A Simple Synthesis of α-D-Ribofuranosides

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The glycosylation of various aglycones with 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl bromide (**2**) has been studied under different reaction conditions. It is possible to obtain high yields of α-linked ribofuranosides using methanol or methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside as the aglycones. However, the use of 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose as the aglycone results in a rather low yield of α 1,3-linked glycoside together with some α 1,6-linked glycoside formed after isopropylidene group migration during the glycosylation reaction.

Several papers have described different approaches to the synthesis of 1,2-*cis* glycosides in the mannopyranose and rhamnopyranose series.[1–6] Some reports have also been concerned with the synthesis of 1,2-*cis* glycosides using mannofuranose[7,8] and ribofuranose[9–11] derivatives. In the present paper we wish to report on an alternative simple approach to the synthesis of 1,2-*cis* glycosides of ribofuranose using the readily available 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl bromide (**2**) as a glycosylating reagent.

Results and discussion

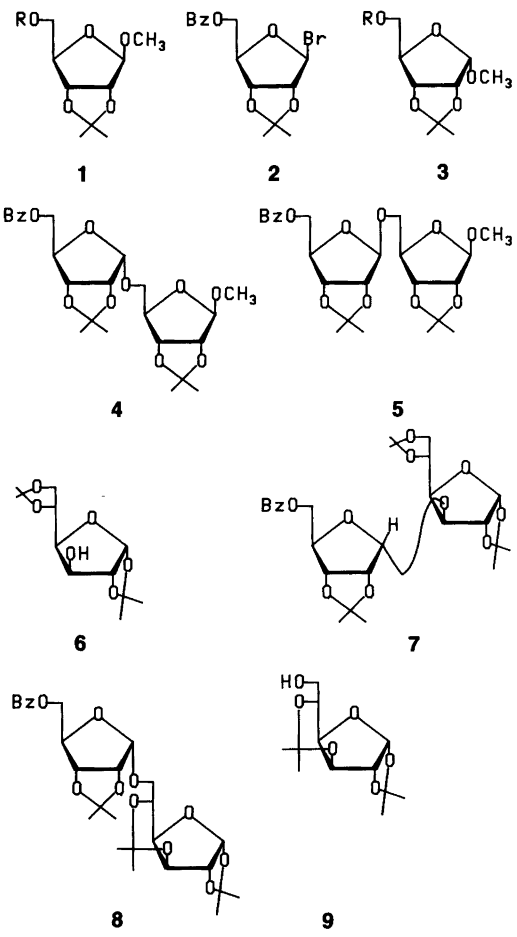
Treatment of D-ribose with methanol, acetone and concentrated sulfuric acid for 24 h at room temperature followed by benzoylation gave a high yield (81 %) of an anomeric mixture of **1a** and **3a** in a ratio of 9 to 1. Treatment of this product with hydrogen bromide in dichloromethane gave a quantitative yield of the unstable glycosyl bromide (**2**), which therefore was only characterized through its spectroscopic data and used directly in the following glycosylation reactions. The corresponding 5-*O*-*p*-nitrobenzoate has been reported to be crystalline.[12,13]

Reaction of the bromide (**2**) with a large excess of methanol in dichloromethane using silver carbonate as the promoter gave a mixture of the glycosides **1a** and **3a** in a ratio of 1 to 5 (total yield 86 %). The α-anomer (**3a**) could be isolated in a crystalline state (50 % yield) after chromatographic separation. Debenzoylation followed by removal of the isopropylidene group gave methyl α-D-ribofuranoside as a syrup, which was characterized by its NMR parameters.

When the glycosylation reaction was conducted in benzene for 3 days at room temperature, using silver carbonate as the promoter and with 6 molar equivalents of methanol, **1a** and **3a** could be isolated in 70 % yield in a ratio of 1 to 6.5. Glycosylation under same reaction conditions using dichloromethane as the solvent gave the same yield, but with a poorer α selectivity (α:β = 3:1).

Glycosylation using methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1b**) as the aglycone under the same reaction conditions as described above gave, after chromatographic separation, the α-linked disaccharide **4** in 76 % and the β-linked disaccharide **5** in 13 % yield. The same results were obtained using benzene as the solvent, although the total yield in this case was somewhat lower. Glycosylation in dichloromethane using silver triflate[14] as the promoter was very rapid and gave a high yield (78 %) of disaccharides, but with an α:β ratio of only 3:1.

Glycosylation with **2** in dichloromethane using 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) as the aglycone and silver carbonate as the promoter gave 30 % of the α 1,3-linked disaccha-



a: R = Bz; **b**: R = H

ride **7**. Careful examination of the reaction mixture showed that no (<2%) β-linked disaccharide was formed in the reaction; however, 6% of an α 1,6-linked disaccharide (**8**) was isolated. The last product was presumably formed by glycosylation of 1,2-3,5-di-*O*-isopropylidene-α-D-glucofuranose (**9**), which may be formed in the reaction mixture by rearrangement of **6**. Similar migration of an isopropylidene group during a glycosylation reaction has been observed previously.[15,16] This result was further confirmed by glycosylation of **9** with **2** under the same reaction conditions as described above. The total yield of disaccharides was rather low (30%), but both α 1,6- and α 1,3-linked disaccharides **7** and **8** in a ratio of about 3:2 were isolated together with 40% of 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**).

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. NMR spectra were obtained on bruker WH-90, HX-270 and WM-400 NMR instruments in deuteriochloroform unless otherwise stated. Dioxane (67.4 ppm) was used as internal reference for ^{13}C NMR spectra in D_2O. TLC was performed on silica gel (Merck PF-254). Microanalyses were performed by Novo microanalytical laboratory.

5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl bromide (**2**). Methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**1a**)[17] (5 mmol) was dissolved in dry CH_2Cl_2 (20 ml) and hydrogen bromide was passed through the solution for 1 h at room temp. under exclusion of moisture. The resulting solution was evaporated and then coevaporated twice with CH_2Cl_2. The unstable glycosyl bromide (**2**) was used for glycosylation without further purification but was characterized by its NMR data. ^1H NMR: δ 6.55 (H-1), 5.33 (H-2), 5.04 (H-3), 4.6–4.8 (H-4, H-5, H-5′). J_{12} 0 Hz, J_{23} 6.0, J_{34} 1.0. ^{13}C NMR: 91.8 ppm (C-1), 88.0 (C-2), 90.2 (C-3), 81.2 (C-4), 62.5 (C-5).

Methyl-5-O-benzoyl-2,3-O-isopropylidene-α-D-ribofuranoside (**3a**). The bromide (**2**) (633 mg) in dry CH_2Cl_2 (20 ml) was added to a suspension of silver carbonate (700 mg) in CH_2Cl_2 (10 ml) and MeOH (5 ml) over a period of 20 min. The reaction mixture was stirred for 1 h at room temp. The mixture was concentrated after filtration through carbon, and a crude product consisting of a mixture of **1a** and **3a** was isolated (542 mg, 86%) in a ratio of 1:6 as determined from a ^1H NMR spectrum. Purification by preparative TLC using Et_2O/pentane (2:1) as eluent gave, as the fastest moving compound, **1a** (51 mg, 8%), identical with the starting material. ^1H NMR: δ 5.02 (H-1), 4.65 (H-2), 4.77 (H-3), 4.52 (H-4), 4.40 (H-5), 4.34 (H-5′). J_{12} 0 Hz, J_{34} 1.0, J_{45} 6.8, $J_{45'}$ 6.8, $J_{55'}$ 12.0. ^{13}C NMR: 109.5 ppm (C-1), 85.2 (C-2), 81.8 (C-3), 84.3 (C-4), 64.9 (C-5), 54.9 (OMe), 112.5, 26.3, 24.9 [$(CH_3)_2C$]. The next

fraction gave **3a** (306 mg, 48 %) as a crystalline product; recrystallization from Et_2O-pentane gave m.p. 44–45 °C, $[\alpha]_D^{20}$ +47.9° (*c* 2.0, $CHCl_3$). Anal. $C_{16}H_{20}O_6$: C, H. ^1H NMR: δ 4.96 (H-1), 47.5 (H-2), 4.69 (H-3), 4.44 (H-4), 4.44 (H-5), 4.51 (H-5′). J_{12} 4.3 Hz, J_{23} 6.8, J_{34} 2.8, J_{45} 4.0, $J_{45'}$ 5.0, $J_{55'}$ 13.0. ^{13}C NMR: 102.6 ppm (C-1), 80.5, 80.4, 78.8 (C-2, C-3, C-4), 64.3 (C-5), 55.7 (OMe), 115.2, 25.8, 25.4 [$(CH_3)_2C$].

Similar results were obtained when the glycosylation reaction was carried out using dry benzene as solvent.

Methyl α-D-ribofuranoside. The glycoside (**3a**) (335 mg) was heated with trifluoroacetic acid (1.5 ml, 90 %) at room temp. for 5 min. The reaction mixture was evaporated *in vacuo* at room temp. The product was purified by preparative TLC using Et_2O as eluent, and 5-*O*-benzoyl-α-D-ribofuranoside was isolated as a syrup (247 mg, 63 %) and characterized by its ^1H NMR spectrum. The product was dissolved in 10 ml of 1 % sodium methoxide in methanol and left overnight at room temp. The reaction mixture was neutralized with an ion-exchange resin (IR 50C) and evaporated, giving 147 mg (97 %) of methyl α-D-ribofuranoside as a syrup; $[\alpha]_D^{20}$ = +142.8° (*c* 2.66, H_2O) (Lit.[18] $[\alpha]_D$ = 146.8°). ^{13}C NMR: 103.9 ppm (C-1), 71.9 (C-2), 70.5 (C-3), 85.3 (C-4), 62.3 (C-5), 56.2 (OMe) are in agreement with those published.[19]

Methyl 5-O-(5-O-benzoyl-2,3-O-isopropylidene-α(β)-D-ribofuranosyl)-2,3-O-isopropylidene-β-D-ribofuranoside (**4**, **5**). The aglycone **1b** (413 mg, 2.02 mmol) was dissolved in dry CH_2Cl_2 containing molecular sieves (3 Å) (2 g) and silver carbonate (700 mg). The bromide (**2**) (from 1.26 g, 4.1 mmol of **1a**) in CH_2Cl_2 (10 ml) was added and the reaction mixture stirred at room temp. for 4 d. Work-up as described above gave the crude product as a syrup (1.63 g). The ratio of **4** to **5** was determined to be 6:1 from a ^1H NMR spectrum. Separation by preparative TLC using Et_2O/pentane (2:1) as eluent gave, as the fastest moving fraction, **5** as a syrup (121 mg, 13 %); $[\alpha]_D^{20}$ −74.5° (*c* 1.94, $CHCl_3$). Anal. $C_{24}H_{32}O_{10}$: C, H. ^1H NMR: δ 5.14 (H-1.1), 4.72 (H-2.1), 4.85 (H-3.1), 4.55 (H-4.1), 4.35 (H-5.1, H-5′.1), 4.90 (H-1.2), 4.50 (H-2.2), 4.57 (H-3.2), 4.27 (H-4.2), 3.44 (H-5.2), 3.66 (H-5′.2). $J_{12.1}$ 0 Hz, $J_{23.1}$ 6.0, $J_{34.1}$ 1.0, $J_{45.1} = J_{45'.1}$ 7.0, $J_{12.2}$ 0, $J_{23.2}$ 6.0, $J_{34.2}$ 1.0, $J_{45.2}$ 8.2, $J_{45'.2}$ 6.8, $J_{55'.2}$ 10.2. ^{13}C NMR: 108.9 ppm (C-1.1, 84.8, 84.4 (C-2.1, C-3.1), 81.8 (C-4.1), 65.0 (C-5.1), 109.2 (C-1.2), 85.3, 85.0 (C-2.2, C-3.2), 81.8 (C-3.2), 68.8 (C-5.2), 112.0, 26.3, 24.9 [2×$(CH_3)_2C$].

The slowest moving fraction gave **4** as a syrup (737 mg, 76 %); $[\alpha]_D^{20}$ −10.9° (*c* 1.49, $CHCl_3$). Anal. $C_{24}H_{32}O_{10}$: C, H. ^1H NMR: δ 5.10 (H-1.1), 4.79 (H-2.1), 4.74 (H-3.1), 4.52 (H-4.1), 4.56 (H-5.1), 4.49 (H-5′.1), 5.01 (H-1.2), 4.74 (H-3.1), 4.52 (H-4.1), 4.56 (H-5.1), 4.49 (H-5′.1), 5.01 (H-1.2), 4.63 (H-2.2), 4.79 (H-3.2), 4.50 (H-4.2), 3.89 (H-5.2), 3.57 (H-5′.2). $J_{12.1}$ 4.5 Hz, $J_{23.1}$ 6.6, $J_{34.1}$ 2.2, $J_{45.1}$ 3.1, $J_{45'.1}$ 3.1, $J_{55'.1}$ 10.5, $J_{12.2}$ 0, $J_{23.2}$ 6.1, $J_{34.2}$ 0, $J_{45.2}$ 6.6, $J_{45'.2}$ 8.7, $J_{55'.2}$ 10.5. ^{13}C NMR 102.1 ppm (C-1.1), 80.9, 80.9, 79.4 (C-2.1, C-3.1, C-4.1), 64.6 (C-5.1), 115.0 $(CCH_3)_2$, 26.1 (CH_3×2), 109.5 (C-1.2), 85.2, 85.1 (C-4.2, C-2.2), 82.2 (C-3.2), 69.4 (C-5.2), 54.8 (OMe), 112.0 [$C(CH_3)_2$], 26.5, 25.0 (CH_3×2).

The glycosylation reaction described above was repeated using benzene as solvent. The reaction was slower and after 7 d the reaction was worked up as described above. The crude product (1.44 g) showed a ratio of **4** to **5** of 6:1. Purification by preparative TLC gave 500 mg (50.3 %) of **4** and 73 mg (7.3 %) of **5**.

To a solution of **1b** (322 mg, 1.58 mmol) in dry CH_2Cl_2 and molecular sieves (3 Å) was added tetramethylurea (0.45 ml, 4 mmol) and silver trifluoromethanesulfonate (505 mg, 1.96 mmol). This mixture was stirred at 0 °C and a solution of **2** (1.18 g, 3.8 mmol) in dry CH_2Cl_2 (15 ml) was added. The reaction mixture was left at room temp. for 4 h. Work-up as described above gave 1.63 g of crude **4** and **5** in a ratio of 3:1, as seen from a ^1H NMR spectrum. Purification by preparative TLC gave 147 mg (19 %) of **5** and 447 mg (59 %) of **4** identical with the products described above.

3-O-(5-O-Benzoyl-2,3-O-isopropylidene-α-D-ribofuranosyl)-1,2-5,6-di-O-isopropylidene-α-D-glucofuranose (**7**). The aglycone (**6**) (526 mg, 2.02 mmol) was dissolved in dry CH_2Cl_2 (15 ml), and molecular sieves (3 Å) and silver carbonate (700 mg) were added. The bromide **2** (from 1.45 g, 4.72 mmol of **1a**) in CH_2Cl_2 (10 ml) was added and the reaction mixture left at room temp. for 3 d. An additional amount of bromide **2** (2.44 mmol) and silver carbonate (100 mg) was

added and the reaction mixture left for 4 d. The mixture was worked up as described above, and gave 2.24 g of crude product which was purified by preparative TLC using Et_2O/pentane (3:1) as eluent. The fastest moving fraction (I) gave 772 mg, the next fraction (II) gave 471 mg and the last fraction gave 90 mg of unreacted aglycone (**6**), as seen from its ^1H and ^{13}C NMR data.

Fraction I was acetylated with acetic anhydride and, after work-up, resubjected to chromatography using ethyl acetate/pentane (1:3) as eluent. The slowest moving fraction gave 306 mg (29 %) of **7** as a syrup; $[\alpha]_D^{20}$ +12.0° (*c* 2.41, $CHCl_3$). Anal. $C_{27}H_{36}O_{11}$: C, H. ^1H NMR: δ 5.24 (H-1.1), 4.70 (H-2.1), 4.65 (H-3.1), 4.53–4.41 (H-4.5,5′-1), 5.86 (H-1.2), 4.64 (H-2.2), 4.28 (H-3.2), 4.10 (H-4.2), 4.34 (H-5.2), 3.97 (H-6.2), 4.12 (H-6′.2). $J_{12.1}$ 4.1 Hz, $J_{23.1}$ 6.6, $J_{34.1}$ 1.8, $J_{12.2}$ 3.3, $J_{23.2}$ 0, $J_{34.2}$ 2.8, $J_{45.2}$ 8.3, $J_{56.2}$ 5.5, $J_{56'.2}$ 6.5, $J_{66'.2}$ 8.8. ^{13}C NMR: 102.4 ppm (C-1.1), 80.8, 80.5, 79.1 (C-2,3,4.1); 64.5 (C-5.1), 115.4 [$C(CH_3)_2$.1], 25.9, 26.7 (CH_3 2.1), 105.2 (C-1.2), 84.1 (C-2.2), 81.1 (C-3,4.2), 72.3 (C-5.2), 67.3 (C-6.2), 111.8, 108.7 [$C(CH_3)_2$.2], 26.7, 26.1, 25.3 (CH_3.2). The fastest moving fraction was the 1-*O*-acetate of the hydrolysed bromide **2**. Fraction II was debenzoylated using 1 % sodium methoxide in methanol and then purified by preparative TLC using pure ethyl acetate as eluent. The fastest moving fraction was re-benzoylated with benzoyl chloride in pyridine, and after work-up purified by preparative TLC using Et_2O/pentane (3:1) as eluent. The yield of **8** was 67 mg (6 %), $[\alpha]_D^{20}$ + 45.7° (*c* 1.25, $CHCl_3$). Anal. $C_{27}H_{36}O_{11}$: C, H. ^1H NMR: δ 5.08 (H-1.1), 4.73 (H-2.1), 4.67 (H-3.1), 4.52–4.42 (H-4,5,5′.1), 5.99 (H-1.2), 4.56 (H-2.2), 4.20 (H-3.2), 4.5 (H-4.2), 3.79 (H-5.2), 3.98 (H-6.2), 3.76 (H-6′.2), $J_{12.1}$ 4.2 Hz, $J_{23.1}$ 6.8, $J_{34.1}$ −0, $J_{12.2}$ 3.9, $J_{23.2}$, $J_{34.2}$ 3.6, $J_{45.2}$ 2.8, $J_{56.2}$ 6.6, $J_{56'.2}$ 2.9, $J_{66'.2}$ 11.6. ^{13}C NMR: 101.4 ppm (C-1.1), 80.8, 80.5, 79.0 (C-2,3,4.1), 64.4 (C-5.1), 115.7 [$C(CH_3)_2$.1], 26.0, 25.8 (CH_3×2.1), 106.2 (C-1.2), 83.9 (C-2.2), 74.8 (C-3.2), 79.0 (C-4.2), 71.2 (C-5.2), 68.0 (C-6.2), 112.0, 100.8 [$C(CH_3)_2$], 27.0, 26.5, 23.9 (CH_3×4.2).

6-O-(5-O-Benzoyl-2,3-O-isopropylidene-α-D-ribofuranosyl)-1,2-3,5-di-O-isopropylidene-α-D-glucofuranose (**8**). 1,2-3,5-Di-*O*-isopropylidene-α-D-glucofuranose (**9**)[20] (511 mg, 1.97 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and glycosylated with the bromide (**2**) (4.1 mmol) as described above. After work-up and separation by preparative TLC as described above, 193 mg of **7** and 110 mg of **8** were isolated together with 218 mg (42.7 %) of 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose. All products were characterized by their ^1H NMR spectra.

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References

1. Garegg, P. J. and Iversen, T. *Carbohydr. Res. 70* (1979) C13.
2. Garegg, P. J. and Ossowski, P. *Acta Chem. Scand., Ser. B37* (1983) 249.
3. Wulff, G. and Wichelhaus, J. *Chem. Ber. 112* (1979) 2847.
4. Paulsen, H., Lebuhn, R. and Lockhoff, O. *Carbohydr. Res. 103* (1982) C7.
5. Srivastava, V. K. and Schuerch, C. *Carbohydr. Res. 100* (1982) 411.
6. Iversen, T. and Bundle, D. R. *J. Org. Chem. 46* (1981) 5389.
7. Dahlhoff, W. V. and Köster, R. *Heterocycles 18* (1982) 421.
8. Bock, K. and Pedersen, C. *Acta Chem. Scand., Ser. B31* (1977) 248.
9. Schmidt, R. R. and Hermentin, P. *Angew. Chem. 89* (1977) 58.
10. Schmidt, R. R. and Hermentin, P. *Chem. Ber. 112* (1979) 2659.
11. Appel, V. R. and Barth, V. *Angew. Chem. 91* (1979) 497.
12. De Bernardo, S. and Weigele, M. *J. Org. Chem. 41* (1976) 287.
13. Sokolova, T. N., Yartseva, I. V. and Preobrazhenskaya, M. N. *Carbohydr. Res. 93* (1981) 19.
14. Hanessian, S. and Banoub, J. *Carbohydr. Res. 53* (1977) C13.
15. Wozny, Y. V., Backinowsky, L. V. and Kochetkov, N. K. *Carbohydr. Res. 73* (1979) 282.
16. Liptak, A. and Nanasi, P. *Carbohydr. Res. 86* (1980) 133.
17. Lerner, L. M. *Carbohydr. Res. 53* (1977) 177.
18. Levene, P. A., Raymond, A. L. and Dillon, R. T. *J. Biol. Chem. 95* (1932) 699.
19. Gorin, P. A. J. and Mazurek, M. *Can. J. Chem. 53* (1975) 1212.
20. Ohle, H. and Vargha, L. *Ber. Dtsch. Chem. Ges. 62* (1929) 2425.

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