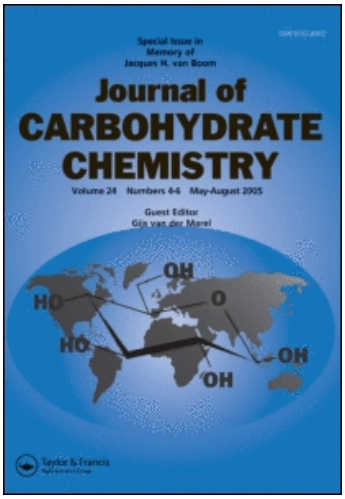

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SELENOGLYCOSIDES 5.[1] STEREOCONTROLLED SYNTHESIS OF SELENO-DISACCHARIDES

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ABSTRACT

Stereocontrolled synthesis of α and β linked seleno-disaccharides is achieved by reaction of a diglycosyl-diselenide with a deoxyhalo sugar derivative under reducing conditions.

INTRODUCTION

In recent years much effort has been devoted to the synthesis of unnatural di- and oligosaccharides in which the bridging oxygen of the glycosidic linkage is replaced by a nitrogen,[2] sulphur[3] or carbon atom[4] because such compounds can act as inhibitors of glycosidases.[5] Compounds exhibiting this property have been used or suggested as antihyperglycemic compounds,[6] inhibitors of tumour metastasis,[7] antiobesity drugs[8] and antivirals.[9]

We now report a versatile methodology for the synthesis of a new class of such compounds in which the bridging atom is a selenium atom. Although

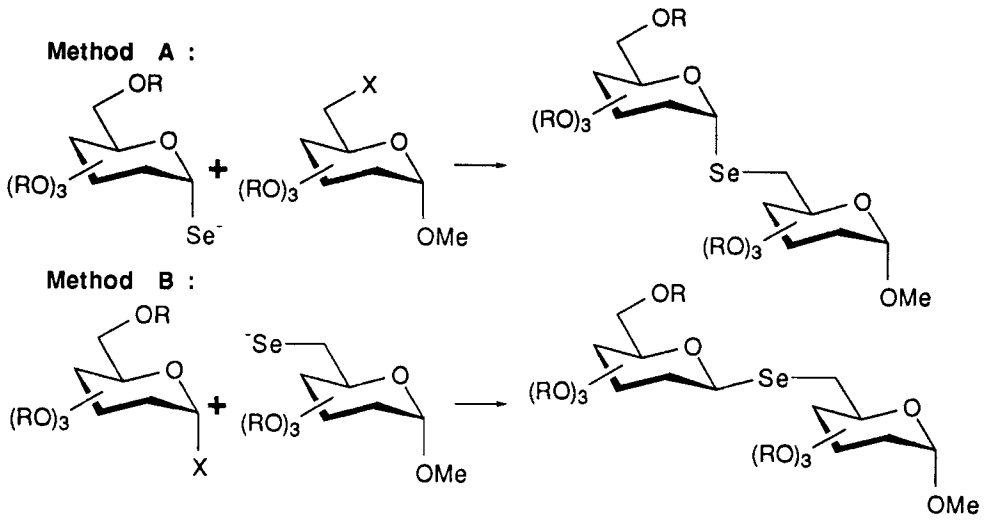

Chart 1

selenoisotrehalose[10] and 6-seleno-bis-(6-deoxy-β-D-glucopyranoside)[11] were reported early in the century, to the best of our knowledge, no < 1, n' > selenodisaccharides containing one reducing unit have been described.[12]

To achieve our goal two strategies were evaluated: Method A - condensation of a glycosyl selenoate of known anomeric configuration with a protected deoxy halo sugar; Method B - condensation of a deoxy seleno sugar derivative with a glycosyl halide.

Treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride[13] **1** with selenourea in acetone afforded an α selenouronium salt **2** in high yield presumably via an S_N1 mechanism. The α configuration of **2**, ascertained by ^1H NMR spectroscopy (H-1, d, δ = 7.25 ppm, $J_{1,2}$ = 5.2 Hz), was in agreement with the previous result obtained by Durette et al. with thiourea.[14] Compound **2** was reacted with potassium hydroxide to afford a diglycosyldiselenide **3** in 70% yield. Preservation of the α-anomeric configuration was confirmed by ^1H NMR (H-1, d, δ = 5.91 ppm, $J_{1,2}$ = 5.00 Hz). The α-selenoate was generated *in situ* by reaction of **3** with potassium borohydride and treated with methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside[15] **7**. The α-selenodisaccharide **10** was obtained in 70% yield. Examination of the ^1H NMR spectrum clearly indicated the α configuration (H-1, d, δ

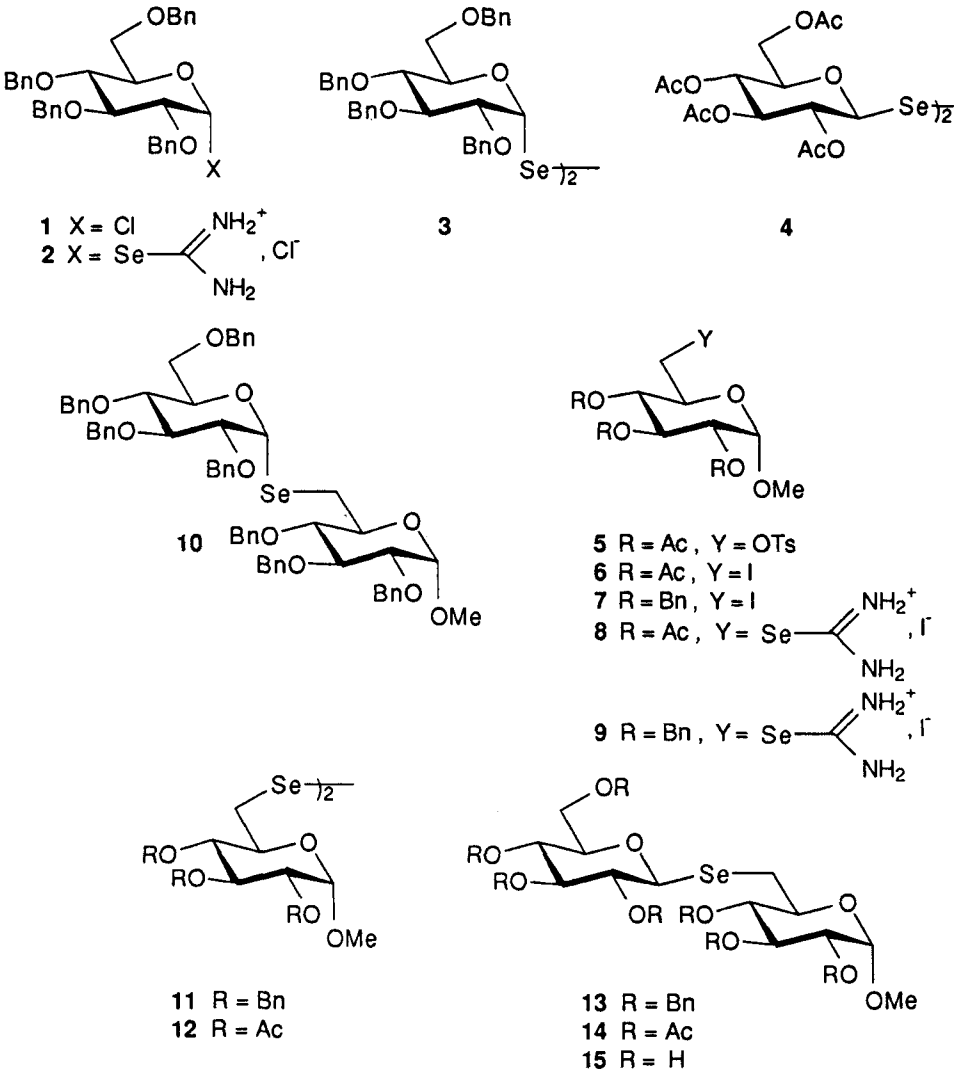

Chart 2

= 6.00 ppm, $J_{1,2}$ = 4.70 Hz) in agreement with previously reported data for α-selenoglycosides by others[16] and by us.[17]

Debenzylation of **10** was not possible under palladium catalysed hydrogenolysis, so another approach with acetyl group as protecting group was considered.

The same route was employed to synthesize peracetylated-β-selenodisaccharide **14.** The known β-β' diglucosyl diselenide[18] **4** was reduced with NaBH3CN (10 equiv)

in a mixture of ethanol and HMPA and treated with methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-tosyl-α-D-glucopyranoside[19] **5**. Deacetylation occurred and reacetylation was necessary. Compound **14** was obtained but the reaction was very slow, HMPA was difficult to remove and separation of **14** from **4** was not easy. Nevertheless, the use of β-β' diglucosyl diselenide **4** leads to β-selenodisaccharide **14**.

For evaluation of Method B, diglycosyl-diselenides **11** and **12** were needed. They were, respectively, prepared in two steps by reaction of 6-deoxy-6-iodo derivatives **7** and **6** with selenourea followed by treatment under basic conditions (see Experimental).

Reaction of **11** with KBH_4 in a mixture of toluene and ethanol afforded the corresponding 6-deoxy-6-selenoate which was directly reacted with **1**. The reaction was very slow and decomposition of **1** was observed before substantial formation of perbenzylated-β-selenodisaccharide **13**. When **12** was transformed into 6-deoxy-6-selenoate with KBH_4 in DMF and reacted with more reactive 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, the desired peracetylated-β-selenodisaccharide **14** was obtained after reacetylation. The NMR spectra of this last compound and of the one obtained by method A showed that the two compounds were identical. Deacetylation (MeO^-Na^+, MeOH) afforded the β-seleno-disaccharide **15** in 70% yield. Evaluation of glucosidase inhibition by **15** is in progress.

EXPERIMENTAL

General methods. Melting points were determined on a Thomas-Hoover apparatus and are reported uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer, using solutions in $CDCl_3$ (internal Me_4Si). Analytical TLC was performed on silica gel 60 F 254 followed by UV detection and by spraying with 1 M ethanolic H_2SO_4 followed by heating. For analytical TLC, the employed solvent systems were: eluent A (1:4 ethyl acetate - hexane), eluent B (5:5:1 acetone - ethyl acetate - acetic acid), eluent C (2:3 ether - petroleum ether), eluent D (3:7 ethyl acetate - hexane), eluent E (1:1 ethyle acetate - hexane), eluent F (3:1 ether - hexane), eluent G (1:1 dichloromethane - methanol). Silica gel 60 (Merck, 230-400 mesh) was used for flash chromatography. Elemental analyses were performed at the "Service de Microanalyse" of the Pierre et Marie Curie University.

Di-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)diselenide (3). A solution of **1**[20] (1.58 g, 2.82 mmol) and selenourea (416 mg, 3.4 mmol) in acetone (8 mL) was strirred at 60 °C under argon for 6 h. The desired compound was precipitating during the reaction. After solvent evaporation, the crude mixture (2.12 g) was dissolved in warm acetone (120 mL), black insoluble impurities were filtered off, and acetone was evaporated to give **2** (1.94 g, 96%), Rf 0.00 (eluent C): Rf 0.50 (eluent B), ^{1}H NMR (500 MHz, DMSO d_6), δ 3.64 (m, 2H, H-4, H-6), 3.72 (m, 2H, H-3, H-6'), 4.06 (dd, 1H, $J_{1,2}$=5.2 Hz, $J_{2,3}$=8.68 Hz, H-2), 4.06 (ddd, 1H, $J_{4,5}$=9.9 Hz, $J_{5,6}$=4.77 Hz, $J_{5,6'}$=1.77 Hz, H-5) 4.40-4.90 (m, 8H, 4 O-CH_2-Ph) , 7.20-7.40 (d included in m, 21H, $J_{1,2}$=5.2, Hz, H-1, Arom.), 8.40 (d, 4H, 2 NH_2). ^{13}C NMR (500 MHz, DMSO d_6) δ 68.03, 72.21, 74.22, 76.02, 81.12, 86.63, 127.48-128.28. Compound **2** (1.49 g, 2.19 mmol) was directly dissolved in acetone (5 mL) and an aqueous solution of KOH (0.71M, 3.7 mL = 2.63 mmol) was added under stirring at room temperature. Precipitation of **3** was observed. After 6 h TLC indicated completion of the reaction. Solvent was evaporated and the residue partitioned between H_2O-Et_2O (40 mL, 1:1) and the aqueous phase extracted with ether (2 x 10 mL). The combined Et_2O layer was washed with H_2O (2 x 10 mL) and dried ($MgSO_4$). After solvent evaporation, the residue was purified by flash chromatography (2:5 ether / hexane) to afford **3** (894 mg, 68%) as white crystals, mp 86-88 °C; Rf 0.40 (eluent C); $[\alpha]_D$ +317° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 3.60-4,00 (m, 6H, H-2, H-3, H-4, H-5, H-6, H-6'), 4.30-4.90 (m, 8H, 4 O-CH_2-Ph), 5.90 (d, 1H, $J_{1,2}$=6 Hz, H-1), 6.90-7.40 (m, 20H, Arom.).

Anal. Calcd for $C_{68}H_{70}O_{10}Se_2$: C, 67.76 ; H, 5.85. Found: C, 67.43 ; H, 5.69.

Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-(selenouronium iodide)-1-α-D-glucopyranoside (9). A solution of compound **7**[15] (670 mg; 1.16 mmol) and selenourea (428 mg; 3.48 mmol = 3 equiv) in acetone (2.5 mL) was refluxed under argon for 72 h. Acetone was evaporated and the crude mixture was used for the next step. Rf: 0.00 (eluent A). Rf: 0.50 (eluent B).

Di-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside)-(6→6)-diselenide (11). Selenouronium salt **9** (809 mg, 1.16 mmol) was dissolved in an aqueous solution of KOH (0.71 M, 2 mL = 1.4 mmol, 1.2 equiv.) and acetone (2.5 mL). After stirring for 24 h the reaction was complete. The solvent was evaporated, the mixture was diluted with ether (15 mL) and washed with water to neutral pH. The aqueous phase was extracted with ether (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue (490 mg) was purified by column chromatography (1:2. ether / hexane) to give **11** as an oil (894 mg; 68%), Rf: 0.50

(eluent A). Rf: 0.80 (eluent B); $[\alpha]_D$ + 96° (*c* 1.0, $CHCl_3$); ^1H NMR δ 3,05 (dd; 1H; $J_{5,6}$ =8.33 Hz; $J_{6,6'}$ = 12.32 Hz; H-6); 3.25-3.35 (m; 5H; H-4; H-6'; -OCH_3), 3.50 (dd; 1H; $J_{1,2}$ =3.52 Hz; $J_{2,3}$ = 9.64 Hz; H-2), 3.85 (m; 1H; H-5), 3.95 (dd; 1H, $J_{3,4}$ = 9.24 Hz, H-3), 4.53 (d, 1H, H-1), 4.55-5.05 (m, 6H, 3 O-CH_2-Ph), 7.20-7.40 (m, 15H, Arom).

Anal. Calcd for $C_{56}H_{62}O_{10}Se_2$: C, 63.87; H, 5.93. Found: C, 63.99; H, 6.01.

Methyl (2,3,4,6-tetra-*O*-benzyl-1-seleno-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (10). Compound **3** (60 mg, 0.05 mmol) and potassium borohydride (27 mg, 0.5 mmol) were dissolved in a mixture of ethanol (2 mL) and toluene (1 mL). After heating for 2 h at 60 °C under argon, methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside **7** (69 mg, 0.12 mmol) was added. After 72 h the solvent was evaporated. The mixture was extracted with ether (15 mL) and washed until neutral pH. The aqueous phase was reextracted with ether (2 x 5 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. Purification by chromatography (1:4 ether/hexane) yielded **10** (74 mg, 70%) as white crystals, mp 100-102 °C; Rf: 0.50 (eluent C); $[\alpha]_D$ + 137° (*c* 1.0, $CHCl_3$); ^1H NMR δ 2.85 (2dd, 2H, $J_{5,6}$ = 2.84 Hz,$J_{5,6'}$ = 7.33 Hz, $J_{6,6'}$ = 12.53 Hz H-6; H-6'), 3.38 (s, 3H, OCH_3), 3.40-4.20 (m, 10H, H-2; H-2'; H-3; H-3'; H-4; H-4'; H-5; H-5'; H-6"; H-6'"), 4.30-5.10 (m, 16H, 7 O-CH2-Ph, H-1), 5.95 (d, 1H, $J_{1',2'}$ = 5.94 Hz, H-1'), 7.10-7.40 (m, 35H, H Arom.).

Anal. Calcd for $C_{62}H_{66}O_{10}Se$: C, 70.91; H, 6.33. Found: C, 70.83; H, 6.50.

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(selenouronium iodide)-α-D-glucopyranoside (8). Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside **6** (860 mg, 2 mmol) and selenourea (320 mg, 2.6 mmol = 1.3 equiv) were dissolved in acetone (4 mL). After heating for 36 h at 50 °C under argon, the solvent was evaporated and the crude mixture was used for the next step. Rf : 0.00 (eluent D), Rf: 0.50 (eluent B).

Di-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside)-(6→6)-diselenide (12). Selenouronium salt **8** (1.1 g, 2 mmol), $Na_2S_2O_5$ (380 mg, 2 mmol) were dissolved in a mixture of acetone (4 mL) and ethanol (3 mL), then potassium carbonate (304 mg, 2.2 mmol = 1.1 equiv) was added. The reaction was complete after 48 h at room temperature. After evaporation of the solvent, the mixture was diluted with ethyl acetate (40 mL) and washed with water (2 x 10 mL). The aqueous phase was reextracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed until neutral pH, dried ($MgSO_4$) and concentrated. (621 mg).

Purification by chromatography (2:1 ether/hexane) yielded **12** (535 mg, 70%) as yellow crystals, mp 139-141 °C; Rf: 0.8 (eluent B), Rf : 0.50 (eluent E); $[\alpha]_D$ + 223.5° (*c* 1.0, $CHCl_3$); ^1H NMR δ 2.00-2.20 (3s, 9H, 3 CH_3CO), 3.15 (m, 2H, H-6, H-6'), 3.40 (s, 3H, -OCH_3), 4.00 (m, 1H, $J_{5,4}$ = 9.86 Hz, $J_{5,6}$ = 6.85 Hz, $J_{5,6'}$ = 4.84 Hz, H-5), 4.80-5.00 (m, 3H, H-1, H-2, H-4), 5.46 (t, 1H, J = 9.56 Hz, H-3).

Anal. Calcd for $C_{26}H_{38}O_{16}Se_2$: C, 40.84 H, 5.01. Found: C, 41.04; H, 5.00.

Methyl (2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranosyl)-(1→6)-2,3,4 tri-*O*-acetyl-α-D-glucopyranoside (14). Compound **12** (183 mg; 0.24 mmol) and potassium borohydride (36 mg; 0.66 mmol) were dissolved in DMF (2 mL). After stirring at 60 °C for 1 h, acetobromoglucose (164 mg, 0.4 mmol) dissolved in DMF (1 mL) was added. After stirring for 72 h, DMF was evaporated. Then acetic anhydride (1 mL) and pyridine (1 mL) were added. After 5 days, pyridine was co-evaporated with toluene. The mixture was diluted with ethyl acetate (15 mL) and washed with water to neutral pH. The aqueous phase was reextracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by chromatography (2:1 ether/hexane followed by 3:1 ether/hexane) yielded **14** (171 mg, 60%) as white crystals; mp 111-113 °C; Rf = 0.35 (eluent F); $[\alpha]_D$ + 37° (*c* 1.0, CH_2Cl_2); ^1H NMR δ 1.90-2.20 (7s, 14H, 7CH_3CO), 2.85 (d, 2H, $J_{6,6'}$ = 5.80 Hz, H-6, H-6'), 3.40 (s, 3H, OCH_3), 3.70 (m, 1H, $J_{4',5'}$ = 9.80 Hz, $J_{5',6''}$ = 2.40 Hz, $J_{5',6'''}$ = 4.90 Hz, H-5'), 4.00 (td; 1H; $J_{4,5}$ =9.80 Hz; H-5); 4,15 (2dd; 2H; $J_{6'',6'''}$ =12.45 Hz; H-6''; H-6'''); 4.80-5.50 (m, 8H, H-1, H-1', H-2, H-2', H-3, H-3', H-4, H-4').

Anal. Calcd for $C_{27}H_{38}O_{17}Se$: C, 45.44 H, 5.37. Found: C, 45.05; H, 5.36.

Methyl (seleno-β-D-glucopyranosyl)-(1→6)-α-D-glucopyranoside (15). A solution of **14** (71 mg, 0.1 mmol) and MeONa (1M, 100 µL) in MeOH (500 µL) was stirred at room temperature until deacetylation was complete (4 h). After neutralisation with Amberlite IRN 77 (H^+ form) and filtration, evaporation of the solvent afforded an oil. Purification by precipitation with ether yielded **15** (28 mg, 70%) as white crystals, mp 79-81 °C; Rf = 0.50 (eluent G); $[\alpha]_D$ - 13° (*c* 1.0, H_2O); ^1H NMR δ 2.80 (dd, 1H, $J_{5,6}$ = 8 Hz, $J_{6,6'}$ = 13.30 Hz, H-6), 3.10 (dd, 1H, $J_{5,6'}$ = 2.75 Hz, H-6'), 3.20-3.80 (s included in m, 13H, OCH_3, H-2, H-2', H-3, H-3', H-4, H-4', H-5, H-5', H-6'', H-6'''), (m, H-1, H-1', H_2O).

Anal. Calcd for $C_{13}H_{24}O_{10}Se$ (2 H_2O) : C, 34.29 H, 6.19. Found: C, 33.85; H, 6.17.

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