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# Synthesis of 5′-seleno-xylofuranosides

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ABSTRACT

The synthesis of selenium derivatives of naturally occurring chiral molecules is becoming increasingly important in recent years. In this context, we describe herein an easy, straightforward synthetic route for the preparation of a series of chiral seleno-furanosides, starting from the readily available carbohydrate D-xylose. In addition, selected compounds were screened as inhibitors of the δ-aminolevulinate dehydratase (δ-ALA-D) enzyme. Diselenide **4** was found to reduce significantly the enzymatic activity, while seleno-furanoside **1a** increased δ-ALA-D activity.



## 1. Introduction

Organoselenium chemistry has continued to attract considerable attention due to its pivotal role in the synthesis of a large number of biological compounds (e.g., seleno-carbohydrates, selenoamino acids, and selenopeptides).[1,2] Dietary selenium is an essential element in human nutrition, playing important roles in cancer prevention, immunology, aging, male reproduction, and other physiological processes.[3] Indeed, organoselenium compounds have also emerged as an exceptional class of structures, which exemplify a role in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[4] However, despite to the growing importance of this field, methods for the incorporation of the selenium atom in carbohydrates and derivatives are limited, compared to the its closest relative sulfur,[5] and there is still a need for further developments toward the synthesis of carbohydrate-derived chiral selenium-compounds, potentially candidates for biological evaluation.[6] In particular, recently seleno-carbohydrates have been described to be effective depigmenting compounds on a mushroom tyrosinase inhibitory assay and some compounds inhibited melanin synthesis in the melan-A cells, in similar levels to phenylthiourea, which is a well-known inhibitor of such process.[7] Besides, carbohydrates presenting an organoselenium group at the anomeric position have also been described to act as selective glycosylating agents in the synthesis of oligosaccharides,[8] and as useful intermediates for the synthesis of functionalized glycals,[9] *C*-glycosides[10] and glycoconjugates.[11]

In this context, by reviewing the current literature we found that studies are mainly focused on the introduction of the organoselenium moiety at the anomeric position of pyranoside sugars. More specifically, Misra and co-workers described the preparation of several selenoglycosides by the reaction between glycosyl bromides and organic diselenides, mediated by powdered zinc, in the presence of catalytic amounts of $ZnCl_2$, delivering preferentially the β-selenoglycoside.[12] The same authors have discovered that changing the $Zn/ZnCl_2$ promoter to indium (I) iodide, the α anomer could be obtained preferentially.[13] Additionally, selenoglycosides have also been obtained in high yields by reaction of glycosyl chlorides or bromides and *p*-methylselenobenzoate.[14]

It is worth to note that the development of methods for the synthesis of furanoside-based seleno-carbohydrates is scarcely studied. Thus, we describe herein a short synthetic route for the preparation of a series of chiral 5′-seleno-furanosides **1**, starting from the readily available carbohydrate D-xylose (Fig. 1).[15]

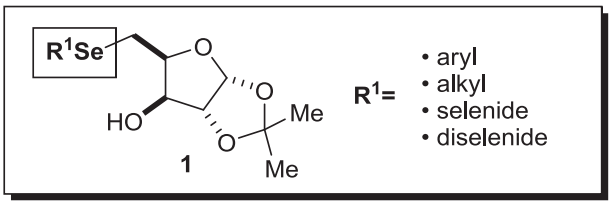


**Figure 1.** General structure of 5′-seleno-xylofuranosides.

An attractive feature related to the structure of seleno-xylofuranosides **1**, is the presence of a free hydroxyl group near to the selenium atom, in a cis relationship. This is relevant, since it

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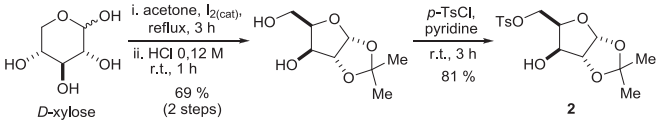
is known that intramolecular non-bonding interaction between selenium and other heteroatoms, such O and N, has a beneficial effect to the glutathione peroxidase (GPx) like activity of numerous simple, synthetic organoselenium compounds.[1,16]

## 2. Results and discussion

For the introduction of the selenium moiety in the carbohydrate framework, we decided to use the known tosylate **2** as the precursor. Thus, this compound was straightforwardly obtained by a short synthetic sequence, as outlined in Scheme 1.

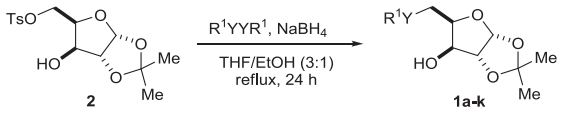



**Scheme 1.** Synthesis of tosylate **2**.

First, the treatment of D-xylose with acetone, in the presence of catalytic amounts of $I_2$ furnished the corresponding di-isopropylidene-D-xylofuranose,[17] which was selectively hydrolyzed with HCl 0.12 M, to the corresponding diol in 69% yield. Important to mention is that the concentration of the HCl solution had to be carefully optimized, since more concentrated solutions hydrolyzed both isopropylidene groups, while more diluted ones did not furnish the desired product. Reaction of the primary hydroxyl group with *p*-TsCl in pyridine as described by Lu and Just[18] delivered the desired tosylate **2** in 81% yield (Scheme 1).

With tosylate **2** in hands, we turned our attention to the incorporation of the organoselenium moiety in the furanoside backbone, through the nucleophilic substitution of the OTs leaving group (Table 1). Studies toward the optimization of this step were performed using phenylselenide nucleophile, which was generated in situ from the corresponding diphenyl diselenide, by reduction with $NaBH_4$, according to our previous work.[19] After screening several reaction parameters, in particular temperature and solvent, we found that the best results were achieved in a 3:1 mixture of THF and ethanol, under reflux. Under these conditions, tosylate **2** was cleanly converted into seleno-carbohydrate **1a** and the product was isolated in 83% yield (Table 1, entry 1). Experiments conducted using either ethanol or THF alone, did not result in any formation of the desired product. Also, when the reaction was carried out at room temperature, the isolated yield of selenide **1a** dropped to 55%.

**Table 1**
Syntheses of seleno-xylofuranoses **1**



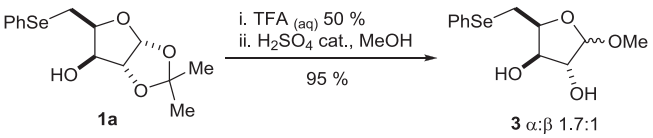

| Entry | $R^1YYR^1$ | $R^1Y$ | Yield[a] (%) |
|---|---|---|---|
| 1 | $(PhSe)_2$ | PhSe (**1a**) | 83 |
| 2 | $(4\text{-ClPhSe})_2$ | 4-ClPhSe (**1b**) | 84 |
| 3 | $(4\text{-}CF_3PhSe)_2$ | 4-$CF_3$PhSe (**1c**) | 79 |
| 4 | $(4\text{-OMePhSe})_2$ | 4-OMePhSe (**1d**) | 84 |
| 5 | $(4\text{-MePhSe})_2$ | 4-MePhSe (**1e**) | 83 |
| 6 | $(2\text{-thienylSe})_2$ | 2-thienylSe (**1f**) | 81 |
| 7 | $(BnSe)_2$ | BnSe (**1g**) | 72 |
| 8 | $(n\text{-BuSe})_2$ | *n*-BuSe (**1h**) | 88 |
| 9 | $(PhS)_2$ | PhS (**1i**) | 64 |
| 10 | $(4\text{-MePhTe})_2$ | 4-MePhTe (**1j**) | 54 |

[a] Isolated yields.

Next, we extended our studies to a broader range of selenium nucleophiles, in order to prepare a small library of compounds, which would be highly desirable for biological evaluation of such compounds. Thus, we extended the optimal conditions to a wide range of selenium nucleophiles, as depicted in Table 1. The reaction is tolerant to a variety of substituents at the aromatic ring of the organoselenium moiety, allowing the preparation of a series of seleno-carbohydrates.

We could successfully perform the reaction starting with aromatic diselenides possessing electron-withdrawing groups, such as 4-ClPh (entry 2, 84% yield), 4-$CF_3$Ph (entry 3, 79% yield) and the electron-donating groups, 4-MeOPh (entry 4, 84% yield) and 4-MePh (entry 5, 83% yield). Moreover, the introduction of heteroaromatic (2-thienyl, entry 7, 81% yield) and aliphatic groups (Bn, entry 6, 72% yield; and *n*-Bu, entry 8, 88% yield) were also achieved in very good yields. It is noteworthy that all reactions proceeded smoothly, with very little by-product formation. Due to the success obtained with the preparation of the seleno-carbohydrates, we decided to extend our studies to sulfur and tellurium analogues, in order to prepare some different chalcogen carbohydrate derivatives, based on the xylose-derived framework. In fact, reduction of diphenyl disulfide or *p*-toluyl ditelluride with $NaBH_4$, under the same conditions used for the diselenides, followed by reaction with **2**, delivered the corresponding thio-carbohydrate **1i** and telluro-carbohydrate **1j** in moderate yields (Table 1, entries 10 and 11).

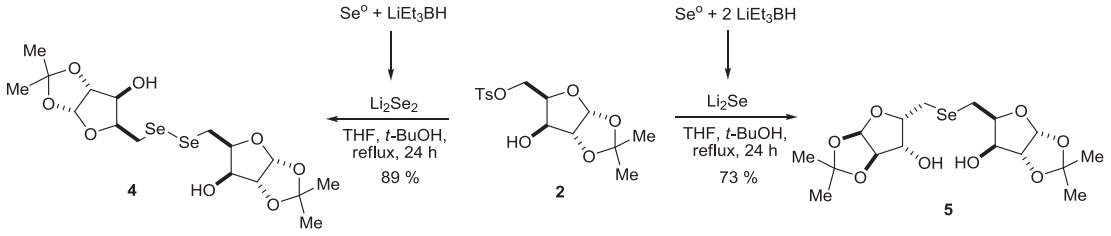
Additionally, the seleno-furanoside **1a**, which presents the isopropylidene protecting group, was converted into methyl seleno-xylofuranoside in a straightforward manner (Scheme 2). First, treatment with aqueous trifluoroacetic acid lead to deprotection of the cis diol, and the crude product was immediately converted into the corresponding methyl glycoside by reaction with MeOH, in the presence of a catalytic amount of acid. The desired product **3** was obtained in 95% yield (two steps), as a 1.7:1(α:β) mixture of anomers, as determined by $^1H$ NMR analysis.




**Scheme 2.** Synthesis of methyl seleno-furanoside **3**.

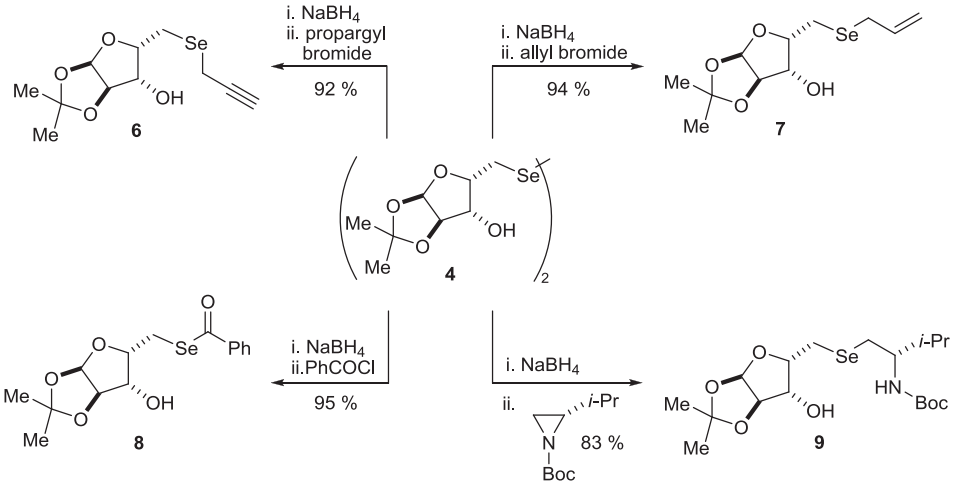
Furthermore, we have also performed the reaction of tosylate **2** with lithium diselenide, prepared by reaction of elemental selenium with $LiEt_3BH$.[20] Using THF/*t*-BuOH as solvent, the tosylate **2** underwent smooth substitution and we were able to prepare carbohydrate-derived diselenide **4** in 89% yield. It is worth mentioning that this compound was already described several years ago by Van Es and co-workers, *en route* to the synthesis of 5-deoxy-5-seleno-D-xylose.[21] In their synthesis, the authors employed a two step procedure, starting from tosylate **2**, with an overall yield of 42%. By our protocol, the diselenide **4** was directly obtained in higher yield, in a single reaction. Besides, changing the stoichiometry between the elemental selenium and $LiEt_3BH$,[22] lithium selenide was generated and its reaction with tosylate **2** furnished the selenide **5** in 73% yield (Scheme 3).

In order to highlight the synthetic utility of diselenide **4**, selected transformations to functionalized seleno-furanosides were performed and are depicted in Scheme 4. For example, cleavage of diselenide **4** with sodium borohydride, followed by trapping of the resulting selenide anion with several electrophiles leads to interesting selenium derivatives possessing the seleno-furanoside nucleus. Thus, the selenide was alkylated with propargyl and allyl




**Scheme 3.** Syntheses of **4** and **5**.

bromide and the corresponding products **6** and **7** were isolated in 92 and 94% yield, respectively. When the electrophile used was benzoyl chloride, the corresponding selenol ester **8** could be cleanly prepared in 95% isolated yield. Selenol esters are important intermediates in organic synthesis and also the investigation of new molecular material, in particular, liquid crystals.[23] Finally, ring-opening of an aziridine, derived from the enantiopure amino acid L-valine, was accomplished in a mild and selective manner, leading to the seleno-glycoconjugate **9** in 83% yield.




**Scheme 4.** Synthesis of functionalized seleno-furanosides.

Although selenium-compounds generally hold promise as potent antioxidant compounds, they are generally poisonous to mammalian systems.[24] Some investigators believe that selenium-compounds exert their toxic effects through interference with certain enzyme systems in the living organism, particularly through mercaptide formation with important sulphydryl enzymes with physiological importance in biological systems.[1b] Thus, we selected seleno-furanosides (**1a**, **1b**, **1g**) and the carbohydrate-derived diselenide (**4**) to evaluate their effect on δ-aminolevulinate dehydratase (δ-ALA-D) activity of rat liver in vitro.

δ-ALA-D catalyzes the asymmetric condensation of two molecules of δ-aminolevulinic acid (δ-ALA) to porphobilinogen in the initial steps of heme biosynthesis.[25] δ-ALA-D is a sulfhydryl containing enzyme and compounds that oxidize sulfhydryl groups modified its activity.[26] Of particular importance, organoselenium compounds like ebselen and diphenyl diselenide demonstrated an inhibitory effect on this enzyme activity in vitro.[24,27] On the other hand, diphenyl diselenide demonstrated many pharmacological properties;[1b] in particular, this compound was able in restoring oxidative parameters changed after cadmium exposure.[28]

Thus, we verified that the compound **4** (carbohydrate-derived diselenide) significantly inhibited the δ-ALA-D activity of rat liver in all tested concentrations. In fact, 50 μM of this compound reduced around 90% of the enzyme activity. The inhibitory potency of compound **1g** (thiophene derivative) was lower than compound **4** because 50 μM reduced the enzyme activity about 16%. Similarly, compound **1b** demonstrated a significant inhibitory effect only at high 400 μM concentrations, indicating an advantage about the possible toxicological properties of these compounds. Thereby, the inhibition caused by these compounds followed the order of **4**>**1g**>**1b**. Compound **4**, a carbohydrate-derived diselenide, demonstrated the strongest potential inhibitory in δ-ALA-D activity (Fig. 2). This enzyme is an important indicator of toxicity since enzyme inhibition may impair heme biosynthesis and can result in the accumulation of ALA substrate, which has some pro-oxidant

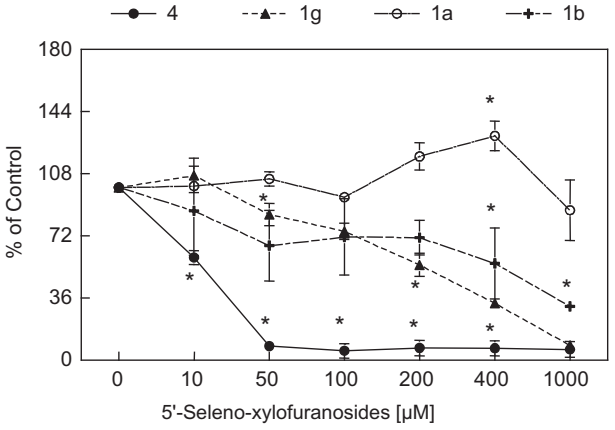



**Figure 2.** Effect of 5′-seleno-xylofuranosides (**1a**, **1b**, **1g**, and **4**) on hepatic δ-ALA-D activity of rat in vitro. *Denoted $p<0.05$ as compared to control group (ANOVA/Duncan).

activity.[29] On the other hand, compound **1a** (seleno-furanoside) did not reduce δ-ALA-D activity and it increased enzyme activity in the concentration of 400 μM (Fig. 2). Considering that δ-ALA-D is extremely sensitive to the presence of pro-oxidants elements, which can oxidize its –SH groups during oxidative stress, we can infer that compound **1a** presents a very low toxicity.

## 3. Conclusions

In summary, the present work describes the preparation of chiral selenium-containing carbohydrates in an easy and efficient strategy. We believe that approach may have significant importance in the design of new selenium-containing carbohydrates for biological screenings. Initial studies in this area reveal that the properties of organoselenium compounds may be related in parts to their observed in vitro *anti*-oxidative activity making them promising candidates as medicaments in the management of a number of diseases in which oxidative stress have been implicated in their etiology.[1b] Taking into account our results we can suggest that the compound **1a** could be a potential candidate for further studies of antioxidant potential as well as toxicological and pharmacological effects. Studies to further evaluate the potential of these compounds are currently underway.

## 4. Experimental

### 4.1. General procedures

$^1$H 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.[30] Thin layer chromatography (TLC) was performed using Merck Silica Gel $GF_{254}$, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. THF was dried over sodium benzophenone ketyl and distilled prior to use. Dichloromethane was distilled from phosphorus pentoxide. All other solvents were used as purchased unless otherwise noted. Tosylate **2** was prepared according to literature procedures.[18] Yields refer to chromatographically and spectroscopically homogeneous materials with purity of >95%, as judged by $^1$H NMR spectroscopy.

### 4.2. General procedure for the preparation of seleno-carbohydrates 1

Under an argon atmosphere, sodium borohydride was added to a solution of the diorganoil diselenide (0.55 mmol) in THF (4 mL). Ethanol (2 mL) was then added dropwise and the clear solution formed was stirred at room temperature for 10 min. After this time a solution of the tosylate **2** (1 mmol in 1 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).

*4.2.1. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-(phenylselanylmethyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1a**).* Yield: 83%; $[\alpha]_D^{20}$ −45.4 (*c* 1.3, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.59–7.56 (m, 2H), 7.28–7.26 (m, 3H), 5.91 (d, *J*=3.7 Hz, 1H), 4.50 (d, *J*=3.7 Hz, 1H), 4.35–4.29 (m, 1H), 4.24 (s, 1H), 3.23–3.10 (m, 2H), 1.42 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=133.3, 129.3, 128.0, 127.6, 111.7, 104.7, 85.1, 80.0, 74.8, 26.6, 26.2, 24.3; HRMS-ESI: *m*/*z* calcd for $C_{14}H_{18}O_4Se+Na^+$: 353.0263; found: 353.0269.

*4.2.2. (3aR,5S,6R,6aR)-5-((4-Chlorophenylselanyl)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1b).* Yield: 84%; $[\alpha]_D^{20}$ −52.2 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.48 (d, *J*=8.0 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 5.91 (d, *J*=3.6 Hz, 1H), 4.50 (d, *J*=3.6 Hz, 1H), 4.31–4.22 (m, 2H), 3.20–3.08 (m, 2H), 1.42 (s, 3H), 1.26 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=134.6, 133.8, 129.4, 127.4, 111.8, 104.8, 85.2, 79.7, 74.9, 26.7, 26.2, 24.7; HRMS-ESI: *m*/*z* calcd for $C_{14}H_{17}ClO_4Se+Na^+$: 386.9879; found: 386.9870.

*4.2.3. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-((4-(trifluoromethyl) phenylselanyl)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1c**).* Yield: 79%; $[\alpha]_D^{20}$ −48.0 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.54 (dd, $J^1$=8.5 Hz; $J^2$=5.5 Hz, 2H), 6.96 (t, *J*=8.5 Hz, 2H), 5.90 (d, *J*=3.6 Hz, 1H), 4.50 (d, *J*=3.6 Hz, 1H), 4.27–4.22 (m, 2H), 3.14–3.0 (m, 2H), 1.40 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=164.3, 161.0, 136.0, 135.9, 123.5, 116.6, 116.3, 111.7, 104.7, 85.2, 79.8, 74.9, 26.6, 26.2, 24.7; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{17}F_3O_4Se+Na^+$: 421.0132; found: 421.0139.

*4.2.4. (3aR,5S,6R,6aR)-5-((4-Methoxyphenylselanyl)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1d**).* Yield: 84%; $[\alpha]_D^{20}$ −56.4 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.53 (d, *J*=8.1 Hz, 2H), 6.81 (d, *J*=8.1 Hz, 2H), 5.88 (d, *J*=3.6 Hz, 1H), 4.47 (d, *J*=3.6 Hz, 1H), 4.30–4.20 (m, 2H), 3.78 (s, 3H), 3.11–2.95 (m, 2H), 1.42 (s, 3H), 1.28 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=159.3, 135.8, 118.1, 114.6, 111.7, 104.2, 84.6, 79.8, 74.8, 54.9; 26.2, 25.8, 24.8; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{20}O_5Se+Na^+$: 383.0374; found: 383.0373.

*4.2.5. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-(p-tolylselanyl-methyl) tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1e**).* Yield: 83%; $[\alpha]_D^{20}$ −30.0 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.54 (d, *J*=7.6 Hz, 2H), 7.15 (d, *J*=7.6 Hz, 2H), 5.96 (d, *J*=3.5 Hz, 1H), 4.55 (d, *J*=3.5 Hz, 1H), 4.40–4.34 (m, 1H), 4.28 (s, 1H), 3.24–3.11 (m, 2H), 2.38 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=137.9, 133.8, 130.1; 125.1; 111.6; 104.7; 85.1; 80.2; 74.9; 26.6; 26.2; 24.7; 21.1; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{20}O_4Se+Na^+$: 367.0425; found: 367.0421.

*4.2.6. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-((thiophen-2-ylselanyl) methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1f**).* Yield: 81%; $[\alpha]_D^{20}$ −31.6 (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.42 (d, *J*=5.3 Hz, 1H), 7.28 (d, *J*=3.7 Hz, 1H), 7.01 (dd, $J^1$=5.3 Hz; $J^2$=3.7 Hz, 1H), 5.92 (d, *J*=3.6 Hz, 1H), 4.52 (d, *J*=3.6 Hz, 1H), 4.35–4.32 (m, 2H), 3.13–2.97 (m, 2H), 1.47 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=136.4; 131.5; 130.7; 128.2; 111.7; 104.6; 85.1; 79.9; 74.9; 27.5; 26.6; 26.2; HRMS-ESI: *m*/*z* calcd for $C_{12}H_{16}O_4SSe+Na^+$: 358.9833; found: 358.9840.

*4.2.7. (3aR,5S,6R,6aR)-5-(Benzylselanylmethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1g**).* Yield: 72%; $[\alpha]_D^{20}$ −55.8 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=7.38–7.23 (m, 5H), 5.90 (d, *J*=3.6 Hz, 1H), 4.51 (d, *J*=3.6 Hz, 1H), 4.33–4.22 (m, 2H), 3.80 (s, 2H), 2.85 (dd, $J^1$=12.0 Hz; $J^2$=5.3 Hz, 1H), 2.70 (dd, $J^1$=12.0 Hz; $J^2$=9.5 Hz, 1H), 2.0 (d, *J*=4.7 Hz, 1H), 1.47 (s, 3H), 1.30 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=139.1, 128.9, 128.7, 127.0, 111.7, 104.8, 85.1, 80.1, 75.2, 28.4, 26.8, 26.2, 20.3; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{20}O_4Se+Na^+$: 367.0425; found: 367.0424.

*4.2.8. (3aR,5S,6R,6aR)-5-(Butylselanylmethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1h**).* Yield: 88%; $[\alpha]_D^{20}$ −48.3 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz, ppm) δ=5.99 (d, *J*=3.6 Hz, 1H), 4.60 (d, *J*=3.6 Hz, 1H), 4.40–4.34 (m, 2H), 2.97–280 (m, 2H), 2.09 (m, 1H), 1.77–1.72 (m, 2H), 1.56 (s, 3H), 1.47 (qui, *J*=7.3 Hz, 2H), 1.37 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm) δ=111.6, 104.8,

85.2, 80.2, 75.3, 32.6, 26.7, 26.2, 24.7, 22.9, 20.1, 13.5; HRMS-ESI: *m*/*z* calcd for $C_{12}H_{22}O_4Se+Na^+$: 333.0581; found: 333.0575.

*4.2.9. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-(phenylthiomethyl)-tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1i**).* Yield: 64%; $[\alpha]_D^{20}$ −44.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz, ppm) $\delta$=7.51–7.48 (m, 2H), 7.22–7,20 (m, 3H), 5.90 (d, *J*=3.6 Hz, 1H), 4.48 (d, *J*=3.6 Hz, 1H), 4.30–4.27 (m, 1H), 4.23 (s, 1H), 3.19–3.11 (m, 2H), 1.40 (s, 3H), 1.27 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=135.2, 130.1, 129.8, 129.1, 126.8, 111.8, 104.7, 85.1, 79.3, 74.6, 31.4, 26.7, 26.2; HRMS-ESI: *m*/*z* calcd for $C_{14}H_{18}O_4S+Na^+$: 305.0824; found: 305.0825.

*4.2.10. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-((p-tolyltellanyl-selanyl) methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**1j**).* Yield: 54%; $[\alpha]_D^{20}$ −40.0 (*c* 1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz, ppm) $\delta$=7.67 (d, *J*=7.9 Hz, 2H), 7.0 (d, *J*=7.6 Hz, 2H), 5.87 (d, *J*=3.7 Hz, 1H), 4.42 (d, *J*=3.7 Hz, 1H), 4.38–4.35 (m, 1H), 4.21–4.19 (m, 1H), 3.07 (dd, $J^1$=11.9 Hz; $J^2$=5.1 Hz, 1H), 2.95 (dd, $J^1$=11.9 Hz; $J^2$=10.2 Hz, 1H), 2.29 (s, 3H), 1.51 (s, 3H), 1.24 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=139.4, 138.5, 130.4; 111.6; 106.7, 104.9, 85.3, 81.8, 75.5, 26.7, 26.3, 21.2, 4,6; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{20}O_4Te+Na^+$: 417.0322; found: 417.0309.

### 4.3. Procedure for the synthesis of (3*R*,4*R*,5*S*)-2-methoxy-5-(phenylselanylmethyl)tetrahydrofuran-3,4-diol (3)

In a round bottomed flask, seleno-carbohydrate **1a** (165 mg, 0.5 mmol) was stirred in an aqueous solution of trifluoracetic acid (50%) for 1 h at room temperature. After this time, the reaction mixture was concentrated in vacuum, co-evaporated with toluene (3×15 mL) and the residue dissolved in a MeOH (10 mL), in the presence of a catalytic amount of sulfuric acid, and stirred for additional 24 h, at room temperature. Following this time, the mixture was neutralized by the addition of sodium bicarbonate. The mixture was filtered and the solvents evaporated to afford the product **3** as a 1.7:1 mixture of anomers. Yield: 95%; $^1H$ NMR ($CDCl_3$, 250 MHz, ppm) $\delta$=7.57–7.50 (m, 2H), 7.29–7.20 (m, 3H), 4.96 (d, *J*=4.3 Hz, 0.37H), 4.82 (s, 0.63H), 4.52 (td, $J^1$=7.3 Hz; $J^2$=4.0 Hz, 0.63H), 4.35 (td, $J^1$=7.0 Hz; $J^2$=5.0 Hz, 0.37H), 4.24–4.17 (m, 1H), 4.14–4.04 (m, 1H), 3.44 (s, 1.1H), 3.34 (s, 1.9H), 3.20–3.00 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz, ppm) $\delta$=132.8, 132.6, 130.0, 129.7, 129.1, 129.0, 127.2, 127.0, 108.5, 101.6, 86.5, 79.6, 78.4, 78.1, 76.8, 76.2, 55.8, 55.1, 27.1, 26.5; HRMS-ESI: *m*/*z* calcd for $C_{12}H_{16}O_4Se+Na^+$: 327.0112; found: 327.0110.

### 4.4. Procedure for the synthesis of (3a*R*,3a′*R*,5*S*,5′*S*,6*R*,6a*R*,6′*R*,6a′*R*)-5,5′-diselanediylbis-(methylene)bis(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]-dioxol-6-ol) (4)

Under an argon atmosphere, dithium diselenide was generated by reaction of gray elemental selenium (95 mg, 1.2 mmol) with lithium triethylborohydride (1.2 mL, 1.2 mmol). The suspension was allowed to stir for at least 20 min, and *t*-BuOH (0.2 mL) and THF (4 mL) were added, followed by dropwise addition of a solution of tosylate **2** (172 mg, 0.5 mmol) in THF (1 mL). The resulting solution was stirred for 24 h under reflux. The mixture was quenched with a saturated $NH_4Cl$ solution (20 mL), extracted with $CH_2Cl_2$ and the combined organic fractions were collected, dried over $MgSO_4$ and filtered, the solvent was removed in vacuo. The crude product was purified by flash chromatography (hexane/ethyl acetate 50:50) to afford the diselenide **4.** Analytical data for **4**: Yield: 89%; $[\alpha]_D^{20}$ +8.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz, ppm) $\delta$=5.93 (d, *J*=3.7 Hz, 1H), 4.55 (d, *J*=3,7 Hz, 1H), 4.41 (td, *J*=7.0 Hz, *J*=2.5 Hz, 1H), 4.30–4.29 (m, 1H), 3.30–3.27 (m, 2H), 2.38–2.36 (m, 1H), 1.51 (s, 3H), 1.31 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=111.8, 104.5, 85.2, 80.9, 74.8, 26.7, 26.5, 26.2; HRMS-ESI: *m*/*z* calcd for $C_{16}H_{26}O_8Se_2+Na^+$: 528.9856; found: 528.9860.

### 4.5. General procedure for the synthesis of functionalized seleno-furanosides 6–9

Under an argon atmosphere, sodium borohydride was added to a solution of diselenide **4** (0.03 mmol, 15 mg) in THF (1 mL). Ethanol (0.3 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 appropriate electrophile (0.12 mmol in 0.3 mL THF) was added dropwise. After stirring for 24 h at room temperature, the reaction mixture was quenched with aqueous saturated $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3×10 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.

*4.5.1. (3aR,5S,6R,6aR)-2,2-Dimethyl-5-((prop-2-ynylselanyl)-methyl)-tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**6**).* Yield: 92%; $[\alpha]_D^{20}$ −36.4 (*c* 1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz, ppm) $\delta$=5.88 (d, *J*=3.7 Hz, 1H), 4.47 (d, *J*=3.7 Hz, 1H), 4.41–4.32 (m, 1H), 4.24 (d, *J*=2.3 Hz, 1H), 3.23–3.20 (m, 2H), 3.07 (dd, $J^1$=12.5 Hz; $J^2$=5.7 Hz, 1H), 2.89 (dd, $J^1$=12.5 Hz; $J^2$=9.3 Hz, 1H), 2.23 (t, *J*=2.3 Hz, 1H), 1.44 (s, 3H), 1.25 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=111.5, 104.6, 85.0, 80.7, 79.8, 75.2, 71.4, 29.4, 26.5, 26.0, 20.9; HRMS-ESI: *m*/*z* calcd for $C_{11}H_{16}O_4Se+Na^+$: 315.0112; found: 315.0108.

*4.5.2. (3aR,5S,6R,6aR)-5-(Allylselanylmethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**7**).* Yield: 94%; $[\alpha]_D^{20}$ −41.4 (*c* 1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz, ppm) $\delta$=5.92–5.74 (m, 2H), 5.01 (dd, $J^1$=16.8 Hz; $J^2$=1.3 Hz, 1H), 4.97 (dd, $J^1$=9.8 Hz; $J^2$=0.8 Hz, 1H), 4.46 (d, *J*=3.8 Hz, 1H), 4.27 (ddd, $J^1$=9.3 Hz; $J^2$=5.5 Hz; $J^3$=2.8 Hz, 1H), 4.23–4.17 (m, 1H), 3.18 (d, *J*=7.8 Hz, 2H), 2.79 (dd, $J^1$=12.0 Hz; $J^2$=5.3 Hz, 1H), 2.65 (dd, $J^1$=12.0 Hz; $J^2$=9.3 Hz, 1H), 1.92 (d, *J*=5.3 Hz, 1H), 1.43 (s, 3H), 1.25 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=134.5, 116.7, 111.5, 104.6, 84.9, 79.7, 75.1, 29.5, 26.6, 26.0, 19.4; HRMS-ESI: *m*/*z* calcd for $C_{11}H_{18}O_4Se+Na^+$: 317.0268; found: 317.0260.

*4.5.3. Se-((3aR,5S,6R,6aR)-6-Hydroxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl benzoselenoate (**8**).* Yield: 95%; $[\alpha]_D^{20}$ −40.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz, ppm) $\delta$=7.92 (d, *J*=8.5 Hz, 2H), 7.64 (tt, $J^1$=7.3 Hz; $J^2$=1.3 Hz, 1H), 7.52–7.43 (m, 2H), 5.97 (d, *J*=3.5 Hz, 1H), 4.59 (d, *J*=3.8 Hz, 1H), 4.33 (ddd, $J^1$=10.3 Hz; $J^2$=4.5 Hz; $J^3$=2.3 Hz, 1H), 4.14 (d, *J*=2.0 Hz, 1H), 3.59 (br s, 1H), 3.44 (dd, $J^1$=13.0 Hz; $J^2$=10.3 Hz, 1H), 3.25 (dd, $J^1$=13.0 Hz; $J^2$=4.5 Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz, ppm) $\delta$=197.2, 138.3, 134.4, 129.0, 127.4, 111.7, 105.0, 84.8, 81.4, 74.2, 26.7, 26.1, 21.1; HRMS-ESI: *m*/*z* calcd for $C_{15}H_{18}O_5Se+Na^+$: 381.0217; found: 381.0218.

*4.5.4. tert-Butyl (S)-1-(((3aR,5S,6R,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl-selanyl)-3-methylbutan-2-ylcarbamate (**9**).* Yield: 83%; $[\alpha]_D^{20}$ −12.7 (*c* 1.1, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz, ppm) $\delta$=5.94 (d, *J*=3.6 Hz, 1H), 4.71 (br s, 1H), 4.56 (d, *J*=3.7 Hz, 1H), 4.39–4.30 (m, 2H), 3.66–3.53 (m, 1H), 3.28 (s, 1H), 3.00–2.75 (m, 4H), 1.97–1.84 (m, 1H), 1.52 (s, 3H), 1.45 (s, 9H), 1.32 (s, 3H), 0.95 (d, *J*=6.6, 3H), 0.88 (d, *J*=6.7, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, ppm) $\delta$=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.

### 4.6. Biological activity

1. Animals: male adult albino Wistar rats (150–200 g) from our own breeding colony were used. The animals were kept in

separate animal rooms, on a 12 h light/dark cycle, at a room temperature of 22 °C, and with free access to food and water. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Medicine, Veterinary, and Animal Science of the University of Sao Paulo, Brazil.

2. Enzyme assay: δ-ALA-D activity was assayed according to the method of Sassa[31] by measuring the rate of product (porphobilinogen) formation. An aliquot of 200 μL of homogenized tissue was added in the reaction medium containing different concentrations of selenium-compounds (10, 50, 100, 200, 400 and 1000 μM). After 10 min the substrate (ALA) was added and incubated for 1 h at 37 °C. δ-ALA-D activity is reported as % of the control value (100%). Data are reported as mean ± SD, $n$=3–5.
3. Statistical analysis: statistical significance was assessed by analysis of variance (Anova) followed by Duncan's test when appropriate. A value of $p<0.05$ was considered to be significant.

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