# *ent*-Kaurene Diterpenoids from *Solenostoma triste* (Nees) K. Müll (Hepaticae)

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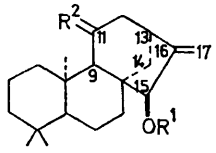
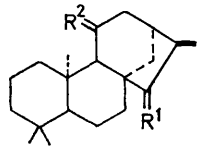
Four new 11β-hydroxylated *ent*-kaurene derivatives have been isolated from the liverwort *Solenostoma triste* (Nees) K. Mull.

FROM the chloroform extract of the liverwort *Solenostoma triste* (Nees) K. Müll, collected in the West of Scotland, we have isolated four related tetracyclic diterpenoids. From chemical and spectroscopic evidence these have been shown to be the *ent*-kaurene derivatives (1)—(4).

The major component of the extract was the hydroxy-acetate (1). The n.m.r. spectrum had signals for three tertiary methyl groups, a secondary acetate [τ 4·72 (t, *J* 3 Hz, H-15)], a secondary hydroxy-group [τ 6·20 (m, $W_{\frac{1}{2}}$ 9 Hz, H-11, after $D_2O$ exchange)], and an exocyclic methylene group (τ 5·07 and 4·88), suggesting a diterpenoid skeleton of the kaurene or 13β-kaurene type. Decoupling experiments confirmed the relative positioning of the secondary acetate and exocyclic methylene groups in ring D. Irradiation at the centre frequency of a multiplet at τ 7·28 (H-13) led to a simplification of the exocyclic methylene signals, which collapsed to doublets (*J* 2 and 3 Hz, respectively) on removal of a small allylic coupling. The carbinol proton (H-11) and the secondary acetate proton (H-15) were unaffected. Irradiation at the frequency of one of the methylene protons (τ 5·07) caused the secondary acetate signal (τ 4·72) to collapse to a doublet (*J* 3 Hz).



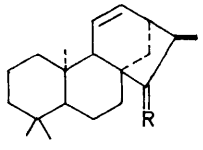


| | $R^1$ | $R^2$ |
|---|---|---|
| (1) | Ac | H,β-OH |
| (4) | H | H,β-OH |
| (5) | Ac | O |
| (6) | Ac | H,β-OAc |
| (7) | Ac | H,β-OTs |

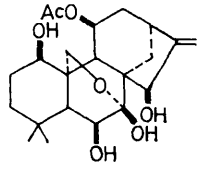
| | $R^1$ | $R^2$ |
|---|---|---|
| (2) | O | H,β-OH |
| (3) | O | H,β-OH 16,17-didehydro |
| (8) | H,β-OH | $H_2$ 16,17-didehydro |
| (11) | H,β-OH | $H_2$ |
| (14) | O | $H_2$ |

Jones oxidation of the hydroxy-acetate (1) gave the keto-acetate (5) [$\nu_{max.}$ ($CCl_4$) 1700 $cm^{-1}$ (cyclohexanone)]. Acetylation of (1) with acetic anhydride in pyridine was slow at room temperature but accelerated on gentle heating to yield the crystalline diacetate (6). Removal of the acetate functions with lithium aluminium hydride afforded the diol (4), identical with one of the natural products from the extract (see later).

To determine the nature of the skeleton of the hydroxy-acetate (1) it was decided to remove the secondary hydroxy-function. Tosylation with tosyl chloride in pyridine was extremely slow at room temperature, but despite this a small amount of the desired tosylate (7) was isolated as a gum. When this was treated with lithium aluminium hydride the product was not the expected deoxy-compound (8) but the diene (9). The latter was obtained in higher yield by heating the hydroxy-acetate (1) with tosyl chloride in pyridine followed by removal of the acetate system of the intermediate acetoxy-diene (10) with lithium aluminium hydride. Evidence for the assignment of the *cis*-disubstituted double bond of the diene to the 11,12-position was again derived from decoupling studies. The prominent features of the n.m.r. spectrum of compound (9) were τ 7·17 (m, H-13), 5·20 and 5·14 (d, *J* 3 Hz and broad s, respectively, exocyclic $CH_2$), 4·50 [dd, *AB*MX, H-11, $J_{BA}$ (obs) 10, $J_{BX}$ (obs) 4, $J_{BM}$ (obs) 0 Hz], and 3·98br [t, *A*BMX, H-12, $J_{AB}$ (obs) 10, $J_{AM}$ (obs) 8, $J_{AX}$ (obs) 2 Hz]. Irradiation at τ 7·17 (H-13) removed a small allylic coupling to the exocyclic methylene protons and collapsed the diffuse triplet at τ 3·98 (H-12) to a diffuse doublet (*J* 10 Hz). Similarly, irradiation at a broad singlet at τ 8·09 (H-9) left H-11 as a clean doublet [one leg of an AB system, *J*(obs) 10 Hz] and indicated the virtual absence of allylic coupling between H-11 and H-13. These results unequivocally place the double bond at the 11,12-position and hence the original hydroxy-group must be either at C-11 or C-12.



(9) R = H,β-OH, 16,17-didehydro
(10) R = H,β-OAc, 16,17-didehydro
(12) R = O



(13)

The diene (9) was hydrogenated over 10% palladium–charcoal for 20 min. The product was not the expected tetrahydro-derivative (11) but, instead, the ketone (12), $\nu_{max.}$ ($CCl_4$) 1740 $cm^{-1}$ (cyclopentanone), τ 8·96 (d, *J* 6 Hz, secondary Me). The n.m.r. spectrum clearly indicated the loss of the exocyclic methylene group with retention of the 11,12-double bond. It was obvious that, under the hydrogenation conditions, the diene had undergone a ready garryfoline–cuauchichicine rearrangement.[1] The same rearrangement was observed with the corresponding 11-hydroxy-derivative (4) (see later). Normally this reaction affects 15β-hydroxy-kaurenes and requires mineral acid.[1] The reason for its occurrence under hydrogenation conditions remains obscure. Subsequent to our observations another

[1] M. F. Barnes and J. MacMillan, *J. Chem. Soc.* (*C*), 1967, 361.

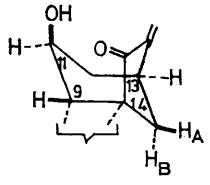
example has been reported.[2] Thus sodoponin (13) is transformed into the corresponding ketone on hydrogenation. This reaction is stereospecific and defines the stereochemistry of the product (12) as shown (16β-Me).

Further hydrogenation of compound (12) over 10% palladium–charcoal for 48 h furnished the known[1] (16*R*)-*ent*-kauran-15-one (14). This transformation of the hydroxy-acetate (1) into (16*R*)-*ent*-kauran-15-one establishes the skeleton, the absolute configuration, and the position and stereochemistry (15β) of the acetate function in the former. The position and configuration of the secondary hydroxy-group remain to be settled.

It is convenient at this stage to consider the other naturally occurring compounds. Chromatography of the more polar fractions of the extract afforded a mixture of two compounds of similar polarity. These were separated on silver nitrate plates. The more polar compound was the diol (4), identical with the diol prepared from the hydroxy-acetate (1). The less polar compound was the hydroxy-ketone (2), identified by comparison with the product of catalytic hydrogenation of the diol (4) (which underwent a garryfoline–cuauchichicine rearrangement).

The most polar compound from the extract was the unsaturated hydroxy-ketone (3). This was converted into the diol (4) by lithium aluminium hydride reduction. Thus the position and configuration of the secondary alcohol are the same in all four natural products. A closer examination of the n.m.r. spectra of these compounds, together with decoupling experiments and the use of benzene-[3] and Eu(dpm)$_3$-[4]induced shifts allowed us to solve these two remaining problems.

A doublet at approximately τ 7·6 was visible in the spectra of several compounds including the keto-acetate (5) and the unsaturated hydroxy-ketone (3). This doublet, one half of an AB quartet ($J_{AB}$ 12 Hz), was assigned to one of the C-14 bridge protons, $H_B$ in




(15)

structure (15) [≡ (3)]. The other H-14 ($H_A$) resonated at τ *ca.* 8·5 but the signal was hidden in the methylene envelope. Irradiation at the frequency of $H_A$ in the unsaturated ketone (15) collapsed the $H_B$ signal (τ 7·63) to a singlet and simultaneously reduced the width of the multiplet at τ 6·90 (H-13) from $W_{\frac{1}{2}}$ 12 to 7 Hz. The carbinol proton (H-11) was unaffected. Irradiation at the frequency of H-13 sharpened the H-14 ($H_B$) doublet slightly, caused a change in the spectrum at τ 8·6 ($H_A$) and had no effect on the exocyclic methylene signals, which were sharp singlets, or that of the carbinol proton (H-11). Fieser models show that the torsion angle between H-13 and $H_A$ is *ca.* 40° and that between H-13 and $H_B$ is *ca.* 80—90°, irrespective of ring c being in a boat or a chair conformation. This requires coupling constants of *ca.* 5 and 0 Hz, respectively, in good agreement with the observed values.

Thus H-13 couples with only one of the bridge (C-14) protons and to an insignificant extent with the exocyclic methylene protons. To account for the remaining coupling ($W_{\frac{1}{2}}$ 7 Hz) there must be vicinal coupling with other protons. Since there is no coupling with the carbinol proton (H-11) at τ 5·90 there must be a methylene group at C-12. Hence the hydroxy-group must be attached to C-11.

This conclusion was reinforced by an examination of the Eu(dpm)$_3$-shifted spectrum of the system (15). With 0·57 mol. equiv. of Eu(dpm)$_3$ the signals for H-9, H-12 (α and β), and $H_A$-14 were clearly visible. Irradiation at the frequency of H-11 (τ −0·84) caused a change in the resonance for H-12α (τ 5·78) but had little effect on H-9 (τ 3·13) or H-12β (τ 4·02). Irradiation at the latter frequency reduced the H-12α signal to a broad singlet by removal of the geminal coupling ($J$ 14 Hz) and also removed a small coupling ($J$ 3 Hz) from H-13 (τ 5·24). Subsequent irradiation at the frequency of H-13 resulted in the loss of small couplings from the C-12 protons and considerable sharpening of the diffuse doublet due to $H_A$-14 (τ 6·97). In the reverse experiment decoupling at $H_A$-14 reduced H-13 to a broad singlet ($W_{\frac{1}{2}}$ 7 Hz), collapsed the $H_B$-14 doublet (τ 5·88) to a singlet, and sharpened the H-9 signal slightly by removal of a small long range W coupling.

In addition to confirming the presence of a hydroxy-group at C-11 these results allow us to assign the configuration of the hydroxy-group and the probable conformation of ring c in system (15). With an 11β-hydroxy-group and ring c in a flattened chair conformation there is good agreement between the observed $J$ values and those calculated from Fieser models. The magnitude of the Eu(dpm)$_3$ shifts is also consistent with this conclusion. Thus, relative to a carbinol proton shift of 6 p.p.m., the signals for H-9 and H-12β, which are both equatorial and *cis* to the 11β-hydroxy-group, move downfield by *ca.* 5 p.p.m., that for H-12α moves by 3 p.p.m., and the exocyclic methylene signals move by 1·7 and 1·1 p.p.m., respectively. One methyl group (C-10 Me) is deshielded by 1 p.p.m. whereas the other two are virtually unaffected. At this molar ratio of Eu(dpm)$_3$ a much larger shift of the C-10 methyl group would be expected from an 11α-hydroxy-group.

The conformation of ring c in the keto-acetate (5) also appears to be a chair. Addition of benzene to a solution of compound (5) in [$^2$H]chloroform caused the signal for H-9 to move from under the acetate resonance at τ 7·88. This signal, a broadened singlet showed

[2] E. Fujita, T. Fujita, M. Taoka, H. Katamaya, and M. Shibuya, *Tetrahedron Letters*, 1970, 421.

[3] J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379; D. H. Williams and N. S. Bhacca, *Tetrahedron*, 1965, **21**, 2021.

[4] J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

long-range coupling with $H_A$-14 (τ 8·60). Irradiation at τ 8·60 caused it to sharpen and simultaneously collapsed the $H_B$-14 doublet (τ 7·60) to a singlet and sharpened the H-13 signal. The W geometry between $H_A$-14 and H-9, necessary for this long-range coupling, is only possible if ring C of the keto-acetate (5) is in a chair conformation.

A number of 11-oxygenated kaurenoid derivatives have already been reported.[2,5-8] In sodoponin (13) [2] ring C is in a boat conformation.

## EXPERIMENTAL

*Extraction.*—The liverwort *S. triste* (900 g) collected in the Renfrewshire hills, was dried, powdered, and extracted (Soxhlet) with chloroform. The crude extract (22 g) was initially chromatographed over alumina (grade H, deactivated). Subsequent separation and purification by preparative t.l.c. afforded four closely related diterpenoids. ent-11α-*Hydroxykauren*-15α-*yl acetate* (1) (450 mg) crystallised from methanol as needles, m.p. 118—120°, $[\alpha]_D$ −89°; $\nu_{max.}$ 3590, 1750, and 1660 cm$^{-1}$; *m/e* 346; τ 9·10, 9·04, and 8·99 (tertiary Me), 7·75 (Ac), 7·28 (m, H-13), 6·20 (m, H-11), 5·07 and 4·88 (m, $CH_2$=), and 4·72 [t, *J*(obs) 3 Hz, H-15] (Found: C, 75·75; H, 9·65. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%). (16R)-ent-11α-*Hydroxykauran*-15-*one* (2) (220 mg) was obtained from ethanol as needles, m.p. 186—188°, $[\alpha]_D$ −85°; $\nu_{max.}$ 3615 and 1735 cm$^{-1}$; τ 9·24, 9·17, and 9·06 (tertiary Me), 8·79 (d, *J* 6 Hz, secondary Me), and 6·09br (d, *J* 4 Hz, H-11) (Found: $M^+$, 304·2399. $C_{20}H_{32}O_2$ requires *M*, 304·2402). ent-*Kaurene*-11α,15α-*diol* (4) (180 mg) crystallised as needles (from ethanol), m.p. 192—194°, $[\alpha]_D$ −62°; $\nu_{max.}$ 3605 and 3480 cm$^{-1}$; τ 9·19, 9·12, and 9·06 (tertiary Me), 7·40 (m, H-13), 6·28 (m, H-11), 6·02br (d, H-15), and 5·02 and 4·92 (each br s, $CH_2$=) (Found: $M^+$, 304·2402. $C_{20}H_{32}O_2$ requires *M*, 304·2402). Recrystallisation from methanol furnished ent-11α-*hydroxykauren*-15-*one* (3) (150 mg) as needles, m.p. 121—124°, $[\alpha]_D$ −118°; $\nu_{max.}$ 3608, 3450, 1730, and 1650 cm$^{-1}$; $\lambda_{max.}$ 238 nm (ε 7100); τ 9·06, 8·98, and 8·87 (tertiary Me), 6·90 (m, H-13), 5·90br (d, *J* 4 Hz, H-11), and 4·71 and 4·11 (s, $CH_2$=) (Found: $M^+$ 302·2187. $C_{20}H_{30}O_2$ requires *M*, 302·2245).

ent-11-*Oxokauren*-15α-*yl Acetate* (5).—The hydroxy-acetate (1) (15 mg) in acetone (3 ml) was treated with an excess of Jones reagent at 0°. Preparative t.l.c. gave the *keto-acetate* (5) (7 mg) as needles, m.p. 120—121° (from methanol); $\nu_{max.}$ 1730 and 1698 cm$^{-1}$; τ 9·16, 9·11, and 8·94 (tertiary Me), 7·88 (Ac), 7·10 (m, H-13), 5·14 and 5·04 (m, $CH_2$=), and 4·86 (m, H-15) (Found: $M^+$, 344·2339. $C_{22}H_{32}O_3$ requires *M*, 344·2351).

ent-*Kaurene*-11α,15α-*diyl Diacetate* (6).—The hydroxy-acetate (1) (10 mg) was heated on a steam-bath for 6 h in dry pyridine (0·5 ml) and acetic anhydride (0·5 ml). Preparative t.l.c. and crystallisation from methanol afforded the *diacetate* (6) (9 mg) as fine needles, m.p. 156—159°; τ 9·18, 9·12, and 9·01 (tertiary Me), 8·12 and 7·86 (2 × Ac), 7·38 (m, H-13), 5·23 and 5·15 (br, s, $CH_2$=), 5·03 [q, *J*(obs) 2, 4 Hz, H-11], and 4·88 [t, *J*(obs) 2 Hz, H-15] (Found: $M^+$, 388·2573. $C_{24}H_{36}O_4$ requires *M*, 388·2613).

*Hydride Reduction of Compounds* (1) *and* (3).—The hydroxy-acetate (1) (18 mg) in dry ether (3 ml) was treated with excess of lithium aluminium hydride for 30 min. Crystallisation of the crude product afforded the diol (4) (12 mg) identical (m.p. and mixed m.p., t.l.c., n.m.r.) with natural material.

Similar reduction of the unsaturated hydroxy-ketone (3) (18 mg) also gave the diol (4) (8 mg), identical with natural material.

*Catalytic Reduction of the Diol* (4).—The diol (4) (10 mg) in ethyl acetate was stirred under hydrogen with 10% palladium–charcoal for 30 min. The product, which crystallised from ethanol as needles, was the hydroxy-ketone (2) (9 mg), m.p. 186—188°, identical with natural material.

ent-*Kaurene*-11α,15α-*diyl* 11-*Tosylate* 15-*Acetate* (7).—The hydroxy-acetate (1) (25 mg) was left with toluene-*p*-sulphonyl chloride (30 mg) in pyridine (0·50 ml) at room temperature for 2 weeks. The *tosylate* (7) (5 mg) was separated from unchanged starting material by preparative t.l.c. and was obtained as a gum, τ 9·10, 9·04, and 8·97 (tertiary Me), 7·92 (Ac), 7·51 (aromatic Me), 5·20 (m, H-11), 5·13 and 5·04 (m, $CH_2$=), 4·82 (m, H-15), and 2·7 and 2·24 (aromatic $A_2B_2$ system).

*Reduction of the Tosylate* (7).—The tosylate (7) was refluxed overnight in the presence of excess of lithium aluminium hydride in ether. The product was the non-crystalline ent-*kaura*-11,16-*dien*-15α-*ol* (9); $\nu_{max.}$ 3610 cm$^{-1}$; τ 9·14, 9·07, and 9·00 (tertiary Me), 7·17 (m, H-13), 6·14br (s, H-15), 5·20 and 5·14 (d, *J* 3 Hz, and s, respectively, $CH_2$=), 4·50 (dd, *ABMX*, H-11, $J_{BA}$ 10, $J_{BX}$ 4, $J_{BM}$ 0 Hz), 3·98br (t, *ABMX*, H-12, $J_{AB}$ 10, $J_{AM}$ 8, $J_{AX}$ 2 Hz) Found: $M^+$, 286·2315. $C_{20}H_{30}O$ requires *M*, 286·2297).

The diene was obtained in much higher yield by heating the hydroxy-acetate (1) with tosyl chloride in pyridine followed by reduction of the intermediate acetoxy-diene (10) with lithium aluminium hydride.

*Catalytic Hydrogenation of the Diene* (9).—The diene (9) (8 mg) in ethyl acetate (10 ml) was stirred with 10% palladium–charcoal in a hydrogen atmosphere for 30 min. The crude product was crystallised from methanol to give (16R)-ent-*kaur*-11-*en*-15-*one* (12) (8 mg) as fine needles, m.p. 124—125°; $\nu_{max.}$ 1740 and 1660 cm$^{-1}$; τ 9·21, 9·13, and 9·07 (tertiary Me), 8·96 (d, secondary Me), 4·43 (dd, *ABMX*, H-11), and 3·97br (t, *ABMX*, H-12) (Found: *M*, 286·2305. $C_{20}H_{30}O$ requires *M*, 286·2297).

(16R)-ent-*Kauran*-15-*one* (14).—The ketone (12) (6 mg) in ethyl acetate (10 ml) was stirred with 10% palladium–charcoal in a hydrogen atmosphere for 2 days. Filtration and removal of solvent yielded (16*R*)-*ent*-kauran-15-one (14) (6 mg), which crystallised from methanol as fine needles, m.p. 147—149°, $[\alpha]_D$ −87° (lit.,[1] m.p. 150°, $[\alpha]_D$ −81°); $\nu_{max.}$ 1735 cm$^{-1}$; τ 9·20 and 9·15 (6H) (tertiary Me), 8·91 (d, *J* 6 Hz, secondary Me) (Found: $M^+$, 288·2450. Calc. for $C_{20}H_{32}O$: *M*, 288·2453).

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