

Preparation and Crystal Structure of (1*S*, 5*S*, 7*S*, 8*R*)-8-Hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one

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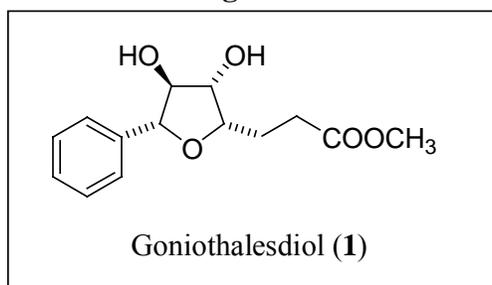
Abstract: The absolute configuration at two newly formed stereogenic centres (5*S*, 7*S*) during the key steps of the total synthesis of naturally occurring goniothalesdiol was established by single-crystal X-ray diffraction analysis relative to stereocentres (1*S*, 8*R*) of the title compound (alternatively named 3,6-anhydro-2-deoxy-6-phenyl-L-*ido*-1,4-hexonolactone, C₁₂H₁₂O₄). The conformation of both 5-membered lactone and furanose fused rings is also discussed.

Keywords: Lactones, palladium(II)-catalysis, oxycarbonylation, X-ray diffraction analysis, conformation.

Introduction

As a part of our long-term programme on palladium(II)-catalyzed oxycarbonylation of unsaturated polyols [1], we are interested in the preparation of naturally occurring biologically active lactones [2–5] structurally related to precursors of goniotaldesdiol (**1**) (Figure 1). Recently, this compound was isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae) and was shown to have a significant cytotoxicity against P388 mouse leukemia cells and insecticidal activities [6].

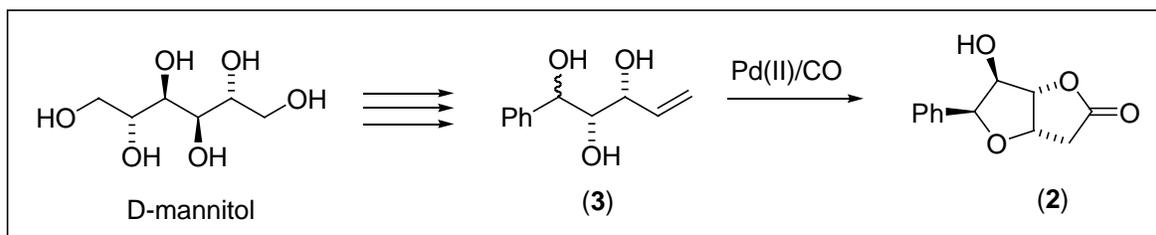
Figure 1.



Results and Discussion

The title compound 3,6-anhydro-2-deoxy-6-phenyl-L-ido-1,4-hexonolactone (**2**), representing the key intermediate in the first total synthesis of goniotaldesdiol [5], was prepared by palladium(II)-catalyzed oxycarbonylation of diastereomeric mixture of (1*S*, 2*S*, 3*R*) and (1*R*, 2*S*, 3*R*)-1-phenylpent-4-ene-1,2,3-triol (**3**) (Scheme 1). The products were separated by column chromatography.

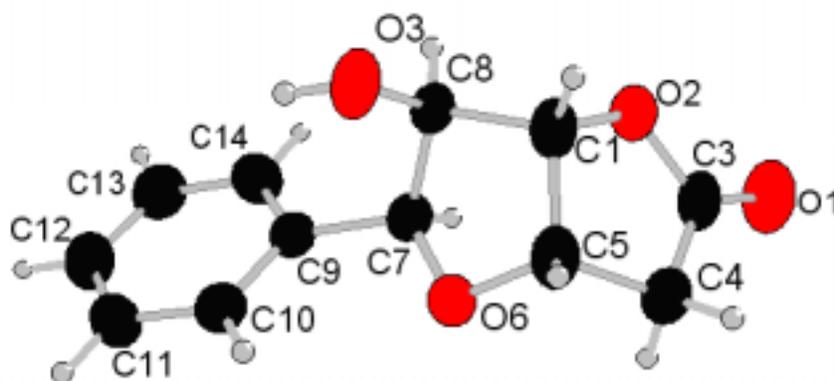
Scheme 1



From the point of view of the synthetic project, it is very important to know its correct configuration at the C-1, C-5, C-7, and C-8 atoms. Because of the obvious difficulties in unambiguously establishing the configuration at two newly formed stereogenic centres C-5 and C-7 (*R* versus *S*) by NMR methods, suitable crystals of compound **2** were subjected to X-ray analysis. This confirmed 5-*S* and 7-*S* (relatively to the known 1-*S* and 8-*R*) configuration of **2** thus indicating a *cis*-fusion of the five-membered lactone and tetrahydrofuran rings. The relevant $^1\text{H-NMR}$ coupling constants $J_{7,8} = 2.6$ Hz

and $J_{1,5} = 4.3$ Hz are also confirmative of the established structural arrangement. A perspective view and the numbering scheme adopted for molecule of **2** is depicted in Figure 2. The relevant crystallographic and structure refinement data for lactone **2** are given in Table 1. The selected bond lengths and bond angles are listed in Table 2. A list of selected torsion angles is given in Table 3. The hydrogen bond geometry is shown in Table 4. Atomic coordinates and equivalent anisotropic displacement parameters have been deposited with CCDC as supplementary information [7].

Figure 2. Thermal ellipsoids plot at 50% probability level and atomic numbering of lactone **2**.



The presence of a five-membered lactone ring fused to a furanose ring at the 2,3-position (C-5 and C-1 in Figure 2 or C-3 and C-4 according to carbohydrate nomenclature of **2**) imposes some conformational rigidity on this compound. The values of relevant torsion angles $\text{O-2-C-1-C-5-C-4} = 15.69(14)^\circ$, $\text{C-1-C-5-C-4-C-3} = -12.53(15)^\circ$, $\text{C-5-C-4-C-3-O-2} = 5.14(16)^\circ$, $\text{C-4-C-3-O-2-C-1} = 5.32(16)^\circ$, $\text{C-3-O-2-C-1-C-5} = -13.49(14)^\circ$ and puckering parameters [8] $Q = 0.152(2)$ Å, $\varphi = 55.7(6)^\circ$ indicate that O-2-C-1-C-5-C-4-C-3 five-membered lactone ring adopts the 2E conformation which is significantly deformed (twisted on C-1-C-5 bond) adopting the shape which is very close to the ${}^{C-5}T_{C-1}$ conformation with the C-5 atom oriented *endo* and C-1 *exo* to the reference plane defined by the atoms O-2, C-3, and C-4. Analogously, the puckering parameters $Q = 0.378(2)$ Å, $\varphi = 124.8(2)^\circ$ and the relevant dihedral angles $\text{O-6-C-5-C-1-C-8} = 12.40(15)^\circ$, $\text{C-5-C-1-C-8-C-7} = -30.83(13)^\circ$, $\text{C-1-C-8-C-7-O-6} = 39.33(13)^\circ$, $\text{C-8-C-7-O-6-C-5} = -33.23(15)^\circ$, and $\text{C-7-O-6-C-5-C-1} = 13.00(15)^\circ$ are indicative of E_3 conformation distorted (twisted on C-7-C-8 bond) almost completely to the ${}^{C-7}T_{C-8}$ direction for tetrahydrofuran ring (O-6-C-5-C-1-C-8-C-7) with the C-7 atom lying in the *endo* and C-8 *exo* direction with respect to the plane defined by the atoms C-1, C-5, and O-6.

Table 1. Crystal and experimental data for compound **2**^a

Empirical formula	C ₁₂ H ₁₂ O ₄
Formula weight	220.22
Temperature, <i>T</i> (K)	183(2)
Wavelength, λ (Å)	0.71073
Crystal system	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions (Å)	<i>a</i> = 5.7069(1) <i>b</i> = 8.4010(1) <i>c</i> = 21.2427(4)
Unit cell volume, <i>V</i> (Å ³)	1018.45(3)
Formula units per unit cell <i>Z</i>	4
<i>D</i> _{calcd} (g/cm ³)	1.436
Absorption coefficient, μ (mm ⁻¹)	0.108
<i>F</i> (000)	464
Crystal size (mm)	0.70 × 0.54 × 0.44
Diffractometer	Siemens SMART CCD
θ Range (°)	2.61–28.25
Range of <i>h</i>	−7→7
Range of <i>k</i>	−11→11
Range of <i>l</i>	−27→27
Reflections	11525
Independent reflections	2371 (<i>R</i> _{int} = 0.0328)
Completeness to $\theta = 28.25$ (%)	95.7
Absorption correction	multi-scan
Max. and min. transmission	0.9539 and 0.9281
Refinement method	Full-matrix least-squares on <i>F</i> ²
Data / restraints / parameters	2371 / 0 / 158
Goodness-of-fit on <i>F</i> ²	1.002
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0336, <i>wR</i> ₂ = 0.0798
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0400, <i>wR</i> ₂ = 0.0846
Largest difference peak and hole (e/Å ³)	0.195 and −0.209

^a Standard deviations in parentheses.

Table 2. Selected bond lengths [Å] and bond angles [°] for compound 2^a

O(1)-C(3)	1.2065(17)	C(5)-C(1)-C(8)	104.37(11)
O(2)-C(3)	1.3533(18)	O(1)-C(3)-O(2)	120.39(15)
O(2)-C(1)	1.4474(16)	O(1)-C(3)-C(4)	128.97(14)
O(3)-C(8)	1.4211(15)	O(2)-C(3)-C(4)	110.63(12)
O(6)-C(7)	1.4379(17)	C(3)-C(4)-C(5)	105.48(12)
O(6)-C(5)	1.4382(17)	O(6)-C(5)-C(1)	106.39(11)
C(1)-C(5)	1.540(2)	O(6)-C(5)-C(4)	112.97(13)
C(1)-C(8)	1.5206(18)	C(1)-C(5)-C(4)	103.71(12)
C(3)-C(4)	1.499(2)	O(6)-C(7)-C(9)	112.15(12)
C(4)-C(5)	1.524(2)	O(6)-C(7)-C(8)	104.29(11)
C(7)-C(9)	1.5076(19)	C(9)-C(7)-C(8)	114.36(11)
C(7)-C(8)	1.5315(19)	O(3)-C(8)-C(1)	105.62(11)
C(3)-O(2)-C(1)	111.22(11)	O(3)-C(8)-C(7)	112.58(12)
C(7)-O(6)-C(5)	108.55(11)	C(1)-C(8)-C(7)	101.00(11)
O(2)-C(1)-C(5)	106.51(11)	C(10)-C(9)-C(7)	123.04(13)
O(2)-C(1)-C(8)	109.74(11)	C(14)-C(9)-C(7)	117.78(13)

^a Standard deviations in parentheses.**Table 3.** Selected torsion angles [°] for compound 2^a

O(2)-C(1)-C(5)-C(4)	15.69(14)	O(2)-C(1)-C(5)-O(6)	-103.68(12)
C(1)-C(5)-C(4)-C(3)	-12.53(15)	C(8)-C(1)-C(5)-C(4)	131.77(11)
C(5)-C(4)-C(3)-O(2)	5.14(16)	C(3)-C(4)-C(5)-O(6)	102.24(14)
C(4)-C(3)-O(2)-C(1)	5.32(16)	C(5)-O(6)-C(7)-C(9)	-157.52(11)
C(3)-O(2)-C(1)-C(5)	-13.49(14)	O(2)-C(1)-C(8)-O(3)	-159.61(11)
O(6)-C(5)-C(1)-C(8)	12.40(15)	C(5)-C(1)-C(8)-O(3)	86.59(13)
C(5)-C(1)-C(8)-C(7)	-30.83(13)	O(2)-C(1)-C(8)-C(7)	82.97(13)
C(1)-C(8)-C(7)-O(6)	39.33(13)	O(6)-C(7)-C(8)-O(3)	-72.88(14)
C(8)-C(7)-O(6)-C(5)	-33.23(15)	C(9)-C(7)-C(8)-O(3)	49.98(16)
C(7)-O(6)-C(5)-C(1)	13.00(15)	C(9)-C(7)-C(8)-C(1)	162.18(12)
C(3)-O(2)-C(1)-C(8)	-125.91(12)	C(8)-C(7)-C(9)-C(10)	-106.15(16)
C(7)-O(6)-C(5)-C(4)	-100.14(14)	O(6)-C(7)-C(9)-C(14)	-168.01(12)

^a Standard deviations in parentheses.

Analysis of the molecular packing in the unit cell revealed two hydrogen bonds (Table 4). Atom O(1) acts as a bifurcated acceptor of both hydrogen bonds. The first-level descriptors based on the graph-set theory [9] give chain C1,1(7) for O...O hydrogen bond while C...O hydrogen bond forms

chain C1,1(5). On the second-level, C2,2(12) and C1,2(6) chains are formed by both types of hydrogen bonds. For convenience, the notation $Xa,d(n)$ has also been adopted in this paper, in which (X) is the pattern descriptor, (*a*) is number of acceptors, (*d*) is number of donors and (*n*) is the number of atoms comprising the pattern.

Figure 3. Packing scheme along *a*-axis for lactone **2**. Hydrogen bonds are shown as broken lines.

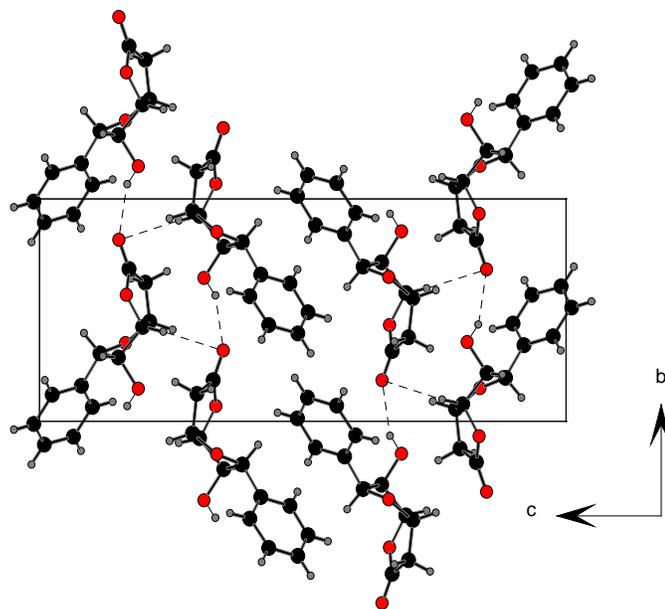


Table 4. Hydrogen bond geometry in compound **2**^a

X–H···Y	Symmetry code	X–H(Å)	H···Y(Å)	X···Y(Å)	X–H···Y(°)
O(3)–H(3)···O(1)	$x, y+1, z$	0.84	2.12	2.8885(14)	151.2
C(1)–H(1)···O(1)	$-x, y+0.5, -z+0.5$	1.00	2.55	3.4976(19)	157.3

^a Standard deviations in parentheses.

Experimental

General

¹H- and ¹³C-NMR spectra (in CDCl₃ with Me₄Si as an internal standard) were recorded on a Bruker Avance DPX 300 instrument operating at working frequencies of 300.13 and 75.46 MHz, respectively. For the assignments of signals, 1D NOESY and C–H heterocorrelated experiments were used. The EI mass spectrum (70 eV) was obtained on a Finnigan MAT SSQ 710 instrument. Specific rotation was determined on a Perkin–Elmer 241 polarimeter (10 cm cell). Microanalyses were performed on a Fisons EA 1108 analyser. Melting point was determined with a Boetius PHMK 05

microscope. Column chromatography was performed as flash chromatography on Silica Gel 60 (E. Merck, 0.063–0.200 mm).

X-ray techniques

Crystal and experimental data for lactone **2** are summarized in Table 1. Preliminary orientation matrix was obtained from the first frames using Siemens SMART software [10]. Final cell parameters were obtained by refinement of 7739 reflections using Siemens SAINT software [10]. The data were empirically corrected for absorption and other effects using SADABS program [11] based on the method of Blessing [12]. The structure was solved by direct methods and refined by full-matrix least-squares on all F^2 data using Bruker SHELXTL [13]. The non-H atoms were refined anisotropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Molecular graphics were obtained using the program DIAMOND [14].

(1S, 5S, 7S, 8R)-8-Hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.0]octan-3-one (2).

A 25-mL flask, purged with CO and connected to a balloon with CO gas, was charged with PdCl₂ (10 mg, 0.05 mol), anhydrous CuCl₂ (200 mg, 1.56 mmol), NaOAc (130 mg, 1.56 mmol), a mixture of (1*S*, 2*S*, 3*R*) and (1*R*, 2*S*, 3*R*)-1-phenylpent-4-en-1,2,3-triol (**3**) (100 mg, 0.52 mmol), and AcOH (10 mL). The mixture was stirred for 20 h at room temperature, then filtered through a short tube filled with cellulose (2 g). The solvent was evaporated under diminished pressure and the residue was purified by chromatography on a column of silica gel using hexane–ethyl acetate (5 : 2, v/v) as an eluent. The fractions with $R_f = 0.4$ (1:1 hexane–ethyl acetate) were collected, evaporated and the product recrystallized from 1:1 EtOAc–hexane affording the title compound **2** (37 mg, 32 %, colourless crystals). M.p. 177–180 °C; $[\alpha]_D + 38^\circ$ (c 0.31, MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 7.46–7.35 (m, 5H, Ph), 5.23 (d, 1 H, $J_{7,8} = 2.6$ Hz, H-7), 5.20 (ddd, 1 H, $J_{1,5} = 4.3$ Hz, $J_{4a,5} = 5.6$ Hz, $J_{4b,5} = 1.4$ Hz, H-5), 5.07 (d, 1 H, $J_{1,5} = 4.3$ Hz, H-1), 4.47 (d, 1 H, $J_{7,8} = 2.6$ Hz, H-8), 2.88 (dd, 1 H, $J_{4a,4b} = 18.8$ Hz, $J_{4a,5} = 5.6$ Hz, H-4a), 2.79 (dd, 1 H, $J_{4a,4b} = 18.8$ Hz, $J_{4b,5} = 1.4$ Hz, H-4b); ¹³C-NMR (75 MHz, CDCl₃): δ 175.4 (C-3), 134.2 (C-1 in Ph), 128.9 (C-3 and C-5 in Ph), 128.6 (C-4 in Ph), 126.6 (C-2 and C-6 in Ph), 87.2 (C-1), 82.9 (C-7), 77.1 (C-5), 75.8 (C-8), 36.0 (C-4); EIMS (70 eV): m/z 220 [M]⁺, 202, 192, 176, 143, 114, 106, 85, 84. Anal. Calcd for C₁₂H₁₂O₄ (220.22): C, 65.40; H, 5.49. Found: C, 65.29; H, 5.52.

Acknowledgements

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References and Notes

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Samples Availability: Compound **2** reported in this paper is available from MDPI.