The Partial Synthesis of Beyergibberellin A_4 and A_9 Methyl Esters

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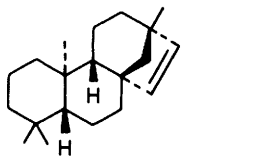
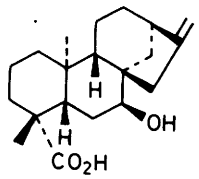
Beyergibberellins A_4 and A_9 methyl esters were synthesized from methyl gibberellate *via* gibberellin A_1 methyl ester and its 3-epimer. The C/D ring junction of the 3-epimer was isomerized to afford the 16-oxo-8,13-isogibberellin and 3-hydroxy group removed by tributyltin hydride reduction of the corresponding chloride. Alternatively the C/D ring junction of the gibberellin A_1 methyl ester was isomerized and the 3-hydroxy group was converted into its trimethylsilylethoxymethyl derivative. Reduction of the 16-ketones and elimination of the corresponding 16-sulphonate esters over alumina or with collidine afforded the title compounds.

The tetracyclic diterpenoids which arise by cyclization of the bicyclic labdadienol pyrophosphate or its enantiomer occur with several different carbon skeleta for rings C and D.[1] Although the kaurenoid group are the most common, a substantial number of compounds have been found with the *ent*-beyer-15-ene skeleton (**1**). The naturally occurring gibberellin plant growth hormones are derived from the *ent*-kaur-16-ene series by contraction of ring B of *ent*-7α-hydroxykaur-16-en-19-oic acid (**2**).[2] Although a number of *ent*-beyer-15-enes are known with hydroxylation patterns reminiscent of gibberellin biosynthetic precursors, no beyergibberellins have hitherto been isolated from plant sources. However there is nothing known concerning gibberellin biosynthesis which would preclude the formation of beyergibberellins. It was therefore our objective† to prepare beyergibberellins A_4 and A_9 methyl esters in anticipation of the possible isolation of the parent acids.



(**1**)



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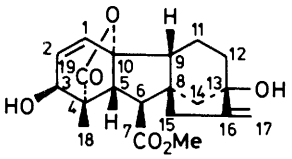

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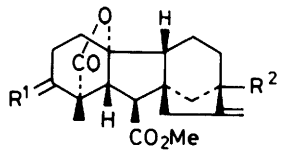
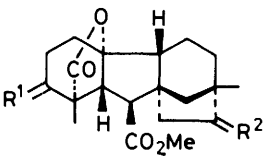
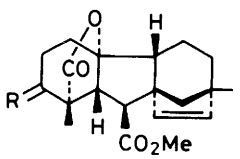


(**4**) R^1 = α-H, β-OH, R^2 = OH
(**5**) R^1 = α-OH, β-H, R^2 = OH
(**6**) R^1 = α-H, β-Cl, R^2 = OH
(**7**) R^1 = H_2, R^2 = OH
(**8**) R^1 = H_2, R^2 = H
(**9**) R^1 = α-H, β-OAc, R^2 = H

The readily available methyl gibberellate (**3**) was converted by oxidation with manganese dioxide and reduction with sodium borohydride–copper chloride into a separable mixture (1:4) of gibberellin A_1 and 3-*epi*-gibberellin A_1 methyl esters [(**4**) and (**5**) respectively].[4,5] Reaction of the 3-*epi*-gibberellin A_1 methyl ester with triphenylphosphine–carbon tetrachloride gave the 3β-chloride which was reduced with tri-n-butyltin hydride to give gibberellin A_{20} methyl ester (**7**).[5] Isomerization of the ring C/D system to afford the 8,13-isogibberellin (**10**) was carried out with trifluoroacetic acid in chloroform in the presence of a catalytic amount of concentrated sulphuric acid. These conditions minimize isomerization at C-9 which occurs to a substantial amount in hydrochloric acid.[6] Isomerization of 3-*epi*-gibberellin A_1 methyl ester (**5**) under the same conditions afforded the 8,13-isogibberellin methyl ester (**11**). When this was carried out in deuteriated media the carbon-13 n.m.r. spectrum of the product (M^+, *m/z* 363, $C_{20}H_{25}{}^2H_1O_6$ requires *M*, 363) showed that deuterium was only incorporated into the C-13 methyl group (δ 19.6) and not at C-9 (δ 53.5). Hence epimerization had not taken place at C-9 and these 8,13-isogibberellins possess the same 9β-H as the natural gibberellins.



(**10**) R^1 = H_2, R^2 = O
(**11**) R^1 = α-OH, β-H, R^2 = O
(**12**) R^1 = α-H, β-Cl, R^2 = O
(**13**) R^1 = H_2, R^2 = α-OH, β-H
(**14**) R^1 = H_2, R^2 = α-OMs, β-H
(**15**) R^1 = H_2, R^2 = α-OTs, β-H
(**16**) R^1 = α-H, β-OH, R^2 = O
(**17**) R^1 = α-H, β-$Me_3SiCH_2CH_2OCH_2O$-, R^2 = O
(**18**) R^1 = α-H, β-$Me_3SiCH_2CH_2OCH_2O$-, R^2 = α-OTs, β-H



(**19**) R = H_2
(**20**) R = α-H, β-OH
(**21**) R = α-H, β-OAc
(**22**) R = α-OH, β-H

The ring A hydroxy group of the 8,13-isogibberellin (**11**) was removed by reaction with triphenylphosphine–carbon tetrachloride to afford the 3β-chloride (**13**). The multiplicity of the CHCl proton resonance and the relatively low-field position of the 5β-H proton resonance (CHCl δ 4.19, dd, *J* 1.5 and 3.5 Hz; 5β-H δ 3.29, *J* 6.5 Hz) compared with the unsubstituted compound (**10**) are in accord with the 3β-stereochemistry of the chlorine atom. Reduction of the chloride with tri-n-butyltin hydride then gave the 8,13-isogibberellin (**10**).[7] A characteristic of the compounds in the 8,13-isogibberellin series is the smaller value of the 5-H,6-H coupling constant compared with the normal series (6.5 *vs.* 10 Hz). However *X*-ray data (see preceding

† Part of this work has appeared in a preliminary communication.[3]

paper) show that there is a relatively small difference in the dihedral angle (5-H, C-5, C-6, 6-H) between the two series (154° in the normal series, 146° in the isogibberellin series).

Reduction of the 16-ketone (**10**) with sodium borohydride took place from the less-hindered face of ring D to generate the *endo*-16α-alcohol (**13**).[8] The alcohol (**13**) gave both a methanesulphonate (**14**) and a toluene-*p*-sulphonate (**15**). Suprisingly, treatment of the toluene-*p*-sulphonate (**15**) with collidine gave predominantly the rearrangement product, gibberellin A_9 methyl ester (**8**). This contrasts with the beyerene series itself in which the C-16 *endo*-toluene-*p*-sulphonate readily gave the Δ^{15}-elimination product.[9] Possibly the 7-methoxycarbonyl group hinders the approach of the collidine to C-15 thus allowing the rearrangement to predominate. Alumina has been recommended[10] for producing elimination without skeletal rearrangement in situations (*e.g.* neopentyl) in which the toluene-*p*-sulphonate is prone to rearrange. Reaction with alumina (Woelm, neutral) in carbon tetrachloride at room temperature for 3 days gave a mixture (2.5:1) of beyergibberellin A_9 methyl ester (**19**) and gibberellin A_9 methyl ester (**8**). Under these conditions the methanesulphonate gave a higher proportion (6:1) of the beyergibberellin A_9 methyl ester.

Beyergibberellin A_4 methyl ester (**20**) was prepared by the isomerization of gibberellin A_1 methyl ester (**4**) with trifluoroacetic acid to afford (**16**). The ring A hydroxy group was protected as the trimethylsilylethoxymethyl ether (**17**)[11] whilst the 16-carbonyl group was reduced with sodium borohydride to the *endo*-16α-alcohol. The latter was then converted into the 16α-toluene-*p*-sulphonate (**18**). Elimination with collidine gave an inseparable mixture. The protecting group was removed with fluoride ion and the ring A hydroxy group acetylated to afford a mixture of acetates. These were separated by careful chromatography on silver nitrate–silica into the 3-acetate of beyergibberellin A_4 methyl ester (**21**) and the acetate of gibberellin A_4 methyl ester (**9**) together with its endocyclic Δ^{15}-double-bond isomer. The 3-acetate of beyergibberellin A_4 methyl ester was hydrolysed with aqueous potassium carbonate to afford the methyl ester of beyergibberellin A_4 (**20**). This hydrolysis was accompanied by some epimerization at C-3 to afford (**22**). An inter-relationship between the two beyergibberellins was established by converting the 3-epimer into its thiocarbonylimidazole derivative[12] and reduction of the latter with tri-n-butyltin hydride which afforded beyergibberellin A_9 methyl ester. (**19**). This was identical with the material obtained above.

Experimental

Rearrangement of 3-epi-*Gibberellin* A_1 *Methyl Ester*.—The methyl ester (**5**) (1.1 g) in chloroform (10 ml) was treated with trifluoroacetic acid (2 ml) and concentrated sulphuric acid (0.2 ml) at room temperature for 15 min. The solution was diluted with chloroform (50 ml), washed with aqueous sodium hydrogen carbonate and water, and then dried. The solvent was evaporated to afford ent-3β,10β-*dihydroxy*-13-*methyl*-16-*oxo*-17,20-*bisnor*-8,13-*isogibberellane*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (1.0 g) which crystallized as needles, m.p. 216—217 °C (Found: C, 65.9; H, 6.9. $C_{20}H_{26}O_6$ requires C, 66.2; H, 7.1%), $\nu_{max.}$ 3 550, 1 765, and 1 740 cm^{-1}; δ 1.05 (3 H, s, 13-Me), 1.26 (3 H, s, 18-H), 2.52 (1 H, d, 6.5 Hz, 5-H), 2.73 (1 H, d, *J* 6.5 Hz, 6-H), 3.66 (1 H, dd, *J* 6 and 10 Hz), and 3.75 (3 H, s, OMe).

Repetition in the presence of trifluoro[^{2}H]acetic acid and [^{2}H]sulphuric acid gave *ent*-[13-methyl-$^2H_1$]-3β,10β-dihydroxy-13-methyl-16-oxo-17,20-bisnor-8,13-isogibberellane-7,19-dioic acid 19,10β-lactone 7-methyl ester which crystallized as needles, m.p. 215—217 °C (M^+, *m/z* 363). In the ^{1}H n.m.r. spectrum the signal at δ 1.05 integrated for 2 protons; δ_C 28.4 (C-1), 29.3 (C-2), 74.2 (C-5), 58.6 (C-4), 50.5 (C-5), 52.2 (C-6), 173.5 (C-7), 50.8 (C-8), 53.5 (C-9), 91.2 (C-10), 19.4 (C-11), 35.5 (C-12), 49.9 (C-13), 47.5 (C-14), 50.2 (C-15), 217.7 (C-16), 12.9 (C-18), 176.8 (C-19), 52.2 (OMe), and 19.6 (13-Me, signal reduced in intensity by ^{2}H).

Preparation of the Chloro Compound (**12**).—The above 3-alcohol (**11**) (800 mg) in carbon tetrachloride (50 ml) was treated with triphenylphosphine (1.6 g) under reflux for 4 h. The solvent was evaporated and the residue chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave ent-3α-*chloro*-10β-*hydroxy*-13-*methyl*-16-*oxo*-17,20-*bisnor*-8,13-*isogibberellane*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (**12**) (790 mg) which crystallized as needles, m.p. 189—191 °C (Found: C, 63.15; H, 6.5; $C_{20}H_{25}ClO_5$ requires C, 63.15; H, 6.57%), $\nu_{max.}$ 1 785, 1 745, and 1 725 cm^{-1}; δ 1.05 (3 H, s, 13-Me), 1.27 (3 H, s, 18-H), 2.65 (1 H, d, *J* 6.5 Hz, 6-H), 3.29 (1 H, d, *J* 6.5 Hz, 5-H), 3.76 (3 H, s, OMe), and 4.19 (1 H, dd, *J* 1.5 and 3.5 Hz, 3-H).

Reduction of the Chloro Compound (**12**).—The above chloro compound (**12**) (700 mg) in benzene (25 ml) was heated under reflux with tri-n-butyltin hydride (1 ml) and azobisisobutyronitrile (20 mg) for 1 h. The solvents were evaporated and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave the ketone (**10**) (485 mg)[7] which was identified from its n.m.r. spectrum.

ent-10β,16β-Dihydroxy-13-methyl-17,20-bisnor-8,13-isogibberellane-7,19-dioic acid 19,10β-lactone 7-methyl ester (**13**) was prepared as described previously.[7] The *toluene*-p-*sulphonate* (**13**), prepared with toluene-*p*-sulphonyl chloride in pyridine, crystallized as needles, m.p. 110 °C (decomp.) (Found: C, 64.6; H, 6.2. $C_{27}H_{34}O_7S$ requires C, 64.5; H, 6.7%), $\nu_{max.}$ 1 780, 1 720, and 1 600 cm^{-1}; δ 0.90 (3 H, s, 13-Me), 1.04 (3 H, s, 18-H), 2.41 (3 H, s, Ar-Me), 2.40 (1 H, d, *J* 6.5 Hz, 5-H), 2.60 (1 H, d, *J* 6.5 Hz, 6-H), 3.64 (3 H, s, OMe), 4.49 (1 H, dd, *J* 5 and 11 Hz, 16-H), 7.35 (2 H, d, *J* 8 Hz, ArH), and 7.77 (2 H, d, *J* 8 Hz, ArH). The *methanesulphonate* was a gum (Found: C, 59.0; H, 6.9. $C_{21}H_{30}O_7S$ requires C, 59.2; H, 7.0%), δ 1.06 (3 H, s, 13-Me), 1.12 (3 H, s, 18-H), 2.44 (1 H, d, *J* 6.5 Hz, 5-H), 2.53 (1 H, d, *J* 6.5 Hz, 6-H), 2.95 (3 H, s, SO_2Me), 3.67 (3 H, s, OMe), and 4.65 (1 H, dd, *J* 5 and 11 Hz, 16-H).

Elimination Reactions.—(*a*) The toluene-*p*-sulphonate (**15**) (100 mg) in freshly redistilled collidine (5 ml) was heated under reflux for 18 h. The solution was poured into dilute hydrochloric acid and the product recovered in ethyl acetate and chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave gibberellin A_9 methyl ester (60 mg) which crystallized as cubes, m.p. 136—138 °C (lit.,[13] 136 °C) identified from its i.r. and n.m.r. spectra.

(*b*) The toluene-*p*-sulphonate (**15**) (120 mg) in carbon tetrachloride (20 ml) was treated with neutral alumina (Woelm, grade 1) (3 g) at room temperature for 3 days. The alumina was filtered off, the solvent evaporated, and the residue chromatographed on silica. Elution with 7% ethyl acetate–light petroleum gave gibberellin A_9 methyl ester (18 mg) followed by ent-10β-*hydroxy*-13-*methyl*-17,20-*bisnor*-8,13-*isogibberell*-15-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (beyergibberellin A_9 methyl ester) (**19**) (45 mg), which crystallized as fine needles, m.p. 93—95 °C (Found: C, 72.6; H, 7.8. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%), $\nu_{max.}$ 1 760, 1 740, 1 170, and 725 cm^{-1}; δ 1.05 (3 H, s, 13-Me), 1.15 (3 H, s, 18-Me), (1 H, d, *J* 6.5 Hz, 5-H), 2.74 (1 H, d, *J* 6.5 Hz, 6-H), 3.79 (3 H, s, OMe), and 5.41 (2 H, m, 15- and 16-H).

Protection of the 3-*Hydroxy Group in* (**16**).—The alcohol (**16**)[6] (200 mg) in dichloromethane (2 ml) was treated with trimethylsilylethoxymethyl chloride (0.3 ml)[10] in di-isopropyl-

ethylamine (1 ml) at room temperature for 28 h. The solution was diluted, washed with water, and chromatographed on silica. Elution with 30% ethyl aceate–light petroleum gave the *trimethylsilylethoxymethyl derivative* (**17**) as a gum [Found: *m/z* 434.2142. $C_{23}H_{34}O_6Si$ ($M^+ - C_3H_6O$) requires *m/z* 434.2124], δ 1.03 (3 H, s, 13-Me), 1.20 (3 H, s, 18-H), 2.62 and 3.20 (each 1 H, d, *J* 8 Hz, 5- and 6-H), 3.74 (3 H, s, OMe), and 4.73 (1 H, m, 3-H).

Reduction of the Derivative (**17**).—The trimethylsilylethoxymethyl derivative (**17**) (160 mg) in methanol (4 ml) was treated with sodium borohydride (28 mg) at room temperature for 80 min. The solution was poured into water and acidified. The product was recovered in ethyl acetate and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave the 3-*trimethylsilylethoxymethyl derivative* of ent-3α,10β,16β-*trihydroxy*-13-*methyl*-17,20-*bisnor*-8,13-*isogibberellane*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (130 mg), m.p. 118—120 °C [Found: M^+, *m/z* 436.2289. $C_{23}H_{36}O_6Si$ ($M - C_3H_6O$) requires *m/z* 436.2281]; δ 0.96 (3 H, s, 13-Me), 1.25 (3 H, s, 18-H), (1 H, d, *J* 8 Hz, 6-H), 3.07 (1 H, d, *J* 8 Hz, 5-H), 3.74 (3 H, s, OMe), and 4.73 (1 H, m, 3-H). The *toluene*-p-*sulphonate*, prepared with toluene-*p*-sulphonyl chloride in pyridine, was a gum [Found: *m/z* 590.2331. $C_{30}H_{42}O_8SSi$ requires *m/z* 590.2331 ($M - C_3H_6O$)], δ 0.90 (3 H, s, 13-Me), 1.10 (3 H, s, 18-H), 2.63 and 3.02 (each 1 H, d, *J* 7 Hz, 6- and 5-H), 3.69 (3 H, s, OMe), 4.50 (1 H, dd, *J* 4 and 11 Hz, 16-H), and 4.71 (1 H, dd, *J* 7 and 11 Hz, 3-H).

Elimination Reaction.—The above toluene-*p*-sulphonate (155 mg) was heated under reflux in collidine (8 ml) for 8 h. The solution was poured into water and the product recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid and water and then dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave a mixture of trimethylsilylethoxymethyl ethers (65 mg) and a second mixture of free alcohols (40 mg). The mixture of ethers (65 mg) in tetrahydrofuran (5 ml) was treated with tetrabutylammonium fluoride (80 mg) at room temperature for 40 h. The solvent was evaporated and the residue chromatographed on silica to give the same mixture of alcohols as obtained above. The mixture of alcohols was combined and acetylated with acetic anhydride in pyridine in the usual manner and chromatographed on silica gel–silver nitrate (20%). Elution with 20% ethyl acetate–light petroleum afforded the acetate of gibberellin A_4 methyl ester (**9**) (16 mg) as a gum (Found: M^+, *m/z* 388.1887. Calc. for $C_{22}H_{28}O_6$: *M*, *m/z* 388.1885), 1.06 (3 H, s, 18-H), 2.16 (3 H, s, OAc), 2.70 and 3.19 (each 1 H, d, *J* 11 Hz, 6- and 5-H), 3.74 (3 H, s, OMe), 4.96 (2 H, m), and 5.00 (1 H, m), (3- and 16-H). Further elution gave the *acetate of* Δ^{15}-isogibberellin A_4 methyl ester (17 mg) which crystallized from ethyl acetate–hexane as needles, m.p. 122—124 °C (Found: M^+, *m/z* 388.1898. $C_{22}H_{28}O_6$ requires M^+, *m/z* 388.1885), δ 1.08 (3 H, s, 18-H), 1.70 (3 H, s, 17-H), 2.15 (3 H, s, OAc), 2.56 and 2.83 (each 1 H, d, *J* 11 Hz, 6- and 5-H), 3.71 (3 H, s, OMe), 4.99 (1 H, m, 3-H), and 5.37 (1 H, br s, 15-H). Elution then afforded the *acetate* of beyergibberellin A_4 methyl ester, δ 1.09 (3 H, s, 13-Me), 1.15 (3 H, s, 18-H), 2.11 (3 H, s, OAc), 2.71 and 3.13 (each 1 H, d, *J* 7 Hz, 6- and 5-H), 3.73 (3 H, s, OMe), 5.00 (1 H, m, 3-H), and 5.48 (2 H, m, 15- and 16-H).

Hydrolysis of the Acetate of Beyergibberellin A_4 Methyl Ester.—The above acetate (30 mg) was treated with aqueous methanolic potassium carbonate (3%) (3 ml) at room temperature overnight. The solution was concentrated, diluted with water, and the product recovered in ethyl acetate and chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave ent-3α,10β-*dihydroxy*-13-*methyl*-17,20-*bisnor*-8,13-*isogibberell*-15-*ene*-7,19-*dioic acid* 19,10β-*lactone* 7-*methyl ester* (beyergibberellin A_4 methyl ester) (**20**) (10 mg), m.p. 149—151 °C (Found: M^+, *m/z* 346.1777. $C_{20}H_{26}O_5$ requires *M*, *m/* 346.1780), δ 1.12 and 1.28 (each 3 H, s, 13-methyl and 18-H), 2.74 and 3.18 (each 1 H, d, *J* 7 Hz, 6- and 5-H) 3.72 (3 H, s. OMe), 3.90 (1 H, m, 3-H), and 5.50 (2 H, m, 15- and 16-H). Further elution gave 3-epi-*beyergibberellin A_4 methyl ester* as a gum (16 mg) (Found: M^+, *m/z* 346.1787 $C_{20}H_{26}O_5$ requires *M*, *m/z* 346.1780), δ 1.08 and 1.28 (each 3 H, s, 13-methyl and 18-H), 2.47 and 2.82 (each 1 H, d, *J* 7 Hz, 6- and 5-H), 3.66 (1 H, m, 3-H), 3.72 (3 H, s, OMe), and 5.51 (2 H, m, 15- and 16-H).

Conversion into Beyergibberellin A_9 Methyl Ester.—3-*epi*-Beyergibberellin A_4 methyl ester (15 mg) and *N,N'*-thiocarbonyldi-imidazole (40 mg) in dry dichloromethane (0.5 ml) were heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed on silica to afford the imidazolethiocarboxylate. This was dissolved in dry toluene (2 ml) and added during 30 min to tri-n-butyltin hydride (0.2 ml) in dry toluene (1 ml) with a trace of azobisisobutyronitrile. The mixture was heated under reflux for 6 h. The solution was concentrated, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water after which the solvent was evaporated. The residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave beyergibberellin A_9 methyl ester (8 mg) (Found: M^+, *m/z* 330.1854. $C_{20}H_{26}O_4$ requires M^+, *m/z* 330.1831) which was identified by its n.m.r. spectrum.

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