Preparation of Some Kaurenolides from 7,18-Dihydroxykaurenolide

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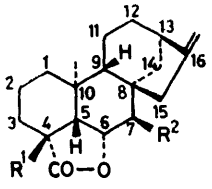
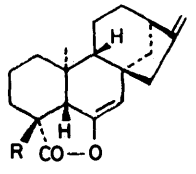
The preparation of 7-hydroxy-, and 18-hydroxy-kaurenolide, the corresponding 18-methyl esters, and 7β-hydroxy-18-norkaurenolide, from 7,18-dihydroxykaurenolide is described.

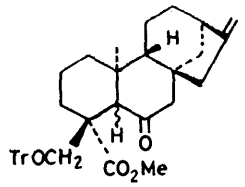
7,18-DIHYDROXYKAURENOLIDE (1) [1] is the major neutral kaurenolide metabolite of *Gibberella fujikuroi* strain ACC 917. It is accompanied by smaller amounts of 7β-hydroxykaurenolide (2).[2] Other kaurenolides such as 3β,7β-dihydroxykaurenolide,[3,4] 7β,11α-dihydroxykaurenolide, and 4β,7β-dihydroxy-18-norkaurenolide [5] have been detected in different strains of the fungus. In connection with biosynthetic studies on the neutral metabolites





(1) R^1 = CH_2OH, R^2 = OH
(2) R^1 = Me, R^2 = OH
(3) R^1 = CH_2OH, R^2 = H
(4) R^1 = CO_2Me, R^2 = OH
(5) R^1 = CO_2Me, R^2 = H
(6) R^1 = H, R^2 = OH
(7) R^1 = CH_2OTs, R^2 = OH
(8) R^1 = CH_2I, R^2 = OH
(9) R^1 = CH_2OMs, R^2 = OMs
(10) R^1 = CH_3, R^2 = OMs
(12) R^1 = CH_2Cl, R^2 = OH
(13) R^1 = CH_2OTr, R^2 = OH
(14) R^1 = CH_2OTr, R^2 = OTs
(18) R^1 = CH_2OTr, R^2 = H
(19) R^1 = CH_2OH, R^2 = OAc
(20) R^1 = CH_2OAc, R^2 = OAc
(21) R^1 = CO_2Me, R^2 = OAc

(11) R = CH_2Cl
(15) R = CH_2OTr



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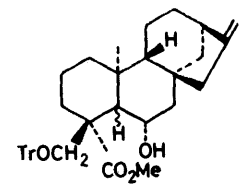

(17)

of *G. fujikuroi*, we have prepared 7β-hydroxykaurenolide (2), 18-hydroxykaurenolide (3), the corresponding 18-methyl esters (4) and (5), and 7β-hydroxy-18-norkaurenolide (6) from the more readily available 7,18-dihydroxykaurenolide (1). These preparations, which form the subject of this paper, necessitated the chemical distinction between the equatorial C-18 primary alcohol and the axial C-7 secondary alcohol. Reaction conditions had to be chosen to avoid the ready Δ^{16}–Δ^{15} double-bond isomerization.

Treatment of 7,18-dihydroxykaurenolide with toluene-*p*-sulphonyl chloride in pyridine afforded an 18-mono-toluene-*p*-sulphonate (7).[1] When an excess of toluene-*p*-sulphonyl chloride was used, a 7,18-bistoluene-*p*-sulphonate was formed. Reduction of the 18-toluene-*p*-sulphonate (7) with sodium iodide and zinc dust [6] afforded 7β-hydroxykaurenolide (2) directly. Alternatively when the toluene-*p*-sulphonate was treated with sodium iodide in acetone, an 18-iodo-lactone (8) was obtained which was reduced in high yield with tri-n-butyl tin hydride [7] to afford 7β-hydroxykaurenolide (2). The reaction with methanesulphonyl chloride was less selective and only a 7,18-dimethanesulphonate was obtained. However the 7-methanesulphonate in (9) was more hindered than C-18 and reduction of this with sodium iodide and zinc dust gave only the 7β-methanesulphonate of 7β-hydroxykaurenolide (10).

When 7,18-dihydroxykaurenolide was treated with triphenylphosphine in carbon tetrachloride containing pyridine,[8] two chloro-compounds were isolated. The n.m.r. of the first of these (11) contained a one-proton olefinic doublet (δ 5.1) showing long-range coupling (J 2 Hz, established by spin-decoupling experiments) to H-5 (δ 2.39). The i.r. spectrum ($\nu_{max.}$ 1 790 and 1 690 cm^{-1}) was typical of an enol-lactone. The second compound was formulated as 18-chloro-7-hydroxykaurenolide (12) on the basis of spectroscopic data [$\nu_{max.}$ 3 530 (OH) and 1 760 cm^{-1} (γ-lactone), δ 3.5 and 3.62 (J 12 Hz, C-CH_2Cl)]. When it was reduced with tri-n-butyltin hydride, it also gave 7β-hydroxykaurenolide (2) in good yield.

18-Hydroxykaurenolide (3) was prepared in the following manner. The primary alcohol was protected as its 18-trityl ether (13). Treatment with toluene-*p*-sulphonyl chloride gave the 7-mono-toluene-*p*-sulphonate (14). This however could not be reduced with zinc and sodium iodide. Treatment of the 18-trityl ether with triphenylphosphine and carbon tetrachloride gave the enol-lactone (15) (δ 7-H, 5.13, J 2 Hz coupled to the 5-H, δ 2.2; $\nu_{max.}$ 1 800 and 1 700 cm^{-1}). The enol-lactone was hydrolysed with sodium methoxide to the 6-keto-ester (16) of undefined stereochemistry at C-5. This was reduced with sodium borohydride to afford the unstable 6α-alcohol (17). The reduction of the kauranoid 6-ketones by sodium borohydride has been shown to occur from the less-hindered β-face of the molecule.[9] Pyrolysis of the alcohol and chromatography of the product gave, in good yield, a separable mixture of 18-hydroxykaurenolide (3) and its 18-trityl ether (18). The trityl group was hydrolysed with acetic acid. Surprisingly the hydroxy-absorption of 18-hydroxykaurenolide lay under the Nujol C–H band. In order to confirm the presence of a free hydroxy-group in the compound, it was acety-

lated to form the 18-monoacetate. Oxidation of the 18-alcohol with the 8N-chromium trixode reagent gave the 18-acid which was purified as its methyl ester (5).

Previous work had shown [1] that C-7 is oxidized more rapidly than C-18. Hence the preparation of the 18-methyl ester (4) involved protecting C-7 as its acetate. This was achieved by acetylation of the 18-trityl ether (13) and then removal of the C-18 protecting group with acetic acid. Apart from the 7β-monoacetate (19), the known [1] 7,18-diacetate (20) was also isolated from this reaction. Subsequently we found that the 7β-monoacetate (19) could be obtained in high yield by partial hydrolysis of the 7,18-diacetate (20) with sodium hydrogen carbonate. Oxidation of this monoacetate with 8N-chromium trioxide and methylation of the resultant acid with diazomethane, gave the 7β-acetoxy-18-methyl ester (21). Hydrolysis of this compound with sodium carbonate in methanol gave the 7β-hydroxy-18-methyl ester (4) in the neutral fraction. The acid fraction contained a mixture of the 7β-acetoxy- and 7β-hydroxy-18-acids which were separated as their methyl esters. Treatment of the methyl ester (4) with sodium carbonate and then boiling the acid fraction with water, gave 7β-hydroxy-18-norkaurenolide (6). The earlier method of preparing this by pyrolysis of 7,18-dihydroxykaurenolide afforded a mixture of Δ^{15} and Δ^{16} double-bond isomers. Thus the differing reactivity of the 7- and 18-hydroxy-groups of 7,18-dihydroxykaurenolide, can be utilized to make available less readily accessible kaurenolides.

EXPERIMENTAL

General experimental details have been described previously.[10] The *bistoluene*-p-*sulphonate* of 7,18-dihydroxykaurenolide was prepared by treatment of 7,18-dihydroxykaurenolide with an excess of toluene-*p*-sulphonyl chloride for 1 week. It crystallized from ethyl acetate–light petroleum as needles, m.p. 155—154 °C (Found: C, 64.0; H, 6.4. $C_{34}H_{40}O_8S_2$ requires C, 63.7; H, 6.3%), $\nu_{max.}$ 1 775, 1 595, 890, 850, 810, and 665 cm^{-1}; δ 0.90 (3 H, s), 2.05 (1 H, d, *J* 7 Hz, 5-H), 2.44 (6 H, s, Ar-CH_3), 3.83 (2 H, s, 18-H), 4.48 (1 H, t, *J* 7 Hz, 6-H), 4.89 and 5.01 (2 H, br, d, 17-H_2), 5.29 (1 H, d, *J* 7 Hz, 7-H), 7.30 (4 H, *J* 9 Hz), 7.68 (2 H, d, *J* 9 Hz), and 7.79 (2 H, d, *J* 9 Hz).

Reduction of the Toluene-p-*sulphonate of* 7,18-*Dihydroxykaurenolide with Sodium Iodide and Zinc Dust.*—The toluene-*p*-sulphonate (7) (100 mg) was heated with a mixture of dry sodium iodide (300 mg) and zinc dust (300 mg) in dry dioxan (100 ml) for 3 days under reflux. The mixture was filtered and the solvent evaporated. The residue was chromatographed on silica. Elution with 17% ethyl acetate–light petroleum gave *ent*-7α-hydroxykaur-16-en-19,6β-σlactone * (60 mg) as needles, m.p. 186—187 °C (lit.,[2] 187—188 °C), which was identified by its i.r. and n.m.r. spectra.

Reaction of the 18-*Toluene*-p-*sulphonate of* 7,18-*Dihydroxykaurenolide with Sodium Iodide.*—The toluene-*p*-sulphonate (7) (100 mg) in dry acetone (30 ml) was heated with dry sodium iodide (500 mg) for 1 day under reflux. The acetone was evaporated, water was added, and the product was extracted with ethyl acetate. The extract was washed with 10% sodium thiosulphate solution and water and then dried (Na_2SO_4). The solvent was removed and the gummy product chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave ent-7α-*hydroxy*-18-*iodokaur*-16-*en*-19,6β-*olactone* (8) (70 mg) which crystallized from acetone–light petroleum as needles, m.p. 151—152 °C (Found: C, 54.3; H, 6.1. $C_{20}H_{27}IO_3$ requires C, 54.3; H, 6.1%), $\nu_{max.}$ 3 580, 1 765, 865, and 720 cm^{-1}; δ 0.88 (3 H, s, 20-H_3), 2.0 (1 H, d, *J* 7 Hz, 5-H), 3.23 and 3.40 (2 H, AB q, *J* 11 Hz, 18-H_2), 4.38 (1 H, d, *J* 7 Hz, 7-H), 4.58 (1 H, t, *J* 7 Hz, 6-H), and 4.88 and 5.0 (2 H, br, d,17-H_2).

Reduction of the Iodo-lactone (8) *with Tri-n-butyltin Hydride.*—The iodo-lactone (100 mg) in dry freshly redistilled tetrahydrofuran (30 ml) was heated with tri-n-butyltin hydride (150 mg) for 0.5 h under reflux. The mixture was cooled and the tetrahydrofuran was evaporated. Water was added and the product was recovered in ethyl acetate and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 7β-hydroxykaurenolide (65 mg) as needles, m.p. 184—186 °C (lit.,[2] 187—188 °C), identified by its i.r. and n.m.r. spectra.

Reduction of the Bismethanesulphonate (9) *with Sodium Iodide and Zinc.*—The *bismethanesulphonate* of 7,18-dihydroxykaurenolide, prepared with methanesulphonyl chloride in pyridine, was a glass, m.p. 72—75 °C (Found: C, 54.2; H, 6.6. $C_{22}H_{32}O_8S_2$ requires C, 54.0; H, 6.6%), $\nu_{max.}$ 1 775, 1 175, and 860 cm^{-1}; δ 1.00 (3 H, s, 20-H), 2.18 (1 H, d, *J* 7 Hz, 5-H), 3.02 and 3.12 (3 H each, singlets, SO_2CH_3), 4.2 (2 H, s, 18-H), 4.91 (1 H, t, *J* 7 Hz, 6-H), 4.88 and 5.0 (2 H, br, d, 17-H), and 5.26 (1 H, d, *J* 7 Hz, 7-H). The methanesulphonate (9) (220 mg) was heated with a mixture of dry sodium iodide (800 mg) and zinc dust (800 mg) in dry dioxan (100 ml) for 1 week under reflux. The mixture was filtered and the dioxan was distilled off. The gummy product was chromatographed on silica. Elution with 20% ethyl acetate in light petroleum gave the *methanesulphonate* (10) of 7β-hydroxykaurenolide (120 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 217—219 °C (Found: C, 64.1; H, 7.65. $C_{21}H_{30}O_5S$ requires C, 64.0; H, 7.7%), $\nu_{max.}$ 1 775, 1 655, 1 162, and 862 cm^{-1}; δ 0.94 (3 H, s, 20-H), 1.31 (3 H, s, 18-H), 1.83 (1 H, d, *J* 7 Hz, 5-H), 3.13 (3 H, s, SO_2CH_3), 4.76 (1 H, t, *J* 7 Hz, 6-H), 4.83 and 5.0 (2 H, br, d, 17-H), and 5.31 (1 H, d, *J* 7 Hz, 7-H).

Reaction of 7,18-*Dihydroxykaurenolide with Carbon Tetrachloride and Triphenylphosphine.*—The kaurenolide (1 g), carbon tetrachloride (100 ml), and pyridine (5 ml) were mixed and heated with triphenylphosphine (2 g) for 90 min under reflux. The mixture was concentrated *in vacuo*. Dilute hydrochloric acid was added and the product was recovered in ether and chromatographed on silica. Elution with 6% ethyl acetate–light petroleum gave ent-18-*chloro*-*kaur*-6,16-*dien*-19,6-*olactone* (100 mg) which was recrystallized from ethyl acetate–light petroleum as needles, m.p. 243—244 °C (Found: C, 72.1; H, 7.5. $C_{20}H_{25}ClO_2$ requires C, 72.2; H, 7.5%), $\nu_{max.}$ 1 790, 1 690, 885, and 730 cm^{-1}; δ 0.8 (3 H, s, 20-H), 2.39 (1 H, d, *J* 2 Hz, 5-H), 3.5 and 3.63 (2 H, AB q, *J* 11 Hz, 18-H), 4.79 and 4.93 (2 H, br, d, 17-H), and 5.1 (1 H, d, *J* 2 Hz, 7-H). Irradiation at δ 5.1 caused the doublet at δ 2.39 to collapse to a singlet. Further elution with 15% ethyl acetate–light petroleum gave ent-18-*chloro*-7α-*hydroxykaur*-16-*en*-19,6β-*olactone* (650 mg) which recrystallized from ethyl acetate–light petroleum as needles, m.p. 193—195 °C, (Found: C, 68.4; H, 7.5.

* Named as *ent*-6β,7α-dihydroxykaur-16-en-19-oic acid 19—6β-lactone in refs. 1,4.

$C_{20}H_{27}ClO_3$ requires C, 68.5; H, 7.7%), $\nu_{max.}$ 3 530, 1 760, 1 650, 895, and 735 cm^{-1}, δ 0.91 (3 H, s, 20-H), 2.12 (1 H, d, *J* 7 Hz, 5-H), 3.5 and 3.62 (2 H, AB q, *J* 12 Hz, 18-H), 4.35 (1 H, d, *J* 7 Hz, 7-H), 4.63 (1 H, t, *J* 7 Hz, 6-H), 4.87 and 4.99 (2 H, br, d, 17-H). Irradiation at δ 4.63 causes the doublet at δ 2.21 to collapse to a singlet.

Reduction of the Chloro-lactone (12) *with Tri-n-butyltin Hydride.*—The lactone (12) (100 mg) in dry tetrahydrofuran (30 ml) was heated with a mixture of tri-n-butyltin hydride (100 mg) and azobisisobutyronitrile (5 mg) for 6 h under reflux. The tetrahydrofuran was distilled *in vacuo*, water was added, and the product was recovered in ethyl acetate. The gummy product was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave the 7β-hydroxykaurenolide (2) (60 mg) which recrystallized from ethyl acetate–light petroleum as needles, m.p. 185—187 °C (lit.,[2] 187—188 °C) and identified by its i.r. and n.m.r. spectra.

Reaction of 7,18-*Dihydroxykaurenolide with Triphenylchloromethane.*—The kaurenolide (6 g) in dry pyridine (50 ml) was heated with triphenylchloromethane (6 g) for 8 h on a boiling water-bath. The mixture was cooled and poured into dilute hydrochloric acid. The product was recovered in ethyl acetate and chromatographed on silica. Elution with 12.5% ethyl acetate–light petroleum gave the 18-*triphenylmethyl ether* (13) of 7,18-dihydroxykaurenolide (5 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 209—211 °C (Found: C, 81.4; H, 7.0. $C_{39}H_{42}O_4$ requires C, 81.5; H, 7.3%), $\nu_{max.}$ 3 598, 1 763, 1 655, 1 595, 885, 770, and 710 cm^{-1}; δ 0.87 (3 H, s, 20-H), 1.75 (1 H, d, *J* 7 Hz, 5-H), 3.14 and 3.33 (2 H, AB q, *J* 9 Hz, 18-H), 4.24 (1 H, d, *J* 7 Hz, 7-H), 4.49 (1 H, t, *J* 7 Hz, 6-H), 4.82 and 4.96 (2 H, br, d, 17-H), and 7.28 (15-H, m, Ar-H).

The 7β-*acetate*, prepared with acetic anhydride in pyridine, crystallized from ethyl acetate–light petroleum as needles, m.p. 215—218 °C (Found: C, 79.9; H, 7.1. $C_{41}H_{44}O_5$ requires C, 79.8; H, 7.2%), $\nu_{max.}$ 1 765, 1 740, 1 655, 1 595, and 890 cm^{-1}; δ 0.99 (3 H, s, 20-H), 2.06 (3 H, s, OAc), 3.08 and 3.38 (2 H, AB q, *J* 9 Hz, 18-H), 4.68 (1 H, t, *J* 7 Hz, 6-H), 4.86 and 4.96 (2 H, br, d, 17-H), 5.71 (1 H, d, *J* 7 Hz, 7-H), and 7.3 (15 H, m, Ar-H).

The 7β-*toluene*-p-*sulphonate*, (14), prepared with toluene-*p*-sulphonyl chloride in pyridine, crystallized from methanol as needles, m.p. 185—187 °C (Found: C, 75.5; H, 6.7. $C_{46}H_{48}O_6S$ requires C, 75.7; H, 6.7%), $\nu_{max.}$ 1 775, 1 600, 876, and 710 cm^{-1}; δ 0.9 (3 H, s, 20-H), 2.41 (3 H, s, Ar-CH_3), 3.04 and 3.24 (2 H, AB q, *J* 8 Hz, 18-H), 4.57 (1 H, t, *J* 7 Hz, 6-H), 4.84 and 4.99 (2 H, br, d, 17-H), 5.3 (1 H, d, *J* 7 Hz, 7-H), 7.32 (15 H, m, Ar-H), and 7.42 and 7.82 (2 H each, d, *J* 8 Hz, Ts-H).

Reaction of the Triphenylmethyl Ether (13) *with Triphenylphosphine and Carbon Tetrachloride.*—The triphenylmethyl ether (13) (4 g) and triphenylphosphine (4 g) in carbon tetrachloride (100 ml) and pyridine (5 ml) were heated for 2 h under reflux. The mixture was then concentrated *in vacuo*, dilute hydrochloric acid was added, and the product was recovered in ethyl acetate. The gummy product was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave the 18-*triphenylmethyl ether* (15) of *ent*-18-hydroxykaur-6,16-dien-19,6-olactone (3.5 g) which crystallized from ethyl acetate–light petroleum as needles, m.p. 203—206 °C (Found: C, 84.1; H, 7.15. $C_{39}H_{40}O_3$ requires C, 84.1; H, 7.2%), $\nu_{max.}$ 1 800, 1 700, 1 655, 1 603, 885, 820, 765, and 710 cm^{-1}; δ 0.76 (3 H, s, 20-H), 2.94 and 3.42 (2 H AB, q, *J* 9 Hz, 18-H), 4.78 and 4.92 (2 H, br, d, 17-H), 5.13 (1 H, d, *J* 2 Hz, 7-H), and 7.30 (15 H, m, Ar-H).

Hydrolysis of the Enol-lactone (15) *with Sodium Methoxide.*—The enol-lactone (15) (3 g) in dry methanol (50 ml) was heated with freshly prepared sodium methoxide (from sodium, 0.35 g) for 1.5 h under reflux. The solution was cooled, concentrated *in vacuo*, and acidified with dilute hydrochloric acid. Water was added and the product recovered in ethyl acetate to afford the 18-*triphenylmethyl ether* (16) of methyl *ent*-18-hydroxy-6-oxokaur-16-en-19-oate (2.6 g) which crystallized from aqueous ethanol as prisms, m.p. 80—82 °C (Found: C, 81.4; H, 7.4. $C_{40}H_{44}O_4$ requires C, 81.6; H, 7.5%), $\nu_{max.}$ 1 715, 1 655, 1 600, 875, 742, and 700 cm^{-1}; δ 1.06 (3 H, s, 20-H), 2.8 (1 H, s, 5-H), 3.22 and 3.41 (2 H, AB q, *J* 9 Hz, 18-H), 3.53 (3 H, s, OCH_3), 4.72 and 4.83 (2 H, br, d, 17-H), and 7.25 (15 H, m, Ar-H).

Reduction of the Ketone (16) *with Sodium Borohydride.*—The *ketone* (16) (2 g) in tetrahydrofuran (50 ml) was treated with a suspension of sodium borohydride (3 g) in methanol (20 ml) for 6 h at room temperature. A mixture of water and ethyl acetate was added and the product was recovered in ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4), and the solvent was evaporated and the gummy product chromatographed on silica. Elution with 6% ethyl acetate–light petroleum gave the 18-*triphenylmethyl ether* (17) of methyl *ent*-6β,18-dihydroxykaur-16-en-19-oate (1.3 g) which crystallized from methanol as prisms, m.p. 87—89 °C (Found: C, 81.5; H, 7.7. $C_{40}H_{46}O_4$ requires C, 81.3; H, 7.85%), $\nu_{max.}$ 3 425br, 1 700, 1 650, 1 595, 870, 760, and 702 cm^{-1}; δ 1.09 (3 H, s, 20-H), 2.89 and 3.58 (2 H, AB q, *J* 8 Hz, 18-H), 3.75 (3 H, s, OCH_3), 3.92 (1 H, m, 6-H), 4.72 (2 H, m, 17-H), and 7.25 (15 H, m, Ar-H).

Pyrolysis of the Hydroxy-ester (17).—The hydroxy-ester (17) (1 g) was heated at 220—230 °C for 1 h under a stream of nitrogen. The mixture was cooled and extracted with ethyl acetate. The solvent was evaporated and the gummy product chromatographed on silica. Elution with 7% ethyl acetate–light petroleum gave the 18-*triphenylmethyl ether* (18) of *ent*-18-hydroxykaur-16-en-19,6β-olactone (600 mg) which crystallized from aqueous ethanol as prisms, m.p. 145—148 °C (Found: C, 83.9; H, 7.6. $C_{39}H_{42}O_3$ requires C, 83.9; H, 7.5%), $\nu_{max.}$ 1 770, 1 655, 1 595, 870, 763, and 710 cm^{-1}; δ 0.91 (3 H, s, 20-H), 3.23 and 3.31 (2 H, AB q, *J* 9 Hz, 18-H), 4.7 (1 H, m, 6-H), 4.8 and 4.94 (2 H, br, d, 17-H), and 7.28 (15 H, m, Ar-H). Further elution with 30% ethyl acetate–light petroleum gave ent-18-*hydroxykaur*-16-*en*-19,6β-*olactone* (3) (200 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 217—219 °C (Found: C, 75.75; H, 8.8. $C_{20}H_{28}O_3$ requires C, 76.0; H, 8.9%), $\nu_{max.}$ 1 754, 1 650, and 875 cm^{-1}; δ 0.98 (3 H, s, 20-H), 3.66 (2 H, m, 18-H), 4.8 (1 H, m, 6-H), and 4.96 (2 H, m, 17-H). The *acetate*, prepared with acetic anhydride in pyridine, was a gum (Found: M^+ 358.214. $C_{22}H_{30}O_4$ requires M^+ 358.214), $\nu_{max.}$ 1 750br 1 650, 1 230, 1 040, and 880 cm^{-1}; δ 0.96 (3 H, s, 20-H), 2.06 (3 H, s, OAc), 4.1 (2 H, s, 18-H), 4.81 (1 H, m, 6-H), and 4.81 and 4.93 (2 H, br, d, 17-H).

Hydrolysis of the 18-*Triphenylmethyl Ether* (18).—The triphenylmethyl ether (18) (500 mg) was heated in acetic acid (10 ml) under reflux for 20 min. The mixture was cooled, poured into aqueous sodium hydrogen carbonate, and the product was recovered in ethyl acetate. The extract was washed with water, dried, and the solvent

evaporated to afford a gum which was chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave *ent*-18-hydroxykaur-16-en-19,6β-olactone (250 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 217—219 °C, identified by its i.r. and n.m.r. spectrum.

Oxidation of the 18-*Hydroxykaurenolide* (3).—The lactone (3) (25 mg) in acetone (5 ml) was treated with the 8N-chromium trioxide reagent (0.5 ml) for 20 min at 0 °C. Methanol was added and the solution was concentrated *in vacuo*. The mixture was diluted with water and the product was extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and the solvent removed at room temperature. The gummy product was treated with ethereal diazomethane. The ether was evaporated and the product chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave ent-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone* (5) (16 mg) which crystallized from methanol as needles, m.p. 115—117° (Found: C, 73.4; H, 8.3. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.1%), $\nu_{max.}$ 1 780, 1 730, 1 235, 1 000, and 880 cm^{-1}; δ 0.92 (3 H, s, 20-H), 2.3 (1 H, d, *J* 6 Hz, 5-H), 3.71 (3 H, s, OCH,), 4.77 (1 H, m, 6-H), and 4.8 and 4.92 (2 H, br, d, 17-H).

Hydrolysis of the 18-*Triphenylmethyl Ether of* ent-7α-*Acetoxy*-18-*hydroxykaur*-16-*en*-19,6β-*olactone*.—The ether (1 g) was heated under reflux with acetic acid (10 ml) for 45 min. The mixture was cooled and the excess of acetic acid was distilled off under reduced pressure. A mixture of water and ethyl acetate was added and the product was recovered in ethyl acetate. The organic phase was washed with water, dried, and the solvent evaporated to afford a gum which was chromatographed on silica. Elution with 20—25% ethyl acetate–light petroleum gave 7,18-diacetoxykaurenolide (400 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 197—198 °C (lit.,[1] 197—202 °C), identified by its i.r. and n.m.r. spectra. Further elution with 30% ethyl acetate–light petroleum gave ent-7α-*acetoxy*-18-*hydroxykaur*-16-*en*-19,6β-*olactone* (19) (300 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 169—171 °C (Found: C, 70.4; H, 8.0. $C_{22}H_{30}O_5$ requires C, 70.6; H, 8.0%), $\nu_{max.}$ 3 450, 1 750, 1 735, and 875 cm^{-1}; δ 1.03 (3 H, s, 20-H), 2.05 (3 H, s, OAc), 3.66 (2 H, s, 18-H), 4.74 (1 H, t, *J* 7 Hz, 6-H), 4.82 and 4.98 (2 H, br, d, 17-H), and 5.74 (1 H, d, *J* 7 Hz, 7-H).

Partial Hydrolysis of 7,18-*Diacetoxykaurenolide*.—The diacetate (1 g) in methanol (25 ml) was treated with aqueous sodium hydrogen carbonate (25 ml) for 4 h at room temperature. The methanol was removed *in vacuo*, water was added, and the product was recovered in ethyl acetate. *ent*-7α-Acetoxy-18-hydroxykaur-16-en-19,6β-olactone (750 mg) crystallized from ethyl acetate–light petroleum as needles, m.p. 169—171 °C, identical (i.r. and n.m.r.) to the material described above.

Oxidation of ent-7α-*Acetoxy*-18-*hydroxykaur*-16-en-19,6β-*olactone* (19).—The alcohol (19) (700 mg) in acetone (50 ml) was treated with the 8N-chromium trioxide reagent (5 ml) for 30 min in an ice-bath. Methanol was added and the mixture was concentrated *in vacuo*. Water was added and the product was recovered in ethyl acetate. The ethyl acetate extract was washed with aqueous sodium hydrogen carbonate. The aqueous sodium hydrogen carbonate was then acidified with dilute hydrochloric acid and the organic acid recovered in ethyl acetate. The solvent was evaporated and the gummy residue methylated with ethereal diazomethane and chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave ent-7α-*acetoxy*-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone* (21) (500 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 181—184 °C (Found: C, 70.4; H, 8.0. $C_{22}H_{30}O_5$ requires C, 70.6; H, 8.0%, $\nu_{max.}$ 1 785, 1 725, and 880 cm^{-1}; δ 0.99 (3 H, s, 20-H), 2.05 (3 H, s, OAc), 2.49 (1 H, d, *J* 7 Hz, 5-H), 3.73 (3 H, s, OCH_3), 4.62 (1 H, t, *J* 7 Hz, 6-H), 4.86 and 5.0 (2 H, br, d, 17-H), and 5.78 (1 H, d, *J* Hz, 7-H). The starting material (100 mg) was recovered from the neutral fraction.

Hydrolysis of ent-7α-*Acetoxy*-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone*.—The above acetate (400 mg) in methanol (50 ml) was treated with aqueous sodium carbonate (15 ml) for 3 h at room temperature. The solution was acidified with dilute hydrochloric acid and the product was extracted with ethyl acetate. This extract was shaken with aqueous sodium hydrogen carbonate. The neutral organic phase was washed with water and dried. The solvent was evaporated and the gummy product chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave ent-7α-*hydroxy*-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone* (4) (150 mg) which crystallized from acetone–light petroleum as needles, m.p. 183—185 °C (Found: C, 69.7; H, 7.8. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%), $\nu_{max.}$ 3 580, 3 480br, 1 765, 1 735, and 885 cm^{-1}, δ 0.99 (3 H, s, 20-H), 3.74 (3 H, s, OCH_3), 4.36 (1 H, d, *J* 7 Hz, 7-H), 4.56 (1 H, t, *J* 7 Hz, 6-H), and 4.86 and 4.99 (2 H, br, d, 17-H). The aqueous phase was acidified with dilute hydrochloric acid and the product was extracted with ethyl acetate. The extract was washed with water, dried, and the solvent evaporated. The residue was methylated with ethereal diazomethane and chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave *ent*-7α-acetoxy-18-methoxycarbonylkaur-16-en-19,6β-olactone (50 mg), m.p. 181—183 °C, identified by its i.r. and n.m.r. spectra. Further elution yielded *ent*-7α-*hydroxy*-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone* (150 mg), m.p. 183—185 °C, identified by its i.r. and n.m.r. spectra.

Hydrolysis of ent-7α-*Hydroxy*-18-*methoxycarbonylkaur*-16-*en*-19,6β-*olactone* (4).—The ester (4) 20 mg) in methanol (10 ml) was treated with aqueous sodium carbonate (10 ml) for 4 h at room temperature. The mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was separated into acidic and neutral fractions with aqueous sodium hydrogen carbonate. The acid fraction was boiled with water (15 ml) for 1 h. The solution was cooled and extracted with ethyl acetate. The extract was dried and the solvent evaporated to afford *ent*-7α-hydroxy-18-norkaur-16-en-19,6β-olactone (6) (13 mg), m.p. 190—192 °C (lit.,[1] 190—192 °C). It was identical to a sample prepared by the pyrolysis of 7,18-dihydroxykaurenolide.

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