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Stereoselective synthesis of a *C*-glycosylic compound (a "methyl *C*-glycoside") through a regioselective free-radical ring-opening reaction. A single-crystal X-ray structure determination

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Abstract

Readily available 3,4,6-tri-*O*-acetyl-D-glucal was converted to 2,6-anhydro-5,7-*O*-benzylidene-1,3,4-trideoxy-D-*arabino*-hept-3-enitol, a methyl *C*-glycosylic compound. Cyclopropanation of 4,6-*O*-benzylidene-D-glucal, followed by tributylstannyl radical-mediated regioselective ring opening of the 1,2-cyclopropano sugar led to a 2,6-anhydro-1-deoxyheptose, (a "methyl *C*-β-D-glycoside"). The stereochemistry of the 1,2-cyclopropano sugar and the "methyl *C*-glycoside" were confirmed by single-crystal X-ray diffraction studies.

Keywords: *C*-Glycoside; 1,2-Cyclopropanated sugar; Radical ring opening; Single-crystal X-ray diffraction

C-Glycosylic compounds, frequently referred to as "*C*-glycosides", are a class of compounds that continue to receive attention in carbohydrate and synthetic organic chemistry. Some of the total syntheses of biologically important macromolecules have been achieved using *C*-glycosides as chiral building blocks.[1] Hence, efficient and stereocontrolled methods for the synthesis of *C*-glycosides and obtaining chiral templates for more complex synthetic targets constitute major challenges in this area.[2]

Our laboratory has earlier reported the synthesis of unsaturated aryl *C*-glycosides and other aryl *C*-deoxyglycosides.[3] An ongoing research project in this area in our laboratory is the development of new methodology for the synthesis of alkyl *C*-glycosides. Because of the attendant problems in regio- and stereoselectivity (observed especially at the anomeric centre of sugars), free-radical reactions have been increasingly employed in organic synthesis.[4] Unsaturated sugars, in particular 3,4,6-tri-*O*-acetyl-D-glucal, have found widespread use as carbohydrate synthons.[5]

Cyclopropanation of appropriately protected glycals paves the way for the introduction of alkyl groups at either C-1 or C-2 of the pyranose ring. Several methodologies have been employed in the last decade for stereocontrolled cyclopropanation in carbohydrates.[6] Although several reactions are known for solvolytic[7] and electrophilic ring opening,[8] there are only a few reports on the free-radical ring-opening of cyclopropanated sugars.[9]

Herein, we report a different approach for synthesis of a *C*-β-D-glycoside via tri-(*n*-butyl)stannyl radical-mediated ring opening of a 1,5-anhydro-1,2-cyclopropylcarbinyl-2-deoxyhexitol system.[10] 3,4,6-Tri-*O*-acetyl-D-glucal (**1**) was converted to 4,6-*O*-benzylidene-D-glucal[11] (**2**) using benzaldehyde dimethylacetal.

Diastereoselective cyclopropanation of **2** was carried out using the Simmons–Smith reaction to furnish 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-1,2-*C*-methylene-D-*glycero*-D-*talo*-hexitol (**3**) (Scheme 1). Although ^{1}H NMR spectral data showed the presence of the cyclopropane ring, the stereochemistry at the bicyclic ring junction still required confirmation.

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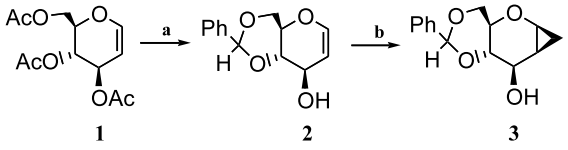
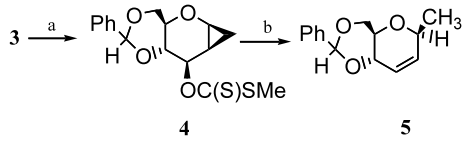
The resulting cyclopropylcarbinol **3** was converted to 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-1,2-*C*-methylene-3-*O*-xanthyl-D-*glycero*-D-*talo*-hexitol (**4**) (Scheme 2) whose NMR spectrum revealed unexpected results. The H-3 [(C-11 as depicted in the ORTEP diagram (Fig. 1)] of **4** at δ 6.16 appeared as a triplet ($J_{2,3} = J_{3,4}$ 11.5 Hz), thus providing no information as to the configuration at C-1 and C-3. Proof for the stereochemistry of the xanthate derivative **4** was obtained by single-crystal X-ray diffraction study (Fig. 1).

The observed stereoselectivity in **4**, based on the X-ray diffraction analysis, is consistent with an oxygen-directed (allylic 3-OH) Simmons–Smith cyclopropanation, while cyclopropanation of 3,4,6-tri-*O*-benzyl-D-glucal using dichlorocarbene is reported to lead to a product with opposite stereochemistry.[12] A summary of the crystallographic data is provided in Table 1, and the selected atomic parameters are shown in Tables 2 and 3.

Free-radical ring-opening reaction of **4** using the standard Barton radical deoxygenation conditions with



Scheme 1. Conditions: (a) (i) Na_2CO_3, MeOH, (ii) Ph-$CH(OMe)_2$, *p*-TsOH, DMF; (b) Zn–Cu, CH_2I_2, Et_2O (45% overall).



Scheme 2. Conditions: (a) NaH, CS_2, MeI, THF, 90% (b) Bu_3SnH, AIBN, toluene, reflux, 80%.

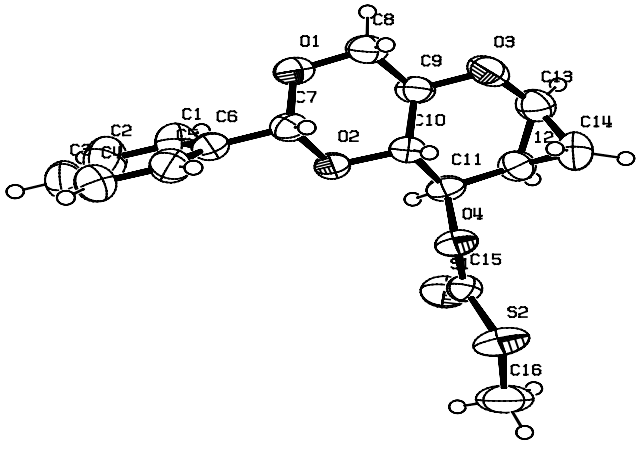


Fig. 1. ORTEP diagram of 1,5-anhydro-4,6-*O*-benzylidine-2-deoxy-1,2-C-methylene-3-*O*-xanthyl-D-*glycero*-D-*talo*-hexitol (**4**).

Table 1
Summary of crystal data and data collection parameters for 1,5-anhydro-4,6-*O*-benzylidine-2-deoxy-1,2-*C*-methylene-3-*O*-xanthyl-D-*glycero*-D-*talo*-hexitol (**4**) and for 2,5-anhydro-5,7-*O*-benzylidene-1,3,4-dideoxy-β-D-*arabino*-hex-3-enitol (**5**)

Chemical formula	$C_{16}H_{18}O_4S_2$ (**4**)	$C_{14}H_{16}O_3$ (**5**)
Formula weight	338.42	232.27
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$
Temperature (K)	293(2)	293 (2)
Wavelength (Å)	1.54160	1.54180
Lattice parameters		
a (Å)	6.4107(9)	9.437(3)
b (Å)	13.991(3)	5.5107(10)
c (Å)	9.2746(2)	23.852(3)
β (°)	95.92(2)	90.110(16)
V (Å^3)	827.43(19)	1240.5(5)
Z	2	4
D_{calcd} (mg m^{-3})	1.358	1.244
Absorption coefficient (mm^{-1})	3.047	0.703
F(000)	356	496
μ (mm^{-1})	3.047	0.703
Index ranges	$0 \le h \le 7$, $0 \le k \le 16$, $-11 \le l \le 11$	$0 \le h \le 10$, $0 \le k \le 6$, $-28 \le l \le 28$
Crystal size (mm)	$0.25 \times 0.1 \times 0.075$	$0.3 \times 0.15 \times 0.15$
Measured data	1628	2758
Unique data	1489	2437
Parameters	220	308
Restraints	1	1
R (all data)	0.0451	0.0614
wR_2	0.1230	0.1704
Goodness-of-fit	1.063	1.136
Mean and maximum shift/esd	0.002–0.000	0.002–0.000
Maximum and minimum difference electron density (e Å^{-3})	0.253, −0.461	0.355, −0.269

Bu_3SnH afforded exclusively the 2,6-anhydro-5,7-*O*-benzylidene-1,3,4-trideoxy-β-D-*arabino*-hept-3-enitol (**5**). NMR (^{1}H, NOE and COSY) spectral studies established the anomeric configuration as β-D.

As expected the free-radical ring opening of **4** stereospecifically afforded the β anomer of the *C*-glucoside **5** with no trace of the seven-membered (i.e., the cyclopropane ring-opened) product.[†] We have established also the stereochemistry of **5** by X-ray crystallographic analysis. Crystallographically **5** shows two nonequivalent molecules in the asymmetric unit. However, stereochemically both the molecules are found to

[†] Ref. 10 reports both the ring opened and ring expanded products in the ratio of 3:2, respectively, in the case of a 4,5-cyclopropanated sugar.

be identical, hence only one of the molecule is represented in the ORTEP diagram (Fig. 2).

The present study provides a potential route for the stereoselective synthesis of *C*-glycosides. Research is underway to extend this approach to the stereoselective synthesis of other *C*-glycosides.

1. Experimental

General procedure.—IR spectra were determined as their solutions in CCl_4 using a SHIMADZU IR 470 model instrument. ^1H and ^{13}C NMR spectra were recorded on a JOEL-GSX 400 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. Electron-impact mass spectra (EIMS) were obtained with a SHIMADZU-QP 5000 instrument.

*1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-1,2-*C*-methylene-*D*-glycero-*D*-talo-hexitol* (**3**).—To a stirred suspension of zinc dust (420 mg, 4.4 mmol) and CuCl (135 mg, 1 mmol) in dry ether (3 mL) was added CH_2I_2 (0.12 mL, 1.5 mmol), followed by acetyl chloride (20 μL). Then a solution of 4,6-*O*-benzylidene-D-glucal (350 mg, 1.5 mmol) in ether (5mL) was added, and the mixture was heated under reflux. After 5 min CH_2I_2 (0.12 mL, 1.5 mmol) was again added, and heating was continued for 45 min. The reaction mixture was diluted with ether

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 1,5-anhydro-4,6-*O*-benzylidine-2-deoxy-1,2-*C*-methylene-3-*O*-xanthyl-D-*glycero*-D-*talo*-hexitol (**4**)

	x	*y*	*z*	U_{eq}
S(1)	−147(2)	4762(1)	2999(1)	69(1)
S(2)	−4385(2)	4067(1)	1720(2)	77(1)
O(1)	3044(6)	5105(2)	−3616(4)	63(1)
O(2)	1372(4)	4505(2)	−1691(3)	44(1)
O(3)	−122(6)	6998(3)	−2313(4)	67(1)
O(4)	−1850(4)	4832(2)	277(3)	49(1)
C(1)	5208(8)	3473(5)	−2347(6)	71(2)
C(2)	6426(11)	2668(6)	−2350(8)	96(2)
C(3)	5727(12)	1861(6)	−3080(8)	91(2)
C(4)	3783(12)	1855(5)	−3837(8)	85(2)
C(5)	2524(9)	2660(4)	−3858(6)	64(1)
C(6)	3198(7)	3458(3)	−3116(4)	48(1)
C(7)	1891(7)	4339(3)	−3128(4)	47(1)
C(8)	1903(10)	5975(4)	−3664(5)	66(1)
C(9)	1243(7)	6197(3)	−2172(5)	51(1)
C(10)	119(6)	5348(3)	−1628(4)	41(1)
C(11)	−270(6)	5515(3)	−88(4)	43(1)
C(12)	−1028(7)	6512(3)	162(5)	53(1)
C(13)	−873(9)	7257(4)	−1003(6)	62(1)
C(14)	−2973(9)	6876(5)	−728(8)	77(2)
C(15)	−1955(6)	4593(3)	1662(4)	47(1)
C(16)	−4343(13)	3712(5)	3553(8)	99(2)

Table 3
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 2,5-anhydro-5,7-*O*-benzylidene-1,3,4-dideoxy-β-D-*arabino*-hex-3-enitol (**5**)

	x	*y*	*z*	U_{eq}
O(1′)	3674(3)	10243(7)	4537(1)	59(1)
O(2′)	5777(3)	6837(6)	3545(1)	56(1)
O(3′)	7285(3)	9386(6)	4048(1)	56(1)
C(1′)	2326(5)	10347(12)	4247(2)	68(1)
C(2′)	2196(6)	8486(12)	3813(2)	78(2)
C(3′)	3286(5)	6984(10)	3649(2)	63(1)
C(4′)	4647(4)	7256(9)	3928(2)	52(1)
C(5′)	4795(4)	9821(8)	4164(2)	50(1)
C(6′)	6205(4)	10038(10)	4446(2)	57(1)
C(7′)	1203(5)	10073(17)	4662(2)	93(2)
C(8′)	7092(4)	7071(9)	3821(2)	51(1)
C(9′)	8229(4)	6589(9)	3399(2)	52(1)
C(10′)	9062(5)	4434(11)	3414(2)	68(1)
C(11′)	10086(6)	4103(11)	3009(3)	83(2)
C(12′)	10279(6)	5660(11)	2589(2)	75(2)
C(13′)	9450(6)	7735(12)	2567(2)	74(2)
C(14′)	8460(5)	8136(10)	2962(2)	64(1)
O(1)	−1326(3)	−1373(6)	459(1)	54(1)
O(2)	789(3)	2053(5)	1461(1)	48(1)
O(3)	2295(3)	−533(6)	950(1)	48(1)
C(1)	−2680(4)	−1458(10)	754(2)	60(1)
C(2)	−2782(5)	430(10)	1193(2)	63(1)
C(3)	−1739(4)	1860(10)	1356(2)	60(1)
C(4)	−350(4)	1633(8)	1069(2)	47(1)
C(5)	−189(4)	−913(8)	845(1)	43(1)
C(6)	1220(4)	−1129(9)	551(2)	51(1)
C(7)	−3819(5)	−1272(18)	310(2)	96(2)
C(8)	2116(4)	1867(7)	1187(1)	43(1)
C(9)	3254(4)	2319(8)	1603(2)	45(1)
C(10)	4070(5)	4399(10)	1577(2)	60(1)
C(11)	5115(5)	4798(10)	1980(2)	72(1)
C(12)	5324(5)	3254(12)	2402(2)	73(2)
C(13)	4514(5)	1153(13)	2441(2)	73(2)
C(14)	3476(5)	694(10)	2041(2)	59(1)

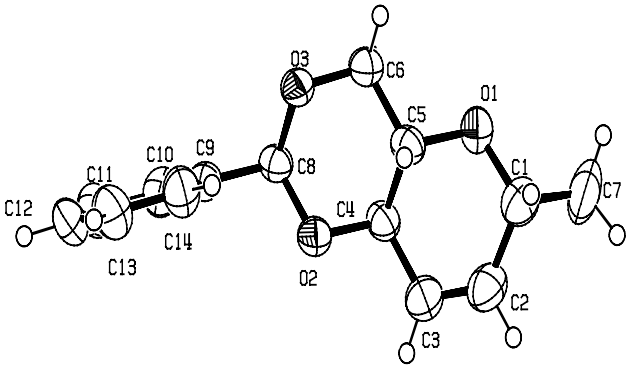


Fig. 2. ORTEP diagram of 2,5-anhydro-5,7-*O*-benzylidene-1,3,4-dideoxy-β-D-*arabino*-hex-3-enitol (**5**).

and washed with 5% NaOH, followed by water. Column chromatography of the crude product using 3:2 EtOAc–hexane yielded 285 mg (75%); mp 133–135 °C; $[\alpha]_D^{30}$ −82.7° (*c* 0.719, CH_2Cl_2); IR cm^{-1}): 3600, 3008, 2928, 2896, 1452, 1379, 1286, 1091, 1030, 966, 872, 598; ^1H NMR: δ 0.77–0.85 (m, 2 H, H-7), 1.34 (dd, 1 H, H-2), 2.77 (bs, 1 H, OH), 3.25–3.5 (m, 3 H, H-4, 5, 1), 3.7 (m, 1 H, H-3), 4.22 (m, 2 H, H-6a, 6b), 5.39 (s, 1 H, benzylidene H), 7.2–7.4 (m, 5 H, Ph); ^{13}C NMR: δ 11.9, 17.61, 54.5, 67.94, 68.53, 68.59, 82.08, 96.19, 101.58, 128.30, 128.20, 129.08, 137.34; EIMS: Anal. Calcd for $C_{14}H_{16}O_4$, 248.27; Found: *m*/*z* 247 [M − 1], 149, 107, 91, 77, 55.

*1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-1,2-*C*-methylene-3-*O*-xanthyl-*D*-glycero-*D*-talo-hexitol* (**4**).—It is important to note that the reaction has to be conducted under a perfectly dry argon atmosphere for good yields. To a solution of **3** (200 mg, 0.8 mmol) in dry THF (10 mL) was added NaH (60 mg, 50% oil dispersion, 1.2 mmol) under dry argon atmosphere, and the mixture was stirred at rt for 1 h. CS_2 (0.14 mL, 2.4 mmol) and a catalytic amount of imidazole (10 mg) was then added, and stirring was continued for 30 min, followed by the addition of MeI (0.1 mL, 2 mmol). After 30 min the reaction was quenched with MeOH. The solvents were evaporated under vacuum, and the reaction mixture was worked up by extracting with CH_2Cl_2. Column chromatography of the crude product using 4:1 EtOAc–hexane yielded 245 mg (90%) of **4**. Recrystallization of the product using 1:9 EtOAc–CCl_4 gave single crystals: mp 147–149 °C; $[\alpha]_D^{30}$ −180.5° (*c* 0.886, CH_2Cl_2); IR (cm^{-1}): 3024, 2992, 2944, 2880, 1452, 1408, 1376, 1235, 1203, 1129, 1049, 915, 694; ^1H NMR: δ 0.90 (m, 2 H, H-7), 2.00 (m, 1 H, H-2), 2.5 (s, 3 H, –SMe_3), 3.2–3.9 (m, 3 H, H-5, 6a, 6b), 4.3 (bs, 1 H, H-4), 5.5 (s, 1 H, benzylidene H), 6.16 (t, 1 H, H-3, $J_{2,3} = J_{3,4}$ 11.5 Hz), 7.2–7.4 (m, 5 H, Ph–); ^{13}C NMR: δ 12.49, 15.12, 19.18, 55.69, 68/6, 76.36, 77.63, 78.76, 79.92, 101.36, 126.13, 128.17, 129.03, 137.04; EIMS: Anal. Calcd for $C_{14}H_{18}O_4S_2$, 338.06; Found: *m*/*z* 338, 277, 231, 125, 107, 91, 81, 67.

*2,6-Anhydro-5,7-*O*-benzylidene-1,3,4-trideoxy-*D*-arabino-hept-3-enitol* (**5**).—About 0.6 mmol of **4** in dry toluene (10 mL) was heated to reflux under a dry nitrogen atmosphere. To this was added dropwise a mixture of Bu_3SnH (209 mg, 0.72 mmol) and a catalytic amount of AIBN in dry toluene, and the mixture was refluxed for 1 h, with monitoring by TLC. The toluene in the reaction mixture was evaporated in vacuum, and the crude product was chromatographed (silica gel column) using 7:3 EtOAc–hexane to yield **5** in about 80% yield. Recrystallization was done in dry MeOH gave single crystals: mp 114–116 °C; $[\alpha]_D^{29}$ +99.4° (*c* 0.767, CH_2Cl_2); IR (cm^{-1}): 3040, 2976, 2944, 2864, 1449, 1385, 1366, 1292, 1136, 1100, 691; ^1H NMR: δ 1.20 (d, 3 H, CH_3, *J* 6.35 Hz), 3.47 (m, 1 H, H-5), 4.0 (d, 1 H, H-4), 4.2–4.3 (m, 1 H, H-6a, 6b), 5.4 (s, 1 H, benzylidene H), 5.59 (d, 1 H, H-2), 5.83 (d, 1 H, H-3), 7.25–7.38 (m, 5 H, Ph–); ^{13}C NMR: δ 21.90, 70.01, 71.81, 72.66, 75.90, 97.00, 102.40, 127.08, 127.20, 128.60, 129.20, 133.14, 138.6; EIMS: Anal. Calcd for $C_{14}H_{16}O_3$, 232.11; Found: *m*/*z* 232 [M], 188, 149, 126, 105, 83, 77, 55, 43.

X-ray crystallography.—Well-grown single crystals of appropriate size were selected for structure determination. The cell dimensions were obtained by the method of short vectors, followed by least-squares refinement of the 25 reflections collected through search routine. The intensity data were collected at room temperature on an Enraf–Nonius CAD4 diffractometer. The data were corrected for Lorentz and polarisation effects, and an absorption correction was applied on the basis of ψ-scans. The structures were solved by direct methods (SHELXS97),[13] and full matrix least-squares refinement was carried out using the program, SHELX-97.[14] Hydrogen atom positions were fixed on geometrically calculated positions (after verifying these positions through a difference Fourier map) and were allowed to ride on their respective carrier atoms. The thermal parameters of the nonhydrogen atoms were anisotropically refined. The final convergence was achieved with $R = 0.0451$ and 0.0614, respectively, for **4** and **5**.

2. Supplementary material

The full crystallographic details of compounds **4** and **5** have been deposited (deposition numbers: 191424 and 191425) with Cambridge Crystallographic Data Centre. These data can be obtained, on request from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; www: http://www.ccdc.cam.ac.uk).

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