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Synthesis of selenium-linked neoglycoconjugates and pseudodisaccharides

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ABSTRACT

The introduction of organoselenium moieties within the structure of carbohydrates has received attention recently. Herein, we report on the synthesis of selenium-containing neoglycoconjugates and pseudodisaccharides by the reaction of nucleophilic selenium species, generated from sugar diselenides, with chiral *N*-Boc aziridines and sugar tosylates. The reaction proceeds with moderate to good yields for various substrates. The introduction of organoselenium moieties within the framework of various sugars, with increased levels of complexity, thus allowing the synthesis of disaccharide and glycoconjugate mimetics.

1. Introduction

The synthesis of small chiral molecules containing a selenium atom has received growing attention, particularly due to the broad range of interesting biological activities displayed by these compounds. Organic selenium compounds have been described to have important roles in biological redox processes, in cancer prevention, immunology and ageing.[1]

Despite the fact that recently selenium has been incorporated in the scaffold of several different classes of molecules, the introduction of selenium within the carbohydrate framework has received less attention. The most commonly encountered modification of carbohydrates with selenium has been the introduction of an organoselenium group at the anomeric position,[2] which has been reported as intermediates for the synthesis of glycoconjugates,[3] oligosaccharides,[4] glycals[5] and *C*-glycosides.[6] In addition, the synthesis of sugars containing selenium in their structures has also been pursued and selenoglycosides[7] and selenodisaccharides[8] have been reported. Seleno pseudodisaccharides, in which the selenium is non-glycosidically linked were recently reported by Cumpstey and co-workers.[9,10] Moreover, the replacement of endocyclic oxygen by selenium to result in selenosugars was also reported.[11] Selenocarbohydrates have already been reported to have interesting biological properties, such as inhibition of melanin synthesis in melan-A cancer cells,[12] inhibition of human maltase glucoamylase (MGA),[13] an enzyme involved in the breakdown of glucose oligosaccharides in the intestine, and of protein tyrosine phosphatases.[14]

In addition, selenium has been incorporated within the sugar moiety in nucleoside chemistry.[15] Selenonucleosides have found extensive application in high resolution determination of three-dimensional structures of DNA and RNA.[16]

In this context, our group has developed efficient strategies for the synthesis of selenium-containing carbohydrates with different structural features.[17] In the present work, we report on the synthesis of more complex selenocarbohydrate derivatives, namely neoglycoconjugates and pseudodisaccharides, linked by a selenium atom (Fig. 1).

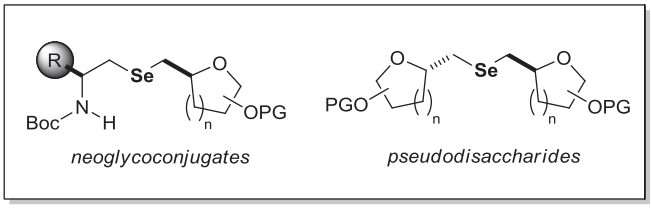

Fig. 1. General structure of selenium-linked neoglycoconjugates and pseudodisaccharides.

2. Results and discussion

Our initial efforts were focused on the synthesis of selenium-linked neoglycoconjugates, and the desired conjugation would be

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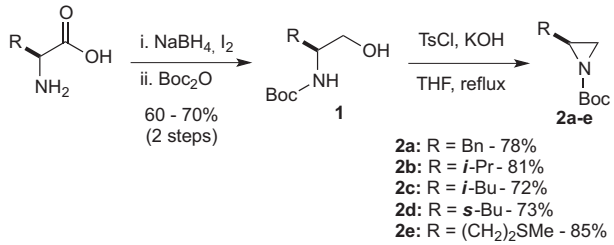
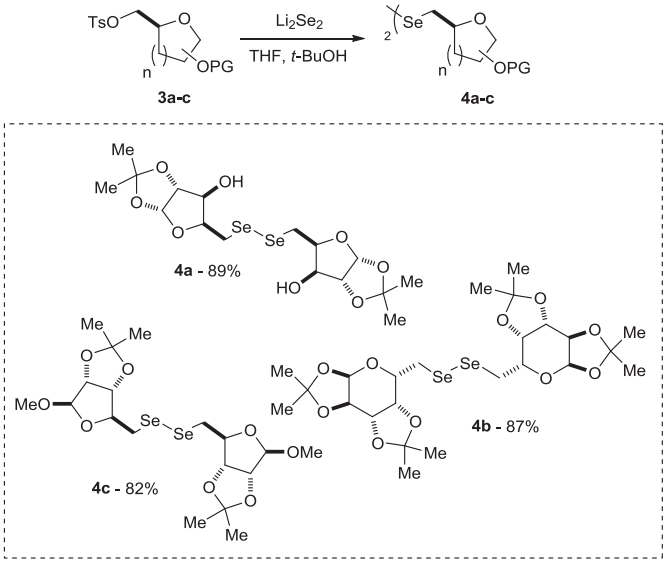
achieved through the nucleophilic ring-opening of chiral *N*-Boc aziridines, derived from amino acids. First, the required aziridines **2a**–**e** were prepared by an efficient synthetic sequence involving reduction of the amino acid to the corresponding amino alcohol,[18] followed by Boc protection of the amino group in good yields for the two step sequence (60–70%). The resulting *N*-Boc amino alcohols **1** were converted to the *N*-Boc aziridines **2a**–**e** in 72–85%, by reaction with TsCl under basic conditions (Scheme 1).[19]



Scheme 1. Synthesis of *N*-Boc aziridines **2a**–**e**.

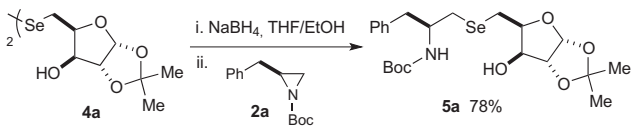
In parallel, the sugar-based diselenides **4a**–**c**, derived from the carbohydrates D-xylose, D-galactose and D-ribose, respectively, were prepared according to our previously reported methodology.[17] The desired sugar-based diselenides were cleanly obtained in high yields (85–89%) by a nucleophilic substitution reaction of a tosylate leaving group in the appropriate carbohydrate derivative with Li_2Se_2[20] (Scheme 2).



Scheme 2. Synthesis of sugar diselenides **4a**–**c**.

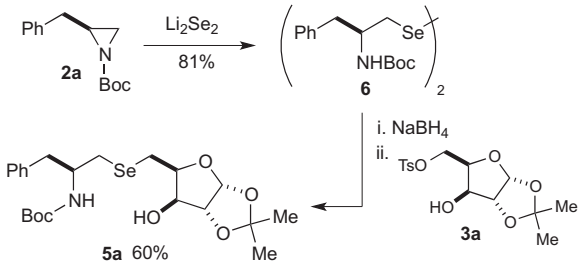
With both required starting materials in hands, we turned our attention to the synthesis of the selenium-linked neoglycoconjugates. We started our studies using furanose-derived diselenide **4a** as the nucleophile, combined with *N*-Boc aziridine **2a**, derived from the amino acid L-phenylalanine. The selenide nucleophile was generated in situ by reduction of the diselenide bond with $NaBH_4$, under our previously described conditions. The nucleophilic ring opening of the *N*-Boc aziridine occurred efficiently, delivering the corresponding *Se*–neoglycoconjugate **5a** in 78% yield (Scheme 3).

For comparison, we have also performed the reaction between the D-xylofuranoside tosylate **3a** and a diselenide possessing the amino group. The diselenide **6** was prepared by ring-opening of



Scheme 3. Synthesis of selenoglycoconjugate **5a**.

N-Boc aziridine **2a** with Li_2Se_2 in 81% yield. Reduction of the diselenide bond under usual conditions, followed by a substitution reaction of the tosylate group resulted in the product **5a** in 60% yield (Scheme 4).



Scheme 4. Reaction between tosylate **3a** and diselenide **6**.

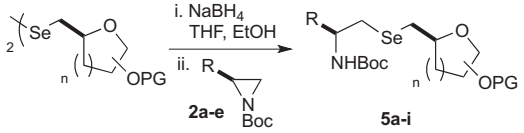
Comparing this result with the reaction shown in Scheme 3, it became clear that the best approach was the use of the sugar diselenide as the nucleophilic partner and the *N*-Boc aziridine as the electrophile, due to higher yield obtained. Therefore we decided to further expand the scope of the reaction between sugar-based diselenide and aziridines to a broader range of substrates in order to prepare a series of selenium-linked neoglycoconjugates. The scope of the reaction was investigated using sugar diselenides with different scaffolds and aziridines **2a**–**e** with varied substituents. The results of these studies are shown in Table 1.

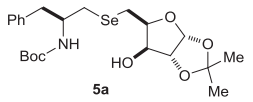
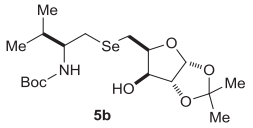
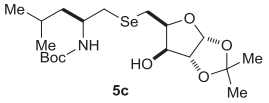
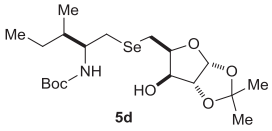
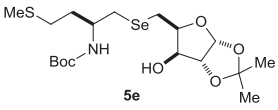
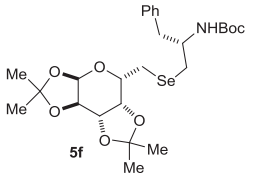
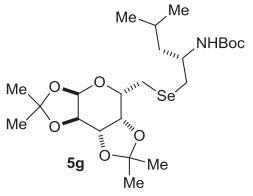
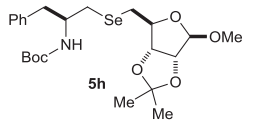
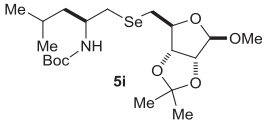
The ring opening reaction of the *N*-Boc aziridines proceeded under mild conditions and with complete regiocontrol, with exclusive attack of the selenium nucleophile at the less hindered carbon of the three membered ring.[21] In general, the products were isolated in moderate to good yields. Five different seleno-neoglycoconjugates **5a**–**e**, with the xylofuranose structure were prepared in yields ranging from 75 to 85% (entries 1–5). Moreover, changing the carbohydrate diselenide to the D-galactose derivative **4b** that contains a pyranoside structure resulted in the syntheses of seleno-neoglycoconjugates **5f** and **5g** in good yields (entries 6 and 7). Finally, the ribofuranose derivative **5h** was also prepared in 30% yield, starting with diselenide **4c** with the *N*-Boc aziridine derived from L-phenylalanine (entry 8). Surprisingly, reaction of the ribofuranose-derived selenium nucleophile with the leucine-derived aziridine did not afford the desired product **5i** (entry 9) and the starting materials were partially recovered alongside with decomposition by-products.

An analogous strategy was pursued for the synthesis of the non-glycosidic selenium-linked pseudodisaccharides **7**. The selenium sugar nucleophile was generated under conventional conditions, by the reduction of the diselenide bond in **4**, followed by nucleophilic displacement of a tosylate leaving group present in a second sugar unit **3** (Scheme 5).

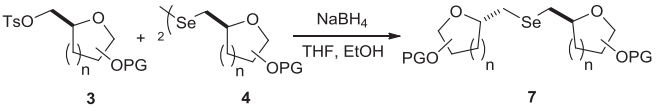
By this approach we were able to prepare selenium-containing pseudodisaccharides with different structural and stereochemical features (Fig. 2). For example, starting with sugar diselenide **4a**, with a xylofuranose backbone and reacting with tosylate **3c**, derived from D-ribose, resulted in the *Se*-pseudodisaccharide **7a** in 70% yield. The opposite combination of reactants (**4c**+**3a**), in order to achieve the same product resulted in 30% yield of compound **7a**. Combination of different scaffolds was also possible and reaction of

Table 1
Synthesis of seleno glycoconjugates **5a–i**



Entry[a]	Product	Yield (%)
1	 **5a**	78
2	 **5b**	83
3	 **5c**	75
4	 **5d**	78
5	 **5e**	85
6	 **5f**	62
7	 **5g**	50
8	 **5h**	30
9	 **5i**	NR

[a] Standard conditions: sugar diselenide **4** (0.3 mmol), $NaBH_4$ (0.75 mmol) and *N*-Boc aziridine (0.5 mmol). NR=no reaction.



Scheme 5. General approach for the synthesis of selenium-containing pseudodisaccharides.

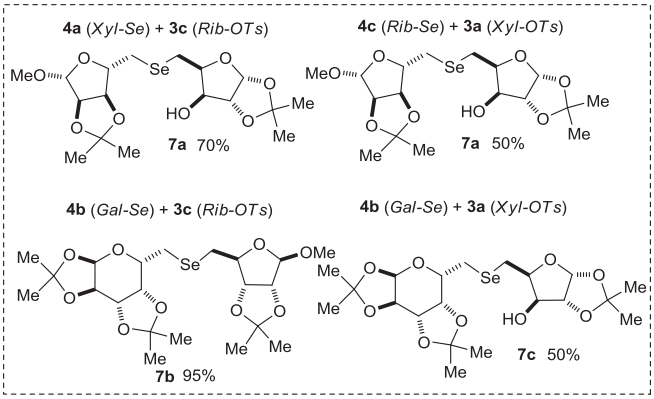


Fig. 2. Structures of selenium-containing pseudodisaccharides prepared.

the galactopyranose-derived diselenide **4b**, with ribo- and xylofuranose tosylates resulted in the corresponding products **7b** and **7c** in 95% and 50% yield, respectively. In an attempt to improve the yield for pseudodisaccharide **7c**, we generated the selenium nucleophile under different reaction conditions. Therefore, reductive cleavage was performed with $NaBH_4$ using DMF as the solvent[22] and the reaction was heated at 80 °C for 24 h. However the product was isolated in a similar 44% yield. Besides, the use of the galactopyranose tosylate **3b** as the electrophile and xylofuranose diselenide **4a** as the nucleophile source proved fruitless and the starting material were almost entirely recovered. This result is in line with our previous observation that tosylate **3b** is more resistant to nucleophilic attack with hindered nucleophiles, probably caused by the axial group at C-4.[17c]

It is worth noting that when the ribofuranose diselenide **4c** was used as the precursor of the selenium nucleophile, the yields were consistently lower for both neoglycoconjugates and pseudodisaccharides, in comparison with the yields obtained with the xylofuranose and galactopyranose derivatives. While at the present moment we still don't have a definitive explanation for this behaviour, a plausible reason might be the lower stability of the selenide anion under the reaction conditions. Further studies are needed to confirm this hypothesis. Conversely, the best electrophile for disaccharide synthesis was the tosylate **3c**, with the ribofuranose framework (Fig. 2).

3. Conclusions

In summary, we have described herein the synthesis of selenium-linked neoglycoconjugates and pseudodisaccharides. The approach further extends the scope of our methodology for the introduction of organoselenium moieties within the framework of various sugars, by this time allowing the synthesis of molecules with increased levels of complexity.

4. Experimental

4.1. General procedures

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with tetramethylsilane as internal standard. High resolution mass spectra were recorded on a Bruker Daltonics

Micro-TOF instrument in ESI-mode. Column chromatography was performed using Merck Silica Gel (230–400 mesh) following the methods described by Still.[23] Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapour, or acidic vanillin or phosphomolibdic acid. THF was dried over sodium benzophenone ketyl and distilled prior to use. DMF was dried over calcium hydride. All other solvents were used as purchased unless otherwise noted.

4.2. General procedure for the preparation of carbohydrate diselenides (4a–c)

Under argon atmosphere lithium diselenide was generated by reaction of elemental selenium (95 mg, 1.2 mmol) with lithium triethylborohydride (1.2 mL, 1.2 mmol–1 M solution in THF) at room temperature. The suspension was stirred for 20 min. After this time *t*-BuOH (0.2 mL) and THF (4 mL) were added at room temperature, followed by dropwise addition of a solution of the respective tosylate (0.5 mmol in 1 mL THF). After stirring for 24 h under reflux, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography eluting with a mixture of hexanes/ethyl acetate (80:20).

Analytical data for carbohydrate diselenides **4a** and **4b** were reported in our previous work.[17b,c]

*4.2.1. bis(Methyl 5-deoxy-2,3-O-isopropylidene-α-D-ribofuranos-5-yl) diselenide (**4c**).* Yellow oil. Yield: 82%; $[\alpha]_D^{20}$–122 (*c* 1.2, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=4.99 (s, 1H, H-1), 4.74 (d, *J*=5.4 Hz, 1H, H-2), 4.61 (d, *J*=6.0 Hz, 1H, H-4), 4.47–4.42 (m, 1H, H-3), 3.35 (s, 3H, OCH_3), 3.22–3.16 (m, 1H, H-5), 3.04–3.00 (m, 1H, H-5), 1.49 (s, 3H, CH_3); 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=112.4, 109.6, 86.8, 85.4, 83.3, 55.0, 32.9, 26.4, 25.0; HRMS-ESI: *m*/*z* calcd for $C_{18}H_{30}O_8Se_2$+Na: 557.0163; found: 557.0164.

4.3. General procedure for the preparation of seleno glycoconjugates 5

Under argon atmosphere, sodium borohydride (0.75 mmol) was added to a solution of the carbohydrate diselenide **4a–c** (0.30 mmol) in THF (3 mL). Ethanol (2 mL) was then dropwise added and the clear pale yellow solution formed was stirred at room temperature for 10 min. After this time a solution of the *N*-Boc aziridine **2** (0.5 mmol in 2 mL THF) was added dropwise. After stirring for 24 h under reflux, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography first eluting with hexanes and then with a mixture of hexanes/ethyl acetate (70:30).

*4.3.1. 5-Se-((S)-2-N-(tert-butoxycarbonyl)-3-phenylpropyl)-5-deoxy-1,2-O-isopropylidene-5-seleno-α-D-xylofuranose (**5a**).* Yellow oil. Yield: 78%; $[\alpha]_D^{20}$–31 (*c* 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.33–7.19 (m, 5H, Ar), 5.95 (d, *J*=3.6 Hz, 1H, H-1), 4.86 (bs, 1H, NH), 4.56 (d, *J*=3.7 Hz, 1H, H-2), 4.39–4.29 (m, 2H, H-3, H-4), 4.06–3.97 (m, 1H, NCH), 3.34 (bs, 1H, OH), 2.98–2.80 (m, 6H, 3× CH_2), 1.53 (s, 3H, CH_3), 1.42 (s, 9H, 3× CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.6, 137.3, 129.4, 128.6, 126.6, 111.6, 104.8, 85.5, 81.2, 79.9, 74.8, 52.3, 39.9, 30.1, 28.3, 26.8, 26.2, 22.0; HRMS-ESI: *m*/*z* calcd for $C_{22}H_{33}NO_6Se$+Na^+: 510.1365, found: 510.1365.

*4.3.2. 5-Se-((S)-2-N-(tert-butoxycarbonyl)-3-methylbutyl)-5-deoxy-1,2-O-isopropylidene-5-seleno-α-D-xylofuranose (**5b**).* Yellow oil. Yield: 83%; $[\alpha]_D^{20}$–13 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.94 (d, *J*=3.6 Hz, 1H, H-1), 4.71 (bs, 1H, NH), 4.56 (d, *J*=3.7 Hz, 1H, H-2), 4.39–4.30 (m, 2H, H-3, H-4), 3.66–3.53 (m, 1H, NCH), 3.28 (bs, 1H, OH), 3.00–2.75 (m, 4H, 2× CH_2), 1.97–1.84 (m, 1H, CH), 1.52 (s, 3H, CH_3), 1.45 (s, 9H, 3× CH_3), 1.32 (s, 3H, CH_3), 0.95 (d, *J*=6.6, 3H, CH_3), 0.88 (d, *J*=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=156.1, 111.6, 104.8, 85.4, 81.1, 79.7, 74.7, 56.3, 29.0, 28.4, 26.8, 26.2, 21.7, 19.8, 17.0; HRMS-ESI: *m*/*z* calcd for $C_{18}H_{33}NO_6Se$+Na^+: 462.1371, found: 462.1368.

*4.3.3. 5-Se-((S)-2-N-(tert-butoxycarbonyl)-4-methylpentyl)-5-deoxy-1,2-O-isopropylidene-5-seleno-α-D-xylofuranose (**5c**).* Colourless oil. Yield: 75%; $[\alpha]_D^{20}$–40 (*c* 1.2, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.94 (d, *J*=3.6 Hz, 1H, H-1), 4.70 (bs, 1H, NH), 4.63 (d, *J*=3.5 Hz, 1H, H-2), 4.36–4.32 (m, 2H, H-3, H-4), 3.61–3.57 (m, 1H, NCH), 3.44 (bs, 1H, OH), 2.97–2.75 (m, 4H, 2× CH_2), 1.93–1.87 (m, 1H, CH), 1.51 (s, 3H, CH_3), 1.44 (s, 9H, 3× CH_3), 1.31–1.24 (m, 5H, CH_2, CH_3), 0.94 (d, *J*=6.5 Hz, 3H, CH_3), 0.87 (d, *J*=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.8, 111.6, 104.9, 85.5, 81.5, 80.0, 74.4, 50.1, 43.4, 32.2, 28.3, 26.8, 26.2, 25.0, 23.3, 22.2, 21.8; HRMS-ESI: *m*/*z* calcd for $C_{19}H_{35}NO_6Se$+Na^+: 476.1522, found: 476.1519.

*4.3.4. 5-Se-((2S,3R)-2-N-(tert-butoxycarbonyl)-3-methylpentyl)-5-deoxy-1,2-O-isopropylidene-5-seleno-α-D-xylofuranose (**5d**).* Colourless oil. Yield: 78%; $[\alpha]_D^{20}$–30 (*c* 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.93 (d, *J*=3.6 Hz, 1H, H-1), 4.72 (bs, 1H, NH), 4.55 (d, *J*=3.6 Hz, 1H, H-2), 4.36–4.31 (m, 2H, H-3, H-4), 3.66–3.62 (m, 1H, NCH), 3.15 (bs, 1H, OH), 2.97–2.74 (m, 4H, 2× CH_2), 1.68–0.88 (m, 21H, 7× CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.2, 111.6, 104.8, 85.3, 81.5, 79.8, 74.6, 51.6, 43.4, 32.1, 28.4, 26.6, 26.2, 25.0, 21.8, 17.6, 13.3; HRMS-ESI: *m*/*z* calcd for $C_{19}H_{35}NO_6Se$+Na^+: 476.1522, found: 476.1519.

*4.3.5. 5-Se-((S)-2-N-(tert-butoxycarbonyl)-4-(methylthio)butyl)-5-deoxy-1,2-O-isopropylidene-5-seleno-α-D-xylofuranose (**5e**).* Colourless oil. Yield: 85%; $[\alpha]_D^{20}$–45 (*c* 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.94 (d, *J*=3.6 Hz, 1H, H-1), 4.70 (bs, 1H, NH), 4.63 (d, *J*=3.5 Hz, 1H, H-2), 4.36–4.32 (m, 2H, H-3, H-4), 3.61–3.57 (m, 1H, NCH), 3.44 (bs, 1H, OH), 2.98–2.52 (m, 6H, 3× CH_2), 2.11 (s, 3H, SCH_3), 1.96–1.92 (m, 2H, CH_2), 1.53–1.33 (m, 18H, 5× CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.8, 111.6, 104.8, 85.4, 81.1, 78.8, 74.8, 54.5, 35.5, 30.7, 30.1, 28.5, 26.8, 26.2, 22.0, 15.8. HRMS-ESI: *m*/*z* calcd for $C_{18}H_{33}NO_6Se$+Na^+: 494.1091, found: 494.1090.

*4.3.6. 6-Se-((S)-2-N-(tert-butoxycarbonyl)-3-phenylpropyl)-6-deoxy-1,2:3,4-di-O-isopropylidene-6-seleno-α-D-galactopy-ranose (**5f**).* Colourless oil. Yield: 62%; $[\alpha]_D^{20}$–37 (*c* 0.9, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.31–7.18 (m, 5H, Ar), 5.53 (d, *J*=4.8 Hz, 1H, H-1), 4.99 (bs, 1H, NH), 4.65–4.60 (m, 1H, H-3), 4.38 (dd, *J*=7.8 Hz, 1.8 Hz, 1H, H-4), 4.33–4.29 (m, 1H, H-2), 4.00 (dt, *J*=7.2 Hz, 1.8 Hz, 1H, H-5), 3.91–3.86 (m, 1H, NCH), 2.93–2.70 (m, 6H, 3× CH_2), 1.55 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.43 (s, 9H, 3× CH_3), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.1, 137.7, 129.4, 128.4, 126.4, 109.2, 108.6, 96.5, 79.2, 72.0, 71.9, 70.9, 70.4, 68.5, 67.7, 51.6, 40.5, 29.8, 28.3, 26.0, 25.9, 25.0, 24.8, 24.6, 24.4, 15.2; HRMS-ESI: *m*/*z* calcd for $C_{26}H_{39}NO_7Se$+Na^+: 580.1784, found: 580.1788.

*4.3.7. 6-Se-((S)-2-N-(tert-butoxycarbonyl)-4-methylpentyl)-6-deoxy-1.2:3,4-di-O-isopropylidene-6-seleno-α-D-galactopy-ranose (**5g**).* Yellow oil. Yield: 50%; $[\alpha]_D^{20}$–31 (*c* 1.3, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.53 (d, *J*=5.1 Hz, 1H, H-1), 4.73 (bs, 1H, NH), 4.61 (dd, *J*=7.8 Hz, 2.4 Hz, 1H, H-3), 4.33–4.29 (m, 3H, H-4, H-2, NCH),

3.90 (dt, J=7.2 Hz, 1.8 Hz, 1H, H-5), 2.88–2.70 (m, 6H, 3× CH_2), 1.68–1.61 (m, 1H, CH), 1.54 (s, 6H, 2× CH_3), 1.44 (s, 9H, 3× CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.91 (d, J=6.3 Hz, 3H, CH_3), 0.90 (d, J=6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.3, 109.2, 108.5, 96.6, 79.0, 71.9, 70.9, 70.4, 68.4, 48.4, 43.9, 31.7, 28.3, 26.0, 25.9, 24.8, 24.4, 22.9, 22.3; HRMS-ESI: m/z calcd for $C_{23}H_{41}NO_7Se+Na^+$: 546.1940, found: 546.1940.

*4.3.8. Methyl 5-Se-((S)-2-N-(tert-butoxycarbonyl)-3-phenylpro-pyl)-5-deoxy-2,3-O-isopropylidene-5-seleno-β-D-ribofuranose (**5h**).* White solid. Yield: 30%; mp 64 °C; $[\alpha]_D^{20}$–45 (c 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.32–7.18 (m, 5H, Ar), 4.98 (d, J=4.2 Hz, 1H, H-1), 4.74 (d, J=5.1 Hz, 1H, H-2), 4.67–4.59 (m, 2H, H-4, H-3), 3.35 (s, 3H, OCH_3), 3.22–3.16 (m, 1H, H-5), 3.04–2.97 (m, 1H, H-5), 2.89–2.80 (m, 2H, CH_2), 2.74–2.55 (m, 2H, CH_2), 1.48 (s, 3H, CH_3), 1.41 (s, 9H, 3× CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=155.1, 137.5, 129.4, 128.5, 126.6, 112.4, 109.6, 86.9, 86.7, 85.5, 85.4, 83.7, 83.3, 55.0, 33.0, 29.7, 29.3, 28.3, 26.5, 26.4, 25.0. HRMS-ESI: m/z calcd for $C_{23}H_{35}NO_6Se+Na^+$: 524.1527, found: 524.1515.

4.4. General procedure for the preparation of seleno disaccharides 7

Under argon atmosphere, sodium borohydride (0.75 mmol) was added to a solution of the appropriate carbohydrate diselenide **4** (0.30 mmol) in THF (3 mL). Ethanol (2 mL) was then dropwise added and the clear solution formed was stirred at room temperature for 10 min. After this time a solution of the tosylate **3** (0.50 mmol in 2 mL THF) was slowly added. After stirring for 24 h under reflux, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography first eluting with hexanes and then with a mixture of hexanes/ethyl acetate (70:30).

*4.4.1. (5-Deoxy-1,2-O-isopropylidene-α-D-xylofuranosyd-5-yl) (methyl 5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl) selenide (**7a**).* White solid. Yield: 70%; mp 122 °C; $[\alpha]_D^{20}$–64 (c 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.92 (d, J=3.7 Hz, 1H, H-1^{xyl}), 4.99 (s, 1H, H-1^{Rib}), 4.72 (d, J=5.9 Hz, 1H, H-2^{Rib}), 4.61 (d, J=5.9 Hz, 1H, H-4^{Rib}), 4.53 (d, J=3.7 Hz, 1H, H-2^{xyl}), 4.38–4.28 (m, 3H, H-3^{Rib}, H-3^{xyl}, H-4^{xyl}), 3.35 (s, 3H, OCH_3), 3.02–2.92 (m, 2H, H-5^{Rib}), 2.84–2.76 (m, 1H, H-5^{xyl}), 2.68–2.60 (m, 1H, H-5^{xyl}), 1.50 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=129.8, 112.6, 111.7, 109.5, 104.9, 86.6, 85.3, 83.3, 80.4, 74.9, 55.1, 27.9, 26.8, 26.5, 26.2, 25.0, 19.9; HRMS-ESI: m/z calcd for $C_{17}H_{28}O_8Se+Na^+$: 463.0842, found: 463.0849.

*4.4.2. (6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyrano-sid-6-yl) (methyl 5-deoxy-2,3-O-isopropylidene-β-D-ribofuranos-5-yl) selenide (**7b**).* Yellow oil. Yield: 95%; $[\alpha]_D^{20}$–71 (c 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.53 (d, J=5.1 Hz, 1H, H-1^{Gal}), 4.97 (s, 1H, H-1^{Rib}), 4.72 (d, J=6.0 Hz, 1H, H-2^{Rib}), 4.61 (dd, J=10.2 Hz, 2.4 Hz, 1H, H-3^{Gal}), 4.61 (s, 1H, H-4^{Rib}), 4.36 (dd, J=7.8 Hz, 1.5 Hz, 1H, H-4^{Gal}), 4.31–4.29 (m, 1H, H-2^{Gal}), 3.91 (dt, J=6.9 Hz, 1.5 Hz, 1H, H-5^{Gal}), 3.34 (s, 3H, OCH_3), 2.94–2.66 (m, 5H, CH_2^{Gal}, CH_2^{Rib}), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=112.2, 109.5, 109.1, 108.5, 96.6, 86.5, 85.3, 83.5, 71.6, 70.9, 70.4, 68.5, 54.8, 29.6, 28.0, 26.4, 26.0, 25.9, 24.9, 24.3, 23.2; HRMS-ESI: m/z calcd for $C_{21}H_{34}O_9Se+Na^+$: 533.1260, found: 533.1260.

*4.4.3. (6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyrano-sid-6-yl)(5-deoxy-1,2-O-isopropylidene-α-D-xylofuranosyd-5-yl) selenide (**7c**).* Colourless oil. Yield: 50%; $[\alpha]_D^{20}$–87 (c 1.0, AcOEt); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.92 (d, J=3.6 Hz, 1H, H-1^{xyl}), 5.53 (d, J=4.8 Hz, 1H, H-1^{Gal}), 4.62 (dd, J=7.8 Hz, 2.4 Hz, 1H, H-3^{Gal}), 4.56 (d, J=3.6 Hz, 1H, H-2^{xyl}), 4.35–4.26 (m, 4H, H-3^{xyl}, H-4^{xyl}, H-2^{Gal}, H-4^{Gal}), 3.98–3.93 (m, 1H, H-5^{Gal}), 3.07 (dd, J=11.9 Hz, 4.5 Hz, 1H), 2.97–2.79 (m, 4H, CH_2^{Gal}, CH_2^{xyl}), 1.55 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.34 (s, 6H, 2× CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ=111.5, 109.4, 108.9, 104.8, 96.4, 85.0, 80.5, 74.6, 72.3, 70.9, 70.5, 69.7, 26.7, 26.1, 26.0, 25.9, 24.9, 24.4, 24.0, 21.2; HRMS-ESI: m/z calcd for $C_{20}H_{32}O_9Se+Na^+$: 519.1104; found: 519.1109.

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