# Exploring the Syntheses of Novel Glycomimetics. Carbohydrate Derivatives with *Se*-*S*- or *Se*-*Se*- Glycosidic Linkages

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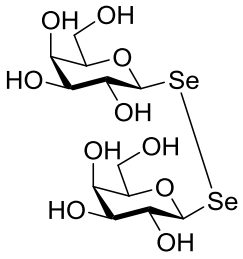
## Abstract

A convenient route to *Se*-*S*-glycoside derivatives was developed using glycosyl isoselenuronium salts as glycosylselenenyl transfer reagents toward thiols. Aliphatic and aromatic thiols were found to react in the presence of *N*,*N*-diisopropylethylamine as a base and furnished alkyl- or aryl glycosylselenenylsulfide derivatives. *S*-glycosylselenenyl-cysteines were obtained similarly via reactions with *O*,*N*-protected cysteine. Reactions with monosaccharide thiols provided disaccharide mimics featuring *Se*-*S*- interglycosidic bonds. Further disaccharide mimics with *Se*-*Se* interglycosidic linkage were obtained from the starting isoselenuronium salts via reactions with protected monosaccharide derivatives bearing selenol groups in 6- or 4-position. The novel glycomimetics are expected to open new perspectives in biological activities and/or mechanistic studies due, i.a., to the rather uncommon *Se*-*S*- or *Se*-*Se* bonds incorporated into a carbohydrate framework.

## Introduction

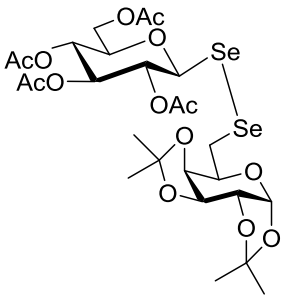
It has been known for some time that synthetic sugar derivatives containing interglycosidic disulfide linkages [1-5] are active in physiologically relevant interactions such as binding to lectins[6-8], enzyme inhibition[9] or acting against human tumor cell lines [8, 10] We have recently found that molecules characterized by the attachment of one or more monosaccharide sugars by disulfide linkages to an aromatic core display remarkable activities against *Trypanosoma cruzi* the etiologic agent of Chagas disease.[11]

Being close analogs of the disulfides, *S-Se* or *Se-Se* derivatives are expected to bear biological activities similar or improved as their *S-S* congeners based on comparison of the physicochemical properties of selenium and sulfur.[12]. Organic symmetrical diselenides were found to display hepatoprotective or antitumour activities presumably via interference in oxidative stress processes.[13] We have recently found that selenoglycosides, including di-β-D-galactopyranosyl-diselenide, **1**, can bind to lectins and exert inhibitory activities on lectin binding to human tumor cell lines.[8] Binding of di-β-D-GlcNAc-diselenide to wheat germ agglutinin including detection by NMR in a plasma environment has also been reported.[14]




**1**

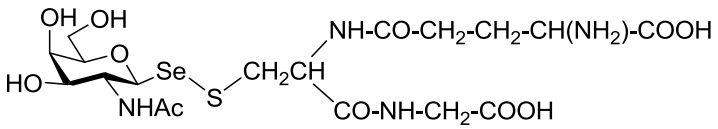
All these structures are symmetric diselenides, i.e., of the Glyc-*Se*-*Se*-Glyc type (where Glyc is protected or unprotected monosaccharide), the *Se*-*Se*-bond serving as a three-bond glycosidic linkage[15] between two monosaccharide units. *Non*symmetrical diglycosyl diselenides, i.e., of the Glyc1-*Se*-*Se*-Glyc2 type, have not been known to date, to the best of our knowledge, with one virtual exception: compound **2** was hypothesized as a side product in a selenoglycosylation reaction; isolation and/or physical characterization have not been reported, however.[16] In the sequel we shall report the synthesis of **2** along with other similar structures.




**2**

Molecules containing S-Se bonds were, apparently, first obtained by Kice & Lee in 1978 through coupling of seleninic acids with thiols and the mechanism of this redox reaction was investigated in detail.[17, 18] Selenenylsulfides are formed in exchange reactions of selenols with disulfides or, vice versa, of thiols with diselenides.[19] Similar reactions take place in selenoenzymes, such as MsrB1[20] or mammalian thioredoxin reductase (TrxR),[21] between contiguous cysteine/Se-cysteine residues.[22] A phenylselenenyl-1-thio-mannopyranoside derivative, apparently the first carbohydrate structure incorporating the S-Se linkage, was observed as a side product by Johnston & Pinto.[23] *N*-Boc-cysteine methyl ester reacted quickly with a glucose 6-seleninic acid derivative to furnish a S-Se-linked sugar-amino acid product in good yield.[24] A phenylselenenyl-1-thio-galcatopyranoside was obtained in an, essentially, thiol-diselenide exchange reaction using thiouronium salt as a thiol precursor.[25] Synthesis of a disaccharide containing a S-Se interglycosidic connection was reported by Pinto et al. in 2005.[26] Glycosyl phenylselenenylsulfides derived from various mono- and oligosaccharides were found to be useful in controlled glycosylation of proteins via generation of disulfide linkages between the reactants[27]. Glycosyl halides react with diphenyl diselenides in the presence of tetrathiomolybdates to furnish carbohydrate derivatives with S-Se bonds.[28]

The discovery of "hepatic Se metabolite A"[29] (**3)** the first natural representative of a *Se*-*S* sugar, in rat and human urine gave particular emphasis to this rare structural motif. Note that this derivative features a sugar-*Se*-*S*-R connection unlike the "inverted" sugar-*S*-*Se*-R structures in most of the examples cited.




**3**

A chemical synthesis of **3** has recently been published by Davis et al.[30] by taking advantage of a thiol-diselenide exchange reaction.

## Results and discussion

Glycosyl thiols, conveniently prepared by hydrolyzing glycosyl-isothiuronium salts,[31] are common starting materials to obtain 1-thiosugar derivatives such as thioglycosides.[15] It has been known for some time, however, that the isothiuronium salts themselves can act as glycosylsulfenyl donors in such reactions thus obviating the step of isolating glycosyl thiols. Syntheses of thioglycosides[32-35], glycosyl alkyl disulfides[36] and a *S*-*Se*-bond-containing selenophenyl thioglycoside[25] have been reported using this "direct" approach.

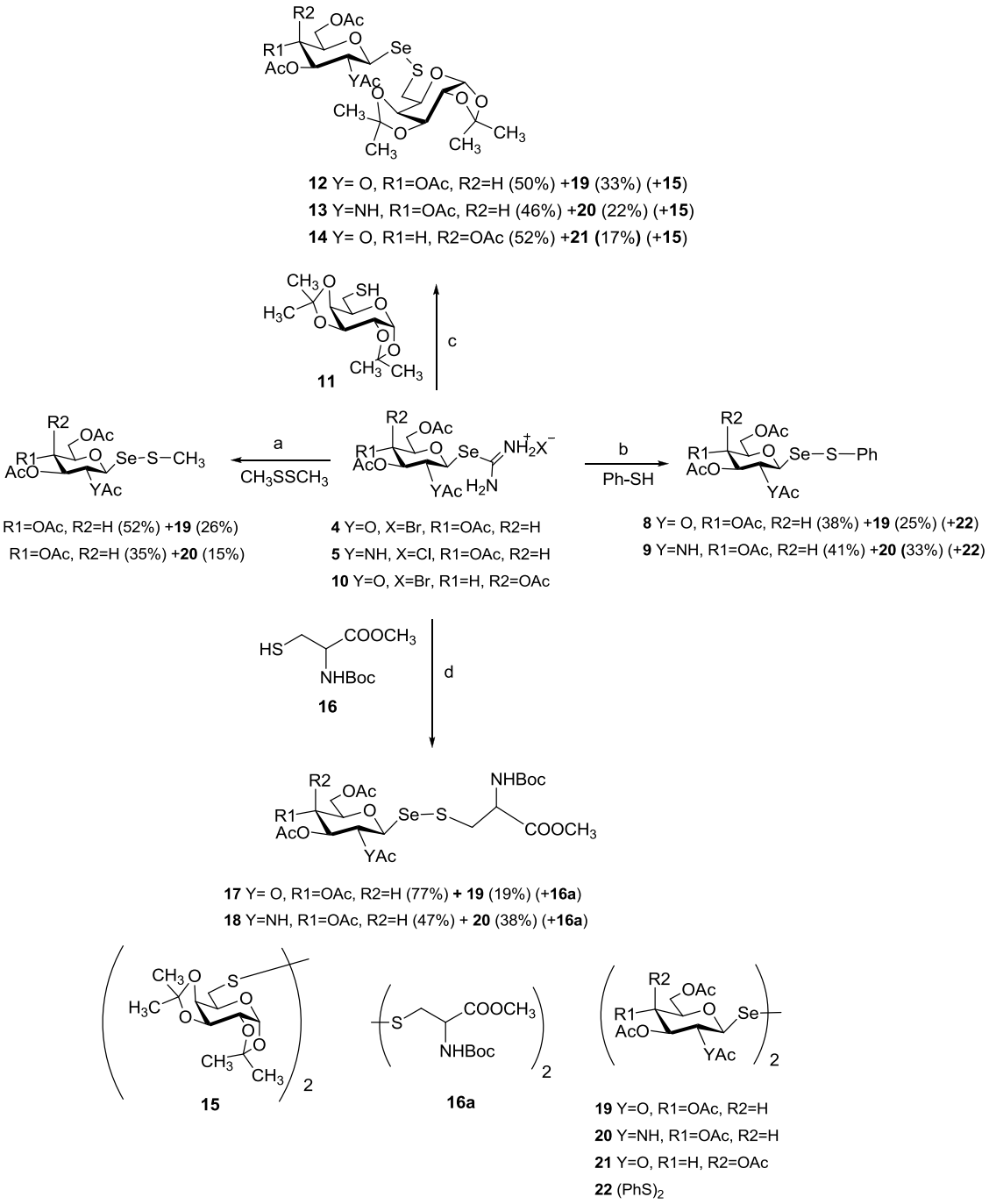
Glycosyl selenols, unlike glycosyl thiols, are much more sensitive toward oxidation and, therefore, cannot be isolated in practice per se.[37] Glycosylisoselenuronium salts, on the other hand, can function as masked selenols and serve as convenient glycosylselenenyl transfer reagents in reactions resulting in the formation of alkyl- and aryl selenoglycosides (Glyc-Se-R) or diglycosyl selenides (Glyc1-Se-Glyc2) as we have recently reported.[38] We have envisioned that these reagents might react with thiols or selenol precursors resulting in the formation of glycosyl derivatives with *Se*-*S* or *Se*-*Se*- glycosidic bonds.

Indeed, we have observed the formation of alkyl- or aryl glycosylselenenylsulfides when dimethyl disulfide or thiophenol were reacted with glycosylisoselenuronium salts in 1:1 molar ratio in concentrated solutions (ca. 0.15-0.20 M) in acetonitrile in the presence 1.1 eq. triethylamine (TEA) at room temperature. Thus, glycosylselenenylsulfides **6, 7, 8** and **9** were obtained from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl *iso*selenuronium bromide **4**[37] or 2-acetamido-2-deoxy-3,4,6,-tri-*O*-acetyl-β-D-glucopyranosyl *iso*selenuronium chloride **5**[38] in poor to moderate yields because of side reactions (see below).

Similarly, reactions of **4** , **5** or 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl *iso*selenuronium bromide **10**[8, 16] with the sugar thiol 1,2:3,4-di-*O*-isopropylidene-6-thio-α-D galactopyranose, **11**[39, 40] furnished *Se*-*S*-linked disaccharides **12, 13** and **14,** respectively**.** Protected cysteine **16** provided glycosylated cysteine derivatives **17** and **18** in analogous reactions.

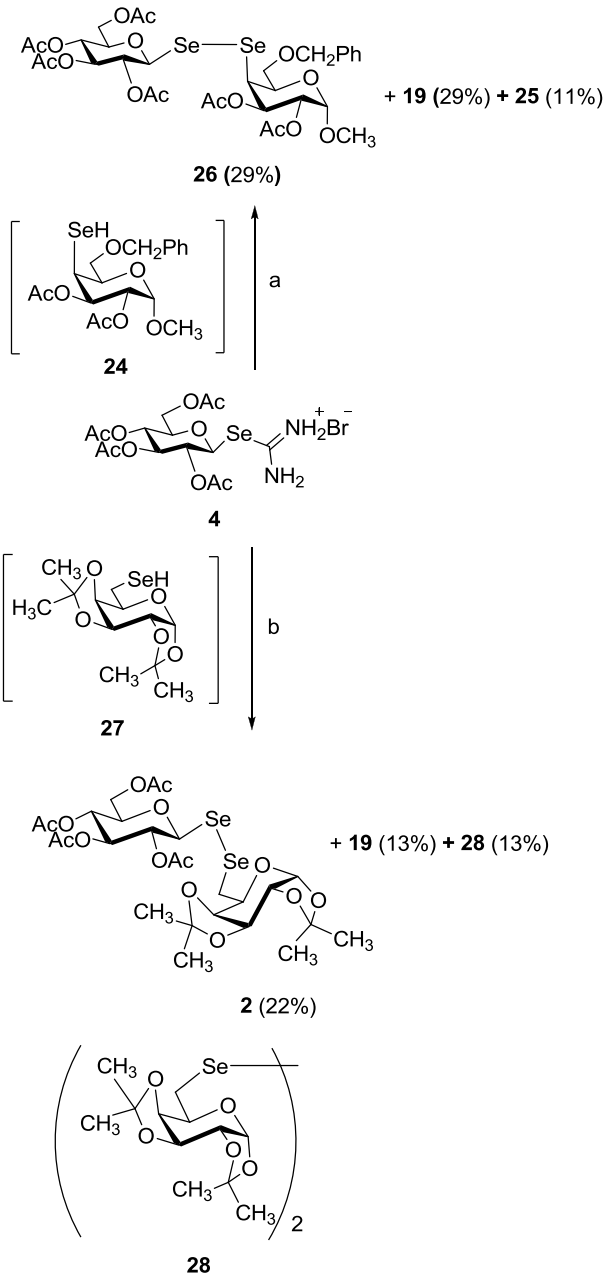
Principal side products in these reactions were symmetric diglycosyl diselenides **19**[37], **20** and **21**[8, 16] formed from the *iso*selenuronium salts. Oxidation of the starting thiols into the corresponding symmetric disulfides was also observed as an additional side reaction. Formation of these side products could not be suppressed, even diminished, by running the reactions in oxygen-free conditions i.e., under argon atmosphere. We have found, however, that performing the reactions in dilute (ca. 3-4 mM) solutions in MeCN with the thiol

components in large excess (5 mol with respect to the *iso*selenuronium salts) and TEA replaced by *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base), also 5 mol in excess, yields of the desired glycosylselenenylsulfides were significantly increased at the expense of the symmetric diselenide side products (see Supporting Information and Scheme 1).




**Scheme 1**. Syntheses of derivatives with glycosyl-*Se*-*S* linkages. *Reagents and conditions*: (a) DIPEA, MeCN, rt, 1.5h; (b) DIPEA, MeCN, rt, 2h; (c) DIPEA, MeCN, rt, 3h; (d) DIPEA, MeCN, rt, 2h. Yields are as indicated.

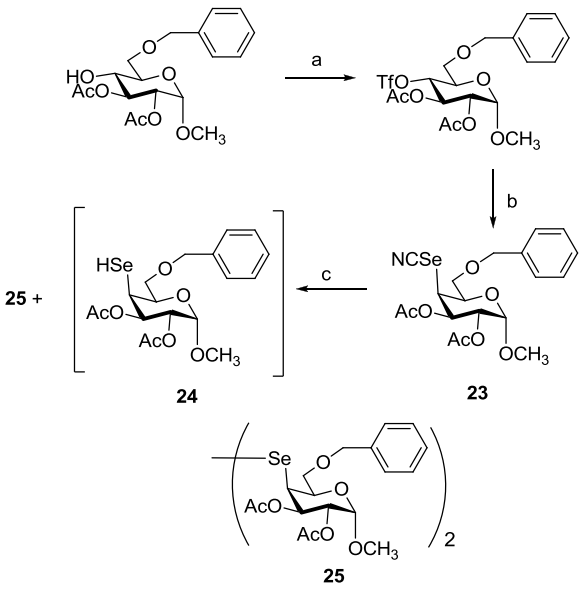
As a further extension to exploit the synthetic potential of glycosyl isoselenuronium salts, 1,4- and 1,6-linked diglycosyl diselenides (**26** and **2,** respectively) were prepared through reactions with sugar selenols or selenol precursors as follow (Scheme 2).




**Scheme 2**. Syntheses of *Se-Se* linked disaccharides. *Reagents and conditions*: (a), (b) $Et_3N$, MeCN, rt, 1h; Yields are as indicated.

The 4-selenogalactose derivative **24** needed for the synthesis of the 1,4-diglycosyl diselenide **26**, was obtained, starting from methyl α-D-glucopyranoside, in analogy with the reaction sequence described for the methyl 2,3,6 tri-O-benzoyl-4-seleno-α-D-

glucopyranoside.[41] The free 4-OH group of methyl 2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranoside[42] was treated with triflic anhydride/pyridine and the 4-triflate directly converted, without isolation, into the 4-selenocyanate **23** by treatment with KSeCN. Reduction of **23** with $NaBH_4$ results in the formation in situ of the 4-selenol **24** which gets oxidized into the symmetric diselenide **25** upon attempted isolation (Scheme 3).




**Scheme 3**. Synthesis of **24**. *Reagents and conditions*: (a) $Tf_2O$, Py / $CH_2Cl_2$, −30°C to rt, 0.5h; (b) KSeCN, DMF, 50°C, 3h, 15% over two steps; (c) $NaBH_4$, EtOH / THF, 0°C to rt, 1h. **24** was utilized without isolation, see Scheme 2.

Therefore **24** was directly reacted with **4** to furnish the 1,4-diglycosyl diselenide **26** in moderate yield. Symmetric diselenides **19** and 4,4'-diselenobis(methyl 4-deoxy-2,3-di-*O*-acetyl- 6-*O*-benzyl-α-D-galactopyranoside) **25** were isolated as byproducts in this reaction (Scheme 3 & Experimental). The 1,6-diglycosyl diselenide **2** was obtained by reacting **4** with in situ generated 6-selenogalactose derivative **27**[43]. Complete conversion could not be achieved and formation of symmetrical diselenides **28**[43, 44] and **19**[37] as byproducts was observed (Scheme 2, Supporting Information).

The structures of three representative disaccharides featuring *Se-S* (**12**) or *Se-Se* (**2** and **26**) interglycosidic linkages have been confirmed by single crystal X-ray diffraction studies as disclosed below.

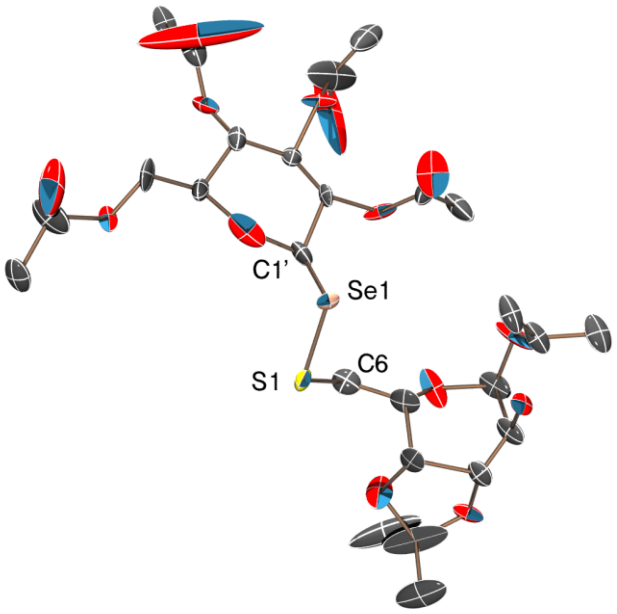



**Fig. 1**
ORTEP view of **12** at 50% probability level with partial numbering scheme. Hydrogen atoms are omitted for clarity. Selected bond length data: (Å) S1—Se1 2.124(3), C1'—Se1 1.774(14), C6—S1 1.830(14), C1'—C2' 1.518(17).

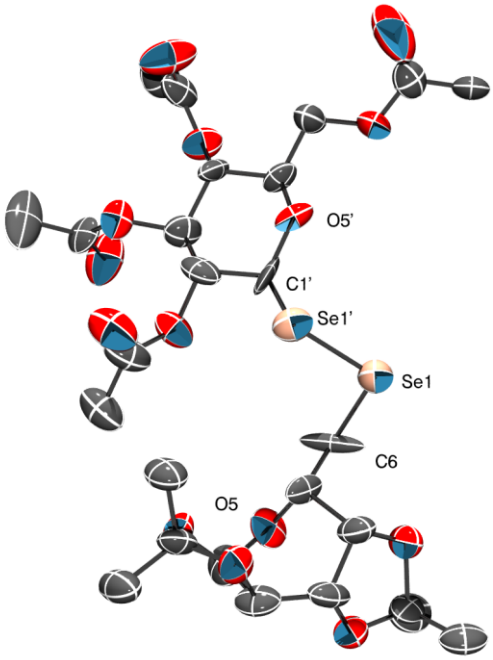



**Fig. 2**
ORTEP view of **2** at 50% probability level with partial numbering scheme. Hydrogen atoms are omitted for clarity. Selected bond length data (Å): Se1—Se1' 2.303(3), C1'—Se1' 1.94(2), C6—Se1 1.97(2).

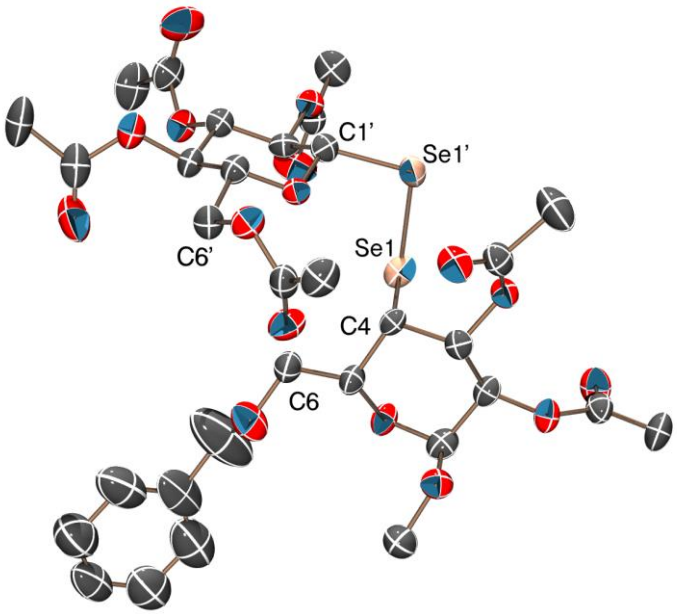



**Fig. 3**
ORTEP view of **26** at 30% probability level with partial numbering scheme. Hydrogen atoms and solvent benzene molecules are omitted for clarity. Selected bond length data (Å): Se1—Se1' 2.3062(16), C1'—Se1' 1.949(9), C4—Se1 1.980(8).

Search in the Cambridge Structural Database (Ver. 5.36 Update May, 2015.)[45] resulted in 360 hits for *Se*-*Se* bond and 27 hits for *S*-*Se* bond. This latter small set of structures does not allow detailed comparisons but in our case the *S*-*Se* bond (*S1—Se1*) length is 2.124(3) Å, somewhat shorter than the average (2.22(4) Å) of the 27 structures. Narrowing the search for glycopyranose derivatives revealed no hits for C1-S-S-C6, C1-S-Se-C6, C6-*S*-*Se*-C1, or C1-*Se*-*S*-C6 isomers. In this way structure **12** is the first representative of a disaccharide featuring an 1,6-selenenylsulfide interglycosidic linkage characterized by single crystal X-ray diffraction. In this structure the C1-*Se*-*S*-C6 torsion angle is + 66$^{o}$ which is lower than values for comparable *S*-*S* or *Se*-*Se* structures (see Supplementary data, Table S1). In the structures listed in Table S1 the respective torsion angles are in the range of +/− 80-96$^{o}$. In spatially nonrestricted structures such as dimethyldisulfane this torsion angle is 86$^{o}$ while for dimethyldiselenane it is 84.7$^{o}$ These data indicate that electronic and steric effects significantly distort the geometry of the selenenosulfide bridge whereas those of diselenides are in the expected range (-82.8 and -82.6 for **26** and **2,** respectively). It is of note therefore that, while **2** and **12** are quasi isosteric structures (differing only by the replacement of a *Se*

atom for *S*) their stereochemistries are distinctly different. This may have implications regarding potential bioactivities.

## Conclusion

In summary, a convenient route to Se-S-glycoside derivatives was developed using glycosyl isoselenuronium salts as glycosylselenenyl transfer reagents toward thiols. Aliphatic and aromatic thiols were found to react in the presence of TEA and furnished selenenylsulfide derivatives with low to moderate yields. *S*-glycosylselenenyl-cysteines were obtained similarly via reactions with *O,N*-protected cysteine. Reactions with monosaccharide thiols provided disaccharide mimics characterized by a selenenylsulfide interglycosidic connection. As a common side reaction, formation of symmetrical diglycosyl diselenides from the starting isoselenuronium salts was observed. We have found that these side reactions can be efficiently controlled and the yields of the desired glycosylselenenylsulfides significantly increased by running the reactions in dilute solutions with the thiol components in large excess and using DIPEA as a base. Disaccharide mimics with *Se-Se* interglycosidic linkage were obtained when the starting isoselenuronium salts reacted with protected monosaccharide derivatives bearing selenol groups in 6- or 4-position. Among the novel derivatives obtained disaccharide mimics with *Se-S*- or *Se-Se*- interglycosidic linkages are of particular interest and their stereostructures were determined by single crystal X-ray diffraction studies. *S*-glycosylselenenylcysteines are also of note as being analogs of "hepatic Se metabolite A",[29] the first glycosylated peptide, isolated from natural sources, featuring a *Se-S*-bond between the sugar and peptide units. The novel glycomimetics are expected to open new perspectives in biological activities and/or mechanistic studies due, i.a., to the rather uncommon *Se-S*- or *Se-Se* bonds incorporated into a carbohydrate framework.

## Supporting Information

Supporting information including detailed experimental procedures, spectroscopic data and original spectra, together with additional crystallographic information is available.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**Keywords:** carbohydrate; selenosugar; selenenylsulfide; *Se-Se*-bond

**TOC text:** Aliphatic or aromatic thiols react with glycosyl isoselenuronium salts to furnish glycosylselenenylsulfide derivatives. *S*-glycosylselenenyl-cysteines were obtained similarly via reactions with *O,N*-protected cysteine. Reactions with monosaccharide thiols provided disaccharide mimics featuring *Se-S*- interglycosidic bonds. Further disaccharide mimics with *Se-Se* interglycosidic linkage were obtained from the starting isoselenuronium salts via reactions with protected monosaccharide derivatives bearing selenol groups in 6- or 4-position.

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