The Influence of a 15-Hydroxy Group on the Rearrangement Reactions of Steviol and its 16,17-Epoxide

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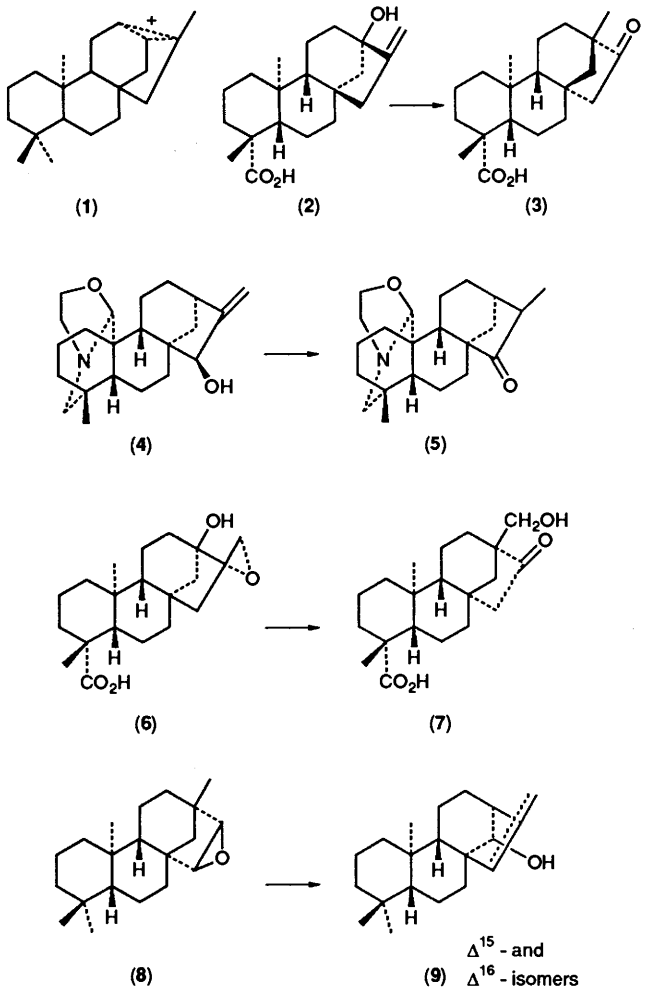
A 15-hydroxy group prevents the steviol/isosteviol rearrangement taking place. In the presence of hydrobromic acid, the 15α-alcohol undergoes rearrangement to a 17-alcohol whilst the 15β-alcohol gives the 15-ketones. Treatment of a 15α-hydroxy-16,17-epoxide gives the 15α,16α-dihydroxy-17-bromide, the structure of which was confirmed by X-ray analysis.

Many of the acid-catalysed rearrangements which inter-relate the C/D ring system of *ent*-kaurene with that of the other tetracyclic diterpenoids may be rationalized in terms of the different modes of collapse of the bridged carbonium ion (**1**).[1–3] The outcome of these rearrangements is strongly influenced by the presence of oxygen functions on the ring system. Thus steviol (**2**) with a 13-hydroxy group readily gives isosteviol (**3**)[4] whilst garryfoline (**4**) with a 15β-hydroxy group gives cuauchichicine (**5**).[5] A similar rearrangement was found[6] with the *ent*-15α-hydroxykaur-16-en-19-oic acid. In a mechanistic study[7] of this rearrangement in the *ent*-kaurene series, it was found that the 15β-alcohol underwent a rapid rearrangement with a 15,16-hydride shift to afford the 16*R*-*ent*-kauran-15-one, whilst the epimeric 15α-alcohol was stable. The epoxide of steviol, compound (**6**), also undergoes an acid-catalysed rearrangement akin to the isosteviol rearrangement.[8] This leads to the 13-hydroxymethyl compound (**7**). The same delocalized carbocation (**1**) can be approached from beyerane derivatives.[9] Thus rearrangement of the 15,16-epoxybeyerane (**8**) afford 14-hydroxykaurenes (**9**).[10,11] The presence of additional oxygen functions at C-14 on the beyerane epoxide has been shown to influence the outcome of these reactions.[12] In this paper we report on the intervention of a 15-hydroxy group in these rearrangements of steviol (**2**).

The allylic hydroxylation of alkenes with selenium dioxide and t-butyl hydroperoxide has been widely used[13,14] and the mechanism has been discussed.[15] Oxidation at C-15 in the kaurene series has been achieved with selenium dioxide and hydrogen peroxide.[16] Hydroxylation of steviol (**2**) with selenium dioxide and t-butyl hydroperoxide[13] gave *ent*-13,15β-dihydroxykaur-16-en-19-oic acid (**10**).[17] The ^{1}H NMR spectrum of the product retained the 17-H_2 alkene resonances (δ 5.19 and 5.22) and showed a new secondary alcohol resonance (δ 3.74) as a broad doublet (*J* 1.8 Hz). An NOE experiment based on irradiation of 20-H_3 (δ 0.97) located the 14-H_α signal at δ 1.95 (*J* 10.9 and 1.8 Hz) (12% enhancement). Decoupling experiments showed that the secondary alcohol resonance (δ 3.74) possessed long-range couplings both to this proton and to the olefinic protons. This led to the assignment of the *ent*-15β-hydroxy stereochemistry to the alcohol. The oxidation of these allylic alcohols to the 15-ketones with chromium trioxide in pyridine, and the subsequent reduction of the ketones with sodium borohydride to the *ent*-15-alcohols, has been described.[6,18] Oxidation of the alcohol (**10**) with chromium trioxide in pyridine gave the unsaturated ketone (**11**) in which the alkene proton resonances had shifted downfield to δ 5.40 and 5.95. Reduction of the ketone with sodium borohydride in ethanol at a low temperature gave the isomeric alcohol (**12**) and a small amount of the original hydroxylation product. The secondary alcohol resonance (δ 4.30) in compound (**12**) did not show any long-range coupling to 14-H_α.



The steviol/isosteviol rearrangement is smoothly effected with cold hydrobromic acid[19] and these conditions were therefore used in this work. Whereas treatment of the alcohol (**10**) with acid gave the allylic alcohol (**13**), its epimer (**12**) smoothly gave the ketone (**14**). This ketone was also obtained from the alcohol (**10**) by hydrogenation over palladium on charcoal and oxidation with chromium trioxide in pyridine. The stereochemistry of the ketone (**14**) at C-16 followed from the

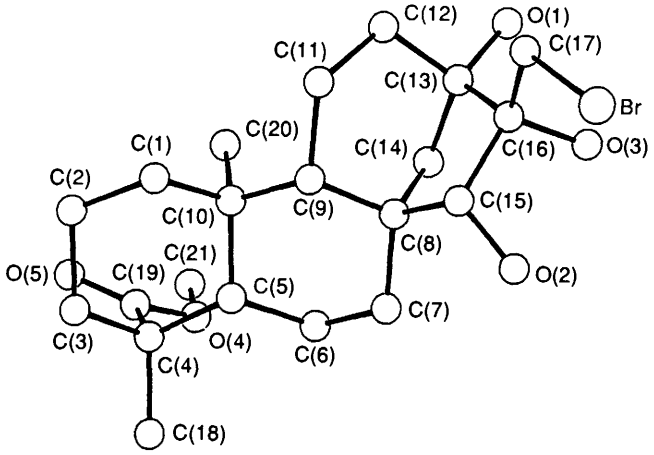


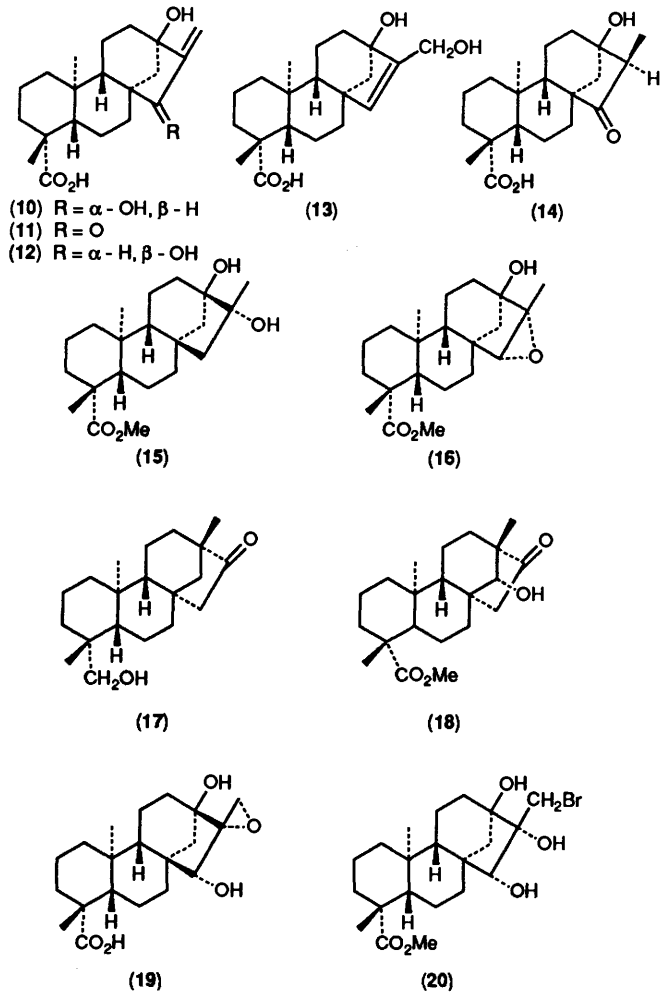
Figure. The X-ray molecular structure of methyl *ent*-17-bromo-13,15β,16β-trihydroxykauran-19-oate (**20**).

^{1}H NMR spectrum of its methyl ester. The 14-H signal (δ 2.47, *J* 11.3 Hz) was identified by an NOE enhancement (10%) observed on irradiation of 20-H_3 (δ 0.87). Decoupling of this signal located the other 14-H signal as a double-doublet (δ 1.56, *J* 11.3 and 2.1 Hz). The 17-H_3 methyl doublet (δ 1.08, *J* 7 Hz) was coupled to a quartet (δ 2.25) (16-H). An NOE experiment based on irradiation of this signal (16-H) produced a 5% enhancement of the double-doublet (δ 1.56) (14-H). Hence the ketone has the stereochemistry shown in structure (**14**) and the hydride shift has proceeded as in the previous examples.

Steviol (**2**) was converted into its epoxide by reaction with *m*-chloroperbenzoic acid (MCPBA). The stereochemistry of the epoxide (**6**) was established by reduction with lithium aluminium hydride to the 13,16-diol (**15**) which is of known stereochemistry.[20] The isomeric 15,16-epoxide, as its methyl ester (**16**), was obtained by epoxidation of a mixture of the 15- and 16-enes isolated[20] from the mild-acid hydrolysis of stevioside. The stereochemistry of the epoxide followed from the presence of a long-range coupling (1.5 Hz) between the 15-H and the 14-H, indicative of a 'W' stereochemical relationship between these protons. This epoxide was less easily reduced by lithium aluminium hydride than was the 16,17-epoxide. The product was the 19-hydroxy-16-oxo-beyerane (**17**), a Wagner–Meerwein rearrangement having occurred on work-up of the reaction mixture.

Whilst the 15- and 16-enes were difficult to separate chromatographically, it was possible to separate their epoxides more easily. Hence their deoxygenation by tungsten chloride[21] was examined with the object of regenerating the alkenes. Whereas the 16,17-epoxide was smoothly deoxygenated producing steviol, the 15,16-epoxide underwent a Lewis acid-catalysed rearrangement to form the 14-hydroxyisosteviol relative (**18**) [ν_{max} 3 487 (OH) and 1 745 cm^{-1} (5-ring ketone); δ 3.38 C*H*OH)]. The stereochemistry of this compound followed from NMR experiments. The 15-H_2 proton resonances appeared at δ 2.15 (doublet, *J* 18.6 Hz) and 2.52 (double-doublet, *J* 18.6 and 1.7 Hz). Irradiation of the C*H*(OH) signal (δ 3.38) removed the long-range coupling (*J* 1.7 Hz) from the signal at δ 2.52.

The influence of a 15-hydroxy group on the rearrangement of the 16,17-epoxide was then examined. The required epoxide (**19**) was prepared from compound (**10**) using MCPBA. On treatment with hydrobromic acid the epoxide produced a compound which had spectral data consistent with the structure (**20**). Thus the ^{1}H NMR spectrum of the methyl ester showed two tertiary methyl-group signals (δ 0.78 and 1.14) and a two-proton singlet (δ 3.61) which was assigned to the 16-CH_2Br. A broad singlet at δ 4.14 was assigned to 15-Hβ. In view of the abnormal opening of the epoxide implicit in this structure, the full structure and stereochemistry at C-16 was established by X-ray crystallography. It is shown in the Figure.



In conclusion we have established that the presence of a 15-hydroxy group substantially modifies the rearrangements of the C/D ring sytem of steviol. These modifications may be rationalized in terms of the participation of a 15-*exo* substituent in the C-12, C-13, C-16 carbocation. In this situation there is the opportunity for overlap between the vacant C-16 p-orbital and the *exo*-grouping.[7] Where this is hydrogen, a hydrogen shift readily occurs leading, in the case of the 15-alcohols, to the formation of the 15-ketone. Where this is a 15-*exo*-alcohol, neighbouring-group participation may occur, thus preventing collapse of the carbocation to form the isosteviol system and thereby allowing the alternative allylic rearrangement to occur. The participation of a 15α-alcohol in the reaction of a C-16 carbocation has been noted in the formation of bromoepoxyatractyligenin.[22] Hydrogen bonding to the epoxide presumably affects its direction of opening.

Experimental

IR spectra were determined as Nujol mulls on a Perkin-Elmer 1710 spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker WM 360 spectrometer for solutions in deuteriochloroform. Light petroleum refers to the fraction boiling in the range 60–80 °C. Silica for chromatography was Merck 9385.

ent-13,15β-*Dihydroxykaur*-16-*en*-19-*oic Acid* (**10**).—Steviol (**2**) (50 mg) was dissolved in a mixture of 1,4-dioxane and water (1:1; 10 ml). Selenium dioxide (3 mg) was added followed by t-butyl hydroperoxide (0.1 ml of a 3.9M solution in toluene) and the mixture was stirred at 60 °C for 5 h. Water (20 ml) was added and the mixture was extracted with chloroform. The extract was filtered through a small column of silica and then dried. The solvent was evaporated off under reduced pressure to afford *ent*-13,15β-dihydroxykaur-16-en-19-oic acid (**10**) (40 mg), which crystallized from methanol as needles, m.p. 271–273 °C (Found: C, 70.0; H, 8.9. Calc. for $C_{20}H_{30}O_4 \cdot 0.5H_2O$: C, 69.9; H, 9.0%); ν_{max} 3 294, 3 400–2 400br, and 1 697 cm^{-1}; δ($CDCl_3$ + CD_3OD) 0.97 (3 H, s, 20-H_3), 1.19 (3 H, s, 18-H_3), 1.95 (1 H, dd, *J* 10.9 and 1.8 Hz, 14-H), 2.12 (1 H, br d, *J* 12.8 Hz, 5-H), 3.74 (1 H, br d, *J* 1.8 Hz, 15-H), and 5.19 and 5.22 (each 1 H, br s, 17-H_2).

ent-13-*Hydroxy*-15-*oxokaur*-16-*en*-19-*oic Acid* (**11**).—A solution of *ent*-13,15β-dihydroxykaur-16-en-19-oic acid (**10**) (143 mg) in pyridine (10 ml) was added to the reagent prepared by the slow addition of pyridine (8 ml) to a solution of chromium trioxide (129 mg) in water (1 ml). The mixture was stirred overnight at room temperature. Water (20 ml) was added and the mixture was extracted with diethyl ether. The extract was dried and the solvent was evaporated off to give ent-13-*hydroxy*-15-*oxokaur*-16-*en*-19-*oic acid* (**11**) (120 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 216–218 °C (Found: C, 69.7; H, 8.7. $C_{20}H_{28}O_4 \cdot 0.5H_2O$ requires C, 70.35; H, 8.7%); ν_{max} 3 514, 3 450br, 1 721, 1 698, and 1 651 cm^{-1}; δ 1.04 (3 H, s, 20-H_3), 1.21 (3 H, s, 18-H_3), 1.46 (1 H, dd, *J* 11.2 and 2.2 Hz, 14-Hβ), 2.47 (1 H, d, *J* 11.2 Hz, 14-Hα), and 5.40 and 5.95 (each 1 H, br s, 17-H_2).

ent-13,15α-*Dihydroxykaur*-16-*en*-19-*oic Acid* (**12**).—The above keto acid (**11**) (52 mg) was dissolved in ethanol (10 ml) and the solution was cooled in an acetone–solid CO_2-bath. Sodium borohydride (30 mg) was added and the mixture was stirred for 3 h. Water (50 ml) was added at room temperature and the solution was acidified with acetic acid. The product was recovered in chloroform and chromatographed on silica. Elution with ethyl acetate–light petroleum–acetic acid (60:39:1) gave ent-13,15α-*dihydroxykaur*-16-*en*-19-*oic acid* (**12**) (30 mg), m.p. 194 °C (Found: C, 68.0; H, 8.9. $C_{20}H_{30}O_4 \cdot H_2O$ requires C, 68.4; H, 9.4%); ν_{max} 3 462, 3 400br, and 1 693 cm^{-1}; δ([$^2H_5$]pyridine) 1.23 (3 H, s, 20-H_3), 1.28 (3 H, s, 18-H_3), 2.41 (1 H, d, *J* 11 Hz, 14-Hα), 4.30 (1 H, s, 15-Hα), and 5.58 and 5.62 (each 1 H, br s, 17-H_2). Further elution gave the alcohol (**10**) (5 mg), identical (TLC, IR, NMR) with that obtained previously.

Reaction of ent-13,15β-*Dihydroxykaur*-16-*en*-19-*oic Acid* (**10**) *with Hydrobromic Acid*.—The dihydroxy acid (**10**) (100 mg) was suspended in 48% hydrobromic acid (15 ml) and the mixture was left for 2 h at room temperature, then diluted with water (100 ml) and the product was filtered off, treated with ethereal diazomethane, and chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave methyl *ent*-13,17-dihydroxykaur-15-en-19-oate (38 mg) as a gum (M^+, 348), ν_{max} 3 480, 3 455, and 1 726 cm^{-1}; δ 0.97 (3 H, s, 20-H_3), 1.22 (3 H, s, 18-H_3), 3.63 (3 H, s, OMe), 4.00 (2 H, br s, 17-H_2), and 5.40 (1 H, br s, 15-H).

Reaction of ent-13,15α-*Dihydroxykaur*-16-*en*-19-*oic Acid* (**12**) *with Hydrobromic Acid*.—The dihydroxy acid (**12**) (30 mg) was suspended in 48% hydrobromic acid (10 ml) and the mixture was left for 2 h at room temperature, then diluted with water (100 ml) and the product was recovered in chloroform. The extract was washed with water, dried, and evaporated to give *ent*-13-hydroxy-15-oxokauran-19-oic acid (**14**) (15 mg), m.p. 156–157 °C, identical (TLC, NMR) with the material described below.

ent-13,15β-*Dihydroxykauran*-19-*oic Acid*.—A selection of the dihydroxy acid (**10**) (540 mg) in methanol (60 ml) was stirred under hydrogen in the presence of 10% palladium on charcoal (50 mg) for 4 h. The catalyst was filtered off and the solvent was evaporated to give the title dihydroxykauranoic acid (500 mg), which was crystallized from methanol as needles, m.p. 280–282 °C. The *methyl ester*, prepared with diazomethane, crystallized from ethyl acetate–light petroleum as needles, m.p. 254–255 °C (Found: C, 71.3; H, 10.0. $C_{21}H_{34}O_4$ requires C, 71.9; H, 9.8%); ν_{max} 3 257br and 1 719 cm^{-1}; δ 0.82 (3 H, s, 20-H_3), 1.09 (3 H, d, *J* 7.2 Hz, 17-H_3), 1.18 (3 H, s, 18-H_3), 3.64 (3 H, s, OMe), and 3.65 (1 H, s, 15-H).

ent-13-*Hydroxy*-15-*oxokauran*-19-*oic Acid* (**14**).—The above dihydroxy acid (174 mg) was dissolved in a mixture of dichloromethane (30 ml) and dimethylformamide (2 ml). Pyridinium dichromate (300 mg) was added and the mixture was stirred at room temperature for 3 h, then filtered through a small column of silica, and the solvent was evaporated off. The *keto acid* (**14**) crystallized from acetone–light petroleum as needles, m.p. 156–158 °C (Found: C, 70.4; H, 9.15. $C_{20}H_{30}O_4 \cdot 0.5H_2O$ requires C, 69.9; H, 9.1%); ν_{max} 3 500br, 1 738, and 1 696 cm^{-1}; δ([$^2H_5$]pyridine) 1.18 (3 H, s, 20-H_3), 1.29 (3 H, d, *J* 7.1 Hz, 17-H_3), 1.30 (3 H, s, 18-H_3), 2.59 (1 H, q, *J* 7.1 Hz, 16-H), and 2.70 (1 H, d, *J* 11.3 Hz, 14-H). The methyl ester, prepared with diazomethane, had δ 0.87 (3 H, s, 20-H_3), 1.08 (3 H, d, *J* 7.1 Hz, 17-H_3), 1.18 (3 H, s, 18-H), 1.56 (1 H, dd, *J* 11.3 and 2.1 Hz, 14-Hβ), 2.25 (1 H, q, *J* 7.1 Hz, 16-H), 2.47 (1 H, d, *J* 11.3 Hz, 14-Hα), and 3.65 (3 H, s, OMe).

ent-17-*Hydroxy*-16-*oxobeyeran*-19-*oic Acid* (**7**).—Steviol epoxide (**6**)[17] (600 mg) was dissolved in aqueous acetone (50 ml), conc. hydrochloric acid (3 drops) was added, and the mixture was heated under reflux for 1 h. The mixture was cooled, then diluted with water, and the product was recovered in chloroform to afford ent-17-*hydroxy*-16-*oxobeyeran*-19-*oic acid* (**7**) (520 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 230–232 °C (Found: C, 71.3; H, 9.2. $C_{20}H_{30}O_4$ requires C, 71.8; H, 9.0%); ν_{max} 3 454, 3 400br, 1 727, and 1 717 cm^{-1}; δ 0.79 (3 H, s, 20-H_3), 1.25 (3 H, s, 18-H_3), 1.86 (1 H, d, *J* 19 Hz, 15-Hβ), 2.17 (1 H, br d, *J* 13.3 Hz, 12-H), 2.67 (1 H, dd, *J* 18.8 and 3.7 Hz, 15-Hα), 3.50 (1 H, d, *J* 11.4 Hz, 17-H), and 3.66 (1 H, d, *J* 11.4 Hz, 17-H).

Methyl ent-13,16β-*Dihydroxykauran*-19-*oate* (**15**).—A solution of methyl *ent*-16,17-epoxy-13-hydroxykauran-19-oate[8] (71 mg) in dry diethyl ether (20 ml) was treated with lithium aluminium hydride (200 mg) for 5 h. Water (100 ml) was added and the product was recovered in ethyl acetate and chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave the glycol (**15**) (51 mg), m.p. 150–151 °C, identical with the material obtained from the acid hydrolysis of stevioside.[20]

Epoxidation of Steviol Methyl Ester and its Δ^{15}-*Isomer*.—The mixture (200 mg) obtained from the hydrolysis of stevioside[20] was esterified with diazomethane, and the product was dissolved in chloroform (20 ml) and treated with MCPBA (200 mg) overnight. The excess of peracid was destroyed with aq. sodium hydrogen sulphite, and the mixture was washed successively with saturated aq. sodium hydrogen carbonate and water, then dried, and the solvent was evaporated off. The residue was chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave methyl *ent*-16,17-epoxy-13-

Table. Fractional atomic co-ordinates (× 10^4), with estimated standard deviations in parentheses.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Br	2 516.7(6)	3 590.1	4 721.9(8)	Br(c)	625.7(7)	6 664.5(37)	518.7(9)
O(1)	3 508(3)	1 457(20)	4 158(4)	O(1c)	1 167(4)	3 136(24)	1 887(5)
O(2)	3 326(3)	5 643(18)	5 233(4)	O(2c)	1 516(3)	7 860(17)	1 172(4)
O(3)	3 211(3)	4 453(19)	4 391(4)	O(3c)	1 295(3)	4 728(20)	1 151(5)
O(4)	5 127(3)	2 834(19)	5 896(4)	O(4c)	2 402(3)	8 751(22)	3 575(5)
O(5)	5 282(4)	503(25)	6 360(6)	O(5c)	2 099(4)	9 818(21)	4 059(5)
C(1)	4 228(5)	−349(31)	6 292(7)	C(1c)	1 223(6)	10 541(33)	2 994(7)
C(2)	4 593(5)	−775(31)	6 627(7)	C(2c)	1 411(6)	11 467(34)	3 457(7)
C(3)	4 784(5)	1 027(31)	6 859(7)	C(3c)	1 746(6)	12 391(35)	3 420(8)
C(4)	4 818(5)	2 441(27)	6 490(6)	C(4c)	2 007(5)	11 102(29)	3 279(7)
C(5)	4 439(4)	2 764(26)	6 149(6)	C(5c)	1 813(4)	10 229(24)	2 816(6)
C(6)	4 416(5)	4 332(27)	5 783(6)	C(6c)	2 039(5)	9 114(26)	2 584(6)
C(7)	4 037(5)	4 863(27)	5 588(6)	C(7c)	1 861(4)	8 810(26)	2 066(6)
C(8)	3 800(4)	3 281(26)	5 352(6)	C(8c)	1 517(5)	7 821(26)	2 010(6)
C(9)	3 861(4)	1 603(26)	5 666(6)	C(9c)	1 287(4)	8 746(26)	2 304(6)
C(10)	4 249(4)	1 029(25)	5 916(6)	C(10c)	1 459(4)	9 210(24)	2 805(6)
C(11)	3 616(5)	4(29)	5 419(7)	C(11c)	924(5)	7 638(32)	2 235(7)
C(12)	3 555(5)	−85(28)	4 871(6)	C(12c)	939(6)	5 592(32)	2 197(7)
C(13)	3 535(5)	1 766(27)	4 651(6)	C(13c)	1 196(6)	5 055(35)	1 925(8)
C(14)	3 872(4)	2 859(25)	4 877(6)	C(14c)	1 576(5)	5 716(29)	2 126(7)
C(15)	3 398(4)	3 752(27)	5 230(6)	C(15c)	1 294(4)	7 727(26)	1 485(6)
C(16)	3 243(5)	2 953(27)	4 721(6)	C(16c)	1 109(5)	5 821(29)	1 405(7)
C(17)	2 908(6)	1 988(30)	4 624(7)	C(17c)	710(5)	5 898(29)	1 168(7)
C(18)	4 961(5)	4 147(31)	6 765(7)	C(18c)	2 338(6)	12 268(35)	3 204(8)
C(19)	5 092(5)	1 838(30)	6 236(7)	C(19c)	2 169(5)	9 838(28)	3 684(7)
C(20)	4 441(5)	92(26)	5 570(6)	C(20c)	1 542(5)	7 594(30)	3 162(6)
C(21)	5 370(6)	2 298(32)	5 611(7)	C(21c)	2 593(6)	7 450(38)	3 932(8)
Br(b)	−2 445.4(6)	3 268.4(35)	−229.3(8)	Br(d)	4 367.7(7)	7 346.6(37)	4 484.7(8)
O(1b)	−1 443(3)	1 274(19)	−783(4)	O(1d)	4 022(4)	3 765(23)	3 086(5)
O(2b)	−1 635(3)	5 161(8)	370(4)	O(2d)	3 477(3)	7 990(18)	3 789(4)
O(3b)	−1 740(3)	4 206(19)	−497(4)	O(3d)	3 789(3)	5 052(19)	3 802(4)
O(4b)	158(4)	2 198(21)	934(5)	O(4d)	2 549(3)	8 546(23)	1 375(5)
O(5b)	318(4)	−273(24)	1 372(6)	O(5d)	2 879(3)	9 726(19)	937(4)
C(1b)	−735(5)	−945(29)	1 351(7)	C(1d)	3 689(5)	11 349(29)	1 999(7)
C(2b)	−354(5)	−1 424(33)	1 674(7)	C(2d)	3 487(5)	12 122(28)	1 535(7)
C(3b)	−171(5)	252(31)	1 903(7)	C(3d)	3 104(5)	12 651(30)	1 554(7)
C(4b)	−139(5)	1 729(30)	1 552(7)	C(4d)	2 885(4)	11 136(26)	1 679(6)
C(5b)	−513(5)	2 132(25)	1 235(6)	C(5d)	3 113(4)	10 310(25)	2 162(6)
C(6b)	−546(4)	3 749(27)	891(6)	C(6d)	2 926(4)	8 802(26)	2 351(6)
C(7b)	−932(5)	4 335(28)	725(6)	C(7d)	3 109(5)	8 659(31)	2 886(7)
C(8b)	−1 161(5)	2 802(26)	451(6)	C(8d)	3 494(4)	7 996(25)	2 942(6)
C(9b)	−1 107(4)	1 046(25)	750(6)	C(9d)	3 693(4)	9 206(25)	2 680(6)
C(10b)	−709(5)	412(27)	974(6)	C(10d)	3 490(5)	9 695(26)	2 154(6)
C(11b)	−1 349(5)	−473(26)	464(6)	C(11d)	4 086(5)	8 667(33)	2 758(7)
C(12b)	−1 401(5)	−429(27)	−70(6)	C(12d)	4 141(6)	6 612(34)	2 793(8)
C(13b)	−1 409(4)	1 463(26)	−281(6)	C(13d)	3 915(6)	5 706(32)	3 070(7)
C(14b)	−1 084(5)	2 487(27)	−32(6)	C(14d)	3 538(5)	6 011(29)	2 813(7)
C(15b)	−1 569(4)	3 301(28)	325(6)	C(15d)	3 708(4)	8 094(25)	3 478(6)
C(16b)	−1 700(4)	2 646(26)	−193(6)	C(16d)	3 944(5)	6 407(28)	3 572(6)
C(17b)	−2 071(5)	1 664(31)	−297(7)	C(17d)	4 347(5)	6 730(30)	3 824(7)
C(18b)	22(5)	3 403(34)	1 831(7)	C(18d)	2 531(5)	11 952(29)	1 750(7)
C(19b)	142(5)	1 104(32)	1 276(7)	C(19d)	2 784(5)	9 775(26)	1 292(6)
C(20b)	−523(5)	−496(28)	620(7)	C(20d)	3 512(5)	8 105(28)	1 814(6)
C(21b)	387(6)	1 638(34)	649(8)	C(21d)	2 448(6)	7 130(34)	1 031(8)

hydroxykauran-19-oate (115 mg), m.p. 137–139 °C (lit.,[8] 144 °C) (Found: C, 72.2; H, 9.4. Calc. for $C_{21}H_{32}O_4$: C, 72.4; H, 9.2%); ν_{max} 3 530 and 1 730 cm^{-1}; δ 0.85 (3 H, s, 20-H_3), 1.17 (3 H, s, 18-H_3), 2.78 and 2.92 (each 1 H, d, *J* 4.5 Hz, 17-H_2), and 3.64 (3 H, s, OMe).

Further elution gave *methyl* ent-15β,16β-*epoxy*-13-*hydroxykauran*-19-*oate* (**16**) (66 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 248–250 °C (Found: C, 72.2; H, 9.4. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.2%); ν_{max} 3 400 and 1 730 cm^{-1}; δ 0.81 (3 H, s, 20-H_3), 1.18 (3 H, s, 18-H_3), 1.38 (3 H, s, 17-H_3), 2.18 (1 H, br d, *J* 14 Hz, 12-Hα), 2.72 (1 H, d, *J* 1.5 Hz, 15-Hβ), and 3.63 (3 H, s, OMe).

ent-19-*Hydroxybeyeran*-16-*one* (**17**).—A solution of methyl *ent*-15β,16β-epoxy-13-hydroxykauran-19-oate (**16**) (32 mg) in diethyl ether (10 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 3 h. There was no reaction. A further amount of lithium aluminium hydride was added and the mixture was heated under reflux for 2 h. The excess of reagent was destroyed with ethyl acetate, dil. hydrochloric acid was added, and the product was recovered in ethyl acetate and chromatographed on silica. Elution with ethyl acetate–light petroleum (1:1) gave ent-19-*hydroxybeyeran*-16-*one* (**17**) (15 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 240–241 °C (Found: C, 74.9; H, 10.5. $C_{20}H_{32}O_2 \cdot H_2O$ requires C, 74.5; H, 10.6%); ν_{max} 3 440 and 1 740 cm^{-1}; δ 0.88 (3 H, s, 20-H_3), 1.00 (3 H, s, 18-H_3), 1.03 (3 H, s, 17-H_3), 2.12 (1 H, d, *J* 18.6 Hz, 15-Hβ), 2.54 (1 H, dd, *J*

18.6 and 1.7 Hz, 15-Hα), 3.43 (1 H, dd, *J* 10.9 and 1.0 Hz, 19-H), and 3.74 (1 H, d, *J* 10.9 Hz, 19-H).

Deoxygenation of the Epoxides.—(*a*) Tungsten(VI) chloride (111 mg; 2.3 ml of a 4.8% solution in diethyl ether) was added to a Schlenk tube (dried and kept under nitrogen) which was immersed in a solid CO_2–acetone-bath. Butyl-lithium (0.2 ml of a 1.6M solution in hexane) was added and the mixture was stirred for 10 min, then allowed to warm to room temperature, and methyl *ent*-16,17-epoxy-13-hydroxykauran-19-oate (50 mg) was added. After 2 h, the mixture was poured into 3M-sodium hydroxide (50 ml). The product was recovered in diethyl ether and chromatographed on silica to afford steviol methyl ester (20 mg), identified by its IR and NMR spectra.

(*b*) Tungsten(VI) chloride (222 mg; 4.6 ml of a 4.8% solution in diethyl ether) was added to a Schlenk tube which was immersed in a solid CO_2–acetone-bath. Butyl-lithium (0.4 ml of a 1.6M solution in hexane) was added and the mixture was stirred for 10 min. Methyl *ent*-15β,16β-epoxy-13-hydroxykauran-19-oate (**16**) (86 mg) was added at room temperature and the mixture was stirred for a further 2 h, then was poured into 3M-sodium hydroxide (50 ml). The product was extracted with diethyl ether and chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave *methyl* ent-14β-*hydroxy*-16-*oxobeyeran*-19-*oate* (**18**) (53 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 243–244 °C (Found: C, 72.1; H, 9.3. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.2%); ν_{max} 3 487, 1 745, and 1 697 cm^{-1}; δ 0.71 (3 H, s, 20-H_3), 1.04 (3 H, s, 17-H_3), 1.20 (3 H, s, 18-H_3), 2.15 (1 H, d, *J* 18.6 Hz, 15-Hβ), 2.19 (1 H, br d, *J* 12.2 Hz, 12-Hα), 2.52 (1 H, dd, *J* 18.6 and 1.7 Hz, 15-Hα), 3.38 (1 H, d, *J* 1.6 Hz, 14-Hβ, and 3.64 (3 H, s, OMe).

ent-16,17-*Epoxy*-13,15β-*dihydroxykauran*-19-*oic Acid* (**19**).—A solution of *ent*-13,15β-dihydroxykaur-16-en-19-oic acid (**10**) (220 mg) in chloroform (50 ml) was treated with MCPBA (200 mg) at room temperature for 24 h. The peracid was destroyed with aq. sodium hydrogen sulphite, the solvent was evaporated off, and the residue was chromatographed on silica. Elution with ethyl acetate–light petroleum–acetic acid (80:29:1) gave ent-16,17-*epoxy*-13,15β-*dihydroxykauran*-19-*oic acid* (**19**) (180 mg), which crystallized from acetone–light petroleum as needles, m.p. 292–294 °C (Found: C, 64.7; H, 8.7. $C_{20}H_{30}O_5 \cdot H_2O$ requires C, 65.2; H, 8.6%); ν_{max} 3 500br and 1 697 cm^{-1}; δ 0.97 (3 H, s, 20-H_3) 1.25 (3 H, s, 18-H_3), 3.05 and 3.10 (each 1 H, d, *J* 4.6 Hz, 17-H_2), and 3.50 (1 H, d, *J* 1.1 Hz, 15-Hβ).

Reaction of ent-16,17-*Epoxy*-13,15β-*dihydroxykauran*-19-*oic Acid* (**19**) *with Hydrobromic Acid.*—The dihydroxy epoxide (**19**) (150 mg) was suspended in 48% hydrobromic acid (20 ml) and the mixture was stirred for 2 h, then diluted with water (100 ml), and the product was recovered in ethyl acetate. The solvent was evaporated off and the residue was esterified with ethereal diazomethane and the product was chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave *methyl* ent-17-*bromo*-13,15β,16β-*trihydroxykauran*-19-*oate* (**20**) (120 mg), m.p. 176 °C (Found: C, 56.9; H, 7.5. $C_{21}H_{33}BrO_5$ requires C, 56.6; H, 7.5%); ν_{max} 3 509, 3 456, 3 305br, and 1 728 cm^{-1}; δ 0.78 (3 H, s, 20-H_3), 1.14 (3 H, s, 18-H_3), 3.60 (3 H, s, OMe), 3.61 (2 H, s, 17-H_2), 4.14 (1 H, s, 15-Hβ).

Crystal Structure Determination of Compound (**20**).—Crystal data: $C_{21}H_{33}BrO_5$, M = 445.4, monoclinic, space group *C*2, a = 39.102(7), b = 7.466(2), c = 29.625(7) Å, β = 104.90(2)°, V = 8 358.2 Å^3, Z = 16, D_c = 1.42 g cm^{-3}, $F(000)$ = 3 744, monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 19.7 cm^{-1}.

A crystal of size *ca.* 0.6 × 0.4 × 0.2 mm was mounted on an Enraf-Nonius CAD4 diffractometer operating in the θ–2θ mode, Δθ = (0.6 + 0.35 tan θ)°, with a maximum scan time of 1 min. 5 589 Reflections were measured for 2 < θ < 22°, $+h, +k, \pm l$. 3 196 Reflections with $|F^2| > 3\sigma(F^2)$ were used in the refinement where $\sigma(F^2) = [\sigma^2(I) + (0.04\ I)^2]^{\frac{1}{2}}/L_p$. The structure was solved using the direct methods routines of SHELXS-86 which revealed the location of 35 atoms, and the remaining non-hydrogen atoms of the four independent molecules were located on successive electron-density maps. Refinement was by full-matrix least-squares with only the Br atoms anisotropic. Hydrogen atoms were omitted. The weighting scheme was $w = 1/\sigma^2(F)$ and the final residuals were R = 0.066, R' = 0.071 (R = 0.070, R' = 0.075 for the opposite absolute structure). Programs from the Enraf-Nonius SDP-Plus package were run on a microVAX II computer. The final atomic co-ordinates are given in the Table.*

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* *Supplementary data* (see 'Instructions for Authors, section 5.6.3, in the January issue). The intramolecular distances, bond angles, torsional angles, and temperature factors have been deposited with the Cambridge Crystallographic Data Centre.

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