Synthesis and Stereoselective Glycosylations of 3-O-Acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl Bromide [1]

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Dedicated to Prof. Dr. Dr. h. c. mult. Günther Wilke on the occasion of his 65th birthday

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3-O-Acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl Bromide, α-D-Ribopyranosides, Stereo-Selective Glycosylation

Crystalline 3-O-acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl bromide (5) is prepared by an easy four-step synthesis from D-ribose (1), the first three steps of which are realised in an one-pot manner. 5 reacts stereoselectively with sodium methoxide and phenoxide to give the pure methyl and phenyl α-D-ribopyranosides 7a and 7b after deboronation and deacetylation.

Introduction

The useful concept of achieving stereoselective syntheses of 1,2-cis-glycosides by reacting certain organoboron protected glycosyl bromides with O-nucleophiles [2] has been applied and shown to be effective for the preparations of various β-D-mannofuranosides [3, 4] and α/β-D-manno-furanosyl-β-D-mannofuranosides [5].

In an extension of that work to pyranoses, the O-phenylboranediylation of D-ribose [6] has been used to achieve an efficient synthesis of 3-O-acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl bromide (5). The preparation of this crystalline halogenose and its highly stereoselective glycosylations to give methyl and phenyl α-D-ribopyranosides 7a and 7b are described below.

Results and Discussion

Condensation of D-ribose (1) with triphenylboroxin in benzene in the molar ratio 3:2 gives a mixture consisting of 65% 1,2:3,4-di-O-phenylboranediyl-α-D-ribopyranose (2) and ca. 35% 1,5:2,3-di-O-phenylboranediyl-β-D-ribopyranose (3) in quantitative yield. The solid mixture of fully protected 2 and 3 is easily converted to partially protected derivatives by transesterification. Thus, on dissolving 2 and 3 in pyridine and adding an equimolar amount of 1, a mixture of the intermediate 2,4-O-phenylboranediyl-D-ribopyranose (Z)

* 1H NMR spectroscopy; ** 13C NMR spectroscopy.

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cannot be separated in such an easy and efficient way. 4 in dichloromethane reacts smoothly with hydrogen bromide/acetic acid at room temperature to give solid 3-O-acetyl-2,4-O-phenyloboranediyl-β-D-ribofuranosyl bromide (5) in 95% yield. Colourless needles of 5 can be obtained from dichloromethane/pentane.

5 in diethyl ether reacts with a stoichiometric amount of sodium methoxide in an exothermic reaction at room temperature and after filtering off the sodium bromide, methyl 3-O-acetyl-2,4-O-phenyloboranediyl-α-D-ribofuranoside (6a) is obtained in >90% yield as a colourless solid of ~99% purity (GC).

Both 6a and 6b are easily deboronated with propane-1,3-diol and then deacetylated with methanol/sodium methoxide giving the pure methyl and phenyl α-D-ribofuranosides 7a and 7b, respectively. 7a is initially isolated as a colourless viscous syrup after vacuum distillation, but it crystallizes on standing after several weeks. Crystalline 7b with m.p. 121 ºC is obtained after crystallization from acetone. The high purities of 7a and 7b were confirmed by GC after converting them to the tri-O-acetates 8a and 8b.

The 1H and 13C NMR data for 2–8b are listed in Tables I and II, respectively. The long-range couplings of 4J2a = 2 Hz in the 1H NMR spectra of 4, 5, 6a, and 6b are consistent with the 1C4-conformations for these rigid derivatives.

Methyl α-D-ribofuranoside (7a) is difficult to prepare by other procedures. Reaction of 2,3,4-tri-O-benzoyl-β-D-ribofuranosyl bromide with methanol for example gives the more stable β-D-ribofuranoside in 88% yield [9]. A laborious multistep synthesis starting from methyl 2-O-benzoyl-3,4-di-O-p-tolylsulfonyl-β-L-arabinofuranoside giving the desired product together with small amounts of methyl β-L-lyxopyranoside has previously been the procedure of choice for the preparation of 7a [10, 11]. The first samples of pure 8a could only be isolated after column chromatography [11]. Phenyl α-D-ribofuranoside 7b has not been described previously and 8b has only been obtained as the minor constituent in a mixture of the anomers formed by condensation of tetra-O-acetyl-β-D-ribofuranose with phenol in the presence of tin tetrachloride [12].

Hence, it is apparent that the easily prepared 5 is a very useful intermediate for the stereoselective preparations of methyl and phenyl α-D-ribofuranoside 7a and 7b. 5 has also been used for preparing some α-D-ribofuranosyl disaccharides in good yields with equally high stereoselectivities [13].

Experimental

All experiments were carried out in dry deoxygenated solvents under an atmosphere of argon. The GC analyses were carried out with a Siemens Sichromat I using glass capillary columns coated with methyl silicone stationary phases such as OV 101. Column lengths 20–25 m. Temperature 60–300 ºC. Pure carrier gas (Helium) was dried by
Table I. $^1$H NMR Data ($\delta$ and $J_{H,H}$) for 2–8b.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Chemical shifts [ppm]</th>
<th>Coupling constants [Hz]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-1</td>
<td>H-2</td>
<td>H-3</td>
</tr>
<tr>
<td>2b</td>
<td>CDCl$_3$</td>
<td>200</td>
<td>5.98</td>
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<td>3b</td>
<td>CDCl$_3$</td>
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<tr>
<td>4</td>
<td>CDCl$_3$</td>
<td>80</td>
<td>6.28</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$D$_6$</td>
<td>80</td>
<td>6.20</td>
</tr>
<tr>
<td>6a</td>
<td>C$_6$D$_6$</td>
<td>80</td>
<td>3.76</td>
</tr>
<tr>
<td>6b</td>
<td>C$_6$D$_6$</td>
<td>80</td>
<td>4.51</td>
</tr>
<tr>
<td>7a</td>
<td>C$_6$D$_6$/DMSO-d$_6$</td>
<td>80</td>
<td>4.43</td>
</tr>
<tr>
<td>7b</td>
<td>DMSO-d$_6$</td>
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<td>5.19</td>
</tr>
<tr>
<td>8a</td>
<td>C$_6$D$_6$</td>
<td>80</td>
<td>4.44</td>
</tr>
<tr>
<td>8b</td>
<td>CDCl$_3$</td>
<td>200</td>
<td>5.34</td>
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</table>

- Instruments: 80 MHz Bruker WP-80-FT, 200 MHz Bruker AM-200; b in mixture of 2 and 3.

Table II. $^{13}$C NMR Chemical shifts for 2–8b.

<table>
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<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>OCH$_3$ B-PhOAc</th>
<th>B-Phenyl</th>
<th>Other signals</th>
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<tbody>
<tr>
<td></td>
<td>$i$</td>
<td>$o$</td>
<td>$m$</td>
<td>$\rho$</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>2b</td>
<td>CDCl$_3$</td>
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<td>72.6</td>
<td>71.2</td>
<td>60.8</td>
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<td>-</td>
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<tr>
<td>3b</td>
<td>CDCl$_3$</td>
<td>104.3</td>
<td>87.3</td>
<td>81.9</td>
<td>87.5</td>
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<td>64.8</td>
<td>64.6</td>
<td>64.7</td>
<td>-</td>
<td>-</td>
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<tr>
<td>6a</td>
<td>CDCl$_3$</td>
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<td>69.9</td>
<td>68.0</td>
<td>66.9</td>
<td>66.8</td>
<td>57.0</td>
<td>131.4</td>
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<td>67.4</td>
<td>66.3</td>
<td>66.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7a</td>
<td>DMSO-d$_6$</td>
<td>100.2</td>
<td>69.1</td>
<td>70.2</td>
<td>67.3</td>
<td>60.6</td>
<td>55.4</td>
<td>-</td>
</tr>
<tr>
<td>7b</td>
<td>DMSO-d$_6$</td>
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<td>69.6</td>
<td>69.2</td>
<td>67.1</td>
<td>61.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8a</td>
<td>CDCl$_3$</td>
<td>97.5</td>
<td>67.6</td>
<td>67.4</td>
<td>66.2</td>
<td>57.9</td>
<td>56.3</td>
<td>-</td>
</tr>
<tr>
<td>8b</td>
<td>CDCl$_3$</td>
<td>94.3</td>
<td>67.6</td>
<td>67.4</td>
<td>66.0</td>
<td>57.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Chemical shifts (ppm) relative to internal TMS. Measurements at 75.5 MHz (Bruker WM 300); b in mixture of 2 and 3; c assignments may be interchanged; d together with other signals.

passing through molecular-sieves. Heating rates 8 °C/min, He 0.8–1.5 bar. The mass spectra were obtained with a Varian CH-5 spectrometer at 70 eV. Optical rotations were measured using a Perkin-Elmer Polarimeter 241. The C, H, B analyses were carried out by Dorris and Kolbe, Mülheim an der Ruhr. Triphenylboroxin was obtained from commercial phenylboronic acid (Heyl and Co., Berlin) by adding toluene and distilling off the toluene/water-azeotrope.
1,3-Di-O-acety1-2,4-O-phenylboranediyl-β-D-ribopyranoside (4)

Triphenylboroxin (27.6 g, 88 mmol) is added to a stirred suspension of 1 (20 g, 133 mmol) in benzen (150 ml) and the benzene/water azeotrope is distilled off. The remaining solvent is removed in vacuo (0.1 torr) to leave 42.9 g (100%) containing ~65% 2 and 35% 3. 1 (20 g, 133 mmol) is then added to this residue and the mixture is dissolved in pyridine (100 ml) by heating to 30 °C. After cooling to room temperature, acetic anhydride in pyridine (100 ml) by heating to 30 °C. After 4 h, the volatile components are removed in vacuo (10 °C) leaving 87.2 g (102%) semi-solid residue to which diethyl ether (20 ml) is added and the crystalline product is filtered off and dried in vacuo.

Phenyl 3-O-acetyl-2,4-O-phenylboranediyl-a-D-ribopyranoside (6b)

5 (7.7 g, 22.6 mmol) in diethyl ether (30 ml) is added dropwise to a stirred suspension of sodium methoxide (1.5 g, 23.7 mmol) in diethyl ether (30 ml) at room temperature so that the flask temperature does not rise above 30 °C. After stirring for a further 1.5 h, insoluble material is filtered off and washed with ether (30 ml). The filtrate is concentrated in vacuo (12 torr) leaving crude crystalline 6b (8 g, 100%), which is recrystallized from diethyl ether to give pure (GC) 6b (7 g, 88%); m.p. 90–92 °C, [α]D^9 33.8° (c 2, CHCl3).

Methyl a-D-ribopyranoside (7a)

6a (3 g, 10.3 mmol) is dissolved in acetone (20 ml) and propane-1,3-diol (2 ml) is added to the solution. The mixture is concentrated in vacuo (10 °C torr) and the residue is treated with acetone (20 ml) and propane-1,3-diol (1 ml). Concentration of the mixture gives pale yellow, highly viscous, boron-free residue, to which methanol (20 ml) and sodium methoxide (0.1 g) are added. After stirring for 2 h at room temperature, the methanol is removed in vacuo (10 °C torr) and the residue is vacuum distilled to give colourless, viscous 7a (1.5 g, 90%) with b.p. 103 °C (10 °C torr), [α]D^20 120° (c 0.5, CH3OH); Lit. [14]: [α]D^20 103.3° (c 1, CH3OH). 7a with m.p. 74 °C crystallizes after standing for several weeks at room temperature.
Phenyl α-D-ribopyranoside (7b)

Propane-1,3-diol (15 ml) and methanol (30 ml) are added to 6b (2.1 g, 5.9 mmol) and all the volatile components are removed in vacuo (10⁻³ torr). Pentane (20 ml) is added to the pale yellow, highly viscous residue which solidifies after 1 d and the colourless 7b is filtered off and dried in vacuo (10⁻² torr). 7b (1.25 g, 93%) is obtained having m.p. 121 °C and [α]_D° 129.6° (c 0.7, CH₂Cl₂), after crystallization from acetone.

MS (m/z, %): 226 (M⁺, 2), 132 (10), 94 (100).

Methyl 2,3,4-tri-O-acetyl-α-D-ribofuranoside (8a)

Pyridine (5 ml) and acetic anhydride (5 ml) are added to 7a (3 mmol) and the stirred mixture is heated to 50 °C (bath temperature) for 2 d in order to achieve per-acetylation. The volatile components are removed in vacuo (10⁻³ torr) and the residue distilled to give colourless 8a (0.75 g, 85% of 99% purity (GC) with b. p. 82 °C (10⁻³ torr), m. p. 99 °C, [α]_D° 90° (c 1.7, CHCl₃); Lit. [11]: [α]_D° 86.6° (c 1.61, CHCl₃).

MS (m/z, %): 259 (M-OCH₃, 1.4), 170 (19), 128 (29), 43 (100).
Calcd C 49.65 H 6.25, Found C 49.61 H 6.20.

Phenyl 2,3,4-tri-O-acetyl-α-D-ribopyranoside (8b)

Pyridine (5 ml) and acetic anhydride (5 ml) are added to 7b (0.7 g, 3.1 mmol) and the stirred mixture is heated to 50 °C (bath temperature) for 2 h. The volatile components are removed in vacuo (10⁻³ torr) and the residue is treated with ethanol (4×10 ml) and diethyl ether (2×10 ml) and concentrated in vacuo (10⁻³ torr) each time to give 8b (1.05 g, 96% of 98% purity (GC) as a highly viscous residue, [α]_D° 119° (c 0.9, CHCl₃).

MS (m/z, %): 352 (M⁺, 0.1), 259 (21), 157 (18), 139 (64), 97 (47), 43 (100).
Calcd C 57.95 H 5.72, Found C 57.76 H 5.91.

[1] Part XV of the Series “Organoboron-Monosaccharides”; for Part XIV see Ref. 5.
[6] Previous reports on the O-phenylboranediyl derivatives of 1 erroneously assigned the a-configuration to the 2,4-O-phenylboranediyl protected Z [7] and it was also claimed that the fully O,BPh protected derivative is solely 3 [8], instead of it being the minor constituent in the mixture of 2 and 3.