*Tetrahedron*. Vol. 28, pp. 2521 to 2526. Pergamon Press 1972. Printed in Great Britain

# THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—XII[1]

## THE LABELLING AND FUNCTIONALIZATION OF THE KAURANOID 6β-POSITION

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(*Received in the UK* 19 *November* 1971; *accepted for publication* 28 *January* 1972)

**Abstract**—The stereochemistry of hydroboronation, osmylation and epoxidation of kaur-6,7-enes are described. The routes yield substances suitably functionalized for study as intermediates in gibberellin biosynthesis.

THE gibberellin plant growth hormones are derived from kauranoid diterpenes.[2] We and others have shown[3] that 7β-hydroxy-(-)-kaur-16-en-19-oic is a precursor of gibberellic acid and that on ring contraction to form the gibbane skeleton, a hydrogen atom migrates from the 6β-position to the extruded C-7. In order to study this biosynthesis we required methods of introducing a 6β-tritium atom and a 6β-hydroxyl group. In this paper we describe the solution of this and some relevant and hitherto undefined aspects of the chemistry of ring B of the kauranoid skeleton.

The dominant stereochemical feature of the chemistry of ring B of the kaurene skeleton is attack from the β-face of the molecule. In earlier parts of this series we showed that this applies to the hydride reduction of C-6[4] and C-7[5] carbonyl functions. Hence, although it was by no means certain, we anticipated that hydroboronation, epoxidation and *cis*-glycol formation from a $\Delta^6$-olefin would yield the 6β,7β- substitution pattern.

A reliable method of preparing the $\Delta^6$-olefin from the fungal metabolite, 7β-hydroxykaurenolide (**1**, R = β-OH, α-H) is as follows. Hydrogenolysis of 7-oxokaurenolide (**1**, R = O) with Ca in liquid $NH_3$ has consistently proved to be a difficult reaction.[6] Modification of the reaction conditions to use calcium amalgam or isopropylamine as solvent gave no reliable improvement. However the 6-deoxy-7-ketone (**2**, R = O, R′ = $CH_2$) is a by-product of the hydrolysis of 7α-hydroxykaurenolide (**1**, R = α-OH, β-H) with methanolic NaOH. This product arises by attack of the base on the β-C-7 hydrogen atom. By employing a large base, t-BuOK in t-BuOH, this reaction was favoured over the sterically more-hindered hydrolysis to afford, after methylation, an 88% yield of the 6-deoxy-7-ketone, 7α-Hydroxykaurenolide may be readily prepared in 75–80% overall yield by the oxidation of 7β-hydroxykaurenolide and reduction of 7-oxokaurenolide with $NaBH_4$.

Reduction of the 6-deoxy-7-ketone with $NaBH_4$ afforded the 7α-hydroxy compound (**2**, R = α-OH, R′ = $CH_2$). Ozonolysis gave a gummy nor-ketone which was converted to its toluene-*p*-sulphonate which as described previously afforded the $\Delta^6$-olefin (**3**, R = O) on refluxing with collidine.[7]

In order to protect the carbonyl group against reduction by borane and against possible exchange at C-15 under tritiating conditions, the C-16 ethylene ketal (**3**,

R = $\overset{O}{\underset{O}{|}}$]) was prepared. Both hydroboronation and tritio-hydroboronation gave a single alcohol. The protecting group was removed and the ester was hydrolysed to give the known 7β-hydroxy-16-oxo-17-norkauranoic acid (**4**, R = H, R′ = O).[5] No isomeric C-6 alcohol was detected. A Wittig reaction using NaH in DMSO as the base, permitted the re-introduction of the 17-methylene group (**4**, R = H, R′ = $CH_2$). This sequence affords a stereospecific method for labelling the kaurene skeleton on ring B.

Hydroxylation of the olefin with $OsO_4$ in pyridine gave the glycol (**5**, R = H, R′ = O), a compound which was described by Cross[7] after our work was completed. In agreement with his work, the coupling constants, $J_{5:6}$ and $J_{6:7}$, correspond to diaxial and axial:equatorial couplings. In further confirmation, the solvent shift data between $CDCl_3$ and $C_5D_5N$ for the diols are diagnostic of the ring B stereochemistry. Thus a 6α-

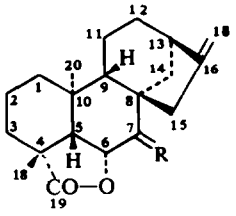
TABLE NMR SOLVENT SHIFT DATA FOR SOME 6,7-DISUBSTITUTED KAURENES

| Compound | Solvent | C-18 | C-20 |
|---|---|---|---|
| Methyl 6α,7β-dihydroxykaur-16-en-19-oate | $CDCl_3$ | 8·72 | 8·94 |
| | $C_5D_5N$ | 8·70 | 8·76 |
| Methyl 7β-acetoxy-6α-hydroxykaur-16-en-19-oate | $CDCl_3$ | 8·80 | 8·94 |
| | $C_5D_5N$ | 8·80 | 8·80 |
| Methyl 7β,18-diacetoxy-6α-hydroxykaur-16-en-19-oate | $CDCl_3$ | 5·72 | 8·92 |
| | $C_5D_5N$ | — | — |
| Methyl 6α,7α-dihydroxykaur-16-en-19-oate | $CDCl_3$ | 8·73 | 8·96 |
| | $C_5D_5N$ | 8·70 | 8·78 |
| Methyl 6β,7β-dihydroxy-16-oxo-17-norkauran-19-oate | $CDCl_3$ | 8·56 | 9·08 |
| | $C_5D_5N$ | 8·29 | 9·05 |

hydroxyl group produces a shift in the C-20 proton resonances between the two solvents and relatively little change in the C-18 proton resonances. On the other hand, the introduction of a 6β-hydroxyl group produces relatively little change in the C-20 proton resonances but a large change in the C-18 proton resonances.

Attempts to re-introduce the C-17 methylene by means of a Wittig reaction on the glycol proceeded in poor yield (1%). Hence in accord with its *cis* 6β,7β-stereochemistry, the diol was protected as its isopropylidene derivative (6, R = Me, R′ = O) prepared using 10% $H_2SO_4$ in acetone at 0°. This derivative rendered the compound more soluble in non-polar solvents and protected the axial:equatorial glycol against epimerization[8] or elimination under the highly basic conditions of the Wittig reaction. The NMR spectrum of the isopropylidene derivative was in accord with the hydroxylation pattern. Thus it showed $J_{5:6}$ 11 Hz and $J_{6:7}$ 6Hz corresponding to dihedral angles of approximately 150° and 40° respectively. This implies that ring B exists in a slightly distorted chair conformation in this compound. It also excludes the 6α,7α-stereochemistry for the glycol. The corresponding couplings in the parent glycol, where the constraint of the isopropylidene derivative is lacking, suggests that ring B then exists in a boat conformation. The Wittig reaction was then succesful and the C-17 methylene was introduced in 60% yield.[9] The C-19 esters are hindered and consequently hydrolysis required the use of dry LiI in collidine. The isopropylidene protecting group was then removed with methanolic 0·05 N HCl to afford the required 6β,7β-dihydroxy-(-)-kaur-16-en-19-oic

acid (5, R = H, R′ = $CH_2$). After this work was complete a similar approach to the glycol without the use of protecting groups, was described.[7] This system has also been prepared by micro-biological transformation.[10]



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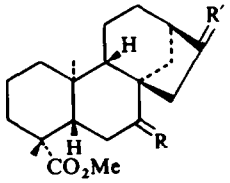

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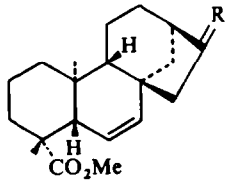

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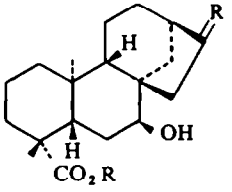

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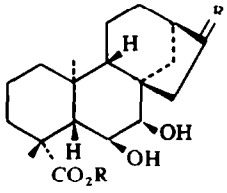

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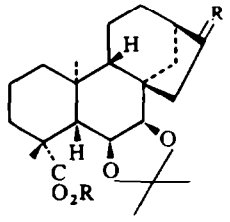

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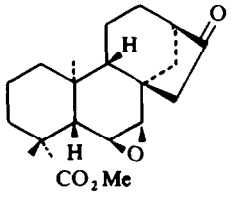

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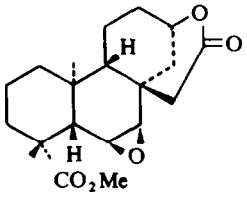

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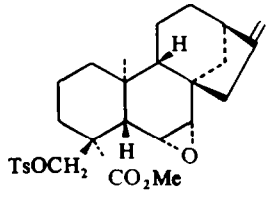

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Treatment of the olefin with m-chloroperbenzoic acid afforded two compounds. $C_{20}H_{28}O_4$ and $C_{20}H_{28}O_5$. The former (7) showed IR absorption at 1710 and 1750 $cm^{-1}$ and the latter showed IR at 1710 and 1725 $cm^{-1}$ suggesting that ring D had been opened to form a $\delta$-lactone(s). In support of this the NMR spectrum of this second compound contained an additional one-proton resonance at $\tau$ 5·20. The epoxide is assigned the β-stereochemistry on the basis of the coupling constant, $J_{5,6}$ 2 Hz, which corresponds to a dihedral angle of approximately 120°. Furthermore the 6α-proton resonance at $\tau$ 6·10 is clearly deshielded by the C-19 methoxycarbonyl group from the expected position of an epoxide resonance (the C-7 proton appears at 6·90) whilst the C-18 proton resonance appears at $\tau$ 8·63 showing the marked effect of an adjacent β-epoxide ring. The α-epoxide in the 7,18-dihydroxy-kaurenolide series, was prepared by the action of NaOMe on the 7β,18-ditoluene-*p*-sulphonate. This afforded methyl 6α,7α-epoxy-18-hydroxy-(−)-kaur-16-en-19-oate 18-toluene-*p*-sulphonate (9) by an internal nucleophilic displace-

ment of the axial 7β-toluene-*p*-sulphonate. In this case the C-6 proton and the C-7 proton resonate at τ 6·77 and 7·17 respectively.

## EXPERIMENTAL

General experimental details have been described previously.

*Methyl 7-oxokaur-16-en-19-oate.* Potassium metal (0·4 g) was dissolved in dry t-BuOH (50 ml). 7α-Hydroxykaurenolide (4·0 g) was added and the solution was refluxed under $N_2$ for 17 hr. After cautious acidification with dilute HCl, the keto-acid was recovered in EtOAc and methylated with $CH_2N_2$. The product was chromatographed on alumina. Elution with 2% EtOAc in light petroleum gave methyl 7-oxokaur-16-en-19-oate (2, R = O, R′ = $CH_2$) (3·2 g) m.p. 108–109° (lit.,[5] 110–112°), $\nu_{max}$ 1734, 1710 and 1666 $cm^{-1}$.

*Methyl 7α-hydroxy-16-oxo-17-norkauran-19-oate toluene-p-sulpnonate.* Methyl 7α-hydroxykaur-16-en-19-oate[4] (2·0 g) in glacial AcOH (50 ml) was treated with ozonised oxygen at 20° for 1 hr. After 1 hr Zn dust (10 g) was added and the solution stirred. The Zn was filtered and the mixture carefully treated with $NaHCO_3$ aq. The product was recovered in EtOAc to give a viscous gum (1·7 g) which did not crystallize. This gum was treated with toluene-*p*-sulphonyl chloride (1·5 g) in pyridine (15 ml) at room temperature for 14 hr. The solution was poured into water and after 1 hr, the product was recovered in EtOAc. Chromatography on silica gave, in the fractions eluted with light petroleum, methyl 7α-toluene-*p*-sulphonoxy-16-oxo-17-norkauran-19-oate (2, R = α-$OTs_A$ R′ = O) which crystallized from ether as plates, m.p. 168–170°, (lit.,[7] 169–172°). (Found: C, 66·5; H, 7·5. Calc. for $C_{27}H_{36}O_6S$ C, 66·4; H, 7·4%). $\nu_{max}$ 1720, 1600 $cm^{-1}$ τ 9·15 (3H, s), 9·01 (3H, s), 7·75 (3H, s), 6·38 (3H, s), 5·6 (1H, m), 2·62 (2H, d, *J* 8 Hz), 2·13 (2H, d, *J* 8 Hz).

*Methyl 16-oxo-17-norkaur-6-en-19-oate.* The above toluene-*p*-sulphonate (1·0 g) in dry collidine (20 ml) was heated under reflux for 5 hr. The collidine was distilled off under reduced pressure and the residue taken up in dil. HCl. The product was recovered in EtOAc and chromatographed on alumina. Elution with light petroleum gave methyl 16-oxo-17-norkaur-6-en-19-oate (3, R = O) (700 mg) which crystallized from light petroleum as prisms, m.p. 166–167°, (lit.,[7] 168–170°). (Found: C, 76·0; H, 8·9. Calc. for $C_{20}H_{28}O_3$ C, 75·9; H, 8·9%). $\nu_{max}$ 1747, 1732 and 730 $cm^{-1}$. τ 9·17 (3H, s), 8·78 (3H, s), 6·38 (3H, s), 4·5 (1H, q, $J_{6:7}$ 10·5 Hz, $J_{5:6}$ 3 Hz), 3·8 (1 H, q, $J_{6:7}$ 10·5 Hz, $J_{5:7}$ 2 Hz).

*Ketalization of Methyl 16-oxo-17-norkaur-6-en-19-oate.* The above ester (400 mg) in dry ethylene glycol (5 ml) and benzene (10 ml) containing toluene-*p*-sulphonic acid (10 mg) was heated under reflux in a Dean and Starke apparatus for 24 hr. The benzene was evaporated and the residue poured into water. The product was recovered in EtOAc. Methyl 16,16-ethylenedioxy-17-norkaur-6-en-19-oate (3, R = $<\!\!\begin{matrix}O\\O\end{matrix}]$) (378 mg) crystallized from 50% aqueous EtOH as plates, m.p. 115–116°. (Found: C, 73·1; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%). $\nu_{max}$ 1717, 725 $cm^{-1}$ τ 9·23 (3H, s), 8·78 (3H, s), 6·36 (3H, s), 6·12 (4H, m), 4·65 (1H, q, $J_{6:7}$ 10·0 Hz, $J_{5:6}$ 2·5Hz), 3·96 (1H, q, $J_{6:7\ 10\ Hz}$, $J_5$ 1·5 Hz).

*Methyl 16,16-ethylenedioxy-7β-hydroxy-17-norkauran-19-oate.* The above ethylene ketal (300 mg) in dry THF (5 ml) was treated with diborane generated externally from $BF_3.Et_2O$ (0·3 ml) and $NaBH_4$ (100 mg) in dry diglyme (10 ml). The borane adduct was hydrolysed with 2 N NaOH (2 ml) and $H_2O_2$ (0·5 ml). The solution was diluted with water and extracted with EtOAc. The solvent was evaporated and the product purified by prep. layer chromatography on silica to give methyl 16,16-ethylenedioxy-7β-hydroxy-17-norkauran-19-oate (4, R = Me, R′ = $<\!\!\begin{matrix}O\\O\end{matrix}]$) (175 mg) which crystallized from acetone as needles, m.p. 154–155°. (Found: C, 69·5; H, 8·7. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·05%). $\nu_{max}$ 3450, 1712 $cm^{-1}$ τ 9·10 (3H, s), 8·89 (3H, s), 6·41 (3H, s), 6·3 (1H, m), 6·19 (4H, m).

*Methyl 7β-hydroxy-16-oxo-17-norkauran-19-oate.* The hydroxy-ketal (100 mg) in acetone (3 ml) was treated with *p*-TsOH (10 mg) at room temperature for 1 hr. The product was purified by prep layer chromatography on silica to give methyl 7β-hydroxy-16-oxo-17-norkauran-19-oate (4, R = Me, R′ = O) (85 mg) which crystallized from acetone : light petroleum as needles, m.p. 194–195°. (Found: C, 71·9; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%). $\nu_{max}$ 3535, 1738, 1710 $cm^{-1}$ τ 9·10 (3H, s), 8·82 (3H, s), 6·37 (3H, s) 6·25 (1H, m).

*7β-Hydroxy-16-oxo-17-norkauran-19-oic acid.* The above methyl ester (80 mg) and LiI (400 mg) in dry collidine (5 ml) were heated under reflux for 1 hr. The collidine was removed *in vacuo* and the residue treated with dil. HCl. The product recovered in EtOAc, washed with water, $Na_2S_2O_3$ aq, dried and the solvent evaporated. The residue was purified by prep TLC to give 7β-hydroxy-16-oxo-17-norkauran-19-oic acid (4, R = H, R′ = O) (56 mg) which crystallized from EtOAc as plates, m.p. 238–240°, (lit.,[5] 239–241°).

7β-*Hydroxykaur*-16-*en*-19-*oic acid.* NaH (50% dispersion in oil) (30 mg) was dissolved in dry DMSO (5 (Found: C, 71·3; H, 8·9. Calc. for $C_{19}H_{28}O_4$: C, 71·2; H, 8·8%). The product was identified by its IR spectrum.

7β-*Hydroxykaur*-16-*en*-19-*oic acid.* NaH (50% dispersion in oil) (30 mg) was dissolved in dry DMSO (5 ml) under $N_2$ at 60°. Methyl triphenylphosphonium iodide (240 mg) in dry DMSO (1 ml) was added and the solution stirred at room temperature for 10 min. The above nor-ketone (50 mg) in dry DMSO (1 ml) was added and the mixture maintained at 50° for 17 hr. The mixture was treated with dil. HCl for 30 min and extracted with EtOAc. The EtOAc was then thoroughly extracted with 2 N NaOH. The extract was acidified and the organic product recovered in EtOAc and purified by prep TLC. 7β-Hydroxykaur-16-en-19-oic acid (**4**, R = H, R′ = $CH_2$) (36 mg) crystallized from ether : light petroleum as needles, m.p. 251–253°, (lit.,[5] 255–258°). The product showed identical IR spectrum to an authentic sample and gave no depression on m.m.p.

*Methyl* 6β,7β-*dihydroxy*-16-*oxo*-17-*norkauran*-19-*oate.* Methyl 16-oxo-17-norkaur-6-en-19-oate (500 mg) was treated with $OsO_4$ (500 mg) in pyridine (10 ml) for 3 days. Sodium metabisulphite (3 g) in pyridine : water (1 : 1) (40 ml) was added and after 1 hr, the product was recovered in EtOAc. After passing through a column of charcoal to remove traces of osmium salts, methyl 6β,7β-dihydroxy-16-oxo-17-norkauran-19-oate (**5**, R = Me, R′ = O) (320 mg) crystallized from ether as needles, m.p. 178–180° (lit.,[7] 180–181°). (Found: C, 68·6; H, 8·3. Calc. for $C_{20}H_{30}O_5$: C, 68·5; H, 8·6%). $\nu_{max}$ 3562, 1745, 1697 $cm^{-1}$ τ 9·09 (3H, s), 8·57 (3H, s), 6·25 (3H, s + 1H, m) 5·61 (1H, 1, $J_{5,6}$ 11 Hz, $J_{6,7}$ 2 Hz).

*Methyl* 6β,7β-*O-isopropylidene*-16-*oxo*-17-*norkauran*-19-*oate.* The above diol (300 mg) was treated with 10% $H_2SO_4$ in dry acetone (5 ml) at 0° for 3 hr. The mixture was cautiously poured into excess NaOH aq and the acetone removed under reduced pressure. The product was recovered in light petroleum and chromatographed on alumina to give *methyl* 6β,7β-O-*isopropylidene*-16-*oxo*-17-*norkauran*-19-*oate* (**6**, R = Me, R′ = O) (265 mg) which crystallized from light petroleum as needles, m.p. 151–152°. (Found: C, 70·9; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). $\nu_{max}$ 1710–1725 $cm^{-1}$ τ 9·12 (3H, s), 8·62 (6H, s), 8·55 (3H, s), 6·30 (3H, s), 6·01 (1H, d, $J_{6,7}$ 6 Hz), 4·88 (1H, q, $J_{5,6}$ 11 Hz., $J_{6,7}$ 6Hz).

*Methyl* 6β,7β-O-*isopropylidenekaur*-16-*ene*-19-*oate.* NaH (50% dispersion in oil) (40 mg) was dissolved in dry DMSO (1 ml) at 65°. Methyl triphenylphosphonium phosphonium iodide (180 mg) was added and the solution stirred at room temp for 10 min. The above norketone (150 mg) in DMSO (2 ml) was added and the mixture stirred at 65° for 1·5 hr. The product was recovered in n-pentane and chromatographed on alumina. *Methyl* 6β,7β-O-*isopropylidenekaur*-16-*ene*-19-*oate* (**6**, R = Me, R′ = $CH_2$) (93 mg) was purified by short path distillation and had m.p. 45–47°. (Found: C, 74·1; H, 9·1. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%). $\nu_{max}$ 1720, 1652 $cm.^{-1}$

6β,7β-O-*Isopropylidenekaur*-16-*ene*-19-*oic acid.* The product from the above reaction (80 mg) in dry collidine (4 ml) was heated under reflux for 1 hr with LiI (400 mg). The collidine was removed *in vacuo* and the product recovered in EtOAc. The extract was washed with dil HCl, water and dried. The solvent was evaporated. 6β,7β-O-*Isopropylidenekaur*-16-*ene*-19-*oic acid* (**6**, R = H, R′ = $CH_2$) (63 mg) crystallized from ether as plates, m.p. 224–225°. (Found: C, 74·5; H, 8·9. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%). $\nu_{max}$ 3200 (br.), 1707, 1657, 890 $cm^{-1}$.

6β,7β-*Dihydroxykaur*-16-*en*-19-*oic acid.* The above acid (50 mg) was heated in 50% aqueous methanolic 0·1 N HCl (5 ml) for 4 hr. MeOH was evaporated and the product recovered in EtOAc. 6β,7β-Dihydroxykaur-16-ene-19-oic acid (**5**, R = H, R′ = $CH_2$) (29 mg) crystallized from acetone as prisms, m.p. 234–236° (lit.,[7] 234–237°). (Found: C, 71·6; H, 8·9. Calc. for $C_{20}H_{30}O_4$: C, 71·8; H, 9·0%). $\nu_{max}$ 3550, 3400 (br.), 1680, 890 $cm^{-1}$.

*Epoxidation of methyl* 16-*oxo*-17-*norkaur*-6-*ene*-19-*oate.* The olefin (100 mg) in $CHCl_3$ (10 ml) was treated with *m*-chloroperbenzoic acid (190 mg) at 0° for 17 hr. The solution was washed with aqueous $FeSO_4$, dil. HCl, $NaHCO_3$ aq, water and dried. The product was purified by prep TLC in 20% EtOAc : light petroleum to give *methyl* 6β,7β-*epoxy*-16-*oxo*-17-*norkauran*-19-*oate* (7) (22 mg) which crystallized from acetone : light petroleum as plates, m.p. 186–187°. (Found: C, 72·4; H, 8·4. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%). $\nu_{max}$ 1750, 1710 $cm^{-1}$ τ 9·10 (3H, s), 8·63 (3H, s), 6·98 (1H, d, *J* 4Hz), 6·32 (3H, s), 6·10 (1H, q, *J* 4Hz and 2Hz). The *epoxy-lactone* (**8**) (36 mg) was a slower moving band which crystallized from acetone : light petroleum as needles, m.p. 198–200°. (Found: C, 68·9; H, 8·1. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%). $\nu_{max}$ 1725, 1710 $cm^{-1}$. τ 9·12 (3H, s), 8·64 (3H, s), 7·15 (1H, d, *J* 4Hz), 6·33 (3H, s), 6·05 (1H, q, *J* 4 and 2 Hz), 5·20 (1H, m).

*Methyl* 6α,7α-*epoxy*-18-*hydroxykaur*-16-*ene*-19-*oate toluene*-p-*sulphonate.* The 7,18-ditoluene-*p*-sulphonate of 7,18-dihydroxykaurenolide (250 mg) was heated with NaOMe (from Na 250 mg) in MeOH (10 ml) for 2 hr. The solution was cooled, acidified with excess dil HCl and the product recovered in EtOAc.

Chromatography on silica gave, in the fractions eluted with light petroleum, *methyl* 6α,7α-*epoxy*-18-*hydroxykaur*-16-*ene*-19-*oate* -18-*toluene*-p-*sulphonate* (9) which crystallized from light petroleum as needles, m.p. 156–158°. (Found: C, 67·3; H, 7·0. $C_{28}H_{36}O_6S$ requires C, 67·2; H, 7·25%). $\nu_{max}$ 1720, 1650, 1600 $cm^{-1}$ τ 9·00 (3H, s), 7·56 (3H, s), 7·17 (1H, d, *J* 4Hz), 6·77 (1H, d, *J* 4Hz), 6·63 (3H, s), 5·80 (2H, s), 5·15 (2H, s), 2·66 (2H, d, *J* 8 Hz), 2·13 (2H, d, *J* 8 Hz).

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