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

Wilhelm V. Dahlhoff*, Gerhard Schroth+, Barbara Gabor++, and Roland Köster

Max-Planck-Institut für Kohlenforschung,
Kaiser-Wilhelm-Platz 1, D-4330 Mülheim an der Ruhr, FRG

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

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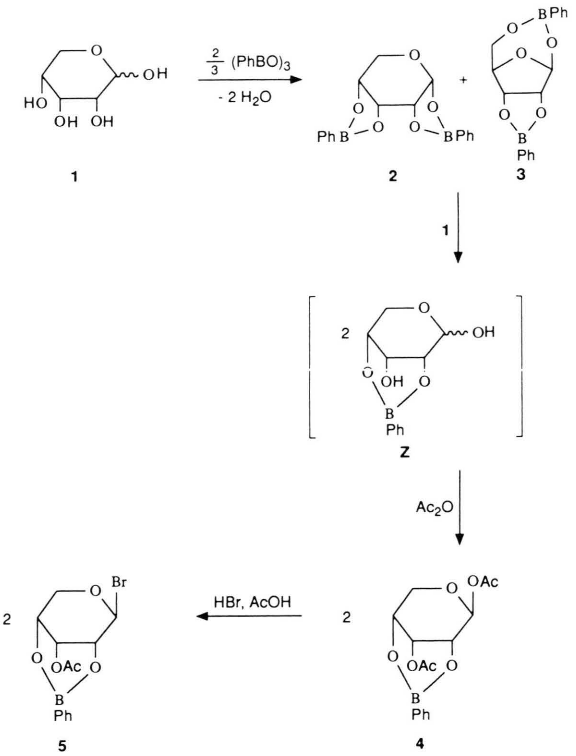
3-O-Acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl Bromide, α-D-Ribopyranosides, Stereoselective Glycosylation

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-mannofuranosyl-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-ribofuranose (**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**) and 2,3-O-phenylboranediyl-D-ribofuranose is formed immediately. This mixture is quantitatively O-acetylated by addition of acetic anhydride. After concentrating *in vacuo* and adding diethyl ether to the residue, colourless solid 1,3-di-O-acetyl-2,4-O-phenylboranediyl-β-D-ribopyranose **4** of 95% purity with 5% anomer (GC) is isolated in 70% yield by filtration and drying *in vacuo*. The O-ethylboranediyl analogues of **2, 3, Z,** and **4** can also be prepared, however the BEt analogue of **4**

+ ^{1}H NMR spectroscopy; ++ ^{13}C NMR spectroscopy.

* Reprint requests to Dr. W. V. Dahlhoff.

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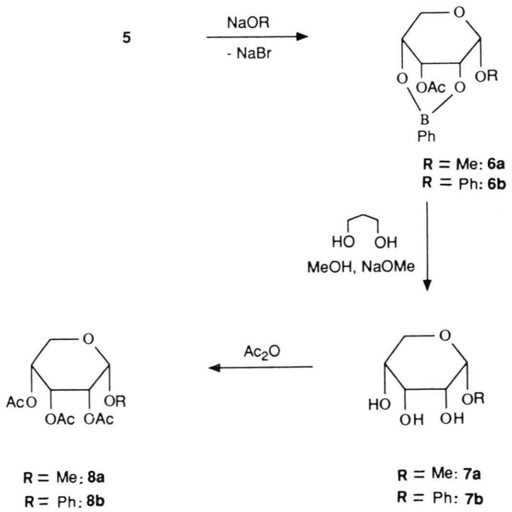
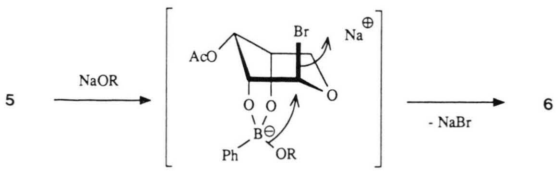
cannot be separated in such an easy and efficient way. **4** in dichloromethane reacts smoothly with hydrogen bromide/acetic acid at room temperature to give solid 3-O-acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl bromide (**5**) in 95% yield. Colourless needles of **5** can be obtained from dichloromethane/pentane.

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-phenylboranediyl-α-D-ribopyranoside (**6a**) is obtained in >90% yield as a colourless solid of ~99% purity (GC).



Likewise, glycosylation of **5** with an equimolar amount of sodium phenoxide is also exothermic at room temperature and pure phenyl 3-O-acetyl-2,4-O-phenylboranediyl-α-D-ribopyranoside (**6b**), is isolated in 88% yield after recrystallization.

The extraordinary high stereoselectivities found in these reactions are possibly due to the formation of labile borate intermediates which react smoothly with inversion at the anomeric centre as shown below.



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-ribopyranosides **7a** and **7b**, respectively. **7a** is initially isolated as a colourless viscous sirup after vacuum distillation, but it crystallizes on standing after several weeks. Crystalline **7b** with m.p. 121 °C 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 ^{1}H and ^{13}C NMR data for **2–8b** are listed in Tables I and II, respectively. The long-range couplings of $^4J_{2,4}$ = 2 Hz in the ^{1}H NMR spectra of **4, 5, 6a,** and **6b** are consistent with the $^1C_4$-conformations for these rigid derivatives.

Methyl α-D-ribopyranoside (**7a**) is difficult to prepare by other procedures. Reaction of 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide with methanol for example gives the more stable β-D-ribopyranoside in 88% yield [9]. A laborious multistep synthesis starting from methyl 2-O-benzoyl-3,4-di-O-*p*-tolylsulfonyl-β-L-arabinopyranoside 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-ribopyranoside **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-ribopyranose 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-ribopyranoside **7a** and **7b. 5** has also been used for preparing some α-D-ribopyranosyl 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 1 using glass capillary columns coated with methyl silicone stationary phases such as OV 101. Column lengths 20–25 m. Temperature 60–300 °C. Pure carrier gas (Helium) was dried by

Table I. ^1H NMR Data (δ and $J_{H,H}$) for **2–8b**[a].

Compound	Solvent	MHz[a]	Chemical shifts [ppm] H-1	H-2	H-3	H-4	H-5a	H-5b	OCH_3	B−Ph	OAc	Coupling constants [Hz] $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$	$^4J_{2,4}$	$^4J_{3,5}$
2[b]	$CDCl_3$	200	5.98	complex			4.27	3.74	–	7.9 7.5	–	5.5	–	–	7.5	9	−12	–	–
3[b]	$CDCl_3$	200	5.92	5.17	complex		4.43	4.30	–	7.9 7.5	–	<1	6	–	1	2.5	−13	–	–
4	$CDCl_3$	80	6.23	4.27	5.32	4.40	4.05	4.01	–	7.87 7.4	2.10 2.16	2.6	2.2	2.0	–	–	−10.8	2.2	–
5	C_6D_6	80	6.05	4.27	5.52	3.93	3.52	3.52	–	8.13 7.3	1.45	2	2	2	–	–	–	2	–
6a	C_6D_6	80	3.76	4.29	4.56	3.94	3.69	2.82	3.23	8.26 7.3	1.51	<1	2	2	2.5	0.5	−12.5	2	–
6b	C_6D_6	80	4.51	4.38	4.59	3.93	3.65	2.86	–	8.26 7.3	1.52	0.5	2	2	2.5	0.5	−12.2	2	–
7a	C_6D_6/ DMSO-d_6	80	4.43	complex					3.29	–	–	3	–	–	–	–	–	–	–
7b	DMSO-d_6	80	5.19	complex					–	–	–	3	–	–	–	–	–	–	–
8a	C_6D_6	80	4.44	4.96	5.57	4.95	3.30	3.89	3.08	–	1.78 1.69 1.62	3.5	3.5	3.5	4.2	8.5	−11	–	1.0
8b	$CDCl_3$	200	5.34	4.97	5.68	4.94	3.33	3.93	–	–	1.80 1.65 1.55	3.8	3.2	3.3	3.3	9.6	−11.1	–	1.1

[a] 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**[a].

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	OCH_3	B-Phenyl *i*	*o*	*m*	*p*	Other signals
2[b]	$CDCl_3$	97.4	73.3[c]	72.6[c]	71.2[c]	60.8	–	–	135.2[d] 134.9	127.8[d]	132.1 131.6[d]	
3[b]	$CDCl_3$	104.3	87.3[c]	81.9[c]	87.5[c]	69.7	–					
4	$CDCl_3$	93.1	67.8[c]	67.7[c]	65.0	65.95	–	131.4 (br)	134.1	127.7	131.2	170.3, 168.6 ($\underline{C}OCH_3$), 20.9 ($CO\underline{C}H_3$)
5	$CDCl_3$	87.4	71.5[c]	64.8[c]	64.6[c]	67.4	–	–	134.4	128.0	131.6	170.2 ($\underline{C}OCH_3$), 20.8 ($CO\underline{C}H_3$)
6a	$CDCl_3$	101.5	69.9[c]	68.0	66.9[c]	66.8	57.0	131.4 (br)	134.2	127.5	131.0	170.2 ($\underline{C}OCH_3$), 20.8 ($CO\underline{C}H_3$)
6b	$CDCl_3$	98.3	69.5[c]	67.4[c]	66.3[c]	66.6	–	–	134.0	127.3	130.8	170.0 ($\underline{C}OCH_3$), 20.6 ($CO\underline{C}H_3$) 156.5, 116.7, 129.2, 122.7 (*i, o, m, p*)
7a	DMSO-d_6	100.2	69.1[c]	70.2[c]	67.3[c]	60.6	55.4	–	–	–	–	–
7b	DMSO-d_6	97.2	69.6[c]	69.2[c]	67.1[c]	61.4	–	–	–	–	–	157.1, 116.7, 129.3, 121.8 (*i, o, m, p*)
8a	$CDCl_3$	97.5	67.6[c]	67.4[c]	66.2[c]	57.9	56.3	–	–	–	–	170.4, 170.0, 169.7 ($\underline{C}OCH_3$), 20.8, 20.74, 20.66 ($CO\underline{C}H_3$)
8b	$CDCl_3$	94.3	67.6[c]	67.4[c]	66.0[c]	57.4		–	–	–	–	156.9, 117.0, 129.6, 122.7 (*i, o, m, p*) 170.4, 169.9, 169.5 ($\underline{C}OCH_3$), 20.8, 20.6 ($COC\underline{C}H_3$)

[a] 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 Dornis and Kolbe, Mülheim an der Ruhr. Triphenylboroxin was obtained from commerical phenylboronic acid (Heyl and Co., Berlin) by adding toluene and distilling off the toluene/water-azeotrope.

1,3-Di-O-acetyl-2,4-O-phenylboranediyl-β-D-ribopyranose (**4**)

Triphenylboroxin (27.6 g, 88 mmol) is added to a stirred suspension of **1** (20 g, 133 mmol) in benzene (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 (100 ml) is added dropwise to the stirred solution at such a rate (~3 h) that the flask temperature does not exceed 40 °C. After 4 h, the volatile components are removed *in vacuo* (10^{-3} torr) leaving 87.2 g (102%) semi-solid residue to which diethyl ether (200 ml) is added and the crystalline product is filtered off and dried *in vacuo* (10^{-3} torr) to give 95% pure **4** (60 g, 70%) with 5% of the anomer; m.p. 155–158 °C, $[\alpha]_D^{20}$ −112.9° (c 0.7, $CHCl_3$).

MS (*m/z*, %): 320 (M^+, 4), 172 (B_1, 32), 159 (B_1, 66), 43 (100). ^{11}B NMR (neohexane): δ = 27.4 (half-width 330 Hz).

$C_{15}H_{17}BO_7$ (320.1)

Calcd	C 56.28	H 5.35	B 3.38,
Found	C 56.20	H 5.41	B 3.48.

3-O-Acetyl-2,4-O-phenylboranediyl-β-D-ribopyranosyl bromide (**5**)

A solution of hydrogen bromide in acetic acid (40 ml with 35 wt-% HBr) is added to a stirred solution of **4a, b** (22.2 g, 69.4 mmol) in dichloromethane (80 ml) at room temperature and after 5 h, all the volatile components are removed at 12 torr and finally at 10^{-3} torr. Dichloromethane (20 ml) is added to the residue and removed again *in vacuo* leaving almost colourless **5** (22.4 g, 95%) of 97.6% purity (by GC) suitable for further reactions; m.p. 75 °C, $[\alpha]_D^{20}$ −193° (c 2.7, $CHCl_3$). Colourless needles of 99% pure (GC) **5** are obtained by crystallization from dichloromethane/pentane (1:5); m.p. 80–83 °C, $[\alpha]_D^{20}$ −204° (c 2.2, $CHCl_3$).

MS (*m/z*, %): 341 (M^+, 1), 261 (B_1, 15), 43 (100).

$C_{13}H_{14}BBrO_5$ (341.0)

Calcd	C 45.79	H 4.14	B 3.17	Br 23.43,
Found	C 45.92	H 4.23	B 3.14	Br 23.25.

Methyl 3-O-acetyl-2,4-O-phenylboranediyl-α-D-ribopyranoside (**6a**)

A solution of **5** (6.8 g, 19.9 mmol) in diethyl ether (30 ml) is added dropwise in 1 h to a stirred suspension of sodium methoxide (1.18 g, 21.9 mmol) in diethyl ether (30 ml) at room temperature, the flask temperature rising by max. 7 °C. The mixture is stirred for 24 h before filtering off insoluble material over Kieselgur. The solids are washed with diethyl ether (3×10 ml) and the filtrate concentrated *in vacuo* (12 torr) to give **6a** (5.4 g, 93%) of 99.2% purity (GC) with m.p. 134 °C, $[\alpha]_D^{20}$ 9.1° (c 1.1, $CHCl_3$).

MS (*m/z*, %): 215 ($M-C_6H_5$, 23), 172 (B_1, 19), 155 (B_1, 42), 69 (72), 43 (100).

$C_{14}H_{17}BO_6$ (292.1)

Calcd	C 57.56	H 5.87	B 3.70,
Found	C 57.49	H 5.92	B 3.65.

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

5 (7.7 g, 22.6 mol) in diethyl ether (30 ml) is added dropwise in 1 h to a stirred suspension of sodium phenoxide (2.75 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, $[\alpha]_D^{20}$ −33.8° (c 2, $CHCl_3$).

MS (*m/z*, %): 354 (M^+, 2), 261 (B_1, 8), 43 (100).

$C_{19}H_{19}BO_6$ (354.1)

Calcd	C 64.43	H 5.41	B 3.05,
Found	C 64.47	H 5.34	B 3.01.

Methyl α-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^{-3} 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^{-2} torr) and the residue is vacuum distilled to give colourless, viscous **7a** (1.5 g, 90%) with b.p. 103 °C (10^{-3} torr), $[\alpha]_D^{20}$ 120° (c 0.5, CH_3OH); Lit. [14]: $[\alpha]_D^{20}$ 103.3° (c 1, CH_3OH). **7a** with m.p. 74 °C crystallizes after standing for several weeks at room temperature.

MS (*m/z*, %): 133 ($M-CH_3O$, 3), 86 (5), 73 (40), 60 (100).

$C_6H_{12}O_5$ (164.2)

Calcd	C 43.90	H 7.37,
Found	C 44.09	H 7.44.

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 $[\alpha]_D^{20}$ 129.6° (c 0.7, CH_2Cl_2), after crystallization from acetone.

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

$C_{11}H_{14}O_5$ (226.2)

Calcd	C 58.40	H 6.24,
Found	C 58.37	H 6.20.

Methyl 2,3,4-tri-O-acetyl-α-D-ribopyranoside (**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. 85 °C, $[\alpha]_D^{20}$ 90° (c 1.7, $CHCl_3$); Lit. [11]: $[\alpha]_D^{18}$ 86.6° (c 1.61, $CHCl_3$).

MS (*m/z*, %): 259 ($M-OCH_3$, 1.4), 170 (19), 128 (29), 43 (100).

$C_{12}H_{18}O_8$ (290.3)

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, $[\alpha]_D^{20}$ 119° (c 0.9, $CHCl_3$).

MS (*m/z*, %): 352 (M^+, 0.1), 259 (21), 157 (18), 139 (64), 97 (47), 43 (100).

$C_{17}H_{20}O_8$ (352.3)

Calcd	C 57.95	H 5.72,
Found	C 57.76	H 5.91.

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