Synthesis of 3,4-disaccharides from pyranosides and furanosides monomers, a novel class of potential bioactive disaccharides

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Dedicated to Professor Attar-ur-Rahman on the occasion of his 65th birthday

Abstract
A new class of synthetically and pharmacologically important disaccharides containing epoxide moieties were synthesized from pyranoside and furanoside monomers in good to excellent yields. The scope and limitations for the formation of the linkage were evaluated.

Keywords: Carbohydrates, carbohydrate mimics, bioactive, disaccharides

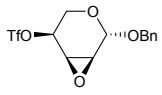
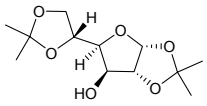
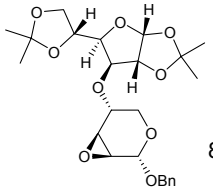
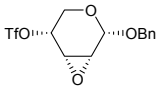
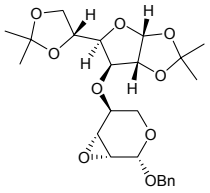
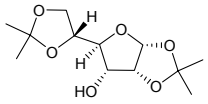
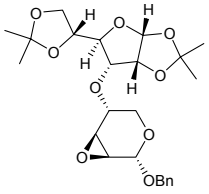
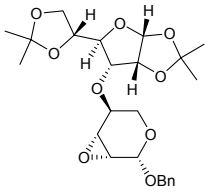
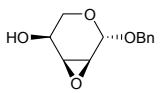
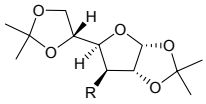
Introduction

The defined topology and stereochemistry of carbohydrate frameworks permit an appealing array to synthesize natural products or natural-like products with interesting biological and pharmaceutical properties.[1,2] Suitable intermediates and building blocks should bear appropriate functional groups for further transformations and in this respect, the oxirane is an ideal functional residue for subsequent regio- and stereoselective manipulations.[3] Amongst others, conversions of the oxirane to trithiocarbonates, thiazolidenes, thiazolines, deoxy sugars, deoxy azido sugars and glycopeptides have been carried out successfully.[4-9] Apart from the synthetic importance epoxide modified carbohydrates have been shown to exhibit several biological activities. [10-16] This has been demonstrated on 2,3-epoxypropyl-β-D-glucosides and its oligomers which are inhibitors of hen's eggs lysozyme.[10,11] Its epimer, the 2,3-epoxypropyl-α-D-glucopyranoside irreversibly inhibits yeast hexokinase.[12] Similarly, derivatives of cellobiose and cellotriose show inhibiting activity against cellulase.[13] Furthermore, 3-*O*-alkyl 1,2-*O*-isopropylidene-α-D-glucofuranoside can reduce *intra*-membrane charge movement, required for signal transduction between the sarcolemma and sarcoplastic reticulum, thereby inhibiting the

excitation-calcium release mechanism (muscle relaxant activity).[14] Oxirane ring-containing carbohydrates and a variety of sugar derivatives have been examined as possible inhibitors for a new thermostable neutral proteinase, isolated from *Saccharomonospora canesencs.*[15] Among all tested compounds, benzyl 2,3-anhydro-β-L-ribopyranoside and benzyl 2,3-anhydro-α-D-ribopyranoside (**11**) exhibited the highest inhibiting activity.

Results and Discussion

Table 1. Synthesis of 3,4-disaccharides

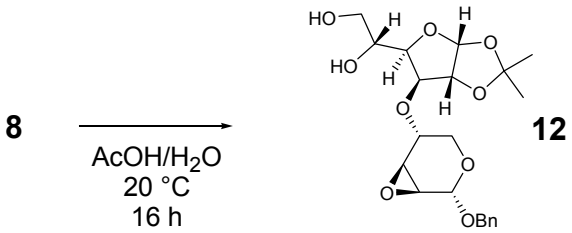
Pyranosides	Furanosides	Disaccharides
 **1**	 **4**	 **8** 82 %
 **2**	**4**	 **9** 71 %
1	 **5**	 **10** 54 %
2	**5**	 **11** 49 %
 **3**	 **6** R = OTs **7** R = OTf	no disaccharide

Reaction conditions: Na_2CO_3, CH_3CN, 0 °C → 20 °C, 7h.

This paper describes the successful coupling of pyranosides (β-L-ribopyranoside **1** and α-D-ribopyranoside **2**) with furanosides (α-D-furanoside **4** and α-D-allofuranoside **5**). The epoxy sugars were prepared according to literature procedures, starting from L-arabinose and D-arabinose, respectively.[16,17] The furanosides **4** and **5** were prepared as according to literature procedures.[18]

As reported earlier by our group, a variety of sugar derivatives exhibit thermostable neutral proteinase inhibition.[3] Considering this, we have decided to couple the glucopyranosides **4**, **5** and **6** with the epoxytriflates **1** and **2**, respectively, to obtain new disaccharides as shown in Table 1. The disaccharides **8 - 11** were synthesized by nucleophilic attack of **4** and **5**, respectively, using mild coupling conditions (Na_2CO_3/CH_3CN) at C-4 of the epoxytriflates **1** and **2**. The yields of these coupling reactions were in the range of 50 - 80%. Employing pyranoside **3** in a reverse reaction setup, no disaccharide formation could be observed via nucleophilic substitution of the tosyl residue in **6** [19] nor triflate residue in **7**.[20]. It can be assumed that steric hindrance at C-3 of the furanoside **6** and **7** is responsible for the unsuccessful reaction.

We have also carried out partial deprotection of **8** leading to glycerol derivative **12**. These deprotected carbohydrate building blocks may find further applications as bidentate ligands (Scheme 1).



Scheme 1. Synthesis of partially deprotected derivatives.

After deprotection, which can be done under classical conditions, the dissaccharides will be further evaluated in biological tests.

Experimental Section

General Procedures. All air and moisture-sensitive reactions were performed under argon using dried glassware. Solvents were dried over standard drying agents. TLC (silica gel 60), precoated aluminium plates (F254) and silica gel 60 (40-630 mesh ASTM) were purchased from Merck, Germany. Mass spectra were measured on JMSHX-110 (Jeol), NMR spectra were obtained using Bruker AMX-250 MHz.

General Method for the synthesis of 3,4-disaccharides

To a suspension of 1.2 mmol of Na_2CO_3 (127 mg) in 5 mL dry CH_3CN was added 1.2 mmol of **4** (312 mg) at 0°C. The mixture was stirred for 30 minutes and then 1.0 mmol (354 mg) of epoxy triflate dissolved in 2 ml of CH_3CN, was added dropwise into the reaction mixture at 0°C which was stirred at this temperature for 30 minutes and then at room temperature for 6.5 h. After completion of the reaction, as indicated by TLC, the reaction mixture was neutralized with a saturated solution of NH_4Cl (50 mL) and extracted with ethyl acetate (2 X 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated to a syrup, and finally purified by column.

Benzyl 2,3-anhydro-4-*O*-(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranos-3-yl)-α-D-lyxopyranoside (8). Purified by column chromatography in 82% yield using ethyl acetate:dichloromethane (1:9, v/v). Colourless oil; ^1H-NMR (250 MHz, $CDCl_3$): δ = 7.35- 7.20 (5H-aromatic), 5.82 (d, *J* = 3.6 Hz, 1H), 4.92 (s, 1H), 4.73 (d, *J* = 11.6 Hz, 1H, -CH_2Ph), 4.51 (1H, d = *J* 3.3 Hz, 1H), 4.48 (d, *J* = 11.6 Hz 1H, -CH_2Ph), 4.16-3.21 (m, 10H), 3.25 (d, *J* = 3.6 Hz, 1H), 3.07 (d, *J* = 3.7 Hz, 1H). 13C NMR (62.8 MHz, $CDCl_3$) δ: 105.3 (C-1′), 93.8 (C-1), 83.9, 82.2, 81.3, 72.2 (C-2′ to C-5′), 69.9 (C-4), 69.8 (C-CH_2Ph), 67.7 (C-6), δ 57.4 (C-5), 54.01 (C-3), 49.9 (C-2), 26.8, 26.8, 26.2, 25.3 (4xCH_3). FAB-MS: e/z 465.3 (M^+), $C_{24}H_{32}O_9$, $[\alpha]^D$ = +36.3° (c = 1, CH_2Cl_2). Calculated C 62.06, H 5.94%, Found C 62.49, H 6.02%

Benzyl 2,3-anhydro-4-*O*-(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranos-3-yl)-β-L -lyxopyranoside (9). Purified by column chromatography in 71% yield using ethyl acetate:dichloromethane (5:95, v/v). Colourless oil; ^1H-NMR (250 MHz, $CDCl_3$) δ: 7.40-7.26 (5H-aromatic), 5.90 (d, *J* 3.6 Hz, 1H, H-1′), 5.06 (d, *J* 3.1 Hz, 1H, H-1), 4.80 (d, *J* 12.2 Hz, 1H, CH_2Ph.), 4.62 (d, *J* 12.2 Hz, 1H, CH_2Ph), 4.65 (d, *J* 3.7 Hz, 1H), 4.62 - 4.34 (m, 1H), 4.15 - 3.86 (m, 6H), 3.35 (br. d, *J* 12.2 Hz, 1H), 3.40 (m, 1H), 1.49 (s, CH_3), 1.41 (s, CH_3), 1.33 (s, CH_3), 1.31 (s, CH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 127.8-128.4 (5xC-Aromatic), 105.5 (C-1′), 92.8 (C-1), 84.0,82.2, 81.3, 72.5 (C-2′ to C-5′), 72.4 (C-4), 69.3 (C-6′), 67.8 (CH_2Ph), 59.1 (C-5), 51.6 (C-3), 50.1 (C-2), 26.9, 26.8, 26.3, 25.4 (4xCH_3). FAB-MS: e/z 465.3 (M^+) $C_{24}H_{32}O_9$. Calculated C 62.06, H 5.94%, Found C 62.09, H 6.08%

Benzyl 2,3-anhydro-4-*O*-(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-allofuranos-3-yl)-α-D-lyxopyranoside (10). Purified by column chromatography in 54% yield using ethylacetate:dichloromethane (1:9, v/v). ^1H-NMR (250 MHz, $CDCl_3$) δ: 7.35 - 7 .20 (5H-aromatic), 5.73 (d, *J* 3.6 Hz, 1H, H-1′), 5.22 (br.-s, 1H), 4.92 (br.-s, 1H), 4.77 (br. d, *J* 11.9 Hz, 1H), 4.56-4.47 (m, 2H), 4.33 - 4.26 (m, 1H), 4.05-3.92 (m, 4H), 3.76 - 3.70 (d, *J* 6.1 and 9.7 Hz 1H), 3.62-3.50 (m, 2H), 3.37 (d, *J* 3.6 Hz 1H), 3.05 (d, *J* 3.3 Hz, 1H), 1.47 (s, CH_3), 1.40 (s, CH_3), 1.29 (s, CH_3), 1.28 (s, CH_3); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: 104.1 (C-1′), 93.9 (C-1), 78.5, 78.1, 78.0, 74.7 (C-2′ to C- 5′), 69.2 (C-4), 69.8 (C-CH2Ph), 65.3 (C-6′), 57.9 (C-5), 53.8 (C-3), 49.9 (C-2), 26.8, 26.7, 26.3, 24.7 (4xCH_3). , FAB-MS: e/z 465.3 (M^+) $C_{24}H_{32}O_9$, $[\alpha]^D$ = +91.2° (c = 1, CH_2Cl_2). Calculated C 62.06, H 5.94%, Found C 62.19, H 6.90%

Benzyl 2,3-anhydro-4-*O*-(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-allofuranos-3-yl)- β-L-lyxopyranoside (11). Purified by column chromatography in 49% yield using ethyl acetate:dichloromethane (1:9, v/v). Colourless oil; ^1H-NMR (250 MHz, $CDCl_3$) δ: 7.32-7.19

(5H-aromatic), 5.77 (d, *J* 3.6 Hz, 1H, H-1´), 4.99 (d, *J* 3.1, 1H, H-1), 4.77 (d, *J* 12.2 Hz, 1H, CH_2Ph), 4.58 (d, *J* 12.2 Hz, 1H, CH_2Ph), 4.01-3.96 (m, 3H), 3.85 (br. s, 2H), 3.52 (s, 3H), 3.29 (m, 1H), 1.49 (s, CH_3), 1.39 (s, CH_3), 1.31 (s, CH_3), 1.29 (s, CH_3). FAB-MS: e/z 465.3 (M^+), $C_{24}H_{32}O_9$, $[\alpha]^D$ = +86.1° (c = 1, CH_2Cl_2). Calculated C 62.06, H 5.94%, Found C 62.40, H 6.00%

Benzyl 2,3-anhydro-4-*O*-(1,2-*O*-isopropylidene-3-deoxy-α-D-glucofuranos-3-yl)-α-D-lyxopyranoside (12). Prepared by stirring overnight 0.1 mmol of **8** (31.2 mg) with 20% acetic acid (2 mL) at room temperature. Purification by column chromatography afforded **12** in 92% yield using ethyl acetate:dichloromethane (2:8, v/v). Colourless oil; ^{1}*H*-NMR (250 MHz), $CDCl_3$) 7.37-7.26 (5H-aromatic), 5.93 (d, *J*= 3.6 Hz, 1H, H-1´), 4.97 (d, *J* = 3.1 Hz, 1H, H-1), 4.85 (d, *J* = 12.2 Hz, 1H, CH_2Ph),4.58 (d, *J* = 12.2 Hz, 1H, CH_2Ph), 4.18-4.12 (m, 3H), 3.95-3.80 (m, 2H), 3.27- 3.57 (m, 3H), 3.32 (s, 1H), 3.30 (s, 1H), 3.16 (brs, 1H), 1.49 (s, CH_3), 1.25 (s, CH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$) 128.5-128.1 (5 x C, aromatic), 105.1 (C-1´), 94.4 (C-1), 83.0, 81.2, 80.0, 70.4 (C-2´) to C-5´), 69.2 (C-4), 68.8 (C-CH_2 Ph), 64.5 (C-6´), 57.2 (C-5), 52.8 (C-3), 26.7, 26.3 (2x CH_3).

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