Tetrahedron, 1966, Vol. 22, pp. 2331 to 2343. Pergamon Press Ltd. Printed in Northern Ireland

TERPENOIDS—XCI

TRANSFORMATION PRODUCTS OF COSTUNOLIDE. STEREOCHEMISTRY OF (—) SANTONIN AND SOLID DIHYDROCOSTUNOLIDE AT C11*

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Abstract—Solid dihydrocostunolide (VI), on metal-amine reduction furnishes an acid, $C_{15}H_{24}O_2$ (VII; R = H), the constitution of which has been decided from spectral evidence and confirmed by conversion into the known primary alcohol (V) and the hydrocarbon (IV). Conclusive evidence in support of VII (R = H), and the stereochemistry at C_4 have been obtained from the ozonolysis of VII (R = CH_3) which gives as one of the products, *S*-(+)-α-methylglutaric acid dimethyl ester (VIIIa), a compound of known absolute configuration. The other product of ozonolysis, (−)-2-methyl-3 (3′-oxo)-butylsuccinic acid dimethyl ester (VIIIb), is converted into (−)-2*S*-methyl-3*S*-butylsuccinic acid dimethyl ester (XV), via desulphurization of its thioketal, which proves the α-orientation of the CH_3 group at C_{11} in both (−)-santonin (X) and dihydrocostunolide (VI). This for the first time provides a chemical proof obtained under mild experimental conditions for the stereochemistry at the centre C_{11}.

Acid catalysed cyclization of VII (R = H), furnishes a bicyclic acid, $C_{15}H_{24}O_2$ (XVII; R = H), and santanolide ‘c’ (IX); the formation of the latter confirms the assignment of stereochemistry at C_4.

α-Cyclodihydrocostunolide (XXVIII), obtainable from both VI and I, has been converted into (+)-isojunenol (XXVII) and dihydro (+)-junenol (XXXIII).

IN ONE of our earlier publications, it has been reported[1] that the metal-amine reduction of the mixture of diols II and III, obtained from costunolide (I) by the action of LAH, leads to the formation of, a hydrocarbon, $C_{15}H_{26}$ (IV); a secondary alcohol, $C_{15}H_{26}O$ (XXV) and a primary alcohol, $C_{15}H_{26}O$ (V). Compounds IV and V are formed from II and III respectively, by the elimination of the hydroxyl groups in the allylic positions, accompanied by migration of the allylic double bond at C_4–C_5 in the original structures, to C_5–C_6 in the reduction products.

In the present communication are described the results of metal-amine reduction of solid dihydrocostunolide (VI), which possesses a potential allylic hydroxyl group in the lactone moiety.

When IV is reduced by lithium in liquid ammonia, an acid, $C_{15}H_{24}O_2$ (VII; R = H) is obtained. The IR spectrum of the methyl ester (VII; R = CH_3) shows peaks at 1660 cm^{-1} due to a trisubstituted double bond and at 980, 970 (shoulder) cm^{-1}, possibly due to a *trans*-disubstituted double bond. Its NMR spectrum shows signals at 9·25, 9·16 τ (3H), due to the methyl group at C_{11}; 8·98, 8·96 τ (3H), due to the methyl group at C_4 and a signal at 8·51 τ (3H) due to the methyl group on a double bond at C_{10}. A signal at 6·46 τ (3H) was observed which is due to the ester methyl group. In the olefinic region, however, the signals were not properly resolved and, as such, the exact nature and number of such protons could not be definitely decided.

As it was not possible to decide definitely, on the basis of spectral data alone,

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[1] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 1301 (1964).

whether hydrogenolysis is accompanied by allylic migration, during the formation of VII ($R = H$) from VI, it was desirable to convert VII ($R = CH_3$) into the corresponding primary alcohol and the hydrocarbon for comparison with V and IV respectively.

The ester VII ($R = CH_3$) is reduced by LAH to the corresponding primary alcohol which is identical with V in its IR spectrum and physical constants. The tosylate of the alcohol V on LAH reduction furnishes a hydrocarbon, $C_{15}H_{28}$, indentified as IV by IR and NMR spectra and other physical constants. These conversions establish the position of double bonds in the acid and the ester as shown in the structure VII.

As the structures assigned to IV, V and hence VII also, are mostly based on spectral data, it was desirable to furnish chemical evidence in support of their structures. In addition, the stereochemistry at C_4, a new asymmetric centre, resulting from migration of the allylic double bond during hydrogenolysis, is also to be determined.

For this purpose, VII ($R = CH_3$), was ozonized, the resulting dicarboxylic acids (obtained by the H_2O_2-oxidation of the aldehydes produced) esterified with diazomethane and the methyl esters fractionated. The lower boiling component, after purification by chromatography and distillation analysed for $C_{18}H_{14}O_4$. It was identified as dimethyl *S*-(+)-α-methylglutarate[2,3] (VIIIa) by its rotation, $[\alpha]_D +16°$, and elemental analysis. This is further confirmed by converting the diester into the slightly impure acid, m.p. 70°, $[\alpha]_D +7°$, and subsequently to its di-anilide, m.p. 175°. (+)-α-Methylglutaric acid[3] has been shown to have the D-configuration by its relation with D-(+)-lactic acid; but according to *R* and *S* conventions, it possesses the *S*-configuration. The formation of *S*-(+)-α-methylglutaric acid, a compound of known absolute configuration, clearly indicates that the C_4-asymmetric centre possesses the *S*-configuration and hence the methyl group at C_4 in VII, as well as in IV and V, is β-orientated. The higher boiling component of ozonolysis of VII ($R = CH_3$), corresponds to the keto dicarboxylic acid dimethyl ester, $C_{11}H_{18}O_5$ (VIIIb), from its elemental analysis, IR and NMR spectra. Its NMR spectrum shows signals at 8·92, 8·95 τ (3H) due to the methyl group at C_2; a signal at 7·92 τ (3H) due to the 4'-CH_3 group adjacent to the carbonyl function. It also shows signals at 7·59, 7·77 τ (2H) due to the two protons of the 2'-CH_2 adjacent to the carbonyl group and a signal at 6·35 τ (6H) due to the two ester methyl groups. It is thus (−)-2-methyl-3,(3'-oxo)-butylsuccinic acid dimethyl ester. It furnishes a semicarbazone, $C_{12}H_{21}O_5N_3$, m.p. 125°.

The formation of VIII a and b clearly establishes the position of the double bonds as shown in VII; and hence in IV and V. In addition, it also establishes the stereochemistry at C_4.

The assignment of stereochemistry at C_4 as described above, is further supported by the acid catalysed cyclization of VII.

The stereospecific nature of the *trans*-annular, acid catalysed cyclizations in costunolide (I) and its derivatives, with the characteristic disposition of the two trisubstituted double bond intact, has already been illustrated with suitable examples.[1,4,5] It invariably leads to selinane compounds with a *trans*-ring juncture.

When VII ($R = H$) is subjected to the reaction, using acetic acid and perchloric

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[2] E. Berner, R. Leonardson, A. T. Grontoft and K. Dahl, *Liebigs Ann.* **538**, 1 (1939); *Chem. Abstr.* 33, 6247[8] (1939).

[3] A. Fredga, *Svensk Kem Tidskr.* **67**, 343 (1955); *Chem. Abstr.* **50**, 10046[h] (1955).

[4] A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya, *Tetrahedron* **18**, 969 (1962).

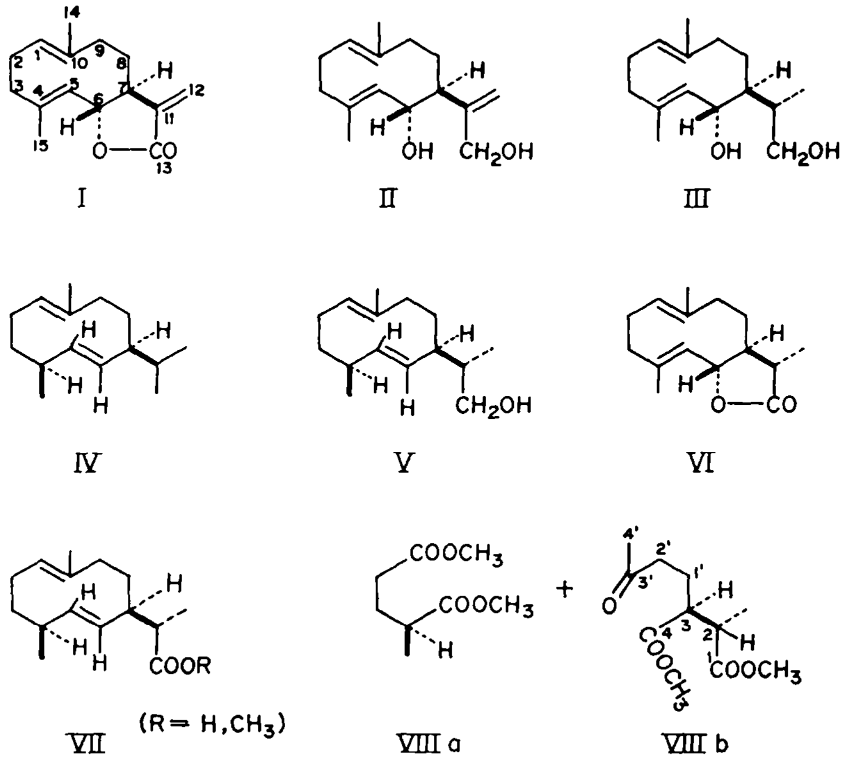

CHART I.

acid, a mixture of bicyclic lactones and acids is obtained, the components of which are separated into acidic and neutral parts by the usual procedure. The neutral part chiefly consists of lactones, from which a solid, m.p. 154–155°, is isolated in about 40% yield, by crystallization from light petroleum and methanol. This has been identified as santanolide ‘c’ (IX) from its m.p., analysis, rotation and IR spectrum. The probable course of reactions leading to santanolide ‘c’ from VII is represented in Chart II. The formation of santanolide ‘c’ from VII is of significance, as it reveals two important aspects of the reaction. It indicates that the C_4-methyl group in VII (and hence in related compounds) is β-oriented. It also indicates that the course of *trans*-annular cyclization in presence of an acid, in the ten-membered carboxyclic ring system with a different arrangement of double bonds as in VII, is also stereospecific and leads to the formation of a selinane compound with a *trans*-ring juncture.

From these results, it is obvious that in the costunolide series metal-amine reduction involving the elimination of the allylic hydroxy group at C_6 is invariably accompanied by the migration of the double bond at C_4–C_5 to C_5–C_6 position. The results of experiments described so far, have also thrown light on a long standing controversial problem regarding the stereochemistry of the lactones of the santonin group.

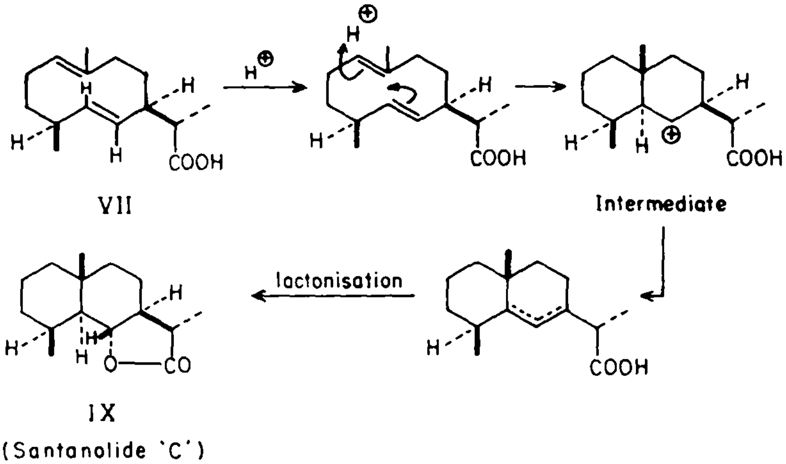

CHART II

The absolute configuration of α-santanin (X) at C_{11} had been under dispute[6,7] for quite some time. The stereochemistry of the methyl group was previously assumed to be β, on stability considerations. It was generally accepted than in α-santonin and related compounds, which contain a *trans*-fused butanolide system, the more stable configuration would be the one, in which the methyl group at C_{11} is *trans-* to the hydrogen at C_7, i.e., it is β-orientated. This was the view held till recently.

The X-ray crystallographic investigations[8] on bromodihydroisophotosantonic lactone acetate (XII), a compound prepared from α-santonin (X) by photochemical transformations, and subsequent acetylation and bromoination, however, revealed that the methyl group at C_{11} is in fact α-oriented, "*provided no inversion occurs at position* C_{11} *during the conversion of* α-*santonin into the compound* (XI)." A chemical proof[9] in support of this was subsequently furnished by the Japanese workers, who converted α-santonin (X) into (5 steps) santinic acid (XIII), which was then transformed by a series of reactions (5 steps) into (+)-benzoylalanine (XIV), a compound of known absolute configuration; and hence assigned the *S*-configuration at C_{11}.

Although this conversion supported the stereochemistry at C_{11}, as revealed by the X-ray crystallographic method, certain reactions involving (i) boiling with acetic acid and iodine, and (2) hydrolysis by hot 20% hydrochloric acid, at some of the stages, are somewhat drastic to be safely applied, for decision on stereochemical problems.

For this reason, a chemical proof carried out under mild conditions, was considered desirable, so that the assignment of configuration at C_{11}, could be made with certainty.

The stereochemistry of solid dihydrocostunolide (VI) at C_6, C_7 has been well established by its conversion by different procedures[4,5] into santonolide 'c' (IX), which also had been prepared from α-santonin (X). This clearly establishes the fact that both the compounds have identical stereochemistry at C_6, C_7 and C_{11}.

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[5] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 2639 (1964).

[6] R. B. Woodward and P. Yates, *Chem. & Ind.* 1391 (1954); W. Cocker and T. B. H. McMurry, *Tetrahedron* **8**, 18 (1960).

[7] Y. Abe, T. Miki, M. Sumi and T. Toga, *Chem. & Ind.* 953 (1956).

[8] J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.* 111 (1962).

[9] M. Nakazaki and H. Arakawa, *Proc. Chem. Soc.* 151 (1962).

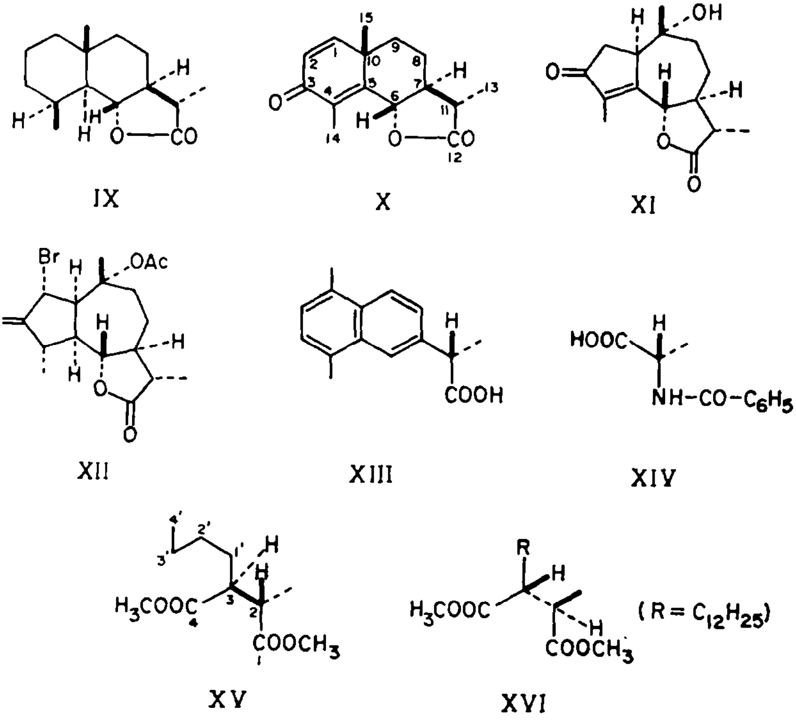

CHART III

The ketodicarboxylic acid dimethyl ester (VIIIb), obtained during ozonolysis of VII (R = CH_3), is converted into its thioketal and the latter on desulphurization with Raney nickel furnishes (—)-2-methyl-3-butylsuccinic acid dimethyl ester (XV) in almost pure condition (GLC 95%).

If the orientation of the methyl group at C_{11} in both solid dihydrocostunolide (VI) and α-santonin (X) be α, it then naturally follows that XV prepared from VIIIb, and also VIIIb, should have the 2*S*, 3*S*-configurations; in terms of D and L conventions, this corresponds in the particular case to 2D and 3D-configurations.

The specific rotation of XV $[\alpha]_D$ $-16°$ (M_D $-34{\cdot}56°$), is in agreement with the assignment made above, when compared with the sp. rotation of $+14{\cdot}5°$ (M_D $+47{\cdot}56°$), of roccellic acid[10] dimethyl ester (XVI), which is 2-methyl-3-dodecylsuccinic acid dimethyl ester. This compound has been shown to possess 2L, 3L-configurations, which in *R* and *S* convention corresponds to 2*R*, 3*R*-configurations. This comparison is made on the assumption that the rotation contribution at C_3 in XV is not much affected by the size of the alkyl group.

Since all the steps involved in the preparation of XV are sufficiently mild, the original stereochemistry must have been retained. Hence, this provides satisfactory chemical evidence for the α-orientation of the methyl group at the C_{11} asymmetric centre. Our present findings are in agreement with those of the previous workers.[8,9]

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[10] Bjorn Akermark (*Kungl. Tekn. Hogskolan, Stockholm*) *Acta. Chem. Scand.* **16**, 599–606 (1962); *Chem. Abstr.*, **57**, 7093h (1962).

Recently, α-santonin (X) has been converted into solid dihydrocostunolide[11] (VI) by photochemical transformations. It thus appears that no inversion at C_{11} occurs, during the photochemical changes reported.[8,11]

The mixture of bicyclic acids obtained during acid catalysed cyclization of VII (R = H) is esterified with diazomethane and the esters chromatographed on alumina to furnish in the earlier fractions, a pure (GLC) bicyclic ester, $C_{16}H_{26}O_2$ (XVIIa).

Although XVIIa does not respond to the tetranitromethane test for unsaturation, the UV end absorption (ε210, 5500) indicates the presence of either a trisubstituted or tetrasubstituted double bond.

This is further supported by its IR spectrum [absorption at 1660 (weak) and 818 cm^{-1}] and especially by its NMR spectrum, which clearly indicates the presence of a trisubstituted double bond, signal at 4·8 τ (1H). It also indicates the presence of three methyl groups, situated on saturated carbon atoms and the absence of any methyl group on a double bond. Signals at 9·16, 9·05, 8·93, 8·83 τ (9H) due to methyls at C_4, C_{10} and C_{11}.

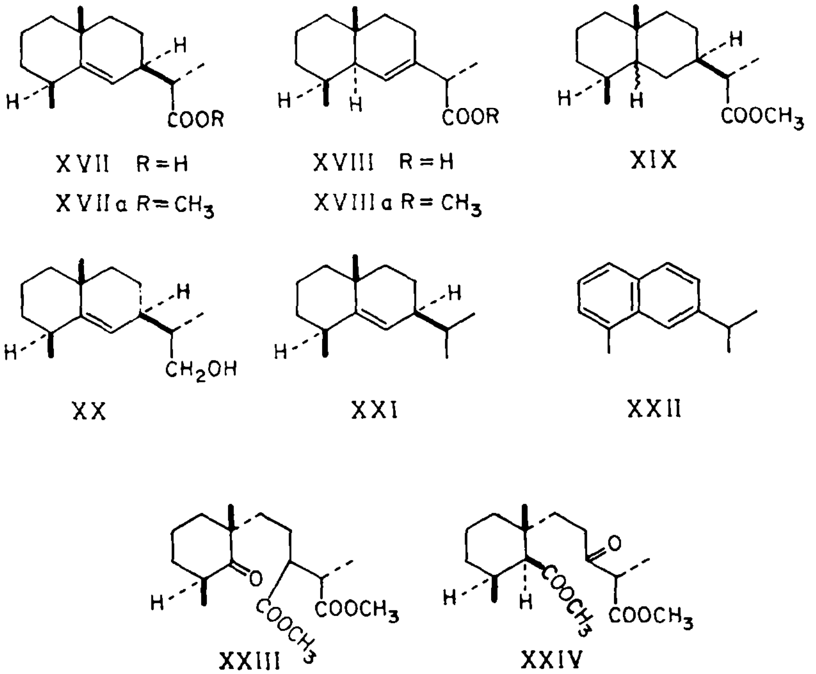

CHART IV

Quantitative catalytic hydrogenation furnishes a saturated dihydro derivative, $C_{16}H_{28}O_2$ (XIX), comparable with tetrahydrocostic acid methyl ester[12] in its IR spectrum and physical constants. The GLC analysis of this product however, indicates the presence of two components, the exact proportion of which could not be ascertained, owing to incomplete resolution. These are presumably C_5-epimeric esters.

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[11] E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.* **85**, 4033 (1963).

[12] A. S. Bawdekar and G. R. Kelkar, *Tetrahedron* **21**, 1521 (1965).

The ester (XVIIa) is converted to the primary alcohol (XX) by LAH reduction, which in its turn is transformed into the unsaturated hydrocarbon (XXI) by LAH reduction of its tosylate. Selenium dehydrogenation of this hydrocarbon (XXI) furnishes eudalene (XXII) in fairly good yield, characterized through its TNB adduct, m.p. and mixed m.p. 110°. These results clearly show the selinanic nature of XVII.

Since, together with XVII under consideration, santanolide 'c' (IX) is also formed, obviously, through an intermediate acid, represented by one of the two structures XVII or XVIII, or possibly through a mixture of both, it is quite probable that the pure ester isolated may correspond to either XVIIa or XVIIIa. That the double bond is more likely to be between C_5 and C_6 is indicated by the moderately high rotations of the ester (XVIIa), alcohol (XX), as selinane compounds[13] with a double bond attached to the C_5 carbon atom show high rotation, whereas the compounds with a double bond between C_6 and C_7[14] show comparatively lower rotations.

Attempts were then made to determine the exact location of the double bond by ozonolysis of XVIIa. A ketodicarboxylic acid monomethyl ester was formed which was converted to a dimethyl ester. This, however, failed to give a semicarbazone, thus excluding structure XVIIIa for the ester, as XVIIIa would furnish a compound on ozonolysis, expected to form a semicarbazone readily. The non formation of the semicarbazone may be attributed to the hindered nature of the carbonyl group in XXIII.

Further support in favour of the structure XXVIII for the ozonolysis product of XVIIa, is furnished by its IR spectrum which does not show the presence of a —CH_2—CO grouping (absence of a peak at 1420 cm^{-1}). In addition it gives the fluorescein test characteristic of a succinic acid derivative, which can be only explained by structure XXIII. These experiments conclusively prove the position of the double bond as in XVIIa.

Synthesis of isojunenol and related compounds. It has already been reported,[1] that the acid catalysed cyclization of the secondary alcohol (XXV), obtained as one of the products of metal-amine reduction of the mixture of diols II and III, yields mainly a mixture of two bicyclic secondary alcohols. One of these was isolated by repeated chromatography over alumina and identified as (+)-junenol (XXVI). Due to paucity of XXV, and also formation of other by products during the reaction, it was not possible to isolate the other alcohol, isomeric with (+)-junenol, viz. isojunenol (XXVII), expected to be formed in the reaction in analogy with other *trans*-annular cyclizations in the same series. Though isojunenol has not yet been known to occur in nature so far, its C_5-epimer, α-verbesinol (having a *cis*-ring juncture) has been obtained from a mixture of α- and β-verbesinol *p*-hydroxycinnamates, present in the plant *verbesina virginica* L.[13]

XXVII was synthesized starting from α-cyclodihydrocostunolide (XXVIII) by a procedure, similar to the one used in the synthesis of (+)-junenol[4] from β-cyclodihydrocostunolide (XXIX). The lactone (XXVIII) can be prepared from VI, by acid catalysed cyclization[4] using either acetic acid and acetic anhydride under refluxing conditions, or acetic acid and perchloric acid at room temperature. It can also be

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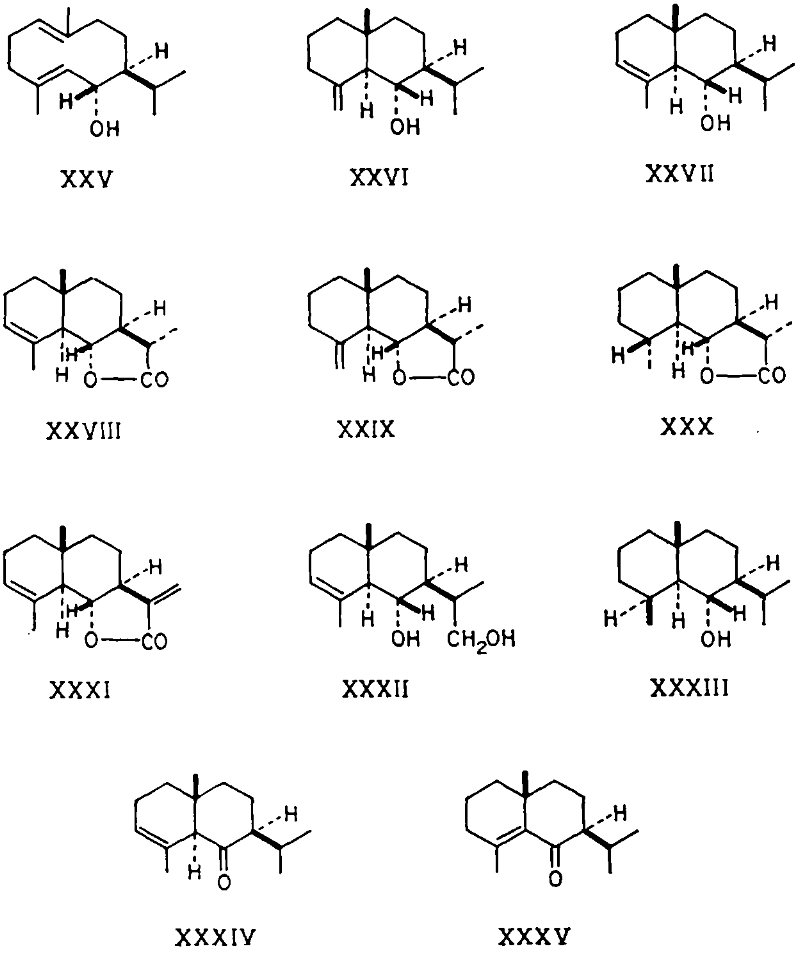
[13] P. D. Gardner, C. J. Park and C. C. Abers, *J. Amer. Chem. Soc.* **83**, 1511 (1961); D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.* 3492 (1954).

[14] G. D. Joshi, S. K. Paknikar, S. N. Kulkarni and S. C. Bhattacharyya, *Tetrahedron.*

obtained more conveniently by $NaBH_4$ reduction of α-cyclocostunolide (XXXI), readily obtainable from costunolide (I).

The lactone (XXVIII) was subjected to controlled LAH reduction to give the hydroxy aldehyde, which, as such, on Huang-Minlon reduction and subsequent purification of the product, by chromatography, vacuum sublimation and crystallization affords a solid, m.p 77–78°, $[\alpha]_D$ +38°. This was identified as isojunenol (XXVII) by IR spectrum (Fig. 1) and NMR spectrum which show the presence of a trisubstituted double bond.

The NMR spectrum of isojunenol shows signals at 9·17, 9·05 and 8·97 τ(9H) due to methyls of the isopropyl group at C_7 and angular methyl group ar C_{10}; at 8·08 τ(3H) due to the methyl group on a double bond at C_4. A broad triplet at 4·65 τ(1H) is due to the olefinic proton at C_3. The physical constants of isojunenol (XXVIII) prepared by us, which definitely possesses a *trans*-ring juncture are entirely different from those of α-verbesinol, which is shown[13] to possess a *cis*-ring juncture.



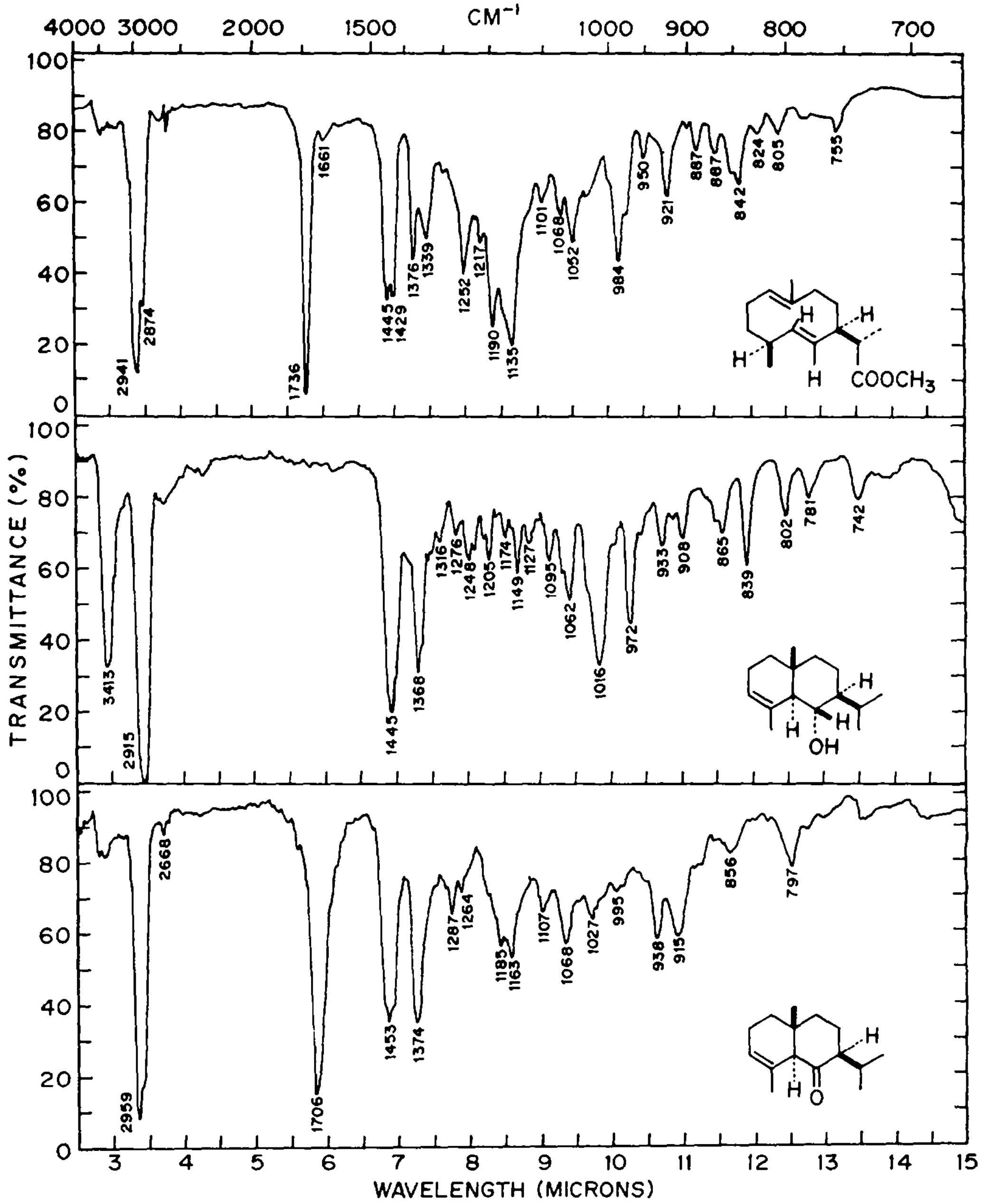
XXV XXVI XXVII

XXVIII XXIX XXX

XXXI XXXII XXXIII

XXXIV XXXV

CHART V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WAVELENGTH (MICRONS)

FIG. I

It is already known that catalytic hydrogenation of lactones (XXVIII and XXIX) in acetic acid using platinum catalyst give santanolide 'c' (IX) and santanolide 'a' (XXX) respectively, in which the methyl group at C_4 is β- and α-oriented respectively. Hydrogenation of (+)-junenol[15] (XXVI) in acetic acid is also reported to give rise to dihydro-(+)-junenol (XXXIII) in which the methyl group at C_4 is β-oriented.

When the catalytic hydrogenation of isojunenol is carried out in alcohol using platinum catalyst, it furnishes mainly the dihydro-(+)-junenol (XXXIII), m.p. and mixed m.p. 114° previously obtained from (+)-junenol (XXVI). The behaviour of (+)-junenol and (+)-isojunenol (XXVIII) on hydrogenation is thus in agreement with Rudloff's results[16] on the hydrogenation of α- and β-eudesmol mixture with platinum catalyst to furnish mainly a product with the methyl group at C_4 β-oriented.

Chromic acid oxidation of isojunenol with Jones reagent gave the ketone isojunenone, $C_{15}H_{24}O$ (XXXIV), the structure of which is supported by IR (1706 cm^{-1}) and UV spectra. The absence of any selective absorption in the region above 220 mμ excluded the possibility of migration of the double bond to give a conjugated ketone (XXXV).

During the formation of isojunenol from XXVIII some diol, $C_{15}H_{26}O_2$ (XXXII), m.p. 167°, was also formed due to the complete reduction of XXVIII by LAH.

Since, the compounds IV, V, VII, XXVII, XXXIII and XXXIV, have all been prepared from solid dihydrocostunolide (VI), a compound, which has been totally synthesized, the above conversions constitute a total synthesis of these compounds.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations were measured in $CHCl_3$ solution. UV spectra were recorded in EtOH solution, on a Beckman DK-II ratio recording spectrophotometer. IR spectra of solids, as nujol mulls and of liquids as liquid films, were taken with Perkin-Elmer Infracord spectrophotometer by Mr. K. G. Deshpande. The NMR spectra were taken in CCl_4 solution using TMS as internal reference on a 60 MC Varian instrument by Dr. P. M. Nair and colleagues and the chemical shifts were measured in τ-units. Microanalyses were carried out by Mr. Pansare and colleagues.

Dihydrocostunolide (VI). Solid dihydrocostunolide was prepared from I as previously reported.[17] It had m.p. 77–78°; $[\alpha]_D$ +113°.

Metal-amine reduction of VI. In a 2 l. three-necked flask, equipped with a Hg sealed stirrer and containing liquid ammonia (1000 ml approx.), Li (2·5 g) was added during 15 min with stirring. A solution of VI (10 g in 100 ml) in ether was then added gradually and the mixture stirred for 3 hr. Ammonia was allowed to evaporate and the residue decomposed by dropwise addition of alcohol under cooling, followed by water. After dilution with water, it was extracted with ether to remove unreacted VI. The aqueous layer was acidified with dil. H_2SO_4 (1:1) and extracted with ether to give the crude acid. This was further purified by Na_2CO_3 treatment to give VII (R = H; 6 g), with the following properties, n_D^{28} 1·4967; $[\alpha]_D$ −82° (*c*, 3). (Found for undistilled sample: C, 74·64; H, 10·34. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%.) IR bands at: 3333, 2941, 2632, 1709, 1445, 1406, 1374, 1332, 1284, 1222, 1043, 984, 971, 950, 923, 841, 803, 753 cm^{-1}.

Methyl ester VII (R = CH_3). The acid VII (R = H; 5 g) esterified with diazomethane yielded a liquid, which was purified by chromatography over alumina (grade III; 125 g) and eluted with pet. ether to give the pure ester (GLC/TLC), n_D^{28} 1·4892, $[\alpha]_D$ −91·4° (*c*, 3·7). (Found for an undistilled sample: C, 75·95; H, 10·52. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47%.) IR spectrum is shown in Fig. 1.

LAH reduction of VII (R = CH_3) *to the alcohol* (V). The ester VII (1·12 g) dissolved in dry ether

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[15] O. Motl, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **12,** 785 (1957).

[16] E. Von Rudloff and H. Erdtman, *Tetrahedron* **18,** 1315 (1962).

[17] A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **9,** 275 (1960).

(25 ml) was added dropwise to a well cooled solution of LAH (0·7 g in 50 ml) under stirring, which was continued for 3 hr yielding V (0·85 g), n_D^{28} 1·5034; $[\alpha]_D$ −98° (*c*, 2·5). (Found: for an undistilled sample: C, 79·79; H, 11·96. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

IR bands at: 3378, 2959, 1658, 1445, 1376, 1224, 1178, 1120, 1101, 1025, 985, 973, 951, 915, 885, 852, 841, 803, 755 cm^{-1}.

Tosylation of V *and LAH reduction of the tosylate.* To a solution of the alcohol (0·6 g) in pyridine (15 ml), toluene-*p*-sulphonylchloride (0·8 g) was added and the mixture kept at room temp for 48 hr. After dilution with water, it was worked up to give the tosylate (0·84 g), which was reduced by an ethereal solution of LAH (0·8 g, in 75 ml). The product (IV) was chromatographed on alumina (gr. I; 40 g) and eluted with pet. ether to give pure IV (GLC), b.p. 110–120° (bath)/0·5 mm, n_D^{25} 1·4913, $[\alpha]_D$ −91° (*c*, 4·2). (Found: C, 86·92; H, 12·61. $C_{15}H_{26}$ requires: C, 87·30; H, 12·7%.) IR bands at: 2994, 2732, 2688, 1667, 1464, 1451, 1385, 1366, 1346, 1300, 1284, 1229, 1196, 1179, 1172, 1126, 1109, 1044, 1019, 988, 975, 952, 934, 917, 888, 854, 841, 816, 797, 755 cm^{-1}. NMR spectrum was identical with the one previously reported.[1]

Ozonolysis of the ester VII (R = CH_3). A stream of ozonized O_2 was passed through an ice-cooled solution of the ester in $CHCl_3$ (4·8 g in 75 ml), till the absorption was complete. $CHCl_3$ was removed (suction) and the ozonide decomposed by heating with water and H_2O_2 (10 ml, 100 vol). The mixture of acids isolated by $NaHCO_3$-extraction was esterified with diazomethane to give mainly a mixture of VIIIa and b which was fractionated.

Fr. No.	*b.p.*	*Yield in g*
1	95–100°/10 mm	0·712
2	101–152°/10 mm	0·618
3	130–140°/2·5 mm	1·813

Fraction 1 was purified by chromatography over alumina (grade III; 15 g) and eluted with pet. ether to give a liquid, identified as VIIIa (95% by GLC), n_D^{24} 1·4213; $[\alpha]_D$ +16° (*c*, 4·5). (Found: C, 54·71; H, 7·90. $C_8H_{14}O_4$ requires: C, 55·16; H, 8·1%.)

A portion of VIIIa (0·3 g) was saponified to give the acid, m.p. 70°, $[\alpha]_D$ +7°, which was converted into the dianilide, m.p. 174–175°. (Found: N, 9·50. $C_{18}H_{20}O_2N_2$ requires: N, 9·45%.)

Fraction 2 was found to contain 85% VIIIa by GLC. Fraction 3 containing VIIIb had the following constants, n_D^{28} 1·4440, $[\alpha]_D$ −8° (*c*, 3·2). (Found: C, 56·56; H, 7·69. $C_{11}H_{18}O_5$ requires: C, 57·38; H, 7·88%.) It gave a semicarbazone, $C_{12}H_{21}O_5N_3$, m.p. 125°. (Found: C, 49·66; H, 7·64; N, 15·12. $C_{12}H_{21}O_5N_3$ requires: C, 50·16; H, 7·37; N, 14·63%.)

Conversion of VIIIb *into thioketal and its desulphurization to* XV. Ethane dithiol (1·5 ml) and BF_3-etherate (1·5 ml) were added to a solution of VIIIb (0·5 g) in glacial AcOH (10 ml) and the reaction mixture kept at room temp for 1 hr. It was then diluted with water and extracted with ether to give the thioketal (0·62 g), which was refluxed in aqueous EtOH (90%; 50 ml) with Raney Ni (8 g) for 14 hr. Ni was filtered off and the filtrate concentrated to give a liquid which was purified by chromatography and distillation to give XV (95%; GLC), b.p. 120–130° (bath)/0·5 mm; $[\alpha]_D$ −16° (*c*, 2·4). (Found: C, 62·08; H, 9·38. $C_{11}H_{20}O_4$ requires: C, 61·09; H, 9·32%.) The NMR spectrum showed signals at 9·20, 9·09, 9·02 τ (3H) due to the primary methyl group at 4′; at 8·94 and 8·97 τ (3H) due to the secondary methyl group at C_2 and at 6·32 τ (6H) due to the two ester methyl groups. A minor signal at 7·98 τ was observed indicating the presence of traces of VIIIb as impurity.

Acid catalysed cyclization of VII (R = H). The acid (VII; R = H; 12 g) was dissolved in glacial AcOH (100 ml) and perchloric acid (3 ml) was added to it. The homogeneous solution was allowed to stand at room temp for 24 hr and then heated on a steam bath for 7 hr. It was then diluted with water and extracted with ether. The ether layer was washed thoroughly with water to remove AcOH. It was then extracted with 10% Na_2CO_3aq to remove the acidic products. The carbonate layer was acidified with dil. H_2SO_4 (1:1) and extracted with ether. Removal of ether furnished a mixture of acids (3·5 g). The ether layer consisting of neutral products gave a solid, which was crystallized twice from pet. ether and subsequently from MeOH to furnish pure IX (4·8 g), m.p. and mixed m.p. 154–155°, $[\alpha]_D$ +57°. (Found: C, 76·10; H, 10·46. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%.) The IR spectrum was superimposable with that of an authentic sample.

The mixture of acids (3·5 g) was esterified with diazomethane and the esters chromatographed on alumina (gr. III; 120 g) and eluted with pet. ether to give pure XVIIa (2·2 g; GLC), b.p. 115–125° (bath)/0·8 mm, n_D^{24} 1·4914; $[\alpha]_D$ +53° (*c*, 3·05). (Found: C, 76·88; H, 10·28. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47%.) UV end absorption; ε 210, 5500. IR spectrum bands at: 1739 (due to ester) and 1660 and 818 cm^{-1} (trisubstituted double bond).

Catalytic hydrogenation of XVIIa. The ester (0·425 g) was hydrogenated in AcOH using Pt catalyst. The volume of H_2 absorbed (40 ml at NTP) corresponded to the presence of one double bond. The hydrogenated product had the following constants, b.p. 110–125° (bath)/0·8 mm, n_D^{28} 1·4819; $[\alpha]_D$ +33°. (Found: C, 75·80; H, 11·01. $C_{16}H_{28}O_2$ requires: C, 76·14; H, 11·18%.) GLC analysis showed two peaks which however were not resolved properly. Lit.[13] records for tetrahydrocostic acid methyl ester, n_D^{28} 1·4849; $[\alpha]_D$ +24·88° (*c*, 2·7). The IR spectrum was identical with that of tetrahydrocostic acid methyl ester.

LAH reduction of XVIIa *to the alcohol* XX. The ester XVIIa (1·2 g) in ether (50 ml) was reduced by a solution of LAH (0·75 g in 100 ml) initially under cooling and stirring. It was then refluxed for 4 hr and yielded XX, b.p. 130–140° (bath)/0·5 mm, n_D^{24} 1·5111; $[\alpha]_D$ +44° (*c*, 1·82). (Found: C, 80·98; H, 11·81. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

Tosylation of XX *and LAH reduction of the tosylate.* The alcohol (0·7 g) was dissolved in pyridine (15 ml) and toluene-*p*-sulphonyl chloride (0·8 g) was added and the mixture kept at room temp for 24 hr. It was diluted with water and the tosylate (0·97 g) was reduced by an ethereal solution of LAH (1 g in 100 ml) to give XXI (0·5 g) which was used as such for selenium dehydrogenation.

Selenium dehydrogenation of XXI. The hydrocarbon (XXI; 0·4 g) was heated with Se (0·5 g) in an atmosphere of N_2 at 280–300° for 12 hr. It was then taken up in pet. ether and chromatographed on alumina (gr. I; 10 g) and eluted with pet. ether to give a liquid (0·26 g) which with *s*-trinitrobenzene gave an adduct purified by crystallization; m.p. and mixed m.p. with an authentic sample of eudalene TNB derivative 110°.

Ozonolysis of ester XVIIa. A stream of ozonized O_2 was passed through an ice-cooled solution of the ester (0·4 g) in $CHCl_3$ till the absorption was complete. $CHCl_3$ was then removed under suction at 40° and the ozonide decomposed by heating with water and H_2O_2 (5 ml; 100 vol). The product was taken up in ether and extracted with 10% Na_2CO_3aq. The aqueous layer was acidified with dil H_2SO_4 (1:1) and extracted with ether to give the keto acid ester, which was esterified with diazomethane to XXIII. This was distilled to give a liquid, b.p. 220–240° (bath)/0·6 mm. It gave the fluorescein test with resorcinol. IR bands at: 1750, 1709 cm^{-1}, due to the ester groups and the keto group respectively. It did not show a peak at 1420 cm^{-1} (shoulder), characteristic of —CO—CH_2— grouping.

Preparation of α-cyclodihydrocostunolide (XXVIII). The preparation of XXVIII from VI using AcOH and Ac_2O has been reported.[4] It was also obtained from VI by using AcOH and perchloric acid at room temp and separating the XXVIII and XXIX as described earlier.[4]

It has now been prepared from XXXI by $NaBH_4$ reduction. The XXXI (9·3 g) was dissolved in MeOH (30 ml) and $NaBH_4$ (0·8 g) was added in small lots with stirring and kept at room temp for 24 hr. A solid (8·2 g), was obtained which was crystallized twice from MeOH to give XXVIII, m.p. 139–140°, $[\alpha]_D$ +82·7° (*c*, 3·8). (Found: C, 76·58; H, 9·48. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.) IR bands at: 2941, 1754, 1656, 1447, 1368, 1309, 1282, 1258, 1232, 1220, 1205, 1188, 1115, 1075, 1057, 1028, 993, 984, 963, 941, 931, 896, 853, 843, 790, 742 and 722 cm^{-1}.

Controlled LAH reduction of XXVIII. An ethereal solution of LAH (0·25 g of 60% activity; in 100 ml) was added to a solution of the lactone (3·39 g) in ether (50 ml) at −10° with stirring. The reaction mixture was stirred for 3 hr at −10° and decomposed with alcohol and water, to give a solid (2·93 g) containing the lactol corresponding to XXVIII as the major product.

Huang-Minlon reduction of the lactol from XXVIII. A mixture of crude lactol (5 g), KOH (5 g), hydrazine hydrate (6 ml) and freshly distilled diethylene glycol (60 ml) was heated at 220–230° for 5 hr, in an atmosphere of N_2. It was diluted with water and extracted with ether to give a solid which was chromatographed on alumina (gr. III; 90 g) and eluted with pet. ether and ether. The fraction eluted with pet. ether was sublimed (at 0·2 mm) to give a solid which on crystallization from pet. ether melted at 77–78°, $[\alpha]_D$ +38° (*c*, 2·7). (Found: C, 81·14; H, 11·93. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.) The IR spectrum is shown in Fig. 1.

The ether eluted fraction gave a solid, m.p. 167°. (Found: C, 75·60; H, 10·96. $C_{15}H_{26}O_2$

requires: C, 75·58; H, 11·00%.) This was identified as XXXII by comparison with an authentic sample prepared from XXVIII by the complete LAH reduction.

Catalytic hydrogenation of isojunenol (XXVII) *to dihydro* (+)-*junenol* (XXXIII). Isojunenol (0·487 g) was hydrogenated in alcohol using Pt catalyst. The volume of H_2 absorbed (55 ml at NTP) corresponded to the presence of one double bond. The hydrogenated product was purified by crystallization from pet. ether to give a solid, m.p. and mixed m.p. with an authentic sample of XXXIII, 114°, $[\alpha]_D$ ±0°. (Found: C, 79·84; H, 12·25. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.) IR bands at: 3356, 2933, 2732, 2681, 1447, 1374, 1302, 1289, 1252, 1238, 1208, 1186, 1167, 1149, 1133, 1074, 1053, 1037, 1010, 1000, 971, 945, 916, 894, 877, 868, 854, 834, 778, 736 cm^{-1}.

Chromic acid oxidation of XXVII *to the ketone* XXXIV. Isojunenol (0·38 g) was dissolved in acetone (10 ml) and Jones' reagent was added drop by drop till a brown colour persisted. The product, a liquid (0·32 g) was purified by chromatography and distillation to give XXXIV (98%; GLC), b.p. 110–120° (bath)/0·5 mm, n_D^{24} 1·4990, $[\alpha]_D$ +12·4° (*c*, 2·4). (Found: C, 81·26; H, 10·90. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.) UV spectrum did not show any maxima between 220–250 mμ. IR spectrum is shown in Fig. 1.