An Unusual C-7 Ortho Ester from 6-*epi*-Gibberellin A_{13}. *X*-Ray Molecular Structure of Gibberellene C-7 Ortho Ester

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Methanolysis of the 7,19-dimethyl ester of 3-acetoxy-6-*epi*-gibberellin A_{13} 20-toluene-*p*-sulphonic anhydride afforded an unusual C-7 ortho ester as the major product. The preparation of 3,6-*epi*-GA_{37} methyl ester and of an interesting C-19 acetal is also described.

In a previous work [1] we published an account of the formation of the 19-ortho ester (**1**) by methanolysis of 3-*O*-acetylgibberellin A_{13} 20-toluene-*p*-sulphonic anhydride 7,19-dimethyl ester (**3**), which revealed an unusual transannular participation between C-19 and C-20. Later we showed [2] how a gibberellin A_{13} methyl ester (**4**) could be epimerized at C-6 to give the 6-*epi*-GA_{13} derivative (**12**) *via* an internal C-7,C-20 anhydride (**5**). This result facilitated the preparation of gibberellin analogues with a carboxylic group, α-orientated at C-6, which can compete with the C-19 C=O group in transannular participation reactions at C-20.

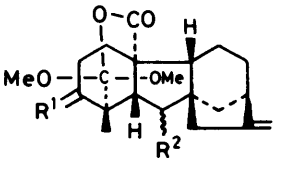
We show in this paper how the formation of C-7 ortho ester (**6**) is preferred to that of the C-19 ortho ester (**2**) in methanolysis of the mixed anhydride (**9**).

The 3-oxo dimethyl ester (**8**) was converted into the 20-toluene-*p*-sulphonic anhydride (**9**) by treatment with tosyl chloride in tetrahydrofuran (THF)–triethylamine. This compound was immediately subjected to methanolysis to give, in low yield, the 3-oxo ortho ester (**6**) and the 3-oxo trimethyl ester (**10**). However, the isomeric ortho ester (**2**) was not detected in the reaction. The 3-oxo ortho ester (**6**) showed, in its ^{1}H n.m.r. spectrum, three methoxy resonances at δ 3.14, 3.27, and 3.63, and 5- and 6-H signals at δ 2.30 and 2.57 (*J* 4 Hz), while in the trimethyl ester (**10**) the signals of the three methoxy groups appeared at δ 3.57, 3.62, and 3.63, and those of 5- and 6-H resonated at δ 2.21 and 2.93 (*J* 8 Hz). The great difference between the coupling constant values of these two methine protons in compounds (**6**) and (**10**) indicated that the ortho ester was formed at C-7 and not at C-19. On the other hand, the 6-*epi*-GA_{13} trimethyl ester derivative (**10**) may be formed by displacement of the tosyl group or by attack on the lactone of (**6**) by methoxide ion. The structure of the ortho ester (**6**) was confirmed by *X*-ray analysis (see later).

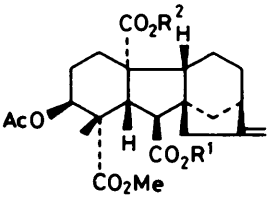
In order to know if the preference in the formation of the C-7 orthoester over that of the C-19 one, in the 6-*epi*-gibberellin is influenced by the presence, in ring A, of a different functional group, we carried out the methanolysis of the 3-acetate mixed anhydride (**11**). In this case also, a C-7 ortho ester (**7**) and the corresponding trimethyl ester (**13**) were formed, but now the two anhydrides (**5**) and (**15**) were also isolated. This difference in the two methanolyses could be a result of the longer length of time of the latter reaction. The structure of the ortho ester (**7**) was confirmed because hydrolysis and oxidation with pyridinium dichromate (PDC) gave ketone (**6**).

The preparation of these C-7 ortho esters offers the possibility of carrying out reactions on C-19, which can prove difficult in the gibberellin A_{13} series because of the presence of the C-20 carboxylic acid.

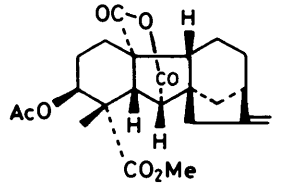
We reduced the lactone (**16**) [2] with lithium borohydride to determine the transannular participation of the C-19 and C-7 carboxylic functions in a reaction at C-20. Thus the 3,6-*epi*-GA_{37} methyl ester (**17**) and the acetal (**18**) were obtained. In the ^{1}H n.m.r. spectrum of ester (**17**) the coupling constant between 5- and 6-H is 9 Hz, the same value observed in 6-*epi*-GA_{13} trimethyl ester (**14**).[2] This excluded an alternative structure such as (**20**), which must have a smaller coupling value between these two protons. Also the ^{13}C n.m.r. spectrum is in accord with the



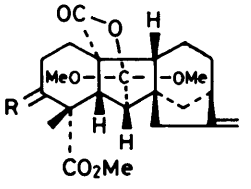
(**1**) R^1 = α-H, β-OAc
R^2 = β-CO_2Me
(**2**) R^1 = O, R^2 = α-CO_2Me



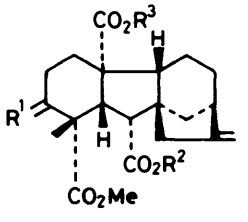
(**3**) R^1 = Me, R^2 = Ts
(**4**) R^1 = R^2 = H



(**5**)

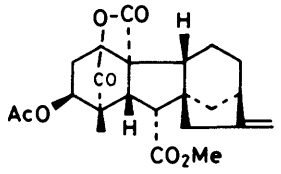


(**6**) R = O
(**7**) R = α-H, β-OAc



(**8**) R^1 = O, R^2 = Me, R^3 = H
(**9**) R^1 = O, R^2 = Me, R^3 = Ts
(**10**) R^1 = O, R^2 = R^3 = Me
(**11**) R^1 = α-H, β-OAc, R^2 = Me, R^3 = Ts
(**12**) R^1 = α-H, β-OAc, R^2 = Me, R^3 = H
(**13**) R^1 = α-H, β-OAc, R^2 = R^3 = Me
(**14**) R^1 = α-H, β-OH, R^2 = R^3 = Me

Ts = *p*-$MeC_6H_4S(O)_2$-



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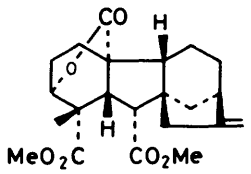

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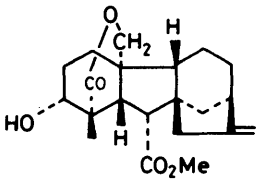
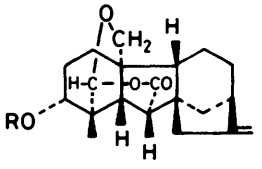
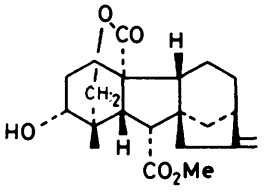


(17)



(18) R = H
(19) R = Ac



(20)

structure (**17**). The structure of the acetal (**18**) was given on the basis of the ^{1}H and ^{13}C n.m.r. spectra of its acetate (**19**). The first spectrum showed signals of the C-18 methyl group at δ 1.18, the 5- and 6-H protons as a broad singlet at δ 2.28, the C-20 methylene hydrogens as a pair of broad doublets at δ 3.48 and 3.85, the geminal proton of the acetate at C-3 as a double doublet at δ 4.64, the hydrogens of the exocyclic double bond as two singlets at δ 4.82 and 4.96, and the acetal proton at C-19 as a narrow triplet at δ 5.45. This acetal hydrogen is coupled with the 5-H. The ^{13}C n.m.r. spectrum showed the resonance for C-19 at δ 97.99. This chemical shift is typical of this group.[1] The acetal (**18**) must be derived from the other compound formed in the reaction, *viz.* lactone (**17**), by reduction of the lactone group.

The 3-oxo ortho ester (**6**) was subjected to *X*-ray analysis (see Figure). This compound consists of a system of five rings; three six-membered rings (A, C, and E) and two five-membered rings (B and D). Rings A, B, C, and D are named in accordance with the tetracyclic diterpene nomenclature, and ring E is the new ring formed in the reaction. The molecular conformation of

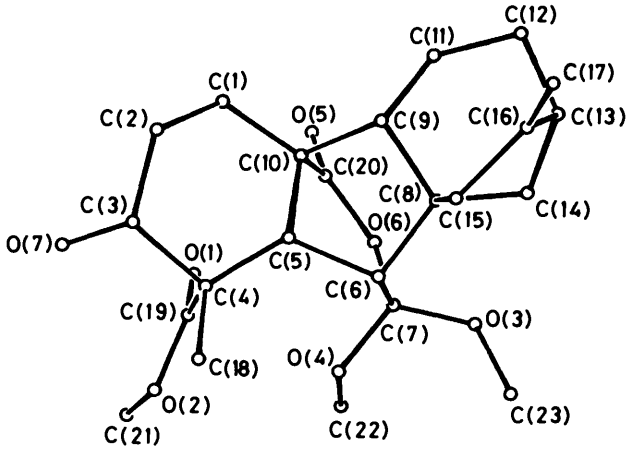


Figure. Molecular structure of the ortho ester (**6**)

Table. Atomic co-ordinates (× 10^4) for compound (**6**) with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
O(1)	5 413(3)	10 098(4)	−876(8)
O(2)	5 709(3)	9 515(5)	1 480(7)
O(3)	2 962(2)	9 499(4)	−11(6)
O(4)	4 113(3)	9 507(4)	1 000(6)
O(5)	4 407(3)	10 328(4)	−3 697(7)
O(6)	3 832(3)	9 937(4)	−1 564(6)
O(7)	6 542(3)	7 942(5)	−1 013(9)
C(1)	5 211(4)	8 496(7)	−3 862(10)
C(2)	5 763(6)	7 800(10)	−3 166(13)
C(3)	5 949(4)	8 025(6)	−1 466(11)
C(4)	5 314(4)	8 268(5)	−381(9)
C(5)	4 616(4)	8 042(5)	−1 305(9)
C(6)	3 846(4)	8 140(5)	−751(9)
C(7)	3 683(4)	9 260(6)	−287(10)
C(8)	3 412(4)	7 695(6)	−2 020(9)
C(9)	3 881(4)	7 917(6)	−3 512(9)
C(10)	4 527(4)	8 564(6)	−2 908(9)
C(11)	3 448(5)	8 361(7)	−4 853(9)
C(12)	2 744(4)	7 741(7)	−5 184(10)
C(13)	2 431(4)	7 335(6)	−3 663(11)
C(14)	2 625(4)	8 037(6)	−2 306(9)
C(15)	3 291(4)	6 506(6)	−1 891(10)
C(16)	2 762(4)	6 295(6)	−3 200(10)
C(17)	2 610(5)	5 388(7)	−3 799(13)
C(18)	5 358(5)	7 548(6)	1 056(12)
C(19)	5 457(4)	9 400(6)	52(11)
C(20)	4 280(4)	9 675(6)	−2 755(10)
C(21)	5 962(5)	10 516(8)	1 899(13)
C(22)	4 056(5)	10 551(7)	1 580(11)
C(23)	2 655(4)	9 011(6)	1 338(11)

the rings in the crystal has been examined in terms of torsion angles, asymmetric parameters,[3] and puckering and phase angle parameters.[4] Rings A and C have a conformation closer to a boat than a twist, while ring E adopts a half-chair conformation. The two five-membered rings B and D show a very similar conformation, closer to an envelope than a half-chair form. The C–C distances in the ring system are in the range 1.49—1.58 Å. The shortest bond is C-1,C-2, while the longest one is C-8,C-9, the bond shared by the *cis*-fused rings B and C. There are no hydrogen bonds, and the only intermolecular contact detected is between O(7) • • • C(23) (3.28 Å). The Table gives the atomic co-ordinates of the absolute molecular structure, and the Figure shows the molecular structure, which also represents the absolute stereochemistry. This was not determined because the absolute configuration of the gibberellins is well known.[5]

Experimental

M.p.s were determined with a Kofler hot-plate apparatus and are uncorrected. I.r. and n.m.r. were taken for solutions in $CHCl_3$ and $CDCl_3$ respectively, on Perkin-Elmer Model 681 and Bruker WP 200 57 spectrometers respectively. Silica gel Merck (0.05—0.2 mm) was used for column chromatography. Light petroleum refers to the fraction boiling in the range 60—80 °C. Thin layer chromatography (t.l.c.) was carried out on silica gel Schleicher–Schüll plates (F 1 500, LS 254).

Preparation of Compounds (**10**) *and* (**6**).—A solution of compound (**8**) (60 mg) in dry THF (3 ml) containing triethylamine (0.4 ml) was treated with toluene-*p*-sulphonyl chloride (40 mg) and the resulting mixture was stirred at room temperature under argon. After 2 h the mixed anhydride (**9**) was quantitatively formed (t.l.c.; light petroleum–ethyl acetate, 50%

v/v). Dry methanol (0.3 ml) was added and the reaction mixture was stirred for 46 h. The solvent was evaporated off, water was added, and the product was recovered in ethyl acetate to afford, on work up, a gum, which was chromatographed on silica gel. Elution with ethyl acetate–light petroleum (20% v/v) gave the ent-3-*oxo*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid trimethyl ester* (**10**) (2 mg) (Found: M^+, 418.2000. $C_{23}H_{30}O_7$ requires M, 418.1990); δ_H (200 MHz) 1.46 (3 H, s, 18-H_3), 2.21 and 2.93 (each 1 H, d, J 8 Hz, together 5- and 6-H), 3.57, 3.62, and 3.63 (each 3 H, s, OMe), and 4.79 and 4.92 (each 1 H, br s, 17-H); *m/z* 418 (M^+, 22%), 390 (22), 386 (33), 358 (35), 326 (97), 298 (100), 270 (48), and 239 (62). Further elution gave the 3-*oxo ortho ester* (**6**) (10 mg), m.p. 199—201 °C (Found: M^+, 418.1995. $C_{23}H_{30}O_7$ requires M, 418.1990); δ_H (200 MHz) 1.40 (3 H, s, 18-H_3), 2.30 and 2.57 (each 1 H, d, J 4 Hz, together 5- and 6-H), 3.14, 3.27, and 3.63 (each 3 H, s, OMe), and 4.87 and 4.98 (each 1 H, br s, 17-H); *m/z* 418 (M^+, 64%), 387 (26), 375 (22), 331 (37), 327 (24), 299 (18), 279 (26), 263 (26), 239 (41), 206 (38), 179 (38), and 165 (100).

Methanolysis of the Mixed Anhydride (**11**).—The anhydride (**11**) was obtained from the corresponding acid (**12**) (270 mg) as described above for the preparation of anhydride (**9**). This was treated with dry methanol (1.8 ml) and the solution was stirred for 4 days. The solvent was evaporated off and the residue was chromatographed over silica gel. Elution with ethyl acetate–benzene (10% v/v) afforded the anhydride (**5**)[2] (6 mg). Further elution gave the *acetate of* 6-epi-*gibberellin* A_{13} *trimethyl ester, compound* (**13**) (5 mg) (Found: M^+, 462.2246. $C_{25}H_{34}O_8$ requires M, 462.2251); δ_H (200 MHz) 1.29 (3 H, s, 18-H_3), 2.08 (3 H, s, OAc), 2.32 and 2.90 (each 1 H, d, J 8 Hz, together 5- and 6-H), 3.52, 3.54, and 3.62 (each 3 H, s, OMe), 4.81 and 4.93 (each 1 H, br s, 17-H), and 4.97 (1 H, t, 3-H); *m/z* 462 (M^+, 7%), 430 (33), 402 (13), 370 (27), 342 (32), 310 (34), 282 (55), 257 (13), 251 (14), 239 (12), 223 (62), 195 (15), and 43 (100). This compound was identical with that obtained by methylation of acid (**12**) with diazomethane. Further elution gave ent-3α-*acetoxy*-6-epi-*gibberell*-16-*ene*-7,19,20-*trioic acid* 19,20-*anhydride* 7-*methyl ester* (**15**) (5 mg) (Found: M^+, 416.1860. $C_{23}H_{28}O_7$ requires M, 416.1833); δ_H (200 MHz) 1.20 (3 H, s, 18-H), 2.10 (3 H, s, OAc), 2.46 and 3.07 (each 1 H, d, J 11 Hz, together 5- and 6-H), 3.62 (3 H, s, OMe), 4.92 (2 H, br s, 17-H_2), and 5.05 (1 H, t, 3-H); *m/z* 416 (M^+, 1%), 374 (2), 356 (25), 328 (42), 310 (14), 296 (59), 284 (72), 268 (50), and 43 (100). Further elution afforded the 3-*acetoxy ortho ester* (**7**) (29 mg) as a gum (Found: M^+, 462.2192. $C_{25}H_{34}O_8$ requires M, 462.2250); δ_H (200 MHz) 1.23 (3 H, s, 18-H_3), 2.08 (3 H, s, OAc), 2.29 and 2.53 (each 1 H, d, J 4 Hz, together 5- and 6-H), 3.11, 3.24, and 3.65 (each 3 H, s, OMe), 4.90 and 5.00 (each 1 H, br s, 17-H), and 4.92 (1 H, t, 3-H); *m/z* 4.62 (M^+, 1%), 431 (4), 418 (32), 283 (13), 223 (13), 193 (10), 179 (21), and 165 (100). When this reaction was carried out under the same conditions but with an increased reaction time for the mixed anhydride formation (24 h) the yields of compounds (**5**) and (**15**) were higher and that of compound (**7**) was lower.

Formation of Ketone (**6**) *from Acetate* (**7**).—The 3-acetoxy ortho ester (**7**) (15 mg) was dissolved in chloroform (1 ml) and the solution was treated overnight with methanolic potassium hydroxide (3%) (5 ml). Usual work-up afforded the corresponding alcohol (9 mg), which was treated with a solution of PDC (13 mg) in dichloromethane (2 ml) and the mixture was stirred for 3 h. The excess of reagent was precipitated with light petroleum and eliminated by filtration. The solvent was evaporated off to afford ketone (**6**) (3 mg), identical with the product reported above.

Reduction of the Lactone (**16**).—A solution of the lactone (**16**) (70 mg) in dry THF (25 ml) was stirred at room temperature with lithium borohydride (70 mg) for 48 h. The reaction mixture was added to 1M-aqueous potassium hydrogen phosphate and the solution was adjusted to pH 2.5. Extraction with diethyl ether in the usual way and evaporation of the solvent afforded a residue, which was chromatographed on silica gel. Elution with ethyl acetate–light petroleum (30% v/v) gave the acetal (**18**), which was purified as its *acetate* (**19**) (16 mg) (Found: M^+, 372.1916. $C_{22}H_{28}O_5$ requires M, 372.1934); δ_H (200 MHz) 1.18 (3 H, s, 18-H_3), 2.02 (3 H, s, OAc), 2.28 (2 H, br s, 5- and 6-H), 3.48 and 3.85 (each 1 H, d, J 13 Hz, 20-H), 4.64 (1 H, dd, J 12 and 5 Hz, 3-H), 4.82 and 4.96 (each 1 H, br s, 17-H), 5.45 (1 H, t, J 2 Hz, 19-H); δ_C (50.32 MHz) 30.66 and 29.54 (C-1 and -12), 25.39 (C-2), 78.61 (C-3), 42.06 (C-5), 49.16 (C-6), 53.87 (C-9), 18.48 (C-11), 39.70 (C-13), 48.80 (C-15), 156.90 (C-6), 107.24 (C-17), 24.01 (C-18), 97.99 (C-19), 62.67 (C-20), and 21.10 (AcO); *m/z* 372 (M^+, 31%), 328 (36), 268 (81), 239 (37), 225 (24), and 43 (100). Further elution gave starting material (**16**) (12 mg) and 3,6-*epi*-gibberellin A_{37} methyl ester (**17**) (25 mg) as a gum, δ_H (200 MHz) 1.21 (3 H, s, 18-H_3), 1.94 (1 H, dd, J 9 Hz, 5-H), 3.05 (1 H, d, J 9 Hz, 6-H), 3.61 (3 H, s, OMe), 4.05 (1 H, dd, J 11 and 2 Hz, 20-H), 4.61 (1 H, dd, J 11 and 3 Hz, 20-H), and 4.72 and 4.87 (each 1 H, br s, 17-H); δ_C (50.32 MHz), 30.73 (C-1), 38.06 (C-2), 78.60 (C-3), 52.27 (C-4), 51.68 and 51.81 (C-5 and -6), 47.07 (C-8), 57.53 (C-9), 42.97 (C-10), 16.05 (C-11), 31.10 (C-12), 39.85 (C-13), 33.44 (C-14), 51.95 (C-15), 156.69 (C-16), 106.34 (C-17), 18.45 (C-18), 173.75 (C-19), and 74.63 (C-20); *m/z* 360 (M^+, 1%), 332 (31), 272 (2), 243 (1), 227 (2), 199 (2), and 45 (100).

Crystal Data for the Ortho Ester (**6**).—The *X*-ray intensity data of compound (**6**) were collected on a four-circle diffractometer (Philips PW-1100), using graphite-monochromated Cu-K_α radiation (λ 1.5418 Å), with a crystal of dimensions 0.2 × 0.25 × 0.15 mm. The crystals are orthorhombic, $P212121$, $Z = 4$, with $a = 18.631\ 1(7)$, $b = 12.947\ 8(4)$, and $c = 8.579\ 1(4)$ Å, $D_c = 1.3463$ g cm^{-3}, and $\mu = 7.745$ cm^{-1}. The intensities of 2 053 reflections to a θ 65° were collected. They were reduced by Lorentz and polarization effects, but absorption and secondary extinction were not applied; 1 084 reflections were considered observed when $I > 2\sigma(I)$, and they were used for structure determination and refinement. The atomic scattering factors and anomalous dispersion corrections were taken from the literature.[6]

The structure was solved by MULTAN,[7] refined isotropically and then anisotropically by full-matrix least-squares.[8] The H-atoms were located on a difference map and were included in the refinement as fixed contributors. A weighting scheme was then applied to normalize $\langle \omega\Delta^2 \rangle$ *vs.* $\langle F_o \rangle$ and *vs.* $\langle \sin\theta/\lambda \rangle$. A weighted full-matrix least-square anisotropic refinement (fixed isotropic H-atoms) using 1 084 observed reflections converged to $R = 4.8$ and $R_w = 5.6$.*

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* *Supplementary data* [see section 5.6.3 of Instructions for Authors (1987), in the January issue]. Full lists of bond lengths and angles, torsion angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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