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# Synthesis of $B_{2,5}$ type conformationally constrained glucopyranosides

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**Abstract**—Isopropyl and *p*-nitrophenyl α- and β-D-glucopyranosides restrained in a conformation close to $B_{2,5}$ have been synthesized. They are all hydrolyzed at similar rates, close to those observed for the parent unlocked glucosides.


The chemical and enzymatic hydrolyses of glycopyranosides are important events in a wide range of chemical and biological glycoprocesses. Glycoside hydrolysis is indeed one of the most studied reactions in carbohydrate chemistry and a wealth of data has been reported.[1] Substantial carbenium ion character is present at the anomeric center in the transition state, which is best accommodated in a sugar conformation in which C-5, O-5, C-1 and C-2 are held in a planar array,[2] ideally set up for the stabilization of the alkoxycarbenium.[3]

Looking at the complete map of pyranoid ring interconversions, including the boat/skew-boat pseudorotational itinerary of the pyranoid ring[4] and as earlier advocated,[5] not only $^4H_3$ and $^3H_4$, but also $B_{2,5}$ and $^{2,5}B$ conformations (Fig. 1) are possible candidates for the conformation of the glucopyranosyl cation, wherein the coplanarity requirement is met. In nature, these boat type conformations have recently been convincingly observed, using kinetic isotope effects or crystal structure analysis of complexes between substrate, substrate analogues and/or inhibitors of the studied enzyme, for some glycosidases that perform substrate distortion away from the ground state $^4C_1$ conformation before enzymatic hydrolysis.[6]

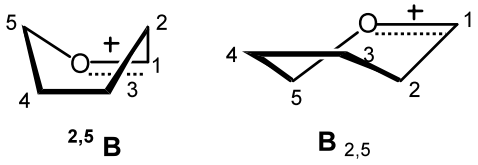


**Figure 1.** The two conformers of the boat/twist-boat pseudorotational itinerary of the pyranoid ring wherein a coplanarity of C-5, O, C-1 and C-2 is met.

If the ground-state conformation prior to oxygen–carbon cleavage is indeed $B_{2,5}$ (or $^{2,5}B$), this implies that the Antiperiplanar Lone Pair effect[7] is not operating in the hydrolytic process. Such a cleavage would rather be compatible with a synperiplanar assistance[8] and be simultaneously in agreement with the relevant least nuclear motion effect.[9]

In this context we thus considered as important to evaluate the ease of acid hydrolysis of monosaccharides conformationally constrained in such a boat conformation. Herein, we would like to report on the synthesis of *p*-nitrophenyl and isopropyl α- and β-D-glucopyranosides locked in a $B_{2,5}$ conformation and disclose preliminary results concerning their hydrolysis under acidic conditions. The selected constrained targets are **1–4** (Fig. 2), with carbon atoms 2 and 5 connected through an oxymethylene bridge.[10] In acid-catalyzed hydrolysis, particularly of conformationally restricted glycosides, the possibility of endocyclic cleavage is always present. The use of isopropyl and *p*-nitrophenyl glycosides will enable us to tell if this mechanism is operative because hydrolysis of nitrophenyl glycosides would be orders of magnitude slower than isopropyl ones in an endocyclic pathway.

*Keywords*: carbohydrates; conformation; hydrolysis.
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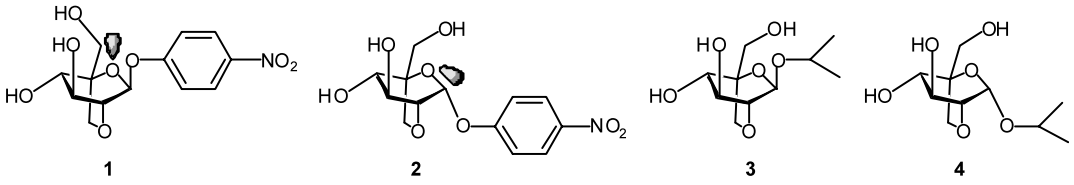
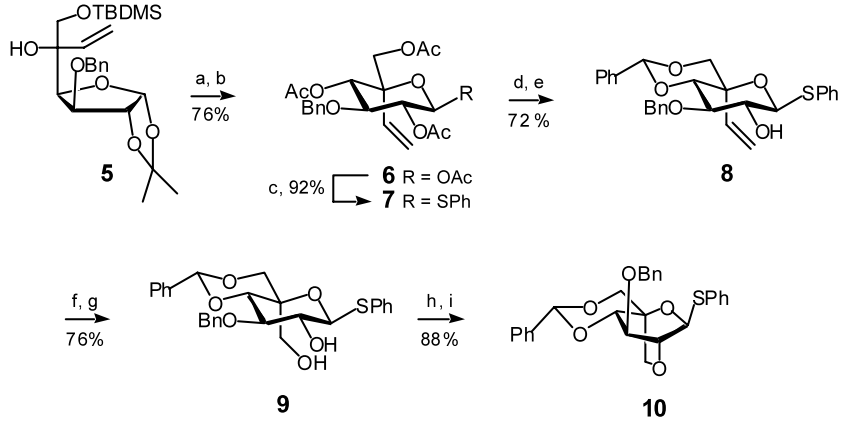


**Figure 2.** Structure of the conformationally constrained α- and β-D-glucopyranosides **1**–**4**, showing the *syn*-periplanarity of one pyranoside orbital of the intracyclic oxygen and of the glycosidic bond.

Compounds **1**–**4** are confined for stringent geometrical reasons to the following conformational domain of the boat/skew-boat itinerary close to $B_{2,5}$: ($^1S_5 \rightleftharpoons B_{2,5} \rightleftharpoons {}^0S_2$).

The strategy used to synthesize compounds **1**–**4** starts from the known vinyl derivative **5**.[11] It was first converted into the protected restrained glycosyl donor **10** as explained in Scheme 1. Compound **10** is an interesting conformationally locked glycosyl donor which can give access to the conformationally locked glycosides **1**, **2** and **4**. When compound **10** was treated with paranitrophenol in the presence of NIS and triflic acid in dichloromethane, the paranitrophenyl β-glycopyranoside **12** and the α-glycopyranoside **13** were obtained in high yield and in a 4/1 ratio (Scheme 2). Treatment of **12** with sodium bromate and sodium dithionite in ethyl acetate/water[12] simultaneously performed the opening of the benzylidene acetal and the cleavage of the benzyl ether to afford a mixture of 4-*O*-benzoate derivative **14** and 6-*O*-benzoate derivative **15** in 74%. Treatment of **14** and **15** with sodium methoxide in methanol afforded the β-*p*-nitrophenyl glucoside **1**† in 73% yield. The same sequence was uneventfully applied to compound **13** to afford the α-*p*-nitrophenyl glucoside **2**‡ in 84% yield over two steps from **13**. Treatment of **10** with dry isopropanol in the presence of NCS gave the α-glucoside **11** along with traces of the corresponding β-glucoside. Hydrogenolysis of **11** under various conditions led only to decomposition products. Reduction with Na-liq. $NH_3$ afforded the pure α-glucoside **4**§ after

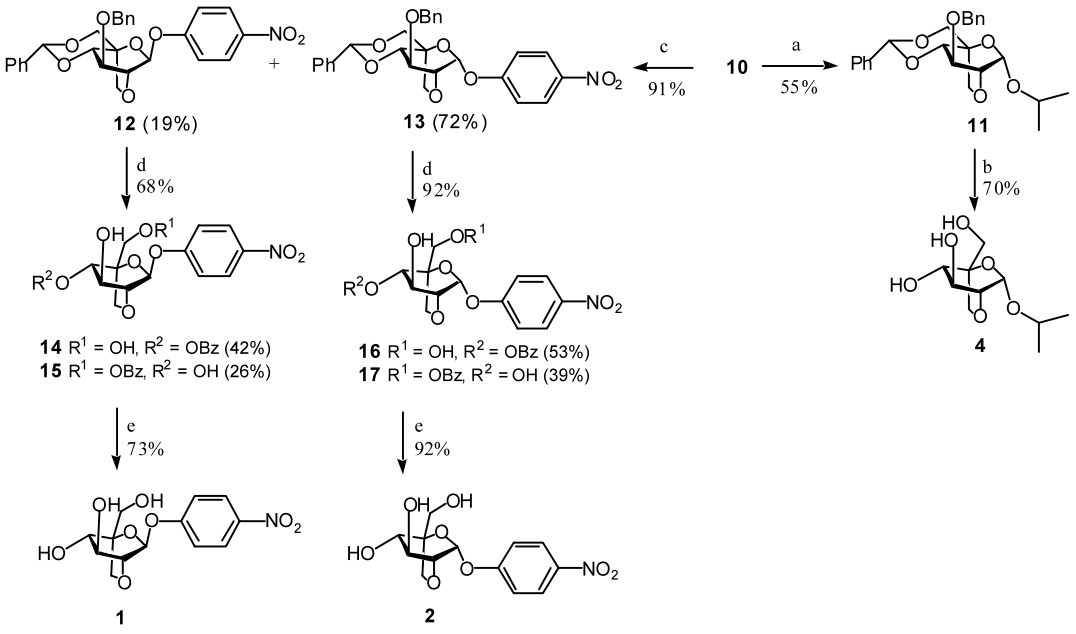


**Scheme 1.** Synthesis of the glycosyl donor **10**. *Reagents and conditions*: (a) IR-120 $H^+$ resin, dioxan, $H_2O$, 90°C, 18 h; (b) $Ac_2O$, DMAP, pyridine, rt; (c) PhSH, $BF_3{\cdot}OEt_2$, anhydrous $CH_2Cl_2$, rt; (d) $CH_3ONa$, $CH_3OH$, rt, 16 h; (e) $PhCH(OMe)_2$, CSA, DMF, rt, 14 h; (f) $O_3$, $CH_2Cl_2$, −78°C, 30 min; (g) $NaBH_4$, EtOH, rt, 18 h; (h) TsCl, DMAP, pyridine, rt, 15 h; (i) NaH, DMF, rt, 18 h.

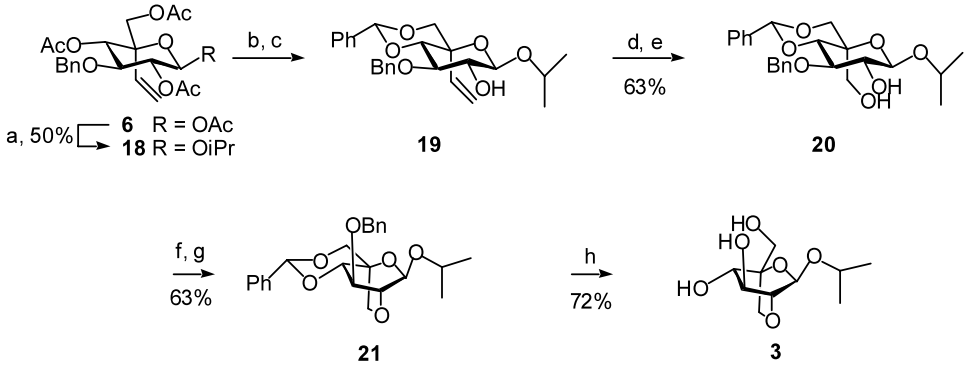
† Selected data for compound **1**: $[\alpha]_D^{22} = -128$ (*c* 0.55 in $CH_3OH$); $^1H$ NMR (400 MHz, $D_2O$): $\delta = 8.21$ (d, 2H, $J = 9.0$ Hz, ($PhNO_2$), 7.21 (d, 2H, $J = 9.0$ Hz, $PhNO_2$), 6.01 (dd, $J = 1.0$ Hz, 2.6 Hz, 1H, H-1), 4.12 (app. t, $J = 2.7$ Hz, 1H, H-2), 4.06 (m, 1H, H-3), 4.02 (dd, $J = 1.6$ Hz, 5.1 Hz, 1H, H-4), 3.91 (d, $J = 9.8$ Hz, 1H, H-7), 3.76 (dd, $J = 1.6$ Hz, 9.8 Hz, 1H, H-7′), 3.68 (d, $J = 12.8$ Hz, 1H, H-6), 3.64 (d, $J = 12.8$ Hz, 1H, H-6′); $^{13}C$ NMR (100 MHz, $D_2O$): $\delta = [161.51, 142.67, (2\times C\textit{ipso})]$, 126.37 (Ph), 116.97 (Ph), 97.09 (CH-1), 76.76 (CH-1), 76.76 (C-5), 74.62, 73.59, 67.99 (CH-2, CH-3, CH-4), 62.46, 60.48 ($CH_2$-6, $CH_2$-7); MS (CI, $NH_3$): *m*/*z* (%): 331 (100) [$M+NH_4^+$]; HRMS (positive-ion CI, $NH_3$): calcd for $C_{13}H_{19}O_8N_2$ ($M+NH_4^+$) 331.1141, found 331.1140.

‡ Selected data for compound **2**: $[\alpha]_D^{22} = +106$ (*c* 0.94 in $CH_3OH$); $^1H$ NMR (400 MHz, $CD_3OD$): $\delta = 8.38$ (d, 2H, $J = 9.2$ Hz, $PhNO_2$), 7.44 (d, 2H, $J = 9.2$ Hz, $PhNO_2$), 6.07 (d, $J = 1.4$ Hz, 1H, H-1), 4.18 (dd, $J = 1.6$ Hz, 4.5 Hz, 1H, H-3), 4.16 (dd, $J = 1.4$ Hz, 4.5 Hz, 1H, H-2), 4.16 (d, $J = 9.4$ Hz, 1H, H-7), 4.12 (dd, $J = 1.0$ Hz, 9.4 Hz, 1H, H-7′), 3.97 (m, 1H, H-4), 3.79 (d, $J = 12.3$ Hz, 1H, H-6), 3.75 (d, $J = 12.3$ Hz, 1H, H-6′); $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta = [164.01, 143.91, (2\times C\textit{ipso})]$, 126.97 (Ph), 118.02 (Ph), 97.16 (CH-1), 79.34 (C-5), 75.36, 74.38, 71.92 (CH-2, CH-3, CH-4), 65.07, 63.18 ($CH_2$-6, $CH_2$-7); MS (CI, $NH_3$): *m*/*z* (%): 331 (52) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{13}H_{15}O_8N$ (313.26): C, 49.84; H, 4.83; N, 4.47; found: C, 49.87; H, 4.87; N, 4.30.

§ Selected data for compound **4**: $[\alpha]_D^{22} = +20$ (*c* 0.44 in $CH_3OH$); $^1H$ NMR (400 MHz, $CD_3OD$): $\delta = 5.36$ (d, $J = 1.6$ Hz, 1H, H-1), 4.27 (m, $J = 6.2$ Hz, 1H, H-8), 4.13 (dd, $J = 1.3$ Hz, 9.0 Hz, 1H, H-7), 4.07 (dd, $J = 1.6$ Hz, 4.5 Hz, 1H, H-3), 4.03 (dd, $J = 0.9$ Hz, 9.0 Hz, 1H, H-7′), 3.85 (dd, $J = 1.6$ Hz, 4.5 Hz, 1H, H-2), 3.83 (m, 1H, H-4), 3.73 (s, 2H, H-6, H-6′), 1.47 (d, $J = 6.2$ Hz, 3H, $CH_3$-9), 1.35 (d, $J = 6.2$ Hz, 3H, $CH_3$-9′); $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta = 95.86$ (CH-1), 77.83 (C-5), 75.72 (CH-3), 74.88 (CH-4), 72.69 (CH-2), 71.12 (CH-8), 65.00 ($CH_2$-7), 63.77 ($CH_2$-6), 24.56 ($CH_3$-9), 22.41 ($CH_3$-9′); MS (CI, $NH_3$): *m*/*z* (%): 252 (100) [$M+NH_4^+$]; HRMS (positive-ion CI, $NH_3$): calcd for $C_{10}H_{22}O_6N$ ($M+NH_4^+$) 252.1447, found 252.1448.




**Scheme 2.** Synthesis of compounds **1**, **2** and **4**. *Reagents and conditions*: (a) NCS, dry isopropanol, rt; (b) Na, liq. $NH_3$; (c) paranitrophenol, NIS, TfOH, $CH_2Cl_2$, −30°C, 30 min; (d) $NaBrO_3$, $Na_2S_2O_4$, EtOAc, $H_2O$, rt; (e) $CH_3ONa$, $CH_3OH$, rt.




**Scheme 3.** Synthesis of compound **3**. *Reagents and conditions*: (a) TMSOTf, dry isopropanol, rt; (b) $CH_3ONa$, $CH_3OH$, rt; (c) $PhCH(OMe)_2$, CSA, DMF, rt, 14 h; (d) $O_3$, $CH_2Cl_2$, −78°C, 30 min; (e) $NaBH_4$, EtOH, rt, 18 h; (f) TsCl, DMAP, pyridine, rt, 15 h; (g) NaH, DMF, rt, 18 h; (h) $H_2$, Pd/C, $CH_3OH$, rt.

careful column chromatography. The last member **3**¶ of the required set was prepared as shown in Scheme 3.

$^1$H NMR data for compounds **1**–**4** are in agreement with a conformation close to $B_{2,5}$.[13] Furthermore, such a conformation was confirmed by the crystal structure[14] in the case of the α-anomer **2** (Fig. 3).

¶ Selected data for compound **3**: $[\alpha]_D^{22} = -58$ (*c* 1.65 in $CH_3OH$); $^1$H NMR (400 MHz, $CD_3OD$): $\delta = 5.47$ (dd, $J = 1.5$ Hz, 2.7 Hz, 1H, H-1), 4.24 (m, $J = 6.2$ Hz, 1H, H-8), 4.05 (dd, $J = 1.8$ Hz, 4.3 Hz, 1H, H-4), 3.99 (d, $J = 9.2$ Hz, 1H, H-7), 3.92 (m, 1H, H-3), 3.87 (app. t, $J = 2.7$ Hz, 1H, H-2), 3.78 (s, 2H, H-6, H-6′), 3.77 (dd, $J = 1.8$ Hz, 9.2 Hz, 1H, H-7′), 1.43 (d, $J = 6.2$ Hz, 3H, $CH_3$-9), 1.34 (d, $J = 6.2$ Hz, 3H, $CH_3$-9′); $^{13}$C NMR (100 MHz, $D_2O$): $\delta = 99.20$ (CH-1), 77.71 (CH-3), 76.79 (C-5), 76.77 (CH-4), 72.15 (CH-8), 69.64 (CH-2), 63.62 ($CH_2$-7), 62.96 ($CH_2$-6), 24.33 ($CH_3$-9), 22.24 ($CH_3$-9′); MS (CI, $NH_3$): *m*/*z* (%): 252 (100) [M+$NH_4^+$]; HRMS (positive-ion CI, $NH_3$): calcd for $C_{10}H_{22}O_6N$ (M+$NH_4^+$) 252.1447, found 252.1450.

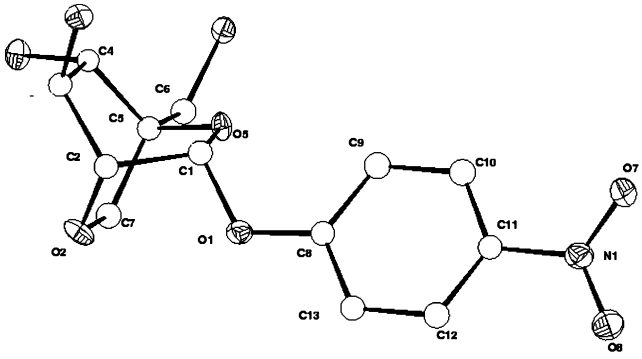



**Figure 3.** Crystallographic structure of the constrained para-nitrophenyl α-D-glucopyranoside **2**

These compounds were then submitted to acidic conditions (1 M aq. HCl) at three temperatures in the ranges 60–70°C and the rate of hydrolysis for each compound was determined.[15] Preliminary results[16] show that the four compounds **1**–**4** are hydrolyzed at a similar rate, the rates observed being close to those reported for the parent unlocked glucosides.[17] This confirms that $B_{2,5}$ transient conformations of glycosides can indeed be acceptable candidates for direct acid hydrolysis. The ongoing piece of work by Davies and Withers[6] indeed nicely brings into light the frequent occurrence of such boat conformations in the context of the enzymatic hydrolysis of glycosides.

## Acknowledgements

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