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ORIGINAL PAPER

Novel Methyl 4,6-*O*-benzylidene-3-ketoglucopyranosid-fused γ-lactam: Synthesis and Crystal Structure

Hong Liu · Fuyi Zhang · Jin-Peng Li · Xuebin Yan · Hong-Min Liu · Yu-Fen Zhao

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Abstract The title compound methyl 4,6-*O*-benzylidene-3-ketoglucopyranosid-fused γ-lactam was synthesized from 2-oxoglucopyranoside in one pot via multi-step reaction sequence under mild conditions. It was characterized by HRMS, ^{1}H and ^{13}C-NMR, IR, elemental analysis and single crystal X-ray diffraction. The crystal belongs to orthorhombic *P*2(1)2(1)2(1) space group with unit cell parameters $a = 6.1840$ (12) Å, $b = 10.372$ (2) Å, $c = 25.702$ (5) Å, $V = 1648.5$ (6) Å^3, $Z = 4$, $D_c = 1.343$ Mg/m^3, $\lambda = 0.71073$ Å, μ(Mo $K\alpha$) = 0.102 mm^{-1}, F(000) = 704. X-ray diffraction analysis reveals that the compound adopts chair-chair conformation. The newly formed γ-lactam moiety is fused to glucopyranoside ring by C2 to form spirosugar. The crystal structure is stabilized by N–H···O2 hydrogen bond.

Keywords 4,6-*O*-benzylidene-3-ketoglucopyranosid-fused γ-lactam · Synthesis · Crystal structure

H. Liu · F. Zhang (✉) · J.-P. Li · X. Yan · Y.-F. Zhao (✉)
Chemistry Department, The Key Lab of Chemical Biology and Organic Chemistry, Phosphorus Chemical Engineering Research Center of Henan Province, Zhengzhou University, 450052 Zhengzhou, People's Republic of China
e-mail: zhangfy@zzu.edu.cn

Y.-F. Zhao
e-mail: zicb@zzu.edu.cn

H.-M. Liu
School of Pharmaceutical Sciences, Zhengzhou University, 100 Science Road, 450001 Zhengzhou, People's Republic of China

Introduction

γ-butyrolactams are biologically relevant as GABA receptor ligands [1–4]. They have also been shown to possess anticonvulsant and antioxidant activity [5–7]. Gabapentinlactam is neuroprotective in retinal ischaemia [8]. Besides, the γ-butyrolactams can be used as the biosynthetic precursors of GABA analogues and the key intermediates for the synthesis of pyrrolidines [9]. The pharmacophore engineered into the carbohydrate is an important method for obtaining biological analogues. Several examples of sugar-fused GABA analogues on a galactose or glucose scaffold have been recently proposed [10, 11]. Sugar lactams including sugar derived γ-butyrolactam are important biological substances and several sugar-biased lactams were synthesized [12–16]. The sugar-fused lactams are GABA analogues and the synthesis of fructose-fused γ-butyrolactams was achieved [17]. Their biological activities as GABA receptor ligands were evaluated. The biological data indicated the carbohydrate moiety can effectively be used to modulate drug pharmacokinetic properties and lipophilicity. These results have stimulated our attempts to find new synthetic route to structurally diverse sugar-fused γ-butyrolactams. In this paper, the novel title compound was synthesized for the first time and its molecular structure was investigated by HRMS, ^{1}H and ^{13}C-NMR, IR, elemental analysis, and X-ray crystallographic techniques.

Experimental

Instrument

Melting points were determined on a WC-1 melting point apparatus and are uncorrected. Infrared spectra were

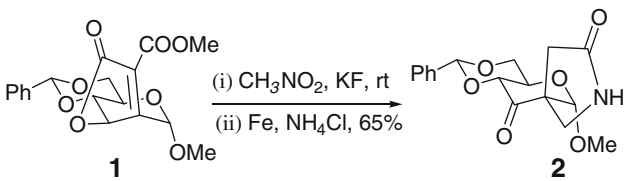
recorded on a Shimadzu IR-435 instrument using KBr disks in the 400–4000 cm^{-1} region. NMR spectra were taken in $CDCl_3$ on a Bruker DPX-400 spectrometer, and the chemical shifts are given in δ values. High resolution mass spectrometry spectrum were taken with a ZAB-2SE double-focusing mass spectrometer (VG Analytical, Manchester, UK).

Synthesis

The starting material **1** (Scheme 1) was prepared by the condensation of 2-oxoglucopyranoside [18–21] with diethyl malonate in the presence of NaOMe as we reported. The title compound **2** was synthesized from **1** reacting with nitromethane followed by reduction.

Synthesis of Methyl 4,6-*O*-benzylidene-3-ketoglucopyranosid-fused γ-lactam, **2**

To a solution of compound **1** (0.50 g, 1.38 mmol) in $MeNO_2$ (5 mL), KF (0.12 g, 2.07 mmol) was added. The mixture was stirred at rt under oxygen atmosphere for 48 h. The solvent was evaporated to dryness and the residue was dissolved in THF (15 mL). Reduced iron powder (0.32 g, 5.79 mmol), NH_4Cl (0.24 g, 4.58 mmol) and H_2O (10 mL) was added. The mixture was heated at 60 °C for 6 h and then filtered. The solid residue was washed with THF and the combined solution was evaporated to remove solvent. The residue was dissolved in EtOAc (25 mL), washed with H_2O (2 × 3 mL) and brine (1 × 3 mL), dried over Na_2SO_4 and evaporated to dryness to afford crude product, which was recrystallized from MeOH to give **2** as a crystalline solid (0.29 g, 63%). The single crystal was obtained after 1 week by slow evaporation of the acetone-methanol solution of **2**. m. p. 135–137 °C; IR ν_{max} (KBr)/cm^{-1}: 3302 (NH), 1752 (C=O), 1703 (CON); δ_H (400 MHz, $CDCl_3$) 7.50–7.49 (m, 2H, Ph), 7.38–7.36 (m, 3H, Ph), 5.60 (s, 1H, PhC*H*), 4.85 (brs, 1H, H-1), 4.38 (dd, 1H, *J* 4.4 and 10.0 Hz, H-6a), 4.16 (dt, 1H, *J* 4.4 and 10.0 Hz, H-5), 4.11 (d, 1H, *J* 10.0 Hz, H-4), 3.96 (t, 1H, *J* 10.0 Hz, H-6b), 3.40 (OMe), 4.18, 3.31 (d, each 1H, *J* 10.0 Hz, CH_2N), 2.8, 2.54 (d, each 1H, *J* 17.2 Hz, CH_2CO); δ_C (100 MHz, $CDCl_3$) 197.3 (C3), 173.2 (CON), 136.3, 129.4, 128.3, 126.4 (Ph),



Scheme 1 The synthesis of 4,6-*O*-benzylidene-3-keto glucopyranosid-fused γ-lactam

Table 1 Crystal data and structure refinement for the title compound

CCDC deposit no.	751673
Empirical formula	$C_{17}H_{19}NO_6$
Formula weight	333.33
Temperature/K	291(2)
Wavelength/Å	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	6.1840(12)
b/Å	10.372(2)
c/Å	25.702(5)
Volume/$Å^3$	1648.5(6)
Z	4
Calculated density/Mg m^{-3}	1.343
Absorptions coefficient/mm^{-1}	0.102
F(000)	704
Crystal size/mm	0.24 × 0.20 × 0.20
Reflections collected/unique	2052/2052 [*R*(int) = 0.0000]
Completeness to $2\theta = 27.51$	93.2%
Max. and min. transmission	0.9798 and 0.9758
Data/restraints/parameters	2052/0/222
Goodness-of-fit on F^2	1.045
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0638$, $wR_2 = 0.0732$
R indices (all data)	$R_1 = 0.1060$, $wR_2 = 0.0837$
Largest diff. peak and hole/e $Å^{-3}$	0.180 and −0.160

Table 2 Selected bond lengths (Å) and bond angles (°)

Bond lengths (Å)	
C(1)–C(2)	1.545(5)
C(2)–C(3)	1.529(4)
C(2)–C(17)	1.537(4)
C(2)–C(8)	1.552(4)
C(8)–C(9)	1.501(4)
C(9)–N(1)	1.340(5)
C(17)–N(1)	1.448(4)
O(3)–C(3)	1.204(3)
O(2)–C(9)	1.222(4)
O(5)–C(1)	1.412(4)
Bond angles (°)	
C(17)–C(2)–C(8)	105.3(3)
C(9)–C(8)–C(2)	108.1(3)
N(1)–C(9)–C(8)	114.8(3)
C(9)–N(1)–C(17)	104.1(3)
N(1)–C(17)–C(2)	102.8(2)
O(2)–C(9)–N(1)	127.0(3)
C(3)–C(2)–C(1)	109.3(3)
C(4)–C(3)–C(2)	111.5(3)
O(5)–C(1)–C(2)	112.5(2)
O(3)–C(3)–C(2)	123.9(3)

105.5 (C1), 102.2 (PhCH), 80.5 (C4), 69.3 (C6), 65.7 (C5), 57.4 (OMe), 55.5 (C2), 42.4 (CH_2N), 38.8 (CH_2CO). HRMS (FAB) *m/z* calcd. for $C_{17}H_{20}NO_6$: 334.1291 (M^++1); found: 334.1296. Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.23; H, 5.74; N, 4.21.

Crystal Structure Determination

Crystallographic data for the title compound was collected at 291(2) K using Mo-Kα radiation ($\lambda = 0.71073$ Å) on a Rigaku RAXIS-IV image plate area detector. The data was corrected for Lorentz and polarization factors and for absorption by using empirical scan data. The structure was solved with the SHELX program, and refined by full matrix least-squares methods based on F^2, with anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms were located theoretically and not refined. Crystal data was summarized in detail in Table 1. Selected bond lengths and bond angles are listed in Table 2.

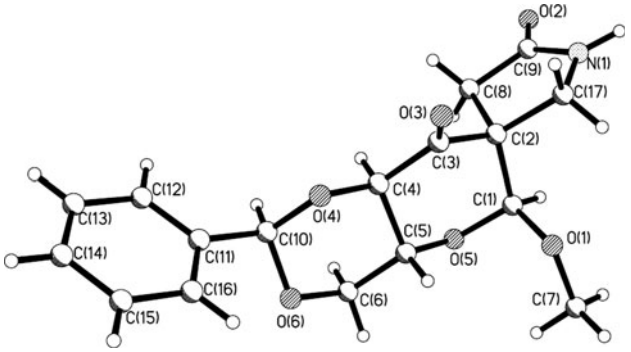


Fig. 1 The molecular structure of the title compound

Results and Discussion

The title compound was synthesized in one pot via multi-step reactions. In the presence of KF, autoxidation and nucleophilic addition of nitromethyl anion to α, β-unsaturated ester **1** followed by iron reduction of intermediate afforded 3-ketoglucopyranosid-fused γ-lactam **2**, which was characterized by HRMS, ^{1}H and ^{13}C NMR, IR, elemental analysis and X-ray crystallographic analysis. The M^++1 peak at 334.1296 in its HRMS spectrum, together with elemental analysis indicate the molecular formula to be $C_{17}H_{19}NO_6$. In the ^{1}H NMR spectrum of the title compound, the proton at δ 4.85 as a singlet was assigned to H-1. The proton at δ 4.11 as a doublet with coupling constant of 10.0 Hz is ascribed to H-4. The two protons at δ 2.80 and 2.54 (d, each 1H, *J* 17.2 Hz) are assigned to α-CH_2 of γ-lactam moiety. Another two protons at δ 4.18 and 3.31 (d, each 1H, *J* 10.0 Hz) are assigned to CH_2N. These assignments are confirmed by DEPT spectrum, showing two secondary carbons at δ 38.8 (C8) and 42.2 (C17) besides δ 69.3 (C6). In ^{13}C NMR spectrum, the quarternary carbon at δ 55.5 is ascribed to C2. The signals at δ 197.3 and 173.2 are assigned to C3 and C9, respectively. All the assignments are based on 2D NMR.

The title compound adopts chair-chair conformation as shown in Fig. 1. The newly formed γ-lactam moiety is

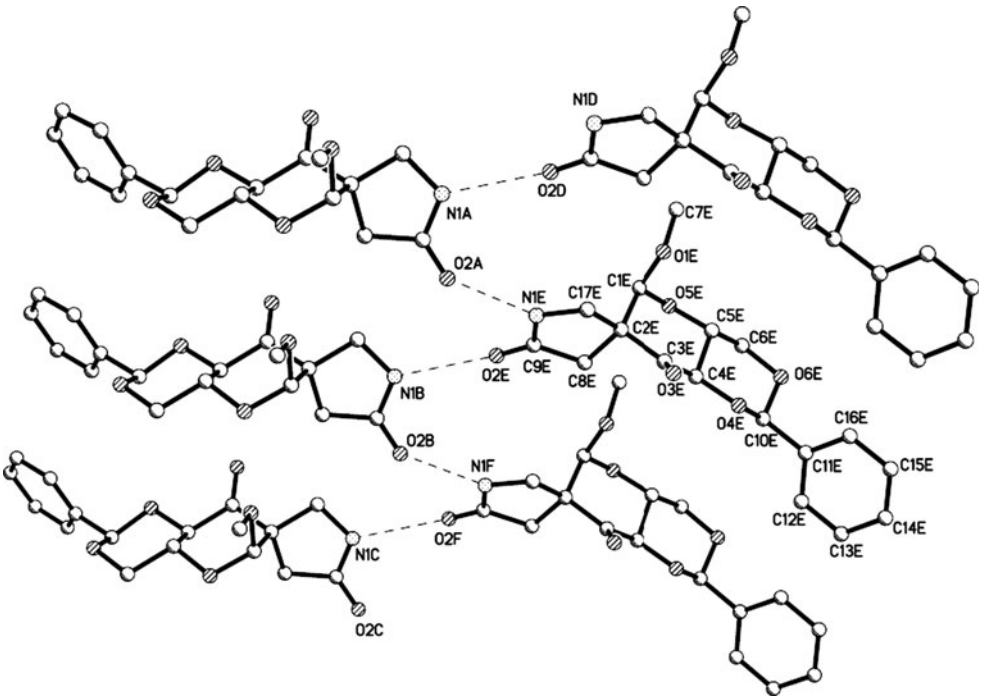


Fig. 2 The intermolecular hydrogen bonds of the title compound

fused to glucopyranoside ring by C2 to form spirosugar. Atoms C2 and C5 are displaced by −0.6354 and 0.7153 Å, respectively, from C3–C4–O5–C1 least-squares plane (r. m. s. deviation 0.0004 Å), giving a flattened chair conformation. Atoms C5 and C10 deviate by 0.6704 and −0.6827 Å from the C4–O4–C6–O6 plane (r. m. s. deviation 0.0149 Å), resulting in another chair conformation. The phenyl ring is nearly perpendicular to these two planes, forming interplanar angles of 92.8° and 75.5°, respectively. As expected, in the newly formed γ-lactam moiety, C8, C9, O2 and N1 locate in one plane (r. m. s. deviation 0.0002 Å) because of sp^2 hybridization of C9. However, atoms C2 and C17 are displaced by −0.3372 and 0.0265 Å respectively from this plane. Similarly, C3 in the newly formed carbonyl group also adopts sp^2 hybridization and the plane C4–C3–O3–C2 is formed (r. m. s. deviation 0.0011 Å).

The crystal structure is stabilized by intermolecular hydrogen bonds N–H···O2 among the γ-lactam moieties (Fig. 2). The title molecule forms hydrogen bonded molecular chains, which stack along the *a* direction in an efficient manner. The absolute structure of the title compound was deduced based on the starting material α-D-2-oxoglucopyranoside [18].

Supplementary Material

X-ray crystallographic file in cif format for the structure determination of the title compound has been deposited with the Cambridge Crystallographic Data Centre, CDCC: 751673. Copies of this data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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