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A Lactone Derived from an Amino Acid with a Cyclohexyl Skeleton: (1*S*,6*R*,9*S*)-6-Benzamido-9-hydroxymethyl-8-oxabicyclo-[4.3.0]non-3-en-7-one

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Abstract

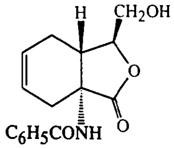
In the title compound, $C_{16}H_{17}NO_4$, the five-membered lactone ring is *trans*-fused to the cyclohexene ring. The cyclohexene ring exhibits a half-chair conformation with the benzamido group in an axial position. The γ-butyrolactone adopts an envelope conformation with the hydroxymethyl substituent in a pseudo-equatorial position. The crystal structure is stabilized by two intermolecular hydrogen bonds (O—H···O and N—H···O) involving the benzamido and hydroxy groups.

Comment

The use of uncommon amino-acid residues in the synthesis of peptides with restricted conformational flexibility has acquired increasing importance in the design of specifically folded analogues of biologically active peptides (Giannis & Kolter, 1993; Liskamp, 1994). Cyclic amino-acid analogues have proved valuable in the construction of conformationally constrained peptide backbones (Holladay *et al.*, 1991; Kazmierski *et al.*, 1988; Hsieh, LaHann & Speth, 1989). In this context, we are interested in the asymmetric synthesis, by Diels–Alder reaction, of new amino-acid derivatives having a cyclic skeleton (Buñuel, Cativiela & Díaz-de-Villegas, 1995).

In the course of experiments directed at the synthesis of cyclic amino-acid analogues having a cyclohexane skeleton, we have found that the isolation of cycloadducts resulting from the reaction between (*Z*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-2-phenyl-5(4*H*)-oxazolone and 1,3-butadiene in the presence of $LiClO_4$ under certain conditions afforded an unexpected byproduct whose chemical and spectroscopic data pointed to a cyclic lactone derived from one of the initially formed cycloadducts. The X-ray analysis was carried out in order to determine unambiguously the absolute configuration at the two new chiral C atoms formed in the Diels–Alder reaction and also to confirm the structure previously assigned to this unexpected compound on the basis of chemical and spectroscopic evidence.

The molecular structure for the title lactone, (I), is shown in Fig. 1. The X-ray analysis confirms the proposed molecular structure and establishes the stereochemistry at the two new chiral C1 and C4 atoms as *R* and *S*, respectively. The absolute configuration is deduced from the known *S* stereochemistry of the chiral centre at C3, which originates from (*R*)-isopropylideneglyceraldehyde; it could not be established from anomalous-dispersion effects in the present work.



(I)

The five-membered lactone ring is *trans*-fused to the cyclohexene ring; the torsion angles C2—C1—C4—C5 and C8—C1—C4—C3 have values of 168.3 (3) and 160.0 (3)°, respectively. The dihedral angle between the best least-squares planes through these two rings is 11.96 (18)°.

The cyclohexene ring exhibits a half-chair conformation [puckering parameters (Boeyens, 1978): Q = 0.529 (5) Å, θ = 50.5 (6), φ = 26.2 (8)°] in which the

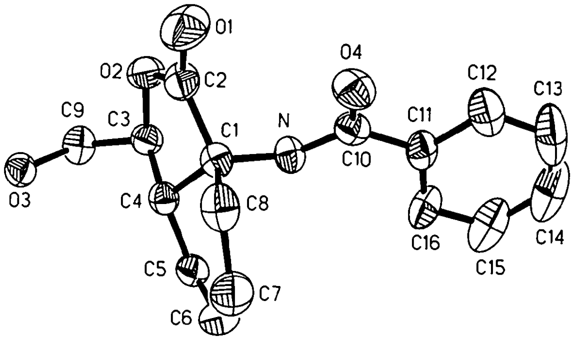


Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids, with H atoms omitted for clarity.

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C5—C6—C7—C8 group is planar and the other C atoms of the ring (C1 and C4) are displaced on opposite sides of the plane by −0.451 (5) and 0.355 (5) Å, respectively.

The benzamido group on the cyclohexene ring is in an axial position [the angle between the C1—N bond and the normal to the least-squares plane of the cyclohexene ring is 5.69 (19)°]. The C1—N—C10—C11 torsion angle is 159.6 (3)°, indicating that the amide linkage adopts the usual *trans* conformation, and the angle between the mean planes of the amide and the phenyl groups is 18.71 (19)°.

The conformation of the five-membered lactone ring is defined by the puckering parameters (Cremer & Pople, 1975) Q = 0.370 (5) Å and φ = 43.0 (7)°. The ring adopts an envelope conformation with atom C4 deviating by 0.569 (5) Å from the plane formed by the remaining four ring atoms (Matijasic, Bocelli, Ugozzoli & Sgarasotto, 1988, 1989; Kopf & Shulz, 1995). The substituents on the lactone ring can be classified as pseudo-axial and pseudo-equatorial by virtue of the resemblance between the envelope form of a five-membered ring system and the chair conformation of cyclohexane (Eliel, 1962). In the present case, the hydroxymethyl group occupies the pseudo-equatorial position [the angle between the C3—C9 bond and the normal to the least-squares plane of the lactone ring is 58.7 (3)°]. The exocyclic bond angles about the carbonyl O1—C2 group differ by 9.1°, with the larger value for the O1—C2—C1 angle [129.8 (3)°]. This is in agreement with published data on other lactones (Soriano-García, Rodríguez-Romeros, Villena & Yuste, 1994; Rychlewska, Szczepànska & Serkerov, 1992).

The three-dimensional packing of the molecules in the unit cell is shown in Fig. 2. The crystal structure is stabilized by two intermolecular hydrogen bonds (O—H···O and N—H···O) involving the benzamido and hydroxy groups [O3···O4^{i} 2.756 (4), H′···O4^{i} 1.864 (4) Å, O3—H′···O4^{i} 156.5 (3)°; N···O3^{ii} 2.929 (5), H···O3^{ii} 2.024 (5) Å, N—H···O3^{ii} 168.2 (3)°; symmetry codes: (i) $-x, \frac{1}{2}+y, 1-z$; (ii) $1-x, -\frac{1}{2}+y, 1-z$]. The hydrogen-bonded molecules form an infinite layer perpendicular to the crystallographic c axis. The layers are held together by van der Waals forces between phenyl groups interacting in a typical herringbone pattern.

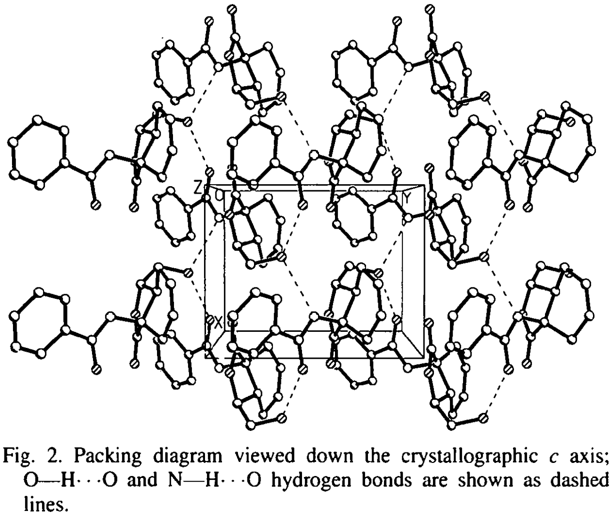

Fig. 2. Packing diagram viewed down the crystallographic c axis; O—H···O and N—H···O hydrogen bonds are shown as dashed lines.

Experimental

The title compound was obtained as a minor byproduct *via* the diastereoselective Diels–Alder reaction of homochiral (*Z*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-2-phenyl-5(4*H*)-oxazolone (1 mmol) (Cativiela, Díaz-de-Villegas & Jiménez, 1994) with 1,3-butadiene (6 mmol) in the presence of 5 *M* $LiClO_4$ in ether (4 ml) as a Lewis-acid catalyst, followed by aqueous work-up. The compound was isolated from the reaction mixture by column chromatography. Crystals were obtained by slow evaporation of a hexane solution.

Crystal data

$C_{16}H_{17}NO_4$
M_r = 287.31
Monoclinic
$P2_1$
a = 6.8840 (10) Å
b = 8.809 (2) Å
c = 12.170 (2) Å
β = 91.99 (3)°
V = 737.6 (2) Å^3
Z = 2
D_x = 1.294 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 40 reflections
θ = 5.7–12.5°
μ = 0.093 mm^{-1}
T = 293 (2) K
Prism
0.42 × 0.26 × 0.24 mm
Colourless

Data collection

Siemens P4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
1970 measured reflections
1562 independent reflections
1227 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0399

θ_{max} = 25.00°
$h = -1 \rightarrow 8$
$k = -1 \rightarrow 10$
$l = -14 \rightarrow 14$
3 standard reflections monitored every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0396
$wR(F^2)$ = 0.1330
S = 1.039
1561 reflections
191 parameters
H atoms riding with a common U_{iso}
$w = 1/[\sigma^2(F_o^2) + (0.0450P)^2 + 0.0454P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.022
$\Delta\rho_{max}$ = 0.145 e Å^{-3}
$\Delta\rho_{min}$ = −0.157 e Å^{-3}

Extinction correction: *SHELXL*93
Extinction coefficient: 0.0982 (88)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983) parameter = −1 (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}
O1	−0.1279 (4)	0.0859	0.4901 (2)	0.0732 (10)
O2	0.1751 (3)	0.0775 (5)	0.5609 (2)	0.0470 (7)
O3	0.4391 (3)	0.3397 (5)	0.6391 (2)	0.0421 (6)
O4	−0.1159 (3)	−0.0561 (5)	0.2568 (2)	0.0527 (7)
N	0.1950 (4)	0.0000 (6)	0.3125 (2)	0.0373 (7)
C1	0.1505 (5)	0.1420 (6)	0.3727 (3)	0.0359 (8)
C2	0.0437 (5)	0.1009 (6)	0.4767 (3)	0.0446 (9)
C3	0.3745 (5)	0.1121 (6)	0.5268 (3)	0.0388 (8)
C4	0.3386 (4)	0.2095 (6)	0.4251 (2)	0.0338 (7)
C5	0.4956 (5)	0.2326 (7)	0.3408 (3)	0.0447 (9)
C6	0.4042 (6)	0.3085 (6)	0.2409 (3)	0.0584 (12)
C7	0.2139 (7)	0.3215 (7)	0.2218 (3)	0.0613 (11)
C8	0.0581 (5)	0.2596 (7)	0.2954 (3)	0.0501 (10)
C9	0.4863 (5)	0.1843 (7)	0.6229 (3)	0.0453 (9)
C10	0.0614 (5)	−0.0775 (6)	0.2501 (3)	0.0391 (8)
C11	0.1356 (5)	−0.1847 (6)	0.1650 (2)	0.0425 (8)
C12	0.0046 (6)	−0.2858 (7)	0.1164 (3)	0.0625 (11)
C13	0.0600 (10)	−0.3764 (7)	0.0296 (4)	0.085 (2)
C14	0.2418 (10)	−0.3702 (8)	−0.0085 (4)	0.090 (2)
C15	0.3724 (8)	−0.2712 (9)	0.0384 (3)	0.080 (2)
C16	0.3221 (6)	−0.1757 (7)	0.1248 (3)	0.0566 (11)

Table 2. *Selected geometric parameters (Å, °)*

O1—C2	1.206 (4)	O4—C10	1.240 (4)
O2—C2	1.359 (4)	N—C10	1.356 (4)
O2—C3	1.479 (4)	N—C1	1.487 (4)
O3—C9	1.423 (4)	C10—C11	1.505 (5)
C2—O2—C3	110.9 (2)	O2—C2—C1	109.5 (3)
C10—N—C1	123.5 (3)	O4—C10—N	122.5 (3)
O1—C2—O2	120.7 (3)	O4—C10—C11	119.9 (3)
O1—C2—C1	129.8 (3)	N—C10—C11	117.5 (3)
C3—O2—C2—C1	4.9 (4)	C5—C6—C7—C8	−1.4 (7)
C8—C1—C4—C3	160.0 (3)	C1—N—C10—C11	159.6 (3)
C2—C1—C4—C5	168.3 (3)		

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1992). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus* (Sheldrick, 1989). Software used to prepare material for publication: *SHELXL*93. Molecular geometry: *PARST* (Nardelli, 1983).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: CF1053). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Trinervinol†

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Abstract

This X-ray diffraction study establishes the molecular structure of the title compound, 4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-α-(hydroxymethyl)-4b,8,8-trimethyl-2,2(3*H*)-phenanthrenedimethanol, $C_{20}H_{34}O_4$. The molecule consists of three six-membered rings (*A*, *B* and *C*). The *A*/*B* and *B*/*C* rings are *trans*-fused. The *A*, *B* and *C* rings adopt a distorted chair $^1C_4$ conformation. The crystal structure is stabilized by a network of intra- and intermolecular hydrogen bonds.

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