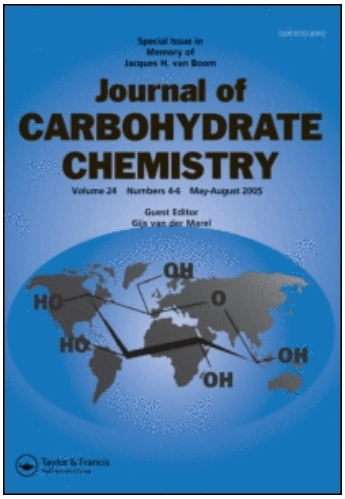

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An Efficient Synthesis of the α-D-Glucopyranosyl-(1->2)-α-L-Rhamnopyranosidic Unit

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COMMUNICATION

AN EFFICIENT SYNTHESIS OF THE α-D-GLUCOPYRANOSYL-(1->2)-α-L-RHAMNOPYRANOSIDIC UNIT

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INTRODUCTION

The α-D-glucopyranosyl-(1->2)-L-rhamnopyranosyl sequence is present in some repeating units of bacterial polysaccharides,[1] as those found in the Shigella type or in various Streptococcal strains.

Efforts towards the synthesis of such repeating units have been developed in the recent years owing to their biological interest. In particular, some groups recently described the synthesis of α-D-glucopyranosyl-(1->2)-L-rhamnopyranosidic compounds;[2,3] however the yields and the stereoselectivity of the coupling reaction were not so satisfactory.

During the synthesis of the trisaccharide component of the repeating unit of the capsular polysaccharide of Streptococcus pneumoniae type 19F[4] we studied the glucosylation of benzyl 3,4-di-O-benzyl-α-L-rhamnopyranoside[5] (1) by 6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl bromide[6,7,8] (2) and developed an efficient and stereoselective

synthesis of benzyl 2-O-(6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranoside (3) which is herein described.

RESULTS AND DISCUSSION

The preparation of the glucosyl donor 2 was effected starting from 1,6-di-O-acetyl-2,3,4-tri-O-benzyl-D-glucopyranose[9,10,11] by treatment with hydrogen bromide in acetic acid at 0 °C. The coupling between the glucosyl donor 2 and the glycosyl acceptor, benzyl 3,4-di-O-benzyl-α-L-rhamnopyranoside (1), synthesized according to Lipták et al.,[5] was strongly dependent on the coupling conditions.

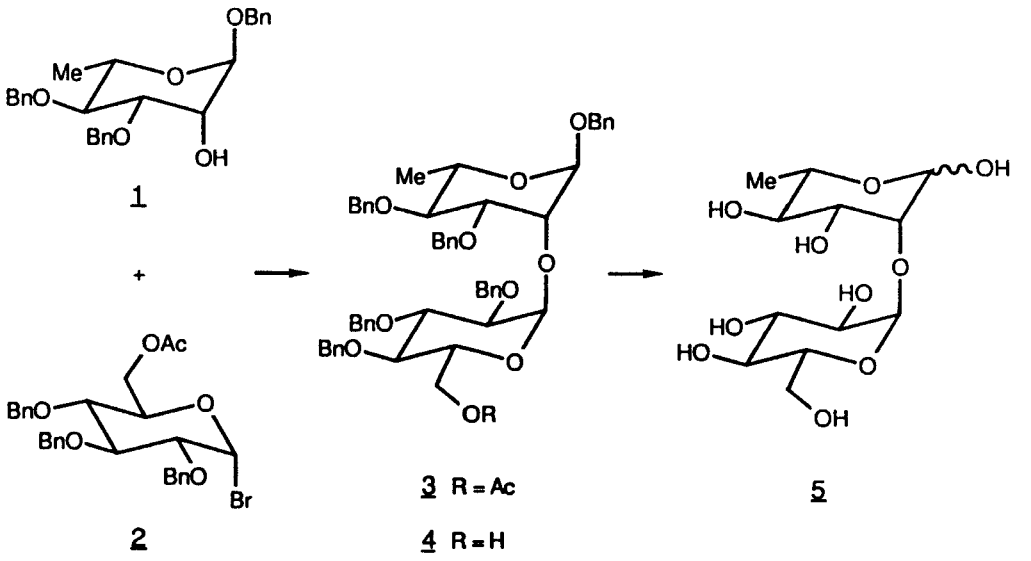
Preliminary experiments using silver trifluoromethanesulfonate, or tetraethylammonium bromide, or silver carbonate/silver perchlorate (10:1) as the glycosylation promoters yielded only very low yields of the desired disaccharide. In contrast, mercury(II) cyanide was found to be the best coupling promoter; in fact, when it was used in molar amount in methylene chloride at -40 °C/room temperature in the presence of 4Å molecular sieves, the pure α-compound 3 was obtained in 74% yield after column chromatography on silica gel.

The α-configuration of the newly formed anomeric linkage was established through a ^1H shift correlated 2D NMR (COSY) experiment performed in C_6D_6. In this way, a doublet (J=1.5Hz) located at 5.02 ppm could be unambiguously assigned to the rhamnose anomeric proton (H-1), and a 4.92 ppm doublet (J=3.5Hz) to the glucose anomeric proton (H-1').

The ^{13}C-NMR spectrum of 3, recorded in C_6D_6, showed two anomeric signals at 96.7 and 95.8 ppm which were assigned to C-1 and C-1' by heteronuclear ^1H-^{13}C decoupling experiments, respectively.

The obtained disaccharide 3 corresponds to a α-D-glucopyranosyl-(1->2)-L-rhamnopyranosyl unit in which all the hydroxyl groups are pro-

tected as benzyl ethers except the 6'-OH which is acetylated. The last protecting group was selectively removed by O-deacetylation with methanolic sodium methoxide[12] to give 4, which could be used for selective



elaboration at the only unprotected position.

Hydrogenolysis of 4 on palladium-charcoal afforded the free disaccharide 5 as a 65:35 mixture of α,ß-anomers at the reducing terminus. The ^1H chemical shifts values (two doublets, one at 5.04 δ for H-1'in the ß-anomer and one at 4.96 δ for H-1 in the α-anomer) and the coupling constant ($J_{1',2'}$ 3.5 Hz) once more indicate the α-configuration of the glcp(1->2)rhap glycosidic linkage.

EXPERIMENTAL

General procedures. The ^1H- and ^{13}C-NMR spectra were obtained at 30 °C using a Varian XL-200 or a Bruker AM-500 spectrometer. Optical rotations were obtained at 25 °C using a Perkin Elmer 241 polarimeter. Column chromatography was performed on Merck 60 silica gel (70-230 mesh).

Evaporation of solvents under reduced pressure was always effected with the bath temperature kept below 40 °C.

Benzyl 2-O-(6-O-Acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranoside (3). A solution of 6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl bromide[6,7,8] (2, 120 mg, 0.216 mmol), obtained from the corresponding 1,6-diacetate[9,10,11] by treatment in CH_2Cl_2 with hydrogen bromide in acetic acid at 0 °C for 30 min, in dry methylene chloride (5 mL) was added at -40 °C under argon to a mixture of benzyl 3,4-di-O-benzyl-α-L-rhamnopyranoside[5] (1, 94 mg, 0.216 mmol) in dry methylene chloride (5 mL) in the presence of 4Å molecular sieves, using mercury(II) cyanide (54 mg, 0.216 mmol) as the promoter. After 48 h under stirring at room temperature the reaction mixture was diluted with methylene chloride and filtered, then the solution washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product (170 mg) was chromatographed on silica gel using hexane-ethyl ether (6:4, v/v) as eluant to give 145 mg (0.159 mmol, 74%) of benzyl 2-O-(6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranoside (3) as an oil, $[\alpha]_D$ +46.2° (c 1.3 in $CHCl_3$). ^1H NMR data (200 MHz, C_6D_6) δ 1.44 (3H, d, $J_{5,6}$=6 Hz, Me-6), 1.66 (3H, s, $COCH_3$), 3.57 (1H, dd, $J_{1',2'}$=3.5 Hz, $J_{2',3'}$=9.5 Hz, H-2'), 3.70 (1H, dd, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=10 Hz, H-4'), 3.90 (1H, dd, $J_{3,4}$=9 Hz, $J_{4,5}$=9 Hz, H-4), 4.00 (1H, dq, $J_{4,5}$=9 Hz, $J_{5,6}$=6 Hz, H-5), 4.13 (1H, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=9 Hz, H-3), 4.30 (1H, dd, $J_{1,2}$=1.5 Hz, $J_{2,3}$=3.5 Hz, H-2), 4.38 (1H, dd, $J_{2',3'}$=9.5 Hz, $J_{3',4'}$=9.5 Hz, H-3'), 4.16-4.58 (3H, m, H-5', H_2-6'), 4.92 (1H, d, $J_{1',2'}$=3.5 Hz, H-1'), 5.02 (1H, d, $J_{1,2}$=1.5 Hz, H-1), 4.30-5.15 (12H, m, 6 benzylic CH_2), 7.04-7.44 (30H, m, H_{arom}). ^{13}C NMR data (200 MHz, C_6D_6) δ 95.8 (C-1'), 96.7 (C-1).

Benzyl 2-O-(2,3,4-Tri-O-benzyl-α-D-glucopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranoside (4). Compound 3 (120 mg) was dissolved in methanol (12 mL) and a 1% sodium methoxide solution (0.4 mL) was added. After 18 h under stirring the solution was neutralized with Dowex 50 (H^+). The resin was filtered off and the solvent was evaporated in vacuo to afford 116 mg of crude 4, which was chromatographed on silica gel using hexane-ethyl acetate (7:3, v/v) as eluant, to give 108 mg (94%) of oily 4, $[\alpha]_D$ +45.4° (c 1.6 in $CHCl_3$). ^1H NMR data (500 MHz, $CDCl_3$) δ 1.35 (3H, d, $J_{5,6}$=6.5 Hz, Me-6), 1.57 (1H, bt, J=6 Hz, OH), 3.43-3.53 (2H, m, H_2-6'), 3.49 (1H, dd, $J_{1',2'}$=3.5 Hz, $J_{2',3'}$=9.5 Hz, H-2'), 3.50 (1H, dd, $J_{3',4'}$= 9.5 Hz, $J_{4',5'}$=9.5 Hz, H-4'), 3.58 (1H, dd, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 3.77 (1H, dq, $J_{4,5}$=9.5 Hz, $J_{5,6}$=6.5 Hz, H-5), 3.90 (1H, dd, $J_{2,3}$=3 Hz, $J_{3,4}$=9.5 Hz, H-3), 3.98 (1H, dd, $J_{1,2}$=1.2 Hz, $J_{2,3}$= 3 Hz, H-2), 4.04 (1H, dd, $J_{2',3'}$=9.5 Hz,$J_{3',4'}$=9.5 Hz, H-3'), 4.04 (1H, ddd, $J_{4',5'}$=9.5 Hz, $J_{5',6'a}$=3.5 Hz, $J_{5',6'b}$=3.5 Hz, H-5'), 4.82 (1H, d, $J_{1',2'}$ =3.5 Hz, H-1'), 4.89 (1H, d, $J_{1,2}$=1.2 Hz, H-1), 4.40-5.00 (12H, m, 6 benzylic CH_2), 7.20- 7.40 (30H, m, H_{arom}).

Anal. Calcd for $C_{54}H_{58}O_{10}$: C, 74.80; H, 6.74. Found: C, 74.41; H, 6.83.

2-O-(α-D-Glucopyranosyl)-α,ß-L-rhamnopyranose (5). The disaccharide (4, 100 mg, 0.115 mmol) was dissolved in methanol (10 mL), treated with Pd/C (10%, 50 mg) and shaken under hydrogen atmosphere for 18 h. The catalyst was filtered off and the solvent evaporated in vacuo to yield 5 (36 mg, 96%) as an anomeric α,ß-mixture; $[\alpha]_D$ +84° (c 0.7 in CH_3OH).

^1H NMR data of the α-anomer (500 MHz, D_2O) δ (relative to HDO at 4.55) 1.23 (3H, d, $J_{5,6}$=6.5 Hz, Me-6), 3.39 (1H, dd, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=10 Hz, H-4'), 3.44 (1H, dd, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4),

3.48 (1H, dd, $J_{1',2'}$=3.5 Hz, $J_{2',3'}$=10 Hz, H-2'), 3.71 (1H, dd, $J_{2',3'}$=10 Hz, $J_{3',4'}$=9.5 Hz, H-3'), 3.72 (1H, dd, $J_{5',6'b}$=4.5 Hz, $J_{6'a,6'b}$=12.5 Hz, H-6'b), 3.76 (1H, dd, $J_{5',6'a}$=2.5 Hz, $J_{6'a,6'b}$=12.5 Hz, H-6'a), 3.83 (1H, dq, $J_{4,5}$=9.5 Hz, $J_{5,6}$=6.5 Hz, H-5), 3.85 (1H, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=9.5 Hz, H-3), 3.89 (1H, dd, $J_{1,2}$=1.5 Hz, $J_{2,3}$=3.5 Hz, H-2), 3.96 (1H, ddd, $J_{4',5'}$=10 Hz, $J_{5',6'a}$=2.5 Hz, $J_{5',6'b}$=4.5 Hz, H-5'), 4.96 (1H, d, $J_{1',2'}$=3.5 Hz, H-1'), 5.18 (1H, d, $J_{1,2}$=1.5 Hz, H-1).

^{1}H NMR data of the ß-anomer (500 MHz, D_2O) δ (relative to HDO at 4.55) 1.25 (3H, d, $J_{5,6}$=6.5 Hz, Me-6), 3.30 (1H, m, H-4), 3.37 (1H, m, H-5), 3.40 (1H, dd, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=10 Hz, H-4'), 3.53 (1H, dd, $J_{1',2'}$=3.5 Hz, $J_{2',3'}$=10 Hz, H-2'), 3.61 (1H, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$= 9.5 Hz, H-3), 3.72 (1H, dd, $J_{2',3'}$=10 Hz, $J_{3',4'}$=9.5 Hz, H-3'), 3.95 (1H, m, H-5'), 3.96 (1H, bd, $J_{2,3}$=3.5 Hz, H-2), 4.88 (1H, bs, H-1), 5.04 (1H, d, $J_{1',2'}$= 3.5 Hz, H-1').

Anal. Calcd for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 43.92; H, 6.72.

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