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MARINE ALGAL CHEMISTRY

I. HALOGENATED CONSTITUENTS OF *CHONDROCOCCUS HORNEMANNI* (MERTENS)SCHMITZ

II. HALOGENATED CONSTITUENTS OF *ASPARAGOPSIS TAXIFORMIS* (DELILE) TREV.

III. STUDIES ON THE BIOGENESIS OF THE DICTYOPTERENE HYDROCARBONS AND SULFUR COMPOUNDS

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAII IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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By

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ABSTRACT

I. Five halogenated acyclic monoterpenes related to myrcene[1] and six halogenated cyclic compounds related to myrcene, viz. chondrocole A,[2] chondrocole furan, chondrocolactone, hornediol monoacetate, hornediol diacetate and 4,5-dimethylbenzofuran, have been isolated from the extract of dried plants of Chondrococcus hornemanni collected from the Halona Blowhole (Oahu, Hawaii) and the structures elucidated primarily from spectral data. The structure of chondrocolactone was confirmed and the absolute configuration determined by single crystal X-ray analysis. The structure of chondrocole A was revised from the one published in the literature.[2]

Examination of the methylene chloride extract of dried plants from Black Point (Oahu, Hawaii) resulted in the isolation of two new compounds, chondrene and bromo-4-hydroxybenzaldehyde.

The ether extract of Sri Lankan C. hornemanni was found to contain a large amount (13.5%) of one halogenated acyclic derivative of myrcene[3] plus smaller amounts of several new unidentified halogenated compounds.

II. The methylene chloride extract of dried Hawaiian Asparagopsis taxiformis has been found to contain five dihaloacetamides, seven halogenated but-3-en-2-ols and twenty halogenated 2-propanols.[4] The aqueous extract has

been shown to contain nine halogenated acetic acids and nine halogenated acrylic acids.[5] Biomimetic syntheses of the haloacetic and haloacrylic acids from polyhaloacetones and polyhalo-2-propanols have been studied.

III. The numerous odoriferous C_{11} hydrocarbons and related sulfur-containing compounds produced by Dictyopteris plagiogramma and D. australis have been proposed to originate from cis-1,5-undecadien-3-ol and cis,cis-undecatrien-3-ol. cis-1,5-Undecadien-3-ol was prepared by two routes and attempts to convert the alcohol into C_{11} hydrocarbons are described. The related alcohol, cis-1,5-octadien-3-ol, isolated from the essential oil of Chondrococcus hornemanni,[6] was also prepared. The methanol extract from Dictyopteris was examined for the naturally occurring C_{11} alcohols but neither alcohol could be detected in the algal samples in this study. Synthesis of the sulfur-containing compounds are also described.

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P A R T O N E

HALOGENATED CONSTITUENTS OF *CHONDROCOCCUS HORNEMANNI* (MERTENS) SCHMITZ

I. INTRODUCTION

A. Initial Studies on the Essential Oil of *Chondrococcus hornemanni*

Chondrococcus hornemanni (Mertens) Schmitz, a red alga belonging to the family Rhizophyllidaceae, is found in the subtropical and tropical regions of the Pacific Ocean. This alga does not grow abundantly in Hawaii, but moderate amounts can be found on the island of Oahu during the winter months in the vicinity of the Halona Blowhole and Black Point. In these areas small tufts of *C. hornemanni* are primarily concentrated in shallow water (0.1-2.5 m) on rocky substrates that are exposed to heavy surf and surge. Isolated tufts growing on dead coral have also been observed in moderately deep water (~15 m) near the mouth of Hanauma Bay (Oahu).

Our interest in *C. hornemanni* was initially aroused by the sharp pleasant odor that is released when the alga is crushed. Unlike terrestrial plants only one essential oil from a marine alga had been previously investigated[1] and it was hoped that the essential oil produced by *C. hornemanni* would be a source of new and interesting compounds. Vacuum drying the wet plants collected at the Blowhole in a vacuum desiccator and trapping the volatiles in a cold finger trap afforded a pale yellow odorous oil (0.3-0.8% yield based on dry weight of seaweed) whose pmr spectrum indicated a complex mixture of compounds. Analysis of the oil by gc-ms

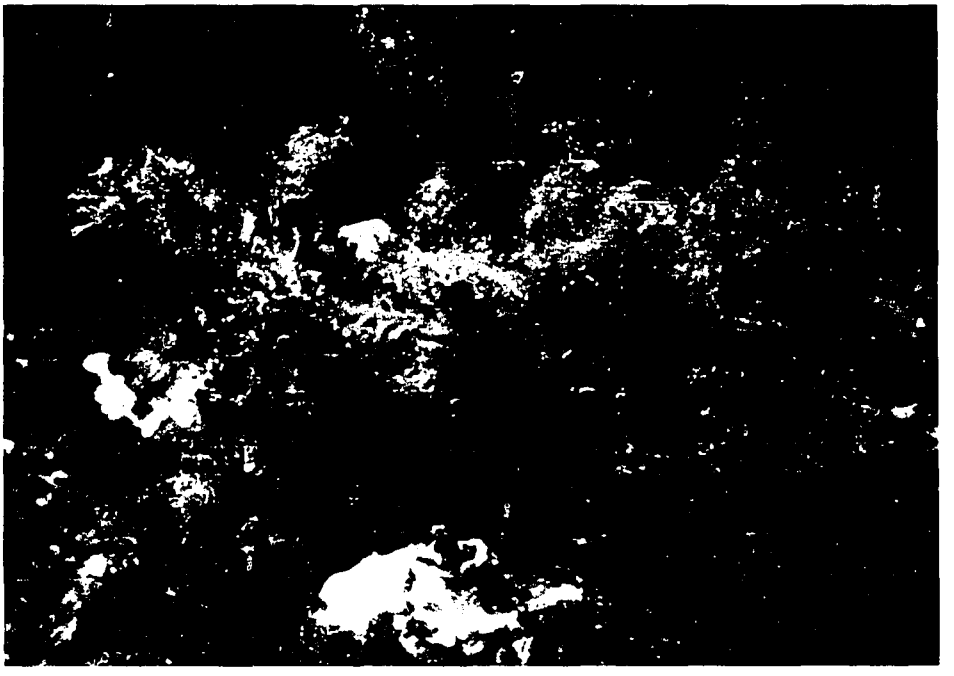


Figure I-1. Photograph of C. hornemanni in its natural habitat.

revealed the presence of approximately 15 halogenated monoterpenes of which three were major. Interestingly, the pmr spectrum and gc trace of the oil isolated in an identical manner from plants collected at Black Point were very different from those of the Blowhole oil. Both oils contained the same halogenated monoterpenes but in radically different amounts.

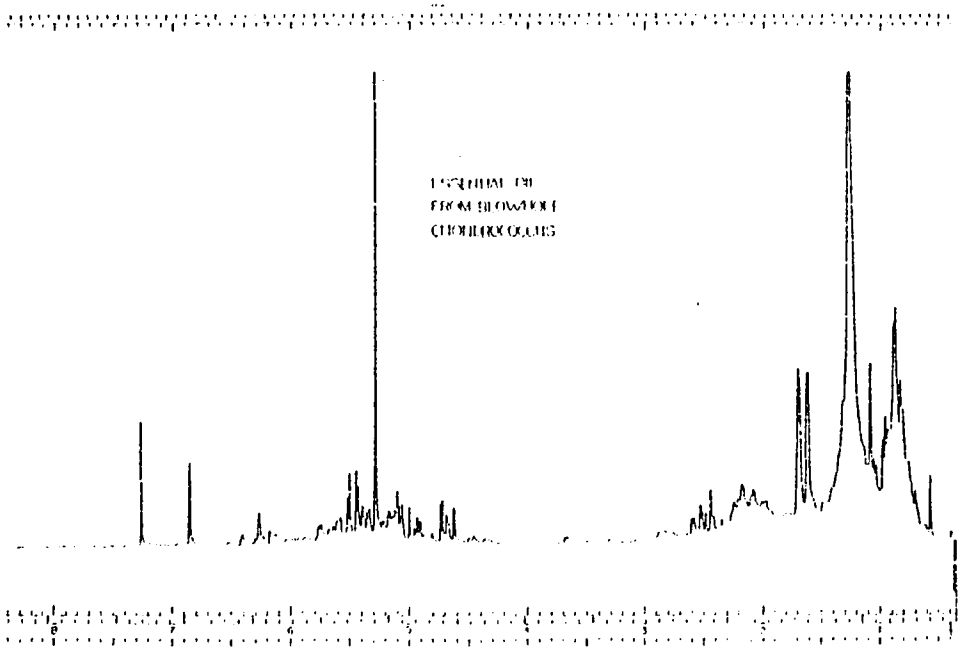


Figure I-2. Pmr spectrum ($CDCl_3$) of the essential oil from Blowhole C. hornemanni.

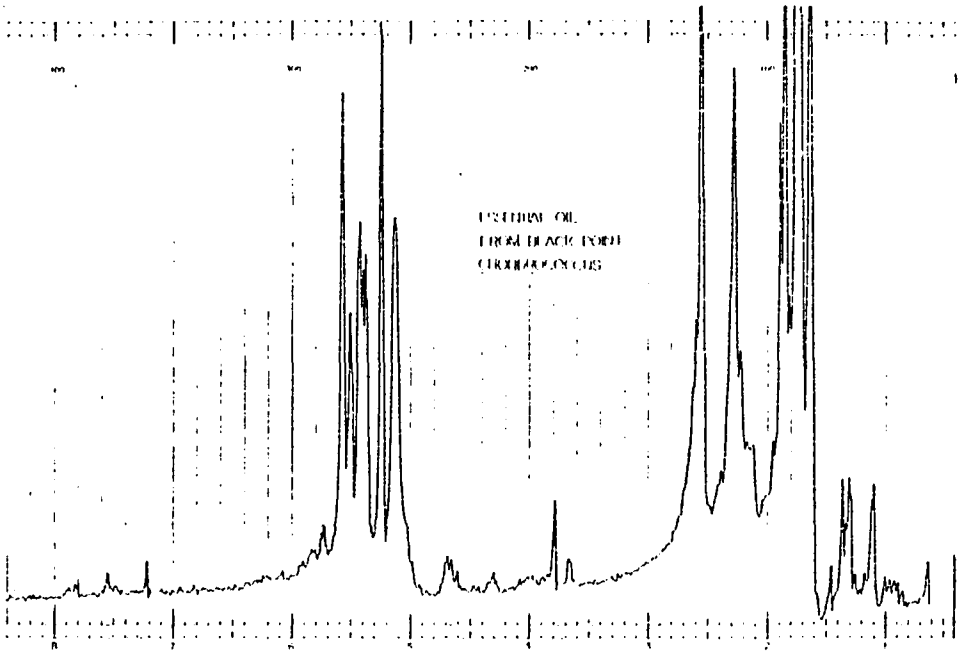
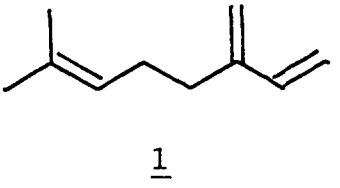


Figure I-3. Pmr spectrum ($CDCl_3$) of the essential oil from Black Point C. hornemanni.

The oils were found to separate nicely on silica gel and tentative structures had been assigned for five compounds when a group of Japanese investigators reported the results of their work on the essential oil of C. hornemanni collected from the Amami Island coasts of southern Japan.[2] The Japanese oil was found to contain the common monoterpene myrcene (1) and seven halogenated derivatives (2-8). Compounds 2-8 were shown to be present in the Blowhole and Black point oils by comparison of the reported pmr spectra and the spectra of the various essential oil fractions.



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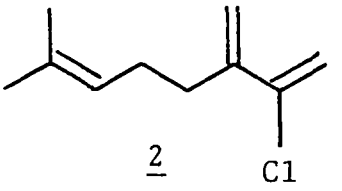

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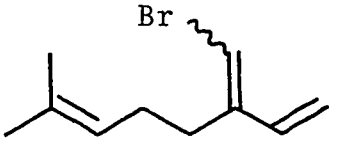
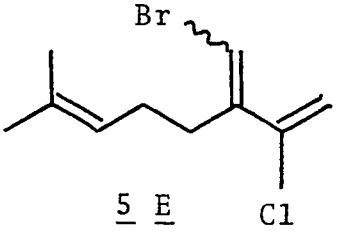


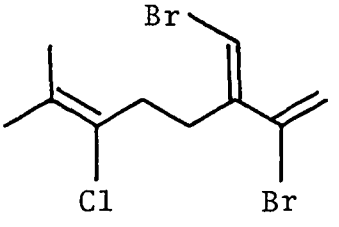
3 E

4 Z



5 E

6 Z



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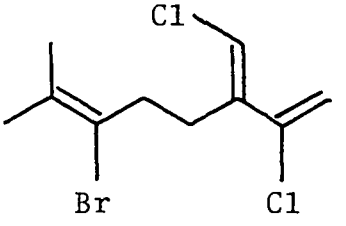

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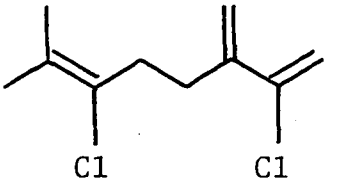
A major component (20%) of the Black Point oil, however, was found to be 2,6-dichloromyrcene (9)[3] which was not found in Japanese C. hornemanni.

The Black Point and Blowhole oils also contained a small amount (1%) of the unrelated (3S)-cis-octa-1,5-dien-3-ol (10)[4] whose structure was determined by synthesis (see Part III, p. 261) and catalytic hydrogenation to the known[5] L-(3R)-octan-3-ol (11).



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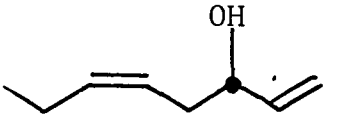

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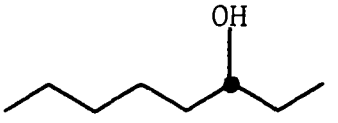

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A major constituent (15%) of the Blowhole oil was a novel, cyclic bromochloromonoterpene, chondrocole A which was accompanied by a small amount (~1%) of the epimeric chondrocole B. Chondrocoles A and B were found in small (~1%) amounts in the Black Point oil but neither was reported to be present in Japanese C. hornemanni. The relative amounts of the various constituents of the three essential oils are summarized in Table I.

The differences between these three essential oils were at first regarded as highly unusual, but more recent work[6,7] has shown other genera of red algae to exhibit this same phenomenon. For example, the nonvolatile halogenated terpenes from extracts of Microcladia species and the essential oil of Asparagopsis taxiformis[7] and A. armata[7] also vary greatly depending on the collection site. In the

TABLE I-1.

RELATIVE AMOUNTS OF CONSTITUENTS OF

C. HORNEMANNI ESSENTIAL OILS

Compound	Plant Collection Site		
	Amami Is.[a] %	Black Point[b] %	Blowhole[b] %
1	0.14	–	–
2	75.4	70	trace
3	3.56	1	trace
4	7.60	1	20
5	3.51	1	trace
6	0.68	4	50
7	0.76	trace	trace
8	1.57	trace	trace
9	–	20	trace
10	–	1	1
chondrocole A (25)	–	1	15
chondrocole B (24)	–	1	1

[a]by gc analysis

[b]estimated

case of Hawaiian C. hornemanni the two collection sites, i.e. Black Point and the Halona Blowhole, are about six miles apart and do not appear to differ significantly. Environmental parameters that might affect the metabolism of the algae such as incident sunlight, wave action, water

clarity and water temperature are comparable and both areas contain roughly equal amounts of male, female and asexual plants. Therefore, in the absence of detailed environmental and/or culturing studies, no conclusions can be drawn as to the reasons for the differences in metabolism exhibited by the two varieties of C. hornemanni.

B. Statement of Objectives

For this study the structures of the remaining unidentified constituents (chondrocoles A and B) of the essential oil of C. hornemanni were to be elucidated. In addition, the nonvolatile extracts of Black Point and Blowhole C. hornemanni were to be examined for new halogenated secondary metabolites of novel structure that might shed light on the biogenesis of the constituents of the essential oil.

II. RESULTS AND DISCUSSION

A. Fractionation of Halona Blowhole *Chondrococcus* Extract

1. Batch 1

The nonvolatile extracts from Blowhole *C. hornemanni* were obtained by extracting the vacuum dried plants with methanol followed by ether. The solvents were removed and the residue partitioned between methanol and heptane. The signals in the pmr spectrum of the heptane soluble oil (2.6%, see experimental section, p. 91) were largely attributable to compounds present in the essential oil (mostly 6 and chondrocole A) but several unidentified signals were also present in the olefinic region. The pmr spectrum of the methanol soluble oil showed only signals attributable to fatty acids and other common lipids.

Chromatography of the heptane soluble oil on a silica gel column with gradient elution gave 23 fractions (A-W) that were monitored for new compounds by pmr spectroscopy. The pmr spectrum of fraction B (19.0%) showed that it consisted almost entirely of 6 as evidenced by a sharp singlet at δ6.83, doublets (J=2 Hz) at 5.48 and 5.41 and broadened methyl singlets at 1.63 and 1.70. The pmr spectrum of fraction C (34.0%) showed small amounts of 3 and 9 and major amounts of two compounds that contained vinyl groups. Repeated chromatography of fraction C on silica gel with hexane removed

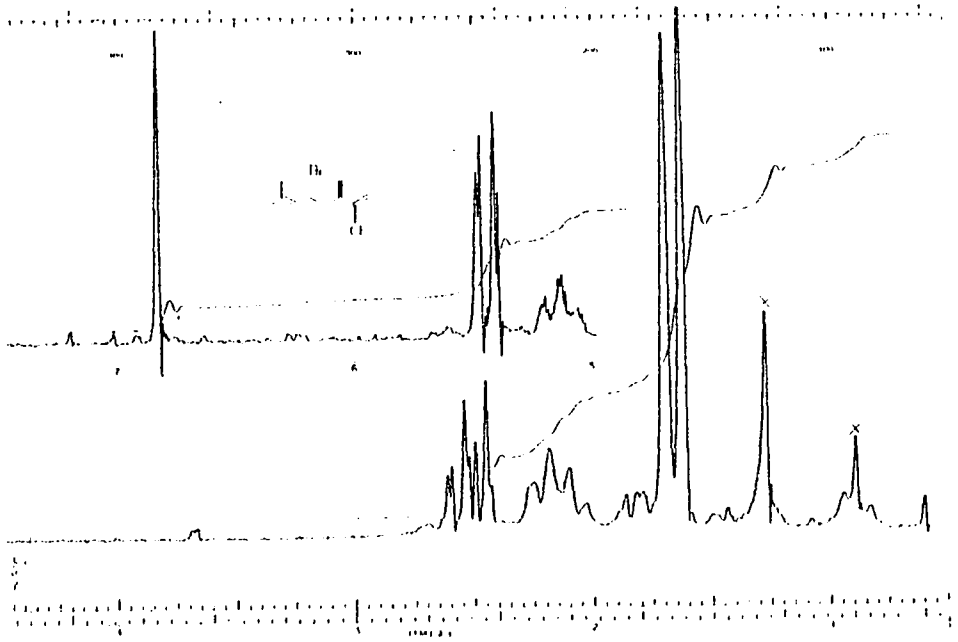


Figure I-4. Pmr spectrum ($CDCl_3$) of Compound 6.

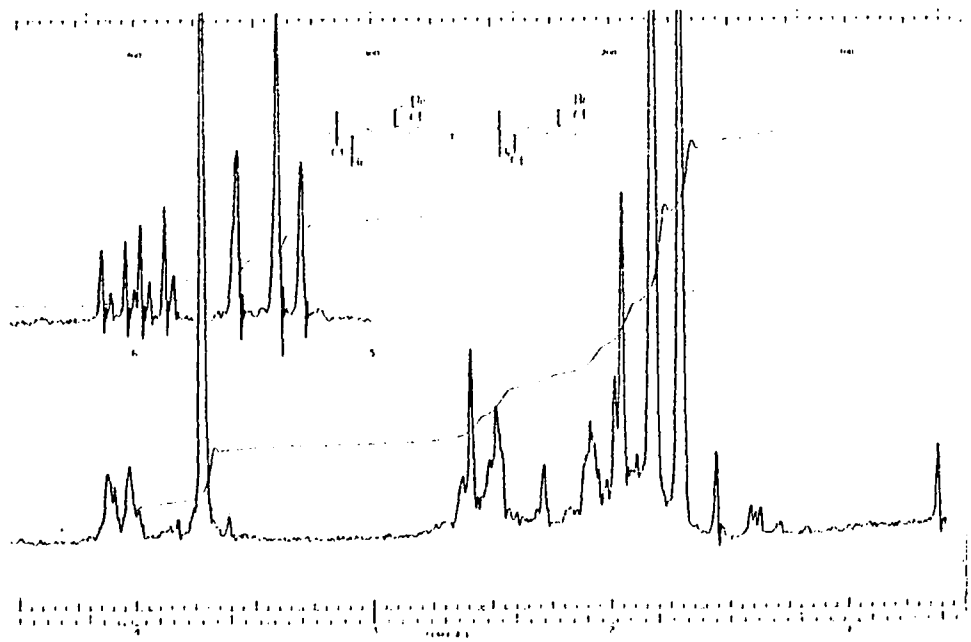


Figure I-5. Pmr spectrum ($CDCl_3$) of compounds 13 and 14.

most of the contaminants but failed to separate the two compounds. All further attempts to separate the mixture (silica gel and alumina tlc) failed. The pmr spectrum of the mixture (~3:1 ratio) exhibited an AMX pattern with two sets of doublets of doublets (X protons, J=10 and 17 Hz) at δ6.01 (major) and 5.97 (minor). The A and M protons of the two compounds were superimposed at δ5.48 (d, J=17 Hz) and 5.35 (d, J=10 Hz). The remainder of the spectrum contained two broadened doublets (J=9.5 Hz) at δ4.07 and 4.04, an AB quartet at 3.69, multiplets at 2.5 and 3.0 and three methyl singlets at 1.95 (minor), 1.80 (major and minor superimposed) and 1.70 (major). The mass spectrum of the mixture showed no molecular ions

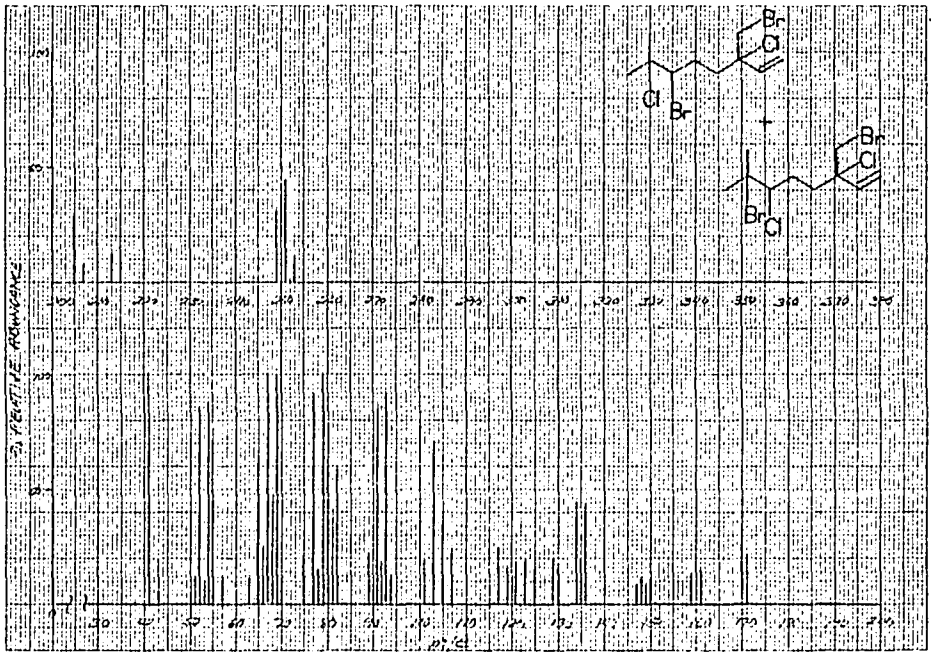
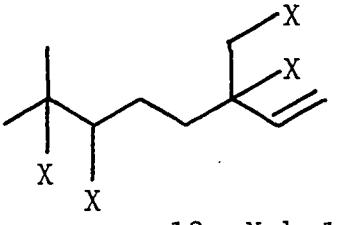


Figure I-6. Mass spectrum (70eV) of compounds 13 and 14.

but did contain a high mass cluster at 293,295,297 (1:3:1) for $C_{10}H_{15}Br_2$. Combustion analysis confirmed the molecular formulae of the two compounds as $C_{10}H_{16}Br_2Cl_2$. These data strongly suggested that the compounds were isomers of the tetrahalotetrahydromyrcene 12. The cmr



12 X=halogen

spectrum of the mixture showed the major component to possess two quaternary carbons bearing chlorine (71.8, s and 71.9, s), a bromomethine carbon (64.9, d) and a bromomethyl group (40.2, t) which confirmed 14 as the structure.

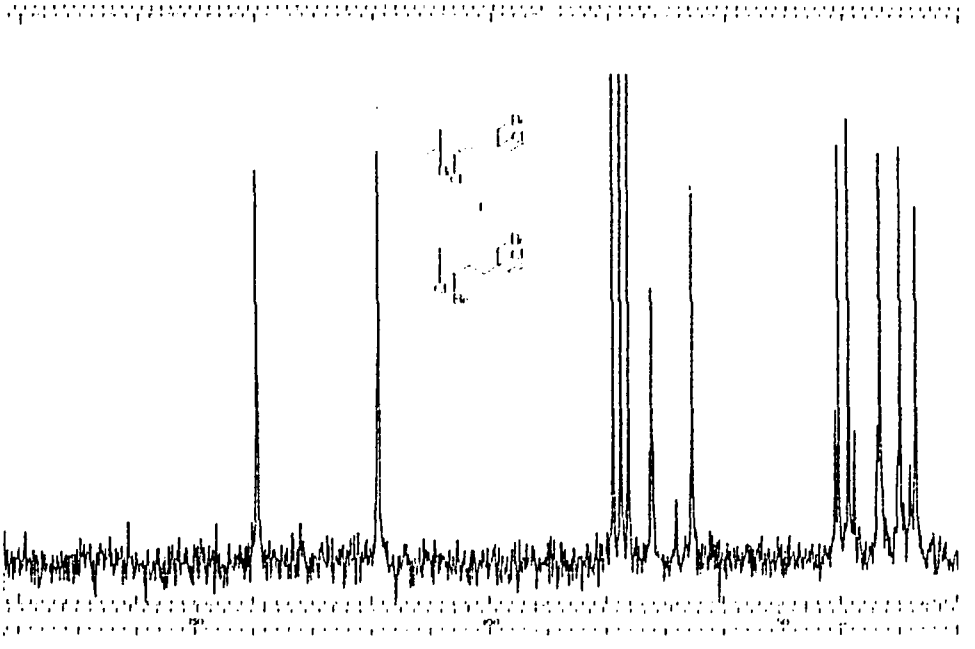


Figure I-7. Cmr spectrum ($CDCl_3$) of compounds 13 and 14.

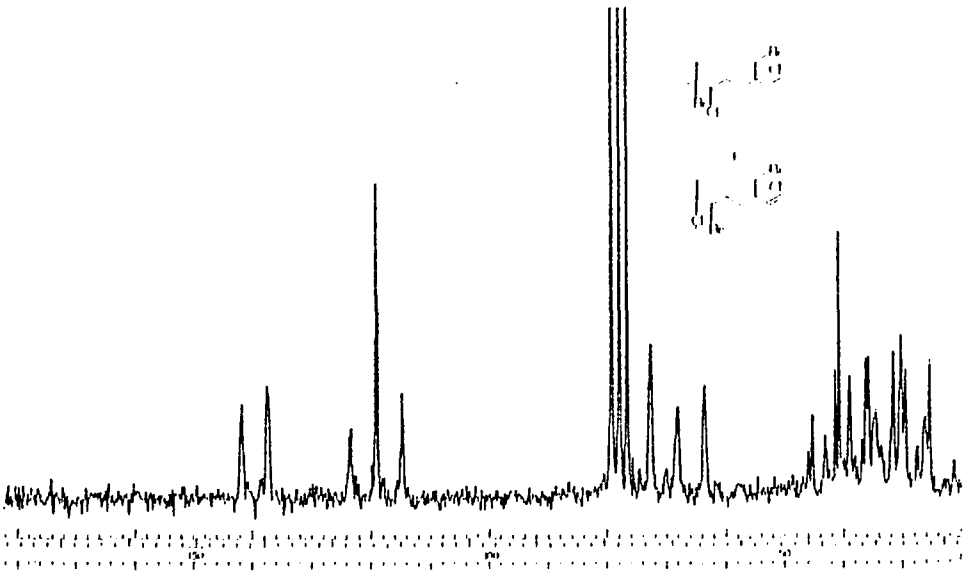
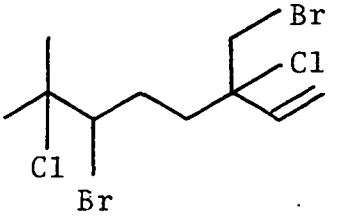
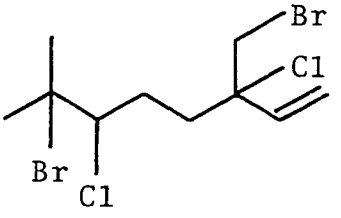


Figure I-8. Cmr off-resonance spectrum ($CDCl_3$) of compounds 13 and 14.



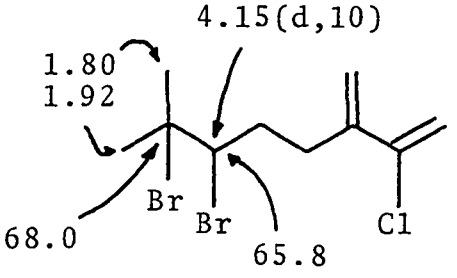
13



14

The downfield positions of the methyl groups of the minor component implied that the bromine atom at C-6 and chlorine atom at C-7 of 14 were reversed as shown in structure 14. In support of this argument the cmr spectrum of the minor component showed a bromomethyl group at 40.8, bromine and chlorine bearing quaternary carbons at 67.5 and 72.1 respectively and a chloromethine

carbon at 71.4 ppm. Final confirmation for structures 13 and 14 was obtained by comparing their pmr and cmr spectra with those of model compounds 15 (from 2 and bromine) and 16 (from 1 and sulfuryl chloride) prepared by Dr. B. J. Burreson.[8]



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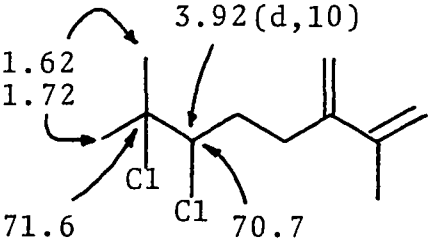
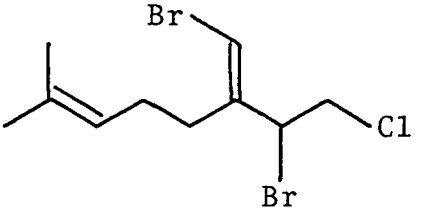


16

Also obtained by repeated chromatography of fraction C on silica gel was a small amount (1%) of (Z)-1-bromo-2-(1-bromo-2-chloroethyl)-6-methyl-1,5-heptadiene (17).



17

The pmr spectrum of 17 showed broadened methyl singlets at δ1.67 and 1.73 and a broad multiplet at 5.2 characteristic of the isopropenyl group and a sharp singlet at 6.46 for the olefinic bromomethine proton. Also

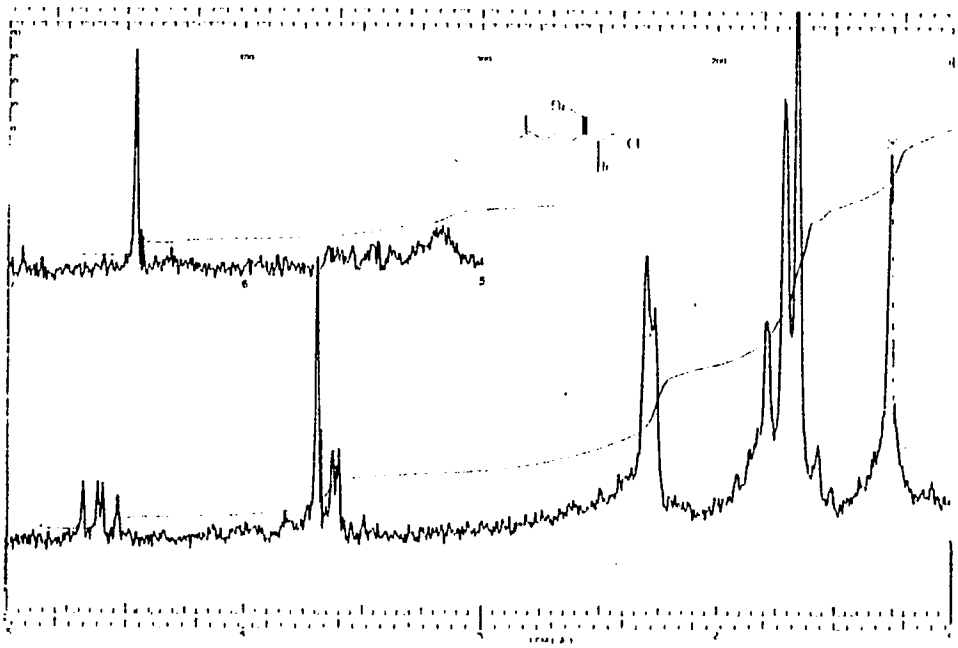


Figure I-9. Pmr spectrum ($CDCl_3$) of compound 17.

present in the spectrum was an ABX pattern at δ4.61 (dd, X part, J=6.5 and 8.5 Hz, 1H) and 3.6 (AB part, J_{gem} = -11 Hz, 2H). The mass spectrum exhibited a weak

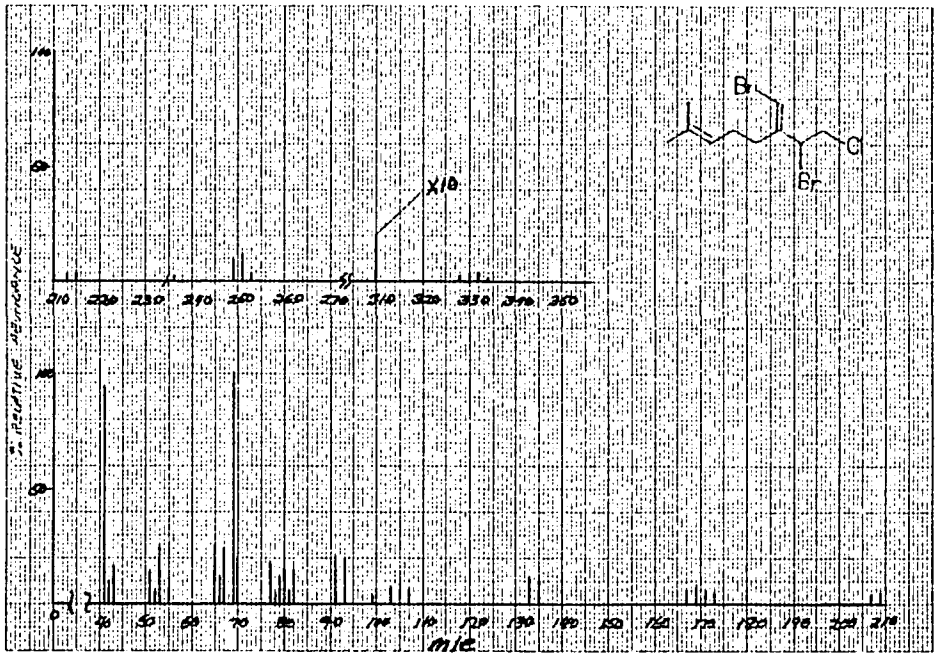


Figure I-10. Mass spectrum (70eV) of compound 17.

molecular ion at m/e 328,330,332,334 ($C_{10}H_{15}Br_2Cl$) and a strong ion cluster at m/e 249,251,253 that corresponded to a loss of the allylic bromine atom. The cmr spectrum showed a bromomethine carbon at 62.7 and a chloromethylene carbon at 60.2 ppm. Finally, the geometry of the

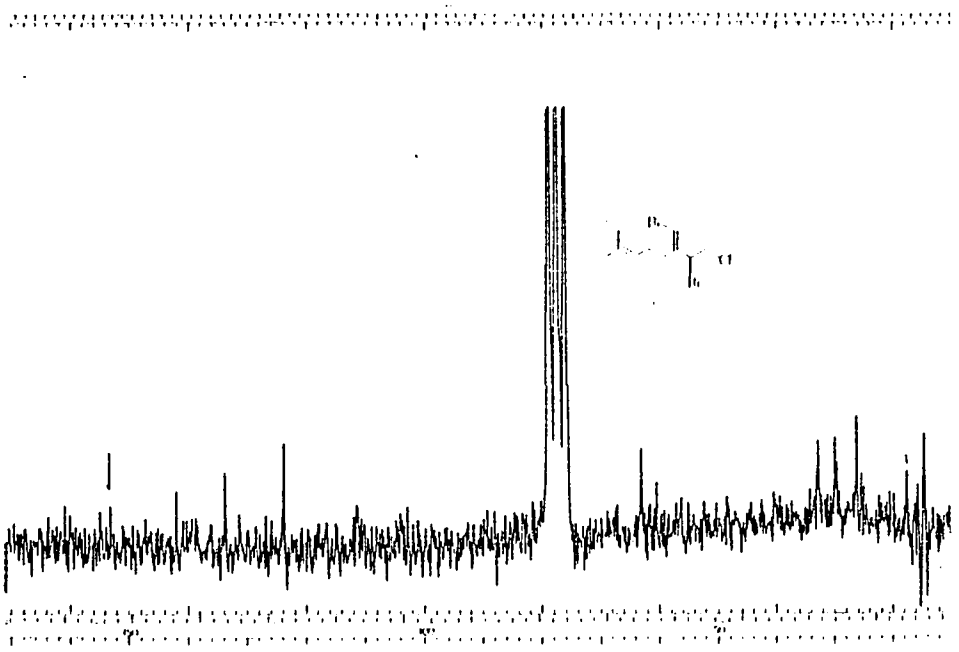


Figure I-11. Cmr spectrum ($CDCl_3$) of compound 17.

bromomethylene group was shown to be Z by chromous sulfate dehalogenation of 17 to 4 which had a retention time identical to that of the naturally occurring compound.

Fraction F (3%), eluted with 2% methylene chloride/hexane, was rechromatographed on silica gel to give a small amount of an unstable compound. The pmr spectrum exhibited a sharp singlet at δ6.89 (1H) and broadened

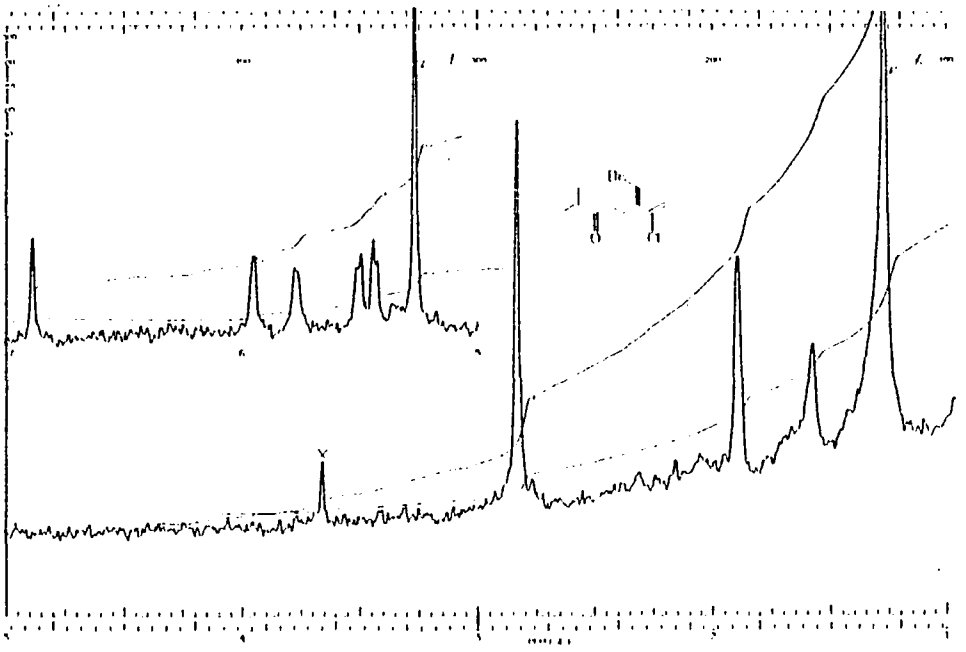
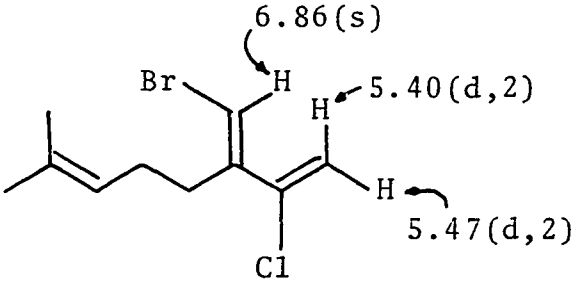
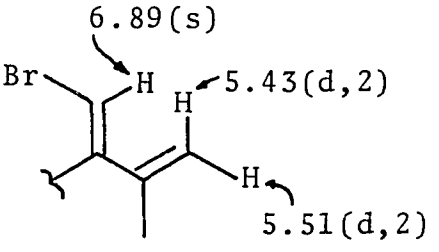


Figure I-12. Pmr spectrum ($CDCl_3$) of compound 21.

doublets (J=2 Hz) at 5.51 and 5.43. Partial structure 18 was assigned to the molecule by comparing these chemical shifts with those of the Z-bromochloro-butadiene moiety of 6. The remainder of the spectrum

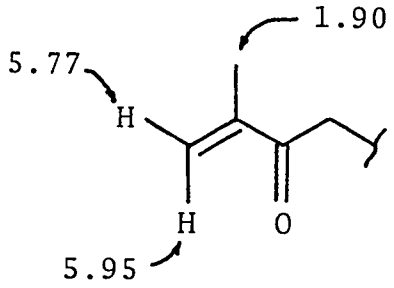


6

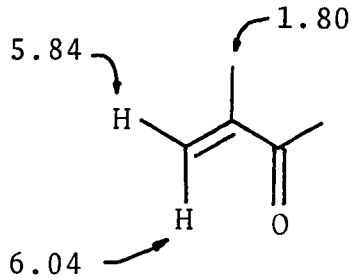


18

contained two broadened 1H singlets at δ5.95 and 5.77, a singlet (4H) at 2.74 and a broadened methyl singlet at 1.90. These latter signals were suggestive of partial structure 19 and compared favorably with the published[9] spectrum of 2-methyl-1-buten-3-one (20).



19



20

The infrared spectrum showed a strong absorption at 1680 cm^{-1} and confirmed the presence of an

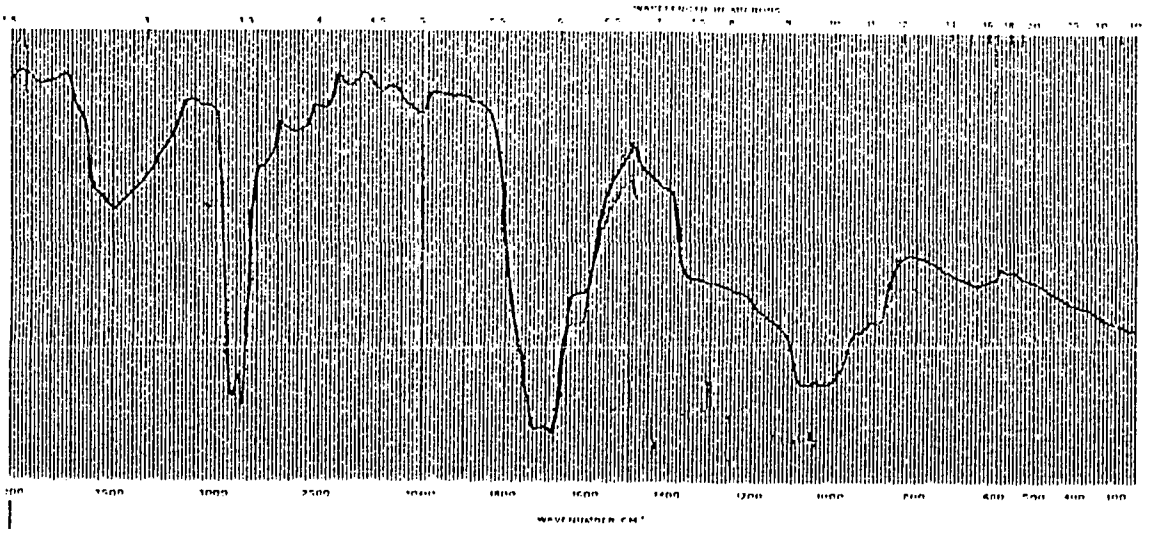
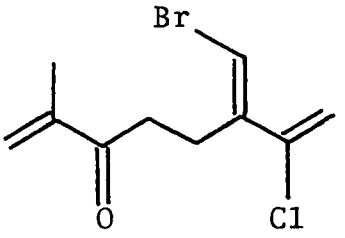


Figure I-13. Ir spectrum (neat) of compound 21.

α,β-unsaturated carbonyl system. Combining partial structures 18 and 19 with an additional methylene group provided 21 as the structure for the new compound.



2.74(s)

21

Unfortunately 21 decomposed before additional data could be obtained.

Fractions I-L (23.5%), eluted with 10% methylene chloride/hexane, contained nearly pure chondrocole A whose structure was determined by complete spectral analysis. The mass spectrum showed a molecular ion at m/e (rel. intensity) 264 (12), 266 (14), 268 (5) for $C_{10}H_{14}BrClO$ that readily loses bromine to give the base peak at m/e 185 (100), 187 (33) which in turn loses hydrochloric acid to give a peak at m/e 149 (28). The infrared spectrum was devoid of hydroxyl and carbonyl absorptions but did contain a strong C–O stretching band at 1080 cm^{-1} for an ether linkage and a doublet at 1360 and 1370 cm^{-1} for a geminal dimethyl group. The pmr spectrum showed two 3H singlets at δ1.15 and 1.33 for

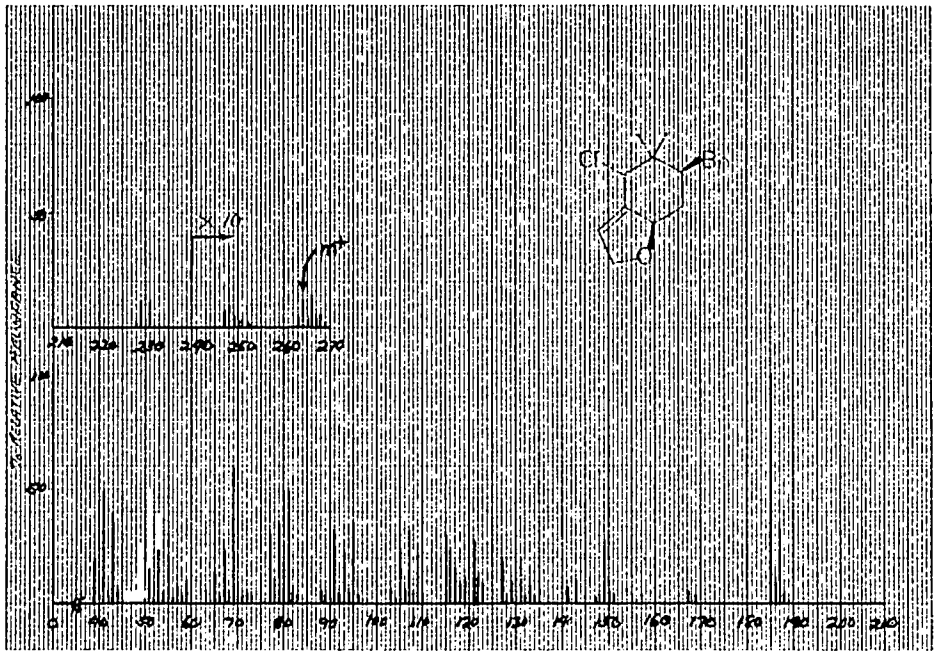


Figure I-14. Mass spectrum (70eV) of chondrocole A (25).

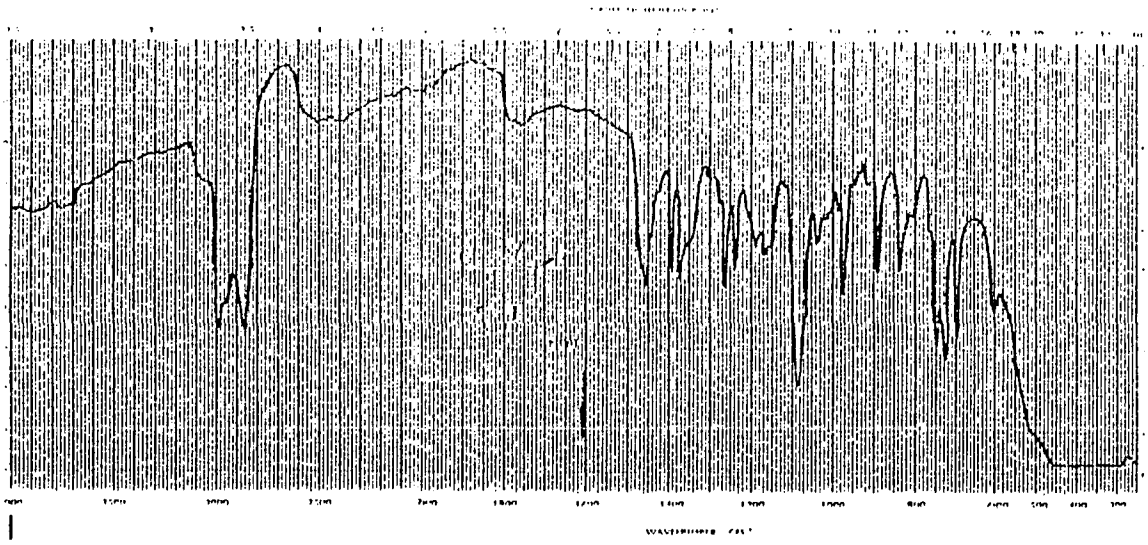


Figure I-15. Ir spectrum (neat) of chondrocole A (25).

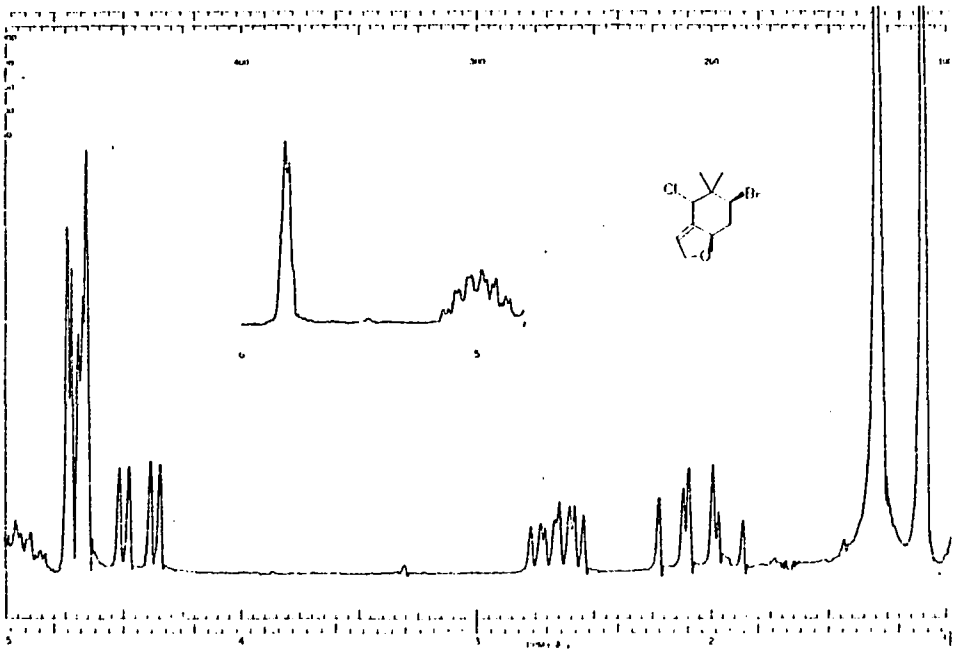
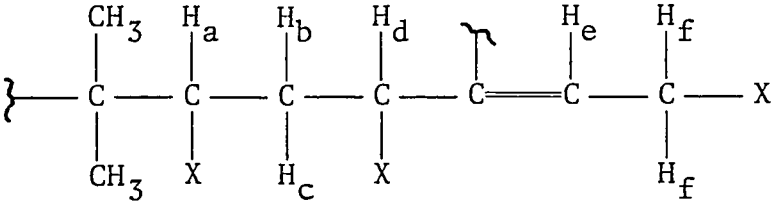


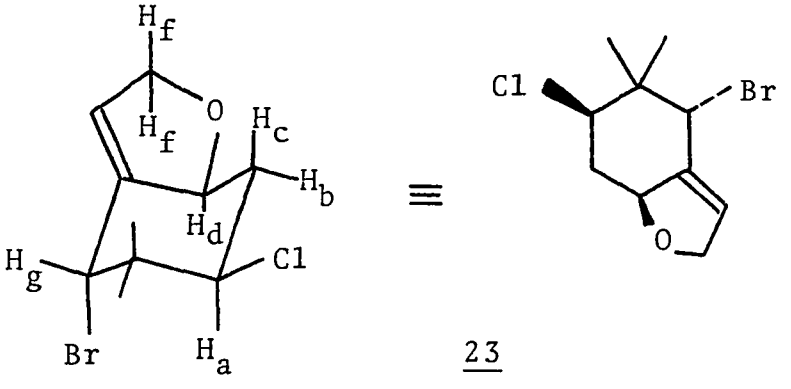
Figure I-16. Pmr spectrum ($CDCl_3$) at chondrocole A (25).

the geminal methyl groups and 1H multiplets at 2.65 and 2.05 for the nonequivalent protons of a methylene group in a six-membered ring. Complete decoupling of the pmr spectrum revealed the presence of partial structure 22 in which X denotes an electronegative substituent. Proton a (δ4.45, dd) was coupled by



22

4 and 13 Hz to H_b and H_c which were also coupled to each other by 12 Hz. In addition, H_b and H_c were coupled by 6 and 10 Hz to H_d (δ5.0, m) which was in turn coupled allylically by 2 Hz to H_e (δ5.78, m) and homoallylically to H_f (δ4.72, dd) by 5 Hz. The magnetically equivalent H_f protons were found to be vicinally coupled to H_e by 2 Hz. The remaining proton in the spectrum (H_g) resonated as a sharp singlet at δ4.64. With these data structure 23 was assigned to chondrocole A.[3] The



23

relative stereochemistry of the chlorine and ether linkage in 23 was deduced from the appropriate coupling constants and the bromine atom was placed in the allylic position to explain the facile loss of bromine from the molecular ion in the mass spectrum. The absence of allylic coupling between H_g and H_e in 23 could only be explained if the bromine atom was axially disposed.[10] In the epimeric chondrocole B (24), which was not found in the extract, H_g and H_e are coupled allylically by 2 Hz.

The cmr spectrum was consistent with 23 and exhibited

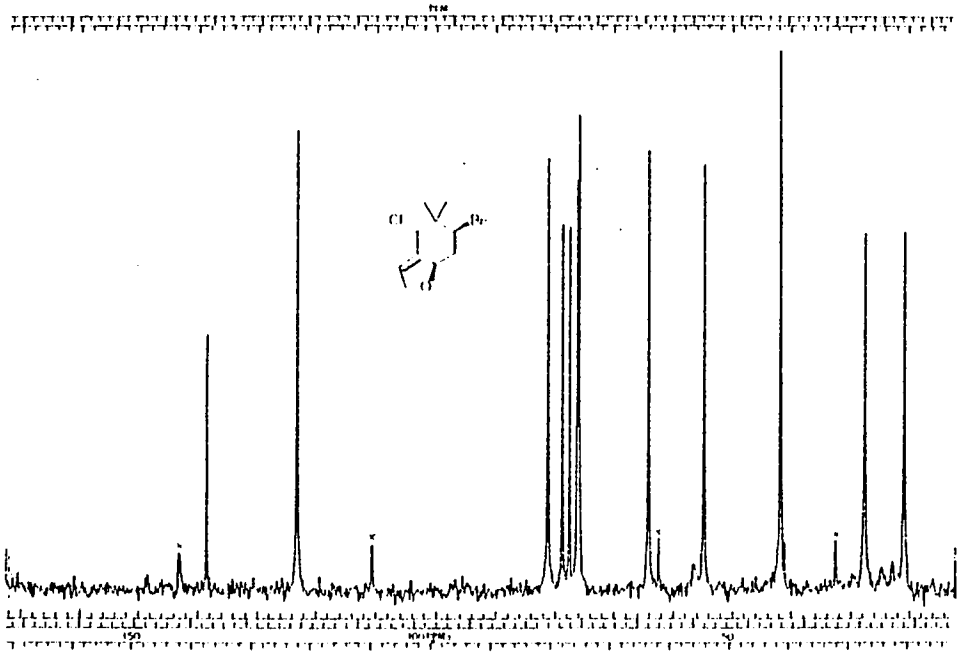


Figure I-17. Cmr spectrum ($CDCl_3$) of chondrocole A (25).

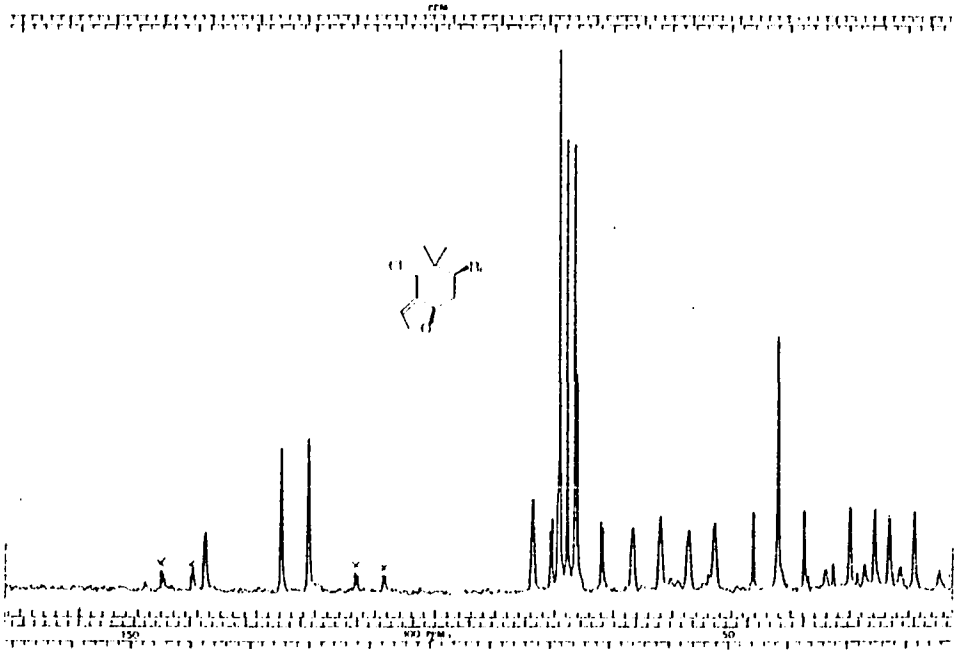
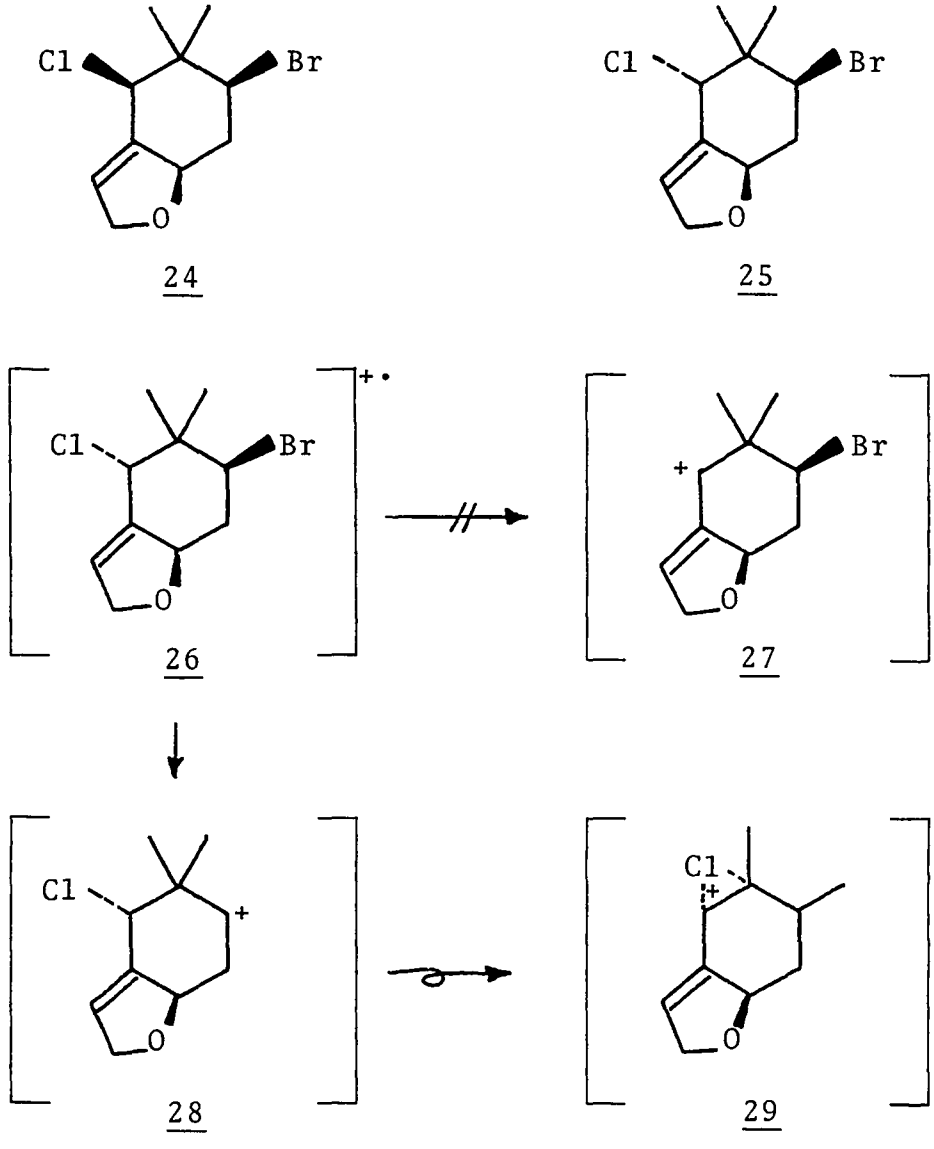


Figure I-18. Cmr off-resonance spectrum ($CDCl_3$) of chondrocole A (25).

two quartets at 21.0 and 27.6, two triplets at 41.7 (C-7) and 75.4 (C-2), four doublets at 54.4 (C-4), 63.8 (C-6), 80.7 (C7a) and 122.3 (C-3) and two singlets at 41.7 (C-5) and 137.6 (C-3a) ppm.

Although all of the data presented above supported structure 23, an x-ray crystallographic study of the related compound chondrocolactone (see pp. 49-50) showed that the actual structures of chondrocoles A and B are 25 and 24 respectively in which the bromine and chlorine are reversed. Structure 25 shows the absolute configuration of chondrocole A in which the configurations of C-4, C-6 and C-7a are R, S and R respectively. The facile loss of bromine from the molecular ion of 25 (26) in the mass spectrum rather than the expected loss of the allylic chlorine is partially explained by close examination of a model of 25. The resulting allylic carbonium ion (27) cannot achieve planarity without moderate distortion of the cyclohexane ring. In addition, loss of the bromine atom followed by rapid methyl group migration would give the stable tertiary carbonium ion which could be further stabilized by the neighboring chlorine atom (28 → 29).



Fraction R (1.0%) contained a compound whose pmr spectrum exhibited a singlet at δ6.87 and doublets (J=2 Hz) at 5.54 and 5.44 that again indicated the presence of partial structure 19. In addition, the chromatographic behavior of the compound, which eluted

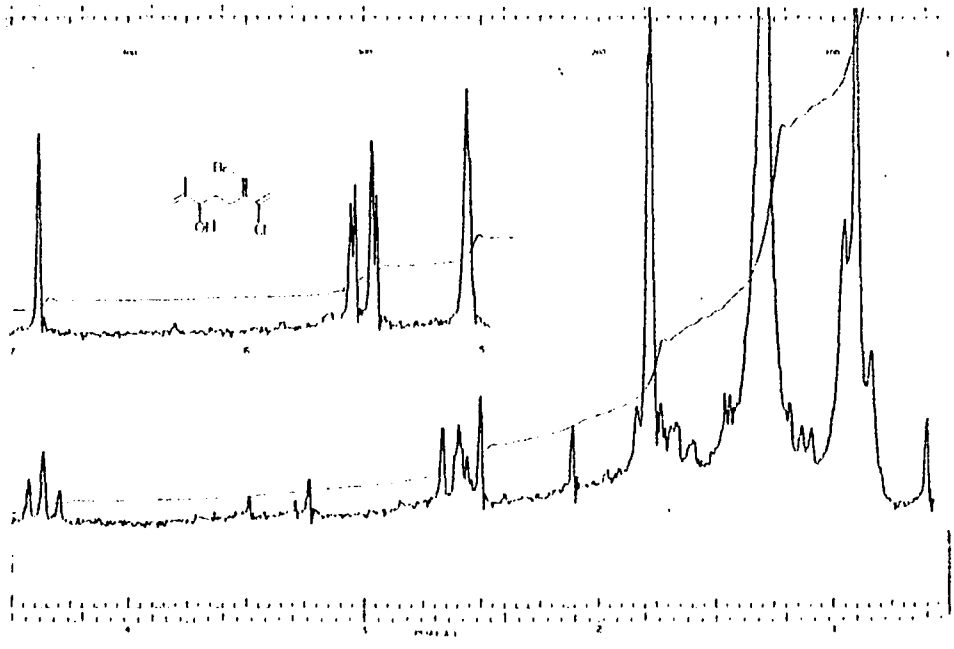
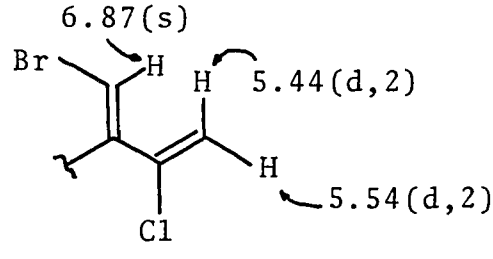


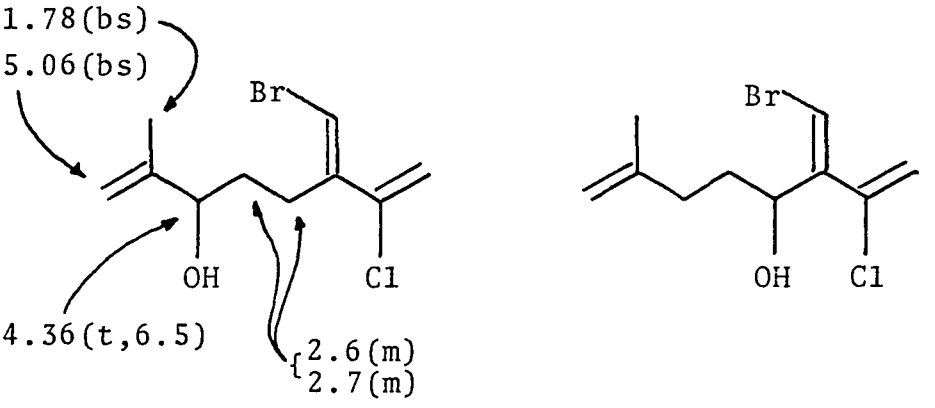
Figure I-19. Pmr spectrum ($CDCl_3$) of compound 30.



19

with 1:1 methylene chloride/hexane, and the presence of a 1H triplet (J=6.5 Hz) at δ4.36 in the pmr spectrum indicated the presence of a hydroxy group. The remainder of the pmr spectrum contained a broadened 2H singlet at δ5.06, 2H multiplets at 2.6 and 2.7 and

a methyl singlet at 1.78. These data were consistent for both structures 30 and 31. Structure 30 is most



30 31

likely correct in light of the isolation of ketone 21 but 31 cannot be ruled out without additional evidence since C-4 hydroxymyrcene derivatives may be precursors of the chondrocoles. As with fraction F, fraction R rapidly decomposed in solution ($CDCl_3/CH_2Cl_2$) at -20° before additional data could be obtained.

Fractions S and T (4.5%) also eluted with 1:1 methylene chloride/hexane and contained a small amount of 30 (or 31) along with substantial amounts of a new compound. The pmr spectrum showed evidence for partial structure 19 for the new compound by exhibiting a singlet at δ6.98 and two 1H doublets (J=2 Hz) at 5.47 and 5.54. However, an additional 2H doublet (J=2 Hz) was also

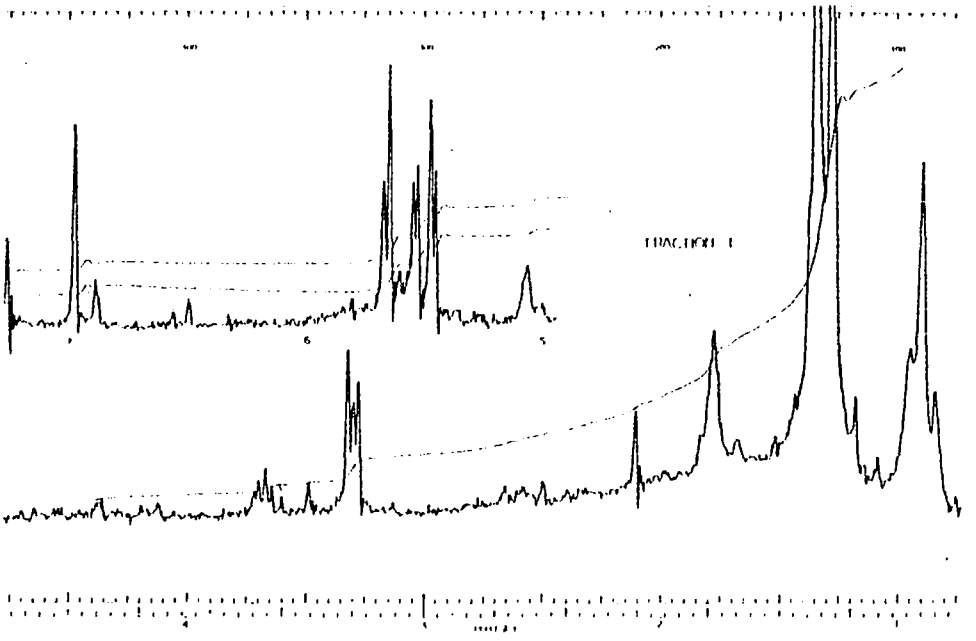
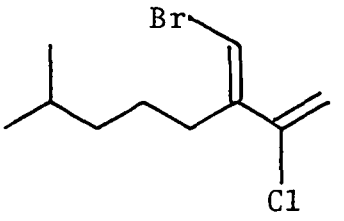


Figure I-20. Pmr spectrum ($CDCl_3$) of fraction T.

present at δ5.66 which indicated the presence of a second terminal methylene group. The remainder of the spectrum contained an ABX pattern at δ3.67 (X part) and 3.30 (AB part), a 2H multiplet at 1.78 and two methyl singlets at 1.45 and 1.38. These data are contradictory in that a single myrcene carbon skeleton will not accommodate all of the functional groups that appear to be present. For example, partial structure 32 incorporates partial structure 18 but the addition of another double bond for the second terminal methylene group and a halogen to account for the ABX pattern removes three of the required 16 hydrogens.



32

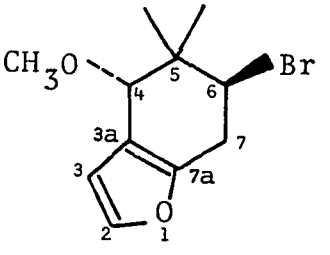
In addition the presence of the two methyl groups at high field precludes a double bond at the terminus of 32. Therefore fractions S and T most likely contain a mixture of closely related compounds but, unfortunately, they were highly unstable and decomposed before further fractionation could be attempted.

2. Batch 2

To reisolate and identify the unstable compounds found during the first fractionation of Blowhole C. hornemanni small amounts of plants were collected between September 1975 and March 1976. Approximately 50% of the plants were collected from rocky shelves in the cove near the Halona Blowhole and the remainder were collected at a depth of 3 m while Scuba diving near the mouth of the cove. The plants from the various collections were quickly frozen and stored at -20° in a freezer until needed. The plants collected from the

rocky shelves were kept separate from those collected from the bottom until it was found that the respective essential oils had identical pmr spectra. The vacuum dried plants were then combined and extracted as before but this time the crude extract was partitioned between methylene chloride and water instead of methanol and hexane. In this manner 12.8 g of salt-free extract was obtained.

Fractions 1 (33.5%), 2 (9.0%) and 3 (2.3%) contained large amounts of 6, 13 and 14 and were not investigated further. Close examination of the fractions eluting with 2-5% methylene chloride/hexane revealed no trace of ketone 21 but fractions 10 and 11 (3.1%), which eluted with 25% methylene chloride/hexane, did contain a new compound that was not found in the first fractionation of the extract. Rechromatography of these fractions on Sephadex LH-20 gave a small amount (0.9%) of methoxychondrocole furan (33). The molecular formula



33

of 33 was established as $C_{11}H_{15}BrO_2$ by high resolution mass measurement of the weak molecular ion cluster at m/e 258,260. Like chondrocole A (25) the molecular ion

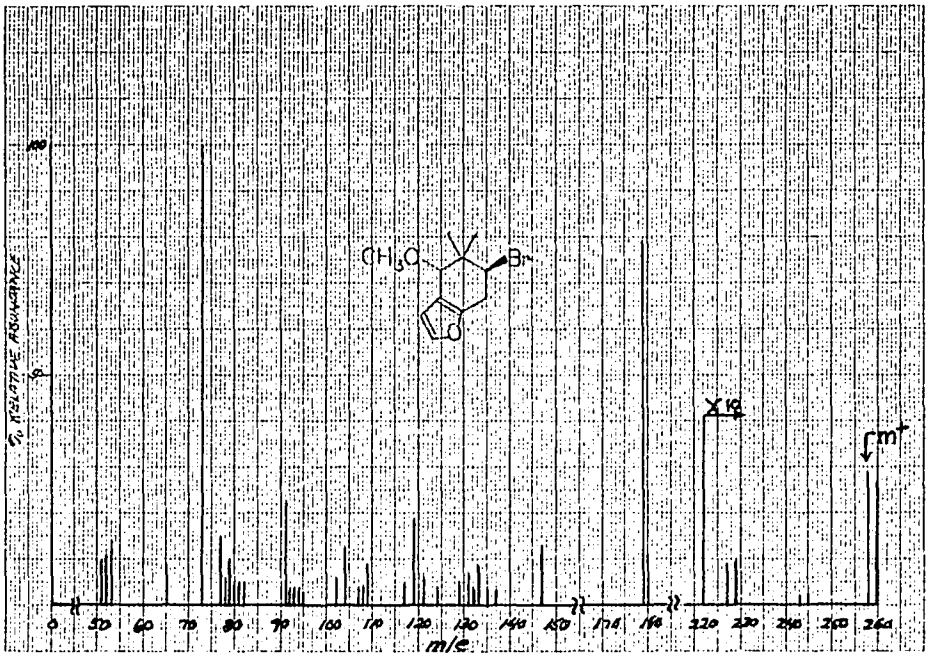


Figure I-21. Mass spectrum (70eV) of methoxychondrocole furan (33).

of 32 readily loses bromine to give a strong peak at m/e 179 and also loses OCH_3 to give a weak cluster at m/e 227,229. The pmr spectrum of 33 exhibited singlets at δ0.99 and 1.20 for the geminal methyl groups, a singlet at 3.36 for the methoxy methyl and doublets (J=1.5 Hz) at 6.30 and 7.13 for the two furan protons. Supporting the presence of the furan ring was a maximum at 223 nm (ε=4300) in the ultraviolet spectrum and two strong absorptions at 1075 and 1090 cm^{-1} in the infrared

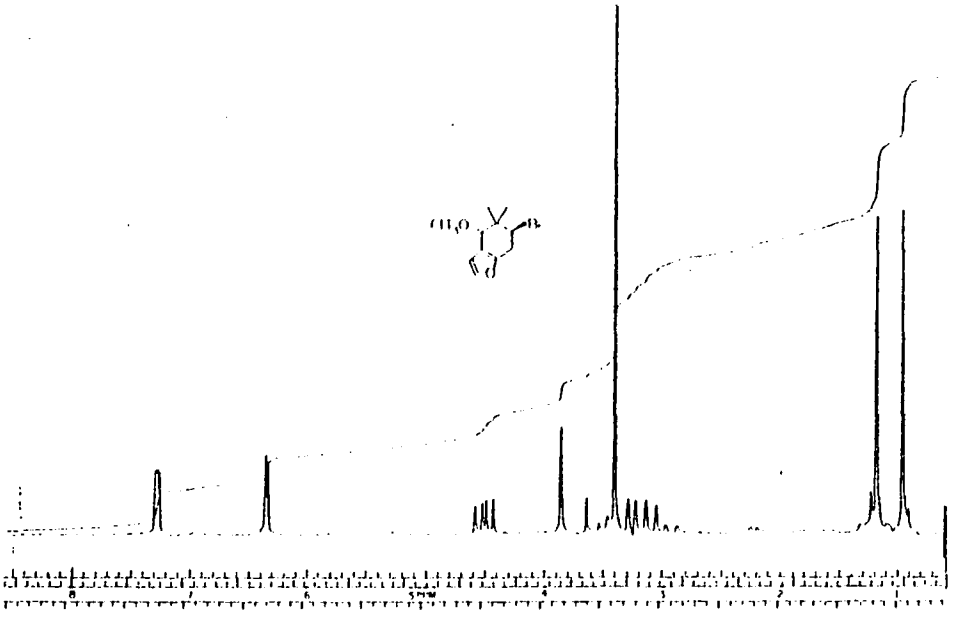


Figure I-22. Pmr spectrum ($CDCl_3$) of methoxychondrocole furan (33).

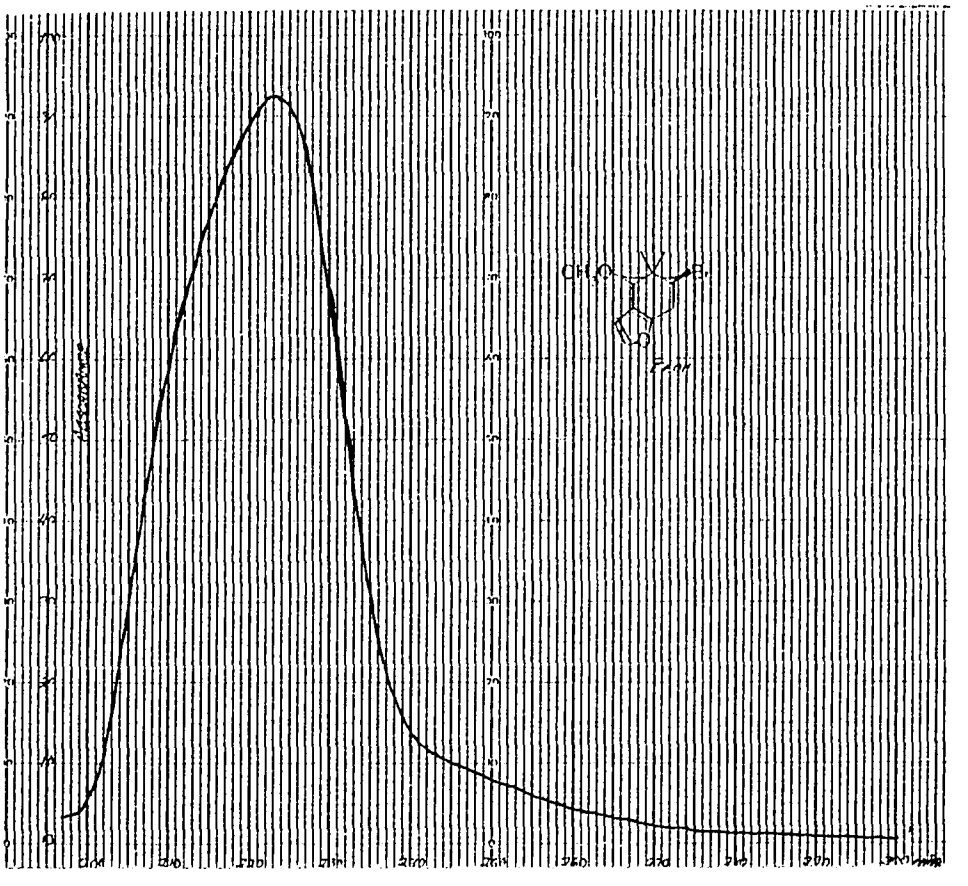


Figure I-23. Uv spectrum (EtOH) of methoxychondrocole furan (33).

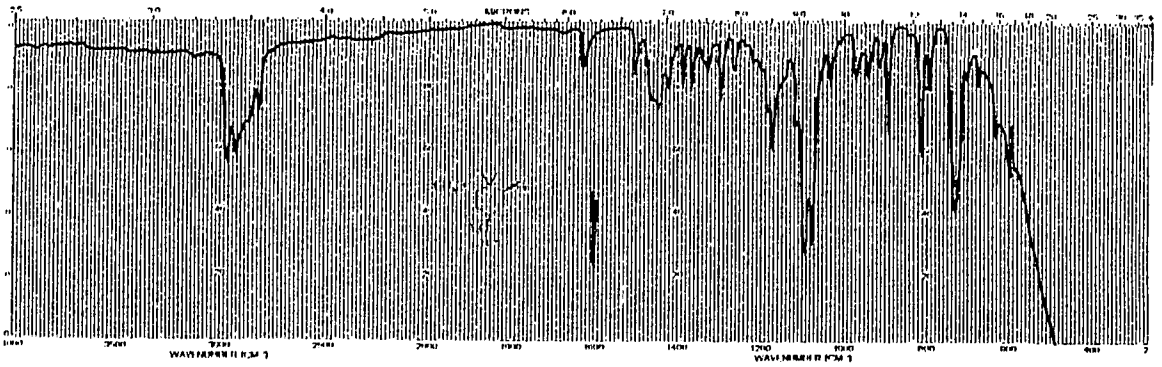


Figure I-24. Ir spectrum (neat) of methoxychondrocole furan (33).

spectrum. The cmr off-resonance spectrum was consistent with structure 33 and contained three singlets at 148.6 (C-7a), 117.0 (C-3a) and 40.9 (C-5), four doublets at 141.3 (C-2), 110.3 (C-3), 80.0 (C-4) and 56.4 (C-6), one triplet at 33.1 (C-7) and three quartets at 57.8 (OCH_3), 24.7 and 20.4 (geminal methyls) ppm.

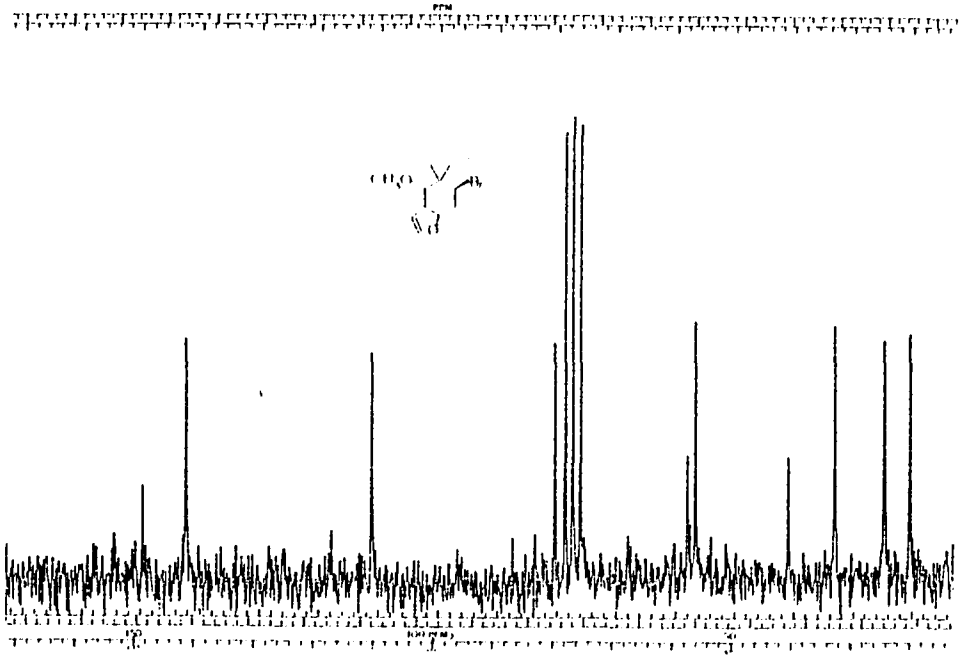


Figure I-25. Cmr spectrum ($CDCl_3$) of methoxychondrocole furan (33).

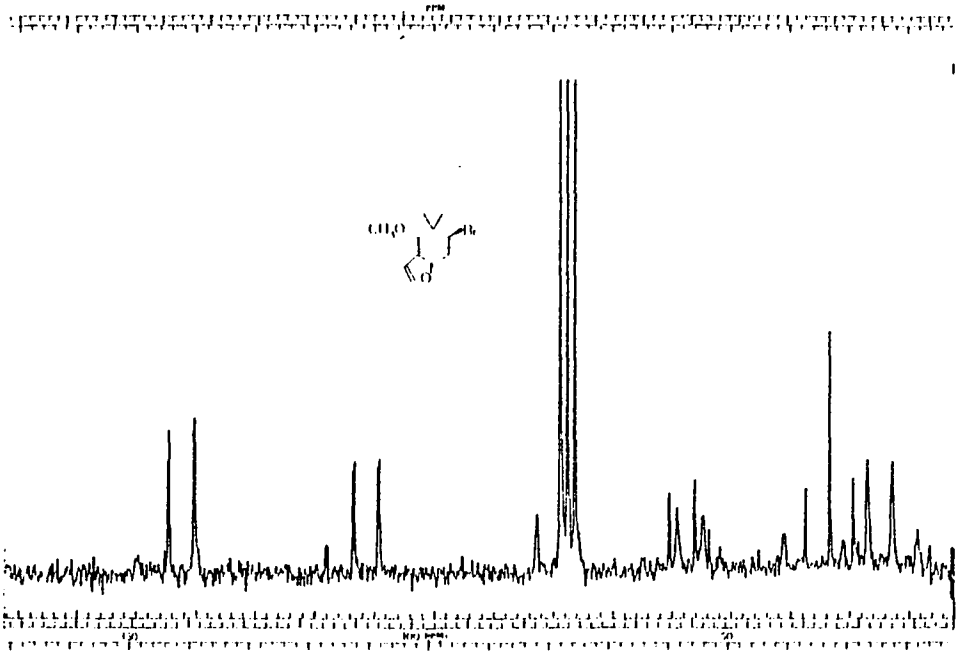
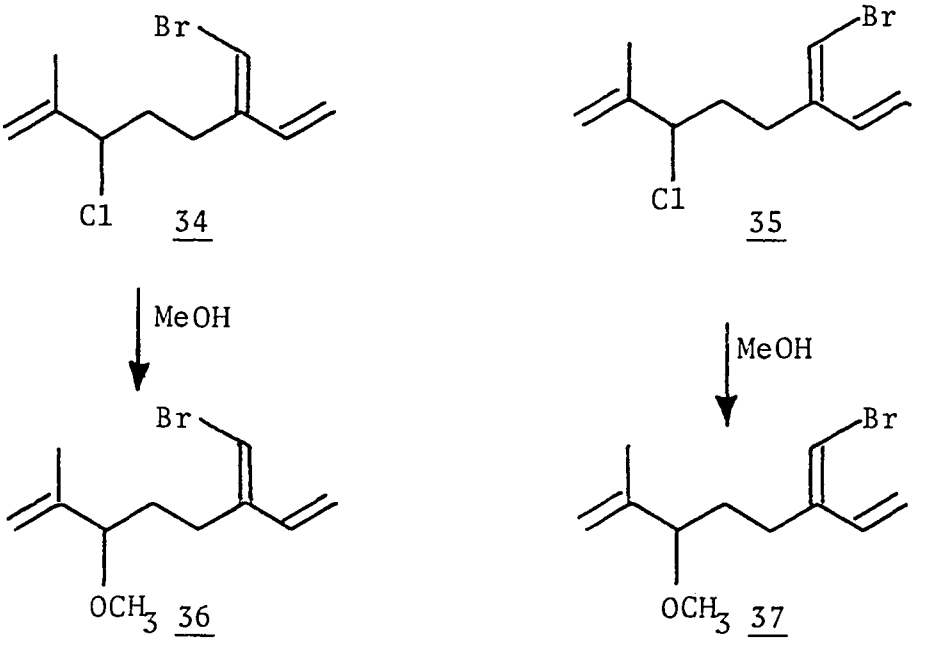


Figure I-26. Cmr off-resonance spectrum ($CDCl_3$) of methoxychondrocole furan (33).

The positions of the bromine and methoxy group in 33 were defined by single frequency off-resonance decoupling experiments. Irradiation of the doublet of doublets (J=6 and 10 Hz) at δ4.46 in the pmr spectrum caused the doublet at 56.4 ppm in the cmr spectrum to collapse to a singlet whereas irradiation of the singlet at δ3.87 collapsed the doublet at 80.0 ppm. Thus the bromine was placed on C-6 and the methoxy group on C-4. The bromine was concluded to be held equatorial due to the large coupling between the bromomethine and adjacent methylene protons (δ3.1, m, 2H). The methoxy group was tentatively assigned to an axial position due to the absence of allylic coupling between

the methoxy methine and the C-4 olefinic proton.

The presence of the methoxy group in 33 initially led to speculation that this compound might be an artifact formed during the extraction of the dried seaweed with methanol. For example, Naya and coworkers found that compounds 34 and 35, isolated from Desmia (Chondrococcus) japonicus, rapidly react with methanol to form methoxy derivatives 36 and 37.[11] However, refluxing chondrocole A (25) in methanol for 16 hours provided only unchanged starting material and therefore the formation of 33 from a chondrocole-like precursor during the extraction process seems rather unlikely.



Fractions 12-16 (23.1%) contained mostly chondrocole A (25) but the pmr spectra of fractions 15 and 16 contained an additional doublet of doublets (J=4 and 13 Hz) at δ3.87 that was not attributable to 25. Rechromatography of fractions 15 and 16 on silica gel with 40% methylene chloride/hexane gave six fractions in which the new compound was concentrated in fraction 4. However, this fraction rapidly decomposed before further purification could be attempted.

The fractions eluting from the column with 1:2 and 1:1 methylene chloride/hexane were carefully examined for the unstable compounds present in fractions R-T in the first extraction (see pp. 25-29). The pmr spectra of the crude oils were recorded in methylene chloride-d_2 to prevent acid catalyzed decomposition but no trace of these compounds could be found. Instead, fractions 19 and 20 (4.4%) were found to contain a cyclic diacetate that was also found in trace amount (ca. 5 mg crude) but not identified in the first extraction. Chromatography of fractions 19 and 20 on Sephadex LH-20 provided a small amount (1.1%) of nearly pure oil whose pmr spectrum showed a 6H singlet at δ2.07 for the two acetate methyl groups and a 6H singlet at 1.15. The compound did not show a molecular ion in the mass spectrum but did exhibit an ion cluster at m/e 331,333 for $C_{14}H_{20}BrO_4$. Subtracting the contribution of the two acetate groups ($C_4H_6O_4$) from

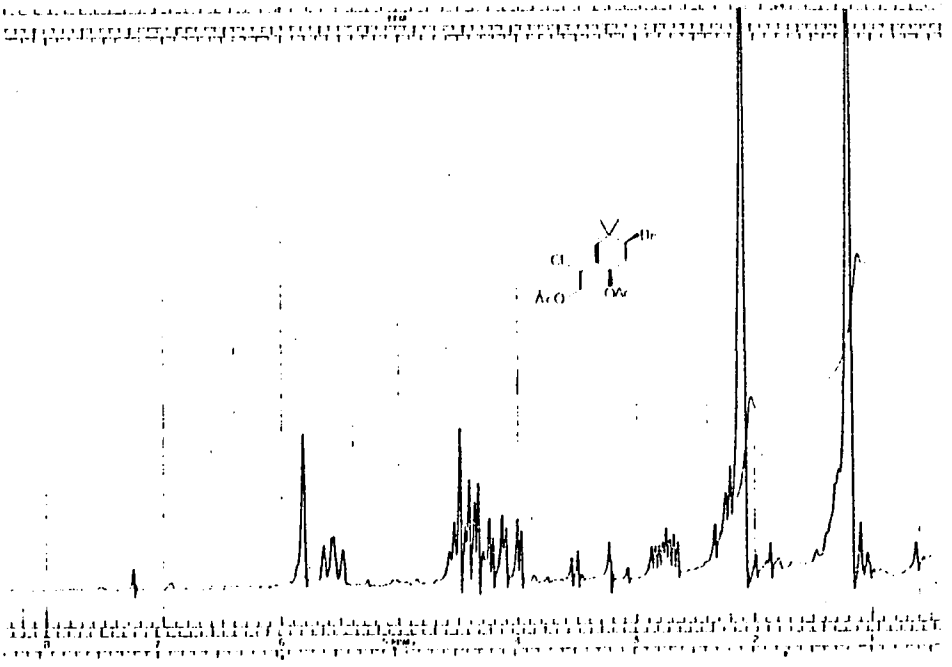


Figure I-27. Pmr spectrum ($CDCl_3$) of hornediol diacetate (41).

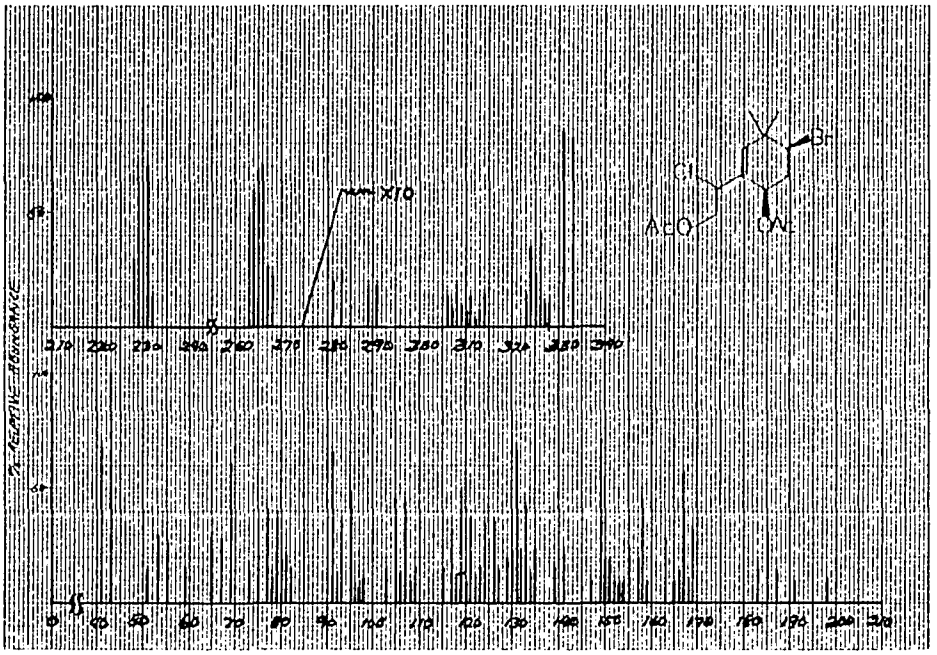


Figure I-28. Mass spectrum (70eV) of hornediol diacetate (41).

this formula left $C_{10}H_{14}Br$ which implied that a halogen was most likely being lost from the molecular ion. Assuming this to be correct the molecular formula was assigned as $C_{14}H_{20}O_4BrX$. The compound has an unsaturation number of four and since the cmr spectrum showed the presence of two acetate carbonyl carbons at 170.1 and 169.8 ppm and two olefinic carbons at 138.3 (s) and 131.5 (d), one ring was present. Partial structure 38 was deduced from nmdr experiments which showed H_a (δ4.02, dd) to be coupled to the axial (H_c, δ2.18, m) and equatorial (H_b, δ2.72, ddd) protons of a nonequivalent methylene group by 13 and 4 Hz, respectively.

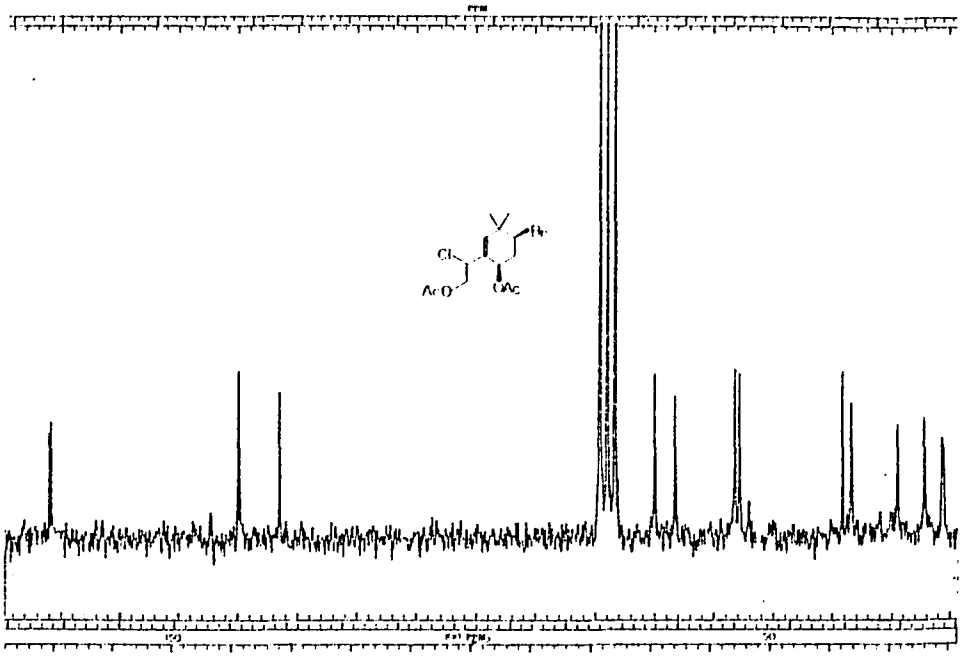


Figure I-29. Cmr spectrum ($CDCl_3$) of hornediol diacetate (41).

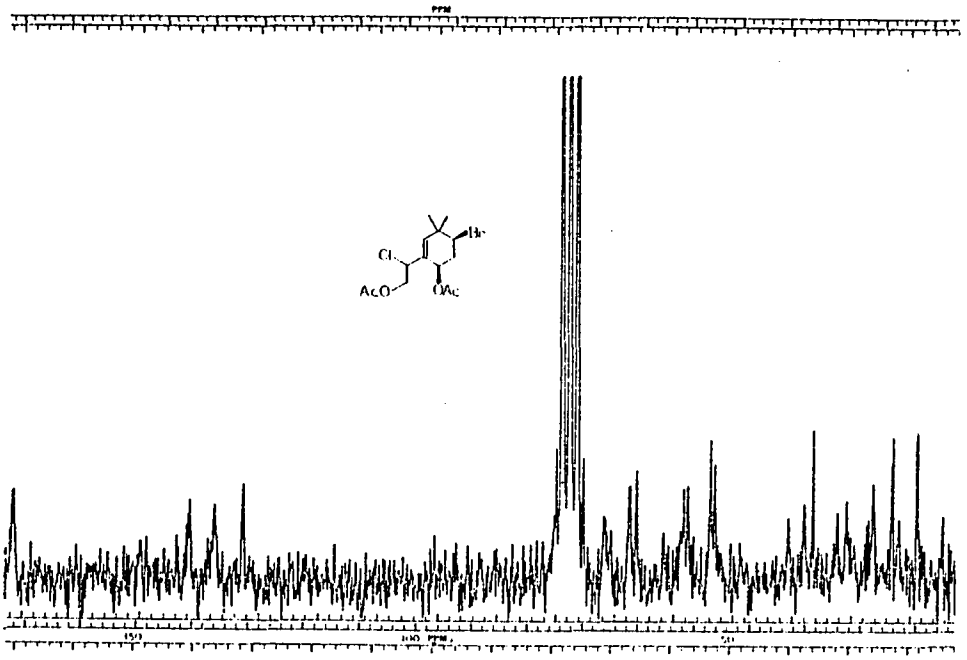


Figure I-30. Cmr off-resonance spectrum ($CDCl_3$) of hornediol diacetate (41).

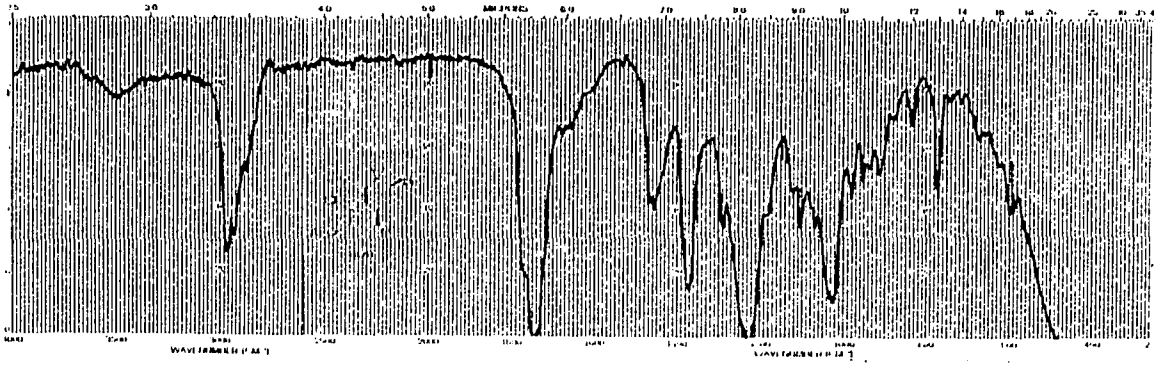
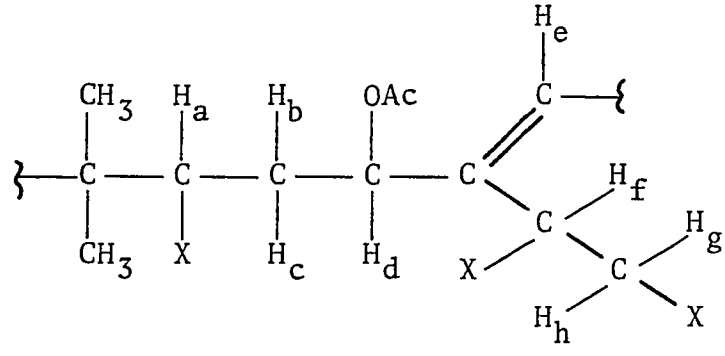
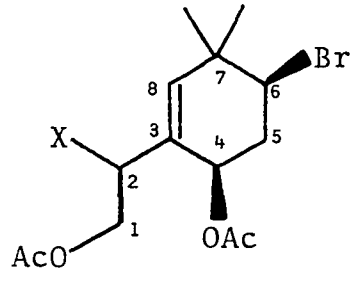


Figure I-31. Ir spectrum (neat) of hornediol diacetate (41).



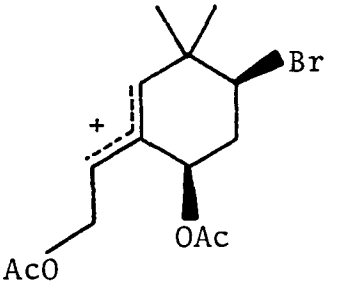
38

Protons b and c were also coupled by 6 and 9 Hz to a proton of an acetoxyl-bearing methine (H_d, dd) at δ5.53 which was further coupled allylically to H_e (δ5.78, bs) by 1 Hz. The olefinic proton (H_e) was also allylically coupled by 1 Hz to a complex 3H multiplet centered at δ4.4 which contained H_f and the magnetically nonequivalent protons H_g and H_h. Cyclization as shown in 39 gave a partial structure in which the bromine was placed on C-6 in analogy with



39

chondrocole A (25) and methoxychondrocole furan (33). The magnitudes of the appropriate coupling constants indicated the bromine and C-4 acetoxy group to be equatorially disposed. The unidentified halogen (X) was placed on C-2 to explain its facile loss from the parent ion in the mass spectrum and therefore the remaining acetoxy group had to be placed on C-1. Unlike chondrocole A (25) loss of the allylic halogen from the molecular ion of 39 would give allylic carbonium ion 40 which can readily achieve planarity.



40

The allylic halogen in 39 was not identified until a small amount of the monoacetate was isolated from later fractions. The monoacetate, eluted from silica gel with 1% methanol/ methylene chloride, had a pmr spectrum that was identical to that of the diacetate with the exception that only one acetate methyl was present at δ2.07 and the 3H multiplet at δ4.4 in the spectrum of 39 was absent. Instead, a 2H multiplet was observed at δ3.9

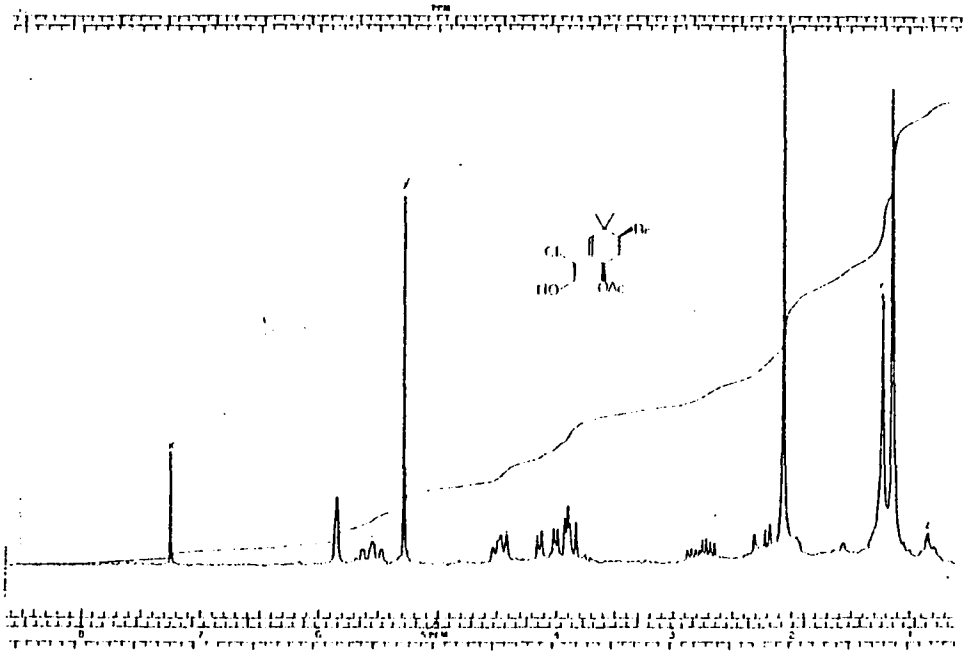


Figure I-32. Pmr spectrum ($CDCl_3$) of hornediol monoacetate (42).

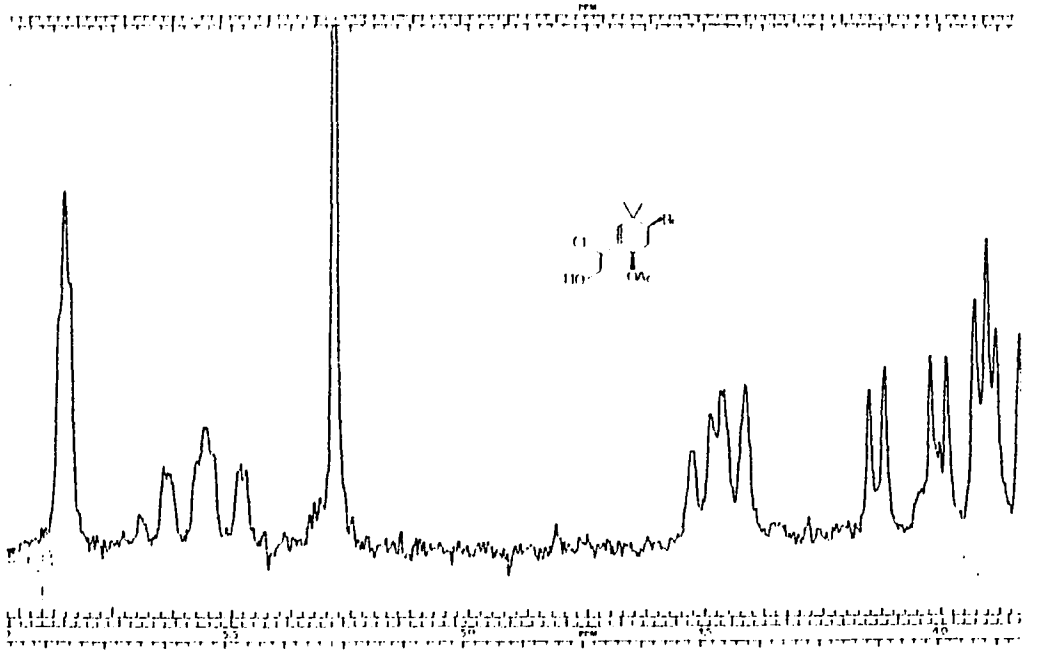


Figure I-33. Expanded pmr spectrum ($CDCl_3$) of hornediol monoacetate (42).

along with a 1H doublet of doublets (J=4 and 7 Hz) at 4.48 that indicated the hydroxyl group to be present at C-1 of 39. The monoacetate exhibited a weak molecular ion cluster at m/e 324,326,328 (1:2.5:0.4) for $C_{14}H_{20}BrClO_4$ in the mass spectrum. Acetylation of the monoacetate with acetic anhydride and pyridine gave a diacetate whose pmr spectrum was identical to that of the material isolated from fractions 19 and 20. With these data the compounds were given the trivial names hornediol diacetate and hornediol monoacetate and assigned structures 41 and 42, respectively.

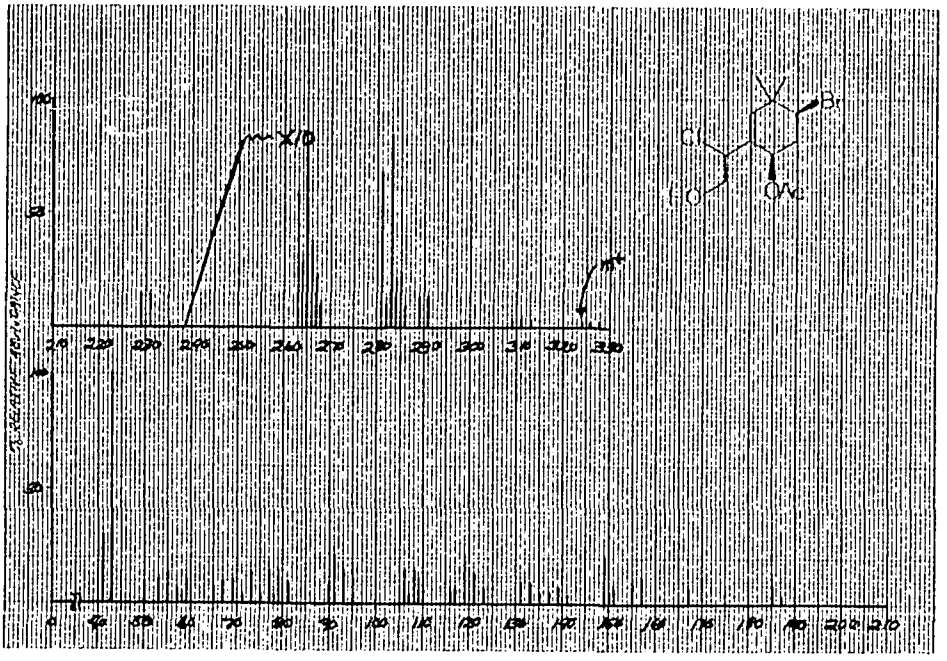


Figure I-34. Mass spectrum (70eV) of hornediol monoacetate (42).

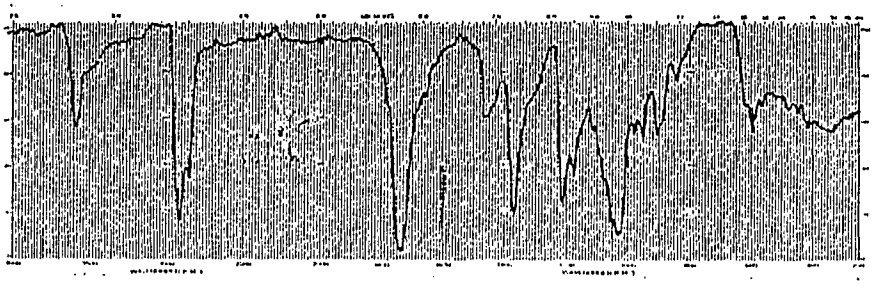
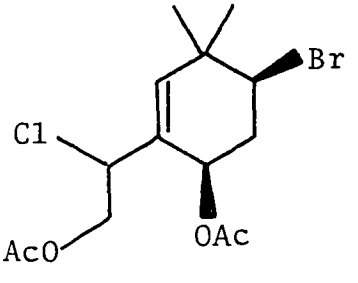
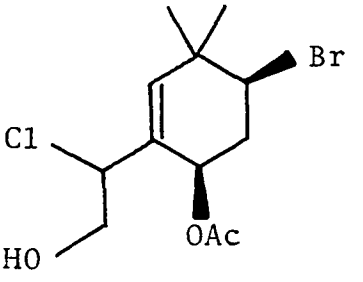


Figure I-35. Ir spectrum (neat) of hornediol monoacetate (42).



41



42

Fraction 21 (2.0%), which was also eluted from silica gel with 1:1 methylene chloride/hexane, was rechromatographed on a silica gel G column to give a solid material. Recrystallization with methylene chloride/hexane gave optically active ([α]= -48°) white needles that had a melting point of 107.0-108.0°. Excluding small differences in chemical shifts the pmr spectrum of the crystalline material was identical to that of chondrocole A (25) except for the absence of the C-2 methylene absorption. The compound was shown

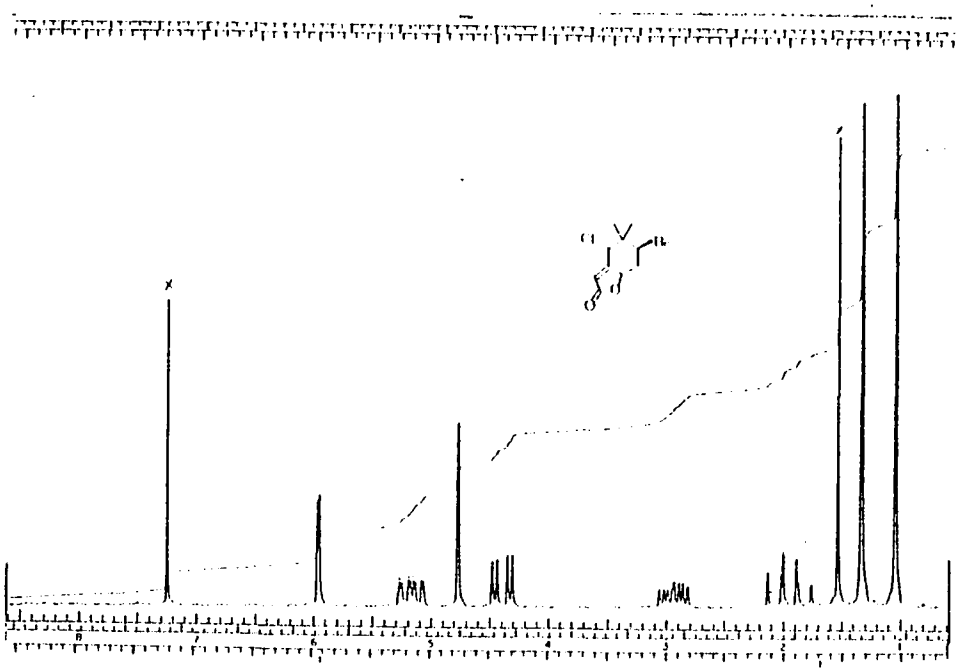


Figure I-36. Pmr spectrum ($CDCl_3$) of chondrocolactone (43).

to be an α,β-unsaturated γ-lactone by a strong absorption at 1760 cm^{-1} in the infrared spectrum and a maximum at 229.5 nm (ε=3900) in the ultraviolet spectrum. The mass spectrum of the molecule, trivially named chondrocolactone (43), exhibited a weak molecular ion cluster at m/e 278,280,282 (1:2.5:0.4) for $C_{10}H_{12}BrClO_2$ that

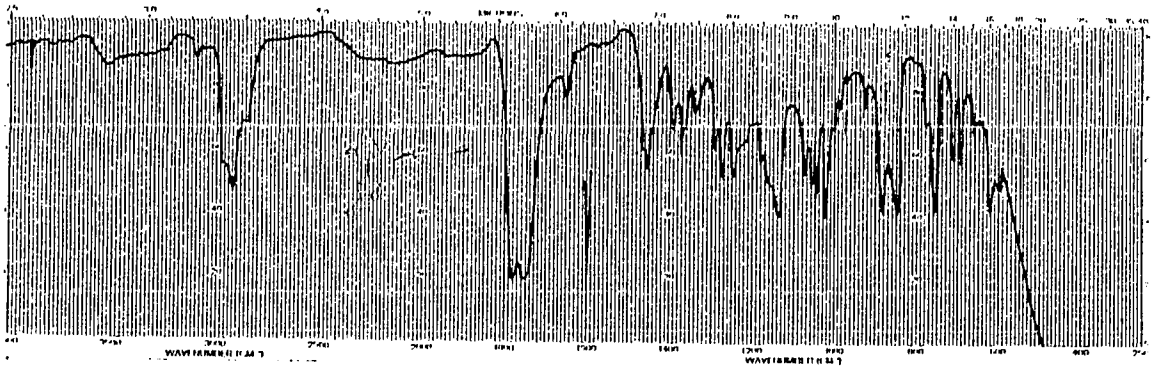


Figure I-37. Ir spectrum (nujol) of chondrocolactone (43).

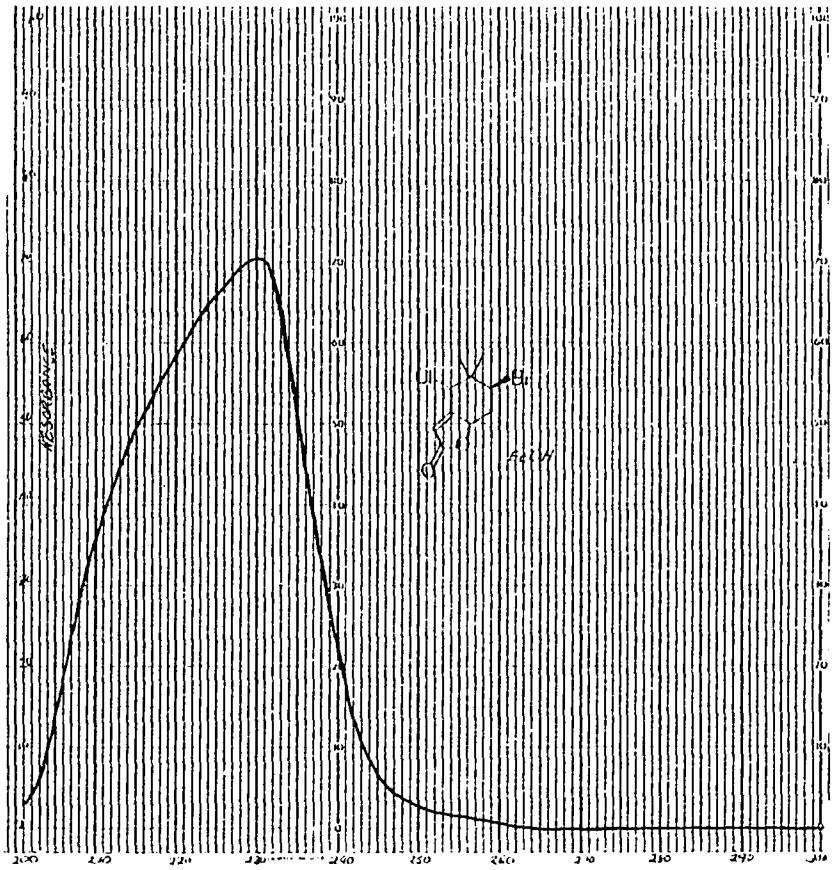


Figure I-38. Uv spectrum (EtOH) of chondrocolactone (43).

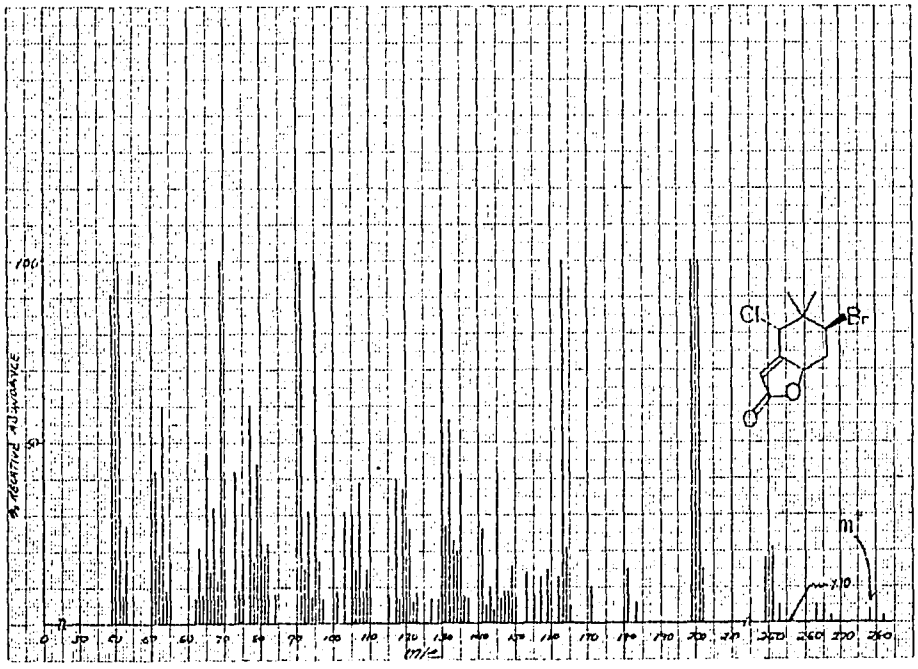


Figure I-39. Mass spectrum (70eV) of chondrocolactone (43).

readily loses bromine to give a cluster at m/e (rel. intensity) 199 (100), 201 (46). An X-ray analysis of chondrocolactone (43) showed that the positions of the bromine and chlorine were on C-6 and C-4, respectively,

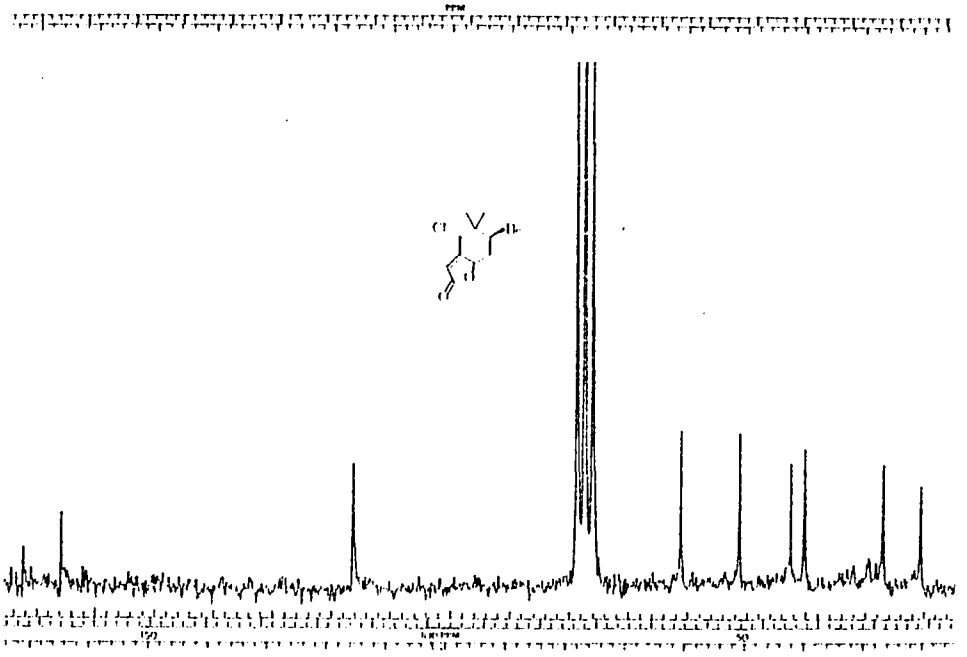


Figure I-40. Cmr spectrum ($CDCl_3$) of chondrocolactone (43).

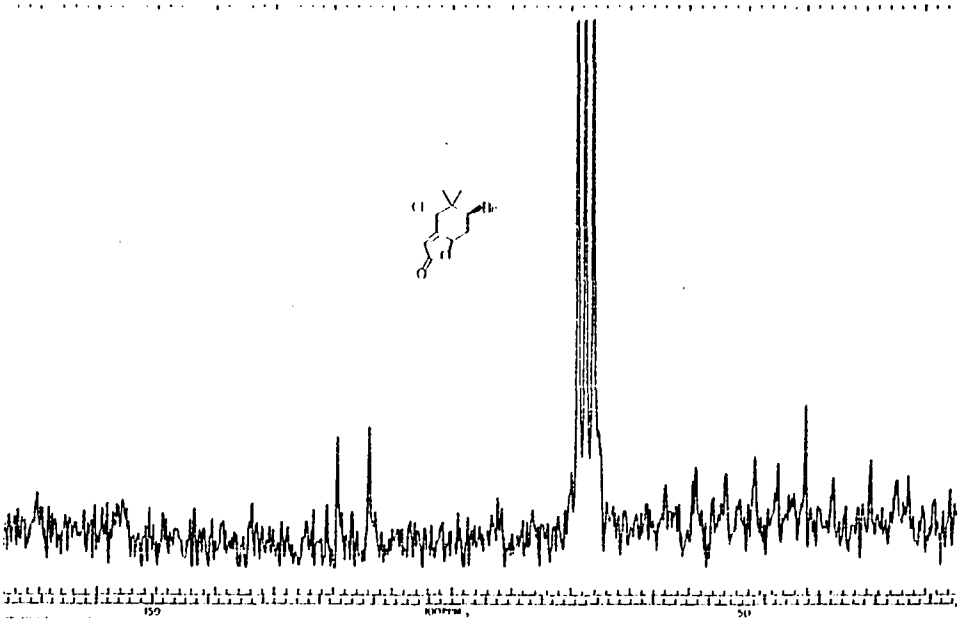


Figure I-41. Cmr off-resonance spectrum ($CDCl_3$) of chondrocolactone (43).

and established the absolute configurations of C-4, C-6 and C-7a to be R, S, and R, respectively.

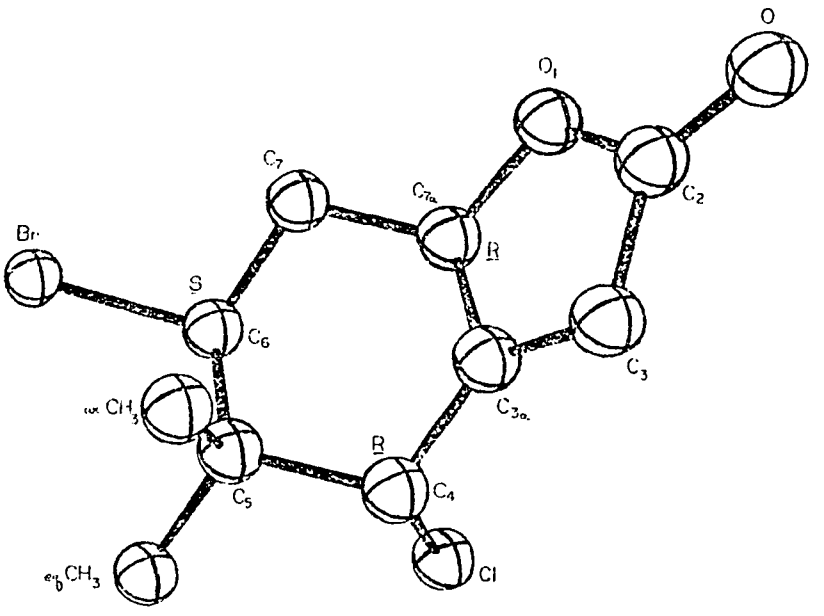
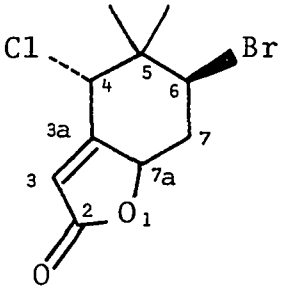


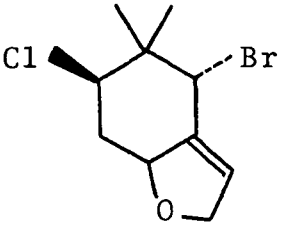
Figure I-42. Computer generated drawing of chondrocolactone (43).



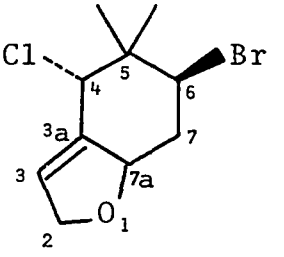
43

The X-ray structure of chondrocolactone (43) now made it possible to establish with certainty the position of the halogens in chondrocole A as well as its absolute configuration. Oxidation of chondrocole A with chromic acid gave a crystalline lactone in 24% yield that had a

melting point, optical rotation ([α]= -50°) and pmr spectrum identical to those of naturally occurring 43. The published structure of chondrocole A (23)[3] was therefore revised to 25.



23



25

Fractions 32 and 33 (2.1%), eluted with 3% methanol/methylene chloride, were rechromatographed on a silica gel column to give a pale yellow oil. Final purification was achieved by silica gel preparative layer chromatography which gave an oil whose pmr spectrum contained two furan doublets (J=2.5 Hz) at δ6.72 and 7.53 and two aromatic doublets (J=8 Hz) at 7.04 and 7.22. The remainder of the spectrum showed only two aromatic methyl singlets at δ2.36 and 2.42. The molecular formula of the compound was established from the molecular ion (m/e 146) as $C_{10}H_{10}O$ by high resolution mass measurement. These data indicated the structure of the new compound to be a dimethylbenzofuran in which the two protons on the aromatic ring were ortho to one another.

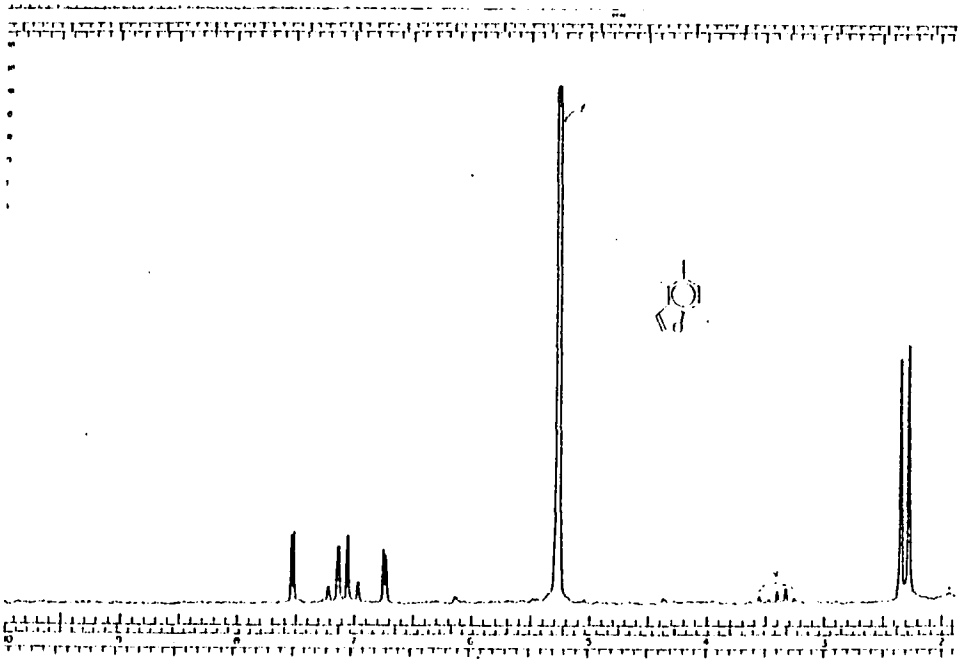


Figure I-43. Pmr spectrum ($CDCl_3$) of compound 45.

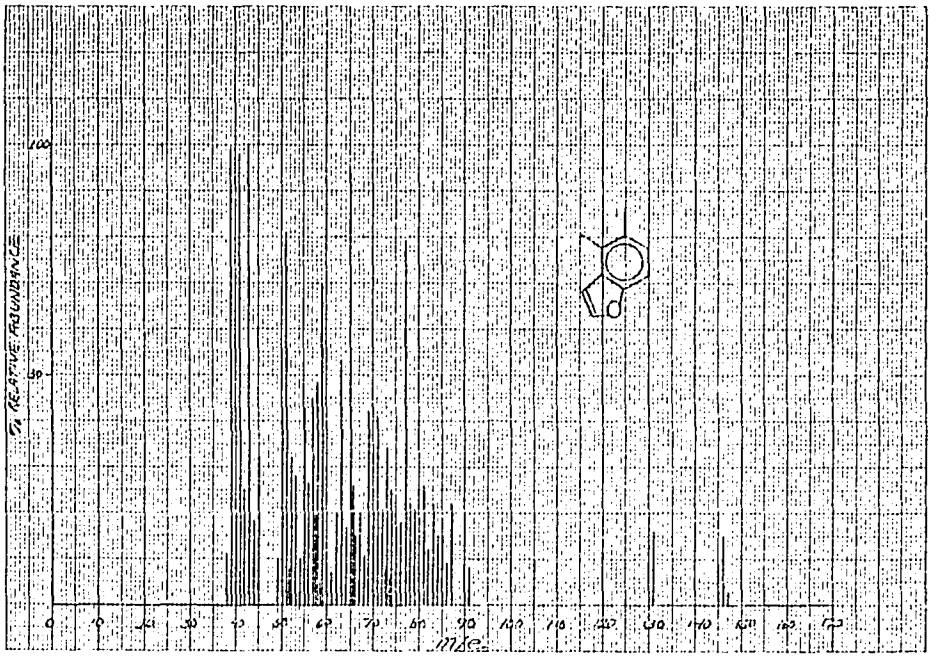
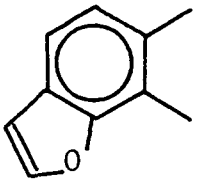
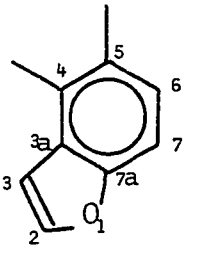


Figure I-44. Mass spectrum (70eV) of compound 45.

Both 6,7-dimethylbenzofuran (44) and 4,5-dimethylbenzofuran (45) met this requirement. Compound 44 has been

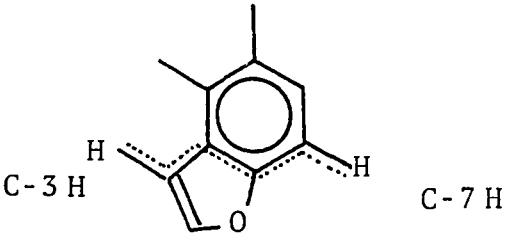


44



45

found to be a constituent of tobacco smoke and exhibits a pmr spectrum[12] that closely resembles that of the oil obtained from fractions 32 and 33. However, the aromatic protons of 44 appear as doublets (J=8 Hz) at δ6.94 and 7.25 and the furan protons resonate as doublets (J=2.5 Hz) at 6.59 and 7.45. In addition, the naturally occurring furan exhibited long-range coupling (~ 0.5 Hz) between the furan doublet (C-3H) at δ6.72 and the aromatic proton (C-7 H) at 7.22. This would not be expected to be observed in 44 and therefore 45 appeared to be the better structure.



46

Fraction 38 (9.4%), eluted with 25% methanol/ methylene chloride, was rechromatographed on Sephadex LH-20 to give an oil whose pmr spectrum contained four methyl singlets of varying intensity at δ1.61 (major), 1.68 (major), 1.78 (major) and 1.92 (minor). The chromatographic behavior of this oil and a complex set of multiplets between δ3.2 and 4.4 in the pmr spectrum suggested that it was a mixture of alcohols. Numerous

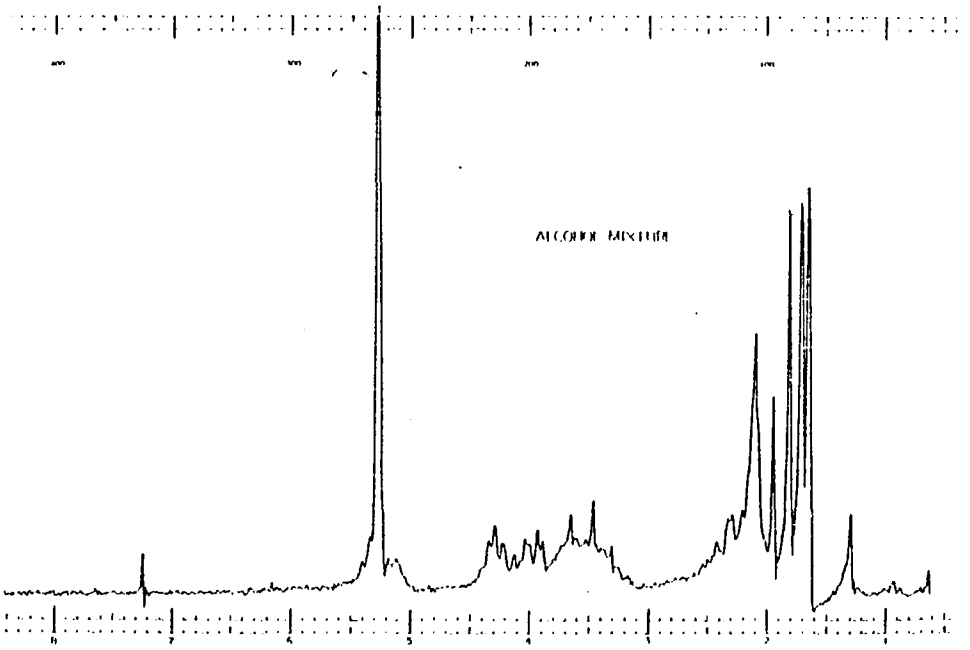


Figure I-45. Pmr spectrum ($CDCl_3$) of alcohol mixture.

attempts were made to separate this mixture by silica gel thin layer chromatography but all were unsuccessful (excessive plate streaking).

A small amount of the oil was treated with acetic anhydride in pyridine with the hope that the resulting

mixture of acetates might be easier to separate. The pmr spectrum of the acetate mixture was somewhat simpler than that of the alcohols and showed four methyl singlets

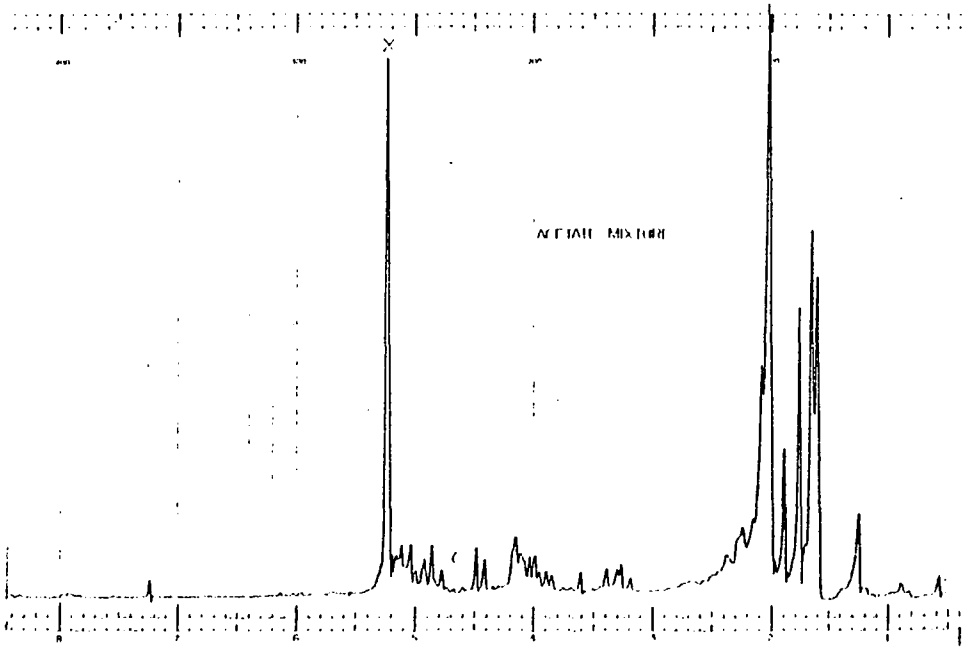


Figure I-46. Pmr spectrum ($CDCl_3$) of acetate mixture.

at δ1.60 (major), 1.66 (major), 1.76 (major) and 1.90 (minor), an acetate singlet at 2.05, a doublet of doublets (J=9 and 12 Hz) at 3.29 and a doublet (J=7 Hz) at 4.45. The remainder of the spectrum consisted of complex multiplets centered at δ3.0 and 5.0. Column chromatography of the mixture on silica gel G, Sephadex LH-20 and alumina HF-254 failed to separate the various components as did all attempts by HPLC using a μ-Porasil column. With these results it was thought that the mixture might actually be a single compound whose pmr

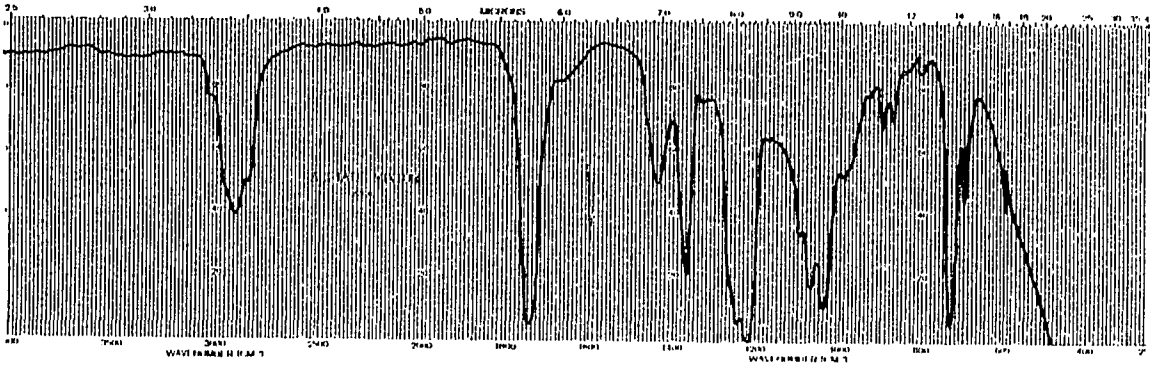


Figure I-47. Ir spectrum (neat) of acetate mixture.

spectrum was complicated by the presence of conformational effects. However, rerunning the spectrum at elevated temperatures (RT → 140°) in DMSO-d_6 did not change the appearance of the various signals. The mass spectrum of the mixture showed two apparent

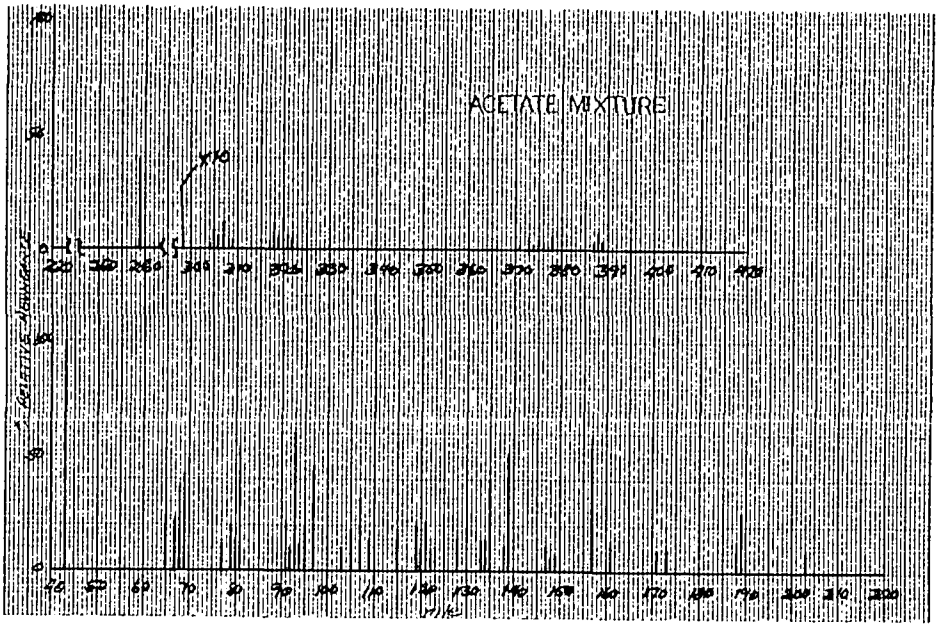
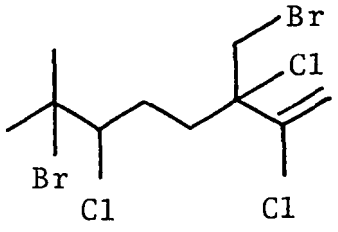


Figure I-48. Mass spectrum (70eV) of acetate mixture.

molecular ion clusters at m/e 318,320,322 (1:1.2:0.4) and 386,388,390 (1:1.3:0.4) whose relative intensities indicated the presence of one bromine and one chlorine. Also present was a cluster containing two bromines and one chlorine at m/e 371,373,375,377 (1:2.5:2.0:0.7) and a cluster at m/e 305,307,309 (1:1.4:0.4) that contained one bromine and one chlorine. None of these high mass clusters appeared to be related and no halogen-containing signals were observed below m/e 305. No further work was done on the acetate mixture.

B. Fractionation of Black Point Chondrococcus Extract

The nonvolatile extract from C. hornemanni collected at Black Point was first fractionated by Dr. B. J. Burreson in 1975 and his study resulted in the isolation and identification of seven new compounds (47-53). These compounds were obtained by extracting the dried plants with ether and chromatographing the resulting extract on a large silica gel column with gradient elution. However, the column was not washed with solvents more polar than methylene chloride and it was later thought that polar compounds such as 46 and the mixture of unidentified alcohols isolated from the Blowhole extract may have been present but not eluted from the column.



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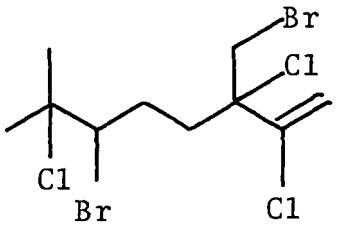

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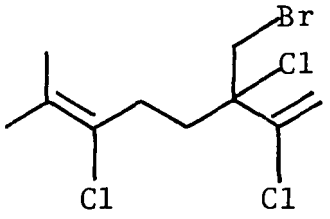

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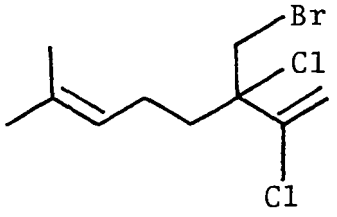

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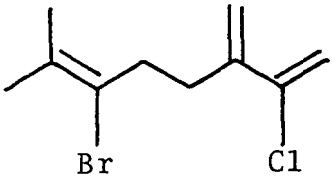

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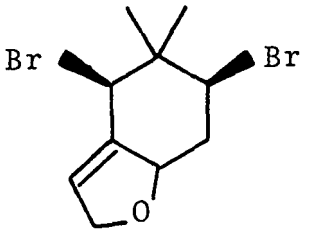
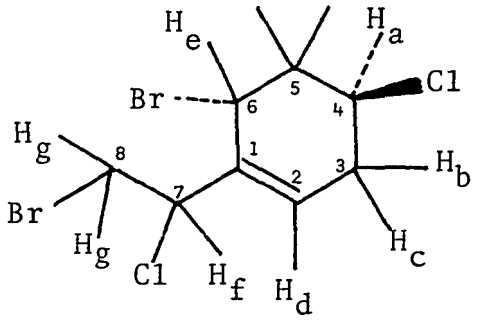


52



53

To more thoroughly investigate the Black Point extract fresh plants were collected between September 1975 and January 1976 and vacuum dried to remove the essential oil. the dried alga was then extracted with methanol and methylene chloride. The crude extract was partitioned between methylene chloride and water and the resulting dark methylene chloride soluble oil chromatographed on silica gel with gradient elution to give 40 fractions.

Fractions 1-4 (32.8%), eluted with hexane, contained mostly 47 with minor amounts of 13, 14 and 47-51. The pmr spectrum of 47 exhibited two methyl singlets at δ1.78 and 1.91, two 2H multiplets at 2.0 and 2.6, an AB quartet at 3.80 and three doublets at 3.98 (J=10 Hz), 5.58 (J=3 Hz) and 5.80 (J=3 Hz). None of these fractions were further investigated.

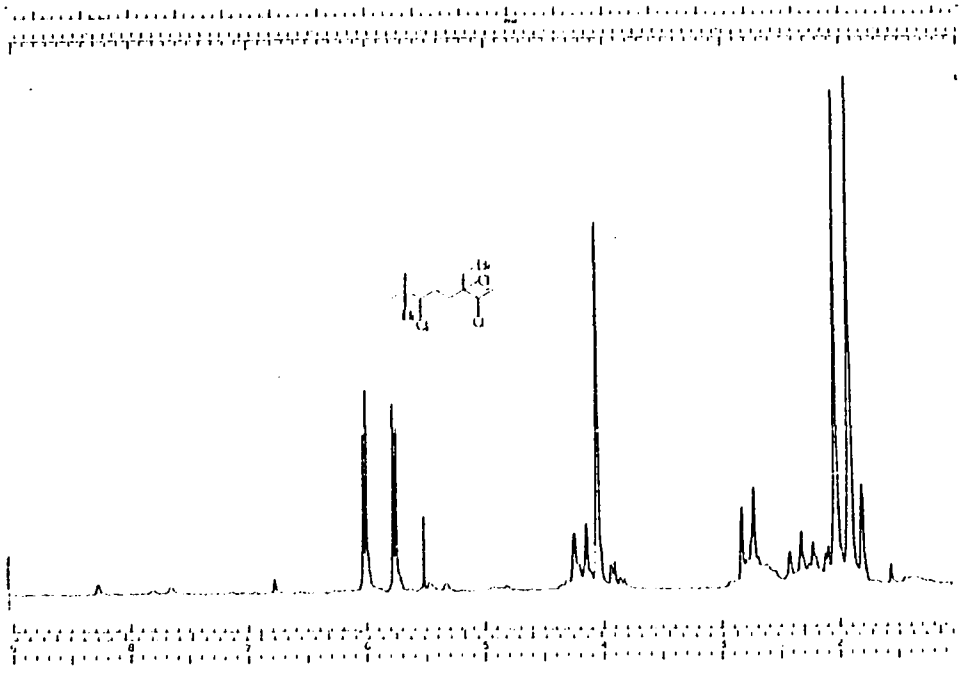


Figure I-49. Pmr spectrum ($CDCl_3$) of compound 47.

Fraction 5 (0.7%), eluted with 10% methylene chloride/hexane, contained compound 53 that was given the trivial name chondrene. Rechromatography of this fraction on Sephadex LH-20 gave pure 53 whose pmr spectrum showed two methyl singlets at δ1.25 and 1.36 and a 2H multiplet (H_b and H_c) at δ2.76 that was coupled vicinally to H_a (δ4.13, t) by 7 Hz, to H_d (δ5.92, m) by 4 Hz and homoallylically coupled to H_e (δ4.86, bs) by 2.5 Hz. The bromomethylene protons (H_g) appeared as a doublet at δ3.78 and were vicinally coupled by 6 Hz to a broadened triplet (H_f) at δ5.10 which was in turn allylically coupled to H_d by 1 Hz. The mass spectrum of 53 did not show a molecular ion but exhibited clusters at m/e 327,329,331,333 ($C_{10}H_{14}Br_2Cl$) and 283,285,287,289 ($C_{10}H_{14}BrCl_2$) that implied a molecular formula in which a bromine and chlorine occupy allylic positions. The cmr spectrum supported the presence of two bromines and two chlorines by exhibiting two chloromethines at 61.2 and 60.0, a bromomethine carbon at 56.2 and a bromomethylene carbon at 48.0 ppm. With these data a bromine was placed on C-8 and a chlorine on C-7 with the remaining bromine and chlorine assigned to C-6 and C-4 respectively in analogy with the original structure of chondrocole A (23).[8] However, in single frequency decoupling experiments, irradiation of the singlet at δ4.86 (H_e) collapsed the doublet at 60.0 in the cmr spectrum and irradiation of H_a collapsed the doublet at 56.2 ppm. This data demonstrated that the ring halogens

were reversed in position from 53 and the structure of chondrene was revised to 54.

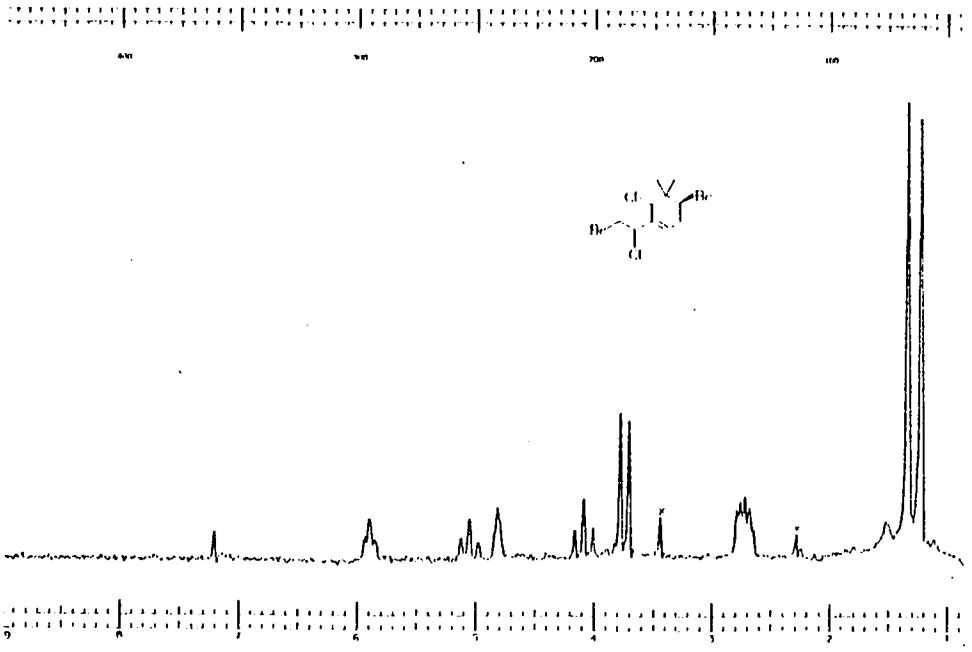


Figure I-50. Pmr spectrum ($CDCl_3$) of chondrene (54).

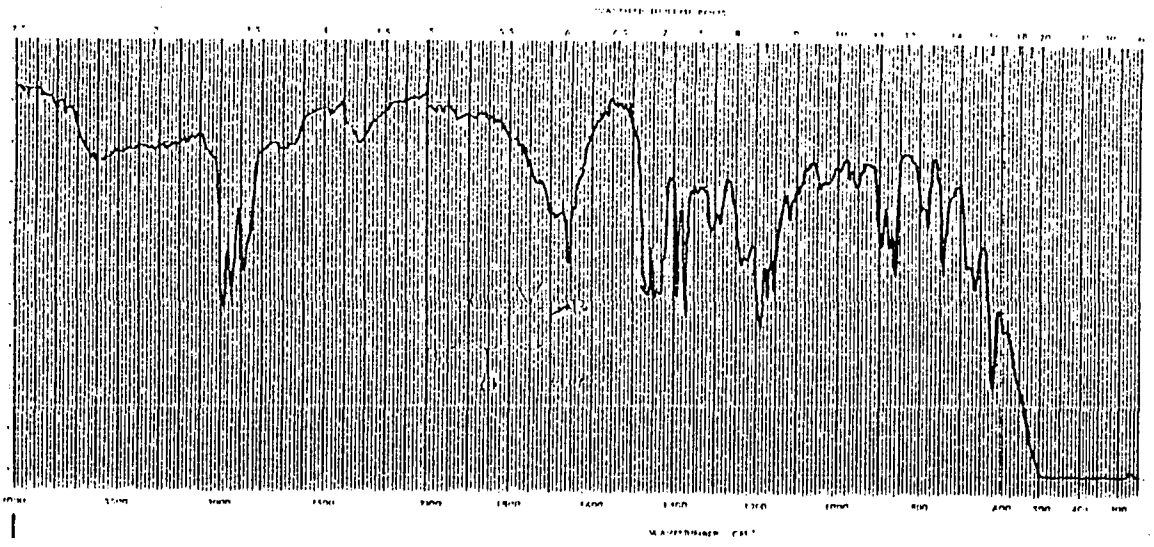


Figure I-51. Ir spectrum (neat) of chondrene (54).

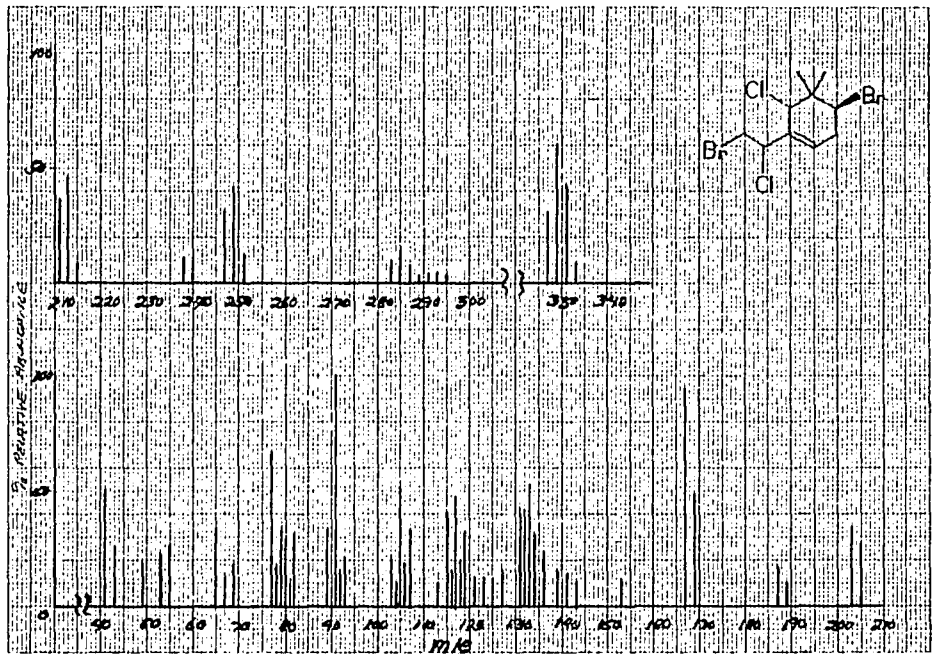


Figure I-52. Mass spectrum (70eV) of chondrene (54).

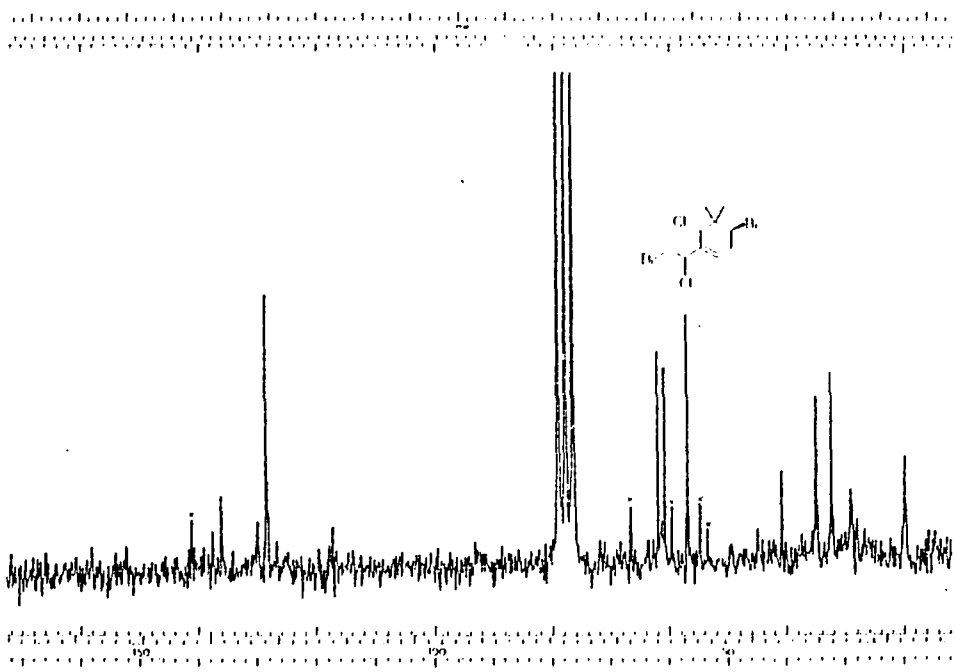


Figure I-53. Cmr spectrum ($CDCl_3$) of chondrene (54).

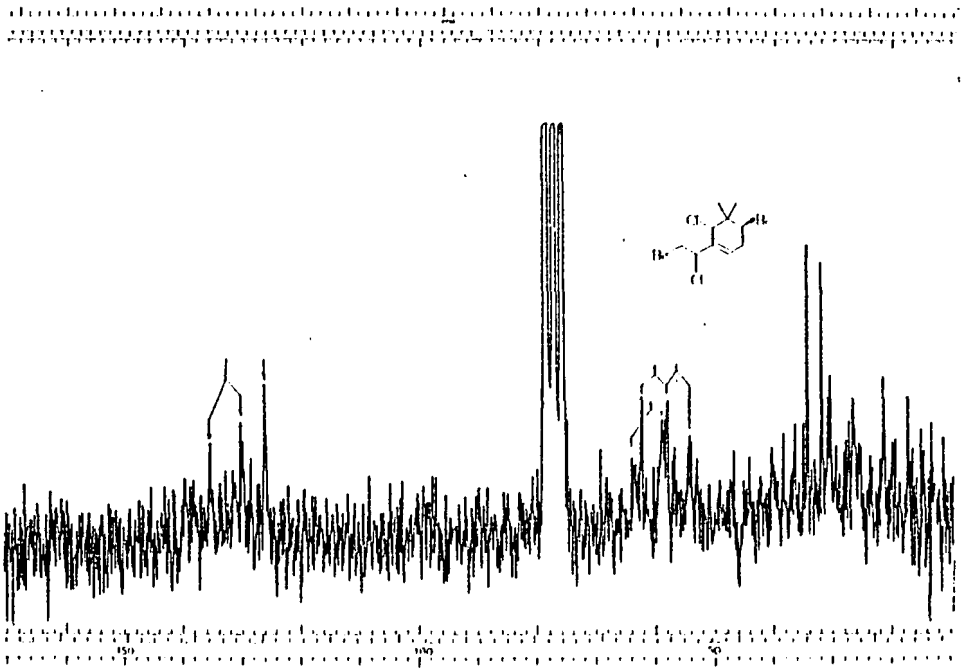
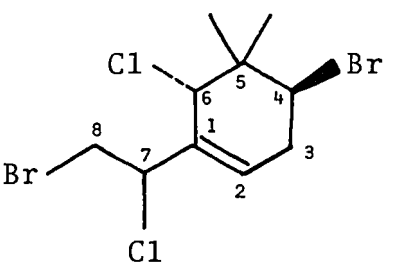


Figure I-54. Cmr off-resonance spectrum ($CDCl_3$) of chondrene (54).



54

Fractions 11 and 12 (1.4%) contained methoxychondrocole furan (33) which was followed by a small amount (1.1%) of chondrocole A (25) in fraction 13. Fractions 14 and 15 (6.7%) eluted with 50% methylene chloride/hexane and contained chondrocole C (52) whose pmr spectrum was nearly

identical to that of 25 with the exception of chemical shifts.[8] Both bromines were concluded to be held equatorial

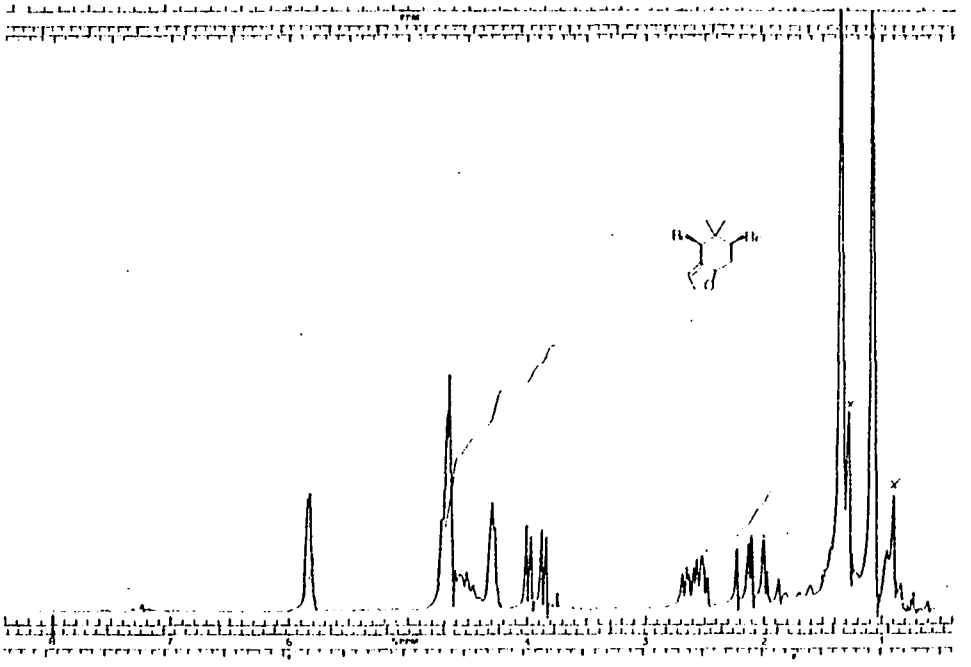


Figure I-55. Pmr spectrum ($CDCl_3$) of chondrocole C (52).

due to the presence of allylic coupling (2 Hz) between the C-4 and C-7a methine protons and the large vicinal coupling (12 Hz) observed for the C-6 methine and C-7 methylene protons. The molecular formula of 52 was established as $C_{10}H_{14}Br_2O$ by high resolution mass measurement of the molecular ion (m/e 308,310,312) which readily loses bromine to give the base peaks at m/e 229,231. The cmr spectrum was consistent with the assigned structure and showed two singlets at 138.3 (C-3a) and 43.6 (C-5), four doublets at 124.8 (C-3), 82.6 (C-7a), 55.7 (C-4) and 54.8 (C-6), two triplets at 75.3 (C-2) and 41.4 (C-7) and two quartets (methyl groups) at 29.1 and 16.0 ppm.

Figure I-56. Mass spectrum (70eV) of chondrocole C (52).

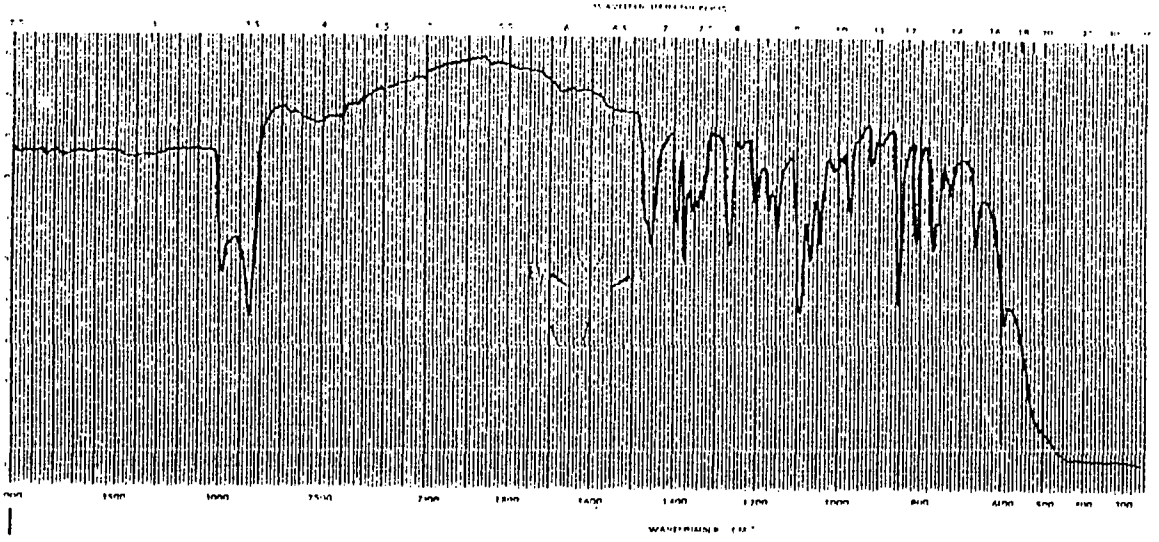


Figure I-57. Ir spectrum (neat) of chondrocole C (52).

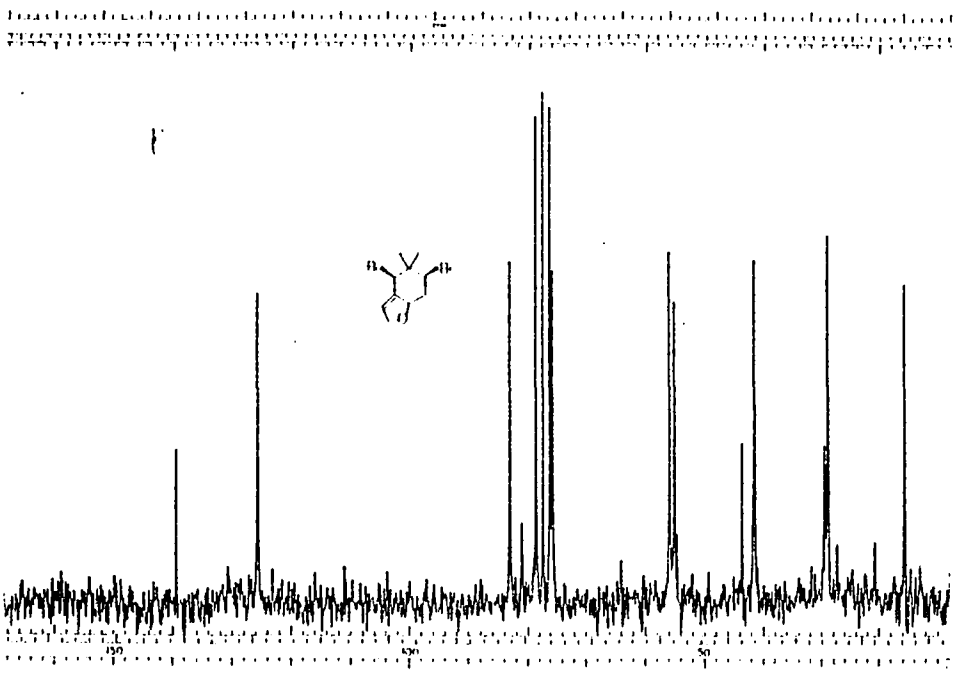


Figure I-58. Cmr spectrum ($CDCl_3$) of chondrocole C (52).

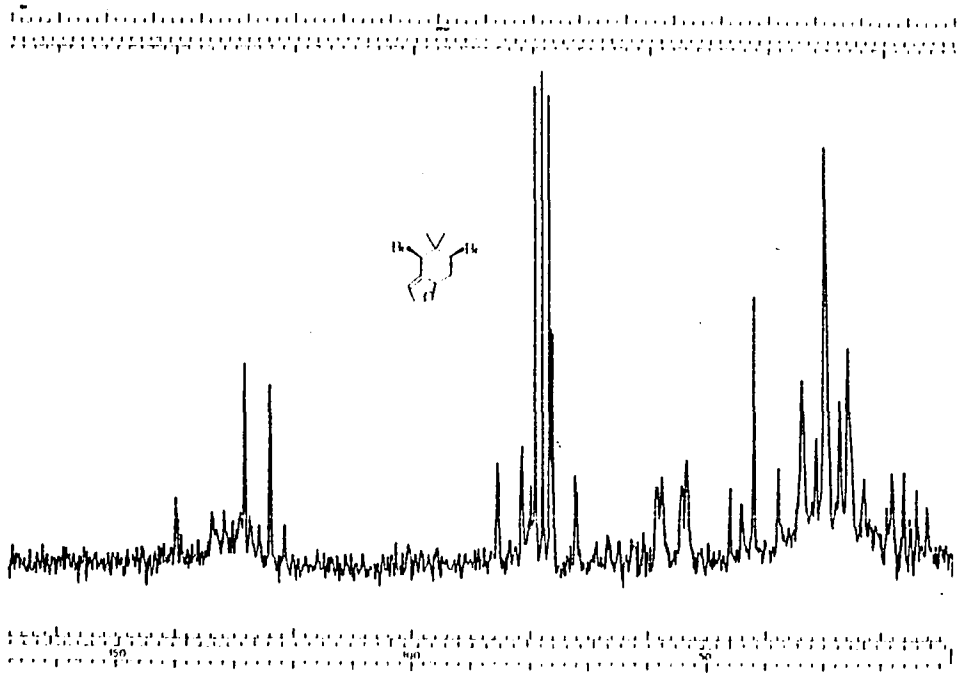


Figure I-59. Cmr off-resonance spectrum ($CDCl_3$) of chondrocole C (52).

The more polar fractions from the Black Point extract did not contain any of the compounds found in the Blowhole extract but fractions 23-29 (7.4%), eluted with 3% methanol/ methylene chloride, did contain a new compound that appeared to be an acyclic myrcene derivative. Rechromatography of these fractions on Sephadex LH-20 gave a fairly pure oil (0.9%) whose pmr spectrum showed a 1H doublet of doublets (J=11 and 17 Hz) at δ5.96 and a 2H multiplet at 5.20 that were characteristic of a vinyl group. The spectrum also contained a 2H multiplet at δ4.95 for a terminal methylene group, a 1H quartet (J=6 Hz) at 4.44, an AB quartet (2H) at 3.44 and a vinyl methyl singlet at 1.76. These data suggested a partial structure 55 for the unknown compound.

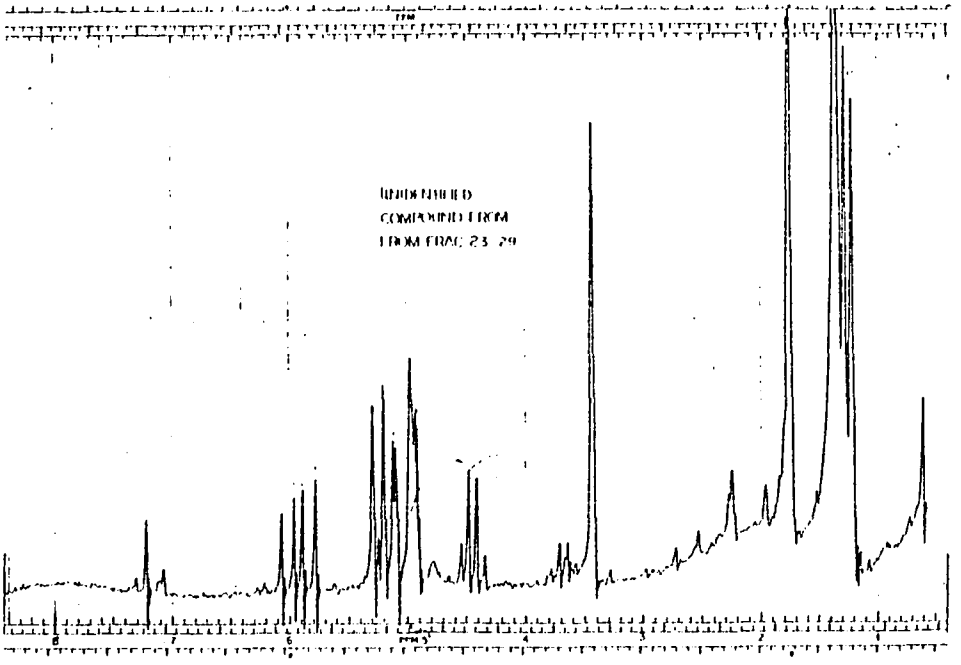
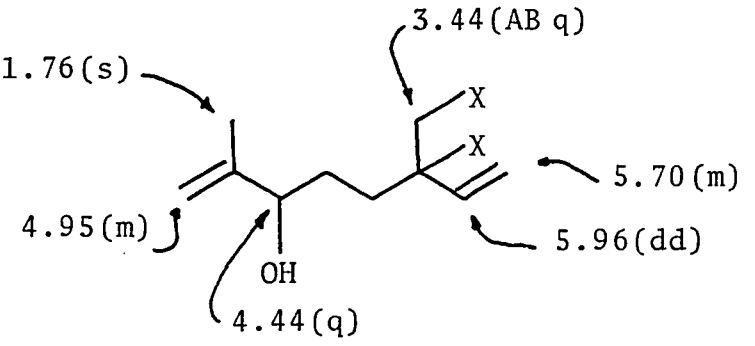
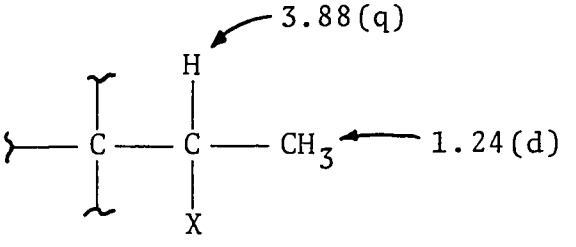


Figure I-60. Pmr spectrum ($CDCl_3$) of unidentified compounds from fractions 23-29.



55

The pmr spectrum also exhibited minor signals for a second compound at δ1.24 (d, J=6 Hz, 3H) and 3.88 (q, J=6 Hz, 1H) which were indicative of partial structure 56. Unfortunately,



56

the fraction containing these two compounds was accidently discarded before the structures could be assigned.

Also isolated from fractions 23-29 during the Sephadex chromatography was a small amount of compound whose pmr spectrum contained a 1H singlet at δ9.74, two 1H doublets at 7.98 (J=2 Hz) and 6.99 (J=8 Hz) and a doublet of doublets (J=2 and

8 Hz) at 7.66. This data, along with a molecular formula of $C_7H_5BrO_2$, established by high resolution mass measurement,

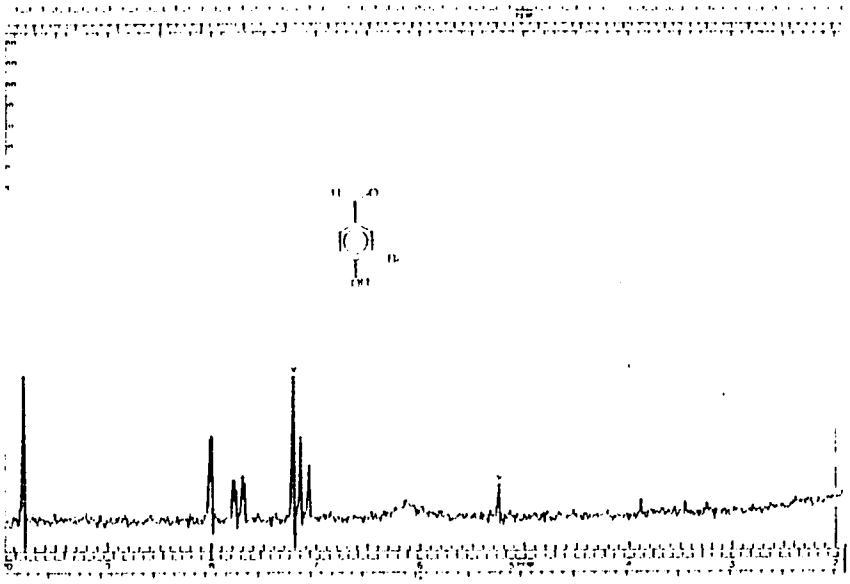


Figure I-61. Pmr spectrum ($CDCl_3$) of compound 57.

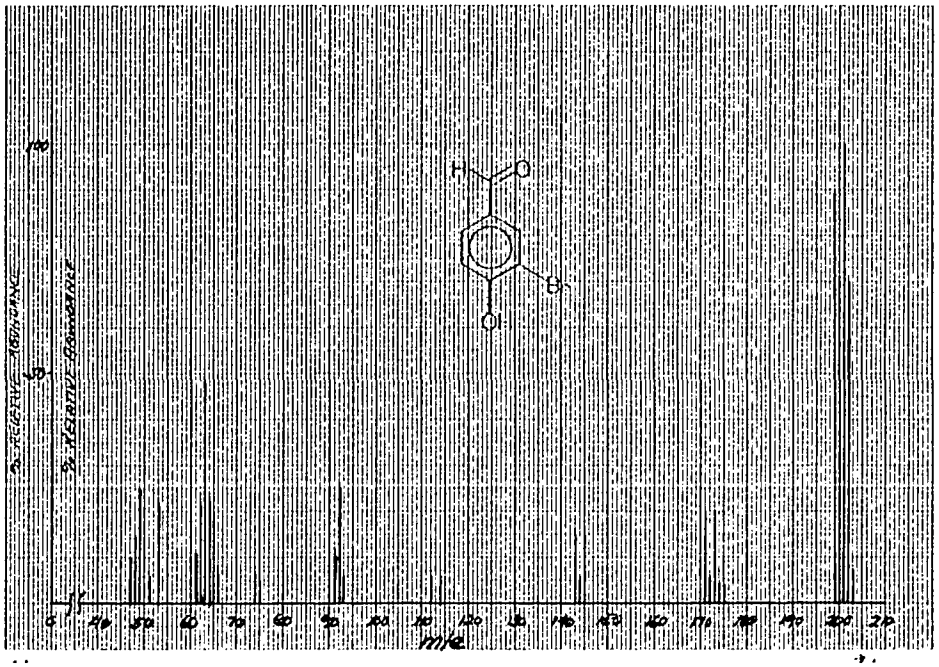
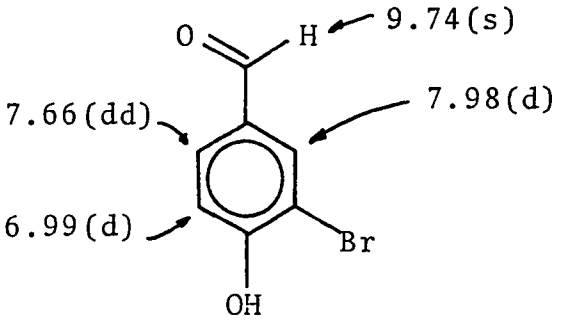


Figure I-62. Mass spectrum (70eV) of compound 57.

indicated the compound to be a bromohydroxybenzaldehyde. The structure was confirmed as 3-bromo-4-hydroxybenzaldehyde (57) by comparing the pmr spectrum with that of a synthetic sample.



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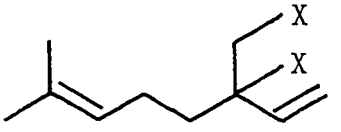
C. Fractionation of Sri Lankan Chondrococcus Extract

1. Batch 1

The ether extract (2.0 g) from wet plants of C. hornemanni collected in tropical Sri Lanka was kindly provided by Prof. M. Mahendran of the University of Sri Lanka. Surprisingly, the pmr spectrum of the crude oil showed no evidence of the halogenated myrcenes produced by Hawaiian and Japanese C. hornemanni and was nearly odorless. The extract was fractionated as before on a silica gel column using gradient elution to give 25 fractions.

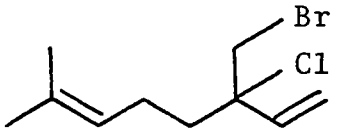
Fraction 1 (26.0%) contained a large amount of a new compound and was rechromatographed on a silica gel column

to give a colorless oil (13.5%). The pmr spectrum of the oil exhibited a doublet of doublets (J=10.5 and 18.0 Hz) at δ5.95, a doublet (J=18.0 Hz) at 5.41 and a doublet (J=10.5 Hz) at 5.26 for a vinyl group. The spectrum also contained a multiplet at δ5.1, an AB quartet at 3.68, a multiplet centered at 2.0 and two broadened methyl singlets at 1.70 and 1.64. These data immediately suggested the compound to be a myrcene derivative (58)



58

which contained a halogen and halomethyl group attached to C-3. The mass spectrum showed a weak molecular ion at m/e 250,242,254 (1:1.4:0.4) for $C_{10}H_{16}BrCl$ which lost chlorine to give an ion cluster at m/e 215,217 (1:1) and bromine to give an ion cluster at m/e 171,173. The positions of the halogens were assigned with data obtained from the cmr spectrum which showed a chlorine-containing quaternary carbon at 72.4 and a bromomethylene carbon at 40.6 ppm. The structure of the compound from fraction 1 was therefore assigned as 59.[13]



59

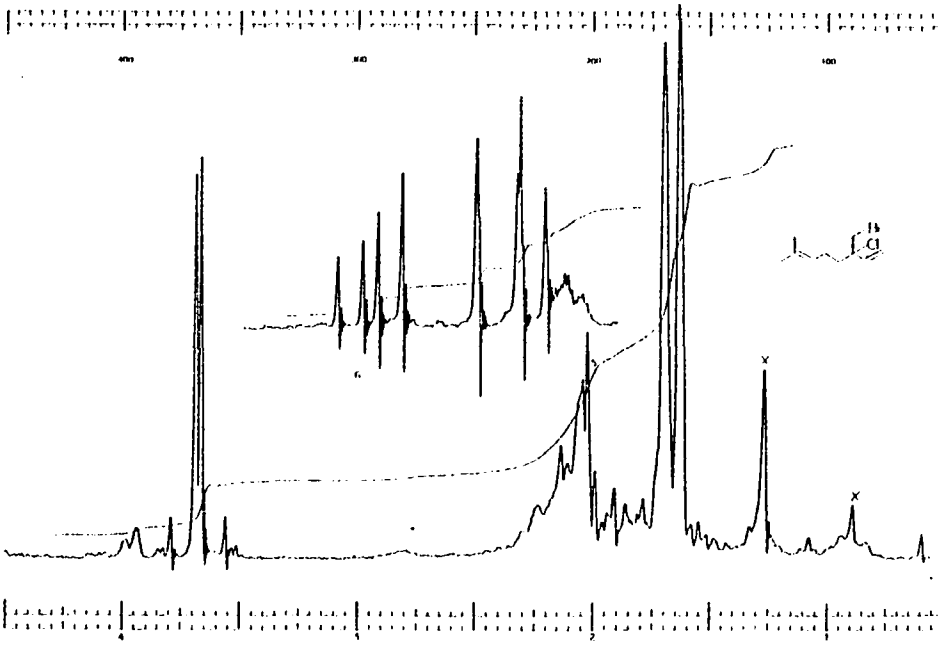


Figure I-63. Pmr spectrum ($CDCl_3$) of compound 59.

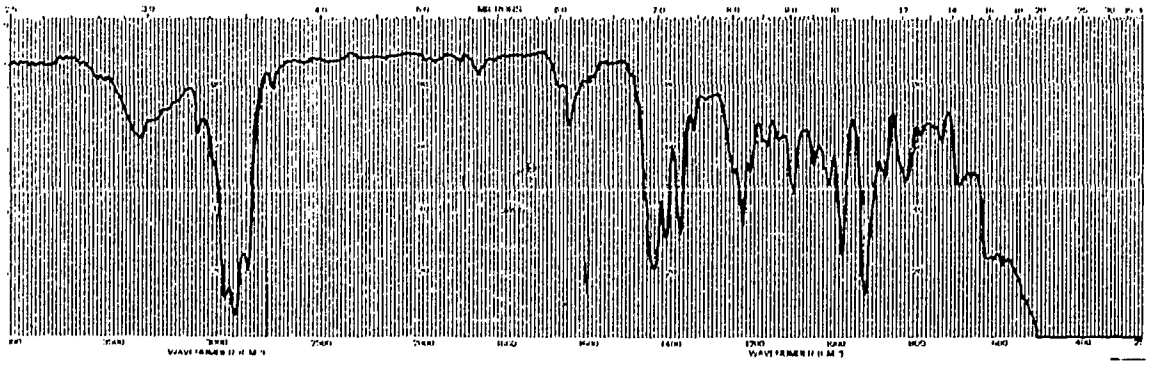


Figure I-64. Ir spectrum (neat) of compound 59.

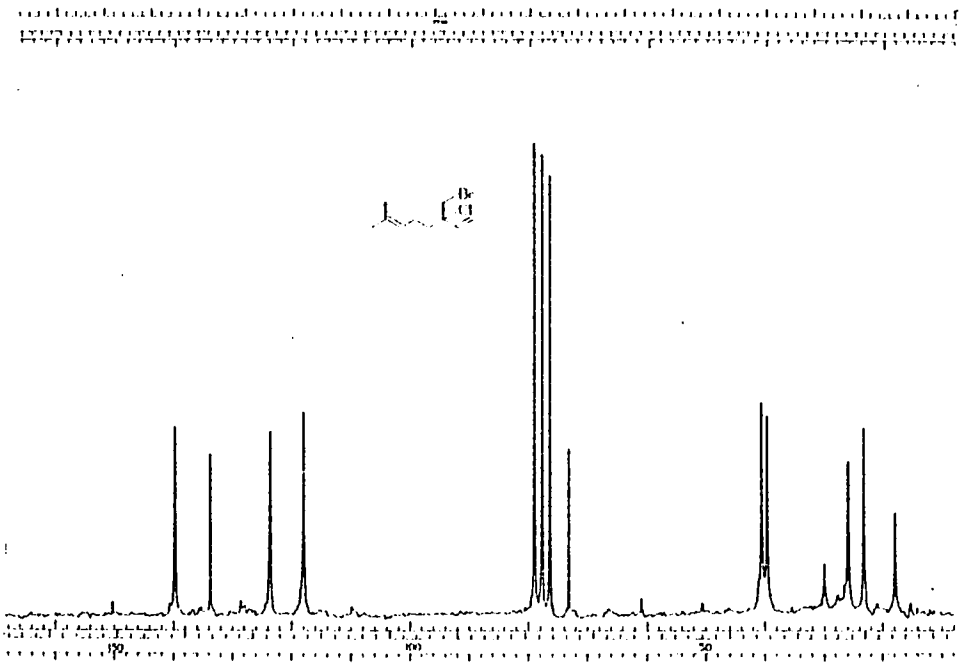


Figure I-65. Cmr spectrum ($CDCl_3$) of compound 59.

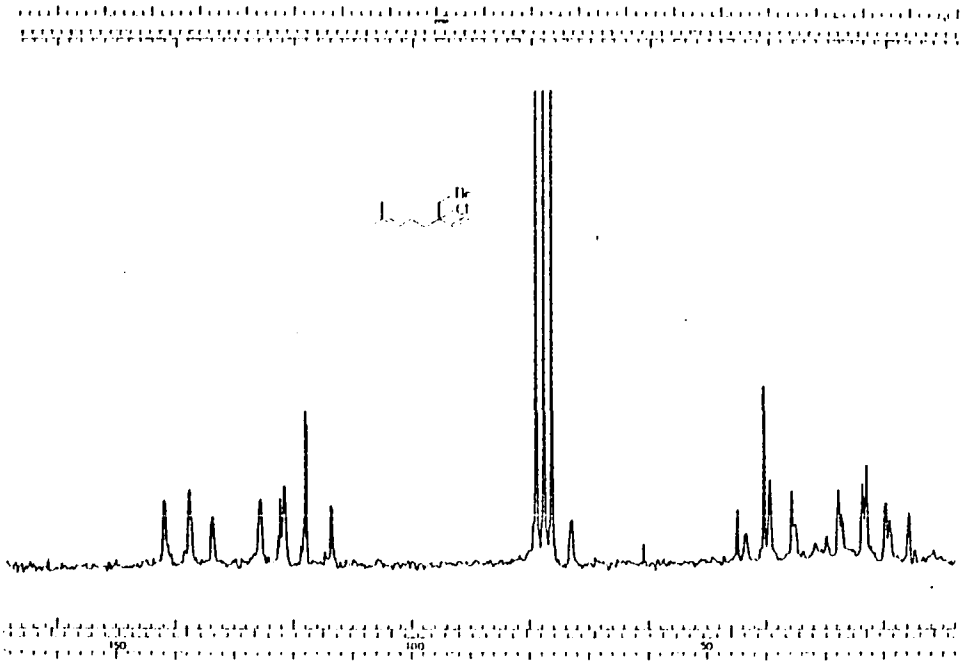
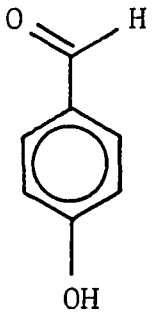


Figure I-66. Cmr off-resonance spectrum ($CDCl_3$) of compound 59.

Repeated chromatography of fraction 11 (7%) on silica gel provided p-hydroxybenzaldehyde (60, 0.03%) and a small amount (0.06%) of an oily compound that contained a vinyl



60

group. The pmr spectrum of the oil exhibited three sets of doublets of doublets at δ5.92 (J=10 and 17 Hz), 5.18 (J=2 and 10 Hz) and 5.32 (J=2 and 17 Hz), two 1H broad

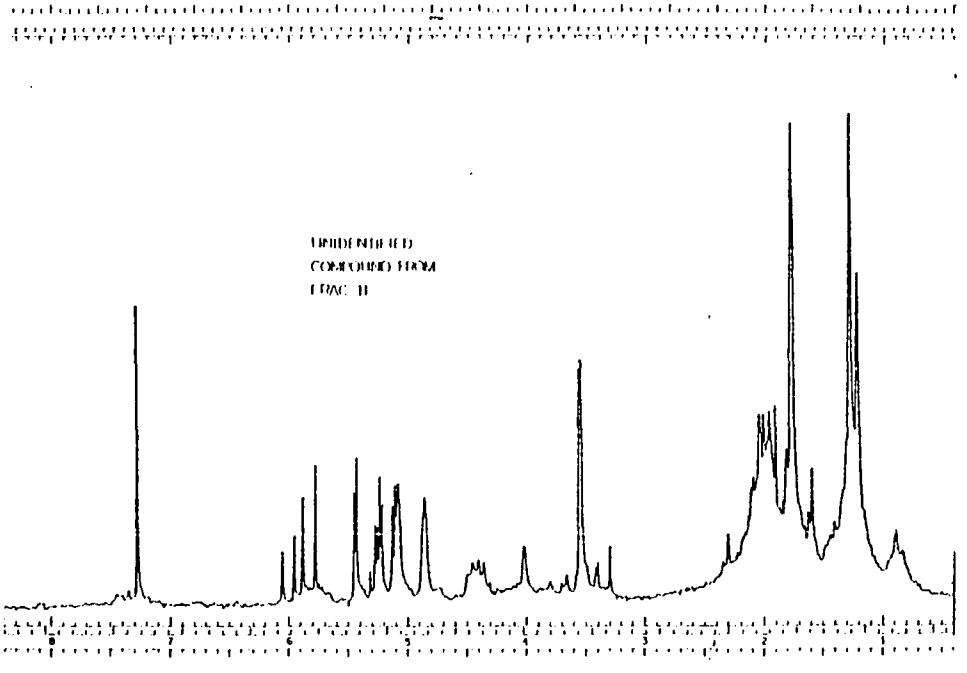
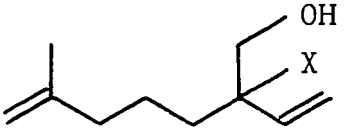
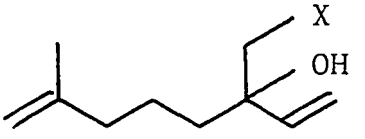


Figure I-67. Pmr spectrum ($CDCl_3$) of unidentified compounds from fraction 11.

singlets at 5.10 and 4.87, an AB quartet at 3.56, a broad multiplet contered at 2.0 and a vinyl methyl singlet at 1.79. These data, along with the chromatographic behavior of the compound, suggested 61 and 62 as possible structures. However, the oil decomposed before further purification could be attempted and additional spectra obtained.



61



62

2. Batch 2

A larger batch of Sri Lankan C. hornemanni ether extract was obtained in the fall of 1976 and it was hoped that any minor components present would be obtained in sufficient quantities to permit identification. However, removal of the ether solvent gave 5.2 g of crude extract that was heavily contaminated (30-40%) with diethyl acetal, a common contaminant in commercial ether. Chromatography of this oil on a silica gel column did provide several fractions containing compounds not found previously but most were isolated in

very small amounts. For example, repeated silica gel chromatography of fraction 6 gave 6 mg (0.01%) of an oil whose pmr spectrum contained two methyl singlets

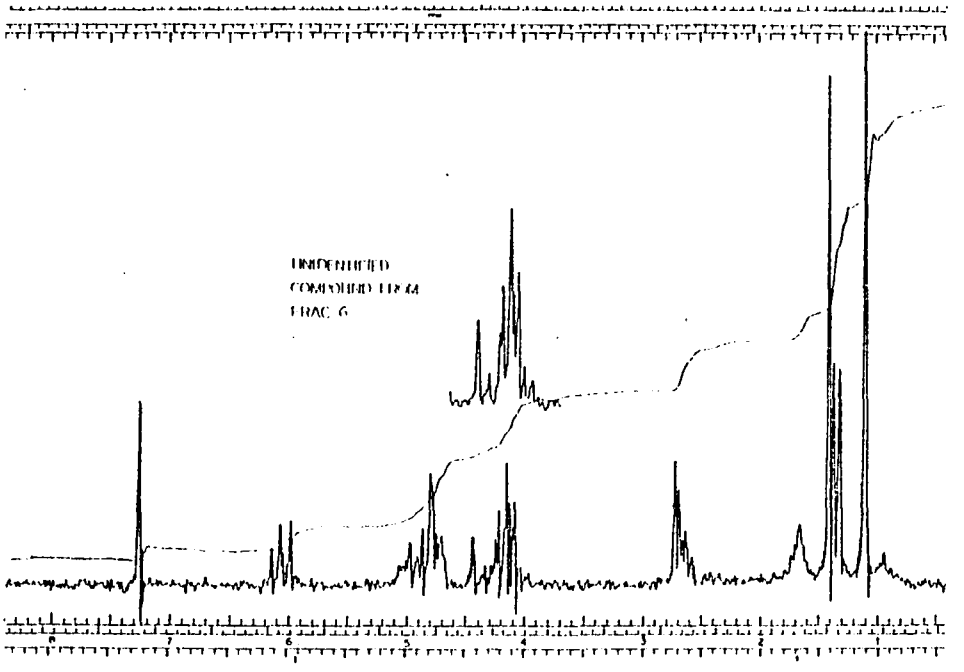
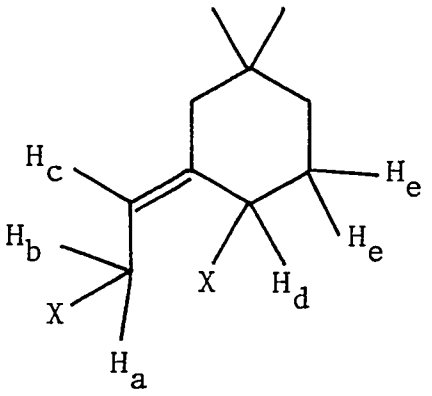


Figure I-68. Pmr spectrum ($CDCl_3$) of unidentified compound from fraction 6.

at δ1.02 and 1.24 that were indicative of a cyclic structure. The remainder of the spectrum contained a doublet (possibly two singlets) at δ1.18, multiplets at 1.6 (1H), 2.6 (2H), 4.1 (2H), 4.8 (3H) and a 1H doublet of doublets (J=6 and 10 Hz) at 6.00. Partial structure 63 was deduced from nmdr experiments which showed the multiplet at δ4.8 (H_d) to be coupled to the multiplet at 2.6 (H_e). Irradiation of the doublet of doublets (H_c) at δ6.00 collapsed the multiplet at 4.1 to an AB quartet which demonstrated H_a and H_b to be the magnetically



63

nonequivalent protons of a halomethyl group. From the appearance of the pmr spectrum it is quite possible that the oil is a mixture of isomeric compounds but due to the small quantity in hand no further separation was attempted.

Fractions 3 (2.4%) and 13 (13.8%) both contained very small signals in their pmr spectra that were not seen in previous extracts but the compounds responsible for them did not survive purification attempts.

Fractions 16-20 (16.3%) were rechromatographed on silica gel to give a small amount (1.1%) of a compound whose pmr spectrum was nearly identical to that of compound 55 isolated from Black Point fractions 23-29 (see pp. 64-67). The X proton of the vinyl group was shifted slightly upfield (ca. 0.3 ppm) from the X proton of 55 and there was no AB quartet at δ3.44. Instead a singlet

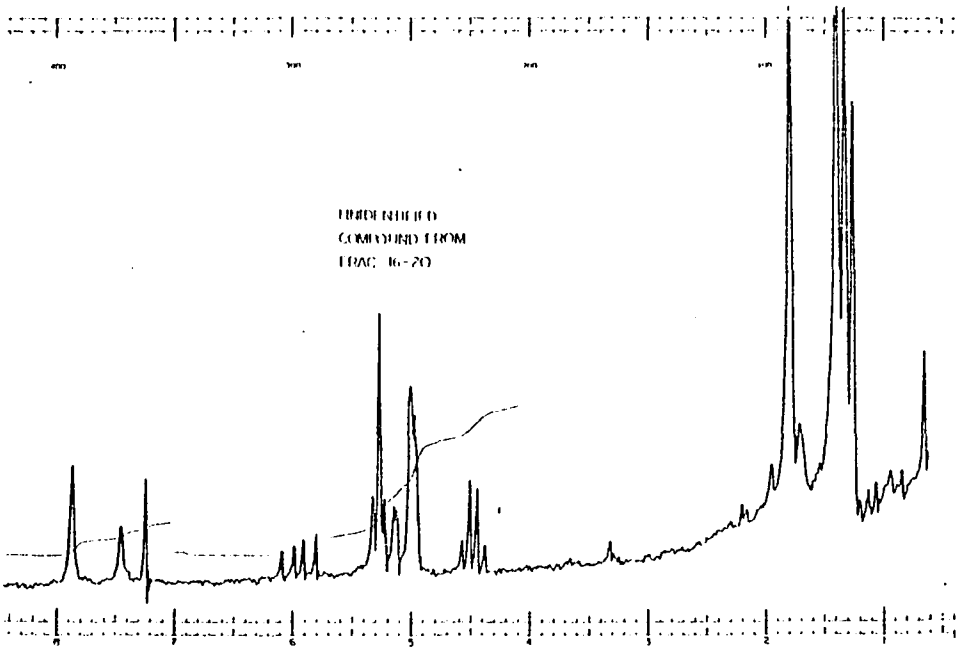
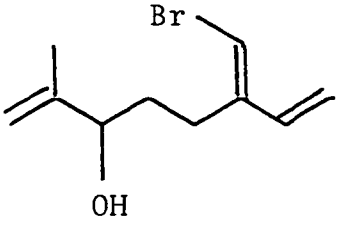


Figure I-69. Pmr spectrum ($CDCl_3$) of unidentified compounds from fractions 16-20.

was present at δ6.86 and 64 was assigned as the tentative structure.



64

D. Biogenesis of the Constituents of C. hornemanni

The exact pathways by which C. hornemanni produces the large number of halogenated monoterpenes found in the essential oils and nonvolatile extracts are not known at this time. However, the similarity of the isolated compounds for which unambiguous structures were assigned does permit speculative conclusions to be drawn with respect to their origins. For example, the presence of the polyhalogenated myrcene derivatives in the nonvolatile extracts indicates that the halogens are introduced exclusively by the enzymatic addition of bromine chloride (BrCl) to myrcene. Molecular bromine and chlorine are evidently not utilized by the plant since compounds containing vicinal bromine atoms and vicinal chlorine atoms were not found. In vivo BrCl is added in both Markovnikov and anti-Markovnikov fashion to the Δ^1 and Δ^6 double bonds of myrcene but predominantly Markovnikov to the 3-methylene group. In vitro, reaction of one equivalent of BrCl with myrcene resulted in a complex mixture of products but large methyl singlets at δ1.79 and 1.98 in the pmr spectrum of the mixture indicated the addition at the Δ^6 double bond to be predominately anti-Markovnikov. Apparently, in the absence of enzymatic systems the two methyl groups of 65 sterically hinder the backside approach of chloride ion to the tertiary center.

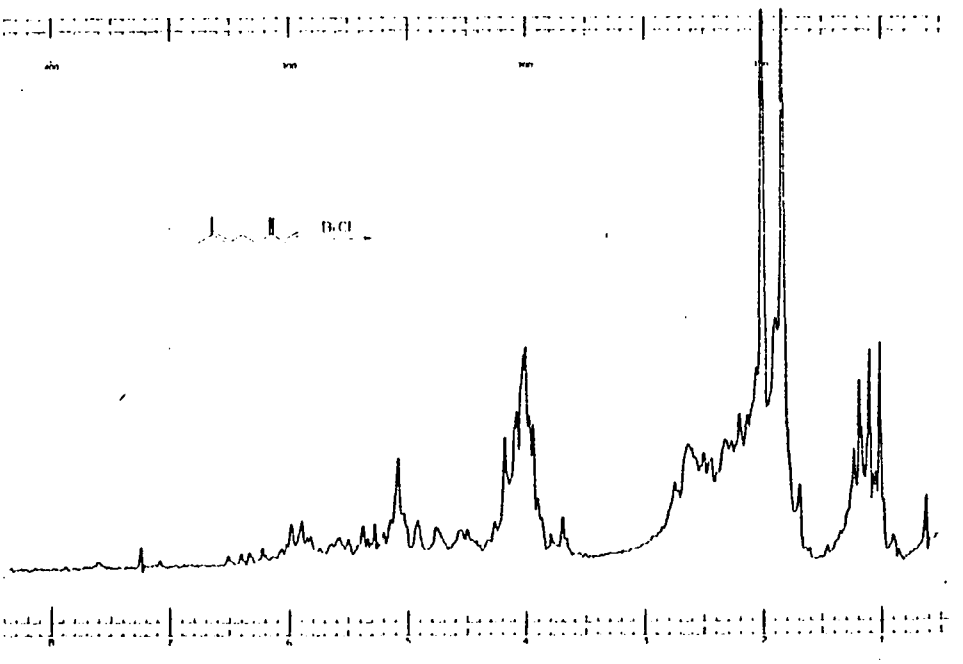
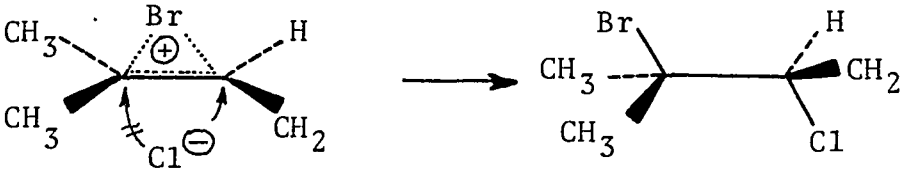
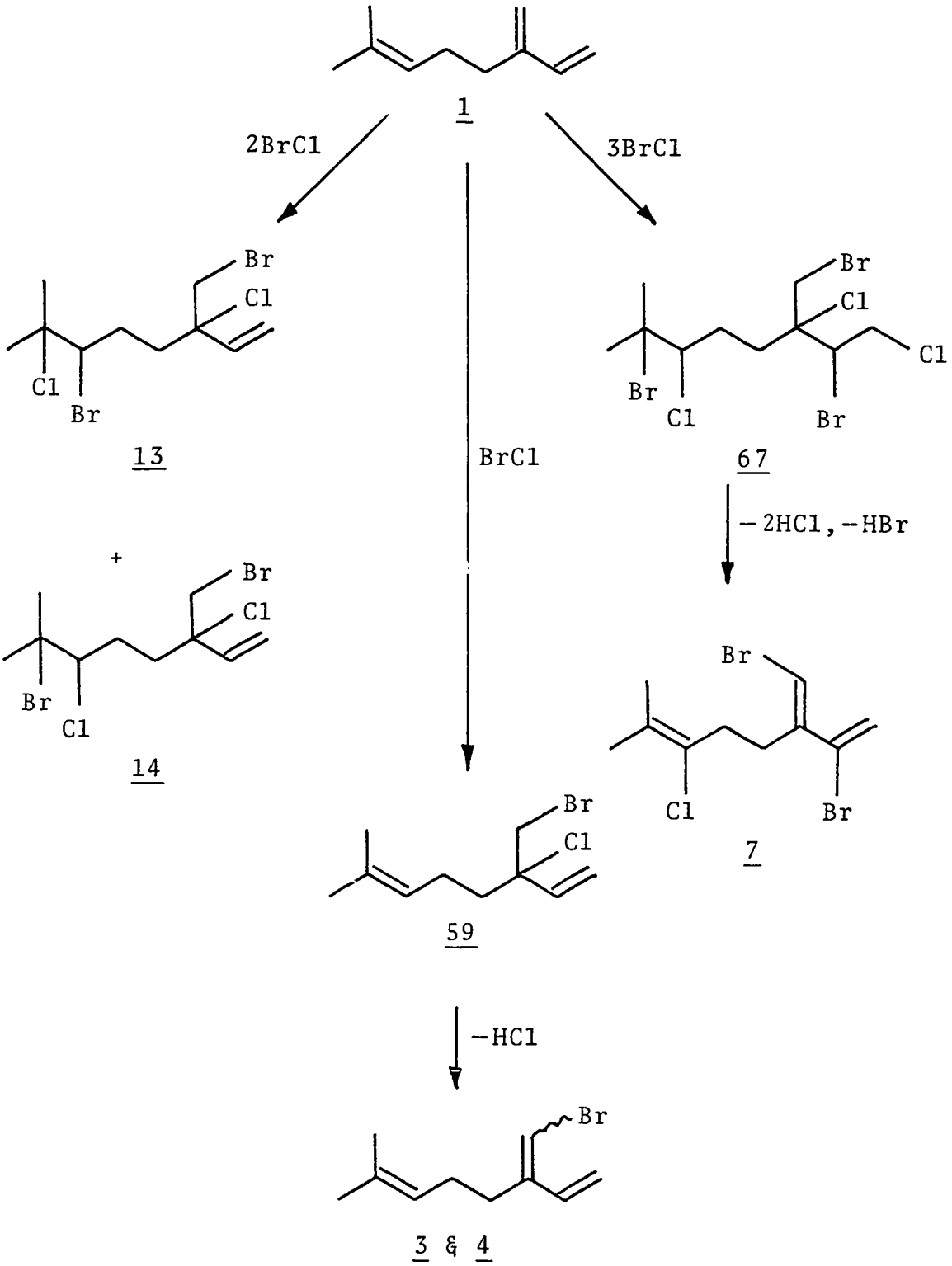


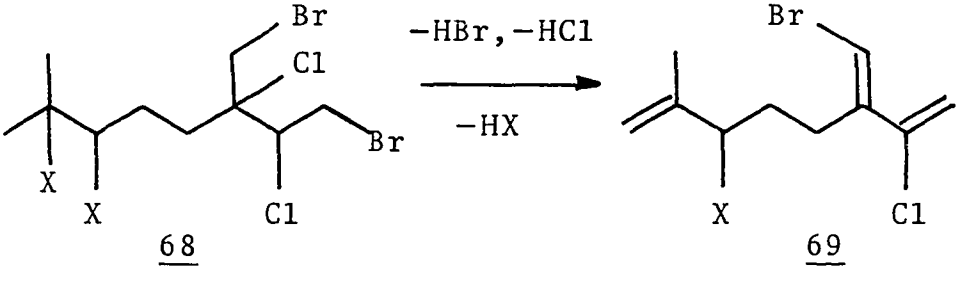
Figure I-70. Pmr spectrum ($CDCl_3$) of product mixture from the addition of BrCl to myrcene.



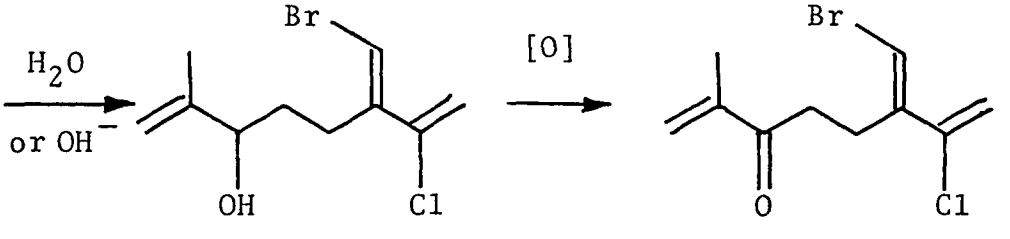
65 66


1
2BrCl
3BrCl
BrCl
Br
Cl
Cl
Br
13
+
Br
Cl
Br
Cl
14
Br
Cl
Cl
Br
67
−2HCl, −HBr
Br
Cl
Br
7
Br
Cl
59
−HCl
Br
3 & 4

The halogenated myrcenes that make up the essential oil undoubtedly arise by elimination of hydrogen halides from the polyhalomyrcene derivatives. For example, elimination of HCl from 59 would give 3 and 4 whereas elimination of HCl and HBr from 67, which was not found in C. hornemanni, would give 7. Alcohol 30 may also be formed from an intermediate resembling 67 in which BrCl had been added Markovnikov to the Δ^1 double bond (68). Elimination of HBr, HCl and HX from 66 forming allylic halide 69 followed by substitution with water or hydroxide ion at C-6 would give alcohol 30. Simple oxidation of 30 would form ketone 21.

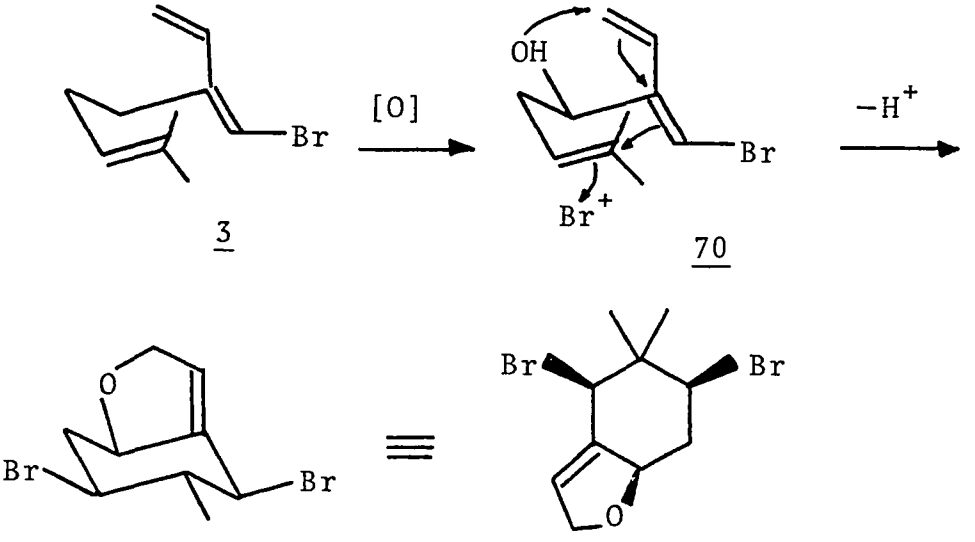


68 69



30 21

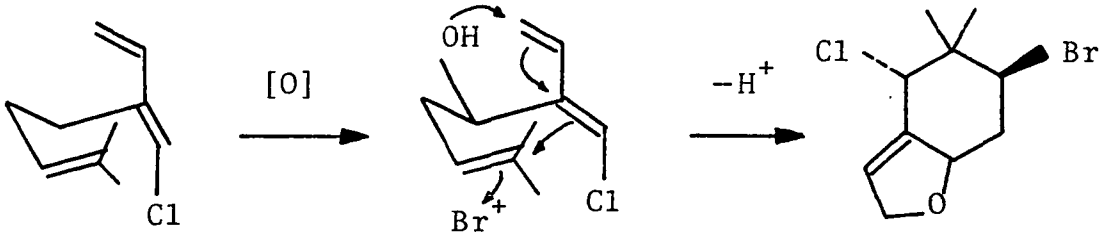
The chondrocoles and related compounds are also based on the myrcene skeleton and are probably formed by cyclization of halogenated myrcenols. For example, oxidation of 3 to the C-4 alcohol (70) followed by concomitant bromonium ion induced cyclization would give chondrocole C (52).



3 70

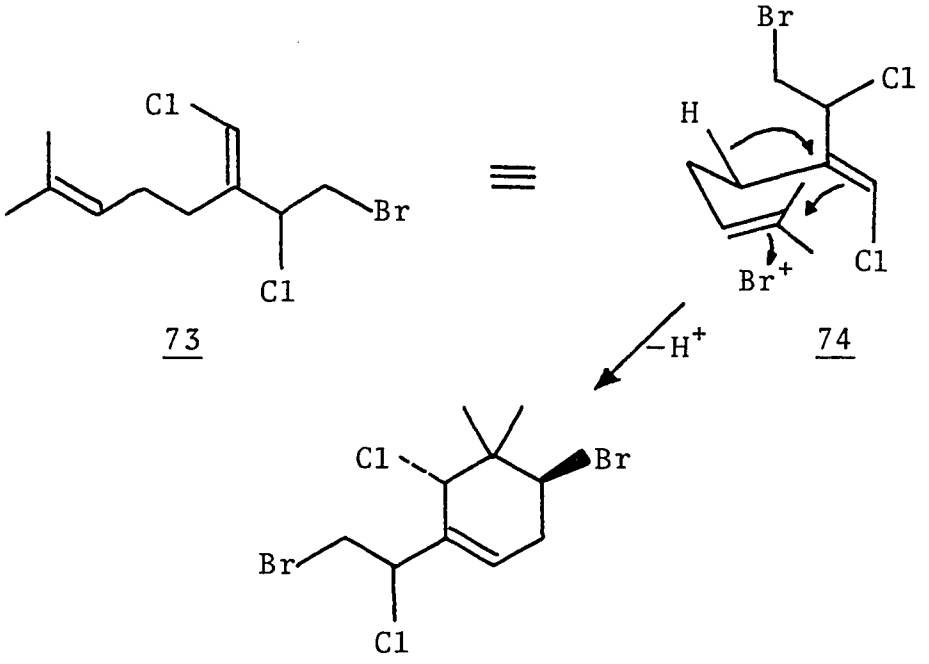
52

In a similar manner, oxidation of 71, which was not found in C. hornemanni, followed by cyclization would give chondrocole A (25). Bromonium ion induced cyclization



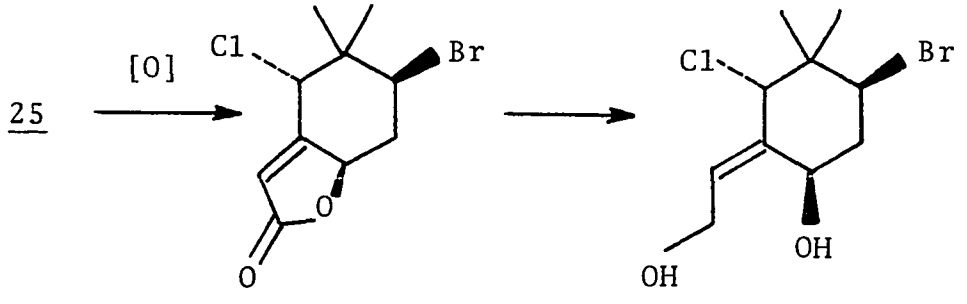
71 72 73

of 73, an analog of 17, would easily explain the formation of chondrene (54).



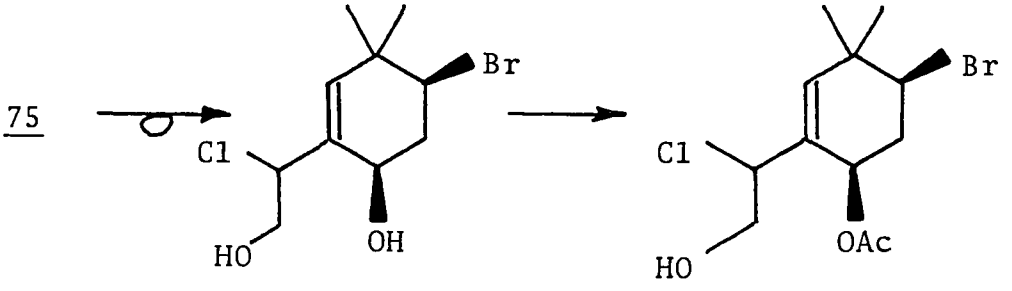
73 74 54

Oxidation of chondrocole A (25) to chondrocolactone (43) followed by reductive ring opening (43 → 75),

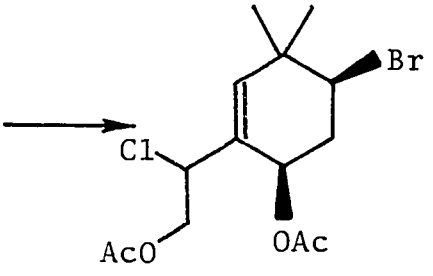


43 75

rearrangement of the double bond and chlorine atom (75 → 76) and stepwise acetylation would give 42 and 41.

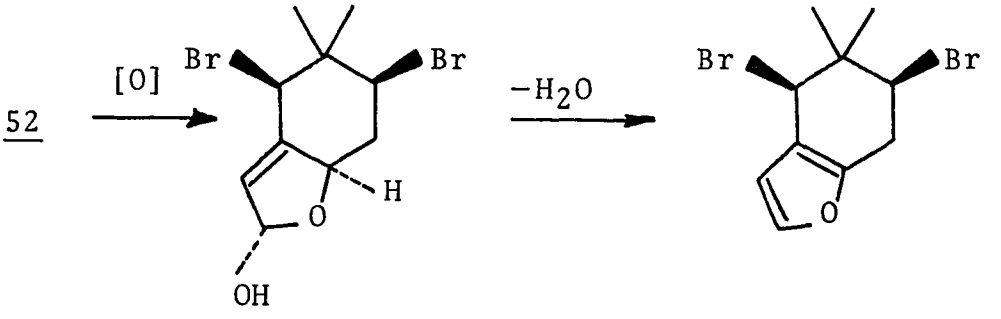


76 42

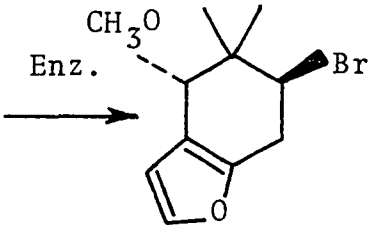


41

On the other hand, methoxychondrocole furan (33) is probably derived from chondrocole C (52) via hemiacetal 77 which undergoes a 1,4-elimination of water (77 → 78) and enzymatic substitution at C-4 to introduce the methoxy group.

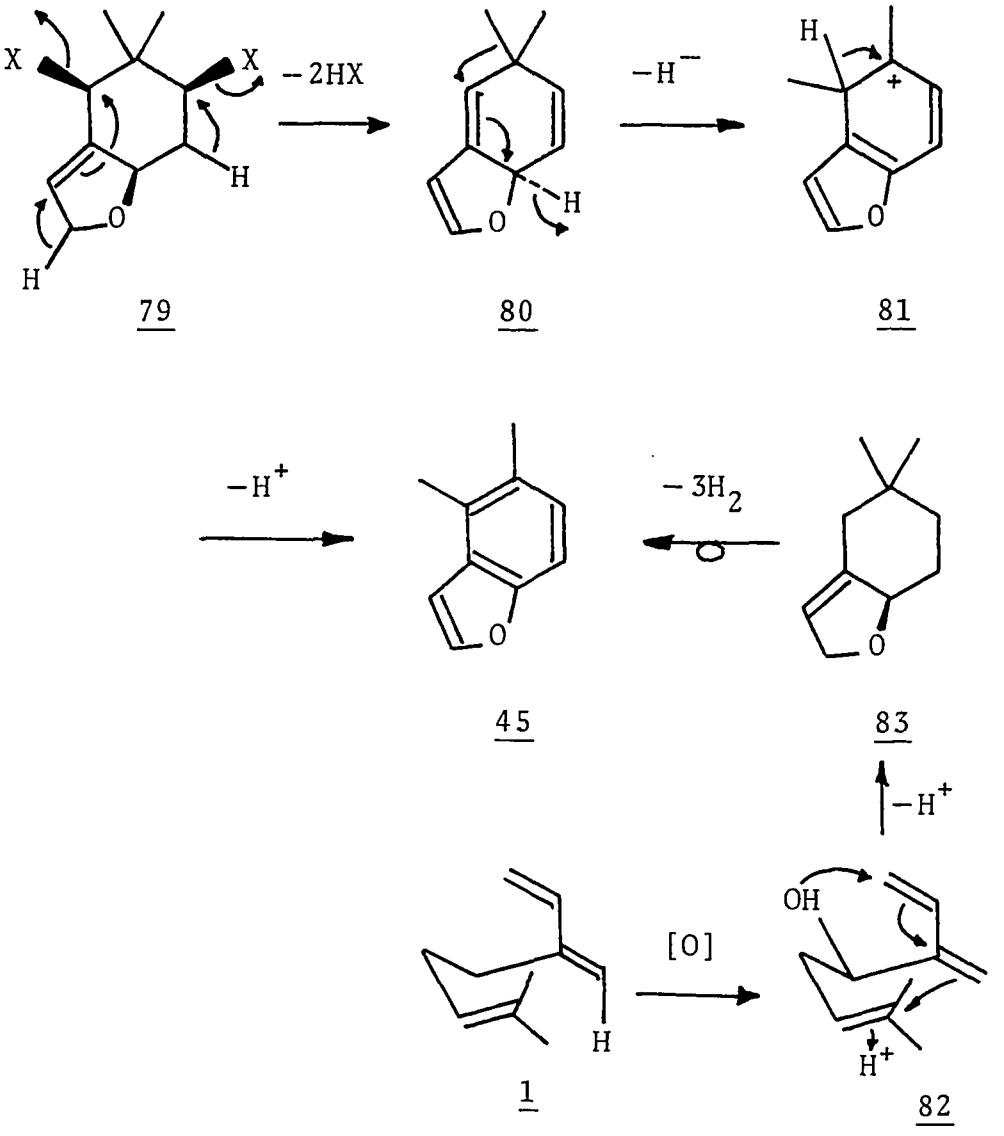


77 78

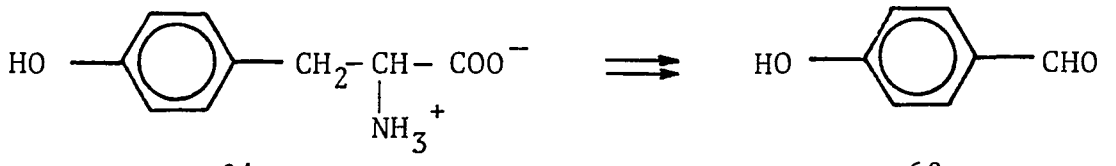


33

Benzofuran 45 may also be derived from a chondrocole (79) by stepwise dehydrohalogenation and aromatization or from cyclization of myrcenol 82 to 83 followed by aromatization. The former route seems more likely since aromatization of 83 requires the abstraction of three moles of hydrogen and therefore more energy.

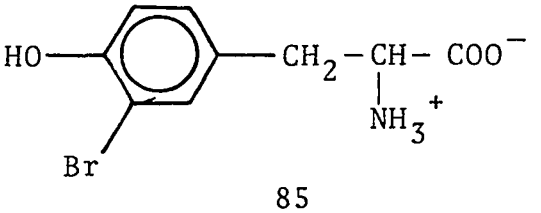


The isolation of p-hydroxybenzaldehyde (60) from C. hornemanni is not unusual since it is a common degradation product of tyrosine (84) and almost always found in plant extracts. The 3-bromo derivative (57), isolated from Black Point C. hornemanni, is almost certainly a degradation product of 84 but it is not clear when the bromination



84 60

of the aromatic ring takes place. It may be that 60 is brominated to give 57 but it is also possible that 57 is directly derived from m-bromotyrosine (85).



85

If the latter is the actual mode of formation the interesting question is then raised as to whether or not C. hornemanni utilizes halogenated amino acids such as 85 in protein synthesis. However, this aspect of the alga's metabolism was not investigated.

E. Summary

In this study on Chondrococcus hornemanni the structures of chondrocole A (25) and condrocole B (24) were elucidated. In addition, fractionation of the nonvolatile extract from plants collected at the Halona Blowhole resulted in the isolation and structure determination of five new acyclic halogen-containing myrcene derivatives (13, 14, 17, 21, 30) and five new halogen-containing cyclic monoterpenes (33, 41, 43, 45). Fractionation of the nonvolatile extract from plants collected at Black Point resulted in the isolation of only two new compounds (54 and 57). The ether extract of Sri Lankan C. hornemanni was found to contain a large amount of 59 and several compounds whose structures were not determined because of insufficient quantities.

The isolation of compounds 13, 14, 17 and 57 strongly suggested that the halogenated monoterpenes present in the essential oil are formed in vivo by enzymatic addition of BrCl to myrcene followed by one or more dehydrohalogenation steps. The in vitro addition of BrCl to myrcene resulted in a complex product mixture consisting of highly halogenated myrcene derivatives. The compounds could not be separated by column chromatography but the pmr spectrum of the crude mixture indicated that BrCl had been predominately added anti-Markovnikov to the $\Delta^{6,7}$-double bond of myrcene.

III. EXPERIMENTAL

A. General

1. Instruments

Continuous wave (cw) pmr spectra were determined on a Varian A-60 spectrometer or a Varian HA-100 spectrometer. Fourier transform (ft) pmr and cmr spectra were determined on a Varian XL-100 spectrometer equipped with a Digilab fourier transform system. Single frequency off-resonance decoupling experiments were carried out with the proton decoupler at δ14. All chemical shifts are reported in δ units (parts per million) relative to tetramethylsilane (TMS, δ=0) as an internal standard in deuteriochloroform unless otherwise noted. Signal multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (b).

Infrared (ir) spectra were determined either on a Perkin-Elmer 467 spectrometer or a Beckman IR-10 spectrometer. Liquids were recorded neat between sodium chloride plates and solids were determined either as nujol mulls or dilute solutions. Absorption bands are designated as strong (s), medium (m), weak (w) and broad (br).

Ultraviolet (uv) spectra were recorded in ethanol solvent either on a Carey 14 spectrometer or a Beckman C III ACTA spectrometer using quartz cells.

Mass spectra (ms) were recorded on a Varian MAT high resolution mass spectrometer operating at 70 eV. Gas chromatography-mass spectrometry (gc-ms) was carried out with a Hewlett-Packard 5700 gas chromatograph coupled through a double-stage jet separator to a JEOL JMS-01SG-2 double focusing mass spectrometer operating at 70 eV.

Melting points were determined on a Thermolyne MP-12600 melting point apparatus and are uncorrected.

Optical rotations were determined on an ETL-NPL automatic polarimeter (Type 143 A) using a sodium vapor lamp. The concentrations of the substrates are presented as grams per 100 ml of solvent.

2. Solvents

All solvents employed were reagent grade or better and were distilled prior to use.

Tetrahydrofuran (THF) was dried by refluxing overnight with calcium hydride and then distilled from red-al [$NaAlH_2(OCH_2CH_2OCH_3)_2$, Aldrich Chemical Co.] under nitrogen or argon.

Benzene and pyridine were dried by distilling over barium oxide.

Boron trifluoride etherate (Eastman Organic Chemicals, Rochester, New York) was distilled under aspirator pressure and stored under nitrogen in sealed

glass ampoules at -20° until needed.

3. Sorbents

Sephadex LH-20 (Pharmacia Fine Chemicals, Piscataway, N. J.), silica gel (Bio-Sil A, 200-400 mesh, Bio-Rad Laboratories, Richmond California), silica gel G (for tlc acc. to Stahl, distributed by Brinkmann Instruments Co.) and alumina (M. Woelm, Germany) were used without further treatment.

B. Fractionation of the First Batch of Halona Blowhole Chondrococcus Extract

1. Extraction of Plants

Frozen plants of C. hornemanni collected at the Halona Blowhole were thawed and placed in a large vacuum desiccator equipped with a series of two cold finger traps cooled with dry ice. The alga was then subjected to high vacuum (0.1 torr) until dry. The dried plants (76.8 g) were steeped in 0.5 l of methanol for 16 hours and the solvent decanted. The extraction procedure was repeated with an additional 0.5 l of methanol and two 0.5 l portions of distilled ether. The solvents were evaporatively removed in a common flask to give a dark oil that was dissolved in 400 ml of methanol and filtered. The methanolic solution was then extracted with heptane (3 X 200 ml), the heptane layers combined and the solvent

removed *in vacuo* to give 2.0 g (2.6%) of dark oil. Evaporation of the methanol layer gave 14.6 g (19.6%) of an oily solid that was mostly inorganic salts with a small amount of fatty material (by pmr).

2. Isolation of Compounds from Heptane Soluble Oil

The heptane soluble oil from above was applied to a 41" X 1" column of Bio-Sil A (200-325 mesh) with hexane and the column successively eluted with hexane, methylene chloride/hexane mixtures and finally 100% methylene chloride to give 23 fractions (A-W) which were monitored for new compounds by pmr.

a. *6-Bromo-3-bromomethyl-3,7-dichloro-7-methyloct-1-ene (13) and 7-bromo-3-bromomethyl-3,6-dichloro-7-methyloct-1-ene (14)*.

Fraction C (680 mg, 34.0%) eluted with hexane and was rechromatographed on a 44" X 5/8" column of Bio Sil-A with hexane to give 100 mg of a 3:1 mixture of *13* and *14*. Repeated chromatography on silica gel G, Sephadex LH-20 and alumina HF-254 failed to separate the mixture; pmr δ1.70 (s, 3H, major), 1.80 (s, 3H, major), 1.95 (s, 3H, minor), 2.5 (m), 3.0 (m), 3.69 (ABq), 4.04 (d, J=9.5 Hz, major), 4.07 (d, J=9.5 Hz, minor), 5.35 (d, J=10 Hz), 5.48 (d, J=17 Hz), 5.97 (dd, J=10 and 17 Hz, major),

6.01 (dd, J=10 and 17 Hz, major); cmr (14) 138.1 (d), 117.6 (t), 71.8 (s), 71.9 (s), 64.9 (d), 40.2 (t), 38.4 (t), 33.1 (q), 29.8 (t), 27.0 (q) ppm; cmr (15) 137.9 (d), 117.8 (t), 72.1 (s), 71.4 (d), 67.5 (s), 40.8 (t), 37.4 (t), 33.5 (q), 29.9 (t), 28.0 (q); ms m/e (rel. intensity), no M^+ ion, 253 (11), 251 (44), 249 (31), 215 (15), 213 (12), 207 (18), 205 (29), 79 (100).

Anal. calcd. for $C_{10}H_{16}Br_2Cl_2$: C, 32.82; H, 4.41; Br, 43.67; Cl, 19.38. Found: C, 32.85; H, 4.27; Br, 43.42; Cl, 19.26.

b. Z-1-Bromo-2-(1-bromo-2-chloroethyl)-6-methylhepta-1,5-diene (17).

Repeated chromatography of the mixture of 13 and 14 provided 10 mg (0.5%) of 17 as a pale yellow oil; pmr δ1.67 (s, 3H), 1.73 (s, 3H), 2.3 (m, 4H), 3.6 (AB part, J_{gem}= -11 Hz, 2H), 4.61 (dd, X part, J=6.5 and 8.5 Hz, 1H), 5.2 (m, 1H); cmr 152.0, 141.9, 134.0, 122.9, 62.7, 60.2, 33.0, 32.8, 30.0, 26.4 ppm; ms m/e (rel. intensity) 328,330,332,334 (1:1.5:2:0.5, <1), 253 (4), 251 (12), 249 (11), 215 (3), 213 (3), 69 (100).

Compound 17 was reacted with chromous sulfate in DMF by the procedure of Mynderse[14] to give a small amount (~ 3 mg) of highly odorous oil. Gas chromatographic analysis of the oil on a 30' X 1/8"

copper column of 30% DEGGS on Varaport 30 (70/80) showed it to consist of starting material (17) and 4. The retention time of synthetic 4 (4.2 min) was identical to that of the naturally occurring material.

c. Z-3-Bromomethylene-2-chloro-7-methyl-1,7-octadien-3-one (21).

Fraction F (60 mg, 3.0%) eluted with 2% methylene chloride/hexane and was rechromatographed on a 35 cm X 1 cm column of silica gel G with hexane followed by methylene chloride to give 15 mg (0.7%) of impure 21; pmr δ1.90 (bs, 3H), 2.74 (m, 4H), 5.43 (d, J=2 Hz, 1H), 5.51 (d, J=2 Hz, 1H), 5.77 (bs, 1H), 5.95 (bs, 1H), 6.89 (s, 1H); ir (CH_2Cl_2) 2920 (br, s), 2870 (br, s), 1680 (br, s) cm^{-1}.

d. Chondrocole A (25).

Fractions I-K (21.0%) eluted with 10% methylene chloride/hexane and contained essentially pure 25; $[\alpha]_D^{24.0} = -16°$ (c=6.2, CH_2Cl_2); pmr δ1.15 (s, 3H), 1.33 (s, 3H), 2.05 (ddd, J=10, 12 and 13 Hz, 1H), 2.65 (ddd, J=4, 6 and 12 Hz, 1H), 4.64 (s, 1H), 4.72 (dd, J=2 and 5 Hz, 2H), 5.0 (m, 1H), 5.78 (m, 1H); cmr 137.6 (s, C-3a), 122.3 (d, C-3), 80.7 (d, C-7a), 75.4 (t, C-2), 63.8 (d, C-6), 54.4 (d, C-4), 41.7 (t, C-7), 41.7 (s, C-5), 27.6 (q), 21.0 (q) ppm;

ir (neat) 2980 (s), 2860 (s), 1455 (m), 1390 (m), 1370 (m), 1260 (m), 1235 (m), 1190 (w), 1165 (w), 1080 (s), 1035 (w), 990 (w), 970 (m), 890 (m), 835 (m), 750 (s), 730 (s), 695 (s) cm^{-1}; ms m/e (rel. intensity) 268 (0.5), 266 (1.4), 264 (1.2), 251 (0.5), 249 (1.1), 247 (0.5), 231 (11), 229 (1.1), 187 (33), 185 (100).

e. Z-6-Bromomethylene-7-chloro-2-methylocta-1,7-diene-3-ol (30).

Fraction R (20 mg, 1.0%) eluted with 1:1 methylene chloride/hexane and contained nearly pure 30; pmr δ1.78 (bs, 3H), 2.6 (m, 2H), 2.7 (m, 2H), 4.36 (t, J=6.5 Hz, 1H), 5.06 (bs, 2H), 5.44 (d, J=2 Hz, 1H), 5.54 (d, J=2 Hz, 1H), 6.87 (s, 1H).

f. Compound 32.

Fractions S and T (90 mg, 4.5%) eluted with 1:1 methylene chloride/hexane and contained mostly 32 and a small amount of 30; pmr δ1.45 (s, 3H), 1.38 (s, 3H), 1.78 (m, 2H), 3.30 (m, AB part, 2H), 3.67 (m, X part, 1H), 5.47 (d, J=2 Hz, 1H), 5.54 (d, J=2 Hz, 1H), 5.66 (d, J=2 Hz, 2H), 6.98 (s, 1H).

C. Fractionation of the Second Batch of Halona Blowhole *Chondrococcus* Extract

1. Extraction of Plants

For the second extraction plants of *C. hornemanni* were collected in small amounts (~ 50 g wet) from the rocky shelves in the cove near the Halona Blowhole and at a depth of ca. 3 m near the mouth of the cove between September 1975 and March 1976. The plants were then quickly frozen and stored at -20°. The plants from the shelves were vacuum dried as previously described to give 1.26 g (0.33%, based on dry weight of seaweed) of essential oil. Similar treatment of the plants collected from the bottom afforded 0.42 g (0.24%) of essential oil whose pmr spectrum was identical to that of the shelf material. The dried seaweed was then combined (377 g) and extracted with methanol as described on page 88 with the exception that methylene chloride was substituted for ether. Removal of the solvents *in vacuo* gave a dark oil that was slurried in 300 ml of water and the oily suspension extracted with methylene chloride (6 X 30 ml). The extracts were combined and the solvent removed *in vacuo* to give 12.8 g (3.4%) of dark oil.

2. Isolation of Compounds from the Methylene Chloride Soluble Oil

The methylene chloride soluble oil was applied to

a 1 m X 2.5 cm column of Bio-Sil A (200-400 mesh) and the column successively eluted with hexane, methylene chloride/hexane mixtures, methylene chloride, methanol/methylene chloride mixtures and methanol to give 40 fractions. As before, all fractions were monitored for new compounds by pmr.

a. Fractions 1 (4.29 g, 33.5%), 2 (1.15 g, 9.0%) and 3 (0.30 g, 2.3%) contained large amounts of 6, 13 and 14 and were not investigated further.

b. Methoxychondrocole Furan (33).

Fractions 10 and 11 eluted with 25% methylene chloride/hexane and upon removal of the solvent afforded 400 mg (3.1%) of oily residue. Rechromatography of the oil on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform afforded 123.4 mg (0.96%) of pure 33 as a pale yellow oil; $[\alpha]_D^{24.0} = +80.5°$ (c=4.91, CH_2Cl_2); uv(EtOH) λ_{max} = 223 nm (ε=4300); pmr δ0.99 (s, 3H), 1.20 (s, 3H), 3.1 (m, 2H), 3.36 (s, 3H), 3.82 (s, 1H), 4.46 (dd, J=6 and 10 Hz, 1H), 6.30 (d, J=1.5 Hz, 1H), 7.13 (d, J=1.5 Hz, 1H); cmr 148.6 (s, C-7a), 141.3 (d, C-2), 117.0 (s, C-3a), 110.3 (C-3), 80.0 (d, C-4), 57.8 (q, methoxy methyl), 56.4 (d, C-6), 40.9 (s, C-5), 33.1 (t, C-7), 24.7 (q), 20.4 (q) ppm;

ir (neat) 2960 (m), 2920 (m), 2820 (m), 1630 (w), 1505 (w), 1450 (w), 1420 (w), 1390 (2), 1370 (w), 1330 (w), 1295 (w), 1265 (w) 1170 (m), 1090 (s), 1075 (s), 1030 (w), 970 (w), 940 (w), 915 (w), 890 (m), 815 (m), 790 (w), 730 (s) cm^{-1}; ms, calcd. for $C_{11}H_{15}BrO_2$, 258.0254. Found, 258.0255, m/e (rel. intensity) 260 (4), 258 (4), 245 (<1), 243 (<1), 229 (2), 227 (2), 180 (10), 179 (79), 177 (12), 129 (18), 109 (8), 104 (7), 91 (22), 73 (100).

c. Chondrocole A (25).

Fractions 12-14 (2.96 g, 23.3%), which eluted with 25% methylene chloride/hexane, were combined and rechromatographed on an 87 cm X 1.5 cm column of Bio-Sil A with 40% methylene chloride/hexane to give 2.43 g (19.0%) of pure 25. $[\alpha]_D^{24.0} = -48°$ (c=0.62, CH_2Cl_2); pmr δ1.15 (s, 3H), 1.33 (s, 3H), 2.05 (m, 1H), 2.65 (m, 1H), 4.45 (dd, J=4 and 13 Hz, 1H), 4.64 (s, 1H), 4.72 (dd, J=2 and 5 Hz, 1H), 5.0 (m, 1H), 5.78 (m, 1H); cmr 137.6 (s, C-3a), 122.3 (d, C-3), 80.7 (d, C-7a), 75.4 (t, C-2), 63.8 (d, C-6), 54.4 (d, C-4), 41.7 (s, C-5), 41.7 (t, C-7), 27.6 (q), 21.0 (q) ppm; ir (neat) 2980 (s), 2860 (s), 1455 (m), 1390 (m), 1370 (m), 1260 (m), 1235 (m), 1190 (w), 1165 (w), 1080 (s), 1045 (w), 990 (w), 970 (m), 910 (w), 890 (m), 935 (m),

750 (s), 730 (s), 695 (s), 605 (m); ms m/e (rel. intensity) 264,266,268 (1:1.2:0.4, M^+ ion cluster <1%), 249 (11), 251 (11), 185 (100), 187 (33).

d. Hornediol Diacetate (41).

Fractions 19 and 20 (560 mg, 4.4%) were combined and rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give 137.1 mg (1.1%) of pure 41 as a pale yellow oil; $[\alpha]_D^{24.0}$= -23.1° (c=7.6, CH_2Cl_2); pmr δ1.15 (s, 3H), 2.07 (s, 6H), 218 (m, 1H), 2.72 (ddd, J=4, 6 and 13 Hz, 1H), 4.02 (dd, J=4 and 13 Hz, 1H), 4.4 (m, 3H), 5.53 (dd, J=6 and 9 Hz, 1H), 5.78 (bs, 1H); cmr δ170.1 (s, acetate carbonyl), 169.8 (acetate carbonyl), 136.3 (s, C-3), 131.5 (d, C-8), 68.9 (d, C-4), 65.6 (t, C-2), 55.7 (d, C-1), 54.9 (d, C-6), 37.6 (s, C-7), 36.2 (t, C-5), 28.4 (q, gem methyl), 28.4 (q, gem methyl), 23.9 (q, acetate methyl), 20.7 (q, acetate methyl) ppm; ir (neat) 2960 (m), 2930 (m), 1745 (s), 1460 (m), 1370 (s), 1290 (m), 1230 (br, s), 1100 (w), 1070 (w), 1025 (s), 980 (w), 950 (w), 910 (w), 835 (w), 770 (m) cm^{-1}; ms, calcd. for $C_{14}H_{20}BrO_4$, 331.0545. Found, 331.0488, m/e (rel. intensity) 331 (13), 333 (12), 328 (3), 327 (2), 326 (9), 325 (5), 324 (7), 323 (4), 285 (2), 283 (7), 281 (5),

268 (22), 267 (27), 266 (74), 265 (69), 264 (60), 263 (40), 231 (62), 229 (62), 43 (100).

e. Chondrocolactone (43).

Fraction 21 (260 mg, 2.0%) eluted with 100% methylene chloride and was rechromatographed on a 180 mm X 10 mm column of silica gel G with 75% methylene chloride/hexane to give 98 mg (0.8%) of crude 43. Recrystallization from methylene chloride/hexane gave 43 mg (0.3%) of 43 as white needles; mp 107.0-108.0°; $[\alpha]_D^{24.0} = -48°$ (c=0.62, CH_2Cl_2); uv(EtOH) $\lambda_{max} = 229.5$ (ε=3900); pmr δ1.07 (s, 3H), 1.32 (s, 3H), 1.95 (ddd, J=11, 12 and 13 Hz, 1H), 2.94 (ddd, J=4, 6 and 12 Hz, 1H), 4.40 (dd, J=4 and 13 Hz, 1H), 4.78 (s, 1H), 5.17 (ddd, J=2, 6 and 11 Hz, 1H), 6.97 (d, J=2 Hz, 1H); cmr 171.0 (s), 164.4 (s), 115.4, (d), 60.8 (d), 51.0 (d), 42.3 (s), 40.0 (t), 26.9 (q), 20.5 (q) ppm; ir (nujol) 2960 (m), 2920 (m), 1760 (s), 1650 (w), 1450 (m), 1390 (w), 1370 (m), 1330 (w), 1290 (w), 1270 (w), 1245 (w), 1140 (m), 1075 (w), 1060 (m), 1020 (m), 870 (m), 845 (m), 780 (w), 760 (m), 710 (m), 690 (m) cm^{-1}; ms, m/e (rel. intensity) 278,280,282 (1:2.5:0.4, M^+ ion cluster <1), 253 (2), 251 (7), 249 (6), 245 (2), 243 (2), 201 (46), 199 (100, off scale), 163 (47), 130 (47).

f. Hornediol Monoacetate (42).

Fractions 27 and 28 (320 mg, 2.5%) eluted with 1% methanol/methylene chloride and were rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give 10 mg of 42 as a pale yellow oil; $[\alpha]_D^{24.0} = -35°$ (c+1.0, CH_2Cl_2); pmr δ1.14 (s, 6H), 2.07 (s, 3H), 2.2 (m, 1H), 2.78 (ddd, J=4, 6 and 13 Hz, 1H), 3.9 (m, 2H), 4.08 (dd, 4 and 13 Hz, 1H), 4.48 (dd, J=4 and 7 Hz, 1H), 5.55 (bt, J=8 Hz, 1H), 5.85 (bs, 1H); ms, m/e (rel. intensity) 324,326,328 (1:2.5:0.4, M^+ ion cluster <1%), 309,311,313 (1:2.5:0.4, <1), 291 (3), 289 (3), 285 (4), 283 (10), 281 (8), 267 (4), 265 (10), 263 (8), 231 (14), 229 (14), 187 (3), 185 (9), 43 (100).

g. 4,5-Dimethylbenzofuran (45).

Fractions 32 and 33 (270 mg, 2.1%) eluted with 3% methanol/methylene chloride and were rechromatographed on a 130 mm X 10 mm column of silica gel G using the same solvent system to give 45 mg of crude 45 as a pale yellow oil. The oil was chromatographed on a 10 cm X 15 cm X 2 mm silica gel preparative layer plate with 1% methanol/methylene chloride to give 37 mg (0.3%) of 45 as a colorless oil (R_f=0.79); pmr δ2.36 (s, 3H), 242 (s, 3H),

6.72 (d, J=2.5 Hz, 1H), 7.04 (d, J=8 Hz, 1H), 7.22 (d, J=8 Hz, 1H), 7.53 (d, J=2.5 Hz, 1H); ms, calcd. for $C_{10}H_{10}O$, 146.0732. Found,146.0725, m/e (rel. intensity) 146 (20), 145 (10), 131 (19), 115 (11), 77 (100), 65 (55).

h. Fraction 38 (1.20 g, 9.4%) eluted with 25% methanol/methylene chloride and was rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/methylene chloride to give 800 mg (6.2%) of an oily alcohol mixture; pmr δ1.61 (s), 1.68 (s), 1.78 (s), 1.92 (s), 3.2-3.4 (m). Further attempts to separate the mixture by silica gel tlc with 17% methanol/methylene chloride, chloroform and 2% methanol/chloroform failed.

A portion (118 mg) of the alcohol mixture was dissolved in 3 ml of pyridine and the solution cooled to 0°. Acetic anhydride (250 mg) was added, the mixture stored in a refrigerator overnight and then poured into 25 ml of water. The mixture was extracted with methylene chloride (3 X 15 ml) and the extracts combined, washed with 3% aqueous hydrochloric acid (6 X 20 ml), dried ($MgSO_4$) and the solvent removed <u>in vacuo</u> to give 131 mg of pale yellow oil; pmr δ1.60 (s), 1.66 (s), 1.76 (s), 1.90 (s), 2.05 (s), 3.0 (m), 3.29 (dd, J=9 and 12 Hz),

4.45 (d, J=7 Hz), 5.0 (m); ms, m/e (rel. intensity) 391 (1), 390 (1.5), 389 (2), 388 (4), 387 (1.5), 386 (3), 377 (1), 376 (1), 375 (2), 374 (1), 373 (3), 371 (1), 323 (1.5), 322 (2), 321 (3), 320 (7), 319 (3), 318 (6), 317 (1.5), 309 (1.5), 308 (2), 307 (6), 306 (3), 305 (4), 303 (1). Numerous attempts were made to separate the mixture by column chromatography on silica gel G, Sephadex LH-20 and alumina HF-254 and by HPLC using a μ-Porasil column but all resulted in failure.

D. Fractionation of Black Point Chondrococcus Extract

1. Extraction of Plants

Thawed plants of Black Point C. hornemanni were dried as described on page 88 to give 1.27 g (0.26%, based on dry weight of seaweed) of pale yellow essential oil. The dried plants (491 g) were extracted as described on page 93 to give 8.6 g (1.9%) of methylene chloride soluble oil.

2. Isolation of Compounds from the Methylene Chloride Soluble Oil

The methylene chloride soluble oil was applied to a 1 m X 2.5 cm column of Bio-Sil A and the column eluted as described on page 94 to give 40 fractions.

a. Fractions 1-4 (2.65 g, 32.8%) eluted with hexane and contained primarily 47 with minor amounts of 13, 14, 48-51 and some fatty material. None of these fractions were investigated further.

b. Chondrene (54).

Fraction 5, which eluted with 10% methylene chloride/hexane, was rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give 23 mg (0.3%) of 54 as a colorless oil; $[\alpha]_D^{24.0} = +33°$ (c=2.3, CH_2Cl_2); pmr δ1.21 (s, 3H), 1.32 (s, 3H), 2.71 (m, 2H), 3.72 (d, J=7 Hz, 2H), 4.07 (t, J=7 Hz, 2H), 4.80 (bs, 1H), 5.04 (t, J=7 Hz, 1H), 5.88 (dd, J=4 and 4 Hz, 1H); cmr 134.7 (s, C-1), 127.2 (d, C-2), 61.2 (d, C-7), 60.0 (d, C-6), 56.2 (d, C-4), 40.2 (s, C-5), 34.5 (t, C-8), 32.0 (t, C-3), 28.8 (q, methyl), 19.5 (q, methyl) ppm; ms, m/e (rel. intensity), no M^+ ion, 333 (9), 331 (43), 329 (60), 327 (31), 295 (3), 293 (5), 291 (4), 287 (7), 285 (15), 283 (8), 91 (100); ir (neat) 2980 (m), 2940 (m), 2890 (m), 1655 (m), 1460 (m), 1440 (m), 1390 (m), 1370 (m), 1310 (w), 1290 (w), 1235 (m), 1190 (m), 1170 (m), 1150 (m), 1115 (w), 1040 (w), 975 (w), 950 (w), 895 (w), 875 (m), 860 (w), 800 (w), 780 (w), 740 (w), 760 (w), 620 (s) cm^{-1}.

c. Methoxychondrocole Furan (33).

Fractions 11 and 12 eluted with 25% methylene chloride/hexane and contained small amounts of 33.

d. Chondrocole A (25).

Fraction 13 eluted with 50% methylene chloride/hexane and contained a small amount of 25.

e. Chondrocole C (52).

Fractions 14-16 (625 mg, 7.3%) eluted with 1:1 methylene chloride/hexane and were rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give 520 mg (6.9%) of 52 as a pale yellow oil; $[\alpha]_D^{24.0} = -10°$ (c=48.0, CH_2Cl_2); pmr δ1.08 (s, 3H), 1.34 (s, 3H), 2.05 (ddd, J-10, 12 and 12 Hz, 1H), 2.58 (ddd, J=3, 6 and 12 Hz, 1H), 3.92 (dd, J=3 and 12 Hz, 1H), 4.28 (bd, J=2 Hz, 1H), 5.56 (m, 1H), 5.66 (m, 2H), 5.83 (bd, J=2 Hz, 1H); cmr 138.3 (s, C-3a), 124.8 (d, C-3), 82.6 (d, C-7a), 75.3 (t, C-2), 55.7 (d, C-4), 54.8 (d, C-6), 41.4 (t, C-7), 43.6 (s, C-5), 29.1 (q, methyl), 16.0 (q, methyl) ppm; ir (neat) 2990 (m), 2860 (m), 1460 (m), 1460 (m), 1390 (m), 1370 (m), 1350 (w), 1270 (m), 1200 (m), 1170 (w), 1150 (w), 1090 (w), 1070 (m), 1040 (m), 970 (m), 915 (w), 850 (s), 810 (w), 665 (w) cm^{-1}; ms, calcd. for $C_{10}H_{14}Br_2O$, 307.9411.

Found 307.9411, m/e (rel. intensity) 312 (9), 310 (20), 308 (9), 297 (1), 295 (2), 293 (1), 231 (100), 229 (100), 159 (81), 149 (90), 79 (90), 81 (94), 80 (35).

f. Compound 55.

Fractions 23-29 (0.64 g, 7.4%) eluted with 3% methanol/methylene chloride and were rechromatographed on a 1 m X 2.5 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give 77 mg (0.9%) of 55 as a light yellow oil; pmr δ1.24 (d, J-6 Hz, 3H), 1.76 (s, 3H), 1.9 (m, 4H), 3.44 (ABq, 2H), 3.88 (q, J=6 Hz, 1H), 4.44 (q, J=6 Hz, 1H), 4.95 (m, 2H), 5.70 (m, 2H), 5.96 (dd, J=11 and 17 Hz, 1H).

g. 3-Bromo-4-hydroxybenzaldehyde (57).

Eluting just prior to 55 on Sephadex LH-20 was a small amount (49 mg, 0.6%) of 57; pmr δ6.98 (d, J=8 Hz, 1H), 7.66 (dd, J=2 and 8 Hz, 1H), 7.98 (dd, J=2 Hz, 1H), 9.74 (s, 1H); ms, calcd. for $C_7H_4BrO_2$ (M-1), 198.9402. Found 198.9395, m/e (rel. intensity), 202 (61), 200 (61), 201 (100), 199 (97), 171 (18), 173 (19), 143 (18), 145 (19).

E. Fractionation of the First Batch of Sri Lankan *Chondrococcus* Extract

1. Extraction of Plants[13]

Dried plants (100 g) of *C. hornemanni*, collected at Trincomalee (Foul Point) Sri Lanka, were extracted with ether to give 2.0 g (2.0% based on dry weight of seaweed) of dark oil.

2. Isolation of Compounds from the Ether Extract

The ether extract was applied to a 1 m X 1.5 cm column of Bio-Sil A (200-325 mesh) with hexane and the column eluted as described on page 94 with acetone substituted for methanol. In this manner 25 fractions were obtained.

a. 3-Bromomethyl-3-chloro-7-methyl-1,6-octadiene (59).[13]

Fraction 1 (520 mg, 26.0%) eluted with hexane and was rechromatographed on a 140 mm X 10 mm column of silica gel G with hexane to give 270 mg (13.5%) of 59 as a colorless oil; $[\alpha]_D^{25} = -3.7°$ (c=14.69, CH_2Cl_2), pmr δ1.63 (s, 3H), 1.69 (s, 3H), 1.9-2.3 (m, 4H), 3.68 (ABq, 2H), 5.12 (m, 1H), 5.21 (dd, J=1 and 10.0 Hz, 1H), 5.40 (dd, J=1 and 16.5 Hz, 1H), 5.94 (dd, J=10.0 and 16.5 Hz, 1H); cmr 138.6 (d), 132.6 (t), 122.5 (d), 116.9 (t), 72.4 (s), 40.1 (t),

39.2 (t), 25.6 (q), 23.0 (t), 17.7 (q) ppm; ir (neat) 2960 (s), 2915 (s), 2850 (s), 1644 (m), 1440 (s), 1410 (m), 1379 (m), 1230 (m), 1105 (m), 980 (s), 929 cm^{-1}; ms, m/e (rel. intensity) 250,252,254 (0.8:1:0.2, M^+ ion cluster <1), 217 (4), 215 (4), 135 (73), 93 (63), 91 (29), 69 (100), 41 (84).

b. Compound 61 (or 62).

Fraction 11 (140 mg, 7.0%) eluted with 15% acetone/methylene chloride and was rechromatographed twice on silica gel G with the same solvent system to give a dark yellow oil. Chromatography of this oil on a 140 mm X 10 mm column of silica gel G with 2% methanol/methylene chloride gave 12 mg (0.6%) of crude 61 (or 62) as a brownish yellow oil followed by 7 mg (0.3%) of p-hydroxybenzaldehyde (60). The pmr spectrum of 61 (or 62) was as follows: δ1.79 (s, 3H), 2.0 (m, 6H), 3.56 (ABq, 2H), 4.87 (bs, 1H), 5.10 (bs, 1H), 5.18 (dd, J=2 and 10 Hz, 1H), 5.32 (dd, J=2 and 17 Hz, 1H), 5.92 (dd, J=10 and 17 Hz, 1H).

F. Fractionation of the Second Batch of Sri Lankan Chondrococcus Extract

1. Extraction of plants

Dried plants of Sri Lankan C. hornemanni were

extracted with ether as described on page 104 to give 5.2 g of crude extract.

2. Isolation of Compounds from the Ether Extract

The ether extract (5.2%), which contained approximately 30-40% diethyl acetal, was applied to a 1 m X 2.5 cm column of Bio-Sil A with hexane and chromatographed as described on page 104 to give 31 fractions.

a. Fraction 2 (360 mg, 6.9%), which eluted with hexane, was nearly pure 58 and was not investigated further.

b. Fraction 3 (120 mg, 2.4%), which eluted with hexane, contained a doublet (J=8 Hz) at δ3.68 in its pmr spectrum. However, rechromatography of the fraction on a 150 mm X 10 mm column of silica gel G with hexane provided only fatty materials.

c. Compound 63.

Fraction 6 (120 mg, 2.4%) eluted with 20% methylene chloride/hexane and was rechromatographed on a 150 mm X 10 mm column of silica gel G with 5% methylene chloride/hexane to give 6 mg (0.01%) of 63 as an oil; pmr δ1.02 (s, 3H), 1.18 (d ?), 1.24 (s, 3H), 1.6 (m, 1H), 2.6 (m, 2H), 4.1 (m, 2H),

4.8 (m, 3H), 6.00 (dd, J=6 and 10 Hz, 1H).

d. Fraction 13 (720 mg, 13.9%) eluted with 100% methylene chloride and contained multiplets between δ5.6 and 6.1 in its pmr spectrum. However, rechromatography of the fraction on a 170 mm X 10 mm column of silica gel G with methylene chloride provided only diethyl acetal and fatty compounds.

e. Compound 64.

Fractions 16-20 (848 mg, 16.3%) eluted with 15% acetone/methylene chloride and were rechromatographed on a 165 mm X 10 mm column of silica gel G with methylene chloride to give 60 mg (1.1%) of 64 as a pale green oil; pmr δ1.7 (m, 4H?), 1.71 (s, 3H), 4.47 (q, J=6 Hz, 1H), 5.0 (m, 2H), 6.2 (m, 2H), 5.95 (dd, J=11 and 18 Hz, 1H), 6.86 (s, 1H).

G. Synthesis of Compounds

1. Chondrocolactone (44) from Chondrocole A (25).

To a cooled (0°) solution of 120 mg (0.45 nmol) of chondrocole A (25) in 12 ml of ether was added 0.35 ml of dichromate solution [prepared by dissolving 10 g (33 nmol) of $Na_2Cr_2O_7 \cdot 2H_2O$ in 3 ml of water followed by the addition of 13.6 g (0.134 mol) of 97% H_2SO_4 and dilution to 50 ml with water]. After stirring at

4° for 13.5 hours 20 ml of water was added and the layers separated. The aqueous layer was extracted with ether (3 X 15 ml), the extracts combined, washed with 5% sodium bicarbonate solution (2 X 10 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give 95 mg of nearly colorless oil. The oil was chromatographed on a 20 cm X 20 cm X 2 mm silica gel preparative layer plate with 25% methylene chloride/hexane to give 50 mg of 25 and 26 mg (24%) of 44 (R_f=0.22) that was identical in all respects to naturally occurring 44; $[\alpha]_D^{24.0}$= -50° (c=1.17, Ch_2Cl_2).

2. 3-Bromo-4-hydroxybenzaldehyde (57).

Compound 57 was prepared in 69% yield by the procedure of Gattermann[15] and had a pmr spectrum identical to that of the naturally occurring material.

3. Addition of BrCl to Mrycene (1).

A 100 ml three-necked round-bottomed flask equipped with a 50 ml pressure equalizing addition funnel and efficient magnetic stirrer was charged with 2.00 g (16.6 nmol) of myrcene and 20 ml of carbon tetrachloride. The temperature was maintained at 0° and a solution of 2.65 g (16.6 nmol) of BrCl[16] in 25 ml of carbon tetrachloride added dropwise over 1.5 hours with rapid stirring. When the addition was complete the mixture

was washed with 5% sodium bicarbonate solution (2 X 15 ml), water (2 X 15 ml) and brine (2 X 15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give 5.51 g of brownish yellow oil; pmr δ1.1 (m), 1.79 (s), 1.89 (m), 1.8-2.8 (complex m), 4.0 (m), 4.4-6.5 (complex m). Chromatography of the crude oil on a 1 m X 2.5 cm column of Bio Sil-A with hexane failed to separate the complex mixture.

4. *Acetylation of Hornediol Monoacetate (42).*

To 10.0 mg (3.1×10^{-5} mol) of *42* in 0.4 ml of pyridine was added 0.1 ml of acetic anhydride. The mixture was allowed to stand at 4° for 47 hours and then dissolved in 15 ml of water. The aqueous mixture was extracted with methylene chloride (4 X 10 ml), the extracts combined, washed with 3% HCl solution (2 X 5 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give 11.2 mg (98%) of *41* whose pmr spectrum was identical to that of the naturally occurring material.

5. *Attempted Methoxylation of Chondrocole A (25).*

Chondrocole A (*25*, 49 mg, 0.18 nmol) was dissolved in 7 ml of methanol and refluxed for 12 hours. Removal of the solvent *in vacuo* afforded 47 mg of unchanged *25*.

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P A R T T W O

HALOGENATED CONSTITUENTS OF *ASPARAGOPSIS TAXIFORMIS* (DELILE) TREV.

I. INTRODUCTION

A. General

Of the twelve common species of edible seaweeds found in Hawaii the most sought after is a red alga of the Bonnemaisoniaceae family, Asparagopsis taxiformis (Delile) Trev. This alga was so highly prized as a spice in old Hawaii that it was given the name limu kohu, the supreme seaweed, and today it still commands premium prices in the local markets when in season. Although most abundant on the island of Kauai, A. taxiformis can be found on all of the Hawaiian islands in shallow reef areas exposed to wave action.[1] On Oahu the alga grows in significant amounts in shallow water at Waikiki, Black Point and the Halona Blowhole area but small amounts have also been found growing as deep as 30 m where water motion is produced by strong tidal currents. Also present in these areas in the springtime is the sporophytic form of A. taxiformis, Falkenbergia rufanolosa (Harvey) Schmitz, which bears no physical resemblance to the male and female plants. The epiphytic F. rufanolosa, unlike the gametophytic and spermatophytic plants, is not known to be edible.

B. Halogenated Compounds from the Essential Oil of A. taxiformis

A. taxiformis is faintly odoriferous when wet and harvested plants rapidly develop a sharp iodine-like odor upon

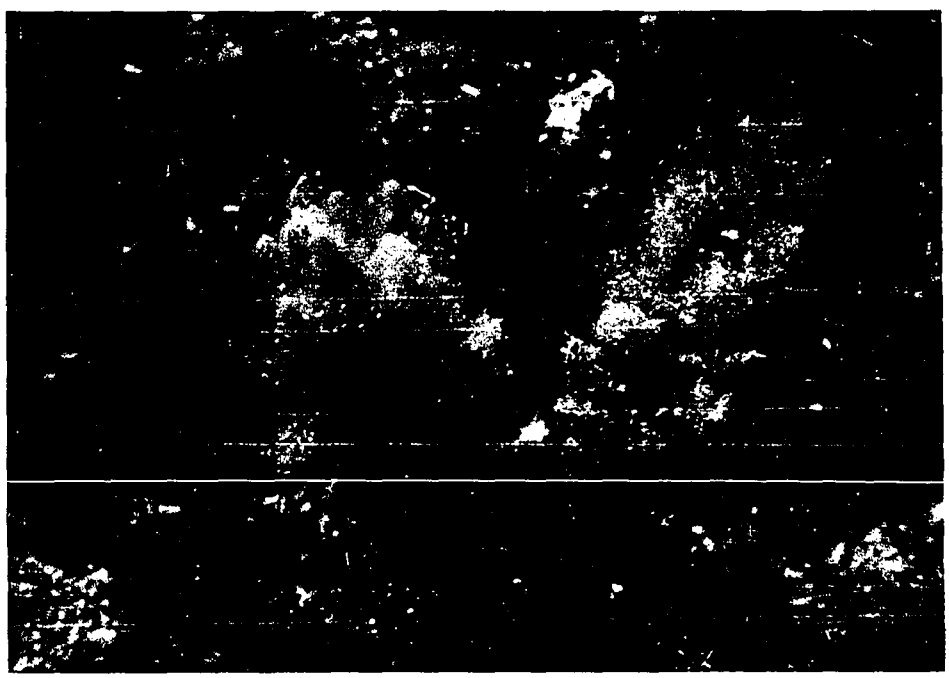


Figure II-1. Male Plants of A. taxiformis in their natural habitat.

standing. To identify the source of this odor Dr. B. J. Burreson in 1975 isolated the essential oil by vacuum drying the wet plants and collecting the volatile materials in dry-ice cooled traps. Once isolated the initially colorless oil rapidly turned deep purple in solution indicating the presence of compounds containing iodine.[2] Column chromatography of the oil on silica gel and analysis of the various fractions by pmr and gc-ms resulted in the identification of many halogenated compounds. However, many of the iodinated compounds such as iodoform (4), clearly visible in the pmr and mass spectrum of the essential oil, decomposed on the silica gel column. Iodoform (4) and iodinated compounds 6, 8, 18, 19, 23, 33, and 37 were detected by gc-ms analysis in fractions obtained by gel filtration and molecular distillation of the essential oil. A complete list of the compounds that compose the essential oil of A. taxiformis is presented in Table II-1. In addition to pmr and mass spectral evidence structural confirmation for compounds 1-7, 9, 10, 12-18, 20-22, 24, 25, 30-32 and 34 was obtained by comparison with commercial or synthetic samples. Carbonyl diiodide was not compared with a synthetic sample but it eluted with the ketone fraction on silica gel and had a molecular ion in the mass spectrum at m/e 282 and peaks at m/e 155 and 127 for $IC{\equiv}O^+$ and I^+ respectively. However, 11 is probably an artifact formed by the decomposition of 4 on the silica gel column since it was not present in any of the fractions

TABLE II-1.

HALOGENATED COMPOUNDS FROM THE ESSENTIAL OIL OF HAWAIIAN ASPARAGOPSIS TAXIFORMIS[2]

Type of Compound	Text No.	Structure
Haloforms	1	$CHBr_3$
	2	$CHBr_2I$
	3	$CHBrI_2$
	4	CHI_3
	5	$CHBr_2Cl$
	6	CHBrClI
Dihalomethanes	7	CH_2Br_2
	8	CH_2BrI
	9	CH_2I_2
Carbon tetrahalides	10	CBr_4
Carbonyl dihalides	11	COI_2
2-Haloethanols	12	ICH_2CH_2OH
1,2-Dihaloethanes	13	$BrCH_2CH_2I$
Halogenated acetaldehydes	14	Br_2CHCHO
Halogenated acetones	15	CH_3COCH_2Br
	16	CH_3COCH_2I

TABLE II-1. (Continued) HALOGENATED COMPOUNDS FROM THE ESSENTIAL OIL OF HAWAIIAN *ASPARAGOPSIS TAXIFORMIS*[2]

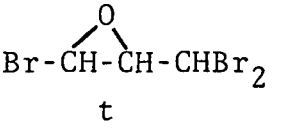
Type of Compound	Text No.	Structure
Halogenated acetones (cont'd)	17	$CH_3COCHBr_2$
	18	$BrCH_2COCH_2Br$
	19	$BrCH_2COCH_2I$
	20	CH_3COCBr_3
	21	CH_3COCBr_2Cl
	22	$BrCH_2COCHBr_2$
	23	$ICH_2COCHBr_2$
	24	$Br_2CHCOCHBr_2$
	25	$Cl_3CCOCCl_3$
Halogenated 2-acetoxypropanes	26	$BrCH_2CH(OAc)CHBr_2$
	27	$Br_2CHCH(OAc)CHBr_2$
Halogenated 1,2-epoxypropanes	28	
1,1,3,3-Tetrahalopropenes	29	$Br_2C=CHCHBr_2$
	30	$Br_2C=CHCHBrCl$
	31	$Br_2C=CHCHCl_2$
	32	$BrIC=CHCHBr_2$

TABLE II-1. (Continued) HALOGENATED COMPOUNDS FROM THE ESSENTIAL OIL OF HAWAIIAN *ASPARAGOPSIS TAXIFORMIS*[2]

Type of Compound	Text No.	Structure
3,3-Dihaloacroleins	33	$Br_2C=CHCHO$
Halogenated butenones	34	$Br_2C=CHCOCH_3$
	35	$Br_2C=CHCOCH_2Br$
	36	$Br_2C=CHCOCH_2I$
	37	$Br_2C=CHCOCHBr_2$
	38	$Br_2C=CHCOCHBrCl$
	39	$BrClC=CHCOCHBr_2$
	40	$Cl_2C=CHCOCHBr_2$
	41	$BrClC=CHCOCHBrCl$

obtained by molecularly distilling the oil. On the other hand, 2-iodoethanol (12), a potential artifact, could not have been formed on the silica gel column since it was clearly visible in the pmr spectrum of the crude essential oil. Curiously, the sporophytic F. rufanolosa was found to produce no essential oil and an examination of the extract revealed no halogenated compounds to be present.

In a simultaneous study Fenical[3] examined the extracts of air-dried Mexican A. taxiformis and identified seven halogenated acetones (18, 22, 24, 48, 51, 52, 55) and four halogenated butenones (60-63). Interestingly, the pmr spectra of 60-63 indicated the olefinic halogens to be vicinally disposed. In later work McConnell and Fenical[4] examined A. taxiformis collected from three locations in the Gulf of California and A. armata from the Spanish Mediterranean. The fresh plants were immediately placed in ethanol and the ethanol decants extracted with purified pentane. Examination of the pentane extracts from A. armata by gc-ms revealed the presence of nine chlorinated acetones (49, 50, 53-55, 56-59) and one halogenated butenone (62). In addition, a halomethane (42) was also identified along with a new dihalomethane (43), two new haloforms (44, 45), a new carbon tetrahalide (46), a haloacetaldehyde (47) and several compounds previously identified in Hawaiian A. taxiformis. The new compounds from Mexican A. taxiformis and Spanish A. armata are presented in Table II-2.

TABLE II-2.

HALOGENATED COMPOUNDS FROM MEXICAN AND/OR SPANISH ASPARAGOPSIS[6]

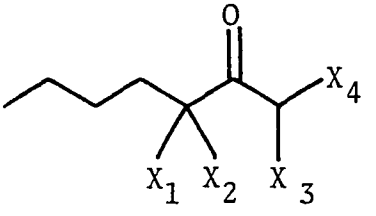
Type of Compound	Text No.	Structure
Methyl halides	42	CH_3I
Dihalomethanes	43	CH_2ClI
Haloforms	44	$CHCl_2Br$
	45	$CHCl_3$
Carbon tetrahalides	46	CCl_4
Haloacetaldehydes	47	$BrCH_2CHO$
Dihaloacetones	48	$BrCH_2COCH_2Cl$
	49	$ClCH_2COCH_2Cl$
	50	$ClCH_2COCH_2$
Trihaloacetones	51	$Br_2CHCOCH_2Cl$
	52	$BrClCHCOCH_2Br$
	53	$Cl_2CHCOCH_2Br$
	54	$Cl_2CHCOCH_2Cl$

TABLE II-2. (Continued) HALOGENATED COMPOUNDS FROM MEXICAN AND/OR SPANISH ASPARAGOPSIS[6]

Type of Compound	Text No.	Structure
Tetrahaloacetones	55	$Br_2CHCOCHBrCl$
	56	$BrClCHCOCHBrCl$
	57	$BrCHCOCHCl_2$
	58	$BrClCHCOCHCl_2$
	59	$Cl_2CHCOCHCl_2$
Halogenated butenones	60	$BrCH=CBrCOCH_2Br$
	61	$BrCH=CBrCOCH_2Cl$
	62	$BrCH=CBrCOCHBr_2$
	63	$BrCH=CBrCOCHBrCl$

C. Related Compounds from other Members of the Bonnemaisoniaceae

Halogenated compounds related to those present in Asparagopsis have been found in several other genera belonging to the Bonnemaisoniaceae family. For example, Bonnemaisonia hamifera has been found to elaborate heptanones 64-68[5] which are the respective C-7 homologs



64 $X_1 = X_2 = X_3 = X_4 = Br$

65 $X_1 = X_2 = X_3 = Br$, $X_4 = H$

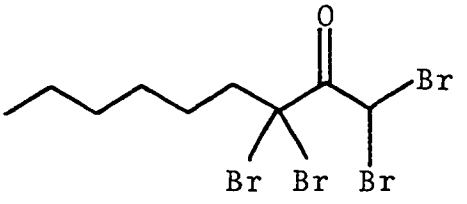
66 $X_1 = H$, $X_2 = X_3 = X_4 = Br$

67 $X_1 = X_3 = H$, $X_2 = X_4 = Br$

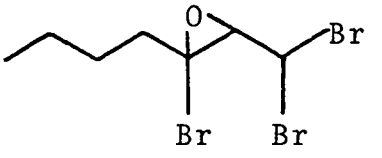
68 $X_1 = X_2 = Br$, $X_3 = H$, $X_4 = I$

of acetones 24, 22, 18 and 23 in Table II-1. McConnell and Fenical[6] have found B. nootkana to contain the C_9 homolog of 24 (69) along with two related epoxides (70, 71).

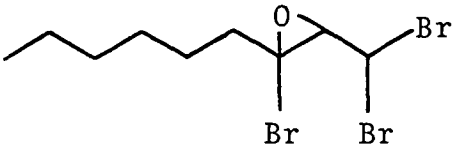
Compounds closely related to the halogenated methyl vinyl ketones from Asparagopsis have been found in Antarctican Delisia fimbriata by Sims and coworkers.[7] Examination



69

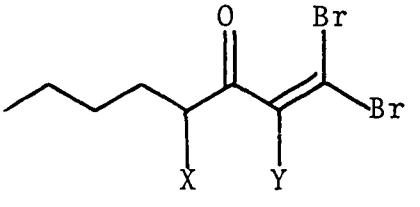


70



71

of the methylene chloride extract provided five halogenated octenones (72-76) whose structures were confirmed by synthesis.



72 X = H, Y = Br

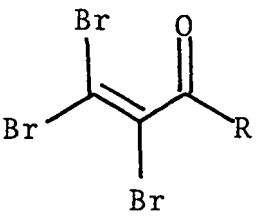
73 X = Y = Br

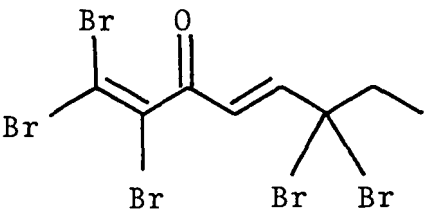
74 X = Cl, Y = Br

75 X = H, Y = I

76 X = Cl, Y = I

In addition, Wells and coworkers[8] have isolated 73 and identified five new vinyl ketones (76-80) from the volatile fractions of Ptilonia australascia.





80

76 R = CH_3

77 R = CH_2Br

78 R = $(CH_2)_4CH_3$

73 R = $CHBr(CH_2)_3CH_3$

79 R = $CBr_2(CH_3)_3CH_3$

To date species of the remaining two genera of the Bonnemaisoniaceae family, Leptophyllis and Pleuroblepharis have not be examined for halogenated constituents.

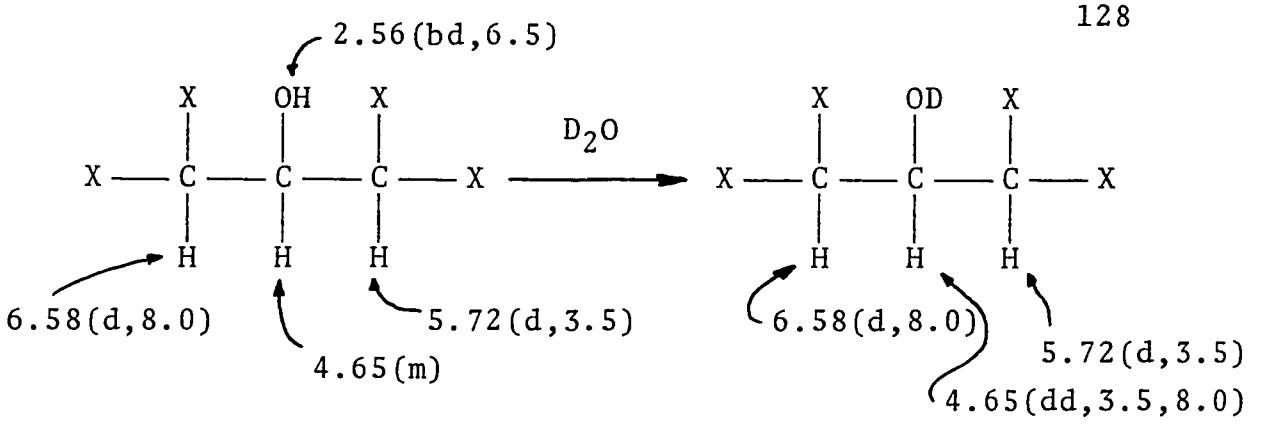
D. Statement of Objectives

The isolation of the essential oil from A. taxiformis resulted in the accumulation of a large quantity of dried plants (~ 300 g). In this study an examination of the nonvolatile extract was undertaken to find out if halogenated compounds related to those identified in the essential oil were present.

II. RESULTS AND DISCUSSION

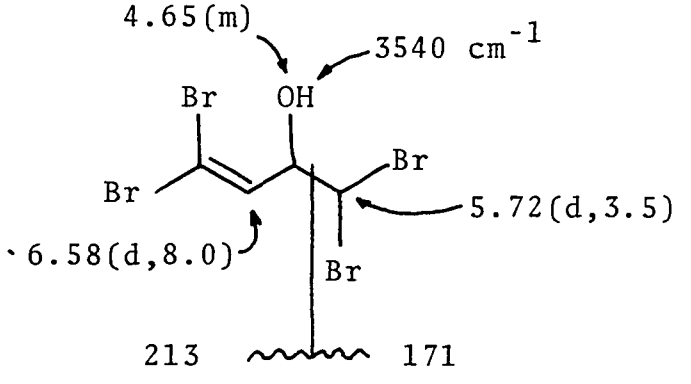
A. Fractionation of the Methylene Chloride Extract of Hawaiian A. taxiformis

The vacuum dried plants of A. taxiformis were extracted with methylene chloride to give a dark oil that was chromatographed on a silica gel column. Gradient elution of the column with hexane followed by ether/hexane mixtures gave 26 fractions that were monitored for new compounds by pmr. Fraction 11 (2.9%), which eluted with 25% ether/hexane, contained numerous low field signals in its pmr spectrum which indicated the presence of a mixture of halogenated compounds. Rechromatography of this fraction on silica gel with the same solvent system provided a solid material that was recrystallized from pentane to give optically active colorless needles. The pmr spectrum of the recrystallized material exhibited three 1H doublets at δ6.58 (J=8.0 Hz), 5.72 (J=3.5 Hz) and 2.56 (J=6.5 Hz) and a 1H multiplet at 4.65. Upon deuterium exchange the doublet at δ2.56 disappeared and the multiplet at 4.65 simplified to a doublet of doublets (J=3.5 and 8.0 Hz). From these data partial structure 81 was assigned to the molecule in which the X's represent electronegative substituents. The mass spectrum of the compound showed a weak molecular ion at m/e 384,386, 388,390,392 (1:2:4:2:1) for $C_4H_4Br_4O$ and clusters at m/e 213,215,217 (1:2:1) and 171,173,175 (1:2:1) for $C_3H_3Br_2O^+$ and $CHBr_2^+$, respectively. The presence of the hydroxyl



81 82

group was confirmed by a strong stretch at 3540 cm^{-1} in the infrared spectrum. With these data the structure of the compound was tentatively assigned as shown in 83.



83

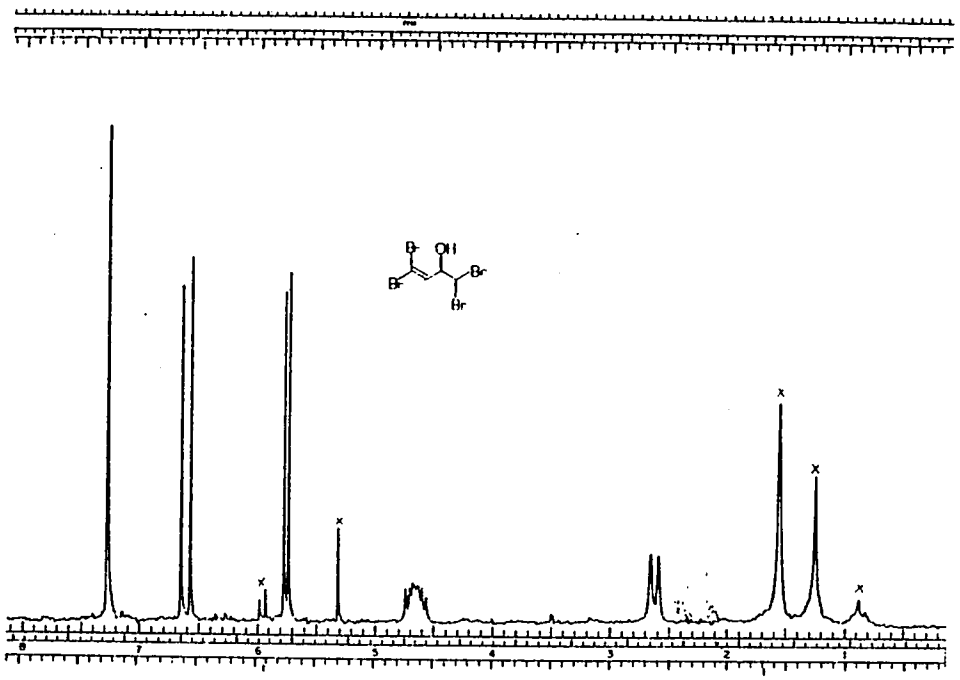


Figure II-2. Pmr spectrum ($CDCl_3$) of compound 83

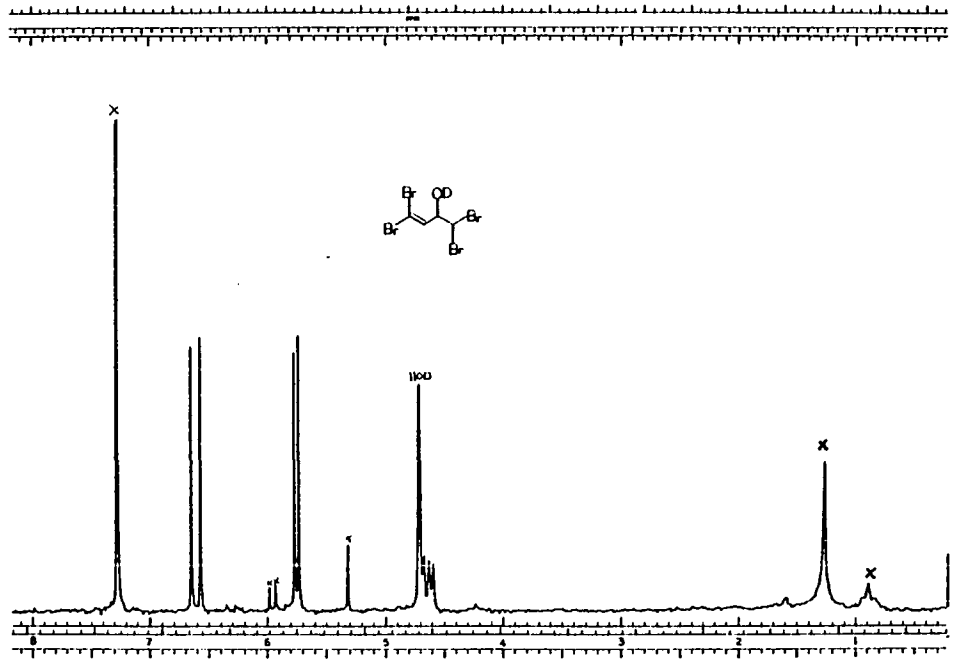


Figure II-3. Pmr spectrum ($CDCl_3$) of deuterium exchanged 83.

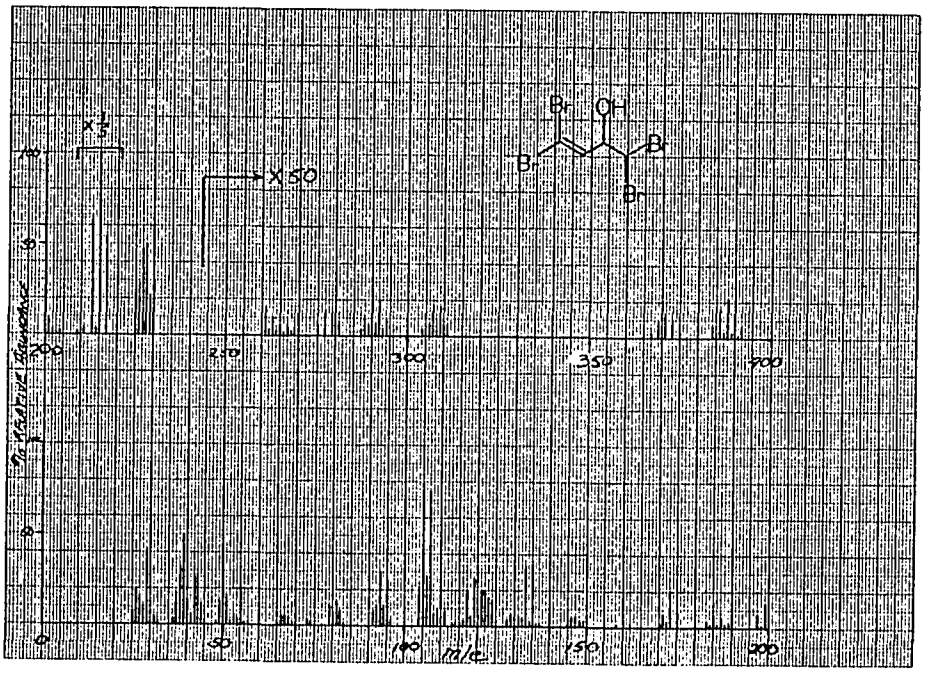


Figure II-4. Mass spectrum (70eV) of compound 83.

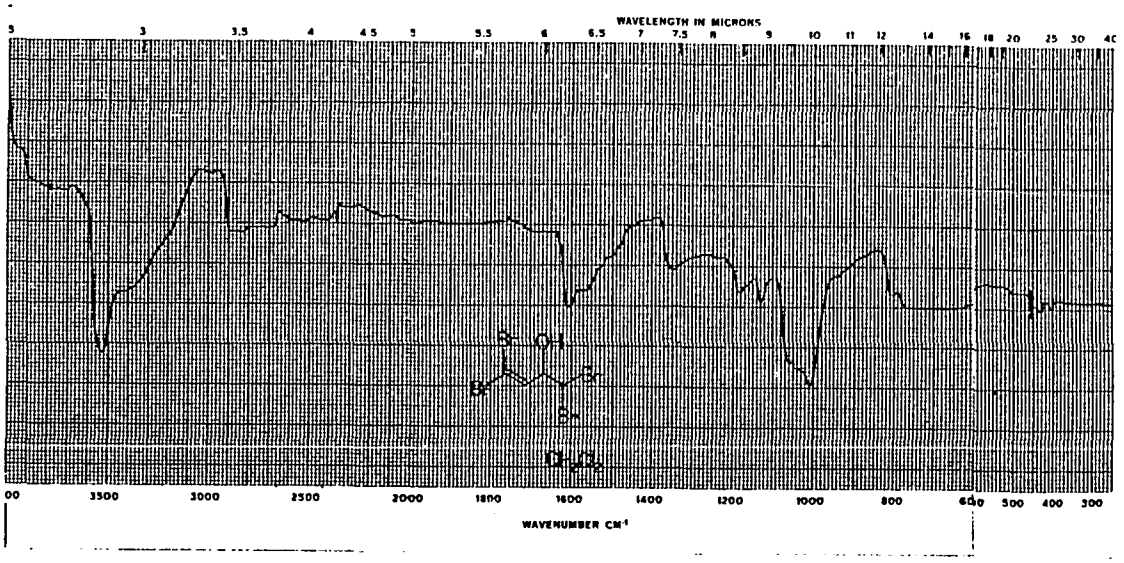
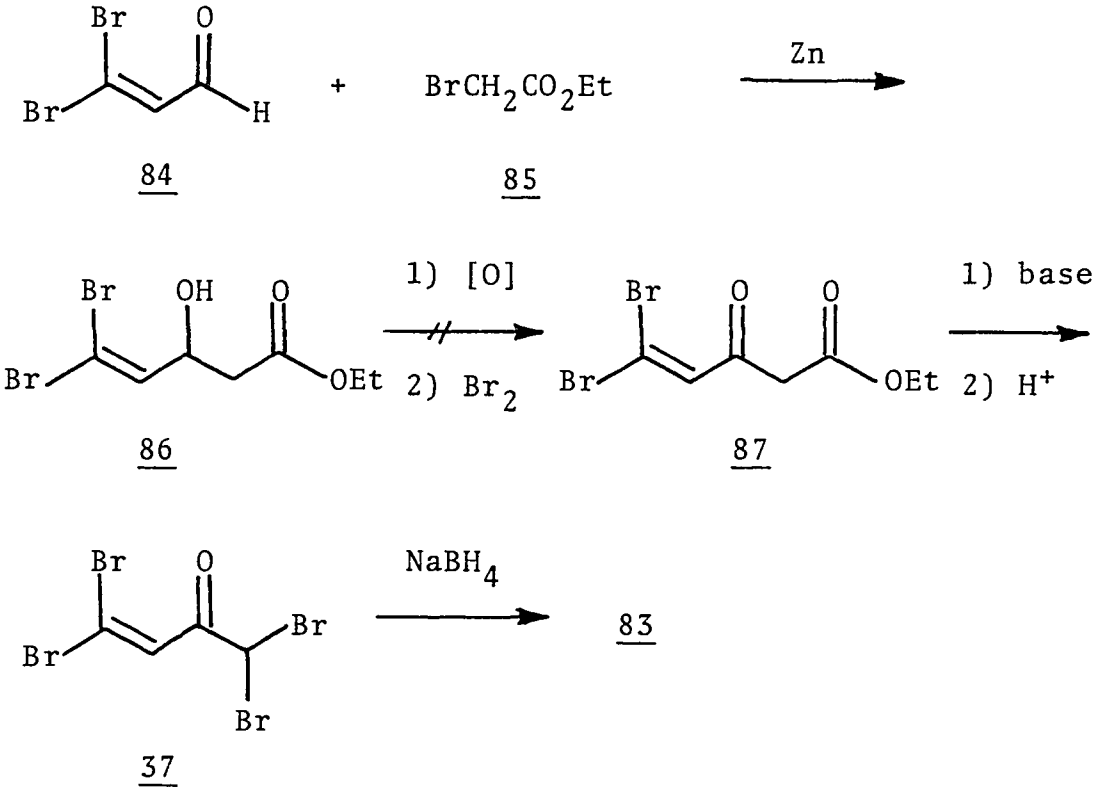


Figure II-5. Ir spectrum (CH_2Cl_2) of compound 83.

To verify the positions of the bromines on the double bond in 83 a synthesis beginning with 3,3-dibromoacrolein (84) was attempted by the route shown in Scheme II-1. The

Scheme II-1

Attempted Synthesis of Compound 83



Reformatsky reaction (84 + 85 → 86) proceeded to give a small amount (7.3% yield) of 86 whose pmr spectrum showed a doublet (J=8.0 Hz) at δ6.33 for the olefinic proton, a doublet of triplets (J=6.0 and 8.0 Hz) at 4.55 for the alcohol methine, a doublet (J=6.0 Hz) at 2.49 for the methylene proton and signals at 4.02 (q, J=6.0 Hz) and 1.21 (t, J=6.0 Hz) for the ethyl ester. All attempts to

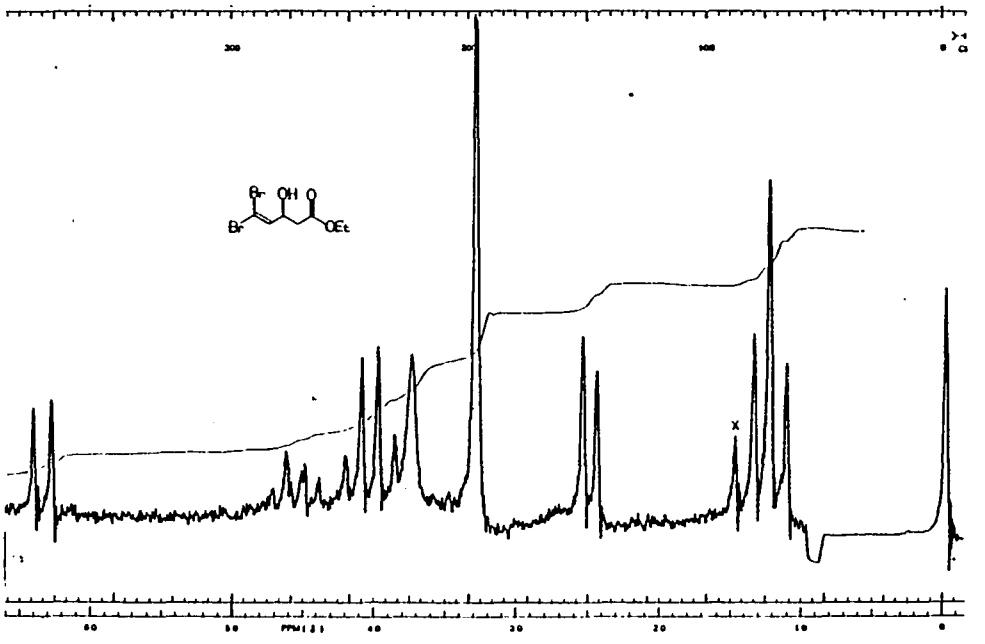
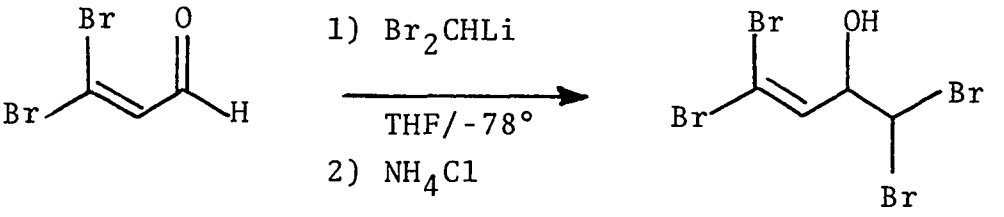


Figure II-6. Pmr spectrum ($CDCl_3$) of compound 86.

oxidize 86 with either activated manganese dioxide, 2,3-dichloro-1,4-dicyano-quinone (DDQ) and pyridinium chlorochromate, however, resulted in the isolation of either starting material or polymeric products and Scheme II-1 was abandoned.

A simple one-step synthesis of 83 was achieved with a procedure developed by Yamamoto and coworkers[9] for the preparation of α-haloalcohols from ketones and aldehydes in the presence of halomethyl lithium reagents. The reaction of dibromomethyl lithium, prepared by reacting methylene bromide with lithium dicyclohexyl amide (LDA), with 84 gave a 24% yield of racemic 83 that had a pmr spectrum and melting point identical to that of the naturally occurring



84 83

material. In addition, sodium borohydride reduction of a sample of tetrabromobutenone 37 also gave 83 whose pmr spectrum was identical to that of the natural compound.

The mother liquor from the recrystallization of 83 was evaporated to give a pale yellow oil whose pmr spectrum revealed the presence of a mixture of compounds. The major

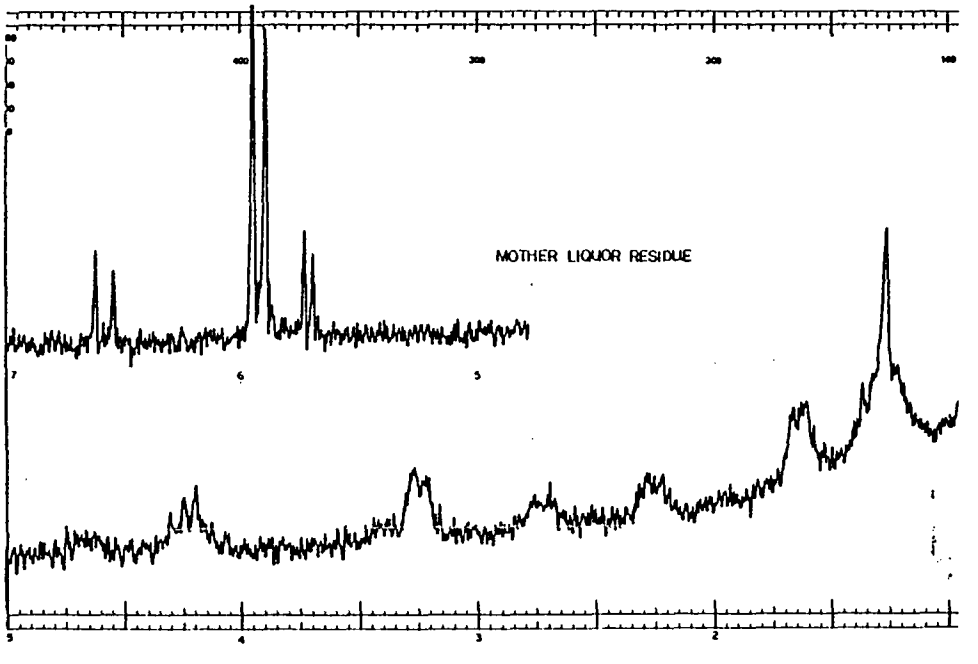


Figure II-7. Pmr spectrum ($CDCl_3$) of the mother liquor residue from the recrystallization of 83.

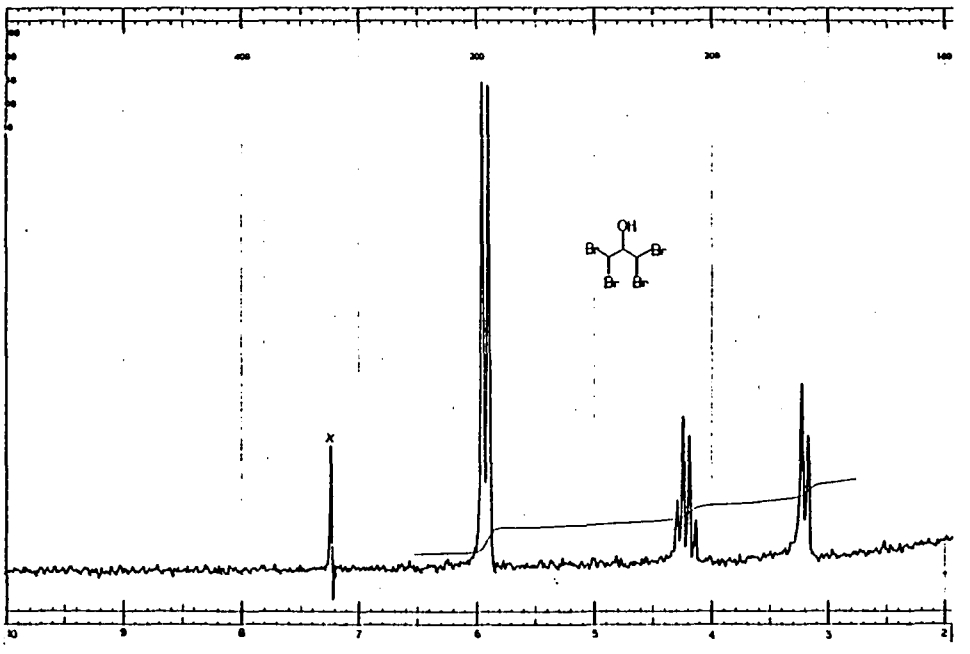
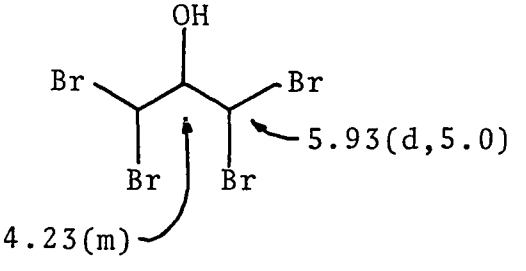


Figure II-8. Pmr spectrum ($CDCl_3$) of synthetic 88.

component exhibited a doublet (J=5.0 Hz) at δ5.93 and a multiplet at 4.23 and was shown to be 1,1,3,3-tetrabromo-2-propanol (88) by comparison with the pmr spectrum of a synthetic sample. Further analysis of the oil by gc-ms revealed the presence of nine other halogenated 2-propanols



88

(99-107) and four halogenated but-3-en-2-ols (110, 111, 113, 114).

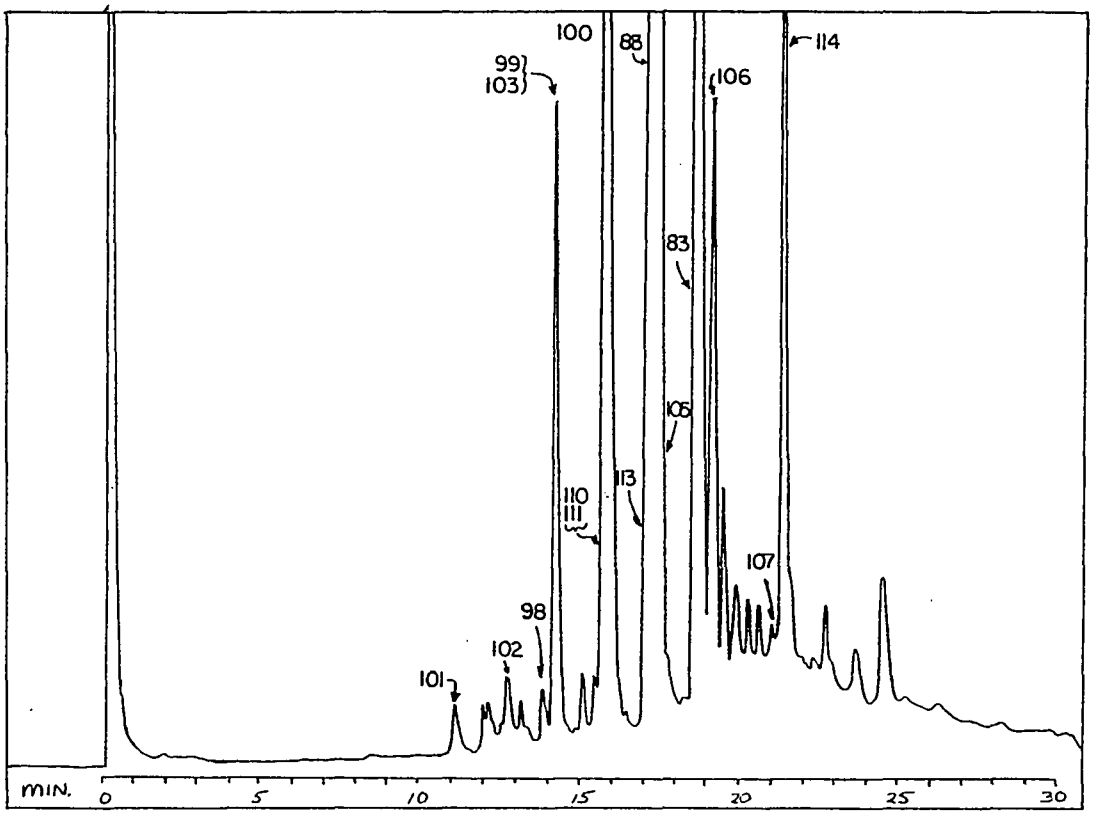


Figure II-9. Gc trace of the mother liquor residue from the recrystallization of 83.

The major components of fraction 12 (4.8%) were found to be 1,1,3-tribromo-2-propanol (98) and 1,1-dibromo-3-chloro-2-propanol (97). The pmr spectrum of 98 showed doublets at δ3.30 (J=5 Hz), 3.66 (J=5 Hz) and 5.40 (J=4 Hz) and a multiplet at 4.15. The spectrum of 97 was identical to that of 98 with the exception that the doublet (J=5 Hz) at δ3.66 was shifted downfield and appeared at 3.76. Gc-ms analysis of the fraction resulted in the identification of nine

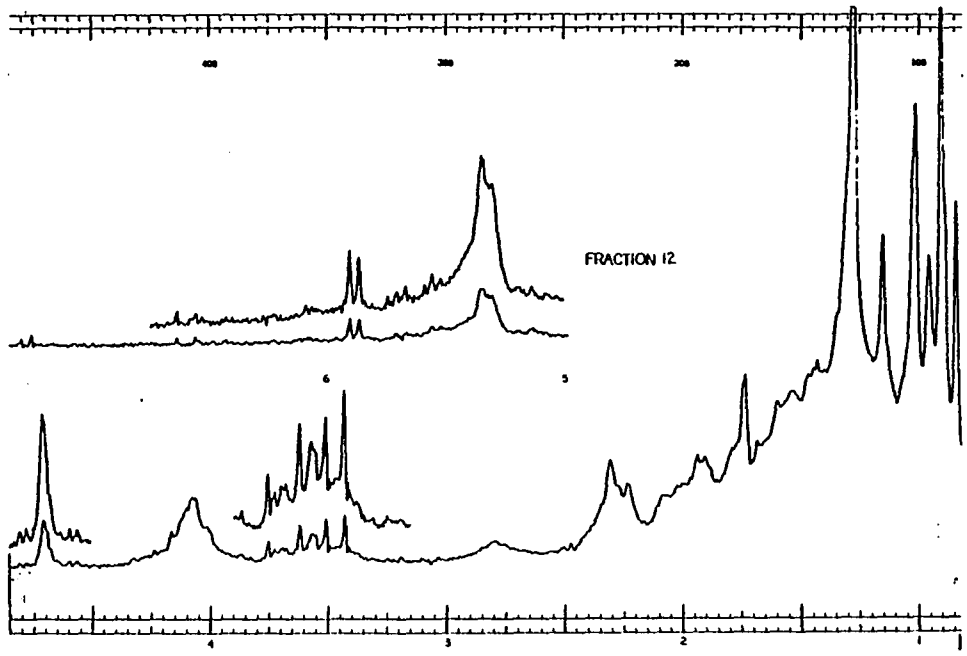


Figure II-10. Pmr spectrum ($CDCl_3$) of fraction 12.

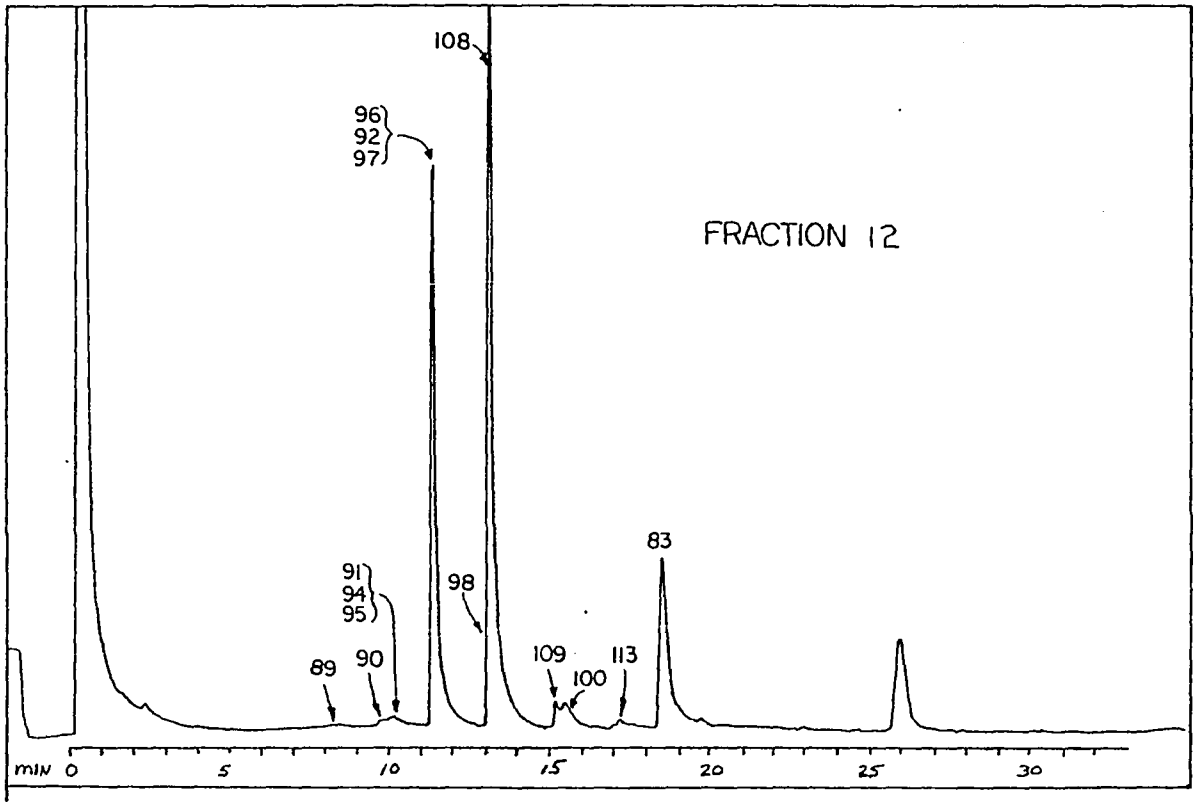
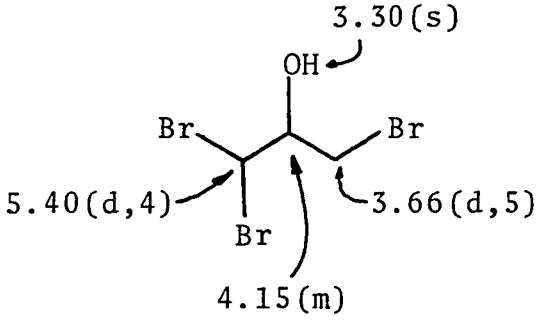
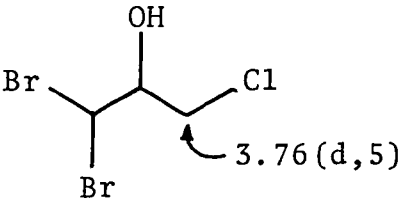


Figure II-11. Gc trace of fraction 12.



98



97

additional halogenated 2-propanols (89-97) and three additional halogenated but-3-en-2-ols (108, 109, 112). The various compounds identified in fraction 12 and the mother liquor from the recrystallization of 83 are presented in Table II-3.

The identification of the individual halogenated 2-propanols in the mixtures by gc-ms analysis was relatively straightforward. The retention times were found to increase with increasing molecular weight (see Table II-3) but many of the compounds did not exhibit molecular ions in their mass spectra. However, all exhibited oxonium ions and halomethyl ions produced by α-cleavage and the structures were obtained by simply combining the two fragments. For example, the mass spectrum of 1,1,1-tribromo-3-chloro-2-propanol (105) exhibited no molecular ion but contained clusters at m/e 249,251,253,255 (1:2:2:1) for Br_3C^+ and 79,81 (3:1) for $ClCH_2CHOH^+$. Combination of these fragments gives 105.

TABLE II-3.

HALOGENATED 2-PROPANOLS AND BUT-3-EN-2-OLS

FROM DRIED HAWAIIAN A. TAXIFORMIS

Type of Compound	Text No.	Structure	GC Retention Time (min)[a]
Dihaloisopropanols	89	$Br_2CHCH(OH)CH_3$	8.3
	90	$BrCH_2CH(OH)CH_2Br$	9.8
	91	$ClCH_2CH(OH)CH_2I$	10.1
	92	$BrCH_2CH(OH)CH_2I$	11.4
	93	$ICH_2CH(OH)CH_2I$	13.3
Trihaloisopropanols	94	$BrClCHCH(OH)CH_2Cl$	10.1
	95	$Cl_2CHCH(OH)CH_2Br$	10.1
	96	$BrClCHCH(OH)CH_2Br$	11.3
	97	$Br_2CHCH(OH)CH_2Cl$	11.3
	98	$Br_2CHCH(OH)CH_2Br$	13.8
	99	$BrClCHCH(OH)CH_2I$	14.3
	100	$Br_2CHCH(OH)CH_2I$	15.8
Tetrahaloisopropanols	101	$Cl_2CHCH(OH)CHCl_2$	11.2
	102	$BrClCHCH(OH)CHCl_2$	12.8
	103	$Br_2CHCH(OH)CHCl_2$	14.3
	104	$Br_2CHCH(OH)CHBrCl$	15.8
	88	$Br_2CHCH(OH)CHBr_2$	15.8
	105	$Br_3CCH(OH)CH_2Br$	17.4

TABLE II-3. (Continued) HALOGENATED 2-PROPANOLS AND BUT-3-EN-2-OLS FROM DRIED HAWAIIAN *A. TAXIFORMIS*

Type of Compound	Text No.	Structure	GC Retention Time (min)[a]
Tetrahaloisopropanols (cont'd)	106	$Br_2CHCH(OH)CHBrI$	19.3
	107	$Br_2CHCH(OH)CHI_2$	21.0
1,4,4-Trihalobut-3-en-2-ols	108	$Br_2C{=}CHCH(OH)CH_2Cl$	13.2
	109	$Br_2C{=}CHCH(OH)CH_2Br$	15.2
1,1,4,4-Tetrahalobut-3-en-2-ols	110	$Br_2C{=}CHCH(OH)CHCl_2$	15.8
	111	$Cl_2C{=}CHCH(OH)CHBr_2$	15.8
	112	$Br_2C{=}CHCH(OH)CHBrCl$	17.2
	113	$BrClC{=}CHCH(OH)CHBr_2$	17.4
	83	$Br_2C{=}CHCH(OH)CHBr_2$	18.8
1,1,1,4,4-Pentahalobut-3-en-2-ols	114	$Br_2C{=}CHCH(OH)CBr_3$	21.4

[a] Determined on a 6' X 1/8" stainless steel column of 3% OV-17 on 80-100 Supelcoport heated isothermally at 60° for 4 min after injection, then temperature programmed from 60° to 170° at 8° per minute, and finally heated isothermally at 170° using a helium flow rate of 30 ml per minute.

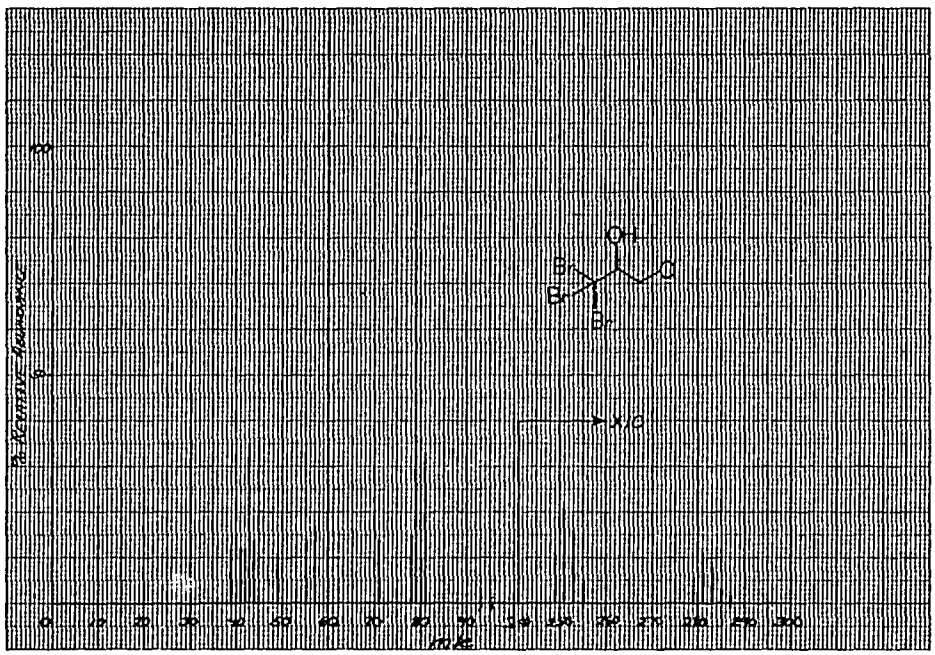
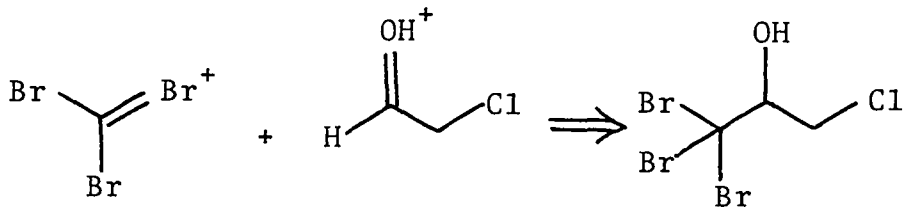


Figure II-12. Mass spectrum (70eV) of compound 105.



105

On the other hand all of the iodine-containing 2-propanols exhibited molecular ions in their respective mass spectra but for two of them, 106 and 107, α-cleavage was not the primary fragmentation pathway. Both of these compounds

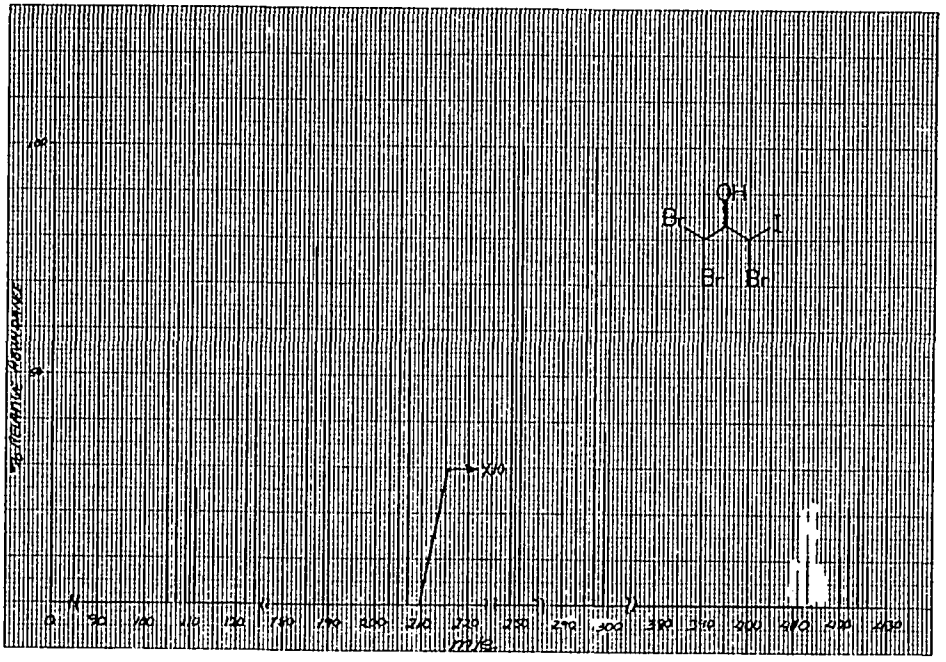


Figure II-13. Mass spectrum (70eV) of compound 106.

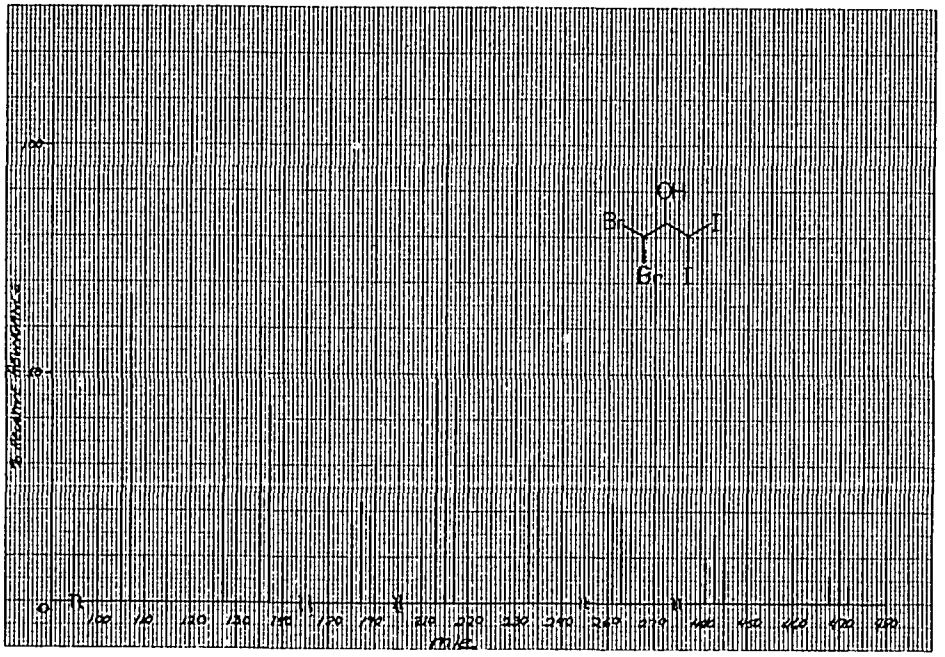
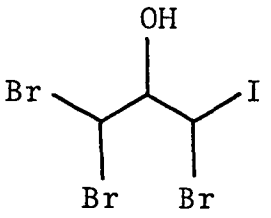
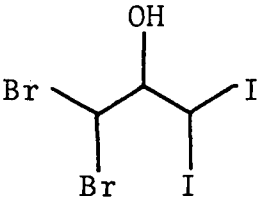


Figure II-14. Mass spectrum (70eV) of compound 107.



106

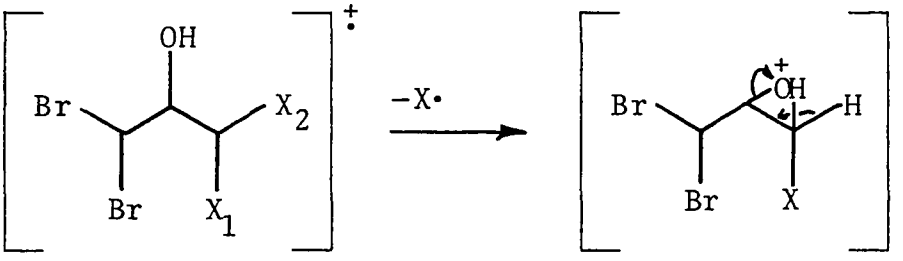


107

(106 and 107) exhibited base peaks at m/e 213,215,217 (1:2:1) for $C_3H_3Br_2O^+$ which loses CO to give a cluster at m/e 185,187, 189 (1:2:1). These data indicated the primary fragmentation pathway for 106 and 107 to be as shown in Scheme II-2.

Scheme II-2.

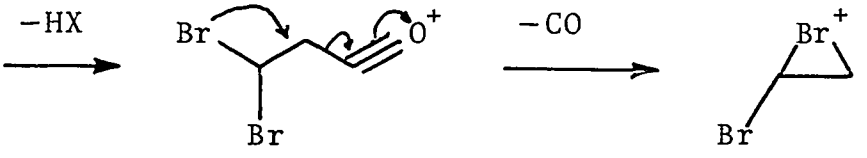
Proposed Fragmentation Pathway for Compounds 106 and 107



115 $X_1=X_2=1$

116 $X_1=Br$, $X_2=I$

117



118

m/e 213,215,217

119

m/e 185,187,189

Apparently, the molecular ions (115 and 116) first lose a halogen (X_1 or X_2) and form epoxide 117 which then undergoes a 1,2-hydride shift followed by loss of CO.

The gc retention times of the halogenated but-3-en-2-ols also correlated nicely with their respective molecular weights but, as with the halogenated 2-propanols, molecular ions were not observed for all compounds. However, all underwent α-cleavage to give oxonium ions in their mass spectra and their respective structures were assigned by combining these fragment ions.[10] For example, the mass spectrum of 108 showed clusters at m/e 213,215,217 (1:2:1) and 123,125 (1:0.3) for $C_3H_3Br_2O$ and $C_2H_4ClO^+$, respectively, which implied the compound to be 4,4-dibromo-1-chlorobut-3-en-2-ol (108).

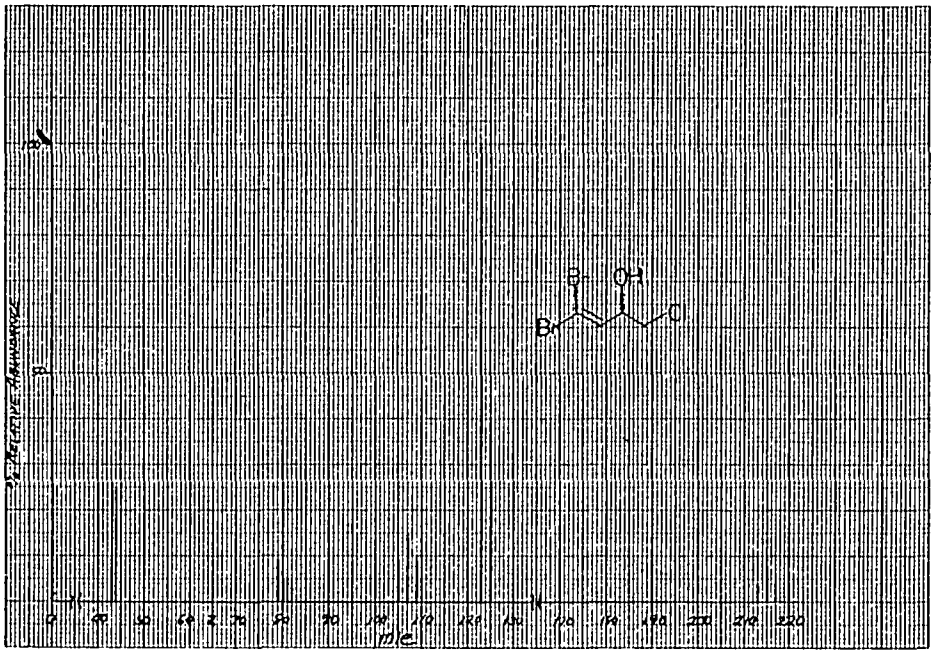
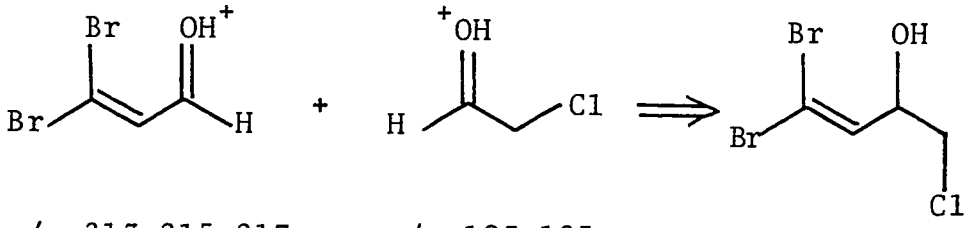


Figure II-15. Mass spectrum (70eV) of compound 108.



m/e 213,215,217 m/e 123,125

108

The major halogenated but-3-en-2-ol (83) and a minor component 1,1,1,4,4-pentabromobut-3-en-2-ol (114) were found to have mass spectra and gc retention times identical to those of synthetic samples. The latter compound (114) was prepared by the addition of 84 to a mixture of bromoform and LDA in THF at -78°. By analogy with 83 and 114 the olefinic

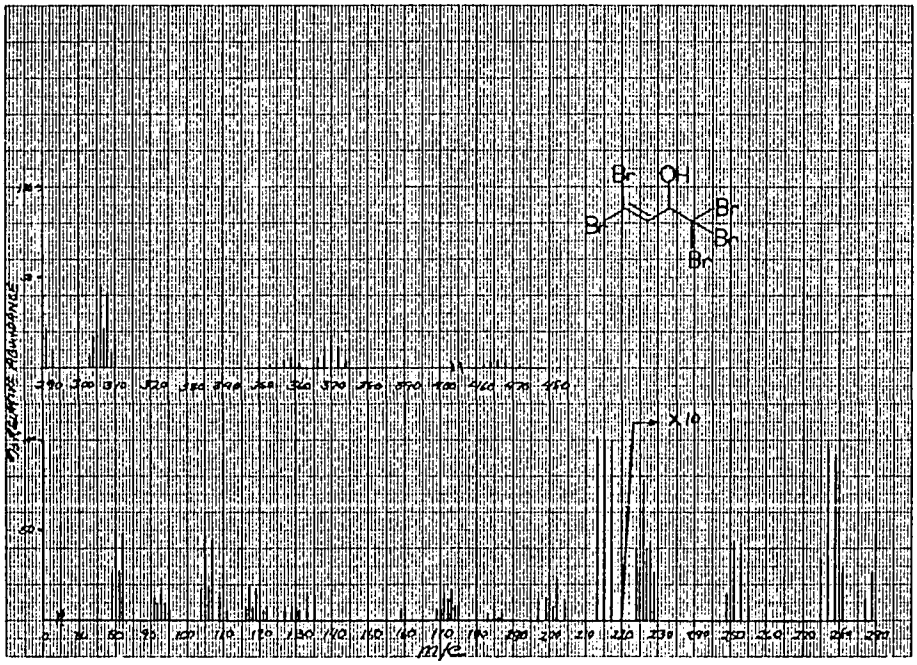


Figure II-16. Mass spectrum (70 eV) of compound 114.

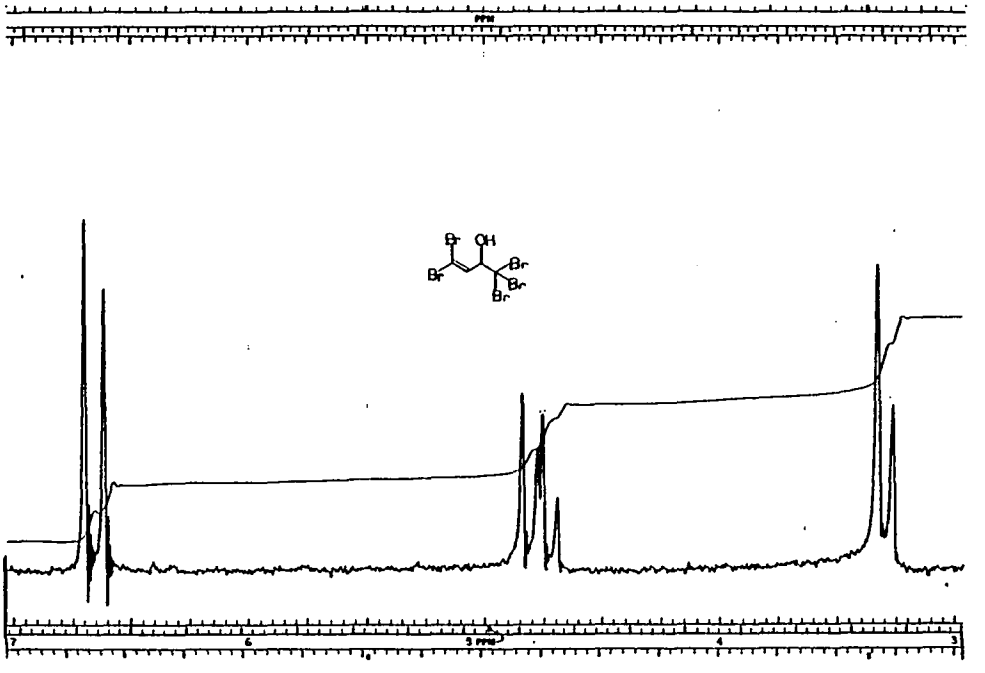


Figure II-17. Pmr spectrum ($CDCl_3$) of compound 114.

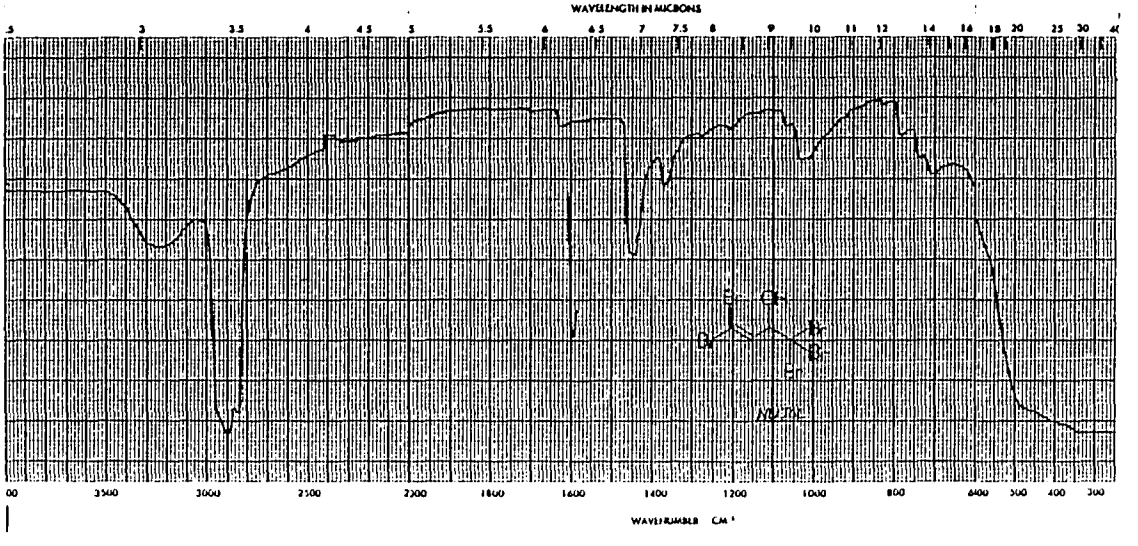
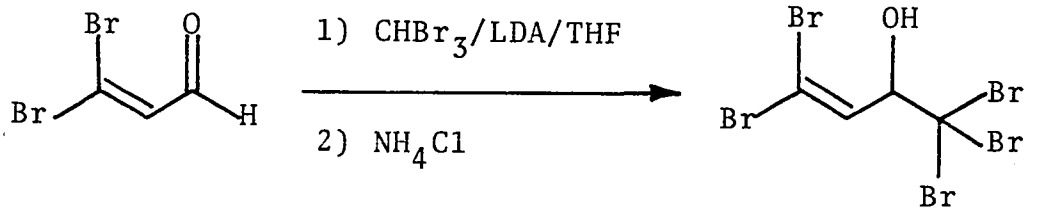


Figure II-18. Ir spectrum (nujol) of compound 114.

halogens of the but-3-en-2-ols not compared with authentic samples (108-113) were assigned to C-4.



84 114

Fraction 19, which eluted with 100% ether, was dissolved in methylene chloride and stored in a freezer. After standing at -20° for four days a greenish solid precipitated that was recrystallized from methylene chloride to give optically inactive colorless needles. Analysis of this mixture by gc-ms revealed the presence of five dihaloacetamides (120-124) which are presented in Table II-4. All of the compounds

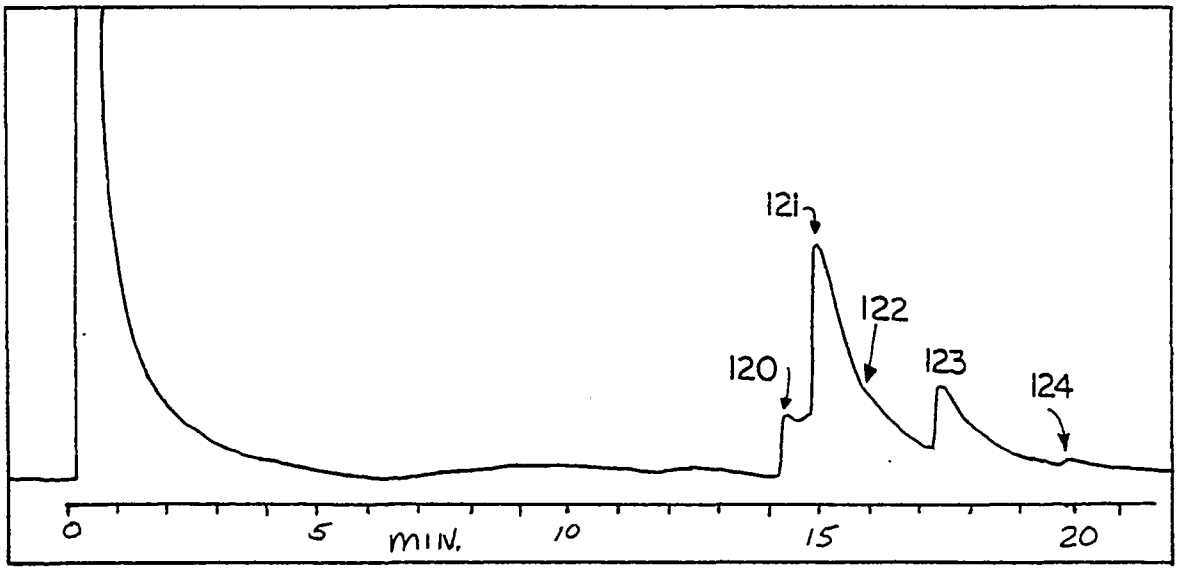


Figure II-19. Gc trace of the acetamide mixture.

TABLE II-4.

DIHALOACETAMIDES FROM DRIED HAWAIIAN A. TAXIFORMIS

Text No.	Structure	Gc Retention Time (min)[a]
120	$BrClCHCONH_2$	13.7
121	$Br_2CHCONH_2$	14.5
122	$ClICHCONH_2$	14.9
123	$BrICHCONH_2$	16.7
124	$I_2CHCONH_2$	19.2

[a] See footnote (a) Table II-3.

in Table II-4 exhibited weak molecular ions in their mass spectra and base peaks at m/e 44 for the $NH_2C{\equiv}O^+$ ion. The pmr spectrum of the mixture in acetone-d_6 exhibited broad multiplets between δ7.5 and 6.5 for the amide protons and five sharp singlets at 6.30, 6.26, 6.16, 6.09 and 5.66 for the dihalomethyl protons of 120, 122, 121, 123 and 124, respectively. A synthetic sample of dibromoacetamide (121), the major component of the mixture, had a pmr spectrum, mass spectrum and gc retention time identical to those of the naturally occurring material.

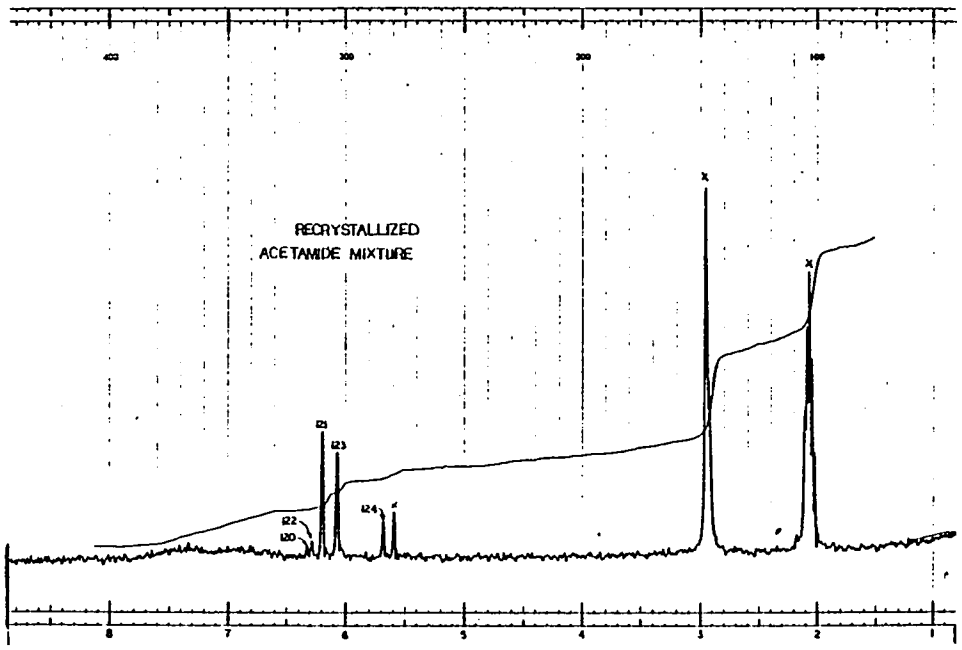


Figure II-20. Pmr spectrum (acetone-d_6) of the acetamide mixture.

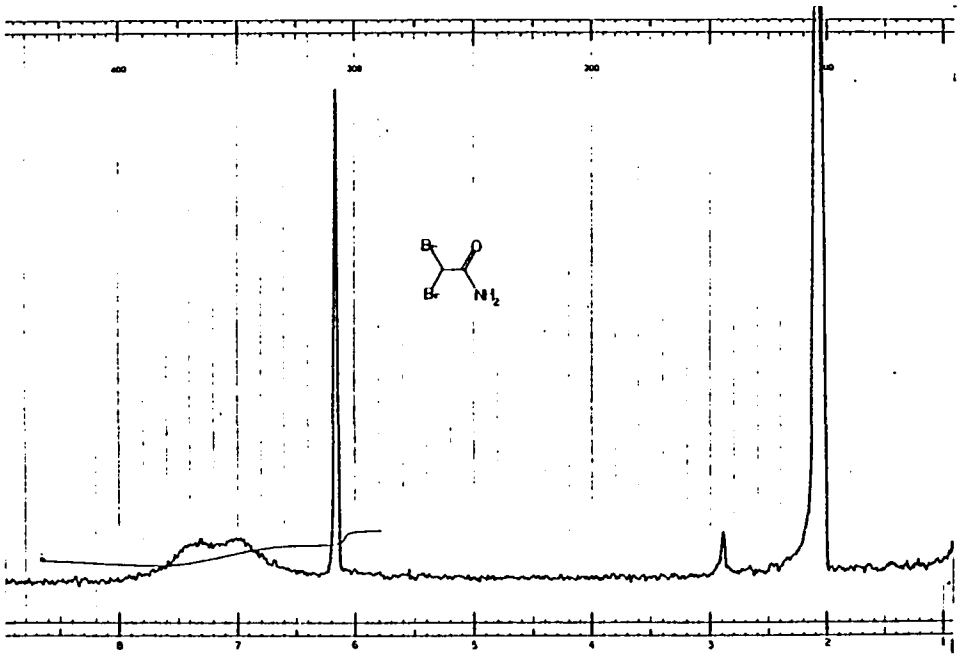


Figure II-21. Pmr spectrum (acetone-d_6) of compound 121.

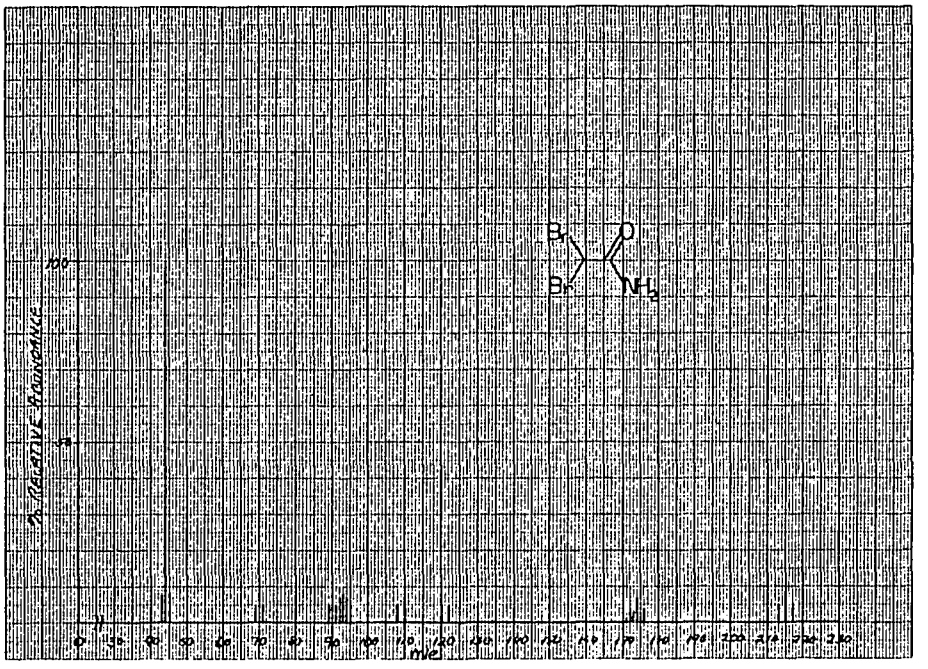


Figure II-22. Mass spectrum (70eV) of compound 121.

A methylene chloride solution of fraction 20 also deposited a greenish solid upon standing at -20° for four days. Gc-ms analysis of this material showed it to be a 2:2:1 mixture of 123, 124 and 121, respectively.

B. Fractionation of Hawaiian A. taxiformis Aqueous Extract

To obtain the aqueous extract vacuum dried plants of A. taxiformis were extracted with methanol and chloroform and the solvents evaporatively removed in a common flask. The crude residue was partitioned between water and chloroform and the layers separated to give an orange aqueous

solution. Acidification of a small amount of the aqueous solution with conc. phosphoric acid followed by continuous ether extraction gave a small amount of oil whose pmr spectrum showed numerous signals between δ5.8 and 7.9 and a large broadened singlet at 9.9 indicative of carboxyl protons. Gc-ms analysis of the mixture showed several sharp peaks for halogenated acrylic acids and several peaks for halogenated acetic acids that were poorly resolved due to excessive trailing. Esterification of the mixture with methanol and sulfuric acid improved the resolution considerably and nine halogenated acetic acids and nine halogenated acrylic acids were identified (Table II-5). The mixture of

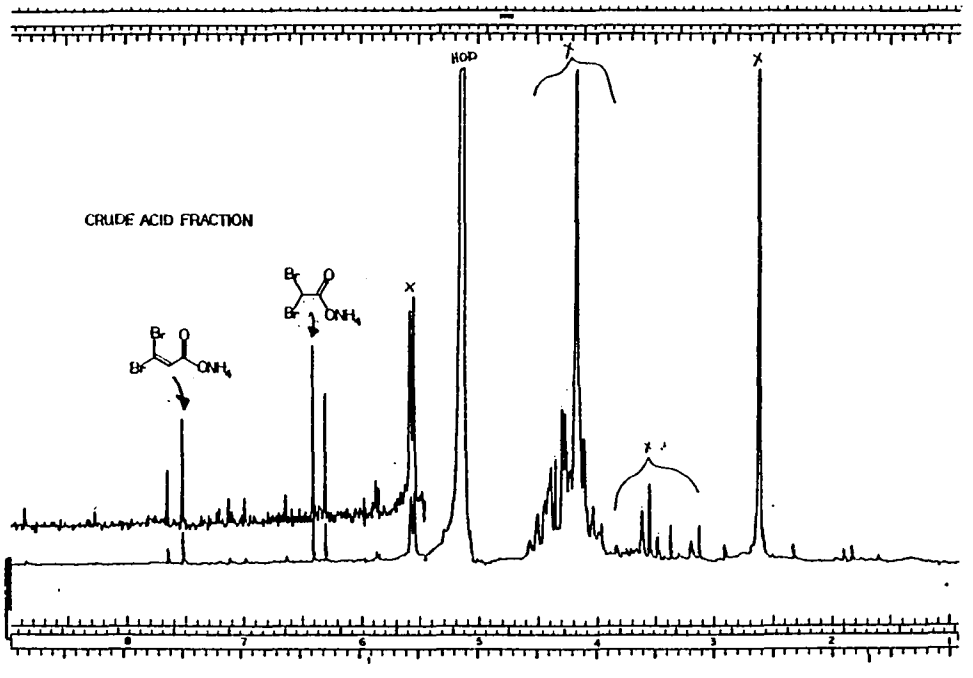


Figure II-23. Pmr spectrum (D_2O) of the crude acid mixture from continuous ether extraction.

TABLE II-5.

HALOGENATED ACIDS FROM DRIED HAWAIIAN A. TAXIFORMIS[11]

Type of Compound	Text No.	Structure	GC Retention Time (min) Acid[a]	Methyl Ester[b]
Haloacetic Acids	125	$ClCH_2CO_2H$		4.5
	126	$BrCH_2CO_2H$		8.4
	127	ICH_2CO_2H		12.6
Dihaloacetic Acids	128	Cl_2CHCO_2H		
	129	$BrClCHCO_2H$		12.3
	130	$ClICHCO_2H$		15.7
	131	Br_2CHCO_2H		14.6
	132	$BrICHCO_2H$		17.6
	133	I_2CHCO_2H		21.2
Haloacrylic Acids	134	$ClCH{=}CHCO_2H$[c]		9.5
	135	$BrCH{\overset{Z}{=}}CHCO_2H$	9.2	12.6
	136	$ICH{=}CHCO_2H$[c]	11.5	14.3
Dihaloacrylic Acids	137	$Cl_2C{=}CHCO_2H$[c]		11.8
	138	$Br_2C{=}CHCO_2H$	12.7	17.0
	139	$BrIC{=}CHCO_2H$[c]	15.6	19.1
	140	$I_2C{=}CHCO_2H$[c]		22.5

TABLE II-5. (Continued) HALOGENATED ACIDS FROM DRIED HAWAIIAN A. TAXIFORMIS[11]

Type of Compound	Text No.	Structure	GC Retention Time (min) Acid[a]	Methyl Ester[b]
Trihaloacrylic Acids	141	$Br_2C=CBrCO_2H$		20.8
	142	$BrIC=CBrCO_2H$ or $Br_2C=CICO_2H$		23.7

[a] Determined on a 6' X 1/8" stainless steel column of 3% OV-17 on 80/100 Supelcoport heated isothermally at 60% for 4 minutes after injection, then temperature programmed from 60° to 200° at 8° per minute, and finally heated isothermally at 200° using a flow rate (He) of 30 ml per minute.

[b] Same column and flow rate as above. Heated isothermally at 40° for 8 minutes after injection, then temperature programmed from 40° to 200° at 8° per minute, and finally heated isothermally at 200°.

[c] Structure has not been rigorously established by synthesis.

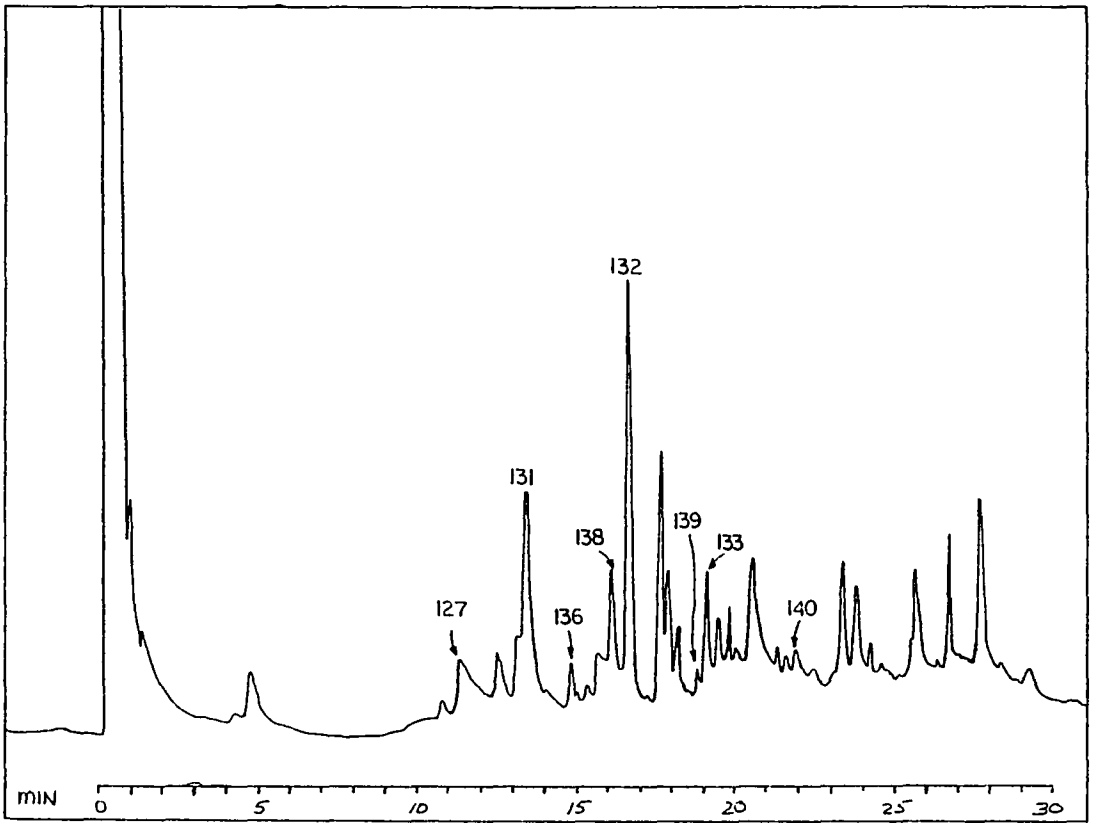


Figure II-24. Gc trace of the crude acid mixture esterified with methanol and sulfuric acid.

esters that resulted from treatment of the acids with diazomethane also contained appreciable amounts of iodo-, bromoiodo- and diiodomethane which, presumably, were formed by reaction of diazomethane with bromoiodo- (132) and diiodoacetic acid (133).

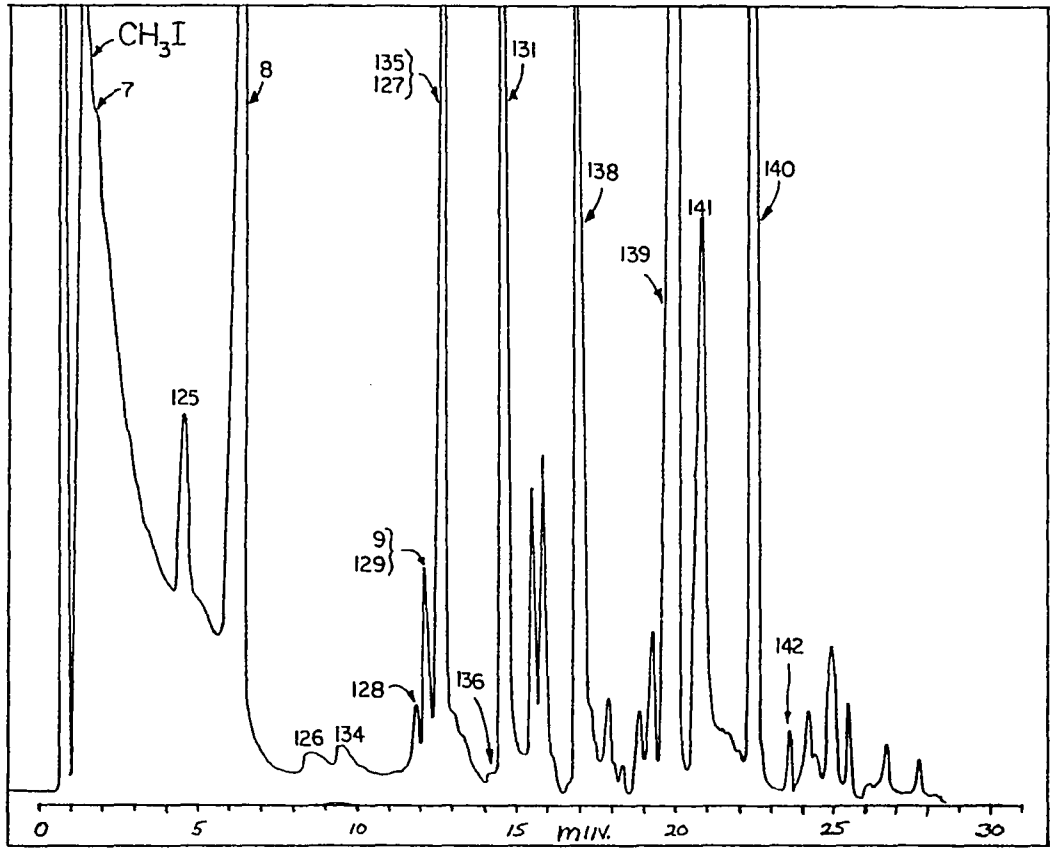


Figure II-25. Gc trace of the crude acid mixture esterified with diazomethane.

The identification of the methyl acetates and acrylates was straightforward since all compounds exhibited molecular ions in their mass spectra. The base peak in the spectrum of the halogenated acetates was generally observed at m/e 59 ($CH_3O\text{-}C{\equiv}O^+$) whereas the base peaks of the halogenated acrylates generally corresponded to loss of OCH_3 from the molecular ions. The position of the bromine and geometry of the double bond in 135 were established by comparison

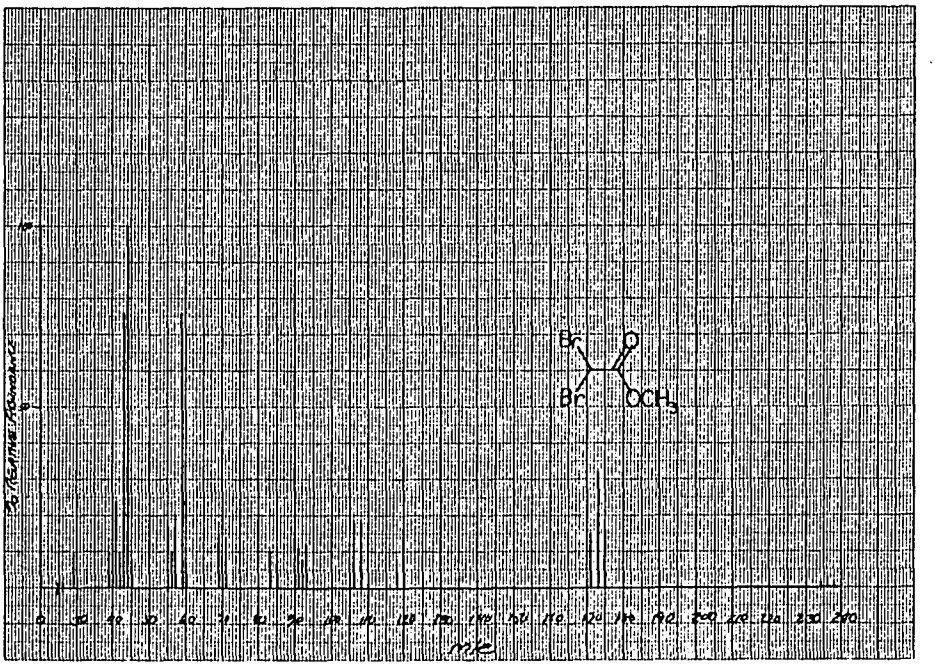


Figure II-26. Representative mass spectrum (70eV) of the halogenated methylacetates; methyl dibromoacetate.

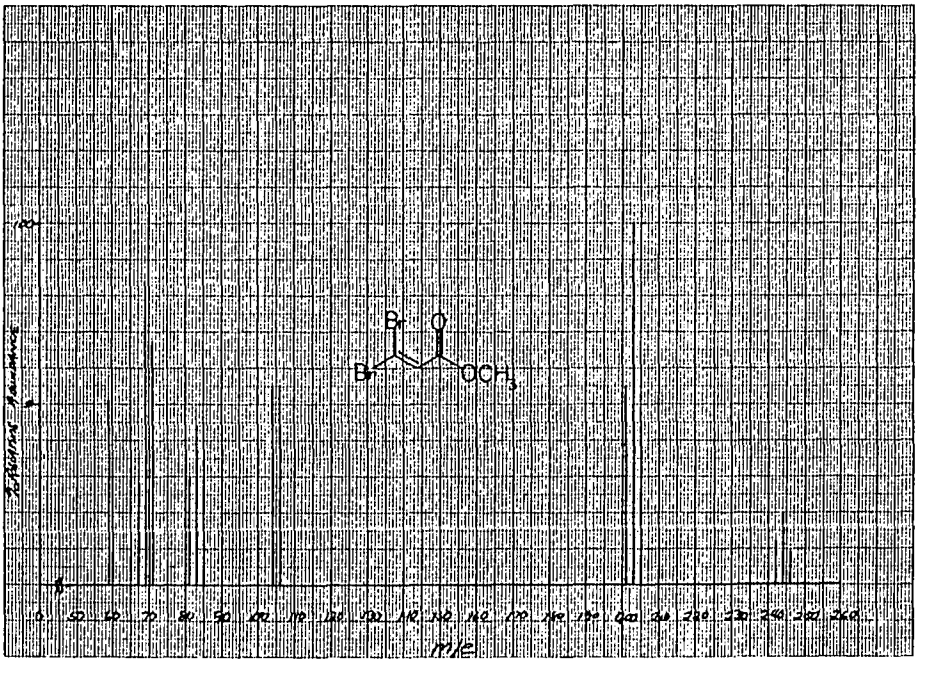
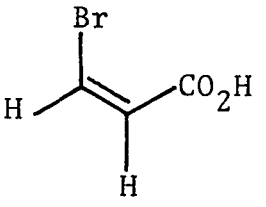
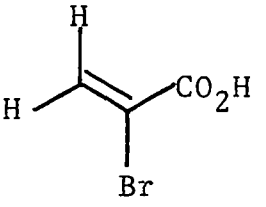


Figure II-27. Representative mass spectrum (70eV) of the halogenated methyl acrylates; methyl dibromoacrylate.

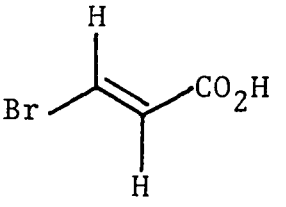
with a synthetic sample. The gc retention times of the methyl esters of the other two isomers (143 and 144) were found to be much shorter than that of the methyl ester of 135. The



135

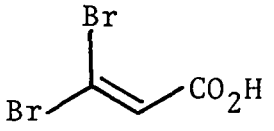


143

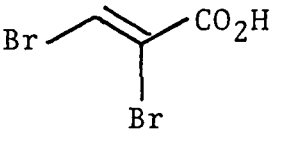


144

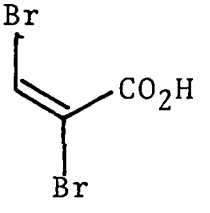
positions of the two bromine atoms of the major halogenated acrylic acid (138) were assigned by comparing its gc retention time with those of the methyl esters of 3,3-dibromoacrylic acid (138), prepared by chromic acid oxidation of 84, and E- and Z-2,3-dibromoacrylic acid (146 and 147, respectively) obtained by adding bromine to propiolic acid.



138



145



146

The halogens of the monohalo- and dihaloacrylic acids not compared with authentic samples (134, 136, 137 and 140) were assigned to C-3 in analogy with 135 and 138.[11]

An attempt to separate the acids in the aqueous fraction on DEAE Sephadex gave only partial separation. The column was initially eluted with water to remove the sugars and inorganic salts followed by 0.01N hydrochloric acid which removed the acrylic and acetic acids in overlapping fractions. The acids were converted to their ammonium salts and identified by pmr. The pmr spectrum (D_2O) of the acrylate fraction contained a singlet at δ7.52 for ammonium 3,3-dibromoacrylate which was identical to the spectrum of a synthetic sample. The pmr spectrum (D_2O) of the acetate fraction contained five singlets at δ5.83, 6.28, 6.38 and 6.46 in a ratio of 3:20:4:1 for ammonium diiodo-, bromoiodo-, dibromo- and dichloroacetate, respectively. The chemical shifts of ammonium dibromo- and dichloroacetate were found to be

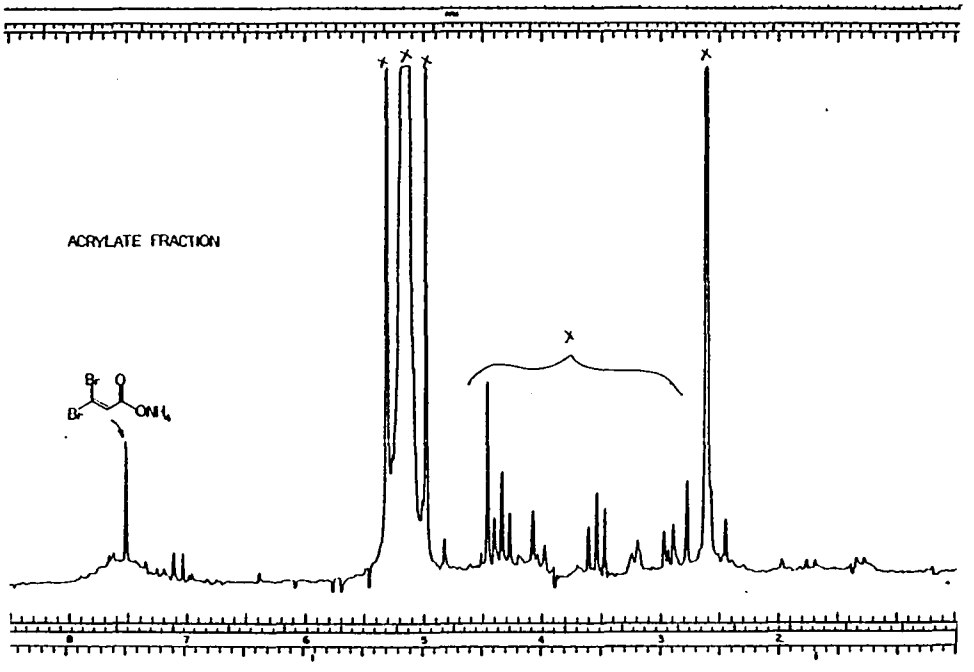


Figure II-28. Pmr spectrum (D_2O) of the acrylate fraction.

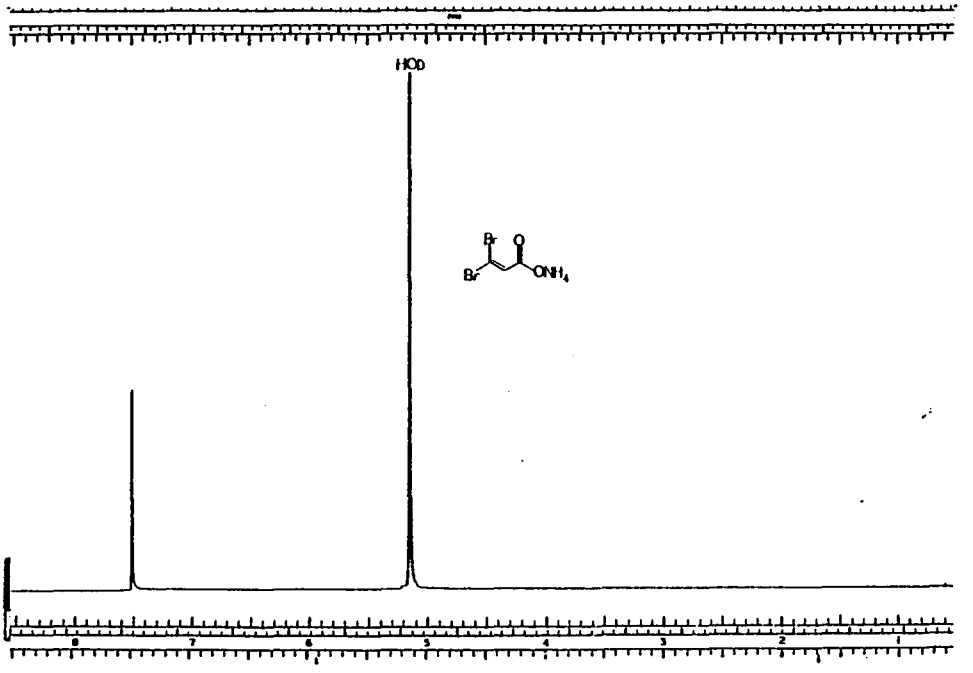


Figure II-29. Pmr spectrum (D_2O) of ammonium dibromoacrylate.

identical with those of the ammonium salts of commercial samples.

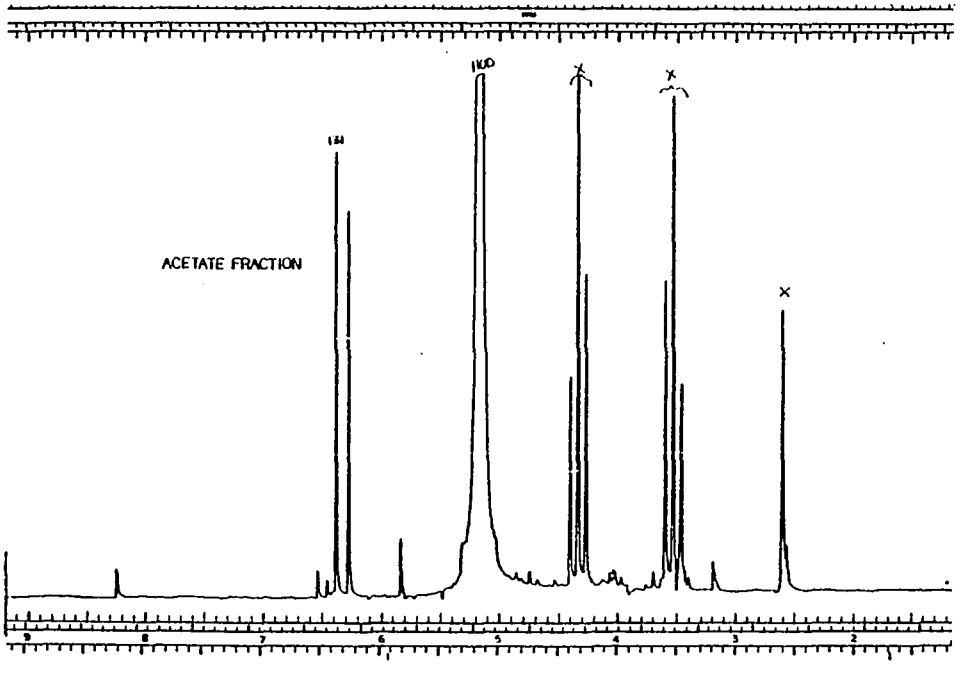


Figure II-30. Pmr spectrum (D_2O) of the acetate fraction.

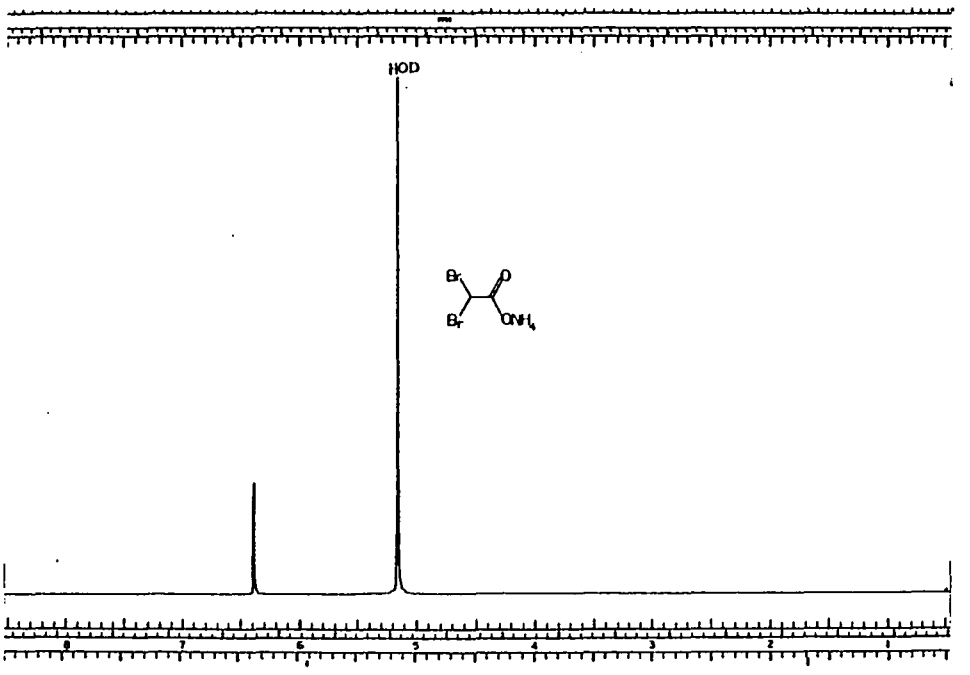
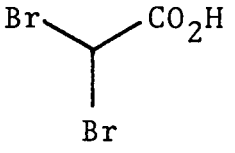
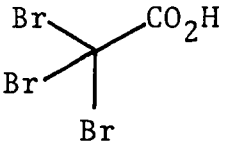


Figure II-31. Pmr spectrum (D_2O) of ammonium dibromoacetate.

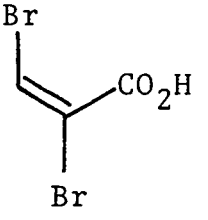
Halogenated acetic and acrylic acids have also been found recently by McConnell and Fenical[4] in Asparagopsis taxiformis from the Gulf of California and A. armata from the Spanish Mediterranean. Ethanol was used to preserve the plants and rapidly converted the acids to ethyl esters that were isolated by extracting the ethanol preservants with purified pentane. Concentration of the pentane extracts from A. armata by careful fractional distillation and gc-ms analysis of the concentrates revealed the presence of two halogenated acetic acids (131, 147) and three halogenated acrylic acids (146, 148, 149). Similar to Hawaiian A. taxiformis 131 was the major halogenated acetic acid but the major halogenated acrylic acid was the E-2,3-dibromo isomer of 138 (146).



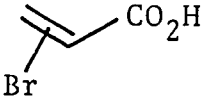
131



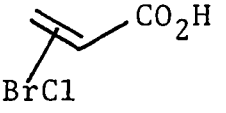
147



146

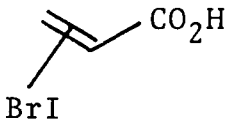


148

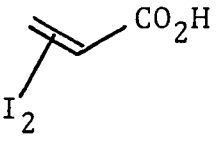


149

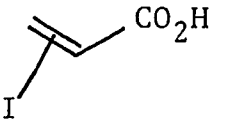
The structure of 146 was rigorously proven by synthesis. Plants of A. taxiformis collected at Isla Carmen and Isla Angel de la Guarda (Gulf of California) were found to contain 146, 148, 149 in differing amounts as well as 150-152 which were not found in A. armata. On the other hand A. taxiformis from Cabo San Lucas (Gulf of California) contained only 146, 148, 149 and 151.



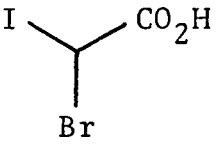
150



151



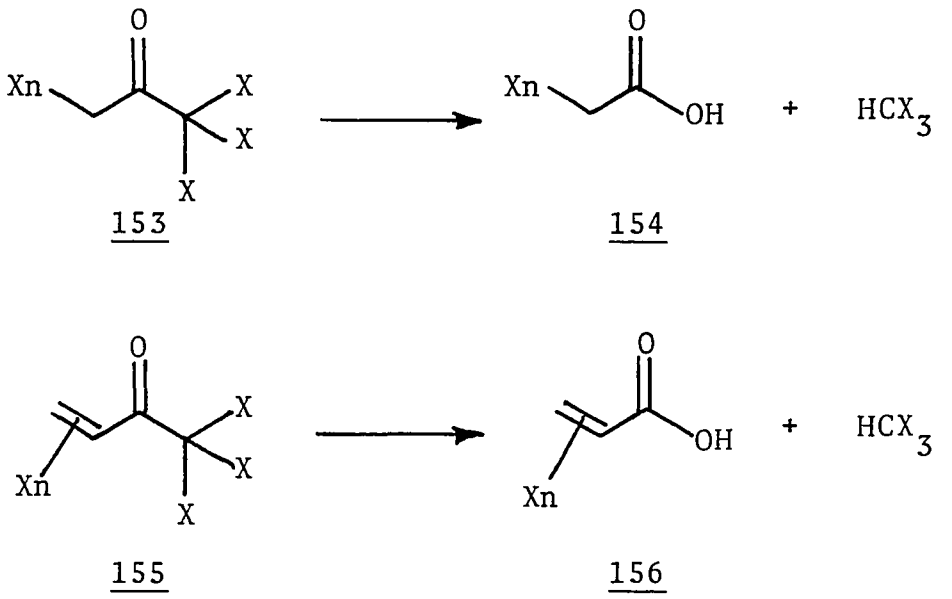
152



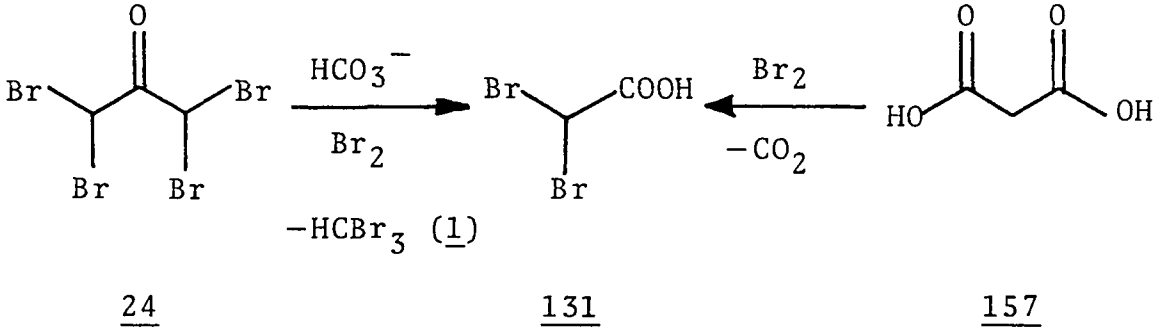
137

C. Biogenesis of the Constituents of A. taxiformis and Biomimetic Syntheses

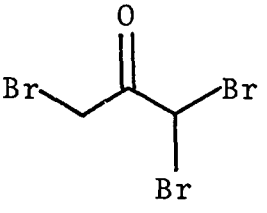
In the absence of radioactive labelling studies the biogenesis of the large number of compounds identified in Hawaiian A. taxiformis is largely speculative. However, it has been postulated that the haloforms may be derived from the halogenated acetones (153 → 154) and may also be derived in part from the halogenated butenones (155 → 156) via the haloform reaction.[2] In his studies on the essential oil Dr. Burreson found that synthetic 1,1,1-trihaloacetones (153) rapidly decompose to form haloforms and acetic acids upon standing in solution. In the present study it was found that base catalyzed bromination of 1,1,3,3-tetrabromoacetone (24) produced primarily dibromoacetic acid



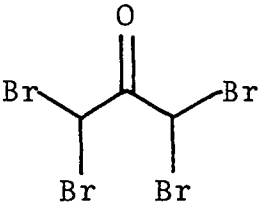
(131) and bromoform (1). Malonic acid (157), another possible source of the halogenated acetic acids, is also rapidly converted to 131 with bromine at pH 7. The instability of the 1,1,1-trihaloacetones (153) indicates that, in vivo, haloform production may not be an enzymatically controlled process.[12] On the other hand, McConnell and



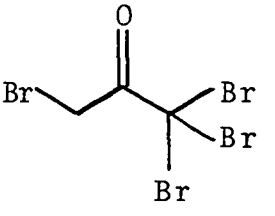
Fenical[4] proved that the ethyl esters isolated from A. taxiformis and A. armata were not artifacts formed by the reaction of 1,1,1-trihaloacetones with ethanol during the extraction process. Treatment of a mixture of 22, 24, 158 and 159 with 99% ethanol and hydrobromic acid at room temperature for 12 hours did not produce bromoacetic acids and bromoform. Treatment of bromoacetic acid under identical conditions, however, resulted in quantitative conversion to ethyl bromoacetate.



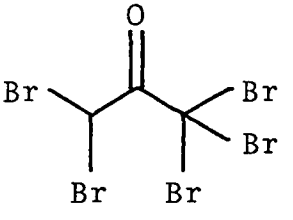
22



24



158



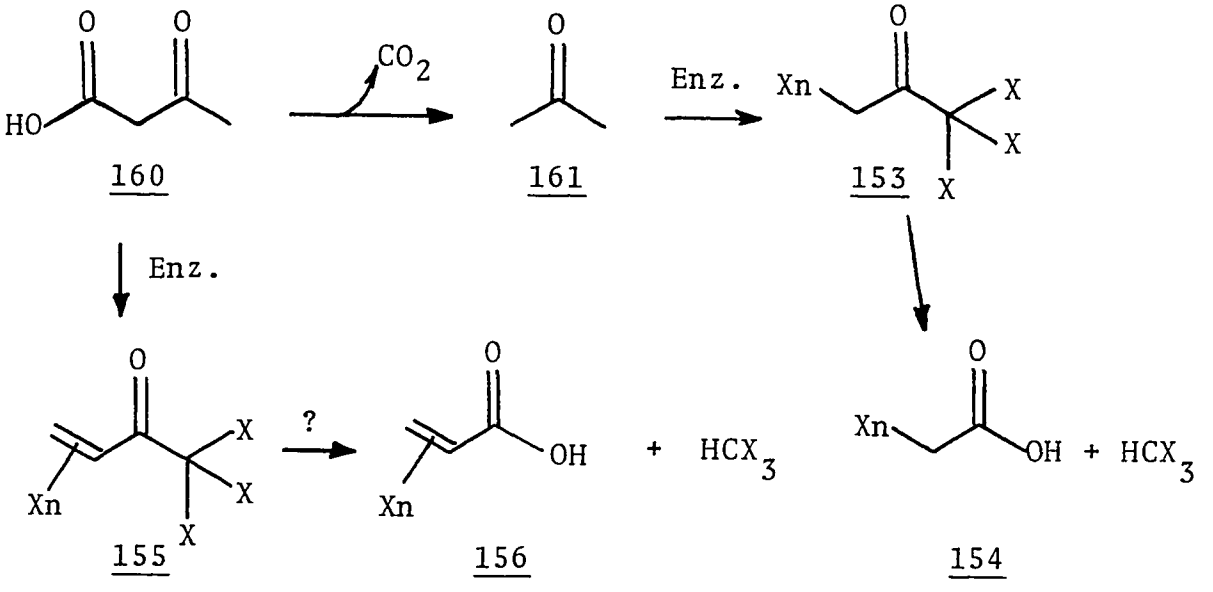
159

McConnell and Fenical[4] also found significant amounts of acetone in these two algae as well as a normal distribution of plant acids. These findings led them to suggest that the halogenated compounds are derived from acetocetic acid as shown in Scheme II-3. The halogenation of 160, 156

Scheme II-3.

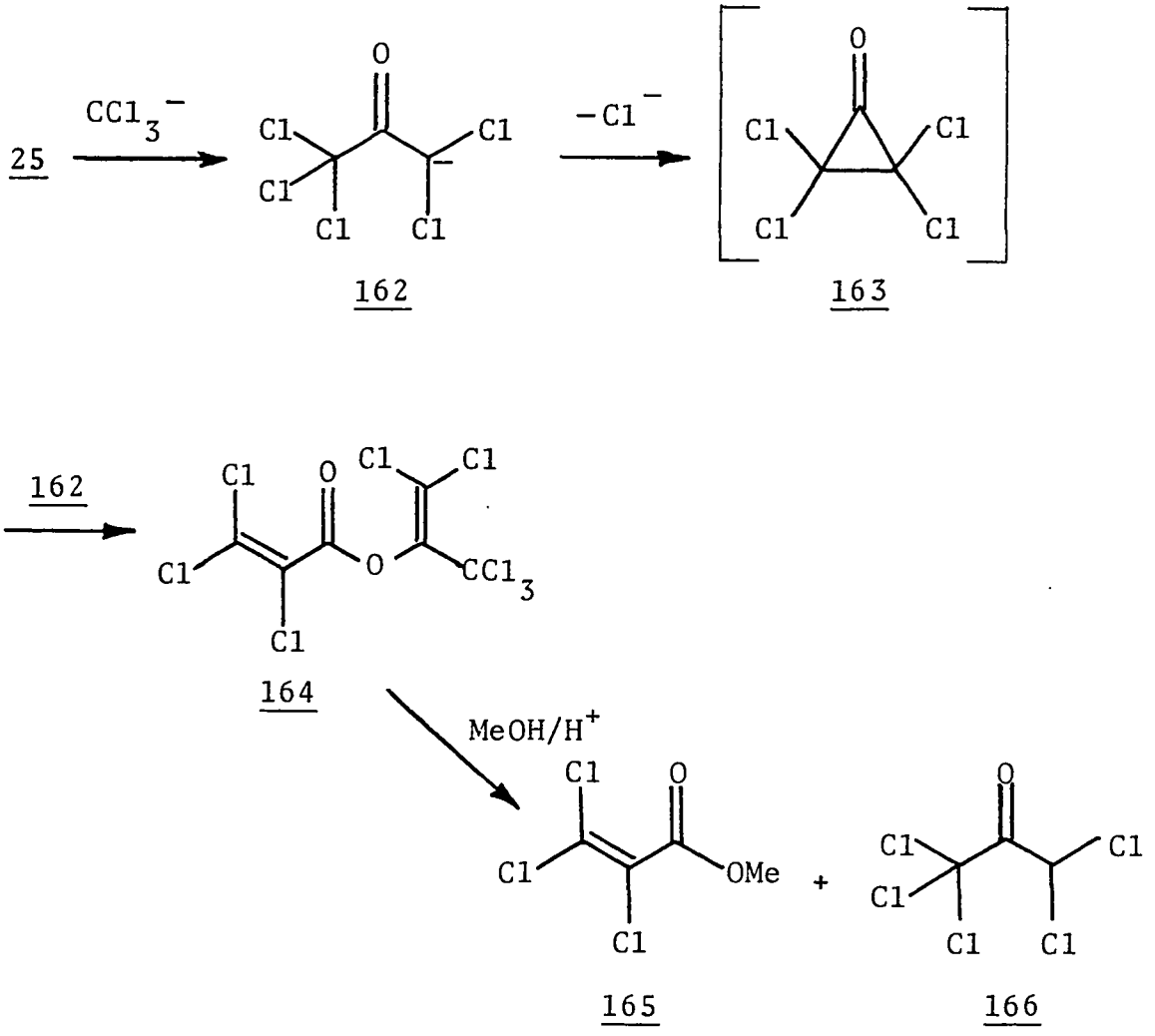
Proposed Biosynthesis of Compounds from

Mexican and Spanish Asparagopsis

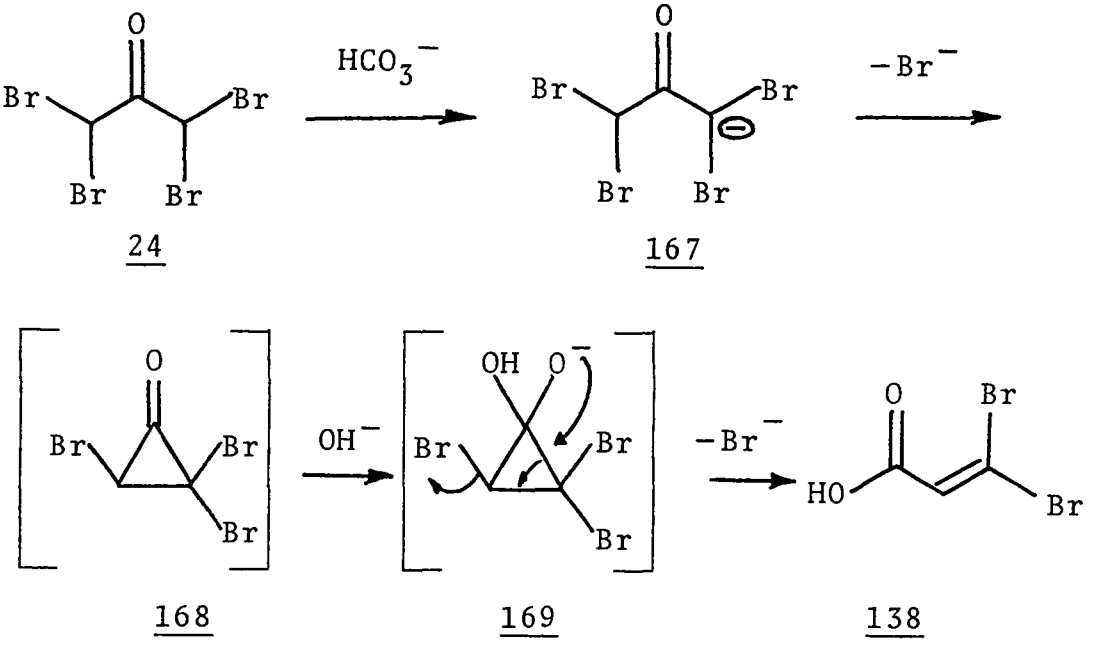


and 161 is undoubtedly enzymatically controlled and may involve a peroxidase similar to that found in the marine alga Enteromorpha linza which catalyzes the formation of mono- and diiodotyrosine.[13]

We have recently proposed that the halogenated acrylic acids are derived primarily from the halogenated acetones via Favorski type rearrangements.[11] Wagner and coworkers[14] have found that thermal decomposition of hexachloroacetone (25) in dimethoxyethane with sodium trichloroacetate produces methyl trichloroacrylate (165) and pentachloroacetone 166 after transesterification of intermediate 164 with methanol. We have found that 1,1,3,3-tetrabromoacetone (24)



readily undergoes a Favorski rearrangement with bicarbonate in 1:1 acetone/water solution at room temperature to give 3,3-dibromoacrylic acid (138) in 50% yield. Examination of the pmr spectrum of the crude product revealed no trace of the E and Z-2,3-dibromo isomers which indicates that the ring opening step and elimination of bromide ion (169 → 138) is concerted or nearly so. The pmr spectrum (acetone-d_6) of recrystallized 138 exhibited a sharp singlet at δ7.08 and a



broad singlet at 10.22 and was identical to the spectrum of 138 prepared by chromic acid oxidation of 84. Interestingly,

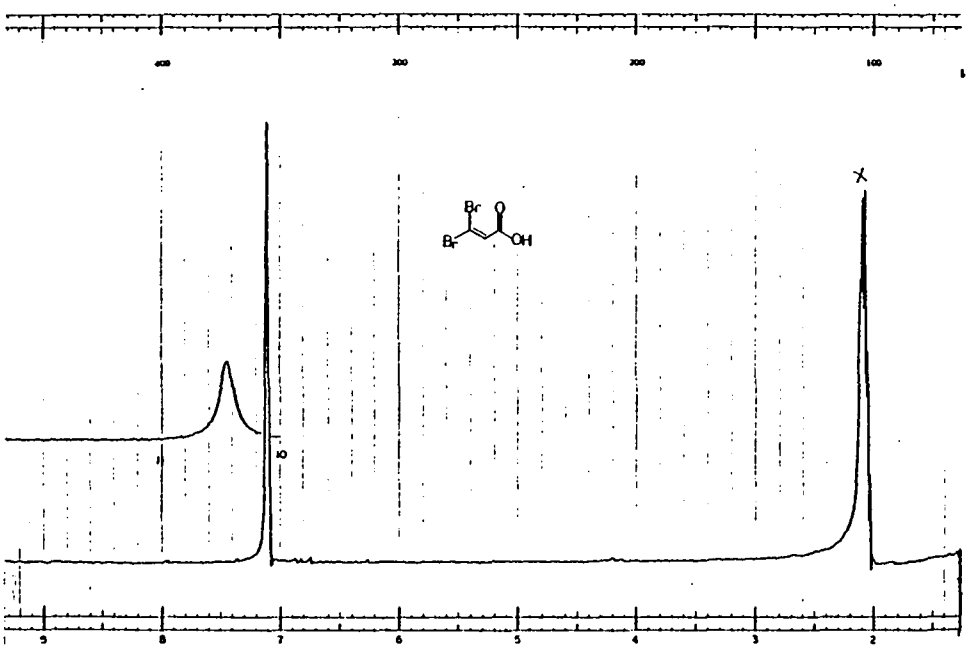


Figure II-32. Pmr spectrum (acetone-d_6) of compound 138.

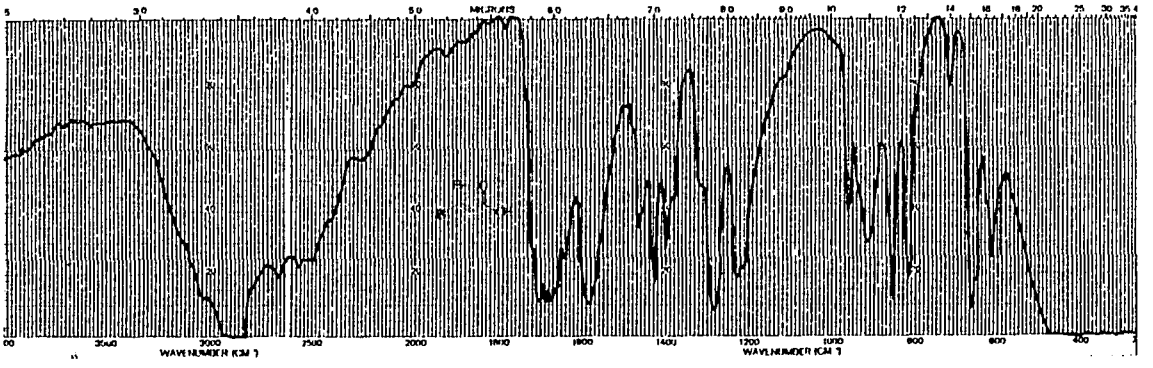
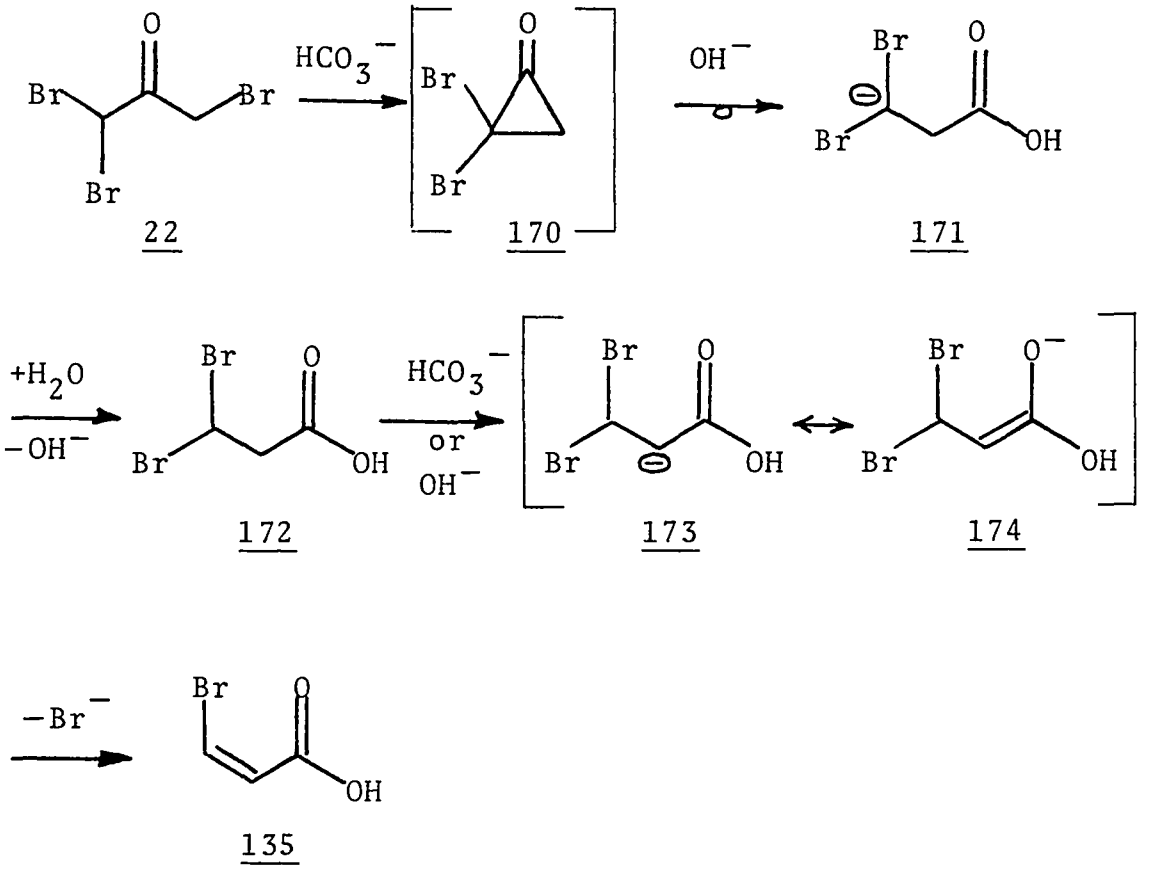


Figure II-33. Ir spectrum (nujol) of compound 138.

under the same conditions 1,1,3-tribromoacetone (22) is sterospecifically converted to Z-3-bromoacrylic acid and not the expected E-isomer. This result indicates that of



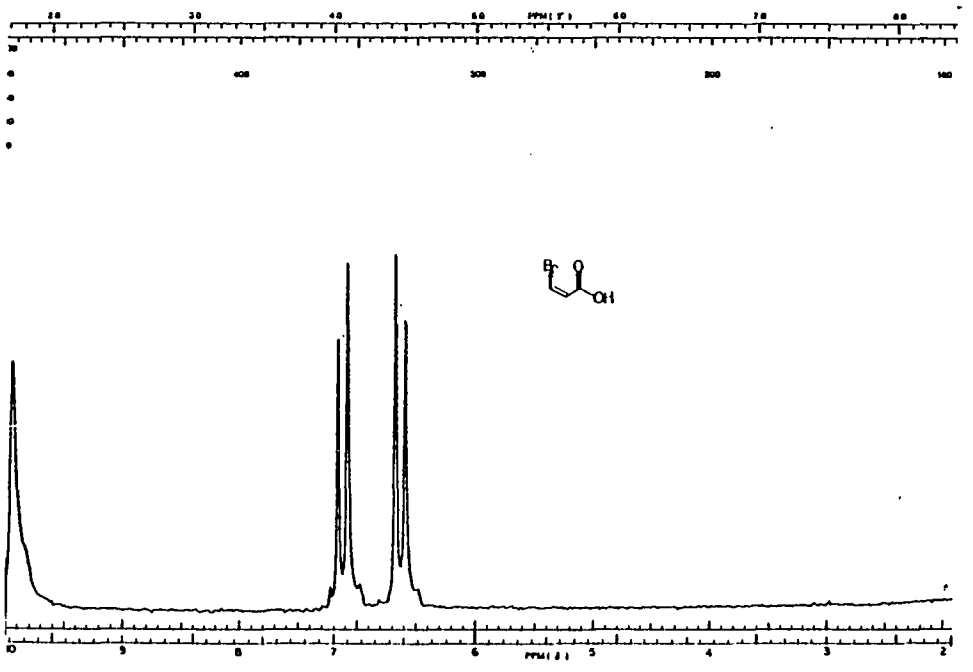
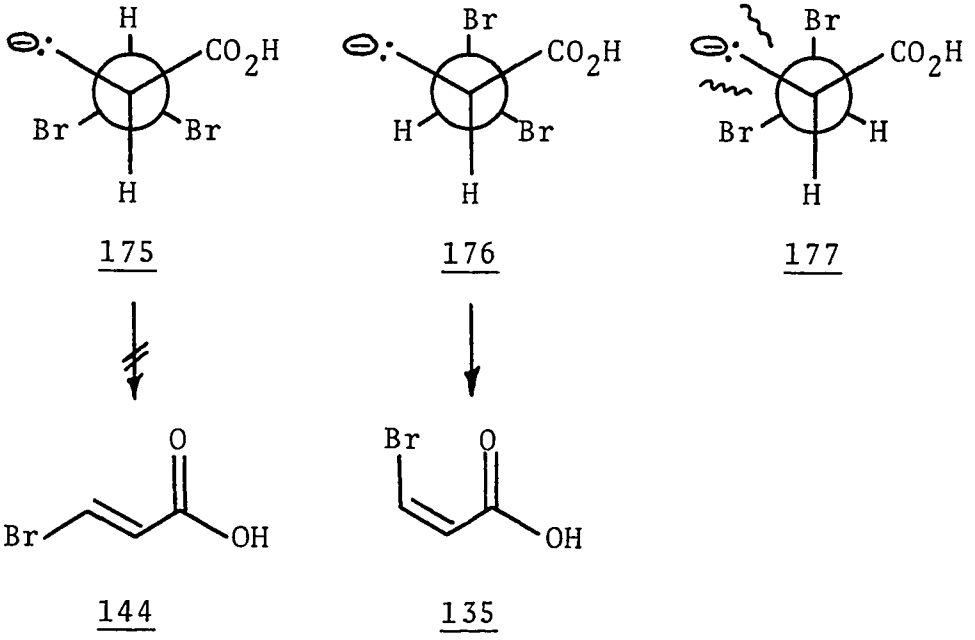


Figure II-34. Pmr spectrum ($CDCl_3$) of compound 135.

the three possible conformations of 173 (175-177) elimination occurs only from 176. This is unusual in that the energies of the conformers would be expected to increase in the order of 175 < 176 < 177 and therefore 144 should be the predominant product. However, the predominance of 176 over 175 may be due to hydrogen bonding between the carbonyl group and the two bromine atoms. This effect, if it exists at all, would be expected to be very weak but it may be just strong enough to lower the overall energy of 176 below that of 175.



Favorski rearrangement of 1,1,3,3-tetraiodoacetone (178), prepared by the method of Lederer,[15] gave a very poor yield of E-2,3-diiodoacrylic acid (184) which exhibited a sharp singlet at δ7.83 in the pmr spectrum and no trace of the expected 3,3-diiodo isomer (140). Apparently, in this case, elimination of iodide ion is not concurrent with the ring opening step and the intermediate carbanion (181) survives long enough to be protonated (181 → 182). The resulting triiodopropanoic acid (182) then undergoes normal base catalyzed β-elimination of HI to give 184.

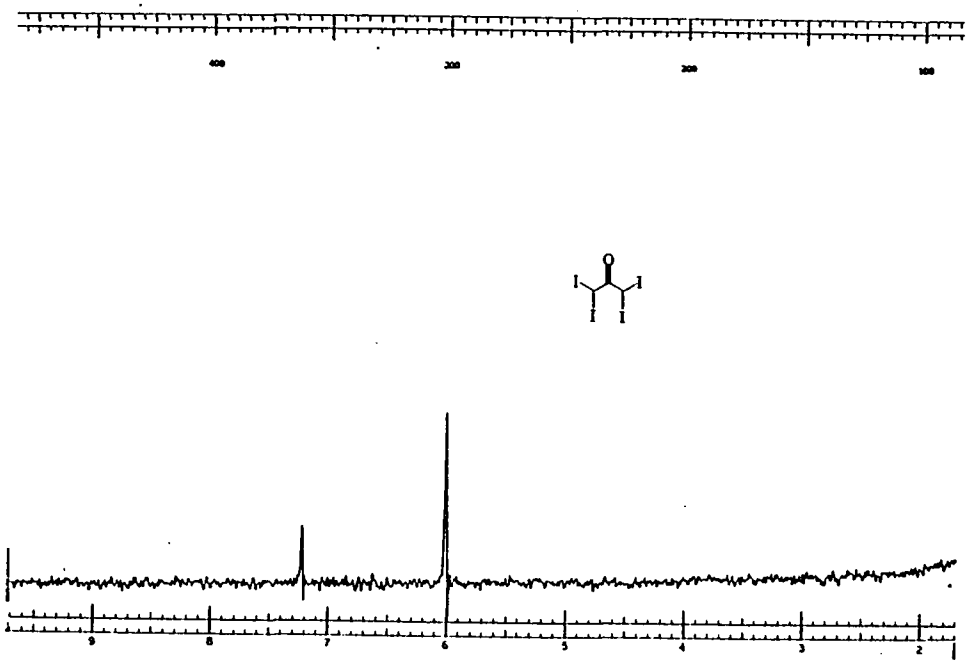


Figure II-35. Pmr spectrum ($CDCl_3$) of compound 178.

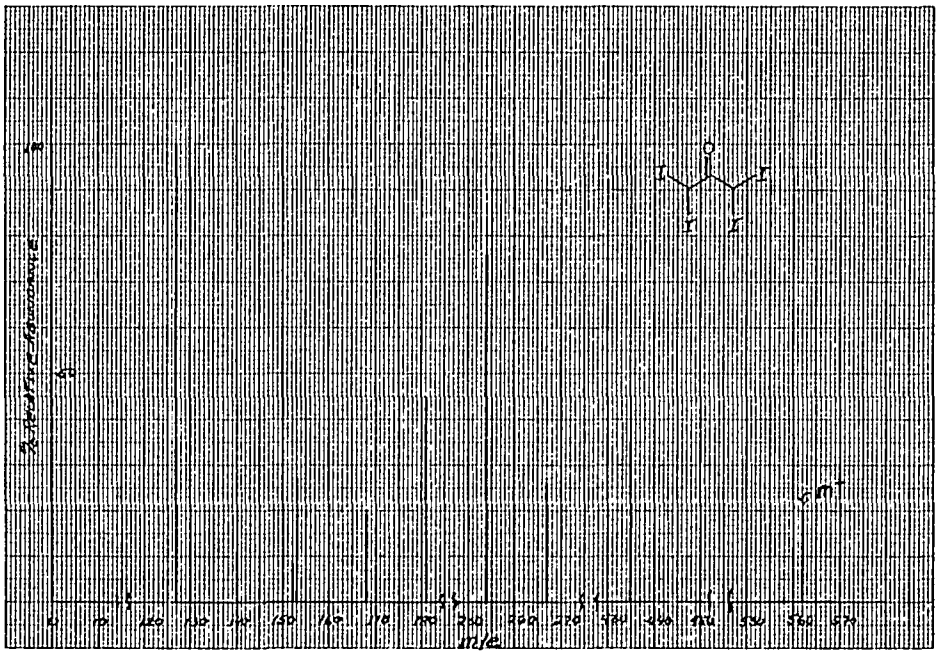
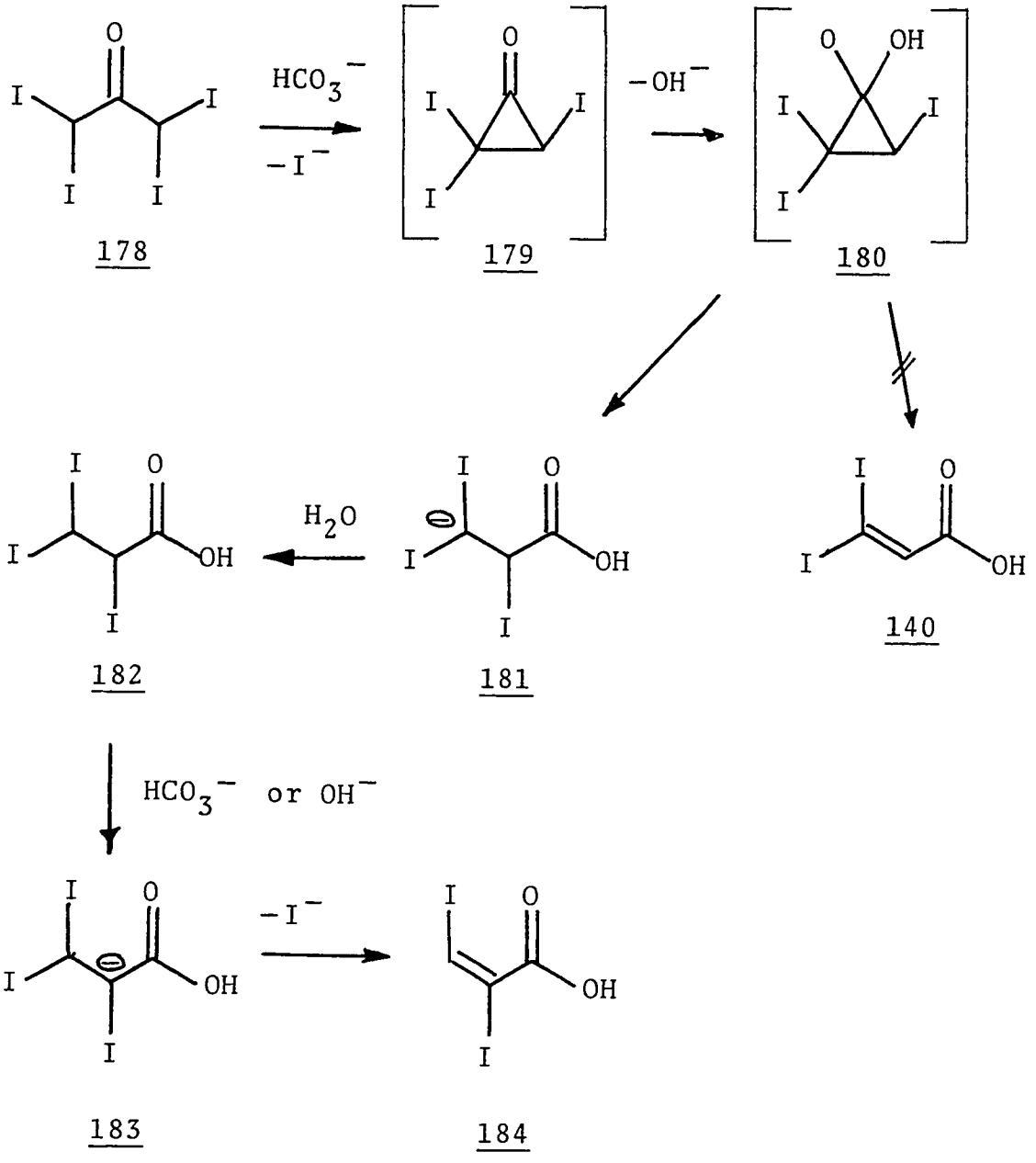


Figure II-36. Mass spectrum (70eV) of compound 178.


178
179
180
140
181
182
183
184
HCO_3^-
$-I^-$
$-OH^-$
H_2O
HCO_3^- or OH^-
$-I^-$

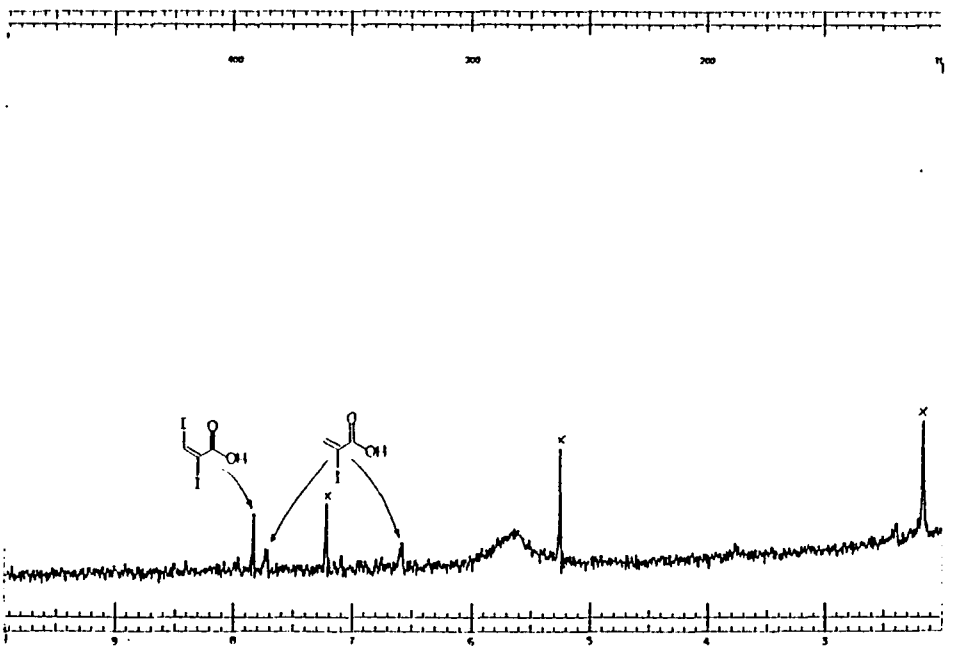
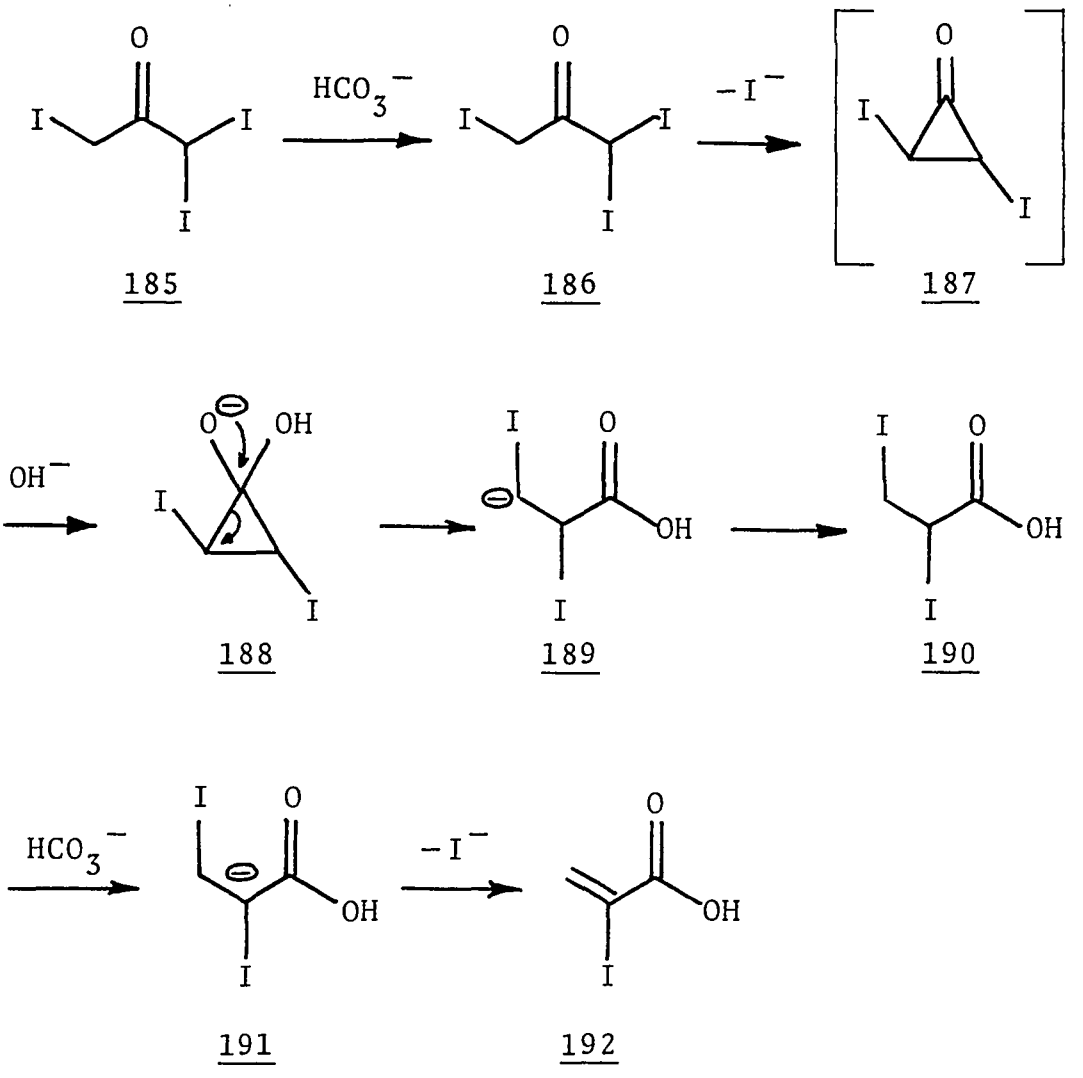
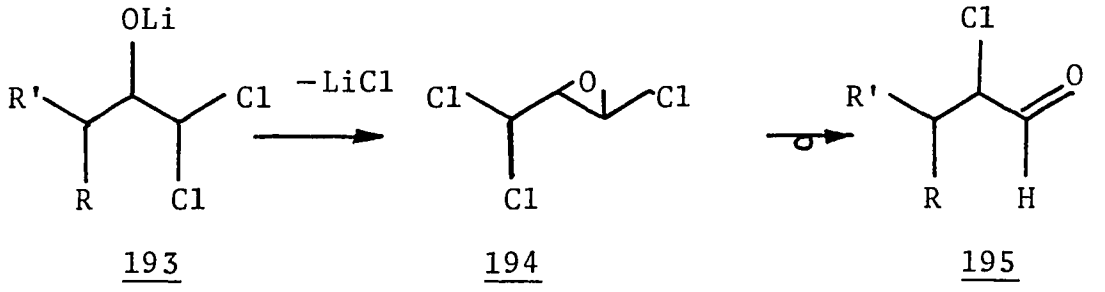


Figure II-37. Pmr spectrum ($CDCl_3$) of compounds 184 and 192.

Also present in the product from the Favorski rearrangement of 178 was 2-iodoacrylic acid (192). Apparently, 178 was contaminated with a small amount of 1,1,3-triiodoacetone (185) which undergoes the favorski sequence shown below. As with carbanion 181, carbanion 187 apparently does not immediately decompose by elimination but, instead, is protonated to give 190. Intermediate 190 evidently then undergoes normal bicarbonate-induced β-elimination of HI to give 192. These results indicate that if the Favorski rearrangement of halogenated acetones is indeed the source of the haloacrylic acids then it is probably a concerted process in Hawaiian A. taxiformis and not concerted in A. armata and Mexican A. taxiformis.

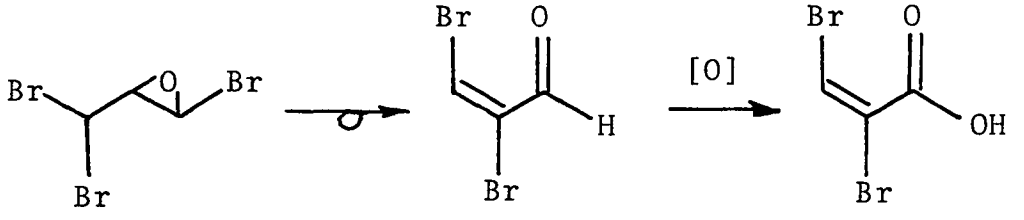


The halogenated isopropanols are most likely simple reduction products of the haloacetones and may also serve as precursors to the haloacrylic acids. For example Köbrich and Werner[16] have found that α,α-dichloro lithium alkoxides (193) rearrange to α-chloroaldehydes (195) via α-chloroepoxides (194) when refluxed in THF. Tribromo-epoxide 29 is a constituent of the essential oil of Hawaiian A. taxiformis and may, through this same type of



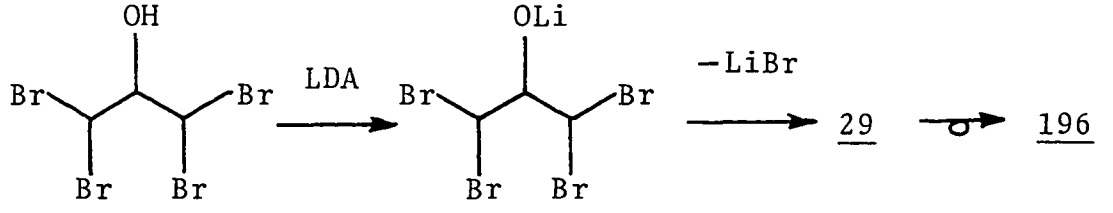
193 194 195

rearrangement, lead to E-2,3-dibromoacrylic acid (146) found in A. armata and Mexican A. taxiformis. The



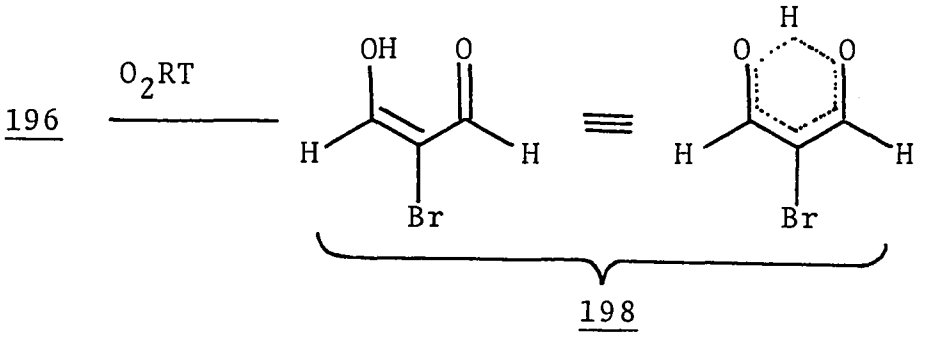
29 196 146

reaction of 1,1,3,3-tetrabromo-2-propanol (105) with LDA formed alkoxide 197 which, in refluxing THF, rearranged to give crude 196 in low yield (~ 36%). Interestingly, neat



105 197

196 rapidly decomposed to 2-bromo-malonodialdehyde (198) upon exposure to moist air. The structure of 198 was deduced



from its pmr spectrum (acetone-d_6) which showed a singlet at δ8.68 and the mass spectrum which exhibited a strong molecular ion cluster at m/e 150,152 (1:1) that readily loses a proton and CO to give clusters at m/e 149,150 (1:1) and 122,124 (1:1), respectively.

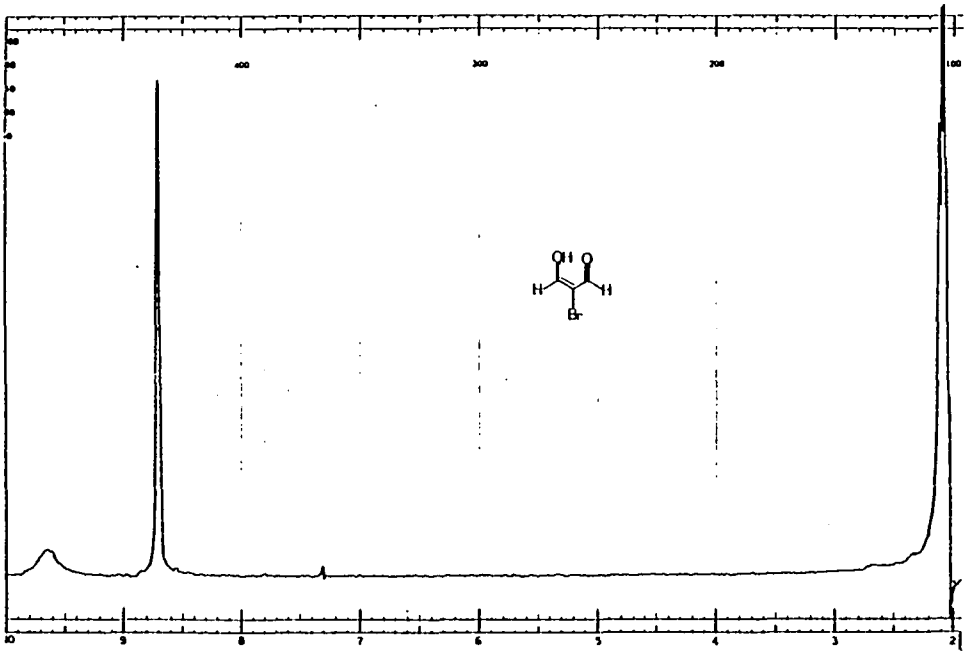


Figure II-38. Pmr spectrum (acetone-d_6) of compound 198.

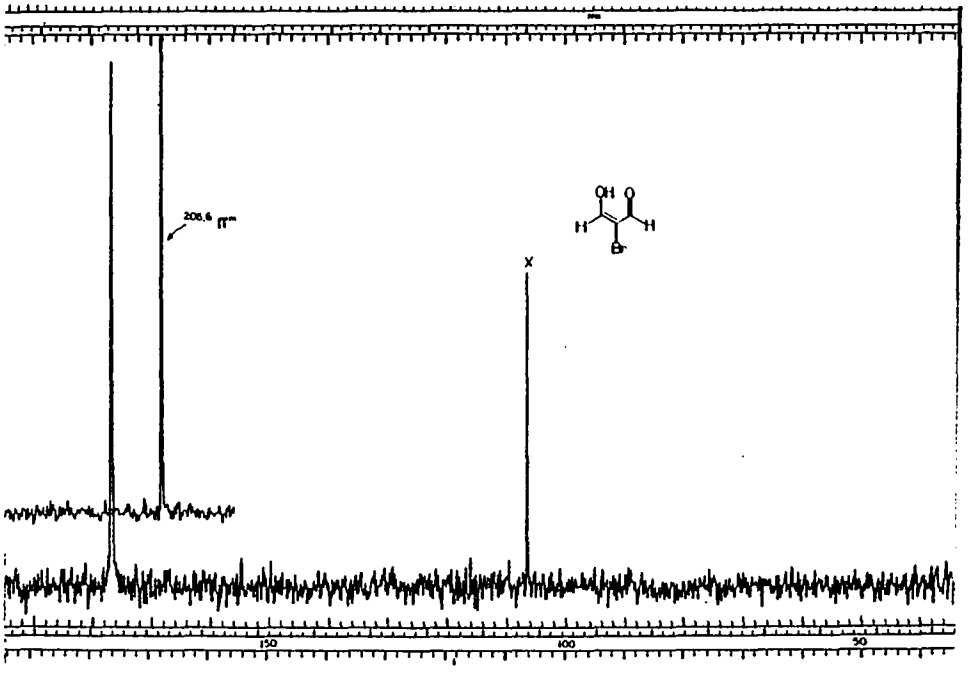


Figure II-39. Cmr spectrum (acetone-d_6) of compound 198.

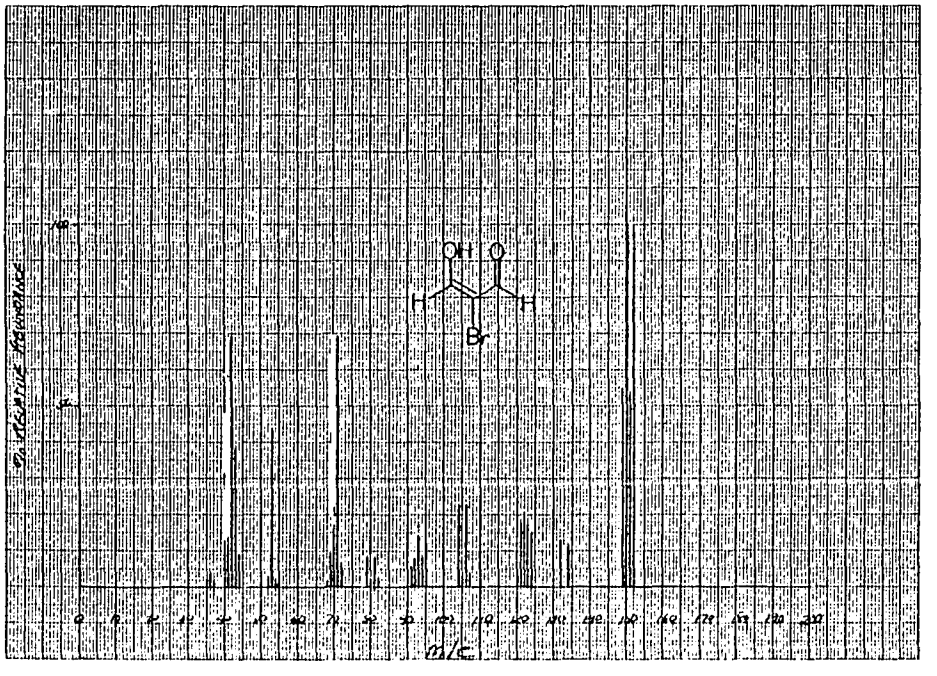


Figure II-40. Mass spectrum (70eV) of compound 198.

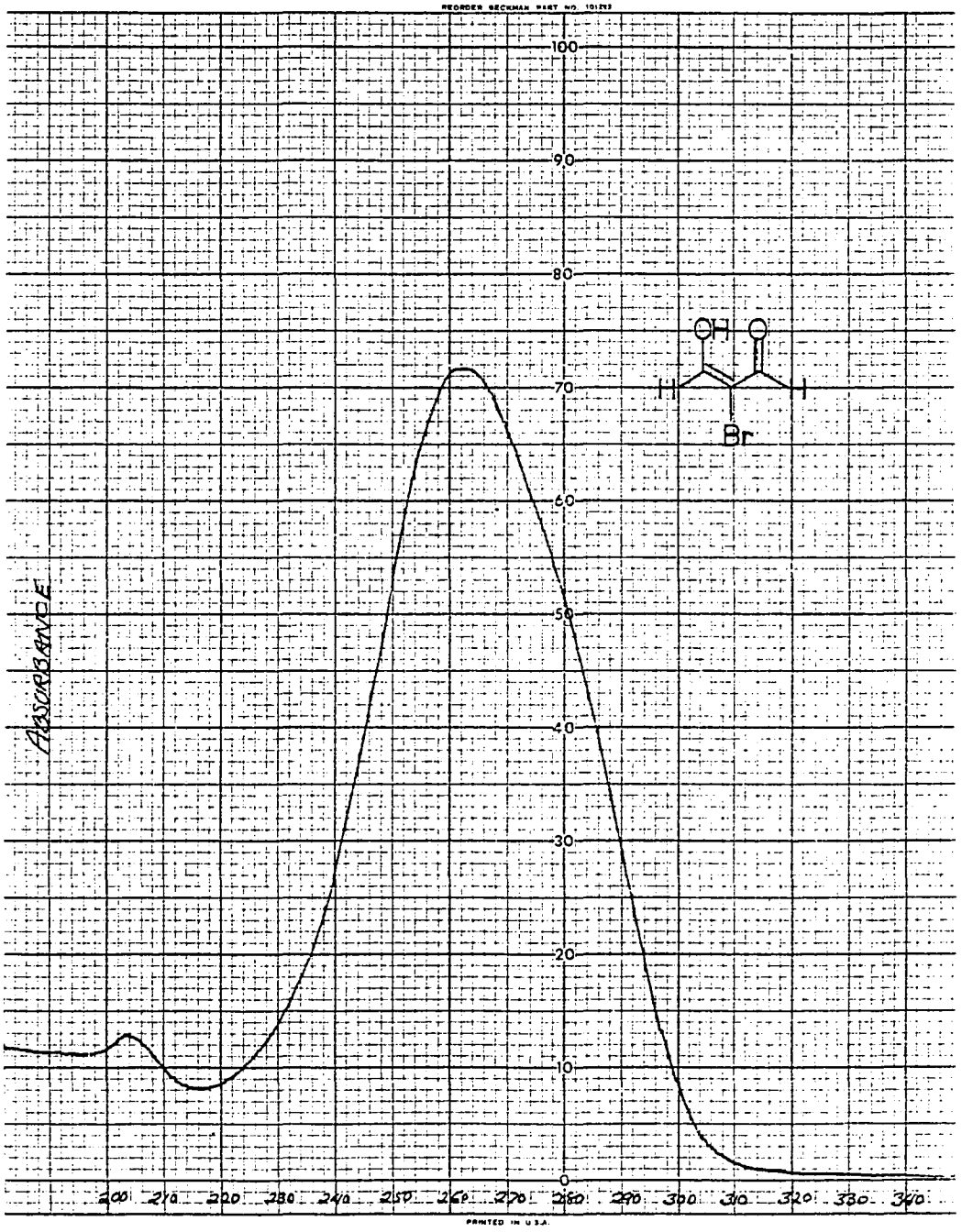


Figure II-41. Uv spectrum (EtOH) of compound 198.

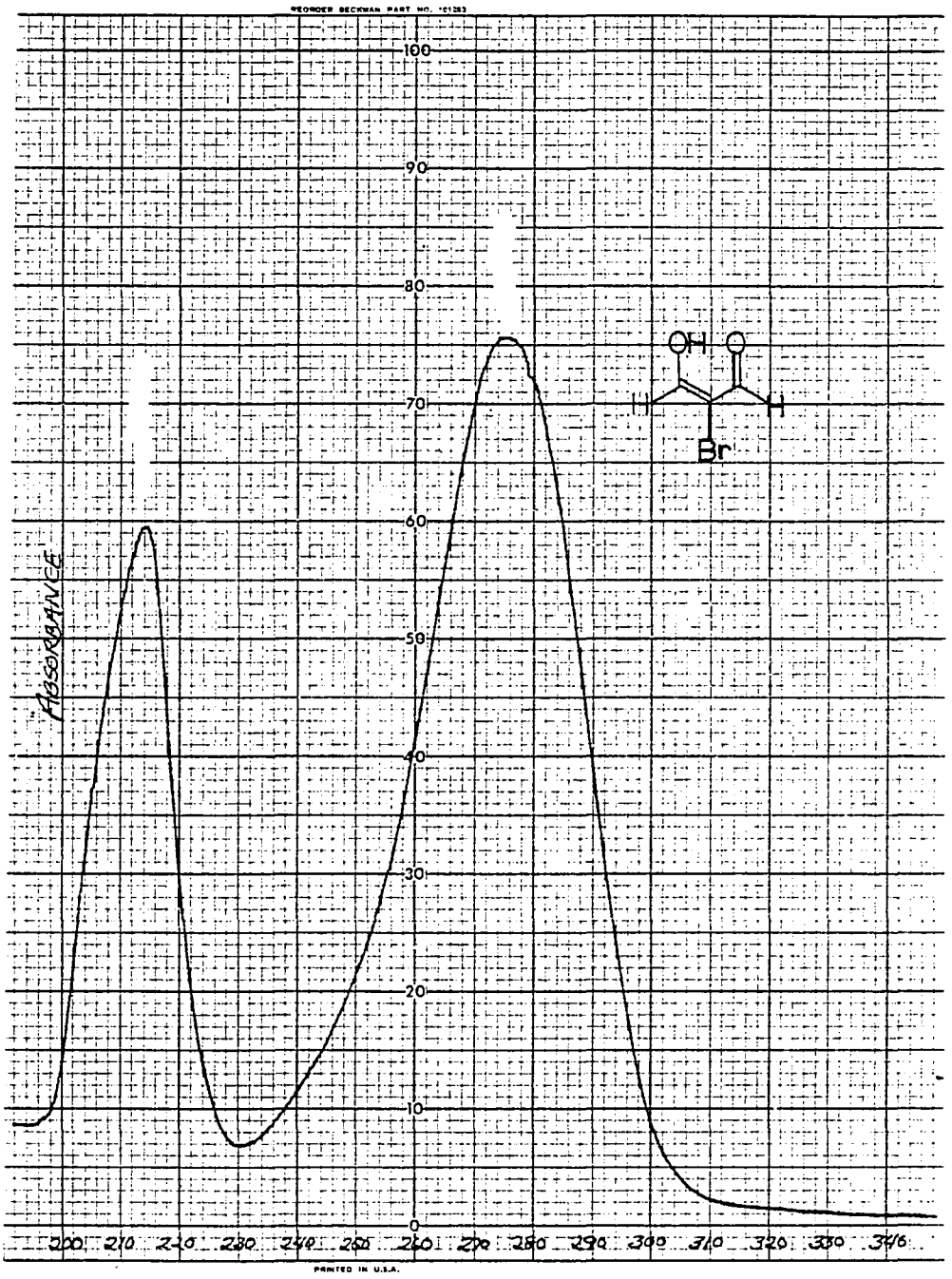


Figure II-42. Uv spectrum (EtOH + base) of compound 198.

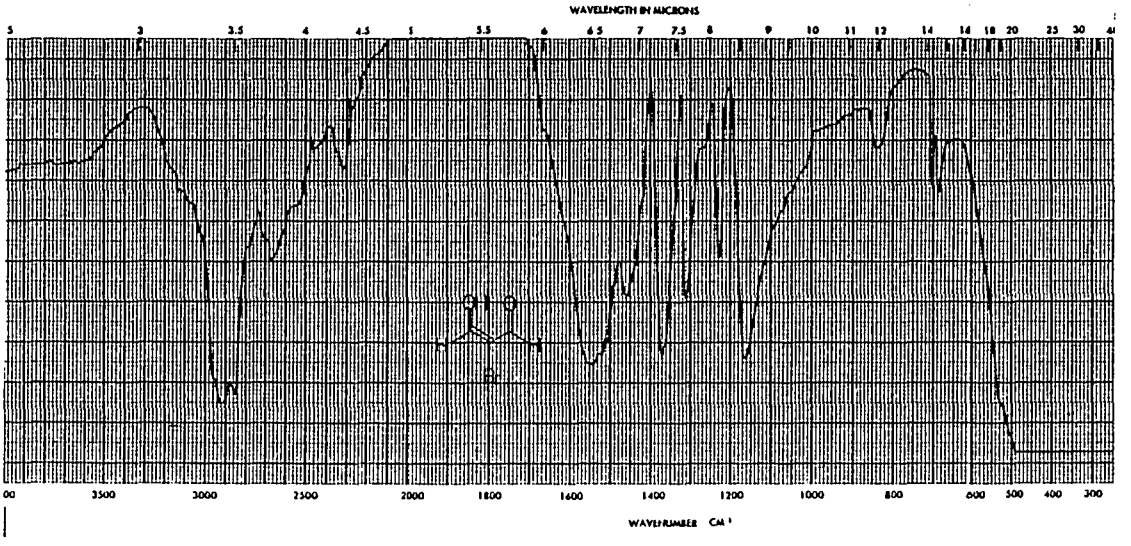


Figure II-43. Ir spectrum (nujol) of compound 198.

Epoxide 29 was also prepared in 21% yield by stirring 105 in 1:1 acetone/water solution with bicarbonate at room temperature for 24 hours. Stirring 29 in 60/40 dioxane/water for 77 hours at room temperature resulted in a 6:3:1 mixture (by pmr integration) of 105, 196 and Z-2,3-dibromoacrolein (199), respectively, plus a small amount of 198. This result demonstrated that exceedingly strong bases such as LDA are not required for the formation of 2,3-dibromoacroleins from 105.

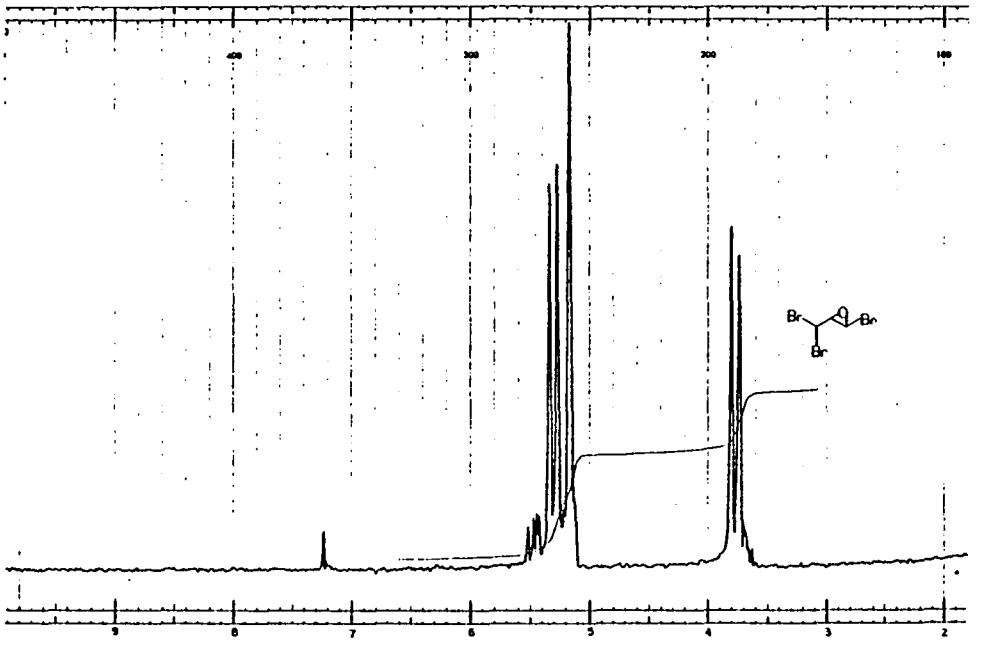


Figure II-44. Pmr spectrum ($CDCl_3$) of compound 29.

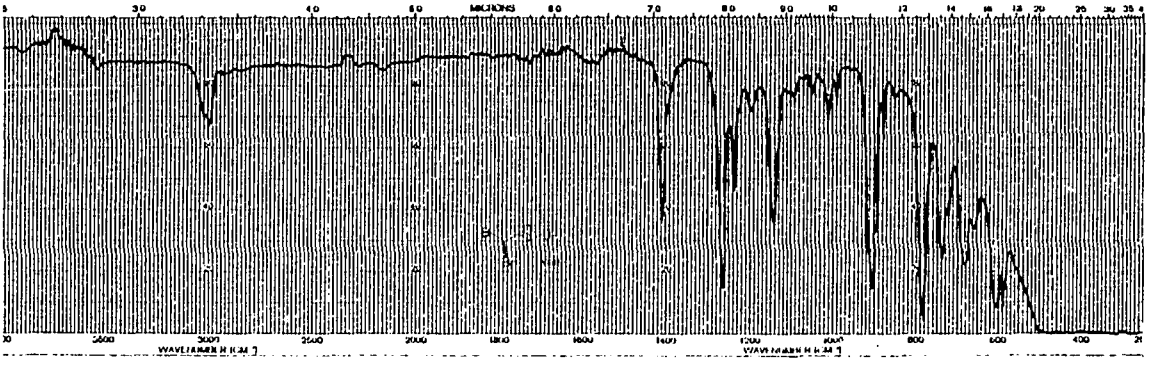
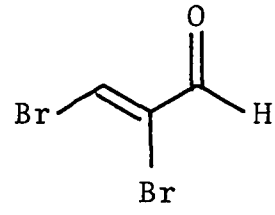


Figure II-45. Ir spectrum (neat) of compound 29.

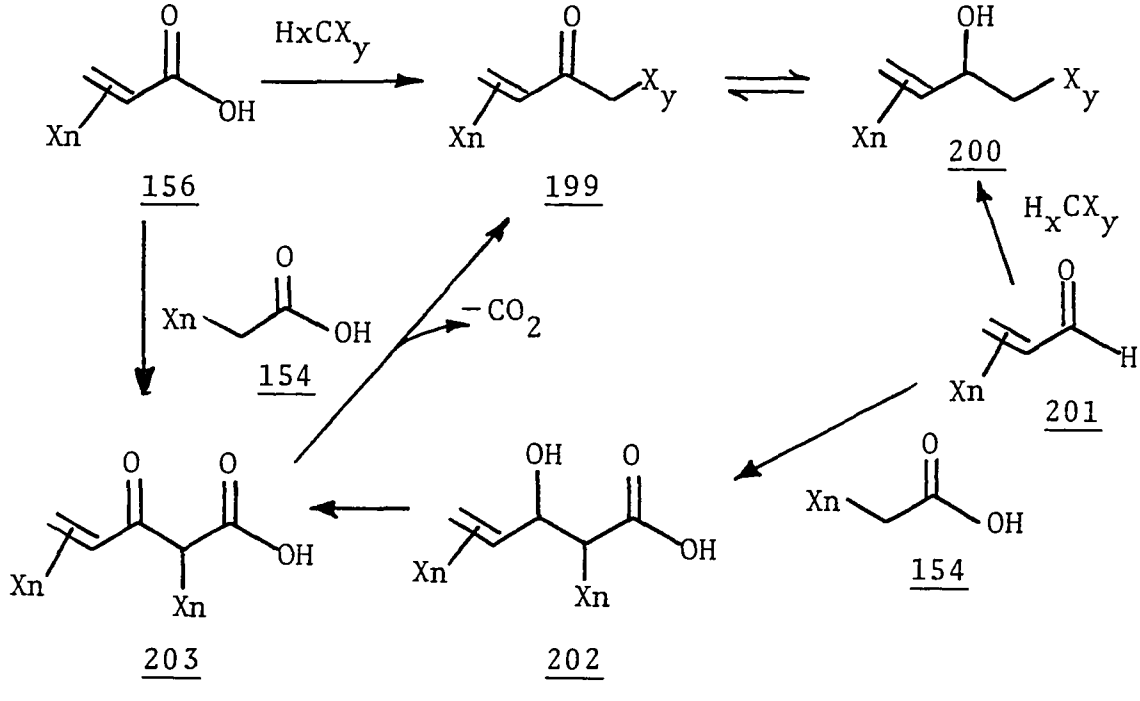


199

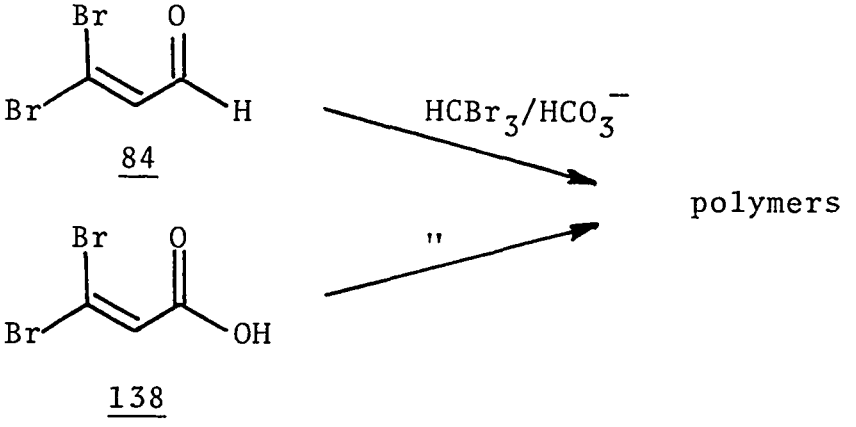
The halogenated butenols and butenones may be derived directly from acetoacetic acid (Scheme II-3) or from addition of halomethanes and acetic acids to halogenated acrylic acids and/or haloacroleins (Scheme II-4).

Scheme II-4.

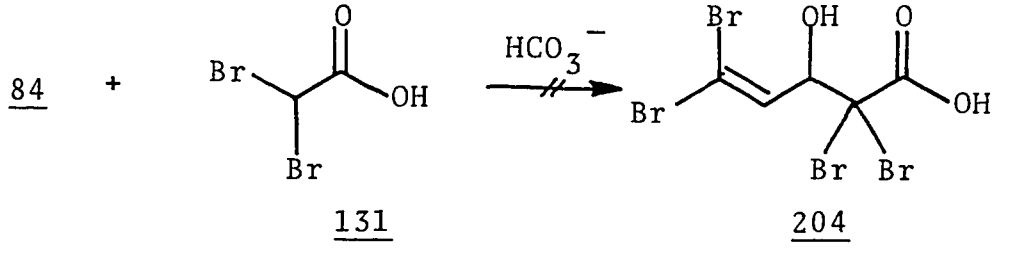
Proposed Biosynthesis of Butenols and Butenones in Hawaiian Asparagopsis

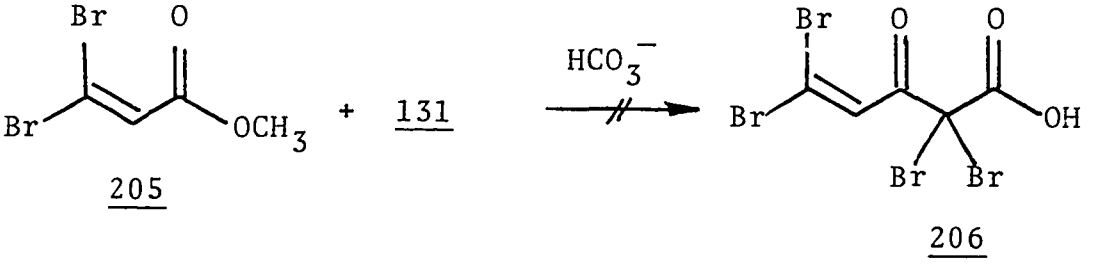


At low temperature, in the presence of strong base (LDA), methylene bromide and bromoform can be added to 3,3-dibromoacrolein (84) to form 83 (p. 133) and 114 (p. 146), respectively. However, stirring mixtures of 84 and 138 and bromoform in aqueous bicarbonate solution at room temperature produced only polymeric products. Attempted reaction of dibromoacetic



acid with 84 and 186 in aqueous bicarbonate solution resulted only in the isolation of starting materials.





D. Summary

In this study the nonvolatile extracts of Asparagopsis taxiformis were to be examined for halogenated compounds related to those found in the essential oil. Silica gel chromatography of the methylene chloride extract and gc-ms analysis of the various fractions resulted in the identification of twenty halogenated isopropanols (88-107), eight halogenated but-3-en-2-ols (83, 108-114) and five halogenated acetamides (120-124). Continuous ether extraction of the aqueous extract provided a small amount of oil that was esterified with diazomethane and methanol:sulfuric acid in separate experiments. Analysis of the resulting crude mixtures of esters by gc-ms revealed the presence of nine halogenated acetic acids (125-133) and nine halogenated acrylic acids (134-142).

The halogenated acetic acids are believed to arise from decomposition of 1,1,1-trihaloacetones and/or halogenation-decarboxylation of malonic acid. On the other hand, the halogenated acrylic acids appear to be derived from halogenated acetones via Favorski rearrangement. Supporting these hypotheses were several biomimetic syntheses. Bromination of 1,1,3,3-tetrabromoacetone (24) and malonic acid gave high yields of dibromoacetic acid. Treatment of 24 with aqueous bicarbonate solution resulted in the formation of 3,3-dibromoacrylic acid whereas similar treatment of 1,1,3-tribromoacetone produced Z-3-bromoacrylic acid.

Favorski rearrangement of 1,1,3,3-tetraiodoacetone and 1,1,3-triiodoacetone gave Z-2,3-diiodoacrylic acid and 2-iodoacrylic acid, respectively.

III. EXPERIMENTAL

A. General

1. Instruments

See page 89.

2. Solvents

See page 90.

3. Sorbents

See page 91.

B. Fractionation of the Methylene Chloride Extract from Hawaiian A. taxiformis

Vacuum dried[2] plants (286 g) of A. taxiformis, collected at Waikiki in the spring of 1975, were extracted with methylene chloride by Dr. B. J. Burreson. Evaporation of the solvent afforded 6.5 g (2.4%) of dark oil that, for this study, was applied to a 1 m X 2.5 cm column of silica gel. The column was first eluted with hexane followed by hexane/ether mixtures and finally 100% ether to give 26 fractions.

Fraction 11 (190 mg, 2.9%) eluted with 75% hexane/ether and was rechromatographed on a 120 X 10 mm column of silica gel G with the same solvent system. A crystalline substance (70 mg) was obtained which upon recrystallization from pentane gave 26 mg (0.4%) of 1,1,4,4-tetrabromobut-3-en-2-ol (83) as colorless needles; mp 84.5-85.5°; $[\alpha]_D^{24} = +7.9°$ (CH_2Cl_2, c=2.61); ir (CH_2Cl_2) 3540 (s), 3380 (m), 1610 (m), 1450 (w), 1185 (w), 1130 (w), 1010 (s) cm^{-1}; uv(EtOH) λ_{max}

212.5 nm (ε=8400); pmr ($CDCl_3$) δ2.68 (bd, J=6.5 Hz, OH, disappears on addition of D_2O), 4.65 (m, C-2 H, signal becomes dd, J=3.5 and 8.0 Hz, on addition of D_2O), 5.72 (d, J=3.5 Hz, C-1 H), 6.58 (d, J=8.0 Hz, C-3 H); cmr ($CDCl_3$) 47.2 (d, C-1), 76.7 (d, C-2), 96.2 (s, C-4), 135.3 (d, C-3) ppm; ms m/e (rel. intensity) 384, 386, 388, 390, 392 (1:4:6:4:1 ion cluster <1%), 213 (56), 215 (100), 217 (50), 171 (6), 173 (9), 175 (5), 105 (19), 107 (17). The mother liquor was evaporated to give 43 mg of yellow oil which was mainly a mixture of 83 and 1,1,3,3-tetrabromo-2-propanol [pmr ($CDCl_3$) 3.25 (bd, J=5 Hz, OH), 4.23 (m, C-2 CH), 5.93 (d, J=5 Hz, C-1 and C-3 CH)] with smaller amounts of other halogenated 3-buten-2-ols and 2-propanols. Analysis of the mixture by gc-ms revealed the presence of the following compounds: 1,1,3,3-tetrachloro-2-propanol (101), <1% retention time 11.2 min, m/e (rel. intensity) no M^+ ion cluster, 113 (100), 115 (68), 117 (7), 83 (23), 85 (20), 87 (6); 1-bromo-1,3,3-trichloro-2-propanol (102), <1%, 12.8 min, no M^+ ion cluster, 157 (56), 159 (56), 161 (20), 127 (16), 129 (13), 131 (6), 113 (100), 115 (67), 117 (7), 83 (24), 85 (18), 87 (6); 1,1,3-tribromo-2-propanol (98), <1%, 13.8 min, 294 (0.1), 296 (0.3), 298 (0.3), 300 (0.1), 201 (6), 203 (7), 205 (4), 171 (4), 173 (7), 175 (4), 123 (100), 125 (95), 93 (17), 95 (16); 1,1-dibromo-3,3-dichloro-2-propanol (103), <1%, 14.3 min, no M^+ ion cluster, 201 (52), 203 (95), 205 (49), 113 (100), 115 (67), 117 (14);

1-bromo-1-chloro-3-iodo-2-propanol (99), 4%, 14.3 min, 298 (5), 300 (5), 302 (3), 171 (100), 157 (72), 159 (82), 161 (24), 127 (48), 129 (50), 131 (14); 4,4-dichloro-1,1-dibromobut-3-en-2-ol (111), <1%, 15.8 min, no M^+ ion cluster, 171 (2), 173 (6), 175 (2), 125 (100), 127 (62), 129 (16); 4,4-dibromo-1,1-dichlorobut-3-en-2-ol (110), <1%, 15.8 min, no M^+ ion cluster, 213 (65), 215 (100), 217 (60), 83 (40), 85 (70), 87 (15); 1,1-dibromo-3-iodo-2-propanol (100), 5%, 15.8 min, 342, 344, 346 (0.6:1.0:0.5 ion cluster, <1%), 201 (49), 203 (89), 205 (45), 171 (100); 1,1,1-tribromo-3-chloro-2-propanol (105), <1%, 15.8 min, no M^+ ion cluster, 279 (3), 281 (5), 283 (5), 285 (2), 249 (5), 251 (8), 253 (6), 255 (4), 79 (>100), 81 (>100), 49 (11), 51 (5); 1,1,3-tribromo-3-chloro-2-propanol (104), <1%, 15.8 min, no M^+ ion cluster, 201 (55), 203 (96), 205 (47), 157 (80), 159 (100), 161 (28); 1,1,4-tribromo-4-chlorobut-3-en-2-ol (113), 5%, 17.4 min, 340, 342, 344, 346, 348 (0.5:0.7:1.0:0.6:0.1 ion cluster <1%), 169 (76), 171 (100), 173 (34), 175 (6); 1,1,3,3-tetrabromo-2-propanol (88), 43%, 17.4 min, 372, 374, 376, 378, 380 (1:4:6:4:1 cluster <1%), 213 (4), 215 (7), 217 (4), 201 (53), 203 (100), 205 (48), 185 (4), 187 (7), 189 (4); 1,1,4,4-tetrabromobut-3-en-2-ol (83), 31%, 18.8 min, 1,1,3-tribromo-3-iodo-2-propanol (106), 5%, 19.3 min, 420, 422, 424, 426 (1:3:3:1 ion cluster <1%), 293 (8), 295 (15), 297 (15), 299 (8), 213 (55), 215 (100), 217 (50), 201 (12), 203 (20), 205 (10), 185 (49), 187 (79), 189 (40);

1,1-dibromo-3,3-diiodo-2-propanol (107), 1%, 21.0 min, 468, 470, 472 (1:2:1 ion cluster, <1%), 341 (11), 343 (17), 345 (11), 213 (52), 215 (100), 217 (48), 201 (26), 203 (38), 205 (25), 185 (20), 187 (33), 189 (20), 127 (43); 1,1,1,4,4-pentabromobut-3-en-2-ol (114), 6%, 21.4 min, 472, 474, 476, 478, 480, 482 (0.1:0.6:1.0:0.9:0.5:0.2 ion cluster <1%), 275 (2), 277 (3), 279 (3), 281 (2), 249 (1), 251 (2), 253 (2), 255 (1), 213 (61), 215 (100), 217 (47).

Fraction 12 (310 mg, 4.8%) eluted with 75% hexane/ether and was rechromatographed on silica gel G with 60% hexane/methylene chloride to give 30 mg of oil which contained mostly 98 [pmr ($CDCl_3$) δ3.30 (d, J=5 Hz, OH), 3.66 (d, J=5 Hz, C-3 CH_2), 4.15 (m, C-2 H), 5.40 (d, J=4 Hz, C-1 H)] and 1,1-dibromo-3-chloro-2-propanol (97) [pmr ($CDCl_3$) δ3.30 (bd, OH), 3.76 (d, J=5 Hz, C-3 CH_2), 4.15 (m, C-2 H), 5.40 (d, J=4 Hz, C-1 H)] plus small amounts of other halogenated 2-propanols and 3-buten-2-ols. Analysis of the mixture by gc-ms (See Table II-3, footnote (a), page 139 for conditions) showed the presence of the following compounds: 1,1-dibromo-2-propanol (89), <1%, retention time 8.3 min, m/e (rel. intensity) 216, 218, 220 (1:2:1 ion cluster <1%), 201 (9), 203 (13), 205 (10), 171 (4), 173 (20), 175 (13), 44 (>100); 1,3-dibromo-2-propanol (90), <1% 9.8 min, 216 (3), 218 (4), 220 (3), 123 (97), 125 (100), 93 (11), 95 (9); 1-bromo-1,3-dichloro-2-propanol (94), <1%, 10.1 min, no M^+ ion cluster, 157 (8), 159 (10), 161 (3), 79 (100), 81 (32);

1-bromo-3,3-dichloro-2-propanol (95), <1%, 10.1 min, no M^+ ion cluster, 123 (100), 125 (95), 113 (8), 115 (6), 117 (2); 1-chloro-3-iodo-2-propanol (91), <1%, 10.1 min, 220, 222 (1:0.3 ion cluster <1%), 171 (3), 79 (100), 81 (32); 1,3-dibromo-1-chloro-2-propanol (96), 3%, 11.3 min, no M^+ ion cluster, 157 (11), 159 (14), 161 (4), 123 (>100), 125 (>100), 93 (39), 95 (37); 1,1-dibromo-3-chloro-2-propanol (97), 20%, 11.3 min, 250, 252, 254, 256 (0.5:1.0:0.7:0.3 ion cluster, <1%), 201 (7), 203 (14), 205 (7), 171 (3), 173 (6), 175 (3), 79 (100), 81 (40), 49 (10), 51 (3); 1-bromo-3-iodo-2-propanol (92), 3%, 11.4 min, 264 (12), 266 (11), 171 (45), 123 (>100), 125 (100), 93 (39), 95 (36); 1,1,3-tribromo-2-propanol (98), 55%, 13.1 min; 4,4-dibromo-1-chlorobut-3-en-2-ol (108), 3%, 13.2 min, 262, 264, 266, 268 (0.6:1.0:0.8:0.4 ion cluster <1%), 213 (55), 215 (100), 217 (53), 49 (15), 51 (5); 1,3-diiodo-2-propanol (93), 2%, 13.3 min, 312 (35), 185 (85), 171 (100), 141 (30); 1,4,4-tribromobut-3-en-2-ol (109), 7%, 15.2 min, 306 (1), 309 (3), 310 (4), 312 (1), 213 (64), 215 (>100), 217 (61), 93 (7), 95 (5); 1,1-dibromo-3-iodo-2-propanol (100), <1%, 15.5 min, 342 (7), 344 (13), 346 (6), 213 (6), 215 (16), 217 (17), 219 (6), 201 (3), 203 (4), 205 (2), 171 (100); 1,1,4-tribromo-1-chlorobut-3-en-2-ol (112), <1%, 17.2 min, 340, 342, 344, 346, 348 (0.5:0.7:1.0:0.6:0.2 ion cluster <1%), 213 (53), 215 (100), 217 (48), 127 (4), 129 (6), 131 (2); 1,1,4,4-tetrabromobut-3-en-2-ol (83), 5%, 18.5 min.

Fraction 19 (600 mg, 9.2%) eluted with 100% ether and was dissolved in methylene chloride. On standing for four days at -20° 80 mg of a greenish solid precipitated. Recrystallization from methylene chloride afforded 75 mg of an optically inactive mixture of dihaloacetamides as colorless needles. Analysis of the mixture by gc-ms (see Table II-3, footnote (a), page 139 for conditions) revealed the presence of the following dihaloacetamides; bromochloroacetamide (120), 15%, retention time 14.4 min, m/e (rel. intensity) 171 (9), 173 (13), 175 (3), 127 (3), 129 (5), 131 (2), 44 (>100); dibromoacetamide (121), 51%, 14.9 min, 215 (3), 217 (6), 219 (3), 172 (2), 174 (4), 176 (2), 171 (1), 173 (2), 175 (1), 120 (2), 122 (2), 91 (2), 92 (3), 93 (3), 94 (3), 95 (2), 79 (2), 81 (2), 44 (>100); chloroiodoacetamide (122), 5%, 15.9 min, 219 (4), 221 (1), 127 (2), 92 (7), 94 (4), 44 (>100); bromoiodoacetamide (123), 22%, 17.4 min, 263 (26), 265 (24), 220 (35), 136 (55), 138 (59), 127 (24), 44 (>100); diiodoacetamide (124), 6%, 19.9 min, 311 (55), 268 (20), 184 (91), 127 (37), 44 (>100). The pmr spectrum of the mixture in acetone-d_6 showed singlets at δ5.66, 6.09, 6.16, 6.26 and 6.30 for the CH protons of 124, 123, 122, 121 and 120, respectively, and several broad multiplets for the NH_2 protons in the 6.5-7.5 ppm region (7.5-8.5 in DMSO-d_6).

Fraction 20 (610 mg, 9.4%) also eluted with 100% ether and deposited a mixture of dihaloacetamides (30 mg) from methylene chloride; pmr and gc-ms analysis showed that it was essentially a 2:2:1 mixture of 124, 123 and 121, respectively.

C. Isolation of Acids from the Aqueous Extract of A. taxiformis

1. Extraction and Identification as Methyl Esters

Dried plants of A. taxiformis (97 g) were soaked in methanol (1 ℓ) for 48 hr. The solvent was decanted and the extraction was continued successively with methanol (1 ℓ) and chloroform (2 x 1 ℓ). The extracts were combined and the solvents removed in vacuo to give a dark oil which was then partitioned between water and chloroform. The aqueous layer (400 ml) was separated and filtered. A small portion (25 ml) of the aqueous extract was acidified with conc. H_3PO_4 (3 ml) and extracted continuously for 48 hr with ether. Removal of the ehter in vacuo afforded 170 mg of an orange oil. A sample of this oil was esterified with excess diazomethane and another one was esterified with methanolic HCl. Analysis of the resulting two mixtures of esters by gc-ms (see Table II-5, footnote (a), page 152, for conditions) indicated the presence of the following methyl esters: methyl chloroacetate, retention time

4.5 min, 1%, m/e (rel. intensity) 108 (12), 110 (5), 77 (35), 79 (14), 73 (19), 59 (100), 49 (48), 51 (16); methyl bromoacetate, 8.4 min, 2%, 152 (20), 154 (20), 121 (30), 123 (30), 93 (45), 95 (45), 59 (100); methyl chloroacrylate, 9.5 min, <1%, 120 (14), 122 (6), 89 (100), 91 (39), 85 (25), 61 (31), 59 (31); methyl dichloroacrylate, 11.8 min, 2%, 154 (15), 156 (9), 158 (2),123 (100), 125 (65), 127 (15), 95 (21), 97 (10), 99 (6), 59 (40); methyl bromochloroacetate, 12.3 min, 4%, 186 (2), 188 (1), 190 (0.5), 155 (3), 157 (4), 159 (1), 127 (69), 129 (58), 131 (15), 59 (100); methyl iodoacetate, 12.6 min, 8%, 200 (34), 169 (18), 141 (35), 73 (78), 59 (100); methyl bromoacrylate, 12.6 min, <1%, 164 (12), 166 (11), 133 (100), 135 (99), 105 (35), 107 (34), 85 (47), 59 (22); methyl dibromoacetate, 14.6 min, 22%, 230 (3), 232 (5), 234 (3), 199 (2), 201 (4), 203 (2), 171 (36), 173 (66), 175 (32), 120 (18), 122 (17), 79 (10), 81 (10), 59 (>100); methyl iodoacrylate, 15.5 min, <1%, 212 (83), 181 (100), 153 (39), 127 (39), 59 (89); methyl chloroiodoacetate, 15.7 min, 2%, 234 (30), 236 (15), 175 (40), 177 (20), 127 (50), 107 (90), 109 (40), 59 (100); methyl 3,3-dibromoacrylate, 17.0 min, 10%, 242 (9), 244 (16), 246 (8), 211 (53), 213 (100), 215 (49), 183 (13), 185 (23), 187 (11), 163 (13), 165 (12), 135 (22), 137 (18), 104 (57), 106 (56), 79 (9), 81 (9), 59 (32); methyl bromoiodoacetate, 17.6 min,

15%, 278 (55), 280 (55), 247 (9), 249 (9), 219 (50), 221 (50), 168 (28), 151 (100), 153 (100), 140 (31), 127 (62), 120 (23), 122 (24), 59 (42); methyl 3-bromo-3-iodoacrylate, 19.1 min, 25%, 290 (72), 292 (70), 259 (60), 261 (58), 231 (20), 233 (19), 211 (10), 163 (50), 165 (49), 127 (40), 59 (100); methyl tribromoacrylate, 20.8 min, <1%, 320 (4), 322 (9), 324 (8), 326 (3), 289 (6), 291 (15), 293 (15), 295 (7), 241 (15), 243 (25), 245 (15), 59 (>100); methyl diiodoacetate, 21.2 min, 8%, 326 (69), 295 (10), 267 (21), 254 (16), 199 (100), 127 (84), 59 (63); methyl 3,3-diiodoacrylate, 22.5 min, 7%, 338 (30), 307 (10), 279 (5), 254 (3), 211 (78), 152 (56), 127 (45), 59 (100); methyl dibromoiodoacrylate, 23.7 min, <1%, 368 (1), 370 (2), 337 (1), 339 (2), 341 (1), 127 (15), 59 (100).

2. Ion Exchange Chromatography of the Aqueous Extract

A small portion of the aqueous solution [pmr spectrum between 5-9 ppm (D_2O): singlets at δ (intensity relative to peak at 5.55 ppm) 5.55 (100), 5.58 (93), 5.85 (13), 5.87 (17), 6.30 (58), 6.40 (80), 6.47 (3), 6.52 (5), 6.59 (5), 6.64 (12), 6.98 (12), 7.12 (12), 7.52 (46), 7.65 (25), 8.26 (7), and 8.86 (10)] was introduced onto a 15 cm X 3 cm column of DEAE Sephadex A-25 (chloride form). After washing the column with 400 ml of water, elution with 0.01N aqueous HCl gave

three fractions (monitored by uv) which were neutralized with dilute NH_4OH solution and lyophilized. Fraction 1 contained ammonium 3,3-dibromoacrylate [pmr spectrum (D_2O) δ7.52]. None of the compounds in fraction 2 were identified. Fraction 3 contained ammonium diiodoacetate [pmr spectrum (D_2O) δ5.83], bromoiodoacetate (δ6.28), dibromoacetate (δ6.38), and dichloroacetate (δ6.46) in a 19:87:100:4 ratio.

Halogenated Acetic Acids. Chloro-, bromo-, iodo-, and dichloroacetic acids were obtained from commercial sources. Pmr (D_2O) of ammonium salts: iodoacetate, δ4.02; dichloroacetate, 6.47.

D. Synthesis of Compounds

1. 1,1,4,4-Tetrabromobut-3-en-2-ol (83).

a. From 3,3-Dibromoacrolein and Methylene Bromide.

3,3-Dibromoacrolein (2.52 g, 10.1 mmol) and freshly distilled methylene bromide (1.74 g, 10.0 mmol) were reacted with lithium dicyclohexylamide (3.74 g, 20.0 mmol) using the generalized procedure of Yamamoto.[9] The mixture was quenched with 50 ml of 2N ammonium chloride solution and the organic solvents were removed in vacuo. The oily solid was extracted with methylene chloride (3 X 40 ml), the extracts combined, dried ($MgSO_4$) and the solvent removed in vacuo to give a dark oil. Chromatography

of the oil on a 1 m X 1.5 cm column of silica gel with 50:50 methylene chloride/hexane followed by vacuum sublimation (78°, 0.025 torr) afforded 1.06 g (27%) of 83 as colorless needles, mp 84-85°.

Anal. calcd. for $C_4H_4Br_4O$: C, 12.4; H, 1.0. Found: C, 12.2; H, 1.0.

b. From 1,1,4,4-Tetrabromobutenone (37).

Fraction 4 (11 mg, essentially a 2:1 mixture of 37 and 1,1,1-tribromoacetone) from chromatography of the essential oil of A. taxiformis on silica gel at 5°[2] was treated with 20 mg of $NaBH_4$ in 1 ml of ethanol at 0° for 30 minutes. One ml of 2N ammonium chloride solution followed by 20 ml of water were added and the mixture was extracted with methylene chloride. The dried ($MgSO_4$) extract was evaporated to give 83. The pmr spectrum was identical with that of 83 from method (a) and signals for 1,1,1-tribromo-2-propanol were not present.

2. Z-3,4-Dibromobut-3-en-2-ol.

Z-3,4-Dibromobutenone (0.5 g, 1.6 mmol) was added to a solution of 100 mg $NaBH_4$ (excess) in EtOH (5 ml) at 0° and stirred for 10 minutes. Water (75 ml) was added and the solution extracted with methylene chloride (3 x 15 ml). The extracts were combined, dried ($MgSO_4$)

and the solvent removed in vacuo to give 0.49 g (97%) of crude Z-3,4-dibromo-but-3-en-2-ol: pmr ($CDCl_3$) δ1.41 (d, J=6.5 Hz, Me), 2.9 (bs, OH), 4.41 (q, J=6.5 Hz, C-2 H), 7.00 (s, C-4 H).

3. 1,1,1,4,4-Pentabromobut-3-en-2-ol (114).

3,3-Dibromoacrolein (1.07 g, 4.2 mmol), freshly distilled bromoform (2.52 g, 5.0 mmol) and lithium dicyclohexylamide (1.73 g, 10 mmol) were reacted together using the general procedure of Yamamoto.[9] Workup as described above for 83 gave after vacuum sublimation (85°, 0.025 torr) 1.35 g (69%) of 114 as colorless needles, mp 94.0-95.5°; ir (nujol) 3260 (s), 1630 (w), 1460 (m), 1380 (m), 1140 (m), 790 (w), 740 (w), 710 (m) cm^{-1}; uv (EtOH) λ_{max} 215 nm (ε=12,000); pmr ($CDCl_3$) δ6.64 (d, J=8.0 Hz, C-3 H), 4.75 (dd, J=6.0 and 8.0 Hz, C-2 H), 3.28 (d, J=6.0 Hz, OH); cmr ($CDCl_3$) 133.4 (d, C-3), 97.9 (s, C-4), 83.7 (d, C-2), 48.7 (s, C-1) ppm.

Anal. calcd. for $C_4H_3Br_5O$: C, 10.3; H, 0.7. Found: C, 10.6; H, 0.7.

4. 1,1,3,3-Tetrabromoacetone (24).

Compound 24 was prepared by the method of Rappe.[17]

5. 1,1,3,3-Tetrabromo-2-propanol (105).

A 500 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 50.0 g (0.14 mol) of 1,1,3,3-tetrabromoacetone (24) and 200 ml of absolute ethanol and cooled to 0°. Sodium borohydride (2.65 g, 0.07 mol) was added and the mixture stirred at 0° for one hour. The reaction was quenched with 50 ml of 2F ammonium chloride solution, the ethanol removed in vacuo and the oily aqueous residue extracted with methylene chloride (3 X 30 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give a pale yellow oil. The oil was chromatographed on a 1 m X 2.5 cm column of silica gel with 1:1 hexane/methylene chloride to give 36.2 g (68.7%) of 105 as a very pale yellow oil; pmr ($CDCl_3$) δ3.52 (d, J=5 Hz, OH), 4.22 (q, J=5 Hz, C-2 H), 5.93 (d, J=5 Hz, C-1 and C-3 H); ms m/e (rel. intensity) 372, 374, 376, 378, 380 (1:4:6:4:1 ion cluster <1%), 213 (5), 215 (9), 217 (5), 201 (53), 203 (100), 205 (50), 185 (5), 187 (9), 189 (4), 171 (12), 173 (22), 175 (12).

6. 2,2-Dibromoacetamide (121).

A 100 ml three-necked round-bottomed flask, nitrogen inlet and exit tubes and glass stopper were heated in a drying oven at 110° for ten minutes, assembled hot and flushed with a rapid stream of dry nitrogen. The flask

was then charged with 1.0 g (4.6 mmol, Aldrich) of dibromoacetic acid, 25 ml of dry benzene and 0.16 cc (0.27 g, 2.3 mmol) of thionyl chloride. The mixture was stirred magnetically and refluxed for eight hours. At the end of this time the flask was cooled to 10° in a water bath and a stream of anhydrous ammonia introduced via a fritted gas inlet tube. After ten minutes the benzene was removed under reduced pressure and the solid residue recrystallized from methylene chloride to give 121 as fine white needles; pmr (acetone-d_6) δ6.16 (s), 6.6-7.6 (m, NH_2); ms m/e (rel. intensity) 215 (3), 217 (6), 219 (3), 172 (2), 174 (4), 176 (2), 171 (1), 173 (2), 175 (1), 120 (2), 122 (2), 91 (2), 92 (3), 94 (3), 95 (2), 79 (2), 81 (2), 44 (>100).

7. Z-3-Bromoacrylic Acid (135).

   a. From Propiolic Acid.

   Using a modified procedure of Kurz,[18] 94 mg of cuprous bromide was added to 5 ml of conc. hydrobromic acid, propiolic acid (1.00 g, 0.015 mol) added dropwise at 0° over 5 minutes, and the mixture stirred at 0° for an additional 15 minutes. After standing overnight at 4°, ten ml of water was added and the mixture extracted with methylene chloride (4 X 10 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo

to give a light tan solid. Recrystallization from hexane gave 1.83 g (18%) of 135 as colorless needles, mp 57.0-58.5°; pmr ($CDCl_3$) δ6.62 (d, J=8 Hz, 1H), 7.12 (d, J=8 Hz, 1H), 9.92 (bs, 1H); ir (nujol) 2900 (br, s), 1700 (br, s), 1610 (s), 1455 (s), 1375 (s), 1230 (s) cm^{-1}.

b. From 1,1,3-Tribromoacetone (22).

To 574 mg (6.8 mmol) of sodium bicarbonate and 50 ml of 1:1 acetone/water was added 1.00 g (3.4 mmol) of 1,1,3-tribromoacetone (22). The mixture was stirred for 14 hours at room temperature and the acetone removed in vacuo. Acidification of the aqueous mixture followed by extraction with methylene chloride afforded an oily solid. Crystallization from hexane gave 380 mg (74%) of 135 as white needles; mp 57.0-58.5°.

8. E-3-Bromoacrylic Acid (144).

Z-3-Bromoacrylic acid (135, 690 mg) was dissolved in six ml of 6N hydrobromic acid and stirred at 105° for five hours. The mixture was cooled, five ml of water added and the mixture extracted with methylene chloride (3 X 10 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give a light tan solid. Recrystallization from hexane gave 310 mg

(45%) of 144 as colorless needles; mp 115.0-116.2°; pmr ($CDCl_3$) δ6.48 (d, J=14 Hz, 1H), 7.70 (d, J-14 Hz, 1H), 10.70 (bs, 1H); ir (nujol) 2900 (br, s), 1655 (br, s), sh 1600, 1435 (br, m), sh 1470, 1270 (s) cm^{-1}.

9. 2-Bromoacrylic Acid (143).

Acrylic acid (5.00 g, 69 mmol) and sodium bicarbonate (17.39 g, 207 mmol) were dissolved with stirring in 100 ml of water. Bromine (11.03 g, 69 mmol) was added dropwise over five minutes and the solution stirred overnight at room temperature. The solution was then acidified with hydrochloric acid and extracted with methylene chloride. Removal of the methylene chloride in vacuo gave a colorless oil which was dissolved in 25 ml of 5% aqueous sodium hydroxide and the mixture stirred at room temperature for one hour. Acidification with hydrochloric acid followed by extraction with methylene chloride afforded 4.10 g of a pale yellow oil which consisted of approximately 30% 143 and 70% 2,3-dibromopropionic acid by gc-ms analysis. 2-Bromoacrylic acid: pmr ($CDCl_3$) δ6.93 (d, J=2 Hz, 1H), 7.06 (d, J=2 Hz, 1H), 11.46 (bs, 1H).

10. Comparison of Methyl Esters of Synthetic Bromoacrylic Acids with the Methyl Ester of Natural Z-3-Bromoacrylic Acid.

Small amounts of 2-, E-3-, and Z-3-bromoacrylic acid were converted to the methyl esters with diazomethane. The methyl esters were examined by gc-ms on a 10' X 1/8" column of 10% SP-1000 (Carbowax) on 100/120 acid-washed Chromosorb W heated isothermally at 80° for two minutes after injection, then temperature programmed from 80° to 200° at 8° per minute using a gas flow rate of 20 ml per minute. Methyl E-3-bromoacrylate: retention time 6.7 minutes; ms m/e (rel. intensity) 164 (24), 166 (24), 133 (100), 135 (100), 119 (2), 121 (2), 105 (56), 107 (56), 85 (100), 59 (29). Methyl 2-bromoacrylate: 7.2 minutes; 164 (59), 166 (58), 133 (88), 135 (92), 119 (2), 121 (2), 105 (100), 107 (94), 85 (80), 59 (47). Methyl Z-3-bromoacrylate: 10.0 minutes; 164 (12), 166 (11), 133 (100), 135 (99), 105 (35), 107 (34), 85 (47), 59 (22).

11. 3,3-Dibromoacrylic Acid (138).

a. From 3,3-Dibromoacrolein (84).

The aldehyde[19] (250 mg) was oxidized by Procedure B of Brown et al.[20] The dark reaction mixture was stored in the freezer overnight and 138 crystallized from the reaction mixture as white plates; mp 82.0-84.0°;

pmr (acetone-d_6) δ7.08 (s, 1H), 10.22 (bs, 1H); ir (nujol) 2800 (vbr, s), 1685 (br, s), 1580 (s), 1460 (m), 1430 (s), 1400 (s), 1280 (s), 1230 (s), 960 (m), 855 (s), 815 (s), 720 (w), 655 (s), 615 (s) cm^{-1}.

b. From 1,1,3,3-Tetrabromoacetone (24).

A mixture of 24 (2.0 g, 5.4 mmol), sodium bicarbonate (0.90 g, 10.7 mmol) and 100 ml of 1:1 acetone/water was stirred at room temperature for 20 hours. The acetone was removed in vacuo and the concentrate was washed with methylene chloride, acidified with hydrochloric acid and extracted with methylene chloride. The extract was evaporated and the resulting tan solid was sublimed (75°, 0.1 torr) to give 610 mg (50%) of 138 as thick white needles; mp 82.0-84.0°.

12. E- and Z-2,3-Dibromoacrylic Acids (146 and 145).

Propiolic acid (500 mg, 7.15 mmol) was brominated using the procedure of Baudrowski[21] to give 1.27 g (78%) of a mixture of E and Z-2,3-dibromoacrylic acids; pmr (D_2O) δ7.04 (s, 1H, Z, 68% by integration), 8.30 (s, 1H, E, 32% by integration).

13. Comparison of Methyl Esters of Synthetic Dibromoacrylic Acids with the Methyl Ester of Natural 3,3-Dibromoacrylic Acid.

Small amounts of 3,3-dibromoacrylic acid and a mixture of E- and Z-2,3-dibromoacrylic acid were converted to the methyl esters with diazomethane. The methyl esters were examined by gc-ms using the conditions outlined in Table II-1, footnote (b). Methyl E-2,3-dibromoacrylate: retention time 11.7 minutes; ms m/e (rel. intensity) 242 (19), 244 (32), 246 (19), 211 (32), 213 (64), 215 (32), 183 (20), 185 (40), 187 (20), 163 (100), 165 (100), 104 (34), 106 (34), 59 (61). Methyl Z-2,3-dibromoacrylate: 12.4 minutes; 242 (19), 244 (32), 246 (19), 211 (32), 213 (64), 215 (32), 183 (20), 185 (40), 187 (20), 163 (100), 165 (100), 104 (34), 106 (34), 59 (61). Methyl 3,3-dibromoacrylate: 17.0 minutes; 242 (9), 244 (16), 246 (8), 211 (53), 213 (100), 215 (49), 183 (13), 185 (23), 187 (11), 163 (13), 165 (12), 135 (22), 137 (18), 104 (57), 106 (57), 59 (32).

14. Dibromoacetic Acid (131).

a. From 1,1,3,3-Tetrabromoacetone (24).

To a suspension of 374 mg (1.0 mmol) of 1,1,3,3-tetrabromoacetone (24) in a solution of 252 mg (3.0 mmol) of sodium bicarbonate in 15 ml of water was added 0.053 ml (160 mg, 1.0 mmol) of

bromine. After 1.5 hours of stirring the mixture was basified, washed with methylene chloride (3 X 10 ml) to remove bromoform and a small amount of 3,3-dibromoacrylic acid (40 mg) and lyophilized. The pmr spectrum (D_2O) of the residual white solid (460 mg) showed a singlet at δ6.38 for dibromoacetate.

b. From Malonic Acid (157).

Malonic acid (104 mg, 1.0 mmol) in 26 ml of pH 7 buffered phosphate solution (16 ml of 0.02N potassium dihydrogen phosphate and 10 ml of 0.01N sodium hydroxide) was treated with 0.10 ml (320 mg, 2.0 mmol) of bromine. The mixture was stirred until gas evolution ceased (one hour). The solution was basified with one ml of conc. ammonium hydroxide and lyophilized. The pmr spectrum (D_2O) of the residue (480 mg) exhibited only one signal, a singlet at δ6.38 for dibromoacetate.

15. Tetraiodoacetone (178).

Compound 178 was obtained in 5.7% yield as yellow needles using the procedure of Lederer;[15] 151.2-152.0°; pmr ($CDCl_3$) δ6.00 (s); ms m/e (rel. intensity) 562 (20, calcd. for $C_3H_2I_4O$: 561.6284, found: 561.6255) 435 (35), 267 (26), 254 (76), 181 (45), 168 (19), 153 (20), 152 (27), 140 (11), 127 (100).

16. E-2,3-Diiodoacrylic acid (184) and 2-Iodoacrylic Acid (192).

Tetraiodoacetone (178, 175 mg, 0.31 mmol) and 78 mg (0.93 mmol) of sodium bicarbonate were dissolved in ten ml of 1:1 acetone/water solution. The mixture was protected from light and stirred magnetically at room temperature for 24.5 hours. The acetone was removed in vacuo and 100 mg of sodium bicarbonate added to the oily aqueous residue. The mixture was extracted with methylene chloride (3 X 10 ml), acidified with hydrochloric acid and extracted again with methylene chloride (5 X 15 ml). The acidic extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give 20 mg of a 3:2 mixture of 184 [pmr ($CDCl_3$) δ7.93 (s)] and 192 [pmr ($CDCl_3$) δ7.72 (d, J=2 Hz), 6.58 (d, J=2 Hz)] as a brown gum.

17. E-2,3-Dibromoacrolein (196) from 1,1,3,3-Tetrabromo-2-propanol (105).

The alcohol (8.20 g, 21.8 mmol) in 200 ml of dry tetrahydrofuran at -100° was treated with lithium dicyclohexylamide (21.8 mmol). After stirring at -100° for 15 minutes the solution was allowed to warm to room temperature and then refluxed for one hour.[16] The THF was removed in vacuo and the black residual oil chromatographed on a 20 cm X 3 cm column of silica gel with 10% methylene chloride/hexane. Evaporation of the solvent

afforded 2.84 g of crude 196; pmr ($CDCl_3$) δ8.28 (s, 1H), 9.28 (s, 1H).

18. 1,1,3-Tribromo-1,2-epoxypropane (29).

A solution of 1,1,3,3-tetrabromo-2-propanol (105) (6.17 g, 16.4 mmol) and sodium bicarbonate (1.38 g, 16.0 mmol) in 100 ml of 1:1 acetone/water was stirred at room temperature for 36 hours. The acetone was removed in vacuo and the oily aqueous mixture was extracted with methylene chloride. Evaporation left a yellow oil which was chromatographed on a 25 cm X 3 cm column of silica gel with 10% methylene chloride/ hexane. The forerun of the effluent afforded 1.02 g (21%) of 29 as a colorless oil; pmr ($CDCl_3$) δ3.73 (d, J=7.0 Hz, 1H), 5.14 (s, 1H), 5.28 (d, J=7.0 Hz, 1H); ir (neat) 2990 (w), 1410 (m), 1264 (s), 1236 (m), 1140 (m), 1010 (w), 905 (s), 878 (w), 780 (s), 740 (s), 680 (s), 605 (s), 590 (s) cm^{-1}; ms m/e (rel. intensity) 292, 294, 296, 298 (0.6:1.0:1.0:0.4, molecular ion cluster <1%), 213 (28), 215 (49), 217 (22), 184 (7), 185 (23), 186 (15), 187 (37), 188 (8), 189 (19), 171 (6), 173 (12), 175 (7), 157 (1), 159 (3), 161 (1), 133 (7), 134 (4), 135 (6), 137 (4), 105 (99), 107 (100), 79 (16), 80 (7), 81 (17), 82 (7).

An analytical sample was prepared by hplc on a μ-Porasil column using 5% methylene chloride/95% hexane.

Calcd. for $C_3H_3Br_3O$: C, 12.2; H, 1.0. Found: C, 12.4; H, 1.1.

19. 2-Bromomalonodialdehyde (198).

a. From E-2,3-Dibromoacrolein (196).

E-2,3-dibromoacrolein (196) was stirred neat in moist air for 48 hours. The resulting black semi-solid was extracted with methylene chloride. The resulting brown solid was sublimed (100°, 0.1 torr) and crystallized from benzene to give 450 mg of 198 as white needles; mp 137-139° dec (lit.[22] 155° dec); pmr (acetone-d_6) δ8.68 (s); uv (EtOH) λ_{max} 262 nm (ε=14,200) shifted to 215.5 nm (ε=17,700), 278 (22,600) in base; cmr (acetone-d_6) δ206.6 (d), 175.3 (s); ms m/e (rel. intensity) 150 (100), 152 (100), 149 (55), 151 (54), 132 (14), 134 (13), 122 (21), 124 (16), 121 (18), 123 (16), 104 (23), 106 (23), 93 (18), 95 (16), 79 (8), 81 (8), 71 (68), 53 (45), 42 (70).

Anal. Calcd. for $C_3H_3BrO_2$: C, 23.9; H, 2.0. Found: C, 24.1; H, 2.1.

b. From 1,1,3-Tribromo-1,2-epoxypropane (29).

A mixture of 588 mg (2.0 mmol) of epoxide, 252 mg (3.0 mmol) of sodium bicarbonate and 20 ml of 60/40 dioxane/water was stirred for 77 hours at

room temperature. Extraction of the mixture with methylene chloride and evaporation of the solvent afforded 181 mg of an oil which was a 6:3:1 mixture of starting material, E-2,3-dibromoacrolein [δ9.28 (s, 1H), 8.28 (s, 1H)] and Z-2,3-dibromoacrolein [δ9.29 (s, 1H), 7.96 (s, 1H)], respectively. The aqueous portion above was acidified with conc. hydrochloric acid and extracted with methylene chloride to give 28 mg of crystalline 198.

20. Ethyl 5,5-Dibromo-3-hydroxy-4-pentenoate (86).

Using the general procedure of Hauser and Breslow[23] compound 86 was obtained as a dark oil. Chromatography of the oil on a 16 cm X 3 cm column of silica gel with hexane followed by 3:2 methylene chloride/hexane afforded 2.6 g (7.3%) of 86 as a yellow oil; pmr ($CDCl_3$) δ1.21 (t, J=6 Hz, 3H), 2.49 (d, J=6 Hz, 2H), 3.73 (bs, 1H), 4.02 (q, J=6 Hz, 2H), 4.55 (dt, J=6.0 and 8.0 Hz, 1H), 6.33 (d, J=8.0 Hz, 1H).

21. Attempted Oxidation of 86 with Manganese Dioxide.

A 50 ml Erlenmeyer flask equipped with a stopper and efficient magnetic stirrer was charged with 500 mg (1.7 mmol) of 86, five g of activated manganese dioxide (previously heated in a drying oven at 100° for 12 hours), 5.5 g of benzene and 19 g of hexane.[24] The

mixture was vigorously stirred at room temperature for 14 hours and then filtered through Celite. The solvents were removed *in vacuo* to give 300 mg of dark tar.

Repeating the reaction as described above with a reaction time of one hour resulted in the isolation of 400 mg of starting material.

22. *Attempted Oxidation of 86 with DDQ.*

A 50 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 302 mg (1.3 mmol) of DDQ and five ml of benzene. The mixture was stirred and when solution was effected 400 mg (1.3 mmol) of *86* and 1.6 ml of benzene were added all at once. The reaction mixture was stirred at room temperature for 20 minutes and the solvent removed *in vacuo*. The resulting red semisolid was dissolved in ~ one ml of acetone and chromatographed on a short (40 mm X 30 mm) column of neutral alumina to give 120 mg of starting material.

Reacting 500 mg (1.7 mmol) of *86* and 377 mg (1.7 mmol) of DDQ as described above for 6.5 hours resulted in the isolation of 370 mg of starting material.

23. *Attempted Oxidation of 86 with Pyridinium chlorochromate.*[25]

A ten ml round-bottomed flask equipped with a drying

tube and efficient magnetic stirrer was charged with 323 mg (1.5 mmol) of pyridinium chlorochromate and 301 mg (1.0 mmol) of 86 in three ml of methylene chloride. The orange heterogeneous mixture was stirred at room temperature and turned black after 15 minutes. The stirring was continued for an additional hour and then filtered through Celite, treated with charcoal and the solvent removed in vacuo to give ~ 200 mg of dark tar.

24. Attempted addition of Bromoform to 3,3-Dibromoacrolein (84) with Bicarbonate.

A 100 ml Erlenmeyer flask equipped with an efficient magnetic stirrer was charged with 60 ml of 1:1 dioxane/water solution, 1.09 g (13.0 mmol) of sodium bicarbonate 1.77 g (7.0 mmol) of bromoform and 1.00 g (4.7 mmol) of 84. The mixture was stirred at room temperature for 142 hours, neutralized with hydrochloric acid and extracted with methylene chloride (3 X 25 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give ~ one g of a highly viscous yellow-brown oil whose pmr spectrum revealed the presence of only polymeric products.

25. Attempted Addition of Bromoform to 3,3-Dibromoacrylic Acid (138) with Bicarbonate.

a 100 ml Erlenmeyer flask equipped with an efficient magnetic stirrer was charged with 60 ml of 1:1 THF/water solution, 1.09 g (13.0 mmol) of sodium bicarbonate, 1.77 g (7.0 mmol) of bromoform and 1.00 g (4.7 mmol) of 138. The mixture was stirred at room temperature for 185 hours, neutralized with hydrochloric acid and the THF removed in vacuo. The resulting oil aqueous mixture was extracted with methylene chloride (3 X 25 ml), the extracts combined, dried ($MgSO_4$) and the solvent removed in vacuo to give 1.1 g of tar.

26. Attempted Addition of Dibromoacetic Acid (131) to 3,3-Dibromoacrolein (84) with Bicarbonate.

A 250 ml Erlenmeyer flask equipped with an efficient magnetic stirrer was charged with 100 ml of 1:1 acetone/water solution, 0.79 g (9.4 mmol) of sodium bicarbonate, 1.02 g (4.7 mmol) of 131 and 1.00 g (4.7 mmol) of 84. The mixture was stirred at room temperature for 148 hours and the acetone removed in vacuo. The oily aqueous residue was acidified with hydrochloric acid and extracted with methylene chloride (3 X 20 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give 2.24 g of brown oil. Gc-ms and pmr analysis showed the oil to consist of

equal amounts of 131 and 84 plus a small amount of acetone condensation products.

27. Attempted Addition of Dibromoacetic Acid (131) to Methyl 3,3-Dibromoacrylate with Bicarbonate.

A 50 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 20 ml of 1:1 acetone/water solution, 176 mg (2.1 mmol) of sodium bicarbonate, 229 mg (1.0 mmol) of 131 and 240 mg (1.0 mmol) of 146. The mixture was stirred at room temperature for 133 hours, the acetone removed in vacuo and the oily aqueous residue extracted with methylene chloride (3 X 15 ml). The aqueous layer was acidified with hydrochloric acid and extracted with methylene chloride (3 X 15 ml). The acidic extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give 330 mg of a 3:2 mixture of 131 and 3,3-dibromoacrylic acid (138).

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P A R T T H R E E

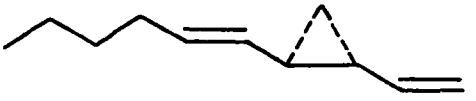
STUDIES ON THE BIOGENESIS OF THE DICTYOPTERENE HYDROCARBONS AND SULFUR COMPOUNDS

I. INTRODUCTION

A. Historical Background and Early Chemical Studies on Hawaiian *Dictyopteris*

Along the eastern and southern shores of Oahu in the summertime the air possesses a very distinct pleasant odor. The source of this odor is known to the Hawaiians as *limu lipoa* (*limu* that is gathered from the deep), which is the local name for two species of edible brown algae belonging to the family *Dictyotales*. These algae are known scientifically as *Dictyopteris plagiogramma* (Montagne) Vickers and *D. australis* Sonder and can be found growing together in large beds in the sublittoral zones of all the Hawaiian Islands. Historically and up to the present time these algae have been used by the people of Hawaii as seasonings because of their aroma and flavor.[1]

In 1966 Moore and coworkers began an investigation of the odor of *D. plagiogramma* and *D. australis*. The essential oils were isolated and were found to contain nearly identical amounts of the same C_{11} hydrocarbons (*1*-*10*).[2-5] The structures of these compounds were established by rigorous analysis of the various pmr spectra and chemical degradation. From a structural standpoint these compounds were exceedingly interesting since dictyopterenes A and B (*1* and *2*, respectively) were the first divinylcyclopropanes to be found in nature.[2] Lemieux oxidation of *1* and *2* gave (+)-*trans*-cyclopropane-1(*R*),2(*R*)-dicarboxylic acid and established



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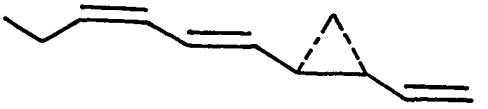

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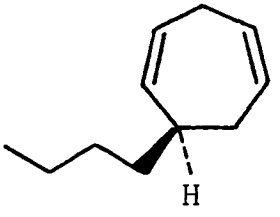

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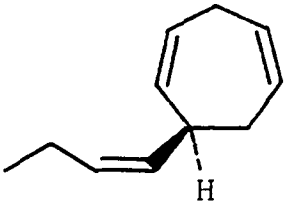

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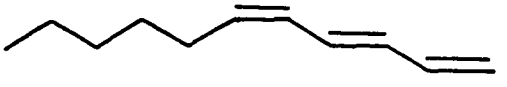

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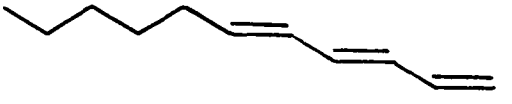

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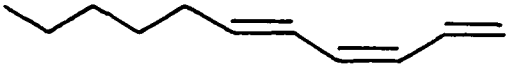

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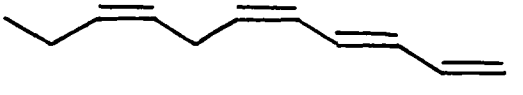

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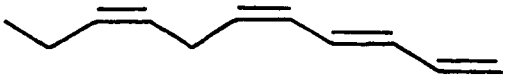

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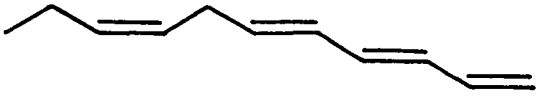

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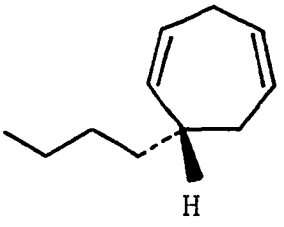

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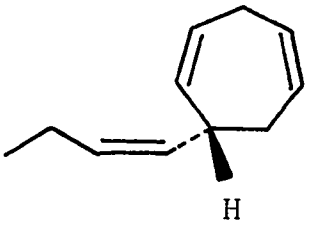
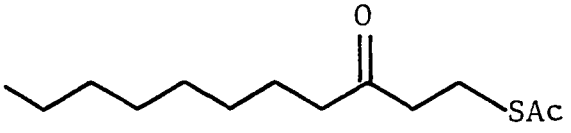


12

the cyclopropane carbons as R,R. Gas chromatographic separation of 1 and 2 at temperatures above 160° caused extensive Cope rearrangement to take place which formed cycloheptadienes 11 and 12. Comparison of the cmr spectra of 11 and 12 with the cmr spectrum of the essential oil led to the isolation of dictyopterene C' (3) and dictyopterene D' (4) which had optical rotations opposite in sign to those of 11 and 12. Partial reduction of 11 to 12 and oxidation of 3 and 11 to the optically active butylsuccinic acids established the absolute configuration of C-6 in 3 as R and C-6 of 4 as S. Interestingly, 4 is identical in all respects to ectocarpene, the sperm attractant in the isogamous seaweed Ectocarpus siliculosis found in the

Mediterranean Sea.[7,8] It is not known at this time whether 4 or any of the other hydrocarbons are involved in the sexual reproduction of Dictyopteris.

Examination of the nonvolatile extracts from Dictyopteris produced a number of sulfur compounds (13-20) that are biogenetically related to the hydrocarbons.[5,9-11] The structures of these compounds were determined by complete spectral analysis but the absolute configurations of 15, 19 and 20 were not determined.



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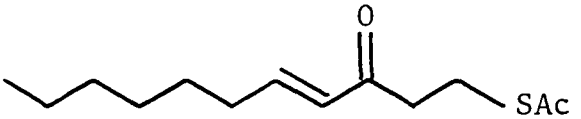

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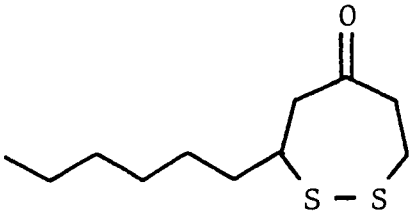

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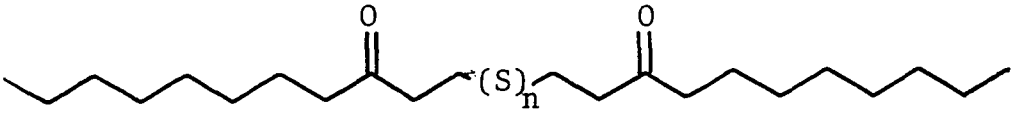
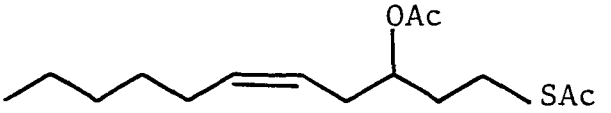


16 n=2

17 n=3

18 n=4



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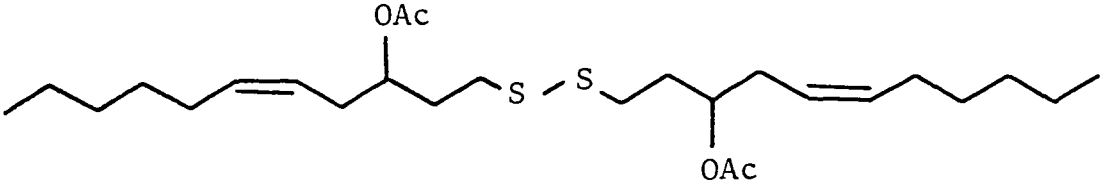
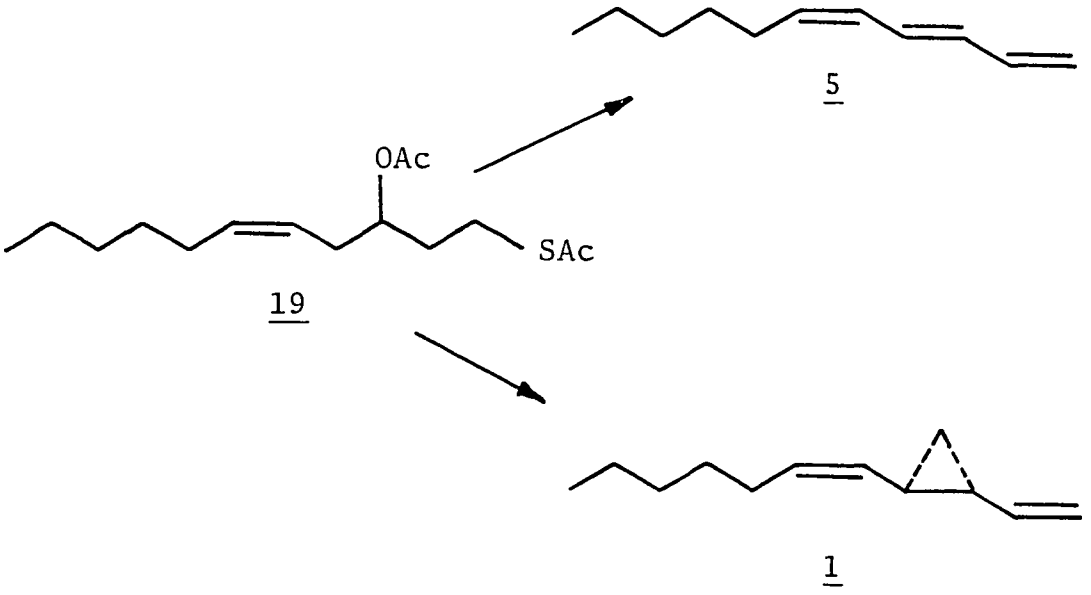


20

B. Biogenesis of the Dictyopterene Hydrocarbons and Sulfur-Containing Compounds

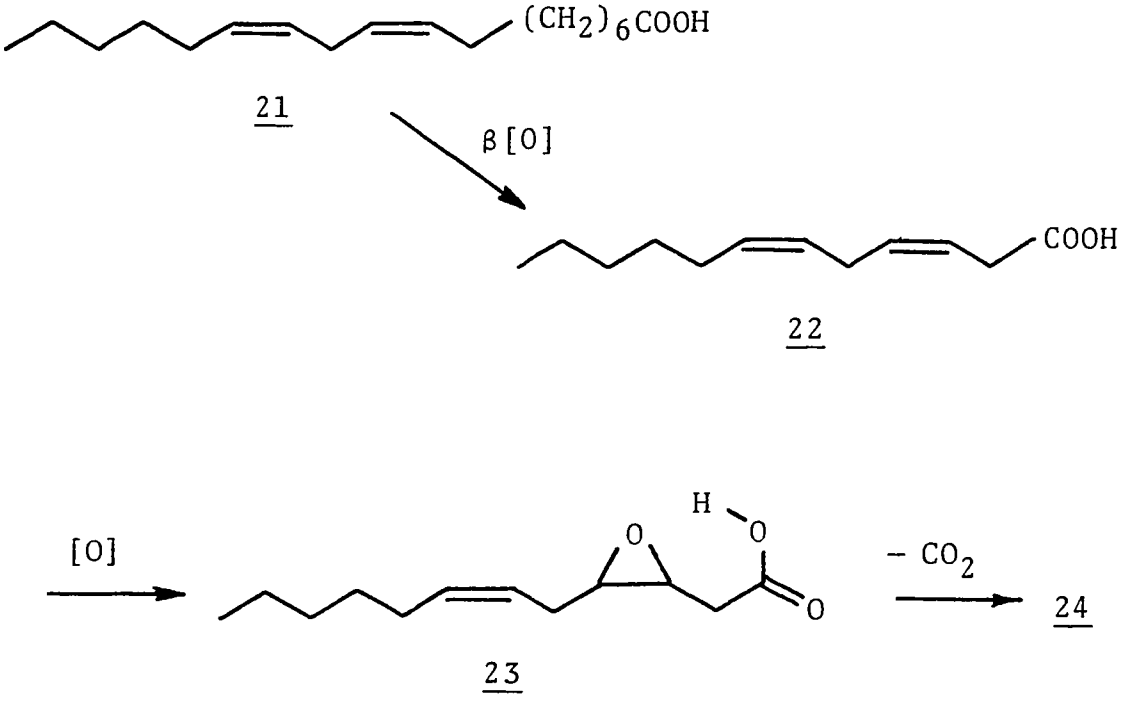
The abundance (1-2% based on wet weight of seaweed) and structural similarity of the hydrocarbons and sulfur-containing compounds as well as their potential activity in chemotaxis raises a number of questions concerning their biogenesis. Are the hydrocarbons derived from the sulfur

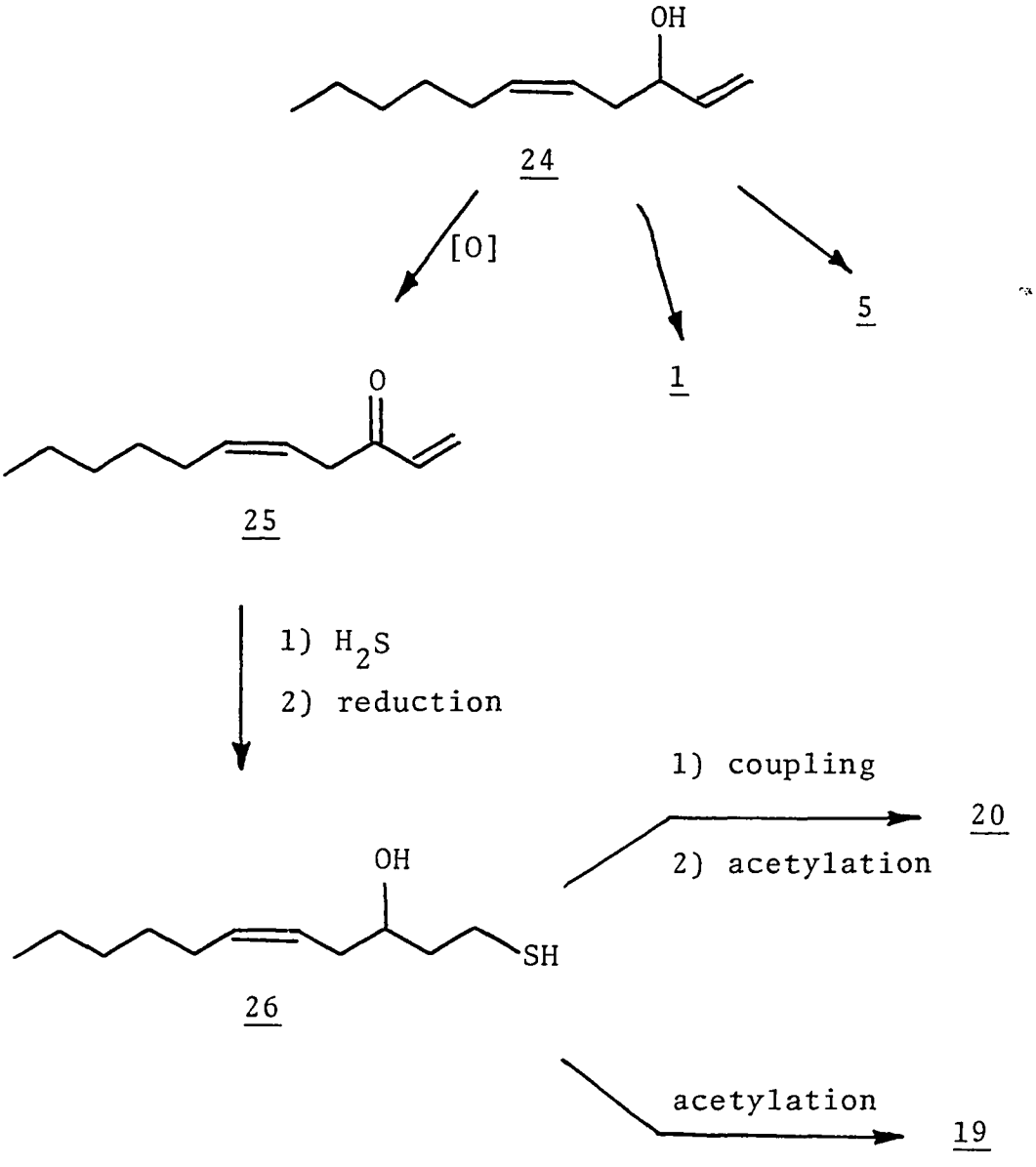
compounds or are both derived from common intermediates? If common intermediates are responsible what types of functional groups are involved and what is their origin? Originally it was postulated that hydrocarbon production could proceed from intermediates such as 19.[5,9] For example,



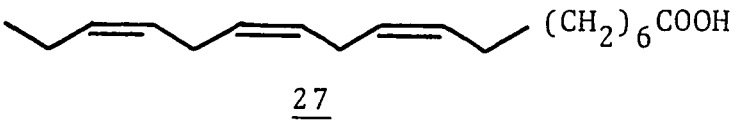
a 1,2-dielimination of the acetoxy and thiolacetoxy groups from 19 would give 5 whereas 1,2-elimination of the thiol-acetoxy group and 1,5-homoallylic elimination of the acetoxy group would form 1. However, the disadvantage of this scheme is that it does not shed any light on the origin of the sulfur containing compounds.

Recently it has been proposed that normal β-oxidation of unsaturated fatty acids to C_{12} acids followed by β,γ-epoxidation and decarboxylation would give unsaturated alcohols which could be the precursors for the hydrocarbons and sulfur containing compounds.[12] For example, linoleic acid (21) would give cis-1,5-undecadien-3-ol (24) which could undergo 1,2-elimination of water to form 5 or 1,5-homoallylic elimination to form 1. Oxidation of 24 to 25 followed by addition of hydrogen sulfide and acetylation would give 19. Reductive coupling of 26 followed by acetylation would give disulfide 20. Oxidative degradation





of linoleic acid (27) would give cis, cis-undeca-1,5,8-trien-3-ol (28) which upon dehydration would yield hydrocarbons 2, 3 and 9. By performing similar reactions with alcohols 24 and 28 formation of all C_{11} hydrocarbons and sulfur containing compounds isolated from Dictyopteris can be rationalized.



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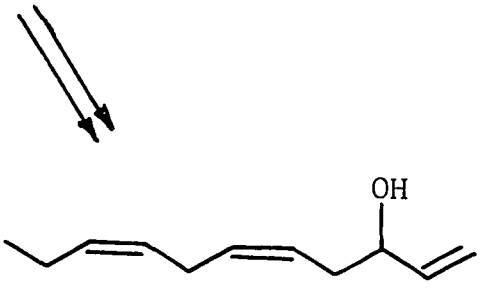
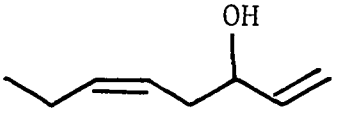


28

2 3 9

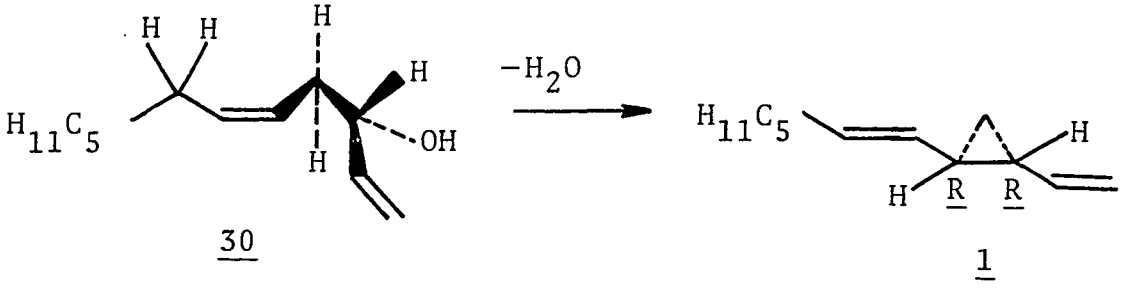
Interestingly (3S)-cis-1,5-octadien-3-ol (29) a lower



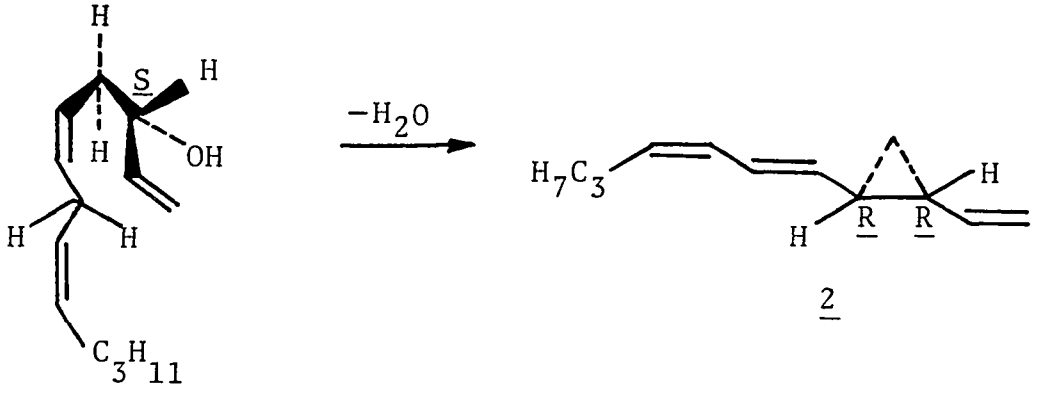
29

homolog of 24, has been isolated from the essential oil of the red alga Chondrococcus hornemanni.[13] However,

C_8 hydrocarbons analogous to those found in Dictyopteris were not detected. If the S configuration at C-3 of 29 is extrapolated to 24 (30) and 28 (31) the stereochemistry of 1 and 2 can be rationalized.



30 1



31 2

C. Statement of Objectives

The ease with which 24 and 28 can, in theory, be converted to the various constituents of Dictyopteris makes them very attractive as the actual intermediates. However, this can only be proved by feeding radioactively labeled 24 and 28 to the living plants or cell-free homogenates and observing incorporation of the label into the secondary metabolites. Toward this end one of the major objectives of this study was to prepare 24 and 28 by routes that would facilitate the eventual introduction of a radioactive label for the feeding experiments. A second objective was to carry out biomimetic dehydration reactions with 24 and 28 to determine whether or not 1,5-elimination would accompany 1,2-elimination. Once synthesized the solubility properties and adsorption characteristics of 24 and 28 were to be studied to aid the search for the naturally occurring alcohols in Dictyopteris extracts.

To date most of the work on Dictyopteris has centered on the isolation and structure elucidation of the numerous constituents. Syntheses of trienes 5, 6 and 7[14] and racemic 1[15] and 2[16] have been reported but only one sulfur compound (15) has thus far been prepared.[11] Preparation of 13, 14, 16-20 and degradative reactions on the naturally occurring materials is needed to assign absolute configurations and fully verify the proposed structures. Therefore, the final objective of this work was to synthesize the remaining sulfur containing compounds.

II. RESULTS AND DISCUSSION

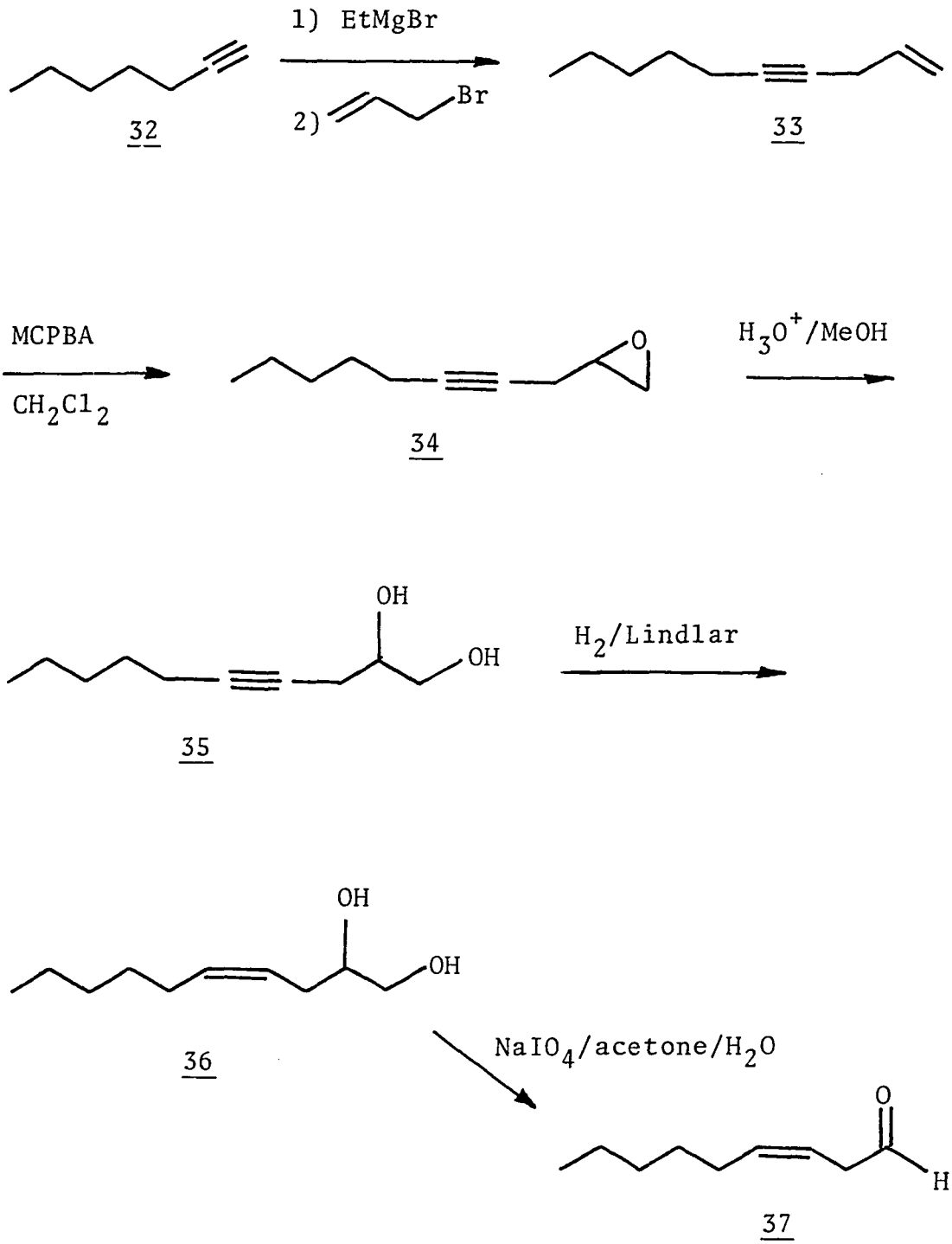
A. Preparation of cis-1,5-Undecadien-3-ol (24)

Before the biomimetic elimination reactions of 24 and 28 could be attempted both compounds had to be synthesized by routes that would yield gram quantities of the final products. In addition, synthetic schemes were required that would allow introduction of a tritium label, preferably in the last step, for eventual feeding experiments. Synthetic schemes employing acetylenic intermediates were attractive since terminal acetylenes are readily alkylated and the resulting internal acetylenes can be stereospecifically reduced to give double bonds with the required cis-geometry. Also, the introduction of a radioactive label could be achieved by partial catalytic reduction of the acetylene with tritium gas. Because of these advantages several synthetic routes to 24 employing acetylenic intermediates were devised.

A moderately successful synthesis of 24 using acetylenes was completed by Dr. Alfred Asato and is shown in Scheme III-1.[17] However, little was done to characterize the intermediate compounds and many steps employed crude starting materials. To further investigate Scheme III-1 for this study large quantities of 33[18] were prepared from heptynyl magnesium bromide and allyl bromide and then reacted with m-chloroperbenzoic acid (MCPBA). For simplification the intermediate epoxide (34) was hydrolized without

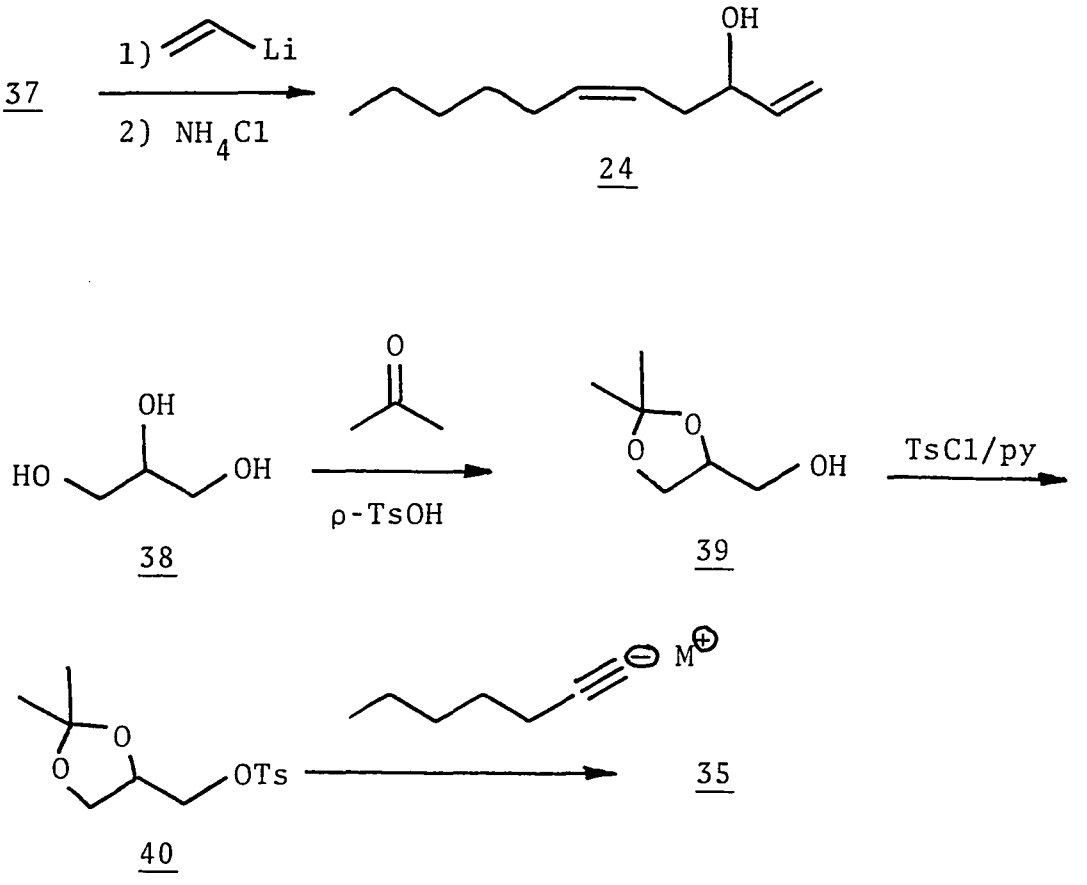
Scheme III-1.

Synthesis of Compound 24



Scheme III-1. (Continued)

Synthesis of Compound 24



purification to diol 35 by stirring with 2:1 acetone/3N sulfuric acid solution overnight or by heating in the same acidic medium for one hour at 50°.

The conversion of 33 to 35 was carried out nine times in an effort to maximize the yield. When the reaction was run at room temperature in methylene chloride for 16 hours

followed by hydrolysis and distillation of the crude product only mediocre yields (~ 40%) were achieved. Extending the reaction time to 48 hours did not appreciably increase the yield. However, purifying the MCPBA by the method of Blumbergs[19] and refluxing the reaction mixture for 12 hours in methylene chloride increased the distilled yield of 35 to 54%. Purification of the crude product by distillation was most likely the principal cause of the low yields since high temperatures were required and substantial pot residues remained after the distillations were complete.

The highest yields of 35 were achieved by refluxing 33 with a one mole excess of 85% MCPBA in ethyl acetate for 12 hours followed by hydrolysis. Purification of the crude reaction mixture was achieved by silica gel column chromatography. The crude oil was applied to the column in 5% ethyl acetate/95% pentane which eluted the unreacted 33. The column was then washed with absolute ethanol which cleanly removed the more strongly held 35 while the traces of unreacted MCPBA were retained by the column. Using this procedure the yield of pure 35 was increased to 70%. The pmr spectrum of D_2O exchanged 35 shows a complex 3H multiplet centered at δ3.6 for the hydroxy methylene and methine protons. The methylene between the acetylene and hydroxy methine groups appears as a doublet of triplets (J=2.5 and 6 Hz) at δ2.37 while the methylene on the opposite side of the triple bond resonates as a multiplet at 2.14. A satisfactory combustion analysis was obtained for 35.

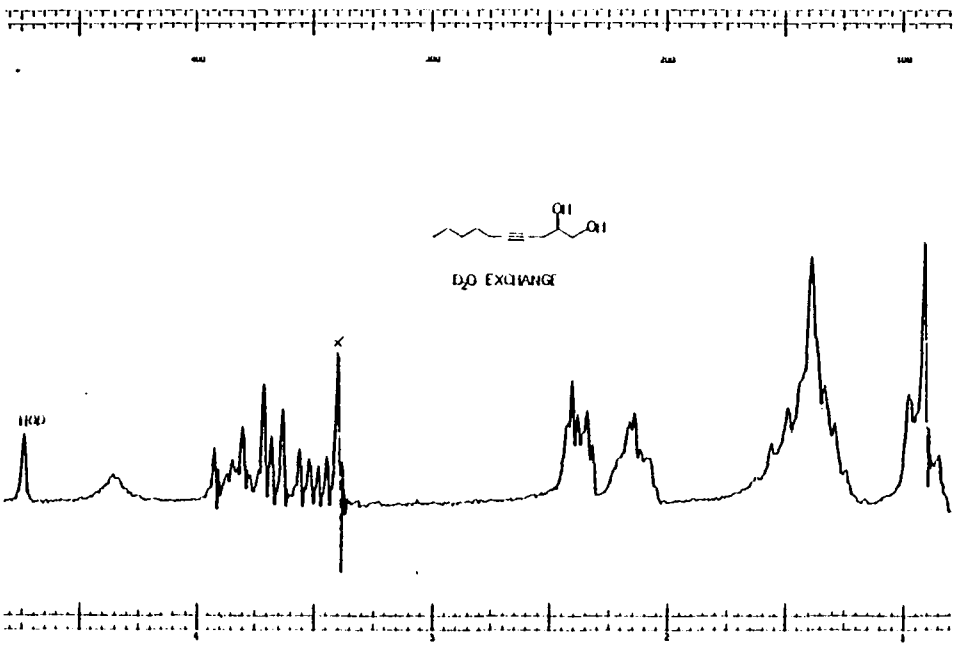


Figure III-1. Pmr spectrum ($CDCl_3$) of D_2O exchanged 35.

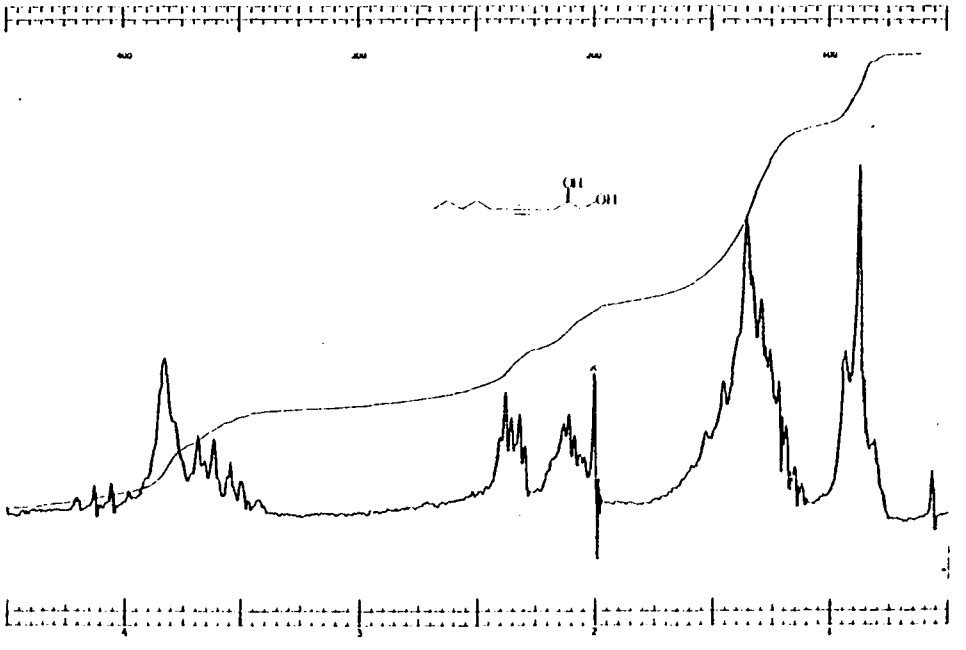


Figure III-2. Pmr spectrum ($CDCl_3$) of compound 35.

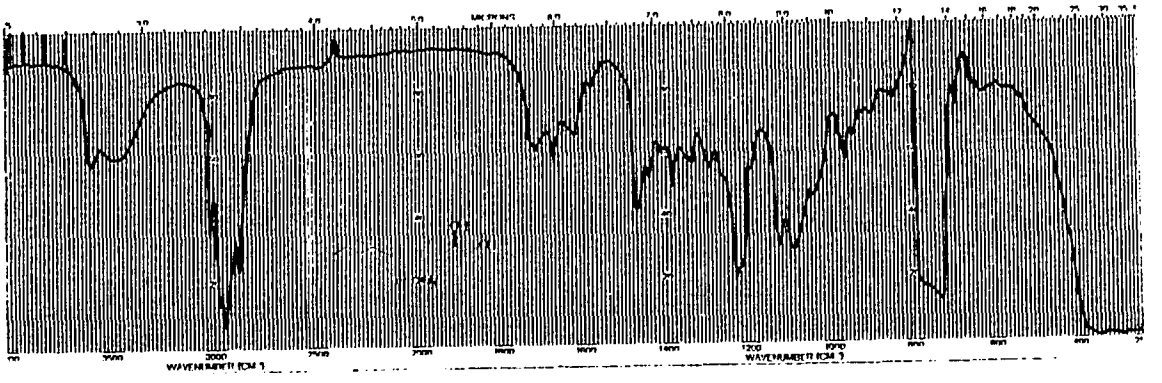


Figure III-3. Ir spectrum ($CHCl_3$) of compound 35.

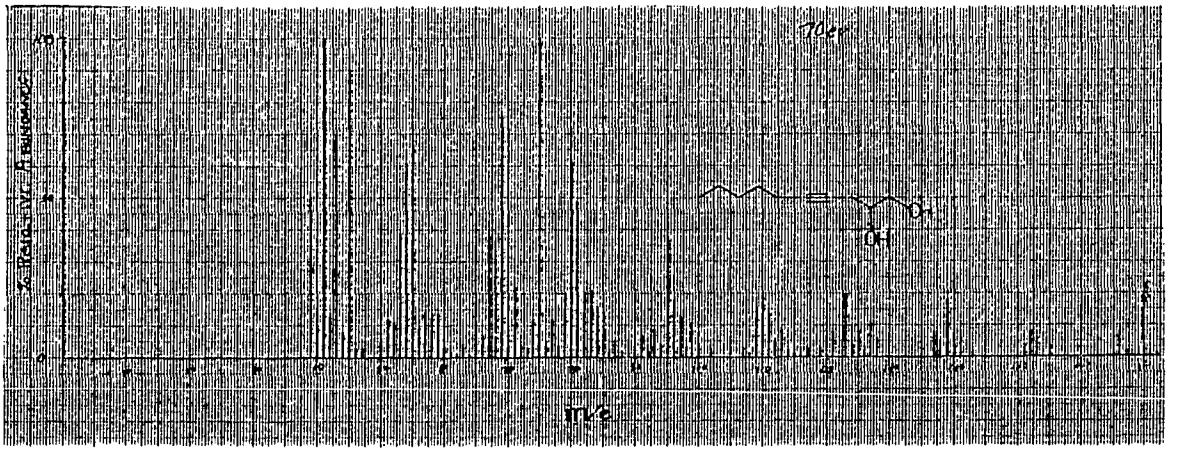


Figure III-4. Mass spectrum (70eV) of compound 35.

A less successful route to 35 involved reacting the tosylate of the acetone ketal of glycerine (40) with heptynyl magnesium bromide. When the reaction was carried out in THF at room temperature for 24 hours only starting materials were isolated. Refluxing the reaction mixture for 18 hours followed by acid hydrolysis resulted in approximately 5% conversion to 35. Increasing the reflux time to 24 hours

did not increase the yield. Due to these poor results no further work with 40 was attempted.

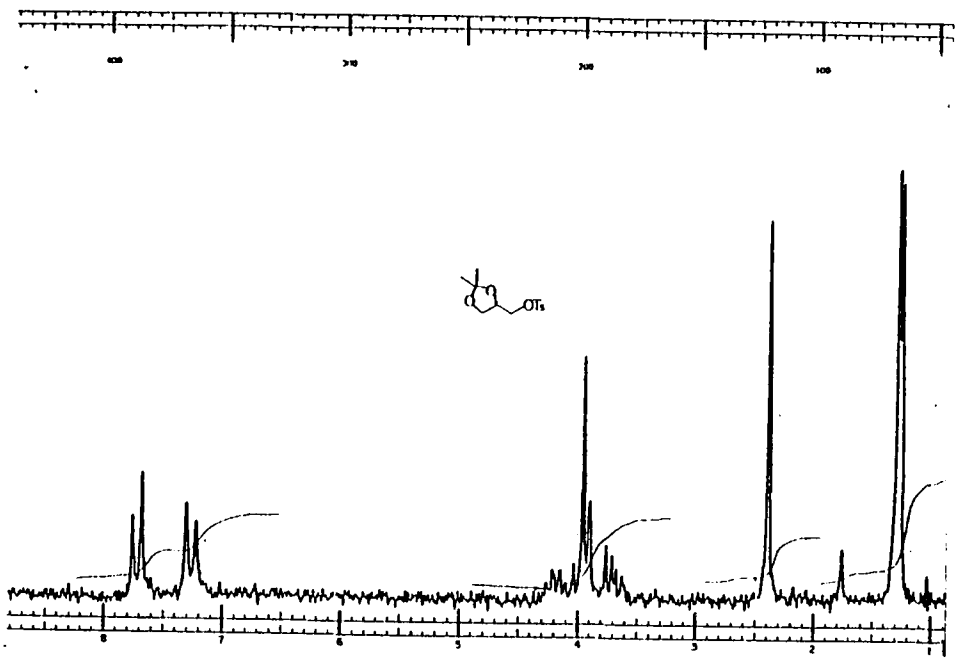


Figure III-5. Pmr spectrum ($CDCl_3$) of compound 40.

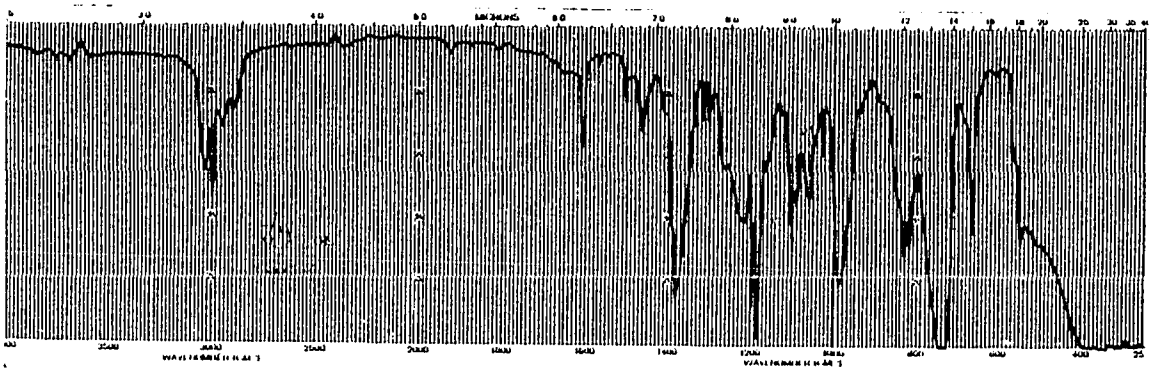


Figure III-6. Ir spectrum ($CHCl_3$) of compound 40.

Small scale (100 mg) catalytic reduction of 35 to cis-diol 36 proceeded in near quantitative yields using Lindlar's catalyst[20] with hexane as the reaction solvent. However, when the reduction was scaled up to gram quantities the initially rapid hydrogen uptake gradually slowed and then stopped completely well before the reaction was complete. Hexane and other non-polar hydrocarbons are the solvents of choice when using Lindlar's catalyst since alcohols (e.g. methanol, ethanol etc.) greatly retard reaction rates, presumably due to complexation with the catalyst.[20] Since 35 contains a vicinal diol moiety it was reasoned that 35 complexes with the catalyst in the same manner. Reduction is rapid at first but once the adsorbed diol is reduced the reaction slows to a stop. Using the more polar benzene as the solvent to improve the equilibrium between adsorbed and solvated 35 hydrogen uptake was again initially rapid. The reduction then slowed but did not stop. In this manner three to five gram quantities of 35 could be completely reduced to 36 within 24 hours.

The extent of the hydrogenation of 35 to 36 was easily monitored by noting the appearance of an olefinic multiplet at δ5.43 and the disappearance of the doublet of triplets at 2.37 in the pmr spectrum. The methylene between the cis-double bond and alcohol methine in 36 appears as a triplet (J=6 Hz) at δ2.18. Although the pmr spectrum of 36 was very clean a satisfactory combustion analysis could not be obtained.

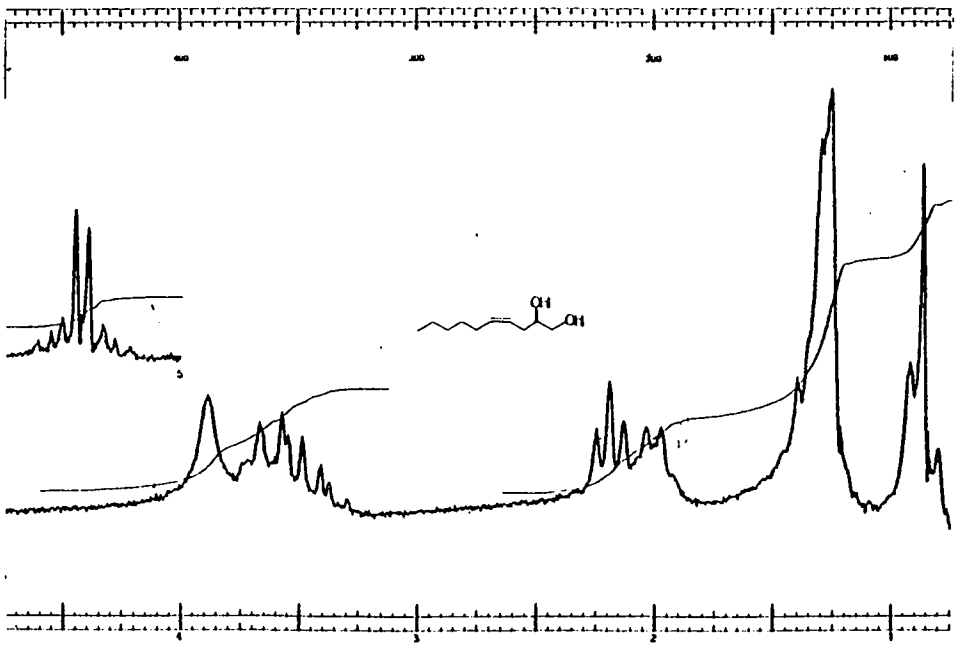


Figure III-7. Pmr spectrum ($CDCl_3$) of compound 36.

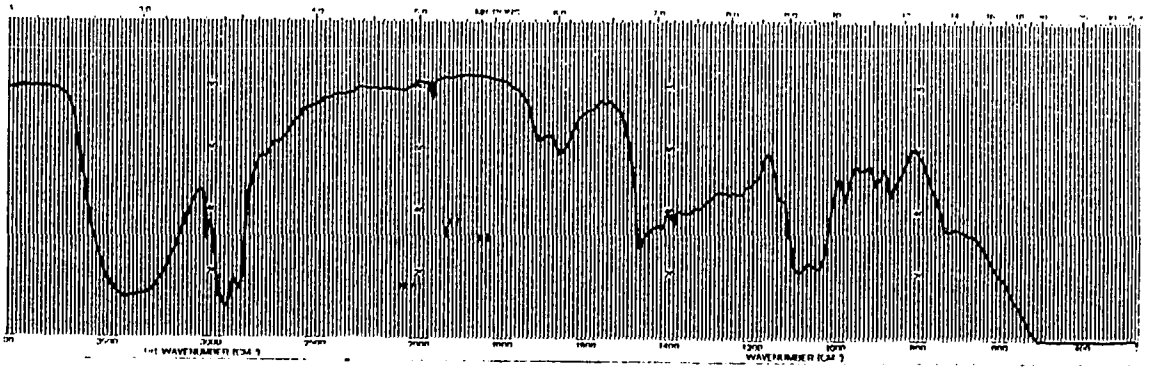


Figure III-8. Ir spectrum (neat) of compound 36.

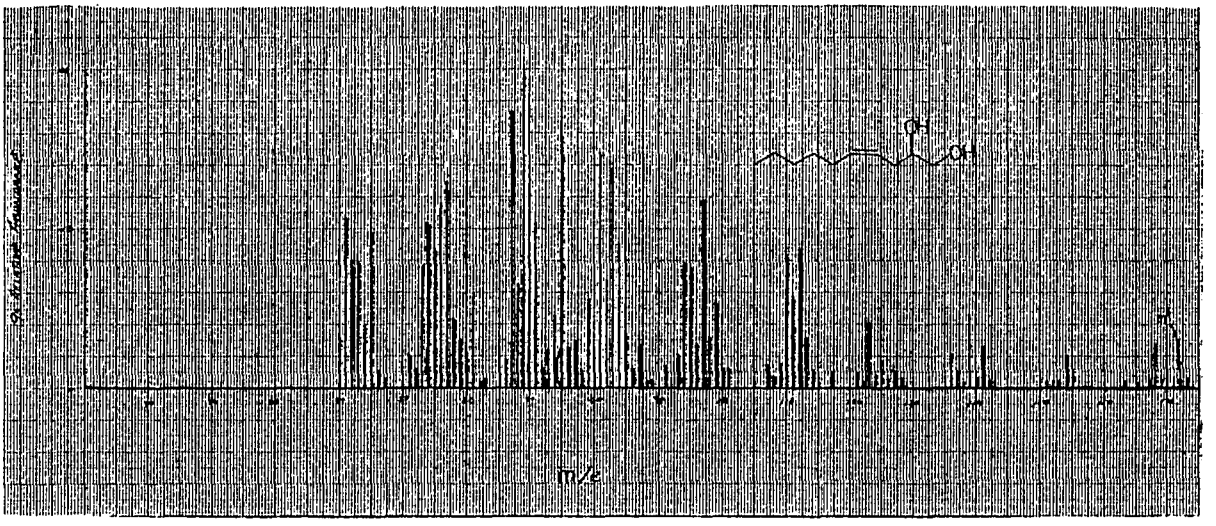
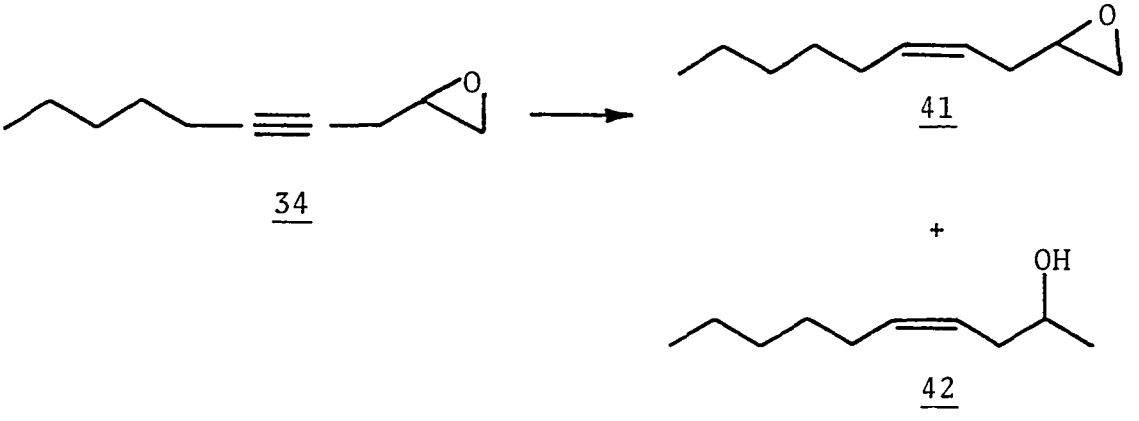


Figure III-9. Mass spectrum (70eV) of compound 36.

In another approach to 36 an attempt was made to reduce epoxide 34 to 41 which could then be hydrolyzed to the diol. It was found, however, that reaction times sufficient to completely reduce the acetylene linkage (3 hours) also caused some reduction of the epoxide to form 42. Purification of the crude hydrogenation mixtures by silica gel chromatography afforded poor yields (~ 25%) of 41 and the sequence 34 → 41 was abandoned.



34 41 + 42

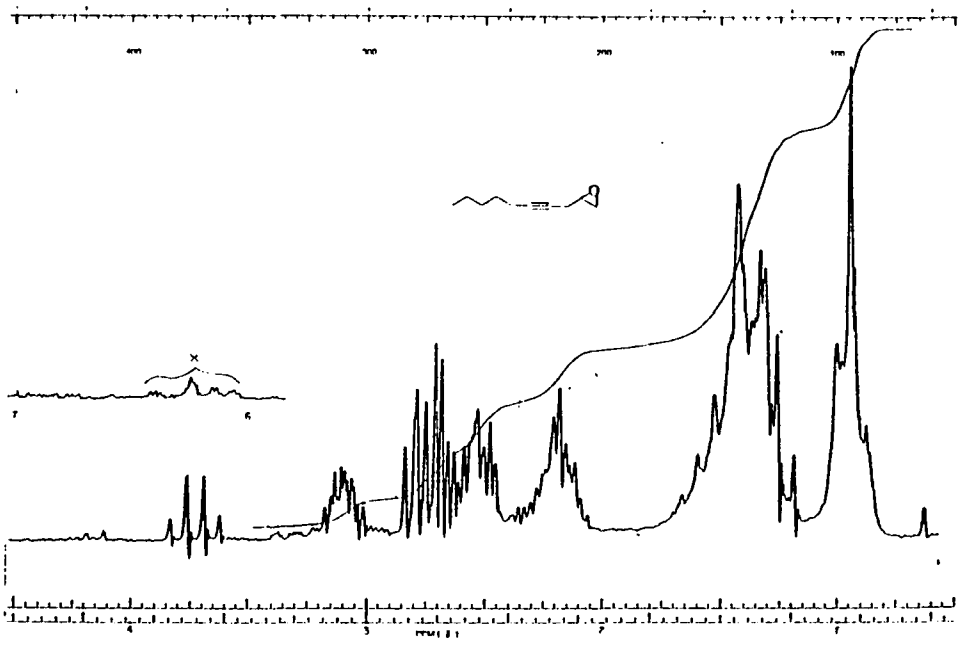


Figure III-10. Pmr spectrum ($CDCl_3$) of compound 34.

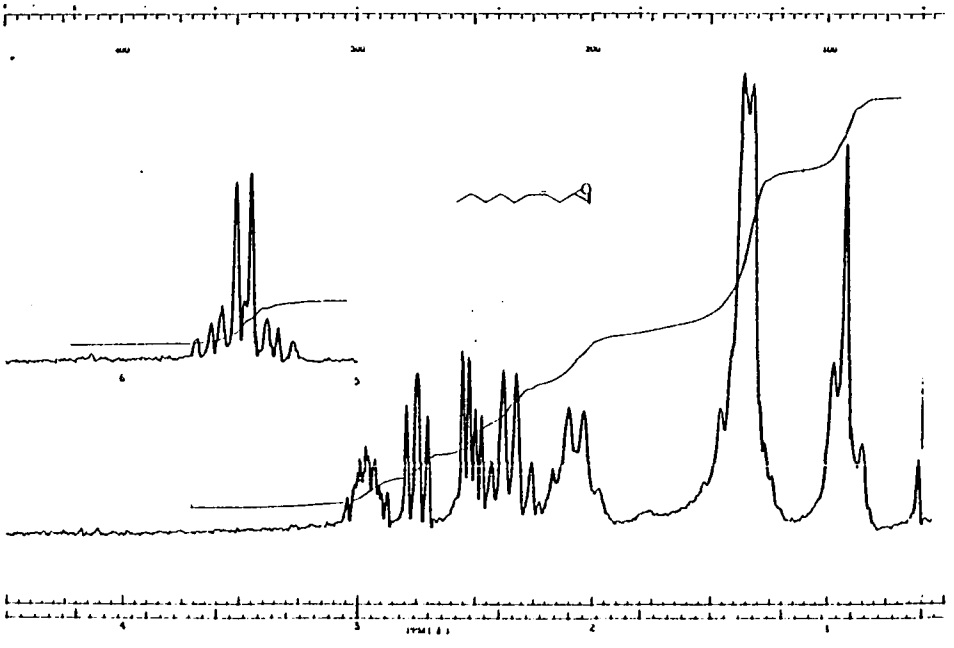


Figure III-11. Pmr spectrum ($CDCl_3$) of compound 41.

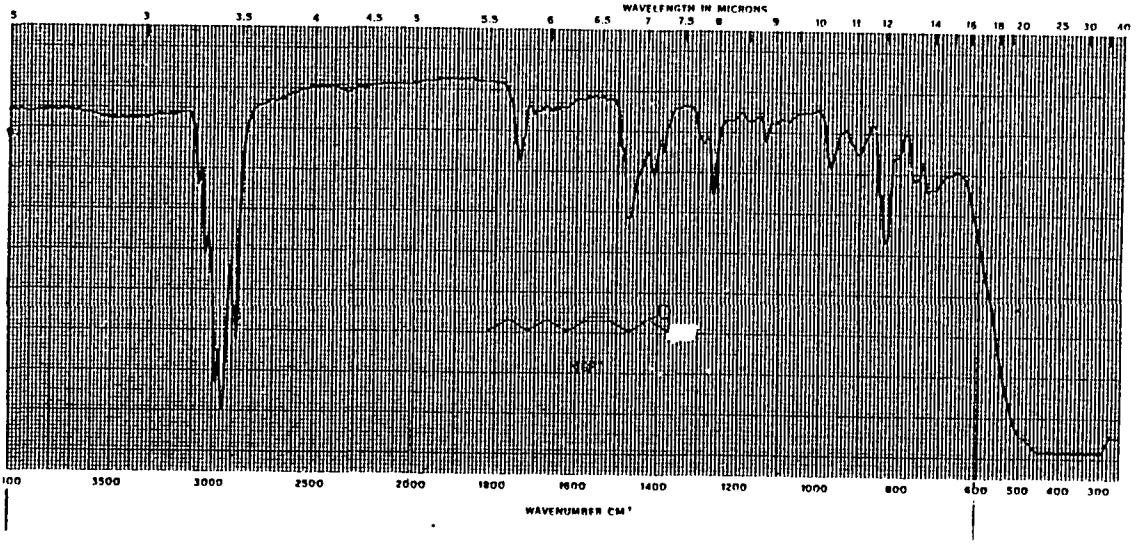


Figure III-12. Ir spectrum (neat) of compound 41.

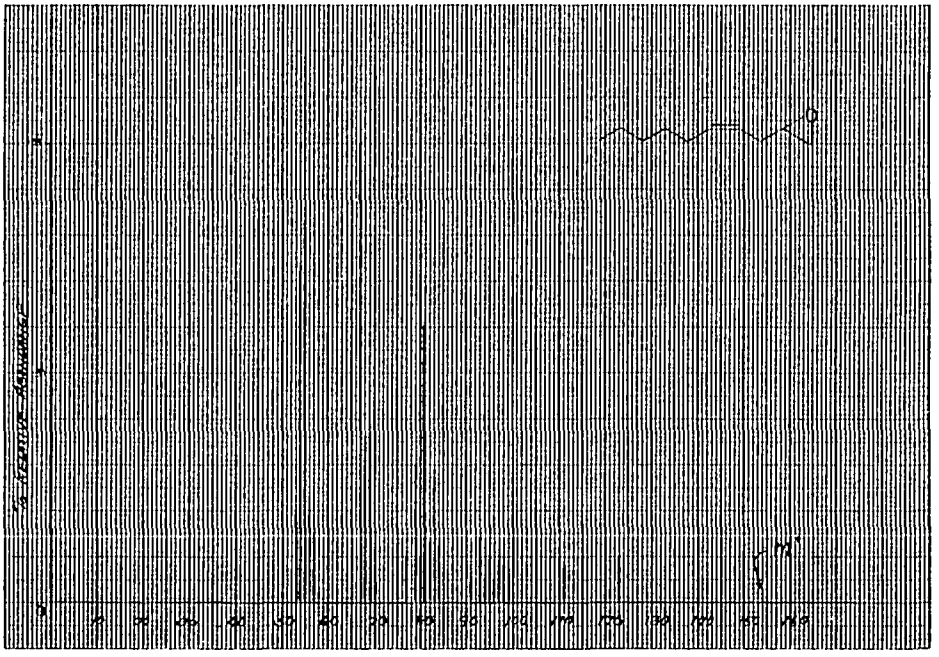


Figure III-13. Mass spectrum (70 eV) of compound 41.

Eight attempts were made to find optimum conditions for the cleavage of diol 36 to aldehyde 37 but the highest yields obtained were never more than 50%. Initial runs involved reacting equimolar amounts of 36 and sodium metaperiodate at room temperature and resulted in mixtures of 37 and starting material. Purification of these mixtures by silica gel column chromatography using 9:1 pentane/ethyl acetate resulted in 30-40% yields of 37. When a one-molar excess of periodate was used with a reaction time of 12 hours at room temperature cleavage of the diol was complete but extensive isomerization to the α,β-unsaturated aldehyde had occurred. The highest yields of 37 (~ 50%) were obtained by stirring 36 with an equimolar amount or 10% excess of periodate at low temperature (0-4°) for two hours. The pmr spectrum of the purified product (37) was consistent with the structure of 37 and exhibited an aldehyde triplet (J=2 Hz) at δ9.62 and a 2H multiplet at 5.59 for the olefinic proton. The methylene group α to the aldehyde carbonyl resonates as a broadened 2H doublet (J=6 Hz) at δ3.16. The infrared spectrum of 37 exhibits a strong carbonyl stretch at 1735 cm^{-1}.

Because of the low yields of 37 from 36 an alternate preparation of 37 from the commercially available 41 was attempted. The hydrogenation of 41 in acetone with Lindlar's catalyst proceeded to give 42 in quantitative yield but oxidation of 42 to 37 proved to be more difficult

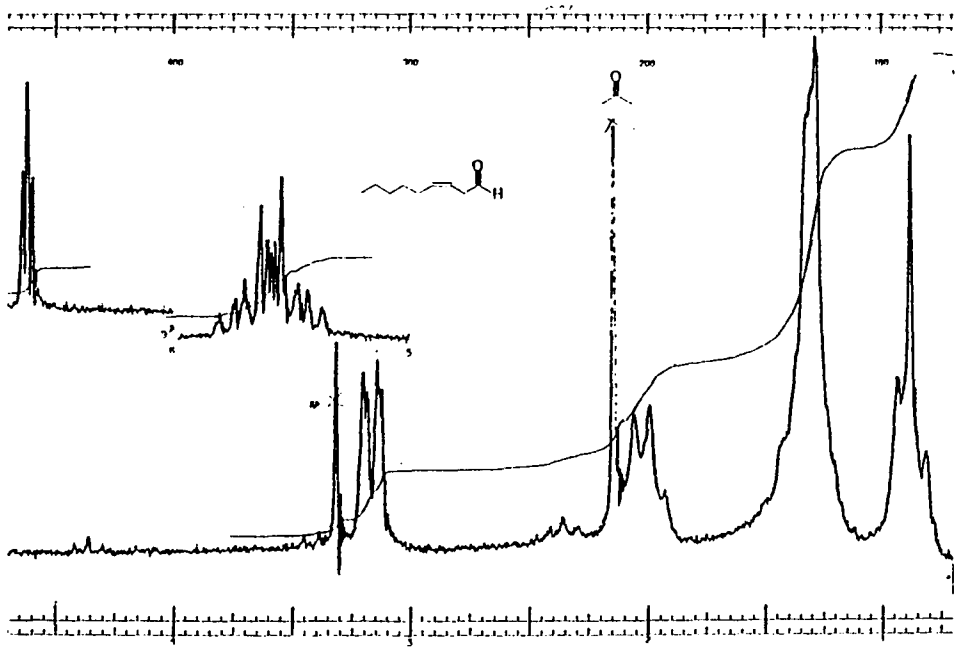
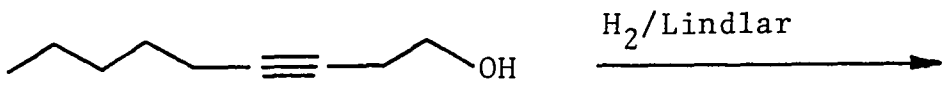
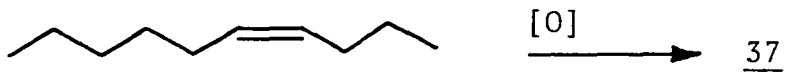


Figure III-14. Pmr spectrum ($CDCl_3$) of compound 37.



41



42

to achieve. The first attempt which employed chromic acid and the procedure B of Brown[21] resulted in isomerization of 37 to the α,β-unsaturated isomer followed by extensive polymerization. The milder procedure of Corey[22] which uses N-chlorosuccinimide and triethyl amine gave a crude product which consisted of 42 and 37 in an approximate ratio of 1:1. However, the N-chlorosuccinimide was not purified before use and may have been the cause of the incomplete reaction.

Using the various procedures discussed above a sufficient quantity of pure 37 was eventually obtained for the conversion to 24 with vinyl lithium. In the first attempt a 10% excess

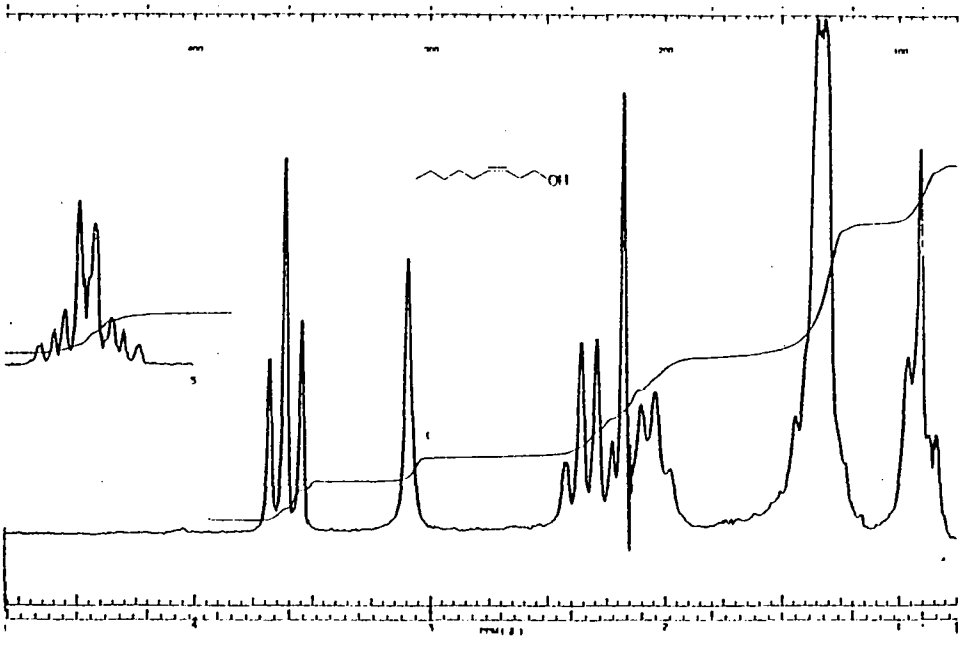


Figure III-15. Pmr spectrum ($CDCl_3$) of compound 42.

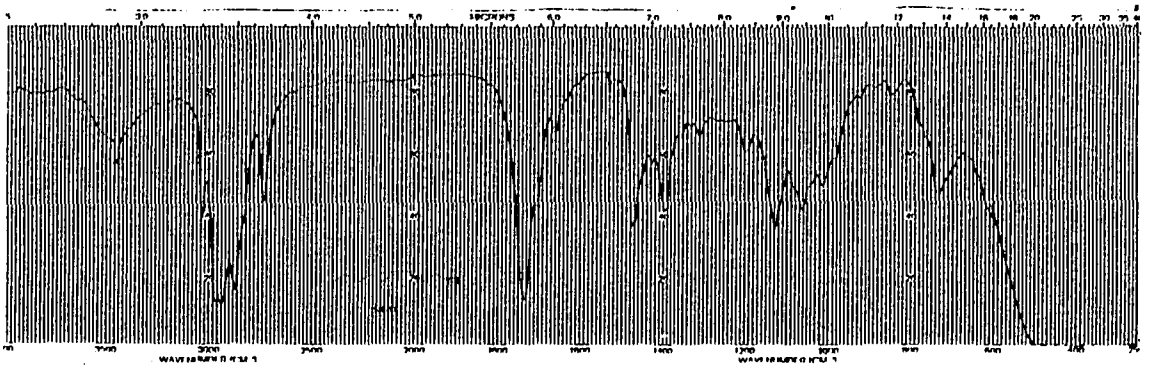


Figure III-16. Ir spectrum (neat) of compound 42.

of vinyl lithium was added via syringe to a stirring solution of 37 in THF at -78°. The product isolated from this reaction was largely polymeric since the pmr spectrum showed only very broad nondescript signals. In the second run a solution of 37 in THF was added to a rapidly stirring solution of vinyl lithium at -78°. This procedure afforded a crude oil that was mostly 24 along with unidentified side products that could not be completely removed by Sephadex column chromatography. The pmr spectrum of the cleanest fraction (~ 90% yield) possesses the expected AMX pattern for the vinyl group with a doublet of doublets of doublets (J=6, 10 and 17 Hz, X part) at δ5.86, a doublet of triplets (J=1.5 and 17 Hz, A part) at 5.35 and a doublet of triplets (J=1.5 and 10 Hz, M part) at 5.07. The cis-double bond protons appear as a multiplet centered at δ5.44 and the alcohol methine proton resonates as a broadened quartet (actually overlapping doublet of triplets) at 4.11.

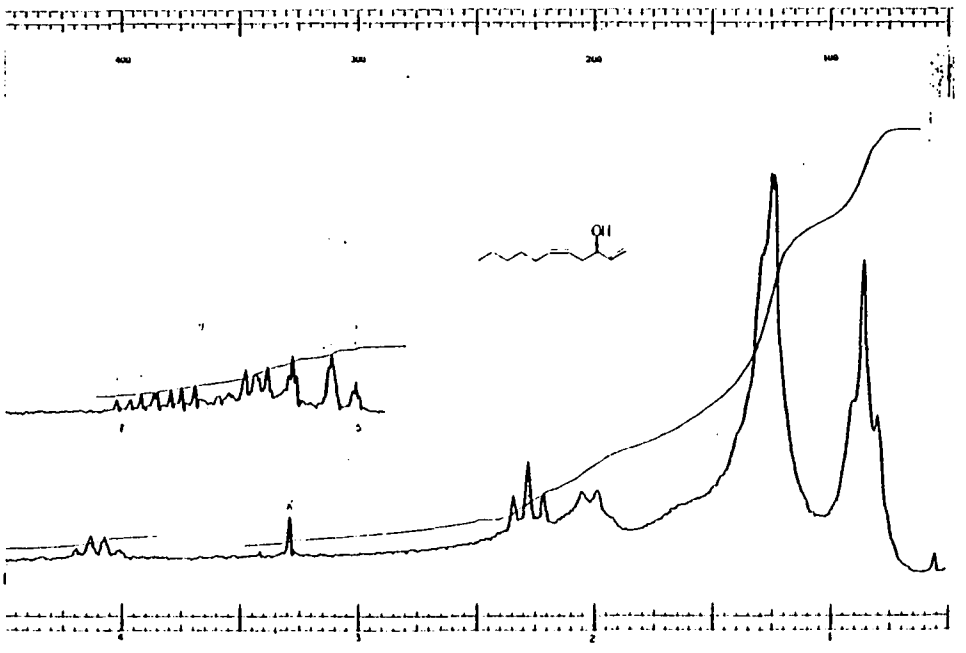
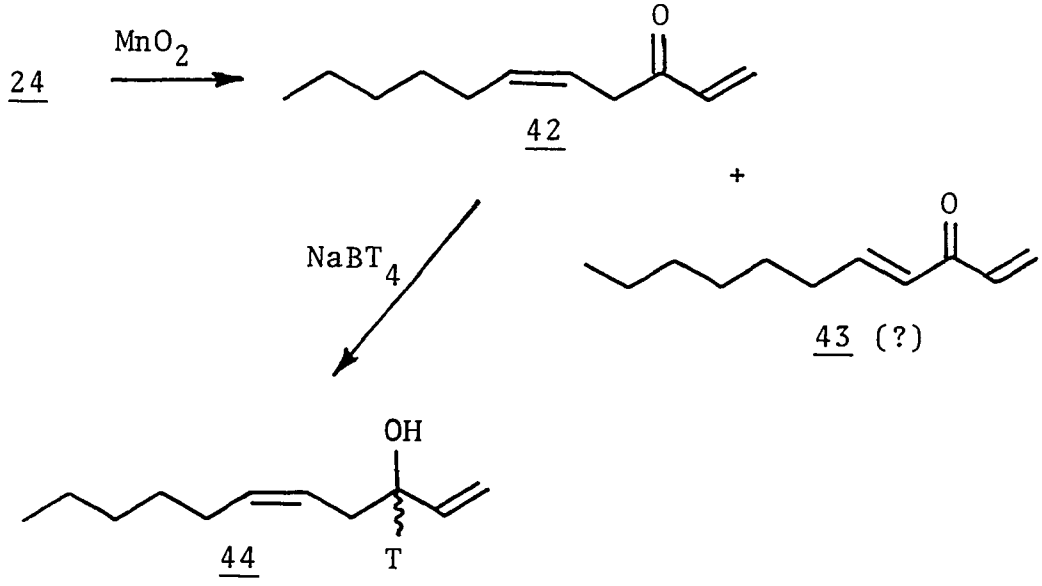


Figure III-17. Pmr spectrum ($CDCl_3$) of compound 24.

Although Scheme III-1 did provide small amounts of 24 the difficulties encountered with the conversion of 36 to 37 made it unattractive for large scale preparations of 24. In addition, the introduction of a radioactive label would involve reducing 35 with tritium gas or oxidation of 24 to the ketone (43) followed by reduction with sodium borotriteride. Neither of these procedures was particularly attractive since reduction of 35 with tritium would require handling radioactive intermediates for two additional steps and manganese dioxide oxidation of 24 involves the strong possibility of double bond migration (43). The placement of the label on the carbinol carbon of 24 (44) also makes it potentially labile to oxidative pathways within the algae.



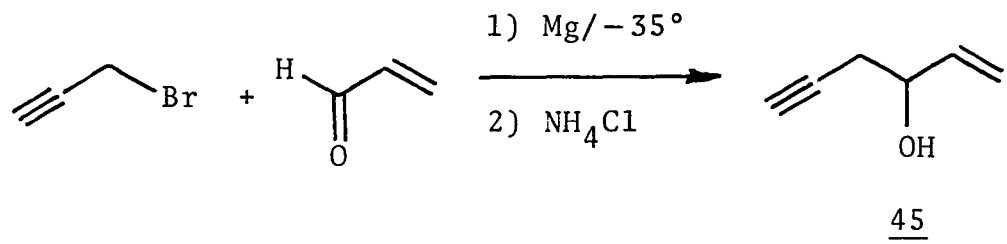
For these reasons Scheme III-1 was abandoned.

To circumvent these problems another approach to 24 (Scheme III-2) starting with a 3-hydroxy-1-hexen-5-yne (45) was devised. Scheme III-2 contains the same number of steps as Scheme III-1 but it has the advantage that a tritium label can be introduced in the last step by reducing 48a to 24 with tritium gas. Using the procedure of Viola and MacMillan[22] 45 was prepared in 76% yield. Protection of the alcohol group of 45 was accomplished by stirring with dihydropyran in benzene at room temperature with a catalytic amount of p-toluene sulfonic acid and resulted in a 97% yield of distilled product. The pmr spectrum of 46 is interesting in that it clearly shows doubled signals for four of the 16 protons. The olefinic region contains a 16 line multiplet centered at δ5.8 for the X proton of the

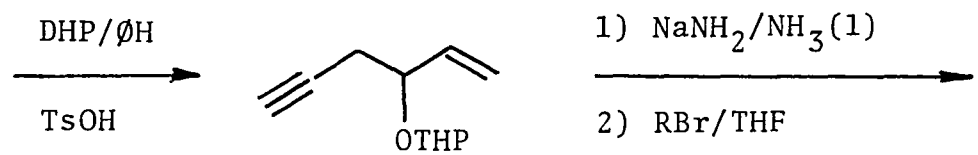
Scheme III-2.

Synthesis of Compound 29 and

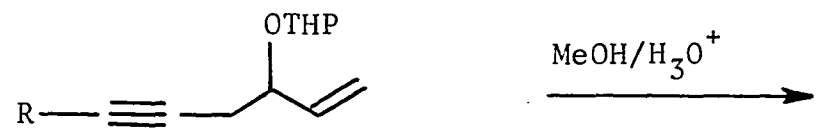
Alternate Synthesis of Compound 24



45

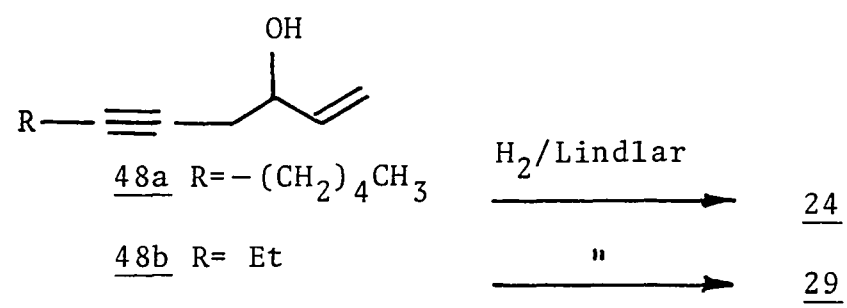


46



47a R=−$(CH_2)_4CH_3$

47b R= Et



48a R=−$(CH_2)_4CH_3$ → 24

48b R= Et → 29

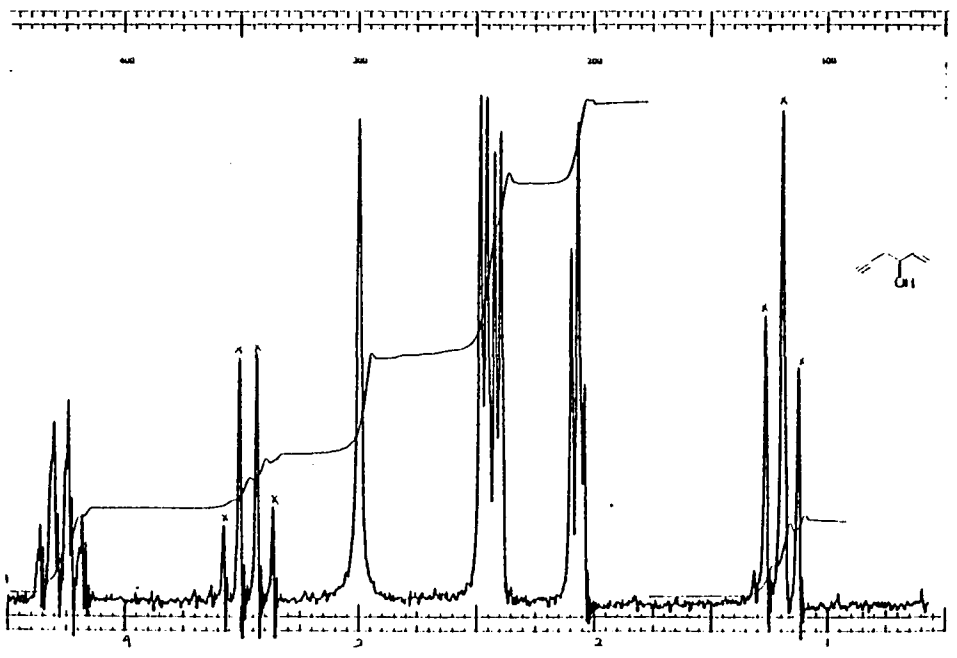


Figure III-18. Pmr spectrum ($CDCl_3$) of compound 45; high field region.

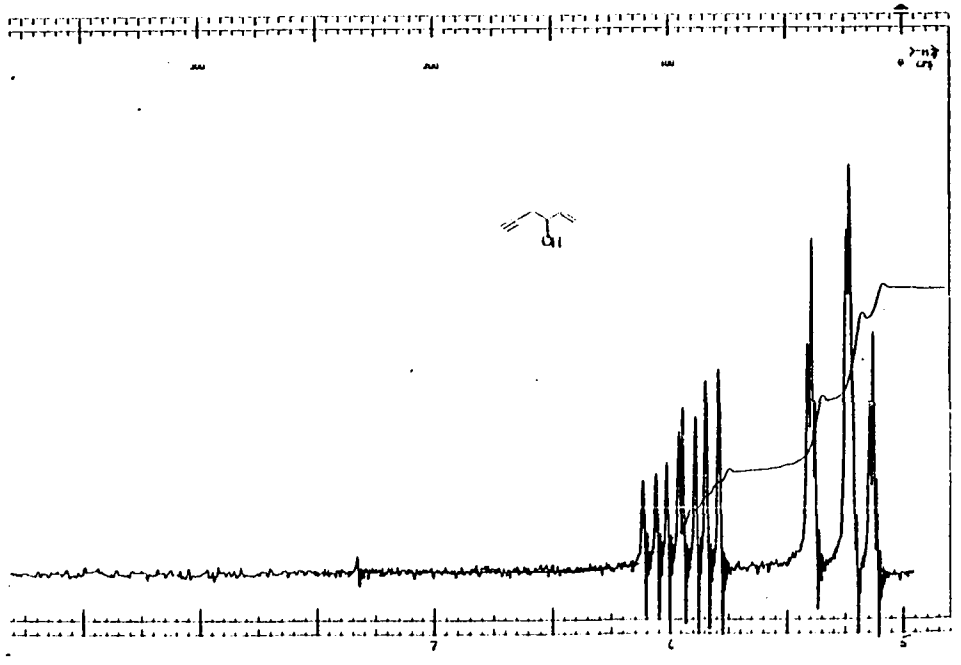


Figure III-19. Pmr spectrum ($CDCl_3$) of compound 45; low field region.

vinyl group and a complicated multiplet at 5.25 for the AB protons. The effect is most pronounced with the acetal methine proton which resonates as two broadened ½H triplets at δ4.82 and 4.55. The remainder of the signals show a decreasing degree of doubling with increasing distance from the acetal methine. The doubling effect was also observed in the cmr spectrum of 46 in which nine of the eleven carbons appear as doublets. These data suggest that a solution of 46 at ambient temperatures contains equal populations of two slowly interconverting anomers (49 and 50). However, this was not proven by rerunning the pmr and cmr spectra at elevated temperatures.

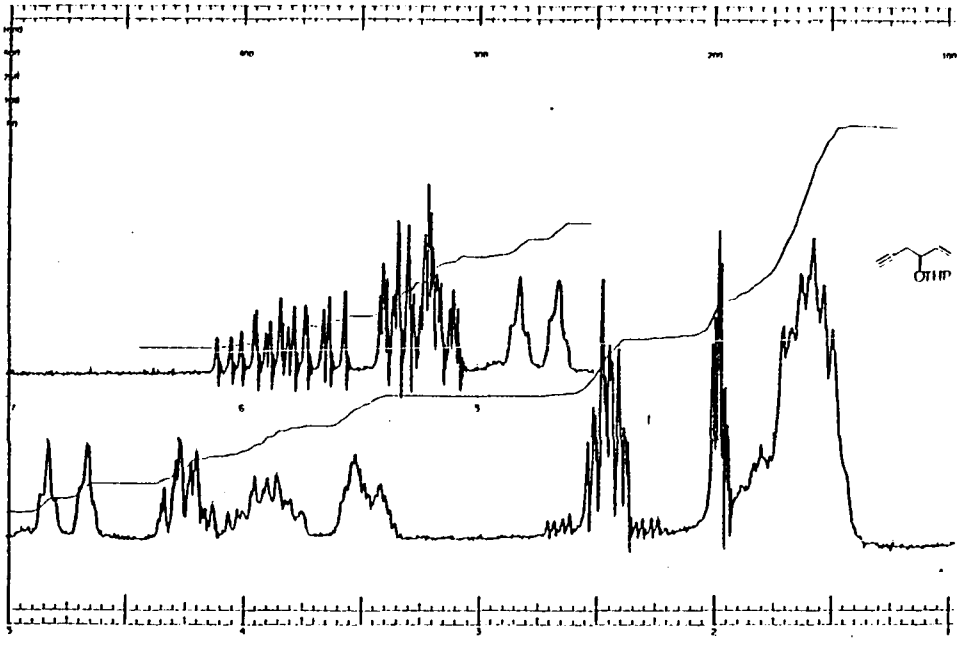


Figure III-20. Pmr spectrum ($CDCl_3$) of compound 46.

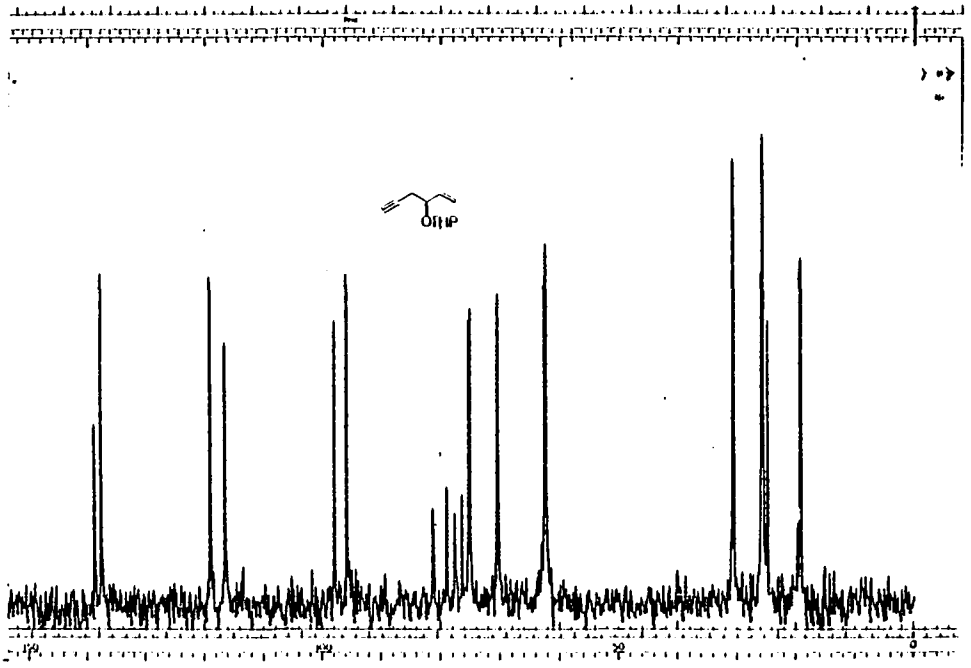


Figure III-21. Cmr spectrum ($CDCl_3$) of compound 46.

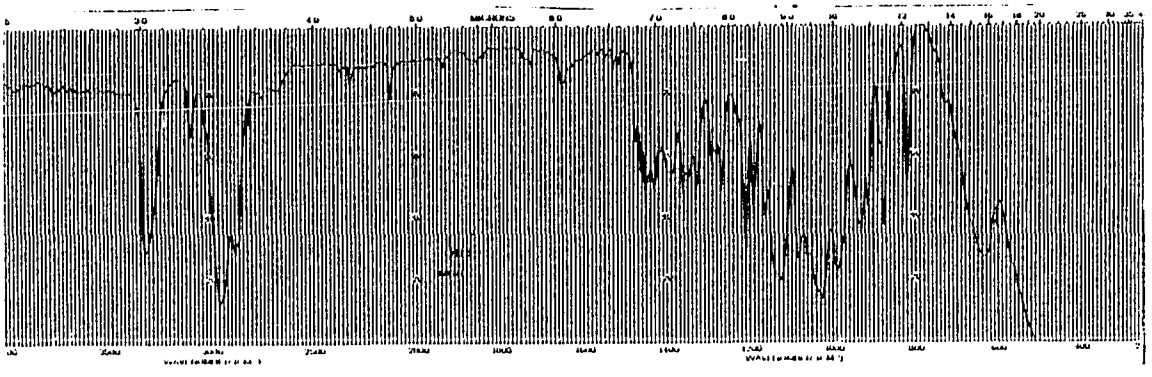


Figure III-22. Ir spectrum (neat) of compound 46.

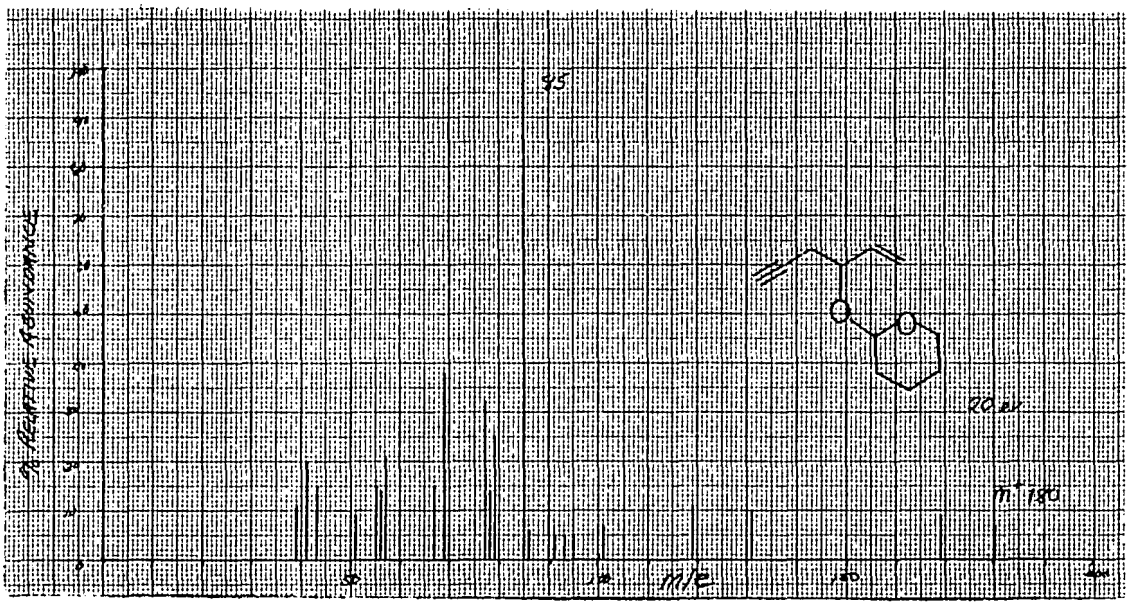
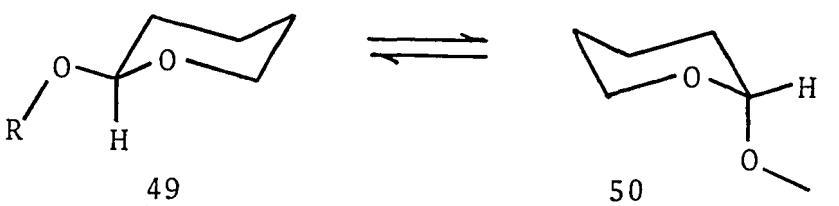
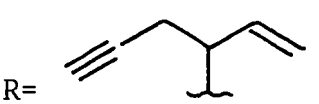


Figure III-23. Mass spectrum (70eV) of compound 46.



49 50



The alkylation of the sodium salt of 46 with n-amyl bromide in liquid ammonia proceeded smoothly to give a 61% yield of 47a after purification on a silica gel column. The prm spectrum of 47a also shows the anomeric effect as evidenced by the doubling of the olefinic and acetal methine

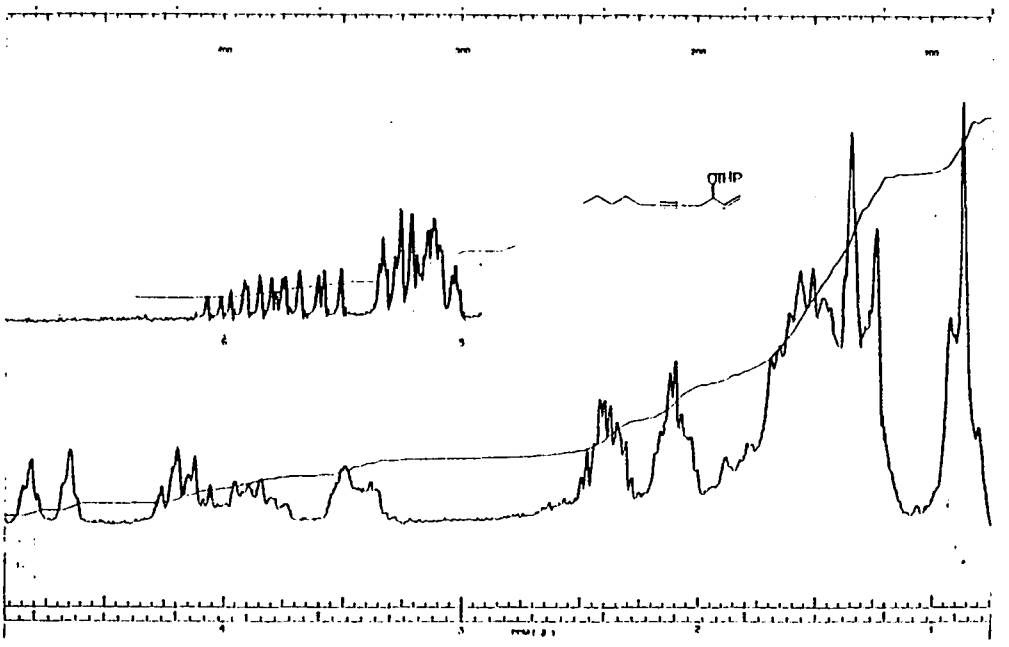


Figure III-24. Pmr spectrum ($CDCl_3$) of compound 47a.

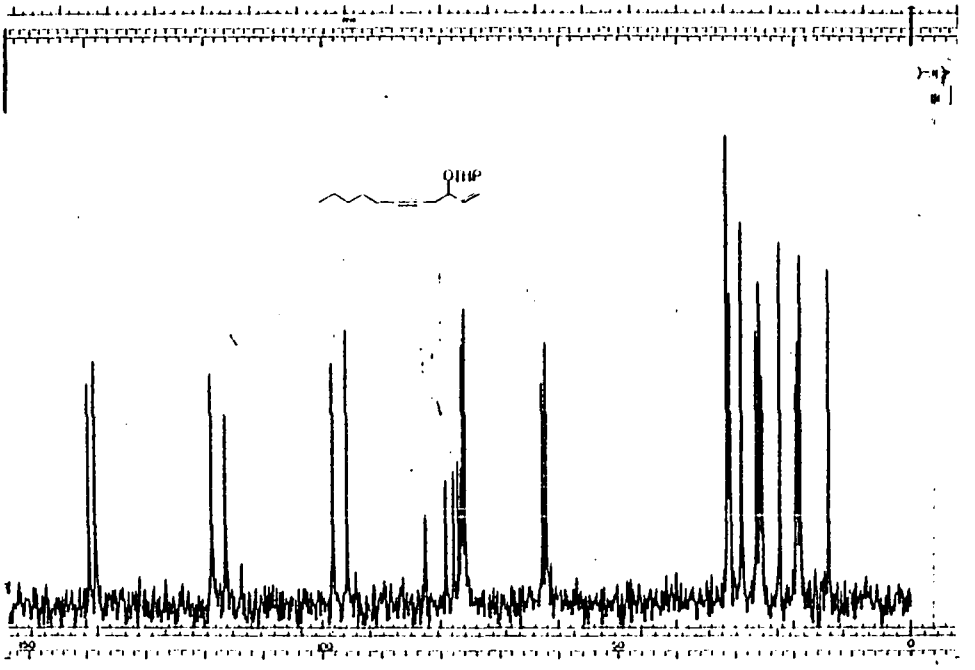


Figure III-25. Cmr spectrum ($CDCl_3$) of compound 47a.

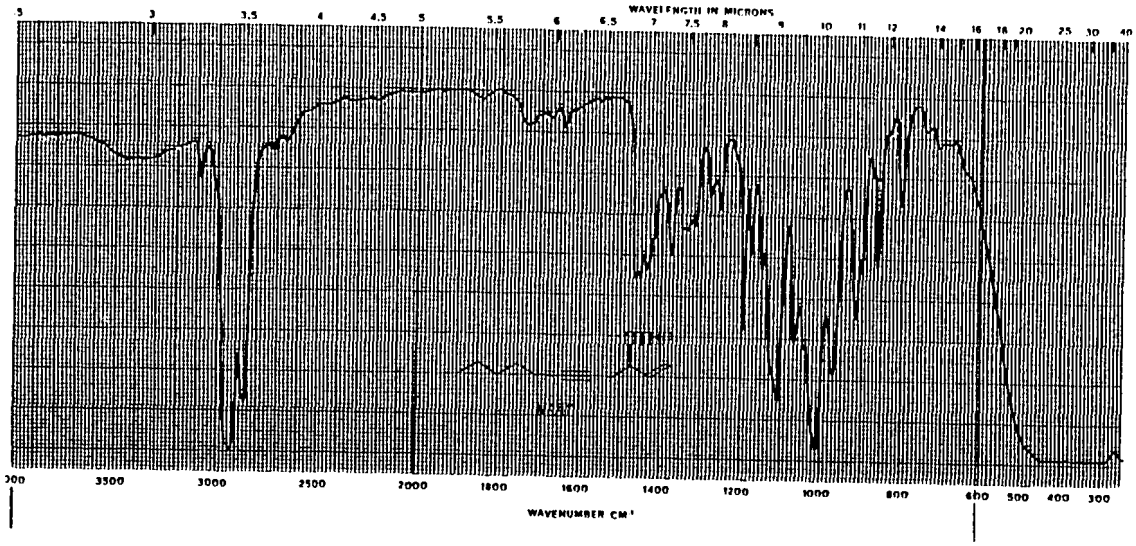


Figure III-26. Ir spectrum (neat) of compound 47a.

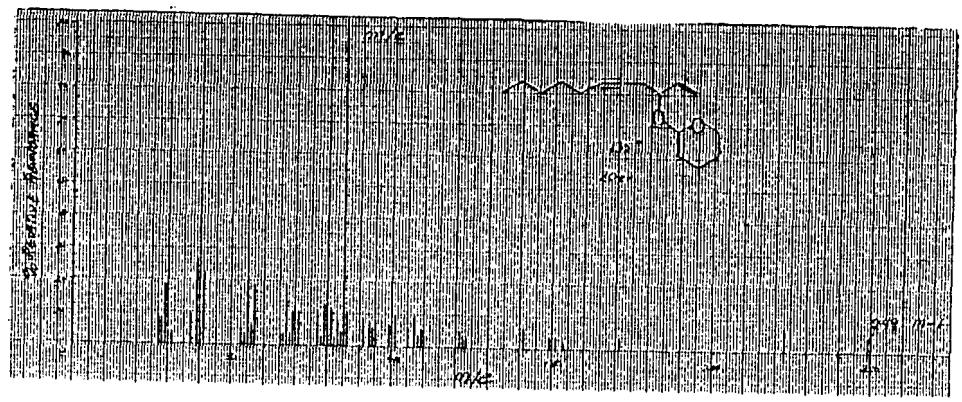


Figure III-27. Mass spectrum (70eV) of compound 47a.

protons. The spectrum also contains a broad 3H triplet at δ0.86 for the terminal methyl group, a methylene envelope at 1.23 and two finely split multiplets at 2.11 and 2.40 for the methylene groups adjacent to the acetylene.

Removal of the protecting group from 47a was achieved with hydrochloric acid in aqueous methanol and gave 48a in quantitative yield. The pmr spectrum of crude 48a was extraordinarily clean and therefore it was not further purified before conversion to 24.

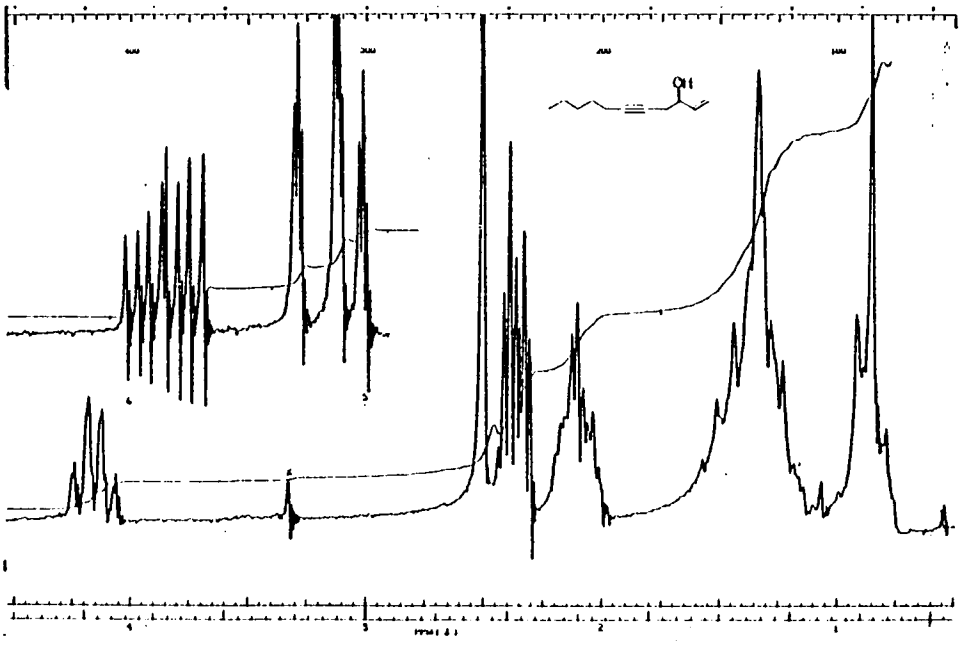


Figure III-28. Pmr spectrum ($CDCl_3$) of compound 48a.

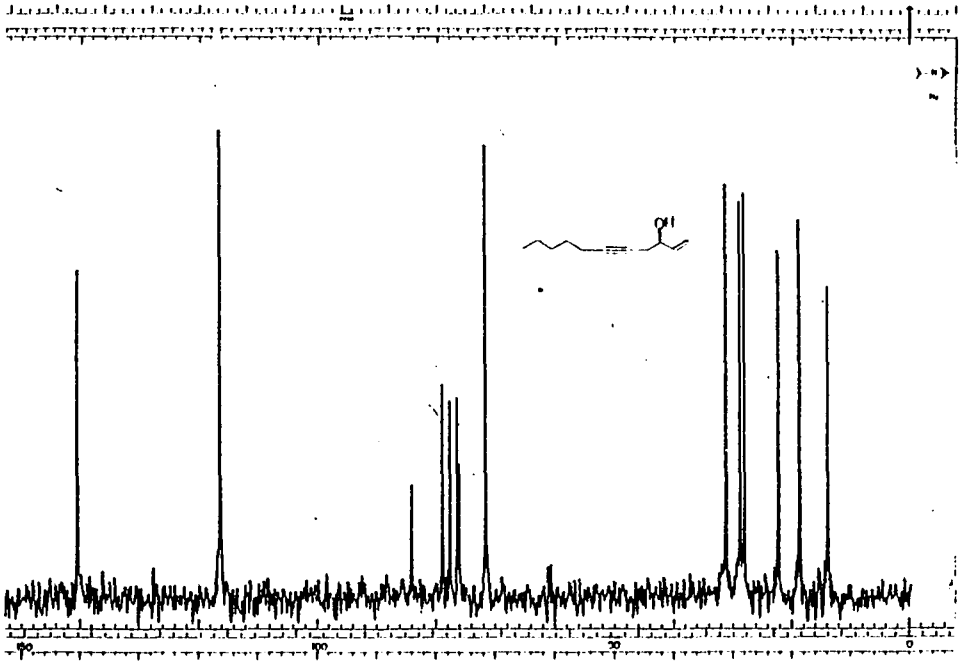


Figure III-29. Cmr spectrum ($CDCl_3$) of compound 48a.

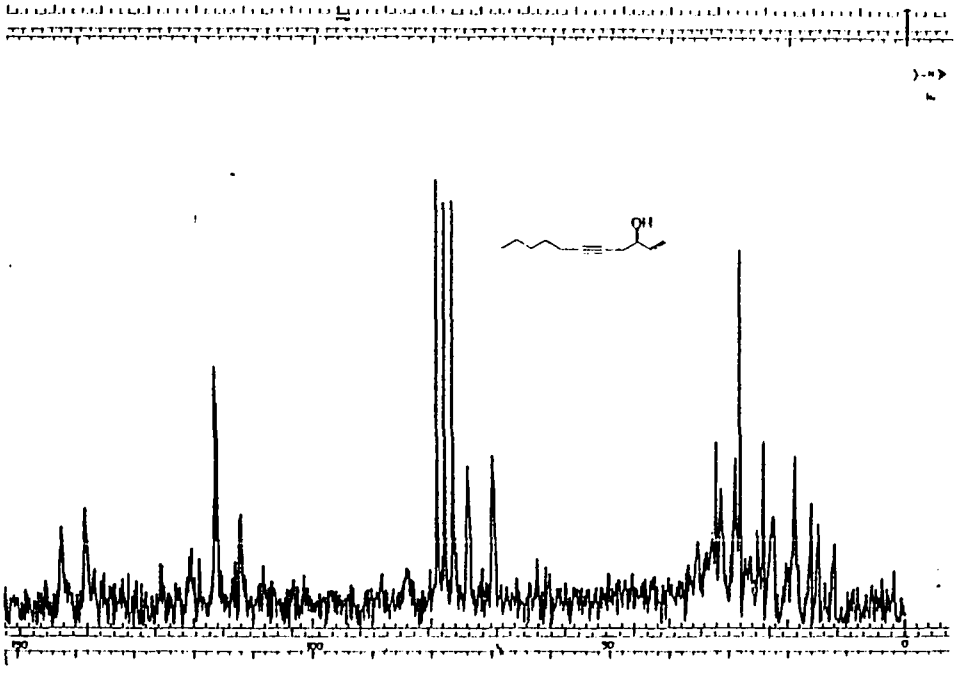


Figure III-30. Cmr off-resonance spectrum ($CDCl_3$) of compound 48a.

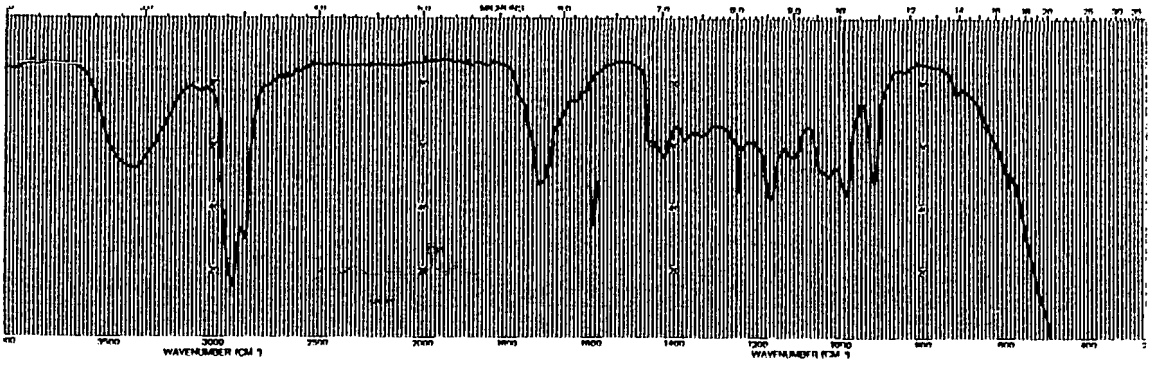


Figure III-31. Ir spectrum (neat) of compound 48a.

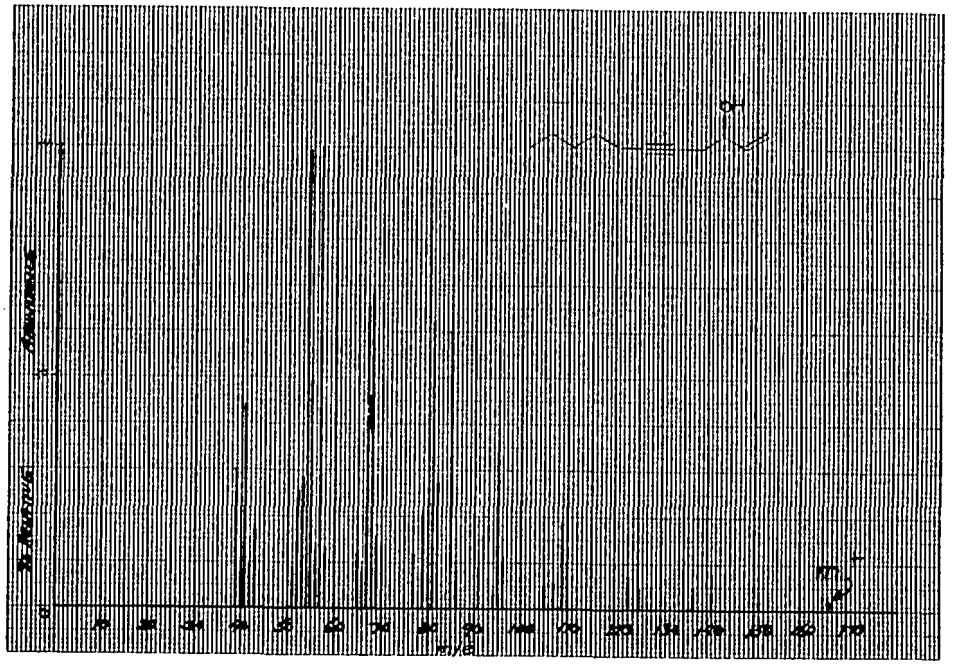
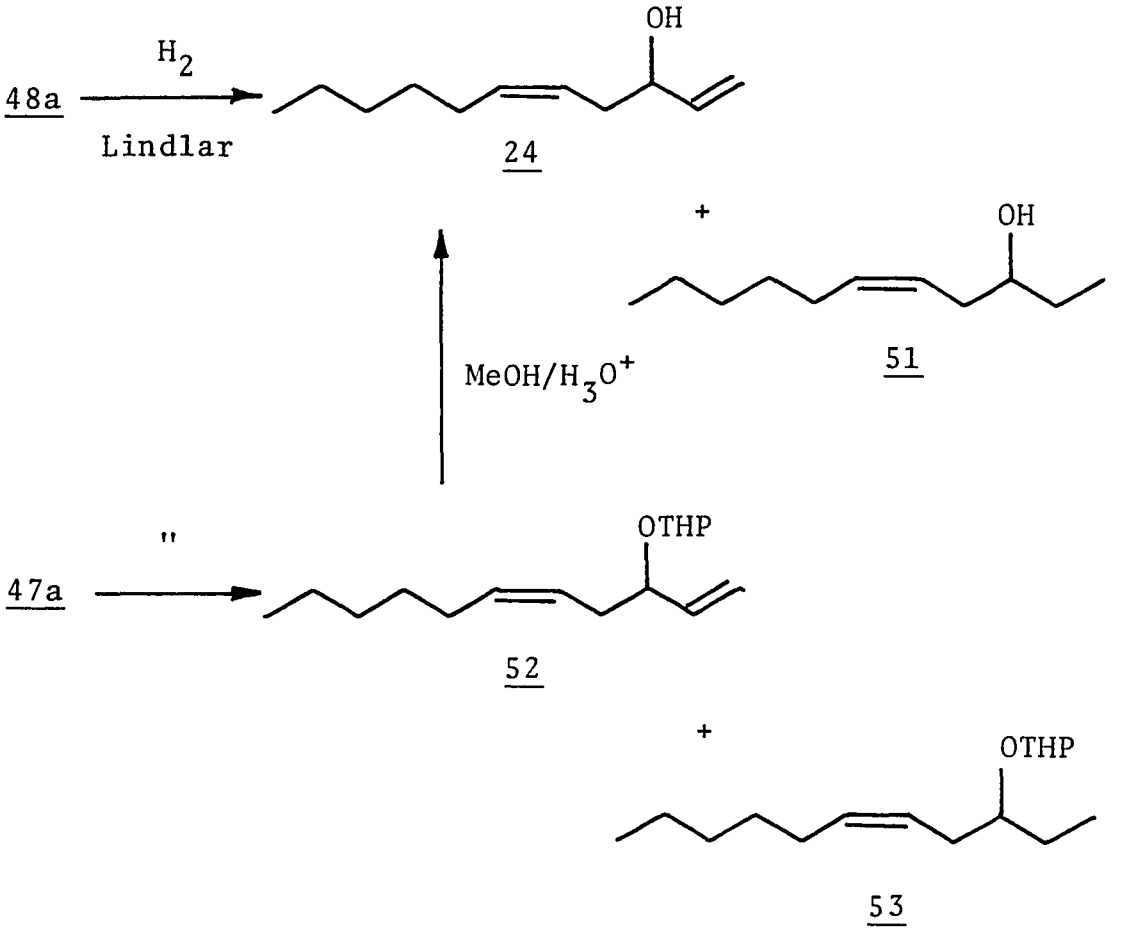


Figure III-32. Mass spectrum (70eV) of compound 48a.

With a 42% overall yield of 48a from acrolein Scheme III-2 appeared to alleviate the problem of obtaining sufficient quantities of 24. However, difficulties in reducing 48a cleanly to 24 at ambient pressures of hydrogen



were encountered in that reaction times sufficient to totally reduce the acetylene also caused partial loss of the terminal olefin (51). The hydrogenation of 47a to 52 was also attempted with the belief that the steric bulk of the tetrahydropyranyl group might hinder the approach of the terminal double bond to the surface of the catalyst thus making it less subject to reduction. The hydrogenation of 47a and 48a was carried out a total of 19 times and the results are summarized in Table III-1.

TABLE III-1.

HYDROGENATION DATA[a]

Run	Acetylene (mg)	Text no.	Solvent	Amt(ml)	Cat(mg)	Quin(µl)	T(min)	T(o)	Yields[b] 47a	48a	24	51	52	53
1	100	48a	c/ØH	10/4	10	5	30	RT	-	100				
2	100	48a	ace	10	10	4	45	RT	-	50	50	-	-	-
3	100	48a	ace	10	10	5	120	O	-	50	50	-	-	-
4	100	48a	ace	10	10	-	45	RT	-	10	90	-	-	-
5	100	48a	ace	10	15	-	65	RT	-	-	20	80	-	-
6	250	48a	ace	25	50	-	90	RT	-	-	5	95	-	-
7	250(THP)	47a	ace	25	25	-	40	RT	5	-	-	-	-	95
8	250 "	47a	c	25	20	-	15	RT	90	-	-	-	10	-
9	250 "	47a	hex	25	20	-	15	RT	100	-	-	-	-	-
10	250 "	47a	c	25	20	-	15	RT	75	-	-	-	25	-
11	250 "	47a	c	25	5	-	45	RT	90	-	-	-	10	-
12	550 "	47a	c	50	27	-	37	RT	10	-	-	-	80	10

TABLE III-1. (Continued)

HYDROGENATION DATA[a]

Run	Acetylene (mg)	Text no.	Solvent	Amt(ml)	Cat(mg)	Quin(μl)	T(min)	T(o)	Yields[b] 47a	48a	24	51	52	53
13	750(THP)	47a	chl	75	37	-	30	RT	100	-	-	-	-	-
14	750 "	47a	c	75	37	-	32	RT	100	-	-	-	-	-
15	750 "	47a	c	75	37	-	38	RT	100	-	-	-	-	-
16	750 "	47a	ace	75	37	-	37	RT	100	-	-	-	-	-
17	750 "	47a	ØH	75	38	-	37	RT	100	-	-	-	-	-
18[c]	250 "	47a	c	25	25	-	45	RT	100	-	-	-	5	-
19[d]	750 "	47a	ace	50	50	-	60	RT	50	-	-	-	50	-

[a] Abbreviations: ace-acetone, c-cyclohexane, chl-chloroform, ØH-benzene, quin-quinoline.

[b] % of reaction mixture based on pmr integration.

[c] New catalyst.

[d] Dried original catalyst.

Comparison of the reaction times for 47a and 48a shows that 47a is much more reactive due to the absence of the hydroxyl group which, in 48a, complexes with the catalyst. However, as can be seen in Table III-1, the terminal double bond of 47a is also labile to hydrogenation and small to moderate amounts of 53 were often present in the product mixtures. The best results were achieved in runs 4 and 12 with the desired products composing 90 and 80% of the respective reaction mixtures. The sensitivity of the reduction of 47a is illustrated by runs 4 and 5 in which the amount of catalyst and reaction time were varied only slightly. In the former case the reaction mixture still contained unreacted 47a while the latter was mostly side product (51).

After run 12 it was decided to reduce the catalyst-substrate contact time by using a more polar solvent ($CHCl_3$, run 13) and thereby avoid the formation of 53. The reaction failed completely and afforded a quantitative recovery of 47a. Run 12 had exhausted the supply of SpectrAR grade cyclohexane and for runs 14 and 15 distilled reagent grade cyclohexane was used instead. These reactions also resulted in failure. Subsequent runs with either acetone or benzene (16 and 17) again produced no reaction and it was assumed that the catalyst was no longer active. A new batch of catalyst was then prepared[20] and found to be less reactive than the original (run 18). In a final effort the original

catalyst was dried in an oven at 100° for two hours which completely restored its activity (run 19).

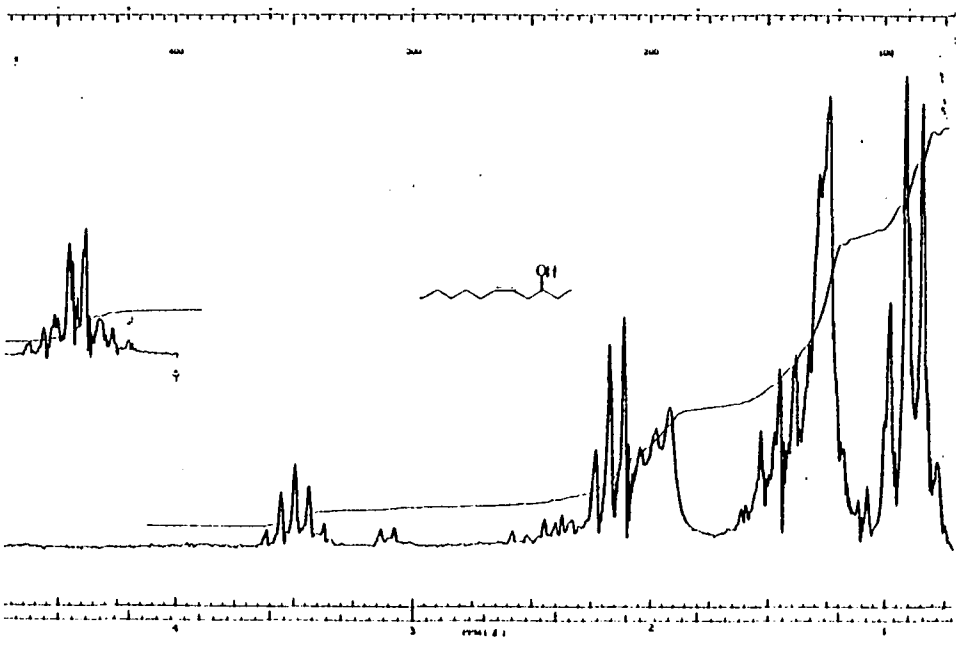


Figure III-33. Pmr spectrum ($CDCl_3$) of compound 51.

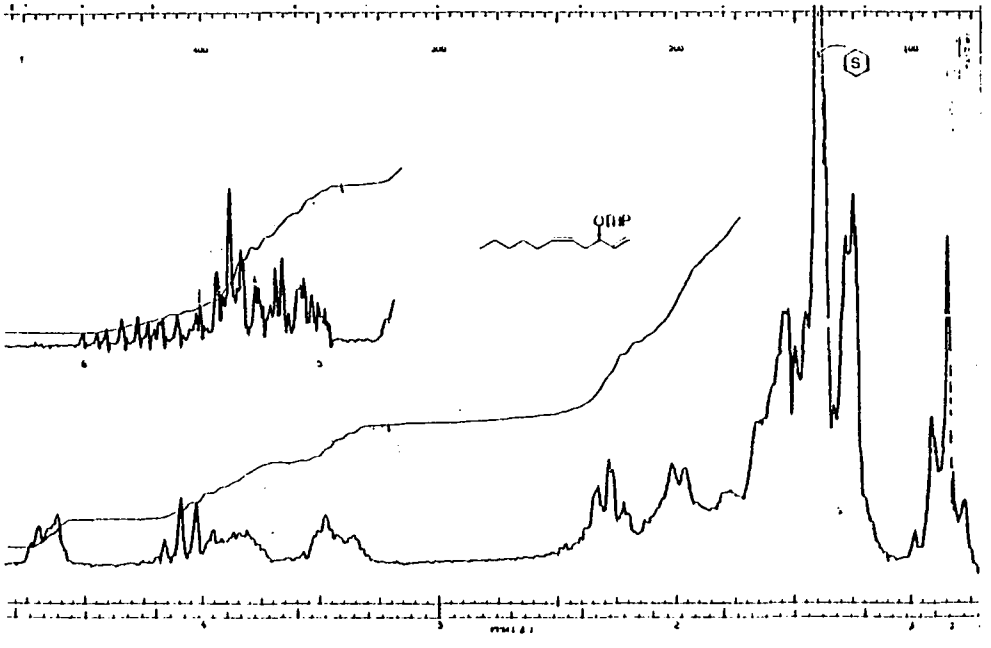
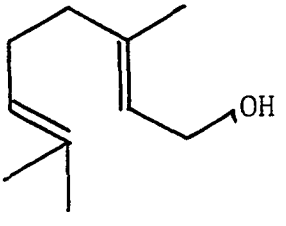
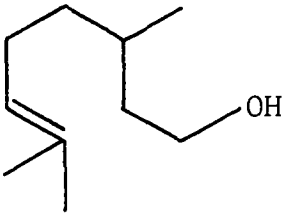


Figure III-34. Pmr spectrum ($CDCl_3$) of compound 52.

In future work, if it proves impossible to eliminate the saturated compound (51), attempts should at least be made to minimize its yield. Purification of the crude reaction mixtures could then possibly be achieved by chromatography on silver nitrate impregnated silica gel or by the recently developed procedure of Sharpless.[23] In this latter procedure the alcohol mixture is slurried with anhydrous calcium chloride in hexane. The most abundant component usually forms a solid complex with the calcium chloride excluding the minor components. The complex is then filtered, washed with hexane and dissolved in water to liberate the purified alcohol. It is not known what factors govern the selectivity of complexation but mixtures of such similar alcohols as 54 and 55 can be cleanly separated by this method. If this procedure will separate mixtures of 47a and 48a then it would still be possible to use Scheme III-2 for the preparation of pure tritium labeled 24.



54



55

Octadienol 29, isolated from the essential oil of Chondrococcus hornemanni, was also prepared by the general route shown in Scheme III-2. Reaction of 46 with sodamide in a liquid ammonia followed by alkylation with ethyl iodide gave a 35% yield of 47b whose pmr spectrum contained a triplet (J=7 Hz) at δ1.04 and a doublet of quartets (J=2 and 7 Hz) at 2.0 for the ethyl group. Hydrolysis of 47b with aqueous methanol and hydrochloric acid gave 48b which was reduced with hydrogen and Lindlar's catalyst to give a 78% yield of racemic 29. The pmr spectrum of synthetic 29 was identical to that of the naturally occurring material.

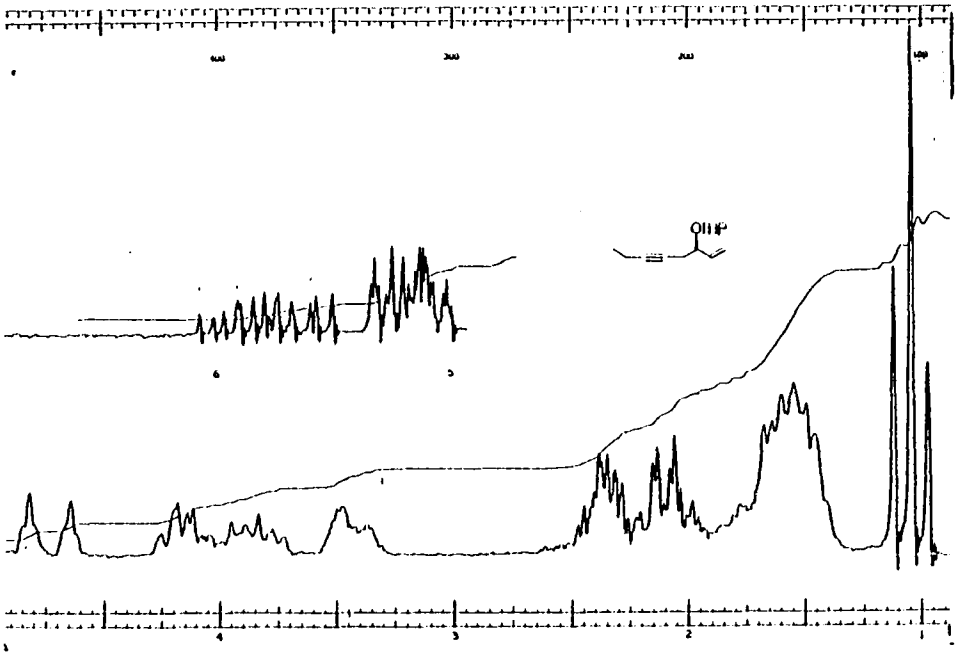


Figure III-35. Pmr spectrum ($CDCl_3$) of compound 47b.

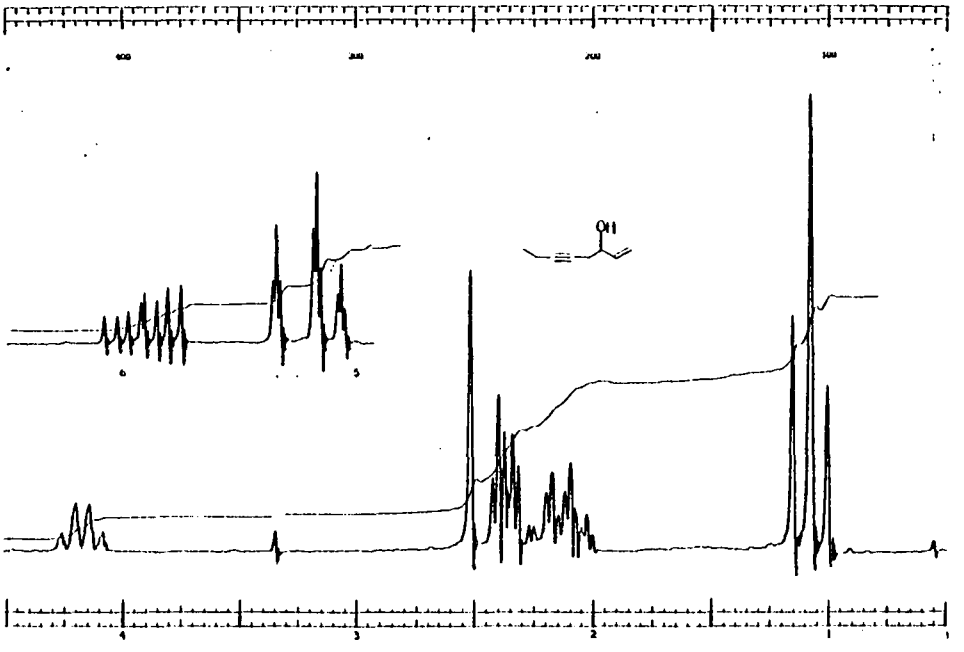


Figure III-36. Pmr spectrum ($CDCl_3$) of compound 48b.

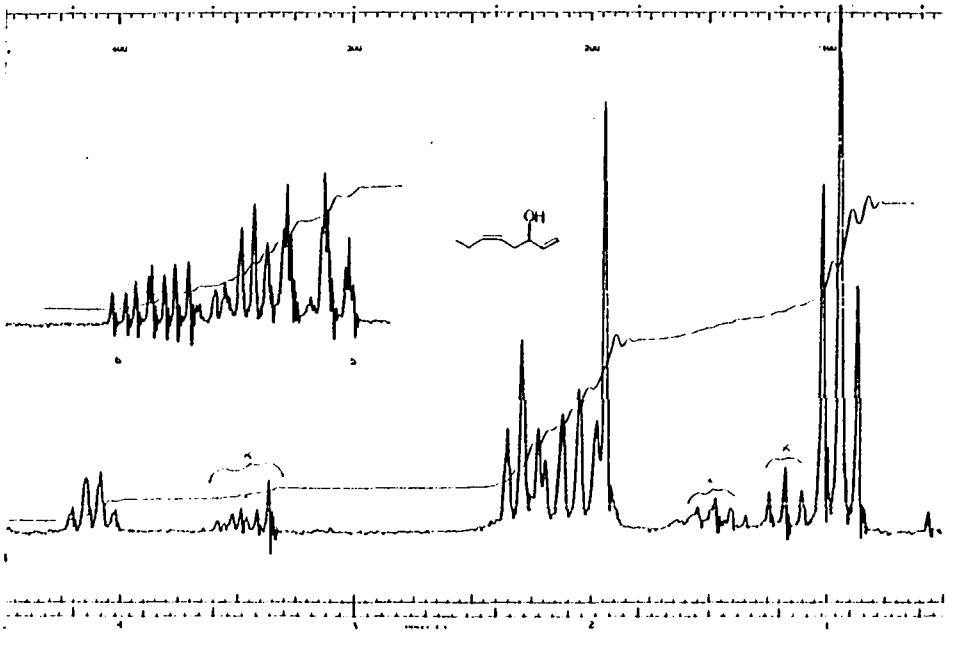


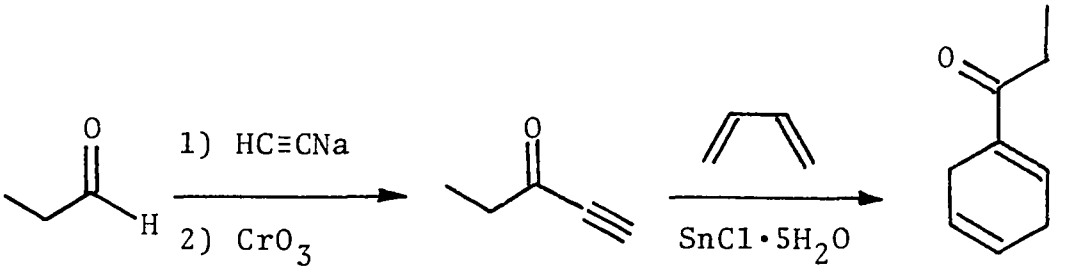
Figure III-37. Pmr spectrum ($CDCl_3$) of compound 29.

B. Attempted Synthesis of cis,cis-1,5,7-Undecatrien-3-ol (28)

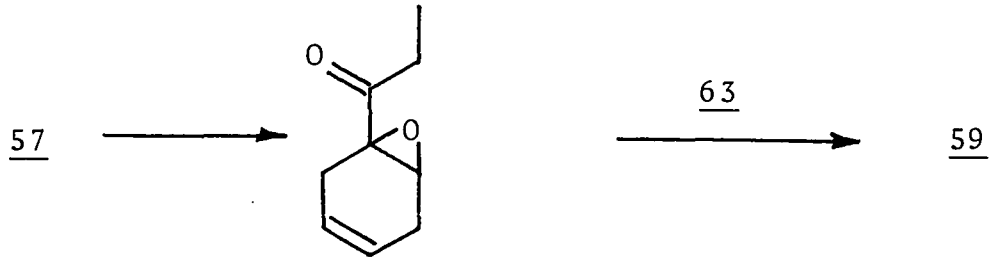
The synthesis of dienol 28 was not achieved but several routes leading to its formation were investigated. The first route attempted was aimed at the synthesis of cis-3-nonen-1-al-5-yne (60) using a slightly modified procedure of Eschenmoser[24] (Scheme III-3). In the original

Scheme III-3.

Unsuccessful Synthetic Route to Compound 28



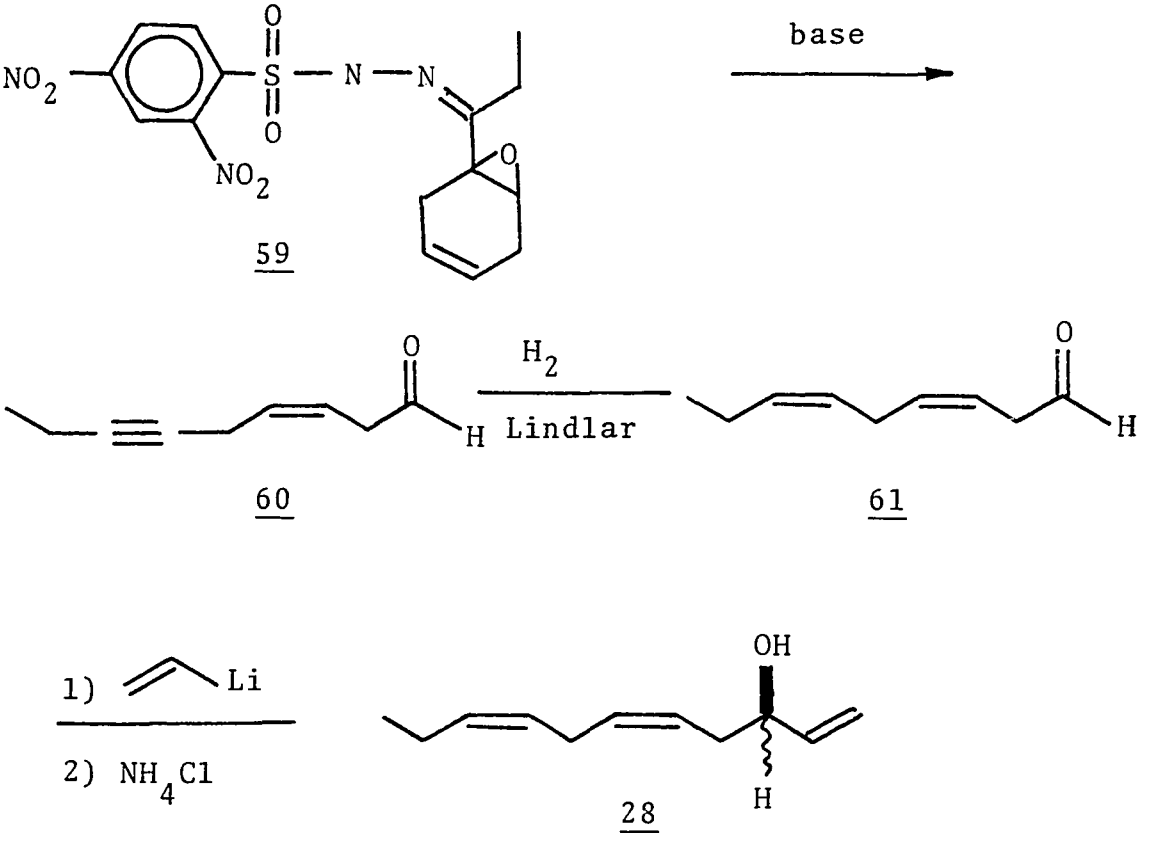
56 57



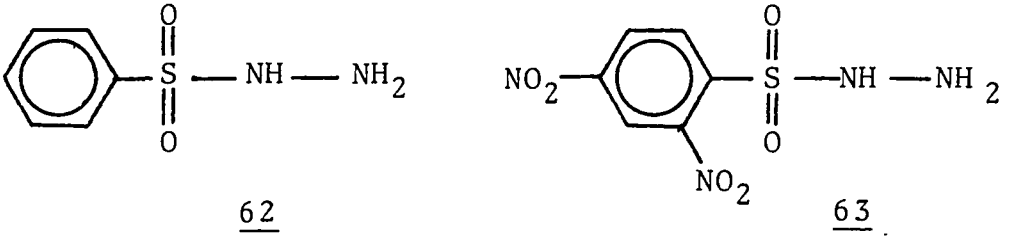
58

Scheme III-3. (Continued)

Unsuccessful Synthetic Route to Compound 28



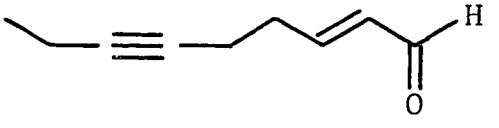
procedure benzene sulfonylhydrazine (62) was employed in the fragmentation of epoxyketone 58. However, Corey[25] has shown that 2,4-dinitrobenzenesulfonylhydrazine (63) gives much



higher yields of fragmentation products from α,β-epoxyketones and therefore it was decided to use 63 in place of 62 for the formation of 60. Once in hand 60 was to be reduced to 61 and then converted to 28 with vinyl lithium.

Preparation of the required ethyl ethynyl ketone (56) from propionaldehyde was achieved in a disappointing 9% yield using the procedures of Heilbron.[27,28] The tin tetrachloride catalyzed Diels-Alder reaction of 56 with butadiene was tried only once and gave a crude oil which contained 56 and 57 in an approximate ratio of 1:1. Column chromatography of the mixture on silica gel failed to separate the two components.

Apart from these discouraging results it was learned from Prof. Eschenmoser[29] that a reexamination of the product obtained from the fragmentation of 58 (as the benzensulfonyl hydrazone) as done in his laboratory revealed a mixture of isomers. Apparently the basic conditions necessary to induce the fragmentation of the benzenesulfonyl hydrazone of 58 also caused isomerization of the product (60) to the α,β-unsaturated isomer (64). Because of the uncertainties in the conversion of 58 to 60 and the difficulties experienced in reacting 37 with vinyl lithium no further attempt was made to prepare 28 via Scheme III-3.

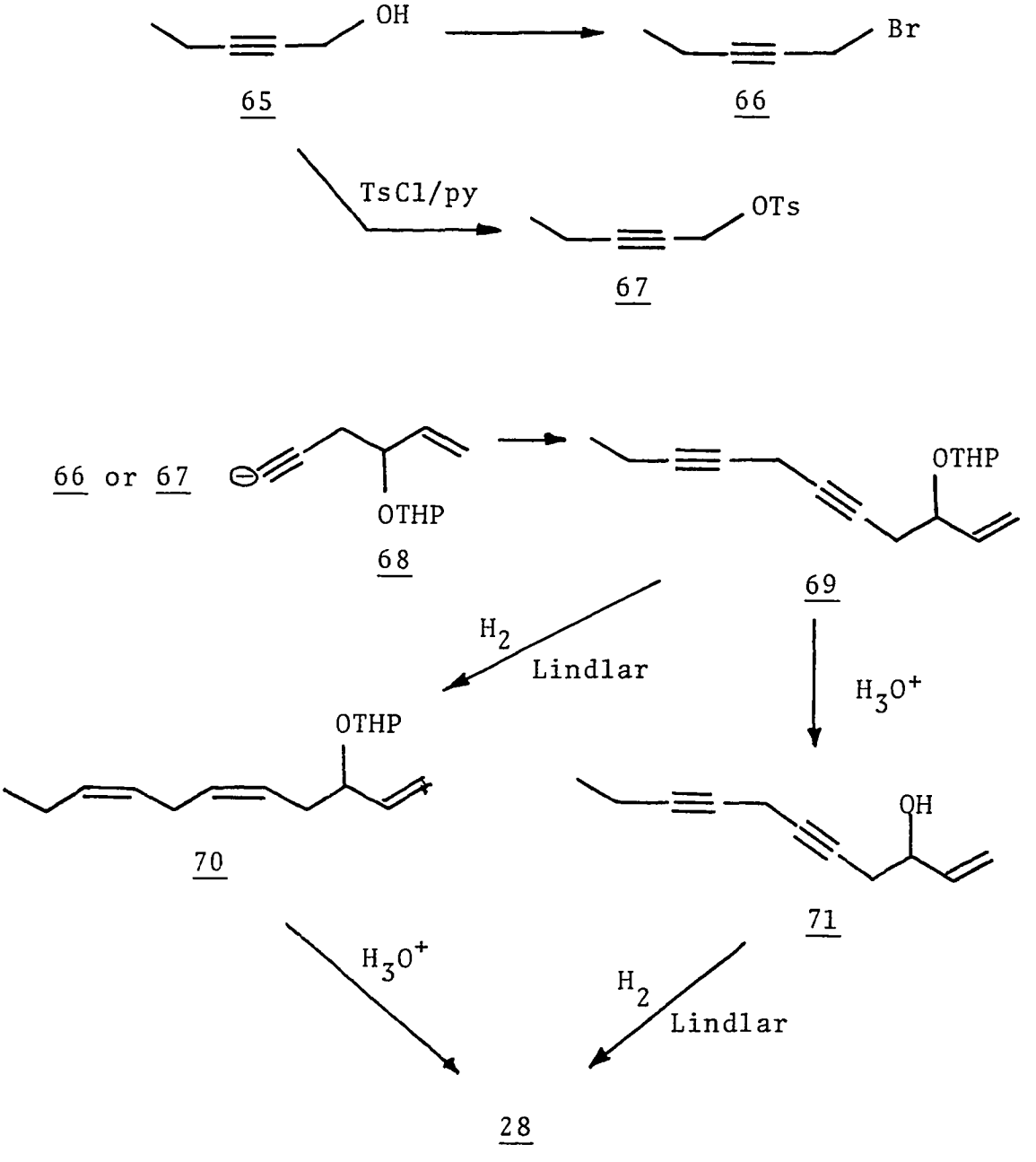


64

A more straightforward approach to 28 utilizing 68 as the key intermediate is outlined in Scheme III-4. The advantage

Scheme III-4.

Alternate Synthetic Route to Compound 28



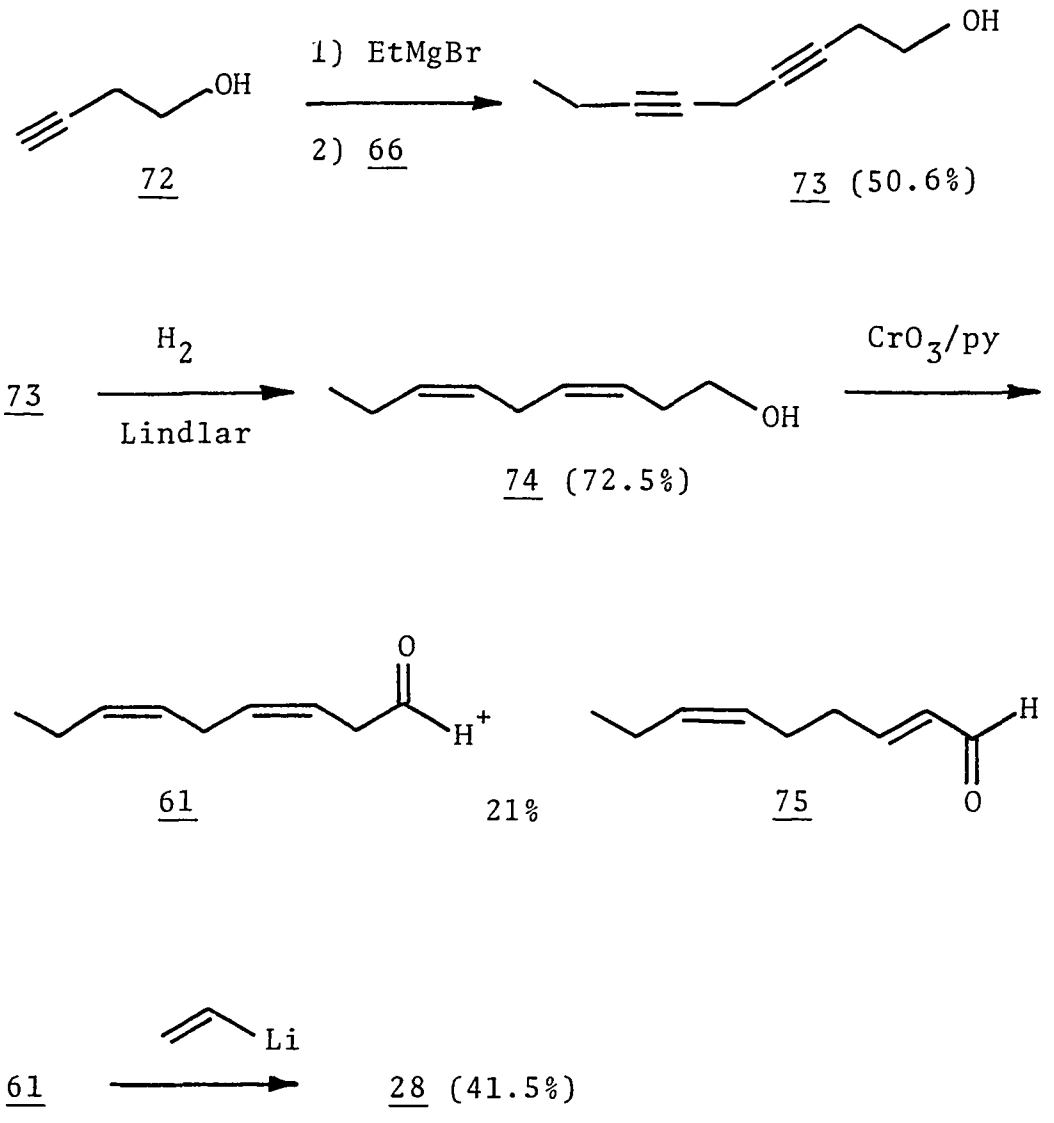
of Scheme III-4 over Scheme III-3 is that coupling of the readily available 48 with either 66 or 67 would quickly assemble the C_{11} backbone with acetylenic linkages at the 5 and 8 positions required for conversion to the cis-double bonds. In addition, tritium labeling of 28 could be achieved in the last step of the synthesis if the proper conditions for reduction of 69 or 71 could be worked out.

A lack of time limited work on Scheme III-4 to the preparation of starting materials (66 and 67). An attempt to prepare tosylate 67 from 65 by standard methods[29] resulted in failure by giving a dark oil whose pmr spectrum showed only the presence of starting materials. The conversion of 65 to 66 with phosphorus tribromide is described in the literature[30] but a lack of the inorganic reagent led us to try other methods. The reaction of 65 with triphenylphosphite-bromine complex[31] in ether gave a colorless oil that apparently contained none of the desired 66 since attempted distillation of the oil at 90° (0.1 mm) produced no distillate (66 bp 38° @ 10 mm[31]). Stirring 65 with triphenylphosphine and carbon tetrabromide[32] in THF for 72 hours did produce a small amount of 66 but also present in the crude product were large amounts of what appeared to be higher brominated derivatives of 65 and a substantial amount of triphenyl phosphine. In future work 66 should be prepared from 65 by the method of Brandsma[30] which uses phosphorus tribromide.

Recently, Marner[33] achieved the synthesis of 28 using the route outlined in Scheme III-5. The most difficult step in this scheme was the oxidation of 74 to 61 with chromium

Scheme III-5.

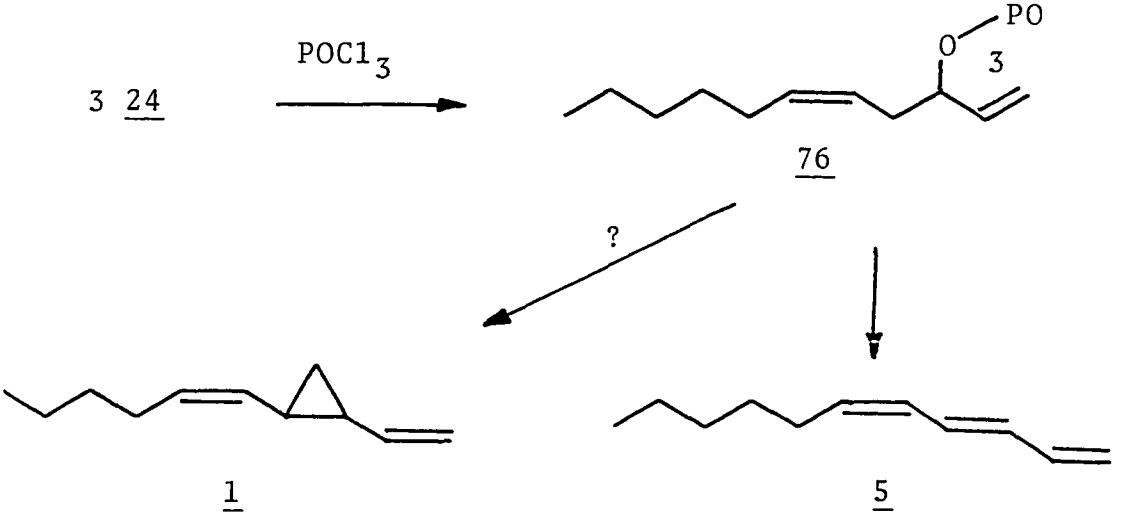
Marner's Synthesis of Compound 28



Trioxide-pyridine complex. Approximately 20% of the product isolated was the isomeric aldehyde 75 which had to be separated by preparative glc before proceeding with the final step (61 → 28). Although the overall yield was very low (3% from 72) Scheme III-5 does represent the first successful route to 28.

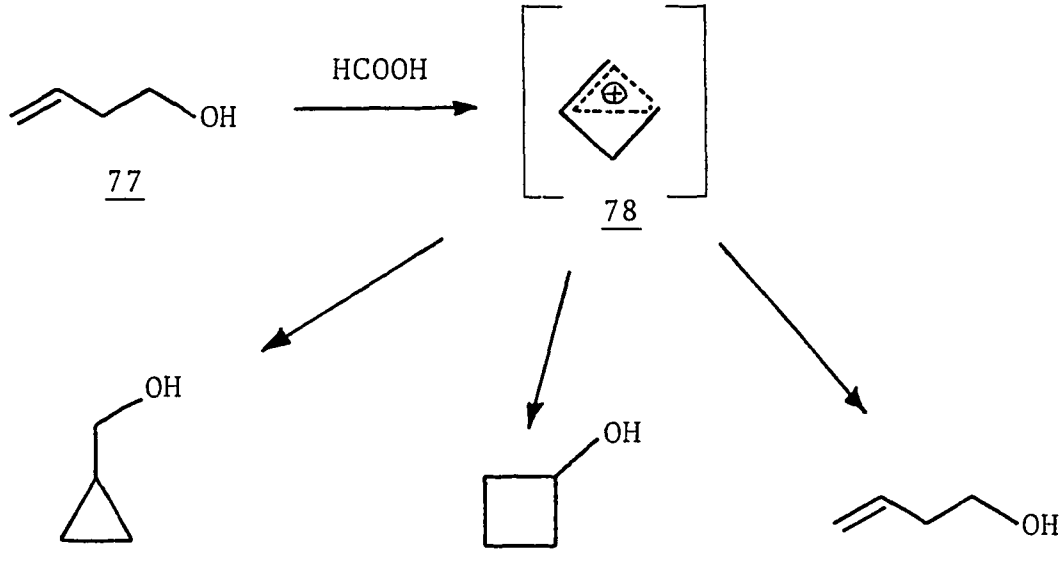
C. Dehydration Reactions of 24

Although Schemes III-1 and III-2 were not successful in producing large amounts of 24 sufficient quantities were obtained to conduct several dehydration experiments. Phosphorus oxychloride ($POCl_3$) was initially attractive as a dehydrating reagent since the elimination of phosphoric acid from 76 would closely mimic biological systems. The reaction of 24 with a stoichiometric amount



of $POCl_3$ gave a dark brown oil that had the characteristic odor of Dictyopteris but the pmr spectrum showed only broad nondescript signals. The hydrochloric acid liberated from the reaction apparently caused the product(s) to rapidly polymerize.

Roberts[34] has shown that formolysis of allyl carbinyl tosylate (77) gives varying yields of cyclopropyl carbinol (79) and cyclobutanol (78) via the cyclobutonium ion 79.

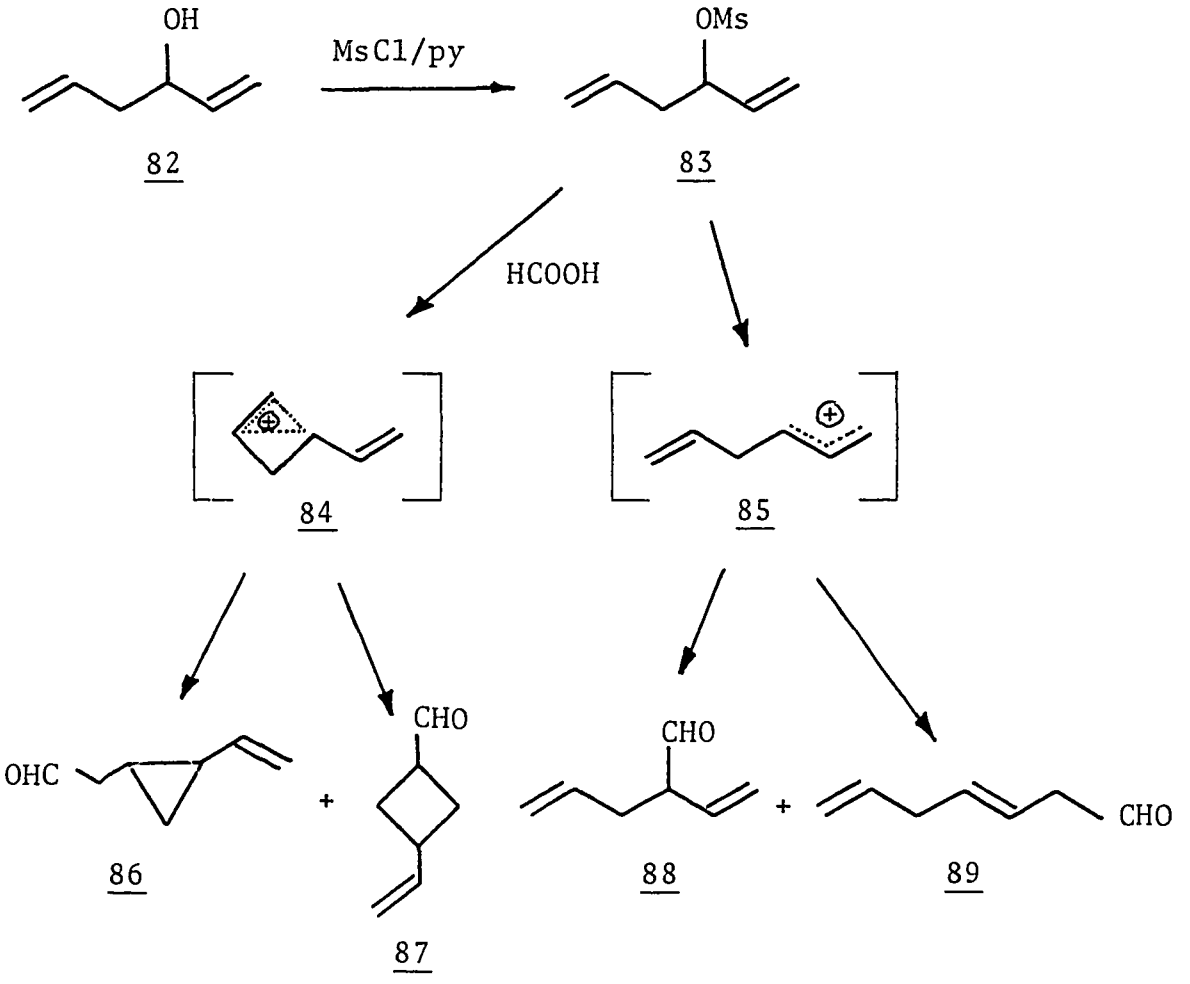


79 3.3-23.1%

80 13.4-70-2%

82 26.5-74.3%

The tosylate group and double bond of 77 occupy the same relative positions as the hydroxy group and cis-double bond of 24 and it was hoped that formolysis of the tosylate of 24 would produce hydrocarbons 1 and 5. For a model study of this system the mesylate (83) of 1,5-hexadien-3-ol (82) was



prepared and heated at 68° for 55 minutes in 99% formic acid solution. The pmr spectrum of the resulting mixture exhibited triplets at δ2.34 (J=7 Hz) and 2.74 (J=7 Hz), a doublet (J=7 Hz) at 4.31 and complex olefinic signals between 4.8 and 5.9. This data along with decoupling experiments showed the mixture to consist of 88 and 89 in an approximate 1:1 ratio along with some polymeric material. Apparently, in this system, the allylic carbonium ion (85) predominates strongly over the cyclobutonium species as there was no evidence for either cyclopropane or cyclobutane formation.

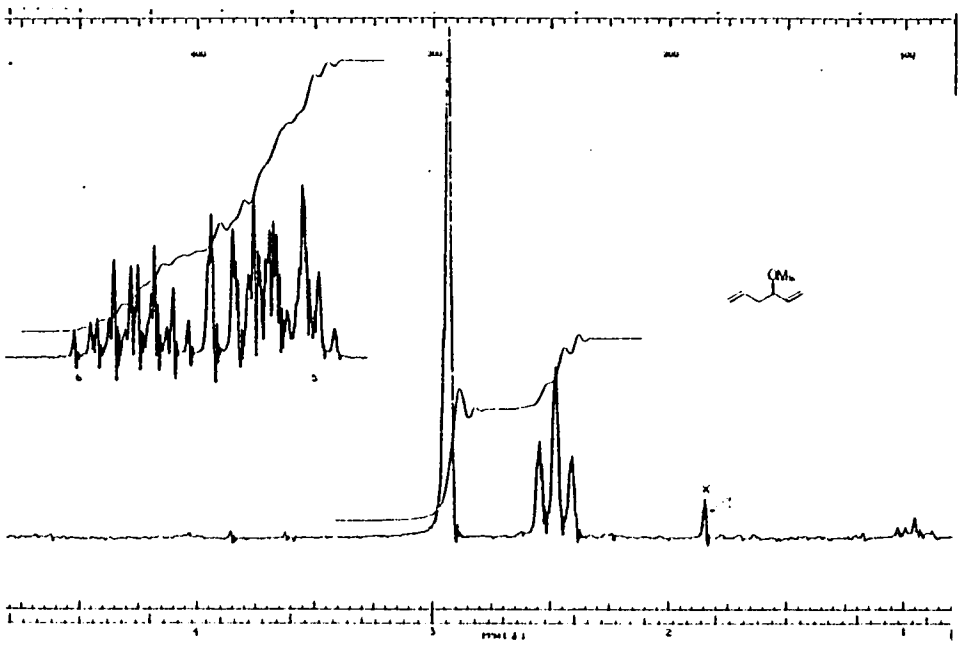


Figure III-38. Pmr spectrum ($CDCl_3$) of compound 83.

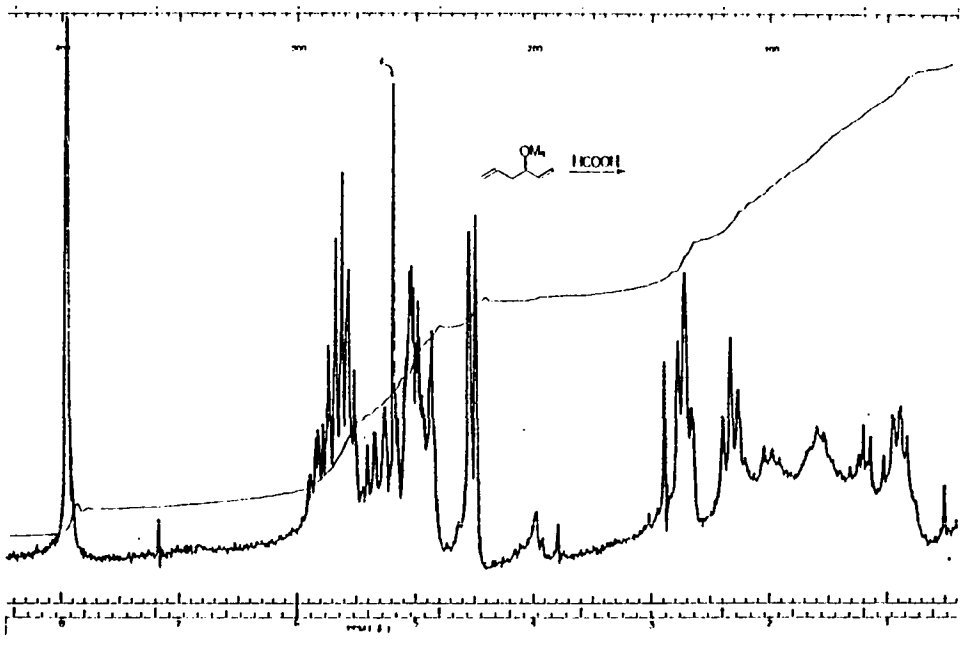
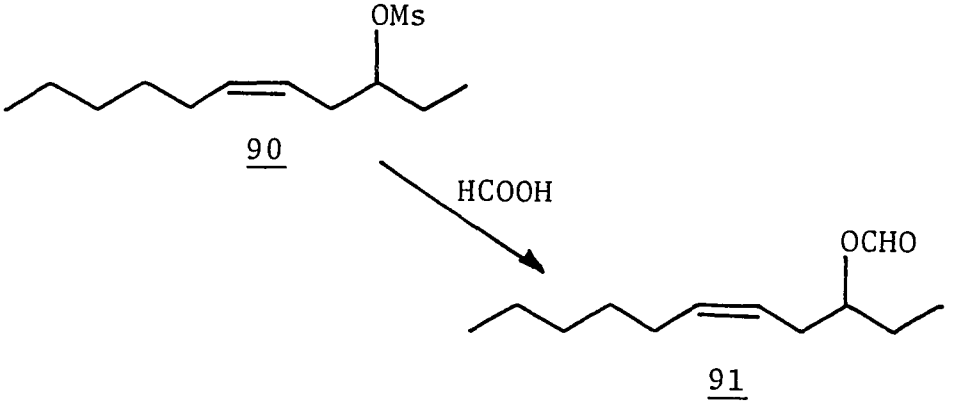


Figure III-39. Pmr spectrum ($CDCl_3$) of formolysis products from 83.

In another model study the mesylate of 51 (90) was reacted with formic acid to observe whether or not cyclobutonium ion derived products would be formed in the absence of the vinyl group. After heating 90 in 88% formic acid at 68° for 55 minutes the only product visible in the pmr spectrum of the reaction mixture was 91. The half-lives



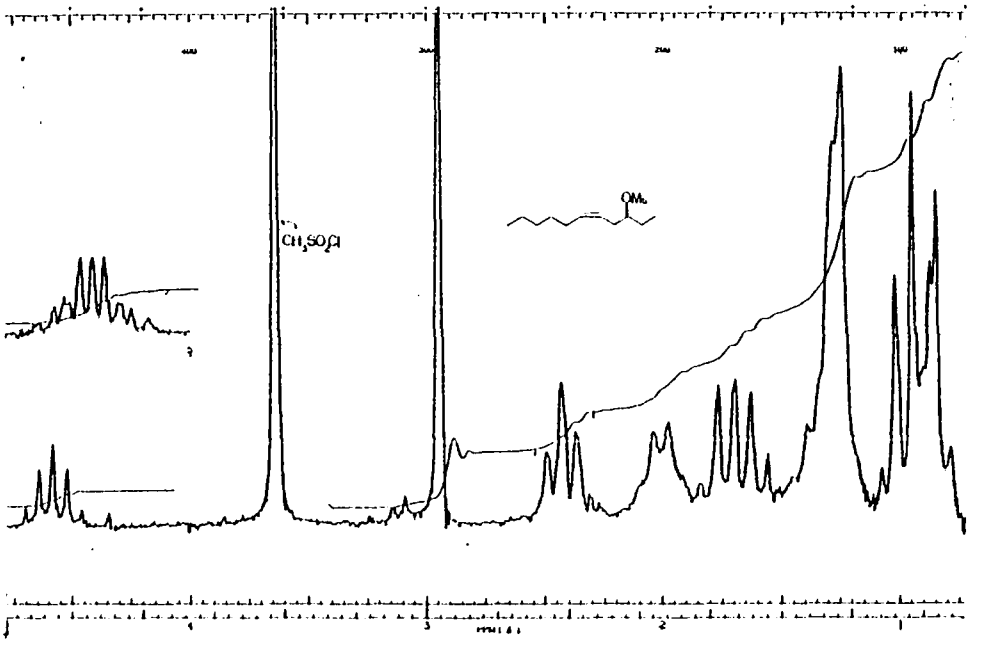


Figure III-40. Pmr spectrum ($CDCl_3$) of compound 90.

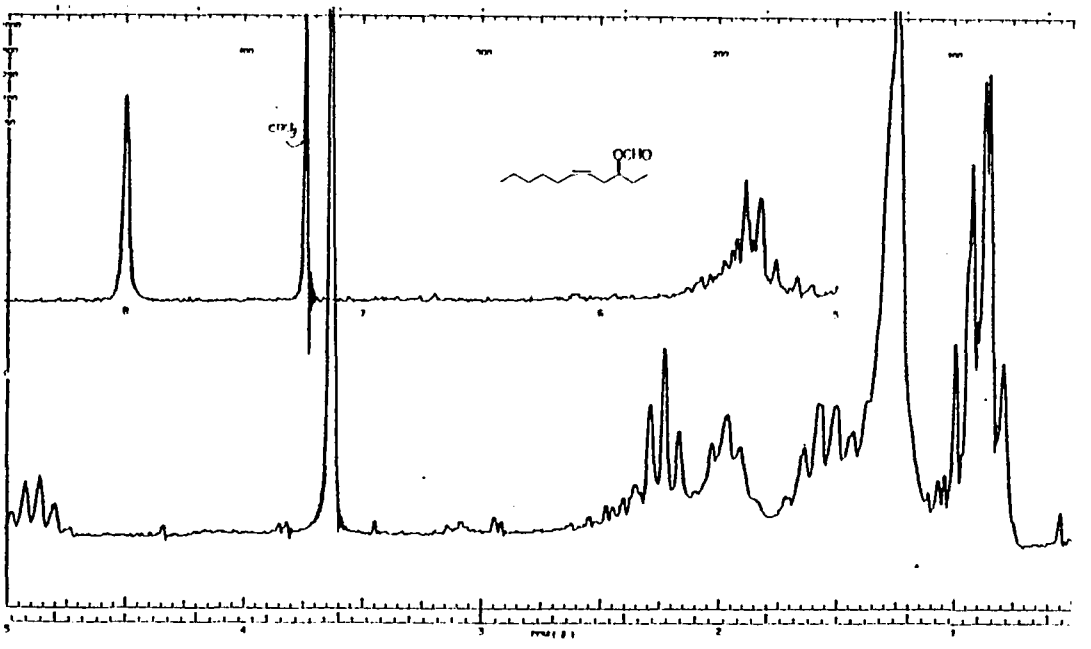
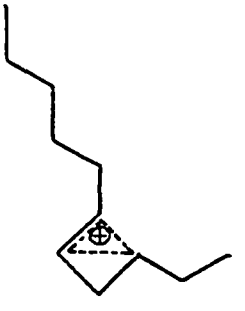


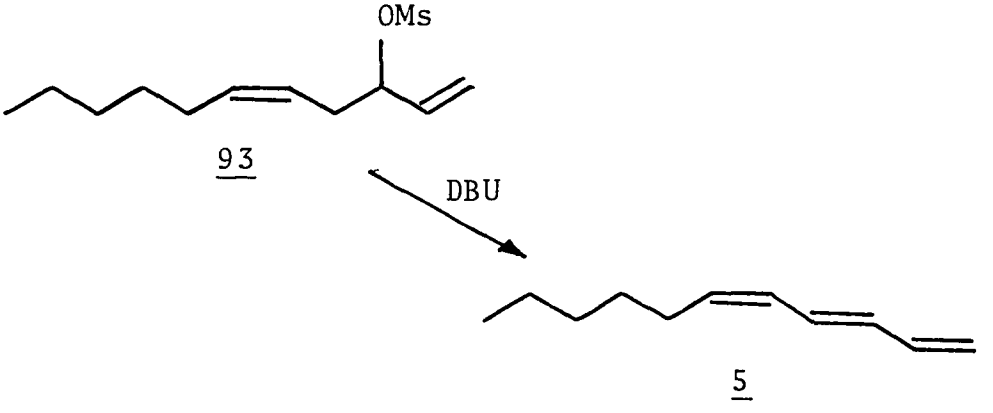
Figure III-41. Pmr spectrum ($CDCl_3$) of compound 91.

of the allyl carbinyl tosylate reactions performed by Roberts[34] are extremely short and it may be that the bulk of the n-pentyl group attached to the cis-double bond of 90 prevents the latter from moving into the proper position to form the cyclobutonium species (92) during the lifetime of the cation.



92

Since acidic conditions did not provide positive results with the model compounds several experiments with 93 using basic conditions were conducted. Reaction of 93 with a 10%



excess of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in methylene chloride at -78° for one hour and then room temperature for three hours produced no visible reaction. Repeating the

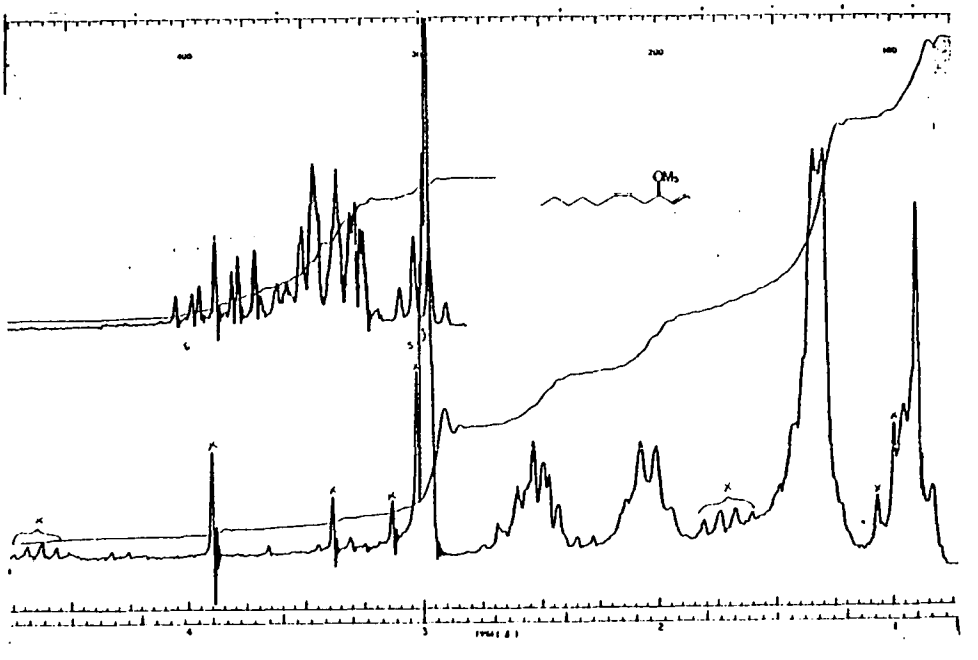
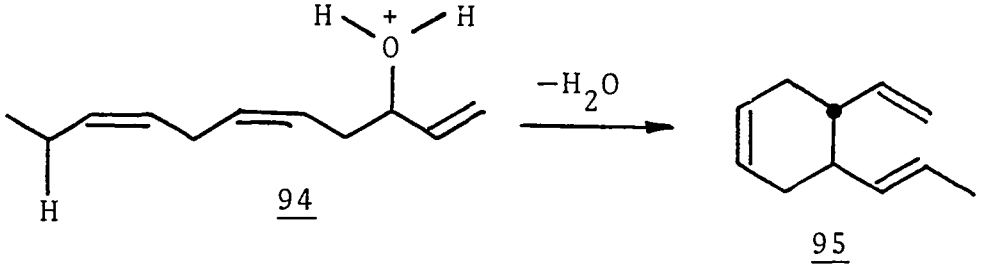


Figure III-42. Pmr spectrum ($CDCl_3$) of compound 93.

reaction at the reflux temperature of chloroform (61°) for two hours again produced no reaction. The reaction of 93 with other bases such as t-butoxide and lithium dicyclohexyl amide were not attempted.

Although the few attempts to effect hydrocarbon formation from 24 and its mesylate (89) gave discouraging results Marner[35] successfully dehydrated trienol 28 by heating in carbon tetrachloride with a small amount of anhydrous oxalic acid. Analysis of the complex product mixture, which rapidly polymerized, by glc showed the presence of a small amount of material that had a retention time identical to that of aucantene (95), a constituent of the brown alga



94 95

Cutleria multifida.[8] Aucantene (95) could only have been formed by a 1,8-elimination of water from the protonated 28 (94) which means that 1,5-elimination may also have taken place to form the cyclopropane (2). However, this could not be verified due to the lack of an authentic sample of 2.

D. Attempted Isolation of 24 and 28 from Dictyopteris

The procedure used to isolate the nonvolatile compounds from Dictyopteris involved successive extraction of the wet algae with methanol and chloroform followed by evaporative removal of the solvents in a common flask. The crude extract was then partitioned between methanol and heptane to give, after removal of the solvents, polar and non-polar extracts respectively. All of the nonvolatile compounds identified from Dictyopteris to date have been isolated from the heptane soluble oil.

To determine in which extracts the alcohols (24 and 28) were likely to be found a partitioning experiment was carried out by placing 500 mg of 48a in a separatory funnel with ten milliliters of heptane and ten milliliters of methanol. The mixture was shaken vigorously for 20 minutes to establish equilibrium and the layers separated. The methanol layer was found to contain 490 mg of 48a after evaporative removal of the solvent. The remaining ten milligrams of 48a was presumed to have been lost during the evaporation of the methanol since evaporation of the heptane layer afforded no residue. This result was very encouraging since only the heptane soluble extract from Dictyopteris had been extensively examined.

Before fractionating the methanol extract a mixture of 48a and 24 was chromatographed on the silica gel and Sephadex columns to be used in order to obtain their retention volumes.

With this data in hand 167 g of Dictyopteris methanol soluble extract was fractionated (see experimental section, p. 360) first on silica gel and then Sephadex. The final fractions weighed less than one milligram and, by pmr analysis, did not contain either 24 or 28.

The failure to find 24 and 28 in the methanol extract may mean that the pool sizes of these compounds within the plants are extremely small or that, once formed, they are not liberated from the enzyme surface before being converted to hydrocarbons and/or sulfur compounds. In addition, the extract used for this experiment was isolated several years previously from drifting plants that had been torn loose from the bottom during periods of heavy surf. Drifting algae is not necessarily in a normal metabolic state[36] and the relative pool sizes of the various constituents may be substantially different from those in algae attached to the sea floor. Future attempts to isolate 24 and 28 should therefore use extracts isolated from Dictyopteris collected from its natural habitat.

E. Synthesis of the Sulfur Containing Compounds

Most of the exploratory work on the synthesis of the sulfur containing compounds was carried out by Dr. Asato[11,17] during the years 1972-3 and resulted in the preparation of compounds 13-16. However, in this early work, few of the intermediates or final products were subjected to complete

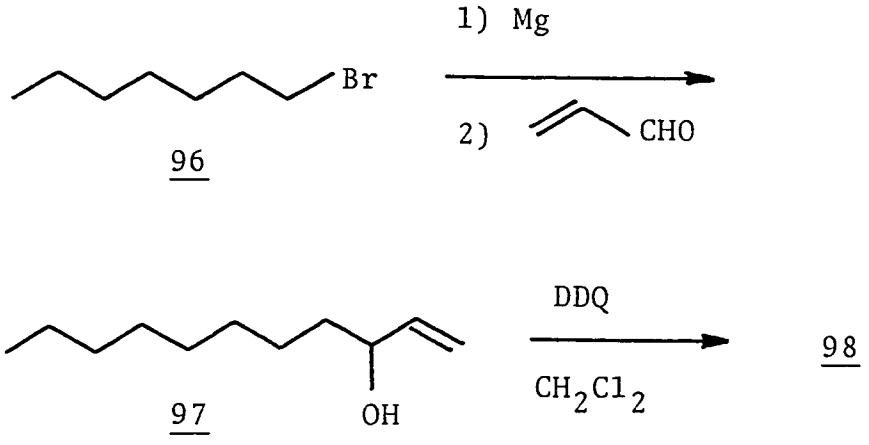
spectral and chemical analysis. In addition, most of the steps leading to the sulfur compounds employed crude starting materials and several gave poor yields of products. For this study the synthetic schemes developed by Asato[11,17] were to be repeated in an attempt to increase yields and fully characterize all intermediate and final compounds.

1. S-(3-Oxoundecyl) Thiolacetate (13) and Bis-(3-Oxoundecyl) Disulfide (16)

The synthesis of S-(3-oxoundecyl) thiolacetate (13, Scheme III-6) was reexamined first since it is the simplest of the sulfur compounds. The reaction of n-octyl magnesium bromide with acrolein proceeded smoothly and gave a 72% yield of 1-undecen-3-ol (97)

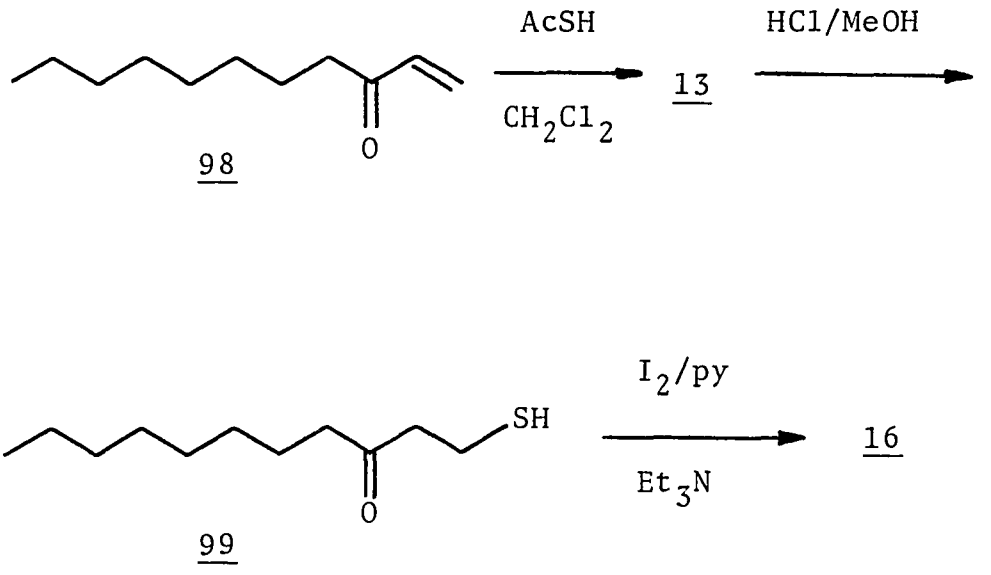
Scheme III-6.

Synthesis of Compounds 13 and 16



Scheme III-6. (Continued)

Synthesis of Compounds 13 and 16



which was completely characterized by Asato.[17] The pmr spectrum of 97 exhibits a typical AMX pattern for the vinyl group with an overlapping doublet of doublets of doublets (J=6, 10 and 16 Hz) at δ5.92 for the X proton. The AM protons appear as doublets of doublets at δ5.25 (J=1.5 and 16 Hz) and 5.12 (J=1.5 and 10 Hz) that are broadened by allylic coupling with the alcohol methine proton (broad q, J=6 Hz, 4.09).

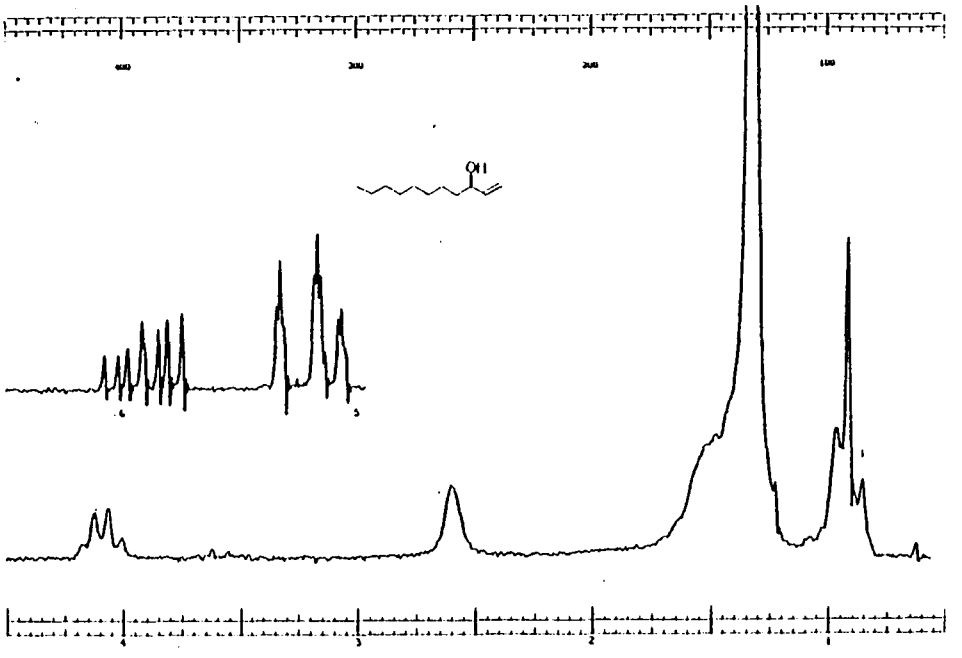


Figure III-43. Pmr spectrum ($CDCl_3$) of compound 97.

The conversion of 97 to 1-undecen-3-one (98) with manganese dioxide or chromic acid was found to proceed in poor yield but oxidation with 2,3-dichloro-5,6-dicyano-quinone (DDQ) gave high yields of crude 98.[17] However, in this study it was found that purification of 98 by vacuum distillation (bp 64.2-65.0°, 0.35 torr) caused substantial polymerization of the product as evidenced by a large amount of nonvolatile pot residue. The yields of pure 98 obtained in this manner were never higher than 30%. Purification of 98 by column chromatography on alumina with chloroform as the eluting solvent increased the yield to 89%. The pmr spectra of distilled and

chromatographed 98 were identical and showed a complex ABC pattern between δ5 and 6 for the vinyl protons.

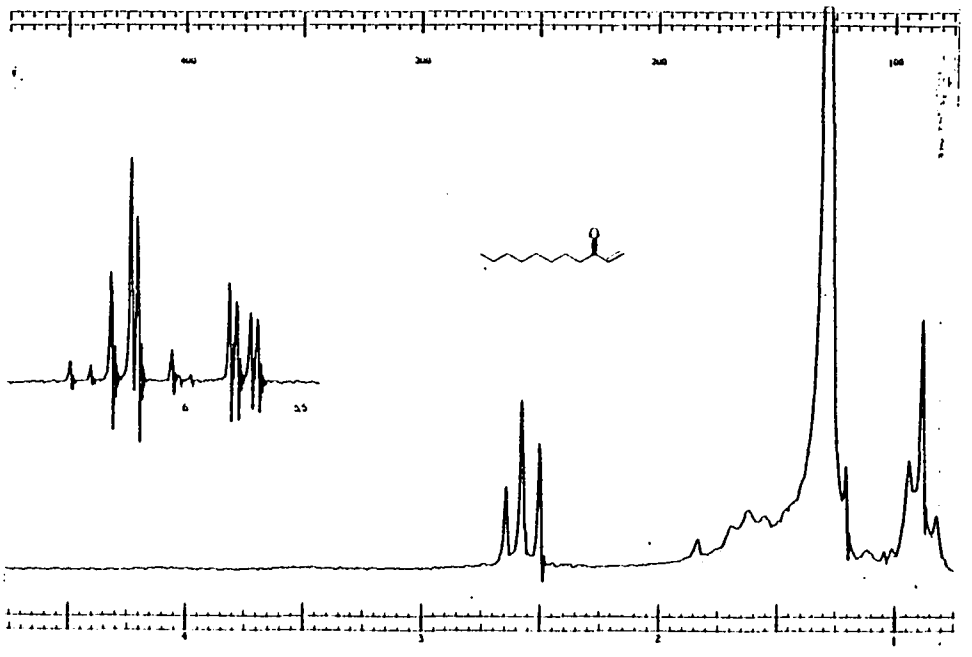


Figure III-44. Pmr spectrum ($CDCl_3$) of compound 98.

The addition of thiolacetic acid to 98 in methylene chloride at 0° followed by chromatography of the resulting crude oil on Sephadex LH-20 with 1:1 methanol/chloroform gave the desired 13 in 81% yield. The synthetic product obtained in this manner gave a satisfactory elemental analysis and was identical in all respects to the naturally occurring material.

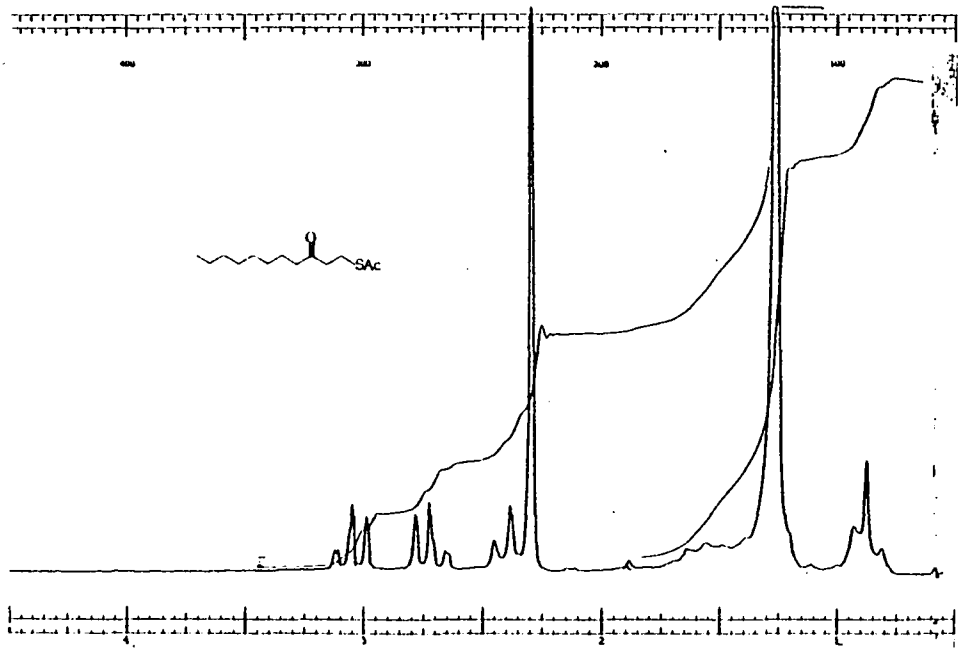


Figure III-45. Pmr spectrum ($CDCl_3$) of compound 13.

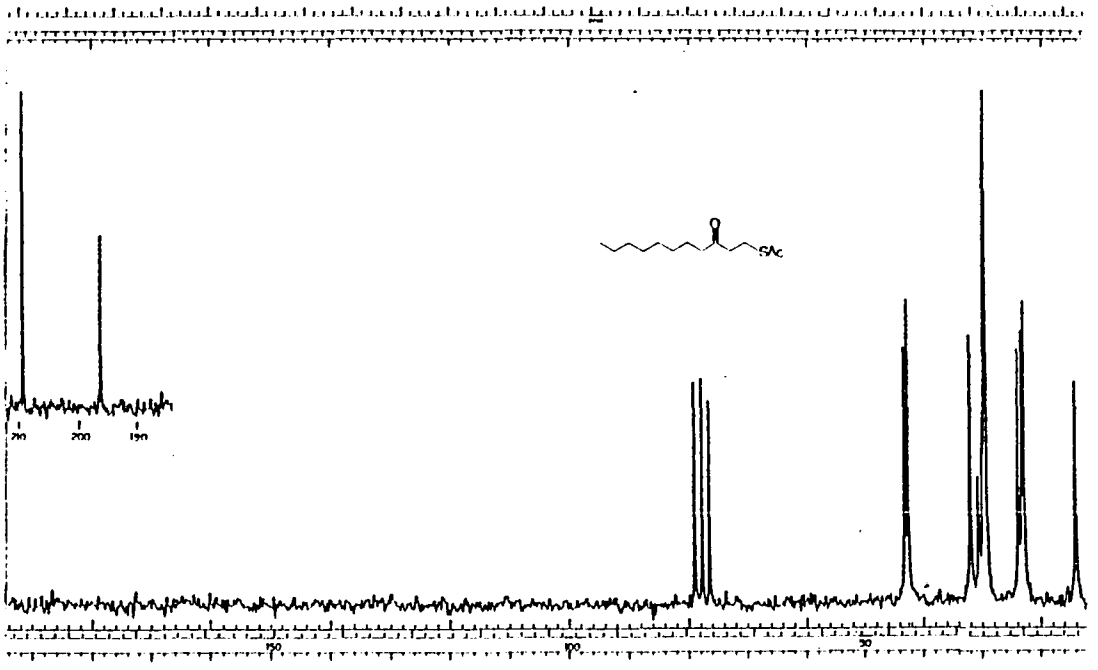


Figure III-46. Cmr spectrum ($CDCl_3$) of compound 13.

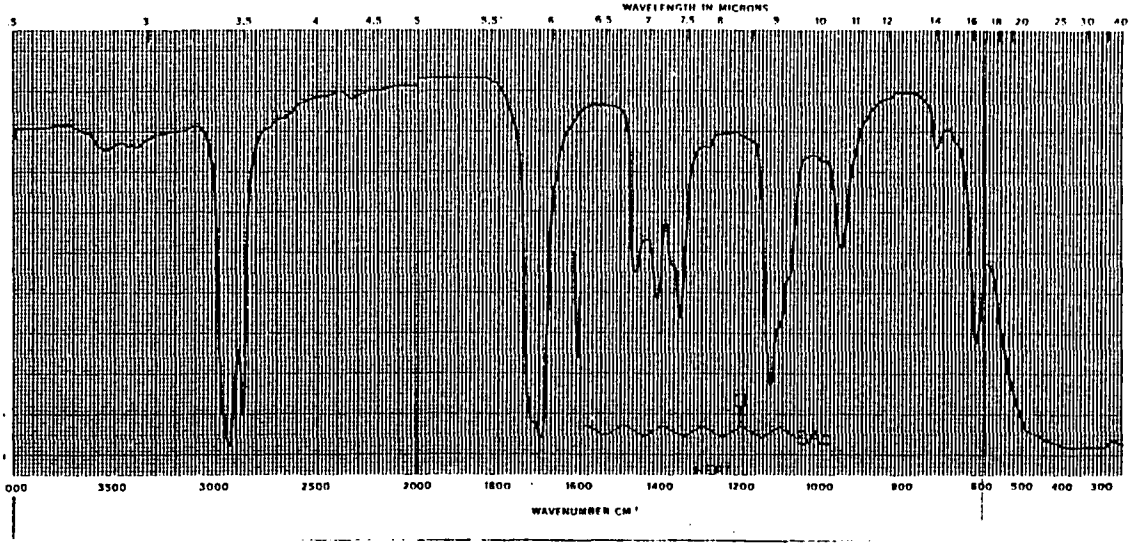


Figure III-47. Ir spectrum (neat) of compound 13.

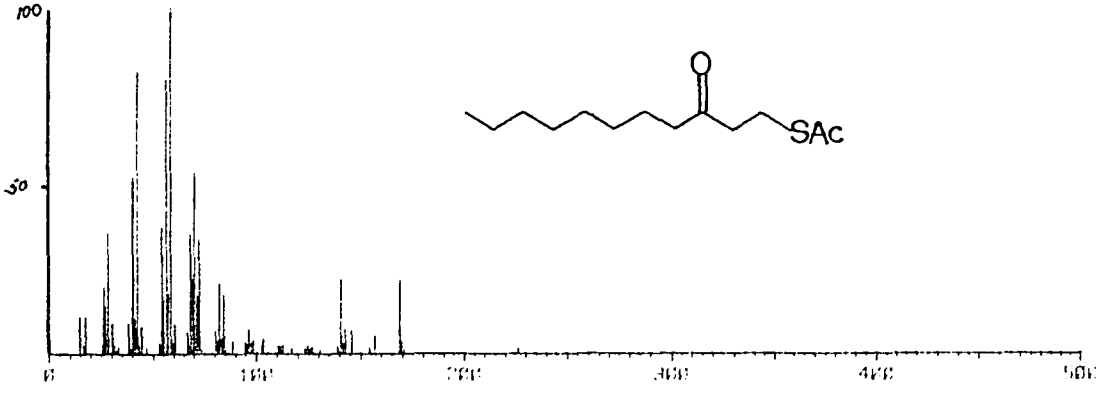
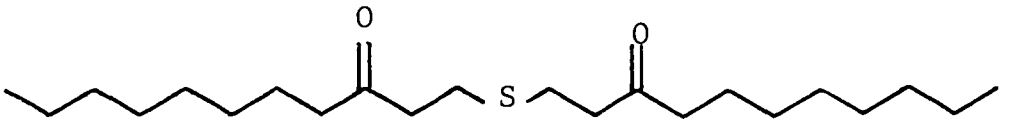


Figure III-48. Mass spectrum (70eV) of compound 13.

Mercaptan 99, required for the formation of disulfide 16, could not be generated from 13 by hydrolysis with borontrifluoride etherate or acid-washed Amberlite IR-20.[17] However, transesterification occurred in refluxing 3% hydrochloric acid/methanol solution to

give a product mixture that was mostly 99 contaminated with a small amount of bis-sulfide 100. Chromatography



100

of the crude product on a Sephadex LH-20 column with 1:1 methanol/chloroform resulted in an 85% yield of pure 99 and a 4% yield of 100. The pmr spectrum of 99 in benzene-d_6 shows a broad triplet (J=6 Hz) at δ0.89, a 12H methylene envelope at 1.21 and a sharp triplet (J=8 Hz) at 1.47 for the mercaptan proton. The four methylene protons between the carbonyl and mercapto groups appear as a complex multiplet between δ3.2 and 3.6 with the methylene group on the opposite side of the carbonyl present as a broadened triplet (J=7 Hz) at 2.03. The infrared spectrum of 99 shows a very weak SH stretch at 2560 cm^{-1} and a strong carbonyl absorption at 1715 cm^{-1}. The mass spectrum exhibits a weak molecular ion at m/e 202 and a strong peak at m/e 169 for loss of the sulfhydryl group.

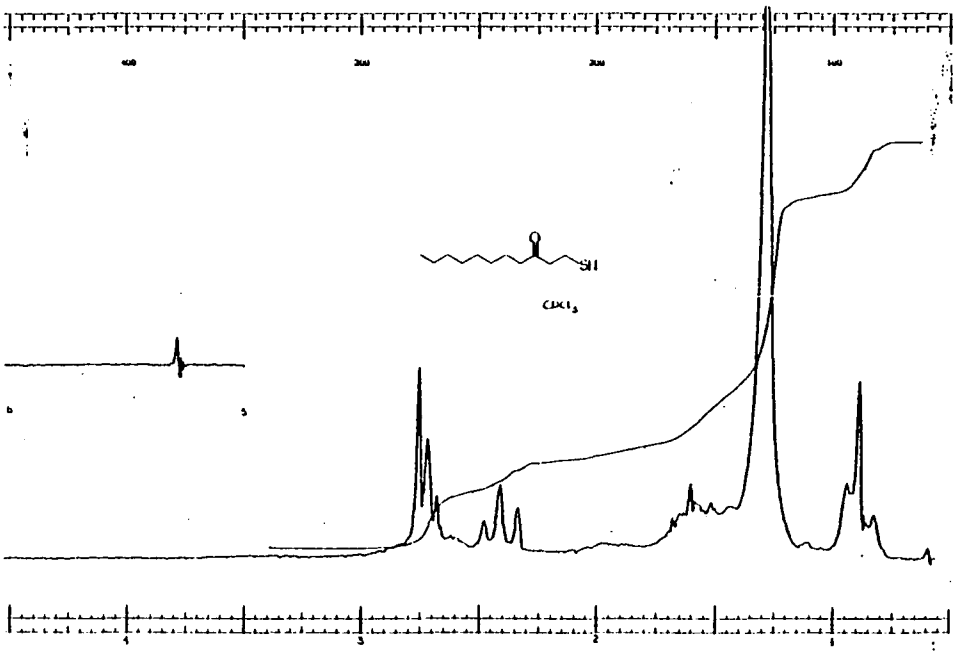


Figure III-49. Pmr spectrum ($CDCl_3$) of compound 99.

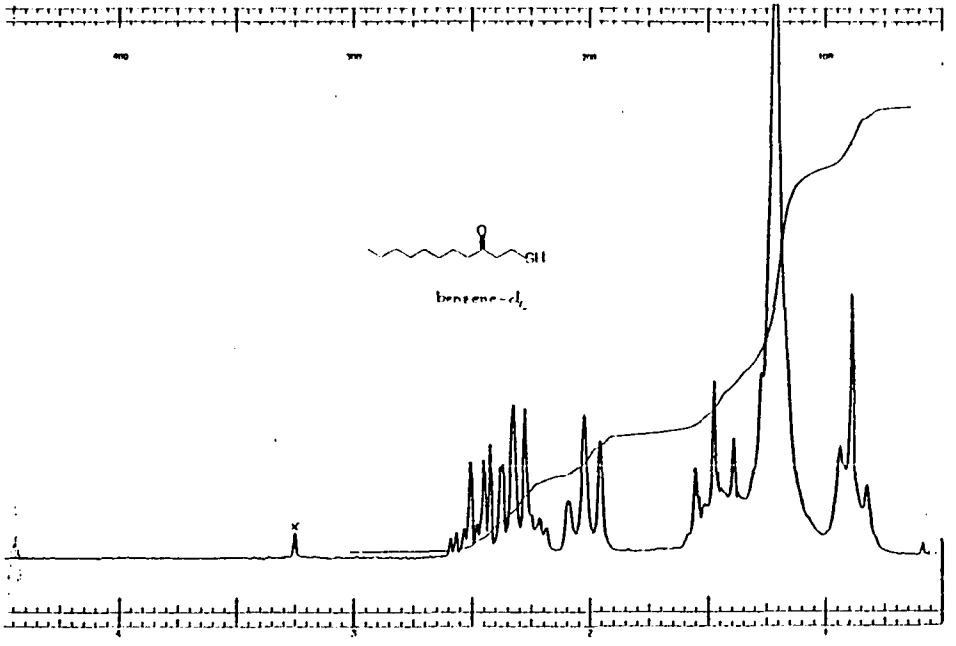


Figure III-50. Pmr spectrum (benzene-d_6) of compound 99.

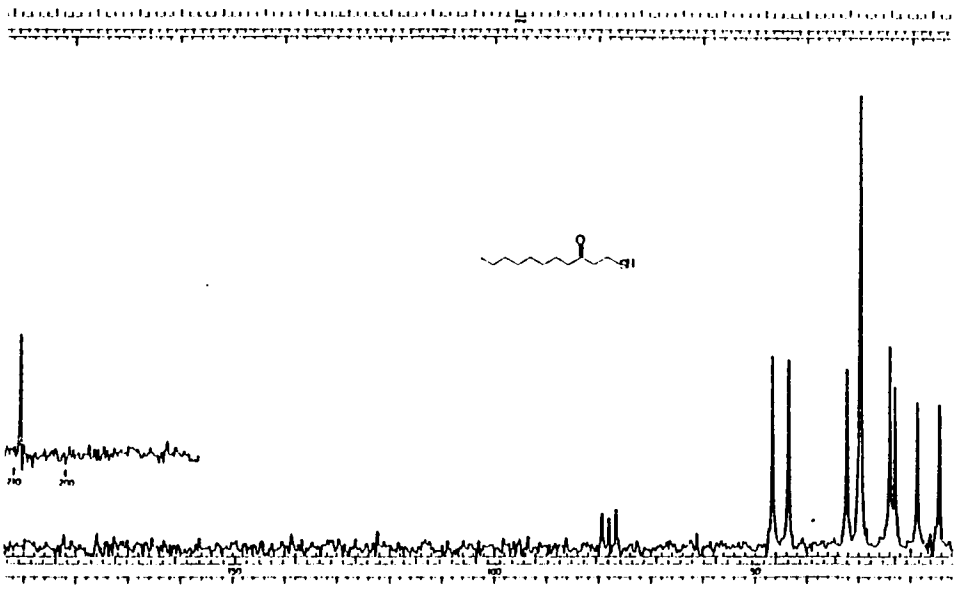


Figure III-51. Cmr spectrum ($CDCl_3$) of compound 99.

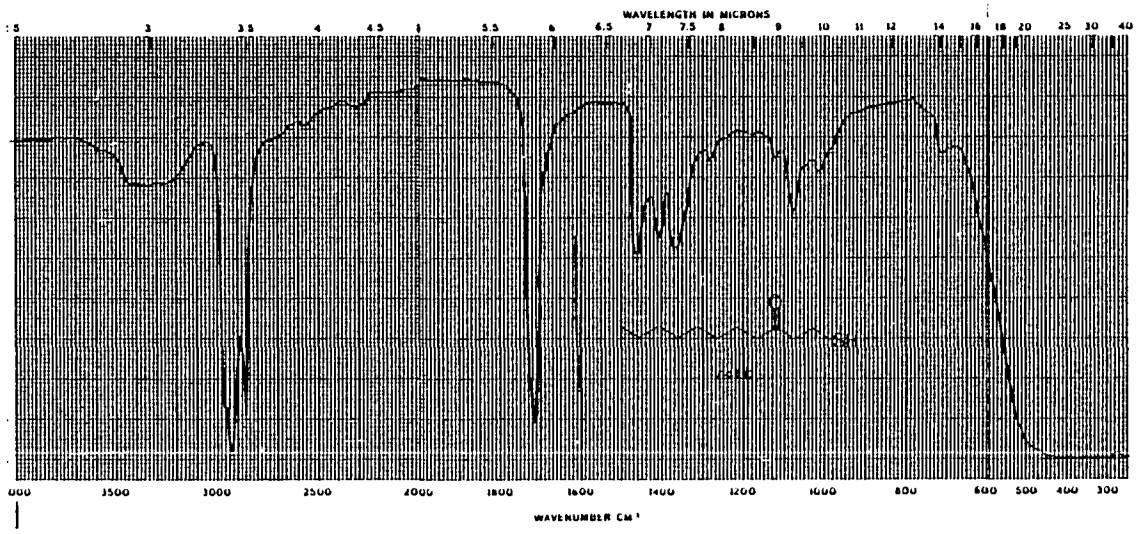


Figure III-52. Ir spectrum (neat) of compound 99.

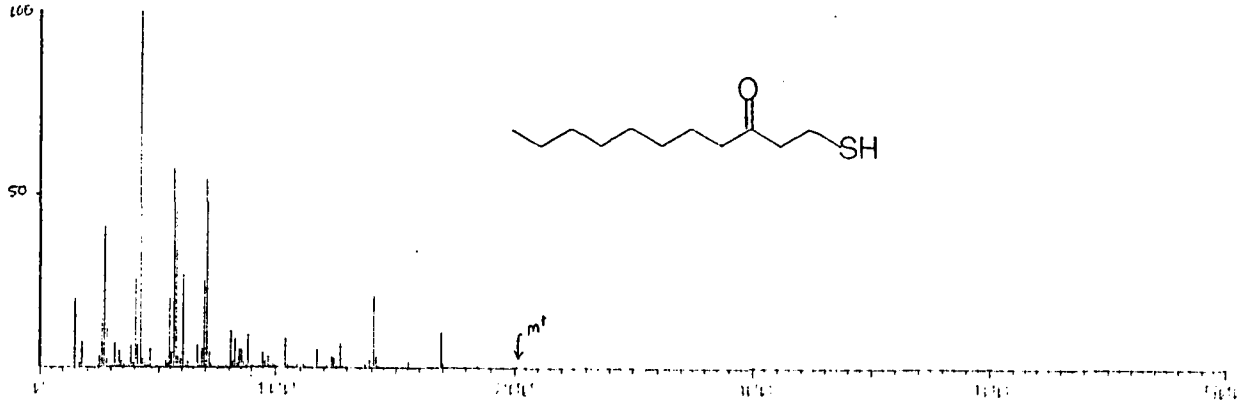


Figure III-53. Mass spectrum (70eV) of compound 99.

Asato[17] found that 100 could be formed directly by stirring mercaptan 99 with basic aluminum oxide. With this procedure pure bis-sulfide 100 was obtained in 37% yield after chromatography on Sephadex LH-20 and recrystallization from hexane. The pmr spectrum of recrystallized 100 (mp 118.0-119.5°) is very similar to the pmr spectrum of 99 but the sharp triplet of the mercaptan proton at δ1.47 is absent. The mass spectrum of 100 shows a weak molecular ion at m/e 370 that cleaves to give peaks at m/e 201 and 169 which are attributed to fragment ions 101 and 102 respectively.

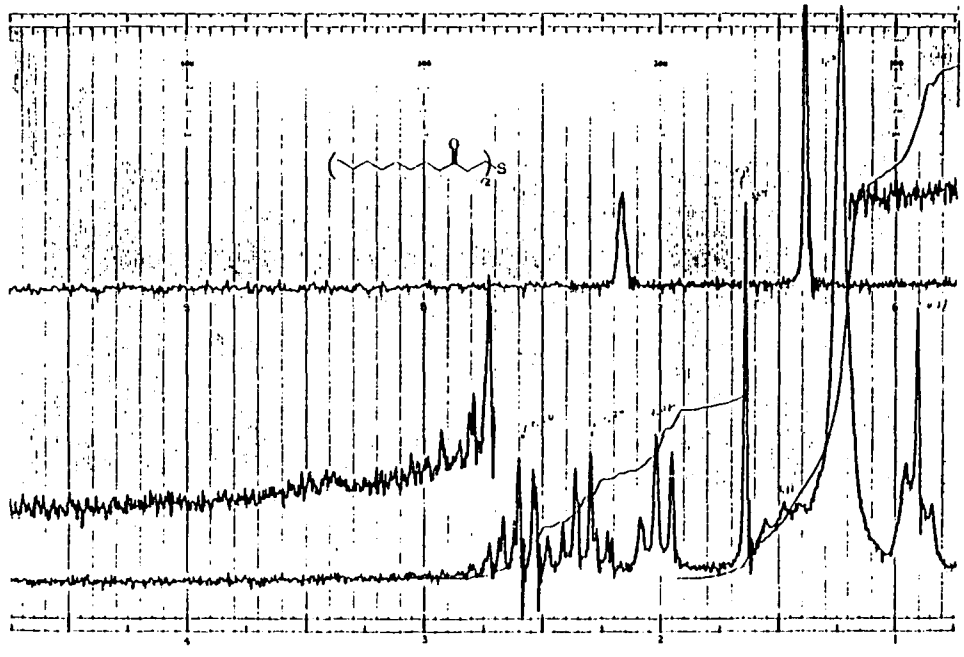
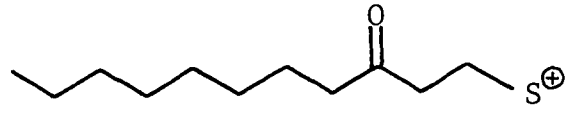
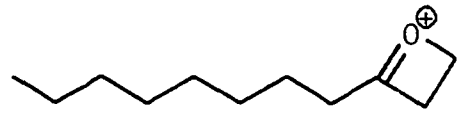


Figure III-54. Pmr spectrum (benzene-d_6) of compound 100.



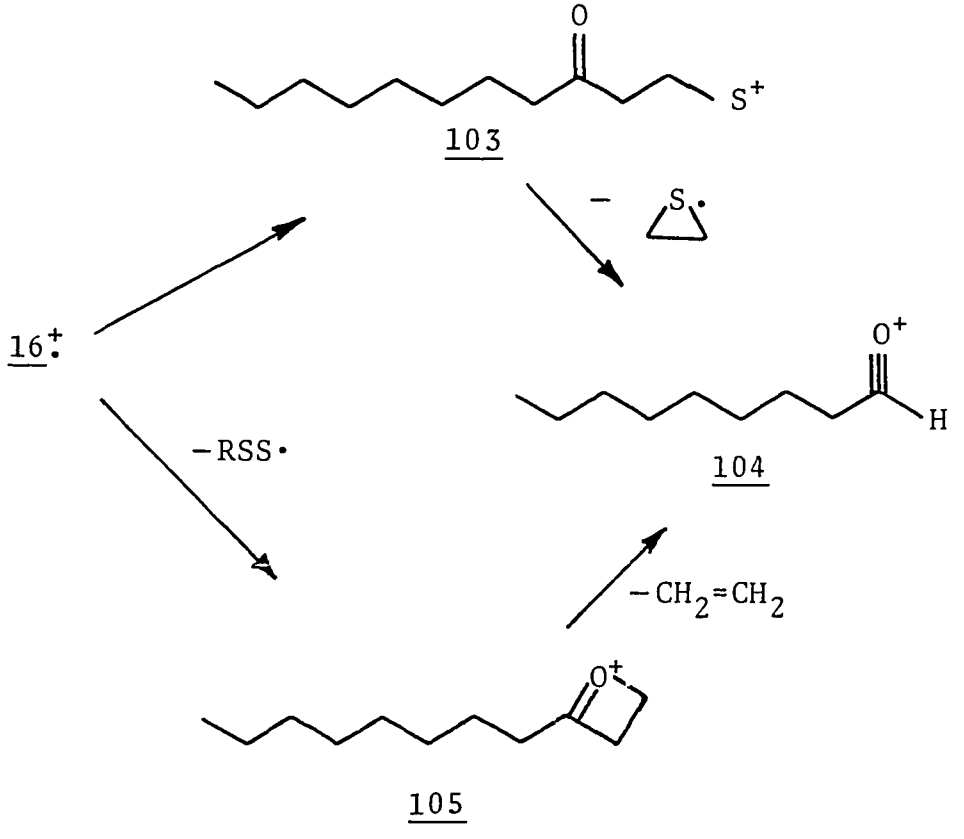
101



102

The reaction of mercaptan 99 with triethyl amine and elemental iodine in chloroform for five minutes at 0° gave bis-disulfide 16 in 39% yield.[17] In this study it was found that increasing the reaction time to one hour gave a lower yield (26%) of 16 and a 60% recovery of starting material (99). A slightly lower yield of 16

(24%) was obtained when the reaction time was increased to seven hours but in this run very little starting material was recovered. The product crystallized from hexane as colorless plates and had a melting point of 66.0-66.3° which is one degree lower than the melting point reported for the naturally occurring material.[9] The pmr spectrum of the recrystallized material was identical to that of natural 16. The mass spectrum of 16 exhibited a molecular ion at m/e 402 which decomposes to give fragment ions 103, 104 and 105 which appear at m/e 201, 141 and 169, respectively.



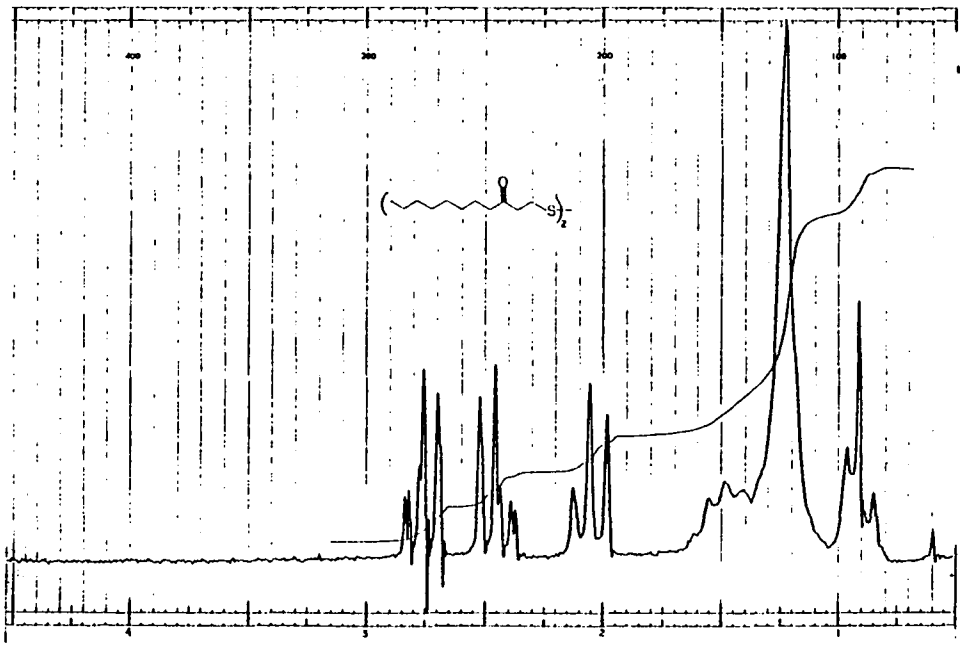


Figure III-55. Pmr spectrum (benzene-d_6) of compound 16.

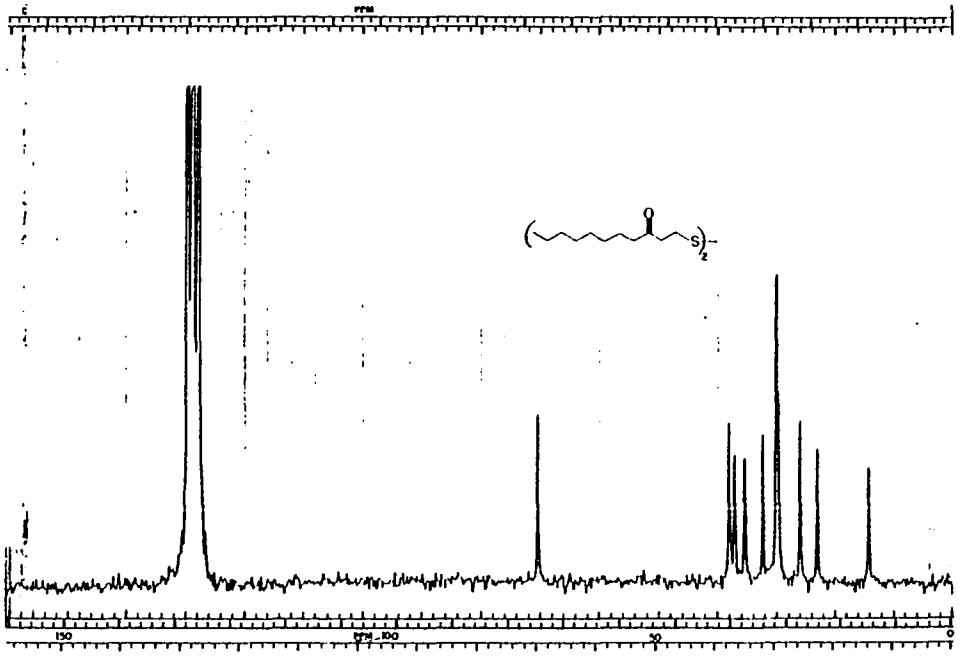


Figure III-56. Cmr spectrum (benzene-d_6) of compound 16.

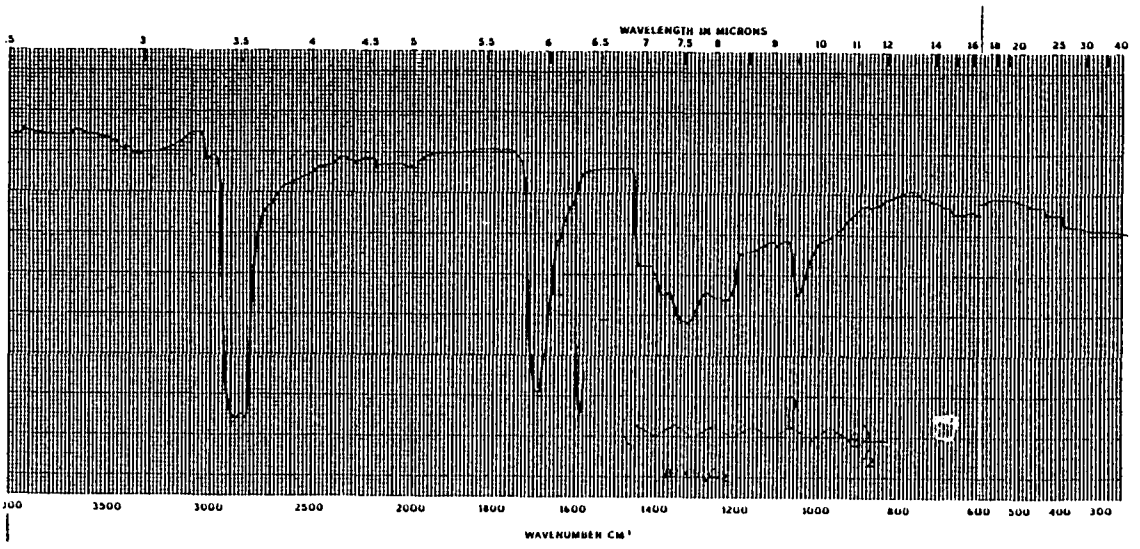


Figure III-57. Ir spectrum (CH_2Cl_2) of compound 16.

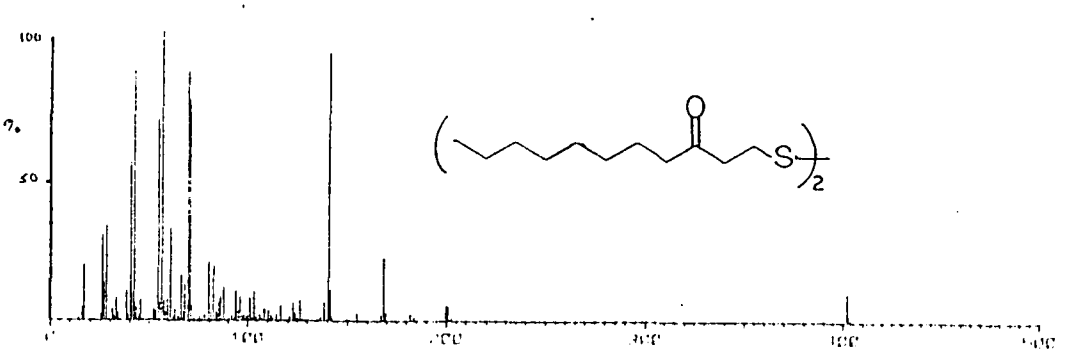


Figure III-58. Mass spectrum (70eV) of compound 16.

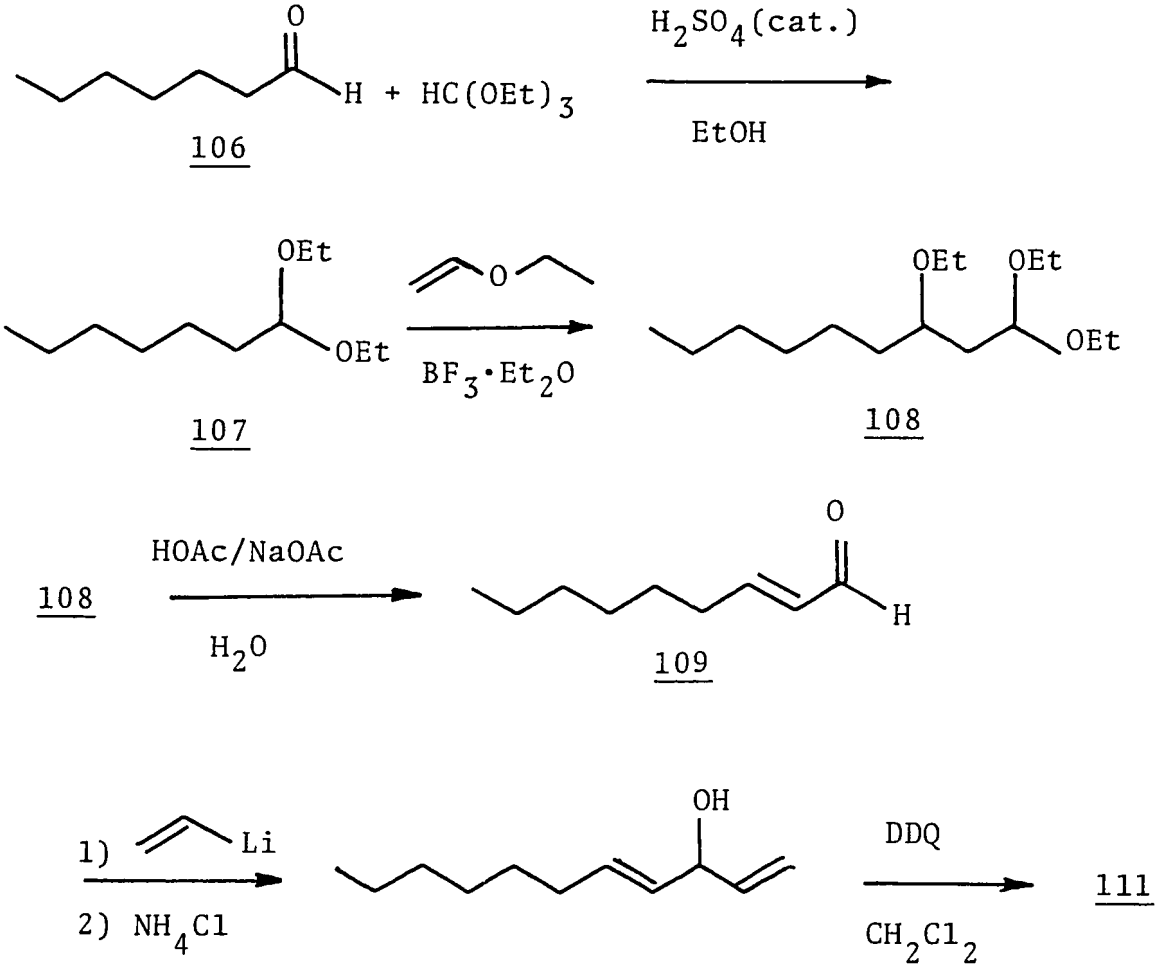
Although the various spectra of 16 showed no evidence of contamination a satisfactory combustion analysis was not obtained. Three attempts were made and in each case the samples proved to be low in carbon and high in hydrogen. These results suggest that the crystals of 16 may either adsorb water from the atmosphere or form a partial hydrate during the recrystallization process.

2. 3-Hexyl-4,5-dithiacycloheptanone (15) and S-(trans-3-Oxoundec-4-enyl) Thiolacetate (14)

The synthesis of cyclic disulfide 15 and thiolacetate 14 was achieved by Asato[11] as outlined in Scheme III-7. This work was repeated for this study to obtain additional spectral data for the intermediate compounds.

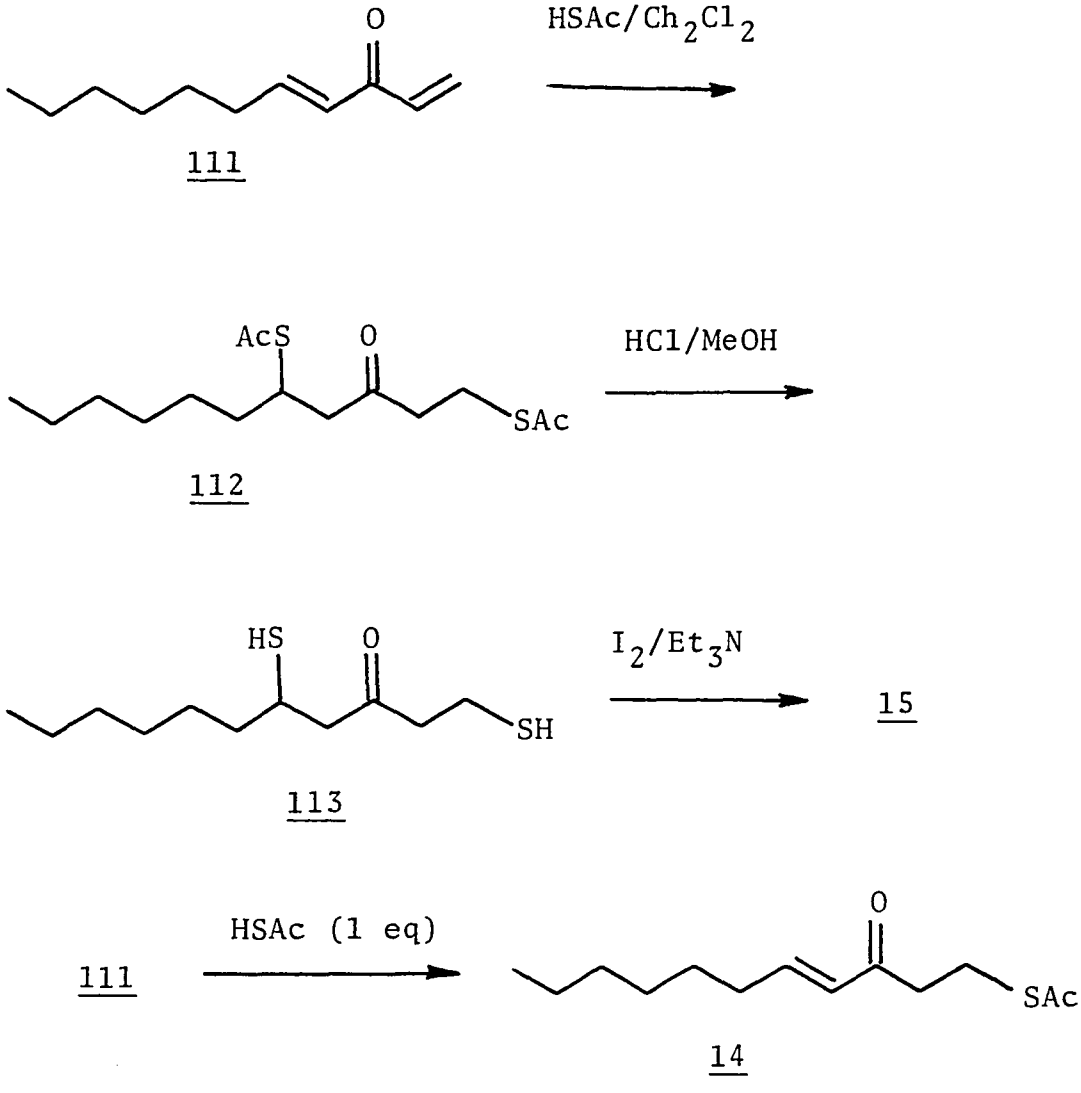
Scheme III-7.

Synthesis of Compounds 14 and 15



Scheme III-7. (Continued)

Synthesis of Compounds 14 and 15



Aldehyde 109 was prepared by buffered hydrolysis of 1,1,3-triethoxynonane (108)[37] and was isolated in 39% overall yield from n-heptanal (106). The addition of vinyl magnesium chloride to 109 proceeded to give dienol 110 in poor yield (~ 10%) presumably due to difficulty

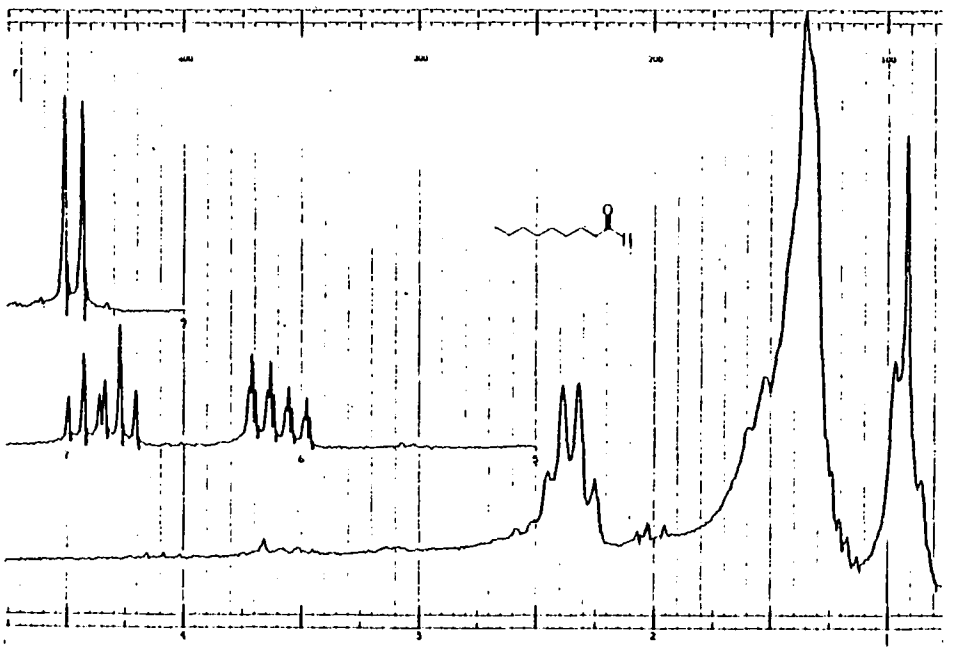
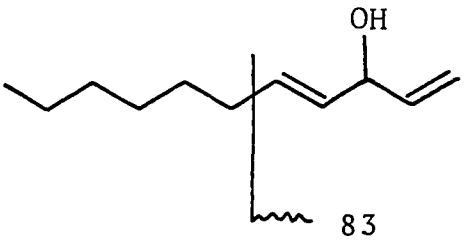


Figure III-59. Pmr spectrum ($CDCl_3$) of compound 109.

in forming the Grignard reagent. Reacting 109 with vinyl lithium in THF at -78° increased the yield of 110 to 91%. The pmr spectrum of the distilled product exhibits a broad triplet (J=6 Hz) at δ4.54 for the alcohol methine and signals characteristic of the n-hexyl side chain. The vinyl group gives an AMX pattern with a complex X portion centered at δ5.7 that also contains signals for the two protons of the trans-double bond. The AM protons are allylically coupled to the alcohol methine and appear at δ5.20 (dt, J=2 and 17 Hz) and 5.06 (dt, J=2 and 10 Hz) respectively. The mass spectrum of 109 shows a weak molecular ion at m/e 168 which readily loses n-hexyl radical to give the base peak at m/e 83.



110

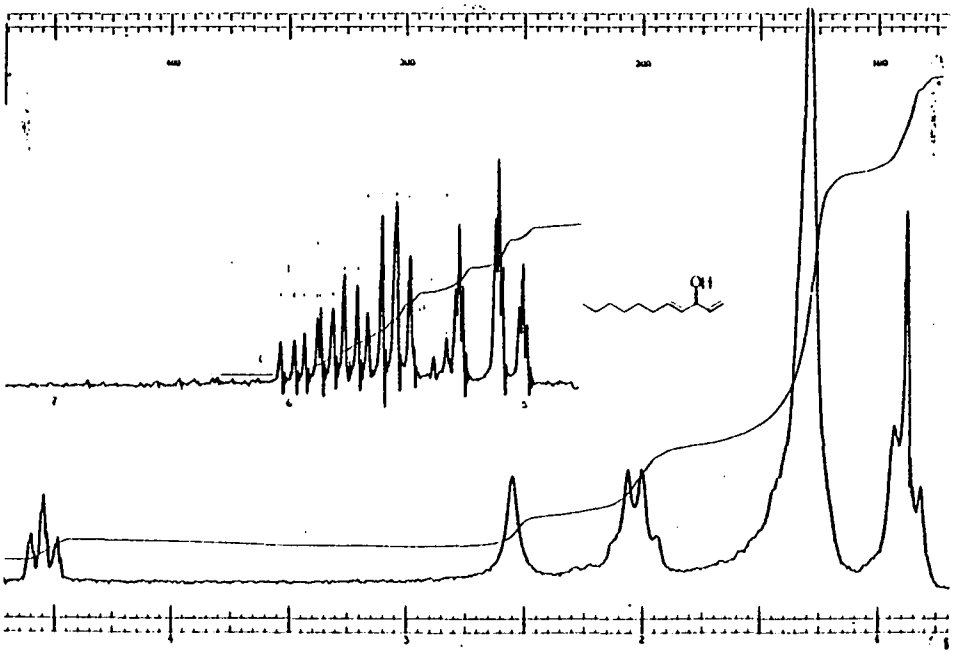


Figure III-60. Pmr spectrum ($CDCl_3$) of compound 110.

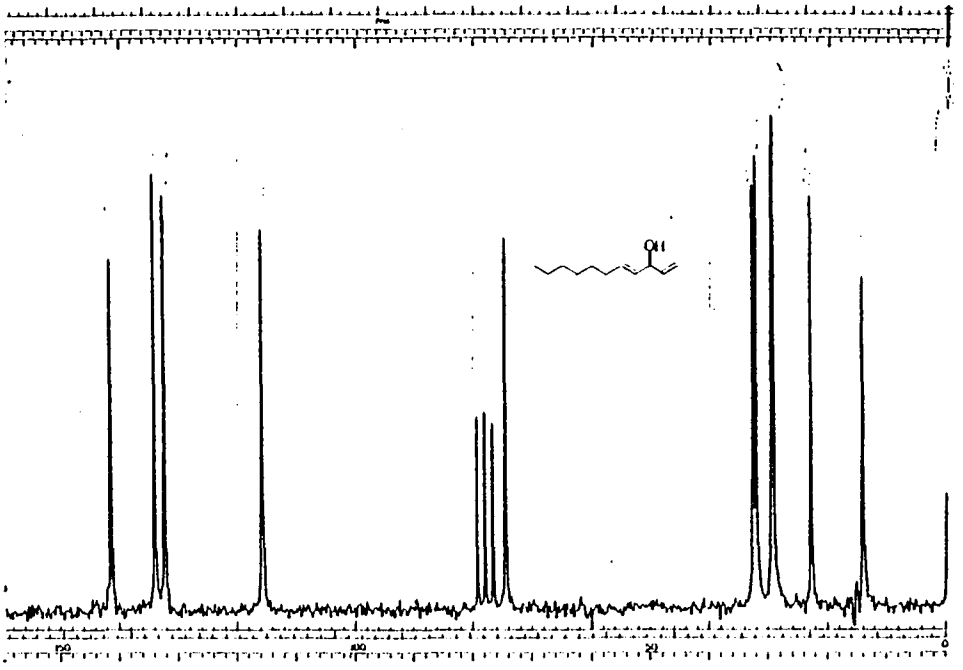


Figure III-61. Cmr spectrum ($CDCl_3$) of compound 110.

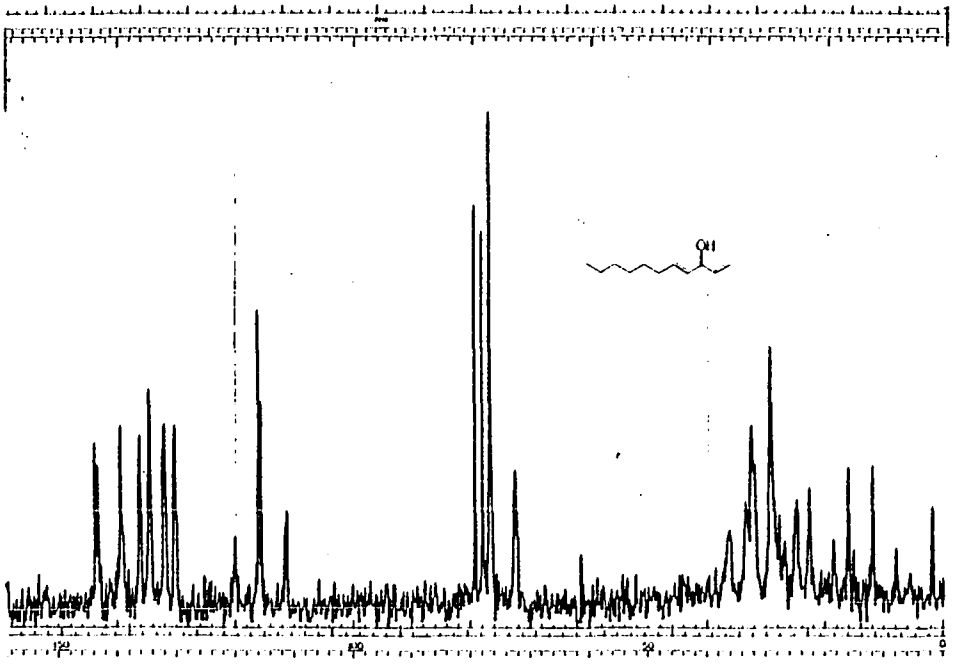


Figure III-62. Cmr off-resonance spectrum ($CDCl_3$) of compound 110.

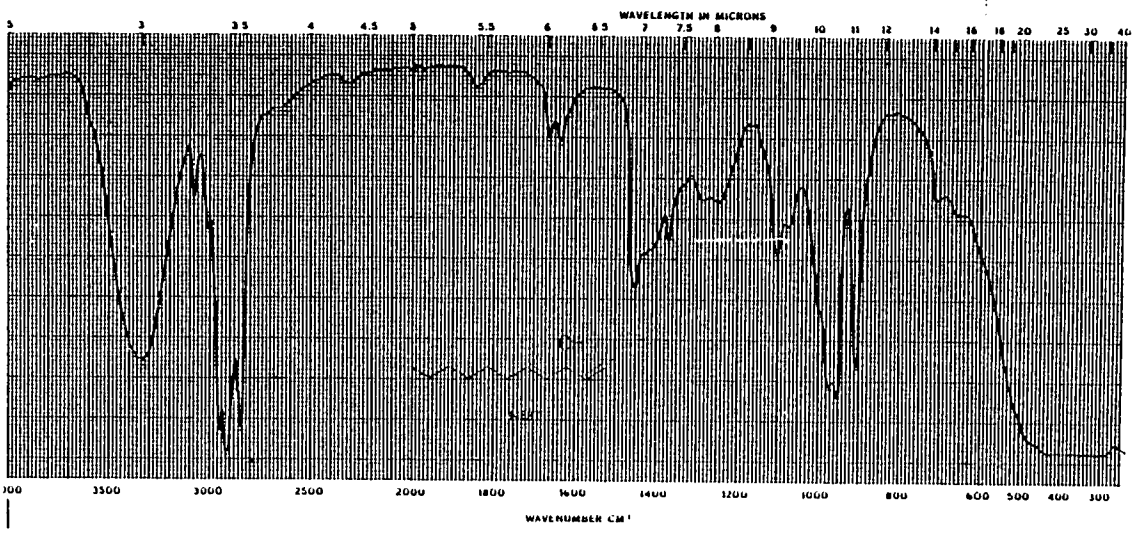


Figure III-63. Ir spectrum (neat) of compound 110.

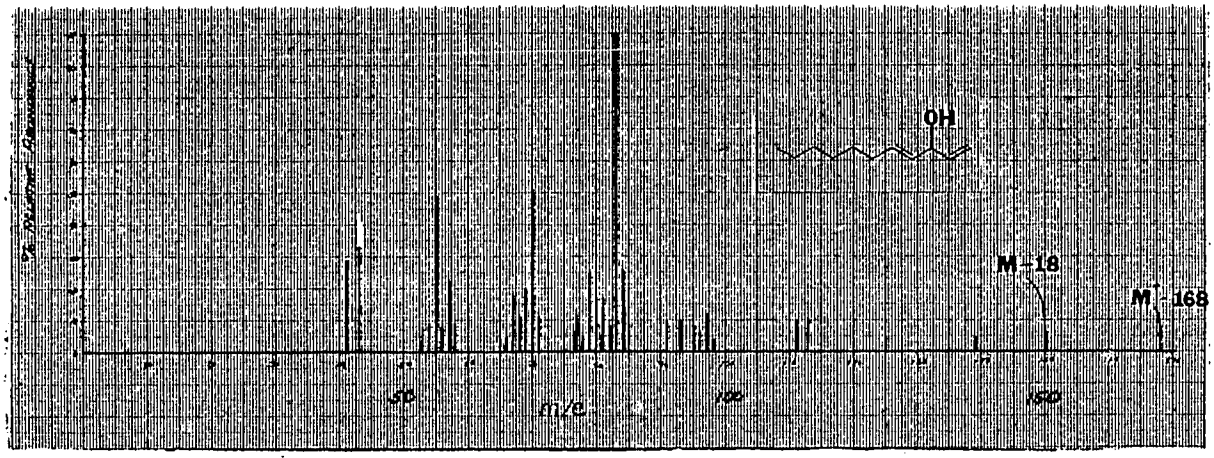


Figure III-64. Mass spectrum (70eV) of compound 110.

Alcohol 110 was inert to oxidation with Chloranil and was only partially oxidized to cross-conjugated ketone 111 with activated manganese dioxide.[17] As with the conversion of 97 to 98 oxidation of 110 was best

achieved with DDQ in methylene chloride at room temperature. The oxidation was found to go to completion within 45 minutes with longer reaction times leading to polymerization of the product (111). Substantial product loss through polymerization was also observed when attempts were made to purify it by vacuum distillation. The purified ketone was highly unstable as a neat liquid and rapidly decomposed even when stored at -20°. For this reason 111 could not be fully characterized but did give satisfactory pmr and cmr spectra. The former shows a complex olefinic region with vinyl doublets of doublets at δ5.75 (J=2 and 10 Hz, A part), 6.62 (J=2 and 18 Hz, M part) and 6.60 (J=10 and 18 Hz, X part). The proton of the trans-double bond adjacent to the carbonyl group appears as a doublet of triplets (J=1.5 and 15.5 Hz) at δ6.31. The remaining trans-olefinic proton (β to the carbonyl group) resonates as a doublet of triplets (J=6.5 and 15.5 Hz) at δ6.93.

The pmr spectrum of 111 after passage of the crude product through a neutral alumina column was identical to that of distilled 111 and it was therefore decided to use this material without further purification for the subsequent formation of 112. The addition of excess

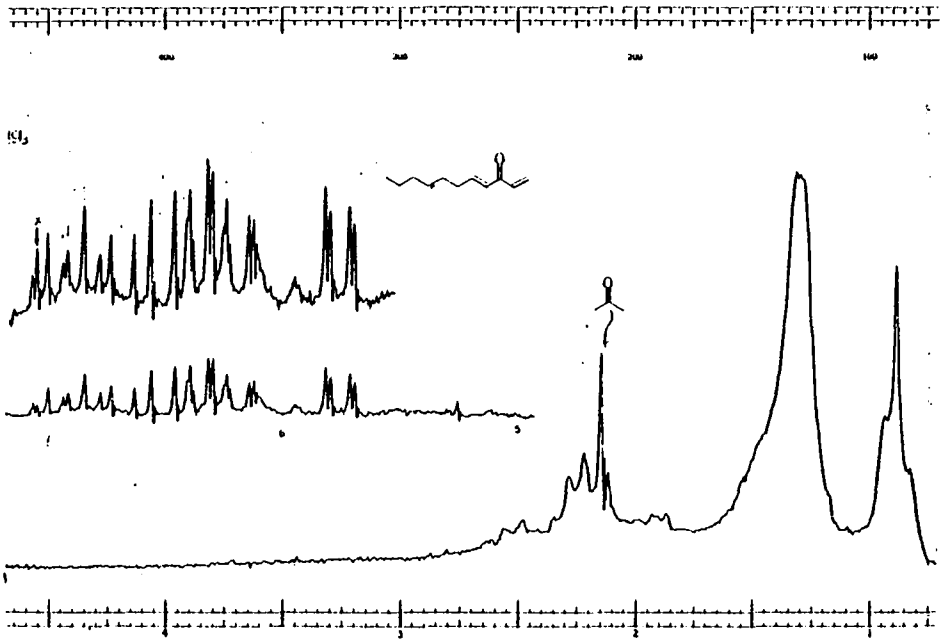


Figure III-65. Pmr spectrum ($CDCl_3$) of compound 111.

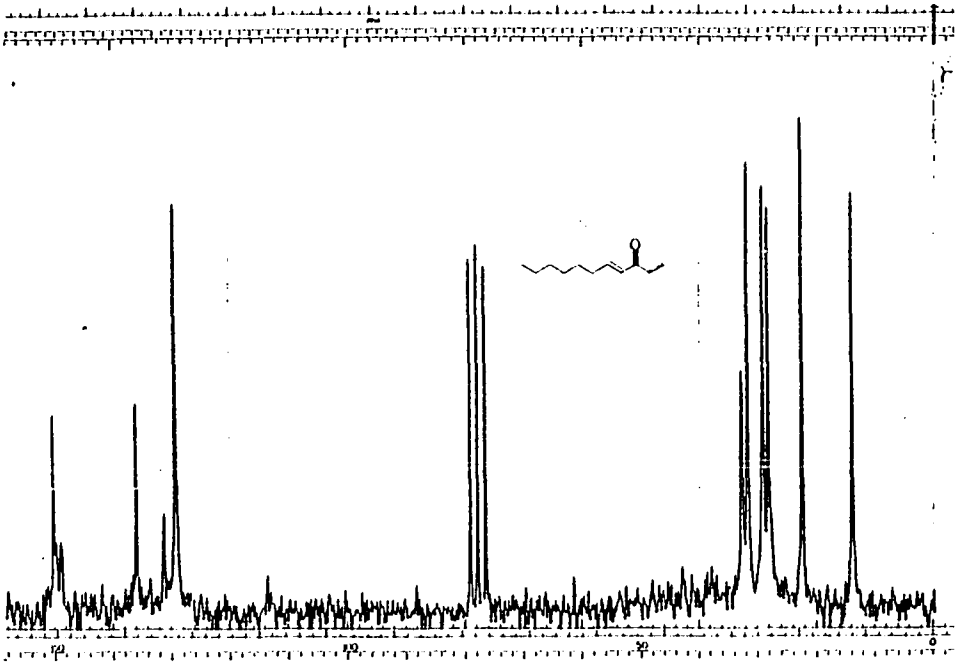


Figure III-66. Cmr spectrum ($CDCl_3$) of compound 111.

thiolacetic acid to 111 proceeded smoothly at 4° to give 112 in 75% yield after purification by column chromatography on Sephadex LH-20. The pmr spectrum of the purified product exhibits a pentet (J=6 Hz) at δ3.80 for the thiolacetoxy methine and a triplet (J=6 Hz) at 3.03 for the thiolacetoxy methylene protons. The infrared spectrum shows a broad carbonyl absorption centered at 1700 cm^{-1} and the mass spectrum contains a weak molecular ion at m/e 318.

When 112 was treated with a small amount of 3% methanolic HCl in refluxing chloroform for 1.5 hours a complex mixture of polymeric products resulted.[17]

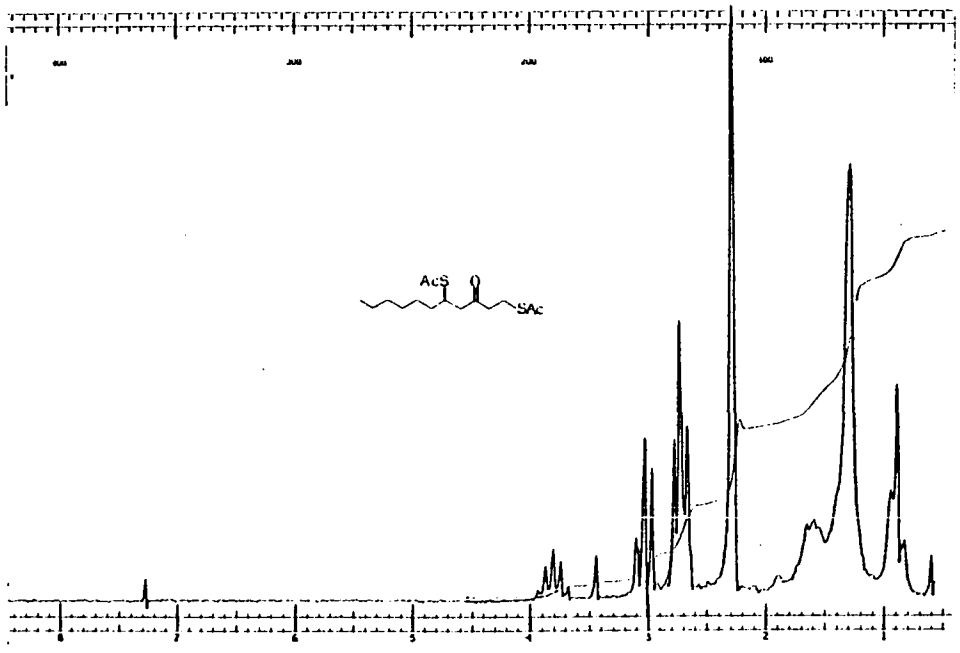


Figure III-67. Pmr spectrum ($CDCl_3$) of compound 112.

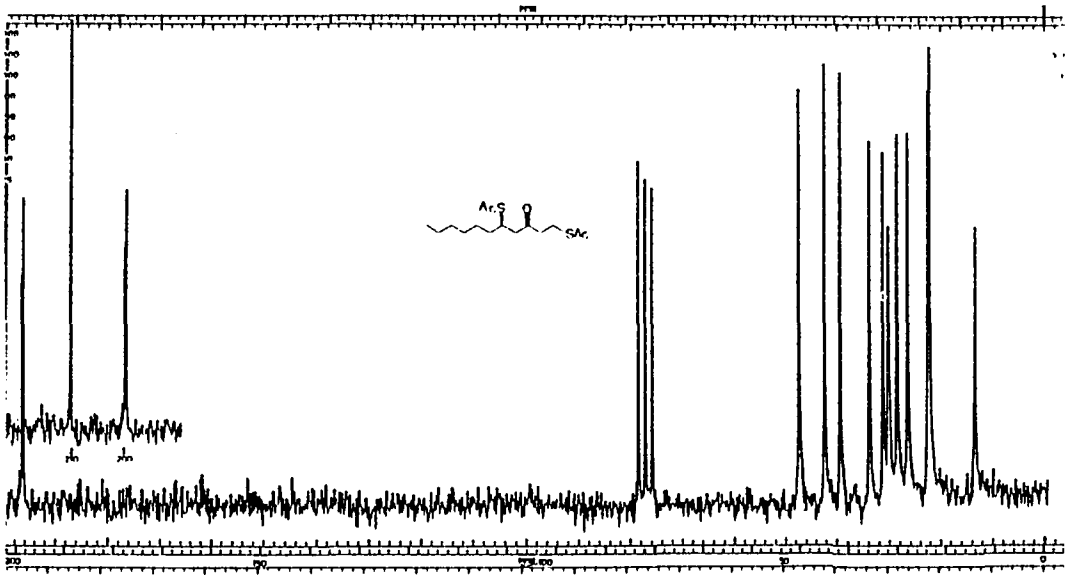


Figure III-68. Cmr spectrum ($CDCl_3$) of compound 112.

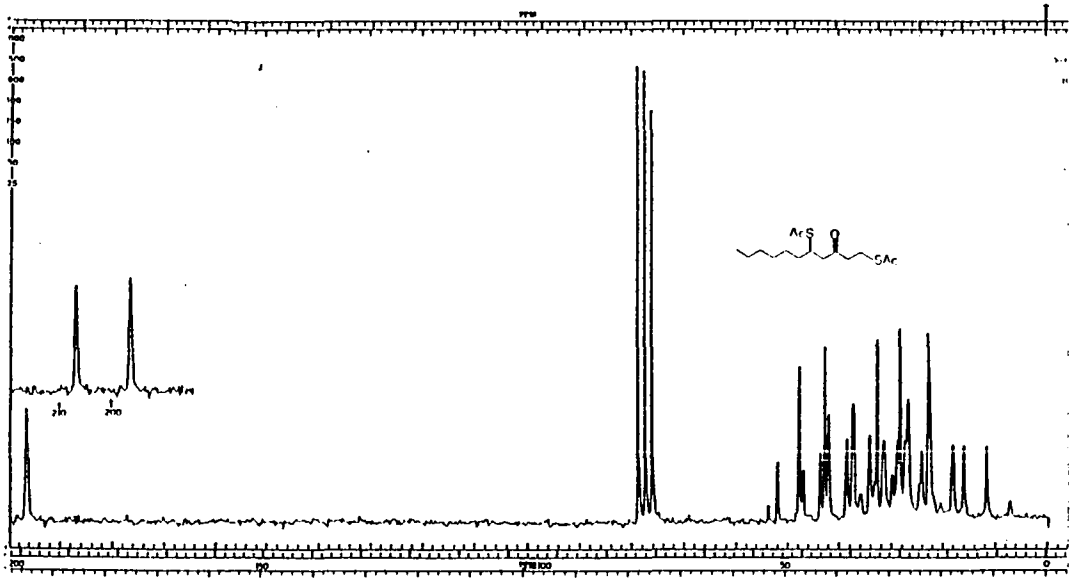


Figure III-69. Cmr off-resonance spectrum ($CDCl_3$) of compound 112.

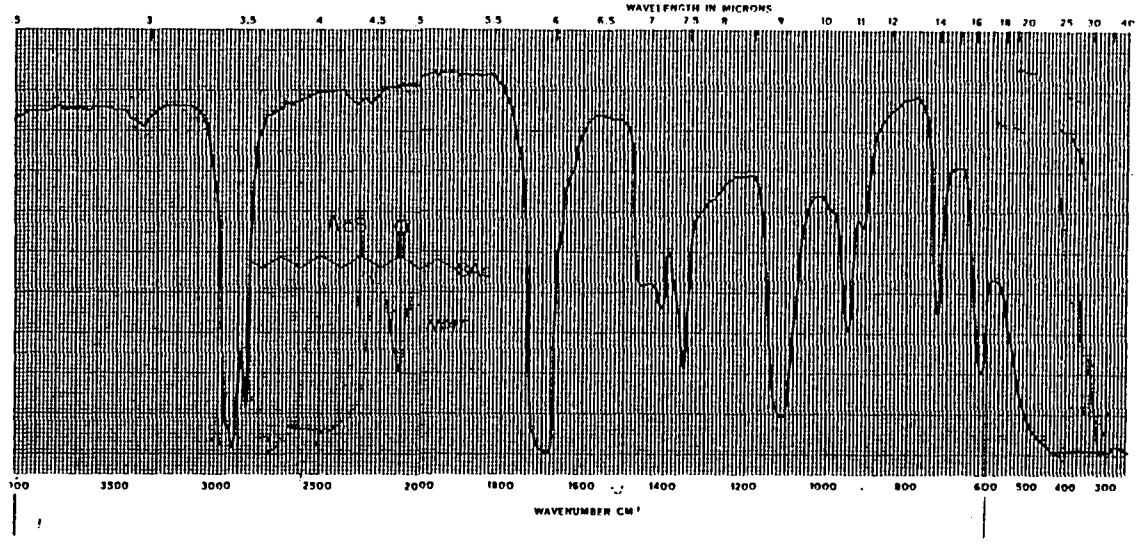


Figure III-70. Ir spectrum (neat) of compound 112.

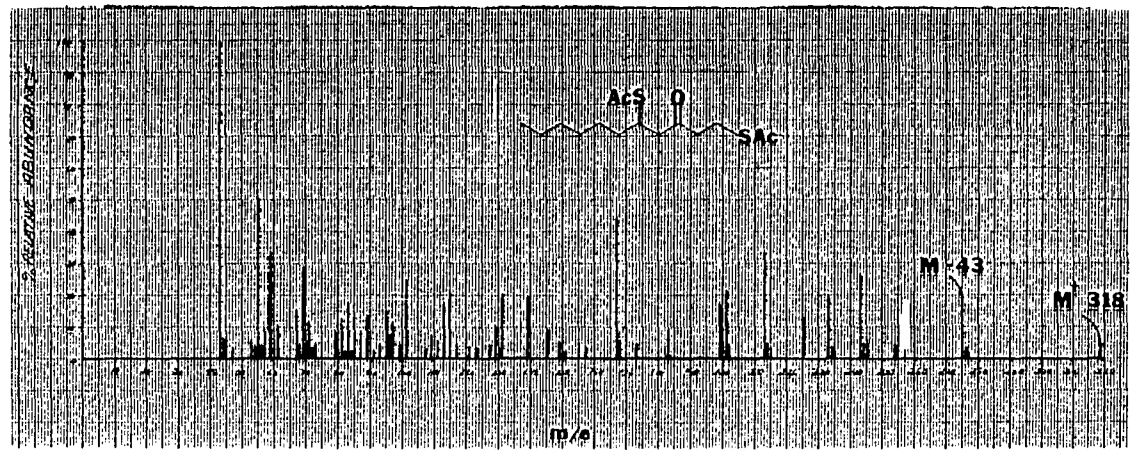
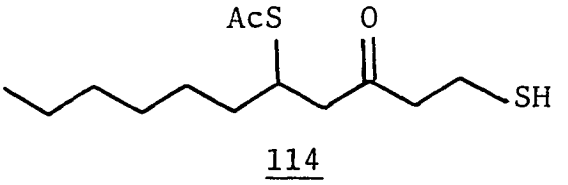
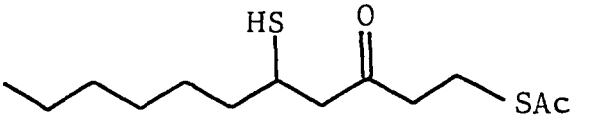


Figure III-71. Mass spectrum (70eV) of compound 112.

Repeating the experiment by stirring 112 with 3% methanolic HCl without a cosolvent for four days at room temperature resulted in a crude product that consisted of 19% polymeric coupling products, 41% partially



114



115

hydrolyzed 109 (114 and 115), 12% starting material (112) and 23% desired 113. Purification of this mixture on a column of Sephadex LH-20 resulted in a 32% yield of 113. The pmr spectrum of purified 113 shows an absence of the thiolacetate methyl singlet and contains a sharp triplet (J=7.5 Hz) at δ2.04 for the C-1 mercaptan proton with

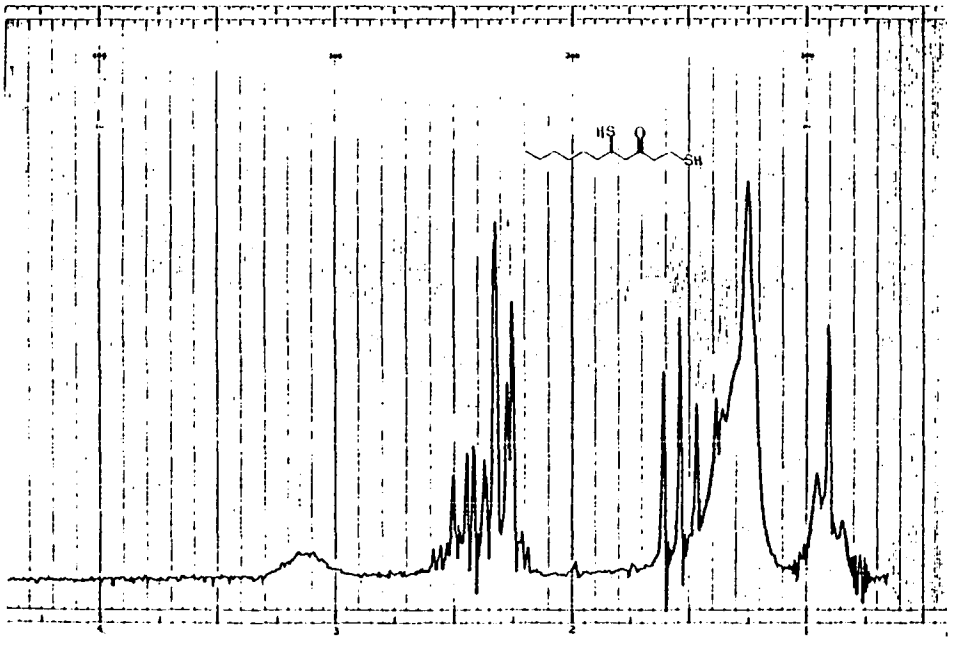
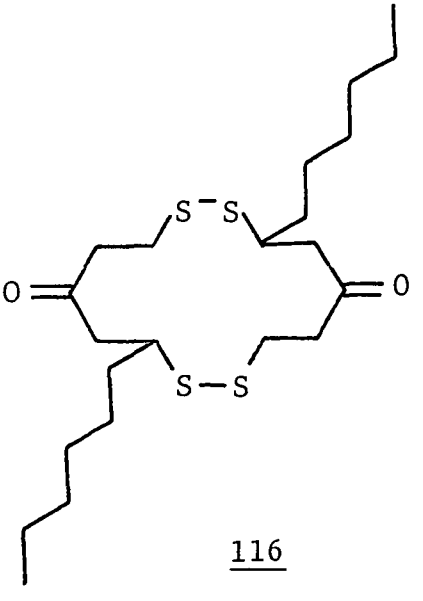


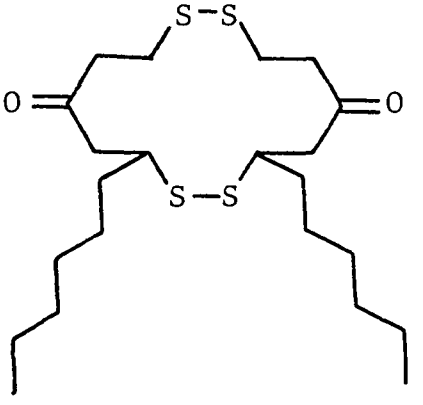
Figure III-72. Pmr spectrum (benzene-d_6) of compound 113.

the methylene enevelope (δ1.25 partially obscuring the C-5 mercaptan proton.

The reductive cyclization of 113 with iodine and pyridine in ether was carried out by Asato[17] and proceeded to give 60-70% yields of disulfide 15 whose spectral properties, with the exception of optical rotation, were identical to those of the naturally occurring material.[11] Also isolated from the reaction mixtures were small amounts (6-10%) of solid materials whose complex pmr spectrum implied a mixture of compounds. Chromatography on an analytical silica gel thin layer plate with 3:2 chloroform/heptane resulted in two closely spaced spots but the mixture could not be separated by preparative layer chromatography. These data along with a weak molecular ion at m/e 464 ($C_{22}H_{40}O_6S_4$) in the mass spectrum implied the side product to be a mixture of isomeric disulfides 116 and 117.



116



117

Using the conditions for the preparation of 112 the reaction of 111 with one equivalent of thiolacetic acid proceeded smoothly to give a 67% yield of 14 after purification by column chromatography with Sephadex LH-20. The various spectra of synthetic 14 were identical to those of the natural material.

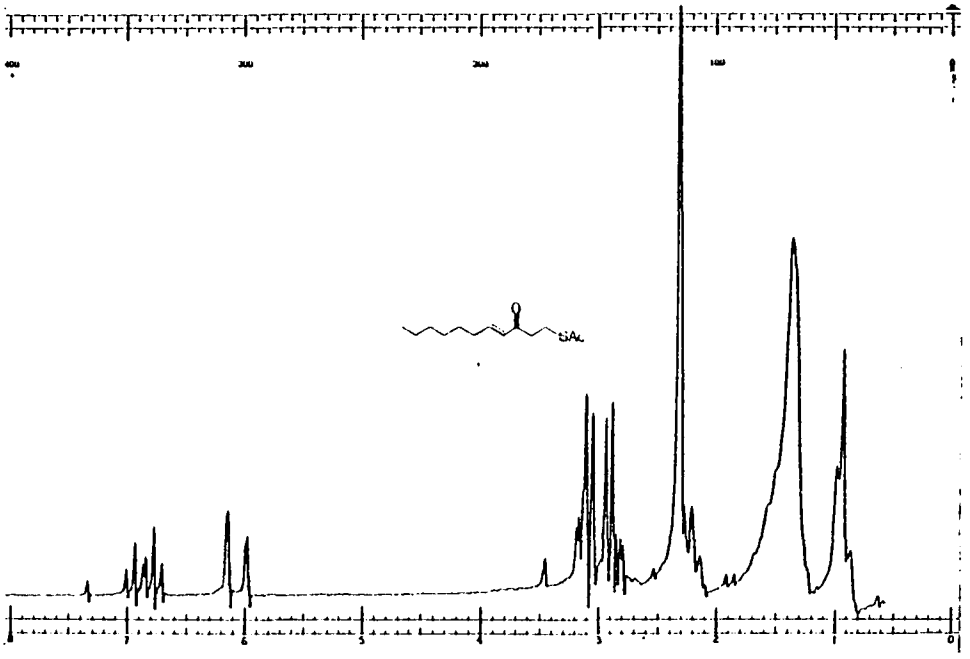


Figure III-73. Pmr spectrum ($CDCl_3$) of compound 14.

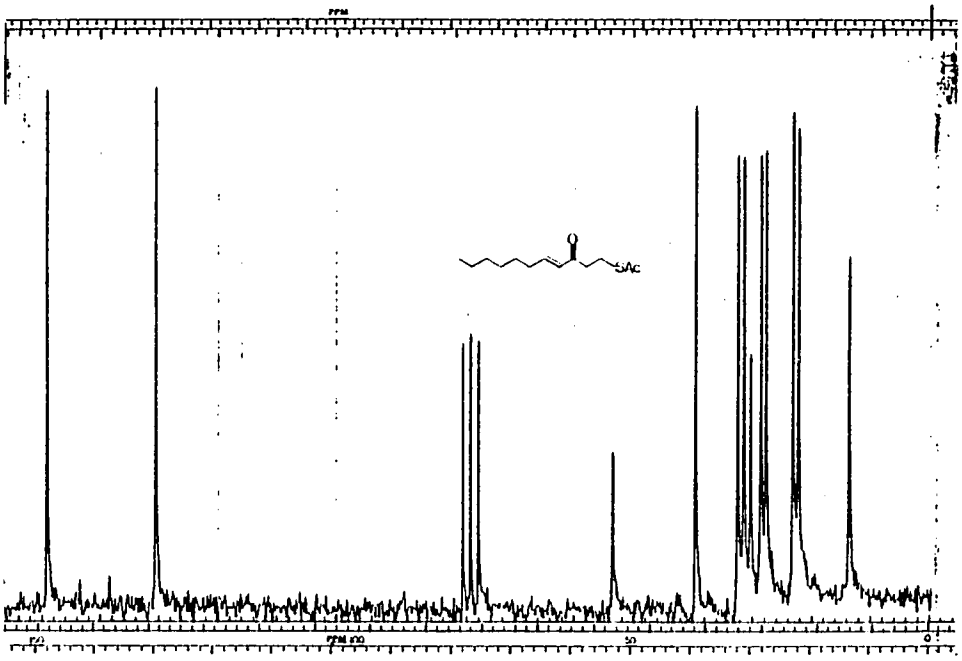


Figure III-74. Cmr spectrum ($CDCl_3$) of compound 14.

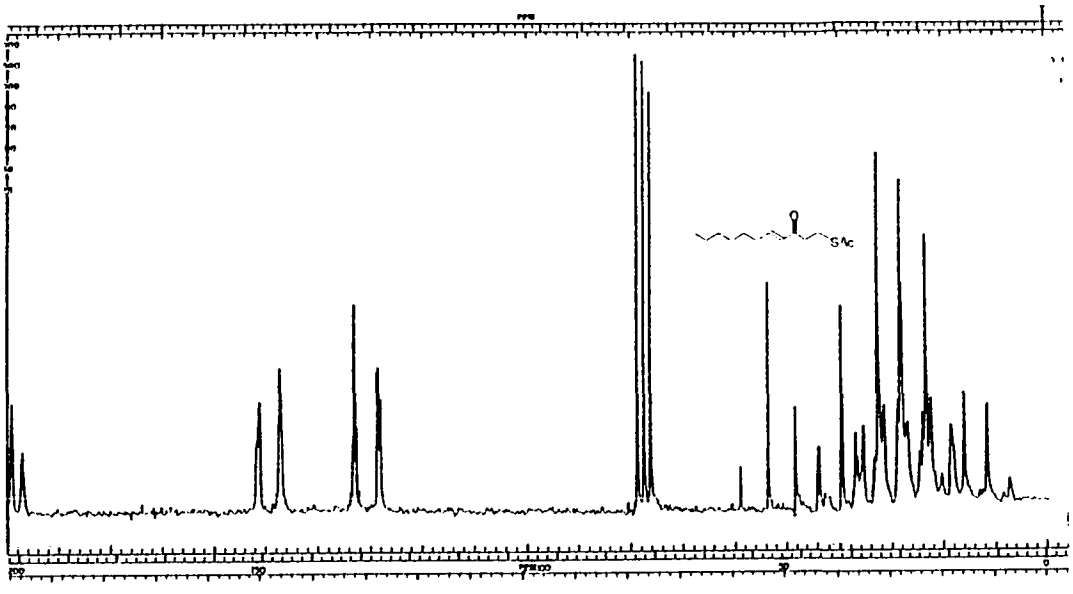


Figure III-75. Cmr off-resonance spectrum ($CDCl_3$) of compound 14.

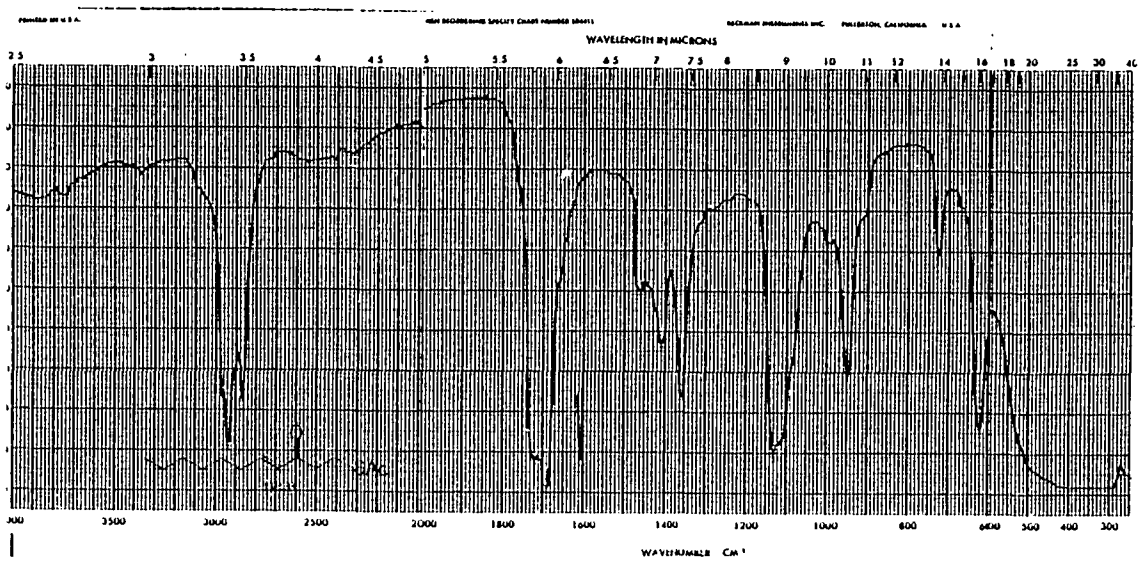


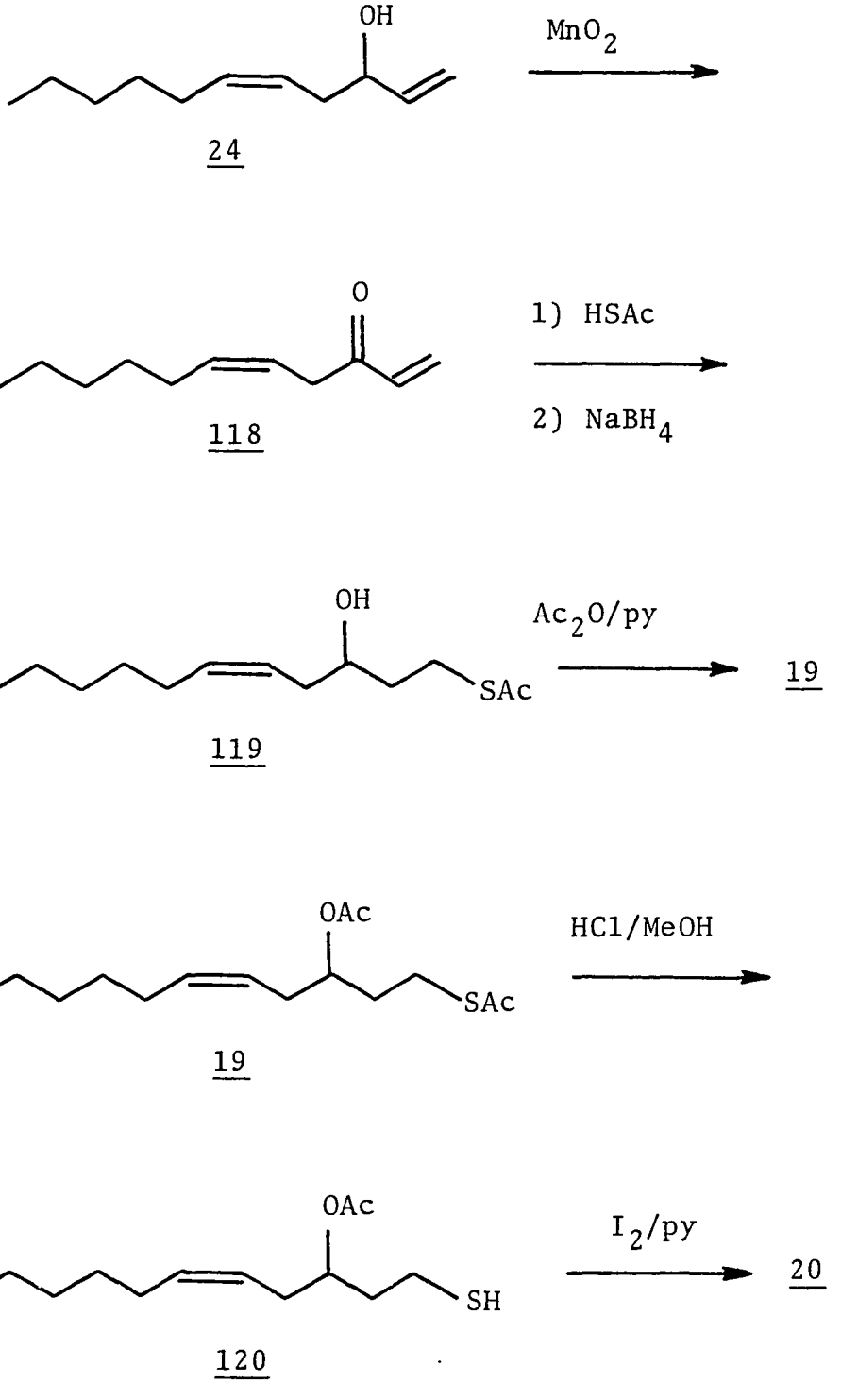
Figure III-76. Ir spectrum (neat) of compound 14.

3. Attempted Synthesis of S-(cis-3-Acetoxyundec-5-enyl) Thiolacetate (19) and Bis-(cis-3-Acetoxy-undec-5-enyl) Disulfide (20)

The synthesis of compounds 19 and 20 was first attempted by Asato[17] by the route outlined in Scheme III-8. Only one attempt was made to oxidize 24 with manganese dioxide and resulted in a quantitative recovery of starting material. Although attractive from a biosynthetic standpoint Scheme III-8 was not reinvestigated for this study due to difficulties encountered in obtaining large amounts of 24 (see page 225). In addition, it was feared that migration of the Δ^5-cis-double bond of 118 would be catalyzed by either manganese dioxide or the acidic conditions present during the addition of thiolacetic acid (118 → 119).

Scheme III-8.

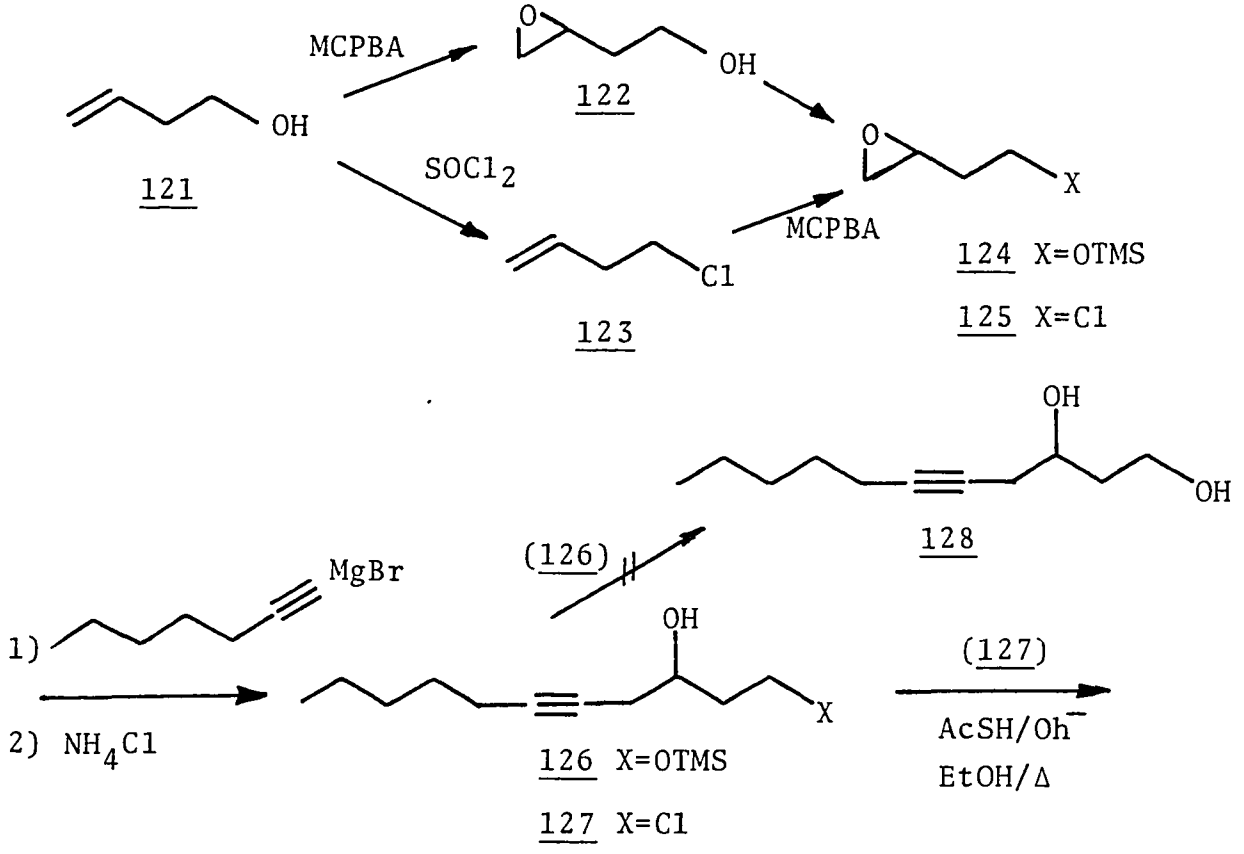
Attempted Synthesis of Compounds 19 and 20 from Dienol 24



Scheme III-9 was also designed by Asato and was much more successful than Scheme III-8. The reaction of 3-buten-1-ol (121) with MCPBA gave a 30% yield of epoxide 122 which was silylated to give 124 in 67% yield.[17] The addition of heptynyl magnesium bromide to 124 gave an oil that was presumed to be 127 but hydrolysis of the crude product by heating in aqueous methanol did not

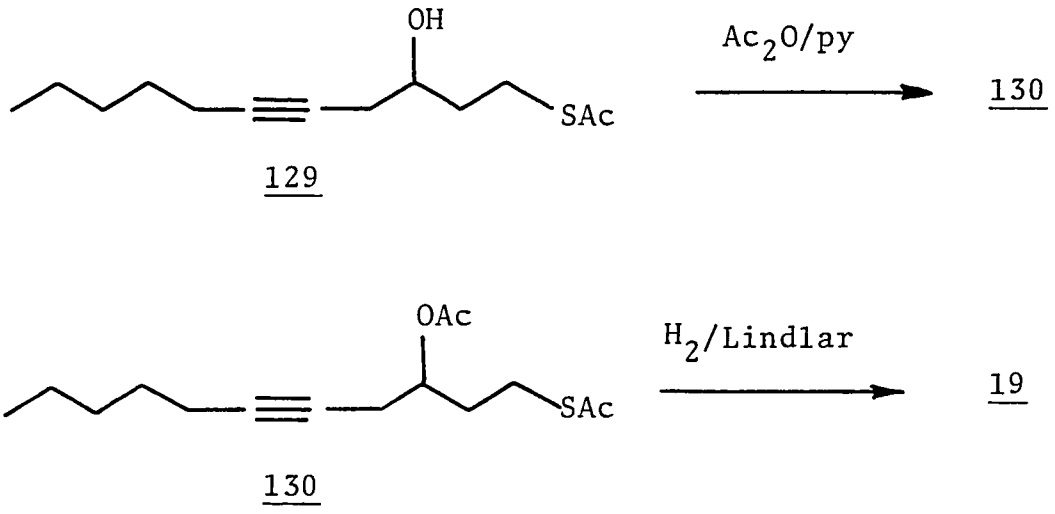
Scheme III-9.

Attempted Synthesis of Compounds 19 and 20 from Compound 121

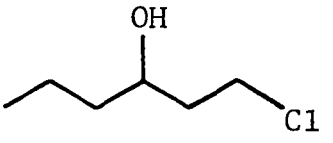


Scheme III-9. (Continued)

Attempted Synthesis of Compounds 19 and 20 from Compound 121



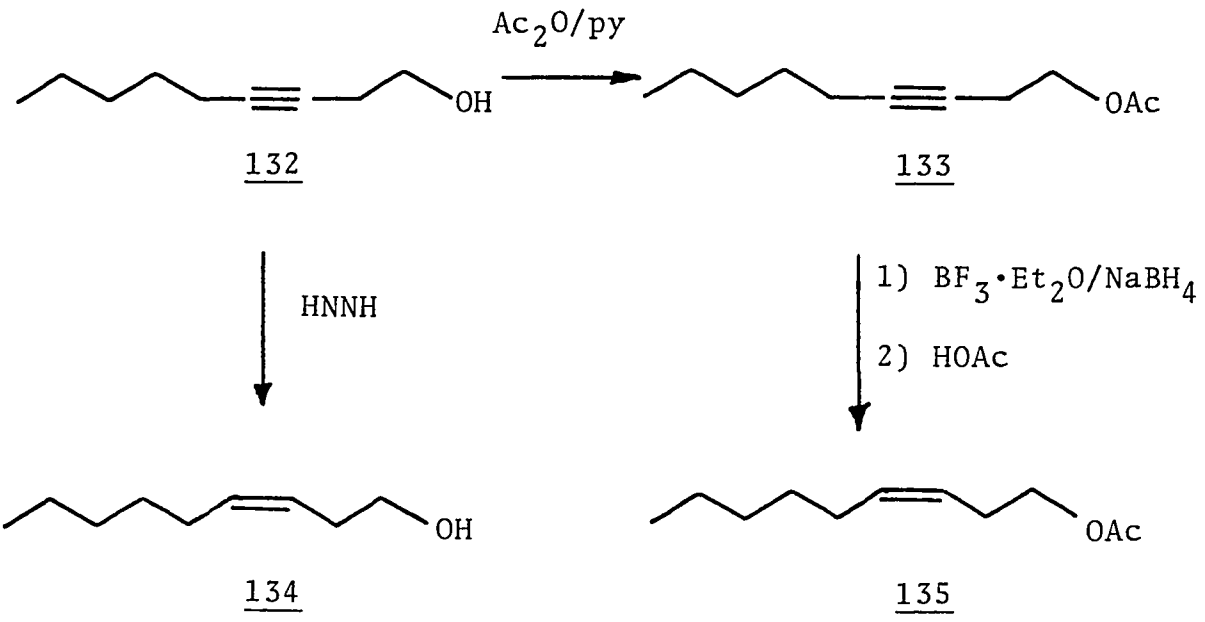
give diol 128. In a slightly different approach 123 was prepared from 121 in 76% yield by the procedure of Roberts[38] and then converted to epoxide 125 in 68% yield with MCPBA in methylene chloride. The crude product isolated from the reaction of heptynyl magnesium bromide and 121 at room temperature was vacuum distilled to give a large amount of by-product instead of the expected chloroacetylene 127. Asato[17] concluded that the Grignard reagent (ethyl magnesium bromide) reacted with 125 before



131

the formation of the acetylide was complete and therefore the by-product was presumed to be 131. The pot residue from the vacuum distillation was found to contain a small amount of the desired 127 and this was reacted crude with thiolacetic acid in basic ethanol solution to give 129. Acetylation of crude 129 gave 130 which could not be reduced to 19 with Lindlar's catalyst. Apparently the presence of the single sulfur atom in 130 was sufficient to completely poison the catalyst and prevent hydrogenation.

Since Scheme III-9 came within one step of giving the desired 19 it was decided for this study to explore alternate methods of reducing the triple bond of 130 using homogeneous reagents. Only a small amount of 130 remained on hand so for these studies model compound 133 was prepared from the commercially available 3-nonyn-1-ol (132).



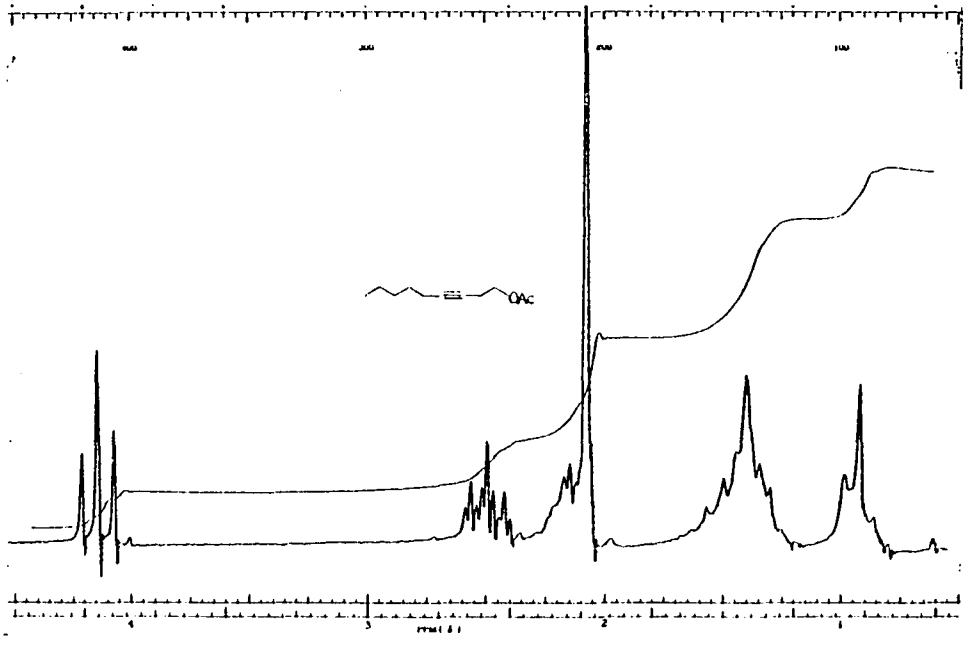


Figure III-77. Pmr spectrum ($CDCl_3$) of compound 133.

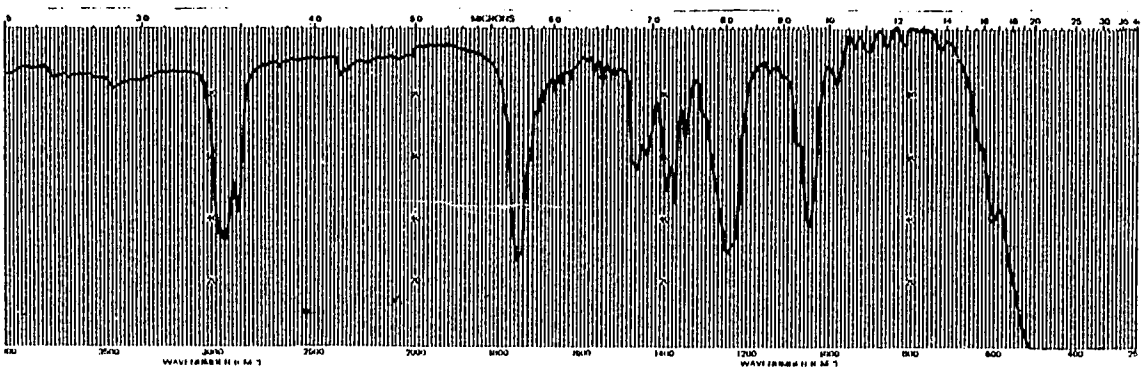
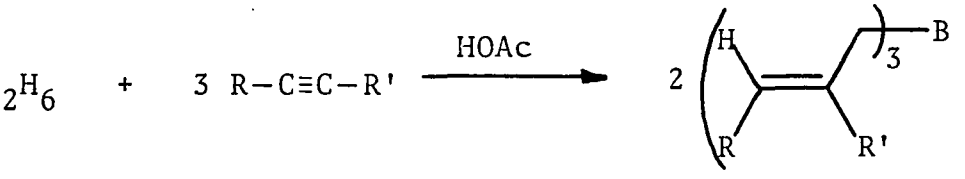
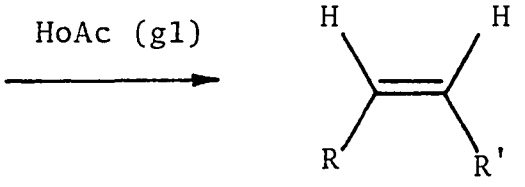


Figure III-78. Ir spectrum (neat) of compound 133.

One attempt was made to reduce alcohol 132 directly to 134 with diimide using the procedure of Hoffman and Schleisinger[39] but very little reduction took place. A more attractive route was developed by Brown[40] who found that diborane reacts with internal acetylenes to give organoboranes (136) which can be hydrolyzed with glacial acetic acid to give cis-olefins (137) in high



136



137

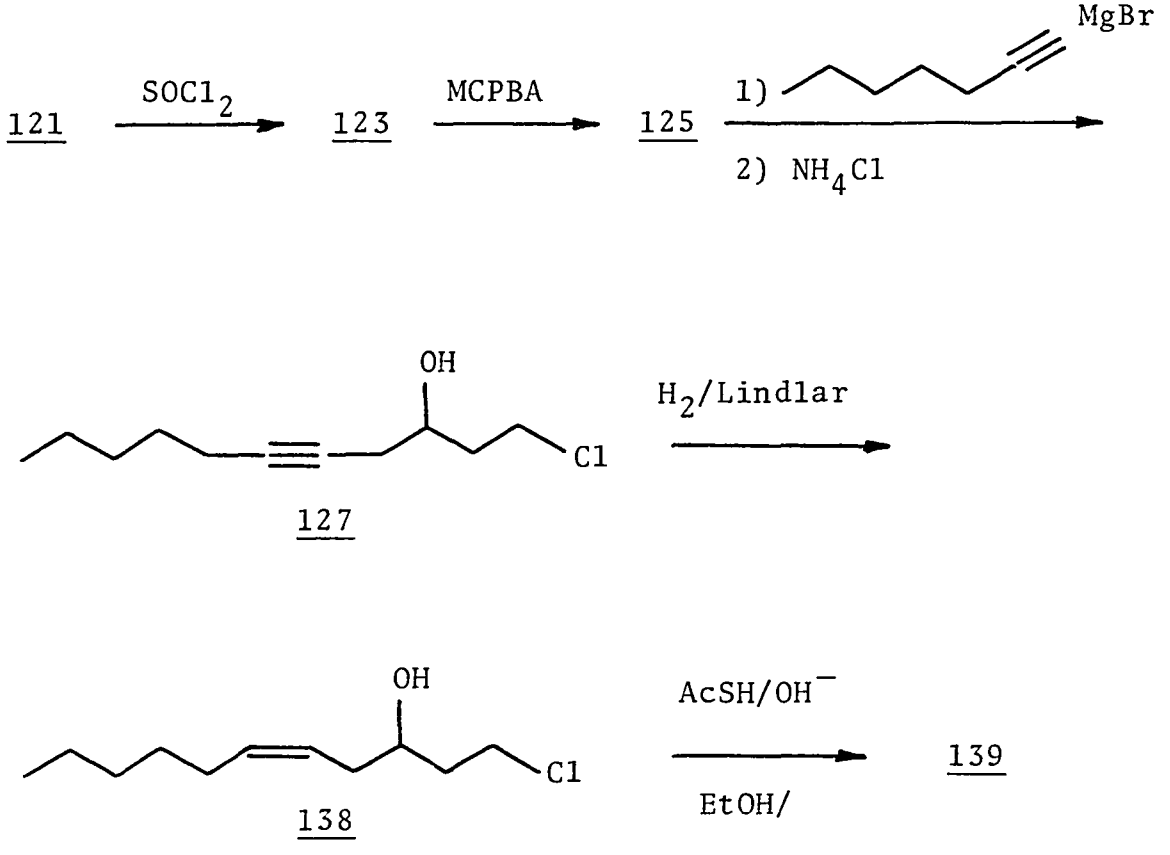
yields (60-70%). The reaction of 133 with diborane under the conditions specified by Brown[40] with diglyme as the reaction solvent gave a colorless oil that, by pmr analysis, consisted of starting material and diglyme. Repeating the reaction with the more easily removable THF as the solvent gave a mixture of 133 and 135 in a ratio of approximately 3:2 (by pmr integration). In trying to increase the amount of reduction the reaction was repeated five more times but in each case only trace amounts of 135 were formed with near quantitative recovery of 133. The reason for these failures probably lies

in the generation of the diborane. Since this reagent is highly reactive towards acetylenes[40] reduction almost certainly would have taken place had it been generated in sufficient quantities. No further reductions of 133 with this method were attempted.

Since the thiolacetoxy group prevents reduction of 130 to 19 Scheme III-9 was modified as shown in Scheme III-10 in order to reduce the triple bond before the

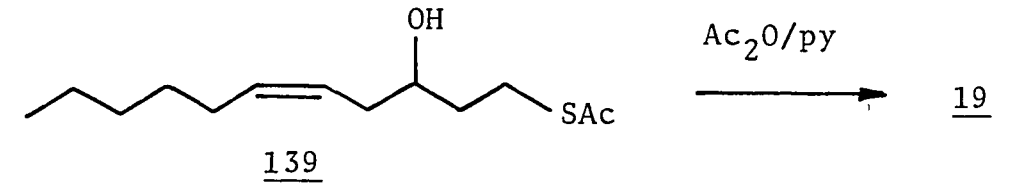
Scheme III-10.

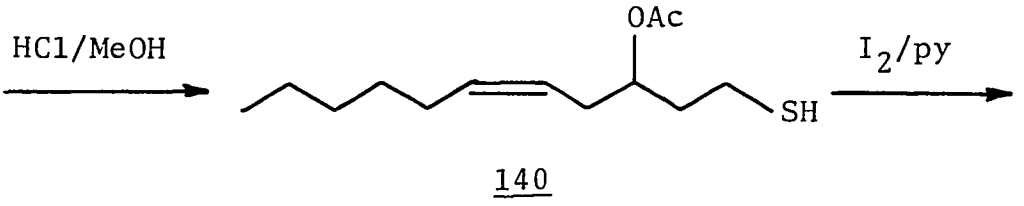
Modification of Scheme III-9



Scheme III-10. (Continued)

Modification of Scheme III-9





thiolacetoxy group was introduced. The preparation of

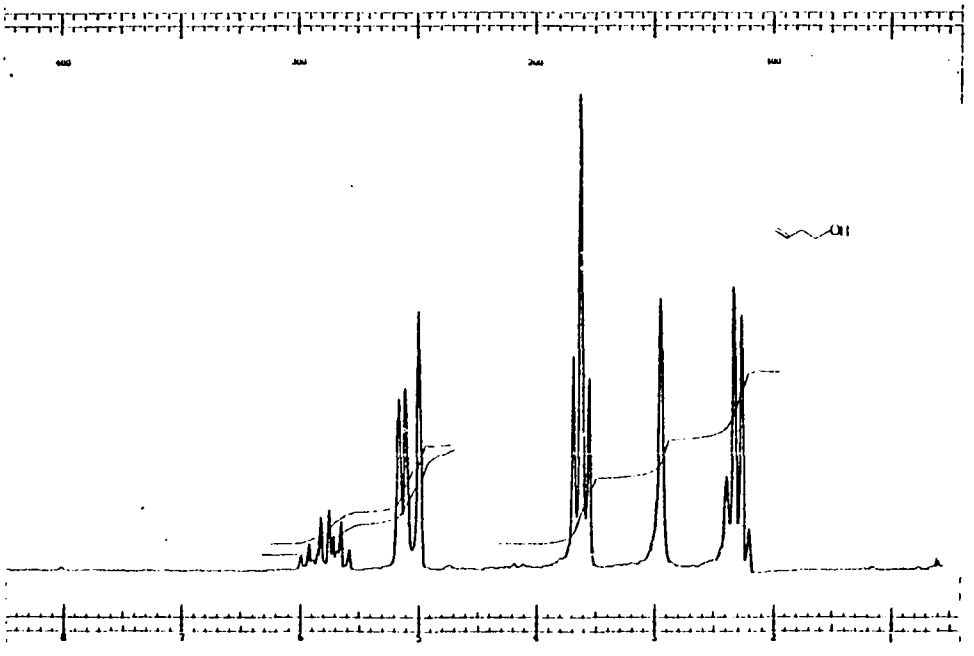


Figure III-79. Pmr spectrum ($CDCl_3$) of compound 121.

olefin 123 and epoxide 125 proceeded smoothly and in yields comparable to those obtained by Asato.[17] The

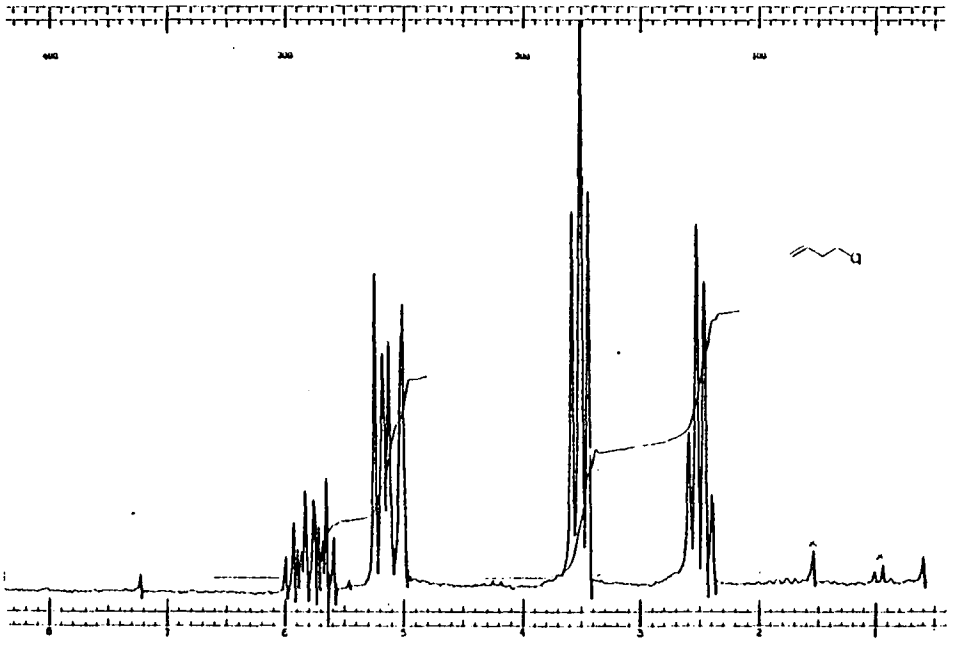


Figure III-80. Pmr spectrum ($CDCl_3$) of compound 123.

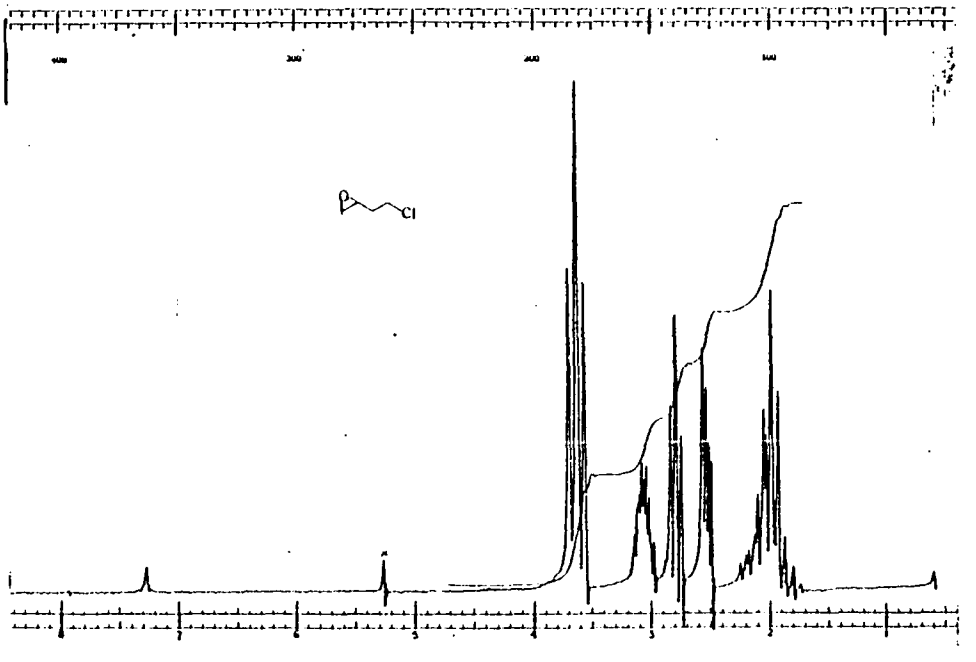
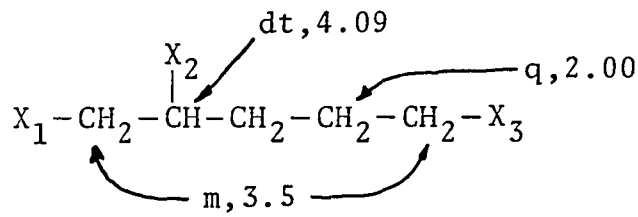
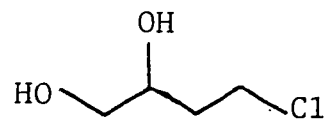


Figure III-81. Pmr spectrum ($CDCl_3$) of compound 125.

epoxide (125) was again reacted with heptynyl magnesium bromide but with a reaction temperature of -78° to minimize the production of side products. However, the pmr spectrum of the crude reaction mixture showed the presence of very little 127 and a substantial amount of an unknown compound. The pmr spectrum of the purified (silica gel column) side product is identical to the spectrum of the material isolated by Asato and exhibits a 2H quartet (J=7 Hz) at δ2.00, a complex 4H multiplet at 3.5 and a broadened doublet of triplets (J=8 and 10 Hz) at 4.04. This spectrum does not support structure 131 proposed by Asato since there is no evidence for a methyl group. Instead this data suggests partial structure 141, a derivative of 125, in which the X's denote electronegative substituents. During the hydrolysis of the reaction mixture with ammonium chloride a strong odor of ammonia was present and it was thought that unreacted 125 had then hydrolyzed to diol 142. This structure is consistent with the pmr spectrum but the chromatographic



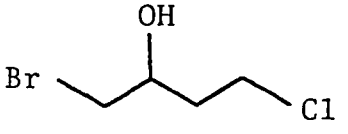
141



142

behavior of the compound is not consistent with a diol. The compound elutes from a silica gel column with 25% methylene chloride/hexane whereas a diol (cf. 35, p. 230 is only eluted with much more polar solvents.

The mass spectrum of the side product exhibits a weak molecular ion cluster at m/e 186,188,190 with a more intense M-1 cluster at m/e 185,181,189. The relative peak intensities of the M and M-1 ion clusters suggest 143 as the correct structure. The expected α-cleavage products[41]



143

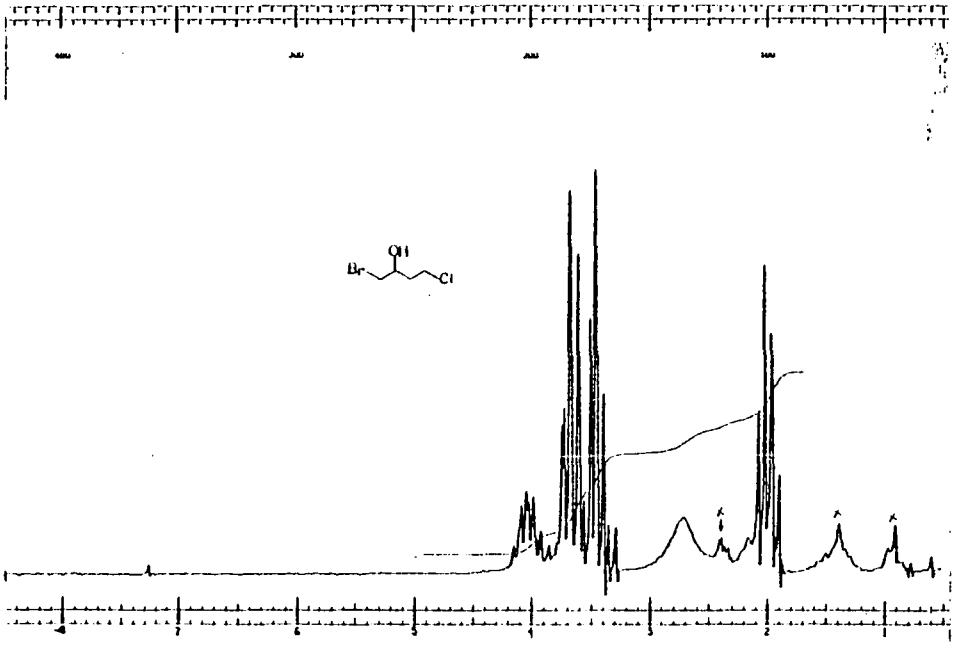


Figure III-82. Pmr spectrum ($CDCl_3$) of compound 143.

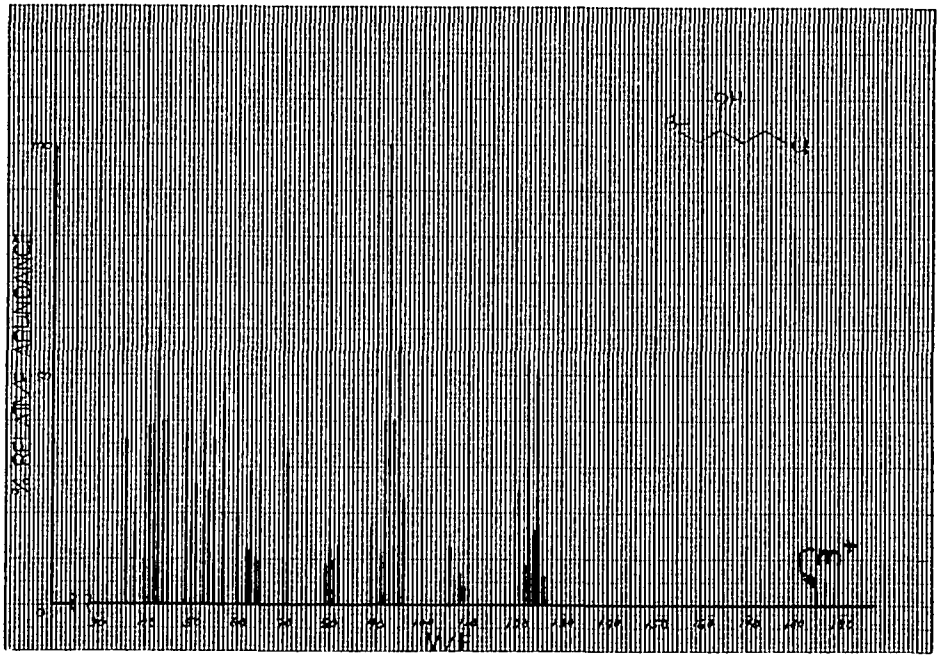
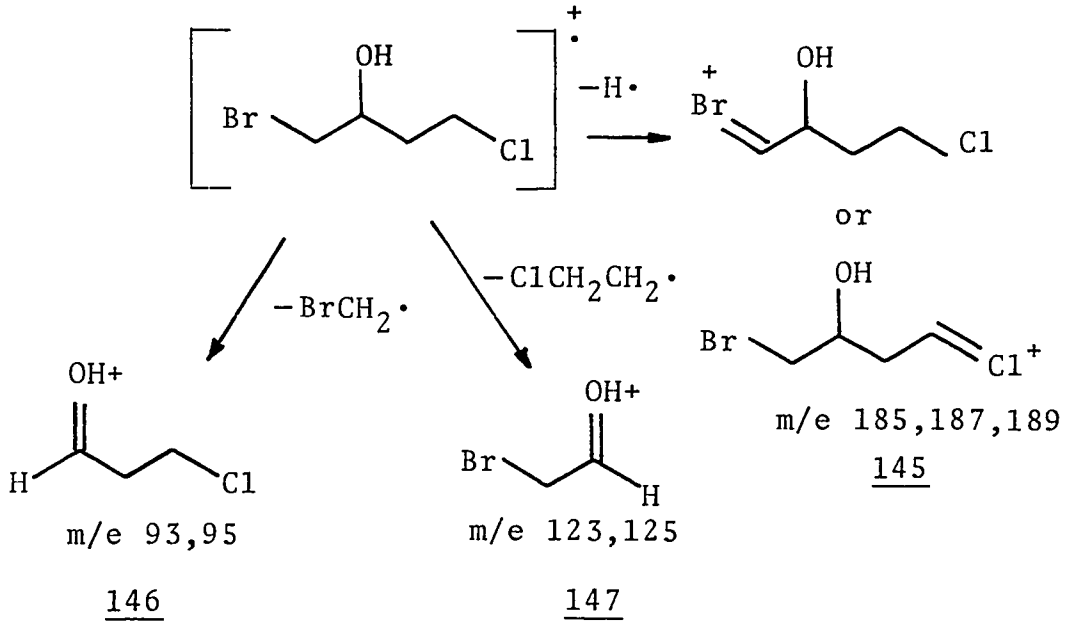
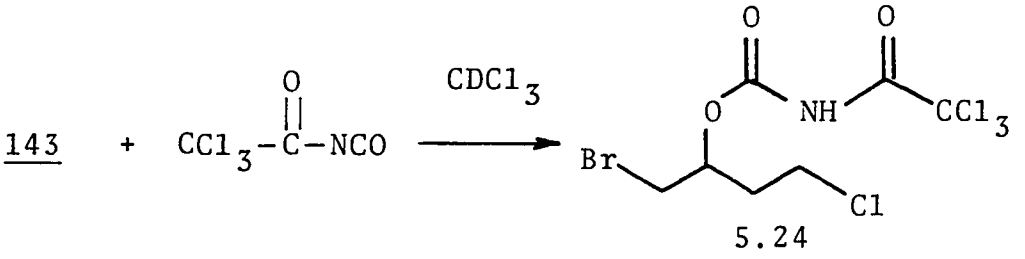


Figure III-83. Mass spectrum (70eV) of compound 143.

from the molecular ion of 143 (144) are observed at m/e 93,95 (146) and m/e 123,125 (147) and possess the proper intensity ratios for the respective halogens.



The reaction of the side product with trichloroacetyl isocyanate[41] rapidly forms a derivative whose pmr spectrum is consistent with structure 148. The alcohol methine of



148

143 is shifted downfield to δ5.24 in 148 and the halomethine and methylene protons appear as a simplified multiplet at 3.62. The absence of signals for an ester methylene group confirms the position of the hydroxy group in 143.

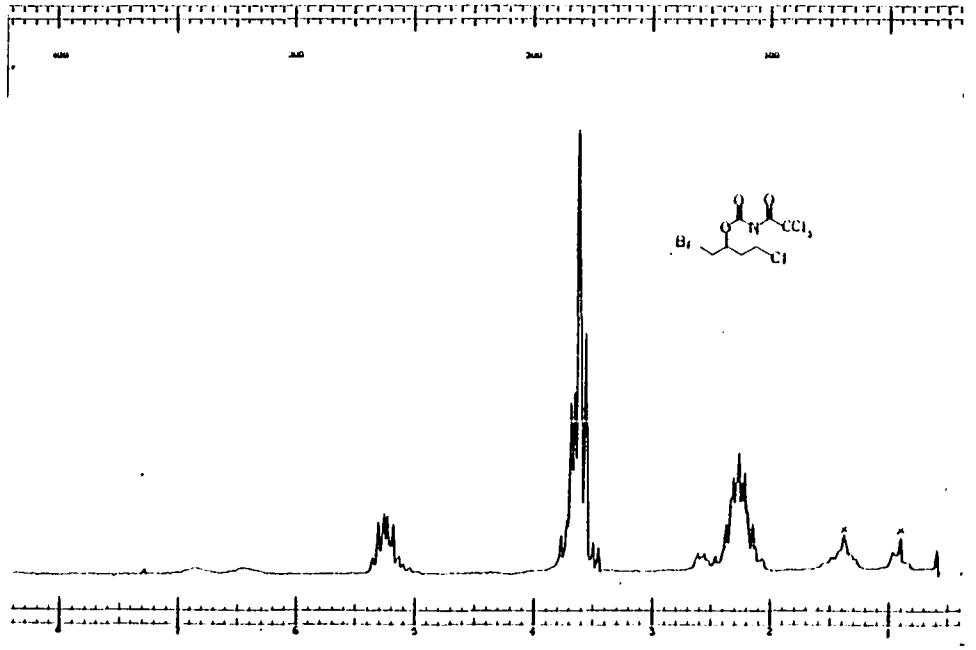
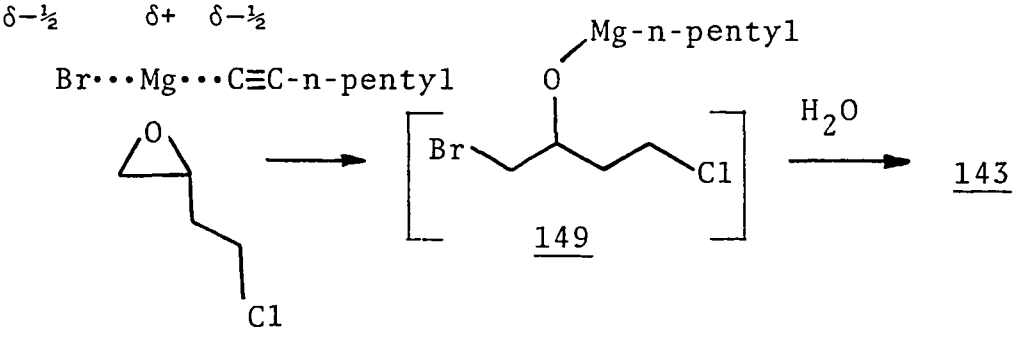
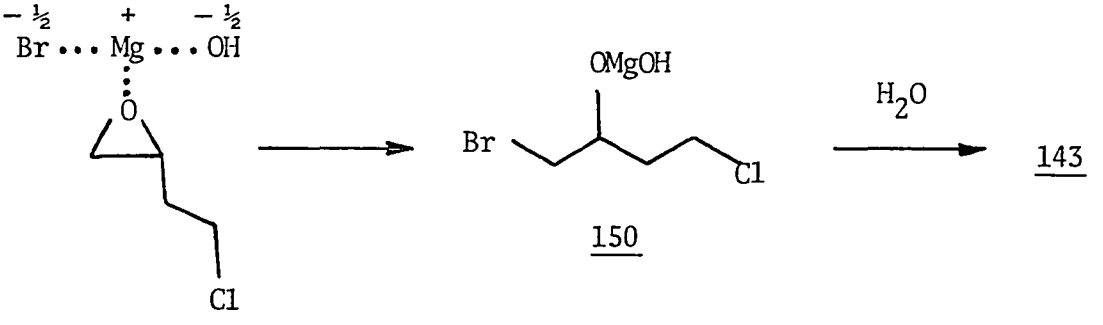


Figure III-84. Pmr spectrum ($CDCl_3$) of compound 148.

The origin of 143 is still speculative at this time but there are, at first glance, two possible explanations. The first is that the acetylide may be bound very tightly to the magnesium ion and therefore only weakly nucleophilic. The coupling reactions between acetylides and alkyl halides are normally catalyzed by cuprous salts which make the former more reactive.[43] In this case the complexation of heptynyl magnesium bromide with the epoxide oxygen leads to nucleophilic attack by bromide ion giving 149.[45] The other possibility is that no reaction takes place at -78° and during hydrolysis the mixed magnesium salt (MgBrOH) reacts in the same manner



to give 150. Under normal conditions hydroxide ion is more nucleophilic than bromide ion[44] but the hydroxide may be more strongly held to the magnesium ion.



In spite of the failure to convert 125 to 127 Scheme III-10 remains a viable route to 19 and 20 because of its simplicity. Future attempts to prepare 127 should use heptynyl acetylide formed from 1-heptyne with n-butyl lithium or other strong base that does not include an additional nucleophilic anion. If the reaction is then run at low temperature (e.g. -78°) the highly nucleophilic lithium acetylide should selectively react with the epoxide of 125 without formation of side products.[45]

F. Summary

The major objectives of this study were to synthesize and characterize alcohols 24 and 28 and sulfur compounds 13-20. In addition, the biomimetic dehydration reactions of synthetic 24 and 28 were to be studied to determine whether or not hydrocarbons could be formed from them under mild conditions. Finally, the solubility properties and chromatographic behavior of synthetic 24 and 28 were to be studied in order to simplify the search for the naturally occurring compounds. Toward these goals two routes were found to be moderately successful in producing 24 but a synthesis of 28 was not achieved. With 24 in hand a partitioning experiment was conducted which demonstrated that the natural compound should be present in the methanol extract of Dictyopteris. Exhaustive examination of 167 g of methanol extract, however, revealed no trace of either 24 or 28.

Although prepared with difficulty sufficient quantities of 24 were obtained to permit several small scale dehydration reactions to be conducted. Treating 24 with phosphorus oxychloride effected elimination but the resulting hydrocarbons were rapidly polymerized by the hydrochloric acid liberated during the course of the reaction. Reaction of either 24 or its mesylate (93) with DBU resulted only in the isolation of starting materials.

The syntheses of sulfur containing compounds 13-16 were completed but only compound 13 gave a satisfactory combustion analysis. Compounds 17-20 were not prepared.

III. EXPERIMENTAL

A. General

1. Instruments

See page 89.

2. Solvents

See page 90.

3. Sorbents

See page 91.

B. Preparation of Compounds

1. 1-Decen-4-yne (33)

Compound 33 was prepared in 69% yield by the method of Brandsma.[18]

2. 1,2-Dihydroxydec-4-yne (35)

A one liter three-necked round-bottomed flask fitted with an efficient mechanical stirrer, reflux condenser and heating mantle was charged with 24.40 g (0.12 mol) m-chloroperbenzoic acid (85% Aldrich) in 200 ml of freshly distilled ethyl acetate. To the stirring solution was added all at once 10.88 g (0.08 mol) of 1-decen-4-yne (33) in 50 ml of ethyl acetate. The mixture was stirred and refluxed for 15 hours. At the end of this time the solvent was stripped in vacuo and 100 ml of acetone added. The mixture was stirred to effect solution and 50 ml of 3N sulfuric acid added all at once. The solution

was heated to 50° and stirred for one hour. At the end of this time the mixture was neutralized to pH 7 with aqueous sodium hydroxide, the acetone removed *in vacuo* and the oily solid residue dissolved in 200 ml of aqueous sodium hydroxide. The oily, basic solution was then extracted with three 60 ml portions of methylene chloride. The extracts were combined, washed twice with saturated bicarbonate solution, dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The residual oil was placed on a silica gel column and the starting material and colored impurities eluted with pentane/ ethyl acetate, 9:1. The product was eluted with absolute ethanol. Evaporation of the ethanol under reduced pressure afforded 9.33 g (70%) of **35** as a yellow oil; pmr δ0.87 (bt, terminal CH_3), 1.86 (m, $-CH_2-$), 2.00-2.23 (m, $-CH_2-C\underline{H}_2-C\equiv$), 2.27-2.45 (m, $\equiv C-C\underline{H}_2-CHOH-$), 3.36 (s, OH), 3.25-3.95 (m, $-C\underline{H}OH-C\underline{H}_2OH$); ir (neat) 3590 (m), 3480 (m), 3101 (m), 2950 (s), 2940 (s), 2880 (s), 2875 (s), 1720 (m), 1670 (m), 1620 (w), 1470 (m), 1440 (w), 1385 (w), 1340 (w), 1290 (w), 1230 (s), 1130 (s) and 1090 (s) cm^{-1}; ms m/e (rel. intensity) 170 (M^+, 2.4), 152 (10), 139 (18), 75 (100), 41 (100).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.27; H, 10.89.

3. dl-Isopropylidineglycerol (39)

Compound 39 was prepared in 84% yield by the method of Renoll and Newman.[46]

4. dl-Tosylisopropylidineglycerol (40)

Into a 250 ml Erlenmeyer flask was placed 6.6 g (0.05 mol) of 39 followed by 100 ml of freshly distilled (over BaO) pyridine. The flask was cooled to 3° in an ice bath and 19.1 g (0.10 mol) of tosyl chloride added. The flask was swirled to effect solution and then placed in the cold room at 4°.

At the end of 48 hours of standing at 4° the solution was decanted over 500 g of cracked ice causing a white solid to precipitate. The aqueous solution was stirred for ten minutes to complete the precipitation. The solution was filtered and the solid washed with 100 ml of ice cold water. The solid was then transferred to a round-bottom flask where the remaining water and pyridine were removed under high vacuum. Recrystallization of the product was achieved by dissolving the crude, dried tosylate in 20 ml of ether followed by dilution with 200 ml of petroleum ether (30-60). This procedure afforded 11.72 g (82%) of 40 as colorless needles; pmr δ1.29 (d, J=1 Hz), 2.40 (s), 3.97 (m), 7.27 (d, J=4 Hz), 7.73 (d, J=4 Hz); ir ($CHCl_3$) 3200 (w), 3000 (w), 2940 (w), 2900 (w), 1610 (m), 1090 (m), 840 (m) and 830 (m) cm^{-1}.

5. cis-1,2-Dihydroxy-4-decene (36)

a. Small Scale

A 100 ml round-bottomed flask was charged with 25 mg of Lindlar's catalyst followed by 0.250 g (1.45 mmol) of 1,2-dihydroxydec-4-yne (35) in 15 ml of hexane. The flask was then placed on the hydrogenation apparatus, evacuated and charged with hydrogen gas at atmospheric pressure. The evacuation/charging procedure was repeated twice more and the reaction mixture stirred under a slight positive pressure of hydrogen. At the end of 4.5 hours the hydrogen uptake was completed and the reaction mixture was filtered through celite and the hexane removed *in vacuo*. Chromatography of the residual oil on Sephadex LH-20 (chloroform/methanol, 1:1) afforded 0.250 g (99.6%) of 36 as a pale yellow oil; pmr δ0.87 (bt, 3H), 1.28 (bs, 6H), 2.02 (m, 2H), 2.18 (t, J=6 Hz, 2H), 3.20-3.80 (m, 3H), 4.27 (bs, 2H), 5.41 (AB, J=10 Hz, 2H), ir (neat) 3400 (b,s), 3010 (m), 2880 (s), 2840 (s), 1730 (w), 1660 (w), 1475 (b,s), 1190 (b,s), 1140 (b,s), 970 (w), 900 (w) cm^{-1}; ms m/e (rel. intensity) 172 (M^+, 3), 154 (10), 151 (13), 97 (59), 69 (100).

b. Large Scale

A 250 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 400 mg of Lindlar's catalyst, 100 ml of thiophene-free benzene, and 4.89 g (28.7 mmol) of 35. The flask was evacuated and charged with hydrogen three times and then stirred under hydrogen (balloon technique) for 24 hours. The mixture was filtered and the benzene removed in vacuo to give 4.59 g (93%) of 36 as a very pale yellow oil. The spectral properties of this material were identical to those of the product obtained above in the small scale reduction.

6. 1,2-Epoxydec-4-yne (34)

A one liter three-necked round-bottomed flask equipped with a mechanical stirrer, heating mantle and reflux condenser was charged with a solution of 19.7 g (97.0 mmol) of 85% MCPBA (Aldrich) in 200 ml of freshly distilled ethyl acetate and 6.62 g (48.5 mmol) of 33. The mixture was stirred at room temperature for 14 hours and then refluxed for two hours. The reaction mixture was then cooled to room temperature, washed with saturated sodium bicarbonate solution (2 X 100 ml), saturated brine solution (1 X 100 ml), dried ($MgSO_4$) and the solvent removed in vacuo to give a pale yellow oil. The crude product was chromatographed on a 33" x 1" column of

silica gel with hexane to give 2.11 g (29%) of 34 as a nearly colorless oil; pmr δ0.90 (bt, 3H), 1.38 (m, 6H), 2.14 (m, 2H), 2.49 (m, 2H), 2.71 (m, 2H), 3.07 (m, 1H).

7. cis-1,2-Epoxydec-4-ene (41)

A 100 ml round-bottomed flask was charged with 250 mg (1.64 mmol) of 34, 25 ml of hexane and 15 ml of benzene and 25 mg of Lindlar's catalyst. The reaction vessel was placed on the hydrogenation apparatus, purged with hydrogen and stirred magnetically at room temperature for three hours. The mixture was filtered through celite and the solvent removed in vacuo, leaving a colorless oil. The oil was chromatographed on a 33" X 1" column of silica gel with hexane to give 60 mg (24%) of 41 as a colorless oil; pmr δ0.87 (bt, 3H), 1.31 (m, 6H) 2.04 (m, 2H), 2.32 (AB q, 2H), 2.49 (dd, J=5 and 3 Hz, 1H), 2.72 (t, J=5 Hz, 1H), 2.93 (m, 1H), 5.45 (AB dt, J=12 Hz, 2H); ir (neat) 3180 (w), 3140 (w), 2980 (s), 2950 (s), 2880 (s), 1740 (w), 1470 (m), 1410 (w), 1390 (w), 1290 (w), 1260 (m), 970 (w) and 835 cm^{-1}; ms m/e (rel. intensity) 154 (M^+, <1), 123 (10), 111 (8), 81 (60), 67 (100), 55 (83), 54 (72).

8. cis-3-Nonen-1-al (37)

A 100 ml round-bottomed flask equipped with a 25 ml addition funnel and efficient magnetic stirrer was charged

with 0.50 g (2.9 mmol) of cis-1,2-dihydroxy-4-decene (36) in 50 ml of acetone. A solution of 0.62 g (2.6 mmol) of sodium metaperiodate in 25 ml of water was added dropwise with stirring at 40° over one hour. When the addition was complete the mixture was stirred an additional hour at 4°. At the end of this time the reaction mixture was filtered and the acetone removed in vacuo. The oily aqueous residue was extracted with three 15 ml portions of methylene chloride. The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The residual oil was column chromatographed on silica gel with pentane/ethyl acetate (9:1). Evaporation of the solvent under reduced pressure afforded 0.21 g (51%) of 37 as a very pale yellow, odorous oil; pmr δ0.88 (bt, 3H), 1.30 (bs, 6H), 2.03 (dt, J=6.5 Hz, 2H), 3.17 (dd, J=6.5 and 2.0 Hz, 2H), 5.59 (AB dt, J=11 Hz 2H), 9.62 (t, J=2.0 Hz, 1H); ir (neat) 3120 (m), 2980 (s), 2970 (s), 2870 (s), 2740 (m), 1735 (s), 1460 (m), 1400 (m), 1200 (w), 1130 (m), 1060 (m) and 740 (w) cm^{-1}.

9. cis-3-Nonen-1-ol (42)

A 100 ml round-bottomed flask equipped with a magnetic stirring bar was charged with 50 mg of Lindlar's catalyst and a solution of 500 mg (3.78 mmol) of 41 in 25 ml of acetone. The flask was placed on the hydrogenation apparatus and evacuated and charged with hydrogen three times. The mixture was then stirred under hydrogen at

ambient pressure for 45 minutes. The suspension was filtered through celite and the solvent removed *in vacuo* to give 550 mg of *42* as a colorless oil contaminated with a small amount of acetone; pmr δ0.91 (bt, 3H), 1.33 (m, 6H), 2.06 (m, 2H), 2.71 (s, acetone), 2.33 (q, J=7 Hz, 2H), 3.09 (bs, 1H), 3.61 (t, J=7 Hz, 2H), 5.46 (AB dt, 2H).

10. *Oxidation of 42 with Chromic Acid*

Following the procedure B of Brown[21] 397 mg (3.0 mmol) of *42* in ten ml of ether were oxidized with chromic acid solution. The pmr spectrum of the crude product showed only a mixture of starting *42* and polymeric material.

11. *Oxidation of 42 by the Procedure of Corey*[25]

Oxidation of 284 mg (2.0 mmol) of *42* with N-chlorosuccinimide and triethylamine by the procedure of Corey[25] gave 300 mg of crude product. The pmr spectrum showed the presence of *42* and *37* in an approximate 1:1 ratio and a small amount of the reaction solvent (toluene).

12. *cis-1,5-Undecadien-3-ol (24)*

A 100 ml four-necked round-bottomed flask, ten ml pressure-equalizing addition funnel, drying tube and

one ml syringe were heated in a drying oven at 115° for 15 minutes. The apparatus was assembled hot and flushed with a rapid stream of high purity nitrogen for five minutes. The flask was cooled to -78° and charged with 25 ml freshly distilled THF (over calcium hydride then Redal) and 0.355 ml of 2.2 M vinyl lithium solution (Alpha Inorganics-via syringe). cis-3-Nonenal (37, 0.100 g, 0.71 mmol) in ten ml of THF was added to the rapidly stirring solution over one-half hour under a rapid stream of nitrogen (~ 150 ml per minute). When the addition was complete the reaction mixture was allowed to come to 0° over one-half hour. At the end of this time 1.04 g of ammonium chloride in five ml of water was added to the reaction mixture with rapid stirring. The THF was removed under reduced pressure and the oily aqueous residue extracted with four 15 ml portions of methylene chloride. The extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure leaving a pale yellow oil. The oil was chromatographed twice on Sephadex LH-20 (chloroform/methanol, 1:1) to give 0.14 g (116%) of 24 as an impure pale yellow oil; pmr δ0.87 (bt, 3H), 1.28 (bs), 2.29 (t, J=6.5 Hz, 2H), 3.31 (s, 1H), 4.15 (overlapping dt, J=6.5 and 1.5 Hz, 1H), 5.06 (A part of AMX, dt, J=10.0 and 1.5 Hz, 1H), 5.30 (AB dt, J=11 Hz), 5.45 (M part of AMX, dt, J=15.0 and 1.5 Hz, 1H), 6.58-6.02 (X part of AMX, ddd, J=6.5, 10.0 and 15.0 Hz, 1H).

13. 3-Hydroxy-1-hexen-5-yne (45)

Compound 45 was prepared in 76% yield by the procedure of Viola and MacMillan.[22]

14. 3-O-Tetrahydropyranyl-1-hexen-5-yne (46)

To a 500 ml three-necked round-bottomed flask equipped with an efficient magnetic stirrer and 100 ml addition funnel was added 22.2 g (0.23 mol) of 45, 200 ml of benzene and ten mg of p-toluenesulfonic acid. The solution was stirred and 54.5 g (0.65 mol) of freshly distilled dihydropyran in 50 ml of benzene added dropwise over one hour at room temperature. The stirring was continued for an additional six hours. Ten ml of saturated bicarbonate solution were added and the solvent removed in vacuo. The oily aqueous residue was added to 100 ml of water and the mixture extracted with ether (3 X 75 ml). The extracts were combined, dried (NaOH pellets) and the ether removed in vacuo to give a pale yellow oil. The crude product was vacuum distilled to give 40.5 g of 46 as a colorless oil, bp 60.8° (0.94 torr); pmr δ1.83-1.95 (m, 6H), 1.98 (m, 1H), 2.43 (m, 2H), 3.35-3.60 (m, 1H), 3.70-4.05 (m, 1H), 4.11-4.36 (m, 1H), 4.66 (bt, ½H), 4.84 (bt, ½H), 5.05-5.40 (m, 2H), 5.55-6.10 (M, 1H); ir (neat) 2960 (s), 2880 (s), 2150 (w), 1475 (w), 1463 (w), 1450 (w), 1430 (w), 1390 (w), 1360 (w), 1330 (w),

1290 (w), 1270 (w), 1210 (s), 1190 (s), 1060 (s), 1130 (s), 1080 (s), 1030 (s), 990 (s), 930 (m), 875 (s), 820 (m); ms m/e (rel. intensity) 180 (M^+, 7), 169 (9), 131 (9), 85 (100); cmr δ137.6, 136.5, 118.0, 115.5, 97.1, 95.0, 80.5, 80.7, 74.7, 74.4, 69.8, 61.7, 61.4, 30.5, 25.9, 25.4, 24.6, 19.2, 19.1.

15. 3-O-Tetrahydropyranyl-1-undec-5-yne (47a)

A one liter three-necked round-bottomed flask, dry ice trap, nitrogen inlet tube, mechanical stirrer and 100 ml addition funnel were dried in an oven at 120° for one hour. The apparatus was assembled hot and flushed with a rapid stream of nitrogen for ten minutes. The trap was filled with dry-ice and acetone and a stream of anhydrous ammonia introduced until the flask contained approximately 125 ml of liquid ammonia. Approximately 0.1 g of sodium metal was added to get a persistent blue color and then 50 mg of $Fe(NO_3)_3 \cdot 9H_2O$ was added. When the mixture had turned brown 1.03 g (0.045 g-at) of sodium metal was added in 0.1 g pieces over 20 minutes. The suspension was stirred for an additional hour at which time the color changed from blue to brown. The flask was swirled to remove the sodium mirror and 7.75 g (43 mmol) of 46 in 50 ml of THF added dropwise over 20 minutes followed by an additional 50 ml of THF. The mixture was stirred for 30 minutes and 15.11 g (100 mmol)

of n-amyl bromide in 50 ml of THF added dropwise over 15 minutes. The reaction was maintained at -33° for 2.5 hours. The ammonia was allowed to evaporate and the reaction mixture stirred under nitrogen at room temperature overnight. A small amount of water (~ 20 ml) was added and the THF removed in vacuo. Approximately 100 ml of water were added to the oily aqueous residue and the mixture extracted with chloroform (3 X 40 ml). The extracts were combined, washed with brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude oil was chromatographed on a 33" X 1" column of silica gel with hexane to give 6.55 g (61%) of 47a as a colorless oil; pmr δ0.89 (bt, 3H), 1.1-1.9 (m, 12H), 2.14 (m, 2H), 2.40 (m, 2H), 3.2-3.5 (m, 2H), 4.20 (q, J=6.5 Hz, 1H), 4.70 (bt, ½H), 4.86 (bt, ½H), 5.05-5.35 (m, 2H), 5.5-6.1 (m, 1H); ms (rel. intensity) 249 (M-1, 2), 223 (8), 107 (10), 101 (10), 85 (100); ir (neat) 2930 (s), 2860 (s), 1460 (m), 1375 (m), 1330 (m), 1280 (m), 1250 (m), 1200 (m), 1180 (w), 1110 (s), 1070 (m), 1010 (s), 860 (m), 805 (m); cmr 138.1, 137.0, 117.6, 115.1, 97.2, 94.8, 81.6, 76.3, 76.1, 75.4, 75.0, 62.1, 61.5, 30.9, 30.7, 30.6, 28.6, 26.1, 25.5, 25.4, 25.2, 22.2, 19.0, 18.9, 18.7, 13.9 ppm.

16. 1-Undecen-3-ol-5-yne (48a)

To a 50 ml round-bottomed flask equipped with a magnetic stirrer was added 15 ml of methanol, two ml of water, 0.25 ml of conc. hydrochloric acid and 500 mg (2.0 mmol) of 47a. The mixture was stirred at room temperature for 1.5 hours. At the end of this time the methanol was removed in vacuo followed by addition of 25 ml of water. The aqueous mixture was extracted with three 15 ml portions of ether. The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo affording 330 mg (100%) of essentially pure 48a; pmr δ0.91 (bt, 3H), 1.2-1.7 (bm, 6H), 2.42 (dt, J=6 Hz, 2H), 3.10 (bs, 1H), 4.22 (q, J=6 Hz, 1H), 5.14 (B portion of ABX, dt, J=10.5 Hz, 1.0 Hz, 1H), 5.28 (A portion of ABX, dt, J=17.0, 1.0 Hz, 1H), 5.44 (X portion of ABX, ddd, J=17.0, 6.0, 10.5 Hz, 1H); ir (neat) 3400 (br, m), 2920 (s), 2850 (s), 1730 (br), 1460 (m), 1430 (m), 1165 (m), 1110 (w), 985 (m), 920 (m); cmr δ139.1 (d), 115.2 (t), 89.3 (s), 75.3 (s), 71.0 (d), 31.0 (t), 28.6 (t), 27.8 (t), 22.2 (t), 18.7 (t), 13.9 (q) ppm; ms m/e (rel. intensity) 166 (M^+, 2), 165 (3), 110 (10), 109 (18), 95 (24), 85 (54), 81 (62), 68 (68), 67 (65), 57 (100), 64 (97).

17. Partial Reduction of 48a

To a 100 ml round-bottomed flask were added 10 mg of Lindlar's catalyst, 100 mg (0.59 mmol) of 48 and 25 ml of anhydrous ether. The reaction vessel was placed on the hydrogenation apparatus, cooled in an ice bath and the apparatus subjected to three evacuation/hydrogen flush cycles. The mixture was stirred for 45 minutes under one atmosphere of hydrogen. At the end of this time the mixture was filtered and the solvent removed in vacuo to give 90 mg of an oil whose pmr spectrum showed approximately 80% conversion to 24 with moderate loss of allylic olefin.

18. Partial Reduction of 47a

To a 100 ml round-bottomed flask were added 20 mg of Lindlar's catalyst, 250 mg (1.0 mmol) of 47a and 25 ml of cyclohexane. The reaction vessel was placed on the hydrogenation apparatus and subjected to three evacuation/hydrogen flush cycles. The mixture was then stirred under hydrogen at room temperature for 15 minutes. The mixture was filtered and the solvent removed in vacuo to give 210 mg of 52 contaminated with a small amount of cyclohexane; pmr δ0.89 (bt, 3H), 129 (m, 6H), 2.5 (m, 6H), 3.04 (m, 2H), 3.32 (bt, J=6 Hz, 2H), 3.47 (m, 1H), 3.87 (m, 1H), 4.10 (q, J=6.5 Hz, 1H), 4.70 (m, 1H), 6.56 (m, 2H), 5.88 (m, 2H), 6.0-6.5 (m, 1H).

19. 3-O-Tetrahydropyranyl-1-octen-5-yne (47b)

Crude 47b was prepared using the procedure for 47a outlined on page 339. Vacuum distillation of the crude product afforded 2.02 g (35%) of 47b as a colorless oil, bp 79-81° (0.35 torr); pmr δ1.04 (t, J=7 Hz, 3H), 1.35-1.80 (m, 6 Hz), 2.10 (dq, J=2 and 7 Hz, 2 H), 2.86 (m, 2H), 3.45 (bm, 1H), 3.7-4.0 (bm, 1H), 4.17 (dt, J=2 and 6 Hz, 1H), 4.72 (dt, J=2 and 17 Hz, 1H), 5.0-5.4 (AB portion of ABX, 2H), 5.00-6.08 (X portion of ABX, 1H).

20. 1-Octen-5-yne-3-ol (48b)

Hydrolysis of 47b (0.5 g, 2.4 mmol) as described for 47a on page 339 resulted in the isolation of 180 mg (57%) of pure 48b as a colorless oil; pmr δ1.08 (t, J=7 Hz, 3H), 1.15 (dq, J=2 and 7 Hz, 2H), 4.02 (s, 1H), 4.17 (dq, J=6 Hz, 1H), 5.12 (B portion of ABX, dt, J=1.5 and 10 Hz, 1H), 5.25 (A portion of ABX, dt, J=1.5 and 17 Hz, 1H), 5.90 (X portion of ABX, ddd, J=1.5, 10 and 17 Hz, 1H).

21. cis-1,5-Octadien-3-ol (29)

A 25 ml round-bottomed flask was charged with 90 mg (0.68 mmol) of 48b, 9.6 mg of Lindlar's catalyst and ten ml of ether. The flask was placed on the hydrogenation apparatus, cooled in an ice bath and flushed with hydrogen. The reaction mixture was stirred at 0°

for 45 minutes under one atmosphere of hydrogen. The catalyst was removed by filtration and the solvent removed *in vacuo* to give 70 mg (78%) of **29** as a colorless oil; pmr δ0.95 (t, J=7 Hz, 3H), 1.94 (s, 1H), 2.05 (p, J=7 Hz, 2H), 2.29 (t, J=6 Hz, 2H), 4.11 (bq, J=6 Hz, 1H), 5.06 (B portion of ABX, dt, J=1.5 and 10 Hz, 1H), 5.20 (A portion of ABX, dt, J=1.5 and 16 Hz, 1H), 5.42 (dt, J=5.5 and 11 Hz, 2H), 5.70-6.02 (X portion of ABX, ddd, J=1.5, 10 and 16 Hz, 1H).

22. 3-Hydroxypent-5-yne

This compound was prepared in 31% yield by the procedure of Heilbron.[27]

23. 1-Pentyne-3-one (56)

Compound **56** was prepared in 30% yield by the procedure of Heilbron.[28]

24. 1-(1-Oxopropyl)cyclohexa-1,4-diene (57)

Ethyl ethynyl ketone (**56**, 7.56 g, 92 mmol), 16.1 g (46 mmol) of $SnCl_4 \cdot 5H_2O$ in 25 ml of acetonitrile and ten ml of butadiene (excess) were combined in a thick-walled glass tube. The tube was sealed and allowed to stand at room temperature for 48 hours with periodic shaking. The tube was then opened, the contents poured into 500 ml of water and the mixture extracted with methylene

chloride (3 X 50 ml). The extracts were combined, washed with water (2 X 100 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 4.97 g of a dark green oil whose pmr spectrum showed an approximate 1:1 ratio of starting material (56) and product (57). Chromatography of the oil on a 33" X 1" column of silica gel with hexane did not separate the mixture.

25. 1-Bromoprop-2-yne (66)

a. Attempted Preparation with Triphenyl Phosphite: Bromine Complex[31]

A 100 ml four-necked round-bottomed flask, two ten ml addition funnels, nitrogen inlet tube and drying tube were dried in oven overnight at 110°, assembled hot and flushed with a rapid stream of nitrogen. The flask was then charged with 11.4 g (37 mmol) of triphenyl phosphite and 50 ml of ether. Bromine (5.7 g, 36 mmol) was then added dropwise over 20 minutes with rapid stirring. Pyridine (2.5 g, 37 mmol) was then added followed by a dropwise addition of 2.0 g (37 mmol) of 65 in ten ml of ether. When the addition was complete (~ 15 minutes) the reaction mixture was stirred for an additional 30 minutes and then poured into 200 ml of ice water. The mixture was extracted with pentane (3 X 20 ml), the extracts were combined,

dried ($MgSO_4$) and the solvent removed *in vacuo* to give 15 g of colorless oil. The pmr spectrum of the oil showed only triphenyl phosphite, pyridine and a small amount of 65.

b. Attempted Preparation with Triphenyl Phosphine: Carbon Tetrabromide Complex[32]

A 50 ml round-bottomed flask equipped with a drying tube and efficient magnetic stirrer was charged with 1.80 g (7.0 mmol) of triphenyl phosphine, 1.71 g (5.17 mmol) of carbon tetrabromide and 35 ml of THF. The mixture was stirred for five minutes and 0.58 g (6.8 mmol) of 65 in ten ml of THF added all at once. The reaction mixture was allowed to stir at room temperature for 72 hours and the THF removed under reduced pressure. The crude oil was combined with 20 ml of water and extracted with chloroform (3 X 15 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 4.23 g of pale yellow oil. The pmr spectrum showed a small amount of the desired product (66), triphenyl phosphine and numerous side products. No attempt was made to separate the mixture.

26. 3-Mesyl-1,5-hexadiene (83)

A 100 ml four-necked round-bottomed flask, 10 ml addition funnel, drying tube and two glass stoppers were dried in an oven at 110° for 30 minutes, assembled hot and flushed with a rapid stream of nitrogen for 15 minutes. The apparatus was then charged with 1.00 g (10.4 mmol) of 82, 1.58 g (11.4 mmol) of triethyl amine and 50 ml of methylene chloride and cooled to 0° with an ice bath. Methanesulfonyl chloride (98%, Aldrich) was then added dropwise over two minutes and the reaction mixture stirred for an additional 45 minutes at 0°. The reaction mixture was then poured into a cold separatory funnel and washed with ice water (2 X 25 ml), cold 10% aqueous hydrochloric acid solution (2 X 25 ml), saturated sodium bicarbonate (2 X 25 ml) and brine (2 X 25 ml). The solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to give 1.62 g (90%) of 83 as a colorless oil; pmr δ2.48 (t, J=7 Hz, 2H), 2.93 (s, 3H), 4.91-5.44 (m, 5H), 5.53-6.02 (m, 2H).

27. Formolysis of 83[34]

To a three-necked pear-shaped flask equipped with a magnetic stirring bar, glass stopper and reflux condenser were added 500 mg (2.8 mmol) of 83 and ten ml of 88% formic acid. The flask was immersed in a heating bath to a depth sufficient to maintain the reaction

temperature at 68°. The mixture was stirred at 68° for 55 minutes then cooled to 0° in an ice bath and neutralized to pH 7 with 20% sodium hydroxide solution. During the neutralization the temperature of the mixture was not allowed to rise above 5°. The mixture was then subjected to extractive workup with methylene chloride. The solvent was then removed under reduced pressure to give 0.30 g of a pale brownish orange oil. The pmr spectrum of the oil showed a small amount of polymeric material and an approximate 1:1 ratio of 88 and 89; δ7.96 (s, $-OC\underline{H}O$), 4.86-4.90 (complex m, olefinic), 4.53 (d, J=7 Hz, $=CH-C\underline{H}_2-O$ of 89), 2.72 (bt, J=6 Hz, $=CH-CH_2-CH=$ of 89), 2.24 (t, J=6 Hz, $=CH-C\underline{H}_2-OH-O$ of 88).

28. cis-3-Mesyl-5-undecene (90)

Compound 90 was prepared using the procedure outlined above for compound 83. The yield was not determined. The pmr spectrum of 90 is as follows: δ0.90 (bt, 3H), 1.00 (t, J=7 Hz, 3H), 1.39 (m, 6H), 1.74 (p, J=7 Hz, 2H), 2.05 (m, 2H), 3.48 (bt, J=5.5 Hz, 2H), 2.99 (s, 3H), 4.63 (p, J=6.5 Hz, 1H), 5.45 (m, 2H).

29. Formolysis of 90

Using the procedure outlined above for the formolysis of 83 250 mg (1.0 mmol) of 90 was treated with 88% formic acid at 68° for 55 minutes. The reaction mixture was

worked up to give 370 mg of crude oil that consisted almost entirely of 91; pmr δ0.89 (bt, 3H), 0.96 (t, J=7 Hz, 3H), 1.29 (m, 6H), 1.61 (p, J=7 Hz, 2H), 2.01 (m, 2H), 2.27 (t, J=6 Hz, 2H), 4.90 (p, J=6 Hz, 1H), 5.40 (m, 2H).

30. 3-Mesyl-1,5-undecadien (93)

Compound 93 was prepared in 67% yield using the procedure outlined above for compound 83. The pmr spectrum of 93 is as follows: δ0.90 (bt, 3H), 1.33 (m, 6H), 2.05 (m, 2H), 2.54 (t, J=7 Hz, 2H), 2.97 (s, 3H), 5.00 (q, J=7 Hz, 1H), 5.24-5.62 (m, 4H), 5.88 (ddd, J=6, 10 and 17 Hz, 1H).

31. Reaction of 93 with 1,5-Diazabicyclo [5.4.0] undec-5-ene (DBU)

A 50 ml three-necked round-bottomed flask, two nitrogen inlet tubes and a ten ml addition funnel were dried in an oven at 110° for 30 minutes. The apparatus was assembled hot, flushed with a rapid stream of nitrogen and charged with 0.19 g (1.23 mmol) of DBU in ten ml of freshly distilled methylene chloride. The mixture was cooled to -78° and 0.25 g (1.12 mmol) of 93 in ten ml of methylene chloride added dropwise over 15 minutes. When the addition was complete the mixture was stirred for an additional hour at -78° and then at room temperature for three hours. The mixture

was then washed with 1% hydrochloric acid solution, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 0.24 g of unchanged 93. Repeating the reaction in refluxing chloroform again gave only starting material (93).

32. 1-Undecen-3-one (97)

A 500 ml three-necked round-bottomed flask equipped with a nitrogen inlet tube, reflux condenser topped with a drying tube, heating mantel and efficient magnetic stirrer was flushed with a rapid stream of nitrogen for ten minutes and then charged with 6.81 g (30 mmol) of DDQ and 150 ml of benzene. The mixture was stirred and 5.00 g (29.4 mmol) of 97[17] added all at once. The solution was heated to a gentle reflux for 13 hours, cooled to room temperature and triturated with 100 ml of hexane. The resulting suspension was filtered and the solvent removed under reduced pressure to give a dark red oil. The oil was dissolved in 50 ml of ether and washed with 5% bisulfite solution (100 ml), saturated bicarbonate solution (2 X 50 ml) and brine (2 X 50 ml), dried ($MgSO_4$) and the ether removed in vacuo. The resulting oil was chromatographed on a 10" X 1" column of neutral alumina with chloroform to give 4.38 g (89%); pmr δ0.88 (bt, 3H), 1.39 (bs, 12H), 1.12 (bt, 2H), 2.57 (t, J=7.5 Hz, 2H), 5.75 (dd, J=3 and 10 Hz, 1H), 6.27 (m, 2H).

33. S-(3-Oxoundecyl) Thiolacetate (13)

A 50 ml stoppered Erlenmeyer flask equipped with an efficient magnetic stirrer was charged with 1.16 g (6.89 mmol) of 97 and 20 ml of freshly distilled methylene chloride. The flask was cooled to 0° and 0.70 cc (0.76 g, 10.5 mmol) of thiolacetic acid added all at once. The mixture was stirred at 0° for 30 minutes and the solvent removed under reduced pressure to give a pale yellow foul-smelling oil. The oil was chromatographed on a 1 m X 2 cm column of Sephadex LH-20 with 1:1 methanol/chloroform to give, after evaporation of the solvent, 1.36 g (81.0%) of 13 as a very pale yellow oil; ir (neat) 2930 (s), 2860 (s), 1690 (s), 1460 (m), 1410 (m), 1355 (m), 1130 (s), 950 (m), 620 (m) cm^{-1}; uv (EtOH) λ_{max} 231 nm, ε=391; pmr δ0.88 (bt, 3H), 1.26 (s, 10H), 1.5 (bm, 2H), 2.29 (s, 3H), 2.38 (t, J=7 Hz, 2H), 2.72 (t, J=7 Hz, 2H), 3.05 (t, J=7 Hz, 2H); ms m/e (rel. intensity) 244 (M^+, 1), 226 (5), 169 (54), 157 (12), 146 (18), 143 (18), 141 (52), 59 (100); cmr δ208.4, 195.4, 42.7, 42.2, 31.7, 30.4, 29.7, 29.2, 29.1, 23.6, 22.8, 22.5, 14.0 ppm.

An analytical sample was prepared by molecularly distilling a small amount of the oil: Calcd. for $C_{13}H_{24}O_2S$: C, 63.89; H, 9.90. Found: C, 64.11, H, 10.09.

34. 1-Mercaptoundecan-3-one (99)

A 100 ml round-bottomed flask equipped with an efficient magnetic stirrer, heating mantel and reflux condenser was charged with 0.50 g (2.0 mmol) of 13 and 50 ml of 3% methanolic HCl solution (prepared by diluting 3.5 ml of conc. hydrochloric acid to 50 ml with methanol). The mixture was refluxed for six hours and the methanol removed in vacuo. The oily aqueous residue was combined with 20 ml of water and extracted with methylene chloride (3 X 15 ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give a pale yellow oil. The oil was chromatographed on a 110 mm X 10 mm column of silica gel G with hexane to give 260 mg (64%) of 99 as a pale yellow oil; pmr δ0.89 (bt, 3H), 1.28 (bs, 12H), 2.05 (m, 2H), 2.10 (t, J=8 Hz, 1H), 2.41 (t, J=7 Hz, 2H), 2.72 (m, 2H); cmr δ209.0, 46.0, 43.1, 32.1, 31.8, 29.1 (3 C's), 23.7, 23.1, 22.6 ppm; ir (neat) 2930 (s), 2860 (s), 2570 (w), 1715 (s), 1460 (m), 1410 (m), 1370 (m), 1280 (w), 1120 (w), 1075 (m), 1015 (w); ms m/e (rel. intensity) 202 (M^+ <1), 169 (10), 141 (20), 71 (53), 70 (25), 61 (26), 58 (44), 57 (55), 55 (19), 43 (100).

An analytical sample was prepared by molecularly distilling a small amount of the oil: Calcd. for $C_{11}H_{22}OS$: C, 65.29; H, 10.96. Found: C, 65.43; H, 10.71.

35. Bis-(3-Oxoundecyl) Disulfide (16)

A solution of 250 mg (1.23 mmol) of 99 in ten ml of methylene chloride was added all at once to a stirring solution of 312 mg (1.23 mmol) of iodine and 311 mg (3.07 mmol) of triethyl amine in 15 ml of methylene chloride. The reaction mixture was stirred for seven hours at room temperature then washed with sodium thiosulfate solution (1 X 20 ml), water (2 X 10 ml) and the solvent removed under reduced pressure. The resulting dark solid mass was chromatographed on a 120 mm X 10 mm column of silica gel G with 25% methylene chloride/hexane followed by 100% methylene chloride to give a white solid. Recrystallization from hexane gave 120 mg (24%) of 16 as colorless plates, mp 66.0-66.3° (Lit[9] 67.0-67.5°); pmr δ0.91 (bt, 6H), 1.23 (bs, 24H), 1.48 (m, 4H), 2.06 (t, J=7.5 Hz, 4H), 2.46 (t, J=6 Hz, 4H), 2.76 (t, J=6 Hz, 4H); cmr (benzene-d_6) 70.0, 38.0, 37.0, 35.4, 32.2, 29.9, 29.6, 26.0, 23.0, 14.3 ppm; ir (CH_2Cl_2) 2980 (s), 2920 (s), 1705 (s), 1400 (m), 1340 (m), 1240 (m), 1060 (m); ms m/e (rel. intensity) 402 (10), 201 (10), 200 (10), 169 (22), 142 (10), 141 (93), 95 (10), 87 (11), 83 (19), 81 (20), 71 (77), 70 (86), 57 (100), 55 (70), 43 (87).

36. 1,1-Diethoxyheptane (107)

Compound 107 was prepared in 86% yield from n-heptanal using the procedure of Isler.[37]

37. trans-2-Nonen-1-al (109)

Using the procedure of Isler[37] 107 was reacted with ethyl vinyl ether in the presence of borontrifluoride etherate to give crude 108. Distillation of the crude product gave a 1:1 mixture of 107 and 108. The mixture was stirred and refluxed for 2.5 hours with 18.3 g (0.23 mol) of sodium acetate, 170 ml of glacial acetic acid and 11 ml of water. The solution was cooled and poured into a beaker containing 500 g of cracked ice. The organic layer was separated and the aqueous layer extracted with methylene chloride (2 X 100 ml). The organic phases were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was distilled under reduced pressure to give 25.6 g (39%, based on 107) of 109 as a colorless oil, bp 66.0-69.0° (2.8 torr); pmr δ0.90 (bt, 3H), 1.33 (bs, 8H), 2.34 (q, J=7 Hz, 2H), 6.07 (ddt, J=1.5, 6 and 16 Hz, 1H), 6.85 (dt, J=6 and 16 Hz, 1H), 9.48 (d, J=6 Hz, 1H).

38. trans-1,4-Undecadien-3-ol (110)

A 500 ml three-necked round-bottomed flask equipped with a nitrogen inlet tube, nitrogen exit tube connected to a mercury bubbler, rubber septum and efficient magnetic stirrer was flushed with a rapid stream of nitrogen and flame dried. After cooling, the apparatus was charged with 4.00 g (28.5 mmol) of 109 and 100 ml of

dry ether and cooled to -78°. Vinyl lithium (Alfa Inorganics, 2.2 mol solution in THF, 15.5 ml, 34.2 mmol, 20% excess) was added dropwise via syringe with stirring over ten minutes. When the addition was complete the reaction mixture was stirred at -78° for one hour, allowed to warm to room temperature over one hour and then stirred for an additional hour. Ammonium chloride solution (2F, 100 ml) was then added and the ether layer separated. The aqueous layer was then extracted with ether (2 X 60 ml). The organic phases were combined, dried ($MgSO_4$) and the ether removed under reduced pressure. Short path distillation of the residual oil afforded 4.34 g (84.0%) of 110 as a colorless oil, bp 67.5-68-5 (0.45 torr); ir (neat) 3340 (s), 2950 (s), 2920 (s), 2840 (s), 1450 (m), 1100 (m), 970 (m), 950 (m), 905 (m) cm^{-1}; pmr δ0.88 (bt, 3H), 1.29 (bs, 8H), 2.03 (bdt, J=5.5 and 6.0 Hz, 2H), 2.55 (bs, 1H), 4.54 (bt, J=5.5 Hz, 1H), 5.06 (dt, J=10.0 and 2.0 Hz, 1H), 5.19 (dt, J=17.0 and 2.0 Hz, 1H), 5.33 (m, 1H), 5.49-6.04 (m, 4H); cmr 14.1, 22.6, 28.9, 31.7, 32.2, 73.7, 114.4, 131.0, 132.6, 139.8 ppm; ms m/e (rel. intensity) 168 (M^+, 1), 150 (8), 139 (5), 125 (5), 113 (11), 111 (10), 83 (100), 70 (49), 55 (43).

Anal. calcd. for $C_{11}H_{20}O$: C, 78.49; H, 12.00. Found: C, 78.56; H, 12.03.

39. trans-1,4-Undecadien-3-one (111)

A 250 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 1.36 g (6.0 mmol) of DDQ and 100 ml of methylene chloride. The solution was stirred and 1.00 g (5.9 mmol) of 110 in 15 ml of methylene chloride added all at once. The mixture was stirred at room temperature for 45 minutes then filtered and the solvent removed in vacuo. The dark red residue was chromatographed on a 20 cm X 3 cm column of neutral alumina with methylene chloride to give 0.87 g (88%) of 111 as a colorless oil; pmr δ0.89 (bt, 3H), 1.30 (bs, 8H), 2.21 (m, 2H), 5.75 (dd, J=2 and 10 Hz, 1H), 6.22 (dd, J=2 and 18 Hz, 1H), 6.32 (dt, J=1.5 and 15.5 Hz, 1H), 6.60 (dd, J=10 and 18 Hz, 1H), 6.93 (dt, J=6.5 and 15.5 Hz, 1H); cmr δ189.4, 148.9, 134.7, 128.0, 32.6, 32.5, 31.6, 28.9, 28.1, 22.5, 14.1 ppm.

40. S,S-1,5-Dithiolacetoxyundecan-3-one (112)

A stoppered 25 ml Erlenmeyer flask equipped with an efficient magnetic stirrer was charged with 310 mg (1.86 mmol) of 111 and ten ml of freshly distilled methylene chloride. The mixture was stirred, cooled to 0° and 278 μl (297 mg, 1.95 mmol) of thiolacetic acid added all at once. After 14 hours of stirring at 4° the solvent was removed in vacuo affording a foul-smelling, pale yellow oil. The oil was chromatographed on a 1 m X 2.5 cm

column of Sephadex LH-20 with 1:1 methanol/chloroform. Evaporation of the solvent afforded 420 mg (67.6%) of 112 as a pale yellow oil; ir (neat) 2930 (m), 2860 (m), 1690 (s), 1405 (m), 1350 (m), 1110 (s), 940 (m), 720 (m), 620 (m) cm^{-1}; uv (EtOH)λ_{max} 237 nm, ε=516 and 280 nm (ε=52); pmr δ0.87 (bt, 3H), 1.26 (bs, 8H), 2.30 (s, 6H), 2.75 (bt, J=6 Hz, 2H), 3.04 (bt, J=6 Hz, 2H), 3.83 (m, 1H); ms m/e (rel. intensity) 318 (M^+, 1), 275 (17), 243 (27), 213 (34), 167 (45), 43 (100); cmr 205.4, 195.2, 195.0, 47.5, 42.4, 39.5, 34.0, 31.4, 30.4, 30.2, 28.7, 26.7, 22.7, 22.4, 13.9 ppm.

41. S-(trans-3-Oxoundec-4-enyl) Thiolacetate (14)

A 50 ml round-bottomed flask equipped with an efficient magnetic stirrer was charged with 0.87 g (5.2 mmol), of 111 and 20 ml of methylene chloride. The solution was cooled to 0° and 0.390 ml (0.42 g, 5.5 mmol) of thiolacetic acid added all at once. The mixture was stirred at 4° (cold room) for 24 hours. Removal of the solvent in vacuo gave a crude oil that was chromatographed on a 160 mm X 10 mm column of silica gel G with 1:1 methylene chloride/hexane. Removal of the solvent under reduced pressure gave 0.85 g (69%) of 14 as a pale yellow oil; pmr δ0.88 (bt, 3H), 1.32 (bs, 8H), 2.22 (q, J=6 Hz, 2H), 3.26 (s, 3H), 3.0 (m, 4H), 6.02 (d, J=16 Hz, 1H), 6.82 (dt, J=6 and 16 Hz, 1H);

cmr δ197.4, 195.4, 148.0, 129.6, 53.3, 39.4, 32.3, 31.4, 28.7, 27.8, 23.2, 22.4, 13.9; ir (neat) 2970 (s), 2940 (s), 2860 (s), 1720 (s), 1690 (s), 1460 (m), 1410 (s), 1355 (s), 1120 (s), 1050 (s), 925 (w), 620 (s).

42. 1-Acetoxy-3-nonyne (133)

A 250 ml round-bottomed flask and drying tube were dried in an oven at 110° for ten minutes, assembled hot and allowed to cool. The flask was then equipped with a magnetic stirrer and charged with 14.0 g (0.10 mol) of 1-hydroxy-3-nonyne, 20.4 g (0.20 mol) of acetic anhydride and 60 ml of dry pyridine. The mixture was then stirred at room temperature for eight hours. The bulk of the pyridine and acetic anhydride was then removed under high vacuum. The dark residue was transferred to a separatory funnel and 40 ml of 5% sodium bicarbonate solution cautiously added. The mixture was extracted with three 20 ml portions of methylene chloride, the extracts combined, washed with brine, dried ($MgSO_4$), treated with Norit and the solvent removed *in vacuo* leaving a pale yellow oil. The oil was vacuum distilled to give 16.79 g (92%) of 133 as a green-yellow oil, bp 82-85° (0.4 torr); pmr δ0.92 (bt, 3H), 1.40 (m, 6H), 2.06 (s, 3H), 2.15 (m, 2H), 2.49 (dt, J=2 and 7 Hz, 2H), 4.14 (t, J=7 Hz, 2H); ir (neat) 2970 (s), 2940 (s), 2870 (s), 1750 (s), 1465 (m), 1440 (m), 1390 (m), 1375 (m), 1350 (w), 1245 (s), 1050 (s).

43. Reaction of 133 with Diborane[40]

A 100 ml four-necked round-bottomed flask, drying tube, pressure equalizing addition funnel, nitrogen inlet tube and thermometer were heated in an oven at 110° for ten minutes. The apparatus was assembled hot, fitted with a magnetic stirrer and flushed with a rapid stream of nitrogen for five minutes. The flask was charged with 5.46 g (0.03 mol) of 1-acetoxy-3-nonyne in 15 ml of anhydrous THF followed by 0.341 g (0.0083 mol) of sodium borohydride. The reaction vessel was cooled to 0° with an ice bath and 1.24 g (0.011 mol) of boron trifluoride etherate in five ml of THF added dropwise with stirring over one hour. After the addition was complete the reaction was stirred for an additional one-half hour at 0°. At the end of this time four ml of glacial acetic acid were added and the reaction stirred at room temperature for 14 hours. The reaction mixture was then poured into 30 ml of water and the organic layer separated. The organic layer was washed with two 15 ml portions of 5% sodium bicarbonate solution followed by two 20 ml portions of brine. The organic layer was dissolved in 40 ml of chloroform, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a colorless oil. The pmr spectrum showed the starting material to be approximately 40% converted (by integration) to 135. No attempt was made to separate the mixture.

44. 3-Buten-1-ol (121)

A five liter three-necked round-bottomed flask, mechanical stirrer, reflux condenser, 200 ml pressure equalizing funnel and two gas inlet tubes were dried in an oven at 110° for two hours. The apparatus was assembled hot, flushed with argon and charged with two liters of ether and 24.3 g (1.0 g-at) of magnesium shavings. Allyl bromide (121.0 g, 1.0 mol) was added dropwise with rapid stirring at a rate sufficient to maintain a gentle refluxing. When the addition was complete a 1000 ml round-bottomed flask containing 35 g (excess) of paraformaldehyde was attached to the reaction vessel by a glass inlet tube. The tube was extended approximately four cm into the etherial solution of allyl magnesium bromide and the flask containing the paraformaldehyde heated with a small bunsen burner. When the paraformaldehyde had completely sublimed the mixture was allowed to stir for an additional 30 minutes and then quenched with 200 ml of aqueous ammonium chloride solution. The ether layer was separated and the aqueous layer subjected to continuous ether extraction for 72 hours. The organic phases were combined, dried ($MgSO_4$) and the ether removed by distillation through a vigreux column. Distillation of the residue gave 40.3 g (56%) of 121 as a colorless oil, by 110-113° (lit.[47] 113°);

pmr δ2.30 (q, J=7 Hz, 2H), 2.97 (s, 1H), 3.62, (t, J=7 Hz, 2H), 5.05 (d, J=10 Hz, 1H), 5.08 (d, J=16 Hz, 1H), 5.77 (m, 1H).

45. 4-Chloro-1-butene (123)

Compound 123 was prepared from 121 in 84% yield using the procedure of Roberts.[38]

46. 1,2-Epoxy-4-chlorobutane (125)

a 1000 ml round-bottomed flask was charged with 27.8 g (0.142 mol) of MCPBA (85%, Aldrich) and 450 ml of methylene chloride. When solution had been effected 12.9 g (0.142 mol) of 123 were added and the solution stirred at room temperature for 18.5 hours. The reaction mixture was then filtered, washed with 5% bicarbonate solution (2 X 50 ml), dried ($MgSO_4$) and the methylene chloride removed by distillation through a vigreux column. Distillation of the residue under reduced pressure gave 8.1 g (54%) of 125 as a colorless oil, bp 59-60° (40 torr); pmr δ2.00 (m, 2H), 2.33 (dd, J=2 and 6 Hz, 1H), 2.80 (t, J=4 Hz, 1H), 3.07 (m, 1H), 2.64 (t, J=6 Hz, 2H).

47. Reaction of 125 with Heptynyl Magnesium Bromide

A 500 ml three-necked round-bottomed flask, reflux condenser, 100 ml pressure equalizing funnel and two

gas inlet tubes were dried in an oven at 110° for three hours, assembled hot, fitted with an efficient magnetic stirrer and flushed with argon. Magnesium (0.91 g, 0.037 g-at) and 15 ml of ether were added to the flask followed by approximately five ml of ethyl bromide in 35 ml of ether. When the reaction had started the remainder of the ethyl bromide (4.1 g, 0.037 mol) was added at a rate sufficient to maintain a gentle refluxing. When the addition was complete 3.61 g (37 mmol) of 1-heptyne in 35 ml of ether were added dropwise over 15 minutes. When the addition was complete the mixture was heated to a gentle reflux for one hour. The mixture was then cooled to -78° and 4.0 g (37 mmol) of 125 in 40 ml of ether were added over 15 minutes and the mixture stirred at -78° for an additional six hours. The mixture was then allowed to warm to room temperature and quenched with saturated ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether (2 X 50 ml). The ether phases were combined, dried ($MgSO_4$) and the solvent removed in vacuo. Chromatography of the residue on a 31 cm X 3 cm column of silica gel with 25% methylene chloride/hexane to give approximately 1.5 g of colorless oil; pmr δ2.00 (q, J=7 Hz, 2H), 3.5 (m, 4H), 4.09 (dt, J=8 and 10 Hz, 1H); ms m/e (rel. intensity) 186, 188, 190 (M^+ ion cluster <1), 189 (2), 187 (4), 185 (3), 125 (50), 123 (53), 95 (56), 93 (100).

48. Reaction of 143 with Trichloroacetyl Isocyanate

To an nmr tube containing approximately 20 mg of 143 and approximately 0.5 ml of deuteriochloroform were cautiously added five drops of trichloroacetyl isocyanate. When the exothermic reaction had subsided one drop of TMS was added and the pmr spectrum recorded; pmr δ2.26 (m, 2H), 3.62 (m, 4H), 5.24 (m, 1H).

C. Attempted Isolation of 24 and 28 from Dictyopteris Methanol Soluble Extracts

1. Partitioning of 48 between Methanol and Heptane

To a separatory funnel were added ten ml of methanol, 500 mg of 48 and ten ml of heptane. The separatory funnel was shaken vigorously for 20 minutes to establish equilibrium and the layers separated. The methanol layer was found to contain 490 mg of 2 after removal of the solvent in vacuo.

2. Chromatography of Synthetic 24 and Fractionation of Dictyopteris Methanol Extract

A mixture of 48 and 24 from various hydrogenation attempts (48a → 24) was chromatographed on a 100 cm X 2.5 cm column of Bio-Sil A using a mixture of chloroform and heptane as the eluting solvent. The mixture did not move appreciably with 20% chloroform/80% heptane solution but in a separate experiment eluted (poorly separated) after

passage of 460 ml of 75% chloroform/25% heptane. The mixture was completely eluted after passage of 480 ml of solvent. The crude methanol extract (167 g) was then chromatographed on a 50 cm X 4.5 cm column of Bio-Sil A and exhaustively eluted with chloroform to give 47 g of oil. This oil was rechromatographed on a fresh Bio-Sil A column of similar dimensions with 20% chloroform/8% heptane to remove the hydrocarbons and carotenoids and then exhaustively eluted with chloroform to give 25 g of oil. This oil was then chromatographed in three g portions on a 55 cm X 3 cm column of Sephadex LH-20 with 1:1 methanol/ chloroform and fractions collected that corresponded to the elution volumn of synthetic 24 chromatographed previously with this system. The oil obtained after removal of the solvent (9.9 g) was divided in two halves and chromatographed on the 100 cm X 2.5 cm column of Bio-Sil A with 75% chloroform/25% heptane and the fraction eluting between 450 and 500 ml collected and evaporated. A pmr spectrum of the residual oil did not confirm the presence of either 24 or 28. This fraction (420 mg) was rechromatographed on the above column with 75% chloroform/25% heptane and the fraction corresponding to the elution volumn of synthetic 24 isolated. This fraction weighed less than one milligram and did not contain natural 24 or 28 (by pft analysis).

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