SYNTHETIC STUDIES IN SPIROAXANE SESQUITERPENOIDS

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ABSTRACT

SYNTHETIC STUDIES IN SPIROAXANE SESQUITERPENOIDS

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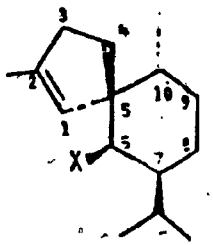
Sesquiterpenoids of a novel spiro[4.5]decane carbon skeleton (the "spiroaxanes") have recently been isolated and characterized from marine (e.g. axisonitrile-3) as well as terrestrial (glehnol) sources. In this study a number of approaches to the total synthesis of the spiroaxane derivatives has been investigated using optically active α-formyl menthone (166) and α-cyanomenthone (168) as starting materials.

All strategies tried for the spiropentannelation using α-cyanomenthone as the starting point were unsuccessful on account of the difficulty encountered in converting the cyano group to an aldehyde group, a result which has been attributed to the sterically encumbered nature of the cyano group in the derivatives. Aspects of the alkylation reactions of α-cyanomenthone and α-formyl menthone are discussed.

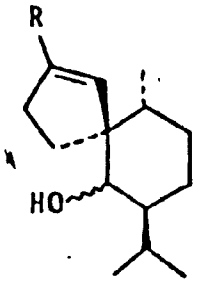


24 X = $N\equiv\overset{+}{C}\overset{-}{}$ (axisonitrile-3)

25 X = N=C=S (axisothiocyanate-3)

26 X = NHCHO (axamide-3)

32 X = OH (glehnol)



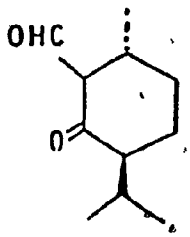
R = CH_3, 202

R = CHO, 201

R = COOEt, 218

A = α-OH

B = β-OH



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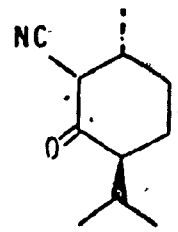

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Two approaches to the spiropentannelation employing α-formyl menthone as the starting point were successful. However, both the spiro[4.5]decane systems produced had the stereochemistry at the spirocarbon which was epimeric to that in the natural spiroaxanes. One of the approaches involved the reaction of the sodium salt of 166 with 1-carbethoxytriphenylphosphonium tetrafluoroborate (133), and generated the spiroester 200B. The other approach which involved the Michael reaction of methyl vinyl ketone with the enolate of 166, followed by aldol cyclization to a spirocyclohexanone derivative and subsequent ring contraction and appropriate functional group transformations led to the epimeric alcohols 202. One of these epimers

(202B) has been shown to be identical to the alcohol obtained via the reaction involving the phosphonium salt 133. The stereochemistry at C-5 in 201B has been assigned as epimeric to that in glechnol. These results showed that in the reaction of both the phosphonium salt 133 and methyl vinyl ketone exclusive "axial alkylation" of the most stable conformer of the enolate of α-formyl menthone had occured. The stereochemical aspects of these reactions as well as the configurational assignments of the hydroxyl groups in the spiroderivatives, based on their IR and NMR spectra are described.

TO MY PARENTS

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. Z. Hamlet for suggesting this research project and for his continued guidance and encouragement throughout the course of this study.

He also wishes to thank his research committee for their cooperation and understanding. The author is also indebted to Mr. Walter Chazin for obtaining the 400 MHz NMR spectra and to Mr. Lalchan Persaud for obtaining the UV spectra. Special thanks are also due to Mr. Thomas Chaly at McGill University for the assistance he provided during the later stages of this study.

The author is also indirectly indebted to Professor D. J. Hart of The Ohio State University and to Professor D. Caine of Georgia Institute of Technology who have communicated to Dr. Hamlet during the course of this study providing some experimental details and NMR spectra of some authentic samples.

Further, he extends his gratitude towards the technical staff of the Department of Chemistry for their support and cooperation.

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LIST OF ABBREVIATIONS

Ac	Acetyl
BT	Benzothiazole
DBU	1,5-Diazobicyclo[5.4.0]undec-5-ene
Dibal-H	Diisobutyl aluminum hydride
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
HMPT	Hexamethylphosphoramide
LDA	Lithium di-isopropylamide
LAH	Lithium aluminum hydride
MCPBA	meta-chloroperbenzoic acid
MIP	Methoxyisopropylidine-
MVK	Methyl vinyl ketone
THF	Tetrahydrofuran
Triton-B	N-Benzyltrimethylammonium Hydroxide
Ts	para-Toluenesulfonyl

LIST OF SCHEMES, TABLE AND FIGURE

INTRODUCTION

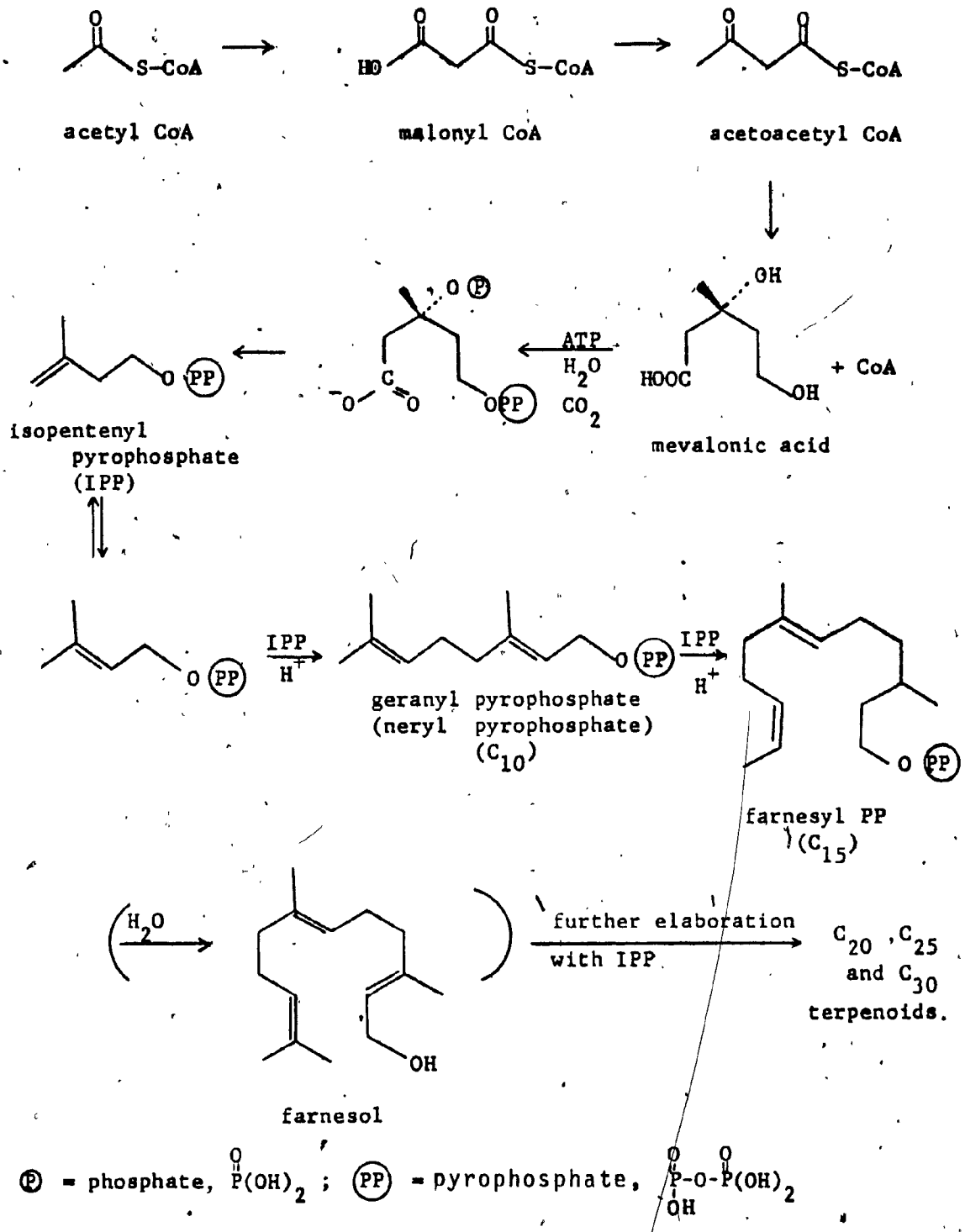
It cannot be denied that some of the major advances in organic chemistry have stemmed from work in the field of chemistry of natural products. Such fundamental concepts as conformational analysis and the principle of conservation of orbital symmetry are but two examples of such major advances within the last three decades, evolving from synthetic studies in natural products, not to mention significant contributions to the advancement of spectroscopic techniques, mechanistic insights, and synthetic methodologies. One of the most interesting groups of natural compounds which continues to fascinate organic chemists, and where much vigorous activity still continues, is that of the terpenes and terpenoids.[1]

Following the first perceptive observation of Wallach[2] that terpenoids are formally constituted of branched five-carbon units (isoprene units), Ruzicka and Stoll[3] hypothesized that the terpenoids are also biosynthesized from these five carbon modules. This hypothesis had a far-reaching effect on the understanding and the development of the chemistry of terpenes and terpenoids. According to the currently accepted view of terpene biogenesis,[4] the true universal precursor of all terpenoids is mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid; R-enantiomer), which was isolated from nature only in 1956, and which in turn is derived from

acetyl coenzyme A ("active" acetate). These biosynthetic pathways of the terpenes are outlined in Scheme 1. The monoterpenes (C_{10}) are derived from geranyl pyrophosphate (geranyl PP), the sesquiterpenes (C_{15}) from farnesyl PP, the diterpenes (C_{20}) from geranyl geranyl PP, the sesterterpenes (C_{25}) from geranyl farnesyl PP, and the triterpenes (C_{30}) from farnesyl farnesyl PP.

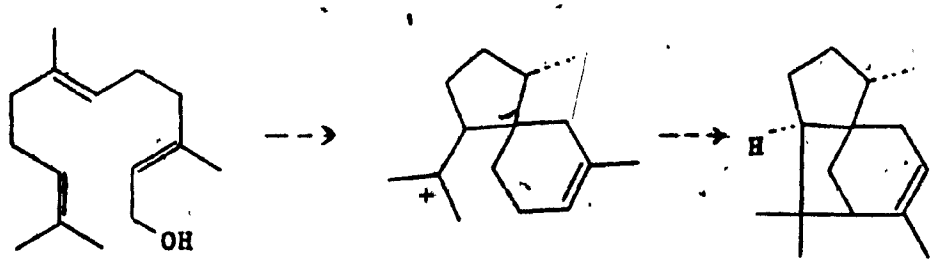
The biogenesis of sesquiterpenes has been the subject of a recent review.[5] Although containing only 15 carbons, the sesquiterpenes provide an amazing variety of carbon skeletons that can be derived from rational chemical transformations of farnesol. In 1953 Ruzicka postulated that the biosynthesis of cedrene from farnesol might proceed through the intermediacy of the cation 1 having the spiro[4.5]decane carbon skeleton,[6] as shown in Scheme 2. The actual occurrence of natural sesquiterpenes having the spiro[4.5]decane system has been established in 1956 by the work of Sorm and coworkers.[7-9] Since then a large number of naturally occurring spiro[4.5]decane sesquiterpenes has come to light, and a review[10] of the chemistry of these compounds appeared in 1974. At the time of this review three different classes of these spiranes were known, the classification being based on the location of the alkyl substituents on the spiro[4.5]decane system.

The first and the largest of these class of naturally



Ⓟ = phosphate, $\overset{O}{\overset{\|}{P}}(OH)_2$; (PP) = pyrophosphate, $\overset{O}{\overset{\|}{P}}(OH)-O-\overset{O}{\overset{\|}{P}}(OH)_2$

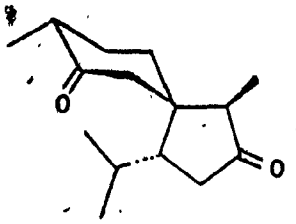
Scheme 1.



farnesol 1 cedrene

Scheme 2

occurring spirodecanes are the acoranes, exemplified by aco-



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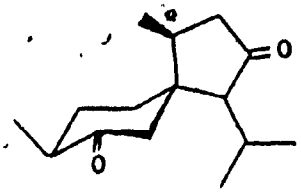

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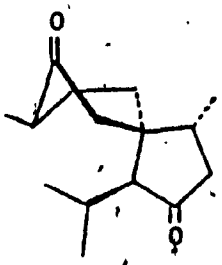

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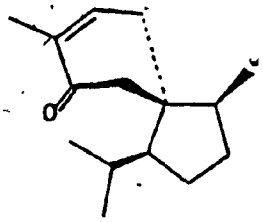

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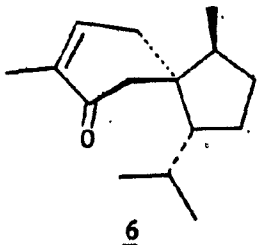

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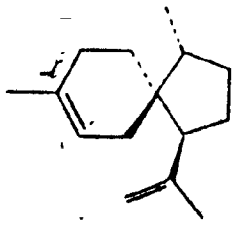
rone (2), isoacorone (3), cryptoacorone (4), acorenone (5), and acoronene (6), which are constituents of sweet flag oil (Acorus calamus L.).[7,9,11] Acoronene (6) which differs from

acorenone (5) has been characterized recently by Japanese



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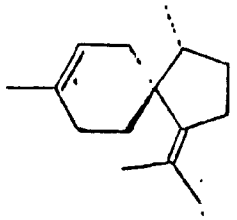

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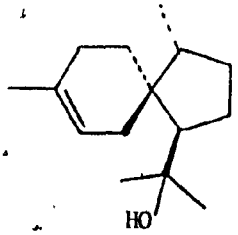

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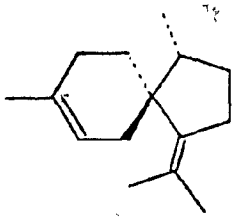

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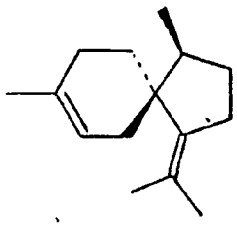

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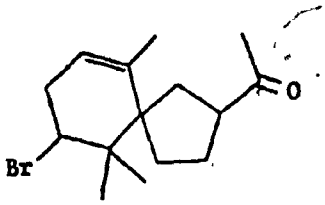
workers.[12]

Spiranes with the absolute stereochemistry of natural (-)-α-cedrene, and therefore related enantiomerically to acoranes have also been isolated from conifer essential oils. These spiranes are referred to as alaskanes, and are exemplified by α-acoradiene (7), δ-acoradiene (8), and α-acorenol (9) isolated from the conifer Juniperus rigida,[13,14] a cedrene-producing species. From a related conifer Chamaecyparis nootkatensis α-alaskene (γ-acoradiene, 10) and β-alaskene (11) were isolated.[15,16] In both the acoranes and the alaskanes the five-membered ring of the

spirodecane system accommodates the branched three-carbon substituent as well as a methyl group.

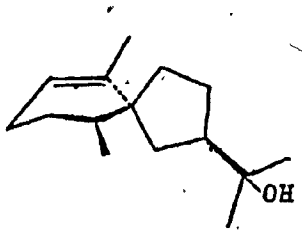
A second class of spiro[4.5]decane sesquiterpenoid was isolated from the marine alga Laurencia glandulifera Kutzing and has been named spirolaurenone.[17] Based on spectral analysis, and chemical degradation its structure was assign-



12

ed as 12. This is the only member of this class of spirane known so far, and one of the few known natural products containing bromine.

A third class of spiro[4.5]decanes where the placement of the alkyl substituents differs from that of the two types mentioned above, is the spirovetivanes which have been isolated from a variety of plant sources. The first of these, agarospirol (13), has been isolated from the oil of fungus-infected agarwood (Aquillaria agollocha Roxb.).[18] Although this sesquiterpenoid was the first reported example having this carbon skeleton, another member, β-vetivone (14), isolated from the essential oil of the Indian grass Vetiveria zizanioides was the first member of this class to come under



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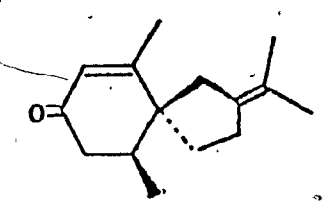

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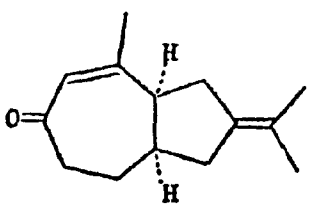

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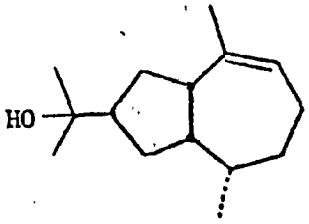
extensive chemical scrutiny.[10] On account of an undetected skeletal rearrangement during degradative studies the hydroazulene structure 15 was wrongly assigned in 1940 to this substance.[19] That β-vetivone did actually have the spiro-[4.5]decane structure 14 was established only in 1967 by the work of Marshall.[20,21] This prompted the revision of another member of this class of spiranes, hinesol, from 16[22] to 17.[21,23,24] Other spirovetivanes isolated from vetiver oil



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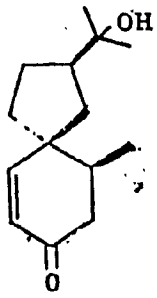

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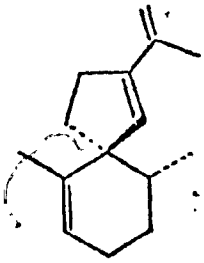

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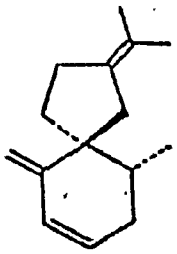

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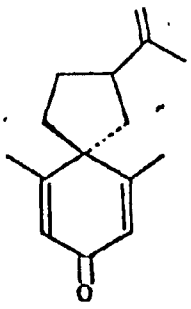
are α-vetispirene (18) and β-vetispirene (19).[25]

More recently, anhydro-β-rotunol (20),[26,27] solavetivone (21),[26,27] lubimin (22),[28-30] and oxylubimin (23)[28,31]

have been isolated as stress metabolites from potato tubers



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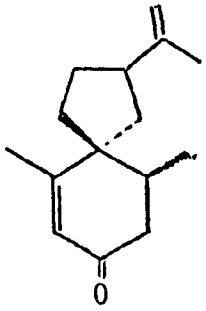

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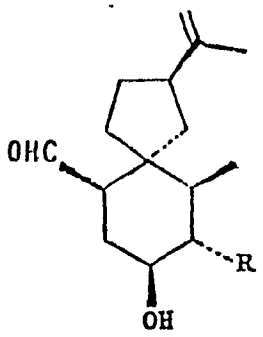


22, R = H
23, R = OH

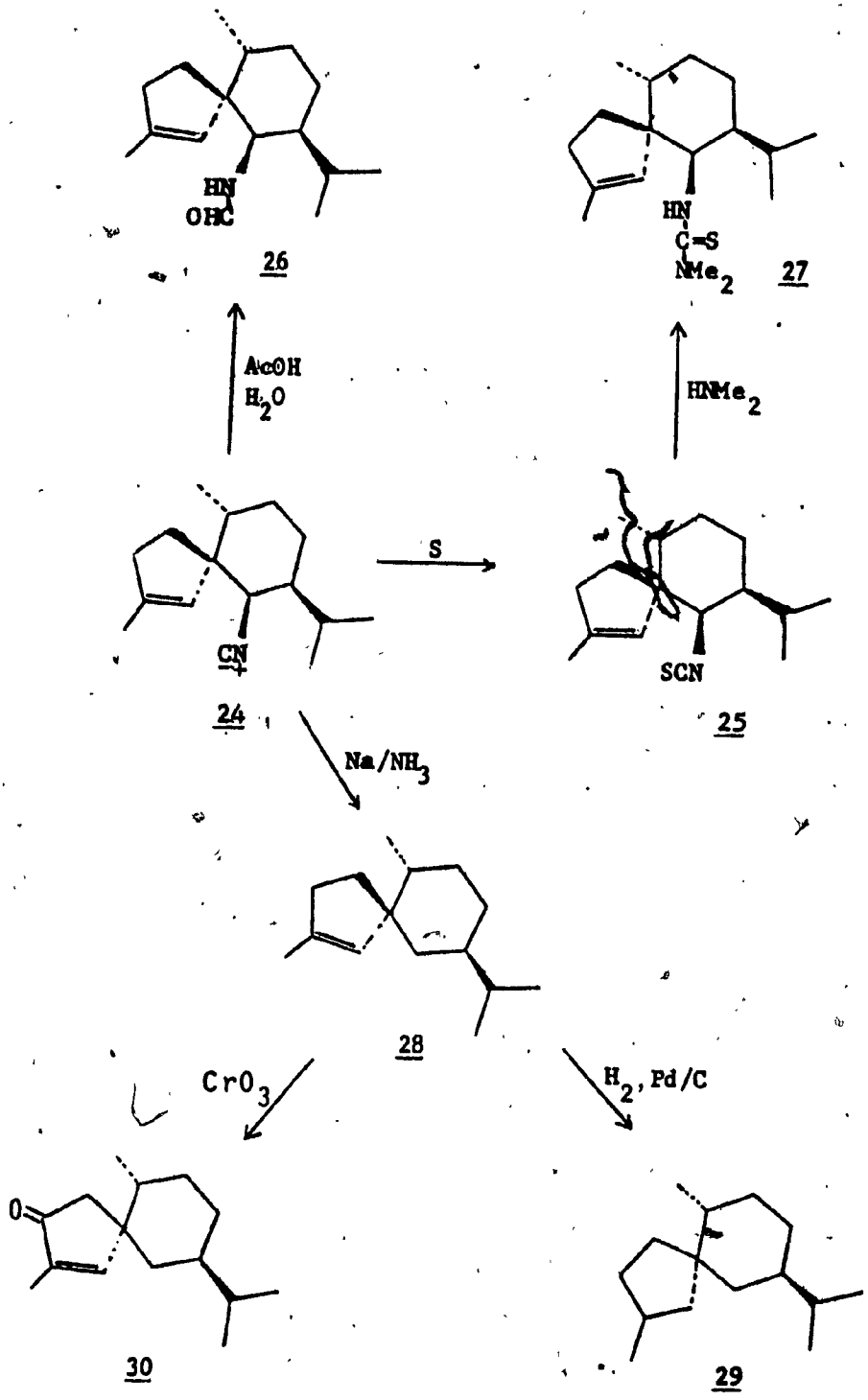
infested with the blight fungus Phytophoria infestans. Lubimin (22), and oxylubimin (23) have also been isolated from egg plants infested with various fungi.[28,29,31] The stereochemical assignments of these stress metabolites have been made solely on the basis of NMR data. It has been shown that lubimin (22) has antifungal activity and it has been suggested that this as well as other spirovetivanes produced by the potatoes may be involved in the defence mechanism of the potato against various pathogens.[32]

Spiro[4.5]decane sesquiterpenoids of yet another carbon skeleton (the fourth class so far identified) have been isolated recently from marine as well as terrestrial sources. From the marine sponge Axinella cannabina, Italian workers[33] have isolated, among other products, spiranes belonging to this new carbon skeleton with isonitrile, or formamido, or isothiocynate functional group in the six-membered ring. The authors have designated the new carbon skeleton "spiro-

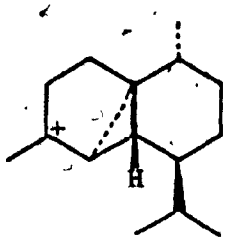
axane",[33] which differs from the other spirodecanes in having the isopropyl group in the six-membered ring rather than in the five-membered one. Based on chemical and spectral data, and single crystal x-ray crystallography the isonitrile derivative, called axisonitrile-3 (mp 101-103°C, $[\alpha]_D$+68.44°), has been assigned the structure 24. The absolute stereochemistry, however, has not been established. This substance could be converted into the isothiocyanate derivative, called axisothiocyanate-3 (25) as well as the formamido derivative, axamide-3 (26). These and other transformations reported by the authors[33] are outlined in Scheme 3.

The co-occurrence in the same marine organism of the isonitrile 24, the isothiocyanate 25, and the formamide 26 has been considered as evidence that the formamide is the biosynthetic precursor of the isonitrile, and the isothiocyanate.[33-36] It was also suggested by the authors[33] that the cation 31, postulated earlier by Japanese workers[37] to be the precursor of cubenes, might be one of the intermediates in the biogenesis of axisonitrile-3 (24).

Almost immediately after the report of the isolation of the spiroaxanes from the marine source by the Italian workers,[33] Soviet workers reported the isolation and characterization of a sesquiterpene alcohol having the same carbon skeleton from a terrestrial source.[38] They named the sub-


HN
OHC
26
HN
C=S
NMe2
27
AcOH
H2O
HNMe2
CN
24
S
SCN
25
Na/NH3
28
CrO3
H2, Pd/C
O
30
29

Scheme 3.



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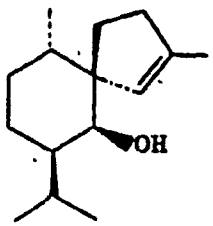
stance glehnol which was a very minor component of the oleoresin of the Sakhalin spruce Picea glehnii.[39] By far the



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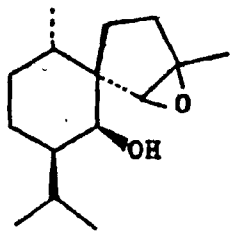
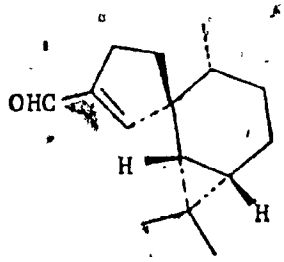


33

major components of the resin were α- and β-pinenes (90-93%) with minor amounts of other mono- and sesquiterpenoids. Glehnol had $[\alpha]_D^{20}$ +10° ($CHCl_3$), and gave a paranitrobenzoate mp 85°. Based on spectroscopic properties (IR, PMR and CMR) of the alcohol itself, and on single crystal x-ray crystallography of its epoxide 33, glehnol was assigned the structure 32. The absolute stereochemistry of the compound has not been established yet. Apparently the Soviet workers were not aware of the report by the Italian workers,[33] as no reference to this is given in their paper.[38]

The newest and the fifth type of spirane sesquiterpeno-

id to join the expanding list of spiranes is (+)-vitrenal (34), which has been unveiled in 1980 by Japanese workers.[40] This substance was isolated from the liverwort Lepidozia vitrea Steph., and has been shown to be a plant-growth in-



34

hibitor. Based on chemical and spectral evidence, as well as on x-ray crystallography, the compound was assigned the tricarbocyclic structure with the absolute configuration as shown in 34. The structure incorporates the spiro[4.5]decane system with an additional gem dimethyl cyclopropyl group bridging C-6 and C-7. The carbon skeleton of this compound is closely related to that of glehnol as well as the marine sesquiterpenoids axisonitrile-3 axisothiocyanate-3, and axamide-3. Still newer types of spirane sesquiterpenoids are bound to enter the arena in the future from both terrestrial and marine sources.

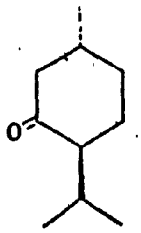
Although very modest in comparison to the number isolated from terrestrial sources, the sesquiterpenoids still constitute the largest number of terpenoids isolated from marine sources. As in axisonitrile-3 the isonitrile functionality is occasionally encountered in terpenoids from ma-

rine organisms.[35,41-44] One explanation for the presence in marine organisms of isonitriles (compounds which are generally associated with unpleasant odors) is that they are utilized as defensive secretions against predators.[45] Marine natural product chemistry is still very young and the number of terpenoids isolated from the marine environment is steadily increasing. When the extent of our knowledge of the marine-derived compounds reaches a level comparable to that of the terrestrially derived ones, it will be interesting to compare such aspects as the oxidation states and distribution patterns with a view to relating these to other aspects of the evolutionary theory. An intriguing observation, in this connection, has been that a number of marine sesquiterpenes are enantiomers of the corresponding terrestrial compounds.[45]

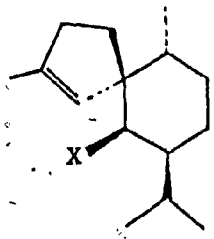
It is interesting to note that, in the novel class of spirane sesquiterpenoids recently come to light, the marine-derived spiroaxanes (24,25 and 26) and the terrestrially derived glehnol (32) have the identical 2,10-dimethyl-7-isopropylspiro[4.5]deca-1-ene system with a substituent in the 6-position. As the absolute stereochemistry of these compounds are still undetermined, it is still unknown whether the carbon skeleton of glehnol is enantiomerically related to that of the spiroaxanes. Therefore, to attempt a total synthesis of these compounds would be a worthwhile and challenging endeavor.

OBJECTIVES OF PRESENT STUDY

The original objective of the present study was to achieve a total synthesis of optically active axisonitrile-3 (24) with a view to establishing the absolute stereochemistry of the marine natural product (+)-axisonitrile-3. Once the synthesis of axisonitrile-3 is achieved it can be easily converted to its congeners axisothiocyanate-3 (25) and axamide-3 (26) by known reactions, as has already been shown



35



24, X = $\overset{+}{N}\equiv\bar{C}$
25, X = N=C=S
26, X = NH-CHO
32, X = OH

by the workers who isolated these natural products.[33]

At the outset it was supposed that in axisonitrile-3 the stereochemistry of the 6-membered ring at carbons carrying the methyl and isopropyl substituents was identical to that of the corresponding carbons in (-)-menthone (35). Taking advantage of the carbonyl functionality in 35, the plan was to examine various approaches to the construction of the required methylcyclopentenyl spirocycle with the proper orientation relative to the substituents in the 6-membered ring. To this end several schemes of spiro-

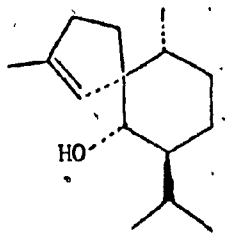
annelation were to be attempted. The spectral properties as well as the sign and the magnitude of the optical rotation of the synthetic product were then to be compared with those reported[33] for the natural product to ascertain whether one is identical to or enantiomeric with the other.

While the present studies were in progress there appeared a communication, reporting a total synthesis (by an entirely different route) and x-ray structure determination of (−)-axisonitrile-3, which seemed to establish that the synthetic material had the absolute stereochemistry as depicted in structure 24 indicating that the natural product had the enantiomeric structure.[46] However, there were still small discrepancies between the NMR chemical shifts observed for the methyl groups of the isopropyl substituent of the synthetic material and those of natural product.

Soon after the communication announcing the synthesis of (−)-axisonitrile-3, a Soviet group reported the isolation from a terrestrial source of a sesquiterpenoid, glehnol (32), and the structure determination by x-ray crystallography of its epoxide derivative.[38] Although the absolute stereochemistry of glehnol was not established, the x-ray study showed that it possessed the same novel spiro[4.5]-decane system as in axisonitrile-3.

The appearance of the two publications mentioned above

necessitated some modified perspectives of the objectives of the present study. It was interesting to note that the published scheme[46] involved the synthesis of the alcohol 36 (with the absolute stereochemistry as shown), which was then converted in four steps to 24 by known reactions. It seemed, at this stage, that one of the logical objectives now would be to achieve the total synthesis of the alcohol 36 by



36

independent pathways. During the course of the present studies it also seemed possible that the synthesis of 36 and its C-6 epimer could be achieved. It should be pointed out that the epimer of 36 is going to be identical to or enantiomeric with glehnol (32).

The pursuit of the alcohol 36 and its epimer thus became all the more interesting. The synthesis of the alcohol 36 now will constitute a formal total synthesis of axisonitrile-3 and will establish the stereochemistry of the natural compound. Synthesis of the alcohol epimeric to that of 35 (i.e., 32) and comparison of its spectral properties as well as the magnitude and sign of the specific rotation with those reported for glehnol will help to establish the

absolute stereochemistry of this natural product. Another dividend expected out of the syntheses of these compounds would be answering the curiosity whether or not the carbon skeleton of the terrestrially occuring glehnol is the optical antipode of the marine derived axisonitrile and its derivatives.

DISCUSSION

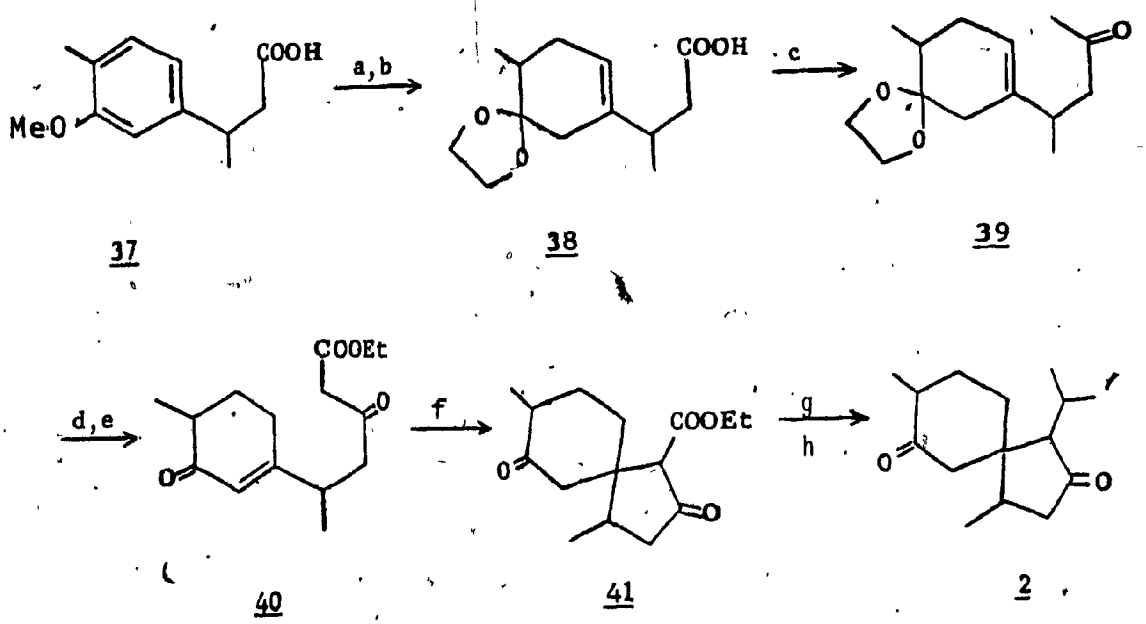
A. APPROACHES USED BY OTHERS FOR SPIROPENTANNELATION.

A variety of synthetic methods are available for the construction of spirocyclic systems of various ring sizes, and two rather extensive surveys of this topic have appeared recently.[47,48] In both reviews only the spiroannelation routes which led to a free carbocyclic linkage are surveyed. A number of methods for constructing spiro[4.5]decane systems are discussed in Marshall's review[10] of the chemistry of spiro[4.5]decane sesquiterpenoids, which covers the literature up to 1973. Nevertheless, it seems appropriate to present here very briefly some selected approaches which led specifically to spiropentannelation, as a prelude to the discussion of the approaches used in the present study.

1. Non-Photochemical Approaches

Acorone (2) has been synthesized by using the sequence outlined in Scheme 4.[10,49] A noteworthy aspect of this approach is the spiropentannelation by making use of an internal Michael addition (40 ⟶ 41). The major disadvantage in this approach had been that the final alkylation step did not give reproducible results.[49]

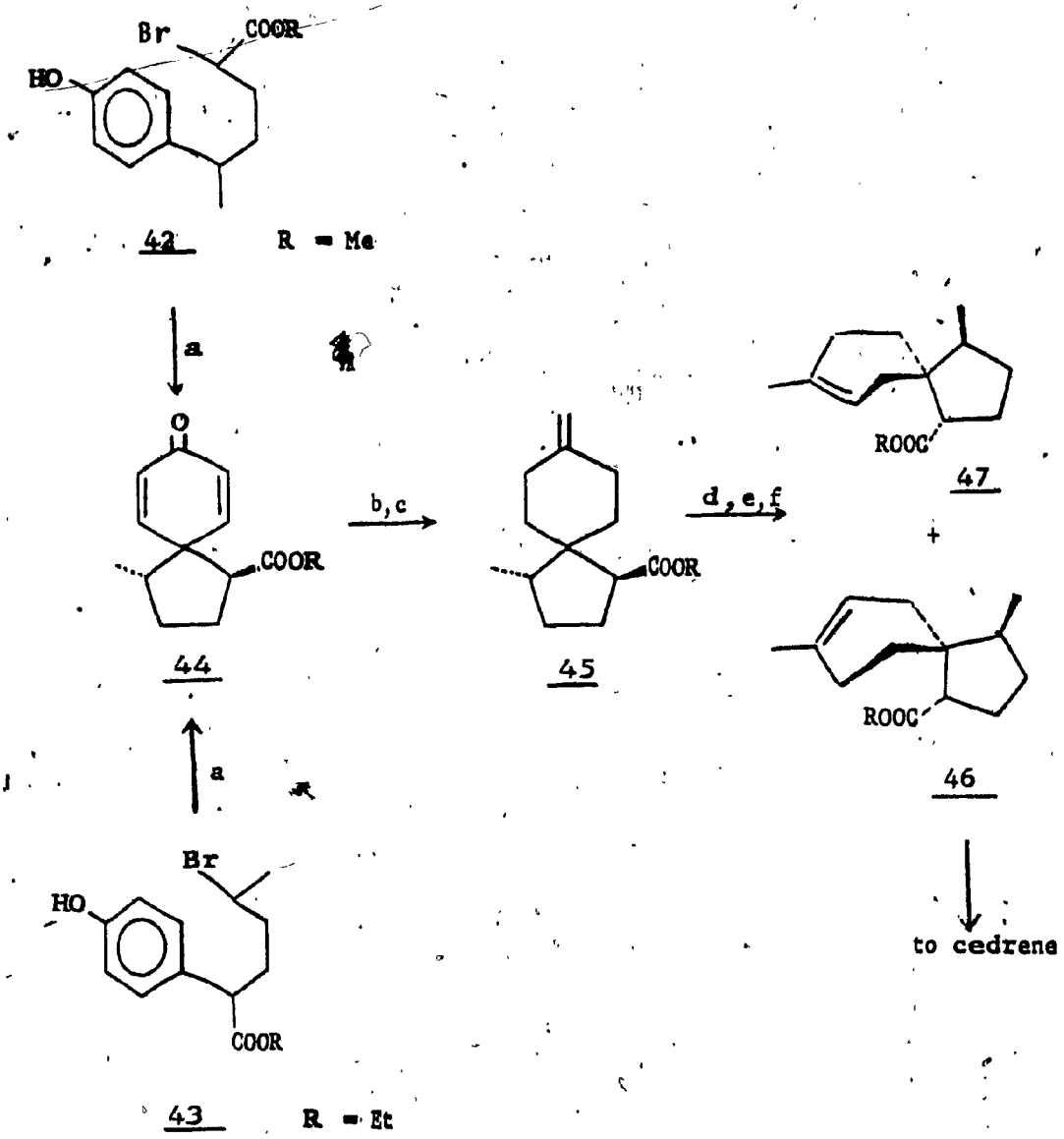
Several syntheses employing phenols appropriately substituted in the 4-position have been used for spiropentannelation. The approach makes use of the principle of "aryl



a. Li,NH_3; b. $(CH_2OH)_2,H^+$; c. MeLi; d. Et_2CO_3,NaH; e. H_3O^+; f. "base"; g. "alkylation"; h. $OH^-,-CO_2$

Scheme 4

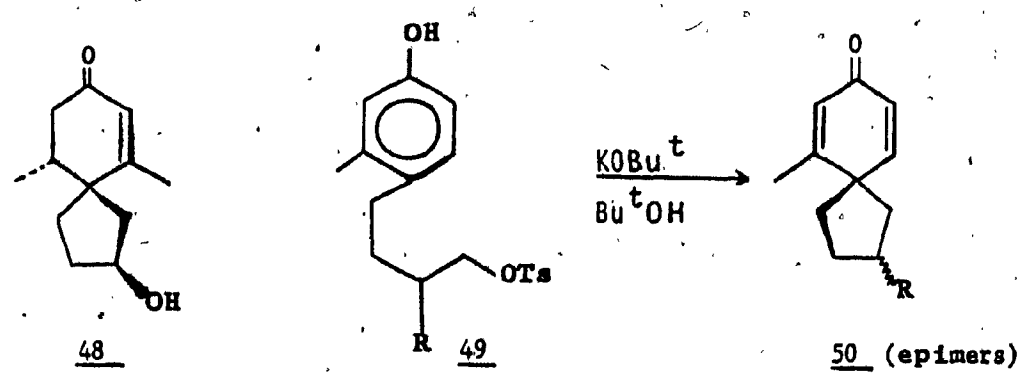
1,5-participation" originally demonstrated by Winstein,[50] whereby electron participation from the phenolic oxygen via the 4-carbon atom occurs in a reaction at the δ-carbon atom in the para-substituent producing a spiro[4.5]decane system having a cross-conjugated cyclohexadienone moiety. Scheme 5 illustrates this approach used independently by two groups in the synthesis of cedrene and cedrol.[51,52] Recently Japanese workers have developed an effective spiroannelation reaction starting with a phenol having a suitable α-diazo-ketone substituent in the para-position.[53] The same workers have used a stereochemically controlled Birch reduction following the spiroannelation to produce the spiranyl



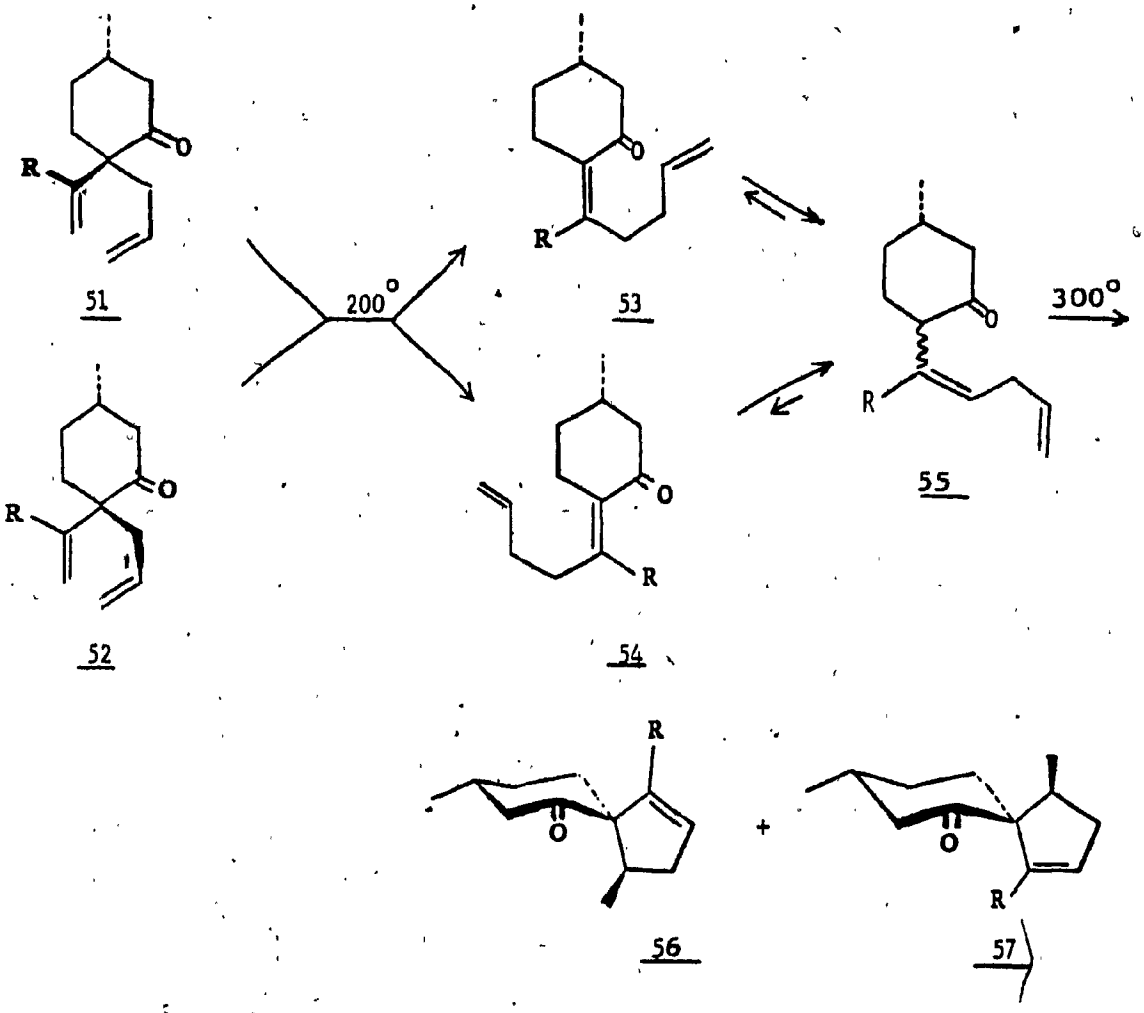
a. $KOBu^t$; b. H_2/Pd; c. $CH_2=PPh_3$; d. KOH; e. HCl; f. NaOMe

Scheme 5

ketoalcohol 48[54] which was a key intermediate in the synthesis of hinesol and agarospirol.[55] Base-catalyzed spiroannelation of phenolic tosylates (49 ⟶ 50) has been



one of the crucial steps in the synthesis of spirovetivane derivatives reported by another Japanese group.[56]



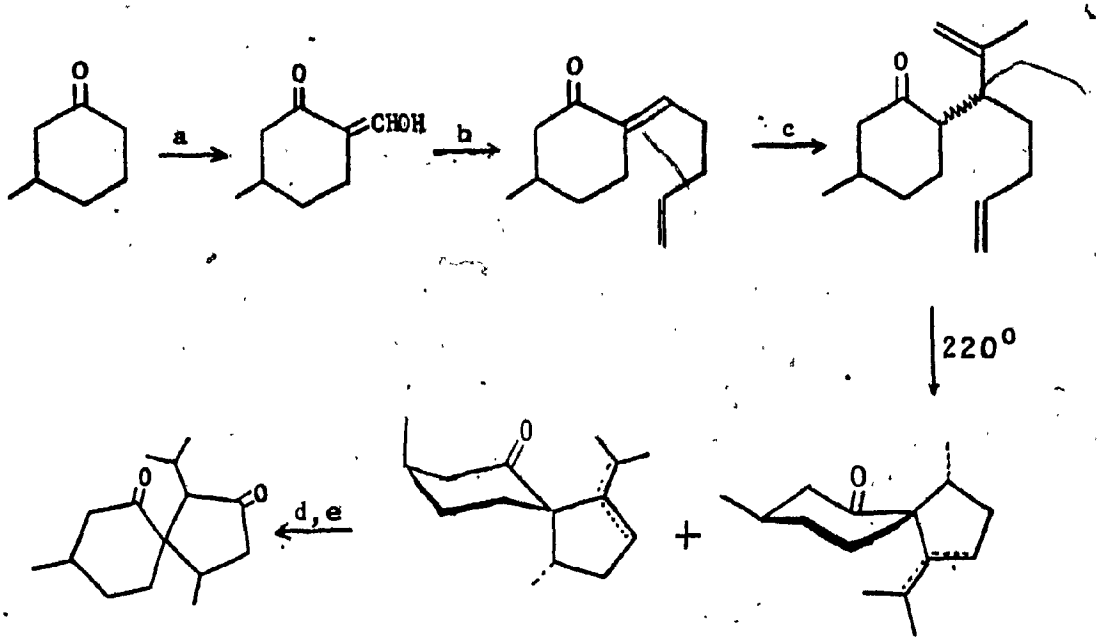
Scheme 6

A thermal cyclization route to the spiro[4.5]decane system has been developed by Conia's group. In one approach[57,58] (Scheme 6) enones of the type 55 (obtained from cyclohexanones of the type 51 and 52) were subjected to temperatures above 300°C whereupon they cyclized to give spiro[4.5]decanes 56 and 57. The same approach has also been used for the synthesis of acorones (Scheme 7).[59]

Another route to spiro[4.5]decanes is the chloroolefin spiroannelation developed by Lansbury,[60] which is outlined in Scheme 8. Here the cyclization is initiated by the cation produced upon the acid treatment of the cyclohexanol 58, producing the spiro system 59 after hydrolysis. The stereochemical aspects of such cyclizations have not been fully elucidated as yet.

Marshall's approach to the synthesis of hinesol[61,62] (Scheme 9) started with a known tricyclic dienone 60[63] incorporating a subdued spiro[4.5]decane system, which is unleased at a later stage. The diol 61 was converted to its monomesylate which was subjected to solvolytic fragmentation in the presence of base to liberate the spiro[4.5]decane derivative 61 which was taken further to hinesol acetate.

What can be viewed as intramolecular alkylation approaches to spiroannelation have been used recently by several workers. A β-vetivone synthesis by Stork (Scheme

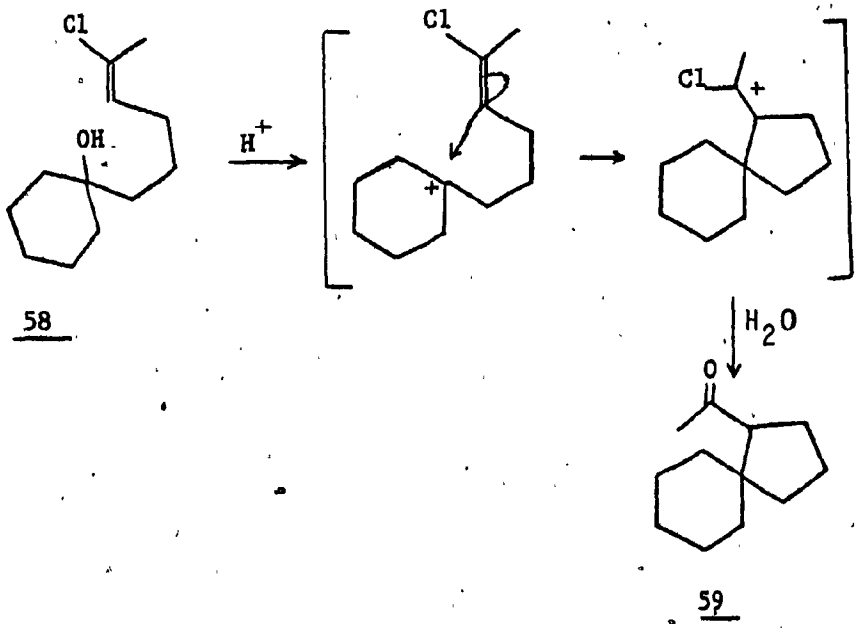


(acorones)

a. $HCOOEt, NaH$; b. $CH_2=CH-CH_2-CH_2-MgBr$; c. $CH_3-C(MgBr)=CH_2$;

d. BH_3; e. CrO_3

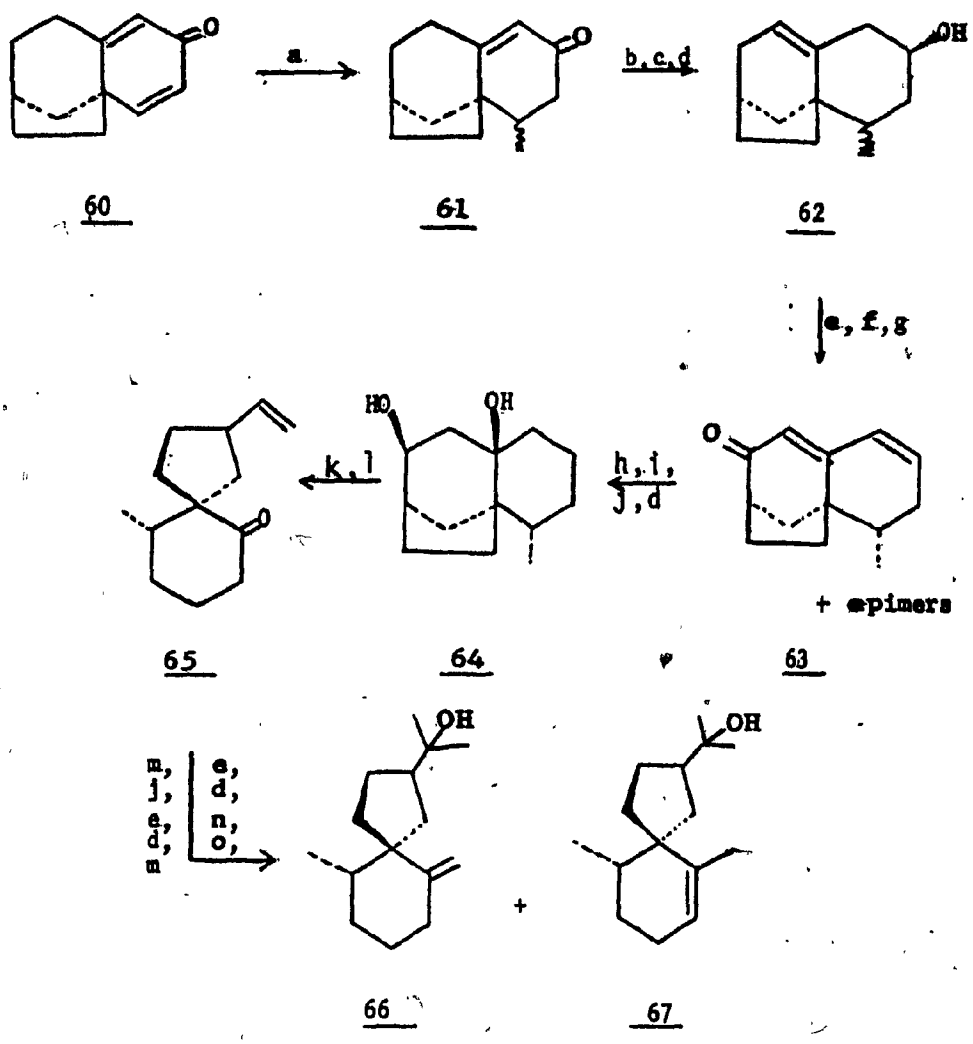
Scheme 7



58

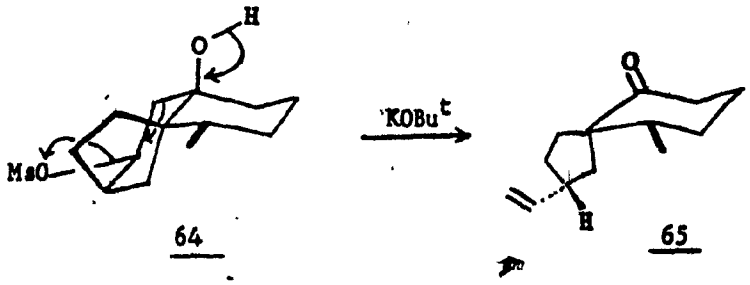
59

Scheme 8



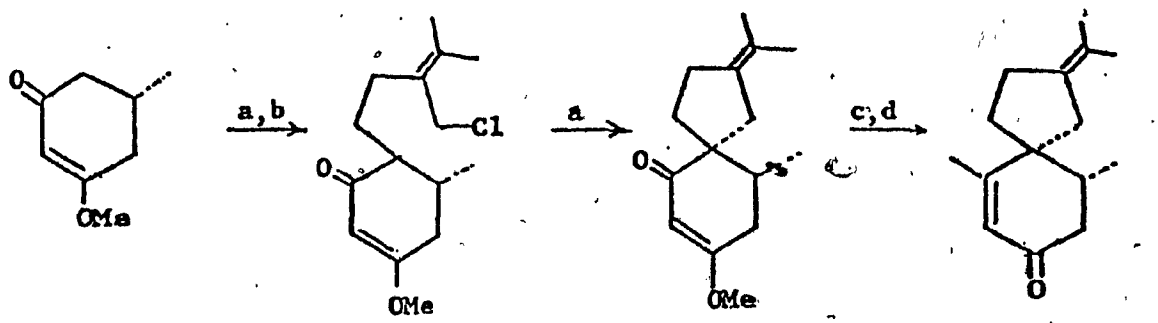
60 61 62 63 64 65 66 67

a. Me_2CuLi; b. NaH; c. NaH_2PO_4; d. LAH; e. Ac_2O; f. H_2CrO_4, AcOH, Ac_2O; g. HCl, EtOH; h. H_2, Pd/C; i. $LiAl(OBu^t)_3H$; j. RCO_3H; k. MsCl; l. $KOBu^t$; m. MeLi; n. $POCl_3$; o. CrO_3.



64 65

Scheme 9

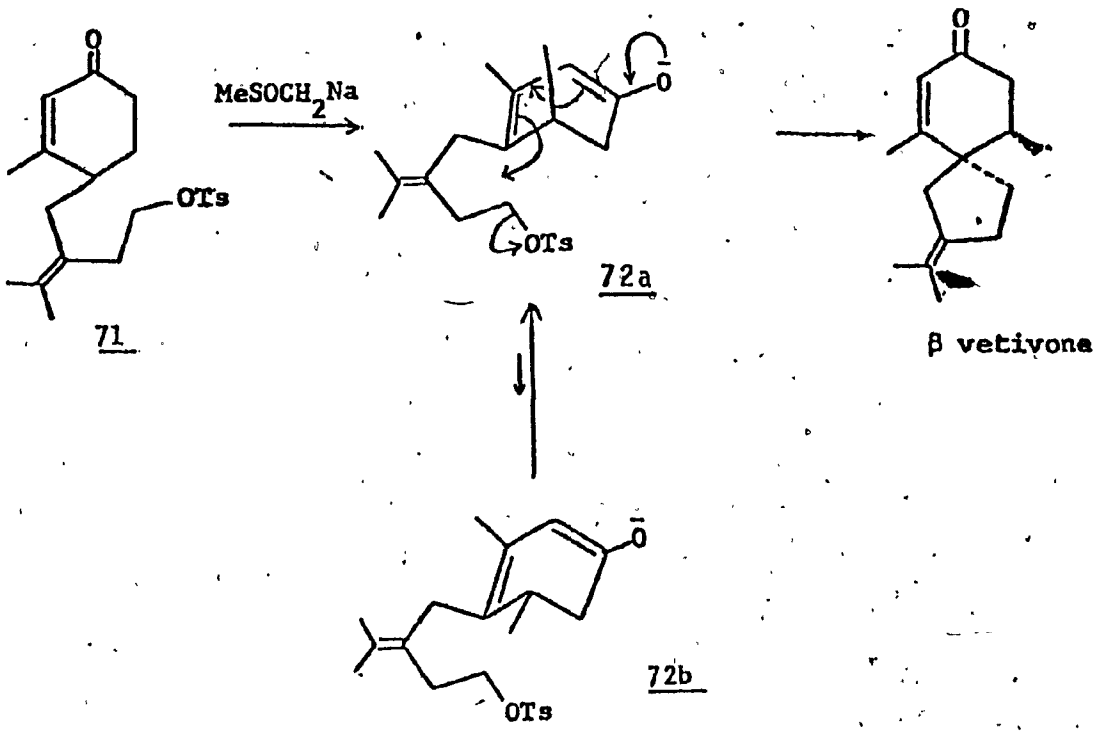


68 69 70 β vetivone

a. $LiN(Pr^i)_2$; b. $Cl-CH_2CH_2C(CH_2Cl)=CMe_2$; c. MeMgI;

d. H^+, H_2O

Scheme 10

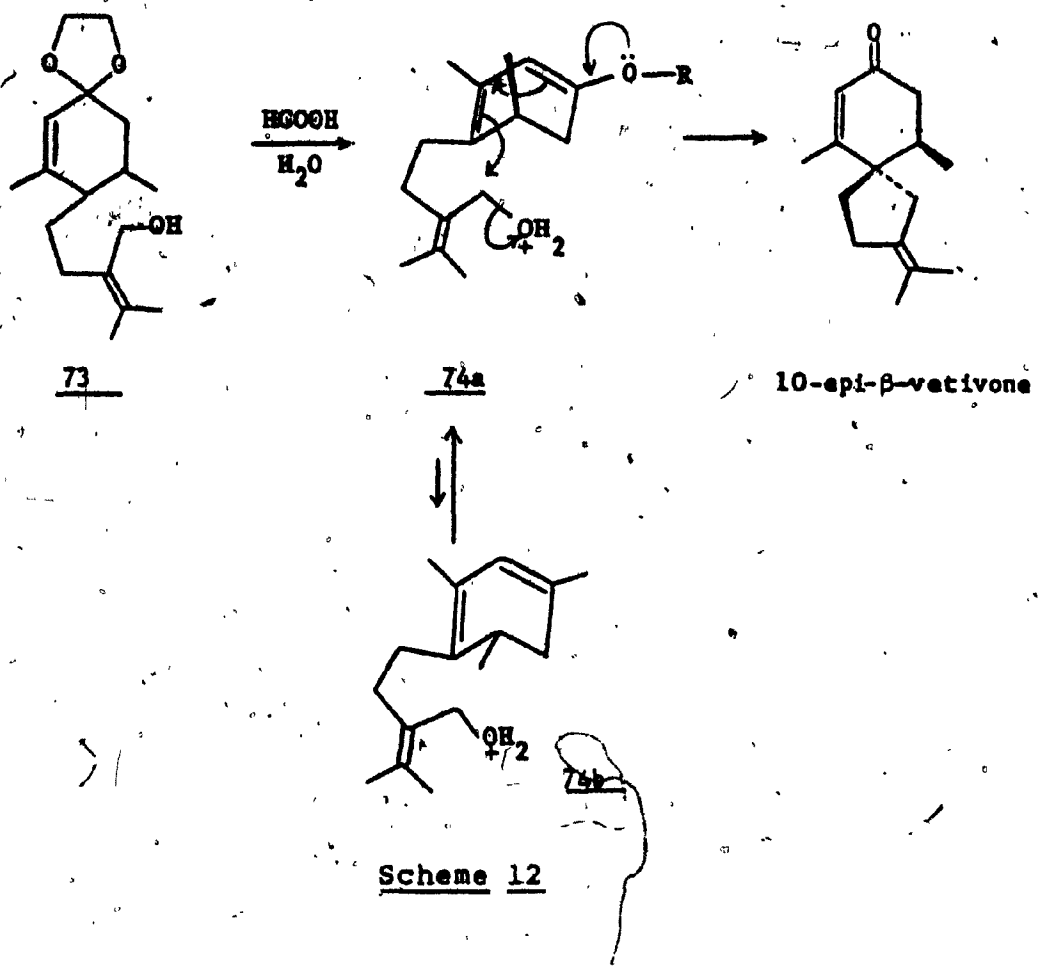


71 72a β vetivone

72b

Scheme 11

11; only final step shown)[65] employs this route. An approach similar to that of Johnson was used by McCurry (Scheme 12)[66] in the cyclization of the allylic alcohol 73. In this case

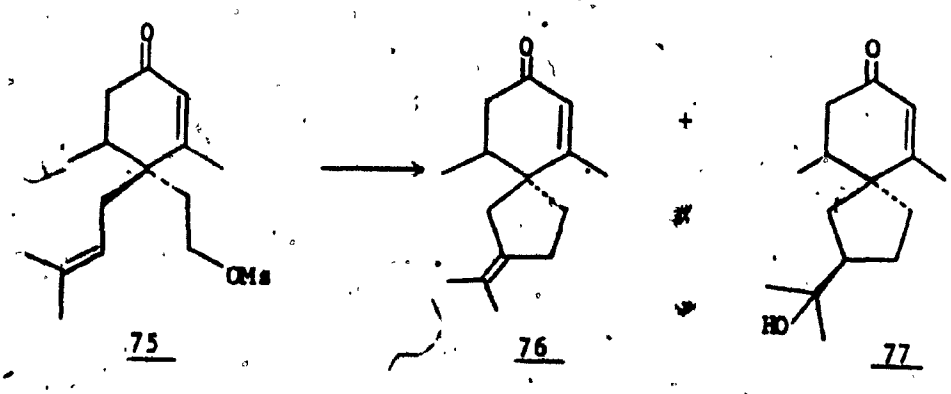


73 74a 10-epi-β-vetivone

74b

Scheme 12

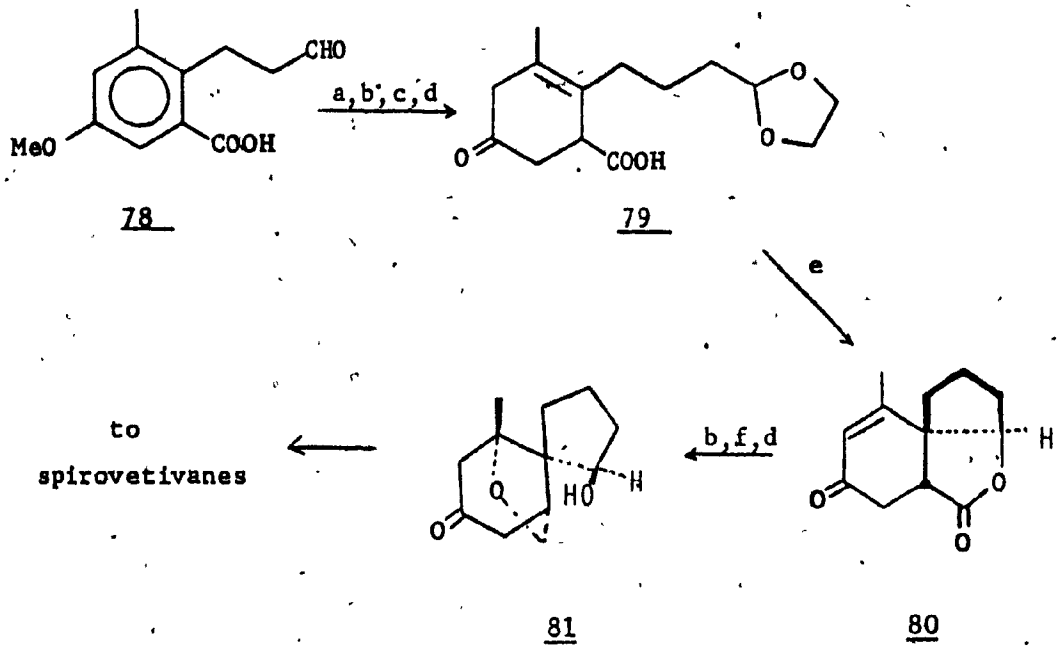
10-epi-β-vetivone was the sole product. Preferential axial alkylation from conformations 72a and 74a has been postu-



75 76 77

Scheme 13

lated[10] as the reason for the stereochemical outcome of the reactions shown in Scheme 11 and Scheme 12, as well as those of Scheme 10. A more recent addition to the same approach is that used by the Japanese group[67] where the intermediate



78 79 81 80

a. $Ph_3P{=}CH{-}OMe$; b. $(CH_2{-}OH)_2, H^+$; c. Li/NH_3 d. H_3O^+; e. HCl, H_2O, DME; f. LAH

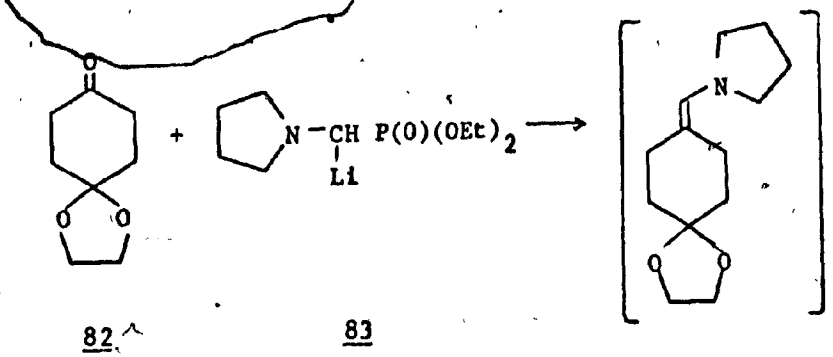
Scheme 14

75 was cyclized to 76 and 77 as shown in Scheme 13.

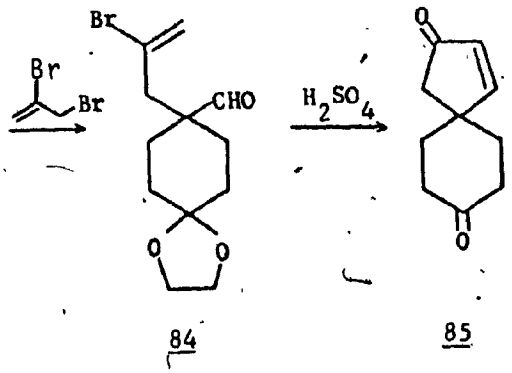
What can be considered as a vinylogous aldol condensation has been the key step in the spirocyclization employed by the Yamada group[68] in the synthesis of spirovetivanes (Scheme 14). The noteworthy aspect of this annelation is that, because of the reversibility of the aldol condensation, the stereochemistry of the product is governed by the

product stability rather than the conformational stability of the reacting species.

Enamine routes to spiroannelation have also been used recently. For example, Martin and co-workers[69] have employed this route in their syntheses of acoranes (Scheme 15a and Scheme 15b). The yield of the spiroproduct 85 in Scheme 15a



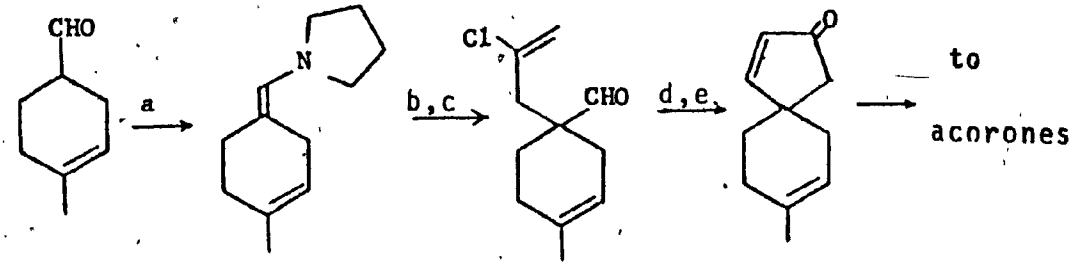
82 83



84 85

Scheme 15a

was only 43% while that of (89) in Scheme 15b was 64%. It must be mentioned that McCurry[70] had earlier used an enamine route to spiroannelation in his synthesis of spirovetivanes.



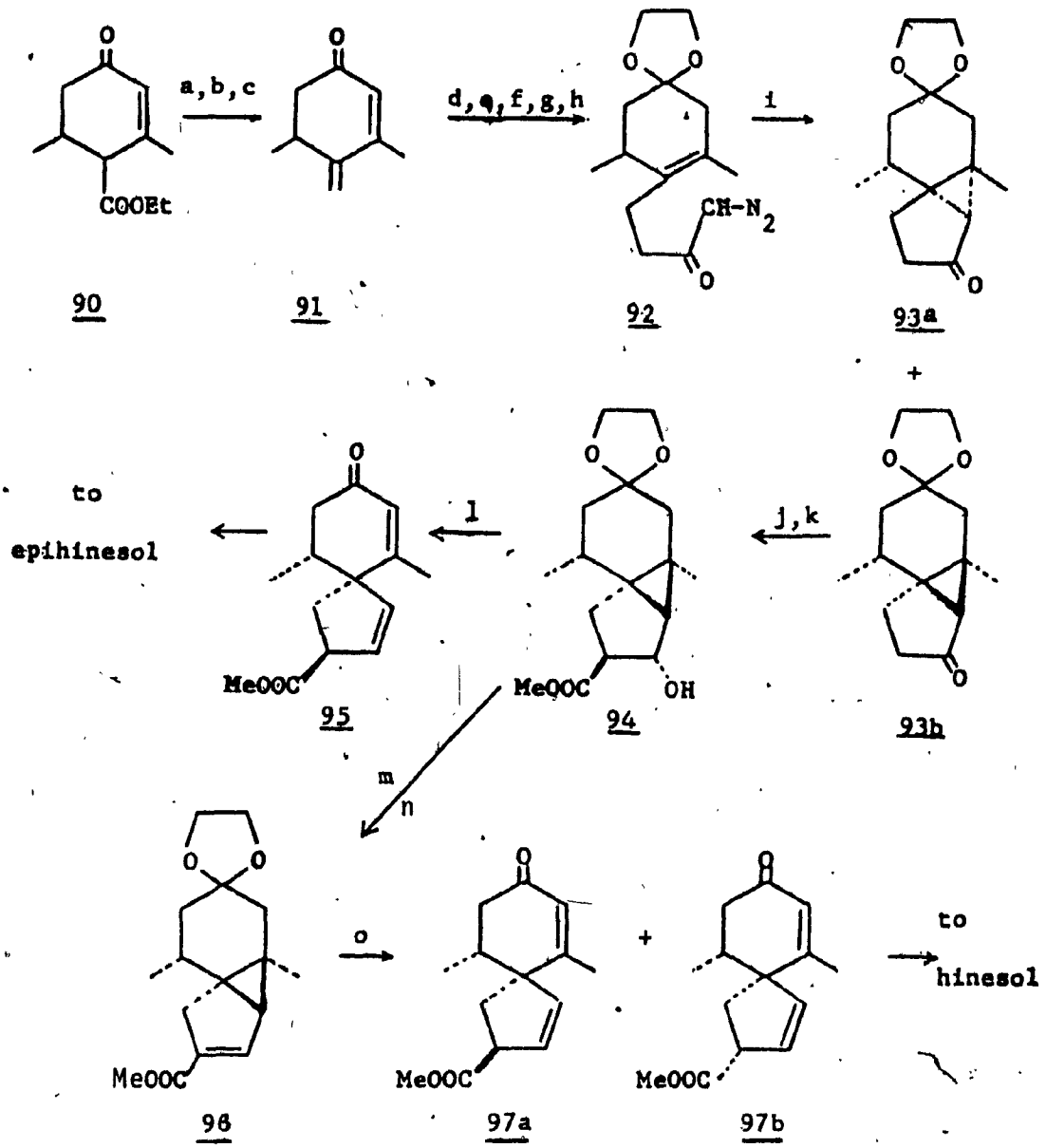
86 87 88 89

a. pyrrolidine,TsOH,PhH; b. $I-CH_2-CH(Cl)=CH_2$, CH_3CN; c. H_2O d. $Hg(OAc)_2, BF_3, Et_2O, AcOH$; e. KOH

Scheme 15b

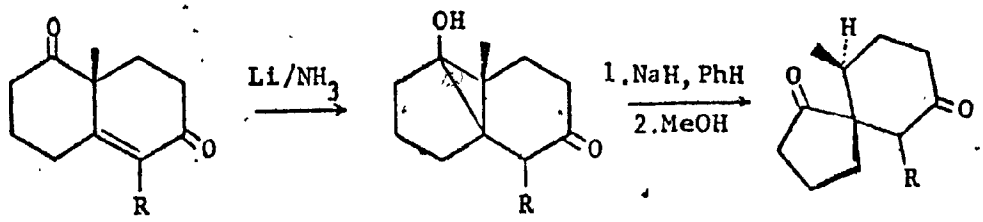
In the total synthesis of hinesol and epihinesol (agarospirol) the Deslongchamps group[71,72] used a different approach for constructing the spirodecane system (Scheme 16). The novel aspect of this synthesis is the use of an intramolecular carbene insertion reaction (92 ⟶ 93) which produced a tricyclic derivative possessing an α-keto-cyclopropyl system from which the spiro[4.5]decane system is liberated by acid-catalysed cleavage of a cyclopropyl σ-bond.

Base-catalysed rearrangement of a tricarbocyclic system which incorporates a spiro[4.5]decane as well as a cyclopropanol system has been the basis of the synthesis of spirovetivane intermediates in the approach used by Reusch and coworkers.[73,75] As outlined in Scheme 17 the bicyclic ketone 98 gave the tricyclic cyclopropanol 99, which on treatment with sodium hydride followed by methanol gave a



a. $(CH_2\text{-}OH)_2, H^+$; b. LAH; c. H_3O^+; d. $CH_2(COOEt)_2$, NaOEt; e. H^+; f. $(CH_2OH)_2, H^+$; g. --->acid chloride; h. CH_2N_2; i. Cu; j. $O{=}C(OMe)_2$, NaH; k. $NaBH_4$; l. HCl, MeOH; m. Ac_2O, PyH; n. Bu^tOH, Bu^tOK; o. THF, HCl

Scheme 16



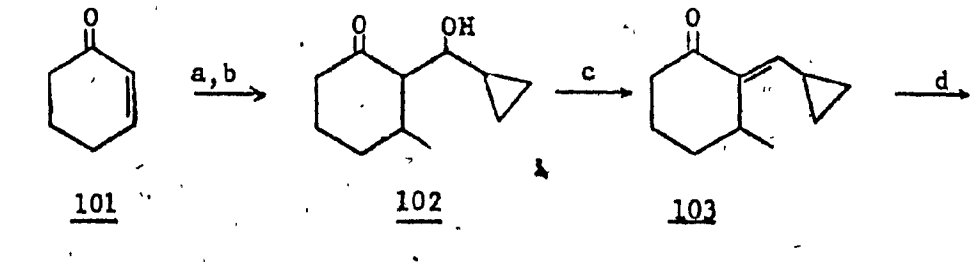
98 99 100

a. R = H
b. R = Me

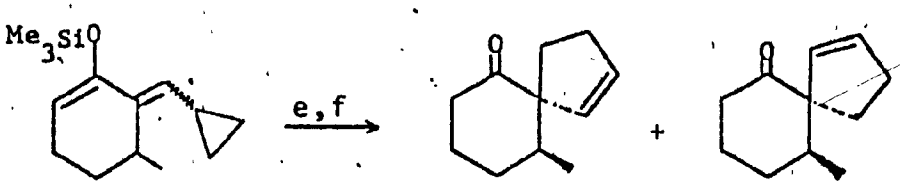
Scheme 17

good yield of spirodiketone 100, a potentially useful intermediate in spirovetivane synthesis.

Spiropentannelation involving a different kind of cyclopropyl system has been developed by Piers.[76] The noteworthy aspect of this methodology is the thermal rearrangement of suitable α-(cyclopropylmethylene)cycloalkanones



101 102 103



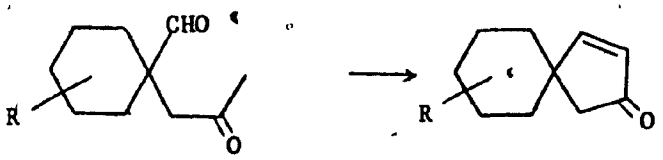
104 105a 105b

a. MeMgI, CuI; b. ▷—CHO; c. TsOH, PhH, ;
d. LDA, Me_3SiCl, Et_3N; e. 380°C/argon; f. HCl, MeOH

Scheme 18

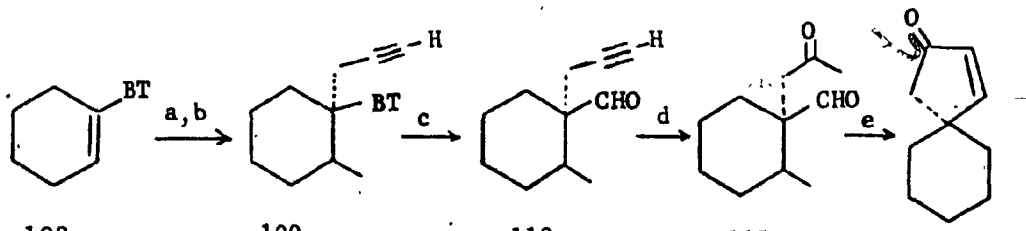
(Scheme 18). The enone 103 was converted into the silyl enol ether 104 by standard methodology. Thermolysis of the latter at 380°C followed by hydrolysis gave the epimeric spiroenones 105a and 105b which were further converted to intermediates suitable for the synthesis of spirovetivanes.

An intramolecular aldol condensation of keto aldehydes



106 107

of the type 106 to spiroenones of the type 107 has been the key step in several methodologies recently developed by Corey's group. Synthesis of the required ketoaldehyde has been achieved by employing several methodologies. One of these is based on the chemistry of benzothiazoles, and several types of spiro and fused 5- and 6-membered rings have been generated using this method,[77] an example of which is outlined in Scheme 19a. The required ketoaldehyde for

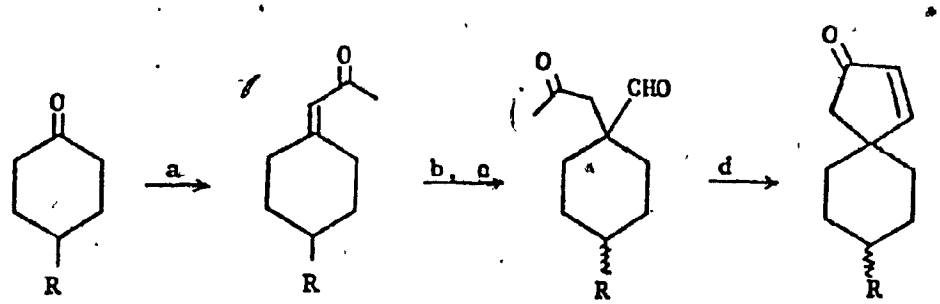


108 109 110 111 112

a. MeLi, THF-HMPT; b. $Br-CH_2-C\equiv CH_2$; c. BT ⟶ CHO;
d. H_2SO_4, Hg^{++}, e. NaOH/EtOH

Scheme 19a

spiroannelation has also been obtained by another route as



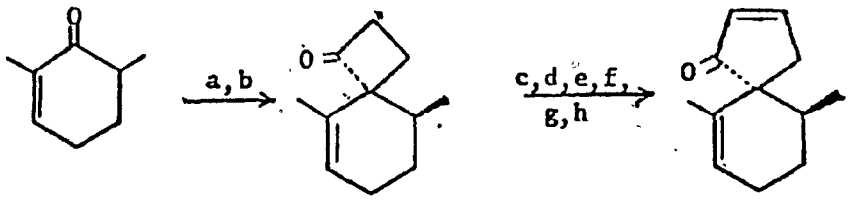
113 114 115 116

a. CH_3-CO-CH_2-P(O)$(OEt)_2$, NaOH; b. CuI, CH_2=CH-MgBr; c. OsO_4, $NaIO_4$, PyH; d. NaOH, MeOH

Scheme 19b

illustrated in Corey's synthesis of an intermediate 116 (Scheme 19b) for the synthesis of gibberellic acid.[78]

In another approach used by Trost and coworkers, a spirotetrannelation using cyclopropyl sulfide derivatives on cycloalkanones followed by ring expansion to a five-membered ring (Scheme 20a)[80] or a six-membered ring (Scheme 20b)[79]

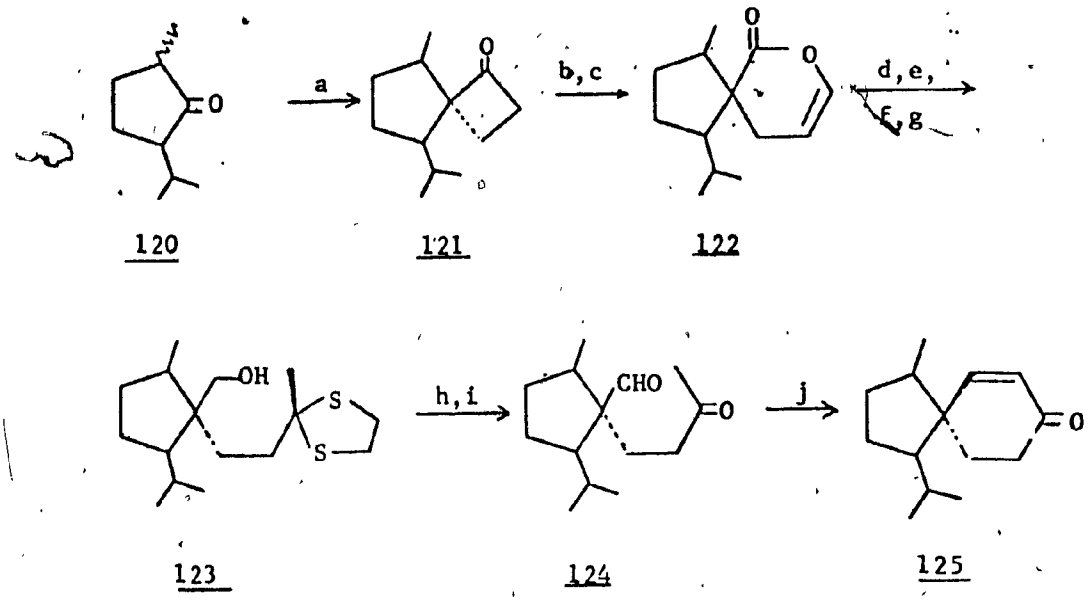


117 118 119

a.  ; b. H^+; c. $(Me_2N)_2CHOBu^t$; d. Ts-S-$(CH_2)_3$-STs, KOAc; e. MeLi; f. NaOMe; g. MeI; h. NaOH

Scheme 20a

has been used for the construction of spirocycles.



120 121 122

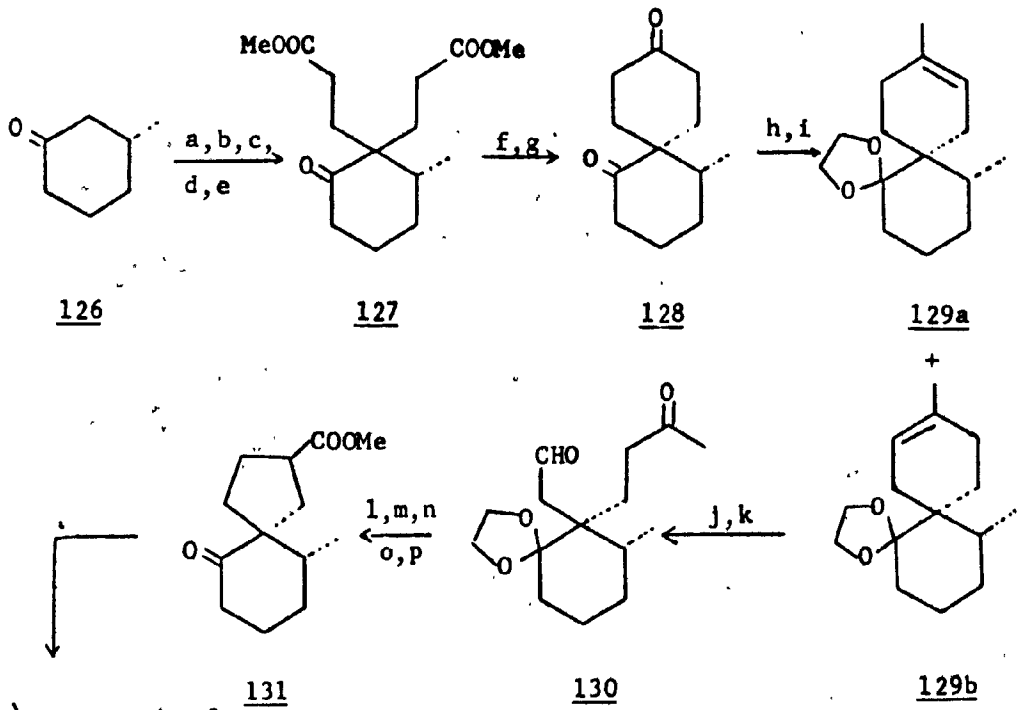
123 124 125

a. $\triangleright\!\!\times^{H}_{S(Ph)2}\ BF_4^-$; b. NaH,HCOOEt,PhH,MeOH:
c. TsOH,PhH,H_2O; d. DIBAL-H; e. CrO_3,H_2SO_4; f. MeLi
g. $(HS\text{-}CH_2)_2$,BF_3,ether; h. PyH.SO_3,DMSO,Et_3N;
i. $HgCl_2$,MeCN,H_2O, ; j. KOH,MeOH

Scheme 20b

The methodology employed by Ramage and coworkers[81] involves a spiroannelation followed by ring contraction for the production of 5-carbon spirocycles. This approach is outlined in Scheme 21. The cyclohexane derivative 129b is cleaved by ozone to produce the ketoaldehyde 130 which was subjected to aldol cyclization, followed by other steps to produce the spiro[4.5]decane derivative 131.

Yet another approach to spiropentannelation is that developed recently by Dauben and Hart[32] where the reaction between sodium enolates of α-formylcycloakanones and 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (133) has been found to produce moderate yields of spiranyl vinylogs of β-ketoesters (e.g. 135). Scheme 22 illustrates this approach starting with α-formyl cyclohexanone. A



to (-) agarospirol
and (-) β-vativone

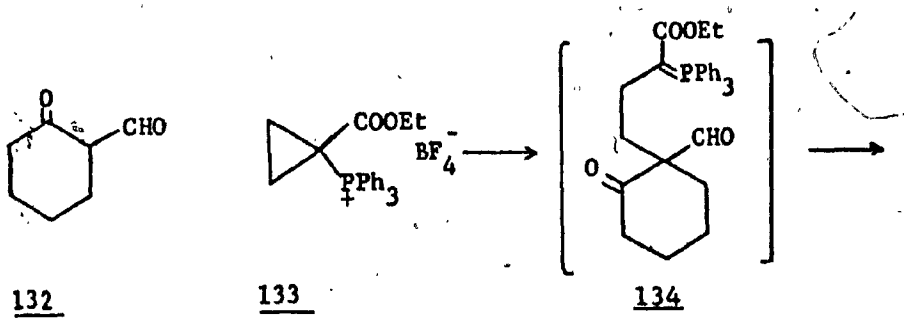
a. base, HCOOEt; b. PhNHMe; c. Triton B, $CH=CH_2CN$; d. OH^-; e. esterification; f. Na, PhH; g. Li, H_2O; h. $Ph_3P=CH_2$; i. $(CH_2OH)_2, H^+$; j. O_3; k. Me_2S; l. KOH; m. H_2, Pd/C; n. Br_2, OH^-; o. CH_2N_2; p. HCl, DME

Scheme 21

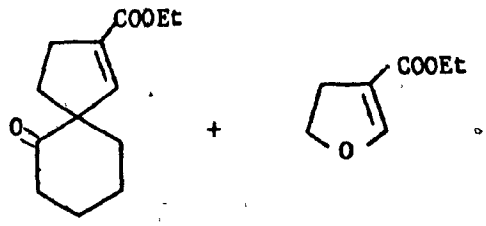
variety of substituted α-formylcycloalkanones have been

employed in this work to produce functionalized spirocyclopentenyl systems. The reaction is presumed to proceed via an ylid of the type 134 which undergoes a regiospecific intramolecular Wittig reaction to produce spiroderivatives of the type 135. In addition to the spiroderivatives the reaction is usually accompanied by small amounts of the dihydrofuran 136 and deformylated starting material.[32]

A related method where the alkylation of enolate anions using suitable stabilized phosphonium ylides followed by spontaneous intramolecular Wittig reaction has also been



132 133 134

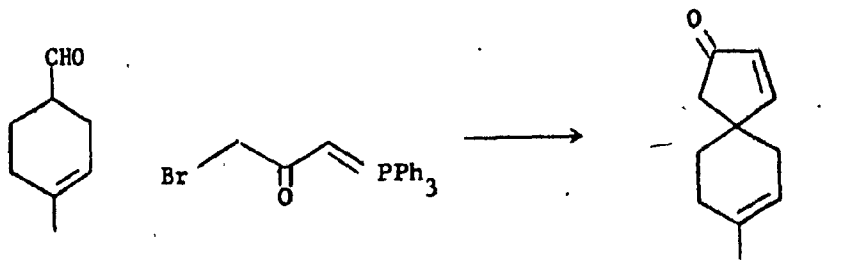


135 136

Scheme 22

recently reported (Scheme 23).[82] In addition to spirocyclopentanones of the type, 139, fused cyclopentanones have also

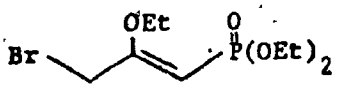
been prepared by this method. However, the reported yields of the annelation products were low. In this connection it must also be mentioned that, recently Piers[83] has employed an annelation procedure using a phosphonate carbanion rather than a phosphorane to annelate fused cyclopentenone systems.



137 138 139

Scheme 23

This approach involves treatment of the phosphonate ester 140 with enolates of cycloalkanones followed by intramolecular Horner-Emmons reaction to produce the fused



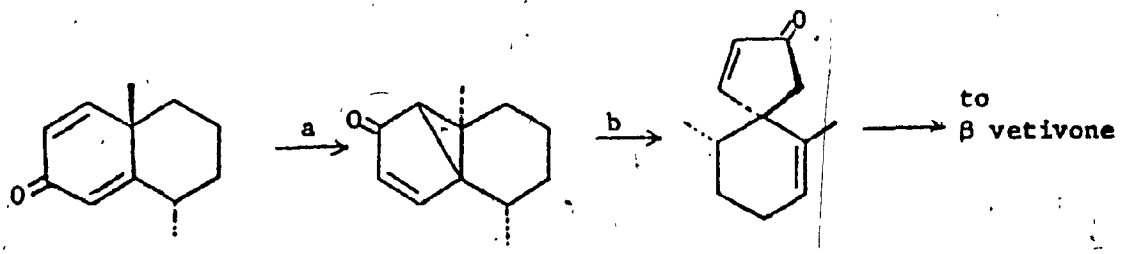
140

cyclopentenones. Although the reagent 140 has not yet been used for spiropentannelation there seems to be no reason why it cannot be used with suitably chosen enolates of cyclic compounds.

2. Photochemical Approaches.

The photochemical rearrangements of cross-conjugated cyclohexadienones have been intensively studied, and an excellent review of the topic has been provided by Kropp.[84] Irradiation of cross-conjugated cyclohexadienones produces a spirocyclopentenone moiety fused to a cyclopropyl system such that the keto group is in conjugation with a C=C bond on one side and the cyclopropyl group on the other. Such ketones are known to undergo acid-catalyzed cleavage of the cyclopropyl ring liberating a spirocyclopentenone system.[85]

The landmark synthesis of β-vetivone by Marshall[86,87] employed this photochemical rearrangement (Scheme 24). The irradiation of the known diketone 141 led to the cyclopropyl ketone 142 which underwent cleavage in strong acid to the isomeric spirodienone 143. The established stereochemistry of 141[88] as well as the established relationships in the related santonin-lumisantonin rearrangement[89] were the basis for the assignment of the stereochemistry of 142. The

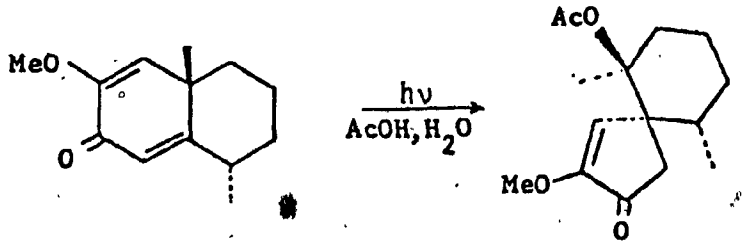


141 142 143

a. hν,dioxane; b. H_2SO_4-AcOH-Ac_2O

Scheme 24

spiroketone was converted to β-vetivone by a further series

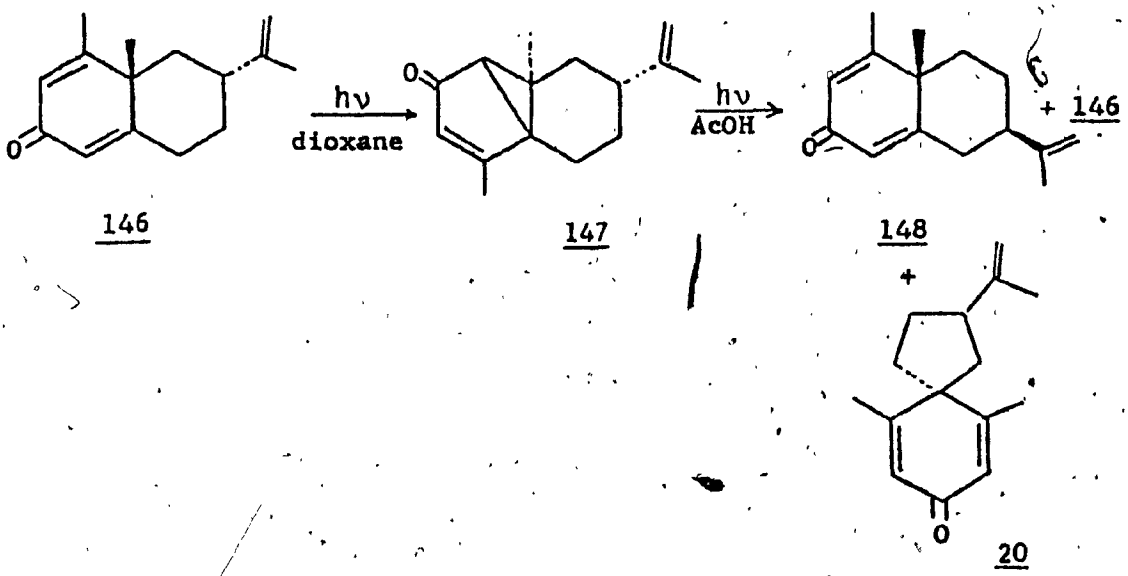


144 145

Scheme 25

of transformations.[86]

Caine and coworkers employed variations of the above-mentioned photochemical rearrangement route to spiro-

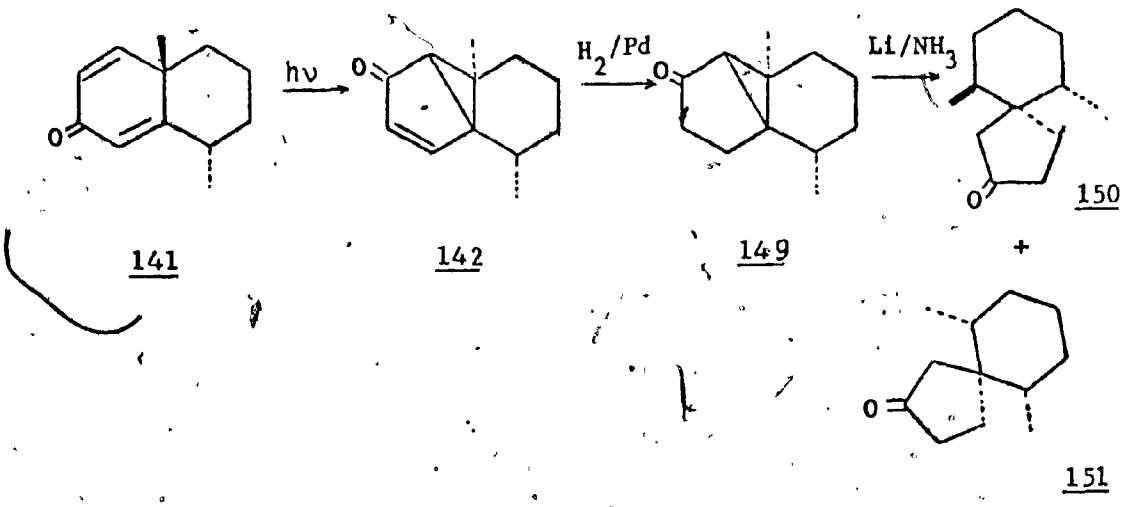


146 147 148

Scheme 26

cyclopentenone in their synthesis of α-vetispirene[90] (Scheme 25), and anhydro-β-rotunol (20; Scheme 26).[91]

Another variation of the photochemical approach was used recently by Piers[92] (Scheme 27). Here the spirovetivane skeleton was produced by the reductive



141 142 149 150 + 151

Scheme 27

cleavage of the conjugated cyclopropyl ketone 142. Dauben and coworkers[93] had shown earlier that this reductive cleavage of conjugated cyclopropyl ketones which is part of a bicyclo[3.1.0]hexane or bicyclo[4.1.0]heptane system proceeds in a stereospecific manner, and that the cyclopropane bond which cleaves is the one possessing greater overlap with the π-system of the carbonyl group. An additional noteworthy facet of Piers' work has been the elucidation of the stereochemical fate of the β-carbon atom. Under the reaction conditions the dissolving metal reduction of 149 occurred with a high degree of inversion at the β-carbon atom (cf. 150).

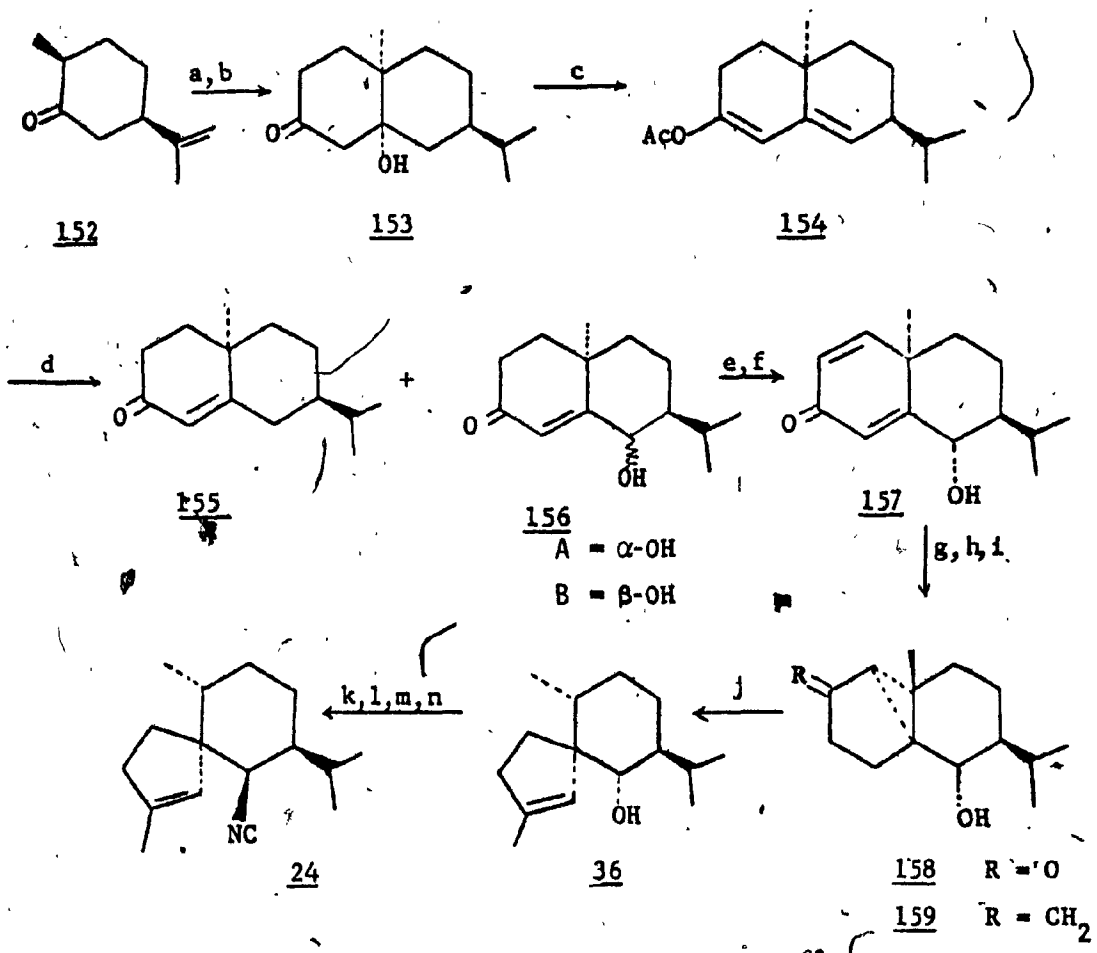
Later work by Caine[46] has shown that in some tricyclodecanones possessing conjugated cyclopropyl ketones the reductive cleavage occurs with 100% inversion. In addition, it was also demonstrated that it is not only the carbonyl-conjugated cyclopropanes that undergo such a reductive cleavage to spirocyclopentyl systems, but also the related vinyl cyclopropanes as well. This approach to spiropentannelation has also been used by Caine[46] in his recent synthesis of (-)-axisonitrile-3 (vide infra).

B. APPROACHES USED BY OTHERS IN THE SYNTHESIS OF SPIROAXANES.

1. Total Synthesis of (-)-Axisonitrile-3

As mentioned earlier, while the present studies were well under way, Caine and Deutsch[46] reported a total synthesis of (-)-axisonitrile-3 using a photochemical approach which also involved the application of the reductive ring opening of a vinylcyclopropane (Scheme 28).

The known ketol 153[94,95] was obtained in 50% yield by annelation with methyl vinyl ketone. Treatment of 153 with acetic anhydride containing catalytic amounts of sulfuric acid gave the dienol acetate 154 (80%) which was reacted with meta-chloroperbenzoic acid in isopropanol-water yielding 42% of enone 155 and 56% of a 6:1 mixture of 156A and its 6-β-epimer. The hydroxyenone 156A was isolated by chromatography on Florisil and was converted into its



a. MVK; b. H_2,cat; c. Ac_2O,H^+; d. MCPBA; e. MIP-protection of OH; f. PhSe-elimination; g. hν, dioxane; h. H_2/cat; i. $CH_2{=}CPPh_3$; j. Li,$EtNH_2$; k. TsCl; l. KN_3 m. LAH; n. NH_2----> NC

Scheme 28

methoxyisopropylidine[96] (MIP) derivative. Introduction of the 1,2-double bond was then achieved by the phenylselenylation-selenoxide elimination procedure,[97] to give 157 (85%).

Irradiation of 157 in anhydrous dioxane gave the tricyclodecenone as the sole product, which upon hydrogenation yielded the hydroxyketone 158 (52%). Treatment of this material with triphenylmethylenephosphorane in DMSO yielded the corresponding exo-methylene compound 159 (92%), the controlled reductive cleavage of which with lithium in ethylamine gave the alcohol 36 (92%). Conversion of this alcohol to its tosylate (60%) followed by S_N2 displacement of the tosyl group by azide using potassium azide in benzene containing 18-crown-6 gave the corresponding β-azide. Reduction of the azide by $LiAlH_4$ gave the corresponding aminoderivative, the NH_2 group of which was converted to the isonitrile function to yield (-)-axisonitrile-3 (24; 85%).

In the communication by Caine[46] it was pointed out that the cyclopropane ring of simple vinylcyclopropanes is not cleaved by metal in liquid ammonia and that conversion of 159 to 36 represented the first example of reductive cleavage of a vinylcyclopropane with lithium in ethylamine. Another point which has been emphasized also was that in the reductive cleavage of 159 there was no 10-β-epimer of 36 detectable, which showed that there was complete inversion of configuration at the carbon carrying the methyl group.

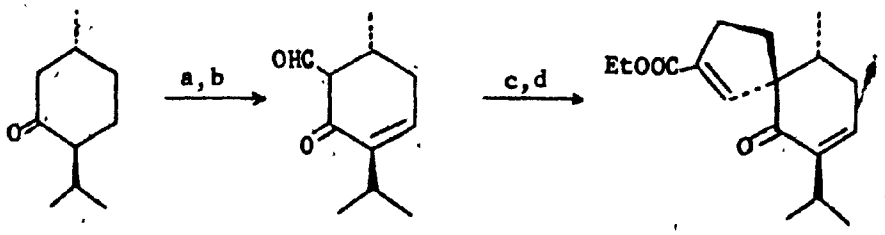
That the synthetic material had indeed the structure shown in 24 was demonstrated by x-ray crystal study. The synthetic material had mp 97-98°C and $[\alpha]_D^{25}$ of -71°. The

natural compound whose structure was also determined by x-ray crystallography had mp 101-103°C and $[\alpha]_D$ of +68.4°. Caine and Deutsch[46] concluded that, "these physical properties generally agreed with those reported for (+)-axisonitrile-3, the enantiomer of 24, except for the sign of the optical rotation". However, there were still some discrepancies between the observed NMR chemical shifts, particularly for the methyl groups of the isopropyl group, and those reported by the Italian workers. A direct comparison of the synthetic material with the natural product was not possible due to the unavailability of pure authentic sample as well as copies of original spectral data.

2. Synthesis of a Spiroaxane Intermediate

The spiroannelation route of Dauben and Hart employing the reaction of enolates of α-formylcycloalkanones with carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (133) has also been used for the synthesis of a compound having the carbon skeleton of spiroaxanes.[32]

In this approach (-)-menthone (35) was converted to the α-formyl ketone 160 using a straightforward bromination-dehydrobromination-formylation sequence. Successive treatment of this product with sodium hydride and 133 afforded 161 as the sole spiroproduct (20%). The structure assignment of 161 was based on spectral data as well as the known stereospecificity of the reaction of 133 with formyl



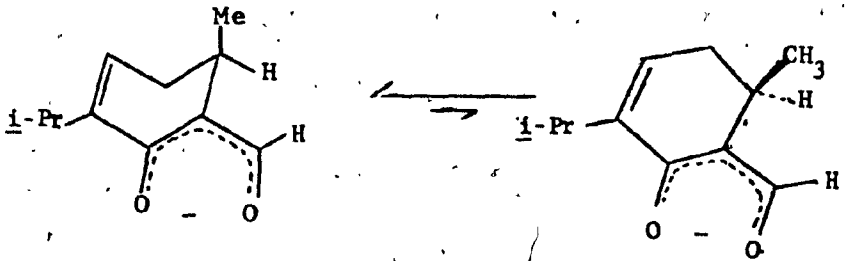
35 160 161

a. bromination-debromination; b. formylation; c. NaH; d. 133

Scheme 29

enones of the type 159.

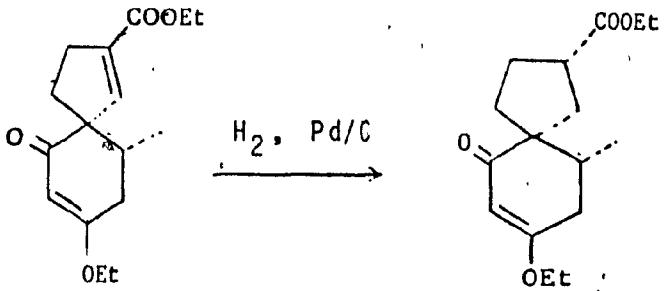
The remarkable stereospecificity in the conversion of 160 to 161 has been attributed by Dauben and Hart to the conformational preference imposed by the juxtaposition of the alkenyl, formyl and the keto groups in the enolate of



162a 162b

160. This enolate can adopt conformations where the methyl group is oriented either axially as in 162a or equatorially as in 162b. Conformation 162a is thermodynamically more stable than 162b, because in the latter the methyl group and the formyl hydrogen lie almost in the same plane causing an interaction approximating a conventional 1,3 diaxial

interaction. This type of interaction, termed "allylic 1,3-interaction" or "$A^{1,3}$ strain", was first recognized by Johnson,[98] who also reviewed the topic later.[99] Thus, during the reaction of 133 with the enolate of 160, the electrophilic cyclopropyl group is expected to approach the more stable conformation 162a from the face opposite the axially disposed methyl group. If the bond formation happens in an irreversible manner, and if the free energy of activation of this mode of attack is equal to or less than



163 164

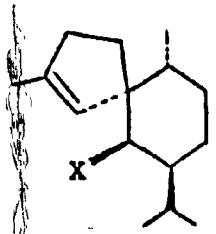
that for the other possible modes of attack, then the formation of 161 necessarily results.

It must be pointed out that the intermediate 161 may not be the most suitable precursor to glehnol or axisonitrile-3 or its derivatives. Even though the relative stereochemistry at C-5 and C-10 in 161 is that of the known spiroaxanes, selective hydrogenation of the double bond in the 6-membered ring may well be a thorny problem. Indeed, it would be easier to hydrogenate the double bond in the five membered ring as has been demonstrated by Dauben and

Hart[32] in the case of a similar spirodienone 163, which underwent catalytic hydrogenation in a regiospecific as well as a stereospecific manner to give 164.

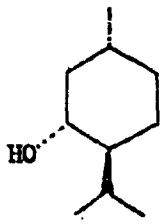
C. APPROACHES USED IN THE PRESENT STUDY

The structures of axisonitrile-3 (24) and glehnol (32), both determined by x-ray crystallography, show the same spiro[4.5]decane carbon skeleton for these compounds. The positions as well as the relative orientations of the alkyl substituents are also the same. One cannot fail to recognize the fact that, but for the appendage of the spirocycle at C-5, either molecule is a neomenthyl derivative. This molecular feature greatly simplifies the design of the schemes for the total synthesis of either molecule. As a starting material one of the choices is naturally (-)menthol (165) which is readily available and



24, X = $\overset{+}{N}\equiv\bar{C}$

32 X = OH



165

(-)-menthol

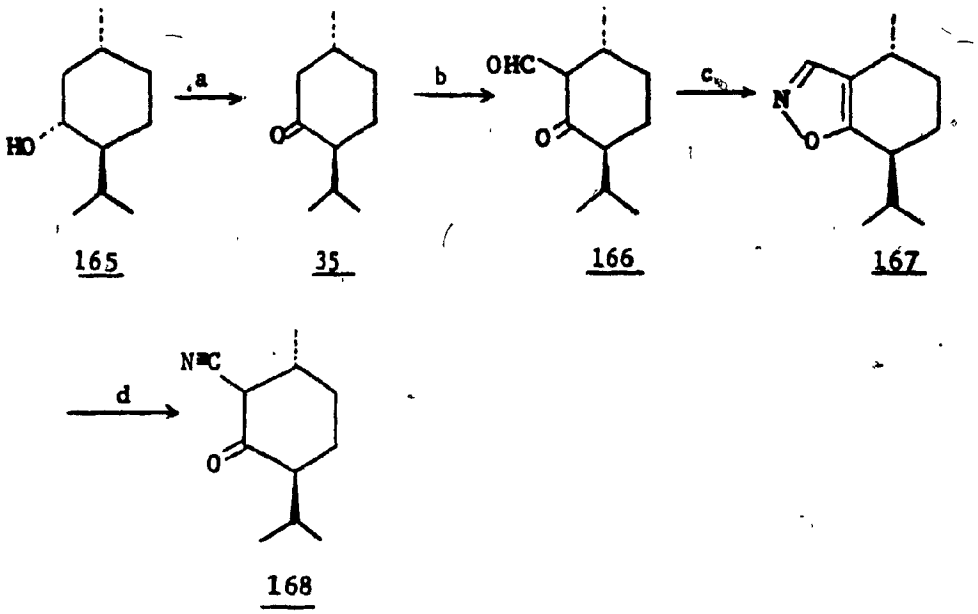
whose absolute stereochemistry is well established.

The selection of (-)menthol as the point of departure was made for several reasons. First, the six membered ring

system of the spiroaxane is already in menthol with the methyl and isopropyl groups in the required positions and with the proper stereochemical relationship. Further, the secondary alcoholic group could be easily converted to a keto group by the standard chromic acid oxidation procedure to give (-)-menthone.[100] By taking advantage of this keto group one could attempt the construction of the spirocyclopentenyl system alpha to it as well as the methyl group. Several other molecular features of the spiroaxanes now need to be attended to. In glehnol as well as in axisonitrile-3 and its congeners the spirocyclopentenyl system has the C-1 in a cis relationship with the C-10 methyl group. The C-6 substituent has the beta orientation. Ideally, one must strive for the appropriate stereochemistry in the transformations that will put on the required appendages, or, failing this, one must be able to separate the epimers which might be produced. If the transformations at those carbon atoms in chiral menthone which would become C-5 and C-6 in the target molecule are such that the required substituents are attached with the proper stereochemistry, then one will have achieved the total synthesis of the natural product or its enantiomer. In either case the absolute stereochemistry of the natural product will be established.

In order to have a suitably activated functionality in menthone such that the above mentioned strategies can be set

in motion, the following preliminary scheme (Scheme 30) was



165 35 166 167

168

a. H_2CrO_4; b. NaH,HCOOEt; c. $HONH_2HCl$,NaOAc; d. NaOMe

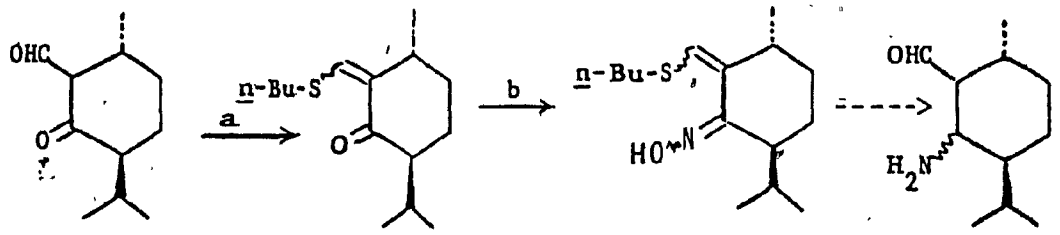
Scheme 30

utilized. Jones' oxidation of (-)-menthol gave (-)-menthone in 89% yield. Formylation of the latter was achieved using ethyl formate and sodium hydride[32] to yield formyl menthone (166) in 86% yield. The IR spectrum of a CCl_4 solution of this material did not reveal any significant hydroxyl bands indicating that it is mostly in the aldehyde form. The aldehyde group is probably in the thermodynamically more stable equatorial orientation; however, this point is of nb significant concern, because all further reactions starting with this compound are to be on its enolate. Being an α-ketoaldehyde it was easy to convert 166 to the isoxazole derivative 167 (77%) by treatment with hydroxylamine

hydrochloride and sodium acetate.[101] In accordance with the well known cleavage of such isoxazoles to α-ketonitriles,[101] treatment of 167 with sodium methoxide and subsequent acidification[102] afforded the cyanomenthone 168 in 67% yield. The NMR spectrum of the product revealed two one-proton doublets at δ 3.35 and δ 3.87 (in a 4 : 3 ratio for their integrated intensities) with coupling constants of 10 Hz and 4.5 Hz respectively. From this it was concluded that 168 was a mixture of epimers with respect to the nitrile group in an equatorial : axial ratio of 4:3.

With the introduction of the formyl or cyano group alpha to the carbonyl group in menthone one now has doubly activated this position in 166 and 168. Subsequent reactions via the carbanions of these derivatives will thus be directed towards this alpha position, rather than to the carbon carrying the isopropyl group. One is cognizant also of the fact that the nitrile group in 168 can, at a later stage in any synthetic scheme, be converted to an aldehyde group by the action of DIBAL-H.[103] One thus has at this stage two potentially useful intermediates as starting points for the synthesis of spiroaxane derivatives. The many approaches which were attempted in the present study had one or the other of these two key intermediates as the point of departure. These approaches are discussed in the remainder of this section.

One plan which was tried out at the early stages of this project had formyl menthone (166) as the starting point



166 169 170 171

a. n-BuSH,p-TsOH,Benzene, ; b. $HONH_2$,NaOAc;

Scheme 31

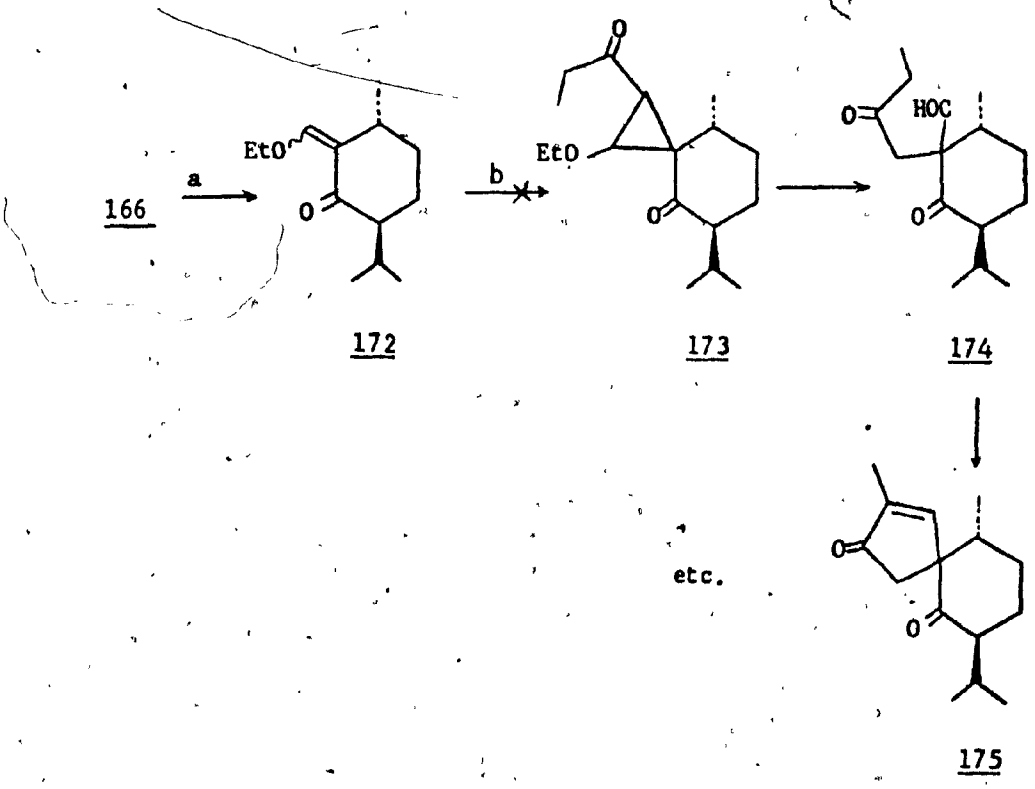
(Scheme 31). It was thought that if the formyl group was suitably protected, then perhaps oximation of the keto group could be achieved. It would be a relatively simple matter to convert the oximino group to an amino group which could then be converted to an isonitrile group. Deprotection of the formyl group would allow one to elaborate the required spirocyclic system by any one of several possible methodologies. Accordingly, the formyl group in 166 was converted to the thiol ether in 83% yield by the action of butanethiol[104] in the presence of catalytic amount of para-toluenesulfonic acid in benzene. The TLC of the product 169 exhibited two spots, and small quantities of the two components were separated by flash chromatography and the spectral properties of these indicated that they are the two possible geometrical isomers of 169. No attempt was made to separate the stereoisomers for the next step as this

was not crucial to the scheme. Attempted oximation of 169 under the standard conditions using hydroxylamine hydrochloride and sodium acetate yielded a multi-component mixture. Column chromatography of the product yielded, as identifiable products, much unreacted starting material and some of the isaoxazole derivative 167. No other attempts at oximation was done and the proposed scheme had to be abandoned at this stage. The reluctance of 169 to undergo oximation is possibly due to the fact that the keto group is in a particularly hindered location.

The protection of the formyl group in 166 was attempted using ethylene glycol and para-toluenesulfonic acid. This resulted in a mixture of products and the starting material, and all attempts to separate the mixture into its components were unsuccessful. It was thought that perhaps the keto group in 169 could be reduced to a hydroxyl group, following which the formyl group could be liberated, and then a way could be sought to elaborate this functionality into the required spirocyclic system. Treatment of 169 with lithium aluminum hydride reduced the keto group as determined by the IR spectrum of the product. However, the TLC of the product indicated two spots of very close R_f values (corresponding possibly to the two diastereomers of the alcohol), and it was not possible to effect a separation of the components. The products also seemed to be labile, as it was observed that the IR spectra of the material obtained at various

intervals revealed carbonyl absorption bands of progressively increasing intensities. It was not possible to establish the identities of the products, and no further work on the thioether derivative 169 was done beyond this stage.

Another approach attempted is given in Scheme 32. Formyl menthone was converted into the enol ether derivative



172 173 174 175

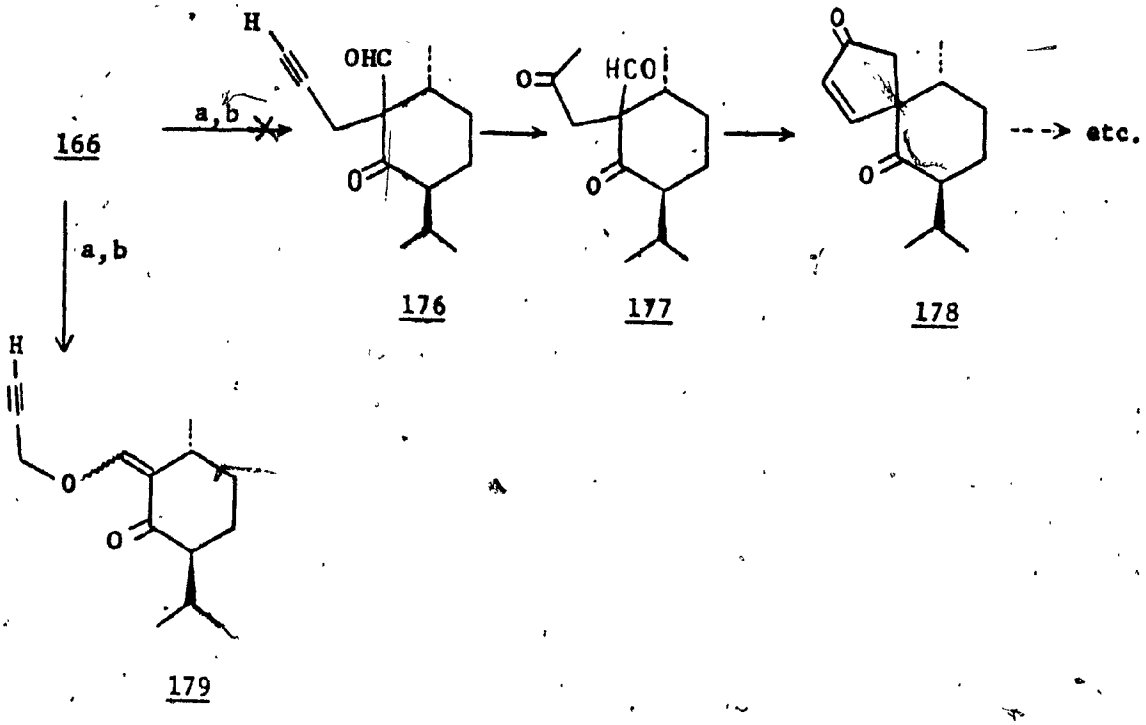
a. NaH, EtBr; b. $CH_3CH_2COCH_2N_2$

Scheme 32

172 as a distillable oil in 91% yield by treating it with sodium hydride in HMPT, followed by reaction with ethyl bromide. It was possible to obtain small quantities of the

two diastereomers of 172 by flash chromatography. The plan was to convert this enol ether into a cyclopropane derivative 173 by an intermolecular insertion of an alpha-ketocarbene into the enol ether double bond. It was hoped that such a cyclopropyl derivative would undergo base-induced cleavage to a 1,4-dicarbonyl derivative 174 which could be made to cyclize to the spiroderivative 175. The idea was prompted by the recent reports by McMurry,[105] and Wenkert and coworkers[106] where similar strategies were employed in making the cyclopropane derivatives which were cleaved to 1,4-diketones and then cyclized to cyclopentene derivatives. Accordingly, 172 was treated with diazomethyl ethyl ketone in the presence of cuprous acetylacetonate[105] in ether. There was an exothermic reaction, and workup of the reaction mixture yielded a product from which was isolated the unreacted starting material and another product identified as oct-4-ene-3,6-dione, the latter undoubtedly arising from the dimerization of the expected alpha-ketocarbene from diazomethyl ethyl ketone. There was no evidence of any of the cyclopropyl derivative in the reaction product.

In the matter of elaborating the required spirocyclopentenyl system at the site carrying the formyl group in 166 several other possibilities were tried. It was hoped that the alkylation of the enolate of 166 with propargyl bromide would produce the alkyne derivative 176



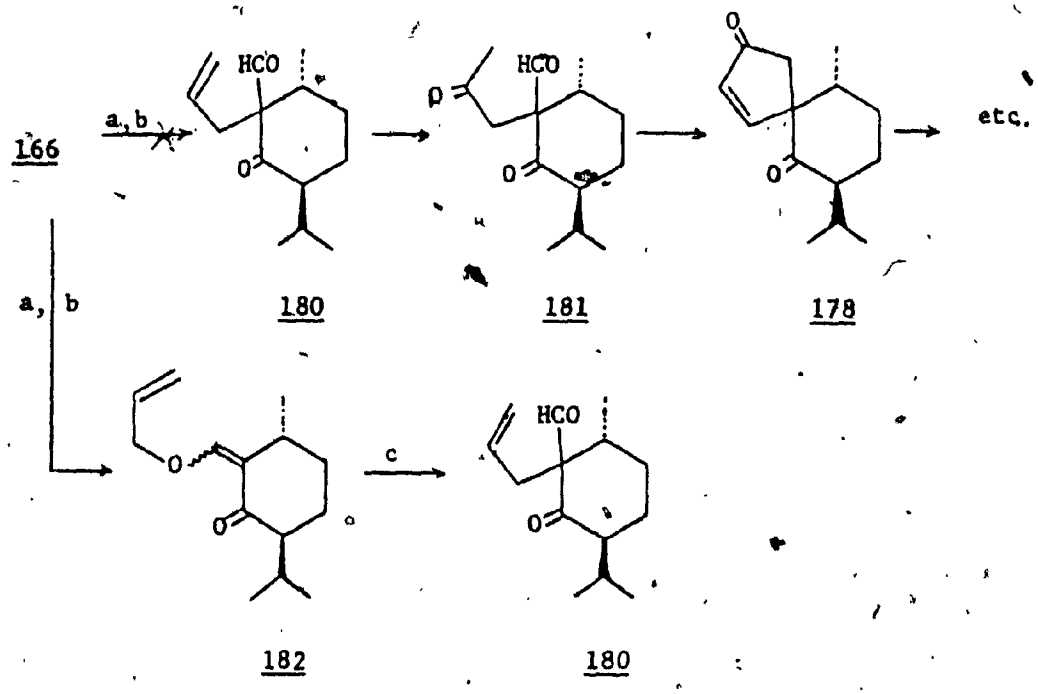
a. NaH; b. $H-C\equiv C-CH_2Br$

Scheme 33

which could be converted to the ketoaldehyde 177, and thence to the spirocyclopentanone derivative 178 by standard methodologies (Scheme 33). From 178 one could find suitable ways of arriving at the target molecule. However, these hopes were crushed at the outset when it was found that the alkylation step did not proceed as expected. The product isolated (86% yield) after treatment of 166 with sodium hydride in HMPT followed by propargyl bromide turned out to be 63% of the O-alkylated derivative 179 and 19% of the expected C-alkylated product 176, as determined by IR and NMR spectroscopy. The scheme was abandoned due to the low

yield of the C-alkylated product.

The alkylation of 166 was also attempted using allyl bromide in the hope that the transformations depicted in Scheme 34 might lead to potential intermediates for the



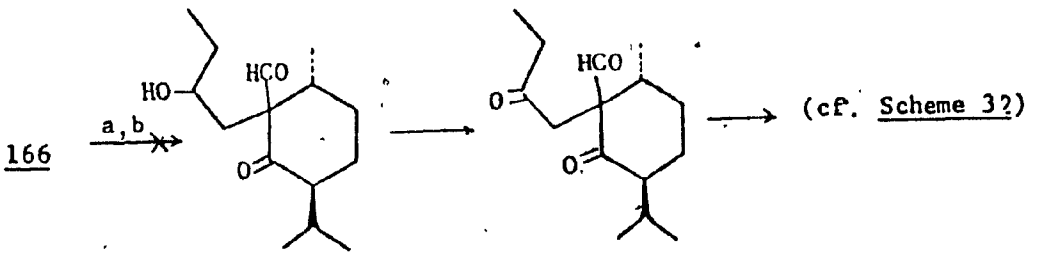
a. NaH, HMPT; b. allyl bromide; c. 210°C, 15min (sealed tube)

Scheme 34

target molecule. Here 65% of O-alkylated product 182 and 22% of C-alkylated product 180 were obtained. This product 182 is an allyl ether suitable for Claisen rearrangement which, if successful, would produce the C-alkylated product 180. Accordingly, when it was heated in a sealed tube at 215°C for 15 min the transformation to the expected products

took place as indicated by the IR and NMR spectra of the product. However, TLC of the product revealed three spots with close R_f values. Two of these are probably the two epimers of 180. The third product, which is not the starting material, remains unknown. Since this step produced a mixture of products which were difficult to separate, the scheme was abandoned.

A further attempt was made for the elaboration of the spirocyclic system according to a plan outlined in

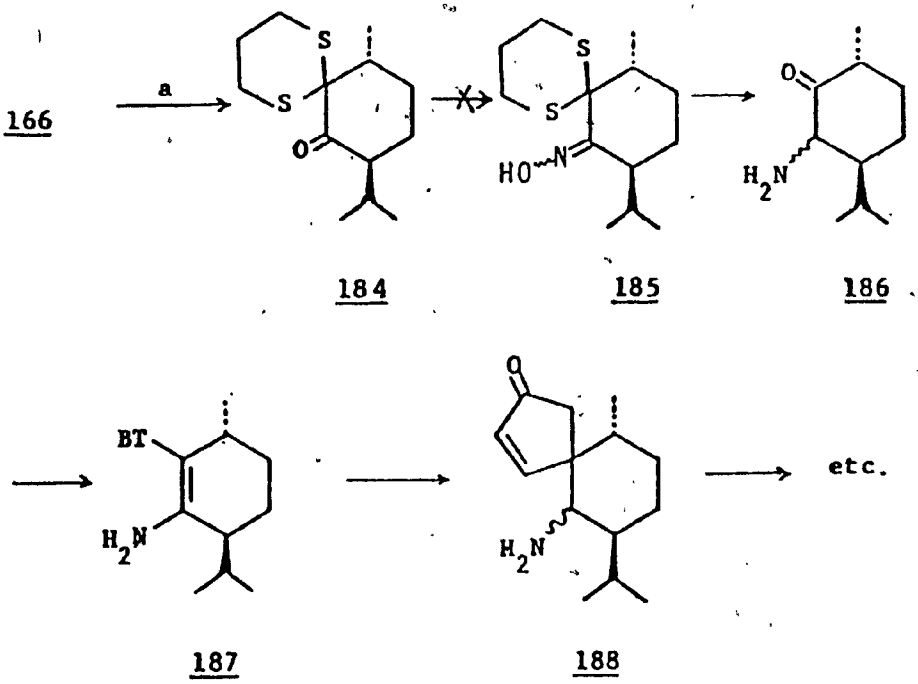


a. NaH, THF-HMPT; b. 

Scheme 35

Scheme 35. It was thought that the anion of 166 might react with 1,2-epoxybutane to give the derivative 183 which could be converted to 174 and thence the plan of Scheme 32 could be pursued. When the anion of 166 was treated with 1,2-epoxybutane there was no evidence for the formation of 183, and the starting material was recovered in near quantitave yield.

As another variation the functionalization of the keto group in 166 was tried in an attempt to obtain a stable grouping which could then be converted to the isonitrile group, prior to the construction of the spirocyclic moiety. To this end a strategy was planned as depicted in Scheme 36.



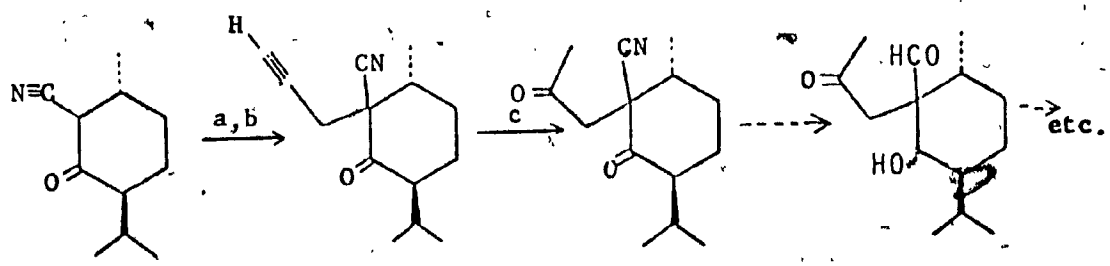
a. $CH_2(CH_2\text{-}STs)_2/NaOAc$

Scheme 36

Following the procedure of Marshall and Roebke[107] formyl menthone was converted to the dithioketal derivative 184 in 53% yield. The plan then was to convert it to its oxime 185, and thence, by following the methodology of Corey and Boger,[108] to the benzothiazole derivative 187 and further to the spiroketone 188. However, all attempts to oximate 184 were unsuccessful. The failure of 184 to undergo oximation

may be attributable to the sterically encumbered nature of the keto group.

The suitability of cyanomenthone (168) as a starting point for the synthesis of spiroaxane derivatives was then explored. One of the approaches planned is outlined in



168 189 190 191

189: A = α-CN, B = β-CN

191: A = α-OH, B = β-OH

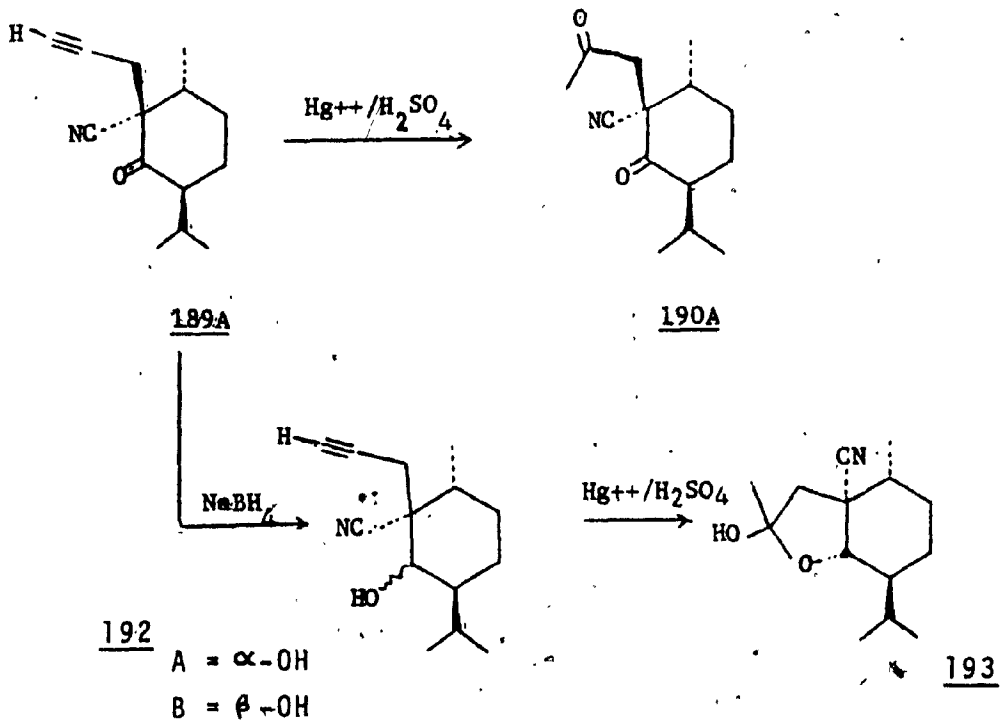
a. NaH /THF-HMPT; b. propargyl bromide ;

c. $HgSO_4$, THF, H_2SO_4, H_2O

Scheme 37

Scheme 37. The anion of 168 was prepared in the mixed solvent system THF-HMPT, and then treated with propargyl bromide. Unlike the case of the alkylation of formyl menthone (166), here there was exclusive C-alkylation producing the cyanoderivative 189 as a mixture of the two possible stereoisomers. It was possible to separate the two isomers by flash chromatography over silica gel. The major component (67%) had mp 92-94°C, and the minor (13%) had mp 54-55°C. The major product was assumed to be the thermodynamically more stable one, and therefore to have the

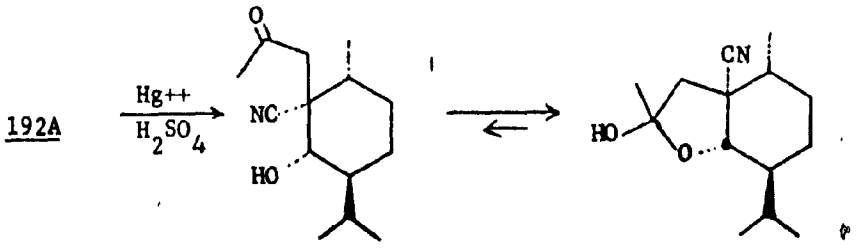
structure 189A. The mercuric ion-catalysed hydration of this material according to the procedure of McCrae and



Dolby[109] gave 190A in 67% yield. The sodium borohydride reduction of 189A resulted in the alcohols 192, the major component being a solid mp 77-79°C (83%) and the minor component an oil (16%). It was assumed that the major product is the thermodynamically more stable one with the OH group in the equatorial position (192A). This is substantiated by the NMR spectrum of the product which shows a doublet at 4.27 (J = 6Hz) for the carbinyl proton. Hydration of the acetylenic group in 192A now yielded a single crystalline product (88%) having a mp 98-100°C, and its IR spectrum showed no carbonyl absorption band, but did show nitrile and hydroxyl absorptions. Based on further

evidence from elemental analysis, NMR and mass spectra the product was assigned the hemiketal structure 193. If the assignment of stereochemistry in 192A is correct, then 193 is expected to have the structure with a trans ring junction. The stereochemistry of the carbon atom carrying the methyl and hydroxyl groups in the five-membered ring is uncertain.

In retrospect, the formation of 193 from 192A is not surprising. Hydroxy aldehydes and ketones are known to exist mostly in the cyclic hemiketal or hemiacetal form, particularly when the ring is five- or six-membered.[110] Indeed, when five- or six-membered rings are possible the cyclization is so facile that it is reported to occur even under neutral conditions. Thus, in the acid-catalyzed



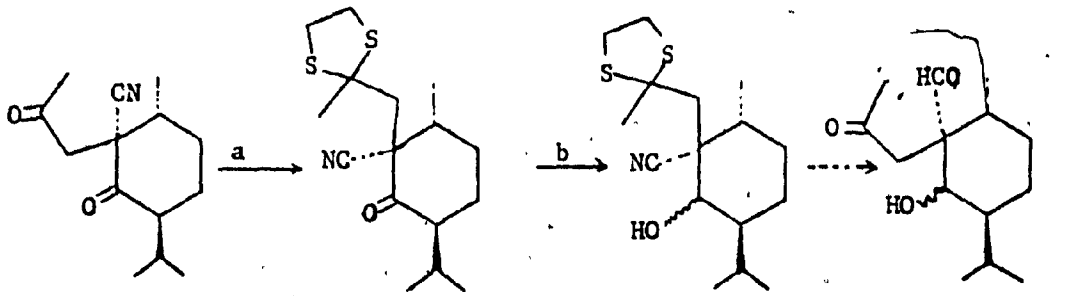
194 193

hydration of 192A the expected keto alcohol 194 was indeed produced, but under the conditions of the reaction did undergo cyclization to 193. The cyclization is considered to be an equilibrium process, with a small amount of the open hydroxy carbonyl form in equilibrium with the ring-closed product.[110] The attempt to protect the hydroxyl

group in 192A was totally unsuccessful. This is attributed to the fact that this group is in a rather sterically encumbered position in the molecule.

Other alkylation reactions of cyanomenthone (168) were also attempted using 1-bromo-2-butanone and 2-bromomethyl-1-butene. In both cases the product consisted predominantly of the corresponding O-alkylated products.

To circumvent the problem of the cyclic hemiketal formation mentioned earlier (cf. 193), another strategy was



190A 195 196 191

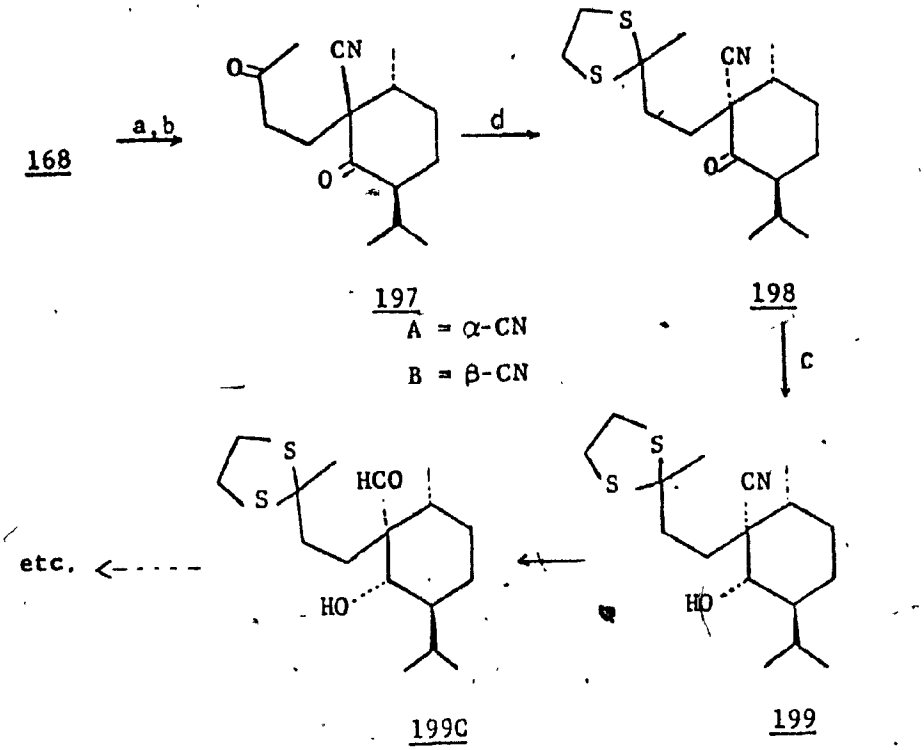
a. $(HS\text{-}CH_2)_2$, TsOH, AcOH; b. $NaBH_4$

Scheme 38

attempted using the cyanomenthone approach (Scheme 38). The keto group in the side chain of 190A was selectively protected[111] as the thioketal 195 (47% yield). Sodium borohydride reduction of this product gave the alcohol 196

essentially as a single product whose stereochemistry is as yet undetermined. The plan at this stage was to convert the nitrile function in 196 to the aldehyde function and then to liberate the carbonyl group from the thioketal masking group to give 191A which was to be cyclized to a spiro-cyclopentenone derivative for further transformation to the target molecule. However, the attempted reaction of the nitrile 196 with DIBAL-H[112] was totally unsuccesful. This result may be attributed to the highly hindered nature of the nitrile group in 196.

A variation of the Scheme 38 was then attempted as illustrated in Scheme 39. Alkylation of the anion of cyanomenthone was achieved via a Michael reaction with methyl vinyl ketone according to the method of Corey and coworkers.[113] There was no evidence of any O-alkylated product being produced under the conditions used, and the C-alkylated cyanoketone 197B was isolated in 73% yield as a single product when the reaction was carried out at -20°C. However, when the reaction was performed at 0°C two products were obtained, the major product being a liquid 197A (64%), and the minor 197B (30%) a solid mp 77-79°C. After selectively protecting the keto group in the substituent of 197A as the dithioketal derivative 198 (89% yield) the ring keto group was reduced using sodium borohydride giving a solid product with a mp 89-91°C. Based on its IR and NMR spectra this product was assigned the structure 199. The



a. DBU-Na_2CO_3, 0°C; b. MVK; c. $NaBH_4$;

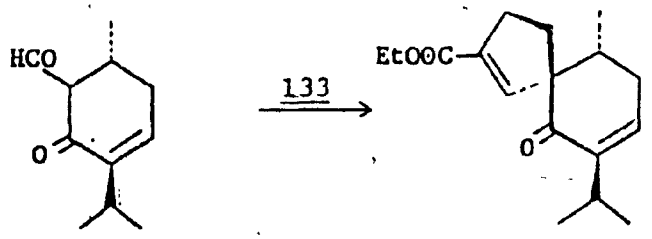
d. $(HS-CH_2)_2$, TsOH, AcOH

Scheme 39

plan then was to convert the nitrile group of each of the epimeric alcohols to the aldehyde group. However, further plans had to abandoned when it was found that the cyano group did not undergo reduction to the aldehyde group when treated with DIBAL-H. The recalcitrance of the nitrile group to DIBAL-H reduction is probably ascribable to its hindered environment. Sterically hindered ester functions are also known to be inert to DIBAL-H.[113]

As mentioned earlier, while the present study was under way, Dauben and Hart[32] demonstrated the utility of

1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (133) in the synthesis of spiroaxane derivatives. For example, the spirocyclic compound 161 was obtained in 17% yield from formyl menthone 160. From their study of the stereochemical course of the reaction between 133 and formyl enones of the type 160 they have concluded that the relative

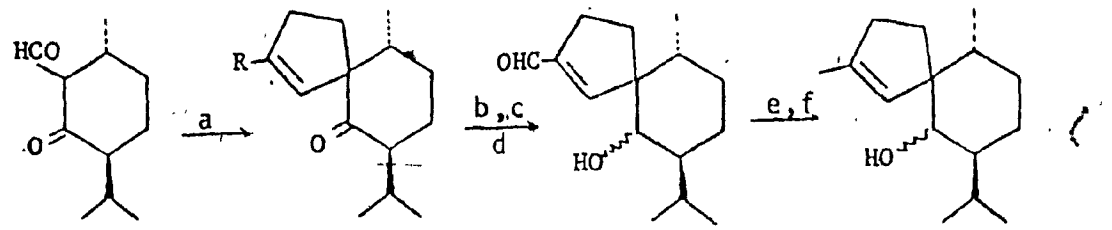


160 161

stereochemistry at C-5 and C-10 should be as shown in 161, and this relative stereochemistry is encountered in the natural products glehnol and other spiroaxanes. It should be noted that in these natural products there is no unsaturation in the six-membered ring, and that catalytic hydrogenation of spirodienones of the type 161 saturates the five-membered ring rather than the six membered one.[32] Thus, the intermediate 161 is not well suited as a key product in the synthesis of glehnol or other spiroaxanes. Dauben and Hart did not pursue this problem further, their objective having been the demonstration of the feasibility of the reagent 133 for a highly stereoselective spiroannelation of α-formyl cycloalkanones having an endocyclic double bond in conjugation with the keto group. In fact, the double bond in conjugation with the keto group is essential in formyl

cyclohexanones to give the indicated relative stereochemistry at C-5 and C-10 (cf. 161).

As the paper of Dauben and Hart did not explicitly report any reaction of the reagent 133 with formyl menthone (166) itself it was decided to study this reaction, and a plan for the synthesis of glehnol (and thence other

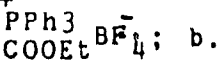


166 200 201 202

R = COOEt

201: A = α-OH, B = β-OH

202: A = α-OH, B = β-OH

a. NaH/HMPT,  ; b. $NaBH_4$; c. LAH;; d. MnO_2; e. $(HS-CH_2)_2$, TsOH, AcOH ; f. Raney nickel

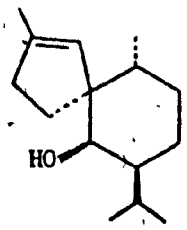
Scheme 40

spiroaxanes) was conceived as outlined in Scheme 40. Accordingly, anion of formyl menthone was treated with propagyl bromide in HMPT and worked up according to the procedure of Dauben and Hart. The oily product (which revealed several spots on TLC) was chromatographed over silica gel which yielded as a non-phosphorus-containing material a product (7%) which had IR and NMR spectra consistent with the structure 200. Reduction of this product with sodium borohydride accomplished the conversion of the keto group to

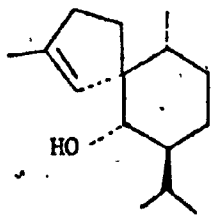
hydroxyl group. The epimeric alcohols were separated by chromatography. By treating the major epimer with excess lithium tetrahydroaluminate followed by oxidation with manganese dioxide[115] it was possible to selectively oxidize the primary allylic alcohol function to the corresponding aldehyde function yielding the alcohol 201B (29%). The hydroxyl group in the epimer is assigned the axial orientation (201B) based on IR and NMR data. (A detailed discussion of the assignments of the OH group of the six-membered ring as axial or equatorial in this and several related derivatives is given in Section D, p 79). The aldehyde group in 201B was converted to a cyclic dithioacetal (90% yield) which was desulfurized using "deactivated" Raney nickel giving 202B as a liquid, $[\alpha]_D$ $+30.23^{\circ}$. This alcohol failed to yield the corresponding tosylate when treated with tosyl chloride in pyridine.[46] Since the OH group in 202B is axially disposed, and since the relative stereochemical relationships of the methyl and isopropyl groups in the six-membered ring are those that exist in menthol the alcohol should be identical to or enantiomeric with glehnol, if the stereochemistry at C-5 in 202B is what would be expected from the work of Dauben and Hart.[32] However, comparison of the available NMR data for glehnol[38] and NMR data of 202B showed that they were not the same.

The chemical shift of the vinylic proton in glehnol is

reported to be at δ 5.06 whereas that in 202B is at δ 5.64. The value for the chemical shift of the methyl group on the double bond is δ 1.76 in glehnol while that in 202B is at δ 1.77. The carbinyl proton appears as a singlet ($W_{1/2}$= 7Hz) at δ 3.57 in 202B, and no value for the corresponding proton is available for glehnol. The English translation of the two papers of Kurvyakov et al. lists opposite signs for the specific rotation of glehnol (32). One[38] reports it as -10° and the other[39] as +10°. No value for the rotation is given in the Chemical Abstracts listing. Incidently, the Chemical Abstracts entry refers to the compound as "gleenol" Since the relative stereochemistries at C-6, C-7 and C 10 in 202b are the same as those of glehnol, the difference between the two may be attributed to difference in the stereochemistry at C-5. Thus, 202B is assigned the absolute



202 B



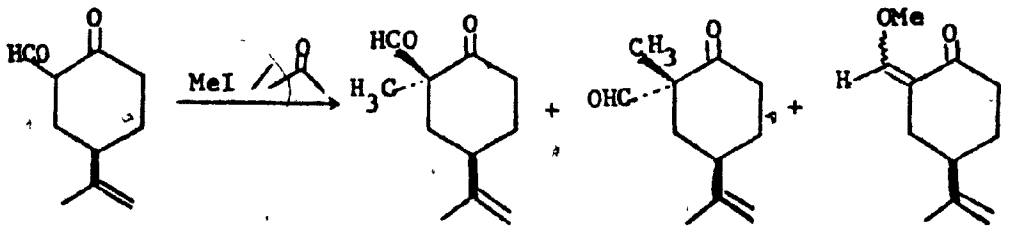
36

stereochemistry as shown below, which makes it 5-epiglehnol.

At this juncture, a comparison of the proton NMR spectrum of 202B was made with that of the alcohol 36 of Caine and Deutsch[46] (kindly supplied by Professor D. Caine

of Georgia Institute of Technology). The vinyl proton of 36 appears as a broad singlet at δ 5.15, the carbinyl proton as a broadened doublet at δ 2.98 (J = 9Hz), and the methyl group attached to the double bond at δ 1.81 as a singlet. The nonidentity of 202B with 36 is thus clear, and coupled with the considerations mentioned in the preceding paragraph it is reasonable to conclude that the stereochemistry at C-5 and C-6 in 202B are epimeric to those in 36.

The structure of 202B illustrates that in the formation of the spiroproduct 200 (cf. Scheme 40) the stereochemical course of the reaction is such that the product is that which results from the "axial approach" of the bulky cyclopropyl group to the thermodynamically most stable conformation of the enolate ion of formyl menthone. This stereochemical outcome of the reaction has been pointed out in the work of Dauben and Hart.[32] The streochemical course of several Robinson annelation reactions has also been explained on the basis of such "axial alkylation" of the most stable enolate ions.[117] Dauben and Hart have also rationalized the major product in the methylation of an α-formyl cyclohexanone derivative 203,[118] by using this approach. In the present study only one spiroannelated product 200 has been isolated. It will be recalled that the opposite stereochemistry results in the same spiroannelation reaction when there is a double bond in conjugation with the keto group in formyl menthone.

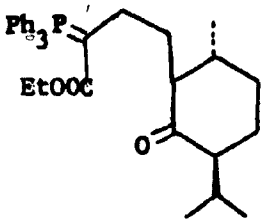


203 204 (55%) 205 (18%) 206 (27%)

Some other facets of the synthetic sequence outlined in Scheme 40 are also worthy of comment. Dauben and Hart have found that the reaction between the sodium salt of α-formyl cycloalkanones and the phosphonium salt 133 produces, in addition to a moderate yield of the spiro keto esters of the type 135 and 200, small amounts of the starting formyl ketones as well as their deformylation products and some 4-carbethoxy-2,3-dihydrofuran (136; cf. Scheme 22, p 36). The dihydrofuran was isolated from most reactions in yields of no greater than 5%, and it was established that this product arose from a reaction between the phosphonium salt and sodium formate which was the other deformylation product.[116] Although it has not been stated how sodium formate arose in these reactions, judging from the yields of the dihydrofuran, it is probable that the hydroxide ion required for the elimination of the formyl group as the formate ion originated as an impurity in the sodium hydride used. The yields of the spiro keto esters in these reactions ranged only from 10-44%, and it was stated that these spiro derivatives were the "major isolable

non-phosphorus-containing compounds."[32] The nature of other products formed in the reaction has not been delineated.

In the present study of the reaction of the phosphonium salt 133 and the sodium salt of formyl menthone, a new type of product, which has not been reported by Dauben and Hart,[32] has been isolated. After the workup of the reaction mixture according to the reported procedure the product mixture was chromatographed over silica gel. After the elution of the spiro keto ester 200, final elution with ether gave a very viscous pale yellow oil (which was difficult to crystallize) as a major phosphorus-containing product (81%). Based on the IR and NMR spectra this product



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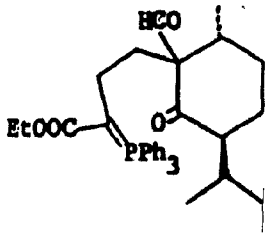


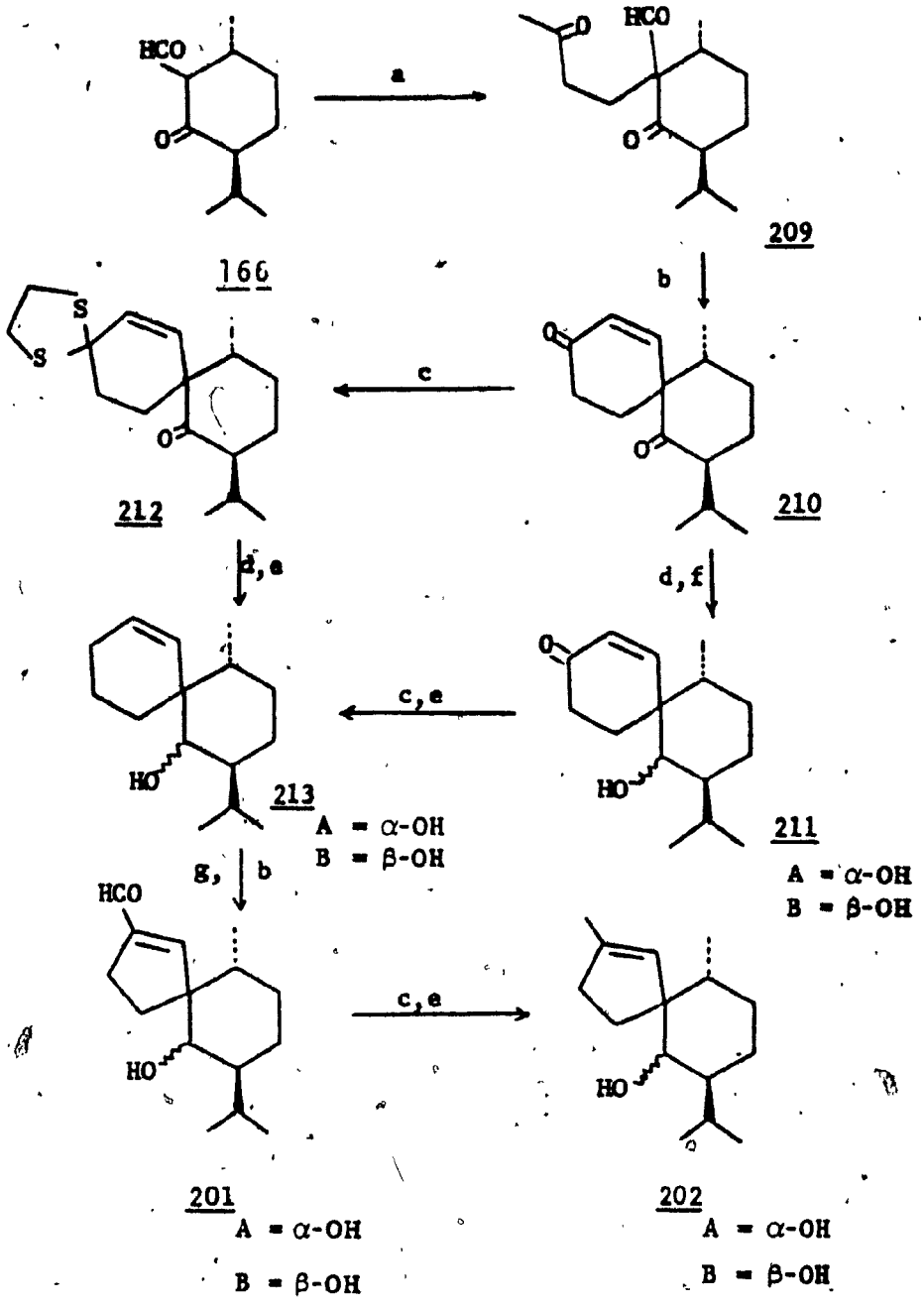
208

is assigned the structure 207. This stabilized phosphonium ylid 207 can be considered as the deformylation product of the phosphorane 208 which must have been formed as the intermediate in the formation of the spiro keto ester 200. Alternatively, 207 could also have arisen by an independent pathway.

As the spiropentannelation procedure of Dauben and Hart

on formyl menthone gave the spiro product with the unwanted stereochemistry, another plan starting with formyl menthone was explored. The essential features of the plan involved the construction of a spirocyclohexenone moiety using the formyl group, and then a ring contraction to a spirocyclopentenyl system by transformations analogous to those used by Ramage and coworkers.[81] Scheme 41 summarizes the sequence of reactions employed in this synthesis. The Michael reaction between formyl menthone and methyl vinyl ketone was achieved at 0°C using the procedure of Corey and coworkers,[113] yielding 85% of the diketo aldehyde 209 as a single product. The aldol spirocyclization of this material using the method of de Groot[119] produced the spiroderivative 210 as a solid (mp 41-43°C) in 63% yield.

In order to remove the carbonyl group in the cyclohexenone moiety of 210 it was decided to convert it to a cyclic dithioketal derivative and to cleave off the thioketal function by one of the standard methodologies. Several procedures were tried for the thioketalization. In one, 210 was treated with propane-1,3-dithiol in the presence of boron trifluoride etherate[119] for 6h at room temperature. Workup of the reaction gave a product whose TLC and NMR spectrum indicated that it was accompanied by an unidentified impurity which was difficult to remove. In another experiment the silicon derivative $(Me_3Si\text{-}S\text{-}CH_2)_2$ was used in the presence of zinc iodide in ether.[120] There was



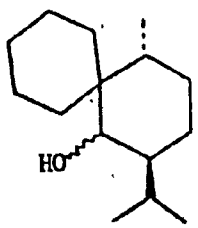
a. DBU-Na_2CO_3, MVK; b. pyrolidine, AcOH;

c. $(HS\text{-}CH_2)_2$, TsOH, AcOH; d. LAH; e. Raney nickel; f. MnO_2;

g. O_3, Me_2S.

Scheme 41

no evidence of the formation of the expected thioketal. Only unreacted starting material was recovered. When 210 was treated with ethanedithiol in acetic acid with catalytic amounts of p-toluenesulfonic acid,[111] the thioketalization proceeded without incident, and a 97% yield of the dithioketal 212 was obtained. Reduction of this product with lithium aluminum hydride gave a 94% yield of a mixture of the epimeric alcohols 215 (A:B = 23:71), the separation of which was achieved by flash chromatography. Early attempts at desulfurization of these alcohols were plagued by unwanted reactions. The procedure involving lithium in ammonia[121] in the presence of tetrahydrofuran resulted in a multi-component mixture (including the starting material) which was difficult to separate. Another attempt was made using the $ZnCl_2$-$CuCl_2$-LAH procedure[122] giving a product (68%) which seemed to be the expected alcohol 213. However, TLC revealed that it was mixed with another product of very close R_f value. This method of desulfurization was therefore deemed unsuitable for the strategy envisioned. So the procedure of using Raney nickel[123] as the desulfurizing agent was tried. However, close examination of the product



214

(IR, NMR, mass spectra and elemental analysis) revealed that it was the saturated product 214. Many attempts were made using both epimers of the alcohol 213, but each time it was found that, concomitant with the desulfurization, the olefinic bond underwent saturation to yield the derivative 214 in 70-75% yields. The literature contains many examples of such unwanted side reactions, and use of Raney nickel partly deactivated by subjecting it to the action of boiling acetone has been found to avoid these side reactions in some cases.[123] However, in the present study this expedient was not found satisfactory in alleviating the problem of the reduction of the olefinic bond alpha to the thioketal function.

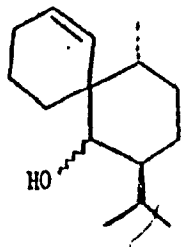
As attempts to desulfurize the reduction product of 212 were frustrated by the formation of the unwanted saturated product 214, it was deemed prudent to put this scheme at abeyance, and the feasibility of other strategies were explored which have already been described in this document. The lack of success of the other approaches led to a re-examination of the Raney nickel reaction, and one last attempt was made using a sample of the catalyst which had been made[124] 9 months earlier. It was a welcome surprise this time to see that not only did the thioketal function cleave off but also that the double bond was preserved. This prompted the idea of looking for other means to "deactivate" the catalyst prior to use in such

desulfurizations. It was found that when the freshly prepared catalyst was stirred briefly with an alkene such as cyclohexene followed by washing with methanol, and then used in the desulfurization reaction, cleavage of the thioketal function went smoothly without affecting the double bond. Thereafter, all desulfurizations of thioketals having alpha-olefinic linkages were carried out without incident by use of the "deactivated" Raney nickel.

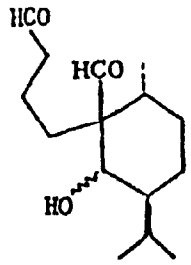
As indicated in scheme 41 the alcohols 213 were also obtained by the sequence involving lithium aluminum hydride reduction of 210 followed by manganese dioxide oxidation. Lithium aluminum hydride converted both carbonyl groups to the secondary alcoholic functions without saturation of the olefinic bond. Selective oxidation of the allylic secondary alcohol function gave an epimeric mixture of the spiroalcohols 211 in an overall yield of 77% from 210 (A:B = 4:7). The separation of the epimers was achieved by flash chromatography over silica gel. The UV spectra of the two epimers were very similar; $\pi \longrightarrow \pi^*$ maximum of 211A appeared at 227nm (ε = 10300), that of 211B at 233 nm (ε = 5320), and the $n \longrightarrow \pi^*$ maxima were at 200 nm and 203 nm respectively. The epimeric alcohols were thioketalized, and then desulfurized using the "deactivated" Raney nickel to the corresponding alcohols 213A and 213B in 70% and 84% yields respectively. It was found that this route was superior to the sequence 210 $\longrightarrow$ 212 $\longrightarrow$ 213 for the preparation of

these epimers. The thioketal of 211B (215B) underwent clean desulfurization with Raney nickel giving a single product 213B, in 84% yield. However, the epimeric thioketal 215A gave two products upon desulfurization. The major component (213A) mp 70-72°C (70%) had an NMR spectrum similar to that of 213B. The carbinyl proton in 213A appeared as a doublet at δ 3.37 (J_{vic}= 9Hz) and the vinylic protons appeared as a complex multiplet between δ 5.30 and δ 6.10, and the corresponding signals in 213B were at δ 3.63 ($W_{1/2} \simeq 6$Hz) and between δ 5.50 and δ 6.20. A noteworthy aspect of the IR spectra (CCl_4 solutions) of 213A and 213B was that neither showed any appreciable C=C stretching band in the 1600-1660 cm^{-1} region. The minor component (213C; mp 89-91°C; 16%yield) had an IR spectrum which revealed a band of moderate intensity at 1655cm^{-1} and strong bands at 655 and 1045 cm^{-1} which were absent in the spectrum of 213A. The NMR spectrum of 213C had a broadened singlet at δ 3.37 (carbinyl proton) and a multiplet at δ 5.50 (2H). The structure of 213C remains to be established.

Having obtained both epimers of 213 attention was directed to methods of ring contraction of the cyclohexenyl moiety. The strategy was to cleave the double bond in 213 so that the dialdehyde 216 could be generated which will be well suited for aldol cyclization to the spirocyclopentenyl aldehyde 201. One methodology tried initially on 213A was the osmium tetroxide-sodium periodate procedure.[125] Workup



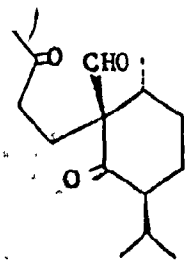
213



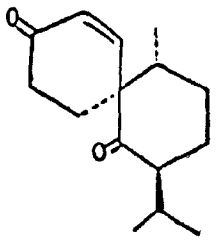
216

of the reaction mixture gave a low yield of a severe mixture containing some starting material as well. Consequently it was decided to use the other standard methodology, viz ozonolysis. The alcohol 213 was dissolved in methanol and excess ozonized oxygen was passed into it at -75°C, followed by treatment with dimethyl sulfide,[126] and after workup a 62% yield of the expected dialdehyde derivative 216 was isolated as confirmed by IR and NMR spectra. After further purification by chromatography this derivative was subjected to the aldol cyclization using pyrrolidine acetate[119] in methanol giving the spirocyclic hydroxy alcohol 201A in 72% yield. Without further purification of the aldehyde, it was converted to the corresponding cyclic dithioketal 217A, mp 68-70°C in 96% yield. Desulfurization using deactivated Raney nickel catalyst gave the expected alcohol 202A in 81% yield (mp 68-70°C $[\alpha]_D^{25}$+14.92°). Following an identical sequence the epimer 213B was also transformed via 217B to the spiro product 202B in 39% yield $[\alpha]_D^{25}$+30.23°. This product had IR and NMR spectra identical to those for the 202B obtained in Scheme 40.

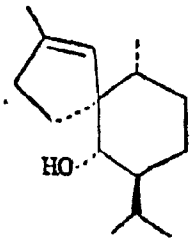
The identity of 202B of Scheme 41 and that obtained according to Scheme 40 points to the fact that in the Michael reaction of methyl vinyl ketone and the enolate of formyl menthone (35), the product was exclusively that which resulted from the axial alkylation[117,118] of formyl menthone. As mentioned earlier 202B is 5-epiglehnol or its enantiomer. The spiro alcohol 201A must be the 5-epimer of the alcohol 36 obtained by Caine and Deutsch.[46] The relevant compounds in Scheme 41 may, therefore, now be assigned the absolute stereochemistries as shown below. The stereochemical assignments of the hydroxyl groups of the various alcohols were made from their IR and NMR data as



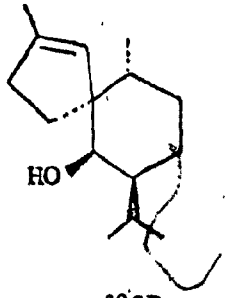
209



210



202A



202B

described in Section D.

D. CONFIGURATIONAL ASSIGNMENT OF HYDROXYL GROUP.

In the area of conformational analysis organic chemists have always relied heavily on various physical methods. Two of the most commonly used physical techniques for conformational studies have been IR and NMR spectroscopies.[114,127] For the conformational assignment of the hydroxyl group IR spectroscopic correlations of the C-O

stretching frequencies[128] as well as O-H stretching frequencies[129] have been examined. Since both possible epimers of several new cyclohexanol derivatives have been synthesized in the present study it was considered interesting and important to attempt such spectroscopic analyses for the conformational assignments of the hydroxyl group.

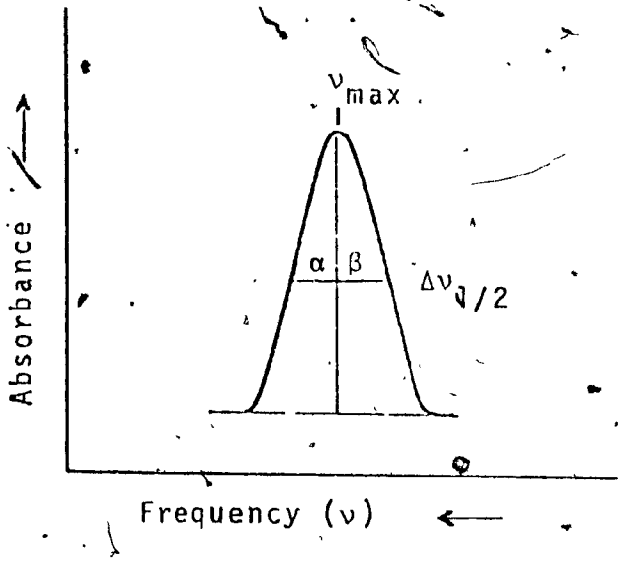
It is known that, in general, an equatorial C-O stretching vibration has a higher frequency than the corresponding axial one, and this has been ascribed to the fact that the equatorial C-O stretching motion has a higher force constant.[114] However, many exceptions to this have been observed even in simple systems.[129,130] It has been observed for several cyclohexanols of known stereochemistry,[127] that the equatorial C-O stretchings were in the region 1037-1044 cm^{-1}, while the axial C-O stretchings were in the region 996-1036 cm^{-1}. Examination of the IR spectra in the region 950-1050 cm^{-1} of the several pairs of epimeric alcohols encountered in the present study showed that the C-O stretching frequency correlation is unreliable as both epimers of several alcohols had sharp, medium intensity bands in the region without any trend in their positions.

An alternative correlation, and a seemingly neglected one, has been based on the the position of the maxima of the fundamental free O-H stretching frequencies. It has been

observed that an axial hydroxyl group has a fundamental free O-H stretching absorption about 5-10 cm^{-1} higher than that of its equatorial epimer,[131] the situation here being the reverse of that of the C-O stretchings. Cole and coworkers[132] have suggested that this is the result of an increase in the force constant of the O-H stretching vibration due to the "steric opposition" of the axial hydrogens. In the present study the IR spectra of dilute carbon tetrachloride solutions (<0.02M) of the epimeric sets of alcohols were measured in the 3000-4000 cm^{-1} region using a slow scan and an expanded abcissa (20 cm^{-1}/cm). The free O-H stretching frequencies are listed in the Table. Examination of the band positions revealed that one epimer in each pair has a consistently higher frequency than the other. The OH group in these epimers has been assigned the axial orientation.

A third approach sometimes used in the conformational assignment of the hydroxyl group has been the band shape of the fundamental free O-H stretching absorption. According to Aaron and Rader,[133] "direct conformational assignment of the hydroxyl group may be made on the basis of its band shape, a symmetrical band for an axial, and an unsymmetrical band for an equatorial hydroxyl group". For quantitative characterization they have expressed the symmetry of the band as the ratio $\gamma = \alpha/\beta$ which results from the measurements of the segments of the half bandwith ($\Delta\nu_{1/2}$) on

the high (α) and low (β) frequency side of the ν_{max} (See



Figure

Figure). The authors have studied a number of epimeric alcohols of various types of known conformations, and have observed that a symmetry ratio which departs from unity by less than 10% would appear to be a firm indication of an axial hydroxyl conformation. The authors did also caution that this simple correlation might not hold "in the case of a vicinally substituted axial alcohol", citing the case of neomenthol which gives a doublet for the free O-H stretching at 3628 cm^{-1} and 3632 cm^{-1} of near equal intensities. The strict application of the method for the characterization of the band symmetry gave an equatorial assignment (Y = 0.60) to this known axial hydroxyl group. When an instrument of lower resolving power was used, neomenthol gave the symmetrical free O-H stretching band expected for its

conformation. In spite of this and several other exceptions[134,135] the free O-H band shape analysis is believed to be an important technique for direct configurational assignments.[133]

In the present study the band shape approach was also examined. Using a Perkin Elmer 599B grating spectrophotometer, spectra in the region of 3000-4000 cm^{-1} of dilute CCl_4 solutions of the epimeric alcohols were recorded in an absorbance mode. The free O-H stretching band of each compound was very slowly scanned on an expanded abscissa (20cm-1/cm) and the symmetry values γ was calculated as described[133] and are given in the Table. As can be seen symmetry ratios close to unity have been obtained even for some equatorial OH groups. It must be noted that all the compounds listed in the Table are vicinally substituted cyclohexanols, and therefore, the band shape approach may not be valid. However, what is clear is that the position of the ν_{max} for the free OH frequencies is consistently higher in one of each pair of epimers in the Table. It seems, therefore, that when the IR spectra of both isomers of an epimeric pair are available, that epimer which shows the higher ν_{max} for the free stretching can be considered to have the OH group axially disposed.

It is interesting to note that the IR spectra of two of the compounds, 190B and 218A exhibit two peaks for the free OH stretching. In 190B the doublets are fairly well

TABLE

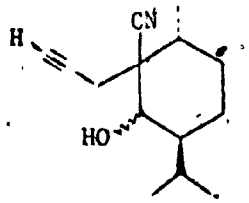
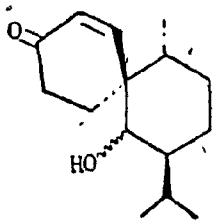
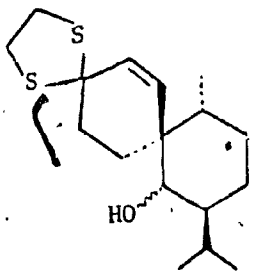
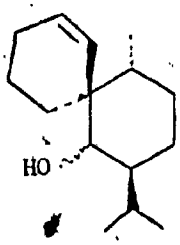
		ν_{max} (cm^{-1})	γ	δ (ppm)*	J (Hz)†
	A	3636	0.97	4.27	6
	B	3642, 3591[b]	0.99, 1.11	¶	
190					
	A	3628	0.98	3.77	9
	B	3642	1.10	3.67	3.8[§]
210					
	A	3598	0.78	3.47	8
	B	3647	0.90	3.42	3[§]
215					
	A	3591	1.00	3.37	9
	B	3647	0.65	3.13	6[§]
213					

TABLE (Cont'd).

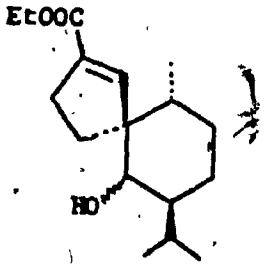
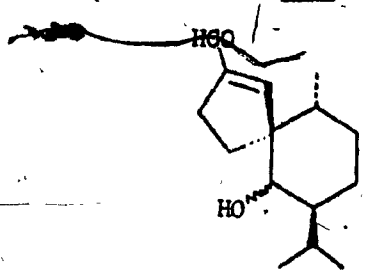
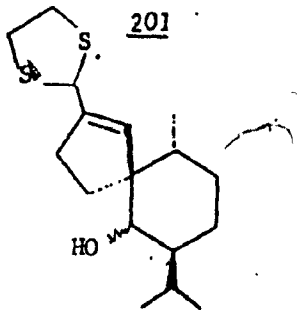
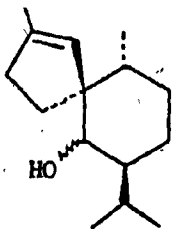
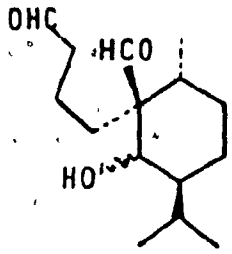
		ν_{max}	γ	δ*	J†
	A	3640, 3605[a]	–	3.57	8.5
	B	3640	1.11	3.58	8[§]
218					
	A	3609	1.90	3.67	9
	B	3640	1.12	3.57	4[§]
201					
	A	3592	0.64	3.58	9
	B	3640	1.40	3.48	9[§]
217					
	A	3584	0.77	3.37	9
	B	3641	0.88	3.45	7[§]
202					

TABLE (Cont'd).

		ν_{max}	γ	δ*	J†
	A[Φ]	3612, 3584[c]	0.68	3.97	9
		3536			
	B	3588	1.10	4.17	4[§]

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* chemical shift of carbinyl proton

† vicinal coupling constant of the carbinyl proton (approximate)

¶ unresolved.

§ width at half height

Φ impure sample

a equal intensities

b higher intensity

c highest intensity

A α-OH

B β-OH

resolved (3642cm^{-1} and 3591cm^{-1}, the integrated intensity of the latter being about twice that of the former), and therefore γ values for both bands are included. In the spectrum of 218A the overlap of the doublets (of near equal intensities) was enough to make the half band widths uncertain. The origin of the two separate bands is not clear at present. As noted before, a similar phenomenon was encountered by Aaron and Rader in the case of the axial hydroxy compound neomenthol.[133]

NMR spectroscopy has also been recognized as a powerful tool for conformational assignments.[114,127,136] Confirmatory evidence for the assignments discussed above based on IR spectral correlations was therefore sought in the NMR spectra of the same set of epimeric alcohols. Two aspects of the NMR spectrum which help to distinguish between axial and equatorial isomers of rigid cyclohexyl systems of chair conformation are the values of the chemical shift (δ) and the coupling constant of an alpha proton. Such factors as the inductive effect of the substituents, anisotropy of the adjacent chemical bonds, and steric interactions, affect the chemical shift, but by and large, an axial alpha proton is observed to have a lower δ value than the corresponding equatorial proton. However, many exceptions are known, and caution has been advised in the use of chemical shift values for conformational assignments.[136] Examination of the chemical shift values listed in the Table shows that they do

not show any clear-cut trend. Some β-epimers in fact exhibit larger values than the corresponding A-isomers.

Perhaps a more important NMR parameter which is useful in distinguishing between axial (a) and equatorial (e) protons is the value of the vicinal coupling constant (J_{vic}) of the alpha proton.[136,137] Although various factors such as the dihedral angle, electronegativity of the substituents, C-C-H angles, and bond lengths are known to affect the coupling constant, the dihedral angle dependance as originally enunciated by Karplus,[138] has been the most commonly used criterion by organic chemists for conformational assignments. According to this approach, in six-membered rings with a chair conformation, the alpha proton can be distinguished by the coupling constants, since $J_{a,a}$ (8-13 Hz) differs substantially from $J_{a,e}$ (2-6 Hz) and $J_{e,e}$ (1-5 Hz). In instances where coupling constants cannot be resolved the width at half height of the signal ($W_{1/2}$) has been recommended,[136] since it is generally larger than 15 Hz for an axial proton, and smaller than 12 Hz for an equatorial proton.

In the present study attention was therefore focussed on the signal due to the carbinyl proton (alpha proton with respect to the OH group) of the epimeric sets of alcohols, and the relevant NMR parameters are given in the Table. In the A-isomers (i.e. α-OH epimers) the carbinyl proton must

be axially disposed and is coupled to the methine proton (also axially disposed) on the carbon carrying the isopropyl group. Consequently, the A-isomers are expected to show larger coupling constants ($J_{a,a}$) for the alpha proton than the corresponding B-isomer where the vicinal protons are in an equatorial-axial ($J_{e,a}$) relationship. As can be seen from the J-values listed in the Table the A-epimer of each pair consistently exhibit larger coupling constants than the corresponding B-epimer. It is clear that the IR correlation based on the position of the ν_{max} of the free OH stretching frequency, and the NMR correlation based on the coupling constant values of the alpha proton are consistent with each other, and thus the conformational assignments of the hydroxyl functions of the alcohols listed are considered reliable.

SUMMARY AND CONCLUSIONS

The original objective of the present study was the total synthesis of optically active axisonitrile-3 which, on account of the isolation and structure elucidation of glehnol and a synthesis of the enantiomer of axisonitrile-3, has been revised to comprise of the total synthesis of glehnol and its 6-epimer. This task was approached from several directions, and a number of strategies were explored, using as a starting point formyl menthone (166) or cyanomenthone (168), both of which were prepared from the readily available (-)-menthol.

In one of the approaches starting from formyl menthone the protection of the formyl group as the n-butyl thioether derivative was achieved relatively easily, and the product consisted of the two possible geometrical isomers. The oximation of this mixture was totally unsuccessful, presumably due to the hindered nature of the carbonyl group. Lithium aluminium hydride treatment produced a mixture of isomeric alcohols which were found to be labile, giving rise gradually to compounds exhibiting carbonyl absorption in the infrared. The nature of the transformation has not been established. An attempt to produce a spirocyclopropyl derivative 173 by an alpha-ketocarbene insertion reaction into the enol ether derivative 172 was unsuccessful.

The alkylation of the enolate of the formyl menthone

using propargyl bromide (Scheme 33) gave mainly the corresponding O-alkylation product, while the alkylation using allyl bromide gave a mixture of the O-allylated (65%) and C-allylated (22%) products. The O-alkylated product in each case was a mixture of the two possible geometrical isomers which were difficult to separate. The O-alkyl derivative (182) was subjected to the Claisen rearrangement yielding a mixture consisting of both stereoisomers of the expected C-alkylated product and a third product of undetermined structure. Due to the difficulty in separating the components the scheme had to be abandoned.

In contrast to the alkylation of the anion of formyl menthone the alkylation of the anion of cyanomenthone with propargyl bromide gave exclusively the C-alkylated products (Scheme 37). The two stereoisomers of the C-alkylated product were solids and were separated by chromatography. The major product (67%) was assumed to have the thermodynamically more stable conformation in which the propargyl and methyl groups are trans with respect to each other (cf. 189A). The murcuric ion-catalyzed hydration of this product yielded the expected diketo derivative 190A. It was possible to reduce the carbonyl group in 189A with sodium borohydride giving a mixture of the two epimeric alcohols which were separated and characterized. The major epimer was a solid which when subjected to the mercuric ion-catalyzed hydration yielded a single crystalline

compound identified as a cyclic hemiketal 193. This result is ascribable to the fact that the initial hydration product is a δ-ketoalcohol which readily formed a 5-membered cyclic hemiketal. The attempt to protect the hydroxyl group prior to the hydration reaction was unsuccessful.

As a variation of the strategy, the keto group in 190A was protected as a cyclic dithioketal and then the ring cabonyl group was reduced using sodium borohydride. However, after this step it was not possible to convert the cyano group to the aldehyde group by treatment with DIBAL-H. The anion of cyanomenthone was also subjected to the Michael reaction with methyl vinyl ketone (Scheme 39) to give the cyanoketone 197. After masking the keto group of the side chain as the dithioketal the ring keto group was reduced with sodium borohydride to the alcohol 199. Subsequent treatment with DIBAL-H failed to convert the nitrile to the aldehyde group. The indolence of the nitrile function to DIBAL-H reduction in both cases mentioned above is attributed to the highly crowded environment of this group.

Two of the schemes used in the present study have been successful in producing spiropentannelated products, and each had formyl menthone as the starting point. In one the sodium salt of formyl menthone was reacted with 1-carbethoxytriphenylphosphonium tetrafluoroborate (133) according to the procedure by Dauben and Hart yielding a

spiropentannelated ester 200 (Scheme 40) as one of the products. The lithium aluminum hydride reduction of this followed by manganese dioxide oxidation gave a mixture of the epimeric hydroxyaldehydes 201 from which the major isomer was isolated in the pure form (201B). The hydroxyl group of this product was shown to be axially oriented by use of IR and NMR spectroscopy. Thioketalization of the aldehyde followed by Raney nickel desulfurization yielded the alcohol 202B. In addition to the spiroester 200 a non-spirocompound has been isolated from the reaction and this constituted the major product of this reaction. Based on spectroscopic evidence, a stable phosphoniun ylid structure 207 has been proposed for this product.

In another approach the Michael reaction of the anion of formyl menthone with methyl vinyl ketone gave the keto aldehyde 209 (Scheme 41) which was cyclized to the spirocyclohexenone derivative 210 in good yield. Lithium aluminum hydride reduction followed by manganese dioxide oxidation gave a mixture of epimeric alcohols 211. After separation of the epimers each was subjected to thioketalization and subsequent desulfurization yielding the spiro alcohols 213A and 213B. Each alcohol was subjected to ozonolysis and the resulting dialdehydes were cyclized to the corresponding spirocyclopentenyl aldehydes 201A and 201B. Conversion of the aldehyde group to the methyl group was achieved by thioketalization followed by Raney nickel

desulfurization yielding the spiro alcohols 202A and 202B. Neither of these was identical to glehnol. The spiroalcohol 202A is considered to be the 5-epimer of the spiro alcohol 36 obtained by Caine and Deutsch[46] en route to their synthesis of (-)-axisonitrile-3, while 202B is considered to be 5-epiglehnol or its enantiomer.

Elucidation of the structures of 202A and 202B indicated that the Michael reaction of methyl vinyl ketone as well as spirocyclization reaction of 1-carbethoxy-triphenylphosphonium tetrafluoroborate with the anion of formyl menthone took place stereospecifically resulting in the "axial alkylation" of the most stable conformation of the enolate.

It was found in the present study that the thioketalization of α,β-unsatuarated cyclic ketones was better done using ethane dithiol than propane-1,3-dithiol, the latter tending to produce more often the corresponding impure thioketals. Another noteworthy finding has been that the desulfurization of the cyclic ketals having α,β-unsaturation using freshely prepared Raney nickel causes the double bond to undergo saturation as well. It was found that a partly deactivated Raney nickel was necessary for desulfurization with the preservation of the α,β-double bond. A convenient method for partial deactivation of the catalyst has been developed during the course of the present

study.

The conformational assignment of the hydroxyl group in the many cyclohexanol derivatives encountered in the present study was made by IR and NMR spectroscopic studies. Of the three parameters generally used in the IR for distinguishing between axial and equatorial OH groups, viz, the position of the "free OH" stretching frequency, and the position of the C-O stretching frequency, and the symmetry of the "free OH" adsorption band, only the ν_{max} of the free OH was found to be a reliable criterion when both epimers are available. In all cases examined in the present study the "free OH" stretching band of the axial epimer had a higher frequency than that of the corresponding equatorial epimer (cf. Table). The chemical shift value of the alpha protons (carbinyl protons) in the alcohols did not reveal any clear-cut trend; however, the vicinal coupling constant correlation was found to be quite reliable, the magnitude of the coupling being greater for $J_{a,a}$ than for $J_{a,e}$ or $J_{e,e}$. The conclusions from the IR and NMR analysis were consistent with each other.

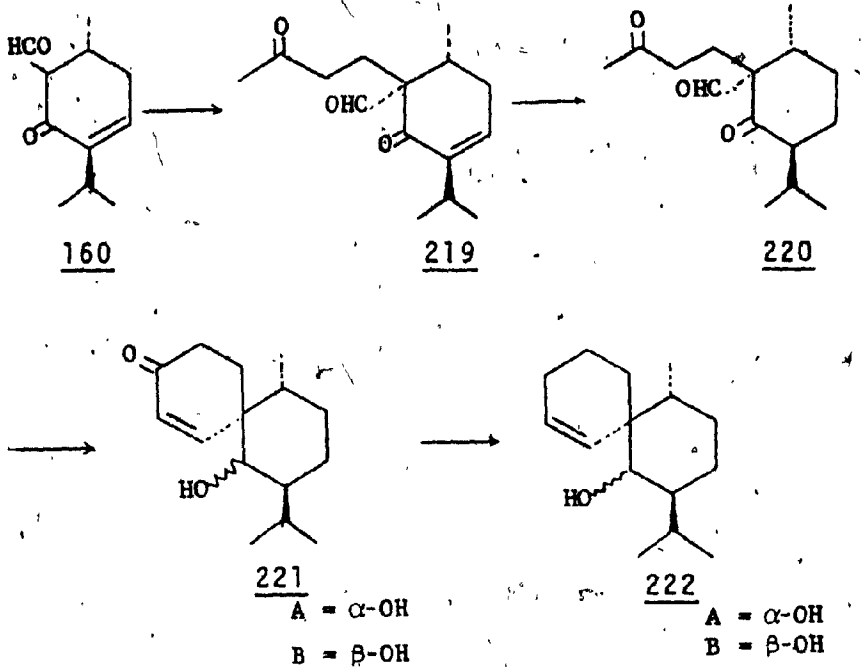
SUGGESTIONS FOR FURTHER STUDY

Several facets of the present study are worthy of further investigation. One of the successful methods of spiropentannelation of formyl menthone (166) was by the use of 1-carbethoxytriphenylphosphonium tetrafluoroborate (133) according to the procedure of Dauben and Hart.[32] This approach (cf. Scheme 40) resulted in producing the 5-epimer of glehnol (or its epimer) which poihted to the fact that in the formation of the spirocyclopentenyl system the anion of the formyl menthone underwent "axial alkylation" with the cyclopropyl reagent. The spirocyclization using this reagent gave only a poor yield of the product. It is worthwhile investigating this reaction further so as to find the optimum reaction conditions for improving the yield of the spirocyclic product, and perhaps even for reversing the direction of the alkylation step.

A more significant observation regarding the reaction of 133 with the anion of formyl menthone was the fact that the major product was a phosphorus-containing product, a thick pale yellow oil which was difficult to crystallize and purify, and whose IR and NMR spectra indicated that it did not contain any formyl group, but did possess COOEt, menthone moiety, and $C{=}PPh_3$ group. Based on these considerations the product was tentatively assigned the stable phosphonium ylide structure 207. In view of the fact that Dauben and Hart did not characterize in their study[32]

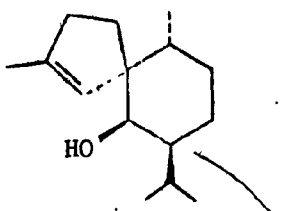
of the reaction of 133 with various formyl cycloalkanones any phosphonium ylide of this type, it is worthwhile investigating this product further so that more insight into the mechanism of the reaction can be gained. If the product is indeed the phosphorane 207, it should undergo reactions characteristic of such phosphoranes, and identifing the products of these reactions will be helpful in characterizing it. One should also be able to achieve an independent unequivocal synthesis of 207 by a series of straightforward transformations.

Another aspect worthy of further attention is the feasibility of the approach outlined in Scheme 42 for the production of the spirocyclohexenone derivative 219. The difference between 219 and 211 is that the chirality of the spirocarbon in the former is opposite to that in the latter. The reaction of the anion of formyl menthone (166) with methyl vinyl ketone resulted in "axial alkylation," and consequently subsequent transformations resulted in 211 (cf. Scheme 41.). The work of Dauben and Hart[32] demonstrated that when a double bond is present in conjugation with the ring keto group the direction of alkylation is reversed. Therefore, the reaction of the anion of formyl menthenone (160) with methyl vinyl ketone is expected to produce 219 where the formyl group and the ring methyl group are cis with respect to each other. At this stage a method has to be found for saturating the olefinic bond of the enone to

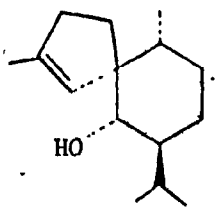


Scheme 42.

the diketo aldehyde 220. This can probably be achieved by hydrogenation using a catalyst such as palladium on carbon. If catalytic hydrogenation is not feasible one has to explore the possibility of bringing about a chemical reduction of the enone system by appropriately protecting the other carbonyl groups. Conversion of 220 to 221 and 222 can be achieved by the same sequence of reactions as were used to obtain 211 and 213 (cf. Scheme 41). Once 222 isomers are produced, reaction sequences identical to those performed on 213 in Scheme 41 should produce the epimeric alcohols 32 (glehnol or its enantiomer) and 36 (6-epiglehnol).

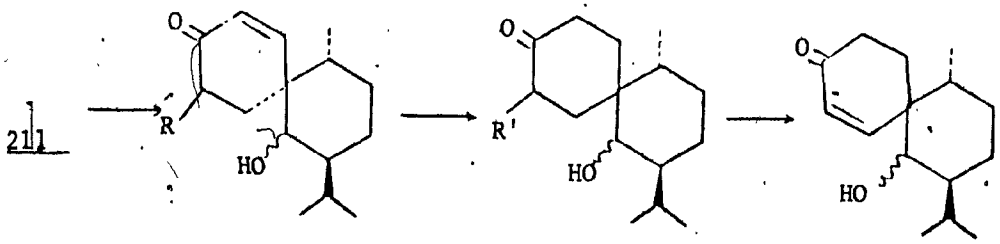


32



36

An alternative route by which 221 could be obtained would be by the sequence outlined in Scheme 43. The idea is to transpose the double bond in the spiro cylohexenone system of each of the epimers of 211 obtained via Scheme 41. One of the ways this could be achieved is by converting 211 to 223 where R = SPh or SePh grouping such that at a later stage this grouping can be oxidized to R' and then eliminated to produce a new α,β-double bond. As shown in Scheme 43, a way has to be found to reduce the olefinic bond in 223 and then to oxidize R to R' so that the subsequent



211 → 223 → 224 → 221

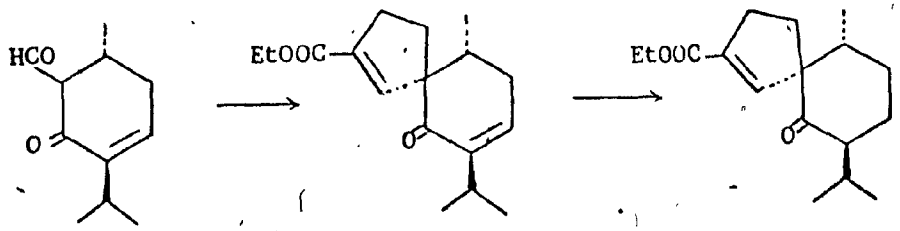
R = SPh or SePh R' = SPh or SePh

Scheme 43

elimination step can be brought about to produce 221. Methodologies are available for introducing a double bond

α,β to a carbonyl group by the use of a phenyl sulfide[139] or a phenyl selenide[97] group alpha to a carbonyl group. Once 221 is thus produced it can be further converted to 32 and 36 by the transformation suggested in the previous paragraph.

Dauben and Hart[32] have shown that the anion of formyl menthenone (160) reacted with the phosphonium salt 133 stereospecifically to produce the spiro ester 161 which has



160 161 225

Scheme 44

the same relative stereochemistry at C-5 and C-10 as that which exists in the spiroaxanes. It was mentioned earlier that selective catalytic hydrogenation of this product to 223 is not feasible because the work of Dauben and Hart has demonstrated that in spiro compounds such as 161 it is the double bond in the five-membered ring that undergoes ready catalytic hydrogenation. However, it might be possible to convert 161 to 223 by a chemical reduction (Scheme 44). Recently Ganem[140] has discovered that certain α,β-unsatuarated cyclohexenones which are unsubstituted at the beta-vinylic carbon undergo exclusive 1,4-reduction in

the presence of potassium tri-sec-butyl borohydride (K-selectride,™ Aldrich Chemical Company) to produce the corresponding saturated ketones in nearly quantitative yields. Other conjugated functional groups such as α,β-unsaturated esters seem to be unaffected by this reagent under the conditions used, as has been shown by the fact that ethyl crotonate was recovered unchanged.[140] Therefore, it would seem that this reagent could bring about the selective reduction of 161 to 225. Once 225 is obtained it can be converted to 32 and 36 by transformations identical to those performed on 200 (which is the 5-epimer of 225) in Scheme 40 (cf. p. 66).

Another point which deserves some further attention concerns the desulfurization of the thioketal 215A. It was found that the Raney nickel desulfurization of 215A resulted in two products 213A and 213C, and the identity of the latter is as yet undetermined. Since 213C is not the epimer of 213A and since the thioketal 215B (epimer of 215A) did produce only the expected desulfurization product 213B it would be an interesting problem to investigate the desulfurization of 215A further and to establish the nature of 213C.

EXPERIMENTAL

TECHNICAL NOTES:

General: Detailed procedures are given only for those reactions which gave identifiable products. Solvent removal from worked up reaction mixtures was effected by using a Buchi rotary evaporator under aspirator vacuum at room temperature (unless otherwise stated). Workup refers to the extraction with ether or other suitable solvent followed by concentration of the sodium sulfate-dried organic extract by rotary evaporation. Unless stated otherwise column chromatography implies the technique of flash chromatography described below. All solvents for reaction, crystallization and chromatography were dried and distilled prior to their use.

Elemental Analysis: These were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Flash Column Chromatography: This was accomplished by the technique described by Still et al.[141] using silica gel 60 as the adsorbent. Fractions were collected and monitored by TLC.

Thin Layer Chromatography(TLC): Analytical TLC was accomplished on standard glass microscope slides coated in this laboratory with Baker aluminum oxide 9F (1-0541) or

E. Merck silica gel $60GF_{254}$. Components were detected by using MINERALIGHT model SL-2537 UV lamp with a short wavelength filter, supplied by Ultra-Violet Products Inc., San Gabriel, California, by use of iodine vapor, or by use of conc. sulfuric acid spray followed by heating the slide on a hot plate.

Melting Points and Boiling Points: All melting points and boiling points reported are uncorrected. Melting points were measured using a Gallenkamp MF-370 instrument.

IR Spectra: These were routinely recorded using a Perkin Elmer Model 559B Infrared Spectrophotometer, using chloroform or carbon tetrachloride as solvent. Most spectra were recorded using a matched set of sodium chloride cells having path lengths of 0.1 mm. Wavenumbers quoted within the experimental section are deemed accurate to $5cm^{-1}$. Details concerning the measurement of spectra for studies related to the conformational assignment of the hydroxyl groups in some cyclohexanol derivatives are given in the Discussion section (Section D; p 79).

Mass Spectra: These were determined on a DuPont 21-492B double focusing unit at 70eV utilizing direct insertion of sample into a heated probe.

NMR Spectra: These were obtained using a Varian A-60A

Spectrometer, or a Varian T-60 Spectrometer, on non-degassed samples (as 5-10% solutions in $CDCl_3$, CCl_4). Spectra at 400 MHz were recorded on a Bruker WH 400 on non-degassed samples (as 0.4-0.1% solutions in $CDCl_3$). All chemical shifts (δ) are expressed in ppm relative to tetramethylsilane used as an internal standard. The peaks are designated as s (singlet), d (doublet), bs (broad singlet), q (quartet), and m (multiplet).

Ultraviolet Spectra: These were obtained on a Perkin Elmer 552 Visible-Ultraviolet spectrophotometer.

Optical Rotation Measurement: These were performed on Perkin Elmer 241 polarimeter.

Ozonizations: Ozonized oxygen for this purpose was prepared by using a Welsbach T-816 series 920 ozonator.

Reagents and Chemicals: All specialty chemicals used in the present study were obtained from commercial sources as listed below, and were purified prior to their use when deemed necessary.

Aldrich Chemical Co. Inc.: Allyl bromide; 1-butanethiol; chlorotrimethyl silane; 1,5-diazabicyclo-[5.4.0]undec-5-ene; dihydropyran; diisobutyl aluminum hydride (1M solution in hexane); 1,2-epoxybutane;

1,2-ethanedithiol; hexamethylphosphoramide; lithium aluminum hydride; manganese(iv)oxide (activated); methyl vinyl ketone; osmium tetroxide; 2,4-pentanedione; propanedithiol; propargyl bromide; propionyl chloride; urea.

Allied Chemicals Canada, Ltd.: Glacial acetic acid.

Alfa Inorganics: Sodium hydride (50%, oil dispersion)

Anachemia Ltd.: Zinc chloride (anhydrous); cupric sulfate.

BDH Chemicals: Silica gel $60GF_{254}$; silica gel 60.

Eastman Kodak Co.: Boron trifluoride etherate; ethyl formate; methylamine hydrochloride; pyrrolidine; triethylamine.

Fisher Scientific Co.: Chromium trioxide; mercuric sulfate; methylamine hydrochloride; sodium metal; tetrahydrofuran; p-toluenesulfonic acid;

W. R. Grace & Co.: Raney nickel alloy powder.

Mallinckrodt Chemical Works: Hydroxylamine hydrochloride.

Pfaltz and Bauer, Inc.: 1,3-dibromopropane.

Ventron Metal Hydride Division: Sodium borohydride.

1-Carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate,[142] cuprous acetylacetonate,[143] nitrosomethylurea,[144] Raney nickel (W-2),[124] and trimethyldithiotosylate[145] were prepared according to the literature methods.

Preparation of l-Menthone(35).[100] To a solution of 26.04 g (0.17 mol) of l-menthol(165) in 125 mL of acetone cooled externally by an ice bath was added, with magnetic stirring, 45 mL of standard chromic acid solution[146] at such a rate that the temperature of the reaction mixture did not exceed 10°C. Stirring was continued for another 15min. The reaction mixture was then poured into water and extracted with ether. The ether layers were washed with 10% sodium bicarbonate, brine and dried over sodium sulfate. After removal of ether under reduced pressure 22.92 g (89%) of l-menthone (35) was obtained as a colorless oil: bp 66-68°C at 3-4 mm; $[\alpha]_D^{25}$-26.91 (c = 10, Et_2O) {lit.[100] $[\alpha]_D^{25}$-25.3}; IR(CCl_4) cm^{-1} 2945, 2920, 2860, 2835, 1710, 1450, 1440, 1365, 1195; NMR(CCl_4) δ 0.85 (d, 3 H, J = 6 Hz), 0.92 (d, 3 H, J = 6 Hz), 1.03 (d, 3 H, J = 6 Hz), 1.37 (m, 1 H), 1.53 (m, 1 H), 1.63-2.50 (m, 7 H).

Preparation of α-Formyl-l-menthone (166). The procedure used was a modification of that of Dauben and Hart.[32] To a magnetically stirred suspension of 3.95 g (0.165 mol) of sodium hydride in 300 mL of anhydrous ether was added dropwise at 0°C, during 45 min, a mixture of 23.14 g (0.15 mol) of l-menthone (35), 0.75 mL of absolute ethanol and 18.9 g (0.22 mmol) of ethyl formate in 25 mL of ether under a nitrogen atmosphere. The reaction mixture was then refluxed for 60 min and was then kept stirring for 12 h at room temperature. The mixture was then treated with 75 mL of water and stirring was continued for another 10 min. The ether layer was decanted, and the aqueous layer was washed twice with 100 mL portions of ether and then acidified with 5N HCl solution and extracted with ether. The combined ether extracts were washed with water, and brine and concentrated using a rotary evaporator to give a crude oil which upon vacuum distillation yielded 23.62 g (86%) of α-formyl-l-menthone (166) as a colorless oil: bp 69-72°C at 0.17 mm; IR (CCl_4) cm^{-1} 2955, 2925, 2865, 1630 (br), 1580 (br), 1452, 1387, 1367, 1340, 1325, 1200, 1160; NMR (CCl_4) δ 0.80 (d, 3 H, J = 7 Hz), 0,93 (d, 3 H, J = 7 Hz), 1.07 (m, 3 H, J = 7 Hz), 14.78 (d, 1 H, J = 3 Hz); $[\alpha]_D^{25}$ +53.59 (c = 10, EtOH).

Preparation of Isoxazole Derivative (167). This was accomplished by the procedure of Kuehne,[102] with minor modifications. Into a solution of 0.765 g (11 mmol) of

hydroxylamine hydrochloride in 4 mL of water was added 0.905 g (11 mmol) of sodium acetate. When all the sodium acetate had been dissolved 1.823 g (10 mmol) of α-formyl-l-menthone (166) was added and the mixture was brought into one phase by adding a minimal amounts of methanol. After heating at reflux for 1 h on a steam bath the reaction mixture was cooled and diluted with 100 mL of water and extracted with two 25 mL portions of ether. The ether extracts were dried over sodium sulfate and concentrated at reduced pressure. Upon flash chromatography of the crude product using 20% ether in hexane as the eluent 1.37 g (77%) of the isoxazole 167 was obtained as a clear liquid: bp 75-76°C at 0.2 mm; IR (CCl_4) cm^{-1} 2960, 2935, 2880, 1640, 1470, 1455, 1390, 1370, 1230, 1165, 1150, 940, 880, 850; NMR (CCl_4) δ 0.89 (d, 3 H, J = 7 Hz), 0.95 (d, 3 H, J = 7 Hz), 1.12 (d, 3 H, J = 7 Hz), 1.13-2.23 (m, 5 H), 2.33-2.97 (m, 2 H), 7.87 (s, 1 H); MS m/z 179 (M^+) 164, 137 (base peak), 122, 109, 108, 94, 81, 55, 43; $[\alpha]_D^{25}$-1.18, $[\alpha]_{578}^{25}$-1.16, $[\alpha]_{546}^{25}$-1.05, $[\alpha]_{436}^{25}$+0.77, $[\alpha]_{365}^{25}$+6.41 (c = 10, EtOH). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81, Found: C,73.45; H, 9.57; N, 7.61.

Preparation of n-Butyl Thioether Derivative of Hydroxymethylene-l-menthone (169). A modification of the procedure reported by Ireland et al.[104] was used for this purpose. A solution of 12.76 g (70 mmol) of α-formyl-l-menthone (166), 6.76 g (75 mmol) of n-butylmercaptan, and

14 mg of p-toluenesulfonic acid monohydrate in 55 mL of benzene was refluxed using a Dean-Stark trap under a nitrogen atmosphere for 5.5 h. At the end of this period approximately 1.2 mL (66 mmol) of water was collected. After the removal of benzene at reduced pressure the residual oil was chromatographed over 200 g of alumina (neutral, activity III) using benzene as the eluent to give 13.8 g (83%) of the thioenol ether as a yellow oil: bp 137-139°C at 0.39 mm. The NMR spectrum of the product indicated it to be a mixture of the two geometrical isomers. Flash chromatography of 0.500 g of the mixture, using 6% ether in hexane as the eluent gave 0.326 g (R_f 0.199) of the major component and 0.156 g (R_f 0.143) of the minor component as yellowish liquids. The major isomer had the following characteristics: IR (CCl_4) cm^{-1} 2960, 2925, 2870, 1660, 1540, 1460, 1450, 1295, 1160, 1140, 1100; NMR (CCl_4) δ 0.80 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 7 Hz), 1.33-3.20 (m, 13 H), 7.23 (s, 1 H); $[\alpha]_D^{25}$ -155 $[\alpha]_{578}^{25}$ -164, $[\alpha]_{546}$ -194, $[\alpha]_{436}^{25}$ -421.5, $[\alpha]_{365}^{25}$ -421.2 (c = 1.6, Et_2O).

The minor isomer had the following characteristics: IR (CCl_4) cm^{-1} 2960, 2925, 2870, 1662, 1540, 1450, 1300, 1070, 1170, 1195; NMR (CCl_4) δ 0.75 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = Hz), 1.08 (d, 3 H, J = Hz), 1.17-2.97 (m, 13 H), 7.09 (s, 1 H); $[\alpha]_D^{25}$ -327.5, $[\alpha]_{578}^{25}$ -345.3, $[\alpha]_{546}^{25}$ -404.8, $[\alpha]_{436}^{25}$ -843.3 (c = 0.6, Et_2O).

Lithium Aluminum Hydride Reduction of 169.[107] A mixture of 4.06 g (16 mmol) of 169 and 0.67 g (17.6 mmol) of lithium aluminum hydride in 50 mL of ether was stirred for 1 h at room temperature under a nitrogen atmosphere. Upon workup 3.81 g (93%) of the crude product was obtained. Thin layer chromatography of this product on alumina using $CHCl_3$ as the eluent showed 2 closely spaced spots: IR (CCl_4) cm^{-1} 3400, 1608 (C=C), 1460, 1382, 1065. No attempt was made to separate the mixture. Periodic examination of the IR spectra of the product which was stored for a prolonged period in the refrigerator revealed the appearance and enhancement of a peak at 1685 cm^{-1} indicating the gradual generation of a C=O group.

Attempted Synthesis of 183 from 166.[147] A solution of 1.21 g (6.6 mmol) of 166 in 5 mL of THF and 3 mL of HMPT was stirred for 1 h with 160 mg (6.7 mmol) of sodium hydride at room temperature under a nitrogen atmosphere. Into the reaction mixture was then added dropwise 1 mL (11.6 mmol) of 1,2-epoxybutane. The reaction mixture was stirred for another 6 h, poured into excess of water, acidified with conc. HCl and then extracted with ether. Concentration of the ether extracts led to the recovery of 1.18 g (97%) of the starting material.

Attempted Synthesis of the Oxime Derivative of 169. A solution of 2.403 g (34 mmol) of hydroxylamine hydrochloride

and 2.664 g (32 mmol) of sodium acetate in 6 mL of water was mixed with a solution of 2.060 g (8 mmol) of 169 in 15 mL of ethanol. The mixture was refluxed on a steam bath for 13 h. Then the mixture was cooled to room temperature, diluted with water, extracted with ether, and worked up to yield 1.80 g of the crude product, the TLC of which showed 4 main spots. Column chromatography of the crude product on neutral alumina (activity III) using benzene as the eluent gave 1.35 g (66%) of the starting material and 123 mg (8%) of the isoxazole 167 as the identifiable products.

Preparation of 184. In a modification of the procedure of Marshall and Roebke,[107] a solution of 1.82 g (10 mmol) of α-formyl-l-menthone (166), 6.33 g (15 mmol) of trimethylene dithiotosylate[145] and 8.25 g (84 mmol) of potassium acetate in 110 mL of absolute ethanol was refluxed for 11 h. The cooled reaction mixture was poured into 500 mL of brine. The workup of the ether extract gave a crude oily product which was chromatographed over 150 g of alumina (neutral, activity III) using benzene as the eluent to give 1.35 g (53%) of an oil 184: bp 140°C at 0.5mm; IR (CCl_4) cm^{-1} 2960, 2925, 2870, 2830, 1700, 1450, 1430, 1422, 1412, 1380, 1375, 1275, 1080, 900, 700; NMR (CCl_4) δ 0.82 (d, 3 H, J = 6 Hz), 0.89 (d, 3 H, J = 7 Hz), 1.03 (d, 3 H, J = 7 Hz), 1.17-3.90 (m, 13 H); $[\alpha]_D^{25}$+20.78, $[\alpha]_{578}^{25}$+21.56, $[\alpha]_{546}^{25}$+27.49, $[\alpha]_{436}^{25}$+76.53, $[\alpha]_{365}^{25}$+263.6 (c = 1.7, Et_2O). Anal. Calcd for $C_{13}H_{22}S_2O$: C, 60.41, H, 8.58. Found: C, 60.34; H, 8.62.

Attempted Oximation of 184. To a solution of 5.2 g (75 mmol) of hydroxylamine hydrochloride and 6.15 g (75 mmol) of sodium acetate in 24 mL of water was added 1.28 g (50 mmol) of 184 in 25 mL of ethanol and the mixture was refluxed for 24 h on a steam bath. The cooled reaction mixture was poured into 200 mL of water and extracted with three 50 mL portions of ether. Workup of the ether extract gave 1.22 g (100%) of the unreacted starting material. (Confirmed by NMR, IR, TLC).

Preparation of Enol Ether of α-Formyl-l-menthone (172). A modification of the procedure of Dauben and Hart[32] was used for this purpose. Into a magnetically stirred suspension of 0.66 g (28 mmol) of sodium hydride in 125 mL of HMPT was added under nitrogen 4.55 g (25 mmol) of α-formyl-l-menthone (166). When the reaction mixture became clear (ca. 0.5 h) it was treated with 2.75 g (25 mmol) of ethyl bromide and the stirring was continued for another 10 h. Then the reaction mixture was poured into ice-cold water and extracted with four 50 mL portions of hexane. The combined organic extracts were worked up to give a crude product which upon distillation gave 4.82 g (92%) of an oil (172): bp 90-92°C at 0.5 mm. The product was shown to consist of two components. Upon flash chromatography using 20% ether in hexane as the eluent, 0.630 g of the mixture gave 0.570 g (83%) of the major component (R_f 0.26) and 0.055 g (8%) of the minor component (R_f 0.43). The major

component had the following properties: IR (CCl_4) cm^{-1} 2960, 2935, 2875, 1675, 1590, 1450, 1382, 1317, 1300, 1210, 1195, 1140, 1115, 1100, 1085, 1040, 1020, 910; NMR (CCl_4) δ 0.78 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz), 1.37 (t, 3 H, J = 7 Hz), 1.57-1.90 (m, 4 H) 1.90-3.33 (m, 3 H), 4.48 (q, 2 H, J = 7 Hz), 7.16 (s, 1 H); $[\alpha]_D^{25}$-23.58, $[\alpha]_{578}^{25}$-25.04, $[\alpha]_{436}^{25}$-42.78, $[\alpha]_{365}^{25}$-47.74 (c = 2, EtOH). The minor component gave: IR (CCl_4) cm-1 2960, 2925, 2870, 1670, 1620, 1380, 1210, 1167, 1150, 1100, 1030.

Reaction of Diazomethyl Ethyl Ketone With Ethyl Ether of Hydroxymethylene-1-menthone (172). Following the method described by Arndt,[148] using 10.3 g (100 mmol) of N-nitrosomethyl urea, 15 g (270 mmol) of potassium hydroxide in 15 mL of water, and 100 mL of ether, a solution of diazomethane in ether was made. To this was added a solution of 2.8 g (30 mmol) of freshly distilled propionyl chloride in 10 mL of ether at 0°C.[150] After stirring for 1 h at room temperature the mixture was diluted with 30 mL of cyclohexane and the ether was removed under reduced pressure. The resulting solution was added dropwise into a mixture of 3.9 g (19 mmol) of 172 and 0.1 g (615 mmol) of cuprous acetylacetonate[105] at 0°C. After the addition was complete the external ice bath was removed and an exothermic reaction was observed. Stirring was continued for another 12 h at room temperature. Workup followed by column chromatography on silica gel using 20% ether in hexane

yielded 3.78 g (97%) of the starting material and 0.200 g of a light yellowish solid, mp 50-53°C, which was identified as oct-4-ene-3,6-dione.[149] NMR (CCl_4) δ 1.15 (t, 6 H, J = 8 Hz), 2.73 (q, 4 H, J = 7 Hz), 7.02 (s, 2 H).

Reaction of Propargyl Bromide with Sodium Salt of α-Formyl-l-menthone (166). Into a magnetically stirred suspension of 68 mg (2.83 mmol) of sodium hydride in 1 mL of HMPT and 2.5 mL of THF was added 500 mg (2.74 mmol) of α-formyl-l-menthone (166) under nitrogen atmosphere. When the mixture become clear (10 min) 257 μL (2.88 mmol) of propargyl bromide was added and the stirring was continued for another 40 min. After adding 25 mL of water the mixture was extracted twice with 20 mL portions of ether. Workup of the ether extract gave 517.6 mg (90%) of crude product which upon flash chromatography using 15% ether in hexane gave 383.4 mg (66%) of the pure O-alkylated isomer(179) as the major product and 115.2 mg (20%) of the pure C-alkylated isomer as the minor product (176) as colorless liquids. The minor component (176) had the following characteristics: IR (CCl_4) cm-1 3320, 2960, 2940, 2875, 2120, 1730, 1710, 1460, 1380, 1370, 1110, 925, 642; NMR (CCl_4) δ 0.78-1.33 (m, 9 H), 1.44-2.61 (m, 8 H), 2.64-2.91 (m, 2 H), 11.58 (s, 1 H); $[\alpha]_D^{25}$+29.62, $[\alpha]_{578}^{25}$+30.20, $[\alpha]_{546}^{25}$+34.55 $[\alpha]_{436}^{25}$+54.23, $[\alpha]_{365}^{25}$+46.60 (c = 1.3, Ether). Spectral data for the major component (179): IR (CCl_4) cm-1 3320, 2970, 2940, 2880, 2122, 1680, 1600, 1452, 1370, 1270, 1170, 1148, 1120, 1085,

1040, 1018, 980, 930, 680, 632; NMR (CCl_4) δ 0.77 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 8 Hz), 1.03 (d, 3 H, J = 8Hz), 1.5-2.07 (m, 5 H), 2.2-3.7 (m, 3 H), 4.58 (m, 2 H), 1.12 (m, 1 H); $[\alpha]_D^{25}$ -35.32, $[\alpha]_{578}^{25}$-36.78, $[\alpha]_{546}^{25}$-42.18, $[\alpha]_{436}^{25}$-68.31, $[\alpha]_{365}^{25}$-112.73. (c = 1.9, Et_2O).

Reaction of Allyl Bromide with Sodium Salt of α-Formyl-l-menthone (166). Into a magnetically stirred solution of 500 mg (2.7 mmol) of α-formyl-l-menthone (166) in 1 mL of HMPT and 2.5 mL of THF was added 68 mg (2.83 mmol) of sodium hydride and stirring was continued for another 15 min. Then the homogeneous reaction mixture was treated with 260 μL (3 mmol) of allyl bromide and stirring was continued for another 15 min. The reaction mixture was poured into water and extracted with 30 mL of ether. Workup of the ether extract gave 590 mg (97%) of crude product, which upon flash chromatography using 16% ether in hexane as the eluent gave 399 mg (65%) of O-alkylated isomer (182; R_f 0.22) as a colorless oil: IR (CCl_4) cm^{-1} 3080, 2960, 2940, 2875, 1680, 1590, 1280, 1185, 1120, 1085, 980; NMR (CCl_4) δ 0.78 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.08 (d, 3 H, J = 7 Hz), 1.50-2.10 (m, 5 H), 2.13-3.77 (m, 2 H), 4.52 (m, 2 H), 5.08-6.33 (m, 3 H), 7.13 (m, 1 H); $[\alpha]_D^{25}$-51.25, $[\alpha]_{578}^{25}$-103.60, $[\alpha]_{546}^{25}$-103.60, $[\alpha]_{436}^{25}$-106.00 (c = 2, Et_2O). As a second fraction 133 mg (22%) of C-alkylated product (180; R_f 0.44) was obtained as a colorless oil: IR (CCl_4) cm^{-1} 3080, 2960, 2875, 1720, 1700, 1640, 1460, 1380, 1368,

1142, 920; NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, 3 H, J = 7 Hz), 0.91 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.62 (m, 1 H), 2.17 (m, 2 H), 2.31 (m, 2 H), 2.65 (m, 1 H), 2.78 (m, 1 H), 5.09 (m, 1 H), 5.50 (m, 1 H), 10.11 (s, 1 H); $[\alpha]_D^{25}$+38.94, $[\alpha]_{578}^{25}$+40.65, $[\alpha]_{546}^{25}$+46.83, $[\alpha]_{436}^{25}$+86.18, $[\alpha]_{365}^{25}$+83.50 (c = 1.2, Et_2O).

Another 20 mg of a compound (R_f 0.31) was isolated. The IR spectrum of this product in CCl_4 showed peaks at 3080, 2960, 2875, 1668, 1620, 1462, 1385, 1370, 1260, 1240, 1210, 1150, 1100, 1002, 970, 930 $cm.^{-1}$ But the sample proved to be unstable and no further characterization of the material was possible.

Claisen Rearrengement of 182.[151] The crude product (182) was sealed in a glass tube and placed in an oil bath maintained at 210°C. After 10 min the tube was removed from the bath and was allowed to come to room temperature and was cut open. TLC of the crude product showed 3 spots with close R_f values. The NMR spectrum of the crude product showed aldehyde proton peaks at δ 10.30 and 10.03 (with 2 : 1 ratio) and disappearance of the peaks at δ 7.13 indicating that complete rearrengement of the allyl ether had taken place. The product was not examined further due to the difficulty of separating the components.

Preparation of α-Cyano-l-menthone (168). An adaptation

of a procedure described by Kuehne[102] was used. A mixture of 2.13 g (89 mmol) of sodium in 98 mL of methanol and 15.11 g (84 mmol) of the isoxazole (167) in 143 mL of benzene was stirred under nitrogen for 3 h, and then poured into ice-water and extracted with eight 80 mL portions of cold 3% sodium hydroxide solution. The combined extracts were acidified with conc. HCl and extracted with three 150 mL portions of ether. Ether extracts were washed with two 50 mL portions of water and finally with brine. Workup of the ether extract afforded 10.15 g (67%) of pure α-cyanomenthone (168) as a colorless oil: bp 88–90°C at 0.20 mm; IR (CCl_4) cm^{-1} 2955, 2920, 2862, 2238, 1722, 1450, 1382, 1365, 1108, 1050; NMR (CCl_4) δ 0.77–1.30 (m, 9 H), 1.63–2.40 (m, 7 H), two overlapping doublets centered at δ 3.56; $[\alpha]_D^{25}$ +34.90, $[\alpha]_{578}^{25}$ +37.20, $[\alpha]_{546}^{25}$ +45.05, $[\alpha]_{436}^{25}$ +112.05, $[\alpha]_{365}^{25}$ +311.20 (c = 2, EtOH)

Reaction of Propargyl Bromide with the Sodium Salt of α-Cyano-l-menthone (166). A magnetically stirred mixture of 500 mg (2.79 mmol) of α-cyano-l-menthone in 1 mL of HMPT and 2.5 mL of THF was treated with 68 mg (2.83 mmol) of sodium hydride. After the reaction mixture became homogeneous (10 min) it was treated with 257 μL (2.88 mmol) of propargyl bromide and stirring was continued for another 1 h. Then the mixture was poured into 20 mL of water and extracted with 30 mL of ether. The ether layer was successively washed with 10 mL portions of 3% NaOH, water, and brine and dried

over sodium sulfate prior to concentration by rotary evaporation at reduced pressure. Flash chromatography of the crude product using 20% ether in hexane as the eluent yielded 409 mg (67%) of a C-alkylated product as the major component (189A; R_f 0.39) An analytical sample was prepared by recrystallization from hexane: mp of 92-94°C; IR (CCl_4) cm^{-1} 3320, 2970, 2940, 2880, 2238, 2115, 1740, 1460, 1422, 1390, 1370, 1110, 655, 630; NMR (CCl_4) δ 0.92 (d, 3 H, J = 7Hz), 0.98 (d, 3 H, J = 7Hz), 1.23 (d, 3 H, J = 6 Hz), 1.57-2.33 (m, 6 H), 2.63-3.43 (m, 4 H); $[\alpha]_D^{25}$ -161.7, $[\alpha]_{578}^{25}$ -170.8, $[\alpha]_{546}^{25}$ -200.7, $[\alpha]_{436}^{25}$ -427.9, $[\alpha]_{365}^{25}$ -1020.7 (c = 0.6, EtOH). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.41; H, 8.66.

Another 82 mg (13%) of a C-alkylated product was isolated as the minor component (189B; R_f 0.23). Crystallization of this material from hexane afforded an analytically pure sample as white needles: mp 54-55°C; IR (CCl_4) cm^{-1} 3300, 2960, 2920, 2860, 2220, 2115, 1720, 1455, 650, 625; NMR (CCl_4) δ 0.93 (m, 4 H), 1.15 (d, 3 H, J = 7 Hz), 1.67-2.60 (m, 8 H), 2.73-3.20 (m, 2 H); $[\alpha]_D^{25}$ +54.50, $[\alpha]_{578}^{25}$ +57.91, $[\alpha]_{546}^{25}$ +66.42, $[\alpha]_{436}^{25}$ +159.0, $[\alpha]_{365}^{25}$ +414.2 (c = 0.8, EtOH). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.58; H, 9.02.

Mercuric Ion-Catalyzed Hydration of 189A.[109] To a stirred mixture of 450 mg (1.5 mmol) of mercuric sulfate and

150 mg of conc. H_2SO_4 was added 1.087 g (5 mmol) of 189A in 30 mL of THF and 6 mL of water, and stirring was continued for 1 h. After dilution with 50 mL of water the mixture was extracted with five 10 mL portions of CH_2Cl_2. Combined organic extracts were washed twice with 20 mL portions of water. The dried (Na_2SO_4) solution was concentrated by rotary evaporation to yield a crude product which upon flash chromatography using 10% ether in chloroform (R_f 0.51) afforded 780 mg (67%) of 190A as a colorless solid as the only isolable product. An analytical sample was prepared by recrystallization of this solid from hexane giving pure white needles: mp 49–51°C; IR (CCl_4) cm^{-1} 3965, 3940, 3880, 2230, 1730, 1460, 1385, 1160, 1170, 960; NMR (CCl_4) δ 0.93 (d, 3 H, J = 7 Hz), 0.97 (d, 3 H, J = 7 Hz), 1.18 (d, 2 H, J = 5 Hz) 1.07–3.28 (m, 7 H), 2.24 (s, 3 H), 2.92 (s, 2 H); $[\alpha]_D^{25}$ −73.56, $[\alpha]_{578}^{25}$ −77.40, $[\alpha]_{546}^{25}$ −90.63, $[\alpha]_{436}^{25}$ −190.4, $[\alpha]_{365}^{25}$ −438.7 (c = 0.4 EtOH). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.61; H, 8.86.

Thioketalization of the Unhindered Keto Group in 190A. In an adaptation of the known procedure,[111] a mixture of 215 mg (0.914 mmol) of 190A, 93 µL (1.1 mmol) of ethane dithiol and 90 mg (0.047 mmol) of p-toluenesulfonic acid monohydrate in 5 mL of glacial acetic acid was stirred for 48 h under a nitrogen atmosphere. The reaction mixture was then poured into 50 mL of water and extracted with two 20 mL portions of ether. The ether layers were washed twice with

10 mL portions of 5% NaOH solution, following which the ether layer was worked up in the usual manner to give a crude product, which upon flash chromatography using 1:1 ether-hexane as the eluent gave 132.8 mg (47%) of the protected compound 195 (R_f 0.64) as a colorless oil. IR (CCl_4) cm^{-1} 2960, 2935, 2875, 2220, 1725 (C=O), 1455, 1445, 1385, 1375, 1230, 1200, 1110, 1120, 940, 920; NMR (CCl_4) δ 0.89 (d, 6 H, J = 7 Hz) 1.20 (d, 3 H, J = 6 Hz), 1.2 (s, 1 H), 1.67-2.33 (m, 6 H), 1.88 (s, 3 H), 2.68-3.5 (m, 6 H). Anal. Calcd for $C_{16}H_{25}NOS_2$: C, 61.69; H, 8.09, Found: C, 61.39; H, 8.03. Further elution gave 112 mg (52%) of the starting material 190A (R_f 0.32).

Sodium Borohydride Reduction of 195. To a solution of 120 mg (0.53 mmol) of 195 in 5 mL of methanol was added 20 mg of sodium borohydride and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and worked up in the usual manner to yield 138 mg (84%) of 196 as a white solid. An analytical sample was prepared by recrystallization from carbon tetrachloride: mp 70-72°C; IR (CCl_4) cm^{-1} 3450, 2960, 2930, 2875, 2220, 1385, 1367, 1275, 1070, 1050. NMR (CCl_4) δ 0.77 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz), 1.80 (s, 3 H), 2.45 (s, 2 H), 2.83 (d, 1 H, J = 6 Hz), 3.28 (s, 4 H)

Attempted Protection of Hydroxyl Group in 192A. Using a general procedure,[152] a solution of 355 mg (1.6 mmol) of

192A and 80 mg (0.32 mmol) of pyridinium-p-toluenesulfonate in 14 mL of methylene chloride was stirred with 300 μL 3.29 mmol) of dihydropyran under a nitrogen atmosphere for 12 h. Upon the workup followed by flash chromatography of the resulting crude product over silica gel using chloroform as the eluent 350 mg (98%) of the starting material was recovered.

Sodium Borohydride Reduction of 189A. To a magnetically stirred solution of 434 mg (2 mmol) of 189A in 10 mL of methanol was added 90 mg (2.4 mmol) of sodium borohydride under nitrogen. The reaction mixture was stirred for 2 h, poured into 50 mL of water and extracted with three 20 mL portions of ether. The ether layers were concentrated by rotary evaporation after drying over sodium sulfate. TLC of the crude product (silica gel; 2% ether in chloroform) showed 2 spots. The components were separated by flash chromatography to give as a first fraction 365 mg (83%) of the alcohol 192A (R_f 0.41). An analytical sample was prepared by crystallization from hexane: mp 77-79°C; IR (CCl_4) cm^{-1} 3635, 3500, 3320, 2965, 2935, 2880, 2235, 2120, 1475, 1460, 1390, 1140, 995, 940, 645, 635; NMR (CCl_4) δ 0.83–1.15 (m, 9 H), 1.15-2.00 (m, 7 H), 2.00-2.33 (m, 2 H), 2.50–2.70 (m, 2 H), 4.27 (d, 1 H, J = 6 Hz). $[\alpha]_D^{25}$ +8.43, $[\alpha]_{578}^{25}$ +8.96, $[\alpha]_{546}^{25}$ +10.19, $[\alpha]_{436}^{25}$ +19.33, $[\alpha]_{365}^{25}$ +35.50 (c = 0.6, Et_2O). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.89; H, 9.80.

The second fraction yielded 71 mg (16%) of 199B (R_f 0.20) as a colorless solid. An analytical sample was obtained by crystallization from hexane: mp 65-67°C; IR (CCl_4) cm^{-1} 3640, 3585, 3470, 3320, 2240, 2120, 1480, 1399, 1370, 1062 (C=C), 650, 625; NMR (CCl_4) δ 0.84 (d, 3 H, J = 7 Hz), 0.98 (d, 3 H, J = 7 Hz), 1.09 (d, 3 H, J = 7 Hz), 1.27-2.78 (m, 10 H), 3.00-3.67 (m, 3 H); $[\alpha]_D^{25}$ +0.12, $[\alpha]_{578}^{25}$ +0.12, $[\alpha]_{546}^{25}$ +0.00, $[\alpha]_{436}^{25}$ -1.40, $[\alpha]_{365}^{25}$ -3.02 (c = 0.9 Et_2O). Anal. Calcd for; $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.79; H, 9.88.

Mercuric Ion-Catalyzed Hydration of 192A. To a magnetically stirred mixture of 18 mg (0.1 mmol) of mercuric sulfate, 6 mg (0.1 mmol) of H_2SO_4, 240 mg (13.3 mmol) of H_2O and 1.2 mL of THF was added 219 mg (1 mmol) of the title compound under a nitrogen atmosphere. After 2 h the reaction mixture was poured into 20 mL of water and extracted twice with 20 mL portions of CH_2Cl_2. The combined organic extracts were washed twice with 10 mL portions of water, and dried over sodium sulfate prior to concentration by rotary evaporation. The crude product was purified by flash chromatography using 40% ether in hexane to yield 209 mg (88%) of pure cyanohemiketal 193. An analytical sample prepared by crystallization from hexane: mp 98-100°C; IR (CCl_4) cm^{-1} 3600, 3455, 2975, 2880, 2240, 1450, 1390, 1150, 1070, 1000, 970, 940, 917; NMR (CCl_4) δ 0.87-1.13 (m, 9 H), 1.20-1.90 (m, 7 H), 1.87 (s, 3 H), 2.0-2.60 (m, 3 H),

3.30 (bs, 1 H), 4.47 (s, 1 H); MS m/z 237 (M^+), 222, 219, 209, 194; 176, 164, 149, 124, 55, 53, 43, 41, 39; $[\alpha]_D^{25}$+80.29, $[\alpha]_{578}^{25}$+80.29, $[\alpha]_{546}^{25}$+94.62, $[\alpha]_{436}^{25}$+155.2, $[\alpha]_{365}$+232.5 (c = 4, Et_2O). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.55; H, 9.47.

Reaction of the Enolate of α-Formyl-1-menthone (166) with Methyl Vinyl Ketone.[113] A mixture of 22.34 g (0.123 mol) of α-formyl-1-menthone (166), 2.598 g (0.025 mmol) of sodium carbonate and 3.7 mL (0.025 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 120 mL of a 1:1 mixture of THF-Bu^{t}OH was stirred at 0°C under a nitrogen atmosphere. To this was added dropwise 11 mL (0.136 mL) of freshly distilled MVK and the stirring was continued for another 2 h at 0°C. Then the reaction mixture was poured into 800 mL of water and extracted 3 times with 100 mL portions of ether. The combined ether extracts were washed succesively with 50 mL portions of water, 5% NaOH and finally with sat. NaCl solutions. Concentration of the dried ($NaSO_4$) extract gave 26.35 g (85%) of 209 as a colorless oil, bp 120-122°C at 0.18 mm: IR (CCl_4) cm^{-1} 2965, 2900, 2880, 1725 (C=O), 1700 (C=O), 1465, 1450, 1385, 1370, 1165; NMR (CCl_4) δ 0.88 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.04 (d, 3 H, J = 8 Hz), 1.25-3.00 (m, 14 H), 9.90 (s, 1 H); $[\alpha]_D^{25}$+22.83, $[\alpha]_{578}^{25}$+23.76, $[\alpha]_{546}^{25}$+27.04, $[\alpha]_{436}^{25}$+45.77, $[\alpha]_{365}^{25}$+24.88 (c = 2, Et_2O).

Spirocyclization of 209. Following a modified version of a procedure reported recently,[119] a magnetically stirred mixture of 25 g (0.1 mmol) of 209, 1.409 g (0.020 mmol) of pyrrolidine, and 1.428 g (0.024 mol) of glacial acetic acid in 100 mL of methanol was refluxed for 1 h under a nitrogen atmosphere. The reaction mixture was then poured into 500 mL of water and extracted with three 125 mL portions of ether. The combined ether extracts were washed with 100 mL portions of water, 10% $NaHCO_3$, and brine and then it was dried over sodium sulfate and concentrated by rotary evaporation. The crude product was stored in the refrigerator overnight and the solid separated at this stage was filtered and washed with hexane to give 9.5 g (41%) of 210 as a white solid. The filtrate was concentrated by rotary evaporation and the residue was further purified by flash chromatography using 50% ether in hexane as the eluent to obtain another 5 g of 210: mp 41-43°C (hexane); IR (CCl_4) cm^{-1} 3040, 2960, 2925, 2875, 1710, 1690, 1380, 920; NMR (CCl_4) δ 0.70-1.10 (m, 9 H), 1.37-2.67 (m, 11 H), 5.88 (d, 1 H, 10 Hz), 7.05 (d, 1 H, J = 10 Hz); $[\alpha]_D^{25}$+54.19, $[\alpha]_{578}^{25}$+57.48, $[\alpha]_{546}^{25}$+68.33, $[\alpha]_{436}^{25}$+141.0, $[\alpha]_{365}^{25}$+140.1 (c = 2, Et_2O). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.06; H, 9.41.

A further fraction (3 g) was eluted which turned out to be a mixture of three components (one of which was 209) of similar R_f values, and was not investigated further.

Thioketalization of 210 Using Ethane-1,2-dithiol. In a modified procedure[111] a mixture of 472 mg (2 mmol) of the diketone 210, 185 μL (2.2 mmol) of ethane-1,2-dithiol and 180 mg (0.9 mmol) of p-toluenesulfonic acid in 10 mL of glacial acetic acid was stirred under nitrogen for 1 h. Then the reaction mixture was poured into 100 mL of water and extracted with three 30 mL portions of ether. The combined ether layers were washed with water, 5% sodium hydroxide and brine and dried over sodium sulfate before concentration by rotary evaporation. The crude product was purified by flash chromatography using 20% ether in hexane as the eluent to obtain 606 mg (97%; R_f 0.46) of 221 as a white solid: mp 90-91°C (hexane); IR (CCl_4) cm^{-1} 3040, 2960, 2925, 2870, 1710 (C=O), 1380, 1270; NMR (CCl_4) δ 0.77-1.03 (m, 9 H), 1.23-2.83 (m, 11 H), 3.30 (s, 4 H), 5.82 (ABq, 2 H); $[\alpha]_D^{25}$+64.29, $[\alpha]_{579}^{25}$+67.86, $[\alpha]_{546}^{25}$+82.37, $[\alpha]_{436}^{25}$+188.8, $[\alpha]_{365}^{25}$+477.1 (c = 0.5, Et_2O). Anal. Calcd for $C_{17}H_{26}OS_2$: C, 65.75; H, 8.44. Found: C, 66.33; H, 8.59.

Lithium Aluminum Hydride Reduction of 212. To a magnetically stirred mixture of 15 mg (0.4 mmol) of lithium aluminum hydride in 7 mL of ether was added at room temperature and under a nitrogen atmosphere, 100 mg (0.32 mmol) of the keto thioketal 212. The mixture was then refluxed for 3 h. Excess water was then cautiously added to the reaction mixture and it was extracted with ether. Work-up of the ether layer in the usual manner yielded a crude

mixture, which was purified by repeated flash chromatography using 15% ether in hexane. The first fraction (R_f 0.24) amounted to 71.3 mg (71%) of 215B as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 56-58°C ; IR (CCl_4) cm^{-1} 3645 (OH, free), 3040, 2960, 2940, 2935, 2880, 1475, 1280, 1160, 1020, 980, 950; NMR (CCl_4) 0.77-2.23 (m, 21 H), 3.13-3.53 (m, 5 H), 5.9 (ABq, 2 H); $[\alpha]_D^{25}$+3.54, $[\alpha]_{579}^{25}$+4.07, $[\alpha]_{546}^{25}$+4.42, $[\alpha]_{436}^{25}$+11.33, $[\alpha]_{365}^{25}$+27.79. (c = 0.6, Et_2O). Anal. Calcd for $C_{17}H_{28}OS_2$: C, 65.33; H, 9.03. Found: C, 65.55; H, 9.04.

The second fraction amounted to 23 mg (23%) of 215A as a white solid (R_f 0.16). An analytical sample was prepared by recrystallization from hexane: mp 66-67°C; IR (CCl_4) cm^{-1} 3995 (OH free), 3020, 2960, 2935, 2880, 1470, 1280, 1050, 870; NMR (CCl_4) δ 0.73-1.53 (m, 14 H), 1.53-2.5 (m, 7 H), 3.13-3.57 (m, 5 H), 5.38 (d, 1 H, J = 10 Hz), 5.97 (d, 1 H, J = 10 Hz); $[\alpha]_D^{25}$-14.96, $[\alpha]_{578}^{25}$-16.01, $[\alpha]_{546}^{25}$-18.92, $[\alpha]_{436}^{25}$-36.96, $[\alpha]_{365}^{25}$-76.18 (c = 1.6, ether). Anal. Calcd for $C_{17}H_{28}OS_2$: C, 65.33; H, 9.03. Found: C, 65.48; H, 9.04.

Preparation of the Ketoalcohols 211A and 211B. A procedure similar to that used earlier for the reduction of α,β-unsaturated aldehydes[153] was used for the initial reduction. To a magnetically stirred solution of 445 mg (11.73 mmol) of lithium aluminum hydride in 80 mL of anhydrous ether was added a solution of 4.5 g (19.2 mmol) of

the diketone 210 in 20 mL of ether dropwise, over 10 min, under a nitrogen atmosphere. The mixture was stirred for 3 h and then treated with 1 mL of water and 5 mL of 10% NaOH and the ether layer was decanted. The residue was washed with 25 mL of ether. The combined ether layers were worked up in the usual manner to yield 4.2 g (92.5%) of a crude product. Without further purification this product was dissolved in 150 mL of $CHCl_3$ and into this solution was added 20 g of active manganese dioxide brown powder. The mixture was stirred for 6 h at room temperature.[115] Then the mixture was filtered and concentrated by rotary evaporation to give the crude product, which upon flash chromatography over silica gel using 10% ether in chloroform as the eluent gave as a first fraction 2.23 g (49% from 210) of 211B as a white solid (R_f 0.32). An analytical sample was obtained by crystallization from hexane: mp 141-143°C; IR ($CHCl_3$) cm^{-1} 3630 (OH, free), 3465 (OH, hydrogen bonded), 3030, 3010, 2970, 2940, 2880, 1675 (C=O), 1610 (C=C), 1475, 1390, 1230; NMR ($CDCl_3$) δ 0.80-2.65 (m, 21 H), 3.67 (s, 1 H), 6.00 (d, 1 H, J = 10.5 Hz), 7.47 (d, 1 H, J = 10.5 Hz); UV (MeOH) λ_{max} nm (ε) 318 (38), 233 (5320), 203 (4060); $[\alpha]_D^{25}$ +27.37, $[\alpha]_{578}^{25}$ +28.56, $[\alpha]_{546}^{25}$ +32.00, $[\alpha]_{436}^{25}$ +34.05 (c = 0.9, Et_2O). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.92; H, 10.44.

The second fraction consisted of 1.27 g (28% from 210) of 211A as a white solid (R_f 0.17). An analytical sample was

prepared by crystallization from hexane: mp 120-121°C; IR ($CHCl_3$) cm^{-1} 3615 (OH free), 3460 (OH hydrogen bonded), 3020, 3000, 2960, 2940, 2895, 2875, 1670 (C=O), 1610 (C=C), 1470, 1380, 1040, 870; NMR ($CDCl_3$) δ 0.83 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz), 1.04 (d, 3 H, J = 6 Hz), 1.17-2.67 (m, 12 H), 3.77 (d, 1 H, J = 9 Hz), 5.98 (d, 1 H, J = 10Hz), 6.85 (d, 1 H, J = 10 Hz); λ_{max} nm (ε) 315 (30), 227 (10345), 200 (4569); $[\alpha]_D^{25}$+6.42, $[\alpha]_{578}^{25}$+5.50, $[\alpha]_{546}^{25}$+5.14, $[\alpha]_{436}^{25}$-19.27, $[\alpha]_{365}^{25}$-213.9. Anal. Calcd for $C_{14}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.36; H, 10.41.

Preparation of Thioketal 215A from 211A. A mixture of 472 mg (2 mmol) of the keto alcohol, 185 μL (2.2 mmol) of ethane-1,2-dithiol and 180 mg (0.9 mmol) of p-toluenesulfonic acid in 10 mL of glacial acetic acid was stirred under nitrogen for 1 h.[111] Then the reaction mixture was poured into water and extracted with ether. Ether extracts were washed with water, 5% NaOH, and brine, and then worked up to give crude product which was purified by passing through a short column of silica gel using 20% ether in hexane as the eluent giving 580 mg (93%) of 215A. (cf. p126)

Preparation of 215B From 211B. Following the procedure described for the preparation of 215A from 211A, from 472 mg of 211B 608 mg (97%) of pure 215B was obtained. (cf. p 126)

Preparation of the Propanedithioketal of the Ketoalcohol 211B.[154] Into a magnetically stirred mixture of 236 mg (1.0 mmol) of dithioketal 211B and 130 mg (1.2 mmol) of propane-1,3-dithiol in 5 mL of ether was added 62 μL of boron trifluoride etherate, at room temperature under nitrogen. After 8 h the reaction mixture was diluted with water and extracted with ether. The ether extracts were washed successively with water, 5% NaOH, water and brine and then dried over Na_2SO_4. Subsequent concentration by rotary evaporation gave 320 mg (98%) of the protected compound as a solid: mp 93-95°C, (hexane; IR (CCl_4) cm^{-1} 3645 (OH, free), 3515 (OH, bonded), 3035, 2960, 2940, 2910, 2875, 2835, 1635 (C=C), 1425, 1280, 975; NMR (CCl_4) δ 0.77-2.33 (m, 23 H), 2.63-3.00 (m, 4 H), 3.30-3.60 (m, 1 H), 5.77 (d, 1 H, J = 10Hz), 6.13 (d, 1 H, J = 10 Hz); $[\alpha]_D^{25}$+1.57 (c = 0.1, Et_2O). Anal. Calcd for $C_{18}H_{30}OS_2$: C, 66.20; H, 9.26. Found: C, 66.64, H, 9.53.

Raney Nickel Desulfurization of Propanedithioketal of the Ketoalcohol 211B. Into a solution of 1.98 g (6.1 mmol) of the thioketal 224A in 162 mL of ethanol and 18 mL of water was added 60 mL (36 g) of W-2 Raney nickel catalyst[124] suspension in ethanol. The mixture was refluxed under nitrogen for 1 h, following which it was cooled to room temperature and filtered. The filtrate was diluted with water and extracted with ether. Workup of the ether extract gave 0.98 g of a colorless liquid, which gave only a

single spot on TLC (silica gel). The product was further purified by flash chromatography over silica gel using 7.5% ether in hexane to yield 0.96 g (71%) of 214B as a colorless liquid: (R_f 0.32); IR (CCl_4) cm^{-1} 3650 (OH, free), 3520 (OH, H-bonded), 2940, 2870, 1475, 1450, 1385, 980; NMR (CCl_4) δ 0.73-2.00 (m, 27 H), 3.5 (m, 1 H); $[\alpha]_D^{25}$ -32.40, $[\alpha]_{578}^{25}$ -33.80, $[\alpha]_{546}^{25}$ -38.25, $[\alpha]_{436}^{25}$ -63.77, $[\alpha]_{365}^{25}$ -97.97 (c = 6.7, Et_2O). Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.13,; H, 12.33.

Desulfurization of 215B with W-2 Raney Nickel. Into a solution of 1.906 g (61 mmol) of 215B in 162 mL of ethanol and 18 mL of water was added 60 mL (36 g) of W-2 Raney nickel[124] catalyst suspension in ethanol. The mixture was refluxed under nitrogen for 1 h. The reaction mixture was then cooled to room temperature and filtered through sodium sulfate. The filtrate was diluted with water and extracted with ether. Workup of the ether extract yielded the crude product which upon flash chromatography on silica gel using 7.5% ether in hexane gave 1.144 g (84%) of pure 214B as a colorless liquid.

Preparation of Partially Deactivated Raney Nickel Catalyst. A general procedure adopted for this is as follows: The W-2 Raney nickel catalyst (30 g) prepared according to the standard procedure[124] was suspended in 150 mL of 95% ethanol (or methanol) and 5 mL of cyclohexene

was added. The mixture was stirred for 20 min following which the nickel catalyst was allowed to settle and the solvent was decanted.

Desulfurization of 215A with "Deactivated" Raney Nickel. In a procedure adapted from that of Pinder and Williams,[154] a solution of 270 mg (0.87 mmol) of the thioketal derivative 215A in 22 mL of EtOH and 1.3 mL of H_2O was treated with 9 mL (ca. 2.7 g) of the "deactivated" Raney nickel dispersion in ethanol and was stirred for 20 min. The mixture was then filtered and the residue was washed with ether. The filtrate collected was concentrated by rotary evaporation. The oily residue was mixed with 20 mL of water and extracted with three 10 mL portions of ether. Workup of the ether extract followed by flash chromatography using 10% ether in hexane gave 135 mg (70%) of a white solid 213A (R_f 0.35) as a fraction mp 70-72°C; IR (CCl_4) cm^{-1} 3595 (OH, free), 3020 (C=C-H), 2965, 2940, 2880, 2845, 1650 (C=C, v. weak), 1470, 1460, 1385, 1120, 1055, 880; NMR (CCl_4) δ 0.75 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 1.18-1.43 (m, 4 H), 1.43-2.43 (m, 10 H), 3.37 (d, 1 H, J = 11.5), 5.82 (m, 1 H); $[\alpha]_D^{25}$ -36.8, $[\alpha]_{578}^{25}$ -38.65, $[\alpha]_{546}^{25}$ -44.66, $[\alpha]_{436}^{25}$ -0.936, $[\alpha]_{365}^{25}$ -147.71 (c = 0.1, Et_2O). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.00; H, 11.70.

The second fraction consisted of 31 mg (16%) of 213C

with mp 89-91°C (R_f 0.25): IR (CCl_4) cm^{-1} 3645, 3620, 3500 (broad), 3025, 2960, 2930, 2875, 2845, 1650 (C=C), 1465, 1450, 1385, 1370, 1180, 1150, 1045, 980, 650; NMR (CCl_4) δ 0.75 (d, 3 H, J = 7 Hz), 0.85 (d, 3 H, J = 8 Hz), 0.90 (d, 3 H, J = 7 Hz), 1.08-2.30 (m, 17 H), 3.33 (bs, 1 H), 5.57 (m, 2 H); $[\alpha]_D^{25}$ -25.41, $[\alpha]_{578}^{25}$ -26.63, $[\alpha]_{546}^{25}$ -30.69, $[\alpha]_{436}^{25}$ -56.40, $[\alpha]_{365}^{25}$ -95.54 (c = 0.9, Et_2O). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.24; H, 11.71.

Desulfurization of 215B with "Deactivated" Raney Nickel. Following the method described in the preceding experiment, from 827 mg (2.67 mmol) of the thioketal 215B and 25 mL (ca. 15 g) of "deactivated" Raney nickel in 71 mL of 95% ethanol and 4 mL of water, 528 mg (89%) of 213B was obtained as a colorless liquid: IR (CCl_4) cm-1 3640 (OH, free), 3025 (C=C-H), 2960, 2930, 2870, 2840, 1640 (C=C, v. weak), 1470, 1450, 1380, 1375, 1365, 1140,1020, 980, 945, 840, 920, 690; NMR (CCl_4) δ 0.84 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz), 1.06 (d, 3 H, J = 7 Hz), 1.40-2.27 (m, 14 H), 3.43 (s, 1 H, broad), 5.50-6.17 (m, 2 H); $[\alpha]_D^{25}$ -5.92, $[\alpha]_{578}^{25}$ -5.92, $[\alpha]_{546}^{25}$ -6.27, $[\alpha]_{436}^{25}$ -5.15, $[\alpha]_{365}^{25}$ +4.49 (c = 0.2, Et_2O). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found C, 81.18; H, 11.66.

Ozonolysis of 213A. A procedure described earlier[126] was used for this purpose. Into a solution of 130 mg (0.6 mmol) of 213A in 2 mL of methanol was passed a stream

of ozonized oxygen at -75°C until the mixture became light persistent blue. At this point the solution was flushed with a stream of nitrogen, treated with 0.5 mL of dimethyl sulfide and allowed to attain room temperature gradually (1 h). After stirring the mixture for another 14 h at room temperature it was mixed with water and extracted with ether. Workup of the extract followed by flash chromatography using 40% ether in hexane gave 95 mg (62%) of the dialdehyde 216A as a colorless liquid: IR (CCl_4) cm^{-1} 3585 (OH, free), 2965, 2900, 2880, 2825, 2720, 1735 (C=O), 1720 (C=O), 1470, 1390, 1320, 1155, 1125, 1060, 875, 650; NMR (CCl_4) δ 0.78 (d, 3 H, J = 7 Hz), 0.88 (overlapping 2d, 6 H, J = 7 Hz), 1.08-1.53 (m, 12 H), 3.22 (s, 1 H), 3.92 (d, 1 H, J = 10 Hz), 9.60 (m, 1 H), 9.70 (m, 1 H); $[\alpha]_D^{25}$-26.89, $[\alpha]_{578}^{25}$-28.17, $[\alpha]_{546}^{25}$-32.48, $[\alpha]_{436}^{25}$-60.70, $[\alpha]_{365}^{25}$-120.17 (c = 2.3, Et_2O). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.90; H, 10.24.

Ozonolysis of 213B. Following the procedure described in the preceding experiment, from 360 mg (1.62 mmol) of 213B was obtained 327 mg (80%) of the dialdehyde 216B as a colorless liquid: IR (CCl_4) cm^{-1} 3580 (OH, free), 2960, 2875, 2820, 2720, 1730, 1715, 1475, 1460, 1410, 1385, 1370, 1350, 1270, 1240, 1170, 1130, 1050, 1020, 660; NMR (CCl_4) δ 0.77-2.00 (m, 20 H), 2.87 (m, 1 H), 4.17 (m, 1 H), 9.37 (s, 1 H), 9.98 (m, 1 H); MS m/z 224(M^+), 206, 197, 163, 149, 123; $[\alpha]_D^{25}$-18.89, $[\alpha]_{589}^{25}$-19.64, $[\alpha]_{546}^{25}$-22.04, $[\alpha]_{436}^{25}$-33.78,

$[\alpha]_{365}^{25}$ -33.78 (c = 2.3, Et_2O). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 69.78; H, 10.48.

Spirocyclization of 216A. Following the procedure of de Groot and Jansen,[119] a mixture of 230 mg (0.9 mmol) 216A in 700 µL of methanol was treated with 7 µL of pyrrolidine and 7 µL of glacial acetic acid. The mixture was refluxed for 1 h, following which it was poured into water and extracted with ether. Ether extract was washed with 10% sodium bicarbonate and brine. Workup of the ether extract followed by flash chromatography yielded 152 mg (72%) of 201A as a colorless solid, the TLC of which indicated it to be mixed with a small amount of a minor impurity which was difficult to remove: mp 152-156°C; IR (CCl_4) cm^{-1} 3605 (OH, free), 3490 (OH, hydrogen bonded), 2960, 2880, 2810, 2708, 1680, 1620, 1460, 1385, 1370, 1290, 1260, 1180, 1075, 1040, 990, 890; NMR (CCl_4) δ 0.83 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3H), 1.03 (d, J = 7 Hz, 3H), 3.70 (d, J = 10 Hz), 6.27 (m, 1 H), 9.70 (s, 1 H).

Spirocyclization of 216B. Following a procedure used by de Groot and Jansen,[119] a mixture of 225 mg (0.88 mmol) of 216B, 10 µL (0.12 mmol) of pyrrolidine and 10 µL (16 mmol) of glacial acetic acid in 8 mL of absolute methanol was refluxed for 40 min, following which it was poured into 40 mL of water and extracted with ether. The organic extract was washed with 10 mL portions each of

water, 10% $NaHCO_3$, and brine, and dried over Na_2SO_4, and was concentrated by rotary evaporation to yield a crude product, which was further purified by flash chromatography using 40% hexane in ether, as the eluent yielding 168.3 mg (81%) of 201B as a white solid. An analytical sample was prepared by recrystallization from hexane: mp 64-66°C; IR (CCl_4) cm^{-1} 3635 (OH, free), 3530 (OH, hydrogen bonded), 3055, 2960, 2935, 2870, 2800, 2705, 1675 (C=O), 1620 (C=C, conj), 1470, 1450, 1380, 1365, 1350, 1260, 1190, 1170, 1150, 1130, 1020, 1000, 940, 880; NMR (CCl_4) δ 0.88 (d, 3 H, J = 6 Hz), 0.95 (d, 3 H, J = 7 Hz), 1.05-1.30 (m, 4 H), 1.37-1.93 (m, 8 H), 2.05 (s, 1 H), 2.47 (m, 2 H), 3.60 (s, 1 H), 7.12 (m, 1 H), 9.70 (s, 1 H); $[\alpha]_D^{25}$+75.07, $[\alpha]_{578}^{25}$+79.27, $[\alpha]_{546}^{25}$+92.57, $[\alpha]_{436}^{25}$+186.94, $[\alpha]_{365}^{25}$+181.25 (c = 1.7, Et_2O). Anal. Calcd for $C_{15}H_{26}O_3$: C, 75.83; H, 10.30. Found: C, 75.65; H, 10.48.

Preparation of the Thioketal Derivative of 216A. A mixture of 35 µL (0.42 mmol) of ethane-1,2-dithiol, 34 mg (0.18 mmol) p-toluenesulfonic acid monohydrate and 89 mg (0.38 mmol) of 216A in 2 mL of acetic acid was stirred under nitrogen, at room temperature, for 0.5 h. The reaction mixture was poured into 20 mL of water and extracted with two 10 mL portions of ether. The ether layer was washed twice with 3 mL portions of 5% NaOH in water. Workup of the ether extract and subsequent flash column chromatography using 10% ether in carbon tetrachloride yielded 113 mg (96%)

of white crystalline thioketal 217A. An analytical sample was obtained by crystallization in hexane: mp 68-70°C; IR (CCl_4) cm^{-1} 3580 (OH, free), 3025 (=C-H), 2955, 2920, 2870, 1640 (C=C v. weak), 1455, 1380, 1365, 1270, 1070, 1040, 990, 905, 885, 875, 720; NMR (CCl_4) δ 0.83 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 1.17-2.70 (m, 12 H), 3.27(s, 4 H), 3.58 (d, 1 H, J = 9.5 Hz), 5.27 (s, 1 H), 5.62 (s, 1 H); $[\alpha]_D^{25}$+6.49, $[\alpha]_{578}^{25}$+6.49, $[\alpha]_{546}^{25}$+8.44, $[\alpha]_{436}^{25}$+14.29, $[\alpha]_{365}^{25}$+22.73 (c = 0.2, Et_2O). Anal. Calcd for $C_{17}H_{28}OS_2$; C, 65.33; H,9.03. Found: C, 65.53; H, 9.31.

Preparation of Thioketal Derivative of 216B. From 84.6 mg (0.36 mmol) of 201B, following the procedure described in the above experiment, 100.7 mg (90%) of thioketal 217B was obtained as a colorless liquid: IR (CCl_4) cm^{-1} 3630 (OH, free), 3500 (OH, bonded), 3040 (C=C-H), 2955, 2920, 2865, 1470,1450, 1380, 1375, 1270, 1130, 1020,940; NMR (CCl_4) δ 0.77-1.17 (m, 9 H), 1.2-2.00 (m, 10 H), 2.26-2.63 (m, 2 H), 3.2 (s, 4 H), 3.48 (bs, 1 H), 5.18 (s, 1 H), 5.93 (s, 1 H); $[\alpha]_D^{25}$+33.20, $[\alpha]_{578}^{25}$+34.90, $[\alpha]_{546}^{25}$+40.50, $[\alpha]_{436}^{25}$+78.50, $[\alpha]_{365}^{25}$+144.30, (c = 0.1, Et_2O).

Raney Nickel Desulfurization of the Thioketal 217A. A solution of 94 mg (0.29 mmol) of the thioketal 217A in 8 mL of absolute ethanol and 1 mL of water was stirred with 3 mL of "deactivated" Raney nickel W-2 dispersion in absolute

ethanol. When the mixture was stirred for 0.5 h all the starting material had been consumed (TLC). The mixture was filtered and the residue was washed with ether. The combined ether extracts were concentrated by rotary evaporation to remove most of the ether. The residue was mixed with water and extracted with ether. Workup of the ether layer gave 54 mg (81%) of pure 202A as a white crystalline solid: mp 68-70°C; IR (CCl_4) cm^{-1} 3560 (OH, free) 3015 (=C-H), 2960, 2930, 2875, 2730, 1660 (C=C), 1465, 1455, 1445, 1380, 1370, 1290, 1260, 1080, 1040, 980, 870; NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, 3 H, J =7 Hz), 0.91 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J =7 Hz), 1.76 (s, 3 H), 3.56 (d, 1 H, J = 10 Hz), 5.21 (s, 1 H); MS m/z 222(M^+); $[\alpha]_D^{25}$+14.28, $[\alpha]_{578}^{25}$+14.92, $[\alpha]_{546}^{25}$+16.83, $[\alpha]_{436}^{25}$+26.03, $[\alpha]_{356}^{25}$+36.82, (c = 0.3, Et_2O). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.73; H, 11.59.

Raney Nickel Desulfurization of 217B. From 95 mg (0.03 mmol) of 217B, following the procedure described in the preceding experiment, 51 mg (67%) of 201B was obtained as a colorless liquid: IR (CCl_4) cm^{-1} 3640, 3040, 2960, 2930, 2870, 1655, 1605, 1470, 1452, 1382, 1378, 1368, 1225, 1140, 1130, 1055, 1018, 940, 862; NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 7.5 Hz), 1.75 (s, 3 H), 3.54 (bs, 1 H), 5.66 (s, 1 H); MS m/z 222 (M^+); $[\alpha]_D^{25}$+30.23, $[\alpha]_{578}^{25}$+31.51, $[\alpha]_{546}^{25}$+36.65, $[\alpha]_{436}^{25}$+70.74, $[\alpha]_{365}^{25}$+132.5 (c = 0.3, Et_2O).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 79.57; H, 11.95.

Reaction of α-Cyano-l-menthone (168) with Methyl Vinyl Ketone in the Presence of DBU. Following the procedure described by Corey et al.,[113] to a solution of 9.72 g (54 mmol) of 168 in 55 mL of a 1:1 mixture of THF-Bu^{t}OH containing 1.64 mL (11 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene and 1.149 g (11 mmol) of anhydrous sodium carbonate was added dropwise 4.8 mL (59 mmol) of freshly distilled methyl vinyl ketone, under a nitrogen atmosphere, at ≈20°C. Then the reaction mixture was poured into 500 mL of water and extracted with three 100 mL portions of ether. The ether layers were washed succesively with 50 mL portions of 5% NaOH, water and brine and worked up. The crude product was dissolved in 100 mL of hexane and refrigerated overnight yielding 9.90 g (73%) of 197B as white crystalline solid. An analytical sample was prepared by recrystallization from hexane: mp 77-79°C; IR (CCl_4) cm^{-1} 2970, 2905, 2880, 2240 (C≡N), 1725 (C=O), 1465, 1420, 1390, 1370, 1170; NMR (CCl_4) δ 0.89 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.15 (d, 3 H, J = 7 Hz), 1.50-2.87 (m, 11 H), 2.47 (s, 3 H); $[\alpha]_D^{25}$ +66.08, $[\alpha]_{578}^{25}$ +69.81, $[\alpha]_{546}^{25}$ +82.26, $[\alpha]_{436}^{25}$ +177.87, $[\alpha]_{365}^{25}$ +433.32 (c = 2, Et_2O). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.39; H, 9.22.

The reaction was also repeated at room temperature. Starting from 346.7 mg (1.93 mmol) of α-cyano-l-menthone was isolated, by flash column chromatography using 40% ether in hexane, 308 mg (64%) of 197B as the first fraction (R_f 0.22) and 179 mg (30%) of 197A (R_f 0.39) as a second fraction: IR (CCl_4) cm^{-1} 2975, 2940, 2880, 2210 (C≡N), 1730 (C=O), 1390, 1370, 1310, 1170, 1120, 930; NMR (CCl_4) δ 0.90 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7Hz), 1.22 (d, 3 H, J = 6 Hz), 1.73-3.00 (m, 11 H), 2.13 (s, 3 H); $[\alpha]_D^{25}$-136.9, $[\alpha]_{578}^{25}$-144.2, $[\alpha]_{546}^{25}$-168.6, $[\alpha]_{436}^{25}$-347.4, $[\alpha]_{365}^{25}$-797.6 (c = 3, Et_2O).

Preparation of the Thioketal 198. Following the procedure described for the preparation of 217A, starting from 499 mg (2 mmol) of 197A, was isolated 579 mg (89%) of the thioketal 198 as a colorless liquid: IR (CCl_4) cm^{-1} 2960, 2925, 2875, 2225, 1725, 1445 (broad), 1382, 1372, 1273, 1200, 1148, 940; NMR (CCl_4) 0.88 (d, 3 H, J = 6 Hz), 0.94 (d, 3 H, J = 7 Hz), δ 3.25 (s, 4 H): $[\alpha]_D^{25}$-79.25, $[\alpha]_{576}^{25}$-83.64, $[\alpha]_{546}^{25}$-97.94, $[\alpha]_{436}^{25}$-205.61, $[\alpha]_{365}^{25}$-486.36 (c = 1.0, Et_2O). Anal. Calcd for $C_{17}H_{27}ONS_2$: C, 62.72; H, 8.36. Found: C, 62.57; H, 8.43.

Attempted Tosylation of 202B. A solution of 200 mg (0.9 mmol) of 202B in 4 mL of pyridine was treated with 205 mg (1.08 mmol) of p-toluenesulfonyl chloride at 0°C under nitrogen. After stirring the reaction mixture for

96 h at 0°C, it was poured into 25 mL of water and extracted with ether. The ether extracts were washed successively with 1 N HCl, 10% $NaHCO_3$, and brine. The ether extract was worked up, and the flash chromatography of the crude product over silica gel afforded 188 mg of the starting material as the only product.

Reaction of 210 with Propane-1,3-dithiol.[154] Into a solution of 235 mg (1 mmol) of 210 and 120 µL (1.2 mmol) of propane-1,3-dithiol in 3 mL of ether was added dropwise 62 µL of borontrifluoride etherate. The reaction mixture was stirred under nitrogen for 6 h. Upon workup followed by flash chromatography using 10% ether in hexane the reaction mixture gave 158 mg of the protected compound whose TLC showed the presence of several impurities. Further purification of this material was not attempted.

Attempted Dethioketalization of 215. The procedure described by Peters et al.[121] was used. Into 100 mL of liquid ammonia was added 260 mg (0.83 mmol) of the epimeric mixture of 215A and 215B in 6 mL of tetrahydrofuran. Into this magnetically stirred mixture was added 327 mg (47 mmol) of lithium in small pieces. After a period of 1 h, 5 mL of methanol was added to the reaction mixture and the ammonia was allowed to evaporate. Upon workup 156 mg of crude product was obtained. TLC of the product showed it to be a multi-component mixture. This product was not investigated

further.

Attempted Protection of the Less Hindered Carbonyl Group in 210. A modification of the procedure described by Evans et al.[120] was used. To a dry, nitrogen-purged, 25 mL flask was added 585.9 g (2.5 mmol) of 210, 2,5 mg of zinc iodide and 1.25 mL of anhydrous ether. To this mixture was added 653.8 mg (2.7 mmol) of propane-1,3-dithiobis-(trimethylsilane) via a syringe over a period of 2 min. After 21 h the mixture was quenched with water and the product was isolated by ether extraction. Upon the concentration of the ether extract followed by flash column chromatography over alumina 580 mg (99%) of the starting material was recovered.

Attempted Desulfurization of Thioketal 215B. A procedure adapted from that of Stutz and Stadler[122] was used. Into a suspension of 134 mg (1 mmol) of anhydrous cupric chloride[155] and 272 mg (2 mmol) of anhydrous zinc chloride in 15 mL of THF was added 304 mg (8 mmol) of lithium aluminum hydride in small portions. The reaction mixture was stirred for 45 min under a nitrogen atmosphere. An exothermic reaction was observed and a black precipitate was formed. Then 164 mg (0.5 mmol) of the thioketal 215B was added in the powdered form. After refluxing for 1 h the mixture was treated with 100 mL of water and filtered. The residue was washed thoroughly with ether and the filtrate

was extracted with ether. Workup of the ether extract gave a crude product which was chromatographed over silica gel, using 5% ether in hexane yielding 84 mg (68%) of the crude 213B whose TLC behavior indicated the presence of impurities. Further purification of the material was not possible.

Osmium Tetroxide Oxidation of 213B. In a procedure adapted from recent literature,[125] a mixture of 111 mg (0.5 mmol) of 215B, 9 mg of osmium tetroxide and 320 mg (1.5 mmol) of sodium metaperiodate in 5 mL of 2 : 1 Bu^tOH-water was stirred for at 0°C for 36 h. The reaction mixture was then poured into 20 mL of 5% sodium bisulfite solution and the resulting mixture was extracted with ether. Workup of the ether extract afforded 80 mg of a crude product whose TLC showed it to be a multicomponent mixture, which was not investigated further.

Attempted Conversion of the Cyano Group in 196 into the Aldehyde Functionality. A procedure modified from that of Marshall et al.[112] was used. Into a suspension of 0.155 mg (5 mmol) of 196A in 5 mL of hexane was added dropwise 1.5 mL (1.5 mmol) of 1 M solution of diisobutyl aluminum hydride in hexane at 0°C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 min, and then quenched with few drops of saturated ammonium chloride solution followed by 5 mL of 5% sulfuric acid. Upon normal

workup 150 mg of (98%) of starting material was recovered as the only product.

Attempted Conversion of the Cyano Group in 199 to the Aldehyde Functionality. In a procedure identical to that of the preceding experiment, from 163.5 mg (0.5 mmol) of 199 160 mg (98%) of it was recovered unchanged.

Sodium Borohydride Reduction of 198. A solution containing 110 mg (0.34 mmol) of 198 in 5 mL of methanol was stirred with 14 mg (0.37 mmol) of sodium borohydride for 1 h. Workup of the reaction led to the isolation of 107 mg (97%) of 199 as a white solid. An analytical sample was prepared by recrystallization from hexane: mp 89-91°C; IR (CCl_4) cm^{-1} 3600, 3475, 2950, 2918, 2860, 2220, 1442, 1380, 1370, 1270, 1140, 988; NMR (CCl_4) δ 1.83-2.07 (m, 4 H), 3.3 (s, 4 H), 3.93 (d, 1 H, J = 6 Hz); $[\alpha]_D^{25}$-0.43, $[\alpha]_{578}^{25}$-0.43, $[\alpha]_{546}^{25}$-0.29, $[\alpha]_{436}^{25}$+1.00, $[\alpha]_{365}^{25}$+6.86 (c = 0.7, Et_2O). Anal. Calcd for $C_{17}H_{29}ONS_2$: C, 62.33; H, 8.92. Found: C, 62.08; H, 8.65.

Reaction of the Sodium Salt of α-formyl-l-menthone 166) with Phosphonium Salt 133. Using a procedure identical to that of Dauben and Hart,[32] to a suspension of 323 mg (14 mmol) of sodium hydride in 70 mL of HMPT was added 2.6 g (14 mmol) of α-formyl-l-menthone (166.). The mixture was stirred for 30 min and then 6.8 g (15 mmol) of solid 133 was

added. The solution was stirred under nitrogen for 24 h. The reaction mixture was poured into water and extracted with ether. Upon concentration of ether extract 7.11 g of crude product was obtained as a yellow oil. This product was subjected to flash chromatography on silica gel using 20% ether in hexane as the eluent to give 550 mg (7%) of crude 200 as a colorless liquid mixed with minor impurities: IR (CCl_4) cm^{-1} 2960, 22935, 2880, 1718 (broad, C=O), 1632 (C=C, conj.), 1370, 1275, 1258, NMR (CCl_4) δ 1.30 (t, CH_3, J = 7 Hz), 4.16 (q, CH_2, J = 7 Hz), 6.7 (s,H).

Then the column was washed with ether to obtain 6.12 g of a phosphorus-containing compound: IR (CCl_4) cm^{-1} 3060, 2960, 2935, 2875, 1670, 1630, 1600, 1585, 1440, 1100, 1090, 712, 692; NMR (CCl_4) δ 1.12 (t, CH_3, J = 7 Hz), 3.25 (q, CH_2, J = 7 Hz), 7.45 (m, aromatic H).

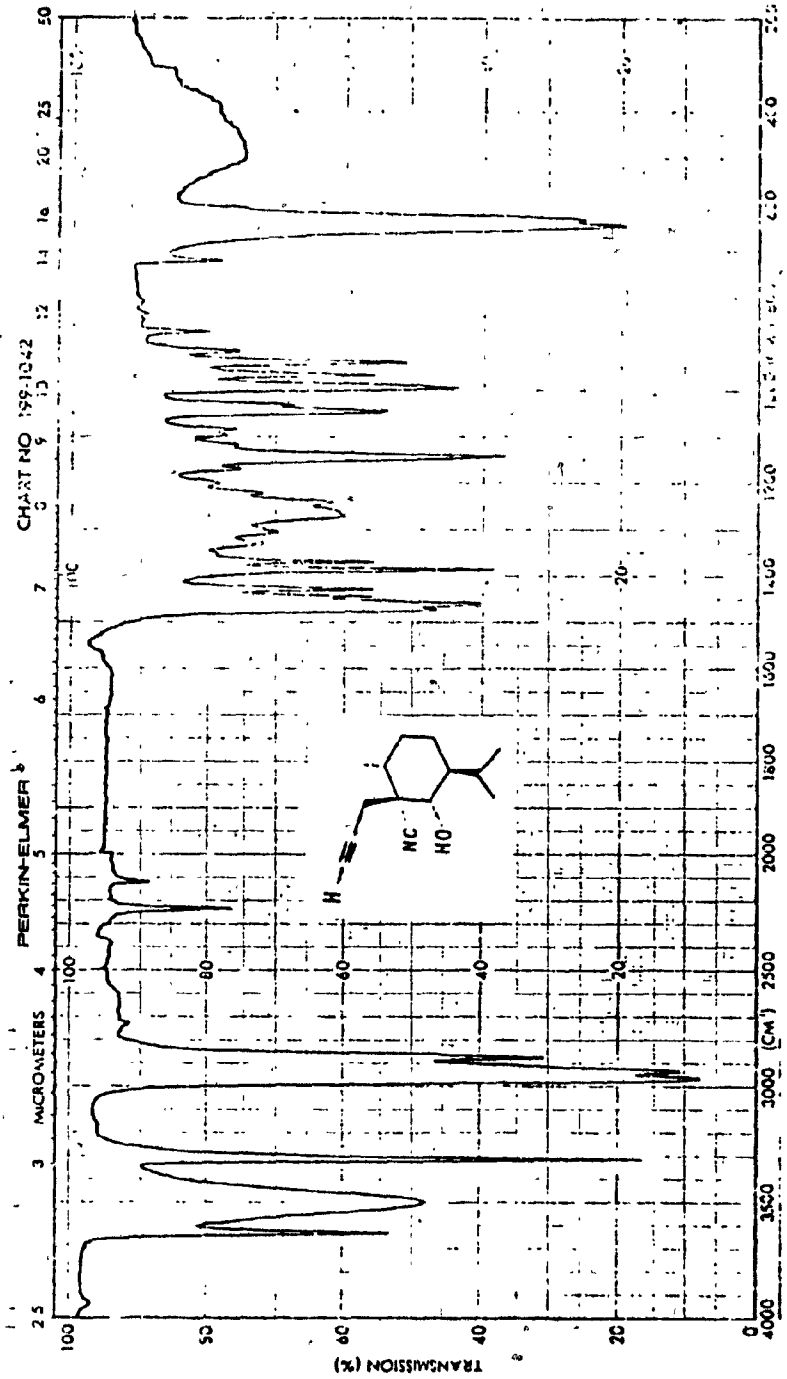
Sodium Borohydride Reduction of 200. A solution containing 500 mg (1.8 mmol) of 200 and 80 mg (2.1 mmol) sodium borohydride in 5 mL of methanol was refluxed for 1 h in a nitrogen atmosphere. Workup followed by flash chromatography of the crude product using 30% ether in hexane gave 300 mg (60%) of a liquid as the major component: IR (CCl_4) cm^{-1} 3640, 3535 (broad), 2965, 2940, 2875,1717, 1630 (C=C, conj.), 1370, 1275, 1212, 1100; NMR (CCl_4) δ 1.24 (t, 3 H, J = 7 Hz), 3.52 (bs, 1 H), 4.10 (q, 2 H, J = 7 Hz), 6.97 (s, 1 H).

The minor component isolated amounted to 70 mg (14%) of a colorless liquid: IR (CCl_4) cm^{-1} 3638, 3600, 3510 (broad), 2960, 2930, 2875,1715, 1640 (C=C, conj.) 1465, 1370, 1297, 1255, 1092; NMR (CCl_4) δ 3.57 (d, 1 H, J = 9 Hz), 4.08 (q, 2 H, J = 7 Hz), 6.13 (s, 1 H).

Both components revealed minor impurities on TLC.

Preparation of 201B. Into a solution of 300 mg (1.1 mmol) of the major product obtained from the preceeding experiment in 5 mL of anhydrous ether was added 50 mg (1.3 mmol) of lithium aluminum hydride. The mixture was stirred under nitrogen for 2 h. Upon the usual workup 200 mg of crude product was obtained, which was dissolved in 3 mL of chloroform, and into this was added 1 g of active manganese dioxide and stirring was continued for 4 h. The reaction mixture was filtered through a bed of sodium sulfate and concentrated under reduced pressure. The crude product thus obtained was purified by flash chromatography using 50% ether in hexane as the eluent to give 132 mg (49%, 2 steps) of a solid, identical in all respects to 201B obtained earlier (cf. p 134).

APPENDIX



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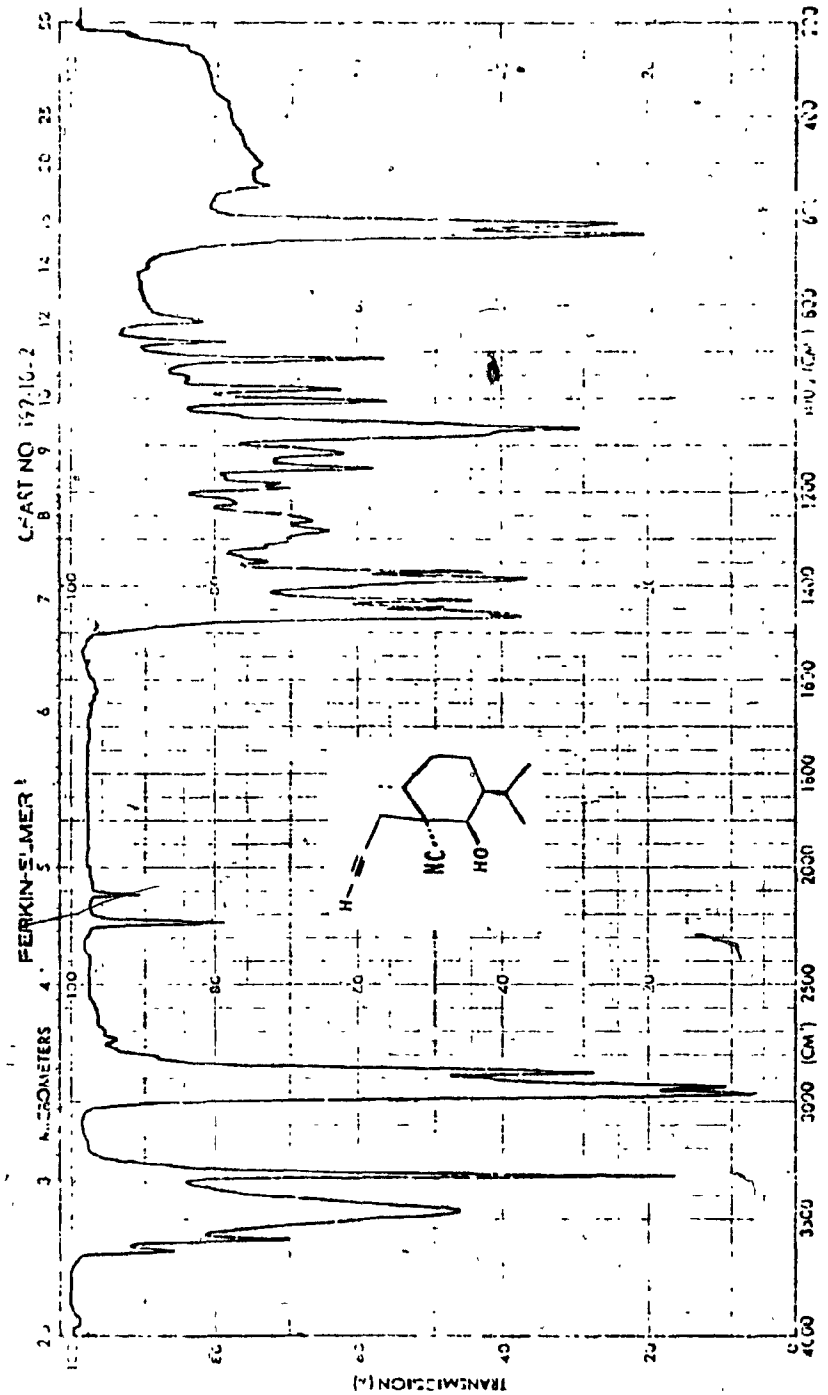

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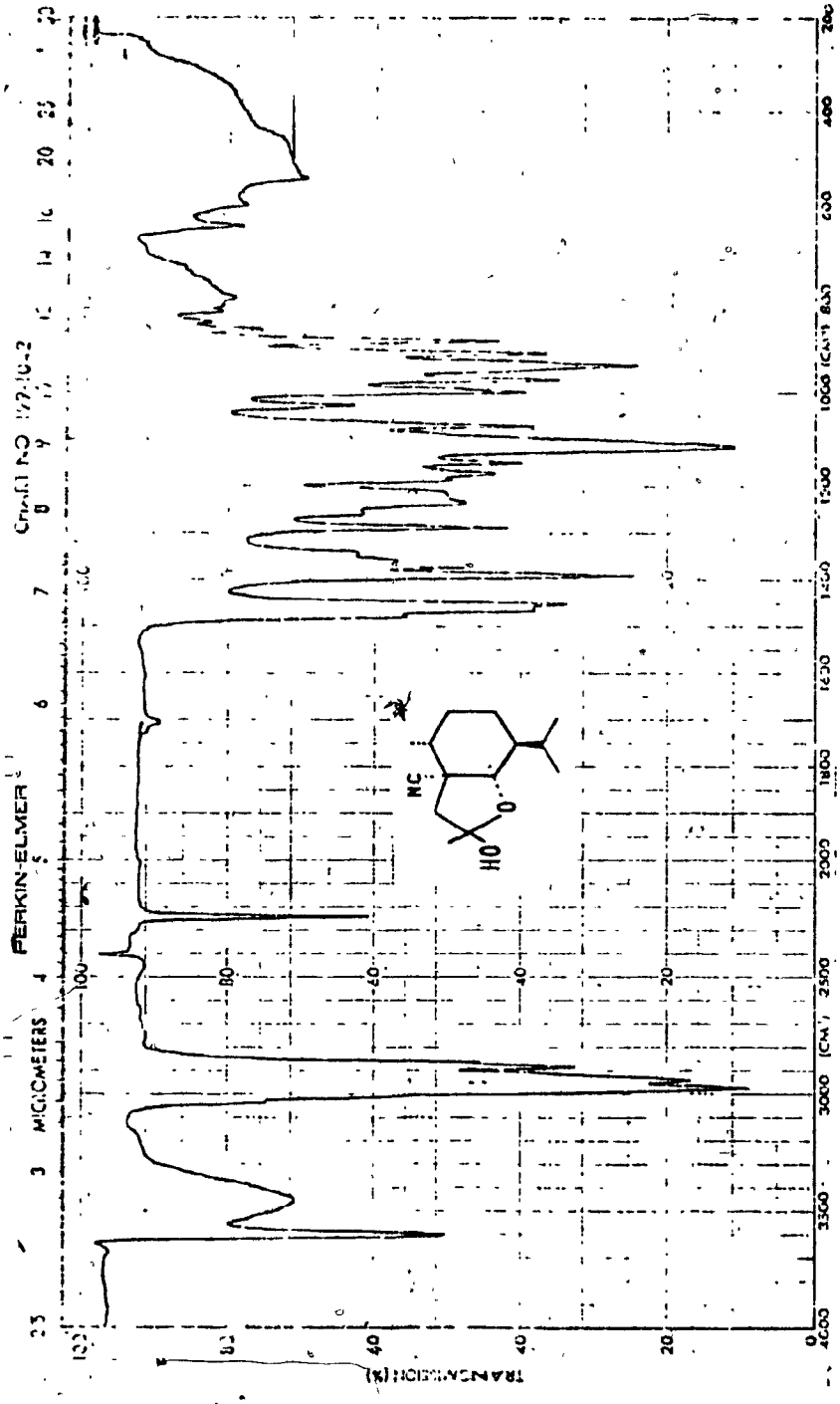
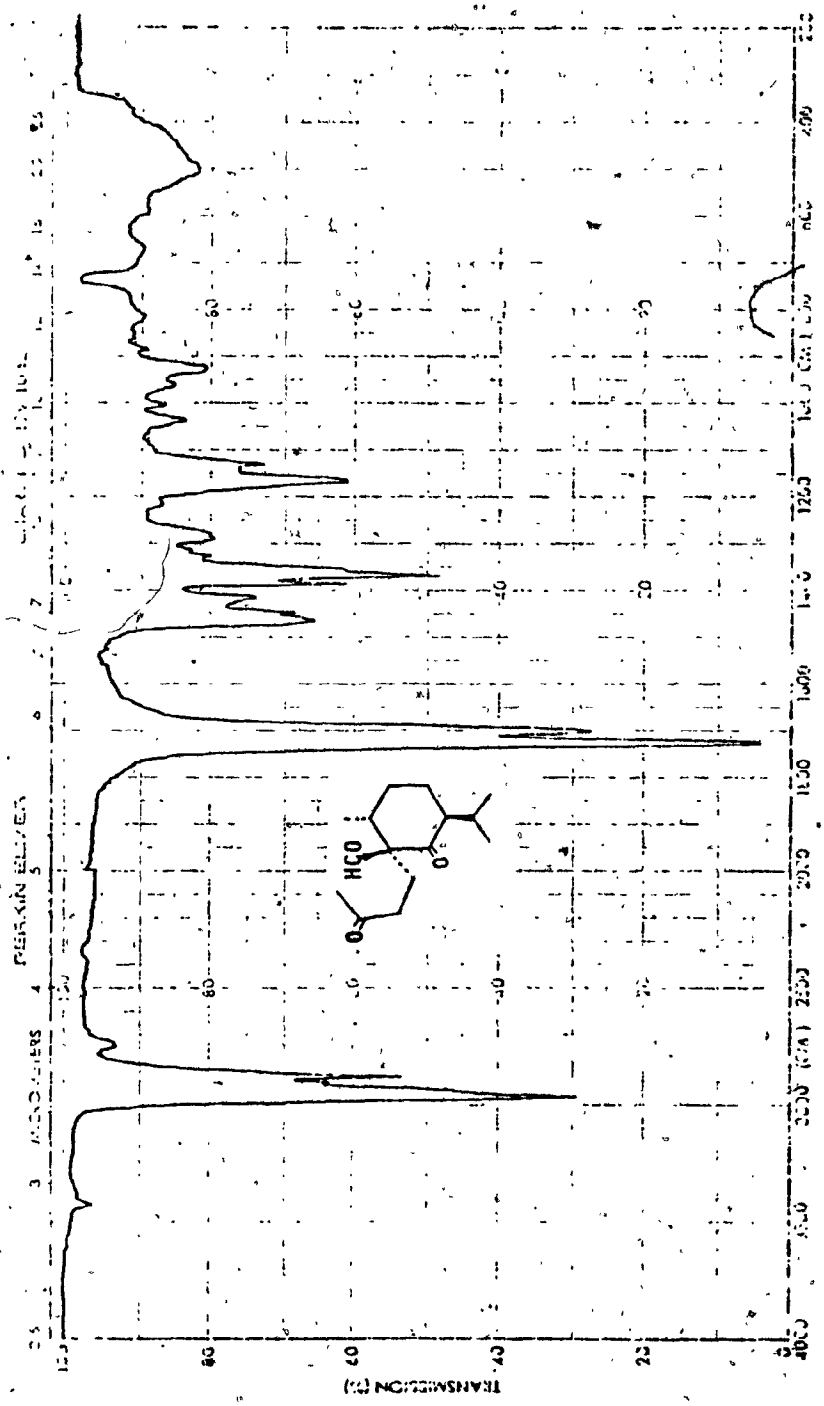
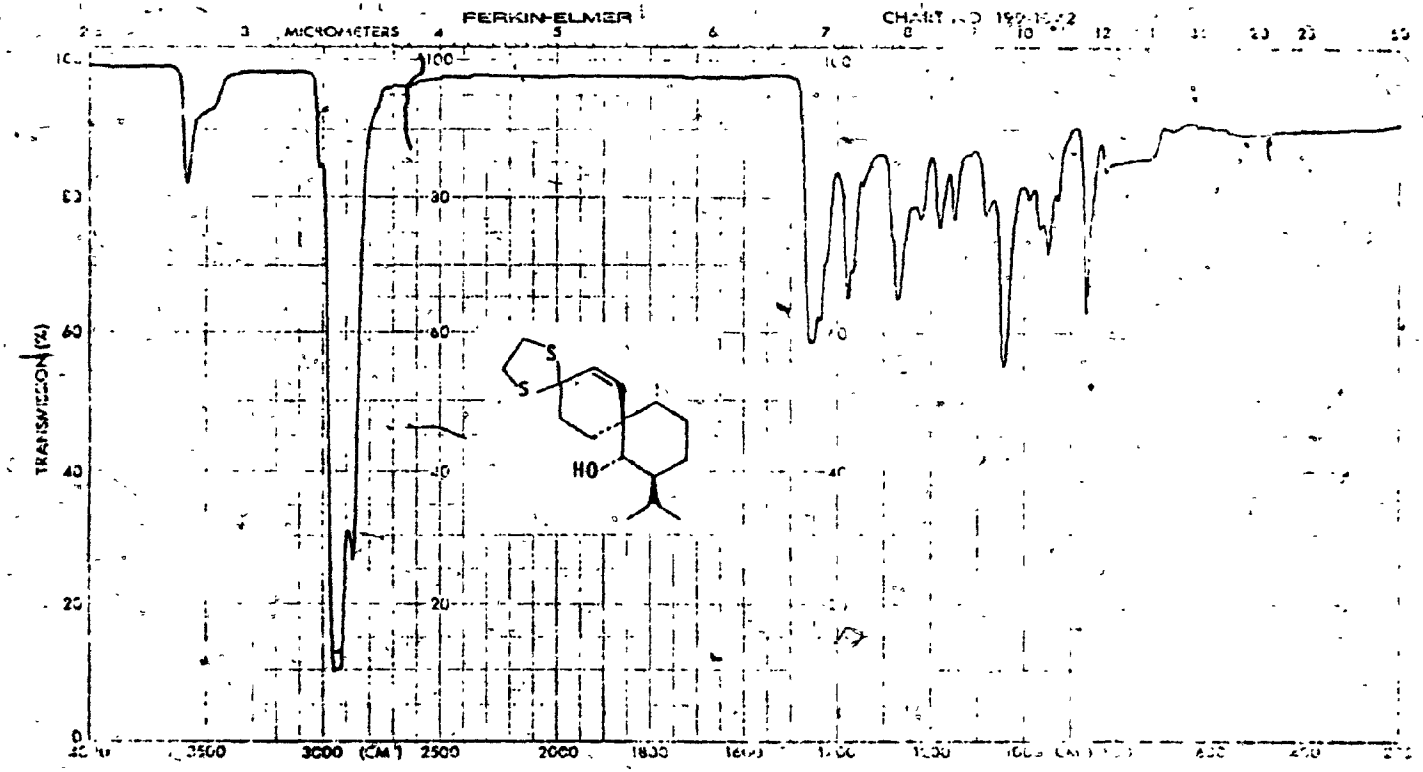


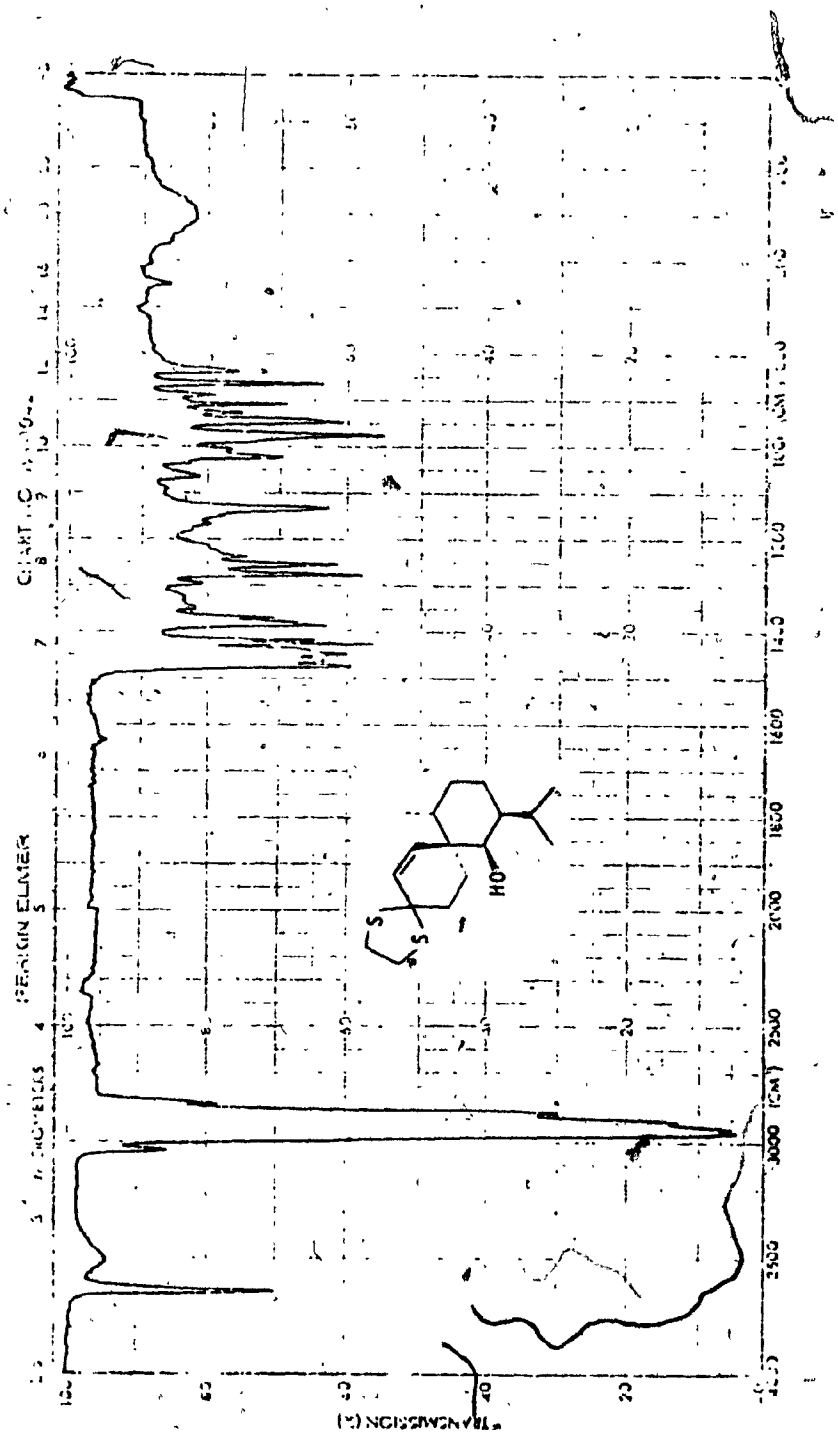
IR Spectrum No 3



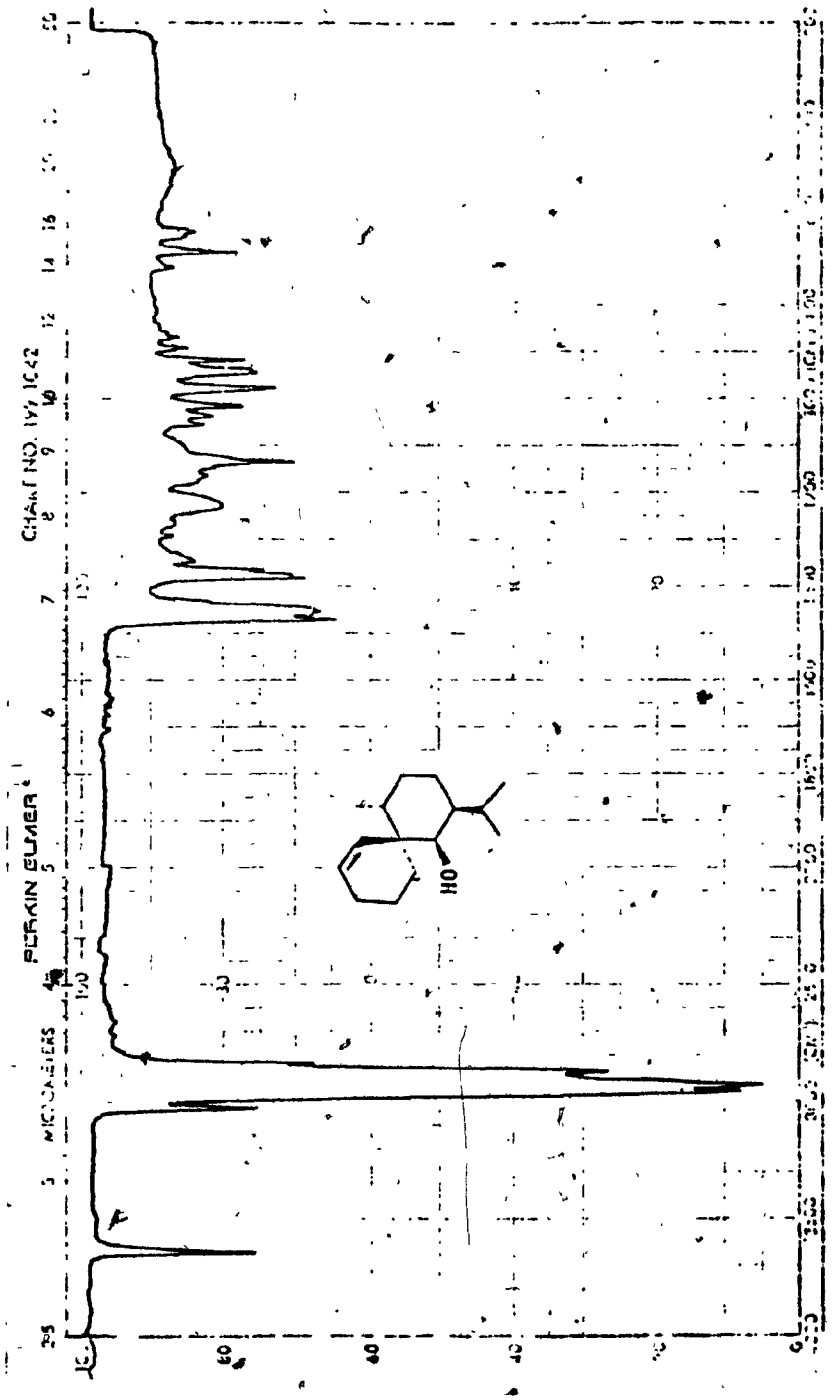
IR Spectrum No 4



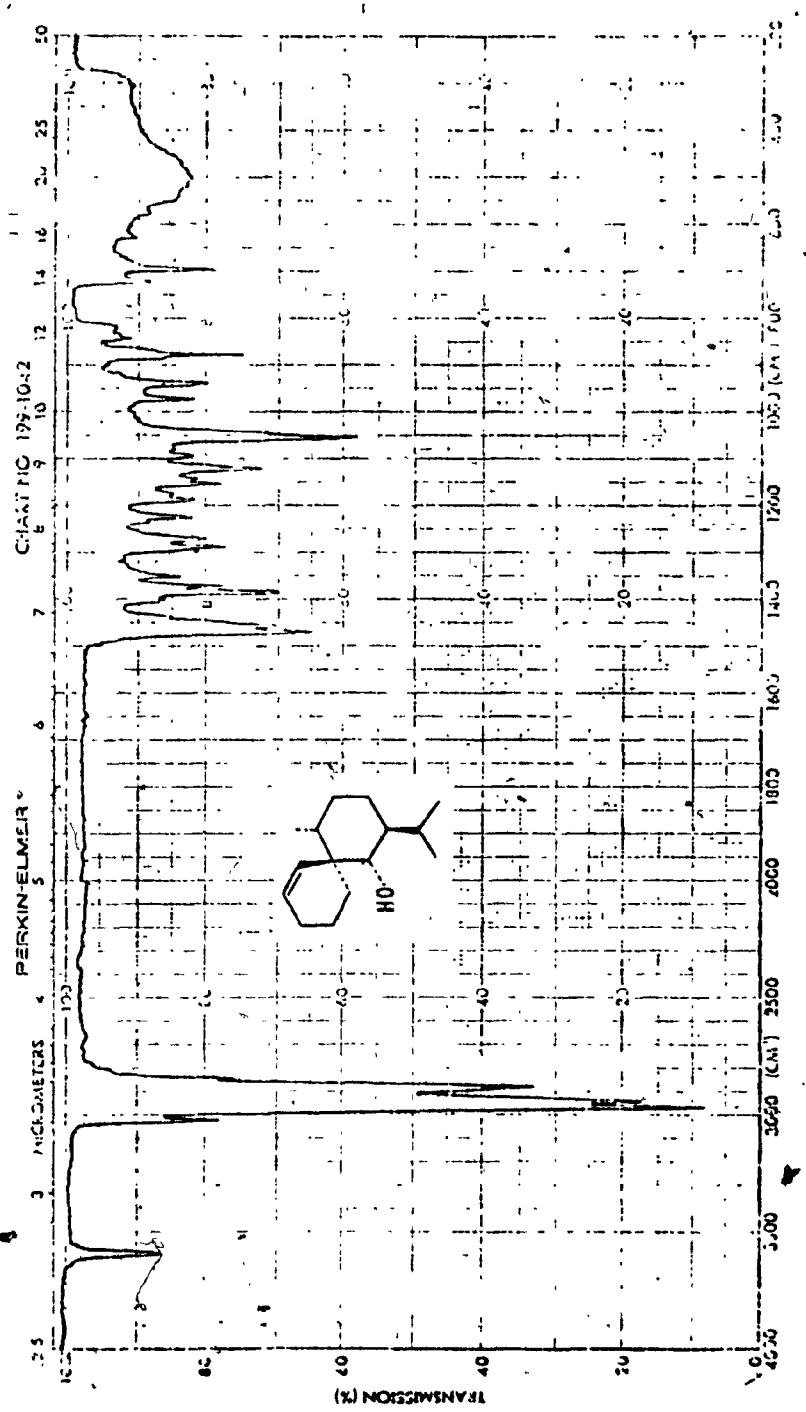
IR Spectrum No 5



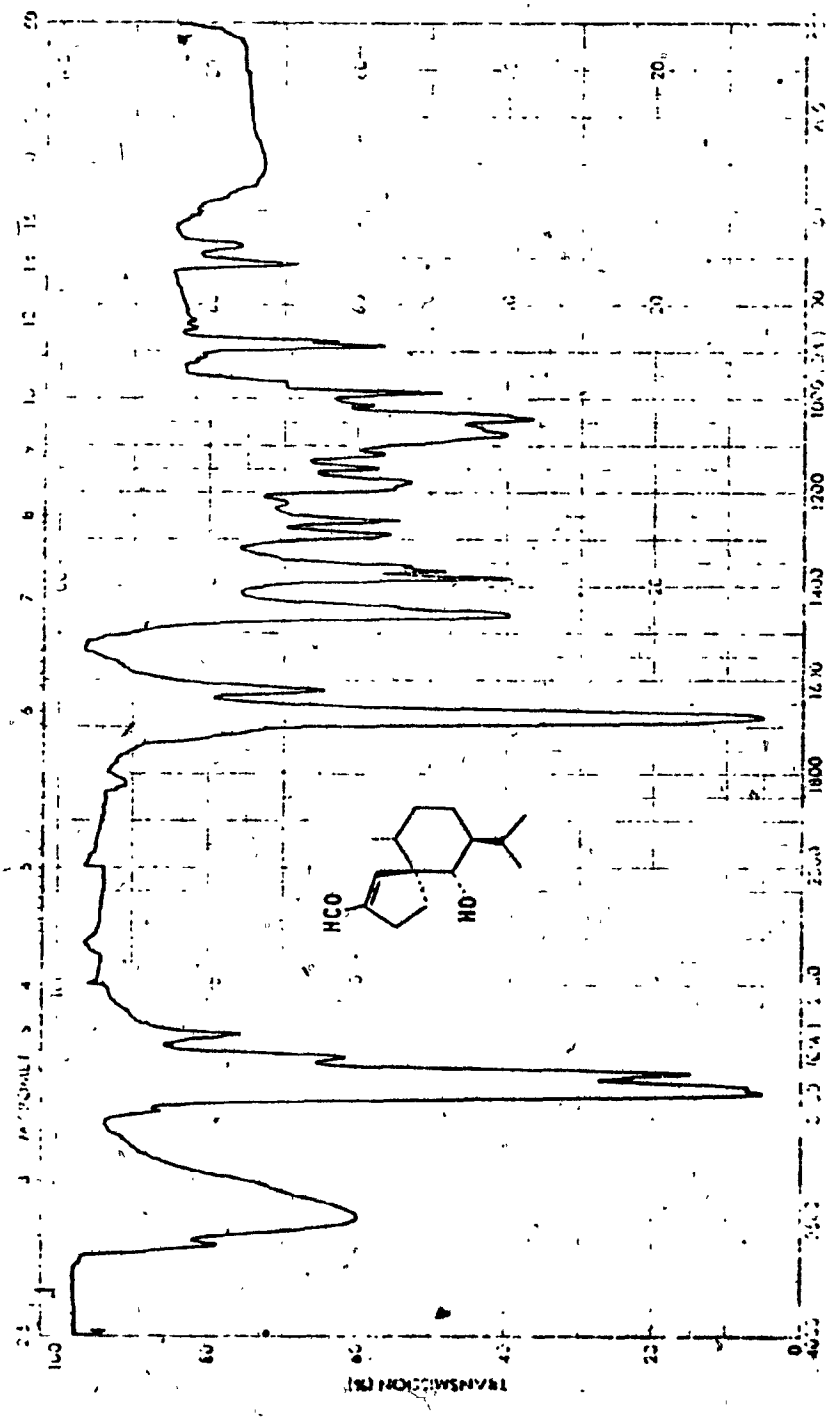
IR Spectrum No 6



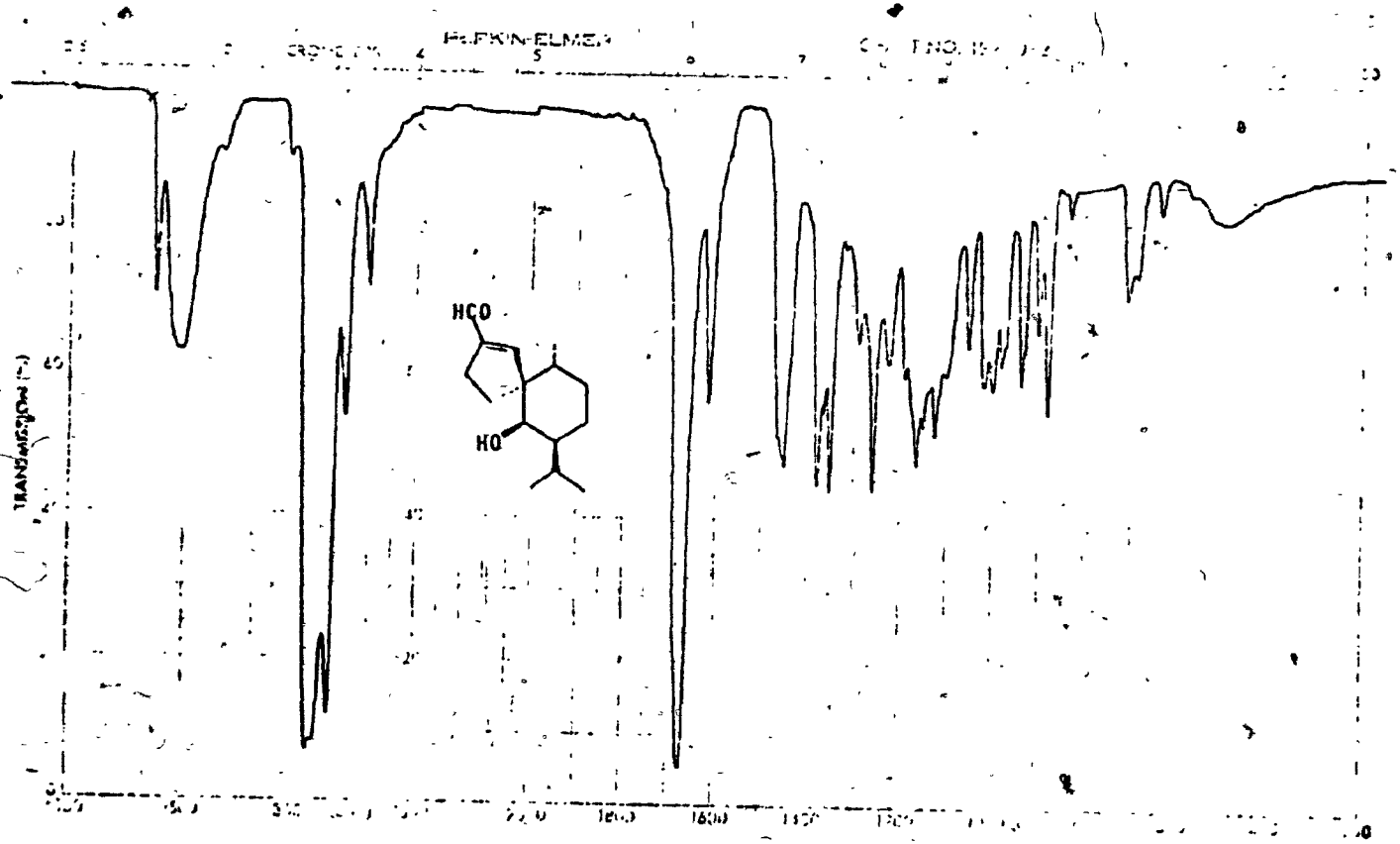
IR Spectrum No 7



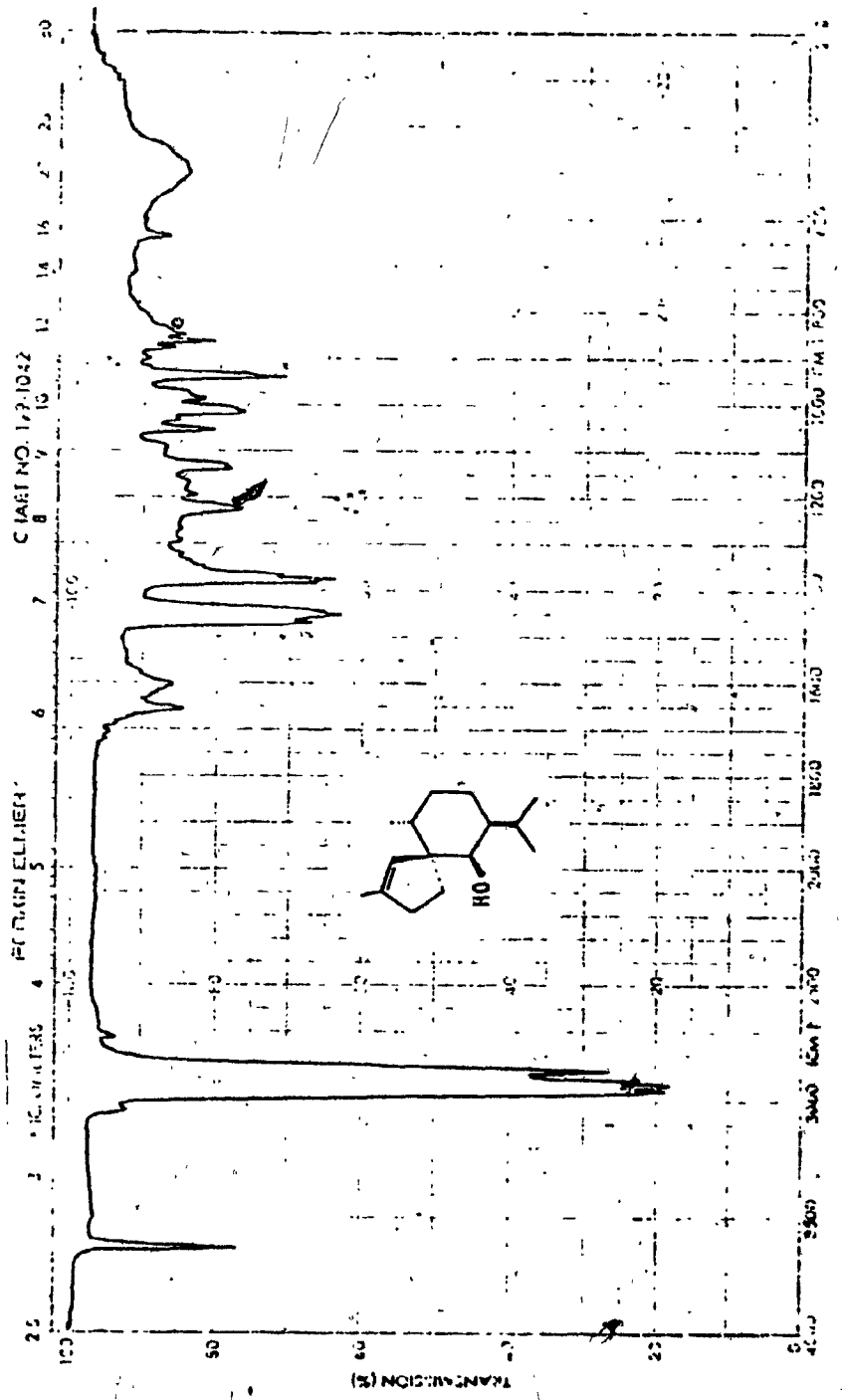
IR Spectrum No 8



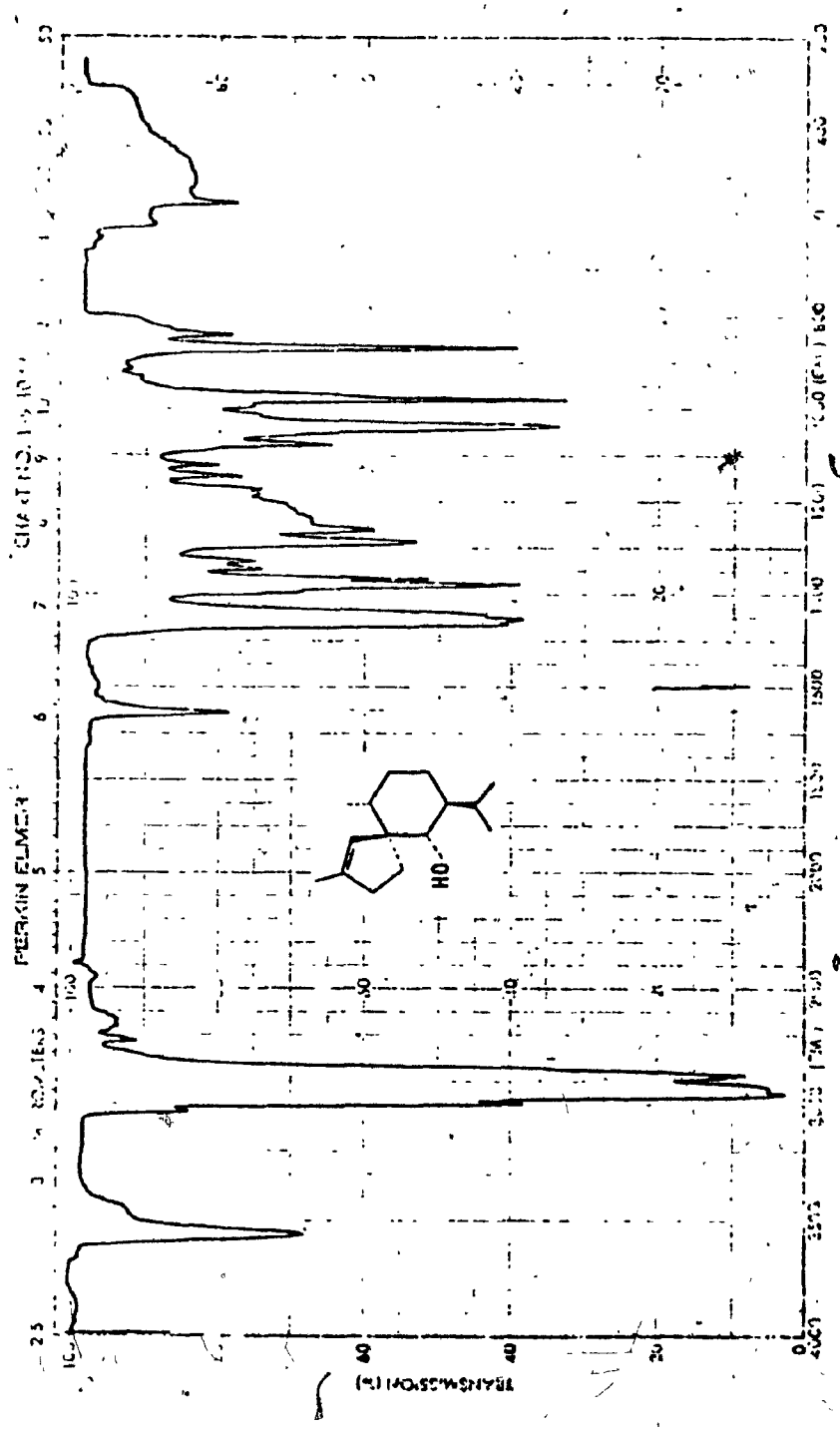
IR Spectrum No 9



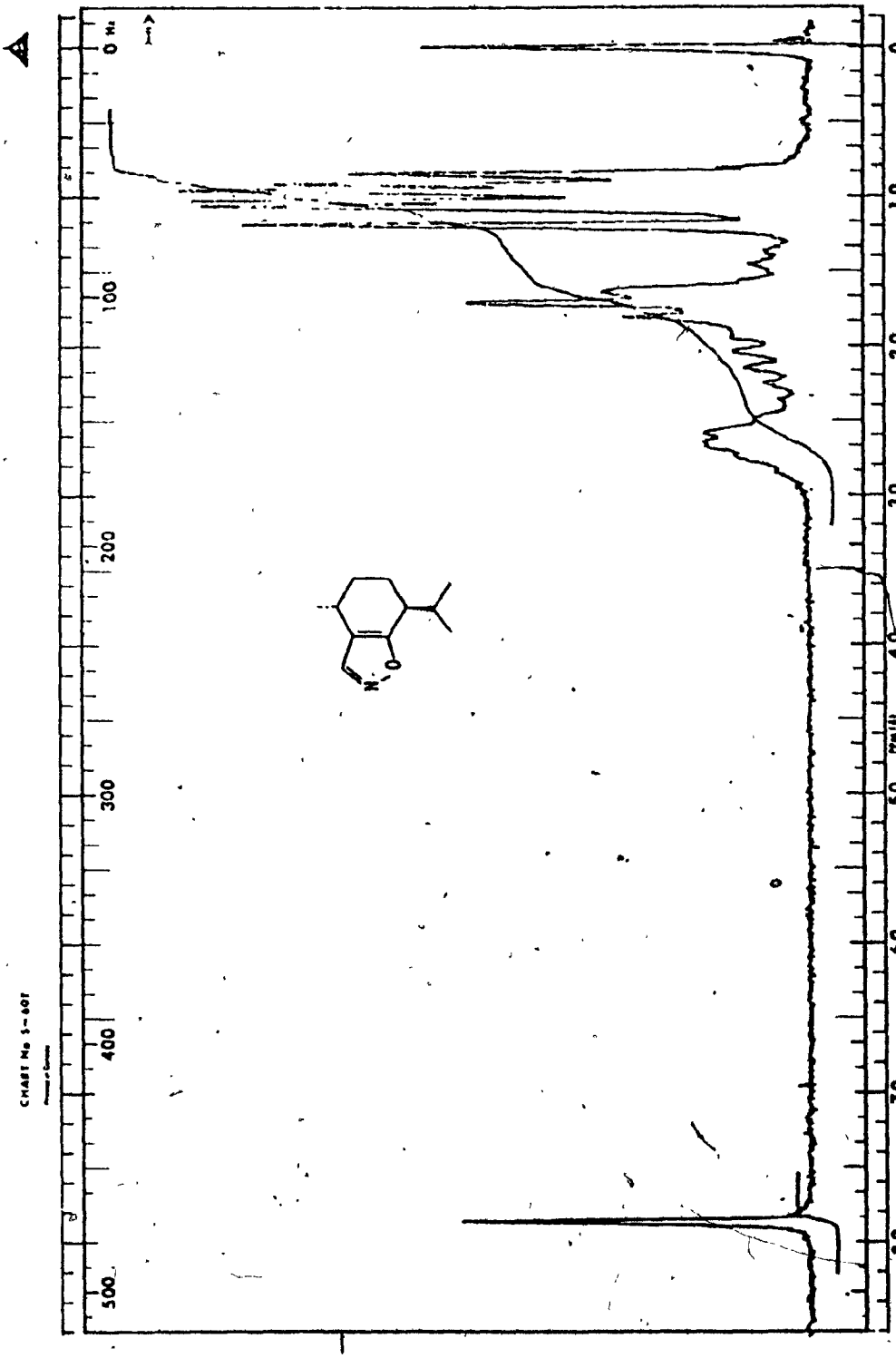
IR Spectrum No 10



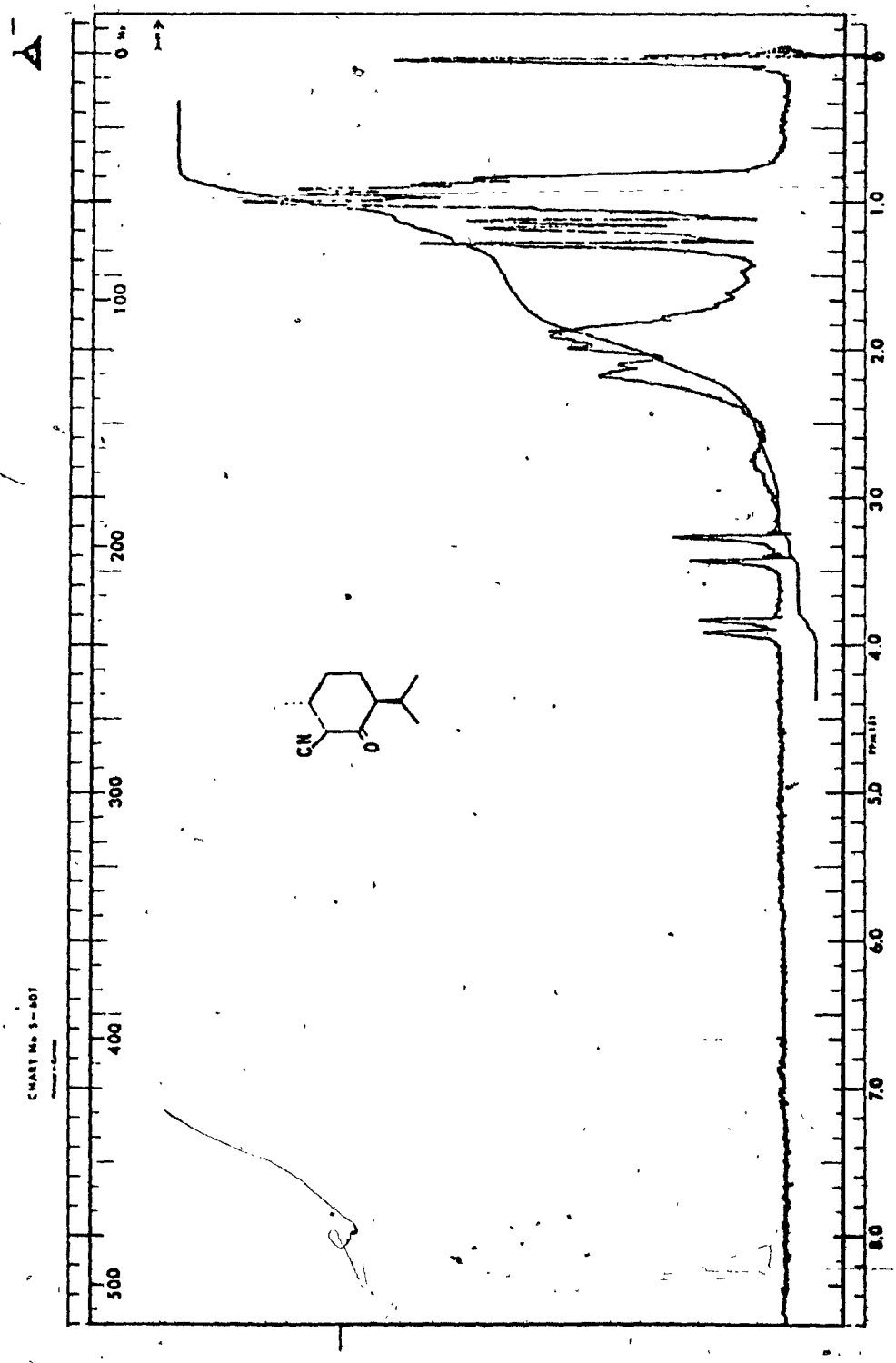
IR Spectrum No 11



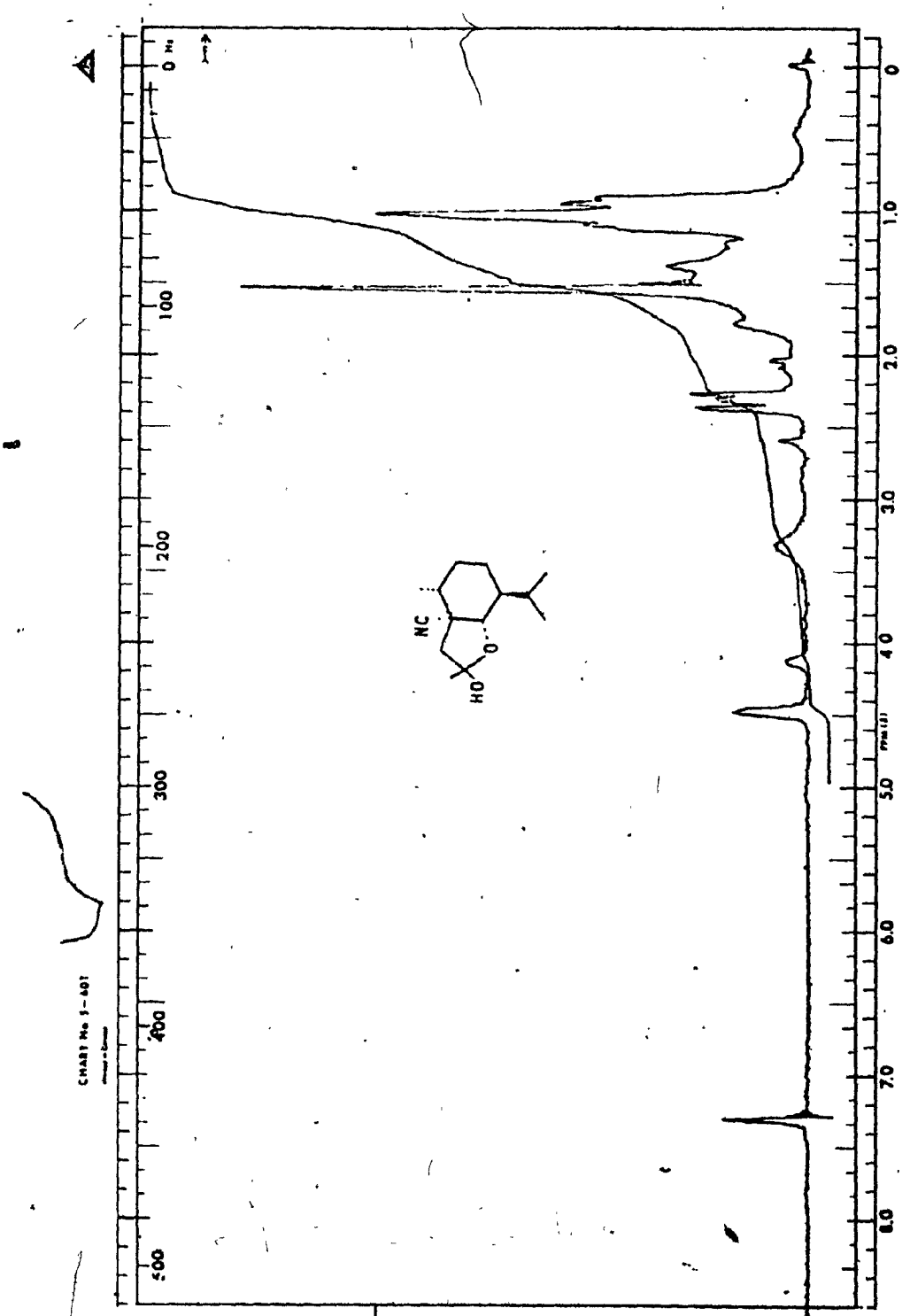
IR Spectrum No 12



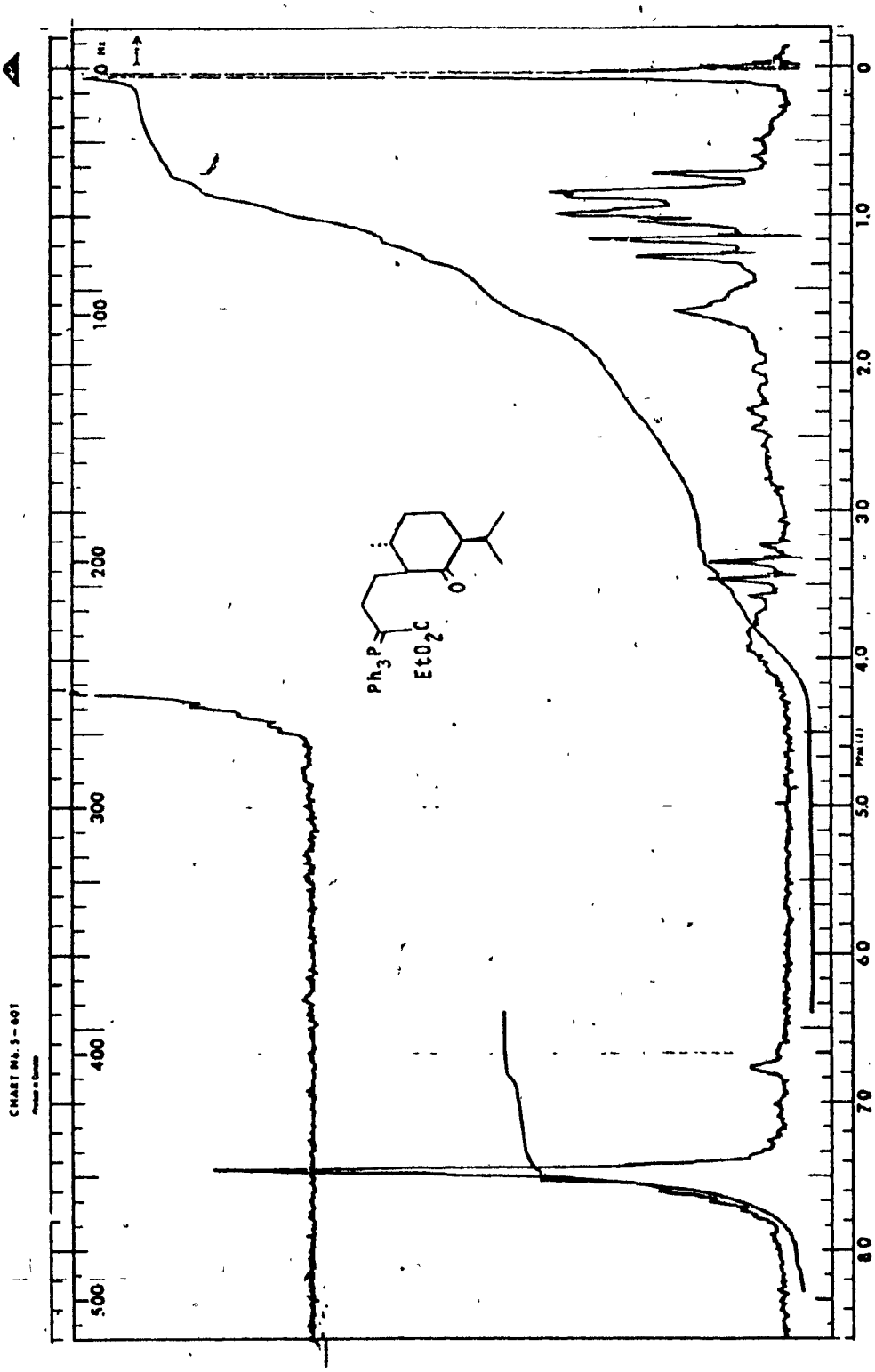
NMR Spectrum No 1



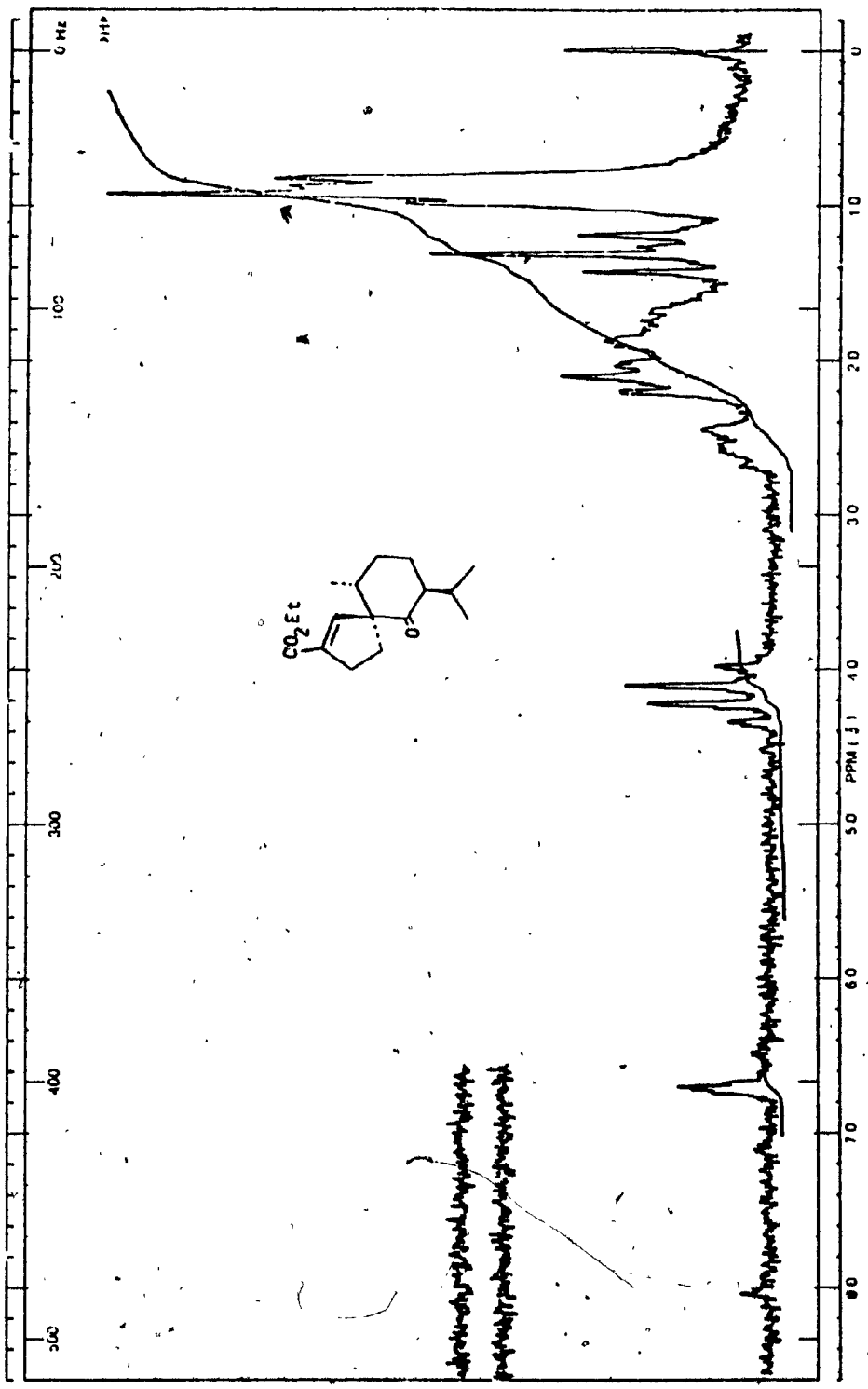
NMR Spectrum No 2



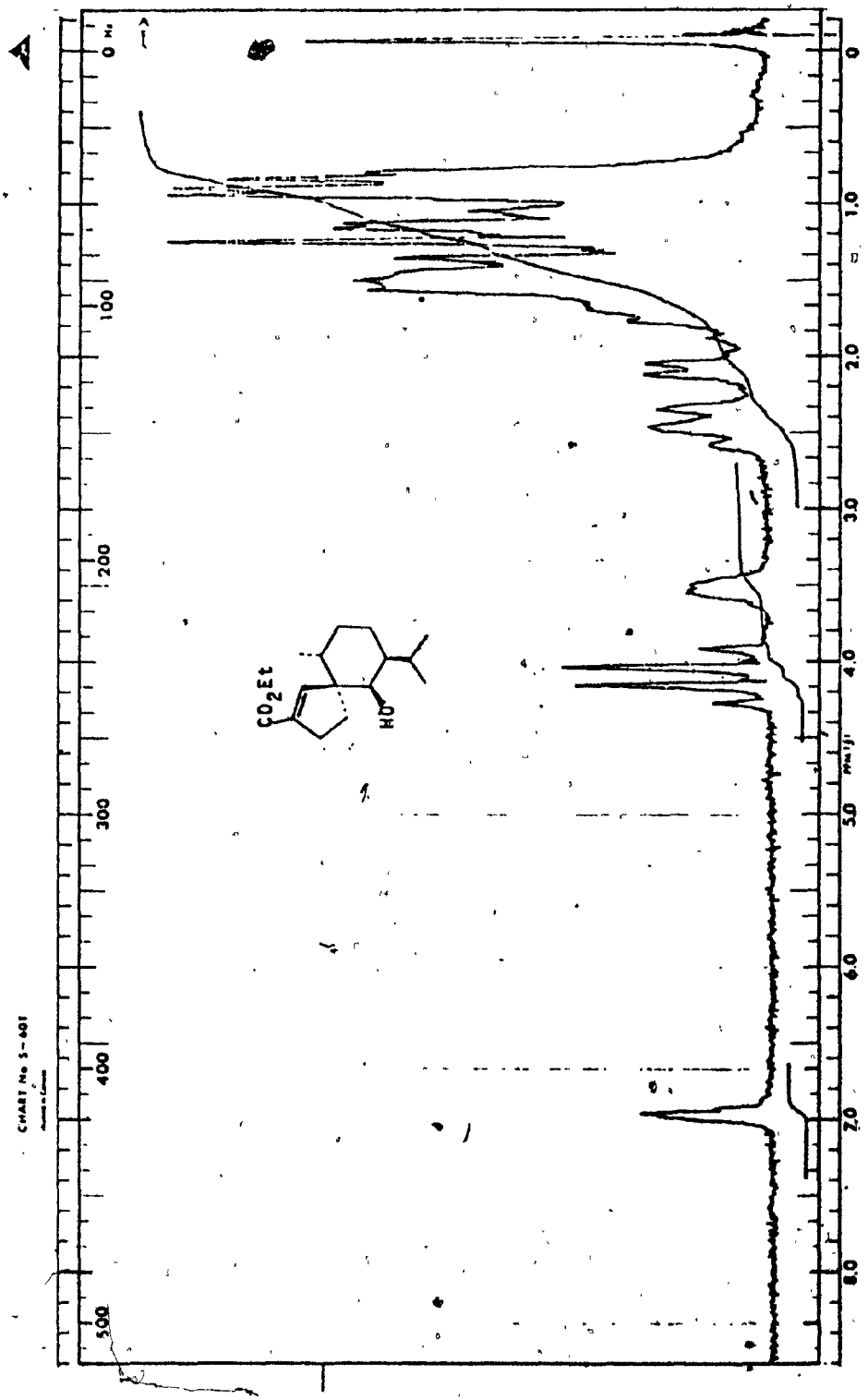
NMR Spectrum No 3



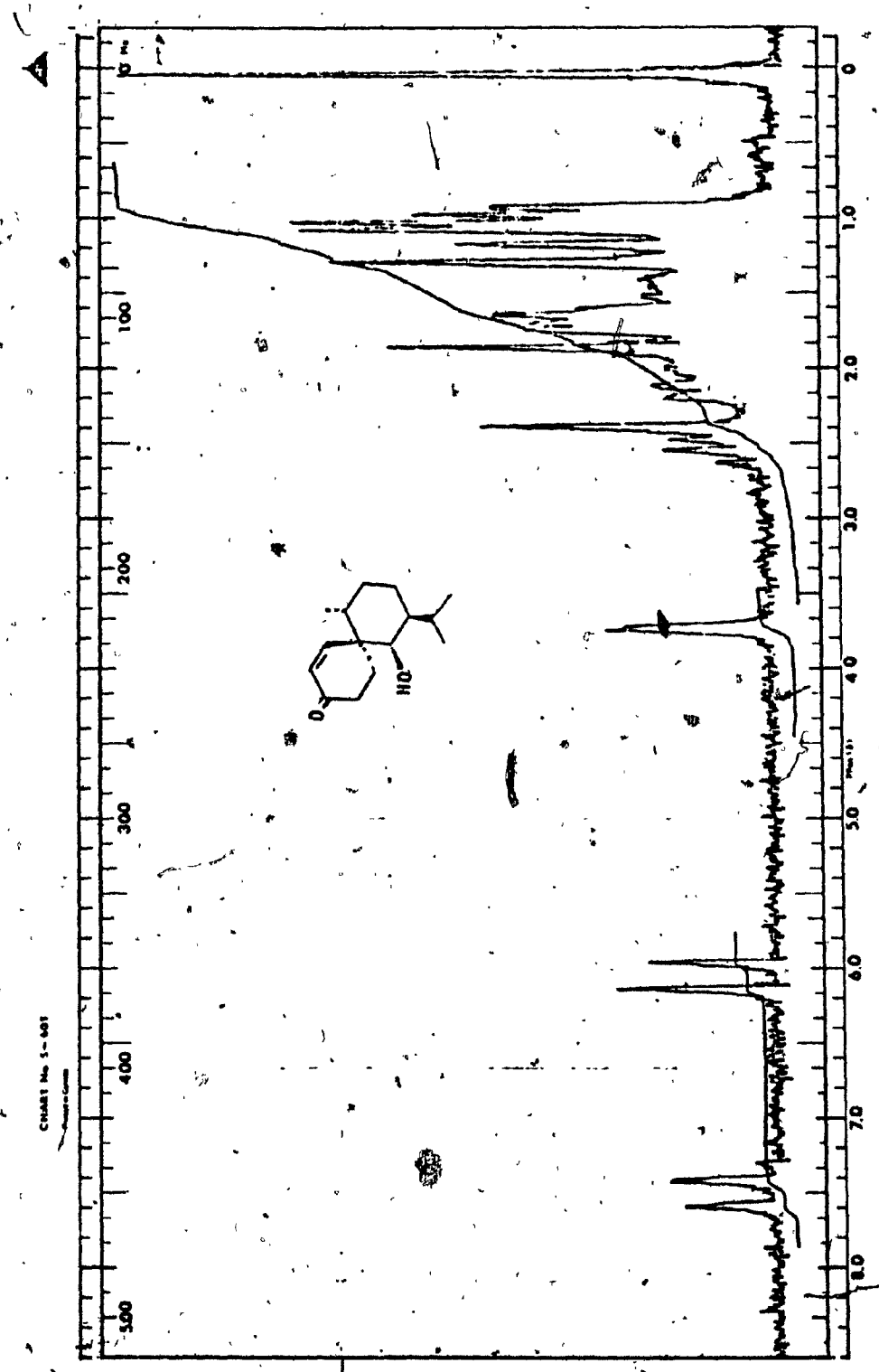
NMR Spectrum No 4



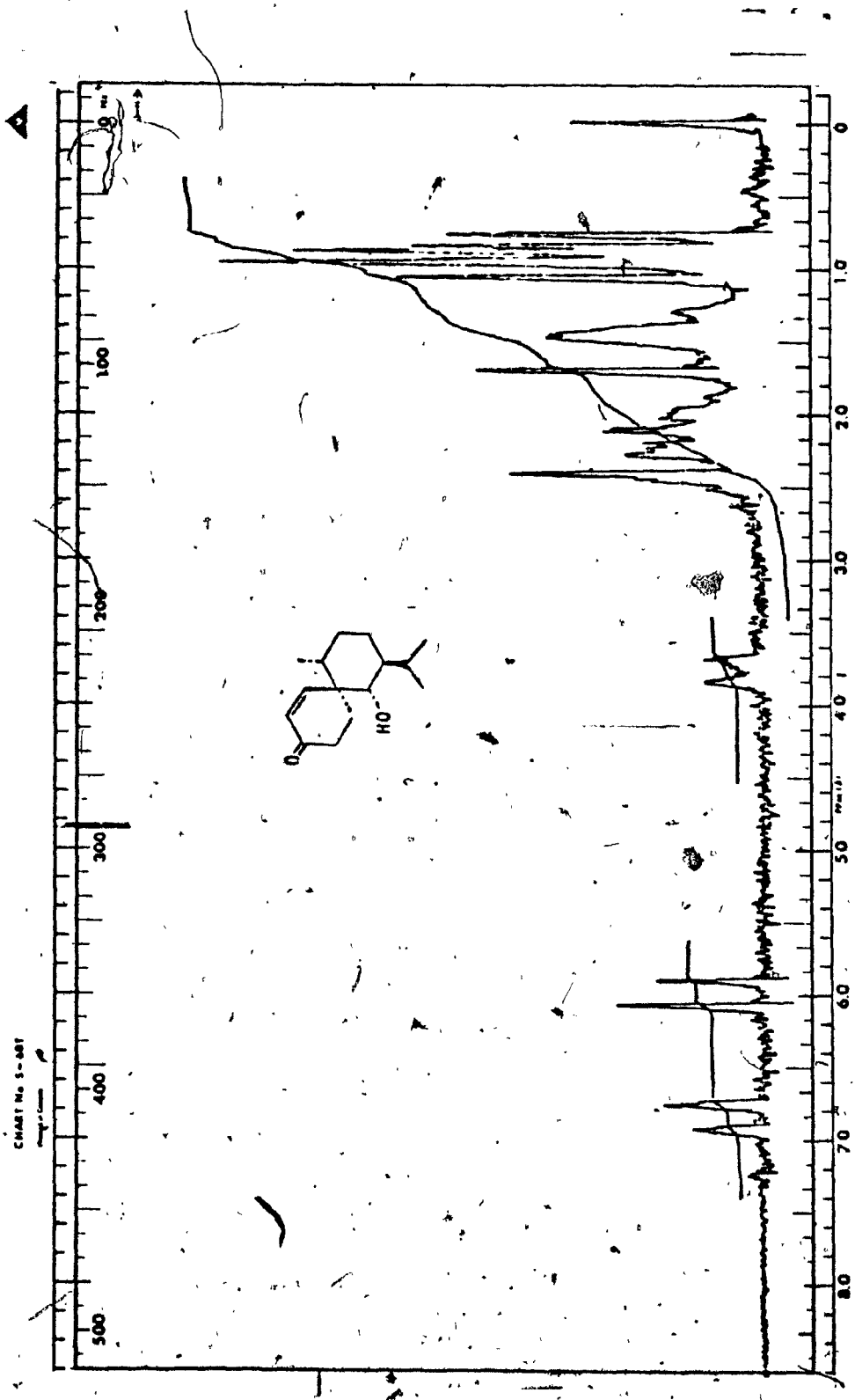
NMR Spectrum No 5



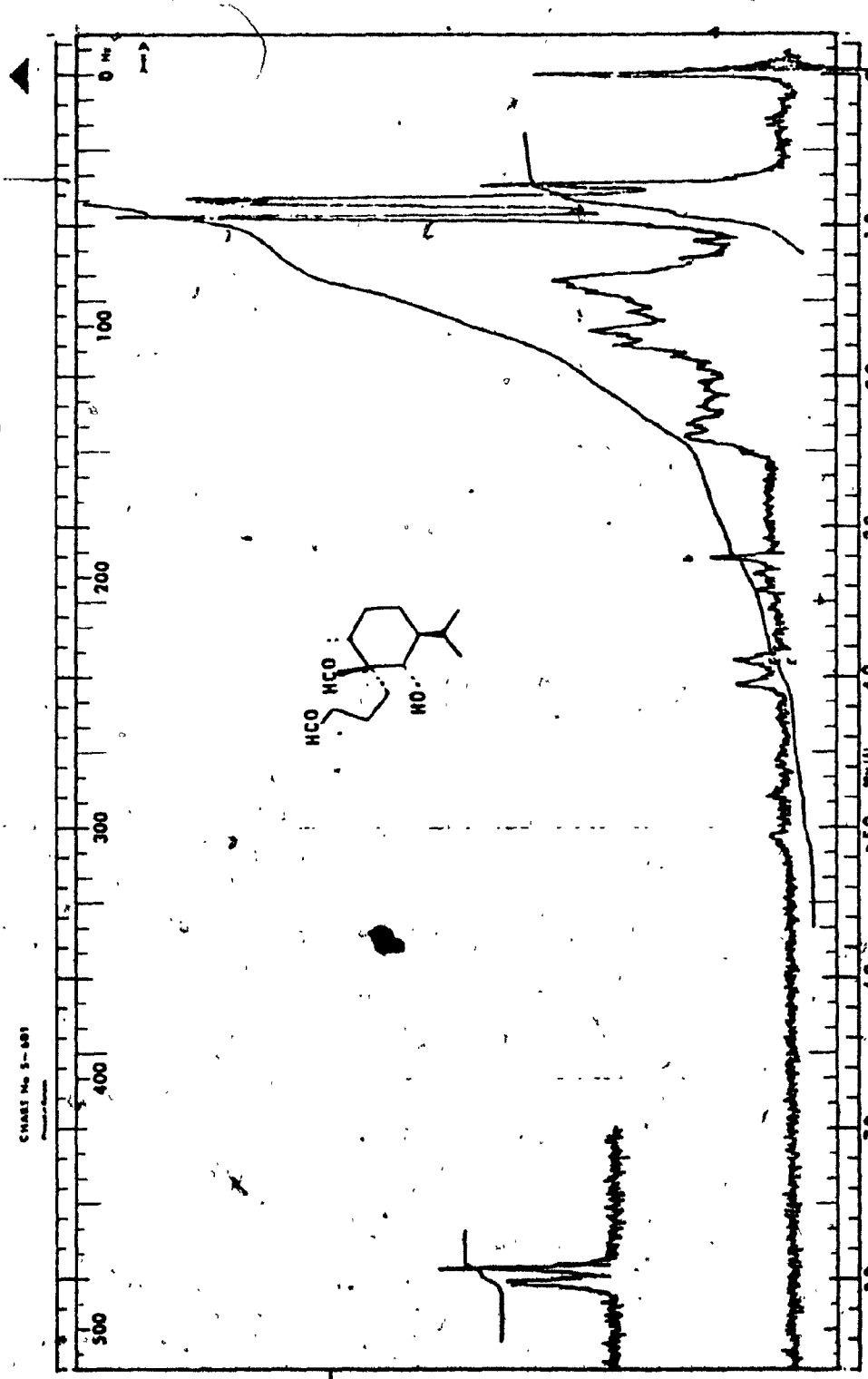
NMR Spectrum No 6



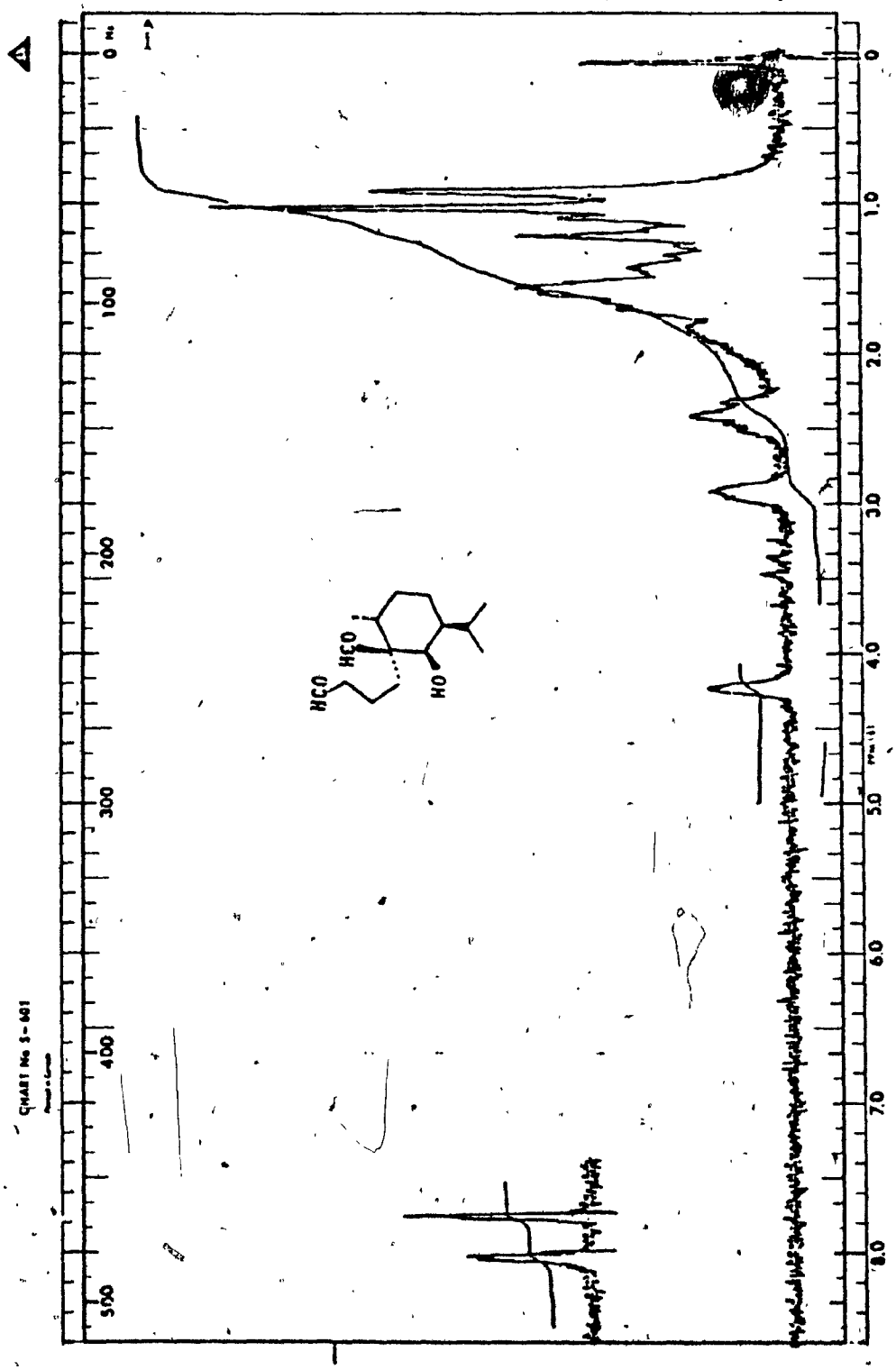
NMR Spectrum No 7



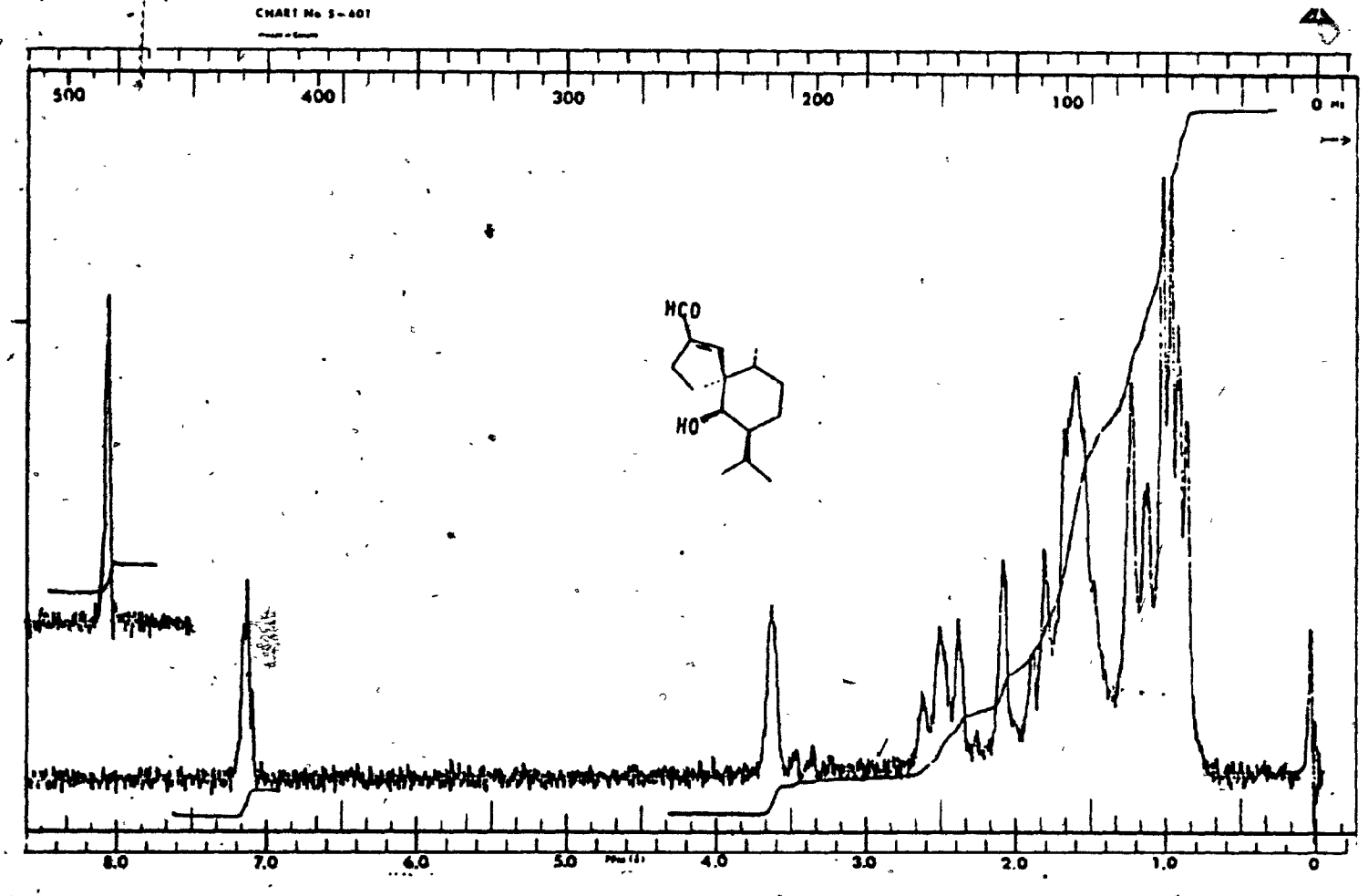
NMR Spectrum No 8



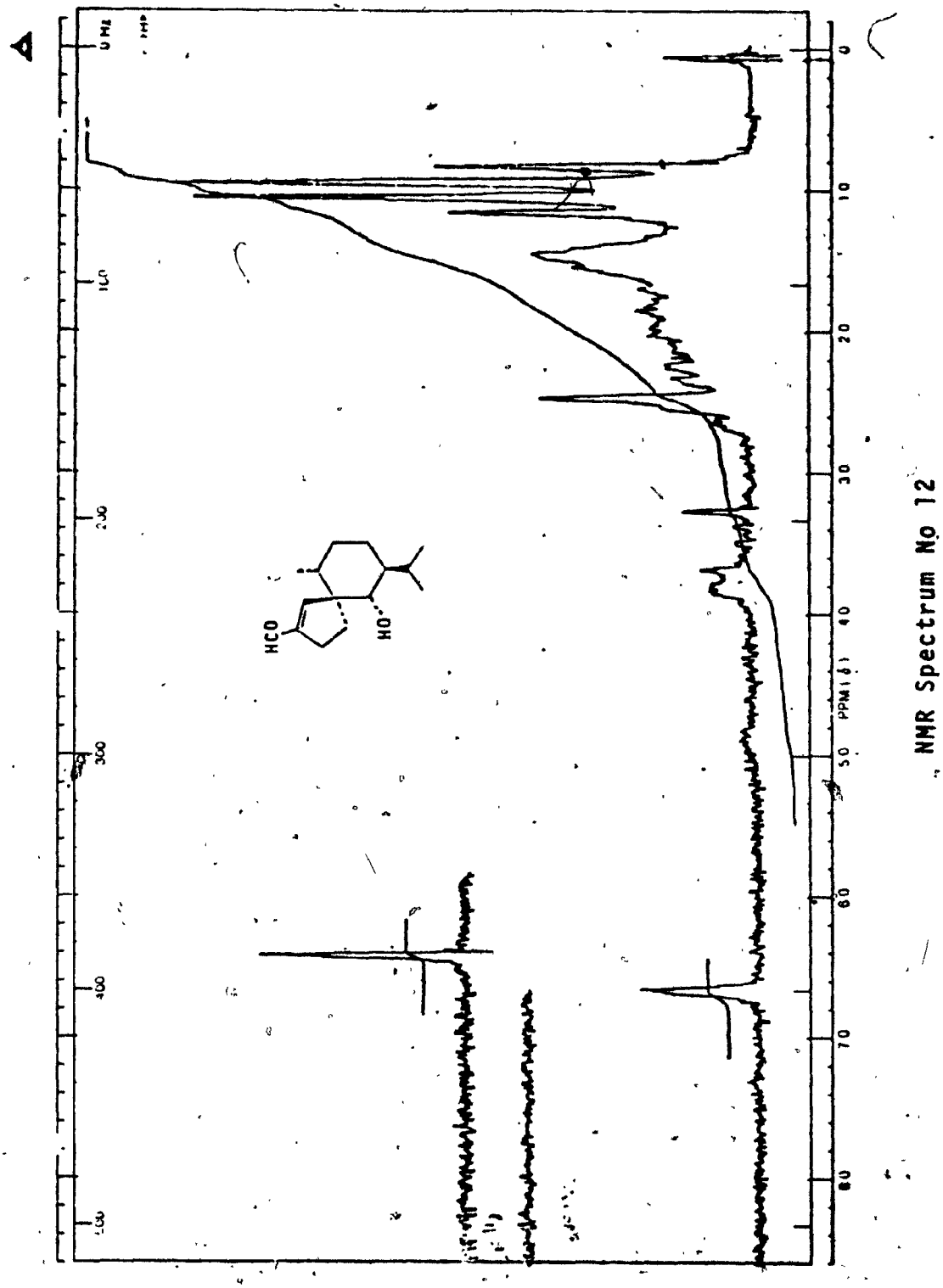
NMR Spectrum No 9



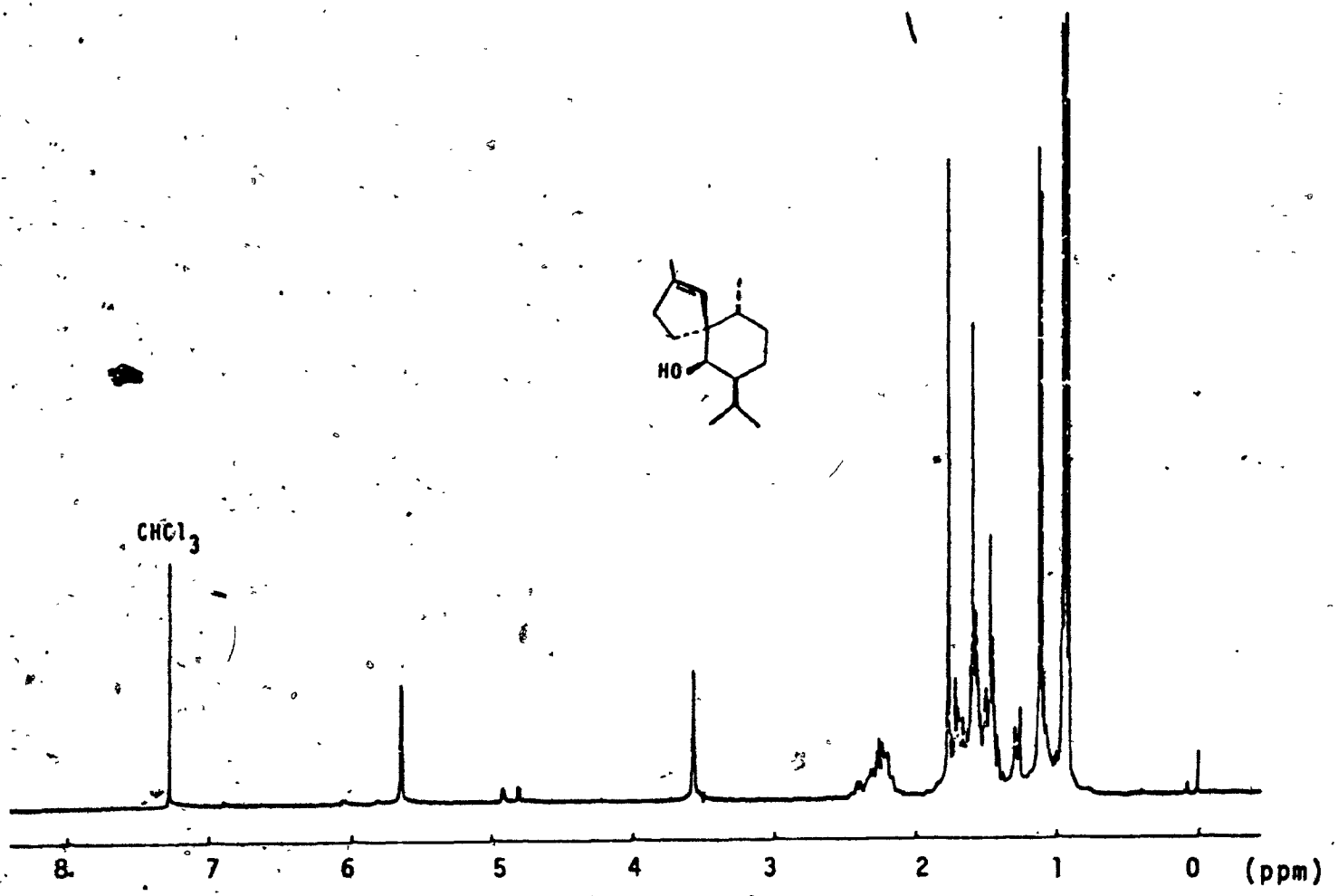
NMR Spectrum No 10



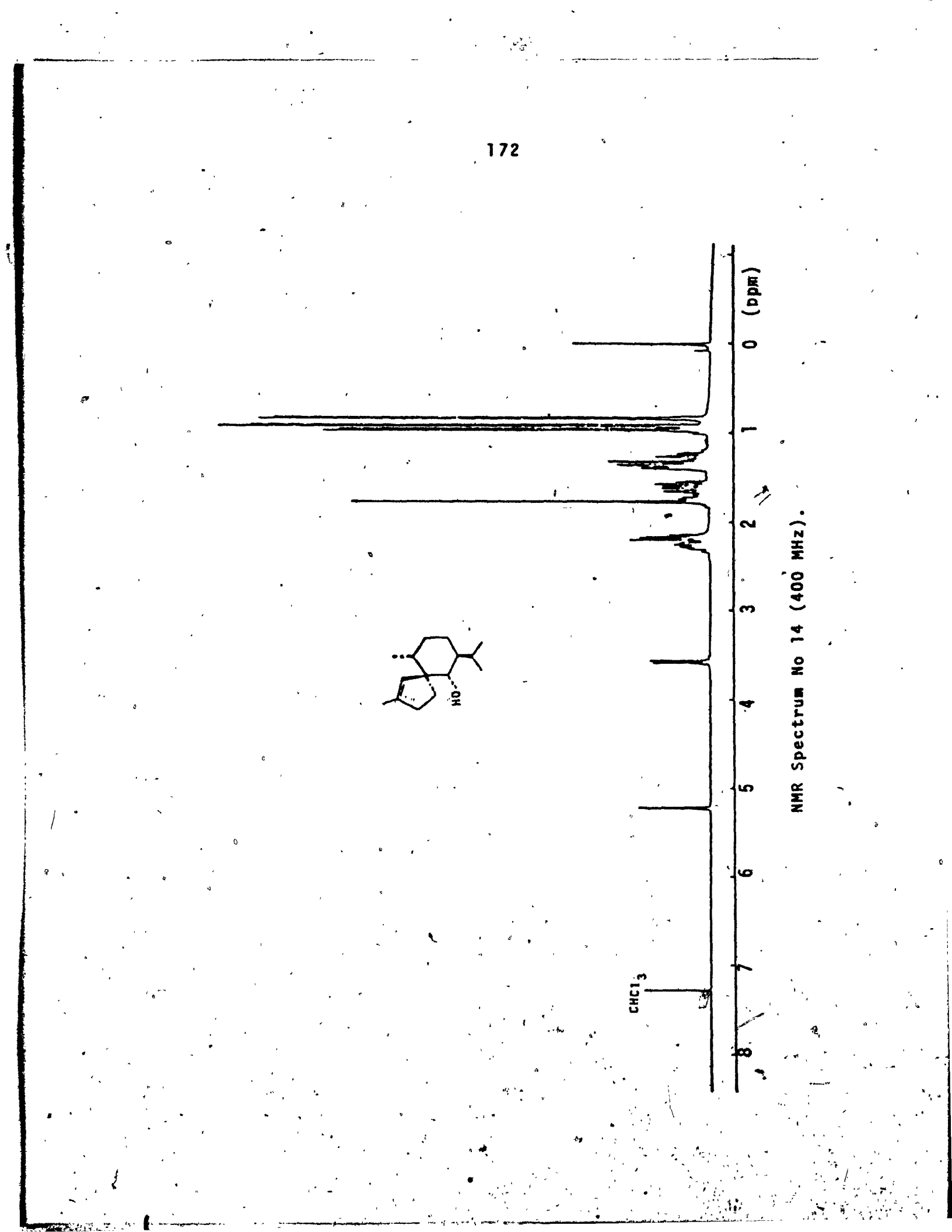
NMR Spectrum No 11



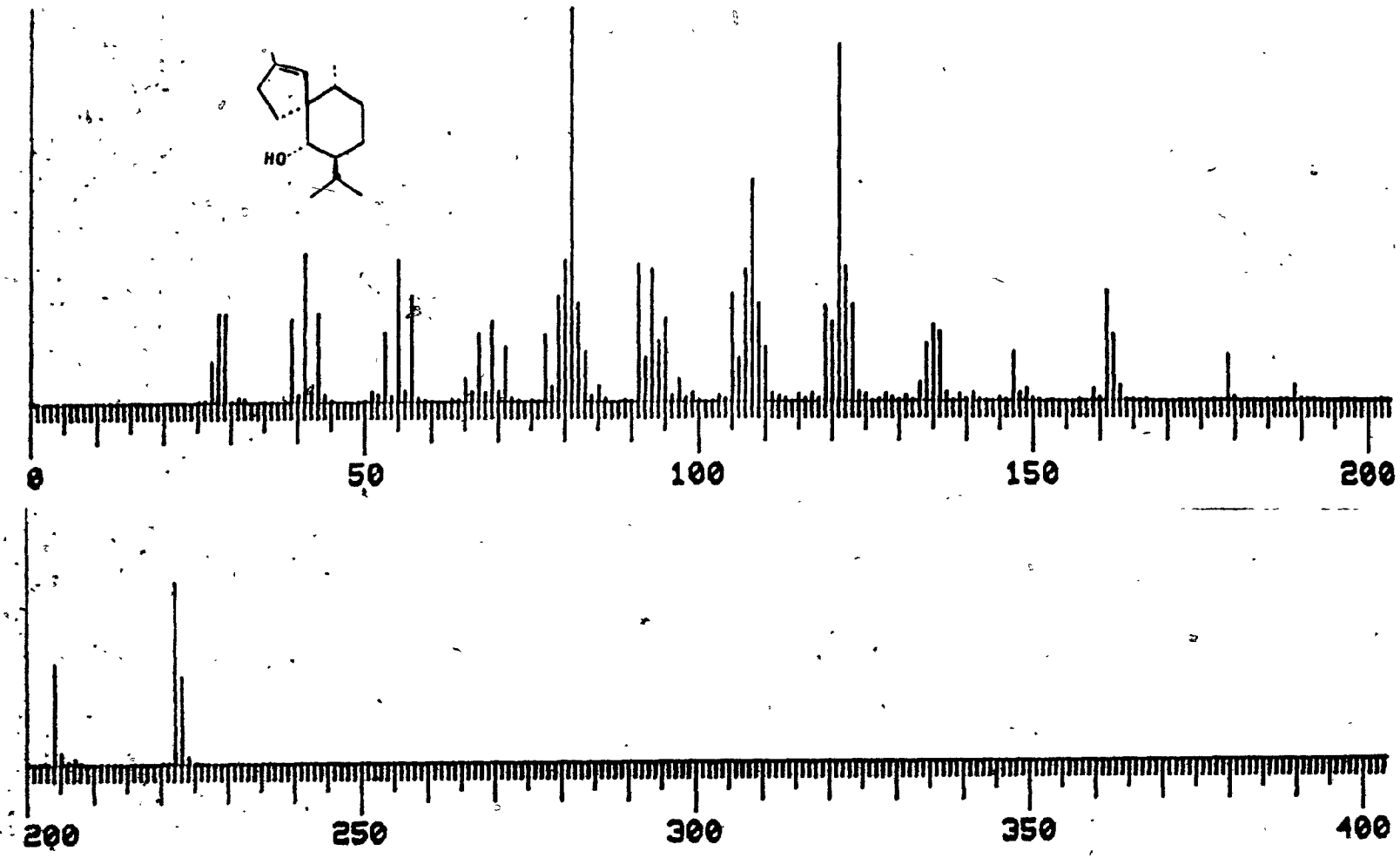
NMR Spectrum No 12



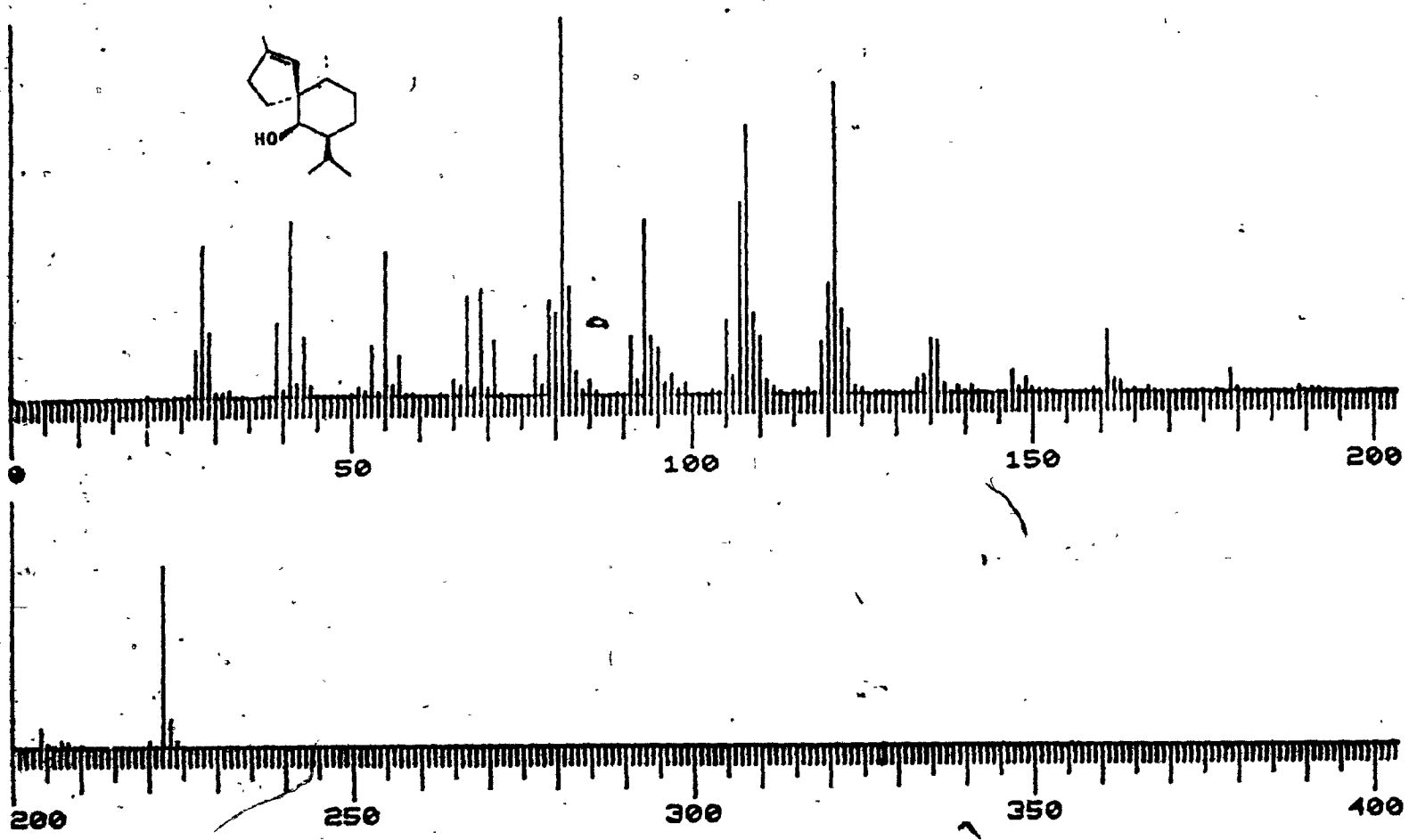
NMR Spectrum No 13 (400 MHz).



NMR Spectrum No 14 (400 MHz).



Mass Spectrum No 1



Mass Spectrum No 2

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