Article

Synthesis of a Novel D-Glucose-Conjugated 15-Crown-5 Ether with a Spiro Ketal Structure

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Abstract: This paper describes a synthetic approach to a novel D-glucose-conjugated 15-crown-5 ether having a spiroketal structure starting from a 1-C-vinylated glucose derivative. The approach consists of the glycosylation of the vinylated glucose derivative to give an ethyleneoxy spacer derivative using bismuth(III) triflate, the conversion of the 1-C-vinyl group of the glucoside produced into a carboxylic acid group, and the intramolecular condensation between the carboxyl group and the terminal hydroxyl group in the ethyleneoxy spacer. A D-glucose-conjugated 15-crown-5 ether having a unique spiroketal structure was thus successfully synthesized.

Keywords: Crown ether; Spiroketal; 1-C-Vinylated glucose; Glycosylation

Introduction

Crown ether molecules with saccharide moieties are interesting as chiral phase-transfer catalysts [1-2]. An enzymatic approach for synthesizing these types of crown ethers provides the cyclofructan family (cyclo$\beta$(2→1)-D-fructooligosaccharides) via the digestion of inulin. The cyclofructan contains a structurally interesting crown ether framework in its central core [3-4]. It is noteworthy that this is the
first example of saccharide-based crown ethers which have spiroketal structures. Many saccharide-based crown ether molecules have also been synthesized by chemical procedures [5-7]. As these chemical methods bind the original hydroxyl groups of the saccharide with an ethyleneoxy spacer, they cannot produce however crown ether compounds having spiroketal structures.

Sugar derivatives (1-C-vinylated sugars) having a vinyl group at the anomeric center, which are readily prepared by the addition of organometallic reagents, such as vinylMgX, to a suitably protected sugar lactone, are a synthetically useful tool in carbohydrate chemistry [8-11]. Our recent studies have shown that these 1-C-vinylated sugar derivatives were good precursors for preparing some functionalized exo-glycal derivatives [12] and naturally occurring anhydroketopyranoses [13]. For the purpose of further exploring the utility of the 1-C-vinylated sugars, we investigated the synthesis of a novel crown ether molecule from a 1-C-vinylated D-glucose derivative 1. The D-glucose-conjugated 15-crown-5 ether 2 that we designed is a dicyclic compound with a unique spiroketal structure derived from the structural characteristic of 1, i.e., its spiro carbon atom corresponds to the anomeric carbon atom. This paper describes our synthetic approach to a novel 15-crown-5 ether 2 having a spiroketal structure from a 1-C-vinylated glucose derivative (1).

Results and Discussion

The synthetic approach to compound 2 from 1 is shown in Scheme 1. It consists of the following reaction steps: 1) introduction of the ethyleneoxy spacer, tetraethyleneglycol monobenzoate (3) onto the vinylated D-glucopyranose derivative 1 by the glycosylation reaction; 2) conversion of the vinyl group at the anomeric center of 4 to a carboxyl group, and 3), intramolecular condensation between the carboxyl group and the terminal hydroxyl group in the ethyleneoxy spacer to produce the desired 2.

The glycosylation of 1 to 3 (1.3 equiv.) using bismuth(III) triflate (Bi(OTf)3) (0.05 equiv.) in the presence of anhydrous CaSO4 in dichloromethane at 0 °C for 24 h afforded the desired glucoside 4 [14], which was purified by preparative TLC (ethyl acetate/hexane = 1/2) in 81% yield. The glycosylation proceeded with an α-stereoselectivity. The high α-stereoselectivity of the glycosylation using 1 was in agreement with our previously reported observation [15]. The α-anomeric configuration of 4 was determined by the NOE interaction between the H-2 and the H-1'.

The ozone oxidation of 4 in dichloromethane at -78 °C for 5 h and treatment with triphenylphosphine (3.4 equiv.) at room temperature for 19 h gave the crude aldehyde product. The subsequent oxidation using NaClO2 (12 equiv.)-NaH2PO4 (3 equiv.) in t-butyl alcohol-H2O (4/1) produced the carboxylic acid derivative 5, which was purified by preparative TLC (CHCl3/MeOH = 5/1) in 85% yield.

Deprotection of the benzoyl group of 5 was performed using 0.5 M NaOH/THF to afford 6 in 83% yield. The cyclization of 6 using (benzotriazol-1-yl oxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (2.5 equiv.) and DIEA (1.8 equiv.) in dichloromethane for 24 h afforded the desired 2, which was purified by preparative TLC (CHCl3/MeOH = 20/1) in 84% yield.

In conclusion, we have demonstrated the synthesis of a novel 15-crown-5 ether 2 having a spiroketal structure from a 1-C-vinylated D-glucose derivative. This compound 2 is expected to function as a chiral phase-transfer catalyst.
Scheme 1. Synthetic approach to 2.

Reagents and conditions: i) Bi(OTf)$_3$ (0.05 equiv.), Bz(OCH$_2$CH$_2$)$_3$OH 3 (1.3 equiv.), CH$_2$Cl$_2$, 0 °C, 24 h, 81%; ii) (a) O$_3$, -78 °C, 5 h, CH$_2$Cl$_2$, then Ph$_3$P (3.4 equiv.), rt, 19 h. (b) Me$_2$C=CHMe (4.5 equiv.), NaClO$_2$ (12 equiv.), NaH$_2$PO$_4$ (3 equiv.), t-BuOH-H$_2$O, rt, 24 h, 85%; iii) 0.5 M NaOH (13 equiv.), THF, rt, 3 h, 83%; iv) PyBOP (2.5 equiv.), DIEA (1.8 equiv.), CH$_2$Cl$_2$, 24 h, 84%.

Experimental

General

$^1$H-NMR (600 MHz) and $^{13}$C-NMR (150 MHz) spectra were recorded using a JEOL ECA-600 spectrometer in CDCl$_3$ with TMS as the internal standard. The optical rotations were recorded by a JASCO DIP-360 digital polarimeter. The HRMS were obtained using a Mariner spectrometer (PerSeptive Biosystems Inc.). Preparative TLC was performed using Merck silica gel 60GF254. Column chromatography was conducted using silica gel 60 N (40–50 μm, Kanto Chemical Co., Inc.). Bi(OTf)$_3$ was purchased from Sigma-Aldrich. All anhydrous solvents were purified according to standard methods.

11-Benzoyloxy-3,6,9-trioxaundecyl 2,3,4,6-tetra-O-benzyl-1-C-vinyl-α-D-glucopyranoside (4): To a stirred solution of Bi(OTf)$_3$ (15 mg, 0.023 mmol) in CH$_2$Cl$_2$ (3.5 mL) were added tetraethyleneglycol monobenzoate (3) (165 mg, 0.55 mmol) and 2,3,4,6-tetra-O-benzyl-1-C-vinyl-α-D-glucopyranose (1) (257 mg, 0.42 mmol) in the presence of anhydrous CaSO$_4$ (280 mg) under an Ar atmosphere. The resulting mixture was stirred at 0 °C for 24 h. The reaction was then quenched by the addition of a sat.
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NaHCO₃ solution (5 mL). The reaction mixture was extracted with CH₂Cl₂ (three times), and the organic layer was washed with water and a sat. NaCl solution. After the organic layer was dried over Na₂SO₄, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane = 1/2) to give 4 (311 mg, 81% yield) as a colorless oil. [α]D<sup>25</sup> = +3° (c 4.7, CHCl₃); ¹H-NMR: δ 3.34 (d, 1H, J = 9.6 Hz, H-2), 3.48-3.70 (m, 14H, H₆-12), 3.75-3.78 (m, 3H, H₅a, H₅b), 3.83 (m, 1H, H-5), 4.09 (t, 1H, J = 9.7 Hz, H-3), 4.42-4.91 (m, 8H, CH₂Ph), 5.27 (dd, 1H, J = 2.0 Hz, J = 11.0 Hz, CH=CH₂H₆), 5.54 (dd, 1H, J = 2.1 Hz, J = 17.9 Hz, CH=CH₂H₅a), 5.99 (m, 1H, CH₂Ph), 7.19-7.54, 8.04-8.05 (m, 25H, Ph); ¹³C-NMR: δ 61.1 (CH₂CH₂), 64.1 (CH₂CH₂), 68.8 (C-6), 69.2 (CH₂CH₂), 70.0 (CH₂CH₂), 70.6 (CH₂CH₂), 70.64 (CH₂CH₂), 70.7 (CH₂CH₂), 71.5 (C-5), 73.4 (CH₂Ph), 75.0 (CH₂Ph), 75.5 (CH₂Ph), 75.8 (CH₂Ph), 78.5 (C-4), 83.0 (C-3), 84.3 (C-2), 99.5 (C-1), 118.8 (CH=CH₂), 125.7-133.0 (Ph), 135.3 (CH=CH₂), 138.1-138.4 (Ph), 166.5 (C=O); HRMS (ESI) m/z calcd for C₅₁H₅₈NaO₁₁ 869.3871 [M +Na]+, found 869.3865.

(11-Benzoyloxy-3,6,9-trioxaundecyl 3,4,5,7-tetra-O-benzyl-α-D-gluco-hept-2-ulopyranosid)onic acid (5): Ozone was bubbled through a stirred solution of 4 (224 mg, 0.26 mmol) in CH₂Cl₂ (15 mL) at -78 °C for 5 h. After triphenylphosphine (230 mg, 0.88 mmol) was added at -78 °C and the reaction temperature was raised to room temperature, the reaction mixture was stirred for 19 h. The solvent was then evaporated under reduced pressure. To a solution of the crude product in t-butyl alcohol (4 mL)-H₂O (1 mL) were added NaClO₂ (277 mg, 3.1 mmol), NaH₂PO₄ (124 mg, 0.8 mmol) and 2-methyl-2-buten (123 μL, 1.2 mmol). After the reaction mixture was stirred for 24 h, the reaction was quenched by adding 2 M HCl (1 mL) and water (5 mL). The reaction mixture was then extracted with CH₂Cl₂ (three times), and the combined organic solvent was dried over anhydrous Na₂SO₄. The organic solvent was filtered and evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (CHCl₃/MeOH = 5/1) to afford 5 (194 mg, 85% yield) as a colorless oil. [α]D<sup>25</sup> = +21° (c 3.9, CHCl₃); ¹H-NMR: δ 3.54-4.08 (m, 20H, H₃-7, H-8, H-9, H-10, H-11, H-12), 4.41-4.49 (m, 2H, CH₂CH₂), 4.51-5.28 (m, 8H, CH₂Ph), 7.03-7.53 (m, 23H, Ph), 8.03-7.53 (d, 2H, J = 6.8 Hz, Ph); ¹³C-NMR: δ 64.0 (CH₂CH₂), 69.1 (C-7), 69.9 (CH₂CH₂), 70.2 (CH₂CH₂), 70.3 (CH₂CH₂), 70.4 (CH₂CH₂), 70.5 (CH₂CH₂), 70.6 (CH₂CH₂), 72.6 (CH₂CH₂), 75.19 (CH₂Ph), 75.20 (CH₂Ph), 75.4 (CH₂Ph), 75.5 (CH₂Ph), 77.6 (C-6), 80.9 (C-5), 82.7 (C-3, C-4), 99.3 (C-2), 126.0-139.2 (Ph), 166.5 (C(O)Ph), 177.7 (C-1); HRMS (ESI) m/z calcd for C₅₀H₅₆NaO₁₃ 887.3613 [M +Na]+, found 887.3653.

(11-Hydroxy-3,6,9-trioxaundecyl 3,4,5,7-tetra-O-benzyl-α-D-gluco-hept-2-ulopyranosid)onic acid (6): A 0.5 M NaOH solution (4 mL, 2 mmol) was added to a solution of 5 (142 mg, 0.16 mmol) in THF (4 mL). After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched by adding 2 M HCl (1 mL) and water (5 mL). After the reaction mixture was extracted with CH₂Cl₂ (three times), the combined organic solvent was dried over anhydrous Na₂SO₄. The organic solvent was filtered and evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (CHCl₃/MeOH = 5/1) to afford 6 (103 mg, 83% yield) as a colorless oil. [α]D<sup>25</sup> = +25° (c 1.8, CHCl₃); ¹H-NMR: δ 3.37-4.00 (m, 22H, H-3, H-4, H-5, H-6, H-7, CH₂CH₂), 4.44-4.84 (m, 8H, CH₂Ph), 6.94-7.43 (m, 20H, Ph); ¹³C-NMR: δ 60.4 (CH₂CH₂), 62.6 (CH₂CH₂), 68.5-70.4 (CH₂CH₂, C-7), 72.4 (CH₂Ph), 80.9 (C-6), 82.4 (C-5), 82.9 (C-3, C-4),
(1R)-2,3,4,6-Tetra-O-benzylspiro[1,5-anhydro-D-glucitol-1,2'-[3,6,9,12]tetraoxatetradecan]-14'-olide (2): To a solution of 6 (20 mg, 0.027 mmol) in CH₂Cl₂ (3 mL) were added 4-dimethylaminopyridine (5.9 mg, 0.048 mmol) and PyBOP (35 mg, 0.067 mmol). After the reaction mixture was stirred for 24 h. The reaction was then quenched by the addition of a sat. citric acid solution (5 mL). The reaction mixture was extracted with EtOAc and the organic layer was washed with water and a sat. NaCl solution. After the organic layer was dried over Na₂SO₄, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (CHCl₃/MeOH = 20/1) to give 2 (17 mg, 84% yield) as a colorless oil. [α]D₂⁵ = +11° (c 0.15, CHCl₃); ¹H-NMR: δ 3.48-3.71 (m, 15H, H-4, H-5, H-6, CH₂CH₂), 3.73-3.75 (m, 1H, CH₂CH₂), 3.81 (d, 1H, J = 9.6 Hz, H-2), 3.87-3.92 (m, 1H, CH₂CH₂), 4.00-4.05 (m, 1H, CH₂H₆CH₂), 4.06-4.07 (m, 1H, H-3), 4.31-4.34 (m, 1H, CH₂H₆CH₂), 4.54-4.65 (m, 4H, CH₂Ph), 4.79-4.89 (m, 4H, CH₂Ph), 7.16-7.35 (m, 20H, Ph); ¹³C-NMR: δ 63.6 (CH₂CH₂), 65.2 (CH₂CH₂), 68.3 (CH₂CH₂), 68.4 (C-6), 69.6 (CH₂CH₂), 70.1 (CH₂CH₂), 70.4 (CH₂CH₂), 70.9 (CH₂CH₂), 71.2 (CH₂CH₂), 73.4 (C-5), 73.44 (CH₂Ph), 75.1 (CH₂Ph), 75.2 (CH₂Ph), 75.6 (CH₂Ph), 78.0 (C-4), 82.2 (C-2), 82.7 (C-3), 99.7 (C-1), 127.5-128.4 (Ph), 137.9-138.5 (Ph), 173.5 (C-1’); HRMS (ESI) m/z calcd for C₄₃H₅₀NaO₁₁ 765.3245 [M +Na]+, found 765.3247.

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Sample Availability: Samples of the compounds are available from the authors

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