Biosynthesis of Natural Products. Part 3.[1] Syntheses of *ent*-[17-^{14}C]-Kaur-16-en-20-ol from Enmein and of *ent*-[17-^{14}C]Kaur-16-ene Derivatives oxygenated at C-3 from *ent*-Kaur-16-ene-3β,19-diol

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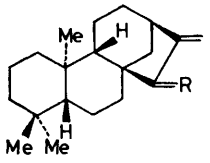
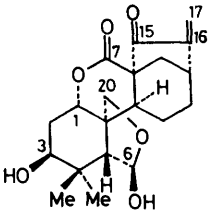
ent-[17-^{14}C]Kaur-16-en-20-ol (5b) was synthesised from enmein (3), and *ent*-[17-^{14}C]kaur-16-en-3β-ol (6b), *ent*-[17-^{14}C]kaur-16-en-3-one (7b), and *ent*-[17-^{14}C]kaur-16-en-3α-ol (8b) were synthesised from *ent*-kaur-16-ene-3β,19-diol (9). These labelled compounds were required for the investigation on the biosynthetic route from *ent*-kaur-16-ene (1) into enmein (3) and oridonin (4).

RECENTLY, we reported the incorporation of *ent*-kaur-16-ene (1) and *ent*-kaur-16-en-15-one (2) into enmein (3) and oridonin (4) in *Isodon japonicus* Hara.[2] All the



(1) R = H_2
(2) R = O



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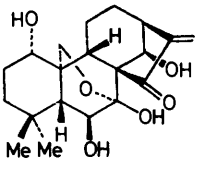

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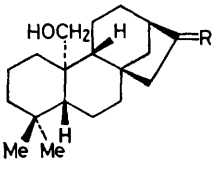
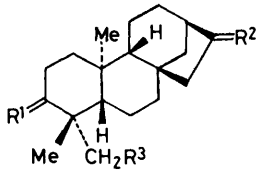


(5a) R = CH^2
(5b) R = $^{14}CH_2$

diterpenoids isolated from *Isodon japonicus* Hara bear the oxygen functions at C-1, C-6, and C-20, in addition to C-7 and C-15 which were discussed in the preceding paper.[1] These positions are very likely oxygenated at relatively early stages in the biosynthetic route from *ent*-kaur-16-ene (1). We thus synthesised *ent*-[17-^{14}C]kaur-16-en-20-ol (5b) from enmein (3), this being an easier synthesis than that of compounds bearing the oxygen functions at C-1 or C-6. On the other hand, little is known about the *Isodon japonicus* diterpenoids bearing the oxygen function at C-3, *i.e.* enmein, enmein 3-acetate, and isodotricin.[3] The possibility that the C-3 position might be oxygenated in preference to the other positions in the biosynthesis of these diterpenes cannot be excluded. Hence, we synthesised *ent*-[17-^{14}C]-kaur-16-en-3β-ol (6b), *ent*-[17-^{14}C]kaur-16-en-3-one (7b), and *ent*-[17-^{14}C]kaur-16-en-3α-ol (8b) from *ent*-kaur-16-ene-3β,19-diol (9), for feeding experiments. Work on the enzymatic biosynthesis of *ent*-kaur-16-en-3-ols was published recently by Coates *et al.*[4]

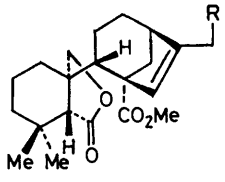
RESULTS AND DISCUSSION

For the synthesis of (5b) from (3), formation of a C-6–C-7 bond, and removal of the C-17 atom and all the oxygen functions except for the one at C-20 are necessary, and it is preferred to introduce the ^{14}C-17 at a later (or the last) step of the synthesis.

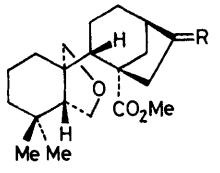


(6a) R^1 = α-OH, β-H, R^2 = CH_2, R^3 = H
(6b) R^1 = α-OH, β-H, R^2 = $^{14}CH_2$, R^3 = H
(7a) R^1 = O, R_2 = CH_2, R^3 = H
(7b) R^1 = O, R_2 = $^{14}CH_2$, R^3 = H
(8a) R^1 = α-H, β-OH, R^2 = CH_2, R^3 = H
(8b) R^1 = α-H, β-OH, R^2 = $^{14}CH_2$, R^3 = H
(9) R^1 = α-OH, β-H, R^2 = CH_2, R^3 = OH

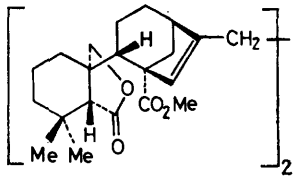
The known unsaturated lactone ester (10),[5] derived from enmein (3), was subjected to allylic bromination to



(10) R = H
(11) R = Br



(12) R = CH_2
(13) R = O
(14) R = α-H, β-OH
(15) R =



(16)

give (11) in 90% yield, which on zinc-dust reduction afforded the desired exocyclic methylene compound (12) in 63—79% yield, together with the dimer (16) in substantial amounts. The exocyclic methylene com-

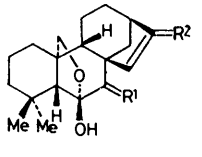
pound (12) on ozonolysis gave the 17-nor-16-one (13) in 90% yield. The ketone (13) on sodium borohydride reduction gave the alcohol (14) in good yield.

Formation of a bond between C-6 and C-7 was accomplished by the acyloin condensation [6-10] of the hydroxy lactone ester (14) with sodium in liquid ammonia under nitrogen. After evaporation of the ammonia by O_2-free nitrogen, two hemiacetals (70%) and a minor by-product were obtained. In the n.m.r. spectrum of one of the major products a doublet (J 4 Hz) was observed at δ 4.18 p.p.m. On the other hand, the n.m.r. spectrum of the other hemiacetal product showed a singlet at δ 3.76 p.p.m. These observations, together with other spectroscopic data, led to the assignments of the 7-hemiacetal structure (17) and the 6-hemiacetal structure (20) to these acyloin products. The minor product was assigned the triol structure (25), on the basis of its

(17) R^1 = R^2 = α-H, β-OH

(18) R^1 = O, R^2 = α-H, β-OH

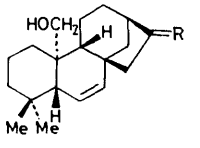
(19) R^1 = α-H, β-OH, R^2 =



(20) R^1 = H, OH, R^2 = α-H, β-OH

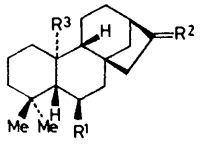
(21) R^1 = O, R^2 = α-H, β-OH

(22) R^1 = H, OH, R^2 =



(23) R = α-H, β-OH

(24) R =



(25) R^1 = OH, R^2 = α-H, β-OH, R^3 = CH_2OH

(26) R^1 = H, R^2 = α-H, β-OH, R^3 = CH_2OH

(27) R^1 = H, R^2 = O, R^3 = CO_2H

(28) R^1 = H, R^2 = O, R^3 = CO_2Me

(29) R^1 = H, R^2 = CH_2, R^3 = CO_2Me

(30) R^1 = H, R^2 = O, R^3 = CH_2OH

spectroscopic data, elemental analysis, consideration of the reaction mechanism, and by analogy with other examples.[6,7,9,10] When the ammonia was allowed to evaporate off in air, an oily compound was obtained in 74% yield together with a small amount of (17). The i.r. spectrum of the oily product suggested the presence of hydroxy-groups and cyclohexanone, and its n.m.r. spectrum showed two singlets due to hydroxy groups at δ 1.78 and 3.55 p.p.m. In addition, its mass spectrum showed the molecular-ion peak at m/e 320 and an intense fragment-ion peak at m/e 292 ($[M - CO]^+$). On acetylation this oil gave a crystalline monoacetate, which was shown to still have a hydroxy group by spectroscopy. Thus, the oxo-hemiacetal structure (18) or (21) was assigned to the oily compound. This oxo-hemiacetal compound is thought to be formed from the initial acyloin product by auto-oxidation.

Huang-Minlon reduction of (17) and (20) yielded the unsaturated diol (23), whose n.m.r. spectrum revealed the AB portion of an ABX spectrum at δ 5.64 and 5.40 p.p.m. (J 1.5, 2.5, and 10 Hz) due to protons on the C-6=C-7 double bond. Catalytic hydrogenation of (23) and subsequent Jones oxidation of the saturated diol (26) gave a keto-acid, which was proved to be identical with *ent*-16-oxo-17-norkaurane-20-carboxylic acid (27).[11,12]

Wittig reaction of the corresponding keto-ester (28) with methyltriphenylphosphonium iodide provided methyl *ent*-kaur-16-ene-20-carboxylate (29) in good yield.

Several unsuccessful attempts to reduce the methoxycarbonyl group of (29) to the hydroxymethyl group were made; (*a*) refluxing of (29) with lithium aluminium hydride in either ether or tetrahydrofuran only recovered the starting material; (*b*) refluxing of (29) with lithium aluminium hydride in glyme recovered the starting material together with the acid; and (*c*) Bouveault–Blanc reduction of the ethylene acetal of (28) with sodium and ethanol only recovered the starting material. The large steric hindrance at C-20 may be the reason why the methoxycarbonyl group can not be reduced. Hence, it was concluded that the original hydroxymethyl group at C-10 should be kept to the last.

For this purpose, the lactone ester (15) was subjected to acyloin condensation. In the first experiment, a mixture of the 16,16-ethylenedioxy-7-hemiacetal (19) and the 16-oxo-7-hemiacetal formed from (19) during work-up was obtained in 68% yield. Reformation of the ethylene acetal of the mixture gave pure (19), the structure of which was supported by its n.m.r. and i.r. spectra and the elemental analysis, and by the spectroscopic data of its acetate. In the second experiment, a mixture of (19) and (22) accompanied by a small amount of their 16-oxo-compounds was obtained. Chromatography resulted in the isolation of only a small amount of (22). The stereochemistry of the hydroxy-group at C-7 in (22) has not been clarified either chemically or spectroscopically.

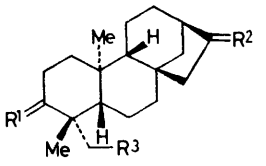
Huang-Minlon reduction of the pure compound (19) or a mixture of (19) and (22) afforded the desired unsaturated alcohol (24) in 60—63% yield. Its catalytic hydrogenation and subsequent deacetalisation gave hydroxyketone (30) in 73% yield.

Finally, the ketone (30), on Wittig reaction with methyltriphenylphosphonium iodide, gave *ent*-kaur-16-en-20-ol (5a). The use of the ^{14}C-labelled reagent in this reaction gave rise to the [17-^{14}C]product (5b).

Subsequently, the syntheses of the 3-oxygenated labelled kaurenes from compound (9) were carried out. The main steps are; (*i*) removal of the C-17 atom; (*ii*) removal of the hydroxy-group at C-19; and (*iii*) introduction of the ^{14}C-17.

Compound (9) on ozonolysis gave the known 17-nor-16-one (31)[13,14] in 48% yield, which on treatment with toluene-*p*-sulphonyl chloride in pyridine afforded the monotoluene-*p*-sulphonate (32) in 37% yield. Its ethylene acetal (33) was treated with sodium benzylsulphide in dimethylformamide to afford the benzyl sulphide (34), which on desulphurisation with Raney nickel gave (35) in 65% yield [based on (33)]. Deace-

talisation and subsequent Wittig reaction transformed compound (35) into *ent*-kaur-16-en-3β-ol (6a) [14] *via* (36).



(31) R^1 = α-OH, β-H, R^2 = O, R^3 = OH

(32) R^1 = α-OH, β-H, R^2 = O, R^3 = $OSO_2C_6H_4Me$-*p*

(33) R^1 = α-OH, β-H, R^2 =  , R^3 = $OSO_2C_6H_4Me$-*p*

(34) R^1 = α-OH, β-H, R^2 =  , R^3 = SCH_2Ph

(35) R^1 = α-OH, β-H, R^2 =  , R^3 = H

(36) R^1 = α-OH, β-H, R^2 = O, R^3 = H

(37) R^1 = O, R^2 =  , R^3 = H

(38) R^1 = α-H, β-OH, R^2 =  , R^3 = H

(39) R^1 = α-H, β-OH, R^2 = O, R^3 = H

In a similar way *ent*-[17-^{14}C]kaur-16-en-3β-ol (6b) was prepared. The radioactive 3-ketone (7b) was derived from (6b) by the Jones oxidation. The preparation of the 3-epimer of (6b) was finally performed as follows. (*i*) Oxidation of (35) with chromic anhydride in pyridine gave (37); (*ii*) Meerwein–Ponndorf reduction of (37) gave the desired 3β-hydroxy-compound (38) (40% yield), accompanied by the minor 3α-epimer (35); (*iii*) deacetalisation of (38) gave (39); and (*iv*) Wittig reactions with (39) gave (8a) [14] and (8b).

The tracer experiments using these materials will be reported elsewhere.

EXPERIMENTAL

General details are given in ref. 2.

ent-17-*Bromo*-20-*hydroxy*-6,7-*secokaur*-15-*ene*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (11).—A solution of (10) (3.8 g) in anhydrous carbon tetrachloride (300 ml) was azeotropically concentrated to 200 ml, and *N*-bromosuccinimide (2.145 g) and dibenzoyl peroxide (45 mg) were added. The mixture was refluxed for 2 h. After cooling, the solid which precipitated was filtered off and the filtrate was washed with water. After drying, the solvent was evaporated off to leave a crystalline residue, which was recrystallised from methylene chloride–methanol to yield the *product* (11) (4.18 g) as crystals, m.p. 138—140 °C; $\nu_{max.}$ 1 765 and 1 730 cm^{-1}; δ 5.83 (1 H, br, s, 15-H), 4.00 and 3.90 (each 2 H, s, 17-H_2 and 20-H_2), 3.73 (3 H, s, CO_2Me), and 1.20 and 0.97 (each 3 H, s, 2 Me) (Found: C, 59.3; H, 7.1. $C_{21}H_{29}O_4Br$ requires C, 59.29; H, 6.82%).

ent-20-*Hydroxy*-6,7-*secokaur*-16-*ene*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (12).—A solution of the bromo-compound (11) (4.1 g) in ethanol (200 ml) was added dropwise to a mixture of zinc dust (45 g), ethanol (40 ml), and acetic acid (0.5 ml) over a period of 1.5 h under vigorous stirring. The reaction mixture was stirred further for 40 min at room temperature. After filtration and washing the zinc with excess of ethanol, the filtrate and washings were combined. The solvent was distilled off *in vacuo* to leave a residue, which was chromatographed on silica gel (methylene chloride–acetone) to afford *compound* (12) (2.63 g), as columnar crystals, m.p. 132—134 °C (from methanol); $\nu_{max.}$ 1 765, 1 725, and 880 cm^{-1}; δ 4.85 (2 H, m, 17-H_2), 4.00 (2 H, s, 20-H_2), 3.72 (3 H, s, CO_2Me), and 1.20 and 0.98 (each 3 H, s, 2 Me) (Found: C, 72.75; H, 8.95. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%): and the *dimer* (16) (550 mg), as needles, m.p. 199—201 °C (from methanol); δ 5.40 (1 H, br s, 15-H), 3.93 (2 H, s, 20-H_2), 3.74 (3 H, s, CO_2Me), and 1.22 and 0.98 (each 3 H, s, 2 Me); M^+, 690.

ent-20-*Hydroxy*-16-*oxo*-17-*nor*-6,7-*secokaurane*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (13).—Ozone was introduced to a solution of (12) (2.05 g) in absolute methanol (135 ml) at −70 °C. When all the (12) had been consumed (t.l.c.) the reaction was stopped. After removal of ozone by passing nitrogen through the solution, a few drops of dimethyl sulphide were added and the mixture was stirred overnight at room temperature. Evaporation *in vacuo* left a residue which was dissolved in chloroform. The usual work-up gave a crystalline substance, which was recrystallised from methanol to yield the *product* (13) as needles (1.8 g), m.p. 172—175 °C; $\nu_{max.}$ 1 770, 1 750, and 1 730 cm^{-1}; δ 4.01 (2 H, s, 20-H_2), 3.80 (3 H, s, CO_2Me), and 1.21 and 1.00 (each 3 H, s, 2 Me) (Found: C, 68.75; H, 8.3. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%).

ent-16α,20-*Dihydroxy*-17-*nor*-6,7-*secokaurane*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (14).—To a solution of (13) (200 mg) in ethanol (15 ml) was added sodium borohydride (75 mg) at 0 °C for 10 min. After stirring at room temperature for 40 min, the mixture was concentrated *in vacuo*. Extraction with methylene chloride and the usual treatment of the extract gave crude product. Recrystallisation from acetone–ether yielded the prismatic *product* (14) (175 mg), m.p. 148—149 °C; $\nu_{max.}$ 3 450, 1 760 sh, 1 740, and 1 725 cm^{-1}; δ 4.29 (1 H, quintet, *J* 5.5 and 10 Hz, 16-H), 3.91 (2 H, s, 20-H_2), 3.67 (3 H, s, CO_2Me), and 1.19 and 0.98 (each 3 H, s, 2 Me) (Found: C, 68.45; H, 8.8. $C_{20}H_{30}O_5$ requires C, 68.54; H, 8.63%).

Acyloin Condensation with the Lactone Ester (14).—(*i*) To a mixture of liquid ammonia (75 ml) and dry ether (35 ml) were added a solution of (14) (0.5 g) in dry ether (35 ml) and then sodium (171 mg) with stirring at −75 °C under oxygen-free nitrogen. The stirring was continued under these conditions for 2.5 h. After addition of a mixture of methanol and ether (1 : 1) to remove the excess of sodium, ammonia was evaporated off by passing through a stream of oxygen-free nitrogen. The remaining mixture was acidified with 10% HCl and extracted with ethyl acetate. The usual work-up gave a crude crystalline product, which was recrystallised from chloroform to yield ent-7β,20-*epoxy*-17-*norkaurane*-6α,7α,16α-*triol* (17) as fine needles (215 mg), m.p. 271—273 °C; $\nu_{max.}$ 3 440 and 3 350 cm^{-1}; δ (C_5D_5N) *ca.* 4.7—4.4 (1 H, m, 16-H), 4.18 (1 H, d, *J* 4 Hz, 6-H), 4.05 (2 H, br s, 20-H_2), and 1.19 and 1.11 (each 3 H, s, 2 Me) (Found: M^+, 322; C, 70.5; H, 9.9. $C_{19}H_{30}O_4$ requires *M*, 322; C, 70.77; H, 9.38%). The *diacetate* had m.p. 194—197 °C (from methanol); δ 5.15—4.73 (1 H, m, 16-H), 4.99 (1 H, d, *J* 4.5 Hz, 6-H), 3.97, 3.77 (2 H, AB quartet, *J* 9 Hz, 20-H_2), 3.53 (1 H, s, OH), 2.07 (6 H, s, 2 COMe), and 1.08 and 0.82 (each 3 H, s, 2 Me) (Found: C, 67.8; H, 8.6. $C_{23}H_{34}O_6$ requires C, 67.95; H, 8.43%).

The mother liquor was subjected to column chromatography to separate three products. Elution with chloro-

form–acetone (8 : 2) gave ent-17-*norkaurane*-6α,16α,20-*triol* (25) as crystals (30 mg) and ent-6β,20-*epoxy*-17-*norkaurane*-6α,7,16α-*triol* (20) as crystals (20 mg), and chloroform–acetone (6 : 4) gave the *hemiacetal* (17) (88 mg). The *triol* (25 was recrystallised from chloroform–methanol to give needles, m.p. 140—145 °C; $\nu_{max.}$ 3 300 cm^{-1}; δ(C_5D_5N) 4.33 (2 H, s, 20-H_2), and 1.54 and 1.36 (each 3 H, s, 2 Me). The *triacetate* had m.p. 107—109 °C (from methanol); $\nu_{max.}$ 1 740 cm^{-1} (Found: C, 69.35: H, 8.9. $C_{25}H_{38}O_6$ requires C, 69.09; H, 8.81%).

The 6-*hemiacetal* (2o) was recrystallised from methylene chloride–methanol to give needles, m.p. 205—210 °C; $\nu_{max.}$ 3 570 and 3 380 cm^{-1}; δ(C_5D_5N) *ca.* 4.77—4.43 (1 H, m, 16-H), 4.07 (2 H, br s, 20-H_2), 3.76 (1 H, s, 7-H), and 1.65 and 1.41 (each 3 H, s, 2 Me) (Found: C, 70.5; H, 9.6. $C_{19}H_{30}O_4$ requires C, 70.77; H, 9.38%). The *diacetate* had m.p. 143—144 °C (from methanol); δ 5.22—4.84 (1 H, m, 16-H), 4.62 (1 H, s, 7-H), 3.99, 3.82 (2 H, AB quartet, *J* 9 Hz, 20-H_2), 3.59 (1 H, s, OH), 2.08 and 2.06 (each 3 H, s, 2 COMe), and 1.29 and 1.07 (each 3 H, s, 2 Me) (Found: C, 67.7; H, 8.6. $C_{23}H_{34}O_6$ requires C, 67.95; H, 8.43%).

(*ii*) The lactone ester (14) (1.75 g) was subjected to acyloin condensation under the same conditions as (*i*). The 6-*hemiacetal* (20) (245 mg), the 7-*hemiacetal* (17) (906 mg), and a mixture (100 mg) of (20) and (17) were obtained together with a trace amount of (25).

(*iii*) To a mixture of liquid ammonia (150 ml) and dry ether (70 ml) were added a solution of (14) (1 g) in dry ether (70 ml) and then sodium (342 mg) with stirring at −75 °C under nitrogen. The mixture was stirred for an additional 2.5 h under the same conditions. After decomposition of the excess of sodium by methanol–ether (1 : 1), ammonia was evaporated off at room temperature overnight. The residue was acidified with 10% HCl and extracted with ethyl acetate. The usual work-up gave a syrup (940 mg), to which was added chloroform–methanol to give the 7-*hemiacetal* (17) (22 mg) as crystals. The mother liquor was chromatographed [chloroform–acetone (95 : 5)] to yield a viscous *oily compound* [(18) or (21)] (677 mg); $\nu_{max.}$ ($CHCl_3$) 3 590, 3 495, and 1 724 cm^{-1}; δ 4.20, 4.45 (2 H, AB quartet, *J* 12 Hz, 20-H_2), 3.55 (1 H, s, OH), 1.78 (1 H, s, OH), and 1.13 and 1.00 (each 3 H, s, 2 Me); M^+ 320. The *monoacetate* had m.p. 174—177 °C as needles (from methanol); $\nu_{max.}$ ($CHCl_3$) 3 495 and 1 725 cm^{-1}; δ 5.2—4.84 (1 H, m, 16-H), 4.20, 4.45 (2 H, AB quartet, *J* 12 Hz, 20-H_2), 3.53 (1 H, s, OH), 2.05 (3 H, s, COMe), and 1.13 and 1.00 (each 3 H, s, 2 Me) (Found: C, 69.8; H, 8.6. $C_{21}H_{30}O_5$ requires C, 69.58; H, 8.34%).

ent-17-*Norkaur*-6-*ene*-16α,20-*diol* (23).—(*i*) The 7-hemiacetal (17) (205 mg) was dissolved in a mixture of 98.5% hydrazine (1.5 ml) and triethylene glycol (9 ml), and heated at 140—160 °C for 6 h under nitrogen. After cooling, pellets of KOH (500 mg) were added and the mixture was slowly heated, so that the temperature was raised up to 210 °C over a period of 4 h. Then, the mixture was heated at 210—220 °C for further 3 h. After cooling, and addition of water (40 ml), it was extracted with ethyl acetate. The extract was worked up as usual to give a crude product, which was chromatographed on a silica gel column. Elution with chloroform gave a crystalline compound (120 mg), which was recrystallised from ether to afford colourless pure crystals of the *unsaturated diol* (23), m.p. 195—196 °C; $\nu_{max.}$ 3 300 and 690 cm^{-1}; δ 5.64 and 5.40 (each 1 H, AB part of ABX pattern, *J* 1.5, 2.5, and 10 Hz, 7-H and 6-H), *ca.* 4.4—4.1 (1 H, m, 16-H), 3.84 (2 H, s, 20-H_2), and 0.94 (6 H, s, 2 Me) (Found: C, 78.3; H, 10.55. $C_{19}H_{30}O_2$ requires C, 78.57; H, 10.41%).

(*ii*) Under the same conditions as in the reduction of (17), the 6-hemiacetal (20) (150 mg) was subjected to Huang-Minlon reduction to afford (23) (80 mg), which was identified by comparison with an authentic sample obtained from (17).

ent-17-*Norkaurane*-16α,20-*diol* (26).—The unsaturated diol (23) (73 mg) was dissolved in methanol (15 ml) and subjected to hydrogenation on PtO_2. The reaction mixture was worked-up as usual to give a crude crystalline product (70 mg). Recrystallisation from methanol–methylene chloride gave pure *compound* (26), m.p. 183—185 °C; $\nu_{max.}$ 3 340 cm^{-1}; δ *ca.* 4.5—4.1 (1 H, m, 16-H), 4.10 (2 H, s, 20-H_2), and 0.90 (6 H, s, 2 Me) (Found: M^+, 292.239. $C_{19}H_{32}O_2$ requires *M*, 292.240).

ent-17-*Nor*-16-*oxokauran*-20-*oic Acid* (27).—A solution of (26) (290 mg) in acetone (55 ml) was subjected to Jones oxidation for 24 h at room temperature. The usual work-up gave a crude product, which was chromatographed. Elution with chloroform gave a crystalline compound (163 mg), which was recrystallised from methanol to afford colourless fine needles of the keto-acid, m.p. 249—250 °C; $\nu_{max.}$ 3 400, 1 750, and 1 690 cm^{-1} (Found: M^+, 304.202; C, 74.4; H, 9.2. Calc. for $C_{19}H_{28}O_3$: *M*, 304.204; C, 74.96; H, 9.27%). This compound proved to be identical with (27) by comparisons of the m.p. and i.r. spectra.

Methyl ent-17-*Nor*-16-*oxokauran*-20-*oate* (28).—The keto-ester (28), prepared from the acid (27) (150 mg) in ether (10 ml) and excess of ethereal diazomethane, was crystallised from chloroform–methanol as rods (100 mg), m.p. 193 °C; $\nu_{max.}$ 1 740 and 1 720 cm^{-1}; δ 3.70 (3 H, s, CO_2Me), and 0.93 and 0.73 (each 3 H, s, 2 Me) (Found: M^+, 318.216. $C_{20}H_{30}O_3$ requires *M*, 318.219).

Methyl ent-*Kaur*-16-*en*-20-*oate* (29).—A solution (0.2 ml) of potassium t-butoxide [from potassium (0.2 g) and t-butyl alcohol (5 ml)] was added to a stirred suspension of methyltriphenylphosphonium iodide (80.8 mg) in dry tetrahydrofuran (THF) (1 ml) under nitrogen, and the mixture was stirred for 15 min. Then, a solution of keto-ester (28) (27 mg) in dry THF (1 ml) was added. The mixture was stirred for a further 30 min. The solvent was evaporated off *in vacuo*, and the residue was extracted with n-hexane–80% aqueous MeOH. The n-hexane layer was washed with brine, dried, and evaporated to yield a crude crystalline *product* (25 mg). Recrystallisation from chloroform–methanol gave pure *prisms* of (29), m.p. 111—112 °C; δ 4.78 (2 H, m, 17-H_2), 3.68 (3 H, s, CO_2Me), and 0.93 and 0.74 (each 3 H, s, 2 Me) (Found: M^+, 316.240. $C_{21}H_{32}O_2$ requires *M*, 316.240).

ent-16,16-*Ethylenedioxy*-20-*hydroxy*-17-*nor*-6,7-*seco*-*kaurane*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (15).—To a solution of (13) (180 mg) in benzene (20 ml) and ethylene glycol (2 ml) was added toluene-*p*-sulphonic acid (20 mg), and the mixture was refluxed for 5.5 h under a water-separator. The usual work-up gave a crude product, which was recrystallised from methanol to afford the *acetal* (15) as fine needles, m.p. 141—142.5 °C; δ 3.95 (2 H, s, 20-H_2), 3.87 (4 H, s, OCH_2CH_2O), 3.72 (3 H, s, CO_2Me), 1.20 and 0.98 (each 3 H, s, 2 Me) (Found: C, 67.05; H, 8.25. $C_{22}H_{32}O_6$ requires C, 67.32; H, 8.22%).

Acyloin Condensation with the Lactone Ester (15).—(*i*) To a mixture of liquid ammonia (75 ml) and dry ether (35 ml) were added a solution of (15) (530 mg) in dry ether (35 ml) and then sodium (162 mg) with stirring at −75 °C under

O_2-free nitrogen. The stirring was continued under these conditions for 3 h. After removal of the excess of sodium by addition of methanol–ether (1 : 1), ammonia was evaporated off at room temperature by the passage through of O_2-free nitrogen. The remaining mixture was acidified with 10% HCl and extracted with ethyl acetate. A crude product obtained by the usual-work-up was chromatographed on a silica gel column [chloroform–acetone (95 : 5—85 : 15)] to give a crystalline product (335 mg) which included a small amount of the 16-oxo-compound; $\nu_{max.}$ 1 740 cm^{-1}. (*a*) A solution of the above-mentioned acyloin product (32 mg) in acetone (3 ml) with 5% HCl (0.5 ml) was set aside at room temperature for 3 h. Evaporation *in vacuo* left a residue which was extracted with chloroform. The usual work-up gave a crystalline product, which was recrystallised from chloroform–methanol to yield ent-7β,20-*epoxy*-16-*oxo*-17-*norkaurane*-6α,7α-*diol* as colourless needles, m.p. 230—235 °C (decomp.); $\nu_{max.}$ ($CHCl_3$) 3 610, 3 450, and 1 740 cm^{-1}; δ 4.11, 3.95 (2 H, AB quartet, *J* 10 Hz, 20-H_2), 3.80 (1 H, d, *J* 4 Hz, 6-H), and 1.10 and 1.03 (each 3 H, s, 2 Me) (Found: C, 71.1; H, 9.05. $C_{19}H_{28}O_4$ requires C, 71.22; H, 8.81%). (*b*) A mixture of the above-mentioned acyloin product (290 mg), ethylene glycol (3 ml), toluene-*p*-sulphonic acid (15 mg), and benzene (30 ml) was refluxed for 4 h under a water-separator. The usual work-up gave a crystalline product (262 mg) which was recrystallised from chloroform–acetone to yield ent-7β,20-*epoxy*-16,16-*ethylenedioxy*-17-*norkaurane*-6α,7α-*diol* (19) as needles, m.p. 216—219 °C (decomp.); $\nu_{max.}$ ($CHCl_3$) 3 600 and 3 450 cm^{-1}; δ *ca.* 3.90 (6 H, m, 20-H_2 and OCH_2CH_2O), 3.72 (1 H, d, *J* 4 Hz, 6-H), and 1.06 and 1.00 (each 3 H, s, 2 Me) (Found: C, 69.1; H, 9.05. $C_{21}H_{32}O_5$ requires C, 69.20; H, 8.85%). The *monoacetate* had m.p. 177—180 °C (from chloroform–methanol) as needles; δ 5.04 (1 H, d, *J* 4.5 Hz, 6-H), *ca.* 3.90 (6 H, m, 20-H_2 and OCH_2CH_2O), 2.10 (3 H, s, COMe), and 1.12 and 0.85 (each 3 H, s, 2 Me), (Found: M^+, 406.236. $C_{23}H_{34}O_6$ requires *M*, 406.236).

(*ii*) Under the same conditions as in (*i*), the lactone ester (15) (530 mg) was subjected to acyloin condensation. The crude product was chromatographed on a silica gel column. Elution with chloroform–acetone (7 : 3) gave a crystalline compound (60 mg), which was recrystallised from chloroform–ether to afford ent-6β,20-*epoxy*-16,16-*ethylenedioxy*-17-*norkaurane*-6α,7-*diol* (22) as needles, m.p. 190—194 °C; $\nu_{max.}$ ($CHCl_3$) 3 600 and 3 450 cm^{-1}; δ 3.90 (6 H, m, 20-H_2 and OCH_2CH_2O), 3.30 (1 H, s, 7-H), and 1.23 and 1.08 (each 3 H, s, 2 Me) (Found: C, 69.2; H, 9.0. $C_{21}H_{32}O_5$ requires C, 69.20; H, 8.85%). The following fraction with the same eluting solvents gave a mixture (316 mg) of (19), (22), and the 16-oxo-compound, whose ethyleneacetalisation as in the case of (*i*)—(*b*) afforded a mixture (297 mg) of (19) and (22).

ent-16,16-*Ethylenedioxy*-17-*norkaur*-6-*en*-20-*ol* (24).—(*i*) A mixture of (19) (150 mg), 98.5% hydrazine (1 ml) and triethylene glycol (7 ml) was heated at 150—160 °C for 5 h under nitrogen. After cooling, 4 pellets of KOH were added and the mixture was heated at 150—160 °C for 2 h. Then the temperature was slowly raised up to 200 °C and heating at 200—210 °C was continued for 8 h. After cooling, water (30 ml) was added, and the reaction mixture extracted with ethyl acetate. The usual work-up gave a crude product, which was chromatographed on a silica gel column (chloroform) to afford *norkaurenol* (24) (83 mg), m.p. 102—103 °C (from chloroform-n-hexane); $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1}; δ 5.65, 5.45 (each 1 H, AB part of ABX, *J* 1, 2, and 10 Hz, 7-H, and 6-H), *ca.* 3.88 (6 H, m, 20-H_2 and OCH_2CH_2O), and 0.90 (6 H, s, 2 Me) (Found: C, 75.8; H, 9.9. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%).

(*ii*) A mixture (484 mg) of (19) and (22) was subjected to Huang-Minlon reduction under the same conditions as in the case of (*i*) to give (24) (280 mg).

ent-16-*Oxo*-17-*norkauran*-20-*ol* (30).—The unsaturated alcohol (24) (246 mg) was subjected to hydrogenation on PtO_2 in methanol at room temperature overnight. The mixture was worked-up as usual to give a saturated acetal, m.p. 127—129 °C (from methylene chloride–n-hexane) (lit.,[11] m.p. 85—86 °C), M^+, 334, which was dissolved in acetone (25 ml) and set aside with 5% HCl (3 ml) at room temperature for 1 h. Evaporation *in vacuo* left a residue which was extracted with chloroform. The usual treatment gave a crude product, which was chromatographed on a silica gel column (chloroform) to give the keto-alcohol (30) (157 mg), m.p. 80—82 °C (from chloroform–n-hexane) (lit.,[11] m.p. 85.5—86.5 °C); $\nu_{max.}$ (Nujol) 3 500 and 1 740 cm^{-1}; δ 4.12 (2 H, s, 20-H_2) and 0.92 (6 H, s, 2 Me) (Found: M^+, 290.225. Calc. for $C_{19}H_{30}O_2$: *M*, 290.225).

ent-*Kaur*-16-*en*-20-*ol* (5a).—A solution (0.25 ml) of potassium t-butoxide [from potassium (0.2 g) and t-butanol (5 ml)] was added to a stirred suspension of methyltriphenylphosphonium iodide (101 mg) in dry THF (1 ml) under nitrogen, and the mixture was stirred for 15 min. A solution of the keto-alcohol (30) (29 mg) in dry THF (1 ml) was then added, and stirring was continued for 40 min. The solvent was evaporated off *in vacuo*, and the residue was extracted with n-hexane–80% aqueous methanol. The n-hexane layer was washed with brine, dried, and evaporated to yield a crude crystalline product (28 mg), which was subjected to preparative t.l.c. [chloroform–acetone (95 : 5)] to afford fine prisms of *kaurenol* (5a) (24 mg), m.p. 75.5—76.5 °C (from aqueous methanol); $\nu_{max.}$ (Nujol) 3 375 and 870 cm^{-1}; δ 4.80 (2 H, m, 17-H_2), 4.10 (2 H, s, 20-H_2), and 0.90 (6 H, s, 2 Me) (Found: C, 83.1; H, 11.3. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

ent-[17-^{14}C]*Kaur*-16-*en*-20-*ol* (5b).—Using [^{14}C]methyltriphenylphsophonium iodide (101 mg), the keto-alcohol (30) (29 mg) was subjected to Wittig reaction under the same conditions as in the synthesis of the unlabelled compound (5a). The crude crystalline product was purified by preparative t.l.c. [chloroform–acetone (95 : 5)], and recrystallisation from aqueous methanol gave ent-[17-^{14}C]*kaur*-16-*en*-20-*ol* (5b) (22 mg) (3.179×10^9 disintegration min^{-1} $mmol^{-1}$), identical with an authentic sample and showing a single radioactive peak on t.l.c.

ent-16-*Oxo*-17-*norkaurane*-3β,19-*diol* (31).—The diol (9) (1 g) in methanol (60 ml) was subjected to ozonolysis at −70 °C. After the usual work-up the crude product was chromatographed [SiO_2; chloroform–acetone (95 : 5)] to yield a crystalline product (31) [13,14] (480 mg), m.p. 203 °C (from chloroform–ether); $\nu_{max.}$ (Nujol) 3 250 and 1 748 cm^{-1} (Found: C, 74.3; H, 9.8. Calc. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%).

ent-16-*Oxo*-17-*norkaurane*-3β,19-*diol* 19-*Toluene*-p-*sulphonate* (32).—The diol (31) (250 mg) in dry pyridine (5 ml) was treated with toluene-*p*-sulphonyl chloride (205 mg) in dry pyridine (2 ml) and the solution was set aside for 2 d. Chromatography (SiO_2; chloroform) of the crude product gave pure *monotoluene*-p-*sulphonate* (32) (138 mg) as needles, m.p. 169 °C; $\nu_{max.}$ 3 430, 1 728, and 1 600 cm^{-1}; δ 7.89—7.28 (4 H, aromatic-H), 4.20 (2 H, s, 19-H_2), *ca.* 3.5—3.10 (1 H, m, 3β-H), 2.48 (3 H, s, Ar-Me), and 1.10 and

1.00 (each 3 H, s, 2 Me) (Found: C, 67.55; H, 7.8. $C_{26}H_{36}O_5S$ requires C, 67.80; H, 7.88%). By elution with acetone, the diol (31) (40 mg) was recovered.

ent-16,16-*Ethylenedioxy*-17-*norkaurane*-3β,19-*diol* 19-*Toluene*-p-*sulphonate* (33).—The acetal (33) (460 mg), prepared from the 16-oxo-compound (32) (464 mg) in benzene (80 ml) and ethylene glycol (6 ml) in the presence of toluene-*p*-sulphonic acid (60 mg) was recrystallised from methanol–n-hexane to give the *acetal* (33) as needles, m.p. 141—142 °C; $\nu_{max.}$ 3 530 and 1 603 cm^{-1}; δ 7.88—7.23 (4 H, aromatic-H), 4.16 (2 H, br s, 19-H_2), 3.89 (4 H, m, OCH_2CH_2O), *ca.* 3.4—3.10 (1 H, m, 3β-H), 2.45 (3 H, s, Ar-Me), and 1.05 and 0.90 (each 3 H, s, 2 Me) (Found: M^+, 504.253. $C_{28}H_{40}O_6S$ requires *M*, 504.255).

ent-19-*Benzylthio*-16,16-*ethylendioxy*-17-*norkauran*-3β-*ol* (34).—To sodium benzyl sulphide prepared from benzyl hydrogensulphide (0.4 ml) and sodium (80 mg), in dimethylformamide (1 ml) was added a solution of (33) (150 mg) in dimethylformamide (4.5 ml). The mixture was heated at 100—110 °C (bath temperature) for 5.5 h under dry nitrogen. The cold solution was added to 5% KOH (40 ml) and extracted with ether. The usual work-up gave a residue, which was subjected to preparative t.l.c. [benzene–ether (9 : 1)] to afford a crystalline product (93 mg). Recrystallisation from chloroform–n-hexane gave the *benzyl sulphide* (34) as columnar crystals, m.p. 116.5—117.5 °C; $\nu_{max.}$ 3 400 cm^{-1}; δ 7.28 (5 H, s, aromatic-H), 3.85 (4 H, m, OCH_2CH_2O), 3.67 (2 H, s, SCH_2Ar), *ca.* 3.35—3.06 (1 H, m, 3β-H), 2.62 (2 H, m, $W_{1/2}$ 4 Hz, 19-H_2), and 1.05 and 0.90 (each 3 H, s, 2 Me) (Found: C, 73.5; H, 8.9. $C_{28}H_{40}O_3S$ requires C, 73.65; H, 8.83%).

ent-16,16-*Ethylenedioxy*-17-*norkauran*-3β-*ol* (35).—The sulphide (34) (650 mg) in ethanol (120 ml) was refluxed for *ca.* 4 h with Raney nickel (W-2) (10 ml, *ca.* 6 g). After filtration the solvent was evaporated off. The crystalline residue was recrystallised from chloroform–methanol to afford ent-16,16-*ethylenedioxy*-17-*norkauran*-3β-*ol* (35) (454 mg) as needles, m.p. 146—147 °C; $\nu_{max.}$ 3 590 and 3 310 cm^{-1}; δ 3.90 (4 H, m, OCH_2CH_2O), *ca.* 3.33—3.10 (1 H, m, 3β-H), and 1.04, 0.97, and 0.78 (each 3 H, s, 3 Me) (Found: C, 75.4; H, 10.3. $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%).

ent-16-*Oxo*-17-*norkauran*-3β-*ol* (36).—The acetal (35) (255 mg) was dissolved in acetone (25 ml) and 10% HCl (2 ml) and set aside at room temperature overnight. Evaporation *in vacuo* left a residue which was extracted with chloroform. The usual work-up gave a crystalline product (177.5 mg), which was recrystallised from methanol to afford (36) [14] as needles, m.p. 181—183 °C; $\nu_{max.}$ 3 510 and 1 728 cm^{-1}; δ *ca.* 3.34—3.06 (1 H, m, 3β-H), and 1.10, 1.01, and 0.82 (each 3 H, s, 3 Me) (Found: C, 78.5; H, 10.6. Calc. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%).

ent-*Kaur*-16-*en*-3β-*ol* (6a).—The crude alcohol (6a) (16.5 mg), prepared from the hydroxyketone (36) (24 mg) in the same manner as in the preparation of (5a), was subjected to preparative t.l.c. [chloroform–acetone (95 : 5)] to afford (6a) [14] as needles, m.p. 170—171 °C; δ 4.77 (2 H, m, $W_{1/2}$ 6 Hz, 17-H_2), *ca.* 3.4—3.07 (1 H, m, 3β-H), and 1.04, 1.00, and 0.80 (each 3 H, s, 3 Me) (Found: M^+, 288.242. Calc. for $C_{20}H_{32}O$: *M*, 288.245).

ent-[17-^{14}C]*Kaur*-16-*en*-3β-*ol* (6b).—Using [^{14}C]methyltriphenylphosphonium iodide (106 mg), hydroxyketone (36) (38 mg) was subjected to Wittig reaction under the same conditions as in the preparation of the unlabelled compound (6a). The crude crystalline product (28.5 mg) was purified by preparative t.l.c. [chloroform–acetone (95 : 5)] and recrystallisation from aqueous methanol to give ent-[17-^{14}C]-*kaur*-16-*en*-3β-*ol* (6b) (21 mg) (2.98×10^9 disintegration min^{-1} $mmol^{-1}$), identical with an authentic sample and showing a single radioactive peak on t.l.c.

ent-[17-^{14}C]*Kaur*-16-*en*-3-*one* (7b).—The labelled alcohol (6b) (12.6 mg) dissolved in acetone (2 ml) was treated dropwise with Jones reagent at 0 °C for 15 min, upon which methanol was added to destroy the excess of reagent. The mixture was extracted with chloroform and the usual work-up gave a crystalline product, which was purified by preparative t.l.c. [chloroform–acetone (95 : 5)] and recrystallised from methanol to give the *labelled kaurenone* (7b) (9.6 mg) (2.83×10^9 disintegration min^{-1} $mmol^{-1}$), identical with an authentic sample of (7a) prepared [14] from (6a), and showing a single radioactive peak on t.l.c.

ent-16,16-*Ethylenedioxy*-17-*norkauran*-3-*one* (37).—The alcohol (35) (50 mg) in pyridine (2.3 ml) was oxidised with chromic anhydride (100 mg) with stirring for 1 h at room temperature. The usual work-up gave a crystalline product (45 mg), which was recrystallised from chloroform–methanol to give the *ketone* (37) as prisms, m.p. 145—146 °C; $\nu_{max.}$ 1 708 cm^{-1}; δ 3.88 (4 H, m, OCH_2CH_2O), 1.08 (6 H, s, 2 Me), and 1.03 (3 H, s, Me) (Found: C, 75.6; H, 9.6. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%).

Meerwein–Ponndorf Reduction of (37).—The ketone (37) (120 mg) in isopropyl alcohol (35 ml) was added to a solution of aluminium isopropoxide in isopropyl alcohol [from aluminium (1.7 g), absolute isopropyl alcohol (34 ml), $HgCl_2$ (0.085 g) and CCl_4 (0.34 ml)], and the mixture slowly distilled over a period of 3.5 h. The residue was diluted with 10% sodium hydroxide (150 ml) and extracted with ether. The usual work-up gave a residue, which was subjected to preparative t.l.c. [chloroform–acetone (95 : 5)] to afford the 3α-hydroxy-compound (35) (33 mg) and the desired ent-16,16-*ethylenedioxy*-17-*norkauran*-3α-*ol* (38) (48 mg) as prisms, m.p. 141—144 °C (from methanol); δ 3.88 (4 H, m, OCH_2CH_2O), 3.40 (1 H, t, *J* 3 Hz, 3α-H), and 1.03, 0.93, and 0.83 (each 3 H, s, 3 Me) (Found: M^+, 334.250. $C_{21}H_{34}O_3$ requires *M*, 334.251).

ent-16-*Oxo*-17-*norkauran*-3α-*ol* (39).—The ethylene acetal (38) (16 mg) in acetone (2 ml) with 10% HCl (0.2 ml) was set aside for 3 h at room temperature. Evaporation *in vacuo* left a residue which was extracted with chloroform. The usual work-up gave a crystalline product (10 mg), which was recrystallised from chloroform–methanol to give the *ketone* (39) as plates, m.p. 185—187 °C; $\nu_{max.}$ 3 550 and 1 737 cm^{-1}; δ 3.43 (1 H, t, *J* 3 Hz, 3α-H) and 1.12, 0.98, and 0.88 (each 3 H, s, 3 Me) (Found: M^+, 290.225. $C_{19}H_{30}O_2$ requires *M*, 290.225).

ent-*Kaur*-16-*en*-3α-*ol* (8a).—The hydroxyketone (39) (25.5 mg) was subjected to Wittig reaction under the same conditions as in the preparation of the epimer (6a). The crude crystalline product was purified by preparative t.l.c. [chloroform–acetone (95 : 5)] and recrystallised from aqueous methanol to give (8a) (18 mg) as needles, m.p. 109 °C; $\nu_{max.}$ 3 490 and 875 cm^{-1}; δ 4.75 (2 H, m, $W_{1/2}$ 7 Hz, 17-H_2), 3.40 (1 H, t, *J* 3 Hz, 3α-H), and 1.03, 0.94, and 0.83 (each 3 H, s, 3 Me) (Found: C, 83.0; H, 11.35. Calc. for $C_{20}H_{32}O$: C, 83.27; H, 11.18%).

ent-[17-^{14}*C*]*Kaur*-16-*en*-3α-*ol* (8b).—Using ^{14}C-labelled reagent (100 mg), (39) (30 mg) was subjected to Wittig reaction under the same conditions as above. The resulting *product* (8b) (14 mg) (3.11×10^9 disintegration min^{-1} $mmol^{-1}$) was identical with the authentic alcohol (8a) on t.l.c. and showed a single radioactive peak.

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