The Formation of Unsaturated Diterpenoid Alcohols from 1,4-Glycols with *N,N*-Dimethylformamide Dimethyl Acetal

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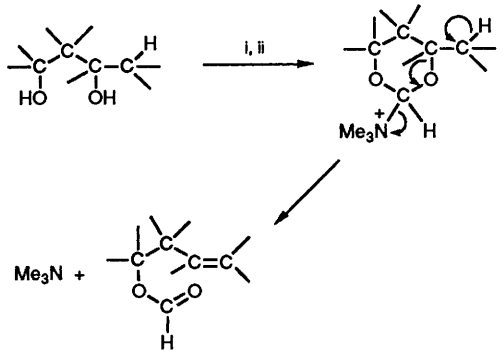
Treatment of the 1,4-diol *ent*-6β,19-dihydroxykaur-16-ene with DMFDMA, quaternization of the resultant formamido–acetal with methyl iodide, followed by elimination and hydrolysis of the resultant formate gives the *ent*-19-hydroxykaur-5,16- and -6,16-dienes. Labelling studies show that the reaction proceeds with the elimination of a hydrogen atom that is *trans* to the axial C-6 alcohol.

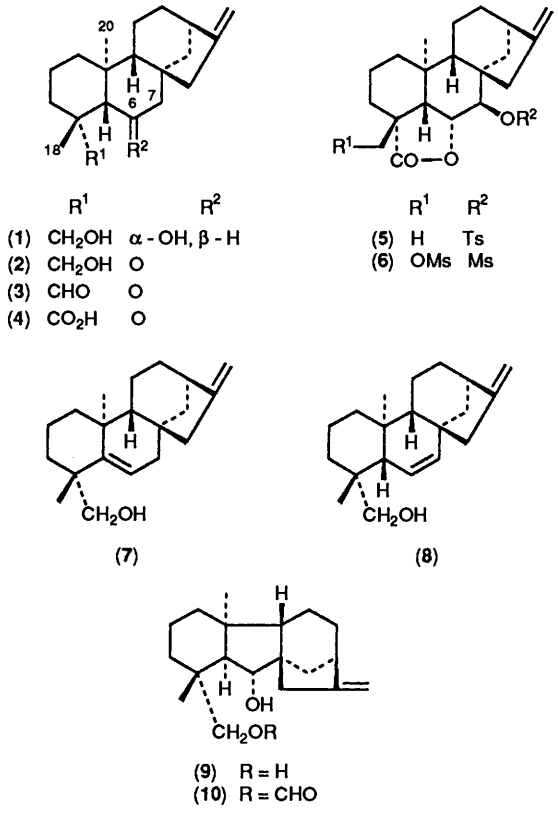
We have recently developed a method for the conversion of 1,3-glycols into unsaturated alcohols using *N,N*-dimethylformamide dimethyl acetal (DMFDMA).[1,†] Activation of the glycol proceeds through the formation of a cyclic *N,N*-dimethylformamido–acetal. Thermolysis of a quaternary salt of the formamido–acetal then leads to elimination of an axial alcohol provided it possesses a suitably disposed *trans* hydrogen atom. The product is the formate of the unsaturated alcohol (Scheme 1). We have now sought to extend this reaction to 1,4-diols.



Scheme 1. *Reagents:* i, DMFDMA; ii, MeI.

The divergence between the kaurenolide and gibberellin biosynthetic pathways in *Gibberella fujikuroi* occurs in the dehydrogenation of *ent*-kaur-16-en-19-oic acid to form *ent*-kaur-6,16-dien-19-oic acid and thence the kaurenolides.[2,3] On the other hand, hydroxylation at C-7 and ring contraction leads to the gibberellins. In order to examine the effect of inhibitors on the oxidative metabolism of *ent*-kaurene, we required a route to kaur-6-enes which might also be open to labelling. The 1,4-diol, *ent*-6β,19-dihydroxykaur-16-ene (**1**) has been obtained[4] by the lithium aluminium hydride reduction of the 7-toluene-*p*-sulphonate of 7-hydroxykaurenolide (**5**) and could consequently be labelled. It was therefore a suitable substrate with which to examine the DMFDMA reaction.

Treatment of *ent*-6β,19-dihydroxykaur-16-ene (**1**) with DMFDMA gave a cyclic formamido–acetal which was methylated with methyl iodide and then heated in toluene to afford a mixture of formates which were hydrolysed and the products separated by chromatography. The major component was *ent*-19-hydroxykaur-5,16-diene (**7**) in which the 6-H proton resonance appeared as a triplet (δ 5.58, *J* 4 Hz). The minor product was identified as the known[5] *ent*-19-hydroxykaur-6,16-diene (**8**) (δ 5.75, 6-H; 5.39, 7-H). Hence although the products were separable, the reaction disappointingly lacked the regiospecificity associated with the dehydration of the 1,3-diols.



	R^1	R^2
(1)	CH_2OH	α-OH, β-H
(2)	CH_2OH	O
(3)	CHO	O
(4)	CO_2H	O

	R^1	R^2
(5)	H	Ts
(6)	OMs	Ms

(7) (8)

(9) R = H
(10) R = CHO

However, the previous work[1] with the 1,3-diols had revealed a strict requirement for a diaxial relationship between the leaving component of the acetal and the proton that was eliminated. The stereochemical requirement was therefore examined by a selective deuteriation.

ent-[7-^{2}H,18-^{2}H,19-^{2}H$_2$]-6β,19-Dihydroxykaur-16-ene was prepared by the reduction of the 7,18-dimethanesulphonate of 7,18-dihydroxykaurenolide (**6**)[6] with lithium aluminium deuteride. In the undeuteriated compound the 7-H resonances (δ 1.70 and 1.74) and the magnitude of the 6-H:7-H coupling constants (2–3 Hz) were too close to permit a reliable assignment to be made of their stereochemistry. However, controlled oxidation of the diol (**1**) with chromium(VI) oxide gave the keto-alcohol (**2**)[4] and the keto–aldehyde (**3**).[4] In the

† 1,1-Dimethoxytrimethylamine.

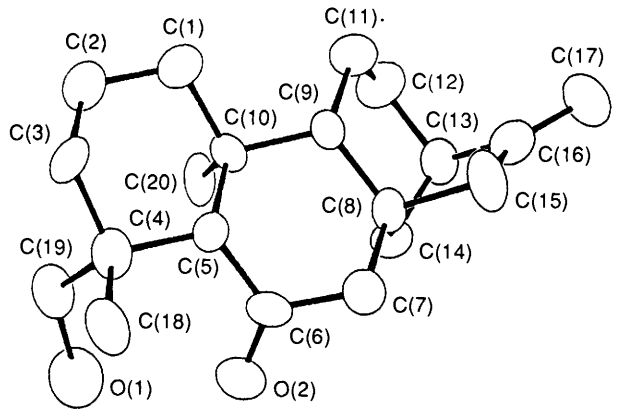


Figure. The crystal structure of *ent*-19-hydroxy-6-oxokaur-16-ene.

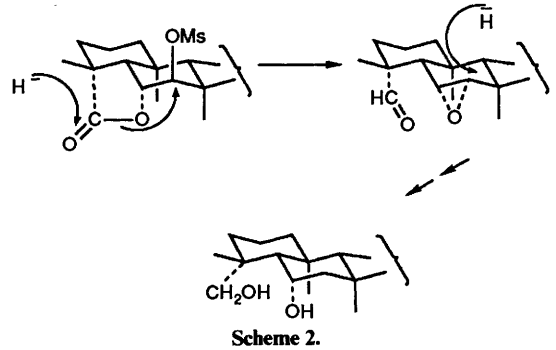
Table 1. Methyl group resonances (determined in $CDCl_3$ at 360 MHz).

Compound	18-H	20-H
(1)	1.00	1.39
(2)	1.01	1.10
(3)	1.05	0.89
(7)	1.06	1.23
(8)	1.02[a]	0.97

[a] Irradiation here produced an NOE enhancement (5%) of the 6-H signal.

unlabelled sample of compound (**2**), it was clearly possible to identify the 7-H resonances at δ 2.13 and 2.83 (*J* 11.8 Hz) and 5-H at δ 2.55 (s). Irradiation of the latter brought about a 4% nuclear Overhauser enhancement of the signal at δ 2.83 which therefore corresponds to 7β-H. Surprisingly it was this signal which bore the deuterium label when the labelled diol was oxidized. The displacement of the methanesulphonate had proceeded with an overall retention of configuration. As it was possible that isomerization of the A/B ring junction had occurred[7] during the purification of the 6-ketone (**2**) (thus invalidating the stereochemical conclusion based on the NOE experiment), the stereochemistry of compound (**2**) was confirmed by an X-ray crystallographic analysis (Figure).

A possible explanation for the anomalous reduction of the methanesulphonate is that attack of hydride on the lactone preceded that on the 7-methanesulphonate. Hydrogenolysis of the lactone was accompanied by an internal displacement of the methanesulphonate with the formation of a 6α,7α-epoxide (Scheme 2). Reduction of the 6α,7α-epoxide by lithium aluminium deuteride would then proceed from the β-face. The formation of a 6α,7α-epoxide by the internal displacement of 7β-toluene-*p*-sulphonate has been noted previously.[8]



Scheme 2.

When the *ent*-[7-^{2}H,18-^{2}H,19-$^2H_2$]-6β,19-dihydroxykaur-16-ene (**1**) was subjected to the DMFDMA reaction sequence and the resultant *ent*-19-hydroxykaur-6,16-diene (**7**) examined, it was found to have lost the deuterium label from C-7, *i.e.* the reaction had proceeded with elimination of the axial hydrogen. As anticipated, the *ent*-19-hydroxykaur-5,16-diene (**7**) retained deuterium at C-7 and the 6-H resonance (δ 5.51) was now a doublet, *J* 4 Hz.

ent-[6-^{2}H,19-$^2H_2$]-6β,19-Dihydroxykaur-16-ene (**1**) was prepared from *ent*-6-oxokaur-16-en-19-oic acid (**4**) by methylation with diazomethane and reduction with lithium aluminium deuteride. When this was subjected to the DMFDMA reaction, *ent*-[6-^{2}H,19-$^2H_2$]-19-hydroxykaur-5,16- and -6,16-dienes, (**7**) and (**8**), were both obtained. Their ^{1}H NMR spectra confirmed the sites of labelling.

These experiments have established the requirement for a diaxial relationship between the hydrogen atom and leaving group in the elimination reaction. The diol, *ent*-6β,19-dihydroxy-5β(*H*)-7-norgibberell-16-ene (**9**)[9] which lacks this relationship, was examined to see if the thermolytic fragmentation might, in the absence of these possibilities, initiate skeletal rearrangement, *e.g.*, migration of the 8:15 bond. However, the product was the 19-formate (**10**) which regenerated the *ent*-6β,19-diol (**9**) on hydrolysis.

In conclusion, we have shown that the formation of unsaturated alcohols through the fragmentation of the quaternary salts of dimethylformamido–acetals may occur with 1,4-glycols. However, whilst retaining the stereospecific requirements, it lacks the regiospecificity which was observed with the 1:3-glycols.

In the course of this work a number of compounds were obtained which bore a deuterium label at C-18. This permitted a distinction to be made between the ^{1}H NMR signals for 18-H and 20-H. It has been assumed that the axial methyl group at C-10 (20-H) was the more shielded and gave the higher field signal. These compounds showed that this is not always the case and in particular that the diaxial interactions with the C-6 and C-19 hydroxyl groups served to deshield the 20-H resonances. The assignments are given in the Table. The deuteriation experiment also permits the assignment of 6-H and 7-H. This revealed a large allylic coupling (*J* 3.2 Hz) between 5-H and 7-H corresponding to an angle of *ca.* 90°[10] and a smaller vicinal coupling (*J* 2 Hz) between 5-H and 6-H associated with a dihedral angle of *ca.* 90°. It also suggests that some assignments[8,11] made on the basis of the observed multiplicity of the ring B alkene resonances, particularly in situations where the smaller 5-H:6-H coupling may not have been resolved, may need to be reversed.

Experimental

IR spectra were determined as Nujol mulls; ^{1}H NMR spectra were determined in deuteriochloroform solution on a Bruker WM 360 spectrometer. Light petroleum refers to the fraction b.p. 60–80 °C and silica for chromatography was Merck 9385.

Reaction of ent-6β,19-*Dihydroxykaur*-16-*ene with DMFDMA.*—The diol (250 mg) in DMFDMA (25 ml) was heated under reflux for 6 h under nitrogen. The solvent was evaporated under reduced pressure and the residue dissolved in dry toluene (15 ml) and treated with methyl iodide (2.5 ml) at room temperature for 1.5 h. The solvent was evaporated, replaced by fresh toluene (20 ml) and the solution heated under reflux under nitrogen for 2 h. The solvent was evaporated, the residue was diluted with water and dil. hydrochloric acid and the organic products recovered in ethyl acetate. The solvent was evaporated to give a mixture of formates [δ 8.14, O–C(H)=O] (205 mg) which was dissolved in methanol (10 ml) and heated with 10% aqueous

sodium hydroxide (5 ml) at 40 °C for 2 h. The methanol was removed under reduced pressure and the remaining aqueous solution was extracted with ethyl acetate. The extract was dried over sodium sulphate, the solvent was evaporated and the residue chromatographed on silica. Elution with 3% ethyl acetate–light petroleum gave ent-19-*hydroxykaur*-5,16-*diene* (75 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 86 °C (Found: C, 83.4; H, 10.7. $C_{20}H_{30}O$ requires C, 83.8; H, 10.5%); ν_{max} 3 300br, 1 655, 1 645, and 870 cm^{-1}; δ_H 1.07 (3 H, s, 18-H), 1.24 (3 H, s, 20-H), 3.19 and 3.77 (each 1 H, d, *J* 10.5 Hz, 19-H), 4.75 and 4.82 (each 1 H, br s, 17-H), and 5.58 (1 H, t, *J* 4 Hz, 6-H). Further elution gave *ent*-19-hydroxykaur-6,16-diene (38 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 119–122 °C (lit.,[5] 119–122 °C); ν_{max} 3 350br, 1 655, and 875 cm^{-1}; δ_H 0.98 (3 H, s, 18-H) 1.01 (3 H, s, 20-H), 3.56 and 3.74 (each 1 H, d, *J* 10.9 Hz, 19-H), 4.80 and 4.84 (each 1 H, br s, 17-H), 5.39 (1 H, dd, *J* 3.2 and 10.1 Hz, 7-H), and 5.75 (1 H, dd, *J* 2.1 and 10.1 Hz, 6-H).

Preparation of ent-[7α,18-^{2}H,19-$^2H_2$]-6β,19-*Dihydroxykaur*-16-*ene*.—The 7,18-di(methanesulphonate) of 7,18-dihydroxykaurenolide (145 mg) in dry tetrahydrofuran (THF) (15 ml) was heated under reflux with lithium aluminium deuteride (200 mg) for 3 h. The mixture was cooled, treated with ethyl acetate and water and the organic solvent was removed under reduced pressure. The residue was acidified and the organic products were recovered in ethyl acetate to give *ent*-[7α,18-^{2}H,19-$^2H_2$]-6β,19-dihydroxykaur-16-ene (72 mg); m.p. 174–175 °C (lit.,[4] 174–175.5 °C); δ_H 1.00 (2 H, s, 18-H), 1.39 (3 H, s, 20-H), 4.31 (1 H, t, *J* 2.6 Hz, 6-H), and 4.75 and 4.81 (17-H).

ent-[6α-^{2}H,19-$^2H_2$]-6β,19-Dihydroxykaur-16-ene was obtained by a similar reduction of methyl *ent*-6-oxokaur-16-en-19-oate[4] with lithium aluminium deuteride.

Reaction of Deuteriated ent-6β,19-*Dihydroxykaur*-16-*enes with DMFDMA*.—(i) The *ent*-[7α,18-^{2}H,19-$^2H_2$]-6β,19-dihydroxykaur-16-ene (115 mg) was heated as above with DMFDMA (20 ml) for 12 h. The resultant acetal was quaternized with methyl iodide (5 ml) in toluene (10 ml) for 2 h. After the quaternary salt in toluene (20 ml) had been heated for 2 h, the recovered formates were hydrolysed with 10% aqueous methanolic sodium hydroxide to afford *ent*-[7α,18-^{2}H,19-$^2H_2$]-19-hydroxykaur-5,16-diene (47 mg) after chromatography; δ_H 1.06 (2 H, s, 18-H), 1.23 (3 H, s, 20-H), 4.75 and 4.82 (each 1 H, br s 17-H), and 5.58 (1 H, d, *J* 4 Hz, 6-H). Further elution gave *ent*-[7,18-^{2}H,19-$^2H_2$]-19-hydroxykaur-6,16-diene (21 mg); δ_H 0.97 (2 H, s, 18-H), 1.02 (3 H, s, 20-H), 4.80 and 4.84 (each 1 H, br s 17-H), and 5.75 (1 H, d, *J* 2.1 Hz, 6-H).

(ii) Similar treatment of *ent*-[6α-^{2}H,19-$^2H_2$]-6β,19-dihydroxykaur-16-ene (115 mg) gave *ent*-6-^{2}H,19-$^2H_2$-19-hydroxykaur-5,16-diene (40 mg); δ_H 1.02 (3 H, s, 18-H), 1.20 (3 H, s, 20-H), 1.95 and 2.25 (2 H, d, *J* 19 Hz, 7-H) and 4.74 (2 H, br s, 17-H) and *ent*-[6-^{2}H,19-$^2H_2$]-19-hydroxykaur-6,16-diene (15 mg); δ_H 0.97 (3 H, s, 18-H), 1.01 (3 H, s, 20-H), 4.78 and 4.84 (each 1 H, br s, 17-H), and 5.40 (1 H, d, *J* 3.2 Hz, 7-H).

Reaction of ent-6β,19-*Dihydroxy*-5β(H)-7-*norgibberell*-16-*ene with DMFDMA*.—The diol (100 mg) in DMFDMA (5 ml) was heated under reflux for 4.5 h. The DMFDMA was distilled off under reduced pressure and the residue was treated with methyl iodide (1 ml) in dry toluene (2 ml) for 2 h. The solvents were then evaporated and fresh toluene (5 ml) was added. The mixture was heated under reflux for 3 h. The solvent was evaporated and the organic product recovered in ethyl acetate and chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave the 19-formate of *ent*-6β,19-dihydroxy-5(*H*)-7-norgibberell-16-ene (56 mg) as an oil; δ_H 1.09 and 1.10 (each 3 H, s, 18-H and 20-H), 3.83 (1 H, d, *J* 10 Hz, 6-H) 4.03 and 4.12 (each 1 H, dd, *J* 10 and 0.8 Hz, 19-H) 4.88 and 4.92 (each 1 H, s, 17-H), and 8.12 [1 H, t, *J* 0.8 Hz, O–C(H)=O]. Hydrolysis with 10% aqueous methanolic sodium hydroxide (10 ml) at room temperature and recovery of the product in ethyl acetate gave *ent*-6β,19-dihydroxy-5β(*H*)-7-norgibberell-16-ene (43 mg), m.p. 158–159 °C (lit.,[9] 161 °C) identified by its IR and ^{1}H NMR spectrum.

Table 2. Fractional atomic co-ordinates (× 10^4) with estimated standard deviations in parentheses.

	x	*y*	*z*
O(1)	7 705(13)	11 462(10)	3 282(5)
O(2)	5 122(16)	9 925(9)	2 797(4)
C(1)	2 124(23)	10 260(12)	4 624(5)
C(2)	3 251(25)	11 452(12)	4 732(5)
C(3)	3 089(25)	12 311(11)	4 227(5)
C(4)	4 083(20)	11 770(11)	3 689(5)
C(5)	2 971(18)	10 530(10)	3 587(5)
C(6)	3 463(20)	9 821(11)	3 056(5)
C(7)	1 841(22)	8 959(12)	2 880(5)
C(8)	1 501(18)	7 994(10)	3 342(5)
C(9)	1 254(18)	8 611(11)	3 934(5)
C(10)	2 944(20)	9 590(10)	4 093(5)
C(11)	992(23)	7 610(12)	4 397(5)
C(12)	2 221(27)	6 449(12)	4 327(6)
C(13)	2 173(22)	6 010(12)	3 688(6)
C(14)	3 234(20)	7 017(11)	3 319(5)
C(15)	−512(22)	7 260(12)	3 195(6)
C(16)	−119(23)	6 045(13)	3 469(5)
C(17)	−1 474(24)	5 107(13)	3 515(7)
C(18)	3 539(23)	12 603(11)	3 186(6)
C(19)	6 588(20)	11 770(12)	3 782(6)
C(20)	5 162(19)	9 044(11)	4 209(5)

Controlled Oxidation of ent-6β,19-*Dihydroxykaur*-16-*ene*.—The diol (22 mg) in acetone (4 ml) was treated dropwise with chromium(VI) oxide (5M) at 0 °C. A sample for TLC was taken after the addition of each drop. The starting material was consumed after 4 drops had been added and only two faster-running TLC spots were apparent. Methanol was added, the solvents were evaporated and the products were recovered in ethyl acetate. Chromatography on silica gave *ent*-6,19-dioxokaur-16-ene (6 mg); m.p. 163–165 °C (lit.,[4] 165–167 °C); ν_{max} 1 738, 1 703, 1 650, and 890 cm^{-1}; δ_H 0.89 (3 H, s, 20-H), 1.06 (3 H, s, 18-H), 2.54 (1 H, s, 5-H), 4.82 and 4.86 (each 1 H, m, 17-H), and 10.02 (19-H). Further elution gave *ent*-19-hydroxy-6-oxokaur-16-ene (6 mg); m.p. 158–159 °C; (lit.,[4] 158–159 °C); ν_{max} 3 310, 1 686, 1 655, and 877 cm^{-1}; δ_H 1.00 (3 H, s, 18-H), 1.09 (3 H, s, 20-H), 2.12 and 2.83 (each 1 H, d, *J* 11.8 Hz, 7α-H and 7β), 2.55 (1 H, s, 5-H), 2.69 (1 H, br s, 13-H), 3.20 and 4.23 (each 1 H, d, *J* 10.6 Hz, 19-H), 4.80 and 4.86 (each 1 H, m, 17-H), and 5.02 (1 H, br s, OH).

Crystal Structure Determination.—Crystal data, $C_{20}H_{30}O_2$, M = 302.5, orthorhombic, space group $P2_12_12_1$, a = 6.349(1), b = 11.106(1), c = 23.812 (1) Å, U = 1 679 Å^3, Z = 4, D_c = 1.20 g cm^{-3}, monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 0.7 cm^{-1}.

A crystal of size *ca.* 0.3 × 0.3 × 0.3 mm was mounted on an Enraf-Nonius CAD4 diffractometer operating in the θ–2 θ mode, Δθ = (0.8 + 0.35 tan θ)°, with a maximum scan time of 1 min. 1 844 Reflections were measured for 2 < θ < 25°, +*h*, +*k*, +*l*. 837 Reflections with $|F^2| > \sigma(F^2)$ were used in the refinement where $\sigma(F^2) = [\sigma^2(I) + 0.04\ (I)^2]^{\frac{1}{2}}/L_p$. The struc-

ture was solved using MULTAN and refined for full matrix least-squares with C and O atoms held anisotropic. Hydrogen atoms were held at fixed calculated positions (C–H, 1.08 Å) except for H(0) which was located on a difference map. All hydrogen atoms had B_{iso} of 6.0 Å^2. The weighting scheme was $w = 1/\sigma^2(F)$ and the final residuals were $R = 0.049$, $R' = 0.056$. A final difference map was featureless. The programs were from the Enraf-Nonius SDP-Plus package. The final atomic co-ordinates are given in Table 2. The intramolecular distances, bond angles, torsional angles, hydrogen atom co-ordinates and temperature factors have been deposited with the Cambridge Crystallographic Data Centre.*

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* For details see 'Introduction for Authors' (1990), *J. Chem. Soc., Perkin Trans. 1*, 1990, issue 1.

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