Synthesis of Octopus Type Trimethylene Glycol β-D-glucopyranosides[*1]

Yong Sik Kim[*2†] and John F. Kadla[*3]

ABSTRACT

The octopus type oligo-hydroxypropylene glycol β-D-glucopyranosides were successfully synthesized in this studies: the sterospecific compound of allyl 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosides (1) was deacetylated with NaOMe in MeOH lead to allyl-β-D-glucopyranoside (2) which was perallylated and followed by hydroboration and subsequent oxidation afforded (3-hydroxy-propyl) 2, 3, 4, 6-tetraO(3-hydroxy-propyl)-β-D-glucopyranoside (4). As a result, not only allylpropylene glycol β-D-glucopyranosides (5, 7, and 9) but also hydroxypropylene glycol β-D-glucopyranosides (6, 8, and 10) were synthesized by repeated sequential perallylation followed by hydroboration/oxidation.

Keywords : hydroboration/oxidation, perallylation, oligo-hydroxypropylene glycol β-D-glucopyranosides

1. INTRODUCTION

Carbohydrates are naturally occurring abundant compounds that have been widely studied for a plethora of applications (Hanessian, 1983; Scott, 1994; Middleton *et al.,* 1993). Of particular interest has been their use as polyfunctional molecules for the design and/or synthesis of carbohydrate-centered multivalent glycoclusters and glycodendrimers (Lindhorst *et al.,* 1998; Lindhorst *et al.,* 2001; Lindhorst *et al.,* 2006). Most of them are based on a multi-step synthesis consisting of oligo-glycosylation in order to achieve a uniform O-hydroxy-spacer, such as ethylene or propylene glycol not only in the 2, 3, 4, 6-tetra hydroxy groups but also at the *a*-anomeric position, turning them into carbohydrate-centered cluster glycosides (Lindhorst *et al.,* 1998; Lindhorst *et al.,* 2001; Lindhorst *et al.,* 2006).

Thus, it became our goal to attempt the synthesis of the exhaustive glycosylation of octopus type β-D-glucopyranosides. This could provide us with a great potential opportunity of a novel class of high-molecular weight monosaccharide mimetics, which could possibly be adapted for the generation of various spacers with different

functionalities at the β-anomeric configuration of monosaccharides in future syntheses. In this article we present the effect of reagents and reaction conditions on the corresponding novel octopus type β-D-glucopyranosides along with the synthetic reaction scheme and characterization.

2. MATERIALS and METHODS

2.1. General

All chemicals were purchased from Aldrich Chemicals and used as received. ^{1}H and ^{13}C NMR were measured using a Bruker Avance-300 MHz spectrometer. Chemical shifts were referenced to tetramethyl silane (TMS; 0.0 ppm). Elemental analysis was measured with a Carlo Erba Elemental Analyzer EA 1108 in the Department of Chemistry at the University of British Columbia.

2.2. Synthesis and Identification of Various β-D-glucopyranosides

2.2.1. Allyl-2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranoside (1)

Acetobromo-a-D-glucose (3.0 g, 7.73 mmol) was dissolved in 5 ㎖ of allyl alcohol to which Ag_2CO_3 (8.0 g, 29.01 mmol) was added and the reaction was left stirring overnight. The reaction mixture was diluted with 200 ㎖ of CH_2Cl_2 and filtered to remove Ag_2CO_3. The filtrate was washed with saturated aqueous NaCl followed by 6 times with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give a pure white solid (2.71 g, 92.3%). The pure compound can be recrystallized from ethanol. ^{1}H NMR (300 MHz, CDCl₃): δ 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 3.68-3.73 (1H, m), 4.09 (1H, dd, J = 6.3, 13.2 Hz), 4.14 (1H, dd, J = 2.7, 12.0 Hz), 4.25 (1H, dd J = 4.8, 12.3 Hz), 4.33 (1H, dd, J = 4.8, 12.9 Hz), 4.56 (1H,

d, J = 8 Hz), 5.01-5.14 (2H, m), 5.20-5.32 (3H, m), 5.80-5.93 (1H, m). ^{13}C NMR (75 MHz, CDCl₃): δ 20.59, 20.62, 20.67, 20.73, 61.96, 68.45, 70.02, 71.30, 71.80, 72.87, 99.57, 117.66, 113.30, 169.32, 169.40, 170.30, 170.69. Elemental analysis ($C_{17}H_{24}O_{10}$) : Calc: C, 52.57; H, 6.23; O, 41.20. measured: C, 52.42; H, 6.20; O, 41.38.

2.2.2 Allyl-β-D-glucopyranoside (2)

Compound 1 (2.5 g, 6.44 mmol) was dissolved in 10 ㎖ of MeOH and 2 ㎖ NaOMe (25% in MeOH) was added and the reaction was left stirring at room temperature overnight. The reaction mixture was neutralized with Amberlite IR 50, diluted with 100 ㎖ of MeOH, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100~200; CHCl₃-MeOH, 3:1) to give a pure white solid (1.27 g, 89.9%). 1H NMR (300 MHz, D2O): δ 3.18-3.44 (4H, m), 3.61 (1H, dd, J = 5.7, 12.3 Hz), 3.82 (1H, dd, J = 2.1, 12.3 Hz), 4.12 (1H, dd, J = 6.3, 12.3 Hz), 4.29 (1H, dd, J = 6.3, 12.3 Hz), 4.42 (1H, d, J = 7.8 Hz), 5.19 (1H, d, J = 10.5 Hz), 5.28 (1H, d, J = 17.7 Hz), 5.84-5.98 (1H, m); ^{13}C NMR (75 MHz, D₂O): δ 60.8, 69.7, 70.6, 73.1, 75.8, 75.9, 101.2, 118.7, 133.3. Elemental analysis ($C_9H_{16}O_6$) Calc: C, 49.09; H, 7.32; O, 43.59. measured: C, 48.16; H, 7.32; O, 44.52.

2.2.3. Allyl-2,3,4,6-tetra-O-allyl-β-D-glucopyranoside (3)

Tetrabutylammonium bromide (TBABr, 1.33 g) was added to the stirring solution of 2 (1.0 g, 4.54 mmol) in 80 ㎖ of aqueous NaOH (33 wt%) at 30°C. Allyl chloride (3 ㎖, 36.7 mmol) was then added dropwise over 30 min and the reaction was left mixing overnight. Toluene (150 ㎖) was then added and the reaction was stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl followed by 3

times with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100~200; 100% toluene → 100% ethyl acetate) to give a pure yellowish oil (1.1 g, 63.7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22-3.27 (1H, m), 3.35-3.43 (3H, m), 3.60 (1H, dd, J = 3.9, 11.4 Hz), 3.70 (1H, d, J = 10.5 Hz), 4.04-4.42 (11H, m), 5.15-5.35 (10H, m), 5.86-6.04 (5H, m); ^{13}C NMR (75 MHz, DMSO-d_6): δ 69.0, 70.1, 72.5, 73.7, 73.8, 74.4, 74.8, 77.6, 81.7, 84.2, 102.5, 116.6, 116.8, 116.9(3x), 134.1, 134.8, 134.9, 135.1, 135.3. Elemental analysis ($C_{21}H_{32}O_6$) Calc: C, 66.29; H, 8.48; O, 25.23. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.4. (3-Hydroxy-propyl)-2, 3, 4, 6-tetra-O-(3-hydroxy-propyl)-β-D-glucopyranoside (4)

9-BBN (20 ㎖, 10 mmol) was then added to stirring solution of 3 (725 mg, 1.91 mmol) in 20 ㎖ dry THF under argon atmosphere and refluxed for 6 h. Excess 9-BBN was hydrolyzed at 0°C with 20 ㎖ of H_2O, followed by aqueous NaOH (3M, 20 ㎖), and subsequently H_2O_2 (30%, 20 ㎖) and left stirring at room temperature overnight. The aqueous layer was saturated with K_2CO_3 and the organic layer was separated. The aqueous layer was further extracted with THF (2 × 50 ㎖) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100~200; 100% ethyl acetate → $CHCl_3$-MeOH, 3:1) to give a pure colorless oil (925 mg, 75.2%). ^{1}H NMR (300 MHz, D_2O): δ 1.74-1.86 (10H, m), 3.04 (1H, t, J = 8.6 Hz), 3.22-3.38 (2H, m), 3.42-3.46 (1H, t), 3.51-3.95 (22H, m), 4.37 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 31.2, 31.4, 31.9 (2x), 32.1, 58.5 (2x), 58.7, 58.7 (2x), 67.4,

68.2, 68.8, 70.3, 70.4, 70.9, 73.6, 77.9, 81.4, 83.7, 102.3. Elemental analysis ($C_{21}H_{42}O_{11}$) Calc: C, 53.60; H, 9.00; O, 37.40. measured: C, 52.45; H, 9.07; O, 38.48.

2.2.5. (3-Allyloxy-propyl)-2, 3, 4, 6-tetra-O-(3-allyloxy-propyl)-β-D-glucopyranoside (5)

NaH (60% suspension in paraffin oil, 680 mg, 17.0 mmol) was added to a reaction mixture of 4 (800 mg, 1.70 mmol) in 15 ㎖ of dry DMF and stirred for 30 min. Allyl chloride (1.5 ㎖, 18.3 mmol) was added dropwise to reaction mixture at room temperature and the reaction was left overnight. Remaining NaH was destroyed with the addition of 10 ㎖ of H_2O at 0°C and then toluene (100 ㎖) was added and the reaction stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl, 3 times with water, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100~200; 100% toluene → 100% ethyl acetate) to give a pure yellowish oil (893 mg, 78.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80-1.95 (10H, m), 3.02 (1H, t, J = 8.4 Hz), 3.16-3.29 (3H, m), 3.48-3.98 (32H, m), 4.19 (1H, d, J = 7.8 Hz), 5.16 (5H, dd, J = 1.4, 10.4 Hz), 5.24 (5H, dd, J = 1.4, 17.3 Hz), 5.86-5.98 (5H, m); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.74, 30.12, 30.62, 30.71, 30.81, 66.40, 66.89, 66.99, 67.05, 67.23 (2x), 68.09, 69.37, 69.51, 69.63, 70.11, 71.31(5x), 74.25, 78.12, 82.40, 84.37, 102.83, 116.48 (2x), 116.53, 116.57 (2x), 135.81 (2x), 135.85 (3x). Elemental analysis ($C_{36}H_{62}O_{11}$) Calc: C, 64.45; H, 9.32; O, 26.23. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.6 (7-Hydroxy-4-oxa-heptyl)-2, 3, 4, 6-tetra-O-(7-hydroxy-4-oxa-heptyl)-β-D-glucopyranoside (6)

9-BBN (6 ㎖, 3 mmol) was added to a stirring solution of 5 (700 mg, 1.04 mmol) in 15 ㎖ dry THF and refluxed under Ar for 1 h. Excess 9-BBN was hydrolyzed at 0°C with 20 ㎖ of H_2O followed by the addition of aqueous NaOH (3M, 6 ㎖) and H_2O_2 (30%, 6 ㎖). The reaction mixture was left stirring at room temperature overnight. The aqueous layer was saturated with K_2CO_3 and the organic layer was separated. The aqueous layer was further extracted with THF (2 × 50 ㎖) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100～200; 100% ethyl acetate → $CHCl_3$-MeOH, 3:1) to give a pure colorless oil (671 mg, 86.4%). ^{1}H NMR (300 MHz, D_2O): δ 1.71-1.90 (20H, m), 3.02 (1H, t, J = 8.5 Hz), 3.21-3.36 (2H, m), 3.40-3.44 (1H, t), 3.51-3.93 (42H, m), 4.34 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 28.73, 29.00, 29.45, 29.49, 29.66, 31.29, 31.32, 58.69, 67.30, 67.34, 67.37, 67.49, 67.55, 68.15, 68.81, 70.15, 70.25, 70.81, 73.64, 77.83, 81.53, 83.77, 102.37. Elemental analysis ($C_{36}H_{72}O_{16}$) Calc: C, 56.82; H, 9.54; O, 33.64. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.7. (7-Allyoxy-4-oxa-heptyl)-2, 3, 4, 6-tetra-O-(7-allyloxy-4-oxa-heptyl-β-D-glucopyranoside (7)

NaH (60% suspension in paraffin oil, 300 mg, 7.5 mmol) was added to a solution of 6 (550 mg, 0.74 mmol) in 10 ㎖ of dry DMF was and stirred for 30 min. Allyl chloride (0.6 ㎖, 7.3 mmol) was added dropwise to the reaction mixture and left overnight at room temperature. The reaction was cooled to 0°C and the remaining NaH was destroyed with the addition of 10 ㎖ of H_2O.

Toluene (100 ㎖) was then added and the reaction was stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl and 3 times with water, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100～200; 100% toluene → 100 % ethyl acetate) to give a pure yellowish oil (488 mg, 69.7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80-1.92 (20H, m), 3.01 (1H, t, J = 7.8 Hz), 3.17-3.28 (3H, m), 3.48-3.98 (52H, m), 4.18 (1H, d, J = 7.8 Hz), 5.16 (5H, dd, J = 1.4, 10.4 Hz), 5.25(5H, dd, J = 1.4, 17.3 Hz), 5.86-5.99 (5H, m); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.14, 30.70, 30.73, 30.87, 66.39, 67.08, 67.48, 67.55, 67.67, 67.69, 68.10, 69.40, 69.54, 69.64, 70.15, 71.29, 74.32, 78.12, 82.40, 84.41, 102.88, 116.50, 135.85 ppm. Elemental analysis ($C_{51}H_{92}O_{16}$) Calc: C, 63.72; H, 9.65; O, 26.63. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.8. (11-Hydroxy-4, 8-dioxa-undecyl)-2, 3, 4, 6-tetra-O-(11-hydroxy-4,8-dioxa-undecyl)-β-D-glucopyranoside (8)

9-BBN (6 ㎖, 3 mmol) was added to a stirring solution of 7 (400 mg, 0.42 mmol) in 15 ㎖ of dry THF under argon atmosphere and refluxed for 1 h. Excess 9-BBN was destroyed at 0°C with 20 ㎖ of H_2O followed by the addition of aqueous NaOH (3M, 6 ㎖) and H_2O_2 (30%, 6 ㎖) and the reaction mixture was stirred at room temperature overnight. The aqueous layer was saturated with K_2CO_3 and the organic layer was separated. The aqueous layer was further extracted with THF (2 × 50 ㎖) and organic phases were combined, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100～200; 100% ethyl acetate → $CHCl_3$-MeOH, 3:1) to give a pure colorless oil (374

mg, 84.2%). ^{1}H NMR (300 MHz, D_2O): δ 1.71-1.90 (30H, m), 3.02 (1H, t, J = 8.5 Hz), 3.21-3.36 (2H, m), 3.40-3.44 (1H, t), 3.50-3.94 (62H, m), 4.34 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 28.76, 28.81, 29.02, 29.48, 29.54, 29.72, 31.30, 58.69, 67.30, 67.50, 68.15, 68.83, 70.12, 70.22, 70.78, 73.67, 77.86, 81.59, 83.83, 102.41. Elemental analysis ($C_{51}H_{102}O_{21}$) Calc: C, 58.26; H, 9.78; O, 31.96. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.9. (11-Allyloxy-4, 8-dioxa-undecyl)-2, 3, 4, 6-tetra-O-(11-allyloxy-4, 8-dioxa-undecyl)-β-D-glucopyranoside (9)

NaH (60% suspension in paraffin oil, 100 mg, 2.5 mmol) was added to a solution of 8 (250 mg, 0.24 mmol) in 10 ㎖ of dry DMF and stirred for 30 min. Allyl chloride (0.3 ㎖, 3.7 mmol) was added dropwise to reaction mixture and left stirring overnight at room temperature. The reaction was cooled to 0°C and the remaining NaH was destroyed with 10 ㎖ of H_2O. Toluene (100 ㎖) was then added and the reaction stirred for 30 min. The organic layer was separated, washed with saturated aqueous NaCl and 3 times with water, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100～200; 100% toluene → 100% ethyl acetate) to give a pure yellowish oil (188 mg, 60.6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79-1.92 (30H, m), 3.01 (1H, t, J = 7.8 Hz), 3.17-3.28 (3H, m), 3.46-4.00 (76H, m), 4.18 (1H, d, J = 7.8 Hz), 5.16 (5H, dd, J = 1.4, 10.4 Hz), 5.26 (5H, dd, J = 1.4, 17.3 Hz), 5.87-5.99 (5H, m); 13C NMR (75 MHz, DMSO-d_6): δ 30.14, 30.70, 30.73, 30.87, 66.39, 67.08, 67.48, 67.55, 67.67, 67.69, 68.10, 69.40, 69.54, 69.64, 70.15, 71.29, 74.32, 78.12, 82.40, 84.41, 102.88, 116.50, 135.85. Elemental analysis ($C_{66}H_{122}O_{21}$) Calc: C, 66.33; H, 9.82; O, 26.83. measured: C, 64.63; H, 8.03; O, 27.34.

2.2.10. (15-Hydroxy-4, 8, 12-trioxa-pentadecyl) -2, 3, 4, 6-tetra-O-(15-hydroxy-4, 8, 12-trioxa-pentadecyl)-β-D-gluco-pyranoside (10)

Compound 9 (100 mg, 0.08 mmol) was reacted in an Ar atmosphere with 9-BBN (6 ㎖, 3 mmol) in 10 ㎖ of dry THF and refluxed for 1 h. Excess 9-BBN was then destroyed at 0°C with 20 ㎖ of H_2O, followed by the addition aqueous NaOH (3 M, 6 ㎖) and H_2O_2 (30 %, 6 ㎖). The reaction mixture was stirred overnight at room temperature. The aqueous layer was saturated with K_2CO_3 and the organic layer was separated. The aqueous layer was further extracted with THF (2 × 25 ㎖) andorganic phases combined, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, Merck, mesh 100～200; 100% ethyl acetate → $CHCl_3$-MeOH, 3:1) to give a pure colorless oil (87 mg, 81.2%). ^{1}H NMR (300 MHz, D_2O): δ 1.71-1.88 (40H, m), 3.02 (1H, t, J = 7.9 Hz), 3.21-3.35 (2H, m), 3.40-3.94 (73H, m), 4.33 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, D_2O): δ 28.76, 28.81, 29.02, 29.48, 29.54, 29.72, 31.30, 58.69. Elemental analysis ($C_{66}H_{132}O_{26}$) Calc: C, 59.08; H, 9.92; O, 31.00. measured: C, 64.63; H, 8.03; O, 27.34.

3. RESULTS and DISCUSSION

3.1 Synthesis and Characterization of β-D-glucopyranoside

Scheme 1 outlines the synthetic protocol to the hydroxypropylene glycol β-D-glucopyranosides. The first step is the sterospecific synthesis of allyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (1) in 92% yield using the Koenigs-Knorr reaction (Koto et al., 2007; Liptak et al., 1989). Deacetylation of 1 with NaOMe in MeOH lead to 2 in 90% yield which was perallylated
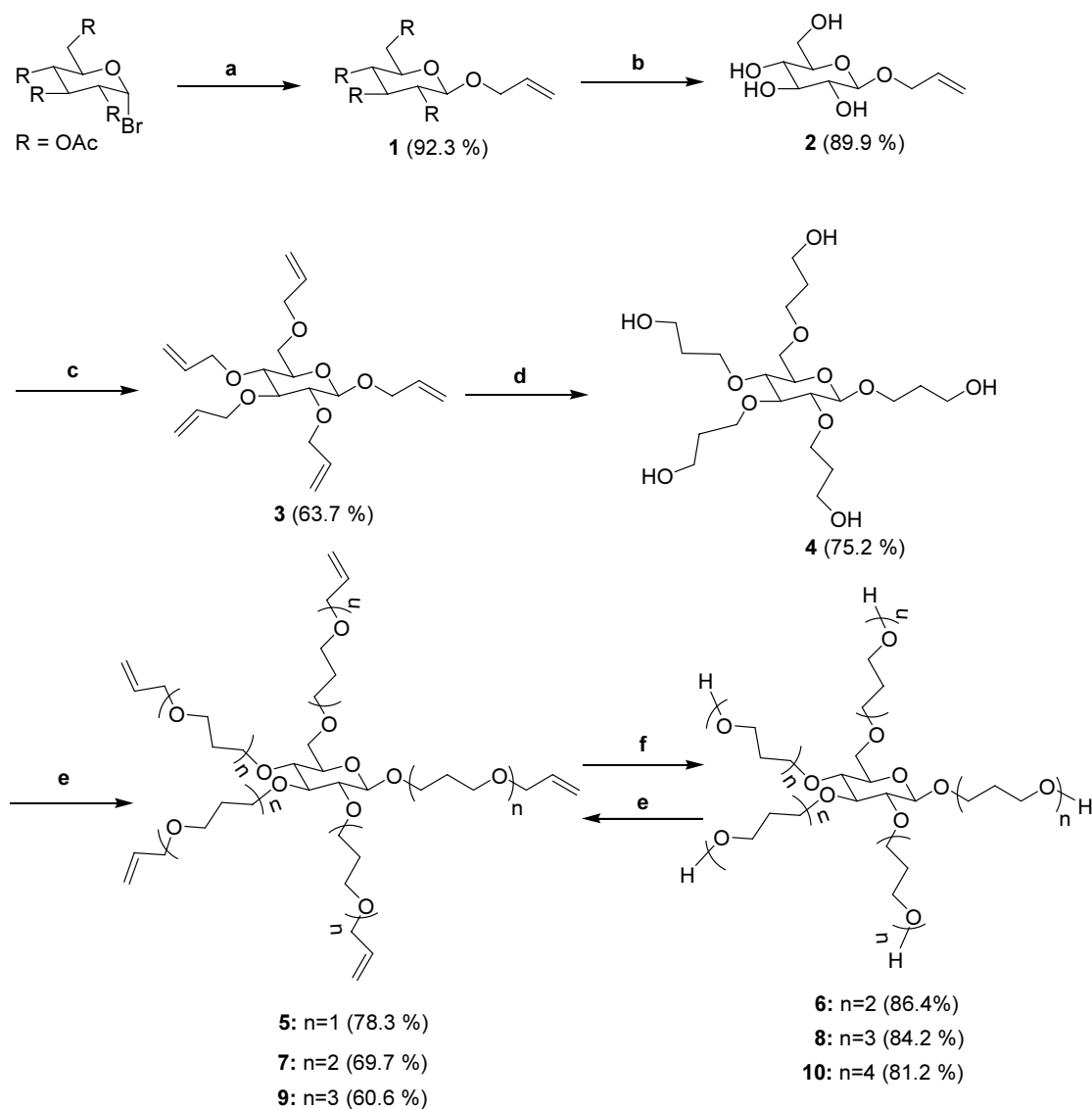
Scheme 1. Regents and conditions: (a) allyl alcohol, Ag₂CO₃, rt, 24 h; (b) NaOMe, MeOH, rt, overnight; (c) allyl chloride, TBABr, aq 33% NaOH, 30°C, 18 h; (d) 9 BBN, THF, reflux, 6 h, 3M NaOH, 30% H₂O₂, rt, overnight;. (e) allyl chloride, NaH, DMF, rt, overnight; (f) 9-BBN, THF, reflux, 1 h, 3M NaOH, 30% H₂O₂, rt, overnight.

using a phase transfer catalyst (TBABr), aqueous NaOH and allyl chloride. Hydroboration and subsequent oxidation afforded 4 in 75% yield. For further extension of the hydroxyl-propyl groups was accomplished by repeated

sequential perallylation followed by hydrobo-ration/oxidation. With each repeated cycle there was a slight decrease in recovered yield, but overall the process was very facile.
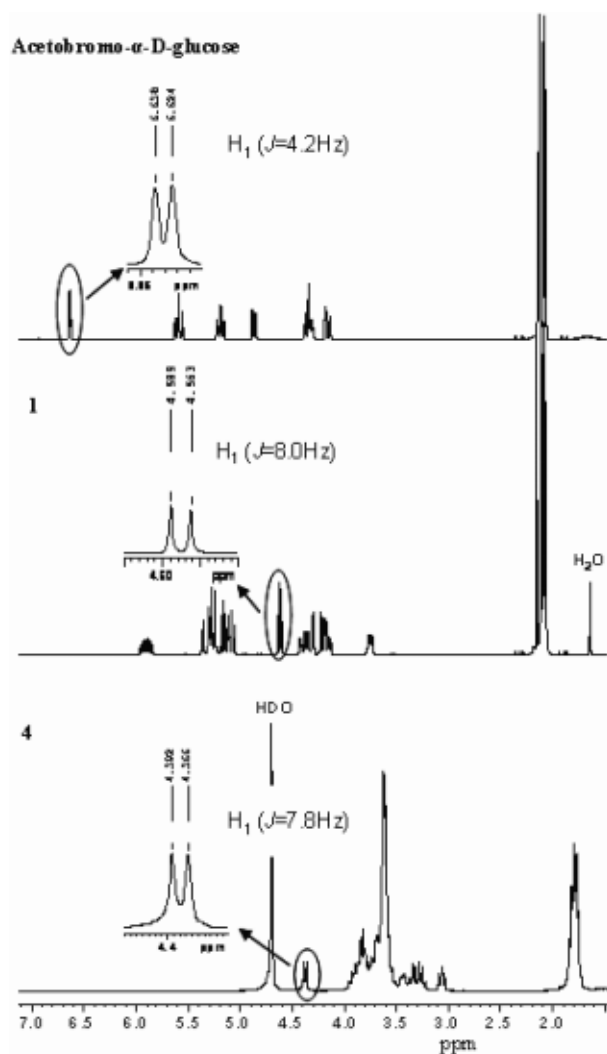
^{1}H NMR confirmed that all of the reaction

Figure 1. ¹H NMR spectra analysis of reaction stereospecificity.

products were β-anomers (Fig. 1). The chemical shift and *J*-coupling constant for anomeric proton (H₁) in 1 and 2, were 4.56 ppm (*J* = 8.0 Hz) and 4.42 ppm (*J* = 7.8 Hz) respectively; *a*-anomer protons are typically further upfield (~ 5.0 ppm) with smaller J-coupling constants (~ 4.0 Hz) (Lindhorst *et al.,* 1998; Lindhorst *et al.,* 2001; Lindhorst *et al.,* 2006). The anomeric proton of acetobromo-*a*-D-glucose can be seen

at ~ 6.63 ppm with a *J*-coupling constant of 4.2 Hz (Fig. 1). In the case of 3 the signal of the β-anomeric proton overlapped with that of the allyl group, but was clearly resolved in 4, appearing at 4.37 ppm with a *J*-coupling constant of 7.8 Hz.

As an example, the chemical structures of 7 and 8 were confirmed by NMR spectra analysis (Fig. 2). In addition, the anomeric configuration
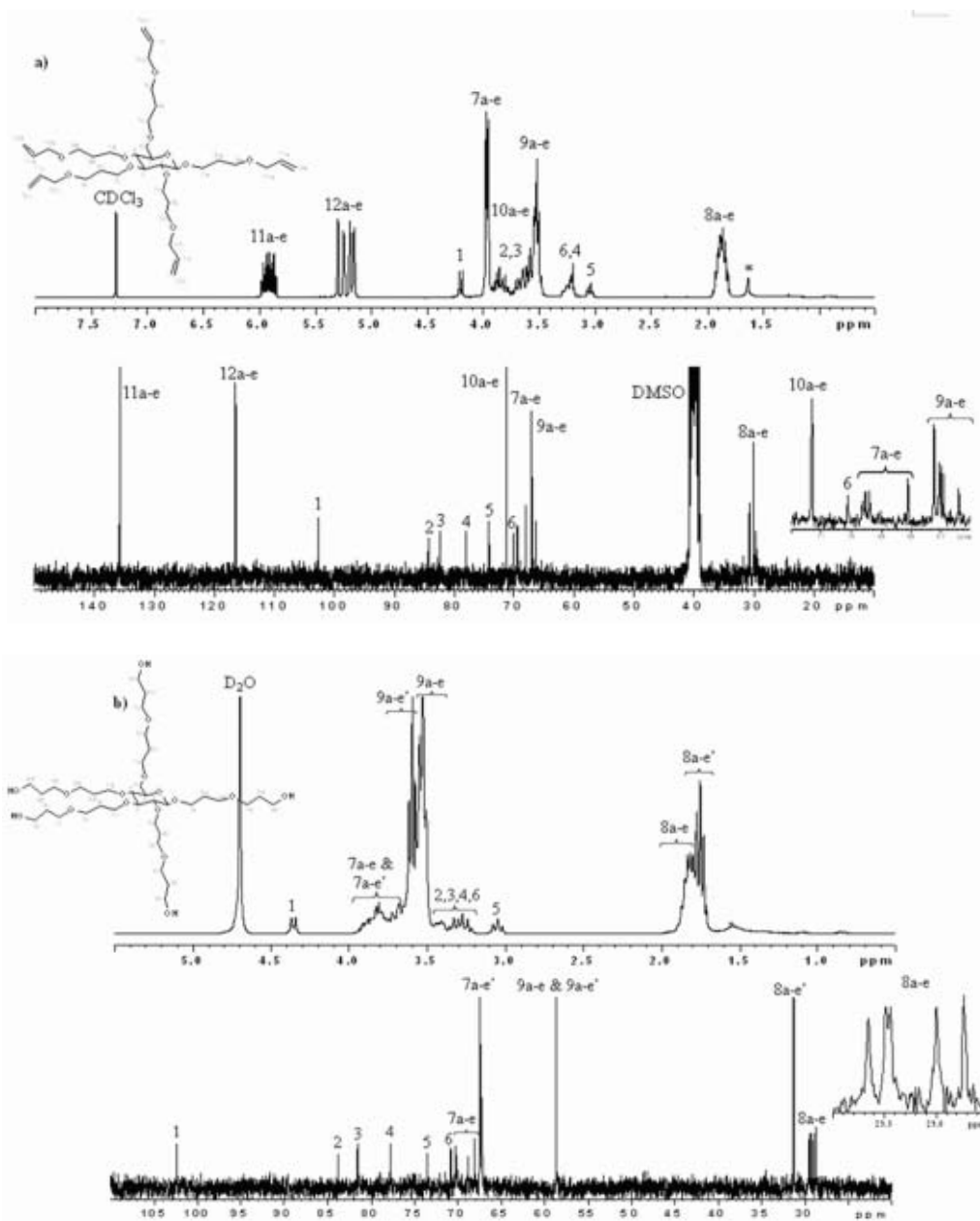
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Figure 2. a) ¹H & ¹³C NMR spectra of 7 and b) ¹H & ¹³C NMR spectra of 8.

by ¹H NMR confirmed the presence of β-ano-meric protons in perallylated 5, 7 and 9, and hydroxypropylene glycol modified 6, 8 and 10

were 4.18 ppm with coupling constant $J = 7.8$ Hz and 4.34 ppm with $J = 7.8$ Hz respectively (data not shown here).

4. CONCLUSIONS

In conclusion, we have attempted the synthesis of the oligo-glycosylation of octopus type β-D-glucopyranosides. The methodology presented in this scheme 1 allows the substitution of not only 2, 3, 4, 6-tetra hydroxy groups but also the anomeric hydroxy group of a sugar into carbohydrate-centered multivalent glycoclusters. Furthermore, above a multi-step synthesis protocol allows us a great potential opportunity of a novel class of carbohydrate-centered multivalent clusters, which could possibly be adapted for the generation various spacer with different functionalities not only in the 2, 3, 4, 6-tetra hydroxyl groups but also at the β-anomeric configuration of monosaccharides in future synthesis developments.

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