Studies on Sesquiterpenoids. Part XV.[1] Structure and Absolute Configuration of Oplodiol, a New Sesquiterpene Alcohol from *Oplopanax japonicus* (Nakai) Nakai [2]

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Oplodiol, a new sesquiterpene alcohol, with a 7-isopropyl-4,10-dimethyldecalin skeleton, has been isolated from *Oplopanax japonicus* (Nakai) Nakai (Japanese name " Haribuki "); its absolute configuration is also discussed.

In a previous Paper,[2] it was reported that oplopanone (I) had been isolated from *Oplopanax japonicus* (Nakai) Nakai (Japanese name " Haribuki "), and its structure and stereochemistry were established. A new sesquiterpene alcohol, oplodiol, was also isolated, and we now describe its structure and stereochemistry.

The n.m.r. spectrum of oplodiol (II) shows one vinyl proton at τ 4·65, two methyl signals at 8·82 (>C(OH)Me) and at 9·03 (angular Me), an isopropyl group (8·91 and 9·03, superimposed two doublets, $J = 7{\cdot}2$ c./sec.), and a quartet ($J = 11{\cdot}1$ and 4·0 c./sec.) due to a proton attached to the carbon carrying the hydroxyl group, at 6·69.

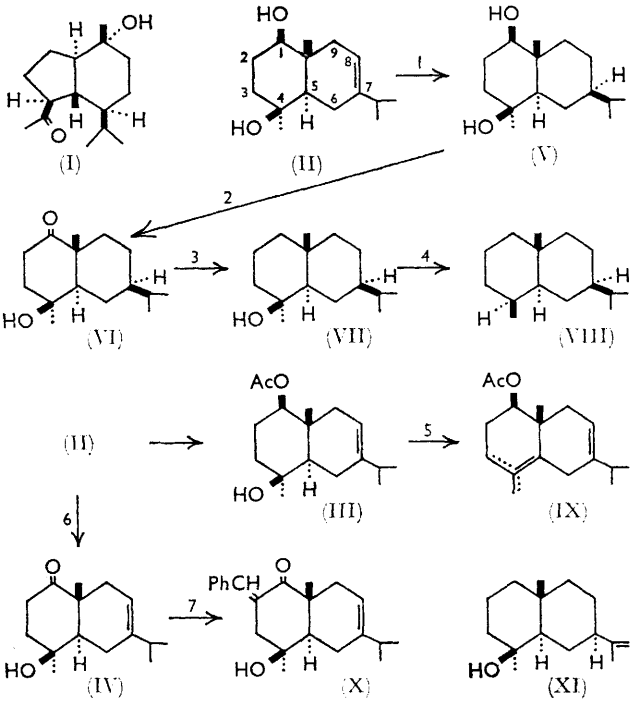
Oplodiol gave a monoacetate (III) on acetylation at room temperature, and a ketone (IV) on oxidation with chromium trioxide. From these results, oplodiol is a bicyclic sesquiterpene having a secondary and a tertiary hydroxyl group and a trisubstituted double bond.

When oplodiol (II) was hydrogenated with Adams catalyst in ethanol, it gave dihydro-oplodiol (V), which was oxidised to a ketone (VI) with chromium trioxide.

[1] Part XIV, H. Minato and T. Nagasaki, *J. Chem. Soc.* (*C*), 1966, 1866.

[2] K. Takeda, H. Minato, and M. Ishikawa, *Tetrahedron*, 1966, Supplement No. 7, 219.

Huang-Minlon reduction of (VI) gave an oily alcohol (VII). If (VII) is dehydrated at the tertiary hydroxyl group and the product is hydrogenated, the skeleton of oplodiol may be clarified. Treatment of (VII) with acetyl chloride in liquid sulphurous acid afforded an oily dehydration product, and not the acetate. This product was hydrogenated with Adams catalyst, to give selinane



1, H_2; 2, CrO_3; 3, Huang-Minlon; 4, MeCOCl in liq. SO_2, then H_2; 5, $SOCl_2$ in pyridine; 6, CrO_3; 7, PhCHO.

(VIII). Therefore, oplodiol has a 7-isopropyl-4,10-dimethyldecalin skeleton, with the tertiary hydroxyl group at C-4, and the double bond is at the 5,6-, 6,7-, or 7,8-position. Treatment of oplodiol monoacetate (III)

TABLE 1

Chemical shift (τ) of methyl group

	(V)	(VII)	(IV)
Angular CH_3 (at C-10)			
$CDCl_3$ soln.	8·99	9·00	8·76
Pyridine soln.	8·48	8·71	9·15 *
Δ value † (c./sec.) ...	+30·9	+17·4	−23·4
CH_3 at C-4			
$CDCl_3$ soln.	8·86	8·86	8·72
Pyridine soln.	8·67	8·68	8·70 *
Isopropyl			
$CDCl_3$ soln.	9·14, 9·04	9·16, 9·06	9·02, 8·91
Pyridine soln.	9·14, 9·05	9·16, 9·06	9·05, 8·94 *

* In benzene solution. † Δ value: difference in chemical shift between the value in $CDCl_3$ and that in pyridine (or benzene).

with thionyl chloride in pyridine gave a dehydrated product (IX) which shows no ultraviolet absorption maximum corresponding to the conjugated diene system above 210 mμ. The double bond is thus not at the 5,6-position.

The n.m.r. spectrum (Table 1) of (VII) shows the angular methyl signal at τ 9·00 in deuteriochloroform and at 8·71 in pyridine. The Δ value of (VII) is +17·4 c./sec., which indicates that the angular methyl and the 4-hydroxyl group are in a 1,3-diaxial relationship, according to the study by Tori and Aono.[3] This leads to the presumption that (VII) has the hydroxyl group in the β configuration and is a *trans*-fused compound or a non-steroid-like *cis*-conformer. The 7-isopropyl group has the β configuration, since selinane (VIII) was derived from (VII). If (VII) has the non-steroid-like *cis* conformation, the isopropyl group should be axial. However, since it is unfavourable for such a bulky group to be axial, the compound is a *trans*-fused derivative (VII). It was shown to be identical with the compound derived from neo-intermedeol (XI), the structure of which was established by Zalkow *et al.*,[4] by comparison of the infrared and the n.m.r. spectra (kindly supplied by Professor L. H. Zalkow).

The n.m.r. spectrum of (V) shows the angular methyl signal at τ 8·99 in deuteriochloroform and at 8·48 in pyridine (Table 1). The large Δ value, +30·9 c./sec., arises from the effects of the secondary hydroxyl group and the tertiary one at C-4. On the basis of the additivity rule [3] for the angular methyl shifts, the effect of the secondary hydroxyl group in (V) is calculated to be +13·5 c./sec., which suggests that it is adjacent to the angular methyl, that is, at C-1 or C-9. Moreover, the angular methyl signal of (IV) appears at τ 8·76 in deuteriochloroform or at 9·15 in benzene, and is shifted upfield by 23·4 c./sec. in the latter. This also indicates that the carbonyl group is at C-1 or C-9 in (IV), according to the study by Williams and Bhacca.[5]

From the following facts, it is improbable that the secondary hydroxyl group of oplodiol (II) is at C-9. Compound (IV) shows carbonyl absorption in the infrared spectrum, and no maximum corresponding to the conjugated enone system in the ultraviolet spectrum; it gave a benzylidene compound (X), $\lambda_{max.}$ 292 mμ (ε 12,300), on treatment with benzaldehyde. On reflux of (IV) with 5% sodium methoxide in methanol for 3 hours, the starting material was recovered, and no αβ-unsaturated ketone was obtained. From these results, it is assumed that the secondary hydroxyl group is at C-1.

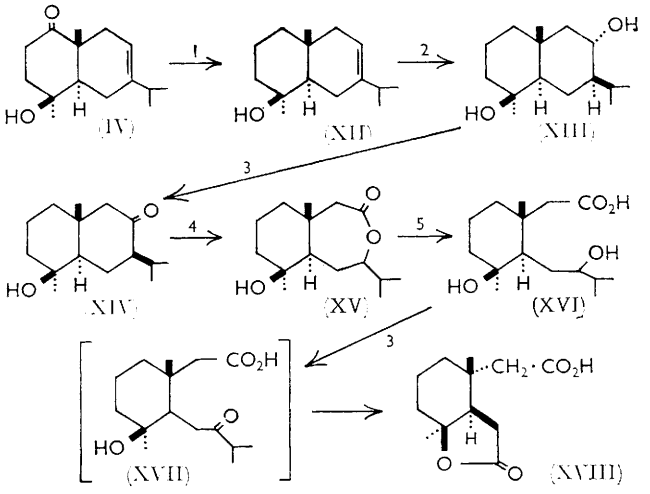
Huang-Minlon reduction of (IV) gave an oil (XII) which was converted into a diol (XIII) by hydroboration followed by hydrogen peroxide oxidation. This diol was oxidised with chromium trioxide to a hydroxy-ketone (XIV), which *m*-chloroperbenzoic acid oxidised to a hydroxy-lactone (XV) whose hydroxyl group resists chromium trioxide oxidation and is the tertiary one of oplodiol (II). When (XV) was hydrolysed and the hydroxy-acid (XVI) was oxidised with chromium tri-

[3] K. Tori and K. Aono, *Ann. Rep. Shionogi Res. Lab.*, 1964, **14**, 136.

[4] V. B. Zalkow, A. M. Shaligram, and L. H. Zalkow, *Chem. and Ind.*, 1964, 194.

[5] D. H. Williams and N. S. Bhacca, *Tetrahedron*, 1965, **21**, 2021.

oxide, the lactone acid (XVIII) was produced, accompanied by oxidative cleavage of the isopropyl group through the intermediate (XVII). The lactone (XVIII) shows γ-lactone and carboxyl absorption, and no hydroxyl absorption, in the infrared spectrum. The n.m.r. spectrum (Table 2) also supports structure (XVIII). Therefore, the γ-lactone function is constructed by use of the tertiary hydroxyl group at C-4, and consequently the double bond of oplodiol (II) should be at the 7,8-position.



1, Huang-Minlon; 2, $(BH_3)_2$; 3, CrO_3; 4, peracid; 5, OH^-.

When oplodiol monoacetate (III) was ozonised and the product was oxidised with chromium trioxide, the γ-lactones (XIX) and (XX) were obtained. The dilactone (XIX) results from oxidative cleavage of the isopropyl group. Its n.m.r. spectrum shows a quartet at τ 5·99 (J = 10·0, 6·3 c./sec.) due to a proton attached to the carbon atom carrying the lactonic oxygen, and two methyl signals (8·97 and 8·61) (Table 2). This

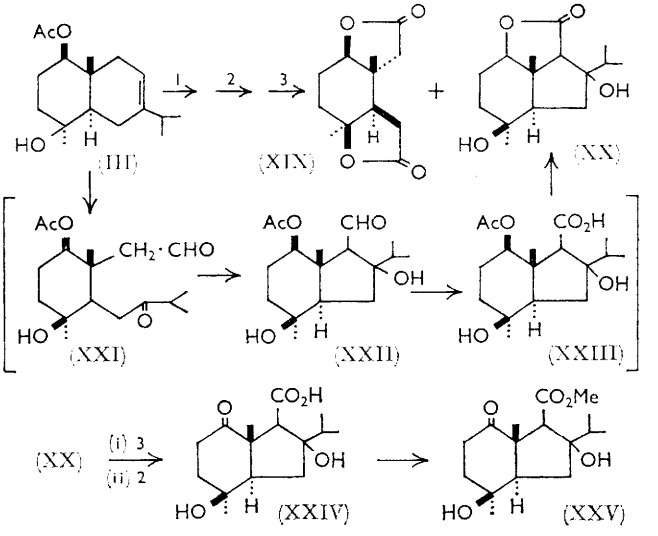
TABLE 2

N.m.r. spectra (τ) in deuteriochloroform

	(XVIII)	(XIX)	
CH_3 at C-10	8·92	8·97	
CH_3 at C-4	8·46	8·61	
H at C-1	—	5·99	(quartet, J = 10·0, 6·3 c./sec.)

indicates that the secondary hydroxyl group of oplodiol (II) plays a part in one γ-lactone function of (XIX). The monolactone (XX) is assumed to be obtained through the intermediates (XXI), (XXII), and (XXIII). Hydrolysis of (XX) followed by chromium trioxide oxidation gave a keto-acid (XXIV), and its methyl ester (XXV) showed ester and ketone bands in the infrared spectrum. It is thus seen that the γ-lactone function of (XX) is also constructed by use of the secondary hydroxyl group. As the γ-lactone function of (XIX) or (XX) was obtained by ozonolysis of the 7,8-double bond in (III), the secondary hydroxyl group of oplodiol should be at C-1.

Since oplodiol (II) was converted into selinane (VIII), and (VII) was identical with the compound derived from neo-intermedeol (XI), the structure of which had been elucidated,[4] the absolute configuration of oplodiol



1, O_3; 2, CrO_3; 3, OH^-.

(II) was clarified, except for the configuration of the 1-hydroxyl group.

The n.m.r. spectrum of oplodiol shows a quartet at τ 6·69 (J = 11·1, 4·0 c./sec.) due to the C-1 proton. A proton with such a large coupling constant should be the axial one at C-1 in the *trans*-decalin system. Therefore, the 1-hydroxyl group in oplodiol possesses a β-equatorial configuration, and the absolute configuration of oplodiol is represented by formula (II).

EXPERIMENTAL

N.m.r. spectra were taken with a Varian A-60 spectrometer. Unless otherwise stated, ultraviolet spectra and rotations were taken in 95% ethanol and dioxan, respectively. M. p.s were measured on a Kofler block and are corrected.

Isolation of Oplodiol (II) *from the Plant.*[2]—The dried and sliced root of *Oplopanax japonicus* (Nakai) Nakai (1 kg.) was extracted with ether (3 × 4 l.) at room temperature for 5 days. The combined ether solution was evaporated, to leave an oily residue (40·77 g.); this was dissolved in ether (500 ml.), washed with 2N-hydrochloric acid, 2N-sodium carbonate, and 2N-sodium hydroxide, and evaporated, leaving an oily neutral residue (28·2 g.). This residue was extracted with light petroleum, and the extract (22·2 g.) was further extracted with 90% ethanol, to give an oil (11·7 g.). This oil was refluxed with Girard reagent T (2·5 g.) in ethanol (70 ml.)–acetic acid (7 ml.) for 46 hr. under nitrogen, to give the ketonic fraction (810 mg.) containing oplopanone (I) and the non-ketonic fraction (9·8 g.). The latter was chromatographed on neutral alumina (activity II), to give an oil (600 mg.) (benzene–chloroform 3 : 1, 1 : 1, and 1 : 3 fractions). With acetic anhydride in pyridine this oil gave an oily acetate, which was chromatographed on neutral alumina, to give an oil (300 mg.) (light petroleum–benzene 3 : 1, 1 : 1, and 1 : 3). The product was saponified with 10% potassium carbonate in methanol,

affording an oil (250 mg.) which was further chromatographed on neutral alumina, to give *oplodiol* (II) (180 mg.) (benzene–chloroform 3 : 1, 1 : 1, 1 : 3) as needles (from ether–light petroleum), m. p. 106—107°, $[\alpha]_D^{24}$ −51·9° (±4°) (*c* 0·540), $\nu_{max.}$ (KBr) 3424 (OH), 3055, 3014, 1668 (double bond), 909, 803, 771 cm.$^{-1}$ (Found: C, 75·9; H, 10·95. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). The *acetate* (III), prisms (from light petroleum), m. p. 72·5—73·5°, had $\nu_{max.}$ ($CHCl_3$) 3574, 1719 cm.$^{-1}$ (Found: C, 72·55; H, 9·9. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·05%).

Oxidation of Oplodiol (II).—Jones reagent [chromium trioxide (2·67 g.) and conc. sulphuric acid (2·3 ml.) in water (10 ml.)] (0·45 ml.) was added to a solution of (II) (213 mg.) in acetone (10 ml.) in an ice-bath, with stirring, during 1 min. and stirred for 3 min. at room temperature. The mixture was poured into ice–water and extracted with chloroform, giving the *product*, (IV) (200 mg.), prisms (from n-pentane), m. p. 80—81° $[\alpha]_D^{24}$ −11·1° (±4°) (*c* 0·467), $\nu_{max.}$ (CCl_4) 3640, 3515, 1712 cm.$^{-1}$ (ketone), o.r.d. $[\phi]_{700}$ −31°, $[\phi]_{317}$ +2612°, $[\phi]_{272}$ −4190°, $[\phi]_{250}$ −3623° (*c* 0·467 in dioxan, 24°) (Found: C, 76·25; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·25%).

Hydrogenation of Oplodiol (II).—Adams catalyst (20 mg.) was added to a solution of (II) (70 mg.) in 90% ethanol (10 ml.) and hydrogenated at room temperature and atmospheric pressure, to give *dihydro-oplodiol* (V) (70 mg.), needles, m. p. 127—129° (from ether) (Found: C, 75·0; H, 11·9. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·75%).

Oxidation of Dihydro-oplodiol (V).—Jones reagent (0·12 ml.) was added to a solution of (V) (44 mg.) in acetone (1 ml.) in an ice-bath and stirred for 3 min. at room temperature. To this mixture was added ice–water, and the mixture was extracted with chloroform, to give the *product* (VI) (42·8 mg.), needles, m. p. 84—86° (from n-pentane), $\nu_{max.}$ ($CHCl_3$) 1701 cm.$^{-1}$, o.r.d. $[\phi]_{318}$ +3964°, $[\phi]_{310}$ +2974°, $[\phi]_{307·5}$ +3126°, $[\phi]_{274·5}$ −2364°, $[\phi]_{225}$ +419° (*c* 0·625 in dioxan, 24°), c.d. $[\theta]_{318}$ 0, $[\theta]_{312}$ +2076, $[\theta]_{310}$ +2044, $[\theta]_{302}$ +3397, $[\theta]_{297·5}$ +3303, $[\theta]_{295}$ +3397, $[\theta]_{245}$ 0 (*c* 0·625 in dioxan, 24°) (Found: C, 75·7; H, 11·0. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%).

Huang-Minlon Reduction of (VI).—The ketone (VI) (18·2 mg.) was dissolved in triethylene glycol (1 ml.), and to this solution were added 80% hydrazine hydrate (200 mg.) and potassium hydroxide (80 mg.). The mixture was heated at 120—130° (inner temperature) for 1 hr., and then the temperature was gradually raised to 190° during 1 hr. and the mixture heated at 210—215° for 3 hr., poured into ice–water, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving an oil (17·8 mg.). The residue was chromatographed on alumina, to give the *product* (VII) as a colourless oil, $[\alpha]_D^{22}$ −3·4° (±4°) (*c* 0·413) (Found: C, 80·3; H, 12·2. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%).

Conversion of (VII) *into Selinane* (VIII).—Acetyl chloride (100 mg.) was added to a solution of (VII) (26 mg.) in liquid sulphurous acid (3 ml.) at −70° and left for 5 min. at the same temperature. The solvent was evaporated and the residue was extracted with ether, washed with 2N-sodium carbonate and water, dried (Na_2SO_4), and evaporated, leaving an oil (23·8 mg.). The residue was chromatographed on alumina, to give a colourless oil (22·7 mg.) which showed no absorption bands corresponding to the acetoxyl group. This oily product was dissolved in acetic acid (10 mg.) and hydrogenated with Adams catalyst (30 mg.), to give an oil, which was chromatographed on alumina, to give a colourless oily product (12·1 mg.), b. p. 115—120°/10 mm., $[\alpha]_D^{22}$ +17·9° (±6°) (*c* 0·296) (Found: C, 86·05; H, 13·8. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·55%), which was identical with selinane (comparison of infrared spectra and $[\alpha]_D$).

Dehydration of (III) *with Thionyl Chloride in Pyridine*.—Thionyl chloride (57 mg.) was added to a solution of (III) (37·7 mg.) in pyridine (0·8 ml.) in an ice-bath, and left for 30 min. at room temperature. The mixture was poured into ice–water, extracted with ether, washed with 2N-sulphuric acid, 2N-sodium carbonate, and water, dried (Na_2SO_4), and evaporated, leaving an oil (34 mg.). The residue was chromatographed on alumina, to give the product (IX) (24·3 mg.), a colourless oil.

Huang-Minlon Reduction of (IV).—The ketone (IV) (198 mg.) was dissolved in triethylene glycol (2·1 ml.), and to this solution were added 80% hydrazine hydrate (2·1 ml.) and potassium hydroxide (800 mg.). The mixture was heated at 120—130° for 1 hr., the temperature was gradually raised to 190° during 1 hr. and the mixture was heated at 210—215° for 2 hr., poured into ice–water, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving an oil (208 mg.). The residue was chromatographed on alumina, to give the *product* (XII) as a colourless oil, b. p. 130—140° (bath)/10 mm., $[\alpha]_D^{25}$ −62·1° (±3°) (*c* 0·715), $\nu_{max.}$ (film) 3477, 3040, 1668, 806 cm.$^{-1}$ (Found: C, 80·9; H, 11·9. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%).

Hydroboration of (XII).—A solution of diborane in dry tetrahydrofuran (2·5 ml., 1 mol.) was added to a solution of (XII) (110·7 mg.) in dry tetrahydrofuran (1 ml.) in an ice-bath in a nitrogen atmosphere, and left for 2·5 hr. at room temperature. To this mixture in an ice-bath, was added water, and 3N-sodium hydroxide (0·5 ml.) and 30% hydrogen peroxide (0·2 ml.) were added to the mixture and stirred for 2 hr. at 35—40°. The mixture was extracted with ether, washed with water and aqueous sodium sulphite, dried (Na_2SO_4), and evaporated, leaving an oil (111 mg.). The residue was chromatographed on alumina, to give a *diol* (XIII) (41 mg.), needles (from ether), m. p. 133—135° (Found: C, 74·7; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·75%), and its oily isomeric diol which gave compound (XIV) on oxidation with chromium trioxide.

Oxidation of (XIII) *with Chromium Trioxide*.—Jones reagent (0·1 ml.) was added to a solution of (XIII) (33·1 mg.) in acetone (1·5 ml.) in an ice-bath and stirred for 3 min. at room temperature. The mixture was poured into ice–water, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving a crystalline substance (33 mg.), which was chromatographed on alumina, to give a *ketone* (XIV) (30 mg.) as prisms (from light petroleum), m. p. 92·5—93·5°, $[\alpha]_D^{25}$ −33·9° (±4°) (*c* 0·548), $\nu_{max.}$ (CCl_4) 1712 cm.$^{-1}$, o.r.d. $[\phi]_{700}$ −38°, $[\phi]_{320}$ −2990°, $[\phi]_{278}$ +2990°, $[\phi]_{250}$ +1823° (*c* 0·548 in dioxan, 23°) (Found: C, 75·65; H, 11·15. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%).

Peracid Oxidation of (XIV).—A solution of (XIV) (10·5 mg.) and *m*-chloroperbenzoic acid (45 mg.) in dichloromethane (1 ml.) was left for 20 hr. at room temperature; to this solution was added toluene-*p*-sulphonic acid (1 mg.) and it was set aside for 27 hr. at the same temperature. Chloroform (10 ml.) was added to the reaction mixture, and it was washed with cold 10% sodium sulphite, water, and aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated, leaving a crystalline substance (9·2 mg.). The residue was chromatographed on alumina, to give a

lactone (XV) (4 mg.), prisms (from ether), m. p. 137—139°, $\nu_{max.}$ (CCl_4) 3605, 3485, 1735 cm.$^{-1}$ (Found: C, 71·0 H, 10·6. $C_{15}H_{26}O_3$ requires C, 70·85; H, 10·3%).

Conversion of (XV) *into* (XVIII).—The lactone (XV) (3·6 mg.) was saponified with 5% potassium hydroxide in methanol (2 ml.) for 30 min., and the mixture was neutralised with acetic acid and extracted with chloroform, to give a hydroxy-acid (XVI). The product was oxidised with Jones reagent for 5 min. at room temperature, to give a *lactone acid* (XVIII) (2·2 mg.), prisms (from ether), m. p. 139—140°, $\nu_{max.}$ ($CHCl_3$) 1757 (γ-lactone), 1711 cm.$^{-1}$ (CO_2H) (Found: C, 63·55; H, 7·65. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

Ozonolysis of (III) *followed by Chromium Trioxide Oxidation.*—A solution of (III) (184 mg.) in dry methanol (2 ml.) was ozonised at −70°, and triethoxyphosphine (214 mg.) was added to this solution at room temperature, with stirring, and stirred for 5 min. at the same temperature. The mixture was evaporated *in vacuo*, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving an oil. The residue was dissolved in acetone (1 ml.) and oxidised with Jones reagent (0·5 ml.), to give an oil (208 mg.). The product was dissolved in 5% potassium hydroxide in methanol (5 ml.) and refluxed for 3 hr. The solution was evaporated, and the residue was dissolved in water and extracted with chloroform. The aqueous layer was acidified with 2N-sulphuric acid, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving a crystalline substance (162·6 mg.). The residue was dissolved in ether (3 ml.) containing toluene-*p*-sulphonic acid (10 mg.), and left for 3 hr. at room temperature. The solution was washed with aqueous sodium hydrogen carbonate, to give a lactone fraction (77 mg.) and an acid fraction (51 mg.). The lactone fraction was chromatographed on alumina, to give a *di-γ-lactone* (XIX) (21 mg.), prisms (from ether–acetone), m. p. 136—138°, $\nu_{max.}$ ($CHCl_3$) 1775 cm.$^{-1}$ (Found: C, 64·25; H, 7·2. $C_{12}H_{16}O_4$ requires C, 63·9; H, 6·95%), and a *mono-γ-lactone* (XX) (24 mg.), plates (from ether–acetone), m. p. 190° (decomp.), $\nu_{max.}$ ($CHCl_3$) 1776 cm.$^{-1}$ (Found: C, 62·55; H, 8·8. $C_{15}H_{24}O_4,H_2O$ requires C, 62·9; H, 9·15%).

Conversion of (XX) *into* (XXV).—The lactone (XX) (21·5 mg.) was saponified with 5% potassium carbonate in methanol (5 ml.), and the mixture was neutralised with acetic acid and extracted with chloroform, to give a hydroxy-acid, which was dissolved in acetone (1·5 ml.) and oxidised with Jones reagent (0·1 ml.), to give a *keto-acid* (XXIV) (19·8 mg.), prisms, m. p. 230° (decomp.) (Found: C, 59·15; H, 8·25. $C_{15}H_{24}O_5,H_2O$ requires C, 59·6; H, 8·65%). The methyl ester (XXV) showed $\nu_{max.}$ 1729 (ester), 1703 cm.$^{-1}$ (ketone).

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