ORGANIC COMPOUNDS

Molecular Geometry of a Pyran–Dioxane–Cyclohexane Tricycle with Linear *cis–trans*-Fusion of Rings

Eckehard Cuny, Frieder W. Lichtenthaler and Hans J. Lindner

Institut für Organische Chemie der Technischen Hochschule, Petersenstrasse 22, D-64287 Darmstadt, Germany

Abstract

The synthetically prepared enantiopure title compound, (2*S*)-(2*α*,4a*β*,5a*β*,9a*α*,10a*β*)-2-benzoyloxy-methyl-4a-hydroxy-4a,5a,6,7,8,9,9a,10a-octahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-yl benzoate diethyl ether solvate, $C_{26}H_{26}O_8 \cdot C_4H_{10}O$ (3), crystallizing as a monoetherate, shows the pyran–dioxane–cyclohexane ring junctions to be *cis–trans*, resembling the steric arrangement of the same three rings in the antibiotic spectinomycin and in a series of cardenolides. The ether molecule with which (3) crystallizes sits in a unique 'horse-saddle' arrangement, hydrogen bonded to the axially oriented tertiary hydroxyl group.

Comment

The antibiotic spectinomycin and a variety of steroidal glycosides of the gomphoside type have linearly linked *cis–trans*-fused pyran–dioxane–cyclohexane skeletons (Cochran, Abraham & Martin, 1972; Ferguson, Parvez, Cheung & Watson, 1983). In development of practical total syntheses of these natural products and their analogs (Lichtenthaler, 1989, 1992), we studied the silver carbonate promoted reaction of the enantiopure bromodihydropyranone (1), readily accessible from D-glucose (Lichtenthaler & Kraska, 1977), with (*R*,*R*)-cyclohexane-1,2-diol (2). This reaction afforded a crystalline tricyclic product in 84% yield. Depending on the stereochemistry of the bromine displacement and cycloacetalization reactions, this product may form one of four possible ring-junction conformations. Although the twofold operation of the anomeric effect points towards a *cis–trans* junction, its proof on the basis of ¹H-NMR and NOE measurements was not possible due to the absence of relevant

protons in the pyran ring. Accordingly, an X-ray structure determination was carried out to determine its stereochemistry unambiguously.
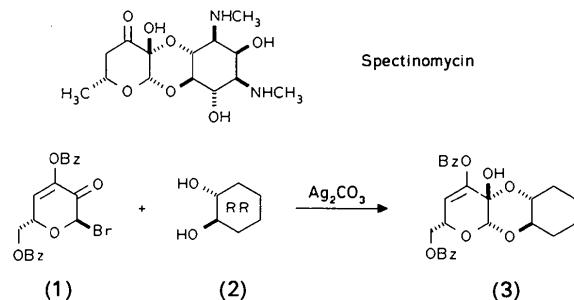
As is clearly apparent from Figs. 1–4, the junction of the pyran and dioxane rings is *cis*, with the tertiary hydroxyl group and the pyranoid ring O atom in axial orientations relative to the dioxane ring; the respective dihedral angles of 165.6 and 166.7° are ample proof of this. The bond distances observed are within standard limits, as are the torsional angles for the three rings (Table 2). There is generally good agreement with the corresponding data for spectinomycin (Cochran, Abraham & Martin, 1972), gomphoside (Ferguson, Parvez, Cheung & Watson, 1983) and other cardenolides (Nishio & Blum, 1982), particularly with respect to the parameters in the cyclohexanoid portions. In (3), due to the presence of a double bond, the pyranoid ring adopts the typical half-chair geometry, which is also seen in a variety of 2,6-*cis*-substituted dihydropyranones (Lichtenthaler, Rönninger, Lindner, Immel & Cuny, 1993).

A characteristic feature of the structure of (3) is the location of the ether molecule; it is hydrogen bonded to the tertiary hydroxyl group. The distance between 4a-OH and OEt_2 is comparatively short (1.995 Å) and, as such, provides a unique 'horse-saddle' arrangements.

In summation, the X-ray structure of (3) provides unequivocal proof of the *cis–trans* junction of the pyran, dioxane and cyclohexane rings. Since saponification of the enol-ester function is likely to liberate readily the carbonyl group at atom C(4), the molecule has all the essential structural and stereochemical features of the antibiotic spectinomycin and the cardenolide glycosides. Thus, the reaction of cyclohexanoid (or steroidal) diols such as (2) with enantiopure bromodihydropyranones of type (1) appears to be a most efficient route to the pyran–dioxane–cyclohexane tricycle seen in these natural products.
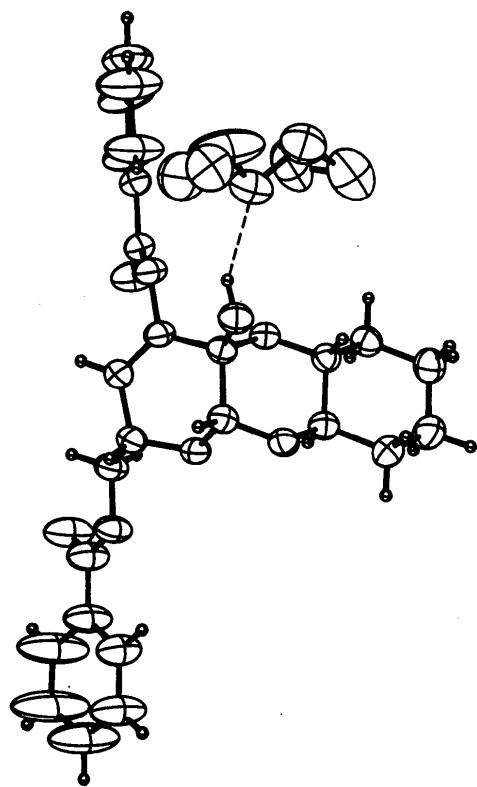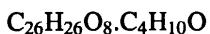
Fig. 1. *ORTEP* plot (Johnson, 1965) of (3) showing 30% probability displacement ellipsoids.


○ = carbon

● = oxygen
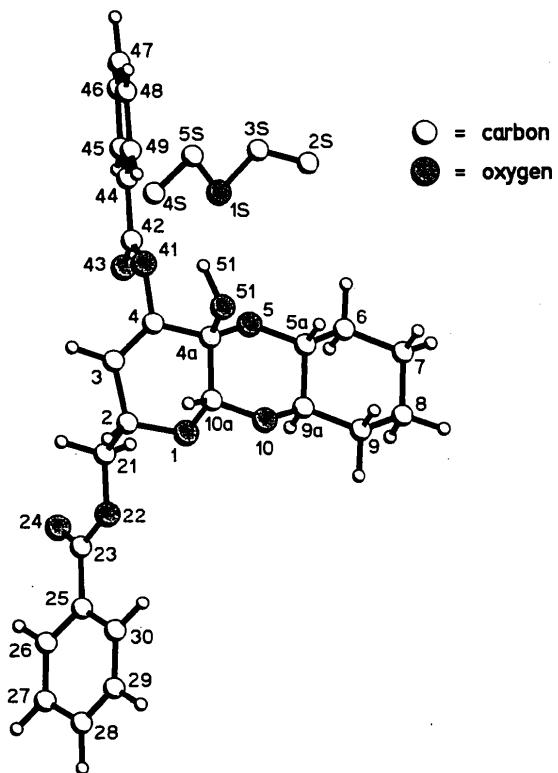
Fig. 2. View of (3) showing the numbering of the atoms.
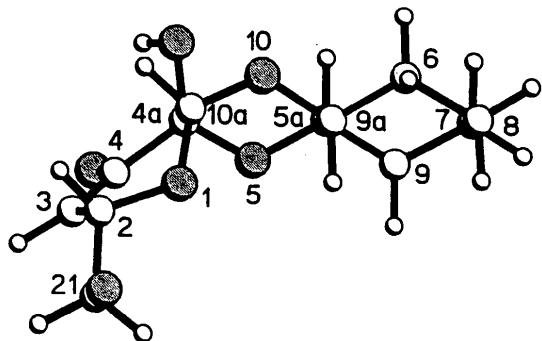
Fig. 3. Side view of (3) with the benzoyl residues omitted for clarity.
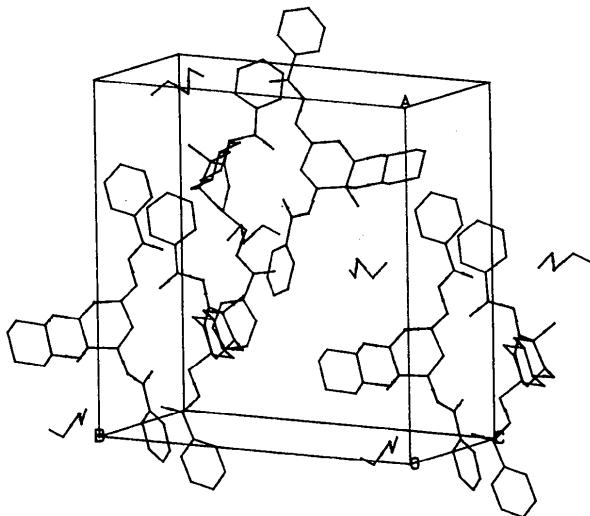
Fig. 4. View of the stereopacking for (3).

Experimental

*Crystal data*

$C_{26}H_{26}O_8.C_4H_{10}O$	Cu $K\alpha$ radiation
$M_r = 540.66$	$\lambda = 1.54178$ Å
Orthorhombic	Cell parameters from 48
$P2_12_12_1$	reflections
$a = 18.752$ (3) Å	$\theta = 13.9–28.3°$
$b = 18.370$ (3) Å	$\mu = 0.66$ mm^{-1}
$c = 8.471$ (2) Å	$T = 293$ (2) K
$V = 2918.0$ (10) Å^3	Needle
$Z = 4$	$0.80 \times 0.20 \times 0.15$ mm
$D_x = 1.231$ Mg m^{-3}	Colourless

Data collection

Stoe Stadi-4 diffractometer	$\theta_{max} = 60°$
$2\theta/\omega$ scans	$h = -20 \rightarrow 21$
Absorption correction:	$k = 0 \rightarrow 20$
none	$l = 0 \rightarrow 9$
4699 measured reflections	3 standard reflections
4207 independent reflections	monitored every 50
3848 observed reflections	reflections
$[I \geq 2\sigma(I)]$	intensity variation: 5%
$R_{int} = 0.021$	

Refinement

Refinement on F^2	$\Delta\rho_{max} = 0.213$ e Å^{-3}
$R(F) = 0.0495$	$\Delta\rho_{min} = -0.205$ e Å^{-3}
$wR(F^2) = 0.1481$	Extinction correction:
$S = 1.076$	SHELXL (Sheldrick, 1993)
4207 reflections	Extinction coefficient:
368 parameters	0.0041 (4)
H-atom parameters not	Atomic scattering factors
refined	from International Tables
$w = 1/[\sigma^2(F_o^2) + (0.0927P)^2$	for Crystallography (1992,
$+ 0.314P]$	Vol. C)
where $P = (F_o^2 + 2F_c^2)/3$	
$(\Delta/\sigma)_{max} = 0.254$	

O(1)—C(2)—C(3)—C(4)	−14.3 (4)
C(2)—C(3)—C(4)—C(4a)	−5.7 (4)
C(3)—C(4)—C(4a)—C(10a)	−9.1 (3)
C(4)—C(4a)—C(10a)—O(1)	44.4 (2)
C(4a)—C(10a)—O(1)—C(2)	−68.2 (2)
C(10a)—O(1)—C(2)—C(3)	51.3 (2)
C(4a)—O(5)—C(5a)—C(9a)	59.0 (2)
C(5a)—C(9a)—O(10)—C(10a)	58.1 (3)
C(9a)—O(10)—C(10a)—C(4a)	−51.8 (3)
O(10)—C(10a)—C(4a)—O(5)	48.3 (2)
C(10a)—C(4a)—O(5)—C(5a)	−51.7 (2)
C(5a)—C(6)—C(7)—C(8)	55.9 (3)
C(6)—C(7)—C(8)—C(9)	−55.9 (3)
C(7)—C(8)—C(9)—C(9a)	55.9 (4)
C(8)—C(9)—C(9a)—C(5a)	−58.2 (4)
C(9)—C(9a)—C(5a)—C(6)	59.9 (2)
C(9a)—C(5a)—C(6)—C(7)	−57.5 (3)
O(1)—C(10a)—C(4a)—O(51)	164.8 (2)
C(3)—C(4)—C(4a)—O(51)	−125.2 (3)
C(5a)—O(5)—C(4a)—O(51)	65.8 (2)
O(10)—C(10a)—C(4a)—O(51)	−72.7 (2)
C(2)—O(1)—C(10a)—O(10)	166.8 (2)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	U_{eq}
C(2)	0.3337 (1)	0.0763 (2)	0.5543 (4)	0.077 (1)
C(2S)	−0.0256 (3)	0.2234 (5)	0.6220 (14)	0.231 (5)
C(3S)	−0.0061 (10)	0.2769 (19)	0.7464 (22)	0.160 (9)
C(3S')	0.0089 (8)	0.2285 (13)	0.7448 (16)	0.157 (5)
C(3)	0.2600 (2)	0.0479 (2)	0.5819 (4)	0.077 (1)
C(4)	0.2046 (1)	0.0789 (1)	0.5182 (3)	0.070 (1)
C(4a)	0.2081 (1)	0.1486 (1)	0.4252 (3)	0.065 (1)
C(4S)	−0.0400 (6)	0.2267 (7)	0.4025 (16)	0.138 (5)
C(4S')	−0.0113 (7)	0.1686 (7)	0.3280 (17)	0.177 (6)
C(5S)	−0.0121 (5)	0.2244 (5)	0.2350 (11)	0.200 (3)
C(5a)	0.2052 (1)	0.1931 (1)	0.1615 (3)	0.068 (1)
C(6)	0.1870 (2)	0.1724 (2)	−0.0053 (4)	0.081 (1)
C(7)	0.2026 (2)	0.2355 (2)	−0.1141 (4)	0.095 (1)
C(8)	0.2790 (2)	0.2606 (2)	−0.1008 (4)	0.102 (1)
C(9)	0.2973 (2)	0.2802 (2)	0.0693 (4)	0.089 (1)
C(9a)	0.2820 (2)	0.2155 (2)	0.1741 (3)	0.071 (1)
C(10a)	0.2829 (1)	0.1812 (1)	0.4425 (3)	0.069 (1)
C(21)	0.3837 (2)	0.0148 (2)	0.5159 (5)	0.086 (1)
C(23)	0.5061 (2)	−0.0090 (2)	0.5159 (7)	0.112 (1)
C(25)	0.5789 (2)	0.0211 (2)	0.5320 (8)	0.128 (2)
C(26)	0.6332 (3)	−0.0258 (2)	0.5644 (16)	0.258 (6)
C(27)	0.7011 (3)	−0.0007 (3)	0.5824 (19)	0.307 (8)
C(28)	0.7164 (3)	0.0712 (3)	0.5644 (15)	0.240 (5)
C(29)	0.6630 (2)	0.1188 (2)	0.5380 (10)	0.160 (3)
C(30)	0.5946 (2)	0.0941 (2)	0.5261 (7)	0.118 (2)
C(42)	0.1149 (2)	−0.0109 (2)	0.4853 (4)	0.078 (1)
C(44)	0.0381 (2)	−0.0248 (2)	0.5064 (4)	0.088 (1)
C(45)	0.0095 (3)	−0.0859 (3)	0.4487 (8)	0.164 (2)
C(46)	−0.0612 (4)	−0.1018 (5)	0.4600 (10)	0.199 (3)
C(47)	−0.1034 (3)	−0.0569 (4)	0.5359 (11)	0.179 (3)
C(48)	−0.0767 (3)	0.0049 (4)	0.6075 (14)	0.224 (5)
C(49)	−0.0041 (2)	0.0205 (3)	0.5884 (11)	0.176 (3)
O(1)	0.3352 (1)	0.1265 (1)	0.4254 (2)	0.071 (1)
O(1S)	0.0145 (1)	0.2003 (2)	0.4959 (4)	0.141 (1)
O(5)	0.1923 (1)	0.1317 (1)	0.2655 (2)	0.067 (1)
O(10)	0.2969 (1)	0.2366 (1)	0.3355 (2)	0.072 (1)
O(22)	0.4557 (1)	0.0423 (1)	0.5227 (3)	0.095 (1)
O(24)	0.4935 (1)	−0.0721 (1)	0.5000 (6)	0.147 (1)
O(41)	0.1344 (1)	0.0553 (1)	0.5404 (3)	0.081 (1)
O(43)	0.1562 (2)	−0.0528 (2)	0.4285 (4)	0.122 (1)
O(51)	0.1618 (1)	0.2013 (1)	0.4841 (2)	0.077 (1)

The structure was solved by direct methods using SHELXS86 (Sheldrick, 1990) and refined by the full-matrix least-squares method using SHELXL93 (Sheldrick, 1993). C(5S) of the ether molecule was disordered with an occupancy factor of 0.5, and C(3S) and C(4S) were disordered with occupancy factors of 0.41 and 0.45, respectively.

Table 2. Selected geometric parameters (Å, °)

O(1)—C(2)	1.429 (3)	C(5a)—C(9a)	1.501 (3)
C(2)—C(3)	1.497 (4)	C(9a)—O(10)	1.448 (4)
C(3)—C(4)	1.302 (4)	O(10)—C(10a)	1.388 (3)
C(5)—C(4a)	1.419 (3)	C(5a)—C(6)	1.502 (4)
C(4a)—C(10a)	1.533 (3)	C(6)—C(7)	1.509 (5)
C(10a)—O(1)	1.411 (3)	C(7)—C(8)	1.509 (4)
C(4a)—O(5)	1.419 (3)	C(8)—C(9)	1.525 (5)
O(5)—C(5a)	1.451 (3)	C(9)—C(9a)	1.511 (4)

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