Synthetic Studies on Terpenoids. Part XVI.[1] Synthesis of 3β,17-Diacetoxyphyllocladen-15-one [2]

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A stereoselective synthesis of 3β,17-diacetoxyphyllocladen-15-one (XIX) from ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate proceeding in ten stages *via* methyl 13,13-ethylenedioxy-3-oxopodocarpa-5,9(11)-diene-8β-carboxylate (V) and methyl 3β-hydroxy-13-oxopodocarpane-8β-carboxylate (XII) is described. The ester (XII) has been correlated with a known degradation product from phyllocladene. Some by-products from the hydrogenation of the diene (V) are discussed.

In a previous publication [3] we described the synthesis of a tricarbocyclic system comprising rings B, C, and D of the phyllocladane nucleus from the keto-ester (I). Subsequently, synthesis of phyllocladene (8β,13β-kaur-16-ene) from an annulated homologue of the keto-ester (I) was completed by Turner,[4] using an identical route to build up ring D. Recently polyhydroxylated diterpenoids have been isolated with oxygen functions at various positions in the bi-, tri-, tetra-, and penta-carbocyclic systems. The 3-hydroxy-group in diterpenoids, which occurs less often than in triterpenoids, is generally associated with compounds possessing these carbocyclic systems [5a-d] and having a *trans*-fused AB ring junction. No naturally occurring 3-hydroxy-derivative of phyllocladene appears to have been isolated and phyllocladene derivatives reported with oxygen functions in ring D are all synthetic compounds.[6]

We became interested in synthesising a 3-hydroxylated phyllocladene derivative with an additional oxygen function in ring D. Existing synthetic methods afford limited [7] scope for introducing a 3-hydroxy-group at any stage of the synthesis, but we have stereoselectively synthesised [2] the hydroxy-keto-ester (XII), a key intermediate for both tetra- and penta-carbocyclic diterpenoids, with the 3-hydroxy-group present in the required configuration. This synthesis also develops the desired stereochemistry at C-8, and avoids the necessity of cleaving and then re-building ring C to generate the correct stereochemistry.[4,8]

Furylacrylic acid was treated with ethanolic hydrogen chloride to afford diethyl 4-oxoheptanedioate and this was converted into diethyl 4,4-ethylenedioxyheptanedioate.[9] Dieckmann cyclisation gave ethyl 3,3-ethylenedioxy-6-oxocyclohexanecarboxylate. This was condensed *in situ* with β-chloroethyl ethyl ketone, and the product was cyclised with sodium methoxide in methanol. The product (II), a viscous liquid, solidified and was isolated in two polymorphic forms, m.p. 68 and 95°. A second condensation of (II) with β-chloroethyl ethyl ketone in the presence of potassium t-butoxide and subsequent ring-closure with sodium methoxide in methanol afforded the lactone (III) and the unsaturated acid (IV) in variable proportions. On alkaline hydrolysis and mild acidification, the lactone (III) furnished the unsaturated acid (IV) as the monohydrate. Identity of the acids was established through the methyl ester (IVa). The AB ring junction in the lactone is expected to be *cis*, from the mechanism of the annulation.[10] The formation of γ- and δ-lactones with a suitably placed ester function is well precedented.[11] The i.r. absorption of the lactone at 1744 cm^{-1} implies some overlap [12] of the carbonyl group with the olefinic double bond, and sterically, this is possible only with a *cis* junction of rings A and B. The combined yield of the lactone (III) and of the acid (IV) was *ca.* 50%, with a considerable recovery of the bicyclic compound (II). That the two asymmetric centres at C-8 and C-10 in the compounds (III), (IV), and (IVa) have the desired configuration follows from the observation of lactone formation, and also from stereoelectronic considerations,[1] and correlation with a degradation product (X) of phyllocladene.[4,8] The methyl ester (IVa) was methylated in the presence of potassium t-pentyloxide to give compound (V) in a satisfactory yield. On a few occasions, a highly crystalline material, m.p. 198°, was also isolated; it appeared from its n.m.r. spectrum and elemental analysis to be an overmethylated compound, and it was not further investigated.

Catalytic hydrogenation of (V) was expected to lead to the corresponding *trans,anti*-perhydrophenanthrene derivative, α-orientation of the C-9 hydrogen being highly

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probable from known analogies.[13] Hydrogenation of the 5,6-double bond would be difficult but would invariably lead to a *trans* AB ring junction,[14] particularly in the presence of the oxygen function [1,15] at C-3. However, hydrogenation of (V) was difficult. The lactone (III) could not be hydrogenated under various conditions, presumably because of the inaccessibility of the double bond (evident from a study of models). This resistance[16] to hydrogenation is due to the highly polar lactonic group being adsorbed on the catalyst surface rather than the olefinic double bond. Hydrogenation of (V) in ethanol over palladium–charcoal (10%) gave a complex mixture of products, which on separation afforded (VI), (VII), and a compound, m.p. 176°, which was tentatively assigned [2] structure (VIII) on the basis of the following data. The n.m.r. spectrum shows signals at δ 0·78 (s, 10-Me), *ca.* 1·0 (*ca.* 12H, >CMe_2, $-CO_2\cdot CH_2\cdot CH_3$, and $-O\cdot CH_2\cdot CH_3$), and 3·35 p.p.m. (q, *J* 6 Hz, $-CO_2\cdot CH_2\cdot CH_3$). The mass spectrum shows a molecular ion peak at *m/e* 364 ($C_{22}H_{36}O_4$). Zeisel estimation of ethoxy-groups (through the courtesy of Professor Prelog) agrees with the proposed molecular formula. Yields of this compound varied with different runs of hydrogenation and different batches of the catalyst. It is difficult to envisage a mechanism leading to this compound, but it may be analogous to hydroboration and chemical reduction where an ethylene acetal undergoes hydrogenolytic fission at one [17] or both [18] of the ether linkages in specific environments.

When hydrogenation of (V) was carried out in ethyl acetate, only compounds (VI) and (VII) were isolated. In the n.m.r. spectrum of (VI), the ethylenedioxy-signal was absent and a >$CH\cdot OH$ signal was present at δ 3·25 p.p.m. The spectrum lacked a vinyl proton signal. The proton at C-13 appeared axial,[19] and this assignment was further confirmed through n.m.r. studies of the corresponding acetate (VIa). The >$CH\cdot OAc$ proton gave a complex signal at δ 4·45 p.p.m., and the width of the band (>25 Hz) supported the assignment (10 Hz is expected for an equatorial proton and 30 Hz for an axial proton). The n.m.r. spectrum of (VII) showed signals at δ 0·68 (s, 10-Me), 1·27 (s, >CMe_2), 3·61 (s, $-CO_2Me$), and 5·68 (olefinic proton at C-6). The compound gave a faint yellow colour with tetranitromethane. The position of the olefinic proton at C-6 was established in the following way. Absence of a signal near δ 2·8 p.p.m. suggests absence of a methylene group (at C-12) flanked by a carbonyl group and an olefinic double bond.[20] During deuteriation * of (VII) in deuteriomethanol (HCl; 80°), isomerisation to the αβ-unsaturated ketone did not occur and this would have happened had the double bond been at the 9(11)-position. Incorporation

(I) (II)

(III) (IV) R = H; (IVa) R = Me

(V)

(VI) R^1 = O, R^2 = <OH H
(VIa) R^1 = O, R^2 = <OAc H
(IX) R^1 = O, R^2 = O
(X) R^1 = H_2, R^2 = O
(XI) R^1 = H_2, R^2 = <OH H
(XIa) R^1 = H_2, R^2 = <OAc H
(XII) R^1 = <H OH, R^2 = O
(XIIa) R^1 = <H OAc, R^2 = O
(XIIb) R^1 = <H OTs, R^2 = O
(XIII) R^1 = <H OAc, R^2 = CH·CN
(XIV) Δ^{12}-isomer of (XIII)
(XV) R^1 = <H OAc, R^2 = <H CH_2·CN
(XVI) R^1 = <H OAc, R^2 = <H $CH_2\cdot CO_2Me$

(VII) R = O
(XVII) R = <H OAc

(VIII)

(XVIII) R^1 = H, R^2 = H_2
(XIX) R^1 = Ac, R^2 = CHOAc

* Kindly carried out by Dr. W. Meir, Hoffman-La Roche Ltd., Basle, Switzerland.

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of deuterium, according to mass-spectral data, was 90%. These findings were confirmed by double-resonance measurements. The saturated diketo-ester (IX) was obtained either from the unsaturated diketo-ester (VII) by catalytic reduction in acetic acid–perchloric acid, or from the hydroxy-ester (VI) by chromic acid oxidation. To ascertain the effect of the acetal group for these abnormal hydrogenations, the ethylenedioxy-group of (V) was removed with toluene-*p*-sulphonic acid in acetone. The crude product had no αβ-unsaturated carbonyl peak in the u.v. region, indicating that there had been no migration of the double bond during deacetalisation. Hydrogenation of the resulting product in ethyl acetate was rapid (uptake 1 mol. equiv.). The sole product (VII) was also obtained quantitatively and at a greater rate, by hydrogenation in ethanol. The axial C-8 methoxycarbonyl group probably participates in the removal of the acetal function, and solvent molecules may also take part during hydrogenation in alcoholic solution, leading to the ethoxy-group in (VIII).

In view of the complexities in the hydrogenation, we decided to obtain a definite proof of the stereochemistry at C-8 and C-9 in one of the hydrogenation products (VI). The keto-ester (X), isolated from phyllocladene and synthesised by Turner and by Ireland, was selected as the reference compound. Huang-Minlon reduction of (VI) gave an impure hydroxy-acid which was esterified to (XI), m.p. 137°. The yield was very low and better results were obtained through desulphurisation of the thioacetal of (VIa), which gave (XIa) in 75% yield. Mild alkaline hydrolysis of (XIa) gave the hydroxy-ester (XI), mentioned earlier. The laevorotatory ester (XIa), m.p. 111—112°, has been reported.[4] Chromic acid oxidation of (XI) afforded the known keto-ester (X) which did not depress the m.p. of an authentic sample (kindly supplied by Professor R. B. Turner), m.p. 132°, and whose i.r. spectrum was identical with that of an optically active sample (m.p. 160—161°).

The keto-ester (X), m.p. and mixed m.p. 132°, was also obtained in low yield through nucleophilic displacement of the tosylate (XIIb) with phenylmethanethiolate anion followed by desulphurisation with Raney nickel.

For the synthesis of the compound (XII), a slightly different path was followed. Reduction of (V) with sodium borohydride was followed by treatment with acid to remove the ethylenedioxy-group; catalytic hydrogenation with palladium–charcoal (10%) in ethyl acetate–perchloric acid gave the desired 3-hydroxy-keto-ester (XII). Its stereochemistry was confirmed (i) by oxidation with chromic acid, which gave the known diketo-ester (IX), also available from oxidation of the 13-hydroxy-keto-ester (VI), and (ii) by dehydration with phosphoryl chloride in pyridine, and subsequent hydrogenation over palladium–charcoal (10%) in ethyl acetate to furnish the keto-ester (X). The β-assignment of the hydroxy-group in (XII) is based on ample analogies,[21] and further confirmed by the n.m.r. data of its acetate (XIIa), which exhibited signals at δ 0·74, 0·80, and 1·00 (3s, $>CMe_2$ and 10-Me), 2·0 (s, $-O\cdot CO\cdot CH_3$), 3·6 (s, $-CO_2Me$), and 4·45 p.p.m. [q, *J* 10 Hz, C(3)-H axial hydrogen].

The bridged CD portion of the molecule was next elaborated. Reformatsky reaction on the carbonyl group of (XIIa) was unrewarding, but Wittig reaction with diethyl cyanomethylphosphonate was satisfactory for inserting a C_2 chain at the site of the carbonyl group. The unsaturated cyano-ester (XIII), isolated as a crystalline solid, melted over a range and was found to be a mixture of isomers from n.m.r. studies. The presence of geometrical isomers was indicated by the splitting of the methoxy-signal (three peaks at δ 3·67—3·7 p.p.m.) due to anisotropic effects of the cyano-group in particular and the olefinic double bond. Another isomer (XIV) was also present. There is evidence in favour of migration of a double bond in Witting reactions with diethyl cyanomethylphosphonate in cyclohexanone systems.[22] Migration [23] of the double bond with triethyl phosphonoacetate but not with diethyl cyanomethylphosphonate has also been observed. The intra-annular position of the double bond in structure (XIV) is facilitated by the B/C *trans* ring junction and is also evident from n.m.r. spectra of the unsaturated cyano-ester. The spectrum reveals the presence of (XIII) and (XIV) approximately in the ratio 2 : 1. Signals appear [for (XIII)] at δ 5·2 (=CH·CN) and [for (XIV)] at δ 5·8 [γ-vinylic C(12)-H] and 3·0 ($C{=}C\cdot CH_2\cdot CN$).[22] The unsaturated cyano-ester was catalytically hydrogenated in high yield. The saturated cyano-ester has structure (XV), hydrogenation most probably occurring at the α-face of the molecule owing to steric interference of the axial methoxycarbonyl group, and leading to the desired configuration at C-13, essential for cyclisation to the five-membered D ring. The cyano-ester (XV) was subjected to alkaline hydrolysis and the free acid, after esterification with diazomethane and acetylation, afforded the pure dimethyl ester (XVI), m.p. 124—125°, which was homogeneous (n.m.r. spectrum of the methyl groups). The same saturated dimethyl ester (XVI) has also been synthesised in improved yield from the Δ^5-keto-ester (XVII), and this is the major product of catalytic hydrogenation of the corresponding doubly-unsaturated $\Delta^{5,9(11)}$ keto-ester under normal conditions. This was subjected to Wittig reaction and the crude product was hydrogenated in ethanolic solution. The keto-ester (XVII) undergoes hydrolysis under mild alkaline conditions by participation [24] of the neighbouring carbonyl group, and could be separated from the Wittig product by dilute alkaline hydrolysis. The Δ^5-cyano-ester was subjected to alkaline hydrolysis, esterification with diazomethane, acetylation, and finally drastic catalytic hydrogenation, whereby the same saturated dimethyl ester (XVI) has

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been obtained in improved yield. Hydrogenation of 5,6-double bond being very difficult, its reduction under drastic conditions at a late stage of the synthesis was found advantageous. The dimethyl ester (XVI) was cyclised with potassium t-butoxide. The resulting β-keto-ester, which did not give a colouration with iron(III) chloride, was subjected to alkaline hydrolysis. The resulting neutral product on chromatographic purification afforded the tetracyclic hydroxy-ketone (XVIII) as a crystalline solid, m.p. 168—169°. I.r. and n.m.r. spectra confirmed the structure. The synthesis may be regarded as stereoselective so far as the ring junctions are concerned, although other products were formed during catalytic hydrogenation.

In order to complete the C_{20} framework by the introduction of one carbon atom at C-16, the ketone (XVIII) was condensed with ethyl formate. The resulting base-soluble hydroxymethylene compound gave an intense violet colouration with iron(III) chloride and was converted into the corresponding acetoxymethylene derivative with acetic anhydride and pyridine. The 3β,17-diacetoxyphyllocladen-15-one (XIX) was isolated as crystalline material. Since the acetoxymethylene function can be readily converted into a methyl [1] or a methylene [25] group, the present work constitutes a total synthesis of the 3,15-dioxygenated phyllocladene nucleus.

EXPERIMENTAL

M.p.s were taken using open capillary tubes in a sulphuric acid bath. U.v. spectra were recorded with a Beckman DU spectrophotometer for solutions in 95% ethanol. I.r. spectra were taken with a Perkin-Elmer 21 instrument. N.m.r. spectra were measured for [^{2}H]-chloroform solutions with tetramethylsilane as internal standard. T.l.c. plates were coated (0·2 mm thickness) with silica gel G (200 mesh). Light petroleum refers to the fraction of b.p. 60—80°.

Methyl 9,9-*Ethylenedioxy*-5-*methyl*-4-*oxobicyclo*[4.4.0]*dec*-5-*ene*-1-*carboxylate* (II).—(*a*) An ethanolic solution (60 ml) containing the methoiodide from 1 diethylaminopentan-3-one (14 g) was slowly added under nitrogen to a cooled (ice–salt) mixture of ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (36 g), sodium ethoxide [from sodium (4·5 g)], and ethanol (150 ml). The mixture was left at 0° for 1 h, and heated under reflux for 3 h. After the usual work-up, the crude product was refluxed with a solution of sodium methoxide [from sodium (2·1 g)] in methanol (50 ml) for 5 h under nitrogen. The solution was cooled to 0° and acidified with acetic acid (6 ml), and the methanol was removed. The residue was worked up and the product, on distillation, afforded keto-ester (II) (24 g) as a thick *liquid*, b.p. 160—165° at 0·5 mmHg, $\lambda_{max.}$ 245 nm (ε 12,560), $\nu_{max.}$ ($CHCl_3$) 1720 and 1660 cm^{-1}. On cooling, the liquid solidified to two polymorphic forms, m.p. 68 and 95° (Found: C, 64·2; H, 7·0. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%); *semicarbazone*, m.p. 216° (from ethanol) (Found: C, 56·9; H, 6·1. $C_{16}H_{23}N_3O_5$ requires C, 57·0; H, 6·2%).

(*b*) To a suspension of dry sodium ethoxide [from sodium (12 g)] in benzene (150 ml), diethyl 4,4-ethylenedioxyheptanedioate (100 g) in benzene (100 ml) was added under nitrogen. The mixture was refluxed for 3 h, and the alcohol liberated during the reaction was removed azeotropically with benzene. β-Chloroethyl ethyl ketone (70 g) was then added slowly at 0° and the mixture was left overnight. It was then refluxed for 6 h, cooled in ice, and poured into an excess of ice-cold 2% acetic acid solution. After working up, the crude and dried material was refluxed again with a solution of sodium methoxide [from sodium (6·4 g)] in methanol (160 ml) for 5 h under nitrogen. Work-up, as described in (*a*), and distillation afforded (II) (48 g), b.p. 162—166° at 0·5 mmHg, identical with the sample obtained in (*a*).

Methyl 13,13-*Ethylenedioxy*-3-*oxo*-15-*norpodocarpa*-4,9(11)-*diene*-8β-*carboxylate* (IVa) *and* 13,13-*Ethylenedioxy*-3-*oxo*-15-*norpodocarp*-9(11)-*ene*-8β,5β-*carbolactone* (III).—A solution of the bicyclic ester (II) (10 g) in benzene (20 ml) was added under nitrogen to an ice-cold suspension of potassium t-butoxide [from potassium (1·5 g)] in benzene (30 ml) with shaking. The mixture was warmed at 70—80° for 1 h, cooled in an ice-bath, and treated slowly with β-chloroethyl ethyl ketone (5·6 g). After refluxing for 6 h, the mixture was cooled, acidified with ice-cold 2% acetic acid, and worked up in the usual way. The crude product was then refluxed with a solution of sodium (0·75 g) in methanol (75 ml) for 6 h under nitrogen. Methanol was removed, the residue diluted with water, and the alkaline solution extracted with ether. The extract afforded the starting material (II) (4 g) on distillation. The alkaline solution was acidified in the cold with dilute acetic acid and extracted with ether. This extract was washed with saturated aqueous sodium carbonate; acidification of the washings with dilute acetic acid furnished the crystalline acid (IV) (3·2 g), as the *monohydrate*, m.p. 196—198°. A sample dried at 140° and 0·1 mmHg had m.p. 200° (from ethyl acetate) (Found: C, 65·3; H, 7·6. $C_{19}H_{24}O_5$,H_2O requires C, 65·2; H, 7·5%).

The neutral ethereal fraction on removal of ether afforded the lactone (III) (3·4 g), m.p. 185—205°. Crystallisation from ethyl acetate furnished *needles*, m.p. 212°, $\nu_{max.}$ (KBr) 1744, 1710, 1400, 1100, and 2900 cm^{-1} (Found: C, 68·6; H, 7·3. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%).

Esterification of (IV) (3·1 g) with an excess of ethereal diazomethane and the usual work-up afforded the *keto-ester* (IVa) (3 g), m.p. 125° (from methanol), $\lambda_{max.}$ 248 nm (ε 10,230), $\nu_{max.}$ 1735, 1710, 1665, and 1150 cm^{-1} (Found: C, 69·4; H, 7·3. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·5%).

Hydrolysis of the Lactone (III).—A mixture of the lactone (III) (1 g), potassium hydroxide (1 g), and methanol (15 ml) was refluxed for 3 h under nitrogen. The usual work-up afforded an acidic product (0·75 g) which was esterified using ethereal diazomethane. The ester had m.p. 125°, alone or on admixture with the sample of (IVa) obtained previously.

Methyl 13,13-*Ethylenedioxy*-3-*oxopodocarpa*-5,9(11)-*diene*-8β-*carboxylate* (V).—To an ice-cold solution of dry potassium t-pentyloxide [from potassium (1·5 g)] in benzene (50 ml) the tricyclic ketone (IVa) (10·3 g) in benzene (50 ml) was added under nitrogen with occasional shaking. The deep brown solution obtained on warming the mixture at 70—80° for 1 h was cooled in an ice-bath and after addition of methyl iodide (4 ml) was left overnight. The mixture was finally refluxed for 4 h. After the usual work-up, the product was chromatographed on neutral alumina (200 g). Fractions eluted with light petroleum–benzene (9 : 1 to 4 : 1) afforded the *monomethylated ketone* (V) (5·5 g), homogeneous by t.l.c.

[25] J. C. Richer and R. Clarke, *Tetrahedron Letters*, 1964, 935.

on silica, m.p. 129° (from methanol), δ 1·21, 1·22, 1·23 (each 3H, s, CMe_2 and Me-17), 3·6 (3H, s, CO_2Me), 3·91 (4H, t, *J* 1 Hz, O·$[CH_2]_2$·O), and 5·65 and 5·7 p.p.m. (each 1H, t, *J* 2 Hz, H-6 and H-11), $\nu_{max.}$ 1735, 1710, and 1150 cm^{-1} (Found: C, 70·1; H, 7·9. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·9%).

Methyl 13α-*Hydroxy*-3-*oxopodocarpane*-8β-*carboxylate* (VI), *Ethyl* 13-*Ethoxy*-3-*oxopodocarpane*-8β-*carboxylate* (VIII), *and Methyl* 3,13-*Dioxopodocarp*-5-*ene*-8β-*carboxylate* (VII).—The methylated compound (V) (3 g) in ethanol (60 ml) was hydrogenated over palladium–charcoal (10%; 1·5 g). Uptake of hydrogen (*ca.* 600 ml) ceased after 24 h. The mixture was filtered and evaporated, and the residue was chromatographed on neutral alumina (110 g). The fractions eluted with light petroleum–benzene (1 : 3) afforded a crystalline solid, tentatively assigned structure (VIII) (70 mg), m.p. 176° (from ethyl acetate–light petroleum), $\nu_{max.}$ 1740, 1710, and 1150 cm^{-1} [Found: C, 72·4; H, 10·1; OEt(Zeisel), 23·4%. $C_{22}H_{36}O_4$ requires C, 72·4; H, 10·0; OEt, 23·5%].

Fractions eluted with benzene–ether (9 : 1) afforded the 13-*hydroxy-compound* (VI) (200 mg), homogeneous by t.l.c. on silica, m.p. 188° (from ethyl acetate–light petroleum) δ 0·74, 0·80, 1·0 (each 3H, s, CMe_2 and Me-17), 2·12 (s, OH), 3·25 (>C*H*·OH), and 3·65 p.p.m. (s, CO_2Me) (Found: C, 70·7; H, 9·4. $C_{19}H_{30}O_4$ requires C, 70·9; H, 9·4%). Fractions eluted with benzene–ether (1 : 1) furnished the *unsaturated diketone* (VII) (150 mg), homogeneous by t.l.c. on silica, m.p. 175° (from methanol), δ 0·68 (3H, s, Me-17), 1·27br (6H, s, Me_2C), 3·61 (3H, s, CO_2Me), 4·45br (1H, $w_{\frac{1}{2}}$ > 25 Hz, C*H*·OAc), and 5·68 p.p.m. (1H, H-6) (Found: C, 71·7; H, 8·4. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·25%).

Catalytic Reduction of (V).—The methylated compound (V) (600 mg) in ethyl acetate (45 ml) was hydrogenated over palladium–charcoal (10%; 1 g) for 18 h. The mixture was filtered and evaporated, and the solid residue on fractional crystallisation from ethyl acetate–light petroleum afforded compounds (VI) (200 mg) and (VII) (125 mg).

Methyl 3,13-*Dioxopodocarpane*-8β-*carboxylate* (IX).—The unsaturated keto-ester (VII) (150 mg) was hydrogenated over palladium–charcoal (10%; 100 mg) in acetic acid (10 ml) containing perchloric acid (5 drops). Uptake was complete in 3 h. The mixture was filtered, neutralised with saturated aqueous sodium hydrogen carbonate, and extracted with ether. Removal of ether afforded the saturated *diketone* (IX) (100 mg) as fine needles, m.p. 172—173° (from ethyl acetate–light petroleum) (Found: C, 71·3; H, 8·9. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

Methyl 13α-*Acetoxy*-3-*oxopodocarpane*-8β-*carboxylate* (VIa).—To an ice-cold solution of the hydroxy-ester (VI) (160 mg) in dry pyridine (3 ml), a mixture of acetyl chloride (1 ml) and acetic anhydride (2 ml) was slowly added. The mixture was treated with dry ether (15 ml) and left overnight at room temperature. The usual work-up gave the *acetate* (VIa) (130 mg), *needles*, m.p. 175° (from ethyl acetate–light petroleum) (Found: C, 69·2; H, 8·8. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%).

Methyl 13α-*Acetoxypodocarpane*-8β-*carboxylate* (XIa).—Boron trifluoride–ether (0·5 ml; freshly distilled) was added dropwise with stirring to an ice-cold mixture of the acetate (VIa) (200 mg), ethane-1,2-dithiol (0·5 ml; freshly distilled), and glacial acetic acid (1 ml). The mixture was kept at room temperature for 18 h. Benzene (15 ml) was added, and boron trifluoride was neutralised with dry sodium carbonate. The mixture was filtered, washed with water, and evaporated. The residue (200 mg), m.p. 170—175°, was refluxed in methanol (30 ml) for 16 h with Raney nickel[26] [from nickel–aluminium alloy (11 g)]. Filtration and evaporation of the solvent afforded the *acetoxy-ester* (XIa) (100 mg), needles, m.p. 85° (from methanol) (Found: C, 72·2; H, 9·9. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%).

Methyl 13α-*Hydroxypodocarpane*-8β-*carboxylate* (XI).—(*a*) The acetoxy-compound (XIa) (50 mg) was refluxed with potassium hydroxide (15 mg) in methanol (4 ml) for 1·5 h. The usual work-up afforded the *hydroxy-ester* (XI) (30 mg), m.p. 136—137° (from aqueous methanol) (Found: C, 74·2; H, 10·5. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·5%), homogenous by t.l.c. on silica.

(*b*) A mixture of the hydroxy-ester (VI) (200 mg), hydrazine (99%; 3 ml), potassium hydroxide (300 mg), and 2,2′-oxydiethanol (30 ml) was heated at 160° for 2 h, excess of hydrazine and water being allowed to escape. The mixture was then refluxed at 210° for 6 h, cooled, diluted with water, and acidified with hydrochloric acid. After the usual work-up, the gummy product (40 mg) was esterified with ethereal diazomethane to give (XI), m.p. 136—137° (from methanol) alone or mixed with the previous sample.

Methyl 3β-*Hydroxy*-13-*oxopodocarpane*-8β-*carboxylate* (XII).—A mixture of the methylated ketone (V) (400 mg), sodium borohydride (300 mg), tetrahydrofuran (10 ml), and water (2 ml) was refluxed for 3 h. Most of the solvent was removed and the gummy residue was heated on a steam-bath for 1 h with acetic acid (10 ml) and water (4 ml). After the usual work-up, the crude product was hydrogenated over palladium–charcoal (10%; 400 mg) in ethyl acetate containing perchloric acid (a few drops). The mixture was filtered, washed with aqueous 5% sodium carbonate, and evaporated. The solid residue, m.p. 170—178°, was chromatographed on neutral alumina (15 g). Fractions eluted with benzene–ether (9 : 1) afforded the 3-*hydroxy-compound* (XII) (200 mg), m.p. 187° (from ethyl acetate–light petroleum) (Found: C, 71·0; H, 9·3. $C_{19}H_{30}O_4$ requires C, 71·0; H, 9·4%).

The *acetyl derivative* (XIIa) (80 mg), obtained from (XII) (100 mg) by treatment with acetic anhydride (2 ml) and acetyl chloride (1 ml) in dry pyridine (4 ml), had m.p. 188° (from ether–light petroleum) (Found: C, 69·0; H, 8·9. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·8%).

Methyl 13-*Oxopodocarpane*-8β-*carboxylate* (X).—(*a*) A mixture of the hydroxy-compound (XI) (10 mg), chromium trioxide (10 mg), and acetic acid (2 ml) was kept at 80—85° for 2 h. The mixture was diluted with water and worked up with ether. Removal of ether afforded the keto-ester (X), m.p. 129—130°, and two recrystallisations from ether–light petroleum raised the m.p. to 134° (Found: C, 74·6; H, 9·9. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·9%). The m.p. was undepressed on admixture with an authentic sample,[4,8] m.p. 132°. The i.r. spectrum was identical with that of the optically active sample, m.p. 160—161°.

(*b*) To a solution of the 3-hydroxy-compound (XII) (150 mg) in dry pyridine (5 ml), phosphoryl chloride (0·5 ml; freshly distilled) was added dropwise. The mixture was refluxed for 3 h, cooled, poured into crushed ice, and acidified with hydrochloric acid. After the usual work-up, the crude material (100 mg) was hydrogenated over palladium–charcoal (10%; 100 mg) in ethyl acetate (20 ml). The mixture was filtered and evaporated, and the residue was chromatographed on neutral alumina (5 g). Elution with

[26] R. Mozingo, *Org. Synth.*, Coll. Vol. III, 1955, p. 181.

benzene and crystallisation from ether–light petroleum afforded the keto-ester (X) (30 mg), m.p. 132°.

(*c*) The hydroxy-ester (XII) (300 mg) was converted into the corresponding tosylate (XIIb) by treatment with toluene-*p*-sulphonyl chloride (300 mg) in pyridine (5 ml) at 0° for 24 h. To dry potassium t-butoxide [from potassium (40 mg)] suspended in dimethyl sulphoxide (3 ml) phenylmethanethiol (120 mg) was added. To this mixture was added a solution of the crude tosylate in dimethyl sulphoxide (3 ml). The resulting mixture was stirred at 80° for 20 h, cooled, diluted with water, and worked up with ether. Removal of ether afforded a gummy residue which was refluxed in methanol (30 ml) under nitrogen for 10 h with Raney nickel [26] [from nickel–aluminium alloy (10 g)]. The mixture was filtered and evaporated, and the residue was chromatographed on neutral alumina (6 g). Fractions eluted with benzene–light petroleum (1 : 2) were recrystallised from methanol to afford compound (X) (30 mg), m.p. and mixed m.p. 132°.

Methyl 3β-*Acetoxy*-13-*cyanomethylenepodocarpane*-8β-*carboxylate* (XIII) *and Methyl* 3β-*Acetoxy*-13-*cyanomethylpodocarp*-12-*ene*-8β-*carboxylate* (XIV).—A solution of diethyl cyanomethylphosphonate (300 mg) in dimethylformamide (3 ml) was added dropwise with stirring under nitrogen to an ice-cold suspension of sodium hydride (50 mg) in dimethylformamide (5 ml). The mixture was stirred at room temperature for 5 h. It was then cooled in an ice-bath and the keto-ester (XIIa) (500 mg) in dimethylformamide (3 ml) was added dropwise. Stirring was continued for another 16 h. The mixture was then diluted with cold water, acidified with hydrochloric acid, and worked up with ether. Removal of ether left a gummy residue (450 mg) which was chromatographed on neutral alumina (15 g). Fractions eluted with light petroleum–benzene (4 : 1) afforded a crystalline material (300 mg), m.p. 170—180°. Recrystallisation from light petroleum afforded a mixture of the isomeric cyano-esters (XIII) and (XIV), m.p. 180—188°, $\nu_{max.}$ 2255, 2230, 1720, and 1670 cm^{-1} (Found: C, 71·2; H, 8·2. Calc. for $C_{22}H_{33}NO_4$: C, 71·2; H, 8·5%).

Methyl 3β-*Acetoxy*-13β-*cyanomethylpodocarpane*-8β-*carboxylate* (XV).—The mixed unsaturated cyano-esters (XIII) and (XIV) (300 mg) in ethanol (15 ml) were hydrogenated over palladium–charcoal (10%; 200 mg) for 2 h. After working up, the product was chromatographed over alumina (10 g). Fractions eluted with light petroleum–benzene (9 : 1) afforded the saturated cyano-ester (XV) (200 mg), m.p. 118—119° (from light petroleum), $\nu_{max.}$ 2255 and 1725 cm^{-1} (Found: C, 69·8; H, 9·2. $C_{22}H_{35}NO_4$ requires C, 69·9; H, 9·3%).

Methyl 3β-*Acetoxy*-13β-*methoxycarbonylmethylpodocarpane*-8β-*carboxylate* (XVI).—A mixture of the cyano-ester (XV) (500 mg), potassium hydroxide (700 mg), ethylene glycol (7 ml), and water (2 ml) was refluxed under nitrogen for 6 h. The usual work-up afforded an acidic product (350 mg) which was esterified using ethereal diazomethane. The methyl ester was acetylated with acetic anhydride (2 ml) and acetyl chloride (1 ml) in pyridine (5 ml) to furnish the *dimethyl ester* (XVI) (300 mg), m.p. 124—125° (from light petroleum), δ 0·83 (9H, s), 2·05 (3H, s), 3·68 (6H, s), and 4·54 p.p.m. (1H, m) (Found: C, 68·1; H, 9·2. $C_{24}H_{38}O_6$ requires C, 68·2; H, 9·1%).

3β-*Hydroxy*-17-*norphyllocladan*-15-*one* (XVIII).—A solution of the dimethyl ester (XVI) (200 mg) in benzene (5 ml) was added under nitrogen to dry potassium t-butoxide [from potassium (300 mg)] suspended in benzene (5 ml). The mixture was refluxed under nitrogen for 2 h. It was then cooled, acidified with dilute hydrochloric acid, and worked up with ether. Removal of ether left a residue which was refluxed under nitrogen for 10 h with potassium hydroxide (150 mg) in methanol (2·8 ml) containing water (0·3 ml). The mixture was diluted with water, acidified with hydrochloric acid, and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The neutral product (100 mg) was chromatographed on alumina (5 g). Fractions eluted with benzene–light petroleum (1 : 1 to 2 : 1) afforded needles (60 mg) of the *hydroxy-ketone* (XVIII), m.p. 168—169° (from ether–light petroleum), $\nu_{max.}$ 3480 and 1735 cm^{-1}, δ 0·81 (9H, s), 1·0 (3H, s), 2·4br (1H, s), and 3·2 p.p.m. (1H, q) (Found: C, 78·7; H, 10·4. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

3β,17-*Diacetoxyphyllocladen*-15-*one* (XIX).—To sodium hydride (200 mg) suspended in dry benzene (10 ml) ethyl formate (2 ml) was added under nitrogen. A solution of the tetracyclic ketone (XVIII) (100 mg) in benzene (20 ml) was then added dropwise with cooling. The mixture was stirred at room temperature for 20 h. The usual work-up afforded a formyl derivative (40 mg), m.p. 216—218°, which was converted into the acetoxymethylene derivative (XIX) by treatment with acetic anhydride (3 ml) and pyridine (1·5 ml) for 18 h at 20°. Crystallisation from light petroleum furnished *needles* (20 mg), m.p. 173—174° (Found: C, 71·6; H, 8·5. $C_{24}H_{34}O_5$ requires C, 71·75; H, 8·45%).

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