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Note

Stereoselective synthesis of methyl 4,6-*O*-benzylidene-2-*C*-methoxycarbonylmethyl-α-D-*ribo*-hexopyranosid-3-ulose, and its X-ray crystallographic analysis

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Abstract

Methyl 4,6-*O*-benzylidene-2-*C*-methoxycarbonylmethyl-α-D-*ribo*-hexopyranosid-3-ulose has been stereoselectively synthesized in 65% yield by reaction of methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose with diethyl malonate. X-ray crystallographic structure analysis reveals that the chain-branch and the OH group are bonded to C-2 in axial and equatorial positions, respectively. The molecules in the crystal lattice are stacked along a one-dimensional chain, with intermolecular hydrogen bonds between O-8 of one molecule and 2-OH of the next as well as intramolecular hydrogen bonds between O-3 and 2-OH. All phenyl groups are parallel as well as the planes of sugar rings in the molecular columnar stacking. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose; Methyl 4,6-*O*-benzylidene -2-*C*-methoxycarbonylmethyl-α-D-*ribo*-hexopyranosid-3-ulose; Molecular stacking

Oxo derivatives of glycosides (glycosiduloses) have biological importance[1,2] and are useful chiral synthons. Some of them have been found in natural glycosides.[3–5] Approaches for the synthesis of branched-chain glycosides are important in carbohydrate chemistry and in biological chemistry. In previous work, such fully protected oxoglycosides as hexopyranosid-4-uloses and an α-D-glucopyranosid-2-ulose were used for synthesis of branched-chain sugars.[6–9] There are no reports on the use of unprotected and partially protected '2-oxoglucopyranosides', because they are difficult to synthesize selectively, and are unstable, particularly in basic medium.[10–13] Here we report a novel reaction of a partially-protected '2-oxoglucopyranoside' (**1**) with diethyl malonate for synthesis of a 2-*C*-branched-chain glycopyranosid-3-ulose (**2**), the structure of which has been determined by spectroscopic data and X-ray crystallographic analysis.

Scheme 1 shows the reaction of compound **1**[12] with diethyl malonate to give **2**. The carbanion derived from diethyl malonate is used for nucleophilic addition to **1** in low temperature, and then $P(OEt)_3$ is added. Air is bubbled through the solution, which is

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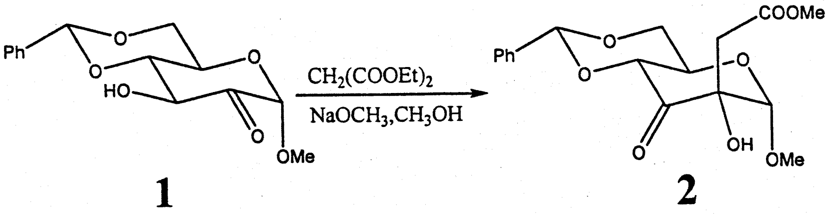

Scheme 1. Synthesis of methyl 4,6-*O*-benzylidene-2-*C*-methoxycarbonylmethyl-α-D-*ribo*-hexopyranosid-3-ulose.

simultaneously heated. In the course of the reaction, some water is added. Table 1 depicts the formation of **2** under various conditions. The temperature and solvent have major influence on the reaction. The optimum temperature is 25–28 °C. Above 35 °C, the yield decreases. The solvent THF is better than $CHCl_3$, and a yield of 65% is attained by use of THF and 2 equiv $P(OEt)_3$. The high-resolution-LSI-MS spectrum of **2** indicates the quasimolecular ion peak $[M^+ + 1]$ at m/z 353.1217, indicating its molecular formula to be $C_{17}H_{20}O_8$. In the ^1H NMR spectrum, two protons giving rise to two doublets at δ 2.90 and 3.41 (each 1 H, J 16.0 Hz) are ascribed to methylene of the 2-*C*-chain branch. The DEPT spectrum exhibits two secondary carbon signals at δ 68.8 and 42.0, corresponding to C-6 and that of the methylene group of the 2-C-chain branch. It also indicates a quaternary carbon at δ 79.8, which is assigned to C-2. The NOESY spectrum shows a correlation between H-4 and the CO_2CH_3 group. The stereochemistry of **2** is shown as Scheme 1.

An ORTEP drawing of compound **2** is shown in Fig. 1 together with the numbering scheme. Selected bond distances and angles are given in Table 2. The chain-branch and 2-OH group are bonded to C-2 in axial and equatorial positions, respectively, displaying a tetrahedral geometry involving C-1, O-2, C-3, C-8, with C-2 in its center. The X-ray diffraction analysis also indicates that the crystal has molecular stacking along a one-dimensional chain. Fig. 2 exhibits the interaction among the molecules in the columnar stacking. The molecules are assembled in polymers through intermolecular hydrogen bonds established between O-8 of one molecule and 2-OH of the next one (distance 2-OH···O-8 2.909 Å, angle 2-OH···O-8 149.86°). Because of this interaction, the O-8–C-10 bond length in each molecule is longer than that of any other C–O bond (Table 2). In the molecular columnar stacking, all phenyl groups are parallel as well as the planes of sugar rings, with the distance of 2.6921 Å between ortho phenyl groups. In addition, in each molecule, an intramolecular hydrogen bond is established between 2-OH and O-3 (distance 2-OH···O-3 2.746 Å, angle 2-OH···O-3 117.49°).

Table 1
Synthesis of compound **2** under various conditions

Temperature (°C)	Time (h) [a]	Solvent	$P(OEt)_3$	Yield (%)
0	5.0	$CHCl_3$	2 equiv	8
	4.5	THF	2 equiv	10
25–28	4.5	$CHCl_3$		35
	4.0	THF		38
25–28	4.0	$CHCl_3$	2 equiv	50
	3.0	THF	2 equiv	65
35–38	4.5	$CHCl_3$	2 equiv	30
	3.5	THF	2 equiv	36

[a] Time of bubbling air through solution.

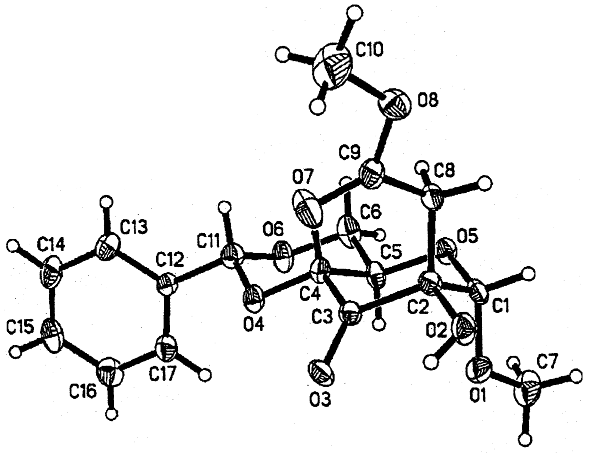

Fig. 1. An ORTEP diagram of the molecular structure of compound **2**, showing the atomic numbering.

Table 2
Selected bond lengths (Å) and bond angles (°) for compound **2**

Bond lengths (Å)			
O-1–C-1	1.420(4)	O-5–C-5	1.448(3)
O-1–C-7	1.449(3)	O-6–C-11	1.434(3)
O-2–C-2	1.427(3)	O-6–C-6	1.449(3)
O-3–C-3	1.220(3)	O-7–C-9	1.214(3)
O-4–C-11	1.424(3)	O-8–C-9	1.342(4)
O-4–C-4	1.446(3)	O-8–C-10	1.464(3)
O-5–C-1	1.426(4)		

Bond angles (°)	
O-2–C-2–C-8	107.4(2)
O-2–C-2–C-3	110.1(2)
C-8–C-2–C-3	114.7(2)
O-2–C-2–C-1	110.6(2)
C-8–C-2–C-1	107.8(2)
C-3–C-2–C-1	106.3(2)

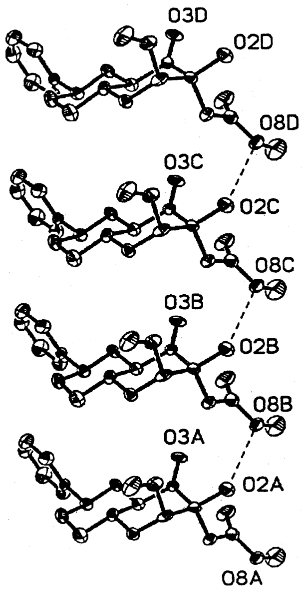

Fig. 2. Perspective ORTEP view of molecules of compound **2**, showing the intermolecular hydrogen bonds. Hydrogen omitted.

1. Experimental

General methods.—TLC was performed on precoated plates of Silica Gel 60 F_{254} (E. Merck). Components were detected by UV light. Elemental analyses were carried out on a MOD 1106 analyzer. Infrared spectra were recorded on a Shimadzu IR-435 instrument using KBr disks in the 400–4000 cm^{-1} region. Melting points were determined on a WC-1 melting-point apparatus and are uncorrected. NMR spectra were taken in acetone-d_6 with Me_4Si as the internal standard on a Bruker DPX-400 spectrometer and the chemical shifts are given in δ values. Liquid secondary-ion mass spectrometry (LSI-MS) spectra were taken with a ZAB-2SE double-focusing mass spectrometer (VG Analytical, Manchester, UK) in the positive mode.

*General procedure for synthesis of methyl 4,6-*O*-benzylidene-2-*C*-methoxycarbonylmethyl-α-*D-ribo-*hexopyranosid-3-ulose* (**2**).—Sodium (200 mg, 8.69 mmol) was dissolved in anhyd MeOH (12 mL), to which diethyl malonate (0.60 mL, 3.90 mmol) was added dropwise at 0 ~ 8 °C with stirring, and after 10 min, **1** (200 mg, 0.714 mmol) dissolved in anhyd THF or $CHCl_3$ (10 mL) was added dropwise, followed in some cases by addition of $P(OEt)_3$ (0.25 mL, 1.45 mmol). Then the mixture was heated and air was bubbled through simultaneously. The solvent was added at regular intervals to supplement the loss of its evaporation by air. The reaction was monitored by TLC. About 2.5 h later, 0.5 mL of water was added. At the end of reaction, the solution was evaporated in vacuo. The residue was dissolved in water, made neutral with AcOH, and then extracted with EtOAc and dried over Na_2SO_4. The solvent was evaporated in vacuo to give **2**, whose formation under various conditions is shown in Table 1. Recrystallization of **2** from EtOAc gave a colorless prism: mp 234–235 °C; IR (KBr); ν 3491 (OH), 2856 (CH_3), 1747 (carbonyl), 997, 770, and 703 cm^{-1} (Ph); ^1H NMR (400 MHz, acetone-d_6): δ 2.90, 3.41 (d, each 1 H, $J_{8a,8b}$ 16.0 Hz, H-8a, H-8b), 3.43 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 3.93 (dt, 1 H, $J_{5,6a} = J_{5,4}$ 10.0, $J_{5,6b}$ 4.8 Hz, H-5), 4.16 (t, 1 H, $J_{6a,6b} = J_{6a,5}$ 10.0 Hz, H-6a), 4.37 (dd, 1 H, $J_{6b,6a}$ 10.0 Hz, H-6b), 4.94 (s, 1 H, H-1), 5.08 (d, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 5.78 (s, 1 H, Ar–CH), 7.42–7.44 (m, 3 H, Ar–H), 7.52–7.55 (m, 2 H, Ar–H); ^{13}C NMR (100 MHz, acetone-d_6): δ 42.0 (C-8), 51.3 (C-7), 55.3 (C-10), 67.2 (C-5), 68.8 (C-6), 79.8 (C-2), 80.7 (C-4), 101.2 (C-11), 106.6 (C-1), 126.6, 128.2, 129.1, 137.7 (Ar), 170.1 (C-9), 198.9 (C-3); HR-LSI-MS Calcd for $C_{17}H_{21}O_8$: m/z 353.1236 $[M^+ + 1]$; Found: m/z 353.1217; Anal. Calcd for $C_{17}H_{20}O_8$ (352.12): C, 57.95; H, 5.72. Found: C, 57.91; H, 5.75.

Crystal structure determination.—A colorless prism, of dimensions $0.30 \times 0.30 \times 0.20$ mm was mounted on R-AXIS-IV diffractometer with graphite-monochromated Mo K_α ($\lambda = 0.71073$ Å) radiation: monoclinic, space group $P2(1)$ with $a = 11.446(2)$, $b = 5.7922(12)$, and $c = 13.364(3)$ Å, $V = 885.8(3)$ Å^3, $Z = 2$, $T = 293(2)$ K, $\mu(\text{Mo } K_\alpha) = 0.106$ mm^{-1}, and $D_{\text{calcd}} = 1.321$ Mg m^{-3}. A total of 2010 reflections were collected. The structure was solved by direct methods using SHELXS-93[14] and successive Fourier-difference synthesis. Refinement (on F^2) was performed by full-matrix least-squares method with SHELXS-97.[15] $R(F) = 0.0672$ for 1473 reflections with $I > 2\sigma I$, $\omega R(F^2) = 0.1079$ for 2010 reflections with $\omega = 1/[\sigma^2(F_o^2) + (0.0240P)^2 + 0.00P]$, where $P = (F_o^2 + 2F_c^2)/3$.

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