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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—IX[1]

THE PARTIAL SYNTHESIS OF 7β-HYDROXY-(−)-KAUR-16-EN-19-OIC ACID

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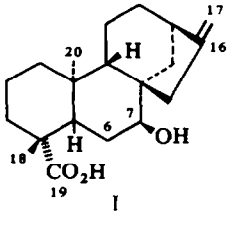
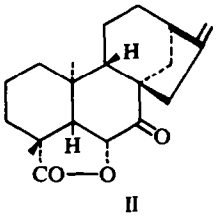
Abstract—A partial synthesis of 7β-hydroxy-(−)-kaur-16-en-19-oic acid from 7β-hydroxykaurenolide is described utilizing the Meerwein–Ponndorf reduction of 7-oxo-(−)-kaur-16-en-19-oic acid. The $NaBH_4$ reduction of some 7-oxo-16,17-dihydroxykauranes is described. The effect of different conformations of ring B on the NMR spectra of these diterpenes is noted.

BIOGENETIC reasoning suggested that 7β-hydroxy-(−)-kaur-16-en-19-oic acid (I) might occur in *Gibberella fujikuroi* and that it could intervene in the biosynthesis of the kaurenolides and the gibberellins. Thus 6α-hydroxylation of the acid would lead to the kaurenolides whilst 6β-hydroxylation would generate an equatorial leaving group and thus permit ring contraction and the formation of the gibbane skeleton by the extrusion of C-7. The acid would thus play a key role in the biosynthesis of the tetracyclic diterpenes. Radiochemical dilution analysis in our laboratories has established the presence of the acid in the mould whilst labelling experiments have confirmed its intervention in the biosynthesis. In order to carry out these experiments, a partial synthesis of 7β-hydroxy-(−)-kaur-16-en-19-oic acid was required. This we now report.



I



II

Reduction of 7-oxokaurenolide (II)[2] and 7-oxo-(−)-kaur-16-en-19-oic acid[1] with $NaBH_4$ leads to the formation of the corresponding 7α-alcohol, attack of the reagent arising from the less-hindered β-face of the molecule. However, Cross has reported[3] that reduction of 7-oxo-16α,17-dihydroxykaurenolide with $NaBH_4$ leads to the formation of the 7β-alcohol. 7-Oxo-(−)-kaur-16-en-19-oic acid was prepared by hydrogenolysis of 7-oxokaurenolide with calcium in refluxing (cf. 4) liquid ammonia. It was then converted to the 16α,17-glycol with OsO_4. The 16α-OH stereochemistry is assigned to this product by analogy with other similar hydroxylations in the kaurene series.[5] Reduction of the keto acid with $NaBH_4$ led to a trihydroxy acid.

However, a 7α-OH stereochemistry had to be assigned to this compound because of a correlation with the known 7α-hydroxy-(−)-kaur-16-en-19-oic acid.[4] Oxidation of the glycol with $NaIO_4$ gave the 17-nor-16-ketone. Reaction with the Wittig reagent from methyl triphenylphosphonium bromide then gave 7α-hydroxy-(−)-kaur-16-en-19-oic acid which was identical with samples obtained both from $NaBH_4$ and dissolving metal reduction of 7-oxo-(−)-kaur-16-en-19-oic acid.

In view of the difference between our results and that obtained by Cross, reduction of the 7-oxo-16α,17-dihydroxykauranolide was repeated. A trihydroxy-lactone was obtained which differed in solution spectra from that obtained by the direct hydroxylation of 7β-hydroxykaurenolide.[6] Oxidation of the trihydroxy lactone with $NaIO_4$ gave 7α-hydroxy-16-oxo-17-nor-kauranolide, i.e. reduction in our hands had followed the typical pattern and produced a 7α-alcohol.

Reduction of 7-oxo-(−)-kaur-16-en-19-oic acid with aluminium isopropoxide in isopropanol gave a mixture of the 7-epimeric alcohols which was separated by preparative TLC. The 7β-(axial)-epimer was, as expected, the faster moving isomer. Examination of the NMR spectra of the esters of the epimers revealed the equatorial proton resonance (in the axial alcohol) at lower field (τ 6·39) than its epimer (τ 6·64). The equatorial 7α-proton resonance corresponds closely to that found for sideridiol.[7] Furthermore, the coupling constants (3,3 and 5, 10·5 Hz respectively) suggest that ring B is closer to a chair form than the twisted boat form of the kaurenolides.[8]

A comparison of the position of various proton resonances between the nonlactonic kauranes and the lactonic kaurenolides reveals a number of differences that may be ascribed to this conformational change. Thus the chemical shift of the C-20 protons is essentially the same for both alcohols in the nonlactonic series, as has been found for the corresponding Me group in the 7-epimeric steroidal alcohols. This is in contrast to the kaurenolides in which the proximity of the 7α-OH group to the angular Me group produces a marked deshielding. Whereas the change from $CDCl_3$ to C_5D_5N as a solvent produces little effect in the non-lactonic series, this change has quite a pronounced effect on this resonance in 7α-hydroxykaurenolide—a feature associated with selective solvation. On the other hand the effect of the 7α-OH group is removed by acetylation. The 7-carbonyl function of methyl 7-oxo-(−)-kaur-16-en-19-oate produces a deshielding in marked contrast to the 7-carbonyl of 7-oxo-kaurenolide in which it produces a shielding effect. Evidently the angular Me group must be closer to the shielding cone of the 7-carbonyl in the keto lactones. The position and solvent shift of the C-6 and C-7 proton resonances appears to depend upon the nature of the C-18 substituent. Another feature of this probable change in shape of the molecule is shown by the C-17 olefinic proton resonances. In the presence of a 19-6α-lactone ring these appear as two distinct but complex resonances whilst in other derivatives they appear as a broad ($W_{\frac{1}{2}}$ c 6 Hz) singlet. Examination of molecular models suggests that the origin of the deformation of ring B in the lactones lies in the rigidity of the lactone ring permitting distortions of ring A, arising by interaction between the axial C-10 substituent and the axial substituent at C-4, to be relayed to ring (B).

Ozonolysis of the 7β-hydroxy acid gave a 17-nor-16-ketone which was suitable for labelling wtth the appropriate Wittig reagents. The results of the feeding experiments will be discussed later within the context of our work on gibberellin biosynthesis. Reduction of 7β-hydroxy-(−)-kaur-16-en-19-oate with LAH gave

TABLE 1. PROTON RESONANCES OF SOME 7-SUBSTITUTED KAURENES

	C.20		C.18		C.17		C.17		C.7		C.6	
	$CDCl_3$	C_5D_5N	$CDCl_3$	C_5D_5N	$CDCl_3$		C_5D_5N		$CDCl_3$	C_5D_5N	$CDCl_3$	C_5D_5N
Methyl (−)-kaur-16-en-19-oate	9·18	—	8·84	—	5·30		—		—		—	
Methyl 7α-hydroxy-(−)-kaur-16-en-19-oate	9·15	9·07	8·82	8·79	5·25		5·12		6·64	6·50	—	
Methyl 7β-hydroxy-(−)-kaur-16-en-19-oate	9·16	9·15	8·85	8·86	5·22		5·12		6·39	6·30	—	
Methyl 7-oxo-(−)-kaur-16-en-19-oate	8·95	—	8·82	—	5·18		—		—		—	
Kaurenolide	9·11	—	8·75	—	5·2	5·05	—		—		5·15	
7α-Hydroxykaurenolide	8·90	8·73	8·68	8·62	5·1	4·9	5·10	4·95	5·94	5·72	5·13	5·02
7β-Hydroxykaurenolide	9·13	9·14	8·72	8·78	5·2	5·1	5·10	4·95	5·65	5·38	5·20	5·03
7-Oxokaurenolide	9·28	9·30	8·70	8·72	5·1	4·9	5·07	4·94	—	—	5·10	4·75
7β,18-Dihydroxykaurenolide	9·08	9·05	6·32	6·1	5·2	5·05	5·30	5·05	5·65	5·50	5·32	4·85
18-Nor-7α-hydroxykaurenolide	8·90	8·72	—	—	5·15	5·03	5·10	4·95	5·95	5·92	5·32	5·36
18-Nor-7-oxokaurenolide	9·29		—	—	5·2	5·05	—	—	—	—	5·32	—
7α,16α:17-Trihydroxykauranolide	—	8·74	—	8·62	—		5·89		—		—	
7β:18-Diacetoxy-16-oxo-17-norkauranolide	9·00	—	5·85	—	—		—		4·18	—	5·31	—
7α-Acetoxy-16-oxo-17-norkauranolide	8·94	—	8·74	—	—		—		4·70	—	5·10	—
7β-Acetoxy-16-oxo-17-norkauranolide	9·00	—	8·72	—	—		—		4·20	—	5·38	—

7β,19-hydroxy-(−)-kaur-16-ene, although reduction of the sterically hindered 19-ester proceeded in only moderate yield.

EXPERIMENTAL

General details have been described previously.[6]

Hydroxylation of 7-oxo-(−)-kaur-16-en-19-oic acid. The acid (734 mg) in Et_2O (20 ml) was treated with OsO_4 (600 mg) in pyridine (6 ml) at room temp for 24 hr. Water (10 ml) and $NaHSO_3$ (2 g) were added and after ½ hr more water and dil HCl were added. The organic product was recovered in EtAc.

16α,17-Dihydroxy-7-oxo-(−)-kauran-19-oic acid (500 mg) crystallized from acetone as needles, m.p. 242–245°. (Found: C, 68·3; H, 8·6. $C_{20}H_{30}O_5$ requires: C, 68·5; H, 8·6%) ν_{max} 3450, 3280, 1698, 1690 cm^{-1}.

Reduction of 16α,17-dihydroxy-7-oxo-(−)-kauran-19-oic acid. The acid (480 mg) in dry MeOH (100 ml) was treated with $NaBH_4$ (800 mg) at room temp overnight. The MeOH was removed *in vacuo*, the residue acidified and the product recovered in EtAc. *7α,16α,17-Triaydroxy-(−)-kauran-19-oic acid* crystallized from EtAc as plates, m.p. 220–223. (Found: C, 68·2; H, 9·2. $C_{20}H_{32}O_5$ requires: C, 68·15; H, 9·15%) ν_{max} 3360, 1690 cm^{-1}.

Oxidation of the triol with sodium periodate. The triol (500 mg) in MeOH (50 ml) was treated with a soln of $NaIO_4$ (3·8 g) in water (10 ml) for 22 hr. The MeOH was removed *in vacuo*, the soln diluted with water and the product recovered in EtAc. *7α-Hydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid* crystallized from EtAc: light petroleum as needles, m.p. 296–299 . (Found: C, 68·7; H, 8·9. $C_{19}H_{28}O_4\frac{1}{2}H_2O$ requires: C, 69·3; H, 8·9%) ν_{max} 3430, 1730, 1690 cm^{-1}.

Wittig reaction of the 7α-hydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid. Methyl triphenyl phosphonium bromide (600 mg) in Et_2O (15 ml) was stirred with 1·6N BuLi (2 ml) for 6 hr under N_2. The above acid (200 mg) in THF (5 ml) was then added and stirring continued for 15 hr. Acetone (5 ml) was added and the solution refluxed for ½ hr. The solvents were evaporated, the residue dissolved in EtAc, washed with dil HCl, water and evaporated. Chromatography on SiO_2 gave in the fractions eluted with 10% EtAc: light petroleum, 7α-hydroxy-(−)-kaur-16-en-19-oic acid (48 mg) which crystallized from EtOH: light petroleum as prisms, m.p. 248–250° identical to material prepared previously.[4,9]

Reduction of 6α,16α,17-trihydroxy-7-oxo-(−)-kauran-19-oic acid 19 → 6α lactone. The lactone (250 mg) in dry MeOH (50 ml) was treated with $NaBH_4$ (357 mg) at room temp overnight. The soln was concentrated, acidified and the organic product (247 mg) recovered in EtAc. *6α,7α,16α,17-Tetrahydroxy-(−)-kauran-19-oic acid 19 → 6α lactone* crystallized from aqueous MeOH as needles, m.p. 223–226°. (Found: C, 68·3; H, 8·8. $C_{20}H_{30}O_5$ requires: C, 68·5; H, 8·6%) ν_{max} 3418, 3180 (br), 1775, 1758 cm^{-1}.

Oxidation of the lactone. The above lactone (220 mg) in MeOH (30 ml) was treated with a soln of $NaIO_4$ (1·2 g) in water (8 ml) overnight. The product was recovered in EtAc. *6α, 7α-Dihydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid 19 → lactone* crystallized from acetone: light petroleum as needles, m.p. 235–237·5, (Found: C, 71·7; H, 8·4. $C_{19}H_{26}O_4$ requires: C, 71·7; H, 8·2%) ν_{max} 3525, 1773, 1730 cm^{-1}, τ (in C_5D_5N) 8·73, 8·62, 5·72 (d. J, 8 Hz) 5·02 (q. J, 6 and 8 Hz).

Reduction of 7-oxo-(−)-kaur-16-en-19-oic acid. The acid (200 mg) in isopropanol (30 ml) was added to a soln of aluminium isopropoxide (10 g—this large excess proved necessary, smaller amounts resulted in recovery of starting material) in isopropanol (60 ml) and the mixture slowly distilled over 4 hr. The residue was diluted with 2N NaOH left for 10 min, and the pH adjusted to 4 with dil HCl, and the residue extracted with Et_2O. The residue (160 mg) was divided into two portions. Portion A (80 mg) was chromatographed on silica gel. Elution with 15% Et_2O: light petroleum gave *7β-hydroxy-(−)-kaur-16-en-19-oic acid* (30 mg) which crystallized from acetone: light petroleum as needles, m.p. 255–258°, (Found: C, 75·2; H, 9·15. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%) ν_{max} 3480, 1694, 890 cm^{-1}. Further elution gave the mixed 7-epimers which were separated by preparative TLC (EtAc: light petroleum, 1:1). The 7α-epimer was identical to the product of $NaBH_4$ reduction. Portion B (80 mg) was methylated with CH_2N_2 and chromatographed on neutral Al_2O_3 (Grade I). Elution with 80% benzene- light petroleum afforded *methyl 7β-hydroxy-(−)-kaur-16-en-19-oate* (37 mg) which crystallized from light petroleum as needles, m.p. 182–184°. (Found: C, 76·3; H, 9·98. $C_{21}H_{32}O_3$ requires: C, 75·9; H, 9·7%) ν_{max} 3600. 1706, 1660, 874 cm^{-1}. Elution with 10% EtAc: benzene gave methyl 7α-hydroxy-(−)-kaur-16-en-19-oate which crystallized from light petroleum as needles, m.p. 148–151° (lit.,[8,9] 145–146°, 149–151°).

Reduction of methyl 7β-hydroxy-(−)-kaur-16-en-19-oate. The ester (20 mg) in dry Et_2O (20 ml) was refluxed with LAH (40 mg) for 3 hr. EtAc was added, followed by dil HCl and the product recovered in EtAc. Preparative TLC gave *7β,19-dihydroxy-(−)-kaur-16-ene* (9 mg) which crystallized from acetone:

light petroleum as needles, m.p. 186–189°, (Found: C, 78·4; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%) ν_{max} 3420, 3325, 1656, and 872 cm^{-1}).

Ozonolysis of 7β-hydroxy-(−)-kaur-16-en-19-oic acid. Ozonized O_2 was passed through a soln of the hydroxy acid (40 mg) in glacial AcOH (10 ml) for 5 min. Zn dust was added and the pH adjusted to 7 with $NaHCO_3$aq. The nor-ketone was recovered in EtAc. *7β-Hydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid* (32 mg) crystallized from EtAc: light petroleum as plates, m.p. 239–241°, (Found: C, 70·8; H, 8·97. $C_{19}H_{28}O_4$ requires: C, 71·2; H, 8·8%) ν_{max} 3480, 1735, 1690 cm^{-1}.

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