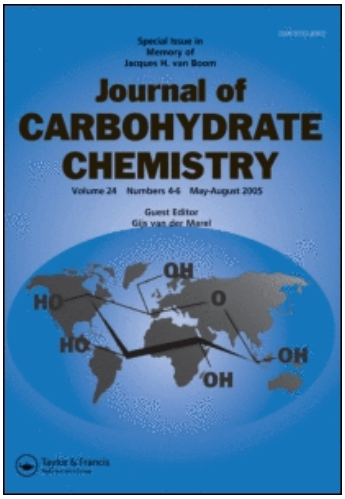

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Pierre Cettour[a]; Gérard Descotes[a]; Jean-Pierre Praly[a]
[a] Laboratoire de Chimie Organique II associé au CNRS, Université Claude-Bernard Lyon I, Villeurbanne, France

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COMMUNICATION

N-BROMOSUCCINIMIDE-MEDIATED TRANSFORMATIONS OF ACETYLATED 1,5-ANHYDRO-1-*C*-PHENYL-D-HEXITOLS

Pierre Cettour, Gérard Descotes and Jean-Pierre Praly*

Laboratoire de Chimie Organique II associé au CNRS
Université Claude-Bernard Lyon I
ESCIL, 43 Boulevard du 11 Novembre 1918
69622 Villeurbanne, France

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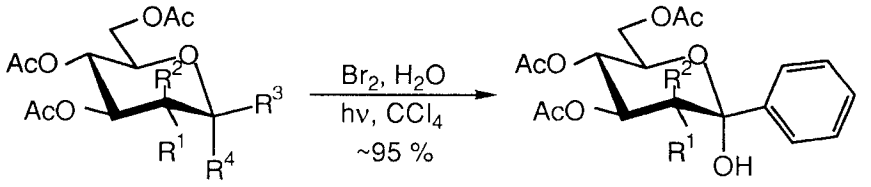
Radical-mediated halogenation constitutes a valuable synthetic tool, in particular for achieving regio and stereocontrolled preparations of brominated or chlorinated sugar derivatives.[1] This chain reaction process involves, as the main steps, the initial homolytic cleavage of an activated C—H bond followed by trapping of the resulting carbon-centered radical with a halogenated species. For cyclic sugar derivatives, halogenation occurs either at C-1 or at C-4 (furanose series) or C-5 (pyranose series) depending on the substituents attached to these carbon atoms.[1] Moreover, trapping of the intermediate carbon-centered free radical occurs with a high stereoselectivity, so that substrates containing an activated C—H bond can be converted under mild conditions and in high yield into halogenated polyfunctional products which are not accessible by other routes. Our recent synthesis of a variety of bromoglycosyl imines[2] from glycosyl azides contitutes a new example of the synthetic value of this method.

In this context, we investigated the free-radical bromination of three 1-*C*-phenyl-1,5-anhydro-D-hexitols **1**, **2** and **3**.[3] Although the phenyl ring was presumed to enhance the susceptibility of the C-1—H bond towards homolysis, it was anticipated that the reactivity of these models might vary, depending on the configuration at either the C-1 position (α or β) or the C-2 position (*gluco* or *manno* configuration). In a study devoted

to debenzylation of carbohydrate benzyl ethers and benzyl glycosides by free-radical bromination, BeMiller et al.[4] observed a fast but unselective transformation of **1** on treatment with *N*-bromosuccinimide (NBS). It was hoped that choice of more appropriate conditions would provide a deeper insight in the reaction, so as to use it, hopefully, for further useful synthetic transformations.

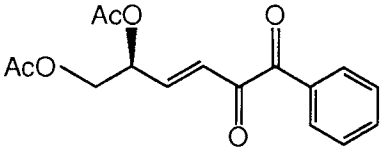
Refluxing a mixture of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-*C*-phenyl-β-D-glucitol **1** and NBS (4 eq) in carbon tetrachloride with a tungsten lamp (250 W) led within 30 min to complete transformation of **1** to a multicomponent mixture as shown by TLC in agreement with BeMiller's report. At a lower temperature (~5 °C), although a single new product was detected by TLC during the first stage of the transformation, complete conversion of **1** resulted again in complex mixtures. Separation of the initial product by column chromatography allowed purification of hemiketal **4** in low yield (~10 %). Since **4** resulted from subsequent hydrolysis of the corresponding benzylic bromide, the reaction was carried out with bromine (4 eq) near 0 °C or below in the presence of water in excess to give **4** almost quantitatively as a crystalline solid. Under these conditions, compounds **2** and **3** led in high yield to the hemiketal **5**. Interestingly, the reaction times required to achieve the complete conversion of **1**, **2** and **3** under the same conditions (85, 15 and 40 min, respectively) were significantly different, suggesting the following sequence of reactivity for the studied hexitols:

β-*manno* **2** > α-*manno* **3** > β-*gluco* **1**



	R^1	R^2	R^3	R^4
1	OAc	H	Φ	H
2	H	OAc	Φ	H
3	H	OAc	H	Φ

	R^1	R^2
4	OAc	H
5	H	OAc



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The same conclusion was reached when mixtures of **1** and **3** or **2** and **3** were treated with bromine (2 eq) since TLC monitoring of each reaction mixture showed that **3** and **2** disappeared, respectively, before **1** and **3**. As compared to their β-D-*gluco* counterparts, the higher reactivity of β-D-mannopyranosyl derivatives, also observed recently in the case of D-*manno* configurated pyranosyl azides,[2] has been explained by the stabilisation resulting from the axial orientation of the C—O bond at C-2.[5]

Treatment of benzyl-protected D-glucono-1,5-lactone with phenyl lithium has been used by several groups to prepare the benzyl analog of **4**.[6-8] Such a compound was obtained as an anomeric mixture, the composition of which was not established. In the case of compound **4**, the ^{1}H NMR spectrum of either the crude or crystallized material corresponded to a single anomer in which the hydroxy group adopted an α orientation. This was deduced by comparison of the NMR data reported for **1**, **2** and **3**[3] and those recorded for **4** and **5**. In each series, a close similarity appeared between the chemical shifts of the H-2 and H-4 signals in either **1** and **4** or **3** and **5** wherein the axial hydroxy group can account for the deshieldings observed for the H-3 and H-5 resonances in **4** and **5**. However, the ^{3}J coupling constants measured for **4** constituted more convincing evidence in favor of its α anomeric configuration (equatorial phenyl ring). In effect, they indicated the *trans*-diaxial relationship of the vicinal ring hydrogen atoms expected for the typical $^4C_1$(D) conformation of the *gluco* pyranose ring, also found for **1**.[3] On the contrary, for its α counterpart (axial phenyl ring), due to the existence of a conformational equilibrium, smaller, solvent-dependent ^{3}J coupling constants were observed.[3]

When the crude reaction mixtures containing essentially **4** or **5** were allowed to warm up to room temperature prior to work-up, acid-catalyzed transformations occurred resulting in multicomponent mixtures from which compound **6** could be separated, in low yield, by column chromatography. This syrupy compound was identified by spectroscopic means. In particular, its NMR spectrum showed the *trans* relationship of the vinylic protons which each were coupled with H-5. This oily compound gave a fast-moving spot on TLC plates which was easily detected under UV light due to the strong absorption of the extended conjugated system.

In conclusion, free-radical bromination of three peracetylated 1,5-anhydro-1-*C*-phenyl-D-hexitols occurred regioselectively at the benzylic position. Hydrolysis of the labile intermediate bromides led in high yield to the corresponding 1-*C*-phenyl-α-D-glycopyranoses. This study confirmed that the C-1—H bond was more susceptible towards homolytic cleavage in *manno*-configurated sugar derivatives as compared to those in the *gluco* series. Furthermore, a mechanism previously proposed[4] to explain the course of debenzylation via free-radical bromination can be applied here.

EXPERIMENTAL

General methods. The NMR spectra were obtained from deuteriochloroform solutions with tetramethylsilane as the internal reference using a BRUKER AM 300 spectrometer. Chemical shifts (δ) are given in ppm, couplings (J) are expressed in Hertz.

2,3,4,6-Tetra-*O*-acetyl-1-*C*-phenyl-α-D-glucopyranose (4). Bromine (48 μL, 0.96 mmol, 4 eq) was added to a mixture of carbon tetrachloride (6 mL) and water (4 mL) containing 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-*C*-phenyl-β-D-glucitol **1** (100 mg, 0.24 mmol). The flask which was immersed in an acetone bath cooled approximately to –20 °C with dry ice was irradiated with a tungsten lamp (60 W) at a distance of ~5 cm. After 85 min, TLC monitoring using *n*-hexane–ethyl acetate 3:2 v/v indicated the complete transformation of **1**. A saturated $NaHCO_3$ solution (15 mL) was added to the cooled reaction mixture which was then extracted with dichloromethane (3 x 25 mL). After washing the organic phase with water (2 x 5 mL) and drying (Na_2SO_4), the solvent was removed under diminished pressure to give 98 mg (94%) of crude **4**, as a single anomer (NMR) which crystallized from diethyl ether-petroleum ether: mp 159-160 °C; Rf 0.28 (*n*-hexane–ethyl acetate 3:2 v/v); $[\alpha]_D$ -4° (*c* 0.54, chloroform); ^1H NMR δ 7.55 (2H, m, aromatic), 7.37 (3H, m, aromatic), 5.62 (1H, t, $J_{3,4}$ 9.7, H-3), 5.29 (1H, t, $J_{4,5}$ 9.8, H-4), 5.08 (1H, d, $J_{2,3}$ 10.1, H-2), 4.44 (1H, dq, $J_{5,6}$ 2.4, H-5), 4.20 (1H, dd, $J_{5,6'}$ 4.2, H-6), 4.34 (1H, dd, $J_{6,6'}$ 12.3, H-6'), 2.95 (1H, exchangeable, OH), 2.12, 2.07, 1.98, 1.90 (12H, 4s, acetyl); ^{13}C NMR δ 170.9, 170.3, 169.7, 169.0 (C=O), 139.7, 129.4, 128.4, 125.6 (respectively, ipso, para, ortho/meta aromatic carbons), 97.2 (C-1), 73.6, 71.5, 68.8, 68.7 (C-2 to C-5), 62.2 (C-6), 20.8, 20.7, 20.7, 20.4 ($CO\underline{C}H_3$).

Anal. Calcd for $C_{20}H_{24}O_{10}$: C, 56.59; H, 5.70; O, 37.71. Found: C, 56.59; H, 5.60.

2,3,4,6-Tetra-*O*-acetyl-1-*C*-phenyl-α-D-mannopyranose (5). This compound was prepared as above and obtained quantitatively from either **2** or **3** which were completely transformed within, respectively, 15 or 40 min: amorphous solid; $[\alpha]_D$ -17° (*c* 0.3, chloroform); ^1H NMR δ 7.54 (2H, m, aromatic), 7.34 (3H, m, aromatic), 5.63 (1H, dd, $J_{3,4}$ 10.0, H-3), 5.47 (1H, d, $J_{2,3}$ 3.3, H-2), 5.36 (1H, t, $J_{4,5}$ 9.9, H-4), 4.37 (1H, m, $J_{5,6}$ 4.8, H-5), 4.33 (1H, dd, $J_{5,6'}$ 2.6, H-6), 4.27 (1H, dd, $J_{6,6'}$ 11.5, H-6'), 3.36 (1H, exchangeable, OH), 2.10, 2.08, 1.96, 1.78 (12H, 4s, acetyl); ^{13}C NMR δ 170.9, 170.1, 170.0, 169.3 (C=O), 139.8, 129.1, 128.1, 126.0 (respectively, ipso, para, ortho/meta aromatic carbons), 97.6 (C-1), 71.7, 70.0, 69.4, 66.2 (C-2 to C-5), 62.9 (C-6), 20.8, 20.8, 20.7, 20.3 ($CO\underline{C}H_3$).

Anal. Calcd for $C_{20}H_{24}O_{10}$: C, 56.59; H, 5.70; O, 37.71. Found: C, 56.28; H, 5.68; O, 37.57.

Competitive brominations. 1/1 mixtures of compounds **1** and **3** or **2** and **3** (50 mg, 0.12 mmol) dissolved in carbon tetrachloride (4 mL) and water (3 mL) containing bromine (12 µL, 0.24 mol, 2 eq) were cooled and irradiated as above. TLC monitoring showed, in the first case, that **3** was completely transformed after 26 min while **1** was still present (diethyl ether-petroleum ether 1:1 v/v). In the second experiment, **2** disappeared after 12 min whereas compound **3** was still visible on the plates.

[*E*-5(*R*)-5,6-Diacetoxy-1,2-dioxohex-3-enyl] benzene (6). This compound was obtained from **1** in a 30 % yield after column chromatography (Silica gel 60 Merck) of a complex reaction mixture, using *n*-hexane-ethyl acetate 3:2 v/v as the mobile phase, Rf. 0.6 (*n*-hexane–ethyl acetate 3:2 v/v): $[\alpha]_D$ +12° (*c* 0.6, chloroform); ^{1}H NMR δ 7.98 (2H, m, aromatic), 7.66 (1H, m aromatic), 7.51 (2H, m, aromatic), 6.94 (1H, dd, $J_{4,5}$ 4.5, H-4), 6.75 (1H, dd, $J_{3,4}$ 16.2, $J_{3,5}$ 1.7, H-3), 5.74 (1H, m, $J_{5,6}$ 4.0, H-5), 4.35 (1H, dd, $J_{5,6'}$ 6.2, H-6), 4.17 (1H, dd, $J_{6,6'}$ 12.0, H-6'), 2.16, 2.07 (6H, 2s, acetyl); ^{13}C NMR δ 192.1, 191.1 (C-1, C-2), 170.5, 169.7 (C=O), 132.3, 130.2, 128,9 127.0 (respectively, ipso, ortho/meta, para aromatic carbons), 134.9, 145.2 (C-3, C-4), 70.3 (C-5), 63.8 (C-6), 20.8, 20.6 ($CO\underline{C}H_3$).

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