RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 93905

Stereoselective glycoconjugation of steroids with selenocarbohydrates†

Ricardo F. Affeldt,[ac] Francisco P. Santos,[a] Rafael S. da Silva,[b] Oscar E. D. Rodrigues,[b] Ludger A. Wessjohann[c] and Diogo S. Lüdtke*[a]

Received 26th August 2016
Accepted 24th September 2016

DOI: 10.1039/c6ra21485a

www.rsc.org/advances

A methodology that brings together sugar and steroid scaffolds linked by a selenium atom is discussed in this work. A series of 6β and 3α glycoconjugated steroids were achieved by stereoselective nucleophilic substitution of cholesterol, pregnenolone, stigmasterol and sitosterol with different seleno-pyranosides and furanosides.

Introduction

Steroidal glycosides including phytosterols are important biomolecules in which one or more carbohydrate units are attached to a steroid skeleton.[1] For example, digitoxin and digoxin, extracted from *Digitalis purpurea* and *lanata*, are cardiac steroidal glycosides applied for heart failure by inhibition of Na^+ K^+ ATPase.[2] They have also shown anti-cancer activity against breast and lung cancer cells.[3] The carbohydrate moiety is known for modulating the binding on ATPase, therefore influencing its efficiency and modifications on these groups has been described to increase its biological activity substantially.[4–6] The metabolism of cardiac glycosides is dependent of the lability of the glycosyl linkage with the steroidal molecule and the carbohydrate moiety being responsible for the appropriate solubility of the molecule in the biological media and to play a role in the binding activity. In addition, recent publications[7] revealed that spirostan saponins (triterpene steroidal glycosides) feature potent cytotoxic activity against human leukemia cell lines HL-60, and antifungal, anti-inflammatory and antiviral activities.[8] The substitution of oxygen by sulfur or selenium in conjugate linkages of biomolecules has been used frequently to reduce or slow down enzymatic breakage of this bond, and to enable bioconjugations not possible otherwise.[9]

Much of the synthetic efforts towards steroid glycosides are based on modification of the sugar moiety and its introduction on the cholesterol framework by selective glycosylation reactions. Few strategies that employ modification on the traditional sugar–steroid linkage are reported for biological evaluation. Some interesting examples involve conjugation of the glycosyl and steroid units by Cu-catalyzed 1,3-dipolar cycloaddition between a sugar azide and an alkynyl steroid.[10] However, the resulting triazole linked products did not maintain the same cytotoxic profile of the parent molecules. In addition, the Ugi multicomponent reaction was also used to construct a pseudo-peptide linkage between the sugar and spirostane moieties.[11] This strategy afforded a library of glycoconjugated derivatives with unique architectures and wide substrate scope.

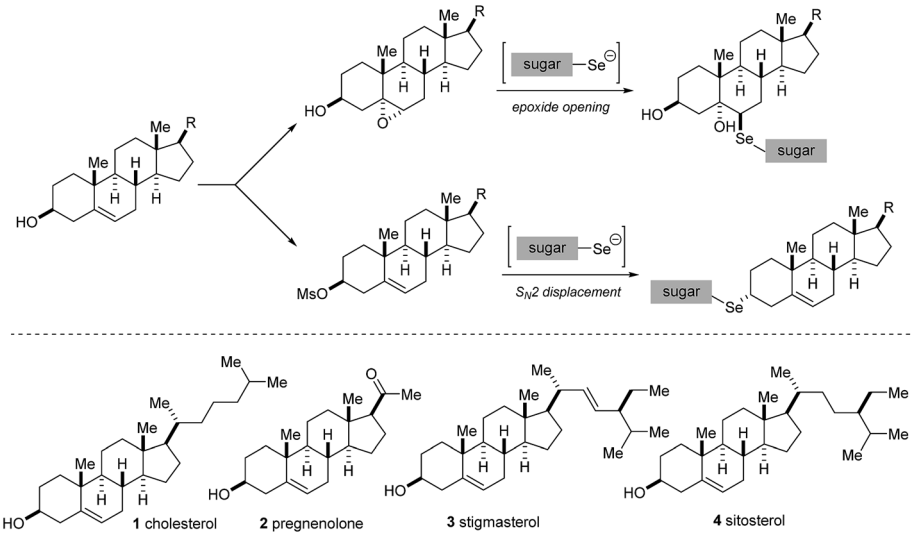
On the other hand, organoselenium compounds have received special attention by the scientific community, especially due the biological activity of sulfur-related molecules such as selenoenzymes.[12] In this context, our groups have been involved with the introduction of organoselenium moieties into the structure of carbohydrates and their derivatives, affording new classes of selenium-containing xylo-furanosides,[13] galacto-pyranosides,[14] uridine derivatives,[15] pseudodisaccharides and neoglycoconjugates.[16] Some of our arylseleno-xylo-furanosides have shown particular bioactivity protecting against Cd and Mn poisoning[17] and promising therapeutic agents for Alzheimer's disease as well.[18]

The introduction of organoselenium groups at the steroid scaffold has been scarcely reported in the literature and the few examples reported were used either as synthetic intermediates for the synthesis of hydroxylated steroids,[19] as a radioactive ^{75}Se imaging agent for the study of the distribution of cholesterol in different animal tissues,[20] and more recently as liquid crystals.[21] A relevant example describes an efficient synthesis of selenosteroids by the reaction of aromatic diselenides with cholesterol epoxides.[22,23]

In this work we report the synthesis of novel selenium-linked steroidal glycoconjugates, starting from protected-D-carbohydrate diselenide derivatives and different modified human steroids (cholesterol and pregnenolone) as well as plant steroids (stigmasterol and sitosterol). A range of selenium-containing products was obtained either by the ring-opening of epoxides

[a]*Institute of Chemistry, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves 9500, 91501-970, Porto Alegre, RS, Brazil. E-mail: dsludtke@iq.ufrgs.br*
[b]*Universidade Federal de Santa Maria, Santa Maria, RS, Brazil*
[c]*Leibniz Institute of Plant Biochemistry, Halle (Saale), Germany*

† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data and copies of NMR spectra. See DOI: 10.1039/c6ra21485a



Scheme 1 Nucleophilic steroid epoxide opening by sugar-derived organoselenium compound.

or S_N2 displacement with selenium–sugar nucleophiles (Scheme 1).

Results and discussion

We began our investigation using the diselenide **5**, derived from D-galactose and cholesterol epoxides **1a** and **1b**, which were prepared by a diastereoselective epoxidation of the double bond with *m*-CPBA.[24] The reactive organoselenium species was generated *in situ* by the reductive cleavage of the diselenide bond, to generate 2 equivalents of the corresponding organoselenium nucleophile (Table 1). By using the traditional $NaBH_4$ to promote reductive cleavage of the Se–Se bond in ethanol or THF/ethanol as solvent, the product was observed in less than 5% yield (entry 1). Since re-oxidation of the selenolate to diselenide was observed, successive additions of the reducing agent and longer reaction time led to increased yield of the desired steroidal selenoglycoconjugate (entry 3).[25] Performing the reaction in the absence of THF afforded the product less effectively (entry 4). Is worth pointing out that 1.8 equivalents of the epoxide were needed to afford reasonable yields of product **6a**. Changing the solvent to DMF, a more polar and aprotic solvent, was also examined (entries 5–8). Gratifyingly, under these conditions the desired product was obtained in 60% yield with a single addition of $NaBH_4$ and using equimolar amounts of the epoxide **1a** and the selenium nucleophile (entry 6). Further additions of the reducing agent did not result in any improvement of product formation (entry 7).

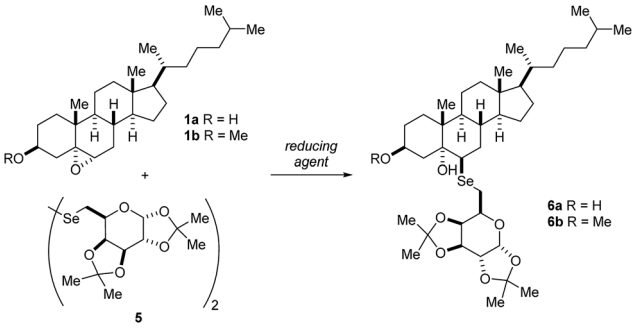
We tried to increase the reaction yield by using $ZnCl_2$ as a Lewis acidic additive (entry 8), however it resulted in almost no reaction at all, presumably due to stabilization of the selenium nucleophile. Additional attempts changing the reducing agent to $LiEt_3BH$ and $LiAlH_4$ only resulted in diminished yields of the product (entries 9 and 10). Thus, the following reaction conditions were defined as optimal and employed for further screenings: 1.0 equiv. of cholesterol epoxide **1a**, 0.5 equiv. of the sugar diselenide **5** (after cleavage, 1.0 equiv. of the corresponding selenolate anion is generated), single addition of $NaBH_4$ as the reducing agent, dry DMF for 48 h at 80 °C (entry 6). When the reaction was performed using cholesterol epoxide derivative **1b**, a slightly better yield was achieved using the THF/ethanol mixture as solvent instead of DMF (compare entries 12 and 15). However, three successive additions of $NaBH_4$ were required in order to achieve a reasonable yield of the product **6b**.

The scope of our reaction was further expanded to additional substrates, and the structures of the products are depicted in Fig. 1. We performed the reaction using the optimized conditions depicted in Table 1, entry 6, to three additional sugar diselenides, which were derived from D-xylose (Fig. 1, compounds **7a** and **7b**), D-ribose (Fig. 1, compounds **8a** and **8b**), and D-mannose (Fig. 1, compound **9a**). All steroidal selenoglycoconjugates were obtained as single isomers through a regioselective nucleophilic epoxide opening (Fig. 1).

Interesting to note is that when pregnenolone epoxide **10** was used as the substrate for the reaction with D-galactose diselenide, a mixture of 6-β-selenoglycoconjugate ketone **11a** and the corresponding alcohol **11b** was obtained in 31% and 61% yield, respectively (Scheme 2). The formation of product **11b** is explained as the result of the reduction of C20 ketone carbonyl of **11a** by the excess of $NaBH_4$.[14] Attempts to lower the amount of the reducing agent in order to maintain the ketone unreacted resulted in slow reaction and unreacted **10** was recovered.

Further application of our methodology for glycoconjugation of selenocarbohydrates with steroid derivatives was carried out using plant steroids. Stigmasterol **3** and sitosterol **4** are abundant phytosteroids found in several plant extracts and are widely used as cholesterol mimics in food additives.[26] In addition, several glycoside forms of these steroids have been reported to possess relevant bioactivities.[27] Diastereoselective epoxidation with *m*-CPBA of both compounds has been performed to deliver the desired corresponding products **12** and **13**

Table 1 Screening of reaction conditions for the reaction of diselenide **5** and cholesterol epoxides **1a** and **1b**[a]



#	Epoxide (equiv.)	Reducing agent (equiv. × additions)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	**1a** (1.8)	$NaBH_4$ (4.0 × 1)	THF/EtOH	66	48	<5
2	**1a** (1.8)	$NaBH_4$ (2.5 × 3)	THF/EtOH	66	24	37
3	**1a** (1.8)	$NaBH_4$ (2.5 × 3)	THF/EtOH	66	48	65
4	**1a** (1.8)	$NaBH_4$ (2.5 × 3)	EtOH	76	48	50
5	**1a** (1.8)	$NaBH_4$ (4.0 × 1)	DMF	80	48	60
6[b]	**1a (1.0)**	**$NaBH_4$ (4.0 × 1)**	**DMF**	**80**	**48**	**60**
7	**1a** (1.0)	$NaBH_4$ (4.0 × 3)	DMF	80	48	53
8[c]	**1a** (1.0)	$NaBH_4$ (4.0 × 3)	DMF	80	48	<5
9	**1a** (1.8)	$LiEt_3BH$ (2.0 × 1)	THF	66	48	50
10	**1a** (1.8)	$LiAlH_4$ (2.0 × 1)	THF	66	48	<5
11	**1b** (1.0)	$NaBH_4$ (4.0 × 1)	DMF	80	48	32
12	**1b** (1.0)	$NaBH_4$ (4.0 × 1)	DMF	120	48	43
13[c]	**1b** (1.0)	$NaBH_4$ (4.0 × 1)	DMF	80	48	<5
14	**1b** (1.0)	$NaBH_4$ (4.0 × 1)	THF/EtOH	66	48	n.r.
15	**1b** (1.0)	$NaBH_4$ (2.5 × 3)	THF/EtOH	66	48	46

[a] Isolated yield. [b] Reaction performed using 0.1 mmol of the sugar diselenide, 0.2 mmol of the epoxide, 0.4 mmol of $NaBH_4$, in 2 mL of dry DMF. [c] With $ZnCl_2$ (1.8 equiv.).

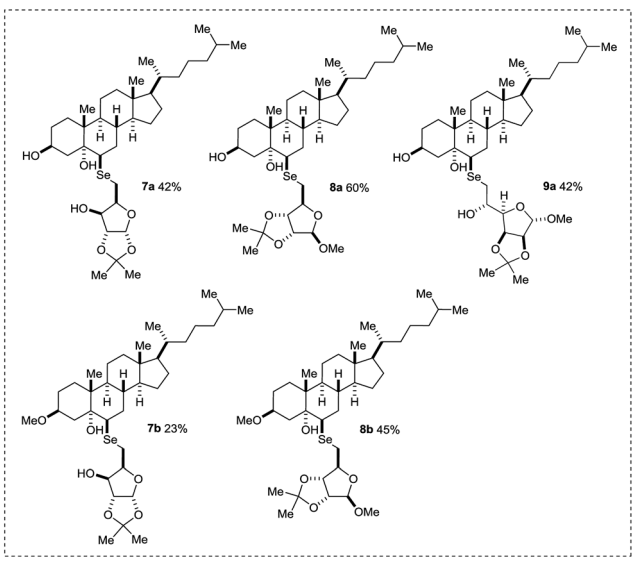
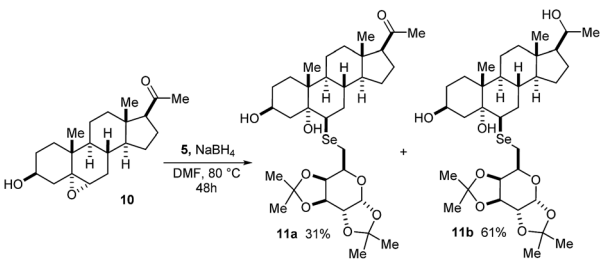


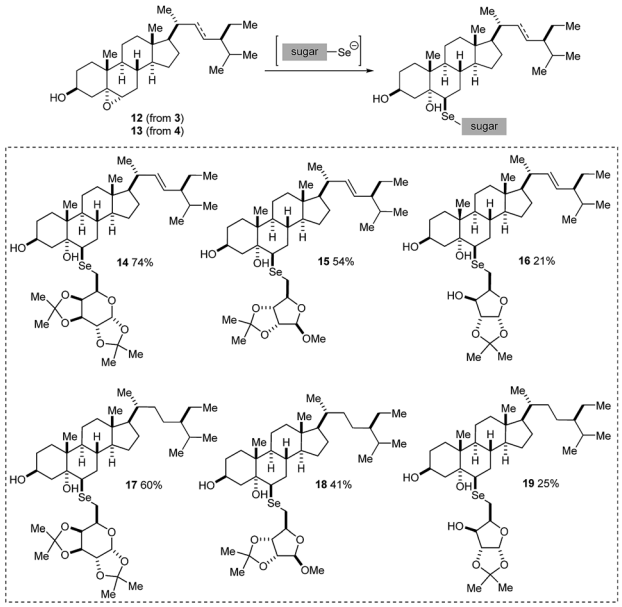
Fig. 1 Cholesterol-derived selenoglycoconjugates.



Scheme 2 Pregnenolone epoxide opening by nucleophilic galactose-derived organoselenium compound.

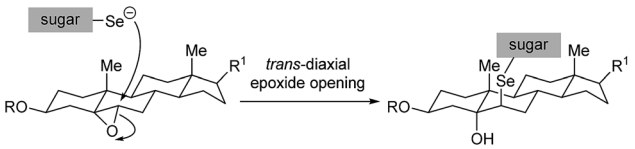
in good yields.[24d] In the case of stigmasterol, traces of a double epoxidation product was also isolated (concomitant epoxidation of the side chain double bond). Therefore, epoxide **12** was reacted with sugar diselenide **5**, under our previously optimized conditions and the corresponding product **14** was isolated in 74% yield (Scheme 3). We have expanded the scope of the reaction by synthesizing six derivatives from stigmasterol and sitosterol through stereoselective epoxide opening with different sugar diselenides. The desired products were obtained in good yields, except when the xylose-derived diselenide was used, which resulted in diminished yields of products **16** and **19**.

In all cases studied, the mechanism of the reaction proceeded through a regio- and stereoselective ring-opening of the

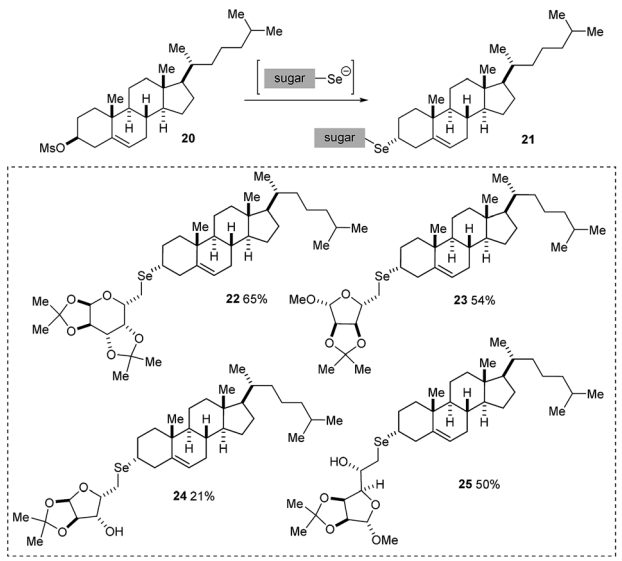


Scheme 3 Glycoconjugates derived from stigmasterol and sitosterol.

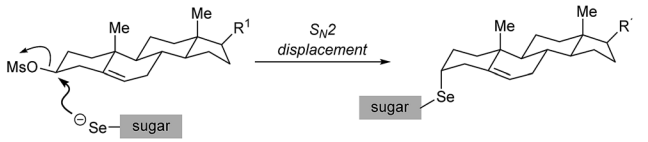
epoxide with the *in situ* generated selenium nucleophile in a *trans*-diaxial fashion therefore delivering the product with the selenium atom attached to the 6β position of the steroid framework (Scheme 4). This assignment has been confirmed by NMR studies (see next section).



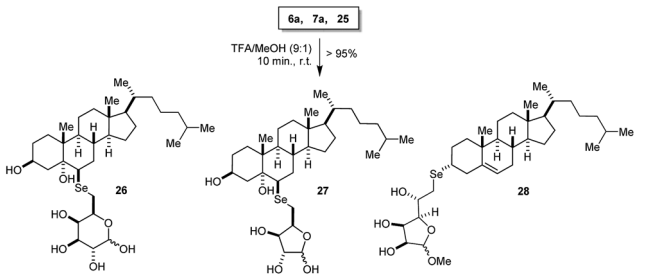
Scheme 4 *trans*-Diaxial epoxide opening by the selenium nucleophile.



Scheme 5 Reaction of sugar diselenides with mesylate **20**.



Scheme 6 Nucleophilic substitution of 3β-mesylate by the selenium nucleophile.



Scheme 7 Acetonide deprotection.

A similar strategy has proved useful for the synthesis of 3-cholesterol derivatives by reacting sugar diselenides with cholesteryl-3-mesylate **20**. In these reactions, we have been able to prepare four new seleno-glycoconjugates in which the sugar moiety is now attached to the α-face of the molecule (Scheme 5).

For the 3α-derivatives, the reaction is believed to proceed through a direct S_N2 displacement, with stereoinversion, delivering the product with the organoselenium moiety at the 3β position of the steroid (Scheme 6). Detailed NMR experiments support this assignment (see next section).

Finally, it is important to highlight that these compounds are readily deprotected in the presence of trifluoroacetic acid and methanol leading to free hydroxyl derivatives (Scheme 7) evidenced by disappearance of the isopropylidene signals on ^{1}H NMR spectra (0.5–1.5 ppm, see ESI†).

NMR studies

Attempts to achieve crystals suitable for X-ray diffractometry of the Se-glycoconjugated products were unsuccessful, leading to oil or semisolid physical states. In order to properly attribute the stereochemistry of the new center formed by the nucleophilic displacement of 3β-cholesteryl mesylate or ring opening of the 5,6α-cholesterol epoxide, two-dimensional NMR experiments were performed (COSY, HSQC, and NOESY) in a 400 MHz magnet. The spectral data for selected compounds **6a** and **25** will be discussed here (complete NMR data achieved are included in the ESI† section), with the atoms labeled according to the official rules for each steroid and carbohydrate moieties (Fig. 2).

For compound **25** which bears 62 hydrogen and 37 carbon atoms, some ^{1}H-NMR signals are easily attributed by comparison with the starting materials X and Y spectra, such as the olefin H6 (d, 5.4 ppm, $^3J_{H6,H7} = 4.6$ Hz) from cholesterol moiety. The presence of this signal showed that no allyl cation

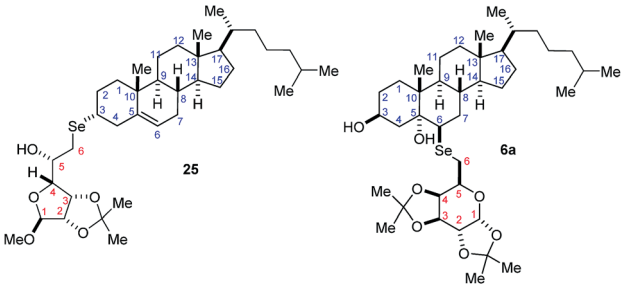


Fig. 2 Atom labeling of sterol selenoglycoconjugates as used for NMR discussion.

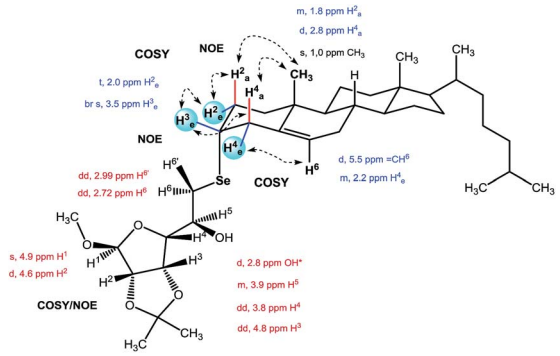


Fig. 3 Relevant data from COSY and NOESY experiments for structure of **25**.

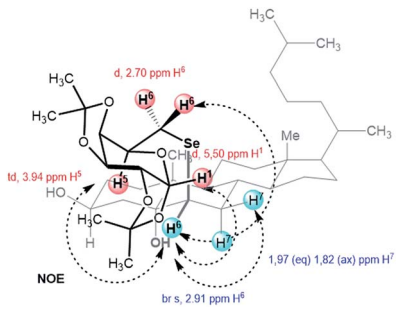


Fig. 4 Relevant data from NOESY experiment for structure of **6a**.

rearrangement has occurred during the reaction as was expected.[28] Furthermore, we have identified a pattern of signals ascribed to the unchanged carbohydrate moiety such as the methoxyl group (s, 3.5 ppm) and the anomeric H1 (s, 4.9 ppm) which does not couple with H2 because of the dihedral angle ($\phi \sim 90°$) imposed by the pyranoside structure. Carbohydrate H3, however, shows coupling with H2 and H4 (5.9 and 3.8 Hz).

The other pair of dd signals between 2.7 and 2.9 ppm are related to the diastereotopic H6 and H6′, showing *gem* and *cis* and *trans* coupling with H5 (13.0, 8.0 and 3.8 Hz, respectively). The 4.0 ppm multiplet could be easily mistaken with the sterol H3 reactive center at first sight, due to its multiplicity and chemical shift, which would mislead to ascribe it to an axial hydrogen position resultant from mesylate retention of the stereocenter. Since inversion of the steroid C3 stereocenter is expected from a bimolecular substitution of selenium nucleophile, the change of H3 to the equatorial position should produce a more shielded and lower multiplicity signal than the axial alternative. This was indeed observed as a broad signal at 3.5 ppm for the whole series **22–25**. Even though the presence of the carbohydrate moiety at the steroid α-face was confirmed by through-space interactions in NOESY experiment. One important observation was made in the phase-sensitive NOE contour map: the hydroxyl hydrogen is ascribed to a doublet signal (d, 2.8 ppm, $^3J_{OH,H5} = 5.0$ Hz) coupling with adjacent H5 which has higher multiplicity (m, 3.9 ppm) and interchanges with DHO (1.6 ppm). It is worth mentioning that none of these couplings where observed in the diselenide spectra or for other unprotected glycoconjugated compounds. Fig. 3 depicts the main correlations between hydrogens that help to corroborate the structure.

For the epoxide opening product **6a**, NMR structural elucidation was more intricate due to the more complex structure. In this case, the diastereotopism related to H6 observed as a pair of double doublets at 3.1 ppm, common to galactopyranosyl structures, is lost after the glycoconjugation to steroid, turning into a coalesced shielded doublet at 2.7 ppm ($\Delta\delta = -0.45$ ppm). Even though the other carbohydrate hydrogens are easily identified by COSY. H5 is also more shielded on the steroid glycoconjugated product by comparison with the signal of the same hydrogen in the diselenide ($\Delta\delta = -0.11$ ppm). The steroid H3 shows the same pattern of multiplicity as the starting materials in the ^{1}H NMR as expected (m, 3.9 ppm) related to the equatorial position and couplings with H4 and H7. Other correlations between the AB fused rings of the steroid moiety were also observed by COSY.

Between 2.1 and 1.6 ppm in the ^{1}H NMR spectra, at least 9 different hydrogen signals are overlapped from both steroid and carbohydrate moieties. However, it was possible to differentiate and assign them to axial or equatorial positions for nuclei connected to the same carbon by HSQC. In contrast to the structure of **25**, no phase inverted hydroxyl signal was observed in the NOESY contour map spectra.

Important NOE weak intensity interactions were observed between both carbohydrate and steroid moieties. The steroid alpha selenium H6, observed in the ^{1}H NMR spectra as a broad signal at 2.9 ppm interacts through space with the following carbohydrate hydrogens: anomeric H1 (d, 5.5 ppm), H5 (td, 3.9 ppm) and H6 (d, 2.7 ppm). These interactions helped us to corroborate the regioselectivity of the *anti*-epoxide nucleophilic ring opening at the sterically less hindered carbon C6 at the steroid beta face. The Fig. 4 depicts the main NOE correlations observed which lead us to assign the carbohydrate moiety on the steroid alpha face.

Conclusions

A method for glycoconjugation by a regioselective epoxide opening or nucleophilic substitution of activated hydroxyls of sterols with different sugar diselenides was developed. The reactions occurred regio and stereoselectively though a *trans*-

diaxial epoxide ring-opening or S_N2-substitution, respectively, affording the corresponding sugar conjugated selenosteroids with several carbohydrate moieties.

Experimental section

General

^{1}H NMR spectra were recorded either at 300 or 400 MHz and ^{13}C NMR 75 or 101 MHz, respectively with tetramethylsilane as internal standard. High resolution mass spectra were recorded on a Micro-TOF instrument in ESI-mode. Flash column chromatography was performed using silica gel (230–400 mesh) following the methods described by Still.[29] Thin layer chromatography (TLC) was performed using supported silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin or phosphomolybdic acid. THF was dried over sodium benzophenone ketyl and distilled prior to use. DMF was dried over calcium hydride. All other solvents were used as purchased unless otherwise noted. Sugar diselenides were prepared by previously reported methods.[16]

General procedure for the synthesis of steroidal selenoglycoconjugates

Epoxide opening. In a Schlenk tube under argon atmosphere, sodium borohydride (0.4 mmol, 38 mg) was added to a solution of the sugar diselenide (0.1 mmol) in dry DMF (2 mL). After heating the mixture for 1 h at 80 °C, a solution of the steroid epoxide (0.2 mmol) in dry DMF (2 mL) was added dropwise and the mixture heated at 80 °C for 48 h. After this time, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The crude mixture was purified by column chromatography with hexanes/ethyl acetate.

Mesylate substitution. In a Schlenk tube under argon atmosphere, sodium borohydride (0.4 mmol, 38 mg) was added to a solution of the sugar diselenide (0.1 mmol) in dry DMF (2 mL). After heating the mixture for 1 h at 80 °C, a solution of the 3-cholesteryl mesylate (0.2 mmol) in dry DMF (2 mL) was added dropwise and the mixture heated at 80 °C for 24 h. After this time, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The crude mixture was purified by column chromatography with hexanes/ethyl acetate.

Deprotection. In a vial the steroidal selenoglycoconjugate (0.1 mmol) and a solution of trifluoroacetic acid/methanol (9 : 1, 1 mL) were added. The mixture was stirred for 10 minutes at room temperature and the solvents were evaporated under reduced pressure, yielding the corresponding products as a mixture of anomers.

Compound 6a

White solid, m.p. 86 °C. $[\alpha]_D^{20}$ −79 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (d, J = 5.0, 1H), 4.61 (dd, J = 7.9, J = 2.4, 1H), 4.34 (dd, J = 1.8, J = 7.9, 1H), 4.29 (dd, J = 2.4, J = 5.0, 1H), 4.08–3.98 (m, 1H), 3.93 (dt, J = 1.6, J = 6.9, 1H), 2.91 (d, J = 3.2, 1H), 2.70 (d, J = 6.9, 2H), 2.38–2.98 (m, 2H), 2.07–1.96 (m, 3H), 1.85–1.70 (m, 7H), 1.55 (s, 6H), 1.44 (s, 6H), 1.34 (s, 6H), 1.33 (s, 6H), 1.13–1.17 (m, 10H), 0.91–0.85 (m, 20H), 0.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.1, 108.6, 98.5, 77.9, 72.0, 70.8, 70.4, 69.0, 68.0, 56.2, 55.5, 49.0, 46.0, 44.0, 42.7, 39.9, 39.4, 39.1, 36.1, 35.7, 34.6, 32.5, 31.1, 30.7, 28.1, 27.9, 26.2, 26.0, 25.9, 24.9, 24.3, 24.1, 23.8, 22.8, 22.5, 21.2, 18.6, 17.6, 12.1. HRMS-ESI: *m*/*z* calcd for $C_{39}H_{66}O_7Se + Na^+$: 749.3871, found: 749.3866.

Compound 6b

White solid, m.p. 53 °C. $[\alpha]_D^{20}$ −75 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (d, J = 5.0, 1H), 5.30 (s, 1H), 4.61 (dd, J = 7.9, J = 2.1, 1H), 4.38 (dd, = 7.9, J = 1.2, 1H), 4.29 (dd, J = 5.0, J = 2.3, 1H), 4.20–4.06 (m, 1H), 3.93 (t, J = 6.9, 1H), 3.60–3.50 (m, 1H), 3.35 (s, 3H), 2.91 (d, J = 2.2, 1H), 2.69 (dd, J = 6.9, J = 2.1, 2H), 2.30–2.22 (m, 1H), 2.04–1.78 (m, 8H), 1.55 (s, 6H), 1.44 (s, 6H), 1.35–1.24 (m, 10H), 1.17–1.18 (m, 10H), 0.91–0.85 (m, 10H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ = 109.1, 108.5, 96.5, 77.8, 71.8, 70.9, 70.5, 68.8, 56.2, 55.7, 55.5, 49.1, 46.3, 42.7, 40.4, 39.9, 39.4, 39.3, 36.1, 35.7, 34.7, 32.4, 31.1, 28.1, 27.9, 27.0, 26.1, 25.9, 25.9, 24.4, 24.1, 23.8, 22.7, 22.5, 21.2, 21.1, 18.6, 17.5, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{40}H_{68}O_7Se + Na^+$: 763.4028, found: 763.4022.

Compound 7a

White solid, m.p. 113 °C. $[\alpha]_D^{20}$ −61 (*c* 0.5, $CHCl_3$). ^{1}H ($CDCl_3$, 300 MHz, ppm) δ = 5.93 (d, J = 3.5, 1H), 4.54 (d, J = 3.5, 1H), 4.37–4.26 (m, 2H), 4.08–3.96 (m, 2H), 3.02–2.80 (m, 4H), 2.42–2.24 (m, 5H), 2.02–1.73 (m, 5H), 1.51–0.70 (m, 40H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ = 111.7, 104.6, 85.1, 81.3, 78.0, 74.8, 68.0, 56.4, 55.4, 51.6, 46.0, 44.0, 42.7, 39.8, 39.4, 39.0, 36.1, 35.8, 34.9, 32.4, 31.3, 30.6, 28.2, 28.1, 27.9, 26.7, 26.1, 24.2, 23.9, 22.7, 22.5, 21.0, 18.5, 17.4, 12.3. HRMS-ESI: *m*/*z* calcd for $C_{35}H_{60}O_6Se + Na^+$: 679.3453, found: 679.3447.

Compound 7b

Yellow oil. $[\alpha]_D^{20}$ −81 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ = 5.93 (d, J = 3.7, 1H), 4.64–4.27, (m, 1H), 4.36–4.17 (m, 2H), 3.70–3.48 (m, 1H), 3.35 (s, 3H), 3.05–2.64 (m, 4H), 2.29–2.20 (m, 1H), 2.05–1.73 (m, 4H), 1.51–1.44 (m, 4H), 1.33–1.25 (m, 20H), 1.13–1.06 (m, 8H), 0.91–0.85 (m, 10H), 0.69–0.68 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ = 112.3, 105.5, 85.8, 80.7, 78.4, 76.0, 56.9, 56.5, 56.1, 50.0, 46.9, 43.4, 41.2, 40.6, 40.2, 40.1, 36.8, 36.5, 35.3, 33.0, 32.6, 31.9, 30.4, 28.7, 27.4, 26.8, 24.9, 24.5, 23.8, 23.5, 23.2, 21.9, 19.3, 18.3, 14.8, 12.9. HRMS-ESI: *m*/*z* calcd for $C_{36}H_{62}O_6Se + Na^+$: 693.3609, found: 693.3604.

Compound 8a

Yellow solid, m.p. 60 °C. $[\alpha]_D^{20}$ −62 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02–4.97 (m, 1H), 4.75–4.59 (m, 2H), 4.32–4.27 (m, 1H), 4.10–4.02 (m, 1H), 3.40 (s, 1H), 3.35 (s, 2H), 2.96 (s, 1H), 2.89 (s, 2.87, 1H), 2.80–2.71 (m, 1H), 2.59–2.45 (m, 1H), 2.37–2.11 (s, 1H), 2.04–1.97 (m, 1H), 1.83–1.58 (m, 4H), 1.48 (s,

3H), 1.32–1.24 (m, 5H), 1.15–1.00 (m, 15H), 0.91–0.85 (m, 20H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm). δ = 133.1, 112.3, 109.57, 86.6, 85.3, 83.7, 77.8, 73.9, 67.9, 56.2, 55.4, 54.9, 53.8, 48.6, 46.0, 44.0, 42.7, 39.9, 39.4, 39.4, 39.1, 36.1, 35.7, 34.6, 32.5, 31.2, 27.9, 26.4, 24.9, 23.8, 22.7, 22.5, 21.2, 18.6, 17.6, 14.5, 12.1. HRMS-ESI: *m*/*z* calcd for $C_{36}H_{62}O_6Se + Na^+$: 693.3609, found: 693.3604.

Compound 8b

Semisolid. $[\alpha]_D^{20}$ −49 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.59–5.56 (m, 1H), 5.43–5.27 (m, 2H), 4.97 (s, 3H), 4.71–4.58 (m, 1H), 4.32–4.27 (m, 1H), 4.17–4.11 (m, 1H), 3.60–3.58 (m, 1H), 3.35 (s, 2H), 2.80–2.74 (m, 1H), 2.57–2.53 (m, 1H), 2.31–2.23 (m, 1H), 2.04–1.74 (m, 4H), 1.51–1.25 (m, 7H), 1.11–1.07 (m, 15H), 0.91–0.84 (m, 20H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ = 133.0, 112.2, 109.6, 86.6, 85.3, 83.6, 77.7, 62.0, 56.2, 55.6, 55.4, 54.9, 48.4, 46.2, 42.7, 40.4, 39.9, 39.4, 36.1, 35.7, 34.8, 32.3, 31.2, 30.1, 28.1, 27.9, 27.0, 26.4, 24.9, 24.1, 23.8, 22.8, 22.5, 21.2, 18.6, 17.5, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{37}H_{64}O_6Se + Na^+$: 707.3766, found: 707.3760.

Compound 9a

Semisolid. $[\alpha]_D^{22}$ −9 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (s, 1H), 4.83 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.57 (d, *J* = 5.9 Hz, 1H), 4.12–3.96 (m, 1H), 3.85 (dd, *J* = 8.1, 3.6 Hz, 1H), 3.32 (s, 3H), 3.01–2.86 (m, 3H), 2.77 (dd, *J* = 13.0, 7.9 Hz, 1H), 2.44–2.29 (m, 2H), 2.08–1.92 (m, 2H), 1.90–1.71 (m, 5H), 1.61–1.05 (m, 26H), 0.90–0.86 (m, 8H), 0.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 107.1, 84.8, 81.6, 80.2, 79.8, 79.1, 77.3, 69.3, 68.0, 64.5, 56.3, 55.5, 46.1, 44.0, 39.5, 36.1, 35.8, 35.0, 33.1, 32.6, 31.2, 28.2, 28.0, 26.0, 24.6, 23.8, 22.8, 22.5, 18.6, 17.7, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{37}H_{64}O_7Se + Na^+$: 723.3715, found: 723.3724.

Compound 11a

Colourless oil. $[\alpha]_D^{22}$ −94 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 5.0 Hz, 1H), 4.63–4.57 (m, 2H), 4.33 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.29 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.02 (ddd, *J* = 15.6, 10.5, 5.1 Hz, 1H), 3.94 (td, *J* = 6.8, 1.2 Hz, 1H), 3.75–3.62 (m, 1H), 2.96–2.86 (m, 2H), 2.70 (d, *J* = 6.9 Hz, 2H), 2.39–2.33 (m, 1H), 2.21–2.07 (m, 2H), 2.04 (s, 3H), 2.00–1.73 (m, 3H), 1.67–0.87 (m, 28H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 109.2, 108.6, 96.6, 82.7, 77.9, 72.1, 70.9, 70.5, 69.1, 68.0, 49.9, 48.9, 46.0, 44.2, 42.8, 39.3, 36.9, 34.3, 32.6, 31.1, 30.7, 27.5, 26.2, 26.2, 26.0, 25.0, 24.4, 23.5, 21.2, 20.7, 17.6, 12.3. HRMS-ESI: *m*/*z* calcd for $C_{33}H_{52}O_8Se + Na^+$: 679.2725, found: 679.2687.

Compound 11b

Colourless oil. $[\alpha]_D^{22}$ −171 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.34 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.29 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.02 (ddd, *J* = 15.5, 10.4; 5.0 Hz, 1H), 3.96–3.92 (m, 1H), 3.77–3.62 (m, 1H), 2.96–2.88 (m, 2H), 2.70 (d, *J* = 6.9 Hz, 2H), 2.37–2.31 (m, 1H), 2.07–1.96 (m, 2H), 1.88–1.10 (m, 36H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 109.2, 108.6, 96.5, 77.9, 72.0, 70.9, 70.5, 70.4, 69.0, 68.0, 58.5, 55.0, 49.0, 46.1, 44.1, 42.7, 40.0, 39.2, 34.7, 32.6, 31.1, 30.7, 26.2, 26.1, 26.0, 25.6, 24.9, 24.4, 23.6, 21.1, 17.6, 12.7. HRMS-ESI: *m*/*z* calcd for $C_{33}H_{54}O_8Se + Na^+$: 681.2882, found: 681.2883.

Compound 14

Semisolid. $[\alpha]_D^{22}$ −73 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 5.0 Hz, 1H), 5.15 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.02 (dd, *J* = 15.1, 8.6 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.35 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.29 (dd, *J* = 4.9, 2.3 Hz, 1H), 4.07–3.99 (m, 1H), 3.93 (t, *J* = 6.9 Hz, 1H), 2.90 (d, *J* = 3.1 Hz, 1H), 2.70 (d, *J* = 7.0 Hz, 2H), 2.39–2.28 (m, 1H), 2.07–1.93 (m, 4H), 1.85–1.61 (m, 19H), 1.55 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.54–1.06 (m, 10H), 1.02–1.00 (m, 3H), 0.86–0.79 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 129.3, 109.3, 108.6, 96.6, 78.0, 72.0, 70.9, 70.5, 69.0, 68.1, 56.0, 55.7, 51.2, 49.1, 46.2, 44.1, 42.7, 40.4, 39.9, 39.2, 34.7, 32.6, 31.8, 31.2, 30.8, 28.8, 26.2, 26.2, 26.0, 25.3, 25.0, 24.4, 24.2, 21.2, 21.2, 21.0, 19.0, 17.7, 12.4, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{41}H_{68}O_7Se + Na^+$: 775.4028, found: 775.4012.

Compound 17

Semisolid. $[\alpha]_D^{22}$ −116 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.35 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.29 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.07–3.99 (m, 1H), 3.93 (td, *J* = 6.9, 1.3 Hz, 1H), 2.96 (s, 3H), 2.91 (d, *J* = 3.2 Hz, 1H), 2.88 (s, 3H), 2.71 (d, *J* = 7.0 Hz, 2H), 2.40–2.27 (m, 1H), 2.06–1.93 (m, 3H), 1.88–1.60 (m, 7H), 1.60 (s, 3H), 1.55 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.29–0.98 (m, 14H), 0.92–0.76 (m, 11H), 0.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 109.2, 108.6, 96.6, 78.0, 72.0, 70.9, 70.5, 68.9, 68.0, 56.2, 55.6, 49.1, 46.2, 45.8, 44.1, 42.8, 40.0, 39.2, 36.1, 34.7, 33.9, 32.6, 31.2, 30.8, 29.1, 28.2, 26.2, 26.0, 25.0, 24.4, 24.2, 23.0, 21.3, 19.8, 19.0, 18.7, 17.6, 15.4, 12.2, 12.0. HRMS-ESI: *m*/*z* calcd for $C_{41}H_{70}O_7Se + Na^+$: 777.4184, found: 777.4182.

Compound 15

Semisolid. $[\alpha]_D^{22}$ −94 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (dd, *J* = 15.2, 8.5 Hz, 1H), 5.02 (dd, *J* = 15.2, 8.6 Hz, 1H), 4.97 (s, 1H), 4.68 (d, *J* = 5.9 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 4.03 (ddd, *J* = 15.5, 10.4, 4.9 Hz, 1H), 3.35 (s, 3H), 2.80 (d, *J* = 3.4 Hz, 1H), 2.76 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.56 (dd, *J* = 12.3, 10.1 Hz, 1H), 2.34 (dd, *J* = 13.3, 11.2 Hz, 2H), 2.10–1.50 (m, 11H), 1.48 (s, 3H), 1.46–1.34 (m, 4H), 1.32 (s, 3H), 1.31–1.11 (m, 10H), 1.11 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.87–0.76 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 129.3, 112.4, 109.6, 86.7, 85.3, 83.7, 77.9, 68.0, 56.0, 55.6, 55.0, 51.2, 48.6, 46.2, 44.2, 42.7, 40.4, 39.8, 39.2, 34.7, 32.6, 31.8, 31.3, 30.8, 30.4, 28.8, 26.5, 25.4, 25.0, 24.2, 21.2, 21.2, 21.1, 19.0, 17.7, 12.4, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{38}H_{64}O_6Se + Na^+$: 719.3766, found: 719.3767.

Compound 18

Yellow oil. $[\alpha]_D^{22}$ −363 (*c* 0.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (d, *J* = 5.9 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 4.03 (ddd, *J* = 15.1, 10.3, 4.7 Hz, 1H),

3.35 (s, 3H), 2.80–2.74 (m, 2H), 2.59–2.53 (m, 1H), 2.37–2.31 (m, 1H), 1.85–1.52 (m, 12H), 1.48 (s, 3H), 1.45–1.34 (m, 5H), 1.32 (s, 3H), 1.28–1.15 (m, 11H), 1.11 (s, 3H), 0.99–0.77 (m, 14H), 0.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 112.4, 109.6, 86.7, 85.3, 83.7, 77.9, 68.0, 56.2, 55.5, 55.0, 48.6, 46.2, 45.8, 44.2, 42.8, 39.9, 39.2, 36.2, 34.7, 32.6, 31.3, 30.8, 30.4, 29.1, 28.2, 26.5, 26.1, 25.0, 24.2, 23.0, 21.3, 19.8, 19.0, 18.7, 17.6, 15.4, 12.2, 12.0. HRMS-ESI: *m*/*z* calcd for $C_{38}H_{66}O_6Se^+$: 698.4025, found: 700.4238.

Compound 16

Yellow oil. $[\alpha]_D^{22}$ −62 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 3.8 Hz, 1H), 5.15 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.02 (dd, *J* = 15.1, 8.6 Hz, 1H), 4.53 (d, *J* = 3.7 Hz, 1H), 4.35 (ddd, *J* = 8.4, 5.8, 2.5 Hz, 1H), 4.27 (s, 1H), 4.03 (ddd, *J* = 15.6, 10.4, 5.1 Hz, 1H), 3.77 (t, *J* = 5.9 Hz, 1H), 2.95–2.89 (m, 1H), 2.87–2.69 (m, 2H), 2.32 (dd, *J* = 13.1, 11.3 Hz, 1H), 2.12–1.58 (m, 14H), 1.51 (s, 3H), 1.49–1.33 (m, 6H), 1.31 (s, 3H), 1.28–1.03 (m, 10H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.87–0.77 (m, 9H), 0.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 129.3, 111.7, 104.8, 85.1, 80.1, 77.9, 75.4, 68.0, 56.0, 55.6, 51.2, 49.1, 46.1, 44.0, 42.7, 40.4, 39.8, 39.2, 34.6, 32.6, 31.9, 31.3, 30.7, 29.7, 28.8, 26.8, 26.2, 25.4, 24.3, 23.2, 21.2, 21.2, 21.1, 19.0, 17.7, 12.4, 12.2. HRMS-ESI: *m*/*z* calcd for $C_{37}H_{62}O_6Se + Na^+$: 705.3609, found: 705.3624.

Compound 19

Yellow oil. $[\alpha]_D^{22}$ −202 (*c* 0.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 3.7 Hz, 1H), 4.53 (d, *J* = 3.7 Hz, 1H), 4.37–4.27 (m, 2H), 4.03 (ddd, *J* = 15.6, 10.4, 5.0 Hz, 1H), 2.91 (d, *J* = 3.1 Hz, 1H), 2.81–2.74 (m, 2H), 2.60 (sl, 1H), 2.35–2.29 (m, 1H), 2.06–1.56 (m, 12H), 1.51 (s, 3H); 1.49–1.33 (m, 6H), 1.32 (s, 3H), 1.30–1.12 (m, 10H), 1.10 (s, 3H), 1.03–0.76 (m, 14H), 0.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 111.7, 104.8, 85.1, 80.2, 77.9, 75.3, 68.0, 56.2, 55.5, 49.0, 46.0, 45.8, 44.0, 42.8, 39.9, 39.2, 36.1, 34.6, 33.9, 32.5, 31.3, 30.7, 29.1, 28.2, 26.8, 26.2, 26.1, 24.2, 23.1, 23.0, 21.2, 19.8, 19.0, 18.7, 17.7, 15.4, 12.2, 12.0. HRMS-ESI: *m*/*z* calcd for $C_{37}H_{64}O_6Se + Na^+$: 707.3766, found: 707.3785.

Compound 22

Semisolid. $[\alpha]_D^{22}$ −53 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (d, *J* = 5.0 Hz, 1H), 5.32 (d, *J* = 4.9 Hz, 1H), 4.60 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.39 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.28 (dd, *J* = 5.0, 2.3 Hz, 1H), 3.88 (td, *J* = 7.3, 1.3 Hz, 1H), 3.49 (s, 1H), 2.79 (d, *J* = 14.3 Hz, 1H), 2.71 (d, *J* = 7.2 Hz, 2H), 2.22 (d, *J* = 14.7 Hz, 2H), 2.02–1.73 (m, 6H), 1.68–1.55 (m, 6H), 1.53 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.26–1.02 (m, 11H), 1.00 (s, 3H), 0.95 (s, 1H), 0.94–0.89 (m, 4H), 0.87 (d, *J* = 1.7 Hz, 3H), 0.86 (d, *J* = 1.7 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3, 122.2, 109.1, 108.4, 96.7, 71.7, 71.1, 70.6, 68.3, 56.7, 56.1, 49.9, 42.3, 41.6, 39.7, 39.5, 39.0, 37.3, 36.2, 35.8, 35.8, 35.0, 31.8, 28.2, 28.0, 27.7, 26.1, 26.0, 24.9, 24.4, 24.3, 23.8, 22.8, 22.6, 22.5, 20.7, 19.3, 18.7, 11.8. HRMS-ESI: *m*/*z* calcd for $C_{39}H_{64}O_5Se + Na^+$: 715.3817, found: 715.3795.

Compound 23

Yellow oil. $[\alpha]_D^{22}$ −37 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.32 (d, *J* = 5.0 Hz, 1H), 4.97 (s, 1H), 4.70 (d, *J* = 5.9 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.30 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.48 (s, 1H), 3.34 (s, 3H), 2.79 (d, *J* = 14.3 Hz, 1H), 2.73 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.53 (dd, *J* = 12.4, 10.2 Hz, 1H), 2.20 (d, *J* = 14.7 Hz, 1H), 2.02–1.49 (m, 10H), 1.48 (s, 3H), 1.44–1.32 (m, 6H), 1.32 (s, 3H), 1.25–1.04 (m, 10H), 1.00 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 1.8 Hz, 3H), 0.86 (d, *J* = 1.8 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1, 122.3, 112.2, 109.6, 86.9, 85.4, 83.7, 56.7, 56.1, 54.9, 50.0, 42.3, 40.8, 39.7, 39.5, 38.8, 37.3, 36.2, 35.8, 34.9, 31.7, 31.7, 28.2, 28.0, 27.6, 26.7, 26.4, 24.9, 24.3, 23.8, 22.8, 22.5, 20.7, 19.3, 18.7, 11.8. HRMS-ESI: *m*/*z* calcd for $C_{36}H_{60}O_4Se + H^+$: 637.3783, found 637.3696.

Compound 24

Semisolid. $[\alpha]_D^{22}$ −31 (*c* 0.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 3.7 Hz, 1H), 5.32 (d, *J* = 5.1 Hz, 1H), 4.53 (d, *J* = 3.8 Hz, 1H), 4.37 (ddd, *J* = 9.6, 5.2, 2.6 Hz, 1H), 4.28 (dd, *J* = 5.3, 2.6 Hz, 1H), 3.55 (s, 1H), 2.83 (dd, *J* = 11.9, 5.3 Hz, 1H), 2.73 (dd, *J* = 11.9, 9.7 Hz, 1H), 2.21 (d, *J* = 14.8 Hz, 1H), 2.07 (d, *J* = 5.5 Hz, 1H), 2.02–1.77 (m, 6H), 1.68–1.52 (m, 6H), 1.50 (s, 3H), 1.46–1.32 (m, 5H), 1.31 (s, 3H), 1.26–1.03 (m, 10H), 1.00 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 1.8 Hz, 3H), 0.86 (d, *J* = 1.8 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0, 122.4, 111.6, 104.9, 85.1, 79.9, 75.5, 56.7, 56.1, 50.0, 42.3, 42.0, 39.7, 39.5, 38.8, 37.3, 36.2, 35.8, 35.0, 31.7, 31.7, 28.2, 28.0, 27.7, 26.7, 26.2, 24.3, 23.9, 22.8, 22.5, 20.7, 19.6, 19.3, 18.7, 11.8. HRMS-ESI: *m*/*z* calcd for $C_{35}H_{58}O_4Se + H^+$: 623.3536, found 623.3335.

Compound 25

Semisolid. $[\alpha]_D^{22}$ +26 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.35 (d, *J* = 4.6 Hz, 1H), 4.89 (s, 1H), 4.83 (dd, *J* = 5.8, 3.8 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 1H), 3.99 (qd, *J* = 8.1, 4.4 Hz, 1H), 3.84 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.50 (sl, 1H), 3.31 (s, 3H), 2.99 (dd, *J* = 12.9, 3.8 Hz, 1H), 2.85 (d, *J* = 5.0 Hz, 1H), 2.79 (d, *J* = 14.0 Hz, 1H), 2.72 (dd, *J* = 12.9, 8.0 Hz, 1H), 2.25 (d, *J* = 14.7 Hz, 1H), 2.08–1.48 (m, 13H), 1.47 (s, 3H), 1.46–1.35 (m, 3H), 1.33 (s, 3H), 1.30–1.03 (m, 10H), 1.00 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1, 122.4, 112.6, 107.2, 84.8, 81.6, 79.9, 68.5, 56.7, 56.1, 54.6, 50.0, 42.3, 42.1, 39.7, 39.5, 38.8, 37.3, 36.2, 35.8, 35.1, 31.7, 31.7, 29.8, 28.3, 28.2, 28.0, 26.0, 24.6, 24.3, 23.8, 22.8, 22.5, 20.7, 19.3, 18.7, 11.8. HRMS-ESI: *m*/*z* calcd for$C_{37}H_{62}O_5Se + Na^+$: 689.3660, found: 689.3664.

Compound 26

Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.4–5.3 (m, 1H), 4.8–4.7 (m, 1H), 4.4–4.3 (m, 1H), 3.5–3.2 (m, 2H), 2.91 (s, 1H), 2.5–2.4 (m, 3H), 2.04–0.8 (m, 21H), 0.7 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.4, 123.8, 121.7, 78.7, 56.7, 56.6, 56.1, 50.2, 49.9, 42.7, 42.3, 39.6, 39.5, 37.4, 36.7, 36.1, 35.8, 31.9, 31.8, 29.7, 28.2, 28.0, 27.2, 24.2, 23.8, 22.8, 22.5, 21.0, 19.4, 19.2, 18.7, 18.6, 11.8.

HRMS-ESI: *m*/*z* calcd for $C_{33}H_{58}O_7Se + H^+$: 647.3429, found 647.3348.

Compound 27

Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.4–5.3 (m, 1H), 4.8–4.7 (m, 1H), 4.1–4.0 (m, 1H), 3.6–2.8 (m, 3H), 2.4–0.9 (m, 44H), 0.7 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.6, 138.4, 123.7, 121.7, 78.7, 71.7, 56.7, 56.6, 56.1, 55.8, 49.8, 42.7, 42.1, 39.5, 39.3, 37.4, 36.6, 36.0, 35.4, 31.8, 31.6, 29.6, 28.2, 27.9, 27.2, 24.2, 23.4, 22.7, 22.3, 21.1, 18.6, 11.7. HRMS-ESI: *m*/*z* calcd for $C_{32}H_{56}O_6Se + H^+$: 617.3323, found 617.3325.

Compound 28

Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39–5.32 (m, 1H), 4.89–4.83 (m, 1H), 4.57–4.52 (m, 1H), 4.07–3.84 (m, 4H), 3.49–3.37 (m, 3H), 3.34–2.81 (m, 5H), 2.39–0.65 (m, 43H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 132.4, 128.9, 126.9, 125.0, 123.1, 56.9, 56.1, 50.1, 48.4, 43.5, 42.4, 42.3, 40.9, 40.3, 39.8, 39.5, 36.2, 35.8, 34.0, 33.8, 31.8, 28.3, 28.2, 28.0, 27.6, 27.5, 24.3, 23.8, 22.8, 22.7, 22.5, 21.5, 18.7, 12.0. HRMS-ESI: *m*/*z* calcd for $C_{34}H_{58}O_5Se + H^+$: 627.3531, found 627.3522.

Notes and references

1 B. Heasley, *Chem.–Eur. J.*, 2012, **18**, 3092.
2 (*a*) M. Slingerland, C. Cerella, H. J. Guchelaar, M. Diederich and H. Gelderblom, *Invest. New Drugs*, 2013, **31**, 1087; (*b*) R. A. Newman, P. Yang, A. D. Pawlus and K. I. Block, *Mol. Interventions*, 2008, **8**, 36; (*c*) J. A. R. Salvador, J. F. S. Carvalho, M. A. C. Neves, S. M. Silvestre, A. J. Leitão, M. C. Silva and M. L. Sá e Melo, *Nat. Prod. Rep.*, 2013, **30**, 324.
3 (*a*) M. Jensen, S. Schmidt, N. U. Fedosova, J. Mollenhauer and H. H. Jensen, *Bioorg. Med. Chem.*, 2011, **19**, 2407; (*b*) H. A. Elbaz, T. A. Stueckle, H.-Y. L. Wang, G. A. O'Doherty, D. T. Lowry, L. M. Sargent, L. Wang, C. Z. Dinu and Y. Rojanasakul, *Toxicol. Appl. Pharmacol.*, 2012, **258**, 51.
4 (*a*) J. M. Langenhan, N. R. Peters, I. A. Guzei, F. M. Hoffmann and J. S. Thorson, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 12305; (*b*) M. Lopez-Lazaro, N. Pastor, S. S. Azrak, M. J. Ayuso, C. A. Austin and F. Cortes, *J. Nat. Prod.*, 2005, **68**, 1642.
5 L. J. Rashan, K. Franke, M. M. Khine, G. Kelter, H. H. Fiebig, J. Neumann and L. A. Wessjohann, *J. Ethnopharmacol.*, 2011, **134**, 781.
6 C. Bobach, S. Tennstedt, K. Palberg, A. Denkert, W. Brandt, A. de Meijere, B. Seliger and L. A. Wessjohann, *Eur. J. Med. Chem.*, 2015, **90**, 267.
7 (*a*) K. Pérez-Labrada, I. Brouard, S. Estévez, M. T. Marrero, F. Estévez and D. G. Rivera, *Bioorg. Med. Chem.*, 2012, **20**, 4522; (*b*) K. Pérez-Labrada, I. Brouard, S. Estévez, M. T. Marrero, F. Estévez, J. Bermejo and D. G. Rivera, *Bioorg. Med. Chem.*, 2012, **20**, 2690.
8 Y. Wang, Y. Zhang, Z. Zhu, S. Zhu, Y. Li, M. Lia and B. Yua, *Bioorg. Med. Chem.*, 2007, **15**, 2528.
9 (*a*) R. M. Phan and C. D. Poulter, *J. Org. Chem.*, 2001, **66**, 6705; (*b*) T. A. Lin, O. Boutureira, L. Lercher, B. Bhushan, R. S. Paton and B. G. Davis, *J. Am. Chem. Soc.*, 2013, **135**, 12156.
10 (*a*) K. Pérez-Labrada, I. Brouard, C. Morera, F. Estévez, J. Bermejo and D. G. Rivera, *Tetrahedron*, 2011, **67**, 7713; (*b*) A. M. Deobald, L. R. S. Camargo, D. Alves, J. Zukerman-Schpector, A. G. Corrê and M. W. Paixão, *Synthesis*, 2011, **24**, 4003.
11 D. G. Rivera, K. Pérez-Labrada, L. Lambert, S. Dorner, B. Westermann and L. A. Wessjohann, *Carbohydr. Res.*, 2012, **359**, 102.
12 L. A. Wessjohann, A. Schneider, M. Abbas and W. Brandt, *Biol. Chem.*, 2007, **10**, 997.
13 (*a*) H. C. Braga, H. A. Stefani, M. W. Paixão, F. W. Santos and D. S. Lüdtke, *Tetrahedron*, 2010, **66**, 3441; (*b*) J. P. Vargas, L. M. Pinto, L. Savegnago and D. S. Lüdtke, *J. Braz. Chem. Soc.*, 2015, **26**, 810.
14 H. C. Braga, A. D. Wouters, F. B. Zerillo and D. S. Lüdtke, *Carbohydr. Res.*, 2010, **345**, 2328.
15 A. L. Braga, W. A. Severo-Filho, R. S. Schwab, O. E. D. Rodrigues, L. Dornelles, H. C. Braga and D. S. Lüdtke, *Tetrahedron Lett.*, 2009, **50**, 3005.
16 R. F. Affeldt, H. C. Braga, L. L. Baldassari and D. S. Lüdtke, *Tetrahedron*, 2012, **68**, 10470.
17 (*a*) S. Wollenhaupt, A. T. Soares, W. G. Salgueiro, S. Noremberg, D. Bohrer, P. Gubert, F. A. Soares, R. F. Affeldt, D. S. Lüdtke, F. W. Santos, C. C. Denardin, M. Aschner and D. S. Avila, *Food Chem. Toxicol.*, 2014, **64**, 192; (*b*) L. M. Vargas, M. B. Soares, A. P. Izaguirry, D. S. Lüdtke, H. C. Braga, L. Savegnago, S. Wollenhaupt, D. S. Brum, F. G. Leivas and F. W. Santos, *J. Appl. Toxicol.*, 2013, **33**, 679.
18 C. C. Spiazzi, M. B. Soares, A. P. Izaguirry, L. M. Vargas, M. Zanchi, N. F. Pavin, R. F. Affeldt, D. S. Lüdtke, M. Prigol and F. W. Santos, *Oxid. Med. Cell. Longevity*, 2016, **65**, 976908, DOI: 10.1016/j.pnpbp.2015.10.008.
19 (*a*) R. Strommer, C. Hödl, W. Strauss, R. Sailer, E. Haslinger, H. W. Schramm and C. Seger, *Monatsh. Chem.*, 2004, **135**, 1137; (*b*) H.-S. Kim and J.-H. Kang, *Bull. Korean Chem. Soc.*, 2001, **22**, 1390; (*c*) E. Ma and T. Choi, *Bull. Korean Chem. Soc.*, 2009, **30**, 245.
20 (*a*) S. D. Sarkar, R. D. Ice, W. H. Beierwaltes, S. P. Gill, S. Balachandran and G. P. Basmadjian, *J. Nucl. Med.*, 1976, **17**, 212; (*b*) S. A. Sadek, S. M. Shaw, W. V. Kessler and G. C. Wolf, *J. Org. Chem.*, 1981, **46**, 3259.
21 T. E. Frizon, J. Rafique, S. Saba, I. H. Bechtold, H. Gallardo and A. L. Braga, *Eur. J. Org. Chem.*, 2015, **16**, 3470.
22 O. E. D. Rodrigues, D. Souza, L. C. Soares, L. Dornelles, R. A. Burrow, H. R. Appelt, C. F. Alves, D. Alves and A. L. Braga, *Tetrahedron Lett.*, 2010, **51**, 2237.
23 M. H. M. Sari, A. C. G. Souza, S. G. Rosa, D. Souza, O. E. D. Rodrigues and C. W. Nogueira, *Eur. J. Pharmacol.*, 2014, **725**, 79.
24 (*a*) E. Ma, H. Kim and E. Kim, *Steroids*, 2005, **70**, 245; (*b*) E. Ma and S. Kim, *Molecules*, 2009, **14**, 4655; (*c*) C. M. Marson, A. S. Rioja, K. E. Smith and J. M. Behan, *Synthesis*, 2003, 535; (*d*) D. A. Foley, Y. O'Callaghan,

N. M. O'Brien, F. O. McCarthy and A. R. Maguirre, *J. Agric. Food Chem.*, 2010, **58**, 1165.

25 The same behaviour was previously observed by our group, see ref. 14.

26 (*a*) R. A. Moreau, B. D. Whitaker and K. B. Hicks, *Prog. Lipid Res.*, 2002, **41**, 457; (*b*) J. Quílez, P. García-Lorda and J. Salas-Salvado, *Clin. Nutr.*, 2003, **22**, 343; (*c*) D. Kritchevsky and S. C. Chen, *Nutr. Res.*, 2005, **25**, 413; (*d*) G. Brufau, M. A. Canela and M. Rafecas, *Nutr. Res.*, 2008, **28**, 217; (*e*) G. García-Llatas and M. T. Rodríguez-Estrada, *Chem. Phys. Lipids*, 2011, **164**, 607.

27 (*a*) S.-S. Huang, K.-L. Jian, R.-J. Li, L.-Y. Kong and M.-H. Yang, *RSC Adv.*, 2016, **6**, 6320; (*b*) X. Lin, L. Ma, R. A. Moreau and R. E. Ostlund Jr, *Lipids*, 2011, **8**, 701; (*c*) X. Lin, L. Ma, S. B. Racette, C. L. A. Spearie and R. E. Ostlund Jr, *Am. J. Physiol. Gastrointest. Liver Physiol.*, 2009, **296**, 931; (*d*) A. Waheed, J. Barker, S. J. Barton, C. P. Owen, S. Ahmed and M. A. Carew, *Eur. J. Pharm. Sci.*, 2012, **47**, 464.

28 Q. Sun, S. Cai and B. R. Peterson, *Org. Lett.*, 2009, **11**, 567.

29 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.