ABSTRACT

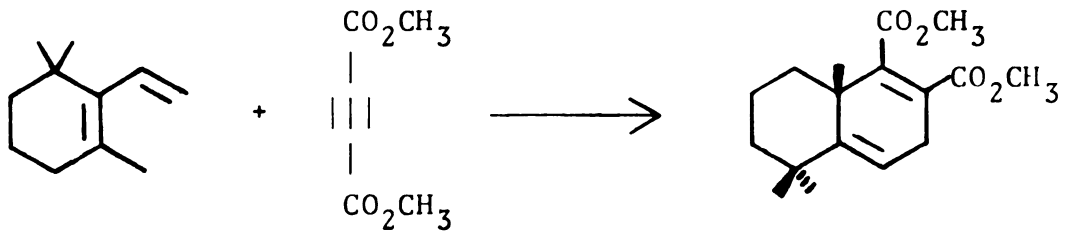
A SYNTHETIC APPROACH TO NONIRESIN-TYPE BICYCLOFARNESOL SESQUITERPENES

By

John C. Loperfido

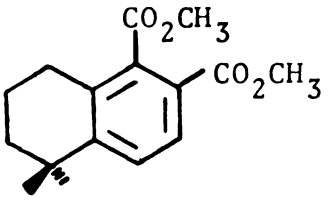
A generally useful route for the synthesis of noniresin-type bicyclofarnesol sesquiterpenes has been investigated.

A facile preparation of 1-vinyl-2,6,6-trimethylcyclohexene (1) has been developed and subsequent reaction of this diene with dimethyl acetylenedicarboxylate effected an efficient synthesis of the key intermediate, dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (3).



1 2 3

Pyrolysis of this angularly substituted dienediester quantitatively generated the aromatic diester 4.



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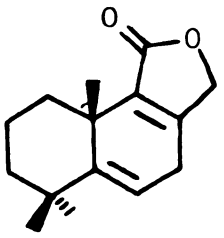
A low temperature reduction of dienediester 3 with sodium bis(2-methoxyethoxy) aluminum hydride followed by treatment with aqueous base yielded 5,6-dehydroisodrimenin (5). Alternatively, reduction with the same reagent in refluxing benzene gave a bis-allylic diol which, on oxidation with silver carbonate, was transformed into 5,6-dehydro-confertifolin (6). Refluxing the diene diacid derived from the saponification of 3 in acetic anhydride gave 5,6-dehydro-winterin (7).



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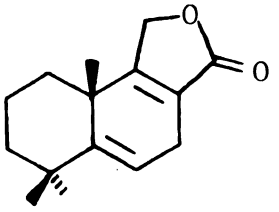

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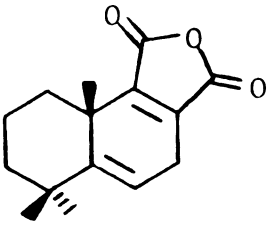
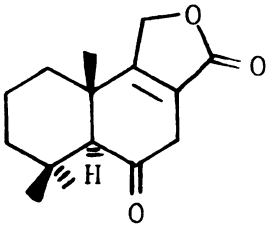


7

The exocyclic double bond of 3 proved difficult to isomerize, but was selectively attacked by electrophilic reagents such as *m*-chloroperbenzoic acid and diborane. Forcing conditions were necessary for the latter reaction.

Potentially useful routes to fragrolide (8) and cinnamosmolide (9) have been proposed and studied.



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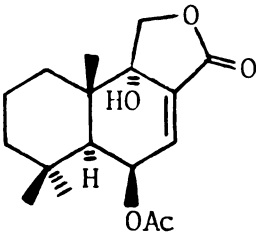

9

A SYNTHETIC APPROACH TO NONIRESIN-TYPE BICYCLOFARNESOL SESQUITERPENES

By

John Charles Loperfido

A THESIS

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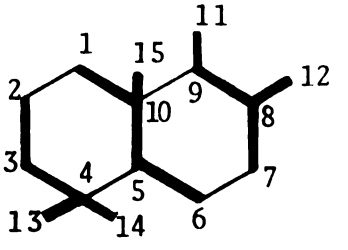
INTRODUCTION

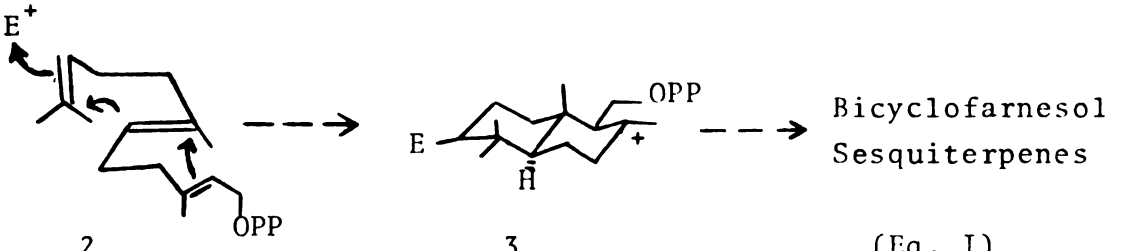
Sesquiterpenes are naturally occurring 15-carbon compounds formally derived from three isoprene units. The skeletal arrangements of these compounds vary from acyclic to tetracyclic and have been generally categorized into approximately forty different classes.[1] Until relatively recently, however, sesquiterpenes possessing the bicyclofarnesol skeleton (1) were unknown.



1

The rarity of sesquiterpenes of the bicyclofarnesol class is somewhat surprising since virtually all of the cyclic di- and triterpenes and, in demethylated form, the steroids have the same skeletal features in their A and B rings. Accordingly, it might have been expected that a biogenetic cyclization of farnesylpyrophosphate (2) would have generated the bicyclofarnesol skeleton. Such a transformation would formally involve an electrophile

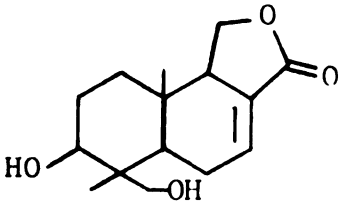
initiated transanti-parallel cyclization (Equation I). The fact that none of these compounds had been discovered prior



2 3 (Eq. I)

to Ruzicka's 1953 review on the biogenesis of terpenes[2] prompted his suggestion that "this appears to indicate that the biogenesis of steroids, diterpenes and triterpenes differs in some fundamental detail from that of the monoterpenes and sesquiterpenes." Shortly thereafter, however, the "missing link" was found.

In 1954 Djerassi and his colleagues isolated a tricyclic sesquiterpene, iresin, from the Mexican plant *Iresine celosioides*.[3,4] That iresin had structure 4 or 5 was deduced



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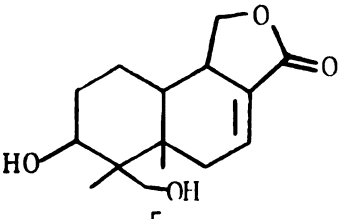
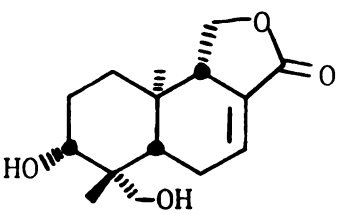


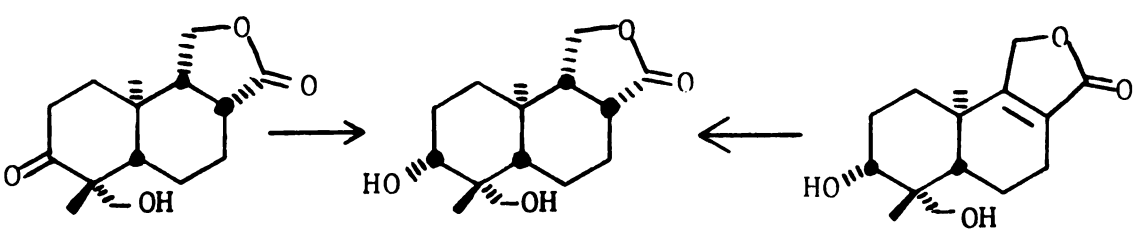
5

from spectroscopic and conventional degradative investigations including dehydrogenation, hydrogenation and ozonolysis.[5] Subsequent bromination-dehydrobromination experiments[6,7] confirmed 4 as the correct structure and this result was

corroborated by the X-ray studies of Rossmann and Lipscomb.[8,9] However, there still existed some doubt as to whether iresin was a biogenetically derived substance or whether it originated from the degradation of di- or triterpenes. This question was resolved by optical rotary dispersion studies,[6,7] which demonstrated that iresin had an absolute configuration (6) antipodal to that normally found in terpenoids or steroids.



IRESIN
6

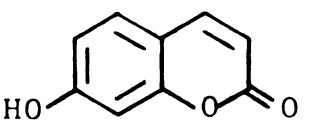


DIHYDROIRESONE 7 | DIHYDROIRESIN 8 | ISOIRESIN 9

A closer examination of the extract from which iresin had been obtained resulted in the isolation of three additional sesquiterpenes of the bicyclofarnesol class.[10] The structures and absolute configurations of these compounds, 7, 8, and 9, were deduced by relating them to iresin through

dihydroiresin (8).

Two additional bicyclofarnesol derivatives which have the atypical 5β,10α stereochemistry characteristic of the iresin group have been reported. The first, farnesiferol A, was isolated from the resin of *Asa foetida* by Jeger *et al.* in 1958.[11] Acid hydrolysis of farnesiferol A gave umbelliferone (10) and a sesquiterpene residue, which degradative studies demonstrated to be the enediol 11. The ketoester 12 derived from 11 was neither identical nor enantiomeric



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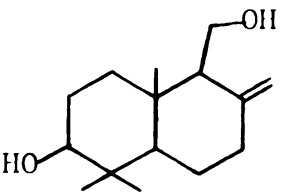
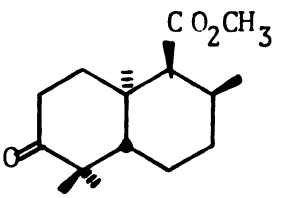


11

with ketoester 13, obtained from the degradation of oleanic acid. However, 12 was further degraded to the dione 14 which



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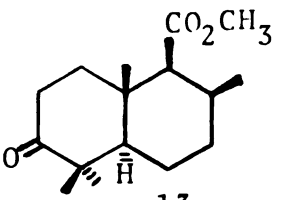
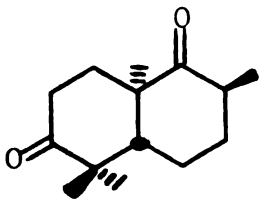


13

was shown by rotary dispersion to be antipodal to the dione (15) derived from α-amyrin. Since oxidation-reduction studies



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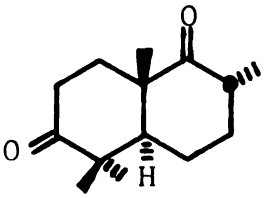
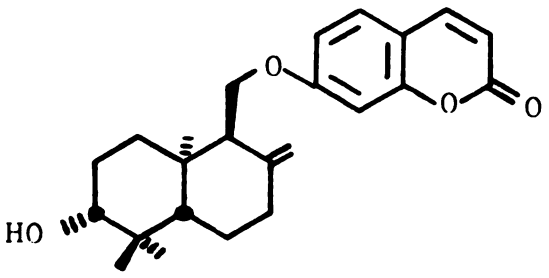


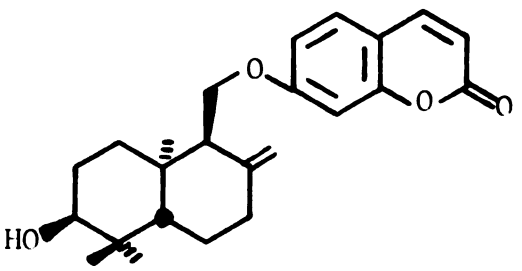
15

indicated an equatorial 3-hydroxyl group, the structure and absolute configuration of farnesiferol A was deduced to be 16. The corresponding 3β-hydroxy compound, gummosine (17), was discovered in 1966[12] in extracts of the roots of *Ferula gummosa*, *F. pseudo-oreoselinum* and *F. samarkandica*.



FARNESIFEROL A

16

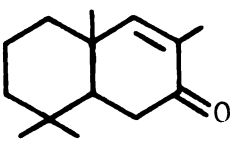


GUMMOSINE

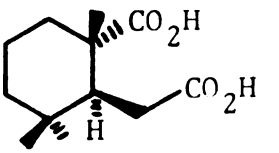
17

The first bicyclofarnesol sesquiterpene identified as having a 5α,10β ring junction was drimenol. Although its isolation from the bark of *Drimys winteri* was accomplished in 1948 by Appel and coworkers,[13] the structure and absolute configuration of drimenol was not deduced until 1959.[14] To this end, chromium trioxide oxidation of drimenol gave the enone 18, which was converted by ozonolysis into drimic acid

(19). This diacid proved identical with the diacid obtained from the degradation of onocerin and abietic acid.

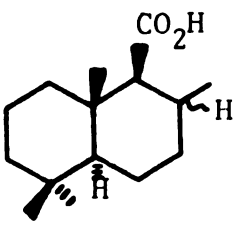


18



19

Furthermore, when drimenol was first hydrogenated and then oxidized by chromium trioxide, drimanic acid (20) identical with a monoacid derived from ambrein and oleanolic acid was obtained. Thus the structure and absolute configuration of drimenol is as formulated in 21.



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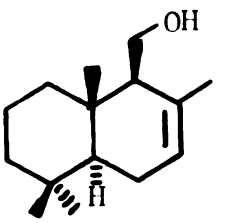
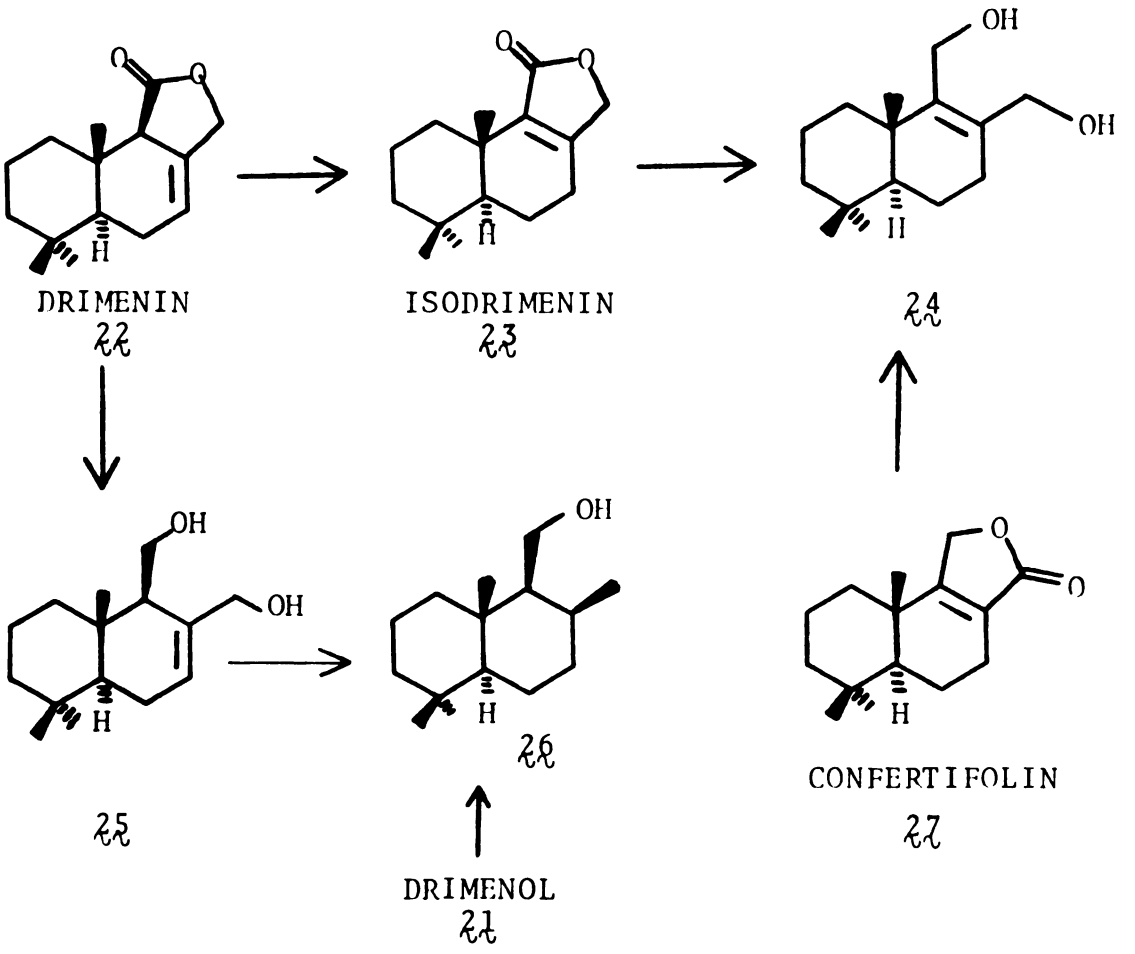


DRIMENOL

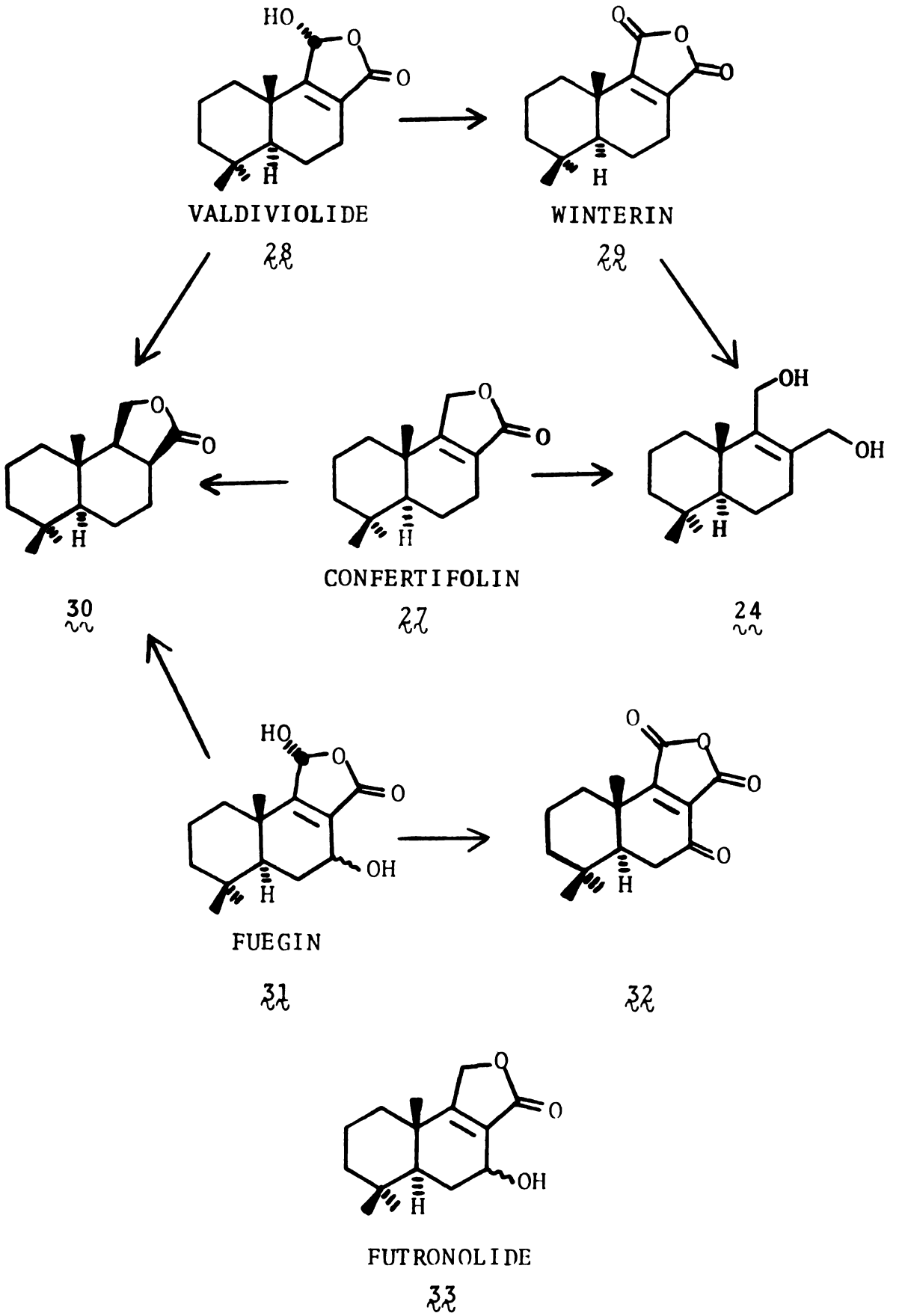
21

After drimenol had been characterized, Appel and his colleagues continued to investigate extracts from the bark of *D. winteri* in search of other bicyclofarnesol sesquiterpenes. Their efforts led to the discovery of the three lactones, drimenin (22), isodrimenin (23) and confertifolin (27).[15]



The latter compound was also isolated, in much lower yield, from *D. confertifolia*.[16] The structures and absolute configurations of these isomeric lactones were determined by relating them to drimenol.

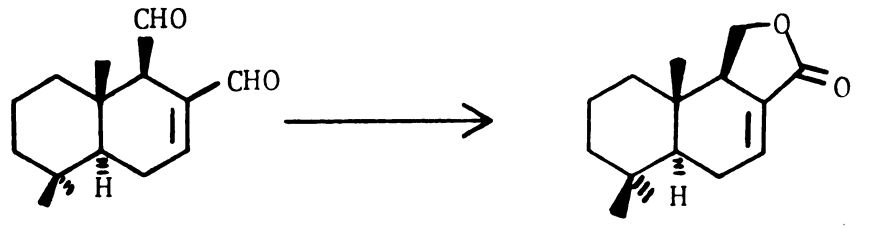
The same authors, working with extracts of *D. winteri* from different regions of Chile, succeeded in isolating four additional bicyclofarnesol derivatives.[17] Three of these compounds, valdiviolide (28), winterin (29), and fuegin (31) were characterized by relating them to confertifolin (27). An insufficient amount of sample precluded a rigorous assignment of the 7-hydroxyl stereochemistry of fuegin (31).


HO
O
O
H
VALDIVIOLIDE
28
O
O
O
H
WINTERIN
29
O
O
H
30
O
O
H
CONFERTIFOLIN
27
OH
OH
H
24
HO
O
O
OH
H
FUEGIN
31
O
O
O
O
H
32
O
O
OH
H
FUTRONOLIDE
33

The fourth compound, futronolide, of which only five milligrams was obtained, was assigned the tentative structure 33 on the basis of spectroscopic evidence. These natural products together with those already discussed constitute an impressive array of oxygenation patterns on C-11 and C-12 of the bicyclofarnesol skeleton.

In 1962 a sesquiterpene possessing yet another oxygenation pattern at C-11 and C-12 of the bicyclofarnesol skeleton was found by Barnes and Loder.[18] Thus, the first sesquiterpene dialdehyde, polygodial, was isolated from the widely distributed plant *Polygonum hydropiper*. Subsequently, the same dialdehyde was found in fresh leaves of the Australian shrub *Drimys lanceolata*.[19] The structure and absolute configuration of polygodial (34) was determined by relating it to confertifolin (27) via *cis*-dihydroconfertifolin (30). Compound 35, derived from an internal crossed Cannizaro reaction of polygodial, was later found to be identical with the naturally occurring sesquiterpene cinnamolide.[20,21]

Canonica and his colleagues isolated cinnamolide and five other bicyclofarnesol derivatives from the bark extracts of the Madagascan plant *Cinnamosma fragrans*.[20,21,22] The crude plant extract contained the major components cinnamolide (35), cinnamosmolide (38) and cinnamodial (36); minor components bemarivolide (42), bemadienolide (44), and fragrolide (39); and trace amounts of other structurally related compounds. The structures and absolute configurations

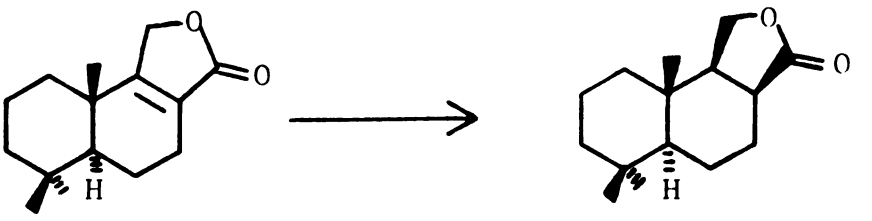


POLYGODIAL

34

CINNAMOLIDE

35



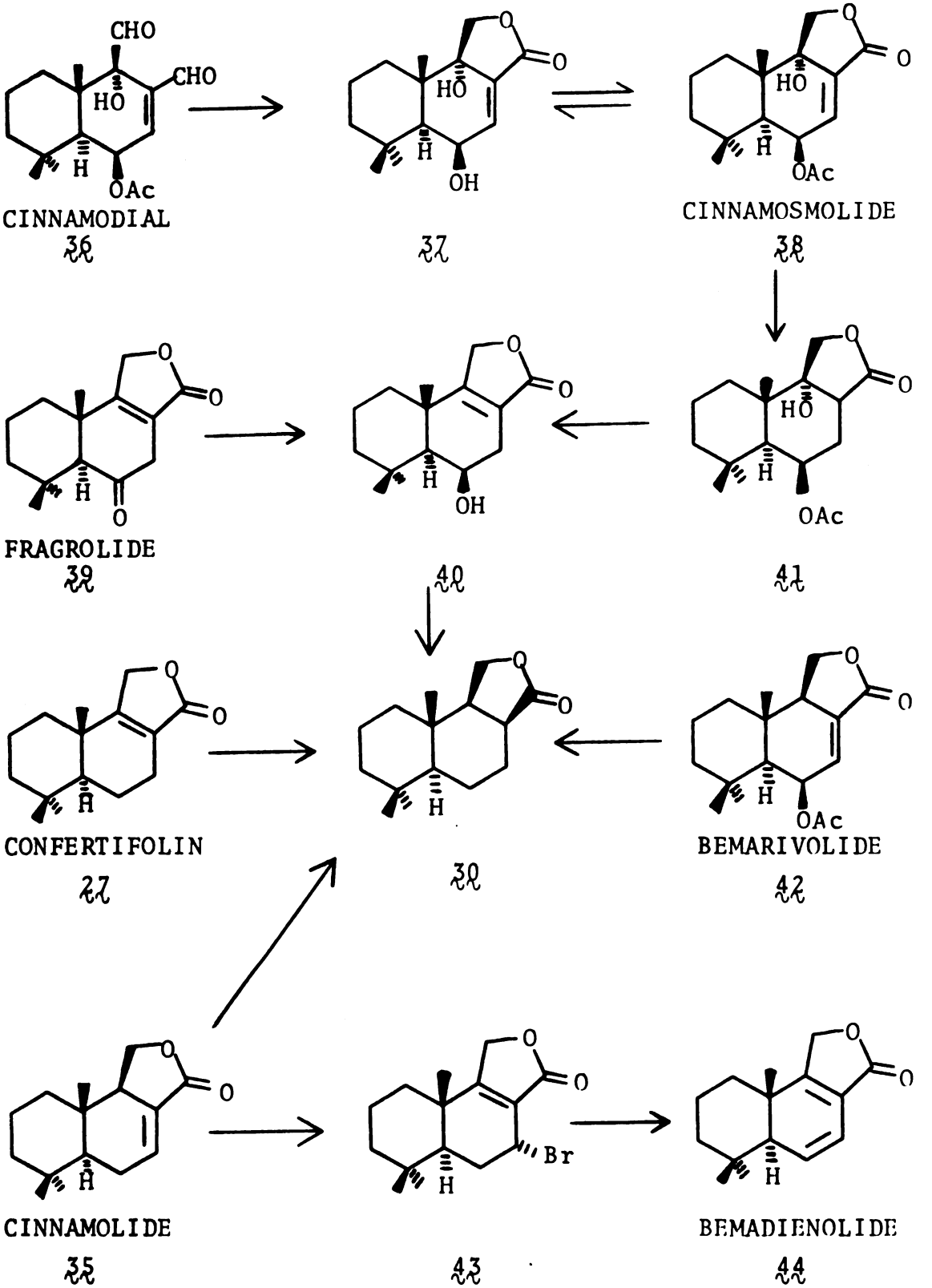
CONFERTIFOLIN

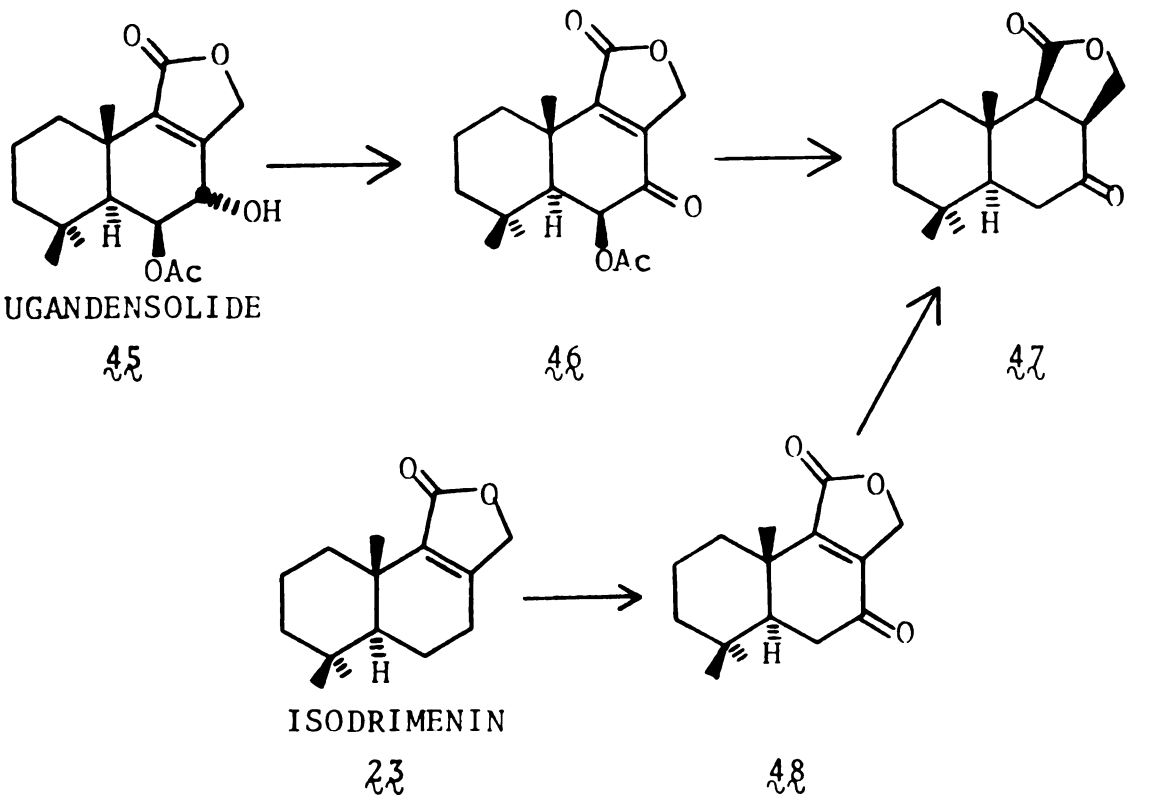
27

30

of the major and minor components were determined through conventional degradative studies and by relating them to confertifolin (27).

Cinnamodial (36) has also been isolated along with ugandensolide (45), the most recently discovered bicyclofarnesol sesquiterpene, from the heartwood of *Warburgia ugandensis*.[23] The latter compound was characterized by chemical degradation and by relating it to isodrimenin (23) through *cis*-dihydrooxoisodrimenin (47).

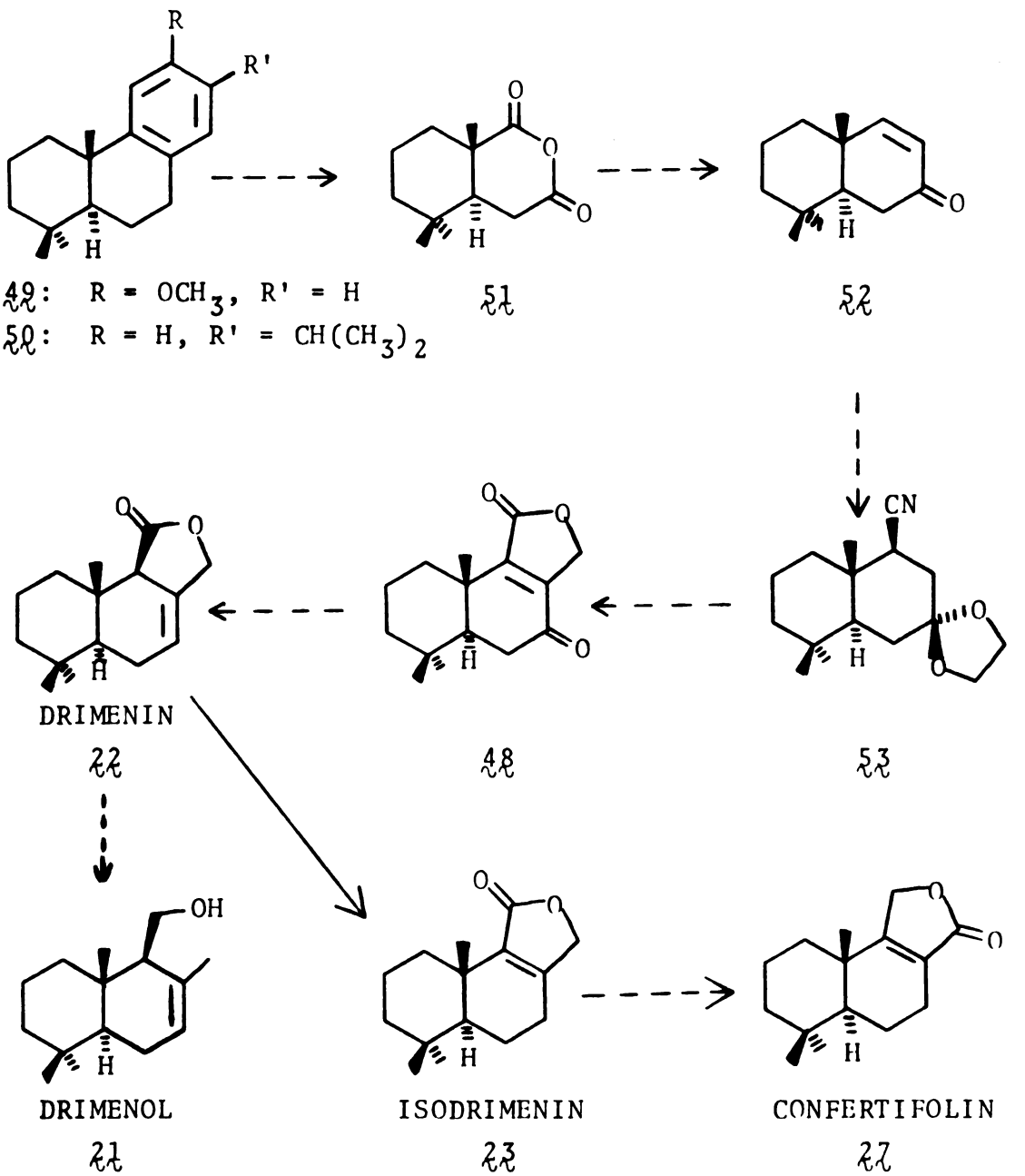

CHO
CHO
HO
H
OAc
CINNAMODIAL
36
HO
H
OH
37
HO
H
OAc
CINNAMOSMOLIDE
38
H
O
FRAGROLIDE
39
H
OH
40
HO
H
OAc
41
H
CONFERTIFOLIN
27
H
39
H
OAc
BEMARIVOLIDE
42
H
CINNAMOLIDE
35
H
Br
43
H
BEMADIENOLIDE
44



The preceding discussion summarizes the isolation and characterization of the twenty-two known bicyclofarnesol sesquiterpenes. Although these compounds are very important to the theory of terpene biogenesis, little else is known of their potential usefulness. This is primarily due to the limited amount of material available for study. Hence, any extensive investigation into the properties of these compounds is dependent on the development of procedures for their synthesis. Unfortunately, few research groups have thus far published work concerned with the synthesis of bicyclofarnesol sesquiterpenes.

In 1964 Wenkert and Strike reported a synthesis of four drimanic sesquiterpenes from O-methylpodocarpane (49) and

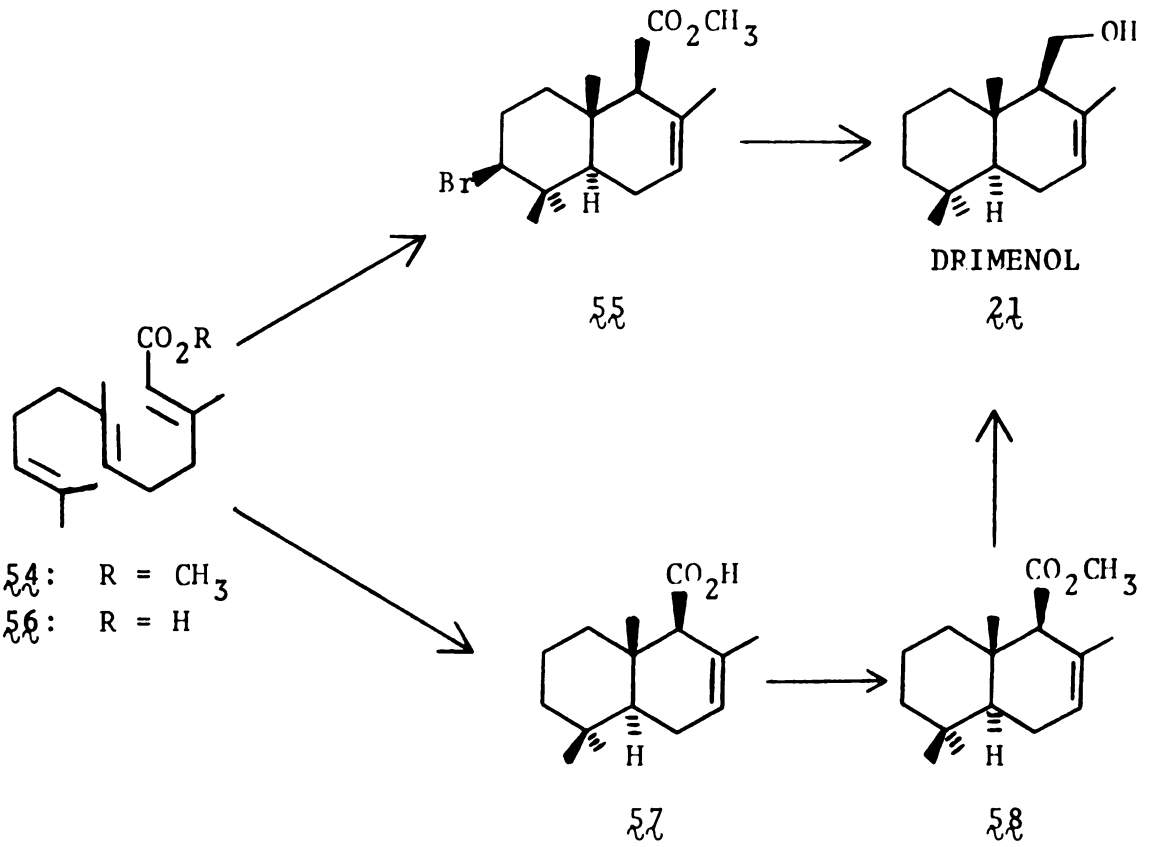
dehydroabietane (50).[24] These resin acid derivatives were chosen as the starting material because of their structural similarity to the sesquiterpenes and because of the principal author's successful completion of total syntheses of podocarpic and abietic acids.[25]



Resin acid derivatives 49 and 50 were oxidatively degraded to drimic anhydride (51). Treatment of this anhydride with dimethyl cadmium formed a mixture of acetyl acids possessing the additional carbon atom necessary to form carbocyclic ring B. The mixture of acetyl esters prepared from the corresponding acids was cyclized and transformed into enone 52. Hydrocyanation of 52 stereospecifically introduced an axial cyano group, which was then isomerized to the desired equatorial cyanoketal 53. Hydrolysis and formylation of 53 followed by cyclization and dehydration of the resulting ketoaldehydo acid effected transformation to the butenolide, oxoisodrimenin (48). Stepwise reduction of the enone system of 48 gave a saturated alcohol which was eliminated via the tosylate to yield drimenin (22). Drimenin was then isomerized to isodrimenin (23), from which confertifolin (27) could be prepared, or reduced to drimenol (21). This synthesis of drimenol from the resin acid derivatives 49 and 50 required twenty-four steps.

Drimenol has also been synthesized in low yield by a short biogenetic-type reaction sequence devised by van Tamelin and Hessler.[26] Cyclization of methyl farnesate (54) by N-bromosuccinimide in tetrahydrofuran gave the bromoester 55, which was reduced to afford a one percent overall yield of drimenol (21).

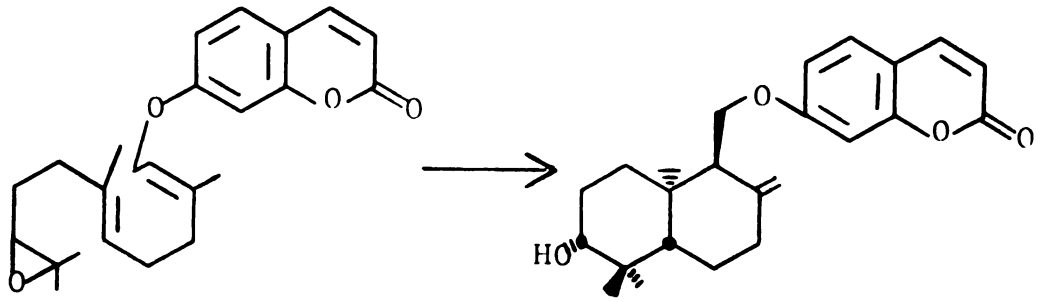
In an earlier study, Schinz and coworkers[27,28,29,30] reacted methyl farnesate (54) with sulfuric acid in formic acid, obtaining a twenty percent yield of drimenic acid (57).



Subsequent esterification and reduction gave a respectable yield of drimenol (21). Stork improved this yield still further by cyclizing farnesic acid (56) with boron trifluoride etherate to form drimenic acid (57) in thirty-five percent yield.[30,31]

Using a similar approach, van Tamelen and Coates have synthesized farnesiferol A (16)[32] by cyclization of *cis*-umbelliprenin terminal epoxide (59) with boron trifluoride

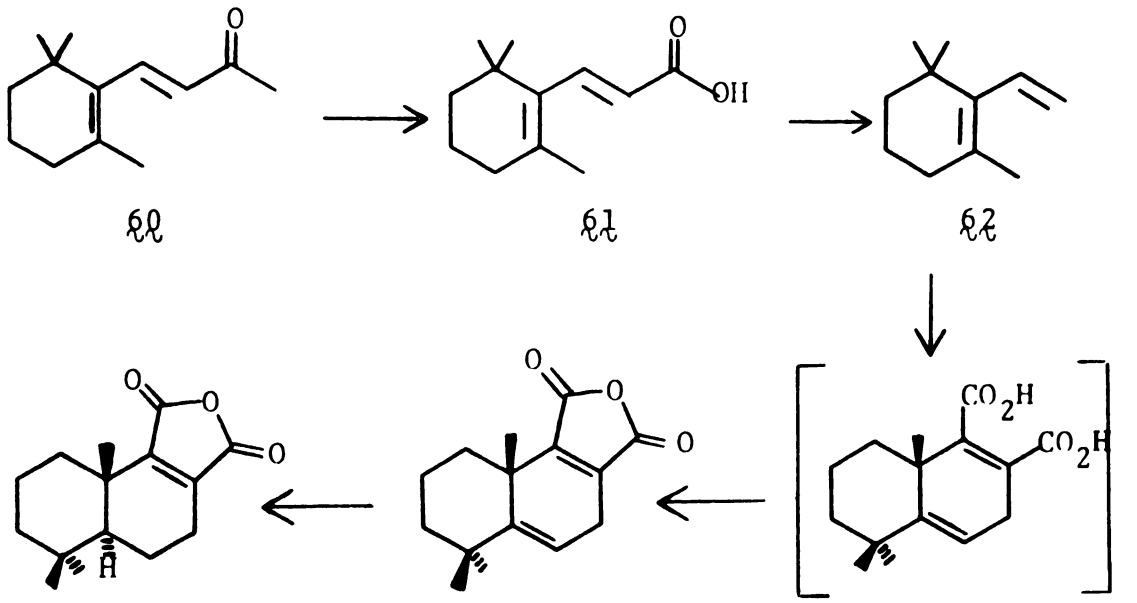
etherate in benzene. A two percent yield of 16 was obtained.



FARNESIFEROL A

59 16

The first synthetic scheme of reasonable length intended as a generally useful route to bicyclofarnesol sesquiterpenes and diterpenes was reported by Brieger in 1965.[33] The approach is illustrated by the following six step synthesis of winterin (29). Unfortunately, the key reaction



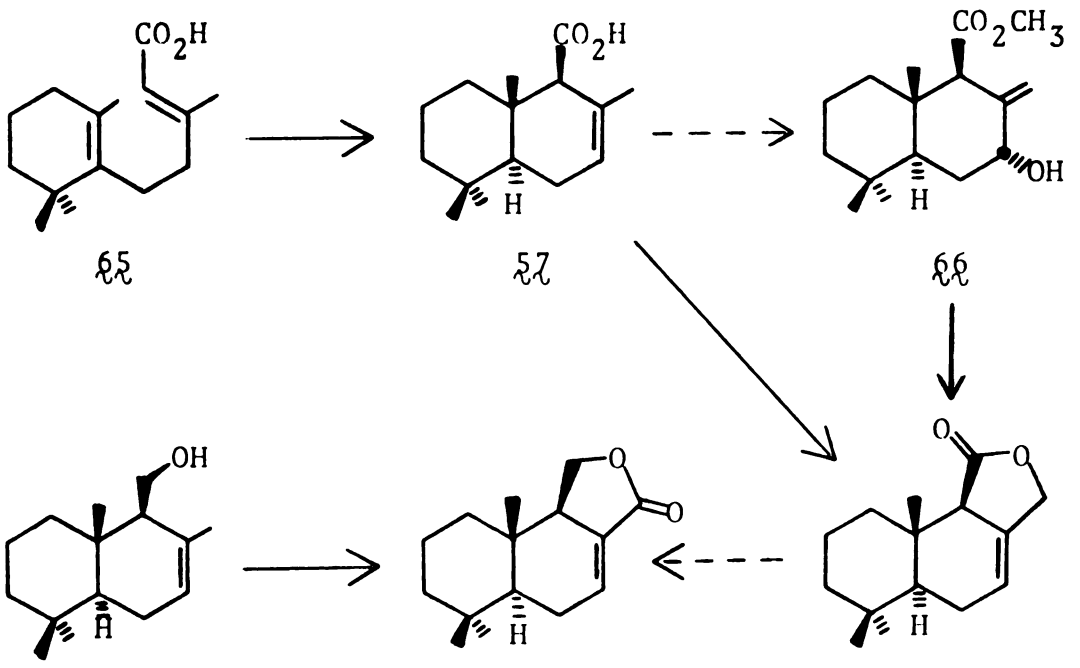
WINTERIN

29 64 63

of the sequence, a Diels-Alder reaction between the diene 62 and acetylenedicarboxylic acid, only gave a four percent yield of the desired adduct 64. Thus, in spite of the brevity of the scheme employed, less than a one percent overall yield of winterin was realized.

The most recent investigations into the synthesis of bicyclofarnesol sesquiterpenes have come from the laboratories of Kitahara, where syntheses of drimenin,[34,35,37] cinnamolide[36,37] and polygodial[37] have been reported during the last two years. The Japanese workers reinvestigated the cyclization of β-dehydroionylideneacetic acid (65) and were able to prepare drimenic acid (57) in sixty-five percent yield, using stannic chloride as a catalyst. Previously, Caliezi and Schinz[29] used sulfuric acid in formic acid while Stork[31] used boron trifluoride etherate in benzene to effect the same transformation in yields of twenty and thirty-five percent respectively. Esterification and photooxidation gave enol ester 66, which underwent an allylic alcohol rearrangement in sulfuric acid to give a good yield of drimenin (22). The reduction of drimenin to the corresponding diol, followed by allylic oxidation gave cinnamolide (35).

Alternatively, drimenin (22) and cinnamolide (35) were synthesized in one step from drimenic acid (57) and drimenol (21), respectively, by the action of palladium chloride. The reactions were designed to mimic enzymatic oxidation of the C-12 methyl group, which is believed to proceed through a π-complex. A ten percent yield was realized in each case.



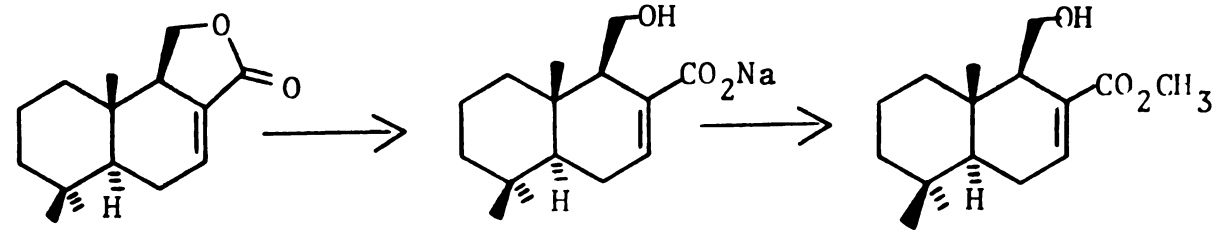
65 57 66

DRIMENOL CINNAMOLIDE DRIMENIN

21 35 22

Finally, cinnamolide (35) was transformed into polygodial (34). Saponification of cinnamolide and treatment of the salt of the resulting hydroxy acid (67) with diazomethane gave hydroxyester 68. Chromium trioxide oxidation of the alcohol and protection of the resulting aldehyde as a dimethyl ketal gave 69, which was subsequently reduced to the ketal aldehyde 70. Deketalization gave polygodial (34).

It is evident from the preceding discussion that there does not exist a generally useful route for the synthesis of bicyclofarnesol sesquiterpenes in high yield. The purpose of this investigation was to develop such a route, and using it, to synthesize cinnamosmolide (38), among the structurally most complex of these derivatives. The reasons for choosing

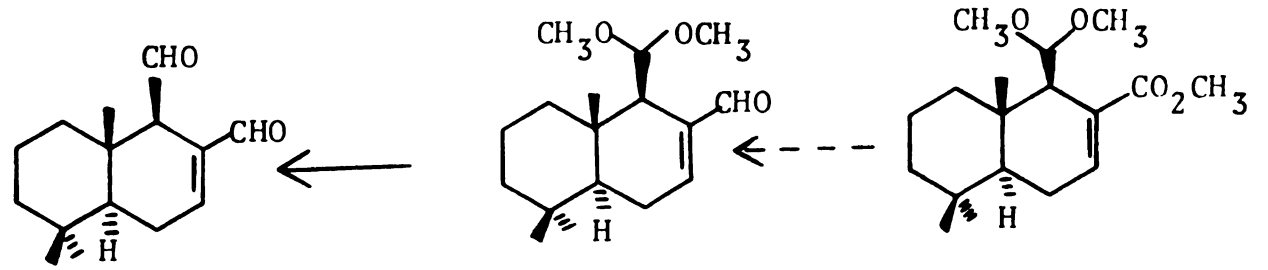


CINNAMOLIDE

35

67

68

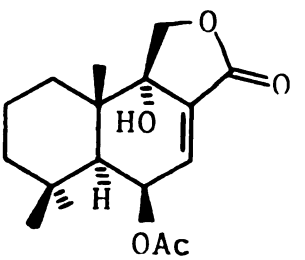


POLYGODIAL

34

70

69



CINNAMOSMOLIDE

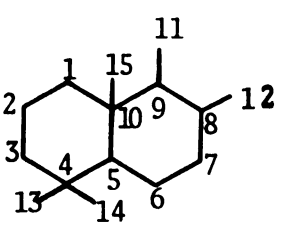
38

cinnamosmolide as the specific target molecule were twofold. First of all, a synthesis of cinnamosmolide constitutes the synthesis of bemadienolide, bemarivolide, cinnamodial, fragrolide, valdiviolide and winterin, since the former has been degraded to each of these compounds, either directly or indirectly, during the course of structure elucidation work. Secondly, in synthesizing the structurally most complex member of a group, intermediates are generated which are often identical with or permit the facile synthesis of less complex derivatives.

RESULTS AND DISCUSSION

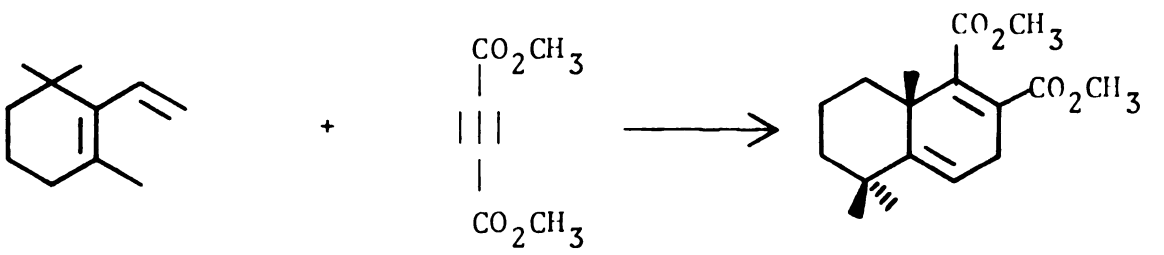
A general synthetic approach to a group of structurally related compounds should provide for the generation of variations in functionality and stereochemistry. This is often accomplished by developing an efficient synthetic route to a key compound, from which each of the specific compounds of the group can be derived. Such an intermediate usually incorporates the characteristic carbon skeleton of the group and sufficient functionality to permit facile modification to any one of the desired products.

Accordingly, a key compound which would be generally useful for the synthesis of noniresin-type bicyclofarnesol sesquiterpenes should have the skeletal framework of 1. Furthermore, since these derivatives are functionalized at C-6, 7, 8, 9, 11 and 12, the same positions in the key compound must be activated by functions which can be



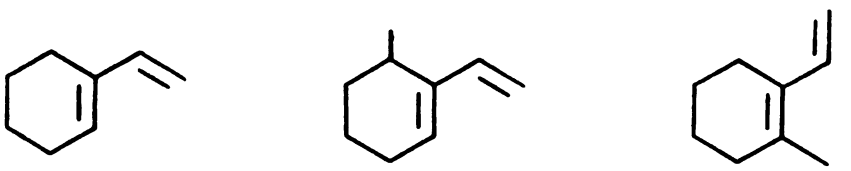
1

selectively manipulated. These requirements are satisfied by dienediester 72 which might be prepared by a Diels-Alder reaction between 1-vinyl-2,6,6-trimethylcyclohexene (62) and dimethyl acetylenedicarboxylate (71).



62 71 72

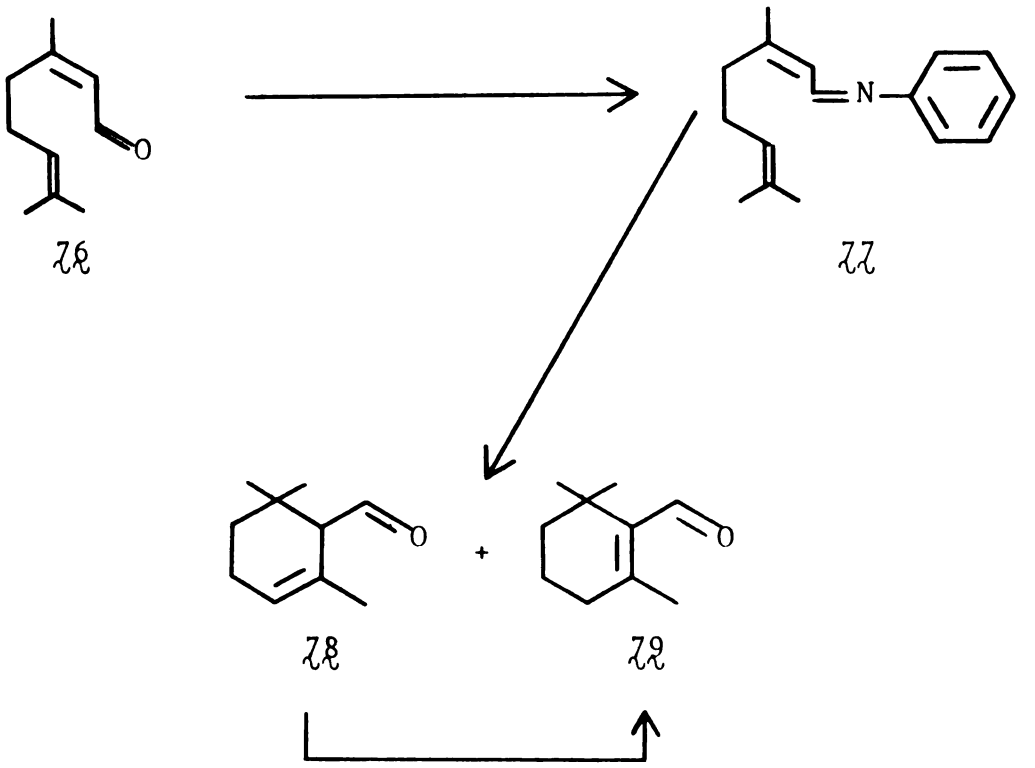
It is not immediately obvious that diene 62 should react with dienophile 71 as proposed, since the capacity of a vinylcyclene to undergo a Diels-Alder reaction is dependent upon its ability to adopt a *cis*-coplanar conformation. Thus, although 1-vinylcyclohexene (73) and 2-vinyl-3-methylcyclohexene (74) react with conventional dienophiles such as maleic anhydride and *p*-quinone, 1-vinyl-2-methylcyclohexene (75) does not.[38] The inertness of the latter diene appears to be due to steric repulsion between the vinyl and methyl substituents which hinders the adoption of a *cisoid*-conformation.



73 74 75

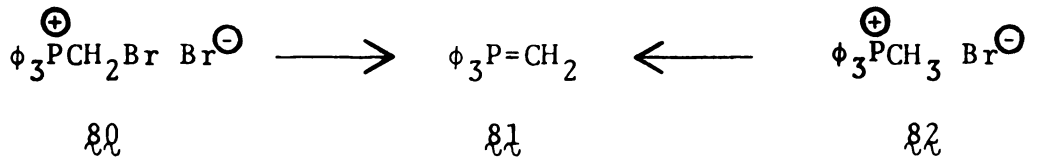
Inspection of a molecular model of 1-vinyl-2,6,6-trimethylcyclohexene (62) suggests, however, that the *cis*-conformation of this diene may be relatively more accessible than in 75, since adoption of the *trans*-conformation is severely inhibited by the geminal methyl groups. Indeed, steric crowding of both sides undoubtedly favors a nonplanar conformation. The geminal methyl groups may also hinder the attack of a dienophile. However, to the extent that the diene system is able to adopt a *cis*-coplanar conformation, diene 62 might be expected to react with a very small and powerful dienophile. Since acetylenedicarboxylic acid derivatives are dienophiles which possess these characteristics, they might be induced to react with diene 62 under forcing conditions.

On the assumption that this key reaction could be made to work, attention was directed to the synthesis of β-cyclocitral (79) from which diene 62 could be prepared by a Wittig reaction. In 1900 Tiemann reported the cyclization of the aniline Schiff base (77) of citral (75) in concentrated sulfuric acid to a mixture of α-cyclocitral (78) and β-cyclocitral (79).[39] Isomerization of enone 78 to the desired β-cyclocitral was then effected by treatment with alkali. This scheme, modified slightly by subsequent investigators,[40] remains the primary synthetic route to β-cyclocitral.

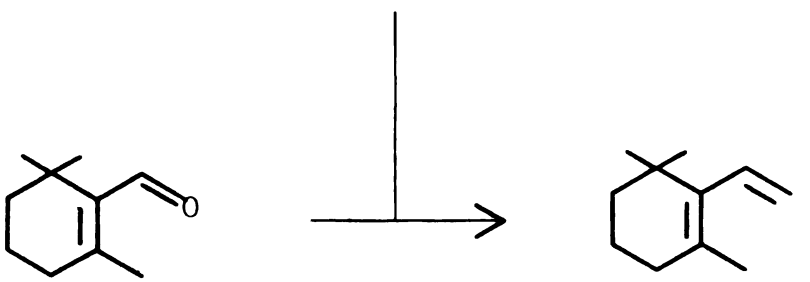


Using the procedure of Schinz and coworkers,[41] a mixture of α- and β-cyclocitral (α:β = 3:1) was prepared in forty-three percent yield. Significant amounts of resinous material and *p*-cymene (from cyclization of hydrolyzed Schiff base) were also formed in this reaction. The necessity of steam distilling the product from the reaction mixture further detracts from the large scale usefulness of this method. Isomerization of this mixture of α- and β-cyclocitral with methanolic potassium hydroxide, as proposed by Koster,[42,43,44] resulted in an eighty-one percent conversion to β-cyclocitral. Due to the hindered nature of the enone system of β-cyclocitral, it could be stored for extended periods without significant decomposition.

Kobrich *et al.* used a Wittig reaction to transform β-cyclocitral into 1-vinyl-2,6,6-trimethylcyclohexene (62).[45,46] They treated an ethereal solution of triphenylbromomethylphosphonium bromide (80) with n-butyl lithium at minus seventy degrees, and reacted the methylenetriphenylphosphorane (81) thus formed with β-cyclocitral (79) to obtain a forty percent yield of diene 62. By using Corey's dimsyl anion method[47] to generate ylid 81 from



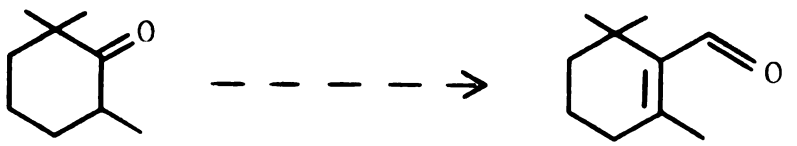
80 81 82



79 62

triphenylmethylphosphonium bromide (82), the reaction with β-cyclocitral has now been effected in a seventy percent yield. The low absorption coefficient (λ_{max} 234.5, ε max 4050; Lit.[46] λ_{max} 233, ε max 5760) of diene 62 is consistent with the *cis*-nonplanar conformations[48,49] suggested by the molecular model studies.

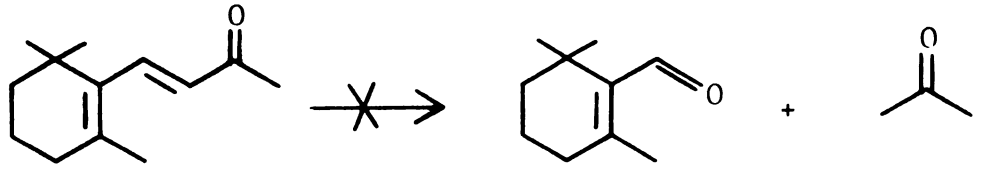
The overall yield of diene 62 from citral (twenty to twenty-five percent) was judged unacceptable for the beginning of a multi-step synthetic route. Since the major source of the low yield was due to the inefficient preparation of β-cyclocitral, efforts were directed towards improving the synthesis of this compound. Although the cyclization of citrylideneaniline (77) was improved by vigorous mixing, the arduous work-up associated with large scale runs prompted the investigation of alternate synthetic routes. Only one other procedure for the synthesis of β-cyclocitral is reported in the chemical literature. This route involves a four-step synthesis of β-cyclocitral (79) from the expensive intermediate 2,2,6-trimethylcyclohexanone (83) in an overall yield of thirty to thirty-five percent.[50] Clearly, this approach was equally undesirable.



83 79

Since β-ionone (60) is as inexpensive and readily accessible as citral (76), it was considered as an alternative source of β-cyclocitral (79). However, all efforts to effect a retroaldol fragmentation of β-ionone (60) by the action of aqueous or alcoholic base or acid

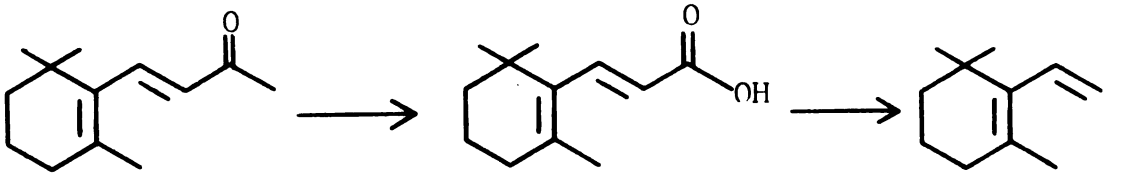
under a variety of conditions were unsuccessful. Nevertheless, these attempts did serve to focus attention



60 79 84

on β-ionone as a possible precursor to diene 62.

In order to transform β-ionone to the desired diene (62) it is necessary to remove the terminal acetyl group. This could be accomplished in a stepwise fashion by converting the acetyl function to a carboxylic acid and subsequently decarboxylating to the diene. Unknown to us at the time, G. Brieger had employed the same scheme in his synthesis of winterin.[33] He did not, however, explicitly describe the method used for the decarboxylation of diene acid 61.

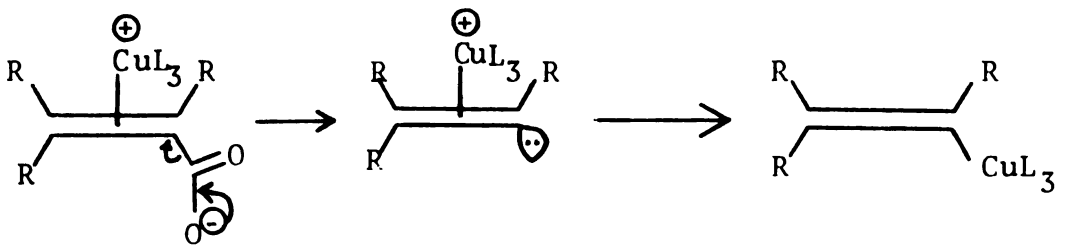


60 61 62

The procedure for the haloform reaction had been previously worked out by other investigators.[51,52,53,54] Thus addition of aqueous sodium or potassium hypochlorite to a methanolic solution of β-ionone (60) gave a seventy

percent yield of the desired acid (61). In this work Clorox, a commercially available solution of sodium hypochlorite, was found to be as effective as a freshly generated hypochlorite solution.

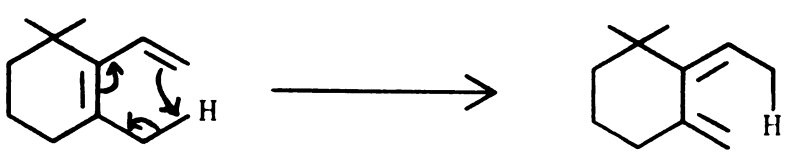
Heating diene acid 61, either neat or dissolved in triglyme, at two hundred fifty degrees gave a poor yield of 1-vinyl-2,6,6-trimethylcyclohexene. Therefore, the alternative copper/quinoline method of decarboxylating aromatic and α,β-unsaturated carboxylic acids was examined. Recent studies have demonstrated that cuprous ion is the catalytic agent in this reaction, and a mechanism has been proposed in which a π-bonded cuprous ion inductively stabilizes the negative charge developing from the loss of carbon dioxide.[55] Preliminary investigations have also



85 86 87

indicated that it is important to maintain an inert atmosphere during this reaction, since the presence of oxygen sharply decreased the cuprous ion concentration and increased that of cupric ion, the latter causing an oxidative decarboxylation.[56]

When a small amount of the diene acid 61 in quinoline was heated at two hundred degrees under nitrogen with an equivalent amount of cuprous oxide or copper chromite ($CuCr_2O_4$) a respectable yield of the desired diene was obtained. However, when the reaction was scaled up, the product was contaminated with a hydrocarbon absorbing strongly in the infrared at 890 cm^{-1} and exhibiting a complex vinyl splitting pattern in the δ 4.5 to 5.5 ppm region of the nmr spectrum. It seemed likely that this contaminant was derived from an ene reaction induced by prolonged heating of diene 62. In an attempt to minimize this reaction, the diene was distilled from the reaction mixture as it was formed



62 88

by continuously sweeping the system with nitrogen, while maintaining a pressure of four hundred to five hundred millimeters of mercury. Unfortunately, the continuous flow of gas also swept the product from the cooled receiver flask so that a very low yield of diene 62, free of contaminant, was obtained.

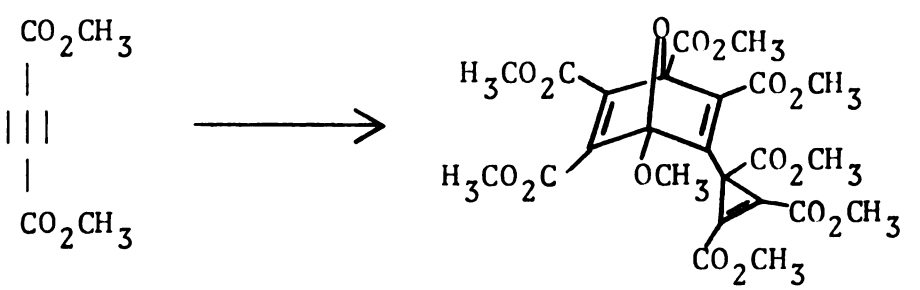
From the latter result it seemed likely that the desired diene could be generated free of contaminant on a large scale by increasing the rate of the decarboxylation

reaction or by lowering the temperature at which it is conducted so as to avoid prolonged heating of the diene. It is known that chelating agents such as 1,10-phenanthroline and 2,2'-bipyridyl will do both,[55] but they are expensive and must be used in equivalent amounts. Thus their use for large scale preparative work would not be practical. An attempt to circumvent this objection was made by using the inexpensive chelating agent, 8-hydroxyquinoline, as the reaction solvent. However, at temperature above its melting point, 8-hydroxyquinoline sublimes profusely, thus rendering it unsuitable for this purpose.

Subsequently, it was found that a ten-fold excess of cuprous oxide significantly increased the rate of decarboxylation. Accordingly, decarboxylation with excess cuprous oxide under nitrogen at two hundred degrees and atmospheric pressure, followed by distillation of the product from the reaction mixture under reduced pressure gave seventy to ninety percent yields of the unrearranged diene.

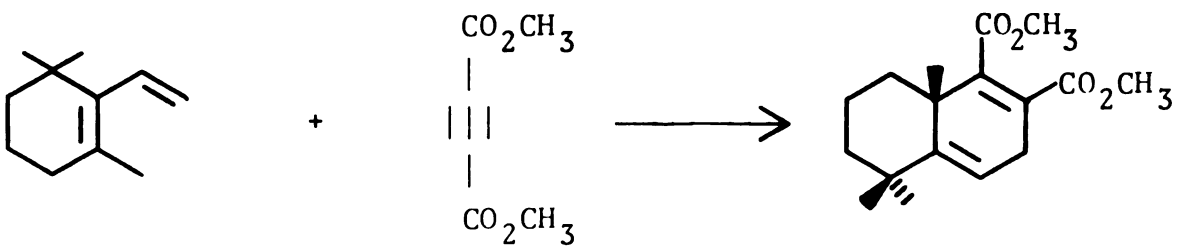
The overall yield of 1-vinyl-2,6,6-trimethylcyclohexene from β-ionone by the above procedure was fifty-five to sixty percent, significantly better than the twenty to twenty-five percent realized from the citral route. Furthermore, the labor required in the new preparation has been halved.

The convenient preparation of large quantities of diene 62 permitted studies of the key step in the synthetic scheme; *i.e.*, the Diels-Alder reaction between this diene and dimethyl acetylenedicarboxylate. Besides being a very small and powerful dienophile, the latter compound has the advantage of being a liquid. Furthermore, there is precedent for its use in reactions where conventional dienophiles fail to react.[57] On the other hand, dimethyl acetylene-dicarboxylate has the disadvantage of tetramerizing to 89 at temperatures above one hundred twenty degrees.[58]



71 89

Refluxing a benzene or toluene solution of diene 62 with a threefold excess of dimethyl acetylenedicarboxylate (71) gave less than a two percent yield of the desired adduct (72). However, if the liquid dienophile was used as the reaction solvent, adduct 72 could be obtained in sixty-nine percent yield. The vinyl region of the nmr spectrum of the distilled product exhibited a doublet of doublets (splitting = 3.0, 2.6, 3.0 Hz) and an AB quartet (splitting =

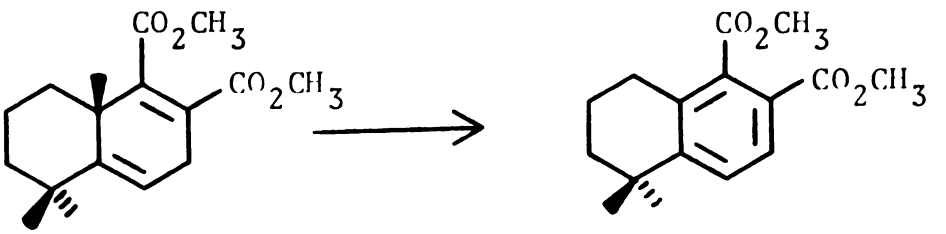


62 71 72

9.0, 13.5, 9.0 Hz) centered at δ 5.71 and 7.59 ppm respectively. Integration of this doublet of doublets showed it was generated by one hydrogen, assigned as the vinyl hydrogen of 72 split by the nonequivalent bis-allylic C-7 hydrogens. Integration of the AB quartet varied from run to run but was consistently less than two tenths of a hydrogen. This signal was therefore attributed to an impurity codistilling with dienediester 72.

Thin layer chromatography (tlc) of the distilled adduct on silica gel, Florisil, alumina (various activities), and silver nitrate impregnated alumina showed only one spot with a variety of solvent systems. However, gas liquid chromatographic (glc) fractionation with a diethylene glycol succinate column showed three peaks corresponding to a major component, a minor component (less than ten percent) and a trace of a third component. Analytical samples of the major and minor components were collected by preparative glc and respectively characterized by spectroscopic means as the

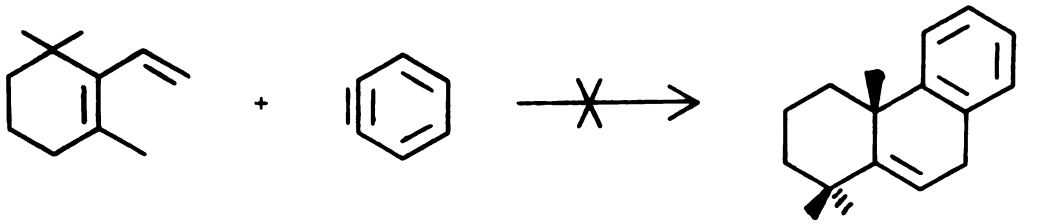
desired adduct 77 and the aromatic diester 99. The AB quartet in the distilled product proved to arise from the two aromatic hydrogens of 99.



77 99

Since the concentration of 99 increased when the product was distilled at higher temperatures, it seemed probable that it was being formed by a pyrolytic dimethylative aromatization of adduct 77. Indeed, heating 77 in triglyme at two hundred degrees gave a quantitative conversion to aromatic diester 99. This aromatic impurity could not be separated from dienediester 77 on a preparative scale, and therefore was carried along in subsequent reactions.

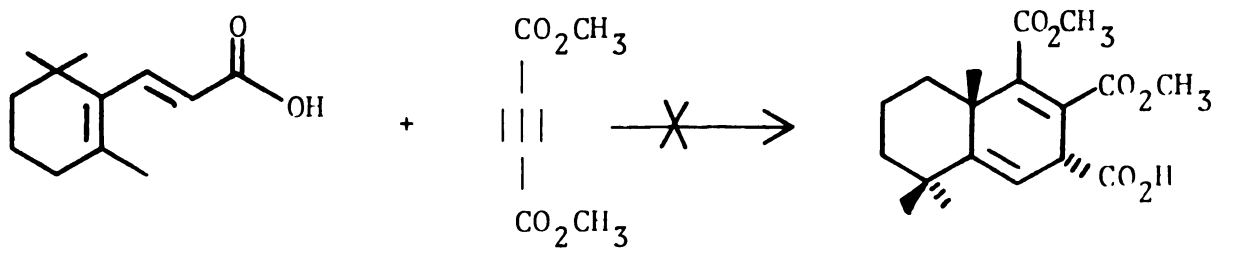
The successful reaction of diene 66 with dimethyl acetylenedicarboxylate suggested that an analogous reaction with benzyne might also work since the latter dienophile, although bulkier, is much more reactive. The adduct of this reaction would be useful for the synthesis of diterpenes. However, when benzyne (91), generated from benzenediazonium-2-carboxylate hydrochloride,[59] was reacted with an equivalent amount of diene 66 in ethylene chloride, a complex mixture of



62 91 92

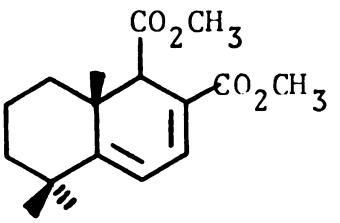
products was obtained. Column chromatographic fractionation of the mixture using silica gel gave what appeared to be mixtures of monosubstituted aromatic products which were not characterized further. No evidence pointed to the formation of adduct 92.

The Diels-Alder reaction of diene acid 61 with dimethyl acetylenedicarboxylate (71) was also attempted. Since the adduct from this reaction would be the β,γ-unsaturated acid 93, it was reasonable to anticipate that it would be readily decarboxylated in high yield to the conjugated dienediesters 94 and/or 95. The latter compound possesses functionality at the same positions as the noniresin-type bicyclofarnesol sesquiterpenes; furthermore, the nature and arrangement of

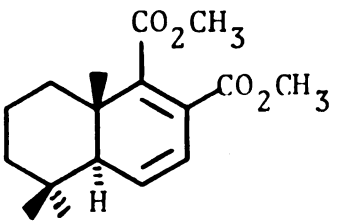


61 71 93

this functionality is such that selective modification should be possible. Unfortunately, the Diels-Alder reaction would not proceed, even when dienophile 71 was used as the



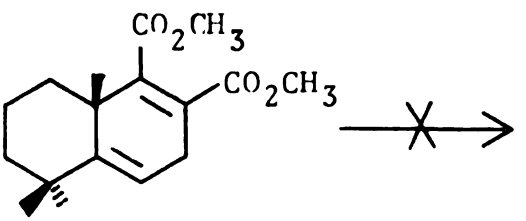
94



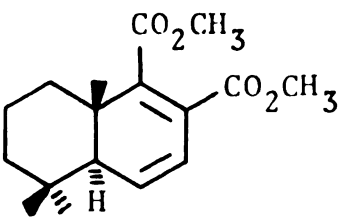
95

reaction solvent. This is not surprising since the carboxyl group of 61 deactivates the diene system to dienophilic attack through both steric and electronic effects.

Although the conjugated dienediester 95 could not be synthesized by the latter sequence, it was anticipated that it could be prepared by isomerizing the 5,6-double bond of adduct. 72.

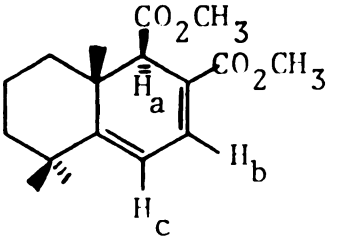


72



95

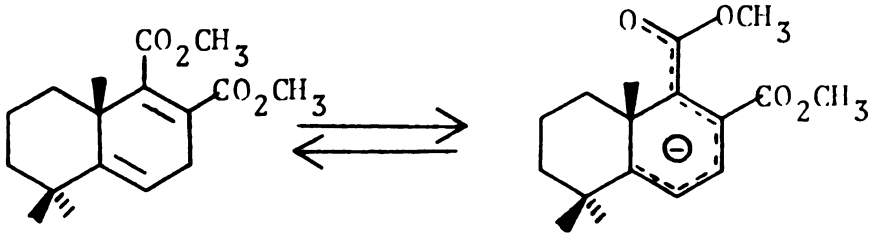
Treatment of dienediester 22 with a variety of acids under mild conditions gave no reaction, whereas forcing conditions caused extensive decomposition. Sodium methoxide, on the other hand, gave a twenty percent yield of a compound which was assigned structure 24 on the basis of



24

the nmr spectrum of the equilibrated mixture. The vinyl region of this spectrum exhibited, in addition to the resonance of the vinyl hydrogen of adduct 22, a one hydrogen doublet of doublets (H_b, J_{ab} = 3.0 Hz, J_{bc} = 6.0 Hz) and a one hydrogen doublet (H_c, J_{bc} = 6.0 Hz) centered at δ 6.79 and 5.93 ppm respectively. Unfortunately, this isomer could not be conveniently separated from the starting material.

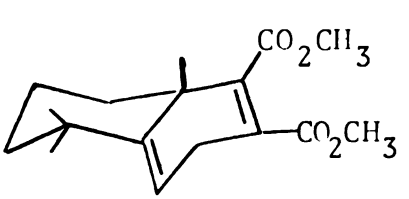
When anion 26 of dienediester 22 was generated with sodium hydride and subsequently quenched wihh a proton source, only starting material was obtained. This result was not



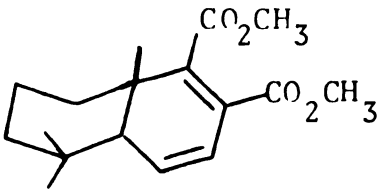
22 26

entirely unexpected since extensively delocalized enolate anions are known to be protonated most rapidly at inner rather than terminal atoms.

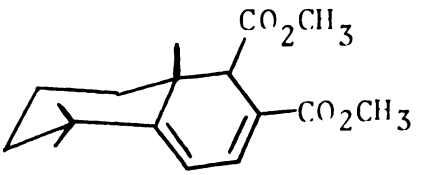
It became apparent from the acid and base catalyzed isomerization reactions that the conjugated dienediester 95 was not the most stable isomer. In fact, a study of molecular models suggested the opposite. The severe 1,3-diaxial interaction between the 14 and 15 methyl groups is



72



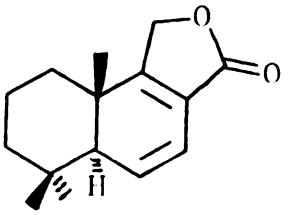
95



94

significantly relieved in isomers 72 and 94 because the exocyclic double bond forces C-4, 5 and 10 to be coplanar thus causing the 14 and 15 axial methyls to adopt a non-parallel orientation. In order to relieve this interaction in isomer 95, the A/B ring system must adopt a twist-boat/nonplanar conformation. Isomers 72 and 95 also suffer an eclipsing of the ester groups. This interaction is somewhat relieved in 94 and possibly accounts for the observed twenty percent isomerization of 72 to 94.

The fact that bemadienolide (44) exists in the conjugated form suggests, however, that additional factors must influence the relative stability of these isomers. One such

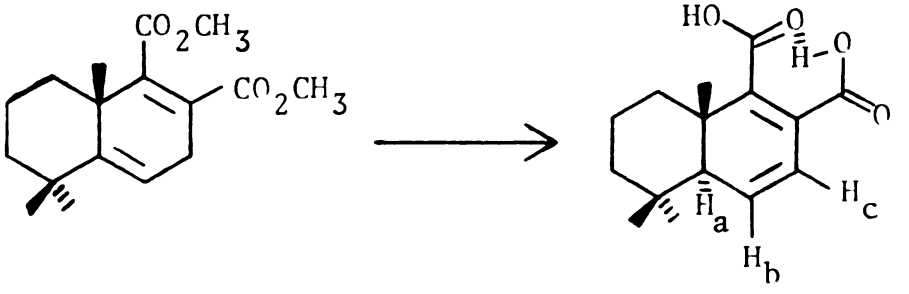


BEMADIENOLIDE

44

factor may be the degree of coplanarity of the C-11 and/or C-12 carbonyl groups with the ene system. Without good π-orbital overlap there would be little incentive for isomerization. Concurrently, nonbonded interaction between the C-1 and C-9 substituents may also be important. In bemadienolide (44) both of these factors must be considered since the lactone ring forces the carbonyl to be coplanar with the diene system and, by constraining C-11, relieves nonbonded interaction with the C-1 hydrogens. Dienediester 95, on the other hand, would be unfavorable on both counts since steric repulsion forces the ester groups to be non-coplanar with the diene system and simultaneously permits nonbonded interaction between the C-1 hydrogens and the C-11 ester.

Saponification of dienediester 77 with alcoholic potassium hydroxide gave a diacid assigned structure 97 on the basis of its nmr spectrum. The vinyl region of the

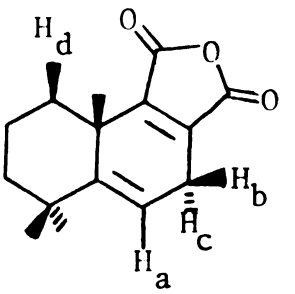


77 97

nmr spectrum of this compound exhibited a pair of one hydrogen doublets (J_{bc} = 6.0 Hz) centered at δ 7.06 and 6.08 ppm. The bridgehead methine hydrogen (H_a) does not interact with H_b because of the orthogonal relationship of the two; a one hydrogen singlet at δ 3.18 ppm is assigned to H_a. Hydrogen bonding of the carboxylic acid groups possibly renders the carbonyl functions coplanar with the 8,9-double bond, thus providing a driving force for the observed isomerization.

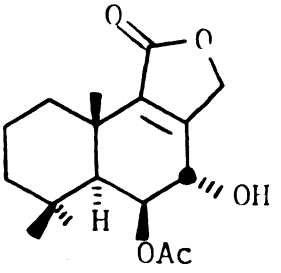
Because it was extremely difficult to separate diene diacid 97 from the corresponding aromatic contaminant, preliminary investigations into the synthetic usefulness of 97 were conducted with a 9:1 mixture of these compounds.

The cyclic anhydride of 97 was not formed in refluxing toluene; however, in refluxing acetic anhydride, a mixture of anhydrides was obtained, from which 5,6-dehydrowinterin (64) was isolated after extensive purification. The nmr spectrum of this product, identical with that reported by



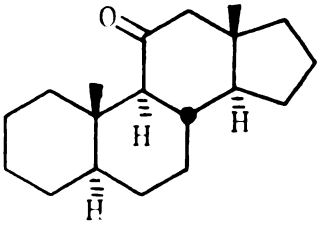
64

Brieger,[33] included a one hydrogen triplet (H_a, J = 4.0 Hz) and a two hydrogen doublet (H_b, H_c; J = 4.0 Hz) centered at δ 5.73 and 3.08 ppm respectively. The spectrum also exhibited a broad one hydrogen doublet (J = 13.0 Hz) centered at δ 2.57 ppm and assigned to the 1β-hydrogen, H_d. Decoupling experiments by Brooks and Draffan[23] have demonstrated that similar doublets in ugandensolide (45) and 5α-androstan-11-one (98) are due to the 1β-hydrogens deshielded by the C-11 carbonyl functions.



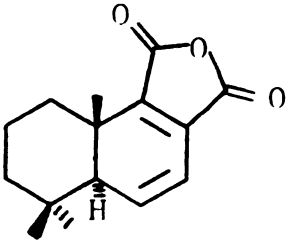
UGANDENSOLIDE

45



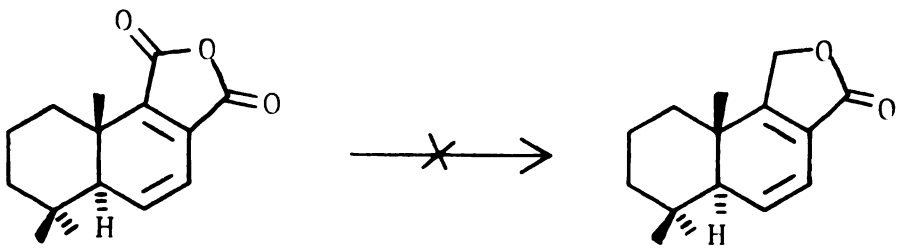
98

Another anhydride present in the acetic anhydride reaction mixture was tentatively assigned structure 99 because of the similarity of the vinyl resonances [pair of one hydrogen doublets (J = 5.8 Hz) centered at δ 7.02 and 6.00 ppm] with those of the starting diacid. This anhydride could be prepared free of 5,6-dehydrowinterin (64) by using the milder tosyl chloride/pyridine method of preparing anhydrides.[60]



99

An attempt to substantiate the assignment of structure 99 by conversion to bemadienolide (44) was unsuccessful.



BEMADIENOLIDE

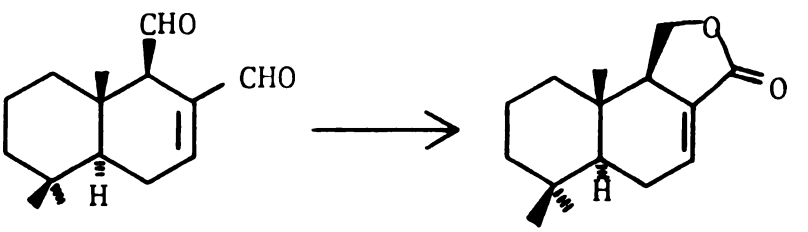
99 44

Sodium borohydride, which has been reported to reduce the most hindered carbonyl of cyclic anhydrides to a methylene group,[61] gave a mixture of products in low yield when reacted with anhydride 99. The infrared spectrum of the reaction mixture indicated that lactonic products had been formed, however, the nmr spectrum showed that extensive double bond isomerization had also occurred.

The difficulty of separating diacid 97 and cyclic anhydride 99 from the corresponding aromatic impurities, and the complex product mixture derived from the sodium borohydride reduction suggested that a re-examination of the synthetic scheme was in order. Two problems needed to be solved. The aromatic impurities had to be removed and another method of selectively generating the desired lactone system was needed. Due to the difference in steric and electronic environments of the two double bonds in diene-

diester 22, it was anticipated that the 5,6-double bond might be selectively oxidized to afford a derivative which could then be separated from the aromatic impurity. Attention was therefore directed to the more difficult problem of generating the desired lactone system.

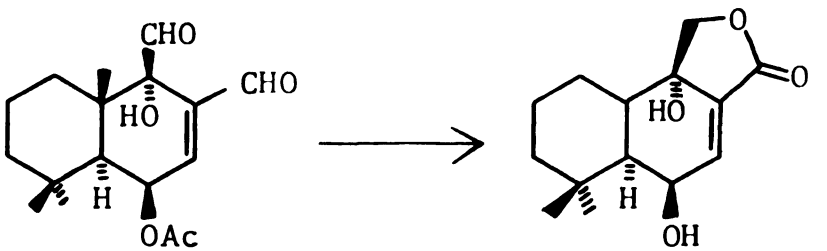
The structure elucidation of polygodial (34) involved the transformation of this dialdehyde into cinnamolide (35) via a crossed Cannizaro reaction.[18,21] Canonica *et al.*



POLYGODIAL — CINNAMOLIDE

34 — 35

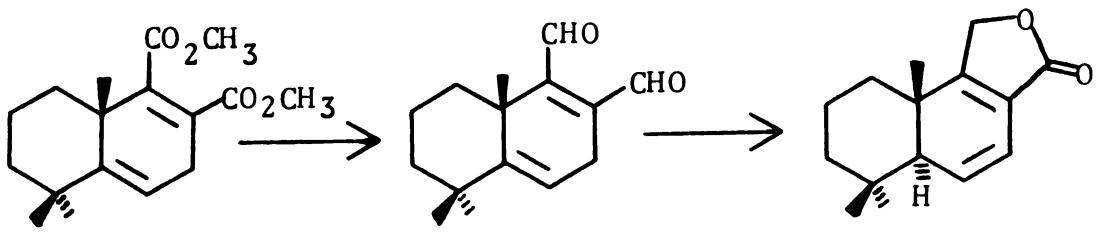
employed the same procedure to lactonize cinnamodial (36)[20,21]



CINNAMODIAL

36 — 37

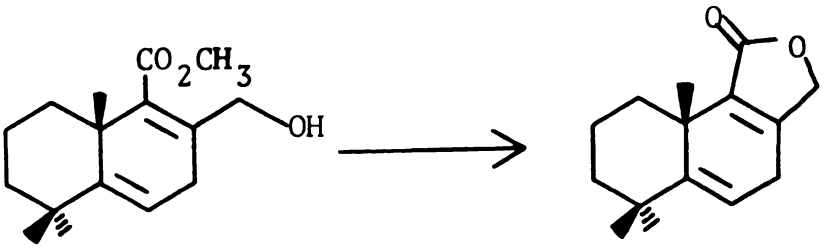
If the dialdehyde derived from dienediester 22 could be made to lactonize in the same manner, and if the alkaline reaction conditions would isomerize the exocyclic double bond into conjugation, bemadienolide (44) could be prepared from adduct 22 in two steps.



BEMADIENOLIDE

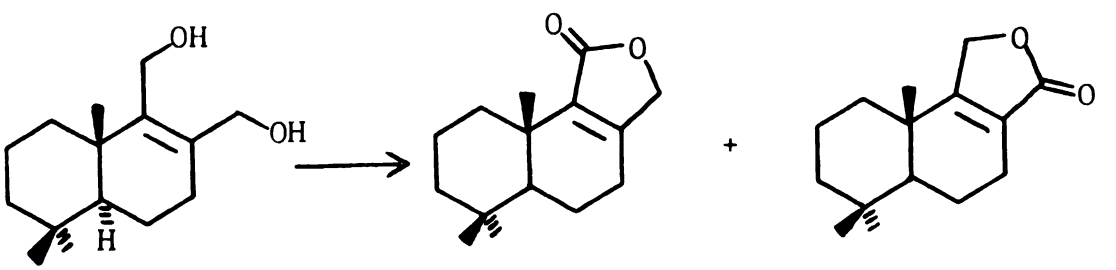
72 100 44

Sodium bis(2-methoxyethoxy) aluminum hydride (SMAH), which has been successfully employed for the low temperature reduction of esters to aldehydes, has proven to be especially useful in cases where the reduction of conjugated double bonds is to be avoided.[62] Accordingly, dienediester 72 was treated with one equivalent of SMAH at minus seventy degrees and, after hydrolysis and filtration of the aluminum salts, the reaction mixture was heated with aqueous sodium hydroxide. Work up gave a low yield of a lactonic product. The nmr spectrum of this lactone exhibited a one hydrogen triplet (J = 4.0 Hz), a two hydrogen singlet, a two hydrogen doublet (J = 4.0 Hz) and a broad one hydrogen doublet (J = 13 Hz) centered at δ 5.62, 4.59, 2.97 and 2.62 ppm respectively. These and additional spectroscopic data are consistent with the structure of 5,6-dehydroisodrimenin (102). Since SMAH reductions are sensitive to steric effects,[63] it is possible that lactone 102 was derived from hydroxyester 101 rather than dialdehyde 100 - hydroxyester 101 being the product of over-reduction of the sterically most accessible C-12 ester.



101 102

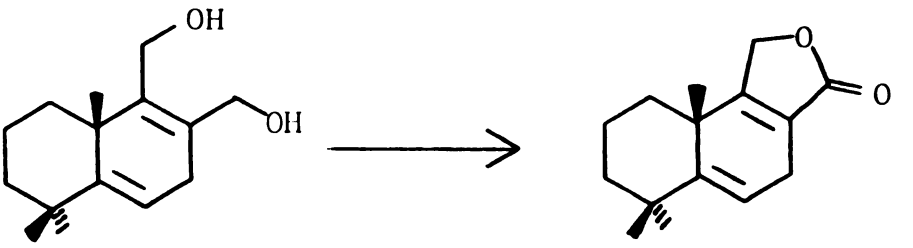
Although 5,6-dehydroisodrimenin (102) could serve as an intermediate in the synthesis of isodrimenin (23) by selectively hydrogenating the exocyclic double bond, it is not a suitable intermediate for the synthesis of the majority of bicyclofarnesol derivatives in which the butenolide system contains the carbonyl function at the C-12 position. Wenkert and Strike, however, were able to generate the latter system by oxidizing the bis-allylic diol 24 to a mixture of isodrimenin (23) and confertifolin (27).[24]



ISODRIMENIN CONFERTIFOLIN

24 23 27

Dienediol 103, prepared from the SMAH reduction of adduct 72 in refluxing benzene,[62,64,65] was converted in low yield to a mixture of lactones when treated with an ethereal suspension of activated manganese dioxide.[66] However, when 103 was refluxed with a benzene dispersion of silver carbonate on celite,[67,68] the desired 5,6-dehydroconfertifolin (104) was obtained in approximately fifty percent yield. In addition to three methyl singlets at



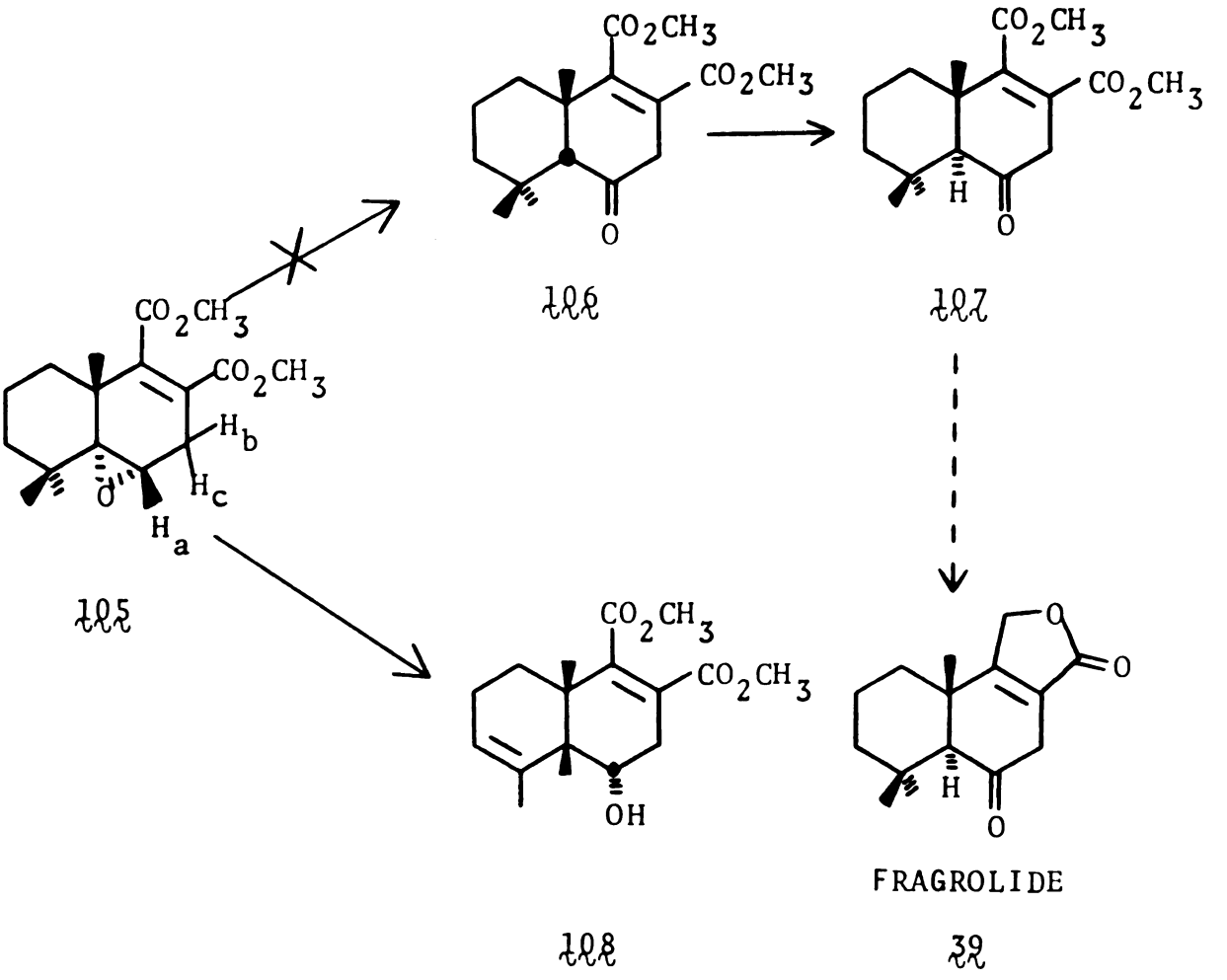
103 104

δ 1.47, 1.30 and 1.20 ppm, the nmr spectrum of lactone 104 exhibited a one hydrogen triplet (J = 4.0 Hz) at δ 5.77 ppm and two two hydrogen multiplets centered at δ 4.70 and 2.80 ppm. The former multiplet is due to the methylene hydrogen atoms of the lactone ring, which exhibit long-range splitting by the bis-allylic C-7 hydrogens (the latter multiplet) through the 8,9-double bond.

With a workable route to the desired butenolide system in hand, attention was redirected to the problem of eliminating the aromatic contaminant which had severely hindered purification of the derivatives of adduct 72

prepared thusfar. The introduction of a polar group at the site of the exocyclic double bond was expected to facilitate separation from aromatic diester 90. Since the 8,9-double bond of dienediester 77 is electronically deactivated by the ester groups and sterically deactivated by tetrasubstitution, it seemed reasonable that the trisubstituted 5,6-double bond would be more susceptible to electrophilic attack. Furthermore, due to the β-orientation of the 14 and 15 axial methyl groups, it was presumed that such an attack would preferentially take place at the α-side of the molecule.

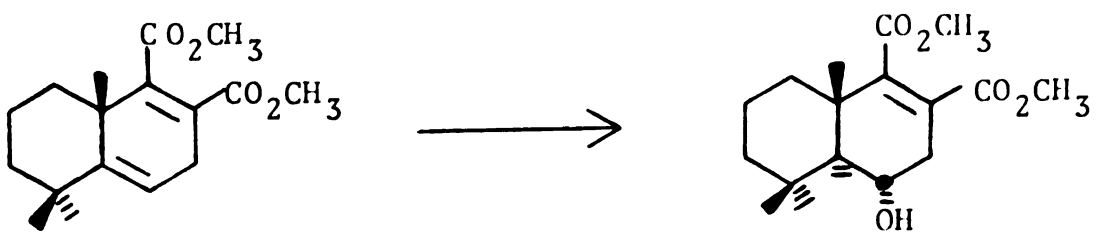
Accordingly, dienediester 77 was epoxidized with *m*-chloroperbenzoic acid in methylene chloride to afford an eighty percent yield of the epoxydiester 105. The nmr spectrum of this epoxide exhibited a complex three hydrogen splitting pattern between δ 3.4 and 2.2 ppm, which was interpreted in the following manner: a broad one hydrogen doublet (J_{ab} = 3 Hz, J_{ac} = 1.5 Hz) centered at δ 3.21 ppm was assigned to the methine hydrogen H_a, while a pair of one hydrogen multiplets (J_{bc} = 19 Hz, J_{ab} = 3 Hz, J_{ac} = 1.5 Hz) centered at δ 3.15 and 2.41 ppm were assigned to the methylene hydrogens H_b and H_c. Recrystallization of epoxydiester 105 from ethyl ether removed all traces of aromatic contaminant.



It was anticipated that the treatment of epoxydiester 105 with boron trifluoride etherate would generate keto-diester 106 via a concerted hydride shift and collapse of the epoxide to a ketone. The latter compound might then be epimerized to 107 and subsequently transformed to fragrolide (39) by the previously developed lactonization procedure. However, this rearrangement did not proceed in the desired fashion, giving instead a product which absorbed at 3500 cm^{-1} in the infrared and which exhibited a one hydrogen multiplet

at δ 5.68 ppm, a six hydrogen singlet at δ 3.63 ppm, a broad three hydrogen singlet at δ 1.72 ppm and two three hydrogen singlets at δ 0.97 and 0.91 ppm in the nmr spectrum. Complex splitting patterns were also observed in the δ 3.5-1.0 ppm region. Although this product was not rigorously characterized, these data are consistent with the hydroxydienediester 108. It is conceivable that the boron trifluoride etherate complex of the epoxide generated sufficient carbonium ion character at C-5 to facilitate migration of the axial C-14 methyl group, followed by proton loss.

Since epoxydiester 105 could not be rearranged to the desired bicyclofarnesol derivative, an oxidative hydroboration[69] of the 5,6-double bond in dienediester 72 was attempted. This reaction was expected to yield a 4-hydroxy substituent directly, thus avoiding the necessity of selectively eliminating a substituent from C-5. In spite of the high reactivity of diborane, forcing conditions (40-50°) were necessary to effect the desired transformation. Unfortunately, at such temperatures reduction of the carbomethoxy functions becomes competitive, resulting in a low yield of hydroxydiester 109. The yield of this product



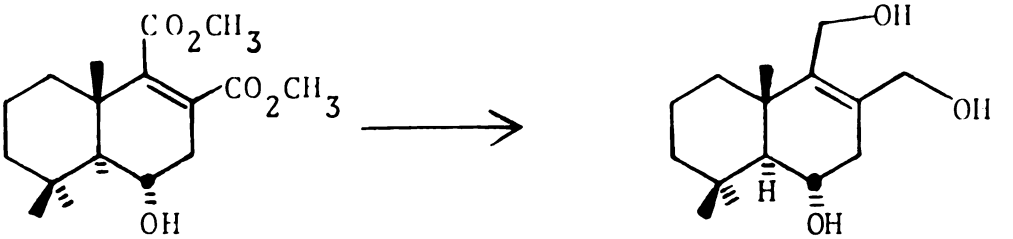
72 109

might possibly be improved by using an inverse addition procedure thereby minimizing the concentration of diborane in the reaction mixture. Column chromatographic fractionation of the reaction mixture (activity III alumina, benzene) efficiently separated the aromatic diester contaminant (90) from hydroxydiester 109.

The nmr spectrum of hydroxydiester 109 exhibited a complex multiplet, assigned to the C-6 hydrogen, centered at δ 4.1 ppm and a six hydrogen singlet at δ 3.75 ppm, assigned to the methoxy hydrogens. The bridgehead hydrogen atom and the two nonequivalent C-7 allylic hydrogens give rise to a complex splitting pattern between δ 3.67 and 2.20 ppm. A singlet at δ 2.13 ppm (absent after exchange with D_2O) is clearly due to the hydroxyl hydrogen, and a six hydrogen multiplet centered at approximately δ 1.5 ppm is attributed to methylene hydrogens. The bridgehead methyl group and the geminal methyl group signals appear at δ 1.28, 1.20 and 1.08 ppm respectively. Other analytical data are also consistent with structure 109. The α-orientation of the C-6 hydroxyl group in tentatively assumed on the basis of steric arguments; however, it should be noted that the forcing conditions employed in this reaction might permit formation of a β-hydroxyl group together with the corresponding *cis*-ring fusion.

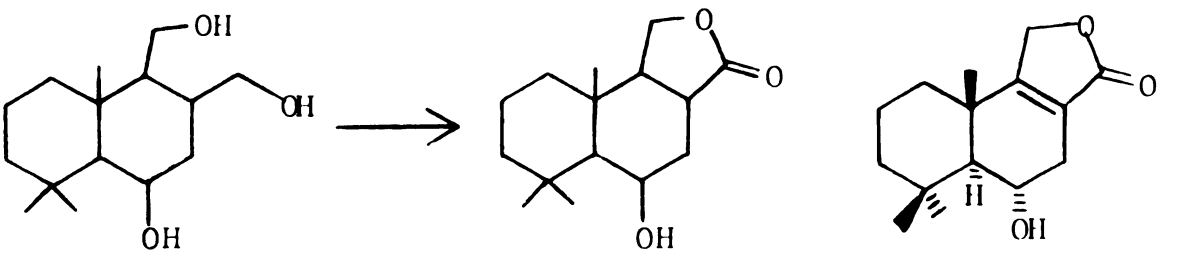
Treatment of purified hydroxydiester 109, with SMAH in refluxing benzene was presumed to have generated triol 110.

This triol was not isolated due to the potentially labile nature



109 110

of the bis-allylic diol system. Instead the crude reaction product was oxidized by a refluxing benzene dispersion of silver carbonate on celite. Work up of this reaction gave a mixture of hydroxy lactones (70% crude yield), which consisted of two major components in a ratio of 2:1. Glc/mass spectrometric analysis of the reaction mixture showed that these components had molecular weights of 252 and 250 respectively, and they are thus assigned structures 111 and 112. The former compound, is apparently generated by oxidation

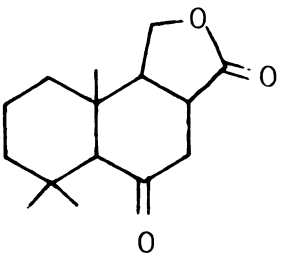


113 111 112

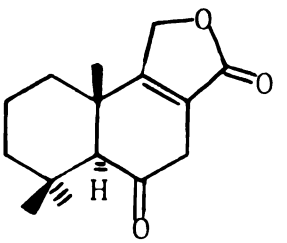
of the saturated triol 113, derived from reduction of the 8,9-double bond of hydroxydiester 109 during the SMAll reaction.

Since this hydroxydiester was reduced under the same conditions as dienediester 72, it is possible that the 6-hydroxyl group was the influential factor in accounting for the reduction of the 8,9-double bond.

Since the hydroxylactone mixture was not readily fractionated by thin layer chromatography and since only a small amount of material was available, the product mixture was oxidized with chromium trioxide/pyridine[70] and then submitted to glc/mass spectrometric analysis. The two major peaks (1:1) of the four component reaction mixture displayed parent masses of 250 and 248 as expected for the tentatively assigned structures 114 and 39. The fragmentation pattern observed for the latter compound is



114

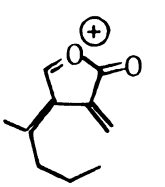
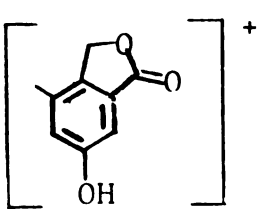
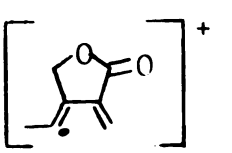
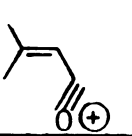


FRAGROLIDE

39

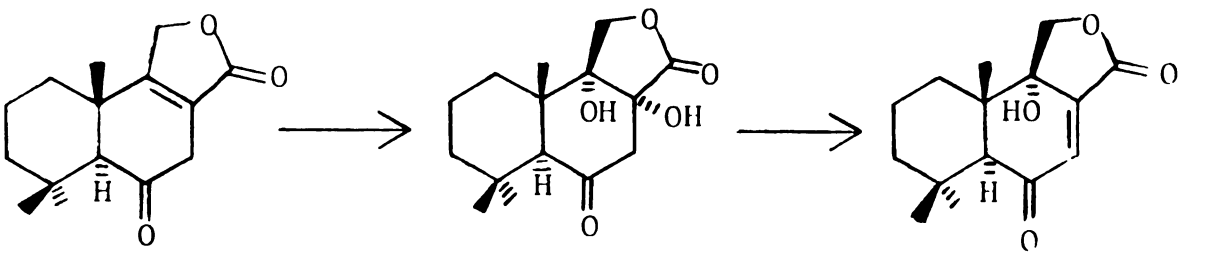
consistent with that expected for fragrolide (39), as shown in the accompanying table:

Table I. Mass Spectral Data for Fragrolide

m/e	Relative Intensity (%)	Relative Intensity (%) (Calcd for $C_{15}H_{20}O_3$)	Fragment Ions
250	3	1.90	$[P + 2]^+$
249	15	16.65	$[P + 1]^+$
248	100	100	$[P]^+$
233	91	-	$[P-CH_3]^+$
220	12	-	$[P-C=O]^+$
205	27	-	$[P-(CH_3 + C=O)]^+$
204	8	-	$[P-CO_2]^+$
165	22	-	
164	20	-	
123	32	-	
83	38	-	

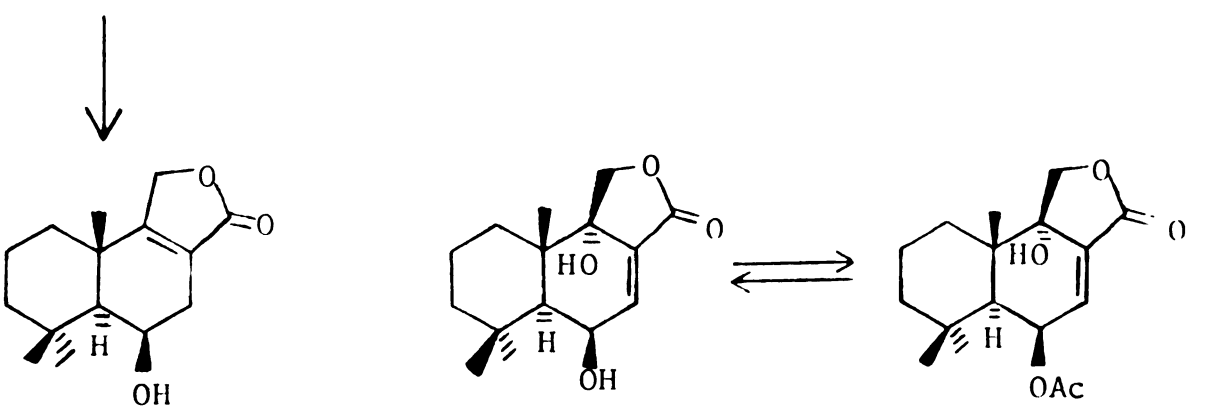
Thus it seems reasonable that fragrolide (or its C-5 epimer) has been prepared in low yield. However, before this reaction sequence can be considered synthetically useful, conditions must be optimized for the oxidative hydroboration reaction and for the SMAH reduction of the hydroxydiester 109. While inverse addition might resolve the problems associated with the former reaction; another reducing agent, such as a dialkyl aluminum hydride, may have to be used for the latter.

Canonica *et al.* have transformed fragrolide (39) to hydroxyketolactone 116 *via* an osmium tetroxide oxidation followed by dehydration with boron trifluoride etherate. The same workers reduced fragrolide with sodium borohydride



FRAGROLIDE

39 115 116



CINNAMOSMOLIDE

40 37 38

to the β-hydroxylactone 40 and have also established conditions for the acetylation of dihydroxylactone 37. It seems reasonable, therefore, that optimization of the fragrolide synthesis presented herein and application of the work of Canonica and colleagues should provide a synthetic route to cinnamosmolide (38).

EXPERIMENTAL

General. Analytical samples were obtained by recrystallization or preparative thin layer- or gas chromatographic techniques. A Varian Aerograph A90-P3 Preparative Gas Chromatograph was employed for the latter.

Melting points (uncorrected) were determined with a Koefler hot stage or a Hoover capillary melting point apparatus. Reported boiling points are also uncorrected.

Infrared absorption spectra were obtained with a Perkin-Elmer 237B Grating Infrared Spectrophotometer. The spectra of liquid samples were determined from neat films of the liquids between sodium chloride plates; solid samples were fused with potassium bromide.

Varian models A-60 and T-60 Nuclear Magnetic Resonance Spectrometers were used to obtain nmr spectra. Tetramethylsilane was employed as an internal standard.

Ultraviolet absorption spectra were taken with a Unicam SP-800 Spectrophotometer.

An Hitachi RMU-6 Mass Spectrometer operating at an ionization potential of 70 eV was used for measuring mass spectra.

Carbon and hydrogen microanalyses were run by Spang Microanalytical Laboratory, Ann Arbor, Michigan or by the Institute of Water Research, Michigan State University, East Lansing, Michigan.

Citrylideneaniline (77). A solution of 171 ml (1.0 mol) of citral and 91 ml (1.0 mol) of aniline in 250 ml of ether was stirred at five degrees for ten minutes and then at room temperature for seven hours. The ethereal solution of the Schiff base was separated from the water which had formed and used without further treatment for the cyclization to α- and β-cyclocitral (78 and 79).

α- and β-Cyclocitral (78 and 79). The previously prepared ethereal solution of 77 (1.0 mol) was added dropwise with vigorous stirring to a pre-cooled (less than -15°, dry ice/carbon tetrachloride) mixture of 700 ml of concentrated sulfuric acid and 36 g of ice under nitrogen. Stirring was continued for one hour beyond the addition period. The resulting thick red slurry was diluted with 1.5 l. of water and subjected to steam distillation.

The two liters of steam distillate was saturated with sodium chloride and extracted with ether. Drying (magnesium sulfate) and concentration of the ether extract left an orangish liquid which was vacuum distilled (36-59°, 0.5 mm) to yield 63.2 g (43%) of a pale yellow mixture of 78 and 79 (78:79 = 3:1).

β-Cyclocitral (79). Twenty-four grams of the previously prepared cyclocitral mixture was added dropwise with stirring over 0.5 hr to one liter of eight percent potassium hydroxide in 80% methanol at -5 to 0° under nitrogen. The reaction mixture was stirred for an additional hour and transferred to a refrigerator (four degrees) for 43 hr. The solution was then diluted with two liters of water and extracted with ether. The dried (magnesium sulfate) extract was concentrated and vacuum distilled (72°, 3.25 mm; Lit.[41]: 91-3°, 12 mm) to give 21.8 g (81%) of 79.

An analytical sample (preparative glc, 20% SE-30) had uv max (EtOH) 247 (ε 8500) and 330 nm (ε 40); ir (neat) 2745 (O=CH), 1670 (C=O), and 1610 cm^{-1} (C=C); nmr (CCl_4) δ 10.8 (s, 1, CHO), 2.19 (m, 2, $=CCH_2$), 2.10 (s, 3, $=CCH_3$), 1.46 [m, 4, $(CH_2)_2$], and 1.15 ppm [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 168 (9), 153 (34), 152 (100), 137 (39), 125 (35), 107 (37), 95 (35), 91 (40), 79 (41), 77 (37), 55 (44), 43 (57), 39 (56).

1-Vinyl-2,6,6-trimethylcyclohexene (62), from β-cyclocitral (79). A three-necked flask containing 2.82 g (0.0625 mol) of 52.8% sodium hydride in mineral oil was alternately evacuated and flushed with nitrogen three times. Thereafter, the system was maintained under a positive nitrogen pressure. Dimethyl sulfoxide (DMSO, 75 ml), freshly distilled from calcium hydride, was injected through a rubber septum and the resulting slurry stirred at room temperature

for ten minutes and then at 75° until evolution of hydrogen had ceased. A pale yellow solution of methylenetriphenylphosphorane was generated by injecting 22.3 g (0.0625 mol) of triphenylmethylphosphonium bromide dissolved in 95 ml of dry DMSO into the cooled solution of the dimsyl anion. The ylid solution was stirred at room temperature for 15 min prior to use.

Injection of 7.7 g (0.05 mol) of enone 79 dissolved in 20 ml of dry DMSO into the ylid solution effected the formation of a dark red betaine solution. After stirring at room temperature for eight hours and at 62° for ten hours, the color faded and the reaction mixture was then poured into 500 ml of cold water. The suspension of triphenylphosphine oxide in aqueous DMSO was extracted with pentane, and the pentane extract was washed with water, dried (magnesium sulfate) and concentrated to a pale yellow oil. Vacuum distillation of the oil gave 5.3 g (70%) of the colorless diene (82), having bp 68° (12.5 mm); Lit.[46]: bp 65-6° (12 mm); ir 1625 (C=C), 995, 917 cm^{-1} ($CH=CH_2$).

An analytical sample (preparative glc, 20% SE-30) had uv max (EtOH) 234.5 nm (ε 4050); ir (neat) 1620 (C=C), 990, 920 cm^{-1} ($CH=CH_2$); nmr (CCl_4) δ 5.31-4.71 (m, 3, $CH=CH_2$), 2.07-1.30 [m, 6, $(CH_2)_3$], 1.65 (m, 3, J = 2 Hz, $=CCH_3$), and 1.00 ppm [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 150 (31), 135 (100), 121 (13), 107 (41), 93 (37), 79 (36), 55 (19), 41 (28).

β-(2,6,6-Trimethyl-1-cyclohexene-1-yl-)acrylic acid (61). Two liters (1.4 mol sodium hypochlorite) of chilled Clorox was added dropwise over five hours to a stirred solution of 60 g (0.31 mol) of β-ionone (60) (Eastman practical grade) in two liters of methanol held at five degrees. The reaction mixture was allowed to warm to room temperature while stirring for 20 hr. Excess sodium hypochlorite was decomposed with sodium sulfite and the methanol evaporated under reduced pressure at a temperature below 50°. The remaining aqueous phase was extracted with ether to remove starting material, acidified to pH 5, and re-extracted with ether. Concentration of the dried (magnesium sulfate) extracts gave, respectively, 17 g of β-ionone (60) and 43 g (71%) of 61. The acid was recrystallized (89% recovery) from aqueous ethanol.

An analytical sample, mp 107-107.5° (Lit.[54]: mp 105.5-108°), exhibited uv max (MeOH) 212 (ε 5200) and 279 nm (ε 8100); ir (KBr) 3200-2500 (CO_2H), 1680 (C=O), and 1625 cm^{-1} (C=C); nmr (CCl_4) δ 12.3 (s, 1, CO_2H), 7.47 (br d, 1, J = 16 Hz, CH=$CHCO_2H$), 5.77 (d, 1, J = 16 Hz, CH=$CHCO_2H$), 2.05 (m, 2, allylic CH_2), 1.82 (s, 3, $=CCH_3$), 1.52 [m, 4, $(CH_2)_2$], and 1.10 ppm [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 194 (44), 179 (100), 161 (16), 138 (46), 133 (33), 119 (16), 107 (18), 93 (59), 79 (17), 77 (17), 55 (16), 41 (29).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.25.

1-Vinyl-2,6,6-trimethylcyclohexene (62), from β-(2,6,6-trimethyl-1-cyclohexene-1-yl-)acrylic acid (61). A mixture of 36 g (0.185 mol) of 61, 125 g (1.75 mol Cu^+) of cuprous oxide and 900 ml of dry (distilled from barium oxide) quinoline was agitated with a vibromixer, flushed with nitrogen and heated at 210-215° in a two liter resin flask. The flask was connected to a receiver flask immersed in an ice bath followed by a dry ice trap. After three hours the pressure within the system was reduced to 400 mm and 150 ml of condensate collected in the receiver flask. This distillate was redistilled (65-109°, 12.5 mm) to afford 30 ml of a mixture of the diene and quinoline which separated into two phases. The upper phase was diluted with ether, washed with 6 N hydrochloric acid to remove quinoline and then with a saturated sodium chloride solution. The dried (magnesium sulfate) ethereal extract was concentrated to yield 19.5 g (70%) of 62.

When 2 g of 61 was decarboxylated as above with the exception that the reaction was worked up immediately after the evolution of carbon dioxide had stopped, a 90% yield of the diene was realized.

Dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (72). A mixture of 12.92 g (0.086 mol) of diene 62 and 25 ml of dimethyl acetylenedicarboxylate (71) was mechanically stirred and heated on a steam bath under nitrogen for 71 hr. Prolonged heating at higher

temperatures causes the dimethyl acetylenedicarboxylate to tetramerize.[58] Vacuum distillation gave 17.35 g (69%) of 77 (bp 135°, 0.13 mm) contaminated with a small amount of dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (90).

An analytical sample (preparative glc, 6% DEGS, 200°) of 77 exhibited uv max (MeOH) end absorption 205 nm (ε 4050); ir (neat) 1725 (C=O), 1670, 1630 (C=C), and 1250 cm^{-1} (C-O); nmr (CCl_4) δ 5.92-5.49 (dd; 1; splitting = 3.0, 2.6, 3.0 Hz; =CH), 3.70 (s, 6, OCH_3), 3.00 (d, 1, J = 5.6 Hz, $=CHCH_2$), 2.85 (d, 1, J = 3.0 Hz, $=CHCH_2$), 1.70-1.27 [m, 6, $(CH_2)_3$], 1.37 (s, 3, bridgehead CH_3), 1.17 (s, 3, geminal CH_3), and 1.13 ppm (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 292 (2), 277 (13), 260 (26), 245 (100), 233 (37), 213 (98), 163 (37).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.03; H, 8.51.

Dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (90). A solution of dienediester 77 (0.5 g) in five ml of triethyleneglycol dimethyl ether was heated at 200° for 14 hr. The reaction mixture was diluted with chloroform and extracted with water. Concentration of the dried (sodium sulfate) chloroform solution gave a quantitative yield of 90, a pale yellow oil.

An analytical sample (preparative glc, 6% DEGS, 200°) of 90 had uv max (pentane) 241 nm (ε 9400), 281 (ε 1500), 289 (ε 1450); ir (neat) 1735, 1725 (C=O), 1590 (aromatic CH), 1290, 1275 cm^{-1} (C-O); nmr (CCl_4) δ 7.75 and 7.38 (ABq, 2, J = 9 Hz, aromatic H), 3.85 (s, 6, OCH_3), 2.86-2.54 (m, 2, benzyl CH_2), 2.13-1.50 [m, 4, $(CH_2)_2$], 1.33 ppm [s, 6, $(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity), 276 (4), 261 (9), 245 (37), 244 (100), 229 (49), 213 (4), 201 (8), 186 (21), 142 (8).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 70.00; H, 7.47.

4a,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylic acid (97). A solution of 2.0 g (6.84×10^{-3} mol) of a 9:1 mixture of dienediester 72 and aromatic diester 90 dissolved in 75 ml of ten percent methanolic potassium hydroxide was refluxed on a steam bath under nitrogen for 8.5 hr. The cooled reaction mixture was diluted with water and the methanol evaporated under reduced pressure at a temperature below 45°. The remaining aqueous solution was extracted with ether to remove unreacted starting material, acidified to pH 1, and re-extracted with ether. Concentration of the dried (sodium sulfate) ethereal extract gave 1.9 g of a foam which could not be crystallized. Elution of the foam through a Florisil column with ether gave 1.7 g (93%) of diene diacid 97 contaminated with the diacid derived from aromatic diester 90

Repeated recrystallization from methanol/water gave an analytical sample of diene diacid 97 having mp 203-4°; uv max (EtOH) 312.5 (ε 6300), 225 nm (sh, ε 2500) and end absorption; ir (KBr) 3400-2500 (CO_2H), 1695 (C=O), 1670 and 1630 cm^{-1} (C=C); nmr (d_6-DMSO) δ 12.6 (br s, 2, CO_2H), 7.06 (d, 1, J = 6.0 Hz, CH-CH=CH), 6.08 (d, 1, J 6.0 Hz, CH-CH=CH), 3.18 (s, 1, CH-CH=CH), 1.8-1.2 [m, 6, $(CH_2)_3$], and 1.2 ppm [br s, 9, $C(CH_3)_2$ and CCH_3]; mass spectrum (70 eV) *m/e* (rel intensity) 264 (3), 246 (17), 230 (28), 215 (41), 213 (20), 205 (21), 201 (18), 189 (21), 187 (37), 159 (21), 149 (65), 128 (20), 115 (23), 105 (45), 104 (65), 91 (24), 88 (34), 84 (35), 77 (28), 76 (56), 73 (38), 70 (71), 69 (32), 61 (100), 56 (83), 55 (39), 50 (32), 45 (89), 43 (89), 41 (66).

5,6-Dehydroisodrimenin (102). A solution of 2.2 g (0.0074 mol) of a 1:1 mixture of dienediester 77 and aromatic diester 90 dissolved in 25 ml of dry tetrahydrofuran (THF) was cooled to -70° under nitrogen. Sodium bis(2-methoxyethoxy) aluminum hydride (SMAH, 2.5 ml of a 70% benzene solution, 8.65×10^{-3} mol) diluted with 15 ml of dry THF was added dropwise over ten minutes and the reaction mixture stirred at -70° for 22 hr. The cooling bath was removed and 15 ml of 20% sulfuric acid added dropwise starting at -70°. The organic layer was separated from the quenched reaction mixture and the aqueous layer extracted with THF. Concentration of the combined organic

phases under reduced pressure at a temperature below 40° left a wet residue which was heated on a steam bath under nitrogen with 50 ml of two normal sodium hydroxide for 2.5 hr. The cooled alkaline solution was extracted with ether, acidified with hydrochloric acid and re-extracted with ether. The dried (sodium sulfate) and concentrated basic and acidic extracts gave 0.45 and 1.55 g respectively, of yellow oils. Column chromatographic fractionation (Florisil, chloroform) of the material recovered from the basic extract yielded 0.13 g of a yellow oil consisting of one major product and two minor products. Sublimation at 78°/0.01 mm gave 10% contaminated with a trace of a colorless oil.

Recrystallization from ether gave an analytical sample of 5,6-dehydroisodrimenin: mp 117°; uv max (MeOH) 209 (ε 5500), 234 (sh, ε 1950), 283 (ε 230) and 292 nm (sh, 200); ir (KBr) 1760 (sh) and 1750 (C=O), 1695 and 1630 (C=C), 1135 and 1025 cm^{-1} (C-O); nmr (CCl_4) δ 5.62 (t, 1, *J* = 4 Hz, =CH), 4.59 (br s, 2, CH_2-O), 2.97 (d, 2, *J* = 4 Hz, =CHCH_2), 2.62 (br d, 1, *J* = 13 Hz, 1β-H), 1.40 (s, 3, bridgehead CH_3), 1.23 (s, 3, geminal CH_3) and 1.15 ppm (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 232 (14), 217 (100), 175 (40), 161 (79), 147 (17), 128 (10), 115 (14), 91 (17), 77 (14), 65 (10), 53 (13), 51 (13), 45 (10), 43 (13), 41 (52), 39 (47).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.35; H, 8.69.

5,6-Dehydroconfertifolin (104). A benzene solution of 1.9 g (0.0065 mol) of a 7:3 mixture of dienediester 72 and aromatic diester 90 was added dropwise to 2.8 g (0.0138 mol) of sodium bis(2-methoxyethoxy) aluminum hydride dissolved in ten milliliters of benzene. The mechanically stirred reaction mixture was refluxed under nitrogen for one hour, cooled and decomposed with two milliliters of 20% sulfuric acid. Methanol was added, the precipitated aluminum salts filtered off and the two phase filtrate separated. The dried (potassium carbonate) organic phase was concentrated to yield 1.6 g (84% crude yield) of a yellow/brown oil which was homogeneous by tlc (alumina, ether) and exhibited strong hydroxyl absorption in the infrared.

The crude diol was dissolved in 400 ml of benzene and slurried with 40 g (0.07 mol) of silver carbonate on Celite. The mechanically stirred reaction mixture, from which water was azeotropically removed, was refluxed for three hours, cooled and filtered. Concentration of the benzene solution gave approximately one gram of a yellow oil which exhibited weak hydroxyl absorption and strong carbonyl absorption in the infrared. Column chromatography (alumina, benzene) of the oil followed by sublimation (100°/0.001 mm) and recrystallization of the major fraction gave 0.15 g of 5,6-dehydroconfertifolin (104).

An analytical sample had mp 104.5-105.5°; ir (KBr) 1760 (C=O), 1695 and 1625 (C=C), and 1060 cm^{-1} (C-O); nmr (CCl_4)

δ 5.77 (t, 1, J = 4.0 Hz, =CH), 4.70 (m, 2, CH_2O), 2.80 (m, 2, =CH-CH_2), 1.47 (s, 3, bridgehead CH_3), 1.30 (s, 3, geminal CH_3) and 1.20 ppm (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 232 (14), 217 (62), 201 (96), 187 (11), 173 (100), 161 (32), 157 (49), 147 (80), 131 (37), 129 (33), 128 (36), 119 (32), 117 (27), 115 (41), 91 (47), 77 (33).

Dimethyl 3,4,4a,5,6,7,8,8a-octahydro-4,4aα-epoxy-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (105). To a stirred solution of 0.58 g (1.95 x 10^{-3} mol) of dienediester 72 in five milliliters of methylene chloride at 25° was added dropwise 0.4 g of 87% (0.002 mol) *m*-chloroperbenzoic acid in ten milliliters of methylene chloride. After stirring for 0.5 hr, excess peracid was decomposed by the dropwise addition of a ten percent sodium sulfite solution until a negative starch-iodide test was obtained. The reaction mixture was then washed with saturated sodium bicarbonate, water and saturated sodium chloride. The dried (sodium sulfate) extract was concentrated to yield 0.5 g (88%) of a nearly colorless oil. Crystallization of the epoxide was induced by diluting with a small amount of ether, cooling and scratching with a glass rod. Recrystallized product (ether) had mp 114-115°.

An analytical sample (preparative glc, 6% DEGS, 200°) exhibited uv max (MeOH) 223 nm (ε 6800); ir (KBr) 3020 and 3000 (epoxy methine), 1725 and 1720 (C=O), 1695 (C=C), and 1260 cm^{-1} (C-O); nmr (CCl_4) δ 3.67 (s, 6, OCH_3), 3.30 and

2.99 (br d's, 1, J_{gem} = 19 Hz, J_{vic} = 3 Hz, $=CCH_2$), 3.23 and 3.18 (br d's, 1, J_{vic} = 3, 1.5 Hz, epoxy methine), 2.57 and 2.25 (br d's, 1, J_{gem} = 19 Hz, J_{vic} = 1.5 Hz, $=CCH_2$), 1.80-1.11 [m, 6, $(CH_2)_3$], 1.43 (s, 3, geminal CH_3), and 0.79 ppm (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 308 (1), 290 (1), 276 (3), 258 (5), 248 (3), 244 (5), 231 (9), 221 (5), 190 (6), 161 (8), 123 (9), 115 (4), 105 (4), 91 (5), 59 (14), 45 (13), 44 (16), 40 (32), 31 (100).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.24; H, 7.85. Found: C, 65.97; H, 7.82.

Dimethyl 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-4α-hydroxy-1,2-naphthalenedicarboxylate (109). To a stirred solution of an 8:2 mixture of dienediester 72 and aromatic diester 90 (10 g, 0.039 mol) in 10 ml of dry tetrahydrofuran (THF) under nitrogen was added 14.2 ml (0.017 mol) of 1.2 M diborane in THF at 0°. The reaction mixture was warmed to 40-50° for 1.5 hr and then cooled with an ice bath. Excess hydride was decomposed with water followed by the dropwise addition of 23 ml of 3N sodium hydroxide and 23 ml of 30% hydrogen peroxide. After heating at 30-50° for one hour to effect oxidation, the reaction mixture was diluted with ether and the resulting two phases separated. The aqueous phase was saturated with sodium chloride and extracted with ether. The combined organic phases were washed with saturated sodium chloride, dried (sodium sulfate) and concentrated to yield

9.4 g of a slightly yellow oil. Column chromatography (activity III alumina, benzene) gave 2.6 g (0.0084 mol, 25%) of hydroxydiester 109, a colorless viscous oil, which could not be crystallized.

An analytical sample of 109 (preparative tlc: alumina, ether) exhibited ir (neat) 3490 (OH), 1720 (C=O), 1640 (C=C) and 1250 cm^{-1} (C-O); nmr (CCl_4) δ 4.4-3.75 (m, 1, CHOH), 3.75 (s, 6, OCH_3), 3.67-2.2 (m, 3, $=CCH_2$ and bridgehead methine), 2.13 (s, 1, absent after exchange with D_2O, OH), 1.8-1.3 [m, 6, $(CH_2)_3$], 1.28 (s, 3, bridgehead CH_3), 1.20 (s, 3, geminal CH_3) and 1.08 ppm (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 310 (2), 292 (2), 279 (16), 278 (11), 263 (12), 260 (22), 250 (18), 245 (23), 233 (47), 219 (26), 201 (30), 191 (14), 185 (13), 177 (21), 173 (26), 163 (41), 140 (28), 135 (15), 119 (26), 109 (28), 105 (29), 95 (23), 93 (19), 91 (38), 83 (24), 81 (24), 79 (30), 77 (30), 67 (25), 59 (34), 57 (29), 55 (65), 53 (21), 43 (39), 41 (100).

4α-Hydroxyconfertifolin (112). Hydroxydiester 109 (2.1 g, 6.75×10^{-3} mol) was reduced with sodium bis(2-methoxyethoxy) aluminum hydride and the resulting crude triol oxidized with silver carbonate on Celite according to the procedures used for the preparation of 5,6-dehydroconfertifolin. Column chromatography (activity III alumina, benzene) gave 0.6 g of a hydroxylactone fraction consisting of five components in the ratios of 1:30:5:1:15. This mixture was

subjected to glc/mass spectrometric analysis.

The component of highest concentration [4α-hydroxy-8,9-dihydroconfertifolin (111)] had mass spectrum (22.5 eV) *m/e* (rel intensity) 252 (25), 237 (37), 234 (40), 219 (47), 195 (20), 182 (15), 179 (15), 178 (52), 175 (12), 169 (75), 167 (36), 166 (64), 164 (15), 153 (50), 151 (28), 148 (30), 135 (24), 129 (62), 127 (100), 123 (68), 109 (64), 107 (35), 100 (61), 95 (35), 85 (38), 82 (50), 69 (53).

The component of second highest concentration [4α-hydroxyconfertifolin (112)] had mass spectrum (22.5 eV) *m/e* (rel intensity) 250 (79), 235 (82), 232 (99), 221 (21), 217 (58), 189 (20), 176 (30), 166 (79), 164 (35), 151 (32), 139 (100), 121 (41), 112 (75), 100 (33), 95 (39), 95 (83), 69 (52).

Fragrolide (39). To a stirred solution of 0.76 g (0.0096 mol) of pyridine in 12 ml of methylene chloride was added 0.48 g (0.0048 mol) of chromium trioxide. The flask was stoppered with a drying tube and the solution stirred at room temperature for 15 min. A solution of the previously prepared hydroxylactone mixture (0.2 g, 0.0008 mol) in methylene chloride was added in one portion and the reaction mixture stirred at room temperature for 15 min. The methylene chloride solution was decanted off of the tarry black deposit which had formed, the residue washed with ether and the combined organic solutions concentrated under vacuum. The residue was triturated with ether, filtered to remove insoluble chromium salts and the ethereal solution washed with 5% sodium

hydroxide and saturated sodium chloride. The dried (magnesium sulfate) solution was concentrated to yield 0.14 g (70% yield) of a ketolactone mixture which was subjected to glc/mass spectrometric analysis.

The major component [8,9-dihydrofragrolide (114)] had mass spectrum (22.5 eV) *m/e* (rel intensity) 252 (1.7), 251 (16.1), 250 (100), 236 (32), 207 (13), 168 (10), 167 (97), 151 (54), 127 (12), 124 (12), 123 (44), 110 (13), 109 (22), 108 (13), 107 (14), 95 (12), 85 (12), 83 (17), 69 (12).

The component of second highest concentration [fragrolide (39)] had mass spectrum (22.5 eV) *m/e* (rel intensity) 250 (3), 249 (15), 248 (100), 234 (14), 233 (92), 220 (12), 205 (27), 204 (8), 166 (11), 165 (22), 164 (20), 150 (12), 137 (10), 124 (11), 123 (32), 121 (18), 83 (38), 82 (14), 69 (16).

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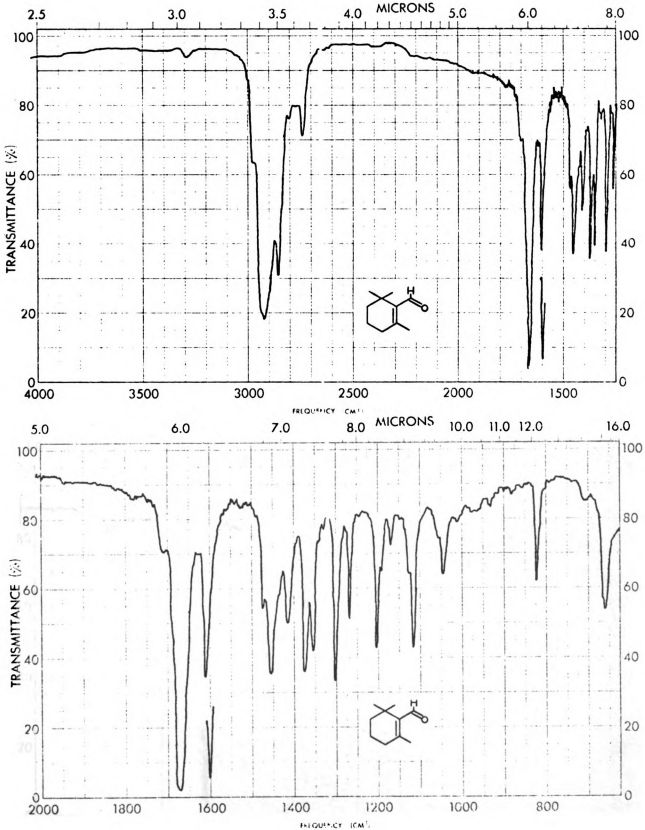

Figure 1. Infrared spectrum of β-cyclocitrial.

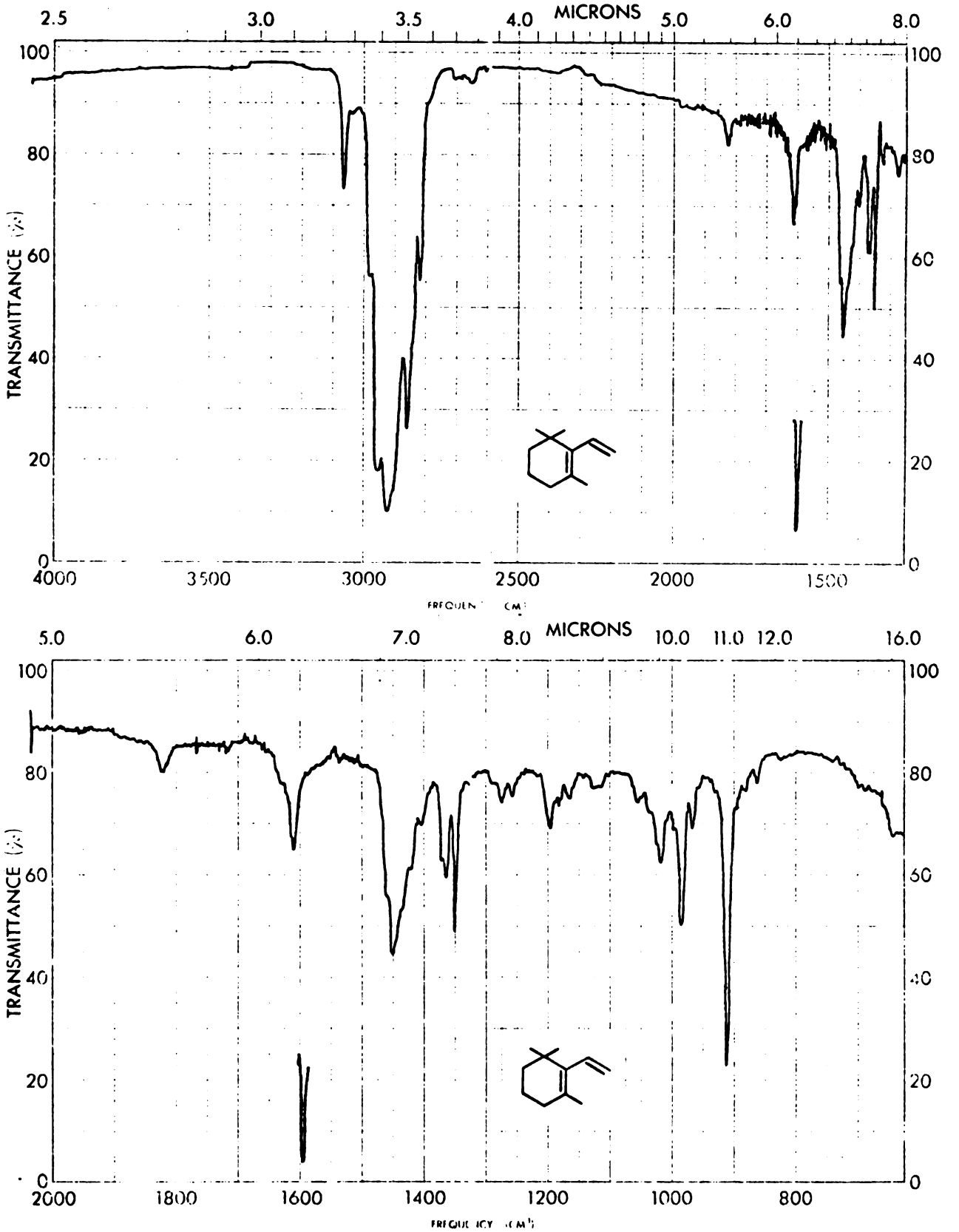

Figure 2. Infrared spectrum of 1-vinyl-2,6,6-trimethylcyclohexene.

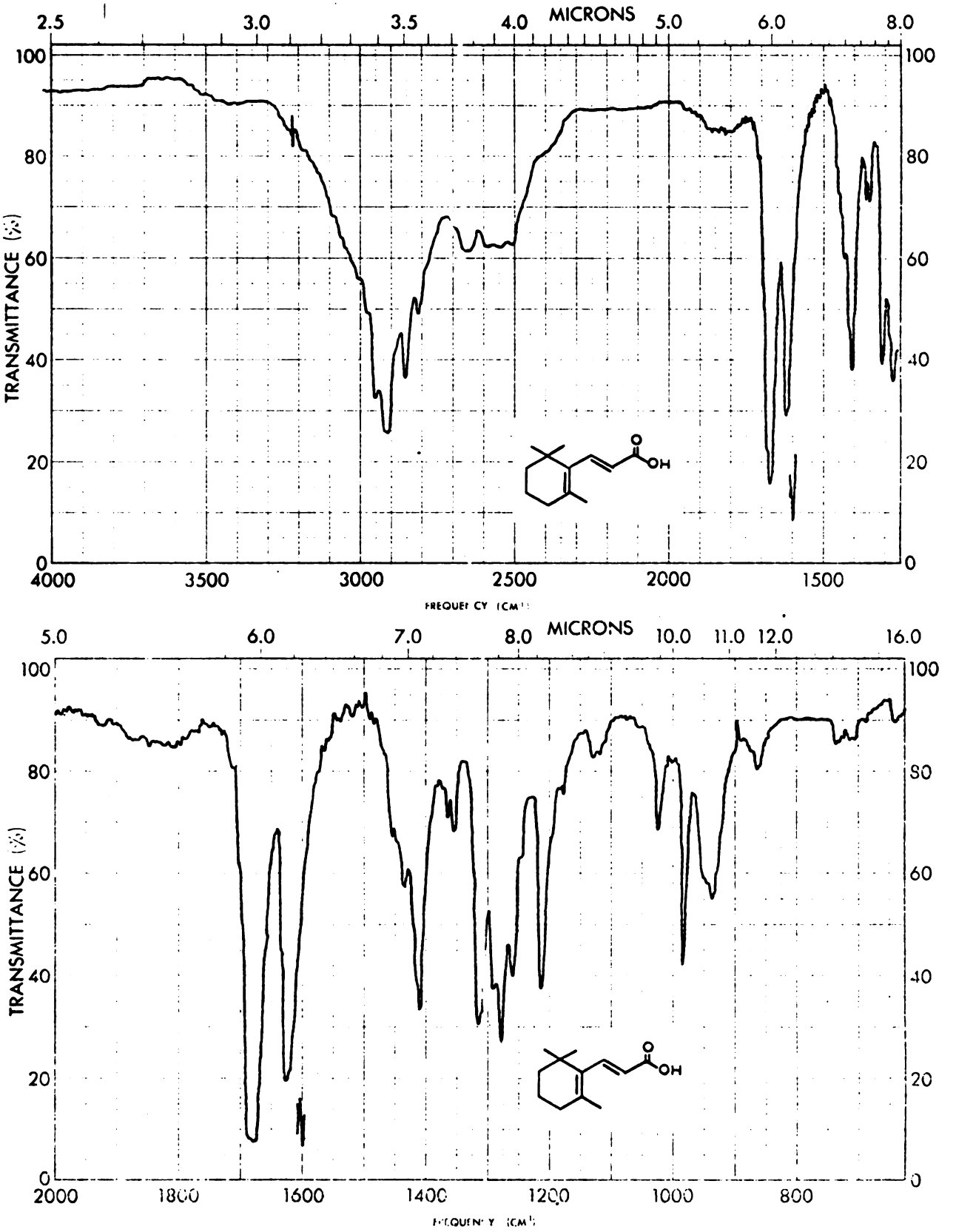

Figure 3. Infrared spectrum of β-(2,6,6-trimethyl-1-cyclohexene-1-yl-)acrylic acid.

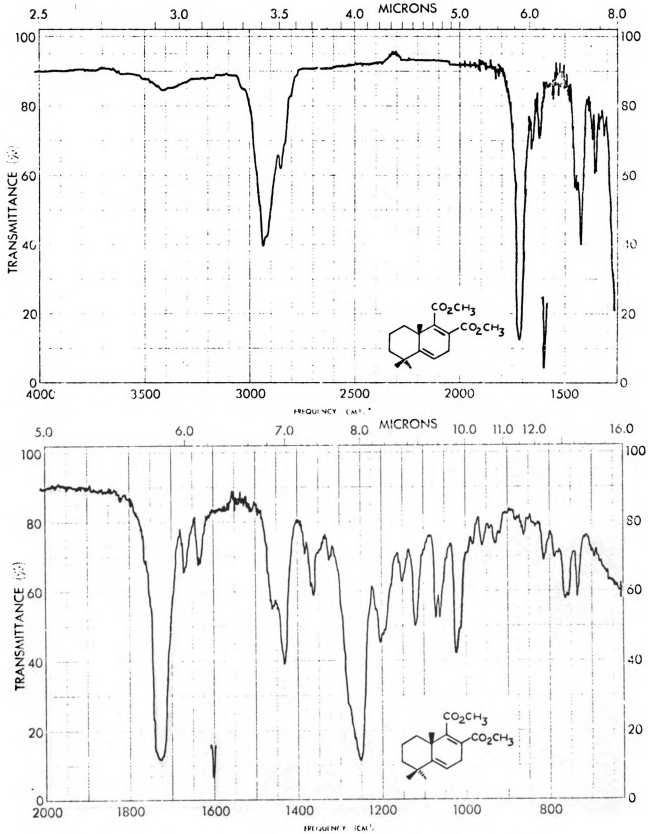

Figure 4. Infrared spectrum of dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate.

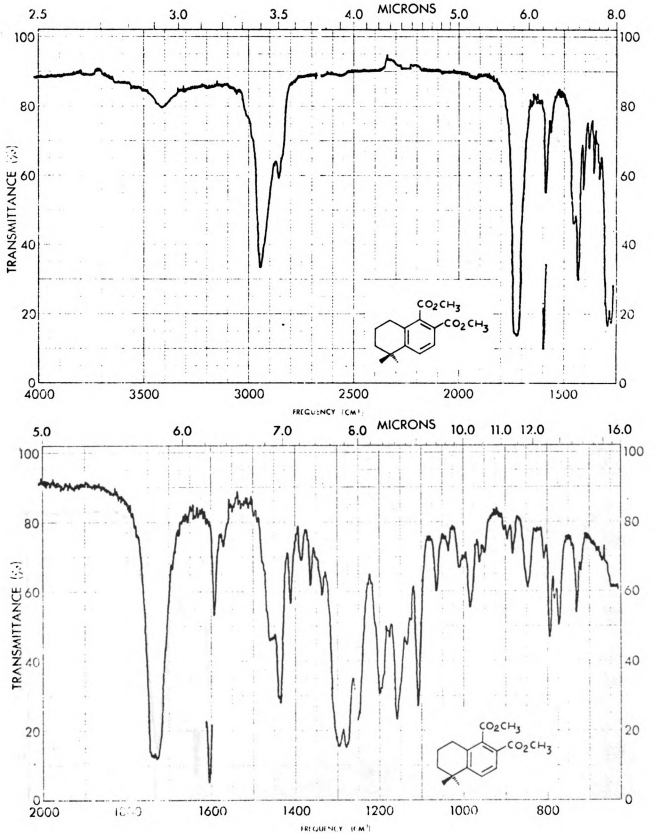

Figure 5. Infrared spectrum of dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate.

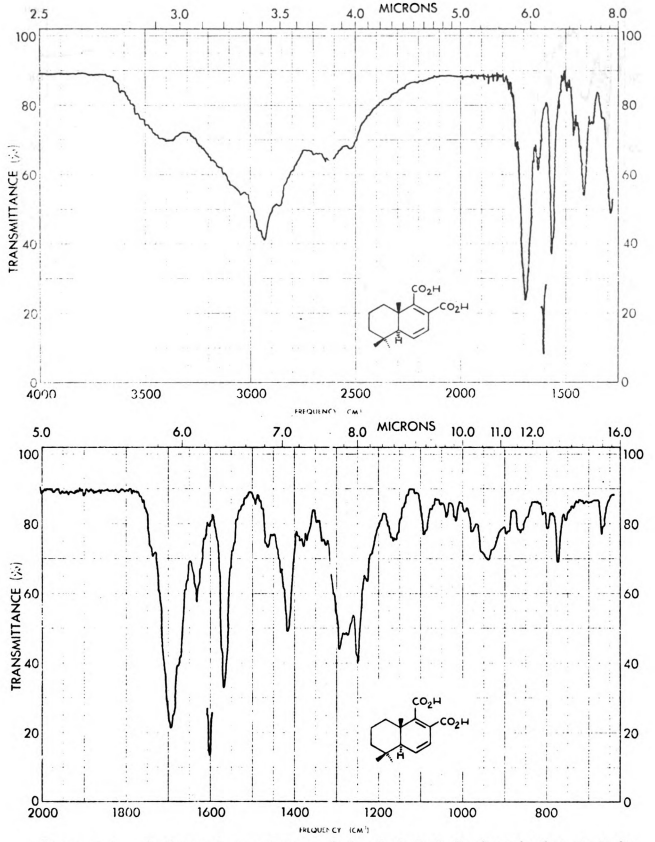

Figure 6. Infrared spectrum of 4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylic acid.

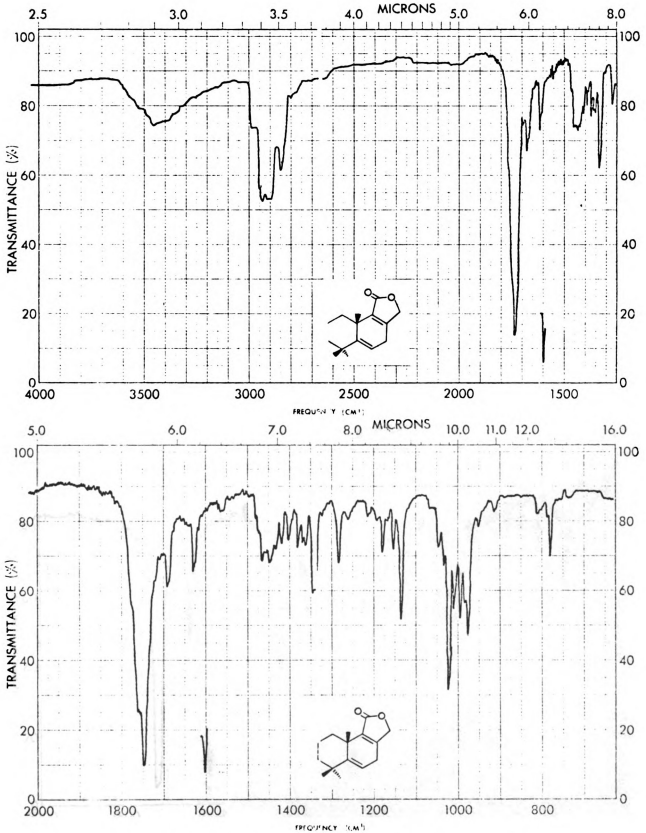

Figure 7. Infrared spectrum of 5,6-dehydroisodrimenin.

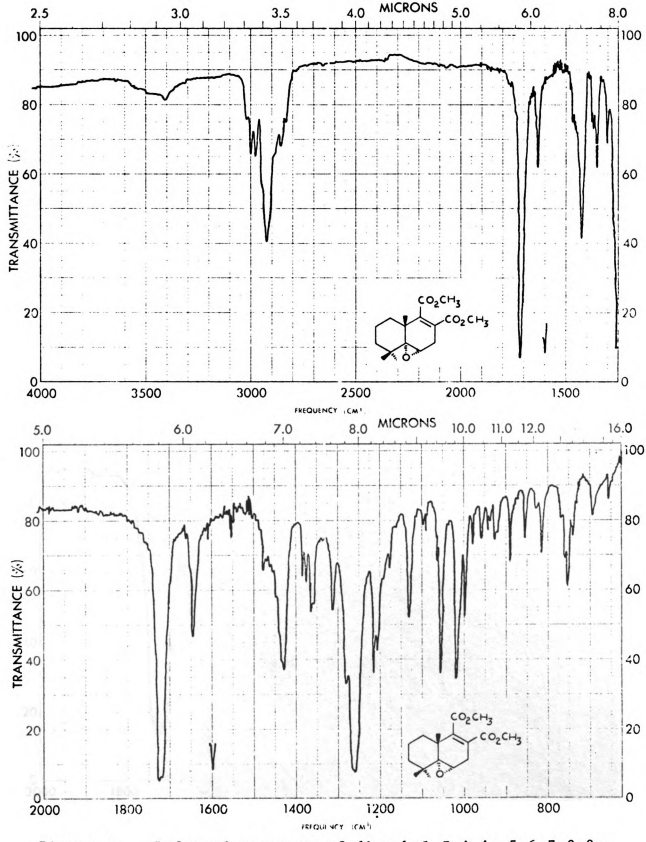

Figure 8. Infrared spectrum of dimethyl 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-4,4aα-epoxy-1,2-naphthalenedicarboxylate.

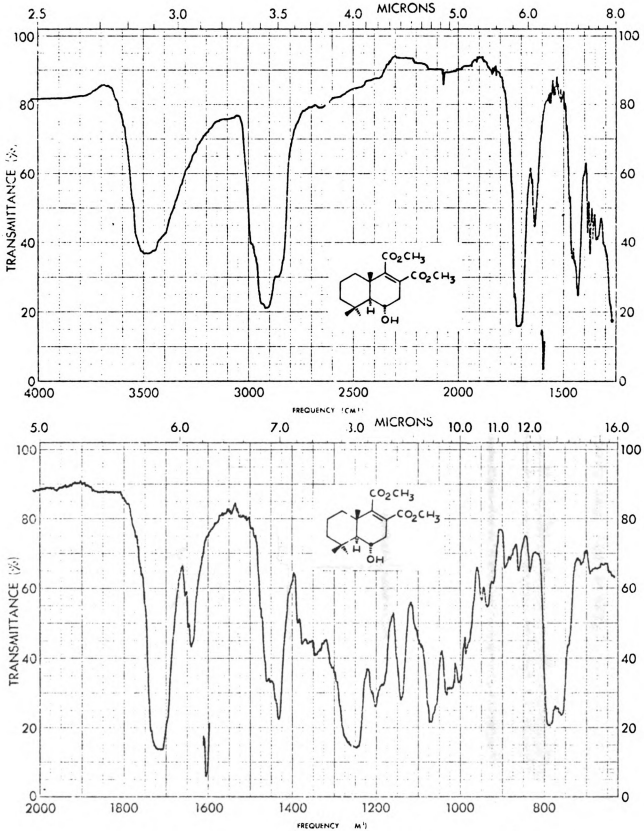

Figure 9. Infrared spectrum of dimethyl 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-4α-hydroxyl-1,2-naphthalenedicarboxylate.

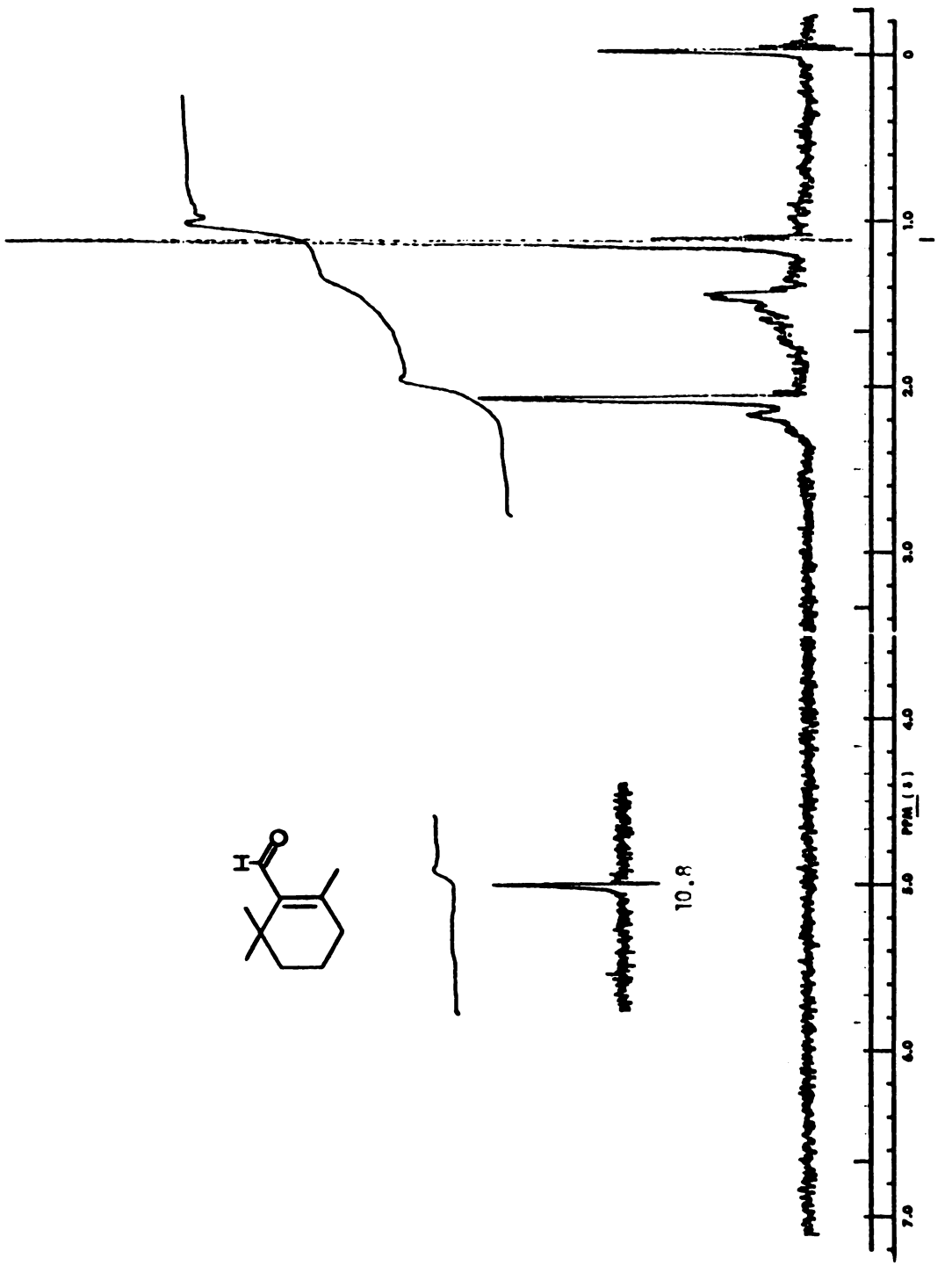

Figure 10. Nmr spectrum of β-cyclocitral.

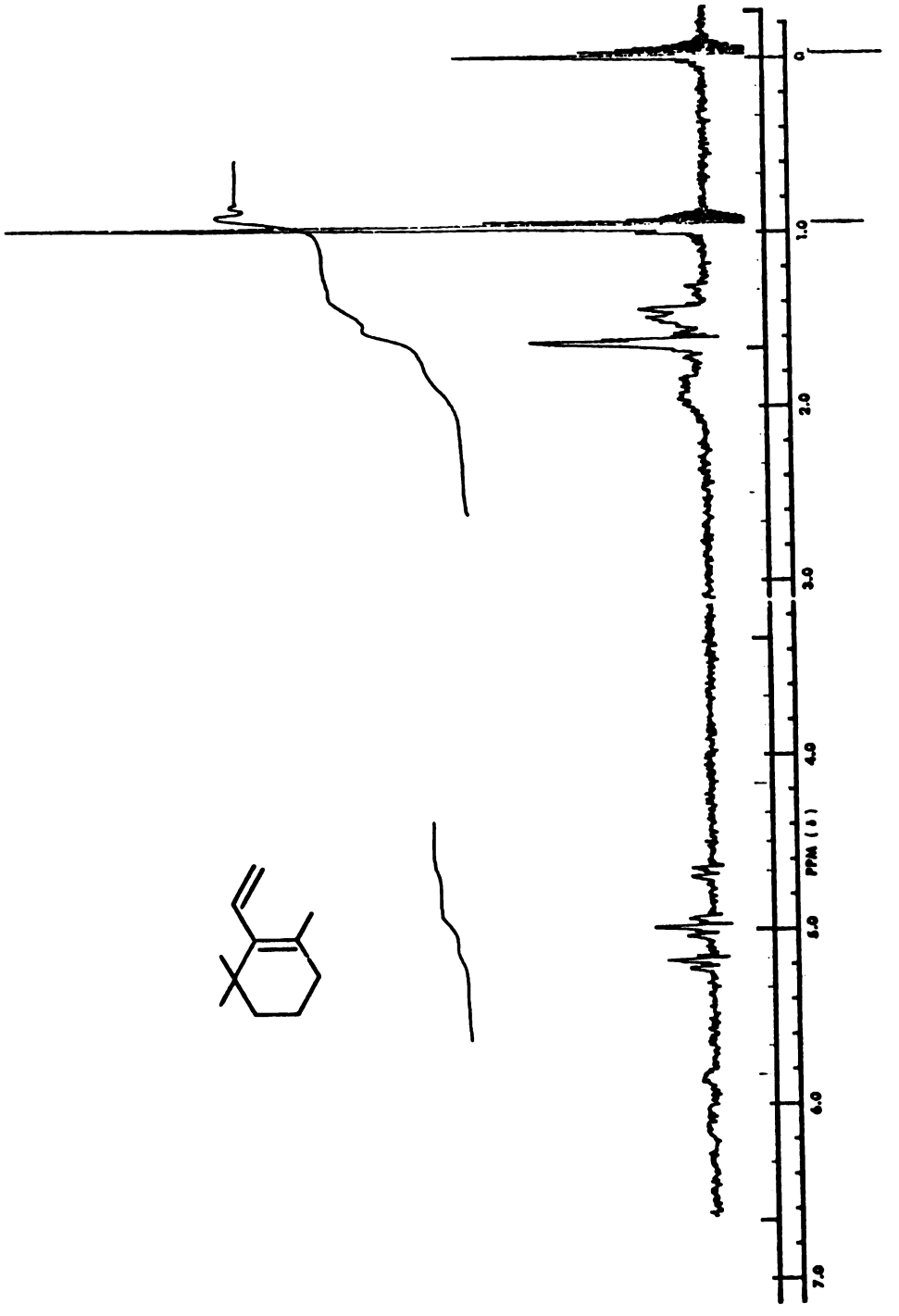

Figure 11. Nmr spectrum of 1-vinyl-2,6,6-trimethylcyclohexene.

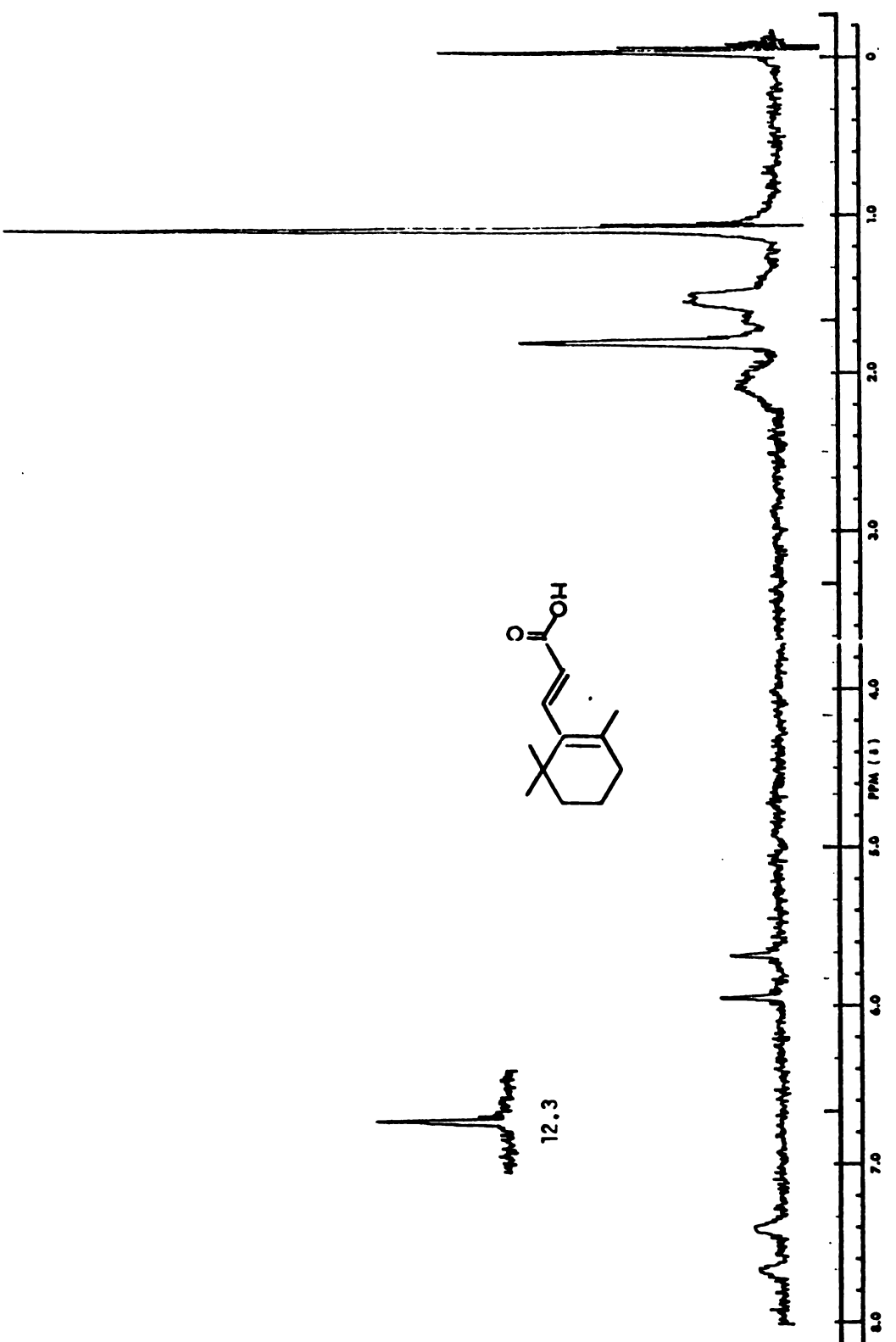

Figure 12. Nmr spectrum of β-(2,6,6-trimethyl-1-cyclohexene-1-yl-)acrylic acid.

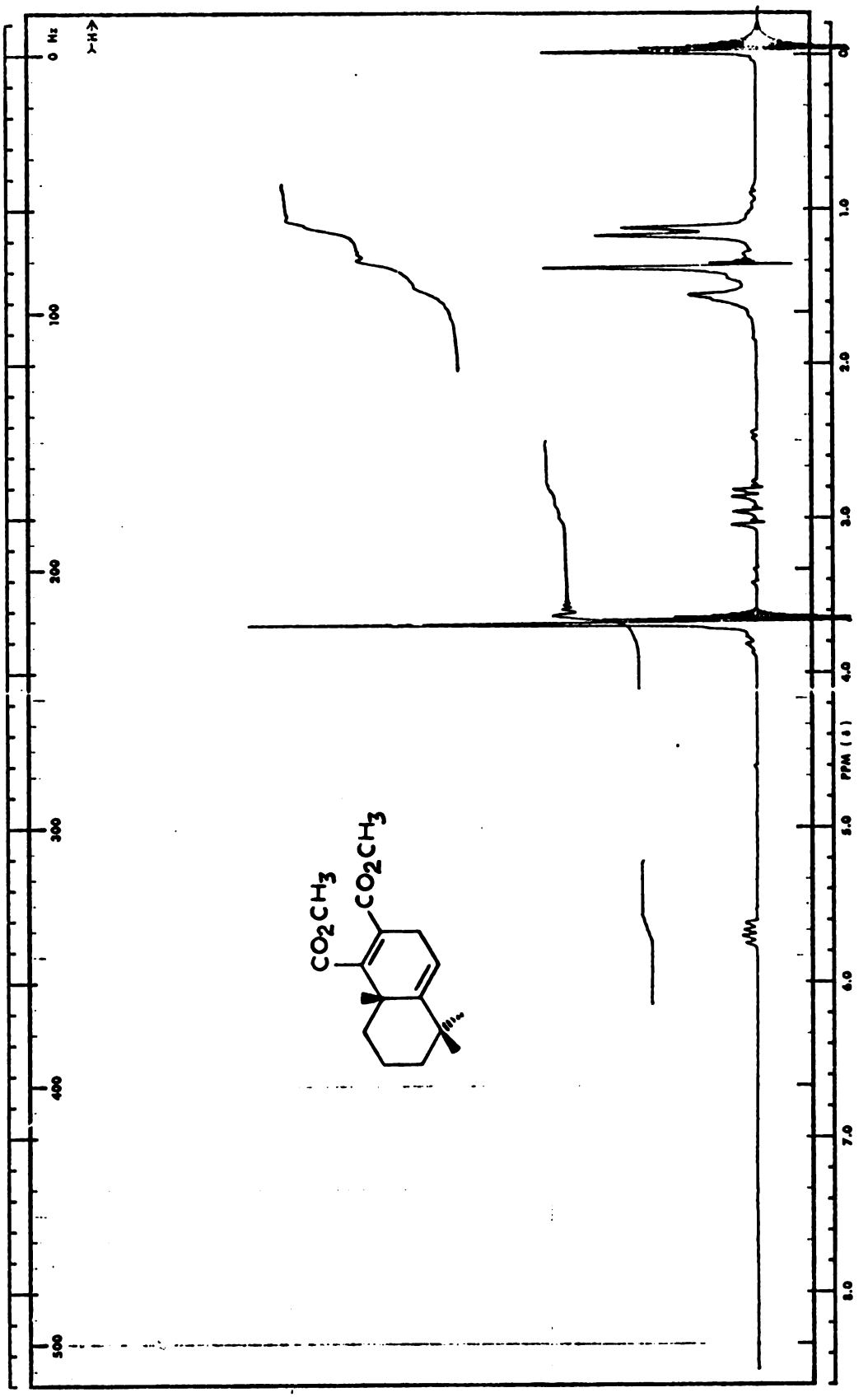

Figure 13. Nmr spectrum of dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate.

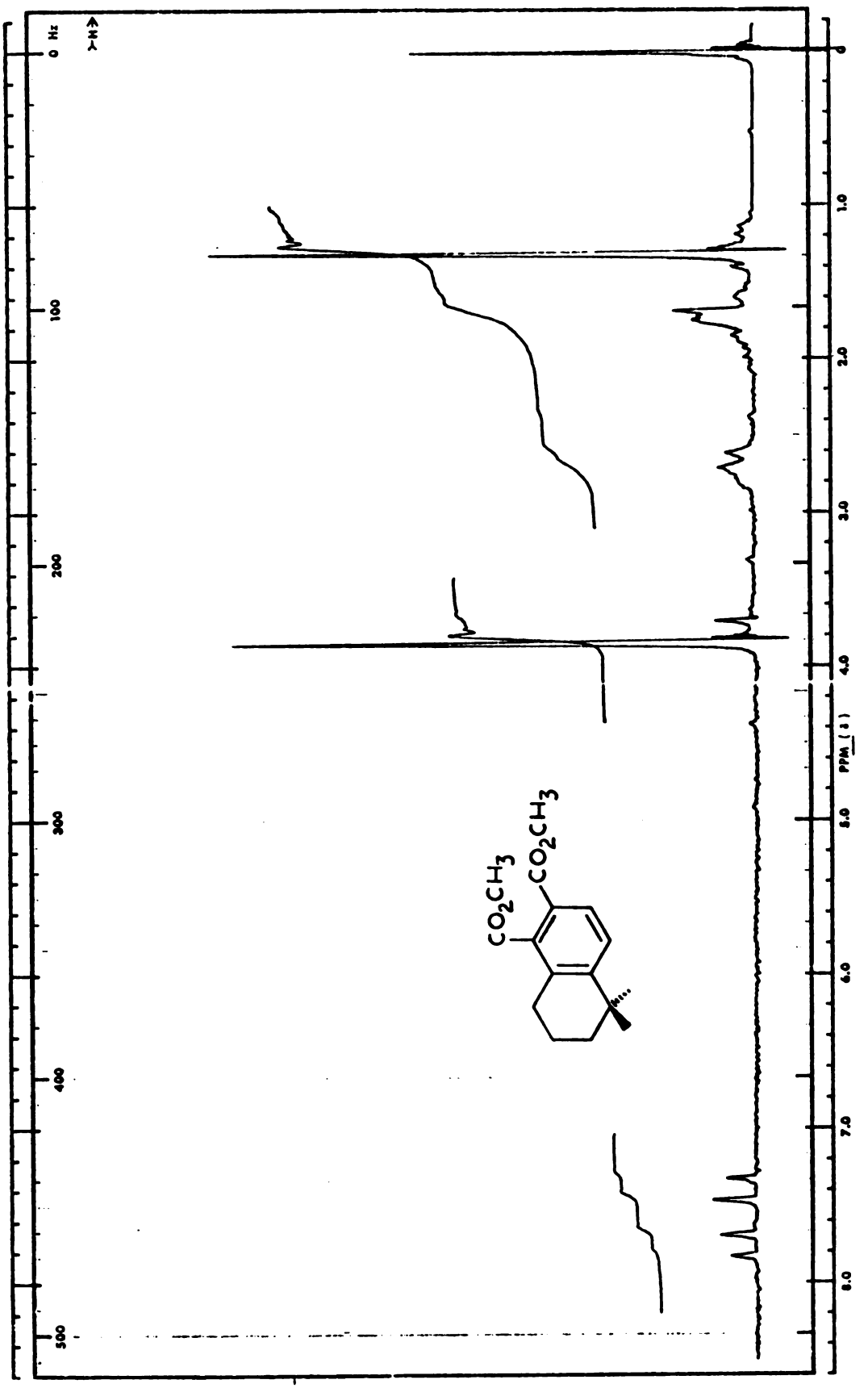

Figure 14. Nmr spectrum of dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate.

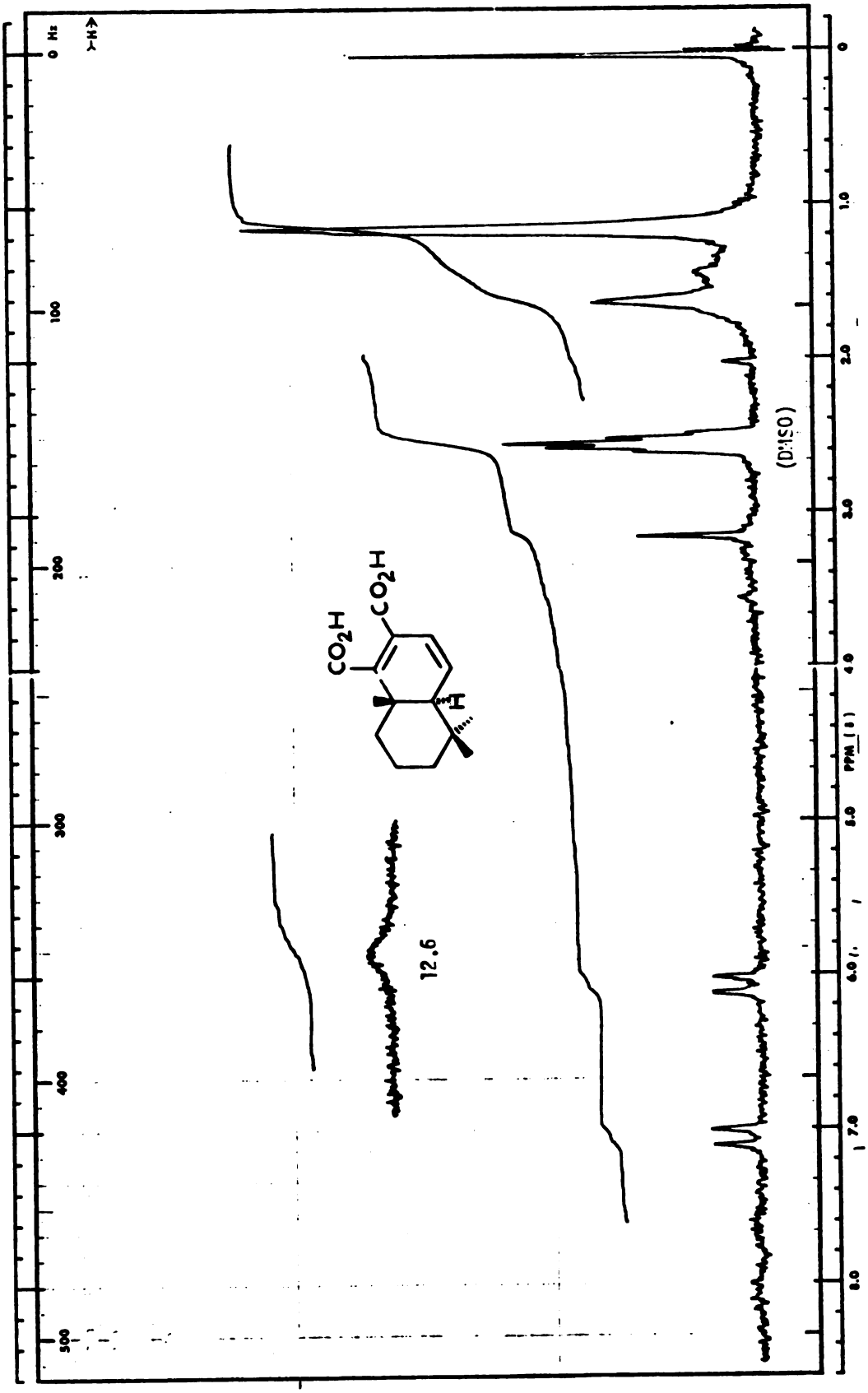

Figure 15. Nmr spectrum of 4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylic acid.

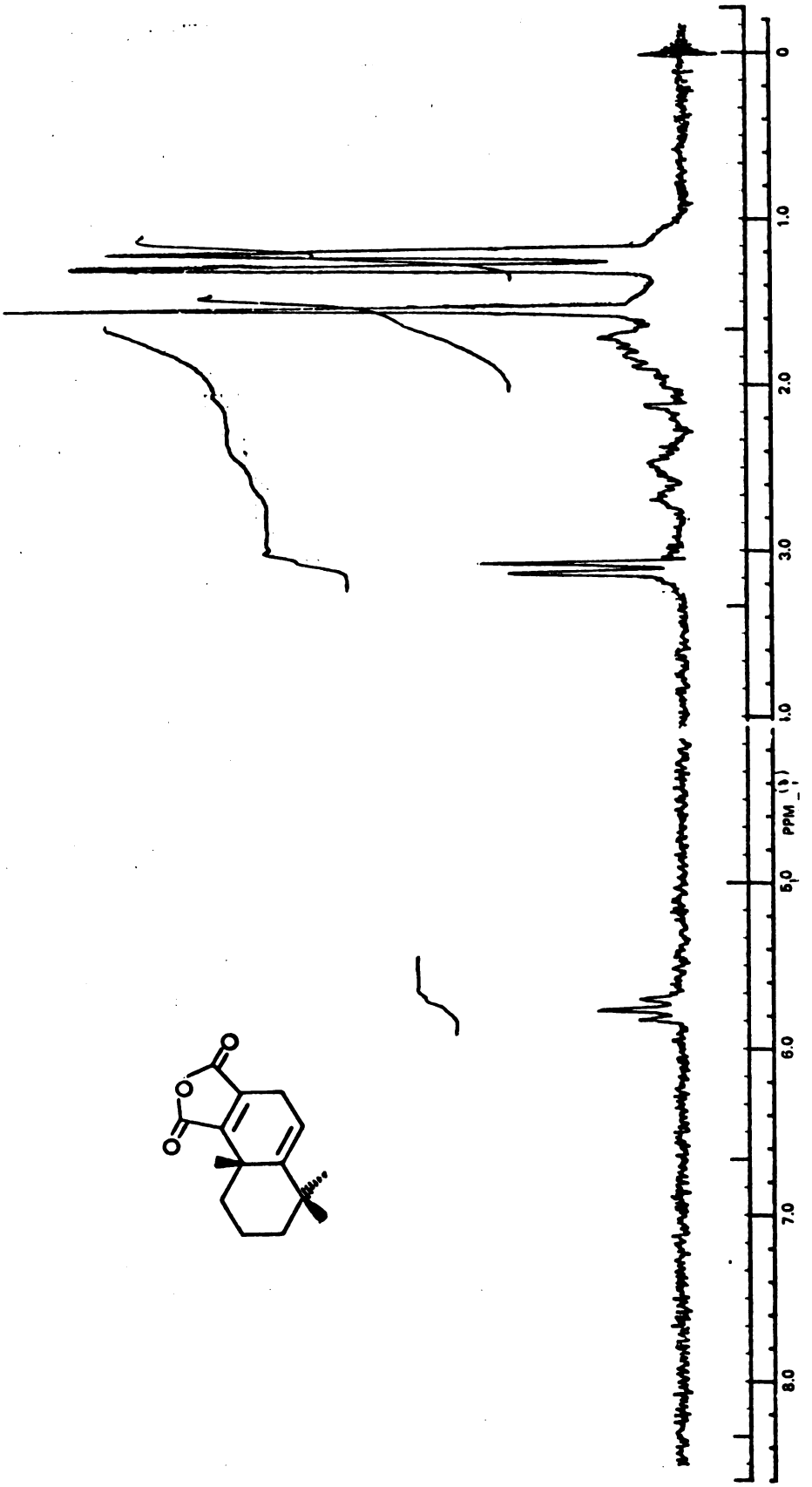

Figure 16. Nmr spectrum of 5,6-dehydrowinterin.

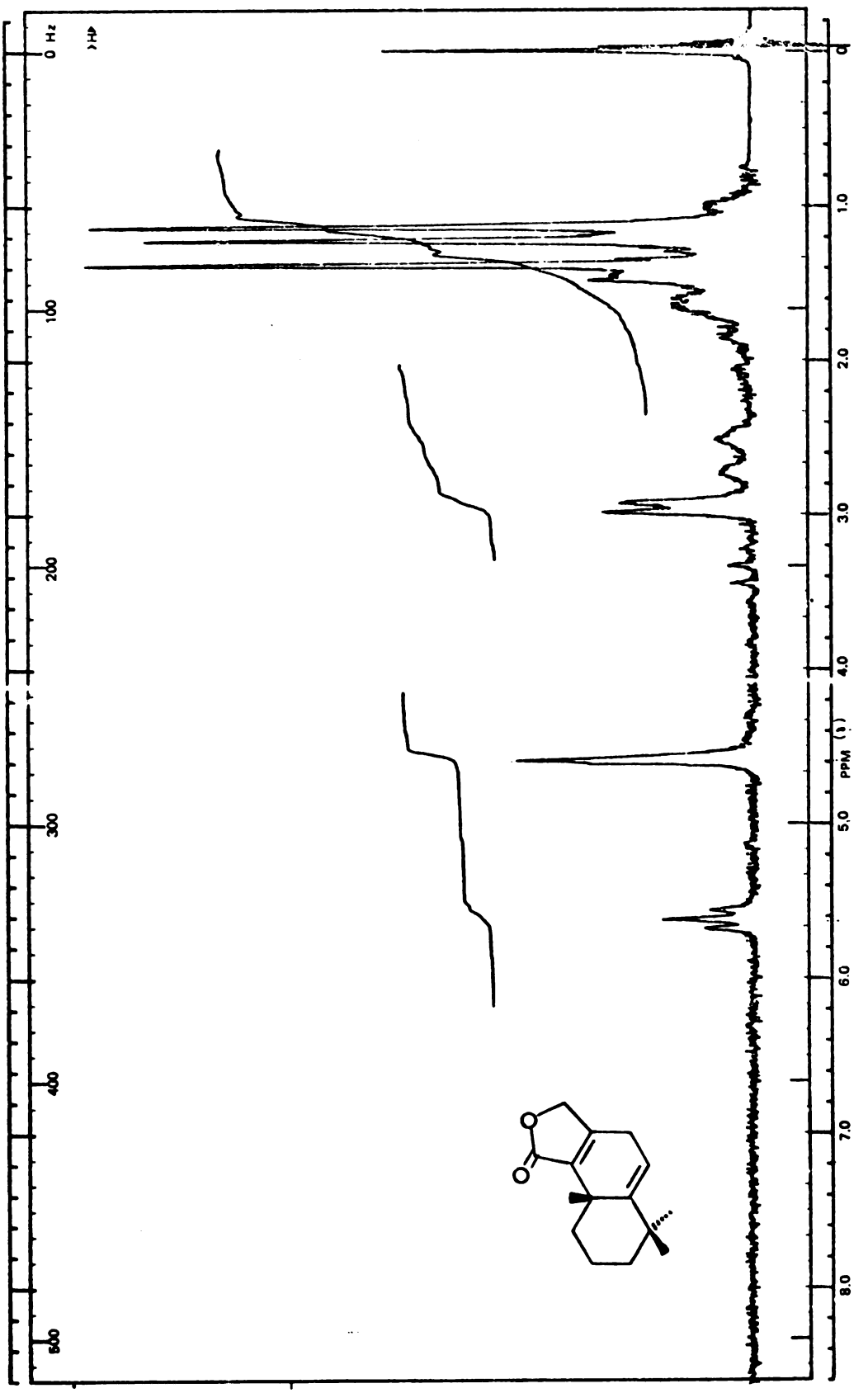

Figure 17. Nmr spectrum of 5,6-dehydroisodrimenin.

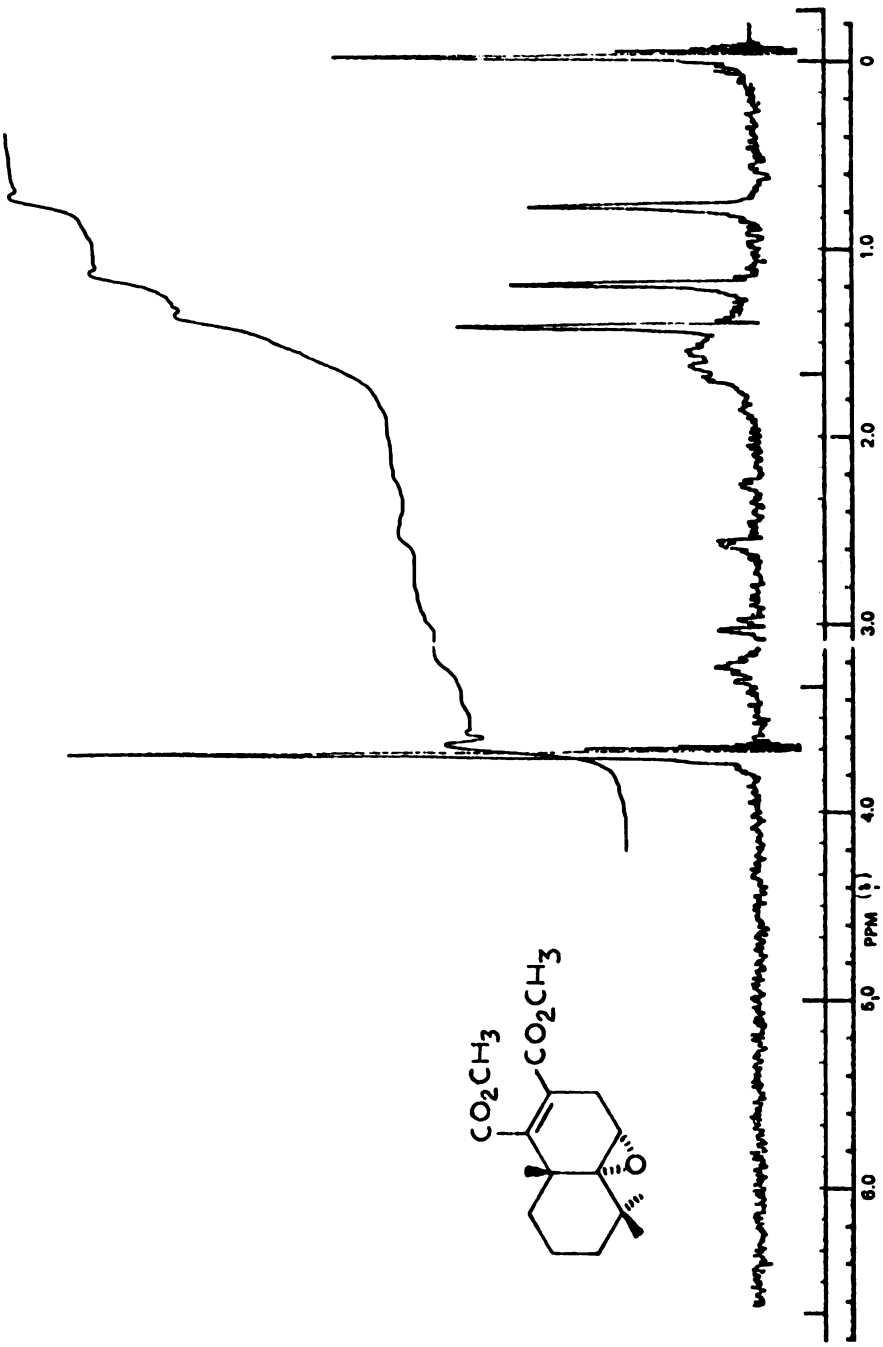

Figure 18. Nmr spectrum of dimethyl 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-4,4aα-epoxy-1,2-naphthalenedicarboxylate.

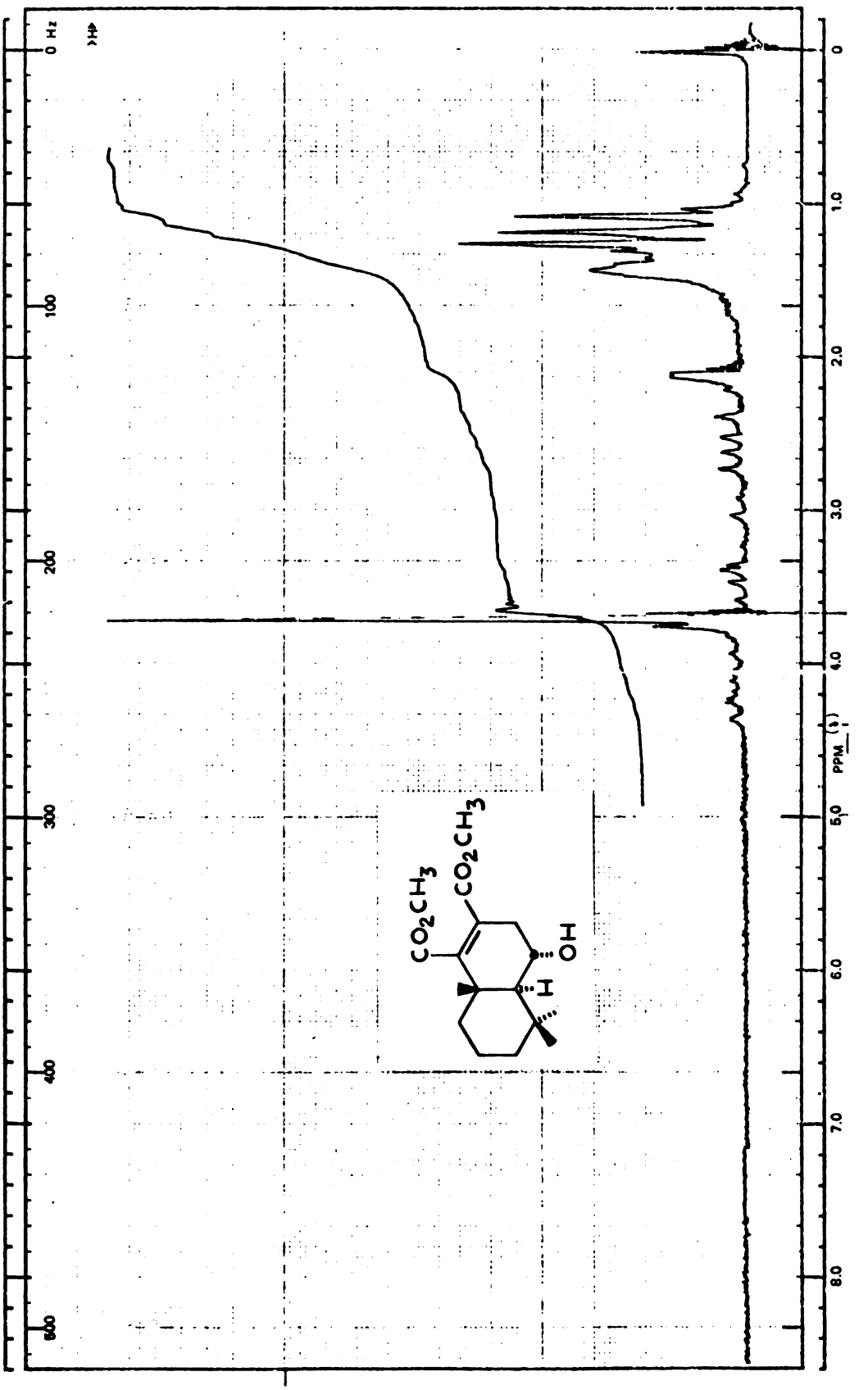

Figure 19. Nmr spectrum of dimethyl 3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-4α-hydroxy-1,2-naphthalenedicarboxylate.