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Synthesis of some drimanic sesquiterpenes

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SYNTHESIS OF SOME DRIMANIC SESQUITERPENES

by

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Dean of Graduate College

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INTRODUCTION

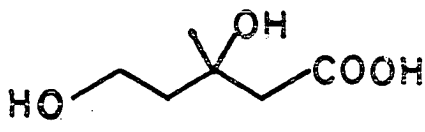
A new class of biogenetically important sesquiterpenes has recently been discovered. The purpose of this research is to confirm the structures of the first four members of this class: drimenol, drimenin, isodrimenin and confertifolin, by total synthesis.

HISTORICAL

In 1920, as the structures of more and more terpenic compounds had become known, Ruzicka noted a basic similarity among them. Despite the variety of structural patterns, Ruzicka[1] pointed out that the carbon skeleta of all terpenes consisted of combinations of the basic isoprene unit. This initial observation was supported by further structure determinations and gradually evolved into the isoprene rule. In 1953, Ruzicka[2] stated a revised version called the "biogenetic" isoprene rule, to account for terpenoids which did not completely follow the "empirical" isoprene rule. He indicated that isoprene units are condensed to the hypothetical precursors geraniol, farnesol, geranylgeraniol and squalene which lead to terpenes by cyclization and rearrangement mechanisms.

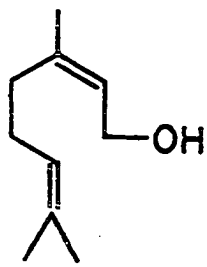
Although the fine points of terpene biogenesis are still being investigated, it is generally accepted that mevalonic acid (I) leads to an active intermediate, isopentenyl pyrophosphate[3](II), which self-condenses in a head-to-tail manner to form unsaturated alcohols. The condensation of two, three or four units of isopentenyl pyrophosphate produces geraniol (III), farnesol (IV) or geranylgeraniol (V), respectively. These alcohols and squalene (VI), the head-to-head dimer of farnesol, are envisioned as terpene precursors.

The transformation of squalene (VI) into cholesterol (VII) was suggested by Robinson[4] in 1934. Later this idea was revised by Woodward and Bloch[5] to explain the isotope distri-

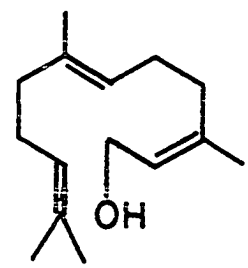


I

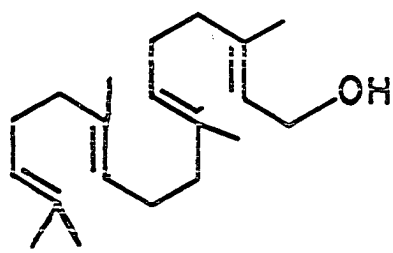
II



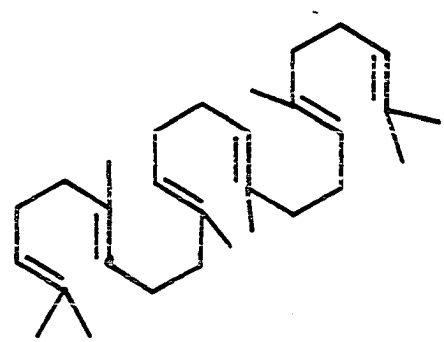
III



IV



V



VI

bution in cholesterol biosynthesized from C^{14}-labeled acetate. They postulated lanosterol (VIII) to be the primary product of oxidative cyclization and the precursor of cholesterol. The cyclization was assumed to be initiated by OH^+ which attacks the terminal double bond starting a concerted cyclization (as in IX) and leading to the cation-olefin complex X which rearranges to lanosterol (VIII).

The cyclization of squalene has been studied in great detail and the experimental results support the above postulates. Tchen and Bloch[6] were successful in proving that the conversion of squalene (VI) to lanosterol (VIII) was a concerted process. When the experiment was carried out in the presence of D_2O no deuterium appeared in the lanosterol, indicating the absence of any intermediate in the cyclization. Furthermore, cyclization in an atmosphere enriched in $O^{18}{}_2$ gave lanosterol containing O^{18} in the hydroxyl group of ring A. This is consistent with a cyclization initiated by a cationic species such as OH^+. The experiments of Maudgal, Tchen and Bloch[7] based on synthetic all-*trans* squalene provided evidence that this stereoisomer is in fact the precursor of lanosterol. The postulate that lanosterol (VIII) is the precursor of the steroids was proven by Clayton and Bloch[8] by the transformation of C^{14}-labeled lanosterol into cholesterol (VII) in liver homogenates.

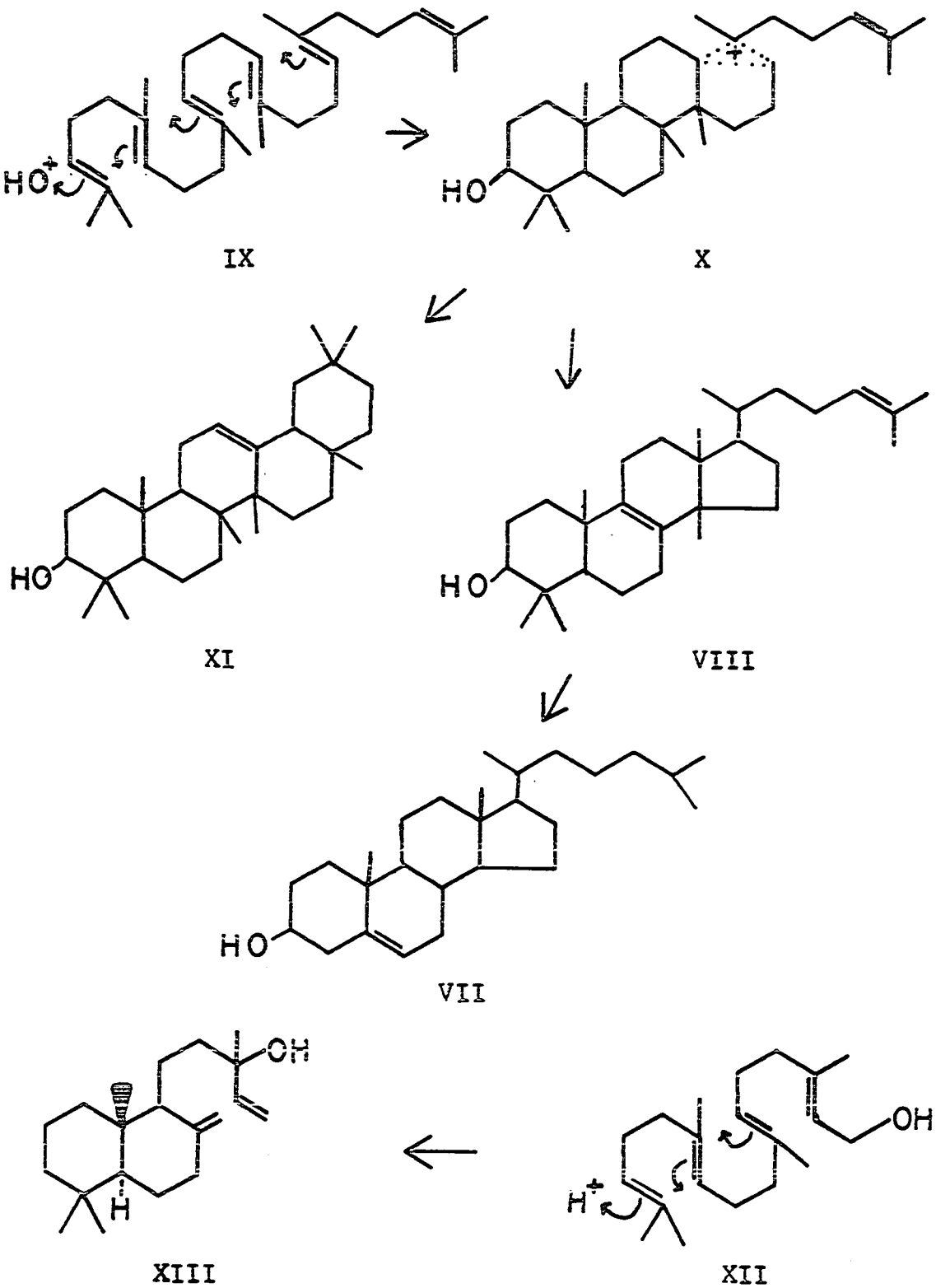
The concerted cyclization of squalene is also involved in the biogenesis of triterpenes. Eschenmoser[9] *et al.*

postulated the biosynthesis of all known pentacyclic triterpenes, such as β-amyrin (XI), from the cation-olefin complex X by accepted cyclization and rearrangement mechanisms. An analogous cyclization of geranylgeraniol (as in XII) is envisioned by Ruzicka[2] to lead to the cyclic diterpenes, such as manool (XIII).

The concept of steroids, triterpenes and diterpenes being formed by similar concerted polyene cyclizations is supported by their similarities in structure and stereochemistry. Investigations[10] have shown that the great majority have the same absolute stereochemistry at the A/B ring juncture, as depicted in manool (XIII).

However, the similarities in structure which are found in the higher terpenes and steroids do not continue into the sesquiterpene group, where a large variety of carbon skeleta are encountered[11]. Two groups contain a decalin ring system, exemplified by cadinene (XIV) and selinene (XV), but their structures and biogeneses are not analogous to those of the higher terpenes. Ruzicka[2], and later Hendrickson[12], proposed the cyclization of farnesol (IV) to intermediates XVI and XVII which could lead to the carbon skeleta of cadinene, selinene and several other sesquiterpenes.

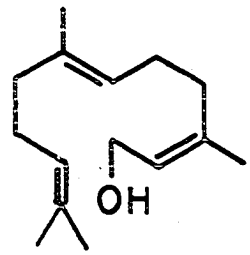
Until most recently the structure patterns characteristic of the higher terpenes could not be found among the sesquiterpenes. In 1953, Ruzicka[2] stated: "The one carbon skeleton which has never been observed is the bicyclofarnesol skeleton


HO
IX
HO
X
HO
XI
HO
VIII
HO
VII
OH
H
XIII
H
OH
XII

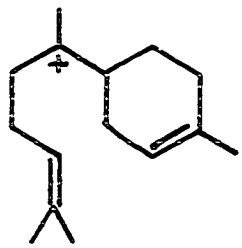
(XVIII), so typical of all cyclic diterpenes and triterpenes. This appears to indicate that the biogenesis of steroids, diterpenes and triterpenes differs in some fundamental detail from that of monoterpenes and sesquiterpenes".

While the expected bicyclofarnesol structure had not been observed yet in nature, investigations of *in vitro* acid-catalyzed cyclizations of farnesol derivatives had been going on for some years. In 1949, Schinz[13] reported that the cyclization of farnesic acid (XVIX) in formic acid gave a mixture from which he isolated α-bicyclofarnesic acid (XX). This acid was reduced with lithium aluminum hydride to α-bicyclofarnesol (XXI). The stereochemistry was not known at this time, but later work by Eschenmoser[14] showed that it was, as indicated in XXI, the same as that observed in higher terpenes.

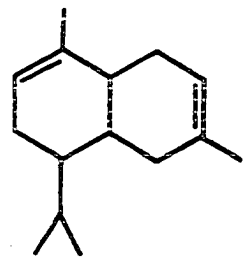
In 1954, Djerassi[15] published the isolation of the first bicyclofarnesol sesquiterpene, called iresin (XXII), from the Mexican plant *Iresine celosioides*. Although the position of the C(10) methyl group was still in doubt, he proposed[16] the correct structure on the basis of the isoprene rule and biogenetic analogy with the higher terpenes. Later work[17] corroborated the structure, but optical rotatory dispersion studies with steroid models showed that the absolute stereochemistry at the A/B ring juncture (indicated in XXII) was the opposite of that found in the higher terpenes. Three related compounds[18] were subsequently found and Djerassi[19] stated: "Iresin (XXII) and its naturally occurring relatives



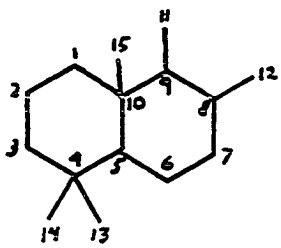
IV



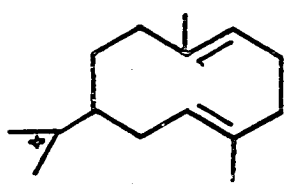
XVI



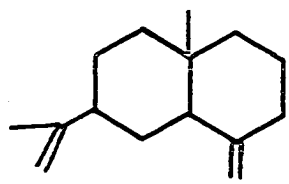
XIV



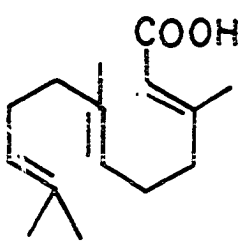
XVIII



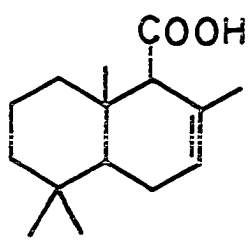
XVII



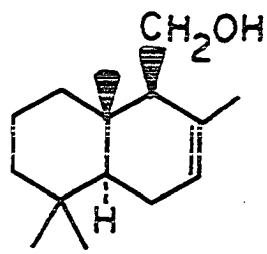
XV



XVIX



XX



XXI

dihydroiresone (XXIII), dihydroiresin (XXIV) and isoiresin (XXV) represent the first group of sesquiterpenes which follow the isoprene skeleton XVIII. This particular bicyclofarnesol skeleton is found in virtually all of the diterpenes and triterpenes and, in demethylated form, in the steroids. The discovery of iresin has thus afforded a missing link between the lower (mono- and sesquiterpenes) and the higher ones".

In 1957, Overton and Brooks[20] published the structure and absolute stereochemistry of the second bicyclofarnesol sesquiterpene found in nature. The new sesquiterpene, named drimenol (XXVI), was isolated from the bark of the South American tree Drimys winteri in 1948 by Appel[21] who also accomplished some preliminary degradations. The structure elucidation was later continued and completed by Overton[21] et al. who proposed the name drimane for the basic hydrocarbon structure XVIII.

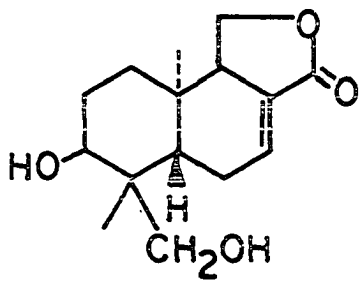
It was determined rapidly that drimenol (XXVI) was an alcohol with a tri-substituted double bond by its ultraviolet and infrared spectra. Moreover, drimenol gave a yellow color with tetranitromethane and consumed one mole of peracid indicating the presence of one double bond. The fact that drimenol was not an allylic alcohol was evident from its inertness to manganese dioxide oxidation. The carbon skeleton was established by dehydrogenation with palladium on charcoal, which afforded 1,2,5-trimethylnaphthalene (XXVII) as the only identified product.

Inferring that drimenol was a bicyclofarnesol sesqui-

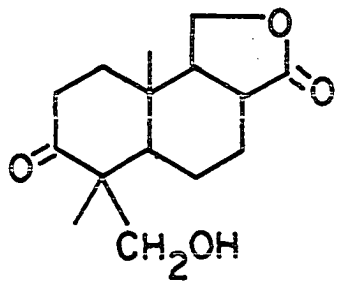
terpene, the final structure and stereochemistry was determined by its oxidation to known degradation products of higher terpenes. Catalytic hydrogenation of drimenol furnished a saturated alcohol, drimanol (XXVIII), which was oxidized by potassium dichromate without the loss of carbon to a monocarboxylic acid, drimanic acid (XXIX). Direct comparison showed that drimanic acid was identical with the known acid XXIX which had been obtained previously by the degradation of oleanolic acid and ambrein[22]. Oxidation of drimenol with chromic anhydride led to an α,β-unsaturated ketone, nordrimenone (XXX), which was ozonized to a dicarboxylic acid, drimic acid (XXXI). Direct comparison of drimic acid and the known degradation product XXXI of onocerin and abietic acid[23] proved that they were identical. As a final point, the infrared spectrum of drimenol (XXVI) was identical with that of α-bicyclofarnesol (XXI) (dl-drimenol), which had been synthesized[13] in vitro in 1949.

Considering the final structure of drimenol, Overton[21] stated: "Drimenol is thus the first representative of this class possessing both the skeletal structure and absolute stereochemistry normally found in ring A and B of the di- and triterpenes, and so constituting a biogenetic link between these three groups".

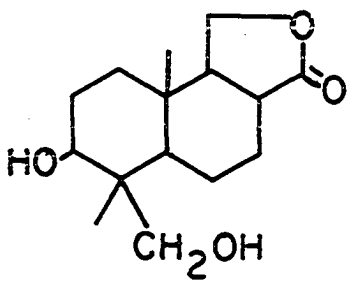
Three isomeric sesquiterpene lactones, drimenin (XXXII), isodrimenin (XXXIII) and confertifolin (XXXIV), were subsequently isolated from Drimys winteri. Their structural and



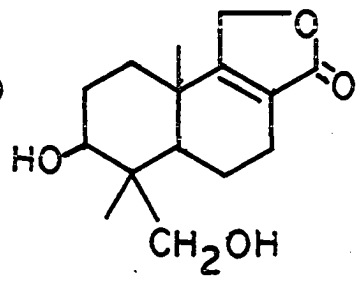
XXII



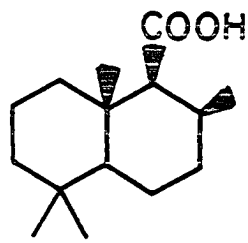
XXIII



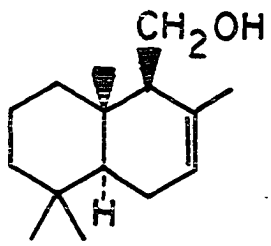
XXIV



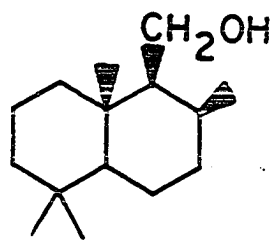
XXV



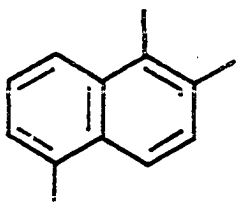
XXIX



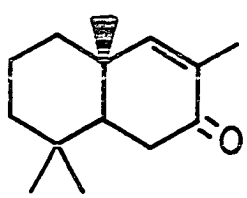
XXVI



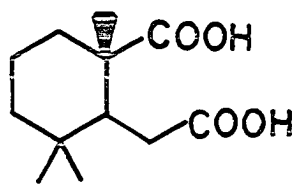
XXVIII



XXVII



XXX



XXXI

stereochemical elucidation by Overton[24] in 1960 showed that they were oxidation derivatives of drimenol.

Investigation of the infrared spectrum of drimenin (XXXII), $C_{15}H_{22}O_2$, indicated the presence of a butanolide and an isolated, triply substituted double bond. Its lactonic nature was supported by reduction with lithium aluminum hydride to an unsaturated diol (XXXV). Both drimenin (XXXII) and the unsaturated diol (XXXV) gave a yellow color with tetranitromethane further supporting the presence of a double bond. Drimenin was also catalytically hydrogenated to a saturated lactone (XXXVI) which was reduced with lithium aluminum hydride to a saturated diol (XXXVII).

Consideration of the analytical data, functional groups and similarity of infrared spectra to drimenol suggested that drimenin (XXXII) had a bicyclofarnesol skeleton. Further work showed this to be correct by the correlation of degradation products with those of drimenol (XXVI).

Oxidation of drimenin (XXXII) with potassium dichromate afforded an α,β-unsaturated ketone (XXXVIII) whose infrared spectrum contained a butenolide absorption band, indicating migration of the previously isolated double bond. The unsaturated ketone (XXXVIII) was readily dehydrogenated by selenium dioxide to a dienone lactone which could be accommodated on the drimane template only as in XXXIX. This evidence defined the constitution of drimenin as in XXXII. Further experiments supported this structure and also defined the

absolute stereochemistry. First, ozonolysis of the unsaturated ketone (XXXVIII) and decomposition of the ozonide with hydrogen peroxide furnished drimic acid (XXXI), previously obtained from drimenol[21]. Secondly, the unsaturated diol XXXV consumed two moles of hydrogen over Adams catalyst to yield drimanol (XXVIII), the hydrogenation product of drimenol[21].

The structure of isodrimenin (XXXIII) was rapidly elucidated when isomerization of drimenin (XXXII), a butanolide, with 10% potassium hydroxide at 20° for 1 hour afforded isodrimenin, whose infrared spectrum indicated it to be a butenolide.

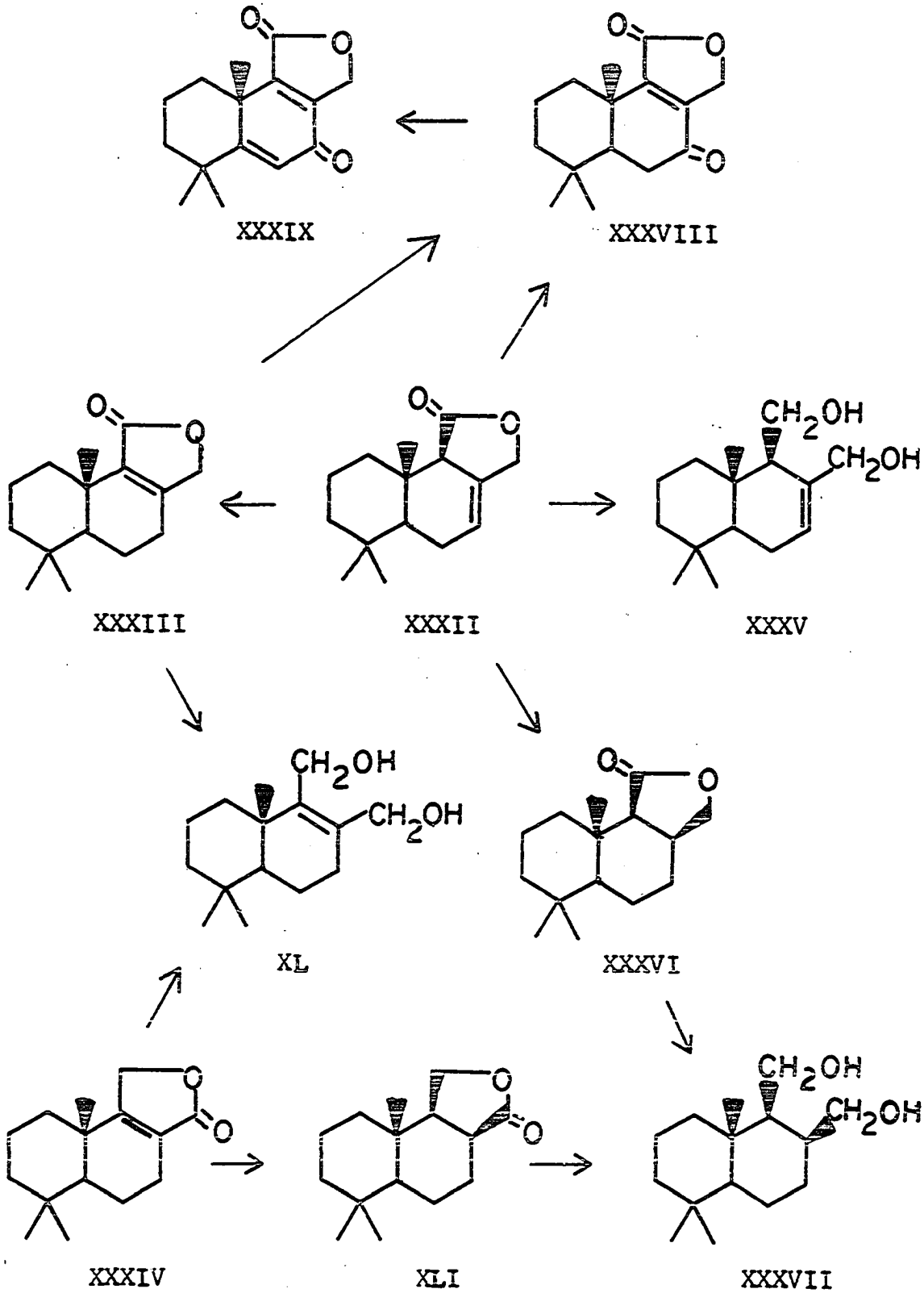
Further evidence was obtained when the oxidation of isodrimenin (XXXIII) with potassium dichromate gave the ketone XXXVIII previously obtained from drimenin (XXXII) and lithium aluminum hydride reduction gave the new unsaturated diol XL. Isodrimenin is probably not an artefact since drimenin was substantially unchanged when subjected to the conditions used in the isolation procedure.

Confertifolin (XXXIV), whose infrared spectrum also suggested a butenolide, did not give a color with tetranitromethane showing the double bond to be tetra-substituted, as in isodrimenin (XXXIII). The infrared and ultraviolet spectra were very similar with those of isodrimenin (XXXIII), suggesting that confertifolin (XXXIV) differed only in the arrangement of the lactone ring. This was confirmed when the lithium aluminum hydride reduction of confertifolin afforded the same unsaturated

diol XL obtained from isodrimenin. Confertifolin was also hydrogenated to a new saturated lactone (XLI) which was reduced with lithium aluminum hydride to the saturated diol XXXVII previously obtained from drimenin.

Several other sesquiterpenes of the bicyclofarnesol skeleton have been reported. The structure of farnesiferol A (XLII) was determined by Jeger[25] in 1958 and has the 5β,10α configuration found in the iresin series. Recently, Barnes and Loder[26] isolated polygodial (XLIII) from both Polygonum hydropiper and Drimys lanceolata[27] and rapidly established the structure as a di-aldehyde of the drimenol series. Firstly, sodium borohydride reduction of polygodial afforded the unsaturated diol XXXV previously obtained from drimenin[24] (XXXII). Secondly, treatment with alkali led to an isomeric α,β-unsaturated lactone (XLIV) by an internal Cannizzaro reaction. Catalytic hydrogenation of the latter afforded a lactone which by direct comparison was shown to be identical with the hydrogenation product XLI of confertifolin[24]. Other reports indicate that a second similar sesquiterpene, tadeonal[28] (XLV), has been isolated from Polygonum hydropiper and the reported sesquiterpene, tadenal[29], has been shown to be polygodial (XLIII).

Very recently, Overton[30] et al. determined the structures of four new sesquiterpenes: winterin (XLVI), valdiviolide (XLVII), fuegin (XLVIII) and futronolide (XLIX). All isolated from Drimys winteri, their structures were elucidated as oxidation derivatives of the drimenol series by their relationship


XXXIX
XXXVIII
XXXIII
XXXII
XXXV
XL
XXXVI
XXXIV
XLI
XXXVII

with confertifolin (XXXIV).

Winterin (XLVI), $C_{15}H_{20}O_3$, was identified as a maleic anhydride by its infrared and ultraviolet spectra. Assuming a structural relationship with confertifolin (XXXIV), winterin was assigned the structure XLVI. This was confirmed by reduction with lithium aluminum hydride to the unsaturated diol XL previously obtained[24] from both isodrimenin (XXXIII) and confertifolin (XXXIV).

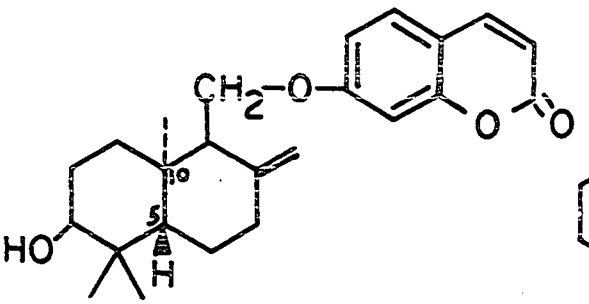
The infrared and ultraviolet spectra of valdiviolide (XLVII), $C_{15}H_{22}O_3$, suggested the presence of a butenolide and one hydroxyl group. The reduction with lithium aluminum hydride to the previously obtained diol XL and the chromic anhydride oxidation to winterin (XLVI) established that the hydroxyl group of valdiviolide (XLVII) was on the lactone ring. The correct structure, XLVII, was determined by its hydrogenolysis over platinum oxide to the known[24] saturated lactone XLI.

The similarity of the infrared and ultraviolet spectra of fuegin (XLVIII) with those of valdiviolide (XLVII) and confertifolin (XXXIV) indicated a lactonol structure as in valdiviolide with the fourth oxygen present as an additional hydroxyl group. The position of a one-proton multiplet at 4.67 ppm in its nuclear magnetic resonance spectrum suggested that the additional hydroxyl group was allylic to the butenolide double bond, hence at C(7). This was confirmed by the conversion of fuegin (XLVIII) to the known[24] saturated lactone XLI by

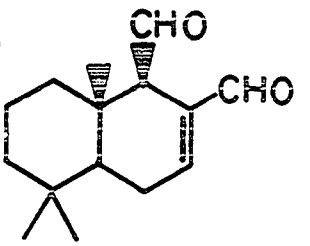
catalytic hydrogenation which hydrogenolized both allylic hydroxyls and reduced the double bond. The stereochemistry of the C(7) hydroxyl group was not deducible from the available data and lack of material precluded further investigation. The C(11) hydroxyl groups in fuegin (XLVIII) and valdivioiide (XLVII) was assumed to be in the thermodynamically more stable α-configuration since equilibration through the aldehydo-acid was considered to have taken place without difficulty.

The fourth sesquiterpene, futronolide, was isolated in very small amounts and only 5 mg. were available for investigation. However, on the basis of mass spectrometry and other spectral properties a tentative structure, XLIX, was assigned to futronolide.

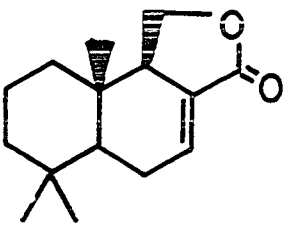
Of all the sesquiterpenes of the drimenol series isolated from the South American Drimys species only drimenol and confertifolin are encountered widely and in major amounts. Isodrimenin appears occasionally while the remaining compounds are found very rarely and only in minor quantities.



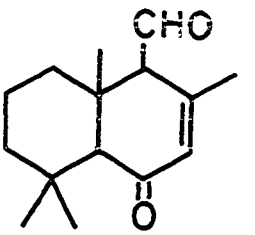
XLII



XLIII



XLIV



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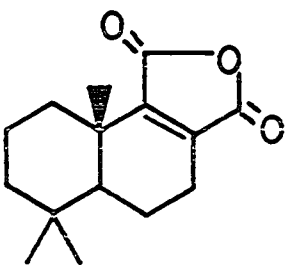

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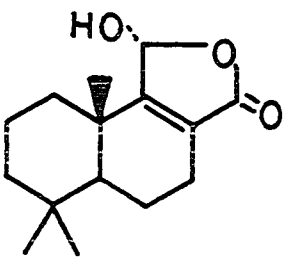

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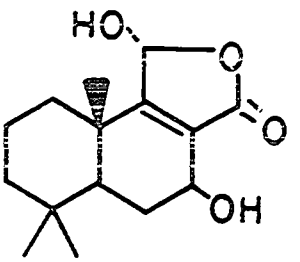
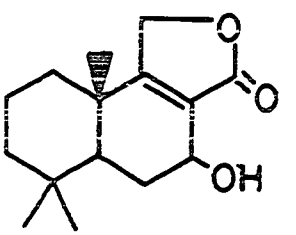


XLVIII



XLIX

DISCUSSION

In view of the biogenetic interest of the bicyclofarnesol sesquiterpenes, it was desirable to confirm the structures of drimenol, drimenin, isodrimenin and confertifolin by total synthesis. Podocarpic acid (L) was chosen as the starting material for several reasons. Firstly, podocarpic acid has the same 5α,10β configuration at its A/B ring juncture as the drimanic sesquiterpenes. Secondly, the gem-dimethyl arrangement at C(4) is potentially available. Thirdly, since d-podocarpic acid has been synthesized[31], any transformations to other natural products constitute their total synthesis also. It was decided to degrade podocarpic acid to the known drimic acid (XXXI) from which the sesquiterpenes would then be synthesized.

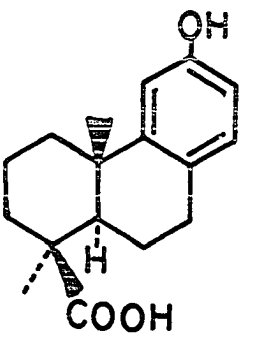
The first objective, reduction of the C(4) acid group to a methyl group, had been previously accomplished. Following known procedures, podocarpic acid was dimethylated with dimethyl sulfate and reduced to O-methylpodocarpol[32] (LI) with lithium aluminum hydride. Oxidation of the alcohol with chromic anhydride-pyridine to the aldehyde followed by Wolff-Kishner reduction afforded O-methylpodocarpane[33] (LII) in good yield.

The second objective, degradation of ring C, was initiated by a benzylic oxidation. Treatment of O-methylpodocarpane with chromic anhydride in acetic anhydride gave 7-keto-O-methylpodo-

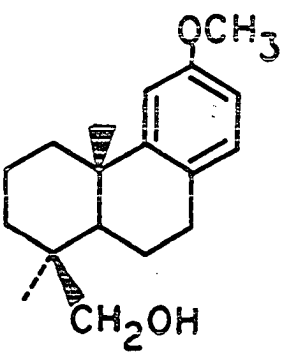
carpane (LIII) as an oil. Attempts to crystallize the latter failed, but its 2,4-dinitrophenylhydrazone, m.p. 235-236°, was prepared and analyzed. These results were repeated subsequently by Fétizon[34] who reported m.p. 236.5-237°.

In order to cleave the C(7)-C(8) single bond, the ketone LIII was subjected to a Baeyer-Villiger oxidation. The reaction of ketone LIII with excess trifluoroperacetic acid was sluggish and after 70 hours at room temperature gave a mixture of products from which the lactone LIV could not be isolated. The product mixture was refluxed in alcoholic sodium hydroxide thereby hydrolyzing the lactone to acid LV. The crude acid LV was reconverted by sublimation to the lactone LIV which was isolated in low yield after extensive purification. The by-products of the Baeyer-Villiger oxidation probably arose from reactions of the aromatic ring C, the only other reactive moiety in LIII. Since it was planned to degrade ring C by ozonolysis, it was decided to ozonize the crude acid LV obtained directly from the Baeyer-Villiger reaction. Exhaustive ozonolysis of the latter and oxidative decomposition of the ozonide in basic hydrogen peroxide afforded crude drimic acid (XXXI). Treatment of the latter with acetic anhydride or sublimation gave drimic anhydride (LVI) which was purified by chromatography and hydrolyzed to drimic acid, m.p. 166-168°; reported[21] m.p. 167-168°. The yield in the conversion of 7-keto-O-methylpodocarpane (LIII) to drimic anhydride (LVI) was 22%.

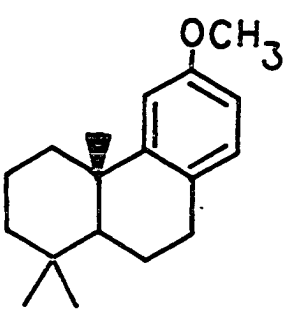
Since podocarpic acid was difficult to obtain and its



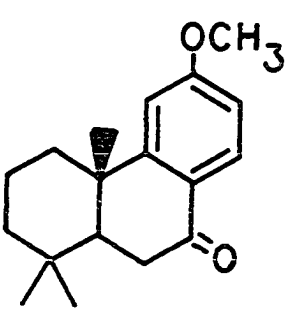
L



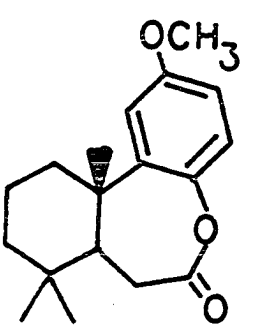
LI



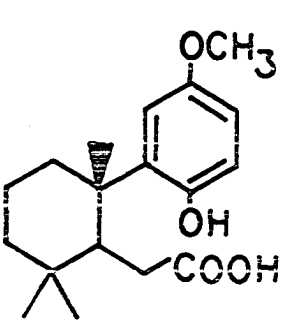
LII



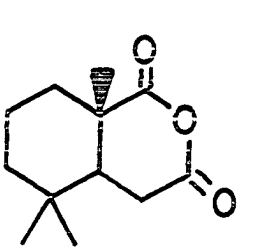
LIII



LIV



LV



LVI

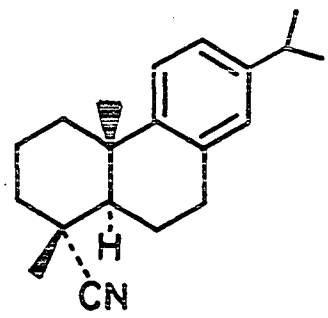
degradation to drimic anhydride had given low yields, it was decided to produce the necessary quantity of drimic anhydride from a more available source. Dehydroabietonitrile (LVII) was chosen as the second starting material since it also has the necessary 5α,10β configuration and the potential gem-dimethyl arrangement at C(4). Since abietic acid (LVIII) has been synthesized very recently[35], the conversion of dehydroabietonitrile to the drimanic sesquiterpenes also constitutes their total synthesis.

The reduction of the nitrile LVII to the aldehyde LIX was accomplished by controlled reduction with lithium aluminum hydride. Treatment of LVII with 1.5 moles of lithium aluminum hydride at room temperature for 10 minutes and rapid acid hydrolysis of the imine intermediate afforded the crude aldehyde in high yield. Wolff-Kishner reduction of the latter and chromatography of the product gave a 70% yield of dehydroabietane (LX), m.p. 38-42°; reported[36] m.p. 41-44°.

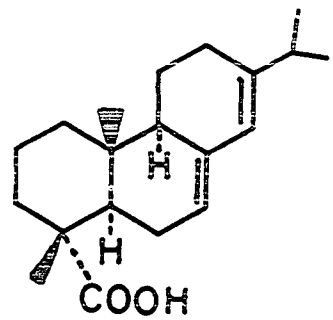
The oxidation of dehydroabietane to the 7-keto compound LXI with chromic anhydride in acetic acid has been accomplished previously[23] in 50% yield. It has also been shown[37] that under stronger conditions dehydroabietane (LX) is oxidized both at C(6) and on the isopropyl side chain. After several experiments it was found that using only 1.5 moles of chromic anhydride still afforded a 50% yield of the ketone LXI and also a 30% yield of starting material. Increasing oxidant, time or temperature simply increased the by-products.

Baeyer-Villiger oxidation of the ketone LXI with trifluoroperacetic acid proceeded cleanly and gave a 51% yield of pure lactone LXII which was characterized by its analysis and infrared spectrum. Hydrolysis of the lactone in alcoholic potassium hydroxide afforded the acid LXIII which analyzed correctly for $C_{20}H_{30}O_3$. The latter was subjected to exhaustive ozonolysis, the resulting ozonide decomposed with basic hydrogen peroxide and the product chromatographed yielding crude drimic acid (XXXI). Refluxing with acetic anhydride converted the acid to drimic anhydride (LVI) which was identical (melting point, mixed melting point, infrared spectrum) with that obtained from podocarpic acid (L).

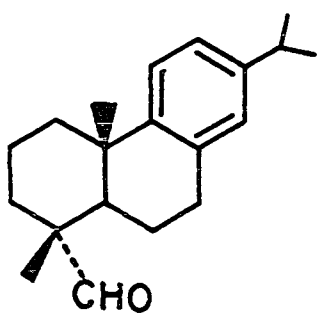
With the source of drimic anhydride secure, an attempt was undertaken to introduce a one-carbon segment into the anhydride and so complete the carbocyclic ring B. This was achieved finally by the use of a reaction with an organocadmium reagent. Although such reactions with cyclic anhydrides are not numerous, an analogous reaction was found in the literature. Cason[38] reacted a substituted glutaric anhydride (LXIV) with di-n-butylcadmium and obtained a mixture of keto-acids LXV and LXVI in high yield. The usefulness of the reaction for the preparation of keto-acids is somewhat decreased, since two products are obtained from unsymmetrical cyclic anhydrides. However, if conversion of the keto-acids into cyclic β-diketones is intended, the creation of two products presents no obstacle since both would be expected to yield the same β-diketone.



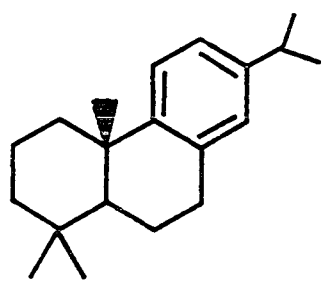
LVII



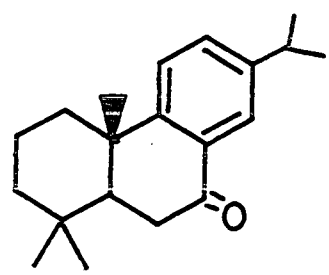
LVIII



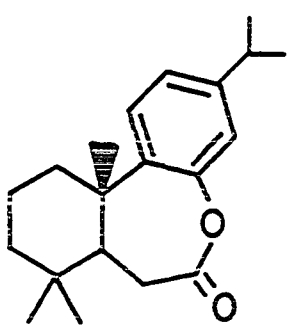
LIX



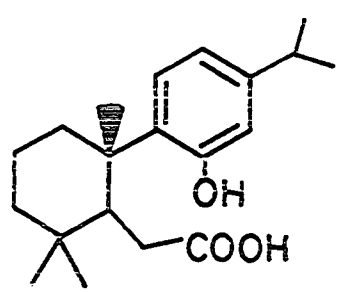
LX



LXI



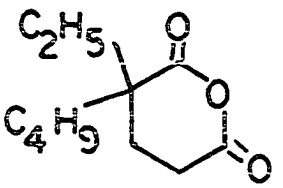
LXII



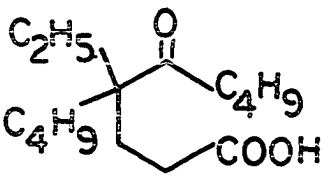
LXIII

Refluxing drimic anhydride (LVI) with three moles of dimethylcadmium in benzene gave an acidic oil. Thin layer chromatography (silica) showed two close spots, presumably the keto-acids LXVII and LXVIII. The crude mixture was esterified with diazomethane and the resulting keto-ester mixture cyclized with potassium t-butoxide affording a 66% yield of trans-5,5,9β-trimethyldecalindione-1,3 (LXIX) (compounds LXIX to CVII are named as decalin derivatives and numbered as in LXIX). Its wide melting point, 194-201°, and infrared spectra indicated ready interconversion with its tautomers. The potassium bromide mull spectrum revealed the compound to be completely enolized in the solid form by a strong 6.25μ band and the absence of any absorption in the normal carbonyl region. Absorption bands at 5.78, 5.88 and 6.20μ indicated the presence of both diketone and enol forms in chloroform solution.

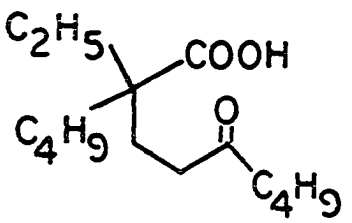
When drimic anhydride (LVI) was treated with 10 moles of dimethylcadmium a 75% yield of a neutral solid was obtained. Its infrared spectrum, a single 5.87μ band in the carbonyl region, and its analysis for $C_{14}H_{24}O_2$ suggested the lactone structure LXX. This would arise from methylation of the keto-acid LXVII with excess dimethylcadmium giving a tertiary alcohol which would lactonize to LXX. Structure LXX rather than the alternate structure LXXI was assigned to the lactone, since C(7) of the anhydride would be expected to be more accessible than its C(9) and the nuclear magnetic resonance spectrum



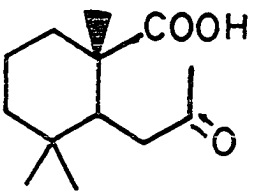
LXIV



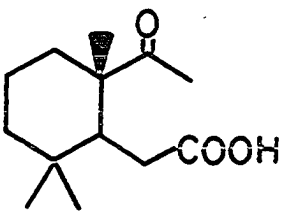
LXV



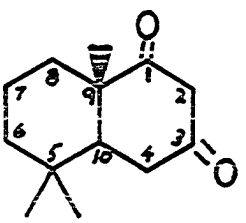
LXVI



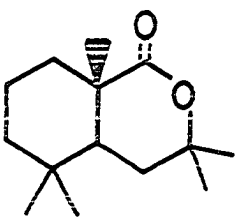
LXVII



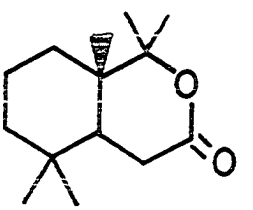
LXVIII



LXIX



LXX



LXXI

of the lactone showed no two-proton signal at 2-3 ppm expected from the C(6) hydrogens in structure LXXI. Although organocadmium reagents do not usually react with ketones, it is known[39,40] that an excess of the reagent with a sufficiently reactive ketone can yield tertiary alcohols.

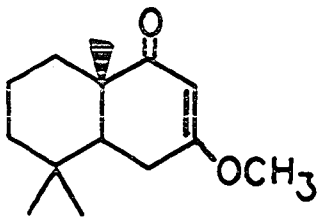
It was desired to introduce a one-carbon segment by formation of the enol ether LXXII, reduction to the enone LXXIII and addition of cyanide at the C(1) position. Refluxing the β-diketone LXIX and p-toluenesulfonic acid in methanol and benzene[41], with slow distillation of the solvent, gave a mixture of the two enol ethers LXXII and LXXIV. Chromatographic separation afforded LXXII in 84% yield and LXXIV in 13% yield, both analyzing correctly for $C_{14}H_{22}O_2$. The structures were assigned by analogy with the yields and chromatographic mobilities of the products in similar systems[42]. The structures were subsequently confirmed by the proper assignment of the structures of their reduction products.

The reduction of an enol ether (e.g. LXXV) of a β-diketone and treatment of the resulting hydroxy enol ether (LXXVI) with acid is a very useful synthesis of an α,β-unsaturated ketone (LXXVII). Previous interpretations[43] of the mechanism of the hydrolysis of the intermediate hydroxy enol ether assumed its primary conversion to a β-ketol (LXXVIII) followed by dehydration to the α,β-unsaturated ketone (LXXVII). The ketol intermediate was never isolated and various acid treatments[41] and even adsorption on alumina[44] were used to effect the presumed

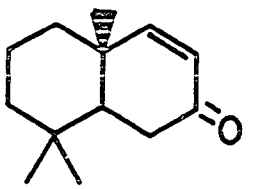
dehydration.

In 1961, Stiles[45] investigated this reaction and proposed a new mechanism. He treated 3-ethoxy-2-cyclohexenone (LXXV) with lithium aluminum hydride and isolated the hydroxy enol ether LXXVI. The latter was converted quantitatively to cyclohexenone (LXXVII) by 10^{-3} M hydrochloric acid at 0° but the proposed ketol intermediate (LXXVIII) was not observed. When the ketol LXXVIII, synthesized by an alternate method, was treated with 10^{-3} M hydrochloric acid under identical conditions there was no measurable reaction. Comparison of the rates of formation of cyclohexenone (LXXVII) from the enol ether LXXVI and the ketol LXXVIII showed that the ketol dehydrated too slowly by a factor of ca. 10^{8} to be an intermediate. With this evidence in hand, Stiles proposed a new mechanism of enone formation involving an allylic rearrangement of the hydroxyl group via intermediates LXXIX and LXXX.

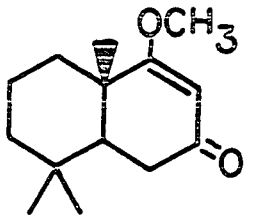
It was decided to investigate this proposed mechanism with respect to the enol ethers LXXII and LXXIV. Reduction of LXXII with lithium aluminum hydride and hydrolysis with water gave a mixture of products. Chromatographic separation afforded a 7% yield of the enone LXXIII, a 41% yield of the hydroxy enol ether LXXXI and an 18% yield of the ketol LXXXII. The structures of the enone and ketol were assigned on the basis of their analyses and infrared spectra. Although the hydroxy enol ether LXXXI was stable in the solid form, m.p. 96-97°, a correct analysis could not be obtained. However, its infrared and



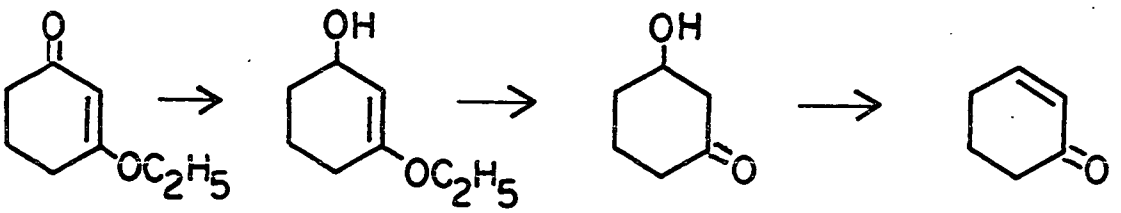
LXXII



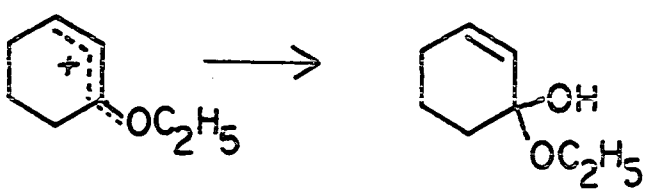
LXXIII



LXXIV



LXXV LXXVI LXXVIII LXXVII



LXXIX LXXX

nuclear magnetic resonance spectra were consistent with the assigned structure. The hydroxyl group at C(1) in both LXXXI and LXXXII was assigned the β position on the assumption that the reduction had occured from the less hindered α-side.

The hydrolysis of the enol ether LXXXI in 0.01 N sulfuric acid in 95% ethanol was very slow and after 36 hours at room temperature a mixture of products was obtained. Thin layer chromatography (silica), with the known compounds as standards, showed the presence of the enone LXXIII, ketol LXXXII and starting enol ether LXXXI. Chromatographic separation afforded yields of 28, 49 and 14%, respectively. When the hydrolysis of LXXXI was carried out in 1.0 N sulfuric acid, under identical conditions, the reaction was complete within 5 minutes and gave a 47% yield of the enone LXXIII and a 45% yield of the ketol LXXXII. Treatment of pure ketol LXXXII with acid under conditions identical with those of the above two experiments led to its recovery in 94 and 100% yields, respectively. However, the ketol LXXXII could be dehydrated to the enone LXXIII in 98% yield by refluxing in 2 N sulfuric acid in 95% ethanol for half an hour. The products of the above reactions were identified by their comparative infrared and thin layer chromatographic properties with known compounds.

These results indicate that both mechanisms of hydrolysis, formation of the ketol and allylic rearrangement, had occurred. The inertness of the ketol (LXXXII) to the conditions which had yielded some enone (LXXIII) excludes it as the precursor of the

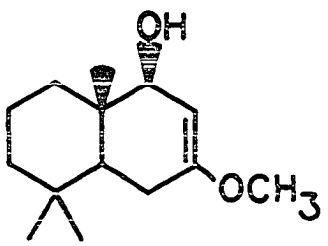
enone LXXIII formed under these conditions. Therefore, the enone LXXIII appears to have been formed through the allylic rearrangement proposed by Stiles, or some similar mechanism. The increase in rate with increasing acidity, especially of the enone formation which increased in yield from 28 to 47%, is also consistent with the results obtained by Stiles.

The reduction of the alternate enol ether LXXIV yielded a solid whose infrared spectrum indicated the expected hydroxy enol ether LXXXIII. Although the solid could be recrystallized, a sharp melting point could not be obtained. On standing at room temperature for 12 hours, the solid became oily and an infrared spectrum indicated that it was decomposing to the enone LXXXIV. The crude enol ether LXXXIII was immediately treated with 0.01 N sulfuric acid in 95% ethanol for a half hour yielding the enone LXXXIV in 98% yield. The failure to detect any ketol LXXXV and the rapid rate of hydrolysis as compared to that of LXXXI suggested that the enol ether LXXXIII had hydrolyzed to the enone LXXXIV completely by the allylic rearrangement mechanism.

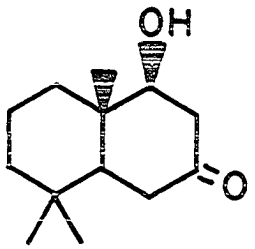
The difference of the rates of allylic rearrangement of LXXXI and LXXXIII under identical conditions of treatment with 0.01 N sulfuric acid can be explained on the basis of a difference of ease of formation of the intermediate methoxy-allyl cations LXXXVI and LXXXVII, respectively. It is known[46] that in a trans-decalin system a double bond at C(2)-C(3) is more stable than at C(1)-C(2). Hence the introduction of double-

bond character into the 1,2-bond (LXXXVI) starting from LXXXI would be expected to require more activation energy than a similar change in the 2,3-bond starting from LXXXIII. Therefore, a parallel, independent reaction, the formation of ketol LXXXII, can take place alongside the rearrangement in the case of LXXXI. The above results indicate that it may be possible to adjust hydrolysis conditions in specific systems to the needs of the synthesis.

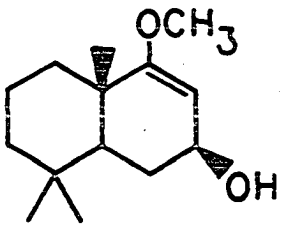
Before proceeding with the sesquiterpene synthesis, it was desirable to establish the structure of the enones LXXIII and LXXXIV. Hydrogenation of the enone LXXIV over palladium-charcoal afforded the saturated ketone LXXXVIII as an oil. The structure LXXXVIII was consistent with the analytical results of the ketone and its 2,4-dinitrophenylhydrazone. The infrared and nuclear magnetic resonance spectra were compared and found identical with those of the known racemic compound[47]. Although the racemic compound was a low melting solid, the ketone LXXXVIII could not be solidified at room temperature even when purified by gas phase chromatography. However, the gas phase and thin layer chromatographic properties along with the spectral properties indicated a pure compound. The ketone LXXXVIII was also obtained by catalytic hydrogenation of the enol ether LXXII in 37% yield along with a 23% yield of the methoxy-alcohol LXXXIX. The structure of the alcohol, which analyzed for $C_{14}H_{27}O_2$, was elucidated by infrared and nuclear magnetic resonance spectra.



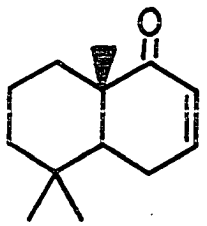
LXXXI



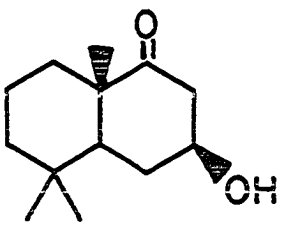
LXXXII



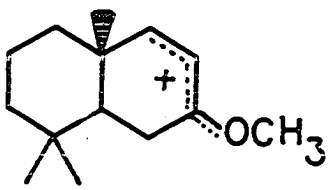
LXXXIII



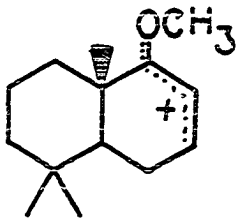
LXXXIV



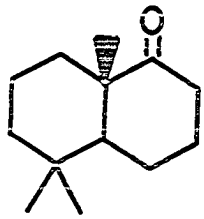
LXXXV



LXXXVI



LXXXVII



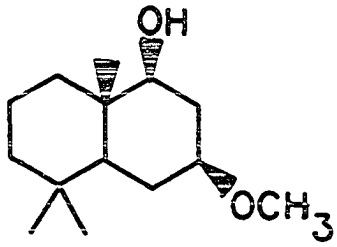
LXXXVIII

The catalytic hydrogenation of enone LXXIII yielded the saturated ketone XC whose analysis agreed with the formula $C_{13}H_{22}O$. The 2,4-dinitrophenylhydrazone of XC melted at 164-165° while the reported[48] melting point of the enantiomeric 2,4-dinitrophenylhydrazone was 169-184°. A sample of the 2,4-dinitrophenylhydrazone of the enantiomer XCI was obtained from Dr. Enzell. Upon recrystallization it melted at 164-166°. The infrared spectrum was identical with that of the 2,4-dinitrophenylhydrazone of XC. These results suggest that the enantiomer XCI reported by Enzell[48] was probably impure.

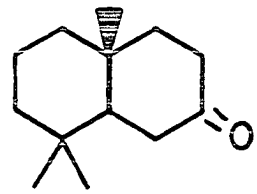
Proceeding with the synthetic route to the drimanic sesquiterpenes, the enone LXXIII was made to react with potassium cyanide and ammonium chloride in dimethylformamide[49] giving an 80% yield of pure α-cyanoketone XCII, m.p. 102-103°. The stereochemistry of the cyano group was determined by its ability to be isomerized to the more stable β-position. To protect against any ketonic interactions during the isomerization, the α-cyanoketone XCII was ketalized with ethylene glycol and the resulting α-cyanoketal XCIII treated with potassium t-butoxide[50,51] at room temperature for 10 hours. Hydrolysis of the resulting β-cyanoketal XCIV afforded the β-cyanoketone XCV, m.p. 100-101°. The analyses of both cyanoketones XCII and XCV checked for $C_{14}H_{21}ON$ and, as expected, their infrared spectra and thin layer chromatographic mobilities were different. The stereochemical assignments of the

cyano group were supported by the nuclear magnetic resonance spectra of the cyanoketals. In the spectrum of the α-cyanoketal XCIII the signal of the hydrogens on the ketal bridge was a 4-proton multiplet centered at 3.94 ppm (deuterochloroform solution with tetramethylsilane as internal standard) while in the spectrum of the β-cyanoketal XCIV, the 4-proton signal was essentially a singlet at 3.96 ppm. The complex multiplet in the α-cyanoketal spectrum can be considered to arise from 1,3 di-axial interactions of the axial cyano and the proximate ketal methylene group. This would change the electronic environment of one methylene group with respect to its neighbor and thus change its chemical shift. In the β-cyanoketal XCIV, in which the cyano group is equatorial there is no 1,3-interaction and the ketal hydrogens are identical, and hence of similar chemical shift.

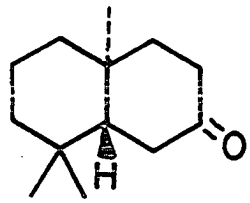
The stereospecificity of the cyanide addition, giving only the α-isomer, prompted a similar reaction with the alternate enone LXXXIV. Treatment of the enone LXXXIV in a manner identical with that of LXXIII again afforded only one isomer, the α-cyanoketone XCVI, in high yield. As in the previous case, the α-cyanoketal XCVII was prepared, isomerized with potassium t-butoxide to the β-cyanoketal XCVIII and hydrolyzed to the β-cyanoketone XCIX. Although the other three isomeric cyanoketones were solids, the β-cyanoketone XCIX, purified by gas phase chromatography, was an oil. However, thin layer chromatography (silica) and its infrared spectrum indicated a pure



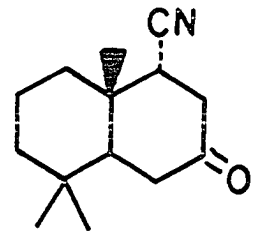
LXXXIX



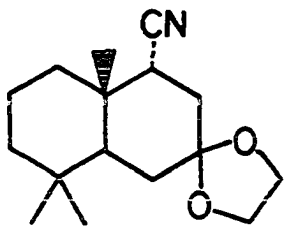
XC



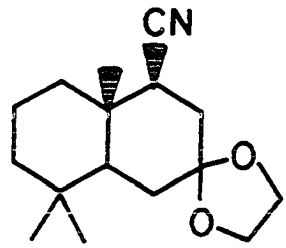
XCI



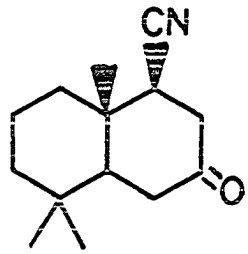
XCII



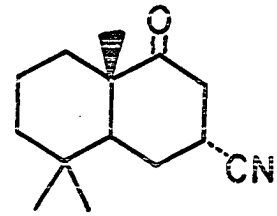
XCIII



XCIV



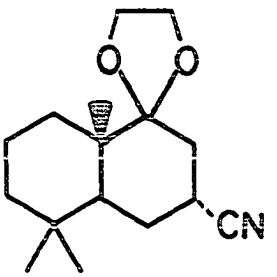
XCV



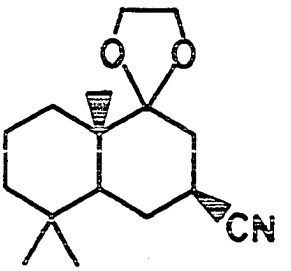
XCVI

compound and definitely the absence of any starting α-cyano-ketone XCVI. As in the previous cyanoketals, the nuclear magnetic resonance spectrum of the α-cyanoketal XCVII, in which the cyano group is axial, contains a complex 4-proton multiplet centered at 4.0 ppm representing the ketal bridge hydrogens. In the spectrum of the β-cyanoketal XCVIII, in which the cyano group is equatorial, the ketal 4-proton signal is essentially a singlet.

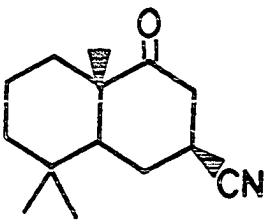
In recent years the stereochemistry of cyanide addition to α,β-unsaturated ketones has been increasingly investigated. Nagata[52] obtained two stereoisomers of the cyanoketone C from the hydrocyanation of the enone CI. Subsequent work by Bowers[53] and Nagata[54,55] in the Δ^4-3-ketosteroid series showed that cyanide addition gives both axial and equatorial isomers, the former in predominance. Very recently cyanide addition has been utilized in the total synthesis of steroids[56,57] and of conessine[58]. These reactions have usually led to mixtures of axial and equatorial nitrile isomers. Meyer and Schnautz[59] have obtained a ratio of 3.6:1 of <u>trans</u> to <u>cis</u> isomers of the cyanoketone CII from hydrocyanation of the enone CIII[60]. Crabbé[61] obtained only the equatorial addition product CIV from the enone CV. Generally[62], it has been found that the cyanide addition to α,β-unsaturated ketones yields both stereoisomers, with the axial isomer predominating. However, all of the above examples concern additions to ring junctures of bicyclic systems (except for the special cyclopentene case) in which the



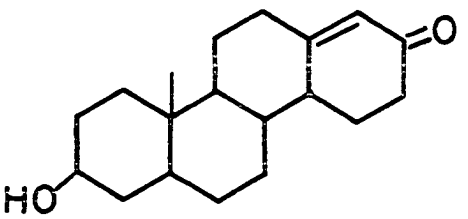
XCVII



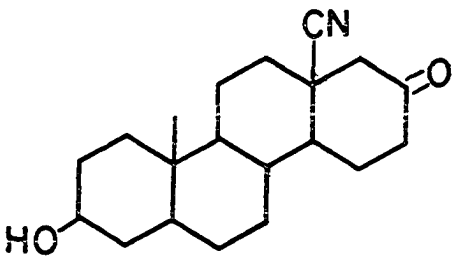
XCVIII



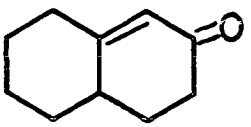
XCIX



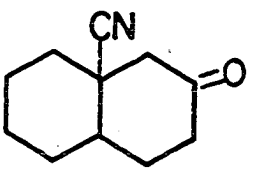
CI



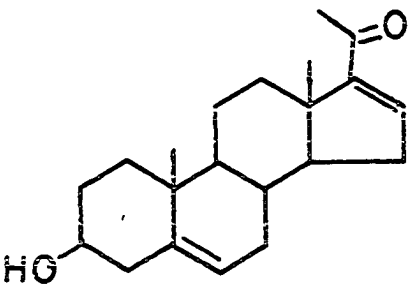
C



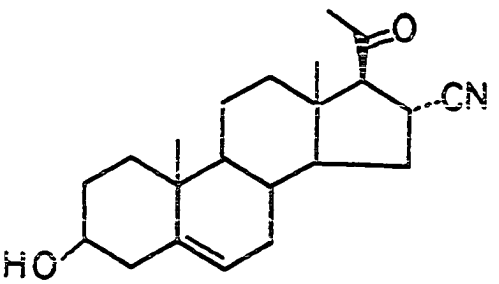
CIII



CII



CV



CIV

stereochemistry of the products may be dependent upon the conformation of more than one ring.

The hydrocyanation of the enones LXXIII and LXXIV represents the first examples of stereospecific addition in rigid cyclohexenones whose stereochemical course must be the result of the conformational requirements of only one ring. Apparently axial approach of cyanide ion to the β-carbon of the unsaturated ketone system is the preferred reaction path. Undoubtedly this is due to maximum orbital overlap[59] in such a reaction process.

Again proceeding with the synthetic route, it was desired to hydrolyze the cyano group in XCV to a carboxyl group. Initial attempts at basic hydrolysis of the β-cyanoketone XCV yielded tars, probably due to reactions of the ketone group. In view of this result, it was decided to hydrolyze the protected β-cyanoketal XCIV. Treatment of either the β-cyanoketal XCIV or the α-cyanoketal XCIII with 20% potassium hydroxide in diethylene glycol at 200° for 24 hours followed by acid hydrolysis of the ketal afforded the β-carboxyketone CVI in 68% yield. The products from both the α- and β-cyanoketals were shown to be identical by their infrared spectra and mixed melting point. The α-cyano group apparently isomerized to the more stable β-orientation during the strongly basic hydrolysis. The structure of the β-carboxyketone CVI was confirmed by analysis and a favorable comparison of the properties of its methyl ester with those reported[63] for the degradation product CVII of

lanosterol.

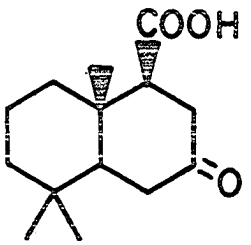
In an attempt to introduce the final one-carbon segment at C(2) in an Aldol condensation, the β-carboxyketone CVI was treated with formaldehyde. However, both acid- and base-catalyzed reactions led to complex oily mixtures and the reaction was discarded. The β-carboxyketone CVI was then subjected to a Claisen condensation with ethyl formate which afforded an oil whose infrared spectrum was consistent with the expected intermediate CVIII. A similar reaction was used in the synthesis of picropodophyllin[64]. Treatment of the intermediate CVIII with acetic anhydride and sodium acetate closed the lactone ring and caused the double bond to migrate yielding 7-ketoisodrimenin (XXXVIII) in 48% yield. The product, XXXVIII, was identified by comparison of its melting point and infrared spectrum with those reported[24] for the oxidation product of isodrimenin (XXXIII). The migration of the double bond, catalyzed by acetate, to a more stable position endocyclic to both rings and conjugated with both ketone and lactone carbonyls is not surprising and has been observed in similar systems[65].

Repeating Overton's procedure, the ketone XXXVIII was reduced with zinc in acetic acid to the dihydro derivative CIX, whose melting point and infrared spectrum were consistent with those previously reported[24]. The dihydroketone CIX was obtained also by the hydrogenation of XXXVIII over palladium/charcoal. Sodium borohydride reduction of the ketone CIX at

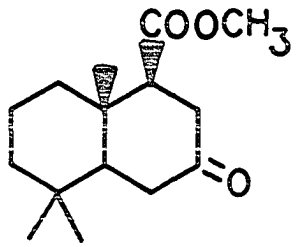
room temperature for 2 hours afforded the β-alcohol CX in 74% yield. The analysis and infrared spectrum were consistent with the proposed structure and the stereochemistry of the alcohol was assumed the more thermodynamically stable β-configuration.

Treatment of the alcohol CX with p-toluenesulfonyl chloride and heating the resulting tosylate in dimethyl sulfoxide[66] at 100° for 1.5 hours effected the desired elimination. The first drimanic sesquiterpene, drimenin[24] (XXXII), was obtained in 40% yield along with 19% of unreacted alcohol CX and 17% of 7-ketoisodrimenin (XXXVIII), arising from the oxidation of the tosylate with dimethyl sulfoxide. A direct comparison of the melting point and infrared spectrum of XXXII with those of the natural product and their undepressed mixed melting point proved that they were identical. Since drimenin (XXXII) has previously been isomerized to isodrimenin (XXXIII)[24], this also constitutes the total synthesis of isodrimenin.

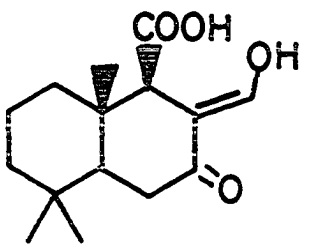
Repeating Overton's procedure, isodrimenin (XXXIII) was reduced with lithium aluminum hydride to the diol XL, whose melting point and infrared spectrum compared favorably with those reported[24]. Treatment of the diol XL with manganese dioxide at room temperature for 12 hours afforded a mixture of isodrimenin (XXXIII) and confertifolin (XXXIV), according to thin layer chromatography. Gradient sublimation of the mixture at 120° (1 mm.) gave long needles of confertifolin (XXXIV), whose melting point and infrared spectrum were identical with those of the natural



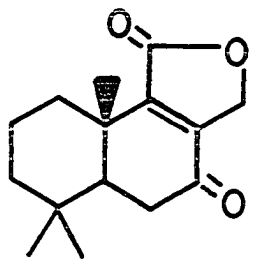
CVI



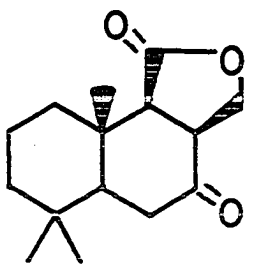
CVII



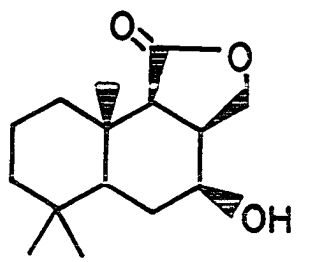
CVIII



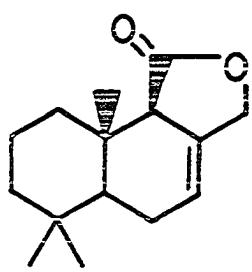
XXXVIII



CIX



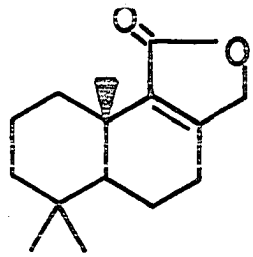
CX



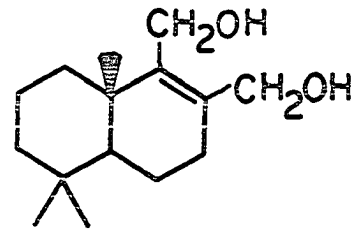
XXXII

product. A mixed melting point of the synthetic and natural products was undepressed.

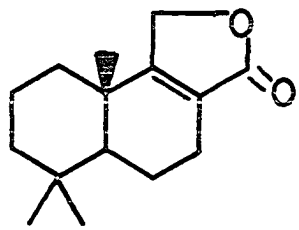
Drimenin (XXXII) was reduced with lithium aluminum hydride to the known diol[24] XXXV. An attempt to reduce the allylic hydroxyl group with sodium in liquid ammonia[67] failed, giving only the starting diol XXXV. However, treatment of the diol XXXV with acetic anhydride and reduction of the resulting crude di-acetate CXI with lithium in liquid ammonia[68] followed by hydrolysis of the acetate CXII afforded drimenol[21] (XXVI) in 41% yield. The melting points and infrared spectra of the synthetic and natural products were identical and their mixed melting point was undepressed.



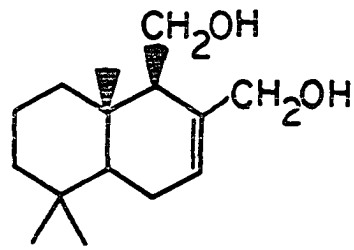
XXXIII



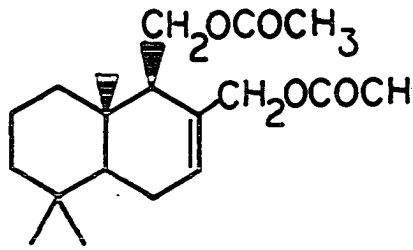
XL



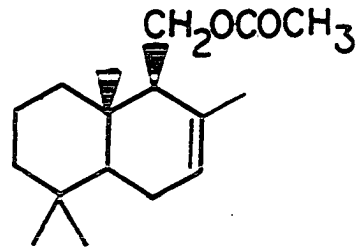
XXXIV



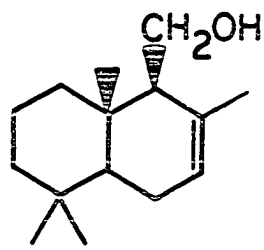
XXXV



CXI



CXII



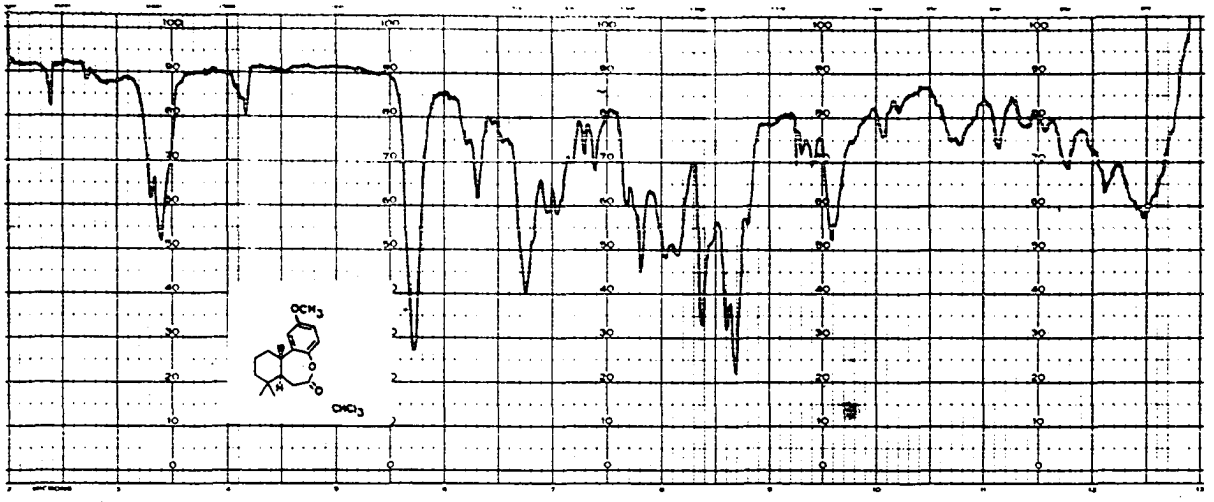
XXVI

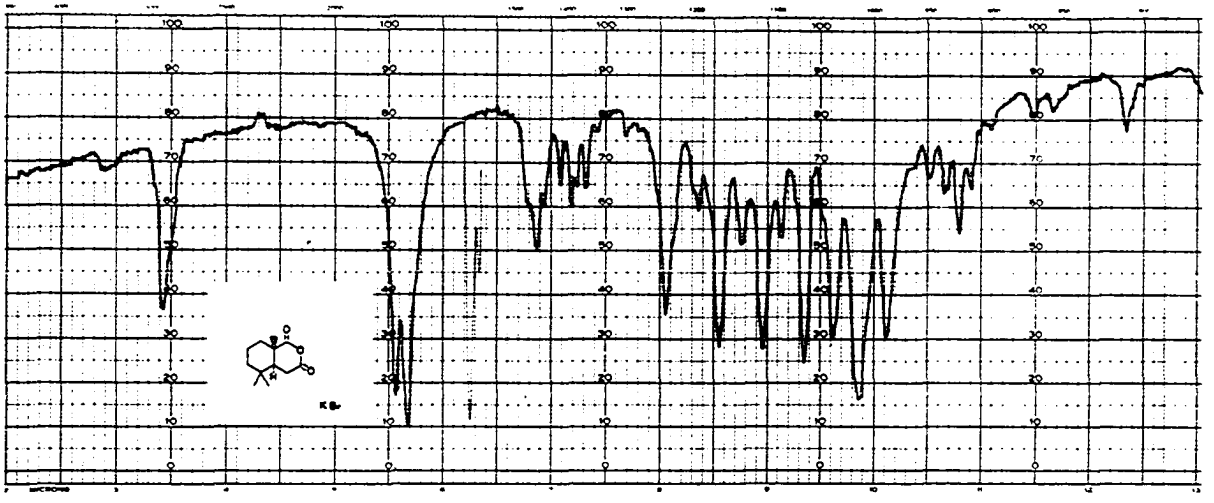
SPECTRA

All infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer unless denoted by the term "Infracord". The latter refers to those spectra taken on a Perkin-Elmer model "Infracord" infrared spectrophotometer.

The nuclear magnetic resonance spectra were obtained from dilute deuterochloroform solutions using a Varian Model A-60 Spectrometer. Resonance positions were determined by pre-calibrated charts relative to tetramethylsilane as an internal standard.

Figure 1. Infrared spectra


OCH3
CHCl3


KBr

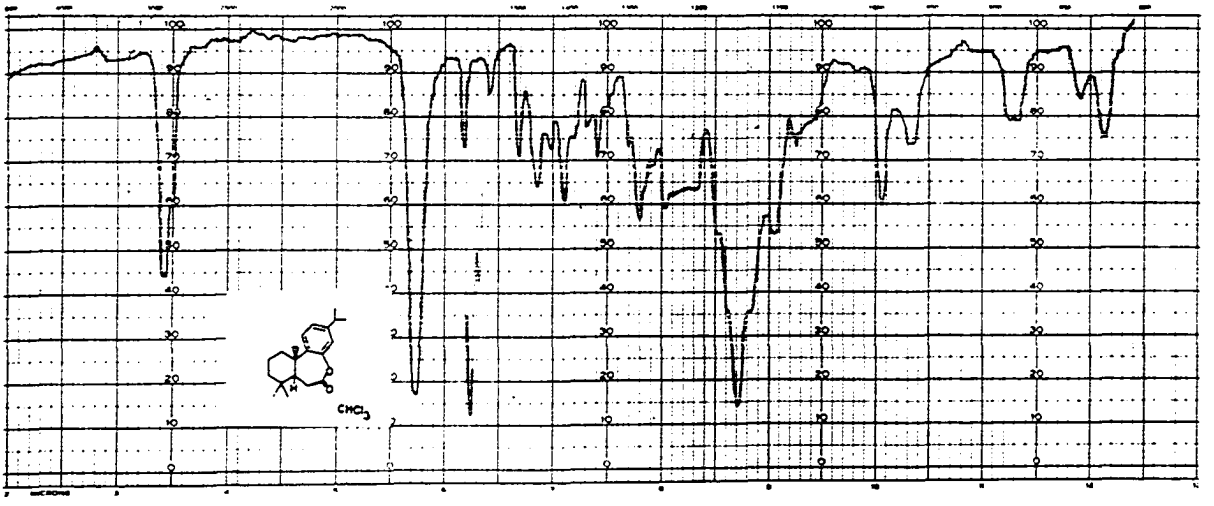
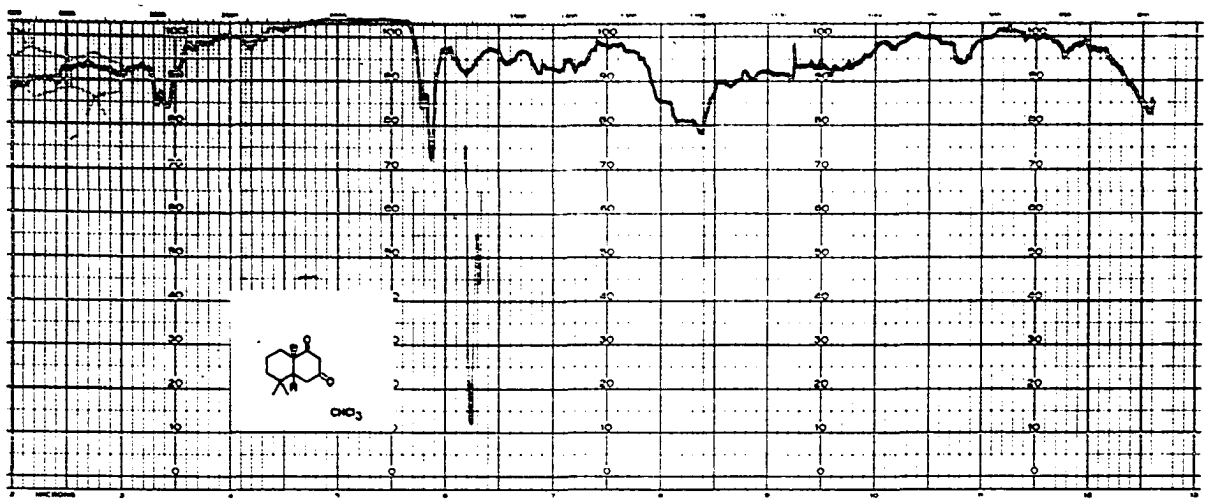
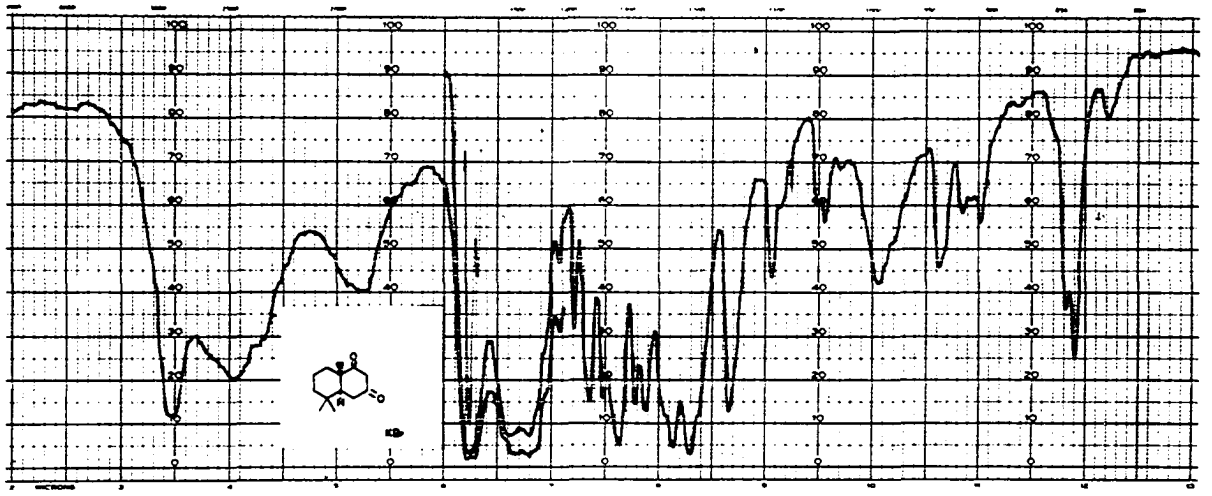

CHCl3

Figure 2. Infrared spectra





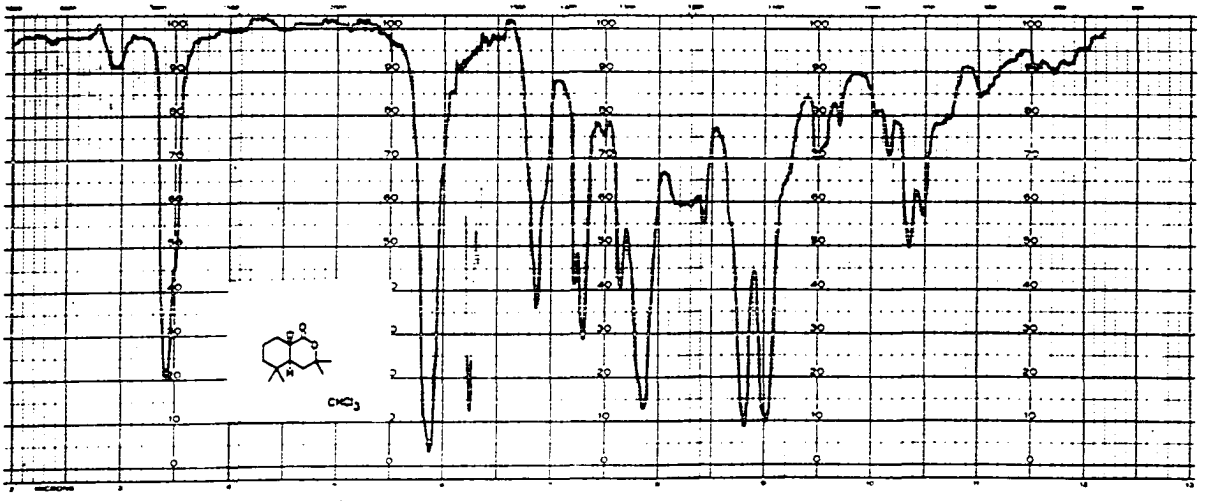
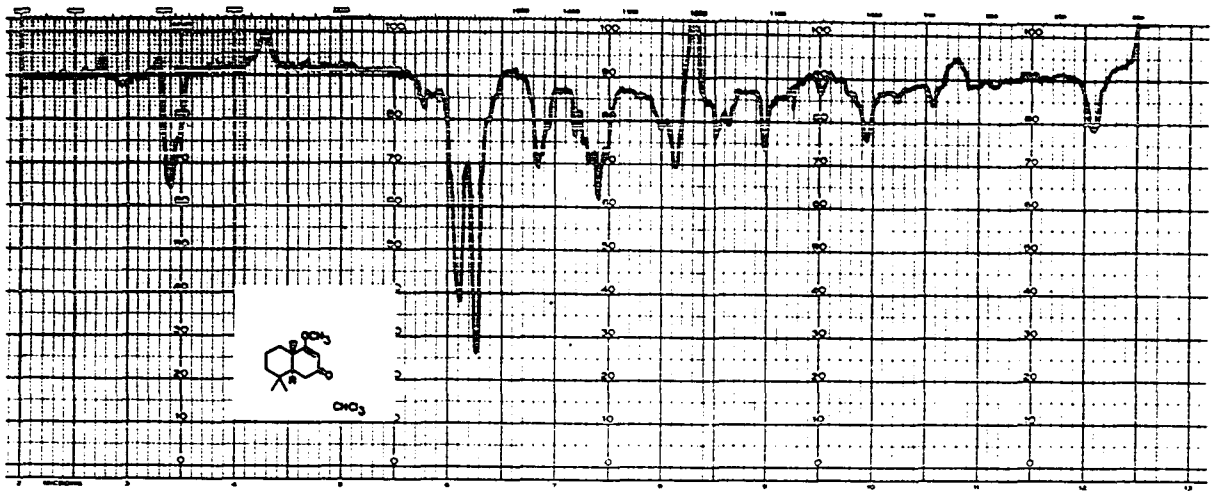
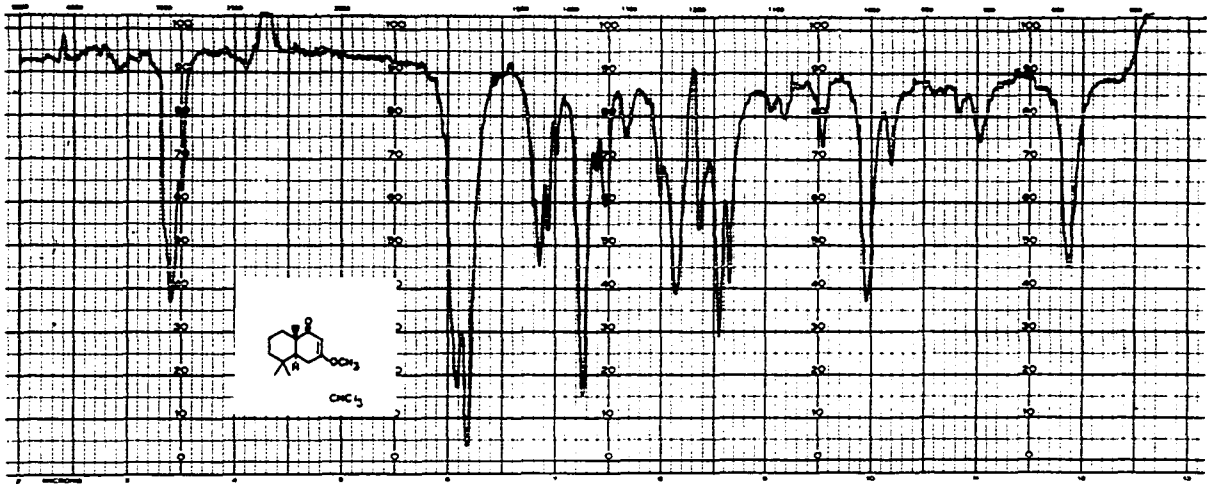


Figure 3. Infrared spectra





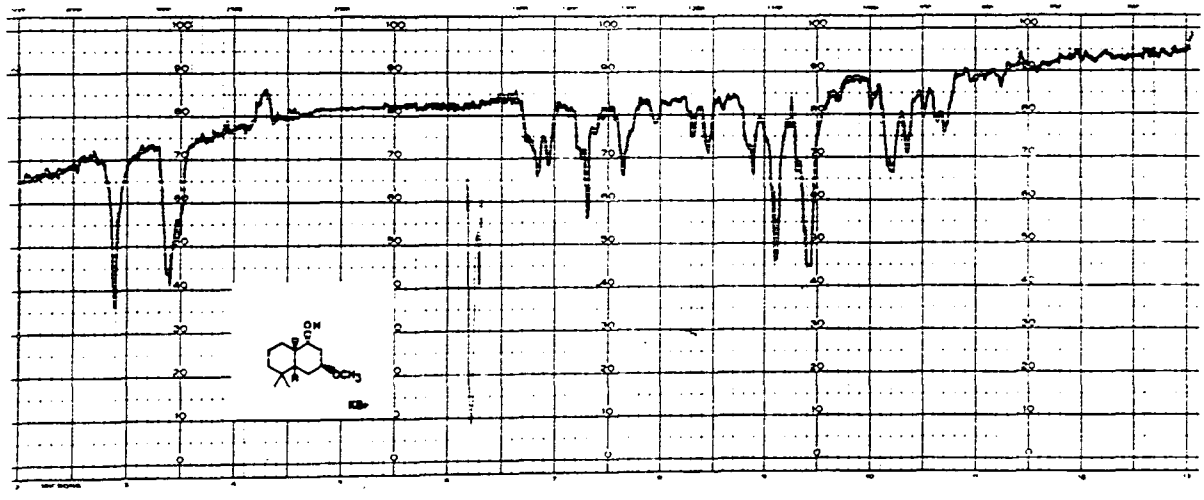
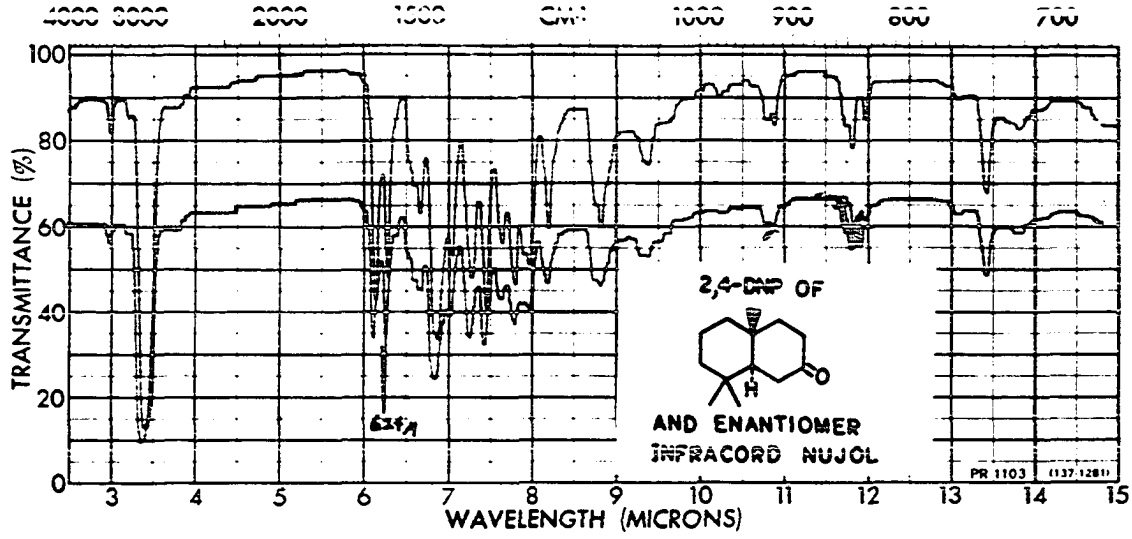
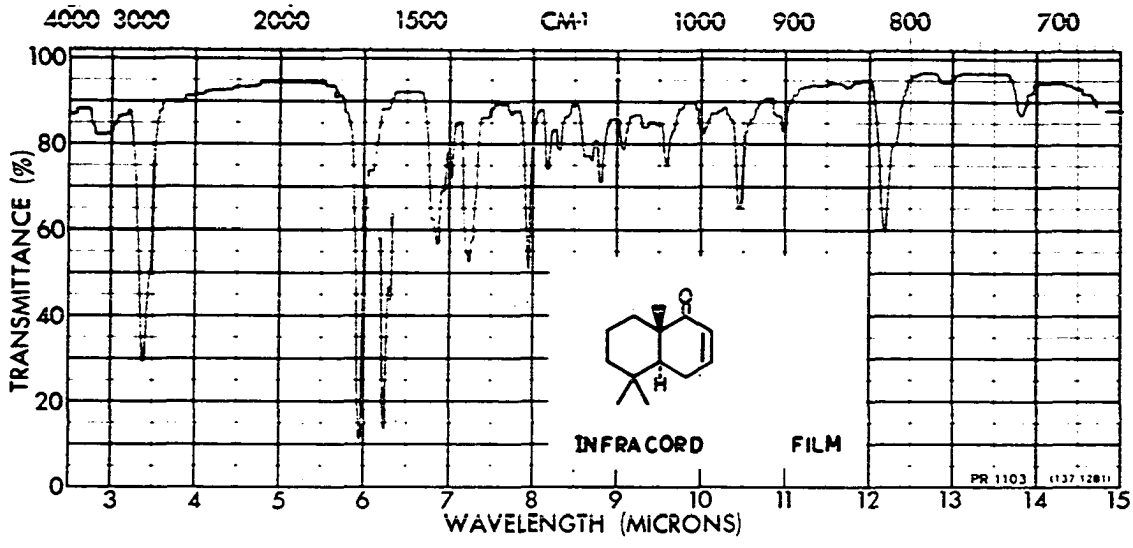


Figure 4. Infrared spectra


4000 3000 2000 1500 CM-1 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
2,4-DNP OF
AND ENANTIOMER
INFRACORD NUJOL
PR 1103


4000 3000 2000 1500 CM-1 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
INFRACORD FILM
PR 1103

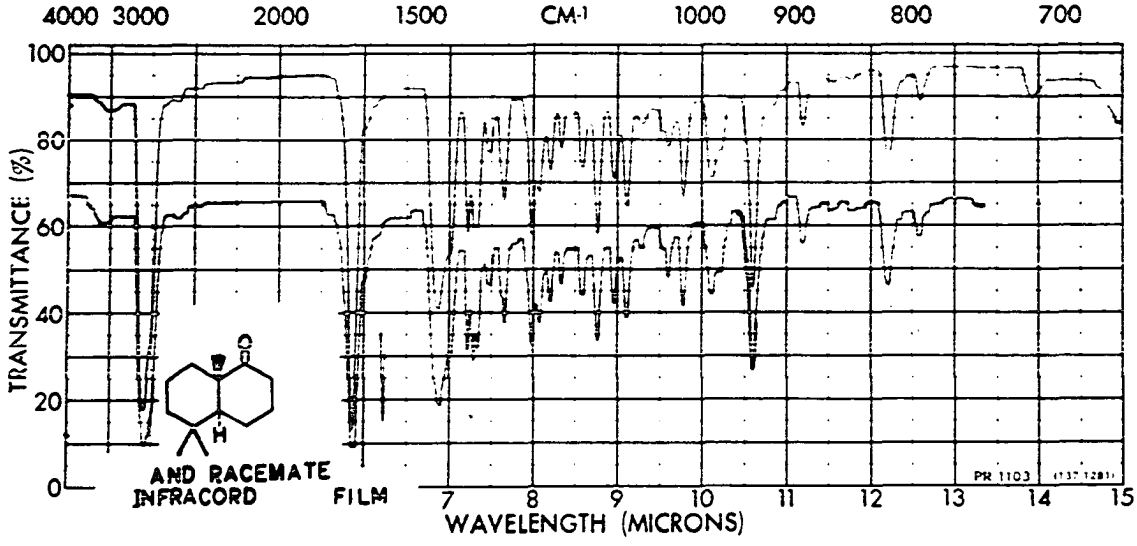
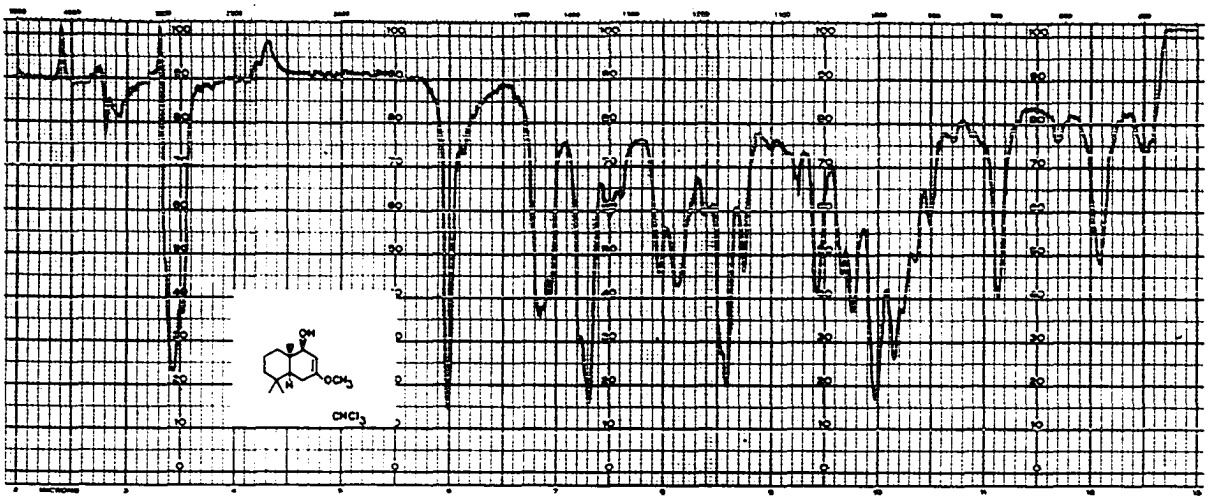
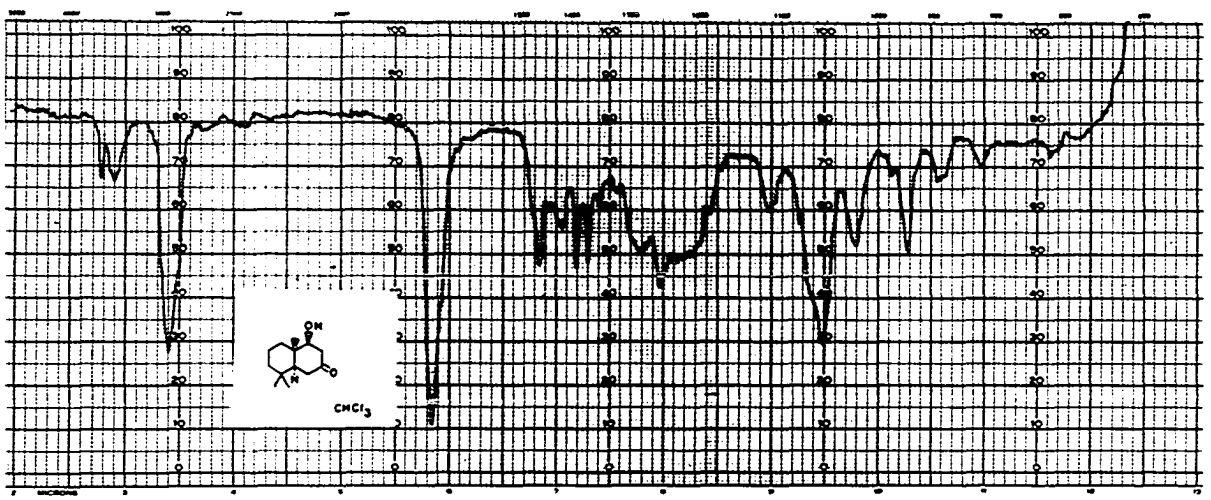

4000 3000 2000 1500 CM-1 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
AND RACEMATE
INFRACORD FILM
PR 1103

Figure 5. Infrared spectra


OH
OCH3
CHCl3


OH
O
CHCl3

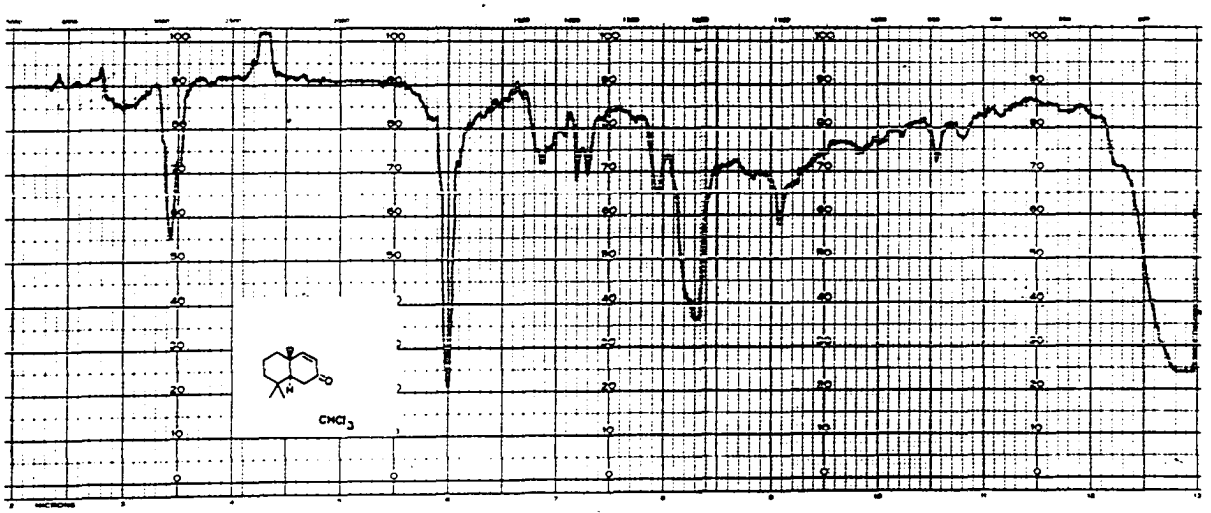
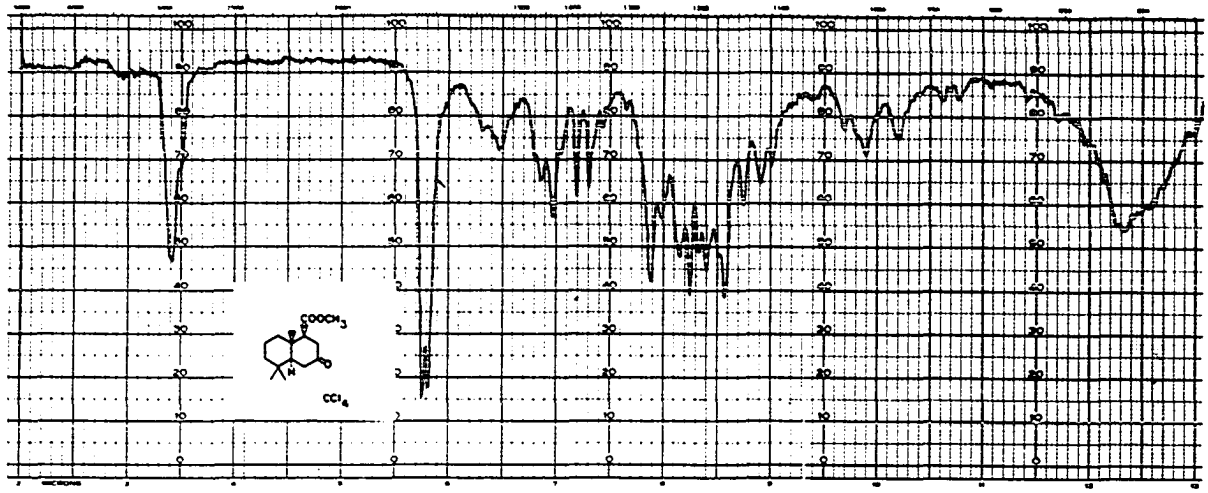
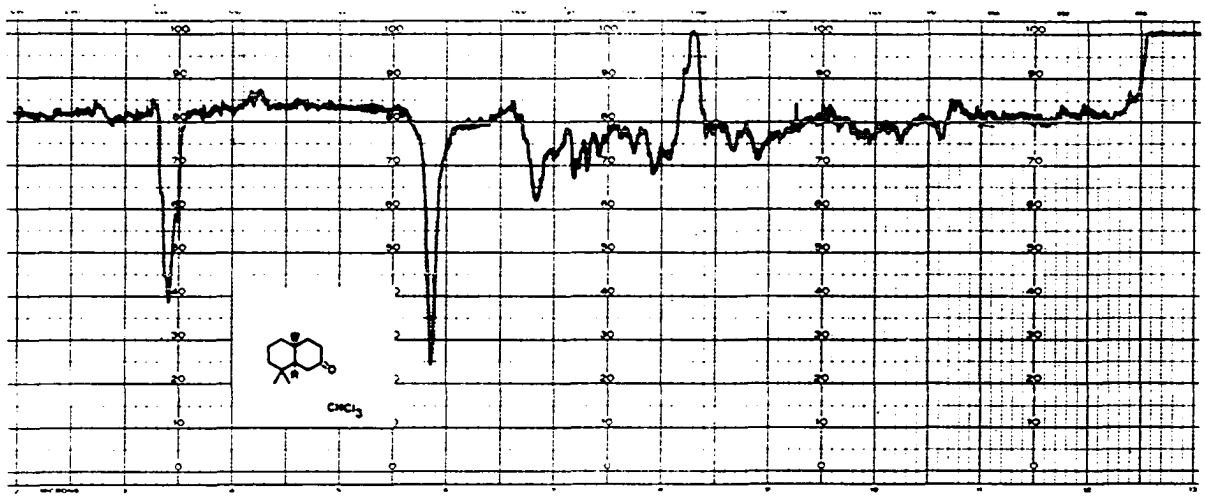

O
CHCl3

Figure 6. Infrared spectra


COOCH3
CCl4


CHCl3

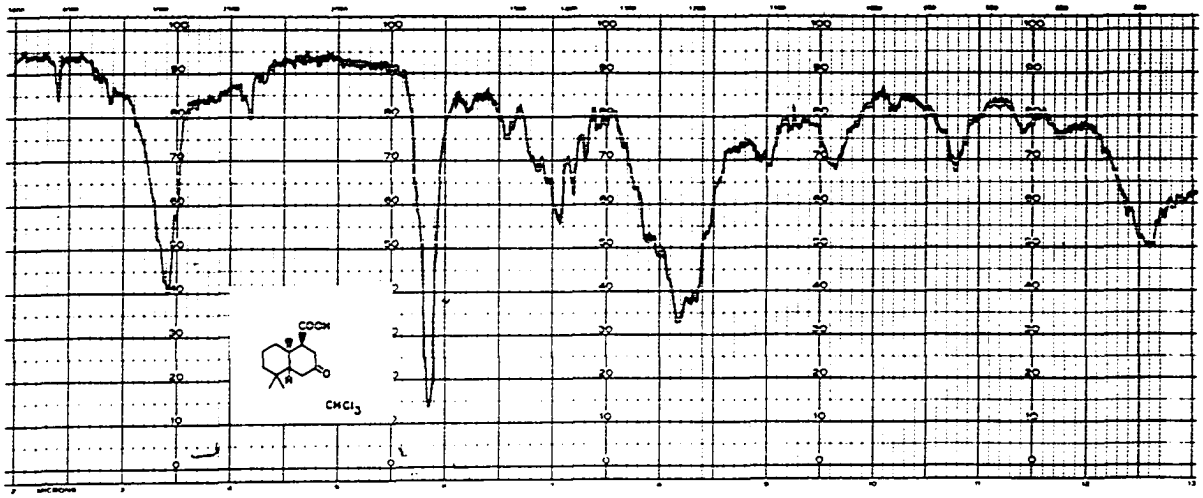
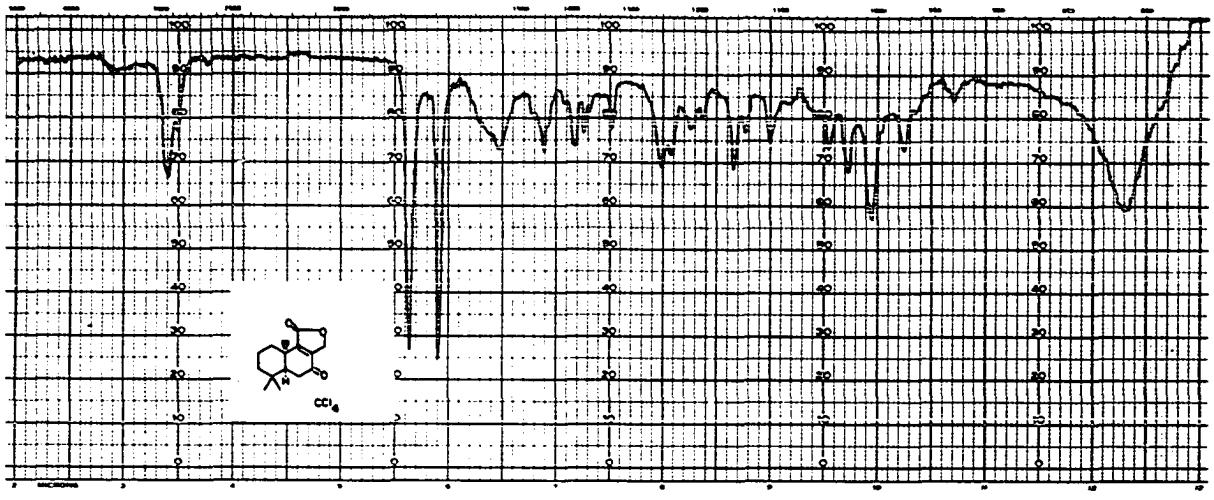
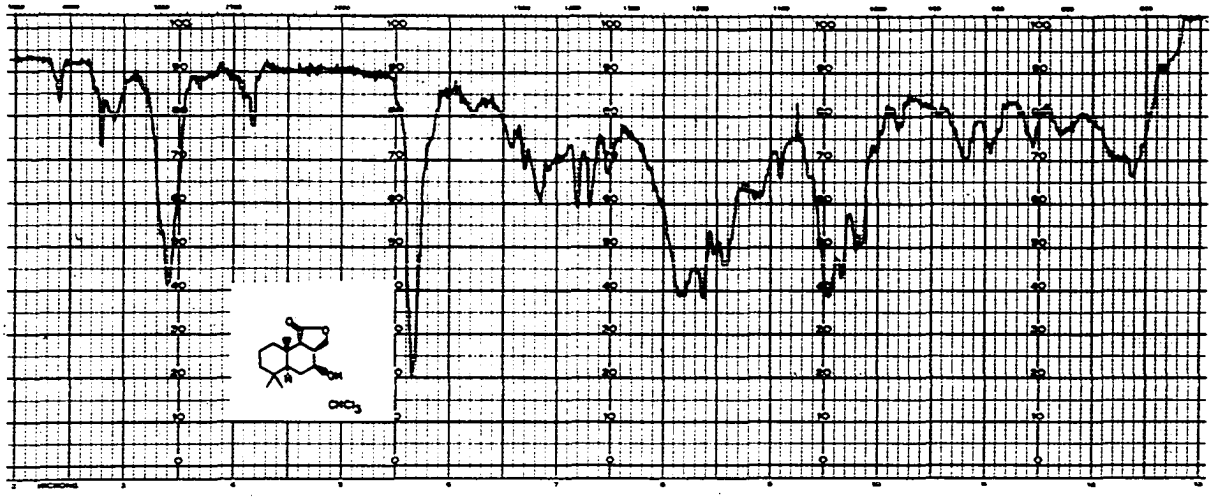

COOH
CHCl3

Figure 7. Infrared spectra





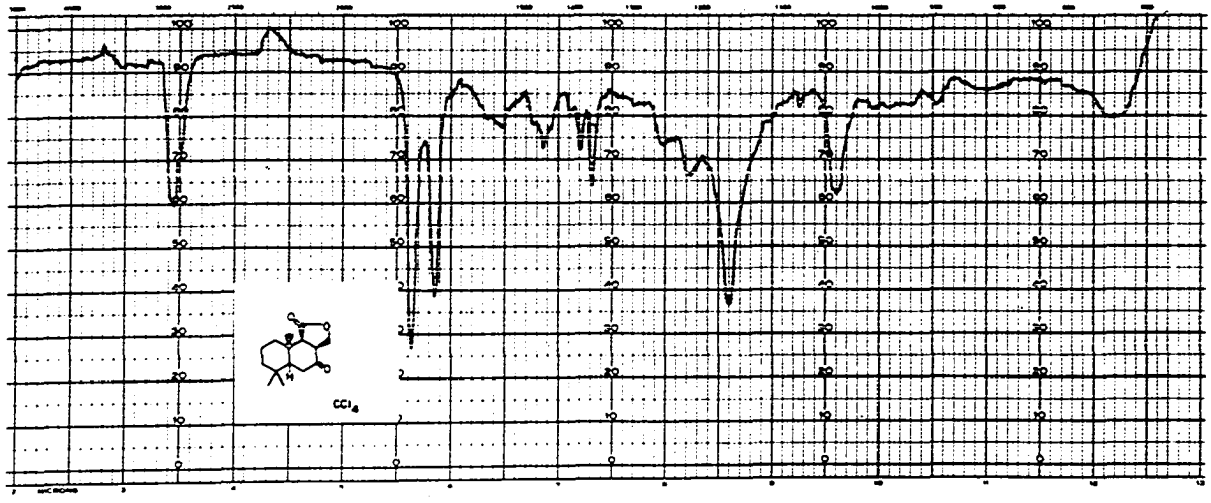
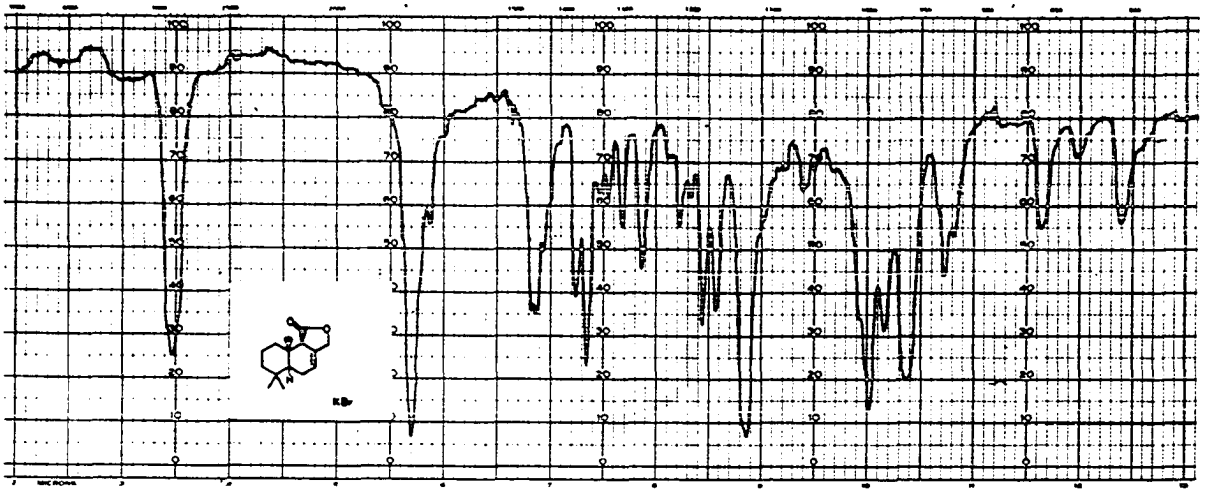
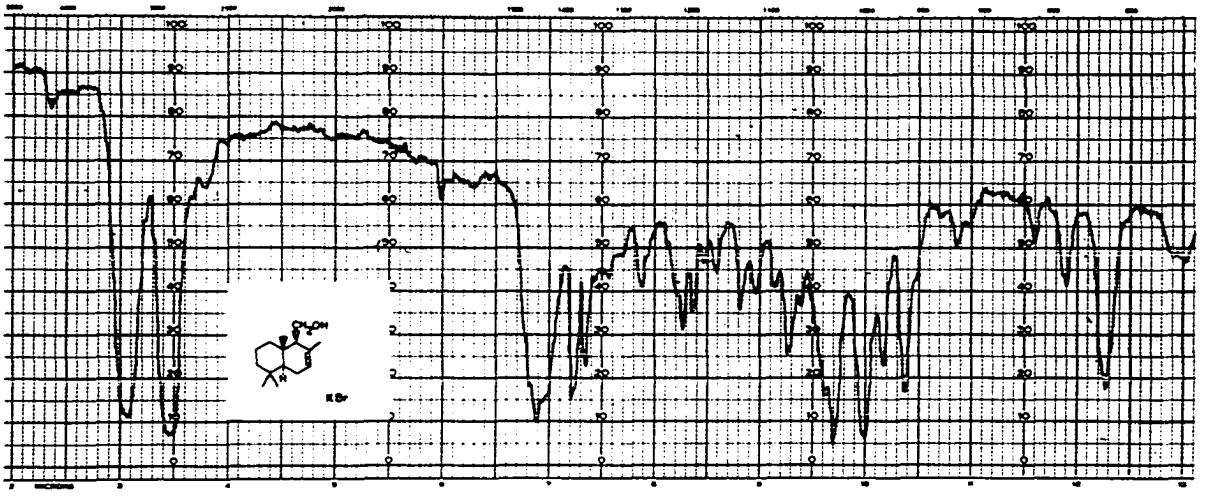


Figure 8. Infrared spectra





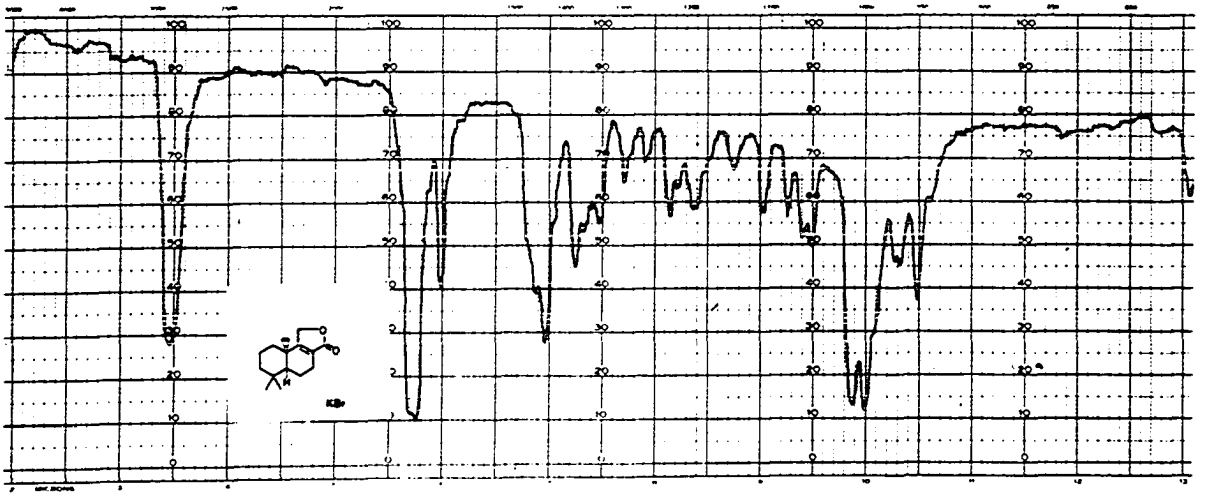


Figure 9. Nuclear magnetic resonance spectra

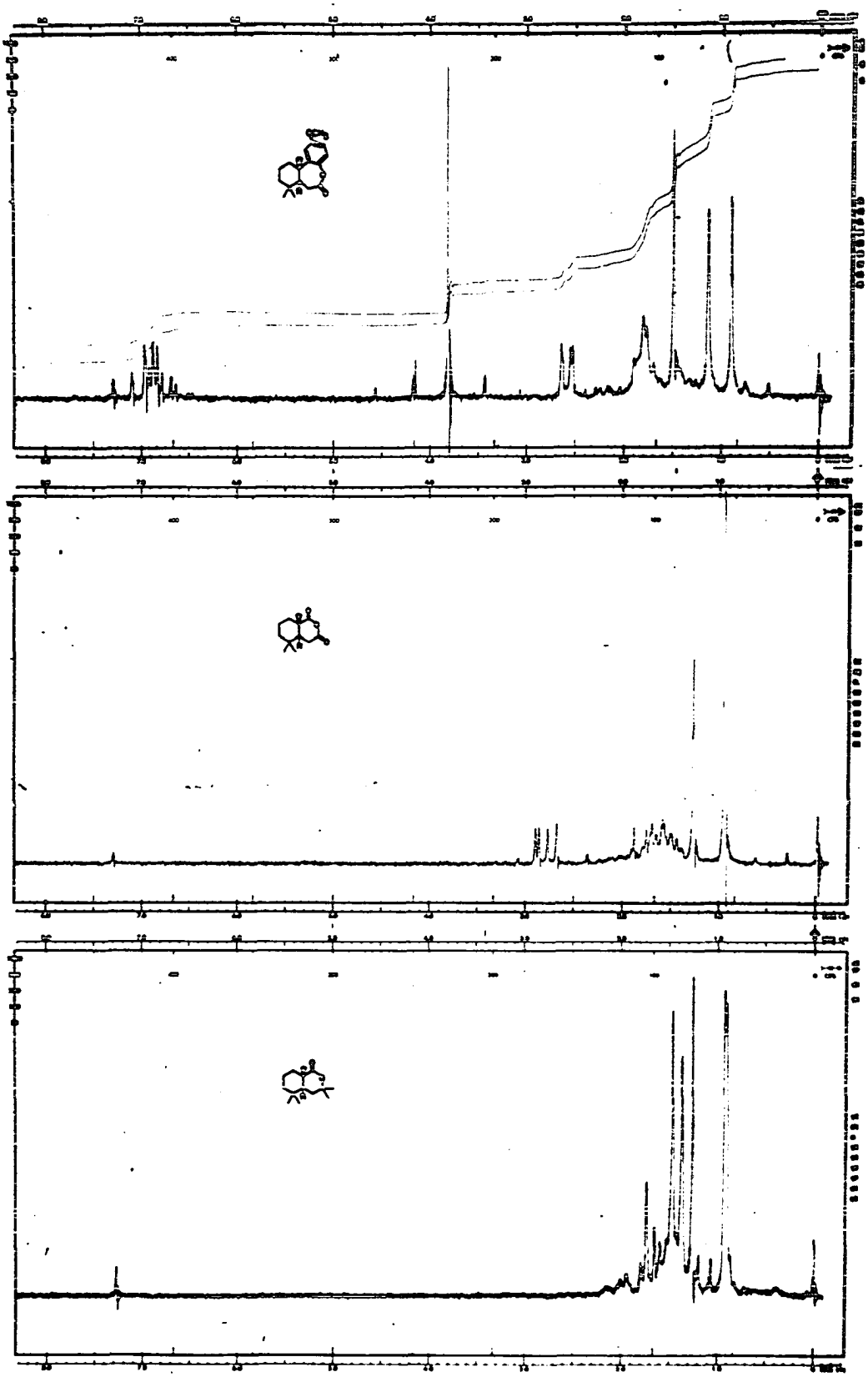


Figure 10. Nuclear magnetic resonance spectra

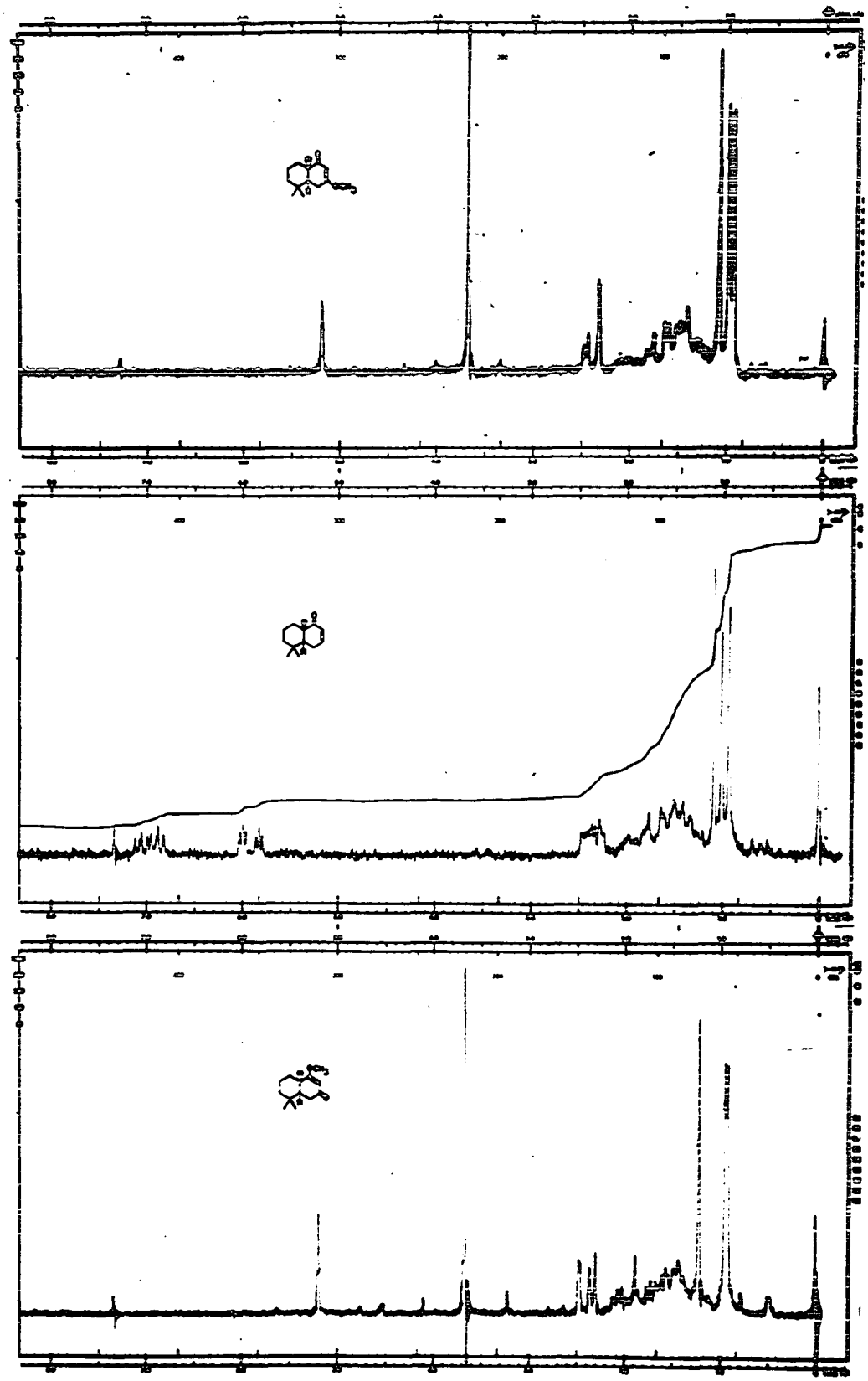


Figure 11. Nuclear magnetic resonance spectra

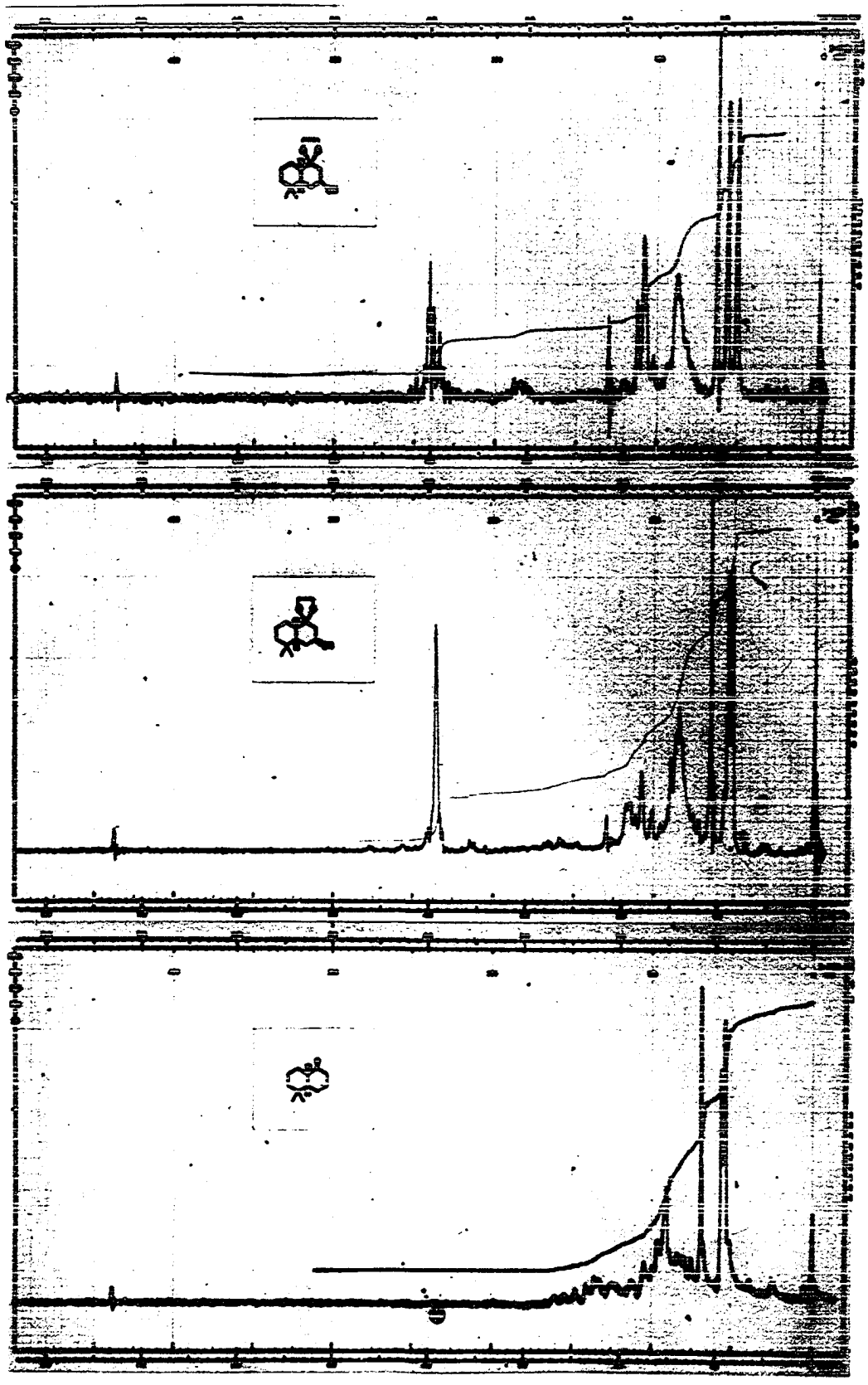


Figure 12. Nuclear magnetic resonance spectra

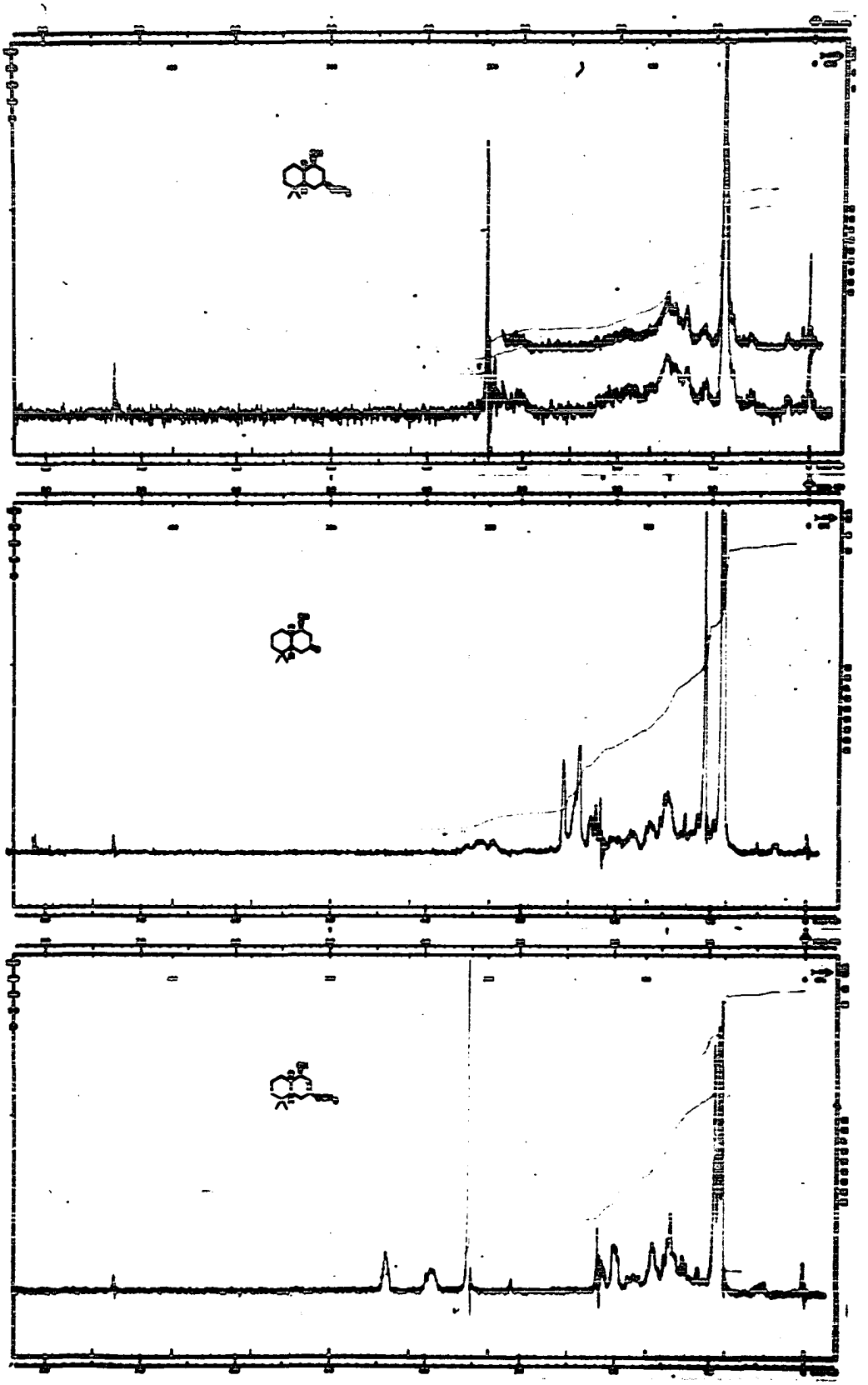


Figure 13. Nuclear magnetic resonance spectra

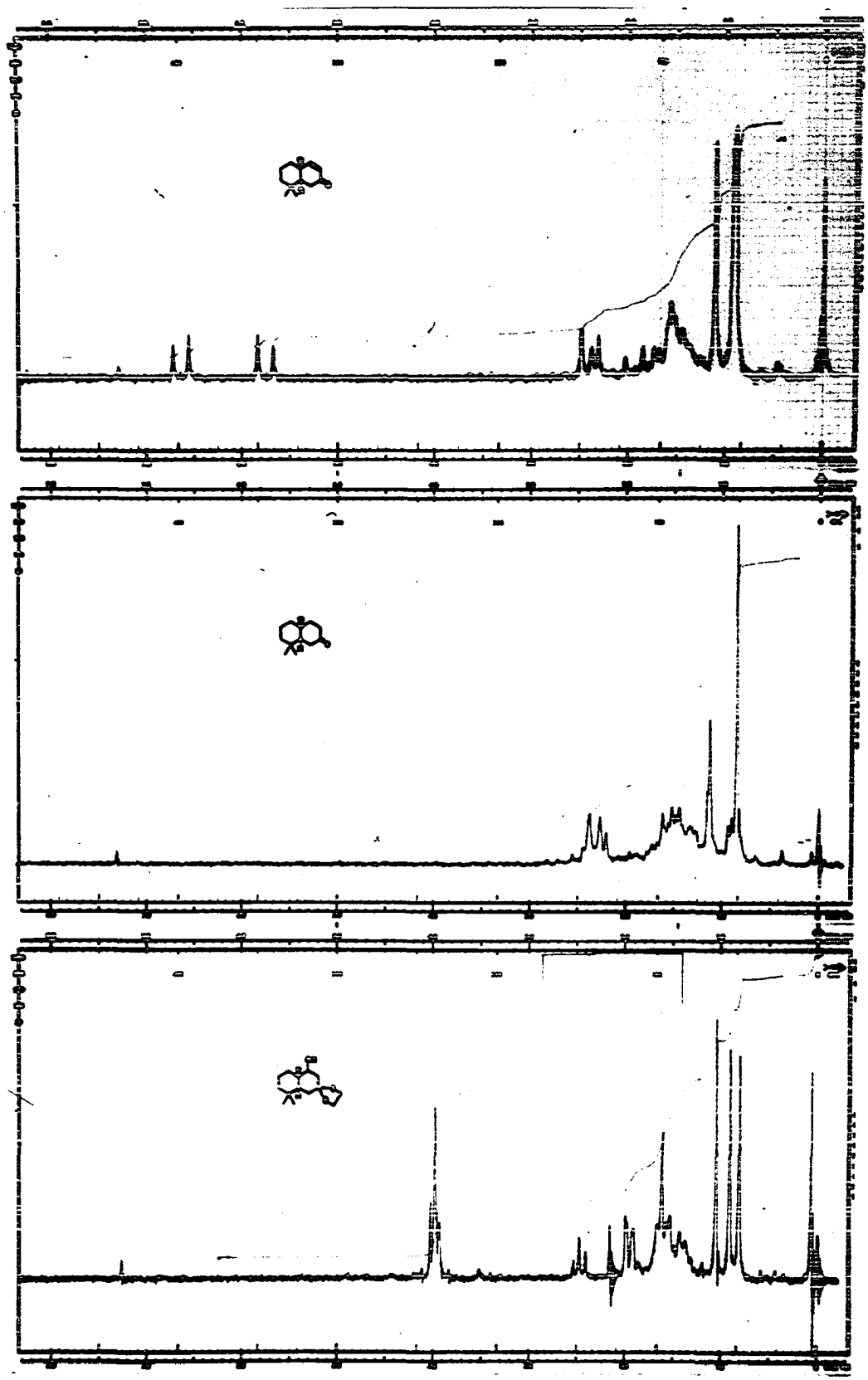
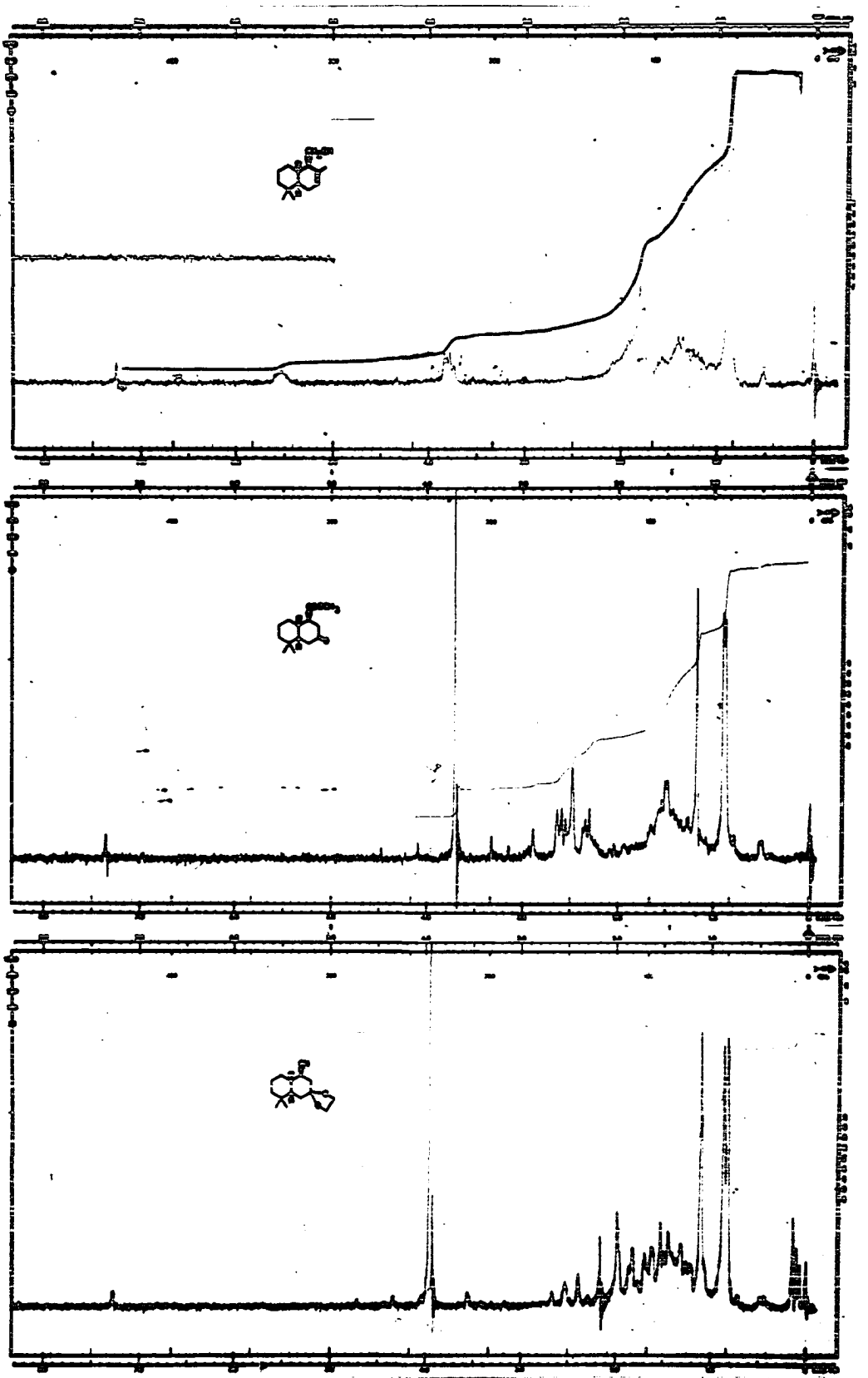


Figure 14. Nuclear magnetic resonance spectra



EXPERIMENTAL

All melting and boiling points are uncorrected. Microanalyses were performed by Midwest Microlabs, Indianapolis, Indiana, and Alfred Bernhardt, Mikroanalytisches Laboratorium, Mulheim (Ruhr), Germany.

Silica for chromatography was 50-200 mesh, supplied by G. Frederick Smith Chemical Co., Columbus, Ohio. Unless otherwise noted, the alumina for chromatography was Aluminum Oxide - Merck, supplied by Merck and Co., Rahway, New Jersey.

Ozonolyses were performed with a 2% weight concentration of ozone in oxygen from a Welsbach T-23 ozonator at a flow rate of 0.04 cfm. Unless otherwise noted, the optical rotations were determined on chloroform solutions with an O. C. Rudolf polarimeter.

O-Methylpodocarpol (LI)

O-Methylpodocarpol was prepared from podocarpic acid (L) by standard methods[32].

O-Methylpodocarpane (LII)

O-Methylpodocarpane was prepared from O-methylpodocarpol (LI) by standard methods[33].

7-Keto-O-methylpodocarpane (LIII)

A solution of 6.0 g. of chromic anhydride in 25 ml. of 80% acetic acid was slowly added to a stirring ice-cooled

solution of 4.8 g. of O-methylpodocarpane (LII) in 100 ml. of acetic acid. The mixture was stirred at room temperature for 12 hours, diluted with 300 ml. of saturated sodium chloride solution and extracted with chloroform. After washing with 5% sodium hydroxide and drying over anhydrous sodium sulfate, the chloroform extract was evaporated yielding a yellow oil. Chromatography of the oil on alumina and elution with 1:1 benzene-hexane gave 3.5 g. (69%) of 7-keto-O-methylpodocarpane (LIII), a clear oil whose 2,4-dinitrophenylhydrazone melted at 235-236°; reported[34] m.p. 236.5-237°.

Analysis of 2,4-dinitrophenylhydrazone

Calculated for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.24; H, 6.32; N, 12.30.

Baeyer-Villiger Oxidation of 7-Keto-O-methylpodocarpane (LIII).

An ice-cold mixture of 0.33 ml. of trifluoroacetic anhydride and 0.83 ml. of 90% hydrogen peroxide in 20 ml. of methylene dichloride was added to 0.287 g. of the ketone LIII in 25 ml. of methylene dichloride and the mixture allowed to stand for 70 hours at room temperature. Evaporation of the methylene dichloride yielded the crude lactone LIV, a red oil, which was hydrolyzed by refluxing for 0.5 hours in 25 ml. of isopropyl alcohol and 10 ml. of 10% sodium hydroxide. The isopropyl alcohol was evaporated under vacuum and the

remaining basic solution washed with ether, acidified with hydrochloric acid and extracted with ether. After drying over anhydrous sodium sulfate, the ether extract was evaporated to yield 0.30 g. of yellow oily acid LV.

The crude acid was chromatographed on silica. Elution with 1:4 ether-benzene yielded an oily solid which was converted to the lactone LIV by sublimation at 175° (2 mm.). Chromatography of the crude lactone on silica and elution with 1:19 ether-benzene, followed by 6 crystallizations from hexane and sublimation at 140° (1 mm.) gave the pure lactone LIV as white crystals, m.p. 114-115°.

Analysis

Calculated for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.32; H, 8.18.

Infrared spectrum

See Figure 1.

Nuclear magnetic resonance spectrum

See Figure 9.

Optical rotation

$[\alpha]_D^{25}$ - 254° (C, 2.59)

Drimic Anhydride (LVI)

A solution of 1.70 g. of crude acid LV, obtained directly from the Baeyer-Villiger oxidation of 7-keto-O-methylpodocarpane (LIII), in 200 ml. of methylene dichloride was ozonized at room temperature for 3 hours. The resulting solution was added slowly to a stirring mixture of 6.0 g. of sodium hydroxide and 40 ml. of 30% hydrogen peroxide in 100 ml. of water. The stirring was continued for 12 hours at room temperature with concommitant evaporation of the methylene dichloride. The basic solution was washed with ether, acidified with hydrochloric acid and extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the ether extract was evaporated yielding 0.47 g. of oily, crude drimic acid (XXXI).

Refluxing of the acid in 25 ml. of acetic anhydride for 1 hour and evaporation of the acetic anhydride under vacuum gave an oily residue which was chromatographed on silica. Elution with 1:20 ether-benzene, followed by sublimation at 120° (1 mm.) gave 0.28 g. (22%) of drimic anhydride (LVI). After four crystallizations from hexane, the anhydride became isotropic at 66-66.5° and melted at 112-113°.

Analysis

Calculated for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.54; H, 8.49.

Infrared spectrum

See Figure 1.

Nuclear magnetic resonance spectrum

See Figure 9.

Optical rotation

$[\alpha]_D^{25}$ - 46.6° (C, 3.77)

Drimic Acid (XXXI)

A solution of 0.182 g. of drimic anhydride (LVI) in 20 ml. of 95% ethanol and 20 ml. of 10% sodium hydroxide was refluxed for 0.5 hours and the ethanol removed by distillation. The remaining basic solution was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield 0.198 g. (100%) of drimic acid (XXXI) which, after recrystallization from hexane, gave a melting point of 166-168°; reported[21] m.p. 167-168°.

Infrared spectrum

Maxima; 5.55 (s), 5.70 (s)μ($CHCl_3$).

Optical rotation

$[\alpha]_D^{25}$ - 6.5° (C, 11.44) (acetone); reported[23] $[\alpha]_D^{25}$ - 5°.

Dehydroabietane (LX)

Lithium aluminum hydride, 1.25 g., was added slowly to a stirring cold solution of 25.0 g. of dehydroabietonitrile (LVII) in 250 ml. of ether. After stirring for 10 minutes, during which time a white precipitate formed, the excess lithium aluminum hydride was decomposed by the dropwise addition of water. The mixture was then acidified with 50 ml. of 5% hydrochloric acid, dropwise at first, and then with concentrated hydrochloric acid. After stirring at room temperature for 0.5 hours, the ether layer was separated, washed with 5% hydrochloric acid, water, and dried over anhydrous magnesium sulfate. Evaporation of the ether afforded 24.9 g. of crude oily aldehyde LIX.

A mixture of the crude aldehyde and 100 g. of 95% hydrazine in 300 ml. of diethylene glycol was refluxed for 6 hours. The excess hydrazine was then distilled off until the temperature of the solution reached 200°. The cooled solution was treated with 150 g. of potassium hydroxide, heated slowly with stirring until the potassium hydroxide had dissolved and refluxed for 3 hours. The cooled mixture was diluted with 1 liter of water and extracted with ether. After washing with

water and drying over anhydrous magnesium sulfate the ether was evaporated yielding 22.0 g. of a green oil. A solution of the latter in 100 ml. of hexane was rapidly chromatographed on 100 g. of alumina and eluted with 500 ml. of hexane. Evaporation of eluant gave 17.4 g. (70%) of dehydroabietane (LX), m.p. 38-42°; reported[36] m.p. 41-44°.

7-Ketodehydroabietane (LXI)

A solution of 13.5 g. of chromic anhydride in 60 ml. of 80% acetic acid was added to a stirring ice-cooled solution of 24.6 g. of dehydroabietane (LX) in 300 ml. of acetic acid. The mixture was stirred at room temperature for 6 hours, diluted with 1.5 liters of water and extracted with ether. After removing the acetic acid by repeatedly washing with 5% sodium hydroxide and drying over anhydrous magnesium sulfate, the ether extract was evaporated yielding 23.8 g. of an orange oil. Chromatography of the resulting oil on alumina and elution with hexane produced 7.4 g. (30%) of unreacted dehydroabietane (LX). Further elution with 1:1 hexane-benzene gave 12.7 g. (48%) of a yellow solid. Crystallization of the latter from hexane yielded pure 7-ketodehydroabietane (LXI), m.p. 92-93°; reported[23] m.p. 83-84°.

Baeyer-Villiger Oxidation of 7-Ketodehydroabietane (LXI)

A stirring ice-cooled mixture of 11.0 g. of 7-ketodehydroabietane and 11.0 g. of anhydrous disodium hydrogen phosphate in 300 ml. of methylene dichloride was treated with a cold solution of 18.5 ml. of trifluoroacetic anhydride and 2.2 ml. of 90% hydrogen peroxide in 100 ml. of methylene dichloride. After warming to room temperature, the mixture was refluxed for 2 hours, washed with 5% sodium hydroxide and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 10.6 g. of red oil which was chromatographed on silica. Elution with benzene produced 7.7 g. of a yellow solid whose two crystallizations from hexane gave 5.9 g. (51%) of white crystalline lactone LXII, m.p. 86.5-87.5°.

Analysis

Calculated for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.27; H, 9.45.

Infrared spectrum

See Figure 1.

Optical rotation

$[\alpha]_D^{25}$ - 234° (C, 1.86)

Hydrolysis of Lactone LXII

A solution of 5.85 g. of lactone LXII in 100 ml. of 10% potassium hydroxide and 200 ml. of isopropyl alcohol was refluxed for 1 hour. The isopropyl alcohol was evaporated under vacuum and the remaining basic solution washed with ether, acidified with hydrochloric acid and extracted with ether. After drying over anhydrous magnesium sulfate, the extract was evaporated to give 6.2 g. of a yellow oily solid which was chromatographed on silica. Elution with 1:9 ether-benzene gave 5.91 g. (95%) of acid LXIII which melted at 147-149° after crystallization from aqueous methanol.

Analysis

Calculated for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.34; H, 9.37.

Infrared spectrum

Maxima; 5.90 (s), 6.20 (w)μ ($CHCl_3$).

Optical rotation

$[\alpha]_D^{25}$ + 28.8° (C, 1.38)

Drimic Anhydride (LVI)

A solution of 1.84 g. of acid LXIII in 100 ml. of methylene dichloride was ozonized at room temperature for 4 hours. The resulting solution was added slowly to a mixture of 100 ml. of 10% sodium hydroxide and 50 ml. of 30% hydrogen peroxide and stirred at room temperature for 12 hours during which time the methylene dichloride evaporated. The remaining solution was washed with ether, acidified with hydrochloric acid and extracted with ether. After washing with water and drying over anhydrous magnesium sulfate the extract was evaporated yielding 1.3 g. of a green oil. Chromatography of the latter on silica and elution with 1:4 ether-benzene gave 0.60 g. of crude drimic acid (XXXI).

Refluxing the acid in 15 ml. of acetic anhydride for 1.5 hours and evaporating the solvent under vacuum afforded a yellow solid residue. Treatment with Norit in hexane followed by crystallization from hexane gave 0.37 g. (31%) of drimic anhydride (LVI), which became isotropic at 66-66.5° and melted at 113-114°. The infrared spectrum was identical with that of drimic anhydride obtained from podocarpic acid and a mixed sample became isotropic at 66-66.5° and melted at 111-113°.

Infrared spectrum

See Figure 1.

Nuclear magnetic resonance spectrum

See Figure 9.

Optical rotation

$[\alpha]_D^{25}$ - 42.8 (C, 8.58)

Trans-5,5,9β-trimethyldecalindione-1,3 (LXIX)

Magnesium turnings, 1.49 g., were added to a solution of 55 ml. of methyl iodide in 150 ml. of ether and the ice-cooled mixture stirred under nitrogen. After the completion of the Grignard reaction, 5.72 g. of powdered anhydrous cadmium chloride was added and the mixture stirred and refluxed under nitrogen for 0.5 hours. After distilling the excess methyl iodide and ether, 300 ml. of sodium-dried benzene and 4.0 g. of drimic anhydride (LVI) was added and the mixture stirred and refluxed under nitrogen for 8 hours. The cooled mixture was treated with 200 ml. of 10% sulfuric acid, stirred for 10 minutes and the layers separated. The aqueous solution was washed with benzene and the combined benzene solution was extracted with 5% sodium hydroxide. The basic extract was acidified with hydrochloric acid, extracted with ether and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 4.3 g. of green oil, presumably a mixture of the keto-acids LXVII and LXVIII.

Repeating the reaction with a 3 fold increase of dimethylcadmium gave a 25% yield of the keto-acid mixture and a 75% yield of a neutral oil. Distillation of the latter at a bath temperature of 155-160° (5 mm.) gave a clear liquid which solidified on standing, m.p. 40-48°. Analysis, infrared and nuclear magnetic resonance spectra showed the neutral product to be lactone LXX.

Analysis

Calculated for $C_{14}H_{24}O_2$: C, 74.70; H, 10.75. Found: C, 74.95; H, 10.75.

Infrared spectrum

See Figure 2.

Nuclear magnetic resonance spectrum

See Figure 9.

Optical rotation

$[\alpha]_D^{25}$ + 24.1° (C, 4.22)

The above keto-acid mixture, 4.3 g., was dissolved in ether, treated with excess diazomethane and allowed to stand at room temperature for 1 hour. The excess diazomethane was decomposed with acetic acid and the solution washed with 5% sodium bicarbonate. After drying over anhydrous magnesium

sulfate, the ether was evaporated leaving 4.3 g. of an oily mixture of the methyl esters of LXVII and LXVIII.

The mixture was added to a previously prepared solution of 1.7 g. of potassium in 300 ml. of t-butyl alcohol and refluxed under nitrogen for 3 hours. The cooled solution was acidified with hydrochloric acid and the solvent evaporated under vacuum. The resulting solid residue was dissolved in chloroform, washed with water and extracted with 5% sodium hydroxide. The basic extract was acidified with hydrochloric acid and extracted with chloroform. After drying over anhydrous magnesium sulfate the solution was evaporated yielding 3.67 g. of a yellow solid. Crystallization from an ethyl acetate-methanol mixture gave 2.64 g. (66%) of trans-5,5,9β-trimethyldecalindione-1,3 (LXIX), m.p. 194-201°.

Analysis

Calculated for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.67; H, 9.52.

Infrared spectrum

See Figure 2.

Optical rotation

$[\alpha]_D^{25}$ - 94.8° (C, 1.43) (methanol)

Trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXII) and Trans-1-methoxy-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIV)

A mixture of 2.0 g. of diketone LXIX, 0.2 g. of p-toluenesulfonic acid, 100 ml. of methanol and 150 ml. of benzene was refluxed with slow distillation for 5.5 hours. The remaining 25 ml. of solution was diluted with 100 ml. of ether, washed with 5% sodium hydroxide and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 2.19 g. of oily solid which was chromatographed on alumina. Elution with benzene gave 1.78 g. (84%) of crystalline trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXII) which after crystallization from hexane gave a melting point of 55.5-57°.

Analysis

Calculated for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.59; H, 9.71.

Infrared spectrum

See Figure 3.

Nuclear magnetic resonance spectrum

See Figure 10.

Optical rotation

$[\alpha]_D^{25}$ - 81.1° (C, 2.55)

Further elution with 1:4 ether-benzene yielded 0.31 g. (13%) of trans-1-methoxy-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIV). Distillation at a bath temperature of 130° (1 mm.) followed by sublimation gave white crystals, m.p. 68-70°.

Analysis

Calculated for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.89; H, 9.78.

Infrared spectrum

See Figure 3.

Nuclear magnetic resonance spectrum

See Figure 10.

Optical rotation

$[\alpha]_D^{25}$ + 78.8° (C, 2.48)

Trans-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXXIV)

A solution of 0.070 g. of enol ether LXXIV in 10 ml. of ether was treated with 0.030 g. of lithium aluminum hydride

and stirred at room temperature for 1 hour. The excess lithium aluminum hydride was decomposed with water and the ether solution filtered and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.063 g. of hydroxy enol ether LXXXIII, a white solid. After 2 crystallizations from hexane and drying in vacuum, the solid melted at 80-94°. On standing at room temperature for 12 hours, the solid became oily due to partial decomposition to the enone LXXIV.

The combined 0.063 g. of crude hydroxy enol ether LXXXIII was dissolved in 10 ml. of 0.01 N sulfuric acid in 95% ethanol and allowed to stand at room temperature for 0.5 hours. The acid was neutralized by adding 5% sodium bicarbonate and the solvent evaporated under vacuum. The residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether afforded 0.060 g. (98%) of crude trans-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXIV) which on distillation at a bath temperature of 95-100° (1 mm.) gave a clear liquid.

Analysis

Calculated for $C_{13}H_{20}O_2$: C, 81.20; H, 10.48. Found: C, 80.91; H, 10.63.

Infrared spectrum

See Figure 4.

Nuclear magnetic resonance spectrum

See Figure 10.

Optical rotation

$[\alpha]_D^{25}$ - 41° (C, 1.38)

Trans-5,5,9β-trimethyldecalone-1 (LXXXVIII)

A mixture of 0.107 g. of enone LXXXIV, 0.030 g. of 10% palladium on charcoal and 15 ml. of ethyl acetate was stirred at room temperature under hydrogen at atmospheric pressure for 1 hour. Filtration of the catalyst and evaporation of the solvent gave 0.105 g. (98%) of crude trans-5,5,9β-trimethyldecalone-1 (LXXXVIII). Distillation at a bath temperature of 80-85° (1 mm.) gave a clear liquid which did not solidify on standing.

Analysis

Calculated for $C_{13}H_{22}O$: C, 80.39; H, 11.41. Found: C, 80.46; H, 10.93.

Infrared spectrum

See Figure 4.

Nuclear magnetic resonance spectrum

See Figure 11.

Optical rotation

$[\alpha]_D^{25}$ - 39.4° (C, 2.14)

2,4-Dinitrophenylhydrazone

Recrystallized from ethyl acetate-methanol, m.p. 165.5-167°. Calculated for $C_{19}H_{26}N_4O_4$: C, 60.94; H, 7.00; N, 14.96. Found: C, 60.83; H, 7.24; N, 15.04.

Trans-3α-cyano-5,5,9β-trimethyldecalone-1 (XCVI)

A solution of 0.078 g. of enone LXXIV in 10 ml. of dimethylformamide was treated with a solution of 0.053 g. of potassium cyanide and 0.032 g. of ammonium chloride in 4 ml. of water. The mixture was stirred at 100° for 3 hours, cooled and added to 100 ml. of ether. After washing with water and drying over anhydrous magnesium sulfate the solution was evaporated yielding 0.093 g. of a white solid. Crystallization from hexane and sublimation at 110° (0.4 mm.) gave crystalline trans-3α-cyano-5,5,9β-trimethyldecalone-1 (XCVI), m.p. 102-103°.

Analysis

Calculated for $C_{14}H_{21}ON$: N, 6.39. Found: N, 6.29.

Infrared spectrum

Maxima; 4.48 (w), 5.84 (s)μ ($CHCl_3$).

Optical rotation

$[\alpha]_D^{25}$ - 43.6° (C, 3.46)

Trans-3β-cyano-5,5,9β-trimethyldecalone-1 (XCIX)

A mixture of 0.190 g. of α-cyanoketone XCVI, 30 ml. of benzene, 5 ml. of ethylene glycol and a trace of p-toluenesulfonic acid was refluxed with a Dean-Stark water separator for 7 hours. The cooled solution was diluted with 50 ml. of ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.226 g. of white, solid α-cyanoketal XCVII.

Nuclear magnetic resonance spectrum

See Figure 11.

The latter was dissolved in a solution of 0.100 g. of potassium in 15 ml. of t-butyl alcohol and stirred at room temperature for 10 hours. The solution was added to 100 ml. of ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.205 g. of oily β-cyanoketal XCVIII.

Nuclear magnetic resonance spectrum

See Figure 11.

The ketal was dissolved in 50 ml. of acetone and 1 ml. of hydrochloric acid and refluxed for 15 minutes. Evaporation of the acetone afforded an oily residue which was dissolved in ether, washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. The solution was evaporated yielding 0.183 g. (96%) of crude trans-3β-cyano-5,5,9β-trimethyldecalone-1 (XCIX).

Distillation at a bath temperature of 135-140° (1 mm.) gave a clear liquid which did not solidify when cooled in a freezer for 24 hours. Thin layer chromatography (silica) indicated the presence of only one compound which was slightly faster than the α-cyanoketone XCVI.

Analysis

Calculated for $C_{14}H_{21}ON$: N, 6.39. Found: N, 6.28.

Infrared spectrum

Maxima; 4.45 (w), 5.86 (s) μ (film, Infracord).

Optical rotation

$[\alpha]_D^{25}$ - 47.4° (C, 2.39)

Hydrogenation of Trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXII)

A mixture of 0.100 g. of enol ether LXXII, 0.100 g. of 10% palladium on charcoal and 10 ml. of ethyl acetate was stirred at room temperature under hydrogen at atmospheric pressure for 13 hours. Filtration of the catalyst and evaporation of the solvent gave 0.084 g. of an oil which was chromatographed on alumina. Elution with 1:4 benzene-hexane afforded 0.032 g. (37%) of trans-5,5,9β-trimethyldecalone-1 (LXXXVIII). Further elution with 1:1 ether-benzene yielded 0.023 g. (23%) of white crystalline solid. Crystallization from hexane and sublimation at 120° (1 mm.) yielded pure trans-3β-methoxy-5,5,9β-trimethyl-decalol-1β (LXXXIX), m.p. 88-90°.

Analysis

Calculated for $C_{14}H_{27}O_2$: C, 74.28; H, 11.58. Found: C, 74.01; H, 11.66.

Infrared spectrum

See Figure 3.

Nuclear magnetic resonance spectrum

See Figure 12.

Optical rotation

$[\alpha]_D^{25}$ - 9.6° (C, 0.96)

Lithium Aluminum Hydride Reduction of Trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalone-1 (LXXII)

A solution of 1.0 g. of enol ether LXXII in 100 ml. of ether was treated slowly with 0.25 g. of lithium aluminum hydride and stirred at room temperature for 1 hour. The excess lithium aluminum hydride was decomposed by the cautious addition of moist sodium sulfate and the ether solution filtered and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 0.988 g. of an oily solid which was shown to be a three component mixture by thin layer chromatography (silica).

Chromatography of the latter on alumina and elution with 1:19 ether-benzene gave 0.058 g. (7%) of trans-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIII). Continued elution with 1:9 ether-benzene afforded 0.416 g. (41%) of a white solid. Crystallization from hexane gave pure trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalol-1β (LXXXI), m.p. 96-97°.

Infrared spectrum

See Figure 5.

Nuclear magnetic resonance spectrum

See Figure 12.

Optical rotation

$[\alpha]_D^{25}$ - 53.3° (C, 1.24)

Further elution with ether gave 0.174 g. (18%) of trans-1β-hydroxy-5,5,9β-trimethyldecalone-3 (LXXXII) which was crystallized from hexane to give fine needles, m.p. 111-112°.

Analysis

Calculated for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.96; H, 10.57.

Infrared spectrum

See Figure 5.

Nuclear magnetic resonance spectrum

See Figure 12.

Optical rotation

$[\alpha]_D^{25}$ - 27.3° (C, 2.43)

Usually, the oily mixture obtained from the reduction was directly hydrolyzed by the following procedure. A solution of the mixture, 0.988 g., in 100 ml. of 95% ethanol was treated with 4 ml. of hydrochloric acid and allowed to stand at room temperature for 10 minutes. The ethanol was evaporated under vacuum and an ether solution of the residue was washed with 5% sodium hydroxide and dried over anhydrous magnesium sulfate. Evaporation of the ether and distillation of the residue at 90-95° (1.5 mm.) gave 0.75 g. (86%) of liquid trans-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIII).

Analysis

Calculated for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.71; H, 10.31.

Infrared spectrum

See Figure 5.

Nuclear magnetic resonance spectrum

See Figure 13.

Optical rotation

$[\alpha]_D^{25}$ + 7.4° (C, 2.81)

Hydrolysis of Trans-3-methoxy-5,5,9β-trimethyl-Δ^2-octalol-1β (LXXXI)

(a) A solution of 0.135 g. of enol ether LXXXI in 10 ml. of 0.01 N sulfuric acid in 95% ethanol was allowed to stand at room temperature for 36 hours. The solution was neutralized with 5% sodium bicarbonate and the ethanol evaporated under vacuum. The residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.121 g. of an oil which was shown by thin layer chromatography (silica) to be a mixture of the starting enol ether LXXXI, enone LXXIII and ketol LXXXII. Chromatography on alumina and elution with benzene gave 0.033 g. (28%) of crude trans-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIII). Continued elution with 1:19 ether-benzene afforded 0.019 g. (14%) of unreacted enol ether LXXXI. Further elution with ether yielded 0.062 g. (49%) of a white solid, trans-1β-hydroxy-5,5,9β-trimethyldecalone-3 (LXXXII), m.p. 110.5-111.5°.

(b) A solution of 0.339 g. of enol ether LXXXI in 25 ml. of 1.0 N sulfuric acid in 95% ethanol was allowed to stand at room temperature for 5 minutes. The solution was neutralized with 5% sodium bicarbonate and the ethanol evaporated under vacuum. The residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether afforded 0.268 g. of oily solid. Thin layer chromatography (silica) showed the presence of enone LXXIII and ketol

LXXXII and the absence of any enol ether LXXXI. Chromatography on alumina and elution with benzene yielded 0.135 g. (47%) of trans-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIII). Continued elution with ether gave 0.144 g. (45%) of trans-1β-hydroxy-5,5,9β-trimethyldecalone-3 (LXXXII), a white crystalline solid.

Dehydration of Trans-1β-hydroxy-5,5,9β-trimethyldecalone-3 (LXXXII)

(a) A solution of 0.035 g. of ketol LXXXII in 5 ml. of 0.01 N sulfuric acid in 95% ethanol was allowed to stand at room temperature for 36 hours. The solution was neutralized with 5% sodium bicarbonate and the ethanol evaporated under vacuum. The residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.033 g. (94%) of unreacted ketol LXXXII.

(b) A solution of 0.090 g. of ketol LXXXII in 10 ml. of 1.0 N sulfuric acid in 95% ethanol was allowed to stand at room temperature for 5 minutes. The solution was neutralized with 5% sodium bicarbonate and the ethanol evaporated under vacuum. The residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.090 g. (100%) of unreacted ketol LXXXII.

(c) A solution of 0.075 g. of ketol LXXXII in 12 ml. of 2 N sulfuric acid in 95% ethanol was refluxed for 0.5 hours. The ethanol was evaporated and an ether solution of the residue washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.067 g. (98%) of trans-5,5,9β-trimethyl-Δ^1-octalone-3 (LXXIII).

Trans-5,5,9β-trimethyldecalone-3 (XC)

A mixture of 0.100 g. of enone LXXIII, 0.040 g. of 5% palladium on charcoal and 15 ml. of ethyl acetate was stirred under hydrogen at atmospheric pressure and room temperature for 4 hours. Filtration of the catalyst and evaporation of the solvent yielded 0.092 g. of oil which was distilled at a bath temperature of 80-90° (1 mm.) to give 0.072 g. (72%) of pure liquid trans-5,5,9β-trimethyldecalone-3 (XC).

Analysis

Calculated for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 79.97; H, 11.28.

Infrared spectrum

See Figure 6.

Nuclear magnetic resonance spectrum

See Figure 13.

Optical rotation

$[\alpha]_D^{25}$ - 11.5° (C, 3.99)

2,4-Dinitrophenylhydrazone

Crystallization from 95% ethanol gave m.p. 164-165°; reported[48] m.p. for the enantiomer, 169-184° (slight decomposition). A sample of the enantiomer obtained from Dr. Enzell, after 3 crystallizations from 95% ethanol, gave a melting point of 164-166° and an infrared spectrum (see figure 4) identical with that of the 2,4-dinitrophenylhydrazone of XC.

Trans-1α-cyano-5,5,9β-trimethyldecalone-3 (XCII)

A solution of 2.19 g. of enone LXXIII in 50 ml. of dimethylformamide was treated with a solution of 1.16 g. of potassium cyanide and 0.84 g. of ammonium chloride in 20 ml. of water. The mixture was stirred at 100° for 3 hours, cooled and added to 500 ml. of ether. After washing with water and drying over anhydrous magnesium sulfate, the solution was evaporated yielding 2.59 g. of yellow oily solid. Chromatography of the solid on alumina and elution with 1:19 ether-benzene afforded 2.19 g. of crude trans-1α-cyano-5,5,9β-trimethyldecalone-3 (XCII). Crystallization from hexane gave 2.00 g. (80%) of the pure crystalline compound, m.p. 102-103°.

Analysis

Calculated for $C_{14}H_{21}ON$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.82; H, 9.45; N, 6.40.

Infrared spectrum

Maxima; 4.50 (w), 5.83 (s)μ (KBr).

Optical rotation

$[\alpha]_D^{25}$ - 33.7° (C, 1.91)

Trans-1β-cyano-5,5,9β-trimethyldecalone-3 (XCV)

A mixture of 1.31 g. of α-cyanoketone XCII, 300 ml. of benzene, 25 ml. of ethylene glycol and 0.030 g. of p-toluenesulfonic acid was refluxed for 7 hours in the presence of a Dean-Stark water separator. The excess benzene was distilled, 200 ml. of ether added and the solution washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 1.66 g. of white crystalline α-cyanoketal XCIII.

Nuclear magnetic resonance spectrum

See Figure 13.

The latter was dissolved in a solution of 0.664 g. of potassium in 75 ml. of t-butyl alcohol and allowed to stand at room temperature for 10 hours. The solution was diluted with 400 ml. of ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 1.63 g. of crystalline β-cyanoketal XCIV.

Nuclear magnetic resonance spectrum

See Figure 14.

The ketal was dissolved in 150 ml. of acetone and 5 ml. of hydrochloric acid and the solution refluxed for 0.5 hours. The acetone was evaporated and an ether solution of the residue washed with water and dried over anhydrous magnesium sulfate. The solution was evaporated yielding 1.28 g. (98%) of crude trans-1β-cyano-5,5,9β-trimethyldecalone-3 (XCV). Treatment of the product with Norit in ether and crystallization from hexane gave white crystals, m.p. 100-101°.

Analysis

Calculated for $C_{14}H_{21}ON$: C, 76.66; H, 9.65. Found: C, 77.03; H, 9.57.

Infrared spectrum

Maxima; 4.48 (w), 5.83 (s)μ (KBr).

Optical rotation

$[\alpha]_D^{25}$ - 4.2° (C, 1.50)

Trans-1β-carboxy-5,5,9β-trimethyldecalone-3 (CVI)

(a) A solution of 0.128 g. of α-cyanoketal XCIII and 3.0 g. of potassium hydroxide in 15 ml. of diethylene glycol was stirred under nitrogen at 200° for 24 hours. The cooled solution was diluted with 50 ml. of water, washed with ether, acidified with hydrochloric acid and extracted with ether. Evaporation of the ether afforded a yellow solid residue which was refluxed in 25 ml. of acetone and 1 ml. of hydrochloric acid for 0.5 hours. The acetone was evaporated and an ether solution of the residue washed with water, dried over anhydrous magnesium sulfate and evaporated. Treatment of the residue with Norit in methanol, followed by crystallization from aqueous methanol and sublimation at 170° (1 mm.), gave 0.73 g. (68%) of trans-1β-carboxy-5,5,9β-trimethyldecalone-3 (CVI), m.p. 210-212°.

Analysis

Calculated for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.07; H, 9.22.

Infrared spectrum

See Figure 6.

Optical rotation

$[\alpha]_D^{25}$ + 37.2° (C, 1.84)

(b) Treatment of 0.052 g. of β-cyanoketal XCIV with 2.0 g. of potassium hydroxide in 10 ml. of diethylene glycol under the conditions stated above gave 0.029 g. (69%) of trans-1β-carboxy-5,5,9β-trimethyldecalone-3 (CVI), m.p. 212-214°. The infrared spectrum was identical with that of the product obtained above from the α-cyanoketal XCII and their mixed melting point was 210-212°.

Trans-1β-carbomethoxy-
5,5,9β-trimethyldecalone-3 (CVII)

An ether solution of 0.095 g. of keto-acid CVI was treated with excess diazomethane in ether and allowed to stand at room temperature for 3 hours. The excess diazomethane was decomposed with acetic acid and the ether solution washed with 5% sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated. Treatment of the residue with Norit in ether followed by crystallization from aqueous methanol and sublimation at 80° (1 mm.) gave 0.083 g. (87%) of trans-1β-carbomethoxy-5,5,9β-

trimethyldecalone-3 (CVII), m.p. 67-68°; reported[63] m.p. "under 50°".

Analysis

Calculated for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.53.

Infrared spectrum

See Figure 6.

Nuclear magnetic resonance spectrum

See Figure 14.

Optical rotation

$[\alpha]_D^{25}$ + 40° (C, 1.75); reported[63] $[\alpha]_D^{25}$ + 38°.

2,4-Dinitrophenylhydrazone

Crystallization from methylene dichloride-methanol gave m.p. 221-223°; reported[63] m.p. 216-217°.

7-Ketoisodrimenin (XXXVIII)

Trans-1β-carboxy-5,5,9β-trimethyldecalone-3 (CVI), 0.070 g., was dissolved in a solution of 0.050 g. of potassium in 2 ml. of t-butyl alcohol and treated with 2 ml. of ethyl formate. After stirring at room temperature for 12 hours, the solvent

was evaporated under vacuum and a dilute hydrochloric acid solution of the residue extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated. The resulting oily residue and 0.030 g. of fused sodium acetate was added to 3 ml. of acetic anhydride and the mixture heated on a steam bath for 0.5 hours. The acetic anhydride was evaporated under vacuum and an ether solution of the residue washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.080 g. of an oil which was chromatographed on alumina (Giulini, Act. III). Elution with 1:4 benzene-hexane and sublimation at 140° (1 mm.) afforded 0.035 g. (48%) of 7-ketoisodrimenin (XXXVIII). Crystallization from hexane gave crystalline plates, m.p. 111-112°; reported[24] m.p. 112-113°.

Infrared spectrum

See Figure 7.

7-Keto-7,8-dihydrodrimenin (CIX)

(a) 7-Ketoisodrimenin (XXXVIII) was reduced with zinc in acetic acid according to the procedure of Overton[24] et al. to give 7-keto-7,8-dihydrodrimenin, m.p. 124-125°; reported[24] m.p. 124-126°.

Infrared spectrum

See Figure 7.

(b) A mixture of 0.010 g. of 7-ketoisodrimenin (XXXVIII), 0.010 g. of 10% palladium on charcoal, 2 drops of sulfuric acid and 5 ml. of ethyl acetate was stirred under hydrogen at atmospheric pressure and room temperature for 12 hours. The catalyst was filtered and the filtrate diluted with ether, washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 0.010 g. of an oil which was sublimed at 140° (1 mm.) and crystallized from hexane. The infrared spectrum and melting point, 124-125°, showed it to be 7-keto-7,8-dihydrodrimenin (CIX).

7β-Hydroxy-7,8-dihydrodrimenin (CX)

A solution of 0.100 g. of 7-keto-7,8-dihydrodrimenin (CIX) in 25 ml. of 95% ethanol was treated with 0.020 g. of sodium borohydride and stirred at room temperature for 2 hours. The ethanol was evaporated and an ether solution of the residue washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.074 g. (74%) of 7β-hydroxy-7,8-dihydrodrimenin (CX) as a white solid. Crystallization from hexane-benzene followed by sublimation at 135° (1 mm.) gave needles, m.p. 159-161°.

Analysis

Calculated for $C_{15}H_{24}O_2$: C, 71.39; H, 9.59. Found: C, 71.89; H, 9.38.

Infrared spectrum

See Figure 7.

Optical rotation

$[\alpha]_D^{25}$ - 66.8° (C, 2.39)

Drimenin (XXXII)

A solution of 0.046 g. of 7β-hydroxy-7,8-dihydrodrimenin (CX) and 0.100 g. of p-toluenesulfonyl chloride in 10 ml. of pyridine was allowed to stand at room temperature for 5 days. The solution was diluted with 50 ml. of water and extracted with ether. The extract was washed with 5% hydrochloric acid, 5% sodium bicarbonate, water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.065 g. of a yellow oil.

A solution of the latter in 15 ml. of dimethyl sulfoxide was stirred under nitrogen at 100° (bath temperature) for 1.5 hours. The cooled solution was added to 70 ml. of water and extracted with ether. After drying over anhydrous magnesium sulfate, the solution was evaporated yielding 0.047 g. of oil which was chromatographed on silica. Elution with benzene afforded 0.017 g. (40%) of drimenin (XXXII) which after crystallization from hexane and sublimation at 120° (0.4 mm.) melted at 132-133°; reported[24] m.p. 133°. The infrared

spectrum (see figure 8) was identical with that of the natural product and their mixed melting point was 132-133°.

Continued elution with 1:4 ether-benzene yielded 0.008 g. (17%) of crude 7-ketoisodrimenin (XXXVIII). Further elution with 1:1 ether-benzene gave 0.008 g. (19%) of unreacted 7β-hydroxy-7,8-dihydrodrimenin (CX).

Lithium Aluminum Hydride Reduction of Isodrimenin (XXXIII)

Isodrimenin was reduced with lithium aluminum hydride according to the procedure of Overton[24] et al. to give the diol XL, m.p. 121-122°; reported[24] m.p. 123-124°.

Confertifolin (XXIV)

A mixture of 0.012 g. of diol XL, 0.100 g. of manganese dioxide and 3 ml. of ether was stirred at room temperature for 12 hours. After filtering the manganese dioxide and washing with methanol, the combined filtrates were evaporated to yield 0.010 g. of yellow solid. Its crystallization from hexane and gradient sublimation at 120° (1 mm.) afforded long needles of confertifolin (XXXIV), m.p. 152.5-153.5°; reported[24] m.p. 152°. The infrared spectrum (see figure 8) was identical with that of the natural product and their mixed melting point was 152-153°.

12-Hydroxydrimenol (XXXV)

Drimenin (XXXII) was reduced with lithium aluminum hydride according to the procedure of Overton[24] et al. to 12-hydroxydrimenol (XXXV).

Drimenol (XXVI)

A mixture of 0.021 g. of 12-hydroxydrimenol (XXXV), 0.003 g. of sodium acetate and 5 ml. of acetic anhydride was heated on a steam bath for 0.5 hours. The acetic anhydride was evaporated under vacuum and the oily residue dissolved in 6 ml. of tetrahydrofuran (sodium-dried). The latter solution was added to 15 ml. of liquid ammonia, cooled in a Dry Ice-ethanol bath, treated with 0.018 g. of lithium wire and stirred for 1.5 hours. The Dry Ice bath was removed and the solvents allowed to evaporate. The resulting residue was dissolved in ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.020 g. of an oil which dissolved in 10 ml. of 95% ethanol and 7 ml. of 5% sodium hydroxide and refluxed for 1 hour. The ethanol was evaporated and the aqueous residue extracted with ether. After drying over anhydrous magnesium sulfate, the ether was evaporated yielding 0.019 g. of an oil. It was chromatographed on a 5 mm. thick silica plate and developed with 1:19 ethyl acetate-benzene. The positions of the products were determined by their fluorescence under ultraviolet light, their silica spots scraped from the

plate and the products extracted by boiling with 1:19 methanol-ethyl acetate. Filtration and evaporation of the eluate gave 0.009 g. of oil which was sublimed at 70° (1 mm.) yielding 0.008 g. (41%) of a white solid. Crystallization of the latter from hexane afforded drimenol (XXXVI), m.p. 94-95°; reported[21] m.p. 97-98°. The infrared spectrum (see figure 8) was identical with that of the natural product and their mixed melting point was 94-95°.

Nuclear magnetic resonance spectrum

See Figure 24.

SUMMARY

The degradation of podocarpic acid and dehydroabietonitrile to drimic acid has been achieved. This acid has been used for the synthesis of the drimanic sesquiterpenes: drimenol, drimenin, isodrimenin and confertifolin and the intermediates characterized. The synthetic sesquiterpenes have been compared and found identical with the natural products, constituting their total synthesis.

The mechanism of the acid hydrolysis of two β-hydroxy enol ethers has been investigated and evidence presented for the co-occurrence of two mechanistic pathways.

The stereochemistry of the cyanide addition to two α,β-unsaturated ketones has been elucidated and the reactions shown to be stereospecific.

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