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Synthesis of non-glycosidically linked selenoether pseudodisaccharides

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ABSTRACT

Non-glycosidically linked disaccharide mimetics with a selenoether functionality linking the two monosaccharide residues have been synthesised. Protected Glc(*Se*3–3)Glc, Glc(*Se*3–6)Glc and Glc(*Se*3–6)Man structures were obtained. Selenium was introduced by displacement of carbohydrate sulfonates with a selenobenzoate anion. Conversion into diselenides by methanolysis of the benzoate and aerial oxidation was followed by reduction of the diselenides to selenolates, and in situ displacement of a second carbohydrate sulfonate in an S_N2 reaction to give selenoethers. Glc(*Se*3–3)Glc and Glc(*Se*3–6)Glc were also obtained in deprotected form.

Hydrolytically stable mimetics of disaccharides are valuable to researchers studying the biological functions of oligo- and polysaccharides, viz. glycobiology.[1] Such stable mimetics may act as enzyme inhibitors or ligands for lectins, and well-studied examples include C-glycosides,[1a] carbasugars[1b] and thiooligosaccharides.[1c] The synthesis of some selenodisaccharides has also recently been reported.[2]

We have begun a research program into the synthesis of pseudodisaccharides, where two monosaccharide units are connected by a formal condensation without involving the anomeric centre (Fig. 1).[3] We have reported some methods for the synthesis of ethers,[4] thioethers,[5] and secondary amines[6] of this type. The presence of a single inter-residue bridging atom means that the resulting pseudodisaccharides are isosteric (sharing the same ring-skeletal arrangement, true for primary–*sec* and *sec*–*sec* linked systems)[7] and potentially bioisosteric with natural disaccharides (i.e., O-glycosides).[8]

Some motivation to synthesise selenoether pseudodisaccharides as biological tools to investigate protein–carbohydrate-binding may be summarised as follows: the bond lengths and bond angles in a selenoether are not expected to be identical to those in an ether or thioether,[9] meaning that the relative orientation of the two monosaccharide residues in space will differ between ethers, thioethers, and selenoethers. The flexibility of C–Se bonds may not be the same as for C–O or C–S bonds, and the hydrogen-bonding ability of a selenoether will not be the same as for an ether or thioether. These differences increase the variety of structures available from two monosaccharide skeletons, which may offer some advantage when studying carbohydrate–protein interactions. Also, the presence of a heavy selenium atom may be beneficial in X-ray crystallographic studies of carbohydrate-binding proteins in complexes with selenium-containing ligands.[10]

We planned to investigate routes to selenoether pseudodisaccharides based on our experience with thioethers,[5] i.e., using nucleophilic selenium:[11] introduction of selenium by displacement of a carbohydrate sulfonate by a selenocarboxylate nucleophile, cleavage of the carboxylate to reveal a selenol and displacement of a second carbohydrate sulfonate would give the selenoether. In fact, we had to modify this approach to obtain optimised coupling results. We were interested in investigating the behaviour of derivatives of primary (C-6) and secondary (C-3) alcohols. The first results from our successful route are described in this Letter.

Displacement of primary carbohydrate 6-*O*-mesylates **1** and **2** by potassium selenobenzoate gave the selenobenzoates **4** and **5**

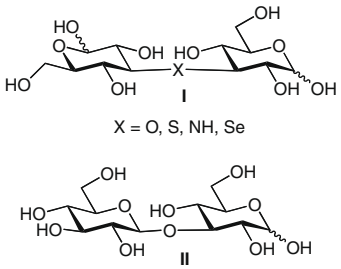

Figure 1. Structures of representative non-glycosidically-linked (3–3)-pseudodisaccharides **I** and comparison with a disaccharide **II**.

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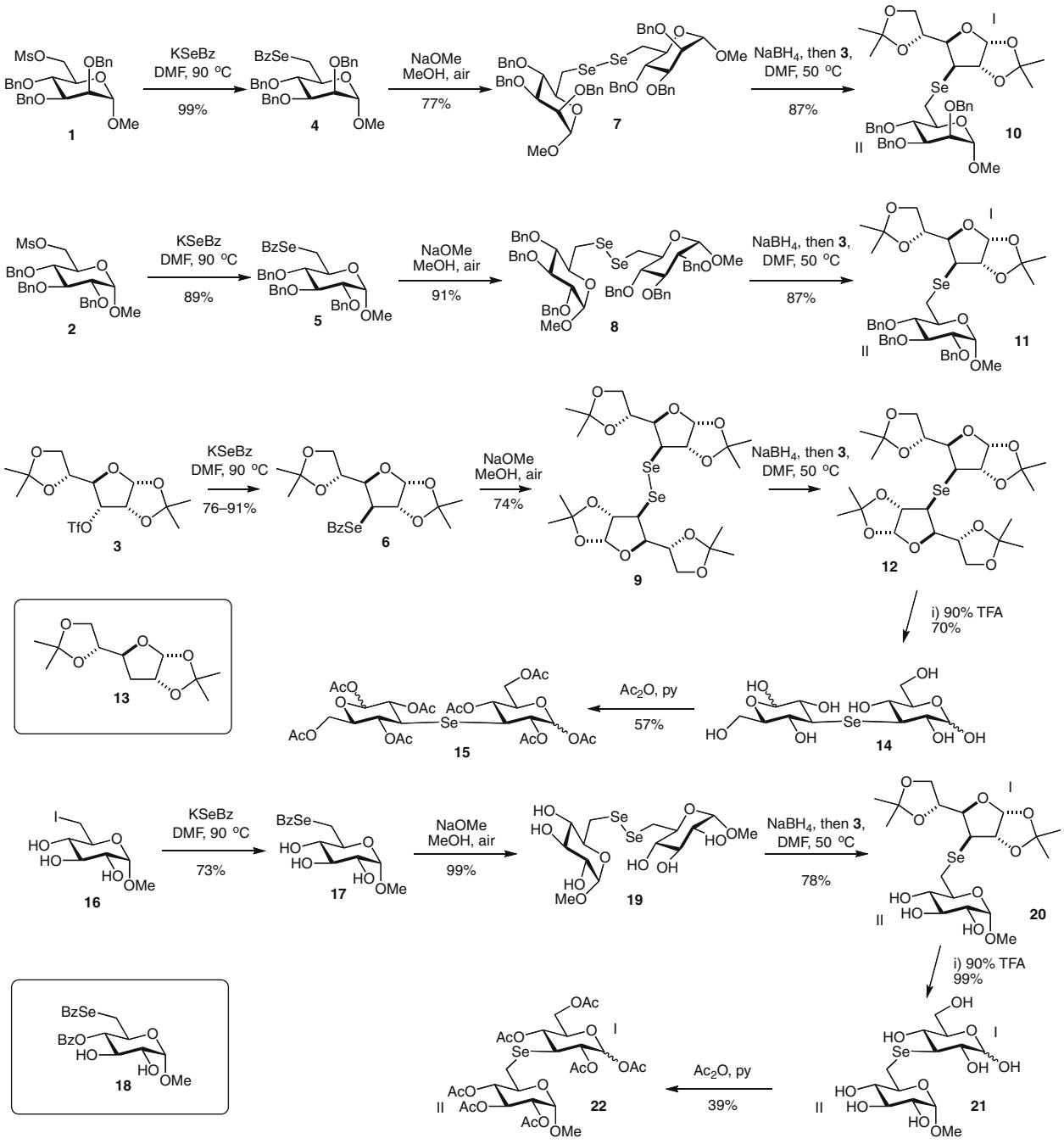

Scheme 1. The labels [I] and [II] are used to distinguish the monosaccharide components of the unsymmetrical pseudodisaccharides in the NMR assignment data (see Supplementary data).

in good yields (Scheme 1). Displacement of the secondary carbohydrate *allo* triflate **3** with the same reagent gave a good yield of the selenobenzoate derivative with inversion of configuration at C-3, i.e., the *gluco* derivative **6**. Potassium selenobenzoate was obtained either by methanolysis[12a] of dibenzoyl selenide[12b] or as a 1:1 mixture with selenium by methanolysis[13a] of dibenzoyl diselenide[13b] as described. No difference was found in the performance of the reagent prepared in these two ways in the displacement reactions. The potassium selenobenzoate decomposes on standing, even after a few weeks in a freezer. We found it best to prepare it freshly from the dibenzoyl selenide or dibenzoyl diselenide, both of which are crystalline solids that may be stored in a freezer without appreciable decomposition after several months.

The benzoyl group could be removed from selenium by treatment with sodium methoxide, but after aqueous work-up, only the diselenides **7–9** were observed. Presumably these were formed by aerial oxidation of the selenols, either in the reaction vessel or during work-up. As these diselenides would be useless as nucleophiles in coupling reactions, we tried an alternative approach based on deliberate formation of the diselenides followed by reduction and in situ alkylation.

The selenobenzoates **4–6** were converted into the diselenides **7–9** in good yield by treatment with sodium methoxide in methanol under air. The diselenides **7–9** were reductively cleaved with sodium borohydride in DMF,[14] and addition of carbohydrate sulfonate **3** to the reducing selenolate solutions resulted in formation of

the selenoethers **10–12** in excellent yield, using almost stoichiometric quantities of the two carbohydrate reaction components, i.e., 1.2–1.3 equiv of triflate with respect to selenolate. The coupling reaction appears to work well for the synthesis of primary–*sec* and one *sec*–*sec* linked systems. One by-product from the reaction was the reduced compound **13**,[15] which was seen in all cases. To investigate the source of this compound, we treated separately the triflate **3** and selenoether **11** with sodium borohydride in DMF at 50 °C. The triflate **3** gave significant amounts of the reduced compound **13** after 3 h,[16] whereas the selenoether **11** was not reduced to **13** under the same conditions (the ^{1}H NMR spectrum of the crude reaction product showed only clean starting material and no trace of **13**). Hence the formation of 3-deoxysugar **13** during the selenoetherification reactions is presumably due to the action of borohydride on the 3-triflate **3**, and not due to reduction of the C–Se bond in the selenoether products.

For the *sec*–*sec* linked compound **12**, this reduced compound **13** was inseparable from the pseudodisaccharide product. Removal of the acetonide protection from **12** gave the free selenoether pseudodisaccharide **14**, which could be purified by column chromatography and which was also characterized as its octaacetate **15**.

Attempted deprotection of **10** and **11** by treatment with sodium in liquid ammonia to cleave the benzyl ethers failed. Even when quenching after very short reaction times (ca. 1 min) at −78 °C, we found that the starting material had undergone comprehensive decomposition to give none of the required debenzylated product. The C–Se bonds are presumably susceptible to reduction under these conditions.

In a second approach to an unprotected Glc(*Se*3–6)Glc derivative, we attempted a synthesis without protection on the glucose C-6-modified fragment. Hence the 6-deoxy-6-iodosugar **16**, available in one step by Garegg iodination[17a] of methyl α-glucoside following Madsen's procedure,[17b] was treated with potassium selenobenzoate to give the 6-deoxy-6-selenoglucose derivative **17**. When excess reagent was used, the 4-*O*-benzoate **18** was formed as a by-product (1.2 equiv KSeBz; **17**, 70%; **18**, 21%) or as the major product (3 equiv KSeBz; **18**, 59%). Treatment of the selenobenzoate **17** with sodium methoxide as before gave the diselenide **19**, and reduction followed by addition of triflate **3** to the reaction vessel gave the coupled product **20**. Removal of the acetonides to give the unprotected pseudodisaccharide **21** was straightforward, and this selenoether was characterised as its heptaacetate **22**.

Non-glycosidically linked selenoether-bridged pseudodisaccharides may be accessed in good yield by reduction of carbohydrate diselenides in DMF to give selenolates that can displace a carbohydrate triflate in situ to give selenoethers. The behaviour of the selenoetherification reactions is similar to the related thioetherification reactions: primary–*sec* and *sec*–*sec* linked structures are obtained in the coupling reactions without difficulty, unlike the preparation of related N-linked structures, where the formation of linkages to secondary centres is difficult.[6] An unprotected selenoether **21** was stable at rt and open to the air for weeks without appreciable degradation. The deprotection of benzyl ethers is problematic, but (*Se*3–6)-linked structures may be formed using a more minimalist protecting group strategy.

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Supplementary data

Supplementary data (Experimental details for all described reactions, including conversion of the respective alcohols[18–20] into the sulfonates **1**–**3**, characterisation data for new compounds, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.064.

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