Acta Cryst. (1997). C**53**, 223–225

The Unusual Structure of a C-Arylated Gibberellin Bis-γ-lactone Formed from a Free Radical-Initiated Cyclization

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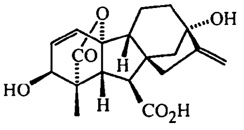
(*Received 20 May 1996; accepted 17 September 1996*)

Abstract

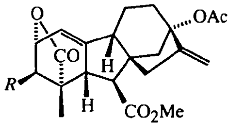
Treatment of the thionocarbonate derivative, *ent*-13-acetoxy-2β-hydroxy-3α-phenoxythiocarbonyloxy-20-norgibberella-1(10),16-diene-7,19-dioic acid 19,2-lactone 7-methyl ester†, (2), with Bu_3SnH and 2,2′-azobis(2-methylpropanenitrile) (AIBN) afforded in very high yield the unusual 10β-phenylgibberellin bis-γ-lactone, *ent*-13-acetoxy-2β,3α-dihydroxy-1α-carboxy-10α-phenyl-20-norgibberell-16-ene-7,19-dioic acid 19,2:1′,3-dilactone 7-methyl ester‡, (4), instead of the expected 3-desoxy product, (3). The crystal structure of (4) as its acetonitrile solvate, $C_{29}H_{30}O_8.C_2H_3N$, shows that the overall shape of (4) is significantly different from that of regular gibberellins, although the *C* ring still retains the boat conformation that is typical of this family of natural products.

Comment

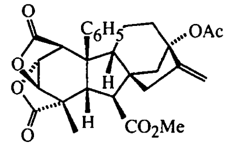
Gibberellic acid, (1), was converted into the phenyl thionocarbonate derivative (2) with a view to studying its deoxygenation (Barton & McCombie, 1975) to (3), which was required as a substrate for a number of planned gibberellin syntheses (Mander & Owen, 1996). We were surprised, however, to find that treatment of (2) with Bu_3SnH and AIBN [2,2′-azobis(2-methylpropanenitrile)] in benzene under reflux for 15 mins afforded in very high yield, a product that was still highly oxygenated and that had incorporated a phenyl group. Structure (4) was deduced from mechanistic considerations and spectroscopic measurements (Mander & Sherburn, 1996). The latter were so unusual when compared with regular gibberellin spectra (Mander, 1992), that we undertook the crystal structure analysis described in this paper so that we could confirm the conclusions made with regard to the constitution of (4). It was also important to determine its conformation in order to rationalize the unusual chemical shifts observed for several protons in its ^1H NMR spectrum.



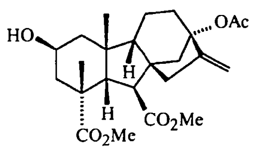
(1)



(2) $R = C_6H_5OC(=S)O$
(3) $R = H$



(4)



(5)

The derived structure (Fig. 1) confirms the original assignment and shows the H5 atom to be in the deshielding zone of the aryl ring, thereby providing a rationalization for the observed downfield shift of *ca* 0.4 p.p.m. in its associated resonance in ^1H NMR spectra, relative to its normal location for standard gibberellins and in the 10-*epi*-gibberellin (5) (Beale, 1985), which serves as the closest structural reference for (4). In contrast, the H15β atom (referred to here as H15*A*) at δ 1.40 is strongly shielded by the phenyl substituent. These shifts are consistent with those calculated from the observed distances of these atoms from the centre of the phenyl ring (3.75 for H5 and 3.79 Å for H15*A*) and their displacements from the least-squares plane of the ring (0.15 and 1.70 Å, respectively) (Haigh & Mallion, 1972). At δ 3.44, the H6 atom occurs at unusually low field, but this shift is probably due to deshielding by the lactone function running from the C2 to the C19 atom. Of further interest was the observation that all five aromatic protons of the 10-phenyl substituent were anisochronous [7.26 (*m*, 2H, ArH); 7.33 (*br. t*, 1H, J = 8.0 Hz, ArH); 7.38 (*br. t*, 1H, J = 8.0 Hz, ArH); 7.84 (*br. d*, 1H, J = 7.5 Hz, ArH)] as a consequence of restricted rotation (Sternhell, 1975).

The two bridging lactone functions in ring *A*, coupled with the stereochemical inversion at C10 that occurs with the introduction of the phenyl group onto the β-face of the gibberellin, impose profound changes on the shape of the gibberellin molecule, tending to make the lower face more concave, with an especially severe nonbonded interaction between C14 and the C19 carbonyl

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† Alternative name: (1α,2β,3α,4bβ,10β)-7-acetoxy-3-hydroxy-1-methyl-8-methylene-10-methoxycarbonyl-2-(phenoxythiocarbonyloxy)-gibb-4-ene-1-carboxylic acid 1,3-lactone.

‡ Alternative name: (1α,2β,3α,4β,4aβ,4bβ,10β)-7-acetoxy-2,3-dihydroxy-1-methyl-8-methylene-10-methoxycarbonyl-4a-phenylgibbane-1,4-dicarboxylic acid 1,3:4,2-dilactone.

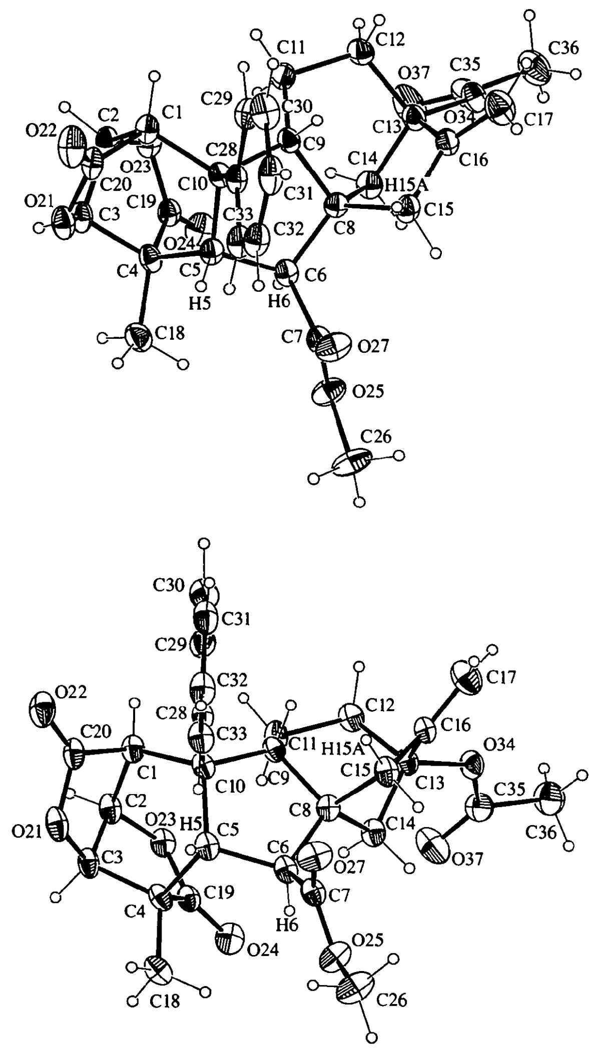

Fig. 1. Two views of compound (4) showing the labelling of the non-H atoms and some H atoms. Displacement ellipsoids are shown at the 20% probability level and H atoms are drawn as small circles of arbitrary radii.

group. This is relieved through the *B* ring adopting an envelope conformation in which the C5, C6, C8 and C9 atoms are almost coplanar [torsion angle −4.4 (5)°]. This change then favours a quasi-boat conformation for the *C* ring that is normal for most gibberellins, but which arises in those other cases in order to relieve non-bonded interactions between the C14 methylene and 10α substituents. There is also a reduction in the H5—C5—C6—H6 torsion angle to 119.9° as reflected in the reduced vicinal coupling between the H5 and H6 atoms, *i.e.* J = 3.6 Hz, compared with 12 Hz for compound (5) and 10–12 Hz for regular gibberellins.

Bond lengths and angles within the structure are similar to corresponding dimensions in related gibberellins (Cambridge Structural Database, 1995), with the exception of the bonds to C10, which tend to be long.

Experimental

Details of the synthesis of compound (4) have been published previously by Mander & Sherburn (1996). Suitable crystals were grown from acetonitrile by slow evaporation.

Crystal data

$C_{29}H_{30}O_8.C_2H_3N$
$M_r = 547.61$
Monoclinic
$P2_1$
$a = 8.350(2)$ Å
$b = 12.570(2)$ Å
$c = 12.945(1)$ Å
$\beta = 92.21(1)°$
$V = 1357.7(4)$ Å^3
$Z = 2$
$D_x = 1.339$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 20–25°$
$\mu = 0.81$ mm^{-1}
$T = 293$ K
Block
0.35 × 0.23 × 0.14 mm
Colourless

Data collection

Rigaku AFC-6*R* diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical
$T_{\min} = 0.823$, $T_{\max} = 0.904$
2343 measured reflections
1741 independent reflections
1741 reflections with $I_{\rm net} > 0$

$R_{\rm int} = 0.02$
$\theta_{\max} = 60.59°$
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 13$
$l = -13 \rightarrow 13$
3 standard reflections every 150 reflections intensity decay: 20%

Refinement

Refinement on F
$R = 0.053$
$wR = 0.073$
$S = 2.017$
1741 reflections
361 parameters
H atoms not refined
$w = 1/[\sigma^2(F) + 0.0009F^2]$
$(\Delta/\sigma)_{\max} = 0.018$

$\Delta\rho_{\max} = 0.309$ e Å^{-3}
$\Delta\rho_{\min} = -0.173$ e Å^{-3}
Extinction correction: Larson (1970); equation 22
Extinction coefficient: 8.1 (13) × 10^4
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °)*

C1—C2	1.541 (7)	C8—C14	1.547 (8)
C1—C10	1.594 (7)	C8—C15	1.545 (7)
C1—C20	1.492 (8)	C9—C10	1.568 (7)
C2—C3	1.499 (11)	C9—C11	1.547 (8)
C2—O23	1.427 (8)	C10—C28	1.562 (8)
C3—C4	1.545 (10)	C11—C12	1.533 (8)
C3—O21	1.455 (8)	C12—C13	1.554 (10)
C4—C5	1.580 (7)	C13—C14	1.541 (10)
C4—C18	1.529 (12)	C13—C16	1.550 (7)
C4—C19	1.485 (8)	C13—O34	1.444 (6)
C5—C6	1.561 (8)	C15—C16	1.512 (9)
C5—C10	1.572 (11)	C16—C17	1.289 (11)
C6—C7	1.516 (9)	C19—O23	1.361 (11)
C6—C8	1.568 (10)	C19—O24	1.204 (10)
C7—O25	1.311 (11)	C20—O21	1.382 (11)
C7—O27	1.206 (7)	C20—O22	1.190 (10)
C8—C9	1.582 (11)		
C2—C1—C10	113.6 (4)	C8—C9—C10	106.2 (6)
C2—C1—C20	97.9 (4)	C8—C9—C11	112.2 (5)
C10—C1—C20	106.7 (4)	C10—C9—C11	121.6 (4)
C1—C2—C3	100.3 (4)	C1—C10—C5	111.2 (4)

C1—C2—O23	118.2 (4)	C1—C10—C9	115.7 (5)
C3—C2—O23	104.8 (7)	C1—C10—C28	106.0 (5)
C2—C3—C4	99.9 (5)	C5—C10—C9	106.7 (5)
C2—C3—O21	105.3 (7)	C5—C10—C28	112.4 (5)
C4—C3—O21	116.1 (4)	C9—C10—C28	104.7 (4)
C3—C4—C5	109.8 (6)	C9—C11—C12	108.3 (4)
C3—C4—C18	115.4 (5)	C11—C12—C13	112.3 (6)
C3—C4—C19	98.1 (5)	C12—C13—C14	108.6 (5)
C5—C4—C18	111.6 (5)	C12—C13—C16	112.0 (6)
C5—C4—C19	108.8 (5)	C12—C13—O34	110.4 (5)
C18—C4—C19	112.2 (6)	C14—C13—C16	101.7 (5)
C4—C5—C6	110.1 (5)	C14—C13—O34	117.6 (6)
C4—C5—C10	115.7 (5)	C16—C13—O34	106.1 (4)
C6—C5—C10	107.6 (5)	C8—C14—C13	100.1 (5)
C5—C6—C7	112.6 (4)	C8—C15—C16	102.6 (4)
C5—C6—C8	107.5 (6)	C13—C16—C15	107.5 (5)
C7—C6—C8	114.0 (4)	C13—C16—C17	123.3 (6)
C6—C7—O25	111.2 (5)	C15—C16—C17	129.3 (5)
C6—C7—O27	125.8 (8)	C4—C19—O23	110.4 (6)
O25—C7—O27	123.0 (7)	C4—C19—O24	129.2 (8)
C6—C8—C9	107.6 (4)	O23—C19—O24	120.4 (6)
C6—C8—C14	112.7 (6)	C1—C20—O21	109.2 (5)
C6—C8—C15	119.1 (5)	C1—C20—O22	130.6 (7)
C9—C8—C14	110.3 (5)	O21—C20—O22	120.3 (6)
C9—C8—C15	108.0 (6)	C3—O21—C20	107.2 (5)
C14—C8—C15	98.8 (4)	C2—O23—C19	108.1 (5)

Data were collected to the maximum θ possible for a Rigaku AFC-6*R* diffractometer equipped with an evacuated exit-beam collimator. The θ-scan width was $(1.6 + 0.3\tan\theta)^\circ$, with a θ-scan rate 32° min^{-1} and up to four scans on weak reflections and background counts for one quarter of scan time on each end of every scan. H atoms were included at calculated positions and methyl groups were aligned to best match peaks observed in difference electron-density maps. The absolute structure was assigned to conform with the known chirality of the compound's precursors.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1992). Cell refinement: *MSC/AFC Diffractometer Control Software.* Data reduction: *Xtal DIFDAT ABSORB SORTRF ADDREF* (Hall & Stewart, 1990). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *Xtal CRYLSQ* (Hall, King & Stewart, 1995). Molecular graphics: *Xtal.* Software used to prepare material for publication: *Xtal BONDLA CIFIO.*

Lists of structure factors, anisotropic displacement parameters, atomic coordinates and complete geometry have been deposited with the IUCr (Reference: TA1104). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1997). **C53**, 225–227

4-Bromo-2,6-dichlorobenzonitrile

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(Received 31 October 1995; accepted 9 October 1996)

Abstract

The molecular structure of 4-bromo-2,6-dichlorobenzonitrile, $C_7H_2BrCl_2N$, is normal. The most striking feature of the crystal packing is a short distance of 3.102 (5) Å between the N and Br atoms of adjacent molecules, which can be thought of as an interaction between the Lewis base, CN, and the Lewis acid, Br.

Comment

We have previously determined the structures of several 2,4,6-trisubstituted benzonitriles, with iodo, bromo, chloro or methyl groups as substituents, in the search for intermolecular interactions between the Lewis-basic N atoms in the nitrile group and the Lewis-acidic halogen atoms; the methyl group was used as a non-acidic comparison group of about the same size as the halogens. The occurrence of $N\cdots X$ distances shorter than the sum of the van der Waals radii was taken as evidence for such interactions.

In the tribromo and trichloro compounds (Carter & Britton, 1972), such short distances are found. In the tribromo compound, both *ortho*-Br atoms are 3.06 Å from the N atoms in adjacent molecules. In the trichloro compound, only one *ortho*-Cl atom is close to an N atom, at a distance of 3.22 Å, consistent with chlorine being a weaker Lewis base than bromine. In the trimethyl compound (Britton, 1979), there are no short $N\cdots CH_3$ distances, as was expected.