[4+1] CYCLOPENTENE ANNULATION IN THE TOTAL SYNTHESIS OF PENTALENENE TYPE SESQUITERPENES

by

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(ABSTRACT)

The generality of the [4+1] cyclopentene annulation was demonstrated by the total synthesis of (±)-pentalenene and its C-9 epimer which were prepared in a stereocontrolled manner in analogy with the synthesis of (±)-isocomene, (±)-hirsutene and (±)-pentalenic acid. The key features of this synthesis involved preparation of acid **161**, its conversion to diazoketone **148**, intramolecular cyclopropanation of this substance to vinylcyclopropane **163** and the vinylcyclopropane-cyclo pentene rearrangement of several derivatives of **195** to triquinanes **147**, **146**, **197**, and **204**. A detailed study of temperature, conformation, and electronic effects on the diradical scission of vinylcyclopropanes of type **195** was carried out under pyrolytic conditions. Conclusive results regarding conformational stability at C-9 were also attained and exploited in the context of stereocontrol at this center. As a result of this synthesis, several new methods of functional transformations emerged, such as the selective reduction of conjugated esters and a new method of preparation of enolethers from carboxylic acids.

Acknowledgements

Heartfelt thanks are extended to my research director and mentor, Tomas Hudlicky, for bringing this research problem to my attention and for guiding me through to its completion. More importantly, I am indebted to him for the personal care and attention which he invested in my professional, and often personal growth.

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Dedicated to my Parents, and

[4+1] CYCLOPENTENE ANNULATION IN THE TOTAL SYNTHESIS OF PENTALENENE TYPE SESQUITERPENES

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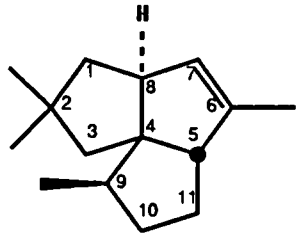
A. Historical

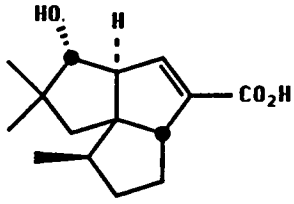
I. Introduction

The angularly fused triquinane sesquiterpene pentalenene **1** is the parent hydrocarbon of the family of sesquiterpene antibiotics to which pentalenic acid **2**[1,2] and pentalenolactone **3**[3,4] both belong (Fig. 1). The first compound which was shown to posses its novel tricyclo [6.3.0.0^{4,8}] undecane moiety was retigeranic acid **4**[5] which eluded the efforts of synthetic chemists for almost 11 years until Corey et al. reported its total synthesis.[6] This moiety was shown to constitute part of the structures of laurenene **5**[7] and crinipellin **6**.[8] Five different types of the angular triquinane framework have been found in Nature and are represented by pentalenene **1**, isocomene **7**,[9,10] silphinene **8**,[11,12] silphiperfolene **9**,[11,13] and subergorgic acid **10**.[14] Hirsutene **11**,[15,16] hirsutic acid **12**,[17,18] and coriolin **13**[19,20] exemplify a closely related family of sesquiterpenes which contain a linearly fused triquinane ring system. In addition to their structural relationship, these two families are related biogenetically through farnesyl pyrophosphate **14** which is believed to be a common metabolic precursor to all cyclic sesquiterpenes[21] (See Scheme II, p. 7). Currently, it is estimated that a total of 80 naturally occuring compounds have been isolated which posses either a linear or nonlinear triquinane ring skeleton.[22]

There has been a great deal of interest in these types of compounds among synthetic chemists due to the challenge of constructing three fused cyclopentane or cyclopentene rings in a regio- and stereocontrolled fashion.[23] A wealth of new cyclopentane annulation



1. Pentalenene



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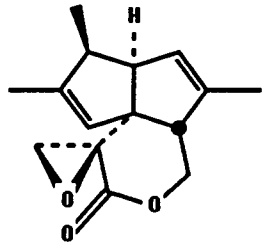
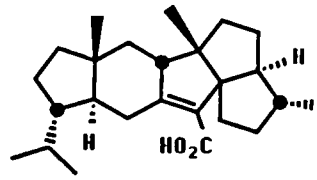


3.Pentalenolactone



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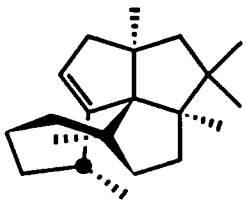

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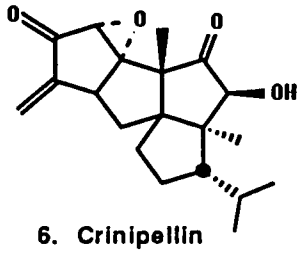

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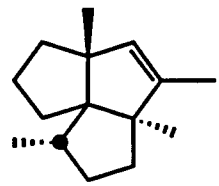

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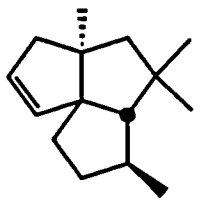

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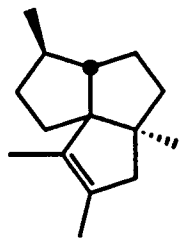
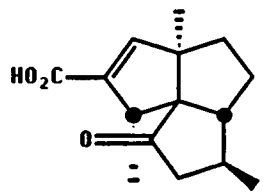
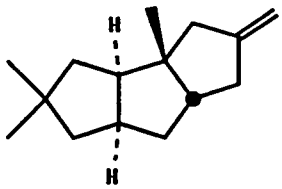


9. Silphiperfolene



10. Subergorgic acid



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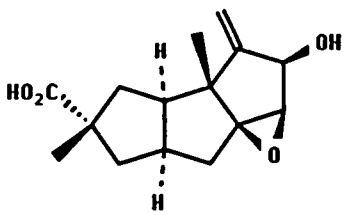
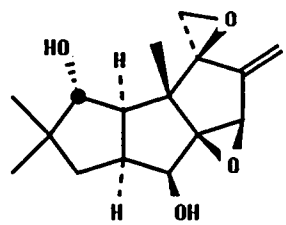


12. Hirsutic acid



13. Coriolin

Figure 1

technologies emerged as a result of increasing interest in triquinane sesquiterpenes as targets and many of these methodologies have been reviewed.[24] Of particular interest in recent years has been the development of general methodologies which allow one to gain entry into a number of different skeletal arrangements from common, mutually interconvertible intermediates. Notable examples include entry into various angularly fused triquinanes containing a 1,5 dimethyl moiety such as pentalenene **1**, isocomene **7**, silphinene **9** and subergorgic acid **10** from 1,5-dimethylcyclooctadiene **79** via a transannulation pathway prosed by Mehta and Rao[25] (see Fig. 6, p. 22). Similarly, Crimmins published a synthetic pathway to construct dione **15** from which pentalenene **1**,

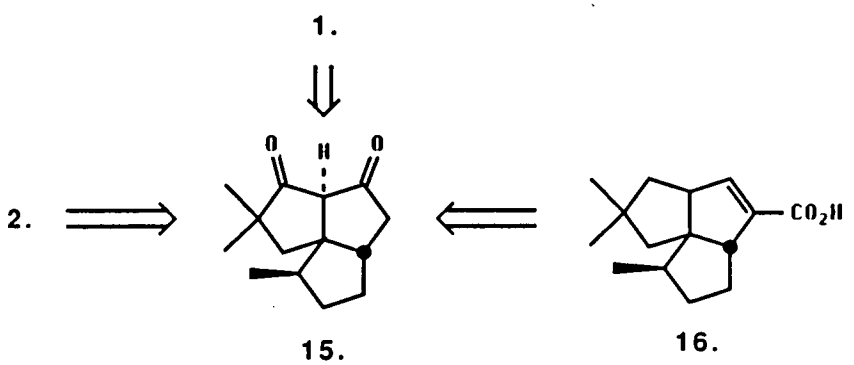


Figure 2

pentalenic acid **2**, and deoxypentalenic acid[2ab] **16** (Fig. 2). One of the most general schemes which have been proposed thus far is the [4+1] cyclopentene annulation proposed by Hudlicky and coworkers which has been applied to the construction of linear triquinane, hirsutene **11**[16c] and the nonlinear moieties isocomene **7**,[10a] isocomenic acid **17**[26] and the triquinane portion of retigeranic acid **4a**[6b] (Fig. 3).

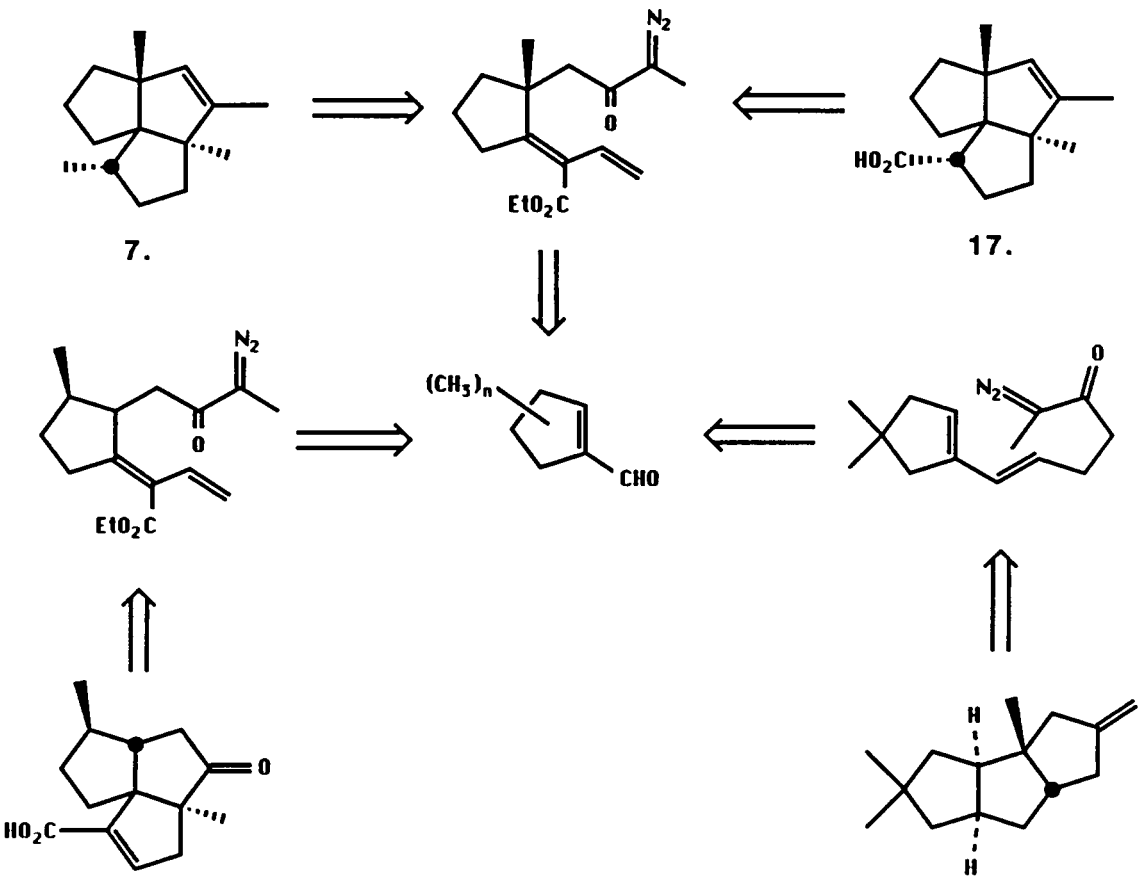
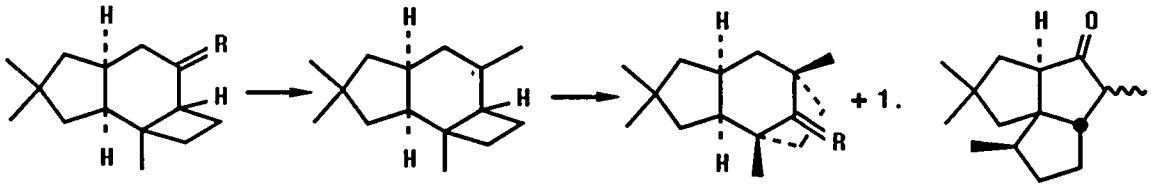


Figure 3

II. Isolation and Structure

In an attempt to gain entry into the Illudane sesquiterpene skeleton[27] via solvolysis of protoilludyl cation **18** (Scheme I), Matsumoto et al.[28] isolated a unique hydrocarbon as a byproduct in addition to the expected bicyclic structure **19**. Initial ^1H NMR, IR and mass spectral data suggested that partial structures H-$\underset{|}{C}$-CH_3, H-C=C-CH_3 and -$\underset{|}{C}$-$(CH_3)_2$ were contained in a tricyclic system and accordingly stucture **1** was suggested and later confirmed by LIS NMR studies of

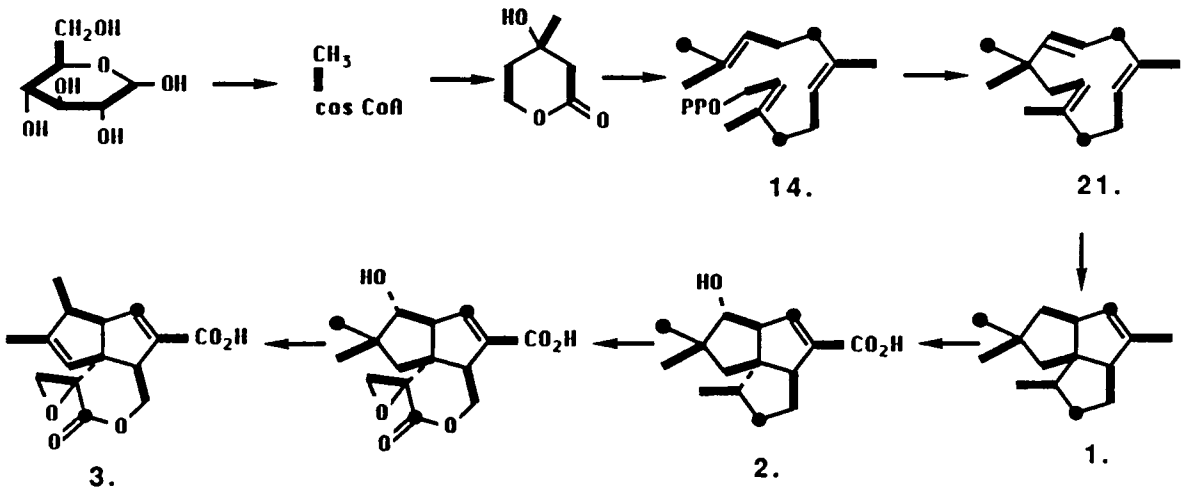


Scheme I

cyclopentanone **20** obtained from **1** by hydroboration-oxidation and subsequent Jones oxidation. The authors did not pay particular attention to the seemingly insignificant byproduct at that time because it had not yet been isolated and identified as a natural product. However, a few years later the same compound was isolated from the neutral broth of an extract from Steptomyces griseochromogenes in an attempt to ascertain what intermediate metabolites might be present as precursors to pentalenelactone **3** which was also found in that species.[29] Initial ^1H and ^{13}C NMR data seemed to suggest structure **1**, and indeed, comparison of spectra confirmed the fact that the newly isolated compound was identical to the synthetic substance **1**. Upon its initial isolation, Seto et al. correctly assumed this compound to be the parent hydrocarbon of the pentalenolactone family of antibiotics and proposed the name Pentalenene.

III. Biosynthetic studies

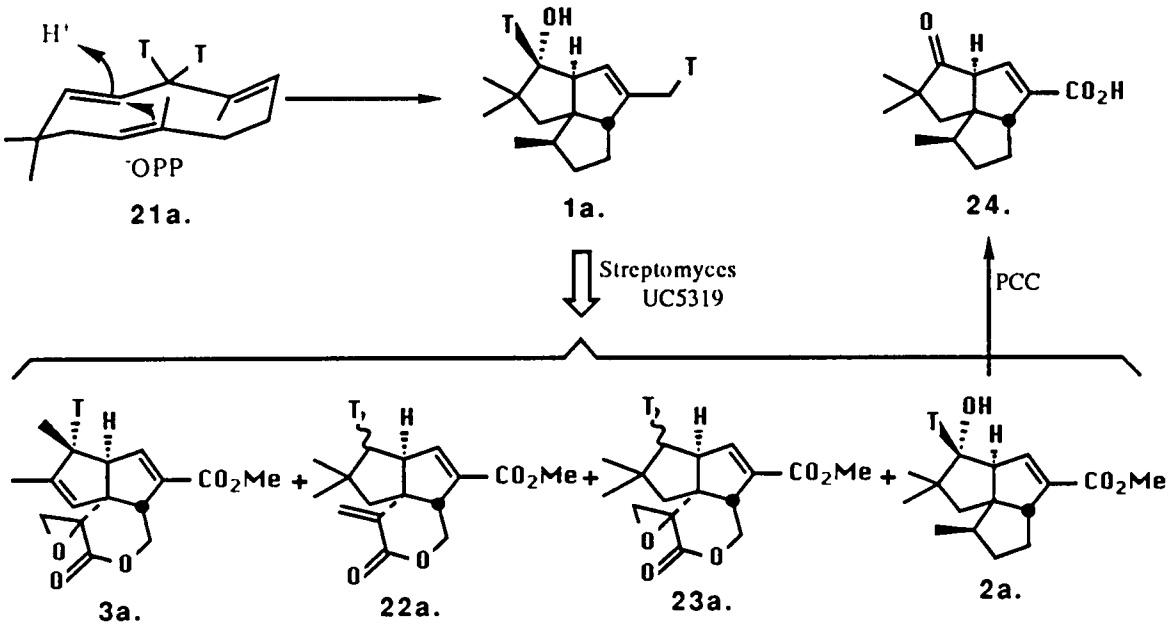
Pentalenolactone 3 has long been a compound of interest to both the biosynthetic[30] and synthetic[4] community as it has been shown to be active against a variety of microorganisms including gram-negative and gram-positive bacteria, pathogenic and saporophytic fungi, and protozoan species.[31] It has also been shown to block glycolysis in target organisms by selective inhibition of glyceraldehyde-3-phosphate dehydrogenase.[32] It has been postulated to arise biogenetically via a mevalonate pathway[33] (Scheme II). Evidence for this assumption was provided when [UL- $^{13}C_6$] glucose, an <u>in vivo</u> precursor to [1,2-$^{13}C_2$]acetyl-CoA, was shown to be incorporated into pentalenolactone[30] when fed to cultures of <u>Streptomyces UC5319</u>. Such a pathway would implicate humulene 21 as an intermediate metabolite, which in turn is derived from 14 as are most other cyclic sesquiterpenes[21]. Evidence for this proposition was given upon initial isolation of the hydrocarbon 1 from <u>Streptomyces griseochromogenes</u>[29] which is also a source of



Scheme II

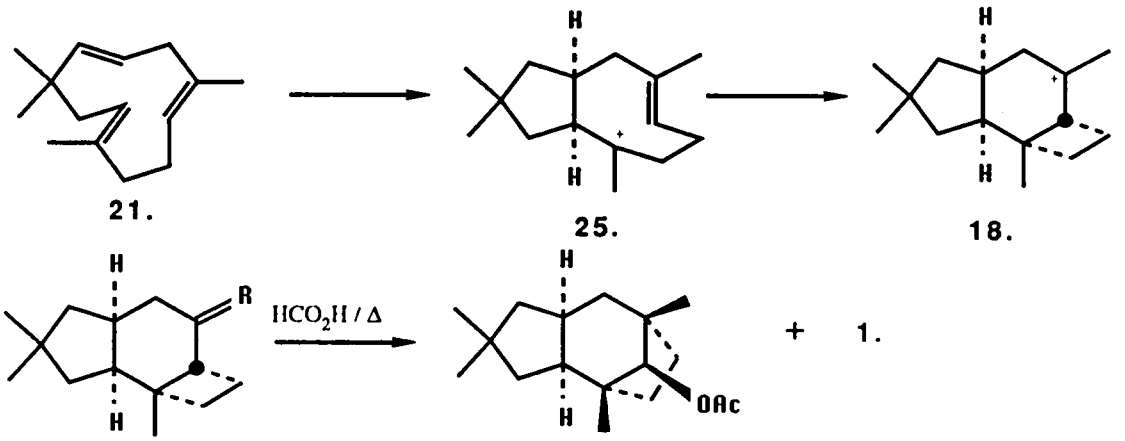
pentalenolactone **3**.

Pentalenene **1** has more recently been shown to be a biosynthetic precursor to a number of members of the pentalenolactone family of antibiotics.[34] Feeding [1,13- ^{3}H] pentalenene **1a** (prepared according to ref. 35 by ^{3}H-$NaBH_4$ reduction of the mercuric nitrate cyclization product of humulene **21a**) to a culture of Streptomyces UC 5319 gave labeled pentalenolactone **3a**, pentalenolactone E **22a**,[36,37] pentalenolactone F **23a**[34] and pentalenic acid **2a** all of which were isolated as their methyl esters (Scheme III). The site of tritium labeling was confirmed by a loss of tritium activity (≤1% of original amount of **2a**) upon pyridinium chlorochromate oxidation of **2a** to the corresponding ketone **24**.



Scheme III

Evidence pertaining to the biosynthesis of pentalenene **1** was obtained even before it was isolated and identified as a natural product. Ohfune et al.[28] were attempting to mimic the biosynthetic conversion of humulene **21** to the illudoid **19** in order to gain evidence for a carbocation based mechanism which has long been thought to first proceed through **25** and then through the protoilludyl cation[38] **18** (Scheme IV). Exocyclic olefin **26** and alcohols **27a** and **27b** were prepared[39,40] as protoilludyl cation equivalents and heated in formic acid to give **19** and the previously unknown hydrocarbon **1** in a 7:3 ratio.



21. **25.** **18.**

26. R = CH_2

27a. R = β-OH, α-CH_3

27b. R = α-OH, β-CH_3

19.

Scheme IV

The apparent ambident character of **18** was explained in terms of two plausible conformations **18a** and **18b.** A Wagner-Meerwein shift with concurrent capture of formate ion would be highly preferred in conformation **18a** due to the favorable stereoelectronic alignment of the neighboring lateral cyclobutane bond with the vacant carbocation orbital; however, the central cyclobutane bond is more adequately aligned with the vacant orbital to undergo fragmentation in conformation

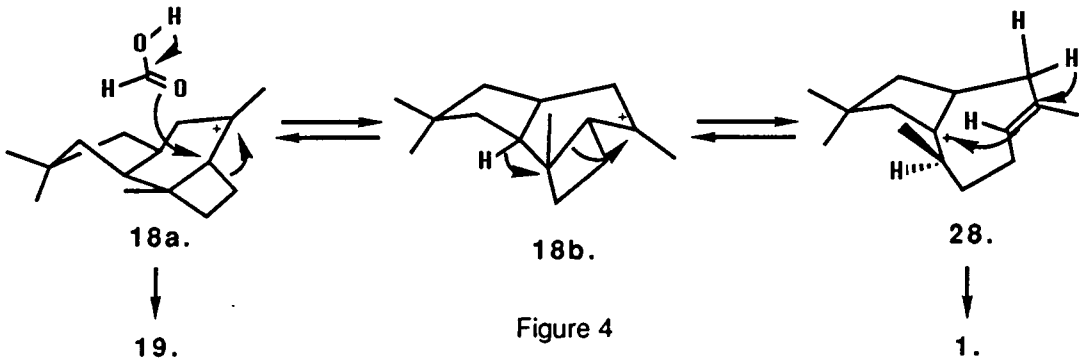
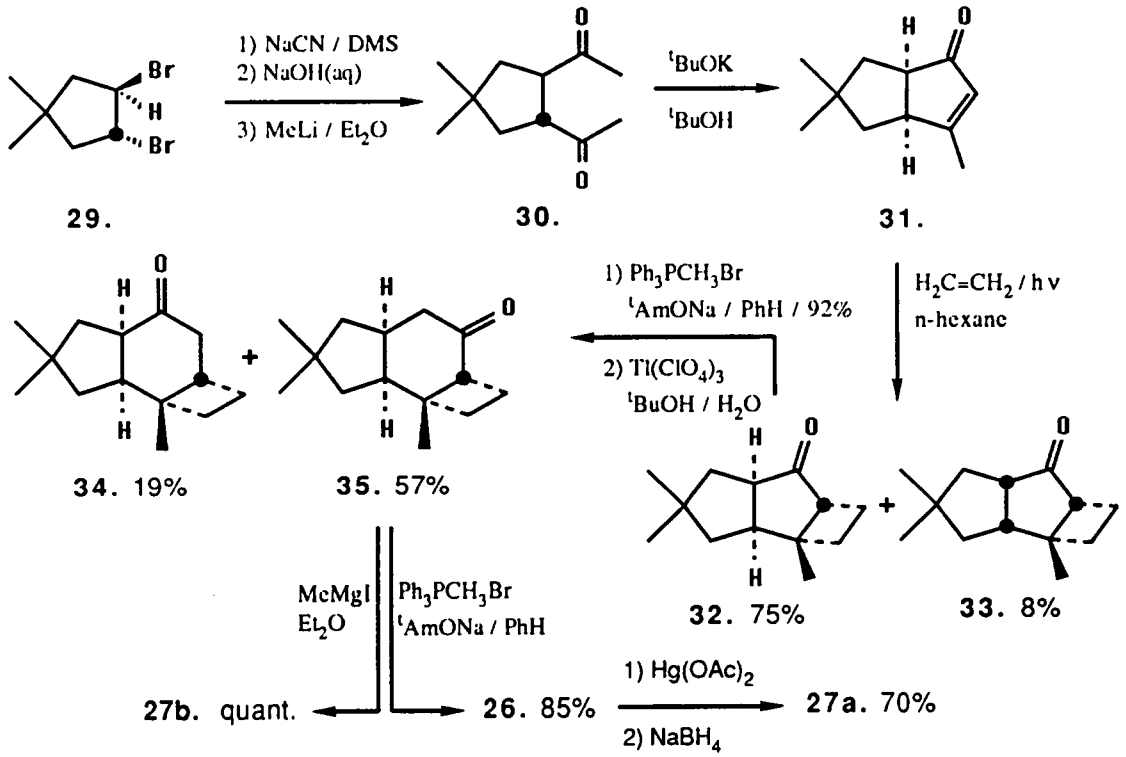


Figure 4

18b with a concomitant 1,2-hydride shift (Fig. 4). Subsequent cyclization of cation **28** to pentalenene **1** can then be expected because of the enforced proximity of the π bond to the cationic center.[41]

The protoilludyl cation equivalents **26**, **27a**, **27b** were prepared using classic organic reactions (Scheme V). The dibromide[42] **29** was converted to a dicyanocyclopentane and subsequently hydrolyzed to a dicarboxylic acid, converted to diketone **30**, and cyclized

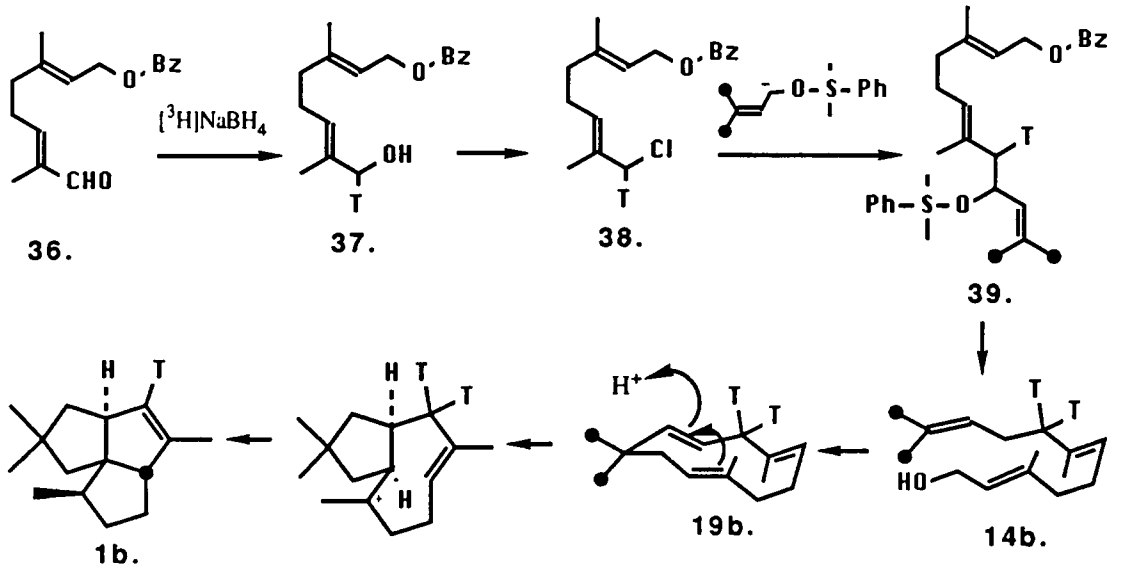


Scheme V

intramolecularly to give diquinane **31**. This diquinane was then subjected to a [2+2] photochemical cycloaddition with ethylene to give 75% of desired cyclobutene **32** in addition to 8% of undesired diastereomer **33**. Conversion of **32** to an exomethylene compound followed by ring enlargement with $Tl(ClO_4)_3$ gave 19% of **34** which resulted from cleavage of the ring junction and 34% of desired **35**. Each of the aforementioned protoilludyl cation equivalents became readily available from **35** in one or two high yield steps.[40]

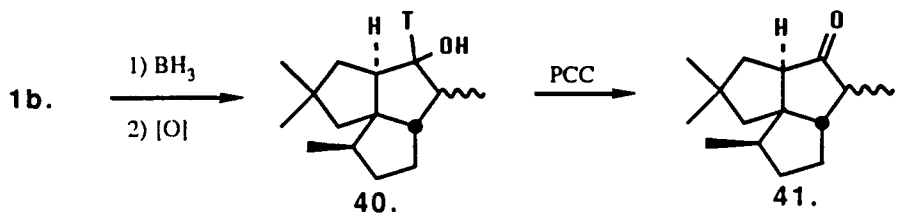
The work done by Ohfune et al.[28] supplied the first piece of evidence that the pentalenolatone lactone family of antibiotics arises via a mevalonate biosynthetic pathway, since it was shown that pentalenene **1** can arise from **21** which is derived from humulene **15**. The isolation of **1** from Streptomyces griseochromogenes by Seto et al.[29] and Cane's biosynthesis[30a] of pentalenolactone from [UL- $^{13}C_6$] glucose also lent support, but the most convincing data came from the biosynthesis of **1**[30,43] (Scheme VI).

In order to study the biosynthesis of pentalenene **1** Cane et al. used cell free extracts of Streptomyces UC5319 in order to prevent problems with precursor permeability and the conversion of pentalenene to higher metabolites. The first labeled precursor, trans, trans-9,^{3}H-farnesol **14b**, was prepared by [^{3}H] $NaBH_4$ reduction of 8-oxogeranylbenzylether **36**[43a] followed by conversion of the resulting [8-^{3}H] alcohol **37** to chloride **38**[43a], coupling with the lithio anion of dimethylallyl-phenylsulfone **39**[43b], and reductive cleavage with lithium in ethylamine.[43] Alcohol **14b** was converted to its corresponding pyrophosphate ester,[44] and was added to a buffered solution which was



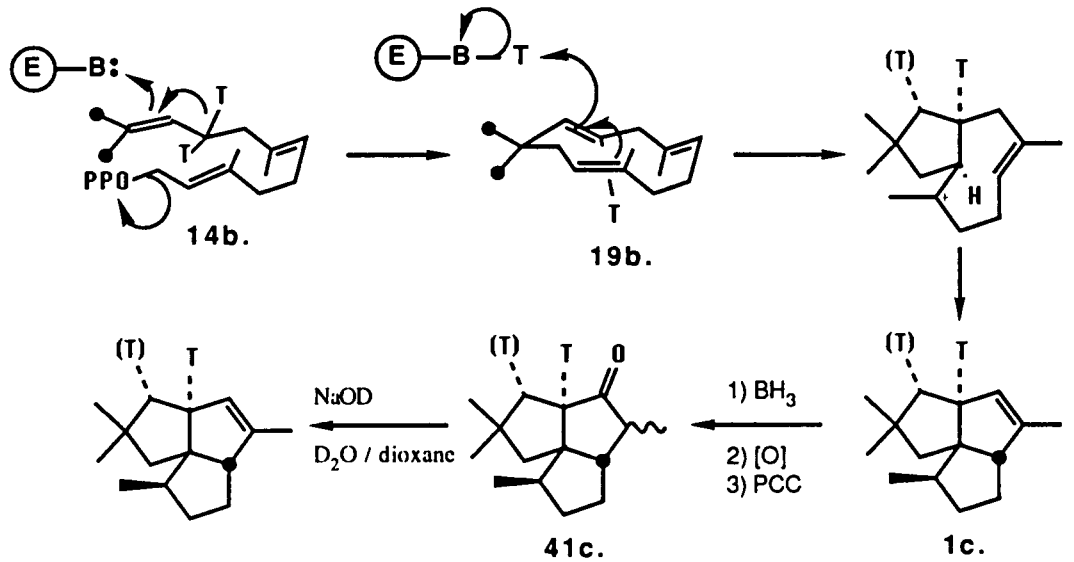
Scheme VI

harvested from the rapid stirring of a 60 hr. culture of Streptomyces UC5319 with glass beads. After 1.5 hr. at 30°C, 44 mg. of (±)-pentalenene was added as a carrier and the solution was extracted with pentane. Based on the activity of the recovered product, a near quantitative amount of tritium was retained compared to the amount of ^{14}C which was retained. In order to establish C-7 as the site of tritiation and confirm enzyme specificity, the recovered pentalenene **1b** was converted to 7-hydroxypentalenene **40** upon hydrobortion-oxidation and followed by pyridinium chlorochromate oxidation to give pentalen-7-one **41** which was devoid of all tritium activity (Scheme VII).



Scheme VII

The resulting location of tritium supported the mechanism which is illustrated in scheme VIII and also suggested the proper configuration of humulene **19b**. Its structural similarity to farnesylpyrophosphate **14b** hinted at the possibility that a single active site is responsible for the conversion of **14b** to **1b**. Circumstantial evidence that **19b** does not accumulate during the course of cyclization became available by repeated



Scheme VIII

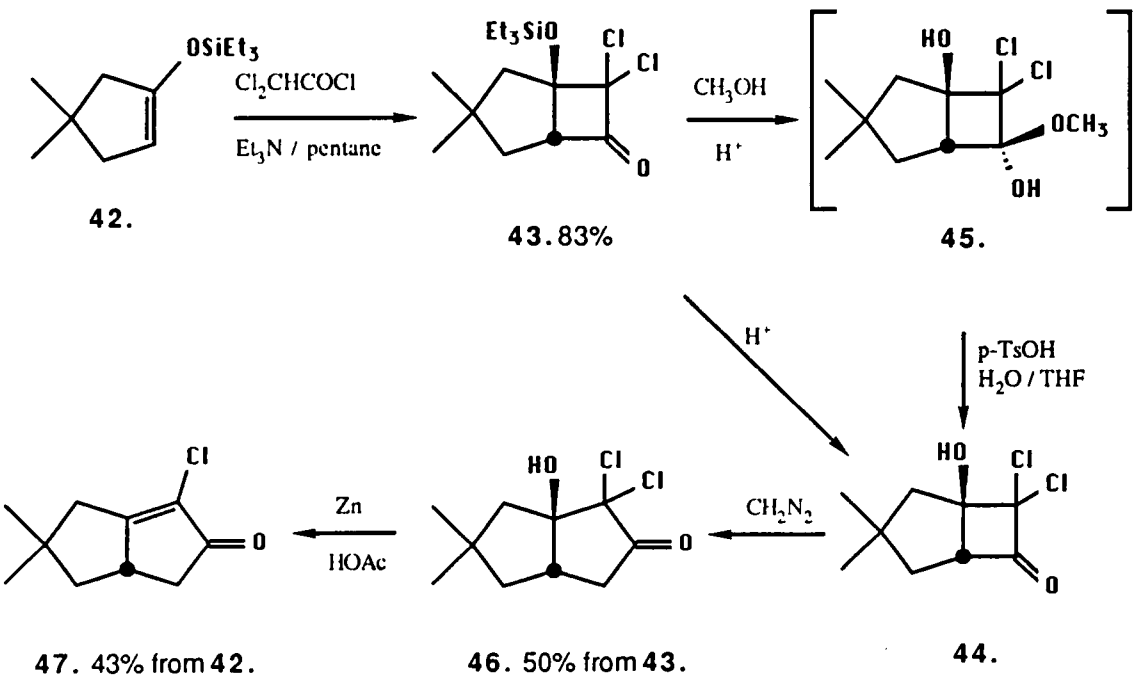
failures to isolate **19b** early in the reaction process. Additional support was realized upon subjecting [9- ^{3}H, 12,13- ^{14}C] farnesyl pyrophosphate **14c** to the same cyclization conditions that were applied to **14b** (Scheme VIII) and a sample of tritium labeled pentalenene **1c** was obtained which was converted to pentalene-7-one **41c**. In this case, tritium activity remained unchanged, however, when the ketone **41c** was subjected to NaOD in D_2O/dioxane the tritium activity decreased to one half of its original value. It was thus shown that C-8 was the site of one tritium site with another (believed to be at H-1α) being present at a base inactive position. This data is consistent with the operation of

a single enzyme mediating pentalenene formation. Support for an enzyme mediated proton transfer would be realized if H-1α was shown to be the second site containing tritium.

IV. Total Synthesis

Upon confirmation by Cane et. al. that pentalenolactone **2** and pentalenene **1** arise via a mevalonate pathway, attention was redirected toward the conversion of protoilludyl cation **18** to pentalenene. Paquette noted in his report on the total synthesis of (±)-pentalenene[45] that **18** rearranges to **28** via a hydride shift. This cast ambiguity on the most thermodynamically stable conformation of the methyl group at C-9 since the stereochemistry at this center is set during a kinetically controlled process. The primary goal in his synthetic plan was to establish which configuration was the more stable.

The overall synthetic strategy involved sequential ring formation beginning with ring A onto which ring B was constructed and



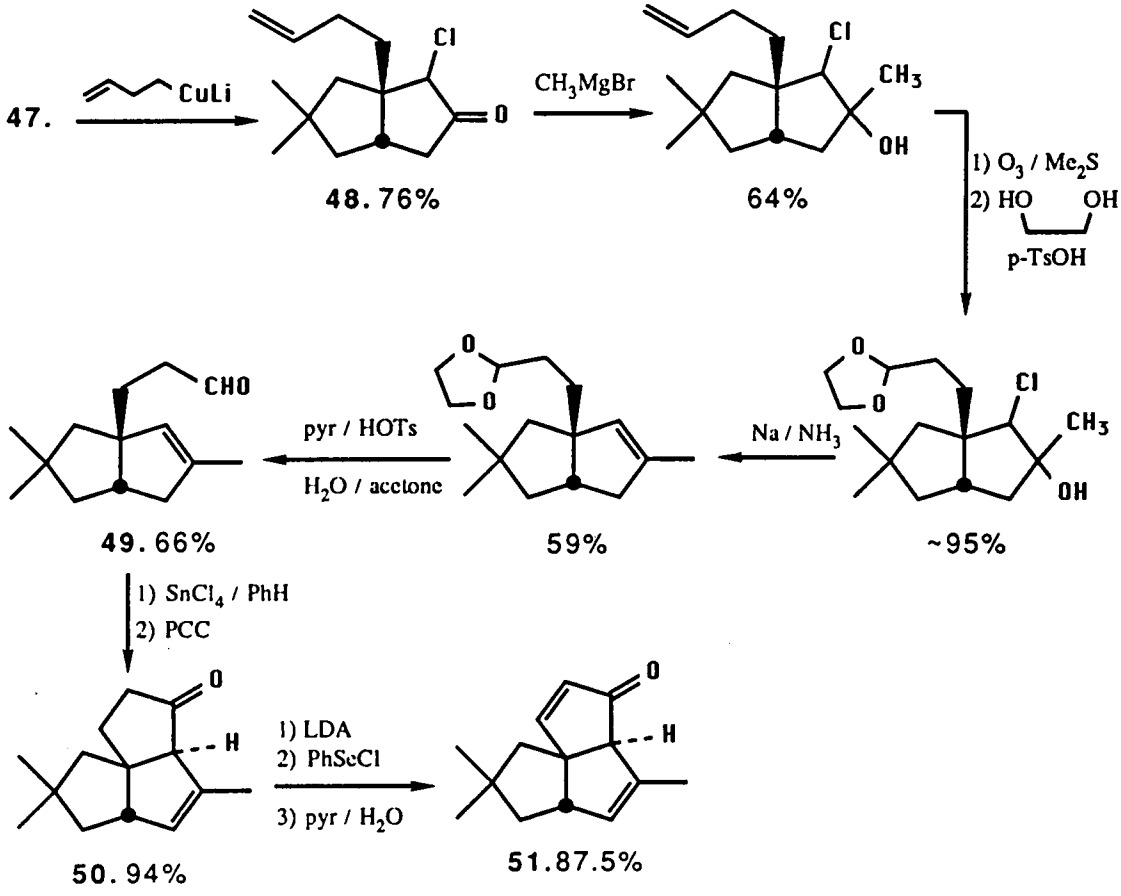
42. **43.** 83% **45.**

47. 43% from **42.** **46.** 50% from **43.** **44.**

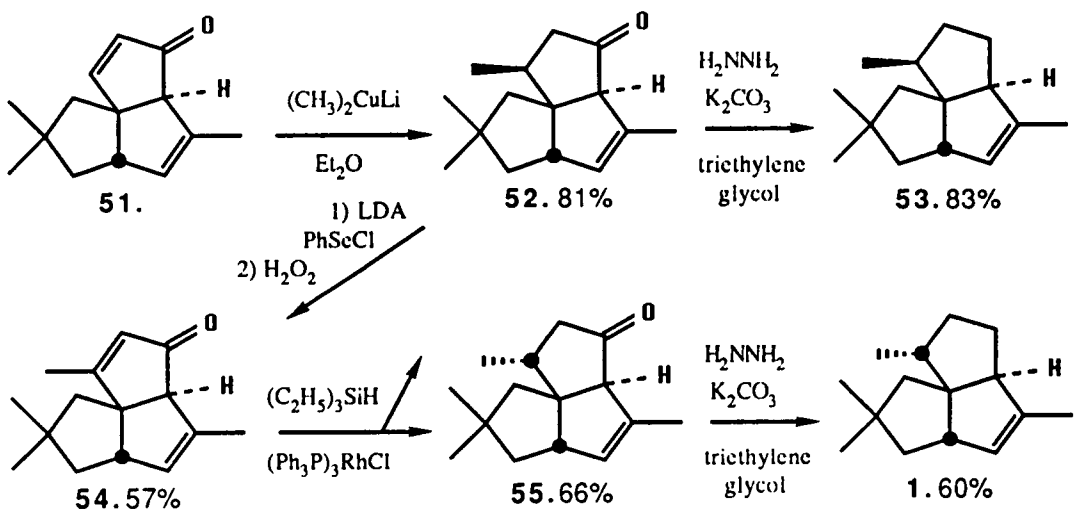
Scheme IX

subsequently served as a foundation for ring C. A convenient template for ring A was available in 3,3-dimethylcyclopentanone since this compound could be readily hydrosilylated[46] to give silyl enolether **42**, which participated in a [2+2] cycloaddition with $Cl_2C=C=O$ with established regiospecificity[47] to give **43** in 83% yield from 3,3-dimethylcyclopentenone (Scheme IX). Aqueous acidic hydrolysis effectively freed the angular hydroxyl group yielding **44**; however, its lability to both heat and chromatography prevented efficient removal of hexaethylsiloxane which was formed as a byproduct. An alternate route proceeded through hemiacetal **45** via solvolysis in acidic methanol, since the resulting siloxane ($MeOSiEt_3$) could be removed from the non-volotile bicyclic product under vacuum. Thus treatment of **43** with aqueous HCl provided pure **44**. Treatment of **44** with diazomethane gave the ring expanded product **46** which quantitatively furnished enone **47** upon exposure to zinc dust in acetic acid.[48] This efficient sequence converted **42** to **47** in 43% overall yield and set the stage for the construction of ring C.

For kinetic and thermodynamic reasons, cuprate addition to **47** was expected to give a cis-fused ring junction. Lithium (di-3-butenyl)-cuprate added to **47** as expected to give **48** in 76% yield after the same reaction had failed with a number of magnesium cuprates. After five steps involving classic functional manipulations, **49** was obtained and a ring closure of ring C was accomplished upon treatment of this substance with stannic chloride to give ketone **50** in 94% yield after PCC oxidation (Scheme X). Dienone **51** became readily available upon kinetically controlled selenation of **50** and selenoxide elimination.



Scheme X



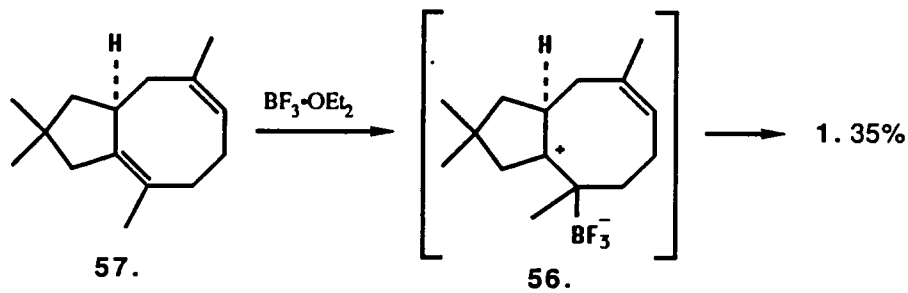
Scheme XI

Upon introduction of the secondary methyl group at C-9, Paquette had planned to determine its most stable thermodynamic configuration. Lithium dimethylcuprate added easily to **51** to yield a single conjugate addition epimer **52** (Scheme XI). Wolff-Kishner reduction with hydrazine hydrate and potassium carbonate in triethylene glycol[49] at 250°C effectively converted the carbonyl to a methylene; however, 300-MHz ^1H NMR did not correspond to the spectrum of natural pentalenene. Delivery of the methyl group to **51** must have occured from the β-face to give **52** which in turn gave epi-pentalenene **53** upon reduction. Since cuprate reactions are generally controlled by kinetic factors,[50] **52** was transformed to **54** and reduced with lithium in liquid ammonia. Again, epi-pentalenene was the exclusive product giving almost unquestionable evidence that the β-configuration of the methyl group at C-9 was thermodynamically preferred in this ketone. Since the β-face seemed to be kinetically favored in **51**, it seemed reasonable to presume that the same would be true in **54**, so a search was initiated to find a reducing agent that would effectively exploit this kinetic preference. Included were CuH,[51] $NaHFe(CO)_4$,[52] NaHTe,[53] $NaHFe_2(CO)_3$,[54] and $Pd/Et_3N/HCO_2H$,[55] but none of these were effective in bringing about reduction of the enone. Finally, the sterically bulky reagent combination $(Ph_3P)_3RhCl/Et_3SiH$[56] reduced the enone with some apparent kinetic control (**52**:**55**=2.24:1). Upon Wolff-Kishner reduction, a mixture of **53** and **1** was obtained and separated by preparative Gas Chromatography.

Aside from total synthesis of the natural product, the most significant information resulting from this work was the suggestion that the natural product possessed the less stable configuration at C-9.

This lent considerable credence to the aforementioned, proposed biogenesis of pentalenene since it suggested that the stereochemistry at C-9 is set via a kinetically controlled hydride shift. One would expect the natural product to posses the more stable β-configuration if such were set during a thermodynamic process.

Pattenden designed a biomimetic synthesis to proceed through **56** which should react analogously to biosynthetic intermediate **28** to effect transannulation and give pentalenene.[59] The synthesis was directed toward **57** which would render **56** accessible upon treatment with boron

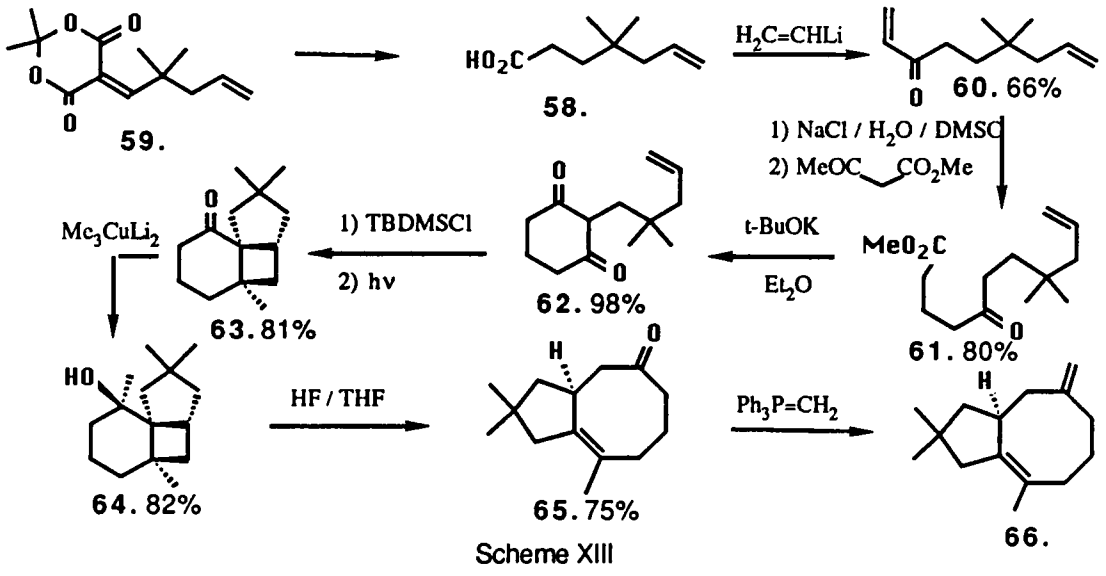


57. **56.**

Scheme XII

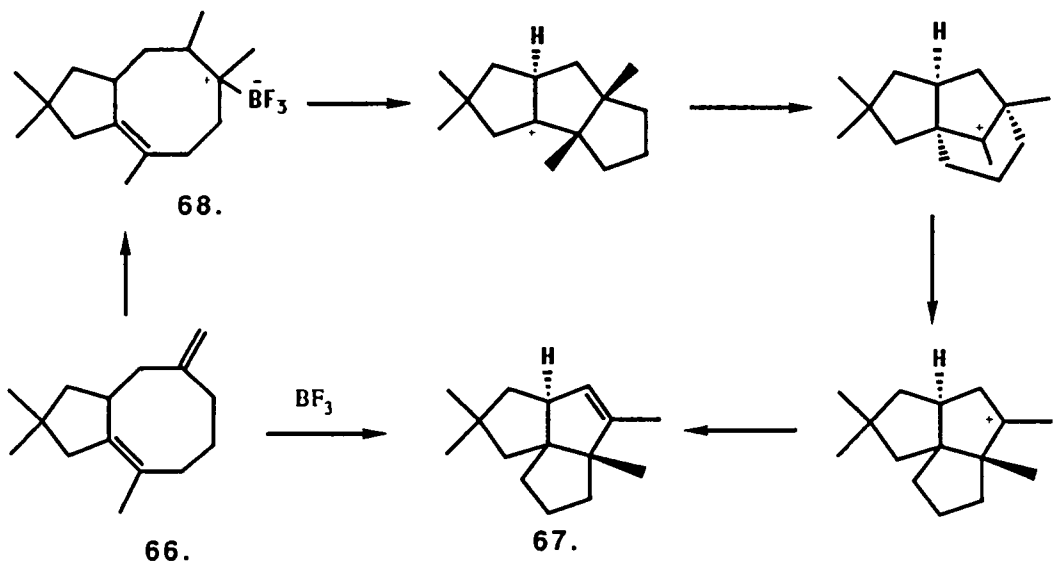
trifluoride etherate (Scheme XII).

The synthesis began with the conversion of **58**, which was readily available form the Meldrum's acid derivative **59** to the corresponding vinyl ketone **60** with vinyl lithium (Scheme XIII). This was followed by Michael addition of dimethyl malonate with subsequent demethoxy-carbonylation to give δ keto ester **61**. Intramolecular acylation gave **62** and, because the cyclohexanedione moiety was symmetrical, **62** could be converted to its corresponding T-butyldimethylsilyl enol-ether which participated in a smooth intramolecular [2+2] photocycloaddition[58] producing tricyclic substance **63** without regiochemical problems.



Scheme XIII

Cuprate addition to tricyclic ketone **63** gave tertiary alcohol **64**[59] stereoselectively, which in turn made the ring cleavage to enone **65** possible upon treatment with hydrofluoric acid in aqueous THF.[60] Enone **65** was then converted to key intermediate **57** via Wittig reaction with the ylide of methylenetriphenylphosphorane, resulting in the production of **66**, which was subsequently isomerized with rhodium chloride

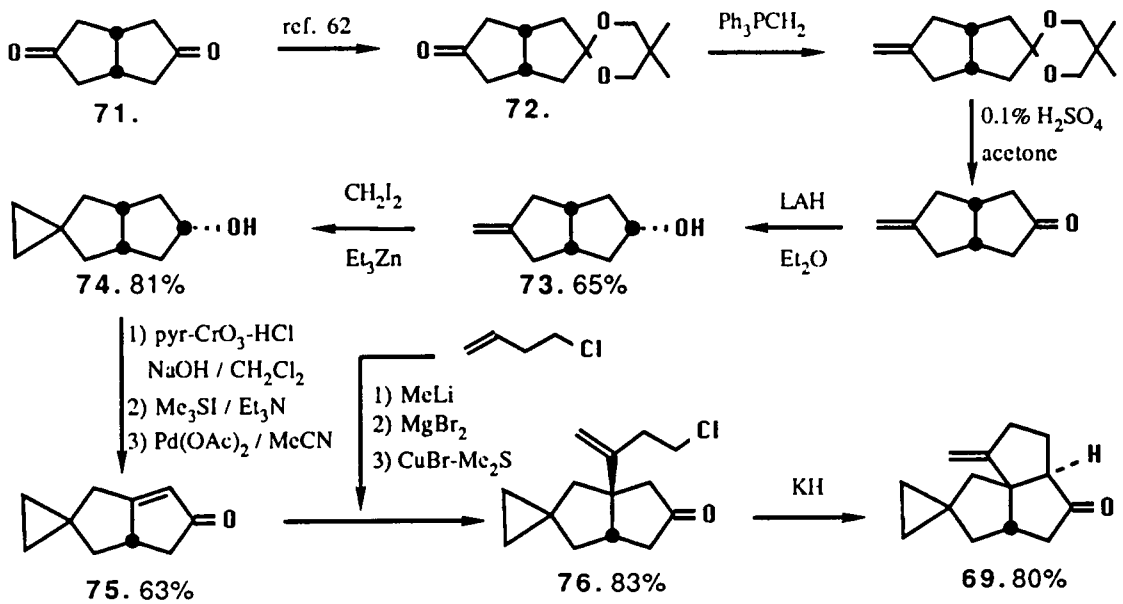


Scheme XIV

trihydrate in hot EtOH.[58a]

With **57** in hand, the final biomimetic conversion to pentalenene was studied. Treatment of **57** with $BF_3 \cdot Et_2O$ in methylene chloride resulted in stereospecific transannulation via the carbocation **56** to give (±)-Pentalenene **1** with no evidence for the formation of its C-9 epimer **53** (Scheme XII); however, an isomeric hydrocarbon **67** was produced in small amounts. It was believed to have arisen via initial transannulation of carbocation **68** with subsequent skeletal rearrangements depicted in Scheme XIV. This hydrocarbon was formed exclusively when **66** was treated in a similar manner with boron triflouride etherate.

Piers reported a total synthesis of (±)-pentalenene[61] during which he studied the conformational stability at C-9 by reducing an sp^2 center to a corresponding sp^3 center using the ketone intermediates **69** and **70** (Scheme XV). His synthesis began with monoprotection of diketone **71** to give **72**[62] followed by classic conversion to olefinic alcohol **73**.



Scheme XV

Treatment of 73 with CH_2I_2-Et_2Zn[63] gave cyclopropane 74; which, upon conversion to the corresponding ketone, gave enone 75 via enol ether formation with subsequent oxidation using $Pd(OAc)_2$ in acetonitrile.[64]

Upon preparation of 75, construction of ring C could begin using a novel methylenecyclopentane annulation method which was described earlier by Piers[65] and which was based on the generalized conversion depicted in (Fig. 5). The cuprate reagent was prepared by successively

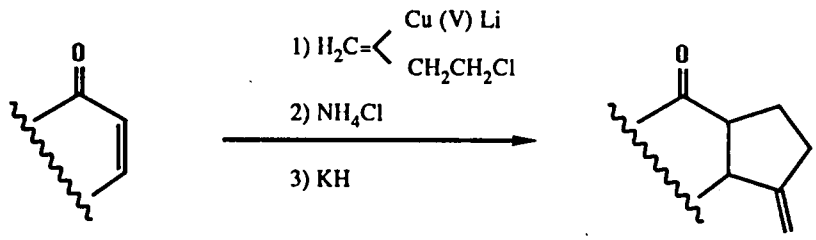
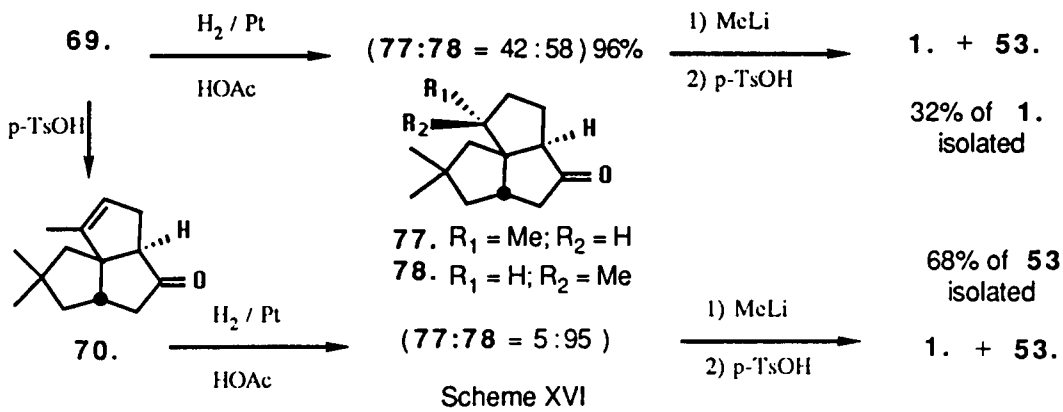


Figure 5

adding MeLi (1.1 eq.), $MgBr_2$ (1.2 eq.) and $CuBr.Me_2S$ to 4-chloro-2-trimethylstannylbut-1-ene[66] at -78°C in THF. Addition of enone 75 to the reagent gave a high yield (83%) of 76. Intramolecular alkylation then provided tricyclic ketone 69 whose preparation demonstrated the utility of this method of annulation.

Hydrogenation of 69 over platinum cleaved the cyclopropane to give the geminal dimethyl group and, more interestingly, reduced the methylene double bond to give saturated ketones 77 and 78 in a 42:58 ratio (Scheme XVI). This result was somewhat curious if one assumes that H_2 approached the less hindered side, since it would tend to indicate that the resulting methyl group enjoys a slightly less crowded environment in the natural configuration. This would be directly in contrast to the result provided by the hydride reduction of 54 by

Paquette et al. Similarly, hydrogenation of endocyclic olefin **70** gave **77** and **78** in a ratio of 5:95. Subjection of this mixture to methyllithium followed by dehydration gave a 68% yield of epi-pentalenene **53** after separation on silver nitrate treated silica gel. Similar operations performed on the aforementioned mixture gave 32% of the natural epimer **1**. Although no definite conclusion can be reached from this data, it does shed some doubt on the claim that the β-configuration of the methyl group at C-9 is more thermodynamically stable than the natural α-configuration of pentalenene.



Scheme XVI

All four syntheses discussed thus far have been directed exclusively toward (±) pentalenene **1** without regard to incorporating any elements of generality so that analogous compounds could be constructed along the same route. However, generality is a goal which has been sought more intensely by synthetic chemists in recent years. In keeping with this trend, Mehta and Rao[25] proposed a synthetic scheme which could also be used to prepare a number of other angularly fused, triquinane terpenes. They suggested that 1,5-dimethyl-1,5-cyclooctadiene **79** could serve as a common intermediate in the synthesis of many nonlinear triquinanes which posses a 1,5-dimethyl moiety such as pentalenene **1**,

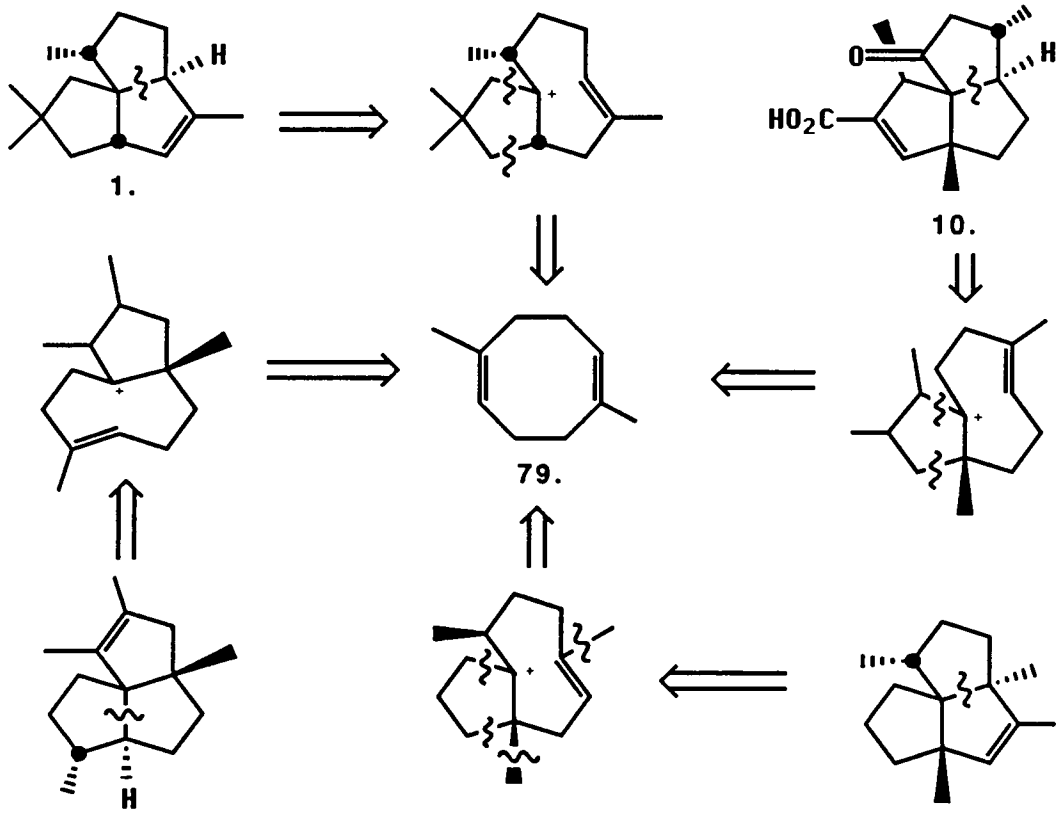


Figure 6

isocomene **7**, silphinene **9** and subergorgic acid **10** (Fig. 6) if a cyclopentannulation and transannulation pathway were followed, similar to the approaches adopted by Pattenden and Teague.[57] In order to demonstrate the viability of this plan, its application to the total synthesis of pentalenene was undertaken.

Initial retrosynthetic analysis revealed **80** (Fig. 7) to be the

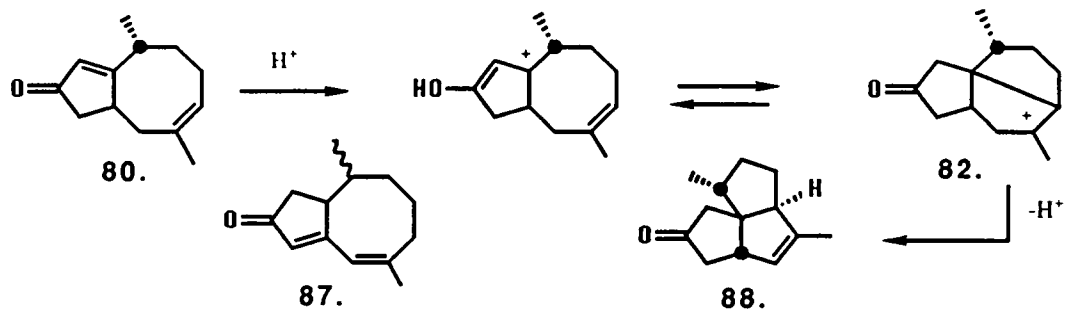
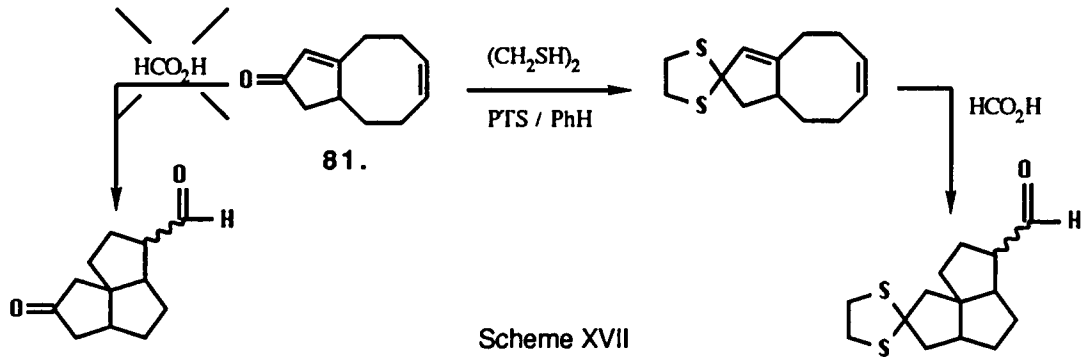


Figure 7

intermediate which would be required for the transannulation step. This generated some concern in view of previous model studies[25b] which indicated that neither formolysis[67] nor treatment with various Lewis acids would effect transannulation of enone **81** unless the carbonyl was first masked as its thioketal (Scheme XVII). However, it was felt that the reaction would be successful with **80** since its rearrangement would

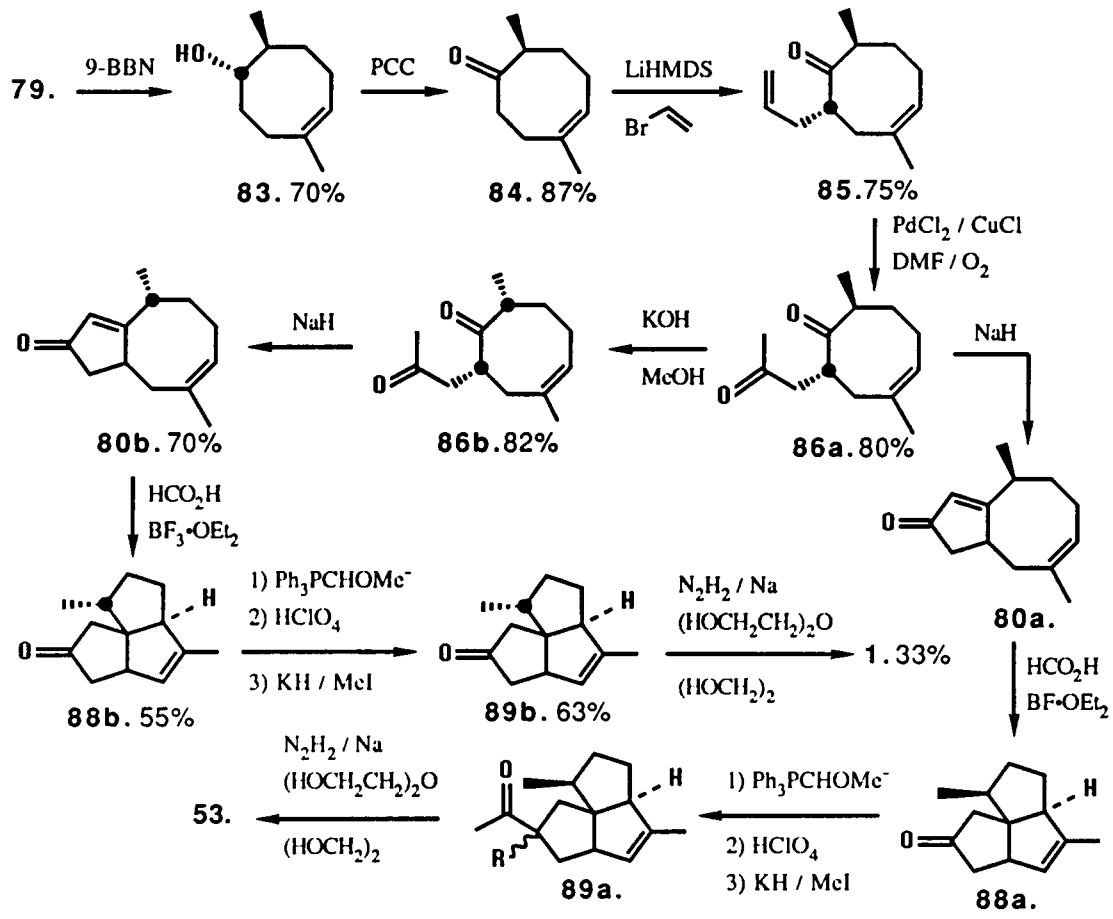


Scheme XVII

generate a stable tertiary cation **82**, (Fig. 7).

The synthesis began with the commercially available key starting material **79** which was selectively hydroborated with 9-BBN giving cyclooctenol **83** followed by **84** after PCC oxidation (Scheme XVIII). The results of Clark Still[68] on the stereo- and regioselective alkylations of cyclooctanone derivatives correctly predicted kinetically controlled alkylation of **84** with LiHMDS which gave **85** with the trans-configuration exclusively. Oxidation with Pd^{2+}/O_2 yielded diketone **86a** which proved to be a pivotal intermediate with respect to stereocontrol since isomerization under basic conditions epimerized the molecule to give **86a:86b** in a 1:4 ratio in accordance with Still's results.[68] Intramolecular aldol cyclization of **86a** and **86b** gave **80a** and **80b** in 4:1 and 1:4 ratios respectively which was suggested to be the result of competitive epimerization.

With key intermediate **80b** in hand, the crucial transannulation process could be tested (Fig. 8). Success was realized upon treatment of **80b** with p-toluenesulfonic acid, BF_3-etherate, Nafion-H, etc.; however, competitive formation of dienone **87** proved to be an irritating

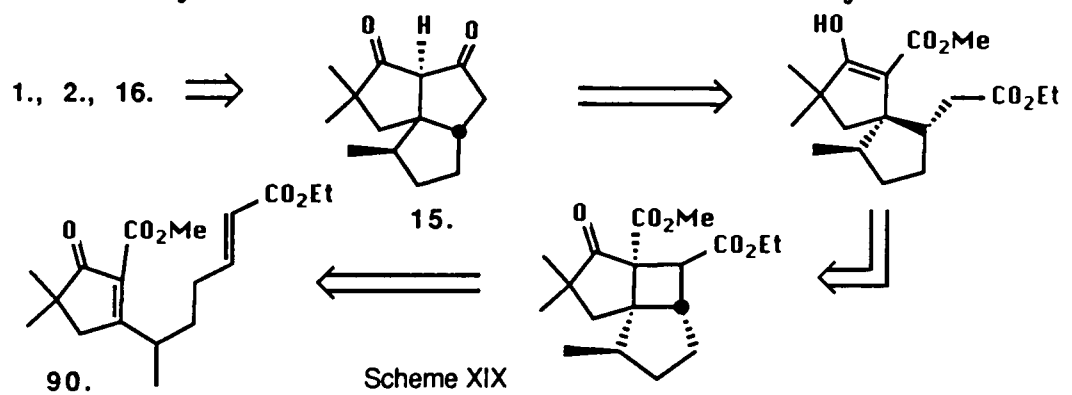


Scheme XVIII

problem which was finally overcome by making use of formic acid in the presence of BF_3-etherate to effect ring closure of **80b** to the desired tricycle **88** exclusively. Upon formation of the triquinane skeleton, geminal dimethylation was attempted according to reports using limethyltitanium dichloride[69] and tetramethylsilane-$AlCl_3$,[70] but neither reagent provided synthetically useful yields of desired product, and a multistep process had to be implemented. Wittig olefination of **88** with

the anion derived from (methoxymethyl) triphyenylphosphonium chloride followed by mild hydrolysis gave **89a** with subsequent MeI addition to provide the requisite quaternary center at C-6. Wolff-Kishner reduction of resulting **89b** completed the sequence and gave (±)-pentalenene. The trans-diketone **86a** was subjected to a parallel series of reactions in a successful attempt to stereoselectively realize (±)-epipentalenene.

Shortly after the efforts of Mehta and Rao appeared a second general approach to (±)-pentalenene was described by Crimmins and DeLoach[70] which rendered (±)-pentalenic acid **2** and (±)-deoxypentalenic acid **16**[71] accessible as well. In order to generalize the approach to the three stucturally related triquinanes, a common intermediate was needed from which all three would be attainable (Scheme XIX). Diketone **15** was chosen since it provides a requisite oxygen funtionality at C-1 and flexibility toward functionalization at C-6. Retrosynthetic



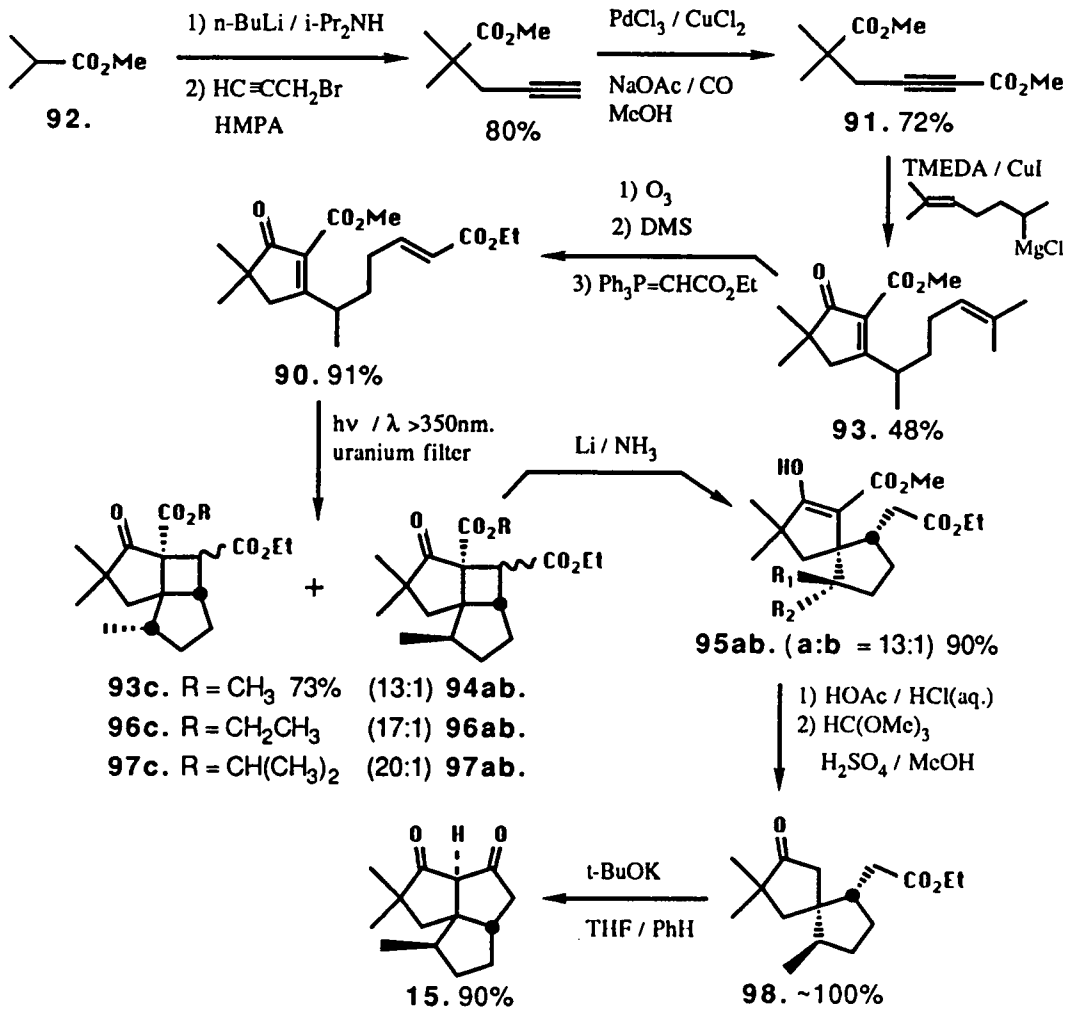
Scheme XIX

analysis suggested **90** as the first key intermediate from which **15** would become accessible via intramolecular [2+2] photocycloaddition and reductive ring cleavage.

The conjugate addition-cycloacylation strategy which was adopted for the preparation of **90** arose from previously published results[72] and applied to propargyl diester **91** which was prepared via alkylation[73] and

subsequent carbomethoxylation[75] of the lithium enolate of methyl isobutyrate **92** (Scheme XX). In the presence of tetramethylethylenediamine and CuI, the Grignard reagent derived from 6-chloro-2-methyl-2-heptene[76] underwent conjugate addition to **91** and spontaneous cyclization resulting in **93**. Conversion of **93** to **90** was not a trivial matter since it required selective ozonolysis of the most electron rich double bond. Fortunately, the electron density of the conjugated double bond was sufficiently depleted by the two carbonyl moieties that it remained inert to treatment with excess ozone in dichloromethane at -78°C and thus allowed exclusive ozonolysis of the uncongugated double bond. After dimethyl sulfide reduction and immediate condensation of the resulting aldehyde with (carboethoxymethylene) triphenyl phosphorane, **90** could be isolated in 91% yield from **93**.

Upon acquisition of diene **90**, attempts at the key photocycloaddition reaction[77] could be initiated. Problems were encountered initially as irradiation of **90** through a pyrex filter resulted in formation of an unidentified secondary cleavage product. Irradiation through a uranium glass filter (λ>350) alleviated the situation and a 73% of photoadducts **94** as a 10:3:1 (**94a:94b:94c**) mixture. Reductive cleavage[78] with lithium in liquid ammonia gave a mixture of C-9 epimers **95a** and **95b** in a ratio of (13:1). The stereoselectivity of photocyclization[79] proved to be dependent upon the size of the vinyl substituent on the cyclopentenone in the order: $-CO_2Me$(**94a:b** = 13:1) to $-CO_3Et$ (**96a:b** = 17:1) to $-CO_2Pr^i$ (**97a:b** > 20:1) which is consistent with Oppolzer's[79a] hypothesis that the observed stereoselectivity is a function of a steric interaction between the

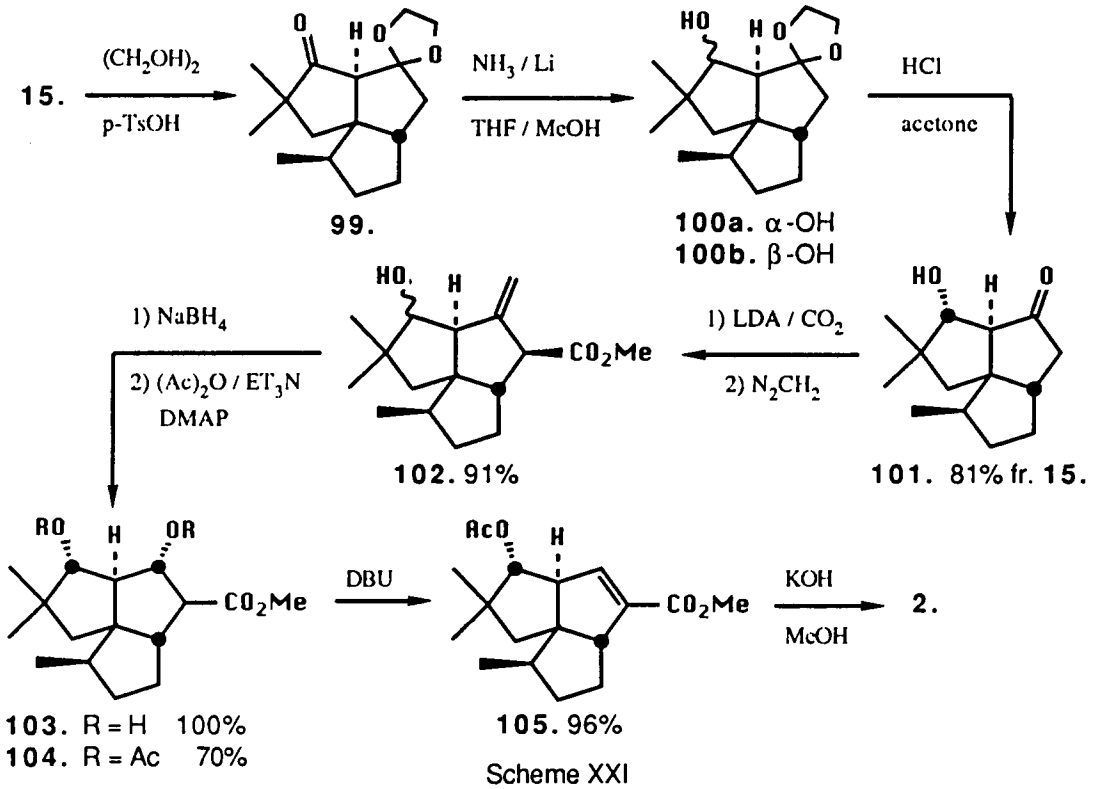


Scheme XX

secondary methyl group and the vinyl substituent during final ring closure causing cycloreversion of the biradical initially formed. Later results by Becker[80] suggested, however, that mechanisms which do not involve cycloreversion cannot be excluded. Irrespective of the mechanism, the control of stereochemistry at C-9, traditionally a troublesome part of the previous syntheses, was achieved with excellent results. After numerous attempts to obtain the triquinane skeleton from 95a and various protected analogs through a Dieckman condensation, dione 15 was realized via quantitative hydrolysis-decarboxylation[81] with

subsequent esterification to give keto ester **98** which cyclized easily upon potassium tert-butoxide treatment.[82]

With the pivotal dione **15** in hand, differentiation of the two carbonyl groups was required before any of the three target compounds could be completed. Since the ketone in ring A suffers from severe steric hindrance, **15** was easily converted to **99** even in the presence of excess ethylene glycol (Scheme XXI). Hydride reduction of **99** proceeded from the less hindered face to give the undesired β-alcohol **100b**,

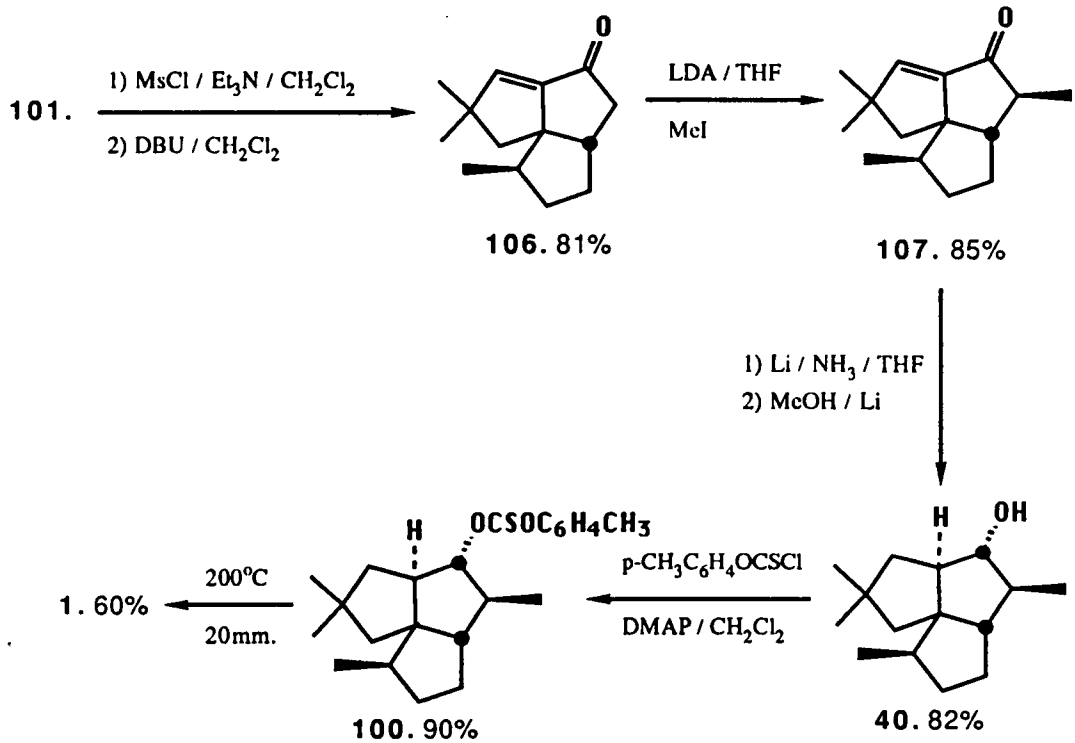


Scheme XXI

however, the problem was easily remedied by employing a lithium-ammonia reducing system which gave the desired α-alcohol **100a** accompanied by only a trace of the undesired β-epimer. Hydrolysis provided the necessary keto alcohol **101** which was directly carboxylated and esterified via lithium diisopropylamide and carbon dioxide treatment

followed by exposure to N_2CH_2 to provide keto ester **102**[83]. Diol **103** was then obtained upon sodium borohydride reduction, but mixtures of sulfonates were obtained in subsequent attempts to selectively convert the C-7 alcohol in its mesylate or tosylate in the presence of the hindered C-1 alcohol. Alternatively, the diacetate **104** was prepared upon exposure of **103** to acetic acid and catalytic amount of 4-(dimethylamino) pyridine.[83] The diacetate provided methyl pentalenate acetate **105** upon treatment with DBU. Concomitant hydrolysis of the two esters yielded (±)-pentalenic acid **2**.

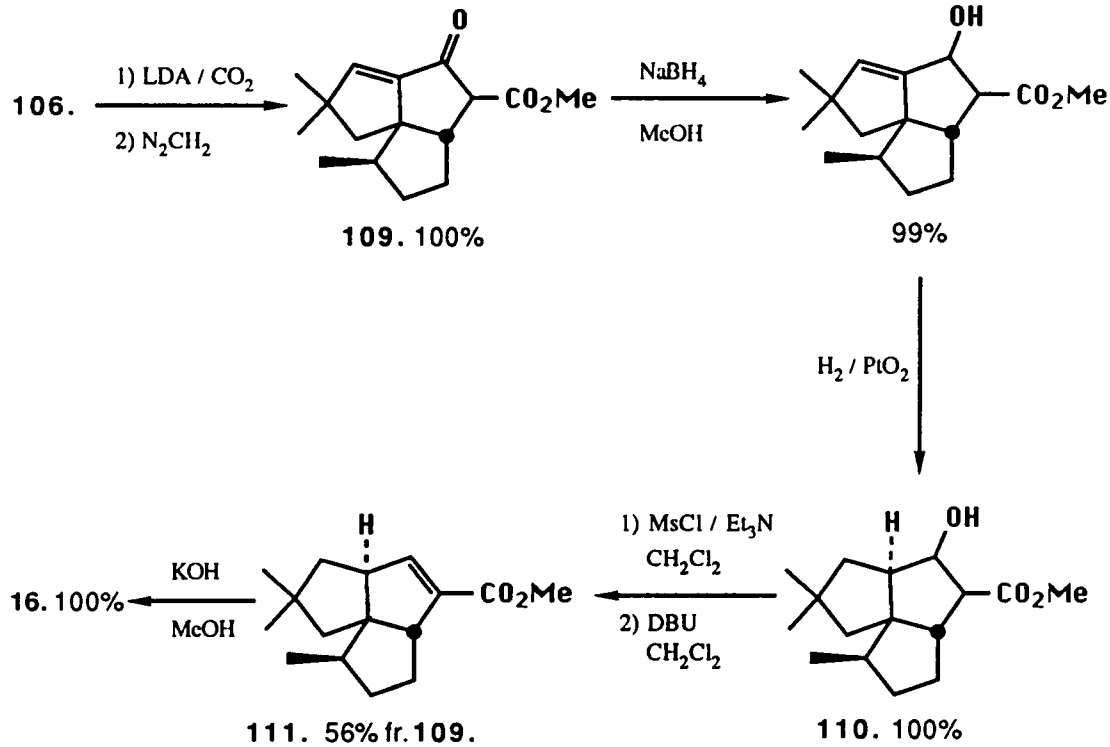
Regression to keto alcohol **101** was necessary to complete the synthesis of pentalenene due to failure of ketal **99** to concede to Wolf-



Scheme XXII

Kishner reduction. DBU treatment cleanly eliminated the mesylate derived from **101** (Scheme XXII) and subsequent alkylation of the resultant enone **106** with LDA/MeI provided **107** as a single epimer in 65% overall yield from dione **15** (five steps). Exposure of **107** to lithium in ammonia-methanol gave **40** which was first reported by Cane et al.[30,43] as a tritiated degredation product of **1b**. Numerous conditions for dehydration of alcohol **101** or elimination of its mesylate failed before the preparation of pententalenene was realized upon pyrolysis of the xanthate derivative of **101**, namely **108**.

The synthesis of deoxypentalenic acid **16** as a final target of the synthesis originated with carboxylation and esterification of

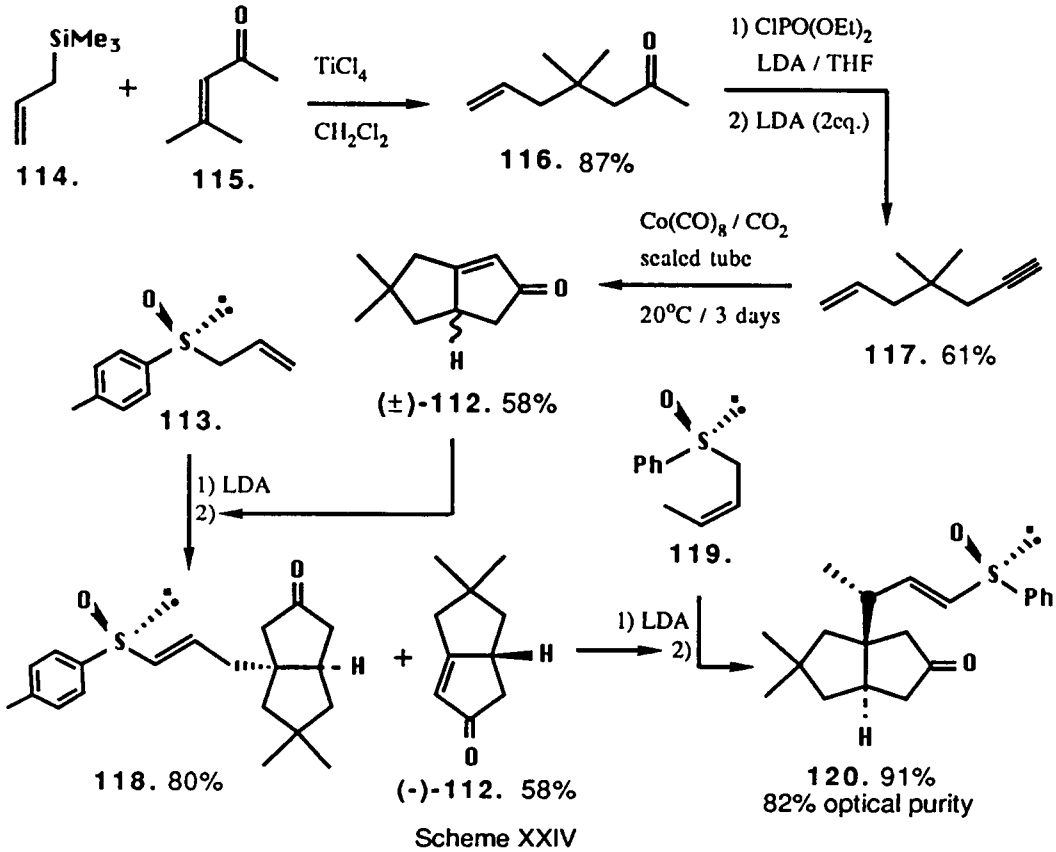


Scheme XXIII

intermediate **106** to keto ester **109** (Scheme XXIII). Successive reductions with $NaBH_4$ and H_2 over PtO_2 generated the C-6 carbomethoxy analog of **40**, **110**, whose mesylate proved to be labile to elimination with DBU and gave the methyl ester **111** of **16** which was hydrolyzed to its acid in refluxing KOH/MeOH.

The only asymmetric synthesis of **1** which has been reported to date was achieved by Hua who succeeded in preparing (+)-Pentalenene.[85] This was a significant accomplishment in view of the increasing interest of the synthetic community in preparing enantiomerically pure compounds. Chirality was achieved by kinetically selective resolution of (-)-**112** with the sulfinylallyl anion derived from **113**.

Enone **112** was prepared in racemic form via a sequence that began with 1,4-addition of **114** to mesityl oxide **115** in the presence of $TiCl_4$[86]

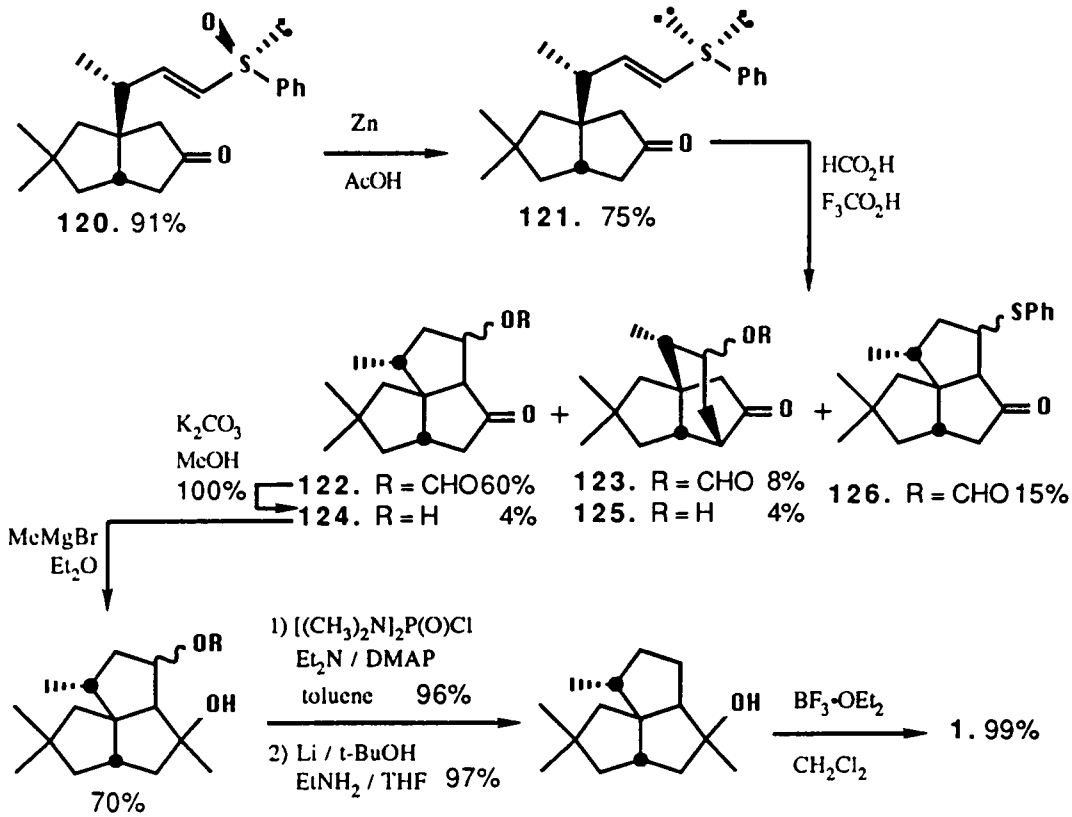


114. **115.** **116.** 87% **117.** 61% **113.** (±)-**112.** 58% **119.** **118.** 80% (-)-**112.** 58% **120.** 91% 82% optical purity

Scheme XXIV

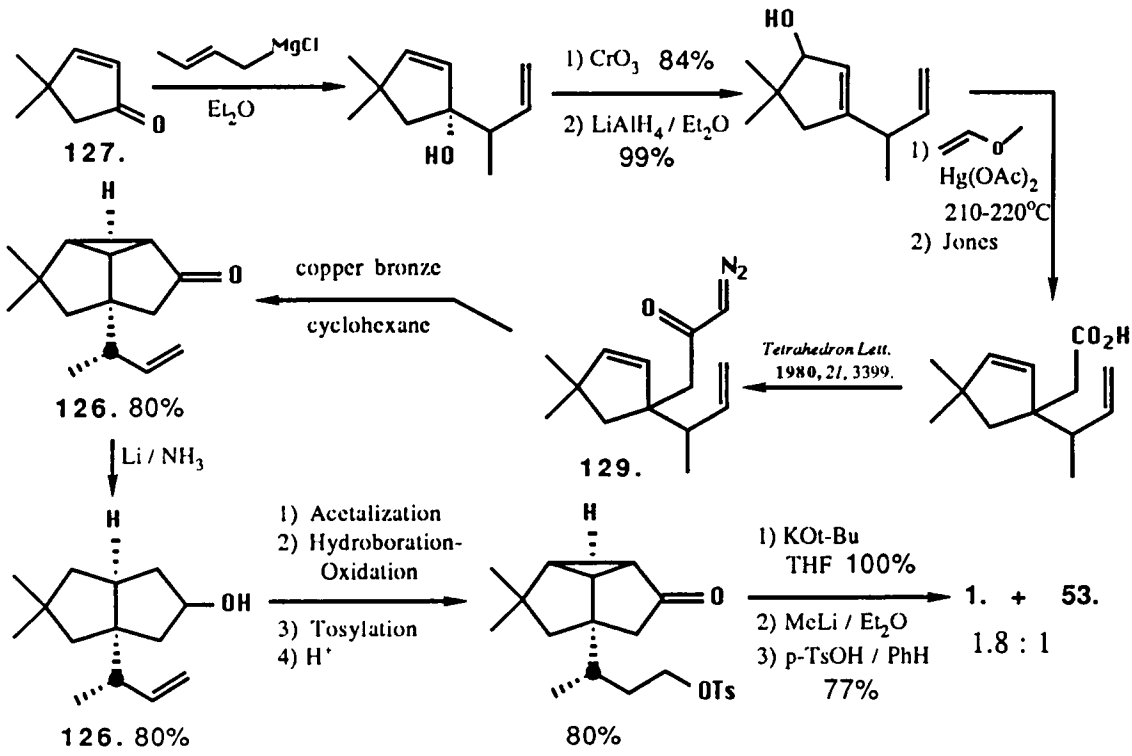
to give ketone **116**, (Scheme XXIV), which was converted to **117** by dehydrophosphonation with LDA of its corresponding enol phosphate obtained from treatment with LDA/$ClPO(OEt)_2$[87]. Intramolecular cyclization of **117** occured in the presence of $Co_2(CO)_8/CO$ in a sealed tube at 120°C providing (±)-**112**[88] which set the stage for the key kinetically selective resolution. The anion of (S)-allyl-p-tolyl sulfoxide[89] was derived upon exposure to 1 eq. of LDA and subsequently exposed to 2 eq. of (±)-**112** giving adduct **118** (80%) and (-)-(S)-**112** (45%, $[\alpha]^{25}_D$=141° (c0.14, $CHCl_3$)). The resolution was thus successful in providing an enantiomerically enriched template making possible the asymmetric synthesis of (+)-**1**.

To complete the synthesis, (-)-**112** was treated with 2 eq. of the



Scheme XXV

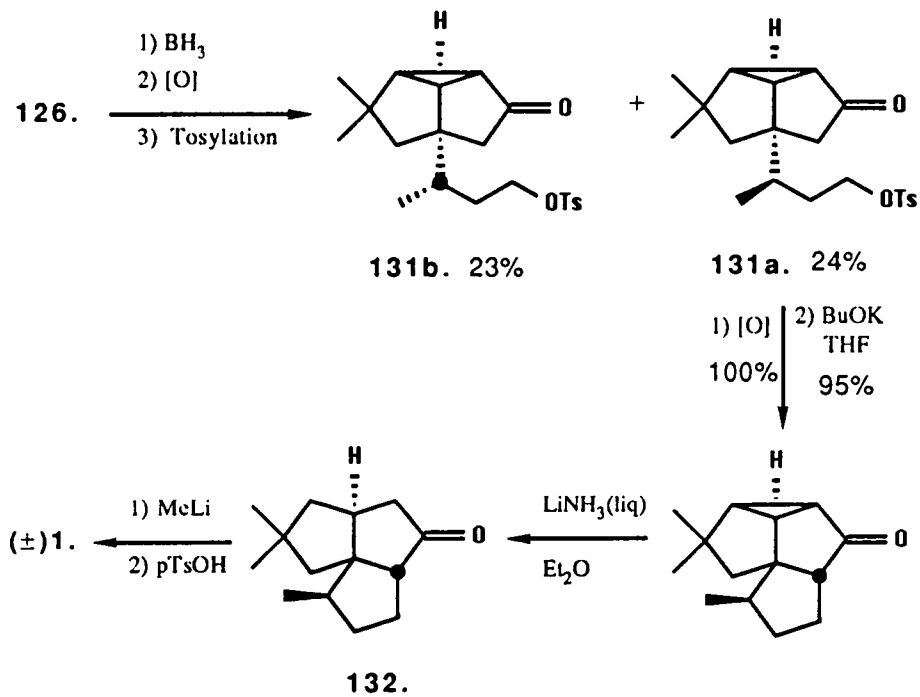
LDA derived anion of **119** (prepared from sodium benzenethiolate and cis-1-chloro-2-butene followed by MCPBA oxidation) to give sulfoxide **120**. In view of the reported difficulty in $HgCl_2$ or acidic hydrolysis of vinyl sulfoxides possessing an α-H,[90] **120** was reduced to the corresponding vinyl sulfide **121** with Zn-HOAc which generated tricycle **122** upon hydrolysis and rapid intramolecular cyclization when **121** was exposed to HCO_2H/CF_3CO_2H in 60% yield along with byproducts **123** (8%), **124** (4%), **125** (2%), and **126** (15%) (Scheme XXV). Formate **122** was converted into alcohol **124** with potassium carbonate. The completion of (+)-**1** was achieved upon addition of methyl Grignard to **124** followed by phosphorylation and deoxyphosphorylation[91] to give **125** which dehydrated smoothly to finish the first assymetric synthesis of (+)-pentalenene.[92] Hua further indicated that this method should be applicable to the construction of isocomene **7**, silphinene **8**, pentalenic acid **2** and



Scheme XXVI

pentalenolactone 3, although he did not substantiate his claim with specific details or explanations.

The most recent synthesis of 1 was reported by Iwata et al.[93] in which the utility of a regioselecticve C_2-C_8 bond cleavage in the tricyclo [3.3.0.$0^{2,8}$] undecane ring system was achieved. In order to study this cleavage the required cyclopropane **126** was prepared from 4,4-dimethycyclopentenone **127** which was converted to dienic acid **128**, using well established chemistry, and closed to form the cyclopropane **126** upon exposure of its corresponding diazoketone **129** to copper bronze in cyclohexane (Scheme XXVI). Cyclopropane cleavage yielded diquinane **130** in a regioselective fashion. Classic functional manipulations were then employed to close the third ring and prepare pentalenene 1 and epipentalenene 53 in a 1.8:1 ratio. A second route was employed in



Scheme XXVII

which a separable diastereomeric pair was encountered **131ab** (a:b ~ 1:1) which allowed isolation of a compound with the natural configuration at C-9 **131a** (Scheme XXVII). Ring cleavage again proceeded regiospecifically to deliver **132** which led to (±)-**1** which was uncontaminated with **53**.

B. Discussion

I. Introduction - Comparison of Synthetic Efforts

Interest in the chemistry of triquinane terpenes was initiated upon elucidation of the unique structural skeleton of retigeranic acid **4** in 1973 which was the first natural compound shown to contain three fused cyclopentane rings.[5] Soon to follow was a rapid growth in the number of triquinanes isolated and tremendous amount of effort was directed toward the total synthesis of many of these compounds. Of special significance was the disclosure that many natural triquinanes possessed important biological properties. Since 1973 most of the principal linear and angular triquinanes have succumbed to total synthesis and many have been approached in the context of generalized synthetic schemes.

In view of the vast number of methodologies which have now been developed, the synthetic community is currently turning its attention away from the total synthesis of single targets. Focus is now being directed toward general methodologies which allow the synthesis of entire classes of compounds. This trend has been clearly exemplified in the preceding section on the history of pentalenene total synthesis.

With the exception of Matsumoto et al.,[28] who synthesized pentalenene purely by accident, Paquette was the first to realize its total synthesis.[45] Although his synthesis was the first, it lacked a great deal of imagination and flexibility. It was based on a straight forward, retrosynthetic type approach in which ring B was built onto ring A and, in turn, served as a foundation for construction ring C. It was in this synthesis which the difficulty of stereocontrol at C-9 was

first realized. No mention was made regarding related compounds which might also be accessible by Paquette's scheme, so the attractiveness of the preparation suffered severely by its high relative yield of epipentalenene **55**. The scheme suggested by Piers[64] was conceptually similar and was useful in that it cast ambiguity on the issue of the most thermodynamically stable configuration at C-9. He arrived at the sp^3 carbon by a reduction of an sp^2 center using catalytic hydrogenation, which event should have delivered hydrogen from the less hindered side thus locking the methyl group on the most sterically crowded side. However, the major diastereomer assumed the β-configuration which was reported to be the most thermodynamically stable, therefore, least crowded. Irrespective of this useful data, the methodology was restricted to the synthesis of pentalenene, and since it generated the unnatural isomer as a major product, it was not synthetically practical.

The approach offered by Pattenden[56] was refreshing in the context of pentalenene total synthesis in that it exploited a transannular approach which was conceptually distinct from those of Piers and Paquette. Rings B and C were formed concurrently from a cyclooctenyl cation without stereochemical problems at C-9.

Soon afterwards Mehta extended this approach to a general methodology for the synthesis of linearly fused triquinanes which contain 1,5-dimethyl substituents;[25] thus, this was the first general approach in which pentalenene was one of a number of proposed possible targets. Indeed, its total synthesis was achieved. In addition, it was the first synthesis to impart stereoselectivity through use of an

epimerizable intermediate to make **1** and **53** available in (1:4) or (4:1) ratios. To date, there have been no reports of other compounds being constructed through this methodology.

The first person to report total synthesis of **1** in conjunction with related analogs, was Crimmins,[72] who also completed pentalenic acid **2** and deoxypentalenic acid **16**. His approach was general since it made use of a pivotal intermediate **15** to render all three compounds accessible. Furthermore, it was conceptually unique from any of its predecessors by virtue of constructing ring C onto ring A with simultaneous formation of the C-4, spiro-, quaternary center and then subsequently closed ring B. Fortunately, there were no stereochemical problems at C-9 as there were none in a subsequent report by Hua who was the first to address asymmetry in his planning.[84] Although asymmetric synthesis represents the latest challenge to synthetic chemists, chirality was induced at a great cost of starting material since it was achieved by resolution of a racemic intermediate with 44% efficiency which calculates to only a 22% recovery of chiral substrate. Despite the inefficiency, Hua's work initiated efforts toward imparting chirality into pentalenene total synthesis.

The most recent reported synthesis by Iwata[93] exemplified regiocontrol during cyclopropane ring cleavage; however, there was no stereocontrol and no attempt was made to use modern or imaginative transformations, so the report was essentially uneventful.

II. Proposed Methodology

In view of the results of previous syntheses, we sought to develop a general approach to angular triquinanes of the pentalenene type that would allow stereocontrol at C-9. In addition, we envisioned extension of such an approach to allow entry into linear triquinane skeletons as well. To achieve this goal, we applied a method equivalent to [4+1] cyclopentene annulation which had been developed in our laboratory[94] and used in the total synthesis of (±)-hirsutene **11**,[16c] (±)-isocomene **7**,[10g] (±)-isocomenic acid **17**,[26] and the triquinane portion of retigeranic acid **4**.[6b] This methodology incorporated the intramolecular addition of carbenes of type **133**, which were derived from their respective

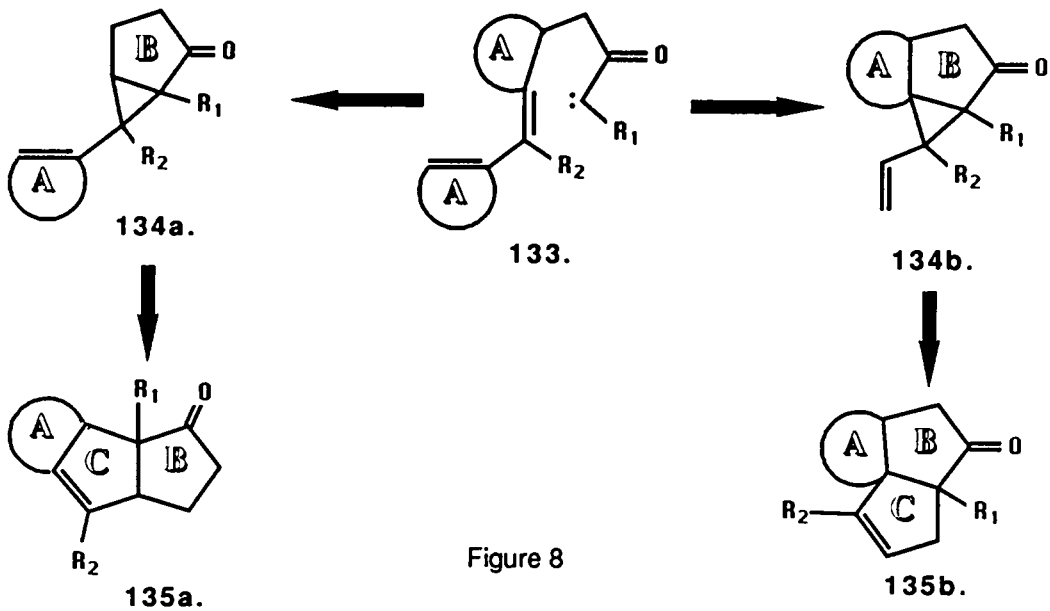


Figure 8

diazoketones, across diene systems to append ring B and form vinylcyclopropanes of type **134** (Fig. 8) with subsequent pyrolytic cleavage via diradical rearrangement and concomitant ring C formation to triquinane units of type **135**. In cases where ring A contained a cyclopentane moiety, the linear triquinane skeleton **135a** or the angular

triquinane skeleton **135b** was obtained as desired depending on the position of ring A in **133**. Thus, utilization of this approach as a general methodology for both ring systems depended upon designing a unified preparation of the precursory dienes.

The first method which was used to prepare requisite dienic-diazoketones made use of the orthoester Claisen rearrangement.[95] Application of this methodology to divinyl alcohol **136** (Fig. 9) delivered the diene system **137** necessary for the synthesis of hirsutene **11**.[16c] Epiisocomene **7a** was similarly obtained via enyne **138** which was

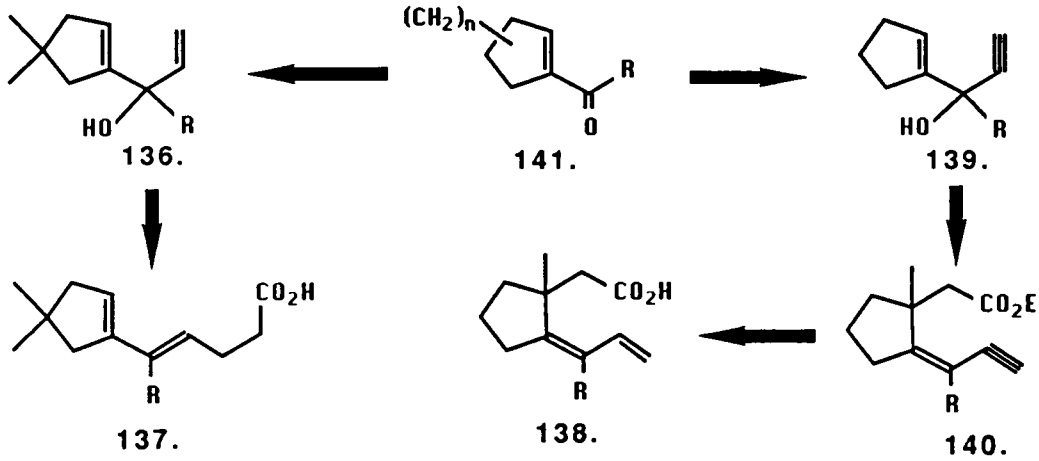
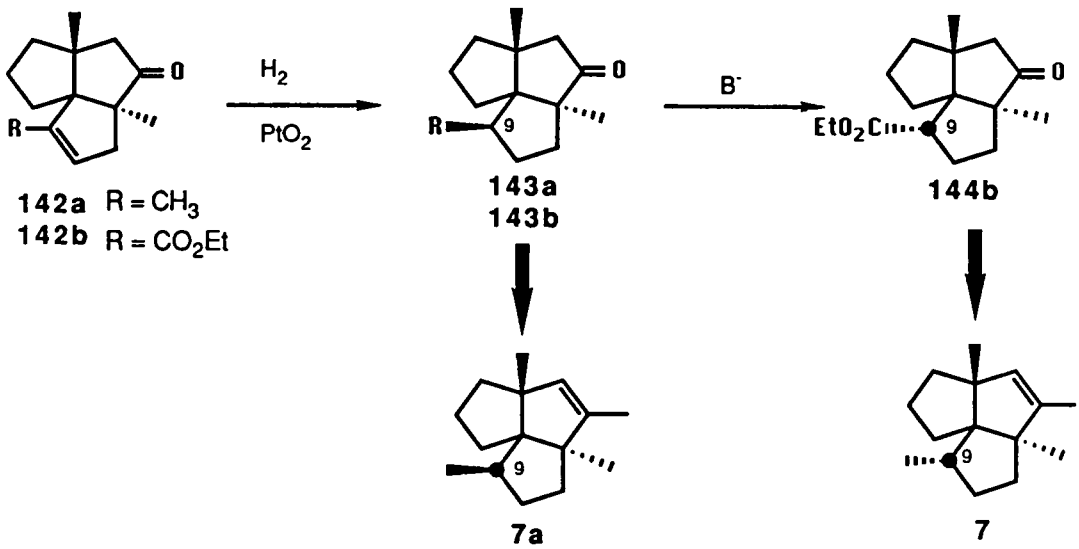


Figure 9

obtained regioselectively from carbinol **139** via the enyne **140**.[10g] Both hydroxy compounds were derived from analogous enones of type **141** thus rendering both dienic systems easily accessible.

The natural epimers of isocomene **7**[10g] and isocomenic acid **17**[26] presented an additional challenge. Catalytic hydrogenation of tricycle **142a**, which was obtained from [4+1] cyclopentene annulation, delivered hydrogen from the least hindered side giving **143a** which possessed the least thermodynamically stable configuration at C-9 (Scheme XXVIII).



Scheme XXVIII

This compound was converted to epi-isocomene **7a**. Therefore, it was advantageous to introduce a functional group which would allow epimerization. This was achieved by adopting an alternate method of preparing the requisite dienes through introduction of a four carbon crotonate unit which provided an acrolate moiety and made possible the epimerization of the saturated tricycle **143b**, obtained by hydrogenation of **142b**, to the natural **144b** configuration.

Inspection of the skeleton of pentalenene **1** reveals a similar stereochemical problem at C-9. It therefore seemed logical to approach its synthesis in analogy with the previously proven scheme which selectively provided both epimers of isocomene **7** and isocomenic acid **17**. It would also provide an intermediate which would finally settle the unanswered question of conformational stability which was originally addressed by Paquette,[45] and, in analogy with the synthesis of isocomenes, all possible C-9 isomers of the title terpenes would become accessible.

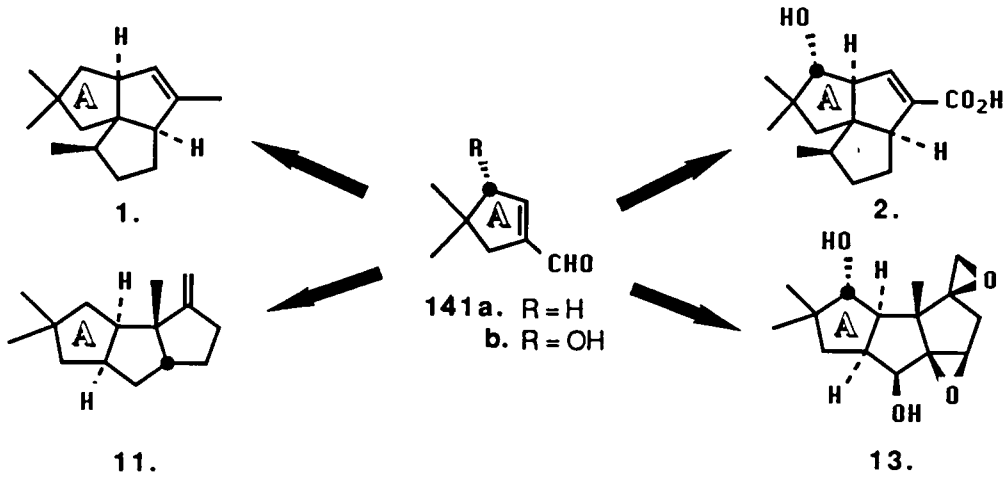


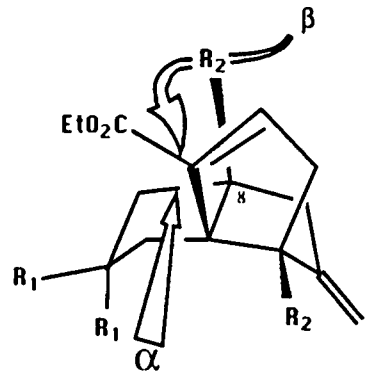
Figure 10

In keeping with the overall theme of generality, the synthesis of pentalenene was designed and undertaken concurrently with that of pentalenic acid 2 (Figure 10). Aldehyde **141a**[96] would become accessible and its oxygenated analog **141b**[97] served as starting points as the former had done in the synthesis of hirsutene. Coriolin **13** was recently chosen as the second target to employ **141b** as starting material. Thus, a general approach was formulated by recognizing that all four compounds share identical functionality in ring A and proper topological relationships in the remaining rings to allow the use of a common intermediate for the construction of each skeleton along similar synthetic pathways. Stereocontrol, a key feature of the approach, was incorporated through the use of an epimerizable intermediate of type **143b**.

The strategic details leading to the construction of pentalenene and pentalenic acid were outlined in direct analogy with those that had already proven to be effective for the total synthesis of isocomene **7**,[10g] isocomenic acid **11**,[26] and their respective C-9 epimers. The

design for the synthesis of pentalenic acid was nearly identical to the one for pentalenene, so mention of it will be made only in those cases where significant variatin existed.

The synthetic design for pentalenene assumed a similar steric environment to that in isocomene **7**; therefore, stereocontrol was expected to be attainable through the use of **145** (Figure 11) in analogy with stereochemical data obtained from **142b.** It was shown in the latter case that the C-8 methyl group hinders the approach of hydrogen from the

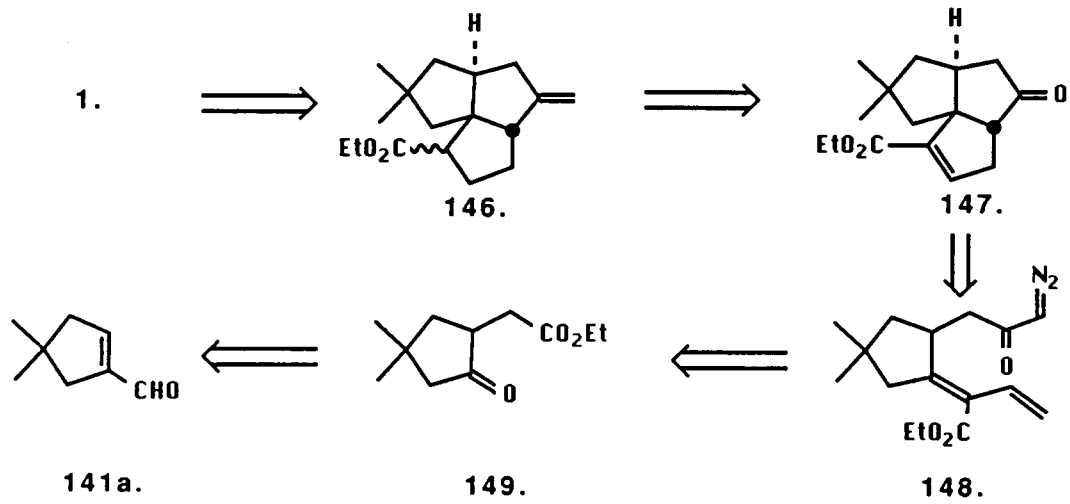


142b. $R_1 = H, R_2 = CH_3$
145. $R_1 = CH_3, R_2 = H$

Figure 11

β face to such an extent that the olefin was attacked only from the α face with the resulting sp^3 hybridized C-8 in the epi- configuration. This left the carboxylate functionality on the β face to interract with the methyl group sufficiently that complete epimerization occured under basic conditions.

The same situation exists in the corresponding pentalenene intermediate **145** except that the C-8 substituent is a hydrogen atom. Although we expected reduction to occur selectively from the α face, we could not anticipate the extent of such selectivity; nor could we predict with certainty the ΔG which would result from crowding of the C-8 hydrogen with the carboxylate unit in **146.** Investigation of these



Scheme XXIX

effects would provide important evidence to accurately assign the more stable configuration of C-9 in pentalenene since that center will be set under equilibrating conditions.

With these goals in mind, we set out to prepare the required tricyclic intermediates **145** and **146** from which both epimers of pentalenene should become accessible (Scheme XXIX). Ketoester **147** was targeted as the key intermediate since similar olefinic tricycles were previously easily attainable and related analogs have resulted from the aforementioned [4+1] cyclopentene annulation of dienic-diazoketones similar to **148** which would be required in this case.

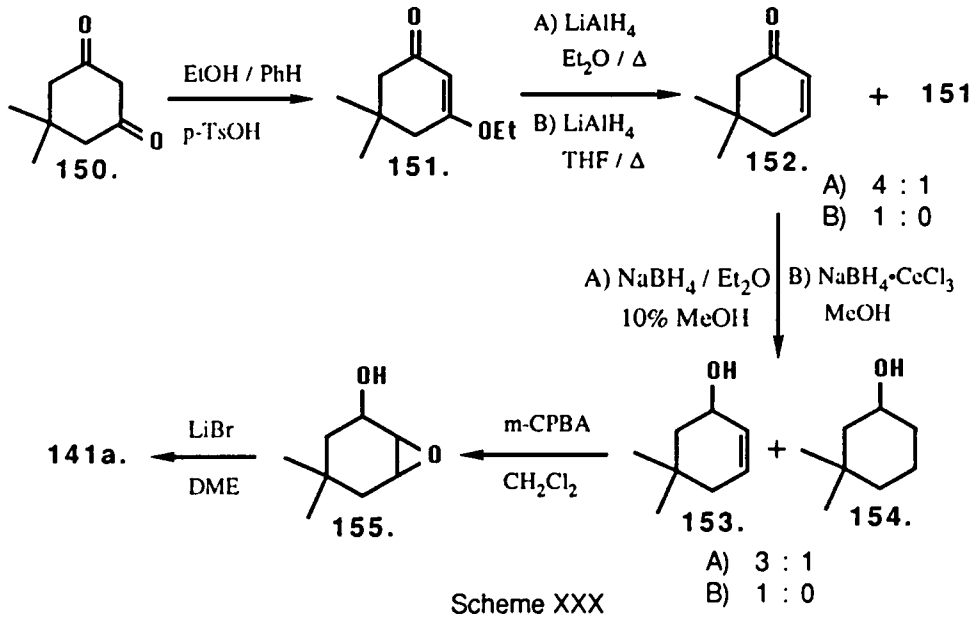
Since pentalenene is an angularly fused triquinane, the exocyclic diene structure was required, affording an opportunity to demonstrate a modified approach to such systems using a vinylogous Reformatsky reaction under conditions which would selectively add a four carbon crotonate unit to ketoester **149** in a regioselective manner. Ketoester **149** was expected to arise from starting aldehyde **141a** via an ortho ester

Claisen rearrangement.

With the successful completion of pentalenene **1**, pentalenic acid **2** and coriolin **13**, we will have demonstrated the utility of [4+1] cyclopentene annulation as a general entry into both linear and angular triquinane ring systems. We will then turn our attention to introduction of chirality which is a goal that has been sought with increasing intensity in recent years.

III. Results

The synthesis began with aldehyde **141a**, and initial efforts were directed toward its preparation, which had been reported in six steps from readily available 5,5-dimethylcyclohexane-1,3-dione **150**[96]



Scheme XXX

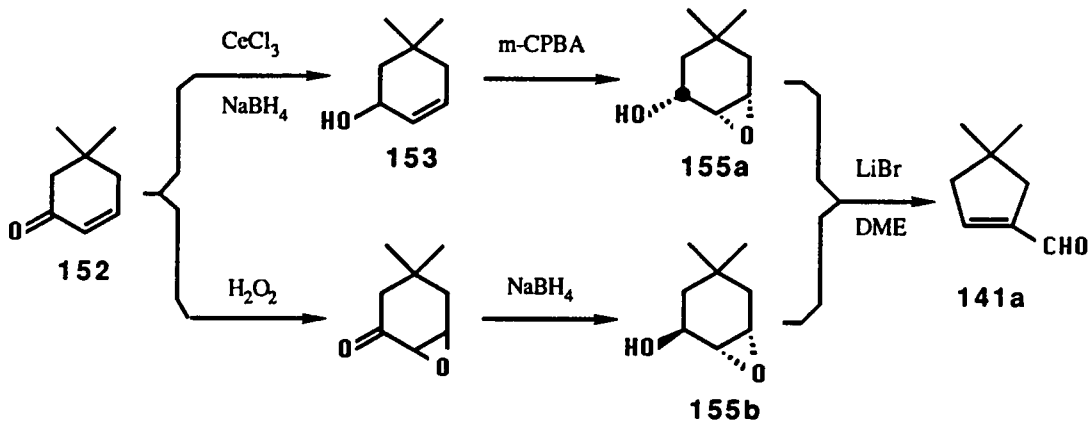
(Scheme XXX). Conversion of **150** to enolether **151** proceeded smoothly as reported; however, lithium aluminum hydride (LAH) reduction of **151** in refluxing ether repeatedly resulted in mixtures of desired enone **152** and starting enol ether **151** in a ratio of approximately 3:1 thus requiring separation by fractional distillation. The problem was easily remedied by running the reaction in refluxing THF. Under these conditions **152** was the only product.

Additional frustration was encountered upon subsequent $NaBH_4$ reduction of **152** in Et_2O with 10% MeOH which provided the desired unsaturated alcohol **153** accompanied by 20% of saturated alcohol **154** as a result of partial 1,4-reduction. This proved to be a major concern because **154** remained as a major, inseparable contaminant throughout the

next four steps. A number of alternatives were investigated to prevent 1,4-addition: these included $NaBH_4$ in MeOH, $NaBH_4$ in i-PrOH and $NaBH_4$ in Et_2O at 0°C and at room temperature. All attempts failed until $NaBH_4$ was added to a solution of the enone **152** and correducing agent cerium chloride heptahydrate in methanol,[98] which procedure cleanly delivered the desired unsaturated alcohol **153** without any evidence of **154.**

Oxidation of allylic alcohol **153** gave epoxy alcohol **155** and set the stage for lithium bromide mediated ring contraction to give the pivotal aldehyde **141a.** The reaction procedure called for the slow addition of **155** in toluene to a refluxing solution of LiBr, solvated with 2 eq. of hexamethyl phosphoramide in toluene. This reaction gave good yields of **141a,** but the volatility of aldehyde **141a** demanded very careful distillation in order to remove the solvents.

The reaction conditions were later modified according to more recent results which were published by Magnusson et al.[99] The new procedure greatly simplified the experiment and increased the yield. In spite of reports that dimethoxyethane renders LiBr inactive toward epoxide rearrangements,[100] complete rearrangement was found to occur upon addition of **155** to a refluxing, 4M solution of LiBr in DME. The explanation which was offered was that the hydroxy functionalities could successfully compete with the solvent for catalytic complexation with lithium ions. Additional mechanistic details were also included as determined by deuterium labeling experiments with this, and other, substituted cyclopentene-carboxaldehydes. The most important finding in regard to this case is the fact that both cis- and trans- epoxy alcohols **155ab** give approximately equal yields of aldehyde **141a** since it is



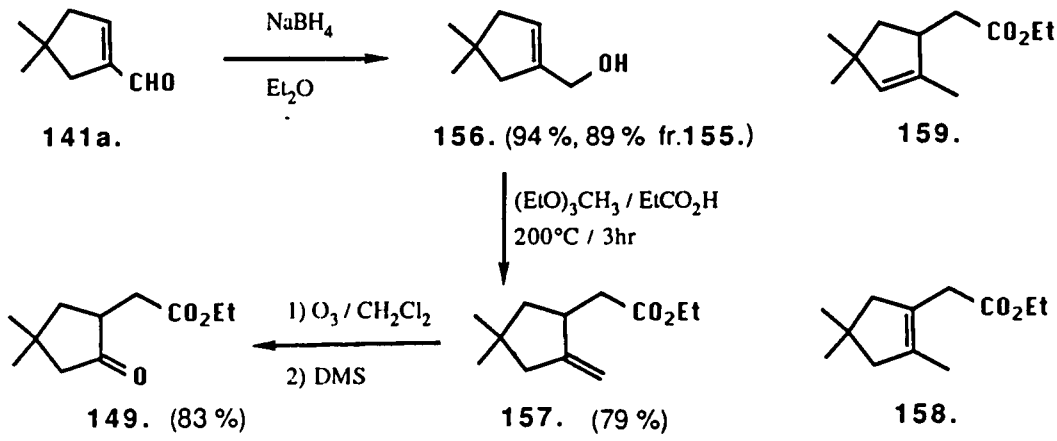
Scheme XXXI

symetrically substituted. One can therefore make use of alternate approaches to the desired epoxy alcohol **155**, such as the ones suggested by Magnusson (Scheme XXXI) without regard to the resulting stereochemistry in order to increase the yield or use cheaper reagents. We did not, however, feel that such alterations would be sufficiently advantageous to merit further time investment, so we continued producing **155** using the preparations with which we had become familiar, with the exception of the ring contraction conditions.

A major advantage of the new conditions was the fact that HMPA was not required as a solubilizing agent, which constituted an improvement in terms of health considerations. Furthermore, DME could be easily removed by rotary evaporation without any decrease in product yield. In our hands, this reaction was run comfortably on scales of up to 30g. Thus, after making the aforementioned modifications, starting aldehyde **141a** could be obtained on large scales and in high overall yields of 50-60% for the entire sequence.

With the starting material in hand, we turned our attention to requisite ketoester **149** which was not available from a sequence

involving normal condensation additions due to its γ-dicarbonyl character. We therefore applied a high yielding approach which we had previously developed for such compounds[101] (Scheme XXXII). Aldehyde



Scheme XXXII

141a was reduced with $NaBH_4$ in ether to deliver allylic alcohol **156** (94%) without evidence of saturated alcohol which would have resulted from 1,4-reduction. The reaction was normally carried out on crude aldehyde **141a** on the same day it was generated due to the instability of α,β-unsaturated aldehydes.

Exposing a solution of alcohol **156** in triethylorthoacetate with catalytic propionic acid to 200°C in a steel autoclave resulted in orthoester Claisen rearrangement to give olefinic ester **157** in surprisingly high yield of 75% considering the harsh reaction conditions. This compound had to be separated on 10% deactivated silica gel to prevent isomerization of the exoolefin to endoolefins **158** and **159**. Ozonolysis of **157** with dimethyl sulfide reduction of the crude ozonide provided the desired keto ester **149** in 83% yield.

With the precursory exocyclic dienic diazoketone **147** in mind, we sought to add a crotonate unit to **149** in a regioselective fashion.

Realization of this goal was made possible by conditions which were established in our laboratory to allow ambidently nucleophilic ethyl-4-

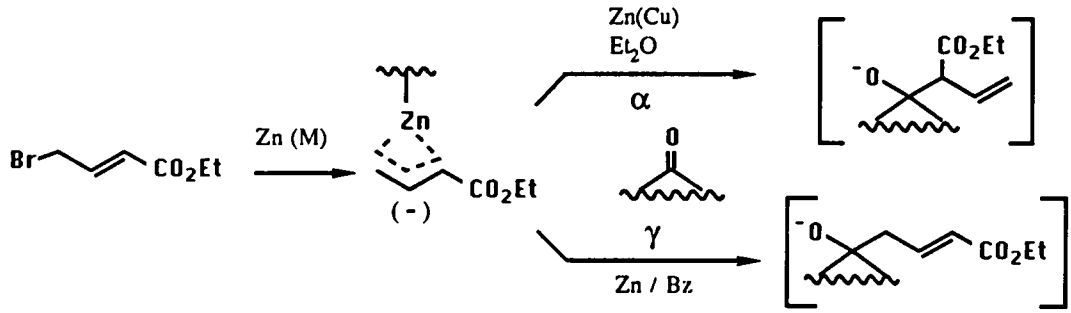
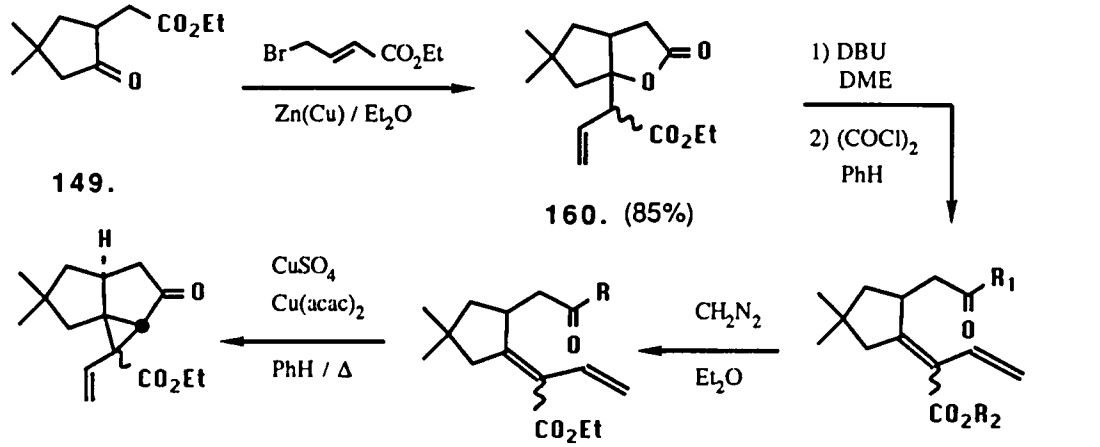


Figure 12

bromocrotonate anions to be added selectively from either the α or the γ carbon[102] (Fig. 12). It was reported that α selectivity increased to the extent of 100% as the polarity of solvents increased and as the Zn-metal couple became harder. When ether was used as a solvent and a zinc copper couple was employed as a catalyst maximum α selectivity was attained. It is believed that a trace of acetic acid is left on the surface of the catalyst as a result of its preparation and its presence also aids regiocontrol. Optimum γ selectivity was obtained with dry zinc in a benzene solution. Time also became a key parameter in this reaction in a later report where four fold regioselectivity was attained in the addition of ambident crotonate nucleophiles to α,β-unsaturated ketones and aldehydes via the Reformatsky reaction.[103] These investigations provided conclusive evidence that the α regioisomer was the kinetic product which would be obtained under almost any conditions using rapid quench.

Since the α-mode of addition was desired, fresh zinc-copper couple in ether was used. Addition of a mixture of ethyl-4-bromocrotonate and keto ester **149** to a suspension of this catalyst in refluxing ether gave

lactone **160** (85%) with 100% regioselectivity (Scheme XXXIII). The mixture of erythro and threo isomers could be separated for spectral identification, but the mixture was normally carried forward as these centers later converged to one. Subsequent treatment with DBU in DME at room temperature gave the desired dienic acid **161** (79%). Upon attempting to purify the acid through extraction with 10% NaOH, the



163a. endo, 163b. exo } 45% fr. **161**.

148. R = CHN_2
165. R = CH_2Cl

161. R_1 = OH, R_2 = Et (72%)
162. R_1 = OH, R_2 = H
164. R_1 = Cl, R_2 = Et

Scheme XXXIII

ester was surprisingly hydrolyzed to give diacid **162** probably due to anion stabilization by the dienic system. It was later found, however, that even though **161** was insoluble in 15% $KHCO_3$, it could be safely extracted into a solution containing 15% K_2CO_3 in 1% KOH and regenerated with HCl in near quantitative yields.

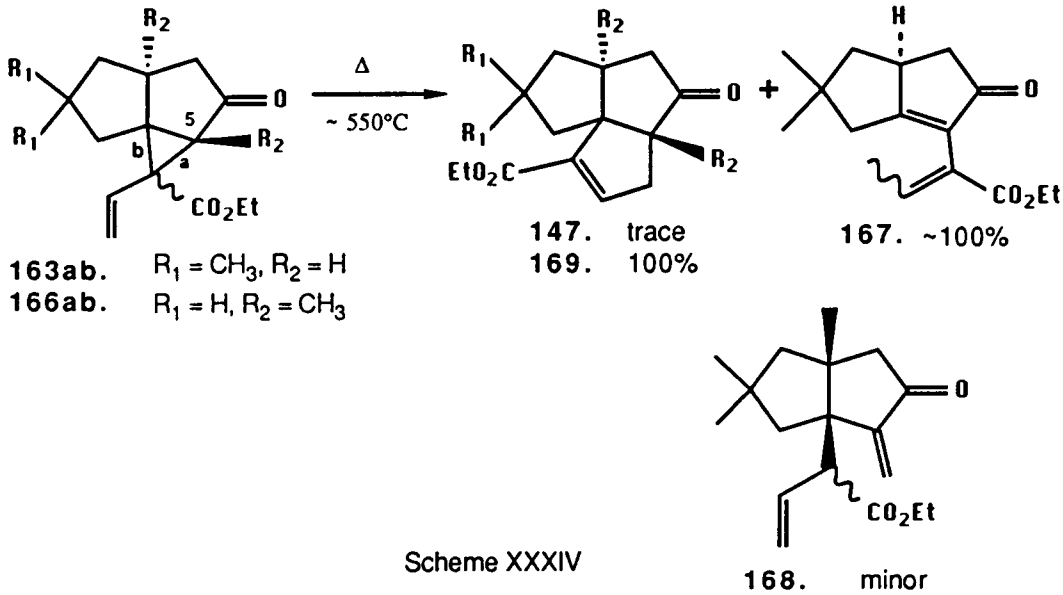
The acid **161** was obtained as a 2:1 mixture of E and Z isomers. The ratio, which was irrespective of the diasteromeric ratio of starting lactone, propagated itself to the stage of vinylcyclopropane **163ab** where it existed in the form of endo- **163a** and exo- **163b** isomers, which could be easily separated by chromatography. The conversion of **161** to **163**

was accomplished through key diazoketone **148** which was obtained by treatment of acid chloride **164** with etheral diazomethane. The acid chloride was derived upon exposure of acid **161** to oxalyl chloride.

Initial attempts to convert **161** to **163ab** generated the desired vinylcyclopropanes, but chloroketone **165** was also obtained as a by-product and composed approximately 25% of the mixture. Its formation not only decreased the yield of desired product, it complicated separation procedures and made the isolation of **163a** almost impossible due to similar R_f values. It was thought to occur as a result of acid catalyzed displacement of nitrogen by Cl^-. The problem was alleviated with the addition of triethylamine to the etheral diazomethane solution before it was added to acid chloride **164** in order to scavenge any acid which may be present. With this change in procedure, the formation of **165** was comletely eliminated.

Early experiments on cyclopropanation of diazoketones in our laboratory were done with a refluxing, homogeneous solution of copper acetylacetonate in benzene.[104] However, poor yields were later obtained when an acrylate unit was contained in the diene system, presumably due to the severe loss of electron density. The yields were improved after realizing that the reaction was proceeding via a nitrogen ylide type addition rather than a carbenoid type addition. Such behavior was reinforced in that case, as well as this one, by using heterogeneos cyclopropanation conditions. Diazoketone **148** was added dropwise to a refluxing suspension of $CuSO_4$ with 10% $Cu(acac)_2$ giving vinylcyclopropanes **163a** and **163b** in a ratio of 2:1 with an overall yield of 45% from dienic acid.

Pyrolysis of the mixture of isomers **163ab** did not meet with the same success which was enjoyed in the cases of isocomene and isocomenic acid intermediates **166ab** as diradical cleavage of bond **b** occurred almost exclusively to give **167** (Scheme XXXIV) with only trace formation of desired tricycle **147**. Some instances of bond **b** cleavage in the isocomene series served to generate **168** in minor yields, but such occurance could be eliminated by employing proper reaction conditions which reproducibly gave **169** as the exclusive product. With this result,



163ab. $R_1 = CH_3, R_2 = H$
166ab. $R_1 = H, R_2 = CH_3$

147. trace
169. 100%

167. ~100%

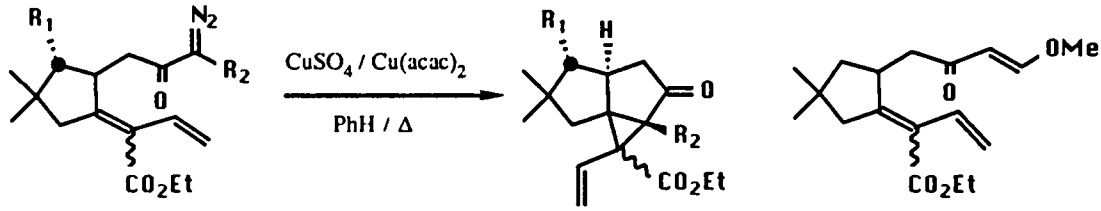
168. minor

Scheme XXXIV

a tedious search for an efficient, selective means of cleaving bond **a** in **163** was initiated and resulted in a detailed study of the factors which control such cleavages.

The major difference between the pyrolysis of isocomene and pentalenene type intermediates is the fact that diradical cleavage gives a stabilized tertiary radical in the former case, whereas a secondary radical is generated in the latter. We therefore reasoned that we could alleviate the problem by placing a removable substituent at C-5. This

possibility was investigated in the case of pentalenic acid using various carboxylate esters (Scheme XXXV). Although attempts to make the methyl ester version of diazoketone **170** were unsuccessful, the t-Butyl and benzyl esters were prepared. Unfortunately, cyclopropanation of these compounds to give **171** did not occur in either case. In an



170. R_1 = OTBDMS, R_2 = CO_2Me, CO_2t-Bu, CO_2CH_2Ph

171. R_1 = OTBDMS

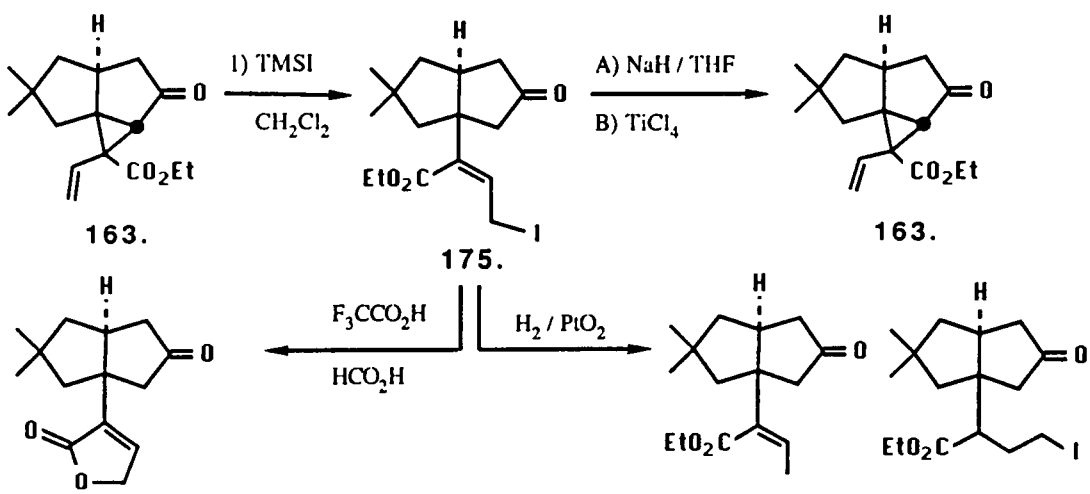
172. R_1 = H, R_2 = CH_2OMe

173. R_1 = H, R_2 = CH_2OMe

174.

Scheme XXXV

alternate attempt, we tried to prepare the methoxy derivative **172** via diazoketone **173**. Again we encountered problems as treatment of acyl chloride **164** with 1,2- diazomethoxyethane in ether led to the formation of enolether **174**. Although this approach did not lead to the desired vinylcyclopropane, it revealed a new method for the formation of enolethers. Investigations into the practicality and utility of this



163.

175.

163.

176.

Scheme XXXVI

177.

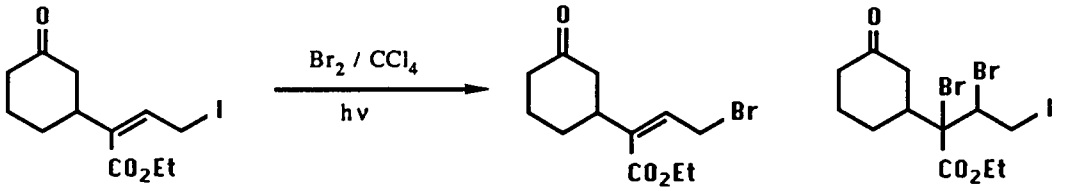
178.

method are currently in progress.

The failure to produce appropriately C-5 substituted vinylcyclopropanes presented a need to develop an alternate strategy for selective scission of bond **a**. Since trimethylsilyl iodide[105] has been shown to selectively cleave α-keto cyclopropanes,[106] an investigation was undertaken primarily by co-workers Gurudas Sinai-Zingde and Alison Fleming who tested this reagent on vinylcyclopropanes **163ab**, which were cleaved to give allylic iodides **175** upon exposure to tetramethylsilyliodide (TMSI) in CH_2Cl_2 at -20°C (Scheme XXXVI). However, upon exposure to NaH, the expected alkylative ring closure to desired tricycle **147** did not occur; rather, starting vinylcyclopropane **163** was regenerated in a ratio of (1:2, **a**:**b**). After closer evaluation, we noticed that cleavage of **163ab** gave the (Z) isomer of **175** exclusively which could not align itself properly to allow intramolecular attack by the enolate anion to the carbon bearing the iodide. An additional attempt at ring closure was made using $TiCl_4$, but this time there was no reaction. Acid catalyzed closure was sought with a solution of triflouroacetic acid in formic acid, but the exclusive product was lactone **176**.

We decided that manipulation of the iodide **175** would be necessary if ring closure was going to occur. Reduction of **175** seemed improbable with the iodide present. Hydrogenation over PtO_2 gave **177** without any evidence of saturated iodide **178** and starting material was recovered from hydrogenation over Wilkinson's catalyst ($Rh(PPh_3)_3Cl$).

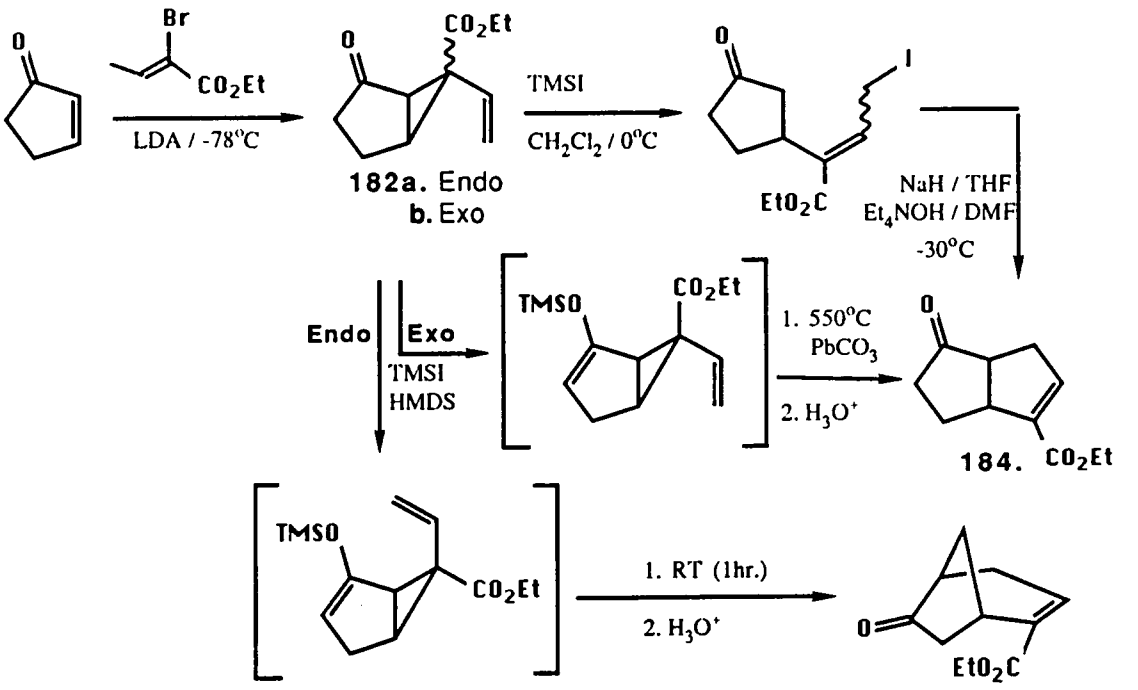
An attempt was made to brominate the double bond and generate **179** (Figure 13) thus allowing free rotation, but to our surprise, halogen



181. Figure 13 180. 179.

exchange occurred to generate allylic bromide **180** during treatment of a model compound **181** with bromine. Further investigations with model compounds did not suggest that the bromide offered any advantage over its corresponding iodide in cyclopentene ring closure, and therefore this alternative was not further investigated.

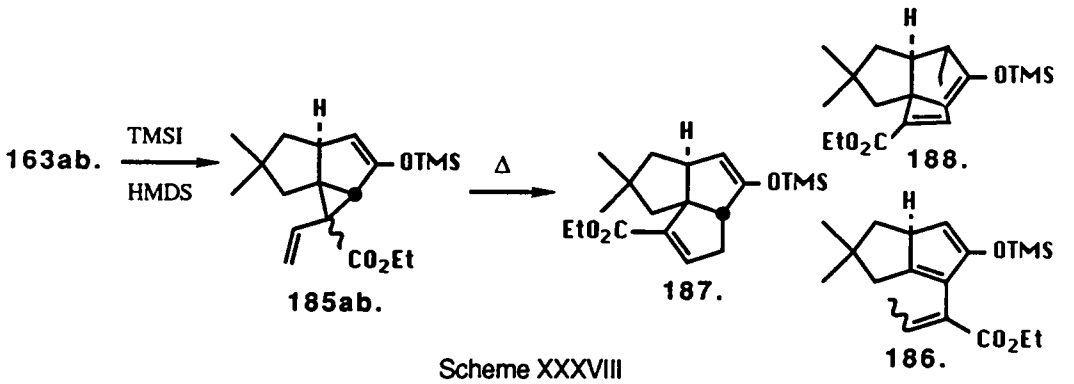
Although ring cleavage with tetramethylsilyl iodide did not lead to subsequent cyclopentene annulation either in the case of pentalenene nor pentalenic acid, endeavors of this type led to a recently published study of [2+3] cyclopentene annulations using this metnodology.[107] A



Scheme XXXVII

number of vinylcyclopropanes were investigated and conditions for ring cleavage and subsequent cyclopentene annulation were described for the endo- **182a** and exo- **182b** isomers of **182** (Scheme XXXVII). In this way each respective diasteromer could be used for selective formation of either bicyclo [3.2.1] octanone **183** or cyclopentene **184**. This information was particularly significant in view of the report on a high yielding synthesis of **182ab** from enones via the addition of lithium dienolate derived from ethyl 2-bromocrotonate as a mixture of endo- **182a** and exo- **182b** isomers.[108] Preliminary experiments indicated that **182a** is obtained specifically with ethyl 2-phenylsulphonylcrotonate. Lower temperatures or harder counter ions favored **182b**. Thus, after optimization of conditions, the reaction was found to be stereospecific for either isomer thus providing a selective entry into either [3.2.1] or [3.3.0] bicyclic ring system.

The most important result which was obtained from our investigation of TMSI mediated vinylcyclopropane ring cleavages in the context of pentalenene and pentalenic acid syntheses followed from treatment of **163ab** with TMSI in the presence of hexamethyldisilazane (HMDS).[109] The major product obtained did not result from cyclopropane cleavage, but rather from the formation of enolether **185ab** (Scheme XXXVIII). Examination of this product proved to be interesting due to the presence of the endocyclic double bond which would tend to disfavor the formation of the previously troublesome elimination product of type **186** during pyrolysis since it would require incorporation of a highly strained cyclopentadiene system into the diquinane framework. The ^{1}H-NMR of the crude product of pyrolysis and acid hydrolysis of **185ab**



Scheme XXXVIII

showed the presence of a major product with a triplet at 6.6 ppm which is the approximate location of the expected olefinic proton in the desired tricycle **147** which could have risen from acid hydrolysis of **187**. Closer inspection of the spectrum, however, revealed a second triplet which represented a minor product present in about 15% yield. We then considered the possibility that the major product might be the corresponding ketone **188a** of **188** which could arise from a Cope type rearrangement of **184ab**[110] (Figure 14). Similar bridged structures **123**, **125** were noticed by Hua[85] in his synthesis of pentalenene and by Piers in his studies of divinylcyclopropyl rearrangements.[61] Since all of the remaining functional manipulations in the sequence should generate analogous structures, we had to carry out the synthesis to completion before the proper assignment could be made (Scheme XXXIX).

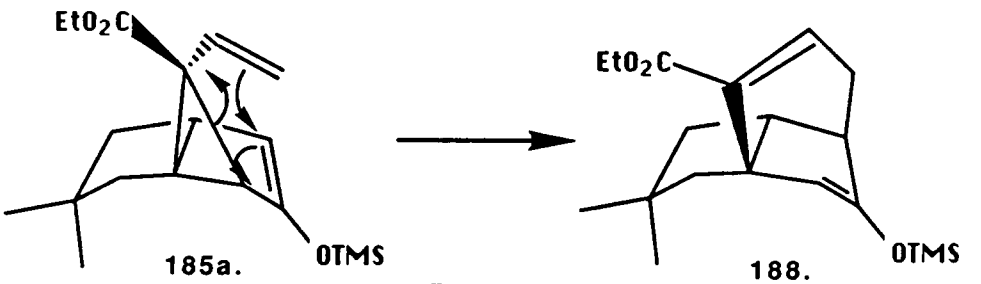
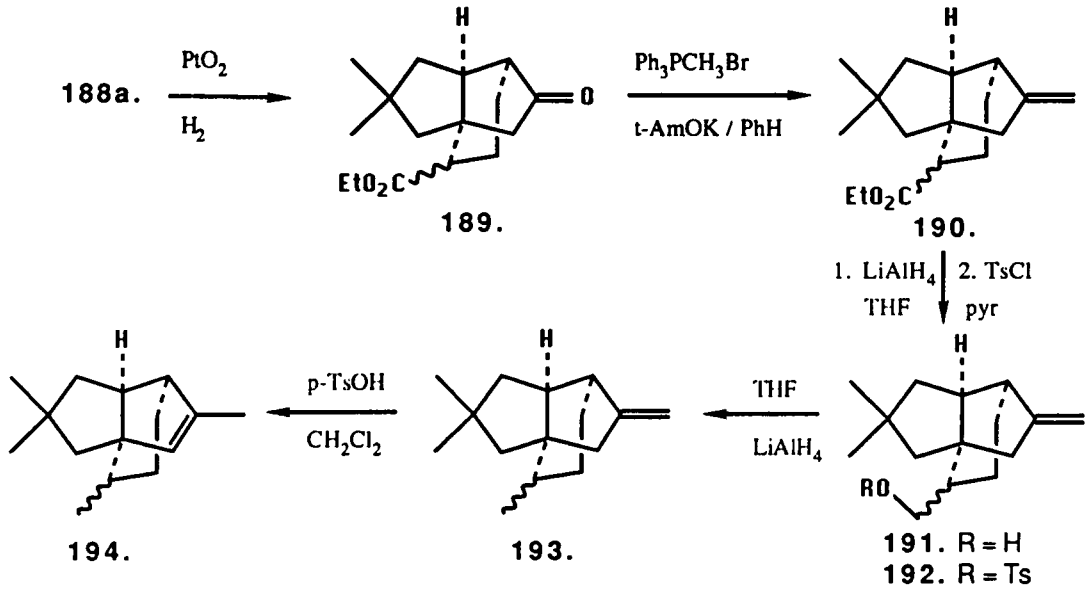


Figure 14

Compound **188a** was hydrogenated to **189** over PtO_2; and since

Professors Paquette and Crimmins had kindly provided us with spectra of pentalenene and epipentalenene, we did not need to concern ourselves with the stereochemistry about the C-9 carbon in order to assign

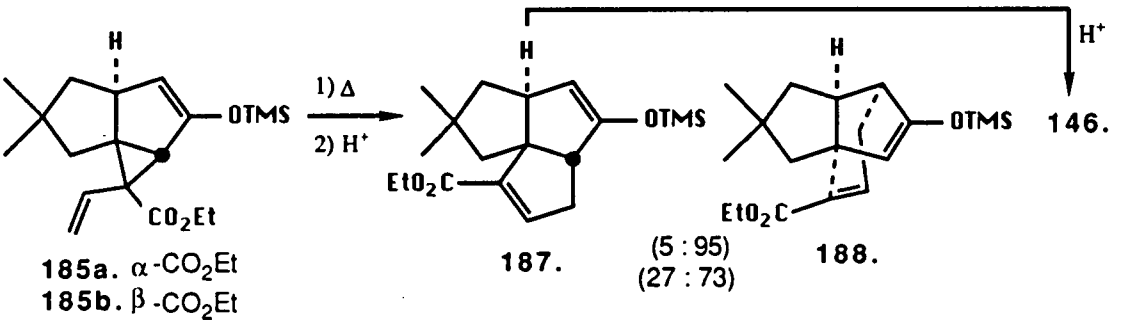


Scheme XXXIX

structure **188a.** Ketone **189** was converted to **190** by means of Dauben-Conia's modification of a Wittig.[111] Alcohol **191** was obtained by LAH reduction in THF, which was converted to its tosylate **192** and reduced with LAH in refluxing THF to hydrocarbon **193.** After p-TsOH catalyzed isomerization, hydrocarbon **194** was obtained. Neither its olefinic ^{1}H or ^{13}C signal matched those of **1** or **53**, so we concluded that the hydrocarbon possessed the structure **194** which in turn had to be derived from the keto ester with structure **188a.**

Inspection of the stereoisomers of **185** revealed that the endo-isomer **185a** is properly aligned to undergo a Cope type rearrangement (Fig. 14). The exo- isomer **185b** on the other hand, could not undergo a similar rearrangement, unless equilibration took place through diradical intermediates, since the vinyl group is too far away from the endocyclic

olefin. We therefore investigated each isomer separately to determine if the final ratio of **187:188** was greatly affected by the difference in configuration (Figure 15). Endo isomer **185a** underwent Cope rearrangement in a ratio of 20:1 compared with diradical cleavage. A surprising result was the discovery that the Cope rearrangement occurred before the compound was subjected to pyrolytic conditions! The vinyl



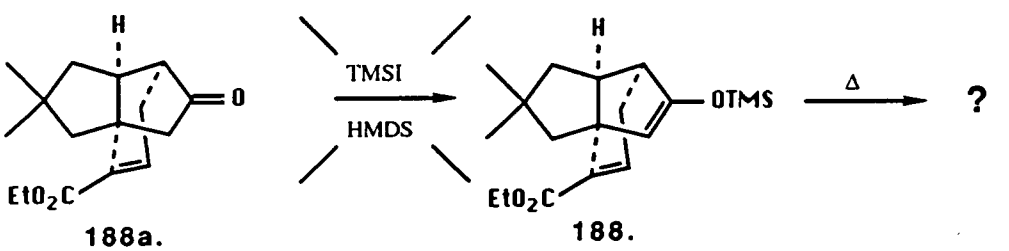
185a. α-CO_2Et
185b. β-CO_2Et

187. **188.**

Figure 15

substituent in the exo- isomer **185b** was not positioned in such a way as to allow a Cope-type process to occur, thus, diradical ring cleavage led to a mixture of **187** (28%) and **188** (72%) giving the first synthetically useful method of forming tricycle **147** despite its low yield.

In an attempt to increase the yield of **146** we attempted to regenerate **188** from **188a** in order to repyrolyze in hopes that pyrolytic cleavage may be reversible (Figure 16). Upon exposure to TMSI and HMDS;



188a. **188.**

Figure 16

however, there failed to be any formation of enolether **187** so the attempt was abandoned. Later observations with **163** suggested that ^1H-

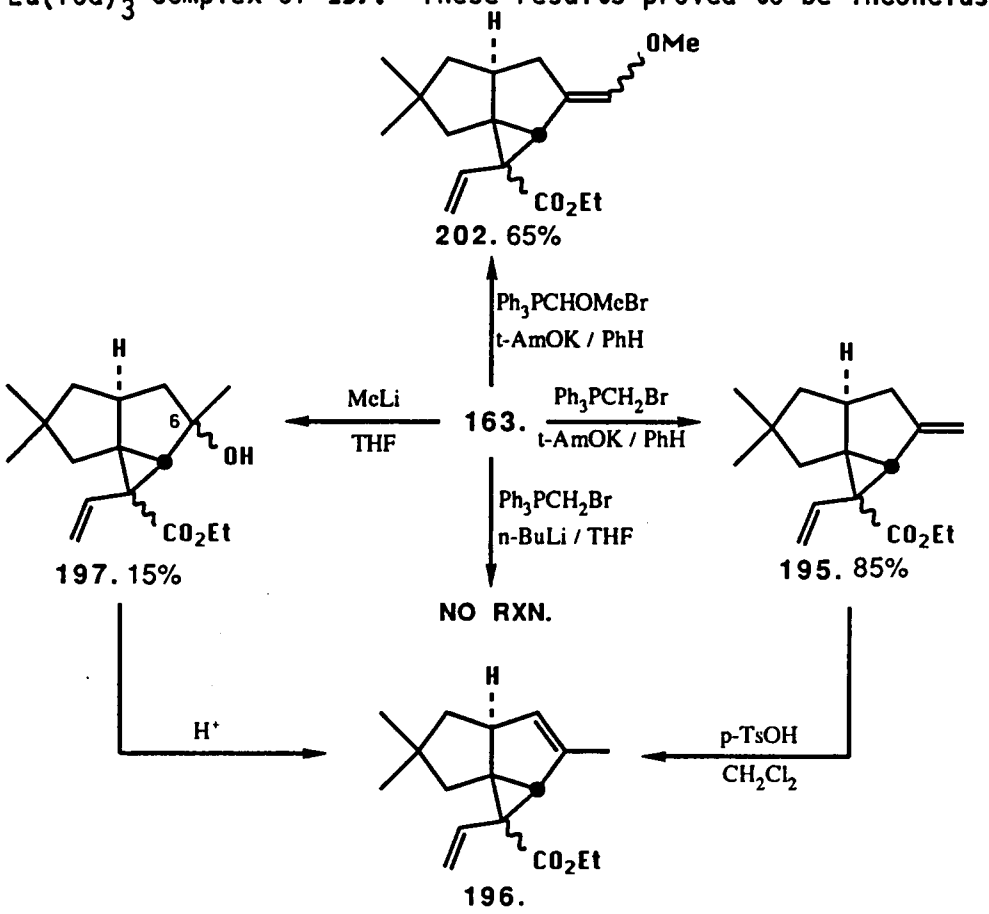
NMR data was not valid since the enolethers tend to hydrolyze in $CDCl_3$, so this study may warrant further investigation.

Approaching the problem of cyclopropane cleavage from a new perspective led to the pursuit of exocyclic olefin **195**. We believed that diradical cleavage at bond **a** would be enhanced since it would result in a stable allylic radical and one incapable of Cope rearrangement since the product of such rearrangement would contain a bridgehead double bond.

We anticipated some problems in the formation of **195** from **163** since cyclopentanones are known to be hindered thus preventing easy Wittig conversion. Irrespective of this, we subjected **163** to PPh_3CH_3Br and n-BuLi in THF, but only starting material was recovered even after 48 hours under these conditions (Scheme XL). An alternative approach was then investigated to generate endocyclic olefin **196** which would afford an allylic radical upon diradical cleavage of bond **a** in analogy with **195**. However, this molecule is similar to **184**, so that even though the elimination product **196** (Scheme XLI) from bond **b** cleavage would be extremely disfavored in this case, this molecule also shares the risk of undergoing a Cope rearrangement.

The synthesis of **196** was to arise from acid hydrolysis of alcohol **197** which was expected from treatment of **163** with MeLi. Disappointingly, **197** was achieved in only 15% yield from **163** with the remainder of the molecule being starting material. Even though this reaction did not prove to be synthetically useful, attempts to prove the stereochemistry at C-6 resulted in some interesting ^1H NMR experiments involving decoupling, lanthanide shift reagent $Eu(fod)_3$, and decoupling

of a $Eu(fod)_3$ complex of **197**. These results proved to be inconclusive



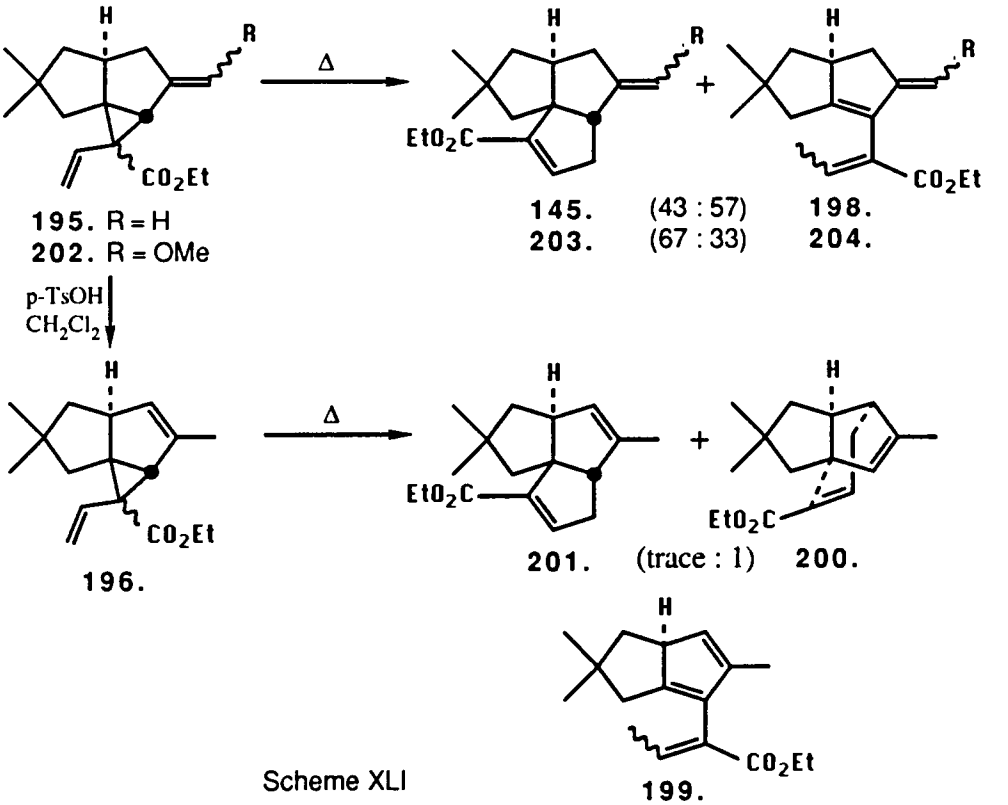
Scheme XL

despite their academic interest.

With the failure to obtain **197** in good yield, we returned our attention to **195**. We applied Dauben-Conia's Wittig[111] conditions to **163** with hopes that the equilibrating medium would allow complete conversion to the exomethylene **195** as in other carbonyls. Fortunately, the reaction proceded in 85% yield to deliver **195** as a mixture of diastereomers which was propagated from **163**.

Exoolefin **195** was subjected to pyrolytic conditions and evaluation of the ^{1}H-NMR of the crude mixture suggested that the desired tricycle **145** was present along with the elimination product from bond **b** cleavage

198 in a ratio of 43:57 respectively (Scheme XLI). This promising result represented the first pentalenene intermediate which underwent pyrolysis in a synthetically useful yield, especially in view of almost



Scheme XLI

quantitative separation on preparative TLC plates and recovery of **145**. An additional advantage which was gained by pyrolyzing **195** was a simpler procedure; since the compound is relatively volatile, it vaporizes rapidly at low temperatures even under moderate vacuum of about 10^{-3} mm. Also, both diasteromers worked equally well and gave identical results. The pyrolysis was performed at 500°C, 585°C, and 630°C giving mass balances which were consistently >90% and product ratios which were essentially independent of reaction temperatures.

Using the same reasoning used in the investigations of TMS enol-ethers **185ab**, exoolefin **195** was isomerized to give endoolefin **196** to

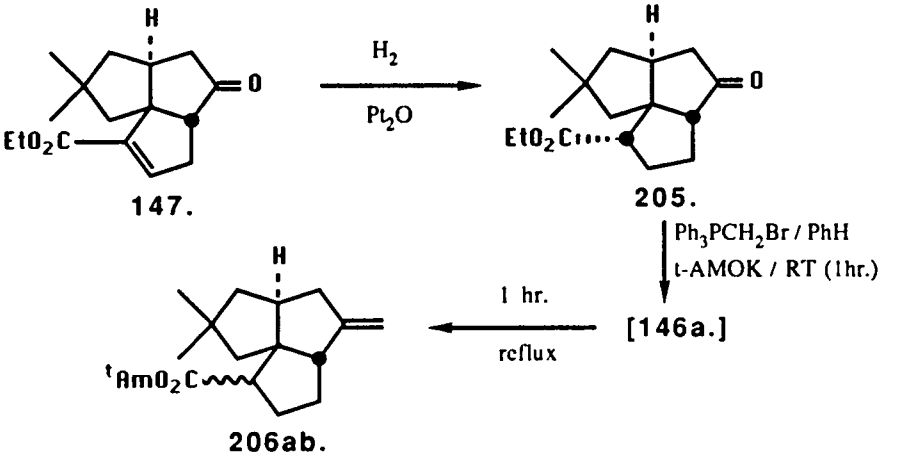
prevent formation of the elimination product **199** which results from cleavage of bond **b**. As in the case of **185ab**, pyrolysis at 550°C and 630°C gave 84% yield of Cope rearrangement product **200** with only trace formation of desired tricycle **201**.

Finally, it was thought that the best result would be obtained from a system similar to **195**, but one which better stabilizes the C-5 radical by contributing more electron density. In this way the pathway to cyclopentene should dominate over that to triene. Methoxyenolether **202** was derived from **163ab** in analogy with the preparation of **195** in order to establish the effect of added electron density in the exoolefin on the stability of the C-5 radical which would result from its pyrolysis (Scheme XLI). As expected, the enolether was more efficient at stabilizing the C-5 radical and gave a higher relative ratio (**67:33**) of desired tricycle **203** compared with elimination product **204**.

In spite of the higher relative yield of tricycle **203** in the enol ether series, there existed problems which decreased its attractiveness as compared with the exoolefin series unless a method of its rapid utilization could be unearthed. Wittig reaction to form **202** worked in only 65% yield as compared with 85% yield of **195**. The enolethers **202** and **203** were easily hydrolyzed to their respective aldehydes on silica which made removal of the Wittig byproducts from the reaction mixtures difficult. Furthermore, the products of pyrolysis could not be separated as enolethers without becoming hydrolyzed, so the crude mixture would have to be converted to a mixture of derivatives stable to silica in order to isolate the tricycle. Thus, the most practical method of preparing the triquinane ring skeleton in terms of isolated

product involved the use of the exocyclic olefin series.

At this point we had the requisite triquinane in hand and available with both ketone and exomethylene functionalities. Beginning with the precedent which was set by work with isocomene type terpenes, we hydrogenated the ketoacrylate **147** to obtain the saturated ester **205** as one diastereomer which was later shown to contain the epi-configuration at C-9 (Scheme XLII). This was the first piece of experimental data that we obtained which showed that the molecule was

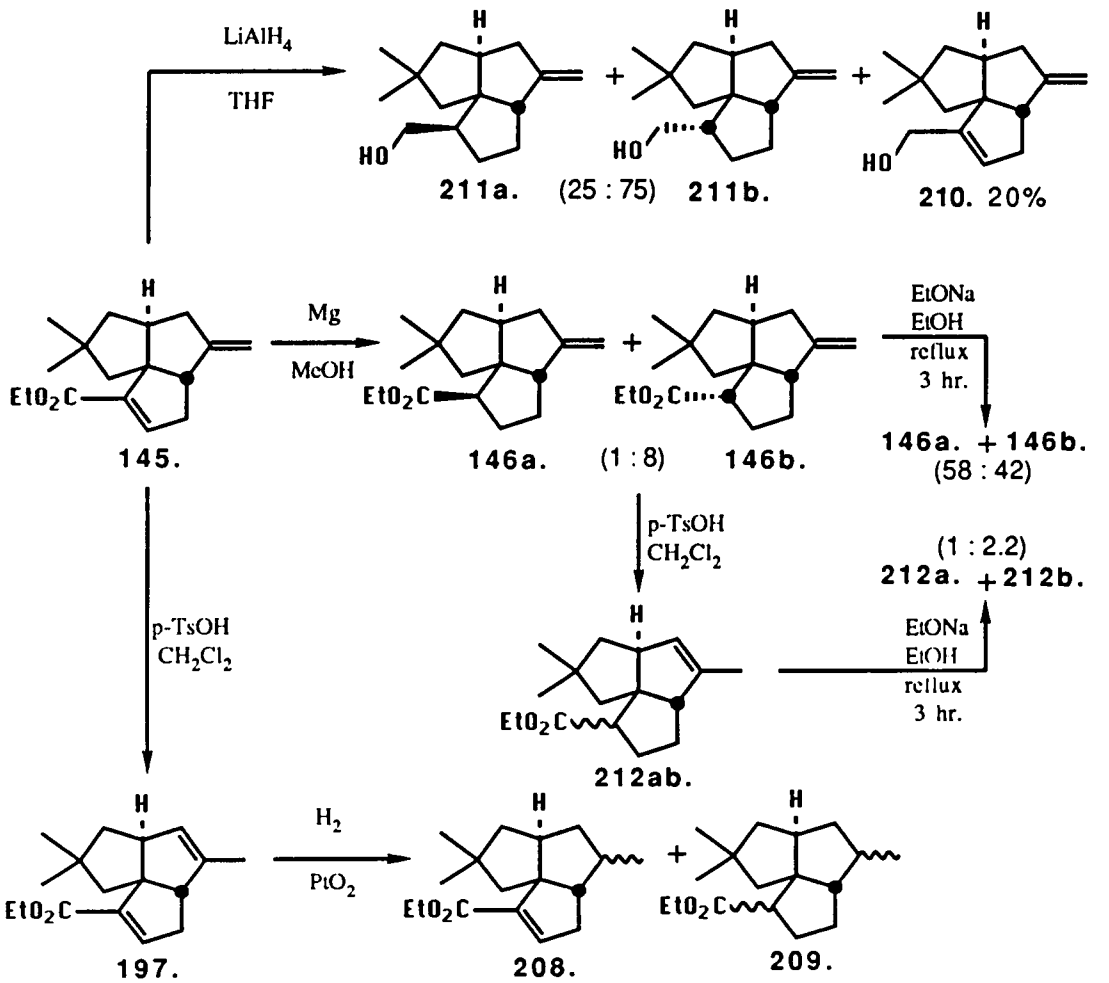


Scheme XLII

least hindered on the **natural**, α face. We then initiated the key stage of the synthesis with respect to stereocontrol. The ester **205** was subjected to Dauben-Conia's conditions for a Wittig at room temperature. We monitored the reaction by subjecting aliquots from the reaction mixture to gas chromatography analysis. These showed complete conversion to exomethylene **146a** in about 1 hr. at room temperature without any change in stereochemistry. No evidence of isomerization was noticed, even after 6 hr. The reaction mixture was then brought to reflux and after 1 hr., **206ab** was formed in an ambiguous epimeric ratio of 55:45. Since the following reaction involved reduction of the ester,

transesterification with isoamylalcohol was not perceived as a major problem.

In order to make use of **195**, we had to devise some method of selective reduction in order to prevent the reduction of the unconjugated double bond. We isomerized **145** to **197** to increase the electron content of the double bond and hydrogenated over PtO_2; unfortunately, the resulting products **209** and **208** demonstrated a lack of

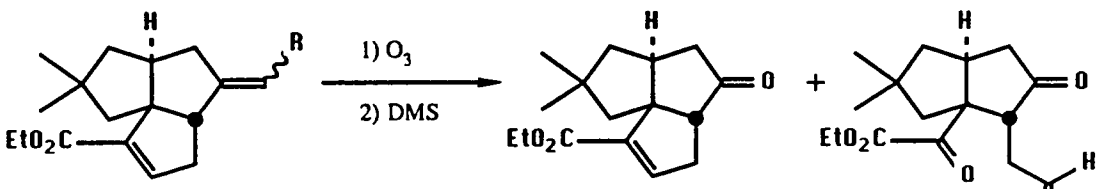


Scheme XLIII

selectivity for the isolated double bond (Scheme XLIII). We next tried $LiAlH_4$ reduction of the ester since it was known to frequently reduce

conjugated esters in a 1,4 fashion and would not reduce isolated double bonds. Exposure of **195** to LAH in THF or ether resulted in the production of allylic alcohol **210** in 20% yield and a mixture of **211a** and **211b** in a 25:75 ratio. This ratio was confirmed by carrying this mixture to the stage of the natural product which generated a 1:3 ratio of **1** and **53**. This route was ineffective in allowing stereocontrol since the epimers delivered from reduction **202ab** are not epimerizable or separable.

In response to our failure to reduce **195** to a synthetically useful intermediate, we attempted a selective ozonolysis of the exomethylene, since it has a much higher electron density than the conjugated olefin, in order to give **147** which we had already shown could be manipulated in a stereoselective manner. Selectivity was attained by Crimmins in a similar system upon exposure to excess ozone in CH_2Cl_2;[70] however in our case, **195** gave **212** under the same conditions which resulted from oxidation of both double bonds (Figure 17). The reaction was repeated on a scale of 6 mg in which a known volume of a saturated ozone solution in CH_2Cl_2 was added with a precooled pipet at -78°C to a stirred



195. R = H
203. R = OMe

147.

212.

Figure 17

solution of CH_2Cl_2 at -78°C. After stirring for 20 min the crude ozonide was reduced with dimethyl sulfide to give starting material

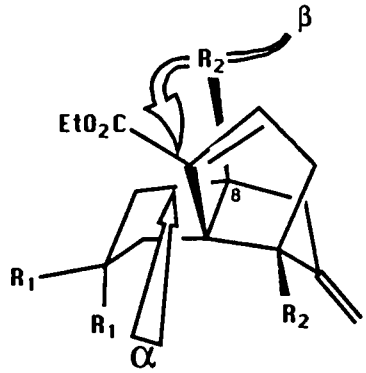
plus about 15% of **147**. The extremely small scale and dilution of the ozone solution both contributed to the low yield, but we did show that the conversion should be possible under better reaction conditions. This should also be possible in the case of enol ether **203**, except that it would have to be selectively ozonized in the presence of **204** which would envoke a need for some type of ozone titration. In spite of the promising results, these ozone studies were postponed in order to pursue an alternate method of selectively reducing the conjugated olefin which we had uncovered in the literature.

Conjugated nitriles and amides have been shown to reduce in the presence of Mg in methanol.[112] Application of this procedure to our conjugated ester **195** gave the desired uncongugated esters **146a** and **146b** in a ratio of 1:8 (Scheme XLIII); thus, in addition to delivering the required ester **146** in a stereoselective manner, we had also developed a method of selectively reducing the olefin in conjugated esters in the presence of isolated double bonds. This method of reduction was investigated in detail with other conjugated esters containing an isolated double bond and the results have been submitted for publication.[113]

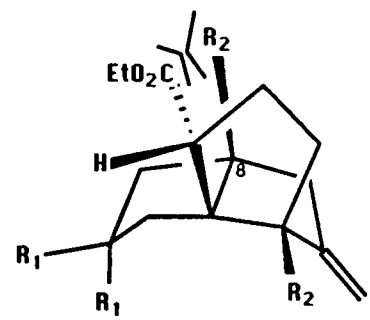
We could test the thermodynamic stability of the exomethylene **146** without risk of transesterification by subjecting the 1:8 epimeric mixture to EtONa. There was no change in the ratio of epimers after 3 hrs. of exposure to EtONa in EtOH at room temperature, so the mixture was heated to reflux and the ratio of **146a:146b** changed gradually over 3 hrs. from 1:8 to a final equilibrium mixture of 58:42 which corresponds to the ratio obtained from Wittig reaction of **146** under basic

conditions. A similar equilibration study of **212ab** which was obtained from isomerization of **146**, was conducted as before, but the equilibrium ratio was 2.2:1 in favor of the epi-configuration.

The results of thermodynamic stability can be explained in conjunction with the isocomene terpenes upon examination of 3-dimensional representations of the molecules. An entering nucloephile



142b. $R_1 = H, R_2 = CH_3$
145. $R_1 = CH_3, R_2 = H$



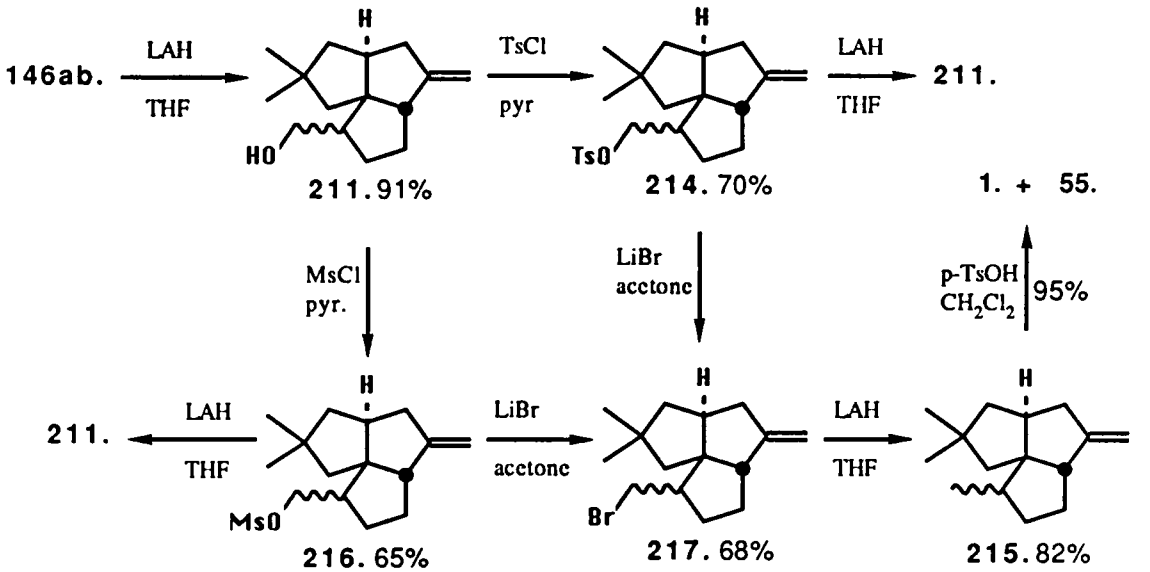
146a.
146b.

Figure 18

can gain easier access to the double bond from the α-face due to steric hindrance of the β-face from the substituent at C-8 which is also responsible for destabilizing the resulting product **146ab** since an interaction with the ester is induced (Figure 18). Since the interaction of the C-8 methyl group in **143b** is greater than the C-8 hydrogen in **146b**, the difference in stability was much more evident in the case of isocomene terpenes than in pentalene terpenes. Thermodynamic calculations were kindly made by Prof. Tanko for both systems and predicted ΔG=2.6 kcal/mole for the isocomene intermediate and ΔG=0.76 Kcal/mole for the pentalenene intermediate which corresponded to ratios of 98.8:1.2 and 78:22 respectively in favor of the natural configurations. These values are relatively close to the observed values of 100:0 and 58:42.

In summary, we have approached the problem of stereocontrol using a number of different methods with varying degrees of success: hydrogenation of gave a <99:1 ratio of the epi- to natural configuration, LAH reduction gave a 3:1 ratio, Mg/MeOH reduction gave an 8:1 ratio, epimerization gave a 58:42 ratio, and epimerization of the endocyclic olefin gave a ratio of 2.2:1. Therefore, we could obtain <100% selectivity for the epipentalenene type configuration and 58% selectivity for the natural pentalenene type configuration.

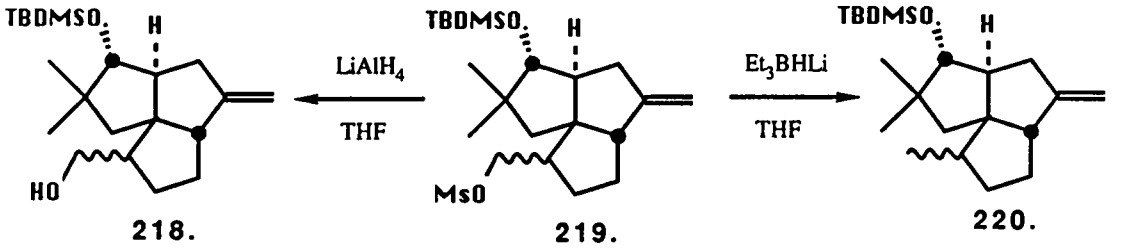
After selecting the desired C-9 configuration, final conversion of **146ab** was initiated upon $LiAlH_4$ reduction of the ester to give alcohol **211** (Scheme XLIV). Tosylation of **211** resulted in an efficient conversion to **214**; however, subsequent treatment with LAH resulted in a



Scheme XLIV

hydride displacement to regenerate **211** rather than reduction of the tosylate to give hydrocarbon **215**. Similar result was given by $LiAlH_4$ reduction of mesylate **216**, so **214** was alternatively converted to bromide **217** via treatment with LiBr in refluxing acetone. Reduction of **217** with

$LiAlH_4$ proceeded easily and gave the desired hydrocarbon **215** which isomerized upon treatment with p-TsOH to give a mixture of pentalenene



218. **219.** **220.**

Scheme XLV

and epipentalenene in a ratio which was propagated from **146ab.**

Analogous problems were encountered by my coworkers in the case of pentalenic acid as alcohol **218** was regenerated from its corresponding mesylate **219** from exposure to $LiAlH_4$ (Scheme XLV). On the other hand, superhydride (Et_3BHLi) reacted with **219** to exclusively generate the desired **220.** Irrespective of the method used to reduce the hydroxy group in **211,** the epimeric ratio of this alcohol is propogated to the final target hydrocarbons, **1** and **53.** These hydrocarbons are thus available in optimum respective ratios of 58:42 and 4:95.

IV. Second Generation Synthesis

As we were progressing toward the total synthesis of pentalenene using the [4+1] cyclopentene annulation route, exciting methodologies were being developed by my coworkers which were applicable to our general synthetic effort. These developments form a basis for a second generation approach to pentalenene type terpenes. The most significant method which was developed provided a novel [2+3] cyclopentene annulation technique.[108] The dianion generated from LDA treatment of 2-bromocrotonate added across enones to give vinylcyclopropanes. When applied to enone **221**, these conditions gave the key vinylcyclopropanes

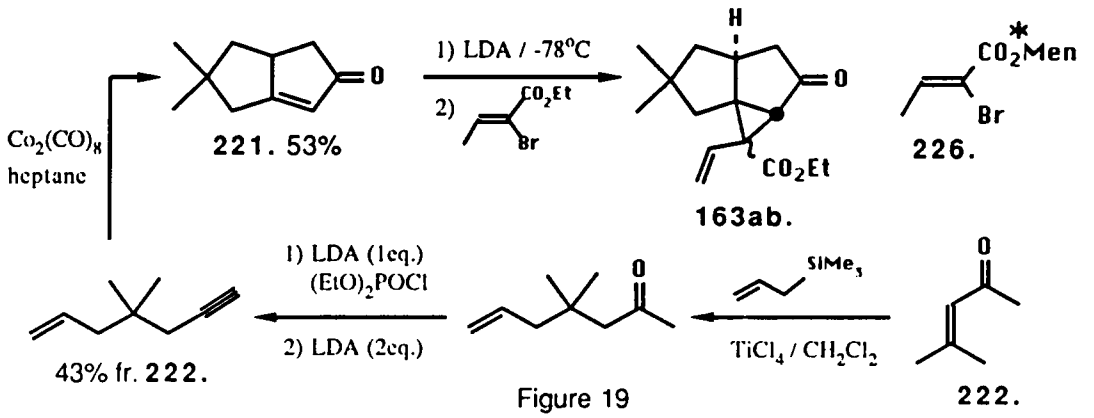


Figure 19

163ab which were used in the previous synthesis (Figure 19). This approach becomes especially attractive in view of the fact that **221** can be made in 3 high yielding steps from readily available mesityl oxide **222**.

Further improvements are expected to arise from our work with TMSI mediated cyclopropane cleavages. We have recently uncovered evidence with model compound **223** that the addition of $SnCl_4$ or $TiCl_4$ to the reaction mixture with TMSI delivers the desired (E)-olefin **224a** in a 13:27 ratio with the unreactive (Z)-olefin **224b** (Figure 20). If this

result also extrpolates to **163ab**, tricycle **147** would be attainable in 5 steps which is a remarkable improvement over the sequence which has been used to synthesize it previously.

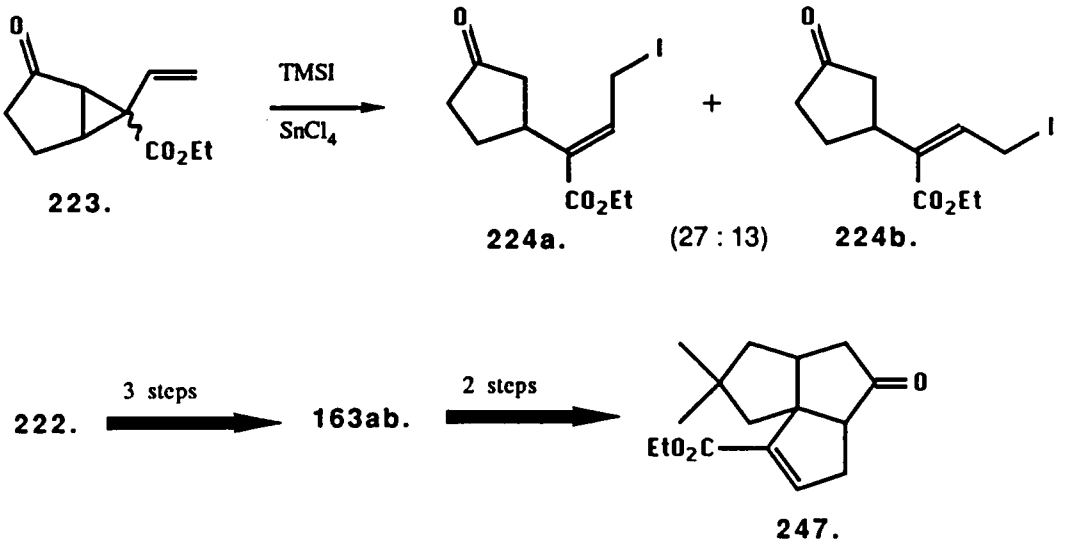


Figure 20

Using the information obtained from stereochemical studies of pentalenene intermediates, we exploited nucleophilic tendencies of **146** to design an alternate method of stereocontrol (Figure 21). We reasoned that nucleophilic attack of an LDA derived anion at C-9 would occur from the least hindered α face in the same way that hydrogen approached selectively from the α face to reduce **195** so that addition of MeI should

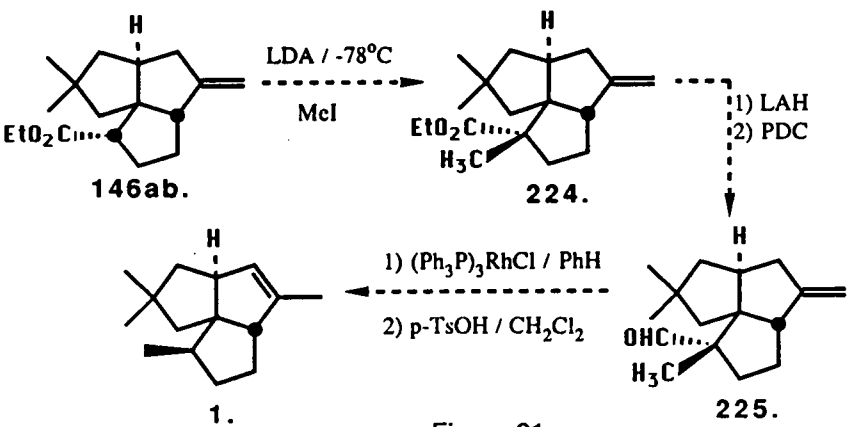


Figure 21

give **224** selectively. Wilkinson's conditions for decarboxylation are known to occur with retention of configuration[113] thus providing a short sequence to convert **147** to **225**. The natural configuration of pentalenene should then become available with simple functional manipulations.

A final improvement which we plan to implement in our second generation sequence should allow the introduction of chirality into the synthesis. We are currently investigating conditions to prepare chiral esters of bromocrotonates with hopes of using them as chiral templates so that the Reformatsky reaction will become a vehicle for chiral induction. Thus, we should be able to prepare a chiral 2-bromocrotonate ester such as **226** (Figure 19) which could then deliver **147** in a chiral - fashion.

V. Conclusion

The total synthesis of pentalenene has been achieved in a stereoselective manner to provide either the **natural** or the **epi**-configuration at C-9 with optimum selectivities of 58:42 and 5:95 in analogy with isocomene-type terpenes which have been previously synthesized by our group. The [4+1] cyclopentene annulation route to triquinane terpenes thus proved to be a general methodology.

In addition to completion of the natural product, efforts toward the synthesis of pentalenene generated exciting new methodologies which include: cyclopentene annulation from TMSI mediated vinylcyclopropane cleavage, enolether formation from acids via diazomethoxyethane, and selective reduction of double bonds which are conjugated to esters in the presence of isolated double bonds with a mixture of magnesium and methanol. These developments should find practical use in many areas of organic chemistry.

The question of thermodynamic stability at C-9 was resolved from equilibration studies of **212ab** which closely resembles the structure of pentalenene. The epi-configuration was found to predominate by a 2.2:1 ratio under equilibrating conditions, and can therefore be assigned as the more stable configuration. This situation was reversed in the case of exomethylene **146ab** where the natural configuration predominated by a 58:42 ratio.

Results acquired from this system showed that diradical cleavage of a cyclopropane is enhanced when stabilized in an allylic system and increases with additional electron density.

Future investigations in this field will be directed toward a

second generation synthesis of pentalenene using new asymmetric, [2+3] cyclopentene annulation techniques which are currently under investigation in our laboratories.

C. Experimental

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere, using standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried with an internal inert gas sweep. All solvents were distilled from benzophenone ketyl, ether from lithium aluminum hydride, and dichloromethane from calcium hydride.

Flash chromatography was performed using Kieselgel 60 (230-400 mesh) by EM reagents. Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double focusing DuPont 21-110C or VGT instruments (exact mass). I. R. spectra were recorded on neat samples on a Perkin-Elmer 257 spectrometer. ^{1}H-NMR spectra were obtained on Varian EM390, or WP-270 instruments. ^{13}C-NMR spectra were recorded on WP-270, or NR-80 instruments.

(5β,8α)-2α,2β-Dimethyl-9-carbethoxy-6-methylenetricyclo[6.3.0.0^{4,8}]undec-9-ene (145).

A sample of **195ab** (160 mg, 0.615 mmol) was evaporated (100°C, 10^{-4}mm) through a horizontally situated Vycor tube (41 cm, 5 mm i.d.) heated to 585°C after having been thoroughly cleaned (nitric acid; 50% KOH) and pretreated with a slurry of $PbCO_3$. The pyrolysate was condensed in a trap cooled with liquid nitrogen. The apparatus was thoroughly rinsed with pentane; the solution filtered to remove inorganic impurities, and the solvent evaporated to give 152 mg (95% mass balance) of orange oil shown by ^{1}H-NMR to consist of **145** (43%) and **198** (57%). The mixture was separated on preparative TLC plates (hexane/Et_2O, 9:3; 3 elutions) to obtain pure **145** as an oil (59 mg, 36.9%) that solidified upon further purification by Kugelrohr distillation, and **198** (71 mg, 44.4%), which had partially decomposed on silica.

145: R_f=0.42 (10% Et_2O, 90% hexane); b.p. 45°/10^{-4} mm Hg (Kugelrohr temp.); **IR** (neat) 3055, 1705, 1650, 1620 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.08 (s, 3H), 1.15 (s, 3H), 1.17-1.38 (m, 4H), 1.62-1.72 (m, 2H), 1.96 (d, 1H, J=13.5 Hz), 2.23 (dd, 1H, J_1=15.9, J_2=1.4 Hz), 2.30-2.46 (m, 2H), 2.79-2.99 (m, 3H), 4.19 (q, 2H, J=7.1 Hz), 4.88 (2H, J=8.9 Hz), 6.70 (t, 1H, J=2.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.26 (CH_3), 29.65 (C), 30.12 (CH_3), 31.17 (CH_3), 31.28 (CH_3), 38.48 (CH_2), 39.43 (CH_2), 46.61 (CH), 48.11 (CH_2), 50.65 (CH_2), 55.44 (CH), 59.75 (CH_2), 69.59 (C), 106.59 (CH_2), 139.51 (C), 143.42 (CH), 158.50 (C), 164.67 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 260 (M^+, 100), 245 (12), 232 (9), 214 (29), 199 (44),

187 (63), 171 (17), 159 (11), 145 (20), 131 (39), 115 (29), 105 (15), 91 (33), 77 (24), 69 (14).

Calcd for $C_{17}H_{24}O_2$: 260.1776. **Found:** 260.1777. **Anal. Calcd:** C, 78.42; H, 9.29. **Found:** C, 78.08; H, 9.29.

198: R_f=0.39 (10% Et_2O, 90% hexane); **^{1}H-NMR** ($CDCl_3$) δ 1.08 (s, 3H), 1.11 (s, 3H), 1.23 (t, 3H, J=7.1 Hz), 1.79 (d, 3H, J=7.0 Hz), 1.80-2.02 (m, 2H), 2.07 (br.s, 2H), 3.00 (br.s, 2H), 4.12 (q, 2H, J=7.1 Hz), 4.34 (br. s, 1H), 4.80 (q, 1H, J=1.2 Hz), 4.93 (q, J=1.2 Hz), 6.90 (q, 1H, J=7.0 Hz).

(5β,8α)-2α,2β-Dimethyl-6-methylene-9α-carbethoxytricyclo[6.3.0.$0^{4,8}$]undecane (146a) and Its 9β-epimer (146b).

Unsaturated ester **147** (15 mg, 0.058 mmol) was dissolved in 1.5 mL of methanol at room temperature with stirring. To this solution was added freshly scratched Mg (7 mg, 0.29 mmol, 70-80 mesh). Bubbles began to evolve almost immediately, and GC analysis of aliquots indicated that the reaction was complete after 95 min giving an 8:1 ratio of epimers with the ester preferentially in the α-position. The reaction mixture was then diluted with 10 mL of hexane and treated with 5 mL of 3M HCl. The layers were separated, and the aqueous solution was extracted 2x with 10 mL of hexane. The combined organic layers were then dried over Na_2SO_4, filtered and evaporated under vacuo to give 13.1 mg (87.3%) of **146** as an 8:1 mixture of inseparable epimers with the ester preferentially on the α-face: R_f=0.63 (1:10, ether-hexane); **IR** (neat) 1725, 1650 cm^{-1}.

major isomer: ^{1}**H-NMR** ($CDCl_3$) δ 0.98 (s, 3H), 1.02 (s, 3H), 1.17-2.73 (m, 16H), 4.16 (q, 2H, J=7.2), 4.85 (d, 2H, J=8.7 Hz); ^{13}**C-NMR** ($CDCl_3$) δ 14.34 (CH_3), 29.63 (CH_2), 30.13 (CH_3), 30.50 (CH_3), 33.96 (CH_2), 40.07 (CH_2), 46.39 (CH), 48.18 (C), 49.02 (CH_2) 55.83 (CH), 56. 83 (CH_2), 59.02 (CH), 59.94 (CH_2), 106.28 (CH_2);

minor isomer: ^{1}**H-NMR** ($CDCl_3$) δ 0.94 (s, 3H), 1.00 (s, 3H), 1.17-2.73 (m, 16H), 4.14 (q, 2H, J=7.1 Hz), 4.79 (br.s, 2H).

Epimerization at C-9. Sodium (5 mg) was added to 2 mL of dry EtOH and the resulting solution was allowed to stir for 1 h after which time all of the sodium had dissolved. Unsaturated ester **146a** (15 mg, 0.058

mmol) was dissolved in 0.5 mL of dry ethanol and added to the NaOEt/HOEt solution. A small aliquot worked up after 3 h indicated that the epimeric ratio remained unchanged. The mixture was then heated to reflux. Analysis of an aliquot after 1 h indicated that the reaction had reached an equilibrium ratio of 42:58 with the ester preferentially in the β-position. This ratio remained unchanged even after 24 h at reflux. The reaction mixture was worked up by partitioning it between 5 mL of hexane and 5 mL of 1N HCl. After separation of the hexane layer, the aqueous layer was extracted 2x with 5 mL of hexane. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the crude epimerized ester. This mixture was separable on TLC using $AgNO_3$ impregnated silica and eluting 2 times with 1:10, ether-hexane (R_f: **146a**=0.56; **146b**=0.58).

(5β,8α)-2α,2β-Dimethyl-9-carbethoxytricyclo[6.3.0.$0^{4,8}$]undec-9-en-6-one (147).

Vinylcyclopropane **163b-exo** or **163b-endo** (340 mg, 1.30 mmol) was dissolved in 10 mL of dry pentane at -20°C with stirring. To this was added 0.33 mL (1.6 mmol) of hexamethyldisilazane (HMDS). After 5 min at -20°C, 0.20 mL (1.4 mmol)of trimethylsilyl iodide was added and the resulting mixture stirred for 10 min at which time it was transferred to a test tube and centrifuged at 5000 rpm for 5 min to remove the white precipitate. The mother liquor was transferred with a pipet to a flask and evaporated to give 480 mg of crude material (TMS enol ether), which was evaporated at 100°C and 10^{-4} mm through a Vycor tube that had been pretreated with $PbCO_3$ and heated to 585°C. The crude pyrolysate was collected in a vacuum trap cooled with liquid N_2. It consisted of enol ethers **185a** and **185b**. The crude material was dissolved in 10 mL of CH_2Cl_2 to which was added 5 mL of 1N HCl. After stirring for 5 min, the organic layer was removed, and the aqueous layer was extracted 3x with 10 mL of CH_2Cl_2. The extact was combined with the first organic layer, dried over Na_2SO_4, filtered, and evaporated to give 292 mg (86%) of crude material. ^{1}H-NMR analysis of crude mixtures consistently showed that **163a-endo** gave a 1:20 ratio of tricycle **147** to Cope product **188a**; whereas **163b-exo** gave a 1:3.7 ratio of these compounds. The crude mixtures were separated on preparative TLC plates using 20% ether in hexane (3 elutions) to give pure samples of each compound.

147: R_f=0.45 (33% Et_2O in hexane); b.p. 80°C/10^{-4}mm Hg (Kugelrohr temp.); **IR** (neat) 1735, 1645 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.11 (s, 3H), 1.22

(s, 3H), 1.25-1.39 (m, 1H), 1.32 (t, 3H, J=7.1 Hz), 1.76 (d, 1H, J=13.5 Hz), 1.93 (dd, 1H, J_1=12.3, J_2=6.5 Hz), 2.07 (d, 1H, J=13.2 Hz), 2.27 (d, 2H, J=5.9 Hz), 2.55-2.80 (m, 3H), 4.21 (q, 2H, J=7.2 Hz), 6.72 (t, 1H, J=2.7 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.23 (CH_3), 30.88 (CH_3), 31.21 (CH_3), 34.47 (CH_2), 39.39 (C), 42.13 (CH), 43.45 (CH_2), 49.78 (CH_2), 49.97 (CH_2), 57.99 (CH), 60.07 (CH_2), 65.73 (C), 138.31 (C), 139.25 (C), 143.47 (CH), 163.87 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 262 (M^+, 23), 245 (8), 232 (19), 214 (33), 186 (18), 149 (40), 129 (96), 123 (43), 112 (136), 91 (48), 55 (100).

Calcd for $C_{16}H_{22}O_3$: 262.1569. **Found**: 262.1570.

188a: R_f=0.40 (33% Et_2O in hexane); **IR** (neat) 1735, 1640 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.01 (s, 3H), 1.10 (s, 3H), 1.22 (t, 3H, J=7.1 Hz), 1.26 (t, 1H, J=13.0 Hz), 1.58 (d, 1H, J=14.1 Hz), 1.64 (dd, 1H, J_1=13.0, J_2=6.9 Hz), 2.07 (d, 1H, J=14.1 Hz), 2.21-2.58 (m, 6H), 4.12 (dq, 2H, J_1=7.1, J_2=1.9 Hz), 6.49-6.52 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 14.13 (CH_3), 32.08 (CH_3), 32.63 (CH_3), 32.86 (CH_2), 39.19 (C), 43.85 (CH_2), 47.65 (CH_2), 50.05 (CH), 51.13 (CH), 52.00 (CH_2), 60.22 (CH_2), 134.96 (CH), 143.02 (C), 165.86 (C), 219.93 (C).

2-Carbethoxymethyl-4,4-dimethylcyclopentanone (149)

Olefinic ester **157** (2.48 g, 12.5 mmol)was dissolved in 100 mL of CH_2Cl_2 and 50 mL of MeOH, and O_2 was passed through the solution for 5 min. Ozone was then bubbled through until the solution turned blue (~3 min) and then for 10 min more. The flow of ozone was replaced with O_2, which was bubbled through the solution until it became clear (~2 min) and then for 10 min more. The solution was transferred to a 250 mL round bottom flask and warmed to 0°C with stirring. Dimethyl sulfide (2 mL) was dropped into the flask and the solution was stirred for 24 h. The CH_2Cl_2 and DMS were removed by rotary evaporation. The crude oil was then dissolved in 20 mL of Et_2O, washed 4x with 5 mL of H_2O, 3x with 5 mL of brine, dried over Na_2SO_4, and evaporated to yield 2.41 g (96.4%) of crude material. This material was suitable for use in the next step. The material was purified on flash silica using 5→10% Et_2O in hexane and then distilled (Kugelrohr; 70°C/0.05 mm) to yield 934 mg (37.4%) of analytically pure ketoester **149**. The yield was low because of to extensive polymerization. R_f=0.47 (20% EtOAc; 80% hexane); **IR** (neat) 1745, 1735, 1180, 1030 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.17 (s, 3H), 1.28 (s, 3H), 1.33 (t, 3H, J=7 Hz), 2.68 (t, 1H, J=12 Hz), 2.13 (dd, 1H, J_1=12, J_2=8 Hz), 2.22 (s, 2H), 2.52 (dd, 1H, J_1=16, J_2=8 Hz), 2.76 (m, 2H), 4.20 (q, 2H, J=7 Hz); **^{13}C-NMR** ($CDCl_3$) δ 13.9 (CH_3), 27.8 (CH_3), 29.5 (CH_3), 33.7 (C), 34.5 (CH_2), 43.3 (CH_2), 44.4 (CH), 52.4 (CH_2), 60.1 (CH_2), 171.5 (C), 217.7 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 198 (M^+) (33), 183 (19), 153 (77), 152 (100), 149 (41), 137 (49), 111 (77), 83 (100), 56 (70), 55 (68);

Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.15. **Found:** C, 66.39; H, 9.28.

1-Hydroxymethyl-4,4-dimethylcyclopentene (156).

LiBr (41.0 g, 0.472 mol) was dissolved in 75 mL of DME and brought to reflux. 5,5-Dimethyl-2,3-epoxycyclohexanol[18,21] (22.1 g, 0.155 mol) in 75 mL of DME was added to the refluxing solution over 30 min. The reaction mixture was refluxed an additional 40 min, then cooled, diluted with 150 mL of pentane and washed 3x with 50 mL of H_2O. The aqueous layer was extracted with pentane and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give 19.3 g (98.4%) of crude 4,4-dimethylcyclopentene-1-carboxaldehyde **141a**. The crude aldehyde was dissolved in 600 mL of Et_2O and 15 mL of MeOH. Sodium borohydride (15 g, 0.4 mol) was added slowly in portions and the reaction mixture was stirred for 24 h. 3N HCl (100 mL) was added dropwise slowly into the flask. The aqueous layer was extracted 2x with 500 mL of Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give 17.82 g (90.8%) of alcohol **156**, pure enough by NMR (>90%) to be used in the next step. An analytical sample was prepared by purification of 503 mg of crude material on flash silica with 10% Et_2O in hexane to yield 355 mg (70.6%) of alcohol **156**: R_f=0.19 (15% EtOAc, 85% hexane). **IR** (neat) 3300, 1658 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.08 (s, 6H) 2.04, (s, 1H), 2.14 (m, 4H), 4.12 (s, 2H), 5.48 (s, 1H); **^{13}C-NMR** ($CDCl_3$) δ 29.9 (CH_3), 38.6 (C), 47.6 (CH_2), 47.8 (CH_2), 62.3 (CH_2), 124.0 (CH), 142.9 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 108 (M^+-H_2O)(20), 96(11), 84(12), 69 (100), 55(20).

Ethyl-2-[4,4-dimethyl-2-methylenecyclopentanyl]acetate (157).

Alcohol **156** (0.240 g, 1.9 mmol) was dissolved in 15 mL of triethylorthoacetate and 0.5 mL of propionic acid was added. The mixture was then sealed in a glass tube and heated at ~200°C for 3 h. The tube was then cooled with liquid N_2 and the seal was broken. The mixture was dissolved in 50 mL of Et_2O, washed 3x with 10 mL of 1N HCl, 3x with 10 mL H_2O, and 2x with 10 mL of brine, dried over Na_2SO_4, filtered, and evaporatd to yield 0.285 g (76.3%) of crude oil. Filtration through a plug of silica gel yielded 0.279 g (74.7%) of product which was >90% pure by NMR and suitable for use in the next step. An analytical sample was then purified on 10% deactivated flash silica gel (to prevent olefin isomerization) with 5% EtOAc in hexane to yield pure olefinic ester **157**. The reaction has been run on scales of up to 20 g of alcohol in a steel autoclave with similar results. R_f=0.63 (15% ethyl acetate, 85% hexane); **IR** (neat) 1738, 1655 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.96 (s, 3H), 1.05 (s, 3H), 1.19-1.28 (m, 1H), 1.26 (t, 3H, J=7.2 Hz), 1.79 (ddd, 1H, J_1=12.4, J_2=8.0, J_3=1.0 Hz), 2.02-2.23 (m, 2H), 2.26 (dd, 1H, J_1=15.2, J_2=9.3 Hz), 2.61 (dd, 1H, J_1=15.3, J_2=5.3 Hz), 2.94-3.02 (m, 1H), 4.13 (q, 2H, J=7.2 Hz), 4.78 (br.q, 1H, J=2.1 Hz), 4.89 (br.q, 1H, J=2.1 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.16 (CH_3), 27.56 (CH_3), 29.08 (CH_3), 37.14 (C), 38.97 (CH), 40.06 (CH_2), 47.34 (CH_2), 48.40 (CH_2), 60.15 (CH_2), 105.74 (CH_2), 155.32 (C), 173.06 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 196 (20, M^+), 181 (20), 165 (25), 153 (100), 149 (35), 121 (55), 107 (60) 93 (60), 79 (40), 67 (50), 55 (85). **Calcd for** $C_{12}H_{20}O_2$: 196.1198. **Found**: 196.1182.

Ethyl 2α-(3-oxo-7,7-dimethyl-2-oxabicyclo[3.3.0]oct-1-yl)-3-butenoate (160).

Dry zinc (1.5 g, 22.9 mmol) was covered with 4.5 mL of a saturated solution of $Cu(OAc)_2$ in acetic acid and allowed to stir for 30 min. The suspension was then washed 15x with 20 mL of Et_2O using an aspirator wand in order to remove the acetic acid. ^{1}H-NMR of the final Et_2O wash showed no acetic acid peak. The catalyst was then covered with 15 mL of dry ether and brought to reflux. A crystal of I_2 was added. A mixture of keto ester **149** (0.5 g, 2.5 mmol) and ethyl 4-bromocrotonate (0.42 mL, 27.5 mmol) was added dropwise slowly over 10 min. No initiation was noticed after 10 min, so another crystal of I_2 was added causing rapid initiation. TLC showed the reaction to be complete after 4 h, whereupon it was quenched with 20 mL of saturated NH_4Cl. The aqueous layer was then extracted 3x with 10 mL of Et_2O; the organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to yield 0.695 g (88.1% including 0.2 equiv of bromocrotonate) of crude oil. The material was then separated on flash silica using 15% EtOAc in hexane to yield 0.577 g (85.8%) of pure lactone **160**. It was then purified by kugelrohr distillation at 150°C and 0.025 mm. to yield 0.449 g (66.8%) of analytically pure lactone **160**. R_f = 0.33 (20% ethyl acetate, 80% hexane). The lactone was obtained as a mixture of erythro and threo isomers in a ratio of 7:3. **Major isomer (160a-erythro)**: **IR** (neat) 1775, 1772, 1635 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.98 (s, 3H), 1.18 (s, 3H), 1.27 (t, 3H, J=7 Hz), 1.44 (m, 1H), 1.91 (m, 3H), 2.35 (d, 1H, J=18 Hz), 2.76 (m, 1H), 2.98 (m, 1H), 3.24 (d, 1H, J=10 Hz), 4.15 (q, 2H, J=6 Hz), 5.31

(m, 2H), 5.91 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 13.9 (CH_3), 29.0 (CH_3), 29.7 (CH_3 double intensity), 36.8 (CH_2), 38.8 (C), 41.1 (CH), 48.1 (CH_2), 50.2 (CH_2), 58.5 (CH), 61.0 (CH_2), 97.2 (C), 121.0 (CH_2), 131.5 (CH), 170.6 (C), 176.5 (C).

Minor isomer (160b-threo): Not isolated in pure form. Peaks were assigned from spectra of threo and erythro mixtures: **IR** (neat) 1775, 1722, 1635 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.02 (s, 3H), 1.18 (s, 3H), 1.27 (t, 3H, J=7 Hz), 1.44 (m, 1H), 1.91 (m, 3H), 2.35 (d, 1H, J=18 Hz), 2.76 (m, 1H), 2.98 (m, 1H), 3.36 (d, 1H, J=10 Hz), 4.15 (q, 2H, J=7 Hz), 5.31 (m, 2H), 5.91 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 13.9 (CH_3), 28.8 (CH_3), 29.7 (CH_3), 37.4 (CH_2), 38.6 (C), 40.8 (CH), 48.5 (CH_2), 49.9 (CH_2), 58.2 (CH), 61.0 (CH_2), 97.5 (C), 121.3 (CH_2), 131.1 (CH), 170.6 (C), 176.8 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 223 (2)(M^++1-CO_2), 205(3), 153 (100), 135(14), 109(13), 83(14), 69(22), 55(18).

Calcd for $C_{11}H_{18}O_3$ (diastereomeric mixture): C, 67.64; H, 8.32. **Found:** C, 67.56; H, 8.29.

(3,3-Dimethyl-5-vinylcarbethoxymethylenecyclopent-1β-yl)acetic acid (161).

A solution of DBU (5.72 g, 37.6 mmol) in 100 mL of DME was added dropwise to a stirred solution of lactone **160** (5.01 g, 18.8 mmol) in 100 mL of DME over 1 h. The solution was stirred for an additional 1 h at which time the volume of the mixture was reduced to approximately 50 mL by evaporation and partitioned between 100 mL of 3N HCl and 100 mL of CH_2Cl_2. The layers were separated and the aqueous layer was washed 2x with 50 mL of CH_2Cl_2. The combined organic layers were extracted 5x with a solution of 20% K_2CO_3 in 5% aqueous KOH. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give 0.88 g (17.6%) of recovered **160**. The basic layer was acidified to pH=1 with 3N HCl and extracted 3x with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated to give 3.3 g (65.1%; 79% based on recovered starting material) of dienic acid **161** as an inseparable 2:1 mixture of E and Z isomers which was clean enough to be used in the next step. For analytical purposes, a portion of **161** was purified on flash silica (10% to 30% EtOAc in hexane containing 2% ACOH). R_f=0.22 (20% EtOAc and 2% HOAc in hexane); **IR** (neat) 3100 v.br., 1715, 1640 cm^{-1}; **Mass Spectrum** (70 eV, m/e (rel. int.)) 266 (M^+, 8), 251 (2), 238 (4), 223 (10), 205 (6), 193 (25), 149 (100), 141 (15), 127 (10), 114 (12), 83 (15), 69 (20).

Calcd for $C_{15}H_{22}O_4$: 266.1518. **Found**: 266.1515.

161 (E, major isomer): ^{1}**H-NMR** ($CDCl_3$) δ 0.86 (s, 3H), 1.12 (s, 3H), 1.30-1.43 (m, 4H), 1.81-2.03 (m, 1H), 2.27-2.49 (m, 3H), 2.82 (dd, 1H,

J_1=15.5, J_2=3.2 Hz), 3.26-3.40 (m, 1H), 4.27 (q, 2H, J=7.2 Hz), 5.18-5.42 (m, 2H), 6.42 (dd, J_1=17.1, 1H, J_2=11.3 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.03 (CH_3), 27.39 (CH_3), 28.78 (CH_3), 37.58 (C), 37.90 (CH), 40.09 (CH_2), 46.69 (CH_2), 47.94 (CH_2), 60.64 (CH_2), 116.39 (CH_2), 127.32 (C), 132.44 (CH), 154.40 (C), 167.60 (C), 178.23 (C).

161 (Z, minor isomer): **^{1}H-NMR** ($CDCl_3$) δ 0.86 (s, 3H), 1.12 (s, 3H), 1.30-1.43 (m, 4H), 1.81-2.03 (m, 1H), 2.27-2.49 (m, 3H), 2.75 (dd, 1H, J_1=15.5, J_2=3.2 Hz), 3.47-3.61 (m, 1H), 4.26 (q, 2H, J=7.2 Hz), 5.18-5.42 (m, 2H), 6.44 (dd, 1H, J_1=17.2, J_2=11.5 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.18 (CH_3), 27.16 (CH_3), 28.56 (CH_3), 38.36 (C), 37.90 (CH), 40.16 (CH_2), 47.16 (CH_2), 47.94 (CH_2), 60.51 (CH_2), 116.62 (CH_2), 126.96 (C), 130.14 (CH), 156.12 (C), 167.38 (C), 177.98 (C).

(1α,6α)-8,8-Dimethyl-2β-carbethoxy-2α-vinyltricyclo[4.3.0.0^{1,3}]nonan-4-one (163a) and its 2α, 2β isomer (163b).

Dienic acid **161** (521 mg, 1.96 mmol) was dissolved in 20 mL of dry benzene and cooled to 5°C. Oxalyl chloride (427 μL, 4.90 mmol) was then added, and the solution was allowed to warm to room temperature. The reaction was monitored by IR which showed complete conversion to acid chloride **165** after 2 h. The solution was then freeze-dried. **IR** (neat) 1795, 1720 cm^{-1}.

Diazomethane was prepared by addition of nitrosomethylurea (2.00g, 19.4 mmol) to a two-phase system consisting of 25 mL of Et_2O and 25 mL of 50% KOH at 0°C. The ether layer was dried for 30 min over KOH pellets, then over Na_2SO_4 for 5 min at 0°C in both cases. Triethylamine (1 mL) was added to the solution which was subsequently filtered through a cotton plug into the round bottom flask which contained the dry acid chloride. The solution was allowed to stir for 45 min at 0°C. IR at this time showed complete coversion to diazoketone **148**. The solution was then gently refluxed for 10 min with a heat gun to remove excess CH_2N_2, filtered through a medium frit and freeze-dried. **IR** (neat) 2100, 1720, 1635 cm^{-1}.

Cupric sulfate (300 mg, 1.88 mmol) and cupric acetylacetonate (30 mg, 0.115 mmol) were suspended in 15 mL of dry benzene and brought to reflux. The crude diazoketone **148** was dissolved in 10 mL of dry benzene and added dropwise over 15 min. to the refluxing suspension. The mixture was refluxed for an additional 40 min, at which time it was cooled to room temperature, evaporated to dryness, and diluted with 20

mL of hexane. This mixture was filtered through celite and evaporated to give 498 mg of crude oil shown by NMR analysis to be a 2:1 mixture of **163a-endo** and **163b-exo**. The crude mixture was separated on flash silica gel using 0→25% EtOAc in hexane as eluant to give a less polar (174 mg, 34%) (**163a-endo**) and a more polar (148 mg, 29%) (**163b-exo**) diastereomer of the desired vinylcyclopropane.

163b-endo (minor diastereomer): R_f=0.33 (Hexane 85%, EtOAc 15%); b.p. 80°/10^{-4}mm Hg (Kugelrohr temp.); **IR** (neat) 1735, 1640 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ, 1.06 (s, 3H), 1.12 (s, 3H), 1.26 (t, 3H, J=7.0 Hz), 1.39 (dd, 1H, J_1=12.5, J_2=10.5 Hz), 1.66 (dd, 1H, J_1=14.0, J_2=1.5 Hz), 1.82 (d, 1H, J=14.0 Hz), 1.93 (ddd, 1H, J_1=13.0, J_2=7.5, J_3=1.5 Hz), 2.00 (m, 1H), 2.22 (ddd, 1H, J_1=20.0, J_2=8.0, J_3=1.0 Hz), 2.66 (m, 1H), 2.70 (s, 1H), 4.16 (m, 2H), 5.24 (dd, 1H, J_1=17.5, J_2=1.0 Hz), 5.34 (dd, 1H, J_1=10.0, J_2=1.0 Hz), 6.08 (dd, 1H, J_1=17.0, J_2=10.0 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.20 (CH_3), 28.76 (CH_3), 29.25 (CH_3), 37.81 (CH), 39.44 (C), 41.70 (C), 43.36 (CH_2), 44.73 (CH_2), 46.00 (CH), 49.22 (CH_2), 53.17 (C), 61.43 (CH_2), 121.44 (CH_2), 130.44 (CH), 169.53 (C), 213.49 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 262 (M^+, 8), 216 (100), 201 (20), 173 (25), 161 (30), 146 (20), 131 (20), 125 (25), 119 (10), 105 (25), 97 (10), 91 (30), 77 (20).

Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. **Found**: C, 73.10; H, 8.45.

163b-exo (major diastereomer): R_f=0.24 (hexane 85%; EtOAc 15%); b.p. 80°/10^{-4}mm Hg (kugelrohr temp.); **IR** (neat) 1735, 1635 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.07 (s, 3H), 1.11 (s, 3H), 1.28 (t, 1H, J=14.0 Hz), 1.83 (dd, 1H, J_1=12.0, J_2=10.0 Hz), 1.54 (d, 1H, J=14.0 Hz), 1.83 (dd, 1H,

J_1=14.0, J_2=1.0 Hz), 1.95 (ddd, 1H, J_1=12.5, J_2=7.5, J_3=1.5 Hz), 2.07 (dd, 1H, J_1=19.5, J_2=3.5 Hz), 2.16 (s, 1H), 2.41 (dd, 1H, J_1=19.0, J_2=8.0 Hz), 2.63 (m, 1H), 4.20 (m, 2H), 5.10 (d, 1H, J=17.5 Hz), 5.18 (d, 1H, J=10.5 Hz), 5.83 (dd, 1H, J_1=17.0, J_2=10.5 Hz); **^{13}C-NMR** ($CDCl_3$) δ, 14.06 (CH_3), 28.50 (CH_3), 29.11 (CH_3), 38.94 (CH_2), 39.79 (C), 42.46 (CH_2), 45.44 (CH_3), 49.68 (CH_3), 53.63 (C), 61.46 (CH_2), 116.22 (CH_2), 133.45 (CH), 169.02 (C), 212.11 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 262 (M^+, 45), 247 (10), 234 (15), 216 (70), 205 (20), 188 (100), 173 (40), 161 (45), 151 (70), 145 (55), 140 (50), 132 (65), 123 (70), 105 (80), 91

80), 77 (45).

Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. **Found:** C, 72.87; H, 8.80.

(1α, 6α)-8,8-Dimethyl-2β-carbethoxy-2α-vinyl-4-methylenetricyclo[4.3.0.0^{1,3}]nonane (195a) and Its 2α, 2β-Isomer (195b).

Methyltriphenylphosphonium bromide (1.34 g, 3.76 mmol) was dissolved with stirring in benzene (15 mL). Potassium tert-amylate/tert-amyl alcohol (3.76 ml, 3.76 mmol, 1.08 M) was then introduced via a syringe and the resulting yellow solution was stirred at room temperature for 20 min. The ketone **163** (both isomers) (492 mg, 1.88 mmol) was then dissolved in 5 mL of benzene and added via a canula to the reaction mixture, which turned to a brownish-orange color. TLC showed no starting material after 2 h. The reaction was worked up with 20 mL of 1M HCl and extracted 3x with 20 mL of hexane, dried over $MgSO_4$, filtered, and evaporated to give 210 mg of crude material. The reaction mixture was then separated over flash silica (hexane→20% Et_2O: 80% hexane) to give one fraction (435 mg, 89.3%) which contained a mixture of endo and exo isomers in the same ratio as the starting ketone **163**. The reaction was later repeated using each of the ketone isomers separately to obtain pure samples of each isomer.

195a-endo: R_f=0.44 (10% Et_2O, 90% hexane); b.p. 70°/0.05 mm Hg (Kugelrohr temp.) **IR** (neat) 3070, 1720, 1645 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.02 (s, 3H), 1.08 (s, 3H), 1.25 (t, 3H, J=7.1 Hz), 1.30 (dd, 1H, J_1=12.1, J_2=10.6 Hz), 1.62 (d, 1H, J=13.0 Hz), 1.67 (dd, 1H, J_1=12.1, J_2=7.5 Hz), 1.78 (d, 1H, J=13.8 Hz), 2.04-2.24 (m, 2H), 2.45-2.55 (m, 1H), 2.65 (s, 1H), 4.13 (q, 2H, J=7.2 Hz), 4.87 (s, 1H), 5.06 (s, 1H), 5.28 (dd, 1H, J_1=10.5, J_2=1.8 Hz), 5.32 (dd, 1H, J_1=17.5, J_2=1.8 Hz), 5.88 (dd, 1H, J_1=17.5, J_2=10.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.25 (CH_3), 29.36 (CH_3), 29.75

(CH_3), 38.42 (CH_2), 39.36(C), 39.37 (C), 42.96 (CH), 43.79 (CH_2), 45.22 (CH), 48.27 (CH_2), 53.44 (C), 60.62 (CH_2), 107.90 (CH_2), 120.18 (CH_2), 131.26 (CH), 151.50 (C), 171.25 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 262 (20, M+), 261 (100), 245 (20), 233 (10), 215 (60), 187 (95), 171 (20), 161 (15), 145 (20), 131 (35), 119 (25), 109 (25).

Anal. Calcd $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. **Found:** C, 78.43; H, 9.41.

195b-exo: R_f=0.39 (10% Et_2O, 90% hexane); b.p. 70°/0.05 mm Hg (Kugelrohr temp.); IR (neat) 3070, 1725, 1650, 1630 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.21-1.30 (m, 4H), 1.50 (d, 1H, J=13.5 Hz), 1.67 (dd, 1H, J_1=12.2, J_2=7.3 Hz), 1.83 (d, 1H, J=13.5 Hz), 1.96 (s, 1H), 1.97 -2.17 (m, 2H), 2.65-2.75 (m, 1H), 4.18 (q, 2H, J=7.1 Hz), 4.87 (br.s, 1H), 5.04 (d, 1H, J=17.1 Hz), 5.06 (br. s, 1H), 5.07 (d, 1H, J=10.6 Hz), 5.51 (dd, 1H, J_1=17.2, J_2=10.8 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.12 (CH_3), 29.69 (CH_3), 30.23 (CH_3), 37.02 (CH_2), 39.14 (C), 42.49 (C), 43.33 (double intensity, CH, CH_2), 45.57 (CH), 48.13 (CH_2), 51.33 (C), 60.58 (CH_2), 107.76 (CH_2), 113.84 (CH_2), 136.07 (CH), 150.23 (C), 169.62 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)) 262 (M^+, 10), 245 (5), 227 (10), 215 (14), 204 (10), 187 (100), 173 (10), 171 (13), 159 (10), 145 (10), 131 (25), 117 (14), 115 (12), 105 (12).

Anal. Calcd $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. **Found:** C, 77.83; H. 9.26.

(E)-(1α, 6α)-8,8-Dimethyl-2β-carbethoxy-2α-vinyl-4-methoxymethylenetricylo[4.3.0.0^{1,3}]nonane (202a) and Its (E)-2α, 2β-(202c), (Z)-2β, 2α-(202b), and (Z)-2α, 2β-(42b) Isomers.

Methoxymethyltriphenylphosphonium chloride (1.21 g, 3.53 mmol) was treated with potassium tert-amylate (2.35 mL, 3.53 mmol, 1.5 M in tert-amyl alcohol) in 10 mL of benzene with stirring at room temperature resulting in a deep orange-red mixture. The mixture was stirred for 30 min, then ketone **163** (185 mg, 0.706 mmol) was added in 5 mL of benzene via canula. TLC indicated substantial starting material was left after 1 h at room temperature, so the reaction was heated to 50°C for 30 min at which time TLC indicated complete consumption of starting material with the appearance of 4 less polar spots. The reaction mixture was worked up with NH_4Cl, extracted with ether, dried over $MgSO_4$, and concentrated to give 960 mg of crude material. Filtration through a short column of flash silica (5 cm x 12 mm) with 10% EtOAc in hexane gave 78 mg (42%) of **202** as a mixture of four diastereomers. The reaction was repeated on a pure sample **163a-endo** to give a mixture of **202a-endo**-E and **202b-endo-Z**; similarly, **202c-exo**-E and **202d-exo-Z** were obtained from **163b-exo**. The clean enol ethers proved to be unstable and decomposed completely within three to four days in $CDCl_3$ at -10°C. **202a-endo-E:** R_f=0.68 (15% EtOAc in hexane); **^{1}H-NMR** ($CDCl_3$) δ 1.01 (s, 3H), 1.07 (s, 3H), 1.25 (t, 3H, J=7.1 Hz), 1.23-1.34 (m, 1H), 1.62 (d, 1H, J=14.0 Hz), 1.69 (ddd, 1H, J_1=12.7, J_2=8.3, J_3=0.8 Hz), 1.78 (d, 1H, J=13.8 Hz), 1.99 (ddd, 1H, J_1=17.5, J_2=8.6, J_3=2.5 Hz), 2.23 (dt, 1H, J_1=17.6, J_2=2.4 Hz), 2.47-2.58 (m, 1H), 2.58 (s, 3H), 4.12 (dq, 2H,

J_1=7.1, J_2=1.1 Hz), 5.28 (dd, 1H, J_1=10.7, J_2=2.0 Hz), 5.31 (dd, 1H, J_1=17.6, J_2=2.0 Hz), 5.81 (dd, 1H, J_1=17.6, J_2=10.4 Hz), 6.07 (t, 1H, J=2.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.35 (CH_3), 29.35 (CH_3), 29.71 (CH_3), 33.90 (CH_2), 39.79 (C), 42.31 (CH), 43.32 (CH), 44.21 (CH_2), 48.73 (CH_2), 52.37 (C), 59.56 (CH_3), 60.61 (CH_2), 120.23 (CH_2), 120.55 (C), 131.56 (CH), 141.41 (CH), 171.54 (C).

202b-endo-Z: R_f=0.51 (15% EtOAc in hexane); not isolated in pure form. NMR data was obtained from a crude mixture. **^{1}H-NMR** ($CDCl_3$) δ 1.01 (s, 3H), 1.07 (s, 3H), 1.25 (t, 3H, J=7.1 Hz), 1.25-1.34 (m, 1H), 1.62 (d, 1H, J=14.0 Hz), 1.62-1.73 (m, 1H), 1.81 (d, 1H, J=14.0 Hz), 2.02-2.06 (m, 1H), 2.42-2.53 (m, 1H), 2.87 (s, 1H), 2.99 (s, 3H), 4.12 (q, 2H, J=7.1 Hz), 5.27 (dd, 1H, J_1=17.4, J_2=2.0 Hz), 5.28 (dd, 1H, J_1=10.5, J_2=2.0 Hz), 5.85 (dd, 1H, J_1=17.6, J_2=10.5 Hz), 5.96 (br. s, 1H).

202c-exo-Z: R_f=0.39 (15% EtOAc in hexane); **^{1}H-NMR** ($CDCl_3$) δ 1.05 (s, 3H), 1.07 (s, 3H), 1.18-1.24 (m, 1H), 1.27 (t, 3H, J=7.1 Hz), 1.49 (d, 1H, J=13.4 Hz), 1.63 (dd, 1H, J_1=11.9, J_2=7.3 Hz), 1.82 (d, 1H, J=13.5 Hz), 1.92 (ddd, 1H, J_1=16.6, J_2=7.7, J_3=2.1 Hz), 2.11 (dt, 1H, J_1=16.4, J_2=1.5 Hz), 2.21 (s, 1H), 2.62-2.72 (m, 1H), 3.58 (s, 3H), 4.17 (q, 2H, J=7.1 Hz), 5.04 (d, 1H, J=17.5 Hz), 5.05 (d, 1H, J=10.2 Hz), 5.55 (dd, 1H, J_1=17.6, J_2=10.3 Hz), 5.95-5.98 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 14.17 (CH_3), 29.76 (CH_3), 30.25 (CH_3), 33.04 (CH_2), 39.22 (C), 40.42 (CH), 42.92 (CH), 43.64 (CH_2), 48.12 (CH_2), 50.44 (C), 59.53 (CH_3), 60.48 (CH_2), 113.77 (CH_2), 119.13 (C), 136. 40 (CH), 141.38 (CH).

202d-exo-E: R_f=0.36 (15% EtOAc in hexane); **^{1}H-NMR** ($CDCl_3$) δ 1.06 (s, 3H), 1.07 (s, 3H), 1.21-1.29 (m, 1H), 1.27 (t, 3H, J=7.2 Hz), 1.50 (d,

1H, J=13.4 Hz), 1.70 (dd, 1H, J_1=12.2, J_2=7.4 Hz), 1.80-1.93 (m, 3H), 2.32 (dt, 1H, J_1=17.7, J_2=1.9 Hz), 2.71-2.81 (m, 1H), 3.57 (s, 3H), 4.18 (dq, 2H, J_1=7.1, J_2=0.7 Hz), 5.01 (d, 1H, J=17.7 Hz), 5.04 (d, 1H, J=10.7 Hz), 5.50 (dd, 1H, J_1=17.2, J_2=10.8 Hz), 6.10 (t, 1H, J=2.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.23 (CH_3), 29.58 (CH_3), 30.12 (CH_3), 32.36 (CH_2), 39.52 (C), 42.38 (CH), 43.63 (CH), 43.80 (CH_2), 48.83 (CH_2), 49.99 (C), 59.50 (CH_3), 60.54 (CH_2), 113.48 (CH_2), 119.63 (C), 136. 39 (CH), 141.38 (CH).

(5β,8α)-2α,2β-Dimethyl-6-methylene-9α-hydroxymethyltricyclo[6.3.0.0^{4,8}]undecane (211a) and Its 9β- epimer (211b).

Lithium aluminum hydride (14 mg, 0.37 mmol) was added to a dry solution of esters **146ab** (16 mg, 0.063 mmol) in 10 mL of dry THF and the mixture was stirred for 20 min after which time the reaction was quenched with 1 mL of water. The mixture was then extracted 3x with 5 mL of ether, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 11 mg (79%) of crude alcohols **211ab** as a mixture of epimers whose ratio was the same as that of the starting ester: R_f=0.42 (ether-hexane, 3:1); **IR** (neat) 3310 br., 3060, 1650, 875 cm^{-1}; **Mass Spectrum** (70 eV, m/e (rel. int.)) 220 (M^+, 15), 205 (12), 187 (28), 173 (5), 161 (24), 146 (28), 131 (100), 119 (22), 105 (32), 91 (42).

Cacld for $C_{15}H_{24}O$: 220.1827. **Found**: 220.1826.

Major isomer (211b): ^{1}**H-NMR** ($CDCl_3$) δ 1.00 (s, 3H), 1.02 (s, 3H), 1.20-2.80 (m, 13H), 3.58 (t, 1H, J=9.3 Hz) 3.76-3.85 (m, 1H), 4.84 (m, 2H); ^{13}**C-NMR** ($CDCl_3$) δ 30.42 (CH_3), 30.87 (CH_3), 33.7 (CH_2), 38.8 (C), 40.64 (CH_2), 43.65 (CH), 49.05 (CH_2), 57.47 (CH_2), 58.97 (CH), 64.08 (CH_2), 87.59 (CH_2), 159.03 (C).

Minor isomer (211a): ^{1}**H-NMR** ($CDCl_3$) δ 0.98 (s, 3H), 1.02 (s, 3H), 1.20-2.80 (m, 13H), 3.47 (t, 1H, J=9.3 Hz), 3.76-3.85 (m, 1H), 4.76 (m, 2H); ^{13}**C-NMR** ($CDCl_3$) δ 26.24 (CH_3), 29.34 (CH_3), 31.4 (CH_2), 58.27 (CH), 64.11 (CH_2), 87.00 (CH_2), 157.73 (C).

(5β,8α)-2α,2β,6-Trimethyl-9α-carbethoxytricyclo[6.3.0.$0^{4,8}$]undec-6-ene (212a) and Its 9β-epimer (212b).

Esters **146ab**, (5.4 mg, 0.021 mmol) were dissolved in 1.5 mL of CH_2Cl_2 with stirring with a catalytic amount of p-TsOH. The mixture was stirred at room temperature for 24 h at which time the reaction was quenched with 2 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous solution was extracted 2x with 10 mL of hexane. The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to give 5.3 mg (98%) of **212ab** as an 8:1 mixture of epimers that were inseparable on silica gel: R_f=0.63 (1:10, ether-hexane); **IR** (neat) 1725 cm^{-1}.

Major isomer: ^{1}H-NMR ($CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 4H), 1.25-1.33 (m, 3H), 1.47 (dd, 1H, J_1=12.7, J_2=9.6 Hz), 1.52-1.81 (m, 8H), 2.18 (d, 1H, J=13.0 Hz), 2.53-2.58 (m, 1H), 2.69-2.81 (m, 2H), 4.04-4.24 (m, 2H), 5.20 (br.s, 1H); **^{13}C-NMR** ($CDCl_3$) δ 14.41 (CH_3), 27.25 (CH_2), 28.17 (CH_2), 28.33 (CH_3), 31.39 (CH_3), 40.19 (C), 45.60 (CH_2), 54.19 (CH), 54.71 (CH_2), 55.52 (CH), 56.68 (C), 59.81 (CH_2), 63.72 (CH), 131.47 (CH), 139.35 (C), 174.28 (C).

Minor isomer: **^{1}H-NMR** ($CDCl_3$) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.21-2.95 (m, 17H), 4.04-4.24 (m, 2H), 5.20 (br.s, 1H); **^{13}C-NMR** ($CDCl_3$) δ 15.03 (CH_3), 28.82 (CH_2), 28.94 (CH_3), 29.66 (CH_2), 29.79 (CH_2), 30.36 (CH_3), 51.14 (CH_2), 59.18 (CH_2), 63.05 (CH), 129.05 (CH).

(5β,8α)-2α,2β-Dimethyl-6-methylene-9α-zoluenesulfonylmethyltricyclo[6.3.0.$0^{4,8}$]undecane (214a) and Its 9β-epimer (214b).

Alcohols **211ab** (54 mg, 0.243 mmol) and p-toluenesulfonyl chloride (117 mg, 0.616 mmol) were dissolved in 1.5 mL of pyridine and stored at -5°C for 24 h after which time the solution was partitioned between 10 mL of hexane and 10 mL of 1M HCl. The organic layer was separated, and the aqueous layer was extracted 2x with 10 mL of hexane. The combined hexane solution was then dried over Na_2SO_4, filtered, and evaporated in vacuo to give 74.7 mg (78%) of crude material, which was filtered through silica gel with 10% Et_2O in hexane. ^{1}H-NMR indicated that the material was a 3:1 mixture of **214ab** which was clean enough for the next reaction: R_f=0.72 (1:10, ether-hexane); **IR** (neat) 3060, 1650, 1660, 1595, 945, 825, 810, 720 cm^{-1}.

major isomer: **^{1}H-NMR** ($CDCl_3$) : δ 0.93 (s, 3H), 0.99 (s, 3H), 1.03-2.35 (m, 12H), 2.45 (s, 3H), 2.58 (br.d, 1H, J=7.4 Hz), 3.99 (dd, 1H, J_1=9.5, J_2=7.9 Hz), 4.10-4.18 (m, 1H), 4.81 (br.d, 2H, J=8.7 Hz), 7.35 (d, 2H, J=8.2 Hz), 7.80 (d, 2H, J=8.2 Hz).

minor isomer: **^{1}H-NMR** ($CDCl_3$) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.03-2.35 (m, 12H), 2.45 (s, 3H), 2.58 (d, 1H, J=7.4 Hz), 3.88 (t, 1H, J=9.1 Hz), 4.10-4.18 (m, 1H), 4.75 (br.s, 2H), 7.35 (d, 2H, J=8.2 Hz), 7.80 (d, 2H, J=8.2 Hz).

(5β,8α)-2α,2β,9α-Trimethyl-6-methylenetricyclo[6.3.0.$0^{4,8}$]undecane (217a) and Its 9α-epimer (217b).

Bromides **217ab** (5.2 mg, 0.018 mmol) were dissolved in 2 mL of THF and this solution was brought to reflux. Lithium aluminum hydride (6.8 mg, 0.18 mmol) was then added and the solution was refluxed for 15 min after which time it was cooled and slowly quenched with 5 mL of water. The aqueous solution was extracted 3x with 10 mL of hexane, and the combined organic solution was dried over Na_2SO_4, filtered through a plug of silica gel, and evaporated to give 2.8 mg (75%) of clean hydrocarbons **215ab** as a 3:1 mixture of epimers in favor of the unnatural diastereomer: R_f=0.80 (hexane).

Unnatural epimer 215b: ^{1}**H-NMR** ($CDCl_3$) δ 0.88-1.60 (m, 22H), 4.75 (br.s, 2H); ^{13}**C-NMR** ($CDCl_3$) δ 14.81 (CH_3), 29.68 (CH_2), 30.46 (CH_3, double intensity), 34.18 (CH_2), 35.44 (C), 39.65 (C), 40.84 (CH_2), 43.32 (CH), 45.03 (CH), 49.34 (CH_2), 56.85 (CH_2), 59.34 (CH), 105.36 (CH_2).

Natural epimer 215a: ^{1}**H-NMR** ($CDCl_3$) δ 0.88-1.60 (m, 22H), 4.80 (br.s, 2H); ^{13}**C-NMR** ($CDCl_3$) δ 14.05 (CH_3), 28.80 (CH_3), 31.23 (CH_2), 35.14 (CH_2), 38.51 (CH_2), 45.03 (CH), 44.61 (CH_2), 48.33 (CH), 58.33 (CH), 105.36 (CH_2).

(5β,8α)-2α,2β-Dimethyl-9α-bromomethyl-6-methylenetricyclo[6.3.0.0.^{4,8}]undecane (217a) and Its 9β-epimer (217b).

LiBr (59 mg, 0.68 mmol) was dissolved in 1.0 mL of dry acetone. The tosylates **214ab** (16.7 mg, 0.045 mmol) were then added at room temperature in 0.5 mL of dry acetone, and the solution was brought to reflux for 15 h after which time the solvent was removed in vacuo. The residue was partitioned between 10 mL of water and 10 mL of hexane. After separation of the organic layer, the aqueous layer was extracted 2x with 10 mL of hexane. The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to give 15.8 mg of crude material which was filtered through a plug of silica with ether-hexane (1:20) to give 8.4 mg (69%) of clean bromides **217ab** as a 3:1 mixture of epimers: R_f=0.68 (ether-hexane, 1:20), **IR** (neat) 3060, 880 cm^{-1}.

major isomer 217b: ^{1}**H-NMR** ($CDCl_3$) δ 1.01 (s, 3H), 1.03 (s, 3H), 1.04-2.70 (m, 13H), 3.32 (t, 1H, J=9.9 Hz), 3.58-3.63 (m, 1H), 4.83-4.87 (m, 1H).

minor isomer 217a: ^{1}**H-NMR** ($CDCl_3$): δ 0.98 (s, 3H), 1.03 (s, 3H), 1.04-2.70 (m, 13H), 3.25 (dd, 1H, J_1=15.5, J_2=9.9 Hz), 4.77-4.80 (m, 1H).

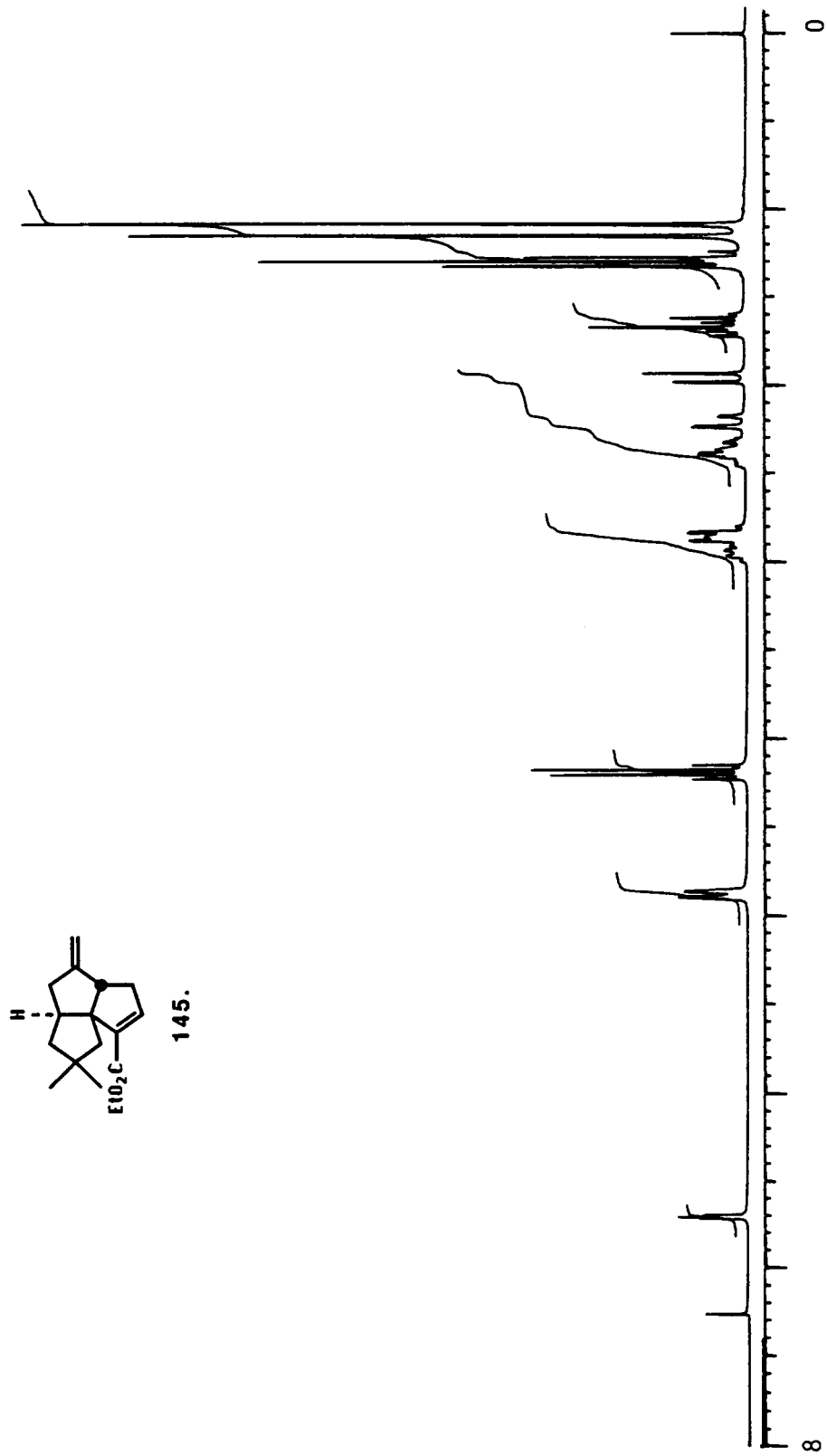
(±)-Pentalenene (1) and Epipentalenene (53).

p-Toluenesulfonic acid (5 mg, 0.0263 mmol) was added to hydrocarbon **215ab** (2 mg, 0.01 mmol) in 1 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 24 h after which time the reaction was quenched with 1 mL of 3N HCl. The mixture was extracted 3x with 5 mL of hexane. The combined layers were dried over Na_2SO_4, filtered through a plug of silica gel, and evaporated to give a near quantitative yield of (±)-pentalenene (**1**) and epipentalene (**53**) as a 1:3 mixture respectively. ^{1}H-NMR of the mixture contains peaks which match those in the spectra of each of the authentic compounds.

For **1**: ^{1}**H-NMR** ($CDCl_3$) δ 5.16 (br s, 1H), 2.7-2.6 (m, 1H).

For **53**: ^{1}**H-NMR** ($CDCl_3$) δ 5.18 (br s, 1H), 2.96-2.75 (m, 1H).

D. Spectra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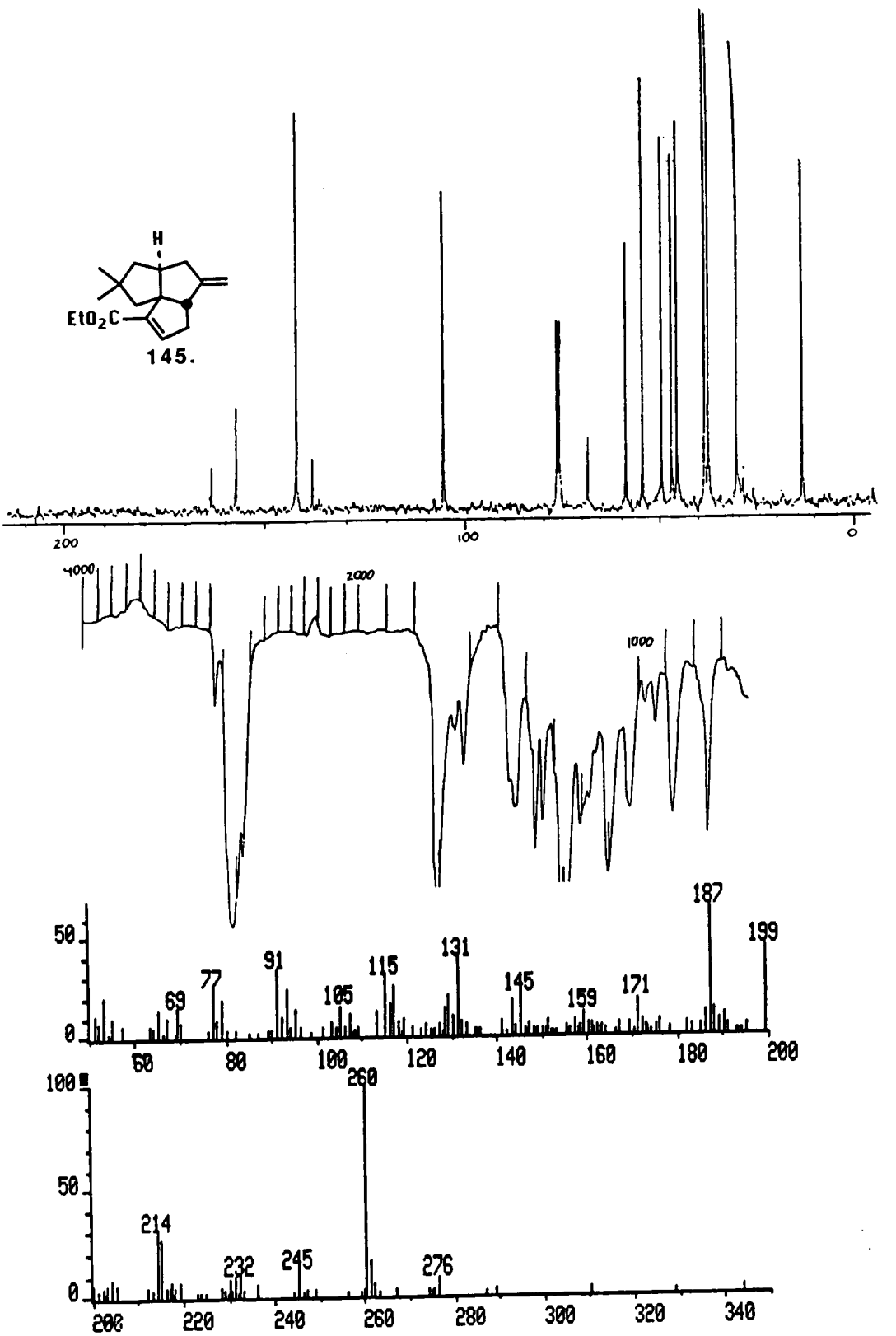
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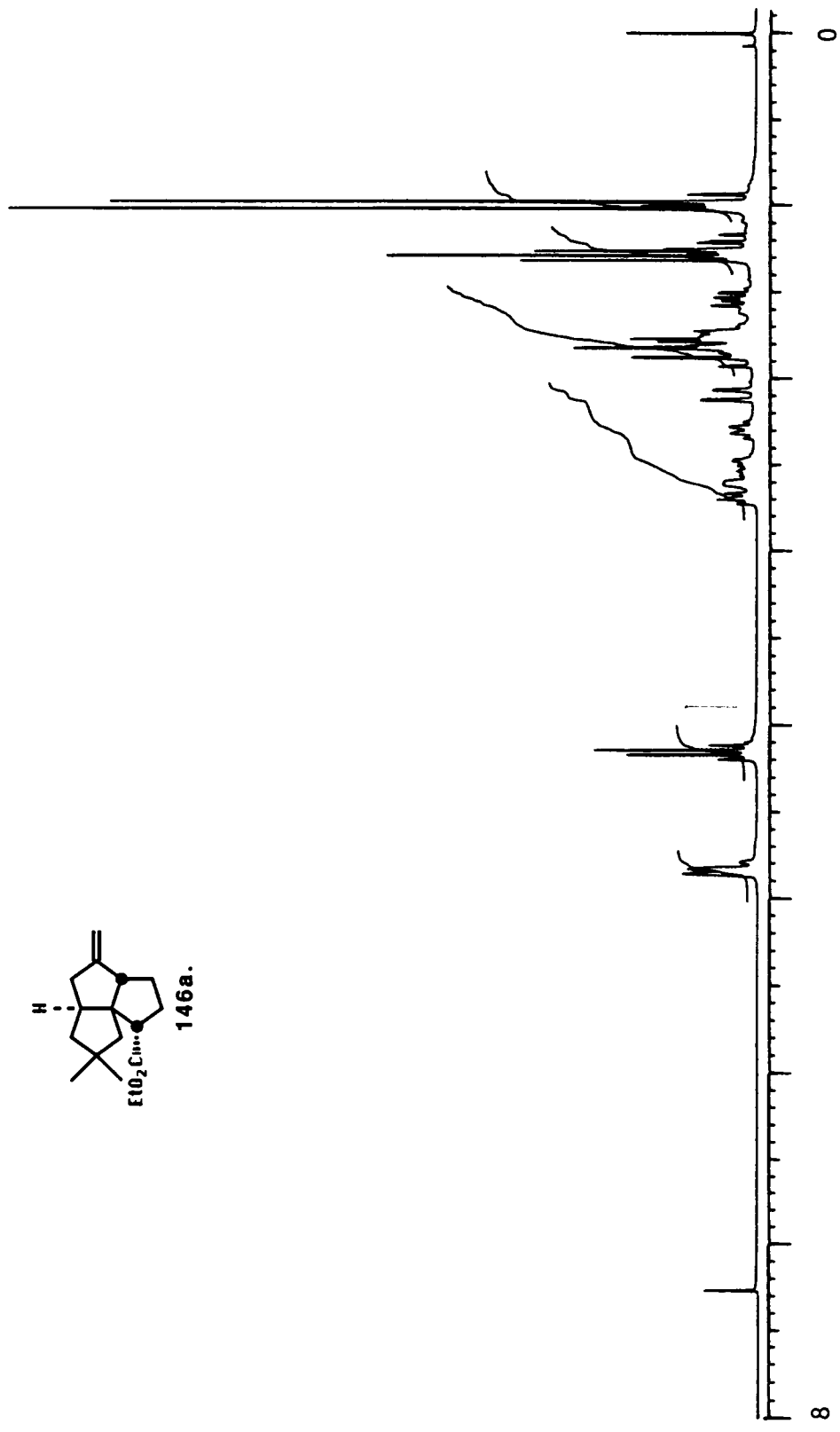

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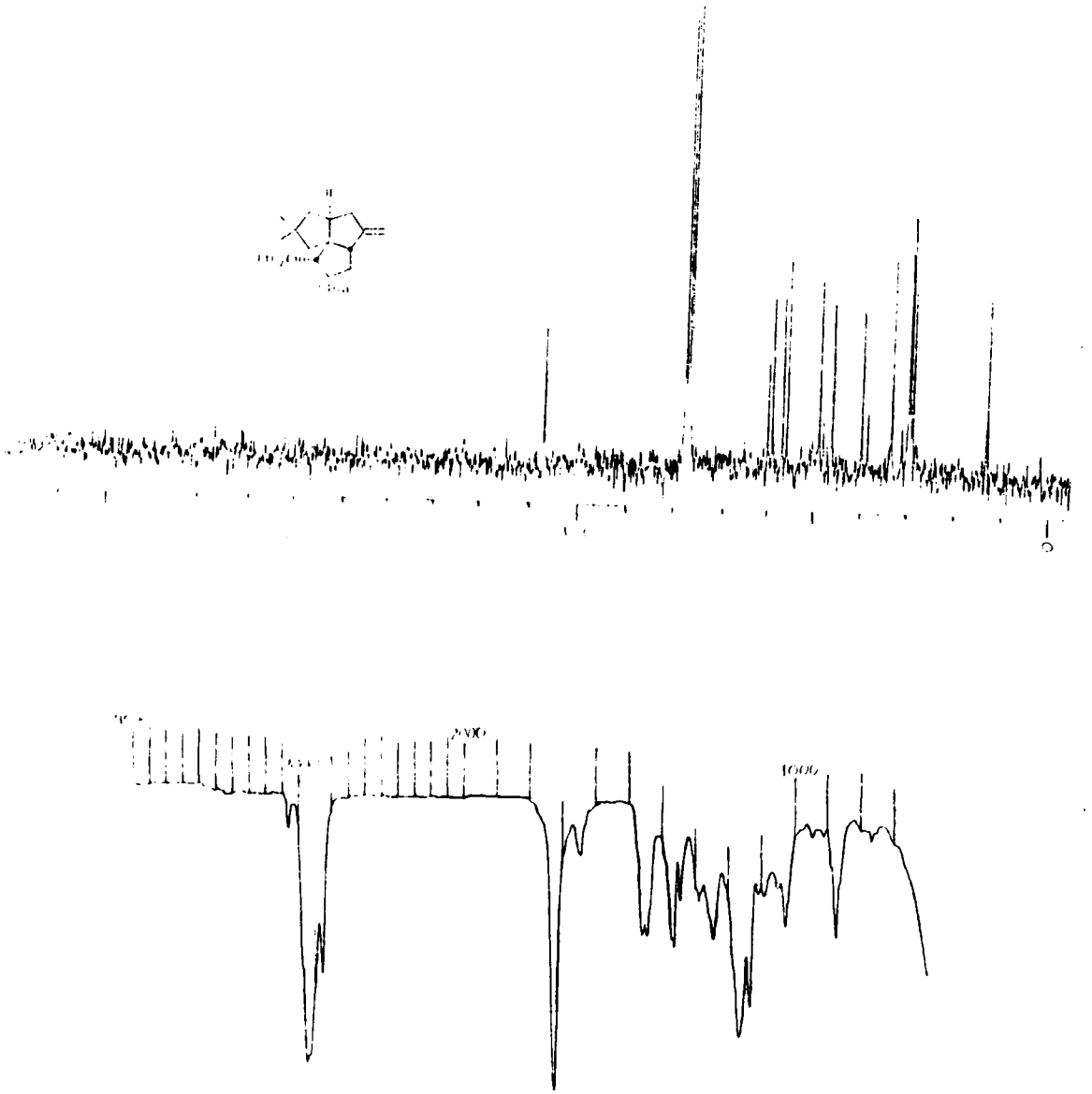

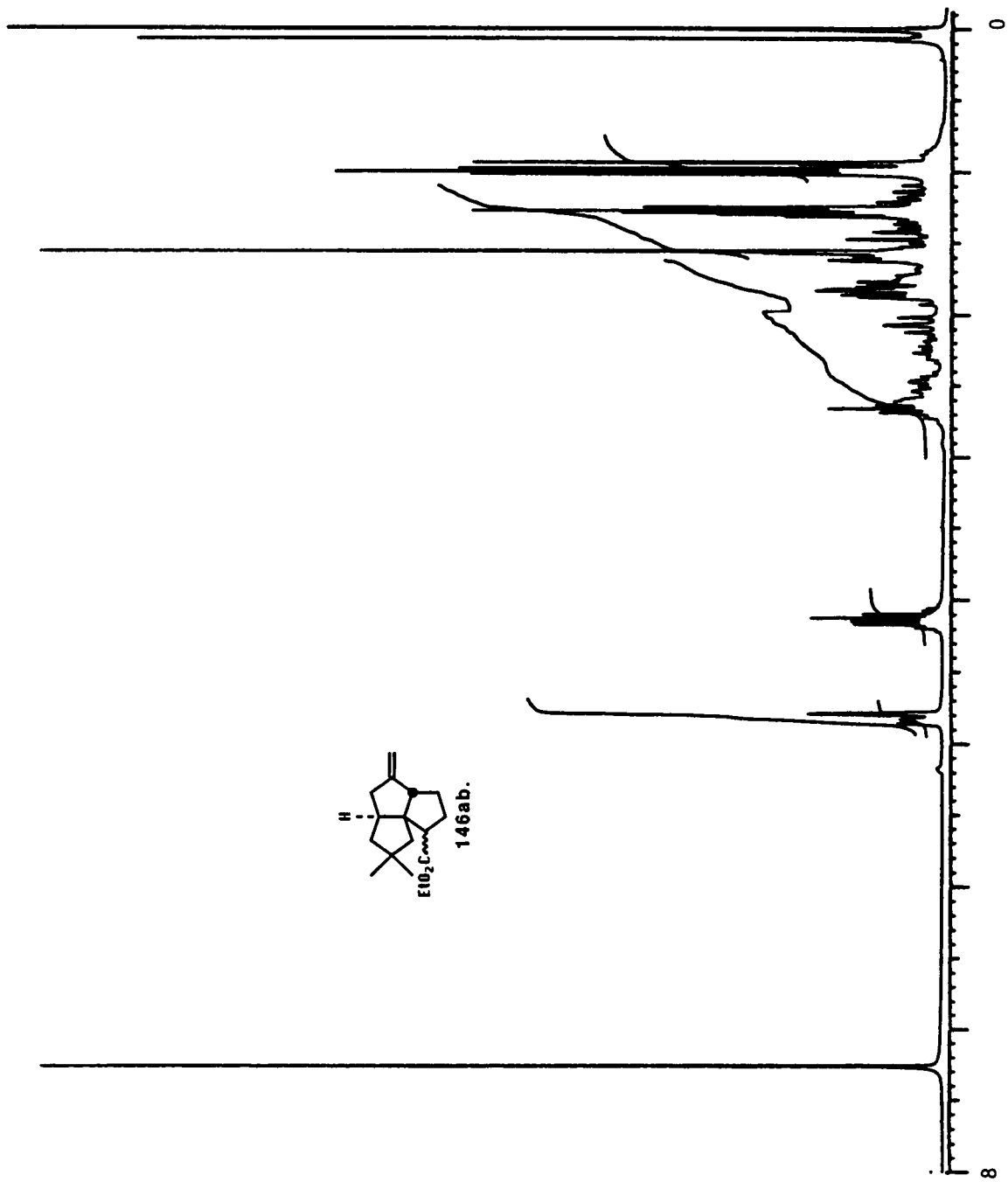
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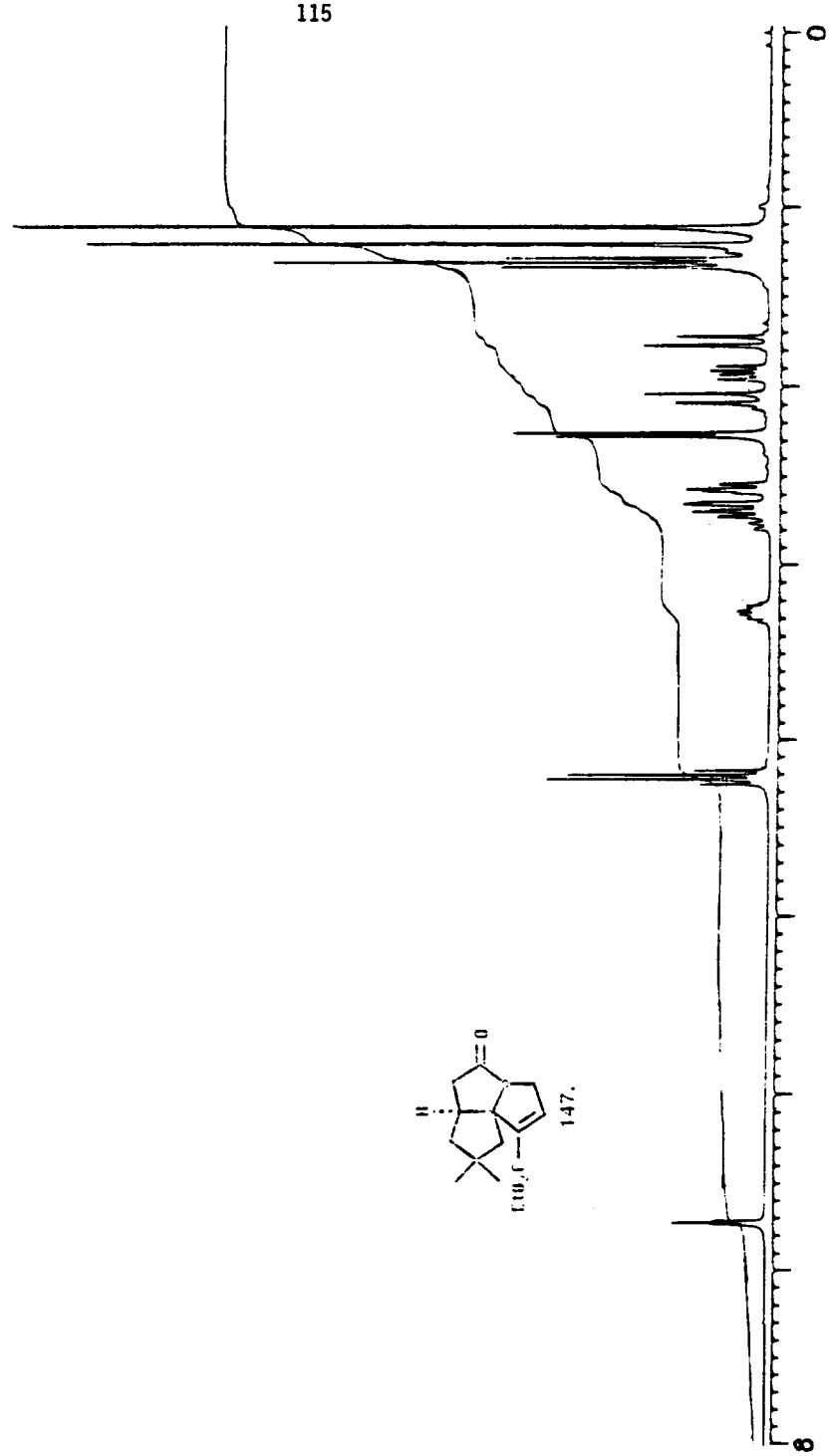
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H
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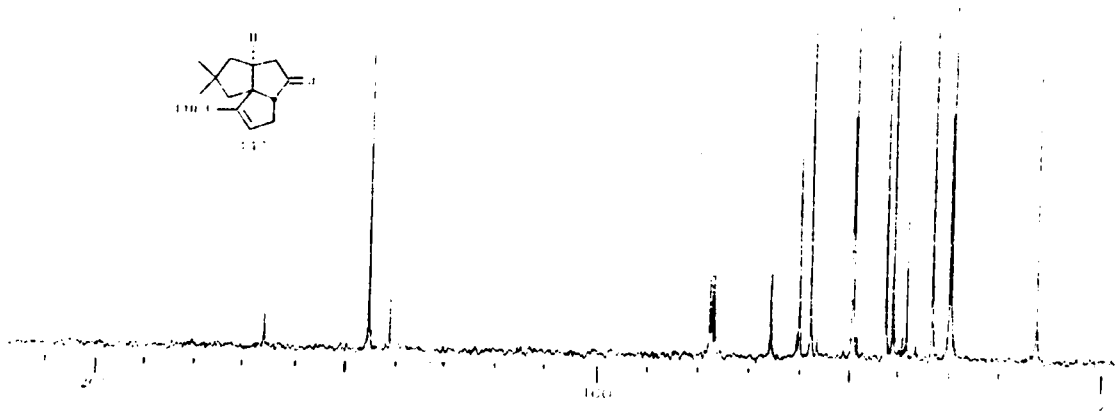

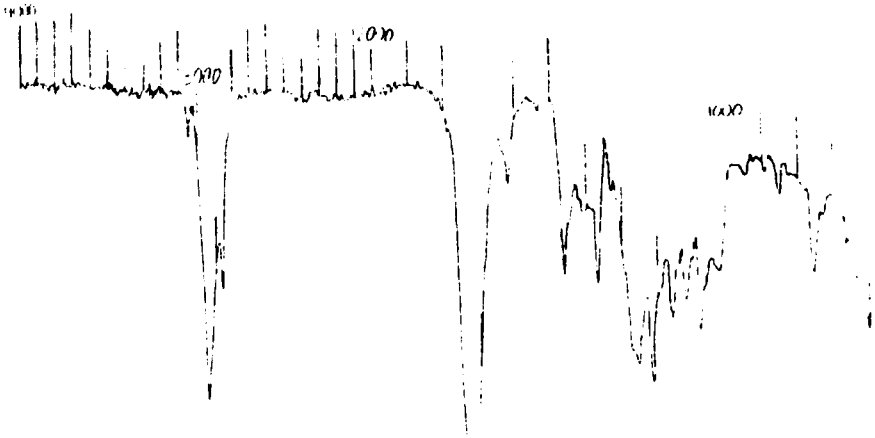

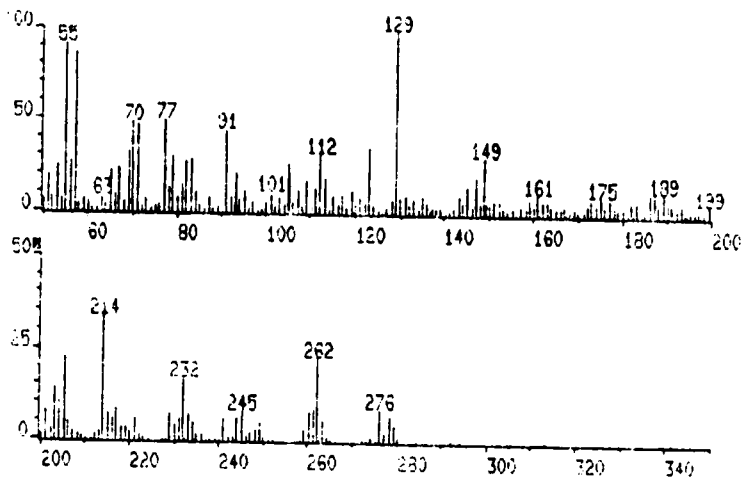
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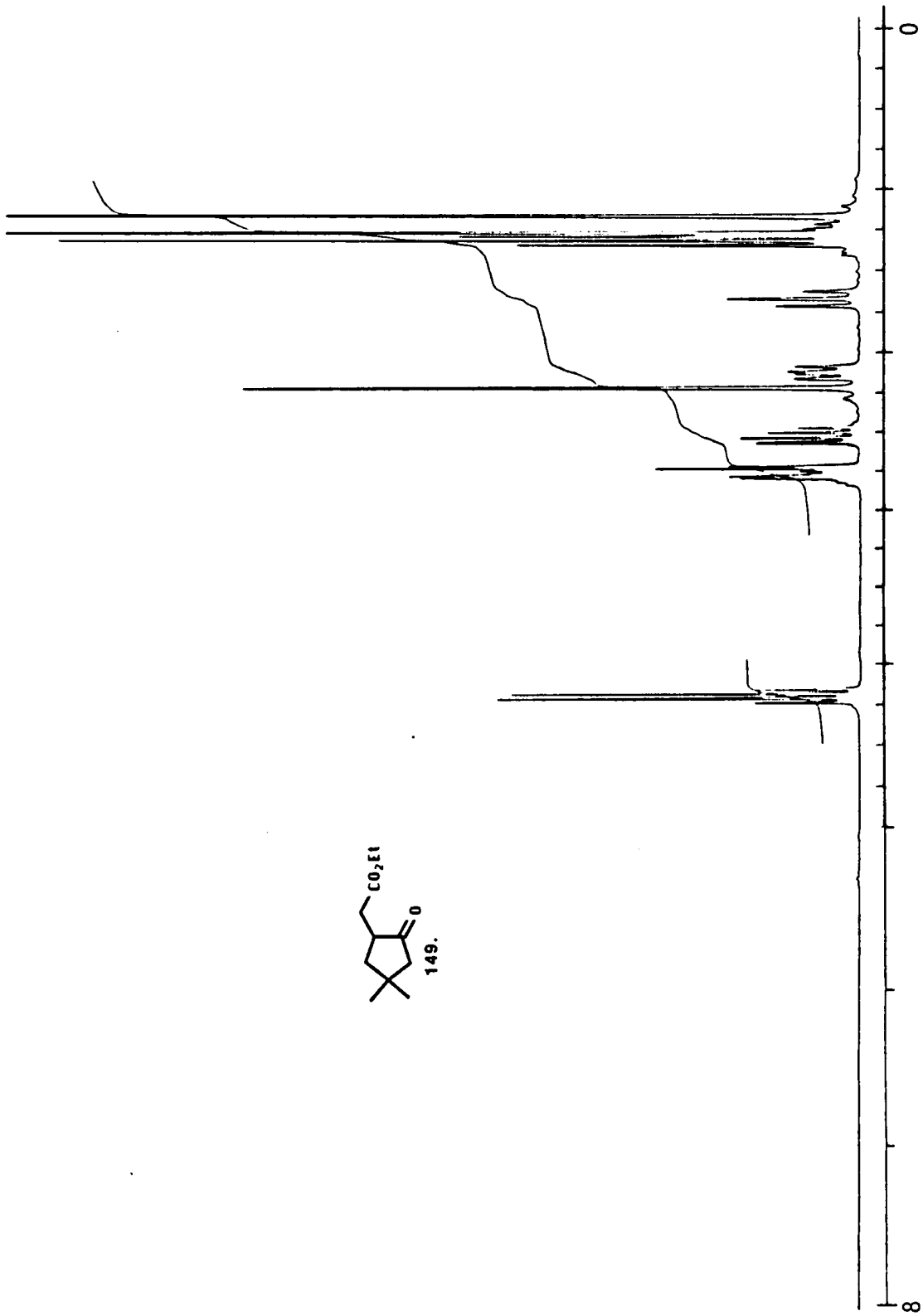

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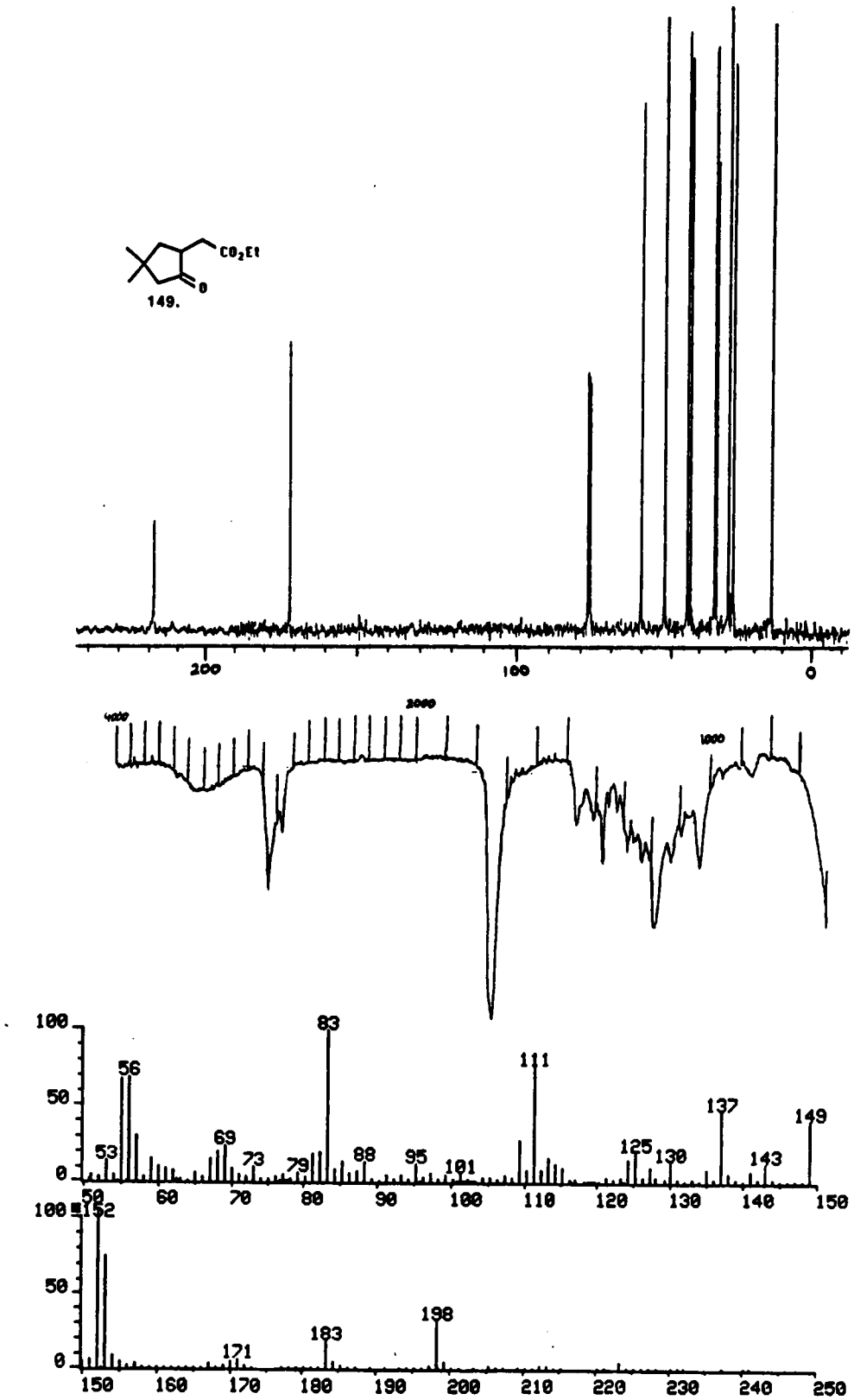
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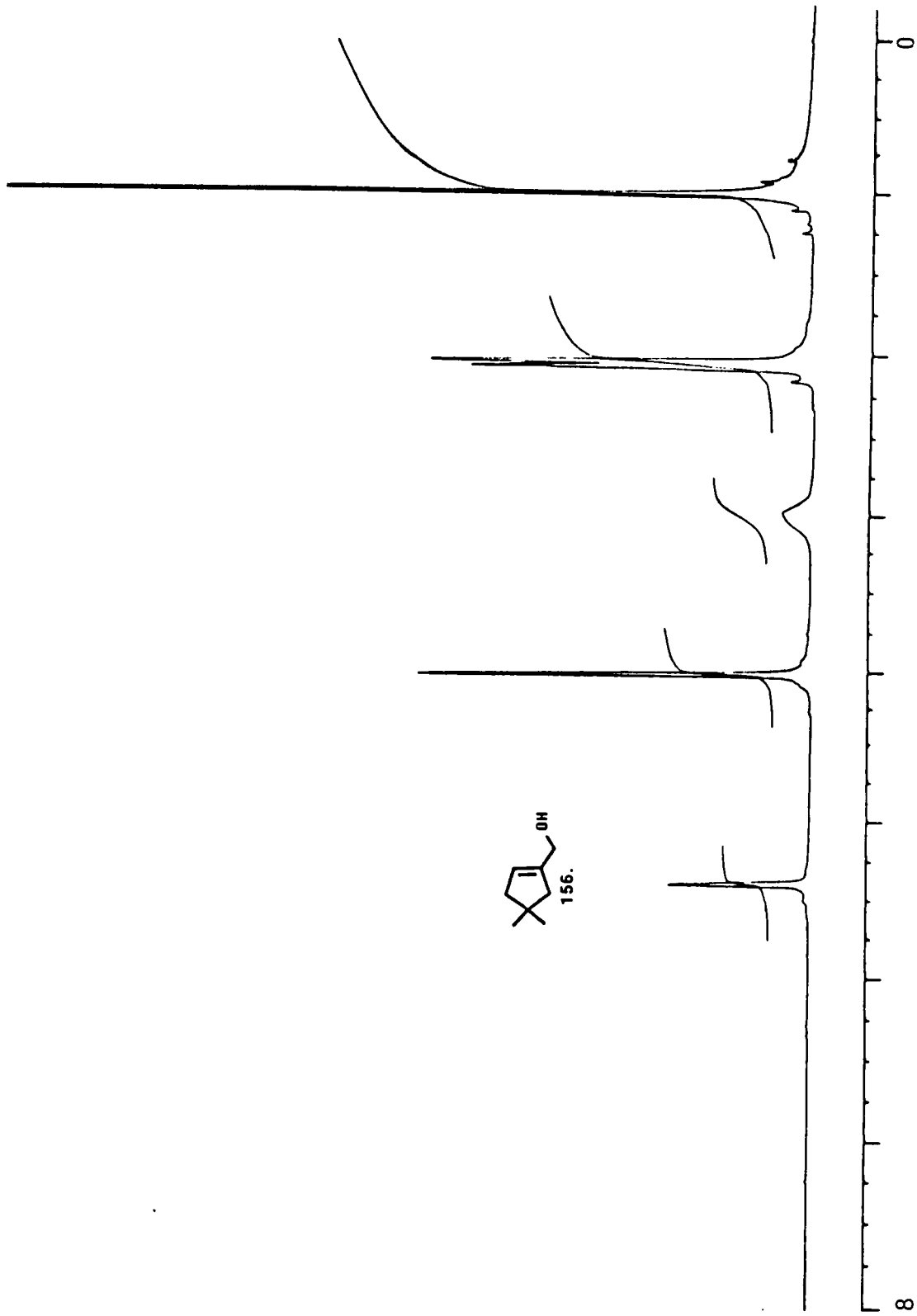
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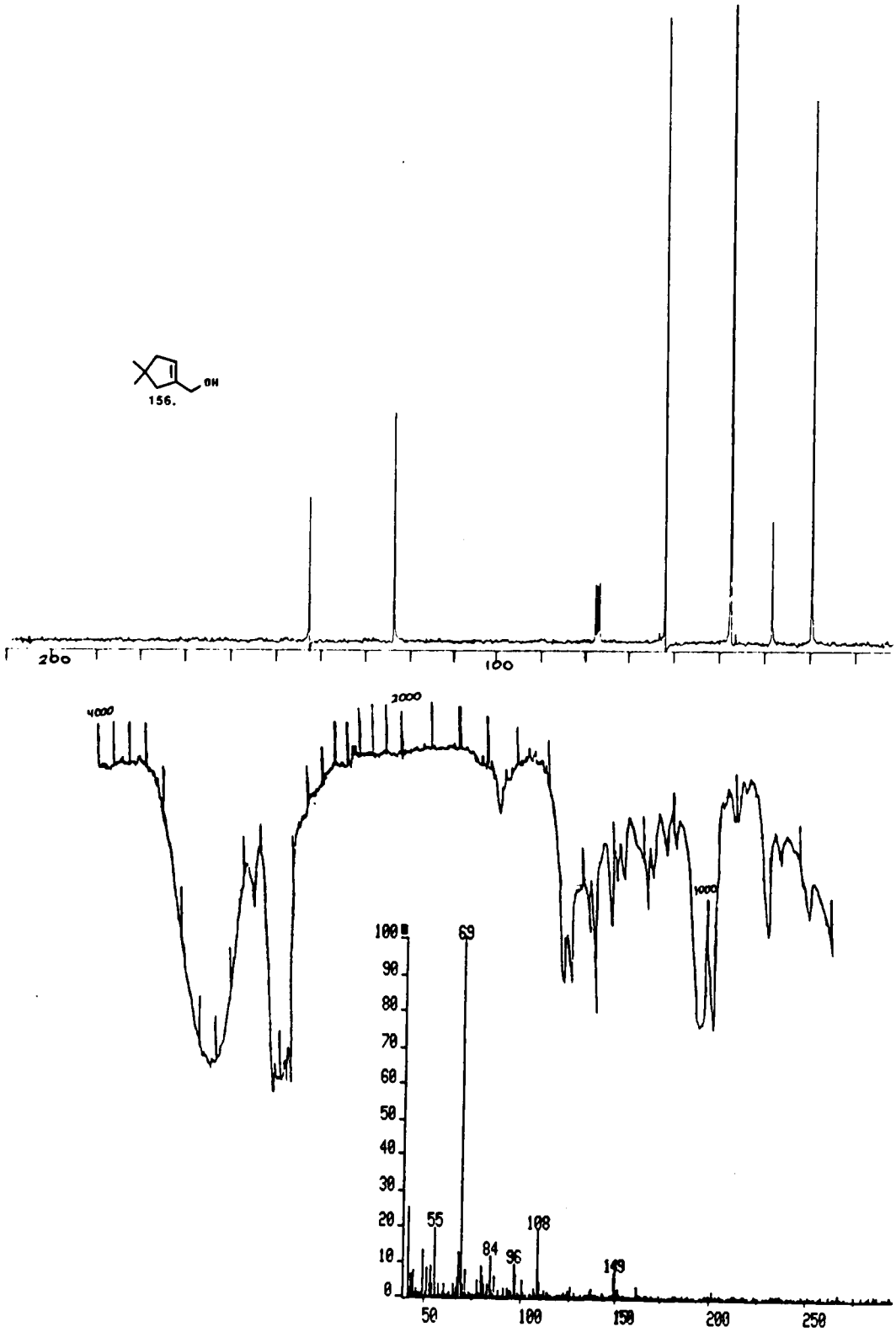
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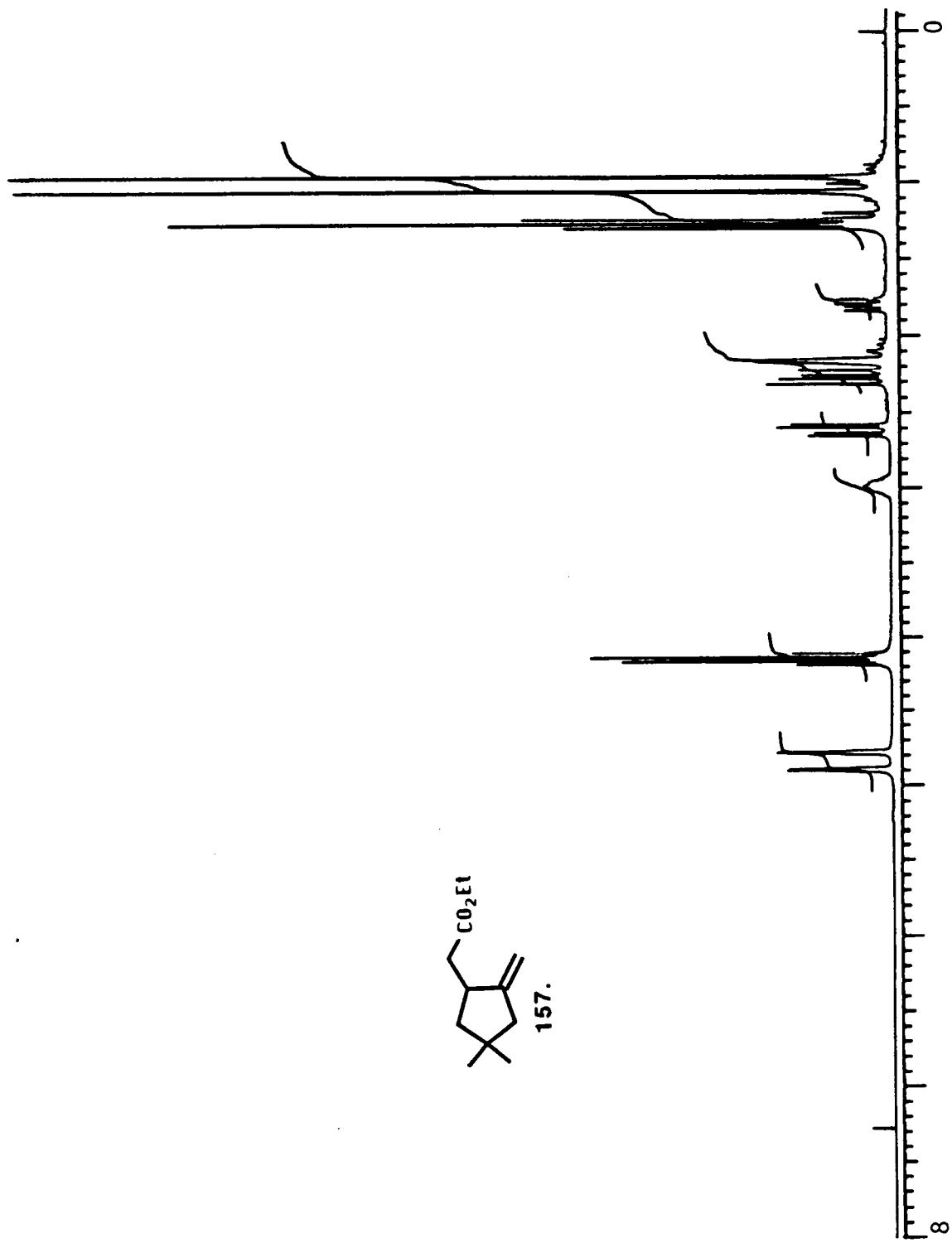

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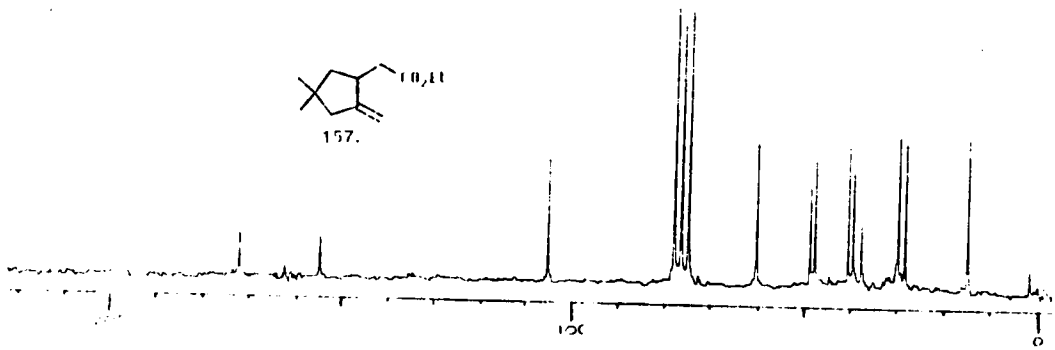
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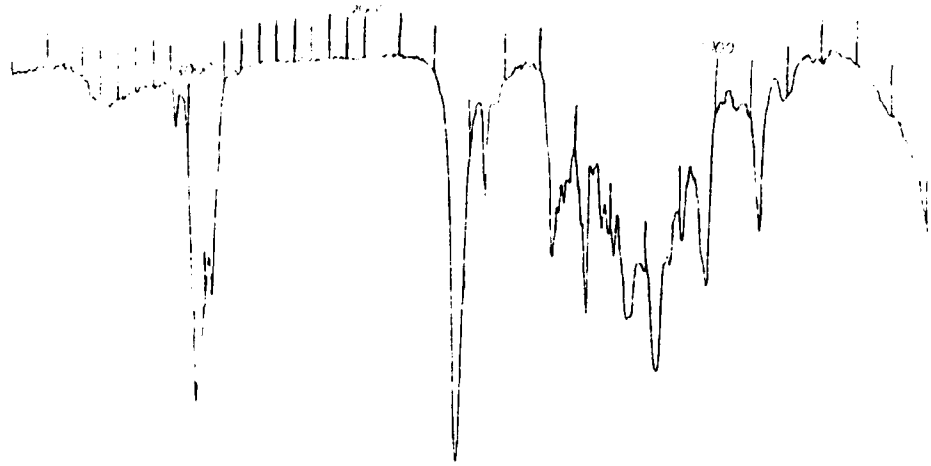

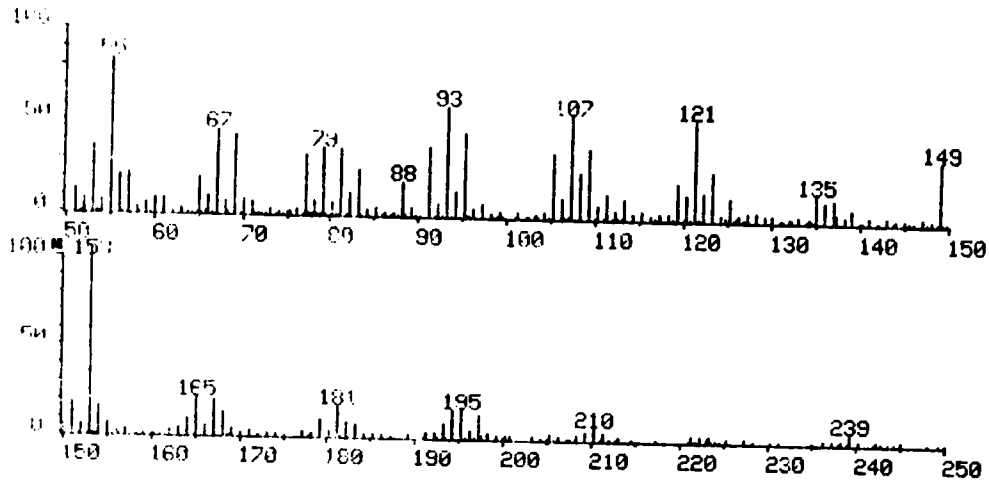
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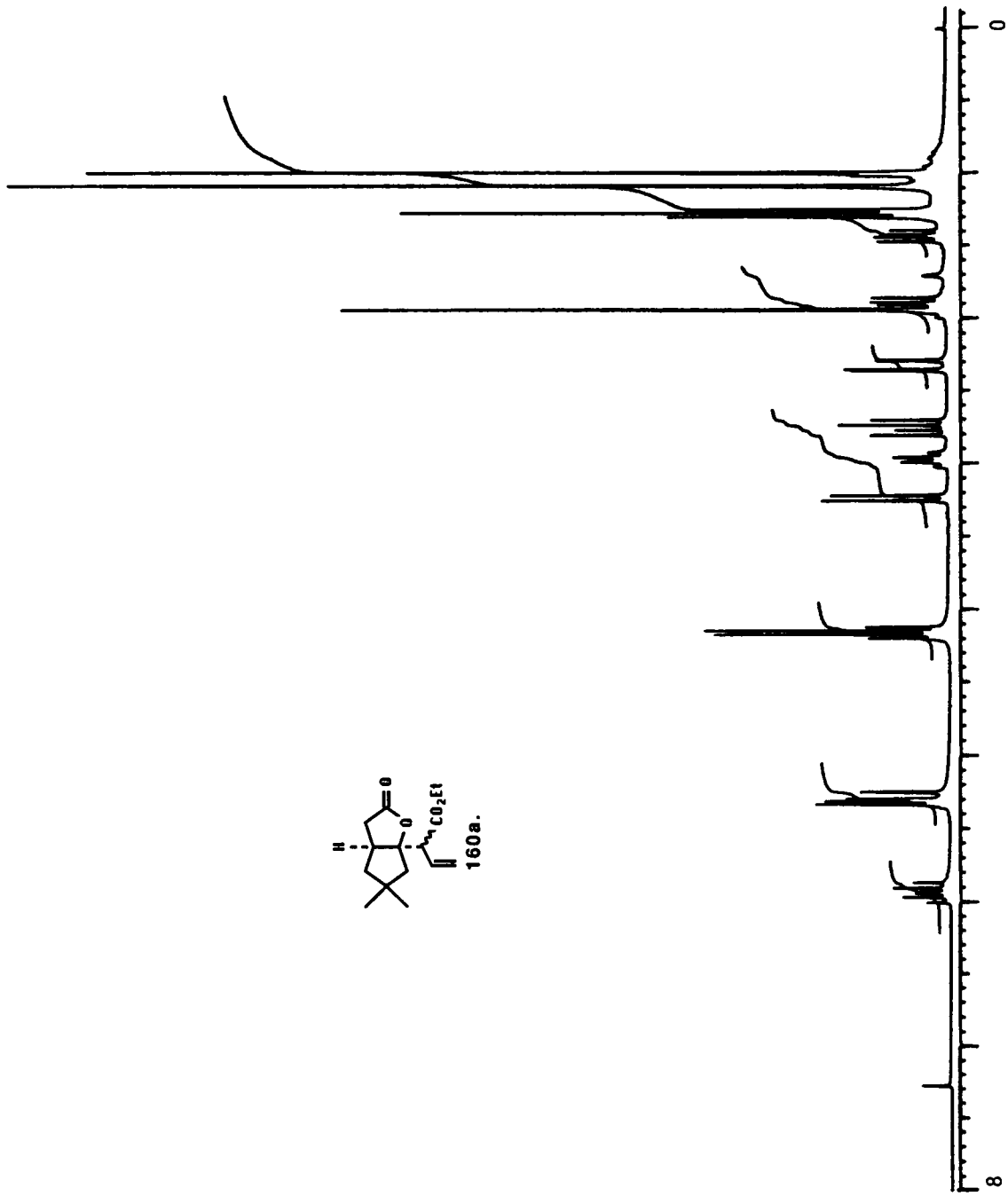
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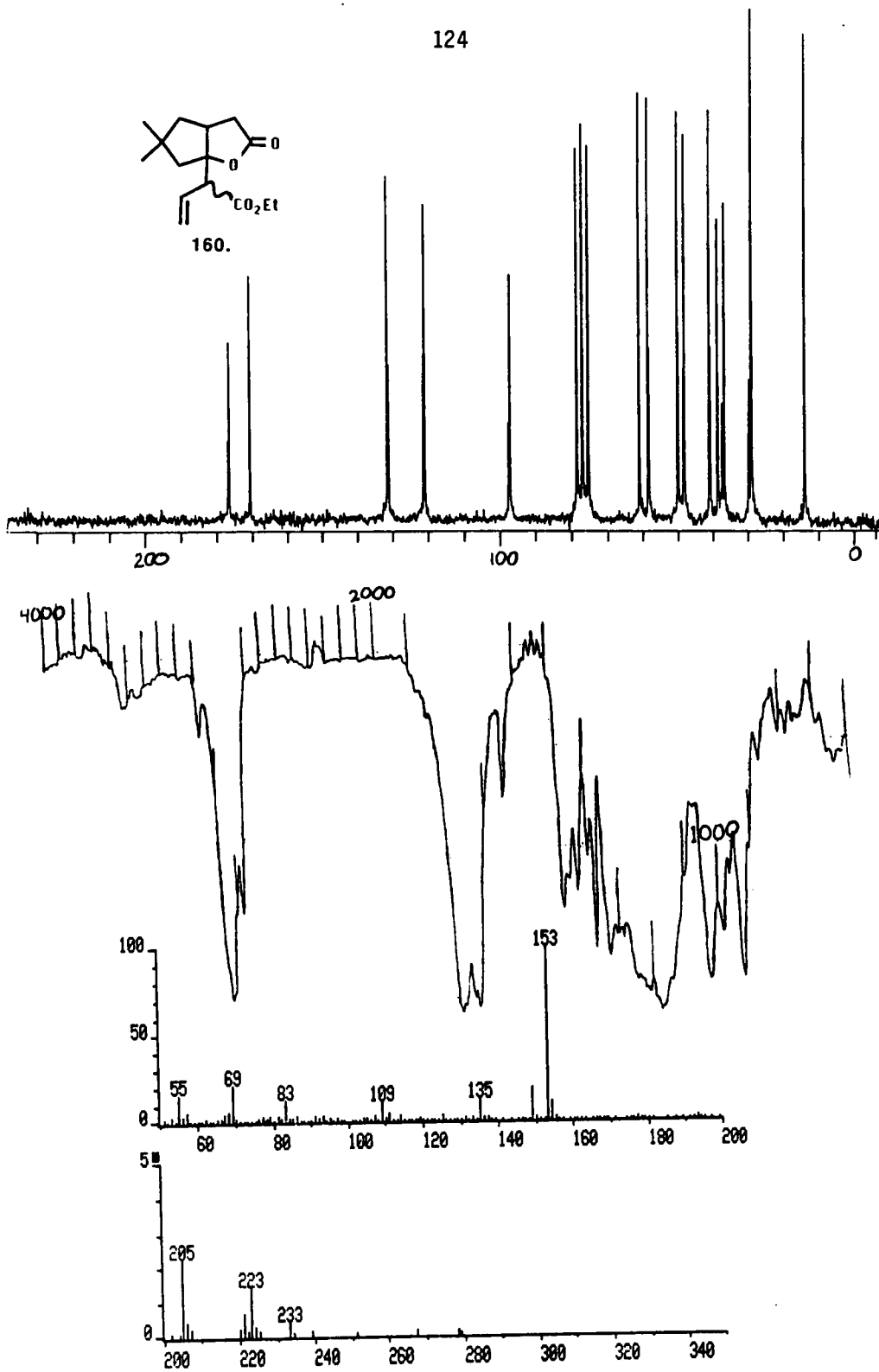
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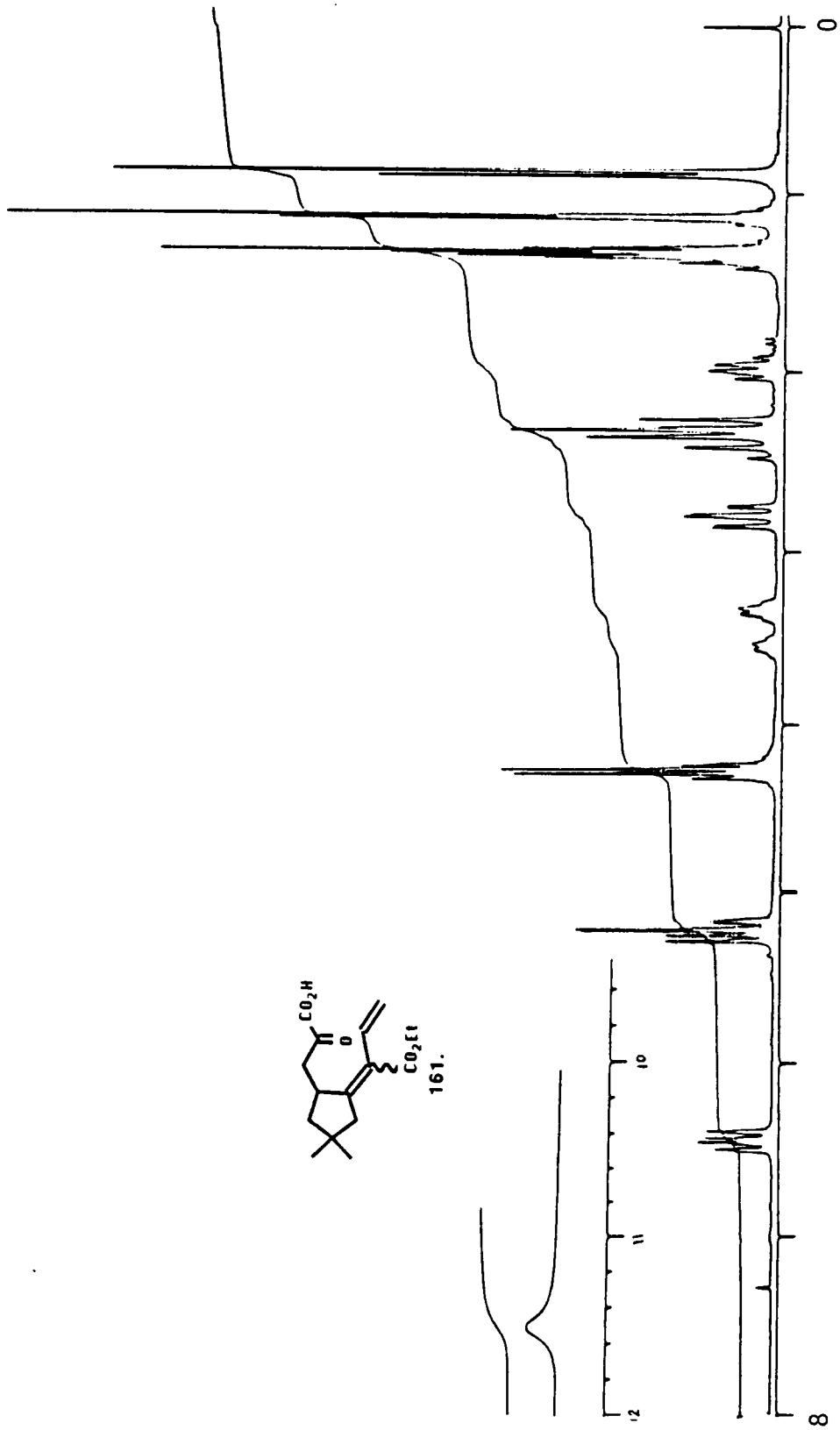
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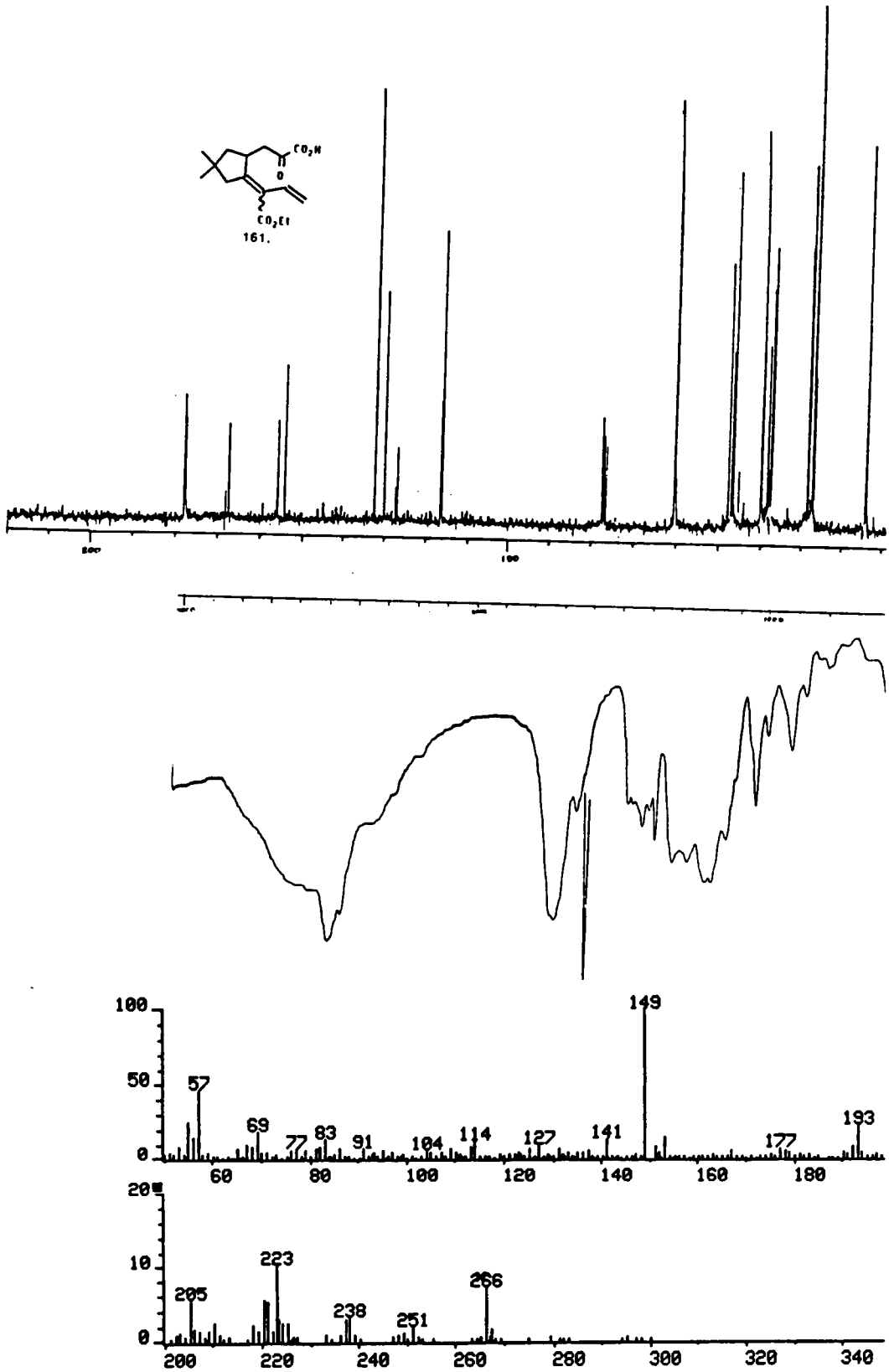
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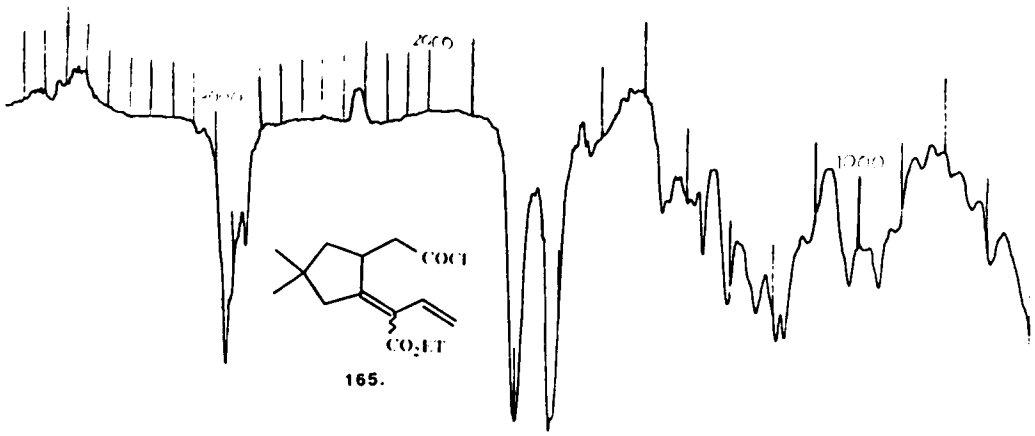

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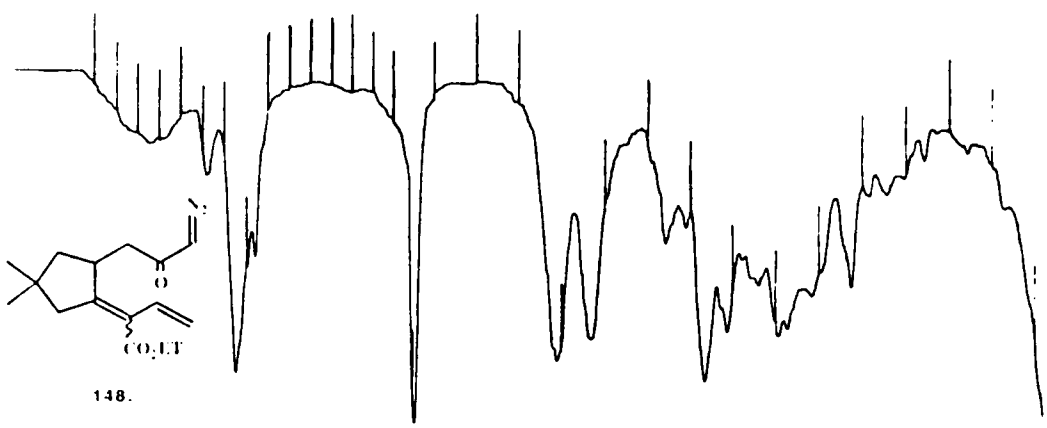

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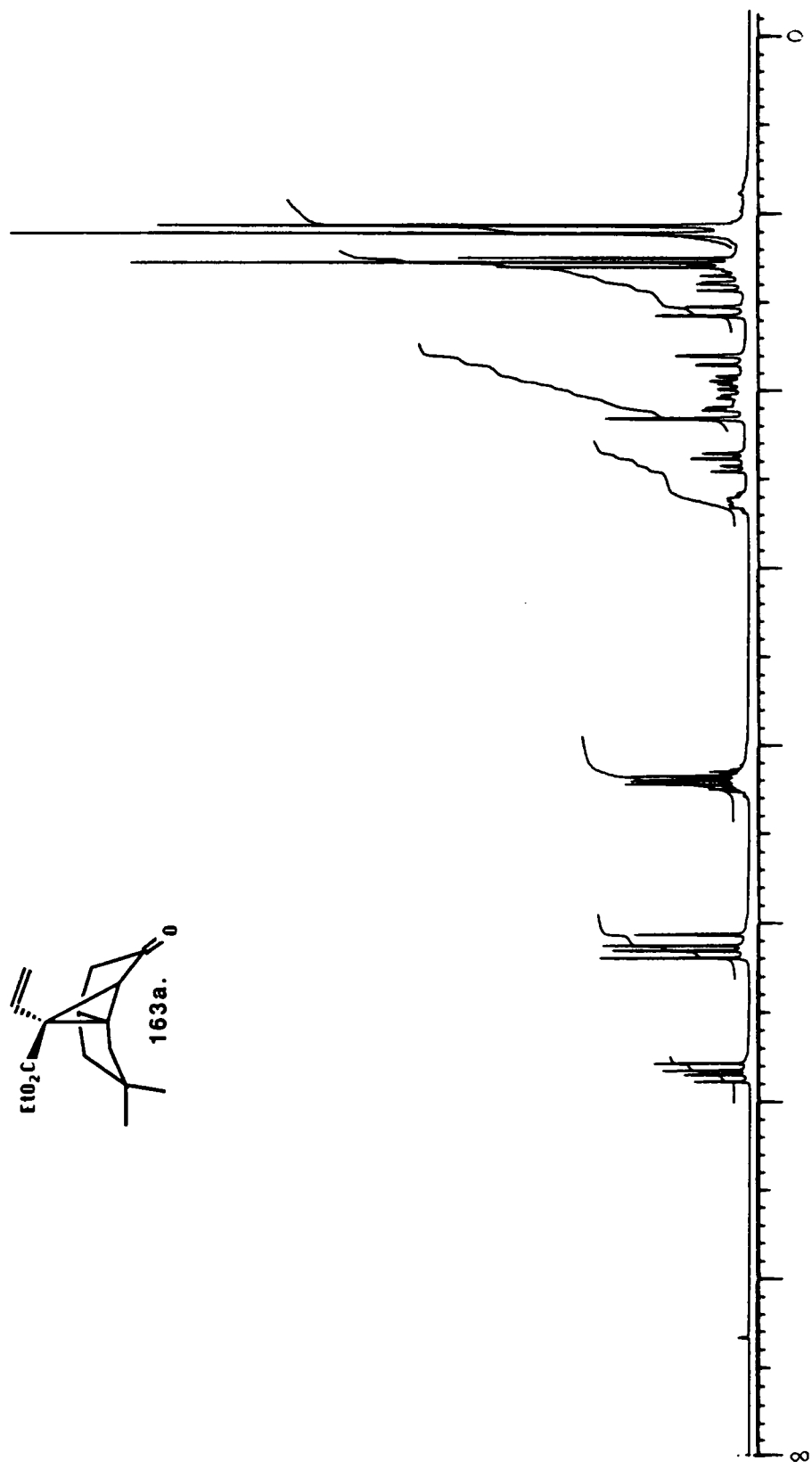
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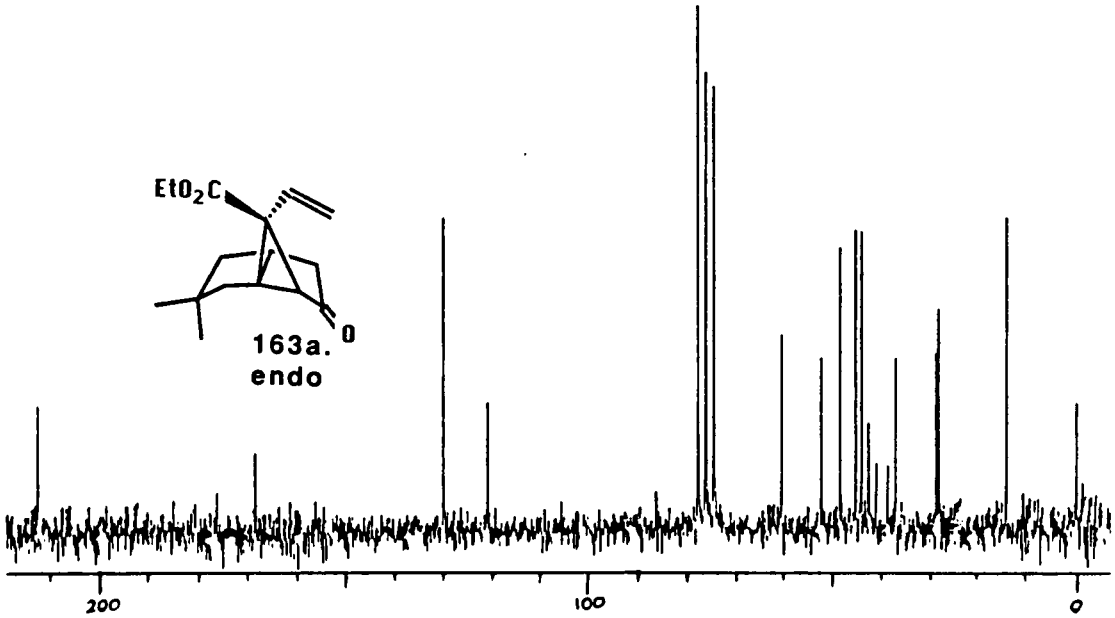
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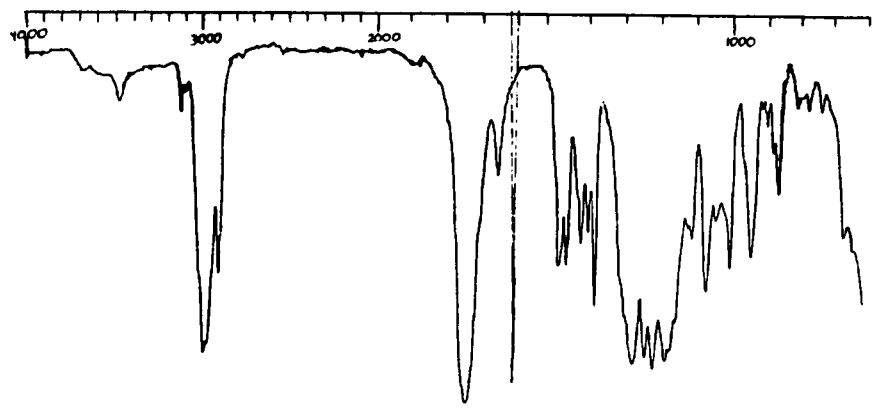
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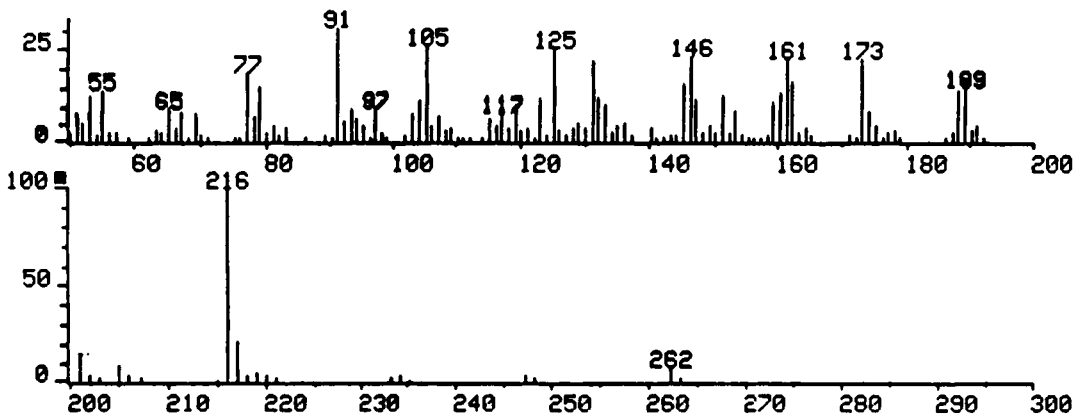
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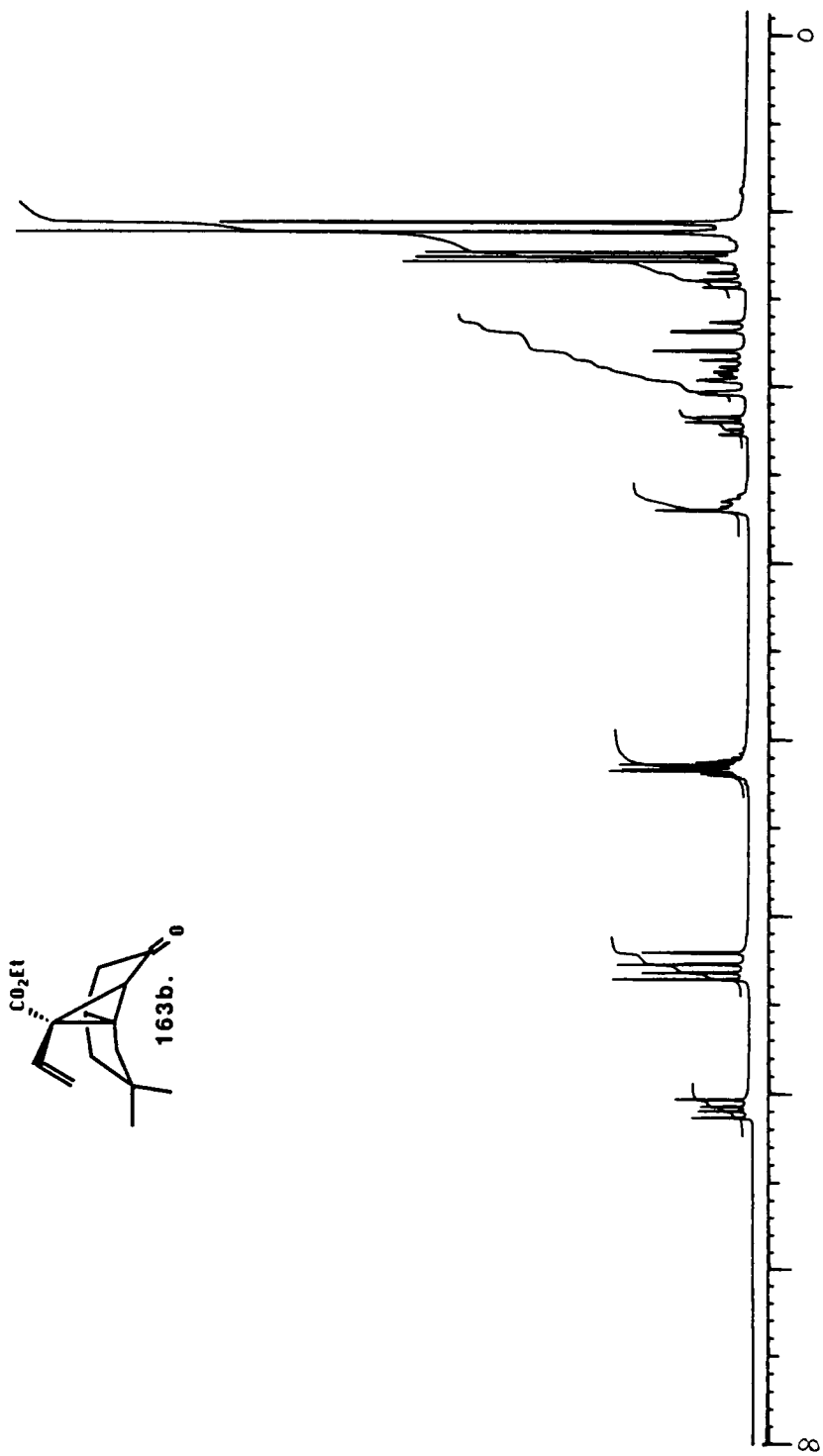
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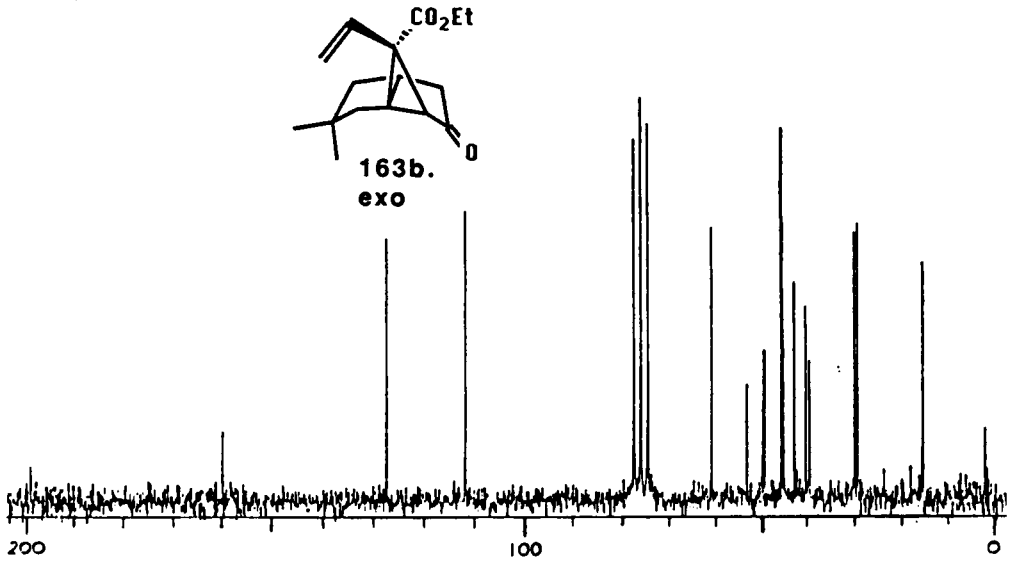
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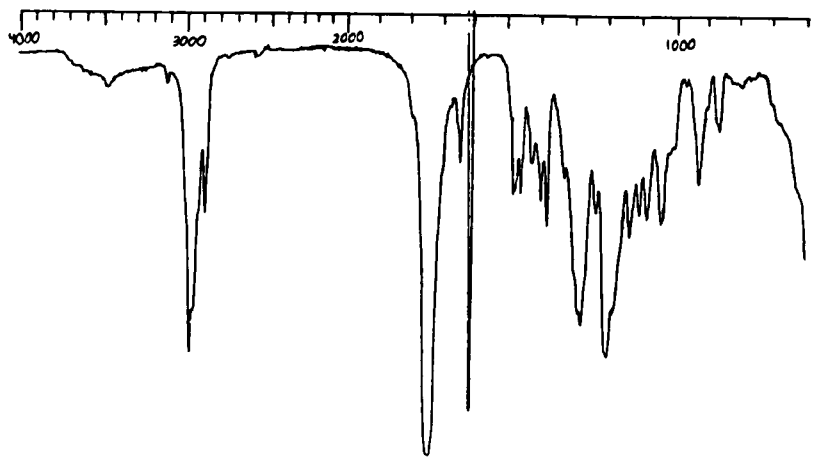
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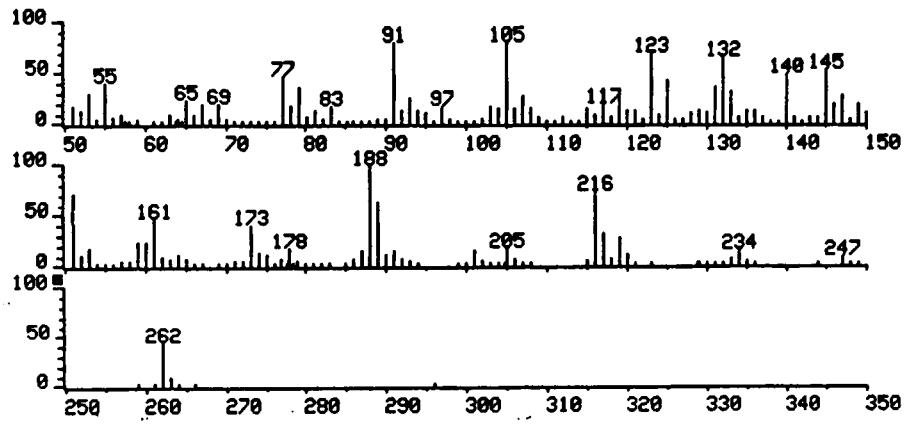
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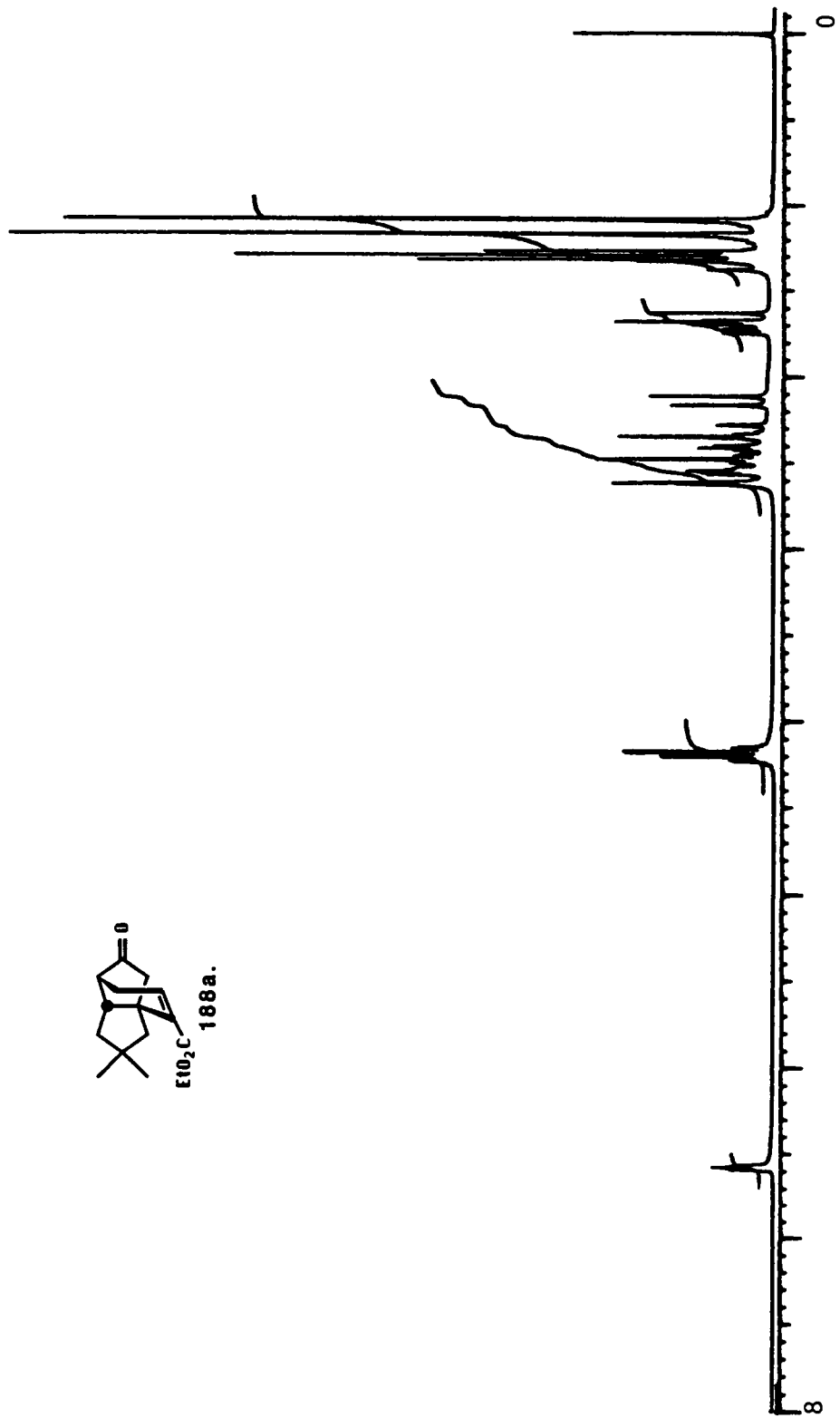
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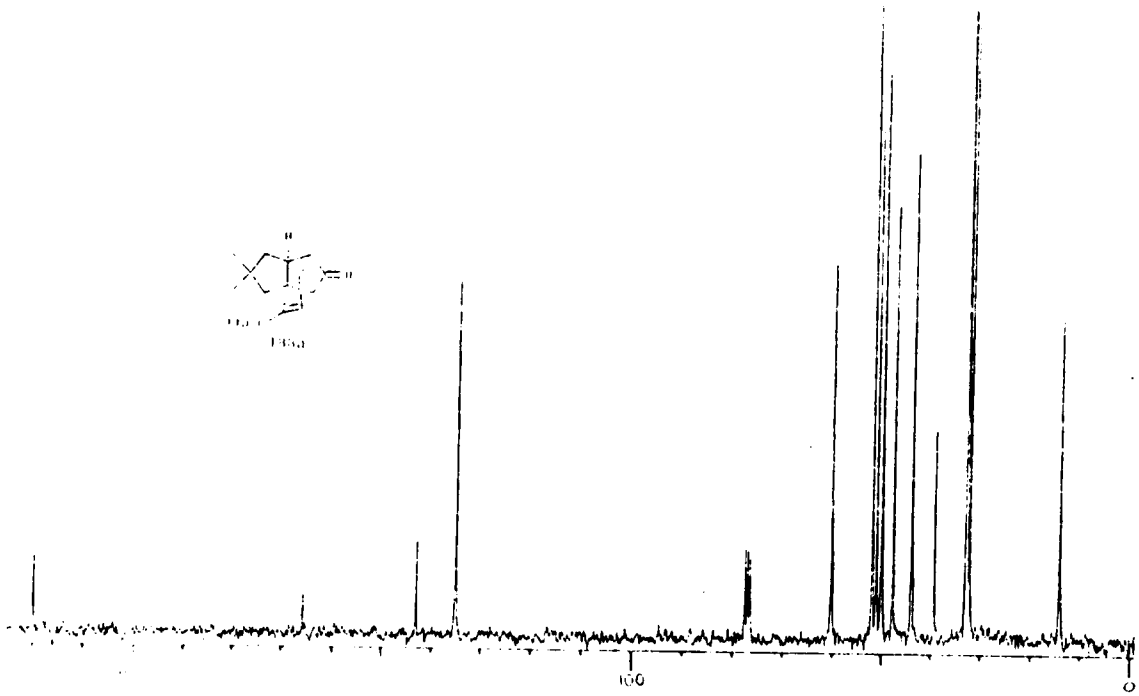
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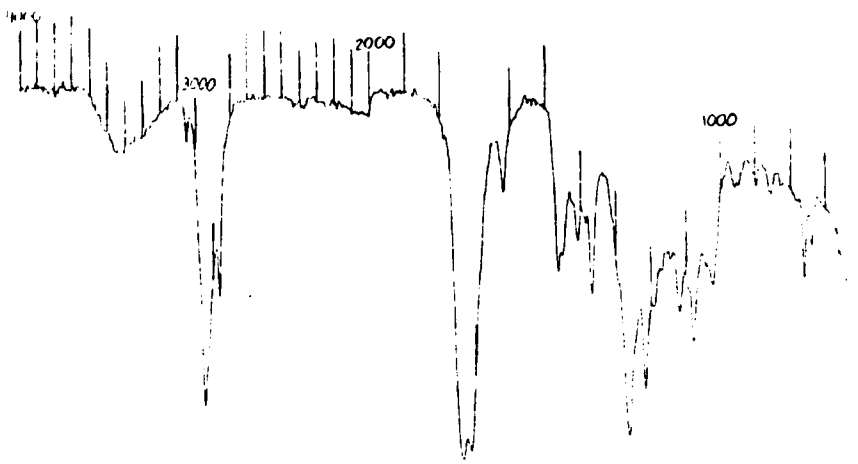
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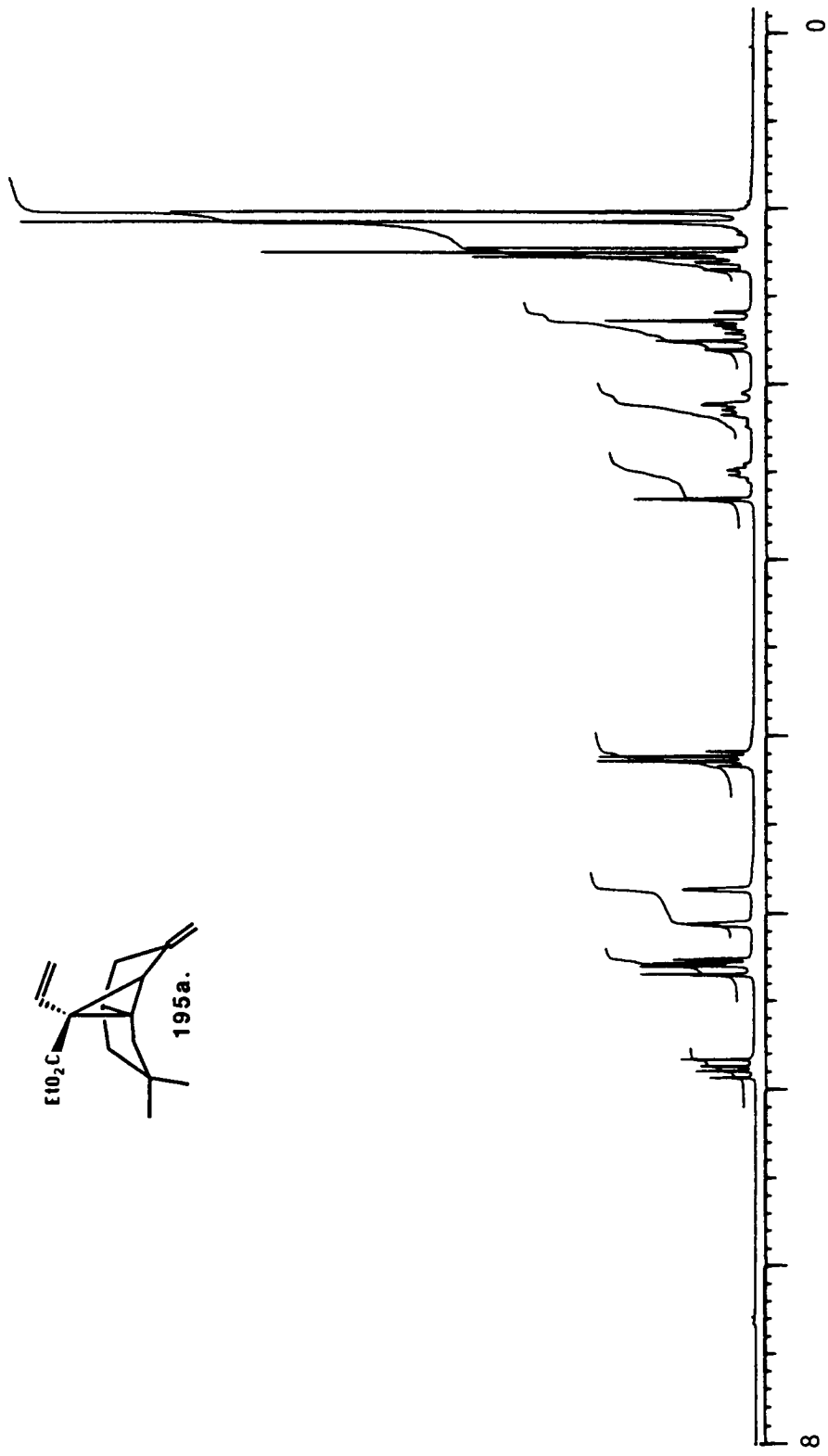
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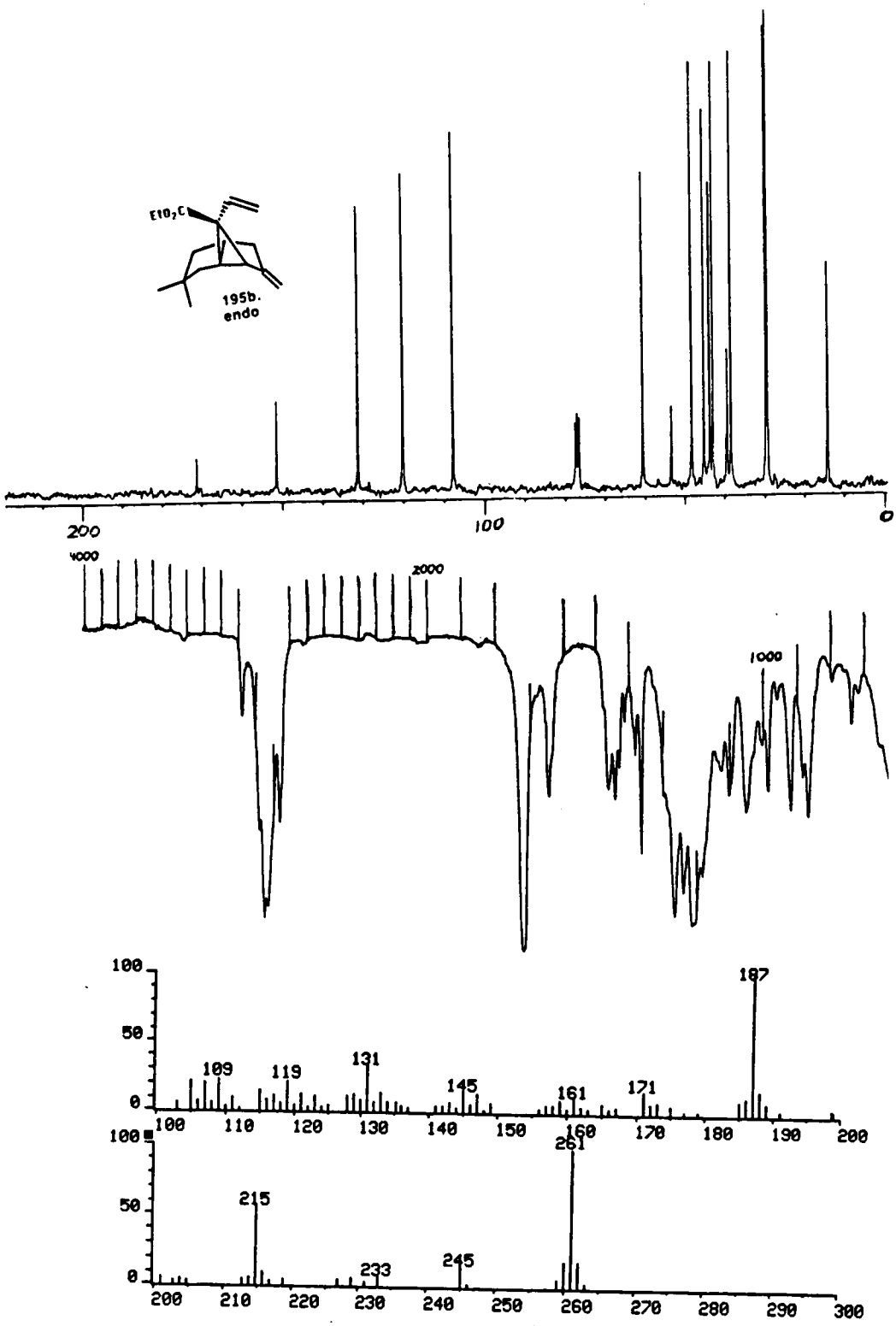
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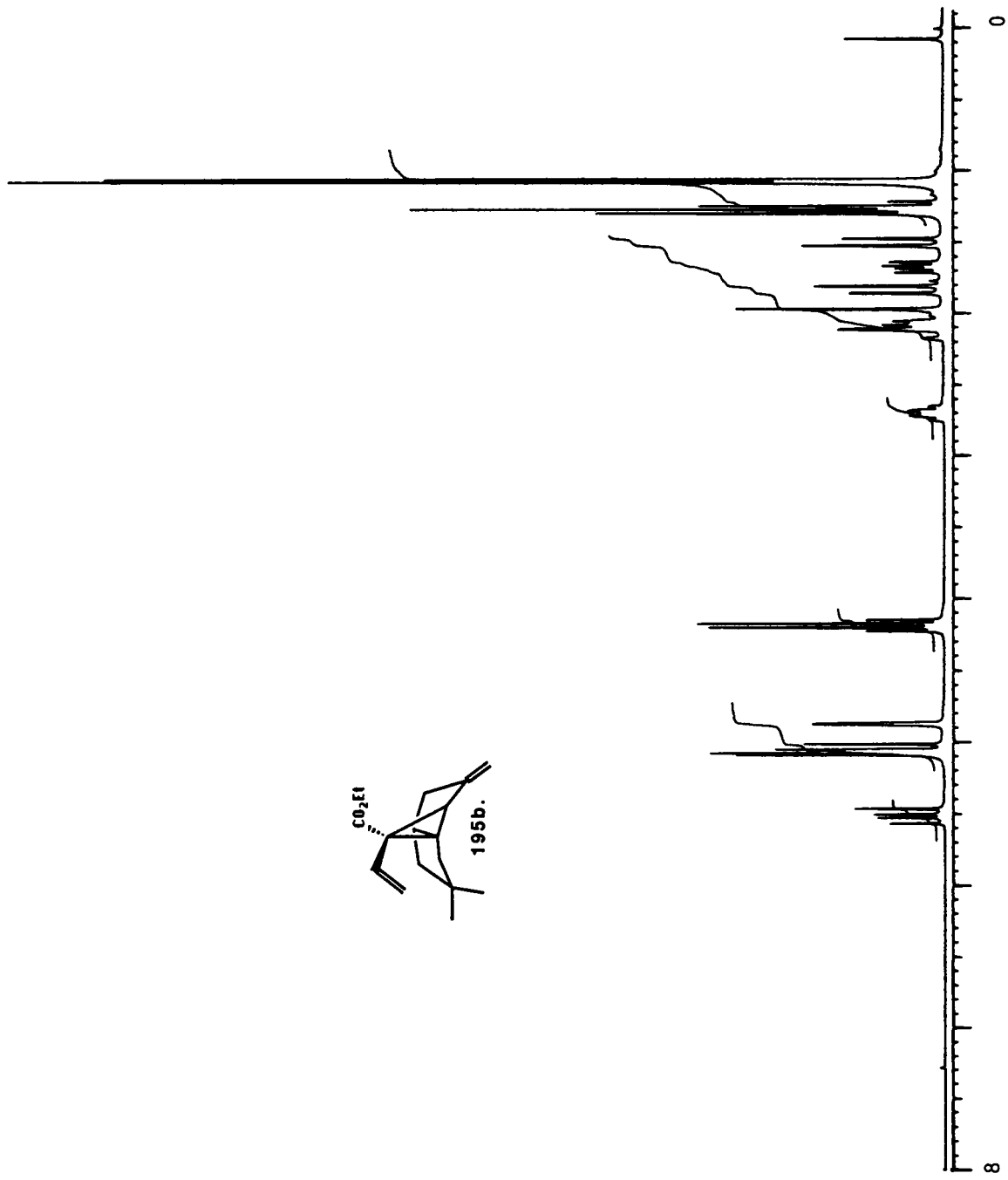
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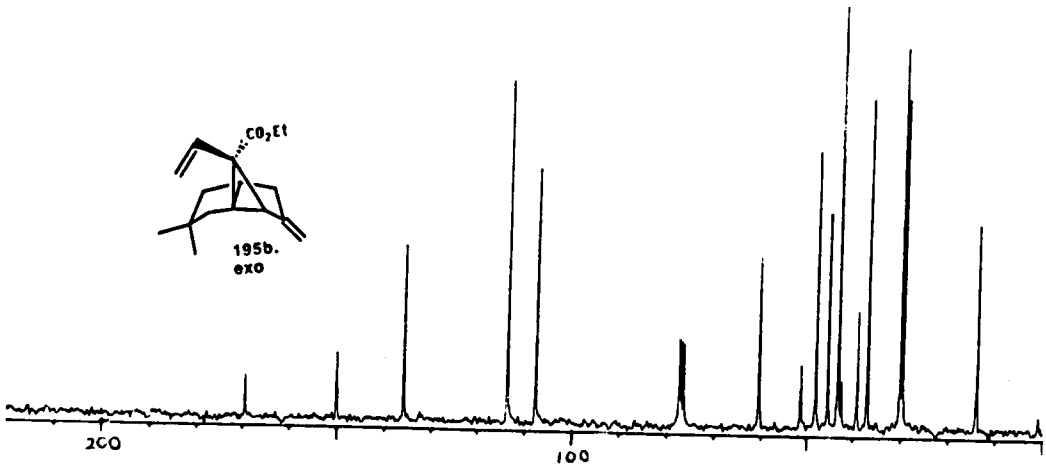
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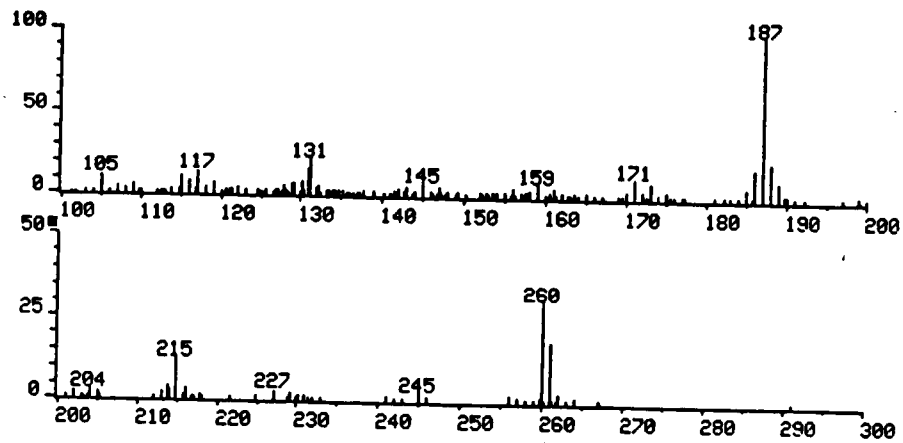
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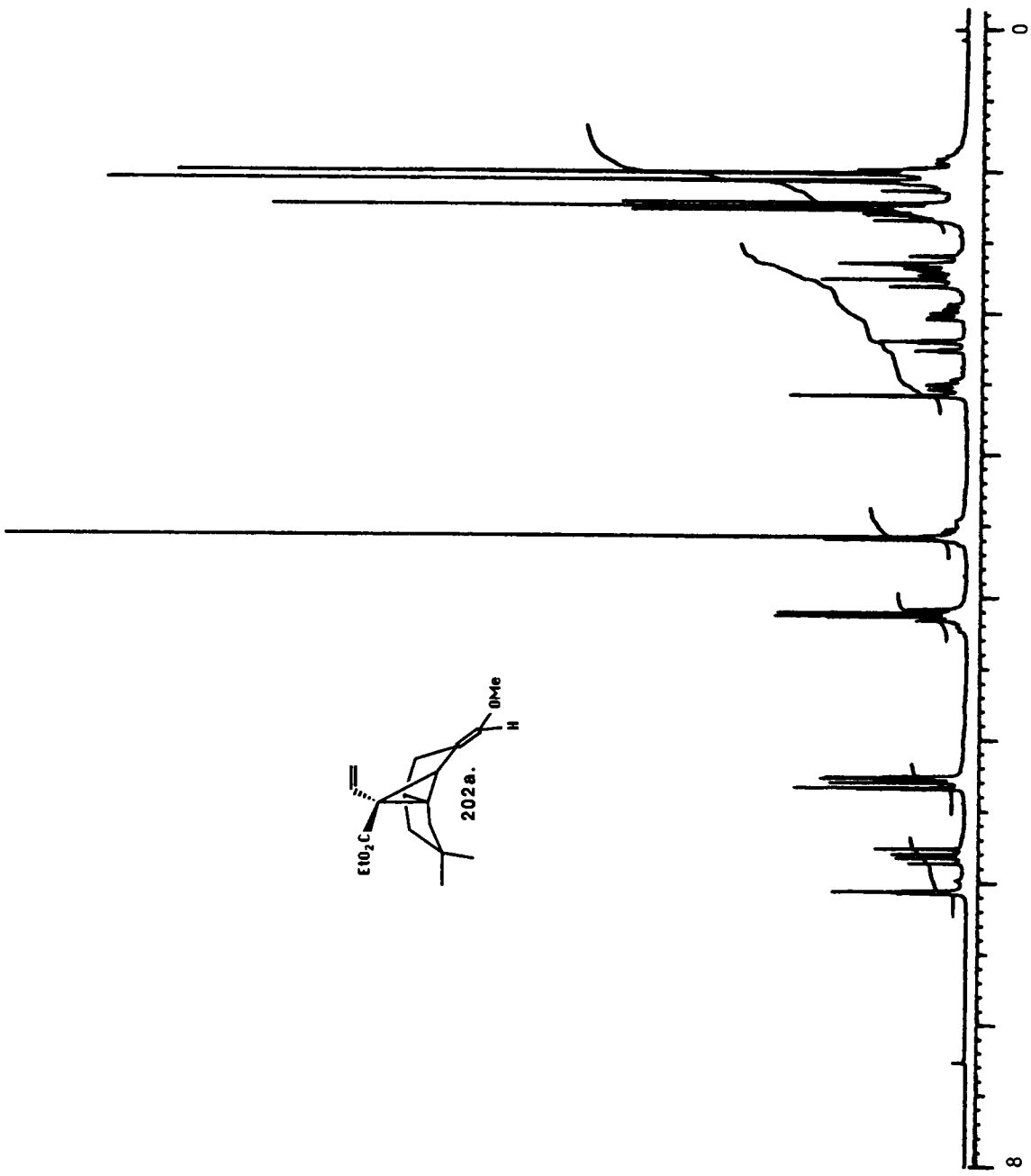
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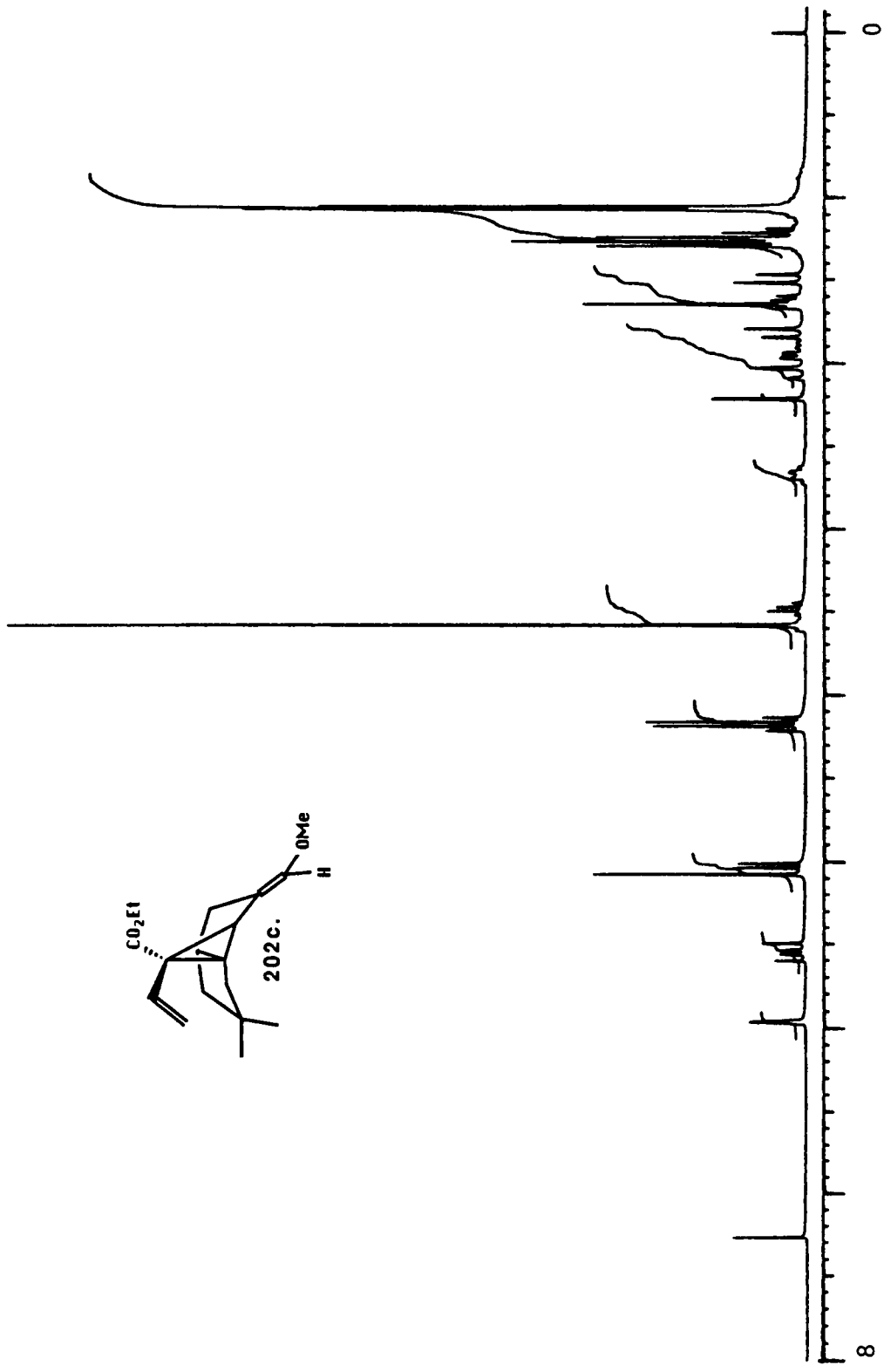
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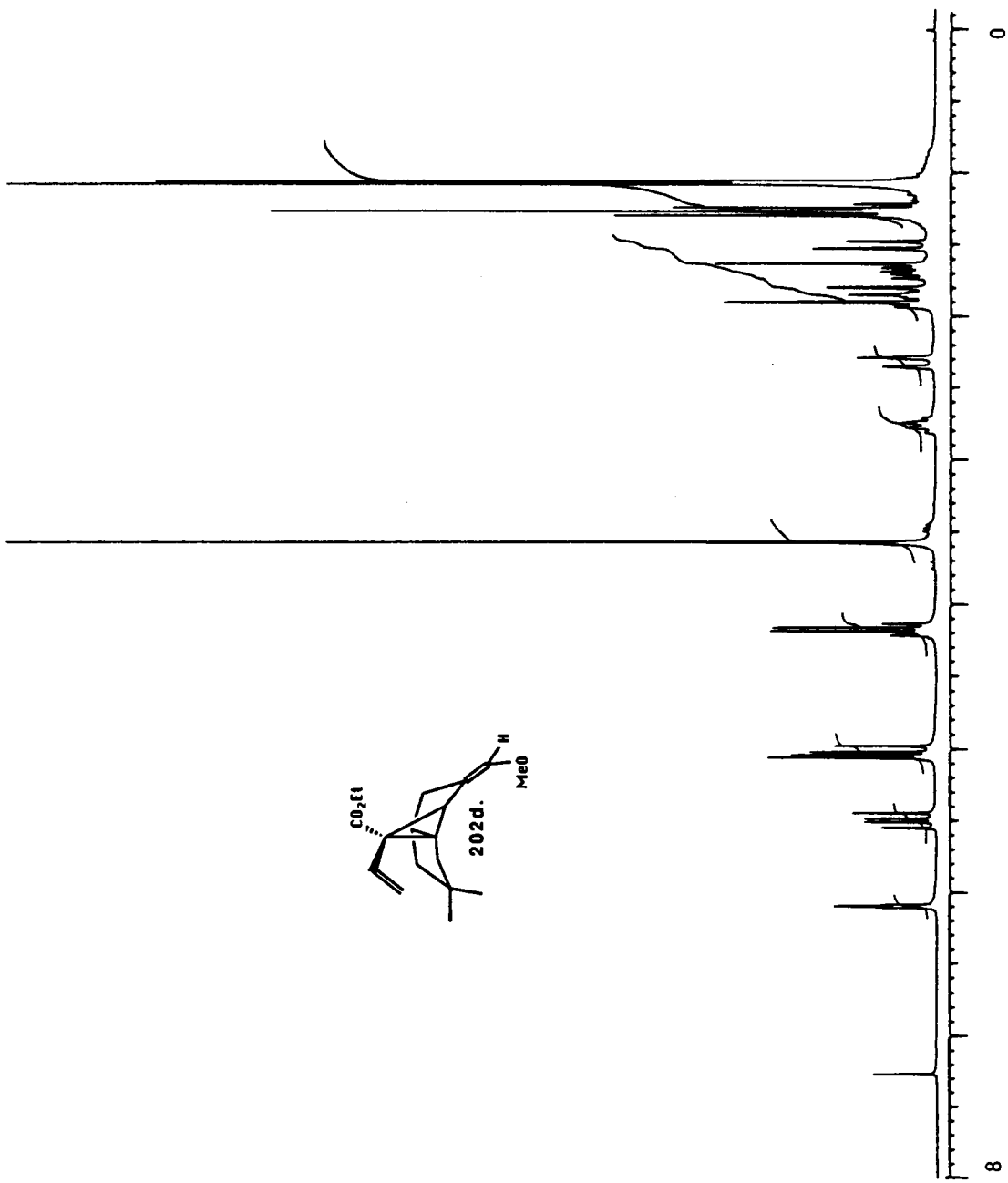
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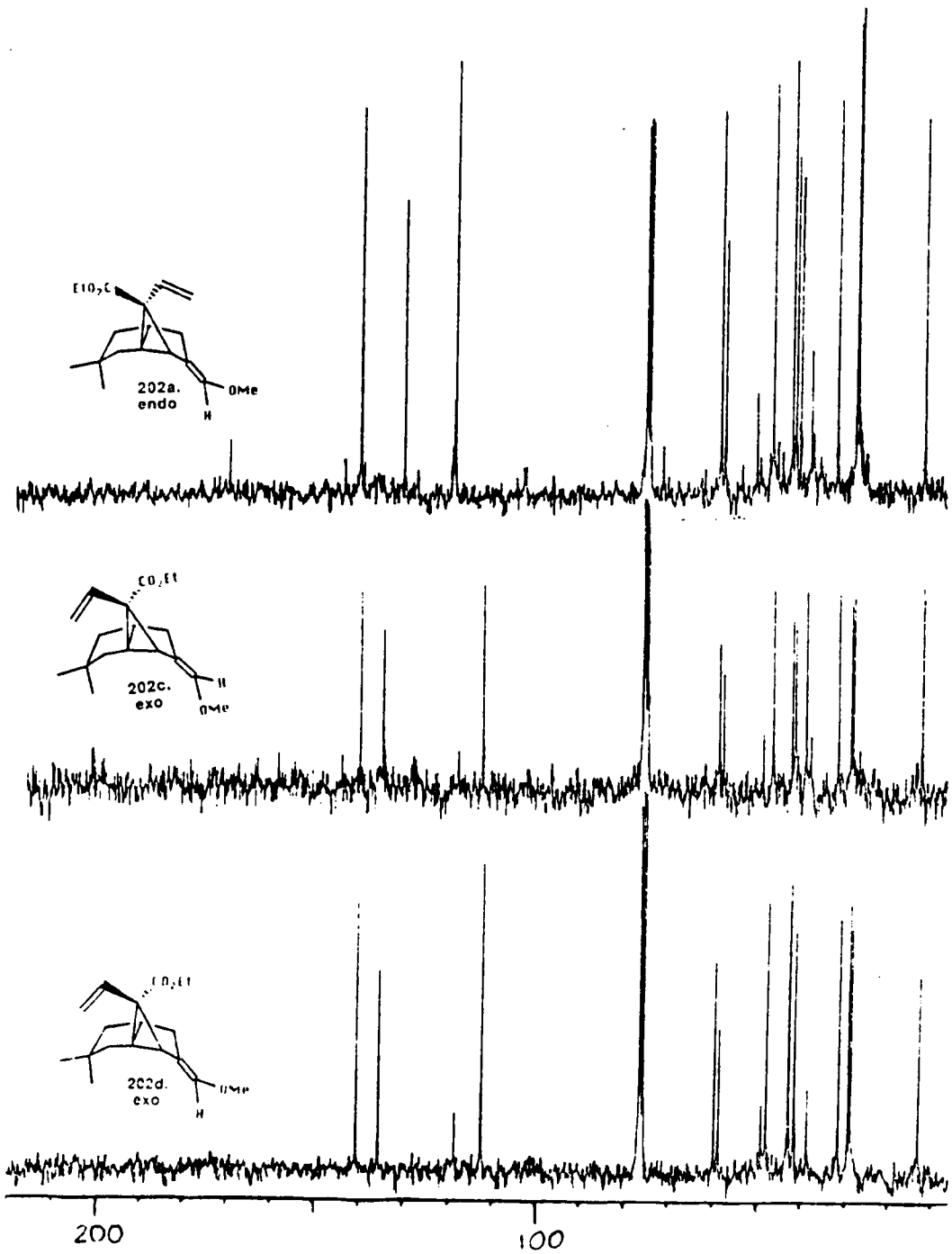
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exo
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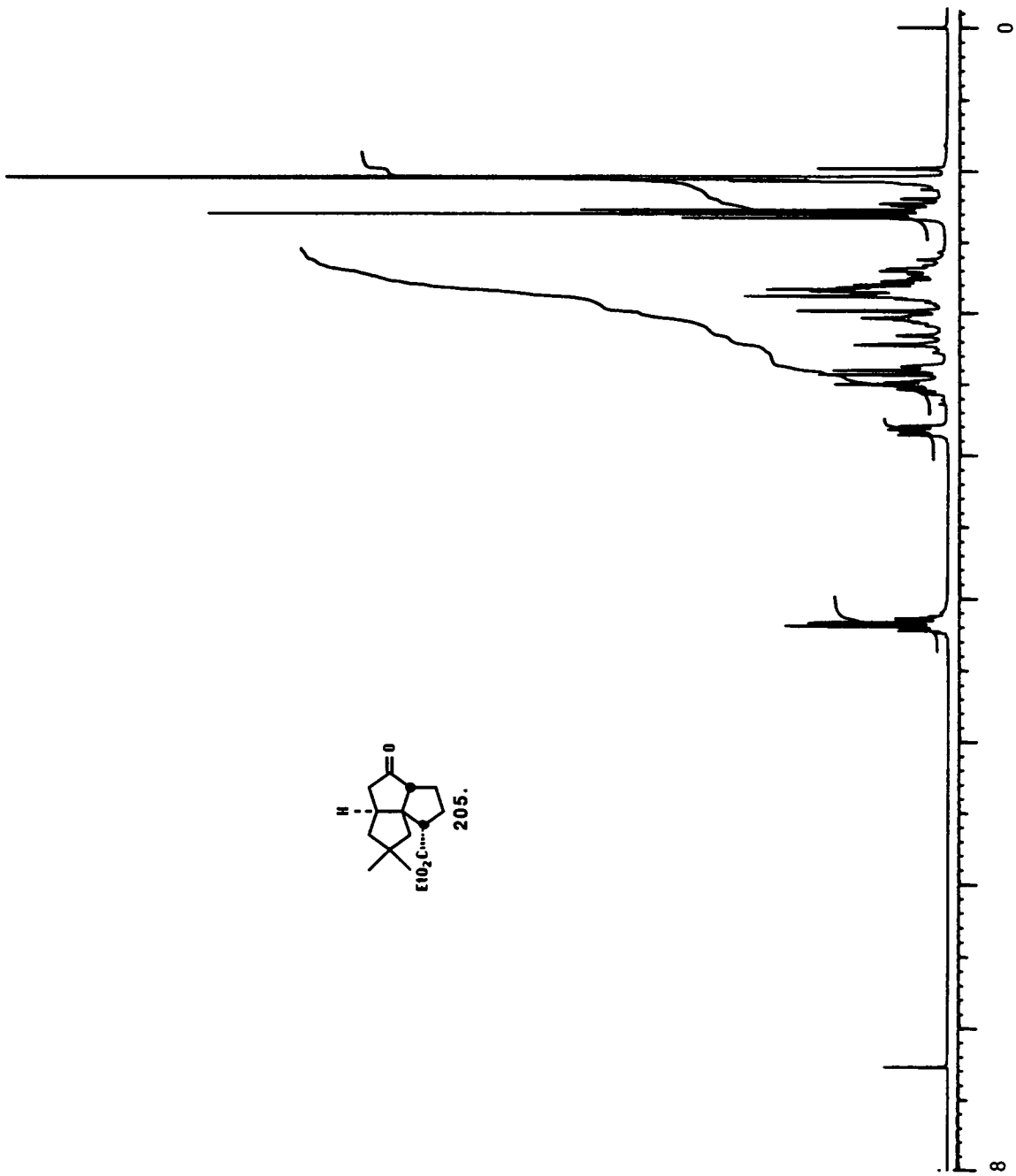
100



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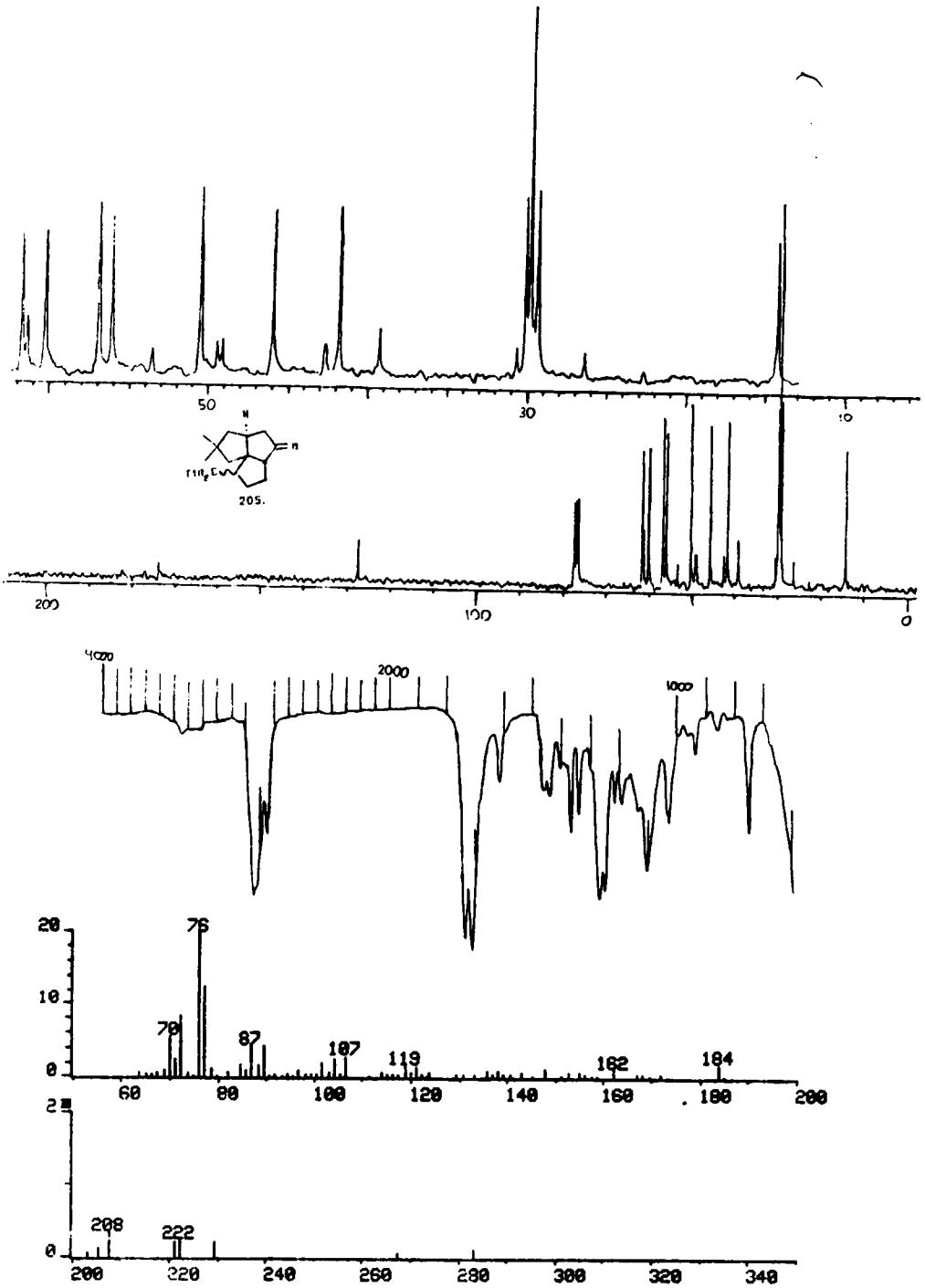
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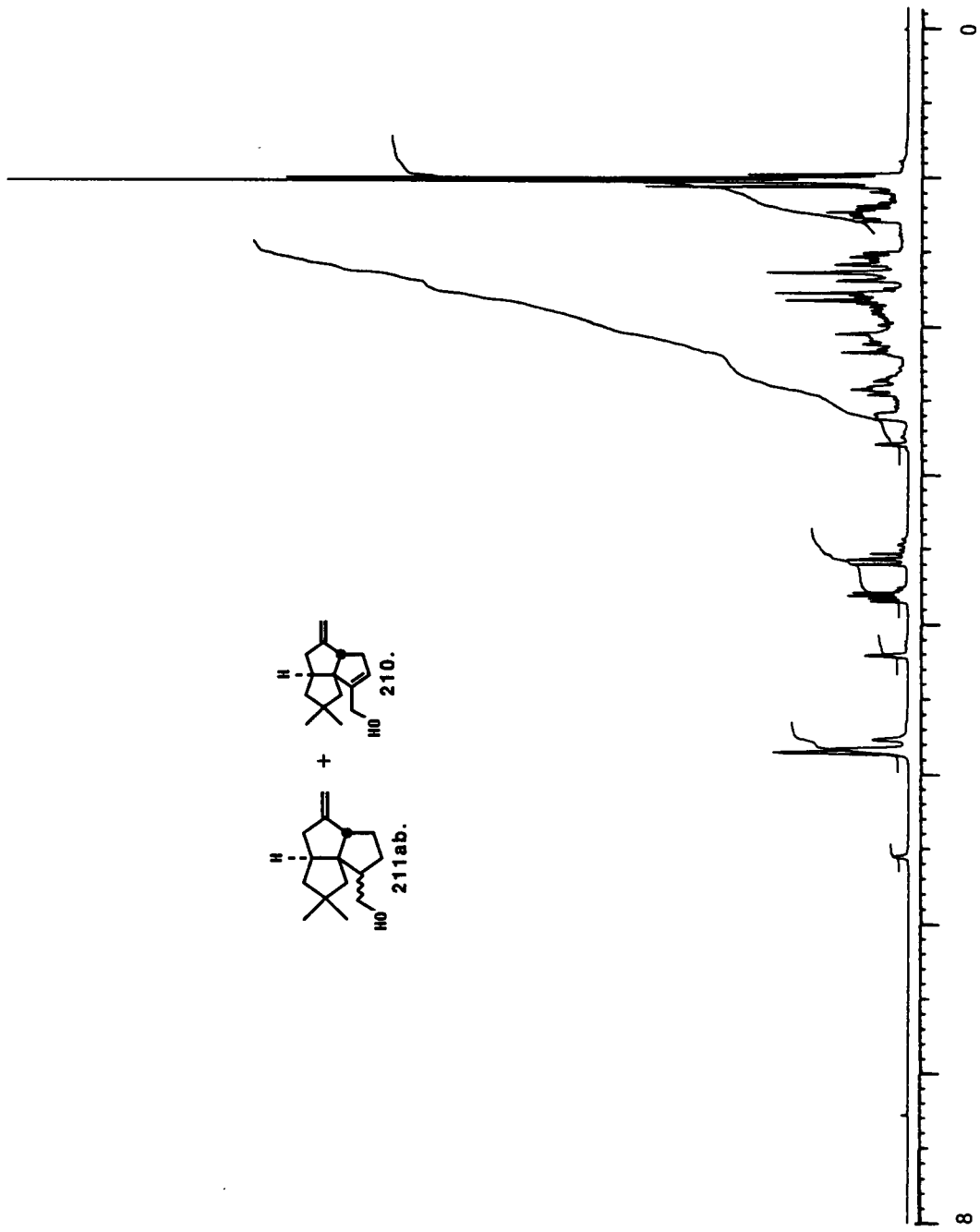
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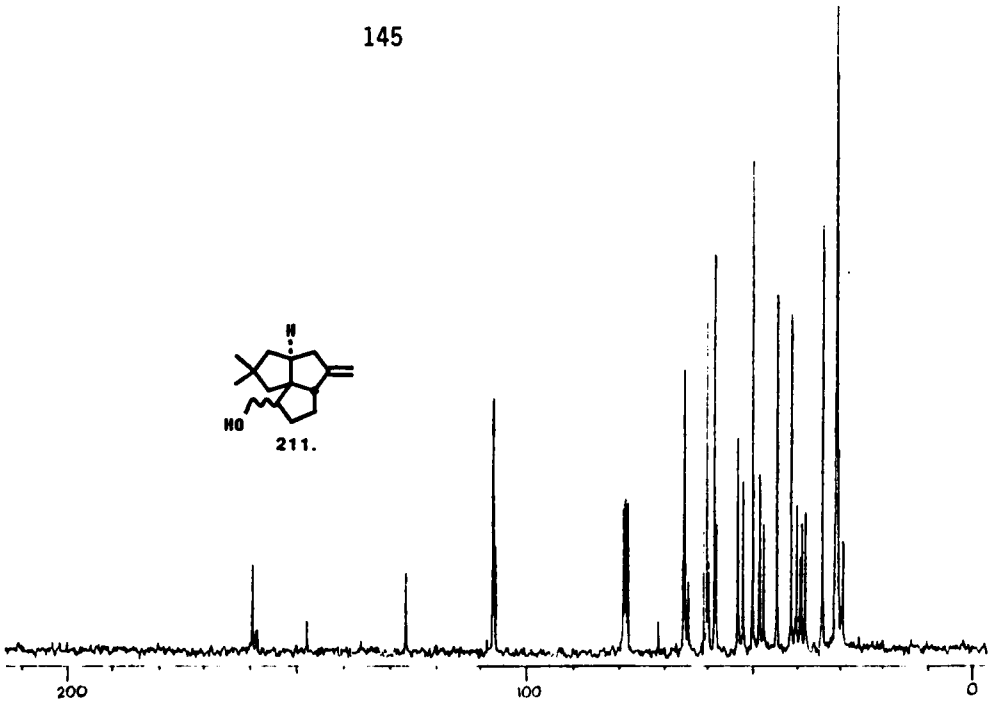
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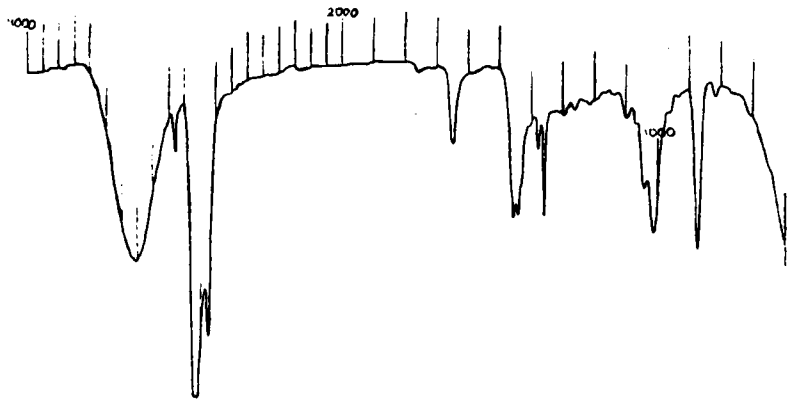
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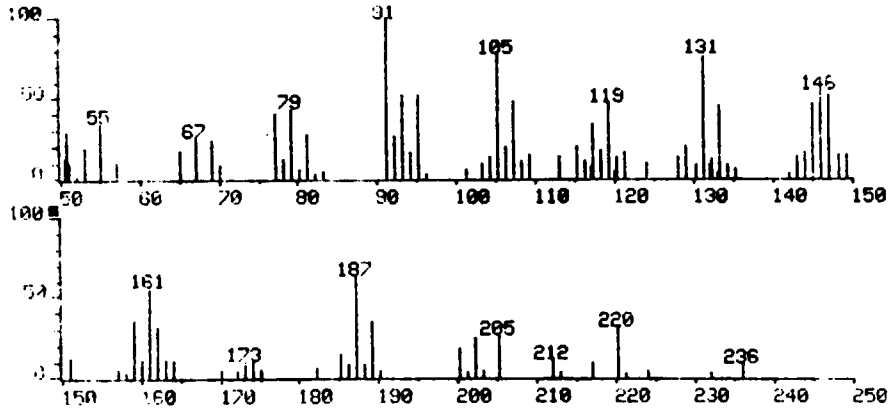
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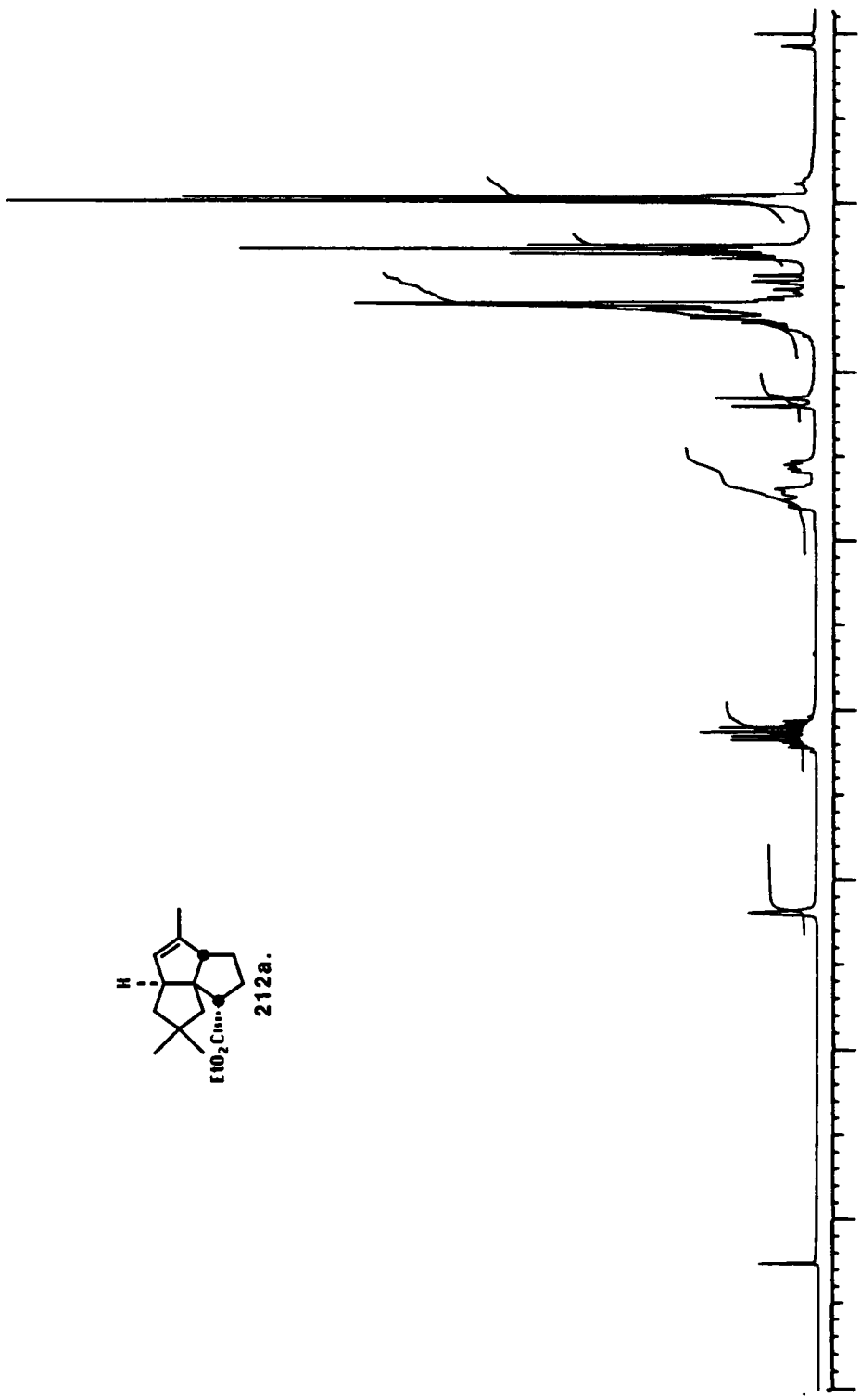

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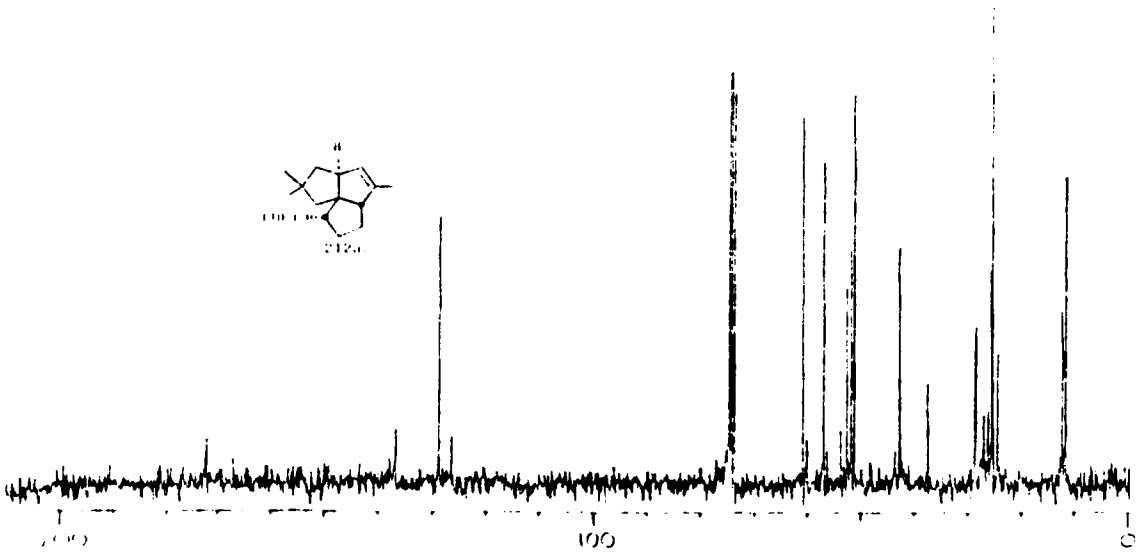

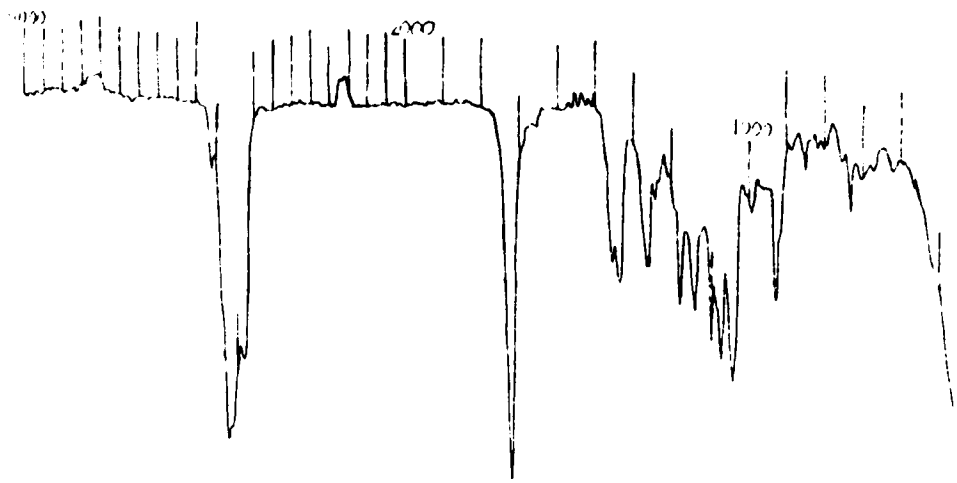

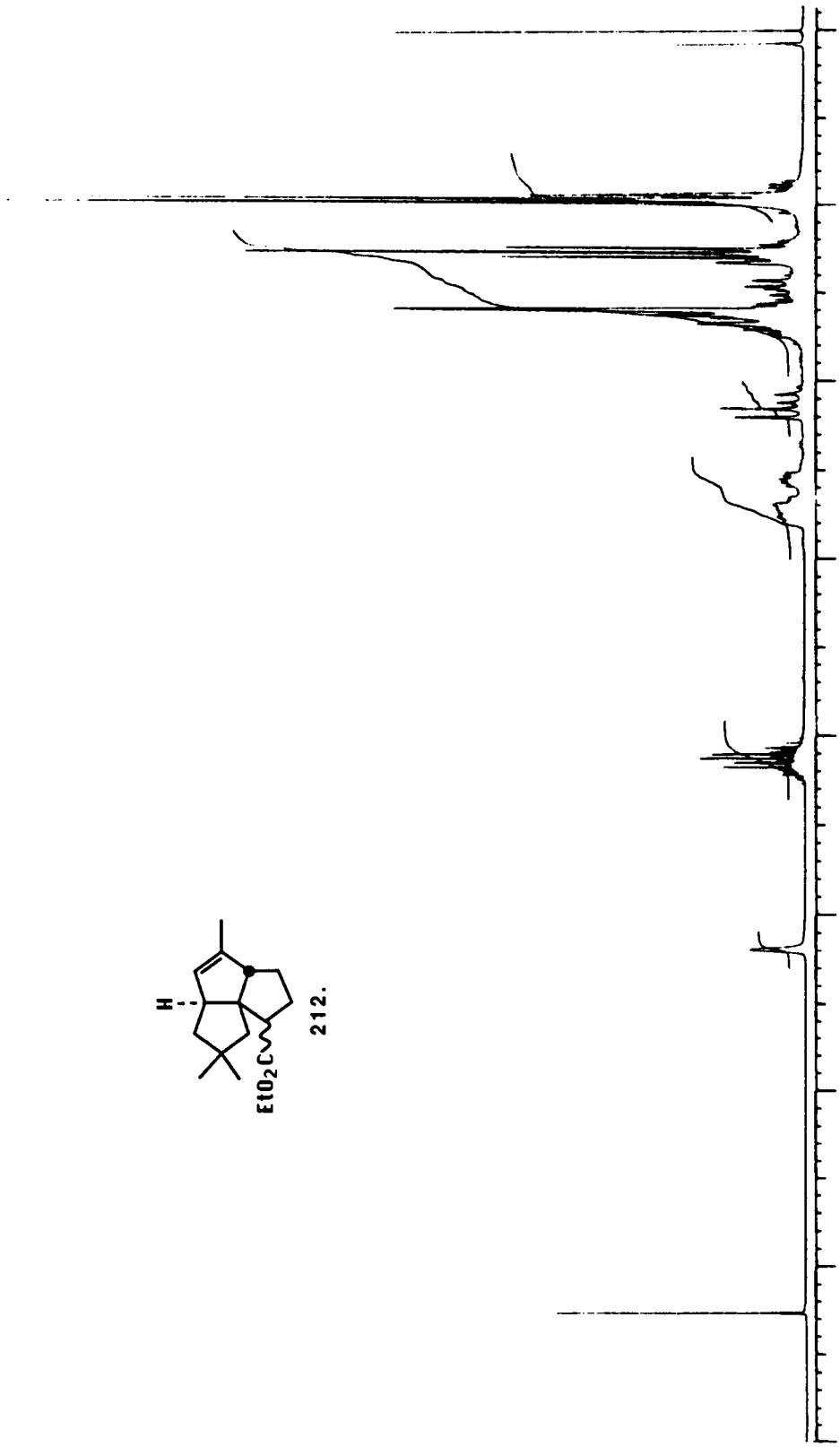

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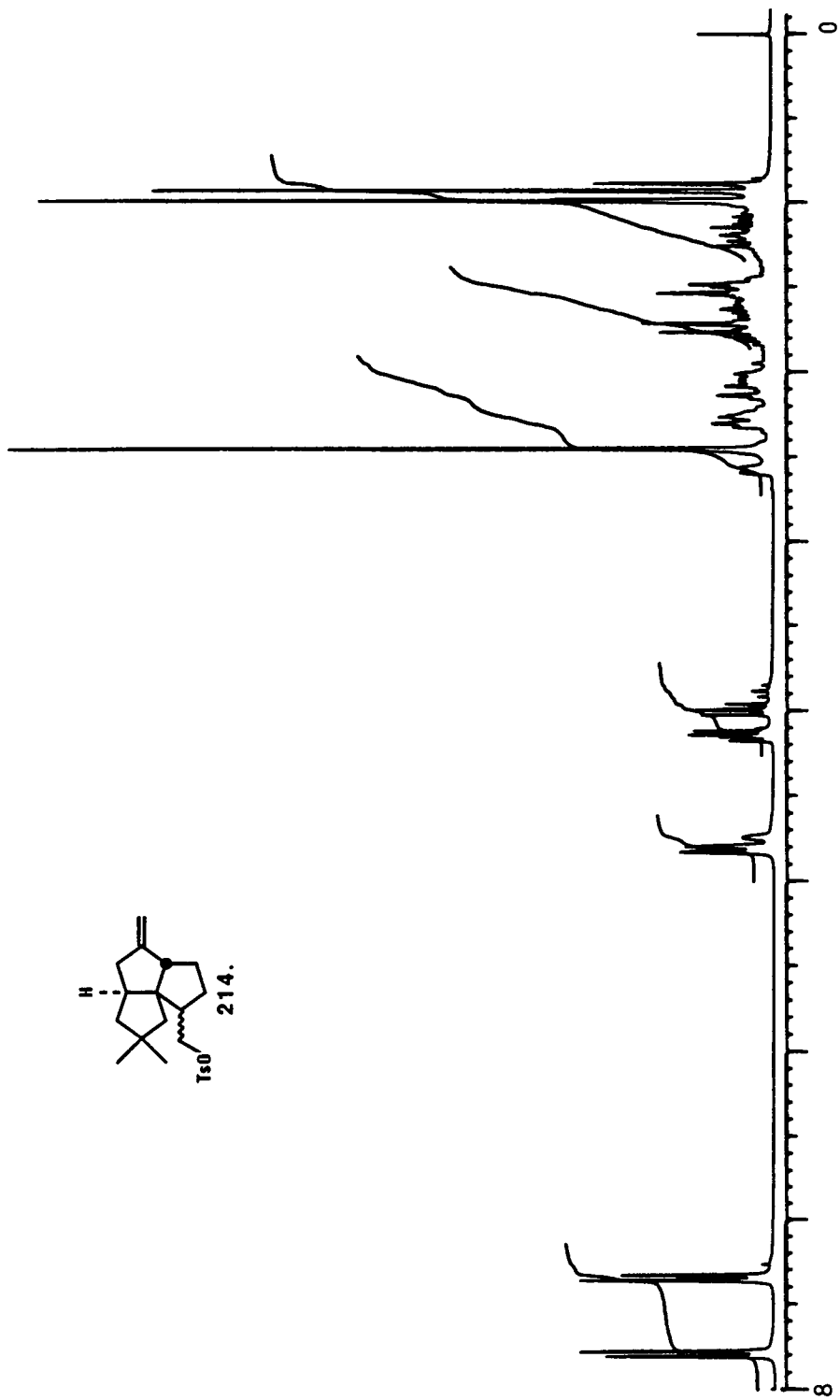
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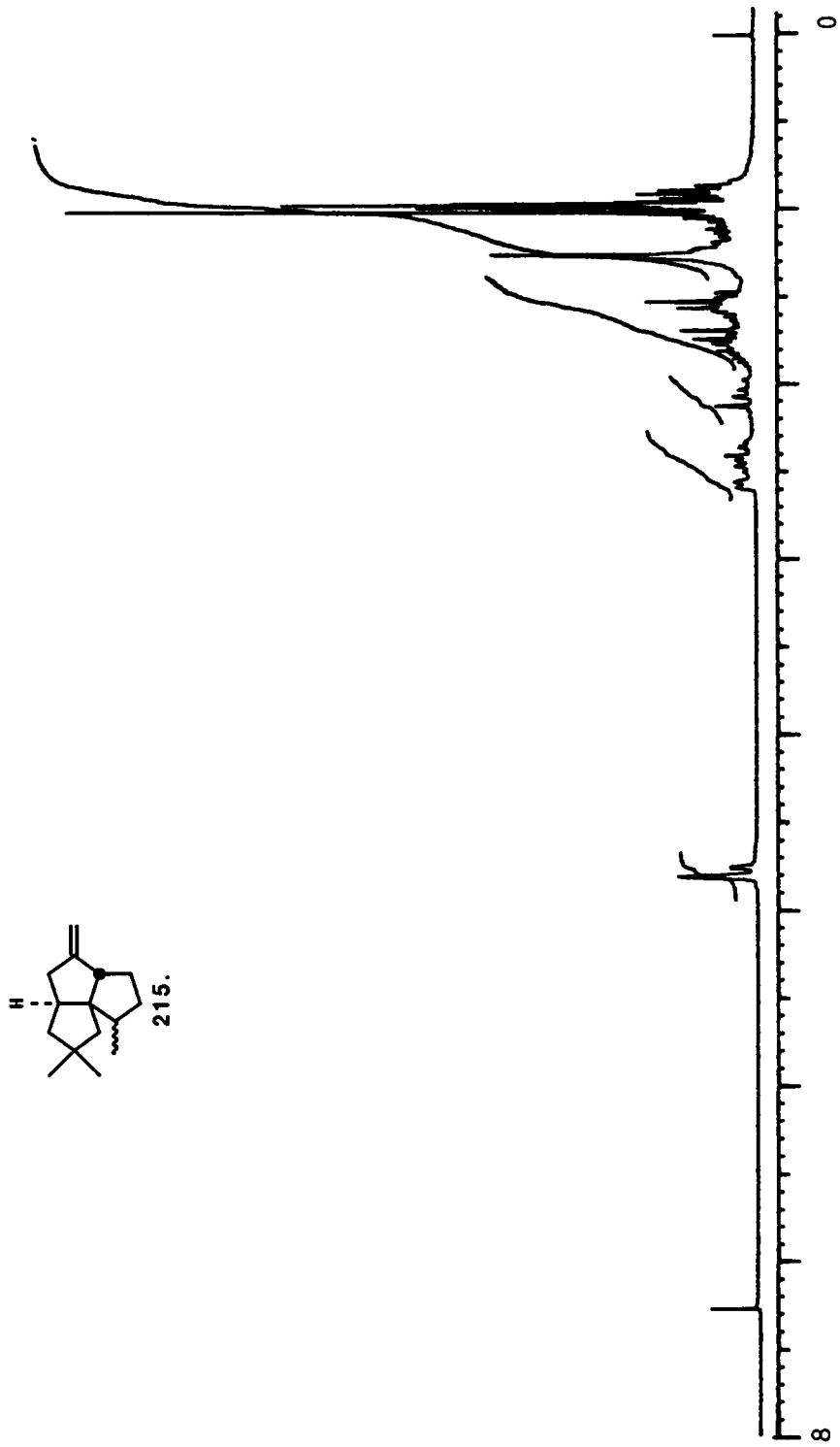
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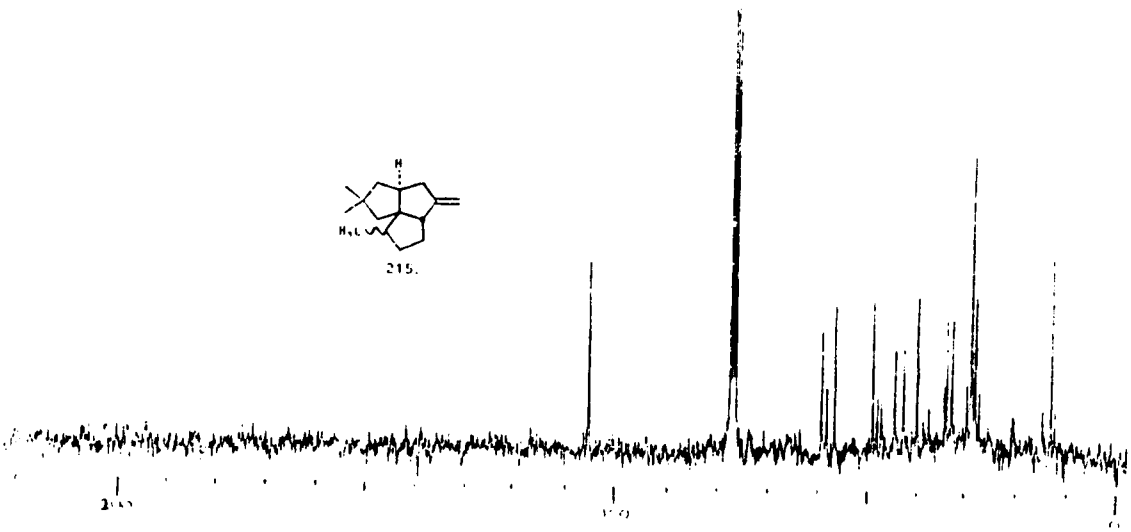

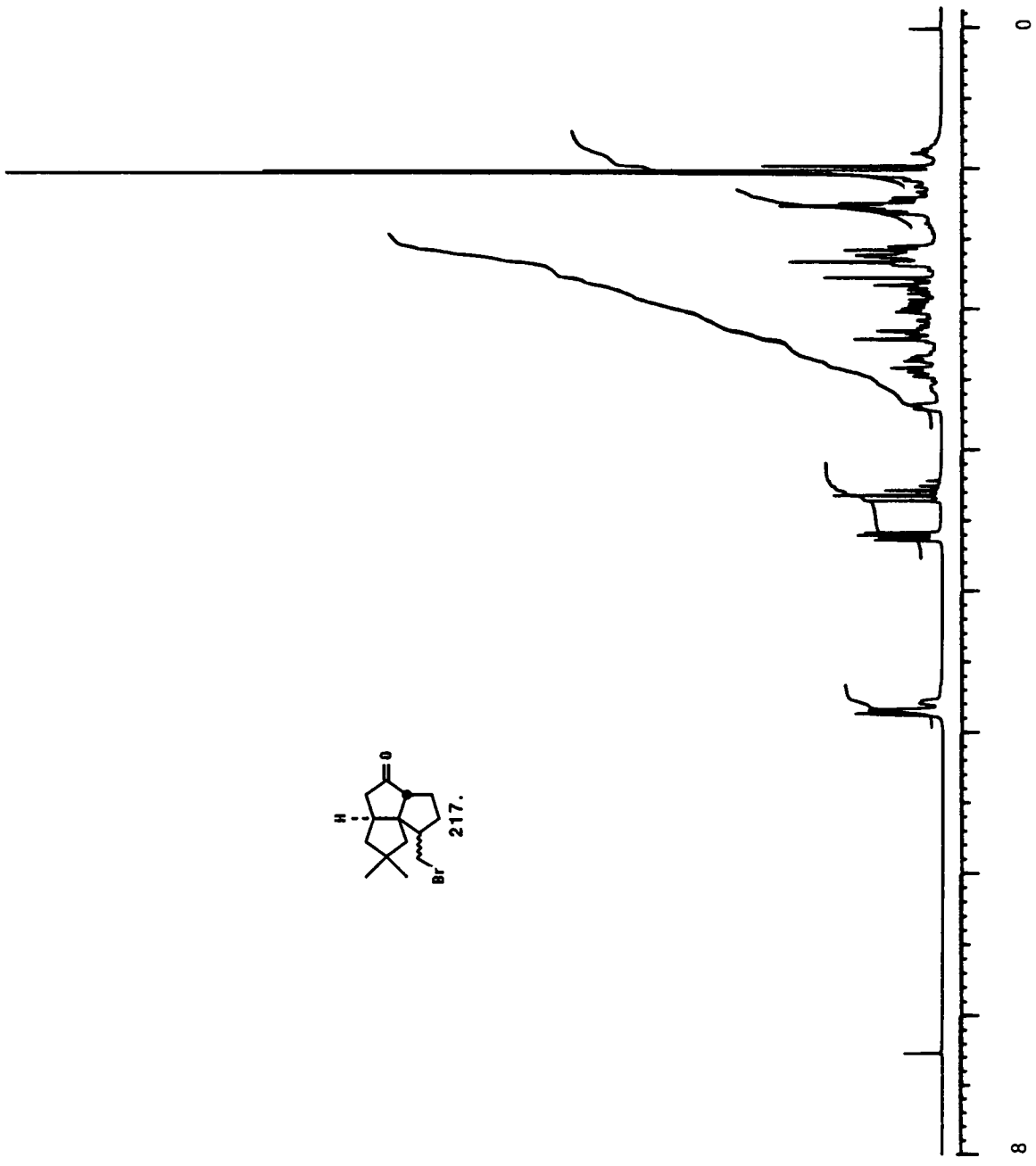

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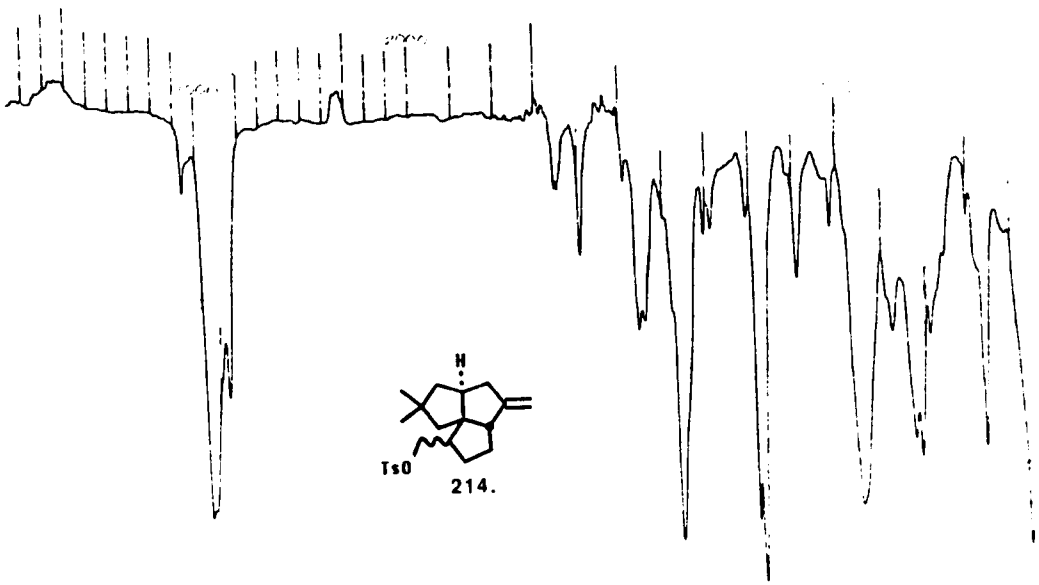

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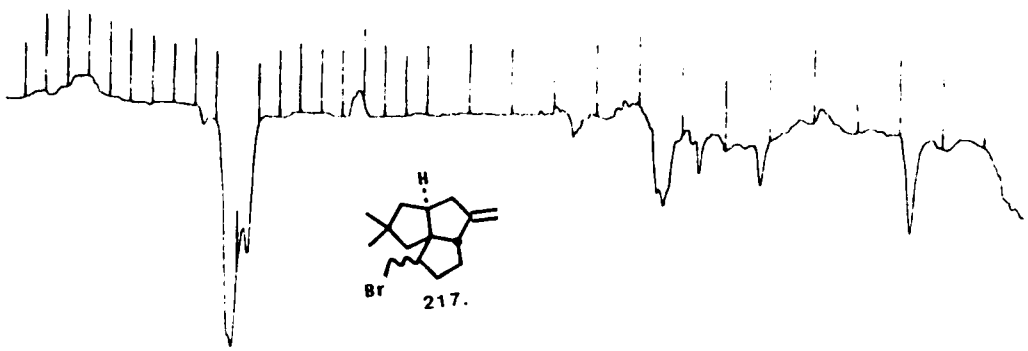

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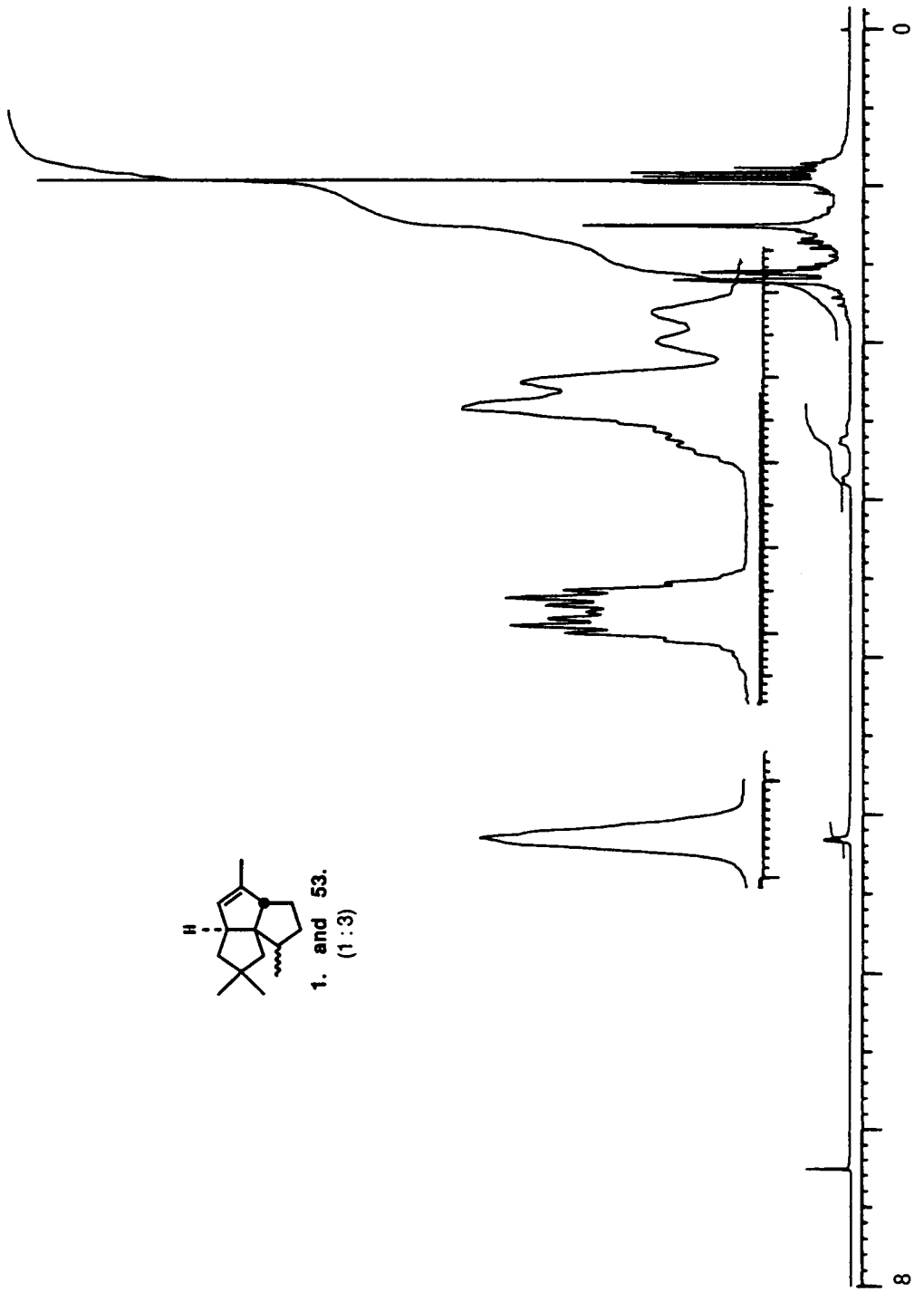

1. and 53.
(1:3)

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