The Stereochemistry of the Chemical Ring-contraction of Kaurenolides to Gibberellins

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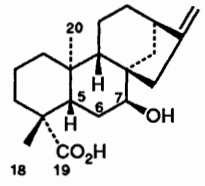
The reductive ring-contraction of the sulphonate ester of 7α,18-dihydroxykaurenolide with lithium aluminium hydride is shown to afford the 6-*epi*-7,19-dihydroxygibberell-16-ene.

The biosynthesis of gibberellic acid by the fungus, *Gibberella fujikuroi*, involves the contraction of the six-membered ring B of *ent*-7α-hydroxykaur-16-en-19-oic acid (**1**) to gibberellin A_{12} 7-aldehyde (**2**).[1,2] This gibberellin biosynthetic intermediate is relatively rare and consequently labelled samples for biosynthetic studies have been prepared[2-5] from more readily available materials. These routes have included the base-catalysed ring contraction of the sulphonate esters of 7α-hydroxykaurenolide (**3**).[5] This affords the C-7 aldehyde (**2**) with



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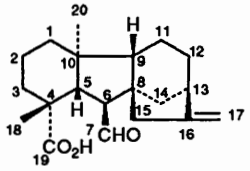

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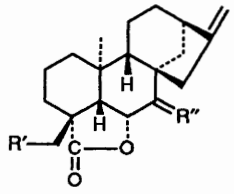
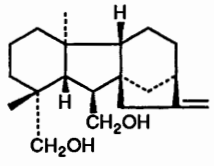


(**3**) R′ = H, R″ = β-H, α-OH
(**4**) R′ = OH, R″ = β-H, α-OH
(**5**) R′ = H, R″ = α-H, β-OH
(**6**) R′ = OH, R″ = α-H, β-OH
(**7**) R′ = OTs, R″ = O
(**8**) R′ = OTs, R″ = β-H, α-OH
(**9**) R′ = OTs, R″ = β-H, α-OMs
(**10**) R′ = OTs, R″ = β-^{2}H, α-OH
(**11**) R′ = OTs, R″ = β-^{2}H, α-OMs

the gibberellin configuration at C-6. However C-6 is an enolisable centre which can be labelled by carrying out the rearrangement in the presence of tritiated water.[4] It is therefore not clear whether the chemical ring contraction generates the gibberellin stereochemistry directly or if this is formed through a subsequent enolization step. The ring-contraction of *ent*-3β,20-epoxy-3,16α-dimethoxy-17-norkaurane derivatives with ring A fixed in a boat conformation, was studied[6] during synthetic work on the gibberellins. However these authors were unable to demonstrate experimentally whether their gibberellin C-7 aldehyde was formed directly or whether, as they presumed, it was formed as a result of an epimerization. Indeed they noted that the stereochemical constraints imposed by the conformation of ring A affected the relationships between the migrating bond and the leaving group and thus the path of the reaction. In connection with the preparation of labelled kaurenes, we examined the reduction of some sulphonate esters of 7α,18-dihydroxykaurenolide (**4**) and observed ring contraction rather than the simple nucleophilic displacement of the sulphonate ester. These results, which shed some light on the stereochemistry of the chemical ring-contraction, form the subject of this paper.

7β-Hydroxykaurenolide (**5**) from which the 7α-epimer was prepared,[3] is no longer readily available and therefore the work was carried out with 7β,18-dihydroxykaurenolide (**6**).[7] This was converted into its known 18-monotoluene-*p*-sulphonate which was then oxidized to the 7-ketone (**7**).[7] Reduction of the 7-ketone with sodium borohydride in methanol gave the 7α-alcohol (**8**) which was converted into its methanesulphonate (**9**). This was then reduced with lithium aluminium hydride. The product was identified as an *ent*-7,19-dihydroxygibberell-16-ene since its ^{1}H NMR spectrum contained two sets of primary alcohol signals. Although this diol possessed the same melting point as a diol (**12**) that had been obtained previously by Cross,[2] we nevertheless examined its stereochemistry by a series of NOE experiments and by comparison with a sample of *ent*-7,19-dihydroxygibberell-16-ene (**12**) prepared from gibberellin A_{14} (**13**), which is of established stereochemistry at C-6.

The dimethyl ester of gibberellin A_{14}[8] was converted into its 3-methylthiocarbonate which was then reduced first with tributyltin hydride and then with lithium aluminium hydride to afford the diol (**12**) of known C-6 stereochemistry. Although this had the recorded literature melting point, it was nevertheless



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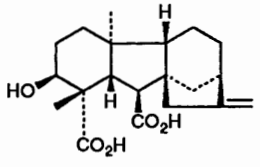

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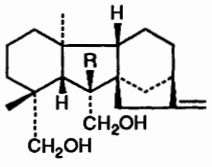
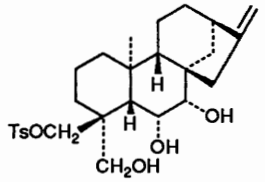


(**14**) R = H
(**15**) R = ^{2}H



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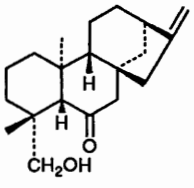
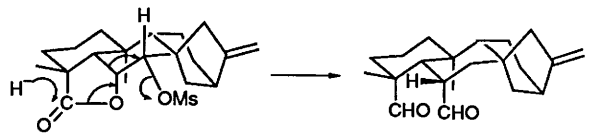


(17)

clearly different to the product of the reductive ring contraction (**14**). The 7-H resonances in (**14**) appeared at δ 3.71 (*J* 4.8 and 11.2 Hz) and 3.89 (*J* 7.3 and 11.2 Hz) whilst in (**12**) they appeared at δ 3.56 (*J* 8.5 and 10.3 Hz) and 3.63 (*J* 2.7 and 10.3 Hz). Spin decoupling experiments located the 5-H and 6-H signals at δ 1.55 and 2.27 in (**14**) ($J_{5,6}$ 7.5 Hz) and at δ 1.02 and 2.20 ($J_{5,6}$ 13.0 Hz) in (**12**). In (**14**) there were NOE enhancements at both 19-H resonances (δ 3.68 and 4.04, 4%) and at the 7-H signal (δ 3.89, 3%) on irradiating the methyl signal at δ 0.92 (20-H). On irradiation of the other methyl signal (δ 1.12) which was assigned to the 18-H, there was an enhancement of one of the 19-H signals (δ 3.68) and both the 5-H (δ 1.55, 5%) and 6-H signals (δ 2.27, 3%). In contrast, in (**12**) there were NOE effects at the 6-H (δ 2.20, 9%) and at the 19-H (δ 4.06, 6%) on irradiation at δ 0.87 (20-H) whilst irradiation at δ 1.15 (18-H) produced NOE effects at the 5-H (δ 1.02, 8%), 7-H (δ 3.56, 2%), and 19-H (δ 3.30, 2%). Thus in the natural series (**12**) the 5- and 6-protons are clearly on opposite faces of the molecule whilst in the product (**14**) of the reductive ring contraction they are on the same face (β) as the 18-H.

The 18-monotoluene-*p*-sulphonate of [7β-^{2}H]-7α,18-dihydroxykaurenolide (**10**) was prepared by reduction of the keto-lactone (**7**) with sodium [$^2H_4$]borohydride in methan-[^{2}H]ol. It showed the 6-H signal as a doublet. The methanesulphonate (**11**) lacked the 7-H resonance of the unlabelled material. Reduction with lithium aluminium hydride then gave the diol (**15**). This compound retained deuterium at C-6. In particular, the 6-H resonance at δ 2.27 was missing from the ^{1}H NMR spectrum whilst the 7-H resonances (δ 3.71 and 3.89) had collapsed to doublets (*J* 11.2 Hz). Hence the ring contraction had proceeded directly without enolization.



(**14**)

When the sodium borohydride reduction of the ketone (**7**) was carried out over a longer reaction time (4 h) it gave the 18-monotoluene-*p*-sulphonate of *ent*-6β,7β,18,19-tetrahydroxykaur-16-ene (**16**). This compound was converted into a gummy dimethanesulphonate which was, in turn, reduced with lithium aluminium hydride. This gave *ent*-19-hydroxy-6-oxokaur-16-ene (**17**)[9] which was identified by its ^{1}H NMR spectrum. There was no ring-contraction. This compound was presumably formed *via* the enol ether with hydrolysis occurring during the work-up.

In conclusion, we have shown that the reductive ring-contraction of the sulphonate esters of 7α-hydroxykaurenolides proceeds directly to the 6-*epi*-gibberellins with participation of the lactone ring. This may be accommodated in the reaction scheme which is shown. The formation of compounds with the gibberellin stereochemistry at C-6 in the base-catalysed ring-contraction probably takes place *via* an enolization step subsequent to the rearrangement. In this context it is also worth noting that the base-catalysed ring-contraction of the 7-chloro 5,6-enol 18,6-lactones in the kaurene series, also generates the 6-*epi*-gibberellin stereochemistry[10] although the reaction proceeds *via* a different mechanism.

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.

Reduction of the 18-*Monotoluene*-p-*sulphonate* (**7**).—The 18-monotoluene-*p*-sulphonate of *ent*-6β,18-dihydroxy-7-oxokaur-16-en-19-oic acid 19,6β-lactone (**7**)[7] (2.0 g) in methanol (125 ml) was treated with sodium borohydride (1.5 g) for 2 h at 0 °C. The solution was acidified with dilute hydrochloric acid and the products were recovered in ethyl acetate. Chromatography on silica in 20% ethyl acetate–light petroleum gave the 18-*toluene*-p-*sulphonate* of ent-6β,7β,18-*trihydroxykaur*-16-*en*-19-*oic acid* 19,6β-*lactone* (**8**) (1.07 g) as a foam (Found: C, 63.9; H, 6.9. $C_{27}H_{34}O_6S{\cdot}H_2O$ requires C, 64.3; H, 7.2%); ν_{max} 3 450br, 1 773, 1 657, and 1 598 cm^{-1}; δ 1.10 (3 H, s, 20-H), 2.46 (3 H, s, Ar-Me), 4.02 (3 H, m, 7-H, 18-H), 4.84 (1 H, t, *J* 7.1 Hz, 6-H), 4.88 and 5.01 (each 1 H, m, 17-H), 7.37 and 7.77 (each 2 H, d, *J* 8 Hz, ArH); *m/z* (CI, NH_3) 504. ($C_{27}H_{34}O_6S + NH_4^+$ requires 504). The methanesulphonate (**9**), prepared with methanesulphonyl chloride in pyridine, was also an unstable gum, δ 1.01 (3 H, s, 20-H), 2.47 (3 H, s, Ar-Me), 3.12 (3 H, s, $MeSO_2O$), 4.01 and 4.06 (each 1 H, d, *J* 10 Hz, 18-H), 4.92 and 5.04 (each 1 H, m, 17-H), 4.93 (1 H, part obscured, 6-H) 4.98 (1 H, d, *J* 7.5 Hz, 7-H).

When the reduction was carried out for 4 h at room temperature, it gave the 18-*monotoluene*-p-*sulphonate of* ent-6β,7β,18,19-*tetrahydroxykaur*-16-*ene* (**16**), m.p. 183–185 °C (Found: C, 66.1; H, 7.7. $C_{27}H_{38}O_6S$ requires C, 66.1; H, 7.8%); ν_{max} 3 520, 3 430br, 1 650, and 1 600 cm^{-1}; δ 1.41 (3 H, s, 20-H), 2.46 (3 H, s, Ar-Me), 3.28 (1 H, br d, *J* 12.1 Hz) and 4.28 (1 H, d, *J* 12.1 Hz) (each 19-H), 3.38 (1 H, m) and 3.89 (1 H, m) (6-H, 7-H), 3.90 and 4.11 (each, 1 H, d, *J* 9.8 Hz, 18-H), 4.79 and 4.84 (each 1 H, m, 17-H) and 7.36 and 7.78 (each 2 H, d, *J* 7.5 Hz, ArH).

The dimethanesulphonate was a gum, δ 1.36 (3 H, s, 20-H), 2.45 (3 H, s, Ar-Me), 3.00 and 3.15 (each 3 H, s, $MeSO_2O$), 3.73 and 4.03 (each 1 H, d, *J* 9.9 Hz, 18-H), 4.53 (1 H, d, *J* 3 Hz), 4.57 (1 H, br s), 4.76 (2 H, br s) (6, 7 and 19-H), 4.82 and 4.86 (each 1 H, br s, 17-H), and 7.37 and 7.85 (each 2 H, s, *J* 7.5 Hz, ArH).

Repetition of the reduction with sodium [$^2H_4$]borohydride (150 mg) and the keto-lactone (**7**) (410 mg) in methan[^{2}H]ol (10 ml) gave the [^{2}H]alcohol (**10**) (200 mg) which was converted into its methanesulphonate with methanesulphonyl chloride (0.5 ml) in pyridine (5 ml). It had δ 1.01 (3 H, s, 20-H), 2.47 (3 H, s, Ar-Me), 3.12 (3 H, s, $MeSO_2O$), 4.00 and 4.05 each 1 H, d, *J* 10 Hz, 18-H), 4.93 and 5.04 (each 1 H, s, 17-H), 4.95 (part obscured by 17-H, 6-H), and 7.38 and 7.78 (each 2 H, d, *J* 7.5 Hz, ArH).

Reductions with Lithium Aluminium Hydride.—(a) The methanesulphonate (**9**) (0.92 g) in tetrahydrofuran (30 ml) was treated with lithium aluminium hydride (0.2 g) for 4 h under reflux. The solution was cooled and carefully treated with aqueous ethyl acetate, acidified, and the products recovered in ethyl acetate. The solvent was evaporated and the residue (700 mg) was chromatographed on silica. Elution with 40% ethyl acetate–light petroleum gave ent-7,19-*dihydroxy*-6-epi-*gibberell*-16-*ene* (400 mg), m.p. 149–151 °C (Found: C, 78.8; H, 10.45. $C_{20}H_{32}O_3$ requires C, 78.9; H, 10.6%); ν_{max} 3 273br, 1 658, and 872 cm^{-1}; δ 0.92 (3 H, s, 20-H), 1.12 (3 H, s, 18-H), 1.57 (d, partially obscured, *J* 7.5 Hz (from NOE spectrum) (5-H), 2.27 (1 H, m, 6-H), 2.29 (1 H, br d, *J* 15.4 Hz), and 2.35 (1 H, d, *J* 15.4 Hz, of t, *J* 2.5 Hz, 15-H) (clarified in the deuteriated sample), 3.71 (1 H, dd, *J* 4.8 and 11.2 Hz) and 3.89 (1 H, dd, *J* 7.3 and 11.2 Hz) (each 7-H) 3.68 and 4.04 (each 1 H, d, *J* 11 Hz, 19-H), 4.77 and 4.90 (each 1 H, br s, 17-H).

(b) Repetition on the [7β-^{2}H]methanesulphonate (**11**) (60 mg) gave the *ent*-7,19-dihydroxy-6-*epi*[6α-^{2}H]gibberell-16-ene (**15**) (20 mg), m.p. 142–146 °C, δ 0.92 (3 H, s, 20-H), 1.12 (3 H, s, 18-H), 1.57 (singlet, 5-H), 2.29 (1 H, br d, *J* 15.4 Hz) and 2.35 [1 H, d (15.4 Hz) of t (2.5 Hz), 15-H], 3.71 and 3.89 (each 1 H, d, *J*

11.2 Hz, 7-H, 3.68 and 4.04 (each 1 H, d, *J* 11 Hz, 19-H), and 4.77 and 4.90 (each 1 H, br s, 17-H).

(c) The dimethanesulphonate of (**16**) (176 mg) in tetrahydrofuran (20 ml) was treated with lithium aluminium hydride (200 mg) for 4 h under reflux. The solution was cooled, acidified and the product recovered in ethyl acetate. The extract was washed and the solvent was evaporated to give a residue which was chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave *ent*-19-hydroxy-6-oxokaur-16-ene (**17**) (100 mg), m.p. 130–134 °C (lit.,[9] 130–135 °C) (M^+, 284), identified by its ^{1}H NMR spectrum.

Preparation of ent-7,19-*Dihydroxygibberell*-16-*ene*(12) *from Giberellin* A_{14}.—Gibberellin A_{14} dimethyl ester (50 mg)[8] in tetrahydrofuran (25 ml) was treated with sodium hydride (100 mg) at 0 °C and carbon disulphide (0.4 ml) for 48 h. Methyl iodide (1 ml) was then added and the solution was left for 5 h. A second portion of methyl iodide (1.5 ml) was added and the solution was left overnight. The flask was cooled, isopropyl alcohol (1 ml) was added, and the solvents were then evaporated. The product was recovered in ethyl acetate. The solvent was again evaporated and the residue (75 mg) dissolved in dry benzene (15 ml) and treated with tributyltin hydride (1.5 ml) and azoisobutyronitrile (15 mg) under reflux for 4 h. The solvents were evaporated under reduced pressure and the residue was chromatographed on silica. Elution with light petroleum removed the tin salts and then elution with 5% ethyl acetate–light petroleum gave the dimethyl ester of gibberellin A_{12}[11] (40 mg) as a gum. The dimethyl ester (30 mg) in dry tetrahydrofuran (15 ml) was heated under reflux with lithium aluminium hydride (25 mg) for 2 h. The suspension was treated with moist ethyl acetate, dilute hydrochloric acid, and water. The organic phase was dried, the solvent was evaporated, and the residue chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave *ent*-7,19-dihydroxygibberell-16-ene (15 mg) as needles, m.p. 143–145 °C (lit.,[2] 145–147 °C); ν_{max} 3 273, 1 655, and 876 cm^{-1}; δ 0.87 (3 H, s, 20-H), 1.02 (d, *J* 13.0 Hz, 5-H), 1.15 (3 H, s, 18-H), 2.20 (1 H, ddd, *J* 13.0, 8.5, and 2.7 Hz, 6-H), 3.30 and 4.06 (each 1 H, d, *J* 10.6 Hz, 19-H), 3.56 (1 H, dd, *J* 8.5 and 10.3 Hz) and 3.63 (1 H, dd, *J* 2.7 and 10.3 Hz) (both 7-H), and 4.69 and 4.85 (each 1 H, br s, 17-H).

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