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Synthesis of sugar-derived isoselenocyanates, selenoureas, and selenazoles

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ABSTRACT

Aryl, alkyl, and sugar-derived isoselenocyanates were prepared by a one-pot procedure starting from the corresponding formamides, using triphosgene as a dehydrating agent, triethylamine, and black selenium powder. The preparation of sugar selenoureas by coupling of *O*-protected sugar-derived isoselenocyanates with different amines, and by coupling of unprotected glycopyranosyl amines with phenyl isoselenocyanate was also accomplished. The synthesis of a glucopyranos-2-yl-selenazole starting from *O*-protected 2-amino-2-deoxy-D-glucose by coupling with benzoyl isoselenocyanate, Se-alkylation with phenacyl bromide, and acid-catalyzed dehydration is also reported. Unprotected *N*-(β-D-glucopyranosyl)-*N*′-phenylselenourea was transformed into a 1,2-*trans*-fused bicyclic isourea upon treatment with aqueous hydrogen peroxide; the same isourea was prepared by a one-pot three-step procedure from β-D-glycopyranosylamine by thiophosgenation, coupling with aniline, and HgO-mediated desulfurization.

1. Introduction

Selenium is a controversial element; it was identified as the active principle causing livestock poisoning through selenium-accumulating plants grown in seleniferous soil.[1] However, in the mid-50s it was considered as an essential nutrient[2] found in some selenoproteins[3] such as glutathione peroxidase, involved in a self-defense mechanism against oxidative stress.[4]

Recent experimental and epidemiological data suggest that many selenium derivatives show an anticancer activity,[5] mainly by inducing apoptosis of tumor cells[6] and by reducing cancerous metastasis in animals.[7] Furthermore, selenium has been found to prevent some age-related pathologies exerting antioxidant, anti-inflammatory, and heavy metal detoxifying activities.[8]

The beneficial effects associated with selenium have encouraged researchers to prepare a plethora of organoselenium derivatives,[9] some of them showing, among others, antihypertensive, antiviral, antibacterial, and antifungal properties.[10]

From a synthetic point of view, organoselenium derivatives have been used extensively as key synthetic intermediates;[11] the use of chiral organoselenium derivatives as ligands in asymmetric synthesis has also been reported.[12]

One of the most promising intermediates in organoselenium chemistry are isoselenocyanates; the intrinsic electrophilicity associated to the heterocumulene moiety makes these compounds suitable for coupling with nucleophiles,[13] giving access to a broad series of selenium-containing derivatives, such as selenocarbamates,[14] selenoureas,[15] and selenoheterocycles.[16]

We have previously reported[17] our preliminary results concerning the synthesis of alkyl and aryl isoselenocyanates starting from the corresponding formamides, and their transformation into glycopyranosyl selenoureas upon coupling with glycopyranosyl amines. Herein we extend this procedure for the preparation of novel aryl isoselenocyanates and also sugar-derived isoselenocyanates and their coupling with alkyl and aryl amines. We also report the synthesis of a D-glucosamine-derived selenazole, using an *N*-benzoyl selenourea as the key starting material.

2. Results and discussion

Although there are some methods in the literature for the preparation of isoselenocyanates,[18] the best procedure turns out to be treatment of isocyanides with elemental black selenium.[19] This procedure was firstly optimized by Barton and co-workers[14c] by the one-pot transformation of alkyl and aryl formamides into isoselenocyanates upon dehydration with phosgene in refluxing toluene in the presence of black selenium. The resulting non-isolated isocyanide reacts with black selenium to afford isoselenocyanates. We have developed[17] a practical modification of this procedure by replacing phosgene by triphosgene,[20] a less hazardous reactant, and toluene by CH_2Cl_2 as solvent.

So, we have carried out the one-pot transformation of alkyl and aryl formamides **1**–**10** into the corresponding isoselenocyanates **11**–**20** by first treatment with triphosgene as a dehydrating agent in refluxing CH_2Cl_2 for 3.5 h in the presence of Et_3N to afford non-isolated isocyanides (Scheme 1). Next, black selenium was one-pot

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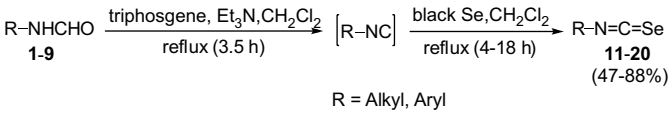
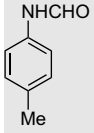
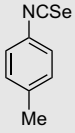
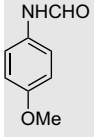
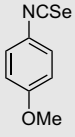
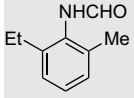
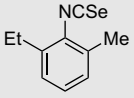
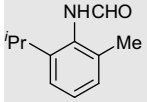
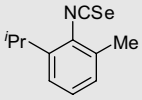
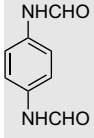
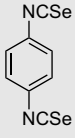
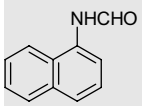
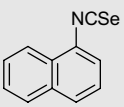


Scheme 1.

added and the corresponding mixture was refluxed for 4–18 h, affording isoselenocyanates **11**–**20** (Table 1) in moderate to good overall yields (47–88%). Su and Liang have reported the preparation of isoselenocyanates[21] using petroleum ether as solvent. Recently, Koketsu and co-workers accomplished the preparation of α-naphthyl isoselenocyanate[22] using the reaction conditions of Ref. 17.

Non-commercial formamides **2**–**5**, **8**, and **9** were prepared in excellent yields (69–98%) by refluxing the amine in ethyl formate in the presence of an equimolecular amount of acetic acid (see Supplementary data). Formamides **6** and **7**, bearing bulky substituents on *o*,*o*′-positions, were prepared by a modification of the original procedure reported by Krishnamurthy,[23] by treatment of the corresponding aryl amines with freshly prepared acetoformic anhydride in a biphasic CH_2Cl_2–satd aq $NaHCO_3$ system (see Supplementary data). When we used refluxing ethyl formate containing AcOH (1.0 equiv), no reaction was observed.

Table 1
Synthesis of alkyl and aryl isoselenocyanates

R–NHCHO	Compound	Yield (%)	R–N=C=Se	Compound	Yield (%)
	**1**	[a]		**11**[14c,21]	75
	**2**	69		**12**	47
	**3**	93		**13**[21]	77
	**4**	98		**14**[21]	88
	**5**	93		**15**[14c,21]	77
	**6**	93		**16**	79
	**7**	88		**17**	80
	**8**	95		**18**	80
	**9**	85		**19**[22]	77
	**10**	[a]		**20**[14c,21]	69

[a] Commercial.

Reactions and purifications involving seleno derivatives must proceed in the darkness, as these compounds are sensible to sunlight, undergoing decomposition with the release of elemental red selenium.

There are numerous procedures for the preparation of selenoureas, such as reaction between diamino carbenes and selenium,[24] carbodiimides and LiAlHSeH,[25] or cyanamides and LiAlHSeH,[26] among others. Nevertheless, direct coupling between an isoselenocyanate and an amine is the most practical procedure.[18]

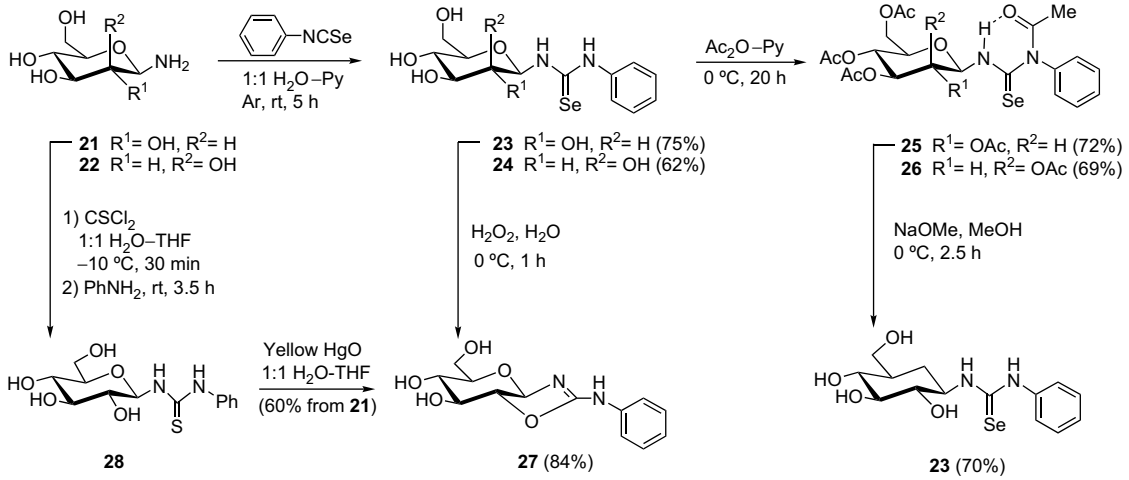
Some selenoureas have been reported to inhibit tyrosinase, the key enzyme in the biosynthesis of melanin and thus they might act as depigmenting agents useful in the case of melasma, freckles, and senile lentigines;[27] furthermore, some selenoureas exert superoxide radical scavenging, and might be potential antioxidants.[28] Moreover, selenoureas are precursors of selenium-containing heterocycles.[16,29]

Phenyl isoselenocyanate was converted into *O*-unprotected glycopyranosyl selenoureas **23** and **24** upon coupling with β-D-*gluco*- and mannopyranosylamine **21** and **22** in aqueous pyridine in a 75 and 62% yield, respectively (Scheme 2). Compound **23** was also prepared recently by Somsák co-workers[30] starting from β-D-glucopyranosylammonium carbamate under the reaction conditions described in our preliminary report.[17] Conventional acetylation afforded penta-acetylated derivatives **25** and **26**, in a completely regioselective fashion, as only the nitrogen in the non-glycosidic position was acetylated, probably due to steric hindrance. Chemical shifts and vicinal coupling constants show that the sugar moiety of both, unprotected and protected, selenoureido derivatives, adopts a non-distorted $^4C_1$ conformation. It is remarkable the high deshielding of the NH protons (12.49 and 10.68 ppm) in derivatives **25** and **26**, a consequence of a strong intramolecular hydrogen bonding with the carbonyl group of the NAc moiety; the values of the H-1–NH coupling constants (7.7 and 8.0 Hz) are in agreement with the selenourea being in the *anti-Z,E* conformation.[31] Deprotection of selenourea **25** under Zemplén deacetylation conditions using a catalytic amount of sodium methoxide in methanol at low temperature (0 °C) afforded unprotected derivative **23** in good yield (70%), without appreciable decomposition.

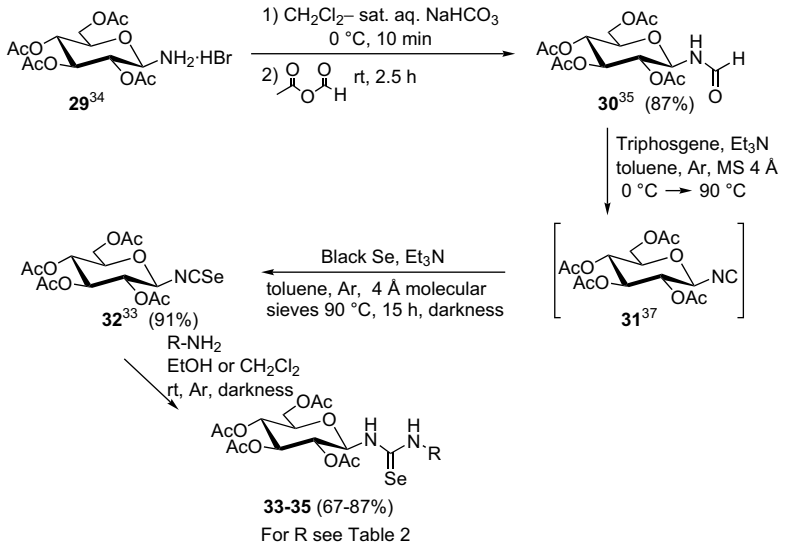
Unprotected glucopyranosyl selenourea **23** was slowly transformed into a product with a higher R_f value when exposed to light, with release of red selenium. This reaction was accelerated by the addition of an equimolecular amount of H_2O_2 and the transformation occurred in a quantitative fashion in less than 1 h (Scheme 2). ^{1}H and ^{13}C NMR spectra of the new product obtained by oxidation of selenourea **23** are in agreement with the bicyclic isourea **27**, presumably obtained by cyclization via a transient carbodiimide and nucleophilic addition of the hydroxyl group on position 2 of the sugar moiety. Oxidation of selenoureas with $NaIO_4$ in refluxing DMF to give carbodiimides has been reported.[18a] The ^{13}C NMR spectrum of **27** showed a strong downfield shift of C-1 and C-2 ($\Delta\delta$=6.9 and 11.8 ppm, respectively), and a shielding of H-1 ($\Delta\delta$ ca. 0.8 ppm) when compared to parent glucopyranosyl selenourea **23**. Furthermore, the resonance of C=N was at 159.8 ppm, a value that agrees with similar bicyclic isoureas.[32] The behavior exhibited by selenourea **23** toward hydrogen peroxide-mediated oxidation suggests that this kind of compounds might be useful as antioxidant agents by eliminating species causing oxidative stress.

The structure of **27** was confirmed by its synthesis starting from β-D-glucopyranosylamine **21** (Scheme 2), using the methodology developed by us.[32] Treatment of **21** with thiophosgene in aqueous THF afforded a non-purified mixture of a glucopyranosyl isothiocyanate and a bicyclic thiocarbamate,[32] which was transformed into glucopyranosyl thiourea **28** by the one-pot reaction with aniline. In situ HgO-mediated cyclodesulfurization of the thiourea afforded **27** in a 60% yield for the three steps, after chromatographical purification. Spectroscopical data of this compound were identical with those of the compound obtained by oxidation of selenourea **23**.

We have extended our method for the preparation of alkyl and aryl isoselenocyanates to the synthesis of sugar-derived isoselenocyanates. For the preparation of glucopyranosyl isoselenocyanate **32**[33] we started from the readily available per-*O*-acetylated β-D-glucopyranosyl amino hydrobromide **29**,[34] which was converted into the known glycopyranosyl formamide **30**[35] by a new procedure consisting of the use of a biphasic medium (CH_2Cl_2–satd aq $NaHCO_3$). Thus, the addition of acetoformic anhydride[36] to the biphasic system containing **29** (Scheme 3) afforded formamide **30** in an 87% yield. Subsequent treatment of **30** with triphosgene as a dehydrating agent in anhydrous toluene at 90 °C afforded non-isolated 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isocyanide **31**[37] that was in situ transformed into isoselenocyanate **32** upon treatment with black selenium, in a one-pot procedure with excellent yield (91% from **30**), after column chromatography. This yield is considerably higher than those reported by Witczak[33] for the synthesis of **32**, starting from purified isocyanide **31** (51 and 65% in $CHCl_3$ and THF, respectively). It is remarkable that our attempts to carry out the synthesis of **32** using CH_2Cl_2 as solvent instead of toluene led to several by-products.



Scheme 2.



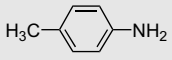
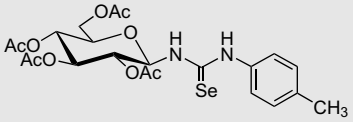
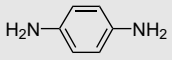
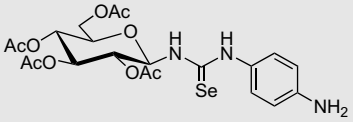
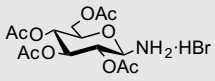
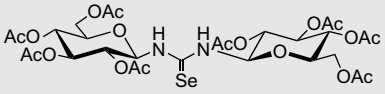
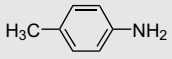
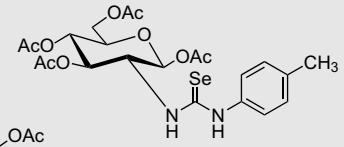
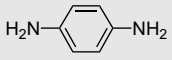
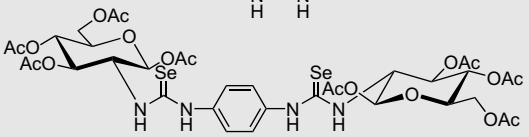
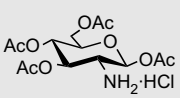
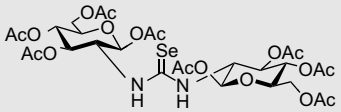
Scheme 3.

A strong IR absorption at 2095 cm^{-1} together with resonance at 141.2 ppm in the ^{13}C NMR spectrum confirms the presence of an –NCSe moiety in compound **32**. These values are close to reported data on *N*-aryl isoselenocyanates.[14,17] Furthermore, the observed coupling constants (see Experimental) are in accordance with the presence of a non-strained glycopyranosyl ring in the $^4C_1$ conformation.

Witczak[33] did not include any ^1H NMR data of **32**, and the ^{13}C NMR resonance data (δ C-1=91.8, C-2=70.5, CSe=140.2 ppm) disagree with our data (δ C-1=83.2, C-2=71.8, CSe=141.2 ppm), what might suggest the presence of a by-product in his spectrum.

Per-*O*-acetylated β-D-glucopyranosyl isoselenocyanate **32** was transformed into glucopyranosyl selenoureas **33**–**35** (Scheme 3) upon treatment with *p*-toluidine, *p*-phenylenediamine, or 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl amino hydrobromide **29** (Table 2). Reactions were carried out at rt, in the darkness using EtOH or CH_2Cl_2 as solvents, and the corresponding selenoureas were isolated in a 67–87% yield, after column chromatography. It is

Table 2
Synthesis of selenoureas **33–35** and **40–42**

Entry	R–NH_2	Product	Selenourea	Solvent	Yield[a] (%)
1			**33**	CH_2Cl_2	87
2			**34**	EtOH	67
3			**35**	CH_2Cl_2	75
4			**40**	EtOH	85
5			**41**	EtOH	71
6			**42**	CH_2Cl_2	74

[a] Yields of isolated products.

remarkable that the use of 1,4-phenylenediamine did not lead to the expected bis-selenourea, and monosubstituted selenourea **34** was obtained (67% yield) despite using an excess of isoselenocyanate **32**.

Analogously, we have also prepared 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isoselenocyanato-β-D-glucopyranose **39** (Scheme 4), starting from hydrochloride **36**[38] and following the same procedure as described for isoselenocyanate **32**. Thus, formylation of **36** with acetoformic anhydride in a biphasic CH_2Cl_2–satd aq $NaHCO_3$ system allowed the preparation of formamido derivative **37**[39] in an 82% yield. Conversion of **37** into 2-isoselenocyanate **39** took place through non-isolated isocyanide **38**[40] by using a one-pot two-step procedure consisting of dehydration with triphosgene, followed by treatment with black selenium (Scheme 4). The yield for the two-step procedure was 84% after column chromatography.

Treatment of isoselenocyanate **39** with *p*-toluidine, *p*-phenylenediamine, and 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride **36** in EtOH or CH_2Cl_2 afforded 2-selenoureido derivatives **40**–**42** in a 71–85% yield (Table 2). For the coupling of **39** with **36**, 1 equiv of Et_3N was added to the reaction mixture. It is remarkable that in contrast with the results obtained for glucopyranosyl isoselenocyanate **32** with 1,4-phenylenediamine, symmetrical bis-selenoureido derivative **41** was obtained as a crystalline product (71% yield) when that diamine was coupled with the 2-isoselenocyanate derivative **39**.

The structures of selenoureas **33**–**35** and **40**–**42** are in accordance with their spectroscopic data. Chemical shifts and coupling constants of the pyranose rings show a non-distorted $^4C_1$ conformation; furthermore, the chemical shift for the C=Se group was roughly 182 ppm, a value close to that described[24,41] for alkyl and aryl selenoureas. The C_2 symmetry present in **35**, **41**, and **42** simplifies both ^1H and ^{13}C NMR spectra, as only one signal for the two sugar moieties is observed. Of the three possible conformations for the selenoureido moiety the *E*,*E* conformation (see Supplementary data) should be discarded due to the unfavorable steric interactions. NMR spectra of carbohydrate-derived thioureas have shown that when the thioureido moiety is located on C1 or C2 the only observed conformer for the sugar-NHCS moiety was the *Z*.[42] So, for symmetrical selenoureas **35** and **42**, *Z*,*Z* conformation should be the major one. The high coupling constants $J_{H1,NH}$ and $J_{H2,NH}$ 8.6–9.6 Hz for selenoureas **33**–**35** and **40**–**42** are in agreement with an antiperiplanar disposition of those protons; analogous values were found for isosteric ureas.[43]

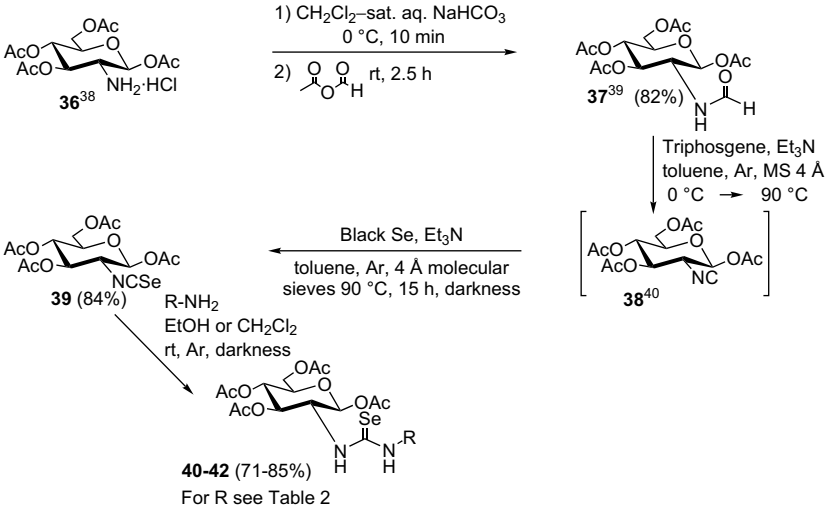
The resonance of the anomeric proton of glucopyranosyl selenourea **35** (δ 5.86 ppm) shows deshielding when compared with the proton of isosteric thiourea[34] (δ 5.68 ppm) and urea[43] (δ 5.02 ppm). The same behavior is observed when comparing H-2 of selenourea **42** (δ 5.23 ppm) with the corresponding isosteric thiourea[42] (δ 4.9–5.2 ppm) and urea[43] (δ 4.10 ppm). The deshielding observed for the selenoureas could be due to the stronger −M effect of the selenocarbonyl moiety compared with the thiocarbonyl and carbonyl groups.[44]

We have also accomplished the preparation of a sugar-derived 1,3-selenazole, encouraged by the biological activities shown by some selenazole derivatives, such as antitumor and antiviral agents.[29b,45] Our key intermediate for accessing such scaffold was *N*-benzoyl isoselenocyanate **44**, easily available using a modification of Douglass' reaction conditions[46] by treatment of potassium selenocyanate with benzoyl chloride (Scheme 5). Coupling of *N*-benzyol isoselenocyanate with hydrochloride **36** in CH_2Cl_2, in the presence of Et_3N, afforded *N*-benzoyl selenourea **45** in an almost quantitative yield (98%) after purification.

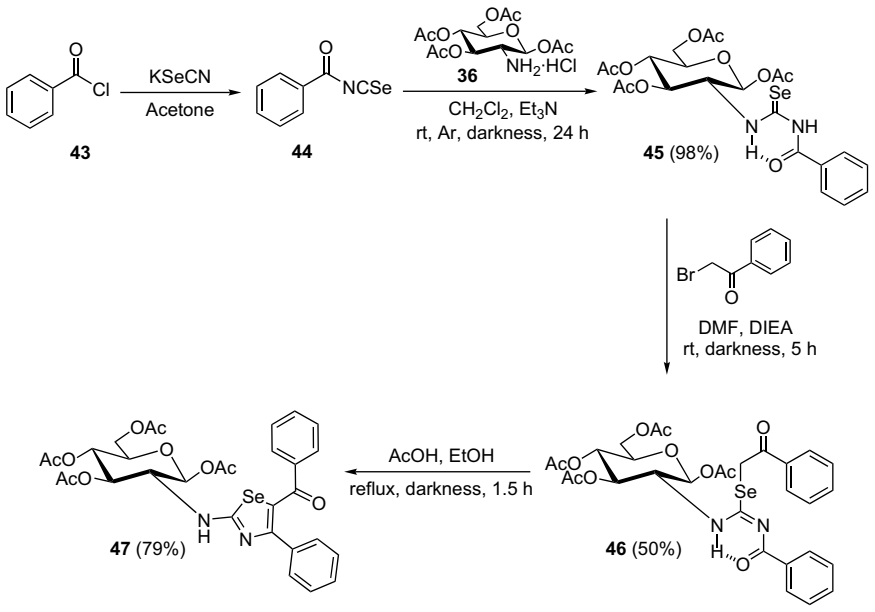
The ^1H NMR spectrum of compound **45** showed a doublet at 11.43 ppm, corresponding to the NH of the selenoureido group attached to the sugar moiety; the high deshielding indicates the presence of a strong intramolecular hydrogen bonding with the carbonyl group of the vicinal *N*-benzoyl group. The resonance for the C=Se group in the ^{13}C NMR spectrum (184.0 ppm) is consistent with the selenoureido moiety.

Treatment of *N*-benzoyl selenourea **45** with phenacyl bromide in DMF at rt, in the presence of diisopropylethylamine (DIEA), afforded the corresponding *Se*-phenacyl isoselenourea **46** in a 50% yield. In the literature some examples of the Se-alkylation of selenocarbonyl derivatives can be found; for instance, selenosemicarbazides react with alkyl halides to give the corresponding *Se*-alkyl derivatives.[47] To the best of our knowledge, the only isoselenourea formed by nucleophilic displacement of phenacyl bromide is derived from unsubstituted selenourea.[48]

The ^1H NMR spectrum of isoselenourea **46** shows a doublet for the NH proton (8.45 ppm); the deshielding is smaller compared with the parent selenourea **45**, indicating a weaker hydrogen bonding for compound **46**. Final acidic treatment of isoselenourea **46** with refluxing ethanolic AcOH led to an intramolecular cyclodehydration to give selenazole **47** in a 79% yield after chromatographic purification. The formation of **47** can be explained considering the mechanism depicted in Scheme 6. This result contrasts with the results of Liebscher and Hartmann[49] who prepared **50** (R=Ph) from



Scheme 4.

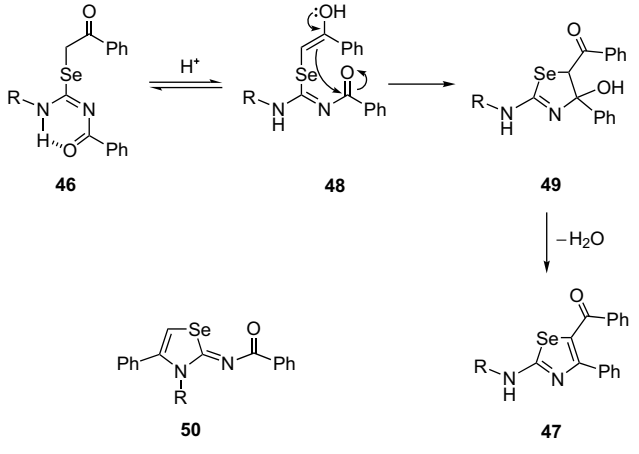


Scheme 5.

BzNHCSeNHPh and phenacyl bromide whereas the same authors obtained 5-aroyl-2-(*N*-methyl-*N*-phenyl)amino-4-phenyl-1,3-selenazoles, similar to **47**, from ArCONHCSeNMePh and phenacyl bromides. No intermediate isoselenoureas were isolated in these reactions.[49] The structure of compound **47** was confirmed by a TOCSY experiment (see Supplementary data).

To the best of our knowledge, no previous examples of 5-acyl-2-(alkyl or arylamino)-1,3-selenazoles with a monosubstituted amino group at C-2 have been described; only 5-acyl-1,3-selenazoles with a disubstituted or unsubstituted amino group at C-2 have been reported, either with an alkyl or aryl group at C4,[49–51] or unsubstituted at that position.[52,53]

In conclusion, we have developed a practical synthesis of alkyl and aryl isoselenocyanates starting from the corresponding formamides. Coupling of aryl isoselenocyanates with fully unprotected glycopyranosyl amines to afford the corresponding selenoureas was carried out in good yields. Furthermore, the mild oxidation of a glucopyranosyl selenourea led to a bicyclic isourea, also formed by spontaneous decomposition, and by desulfurization of the isosteric thiourea. The synthetic approach for the preparation of isoselenocyanates was extended to carbohydrates in order to obtain per-*O*-acetylated sugar-derived isoselenocyanates in excellent yields; they were coupled with aromatic amines and aminosugars to give selenoureas in good yields. We have also accomplished the preparation of the first example of a sugar-derived 2-amino-1,3-selenazole in three steps: coupling of benzoyl isoselenocyanate with *O*-protected glucosamine, Se-alkylation of the corresponding *N*-benzoyl selenourea with phenacyl bromide, and acid-promoted intramolecular cyclization.



Scheme 6.

3. Experimental section

3.1. General procedure for the synthesis of isoseleno cyanates 11–20

To a refluxing mixture of formamides **1**–**10** (1.5 mmol), Et_3N (6.4 mmol), and 4 Å molecular sieves in dry dichloromethane (5 mL) was dropwise added a solution of triphosgene (0.8 mmol) in dry dichloromethane (2 mL), under Ar, over a period of 1 h. After the addition, the resulting mixture was refluxed for 2.5 h and then black selenium powder (3.0 mmol; 6.0 mmol for **8**) was added and refluxed for 4–18 h. Conventional work-up and column chromatography afforded isoselenocyanates **1**–**20**.

*3.1.1. o-Chlorophenyl isoselenocyanate (**12**)*

Column chromatography (hexane) gave **12** as a syrup: 153 mg, 47%; R_f 0.40 (hexane); IR ν_{max} 2056, 1582, 1468, 1368, 1126, 1063, 984, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 1H, H-3), 7.30 (m, 1H, H-6), 7.25 (m, 2H, H-4, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 134.5 (C=Se), 132.1 (C-2), 130.3 (C-3), 128.8 (C-4), 127.8 (C-5), 127.3 (C-6); EIMS *m*/*z* 217 (M^+, 100%); HREI-MS *m*/*z* calcd for $C_7H_4ClN^{80}Se$, M^+: 216.9197, found: 216.9191.

*3.1.2. o-Methylphenyl isoselenocyanate (**13**)*

Column chromatography (hexane) gave **13** as a syrup: 227 mg, 77%; R_f 0.44 (hexane); IR ν_{max} 2922, 2112, 1597, 1483, 1371, 1115, 858, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.15 (m, 4H, ArH), 2.41 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.7 (C-2), 130.8 (C-3), 129.3 (C=Se), 128.3 (C-4), 127.0 (C-5), 126.3 (C-6), 18.5 (CH_3); EIMS *m*/*z* 197 (M^+, 100%); HREI-MS *m*/*z* calcd for $C_8H_7N^{80}Se$, M^+: 196.9744, found: 196.9747.

*3.1.3. 2-Ethyl-6-methylphenyl isoselenocyanate (**16**)*

Column chromatography (hexane) gave **16** as a syrup: 266 mg, 79%; R_f 0.45 (hexane); IR ν_{max} 2926, 2101, 1587, 1461, 1375, 1256, 1060, 853, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, 1H, H-4), 7.07 (m, 2H, H-3, H-5), 2.74 (q, 2H, $J_{H,H}$=7.6 Hz, CH_2CH_3), 2.41 (s, 3H, CH_3), 1.26 (t, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.4, 135.9 (C-2, C-6), 130.8 (C=Se), 128.2 (C-5), 128.0 (C-4), 126.6 (C-3), 25.8 (CH_2CH_3), 18.8 (CH_3), 14.4 (CH_2CH_3); EIMS *m*/*z* 225 (M^+, 100%); HREI-MS *m*/*z* calcd for $C_{10}H_{11}N^{80}Se$, M^+: 225.0057, found: 225.0065.

*3.1.4. 2-Isopropyl-6-methylphenyl isoselenocyanate (**17**)*

Column chromatography (hexane) gave **17** as a syrup: 286 mg, 80%; R_f 0.46 (hexane); IR ν_{max} 2964, 2109, 1584, 1465, 1375, 1261, 1045, 849, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, 1H, $J_{3,4}$=7.8 Hz, $J_{4,5}$=7.3 Hz, H-4), 7.13 (dd, 1H, $J_{3,5}$=1.7 Hz, H-3), 7.07 (dd, 1H, H-5), 3.25 (sept, 1H, $J_{H,H}$=6.9 Hz, $CH(CH_3)_2$), 2.41 (s, 3H, CH_3), 1.27 (d, 6H, $CH(CH_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.4, 136.1 (C-2, C-6), 130.8 (C=Se), 128.1 (C-4), 128.0 (C-5), 123.8 (C-3), 30.0 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$), 19.0 (CH_3); EIMS *m*/*z* 239 (M^+, 36%); HREI-MS *m*/*z* calcd for $C_{11}H_{13}N^{80}Se$, M^+: 239.0213, found: 239.0204.

*3.1.5. Benzene-1,4-diisoselenocyanate (**18**)*

To a refluxing solution of bisformamide **8** (123 mg, 0.75 mmol) and Et_3N (0.90 mL, 6.47 mmol) in dry CH_2Cl_2 (5 mL) in the presence of 4 Å molecular sieves was dropwise added, under Ar, a solution of triphosgene (235 mg, 0.80 mmol) in dry CH_2Cl_2 (5 mL) over a period of 1.5 h. After the addition, the mixture was refluxed for 2 h, and then black selenium powder (236 mg, 3.00 mmol) was added, and the mixture was refluxed in the darkness for 3 h. Conventional work-up and column chromatography (hexane→1:1 hexane−Et_2O) gave diisoselenocyanate **18** as a syrup (182 mg, 85%); R_f 0.69 (1:2 hexane–Et_2O); IR ν_{max} 2922, 2128, 1586, 1485, 1447, 1373, 991, 833, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 4H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.7 (C=Se), 129.3 (ArC), 127.5 (ArCH); CIMS *m*/*z* 288 (M^+, 100%); HRCI-MS *m*/*z* calcd for $C_8H_4N_2^{80}Se_2$, M^+: 287.8705, found: 287.8707.

*3.1.6. 1-Naphthyl isoselenocyanate (**19**)*

Crystallization from EtOH gave **19** as a white solid: 268 mg, 77%; mp: 73–74 °C (EtOH); R_f 0.38 (hexane); IR ν_{max} 2953, 2129, 1587, 1385, 1262, 1156, 795, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, 1H, $J_{6,8}$=1.2 Hz, $J_{7,8}$=8.3 Hz, H-8), 7.89 (dd, 1H, $J_{5,6}$=8.2 Hz, $J_{5,7}$=1.3 Hz, H-5), 7.83 (dd, 1H, $J_{2,3}$=8.2 Hz, H-2), 7.65 (ddd, 1H, $J_{6,7}$=6.9 Hz, H-7), 7.58 (ddd, 1H, H-6), 7.49 (dd, 1H, $J_{2,4}$=1.2 Hz, $J_{3,4}$=7.4 Hz, H-4), 7.43 (dd, 1H, H-3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 131.3 (C=Se), 134.1, 129.5, 126.5 (C-1, C-4a, C-8a), 128.7 (C-2, C-5), 127.9 (C-7), 127.5 (C-6), 125.4 (C-3), 124.1 (C-4), 122.9 (C-8); EIMS *m*/*z* 233 (M^+, 77%); HREI-MS *m*/*z* calcd for $C_{11}H_7NSe$, M^+: 232.9744, found: 232.9758.

3.2. General procedure for the synthesis of selenoureas 23 and 24

To a solution of phenyl isoselenocyanate (1.34 mmol, 1.2 equiv) in pyridine (2 mL) was added a solution of β-D-glucopyranosylamine **21** or of β-D-mannopyranosylamine **22** (200 mg, 1.12 mmol) in water (2 mL) in the darkness under Ar. The mixture was kept at rt for 5 h; then it was concentrated to dryness and purified by column chromatography (CH_2Cl_2→5:1 CH_2Cl_2–MeOH).

*3.2.1. N-(β-D-Glucopyranosyl)-N′-phenylselenourea (**23**)*

Yield: 302 mg, 75%; R_f 0.33 (5:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$ −19 (*c* 1.4, CH_3OH); IR ν_{max} 3317, 3071, 2928, 1545, 1093, 1029, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.39 (m, 5H, Ar), 5.61 (br s, 1H, H-1), 3.88 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=11.9 Hz, H-6a), 3.68 (dd, 1H, $J_{5,6b}$=5.1 Hz, H-6b), 3.47–3.28 (m, 4H, H-2, H-3, H-4, H-5); ^{13}C NMR (75.5 MHz, CD_3OD) δ 182.8 (C=Se), 139.3, 130.3, 127.8, 126.4 (Ar), 88.2 (C-1), 79.4, 78.9 (C-3, C-5), 73.8 (C-2), 73.5 (C-4), 62.6 (C-6); FABMS *m*/*z* 385 ($[M+Na]^+$, 72%); HRFAB-MS calcd for $C_{13}H_{18}N_2NaO_5^{80}Se$, $[M+Na]^+$: 385.0279, found: 385.0267.

*3.2.2. N-(β-D-Mannopyranosyl)-N′-phenylsenourea (**24**)*

Yield: 228 mg, 62%; R_f 0.30 (5:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$ +7 (*c* 0.6, DMSO); IR ν_{max} 3308, 3036, 2920, 1541, 1362, 1121, 1065, 712 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.45–7.30 (m, 5H, Ar), 5.85 (br s, 1H, H-1), 3.88 (m, 1H, H-2), 3.87 (m, 1H, H-6a), 3.70 (dd, 1H, $J_{5,6b}$=6.0 Hz, $J_{6a,6b}$=12.0 Hz, H-6b), 3.54 (m, 2H, H-3, H-4), 3.33 (m, 1H, H-5); ^{13}C NMR (125.8 MHz, CD_3OD) δ 183.4 (C=Se), 138.6, 130.8, 128.2, 126.3 (Ar), 86.0 (C-1), 79.9 (C-5), 75.5 (C-3), 71.9 (C-2), 68.0 (C-4), 62.9 (C-6); FABMS *m*/*z* 363 ($[M+H]^+$, 33%), 385 ($[M+Na]^+$, 62%). Anal. Calcd for $C_{13}H_{18}N_2O_5Se$: C, 43.22; H, 5.02; N, 7.75. Found: C, 42.86; H, 5.09; N, 7.62.

3.3. *N*-Acetyl-*N*-phenyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)selenourea (25)

N-(β-D-Glucopyranosy-l)-*N′*-phenylselenourea **23** (20 mg, 0.055 mmol) was conventionally acetylated in a 1:1 Py–Ac_2O mixture (1 mL). After standard work-up, the residue was purified by preparative TLC (60:1 CH_2Cl_2–MeOH) to afford selenourea **25** (21 mg, 72%); R_f 0.52 (60:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$ +36 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3107, 1759, 1691, 1528, 1379, 1230, 1095, 1047, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.49 (d, 1H, $J_{1,NH}$=9.2 Hz, NH), 7.26–7.20 (m, 5H, Ar), 5.89 (d, 1H, $J_{1,2}$=9.2 Hz, H-1), 5.34 (t, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=9.3 Hz, H-3), 5.26 (t, 1H, H-2), 5.10 (t, 1H, $J_{4,5}$=10.1 Hz, H-4), 4.27 (dd, 1H, $J_{5,6a}$=4.7 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.83 (ddd, 1H, H-5), 2.08, 2.07, 2.01, 1.92 (5s, 3H each, 5×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.1 (C=Se), 174.5 170.7, 170.1, 170.0, 169.5 (5×CO), 143.4, 129.7, 129.4, 129.3 (Ar), 85.9 (C-1), 73.8 (C-5), 73.0 (C-3), 70.4 (C-2), 68.3 (C-4), 61.6 (C-6), 28.3 (NAc), 20.8, 20.7 (×2), 20.6 (4×CH_3CO); FABMS *m*/*z* 573 ($[M+H]^+$, 16%), 595 ($[M+Na]^+$, 7%); HRFAB-MS calcd for $C_{23}H_{28}N_2NaO_{10}^{80}Se$, $[M+Na]^+$: 595.0807, found: 595.0808.

3.4. *N*-Acetyl-*N*-phenyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)selenourea (26)

N-(β-D-Mannopyranosyl)-*N′*-phenylsenourea **24** (61 mg, 0.17 mmol) was conventionally acetylated in a 1:1 Py–Ac_2O mixture (1 mL). After standard work-up, the residue was purified by column chromatography (CH_2Cl_2) to afford selenourea **26** (67 mg, 69%); R_f 0.51 (60:1 CH_2Cl_2–MeOH); $[\alpha]_D^{27}$ +13 (*c* 0.5, CH_2Cl_2); IR ν_{max} 3295, 1750, 1682, 1522, 1368, 1225, 1053, 991, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.68 (d, 1H, $J_{1,NH}$=8.0 Hz, NH), 7.47–7.20 (m, 5H, Ar), 6.14 (dd, 1H, $J_{1,2}$=0.9 Hz, H-1), 5.60 (dd, 1H, $J_{2,3}$=3.4 Hz, H-2), 5.27 (t, 1H, $J_{3,4}$=10.0 Hz, $J_{4,5}$=10.0 Hz, H-4), 5.16 (dd, 1H, H-3), 4.29 (dd, 1H, $J_{5,6a}$=5.4 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b), 3.79 (ddd, 1H, H-5), 2.28, 2.08, 2.03, 1.98, 1.91 (5s, 3H each, 5×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 189.3 (C=Se), 174.9 170.7, 170.3, 169.8, 169.7 (5×CO), 143.2, 129.7, 129.5, 129.3 (Ar), 84.9 (C-1), 74.3 (C-5), 71.1 (C-3), 68.8 (C-2), 65.4 (C-4), 62.2 (C-6), 28.3 (NAc), 20.8, 20.7 (×2), 20.6 (4×CH_3CO); FABMS 573 ($[M+H]^+$, 71%), 595 ($[M+Na]^+$, 60%); HRFAB-MS *m*/*z* calcd for $C_{23}H_{29}N_2O_{10}^{80}Se$ ($[M+H]^+$): 573.0987, found: 573.0972. Anal. Calcd for $C_{23}H_{28}N_2O_{10}Se$: C, 48.34; H, 4.94; N, 4.90. Found: C, 48.14; H, 4.71; N, 4.92.

3.5. 4,5-Dihydro-2-phenylamino-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (27)

Method A. To a solution of phenyl selenourea **23** (26 mg, 0.07 mmol) in water (0.5 mL) was added 3.3% w/v H_2O_2 (76 μL, 0.07 mmol) at 0 °C. The mixture was kept at this temperature for 1 h; then it was diluted with EtOH, filtered over a Celite pad, and the filtrate was concentrated to dryness and purified by column chromatography (CH_2Cl_2→5:1 CH_2Cl_2–MeOH) to give isourea **27** (17 mg, 84%).

Method B. To a suspension of $NaHCO_3$ (169 mg, 2.01 mmol) in 1:1 H_2O–THF (4 mL) were added β-D-glucopyranosylamine (150 mg, 0.84 mmol) and thiophosgene (78 μL, 1.00 mmol; 1.2 equiv). The mixture was stirred at −10 °C for 40 min and then aniline (91 μL, 1.00 mmol; 1.2 equiv) was added and the mixture was stirred at rt for 3.5 h to afford non-isolated thiourea **28**. To the solution of the crude thiourea was added yellow mercury oxide (II) (546 mg, 2.52 mmol, 3.0 equiv). The mixture was stirred at rt for 3 h and then it was filtered through a Celite pad and the filtrate was purified by column chromatography (CH_2Cl_2→5:1 CH_2Cl_2–MeOH) to give isourea **27** (140 mg, 60%, three steps); $[\alpha]_D^{27}$ +67 (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, CD_3OD) δ 7.35, 7.27, 7.01 (m, 5H, Ar), 4.85 (d, 1H, $J_{1,2}$=9.6 Hz, H-1), 3.88 (dd, 1H, $J_{2,3}$=10.5 Hz, $J_{3,4}$=7.6 Hz, H-3), 3.87 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=12.1 Hz, H-6a), 3.73 (dd, 1H, $J_{5,6b}$=5.3 Hz, H-6b), 3.60 (m, 1H, H-2), 3.53 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.40 (dd, 1H, H-4); ^{13}C NMR (125.8 MHz, CD_3OD) δ 159.8 (C═N), 148.5, 129.9, 124.2, 121.2 (Ar), 95.1 (C-1), 85.6 (C-2), 83.1 (C-5), 75.6 (C-3), 73.5 (C-4), 62.7 (C-6); CIMS *m*/*z* 280 (M^+, 31%); HRCI-MS *m*/*z* calcd for $C_{13}H_{16}N_2O_5$, M^+: 280.1059, found: 280.1056.

3.6. General method for the synthesis of sugar isoselenocyanates 32 and 39

To a solution of hydrohalide **29** or **36** (500 mg, 1.17 or 1.30 mmol, respectively) in a 1:1 CH_2Cl_2–satd aq $NaHCO_3$ mixture (20 mL) was added acetoformic anhydride (0.47 or 0.52 mL, respectively, 3.0 equiv), under vigorous stirring at 0 °C. The reaction mixture was kept stirring at rt for 2.5 h and then the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated to dryness. The residue was crystallized from Et_2O to give formamide **30** (391 mg, 87%) or **37** (401 mg, 82%). To a mixture of formamide **30** or **37** (200 mg, 0.53 mmol) and Et_3N (376 μL, 2.66 mmol, 5.0 equiv) in dry toluene (5 mL), containing 4 Å molecular sieves, was dropwise added at 0 °C, under Ar, a solution of triphosgene (131 mg, 0.44 mmol, 2.5 equiv) in dry toluene (5 mL) over a period of 30 min. After the addition, the corresponding mixture was kept stirring at 0 °C for 15 min and then it was heated at 90 °C for 7 h to afford the corresponding non-isolated isocyanides (R_f 0.85, EtOAc). To the crude reaction mixture were added black selenium (63 mg, 0.80 mmol, 1.5 equiv) and Et_3N (75 μL, 0.53 mmol, 1.0 equiv), and the reaction mixture was kept in the darkness at 90 °C for 15 h. Then, it was filtered through a Celite pad and the filtrate was concentrated to dryness. The residue was treated with Et_2O and filtered off, and the filtrate was purified by column chromatography (hexane→1:5 hexane–Et_2O) to afford isoselenocyanates **32** and **39**.

*3.6.1. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isoseleno cyanate (**32**)*

Yield: 210 mg, 91%; R_f 0.43 (1:5 hexane–Et_2O); $[\alpha]_D^{25}$ −6 (*c* 0.8, CH_2Cl_2), lit.[33] $[\alpha]_D^{20}$ +4.8 ($CHCl_3$); IR ν_{max} 2992, 2095, 1744, 1375, 1233, 1107, 1036, 909 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=9.5 Hz, H-3), 5.15 (t, 1H, $J_{1,2}$=8.5 Hz, H-2), 5.10 (dd, 1H, $J_{4,5}$=10.0 Hz, H-4), 5.09 (d, 1H, H-1), 4.23 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.74 (ddd, 1H, H-5), 2.11, 2.10, 2.03, 2.01 (4s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.2, 169.3, 169.1 (4×CO), 141.2 (C═Se), 83.2 (C-1), 74.3 (C-5), 72.5 (C-3), 71.8 (C-2), 67.6 (C-4), 61.5 (C-6), 20.8, 20.7, 20.6 (×2) (4×*C*H_3CO). Anal. calcd for $C_{15}H_{19}NO_9Se$: C, 41.30; H, 4.39; N, 3.21. Found: C, 41.26; H, 4.30; N, 3.17.

*3.6.2. 1,3,4,6-Tetra-O-acetyl-2-deoxy-2-isoselenocyanato-β-D-glucopyranose (**39**)*

Yield: 194 mg, 84%; R_f 0.78 (1:5 hexane–Et_2O); $[\alpha]_D^{24}$ +94 (*c* 1.5, CH_2Cl_2); IR ν_{max} 2926, 2037, 1753, 1370, 1223, 1071, 1040, 903 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, 1H, $J_{1,2}$=8.6 Hz, H-1), 5.29 (dd, 1H, $J_{2,3}$=10.3 Hz, $J_{3,4}$=9.4 Hz, H-3), 5.01 (dd, 1H, $J_{4,5}$=10.0 Hz, H-4), 4.29 (dd, 1H, $J_{5,6a}$=4.4 Hz, $J_{6a,6b}$=12.6 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b), 4.03 (dd, 1H, H-2), 3.85 (ddd, 1H, H-5), 2.19, 2.10, 2.06, 2.02 (4s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.3, 169.4, 169.3, 168.3 (4×CO), 137.1 (C═Se), 91.2 (C-1), 72.8 (C-5), 72.0 (C-3), 67.2 (C-4), 61.0 (C-6), 59.4 (C-2), 20.7, 20.5 (×2), 20.3 (4×*C*H_3CO); FABMS *m*/*z* 460 ([M+Na]$^+$, 32%); HRFAB-MS *m*/*z* calcd for $C_{15}H_{19}NNaO_9^{80}Se$, [M+Na]$^+$: 460.0123, found: 460.0152.

3.7. *N*-(*p*-Methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)selenourea (33)

To a solution of isoselenocyanate **32** (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added *p*-toluidine (15 mg, 0.14 mmol; 1.3 equiv) and the mixture was kept in the darkness, under Ar, at rt for 12 h. Then, it was concentrated to dryness and the residue was purified by column chromatography (hexane→1:5 hexane–Et_2O) to give selenourea **33** (52 mg, 87%) as an amorphous solid; $[\alpha]_D^{32}$ +6 (*c* 0.9, CH_2Cl_2); IR ν_{max} 3308, 2922, 1748, 1534, 1368, 1225, 1125, 1038, 872 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H, NHAr), 7.27–7.03 (m, 4H, Ar), 6.75 (d, 1H, $J_{1,NH}$=9.1 Hz, NH), 5.89 (t, 1H, $J_{1,2}$=9.5 Hz, H-1), 5.35 (t, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=9.7 Hz, H-3), 5.01 (t, 1H, $J_{4,5}$=10.1 Hz, H-4), 4.91 (t, 1H, H-2), 4.32 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.09 (dd, 1H, $J_{5,6b}$=1.9 Hz, H-6b), 3.87 (ddd, 1H, H-5), 2.38 (s, 3H, CH_3Ar), 2.07, 2.06, 2.02, 1.99 (4s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.1 (C═Se), 171.0, 170.8, 170.0, 169.7 (4×CO), 139.1, 132.0, 131.1, 125.7 (Ar), 85.9 (C-1), 73.8 (C-5), 72.7 (C-3), 70.6 (C-2), 68.3 (C-4), 61.7 (C-6), 21.3 (CH_3Ar), 20.9, 20.8, 20.7 (×2) (4×*C*H_3CO); CIMS *m*/*z* 545 ([M+H]$^+$, 34%); HRCI-MS *m*/*z* calcd for $C_{22}H_{29}N_2O_9^{80}Se$, [M+H]$^+$: 545.1038, found: 545.1023.

3.8. *N*-(*p*-Aminophenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)selenourea (34)

To a solution of isoselenocyanate **32** (50 mg, 0.11 mmol) in EtOH (3 mL) was added 1,4-phenylenediamine (8 mg, 0.07 mmol), and the mixture was kept in the darkness at rt, under Ar, for 12 h. Then, the reaction mixture was concentrated to dryness and the residue was purified by column chromatography (Et_2O→5:1 Et_2O–AcOEt) to give selenourea **34** (26 mg, 67%) as an amorphous solid; R_f 0.25 (5:1 Et_2O–EtOAc); $[\alpha]_D^{20}$ −5 (*c* 1.1, CH_2Cl_2); IR ν_{max} 3335, 2924, 1748, 1541, 1433, 1370, 1125, 1040, 872 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H, NHAr), 6.92 (m, 2H, Ar), 6.70 (m, 2H, Ar), 6.63 (br d, 1H, NH), 5.89 (t, 1H, $J_{1,NH}$=$J_{1,2}$=9.1 Hz, H-1), 5.34 (t, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3), 5.01 (t, 1H, $J_{4,5}$=9.8 Hz, H-4), 4.89 (t, 1H, H-2), 4.32 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.09 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.89 (br s, 2H, NH_2), 3.87 (ddd, 1H, H-5), 2.08, 2.06, 2.01, 1.99 (4s, 3H each, 4×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.2 (C═Se), 170.9, 170.8, 169.9, 169.8 (4×CO), 147.3, 128.9 (Ar–C), 127.7, 116.0 (Ar–CH), 85.8 (C-1), 73.8 (C-5), 72.8 (C-3), 70.6 (C-2), 68.3 (C-4), 61.7 (C-6), 20.9, 20.8, 20.7 (×2) (4×*C*H_3CO); FABMS *m*/*z* 546 ([M+H]$^+$, 18%); HRFAB-MS *m*/*z* calcd for $C_{21}H_{27}N_3O_9^{80}Se$, M^+: 545.0913, found: 545.0933.

3.9. *N,N′*-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) selenourea (35)

To a solution of isoselenocyanate **32** (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) were added 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine hydrobromide **29** (49 mg, 0.11 mmol) and Et_3N (14 μL, 0.11 mmol). The mixture was kept in the darkness at rt, under Ar, for 24 h. Then, the reaction mixture was concentrated to dryness and the residue was purified by column chromatography (hexane→1:2 hexane–EtOAc) to give selenourea **35** (65 mg, 75%) as an amorphous solid; R_f 0.62 (1:5 hexane–EtOAc); $[\alpha]_D^{25}$ −21 (*c* 0.7, CH_2Cl_2); IR ν_{max} 3300, 2922, 1750, 1547, 1427, 1368, 1221, 1040, 984 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (br s, 1H, NH), 5.86 (br t, 1H, H-1), 5.34 (m, 1H, $J_{3,4}$=9.6 Hz, H-3), 5.04 (t, 1H, $J_{4,5}$=9.9 Hz, H-4), 4.96 (br t, 1H, $J_{1,2}$=$J_{2,3}$=8.5 Hz, H-2), 4.28 (m, 1H, H-6a), 4.10 (m, 1H, H-6b), 3.89 (m, 1H, H-5), 2.08 (×2), 2.03, 2.01 (3s, 3H each, 4×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.7 (×2), 169.7 (×2) (4×CO), 84.9 (C-1), 73.6 (C-5), 72.6 (C-3), 70.8 (C-2), 68.4 (C-4), 61.8 (C-6), 20.9 (×2), 20.7, 20.6 (4×*C*H_3CO); FABMS *m*/*z* 807 ([M+Na]$^+$, 47%); HRFAB-MS *m*/*z* calcd for $C_{29}H_{40}N_2NaO_{18}^{80}Se$, [M+Na]$^+$: 807.1339, found: 807.1333. Anal. Calcd for $C_{29}H_{40}N_2O_{18}Se$: C, 44.45; H, 5.15; N, 3.58. Found: C, 44.55; H, 5.10; N, 3.58.

3.10. *N*-(*p*-Methylphenyl)-*N′*-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)selenourea (40)

To a solution of isoselenocyanate **39** (50 mg, 0.11 mmol) in EtOH (3 mL) was added *p*-toluidine (15 mg, 0.14 mmol; 1.3 equiv), and the mixture was kept in the darkness at rt, under Ar, for 7 h. Then it was concentrated to dryness and the residue was purified by column chromatography (hexane→1:5 hexane–Et_2O) to give selenourea **40** (51 mg, 85%) as an amorphous solid; R_f 0.24 (1:5 hexane–Et_2O); $[\alpha]_D^{23}$ +15 (*c* 0.8, CH_2Cl_2); IR ν_{max} 3312, 2936, 1748, 1543, 1370, 1225, 1042, 912, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H, NHAr), 7.28–6.99 (m, 4H, Ar), 6.03 (d, 1H, $J_{2,NH}$=9.6 Hz, NH), 5.66 (d, 1H, $J_{1,2}$=8.4 Hz, H-1), 5.24 (m, 1H, H-2), 5.21 (t, 1H, $J_{3,4}$=9.1 Hz, $J_{4,5}$=9.7 Hz, H-4), 5.03 (dd, 1H, $J_{2,3}$=10.2 Hz, H-3), 4.23 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.11 (dd, 1H, $J_{5,6b}$=2.4 Hz, H-6b), 3.70 (ddd, 1H, H-5), 2.38 (s, 3H, CH_3Ar), 2.19, 2.11, 2.09, 1.99 (4s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1 (C=Se), 171.0, 170.7, 169.6, 169.0 (4×CO), 139.1, 131.8, 131.1, 126.0 (Ar), 92.5 (C-1), 73.1 (C-5), 72.3 (C-3), 67.2 (C-4), 61.5 (C-6), 60.8 (C-2), 21.2 (CH_3Ar), 21.1, 20.8, 20.7, 20.5 (4×*C*H_3CO); FABMS *m*/*z* 567 ([M+Na]$^+$, 48%); HRFAB-MS *m*/*z* calcd for $C_{22}H_{28}N_2NaO_9^{80}Se$, [M+Na]$^+$: 567.0858; found: 567.0860.

3.11. 1,4-Bis[3-(1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranos-2-yl)selenoureido]benzene (41)

To a solution of isoselenocyanate **39** (50 mg, 0.11 mmol) in EtOH (3 mL) was added 1,4-phenylenediamine (8 mg, 0.07 mmol), and the mixture was kept in the darkness at rt, under Ar, for 6 h. Selenourea **41** precipitated, and the solid was filtered and washed with EtOH (38 mg, 71%); R_f 0.68 (1:10 hexane–Et_2O); $[\alpha]_D^{25}$ +48 (*c* 0.9, CH_2Cl_2); IR ν_{max} 3306, 2922, 1746, 1543, 1370, 1223, 1040, 993, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H, NHAr), 7.25 (s, 2H, Ar), 6.16 (d, 1H, $J_{2,NH}$=8.9 Hz, NH), 5.75 (d, 1H, $J_{1,2}$=8.2 Hz, H-1), 5.23 (dd, 1H, $J_{2,3}$=10.2 Hz, $J_{3,4}$=9.0 Hz, H-3), 5.18 (t, 1H, $J_{4,5}$=9.5 Hz, H-4), 5.12 (m, 1H, H-2), 4.21 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.09 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b), 3.61 (ddd, 1H, H-5), 2.22, 2.12, 2.08, 2.00 (4s, 3H each, 4×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.6 (C=Se), 172.1, 170.7, 170.1, 168.9 (4×CO), 135.4, 129.1 (Ar), 92.7 (C-1), 73.3 (C-5), 72.3 (C-3), 67.6 (C-4), 61.7 (C-6), 61.0 (C-2), 21.4, 21.0, 20.8, 20.6 (4×*C*H_3CO); FABMS *m*/*z* 1005 ([M+Na]$^+$, 5%); HRFAB-MS *m*/*z* calcd for $C_{36}H_{46}N_4NaO_{18}^{80}Se_2$, [M+Na]$^+$: 1005.1035, found: 1005.1036. Anal. Calcd for $C_{36}H_{46}N_4O_{18}Se_2$: C, 44.09; H, 4.73; N, 5.71. Found: C, 44.01; H, 4.70; N, 5.75.

3.12. *N,N′*-Bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)selenourea (42)

To a solution of isoselenocyanate **39** (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) were added 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride **36** (41 mg, 0.11 mmol) and Et_3N (14 μL, 0.11 mmol). The mixture was kept in the darkness at rt, under Ar, for 24 h. Then, it was concentrated to dryness and the residue was purified by column chromatography (hexane→1:2 hexane–EtOAc) to give selenourea **42** (64 mg, 74%) as an amorphous solid; R_f 0.54 (1:5 hexane–EtOAc); $[\alpha]_D^{24}$ +7 (*c* 1.2, CH_2Cl_2); IR ν_{max} 3335, 2930, 1751, 1545, 1370, 1227, 1040, 901, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, 1H, $J_{2,NH}$=8.6 Hz, NH), 5.83 (d, 1H, $J_{1,2}$=8.2 Hz, H-1), 5.45 (dd, 1H, $J_{2,3}$=10.2 Hz, $J_{3,4}$=9.0 Hz, H-3), 5.23 (m, 1H, H-2), 4.99 (t, 1H, $J_{4,5}$=9.5 Hz, H-4), 4.19 (m, 2H, H-6a, H-6b), 3.95 (m, 1H, H-5), 2.15, 2.08 (×2), 2.04 (4s, 3H each, 4×Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 186.1 (C=Se), 172.1, 170.8 (×2), 170.1 (4×CO), 93.0 (C-1), 72.6 (C-3), 72.4 (C-5), 69.0 (C-4), 61.8 (C-6), 60.0 (C-2), 21.5, 20.9, 20.8 (×2) (4×CH_3CO); FABMS *m*/*z* 807 ([M+Na]$^+$, 10%); HRFAB-MS *m*/*z* calcd for $C_{29}H_{40}N_2NaO_{18}^{80}Se$, [M+Na]$^+$: 807.1339, found: 807.1333.

3.13. 1,3,4,6-Tetra-*O*-acetyl-2-(3-benzoylselenoureido)-2-deoxy-β-D-glucopyranose (45)

To a solution of benzoyl chloride (81 μL, 0.70 mmol) in acetone (1.5 mL) was added dropwise a solution of KSeCN (101 mg, 0.70 mmol) in acetone (2.5 mL) at rt. The mixture was stirred at rt for 2 h, and then, it was concentrated to dryness. The residue was suspended in CH_2Cl_2 and the solids were filtered off. The filtrate was concentrated to dryness and the residue (**44**, 115 mg, 77%) was used for the next step without further purification. To a solution of freshly prepared benzoyl isoselenocyanate (115 mg, 0.55 mmol) in CH_2Cl_2 (8 mL) were added hydrochloride **36** (142 mg, 0.37 mmol) and Et_3N (53 μL, 0.37 mmol). The mixture was stirred in the darkness at rt, under Ar, for 24 h. Then, it was concentrated to dryness and the residue was purified by column chromatography (hexane→3:2 hexane–EtOAc), to give **45** as a yellow solid (202 mg, 98%); mp: 160–162 °C (EtOH); R_f 0.70 (1:2 hexane–EtOAc); $[\alpha]_D^{20}$ +2 (*c* 0.7, CH_2Cl_2); IR ν_{max} 3453, 1749, 1676, 1515, 1370, 1222, 1041, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.43 (d, 1H, $J_{2,NH}$=9.5 Hz, NH), 9.29 (s, 1H, NHBz), 7.85–7.49 (m, 5H, Ar), 5.95 (d, 1H, $J_{1,2}$=8.1 Hz, H-1), 5.39 (t, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=8.9 Hz, H-3), 5.24 (t, 1H, $J_{4,5}$=9.6 Hz, H-4), 5.20 (m, 1H, H-2), 4.33 (dd, 1H, $J_{5,6a}$=4.7 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.18 (dd, 1H, $J_{5,6b}$=2.6 Hz, H-6b), 3.91 (ddd, 1H, H-5), 2.15, 2.11, 2.07 (×2) (3s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 184.0 (C=Se), 170.8, 170.5, 169.4, 169.3 (4×CO), 166.4 (Ph*C*O), 134.2, 130.9, 129.4, 127.8 (Ar), 92.1 (C-1), 73.1 (C-5), 72.2 (C-3), 67.5 (C-4), 61.8 (C-6), 60.9 (C-2), 21.2, 20.9 (×2), 20.7 (4×*C*H_3CO); LSIMS *m*/*z* 581 ([M+Na]$^+$, 10%); HRLSI-MS *m*/*z* calcd for $C_{22}H_{26}N_2NaO_{10}^{80}Se$, [M+Na]$^+$: 581.0650, found: 581.0630. Anal. Calcd for $C_{22}H_{26}N_2O_{10}Se$: C, 47.40; H, 4.70; N, 5.03. Found: C, 47.53; H, 4.64; N, 5.12.

3.14. *N*-Benzoyl-*Se*-phenacyl-*N′*-(1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranos-2-yl)isoselenourea (46)

To a solution of *N*-benzoyl selenourea **45** (200 mg, 0.36 mmol) in DMF (10 mL) were added phenacyl bromide (86 mg, 0.43 mmol, 1.2 equiv) and DIEA (94 μL, 0.54 mmol, 1.5 equiv), and the mixture was kept in the darkness at rt for 5 h. Then, it was concentrated to dryness and the residue was purified by column chromatography (10:1 hexane–EtOAc→2:1 hexane–EtOAc) to give *Se*-phenacyl

isoselenourea **46** as an amorphous solid (122 mg, 50%). R_f 0.43 (1:1 hexane–EtOAc); $[\alpha]_D^{20}$ +60 (*c* 1.1, CH_2Cl_2); IR ν_{max} 3472, 2923, 1750, 1610, 1494, 1347, 1225, 1043, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, $J_{2,NH}$=8.3 Hz, NH), 8.25 (m, 2H, Ar–H*o*), 7.96 (m, 2H, Ar–H*o*′), 7.64 (m, 1H, Ar–H*p*′), 7.52 (m, 1H, Ar–H*p*), 7.50 (m, 2H, Ar–H*m*′), 7.46 (m, 2H, Ar–H*m*), 6.03 (d, 1H, $J_{1,2}$=8.8 Hz, H-1), 5.50 (t, 1H, $J_{2,3}$=$J_{3,4}$=9.8 Hz, H-3), 5.27 (t, 1H, $J_{4,5}$=9.6 Hz, H-4), 5.03 (m, 1H, H-2), 4.40 (dd, 1H, $J_{5,6a}$=4.7 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.18 (dd, 1H, $J_{5,6b}$=2.3 Hz, H-6b), 4.01 (s, 2H, CH_2), 3.99 (ddd, 1H, H-5), 2.14, 2.08, 1.98, 1.94 (4s, 3H each, 4×Ac). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.2 (Ph*C*OCH$_2$), 176.7 (N=*C*–Se), 170.8, 170.6, 169.7, 169.2 (4×CO), 168.0 (Ph*C*ON), 135.7, 134.5 (Ar–C), 134.6 (C*p*′), 132.7 (C*p*), 130.1 (C*o*), 129.2 (C*o*′, C*m*′), 128.4 (C*m*), 92.7 (C-1), 73.2 (C-3, C-5), 68.1 (C-4), 61.9 (C-6), 57.5 (C-2), 28.7 (CH_2), 20.9 (×2), 20.8 (×2) (4×*C*H$_3$CO). LSIMS *m*/*z* 677 ([M+H]$^+$, 50%); HRLSI-MS *m*/*z* calcd for $C_{30}H_{33}N_2NaO_{11}^{80}Se$, [M+H]$^+$: 677.1250, found: 677.1242.

3.15. 5-Benzoyl-4-phenyl-2-(1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranos-2-yl)amino-1,3-selenazole (47)

To a solution of *Se*-phenacyl isoselenourea **46** (61 mg, 0.09 mmol) in EtOH (4 mL) was added AcOH (0.4 mL) and the resulting mixture was refluxed in the darkness for 1.5 h. Then, it was concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2 → 100:1 CH_2Cl_2–MeOH) to give **47** as a syrup (46 mg, 79%); R_f 0.39 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ −10 (*c* 1.0, CH_2Cl_2); IR ν_{max} 2926, 1752, 1544, 1467, 1372, 1326, 1220, 1040, 707 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.83 (d, 1H, $J_{2',NH}$=8.7 Hz, NH), 7.33 (m, 2H, Ar–H*o*), 7.28 (m, 1H, Ar–H*p*), 7.24 (m, 2H, Ar–H*o*′), 7.15 (m, 1H, Ar–H*p*′), 7.11 (m, 2H, Ar–H*m*′), 7.07 (m, 2H, Ar–H*m*), 5.96 (d, 1H, $J_{1',2'}$=8.3 Hz, H-1′), 5.41 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.7 Hz, H-3′), 4.99 (t, 1H, $J_{4',5'}$=9.7 Hz, H-4′), 4.20 (dd, 1H, $J_{5',6a'}$=4.5 Hz, $J_{6a',6b'}$=12.4 Hz, H-6a′), 4.18 (m, 1H, H-2′), 4.12 (ddd, 1H, $J_{5',6b'}$=2.1 Hz, H-5′), 4.01 (dd, 1H, H-6b′), 2.05, 2.01, 1.99, 1.90 (4s, 12H, 4×Ac); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 2H, Ar–H*o*), 7.31 (m, 2H, Ar–H*o*′), 7.23 (m, 1H, Ar–H*p*), 7.13 (m, 1H, Ar–H*p*′), 7.07 (m, 4H, Ar–H*m*′, Ar–H*m*), 5.62 (d, 1H, $J_{1',2'}$=8.5 Hz, H-1′), 5.16 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.6 Hz, H-3′), 5.11 (t, 1H, $J_{4',5'}$=9.6 Hz, H-4′), 4.29 (dd, 1H, $J_{5',6a'}$=4.5 Hz, $J_{6a',6b'}$=12.5 Hz, H-6a′), 4.08 (dd, 1H, $J_{5',6b'}$=2.2 Hz, H-6b′), 3.78 (br t, 1H, H-2′), 3.68 (ddd, 1H, H-5′), 2.11, 2.10, 2.04 (×2) (3s, 3H each, 4×Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.5 (Ph*C*O), 172.9 (C-2), 170.8, 170.7, 169.5, 169.0 (4×CO), 158.2 (C-4), 138.0, 135.2 (Ar–C), 131.6 (C*p*), 130.3 (C*o*′), 129.3 (C*o*), 128.9, 128.8 (C*p*′, C-5), 127.9, 127.8 (C*m*, C*m*′), 92.8 (C-1′), 73.1 (C-3′), 72.9 (C-5′), 67.9 (C-4′), 61.6 (C-6′), 61.3 (C-2′), 21.2, 21.0, 20.9, 20.7 (4×*C*H$_3$CO); LSIMS *m*/*z* 659 ([M+H]$^+$, 10%); HRLSI-MS *m*/*z* calcd for $C_{30}H_{31}N_2O_{10}^{80}Se$, [M+H]$^+$: 659.1144, found: 659.1151.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.038.

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