1026. *Diterpenes. Part VIII.*[1] *Reactions of Epoxides in the (−)-Kaurene and Phyllocladene Series, and a Direct Correlation of the Diterpenes.*[2]

By Lindsay H. Briggs, R. C. Cambie, and P. S. Rutledge.

Treatment of 15,16-epoxykaurane (V) with magnesium bromide etherate effects a rearrangement to kaur-16-en-15α-ol (VIII), and similar treatment of 15,16-epoxyphyllocladane (XI) gives 16-epiphyllocladan-15-one (IV). The structure and stereochemistry of kaur-16-en-15α-ol has been proved by successive hydrogenation to kauran-15α-ol (IX), oxidation to kauran-15-one (VI), and Wolff–Kishner reduction to kaurane (X; R = H). The variation in products from 15,16-epoxykaurane and 15,16-epoxyphyllocladane probably arises from a difference in the relative configurations of the epoxides.

Reduction of 16,17- and 15,16-epoxykaurane with lithium aluminium hydride gives kauran-16-ol (X; R = OH), identical with "γ-kaurene"; similar reduction of 16,17- (XVIII) and 15,16-epoxyphyllocladane gives phyllocladan-16-ol (XVII), identical with a natural alcohol from *Cryptomeria japonica*. The 15,16-epoxides also yield, by rearrangement, kaur-16-en-15α-ol and phylloclad-16-en-15α-ol (XIII), respectively.

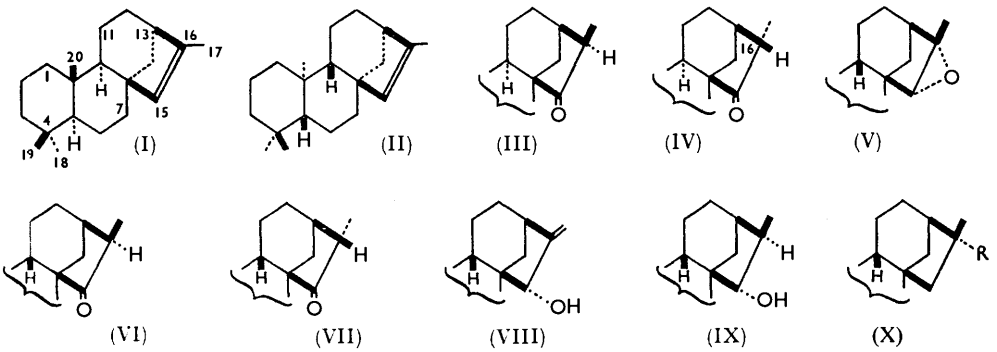
(−)-Kaurene and phyllocladene have been directly correlated by respective conversions into the enantiomeric keto-esters (XXV) and (XXVII).

The structures and absolute configurations of isophyllocladene (I) [3-5] and (−)-isokaurene (II) [1,6-8] have recently been determined. Further derivatives of these diterpenes, particularly those derived from their respective epoxides, are now reported.

In order to prepare a suitable ketone for comparison of its optical rotatory dispersion with that of phyllocladan-15-one [9] (III) and its 16-epi-isomer [9] (IV), 15,16-epoxykaurane (V) was prepared and treated with magnesium bromide etherate in the expectation [10,11] of obtaining kauran-15-one (VI) or its 16-epimer (VII). However, this led to an unsaturated alcohol, $C_{20}H_{32}O$, isomeric with the oxide, with only a trace of ketone. The infrared spectrum of the alcohol showed stretching and bending bands of a vinylidene group (at 3069, 1634, and 897 cm.$^{-1}$) and hydroxyl absorption (at 3571 and 1058 cm.$^{-1}$), consistent with its formulation as kaur-16-en-15α-ol (VIII). Proof of its structure and stereochemistry was provided in the following manner. Hydrogenation gave a saturated alcohol, $C_{20}H_{34}O$ (IX), oxidation of which, with chromium trioxide–pyridine [12] or 8N-chromic acid–sulphuric acid,[13] gave the initially desired kauran-15-one (VI). A peak at 1739 cm.$^{-1}$ in the infrared spectrum of the ketone showed that the carbonyl group was in a five-membered ring, while absence of absorption in the methylene bending region [14] (*ca.* 1400 cm.$^{-1}$) showed that no methylene group was adjacent to the carbonyl group. Wolff–Kishner reduction of the ketone gave kaurane [1] ("α-dihydrokaurene") (X; R = H) as the only product. Since the absolute configuration of kaurane is known,[1,8] and as both

[1] Part VII, Briggs, Cain, Cambie, Davis, Rutledge, and Wilmshurst, *J.*, 1963, 1345.
[2] Preliminary report, Cross, Galt, Hanson, Briggs, Cambie, and Rutledge, *Proc. Chem. Soc.*, 1963, 17.
[3] Briggs, Cain, Cambie, and Davis, *J.*, 1962, 1840, and references therein.
[4] Grant and Hodges, *Tetrahedron*, 1960, **8**, 261.
[5] Turner and Gänshirt, *Tetrahedron Letters*, 1961, 231.
[6] ApSimon and Edwards, *Canad. J. Chem.*, 1962, **40**, 896.
[7] Cross, Galt, Hanson, and Klyne, *Tetrahedron Letters*, 1962, 145.
[8] Vorbrueggen and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2990.
[9] Henderson and Hodges, *Tetrahedron*, 1960, **11**, 226.
[10] Braude, Webb, and Sultanabawa, *J.*, 1958, 3328.
[11] Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737; Winstein and Henderson in "Heterocyclic Compounds," Wiley and Sons, New York, 1950, Vol. I, p. 1.
[12] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[13] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.
[14] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648.

epoxide formation from isokaurene and hydrogenation of the vinylidene group would be expected to occur from the less hindered α-face, the stereochemistry of the αβ-unsaturated alcohol (VIII), the saturated alcohol (IX), and the ketone (VI) is that as shown. The formation of kaurane also establishes that no migration of the methyl group occurred during the treatment of the epoxide (V) with magnesium bromide etherate. As expected, epimerisation of the ketone (VI) with sodium methoxide gave 16-epikauran-15-one (VII).



In these and succeeding diagrams the bracket denotes a derivative of phyllocladane where H_9 has the α-configuration and a kaurane derivative where it has the β-configuration.

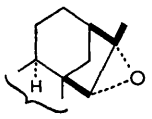
Few reports of the formation of a product analogous to the αβ-unsaturated alcohol (VIII) during acid- and especially Lewis acid-catalysed rearrangement of epoxides have been recorded,[15,16] and it was therefore of interest to examine the reaction of magnesium bromide etherate with 15,16-epoxyphyllocladane (XI). The latter was prepared in quantitative yield by oxidation of isophyllocladene with perbenzoic acid and possessed properties identical with those recorded by Henderson and Hodges [9] who used monoperphthalic acid. Treatment of this epoxide under the conditions used for the preparation of the unsaturated alcohol (VIII) from 15,16-epoxykaurane gave directly 16-epiphyllocladan-16-one (IV), whose melting point was identical with that of a product assigned the same structure and stereochemistry by Henderson and Hodges and prepared by them as one of a mixture of two 16-epimeric ketones by rearrangement of 15,16-epoxyphyllocladane with boron trifluoride etherate. Although it was not epimerised by sodium methoxide, its optical rotation corresponded more closely to that recorded by the latter workers for phyllocladan-15-one (III). Repetition of the rearrangement of 15,16-epoxyphyllocladane with boron trifluoride,[9] however, led to an identical product in 80% yield, thus confirming the structure and stereochemistry assigned. Further confirmation was obtained when Wolff–Kishner reduction of 16-epiphyllocladan-15-one gave 16-epiphyllocladane [3] (" β-dihydrophyllocladene ") (XII), identified by gas–liquid chromatographic comparison with an authentic sample.

Unexpectedly, phylloclad-16-en-15α-ol (XIII), corresponding to the αβ-unsaturated alcohol (VIII) from isokaurene, was obtained as the major product (for minor product, see below) on attempted reduction of 15,16-epoxyphyllocladane with lithium aluminium hydride. It was identical with a compound previously assigned the same structure by us [3] and formed by vigorous benzoylation (with dehydration) of phyllocladane-15α,16-diol (XIV; R = OH) and subsequent saponification, but for which a satisfactory analysis had not been obtained. In the present experiment the compound probably arises from

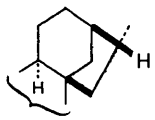
[15] Cf. Syhora, *Tetrahedron Letters*, 1960, No. 17, 34; Kirk, Petrow, Stansfield, and Williamson, *J.*, 1960, 2385; Wendler, Graber, Snoddy, jun., and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476; cf. Alt and Barton, *J.*, 1954, 1356; Grant, Hamilton, Hamor, Hodges, McGeachin, Raphael, Robertson, and Sim, *Proc. Chem. Soc.*, 1961, 444; Gopinath, Govindachari, Parthasarathy, Viswanathan, Arigoni, and Wildman, *Proc. Chem. Soc.*, 1961, 446; Bevan, Rees, and Taylor, *J.*, 1963, 983.

[16] Henbest and Wrigley, *J.*, 1957, 4596.

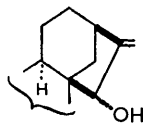
the epoxide by isomerisation before reduction can take place. The αβ-unsaturated alcohol (XIII) has now been fully characterised and its structure confirmed by the following steps. Catalytic hydrogenation gave two epimeric 15α-alcohols. The major product was not obtained crystalline (cf. ref. 9 for the same compound) but was assigned the structure, phyllocladan-15α-ol (XIV; R = H), since hydrogenation would be expected



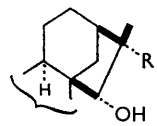
(XI)



(XII)



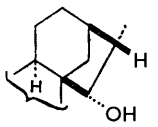
(XIII)



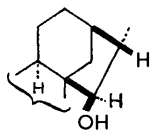
(XIV)

to occur mainly from the α-face. Oxidation of the alcohol (XIV; R = H) with 8N-chromic acid led to phyllocladan-15-one (III), which had the properties reported and was epimerised by Henderson and Hodges's procedure [9] to 16-epiphyllocladan-15-one (IV). The minor and crystalline product of the catalytic reduction, 16-epiphyllocladan-15α-ol (XV), was identical with the minor product of reduction of 16-epiphyllocladan-15-one with sodium borohydride. As expected, the major product of the borohydride reduction was 16-epiphyllocladan-15β-ol (XVI), formed by hydride attack on the α-face. In agreement with the greater stereospecificity of reductions with lithium aluminium hydride [17] a purer sample of the alcohol (XVI) was prepared from 16-epiphyllocladan-15-one by treatment with that reagent. Oxidation of 16-epiphyllocladan-15β-ol with 8N-chromic acid re-formed the 16-epiketone (IV). These interconversions confirm the stereochemical assignments shown.

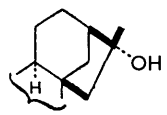
As indicated above, two products were obtained on reduction of 15,16-epoxyphyllocladane with lithium aluminium hydride. The minor product was, as expected, phyllocladan-16-ol (XVII), which was the sole product of similar reduction of 16,17-epoxyphyllocladane (XVIII). This alcohol was identified by direct comparison with a natural phyllocladanol * isolated by Kondo and his co-workers [18] from the heartwood of *Cryptomeria japonica*, thus confirming their structure and proving its stereochemistry at position 16.



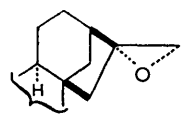
(XV)



(XVI)



(XVII)



(XVIII)

Reduction of 16,17-epoxykaurane with lithium aluminium hydride led to kauran-16-ol (X; R = OH), identical with a natural kauranol from *Gibberella fujikuroi* [7] and with the product ("γ-kaurene") obtained by treatment of kaurene with alcoholic sulphuric acid [19] or by the action of potassium hydroxide on kaurene hydrochloride [20] or hydrobromide (X; R = Br). In the last two reactions it appears that S_N1 replacement of the tertiary halogen atoms proceeds with retention of configuration or only partial racemisation at position 16.

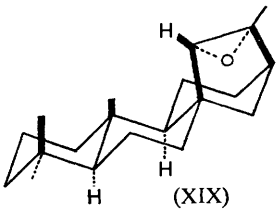
Kauran-16-ol (X; R = OH) was also formed by treatment of 15,16-epoxykaurane

* We are indebted to Professor Kondo for this material.

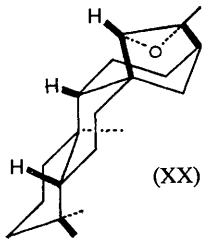
[17] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.
[18] Kondo, Imamura, and Suda, *Yakugaku Zasshi*, 1959, **79**, 1298; *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 65.
[19] Briggs, Cawley, Loe, and Taylor, *J.*, 1950, 955.
[20] Nishida and Uota, *J. Agric. Chem. Soc., Japan*, 1931, **7**, 157, 957.

with lithium aluminium hydride but, as in the corresponding reaction with 15,16-epoxyphyllocladane, the αβ-unsaturated alcohol, kaur-16-en-15α-ol (VIII), was the major product.

The precise reasons for the difference in products of attack by magnesium bromide etherate on 15,16-epoxykaurane and 15,16-epoxyphyllocladane are not clear. However, if we assume that rings A, B, and C in both structures exist in all-chair (or near-chair) conformations, examination of Dreiding models shows that considerable non-bonded interaction occurs between the 15-hydrogen and the 10β-methyl group in 15,16-epoxyphyllocladane (XIX) but not in 15,16-epoxykaurane (XX). Therefore a configurational



(XIX)

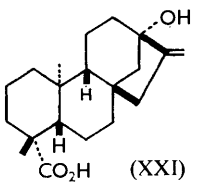


(XX)

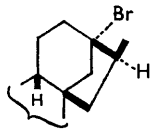
driving force exists in the phyllocladane series (but not in the kaurane series) which will favour relief of this non-bonded interaction where possible. If opening of the epoxide rings under the influence of a Lewis acid is by the process of hydride shift proposed by Henbest and Wrigley [16] then in the case of 15,16-epoxyphyllocladane the formation of a ketone will be favoured. Further investigation of this point is in progress.

Like the corresponding 15-ketones derived from isophyllocladene,[9] both kauran-15-one and its 16-epimer exhibit negative Cotton effects in their rotatory dispersion curves, in accord with a β-configuration for the bridged ring in these compounds. Similar curves are also shown by two 15-keto-derivatives of garryfoline with a β-bridged ring.[8]

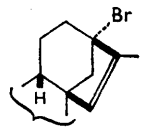
Steviol (XXI) has been correlated with (—)-kaurene by conversion into kaurane (X; R = H).[21] A further link has now been effected by conversion of kaurene into the bromo-compound (XXII) obtained in the penultimate stage of the above correlation. Treatment of isokaurene with *N*-bromosuccinimide gave an allylic bromo-derivative, assigned the structure (XXIII) since it resisted hydrolysis. Hydrogenation of the bromide (XXIII) gave the saturated derivative (XXII) with properties identical with those reported by Dolder *et al.*[21]



(XXI)



(XXII)



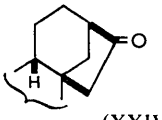
(XXIII)

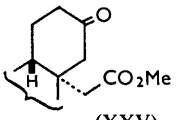
Finally, during this investigation the absolute configuration of (—)-isokaurene (II) was determined mainly on the basis of physical data,[1]* while, earlier, isophyllocladene had been shown unequivocally by degradation [4] and synthesis [5] to have the absolute configuration (I). It was therefore considered desirable to attempt a direct correlation of (—)-kaurene and phyllocladene. This was accomplished by conversions of 17-norkauran-16-one [1] (XXIV) into the keto-ester (XXV), and of 17-norphyllocladan-16-one [3] (XXVI)

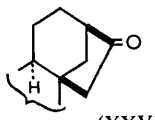
* Confirmation has been provided by Bell, Ireland, and Partyka [22] with a synthesis of (±)-kaurene.

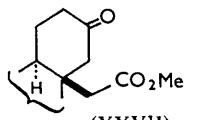
[21] Dolder, Lichti, Mosettig, and Quitt, *J. Amer. Chem. Soc.*, 1960, **82**, 246.
[22] Bell, Ireland, and Partyka, *J. Org. Chem.*, 1962, **27**, 3741.

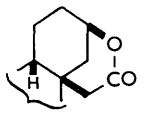
into the enantiomer (XXVII). Oxidation of the ketone (XXIV) with peroxytrifluoroacetic acid gave the δ-lactone (XXVIII) and saponification of this gave the hydroxy-acid (XXIX; R = H) which, however, could not be obtained pure. Methylation of the silver salt of the crude acid afforded the hydroxy-ester (XXIX; R = Me), which was oxidised

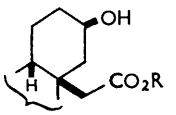

(XXIV)

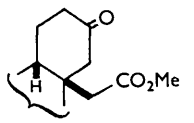

(XXV)

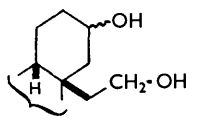

(XXVI)


(XXVII)

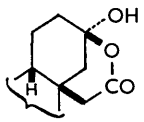

(XXVIII)

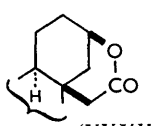

(XXIX)

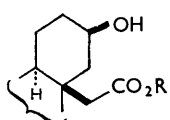

(XXX)


(XXXI)

to the keto-ester (XXX). The epimer (XXV) of the keto-ester (XXX) was obtained through the diol (XXXI) and a lactonol (XXXII) derived from the lactone (XXVIII). These steps, involving in turn, reduction with lithium aluminium hydride, oxidation with 8N-chromic acid-sulphuric acid, and treatment of the lactonol (XXXII) with sodium


(XXXII)


(XXXIII)


(XXXIV)

methoxide and methyl iodide in methanol, had previously been carried out by Mr. J. R. Hanson, to whom we are grateful for providing details before publication. The last step of the sequence involves an inversion at position 8 by an intramolecular Claisen condensation at C-12, followed by fission of the resultant 1,3-diketone.[23] The enantiomer (XXVII) of the keto-ester (XXV) was prepared from 17-norphyllocladan-16-one (XXVI) by a similar sequence to that for the preparation of the keto-ester (XXX), namely, through the δ-lactone (XXXIII), the hydroxy-acid (XXXIV; R = H), and its ester (XXXIV; R = Me). Since the completion of this work Vorbrueggen and Djerassi have prepared the keto-ester (XXVII) by a similar route.[8]

The keto-esters (XXV) and (XXVII) were identical, except for their rotatory dispersion curves which were mirror images. Since the absolute configuration of phyllocladene is known this direct link specifies all centres of asymmetry of (—)-kaurene, the parent hydrocarbon of an increasing number of diterpenoids with the antipodal A/B ring fusion.[24]

Experimental

Infrared spectra, unless otherwise stated, were measured for potassium bromide discs with a Beckman IR2 instrument. Infrared spectra of carbon disulphide solutions were measured with a Perkin-Elmer model 21 spectrophotometer. Optical rotations were determined for chloroform solutions with an ETL-NPL automatic polarimeter of type 143A. Light petroleum was of b. p. 40—60° and alumina for chromatography was P. Spence and Co.'s grade H material. Derivatives of kaurene were prepared from the lævorotatory form. Conditions for gas–liquid chromatography of hydrocarbons were those reported elsewhere.[25]

[23] Cf. Grove and Mulholland, *J.*, 1960, 3007.
[24] Scott, Sim, Fergusson, Young, and McCapra, *J. Amer. Chem. Soc.*, 1962, **84**, 3197; see also ref. 8.
[25] Aplin, Cambie, and Rutledge, *Phytochemistry*, 1963, **2**, 205.

15,16-*Epoxykaurane* (V).—A solution of isokaurene (4·8 g.) in chloroform (50 c.c.) was treated with an excess of a chloroform solution of perbenzoic acid at 0°. Titration with sodium thiosulphate indicated that reaction was complete after 1 hr. Crystallisation of the product from light petroleum gave 15,16-*epoxykaurane* (4·52 g., 89%) as needles, and finally from methanol as plates, m. p. 122—123°, $[\alpha]_D^{23}$ −6° (*c* 1·2) (Found: C, 83·3; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 1263 and 841 cm.$^{-1}$ (epoxide).

Kaur-16-*en*-15α-*ol* (VIII).—A mixture of ethylene dibromide (15 g.), magnesium (2 g.), and ether (50 c.c.) was heated under reflux for 20 min., then cooled, and the liquid was decanted from magnesium. 15,16-Epoxykaurane (1·9 g.) was added and the mixture kept at room temperature for 100 hr., then shaken with water, dried, and evaporated. Treatment of the resulting oil with Girard's reagent P yielded a trace of red oil in the ketonic fraction. The non-ketonic fraction (1·65 g.) afforded *kaur*-16-*en*-15α-*ol* (750 mg.), needles (from ethanol), m. p. 93°, $[\alpha]_D^{20}$ −32° (*c* 2·2) (Found: C, 83·6; H, 11·3. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ 3571 (OH), 3069 (C:CH_2), 1634 (C:C), 1058 (C–O), and 897 cm.$^{-1}$ (C:CH_2), or (in CS_2) 3577 (OH), 1656 (C:C), 1053 (C–O), and 897 cm.$^{-1}$ (C:CH_2).

The compound was unchanged (infrared spectrum and mixed m. p.) after treatment with 10% methanolic hydrochloric acid under reflux for 40 min.

Kauran-15α-*ol* (IX).—Kaur-16-en-15α-ol (500 mg.) in methanol (200 c.c.) was hydrogenated over palladium–charcoal (500 mg.) at room temperature and 42 lb./sq. in. for 20 hr. Crystallisation of the product from light petroleum and finally from methanol afforded *kauran*-15α-*ol* (300 mg.) as needles, m. p. 143—144°, $[\alpha]_D^{16}$ −28° (*c* 0·6) (Found: C, 82·7; H, 11·8. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%), $\nu_{max.}$ 3390 (OH) and 1058 cm.$^{-1}$ (C–O), or (in CS_2) 3571 (OH), and 1047 cm.$^{-1}$ (C–O).

Kauran-15-*one* (VI).—(*a*) A solution of kauran-15α-ol (220 mg.) in pyridine (3 c.c.) was added to the complex of chromium trioxide (300 mg.) and pyridine (3 c.c.), and the mixture was kept at room temperature for 3 hr. A saturated aqueous solution of oxalic acid (90 c.c.) was added and the whole kept at 20° for 30 min. The resultant brown solid was washed with water and chromatographed on alumina (Brockmann's grade I). Elution with light petroleum gave *kauran*-15-*one* (103 mg., 47%) which crystallised from acetone as needles, m. p. 138° with sublimation from 125°, $[\alpha]_D^{20}$ −5° (*c* 0·5) (Found: C, 83·4; H, 10·9. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2), $\nu_{max.}$ 1739 cm.$^{-1}$ (cyclopentanone), or (in CS_2) 1729 cm.$^{-1}$ (C:O). Rotatory dispersion in methanol: $[\alpha]_{500}$ 0°, $[\alpha]_{323}$ −216°, $[\alpha]_{285}$ +300°, $[\alpha]_{250}$ +160°.

Fractions eluted from the column with benzene gave unchanged kauran-15α-ol (124 mg.), m. p. and mixed m. p. 141—142°.

(*b*) Kauran-15α-ol (120 mg.) in dry acetone (5 c.c.) was treated dropwise with 8N-chromic acid–sulphuric acid until a brown colour persisted, and the mixture was kept at room temperature for 30 min. Dropwise addition of water gave needles (86 mg., 59%) which crystallised from aqueous acetone to yield kauran-15-one, m. p. and mixed m. p. 138° (correct infrared spectrum).

Wolff–Kishner Reduction of Kauran-15-*one*.—A mixture of kauran-15-one (60 mg.), semicarbazide hydrochloride (45 mg.), anhydrous sodium acetate (50 mg.), and ethanol (5 c.c.) was heated under reflux for 1 hr. and kept at room temperature for 12 hr. The mixture was filtered, ethanol removed from the filtrate, and the remaining oil washed with warm water and dried. The oil (76 mg.), diethylene glycol (6 c.c.), and hydrazine (1·5 g.) were heated under reflux for 1 hr., potassium hydroxide (30 mg.) was added, and the temperature was raised to 210° by distillation. Refluxing was continued for 6 hr., and the mixture was cooled and added dropwise with stirring to water. The resultant oil was removed in light petroleum, recovered, and crystallised from ethyl acetate at 0°, to yield kaurane (10 mg.) as needles, m. p. and mixed m. p. 81—83°, $[\alpha]_D^{18}$ −30° (*c* 0·4) (correct infrared spectrum and identical R_t^p value [25] on gas–liquid chromatography).

16-*Epikauran*-15-*one* (VII).—Kauran-15-one (30 mg.) was heated under reflux with 2% methanolic sodium hydroxide (5 c.c.) for 6 hr. Isolation of the product, by means of ether and chromatography on alumina, gave 16-*epikauran*-15-*one* (21 mg.) which crystallised from methanol as needles, m. p. 145° (Found: C, 83·3; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 1733 cm.$^{-1}$ (cyclopentanone). Rotatory dispersion in methanol: $[\alpha]_{589}$ −50°, $[\alpha]_{320}$ −581°, $[\alpha]_{300}$ −12°, $[\alpha]_{270}$ −589°.

15,16-*Epoxyphyllocladane* (XI).—Isophyllocladene (2·0 g.), when treated with perbenzoic acid as for isokaurene, afforded 15,16-epoxyphyllocladane (2·1 g.) which crystallised from light

petroleum as plates, m. p. 93°, $[\alpha]_D^{20}$ +35° (*c* 3·0) (lit.,[9] m. p. 92—93°, $[\alpha]_D$ +30°) (Found: C, 83·45; H, 11·2. Calc. for $C_{20}H_{32}O$: C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 835 cm.$^{-1}$ (epoxide).

16-*Epiphyllocladan*-15-*one* (IV).—(*a*) 15,16-Epoxyphyllocladane (490 mg.) was added to magnesium bromide etherate [prepared from ethylene dibromide (9·4 g.), magnesium (4·24 g.), and ether (75 c.c.)], and the mixture was heated under reflux for 10 hr. and then kept at room temperature for 13 hr. Solids were removed, the solution was washed with water and dried, and the solvent removed. Fractional crystallisation of the residue from ethanol gave unchanged epoxide and 16-epiphyllocladan-15-one (82%) as plates, m. p. 129°, $[\alpha]_D^{20}$ −66° (*c* 0·7) (lit.,[9] m. p. 127·5—129°, $[\alpha]_D$ −50°) (Found: C, 83·3; H, 10·95. Calc. for $C_{20}H_{32}O$: C, 83·3; H, 11·2%), $\nu_{max.}$ 1739 cm.$^{-1}$ (cyclopentanone), or (in CS_2) 1727 cm.$^{-1}$ (C:O). Rotatory dispersion in methanol: $[\alpha]_{327·5}$ −1507°, $[\alpha]_{285}$ +1194°.

(*b*) Treatment of 15,16-epoxyphyllocladane (500 mg.) with boron trifluoride etherate (0·5 c.c.) by the recorded procedure [9] gave 16-epiphyllocladan-15-one (400 mg., 80%), plates, m. p. and mixed m. p. 128—129° (from methanol and ethyl acetate) (Found: C, 83·4; H, 11·35%) (correct infrared spectrum). No other crystalline material could be obtained (cf. ref. 9).

The ketone was recovered in quantitative yield after 6 hours' heating under reflux in 2% methanolic sodium hydroxide.

Wolff–Kishner Reduction of 16-*Epiphyllocladan*-15-*one*.—The crude semicarbazide from 16-epiphyllocladan-15-one (30 mg.), in diethylene glycol (5 c.c.), was treated with hydrazine (500 mg.) and potassium hydroxide (20 mg.), as for the semicarbazide of kauran-15-one. Percolation of the resulting oil through deactivated alumina and gas–liquid chromatography indicated that 16-epiphyllocladane ($R_t^{p\ 25}$ 1·01) was the only hydrocarbon present.

16,17-*Epoxyphyllocladane* (XVIII).—Treatment of phyllocladene (1·0 g.) with perbenzoic acid in the usual manner, followed by chromatography of the product on alumina, gave unchanged hydrocarbon in light petroleum eluates. Elution with light petroleum–benzene (1 : 1) gave 16,17-*epoxyphyllocladane* (920 mg., 92%) which crystallised from light petroleum as prisms, m. p. 109—110°, $[\alpha]_D^{20}$ −19° (*c* 1·0) (Found: C, 83·3; H, 11·3. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 782 cm.$^{-1}$ (epoxide).

Phyllocladan-16-*ol* (XVII).—The above epoxide (200 mg.) in dry ether was treated with lithium aluminium hydride (1 mole/mole) at room temperature for 48 hr. The product was chromatographed on alumina and the column eluted successively with light petroleum, benzene, and ether. Material eluted with ether crystallised from light petroleum to yield phyllocladan-16-ol (162 mg.) as needles, m. p. 184—185°, $[\alpha]_D^{20}$ +16° (*c* 0·5) (lit.,[15] $[\alpha]_D$ +14·5°), undepressed by a sample of m. p. 181—182° from *Cryptomeria japonica* (Found: C, 82·3; H, 11·6. Calc. for $C_{20}H_{34}O$: C. 82·7; H, 11·8%), $\nu_{max.}$ (in CS_2) 3532 (OH) and 1120 cm.$^{-1}$ (C–O).

Phylloclad-16-*en*-15α-*ol* (XIII).—15,16-Epoxyphyllocladane (320 mg.) was heated under reflux with lithium aluminium hydride (570 mg.) in dry ether for 5 days and the product chromatographed on alumina. Light petroleum eluted unchanged oxide (104 mg.); benzene eluted phylloclad-16-en-15α-ol (194 mg., 60%) which crystallised from aqueous acetone in plates, m. p. and mixed m. p. 110—111°, $[\alpha]_D^{17}$ −36° (*c* 1·1) [Found (for sample dried at 100°): C, 83·0; H, 11·3. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%] (identical infrared spectra). Elution of the column with ether afforded phyllocladan-16-ol (24 mg.), which crystallised from ether as needles, m. p. and mixed m. p. 184—184·5° (correct infrared spectrum).

Phyllocladan-15α-*ol* (XIV; R = H) *and* 16-*Epiphyllocladan*-15α-*ol* (XV).—Phylloclad-16-en-15α-ol (200 mg.) in ethanol (40 c.c.) was hydrogenated over palladium–charcoal (100 mg.) at room temperature and 25 lb./sq. in for 48 hr. The product was chromatographed on alumina, and the column eluted successively with light petroleum, benzene, and benzene–ether (4 : 1). Benzene eluates afforded 16-*epiphyllocladan*-15α-*ol* (16 mg.) which crystallised from aqueous methanol as needles, m. p. 111—111·5°, $[\alpha]_D^{17}$ −12° (*c* 1·8) (Found: C, 82·8; H, 12·1; O, 5·8. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8; O, 5·5%), $\nu_{max.}$ (in CS_2) 3546 (OH), and 1125 cm.$^{-1}$ (C–O).

Ether eluted phyllocladan-15α-ol (192 mg.) which failed to crystallise (cf. ref. 9). Oxidation by Henderson and Hodges's method [9] gave phyllocladan-15-one (III), plates (from methanol), m. p. 101°, $[\alpha]_D^{20}$ −58° (*c* 1·4) (lit.,[9] m. p. 101—102°, $[\alpha]_D$ −62°) (Found: C, 83·25; H, 11·2. Calc. for $C_{20}H_{32}O$: C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 1727 cm.$^{-1}$ (cyclopentanone).

Epimerisation of the ketone (III) by the recorded method [9] gave 16-epiphyllocladan-15-one, m. p. and mixed m. p. 128—129° (identical infrared spectra).

Hydride Reductions of 16-*Epiphyllocladan*-15-*one*.—16-Epiphyllocladan-15-one (50 mg.) in ethanol (2 c.c.) was treated with an excess of sodium borohydride at room temperature for 48 hr.

Careful chromatography of the product on deactivated alumina and fractional crystallisation from aqueous acetone, ether–methanol, and aqueous ethanol afforded 16-epiphyllocladan-15α-ol, m. p. and mixed m. p. 110—111°, and needles of 16-*epiphyllocladan*-15β-*ol*, m. p. 154—155°, $[\alpha]_D^{17}$ −3° (*c* 0·8).

A purer sample of 16-epiphyllocladan-15β-ol, m. p. 157·5—158°, was obtained by reduction of 16-epiphyllocladan-15-one with lithium aluminium hydride in the normal manner, followed by successive crystallisation of the product from light petroleum, ethanol–dichloromethane, and ethanol (Found: C, 82·9; H, 11·6. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%), $\nu_{max.}$ (in CS_2) 3571 (OH) and 1031 cm.$^{-1}$ (C–O).

16,17-*Epoxykaurane*.—Kaurene (511 mg.), when treated with perbenzoic acid in the usual manner, afforded 16,17-*epoxykaurane* (470 mg., 92%), needles (from light petroleum), m. p. 117°, $[\alpha]_D^{20}$ −12° (*c* 1·8) (Found: C, 83·5; H, 11·05. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ (in CS_2) 840 cm.$^{-1}$ (epoxide).

Kauran-16-*ol* (X; R = OH).—16,17-Epoxykaurane (30 mg.) was treated with an excess of lithium aluminium hydride (50 mg.) in dry ether at 20° for 12 hr. Chromatography of the product on alumina gave kauran-16-ol (15 mg.) which crystallised from light petroleum as needles, m. p. and mixed m. p. 216—217°, $[\alpha]_D^{20}$ −41° (*c* 0·2) (Found: C, 82·7; H, 11·6. Calc. for $C_{20}H_{34}O$: C, 82·7; H, 11·8%) (identical infrared spectra).

Kauran-16-*yl benzoate*, formed by the action of benzoyl chloride–pyridine at 100° for 2 hr., crystallised from methanol as needles, m. p. 74—75° (Found: C, 82·6; H, 9·9. $C_{27}H_{38}O_2$ requires C, 82·2; H, 9·7%).

Saponification of the benzoate with 2N-methanolic potassium hydroxide solution under reflux for 4 hr. regenerated kauran-16-ol, m. p. and mixed m. p. 216—217°, in 81% yield.

Action of Lithium Aluminium Hydride on 15,16-*Epoxykaurane*.—15,16-Epoxykaurane (200 mg.) in dry ether (10 c.c.) was treated with lithium aluminium hydride (750 mg.) at 20° for 4 weeks and the product chromatographed on alumina (grade II—III). Elution with light petroleum gave unchanged oxide (125 mg.); elution with chloroform yielded a yellow oil. Trituration of the oil with acetone yielded kauran-16-ol (8 mg.), which crystallised from light petroleum in needles, m. p. and mixed m. p. 212—215° (correct infrared spectrum). Further chromatography of the soluble portion on alumina and elution with benzene gave kaur-16-en-15α-ol (36 mg.), needles (from methanol), m. p. and mixed m. p. 93—95°, $[\alpha]_D^{17}$ −31° (*c* 0·6) (correct infrared spectrum).

16-*Bromokaurane* (X; R = Br).—Dry hydrogen bromide was passed through a solution of kaurene (250 mg.) in ether (10 c.c.) and glacial acetic acid (10 c.c.) at 0° for 2 hr. After trituration of the precipitated solid with light petroleum the insoluble portion afforded kauran-16-ol (150 mg.), needles (from light petroleum), m. p. and mixed m. p. 216°. The soluble portion, when cooled to 0°, yielded the bromo-compound (100 mg.) as plates, m. p. 128°; it decomposed during analysis and satisfactory values were not obtained.

Similar treatment of isokaurene (250 mg.) gave kauran-16-ol (167 mg.) and the same bromide (96 mg.), m. p. and mixed m. p. 128°.

Treatment of the bromide with 2N-methanolic potassium hydroxide gave kauran-16-ol, m. p. and mixed m. p. 216°, $[\alpha]_D^{20}$ −40°; treatment of the latter compound (200 mg.) with hydrogen bromide for 6 hr. afforded unchanged material (120 mg.) and 16-bromokaurane (57 mg.), m. p. and mixed m. p. 128°.

13-*Bromokaur*-15-*ene* (XXIII).—A solution of isokaurene (2·8 g.) and *N*-bromosuccinimide (1·83 g.) in carbon tetrachloride (40 c.c.) was heated under reflux for 2 hr. and then kept at room temperature for 40 hr. After removal of succinimide and crystallisation of the resulting oil (3·2 g.) from acetone, 13-*bromokaur*-15-*ene* was obtained as needles (180 mg.), m. p. 237—238°, $[\alpha]_D^{17}$ −41° (*c* 0·8) (Found: C, 68·3; H, 9·0. $C_{20}H_{31}Br$ requires C, 68·4; H, 8·9%), $\nu_{max.}$ 3046 and 1672 (C=C), 757 cm.$^{-1}$ (C=CH deformation, shifted by allylic bromine).

The compound was unchanged after being heated with potassium carbonate in aqueous methanol for 6 hr.

13-*Bromokaurane* (XXII).—The above allylic bromide (50 mg.) in ethanol (20 c.c.) was hydrogenated over platinum oxide (20 mg.) at room temperature for 24 hr. The product crystallised from aqueous methanol as needles (45 mg.), m. p. 109—110°, $[\alpha]_D^{16}$ −16° (*c* 0·2) (lit.,[21] m. p. 110—112°, $[\alpha]_D$ −17°) (Found: C, 68·2; H, 9·2; Br, 22·5. Calc. for $C_{20}H_{33}Br$: C, 68·0; H, 9·4; Br, 22·6%); the infrared spectrum showed no double-bond absorption.

Baeyer–Villiger Oxidation of 17-*Norkauran*-16-*one* (XXIV).—To a cooled solution of 17-norkauran-16-one (1·8 g.) in dry dichloromethane (12 c.c.) was added a cooled mixture of trifluoroperacetic anhydride (2·1 c.c.) and 85% hydrogen peroxide (0·3 c.c.) in dichloromethane (10 c.c.). The solution was kept at 20° for 12 hr. and washed with saturated aqueous sodium hydrogen carbonate (50 c.c.) and then water. Solvent was removed from the dried organic phase, to give the δ-*lactone* (XXVIII) of 13β-hydroxy-5β,9β,10α-podocarpan-8β-ylacetic acid (977 mg., 48%) which formed prisms, m. p. 146—148°, from acetone (Found: C, 79·0; H, 10·5. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 1723 (δ-lactone) and 1224 cm.$^{-1}$ (C–O).

Saponification of the lactone with 2N-methanolic potassium hydroxide under reflux for 18 hr., followed by ether-extraction and careful neutralisation of the aqueous layer with N-hydrochloric acid at 0° during 1 hr., gave crude acid (XXIX; R = H), $\nu_{max.}$ 3390, 2778—2703 (broad absorption of bonded acid OH), and 1723 cm.$^{-1}$ (CO_2H), but attempted crystallisation regenerated the lactone (XXVIII). Attempted esterification of the acid with diazomethane or with methyl iodide and potassium carbonate also gave the lactone.

Methyl 13-*Oxo*-5β,9β,10α-*podocarpan*-8β-*ylacetate* (XXX).—The above acid (200 mg.), in 3·5N-ammonia (50 c.c.), was converted into its silver salt which was heated under reflux with methyl iodide (3 c.c.) and dry benzene (20 c.c.) for 10 hr. The mixture was filtered and solvent removed, to yield the crude ester (XXIX; R = Me), $\nu_{max.}$ 3425 (OH), 1729 (ester C:O), and 1231 cm.$^{-1}$ (C–O); this was directly oxidised with 8N-chromic acid-sulphuric acid in acetone at 0° and the mixture kept at room temperature for 12 hr. Crystallisation of the product from aqueous methanol gave the *keto-ester* (15 mg.) as needles, m. p. 127—129°, $[\alpha]_D^{20}$ −10° (*c* 0·2) (Found: C, 74·8; H, 10·3. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%), $\nu_{max.}$ (in CS_2) 1730 (ester C:O), and 1709 cm.$^{-1}$ (cyclohexanone).

Methyl 13-*Oxo*-5β,9β,10β-*podocarpan*-8α-*ylacetate* (XXV).—This *compound* was prepared by way of the diol (XXXI) and the lactonol (XXXII) according to the method outlined previously [2] and for which details are to be published by Mr. J. R. Hanson. It crystallised from methanol as plates, m. p. 176—178°, $[\alpha]_D^{16}$ −22° (Found: C, 75·2; H, 10·2. $C_{20}H_{32}O_2$ requires C, 75·0; H, 10·1%), $\nu_{max.}$ (in CS_2) 1735 (ester C:O) and 1709 cm.$^{-1}$ (cyclohexanone). Rotatory dispersion in methanol: $[\alpha]_{600}$ −17°, $[\alpha]_{589}$ −20°, $[\alpha]_{312}$ −1066°, $[\alpha]_{270}$ +1167°.

Baeyer–Villiger Oxidation of 17-*Norphyllocladan*-16-*one* (XXVI).—A solution of 90% hydrogen peroxide (0·06 c.c.) and trifluoroperacetic anhydride (0·7 c.c.) in dichloromethane (4 c.c.) was added to a stirred and cooled solution of 17-norphyllocladan-16-one (572 mg.) in dichloromethane (4 c.c.). The mixture was heated under reflux for 1 hr. and the solvent removed *in vacuo*. The residue crystallised from aqueous methanol to yield the δ-lactone (XXXIII) (403 mg.) as needles, m. p. 151°, $[\alpha]_D^{20}$ −8° (*c* 1·0) (lit.,[8] m. p. 153—154°, $[\alpha]_D$ −6°) (Found: C, 78·3; H, 10·4. Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4%), $\nu_{max.}$ 1742 (δ-lactone), 1218, and 1203 cm.$^{-1}$ (C–O).

Repeated attempts to saponify the lactone with 2N-methanolic potassium hydroxide, followed by careful acidification, always led to relactonisation.

Methyl 13β-*Hydroxypodocarpan*-8β-*ylacetate* (XXXIV; R = Me).—The above δ-lactone (80 mg.) and potassium carbonate (42 mg.) were heated under reflux in dry methanol (5 c.c.) for 4 hr. Methyl iodide (51 mg.) and acetone (20 c.c.) were added and the mixture was kept at 20° for 48 hr. Solvents were removed *in vacuo* and the remaining solid was stirred with dry acetone at 20° for 2 hr. Filtration and removal of solvent *in vacuo* gave the 13β-hydroxy-ester (73 mg.) which formed plates (from acetone), m. p. 154—155°, $[\alpha]_D^{20}$ +21°. The compound was probably contaminated with a trace of the δ-lactone and satisfactory analyses were not obtained; it had $\nu_{max.}$ 3378 (OH), 1724 (ester C:O), 1235, 1227, 1220, 1096, and 1014 cm.$^{-1}$ (C–O).

Attempts to prepare this hydroxy-ester by treatment of the δ-lactone with potassium carbonate and methyl iodide in dry benzene at 20° for 24 hr. gave 95% of unchanged material.

Methyl 13-*Oxopodocarpan*-8β-*ylacetate* (XXVII).—The last-mentioned ester (42 mg.) in dry acetone (5 c.c.) was treated with 8N-chromic acid–sulphuric acid at 0° and kept at 20° for 12 hr. Fractional crystallisation of the product from aqueous acetone yielded unchanged hydroxy-ester (32 mg.) and the keto-ester (17 mg.) as needles, m. p. 175—176°, $[\alpha]_D^{20}$ +23° (*c* 0·5) (lit.,[8] m. p. 175—176°, $[\alpha]_D$ +18°) (Found: C, 75·4; H, 10·4. Calc. for $C_{20}H_{32}O_2$: C, 75·0; H, 10·1%), $\nu_{max.}$ 1737 (ester C:O), 1709 (cyclohexanone), 1190, 1174, and 1152 cm.$^{-1}$ (C–O). Rotatory dispersion in methanol: $[\alpha]_{600}$ +32°, $[\alpha]_{589}$ +24°, $[\alpha]_{308}$ +943°, $[\alpha]_{270}$ −1153°.

The same compound was prepared in low yield from the lactone (XXXIII) by a reaction

sequence analogous to that detailed above for the preparation of methyl 13-oxo-5β,9β,10α-podocarpan-8β-ylacetate but without rigorous purification of the intermediates.

The authors are grateful to Professors C. Djerassi and W. Klyne for the determination of rotatory dispersion curves and to Mr. J. R. Hanson for details of unpublished work and helpful discussion. We gratefully acknowledge assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, and a Research Fund Fellowship to one of us (P. S. R.).

UNIVERSITY OF AUCKLAND, NEW ZEALAND. [*Received, April* 1*st*, 1963.]