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ORIGINAL PAPER

Synthesis and Crystal Structure of Benzoyloxymethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkauran-18-carbonate Ester

Jin Cai · Wen Zhou · Junqing Chen · Min Sun · Min Ji

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Abstract Isosteviol derivative: benzoyloxymethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkauran-18-carbonate ester was synthesized by esterification of isosteviol with chloromethyl benzoate and its crystal structure was determined by X-ray diffraction method. The compound crystallizes in the triclinic space group P1 with unit cell parameters: a = 8.784(3) Å, b = 9.079(3) Å, c = 15.950(6) Å, α = 79.343(6)°, β = 79.061(5)°, γ = 89.849(5)°, *Z*= 2. The conformation of rings A and B is *chair*, whereas the conformation of ring C is unsymmetrical *twist chair*. The carbonyl group at the C20 is coplanar with the benzene ring. The fragment of the ester group occupying the pseudoaxial site of C1 position adopts a zigzag conformation.

Keywords Crystal structure · Isosteviol · Benzoyloxymethyl ester

Introduction

Isosteviol, (4α,8β,13β)-13-methyl-16-oxo-17-norkauran-18-oic acid **2**, is a tetracyclic diterpenoid with a beyerane skeleton, obtained by acid-catalyzed hydrolysis of stevioside **1**, a constituent of *Stevia rebaudiana*, which is commonly used as a noncaloric sugar substitute [1, 2]. It has been found that isosteviol has good pharmacological activity against a number of significant diseases including ischemia–reperfusion injury, hypertension, and cancer [3–6]. However, study in the Sansom Institute has demonstrated that isosteviol has a short half life for only 30 min and would be removed rapidly from the body, probably owing to glucuronidation of carboxyl in isosteviol. Therefore, the benzoyloxymethyl ester of isosteviol, benzoyloxymethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkauran-18-carbonate ester **6**, was synthesized, which may retain the pharmacological activity while having much more desirable pharmacokinetic properties via hydrolyzed by esterase under biological conditions to release isosteviol step by step. The crystal and molecular structures of benzoyloxymethyl ester was confirmed for future scientific studies, and a conventional synthetic method was also reported in this literature.

Experimental

Synthesis

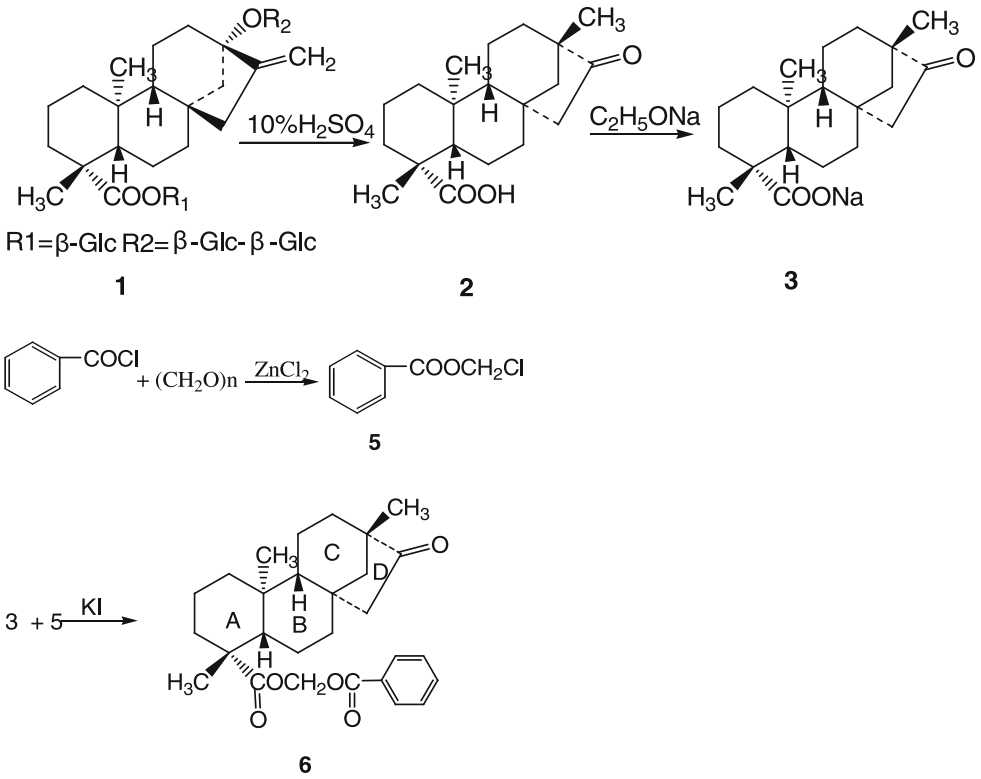
The synthesis of benzoyloxymethyl ester involved condensation of benzoyl chloride and paraformaldehyde, to yield chloromethyl benzoate **5**, which was converted to compound **6** by reacting with the sodium salt of isosteviol (Scheme 1). The structure of **6** was confirmed by MS, IR, ^{1}HNMR, ^{13}CNMR, elemental analysis, and X-ray crystallography.

Synthesis of Sodium Isosteviol

Isosteviol **2** was obtained by hydrolysis of stevioside **1** with 10% sulfuric acid at 95 °C for 7 h and recrystallization from ethanol gave colorless crystals of **2** in 80% yield. To a solution of sodium (0.2 g) in ethanol (20 mL), isosteviol **2** (2.8 g) was added. The mixture was stirred at reflux for

J. Cai · W. Zhou · J. Chen · M. Sun · M. Ji (✉)
Institute of Pharmaceutical Engineering, School of Chemistry and Chemical Engineering, Southeast University, 210096 Nanjing, People's Republic of China
e-mail: jimin@seu.edu.cn

Scheme 1 The synthesis route of compound **6**



2 h. The precipitate was collected by filtration, giving pale yellow solid of **3** (3.6 g) in 95% yield.

Synthesis of Chloromethyl Benzoate

A mixture of benzoyl chloride (12 mL, 0.1 mol), dry paraformaldehyde (3 g), and a minute quantity of zinc chloride were heated at 105 °C for 18 h. After cooling to ambient temperature, the mixture was poured into ice water and extracted with dichloromethane. The organic phase was dried with sodium sulfate and the solvent was removed by evaporation. Then the oil residue was chromatographed on silica gel with ethyl acetate/petroleum ether, and 4 g (23% yield)of chloromethyl benzoate **5** was obtained.

Synthesis of Benzoyloxymethyl Ester

A mixture of sodium isosteviol **3** (3.4 g, 0.01 mol), chloromethyl benzoate **5** (2 g, 0.012 mol), a minute quantity of potassium iodide, and acetonitrile (30 mL) was heated at reflux for 6 h. After cooling to ambient temperature, the solvent was removed in a vacuum and water (20 mL) was added. The organic phase was extracted with ethyl acetate and dried with sodium sulfate, then the solvent was removed by evaporation. Recrystallization from methanol gave colorless crystals of **6** (2.8 g) in 62% yield, m.p. 106–107 °C. The compound was characterized on the basis of spectral data: MS(ES): $[M + Na]^+$ 475.3; IR ν_{max}: 2917.91, 1743.42, 1716.42, 1600.71, 711.64 cm^{-1}; ^{1}HNMR($CDCl_3$) δ: 0.65(s, 3H, 20-H_3), 0.95(s, 3H, 17-H_3), 1.23(s, 3H, 18-H_3), 0.85–1.91(m,18H, 1-H_2, 2-H_2, 3-H_{ax}, 5-H, 6-H_2, 7-H_2, 9-H, 11-H_2, 12-H_2, 14-H_2, 15-H_β), 2.19–2.23(d, 1H, 3-H_{eq}, J = 13.68 Hz), 2.42–2.50(dd, 1H, 15-H_α, J = 18.72, 3.75 Hz), 5.97–6.03(q, 2H, OCH_2O, J = 6.17 Hz), 7.44–7.49(m, 2H, Ph-H), 7.59–7.63(t, 1H, Ph-H, J = 7.49 Hz), 8.03–8.06(m, 2H, Ph-H) ppm; ^{13}C-NMR($CDCl_3$) δ: 13.37, 18.77, 19.80, 20.27, 21.58, 28.65, 37.22, 37.79, 38.09, 39.36, 39.68, 41.43, 44.00, 48.24, 48.61, 54.24, 54.68, 57.09, 128.56, 128.92, 129.87, 133.73, 165.21, 176.12, 222.10 ppm; Anal. calcd for $C_{28}H_{36}O_5$ (%):C, 74.31; H, 8.02; Found: C 74.48, H 7.81.

Crystal Structure Determination

Colorless rhombic crystals of the title compound were grown at room temperature from methanol by slow evaporation technique. A single crystal of dimensions 0.46 × 0.45 × 0.37 mm was chosen for X-ray diffraction studies. X-ray diffraction data were collected on a BRUKER SMART 1000 CCD diffractometer with graphite monochromatized Mo–Kα radiation. The crystal data, data collection details, and refinement parameters for the structures are listed in Table 1.

The structure was solved by direct methods (program SHELX-97) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL-97 programs.

Table 1 Crystal data and other experimental details

CCDC number	CCDC-272526
Crystal description	Colorless rhombic
Chemical formula	C_{28} H_{36} O_5
Molecular weight	452.57
Temperature (K)	298(2)
Radiation, wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	
a (Å)	8.784(3)
b (Å)	9.079(3)
c (Å)	15.950(6)
α (°)	79.343(6)
β (°)	79.061(5)
γ (°)	89.849(5)
Unit cell volume (Å^3)	1226.6(7)
Z	2
Density (calculated) (mg/m^3)	1.225
Absorption coefficient (mm^{-1})	0.083
F(000)	488
θ range for data collection (°)	2.28–25.01
Limiting indices	$-10 \leq h \leq 10$
	$-10 \leq k \leq 9$
	$-16 \leq l \leq 18$
Reflections collected/unique	6493/4264 [R(int) = 0.0336]
Completeness to theta = 25.01	98.8%
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.9701, 0.9630
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4264/3/601
Goodness-of-fit on F^2	1.002
Final R indices [I > 2sigma(I)]	$R_1 = 0.0547$, $wR_2 = 0.1219$
R indices (all data)	$R_1 = 0.0919$, $wR_2 = 0.1410$
Largest different peak and hole (eÅ^{-3})	0.189, −0.172

The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed at geometrically permitted positions and were not refined.

Results and Discussion

The MS, IR, ^{1}HNMR, ^{1}CNMR and elemental analysis for the product were in good agreement with the title compound **6**. Figure 1 shows the molecular structure of the compound **6**. Packing diagram of the compound **6** in a unit cell is shown in Fig. 2. The selected bond lengths and bond angles are listed in Table 2.

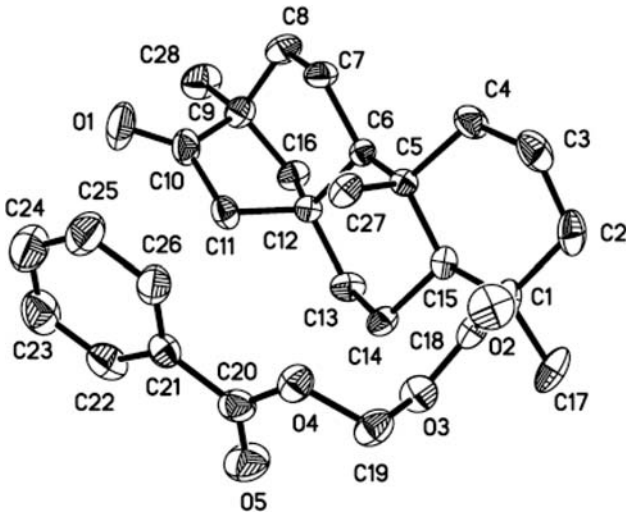


Fig. 1 Thermal motion ellipsoids, shaving crystallographic atom numbering

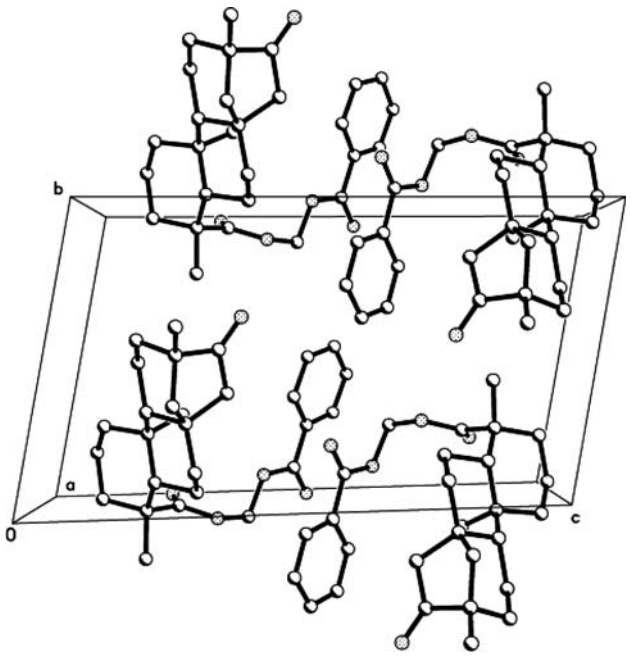


Fig. 2 The crystal packing diagram

The title molecule consists of three six-membered aliphatic rings A, B, and C, and a five-membered aliphatic ring D. The rigid molecular skeleton coincides with that of the parent isosteviol **2** [7]. The conformation of rings A and B is *chair*, whereas the conformation of ring C is unsymmetrical *twist chair* and the values of the torsion angles C12–C6–C7–C8, C6–C7–C8–C9, C6–C12–C16–C9, and C8–C9–C16–C12 show some significant deviation from the ideal value of 60°. Distortion in ring C is because of strain at the junction with the five-membered D ring.

Table 2 Selected bond lengths (Å), bond angle (°) and torsion angles (°) for non-hydrogen atoms

(a) Bond lengths					
O(1)–C(10)	1.217(7)	O(2)–C(18)	1.204(7)	O(3)–C(18)	1.352(7)
O(3)–C(19)	1.421(7)	O(4)–C(20)	1.368(7)	O(4)–C(19)	1.414(7)
O(5)–C(20)	1.195(7)	C(1)–C(17)	1.559(8)	C(1)–C(18)	1.508(8)
C(21)–C(26)	1.393(8)	C(20)–C(21)	1.472(9)	C(21)–C(22)	1.375(8)
C(24)–C(25)	1.366(11)	C(22)–C(23)	1.374(10)	C(23)–C(24)	1.371(11)
(b) Bond angles					
C(18)–O(3)–C(19)	117.3(5)	C(20)–O(4)–C(19)	115.6(5)	C(18)–C(1)–C(17)	106.3(5)
C(2)–C(1)–C(17)	107.4(5)	C(18)–C(1)–C(2)	109.6(5)	O(2)–C(18)–C(1)	125.7(6)
C(17)–C(1)–C(15)	109.2(4)	C(18)–C(1)–C(15)	116.0(4)	O(5)–C(20)–O(4)	122.5(6)
O(3)–C(18)–C(1)	112.5(5)	O(2)–C(18)–O(3)	121.7(5)	C(22)–C(21)–C(26)	118.6(6)
O(5)–C(20)–C(21)	125.5(7)	O(4)–C(19)–O(3)	108.2(4)	C(23)–C(22)–C(21)	120.3(7)
C(22)–C(21)–C(20)	119.0(6)	O(4)–C(20)–C(21)	112.0(6)	C(24)–C(25)–C(26)	120.2(8)
C(25)–C(24)–C(23)	119.8(8)	C(26)–C(21)–C(20)	122.4(6)		
(c) Torsion angles					
C12–C6–C7–C8	−47.3(6)	C6–C7–C8–C9	46.0(7)	C6–C12–C16–C9	−73.8(5)
C8–C9–C16–C12	70.0(5)	C7–C8–C9–C16	−57.6(6)	C7–C6–C12–C16	62.2(5)
O1–C10–C9–C28	−31.3(9)	C19–O3–C18–O2	7.7(7)	C20–O4–C19–O3	77.3(6)
C18–O3–C19–O4	91.3(5)	C19–O4–C20–O5	7.2(8)	C19–O4–C20–C21	−172.1(4)
C19–O3–C18–C1	−174.8(4)	C19–O4–C20–O5	7.2(8)	C19–O3–C18–O2	7.7(7)

The C10–O1 bond, 1.217(7) Å, has a normal value for a carbonyl group. The carbonyl group at the C20 is coplanar with the benzene ring (torsion angle: O5–C20–C21–C26 = 177.2(6)°, O5–C20–C21–C22 = −4.0(9)°), so the C20–O5 distance, 1.195(7) Å, is shorter than normal because of its conjugation with the benzene ring. The torsion angle O1–C10–C9–C28 is −31.3(9)°, minimizing steric interaction. The C1 position is at one top of the chair in ring A, methyl C17 is in the pseudoequatorial site, while carbonyl C18 is in the pseudoaxial site. The C18–O3–C19–O4–C20 fragment of the ester group adopts a zigzag conformation; the corresponding dihedral angles are given in Table 2. The methylene C19 is almost the same torsion angle from two oxygens of the carbonyl groups at C18 and C20 (the torsion angles: C19–O4–C20–O5 = 7.2(8)°, C19–O3–C18–O2 = 7.7(7)°).

The preliminary biological test showed that the title compound exhibited acute antihyperglycemic effect. The compound **6** is found to be more active than isosteviol on depressing the blood glucose during IVGTT in SD rats, respectively at 15.6 μM/kg.

Supplementary Material

CCDC–272526 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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