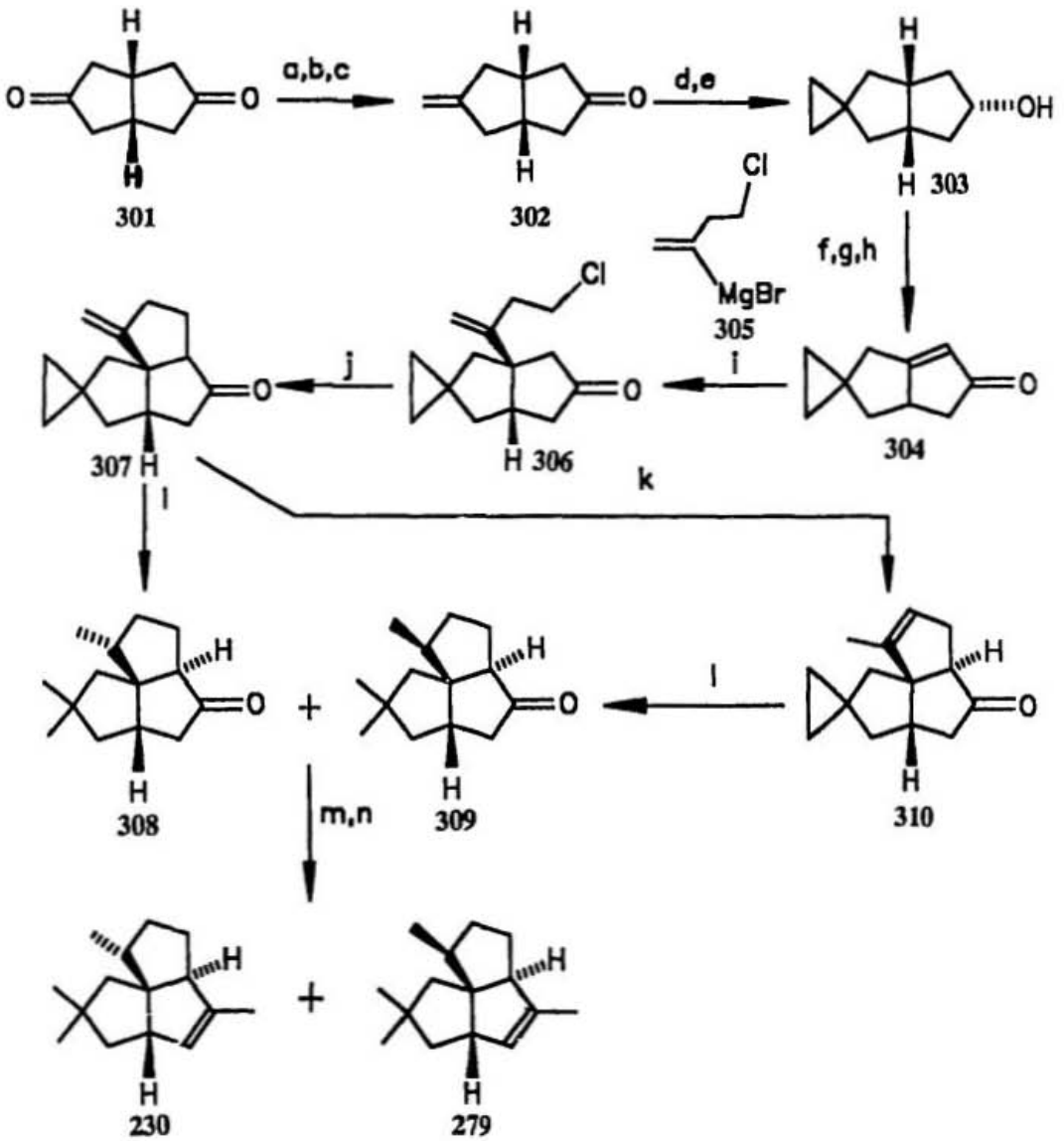


F

Piers and Karunaratne[115] described a total synthesis of pentalenene that employed a novel annulation strategy as shown in Scheme 58. Monoketalization of the bicyclic dione **301** with 2,2-dimethyl-1,3-propanediol, Wittig reaction of the remaining ketone, and deprotection of the ketal provided the enone **302**. Since the cyclopropanation of this compound with diethylzinc-diiodomethane gave a complex mixture of products, the enone **302** was reduced with lithium aluminum hydride, and the resulting alcohol was subjected to cyclopropanation leading to **303** in 81% yield. After oxidation, the resulting ketone, upon treatment with TMSI-Et_3N, was converted to the corresponding silyl enol ether, which was allowed to react with palladium(II) acetate in acetonitrile to produce enone **304** in 63% yield. Addition of the bifunctional Grignard reagent **305** to the enone **304** in the presence of copper(I) bromide-dimethyl sulfide complex led to adduct **306**, which, upon treatment with base, cyclized smoothly to the tricyclic product **307**. Catalytic hydrogenation of **307** resulted in a 5 : 95 mixture of **308** and **309**, of which the former was the desired epimer. In fact, this mixture was converted into *epi*-pentalenene (**279**) by addition with methyllithium followed by dehydration. In order to reach pentalenene (**230**), **307** was isomerized in acid to compound **310**, which on catalytic hydrogenation provided a 42 : 58 mixture of **308** and **309**. To this mixture methyllithium was added and the resulting alcohol was dehydrated to furnish a 32% yield of pentalenene (**230**) and a 33% yield of *epi*-pentalenene (**279**). Piers' synthesis required twelve steps from *cis*-bicyclo[3.3.0]octane-3,7-dione (**301**); it involved one isomer separation, and produced pentalenene in 4.69% overall yield. Unfortunately, the poor stereochemical control at C-9, as in the Paquette's synthesis, made this approach less elegant than it could be.

The Iwata synthesis,[116] outlined in Scheme 59, began with 4,4-dimethyl-2-cyclopenten-1-one (**311**). 1,2-Addition of crotylmagnesium bromide to the enone **311** afforded quantitatively the alcohol **312**, which was subjected to chromic acid

Scheme 58

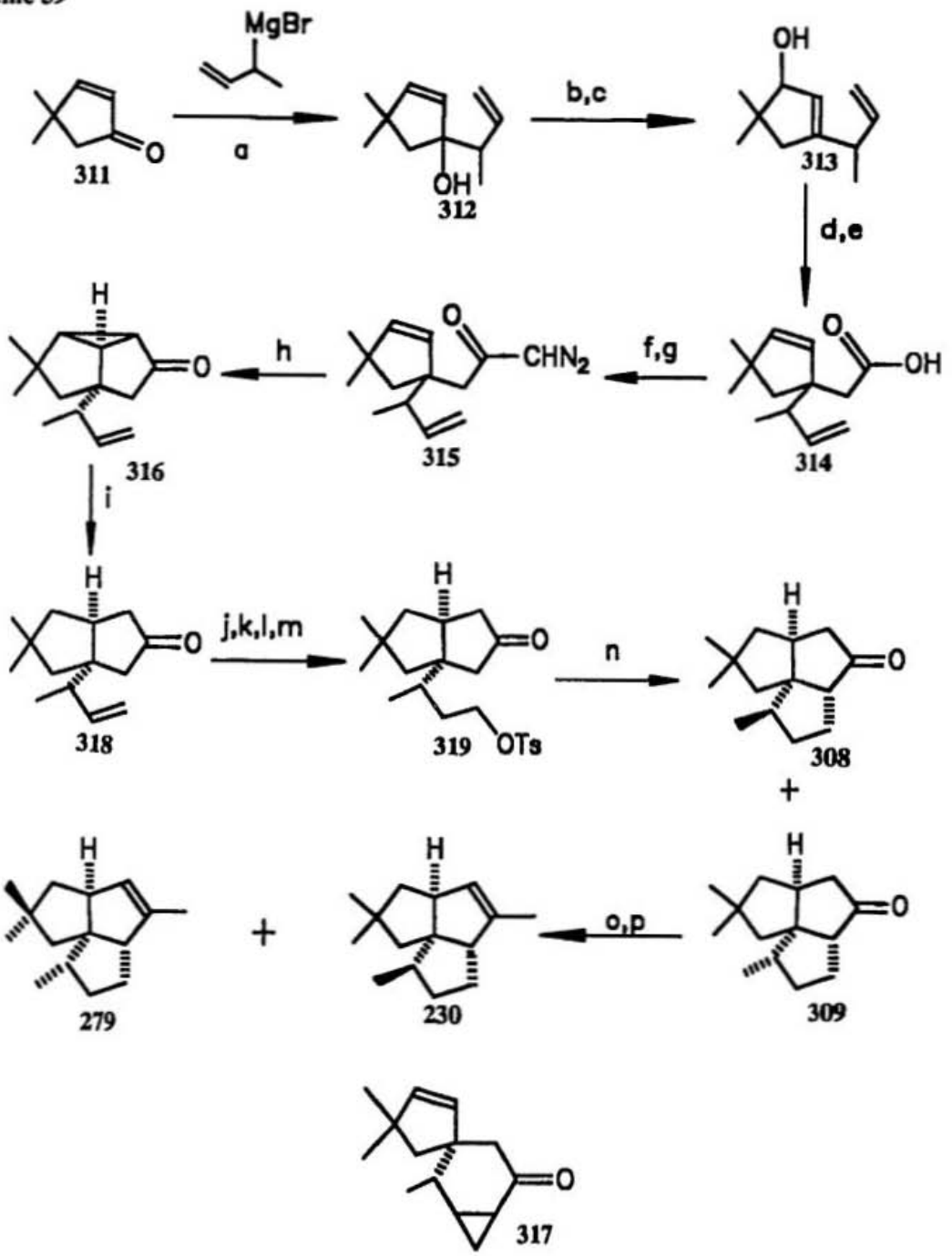


(a) 2,2-dimethyl-1,3-propanedioi, *p*TSA; (b) $Ph_3P=CH_2$; (c) H_2SO_4, acetone; (d) $LiAlH_4$; (e) $CH_2I_2-Et_2Zn$; (f) PCC; (g) TMSI, Et_3N; (h) $Pd(OAc)_2$, MeCN; (i) **305**, $CuBr{\cdot}Me_2S$; (j) KH, THF; (k) *p*TSA, CH_2Cl_2; (l) PtO_2, HOAc, H_2; (m) MeLi; (n) *p*TSA, C_6H_6.

oxidation with allylic rearrangement of the hydroxyl group. The resulting enone was converted into the alcohol **313** by reduction with lithium aluminum hydride. Treatment of the allylic alcohol **313** with ethyl vinyl ether in the presence of mercuric acetate furnished the Cope rearrangement product, an aldehyde, which was oxidized to the acid **314**. Conversion of **314** into its acid chloride, followed by treatment with diazomethane, furnished the diazo ketone **315**. Cyclopropanation of **315** with copper bronze provided the desired product **316** in 82% yield from **314** without any of the structural isomer **317**. Regioselective C_2-C_8 bond cleavage of the cyclopropane ring in **316** was achieved by means of lithium/ammonia reduction leading to **318**. Protection of the ketone as a ketal, hydroboration–oxidation of the alkene, tosylation of the resulting primary alcohol, and deprotection of the ketal furnished the tosylate **319**, which underwent base–induced intramolecular cyclization leading to the mixture of **308** and **309** quantitatively. Following the procedure of Piers, a 1.8 : 1 mixture of pentalenene (**230**) and *epi*–pentalenene (**279**) was obtained in 77% yield. Iwata's synthesis required sixteen steps from enone **311**, and it involved one isomer separation.

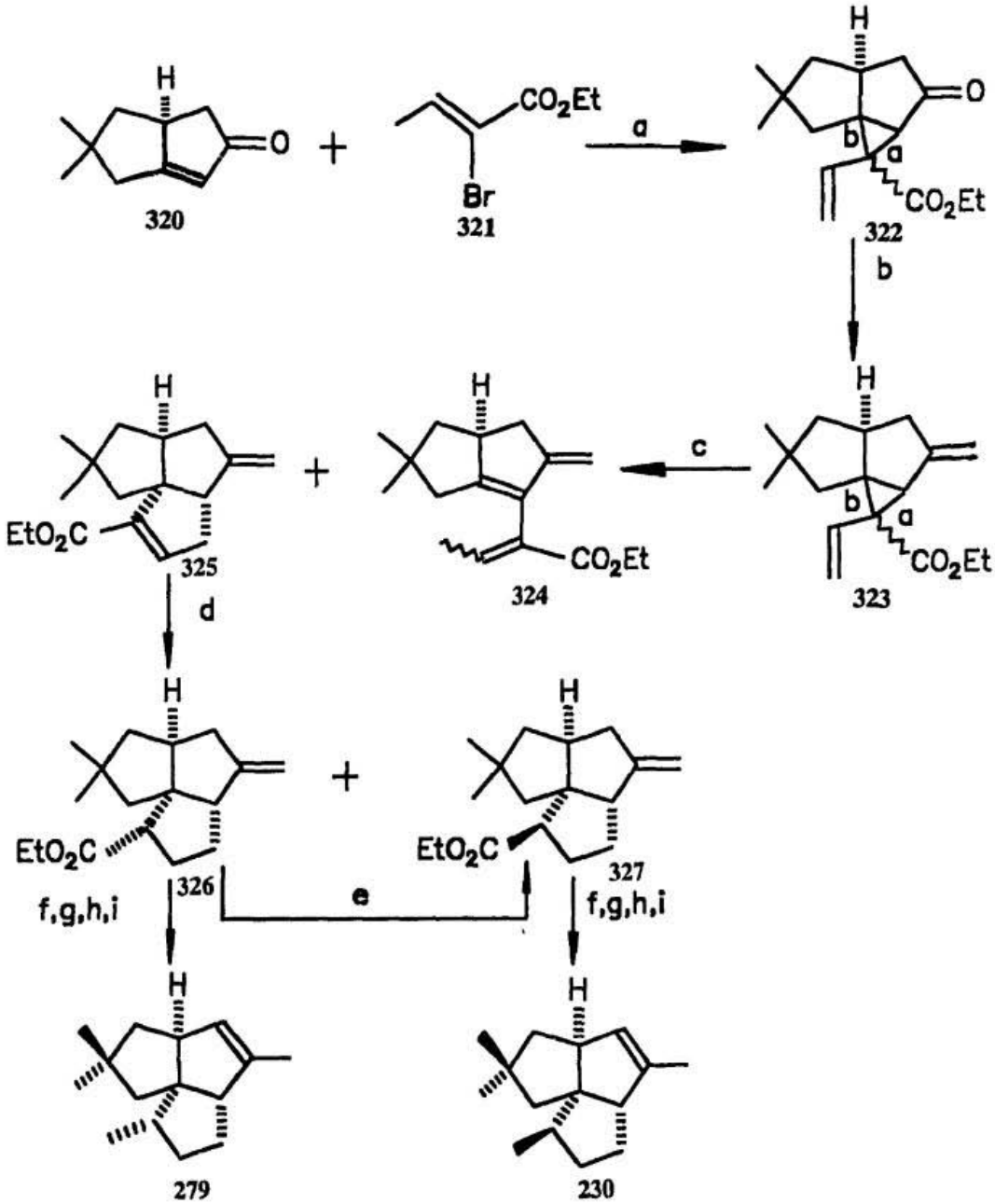
Hudlicky and coworkers[117] completed a total synthesis of pentalenene *via* a [2 + 3] strategy as depicted in Scheme 60. A bicyclic enone **320** was activated with BF_3 at low temperature, and the resulting complex was condensed with the lithio dienolate of ethyl 2–bromocrotonate to provide a 45% yield of vinylcyclopropane **322** (exo / endo = 1 : 1). Direct thermolysis of the cyclopropane **322** gave mainly the undesired bicyclic enone derived from the diradical cleavage of bond b. Therefore, **322** was subjected first to a Wittig reaction leading to **323**, which resulted in a 43 : 57 mixture of the triquinane **325** and the cleavage product **324** under pyrolytic conditions. The selective reduction of the α,β–unsaturated ester in the presence of the isolated olefin was successfully achieved when **325** was reacted with magnesium metal in methanol. The product was a 9 : 1 mixture of epimers **326** and **327**, of which the minor possessed the

Scheme 59



(a) crotyl magnesium bromide; (b) CrO_3; (c) $LiAlH_4$; (d) $CH_2=CH-OEt$, $Hg(OAc)_2$; (e) Jones oxidation; (f) $SOCl_2$; (g) CH_2N_2; (h) Cu; (i) $Li-NH_3$; (j) ethylene glycol, *p*TSA; (k) B_2H_6; NaOH, H_2O_2; (l) TsCl; (m) H_3O^+; (n) *t*-BuOK; (o) MeLi; (p) *p*TSA.

Scheme 60

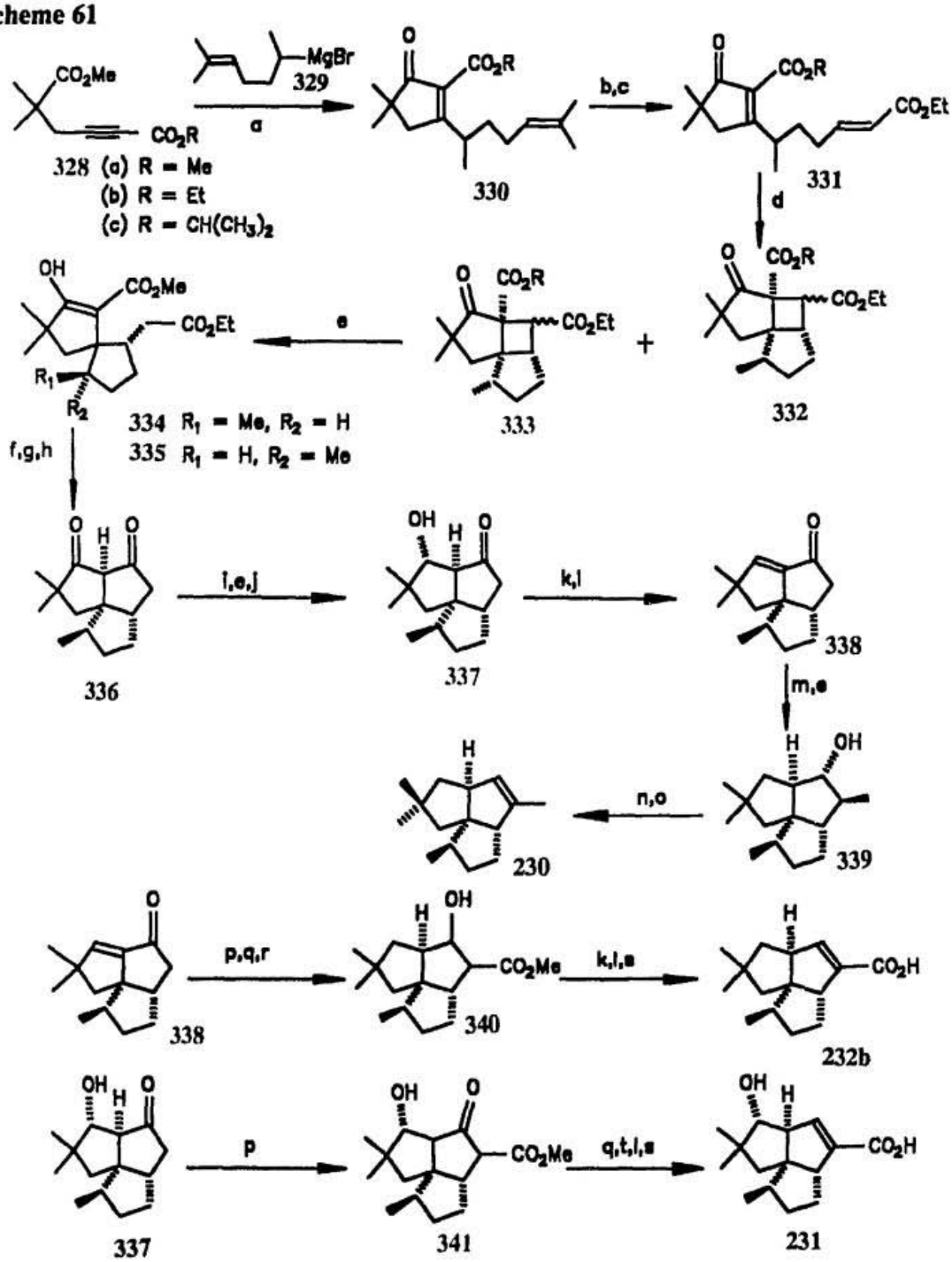


(a) LDA, **321**; then **320**; (b) $Ph_3P{=}CH_2$; (c) 585 °C; (d) Mg, MeOH; (e) EtONa; (f) $LiAlH_4$; (g) MsCl, Et_3N; (h) $LiEt_3BH$; (i) *p*TSA, CH_2Cl_2.

same configuration at C−9 as natural pentalenene. Fortunately, base−catalyzed equilibration of the mixture of **326** and **327** provided a different ratio in which the desired epimer **327** was very slightly favored (55 : 45). After separation, **326** and **327** were individually converted in four steps into *epi*−pentalenene and pentalenene, respectively. These four steps were: reduction of the ester, mesylation of the primary alcohol, reduction of the mesylate, and isomerization of the double bond. Hudlicky's synthesis required nine steps from the bicyclic enone **320**, and it involved one isomer separation. The [2+3] cyclopentene annulation reaction involved in the synthesis was conceptually interesting, but the poor selectivity of the diradical cleavage (i.e. bond a *vs.* b in **322**) rendered this approach less attractive. In addition, the stereochemical control at C−9 was problematic.

Crimmins and Deloach[118] undertook an intramolecular photoaddition−cyclobutane fragmentation approach to pentalenene, pentalenic acid and deoxypentalenic acid, as outlined in Scheme 61. The photoaddition precursor **331** was elaborated from the acetylenic diester **328** by conjugate addition of an organocopper reagent derived from **329** resulting in the product **330**, which was selectively ozonolysized to the aldehyde. A Wittig reaction then gave **331**. Irradiation of **331a** resulted in smooth cycloaddition of the olefinic moieties to provide a 13 : 1 mixture of the photoadducts **332a** and **333a**. The cyclobutane ring of each was reductively cleaved with lithium in ammonia, which led to the β−keto−esters **334** and **335** in a ratio of 13 : 1. The stereoselectivity in the photoaddition could be improved by increasing the size of the vinyl substituent on the cyclopentenone from carbomethoxy (**332a** : **333a** = 13 : 1) to carboethoxy (**332b** : **333b** = 17 : 1) to carboisopropoxy (**332c** : **333c** > 20 : 1). The observed stereoselectivity as well as the effect of the vinyl substituent on the cyclopentenone was interpreted in terms of Oppolzer's[110] hypothesis that the secondary methyl group experiences a steric interaction with the vinyl substituent during the final bond formation of the cyclobutane ring. Next, hydrolysis−decarboxylation of the 13 : 1

Scheme 61



(a) 329, CuI; (b) O_3; (c) $Ph_3P{=}CH{-}CO_2Et$; (d) $h\nu$; (e) Li/NH_3; (f) HOAc–HCl; (g) $HC(OEt)_3$, *p*TSA; (h) *t*-BuOK; (i) ethylene glycol, *p*TSA; (j) 10% HCl, acetone; (k) MsCl, Et_3N; (l) DBU; (m) LDA, MeI; (n) $CH_3C_6H_4OSCl$, pyridine; (o) 200 °C, 20 Torr; (p) LDA, CO_2; CH_2N_2; (q) $NaBH_4$, MeOH; (r) H_2, Pd–C; (s) KOH; (t) Ac_2O–pyridine.

mixture of **334** and **335** in aqueous acid, esterification of the resulting acid, and Dieckmann cyclization produced the dione **336** in high yield. Compound **336** was converted into the keto–alcohol **337** *via* selective protection of the carbonyl, reduction of the remaining carbonyl with lithium in ammonia, and deprotection. Compound **337** underwent mesylation followed by elimination to give enone **338**, which was transformed into alcohol **339** by α–methylation and Birch reduction. Alcohol **339** was elaborated into pentalenene in moderate yield by pyrolysis of the corresponding *p*–cresol thiocarbonate.

For the synthesis of deoxypentalenic acid, enone **338** was converted into **340** by α–carboxylation, reduction of the ketone, and catalytic hydrogenation of the double bond. Mesylation of **340**, elimination, and hydrolysis of the methyl ester furnished deoxypentalenic acid (**232b**).

The synthesis of pentalenic acid was achieved *via* the keto–alcohol **337**. When it was subjected to α–carboxylation followed by esterification with diazomethane, the methyl ester **341** was formed. Sodium borohydride reduction of the ketone function in **341**, acetylation, elimination of the resulting diacetate, followed by base hydrolysis afforded pentalenic acid (**231**).

Crimmins' syntheses of pentalenene, pentalenic acid and deoxypentalenic acid required seventeen, twenty, and seventeen steps, respectively, from the acetylenic diester **328**, and then provided pentalenene in 6.69% overall yield, deoxypentalenic acid in 4.67% overall yield, and pentalenic acid in 10.98% overall yield. For this approach, particularly noteworthy was the excellent stereochemical control of the C–9 methyl group during photoaddition.

Fukumoto and coworkers[119] completed total syntheses of pentalenene, pentalenic acid, and deoxypentalenic acid *via* an intramolecular double–Michael reaction as the key step. The synthesis, as depicted in Scheme 62, began with enone **342**, which

was treated with 5-bromo-1-hexene and lithium under ultrasonic irradiation to give a 70% yield of alcohol **344**. Oxidation of **344** in the presence of Florisil was accompanied by allylic rearrangement of the hydroxyl group to provide enone **345**, which was converted into the primary alcohol **346** by hydroboration-oxidation. The alcohol function of **346** was oxidized with pyridinium chlorochromate (PCC), then the resulting aldehyde was attacked by vinylmagnesium bromide, and the allylic alcohol was oxidized with pyridinium dichromate (PDC) to give the bis-enone **347**. Compound **347** was heated together with chlorotrimethylsilane, triethylamine, and zinc chloride to give, after acidic hydrolysis, a 35% yield of **348** and a 65% yield of **349**. The latter was treated with ethyl formate in the presence of sodium methoxide leading to a 90% yield of hydroxymethylene compound **350**. After diazo-exchange using *para*-toluenesulphonyl azide and triethylamine, the diazo ketone **351** was irradiated to provide a 3.6 : 1 mixture of **352** and **353**.* Reduction of the carbonyl group of compound **352** to methylene was achieved by treatment with ethanedithiol in the presence of $BF_3 \cdot Et_3O$ followed by desulphurization of the dithioketal with Raney nickel. Compound **354** was subjected to selenation followed by oxidative elimination to furnish a 46% yield of methyl deoxypentalenate (**355**), accompanied by a 37% yield of isomer **356**. Reduction of ester **355** with diisobutylaluminum hydride (DIBAL) gave the allylic alcohol, which was treated with a pyridine-sulphur trioxide complex and the resulting product was reduced with lithium aluminum hydride to afford pentalenene (**230**) in moderate yield. Ester **352** was further elaborated into pentalenic acid (**231**) in six steps. Since sodium borohydride reduction of **352** resulted in mainly the undesired stereochemistry of the hydroxyl group, the alternative route to **357** was sought. Thus, hydrolysis of the ester to the acid, reduction of the ketone function with lithium in

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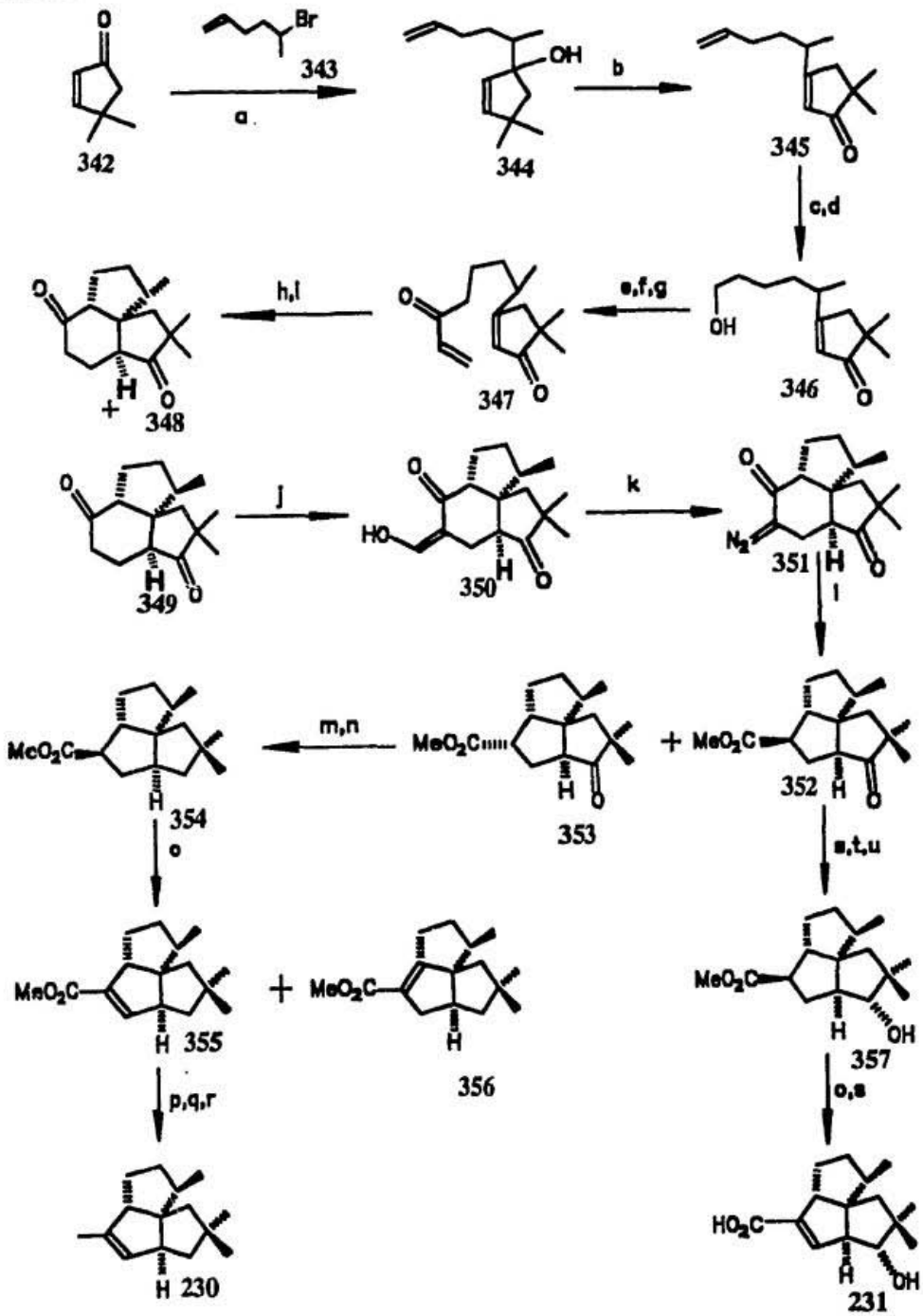
* It is our opinion that ester **353** could have been used in the same fashion as ester **352** for the synthesis of pentalenene, deoxypentalenic acid and pentalenic acid.

Scheme 62

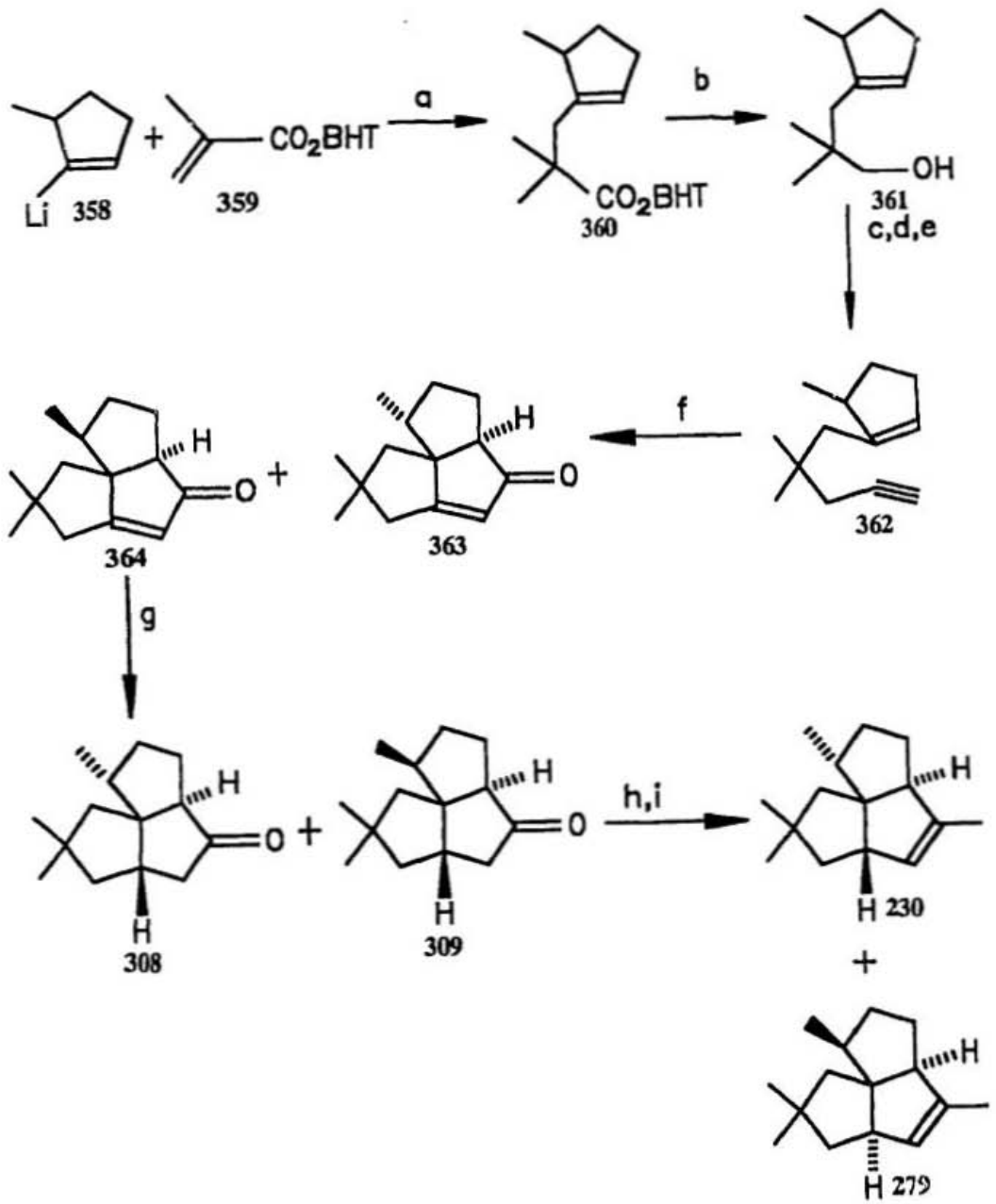


(a) 343, Li, ultrasonic irradiation; (b) PCC, Florisil; (c) $(C_6H_{11})_2BH$; (d) NaOH, H_2O_2; (e) PCC; (f) $CH_2=CH-MgBr$; (g) PDC; (h) E.N, TMSCl, $ZnCl_2$; (i) $HClO_4$; (j) HCO_2Et, NaOMe; (k) TsN_3, Et_3N; (l) $h\nu$; (m) $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$; (n) Raney Ni; (o) LDA, PhSeCl; H_2O_2; (p) DIBAL; (q) SO_3-pyridine; (r) $LiAlH_4$; (s) KOH, MeOH; (t) $Li-NH_3$; (u) CH_2N_2.

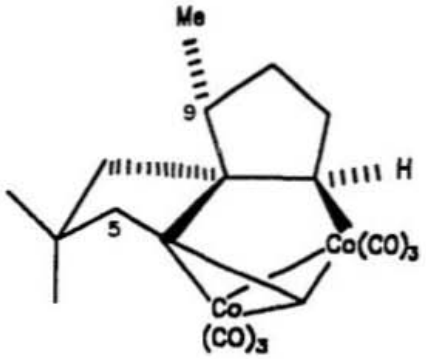
ammonia, and esterification with diazomethane back into the ester yielded **357**, which underwent selenation and oxidative elimination then successive hydrolysis to lead to pentalenic acid (**231**). Fukumoto's synthesis of pentalenene, pentalenic acid and deoxypentalenic acid required eighteen, seventeen and sixteen steps, respectively, from enone **342**; this involved three, two, and three isomer separations, respectively, and produced pentalenene in 2.8% yield, pentalenic acid in 10% yield and deoxypentalenic acid in 6.5% yield. Although the key intramolecular double-Michael reaction was unique, the poor stereoselectivity of this reaction (i.e. **347** → **349**), as well as the poor regioselectivity of the selenation-elimination sequence (i.e. **354** → **355**) made this approach, as a whole, less attractive.

Schore and Rowley[120] developed an efficient synthesis of pentalenene involving an intramolecular Pauson-Khand cycloaddition. The synthesis, as shown in Scheme 63, began with conjugate addition of 2,6-di-*tert*-butyl-4-methylphenyl methyacrylate (BHT ester) (**359**) with 5-methylcyclopentenyllithium (**358**) followed by *in situ* methylation of the resulting enolate to give a 90% yield of **360**. After reduction of the BHT ester **360** with lithium in ammonia, the primary alcohol **361** was converted into the enyne **362** by tosylation, iodide displacement, and then displacement by acetylide. Enyne **362**, when heated with $Co_2(CO)_8$ in heptane, produced a 51% yield of the mixture enones **363** and **364** in an 88 : 12 ratio. The observed stereoselectivity can be rationalised by examining two presumed intermediates **H** and **I** leading to enones **363** and **364**, respectively. The 1,3-pseudodiaxial interaction developed between the C-9 methyl group and the C-5 methylene group in **I** is absent in **H**, thereby directing the cycloaddition in the desired direction. The mixture of enones **363** and **364** was subjected to Birch reduction to give a mixture of ketones **308** and **309**, which were transformed into pentalenene and *epi*-pentalenene according to Piers' procedures. This synthesis of pentalenene required ten steps from the BHT ester **359**; it involved one isomer separation, and produced pentalenene in 3.7% overall yield.

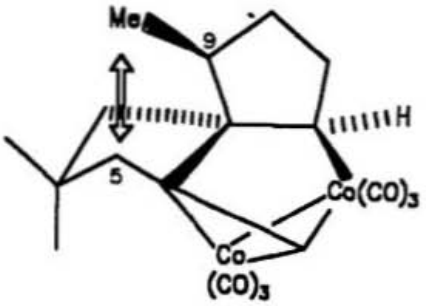
Scheme 63



(a) MeI; (b) $Na-NH_3$; (c) TsCl/pyridine; (d) LiI, HMPA; (e) $Li-C{\equiv}CH{\cdot}en$; (f) $Co_2(CO)_8$, 110 °C; (g) $Li-NH_3$; (h) MeLi; (i) *p*TSA.



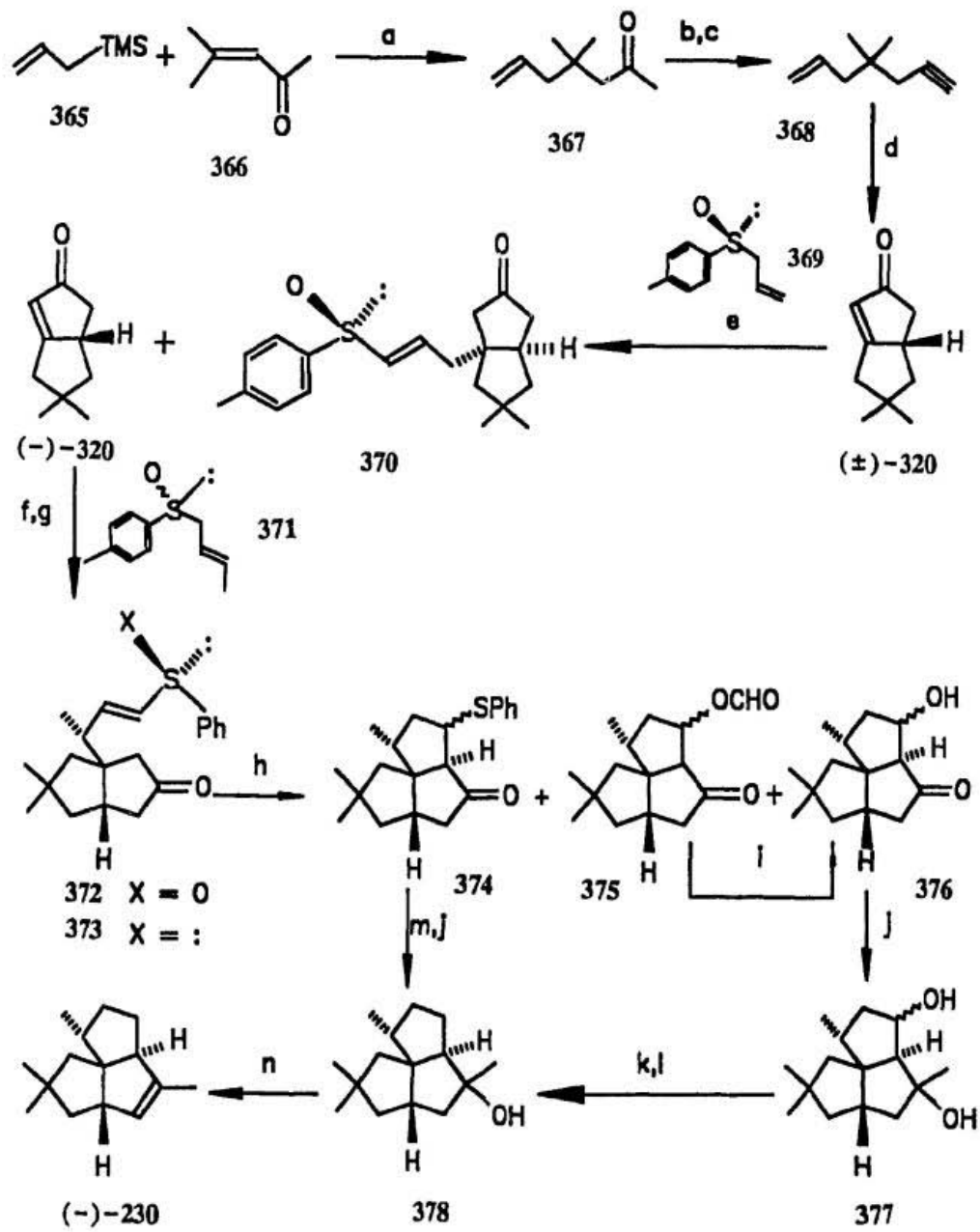
H



I

Hua[121] designed an asymmetric synthesis of (+)−pentalenene that employed chiral sulfinylallyl anions, thus establishing the absolute configuration of pentalenene for the first time. The synthesis, as outlined in Scheme 64, started with the 1,4−addition of allyltrimethylsilane (**365**) to mesityl oxide (**366**) to provide **367** in 87% yield. Formation of the enol phosphate followed by *in situ* dehydrophosphonation with 2 equivalents of LDA gave a 61% yield of **368**. Intramolecular Pauson−Khand cyclization of the α,ω−enyne **368** with $Co_2(CO)_8$ under an atmosphere of carbon monoxide yielded 58% of the racemic enone **320**. The kinetic, selective resolution of **320** was made possible by taking advantage of the fact that the anion derived from (*S*)−allyl−*p*−tolyl sulfoxide (**369**) added to (+)−(*R*)−**320** much more quickly than to (−)−(*S*)−**320**. Thus, treatment of racemic enone **320** with 0.5 equivalents of anion, prepared by the reaction of **369** with LDA, gave a 40% yield of adduct **370**, and the (−)−(*S*)−**320** was recovered to the extent of 45%. Addition of the sulfinylallyl anion, derived from the reaction of two equivalents of racemic *cis*−crotyl phenyl sulfoxide **371** with two equivalents of LDA, to one equivalent of (−)−**320** furnished an 82% optically pure sulfoxide **372** in 91% yield. Reduction of the sulfoxide **372** with zinc in acetic acid provided the vinyl sulfide **373**, which, upon hydrolysis followed by

Scheme 64



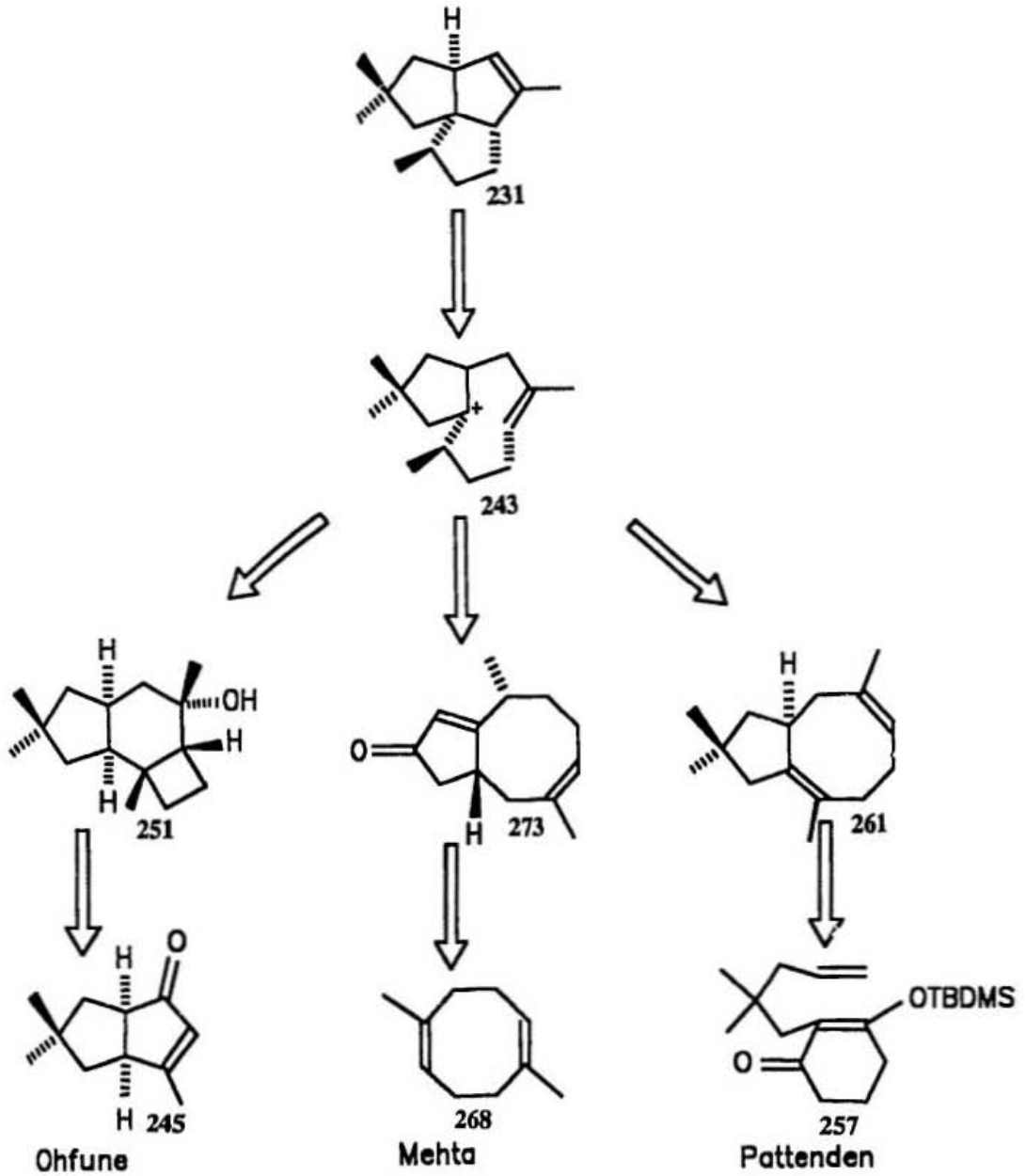
(a) $TiCl_4$; (b) LDA, $ClP(O)(OEt)_2$; (c) LDA; (d) $Co_2(CO)_8$, CO; (e) 369, LDA; (f) racemic 371, LDA; (g) Zn−HOAc; (h) HCO_2H−TFA; (i) K_2CO_3, MeOH; (j) MeMgBr; (k) $[(CH_3)_2N]_2POCl$, Et_3N, DMAP; (l) Li/$EtNH_2$; (m) Raney Ni; (n) $BF_3{\cdot}Et_2O$.

intramolecular cyclization gave 4% of the alcohol **376**, 60% of the formate **375**, and 15% of the sulfide **374**. The transformation of formate **375** into alcohol **376** was easily achieved by treatment with mild base. Addition of a Grignard reagent to **376** furnished a 70% yield of diol **377**, which underwent phosphorylation with *N,N,N',N'*-tetramethyl-diamidophosphorochloridate, triethylamine and 4-dimethylaminopyridine (DMAP), followed by deoxyphosphorylation with $Li/EtNH_2$ to give **378**. Alcohol **378** was also obtained from sulfide **374** by desulfurization with Raney nickel and addition to the carbonyl of methylmagnesium bromide. Finally, dehydration of **378** with $BF_3 \cdot Et_2O$ proceeded smoothly to lead to (+)-pentalenene in 99% yield. Hua's synthesis required twelve steps from enone **366** and produced (+)-pentalenene in 4% overall yield.

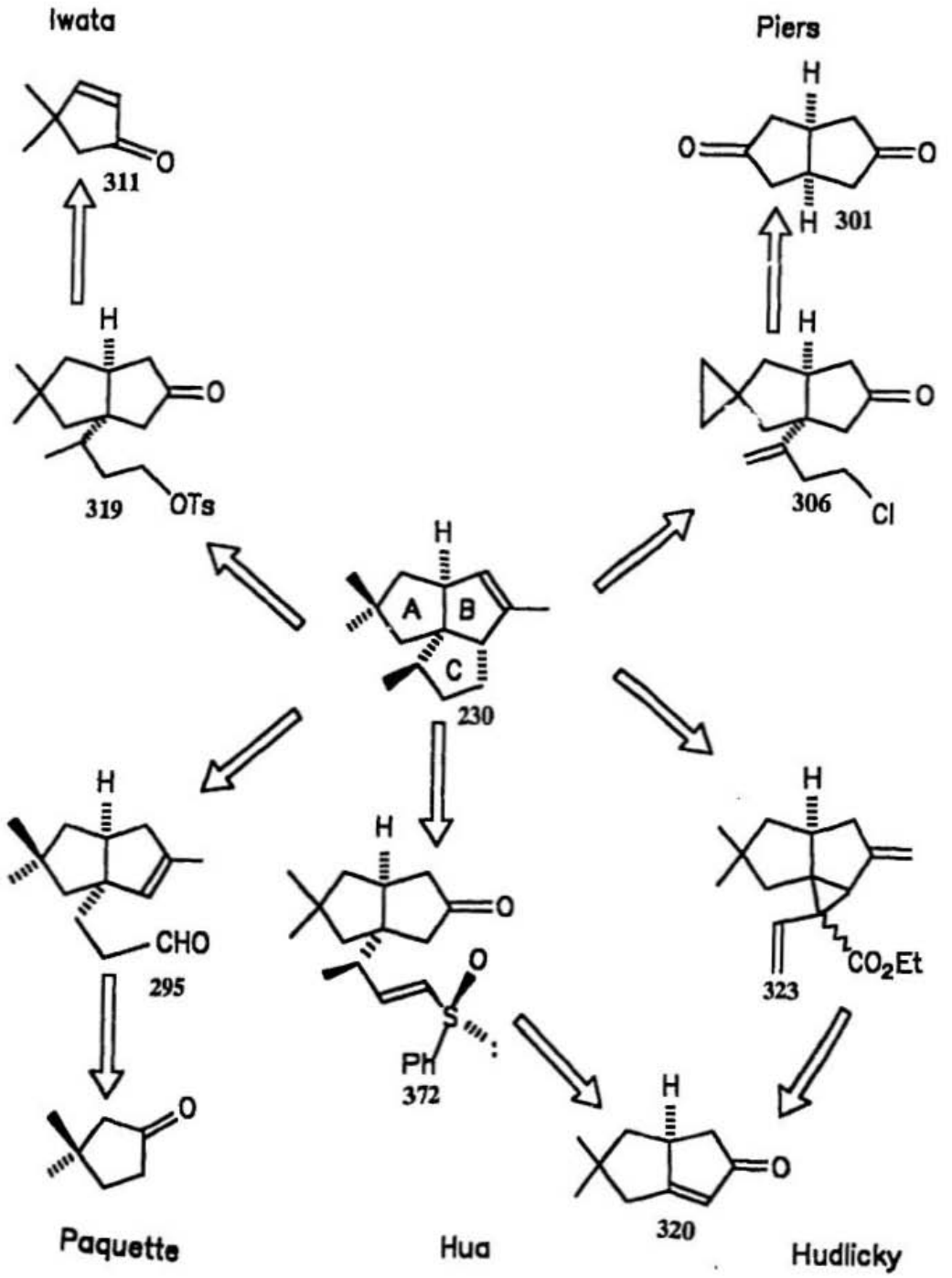
To date, eleven syntheses of pentalenene including one asymmetric synthesis, three syntheses of pentalenic acid, and two total syntheses of deoxypentalenic acid have been reported. Ohfune, Mehta, and Pattenden accomplished their total syntheses through a common carbocation intermediate **243** with a strategy based on biosynthetic considerations (Scheme 65). On the other hand, Paquette, Hudlicky, Hua, Iwata, and Piers designed syntheses that have a common C ring disconnection as shown in Scheme 66. The retrosynthetic analysis of some other approaches is summarized in Scheme 67. Fukumoto constructed the B' and C rings *via* an intramolecular double-Michael addition of dienone **347** and ring contraction of the B' ring led to the B ring. In Schore's synthesis, the A and B rings were constructed simultaneously by means of an intramolecular Pauson-Khand cyclization. Crimmins' approach was based on the B ring disconnection. Photoaddition of **331** provided the C ring and Dieckmann condensation of the spiro-compound **379** built the B ring.

Due to the obvious structural similarities of pentalenene, pentalenic acid and deoxypentalenic acid, it would be more attractive to achieve their syntheses through a

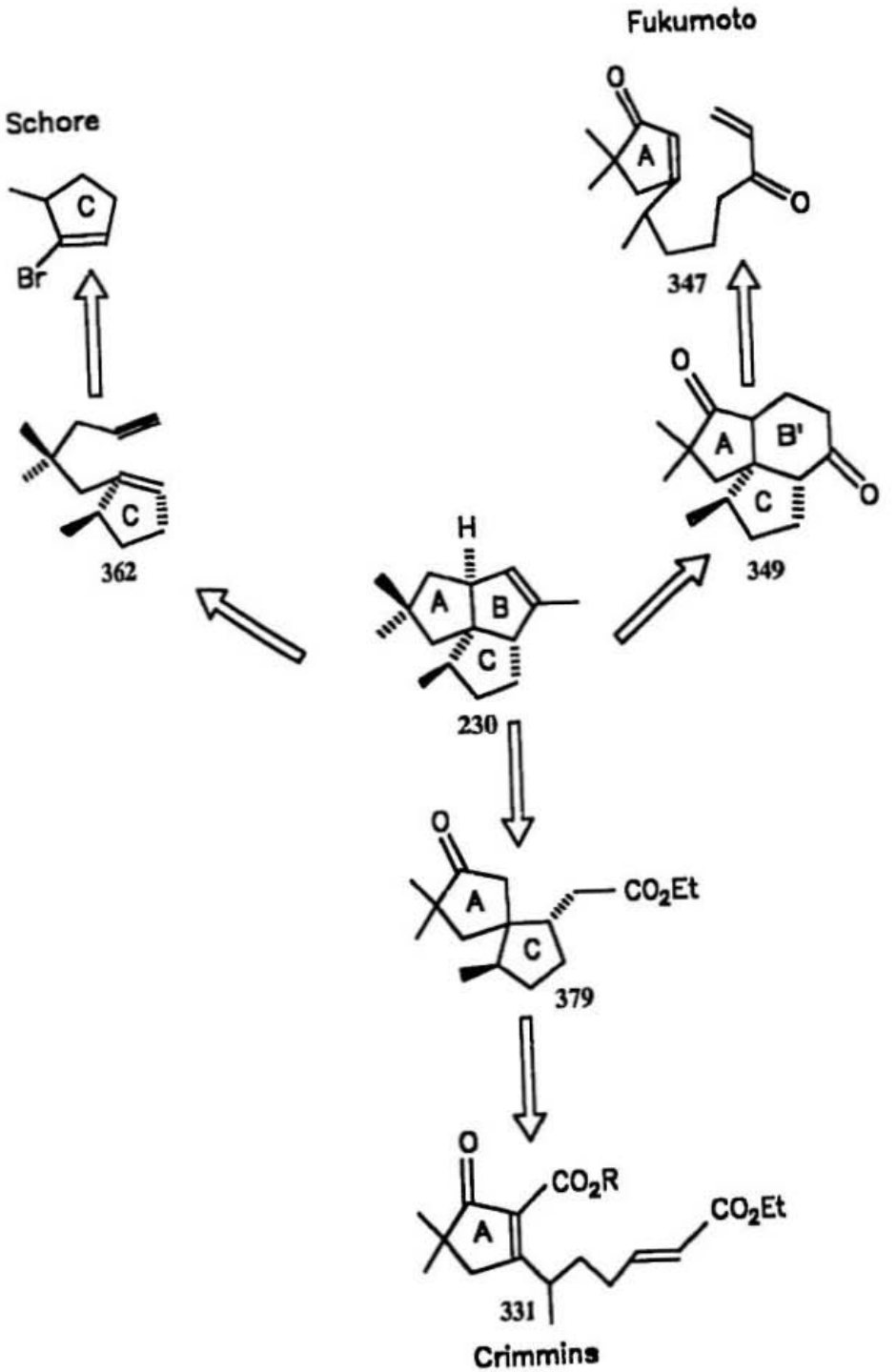
Scheme 65


H
231
243
OH
H
H
251
O
H
273
261
H
O
H 245
Ohfune
268
Mehta
OTBDMS
O
257
Pattenden

Scheme 66

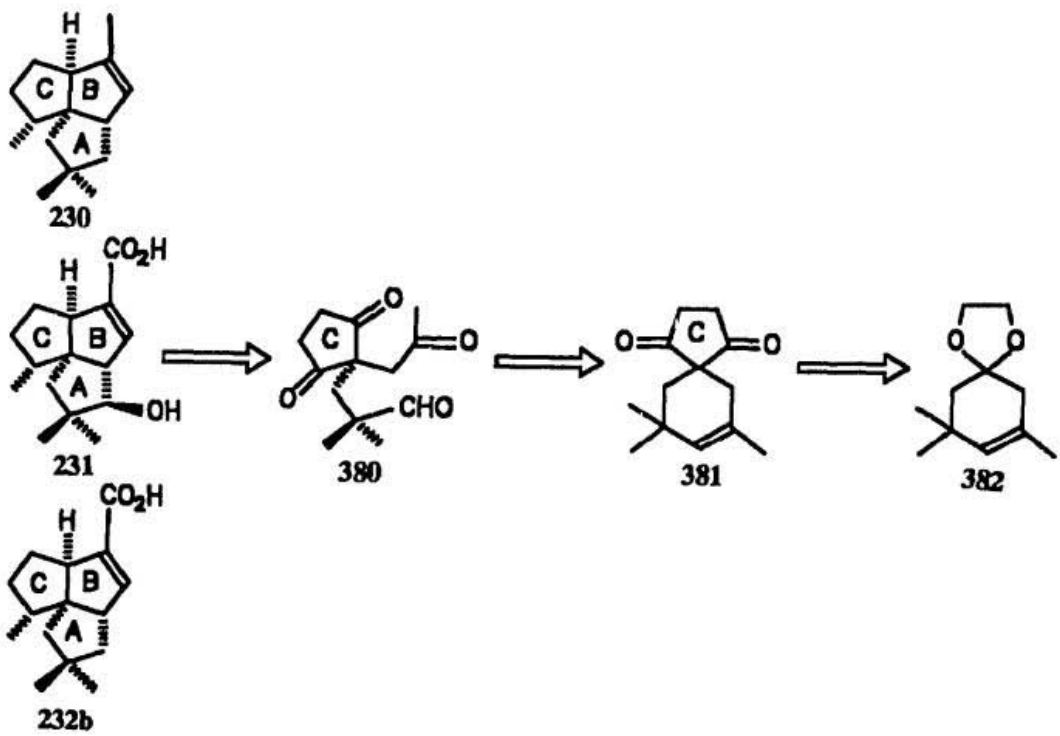

Iwata
311
319
OTs
Piers
301
306
Cl
A
B
C
230
CHO
295
372
Ph
323
CO_2Et
320
Paquette
Hua
Hudlicky

Scheme 67


Fukumoto
Schore
O
A
O
347
C
Br
O
A
B'
O
C
362
H
A
B
C
349
230
O
A
CO2Et
C
379
O
CO2R
CO2Et
A
331
Crimmins

common intermediate. We deemed ketone **380** an appropriate intermediate that might undergo double aldol condensation to generate the A and B rings with appropriate functionalities. The C-9 methyl group might be introduced *via* the corresponding carbonyl group. Obviously, **380** can be derived from a spiro-diketone **381**, which, in turn, can be prepared from the corresponding ketal **382** with cyclobutene **109**. Thus, our synthetic plan was to make **381** utilizing the one-pot spiro-annulation (geminal acylation) procedure that we had developed in the synthetic efforts toward isokhusimone, then to cleave the double bond by ozonolysis, to build the A and B rings by aldol condensations, and finally to manipulate some other functionalities to lead to the target molecules (Scheme 68). In this initial study our synthetic efforts were mainly devoted to the total synthesis of pentalenene. The following is a detailed description of our synthetic studies in this area.[122]

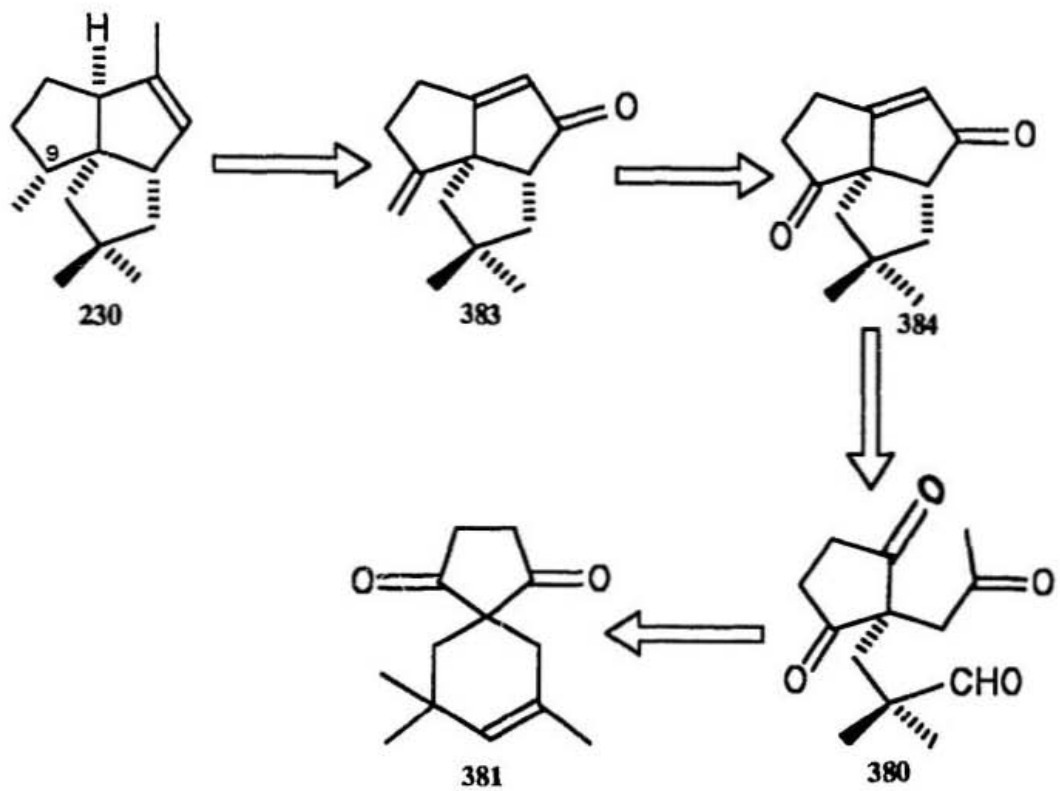
Scheme 68



II. Results and Discussion

As indicated in Scheme 69, our approach to pentalenene was designed with the view that its triquinane unit could be assembled through the use of two intramolecular aldol condensations (i.e. **380** → **384**). We expected that catalytic hydrogenation of the exocyclic double bond of compound **383** would occur from the less sterically hindered face, thereby resulting in the requisite stereochemistry of the C−9 methyl.

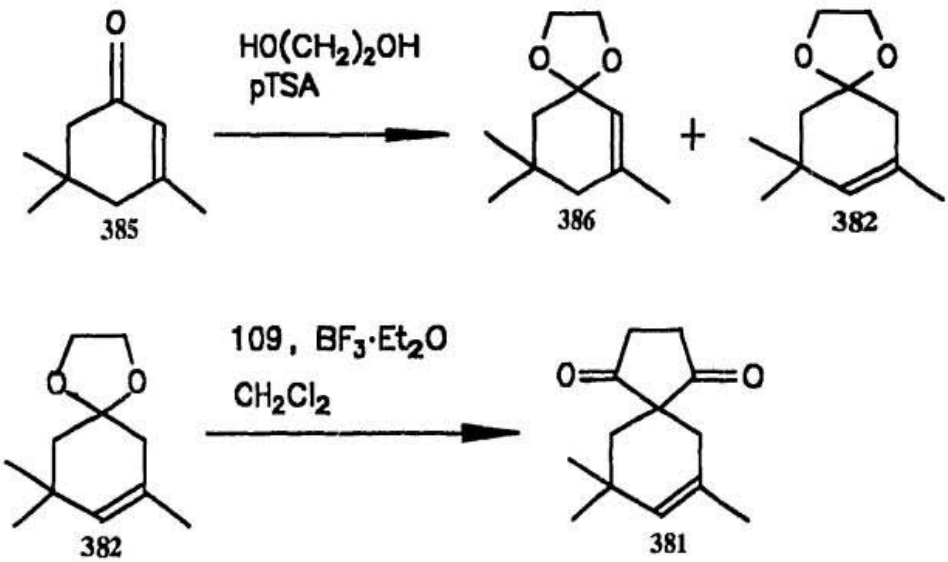
Scheme 69



230 **383** **384** **380** **381**

The preparation of the spiro−diketone **381** required the ethylene ketal **382**. Babler and coworkers[123] reported that the reaction of isophorone with ethylene glycol

Scheme 70



in toluene at reflux with continuous azeotropic removal of water gave a 65% yield of a mixture of ketals **382** and **386** after either vacuum distillation or chromatography on Florisil (Scheme 70). More recently Constantino *et al.*[124] improved the yield up to 88.5% by distilling out the azeotrope, and they separated both ketals by fractional distillation. Our initial efforts were to follow these procedures. However, as indicated by GC–MS analysis, a considerable amount of starting material was still present when the reaction was allowed to run for a few hours. Furthermore, after this time some oligomeric material with a relatively long retention time began to form. We never found an optimized reaction time at which most of the starting material was consumed and only a small amount of high molecular weight by-product was produced. The highest yield of the mixture of ketals that we achieved, after vacuum distillation, was 49%. The major component of the mixture of ketals was always **382**, but the ratio depended on the reaction time. The ketals could be differentiated by their distinctive mass spectra. The mass spectrum of ketal **382** is shown in Figure 6. The fragment at *m/z* 86

Figure 6. Mass spectrum of ketal **382**

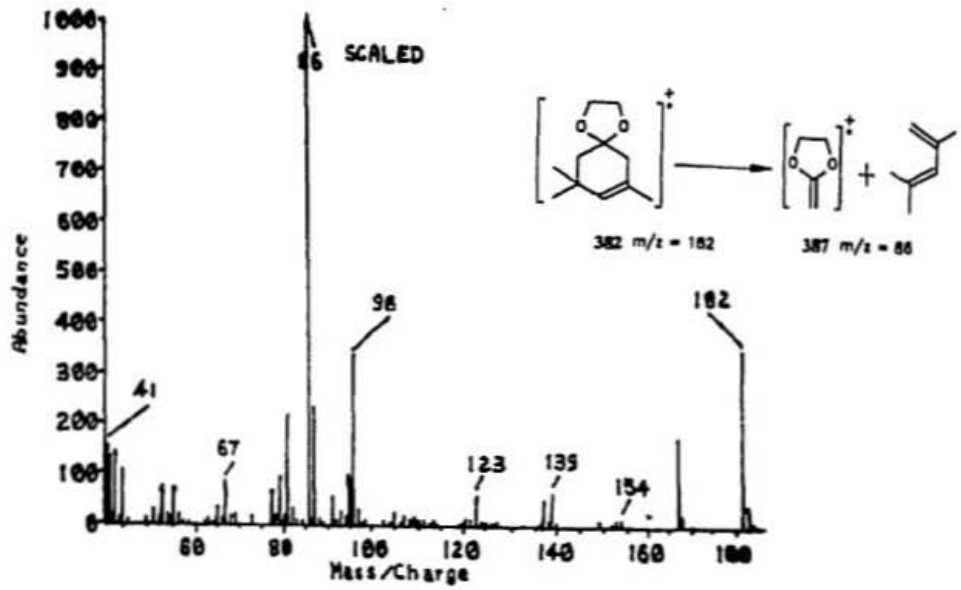
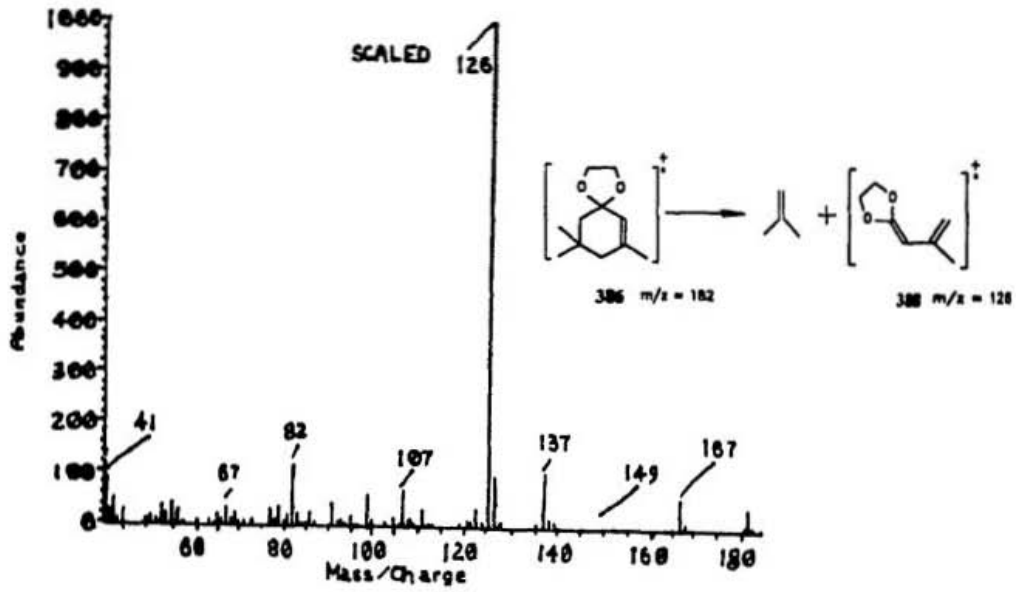


Figure 7. Mass spectrum of ketal 386

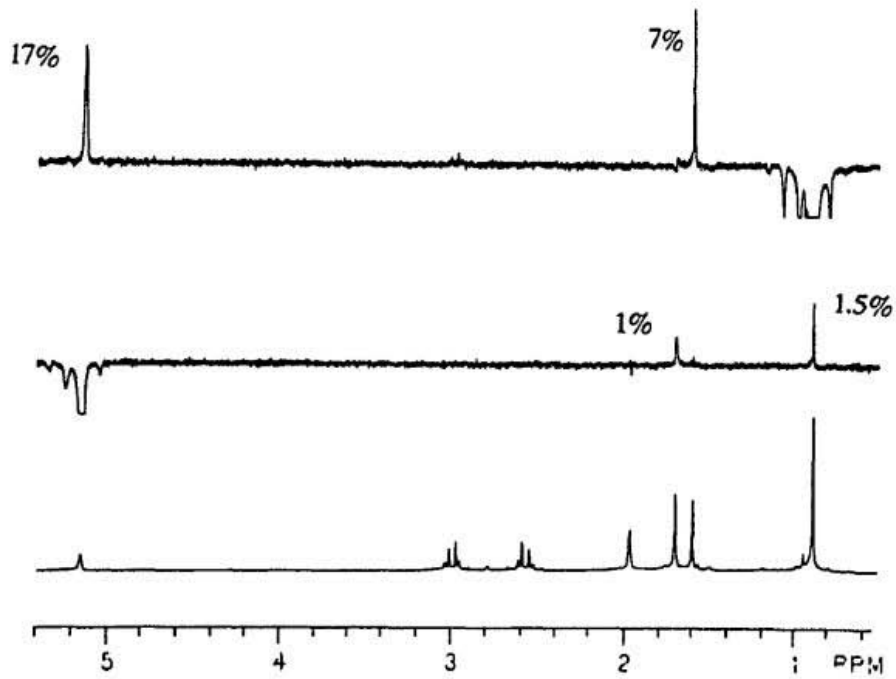


corresponds to **387** which arises *via* the homolytic *retro*-Diels-Alder reaction of **382**.[125] Likewise, the peak at *m/z* 126 in the mass spectrum of **386** shown in Figure 7 can be rationalised as a fragment with the formula $C_7H_{10}O_2^{\ddagger}$ (**388**). We believed that the oligomerization of isophorone might be supressed if benzene were used instead of toluene. With this idea in mind, the reaction mixture was heated in benzene overnight. GC-MC analysis indicated that the crude product consisted of a ketal mixture and isophorone, along with a trace amount of oligomers. After work-up, some of the ketal **386** was hydrolysed back into isophorone as revealed by the GC-MS ratio of **386** to **382**. The colored oligomeric material was easily removed by vacuum distillation and the distillate was subjected to column chromatography on silica gel to give a 62% yield of pure **382** and a 31% recovery of isophorone. Clearly ketal **386** was hydrolysed on silica gel, which was fortunate since **382** was the desired ketal for our synthesis. One recycle of the recovered isophorone provided another 20% yield of ketal **382**, thus the overall yield of **382** was at least 82%. Besides the mass spectrum, the ^1H and ^{13}C NMR spectra of **382** were found to be distinguishable from those of **386**, prepared *via* another route (*vide infra*), thus confirming the position of the double bond.

With supplies of **382** readily available, the crucial geminal acylation reaction was addressed (Scheme 70). Exposure of **382** to three equivalents of the cyclobutene **109** and fifteen equivalents of $BF_3{\cdot}Et_2O$ in dichloromethane following our general spiro-annulation procedure gave, after column chromatography on silica gel, a 72% yield of the spiro-diketone **381**, and the hydrolysed starting material was recovered to the extent of 18%. Compound **381** showed an IR absorption maximum for the ring carbonyls at 1721 cm^{-1}. In the ^1H NMR spectrum, two-proton multiplets at δ 2.632 and 3.054 were attributed to the protons in the five-membered ring. The carbonyls were found at δ 214.2 in the ^{13}C NMR spectrum. The position of the double bond was unequivocally determined by means of an NOE experiment. In the ^1H NMR spectrum, two C-5 methyls appeared as a singlet at δ 0.942 and the vinyl methyl was found as a

singlet at δ 1.759. As shown in Figure 8, irradiation at the olefinic proton at δ 5.205 resulted in NOE's at both δ 0.942 and 1.759, and a positive NOE at δ 5.205 was observed when the six-proton singlet at δ 0.942 was irradiated, which ruled out the possibility of compound **389**.

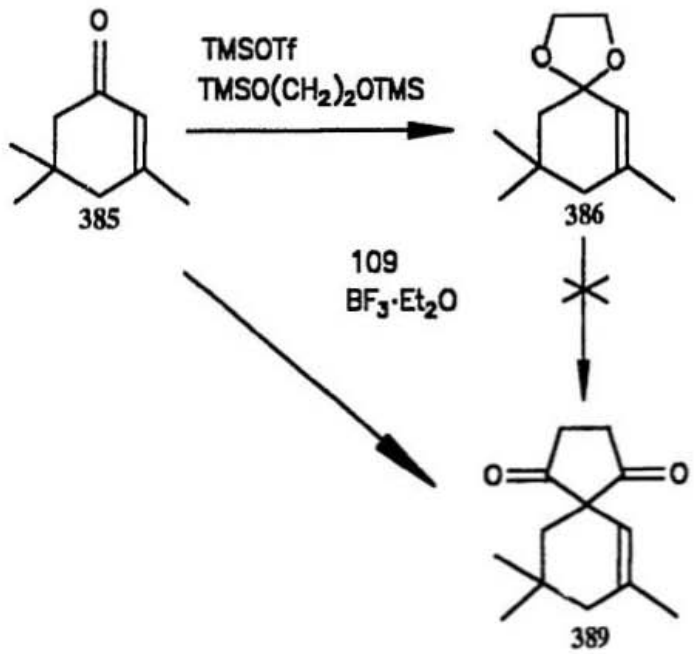
Figure 8. NOE difference spectra of **381**



In order to achieve a direct comparison between **381** and **389**, we intended to prepare **389** from the corresponding ketal **386**. The ketal **386** was conveniently made by the reaction of isophorone with 1,2-bis(trimethylsiloxy)ethane using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst after the method of Tsunoda and Noyori.[126] However, only hydrolysed isophorone was recovered when ketal **386** was subjected to the spiro-annulation reaction. Nevertheless, Mr. Tracy Jenkins[127] of our laboratory discovered that direct treatment of isophorone with the cyclobutene **109** and $BF_3 \cdot Et_2O$ affords a modest yield of **389** after chromatography on silica gel

(Scheme 71). The IR spectrum of **389** showed an absorption maximum for the ring carbonyls at 1719 cm^{-1}. The carbonyl resonances appeared at δ 212.5. The four protons α to the carbonyls appeared as a multiplet at δ 2.850 in ^1H NMR spectrum. In fact, all the spectra of **389** were found to be quite different from those of **381.**

Scheme 71

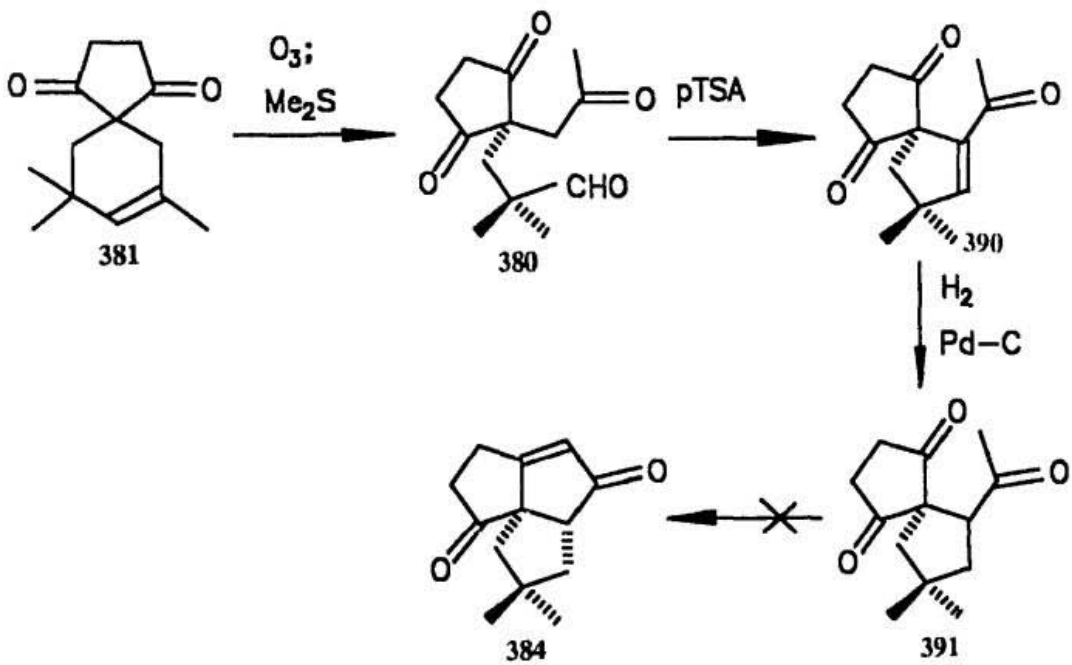


Compound **381** underwent ozonolysis to give **380**, which was converted into enone **390** in a 52% yield on treatment with *p*TSA in benzene at reflux (Scheme 72). The IR spectrum showed absorption maxima for the ring carbonyls at 1725 cm^{-1}, for the conjugated carbonyl at 1664 cm^{-1}, and for the double bond at 1626 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton and the acetyl protons appeared as two singlets at δ 6.761 and 2.252, respectively. Since the ring closure of **390** by intramolecular aldol condensation should be extremely difficult because of the considerable ring strain, compound **390** was converted into trione **391** quantitatively by catalytic hydrogenation

in methanol. The structure of the hydrogenation product was readily proved on the basis of the IR and ^{1}H NMR spectra. The IR spectrum showed broad absorption maxima for the carbonyls in the region of 1715 cm^{-1}. There was no signal for an olefinic proton in the ^{1}H NMR spectrum.

Attempted intramolecular aldol condensation of **391** under several standard conditions was unsuccessful. Neither *p*TSA in benzene at reflux nor alkoxide in hydroxylic solvents ever gave evidence of the production of any tricyclic enedione **384**.

Scheme 72

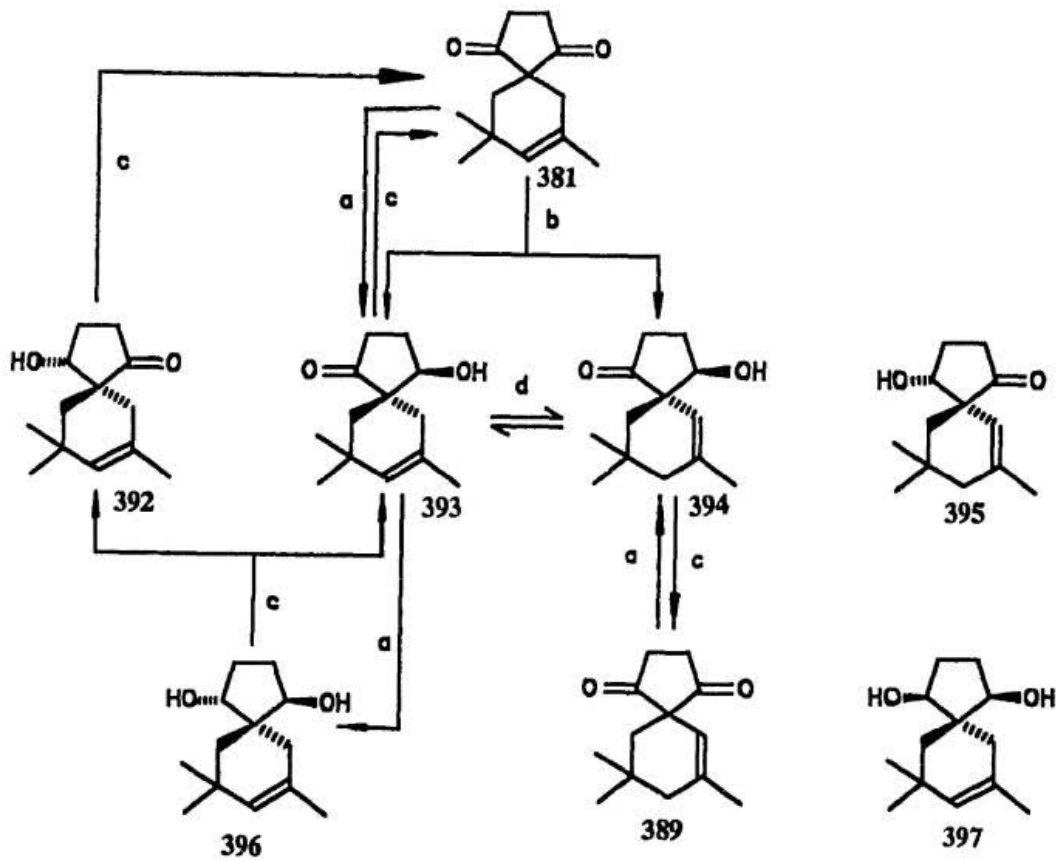


The failure of the intramolecular aldol condensation of the trione **391** might be attributed to the instability of the cyclopentane-1,3-dione moiety. Based on this assumption, we decided to reduce one carbonyl and to protect the resultant alcohol as a *tert*-butyldimethylsilyl ether. Thus, compound **381** was treated with 0.25 equivalents of sodium borohydride in methanol followed by addition of 10% hydrochloric acid* to

* To our knowledge, acidic work-up is generally employed after sodium borohydride reduction.[128]

give, after column chromatography, an 80% yield of monoalcohol. This product appeared to be pure by TLC analysis, but GC–MS showed clearly an approximate 1 : 1 mixture of two compounds with quite different mass spectra. In the ^{1}H NMR spectrum the olefinic protons were observed as broad singlets at δ 5.228 and 4.953 and the protons α to the hydroxyl groups appeared as multiplets at δ 4.230 and 4.222. In the ^{13}C NMR spectrum the signals at δ 222.0 and 219.1 and at δ 131.8, 127.3, 116.4 and 137.7 represented carbonyls and double bond carbons, respectively. The two compounds could have been epimeric alcohols **392** and **393**, or the double bond isomers

Scheme 73

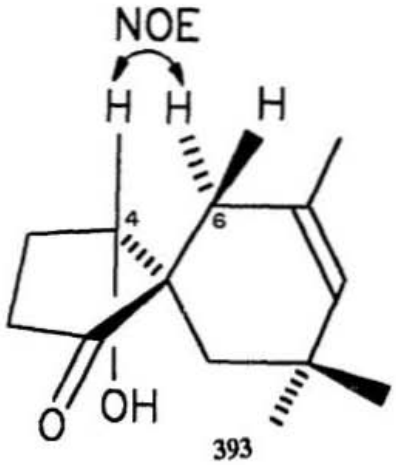


(a) $NaBH_4$; H_2O; (b) $NaBH_4$; 10% HCl; (c) PCC; (d) 10% HCl.

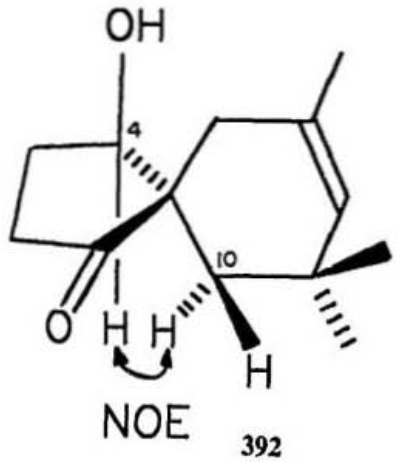
392 and **395**, or **393** and **394** (Scheme 73). In the ^{1}H NMR spectrum, the chemical shifts of the protons α to the hydroxyl groups in both compounds were close (δ 4.230 *vs.* 4.222), in contrast, the chemical shifts of the olefinic protons appeared quite different (δ 4.953 *vs.* 5.228). In addition, PCC oxidation of this mixture afforded an approximate 1 : 1 mixture of two spiro-diketones **381** and **389**. Thus, it could be concluded that the mixture consisted of double bond isomers instead of epimeric alcohols. Double bond isomerization must have occurred during the hydrochloric acid work-up. Indeed, when pure water was used in the work-up, then we were left with only one monoalcohol. To determine the stereochemistry of this product, we performed an NOE experiment. An NOE between the C-4** proton and the C-6 protons was expected for **393**, but not for **392**. On the other hand, there should have been an NOE between the C-4 proton and the C-10 protons in **392**, but not in **393**. Unfortunately, the NOE experiment on this reduction product was inconclusive. Therefore, we turned to an alternative solution.

Recall that $NaBH_4$ reduction followed by acidic work-up gave an approximate 1 : 1 mixture of double bond isomers. As a matter of fact, treatment of the monoalcohol prepared by $NaBH_4$ reduction and water work-up with 10% hydrochloric acid gave the same two double bond isomers as revealed by GC-MS analysis and ^{1}H NMR. Since the C-4 stereochemistry in both double bond isomers must be the same, we attempted to solve the C-4 stereochemistry in another isomer, i.e. **394** or **395**. To achieve this, we required a pure sample of either **394** or **395**. Treatment of **389** with 0.25 equivalents of $NaBH_4$ in methanol gave only one of the two double bond isomers as clearly indicated by ^{1}H NMR analysis. Again, NOE experiments were employed to tell the C-4 stereochemistry. Irradiation at δ 4.953 (olefinic proton) resulted in a 1.4% NOE at δ 4.222 (C-4 proton), and a 4.4% NOE at δ 4.953 was observed when

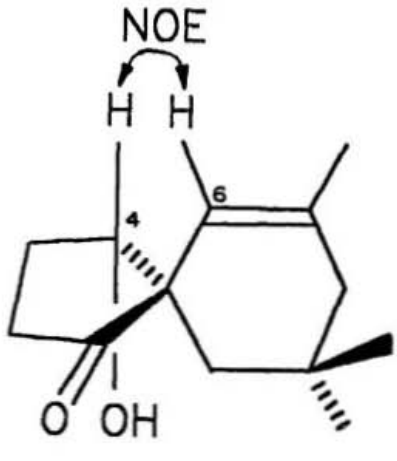
** IUPAC numbering



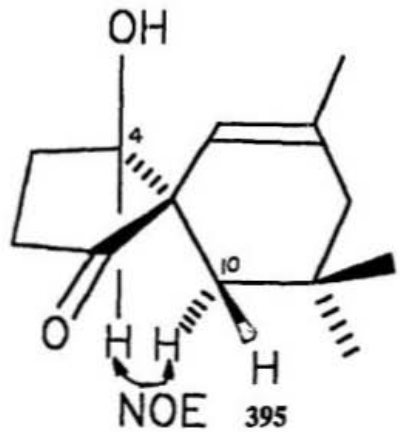
393



392



394



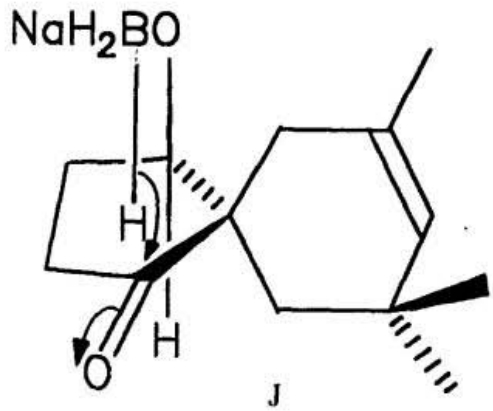
395

the C−4 proton at δ 4.222 was irradiated, which established a *syn* relationship between the C−4 proton and the double bond. Thus, this $NaBH_4$ reduction product was clearly **394**; therefore, the $NaBH_4$ reduction product of **381** could be assigned as **393**. Both **393** and **394** were reconverted into their corresponding diketones **381** and **389** quantitatively upon oxidation with PCC (Scheme 73). It was very interesting to note the remarkable facial selectivity of the $NaBH_4$ reduction of the spiro−diketones **381** and **389**. Steric effects may be partially responsible for the stereochemical outcome of the

$NaBH_4$ reduction of **389**, but in the case of **381**, the facial selectivity cannot be attributed to steric effects. One explanation is as follows. The double bond of the starting material and metal ion of the reagent might form a π-complex, thereby directing the reducing reagent to attack from the face syn to the double bond. The generality of the remarkable facial selectivity observed here is being investigated in more detail.

Further reduction of monoalcohol **393** with $NaBH_4$ provided cleanly the *trans* diol **396** (Scheme 73). Its IR spectrum showed an absorption maximum for hydroxyl groups at 3340 cm^{-1}. The *trans* stereochemistry of two hydroxyl groups was borne out by the fact that the two protons α to the hydroxyl groups appeared at δ 4.098 and 3.960 in the ^1H NMR spectrum. If the product were a *cis* diol **397**, then the chemical shifts of the two protons α to the hydroxyl groups should be the same (they would be chemically equivalent). The *trans* stereochemistry of diol **396** was strictly confirmed by chemical transformation. Oxidation of **396** with one equivalent of PCC in dichloromethane provided an approximate 1 : 1 mixture of the monoalcohols, one of which, as indicated by ^1H NMR spectrum, was **393**. Then another isomer must have been **392**. The chemical shifts of the olefinic protons of **392** and **393** were approximately the same (δ 5.225 *vs.* 5.231), but the carbinol protons in both compounds appeared quite different (δ 4.230 *vs.* 4.308). If the diol were *cis*, then oxidation with one equivalent of PCC would produce only **393**. The *trans* stereochemical outcome might be attributed to the possible intermediate **J** in which the hydride would attack from the face *syn* to the first hydroxyl group.

The *trans* diol **396** can be obtained directly from **381** by reduction with excess $NaBH_4$ (Scheme 74). However, a new substance was formed when 10% hydrochloric acid was used in the work-up procedure instead of pure water. Since treatment of **396** with 10% hydrochloric acid in methanol gave quantitatively the same compound, then the formation of this new compound must go through the *trans* diol **396**. The structure



J

of this new compound was elucidated according to the following spectroscopic evidence. The mass spectrum showed the same molecular ion as the diol **397**, and the IR spectrum displayed an absorption maximum for an hydroxyl group at 3405 cm^{-1}. In the ^{13}C NMR spectrum, we found five methylenes at δ 32.5, 36.6, 42.5, 46,3 and 51.0; two methines bearing oxygens at δ 77.0 and 84.4; three methyls at δ 26.8, 31.5 and 32.5; and three quaternary centers at δ 30.4, 57.6 and 83.0, one of which (δ 83.0) was connected to an oxygen. Comparison of the ^{13}C NMR spectrum of this new compound with that of **396** suggested the connection of the C−4 hydroxyl oxygen with C−7 and the conversion of the C−8 methine into methylene to give the new compound **398**. A mechanism for this acid−catalysed cyclization is outlined in Scheme 75. Protonation of the double bond in **396** can give two carbocations **401** and **402**. Carbocation **402** is expected to be much more stable than the secondary, neopentyl carbocation **401**, thus leading to the tricyclic alcohol **398** exclusively.

The assignment of the C−2 stereochemistry in **398** was based on the *trans* diol **396**. We thought that this assignment could be confirmed by a positive NOE between the C−2 hydroxyl proton* and C−5 proton. In the ^{1}H NMR spectrum of the alcohol

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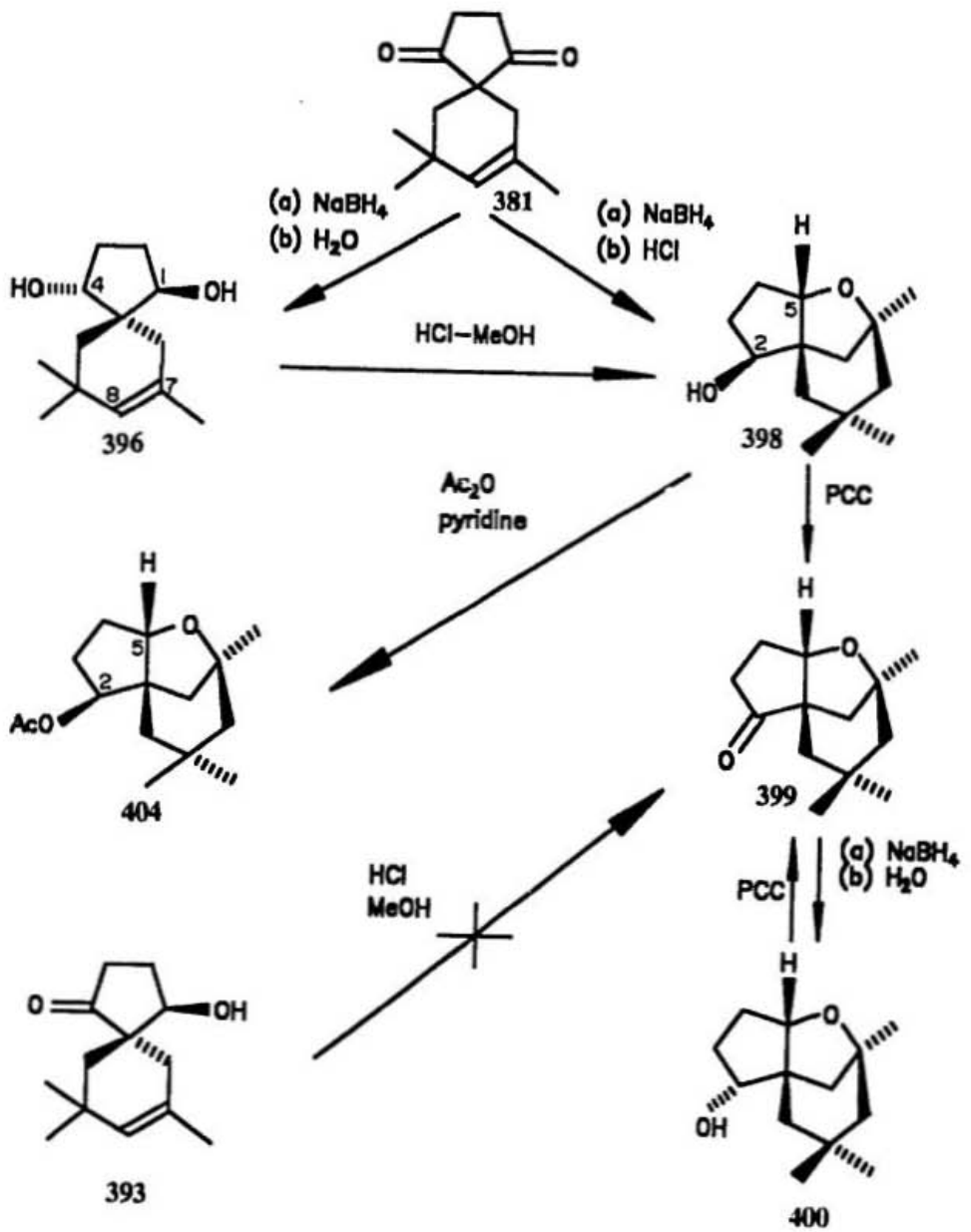
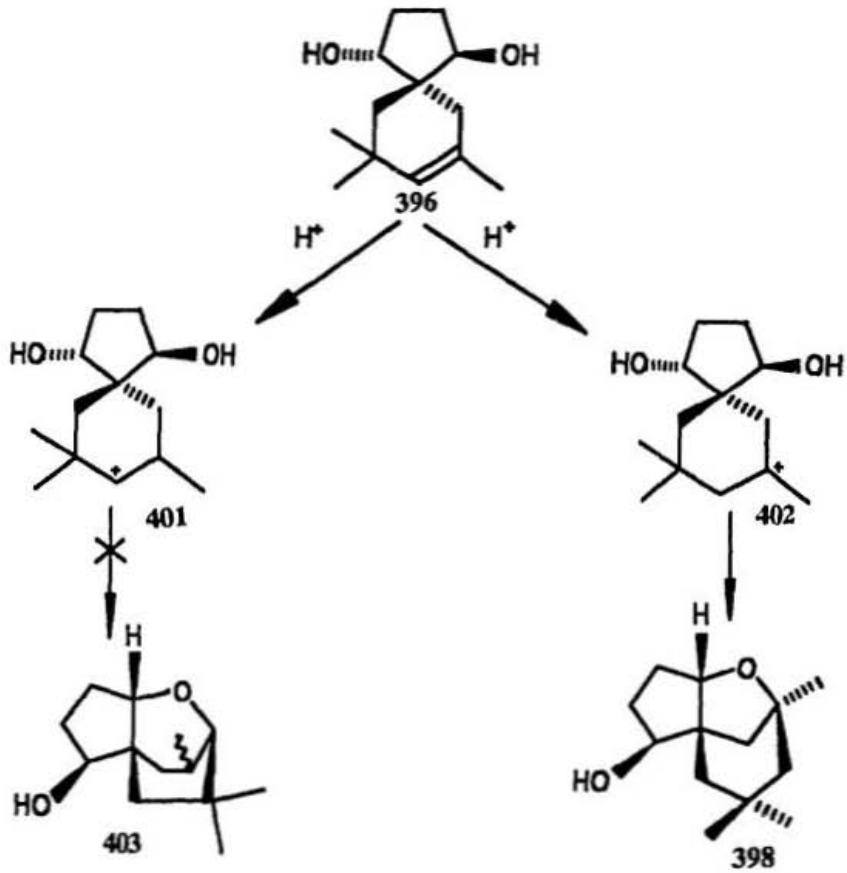
* It is known that an NOE experiment on an hydroxyl proton can be difficult, but it can be carried out by carefully choosing solvent and controlling the temperature.

Scheme 74



398, the two carbinol protons, i.e. the C−2 proton and the C−5 proton, appeared as double doublets at δ 4.026 and 4.524, respectively. In order to achieve the unambiguous assignment for the C−5 proton for the NOE experiment, we prepared the acetate **404** by treatment of **398** with acetic anhydride and pyridine (Scheme 74). It was

Scheme 75



anticipated that the C−2 proton of **398** would shift downfield significantly and the chemical shift of the C−5 proton would change very little. In fact, the C−2 and C−5 protons of the acetate **404** were observed as double doublets at δ 4.505 and 5.084, respectively. Thus, the the C−2 proton and the C−5 proton of acetate **404** were assigned at δ 5.084 and 4.505 and those of alcohol **398** were assigned at δ 4.026 and 4.524. It turned out that no significant NOE was observed between the C−5 proton and the C−2 hydroxyl.

Oxidation of **398** with PCC proceeded cleanly to give ketone **399** (Scheme 74). The IR spectrum of this compound showed an absorption maximum for the carbonyl

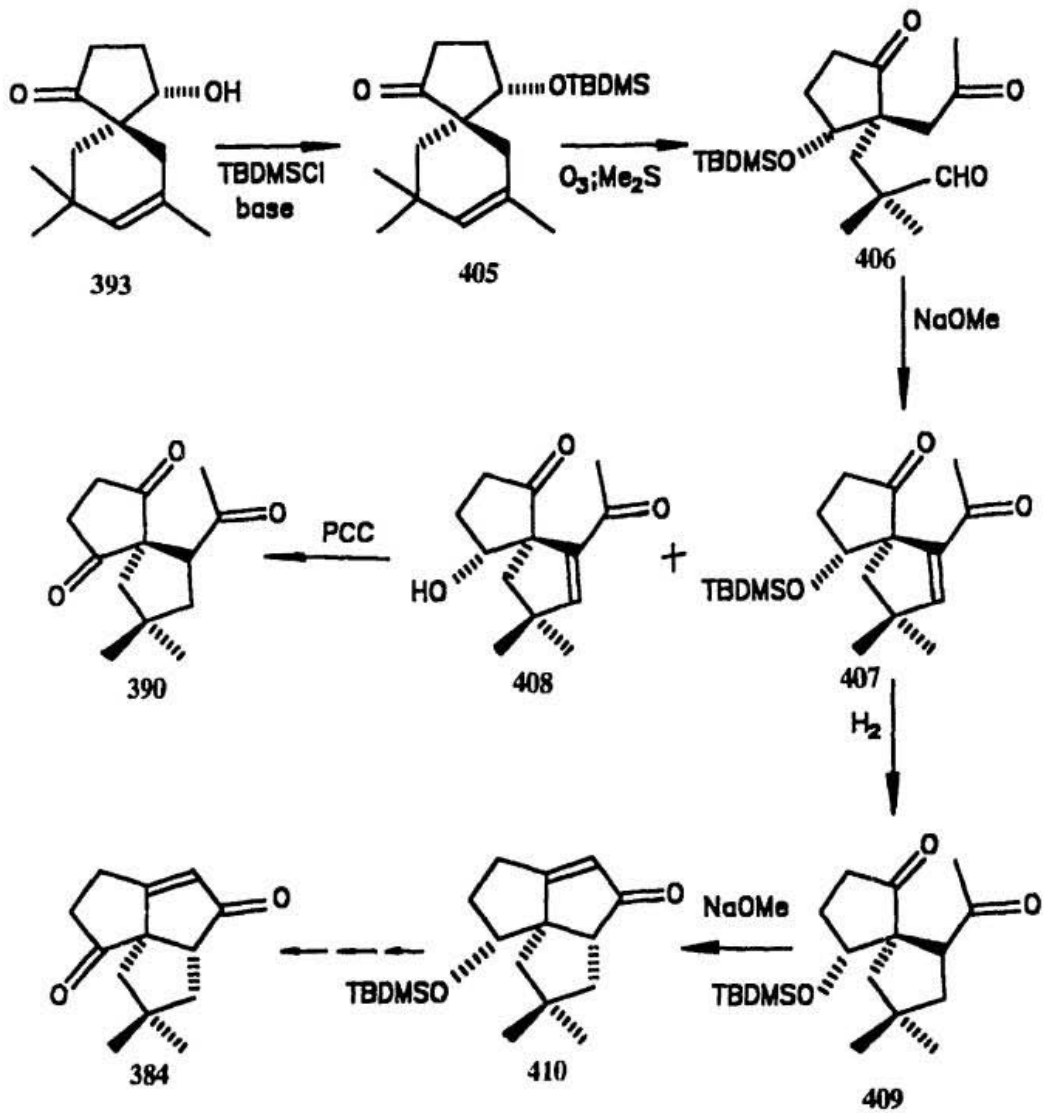
at 1739 cm^{-1}. In addition, the carbonyl appeared at δ 216.3 in the ^{13}C NMR spectrum. The chemical shift of the C-5 proton was δ 4.604, which supported our previous assignment of the C-5 and C-2 protons in alcohol **398**.

Reduction of ketone **399** with sodium borohydride afforded a single product. Although the mass spectrum and R_f value of this product appeared to be the same as for alcohol **398**, ^1H and ^{13}C NMR spectroscopic analysis suggested a different compound. The IR spectrum showed an absorption maximum for the hydroxyl group at 3420 cm^{-1}. Furthermore, the ^{13}C NMR spectrum indicated the same number of primary, secondary, tertiary and quaternary carbons as those in **398**. Clearly, this compound must have been be the epimeric alcohol **400**. The C-5 and C-2 protons of **400** were observed at δ 4.265 and 3.854, respectively. Alcohol **400**, upon treatment with PCC, was oxidized quantitatively back to ketone **399**.

With the stereochemical studies of the sodium borohydride reduction on spiro-diketone **381** finished, we returned our attention to the conversion of the monoalcohol **393** to the tricyclic intermediate **410** (Scheme 76). Treatment of **393** with *tert*-butyl-chlorodimethylsilane (TBDMSCl) and imidazole, using 4-dimethylaminopyridine (DMAP) as a catalyst, provided **405** accompanied by small amount of di-*tert*-butyldimethylsilyl ether ($(TBDMS)_2O$) as revealed by GC-MS analysis of the crude product. However, column chromatography on silica gel gave only a 46% yield of **405**, and **393** was recovered in 47% yield. It was evident that some product was hydrolysed back to the alcohol on silica gel. The IR spectrum of compound **405** showed an absorption maximum for the ring carbonyl at 1740 cm^{-1}. In the ^1H NMR spectrum, two methyl singlets at δ 0.054 and 0.086 and a nine-proton singlet at δ 0.087 were attributed to the protecting group.

After ozonolysis of **405**, the crude product **406** was treated with sodium methoxide in methanol at room temperature. The conjugated enones we isolated were

Scheme 76



407 (21%) and **408** (2%). The IR spectrum of **407** showed absorption maxima for the ring carbonyl at 1746 cm^{-1}, for the conjugated carbonyl at 1670 cm^{-1}, and for the conjugated double bond at 1623 cm^{-1}. In its ^1H NMR spectrum, the one–proton singlet at δ 6.692 and three–proton singlet at δ 2.284 were assigned to the olefinic proton and acetyl group, respectively. The structural assignment of alcohol **408** was based on the

fact that the ^1H NMR spectrum was quite similar to that of **407** except that no signals attributable to the *tert*-butyldimethylsilyl group were evident. Since IR and ^{13}C NMR spectra were not feasible due to the small quantity of **408**, classic chemical transformation was applied to confirm the structural assignment. As expected, PCC oxidation of **408** provided quantitatively the trione **390**, whose ^1H NMR and mass spectra were completely superimposable with those of the authentic sample of **390** prepared previously. Our efforts to optimize the yield of **407** proved to be fruitless.

The conversion of enone **407** to saturated dione **409** was achieved easily by catalytic hydrogenation. Absorption maxima in the IR spectrum were observed at 1738 cm^{-1} for the ring carbonyl and at 1691 cm^{-1} for the acetyl carbonyl. No double bond was present as indicated by the ^1H and ^{13}C NMR spectra.

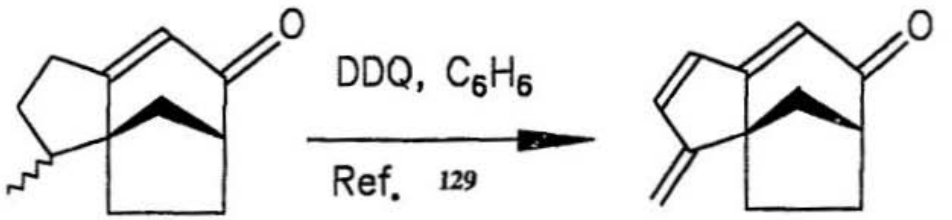
At this stage, the crucial ring closure leading to the tricyclic compound **410** was examined. To our delight, upon treatment with sodium methoxide in methanol at room temperature, a new UV-active substance was formed exclusively. Carbonyl stretching frequency at 1711 cm^{-1} and C=C stretching frequency at 1630 cm^{-1} in the IR spectrum of the product, olefinic resonance at δ 5.808 (1H, s) in the ^1H NMR spectrum, and a prominent peak at *m/z* 263 ($M^+ - (CH_3)_3C$) in the mass spectrum, all suggested that this product was the elusive tricyclic enone **410**. We were able to obtain **410** in yields as high as 85% after column chromatography.

Tricyclic enone **410** can serve as a key precursor to the enedione **384**. However, the poor yield in the conversion of **406** to **407** was deemed unsatisfactory for our synthesis of pentalenene, so an alternative route was sought.

Ms. Peiying Liu[129] in our laboratory discovered that the epimeric mixture **411**, upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *p*TSA in benzene at reflux for several days, gave the trieneone **412** in a modest yield (Scheme 77). Based on this result, we thought that trienone **413** may serve as a possi-

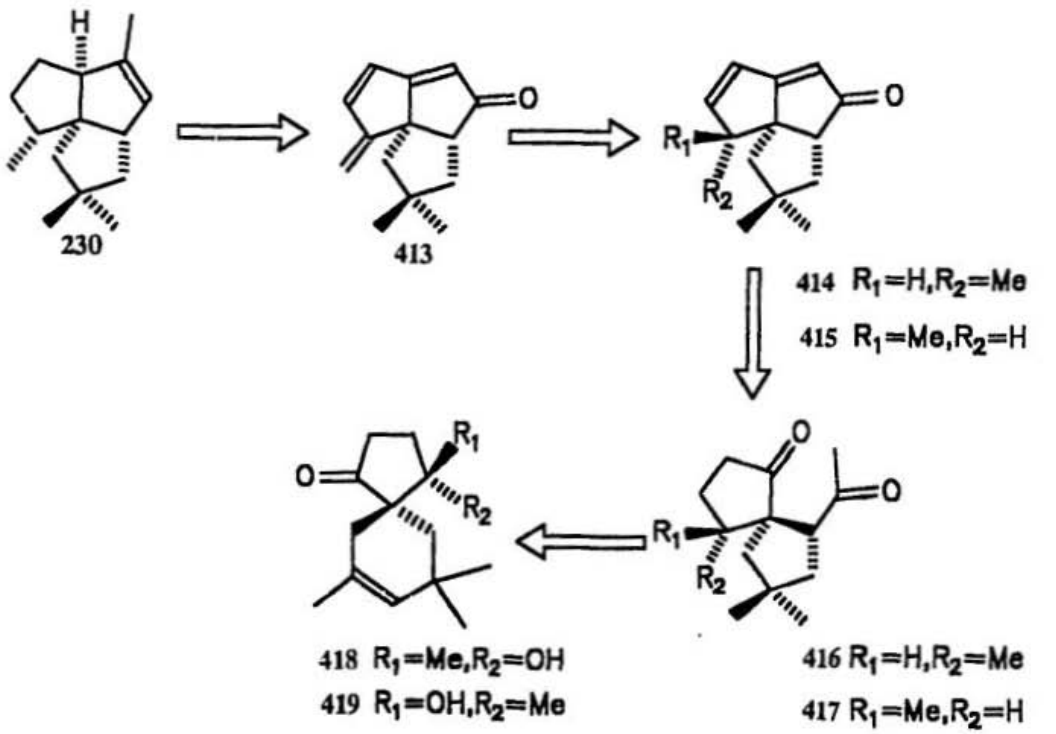
ble precursor to pentalenene, and **413** might be derived from enone **414** and/or **415** as outlined in Scheme 78. The preparation of enone **414** and/or **415** was planned starting from keto–alcohol **418** and/or **419**, *via* diketone **416** and/or **417**.

Scheme 77



411 **412**

Scheme 78

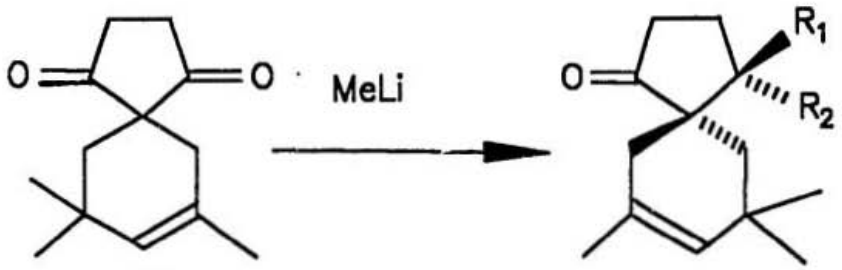


230 **413**

This synthetic study began with the addition of methyllithium to **381** (Scheme 79). Since methyllithium is a very reactive reagent, we were worried about double addition, which would lead to a diol. Thus, compound **381** was treated with only one equivalent of methyllithium in ether at −78°C for two hours. GC−MS analysis of the crude product indicated a mixture of a monoalcohol and starting material. We were relieved that no detectable amount of diol was formed. Since some starting material remained after the above reaction, we tried adding five equivalents of methyllithium to **381**. After column chromatography on silica gel, we were left with two monoaddition products in isolated yields of 86% and 1.4%, accompanied by a 3% recovery of the starting material **376**. Once again, no diol was isolated. (In fact, GC−MS analysis revealed that no diol was formed even when twenty equivalents of methyllithium were applied.) In the IR spectrum of the major product, absorption maxima appeared at 3426 cm^{-1} for the hydroxyl and 1730 cm^{-1} for the ring carbonyl. The three−proton singlet at δ 1.152 in its ^{1}H NMR spectrum was attributed to the C−4 methyl group. The quaternary carbon bearing oxygen was found at δ 78.1 in the ^{13}C NMR spectrum. All these spectroscopic data were in agreement with either **418** or **419**. The relative stereochemistry of C−4 in the major adduct was unambiguously assigned on the basis of NOE data. For adduct **418**, we expected an NOE between the C−4 methyl and the C−6 protons. On the other hand, in the case of **419**, an NOE between the C−4 methyl and the C−10 protons should be observed. In the ^{1}H NMR spectrum, the two−proton AB system at δ 1.690 and 1.727 and two−proton broad singlet at δ 1.789 were attributed to the C−10 and C−6 protons, respectively. This assignment was further proved when a 3−4% NOE at δ 1.690 and 1.727 (C−10 protons) was observed on irradiation at δ 0.896 and 1.003 (the C−9 methyls). When the C−4 methyl at δ 1.152 was irradiated, a 5% NOE at δ 1.789 (C−6 protons) was evident, which established the *syn* relationship of the C−4 methyl and the double bond, i.e. **418**. Regarding the minor product, the mass spectrum was very similar to that of the major adduct **418**, but its ^{1}H

NMR spectrum was different. The three-proton singlets at δ 1.777, 1.293, 0.996 and 0.857 were assigned as the C-7, the C-4 and the two C-9 methyls. The olefinic resonance at δ 5.178 (1H, br s) was quite close to that of **418** at δ 5.182 (1H, br s), suggesting that the two products were not double bond isomers. Thus, the minor adduct was assigned structure **419**. The remarkable facial selectivity observed here in the methyllithium addition was consistent with that of the sodium borohydride reduction discussed previously.

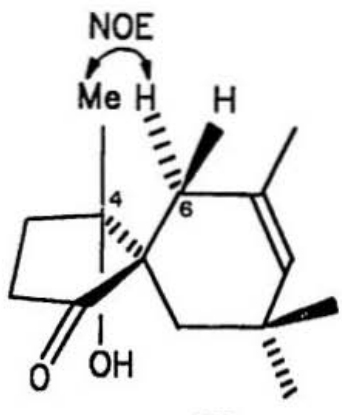
Scheme 79



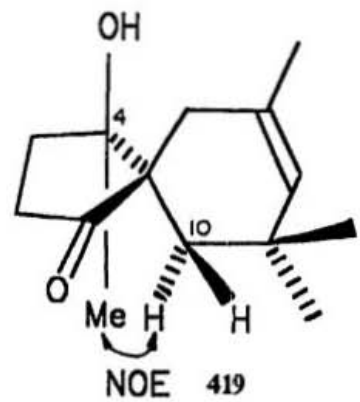
381

418 R_1=Me,R_2=OH

419 R_1=OH,R_2=Me



418

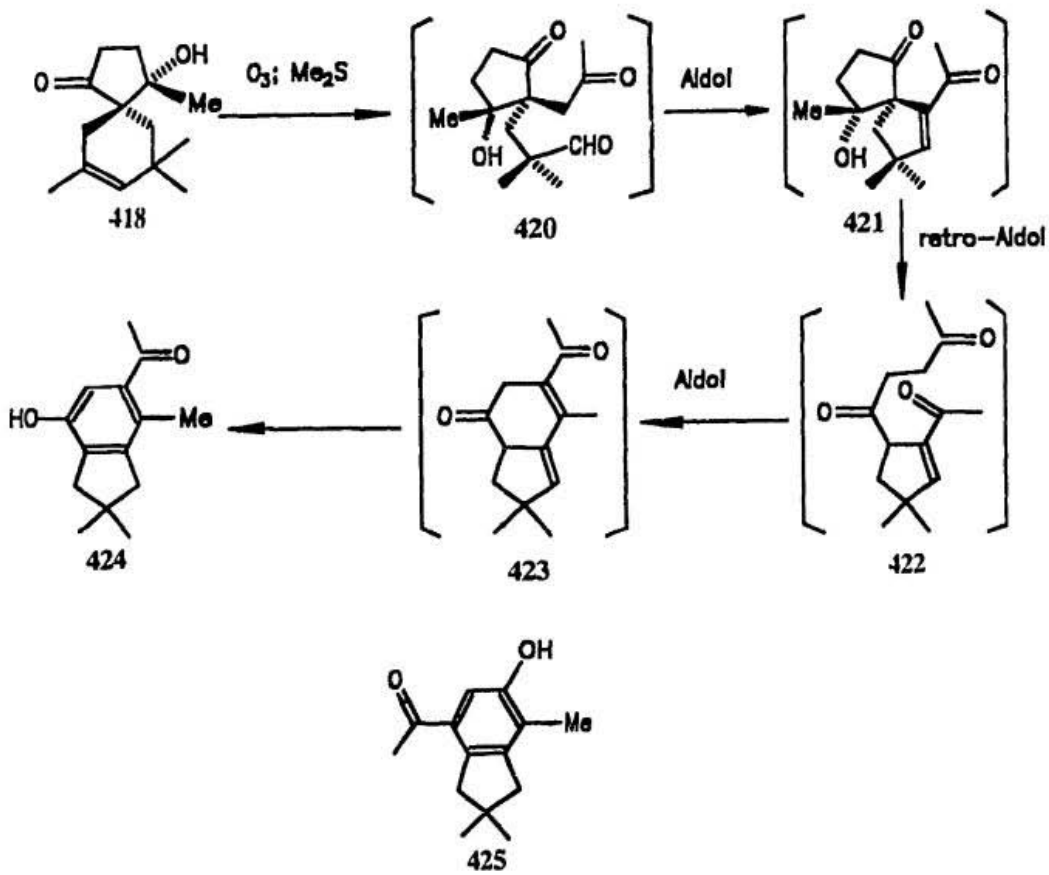


419

With the keto–alcohol **418** in hand, we thought that simultaneous intramolecular aldol condensation and elimination of the tertiary alcohol in **420**, prepared from **418** *via* ozonolysis, would give **426** and/or **427**. After ozonolysis, the crude product **420** was allowed to react with sodium methoxide in methanol at room temperature for twenty minutes. Usual work–up provided a single, very UV–active crystalline substance. In its mass spectrum, a strong peak at m/z 43 suggested a methyl ketone and a prominent molecular ion at m/z 218 implied that this product was derived from **420** by elimination of two equivalents of water. The IR absorption maxima at 3197 (br), 1650, 1595, and 1461 cm^{-1} indicated that this compound contained an hydroxyl, a conjugated carbonyl, and conjugated double bonds or an aromatic moiety. In the ^1H NMR spectrum, two three–proton singlets at δ 2.530 and 2.296 were assigned to two methyls. Another two methyl groups were found as one larger singlet at δ 1.178. A four–proton singlet at δ 2.712 might represent two methylenes attached to an aromatic ring. Carbon resonances at δ 149.5, 146.5, 137.7, 132.5, 126.4 and 114.4 indicated an aromatic ring. This benzene derivative was pentasubsti ıted as evidenced by the single aromatic proton resonance at δ 7.005 (1H, s) and one methine aromatic carbon resonance (δ 114.4). Based on this analysis, we concluded that the product possessed an indane skeleton with methyl, hydroxyl and acetyl groups attached to the benzene ring. Generally, the chemical shift of an aromatic proton is around δ 7.3 ppm. However, if this proton were adjacent to an acetyl group, the proton resonance would be shifted downfield to around δ 8.0 ppm. In contrast, if this proton were next to an hydroxyl group, then the proton resonance would be shifted upfield up to around δ 6.7 ppm. In our case, the aromatic proton resonance at δ 7.005 suggested strongly that this proton be located between acetyl group and hydroxyl group so that the deshielding effect of acetyl group roughly cancelled the shielding effect of the hydroxyl group. Thus, the structure of the product could be either **424** or **425**. However, the reaction mechanism precluded the possibility of structure **425**. The formation of **424** could be rationalized as below

(Scheme 80). The enone **421**, derived from ozonolysis product **420** by intramolecular aldol condensation, underwent *retro*-aldol ring cleavage to give **422**, which led to aromatic compound **424** by a second intramolecular aldol condensation followed by double bond isomerization and enolization of the ring carbonyl *via* **423**.

Scheme 80

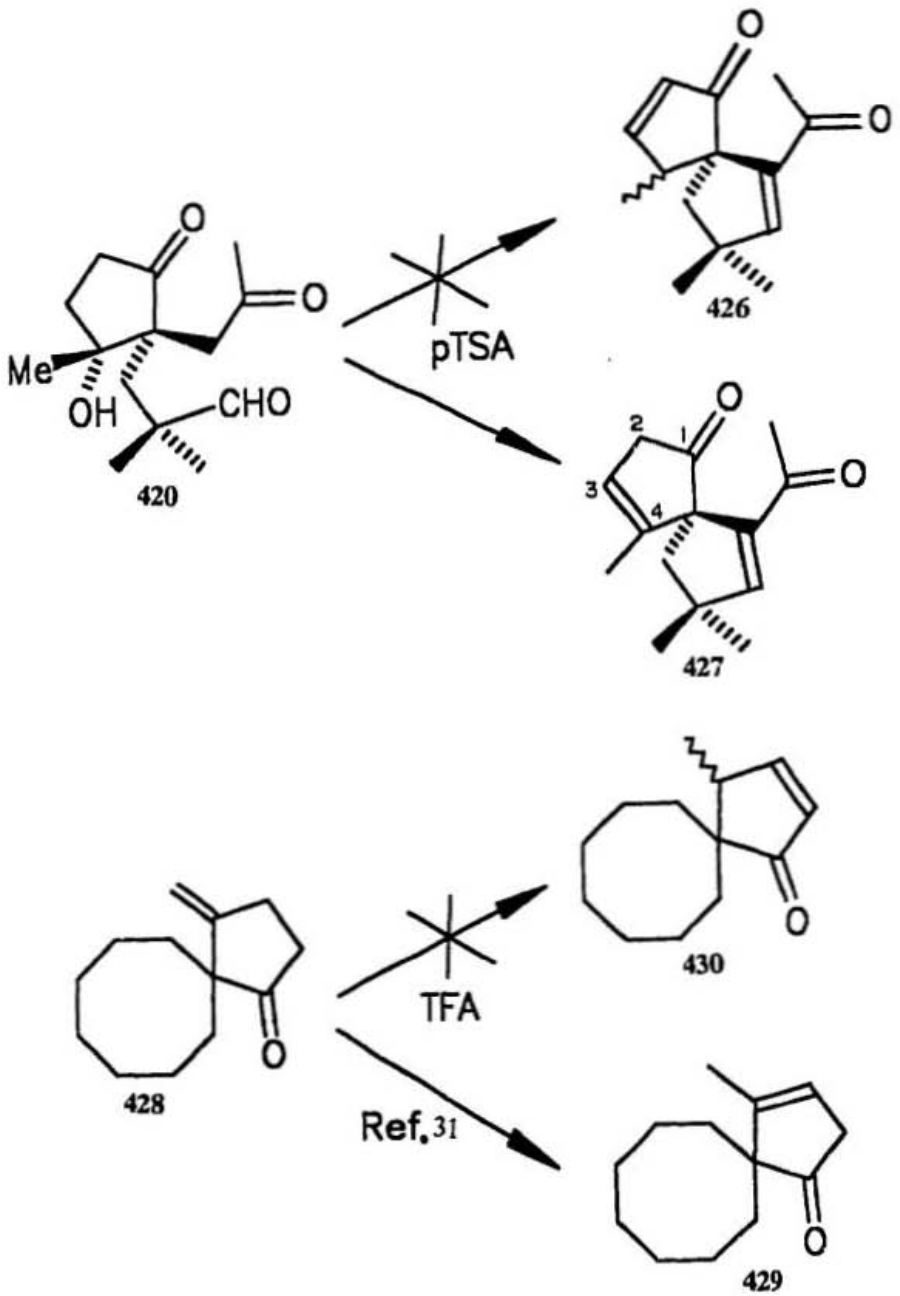


Since treatment of **420** with base resulted in ring cleavage, we turned to acidic conditions. Indeed, crude **420** upon treatment with *p*TSA in benzene at reflux with continuous azeotropic removal of water, gave a single, UV-active product. A strong peak at *m/z* 43 in its mass spectrum implied the methyl ketone moiety and a

prominent molecular ion at *m/z* 218 indicated that the product was derived from **420** by elimination of two equivalents of water. IR absorption maxima appeared at 1741 cm^{-1} for the nonconjugated carbonyl and 1671 cm^{-1} for the conjugated carbonyl, which suggested enone **427** (Scheme 81). Further evidence was derived from ^{1}H and ^{13}C NMR spectra. A methyl singlet at δ 2.260 represented the acetyl group. The integration of the ^{1}H NMR spectrum showed that there were only two olefinic protons, and a vinyl methyl resonance appeared at δ 1.640. Only two sp^2 methines were found at δ 121.5 and 157.1 in the ^{13}C NMR spectrum. These facts ruled out structure **426**. After column chromatography on silica gel, enone **427** was obtained in 69% yield. The reason why the 3,4-double bond in **427** did not isomerize to the conjugated 2,3-position remains uncertain. Nevertheless, some similar examples are known in literature. For instance, Kuwajima and coworkers reported that 3-methylenecyclopentanone **428** readily isomerized to the more stable *endo* olefinic isomer **429** in 54% yield, but none of the conjugated enone **430** was formed in the reaction (Scheme 81).

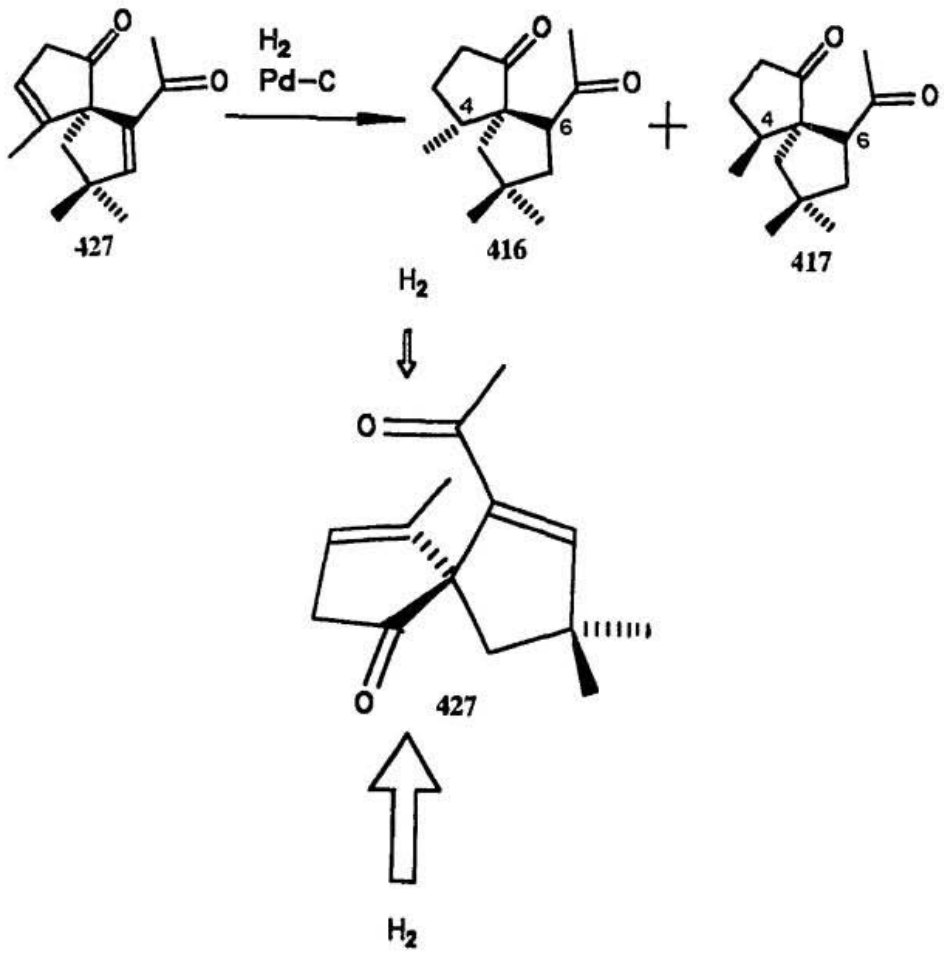
Catalytic hydrogenation of **427** preceeded quantitatively (Scheme 82). The IR spectrum of the crude product showed absorption maxima for the ring carbonyl at 1733 cm^{-1} and the methyl ketone at 1712 cm^{-1}. GC-MS analysis indicated a mixture of two isomers whose mass spectra were almost identical. These two isomers could be easily distinguished from the ^{13}C NMR spectra of the mixture in which one set of signals was much larger than another set. It should be pointed out that there are three chiral centers in **416** or **417**, thus four (racemic) isomers would be expected. However, only two isomers were formed in this case, which suggested either epimers at C-4 or C-6. The three-proton doublets at δ 1.049 and at δ 1.003 in the ^{1}H NMR spectrum of the mixture were attributed to the C-4 methyls in the major isomer and minor isomer, respectively. The C-6 proton resonances in the major isomer and minor isomer appeared as double doublets at δ 3.234 and 2.913, respectively. The relative

Scheme 81



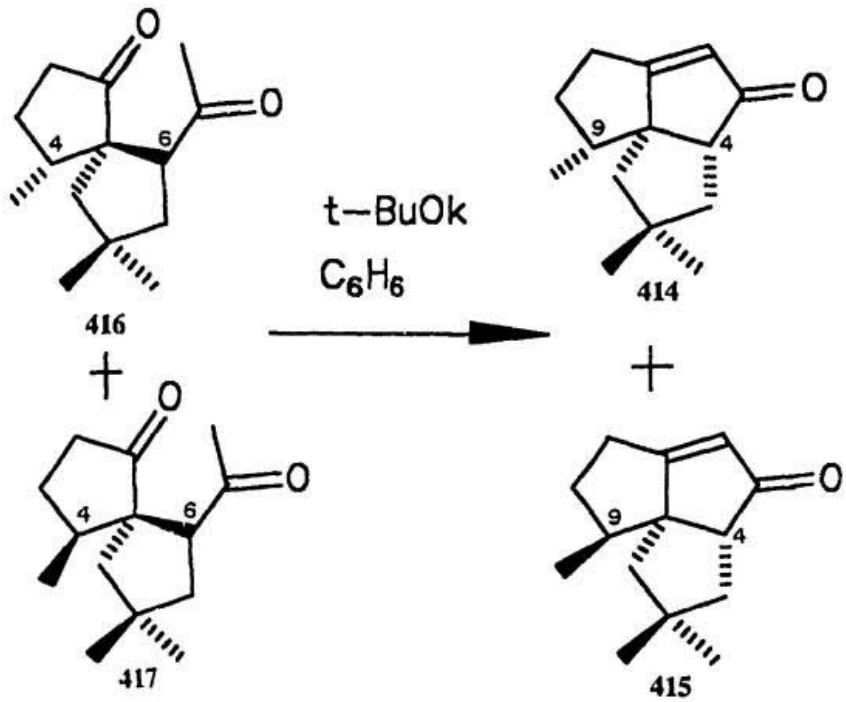
stereochemistry of the two hydrogenation products was established later in the synthesis (*vide infra*).

Scheme 82



The conversion of the hydrogenation products to tricyclic enones **414** and **415** required an intramolecular aldol condensation, which might be troublesome due to the ring strain (Scheme 83). Our attempts to induce this cyclization by using either *p*TSA in benzene at reflux or sodium methoxide in methanol gave no detectable cyclization product. Nevertheless, treatment of the hydrogenation products with potassium *tert* –

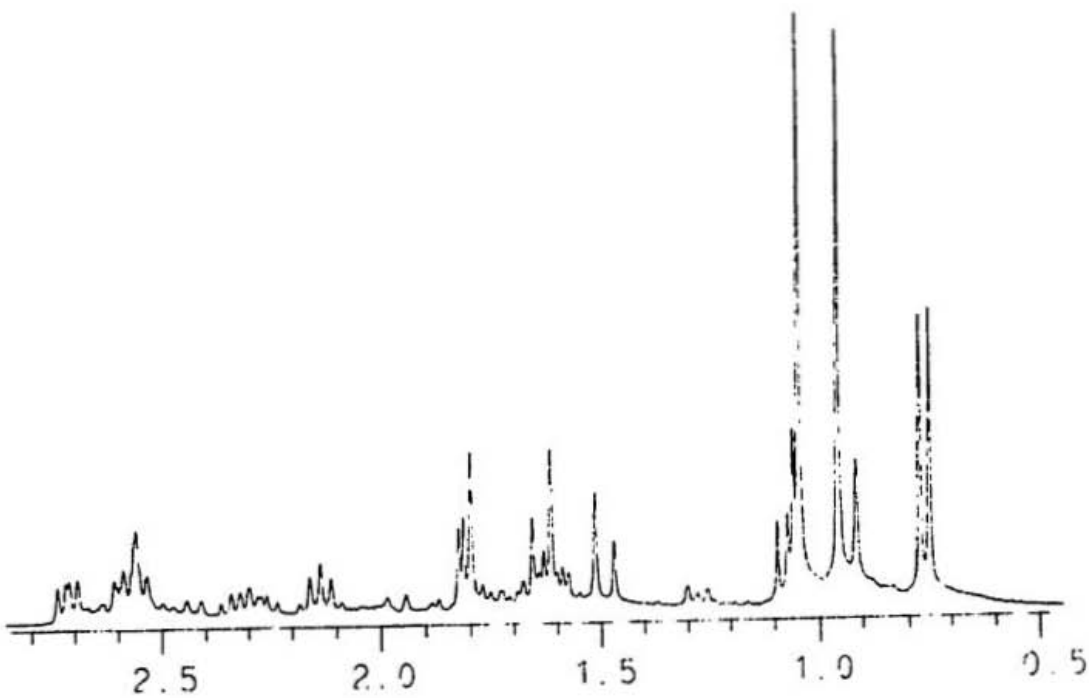
Scheme 83



butoxide in benzene under carefully controlled conditions cleanly produced a UV–active product. When the reaction was carried out in benzene at reflux, then several minutes were long enough for the reaction to be complete. Longer treatment resulted in complete destruction of the UV–active product. The cyclization at room temperature required up to twenty minutes, which provided enough time for TLC analysis. In general, the reaction was performed at room temperature and closely monitored by TLC. When TLC showed complete conversion, the reaction was worked up. The IR spectrum of the product showed absorption maxima for a conjugated carbonyl at 1705 cm^{-1} and for a double bond at 1631 cm^{-1}. Although this product appeared to be pure by TLC analysis, GC–MS analysis revealed clearly a 1 : 3.5 mixture of two isomers whose mass spectra were almost identical. Disappearance of a very strong peak at *m/z* 43 for the methyl ketone moiety as well as a prominent molecular ion at *m/z* 204

implied the cyclization products **414** and **415**. In the ^{13}C NMR spectrum of the mixture, there were two sets of signals, one of which was predominant. In the ^{1}H NMR spectrum ($CDCl_3$), an olefinic proton resonance was observed at δ 5.766. Doublets at δ 0.737 and 1.057 were attributed to the C−9 methyls of the major and minor epimers, respectively (Figure 9). The C−9 methyls of two isomers were shifted upfield in C_6D_6: δ 0.439 (d) for the major and δ 0.756 (d) for the minor isomer. The next issue to be addressed was the relative stereochemistry of each isomer. Examination of molecular models suggested that one cyclization product, **415**, might show an NOE between its C−9 methyl and its C−4 proton. The C−4 hydrogen of the major isomer was found as a double doublet at δ 2.567 (C_6D_6). Irradiation of this double doublet resulted in a 2% NOE of the C−9 methyl at δ 0.439, and an 11% NOE of the C−4 proton at δ 2.567 was observed when the C−9 methyl at δ 0.439 was irradiated. This NOE data indicated

Figure 9. Partial ^{1}H NMR spectrum of the 1 : 3.5 mixture of **414** and **415** ($CDCl_3$)



the *syn* relationship between the C−9 methyl and the C−4 hydrogen in the major epimer, i.e. **415**. No NOE between the C−9 methyl and the C−4 hydrogen was observed for the minor epimer, but, since the major epimer was assigned **415**, then **414** must have been the minor epimer. The ^{13}C chemical shifts of the quaternary double bond carbon in tricyclic enones **414** (δ 194.4) and **415** (δ 192.1) were unusually low−field, a result attributable to the considerable bond strain.[130] It should be pointed out that the relative stereochemistry at C−9 in the major epimer **415** was unfortunately opposite to that of natural pentalenene.

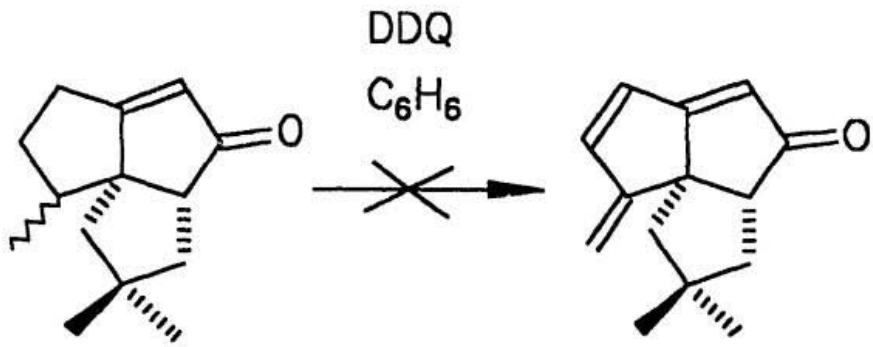
With the relative stereochemistry of the cyclization products **414** and **415** established, we were able to assign the relative stereochemistry of the earlier hydrogenation products. Since the cyclization products **414** and **415** were in a ratio of 1 : 3.5 and the hydrogenation product was composed of only two 1 : 3.5 isomers, it could be concluded that the hydrogenation products were C−4 epimers **416** and **417**, of which the latter was predominant. The relative stereochemistry at C−6 in both **416** and **417** was not established. Actually, the chirality at C−6 made no difference for our synthesis because the basic reaction condition can induce epimerization at C−6 leading to the desired stereochemistry for the cyclization.

The predominant formation of **417** over **416** in the catalytic hydrogenation could be easily rationalized (Scheme 82). If one postulates that the isolated double bond is hydrogenated much faster than the conjugated double bond, then one face of the isolated double bond in **427** would be seriously shielded by the acetyl group, thereby resulting in **417** as the major epimer.

Recall that the cyclization products were a 1 : 3.5 mixture of **414** and **415**, of which only the former possessed the desired stereochemistry at C−9. Our plan was to prepare trienone **413** from the C−9 epimers **414** and **415**, and we hoped that catalytic hydrogenation of **413** would then result in the desired stereochemistry at C−9

(Scheme 84). Therefore, the mixture of **414** and **415** was treated with DDQ and *p*TSA in benzene at reflux for one week. To our disappointment, GC–MS analysis indicated no detectable formation of doubly dehydrogenated product **413**. A longer reaction time and a large excess of DDQ resulted in no improvement. The failure of this reaction might result from much greater ring strain in trienone **413** compared with **412**.

Scheme 84

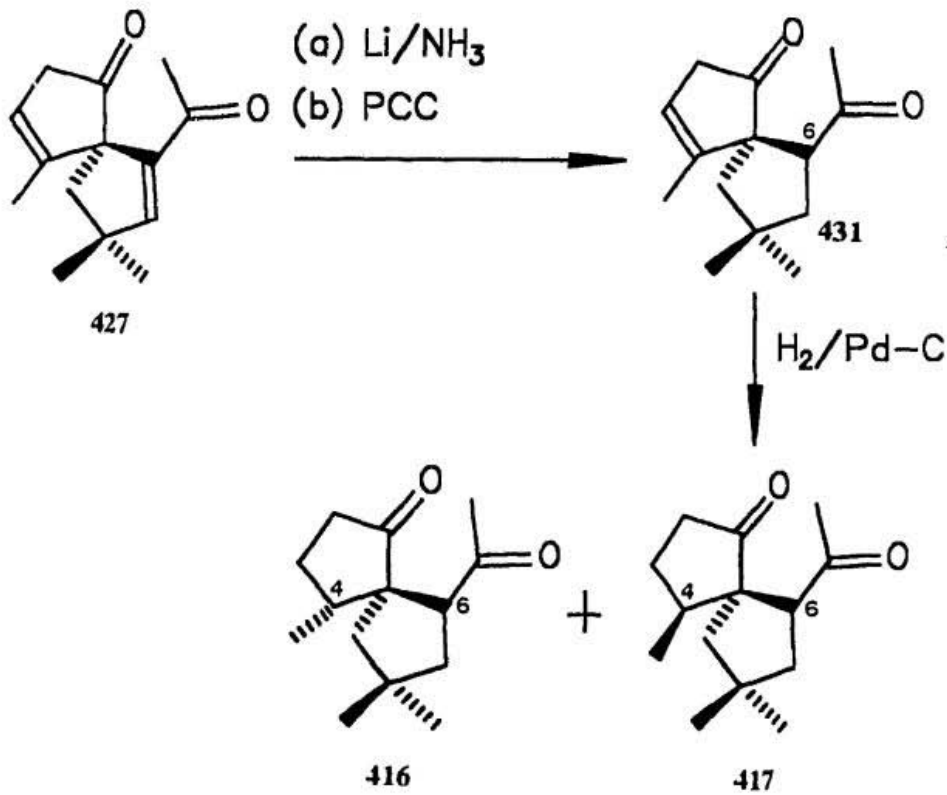


414/415 **413**

The predominant formation of epimer **417** was explained by assuming that the isolated double bond was hydrogenated prior to the conjugated double bond (Scheme 82). Then the ratio of **416** to **417** might be increased if the conjugated double bond were reduced before the isolated double bond. Lithium–ammonia reduction of **427** resulted in a complex mixture of at least three components as indicated by TLC analysis. Since this mixture, upon oxidation with PCC, gave exclusively one product, then it must have contained some overreduced products. The IR spectrum of the product after PCC oxidation showed absorption maxima for the ring carbonyl at 1745 cm^{-1}, for the nonconjugated methyl ketone at 1710 cm^{-1}, and for the double bond at 1643 cm^{-1}. The single olefinic proton resonance at δ 5.690 in the ^1H NMR spectrum confirmed the structure of reduction product **431** (Scheme 85). It is worth mentioning that there are two chiral centers (C–5 and C–6) in **431**, thus two C–6 epimers might

have been expected from the Birch reduction. However, the ^{13}C NMR spectrum was consistent with the presence of only one product. Our attempt to solve the relative stereochemistry at C-6 by using NOE experiments was unsuccessful. Nevertheless, the chirality at C-6 did not matter for our synthesis.

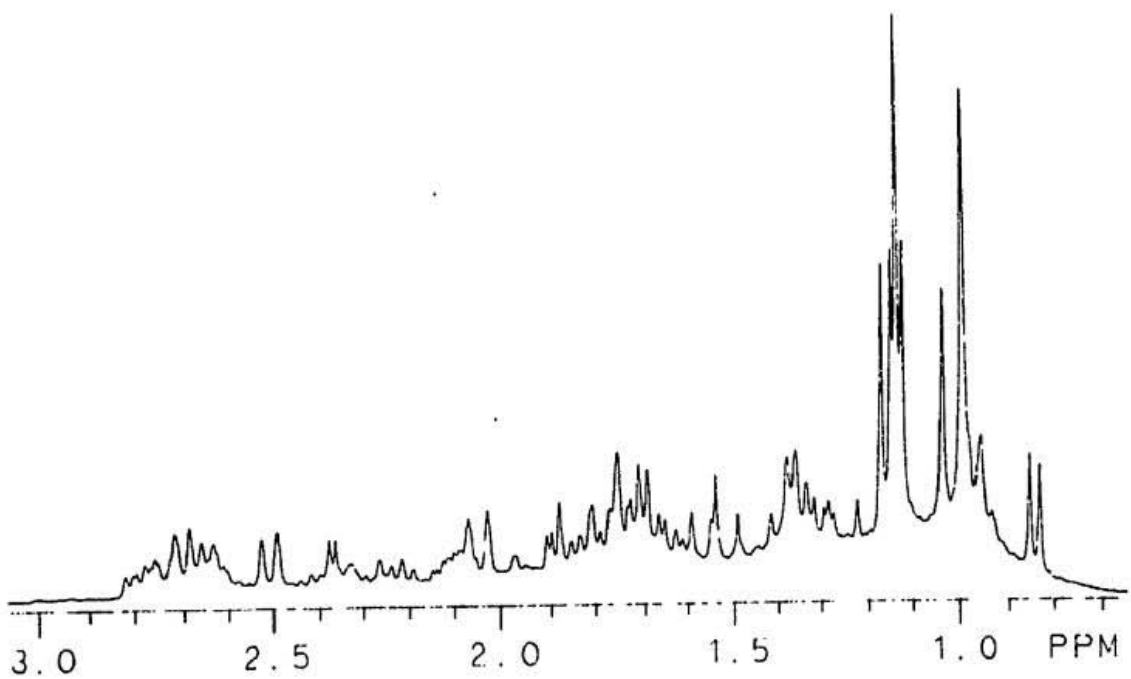
Scheme 85



Since Birch reduction gave only isomer **431**, the catalytic hydrogenation of **431** could only provide two C-4 epimers. Indeed, after catalytic hydrogenation, the resulting C-4 epimers **416** and **417** were treated with potassium *tert*-butoxide in benzene at room temperature for twenty minutes to provide an 84% isolated yield of **414** and **415** in 3.5 : 2 ratio as calculated from the GC-MS data and by integration of the C-9 methyls in the ^1H NMR spectrum (Figure 10). Obviously, the hydrogenation products were a 3.5 : 2 mixture of **416** and **417**. It is important to note that the epimer **416**, a

minor product in the direct hydrogenation of **427**, was predominant after hydrogenation of **431**. The reason for the preferred formation of **416** in the hydrogenation of **431** remains uncertain, but at least we can rationalise the relatively high ratio of **416** to **417**. In compound **431**, whatever the stereochemistry at C-6 is, the acetyl group was located further away from 3,4-double bond than that in **427**, and consequently, the steric hindering effect of the acetyl group must be much less, which would allow other directive effects to become important. Thus, some favorable interaction between the acetyl carbonyl group and the palladium catalyst might direct the hydrogenation preferentially to the face *syn* to the acetyl group.

Figure 10. Partial ^1H NMR spectrum of the 3.5 : 2 mixture of **414** and **415** ($CDCl_3$)



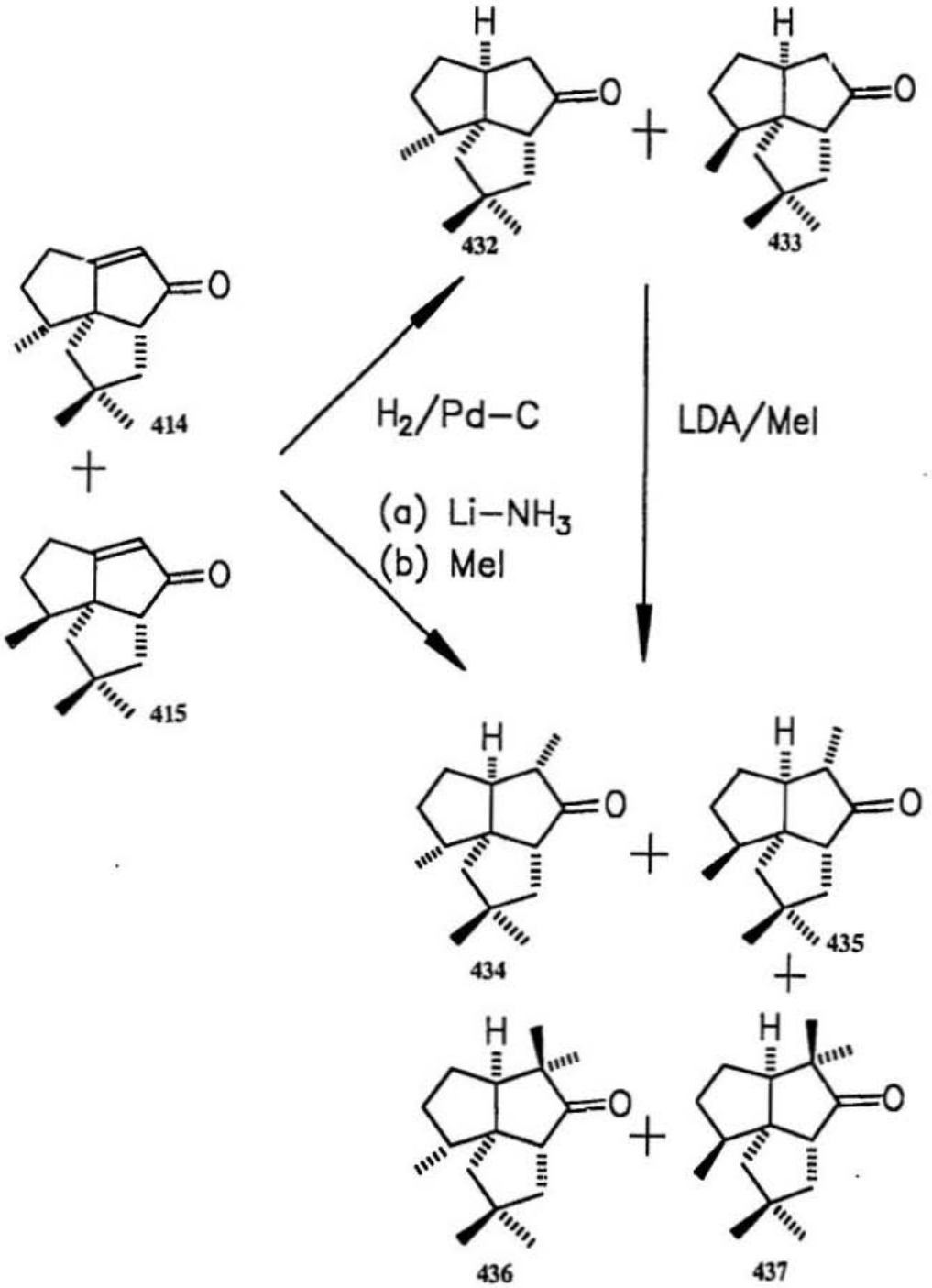
With the key intermediates **414** and **415** in hand, the conversion to pentalenene and *epi*-pentalenene was next addressed (Scheme 86). A 1 : 3.5 mixture of **414** and **415**, derived from the direct hydrogenation route, was subjected to catalytic

hydrogenation to afford quantitatively a mixture of **432** and **433**, in 1 : 3.5 ratio by GC–MS. An IR absorption maximum appeared at 1739 cm^{-1} for the carbonyl. In the ^1H NMR spectrum, no olefinic proton resonance was observed. The two three–proton doublets, at δ 0.965 and 0.949, and two one–proton double doublets, at δ 2.775 and 2.736 were attributed to C–9 methyls in **432** and **433** and the C–4 protons, respectively.

The 1 : 3.5 mixture of **432** and **433** was then allowed to undergo α–methylation. We expected **434** and **435** to be the very predominant products simply due to steric effects. The mixture was treated with 1.1 equivalents of lithium diisopropylamide (LDA) at –78°C followed by the addition of 1.2 equivalents of iodomethane. The resulting mixture was stirred at –40°C for forty minutes. GC–MS analysis showed that the crude product contained both starting material and monomethylated substances, most likely **434** and **435**. Since substantial amounts of starting materials remained, we decided to use three equivalents of iodomethane. As indicated by GC–MS analysis, there were still some starting materials present and some dimethylated compounds **436** and **437** were formed. We attemped the separation of **434** and **435** from the crude product. Unfortunately, the R_f values of the starting materials, the monomethylated products as well as dimethylated products were so close that our efforts to separate them by column chromatography on silica gel employing a variety of eluting solvent systems were not successful.

Alternatively, **434** and **435** could be prepared from **414** and **415** by Birch reduction and subsequent trapping with iodomethane. Lithium–ammonia reduction followed by trapping with one equivalent of iodomathane afforded, once again, some monomethylated products along with a substantial amount of the starting materials. When excess iodomethane was used, the crude product contained mono– and dimethylated prducts **434**, **435**, **436**, and **437** along with some starting materials as

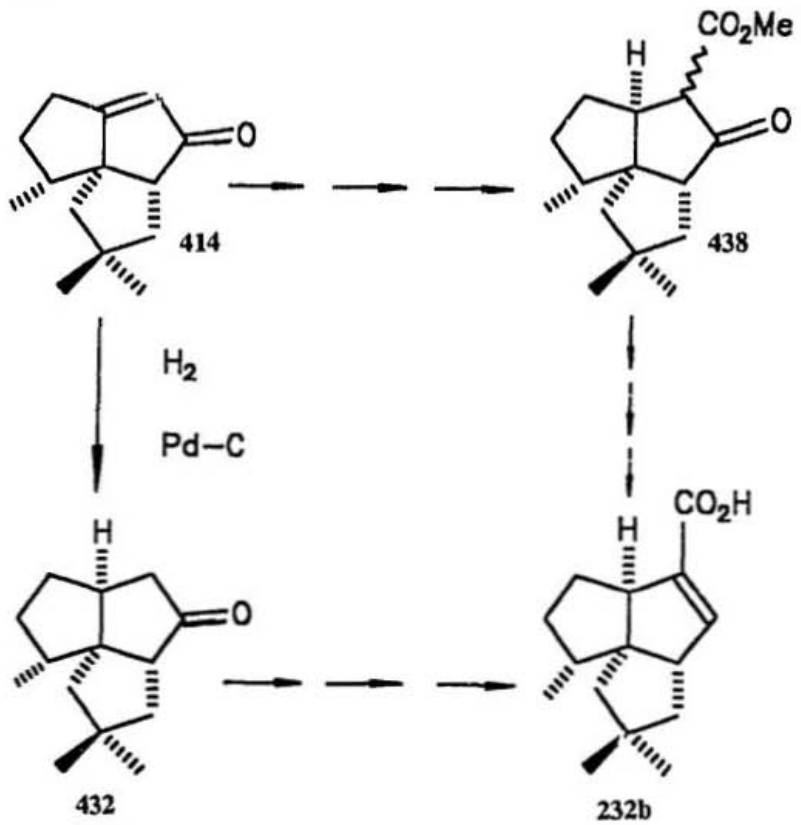
Scheme 86



revealed by GC–MS analysis.

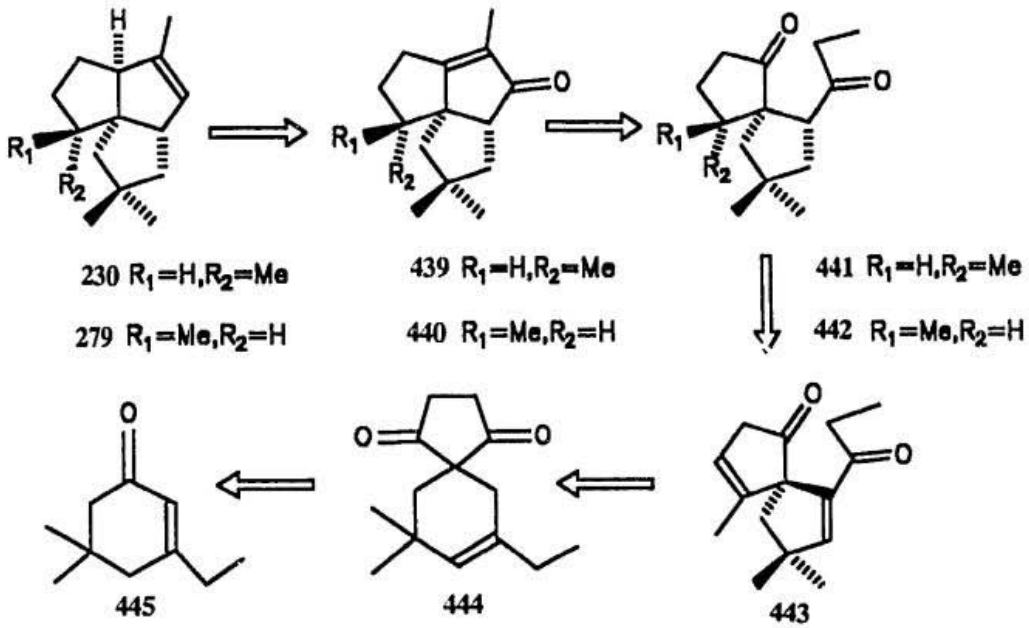
Although we did not convert **414** or **432** into pentalenene (**230**), nevertheless, as shown in Scheme 87, **414** or **432** should be easily transformed into keto–ester **438**, a very promising precursor to deoxypentalenic acid (**232b**). This work will be under way in the near future.

Scheme 87



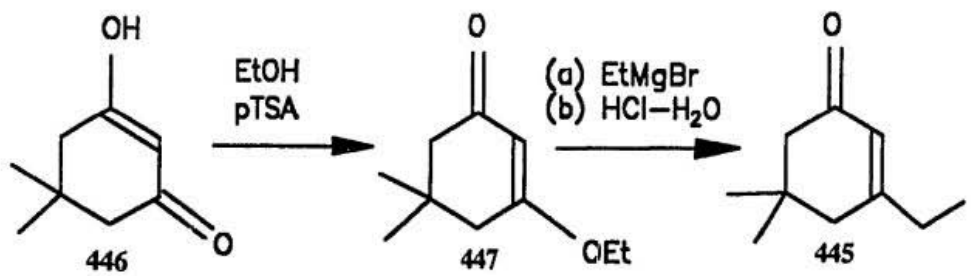
A modified approach to pentalenene (**230**) and *epi*-pentalenene (**279**) is outlined in Scheme 88. We envisioned that enone **445** could be converted into **439** and **440** by following exactly the same reaction sequence as **385** to **414** and **415**. The C–2 methyl in pentalenene and *epi*-pentalenene was derived from the starting material **445**, thus obviating the introduction of the C–2 methyl at the final stage of the synthesis.

Scheme 88



The preparation of cyclohexenone **445** started with with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**446**), which, upon treatment with *p*TSA in benzene and absolute ethanol at reflux with water removal by 4 Å Molecular Sieves in a Soxhlet extractor, gave the crystalline enol ether **447** in quantitative yield (Scheme 89).

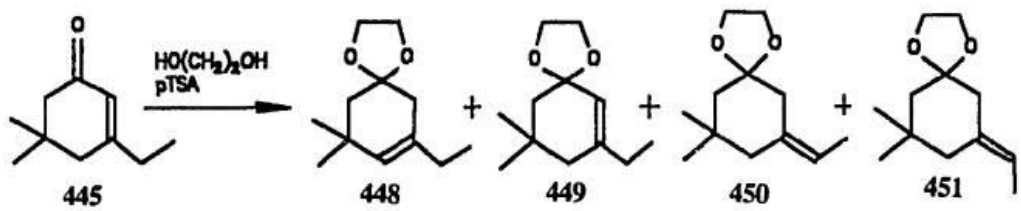
Scheme 89



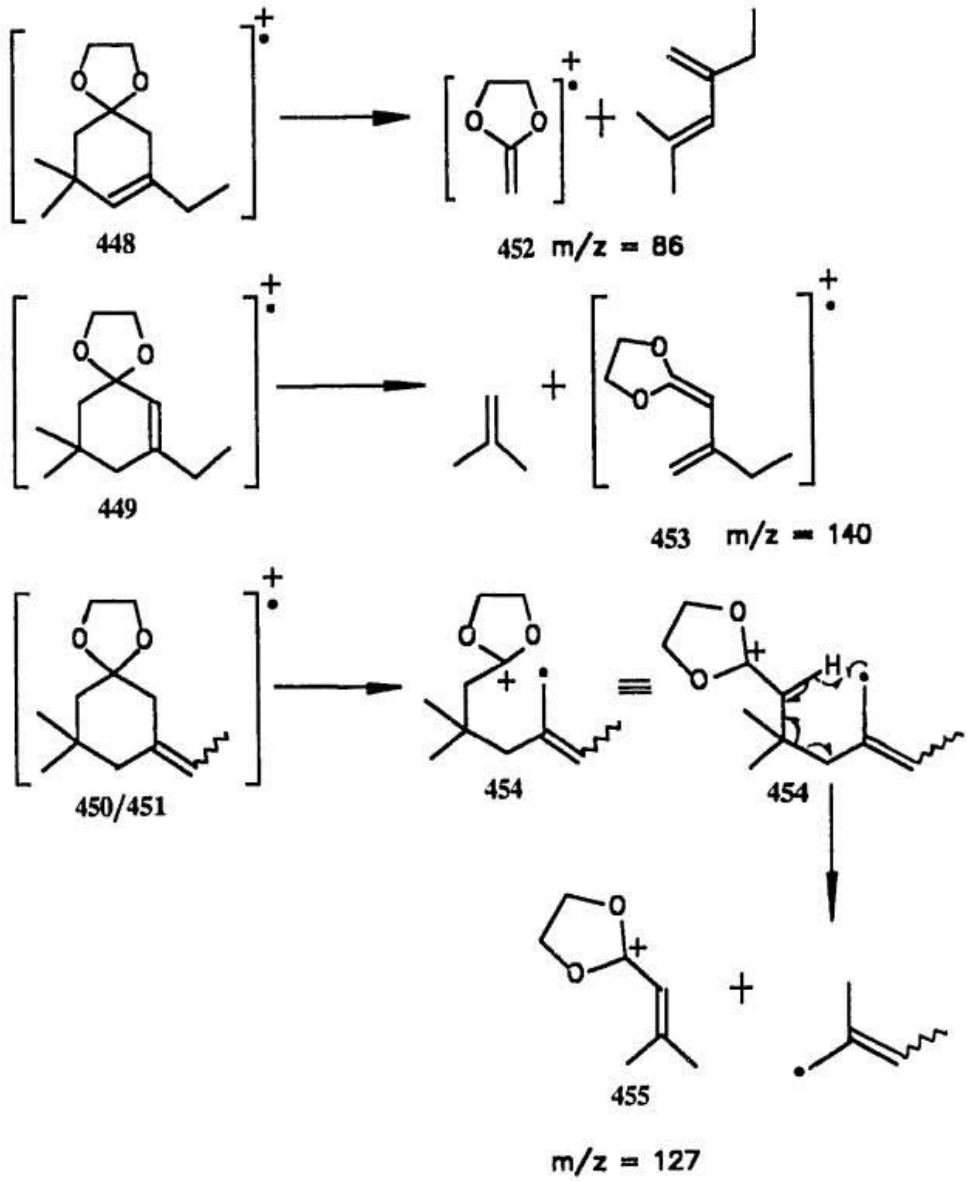
Addition of ethylmagnesium bromide to the enol ether **447** in THF was followed by acidic hydrolysis at room temperature (Scheme 89). Crude **445** was obtained in 98% yield, and it was used for the next ketalisation without further purification. It is worthwhile pointing out that the addition of ethylmagnesium bromide to **447** is a very exothermic reaction, therefore great care should be taken at the initial stage of the addition.

Ketalisation of **445** was carried out with ethylene glycol and *p*TSA in benzene at reflux overnight (Scheme 90). GC–MS analysis indicated the formation of four ketals, a small amount of oligomeric material along with some starting material. The structures of the four ketals were assigned by their mass spectra (Scheme 91). In the mass spectrum of **448**, the strong peak at *m/z* 86 was attributed to the fragment **452** ($C_4H_6O_2^{\ddagger}$) formed *via* homolytic *retro*–Diels–Alder reaction of **448**. Likewise, the strong peak at *m/z* 140 in the mass spectrum of **449** resulted from **453** ($C_7H_{12}O_2^{\ddagger}$). The other two ketals, whose mass spectra were very similar, were (*Z*)– and (*E*)– isomers **450** and **451**. The strong peak at *m/z* 127 in their mass spectra corresponded to a carbocation **455** ($C_7H_{11}O_2^{+}$), which was derived from **450** or **451** by ring cleavage followed by hydrogen transfer *via* **454**. Fortunately, the desired isomer **448** was found to be the major component as shown by GC–MS. After work–up with saturated sodium bicarbonate, most of the ketal **449** was hydrolysed back into starting material. Vacuum

Scheme 90



Scheme 91



distillation of the crude product removed some yellowish materials, and the resultant colorless distillate was subjected to column chromatography on silica gel. We obtained a 62% yield of the ketal mixture, and the starting enone was recovered to the extent of

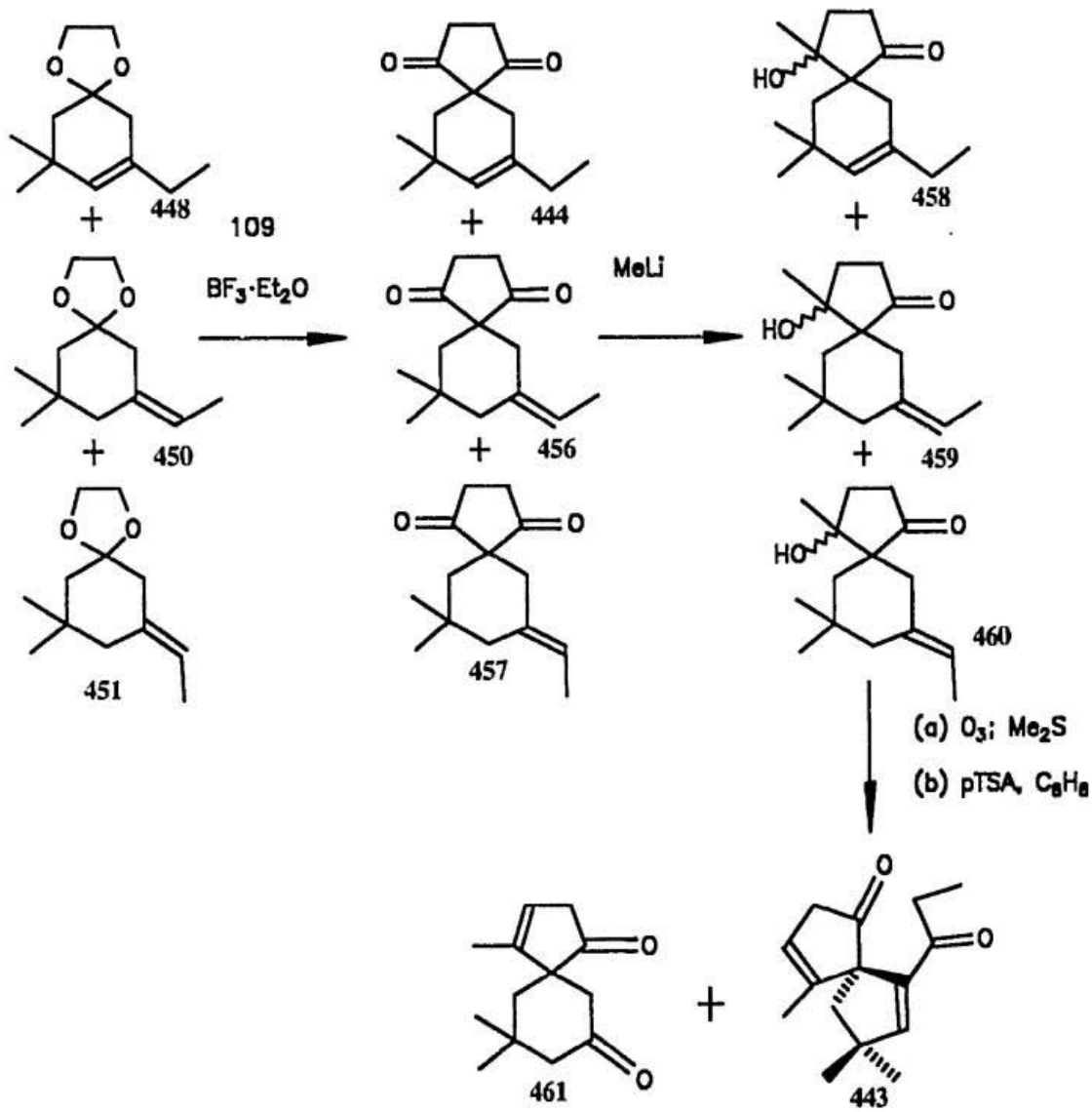
28%. One recycle of the recovered **445** gave another 16% yield of ketal mixture. Thus, the ketal mixture could be prepared in at least 78% yield. The ratio of **448** to **450** plus **451** was 4.5 : 1 on the basis of GC–MS. Since the separation of the desired ketal **448** from **450** and **451** was extremely difficult, we left the purification of the desired compound until a later stage.

Geminal acylation reaction leading to a cyclopentane–1,3–dione moiety was examined next (Scheme 92). Following our general procedure, the ketal mixture was treated with three equivalents of cyclobutene **109** and fifteen equivalents of $BF_3{\cdot}Et_2O$ at –78°C for six hours, and the resulting mixture was allowed to attain room temperature while stirring overnight. The GC–MS analysis showed clean conversion of the mixture of ketals to the spiro–diketones **444**, **456** and **457**. After chromatography on silica gel, we were left with a 77% yield of spiro–diketones **444**, **456** and **457** and an 11% recovery of the hydrolysed starting material **445**. The IR spectrum of the mixture of spiro–diketones showed absorption maxima for the ring carbonyls at 1725 cm^{-1} and for a double bond at 1665 cm^{-1}. Since the major component of the mixture was assigned **444**, then the two minor by–products, whose mass spectra were almost identical, must have been the (*Z*)– and (*E*)– isomers **456** and **457**. According to the GC–MS report and integration of the ^1H NMR spectrum, the ratio of **444** to **456** plus **457** was 4.5 : 1. For **444**, the olefinic proton appeared as a broad singlet at δ 5.042 in its ^1H NMR spectrum, and a three–proton triplet at δ 1.004 and a two–proton quartet at δ 2.049 were attributed to the ethyl group. The olefinic protons in **456** and **457** were found as multiplets at δ 5.866. Indeed, the position of the double bond in **444** was confirmed as our synthesis continued.

The spiro–diketone mixture was treated twice with five equivalents of methyllithium at –78°C for *ca.* two hours to give the keto–alcohol mixture **458**, **459** and **460** along with some starting material as revealed by GC–MS analysis (Scheme 92). The

IR spectrum of the crude mixture showed the absorption maxima at 3457 cm^{-1} for the hydroxyl, and 1726 cm^{-1} for the carbonyl. The separation of the keto–alcohol mixture from the starting material turned out to be quite difficult, therefore, the crude

Scheme 92

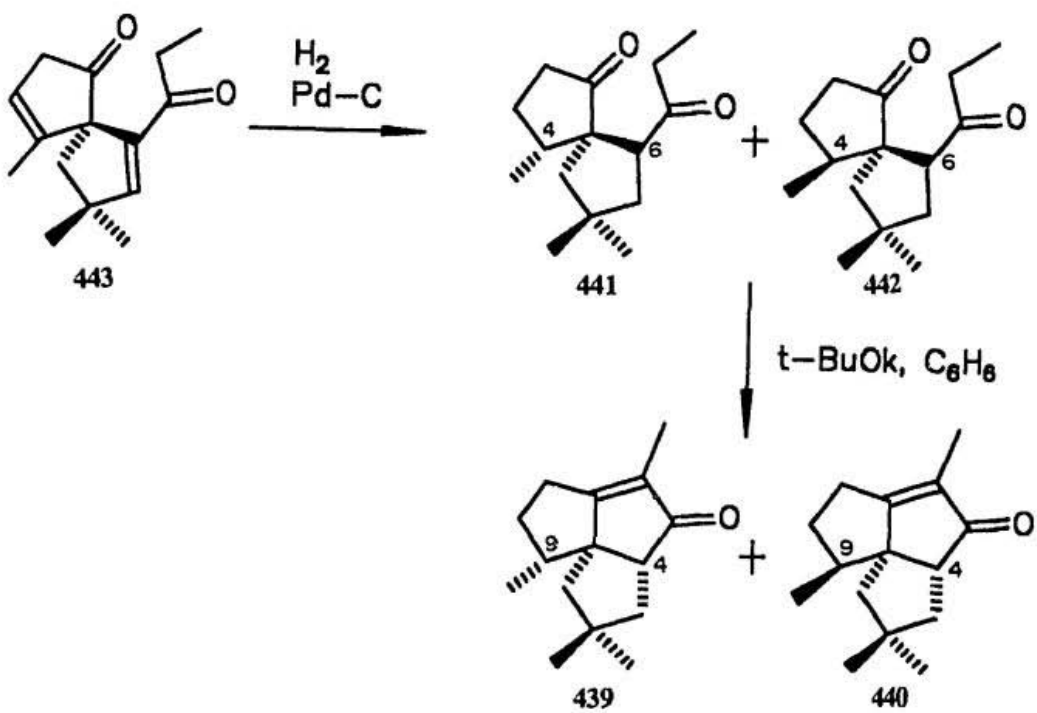


alcohol mixture was subjected to ozonolysis and subsequent treatment with *p*TSA in benzene at reflux. GC–MS analysis indicated compound **443**, accompanied by very small amount of a side product, which was tentatively assigned as **461** based on the prominent molecular ion at *m/z* 206 in the mass spectrum (Scheme 92). The UV–active compound **443** was obtained in an isolated yield of 63% from the mixture of spiro–diketones. Its IR spectrum showed absorption maxima for the conjugated carbonyl at 1672 cm^{-1} and for the ring carbonyl at 1748 cm^{-1}. The strong peak at *m/z* 57 in its mass spectrum implied the ethyl ketone moiety. In the ^{1}H NMR spectrum, a methyl triplet at δ 1.026 and a methylene quartet at δ 2.638 were attributed to the ethyl group attached to the carbonyl. The two olefinic protons were observed as a singlet at δ 6.676 and a multiplet at δ 5.757. Compound **443**, on catalytic hydrogenation, gave quantitatively a mixture of C–4 epimers **441** and **442** in 1 : 5 ratio by integration of its ^{1}H NMR spectrum (Scheme 93). The IR absorption maxima were observed at 1736 cm^{-1} for the ring carbonyl and 1711 cm^{-1} for the side–chain carbonyl. The ^{13}C NMR spectrum showed only two isomers, one of which was very predominant. The two doublets, at δ 1.043 and 0.999, and two double doublets, at δ 3.242 and 2.928 could be assigned to C–4 methyls in **441** and **442** and C–6 protons, respectively. The assignment of the relative stereochemistry at C–4 in **441** and **442** was achieved from their corresponding cyclization products **439** and **440** (*supra infra*). As in the case of **416** and **417**, the relative stereochemistry at C–6 in **441** and **442** was not determined.

The hydrogenation products, **441** and **442**, upon treatment with potassium *tert*–butoxide in benzene at room temperature for *ca.* 20 minutes, underwent intramolecular aldol condensation to provide, after chromatography on silica gel, an 84% yield of the cyclization products **439** and **440** (Scheme 93). The IR spectrum of this mixture showed absorption maxima for the conjugated carbonyl at 1704 cm^{-1} and for the double bond at 1667 cm^{-1}. Although only one peak was observed in the GC–MS spectrum, ^{1}H and ^{13}C NMR spectra indicated clearly a mixture of two C–9 epimers. In

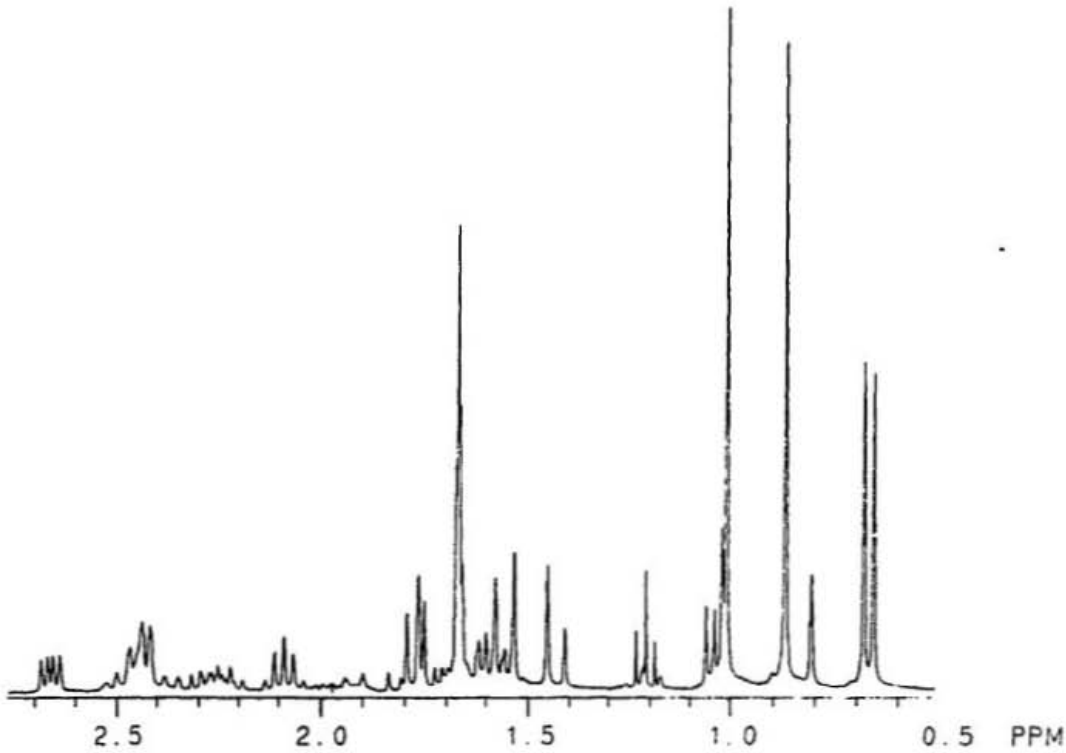
the ^1H NMR spectrum ($CDCl_3$), a broad methyl singlet at δ 1.66, and two methyl doublets, at δ 1.047 and 0.671 could be assigned as vinyl methyls in **439** and **440**, and C−9 methyls, respectively. The proton chemical shifts of the C−9 methyls in **439** and **440** and the C−4 protons in C_6D_6 were 0.756, 0.416 and 1.987, 2.579, respectively. The assignment of the relative stereochemistry at C−9 in **439** and **440** was based the NOE data. Irradiation of the double doublet at δ 2.579 (C−4 proton in **440**) resulted in an 1.2% NOE of the doublet at δ 0.416 (C−9 methyl in **440**), and, *vice versa*, a 13.9% NOE of the double doublet at δ 2.579 was observed when the signal at δ 0.416 was irradiated, which confirmed the relative stereochemistry in **440**. As calculated from the integrations in the ^1H NMR spectrum ($CDCl_3$), the ratio of **439** to **440** was 1 : 5 .

Scheme 93



(Figure 11). It should be pointed out that the major product **440** possessed the stereochemistry at C−9 opposite to natural pentalenene. Nevertheless, it could serve as a precursor to *epi*−pentalenene.

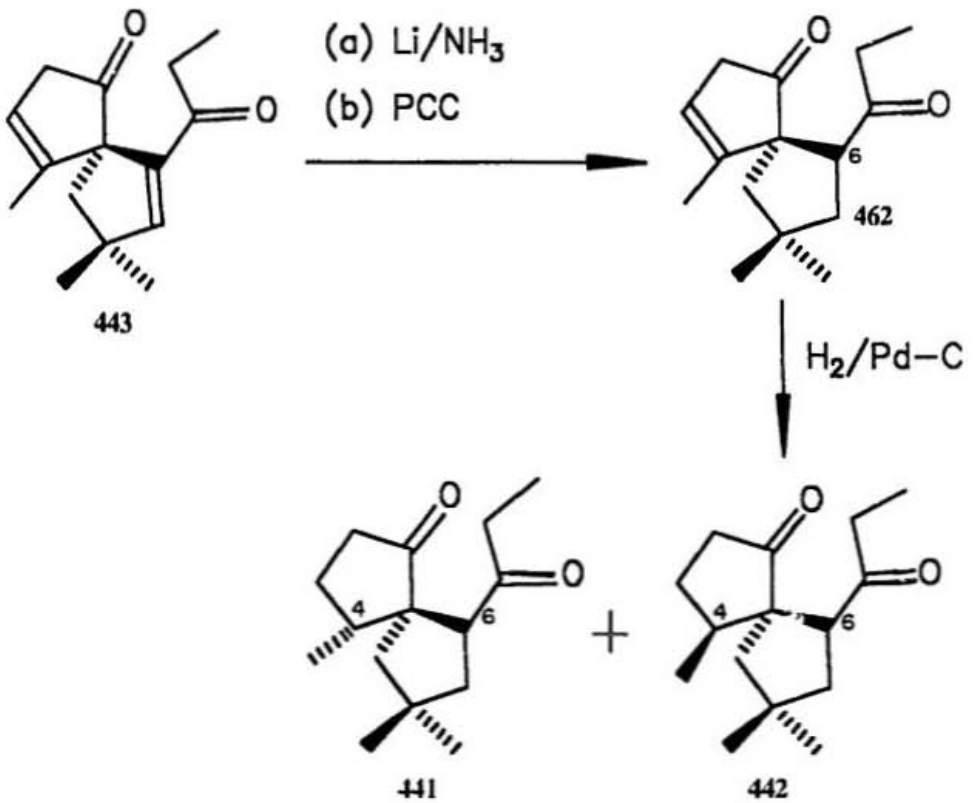
Figure 11. ^{1}H NMR spectrum of the 1 : 5 mixture of **439** and **440** ($CDCl_3$)



It is worthwhile to recall that compound **427**, upon direct hydrogenation followed by aldol condensation, produced a 1 : 3.5 mixture of **414** and **415**, of which only the former possessed the requisite stereochemistry at C−4, but, in contrast, a 3.5 : 2 mixture of **414** and **415** was formed when **427** was subjected to Birch reduction, hydrogenation, and aldol condensation. Therefore, we examined the Birch reduction in this series, also. Lithium−ammonia reduction of **443** followed by oxidation with PCC gave an 81% yield of **462** (Scheme 94). The IR absorption maxima at 1745 cm^{-1} and 1709 cm^{-1} were assigned as the ring carbonyl and the side−chain carbonyl, respectively. In

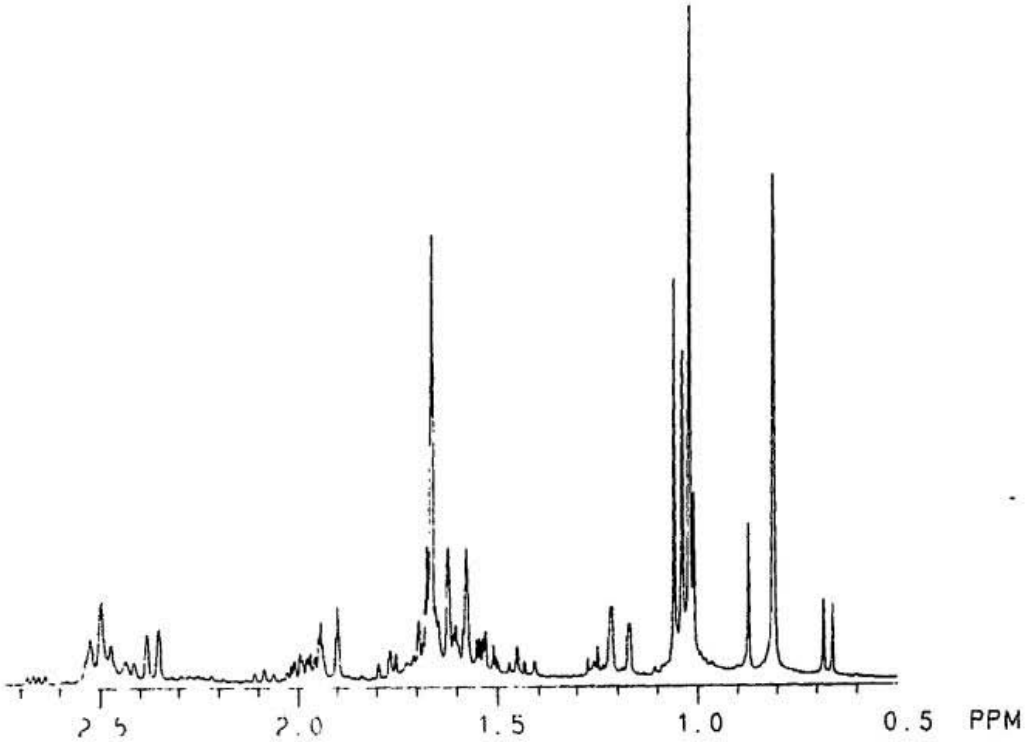
the ^1H NMR spectrum, only one olefinic proton resonance at δ 5.683 (m) was apparent. The ^{13}C NMR spectrum indicated a single compound, whose relative stereochemistry at C–4 was not established.

Scheme 94



Catalytic hydrogenation of **462** proceeded quantitatively, and the resulting mixture was subjected to base–induced intramolecular aldol condensation using potassium *tert*–butoxide in benzene at room temperature. The cyclization products **439** and **440** were isolated in 84% yield. The ratio of **439** to **440**, as calculated by the integration of the ^1H NMR spectrum ($CDCl_3$), was 4 : 1 (Figure 12). The hydrogenation product must have been a 4 : 1 mixture of methyl epimers **441** and **442**.

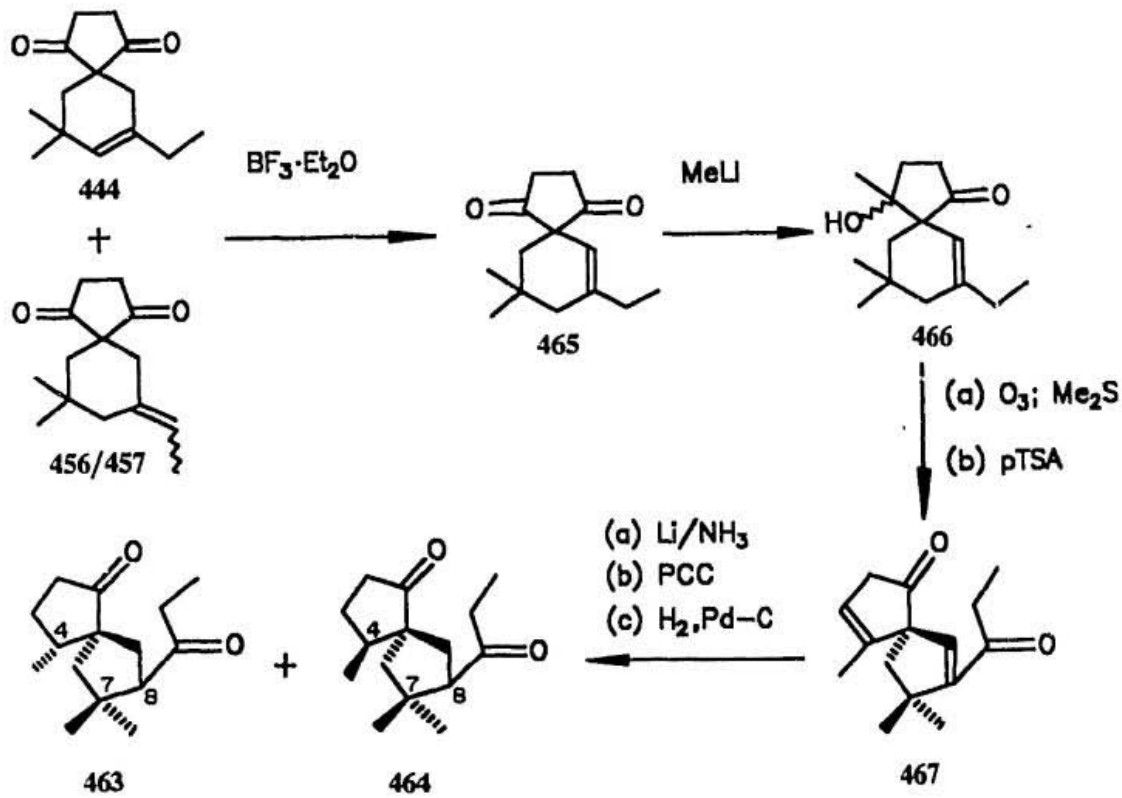
Figure 12. ^{1}H NMR spectrum of the 4 : 1 mixture of **439** and **440** ($CDCl_3$)



It should be mentioned that once, after Birch reduction sequence, we isolated a small amount of some other material along with the desired hydrogenation products **441** and **442**. Its IR spectrum showed absorption maxima at 1740 and 1716 cm^{-1} for the carbonyls, one of which (ν_{max}: 1740 cm^{-1}) appeared to be a five-membered ring carbonyl. The ^{13}C and ^{1}H NMR spectra of this side-product were clearly different from those of **441** and **442**. The ^{13}C NMR spectrum showed two sets of signals, of which one was slightly larger than the other, thus suggesting two isomers. Furthermore, these two isomers possessed the same number of primary, secondary, tertiary, and quaternary carbons as in **441** and **442**. We soon realized that **463** and **464** were the possible side products (Scheme 95). Accordingly, the C-8 hydrogens of the major and minor epimers appeared as double doublets at δ 3.759 and 3.156, respectively. The formation of **463** and **464** was rationalised starting from spiro-diketone **465**, which might

be derived from **444** and **456/457** *via* double bond isomerization. Addition of methyllithium gave alcohol **466**, which underwent ozonolysis followed by intramolecular aldol condensation to provide **467**. Birch reduction followed by PCC oxidation and catalytic hydrogenation resulted in **463** and **464**.

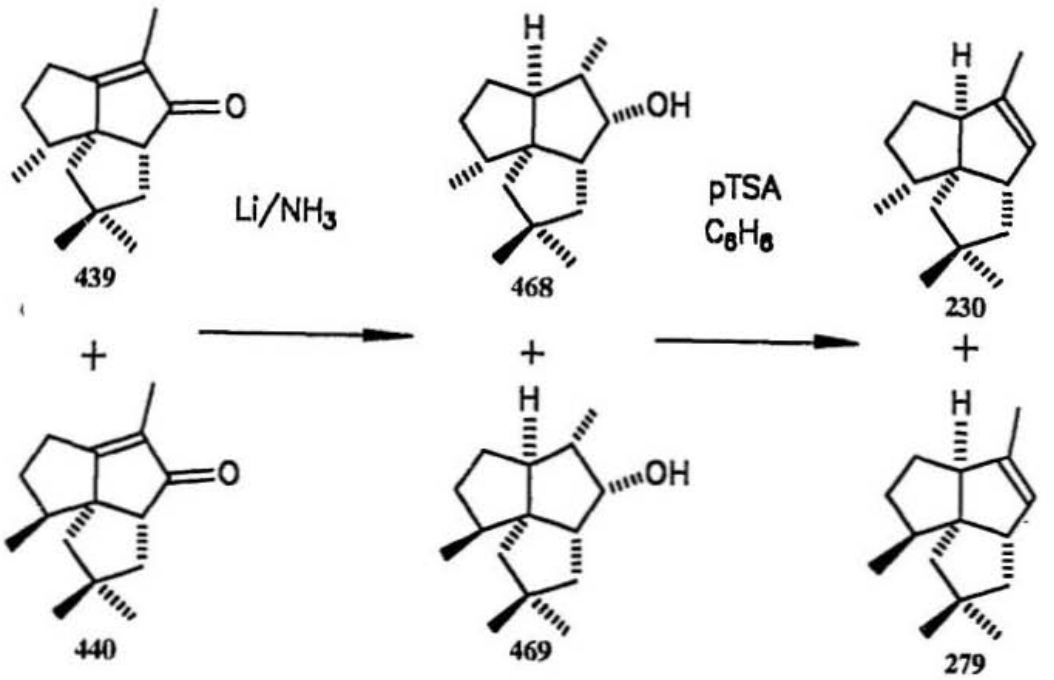
Scheme 95



It was interesting to note that the hydrogenation of **431** gave a 3.5 : 2 mixture of **416** and **417** (Scheme 85), but a 4 : 1 mixture of **441** and **442** was obtained from **462** by catalytic hydrogenation (Scheme 94). In other words, the facial selectivity was higher in the case of **462** than that in the case of **431**. This fact is not yet understood.

With the key intermediates **439** and **440** in hand, the transformation to *epi*–pentalenene and pentalenene was indeed very straightforward. The hydrogenation of

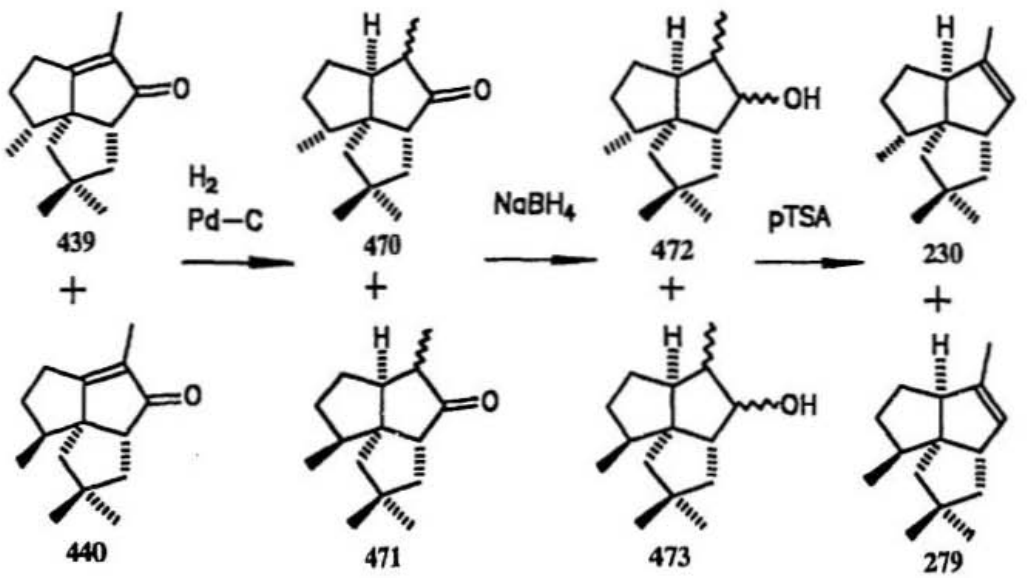
Scheme 96



the double bond and the reduction of the carbonyl can be achieved by either Birch reduction or catalytic hydrogenation followed by sodium borohydride reduction. Lithium–ammonia reduction of the 1 : 5 mixture of **439** and **440**, prepared *via* the direct hydrogenation route, gave a mixture of saturated alcohols, which were assigned as **468** and **469** based on the following findings (Scheme 96). The IR spectrum showed absorption maximum for an hydroxyl at 3436 cm^{-1} (broad). A prominent molecular ion at *m/z* 222 was observed in the mass spectrum. In the ^1H NMR spectrum, two double doublets at δ 3.521 and 3.564 were attributed to the protons α to the hydroxyl in **468** and **469**, respectively. The ^1H NMR spectroscopic data for **468** were in excellent agreement with those reported by Crimmins *et al.*[118] who arrived at this compound by a different route. Since the isolated yield ranged from 45% to 60% in several small scale reactions, the alternative two–step sequence was studied (Scheme 97). The catalytic hydrogenation of the 1 : 5 mixture of **439** and **440** proceeded smoothly to provide

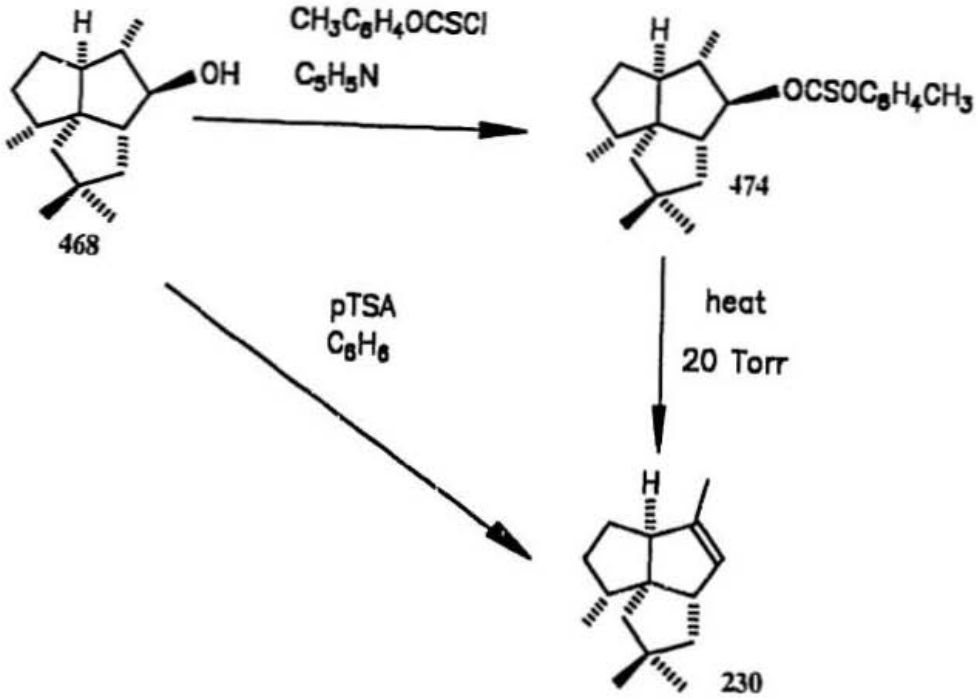
the saturated ketones in nearly quantitative yield. The IR spectrum of the product showed an absorption maximum at 1736 cm^{-1} for a nonconjugated carbonyl. If one assumes that *syn* hydrogenation occurs for **439** and **440**, then only two hydrogenation products are expected, but, GC–MS analysis and the ^{13}C NMR spectrum showed clearly the presence of four compounds. Thus, the hydrogenation products must have been a mixture of four diastereomers (i.e. **470** and **471**). It is most likely that the C–2 methyl group prefers the α position due to steric reasons, thereby resulting in the epimerization on Pd–C catalysis. Treatment of the mixture of ketones **470** and **471** with sodium borohydride in methanol furnished a mixture of alcohols **472** and **473** in nearly quantitative yield.

Scheme 97



The conversion of the alcohol **468** to pentalenene was previously reported by Crimmins *et al.*[118] by pyrolyzing the *p*–cresol thiocarbonate derivative **474** (Scheme 98). Regarding this conversion, Crimmins claimed that the direct dehydration under

Scheme 98



a variety of conditions such as $SOCl_2$ with pyridine, $POCl_3$ with pyridine in benzene, or elimination of the mesylate of **468** (*t*-BuOK, Me_2SO; DBU, benzene) gave either intractable mixtures or recovery of starting material. Since *p*TSA in benzene at reflux, a very common condition for dehydration, was not mentioned in Crimmins' paper, we decided to examine it first. The mixture of alcohols **472** and **473** prepared by catalytic hydrogenation and $NaBH_4$ reduction was treated with *p*TSA in benzene at reflux with continuous azeotropic removal of water. The reactions were closely followed by GC-MS and TLC analysis. As the reaction began, TLC indicated the formation of very nonpolar material which, as identified by GC-MS, were a mixture of *epi*-pentalenene and pentalenene, of which the former was predominant. When GC-MS and TLC showed no starting material, the crude product was passed through a short column of silica gel eluting with anhydrous diethyl ether to get rid of the *p*TSA. GC-

MS analysis of the resulting solution indicated a 1 : 5 mixture of pentalenene and *epi*-pentalenene, whose mass spectra were almost identical. A 1 : 5 mixture of *epi*-pentalenene and pentalenene was also obtained when a mixture of the alcohols **468** and **469** prepared *via* Birch reduction was treated with *p*TSA in benzene under reflux as above. In order to obtain pure samples for spectroscopic analysis, we needed to remove the solvent, which turned out a tough nut to crack because of the high volatility of pentalenene and of *epi*-pentalenene. Evaporation of benzene at room temperature using the vacuum produced by an aspirator resulted in a significant loss of product. Distillation might have been an alternative solution. However, it can be difficult on very small scale. Nevertheless, the loss of product could be minimized when the evaporation of the solvent was carried out by using a very carefully controlled vacuum, and this was stopped when no solvent peaks appeared in the ^{1}H NMR spectrum. In this way, we were able to obtain the mixture of pentalenene and *epi*-pentalenene in yields as high as 96%.

Pentalenene and *epi*-pentalenene proved to be very difficult to separate by column chromatography on silica gel using a variety of eluting solvent systems. Nevertheless, Piers and Karunaratne[115] achieved the separation by chromatography on silver nitrate-impregnated silica gel eluted with petroleum ether. Indeed, column chromatography of the 1 : 5 mixture of pentalenene and *epi*-pentalenene on 20% silver nitrate-impregnated silica gel eluted with pure pentane provided 69% *epi*-pentalenene and 7.5% pentalenene. In their ^{1}H NMR spectra the olefinic protons of *epi*-pentalenene and pentalenene appeared at δ 5.168 (br s) and δ 5.153 (br s), respectively, and the vinyl methyls of *epi*-pentalenene and pentalenene were observed as broad singlets at δ 1.597 and 1.614, respectively. The ^{13}C NMR spectra showed the sp^2 carbons for *epi*-pentalenene, at δ 131.5 and 140.5, and for pentalenene at δ 129.5 and 140.4. Our spectra of both pentalenene and *epi*-pentalenene were in good agreement

with those provided by Professor E. Piers* of University of British Columbia.

Based on our experience, it was quite difficult to evaporate or distill a large volume of petroleum ether under vacuum without any loss of the products. In our case, an alternative solution to obviate the separation of pentalenene and *epi*-pentalenene was to achieve the separation of their precursors at an earlier stage of the synthesis. Since the boiling point of the tricyclic enones **439** and **440** was quite high, we wondered if both isomers might be separated. Not surprisingly, many of our initial efforts to separate them by employing a variety of solvent systems were unsuccessful. The separation was eventually achieved when the mixture was chromatographed on silica gel-impregnated with 20% silver nitrate eluted with 2% diethyl ether and 98% petroleum ether. From the 1 : 5 mixture of **439** and **440**, prepared from the direct hydrogenation route, we were able to obtain a 8% of **439** and a 83% of **440**, along with 5% of an the unresolved mixture of **439** and **440** which could be separated again. In the case of the 4 : 1 mixture of **439** and **440** derived from the Birch reduction sequence, we isolated a 75% yield of **439** and a 12% yield of **440**, accompanied by a 5% yield of the unresolved mixture. With pure samples of **439** and **440** in hand, the previous assignment based on the ^{1}H and ^{13}C NMR spectra of the mixture was indeed fully confirmed. The ^{1}H and ^{13}C NMR spectra of tricyclic enones **439** and **440** are shown in Figure 13, 14, 15, and 16.

The transformation of pure **439** and **440** to pentalenene and *epi*-pentalenene was achieved by following the same reaction sequence as with the mixture of **439** and **440**. Thus, compound **439** underwent catalytic hydrogenation to give a mixture of two epimers **470** as identified by GC-MS analysis. This hydrogenation mixture, without any purification, was treated with sodium borohydride to give the mixture alcohols **472**.

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* We are very grateful to Professor E. Piers for making this comparison possible.

Figure 13. ^{1}H NMR spectrum of **439** ($CDCl_3$)

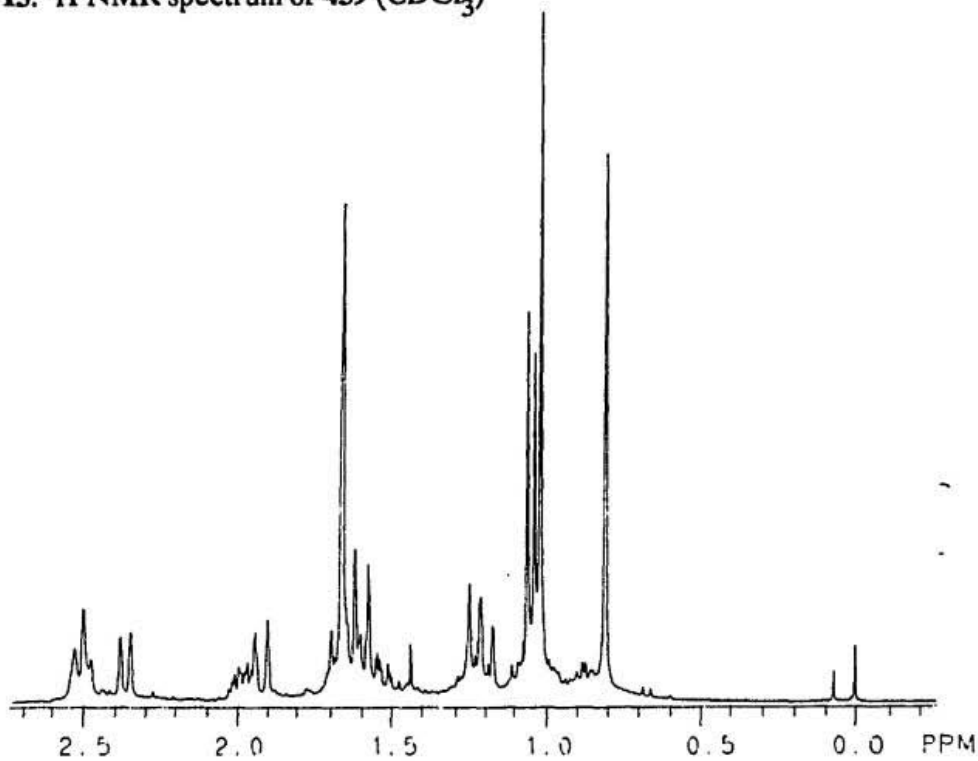


Figure 14. ^{13}C NMR spectrum of **439** ($CDCl_3$)

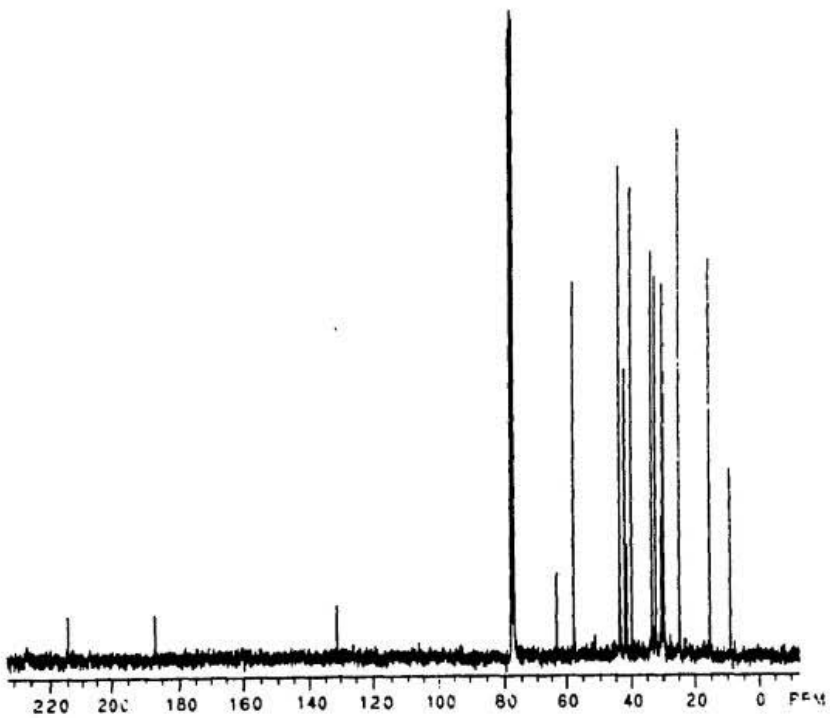


Figure 15. ^{1}H NMR spectrum of **440** ($CDCl_3$)

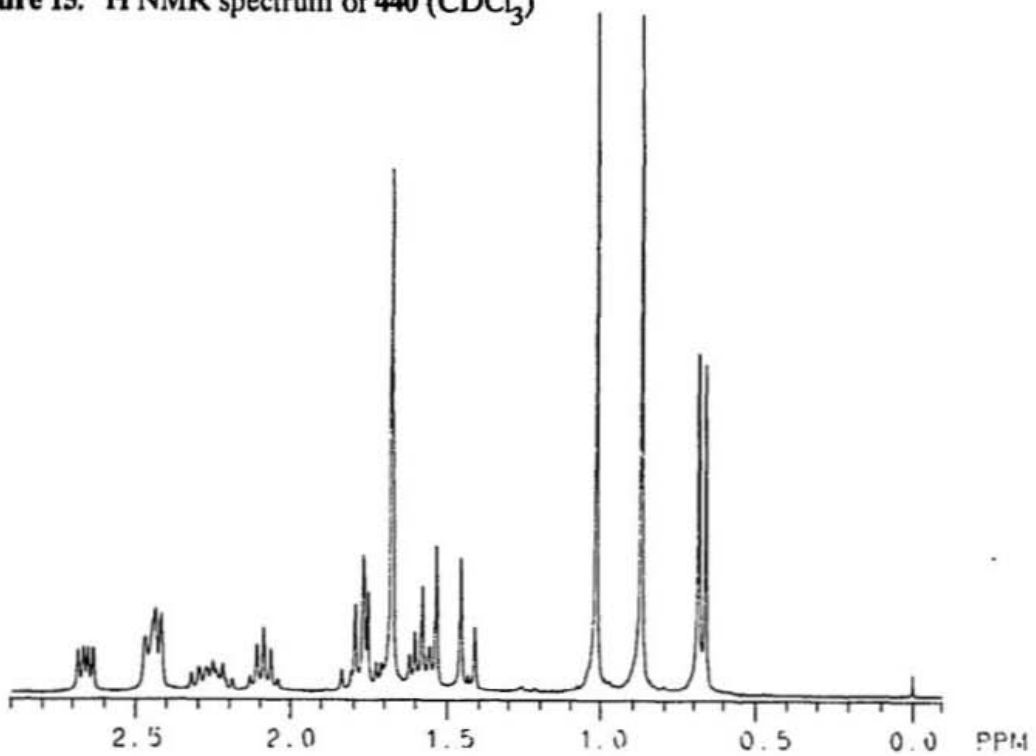
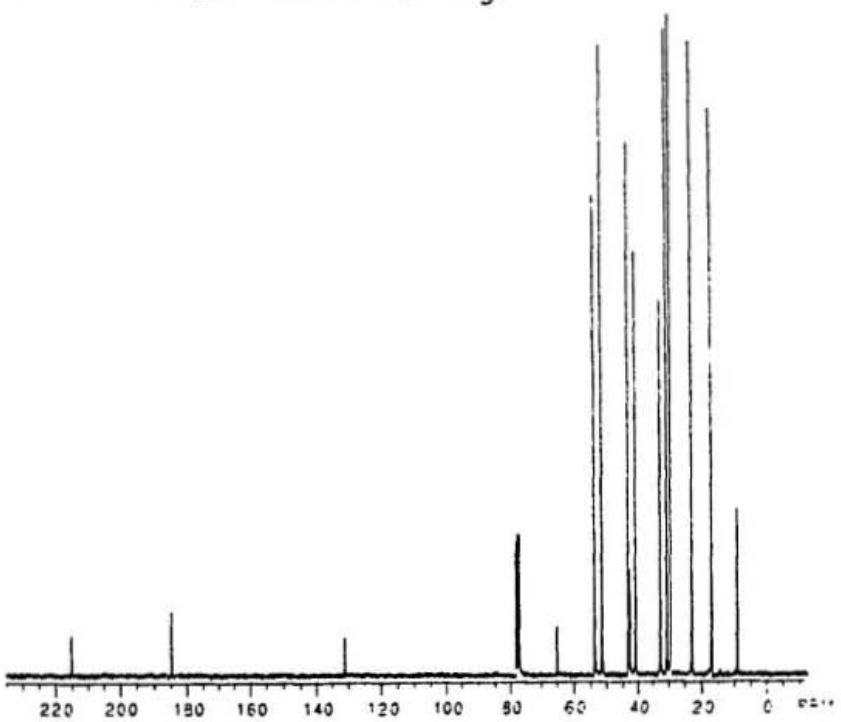


Figure 16. ^{13}C NMR spectrum of **440** ($CDCl_3$)



Next, we subjected the crude mixture of alcohols **472** to dehydration with *p*TSA in benzene. In this way, pentalenene was obtained in 88% overall yield from **439**. Likewise, *epi*-pentalenene was prepared from **440** in roughly the same yield.

In summary, pentalenene and *epi*--pentalenene were synthesized in a stereoselective sense depending on the order in which the double bonds of enone **443** were reduced (i.e. Birch reduction followed by catalytic hydrogenation or direct catalytic hydrogenation). Our synthesis required twelve steps for pentalenene and eleven steps for *epi*-pentalenene from dimedone; it involved one isomer separation, and produced pentalenene and *epi*-pentalenene in 16.4% and 22.4% yields, respectively. Indeed, our synthesis was both short and stereoselective as compared with others. The strategies developed in this synthetic study should be amenable to the synthesis of other angularly fused triquinanes.

III. Experimental*

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene (382)

A solution of isophorone (2.19 g, 15.2 mmol), ethylene glycol (4.2 mL, 76 mmol), and *p*TSA (300 mg) in benzene was heated under reflux overnight with a Barrett water-separator. Solid $NaHCO_3$ was added, and the resulting yellow solution was saturated with water. The aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The solution was dried over anhydrous K_2CO_3 and evaporated *in vacuo* to give a yellow liquid. The yellow color was removed by vacuum distillation, and the resulting colorless distillate was chromatographed (1% acetone in petroleum ether) to provide pure **382** (1.72 g, 62%) as a colorless liquid and recovered starting material, isophorone (651.3 mg, 31%). [The recovered isophorone was treated again with ethylene glycol and *p*TSA in benzene as above to give pure **382** (557.4 mg, 20%) and isophorone (180.1 mg, 9%). The overall yield of the ketal **382** was 82%.] For **382**: ^{1}H NMR δ: 1.037 (6H, s), 1.591 (2H, s), 1.660 (3H, s), 2.123 (2H, s), 3.931 (4H, s), and 5.153 (1H, s); ^{13}C NMR δ (attached H's): 23.1 (3), 30.1 (2C, 3), 33.9 (0), 39.5 (2), 43.3 (2), 63.7 (2C, 2), 108.8 (0), 127.6 (0), and 130.9 (1); MS (from GC-MS) *m/z* (%): 182 (46, M^+), 167 (20), 96 (34), 87 (23), 86 (100), 81 (19), 43 (12), 42 (12), and 41 (13).

7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-dione (381)

A solution of **382** (300.1 mg, 1.65 mmol) in CH_2Cl_2 (60 mL) was cooled to −78°C. Freshly distilled $BF_3{\cdot}Et_2O$ (2.03 mL, 16.5 mmol) was added followed, dropwise, by a solution of **109** (1.10 mL, 4.13 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred overnight, over which time the solution was allowed to attain room

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* For **General Procedures**, see **1.III.**

temperature. This mixture was added slowly to an ice–cooled saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. Chromatography of the residue (3% acetone in petroleum ether) provided pure **381** (244.6 mg, 72%) and hydrolysed starting material isophorone (37.1 mg, 16%). For **381**: mp 85–86°C; IR (film) ν_{max}: 1721 cm^{-1}; ^1H NMR δ: 0.942 (6H, s), 1.654 (2H, s), 1.759 (3H, s), 2.027 (2H, br s), 2.632 (2H, m), 3.054 (2H, m), and 5.205 (1H, br s); NOE data: see Figure 8; ^{13}C NMR δ (attached H's): 23.6 (3), 29.1 (2), 30.1 (2C, 3), 32.8 (0), 34.7 (2C, 2), 43.3 (2), 59.0 (0), 128.6 (0), 129.6 (1), and 214.2 (2C, 0); MS *m/z* (%): 206 (100, M^+), 191 (22, M^+ – Me), 178 (11), 163 (31), 149 (14), 145 (28), 131 (31), 107 (21), 91 (21), 85 (13), 81 (11), 79 (11), 57 (11), 55 (13), 43 (12), and 41 (16). *Exact mass* calcd. for $C_{13}H_{16}O_2$: 206.1306; found: 206.1306.

7,9,9–Trimethyl–1,4–dioxaspiro[4.5]dec–6–ene (386)

To a reaction flask containing CH_2Cl_2 was added trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) (50 μL) and the mixture was cooled to −78°C. 1,2–Bis(trimethylsiloxy)ethane (3.91 g, 19.0 mmol) was added followed by injection of isophorone (1.199 g, 8.62 mmol). The solution was stirred at −78°C for 2 hours and quenched at −78°C by adding dry pyridine (0.21 mL, 2.6 mmol). The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated NaCl (×2), dried over anhydrous K_2CO_3, and concentrated *in vacuo*. The resulting residue was chromatographed (2% acetone in petroleum ether) to provide pure **386** (0.66 g, 42%) as a colorless liquid: ^1H NMR δ: 0.995 (6H, s), 1.662 (2H, s), 1.700 (3H, s), 1.795 (2H, s), 3.932 (4H, m), and 5.535 (1H, br s); ^{13}C NMR δ (attached H's): 23.6 (3), 28.9 (2C, 3), 31.1 (0), 44.3 (2), 45.8 (2), 64.1 (2C, 2), 106.8 (0), 120.8 (1), and 139.5 (0); MS (from GC–MS)

m/z (%): 182 (4, M^+), 167 (6, M^+ – Me), 137 (10), 126 (100), 107 (6), 99 (6), 86 (6), 82 (11), and 41 (7).

7,9,9-Trimethylspiro[4.5]dec-6-ene-1,4-dione (389)[*]

A solution of isophorone (417.2 mg, 3.02 mmol) in CH_2Cl_2 was cooled to −78°C and $BF_3{\cdot}Et_2O$ (5.57 mL, 45.3 mmol) was added, followed dropwise by a CH_2Cl_2 solution of **109** (2.4 mL, 9.06 mmol). The mixture was stirred overnight during which time the reaction was allowed to attain room temperature. This mixture was added slowly to an ice-cooled saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (3% acetone in petroleum ether) to provide **389** (133.3 mg, 21%) along with some starting material. For **389**: mp 64–64.5°C; IR (film) ν_{max}: 1719 cm^{-1}; ^1H NMR δ: 0.995 (6H, s), 1.617 (2H, s), 1.750 (3H, s), 1.818 (2H, s), 2.850 (4H, m), and 5.055 (1H, br s); ^{13}C NMR δ (attached H's): 24.4 (3), 29.2 (2C, 3), 30.1 (0), 34.6 (2C, 2), 38.2 (2), 43.2 (2), 62.8 (0), 112.7 (1), 139.5 (0), and 212.5 (2C, 0); MS *m/z* (%): 206 (100, M^+), 191 (64, M^+ – Me), 163 (26), 150 (23), 149 (15), 145 (13), 135 (21), 131 (12), 121 (24), 107 (84), 105 (14), 93 (14), 91 (35), 85 (28), 79 (24), 77 (17), 65 (14), 55 (18), and 41 (28). *Exact mass* calcd. for $C_{13}H_{18}O_2$: 206.1306; found: 206.1296.

2-(2,2-Dimethyl-3-oxopropyl)-2-(2-oxopropyl)cyclopentane-1,3-dione (380)

Ozone was passed through a solution of **381** (200.3 mg, 0.97 mmol) in CH_2Cl_2 at −78°C until the blue color persisted, indicating the completion of the ozonolysis. The excess O_3 was removed (i.e. the blue color disappeared) when O_2 was bubbled

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[*] We thank Mr. Tracy J. Jenkins for kindly informing us of this experimental procedure.

through the solution for *ca.* 5 min. The reaction system was purged with N_2 for *ca.* 10 min to remove the remaining O_2. Next, Me_2S (3 mL) was added and the mixture was stirred overnight during which time the reaction was allowed to attain room temperature. Evaporation of the solvent *in vacuo* gave the crude **380** (90% pure by GC–MS analysis): MS (from GC–MS) *m/z* (%): no M^+, 210 (1.6, M^+ – CO), 178 (4), 167 (13), 154 (23), 139 (13), 125 (15), 112 (30), 111 (17), 107 (14), 97 (10), 79 (8), 55 (19), 43 (100), and 41 (19). This crude product was used for the next cyclisation without further purification.

6–Acetyl–8,8–dimethylspiro[4.4]non–6–ene–1,4–dione (390)

A benzene solution of the crude **380** from the above reaction in the presence of a small amount of *p*TSA (200 mg) was heated under reflux for *ca.* 2 hours with a Barrett water–separator. Saturated $NaHCO_3$ was added to the cooled solution, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (3% acetone in petroleum ether) of the brown residue provided pure **390** (113.4 mg, 52% from **381**) as a colorless oil: IR (film) ν_{max}: 1725, 1664, and 1626 cm^{-1}; ^1H NMR δ: 1.318 (6H, s), 1.891 (2H, s), 2.252 (3H, s), 2.734 (2H, m), 3.077 (2H, m), and 6.761 (1H, s); MS *m/z* (%): 220 (13, M^+), 205 (5, M^+ – Me), 201 (7), 192 (44, M^+ – CO), 177 (33, M^+ – $COCH_3$), 163 (24), 149 (9), 135 (28), 91 (10), 77 (12), 55 (25), and 43 (100, $COCH_3^+$). *Exact mass* calcd. for $C_{13}H_{16}O_3$: 220.1098; found 220.1087.

6–Acetyl–8,8–dimethylspiro[4.4]nonane–1,4–dione (391)

Compound **390** (54.9 mg, 0.25 mmol), dry methanol (30 mL), and 5% palladium on carbon (2 spatula–tips) were added to an hydrogenation flask, which was then shaken under 51 psi pressure of H_2 for 1 h. The solution was filtered through a small

pad of Celite and concentrated *in vacuo*. Chromatography of the residue (5% acetone in petroleum ether) provided **391** (55.2 mg, 100%) as a colorless oil: IR (film) ν_{max}: 1715 (very br) cm^{-1}; ^1H NMR δ: 1.171 (3H, s), 1.188 (3H, s), 1.505 (1H, d, J = 13.4 Hz) and 1.756 (1H, d, J = 13.4 Hz) (AB quartet, C−9 methylene), 1.998 (1H, dd, J = 7.0, 11.7 Hz), 2.086 (3H, s), 2.351 (1H, dd, J = 11.7, 13.8 Hz), 2.60−3.00 (4H, mm), and 3.642 (1H, dd, J = 7.0, 13.8 Hz, methine); ^{13}C NMR δ (attached H's): 27.9 (3), 29.7 (3), 30.1 (3), 35.6 (2C, 2), 40.2 (0), 43.5 (2), 49.0 (2), 62.3 (0), 65.5 (1), 208.2 (0), 216.3 (0), and 218.0 (0); MS *m/z* (%): 222 (2, M^+), 180 (16), 179 (100, M^+ − $COCH_3$), 138 (9), 137 (38), 123 (11), 96 (9), 95 (9), 85 (9), 43 (52, $COCH_3^+$), and 41 (10). *Exact mass* calcd. for $C_{13}H_{18}O_3$: 222.1255; found: 222.1273; and for $C_{11}H_{15}O_2$ (M^+ − $COCH_3$): 179.1071; found: 179.1055.

***rel*-(4*R*,5*R*)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (393)**

Spiro−diketone **381** (300.2 mg, 1.46 mmol) was dissolved in methanol (10 mL) and cooled in an ice bath. Sodium borohydride (13.8 mg, 0.37 mmol) was added in small portions, and the mixture was stirred for 30 min. Water was added, and much of the methanol was removed *in vacuo*. The solution was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. Chromatography (2% acetone in petroleum ether) of the residue provided the pure monoalcohol **393** (243.1 mg, 80%) as a colorless oil and recovered starting material **381** (28.3 mg, 9%). For **393**: IR (film) ν_{max}: 3460 (br) and 1727 cm^{-1}; ^1H NMR δ: 1.019 (3H, s), 1.043 (3H, s), 1.637 (3H, s), 1.51−2.58 (8H, mm), 4.230 (1H, m), and 5.228 (1H, br s); ^{13}C NMR δ (attached H's): 27.3 (3), 28.0 (2), 30.3 (3), 31.2 (0), 32.0 (3), 33.3 (2), 34.8 (2), 35.0 (2), 54.4 (0), 74.5 (1), 127.3 (0), 131.8 (1), and 222.0 (0); MS *m/z* (%): 208 (53, M^+), 193 (13, M^+ − Me), 175 (87), 149 (79), 133 (86), 131 (32), 121 (42), 119 (55), 107 (50), 105 (38), 91 (62), 81 (32), 79 (34), 77 (37), 55 (47), 53 (33), 43 (74), and 41 (100). *Exact mass* calcd. for

$C_{13}H_{20}O_2$: 208.1462; found: 208.1462. PCC oxidation of this monoalcohol provided the spiro-diketone **381** in nearly quantitative yield.

***rel*-(4*R*,5*S*)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-6-en-1-one (394)**

From spiro-diketone 381

Compound **381** (110.3 mg, 0.54 mmol) in methanol was treated as above with sodium borohydride (5.1 mg, 0.135 mmol). 10% HCl was added to the ice-cooled solution, and much of the methanol was removed *in vacuo*. The product was extracted with diethyl ether (×3), and the combined organic layers were washed with water (×2), saturated $NaHCO_3$ (×2), and saturated NaCl (×2). The solution was dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (3% acetone in petroleum ether) provided an approximate 1 : 1 mixture of double bond isomers **393** and **394** (79.7 mg, 80%) as revealed by GC-MS and spectroscopic analysis. Oxidation of this mixture with PCC provided quantitatively an approximate 1 : 1 mixture of **381** and **389**. For the spectroscopic data for **394**, see below.

From monoalcohol 393

To a methanol solution of monoalcohol **393** (41.7 mg, 0.20 mmol) was added 10% HCl, and the resulting mixture was stirred at room temperature for 10 min. Much of the solvent was evaporated *in vacuo* and the solution was extracted with diethyl ether (×3). The combined organic layers were washed with water (×2), saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo* to give an approximate 1 : 1 mixture of **393** and **394** (41.6 mg, 100%) as indicated by GC-MS and spectroscopic analysis. Oxidation of this mixture with PCC gave an approximate 1 : 1 mixture of **381** and **389**.

From spiro-diketone 389

Spiro-diketone **389** (15.1 mg, 0.073 mmol) in methanol was treated as for **381**

with sodium borohydride (ca. 1 mg, 0.026 mmol) except that water was added in the work-up instead 10% HCl. The crude product was chromatographed (2% acetone in petroleum ether) to give pure **394** (10.4 mg, 69%) as a colorless oil: IR (film) ν_{max}: 3464 (br), 1731 and 1451 cm^{-1}; ^1H NMR δ: 0.966 (3H, s), 1.021 (3H, s), 1.629 (3H, s), 1.680 (2H, s), 1.81-2.54 (6H, mm), 4.215 (1H, m), and 4.957 (1H, br s); NOE data: irradiate 4.957: NOE at 4.215 (1.4%); irradiate 4.215: NOE at 4.957 (4.4%); ^{13}C NMR δ (attached H's): 24.5 (3), 27.4 (2), 27.5 (3), 29.4 (0), 30.8 (3), 32.8 (2), 33.7 (2), 43.8 (2), 58.3 (0), 75.5 (1), 116.4 (1), 137.7 (0), and 219.1 (0); MS (from GC-MS) *m/z* (%): 208 (28, M^+), 175 (72), 149 (100), 137 (26), 133 (30), 123 (28), 121 (69), 119 (33), 109 (21), 107 (74), 105 (30), 93 (44), 91 (51), 81 (28), 79 (43), 77 (38), 69 (28), 57 (29), 55 (47), and 41 (70). *Exact mass* calcd. for $C_{13}H_{20}O_2$: 208.1462; found 208.1462. Oxidation of this monoalcohol with PCC provided cleanly the spiro-diketone **389**.

***trans*-7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-diol (396)**

From the monoalcohol 393

The monoalcohol **393** (63.7 mg, 0.31 mmol) was dissolved in methanol (20 mL) and cooled in an ice bath as sodium borohydride (23.0 mg, 0.62 mmol) was added in several portions. The solution was stirred at 0°C for 30 min, and water was added. Much of the methanol was removed by evaporation *in vacuo*, and the product was extracted with diethyl ether (×3). The combined organic layers were washed with saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. The resulting residue was chromatographed (5% acetone in petroleum ether) to provide the diol **396** (65.1 mg, 100%) as a colorless oil: IR (film) ν_{max}: 3340 (very br) cm^{-1}; ^1H NMR δ: 1.027 (3H, s), 1.060 (3H, s), 1.20-1.75 (3H, mm), 1.662 (3H, s), 2.06-2.23 (3H, mm), 3.960 (1H, m), 4.089 (1H, t, J = 7.9 Hz), and 5.188 (1H, s); ^{13}C NMR δ (attached H's): 24.1 (3), 29.0 (2), 29.7 (2), 31.1 (2C, 2 and 3), 32.1 (2C, 0 and 3), 38.6 (2), 48.5 (0), 76.8 (1), 77.4 (1), 129.4 (0), and 131.4 (1). MS *m/z* (%): 210 (6, M^+), 195 (26, M^+

– Me), 177 (36), 159 (70), 149 (21), 148 (20), 136 (29), 135 (32), 133 (100), 123 (35), 121 (25), 119 (33), 109 (20), 107 (38), 105 (39), 93 (27), 91 (38), 81 (29), 79 (23), 77 (20), 67 (19), 55 (32), 43 (64), and 41 (70). *Exact mass* calcd. for $C_{12}H_{19}O_2$ (M^+ – Me): 195.1384; found: 195.1379.

From spiro–diketone 381

Compound **381** (39.8 mg, 0.19 mmol) was treated as above with sodium borohydride (14.4 mg, 0.38 mmol) to give the pure diol **396** (40.1 mg, 100%).

***rel*–(4*R*,5*S*)–4–Hydroxy–7,9,9–trimethylspiro[4.5]dec–7–en–1–one (392)**

To a solution of the *trans* diol **396** (10.8 mg, 0.05 mmol) in CH_2Cl_2 was added PCC (10.8 mg, 0.05 mmol) and the resulting solution was stirred at room temperature for 3 h. Filtration through a Florisil pad removed a black precipitate. Five volumes of diethyl ether were passed through the pad. The combined organic solutions were evaporated *in vacuo*, and the residue was chromatographed (3% acetone in petroleum ether) to provide an approximate 1 : 1 mixture of epimeric monoalcohols **392** and **393** (7.2 mg, 67%) as a colorless oil and some recovered starting material **396**. For **392**: ^{1}H NMR (from the mixture) δ: 0.984 (3H, s), 1.060 (3H, s), 1.45–2.57 (8H, mm), 4.322 (1H, t, J = 5.8 Hz), and 5.236 (1H, br s); MS (from GC–MS) *m/z* (%): 208 (18, M^+), 175 (78), 149 (87), 133 (100), 131 (40), 121 (62), 119 (63), 107 (60), 105 (51), 93 (31), 91 (71), 85 (23), 81 (37), 79 (42), 77 (46), 69 (37), 67 (26), 65 (32), 57 (31), 55 (61), 53 (33), 44 (36), 43 (82), and 41 (97). This mixture of epimeric alcohols was further oxidized cleanly to spiro–diketone **392** upon treatment with PCC.

***rel*–(1*R*,2*S*,5*S*,7*S*)–7,9,9–Trimethyl–6–oxatricyclo[5.3.1.0^{1,5}]undecan–2–ol (398)**

From spiro–diketone 381

Compound **381** (51.7 mg, 0.25 mmol) was treated as above with $NaBH_4$ (15.0 mg, 0.40 mmol). After the mixture was stirred at 0°C for about 30 min, 10% HCl was

added until pH 2. Much of the solvent was removed *in vacuo* and the product was extracted with diethyl ether (×3). The combined organic extracts were washed with water (×2), saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. The resulting residue was chromatographed (20% acetone in petroleum ether) to provide pure alcohol **398** (52.8 mg, 100%): mp 82–83°C; IR (film) ν_{max}: 3405 (br) and 1463 cm^{-1}; ^1H NMR δ: 0.996 (3H, s), 1.207 (3H, s), 1.282 (3H, s), 1.24–1.76 (8H, mm), 1.888 (1H, br dd, J = 1.8, 13.4 Hz), 2.09–2.24 (1H, m), 2.27–2.41 (1H, m), 4.026 (1H, dd, J = 1.4, 5.0 Hz, C–2 methine), and 4.524 (1H, dd, J = 4.4, 8.6 Hz, C–5 methine); ^{13}C NMR δ (attached H's): 26.8 (3), 30.4 (0), 31.5 (2), 32.5 (2C, 2 and 3), 36.6 (3), 42.5 (2), 46.3 (2), 51.0 (2), 57.6 (0), 77.0 (1), 83.1 (0), and 84.4 (1). *Exact mass* calcd. for $C_{13}H_{22}O_2$: 210.1619; found: 210.1602.

From *trans* diol 396

To a methanol solution of *trans* diol **396** (55.7 mg, 0.27 mmol) was added 10% HCl until pH 2, and the resulting mixture was stirred for 30 min. Work–up as above gave an oily residue which was chromatographed (5% acetone in petroleum ether) to provide pure **398** (55.6 mg, 100%) as a colorless solid.

***rel*–(1*S*,2*S*,5*S*,7*S*)–7,9,9–Trimethyl–6–oxatricyclo[5.3.1.$0^{1,5}$]undecan–2–ol acetate (404)**

To a solution of **398** (7.8 mg, 0.037 mmol) in pyridine (0.5 mL) was added acetic anhydride (0.5 mL), and the resulting solution was stirred at room temperature for 30 min. Water was added, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with water (×2), 5% HCl (×3) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (5% acetone in petroleum ether) of the residue provided the pure acetate **404** (8.3 mg, 89%) as a colorless oil: IR (film) ν_{max}: 1746 cm^{-1}; ^1H NMR δ: 0.964 (3H, s), 1.196 (3H, s), 1.271 (1H, d, J = 11.5 Hz), 1.290 (3H, s), 1.349 (1H, d, J = 8.6 Hz), 1.414 (1H,

d, J = 8.6 Hz), 1.452 (1H, d, J = 11.5 Hz), 1.53–1.75 (4H, mm), 2.00–2.20 (1H, m), 2.056 (3H, s), 2.26–2.43 (1H, m), 4.505 (1H, dd, J = 4.9, 8.4 Hz, C–2 methine), and 5.084 (1H, dd, J = 2.1, 5.5 Hz, C–5 methine); MS (from GC–MS) *m/z* (%): 252 (10, M^+), 192 (34), 165 (19), 136 (27), 135 (54), 109 (24), 57 (49), 56 (27), 43 (100), 42 (21), and 41 (64).

7,9,9–Trimethyl–6–oxatricyclo[5.3.1.$0^{1,5}$]undecan–2–one (399)

To a solution of the alcohol **398** (25.4 mg, 0.12 mmol) in CH_2Cl_2 (30 mL) was added PCC (39.0 mg, 0.18 mmol) in CH_2Cl_2. The solution was stirred at room temperature overnight. Filtration through a Florisil pad removed a black precipitate. Five volumes of diethyl ether were passed through the pad, and concentration of the combined organic solutions *in vacuo* provided pure ketone **399** (25.4 mg, 100%): mp 25°C; IR (film) ν_{max}: 1739 cm^{-1}; ^1H NMR δ: 1.009 (3H, s), 1.197 (3H, s), 1.322 (1H, d, J = 14.4 Hz), 1.363 (3H, s), 1.370 (1H, d, J = 11.2 Hz), 1.494 (1H, br d, J = 14.0 Hz), 1.644 (1H, br d, J = 14.6 Hz), 1.70–1.83 (1H, m), 1.866 (1H, d, J = 14.0 Hz), 1.964 (1H, dt, J = 2.4, 11.2 Hz), 2.17–2.37 (2H, mm), 2.58–2.71 (1H, m), and 4.604 (1H, t, J = 7.6 Hz); ^{13}C NMR δ (attached H's): 26.3 (3), 28.5 (2), 30.1 (0), 32.2 (3), 35.9 (3), 37.3 (2), 41.9 (2), 44.0 (2), 50.7 (2), 58.5 (0), 83.8 (1), 85.5 (0), and 216.3 (0); MS *m/z* (%): 208 (12, M^+), 180 (16), 165 (11), 152 (47), 137 (7), 96 (100), 95 (16), 67 (10), 57 (41), 55 (14), 43 (66), and 41 (31). *Exact mass* calcd. for $C_{13}H_{20}O_2$: 208.1462; found: 208.1463.

***rel*–(1*R*,2*R*,5*S*,7*S*)–7,9,9–Trimethyl–6–oxatricyclo[5.3.1.$0^{1,5}$]undecan–2–ol (400)**

To an ice cooled solution of ketone **399** (80.6 mg, 0.39 mmol) in methanol was added sodium borohydride (14.7 mg, 0.39 mmol) in several portions. The reaction mixture was stirred at 0°C for 30 min. Water was added, and much of the methanol was evaporated *in vacuo*. The solution was extracted with diethyl ether (×3) and the

combined organic layers were washed with water and saturated NaCl (x2), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (5% acetone in petroleum ether) of the residue provided pure alcohol **400** (78.1 mg, 96%) as a colorless oil: IR (film) ν_{max}: 3420 cm^{-1}; ^1H NMR δ: 0.982 (3H, s), 1.186 (3H, s), 1.272 (1H, d, J = 11.1 Hz), 1.320 (1H, d, J = 14.4 Hz), 1.323 (3H, s), 1.438 (1H, br dd, J = 1.9, 13.4 Hz), 1.594 (1H, partially overlapped d, J = 14.4 Hz), 1.76–2.00 (4H, mm), 2.134 (1H, very br, OH), 3.854 (1H, t, J = 7.9 Hz, C–2 methine), and 4.265 (1H, dd, J = 4.8, 7.9 Hz, C–5 methine); ^{13}C NMR δ (attached H's): 26.9 (3), 29.2 (2), 30.5 (0), 30.8 (2), 32.6 (3), 36.3 (3), 41.7 (2), 46.7 (2), 51.1 (2), 56.7 (0), 77.00 (1), 83.8 (1), and 84.4 (0); MS *m/z* (%): 210 (23, M^+), 195 (7, M^+ – Me), 192 (65, $M^+ - H_2O$), 175 (32), 173 (45), 149 (47), 147 (48), 135 (48), 133 (31), 129 (48), 109 (80), 95 (34), 75 (92), 73 (82), 57 (73), 55 (40), 43 (100), and 41 (62). *Exact mass* calcd. for $C_{13}H_{22}O_2$: 210.1619; found: 210.1619. This alcohol was converted cleanly into ketone **399** upon oxidation with PCC.

***rel*-(4*S*,5*S*)-4-(*tert*-Butyldimethylsiloxy)-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (405)**

tert-Butylchlorodimethylsilane (TBDMSCl) (232.0 mg, 1.54 mmol) was added portionwise to a stirred solution of the monoalcohol **393** (160.8 mg, 0.77 mmol), imidazole (157.3 mg, 2.31 mmol) and 4-dimethylaminopyridine (DMAP) (10 mg) in dry DMF (7 mL). The reaction mixture was heated to 80°C in an oil bath overnight. To the cooled solution was added diethyl ether and water. The organic phase was separated, and the aqueous layer was re-extracted with diethyl ether (x3). The combined organic extracts were washed with water (x2) and saturated NaCl (x2), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (4% acetone in petroleum ether) of the residue provided pure **405** (113.4 mg, 46%) as a colorless oil, recovered monoalcohol **393** (75.7 mg, 47%), and a small amount of di-*tert*-butyldimethylsilyl

ether ($(TBDMS)_2O$). For **405**: IR (film) ν_{max}: 1740 cm^{-1}; ^1H NMR δ: 0.054 (3H, s), 0.086 (3H, s), 0.876 (9H, s), 0.910 (3H, s), 0.963 (3H, s), 1.563 (1H, d, J = 14.3 Hz), 1.671 (3H, br s), 1.70–1.82 (3H, mm), 1.93–2.22 (3H, mm), 2.30–2.53 (1H, m), 3.985 (1H, br t, J = 5.6 Hz), and 5.176 (1H, apparent br s, $W_{1/2}$ = 5.4 Hz); ^{13}C NMR δ (attached H's): −4.6 (3), −3.8 (3), 18.1 (0), 23.7 (3), 25.9 (3C, 3), 27.7 (2), 30.0 (3), 31.7 (0), 32.2 (3), 35.5 (2), 33.7 (2), 35.1 (2), 54.2 (0), 76.6 (1), 128.2 (0), 131.7 (1), and 220.1 (0); MS *m/z* (%): 322 (43, M^+), 265 (33, $M^+ - (CH_3)_3C$), 221 (8), 209 (7), 179 (17), 175 (18), 173 (45), 164 (28), 149 (31), 147 (45), 133 (27), 131 (26), 129 (45), 119 (22), 105 (22), 101 (23), 91 (22), 75 (100), 73 (90), 59 (31), 57 (26), and 41 (45). *Exact mass* calcd. for $C_{19}H_{34}O_2Si$: 322.2326; found: 322.2293; and for $C_{15}H_{25}O_2Si$ ($M^+ - (CH_3)_3C$): 265.1623; found: 265.1659. For $(TBDMS)_2O$: MS (from GC–MS) *m/z* (%): 246 (0.6, M^+), 231 (0.8, M^+ – Me), 189 (30, $M^+ - (CH_3)_3C$), 148 (16), 147 (100), 133 (6), 131 (4), 117 (8), 73 (18), 57 (17), and 41 (17).

***rel*-(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(2,2-dimethyl-3-oxopropyl)-2-(2-oxopropyl)cyclopentanone (406)**

Ozone was passed through a solution of the silyl ether **405** (113.5 mg, 0.35 mmol) in MeOH (15 mL) at −78°C until a blue coloration appeared, indicating completion of the reaction. The excess ozone was removed by bubbling O_2 through the solution and the system was then purged with nitrogen. Dimethyl sulfide (2 mL) was added, and the mixture was stirred overnight during which time the reaction was allowed to rise to room temperature. Concentration *in vacuo* provided crude **406** (82% pure by GC–MS analysis): MS (from GC–MS) *m/z* (%): no M^+, 297 (35, $M^+ - (CH_3)_3C$), 279 (32), 239 (25), 225 (23), 213 (20), 211 (25), 205 (31), 197 (24), 195 (22), 169 (40), 163 (34), 151 (29), 145 (17), 139 (16), 137 (18), 109 (19), 95 (18), 75 (100), 73 (72), 59 (17), 43 (89), and 41 (33). This crude product was used for the next cyclisation without further purification.

***rel*-(4*R*,5*S*)-6-Acetyl-4-(*tert*-butyldimethylsiloxy)-8,8-dimethylspiro[4.4]non-6-en-1-one (407)**

To ice-cooled dry methanol (10 mL) was added sodium metal (24.2 mg, 1.05 mmol) followed by a methanol solution of the crude **406** from the above reaction. The resulting solution was stirred at 0°C for 8 min. Water was added, and much of the methanol was evaporated *in vacuo*. The product was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (2% acetone in petroleum ether) to afford, in order of elution, **407** (25.1 mg, 21%) and ***rel*-(4*R*,5*S*)-6-acetyl-4-hydroxy-8,8-dimethylspiro[4.4]non-6-en-1-one (408)** (2.0 mg, 3%). For compound **407**: IR (film) ν_{max}: 1746, 1670, and 1623 cm^{-1}; ^1H NMR δ: −0.046 (3H, s), 0.025 (3H, s), 0.875 (9H, s), 1.210 (6H, s), 1.435 (1H, d, J = 13.3 Hz), 1.580 (1H, m), 2.163 (1H, m), 2.284 (3H, s), 2.32–2.52 (3H, mm), 4.691 (1H, dd, J = 6.4, 10.6 Hz), and 6.692 (1H, s); ^{13}C NMR δ (attached H's): −4.7 (3), −4.5 (3), 18.1 (0), 25.9 (3C, 3), 26.7 (3), 28.9 (3), 29.7 (3), 30.0 (2), 35.6 (2), 39.9 (2), 45.8 (0), 67.6 (0), 72.9 (1), 141.8 (0), 158.4 (1), 196.0 (0), and 217.2 (0); MS (from GC–MS) m/z (%): 336 (4, M^+), 321 (2.3, M^+ − Me), 303 (5.4, M^+ − Me), 281 (7), 280 (23), 279 (100, M^+ − $(CH_3)_3C$), 261 (23), 238 (8), 237 (40), 235 (15), 193 (17), 189 (11), 161 (14), 159 (14), 147 (9), 145 (16), 119 (8), 117 (7), 105 (8), 91 (10), 77 (8), 75 (34), 73 (37), 59 (8), 57 (11, $(CH_3)_3C$), 43 (42, $COCH_3^+$), and 41 (12). For the alcohol **408**: ^1H NMR δ: 1.242 (6H, s), 1.533 (1H, d, J = 13.3 Hz), 2.296 (1H, d, J = 13.3 Hz), 2.298 (3H, s), 1.57–1.71 (1H, m), 2.26–2.65 (3H, mm), and 4.686 (1H, dd, J = 6.5, 4.0 Hz); MS (from GC–MS) m/z (%): 222 (4, M^+), 204 (10, M^+ − H_2O), 179 (10, M^+ − $COCH_3$), 176 (17), 163 (17), 162 (32), 161 (42, M^+ − H_2O − $COCH_3$), 147 (37), 133 (15), 121 (14), 119 (25), 91 (17), 77 (18), and 43 (100, $COCH_3^+$). The alcohol **408** was converted into triketone **390** upon treatment with PCC.

***rel*-(4*R*,5*S*,6ξ)-6-Acetyl-4-(*tert*-butyldimethylsiloxy)-8,8-dimethylspiro[4,4]-nonan-1-one (409)**

Compound **407** (40.1 mg, 0.12 mmol), dry methanol (25 mL), and 5% palladium on carbon (2 spatula-tips) were added to an hydrogenation flask, which was then shaken under 51 psi pressure of H_2 for 1 h. The mixture was filtered through a small pad of Celite, and the filtrate was concentrated *in vacuo*. The crude residue was chromatographed (4% acetone in petroleum ether) to yield pure **409** (41.2 mg, 100%): mp 77-77.5°C; IR (film) ν_{max}: 1738 and 1691 cm^{-1}; ^1H NMR δ: 0.051 (3H, s), 0.085 (3H, s), 0.905 (9H, s), 1.062 (3H, s), 1.114 (3H, s), 1.276 (1H, d, J = 13.5 Hz), 2.040 (1H, br d, J = 13.5 Hz) (AB quartet, C-9 methylene), 1.528 (1H, m), 1.860 (1H, dd, J = 6.9, 11.2 Hz), 2.107 (1H, m), 2.132 (3H, s), 2.248 (1H, dd, J = 11.6, 13.5 Hz), 2.332 (2H, m), 2.949 (1H, dd, J = 6.9, 13.5 Hz), and 4.389 (1H, dd, J = 6.2, 10.0 Hz); ^{13}C NMR δ (attached H's): -4.7 (3), -4.3 (3), 18.0 (0), 25.8 (3C, 3), 29.4 (3), 30.0 (2C, 2 and 3), 30.2 (3), 36.0 (2), 37.9 (0), 41.2 (2), 44.4 (2), 57.7 (1), 62.4 (0), 75.0 (1), 209.9 (0), and 219.4 (0); MS *m/z* (%): no M^+, 295 (5, $M^+ - COCH_3$), 283 (4), 282 (13), 281 (61, $M^+ - (CH_3)_3C$), 263 (16), 239 (10), 189 (22), 161 (17), 147 (34), 131 (15), 121 (15), 75 (100), 73 (88), 62 (25), 59 (16), 45 (71), 44 (22), and 43 (79, $COCH_3^+$). *Exact mass* calcd. for $C_{15}H_{25}O_3Si$ ($M^+ - (CH_3)_3C$): 281.1572; found: 281.1573.

***rel*-(4*R*,8*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-6,6-dimethyltricyclo[6.3.0.0^{4,8}]-undec-1-en-3-one (410)**

To ice-cooled dry methanol (10 mL) was added sodium metal (6.1 mg, 0.267 mmol) followed by a methanol solution of **409** (30.1 mg, 0.089 mmol). The resulting mixture was stirred at 0°C for *ca.* 10 min. Water was added, and much of the methanol was removed *in vacuo*. The product was extracted with diethyl ether (×3), and the combined extracts were washed with saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and evaporated *in vacuo*. Chromatography (4% acetone in

petroleum ether) of the residue provided pure **410** (23.7 mg, 83%) as a colorless oil: IR (film) ν_{max}: 1741, 1711, and 1630 cm^{-1}; ^1H NMR δ: 0.047 (6H, s), 0.873 (3H, s), 0.905 (9H, s), 1.037 (3H, s), 1.03–2.83 (9H, mm), 4.389 (1H, dd, J = 6.3, 9.9 Hz), and 5.808 (1H, s); MS m/z (%): no M^+, 305 (M^+ – Me), 281 (14), 265 (7), 264 (25), 263 (100, M^+ – $(CH_3)_3C$), 207 (6), 189 (7), 161 (12), 147 (10), 145 (12), 105 (15), 91 (19), 77 (15), 75 (94), 73 (71), 59 (21), 43 (26), and 41 (30). *Exact mass* calcd. for $C_{15}H_{23}O_2Si$ (M^+ – $(CH_3)_3C$): 263.1466; found: 263.1464.

***rel*-(4*S*,5*S*)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one (418)**

To a solution of spiro-diketone **381** (89.4 mg, 0.43 mmol) in anhydrous diethyl ether (30 mL) at −78°C in a Dry Ice/acetone bath was added slowly a 1.4 M solution of methyllithium in diethyl ether (1.5 mL, 2.15 mmol). (The solution turned cloudy right after the addition of methyllithium.) The mixture was stirred at −78°C for 2 h. It was poured into an ice-cooled saturated solution of NaCl. Water was added, and the aqueous layer was extracted with diethyl ether (×3). The combined organic layers were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting oily residue was chromatographed (2% acetone in petroleum ether) to afford, in order of elution, the recovered starting material **381** (2.6 mg, 3%), **418** (82.3 mg, 86%) as a colorless oil, and ***rel*-(4*R*,5*S*)-4-hydroxy-4,7,9,9-tetramethyl-spiro[4.5]dec-7-en-1-one (419)** (1.3 mg, 1.4%). For **418**: IR (film) ν_{max}: 3426 (br) and 1730 cm^{-1}; ^1H NMR δ: 0.896 (3H, s), 1.003 (3H, s), 1.152 (3H, s), 1.690 (1H, d, J = 13.4 Hz) and 1.727 (1H, d, J = 13.4 Hz) (AB quartet, C-10 methylene), 1.733 (3H, s), 1.789 (2H, br s), 1.826 (1H, s, OH), 1.86–2.00 (1H, m), 2.13–2.32 (2H, mm), 2.48–2.65 (1H, m), and 5.182 (1H, br s); NOE data: irradiate 0.896: NOE's at 1.690 and 1.727 (AB quartet) (3%), and 5.182 (9%); irradiate 1.003: NOE's at 1.690 and 1.727 (AB quartet) (4%), and 5.182 (14%); irradiate 1.152: NOE at 1.789 (5%); irradiate 5.182: NOE's at 1.733 (1.1%), 1.003 (0.7%), and 0.896 (0.5%); ^{13}C NMR δ

(attached H's): 23.9 (3), 24.3 (3), 28.6 (3), 30.5 (2), 32.2 (0), 32.8 (3), 33.6 (2), 34.1 (2), 37.9 (2), 55.9 (0), 78.1 (0), 128.9 (0), 130.6 (1), and 220.0 (0); MS *m/z* (%): 222 (39, M^+), 189 (14), 164 (22), 149 (21), 147 (20), 131 (22), 123 (22), 107 (20), 99 (44), 91 (19), 83 (18), 55 (18), 43 (100), and 41 (27). *Exact mass* calcd. for $C_{14}H_{22}O_2$: 222.1618; found: 222.1605. For **419**: ^1H NMR δ: 0.857 (3H, s), 0.966 (3H, s), 1.293 (3H, s), 1.361 (1H, apparent d, J = 13.5 Hz), 1.777 (3H, s), 1.560 (1H, apparent dt), 1.81–2.51 (7H, mm), and 5.178 (1H, br s); MS (from GC–MS) *m/z* (%): 222 (14, M^+), 189 (7), 149 (13), 147 (18), 107 (19), 105 (11), 99 (45), 91 (21), 83 (19), 81 (13), 79 (11), 77 (12), 55 (23), 43 (100), and 41 (25).

rel-(2*R*,3*S*)-3-Hydroxy-3-methyl-2-(2,2-dimethyl-3-oxopropyl)-2-(2-oxopropyl)cyclopentanone (420)

Ozone was passed through a solution of the alcohol **418** (63.7 mg, 0.29 mmol) in CH_2Cl_2 (15 mL) at −78°C until the solution became blue. Excess ozone was displaced by a stream of O_2 (solution became colorless), and the system was then purged with nitrogen. Dimethyl sulfide (2 mL) was added at −78°C, and the mixture was stirred overnight during which time the reaction mixture was allowed to attain room temperature. Concentration *in vacuo* provided crude **420**: MS (from GC–MS) *m/z* (%): no M^+, 210 (1.1, $M^+ - COCH_3 - H$), 182 (9, $M^+ - COCH_3 - CHO$), 167 (9), 164 (9), 155 (17), 139 (14), 123 (21), 122 (14), 121 (18), 110 (14), 109 (18), 107 (35), 95 (33), 93 (20), 84 (16), 81 (31), 79 (29), 77 (18), 71 (20), 67 (32), 55 (31), 53 (19), 43 (100, $COCH_3^+$), and 41 (50). This crude product was used for the next cyclisation without further purification.

5-Acetyl-7-hydroxy-2,2,4-trimethylindan (424)

To ice-cooled dry methanol (10 mL) was added sodium metal (26.7 mg, 1.16 mmol) followed by a methanol solution of the crude **420** from the above reaction. The

mixture was stirred at room temperature for *ca.* 1 h. Some water was added and much of the methanol was evaporated *in vacuo*. The product was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow precipitate which was chromatographed (7% acetone in petroleum ether) to provide pure **424** (38.7 mg, 62%) as colorless crystals: mp 138–139°C; IR (film) ν_{max}: 3197, 1650, 1595, and 1461 cm^{-1}; ^1H NMR δ: 1.178 (6H, s), 2.296 (3H, s), 2.530 (3H, s), 2.712 (4H, s), 5.145 (1H, very br s, OH), and 7.005 (1H, s); ^{13}C NMR δ (attached H's): 16.8 (3), 29.2 (2C, 3), 29.8 (3), 39.7 (0), 43.9 (2), 47.2 (2), 114.4 (1), 126.4 (0), 132.5 (0), 137.7 (0), 146.4 (0), 149.5 (0), and 202.4 (0); MS *m/z* (%): 218 (33, M^+), 204 (14), 203 (100, M^+ – Me), 175 (9, M^+ – $COCH_3$), 160 (7), 145 (6), 115 (8), 91 (9), 77 (7), 69 (9), and 43 (52, $COCH_3^+$). *Exact mass* calcd. for $C_{14}H_{18}O_2$: 218.1305; found: 218.1317; and for $C_{13}H_{15}O_2$ (M^+ – Me): 203.1071; found: 203.1072.

6–Acetyl–4,8,8–trimethylspiro[4.4]nona–3,6–dien–1–one (427)

A benzene solution of the crude **420**, prepared from the alcohol **418** (100.3 mg, 0.45 mmol) *via* ozonolysis as above, and *p*TSA (20 mg) was heated under reflux with a Barrett water–separator for 2 h. Saturated $NaHCO_3$ was added to the cooled solution, and the aqueous layers were extracted with diethyl ether (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×3) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo* to give a black oily residue, which was chromatographed (2% acetone in petroleum ether) to provide pure **427** (77.8 mg, 79%) as a colorless oil: IR (film) ν_{max}: 1741, 1671, and 1626 cm^{-1}; ^1H NMR δ: 1.265 (3H, s), 1.309 (3H, s), 1.640 (3H, apparent q, J = 1.6 Hz), 1.723 (1H, d, J = 13.9 Hz) and 1.922 (1H, d, J = 13.9 Hz) (AB quartet, C–2 methylene), 2.260 (3H, s), 2.849 (1H, d of apparent quintets, J = 2.2, 22.7 Hz) and 3.178 (1H, d of apparent quintets, J = 2.2, 22.7 Hz) (C–9 methylene), 5.766 (1H, apparent q), and 6.686 (1H, s); COSY

spectrum confirmed the significant long-range coupling between the C-2 methylene and the C-4 methyl; ^{13}C NMR δ (attached H's): 14.6 (3), 26.5 (3), 29.1 (3), 29.7 (3), 41.9 (2), 45.5 (0), 46.5 (2), 68.3 (0), 121.5 (1), 141.7 (0), 142.7 (0), 157.1 (1), 195.3 (0), and 219.3 (0); MS *m/z* (%): 219 (8, $M^+ + 1$), 218 (37, M^+), 190 (12), 176 (18), 175 (82, $M^+ - COCH_3$), 161 (15), 147 (38), 133 (32), 105 (14), 91 (20), 77 (13), 53 (10), 43 (100, $COCH_3^+$), and 41 (19). *Exact mass* calcd. for $C_{14}H_{18}O_2$: 218.1305; found: 218.1283; and for $C_{12}H_{15}O$: 175.1122; found: 175.1098.

***rel*-(4*R*,5*R*,6ξ)-6-Acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (416) and *rel*-(4*S*,5*R*,6ξ)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (417)**

Compound **427** (89.1 mg, 0.41 mmol), dry methanol (30 mL), and 5% palladium on carbon (2 spatula-tips) were added to an hydrogenation flask, which was shaken under 51 psi pressure of H_2 for 1 h. The mixture was then filtered through a Celite plug and the solution was concentrated *in vacuo*. The crude product was chromatographed on silica gel with 4% acetone in petroleum ether as the eluent to yield a mixture of two isomers **416** and **417** (91.1 mg, 100%) in 1 : 3.5 ratio: IR (film) of the mixture ν_{max}: 1733 and 1712 cm^{-1}; for the major epimer **417**: ^1H NMR (from the mixture) δ: 1.049 (3H, d, J = 6.9 Hz), 1.080 (3H, s), 1.177 (3H, s), 1.306 (1H, d, J = 13.5 Hz) and 1.862 (1H, d, J = 13.5 Hz) (AB quartet, C-9 methylene), 1.46-1.62 (1H, m), 1.77-2.60 (mm), 2.117 (3H, s), and 3.234 (1H, dd, J = 6.4, 13.4 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 15.6 (3), 28.7 (2), 29.3 (2C, 3), 30.7 (3), 37.3 (0), 38.3 (2), 41.4 (1), 45.6 (2), 52.2 (2), 58.8 (1), 59.6 (0), 209.1 (0), and 224.4 (0); MS (from GC-MS) *m/z* (%): 222 (15, M^+), 194 (8), 180 (20), 179 (27, $M^+ - CH_3CO$), 161 (18), 147 (25), 138 (34), 123 (29), 121 (25), 119 (19), 107 (19), 95 (36), 91 (19), 81 (24), 55 (29), 43 (100, $COCH_3^+$), and 41 (36); for the minor epimer **416**: ^1H NMR (from the mixture) δ: 1.003 (3H, d, J = 6.8 Hz), 1.060 (3H, s), 1.125 (3H, s), 1.306 (1H, d, J = 13.5 Hz) and 1.862 (1H, d, J = 13.5 Hz) (AB quartet, C-9 methylene), 1.46-1.62

(1H, m), 1.77–2.60 (mm), 2.122 (3H, s), and 2.913 (1H, dd, J = 6.9, 13.4 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 14.4 (3), 29.1 (2), 29.2 (3), 30.0 (3), 30.2 (3), 37.3 (2), 38.0 (0), 38.8 (1), 41.8 (2), 44.1 (2), 58.2 (1), 59.6 (0), 209.1 (0), and 224.4 (0); MS (from GC–MS) m/z (%): 222 (10, M^+), 179 (23, $M^+ - COCH_3$), 166 (21), 152 (29), 138 (24), 123 (32), 121 (23), 95 (34), 81 (27), 55 (31), 43 (100, CH_3CO^+), and 41 (38). *Exact mass* (epimeric mixture) calcd. for $C_{14}H_{22}O_2$: 222.1618; found: 222.1612;

***rel*-(4*R*,8*R*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (414) and *rel*-(4*R*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (415)**

Potassium *tert*-butoxide (184.0 mg, 1.64 mmol) was added to a solution of epimers **416** and **417** (182.2 mg, 0.82 mmol) in dry benzene (40 mL) at room temperature, and the reaction was closely monitored by TLC. Once TLC showed the complete conversion (it generally required ca. 20 min), water was added. The aqueous layer was extracted with diethyl ether (×3), the combined organic extracts were washed with saturated NaCl (×2), and the resulting solution was dried over $MgSO_4$ followed by concentration *in vacuo* to give a slightly yellow oil, which was chromatographed (2% acetone in petroleum ether) to provide a mixture of C–9 epimers **414** and **415** (141.2 mg, 84%) in 1 : 3.5 ratio: IR (film) of the mixture ν_{max}: 1705 and 1631 cm^{-1}; UV (methanol) of the mixture λ_{max}: 241 nm, ε = 1149 $mol^{-1}\cdot l\cdot cm^{-1}$; for the major epimer **415**: ^1H NMR (from the mixture) δ ($CDCl_3$): 0.737 (3H, d, J = 7.12 Hz), 0.930 (3H, s), 1.020 (3H, s), 1.08–2.73 (mm), 1.632 (1H, d, J = 13.3 Hz) and 1.940 (1H, d, J = 13.3 Hz) (AB quartet, C–7 methylene), 2.534 (2H, m, C–11 methylene), 2.692 (1H, dd, J = 5.8, 2.3 Hz, C–4 methine), and 5.766 (1H, s); ^1H NMR (from the mixture) δ (C_6D_6): 0.439 (3H, d, J = 7.1 Hz), 0.830 (3H, s), 0.864 (3H, s), 1.02–2.23 (mm), 2.567 (1H, dd, J = 3.8, 6.0 Hz, C–4 methine), and 5.664 (1H, s); NOE data (C_6D_6): irradiate 2.567: NOE at 0.439 (2%); irradiate 0.439: NOE at 2.567 (11%); ^{13}C NMR (from

the mixture) δ (attached H's): 16.6 (3), 23.7 (2), 28.9 (3), 30.0 (3), 32.3 (2), 40.1 (1), 42.4 (0), 42.5 (2), 51.0 (2), 53.9 (1), 66.7 (0), 123.8 (1), 192.1 (0), and 215.1 (0); MS (from GC–MS) *m/z* (%): 204 (84, M^+), 189 (18), 176 (6), 162 (47), 161 (28), 148 (100), 147 (64), 134 (37), 133 (53), 120 (53), 119 (46), 107 (70), 105 (46), 91 (60), 77 (39), and 41 (44); for the minor epimer **414**: ^{1}H NMR (from the mixture) δ ($CDCl_3$): 0.889 (3H, s), 1.033 (3H, s), 1.057 (3H, d), 1.15–2.44 (mm), 2.404 (1H, d, J = 9.7 Hz, C–4 methine), 2.612 (2H, m, C–11 methylene), 5.766 (1H, s); ^{1}H NMR (from the mixture) δ (C_6D_6): 0.722 (3H, d, J = 6.5 Hz), 0.889 (3H, s), 0.906 (3H, s), 1.02–2.23 (mm), and 5.649 (1H, s); ^{13}C NMR (from the mixture) δ (attached H's): 14.6 (3), 25.5 (2), 29.2 (3), 31.5 (3), 32.5 (2), 39.3 (2), 41.0 (0), 41.3 (1), 42.9 (2), 57.8 (1), 64.9 (0), 123.8 (1), 194.4 (0), and 214.7 (0); MS (from GC–MS) *m/z* (%): 204 (83, M^+), 189 (22, M^+ – Me), 176 (11), 162 (48), 161 (39), 148 (100), 147 (80), 134 (49), 133 (56), 120 (65), 119 (62), 107 (90), 105 (62), 91 (86), 79 (37), 77 (54), and 41 (56). *Exact mass* (epimeric mixture) calcd. for $C_{14}H_{18}O$: 204.1503; found: 204.1486; and for $C_{13}H_{15}O$ (M^+ – Me): 189.1295; found: 189.1298.

Attempted dehydrogenation of epimers 414 and 415 with DDQ*

DDQ (284 mg, 1.25 mmol) was added to a solution of epimers **414** and **415** (51.7 mg, 0.25 mmol) from the above reaction in dry benzene (30 mL) and the resulting solution was heated under reflux for one week. No detectable formation of **413** was observed as revealed by GC–MS analysis. Longer reaction time and a large excess of DDQ made no difference.

***rel*-(5ξ,6ξ)-6-Acetyl-4,8,8-trimethylspiro[4.4]non-3-en-1-one (431)**

To lithium (30 mg, 4.3 mmol) in liquid ammonia (30 mL) at –78°C was added a

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* We thank Ms. Peiying Liu for kindly informing us of this detailed experimental procedure.

solution of **427** (205.7 mg, 0.95 mmol) in THF (10 mL). The reaction temperature was raised to −33°C, and the mixture was stirred for *ca.* 30 min, whereupon solid NH_4Cl was added cautiously (the blue color disappeared right after the addition), and the ammonia was allowed to evaporate overnight. The residue was extracted with diethyl ether (×4), washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was then treated with PCC (614.3 mg, 2.85 mmol) in CH_2Cl_2 (50 mL) overnight. Filtration through a Florisil pad removed a black precipitate, and five volumes of diethyl ether were passed through the pad. The combined solutions were concentrated *in vacuo* and chromatography (2% acetone in petroleum ether) of the residue provided pure **431** (167.4 mg, 81%) as a colorless oil: IR (film) ν_{max}: 1745, 1710, and 1643 cm^{-1}; ^1H NMR δ: 0.80−0.93 (1H, m), 1.123 (3H, s), 1.133 (3H, s), 1.14−1.76 (6H, mm), 1.913 (3H, s), 2.028 (1H, t, J = 13.1 Hz), 2.848 (1H, d of quintets, J = 2.3, 23.3 Hz) and 2.954 (1H, d of quintets, J = 2.3, 23.3 Hz) (C−2 methylene), 3.492 (1H, dd, J = 6.3, 13.5 Hz), and 5.690 (1H, apparent s); ^{13}C NMR δ (attached H's): 15.6 (3), 28.8 (3), 29.3 (3), 29.7 (3), 37.8 (0), 41.6 (2), 43.6 (2), 49.5 (2), 60.2 (1), 64.1 (0), 121.1 (0), 144.2 (0), 207.8 (0), and 221.0 (0); MS *m/z* (%): 220 (14, M^+), 177 (45, $M^+ - COCH_3$), 149 (20), 107 (43), 93 (48), 91 (21), 77 (20), 43 (100, $COCH_3^+$), and 41 (35). *Exact mass* calcd. for $C_{14}H_{20}O_2$: 220.1462; found: 220.1457; and for $C_{12}H_{17}O$ ($M^+ - COCH_3$): 177.1279; found: 177.1279.

***rel*-(4*R*,5*R*,6ξ)-6-Acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (416) and *rel*-(4*S*,5*R*,6ξ)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (417)**

Compound **431** (45.4 mg, 0.21 mmol), 5% palladium on carbon (2 spatula-tips), and dry methanol (20 mL) were placed in an hydrogenation flask which was then shaken under 51 psi pressure of H_2 for 1 h. The mixture was filtered through a Celite plug, and the solution was concentrated *in vacuo*. The residue was chromatographed (4% acetone in petroleum ether) to yield a mixture of epimers **416** and **417** (45.9 mg,

100%) in 3.5 : 2 ratio as revealed from the following cyclisation described below. For the spectroscopic data for these two epimers: *vide supra*.

***rel*-(4*R*,8*R*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (414) and *rel*-(4*R*,8*R*,9*S*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (415)**

To a solution of epimers **416** and **417** (45.9 mg, 0.21 mmol) in dry benzene (30 mL) was added potassium *tert*-butoxide (47.1 mg, 0.42 mmol), and the resulting mixture was stirred at room temperature for *ca.* 20 min. Water was then added and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The yellow residue was chromatographed (2% acetone in petroleum ether) to provide the methyl epimers **414** and **415** (34.1 mg, 81%) in 3.5 : 2 ratio. For the spectroscopic data for these two epimers: *vide supra*.

***rel*-(1*S*,4*R*,8*S*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (432) and *rel*-(1*S*,4*R*,8*S*,9*S*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (433)**

A 1 : 3.5 mixture of epimers **414** and **415** (61.3 mg, 0.30 mmol) from the direct hydrogenation sequence, 5% palladium on carbon (2 spatula-tips), and dry methanol (30 mL) were placed in an hydrogenation flask, which was shaken under 51 psi pressure of H_2 for *ca.* 1 h. The mixture was then filtered through a Celite plug, and the solution was concentrated *in vacuo*. The residue was then chromatographed (5% acetone in petroleum ether) to provide a mixture of the epimers **432** and **433** (62.3 mg, 100%) in an approximate 1 : 3.5 ratio as revealed by GC-MS analysis: IR (film) of the mixture ν_{max}: 1739 cm^{-1}; for the major epimer **433**: ^{1}H NMR (from the mixture) δ: 0.789 (3H, s), 0.949 (3H, d, J = 6.6 Hz), 1.025 (3H, s), 1.10-2.15 (mm), 2.449 (1H, m), and 2.736 (1H, dd, J = 7.6 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 13.9 (3), 28.1 (3), 29.7 (3), 32.7 (2), 33.2 (2), 39.6 (0), 45.4 (1), 45.9 (2), 46.0 (1), 46.9

(2), 53.6 (1), 56.3 (2), 60.8 (0), and 224.1 (0); MS (from GC–MS) *m/z* (%): 206 (59, M^+), 191 (31, M^+ – Me), 177 (12), 163 (61), 150 (73), 121 (49), 107 (70), 95 (54), 93 (53), 91 (54), 81 (51), 79 (59), 55 (55), and 41 (100); for the minor epimer **432**: ^{1}H NMR (from the mixture) δ: 0.965 (3H, d, J = 6.5 Hz), 0.985 (3H, s), 1.007 (3H, s), 1.10–2.15 (10H, mm), 2.449 (1H, m), and 2.775 (1H, dd, J = 7.6 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 15.5 (3), 29.2 (3), 29.5 (3), 31.3 (2), 34.4 (2), 39.4 (0), 42.9 (1), 44.6 (2), 45.4 (1), 46.8 (2), 47.9 (2), 59.4 (1), 61.8 (0), and 223.9 (0); MS (from GC–MS) *m/z* (%): 206 (60, M^+), 191 (51, M^+ – Me), 163 (63), 150 (48), 149 (46), 135 (36), 121 (54), 109 (50), 107 (80), 95 (87), 93 (65), 91 (67), 81 (58), 79 (72), 77 (54), 55 (58), and 41 (100).

3–Ethoxy–5,5–dimethylcyclohex–2–en–1–one (447)

The following procedure was derived from that of House and Gannon.[131] A solution of absolute ethanol (350 mL), dry benzene (100 mL), 5,5–dimethyl–1,3–cyclohexanedione (dimedone) (31.3 g, 0.22 mol), and *p*TSA (400 mg) was heated under reflux with water removal by 4 Å Molecular Sieves in a Soxhlet extractor overnight. Much of the solvent was removed *in vacuo*, and 15% NaOH was added. The product was extracted with diethyl ether (×3), and the combined organic solutions were washed with 10% NaOH (×3), water (×2), and saturated NaCl (×2). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo* to provide pure **447** (37.5 g, 100%) as a colorless solid: mp: *ca.* 30°C; IR (film) ν_{max}: 1712 and 1607 cm^{-1}; ^{1}H NMR δ: 1.076 (6H, s), 1.369 (3H, t, J = 7.0 Hz), 2.205 (2H, s), 2.280 (2H, s), 3.910 (2H, q, J = 7.0 Hz), and 5.338 (1H, s); ^{13}C NMR δ (attached H's): 13.9 (3), 28.0 (2C, 3), 32.2 (0), 42.6 (2), 50.5 (2), 63.9 (2), 101.2 (1), 175.8 (0), and 199.1 (0); MS (from GC–MS) *m/z* (%): 168 (38, M^+), 112 (67), 84 (100), 69 (84), 68 (63), 55 (22), 43 (51), and 41 (30).

3-Ethyl-5,5- dimethylcyclohex-2-en-1-one (445)

To an ice-cooled solution of **447** (440.2 mg, 2.62 mmol) in anhydrous THF (30 mL) was added cautiously a 3.0 M solution of EtMgBr (1.40 mL, 4.19 mmol) in diethyl ether. The mixture was heated cautiously under reflux for *ca.* 1 h, and the cooled solution was poured slowly into an ice-cooled 10% HCl solution. The mixture was stirred at room temperature overnight. Diethyl ether was added, the aqueous layer was re-extracted with diethyl ether (×3), and the combined organic solutions were washed with water (×3), 10% NaOH (×3), water (×3), and saturated NaCl (×2). The solution was then dried over $MgSO_4$ and concentrated *in vacuo* to give **445** (389.2 mg, 98%): IR (film) ν_{max}: 1720 and 1631 cm^{-1}; ^1H NMR δ: 1.038 (6H, s), 1.102 (2H, t, J = 7.4 Hz), 2.186 (2H, s), 2.215 (2H, q, J = 7.4 Hz), 2.219 (2H, s), and 5.882 (1H, br s); ^{13}C NMR δ (attached H's): 11.1 (3), 28.1 (2C, 3), 30.8 (2), 33.4 (0), 43.8 (2), 50.9 (2), 123.3 (1), 165.5 (0), and 200.9 (0); MS m/z (%): 152 (8, M^+), 96 (47), 81 (35), 77 (22), 68 (70), 67 (100), 55 (22), 53 (27), and 41 (31). For large scale preparation of **445**, the reaction mixture was stirred at room temperature overnight because of the uncontrollable vigorous reaction under reflux.

7-Ethyl-9,9-dimethyl-1,4-dioxaspiro[4.5]dec-7-ene (448)

A solution of the enone **445** (3.4 g, 22.4 mmol), ethylene glycol (6.2 mL, 0.11 mmol), and *p*TSA (400 mg) in benzene was heated under reflux with a Barrett water-separator overnight. Solid $NaHCO_3$ was added to the cooled solution, and water was added until the solution became saturated. The aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The yellow color was removed by vacuum distillation, and the colorless distillate was then chromatographed (1.5% acetone in petroleum ether) to provide a 4.5 : 1 mixture of **448** and **(*Z*)-7-ethylidene-1,4-dioxaspiro[4.5]decane (450)** plus **(*E*)-7-**

ethylidene-1,4-dioxaspiro[4.5]decane (451) (1.3 g, 62%) along with the recovered starting material **445** (1.4 g, 28%). [The recovered **445** was treated again with *p*TSA and ethylene glycol in benzene as above to give the same mixture of ketals **448**, **450** and **451** (0.87 g, 16%) along with the recovered starting material **445** (192.3 mg, 6%).] For **447**: ^{1}H NMR (from the mixture) δ: 1.050 (6H, s), 0.998 (3H, t, J = 7.3 Hz), 1.618 (2H, s), 1.972 (2H, q, J = 7.3 Hz), 2.150 (2H, s), 3.954 (4H, s), and 5.142 (1H, br s); ^{13}C NMR δ (attached H's): 12.0 (3), 30.4 (2C, 3), 30.0 (2), 34.0 (0), 38.3 (2), 43.7 (2), 64.0 (2C, 2), 109.2 (0), 129.3 (1), and 133.4 (0); MS (from GC-MS) *m/z* (%): 196 (11, M^+), 110 (34), 95 (49), 87 (34), 86 (100), and 41 (16). For **450** and **451**: MS (from GC-MS) *m/z* (%): 196 (1, M^+), 140 (6), 127 (100), 86 (11), 83 (17), and 41 (12). For **449** MS (from GC-MS) *m/z* (%): 196 (10), 151 (13), 140 (100), 127 (11), 125 (20), 111 (10), 91 (10), 86 (10), 67 (14), 55 (13), 53 (11), 43 (13), and 41 (20).

7-Ethyl-9,9-dimethylspiro[4.5]dec-7-ene-1,4-dione (444)

A solution of the mixture ketals **448**, **450** and **451** (300.2 mg, 1.53 mmol) from the above reaction in CH_2Cl_2 was stirred at −78°C as $BF_3{\cdot}Et_2O$ (1.88 mL, 15.3 mmol) was introduced, followed over a period of 10 min by a solution of **109** (1.22 mL, 4.59 mmol) in CH_2Cl_2. The mixture was allowed to attain room temperature while stirring overnight. The cooled solution was poured cautiously into an ice-cooled saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×3) followed by saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The black residue was then chromatographed (3% acetone in petroleum ether) to provide a 4.5 : 1 mixture of spiro-diketones **444** and **(*Z*)-7-ethylidene-9,9-dimethylspiro[4.5]decane-1,4-dione (456)** plus **(*E*)-7-ethylidene-9,9-dimethylspiro[4.5]decane-1,4-dione**

(**457**) (259.3 mg, 77%) and hydrolysed starting material, isophorone (25.6 mg, 11%). IR (film) of the mixture ν_{max}: 1770, 1725 and 1665 cm^{-1}; for **444**: ^1H NMR (from the mixture) δ: 0.998 (6H, s), 1.004 (3H, t, J = 7.4 Hz, partially overlapped), 1.630 (2H, s), 1.822 (2H, s), 2.049 (2H, q, J = 7.4 Hz), 2.845 (4H, m), and 5.042 (1H, br s); ^{13}C NMR (from the mixture) δ (attached H's): 11.7 (3), 29.1 (2C, 3), 30.6 (0), 30.8 (2), 34.5 (2C, 2), 37.8 (2), 41.5 (2), 62.7 (0), 111.3 (1), 144.5 (0), and 212.4 (2C, 0); MS (from GC–MS) m/z (%): 220 (88, M^+), 205 (41, M^+ – Me), 192 (24), 177 (84), 163 (62), 159 (57), 145 (81), 93 (57), 91 (100), 79 (57), 77 (82), 55 (94), 53 (50), 43 (65), and 41 (99); for **456** and **457**: MS of one isomer (from GC–MS) m/z (%): 220 (82, M^+), 205 (76, M^+ – Me), 191 (14), 178 (11), 177 (46), 164 (24), 163 (31), 159 (14), 149 (44), 145 (17), 135 (27), 131 (10), 122 (10), 121 (74), 119 (16), 107 (66), 105 (43), 103 (10), 95 (14), 93 (61), 92 (14), 91 (93), 85 (46), 81 (14), 80 (10), 79 (71), 78 (20), 77 (86), 69 (13), 67 (25), 66 (13), 65 (43), 63 (11), 57 (25), 56 (14), 55 (84), 53 (49), 52 (19), 51 (30), 43 (48), 42 (49), and 41 (100); of the other isomer: 220 (33, M^+), 205 (12, M^+ – Me), 192 (32), 178 (30), 177 (89), 163 (34), 159 (15), 149 (15), 145 (17), 135 (24), 121 (31), 119 (10), 109 (19), 107 (30), 105 (23), 95 (18), 93 (34), 91 (49), 85 (15), 81 (17), 79 (50), 69 (19), 67 (36), 65 (27), 57 (28), 56 (15), 55 (76), 54 (13), 53 (47), 52 (13), 51 (20), 43 (50), 42 (19), and 41 (100).

7–Ethyl–4–hydroxy–4,9,9–trimethylspiro[4.5]dec–7–en–1–one (458)

To a solution of the mixture of spiro–diketones **444**, **456** and **457** (200.4 mg, 0.91 mmol) at –78°C was added a 1.4 M solution of methyllithium in diethyl ether (3.25 mL, 4.55 mmol), and the mixture was stirred at –78°C for 2 h. This solution was then poured cautiously into an ice–cooled saturated NaCl solution, and the aqueous layer was extracted with diethyl ether (×3). The combined organic solutions were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting slightly yellow oil was treated again with methyllithium in diethyl ether (3.25 mL, 4.55

mmol) following the same procedure to give a mixture of keto-alcohols **458**, (*Z*)-**7-ethylidene-4-hydroxy-4,9,9-trimethylspiro[4.5]decan-1-one** (**459**), and (*E*)-**7-ethylidene-4-hydroxy-4,9,9-trimethylspiro[4.5]decan-1-one** (**460**): IR (film) of the mixture ν_{max}: 3457 (br), 1726 and 1459 cm^{-1}; for **458**: MS (from GC-MS) *m/z* (%): 236 (54, M^+), 203 (17, $M^+ - H_2O - Me$), 178 (30), 163 (20), 161 (18), 145 (26), 137 (33), 99 (69), 91 (21), 55 (26), and 43 (100). for **459** and **460**: MS of one isomer (from GC-MS) *m/z* (%): 236 (46, M^+), 178 (87), 163 (19), 145 (22), 137 (31), 99 (61), 91 (22), 77 (16), 55 (27), 43 (100), and 41 (34); of the other isomer *m/z* (%): 236 (22, M^+), 178 (100, $M^+ - H_2O - Me$), 163 (17), 153 (43), 135 (16), 121 (11), 99 (37), 69 (13), 55 (22), 43 (76), and 41 (27). Since it was difficult to separate the mixture of keto-alcohols **458**, **459** and **460** from the corresponding spiro-diketones, the crude product was used for the ozonolysis without further purification.

4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]nona-3,6-dien-1-one (443)

Ozone was passed through a solution of the crude keto-alcohol mixture of **458**, **459** and **460** from the above reaction in CH_2Cl_2 (50 mL) at −78°C until the solution turned blue. The excess ozone was removed by bubbling O_2 through the solution, and the system was then purged with nitrogen. Dimethyl sulfide (4 mL) was added, and the mixture was stirred overnight during which time the reaction was allowed to attain room temperature. The solvent was evaporated *in vacuo*. Benzene (50 mL) and *p*TSA (35 mg) were added to the residue. The resulting solution was heated under reflux with a Barrett water-separator for 2 h. Saturated $NaHCO_3$ was added to the cooled solution, the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with saturated $NaHCO_3$ (×2) and saturated NaCl(×2), and the resulting solution was then dried over $MgSO_4$ and concentrated *in vacuo*. The black residue was chromatographed (4% acetone in petroleum ether) to provide pure **443**

(133.1 mg, 63% from the *mixture* of the spiro-diketones **444**, **456** and **457**): IR (film) ν_{max}: 1748 and 1672 cm^{-1}; ^1H NMR δ: 1.026 (3H, t, J = 7.3 Hz), 1.250 (3H, s), 1.707 (1H, d, J = 13.9 Hz) and 1.898 (1H, d, J = 13.9 Hz) (AB quartet, C-9 methylene), 2.638 (2H, m), 2.848 (1H, d of quintets, J = 2.4, 22.7 Hz) and 3.197 (1H, d of quintets, J = 2.4, 22.7 Hz) (C-2 methylene), 5.757 (1H, m), and 6.676 (1H, s); COSY spectrum showed the significant long-range coupling between the C-2 methylene and the C-4 methyl; ^{13}C NMR δ (attached H's): 7.8 (3), 14.5 (3), 29.0 (3), 29.6 (3), 31.6 (2), 41.8 (2), 46.2 (2), 52.0 (0), 68.4 (0), 121.3 (1), 141.6 (0), 142.0 (0), 155.5 (1), 198.1 (0), and 219.1 (0); MS *m/z* (%): 232 (45, M^+), 217 (16, M^+ - Me), 189 (33), 176 (28), 175 (100, M^+ - CH_3CH_2CO), 161 (26), 147 (45), 133 (26), 91 (24), 57 (75, $CH_3CH_2CO^+$), and 41 (20). *Exact mass* calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1460; and for $C_{12}H_{15}O$ (M^+ - CH_3CH_2CO): 175.1123; found: 175.1121. Compound **461** was very tentatively identified in the crude product by its MS (from GC-MS) *m/z* (%): 206 (48, M^+), 191 (2, M^+ - Me), 150 (22), 149 (100), 135 (15), 109 (8), 108 (62), 107 (28), 95 (8), 79 (8), 77 (14), 56 (11), 55 (18), 43 (38), and 41 (18).

rel-(4_R_,5_R_,6ξ)-4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]nonan-1-one (441) and _rel_-(4_S_,5_R_,6ξ)-4,8,8-trimethyl-6-(1-oxopropyl)spiro[4.4]nonan-1-one (442)

Compound **443** (279.1 mg, 1.20 mmol), dry methanol (30 mL), and 5% palladium on carbon (2 spatula-tips) were placed in an hydrogenation flask, which was then shaken at 51 psi pressure of H_2 for *ca.* 1 h. The mixture was filtered through a Celite plug and the solution was concentrated *in vacuo*. The residue was chromatographed (5% acetone in petroleum ether) to yield a 1 : 5 mixture of epimers **441** and **442** (283.9 mg, 100%): IR (film) of the mixture ν_{max}: 1731 and 1711 cm^{-1}; for the major epimer **442**: ^1H NMR (from the mixture) δ: 1.004 (3H, t, J = 7.2 Hz), 1.043 (3H, d, J = 7.0 Hz), 1.077 (3H, s), 1.175 (3H, s), 1.295 (1H, d, J = 13.7 Hz) and 1.852 (1H, d, J = 13.7

Hz) (AB quartet, C-9 methylene), 2.443 (2H, q, J = 7.2 Hz), 1.42-2.52 (mm), and 3.242 (1H, dd, J = 6.4, 7.0 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 7.6 (3), 15.4 (3), 28.7 (2), 29.0 (3), 30.6 (3), 34.7 (2), 37.1 (0), 38.2 (2), 41.2 (1), 45.6 (2), 51.8 (2), 57.8 (1), 59.5 (0), 211.6 (0), and 224.2 (0); MS (from GC-MS) m/z (%): 236 (28, M^+), 180 (66), 179 (49, $M^+ - CH_3CH_2CO$), 162 (31), 161 (42), 147 (48), 138 (58), 123 (27), 121 (28), 109 (27), 95 (35), 81 (28), 57 (100, $CH_3CH_2CO^+$), 55 (47), 43 (25), and 41 (50); for the minor epimer **441**: ^{1}H NMR (from the mixture) δ: 0.987 (3H, t, J = 7.4 Hz), 0.999 (3H, d, J = 7.2 Hz), 1.054 (3H, s), 1.121 (3H, s), 1.295 (1H, d, J = 13.7 Hz) and 1.852 (1H, d, J = 13.7 Hz) (AB quartet, C-9 methylene), 2.433 (2H, q, J = 7.3 Hz), 1.42-2.52 (mm), and 2.928 (1H, dd, J = 6.9, 6.5 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 7.2 (3), 14.3 (3), 28.8 (2), 29.9 (3), 30.1 (3), 34.6 (2), 37.3 (2), 37.9 (0), 38.7 (1), 41.6 (2), 43.7 (2), 57.7 (1), 60.4 (0), 211.9 (0), and 223.4 (0); MS (from GC-MS) m/z (%): 236 (22, M^+), 180 (57), 179 (60, $M^+ - CH_3CH_2CO$), 161 (51), 152 (58), 147 (49), 138 (48), 137 (30), 123 (32), 121 (30), 119 (43), 109 (29), 107 (26), 95 (38), 81 (33), 79 (27), 67 (26), 57 (100, $CH_3CH_2CO^+$), 55 (50), 43 (25), and 41 (49). *Exact mass* (epimeric mixture) calcd. for $C_{15}H_{24}O_2$: 236.1776; found: 236.1773.

rel-(4_R_,8_R_,9_R_)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (439) and _rel_-(4_R_,8_R_,9_S_)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (440)

To a solution of the epimers **441** and **442** (140.2 mg, 0.59 mmol) from the above hydrogenation reaction in dry benzene (40 mL) was added potassium *tert*-butoxide (32.4 mg, 1.18 mmol), and the mixture was stirred at room temperature for *ca.* 30 min. Water was added, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was then chromatographed (2% acetone

in petroleum ether) to provide a 1 : 5 mixture of C-9 epimers **439** and **440** (108.8 mg, 84%) as a colorless oil. For the spectroscopic data for these two epimers, *vide infra*.

***rel*-(5ξ,6ξ)-4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]non-3-en-1-one (462)**

Enone **443** (89.4 mg, 0.39 mmol) in THF (10 mL) was added to lithium (13.5 mg, 1.95 mmol) in ammonia (30 mL) at −78°C, and the temperature was then raised to −33°C, at which temperature the reaction mixture was stirred for *ca.* 35 min. The reaction was quenched by the cautious addition of solid NH_4Cl (the blue color disappeared after the addition), and the ammonia was allowed to evaporate overnight. Diethyl ether and water were added, the aqueous layer was re-extracted with diethyl ether (×3), and the combined extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), and PCC (252.2 mg, 1.17 mmol) was added to this solution. The mixture was stirred at room temperature overnight. Filtration through a small pad of Florisil removed a black precipitate, and five volumes of diethyl ether were passed through the pad. Concentration of the combined solutions *in vacuo* gave a residue which was then chromatographed (3% acetone in petroleum ether) to provide the pure **462** (77.5 mg, 86%) as a colorless oil: IR (film) ν_{max}: 1745 and 1709 cm^{-1}; ^1H NMR δ: 0.954 (3H, t, J = 7.2 Hz), 1.138 (3H, s), 1.150 (3H, s), 1.582 (1H, d, J = 14.1 Hz) and 1.678 (1H, partially overlapped d, J = 14.1 Hz) (AB quartet, C-9 methylene), 1.49-1.74 (4H, mm), 2.151 (2H, q, J = 7.2 Hz), 2.00-2.32 (1H, m), 2.833 (1H, d of quintets, J = 2.3, 25.6 Hz) and 2.975 (1H, d of quintets, J = 2.3, 25.6 Hz) (C-2 methylene), 3.490 (1H, dd, J = 6.1, 7.2 Hz), and 5.683 (1H, m); ^{13}C NMR δ (attached H's): 7.4 (3), 15.4 (3), 28.7 (3), 29.7 (3), 34.9 (2), 37.8 (0), 41.5 (2), 43.5 (2), 49.4 (2), 59.1 (1), 64.1 (1), 120.9 (1), 144.3 (0), 210.1 (0), and 220.9 (0); MS *m/z* (%): 234 (24, M^+), 178 (18), 177 (78, $M^+ - CH_3CH_2CO$), 159 (11), 149 (34), 121 (25), 107 (64), 93 (67), 91 (29), 79

(20), 77 (27), 69 (23), 57 (100, $CH_3CH_2CO^+$), 55 (21), and 41 (47). *Exact mass* calcd. for $C_{15}H_{22}O_2$: 234.1619; found: 234.1614.

rel-(4*R*,5*R*,6ξ)-4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]nonan-1-one (441) and rel-(4*S*,5*R*,6ξ)-4,8,8-trimethyl-6-(1-oxopropyl)spiro[4.4]nonan-1-one (442)

Compound **462** (114.3 mg, 0.49 mmol) from the above Birch reaction, dry methanol (30 mL), and 5% palladium on carbon (2 spatula-tips) were placed in an hydrogenation flask, which was shaken at 51 psi pressure of H_2 for *ca.* 1 h. The mixture was filtered through a Celite plug, and the solution was concentrated *in vacuo*. The residue was chromatographed (4% acetone in petroleum ether) to provide a 4 : 1 mixture of epimers **441** and **442** (111.3 mg, 97%). The ratio was established from the following cyclisation described below. For the spectroscopic data for these two epimers **441** and **442**, *vide supra*. Once, a small amount of a mixture of ***rel*-(4*R*,5*R*,8ξ)-4,7,7-trimethyl-8-(1-oxopropyl)spiro[4.4]nonan-1-one** (**463**) and ***rel*-(4*S*,5*R*,8ξ)-4,7,7-trimethyl-8-(1-oxopropyl)spiro[4.4]nonan-1-one** (**464**) was isolated along with the desired C-9 epimers **441** and **442**. IR (film) of the epimeric mixture of **463** and **464** ν_{max}: 1740 and 1716 cm^{-1}; for the major epimer: ^1H NMR (from the mixture) δ: 0.970 (3H, s), 1.045 (3H, d, J = 7.3 Hz), 1.107 (3H, s), 1.040 (3H, t, J = 7.3 Hz), 1.15-2.62 (mm), and 3.759 (1H, dd, J = 6.3 and 7.3 Hz, C-7 methine); ^{13}C NMR (from the mixture) δ (attached H's): 7.3 (3), 14.7 (3), 27.0 (2), 29.2 (3), 31.5 (3), 32.7 (2), 35.7 (2), 37.3 (0), 39.1 (1), 44.1 (2), 51.2 (2), 54.3 (1), 64.9 (0), 210.8 (0), and 220.2 (0); for the minor epimer: ^1H NMR (from the mixture) δ: 0.729 (3H, d, J = 7.1 Hz), 1.014 (3H, t, J = 7.3 Hz), 1.014 (3H, s), 1.033 (3H, s), 1.15-2.62 (mm), and 3.156 (1H, dd, J = 4.5 Hz); ^{13}C NMR (from the mixture) δ (attached H's): 7.8 (3), 17.2 (3), 26.2 (2), 29.0 (3), 31.6 (3), 35.5 (2), 36.8 (2), 37.8 (0), 38.2 (1), 42.4 (2), 43.0 (2), 53.9 (1), 61.9 (0), 213.1 (0), and 220.9 (0).

rel-(4R,8R,9R)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (439) and rel-(4R,8R,9S)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (440)

Potassium *tert*-butoxide (58.4 mg, 0.52 mmol) was added to a solution of the epimers **441** and **442** (60.4 mg, 0.26 mmol) from the above hydrogenation in dry benzene (35 mL), and the mixture was stirred at room temperature for *ca.* 30 min. Water was added, the aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the residue with 3% acetone in petroleum ether as the eluent provided a 4 : 1 mixture of epimers **439** and **440** (45.8 mg, 82%). For the spectroscopic data for these two epimers, *vide infra*.

rel-(1S,2S,3S,4R,8S,9R)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (468) and rel-(1S,2S,3S,4R,8S,9S)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (469)

A 1 : 5 mixture of epimers **439** and **440** (57.4 mg, 0.26 mmol) from the direct hydrogenation sequence in THF (5 mL) was added to lithium (9 mg, 1.3 mmol) in ammonia (20 mL) at −78°C, and the temperature was raised to −33°C, at which temperature the mixture was stirred for 35 min. The reaction was quenched by the cautious addition of solid NH_4Cl (the blue color disappeared right after the addition), and the ammonia was allowed to evaporate overnight. Diethyl ether and water were added, the aqueous layer was re-extracted with diethyl ether (×3), and the organic solution was washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (4% acetone in petroleum ether) to provide a 1 : 5 mixture of the alcohols **468** and **469** (34.8 mg, 60%): IR (film) of the mixture ν_{max}: 3333 (br) cm^{-1}; for the major epimer **469**: ^1H NMR (from the mixture) δ: 0.949 (3H, d, J = 6.6 Hz), 1.014 (3H, d, J = 6.3 Hz), 1.024 (3H, s), 1.078 (3H, s), 1.13–2.19

(12H, mm), and 3.564 (1H, dd, J = 8.5, 1.2 Hz); MS (from GC–MS) m/z (%): 222 (2.6, M^+), 207 (4), 204 (12, $M^+ - H_2O$), 193 (8), 189 (15, $M^+ - H_2O$ – Me), 166 (12), 165 (21), 162 (13), 161 (9), 151 (11), 149 (15), 148 (8), 147 (12), 137 (9), 136 (10), 124 (8), 123 (18), 121 (14), 119 (8), 110 (17), 109 (67), 108 (15), 107 (39), 105 (17), 95 (45), 94 (10), 93 (31), 91 (30), 81 (35), 79 (33), 77 (24), 69 (23), 67 (28), 65 (12), 67 (28), 65 (12), 57 (24), 55 (59), 53 (23), 43 (56), and 41 (98); for the minor epimer **468**: ^{1}H NMR (from the mixture) δ: 0.876 (3H, d, J = 6.7 Hz), 1.003 (3H, s), 1.016 (3H, d, partially overlapped with the signals of the major epimer **469**), 1.089 (3H, s), 1.13–2.19 (12H, mm), and 3.521 (1H, dd, J = 7.0, 9.0 Hz); MS (from GC–MS) m/z (%): no M^+, 204 (13, $M^+ - H_2O$), 189 (19, $M^+ - H_2O$ – Me), 175 (6), 165 (11), 162 (12), 161 (12), 149 (13), 148 (10), 147 (13), 136 (15), 123 (14), 121 (16), 119 (8), 108 (15), 107 (38), 106 (10), 105 (17), 95 (51), 94 (11), 93 (31), 91 (29), 81 (33), 79 (31), 77 (23), 69 (23), 67 (28), 65 (12), 57 (24), 56 (10), 55 (59), 53 (23), 43 (56), and 41 (98). *Exact mass* (mixture of alcohols) calcd. for $C_{15}H_{26}O$: 222.1982; found: 222.1971; and for $C_{15}H_{24}$ ($M^+ - H_2O$): 204.1876; found: 204.1875.

***rel*-(1*S*,9*R*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (470) and *rel*-(1*S*, 9*S*)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (471)**

A 1 : 5 mixture of epimers **439** and **440** (180.4 mg, 0.83 mmol) from the direct hydrogenation sequence, dry methanol (30 mL), and 5% palladium on carbon (2 spatula-tips) were placed in an hydrogenation flask, which was shaken at 51 psi pressure of H_2 for *ca.* 1 h. The mixture was then filtered through a Celite plug, and the solution was concentrated. The residue was chromatographed (5% acetone in petroleum ether) to provide a mixture of four diastereomers **470** and **471**: (182.0 mg, 100%) as a colorless oil: IR (film) of the mixture ν_{max}: 1736 and 1462 cm^{-1}; the mass spectra (from GC–MS) for all four isomers were almost identical, m/z (%): 220 (77, M^+), 205 (24, M^+ – Me), 202 (9), 177 (31), 164 (75), 163 (87), 149 (41), 148 (82), 137

(20), 136 (28), 135 (30), 124 (81), 123 (25), 122 (22), 121 (64), 109 (72), 108 (31), 107 (67), 105 (24), 96 (21), 95 (66), 93 (54), 91 (50), 82 (36), 81 (52), 77 (42), 69 (27), 68 (18), 67 (34), 65 (19), 55 (64), 53 (29), 43 (25), and 41 (100).

***rel*-(1*S*, 9*R*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (472), and *rel*-(1*S*, 9*S*)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (473)**

To an ice-cooled solution of the mixture ketones **470**, **471** (171.3 mg, 0.78 mmol) from the above reaction in methanol (25 mL) was added portionwise sodium borohydride (59.0 mg, 1.56 mmol), and the mixture was stirred at 0°C for *ca.* 35 min. Water was added and much of the methanol was removed *in vacuo*. The aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (4% acetone in petroleum ether) to provide a mixture of alcohols **472** and **473** (172.1 mg, 100%). Their mass spectra were almost identical with those of **468** and **469** (*vide supra*). *Exact mass* (mixture of alcohols) calcd. for $C_{15}H_{26}O$: 222.1982; found: 222.1976.

***epi*-Pentalenene (279) and pentalenene (230)**

To a solution of the mixture alcohols **468** and **469** (55.2 mg, 0.25 mmol) from the above Birch reduction in benzene (20 mL) was added *p*TSA (8 mg), and the resulting mixture was heated under reflux with a Barrett water-separator filled with 4 Å Molecular Sieves for *ca.* 7 h. The cooled solution was added to a saturated $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The resulting solution was dried over $MgSO_4$, and most of the solvent was removed *in vacuo*. The remaining solvent was evaporated under a very carefully controlled vacuum until the ^1H NMR spectrum of the product showed no solvent peaks. In this case, a 1 : 5 mixture of **pen-**

talenene and ***epi*-pentalenene** (48.3 mg, 96%) was obtained as a colorless oil. Likewise, a mixture of **472** and **473** (20.1 mg, 0.09 mmol) from the above sodium borohydride reduction was treated as above to provide a 1 : 5 mixture of **pentalenene** and ***epi*-pentalenene** (17.6 mg, 96%). For the spectroscopic data for these two final products, *vide infra*.

Preparation of silver nitrate-impregnated silica gel

All operations were performed under dark conditions since silver nitrate is sensitive to light. To a round bottom flask containing silica gel (28 g) was added an aqueous solution of silver nitrate (7 g), and a minimum amount of water was then added until all the silica gel was soaked. The flask was gently shaken, and the resulting slurry was evaporated *in vacuo* for *ca.* 40 min, until most of the water was removed. The flask was placed in an oven at 110°C overnight, and the cooled 20% silver nitrate-impregnated silica gel was ready to use.

Separation of pentalenene and *epi*-pentalenene

A 1 : 5 mixture of pentalenene and *epi*-pentalenene (48.3 mg) was chromatographed on the silver nitrate-impregnated silica gel with pure pentane as eluent to provide **pentalenene** (3.6 mg, 7.5%) and ***epi*-pentalenene** (33.3 mg, 69%).

Separation of two epimeric tricyclic enones: 439 and 440

A 1 : 5 mixture of **439** and **440** (60.4 mg) from the direct hydrogenation route was chromatographed on the silver nitrate-impregnated silica gel with 2% diethyl ether in petroleum ether as eluent to provide pure **439** (4.8 mg, 8%), **440** (50.1 mg, 83%), and an unresolved mixture of **439** and **440** (2.4 mg, 4%). Likewise, chromatography of a 4 : 1 mixture of **439** and **440** (30.5 mg) from the Birch reduction sequence on the silver nitrate-impregnated silica gel gave pure **439** (22.7 mg, 75%), **440** (3.7 mg, 12%), and

an unresolved mixture of **439** and **440** (1.5 mg, 5%). The unresolved mixture of **439** and **440** was rechromatographed in the same fashion. For **439**: IR (film) ν_{max}: 1706 and 1666 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.807 (3H, s), 1.019 (3H, s), 1.047 (3H, d, J = 6.4 Hz), 1.663 (3H, br s), 1.16–2.04 (7H, mm); 2.365 (1H, d, J = 9.7 Hz, C–4 methine), 2.497 (2H, apparent t, J = 6.9, 7.9 Hz, C–11 methylene), ^1H NMR (from the mixture) δ (C_6D_6): 0.756 (3H, d, J = 6.2 Hz), 0.866 (3H, s), 0.904 (3H, s), 1.652 (3H, br s), and 1.03–2.22 (mm); ^{13}C NMR δ: 8.5 (3), 14.7 (3), 24.2 (2), 29.1 (3), 31.5 (3), 32.7 (2), 39.3 (2), 40.8 (0), 41.4 (1), 43.1 (2), 57.0 (1), 62.6 (0), 130.6 (0), 186.6 (0), and 214.3 (0); MS *m/z* (%): 218 (43), 203 (14, M^+ – Me), 176 (15), 175 (12), 163 (12), 162 (72), 161 (20), 147 (27), 134 (10), 133 (17), 121 (100), 119 (13), 105 (17), 91 (24), 77 (13), 55 (12), 53 (11), 43 (20), and 41 (28). *Exact mass* calcd. for $C_{15}H_{22}O$: 218.1669; found: 218.1665. For **440**: IR (film) ν_{max}: 1705 and 1667 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.671 (3H, d, J = 7.1 Hz), 0.870 (3H, s), 1.010 (3H, s), 1.439 (1H, d, J = 12.9 Hz) and 1.551 (1H, d, J = 12.9 Hz) (AB quartet, C–7 methylene), 1.674 (3H, br s), 1.51–2.32 (5H, mm); 2.437 (2H, apparent t, C–11 methylene), 2.659 (1H, dd, J = 4.9 and 4.0 Hz, C–4 methine), ^1H NMR (from the mixture) δ (C_6D_6): 0.416 (3H, d, J = 7.0 Hz), 0.841 (3H, s), 0.849 (3H, s), 1.113 (1H, d, J = 12.7 Hz) and 1.304 (1H, d. J = 12.7 Hz) (AB quartet, C–7 methylene), 1.08–2.08 (7H, mm), 1.669 (3H, br s), and 2.579 (1H, dd, J = 3.7, 6.1 Hz); NOE data (C_6D_6): irradiate 0.416: NOE at 2.579 (14%); irradiate 2.579: NOE at 0.416 (1.2%); ^{13}C NMR δ: 8.5 (3), 16.5 (3), 22.2 (2), 28.8 (3), 30.0 (3), 32.2 (2), 40.2 (1), 42.2 (0), 42.6 (2), 50.8 (2), 53.1 (1), 64.3 (0), 130.6 (0), 184.3 (1), and 214.7 (0); MS *m/z* (%): almost identical with that of **439**. *Exact mass* calcd. for $C_{15}H_{22}O$: 218.1669; found: 218.1669.

***rel*-(1*S*,9*R*)-2,6,6,9-Tetramethyltricyclo[6.3.0.$0^{4,8}$]undecan-3-one(470)**

Compound **439** (25.1 mg, 0.12 mmol), dry methanol, and 5% palladium on carbon (1 spatula-tips) were placed in an hydrogenation flask, which was shaken at 51

psi pressure of H_2 for *ca.* 1 h. The solution was filtered through a Celite plug and concentrated *in vacuo*. Chromatography of the residue (5% acetone in petroleum ether) provided a mixture of two diastereomers **470** (26.2 mg, 100%): IR (film) ν_{max}: 1736 and 1462 cm^{-1}; MS (from GC–MS): see page 219.

***rel*-(1*S*, 9*R*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (472)**

To an ice-cooled solution of the mixture ketones **470** (26.2 mg, 0.12 mmol) from the above reaction was added portionwise sodium borohydride (9 mg, 0.24 mmol), and the resulting mixture was stirred at 0°C for *ca.* 1 h. Water was added, and much methanol was removed *in vacuo*. The product was extracted with diethyl ether (×3), and the combined extracts were washed with saturated NaCl (×2), dried over $MgSO_4$ and concentrated *in vacuo* to provide a mixture of alcohols **472** (26.8 mg, 100%): IR (film) ν_{max}: 3338 (br) and 1463 cm^{-1}; MS (from GC–MS): see page 220. *Exact mass* calcd. for $C_{15}H_{24}$ ($M^+ - H_2O$): 204.1876; found: 204.1852.

Pentalenene (230)

A solution of the mixture alcohols **472** (26.8 mg, 0.12 mmol) from the above reaction in dry benzene (20 mL) was heated under reflux with a Barrett water-separator for *ca.* 2 h. The cooled solution was poured into a saturated solution of $NaHCO_3$, the aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated $NaHCO_3$, saturated NaCl and dried over $MgSO_4$. The solvent was removed under very carefully controlled vacuum to provide **pentalenene** (21.6 mg, 88%): ^1H NMR δ: 0.894 (3H, d, J = 6.8 Hz), 0.977 (3H, s), 0.982 (3H, s), 1.14–1.86 (9H, mm), 1.614 (3H, br s), 2.543 (1H, br d, J = 8.9 Hz), 2.664 (1H, m), 5.153 (1H, br s); ^{13}C NMR δ (attached H's): 15.5 (3), 17.0 (3), 27.6 (2), 29.1 (3), 29.9 (3), 33.5 (2), 40.5 (0), 44.6 (1), 46.8 (2), 48.9 (2), 59.3 (1), 62.0 (1), 64.8 (0), 129.5 (1), and 140.4 (0); MS (from GC–MS) m/z (%): 204 (50, M^+), 189 (43, M^+ – Me), 162

(27), 161 (22), 149 (16), 148 (57), 147 (91), 133 (41), 120 (21), 119 (62), 117 (17), 115 (16), 107 (33), 106 (74), 105 (99), 93 (25), 92 (25), 91 (100), 79 (30), 77 (38), 65 (19), 55 (31), 53 (19), and 41 (69). *Exact mass* calcd. for $C_{15}H_{24}$: 204.1877; found: 204.1879.

rel-(1*S*,9*S*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (471)

Compound **440** (41.5 mg, 0.19 mmol) was hydrogenated as **439** to provide a mixture of two epimers **471** (42.1 mg, 100%): IR (film) ν_{max}: 1736 and 1462 cm^{-1}; MS (from GC-MS): see page 219.

rel-(1*S*,9*S*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (473)

A mixture of ketones **471** (42.1 mg, 0.19 mmol) from the above hydrogenation was treated with sodium borohydride (14 mg, 0.38 mmol) as **470** to provide a mixture of alcohols **473** (43.1 mg, 100%): IR (film) ν_{max}: 3320 (br) and 1461 cm^{-1}; MS (from GC-MS): see page 220. *Exact mass* calcd. for $C_{15}H_{24}$ ($M^+ - H_2O$): 204.1876; found: 204.1879.

***epi*-Pentalenene (279)**

A mixture of alcohols **473** (43.1 mg, 0.19 mmol) was treated with *p*TSA (10 mg) in benzene in the same way as the mixture of the alcohols **472** to provide pure ***epi*-pentalenene (279)** (34.3 mg, 88%): IR (film) ν_{max}: 3027, 1445, 1377, and 1363 cm^{-1}; ^{1}H NMR δ: 0.931 (3H, d, J = 6.7 Hz), 0.969 (6H, s), 1.25-1.70 (9H, mm), 1.597 (3H, br s), 2.625 (1H, br d, J = 8.1 Hz), 2.88 (1H, m) and 5.168 (1H, br s); ^{13}C NMR δ (attached H's): 13.4 (3), 15.3 (3), 28.4 (1), 29.1 (2), 31.5 (3, 2C), 32.8 (2), 39.7 (0), 44.9 (1), 46.0 (2), 50.3 (1), 54.5 (2), 63.2 (1), 131.5 (1), 140.5 (0); MS (from GC-MS) m/z (%): 204 (56, M^+), 189 (48), 162 (30), 161 (24), 148 (61), 147 (96), 133 (43), 120 (22), 119 (63), 107 (33), 106 (74), 105 (100), 93 (25), 92 (25), 91 (98), 79 (29), 77 (37), 55 (30), and 41 (63). *Exact mass* calcd. for $C_{15}H_{24}$: 204.1877; found: 204.1879.

Chapter 4

MODEL STUDIES RELATED TO THE TOTAL SYNTHESIS OF PENTALENOLACTONE

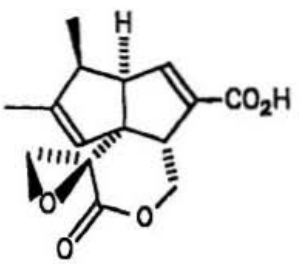
I. Introduction

In 1957, Celmer *et al.*[85a] isolated a new antibiotic from a *Streptomyces* broth culture. This substance, named PA-132, possessed excellent activity against Gram-positive and Gram-negative bacteria as well as against pathogenic and saprophytic fungi. In 1969, Takeuchi[85b] reported the isolation of PA-132 from *Streptomyces* sp. no. 8403-MC. This substance, named pentalenolactone, was found to have inhibitory activity against nucleic acid synthesis in bacterial cells. Based on chemical and spectroscopic studies, structure **475** was tentatively assigned to this antibiotic.

In 1970, Duchamp and coworkers[85c] reported the isolation of pentalenolactone from a fermentation broth of *Streptomyces* UC 5319 during a screening for antitumor agents. Its tetrahydrobromohydrin derivative was unambiguously assigned structure **476** by means of crystallographic analysis. Accordingly, the structure of pentalenolactone was revised as **?33**. More recent studies have shown that pentalenolactone is a potent and specific inhibitor of glyceradehyde-3-phosphate dehydrogenase, a key enzyme in the glycolytic pathway.[85d,105] In addition, pentalenolactone was found to have antiviral activity.[105]

Streptomyces strains from which pentalenolactone was isolated produced a variety of related metabolites, such as pentalenolactones E (**477**), *epi*-F (**478**), G (**479**), H (**480**), P (**481**), and O (**482**). Many of these compounds were considered as

potential biosynthetic intermediates between pentalenene and pentalenolactone. In fact, labelled pentalenene was found to be incorporated into **477**, **478**, and pentalenolactone itself.[105]



Pentalenolactone

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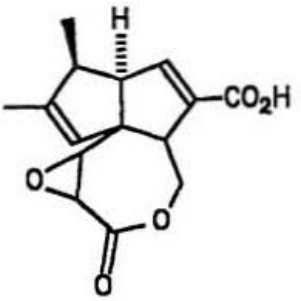
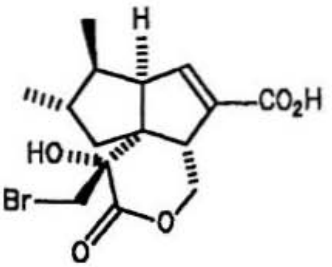
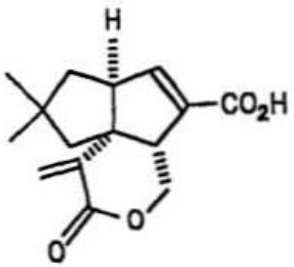


475

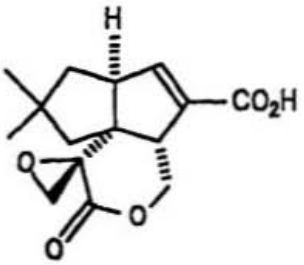


476



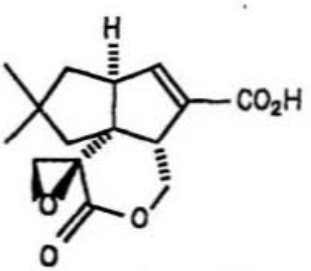
Pentalenolactone E

477



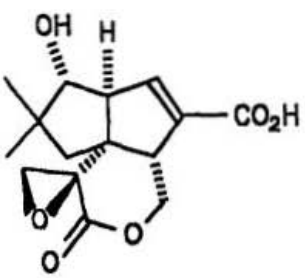
epi – Pentalenolactone F

478



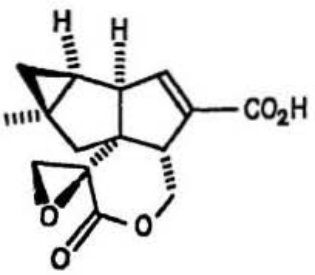
Pentalenolactone G

479



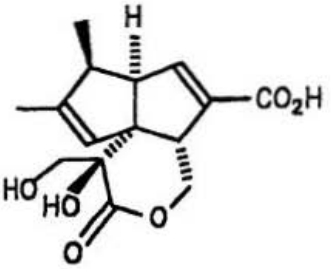
Pentalenolactone H

480



Pentalenolactone P

481



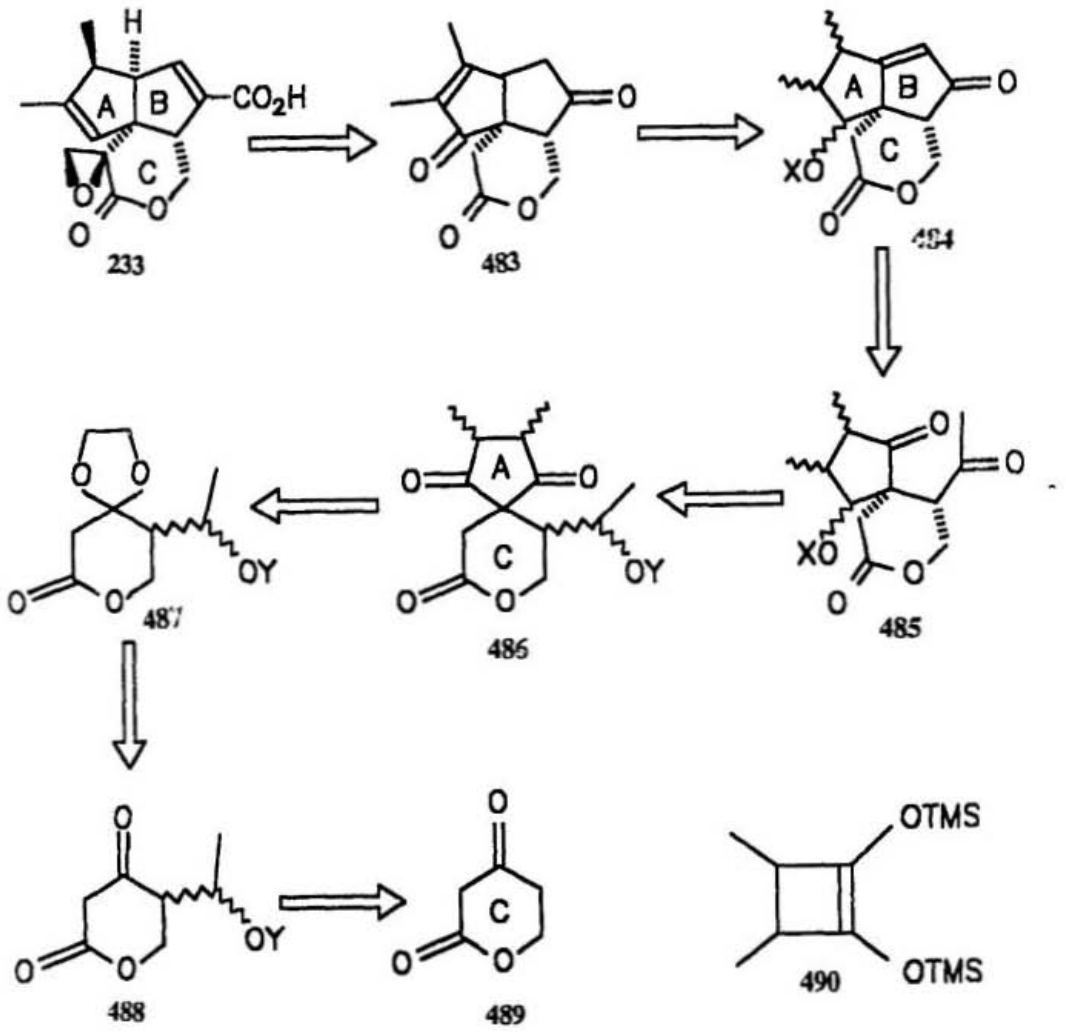
Pentalenolactone O

482

The biological activities and interesting structural features of pentalenolactone have made it an attractive synthetic target. After achieving the total synthesis of pentalenene and *epi*-pentalenene, we initiated a synthetic approach toward pentalenolactone. Our strategic plan for the synthesis is shown in Scheme 99. We deemed that the tricyclic enone **483**, a very promising precursor, might be prepared from enone **484** by deprotection of the hydroxyl, oxidation of the hydroxyl and isomerization of the double bond *via* $RhCl_3 \cdot 3H_2O$. According to our experience in the synthesis of pentalenene, compound **485** should undergo aldol condensation to give enone **484**. We had hoped, naively, that the conversion of **487** to **486** would follow directly *via* a one-pot spiro-annulation reaction with 3,4-dimethylcyclobutene derivative **490**. The transformation of **489** to ketal **487** was expected to be achieved in a straightforward fashion. Thus, our synthesis was designed with the view that the A and B rings of pentalenolactone might be constructed by a spiro-annulation reaction and an intramolecular aldol condensation, respectively.

Herein is provided a brief account of our synthetic endeavors in this area.

Scheme 99



X,Y = protecting group

II. Results and Discussion

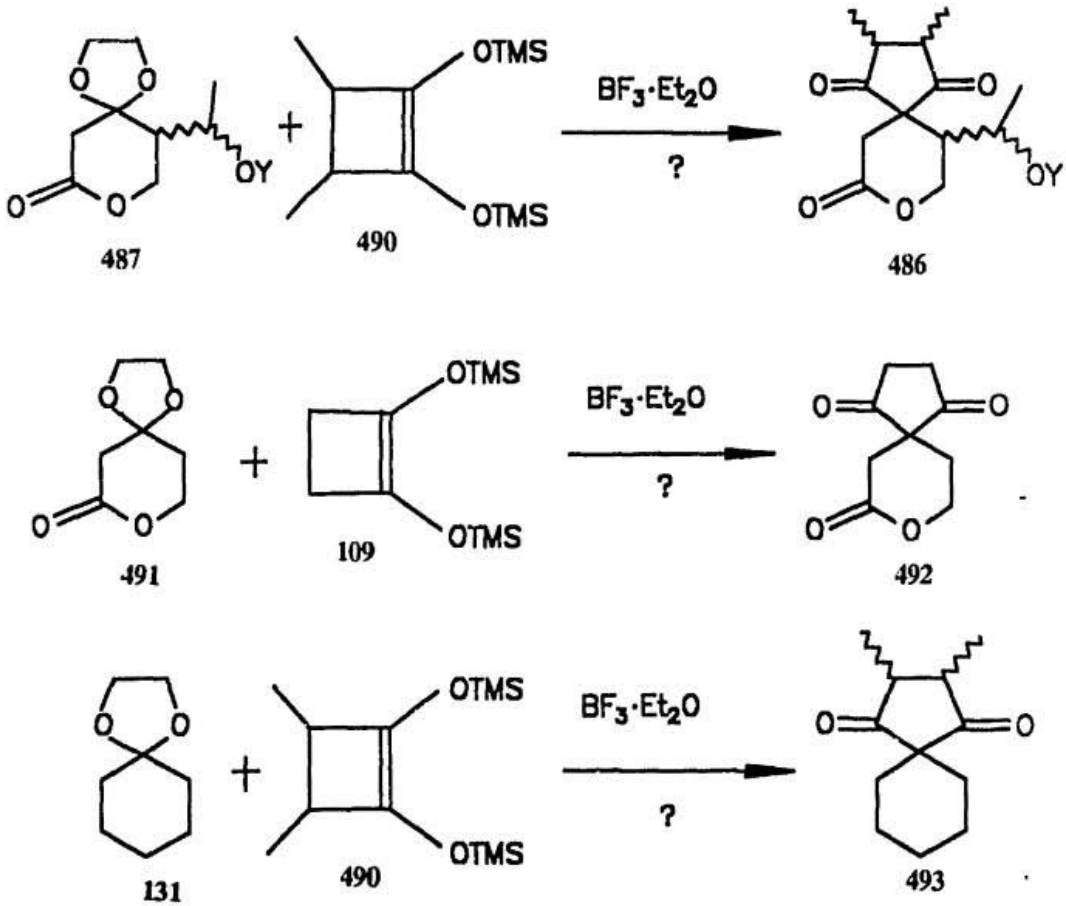
Based on our retrosynthetic analysis, the crucial reaction was the geminal acylation reaction of the ketal **487** with 1,2-bis(trimethylsiloxy)-3,4-dimethylcyclobutene (**490**). Compared with some other spiro-annulation reactions examined previously, this one was of special interest in two respects. First, the ketal moiety in **487** was located at a position β to the lactone carbonyl group. Secondly, the 3,4-dimethylcyclobutene **490** had not been explored in the spiro-annulation reaction. Thus, at the outset, it seemed wise to examine the reactions of the simple lactone ketal **491** as model for **487** with **109** and **490** with cyclohexanone ethylene ketal (**131**) (Scheme 100).

Our initial efforts to prepare ketal **491** were to use Weiler's[132] dianion technique (Scheme 101). Ethyl acetoacetate was treated with sodium hydride followed by n-butyllithium (n-BuLi) and the resulting dianion was bubbled with formaldehyde gas produced from paraformaldehyde. After acidic work-up, we were left with a very complex mixture, in which none of the desired product **494** (or **489**) was detected by GC-MS analysis. Repeating the reaction using water instead of hydrochloric acid in the work-up procedure again gave neither **494** nor **489**.

Our next approach to **491** involved the condensation of the lithium enolate of **495** with formaldehyde to give **496**, which, upon treatment with acid, would afford **489** (Scheme 102). Unfortunately, our attempts to bring about this condensation following the procedure of Schlessinger and Poss[133] were unsuccessful.

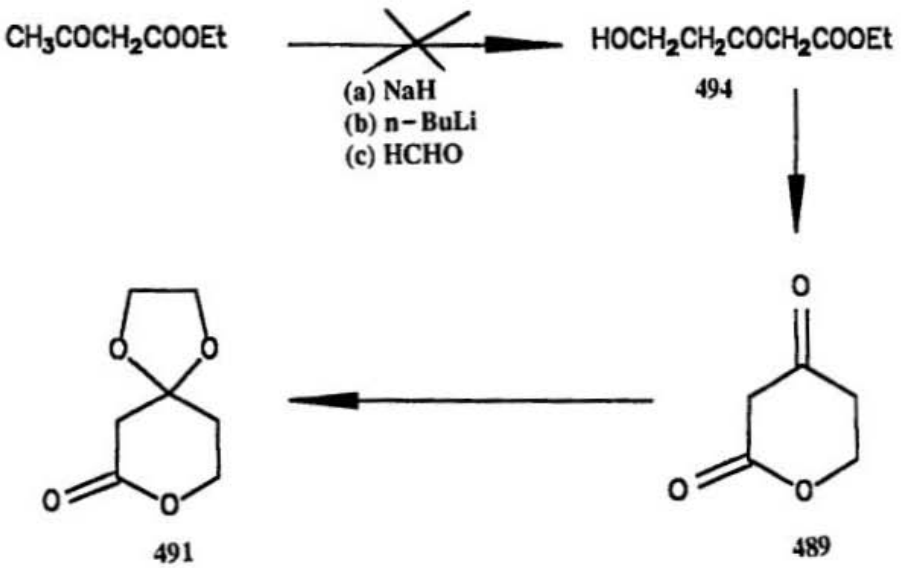
An alternative approach to **491** relied on the mono reduction of diester **498**, which was readily available from the dimethyl 1,3-acetonedicarboxylate (**497**) (Scheme 103). Jung and Miller[134] reported that direct reduction of **498** with 1.5 equivalents of diisobutylaluminum hydride (DIBAL) in dichloromethane at -78°C

Scheme 100

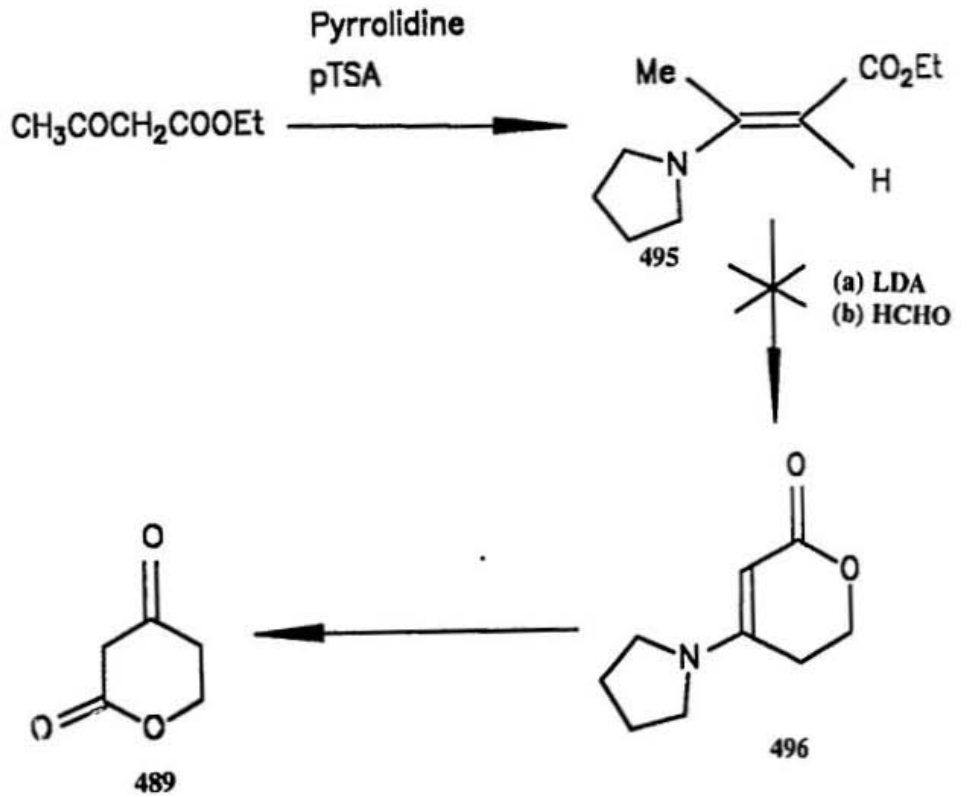


for two hours provided **499** in 82% yield. In our hands, the mono reduction proved to be quite difficult. Reaction of **498** with 1.5 equivalents of DIBAL resulted in the formation of monoaldehyde **499** along with a substantial amount of unreacted starting material as revealed by the ^1H NMR spectrum of the crude product and GC–MS analysis. The proton resonance at δ 9.7 (1H, t) represented the aldehyde. The separation of the monoaldehyde from the starting material was not easy due to the close R_f values under a variety of solvent systems. On the other hand, both ester groups in **498** were reduced when a large excess of DIBAL was applied. As a result, we were unable to achieve the clean conversion of **498** to **499**.

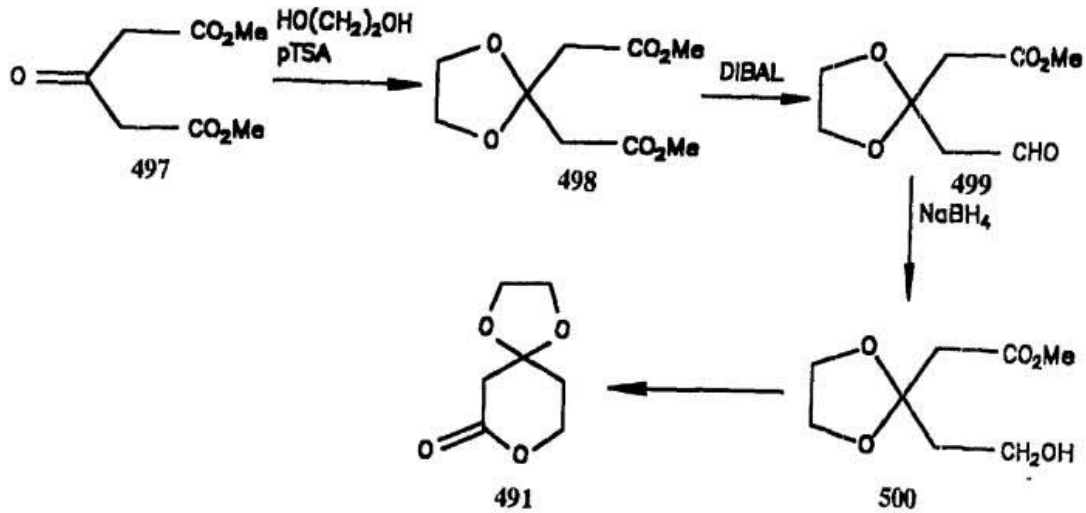
Scheme 101



Scheme 102



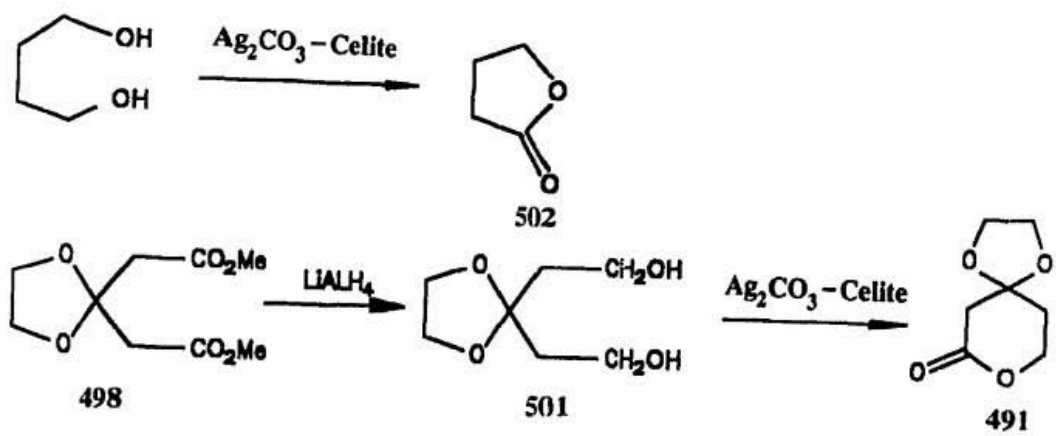
Scheme 103



Fétizon and coworkers[135] reported that γ-, δ-, and even ε-lactones can be prepared from the corresponding diols in good yields using the silver carbonate-Celite reagent (Scheme 104). For example, γ-butyrolactone **502** and lactone **491** had been prepared from butane-1,4-diol and diol **501** in 90% and 60% yields, respectively. Confronted with difficulties preparing **491** or **489** by using simple reagents, we were forced to employ the expensive silver carbonate-Celite reagent. As a model reaction, butane-1,4-diol in benzene was heated under reflux with a large excess of the silver carbonate-Celite reagent. After chromatography, we obtained a 76% yield of lactone **502**. The ^{13}C NMR spectrum showed a lactone carbonyl at δ 177.4 and three methylenes at δ 21.9, 27.5 and 69.0, of which the last one was attached to oxygen. The ketal of dimethyl acetonedicarboxylate (**498**) was reduced with lithium aluminum hydride. However, usual work-up procedures could not be applied in this case owing to the great solubility of the resulting diol **501** in water. Nevertheless, following the method of Mori and coworker,[136] a small amount of water was added dropwise to the crude reduction product followed by 15% sodium hydroxide solution. After filtration,

the filter cake was washed with a large volume of THF. The combined organic solutions were dried over anhydrous potassium carbonate. In this way, we were able to obtain **501** in 94% yield. The IR absorption maximum at 3370 cm^{-1} (broad) represented the hydroxyls. The ^{13}C NMR spectrum showed a ketal carbon at δ 111.7 and three methylenes at δ 39.1, 58.6 and 65.0, of which the last two were connected to oxygens. Treatment of diol **501** with silver carbonate–Celite provided the lactone **491** in an isolated yield of 67%. The IR spectrum showed an absorption maximum at 1740 cm^{-1} for the lactone carbonyl. In the ^1H NMR spectrum, a two–proton singlet at δ 2.618 was assigned to the protons α to the carbonyl.

Scheme 104

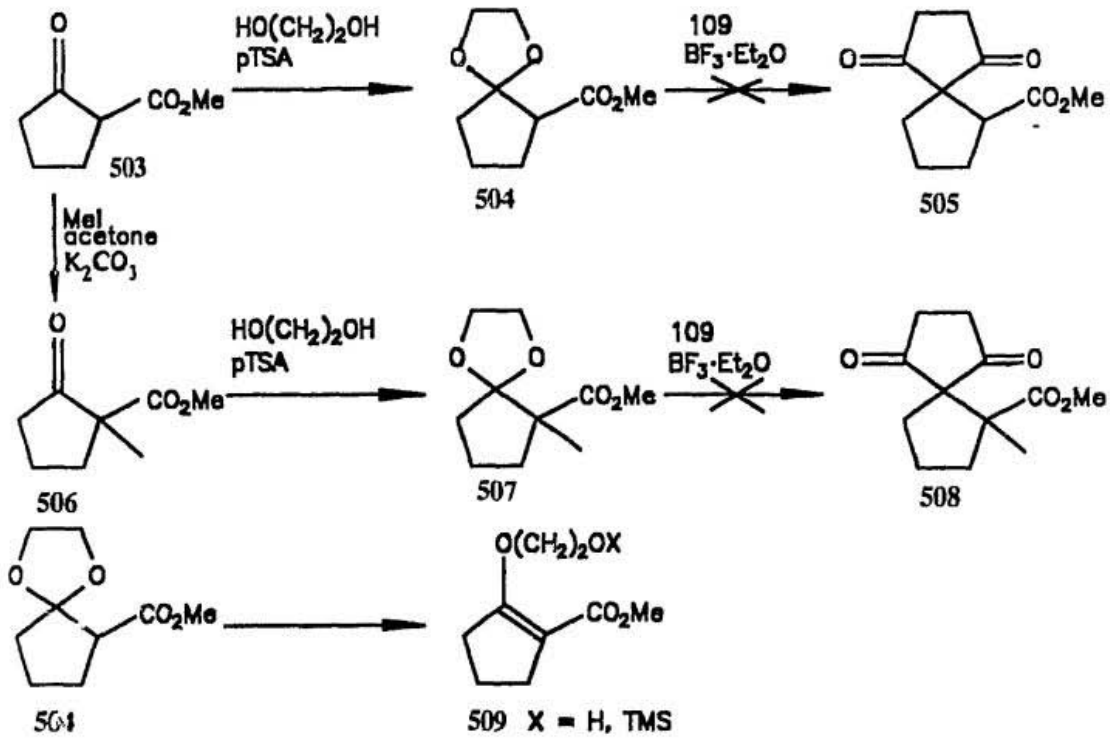


With ketal **491** in hand, the geminal acylation reaction with **109** was next investigated (Scheme 100). To our disappointment, our numerous attempts to bring about this reaction under a variety of conditions including our general one did not give any detectable formation of the spiro compound **492**. In every case, we obtained either the starting material **491** or some other unidentified substances.

The failure of **491** in the geminal acylation reaction might be attributed to the β carbonyl group. The generality of this phenomenon was next studied. The ketal **504**,

obtained easily from **503**, failed to react with **109** to give **505**. It was likely that **504** underwent ketal cleavage under reaction condition to provide **509**, which was not expected to react with **109**. To test this possibility, ketal **507** was prepared from **503** *via* **506**. Unfortunately, no detectable formation of **508** was observed when **507** was subjected to the reaction with **109** (Scheme 105).

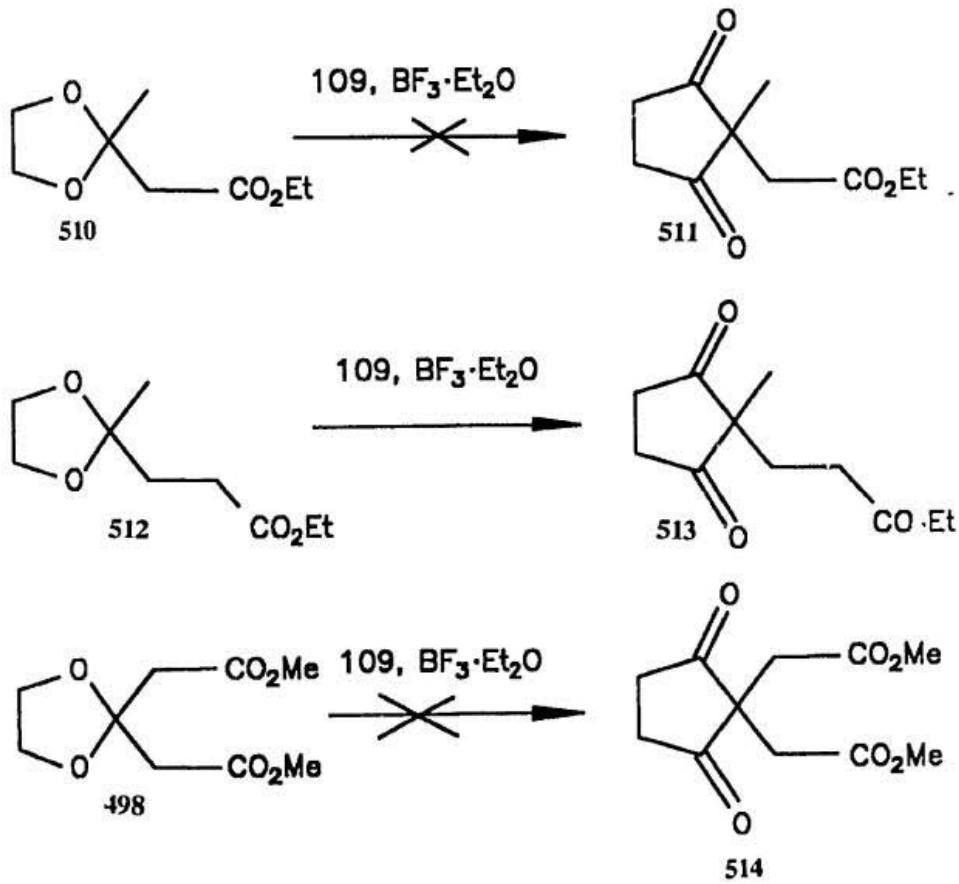
Scheme 105



Steric hindrance might be responsible for the failure of **507** to react with **109**. Thus, we prepared the ketal **510** in which the steric effects should be much smaller. Exposure of **510** to **109** and $BF_3 \cdot Et_2O$ in dichloromethane following our general procedure provided no **511**. In contrast, ketal **512** underwent a smooth geminal acylation reaction leading to a 91% yield of **513** after column chromatography. The IR

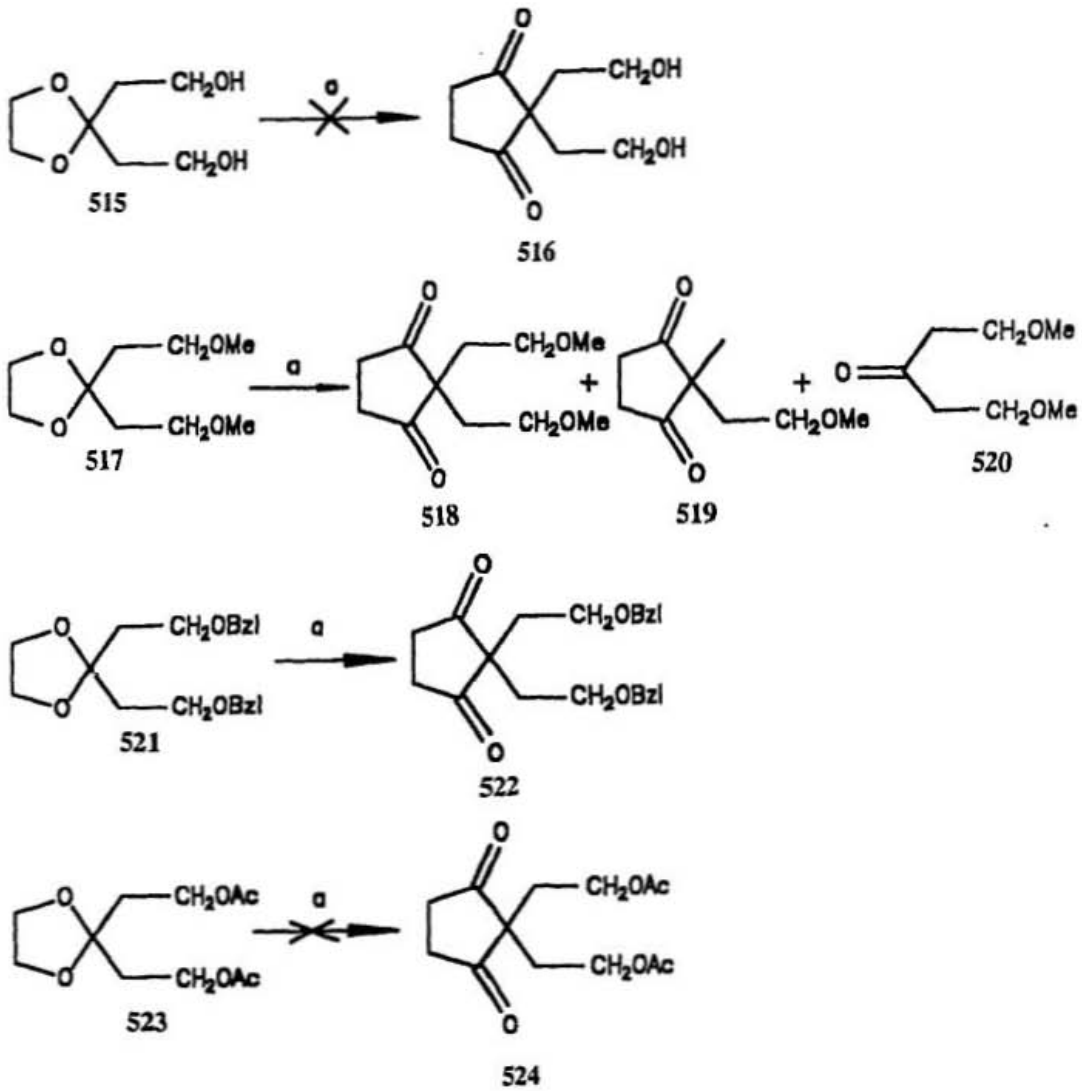
absorption maximum at 1724 cm^{-1} and a four-proton singlet at δ 2.815 in the NMR spectrum confirmed the structure **513**. As expected, no **514** was formed when **498** was allowed to react with **109** (Scheme 106). Based on these studies, we concluded tentatively that a ketal β to a carbonyl does not undergo geminal acylation.

Scheme 106



Diol **515** did not react with **109** to give **516**. In contrast, the geminal acylation reaction of the dimethyl ether **517** proceeded smoothly to furnish, after chromatography, a 74% yield of **518**, a 6% yield of hydrolyzed starting material **520**, and a small

Scheme 107



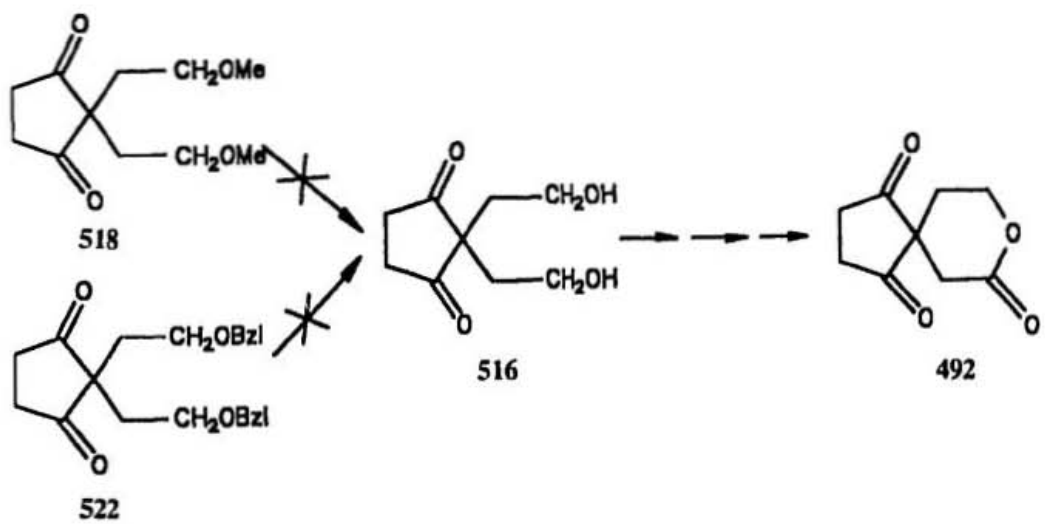
(a) $BF_3 \cdot Et_2O$, **109**, CH_2Cl_2.

amount of some other material (*vide infra*). The IR spectrum of **518** showed an absorption maximum at 1760 cm^{-1} for the ring carbonyls. A four-proton singlet at δ 2.563 in the ^1H NMR spectrum represented two methylenes in the five-membered ring. For the hydrolysed starting material **520**, the IR absorption maximum appeared at 1712 cm^{-1} for the carbonyl. The ^{13}C NMR spectrum showed a carbonyl at δ 207.6,

two methylenes at δ 67.6 and 43.5, and a methyl at δ 59.0. The structure of the other material was derived from the following spectroscopic data. The IR absorption maxima at 1759 (shoulder) and 1715 cm^{-1} indicated the carbonyls in the spiro-diketone system. In the ^1H NMR spectrum, two two-proton triplets at δ 1.995 and 3.199 and a methyl singlet at δ 3.085 may be attributed to methoxyethyl moiety ($CH_3OCH_2CH_2$) attached to a quaternary center. A methyl singlet at δ 1.031 might represent a methyl group attached to a quaternary center. A four-proton singlet at δ 2.673 indicated the two methylenes in the spiro-diketone system. Thus the structure of this substance was tentatively assigned as **519**. Indeed, stucture **519** was in full agreement with its ^{13}C NMR data. The formation of **519** was not understood. Exposure of **521** to **109** and $BF_3{\cdot}Et_2O$ in dichloromethane afforded **522** in 75% yield. However, no **524** was formed when the diacetate **523** was treated with **109** and $BF_3{\cdot}Et_2O$ (Scheme 107).

With **518** and **522** available, we wondered if they could be converted into lactone **492** *via* diol **516**. To our surprise, neither **518** nor **522** underwent deprotection to give **516** under several standard conditions (Scheme 108).

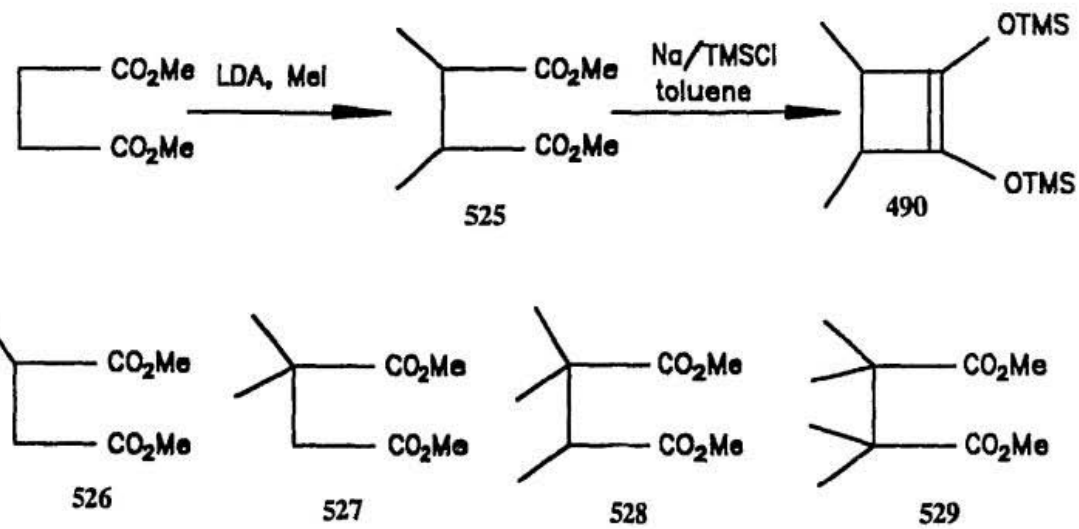
Scheme 108



Although the geminal acylation reaction of **491** with **109** was eventually unsuccessful, we were still interested in the reaction of 3,4-dimethylcyclobutene **490** with simple ketals, which might be applied to the synthesis of some other natural products.

The preparation of **490** began with α, α'-dimethylation of dimethyl succinate.[137] It was anticipated that the products would be a mixture of mono- and multimethylated products. Indeed, it was the case. An optimized condition involved the treatment of dimethyl succinate with 2.2 equivalents of LDA and 2.2 equivalents of iodomethane at a temperature ranging from −40°C to 0°C for three hours. After vacuum distillation, we obtained a 73% yield of 5 : 4 ***R*** and ***S*** isomers **525**, whose mass spectra were almost identical. The ^{1}H NMR spectrum (60 MHz) showed a six-proton singlet at δ 3.74 and a six-proton doublet at δ 1.17, thus ruling out the possibility of the alternative structure **527**. As shown by GC-MS analysis, the mixture of isomers **525** was contaminated with 4% of **526**, 2% of **528**, and 1% of **529**. The 3,4-dimethylcyclobutene **490** was prepared from **525** in 87% yield by following the same procedures as for cyclobutene **109** (Scheme 109).

Scheme 109



Cyclohexanone ethylene ketal (**131**) was treated with four equivalents of **490** and fifteen equivalents of $BF_3 \cdot Et_2O$ in dichloromethane. GC–MS analysis of the crude product indicated a 4 : 3 mixture of *trans* and *cis* isomers **493**, accompanied by 60% unidentified substances (Scheme 100). We were surprised to find that after column chromatography on silica gel the product was much less pure. In fact, neither chromatography on silica gel nor recrystallization from different solvent systems gave any improvement in purity, a result probably attributable to some undefined decomposition of **493**. The troublesome purification was also found in some other spiro–annulation reactions (*vide infra*).

In conclusion, two model reactions, i.e. **491** → **492**, **131** → **493**, turned out to be unsuccessful, which suggested strongly that our further efforts toward pentalenolactone by this exact strategy were unnecessary. Nevertheless, we learned that a ketal β to a carbonyl might refuse to undergo geminal acylation reaction and the purification of 2,2–disubstituted 4,5–dimethylcyclopentane–1,3–dione derivatives such as **493** can be problematic. This information is certainly valuable for a synthetic design involving a spiro–annulation reaction.

III. Experimental*

Attempted preparation of lactone 489 using Weiler's dianion

60% Oil dispersion of sodium hydride (440 mg, 10.0 mmol) was washed with hexane three times, and THF (50 mL) was added. To this solution at 0°C was added slowly ethyl acetoacetate (1.28 mL, 10.0 mmol), and the resulting mixture was stirred at 0°C for 30 min. After addition of 1.60 M n-BuLi in hexane (6.56 mL, 10. 5 mmol), the mixture was kept at 0°C for another 30 min. Formaldehyde gas was bubbled through the solution for 1 h. Work-up with water as usual provided many unidentified products. No improvement was made when 10% HCl was used in the work-up instead of pure water.

Attempted condensation of 495 with formaldehyde

To a solution of LDA (4.4 mmol) in THF (50 mL) at -78°C was added **495** once, and the mixture was stirred at -78°C for 30 min. Paraformaldehyde (180 mg, 6 mmol) in THF (10 mL) was added, and solution was stirred at -78°C for 6 min. The reaction temperature was raised to -22°C, and it was kept at that temperature for another 30 min. The reaction was quenched with saturated NH_4Cl solution and worked up as usual. GC-MS, TLC and ^1H NMR analysis showed no detectable formation of **496**. No improvement was evident when formaldehyde gas was used instead of paraformaldehyde.

Dimethyl 3-oxoglutarate ethylene ketal (498)

A solution of dimethyl 3-oxoglutarate (**497**) (50 g, 0.29 mol), ethylene glycol (24 mL, 0.43 mol) and *p*TSA (500 mg) in benzene was heated under reflux with a Barrett

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* For General Procedures see 1.III.

water–separator overnight. Saturated $NaHCO_3$ was added to the cooled solution, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated $NaHCO_3$ followed by saturated NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. Vacuum distillation of the residue provided pure ketal **498** (26.82 g, 43%): bp 100–105°C/0.25 Torr; ^{1}H NMR (60 MHz) δ: 2.93 (4H, s), 3.70 (6H, s), and 4.05 (4H, s); MS (from GC–MS) *m/z* (%): no M^+, 187 (0.3, M^+ – OMe), 156 (0.3, M^+ – 2 × OMe), 145 (100, M^+ – CH_2COOMe), 126 (1.5), 113 (5), 103 (71), 101 (14), 86 (7), 69 (10), 59 (28), 45 (9), 43 (10), and 42 (23).

Methyl 3,3–(ethylenedioxy)–4–formylbutyrate (499)

To a solution of dimethyl 3–oxoglutarate ethylene ketal (**498**) (722.3 mg, 3.31 mmol) in CH_2Cl_2 (30 mL) at -78°C was added dropwise 1.0 M solution of DIBAL in CH_2Cl_2 (4.97 mL, 4.97 mmol). The reaction mixture was stirred at -78°C for *ca.* 2 h. Water was added, and some precipitate formed. Filtration removed the precipitate, and the filtrate was extracted with CH_2Cl_2 (×3). The combined organic solutions were washed with saturated NaCl (×2), dried over $MgSO_4$ and concentrated *in vacuo*. GC–MS analysis and ^{1}H NMR of the crude product indicated a 3 : 7 mixture of the aldehyde **499** and the starting material **498**. For **499**: ^{1}H NMR (60 MHz) (from the mixture) δ: 2.7 (2H, s), 2.9 (2H, d), 3.9 (4H, s), 4.0 (3H, s), and 9.7 (1H, t); MS (from GC–MS) *m/z* (%): no M^+, 145 (64, M^+ – CH_2CHO), 115 (100, M^+ – CH_2CO_2Me), 103 (70), 86 (15), 71 (21), 69 (17), 59 (34), 45 (39), 43 (98), and 41 (15). Three equivalents of DIBAL resulted in reduction of both aldehyde groups of **498** as shown by the integration of the ^{1}H NMR spectrum of the crude product.

1,5–Dihydroxy–2–pentanone ethylene ketal (501)

A solution of **498** (550.4 mg, 2.53 mmol) in dry diethyl ether (20 mL) was added slowly to a stirred ice–cooled suspension of $LiAlH_4$ (184 mg, 4.85 mmol) in dry

diethyl ether (30 mL). The mixture was stirred overnight during which time the reaction was allowed to attain room temperature. Water (0.60 mL) was then added cautiously to the ice-cooled solution, followed by 15% NaOH (0.20 mL). The mixture was diluted with THF (100 mL) and stirred at room temperature for 30 min. The solution was then filtered, the filter cake was washed with THF (150 mL), and the combined filtrates were dried over K_2CO_3. Evaporation *in vacuo* provided pure diol **501** (410.0 mg, 100%): IR (film) ν_{max}: 3370 cm^{-1}; ^1H NMR δ: 1.781 (4H, t, J = 6.0 Hz), 3.560 (4H, apparent q, J = 5.5 Hz), 3.321 (2H, t, J = 5.1 Hz), and 3.832 (4H, s); ^{13}C NMR δ (attached H's): 39.1 (2C, 2), 58.6 (2C, 2), 65.0 (2C, 2), and 111.7 (0); MS *m/z* (%): no M^+ [illegible] (100, $M^+ - CH_2CH_2OH$), 99 (39), 87 (16), 73 (26), 55 (13), 45 (31), 43 (67), and 42 (13). *Exact mass* calcd. for $C_5H_9O_3$ ($M^+ - CH_2CH_2OH$): 117.1551; found: 117.1556.

Silver carbonate on Celite

Celite was purified by washing it successively with methanol containing 10% concentrated HCl and then with distilled water until neutral. The wet Celite was dried in an oven at 120°C. The purified Celite (50.84 g) was added to a mechanically stirred solution of silver nitrate (57.62 g, 339 mmol) in distilled water (300 mL). A solution of sodium carbonate (18.91 g, 178.42 mmol) in distilled water (400 mL) was added slowly to the homogeneous suspension. The resulting mixture was stirred for another 15 min, and the mixture was filtered. The yellow-green precipitate collected was dried *in vacuo* for *ca.* 3 h. The reagent thus prepared contained about 1 mmol of silver carbonate per 0.56 g. Since the following oxidation was carried out in benzene under reflux with a Barrett water-separator, a small amount of water still within the reagent could be removed by using the same apparatus before the diol was added.

γ-Butyrolactone (502)

A mixture of butane-1,4-diol (201.7 mg, 2.24 mmol) and Ag_2CO_3/Celite (30.62 g, 53.72 mmol) in benzene (200 mL) was heated under reflux with a Barrett water-separator for 24 h. Filtration removed the solids, and diethyl ether (100 mL) was used to wash the solids. The combined filtrates were concentrated *in vacuo*. The residue was chromatographed (5% acetone in petroleum ether) to provide pure lactone **502** (162.5 mg, 84%): IR (film) ν_{max}: 1770 cm^{-1}; ^1H NMR δ: 2.148 (2H, br quintet), 2.352 (2H, br t, J = 7.0 Hz), and 4.212 (2H, t, J = 7.0 Hz); ^{13}C NMR δ (attached H's): 21.9 (2), 27.5 (2), 68.4 (2), and 177.7 (0); MS m/z (%): 86 (10, M^+), 56 (16), 42 (100), and 41 (49). *Exact mass* calcd. for $C_4H_6O_2$: 86.0367; found: 86.0365.

1,4,8-Trioxaspiro[4.5]decan-7-one (491)*

A mixture of diol **501** (410.0 mg, 2.53 mmol) and the silver carbonate-Celite (37.50 g, 65.78 mmol) in benzene was treated as previously with butane-1,4-diol to provide pure **491** (240.4 mg, 60%) as a colorless oil: IR (film) ν_{max}: 1740 cm^{-1}; ^1H NMR δ: 1.901 (2H, t, J = 5.7 Hz), 2.618 (2H, s), 3.847 (4H, m), and 4.238 (2H, t, J = 5.7 Hz); ^{13}C NMR δ (attached H's): 32.9 (2), 41.4 (2), 64.5 (2C, 2), 65.5 (2), 105.2 (0), and 169.1 (0); MS m/z (%): no M^+, 115 (2), 99 (83), 86 (100), 55 (31), 43 (25), and 42 (63).

2-Carbomethoxy-2-methylcyclopentanone (506)

A solution containing β-keto-ester **503** (5.00 g, 35.2 mmol) and potassium carbonate (19.45 g, 0.14 mol) in acetone (70 mL) was heated to 40°C. Iodomethane (4.4 mL, 70.36 mmol) was added dropwise, and the resulting mixture was heated under reflux for 1 h. The cooled solution was filtered and H_2O was added. The aqueous layer

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* Alternative name: spiro(1,3-dioxacyclopentane-2,3'-δ-valerolactone)

was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide **506** (5.51 g, 100%) as a colorless oil: IR (film) ν_{max}: 1762 and 1742 cm^{-1}; ^1H NMR δ: 1.22 (3H, s), 1.75–2.50 (6H, mm), and 3.61 (3H, s); ^{13}C NMR δ (attached H's): 19.2 (3), 19.3 (2), 35.9 (2), 37.4 (2), 52.2 (3), 55.6 (0), 172.5 (0), and 215.5 (0); MS *m/z* (%): 156 (1, M^+), 128 (70, M^+ – CO), 125 (18), 113 (28), 101 (36), 97 (27), 69 (73), 68 (20), 55 (33), and 41 (100). *Exact mass* calcd. for $C_8H_{12}O_3$: 156.0785; found: 156.0778 and for $C_7H_{12}O_2$ (M^+ – CO): 128.0837; found: 128.0837.

2–Carbomethoxy–2–methylcyclopentanone ethylene ketal (507)

A solution of **506** (3.22 g, 20.6 mmol), *p*TSA (200 mg) and ethylene glycol (2.30 mL, 41.3 mmol) in benzene was heated under reflux with a Barrett water–separator overnight. Saturated $NaHCO_3$ was added to the cooled solution, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over K_2CO_3, and concentrated *in vacuo* to give ketal **507** (3.75g, 91%) as a colorless oil: IR (film) ν_{max}: 1736 cm^{-1}; ^1H NMR δ: 1.270 (3H, s), 1.52–1.93 (5H, mm), 2.39–2.53 (1H, m), 3.687 (3H, s), and 3.95 (4H, m); ^{13}C NMR δ (attached H's): 19.0 (3), 20.2 (2), 34.4 (2), 35.4 (2), 51.7 (3), 54.2 (0), 64.8 (2), 65.3 (2), 118.7 (0), and 175.2 (0); MS *m/z* (%): 200 (3, M^+), 169 (7), 157 (1), 155 (1), 141 (10), 128 (1), 113 (26), 112 (13), 100 (52), 99 (100), 55 (24), and 41 (23). *Exact mass* calcd. for $C_{10}H_{16}O_4$: 200.1047; found: 200.1025 and for $C_9H_{13}O_3$ (M^+ – CH_3O): 169.0863; found: 169.0853.

2–(2–Carboethoxyethyl)–2–methylcyclopentane–1,3–dione (513)

The ketal **512** (289.9 mg, 1.54 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.84 mL, 23.1 mmol) and **109** (1.03 mL, 3.85 mmol) following our general spiro–annulation procedure. Chromatography (10% acetone in petroleum ether) of the crude product pro-

vided pure **513** (297.5 mg, 91%) as a colorless oil: IR (film) ν_{max}: 1724 (very br) cm^{-1}; ^1H NMR δ: 1.130 (3H, s), 1.233 (3H, t, J = 7.1 Hz), 1.962 (2H, t, J = 7.5 Hz), 2.815 (4H, s), and 4.065 (2H, q, J = 7.1 Hz); ^{13}C NMR δ (attached H's): 13.9 (3), 19.7 (3), 28.6 (2C, 2), 34.6 (2C, 2), 55.1 (0), 60.5 (2), 172.6 (0), and 215.5 (2C, 0); MS m/z (%): 212 (11, M^+), 184 (9), 167 (15, $M^+ - CH_3CH_2O$), 166 (17), 138 (36), 125 (100), 110 (20), 97 (24), 69 (22), 55 (36), 43 (20), and 41 (34). *Exact mass* calcd. for $C_{11}H_{16}O_4$: 212.1047; found: 212.1046.

1,5-Dimethoxy-3-pentanone ethylene ketal (517)

80% Dispersion of sodium hydride in mineral oil (420 mg, 14 mmol) was washed with hexane (×3), and THF (30 mL) was added followed by a solution of the diol **515** (387.6 mg, 2.39 mmol) in THF (10 ml). The mixture was heated cautiously in a 60°C oil bath for ca. 1 h, iodomethane (0.89 mL, 14.34 mmol) was added to the cooled solution, and the mixture was stirred at room temperature overnight. The cooled solution was poured cautiously into ice-cooled water, and the aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated NaCl (×2), dried over K_2CO_3, and concentrated *in vacuo*. Chromatography (6% acetone in petroleum ether) of the residue provided pure **517** (410.6 mg, 90%) as a colorless oil: IR (film) ν_{max}: 1450 and 1399 cm^{-1}; ^1H NMR δ: 1.806 (4H, t, J = 7.0 Hz), 3.183 (6H, s), 3.340 (4H, t, J = 7.0 Hz), and 3.794 (4H, s); ^{13}C NMR δ (attached H's): 37.6 (2C, 2), 59.0 (2C, 3), 65.1 (2C, 2), 68.8 (2C, 2), and 109.8 (0); MS m/z (%): no M^+, 131 (87, $M^+ - CH_2CH_2OMe$), 99 (76), 55 (15), 45 (100), and 43 (11). *Exact mass* calcd. for $C_6H_{11}O_2$ ($M^+ - CH_2CH_2OMe$): 131.0707; found: 131.0704.

2,2-Di-(2-methoxyethyl)cyclopentane-1,3-dione (518)

A solution of the dimethyl ether **517** (300.7 mg, 1.58 mmol) was treated with $BF_3{\cdot}Et_2O$ (1.94 mL, 15.8 mmol) and **109** (1.26 mL, 4.74 mmol) following our general

procedure. The residue was chromatographed (5% acetone in petroleum ether) to provide pure **518** (250.7 mg, 74%), another substance tentatively identified as **2-methyl-2-methoxyethylcyclopentane-1,3-dione (519)** (17.1 mg), and the hydrolysed starting material **520** (13.1 mg, 6%). For **518** (colorless oil): IR (film) ν_{max}: 1760 and 1720 cm^{-1}; ^1H NMR δ: 1.852 (4H, t, J = 6.0 Hz), 2.536 (4H, s), 3.045 (6H, s), and 3.122 (4H, t, J = 6.0 Hz); ^{13}C NMR δ (attached H's): 36.2 (2C, 2), 37.8 (2C, 2), 55.5 (0), 58.5 (2C, 3), 68.4 (2C, 2), and 217.9 (2C, 0); MS m/z (%): no M^+, 156 (14, M^+ – CH_2=CH–OMe due to McLafferty rearrangement), 141 (42), 125 (7), 112 (8), 109 (23), 81 (10), 55 (12), 53 (10), 45 (100), and 41 (12). *Exact mass* calcd. for $C_8H_{12}O_3$ (M^+ – CH_2=CH–OMe): 156.0785; found: 156.0783. For **519** (colorless oil): IR (film) ν_{max}: 1759 (shoulder) and 1715 cm^{-1}; ^1H NMR δ: 1.031 (3H, s), 1.995 (2H, t, J = 7.2 Hz), 2.673 (4H, s), 3.085 (3H, s), and 3.199 (2H, t, J = 7.2 Hz); ^{13}C NMR δ (attached H's): 21.6 (3), 35.0 (2C, 2), 35.8 (2), 53.6 (0), 58.7 (3), 68.3 (2), and 217.2 (2C, 0); MS m/z (%): 170 (1, M^+), 156 (5), 140 (14), 125 (42), 109 (11), 69 (53), 59 (30), 55 (28), 45 (100), 43 (16), and 41 (61). For **520** (colorless oil): IR (film) ν_{max}: 1712 cm^{-1}; ^1H NMR δ: 2.702 (4H, t, J = 6.2 Hz), 3.325 (6H, s), and 3.643 (4H, t, J = 6.2 Hz); ^{13}C NMR δ (attached H's): 43.5 (2C, 2), 59.0 (2C, 3), 67.6 (2C, 2), and 207.6 (0); MS (from GC–MS) m/z (%): no M^+, 115 (1, M^+ – OMe), 114 (M^+ – MeOH), 103 (2), 87 (11), 83 (5), 71 (3), 59 (4), 58 (4), 55 (10), 45 (100), and 43 (11).

1,5-Dibenzyloxy-3-pentanone ethylene ketal (521)

80% Dispersion of sodium hydride in mineral oil (7.08 g, 0.16 mol) was washed with hexane (×3), and THF (150 mL) was added followed by a solution of the diol **515** (6.37 g, 39.3 mmol) in THF (20 ml). The resulting mixture was heated cautiously under reflux for *ca.* 30 min, and benzyl bromide (18.1 mL, 0.16 mol) was added to the cooled solution. The solution was heated under reflux for *ca.* 5 h, and the cooled solution was poured cautiously into ice-cooled water. The aqueous layer was extracted

with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2), dried over K_2CO_3 and concentrated *in vacuo*. Vacuum distillation of the residue provided pure **522** (11.58 g, 86%): bp 184–185°C/0.3 Torr; IR (film) ν_{max}: 1497, 1453 and 1370 cm^{-1}; ^1H NMR δ: 2.004 (4H, t, J = 7.1 Hz), 3.552 (4H, t, J = 7.1 Hz), 3.823 (4H, s), 4.428 (4H, s), and 7.295 (10H, m); ^{13}C NMR δ (attached H's): 37.2 (2C, 2), 64.5 (2C, 2), 66.0 (2C, 2), 72.8 (2C, 2), 109.3 (2C, 0), 127.3 (2C, 1), 127.4 (4C, 1), 128.1 (4C, 1), and 138.0 (0); MS m/z (%): no M^+, 207 (25, M^+ – $CH_2CH_2OCH_2C_6H_5$), 99 (16), 91 (100), 65 (13), and 43 (15). *Exact mass* calcd. for $C_{12}H_{15}O_3$ (M^+ – $CH_2CH_2OCH_2C_6H_5$): 207.1020; found: 207.1021.

2,2–Di–(2–benzyloxyethyl)cyclopentane–1,3–dione (522)

A solution of the ketal **521** (210.7 mg, 0.62 mmol) in CH_2Cl_2 was treated with $BF_3{\cdot}Et_2O$ (1.14 mL, 9.3 mmol) and **109** (0.33 mL, 1.24 mmol) following our general procedure. The crude product was chromatographed (5% acetone in petroleum ether) to provide pure **522** (194.1 mg, 86%): IR (film) ν_{max}: 1757, 1710, 1495, 1453, 1418, and 1360 cm^{-1}; ^1H NMR δ: 2.151 (4H, t, J = 7.0 Hz), 2.501 (4H, s), 3.483 (4H, s, J = 7.0 Hz), 4.428 (4H, s), and 7.391 (10H, m); ^{13}C NMR δ (attached H's): 35.8 (2C, 2), 37.3 (2C, 2), 65.8 (2C, 2), 72.8 (2C, 2), 55.5 (0), 127.5 (4C, 1), 127.6 (2C, 1), 128.2 (4C, 1), 137.2 (2C, 0), and 217.6 (2C, 0); MS m/z (%): 366 (2, M^+), 169 (18), 141 (14), 126 (8), 125 (4), 108 (3), 107 (3), 92 (13), 91 (100), 78 (3), 77 (4), 65 (10), 55 (3), and 41 (4).

1,5–Diacetoxy–3–pentanone ethylene ketal (523)

To an ice–cooled solution of the diol **515** (1.3470 g, 8.32 mmol) in pyridine (10 mL) was added cautiously acetic anhydride (4.71 mL, 49.92 mmol), and the resulting mixture was stirred at room temperature overnight. Water was added, and the aqueous layer was extracted with diethyl ether (×3). The combined organic solutions were

washed with water, saturated $NaHCO_3$ (×2) and saturated NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (5% acetone in petroleum ether) of the residue provided the pure diacetate **523** (1.3941 g, 71%) as a colorless oil: IR (film) ν_{max}: 1740 and 1370 cm^{-1}; ^1H NMR δ: 1.976 (4H, t, J = 7.1 Hz), 2.010 (6H, s), 3.943 (4H, s), and 4.132 (4H, t, J = 7.1 Hz); ^{13}C NMR δ (attached H's): 20.2 (2C, 3), 35.6 (2C, 2), 59.7 (2C, 2), 64.4 (2C, 2), 108.2 (0), and 170.1 (2C, 0); MS m/z (%): no M^+, 159 (3, $M^+ - CH_2CH_2OCOCH_3$), 100 (6), 99 (100), 55 (24), and 43 (57, CH_3CO^+). *Exact mass* calcd. for $C_7H_{11}O_4$ ($M^+ - CH_2CH_2OCOCH_3$): 159.0657; found 159.0651.

Attempted preparation of the keto-alcohol 516

From the dimethyl ether 518

The dimethyl ether **518** (47.5 mg, 0.22 mmol) was treated with iodotrimethylsilane (TMSI) (83 μL) in CH_2Cl_2 (15 mL) following the procedure of Jung *et al.*[138] No **516** was isolated from the crude product by column chromatography on silica gel.

From the dibenzyl ether 522

No desired diol **516** was isolated from the crude product produced by catalytic hydrogenation of **522** or by treatment of **522** with C_2H_5SH and $BF_3{\cdot}Et_2O$[139].

Dimethyl 2,3-dimethylsuccinate (525)

Dimethyl succinate (7.0 g, 47.95 mmol) in dry THF (15 mL) was added to lithium diisopropylamide (LDA) (105.5 mmol) in THF (350 mL) at −78°C. The solution was stirred at −78°C for *ca.* 20 min during which time a yellow slurry formed. The reaction mixture was warmed to −5°C, and it was stirred at this temperature for 15 min. After the solution was cooled to −40°C, iodomethane (7.76 mL, 124.67 mmol) was added (the yellow slurry was dissolved right after the addition). The solution was stirred at −40°C for 2 h, and the reaction was quenched by the cautious addition of water. The

aqueous layer was extracted with diethyl ether (×3). The combined organic extracts were washed with saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. Vacuum distillation of the residue provided a 5 : 4 mixture of the isomers **525** (15.33 g, 61%): ^{1}H NMR (60 MHz) δ: 1.17 (6H, d), 2.78 (2H, m), and 3.74 (6H, s); MS (from GC–MS) of one isomer *m/z* (%): no M^+, 143 (44, M^+ – OMe), 142 (11), 115 (40), 114 (33), 99 (11), 88 (51), 87 (13), 83 (15), 69 (6), 59 (100), 56 (24), 55 (37), and 41 (23); of the other isomer *m/z* (%): no M^+, 143 (43, M^+ – OMe), 142 (9), 115 (27), 114 (29), 99 (11), 88 (74), 87 (18), 83 (13), 82 (7), 69 (6), 59 (100), 57 (13), 56 (26), 55 (40), 53 (8), and 41 (24). GC–MS analysis indicated that the product contained 4% of **526**, 2% of **528**, and 1% of **529**: MS (from GC–MS) of **526** *m/z* (%): no M^+, 129 (48, M^+ – OMe), 113 (1.1), 101 (26), 100 (25), 87 (12), 85 (4), 74 (5), 73 (5), 69 (18), 59 (100), 55 (10), 42 (23), and 41 (30); of **528** *m/z* (%): no M^+, 157 (14, M^+ – OMe), 129 (28), 128 (17), 113 (13), 102 (21), 101 (18), 97 (13), 88 (42), 73 (100), 70 (16), 69 (40), 59 (40), 55 (33), and 41 (34); of **529** *m/z* (%): no M^+, 171 (7, M^+ – OMe), 143 (13), 127 (6), 102 (100), 87 (34), 83 (34), 73 (64), 70 (14), 69 (25), 59 (25), 55 (18), 43 (11), and 41 (11).

3,4–Dimethyl–1,2–bis(trimethylsiloxy)cyclobutene (490)

A 5 : 4 mixture of the isomers **525** (13.92 g, 80 mmol) was treated with sodium metal (7.9 g, 344 mmol) and chlorotrimethylsilane (44.69 mL, 352 mmol) in toluene (500 mL) following the procedure of Bloomfield and Nelke[61] to provide **490** (18.04 g, 87%): bp 55–56°C/0.30 Torr; ^{1}H NMR (60 MHz) δ: 0.19 (18H, s), 0.85–1.23 (6H, m), and 2.32 (2H, m). The mass spectra (from GC–MS) of both isomers **490** were almost identical, *m/z* (%): 258 (49, M^+), 243 (27), 229 (10), 155 (32), 153 (20), 149 (14), 148 (16), 147 (100), 133 (10), 75 (26), 73 (86), and 45 (32).

Spiro – annulation reaction of 490 with cyclohexanone ethylene ketal (131)

A solution of the ketal **131** (290.5 mg, 2.05 mmol) in CH_2Cl_2 was treated with $BF_3{\cdot}Et_2O$ (3.78 mL, 30.75 mmol) and **490** (1.98 mL, 6.14 mmol) following our general procedure. GC – MS analysis of the crude product indicated a 4 : 3 mixture of the isomers **493**, accompanied by 60% of some unidentified substances. MS (from GC – MS) of one isomer *m/z* (%): 194 (86, M^+), 179 (10), 152 (11), 151 (14), 140 (25), 139 (18), 125 (13), 111 (51), 110 (35), 109 (19), 83 (15), 82 (25), 81 (23), 79 (19), 67 (100), 56 (30), 55 (34), 54 (32), 53 (30), and 41 (62); of the other isomer *m/z* (%): 194 (89, M^+), 152 (10), 140 (31), 139 (18), 125 (11), 111 (64), 110 (40), 109 (18), 93 (14), 82 (26), 81 (30), 79 (22), 77 (15), 69 (26), 67 (100), 56 (46), 55 (46), 54 (35), 53 (42), 43 (18), and 41 (83). Our efforts to separate the desired products by column chromatography on silica gel or recrystalization were unsuccessful.

Chapter 5

INVESTIGATION ON THE FACTORS AFFECTING GEMINAL ACYLATION REACTIONS

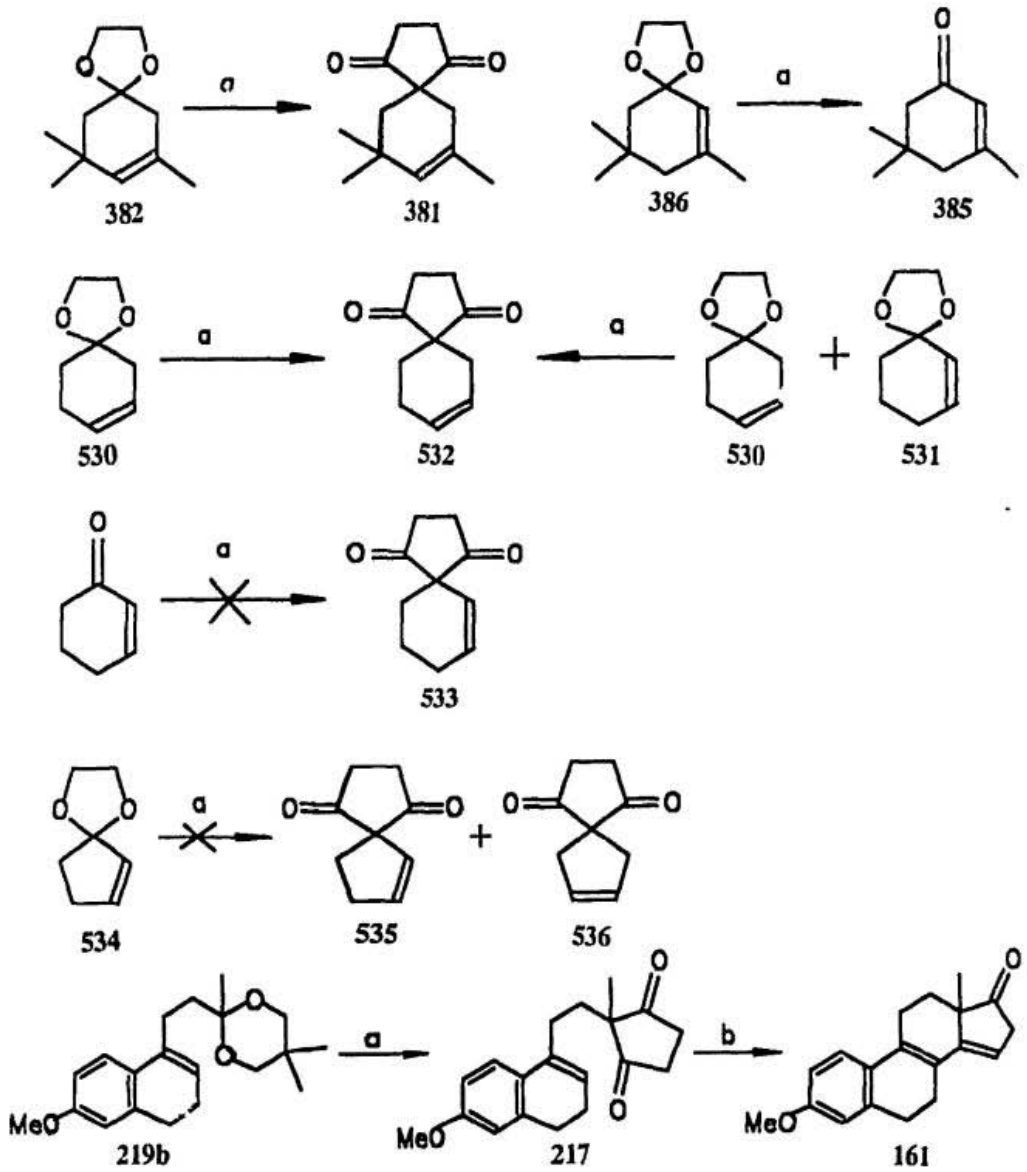
I. Results and Discussion

Our one-pot geminal acylation reactions had been successfully applied to synthesis of isokhusimone (**65**), the steroid diene (**161**), pentalenene (**230**) and *epi*-pentalenene (**279**). On the other hand, as seen from our model studies relevant to the synthesis of pentalenolactone, there are certainly some limitations associated with this geminal acylation reaction. Thus, we initiated the following investigations on some parameters that might affect the reaction.

1. Ketals α-, β-, or γ- to double bonds

As discussed in the pentalenene synthesis, the reaction of ketal **382** with cyclobutene **109** proceeded smoothly to afford **381**. In contrast, ketal **386** failed to react with **109**. We wondered if this were a general phenomenon. For this pursose, we chose to study ketals **530** and **531**. 2-Cyclohexen-1-one was treated with a large excess of ethylene glycol and a catalytic amount of *p*TSA in benzene under reflux overnight. Carefully controlled fractional distillation provided pure **530** and a 4 : 5 mixture of **530** and **531**. The structural assignment of **530** and **531** can be easily achieved in the same manner as that of ketals **382** and **386** (*vide supra*). Exposure of pure ketal **530** to **109** and $BF_3 \cdot Et_2O$ following our general procedure furnished **532** in 75% isolated yield. The IR absorption maximum appeared at 1718 cm^{-1} for the ring carbonyl and at 1420

Scheme 110



(a) $BF_3{\cdot}Et_2O$, **109**, CH_2Cl_2; (b) TFA.

cm^{-1} for the double bond. The two two-proton multiplets at δ 2.724 and 2.920 in the ^1H NMR spectrum clearly indicated the protons of the cyclopentanedione moiety. The position of the double bond in **532** was unambiguously established on the basis of its

^{1}H NMR spectrum. The multiplet at δ 2.154 attributed to the protons α to the double bond and the triplet at δ 1.737 represented the two protons β to the double bond. The ratio of the α protons to β protons was 2 : 1 as calculated from the integration, which allowed structure **532** only. Next, we subjected the 4 : 5 mixture of **530** and **531** to the spiro-annulation reaction. GC-MS analysis of the crude product indicated complete conversion to a single substance. This substance was obtained in 73% yield after column chromatography. ^{1}H and ^{13}C NMR, TLC, IR, and GC-MS analysis showed unequivocally that this material was the spiro-diketone **532**. Clearly, the ketal **531** was converted to **532** under the reaction condition. The double bond isomerization from **531** to **532** can occur either before (i.e. **531** → **530**) or after the spiro-annulation reaction (i.e. **533** → **532**). If after, then treatment of **533** with $BF_3{\cdot}Et_2O$ in dichloromethane should give **532**. Although isophorone directly underwent the spiro-annulation reaction to give **389** in 21% yield, our attempts to prepare **533** by using the same procedure were unsuccessful. Unlike 2-cyclohexenenone ketal **530**, 2-cyclopentanone ethylene ketal (**534**) failed to undergo geminal acylation reaction leading to **535** or **536** (Scheme 110). As described in the steroid synthesis, the reaction of ketal **219b** with **109** and $BF_3{\cdot}Et_2O$ provided **217**, which, upon treatment with TFA, afforded the steroid diene **161**.

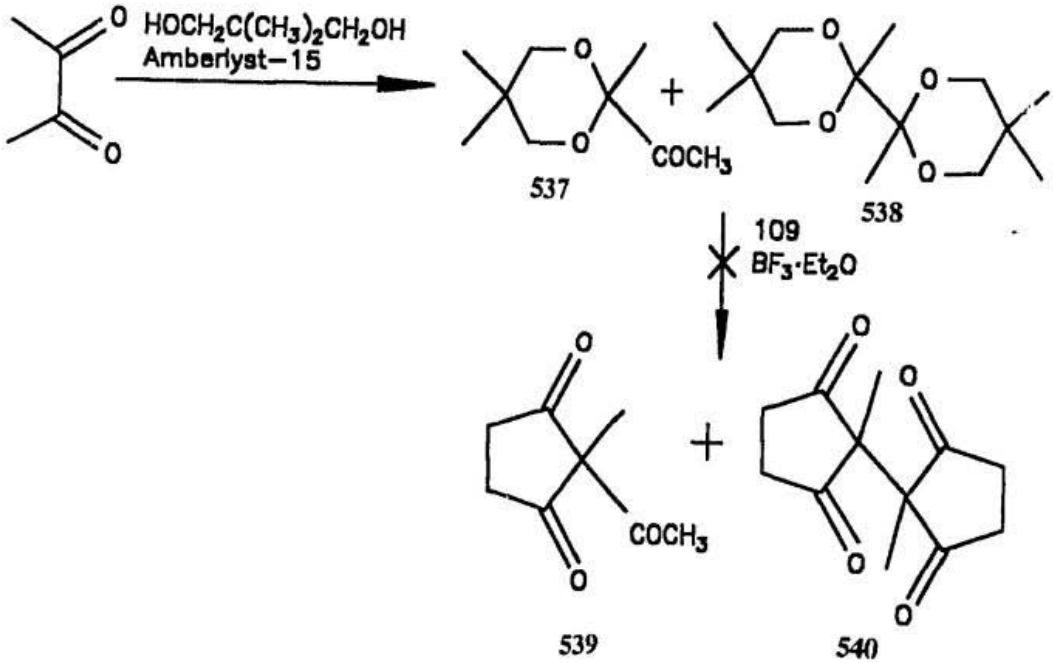
We concluded that a ketal α to a double bond may not be a good substrate for geminal acylation reaction, but double bonds further away are compatible with the reaction.

2. Ketal α to a carbonyl or to another ketal

To test the spiro-annulation reaction of a ketal α to a carbonyl or α to another ketal, we prepared butane-2,3-dione monoketal **537** and diketal **538**. Treatment of butane-2,3-dione with 2,2-dimethylpropane-1,3-diol and Amberlyst-15 in

dichloromethane following the procedure of Levine and Mauney[140] provided a 9 : 1 mixture of **537** and **538** after fractional distillation. Exposure of this mixture to **109** and $BF_3 \cdot Et_2O$ gave neither **539** nor **540** (Scheme 111). The failure of **538** might be partially attributed to steric effects. The reason for the failure of **537** was not clear.

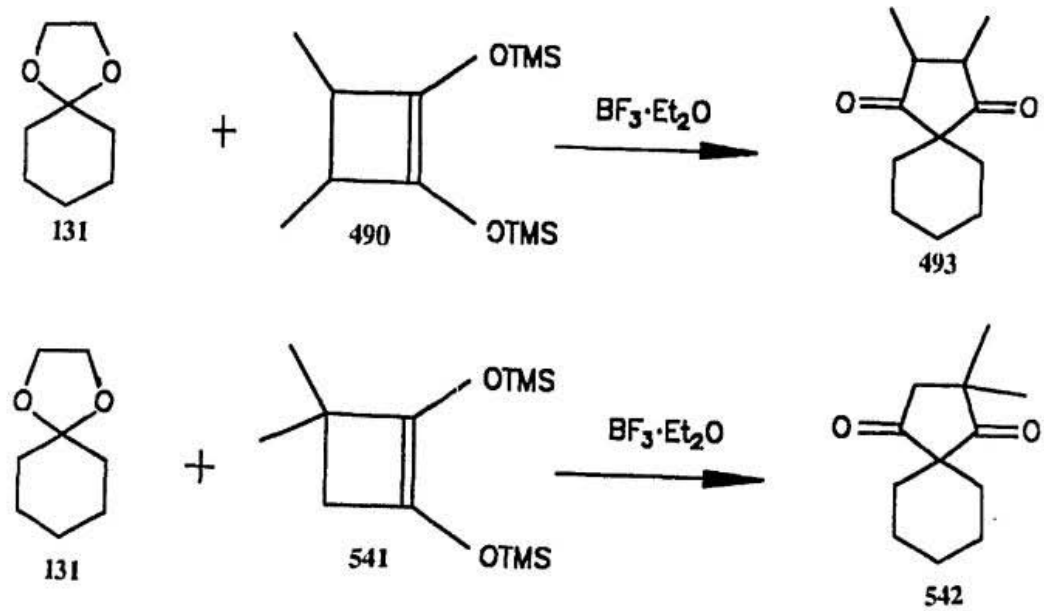
Scheme 111



3. Substituents on the cyclobutene ring

As shown in the synthetic studies toward pentalenolactone, the reaction of 3,4-dimethylcyclobutene **490** with ketals did occur, but the purification of the resulting product such as **493** turned out to be problematic. We were curious about the behaviour of some other cyclobutene derivatives. To this end, 3,3-dimethylcyclobutene **541** was prepared after the method of Bloomfield and Nelke.[61] The geminal acylation of ketal **131** with **541** did seem to produce **542**, along with 50% unidentified material as revealed by GC-MS analysis. However, we were unable to purify **542** by several standard techniques (Scheme 112).

Scheme 112

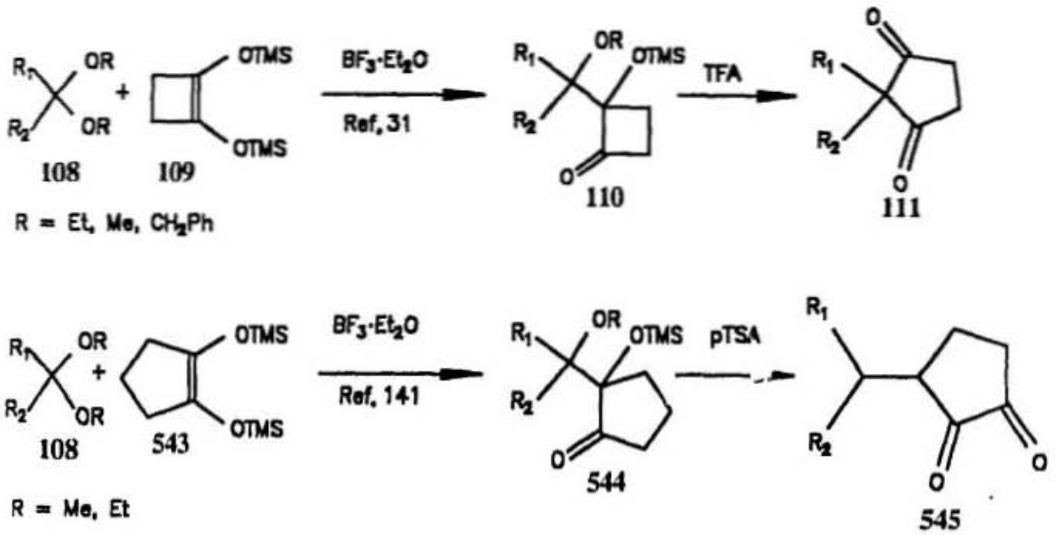


4. 1,2-Bis(trimethylsilyloxy)cyclopentene and its derivative

Kuwajima and coworkers[31] reported that cyclobutene **109** reacted with a ketal **108** using $BF_3{\cdot}Et_2O$ as catalyst, to give a cyclobutanone derivative **110**, which, upon treatment with TFA, underwent rearrangement to a 2,2-disubstituted cyclopentane-1,3-dione **111**. We found that a large excess of $BF_3{\cdot}Et_2O$ and a longer reaction time afforded **111** ***directly*** in a better yield. In contrast, as reported by Pattenden and Teague,[141] 1,2-bis(trimethylsiloxy)cyclopentene (**543**) reacted initially with **108** in an analogous fashion to provide the cyclopentanone derivative **544**, but, when this was treated with *p*TSA in benzene under reflux, rearrangement to 2,2-disubstituted cyclohexane-1,3-dione did not occur; instead the product isolated in low yield was assigned structure **545** (Scheme 113).

We were curious about the difference in behaviour between cyclobutene **109** and cyclopentene **543** in the reaction with ketals using $BF_3{\cdot}Et_2O$ as the catalyst. Thus, we examined the reactions of **543** with a variety of ketals (Scheme 114).[142]

Scheme 113



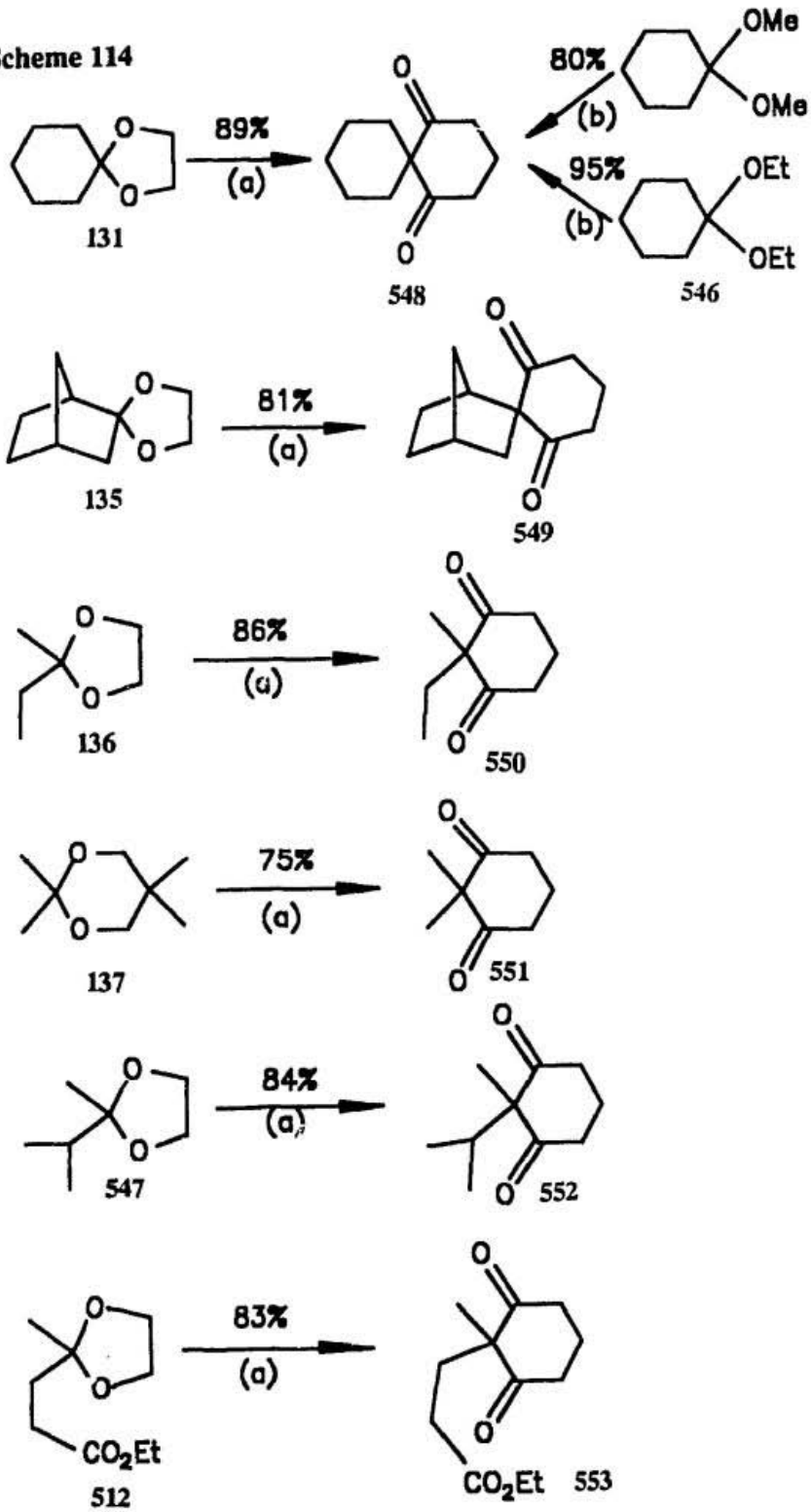
Ketal **131** was treated with three equivalents of **543** and fifteen equivalents of $BF_3{\cdot}Et_2O$ in dichloromethane for six hours and the resulting mixture was stirred overnight while attaining room temperature. TLC and GC–MS analysis of the crude product showed a single substance. After column chromatography on silica gel, this substance was obtained in 89% yield. The ^{13}C NMR spectrum showed seven signals, five methylenes (δ 18.4, 22.4, 25.5, 30.9 and 37.2), one quarternary center (δ 67.6), and one carbonyl (δ 209.6). Without any doubt, this substance was the symmetrical 2,2–disubstituted cyclohexane–1,3–dione **548**. The same product was obtained when cyclohexanone dimethyl ketal or diethyl ketal was subjected to the spiro–annulation reaction with **543**. We next investigated the reaction of **137** with **543**. GC–MS and TLC analysis showed complete conversion to a single product.The ^{13}C NMR spectrum showed five signals, two methylenes (δ 22.1, 37.2), one methyl (δ 17.9), one quarternary carbon (δ 61.6), and one carbonyl (δ 210.3). Accordingly, the structure could be unambiguously assigned **551**. Likewise, when ketals **136**, **547** and **512** were allowed to react with **543**, the products we isolated were undoubtedly the symmetrical 2,2–

disubstituted cyclohexane-1,3-diones **550**, **552** and **553**, respectively, as strictly confirmed by ^{13}C NMR analysis. It should be noted that the product **549**, derived from the norcamphor ethylene ketal (**135**), was an unsymmetrical molecule. Indeed, the ^{13}C NMR spectrum showed twelve signals, seven methylenes (δ 18.2, 25.2, 27.6, 27.7, 37.1, 37.9 and 48.5), two methines (δ 36.5 and 39.3), one quarternary center (δ 76.0), and two carbonyls (δ 207.4 and 206.9). The IR spectrum of each product (**548** → **553**) displayed two bands in its carbonyl region, which was well known for many other 2, 2-disubstituted cyclohexane-1,3-diones reported in literature.[143]

Next, the dimethyl acetal **554** was allowed to react with **543** and $BF_3{\cdot}Et_2O$ (Scheme 115). After column chromatography on silica gel, we obtained a single crystalline substance. Besides the aromatic ring, the ^{13}C NMR spectrum showed three methylenes (δ 17.6, 31.0 and 37.4), one methine (δ 85.4), one quarternary carbon (δ 79.0), one methyl (δ 57.2) and one carbonyl (δ 219.7). We realised that this was the unrearranged adduct **555**. Accordingly, a one-proton singlet at δ 4.313 and a methyl singlet at δ 3.197 were evident in its ^1H NMR spectrum. It should be pointed out that there are two chiral centers in **555**, but the ^{13}C NMR spectrum showed only one adduct. The remarkable stereoselectivity of the addition between acetal **554** and **543** is particularly noteworthy. Since **555** refused to undergo the rearrangement under the reaction condition, we subjected it to *p*TSA in benzene under reflux. GC-MS analysis of the crude product indicated a mixture of several compounds. A similar result was obtained when TFA was employed instead of *p*TSA. Our efforts to separate the components of the crude mixture by chromatography were unsuccessful. Nevertheless, the isolation of **555** confirmed the intermediate proposed for the reaction of ketals with cyclopentene **543**.

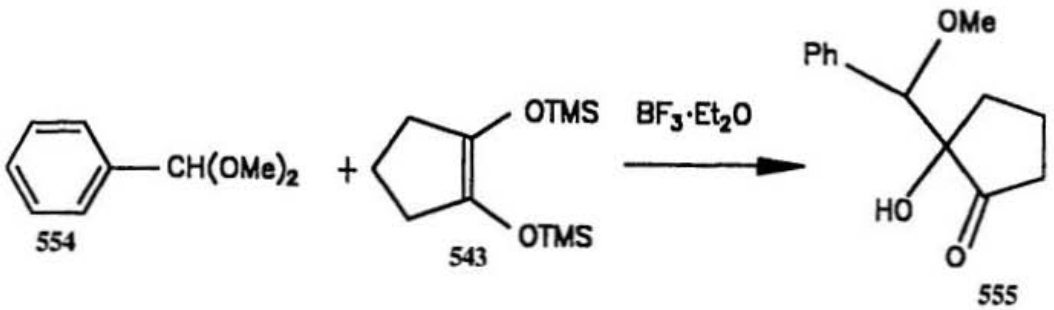
3,4-Disubstituted cyclopentene **557** was readily prepared from dimethyl camphorate (**556**) by using a standard acyloin procedure.[61] However, the reaction of

Scheme 114



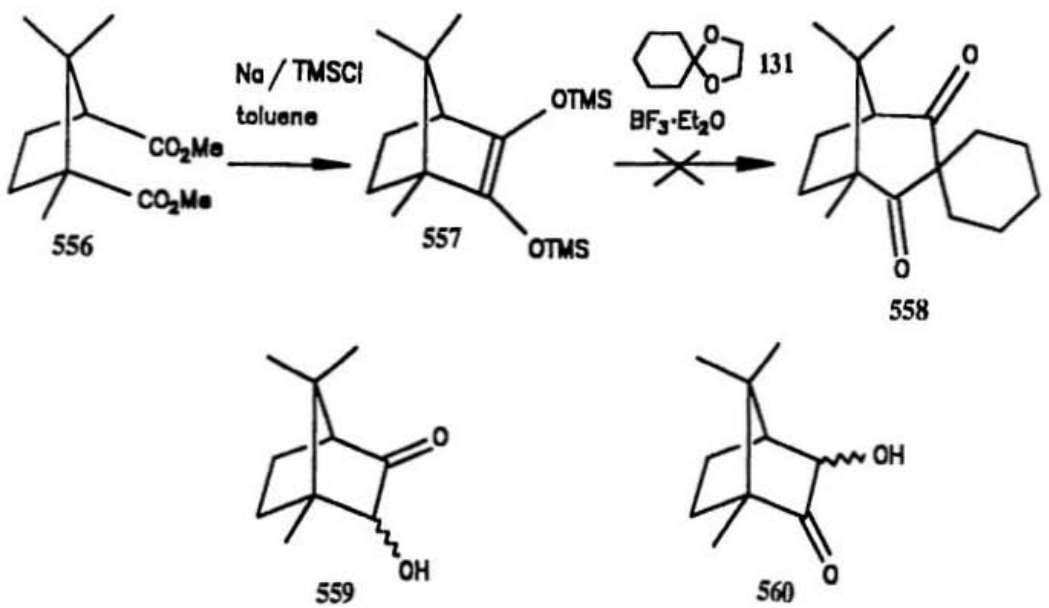
(a) Isolated yield; (b) GC–MS yield.

Scheme 115



this cyclopentene **557** with ketal **131** gave no detectable amount of **558**. The products we obtained were a mixture of **559** and **560**, derived from **557** *via* hydrolysis (Scheme 116). The steric hindrance could be responsible for the failure of **557** to react.

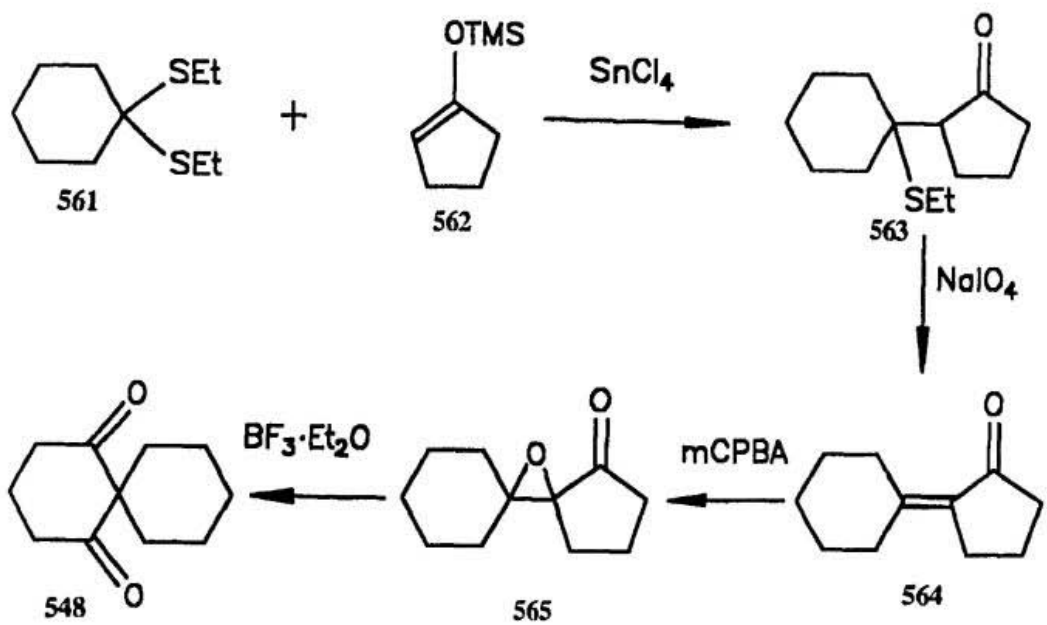
Scheme 116



In general, 2,2-disubstituted cyclohexane-1,3-diones were prepared from

cyclohexane-1,3-diones by double alkylation, but the yields were uniformly poor due to the formation of unwanted O-alkylation as well as ring cleavage.[30] More recently, Bach and Klix[144] developed a four-step synthesis of spirocyclic 1,3-diketones as outlined in Scheme 117. Thus, the Lewis acid initiated α-thioalkylation of silyl enol ether **562** provides **563**, which, upon treatment with $NaIO_4$, undergoes dehydrosulfenylation leading to enone **564**. Oxidation of **564** with *m*CPBA gives α, β-epoxy ketone **565**, which rearranges to **548** in 71% yield. Clearly, the reaction of ketals with **543** provides much more efficient method for the preparation of 2,2-disubstituted cyclohexane-1,3-diones.

Scheme 117

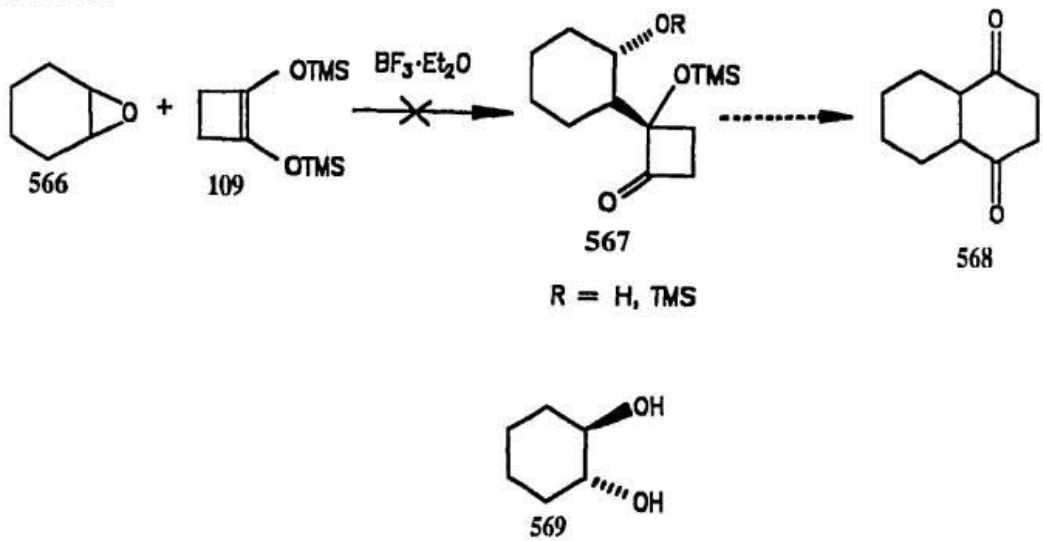


5. Epoxides and ozonides

All the reactions we explored were those between ketals or acetals and cyclobutene derivatives such **109** or cyclopentene **543**. Based on the mechanism of the geminal

acylation reaction, epoxides such as **566** might serve as substrates as well. We postulated that the reaction of **566** with **109** might give **567**, which undergo rearrangement leading to **568** as depicted in Scheme 118. Contrary to our expectation, no reaction was observed under several conditions. In every case, the product we obtained was the *trans* diol **569**.

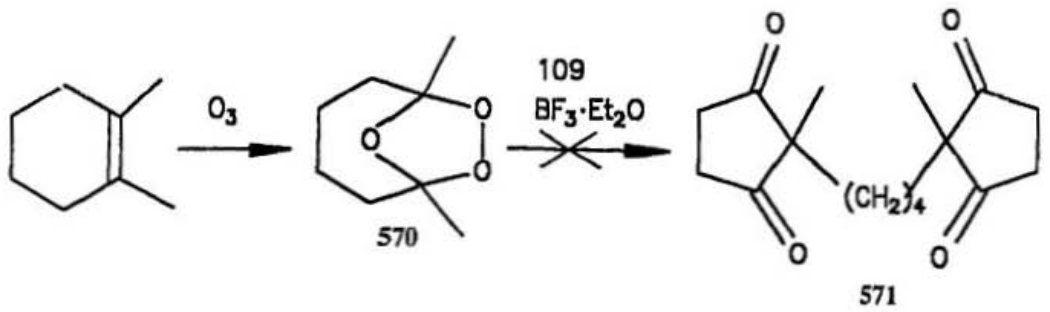
Scheme 118



Next, we examined the geminal acylation reaction of the ozonide **570**, derived from 1,2-dimethylcyclohexene (Scheme 119). Compound **570**, which possessed two "ketal" moieties, might react with **109** leading to the geminal acylation product **571**. Once again, no **571** was formed when **570** was subjected to the standard reaction conditions with **109**.

The failure of epoxides and ozonides as substrates in the geminal acylation reaction is probably due to the fact that epoxides and ozonides are not reactive enough relative to normal ketal.

Scheme 119



II. Experimental*

1,4-Dioxaspiro[4.5]dec-7-ene (530) and 1,4-dioxaspiro[4.5]dec-6-ene (531)**

A solution of 2-cyclohexen-1-one (5 0 g, 0.05 mmol), ethylene glycol (14 mL, 0.25 mmol), and *p*TSA (500 mg) in benzene was heated under reflux overnight with a Barrett water-separator. Saturated $NaHCO_3$ solution was added, the aqueous layer was extracted with diethyl ether (×3), and the combined organic extracts were washed with saturated NaCl (×2). The organic solutions were then dried over K_2CO_3 and evaporated *in vacuo*. Carefully controlled fractional distillation of the resulting residue provided pure **530** (0.9 g, 13%) and a 4 : 5 mixture of **530** and **531** (1.0 g, 14%). For **530** (colorless oil): ^{1}H NMR δ: 1.756 (2H, t, J = 6.5 Hz), 2.262 (4H, m), 3.985 (4H, s), 5.56-5.66 (1H, m), and 5.68-5.78 (1H, m); ^{13}C NMR δ (attached H's): 24.4 (2), 30.9 (2), 35.6 (2), 64.2 (2C, 2), 107.7 (0), 124.1 (1), and 126.3 (1); MS (from GC-MS) m/z (%): 140 (40, M^+), 125 (15, M^+ - Me), 86 (100), 67 (11), 43 (13), 42 (36), and 41 (13). For **531** (colorless oil): ^{1}H NMR (from the mixture) δ: 1.70-1.83 (4H, mm), 1.96-2.07 (2H, mm), 3.92-4.01 (4H, mm), 5.56-5.75 (1H, m), and 5.93-6.05 (1H, m); ^{13}C NMR δ (attached H's): 20.6 (2), 24.7 (2), 33.3 (2), 64.2 (2C, 2), 105.5 (0), 127.3 (1), and 132.7 (1); MS (from GC-MS) m/z (%): 140 (2, M^+), 112 (100), 110 (4), 109 (2), 95 (4), 86 (5), 79 (14), 77 (7), 68 (40), 55 (11), 43 (4), 42 (7), and 41 (9).

Spiro[4.5]dec-7-ene-1,4-dione (532)

A solution of the ketal **530** (119.3 mg, 0.85 mmol) in CH_2Cl_2 (50 mL) was cooled to -78°C. $BF_3{\cdot}Et_2O$ (1.57 mL, 12.8 mmol) was added followed, dropwise, by a solution of **109** (0.57 mL, 2.1 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred

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* For **General Procedures**, see **1.III.**

** We thank Mr. Paul F. Walsh for performing this experiment.

overnight, during which time the solution was allowed to attain room temperature. This mixture was added slowly to an ice-cooled saturated $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed (3% acetone in petroleum ether) to provide pure **532** (91.3 mg, 75%): mp 53-54°C; IR (film) ν_{max}: 1749, 1716, and 1438 cm^{-1}; ^1H NMR δ: 1.733 (2H, t, J = 6.1 Hz), 2.134 (4H, m), symmetrical 16-line pattern centered at 2.824 (4H), and 5.755 (2H, m); ^{13}C NMR δ (attached H's): 20.8 (2), 25.8 (2), 27.0 (2), 34.1 (2C, 2), 55.3 (0), 122.9 (1), 125.4 (1), and 214.4 (2C, 0); MS *m/z* (%): 164 (100, M^+), 149 (11), 136 (44), 135 (36), 122 (28), 121 (24), 108 (22), 107 (43), 93 (12), 91 (12), 81 (17), 80 (53), 79 (93), 78 (15), 77 (37), 56 (17), 55 (25), 54 (11), 53 (15), 52 (12), 51 (17), 43 (17), and 41 (13). *Exact mass* calcd. for $C_{10}H_{12}O_2$: 164.0837; found: 164.0843.

A 4 : 5 mixture of **530** and **531** (114.1 mg, 0.815 mmol) was treated with $BF_3{\cdot}Et_2O$ (1.50 mL, 12.2 mmol) and **109** (0.54 mL, 2.0 mmol) as above to give pure **532** (94.9 mg, 71%).

2-Acetyl-2,5,5-trimethyl-1,3-dioxane (537) and 2,5,5-trimethyl-2-(2,5,5-trimethyl-1,3-dioxa-2-cyclohexyl)-1,3-dioxane (538)

A mixture of butane-2,3-dione (1.96 g, 22.7 mmol), 2,2-dimethyl-1,3-propanediol (3.60 g, 34.6 mmol), and Amberlyst-15 (8 g) in CH_2Cl_2 (70 mL) was stirred at room temperature overnight. The resin was removed by filtration through a Celite pad, and two volumes of diethyl ether were then passed through the pad. The combined solutions were concentrated *in vacuo*. Fractional distillation of the residue provided a 9 : 1 mixture of **537** and **538** (3.71 g, 95%) as a colorless liquid: for the monoketal **537**: ^1H NMR (60 MHz) δ: 0.75 (3H, s), 1.20 (3H, s), 1.45 (3H, s), 2.25 (3H, s), and 3.50 (4H, s); MS (from GC-MS) *m/z* (%): no M^+, 129 (32, M^+ -

$COCH_3$), 69 (33), 56 (4), 43 (100, $COCH_3$), and 41 (26); for the diketal **538**: MS (from GC–MS) *m/z* (%): no M^+, 243 (2, M^+ – Me), 173 (0.2), 129 (100), 115 (4), 69 (58), 56 (7), 43 (91), and 41 (28).

3,3–Dimethyl–1,2–bis(trimethylsiloxy)cyclobutene (541)

Dimethyl 2,2–dimethyl succinate (20.18 g, 0.12 mol) was treated with sodium (11.46 g, 0.50 mol) and chlorotrimethylsilane (70 mL, 0.55 mol) in toluene (600 mL) according to the procedure of Bloomfield and Nelke[61], which gave pure **541** (21.8 g, 73%): bp 90–91°C/0.20 Torr; ^{1}H NMR (60 MHz) δ: 0.21 (9H, s), 0.23 (9H, s), 1.10 (6H, s), and 1.95 (2H, s).

Spiro–annulation reaction of 541 with ketal 131

The ketal **131** (88.5 mg, 0.62 mmol) was treated with $BF_3{\cdot}Et_2O$ (0.76 mL, 6.2 mmol) and **541** (0.75 mL, 2.5 mmol) in CH_2Cl_2 following our general procedure. GC–MS analysis indicated that the crude product consisted *ca.* 50% of **542**: MS (from GC–MS) *m/z* (%): 194 (41, M^+), 111 (15), 110 (100), 82 (27), 81 (12), 79 (16), 67 (86), 55 (20), 54 (19), 53 (16), 43 (10), and 41 (43). Attempts to purify **542** by column chromatography on silica gel or recrystalization were unsuccessful.

1,2–Bis(trimethylsiloxy)cyclopentene (543)

Dimethyl glutarate (26 g, 0.16 mol) was treated with sodium (14.72 g, 0.64 mol) and chlorotrimethylsilane (81.23 mL, 0.64 mol) in toluene following the procedure of Bloomfield and Nelke[61] to provide **543** (27.70 g, 70%): bp 66–67°C/0.4 Torr; ^{1}H NMR (60 MHz) δ: 0.20 (18H, s), 1.80 (2H, m), and 2.30 (4H, t).

Typical procedure for reaction of 1,2-bis(trimethylsiloxy)cyclopentene (543) with a ketal or acetal: Spiro[5.5]undecane-1,5-dione (548)

A solution of cyclohexanone ethylene ketal (**131**) (336.3 mg, 2.37 mmol) in dry CH_2Cl_2 (30 mL) was cooled to −78°C under nitrogen. Freshly distilled $BF_3{\cdot}Et_2O$ (4.4 mL, 36 mmol) was added followed by the dropwise addition of a solution of **543** (1.63 mL, 5.93 mmol) in dry CH_2Cl_2 (8 mL). The mixture was stirred overnight during which time the mixture was allowed to attain room temperature. Water was added, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic solutions were washed with H_2O (×2), saturated $NaHCO_3$ (×2) and saturated NaCl (×2), dried over $MgSO_4$, and concentrated *in vacuo*. The dark residue was chromatographed (5% acetone in petroleum ether) to provide pure **548** (379.4 mg, 89%) as colorless crystals: mp 71-72°C; IR (film) ν_{max}: 1720 and 1690 cm^{-1}; ^1H NMR δ: 1.42 (2H, m), 1.58 (4H, m), 1.90 (6H, m), and 2.687 (4H, apparent t, J = 7.0 Hz); ^{13}C NMR δ (attached H's): 18.4 (2), 22.4 (2C, 2), 25.5 (2), 30.9 (2C, 2), 37.2 (2C, 2), 67.6 (0), and 209.6 (2C, 0); MS *m/z* (%): 180 (100, M^+), 152 (18), 151 (16), 139 (14), 138 (18), 137 (16), 126 (34), 125 (43), 124 (24), 123 (26), 111 (11), 110 (36), 109 (61), 107 (11), 98 (19), 97 (26), 96 (21), 95 (17), 91 (15), 84 (13), 83 (21), 82 (18), 81 (61), 80 (14), 79 (41), 77 (18), 71 (10), 70 (27), 68 (10), 67 (71), 55 (53), 54 (21), 53 (23), 51 (11), 44 (27), 43 (51), 42 (60), and 41 (56). *Exact mass* calcd. for $C_{11}H_{16}O_2$: 180.1149; found: 180.1167.

Spiro(bicyclo[2.2.1]heptane-2,1'-[2,6]cyclohexanedione) (549)

The ketal **135** (168.0 mg, 1.09 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.01 mL, 16.4 mmol) and **543** (0.75 mL, 2.73 mmol) as above to provide pure **549** (169.6 mg, 81%): mp 49-50°C; IR (film) ν_{max}: 1720 and 1690 cm^{-1}; ^1H NMR δ: 1.13-1.31 (3H, m), 1.39-1.51 (3H, m), 1.69 (1H, m), 1.822 (1H, dd, J = 2.6, 12.4 Hz), 2.10-2.24 (2H, m), 2.30 (1H, br s, bridgehead H), 2.54-2.76 (3H, m), 2.74 (1H, br s, bridgehead H), and

2.94 (1H, m); ^{13}C NMR δ (attached H's): 18.2 (2), 25.2 (2), 27.6 (2), 27.7 (2), 36.5 (1), 37.1 (2), 37.9 (2), 39.3 (1), 48.5 (2), 76.0 (0), 206.9 (0), and 207.4 (0); MS *m/z* (%): 192 (60), 164 (16), 163 (88), 137 (13), 136 (24), 135 (64), 127 (20), 126 (100), 125 (14), 122 (13), 121 (12), 109 (10), 108 (20), 98 (31), 97 (19), 95 (11), 93 (42), 91 (21), 80 (14), 79 (39), 77 (20), 67 (39), 66 (29), 65 (28), 55 (47), 53 (22), 43 (21), 42 (48), and 41 (48). *Exact mass* calcd. for $C_{12}H_{16}O_2$: 192.1149; found: 192.1150.

2-Ethyl-2-methylcyclohexane-1,3-dione (550)

The ketal **136** (213.8 mg, 1.84 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.26 mL, 18.4 mmol) and **543** (1.26 mL, 4.60 mmol) as above to provide **550** (242.1 mg, 85%) as a colorless oil: IR (film) ν_{max}: 1725 and 1695 cm^{-1}; ^{1}H NMR δ: 0.796 (3H, t, J = 7.4 Hz), 1.206 (3H, s), 1.847 (2H, q, J = 7.4 Hz), 1.86 (1H, m), 2.05 (1H, m), and 2.675 (4H, m); ^{13}C NMR δ (attached H's): 9.1 (3), 17.7 (2), 17.9 (3), 30.8 (2), 37.9 (2C, 2), 66.2 (0), and 210.4 (2C, 0); MS *m/z* (%): 254 (66, M$^+$), 139 (8), 112 (8), 111 (83), 98 (16), 97 (61), 84 (43), 83 (26), 81 (22), 79 (8), 70 (20), 69 (79), 56 (12), 55 (79), 53 (43 (54), 42 (100), and 41 (86). *Exact mass* calcd. for $C_9H_{14}O_2$: 154.0993; found: 154.0987.

2,2-Dimethylcyclohexane-1,3-dione (551)

The ketal **137** (333.6 mg, 2.32 mmol) was treated with $BF_3{\cdot}Et_2O$ (4.28 mL, mmol) and **543** (1.27 mL, 4.64 mmol) to provide pure **551** (242.1 mg, 75%): mp 34-35°C (lit.[67b] 35°C); IR (film) ν_{max}: 1720 and 1690 cm^{-1}; ^{1}H NMR δ: 1.307 (6H, s), 1.961 (2H, quintet), and 2.710 (4H, t, J = 6.6 Hz); ^{13}C NMR δ (attached H's): 17.9 (2C, 3), 22.1 (2), 37.2 (2C, 2), 61.6 (0), and 210.3 (2C, 0); MS *m/z* (%): 140 (47, M$^+$), 97 (58), 85 (16), 70 (58), 69 (16), 67 (40), 55 (56), 43 (23), 42 (100), and 41 (54). *Exact mass* calcd. $C_8H_{12}O_2$: 140.0837; found: 140.0845.

2-Isopropyl-2-methylcyclohexane-1,3-dione (552)

The ketal **547** (198.7 mg, 1.53 mmol) was treated with $BF_3 \cdot Et_2O$ (2.82 mL, 22.9 mmol) and **543** (1.47 mL, 5.36 mmol) as above to provide the pure **552** (215.7 mg, 84%) as a colorless oil: IR (film) ν_{max}: 1720 and 1690 cm^{-1}; ^1H NMR δ: 0.848 (6H, d, J = 6.7 Hz), 1.059 (3H, s), 1.66 (1H, m), 2.12 (1H, m), 2.54 (3H, m), and 2.83 (2H, m); δ (attached H's): 9.0 (3), 17.2 (2C, 3), 18.3 (2), 34.6 (1), 37.6 (2C, 2), 71.7 (0), and 209.6 (2C, 0); MS (from GC-MS) m/z (%): 168 (47, M^+), 153 (45, M^+ - Me), 126 (25), 125 (100), 107 (10), 98 (37), 97 (38), 83 (66), 81 (10), 70 (32), 69 (17), 67 (13), 55 (88), 53 (18), 43 (51), 42 (82), and 41 (72). *Exact mass* calcd. for $C_{10}H_{16}O_2$: 168.1150; found 168.1147.

2-(2-Carboethoxyethyl)-2-methylcyclohexane-1,3-dione (553)

The ketal **512** (166.6 mg, 0.89 mmol) was treated with $BF_3 \cdot Et_2O$ (1.64 mL, 13.3 mmol) and **543** (0.49 mL, 1.78 mmol) as above to provide pure **553** (165.4 mg, 83%) as a colorless oil: IR (film) ν_{max}: 1725 (br) and 1690 cm^{-1}; ^1H NMR δ: 1.242 (3H, t, J = 7.2 Hz), 1.268 (3H, s), 1.97 (2H, m), 2.16 (4H, m), 2.685 (4H, m), and 4.090 (2H, q, J = 7.2 Hz); ^{13}C NMR δ (attached H's): 14.1 (3), 17.5 (2), 20.8 (3), 29.4 (2), 30.4 (2), 37.7 (2C, 2), 60.5 (2), 64.3 (0), 172.7 (0), and 209.7 (2C, 0); MS (from GC-MS) m/z (%): 226 (30, M^+), 198 (29, M^+ - CO), 182 (11), 181 (95), 180 (43), 153 (17), 152 (100), 139 (69), 138 (91), 137 (13), 127 (13), 125 (13), 124 (51), 111 (61), 110 (14), 109 (12), 99 (21), 97 (36), 96 (59), 95 (12), 69 (36), 55 (93), 53 (12), 43 (36), 42 (84), and 41 (56). *Exact mass* calcd. for $C_{12}H_{18}O_4$: 226.1204; found 226.1201.

2-Hydroxy-2-(α-methoxybenzyl)cyclopentanone (555)

The benzaldehyde dimethyl acetal (**554**) (188.7 mg, 1.24 mmol) was treated with $BF_3 \cdot Et_2O$ (2.28 mL, 18.6 mmol) and **543** (0.70 mL, 2.5 mmol) as above to provide pure **555** (219.7 mg, 81%) as colorless crystals: mp 81-82.5°C; ^1H NMR δ: 1.05-2.48

(7H, mm), 3.197 (3H, s), 4.313 (1H, s), and 7.351 (5H, br s); ^{13}C NMR δ (attached H's): 17.6 (2), 31.0 (2), 37.4 (2), 57.2 (3), 79.0 (0), 85.4 (1), 127.6 (2C, 1), 128.0 (3C, 1), 136.6 (0), and 219.7 (0); MS *m/z* (%): no M^+, 189 (0.2, M^+ – OMe), 188 (1.3, M^+ – MeOH), 160 (3.2), 133 (3.4), 132 (5), 131 (5), 129 (2.2), 128 (2.8), 123 (2.8), 122 (49), 121 (100, $C_6H_5C^+H(OMe)$), 118 (14), 105 (20), 104 (31), 91 (44), 90 (10), 78 (12), 77 (71), 55 (16), 51 (13), 43 (10), and 42 (10). *Exact mass* calcd. for $C_{12}H_{13}O_2$ (M^+ – OMe): 189.0915; found: 189.0892; and for $C_{12}H_{12}O_2$ (M^+ – MeOH): 188.0837; found: 188.0813.

1,7,7-Trimethyl-2,3-bis(trimethylsiloxy)bicyclo[2.2.1]hept-2-ene (557)

Dimethyl camphorate (**556**) (13.7 g, 60.1 mol) was treated with sodium metal (5.94 g, 0.26 mol) and chlorotrimethylsilane (32.79 mL, 0.26 mol) in toluene following the procedure of Bloomfield and Nelke[61] to give **557** (17.08 g, 91 %) as a colorless liquid: 131–132°C/0.30 Torr; MS (from GC–MS) *m/z* (%): 312 (13, M^+), 286 (10), 285 (27), 284 (100), 270 (12), 269 (46), 209 (9), 181 (10), 147 (11), 75 (11), 73 (93), and 45 (24).

Attempted geminal acylation reaction of 557 with ketal 131

A solution of the ketal **131** (277.3 mg, 1.95 mmol) in CH_2Cl_2 (50 mL) was treated with **557** (1.42 mL, 3.90 mmmol) and $BF_3{\cdot}Et_2O$ (3.60 mL, 29.3 mmol) following our general procedure provided a mixture of keto–alcohols **559** and **560** (100% conversion by GC–MS) as colorless crystals: MS (from GC–MS) *m/z* (%): 168 (11, M^+), 153 (6, M^+ – Me), 125 (7), 107 (5), 95 (12), 84 (23), 83 (33), 71 (73), 70 (94), 69 (39), 67 (17), 55 (58), 53 (24), 43 (61), and 41 (100).

1,2 – Dimethyl cyclohexene ozonide (570)

Ozone was passed through a solution of 1,2 – dimethylcyclohexene (99.0 mg, 1.20 mmol) in CH_2Cl_2 (40 mL) at −78°C until the solution turned blue, indicating the completion of the ozonolysis. The excess ozone was removed by bubbling O_2 through the solution for *ca.* 5 min, and the system was then purged with nitrogen. This solution was used directly for the following geminal – acylation reaction.

Attempted spiro – annulation reaction of ozonide 570

To the above solution at −78°C was added $BF_3 \cdot Et_2O$ (1.48 mL, 12 mmol) followed by the dropwise addition of a solution of **109** (1.28 mL, 4.80 mmol) in CH_2Cl_2. The solution was then stirred overnight during which time the reaction was allowed to attain room temperature. No detectable formation of **571** was obtained as revealed by GC – MS analysis of the crude product.

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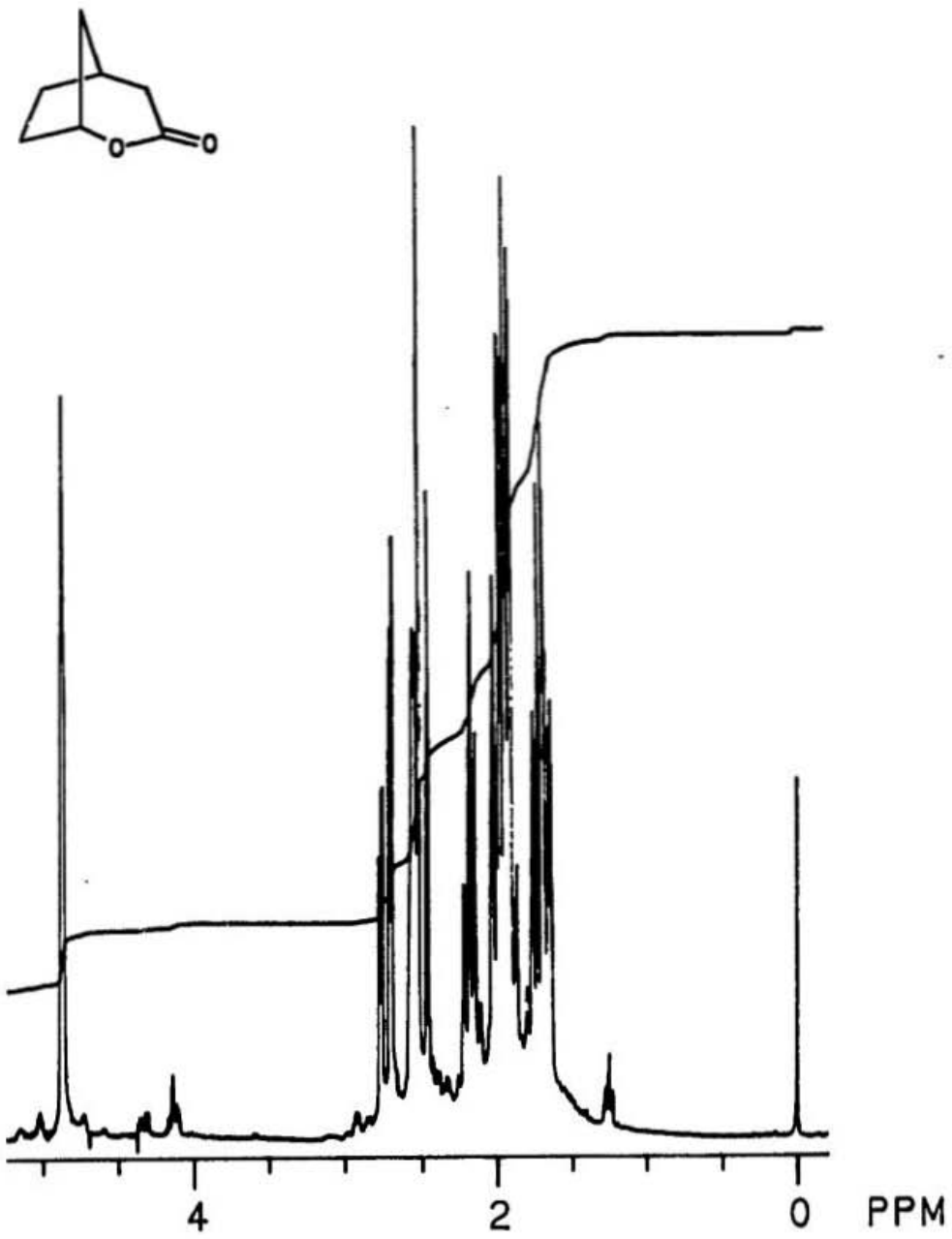
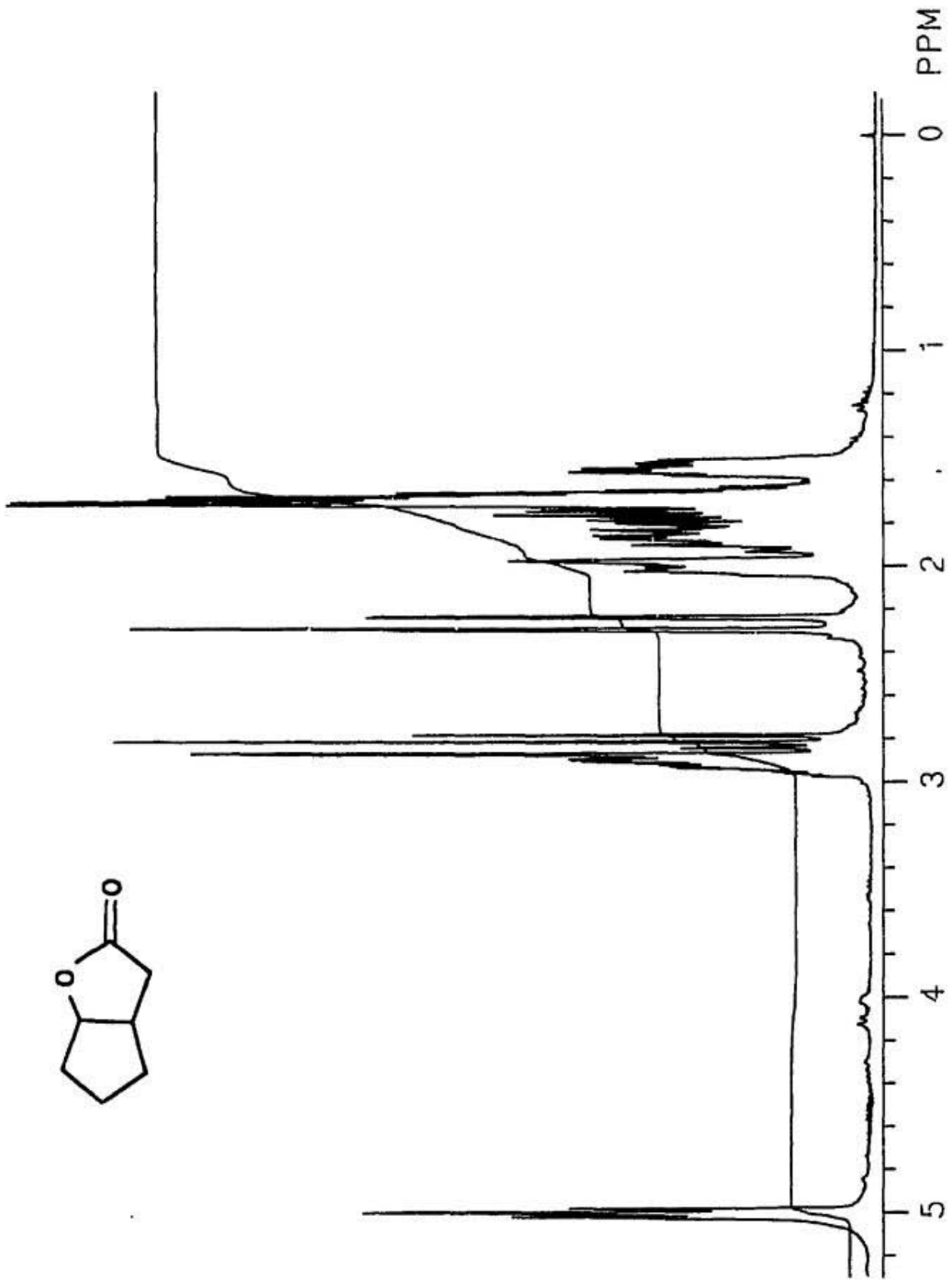
Appendix

The selected ^{1}H NMR spectra and gas chromatograms from the GC–MS of the synthetic samples were arranged according to the order in which they appear in the text. For the instruments employed, see **General Procedures** in **1.III.**

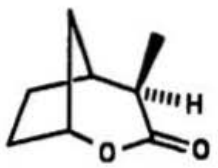
116 ($CDCl_3$)



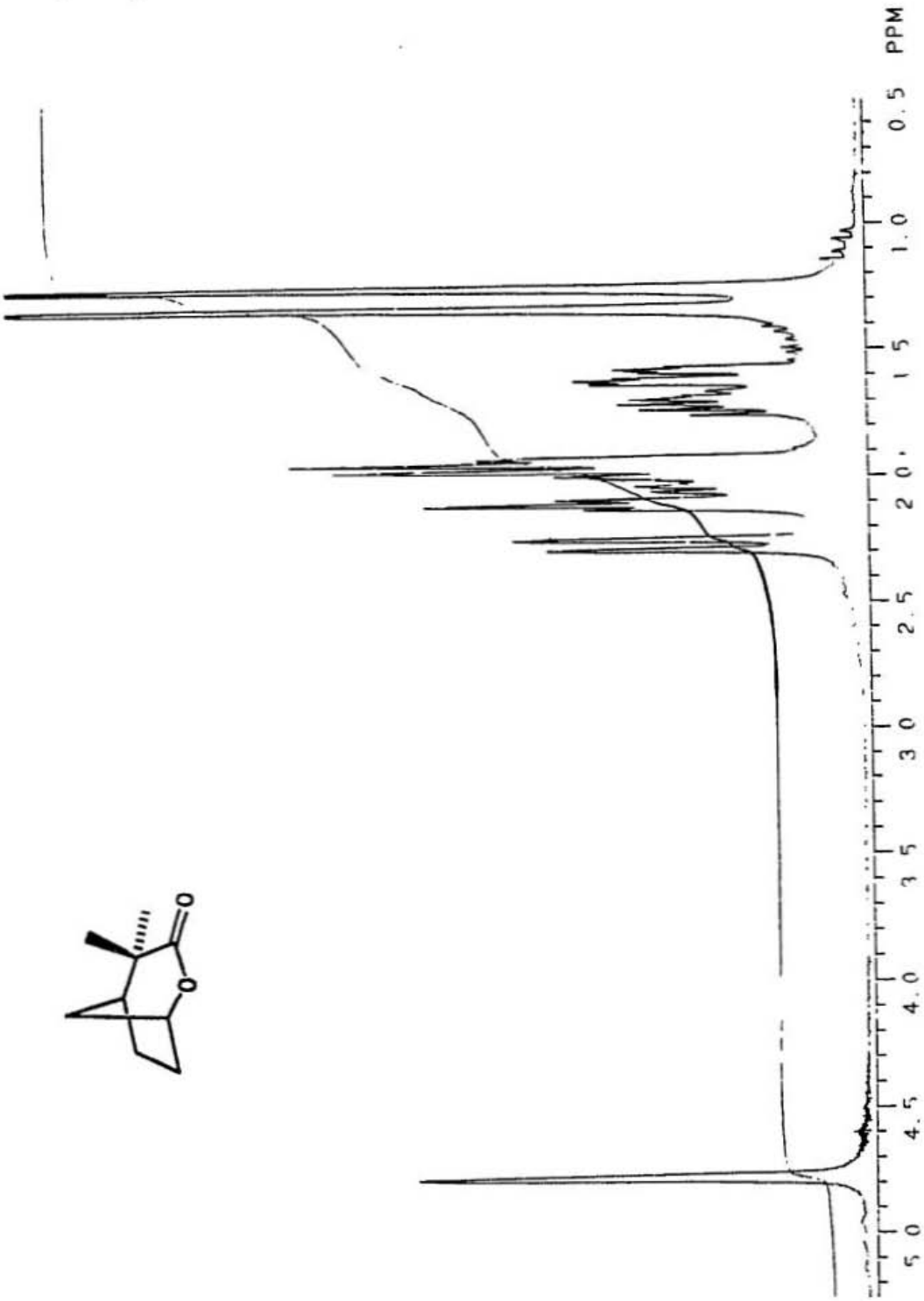
118 ($CDCl_3$)



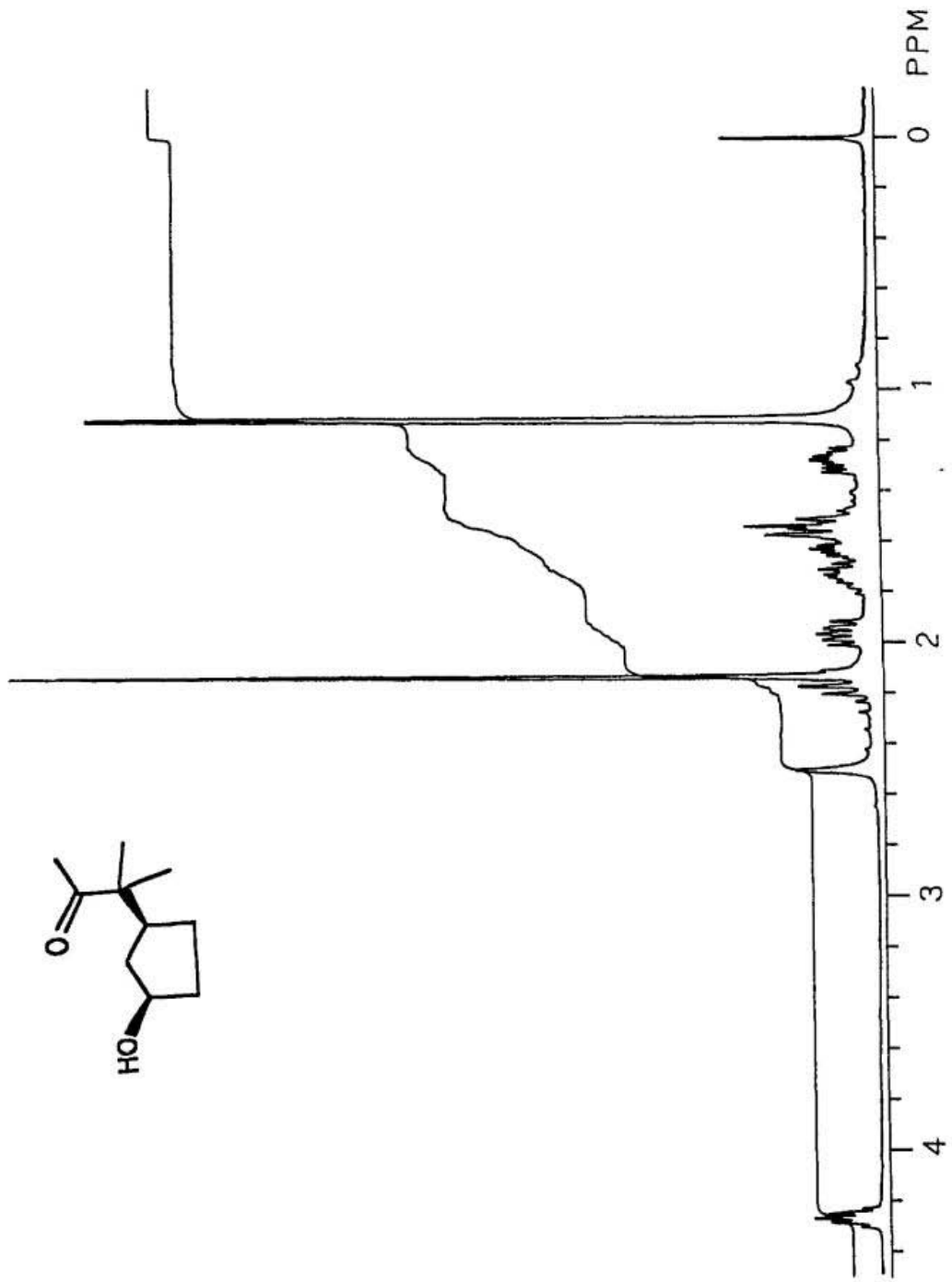
122 ($CDCl_3$)



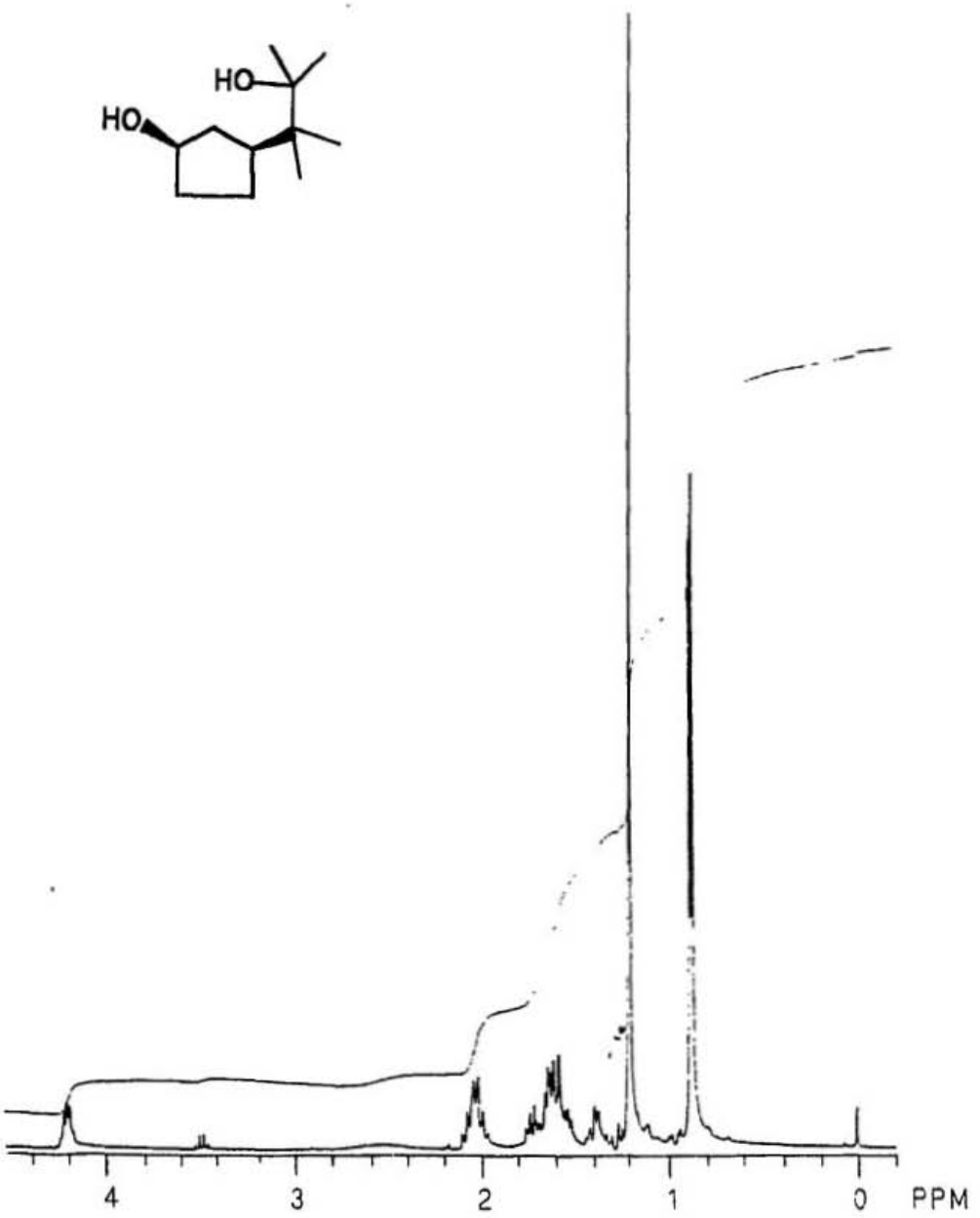
114 ($CDCl_3$)



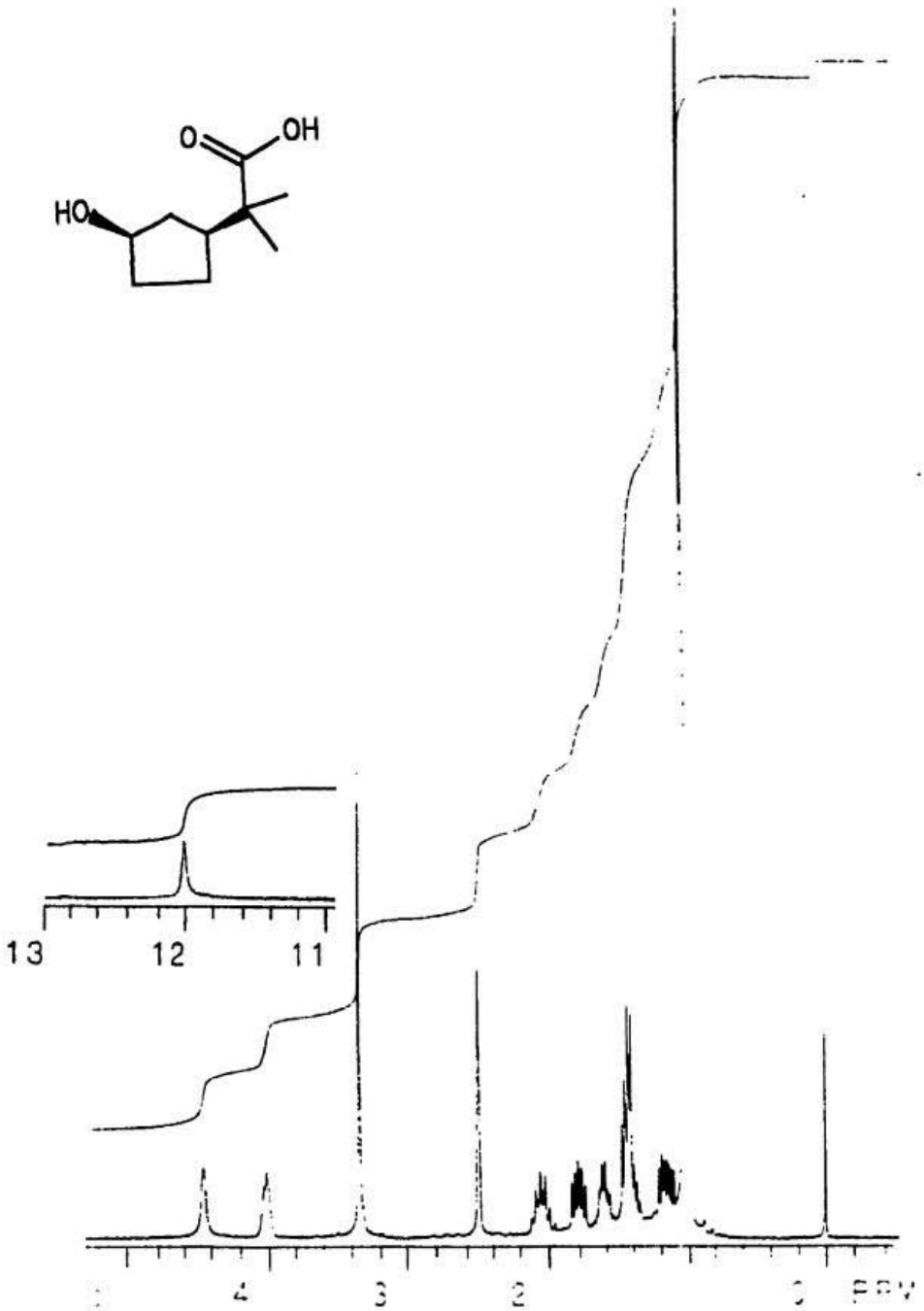
113 ($CDCl_3$)



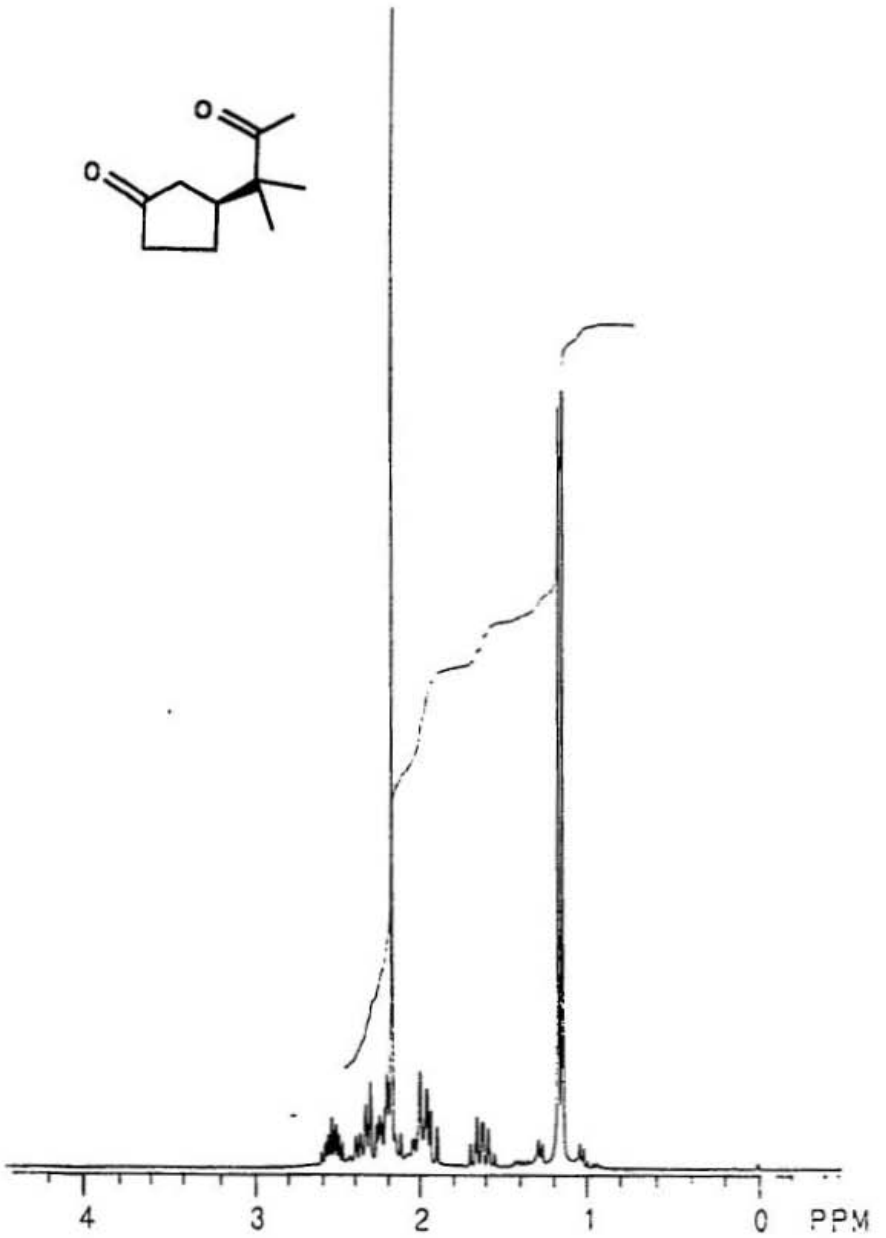
125 ($CDCl_3$)



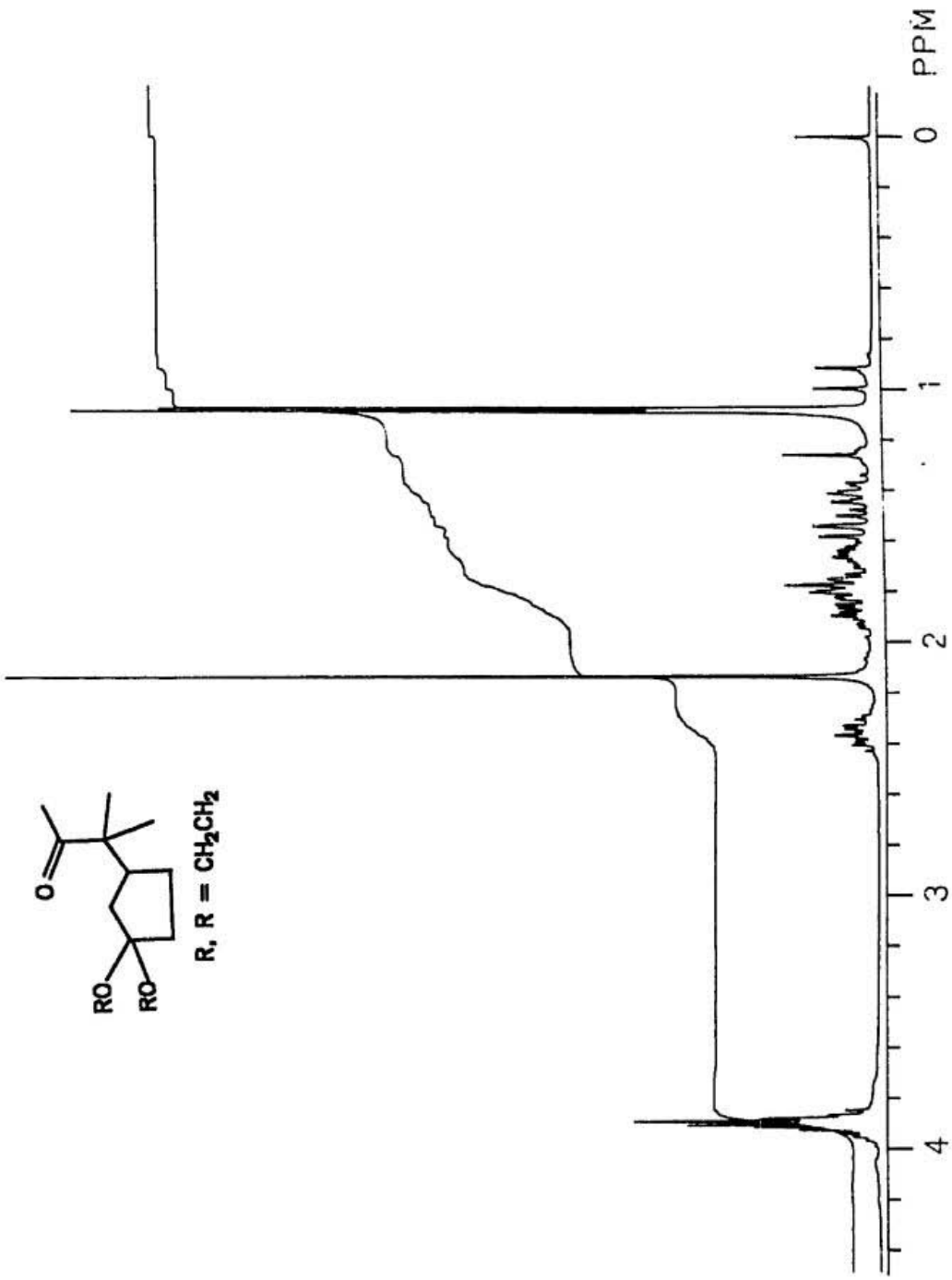
124 (DMSO)



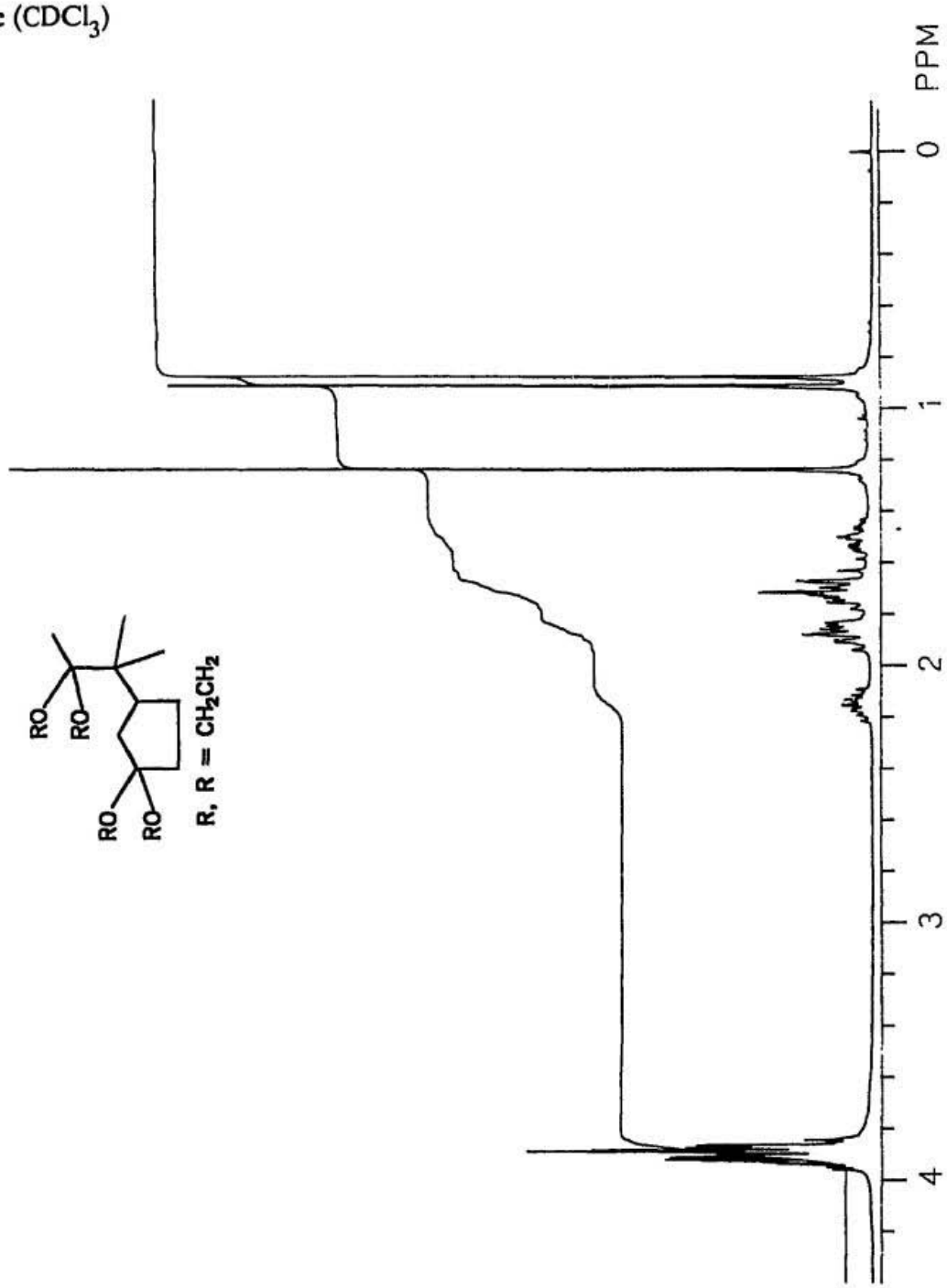
112 ($CDCl_3$)



107c ($CDCl_3$)



130c ($CDCl_3$)



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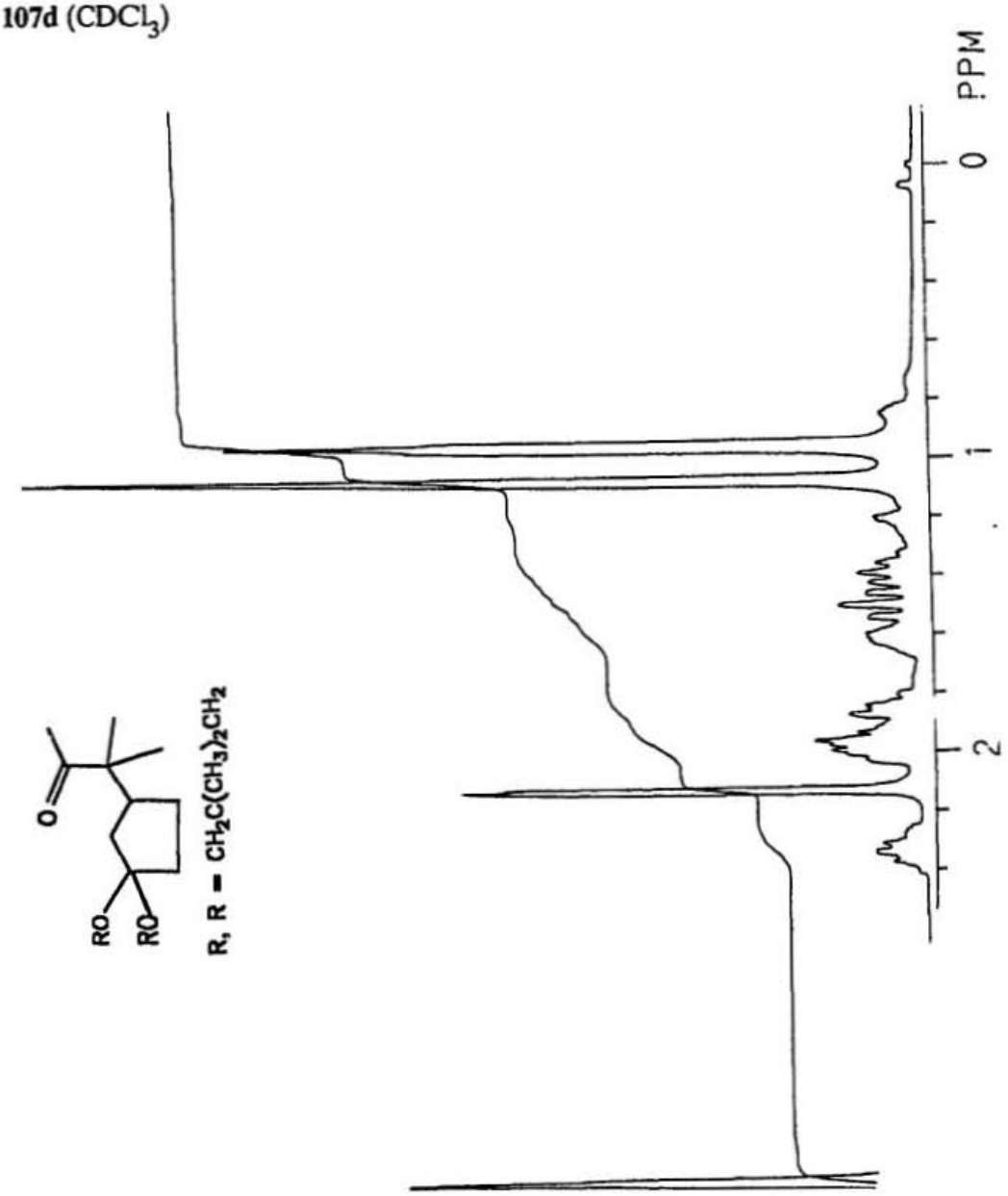
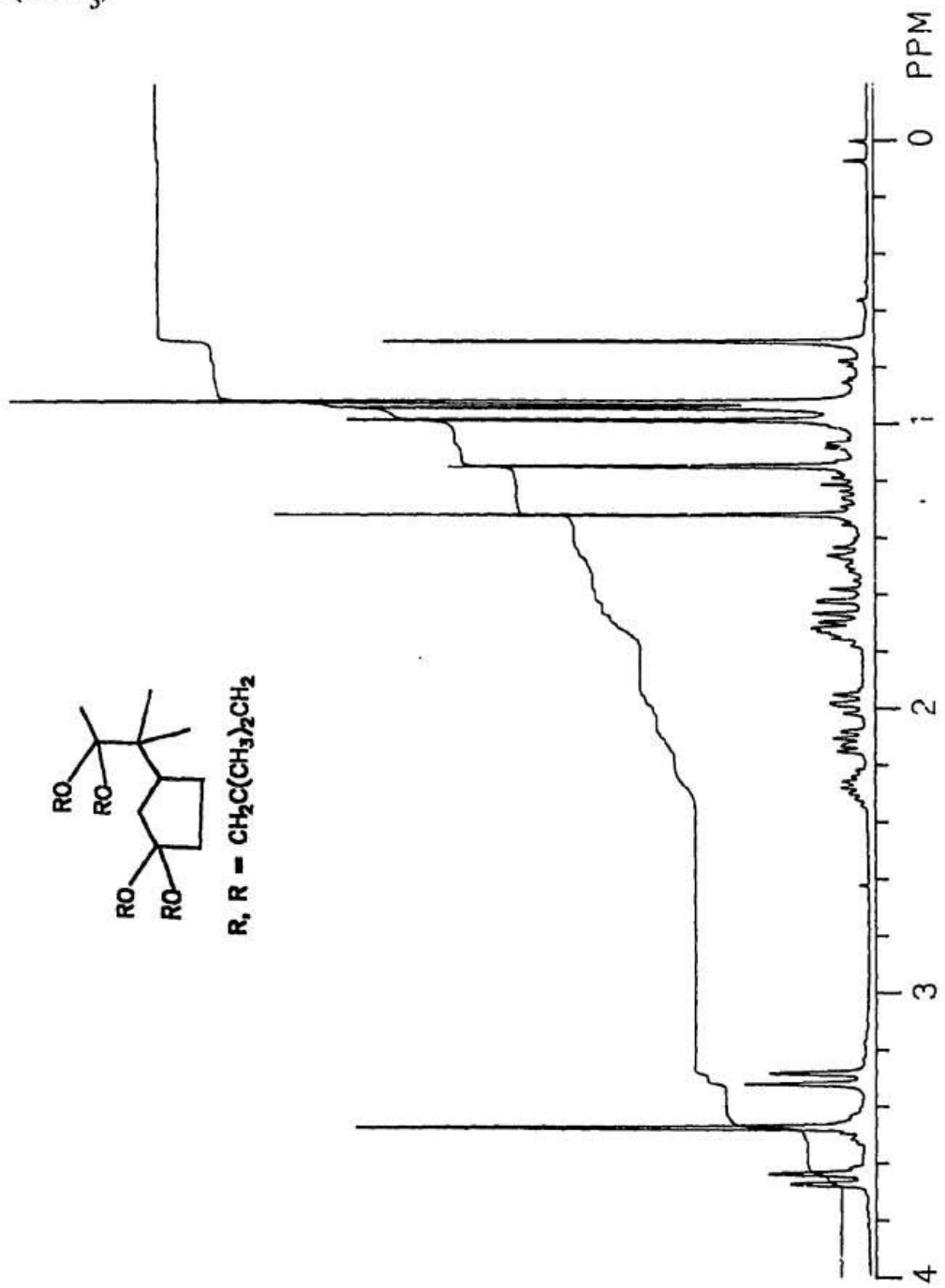
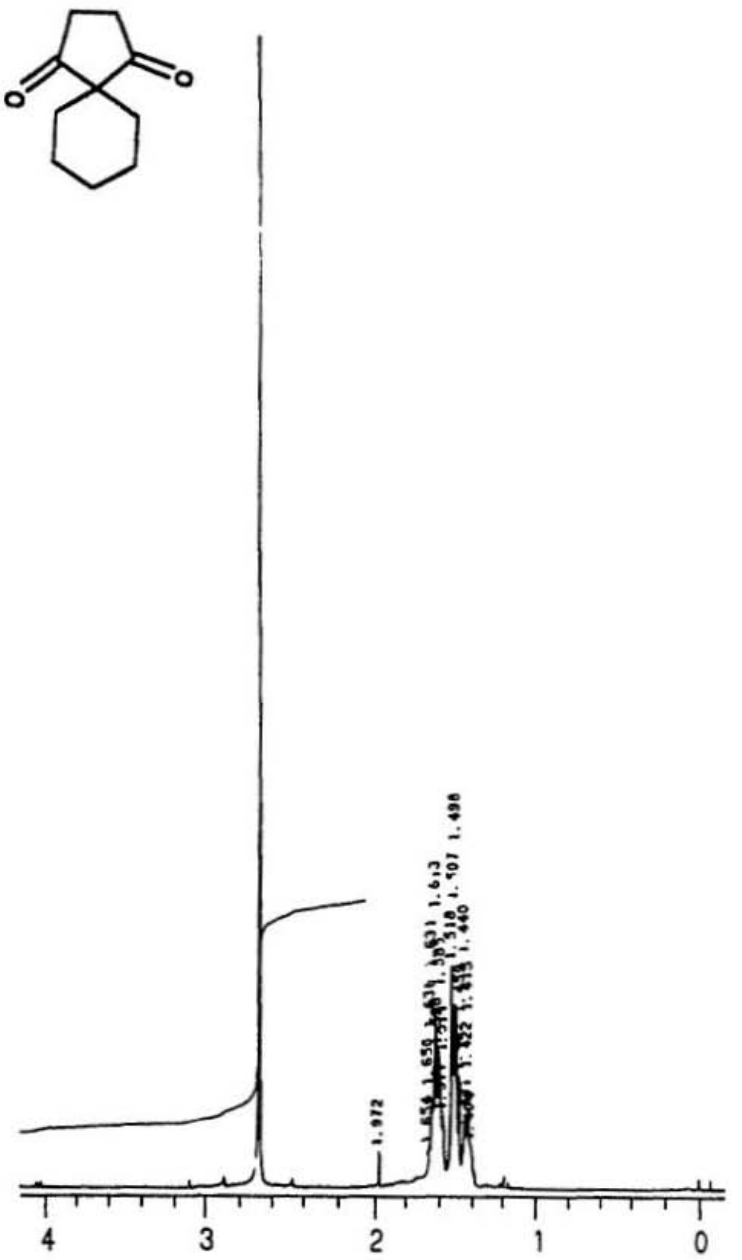


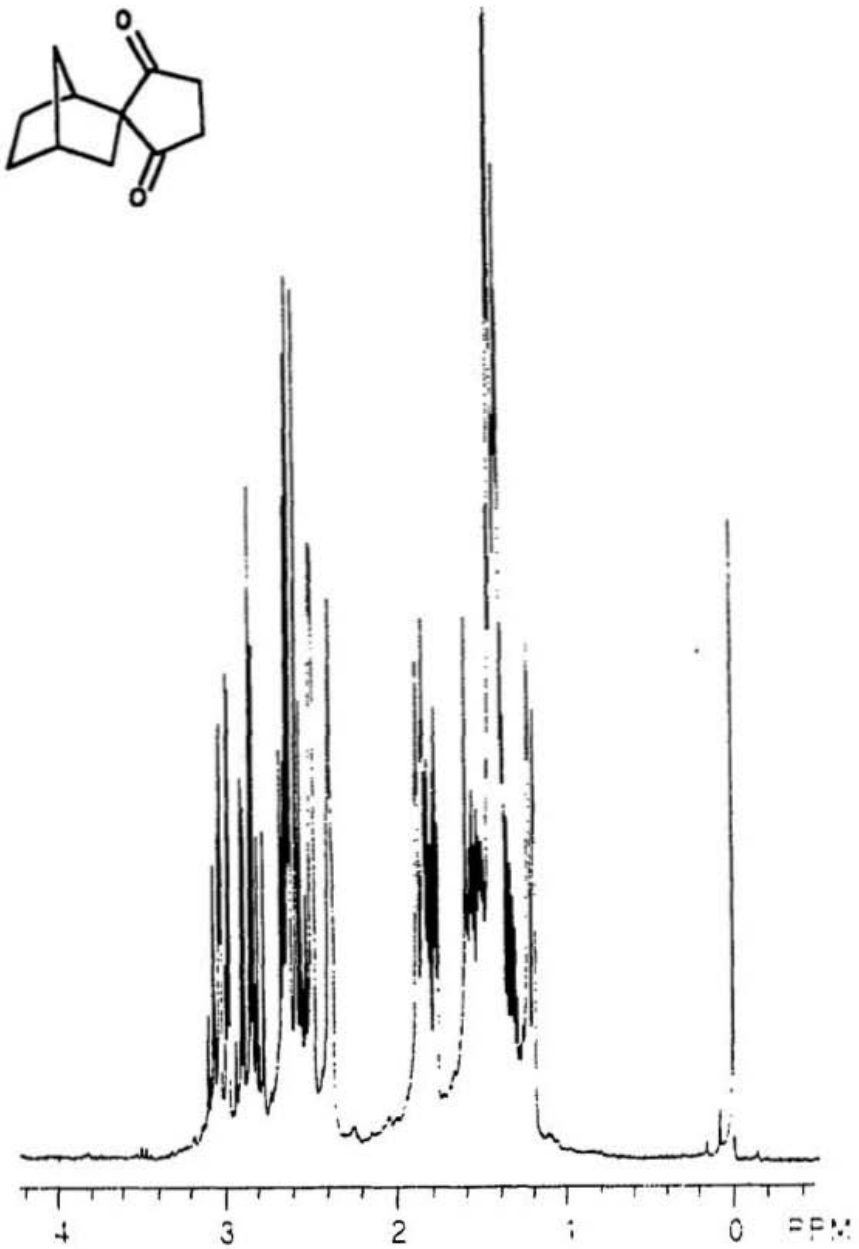
130d ($CDCl_3$)



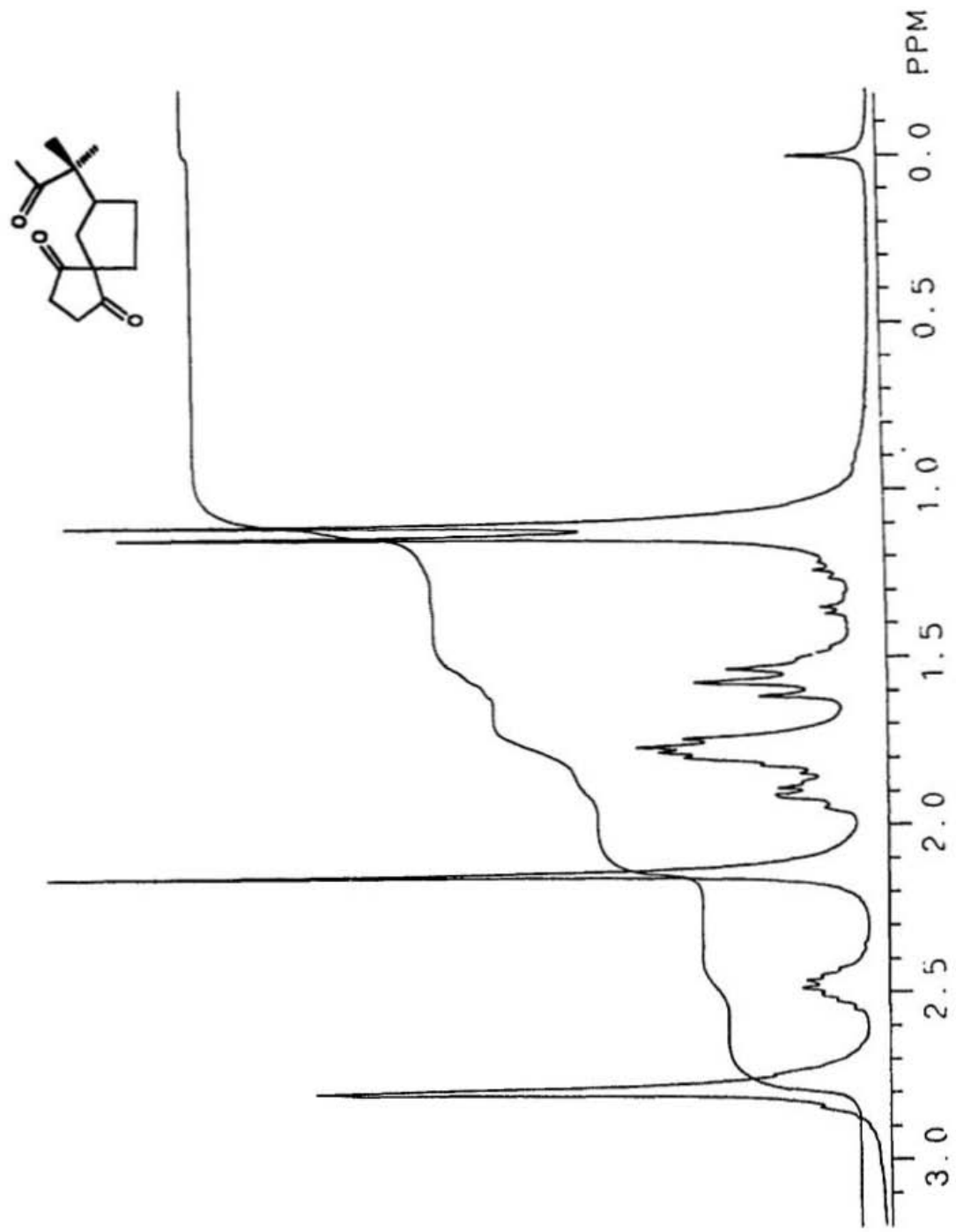
133 ($CDCl_3$)



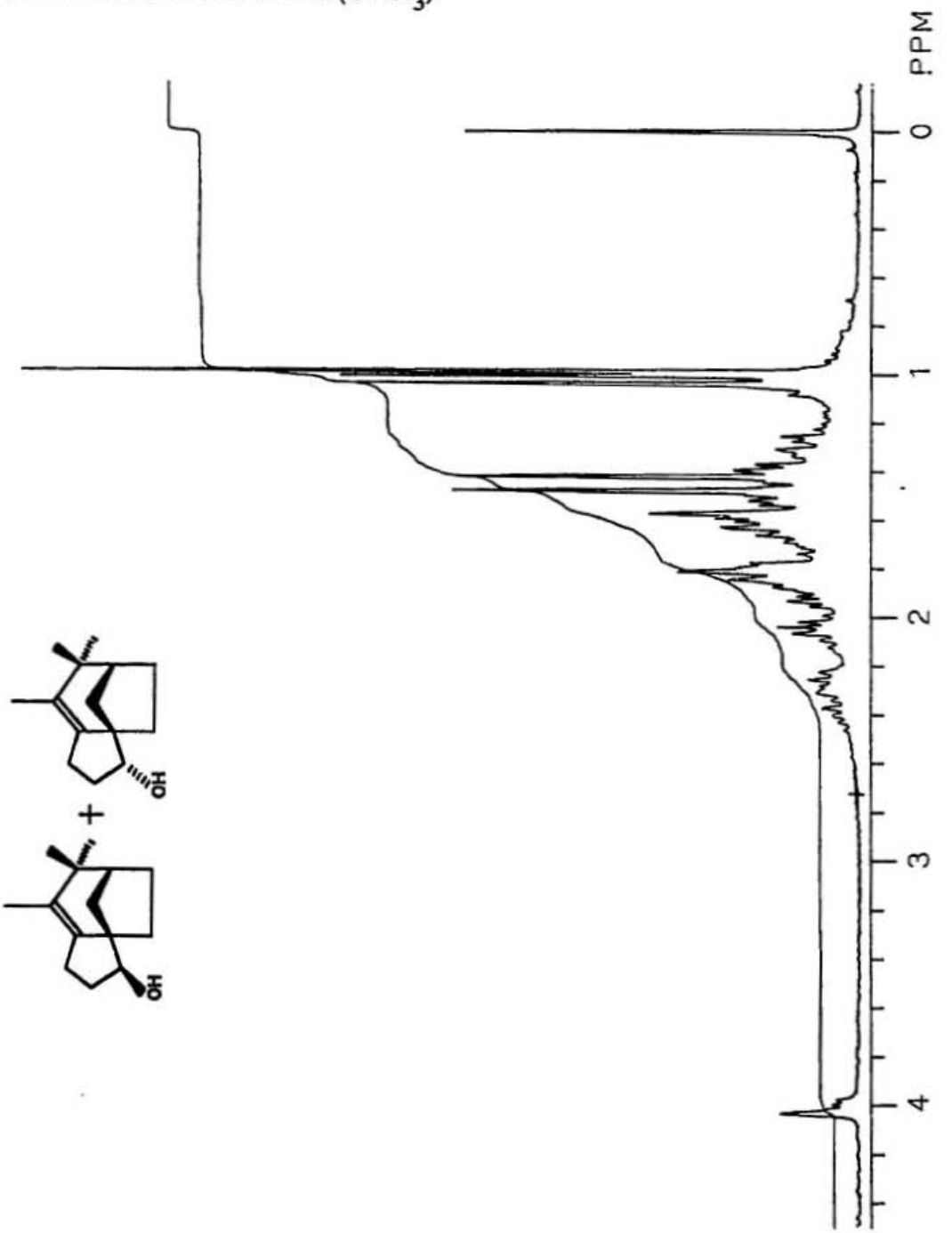
139 ($CDCl_3$)



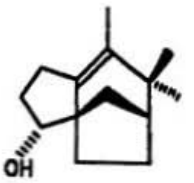
106 ($CDCl_3$)



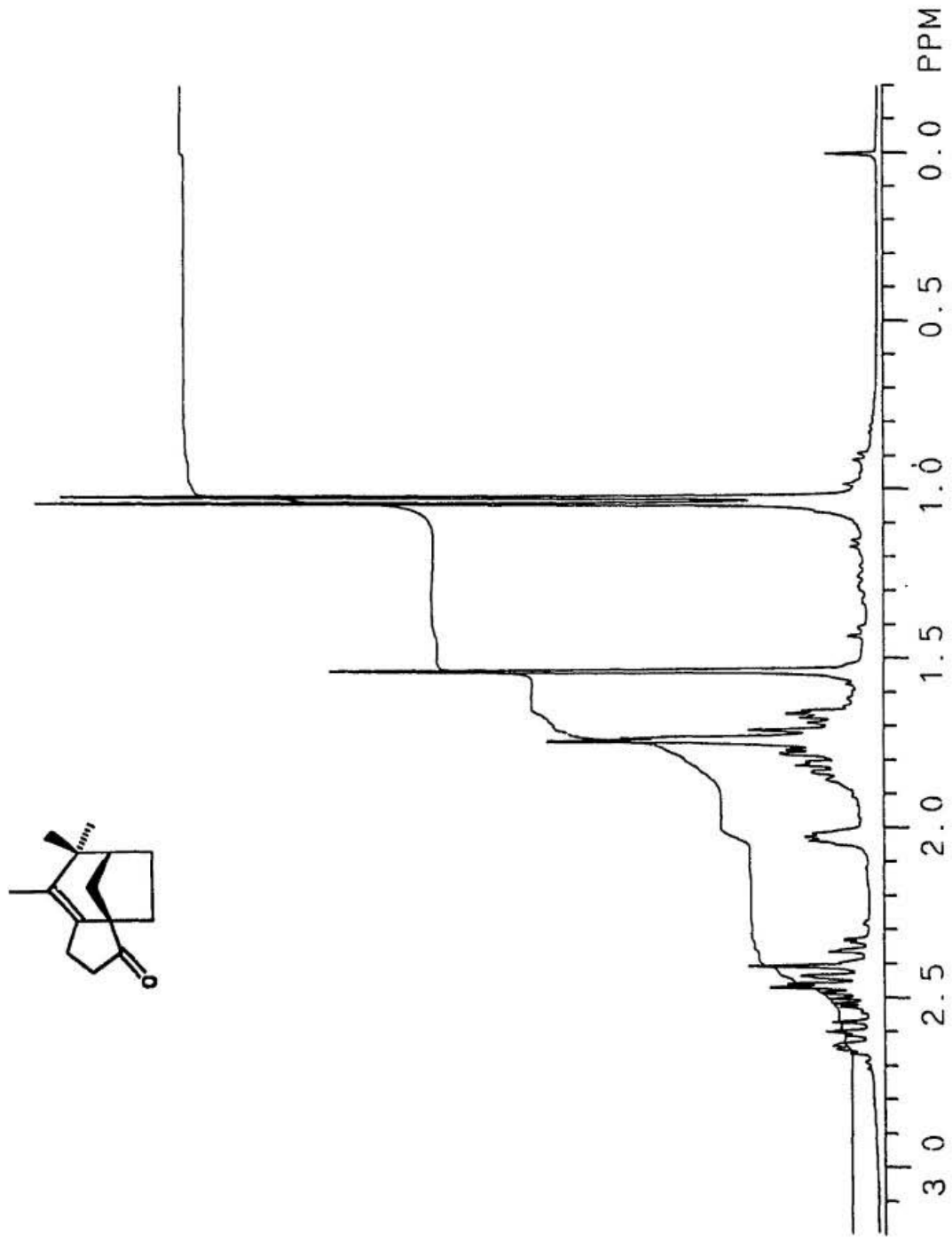
1 : 1 Mixture of 144a and 144b ($CDCl_3$)



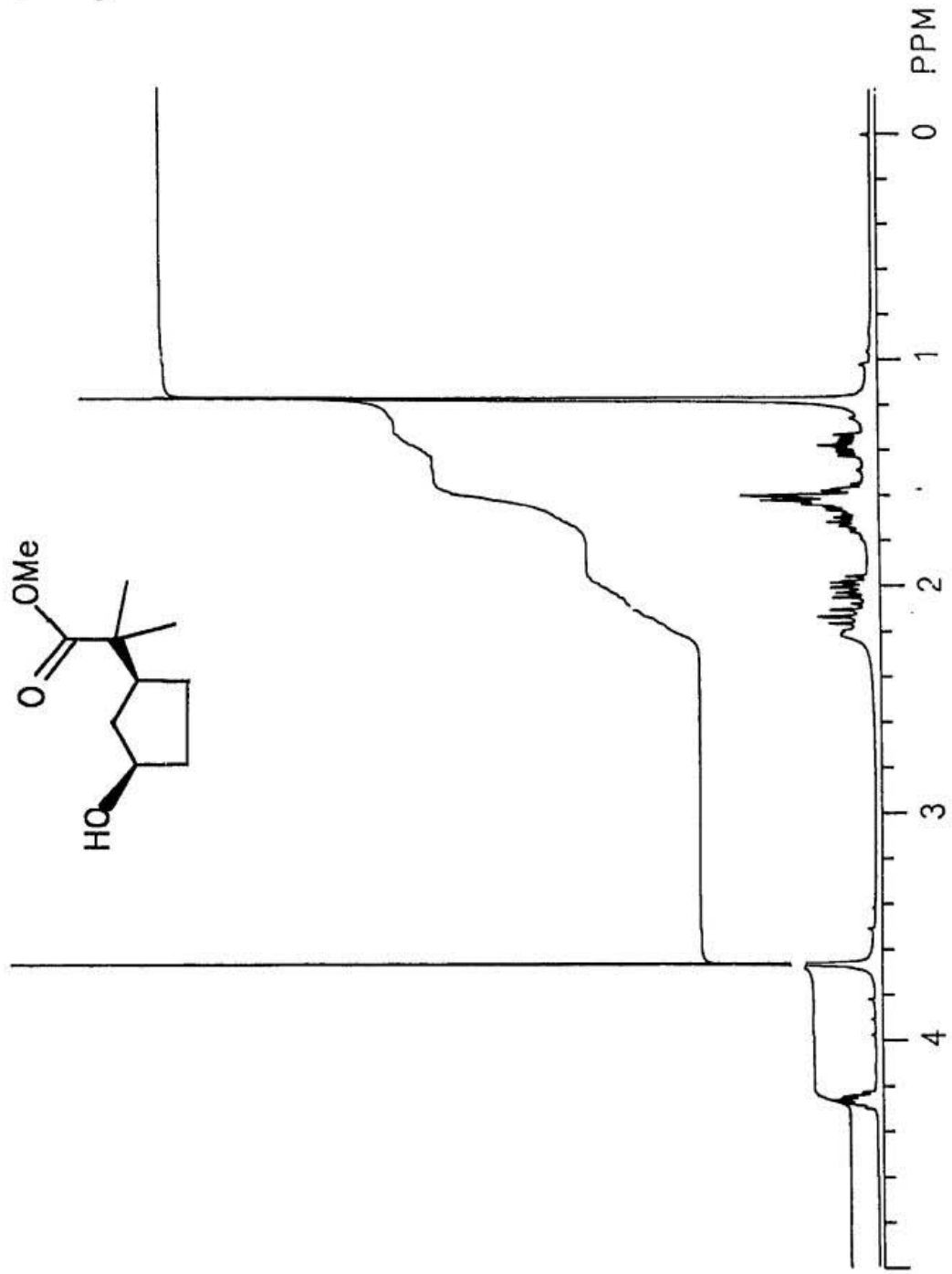
144b ($CDCl_3$)



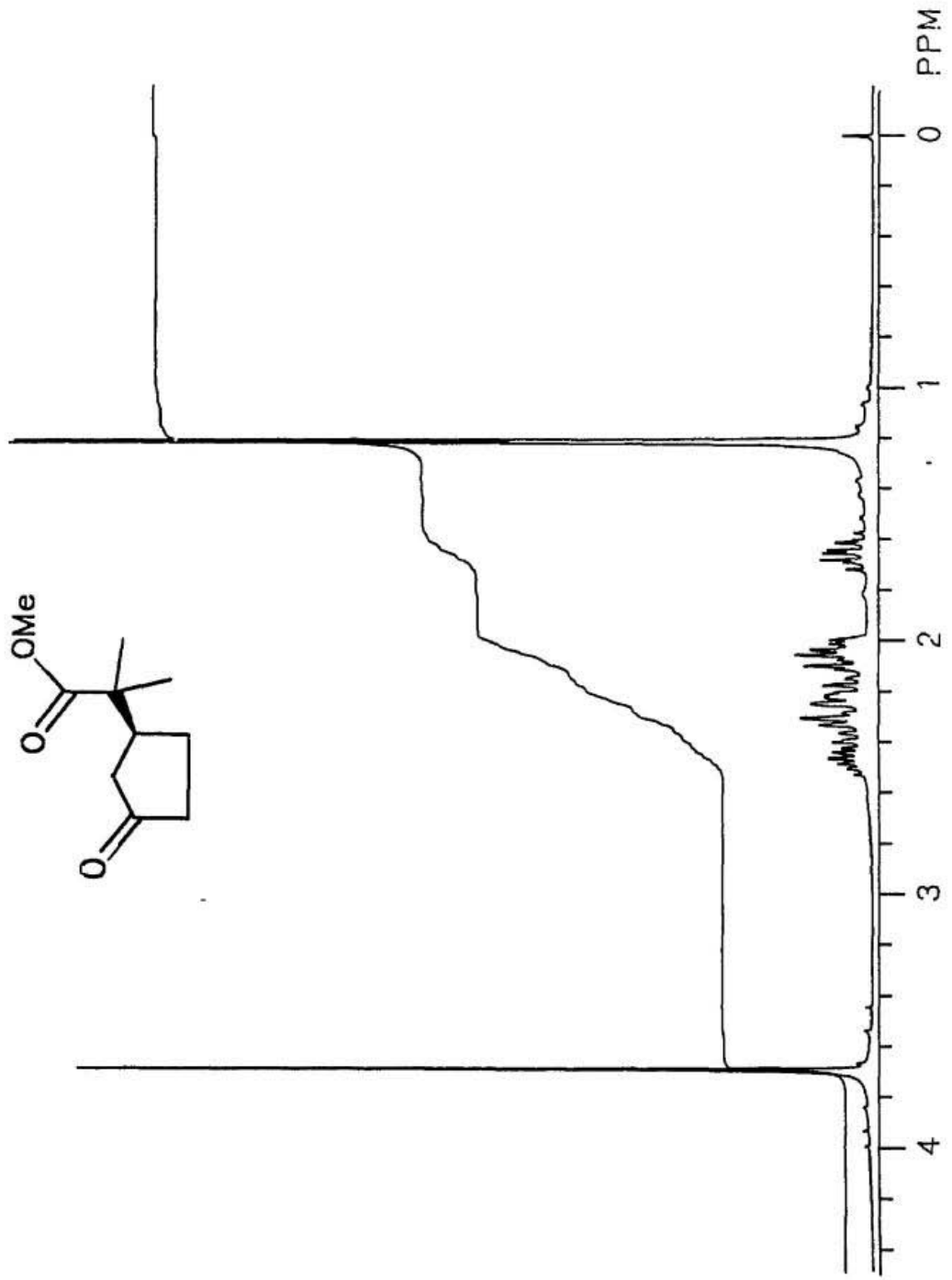
65 ($CDCl_3$)



150 ($CDCl_3$)



151 ($CDCl_3$)



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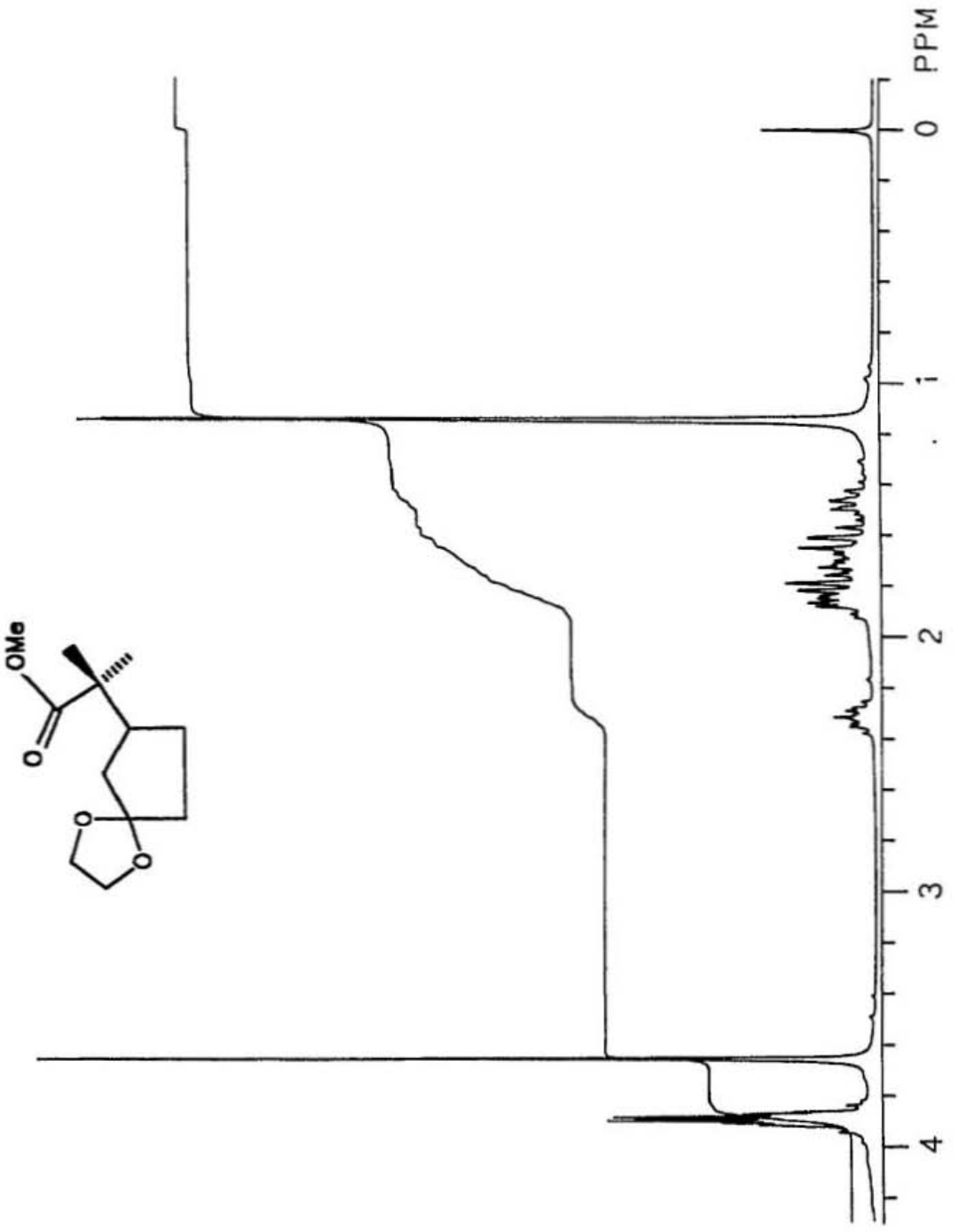
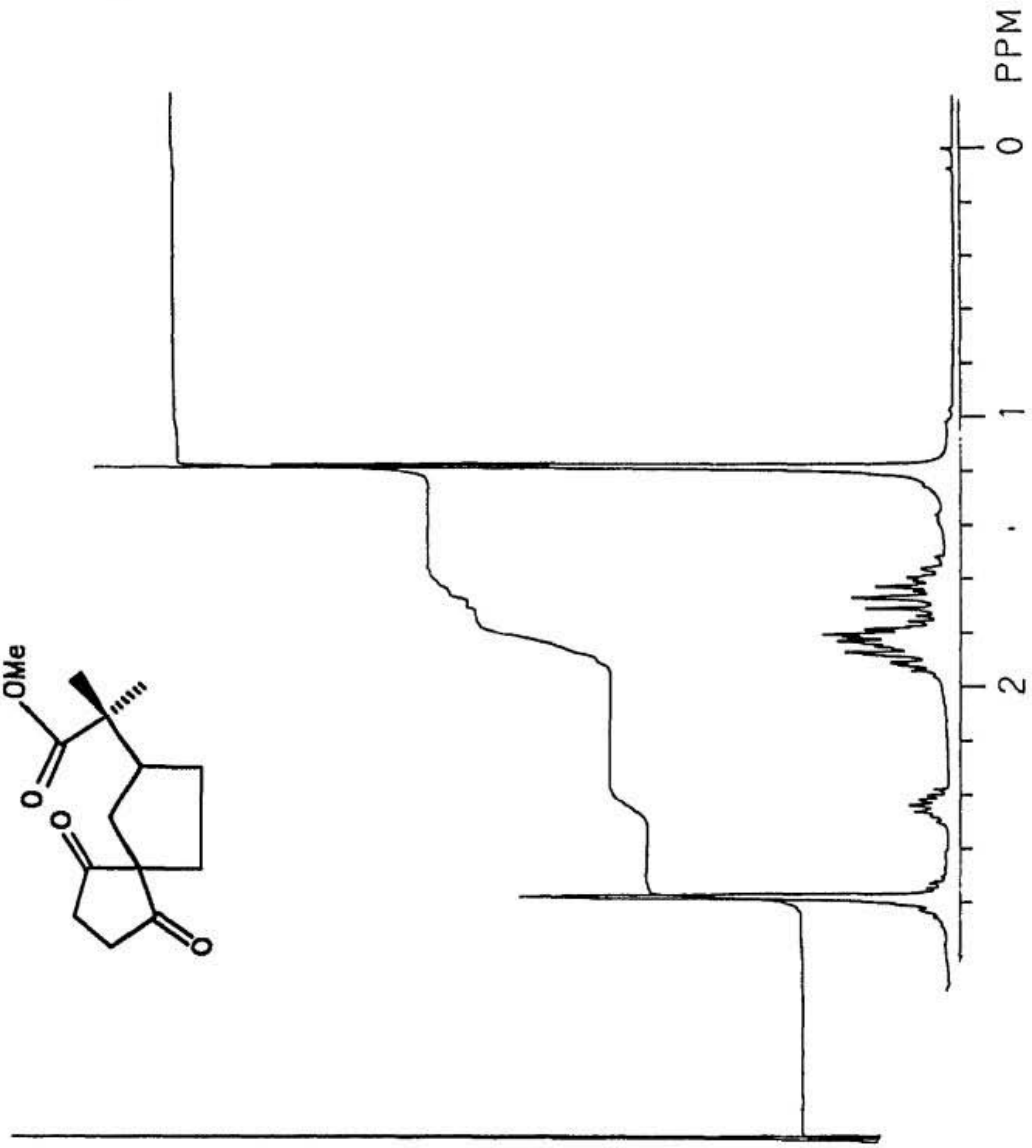
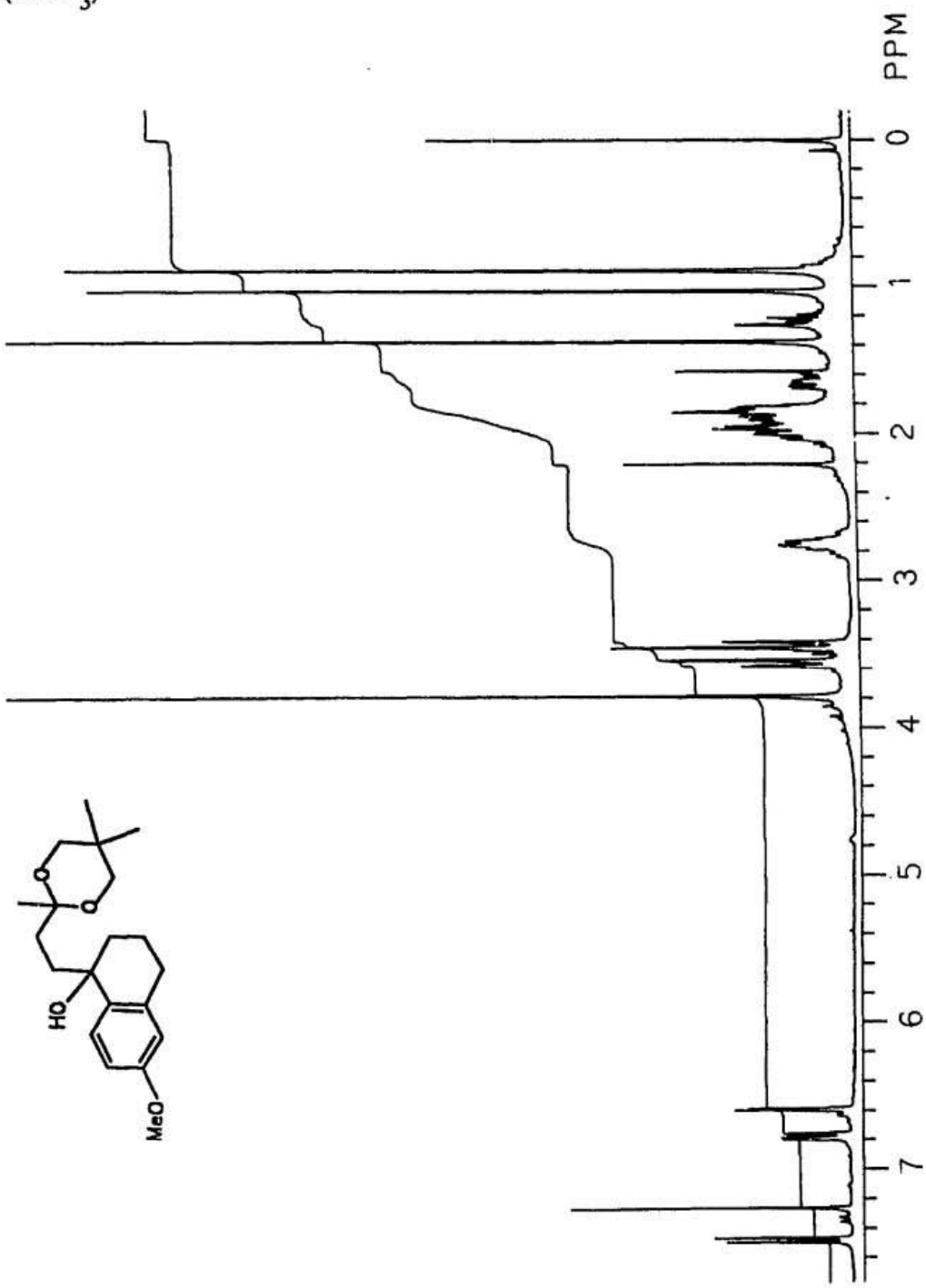


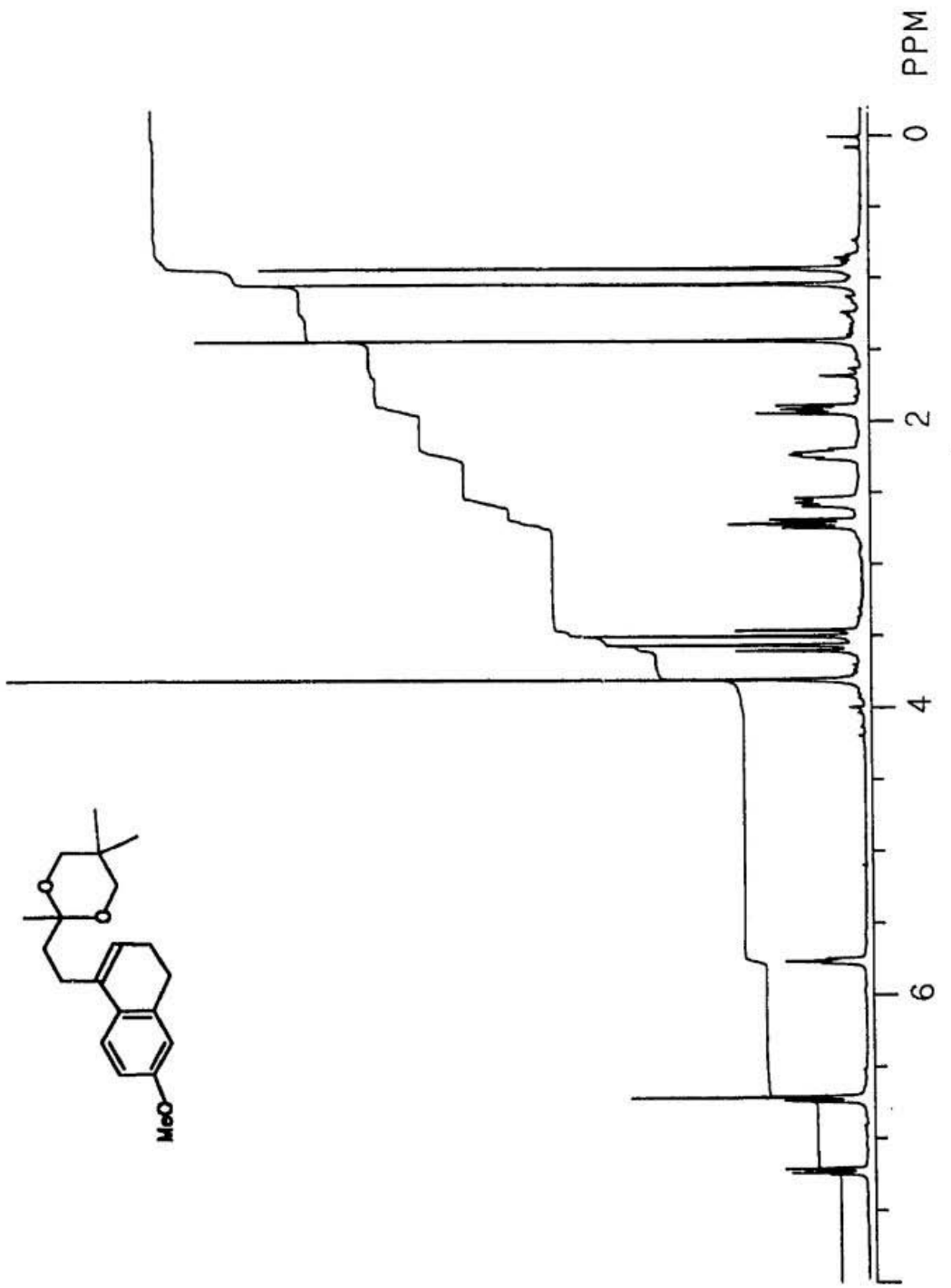
148 ($CDCl_3$)



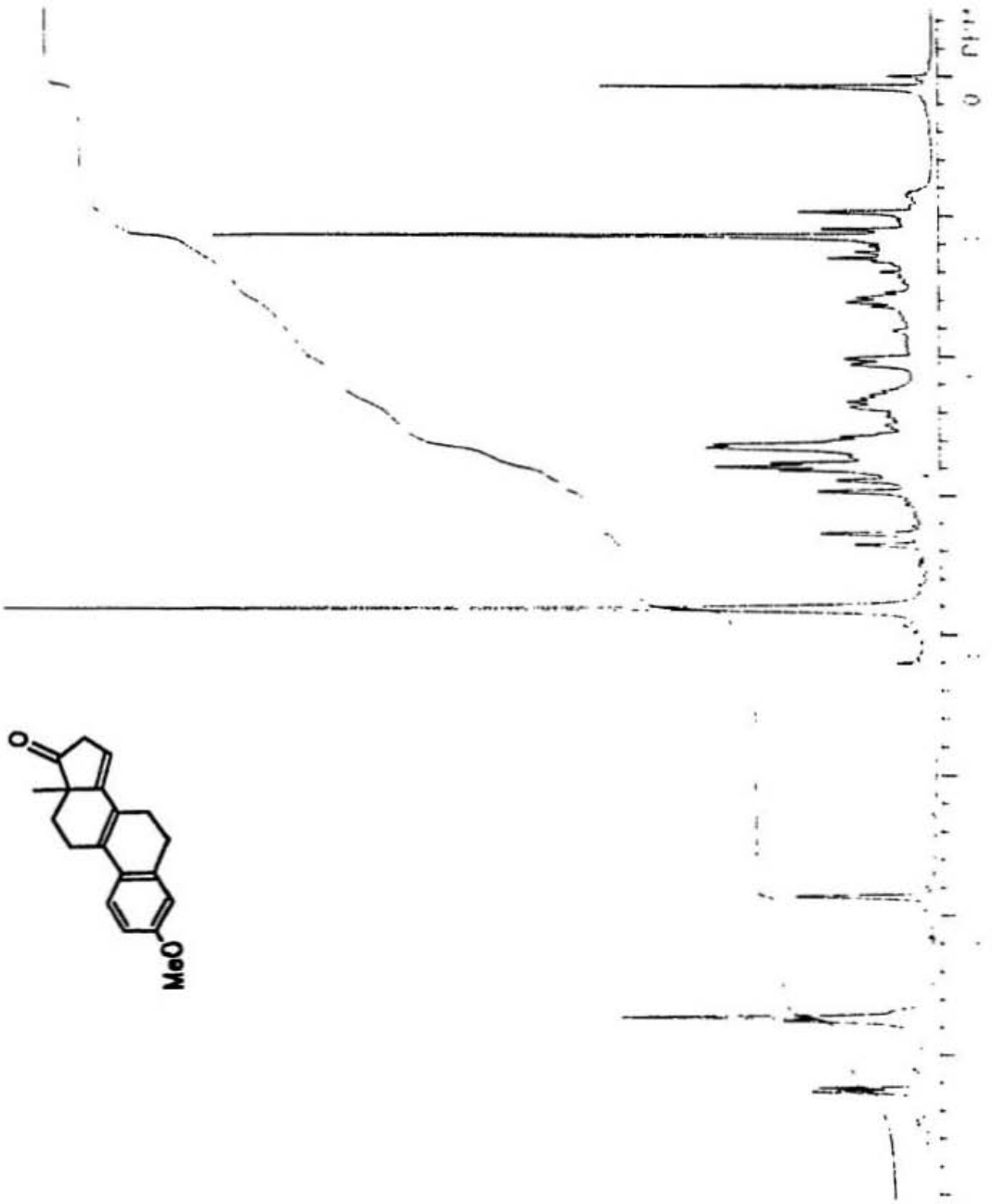
226 ($CDCl_3$)



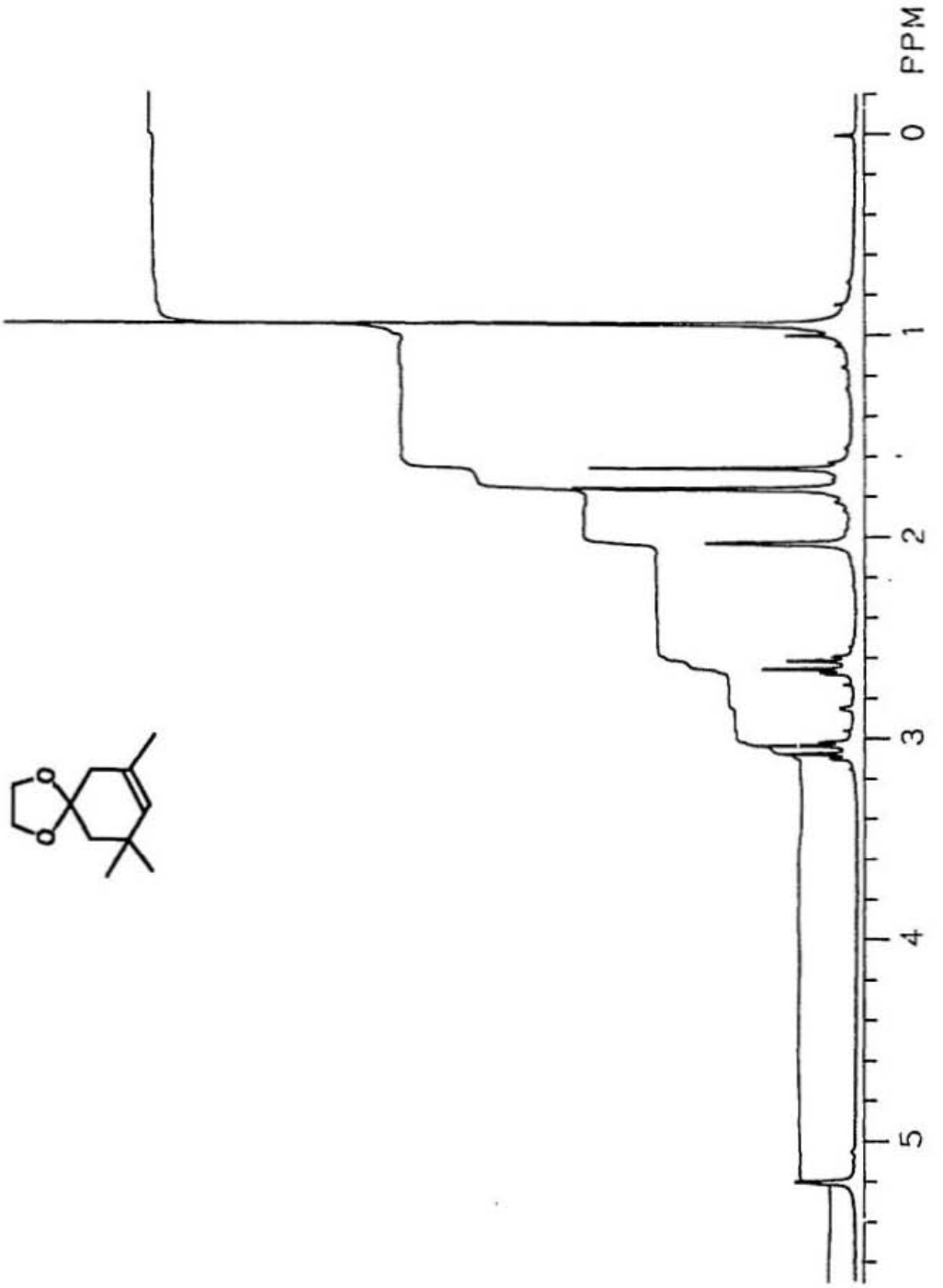
219b ($CDCl_3$)



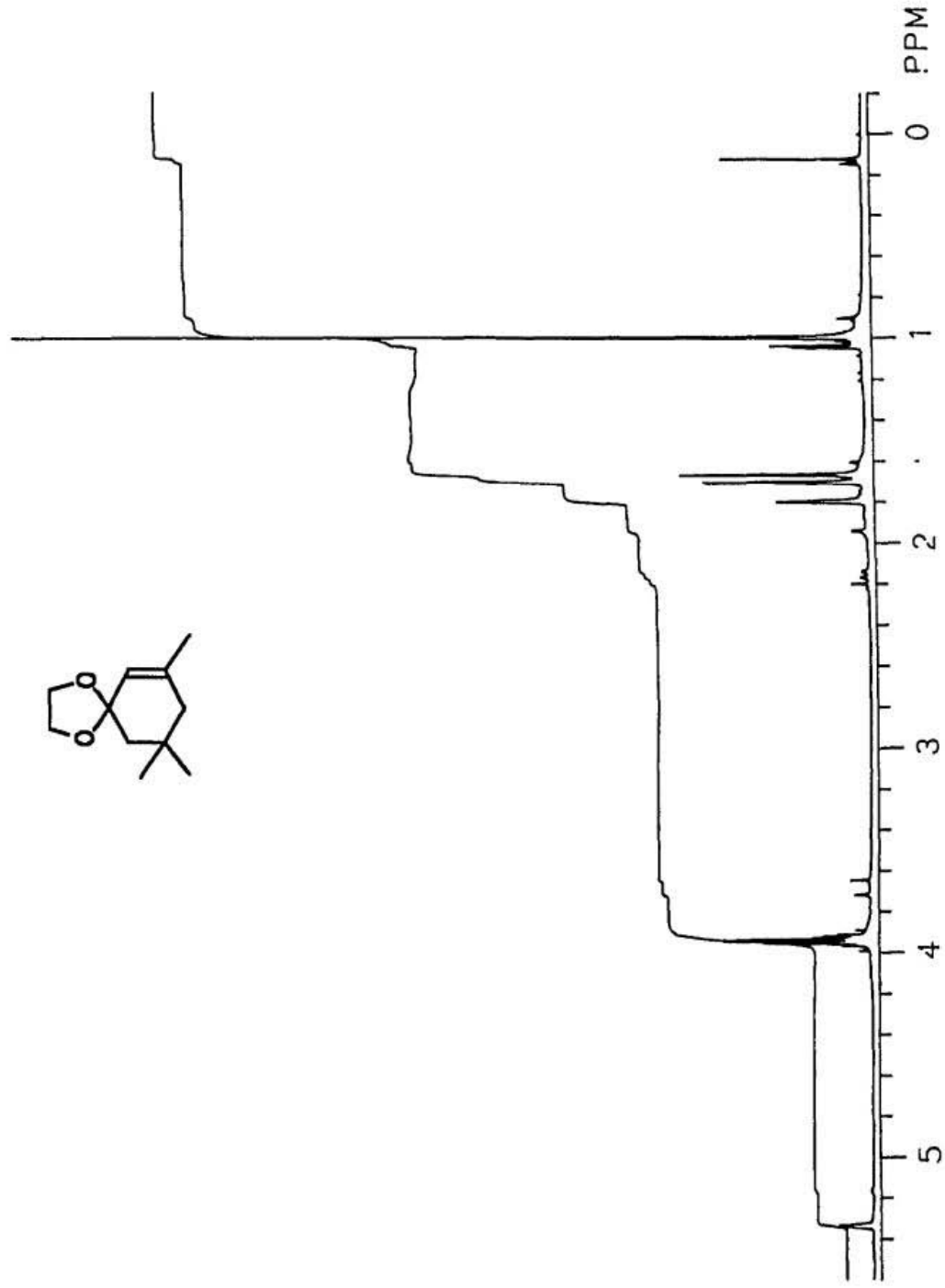
161 ($CDCl_3$)



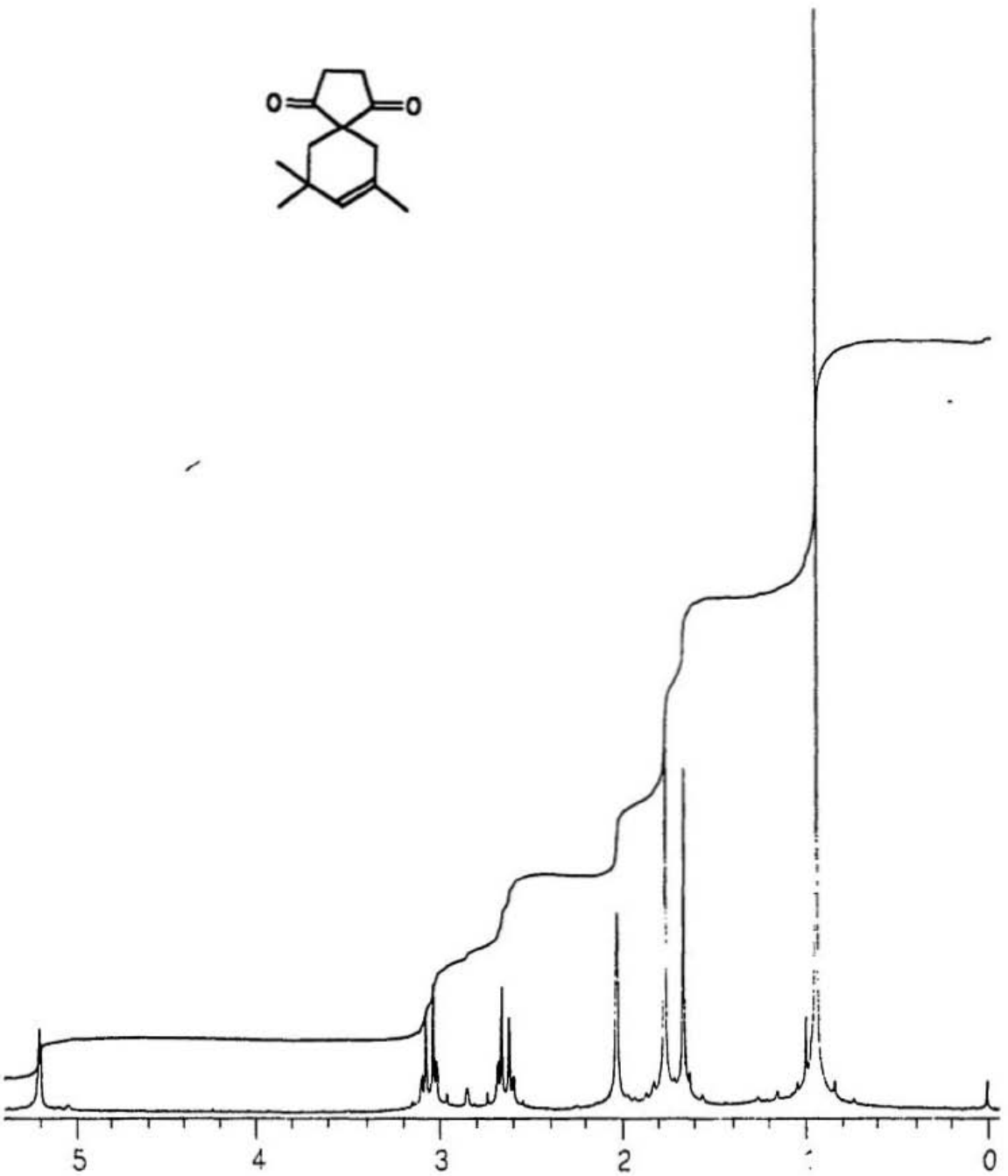
382 ($CDCl_3$)



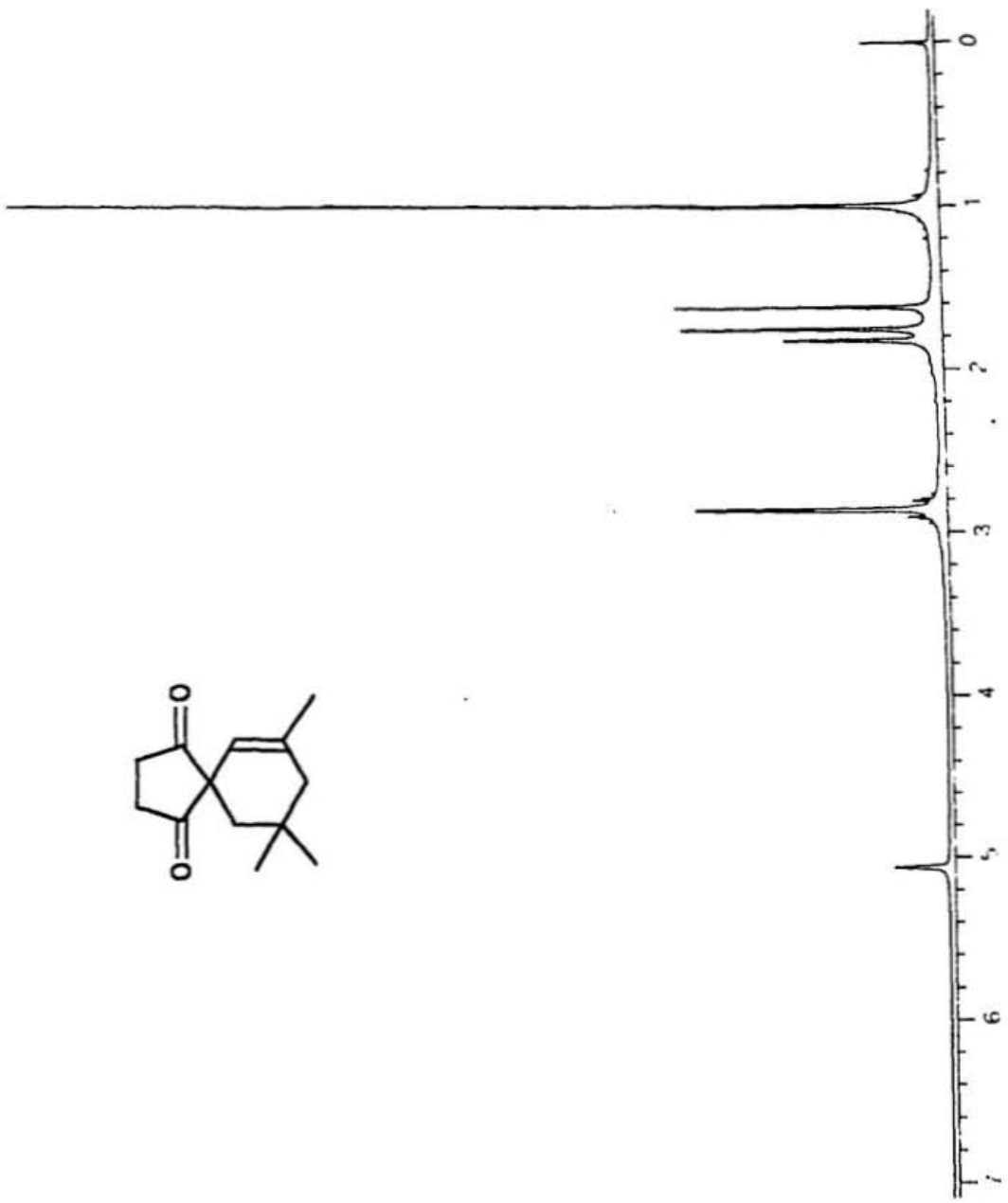
386 ($CDCl_3$)



381 ($CDCl_3$)



389 ($CDCl_3$)



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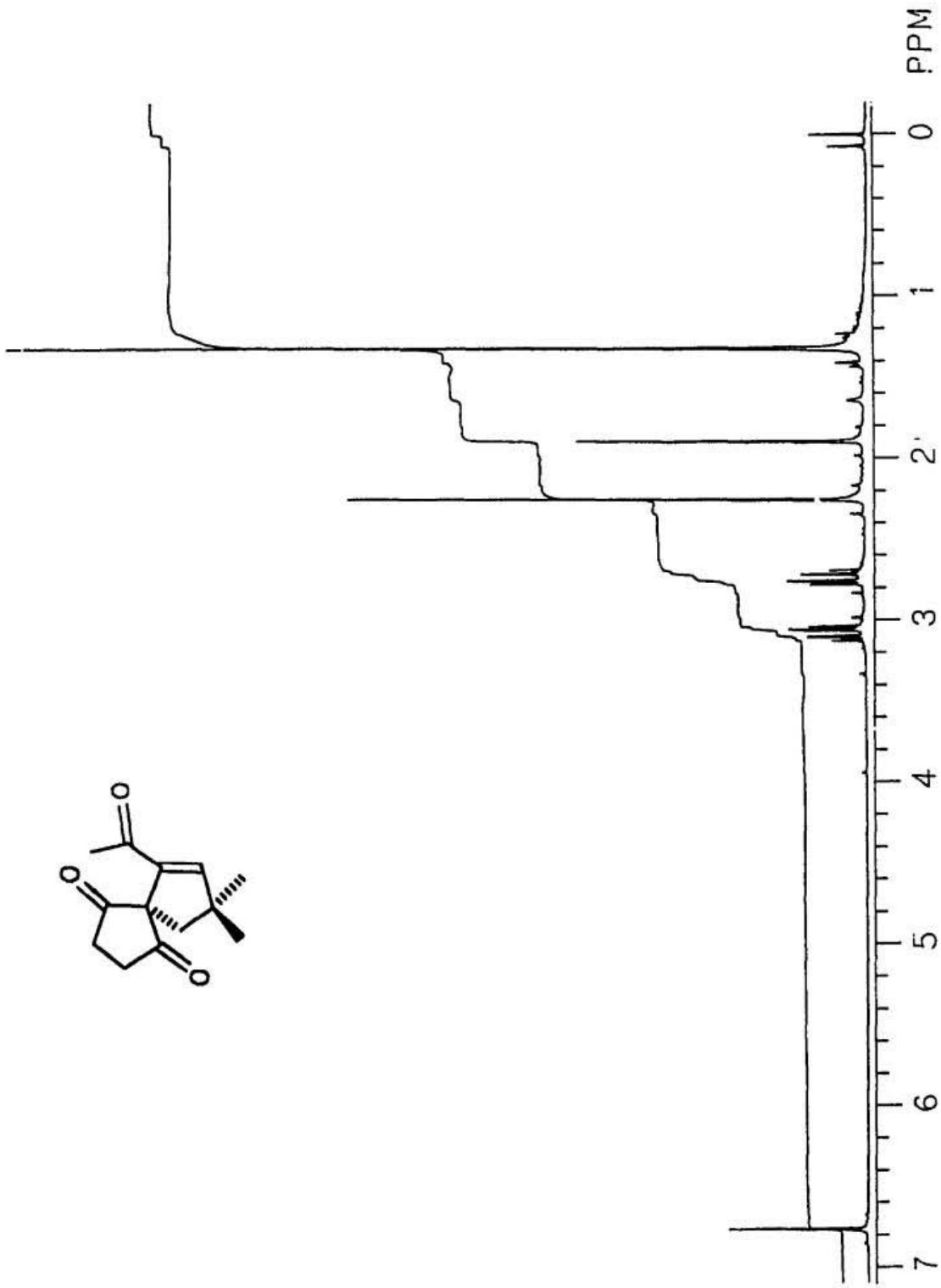
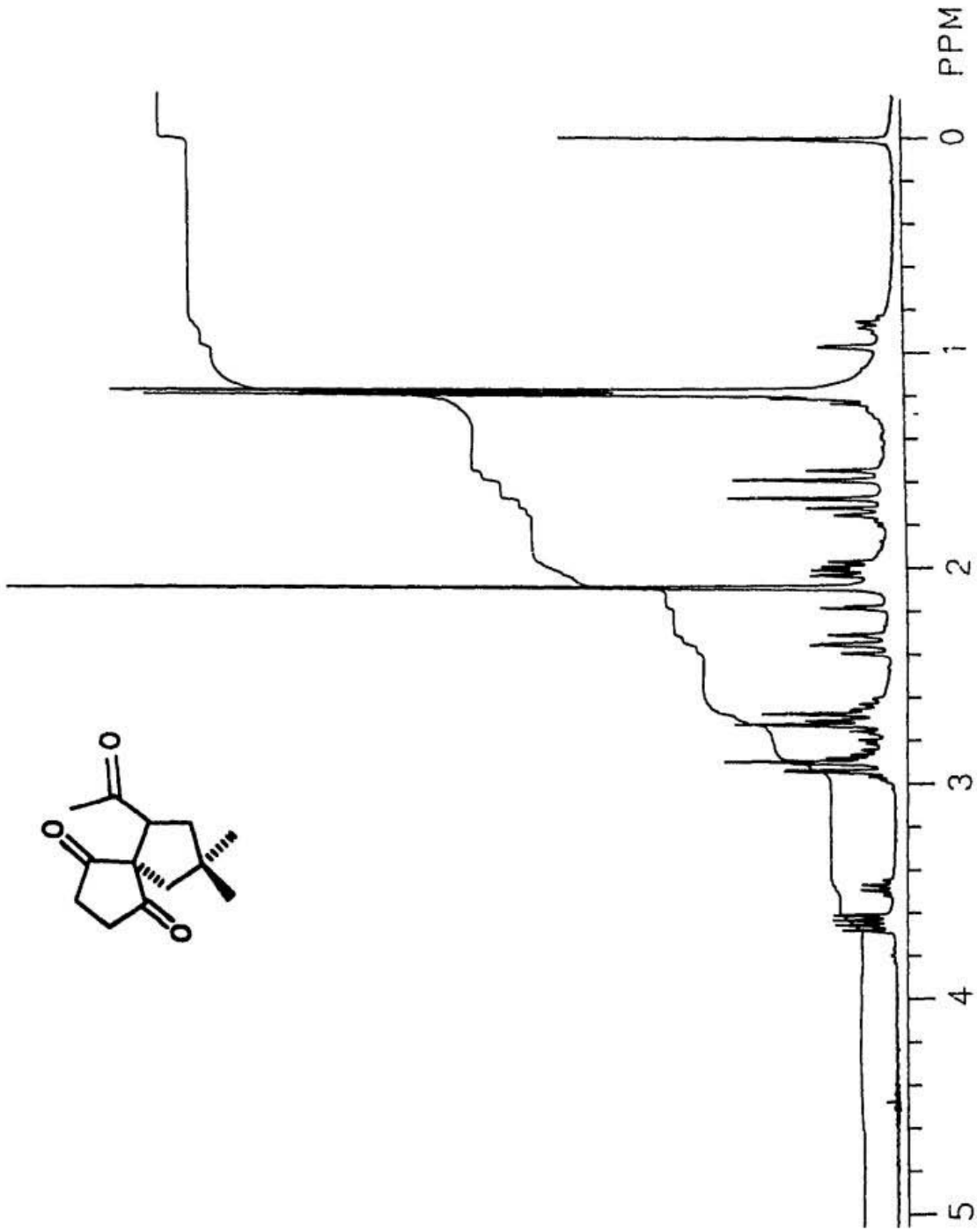
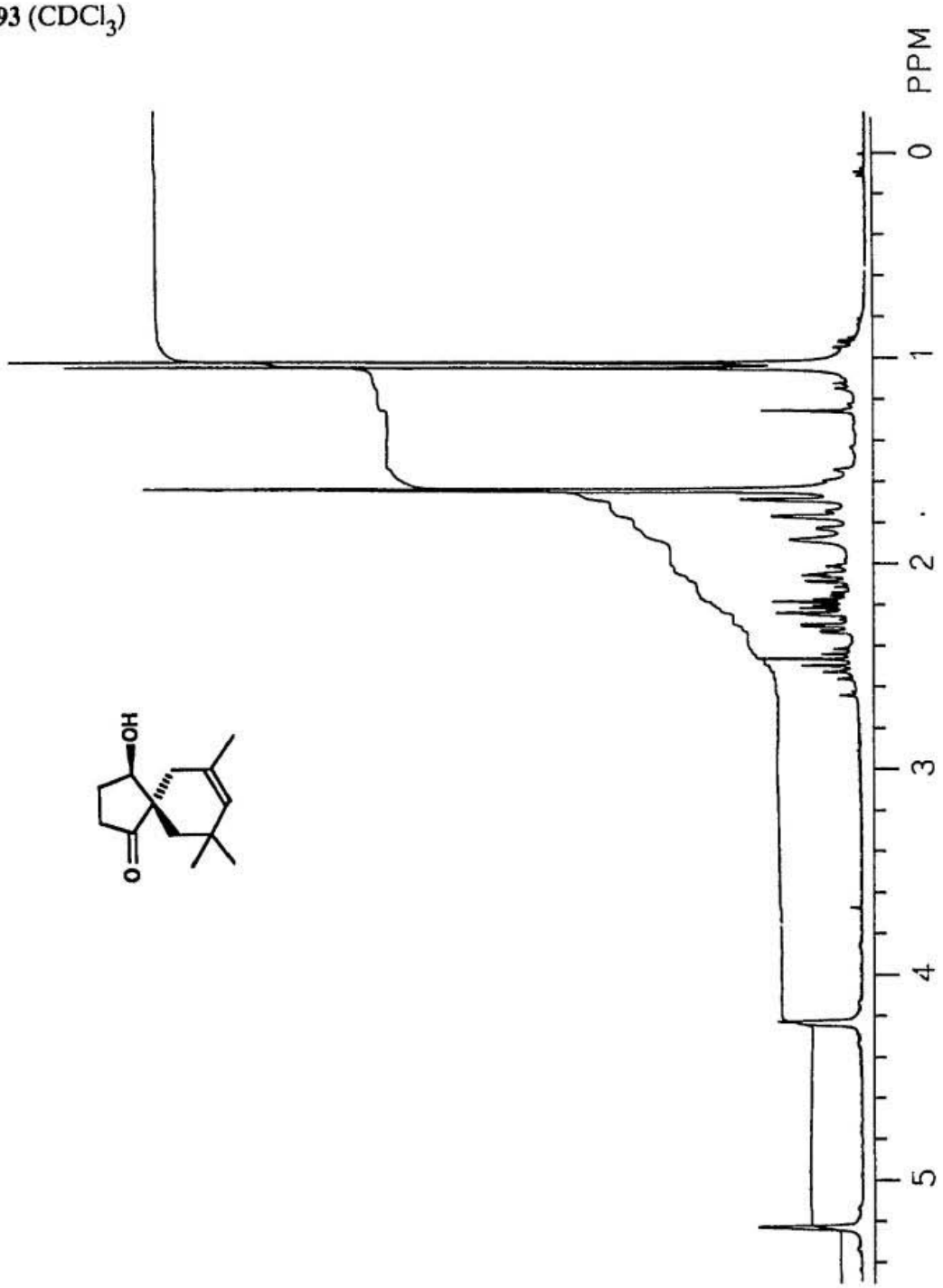


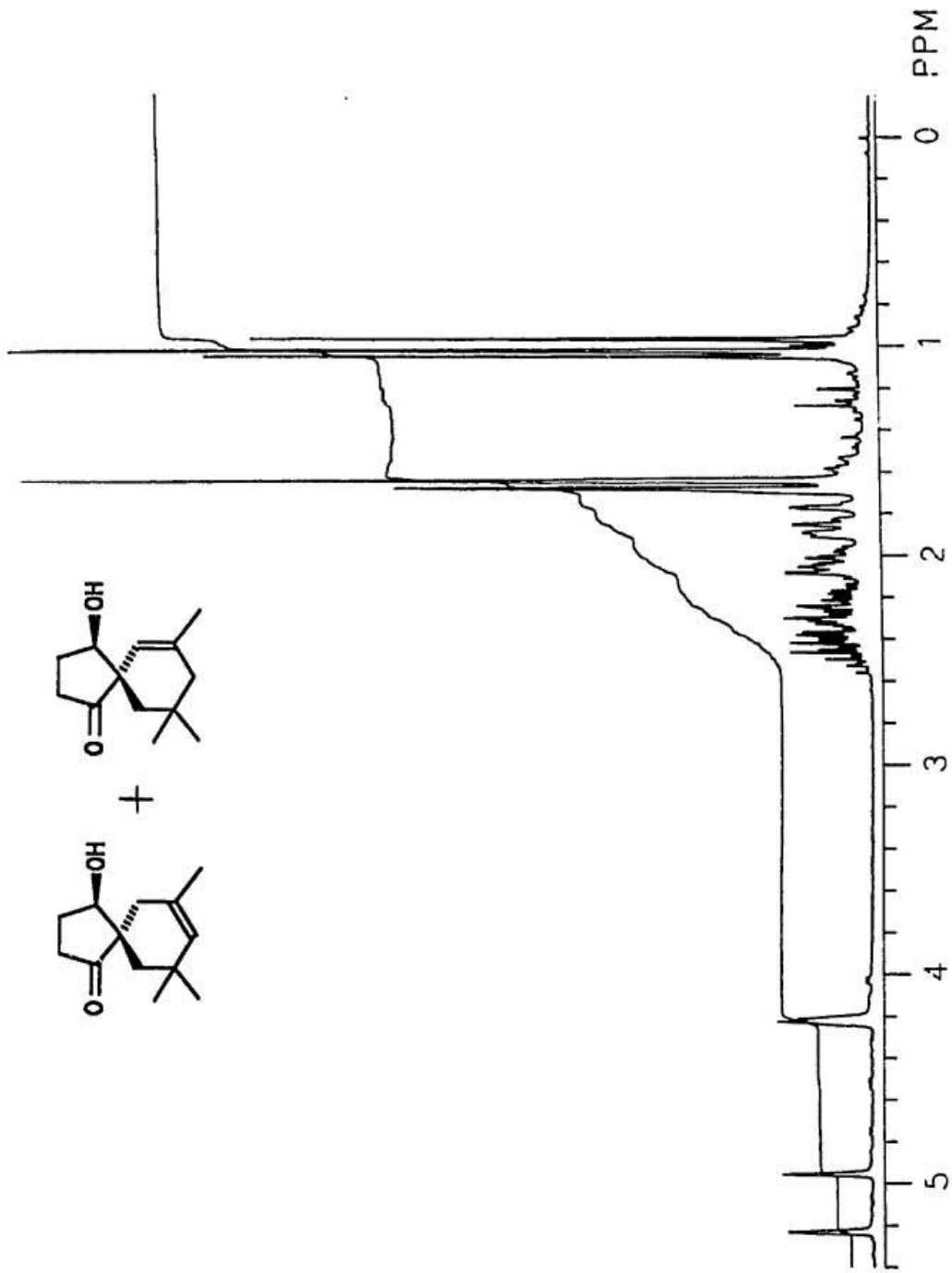
391 ($CDCl_3$)



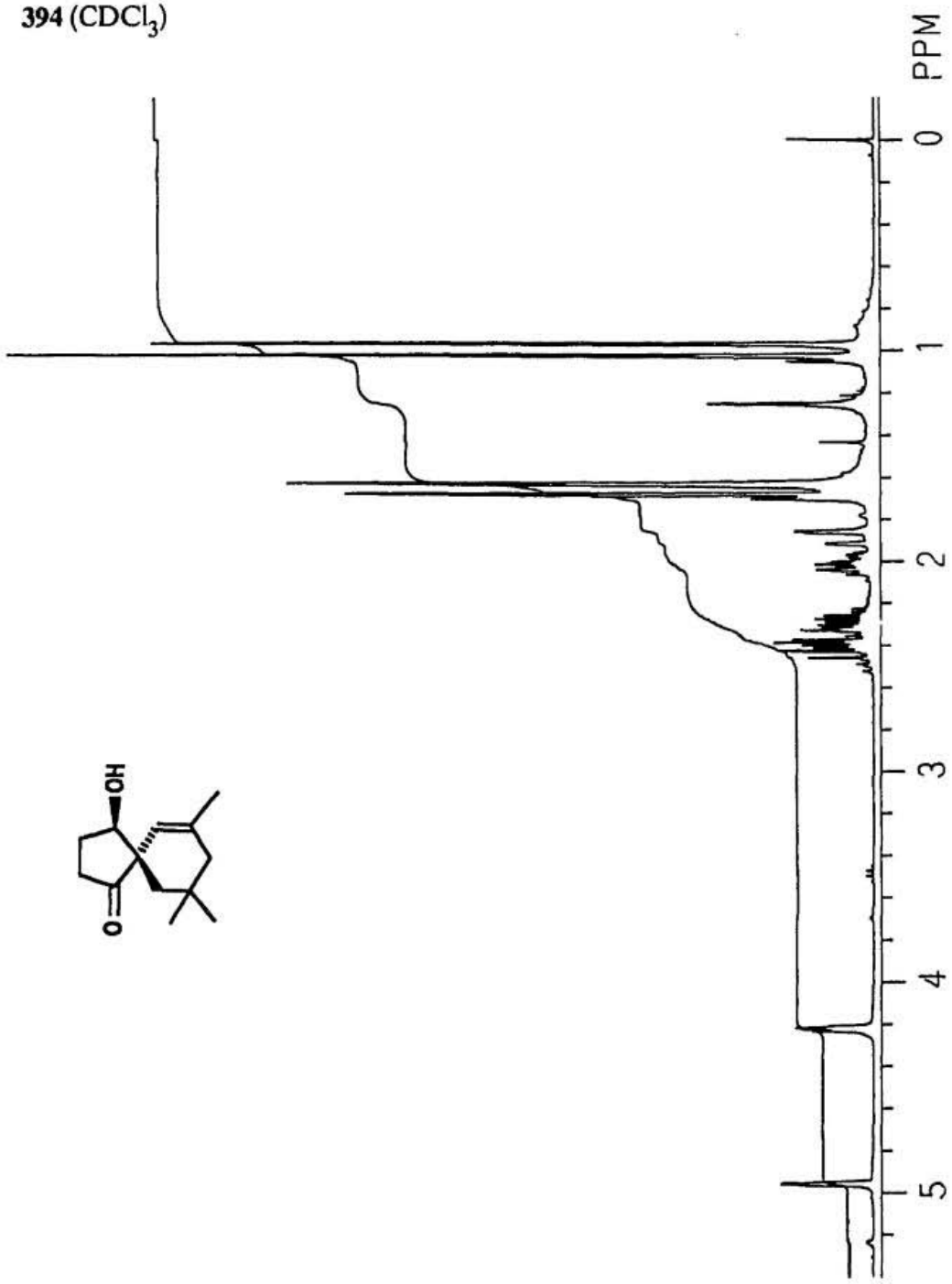
393 ($CDCl_3$)



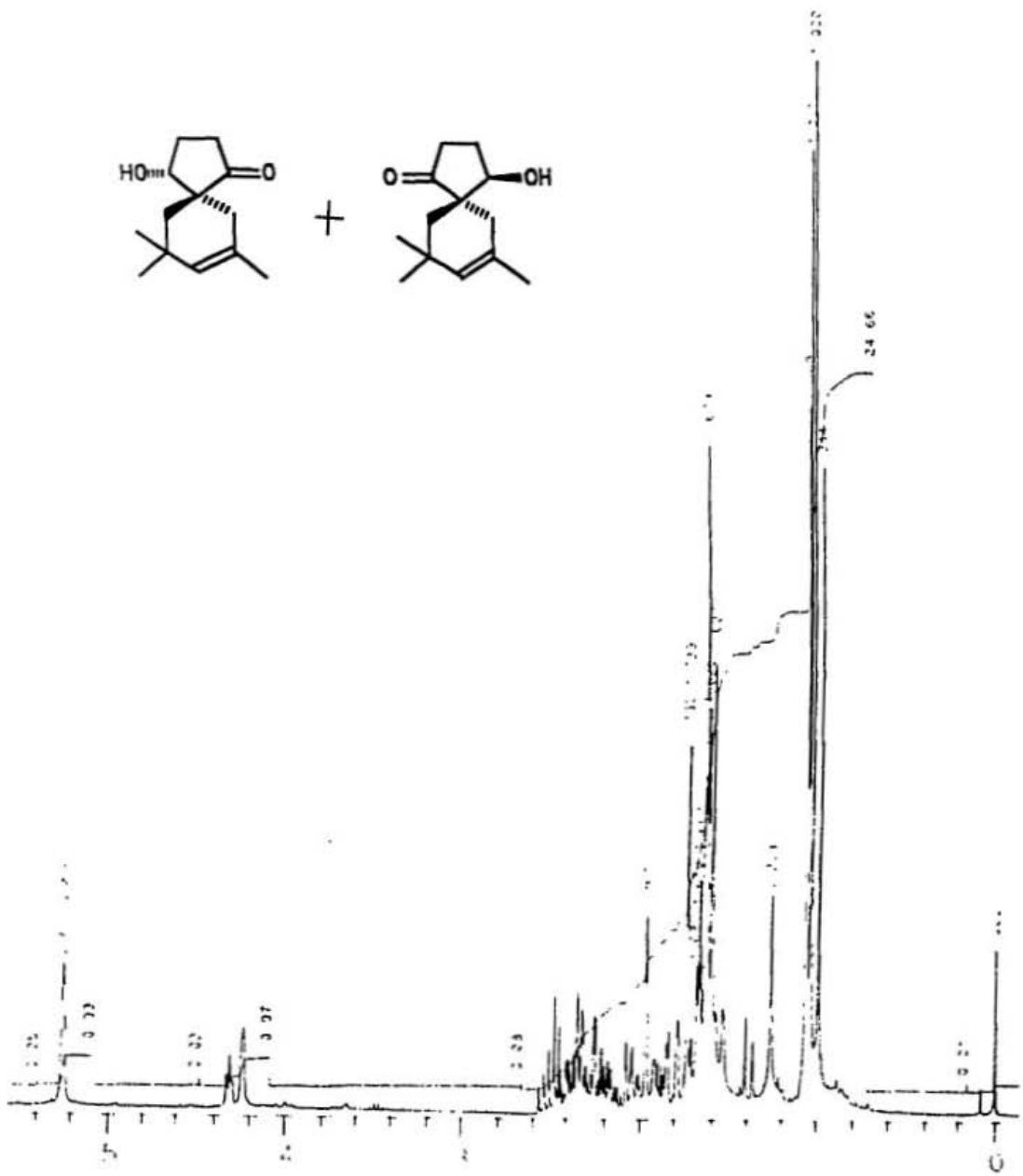
1 : 1 Mixture of 393 and 394 ($CDCl_3$)



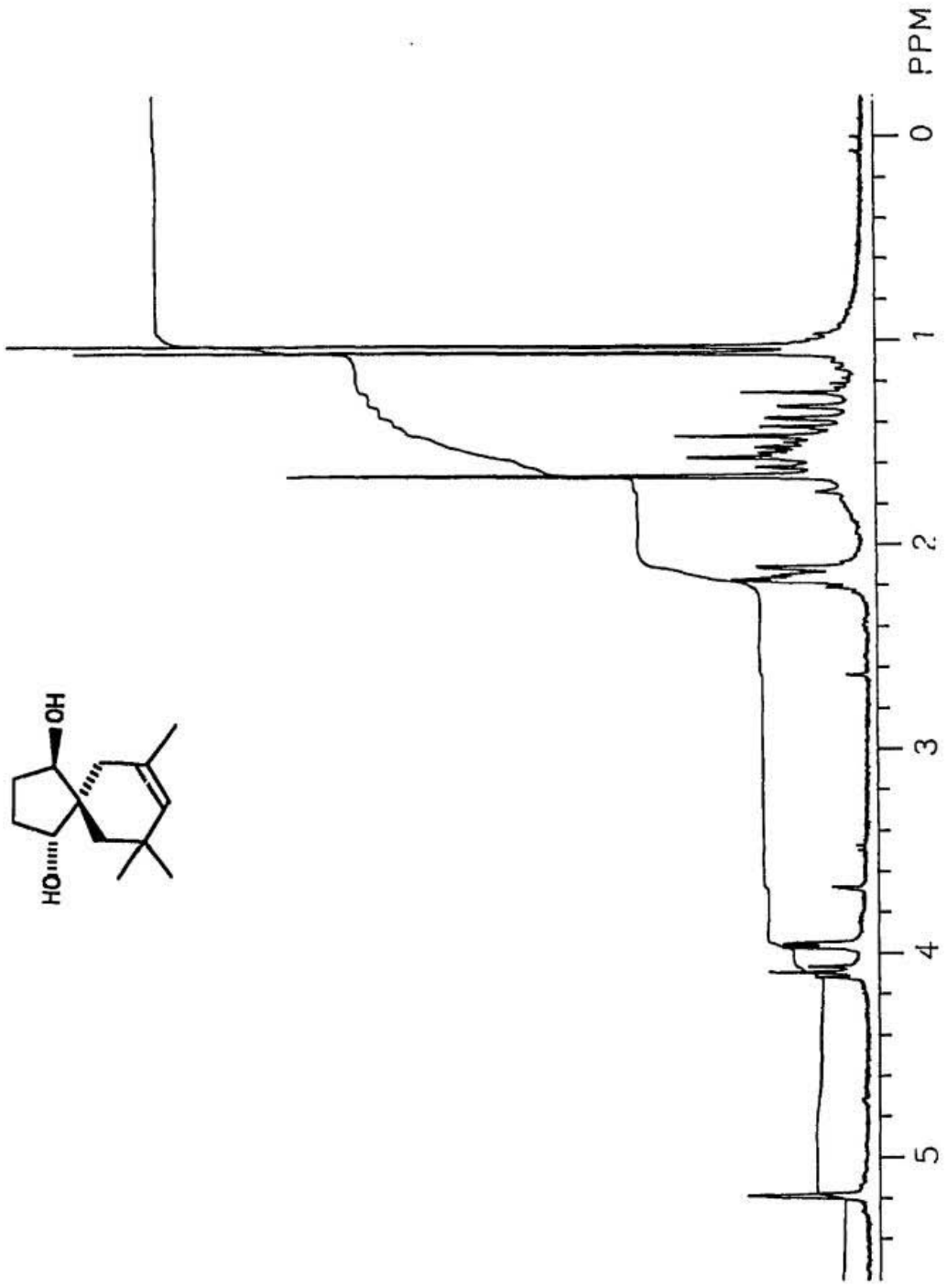
394 ($CDCl_3$)



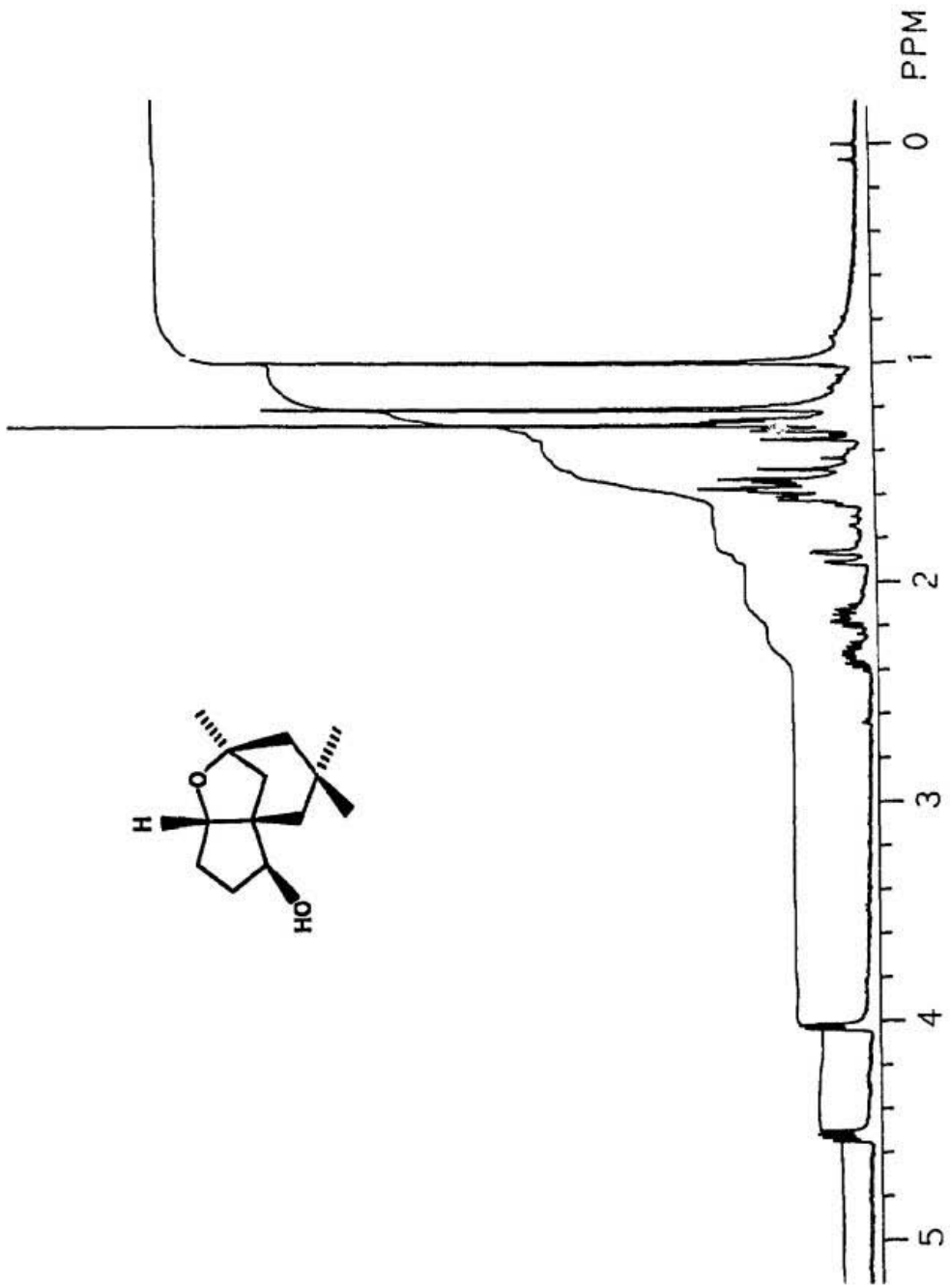
1 : 1 Mixture of 392 and 393 ($CDCl_3$)



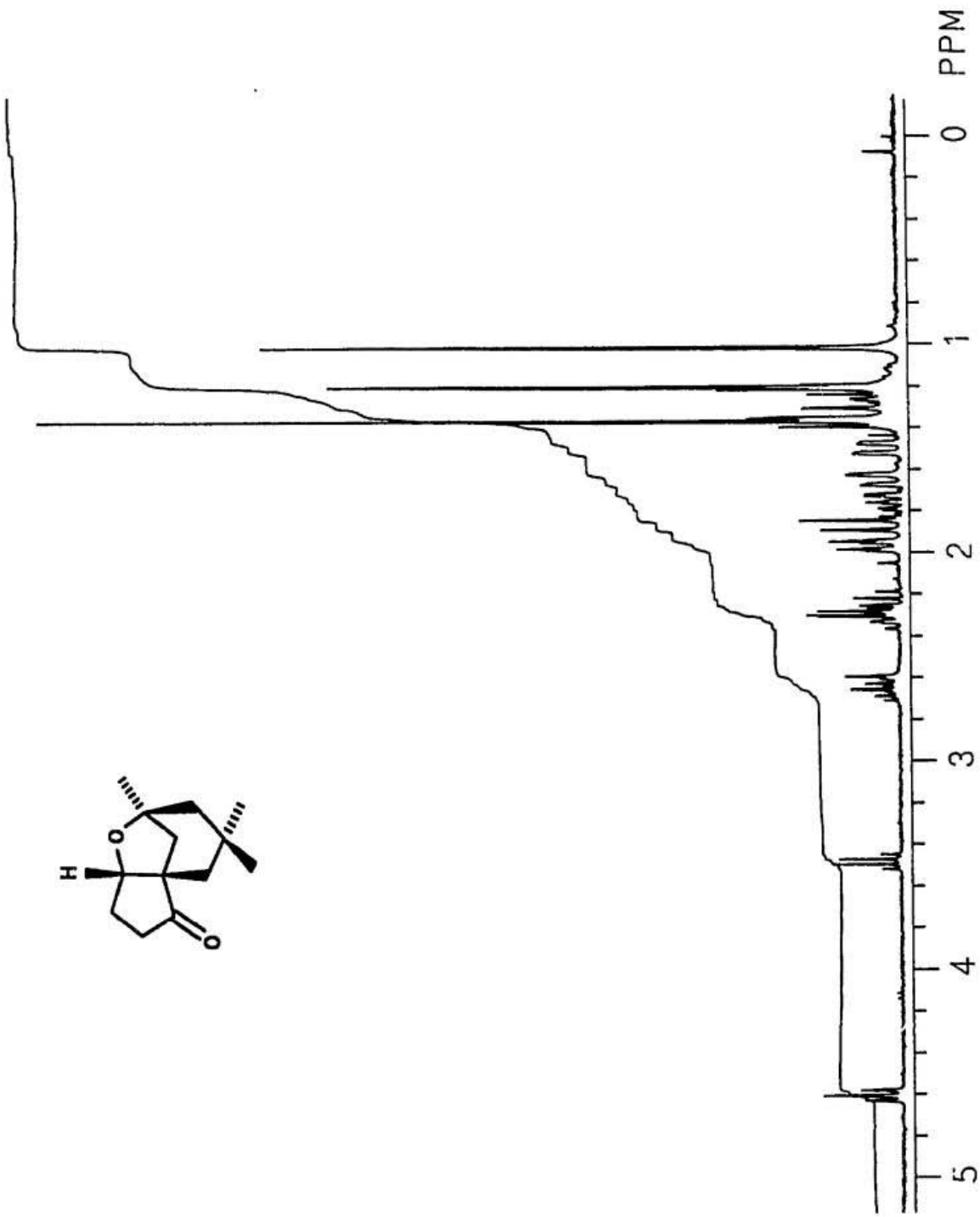
396 ($CDCl_3$)



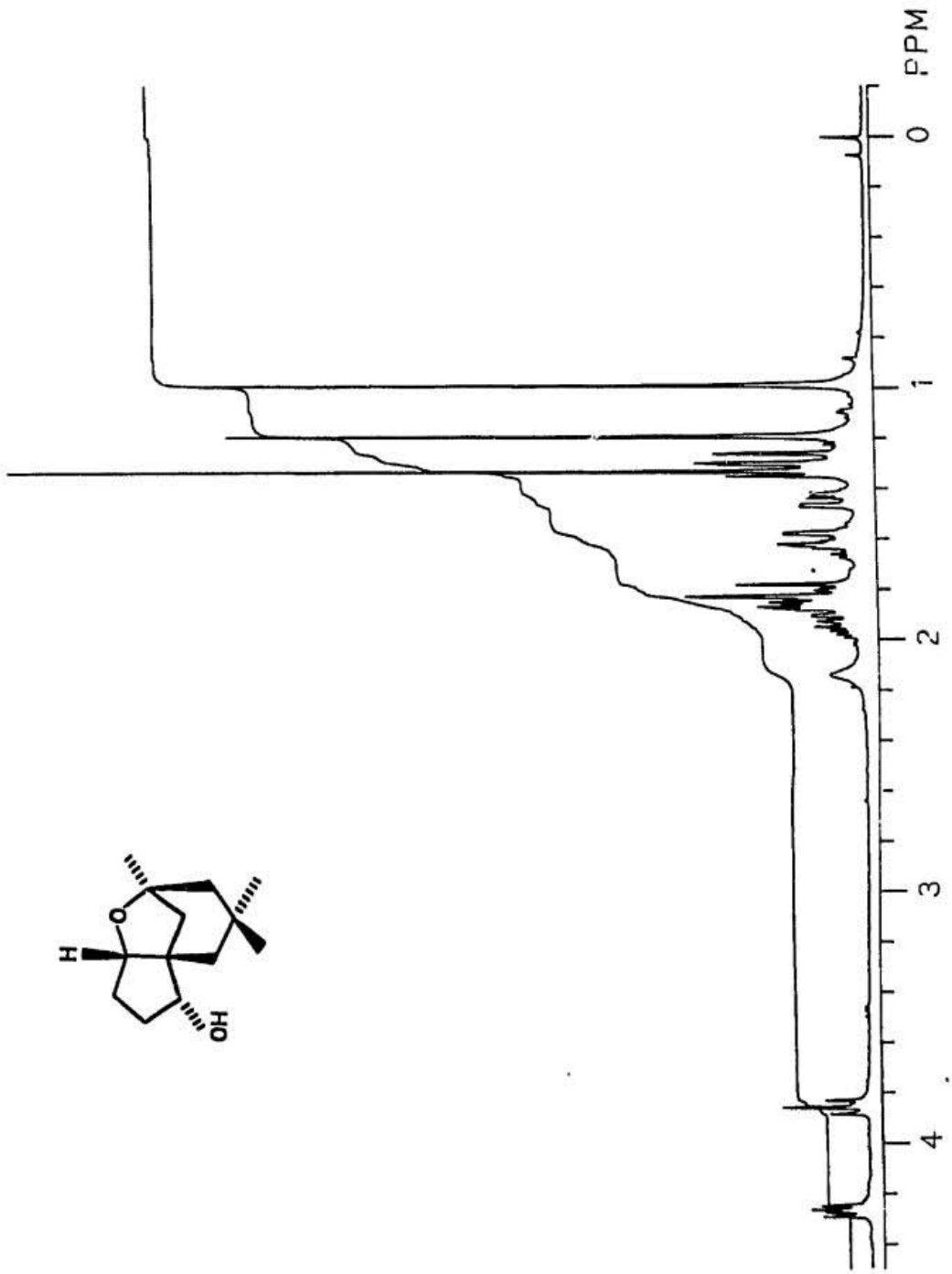
398 ($CDCl_3$)



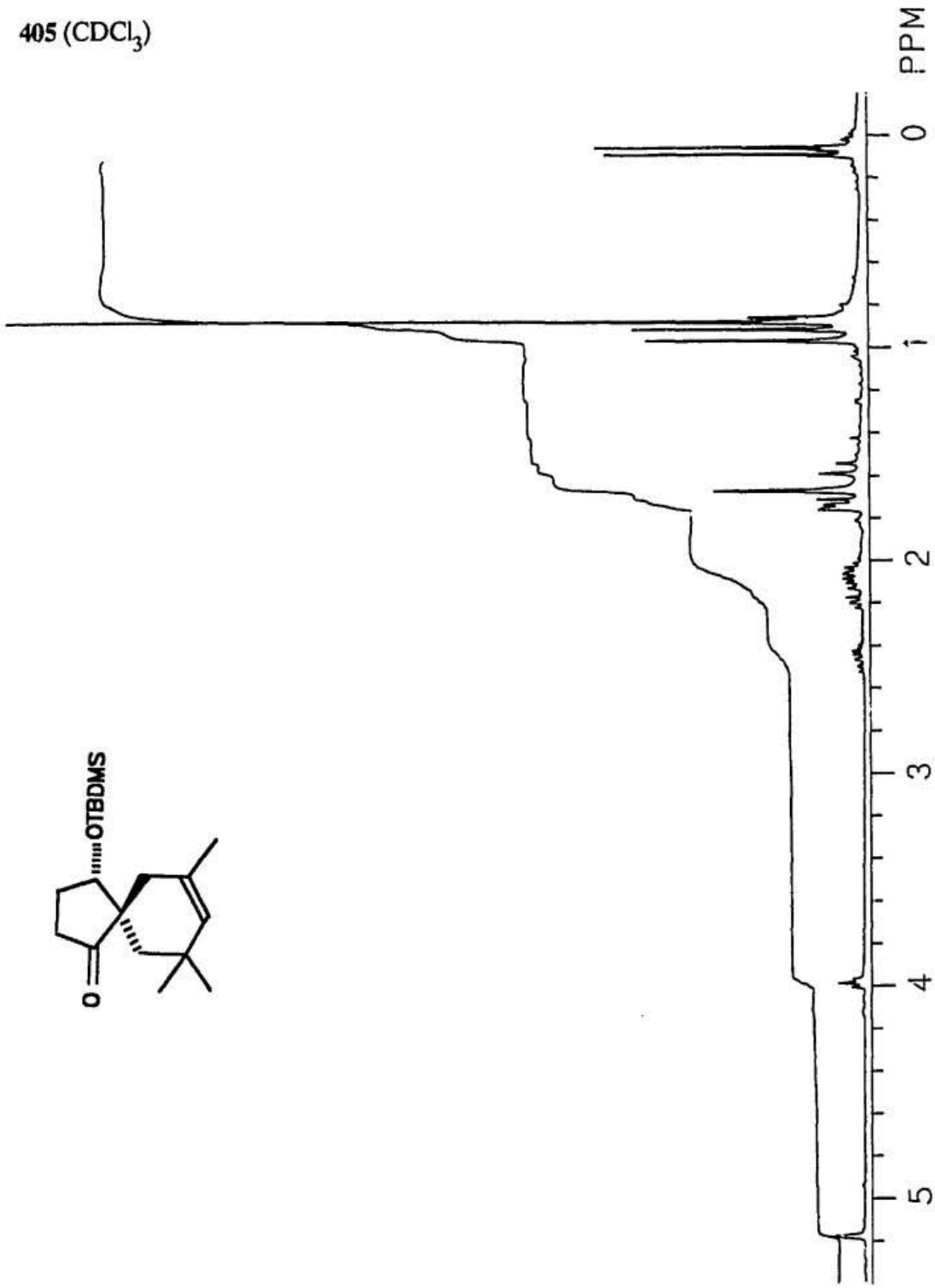
399 ($CDCl_3$)



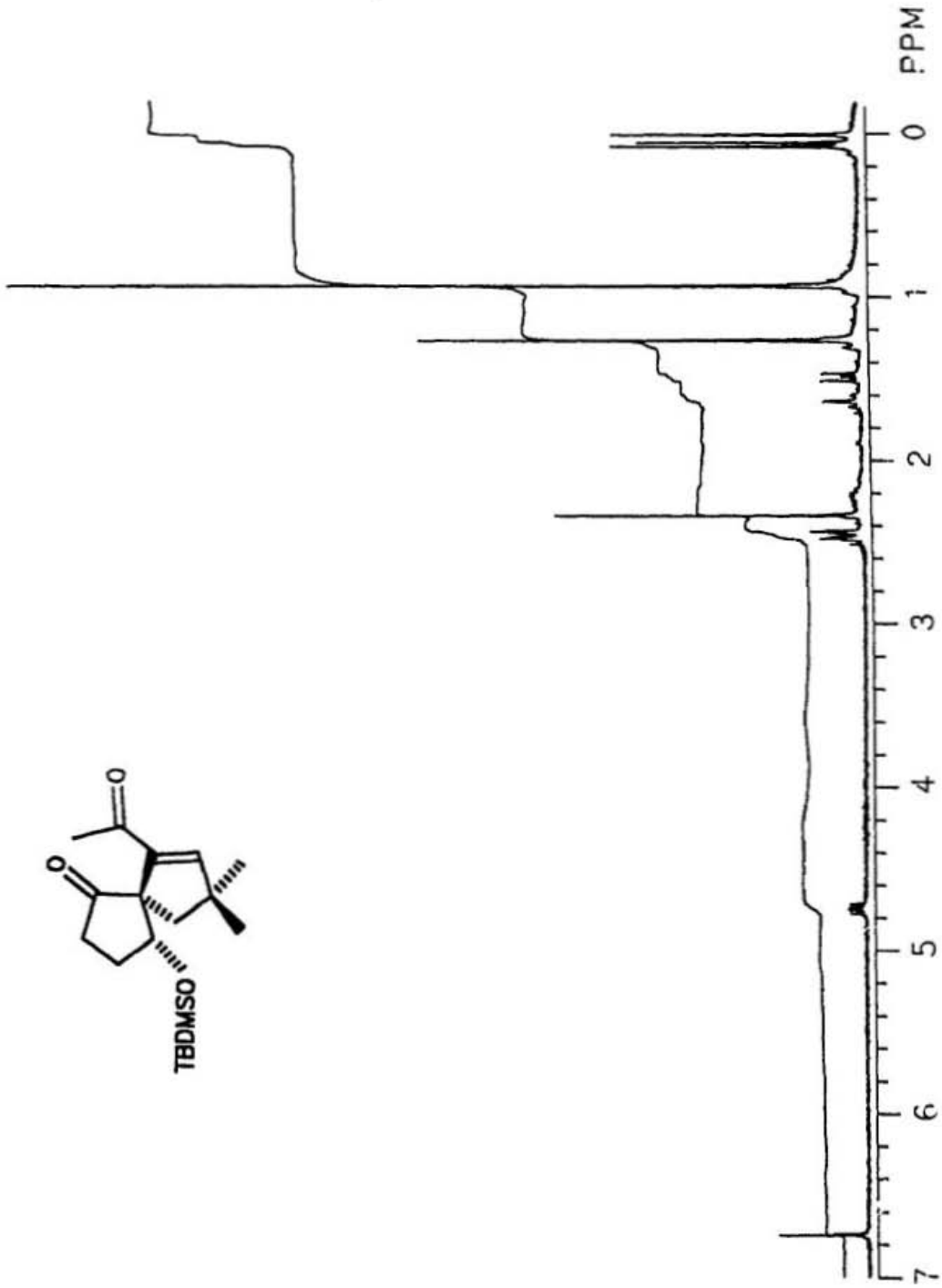
400 ($CDCl_3$)



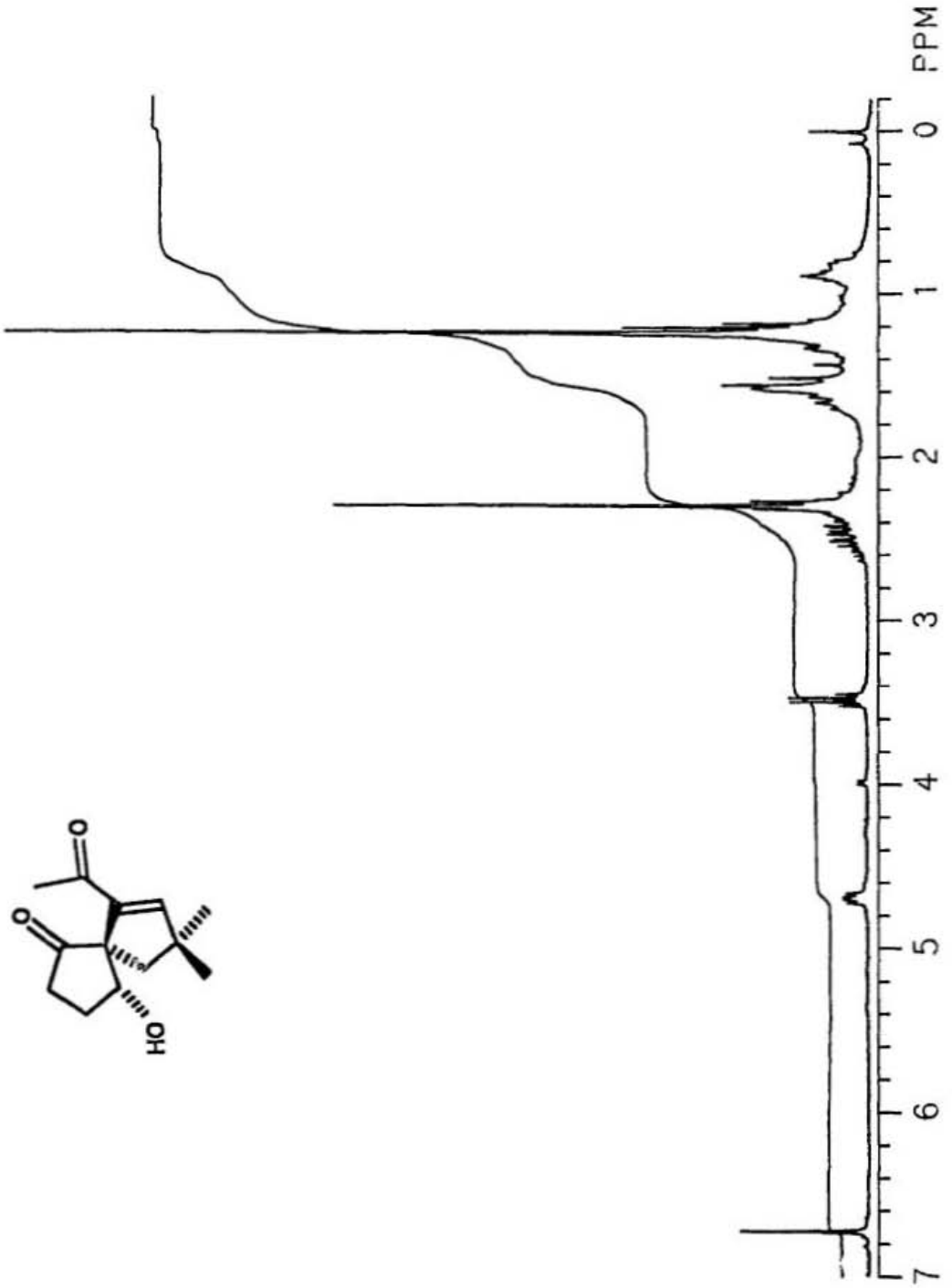
405 ($CDCl_3$)



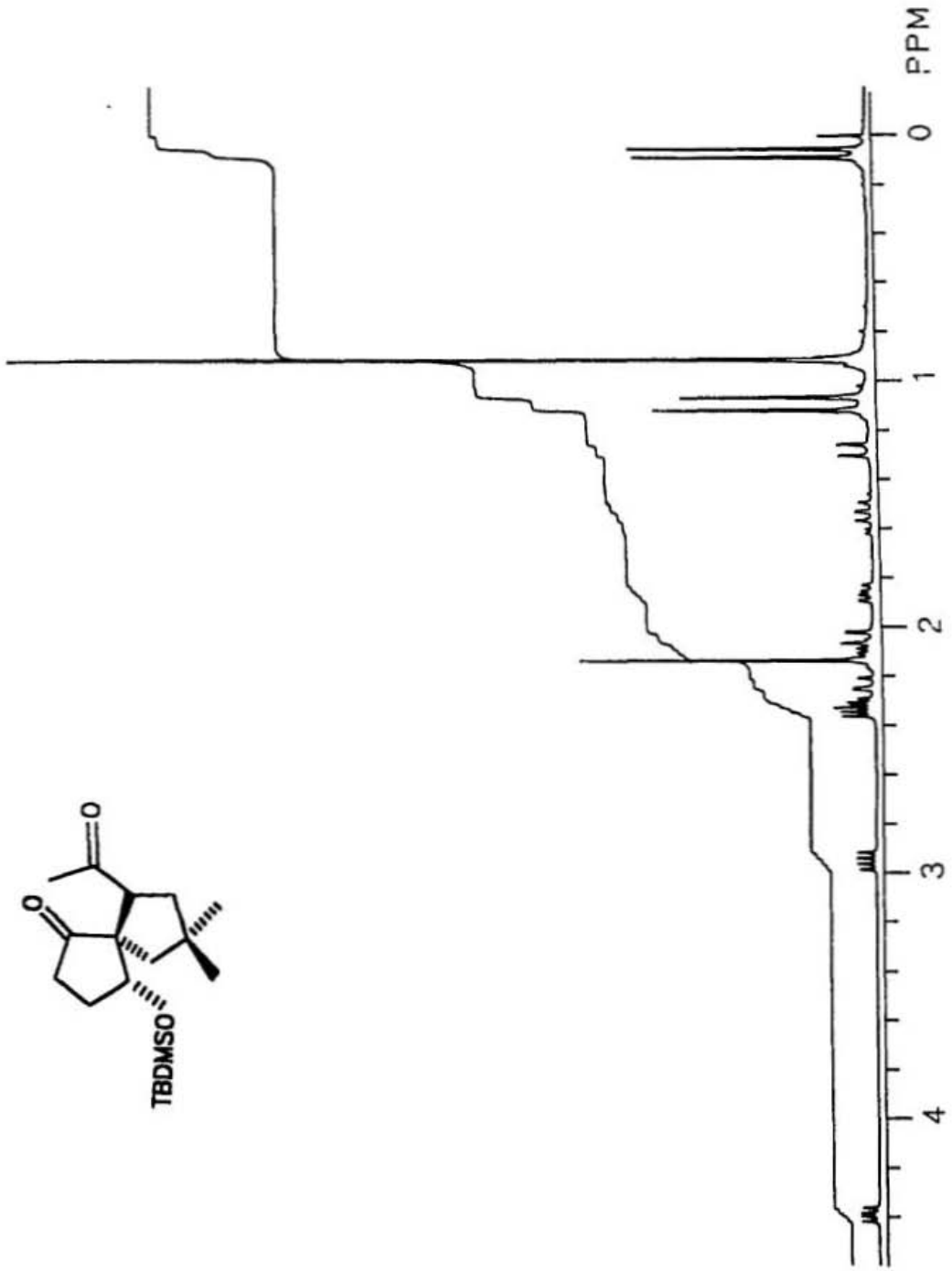
407 ($CDCl_3$)



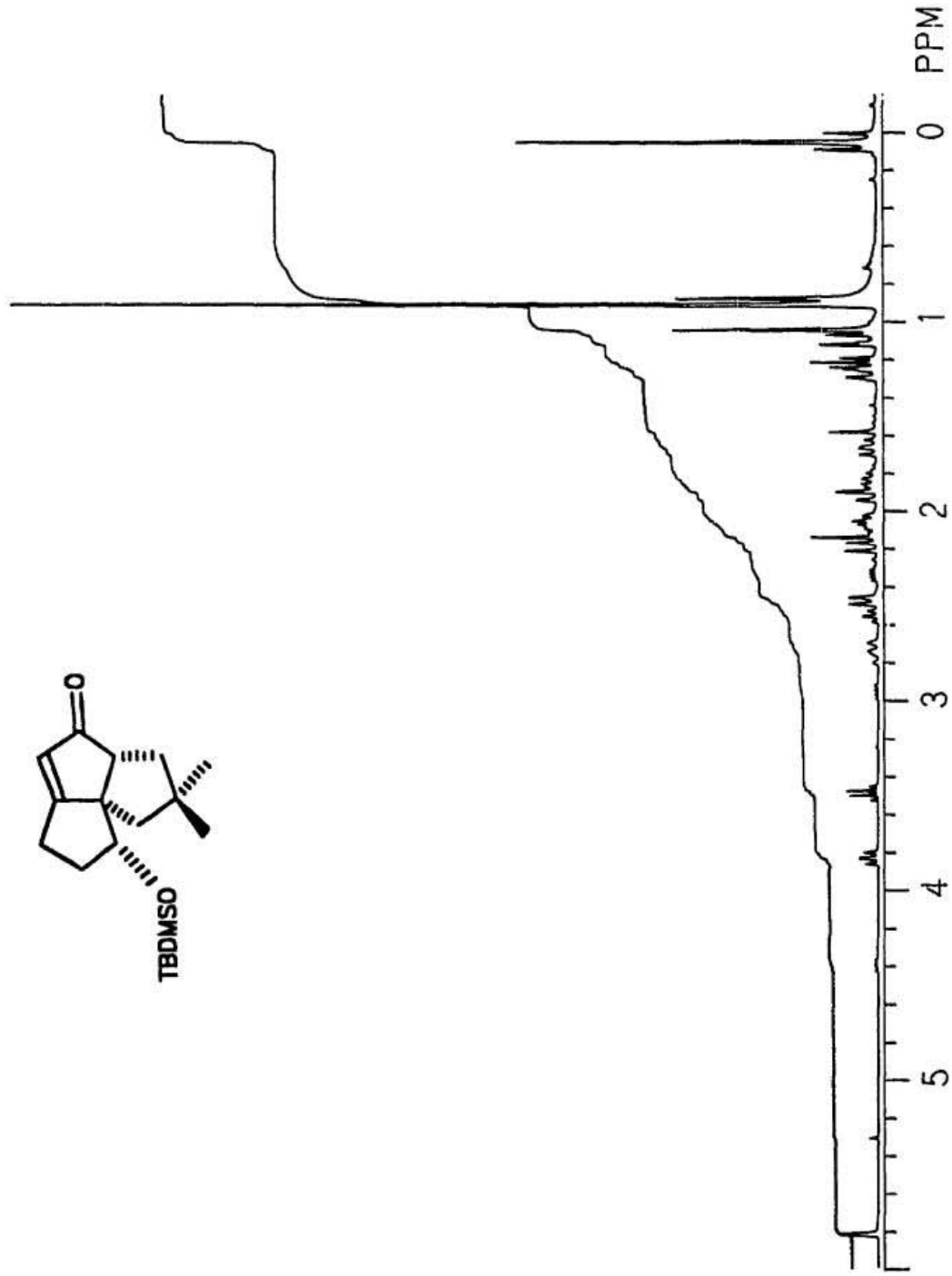
408 ($CDCl_3$)



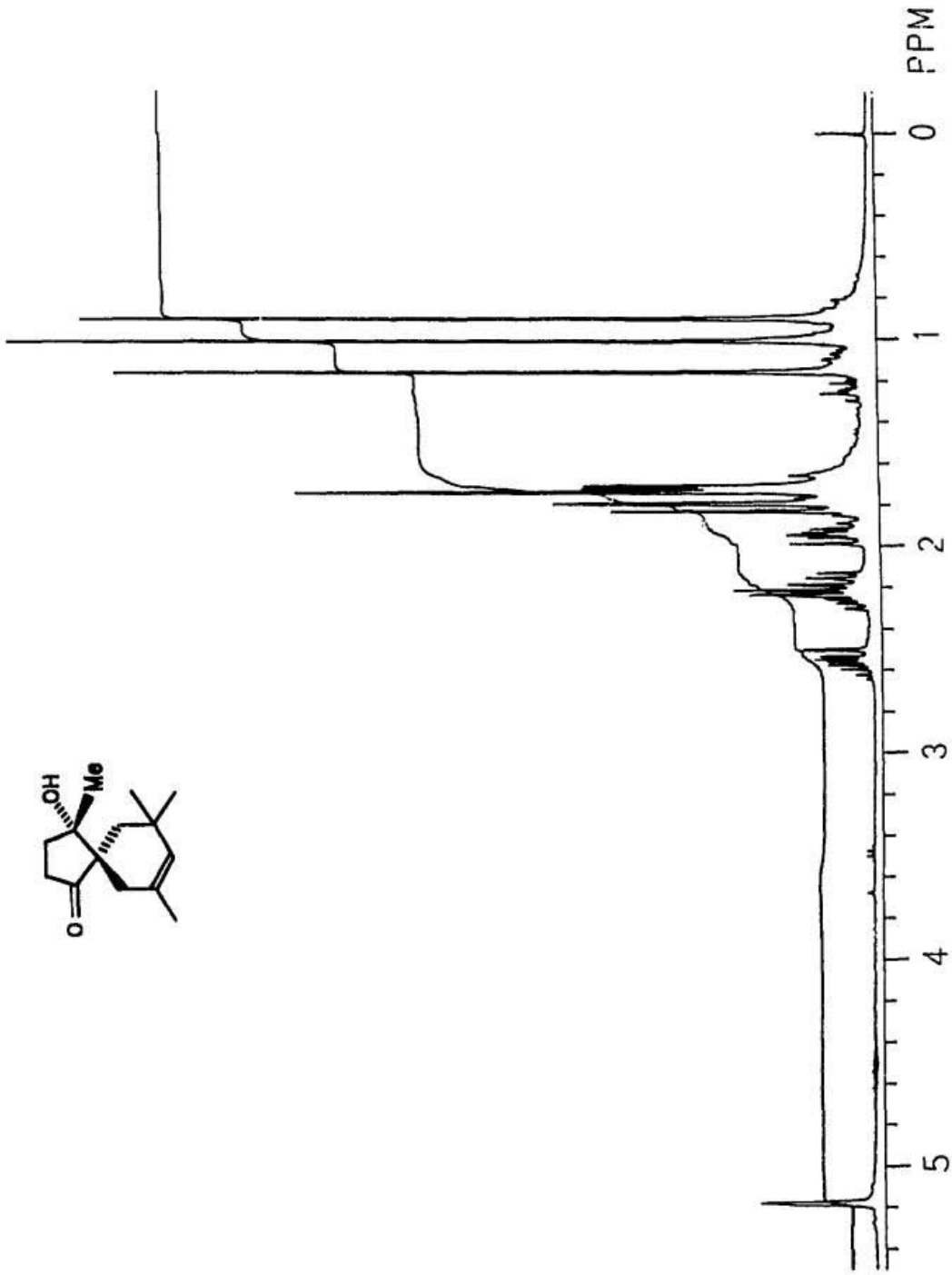
409 ($CDCl_3$)



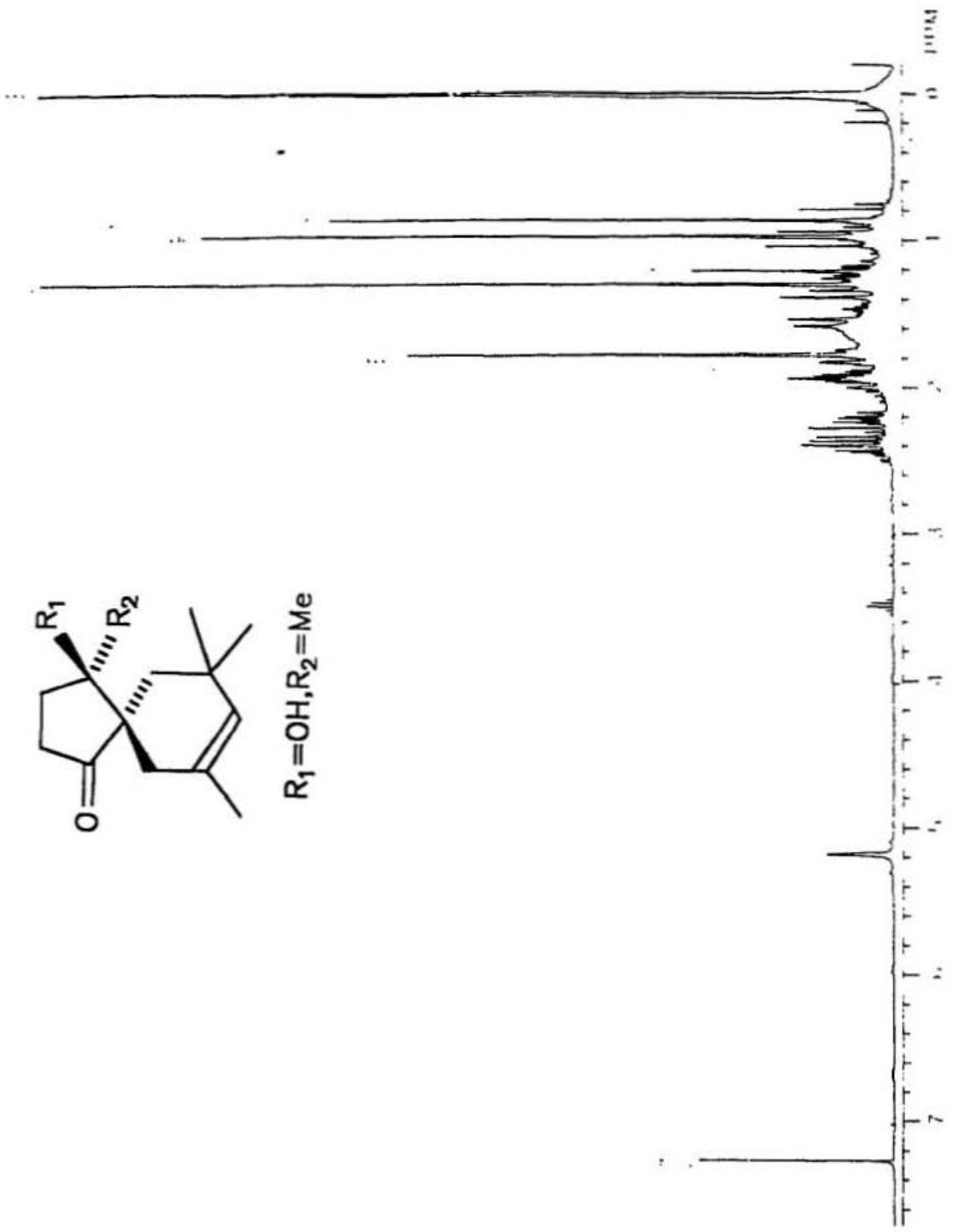
410 ($CDCl_3$)



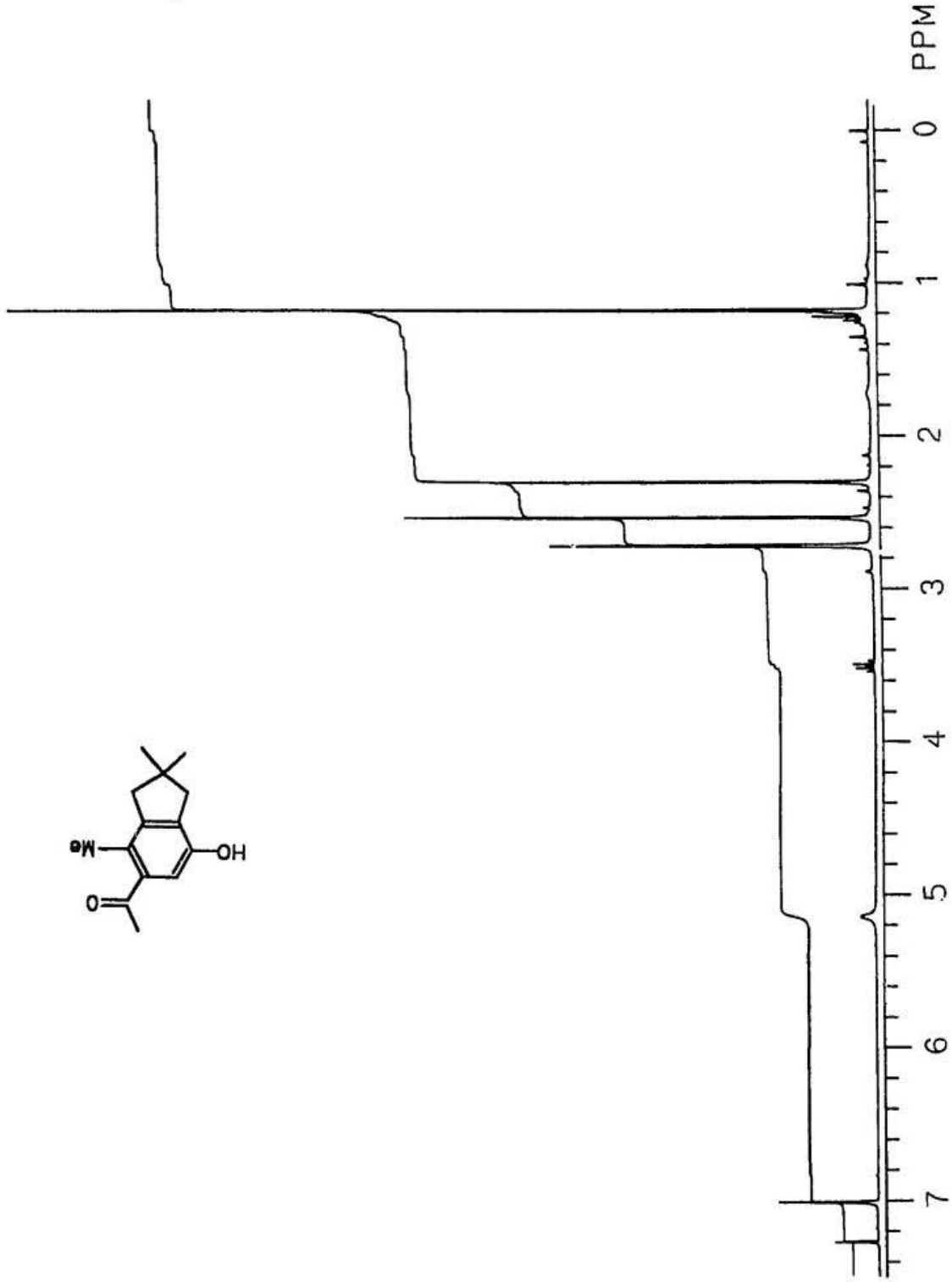
418 ($CDCl_3$)



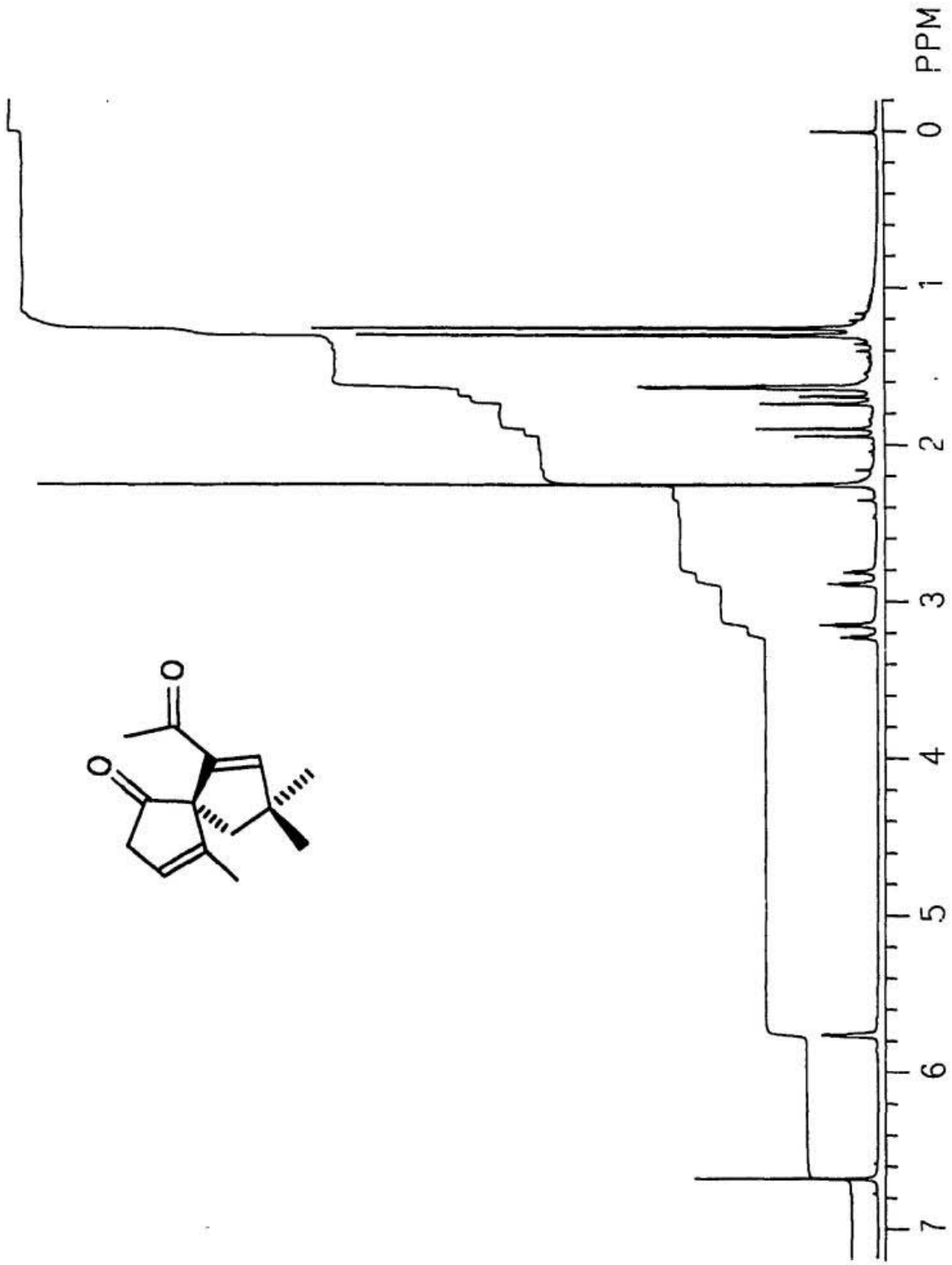
419 ($CDCl_3$)



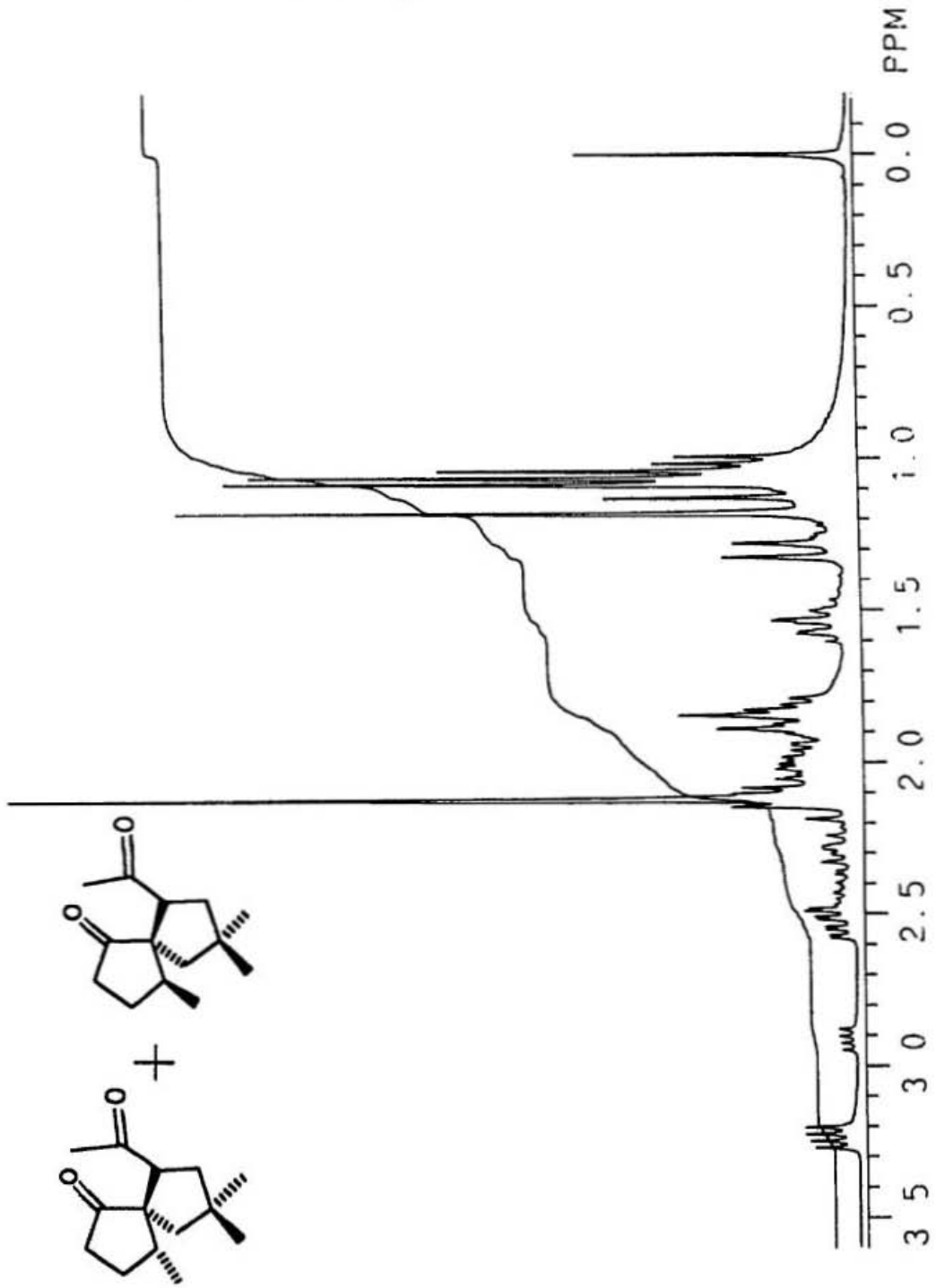
424 ($CDCl_3$)



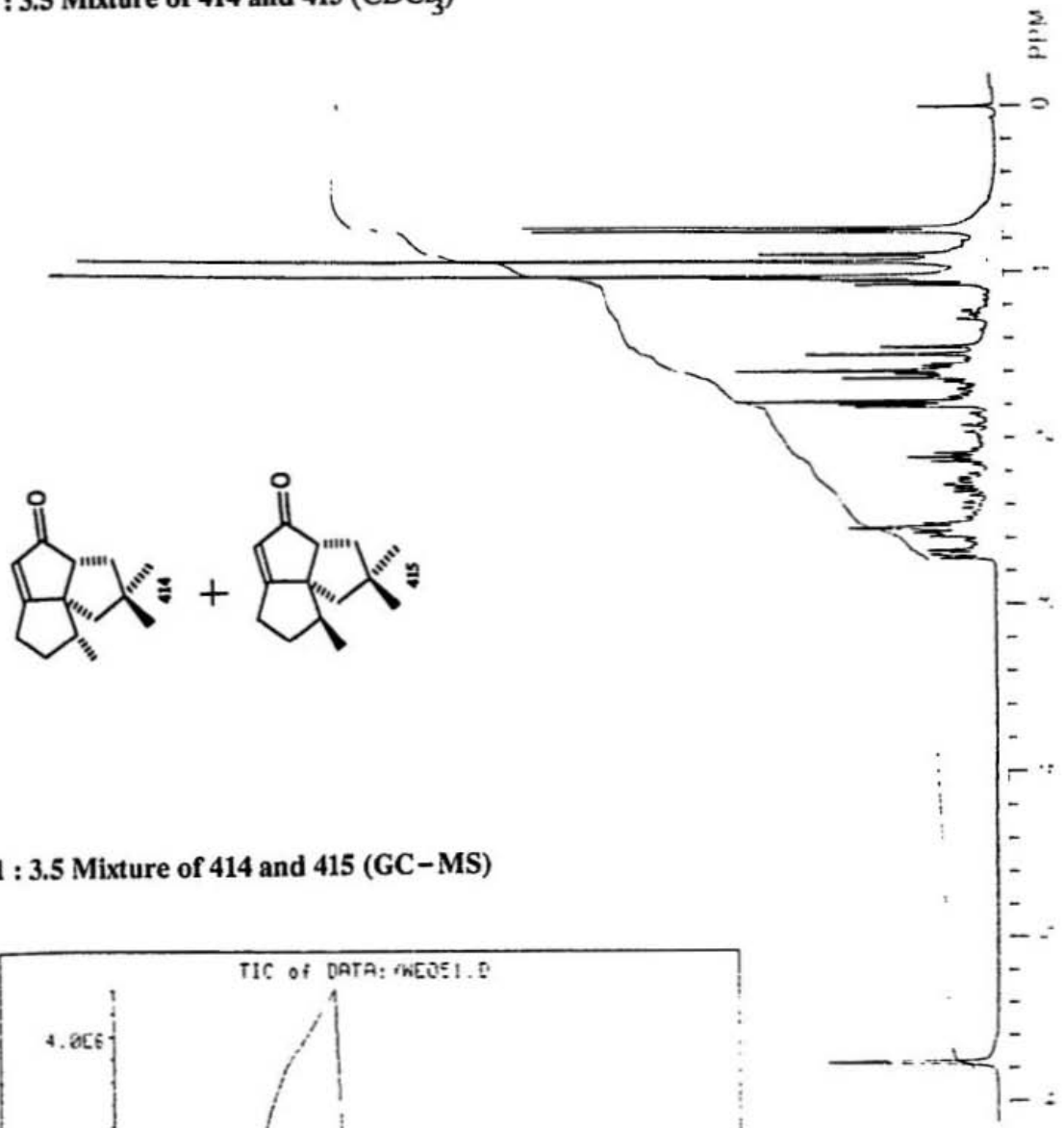
427 ($CDCl_3$)



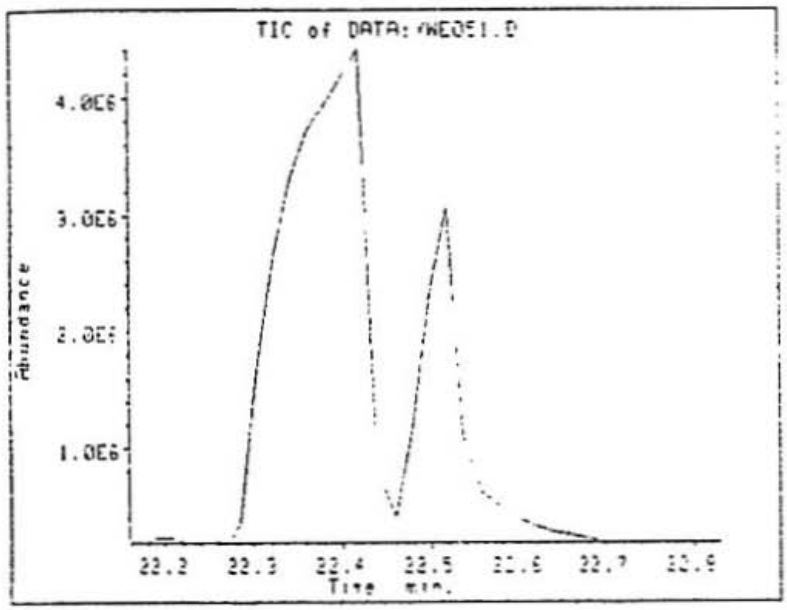
1 : 3.5 Mixture of 416 and 417 ($CDCl_3$)



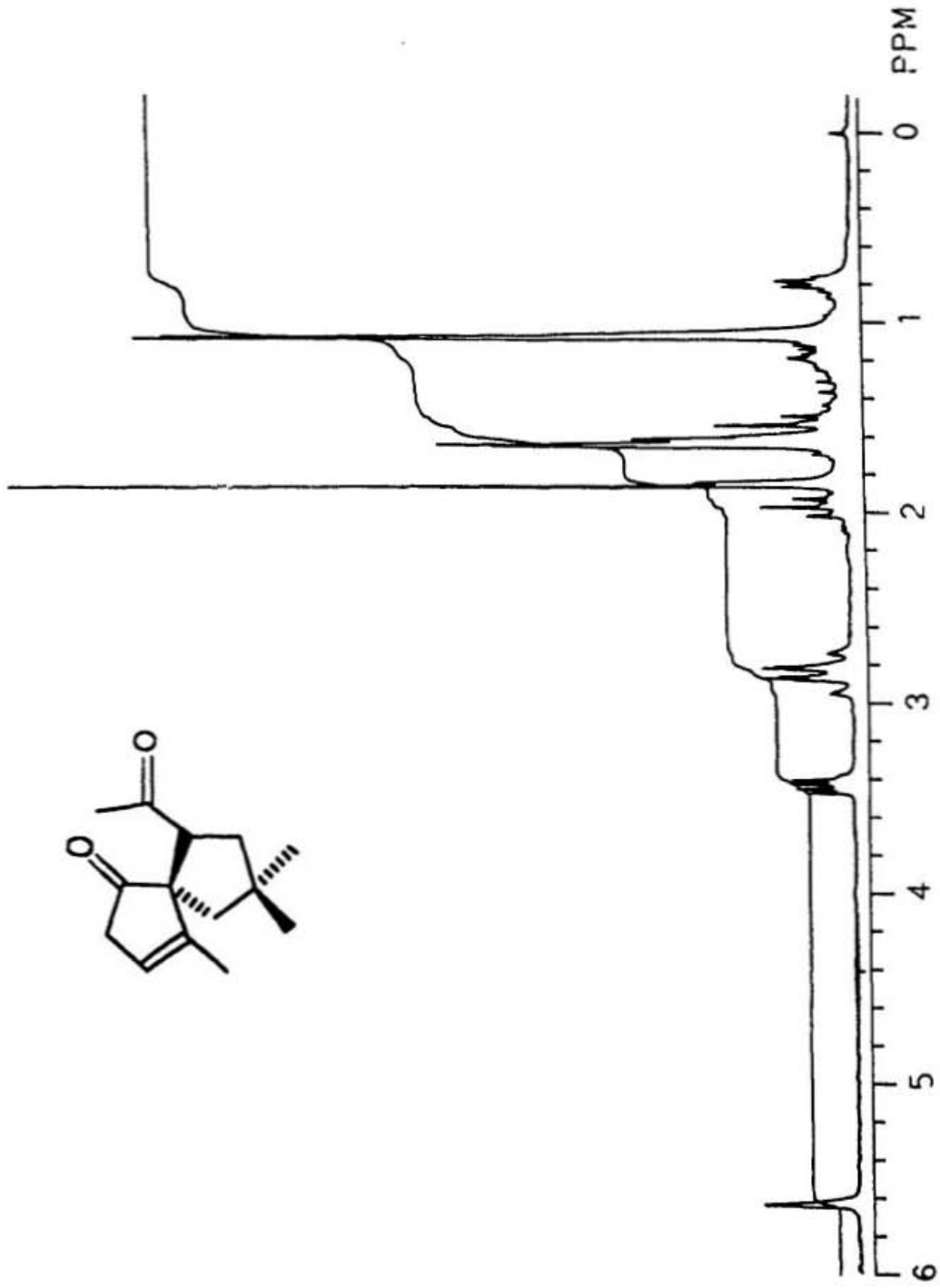
1 : 3.5 Mixture of 414 and 415 ($CDCl_3$)



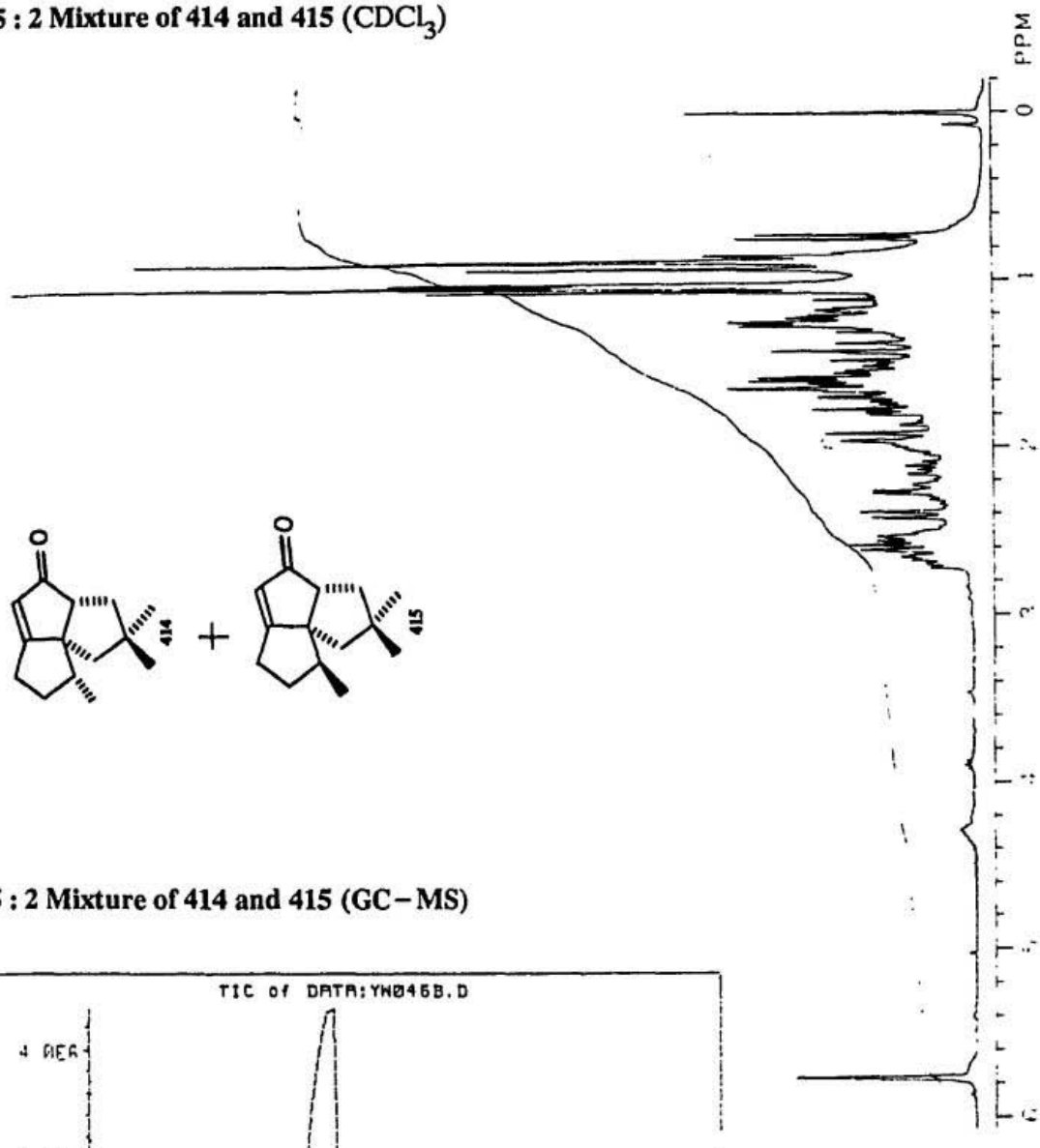
1 : 3.5 Mixture of 414 and 415 (GC–MS)



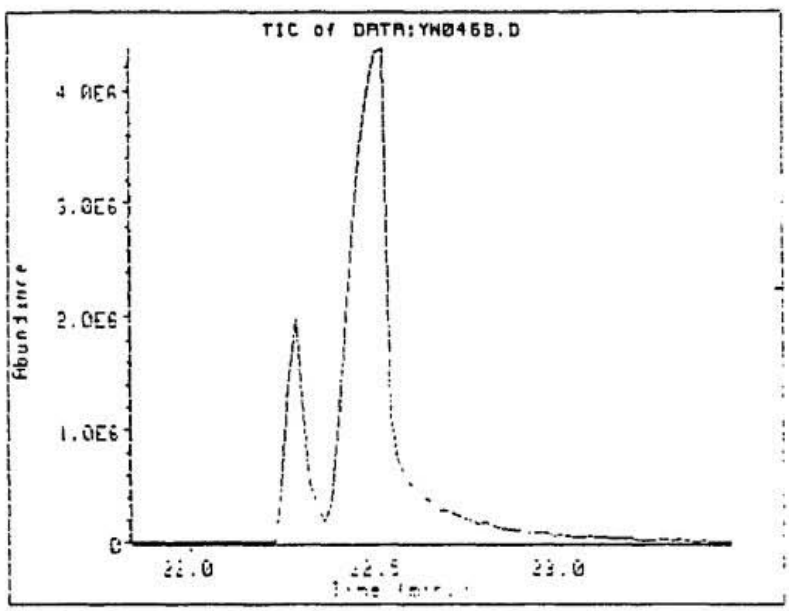
431 ($CDCl_3$)



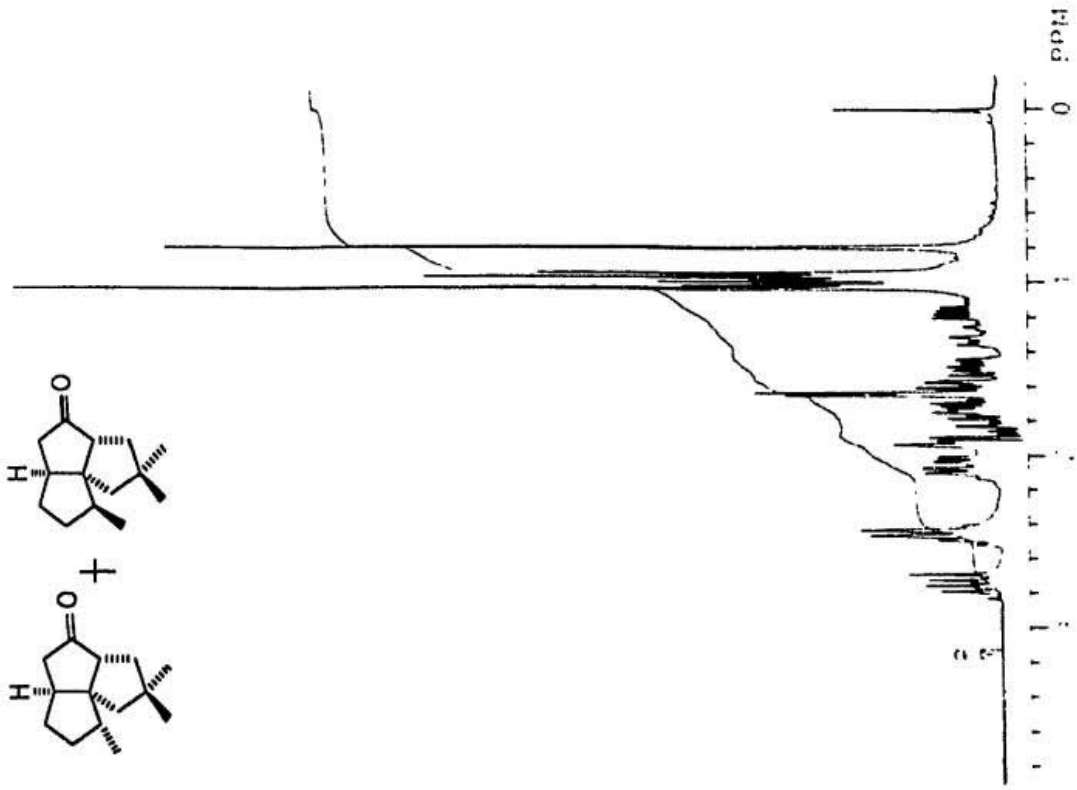
3.5 : 2 Mixture of 414 and 415 ($CDCl_3$)



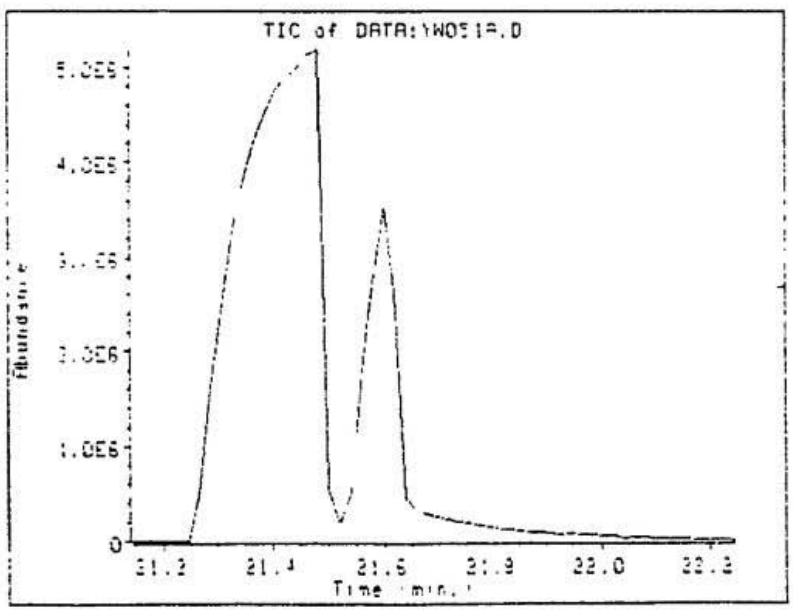
3.5 : 2 Mixture of 414 and 415 (GC – MS)



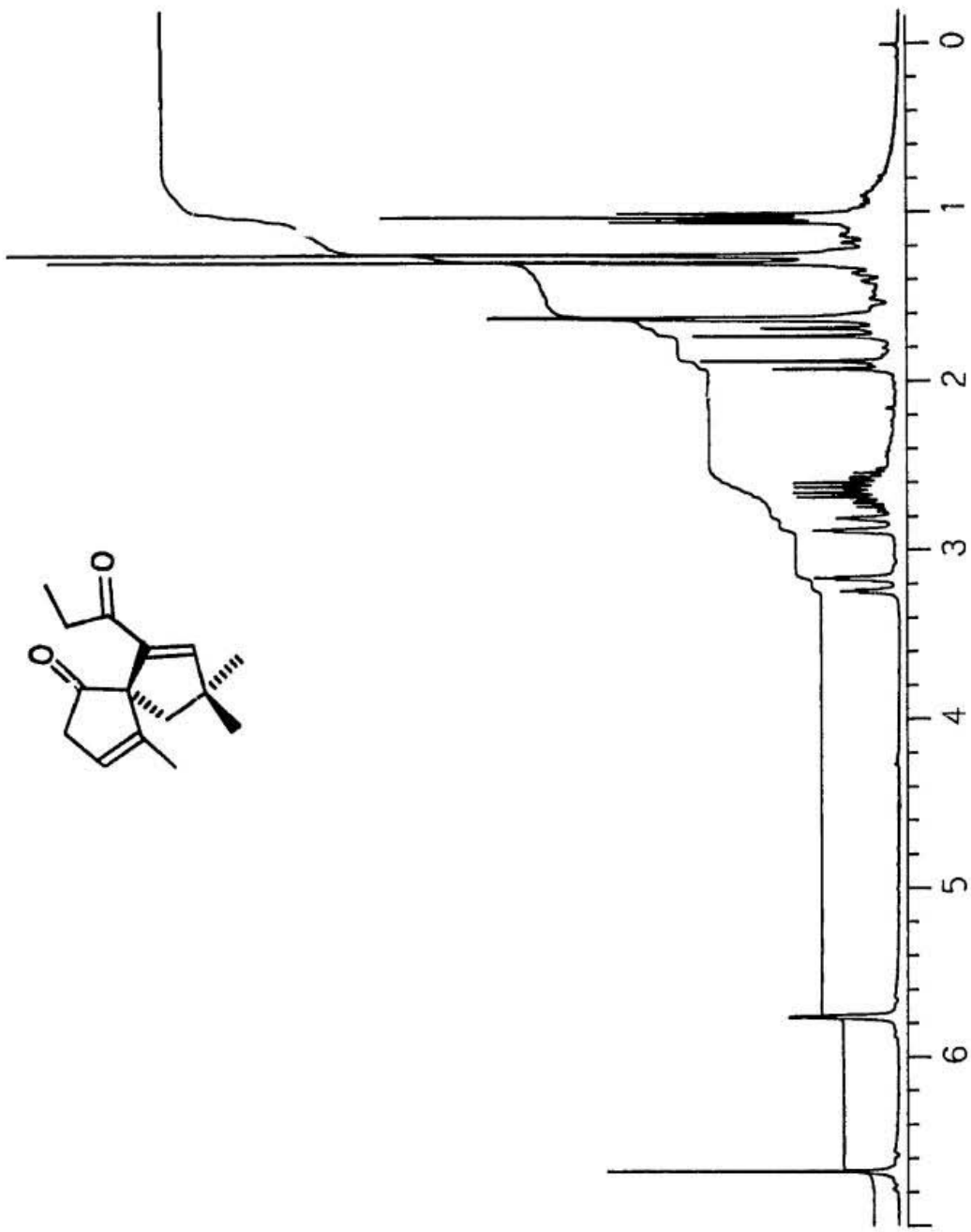
1 : 3.5 Mixture of 432 and 433 ($CDCl_3$)



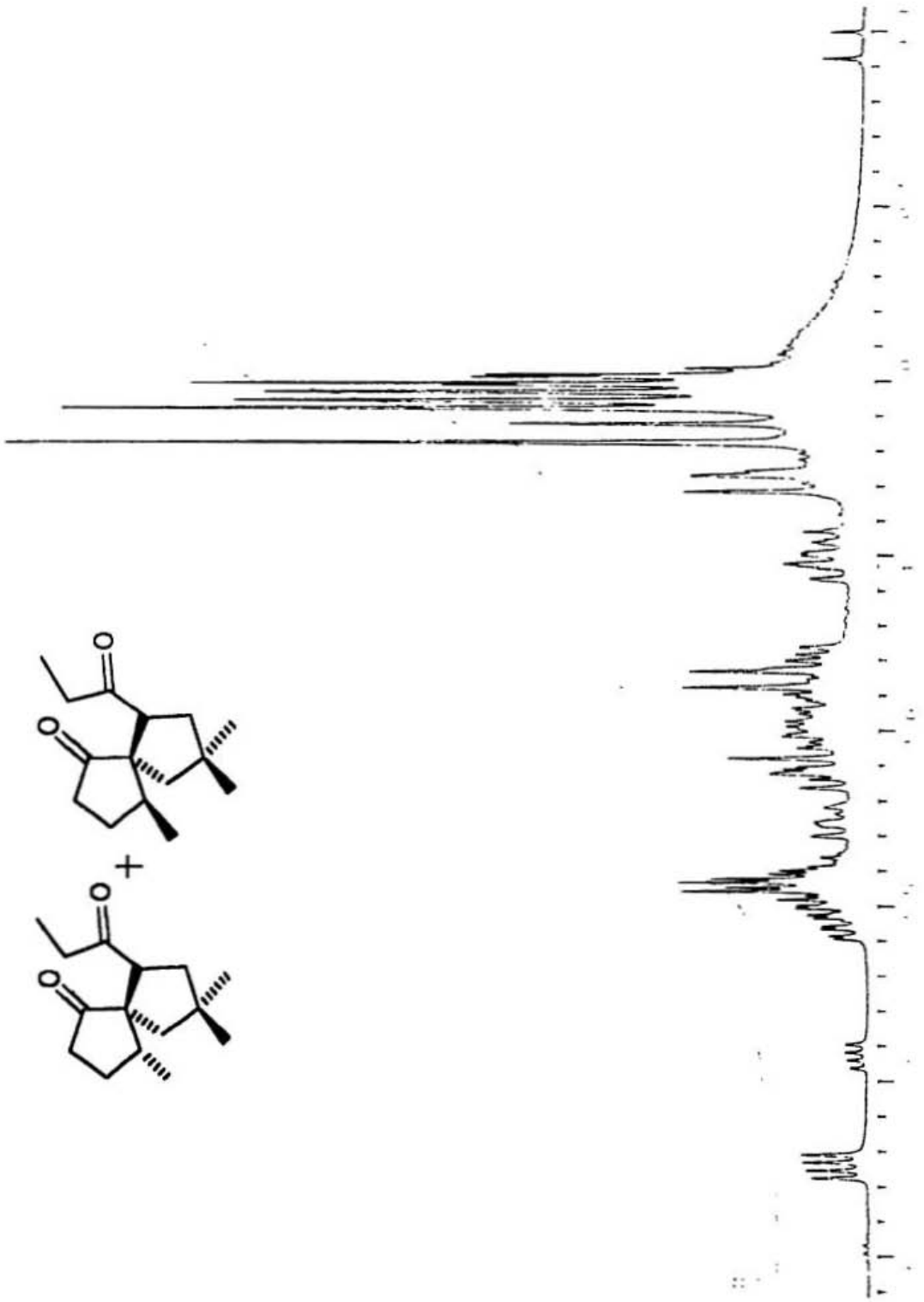
1 : 3.5 Mixture of 432 and 433 (GC–MS)



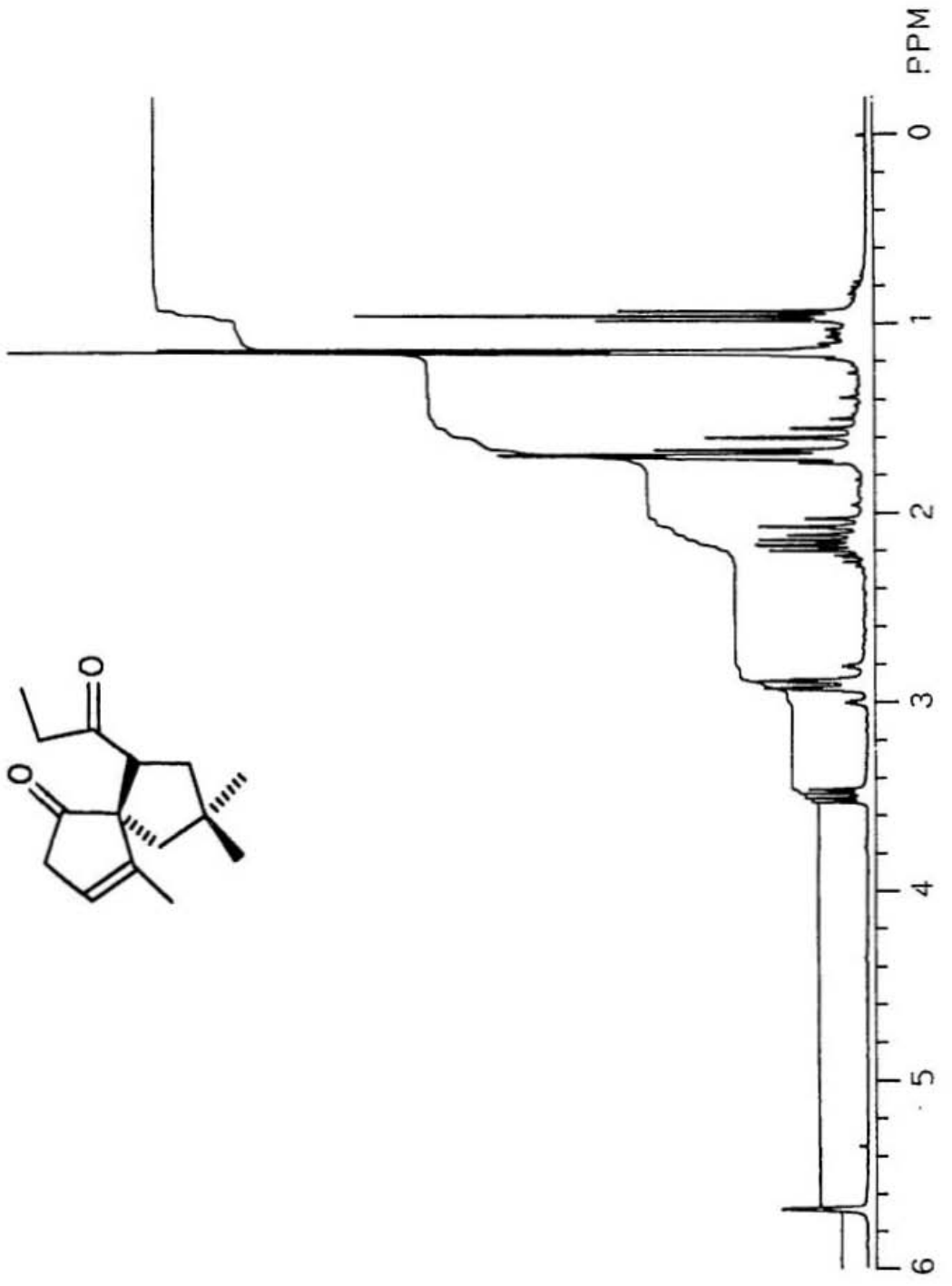
443 ($CDCl_3$)



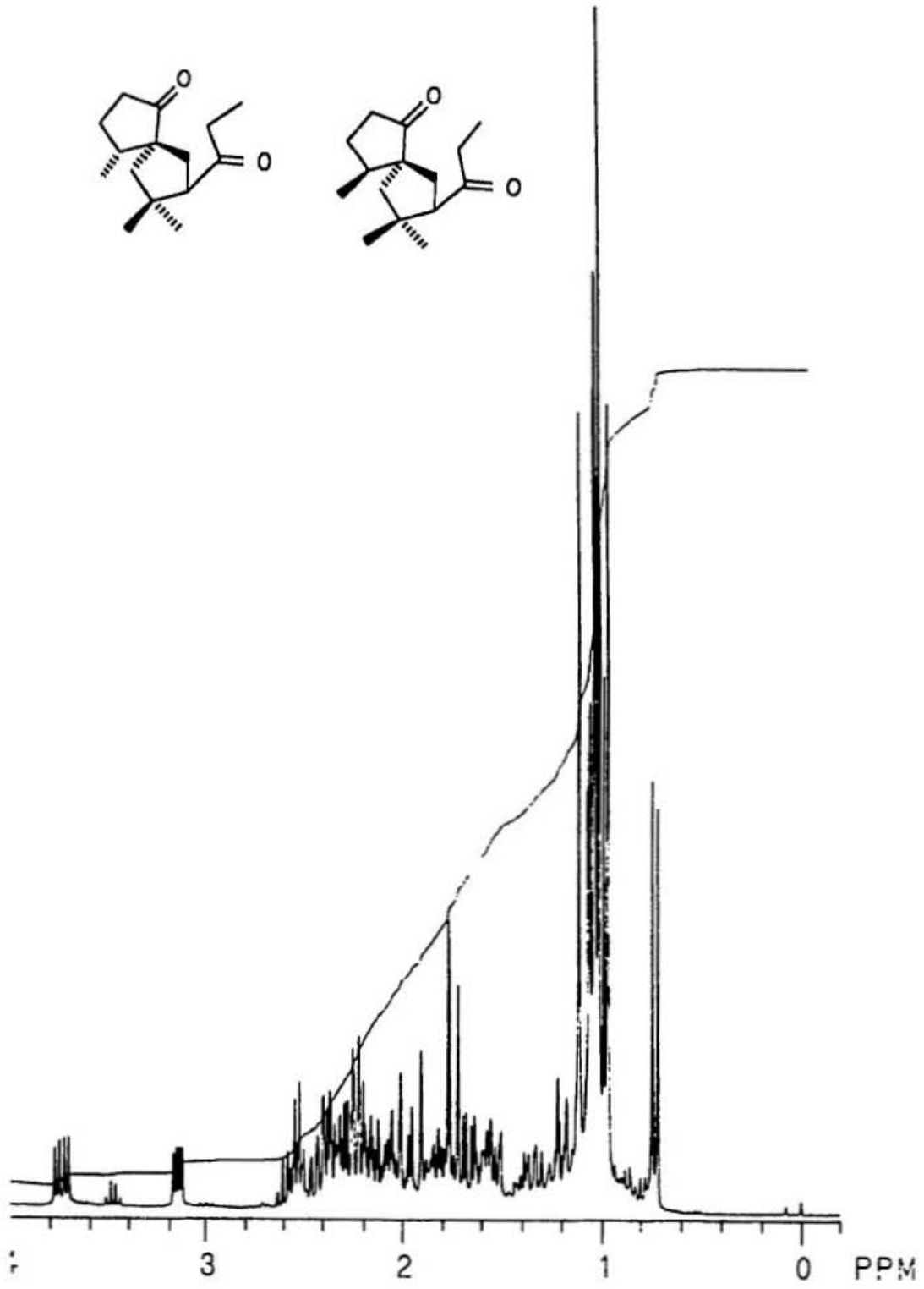
1 : 5 Mixture of 441 and 442 ($CDCl_3$)



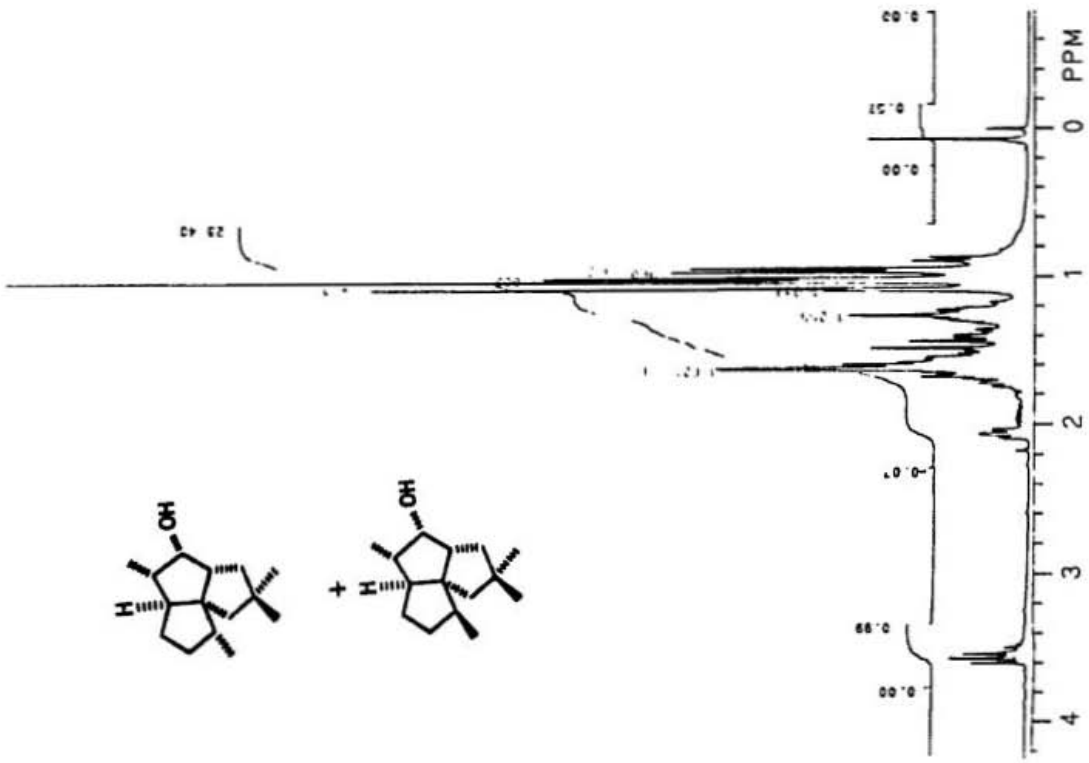
462 ($CDCl_3$)



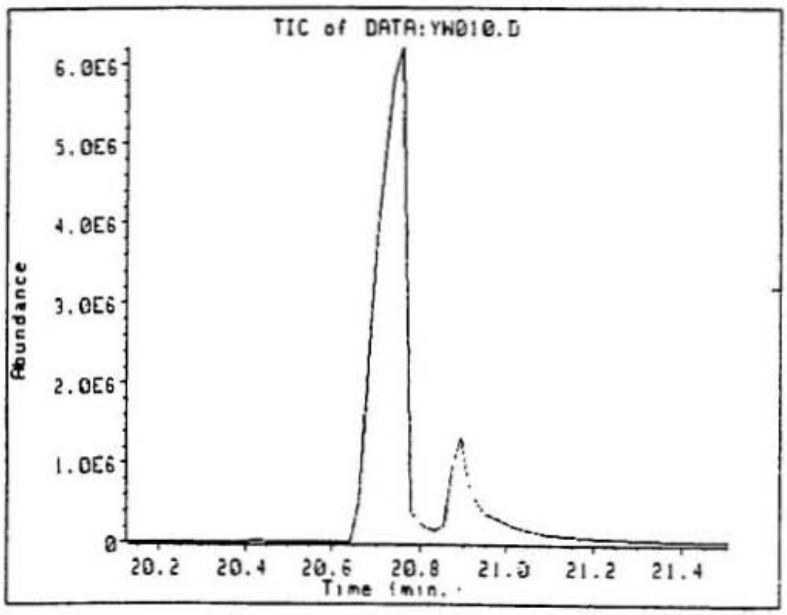
A mixture of 463 and 464 ($CDCl_3$)



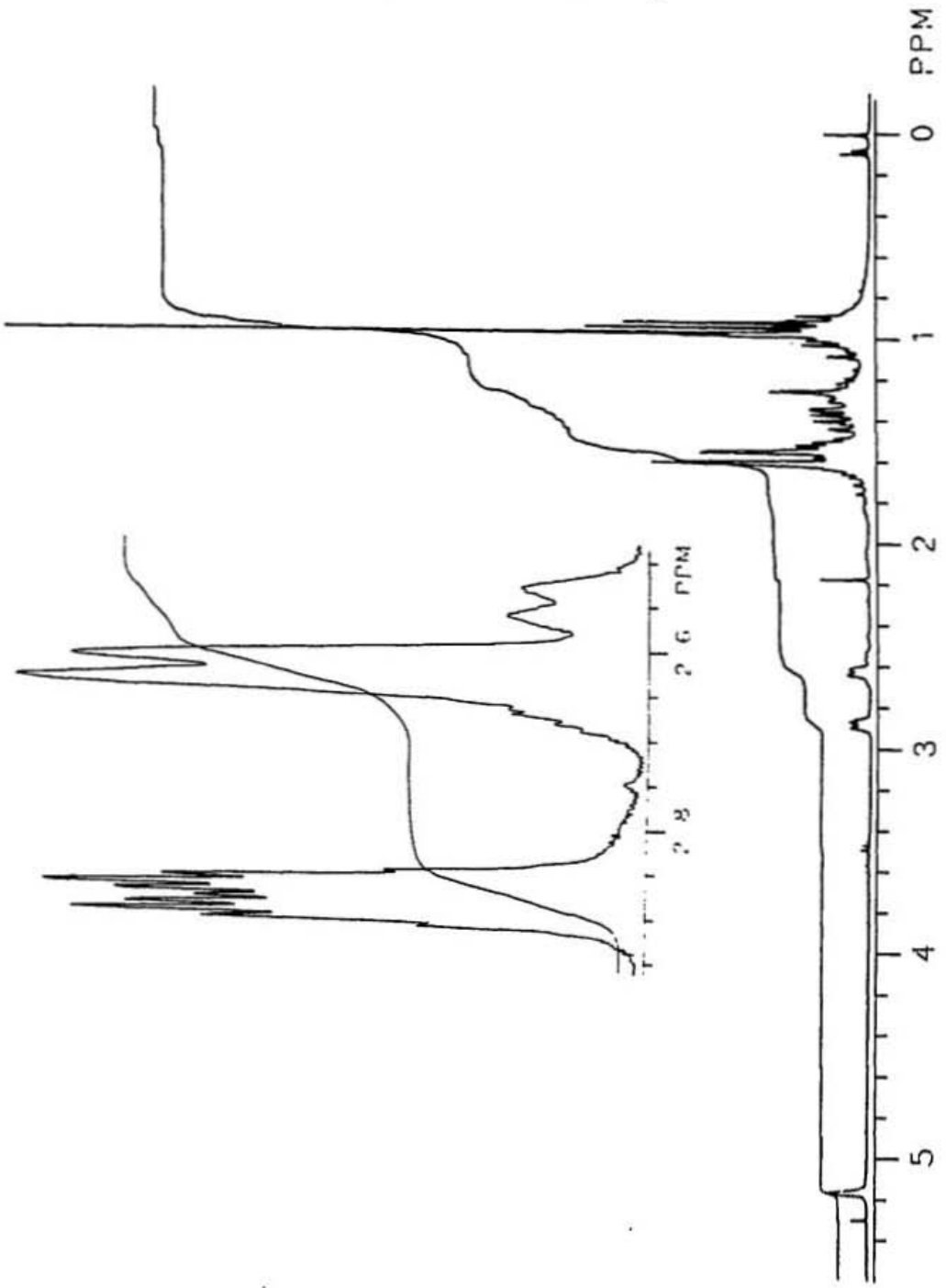
1 : 5 Mixture of 468 and 469 ($CDCl_3$)



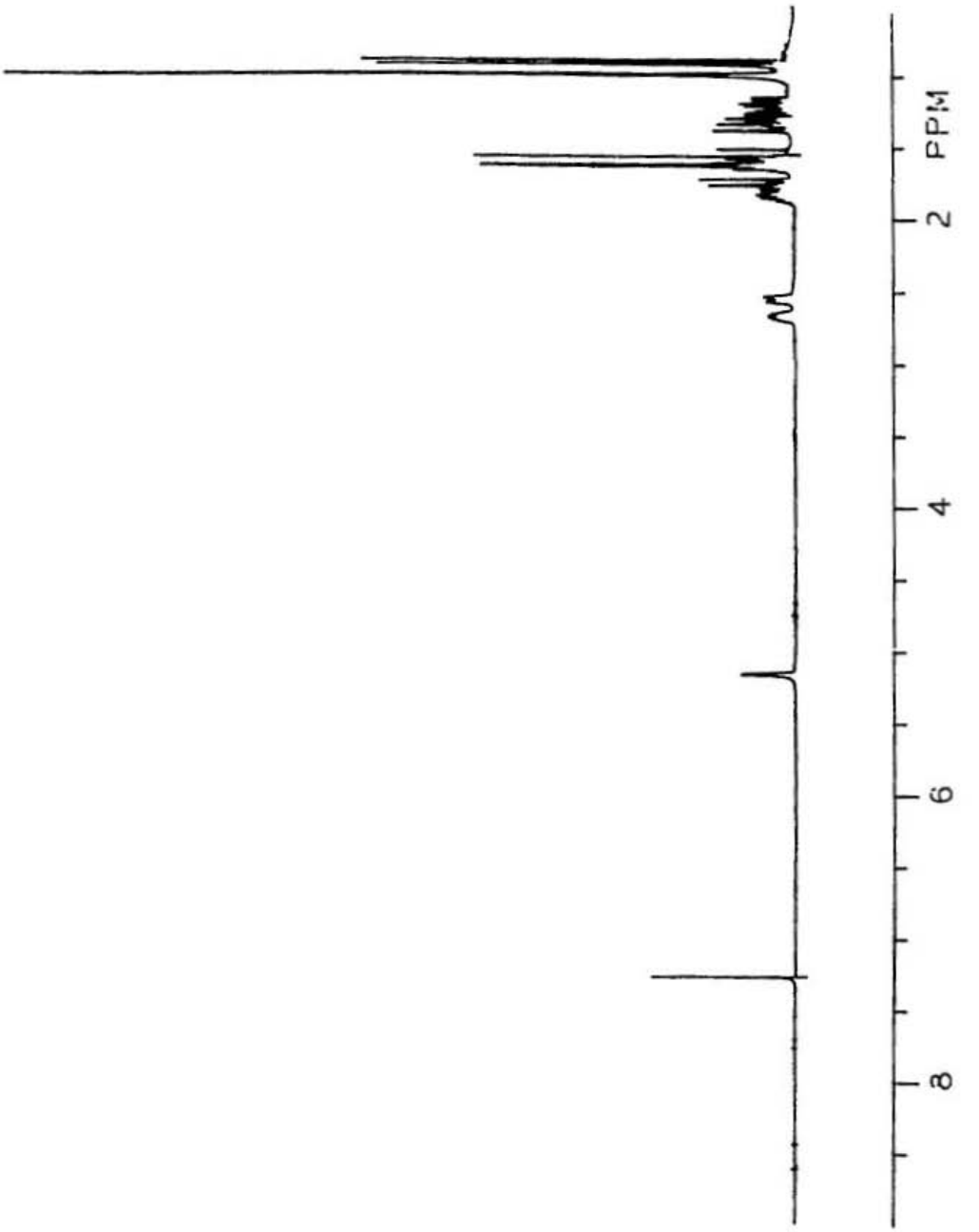
1 : 5 Mixture of 468 and 469 (GC–MS)



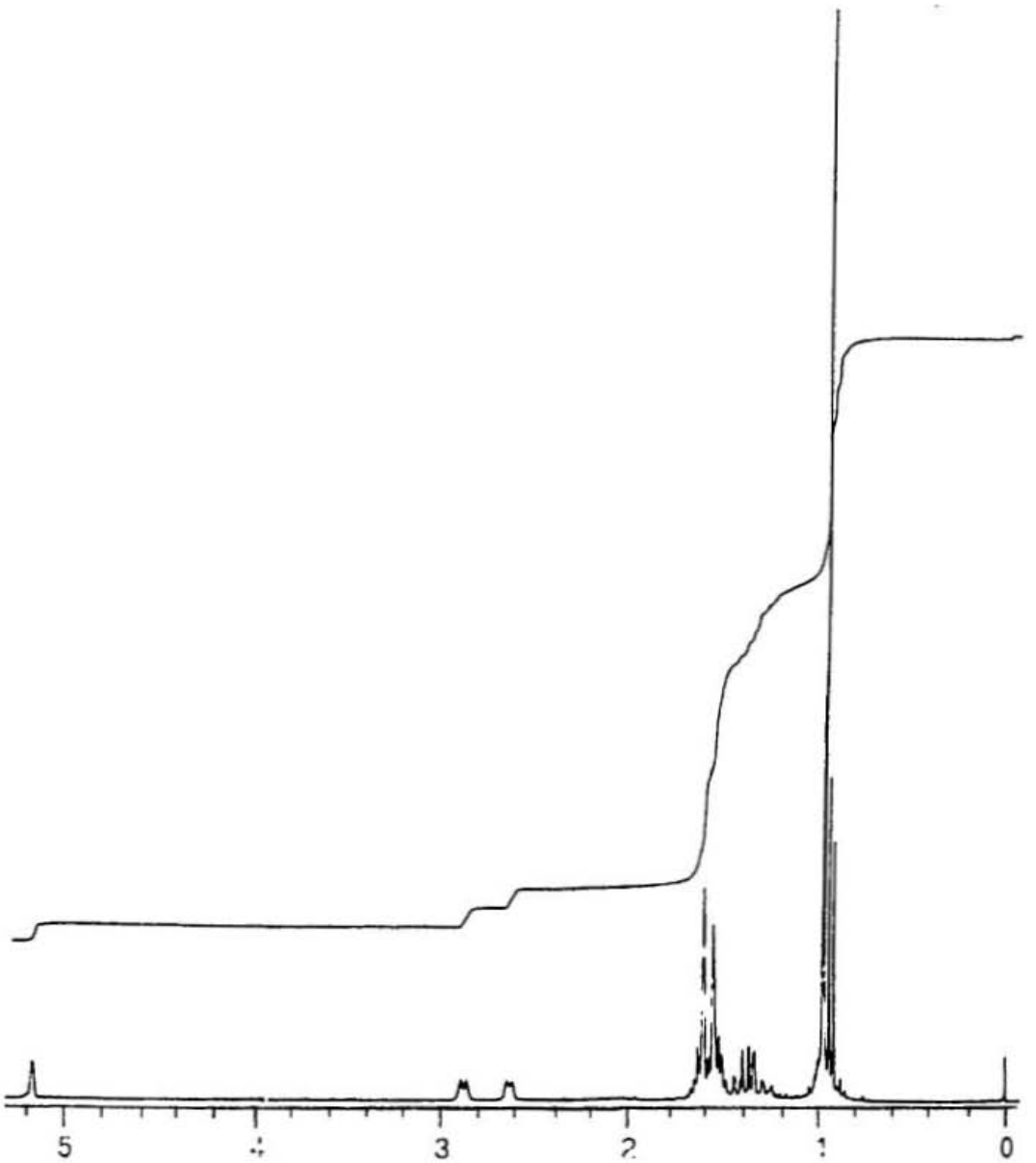
1 : 5 Mixture of pentalenene and *epi*-pentalenene($CDCl_3$)



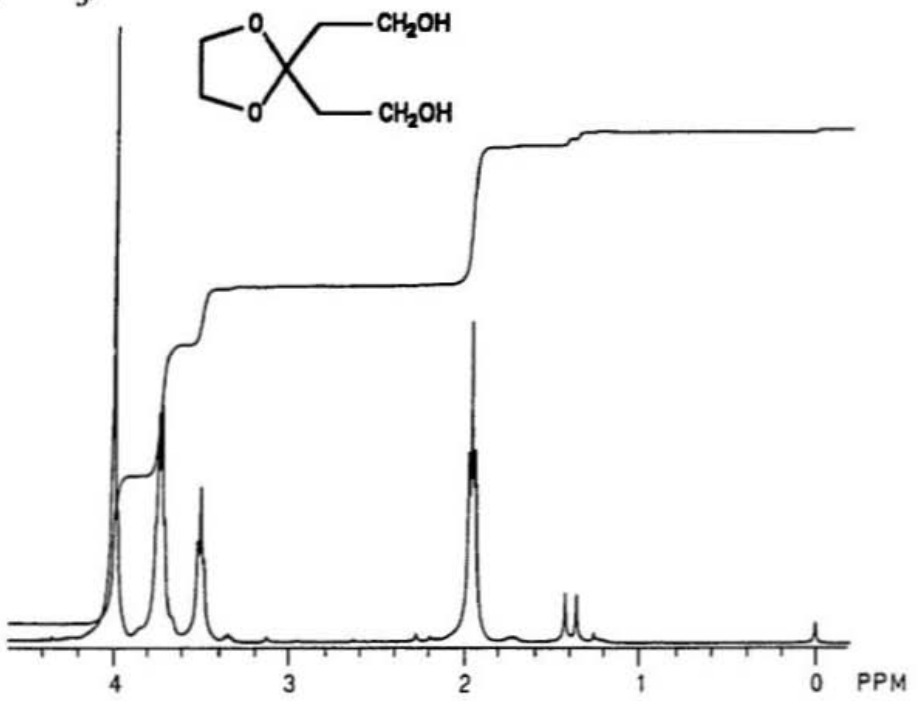
Pentalenene ($CDCl_3$)



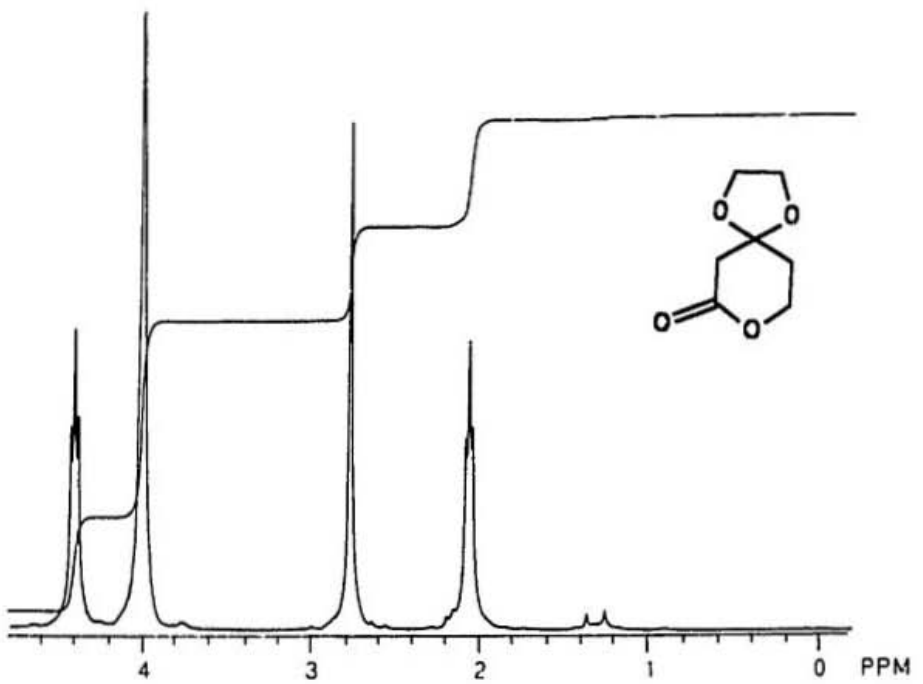
***epi*-Pentalenene** ($CDCl_3$)



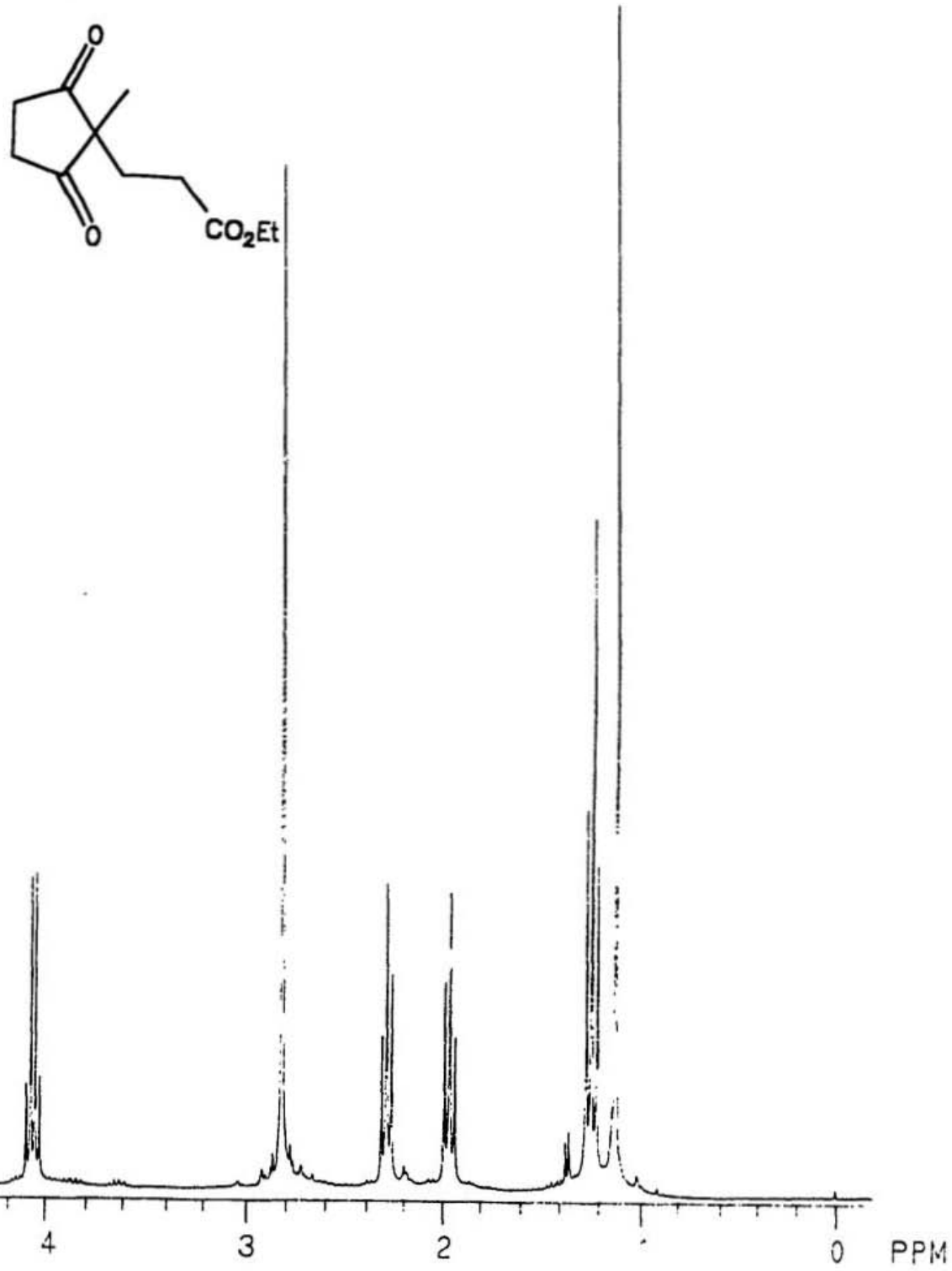
501 ($CDCl_3$)



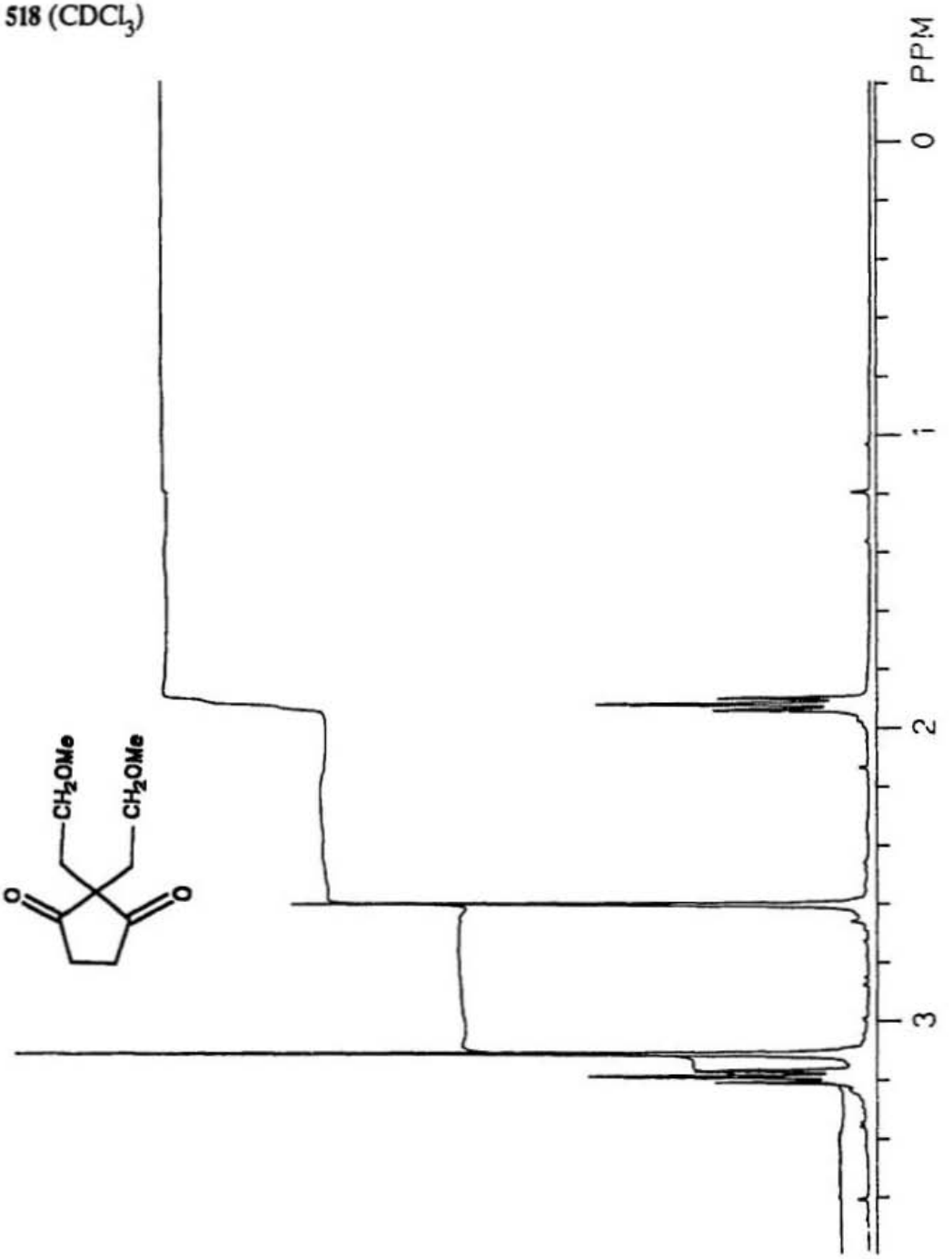
491 ($CDCl_3$)



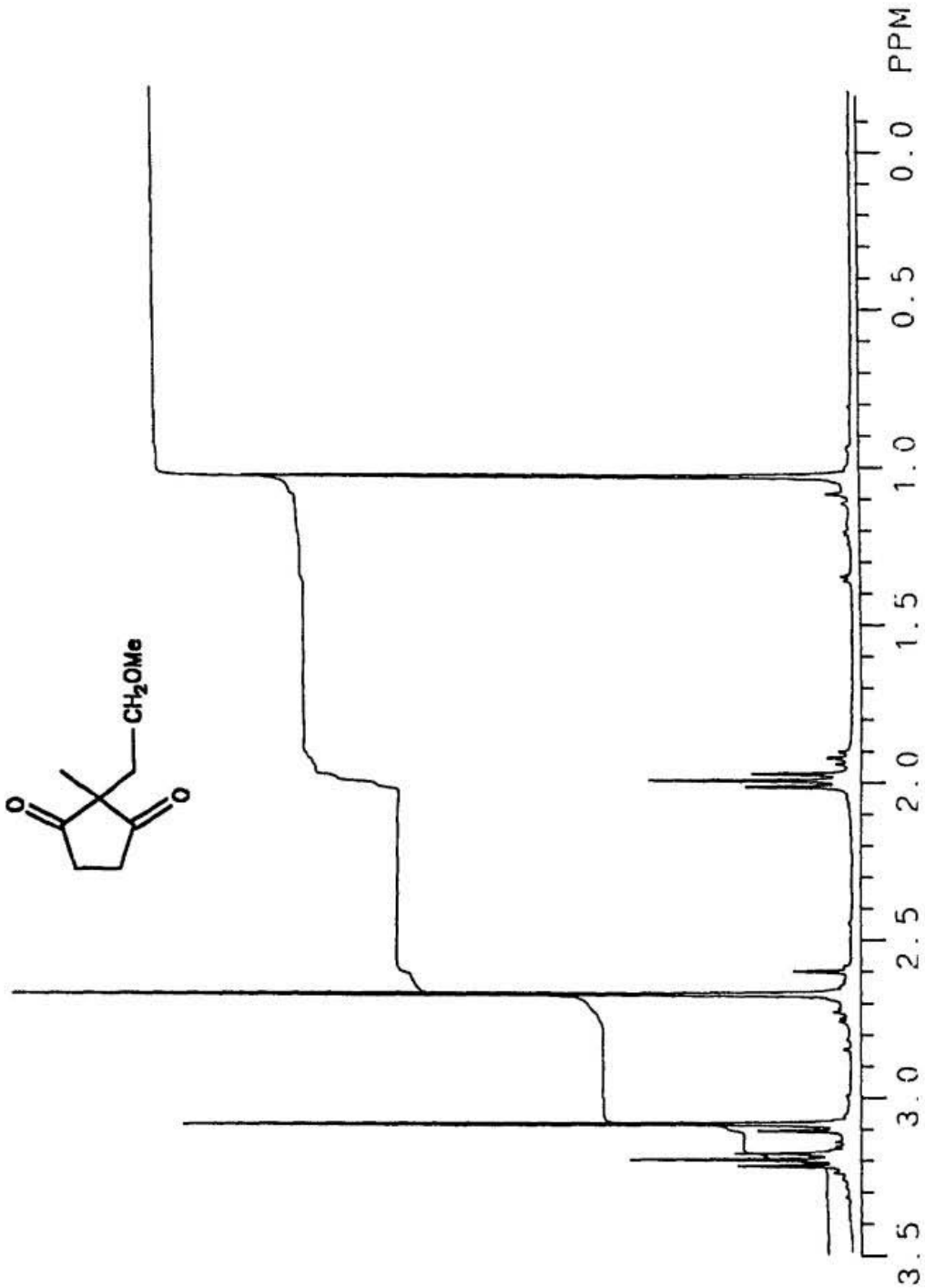
513 ($CDCl_3$)



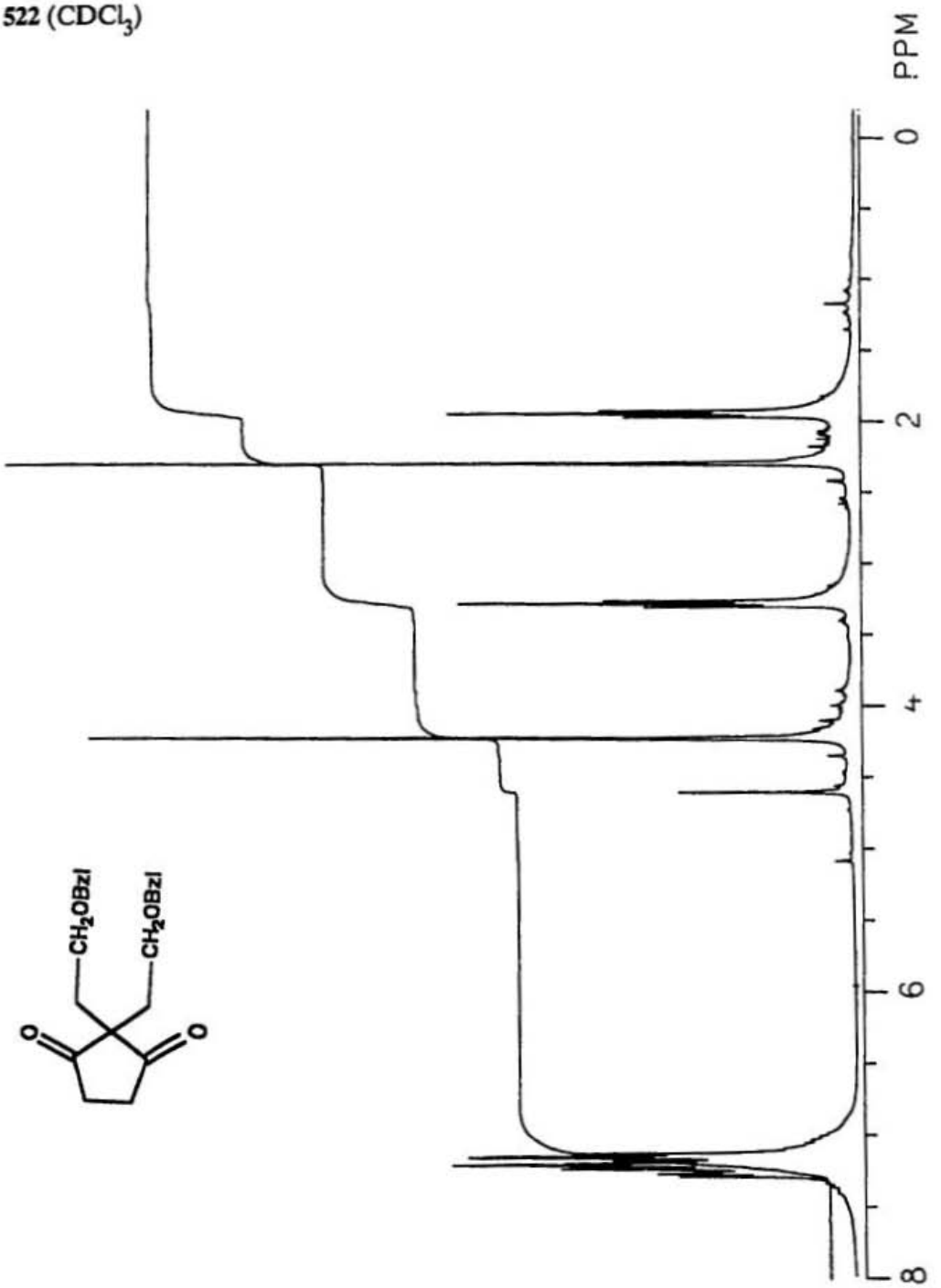
518 ($CDCl_3$)



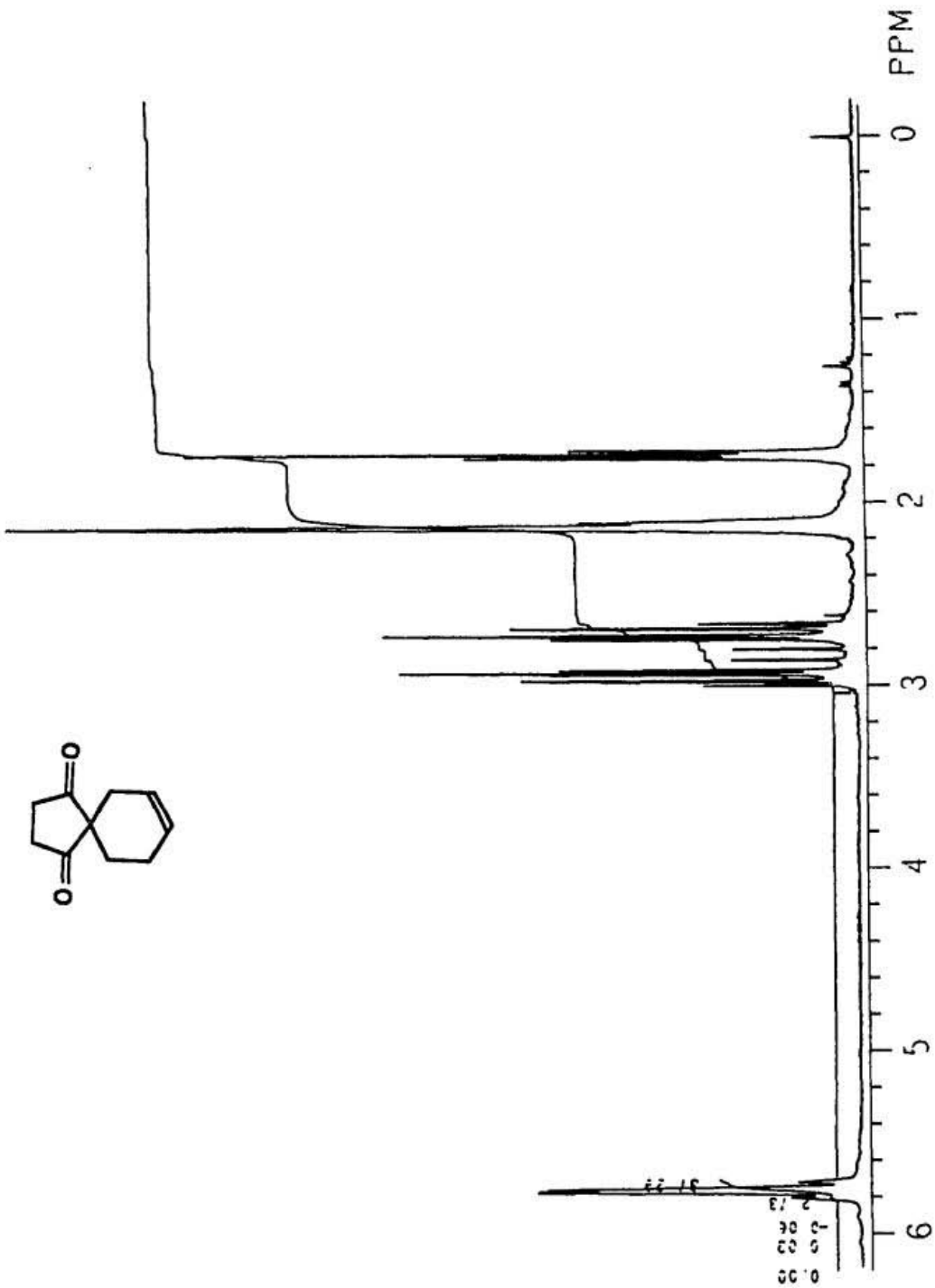
519 ($CDCl_3$)



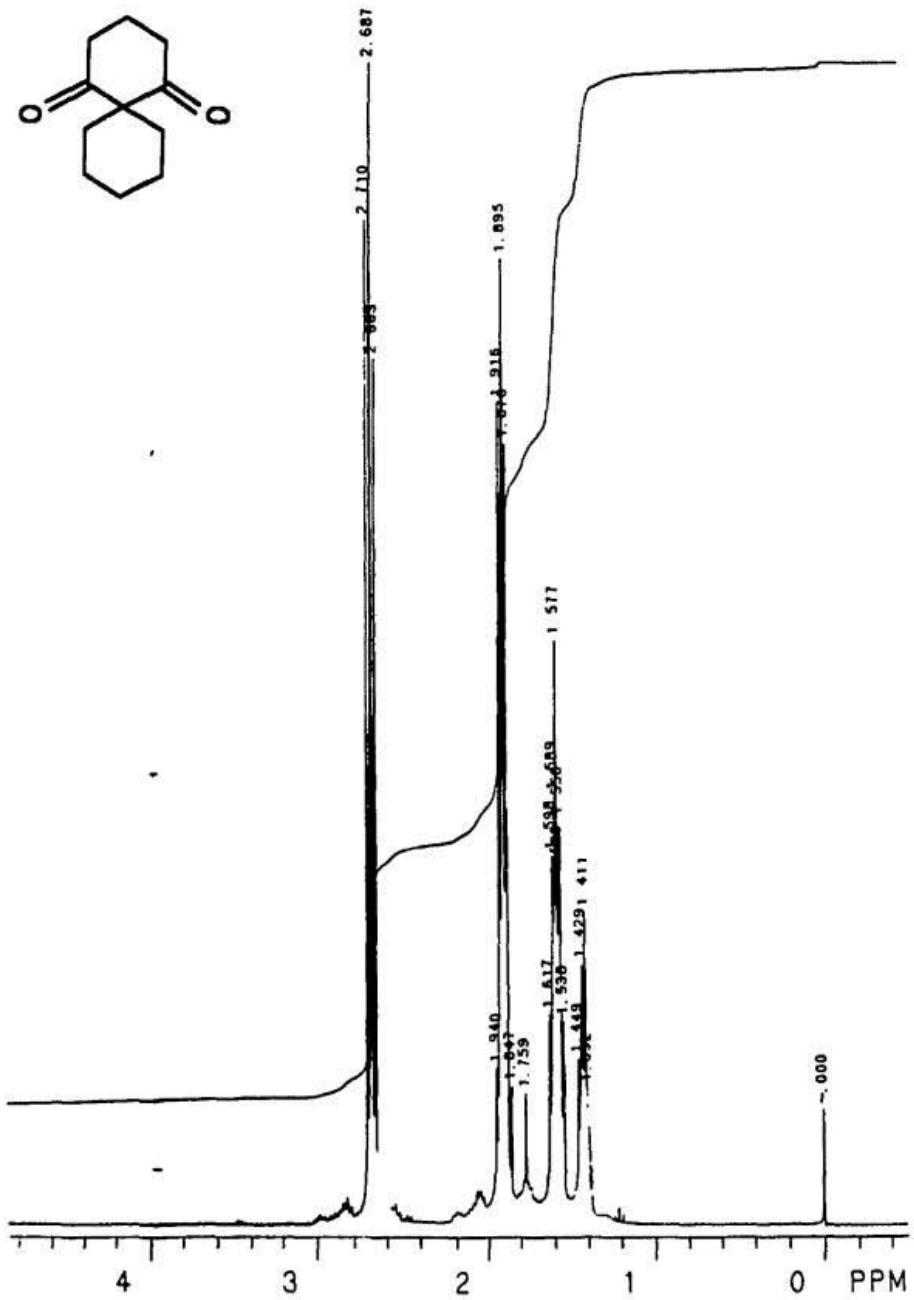
522 ($CDCl_3$)



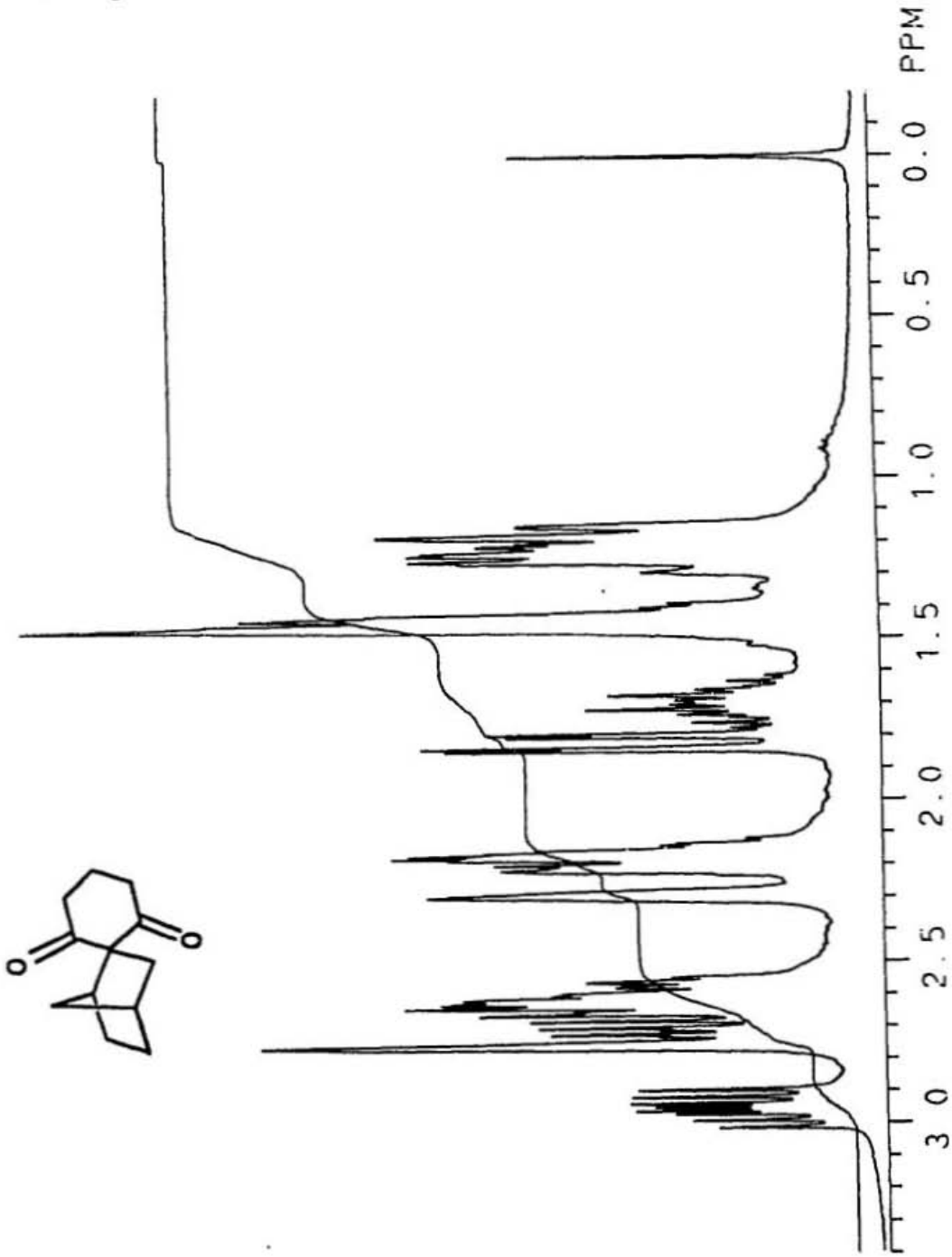
532 ($CDCl_3$)



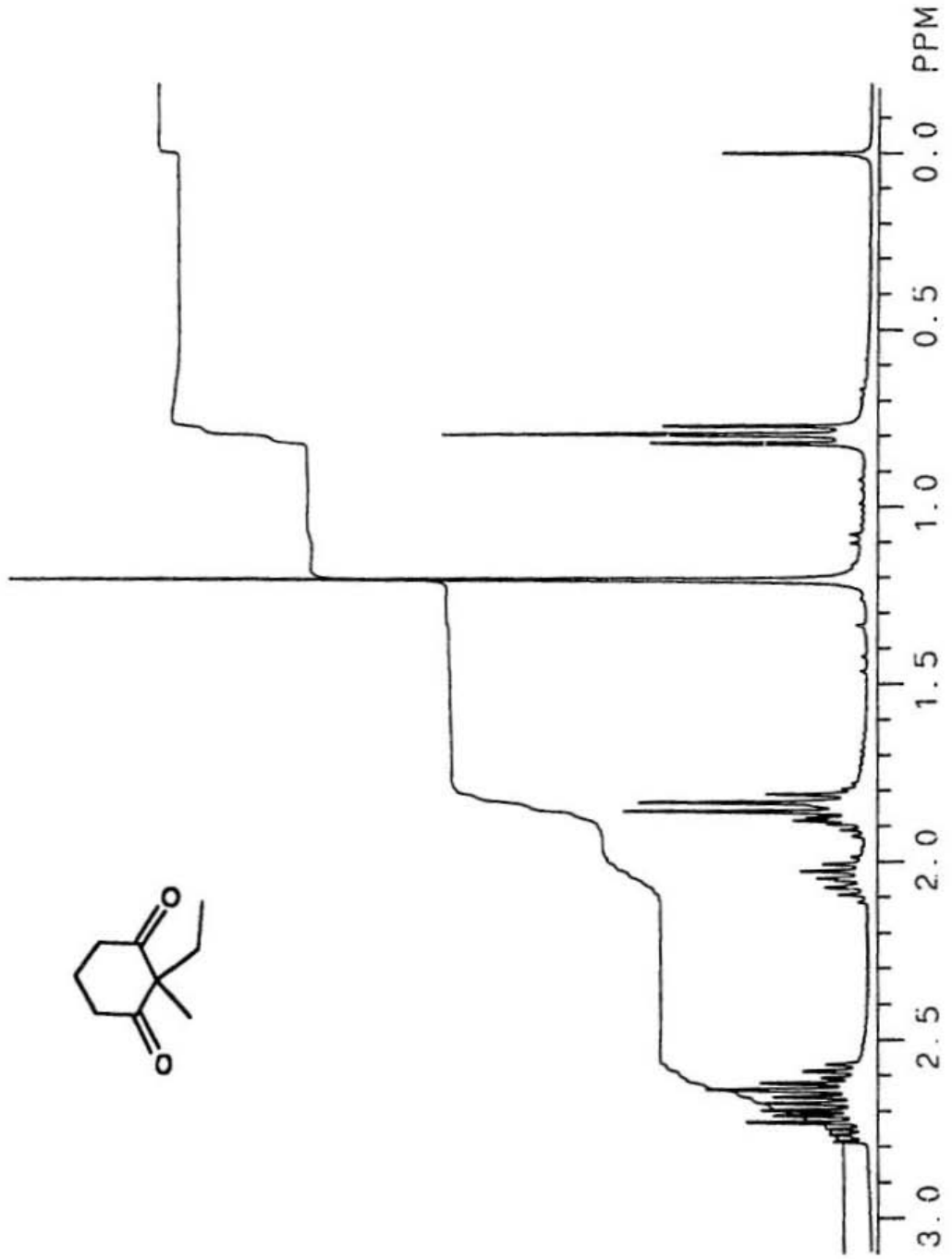
548 ($CDCl_3$)


2.687
2.110
1.895
1.517
1.411
1.429
1.617
1.538
1.449
1.940
1.759
.000
4
3
2
1
0
PPM

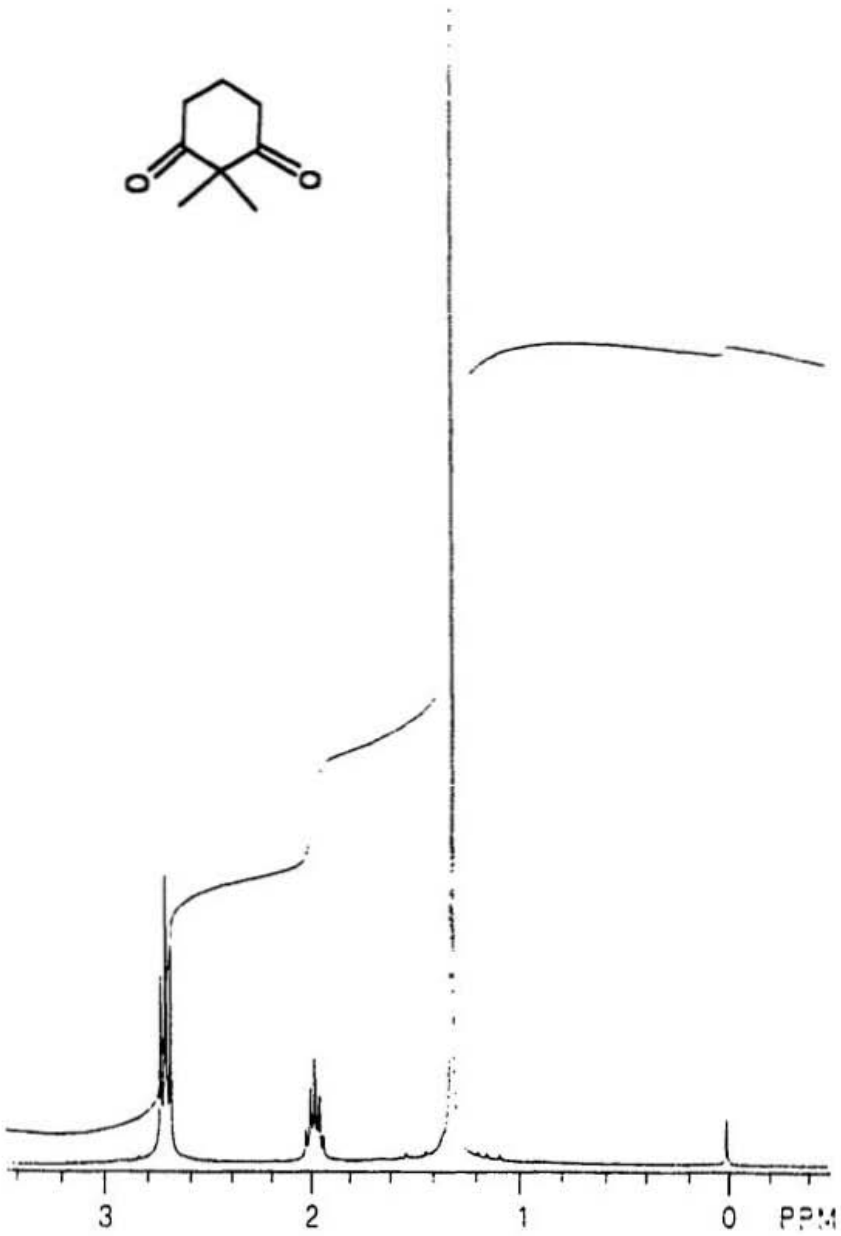
549 ($CDCl_3$)



550 ($CDCl_3$)



551 ($CDCl_3$)



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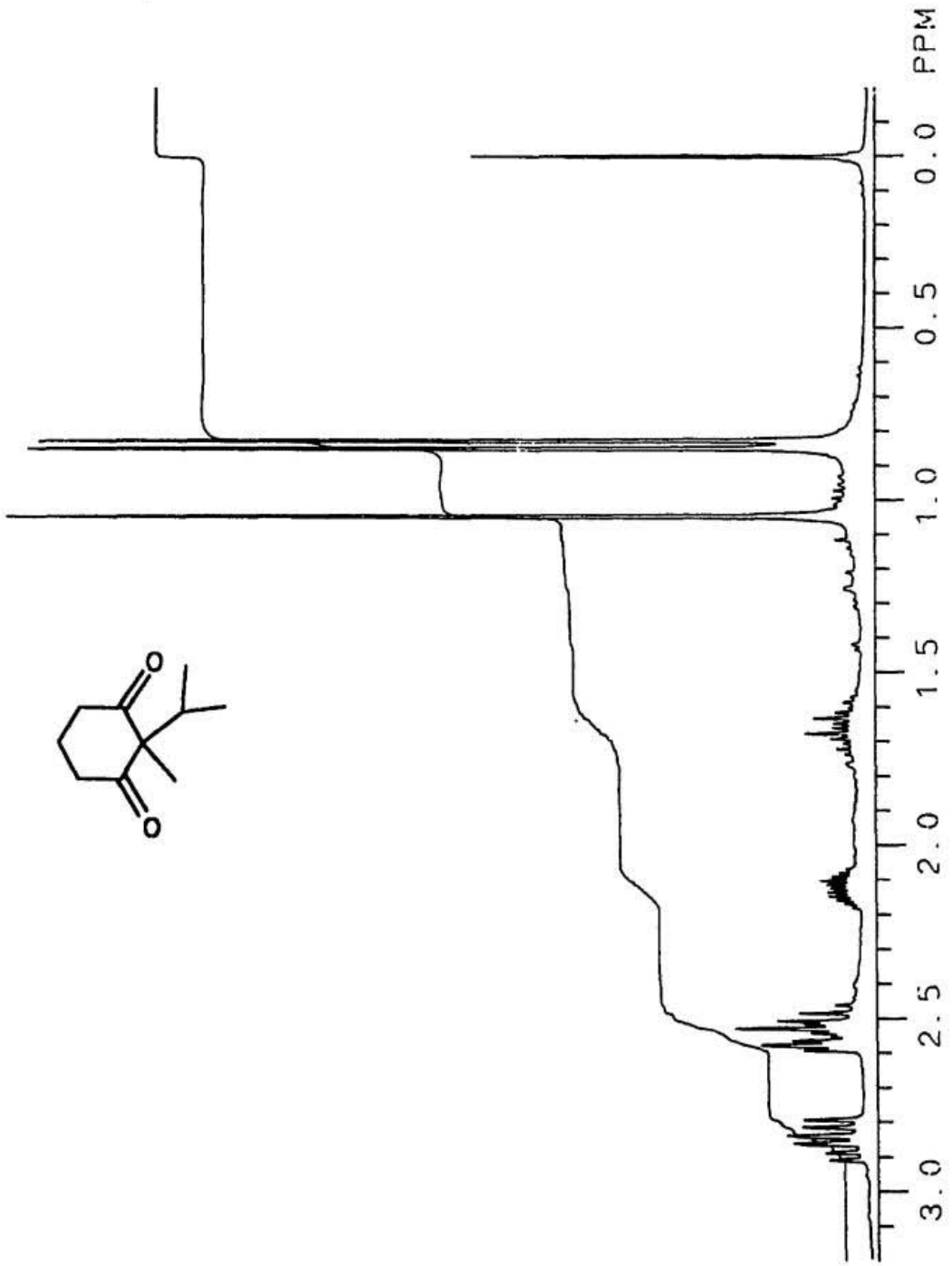
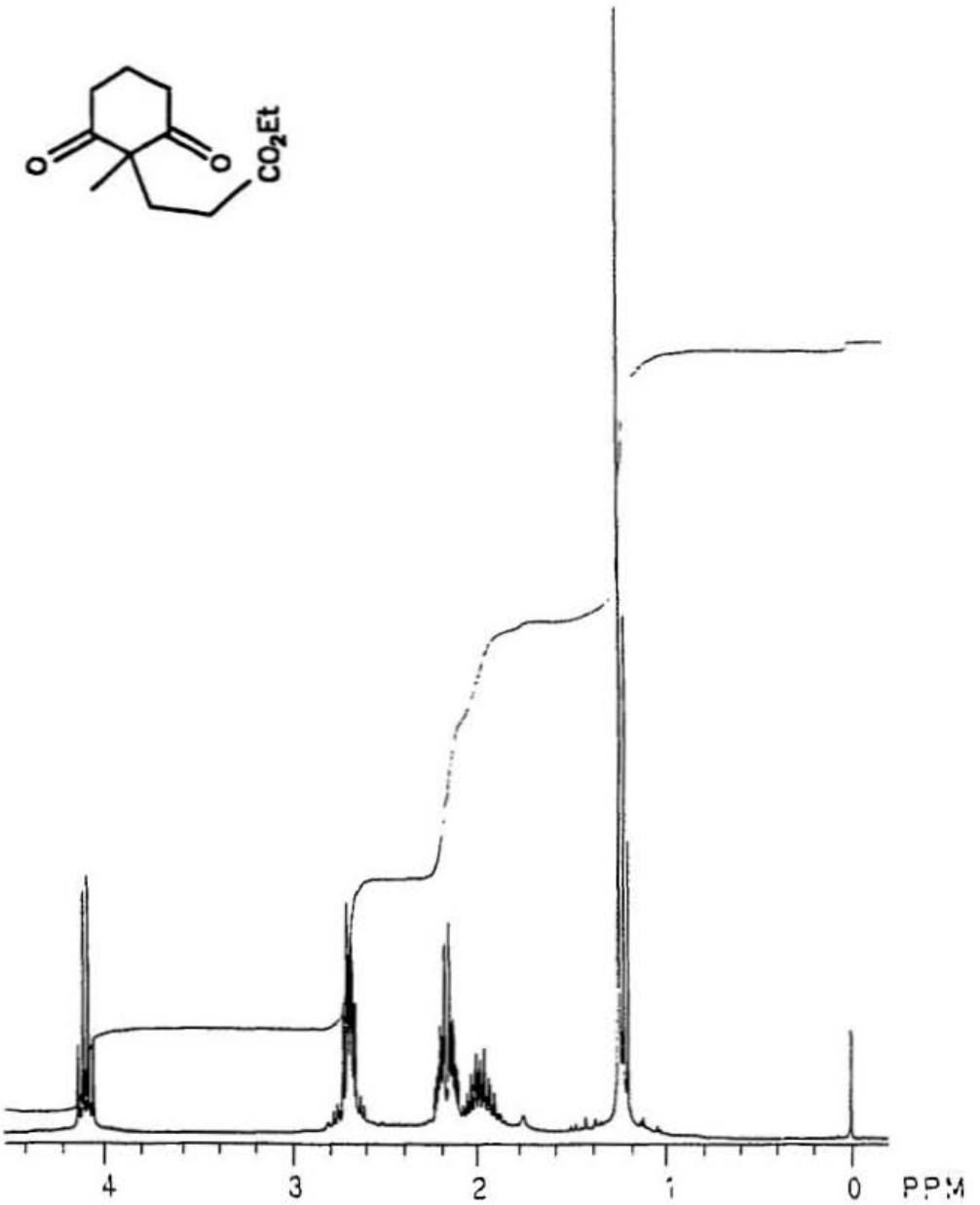


553 ($CDCl_3$)



555 ($CDCl_3$)