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On reactions of spirostane sapogenins with benzeneseleninic anhydride

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ABSTRACT

Direct dehydrogenation of spirostane sapogenins with benzeneseleninic anhydride/iodoxybenzene afforded the Δ^{22} derivatives in low yields. The reactions catalyzed by BF_3/Et_2O produced the 23-oxo-sapogenins in addition to their 22-oxo-23-spiro-isomers. The reactions of sapogenins with benzeneseleninic anhydride carried out in the presence of $TiCl_4$ afforded products chlorinated at C23.

1. Introduction

Steroidal saponins are frequently occurring natural products with diverse biological activity.[1] Upon hydrolysis, these compounds yield sugars and aglycones called sapogenins with cholestane, furostane or spirostane frameworks. The spirostane sapogenins (SS) obtained from natural saponins always have an *R* configuration at the spiro carbon atom. The 21-methyl group is usually α-oriented (20*S*). However, the SS differ in configuration at C25. In compounds with an equatorial α-methyl group (e.g., hecogenin) this stereocenter has a 25*R* configuration, while compounds with an axial β-methyl group, such as sarsasapogenin, have the 25*S* configuration. Of course, apart from the side chain there are further structural differences between SS in the type of functionalization and stereochemistry at the A/B ring junction (5α- and 5β-steroids). The SS are relatively cheap raw materials for the synthesis of various medicinally important compounds.[2] Among them are steroidal hormones, which may be obtained by Marker degradation of spirostane side chain into C_{21} or C_{19} steroids, followed by further transformations.[3] Functionalization of SS in the side chain was a matter of many recent reports. Syntheses of some natural products with important biological activity (e.g., cephalostatins),[4] spirostanic analogues of brassinosteroids,[5] glycospirostanes,[6] etc., involved modification of the SS side chain. The most common reactions of SS are transformations at the α position to the spiro carbon atom (C23).[7] This is so, because the spiroketal system of SS easily undergoes ring F cleavage to a reactive enol ether susceptible to an electrophilic attack at C23. There are several papers dealing with halogenation[8] or oxidation[9] at this position. However, none of these are devoted to direct dehydrogenation leading to the 23(24)-unsaturated SS, potentially useful in various syntheses. The syntheses of these compounds have been reported in the literature only by rather inefficient routes, e.g., dehydrobromination of the 23-bromo-SS,[10] denitroamination of the 23-nitroamino-SS,[11] the Shapiro reaction of tosylhydrazones of the SS 23-oxo-derivatives[6a] or using lengthy procedures, e.g., phenylselenylation of SS followed by oxidation of phenylselenide to its selenoxide and subsequent elimination.[12]

2. Results and discussion

The spiroketal moiety of SS is sensitive to protic and Lewis acids. The acids catalyze reversible opening of ring F of SS to form the enol ether that has been postulated as an intermediate of several reactions proceeding at C23. The enol form is also a reactive intermediate of various ketone dehydrogenation procedures. Therefore we thought that it might be possible to carry out direct dehydrogenation of SS to the 23(24)-unsaturated derivatives in acid medium. Here we present the results of our study on benzeneseleninic anhydride (BSA) oxidation of SS under various conditions. BSA[13] is a convenient reagent for dehydrogenation of ketones and possesses certain advantages over the commonly used methods employing *o*-iodoxybenzoic acid (IBX),[14] dicyanodichloroquinone (DDQ)[15] and other high-potential quinones, bromination/dehydrobromination or palladium-catalyzed oxidation of the enol ethers.[16]

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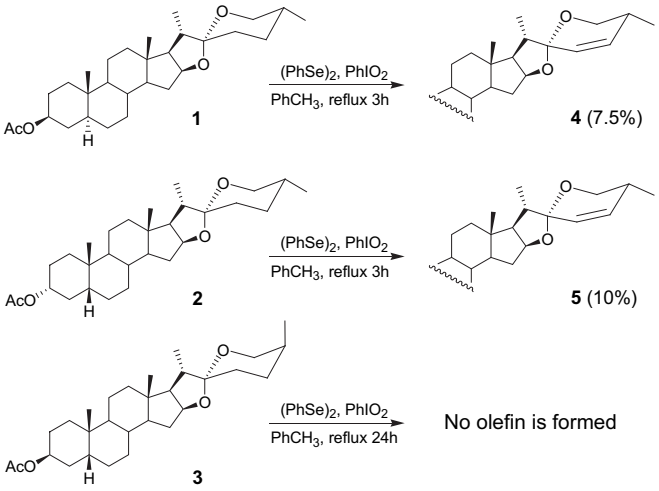
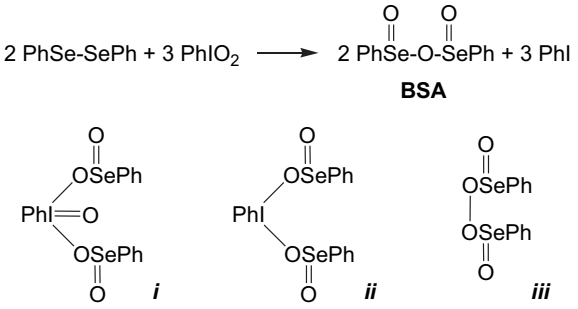
At the beginning of this study it was checked that SS are resistant to IBX and iodoxybenzene oxidation (no reaction occurred). However, without acid catalysis there was no oxidation of tigogenin acetate (**1**) with BSA (in refluxing benzene, toluene or chlorobenzene) either. The reactions with BSA in the presence of *p*-TsOH led to a complex mixture of several products but none of them was the desired 23(24)-unsaturated derivative. Unexpectedly, when the reaction was carried out by a catalytic method[17] with only small amount of BSA and iodoxybenzene (in excess) as a cooxidant in refluxing toluene in the absence of *p*-TsOH dehydrogenation to 23-dehydrotigogenin acetate (**4**) took place, albeit in low yield (7.5%). Exactly the same result was obtained when catalytic amount of diphenyl diselenide was used instead of BSA (Scheme 1). The analogous reaction of epismilagenin acetate (**2**) also afforded the corresponding 23-dehydrogenated **5** product in a slightly better yield (10%). Most of the unreacted sapogenin could be recovered, if the reaction time was not too long. However, attempts to increase yields by optimizing the reaction conditions failed. The problem is that the olefinic products (**4** and **5**) slowly react further and the reactions become messy over time. Sarsasapogenin acetate (**3**) containing an axial methyl group at C25 did not form an olefin at all under these conditions (23-oxosarsasapogenin acetate was obtained instead in very low yield).



Scheme 1.

The previous study[17] has proved that oxygen atom transfer from the iodine–oxygen bond into selenium atom is fast and BSA is formed from diphenyl diselenide and iodoxybenzene. The catalytic ketone dehydrogenation reactions with $Ph_2Se_2/PhIO_2$ generally give yields equal or superior to those obtained by use of the anhydride (BSA) in stoichiometric amount. This is so, because the catalytic approach prevents formation of reduced forms of the anhydride generated in the elimination step, which may give rise to unwanted secondary reactions. However, there are also reports[18] that during reaction between Ph_2Se_2 and $PhIO_2$ some peroxy species (e.g., *iii*) may be formed (Scheme 2), responsible for the side reactions of the Beyer/Villiger oxidation type. It is possible, that apart from the major reaction product (BSA), iodoxybenzene dibenzeneseleninate (*i*), iodosobenzene dibenzeneseleninate (*ii*), and peroxybenzeneseleninic anhydride (*iii*) are also formed.



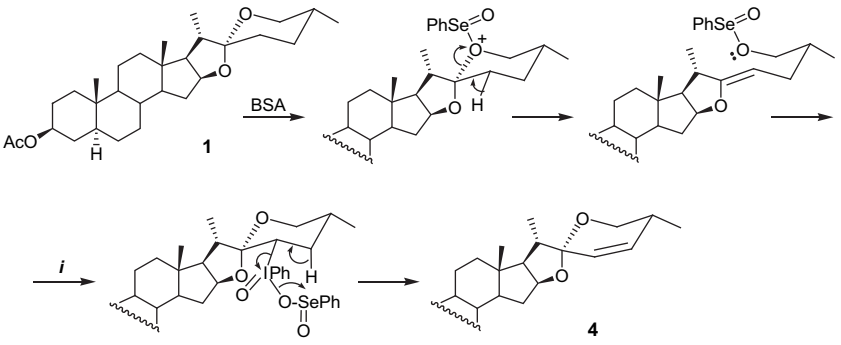
Scheme 2.

Since the blank experiments showed that SS do not react with BSA or $PhIO_2$ in toluene at reflux, it can be concluded that one of the above mentioned species formed in situ may play an important role in dehydrogenation. In view of the known disproportionation of iodosobenzene into iodobenzene and iodoxybenzene at elevated temperatures, iodosobenzene dibenzeneseleninate (*ii*) seems to be a less likely candidate for a reactive intermediate than compound *i*.

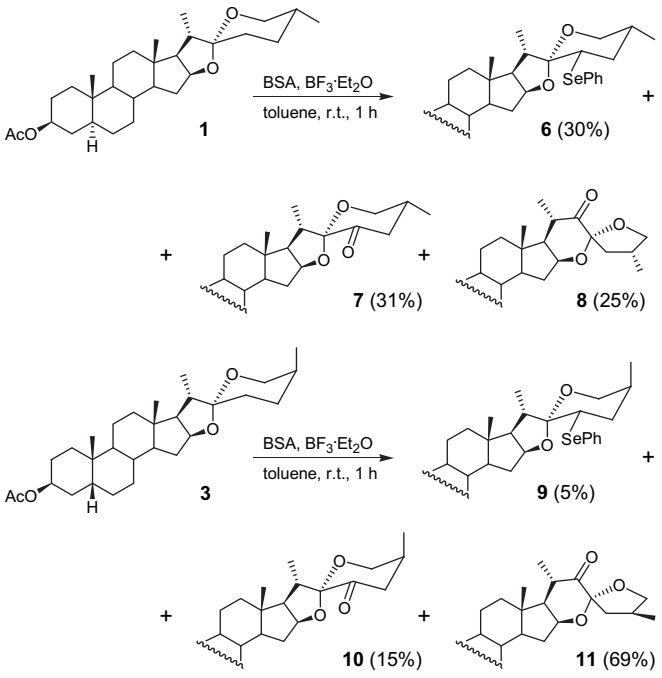
A tentative mechanism of dehydrogenation is shown in Scheme 3. It is suggested that BSA in refluxing toluene behaves similarly to anhydrides of carboxylic acids promoting opening of the ring F. The enol ether formed in this way reacts with oxidizing agent, such as *i*. The capability of hypervalent iodine compounds to react with enols is well documented.[19]

Considering that a hypervalent iodine moiety, after its electrophilic attack to enol ether, may undergo *syn*-elimination similarly to selenoxides, the reaction with a species like *i* is an alternative to the reaction of enol ether with BSA. However, it is not clear why the latter reaction does not work in this case. Therefore an alternative mechanism assuming that a hypervalent iodine compound assists in F-ring opening (serves as a weak Lewis acid) and BSA attacks enol ether can be also envisaged.

A further study of SS reactions with BSA was performed in the presence of strong Lewis acids at room temperature. The reaction of tigogenin acetate (**1**) with BSA/$BF_3\cdot Et_2O$ afforded three products in comparable yields: 23-phenylselenide **6**, the 23-oxotigogenin acetate (**7**), and its 22-oxo-23-spiro-isomer **8** (Scheme 4). A similar reaction of sarsasapogenin acetate (**3**) gave analogous products but in



Scheme 3.



Scheme 4.

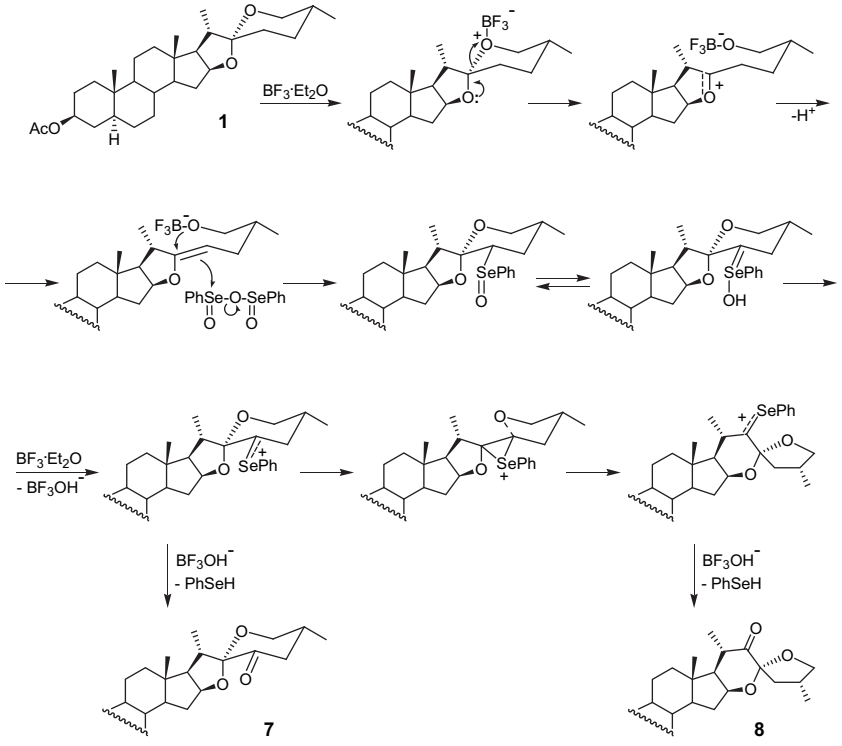
different yields. The major reaction product (69%)—the 23-spiro-22-ketone **11** was accompanied by 23-oxosarsasapogenin acetate (**10**;15%) and small amount of 23-phenylselenide **9**. A likely mechanism of compound **1** reaction is outlined in Scheme 5. It seems reasonable to postulate that under the reaction conditions enolization of the initially formed selenoxide is faster than *syn*-elimination. Migration of a hydroxyl group from selenium atom into C23 followed by elimination of benzeneselenol resulted in formation of 23-ketone **7**. The intermediate cation may rearrange to the more thermodynamically stable isomeric spiro system before hydrolysis to a ketone.[20]

Partial isomerization of **7** into **8** catalyzed by $BF_3 \cdot Et_2O$ is a known reaction. However, this transformation requires very harsh conditions (reflux 7 days in THF).[20a] In the present case isomerization of a selenium species occurred quickly at room temperature. The equilibration of the isomeric spiro systems in the case of a sarsasapogenin derivative proved to be much more efficient. The minor reaction products, 23-phenylselenides, were formed as a result of an enol ether reaction with reduced forms of BSA. Formation of these by-products may be suppressed by using BSA in larger excess.

The reaction of SS with BSA carried out in the presence of $TiCl_4$ afforded only chlorinated products. BSA appeared to be a very strong oxidizing agent in acid medium. It seems that a new hypervalent iodine species containing chlorine atom[21] was generated in situ by the reaction of BSA with $TiCl_4$. This species was a source of electrophilic 'Cl^+', which reacted with enol ether obtained upon treatment of SS with $TiCl_4$. Tigogenin acetate (**1**) afforded two monochlorides (**12** and **13**) and dichloride **14**, while sarsasapogenin acetate (**3**) yielded only dichloride **15**. In the latter case the second chlorination is probably faster than the first one (Scheme 6).

3. Conclusions

All reactions of SS with BSA proceed via an enol ether intermediate. Direct dehydrogenation of tigogenin acetate at C23 was achieved using a catalytic method ($Ph_2Se_2/PhIO_2$) but yield was unsatisfactory. The reactions of SS with BSA in the presence of $BF_3 \cdot Et_2O$ afforded 23-ketones in addition to their 22-oxo-23-spiro isomers. In the case of sarsasapogenin acetate the latter product was obtained in 69% yield. When $TiCl_4$ was used as a Lewis acid in the SS reactions with BSA only chlorinated at C23 products were formed.

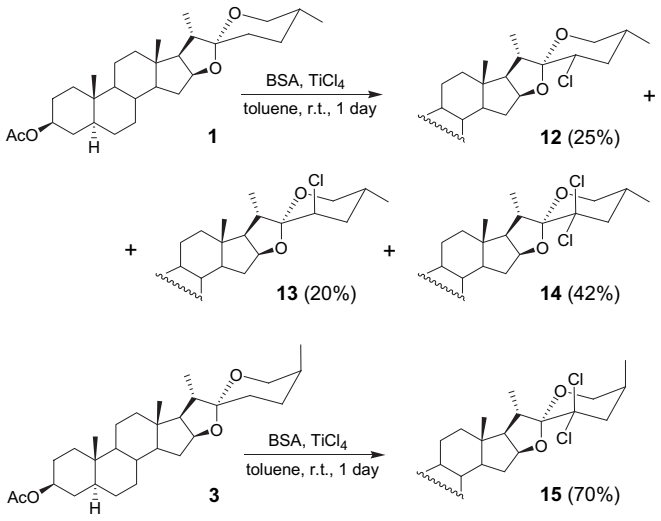


Scheme 5.

4. Experimental section

4.1. General

Melting points were determined on a Kofler apparatus of the Boetius type. NMR spectra were recorded with a Bruker Avance II



Scheme 6.

400 MHz spectrometer in $CDCl_3$ as a solvent with TMS as internal standard (only selected signals in the ^1H NMR spectra are reported). Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer in chloroform solutions. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70–230 mesh silica gel (Baker). The TLC silica gel 60 F_{254} sheets (Merck) were used.

4.2. Reaction of tigogenin acetate (1) with Ph_2Se_2 and $PhIO_2$

To a solution of Ph_2Se_2 (11 mg, 0.03 mmol) in dry toluene (20 ml), $PhIO_2$ (135 mg, 0.68 mmol) was added. The reaction mixture was stirred and refluxed until the yellow color disappeared (about 10 min). Then tigogenin acetate (**1**, 80 mg, 0.17 mmol) was added. After 24 h the reaction mixture was poured into water and extracted with dichloromethane. Combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. Silica gel column chromatography with ethyl acetate/hexane 10:90 elution afforded the unreacted substrate (**1**, 42 mg) and the more polar product **4** (6 mg, 7.5%).

*4.2.1. (25R)-5α-Spirost-23-en-3β-ol acetate (**4**).* Mp 198–200 °C (CH_2Cl_2-hexane); R_f (15% AcOEt/hexane) 0.33; $[\alpha]_D^{20}$ −51.1 (*c* 0.75, $CHCl_3$); IR ν_{max} (cm^{-1}): 1724, 1654, 1255, 981; ^1H NMR ν (ppm): 5.86 (dd, J_1=10.0, J_2=1.5 Hz, 1H), 5.57 (dd, J_1=10.0, J_2=2.6 Hz, 1H), 4.69 (m, 1H), 4.57 (m, 1H), 3.69 (ddd, J_1=10.9, J_2=5.6, J_3=1.3 Hz, 1H), 3.49 (t, J=10.9 Hz, 1H), 2.37 (m, 1H), 2.03 (s, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.89 (d, J=7.2 Hz, 3H), 0.85 (s, 3H), 0.81 (s, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 136.8 (CH), 126.8 (CH), 107.2 (C), 81.9 (CH), 73.6 (CH), 65.4 (CH_2), 62.4 (CH), 56.2 (CH), 54.2 (CH), 44.6 (CH), 41.9 (CH), 40.7 (C), 39.9 (CH_2), 36.7 (CH_2), 35.6 (C), 35.0 (CH), 34.0 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 29.1 (CH), 28.4 (CH_2), 27.4 (CH_2), 21.4 (CH_3), 21.0 (CH_2), 16.5 (CH_3), 15.7 (CH_3), 14.4 (CH_3), 12.2 (CH_3); EIMS, *m*/*z* 456 (M^+, 4%); HRMS calcd for $C_{29}H_{44}O_4$: 456.3240, found: 456.3255.

Analogous reaction of epismilagenin acetate (**2**) with Ph_2Se_2 and $PhIO_2$ afforded (25*R*)-5β-spirost-23-en-3α-ol acetate (**5**) in 10% yield.

*4.2.2. (25R)-5β-Spirost-23-en-3α-ol acetate (**5**).* Mp 159–162 °C (CH_2Cl_2-methanol); R_f (15% AcOEt/hexane) 0.36; $[\alpha]_D^{20}$ −28.2 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 1721, 1663, 1261, 980; ^1H NMR δ (ppm): 5.87 (dd, J_1=10.0 Hz, J_2=1.5 Hz, 1H), 5.57 (dd, J_1=10.0 Hz, J_2=2.6 Hz, 1H), 4.73 (m, 1H), 4.54 (m, 1H), 3.70 (ddd, J_1=10.9 Hz, J_2=6.3 Hz, J_1=1.3 Hz, 1H), 3.49 (t, J=10.9 Hz, 1H), 2.37 (m, 1H), 2.04 (s, 3H) 0.96 (s, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.90 (d, J=7.2 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR δ (ppm): 170.6 (C), 136.8 (CH), 126.8 (CH), 107.2 (C), 81.9 (CH), 74.3 (CH), 65.4 (CH_2), 62.4 (CH), 56.3 (CH), 41.9 (CH), 41.8 (CH), 40.8 (C), 40.5 (CH), 40.2 (CH_2), 35.4 (C), 35.0 (CH), 34.7 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.1 (CH), 26.9 (CH_2), 26.6 (CH_2), 23.3 (CH_3), 21.5 (CH_3), 20.6 (CH_2), 16.4 (CH_3), 15.7 (CH_3), 14.4 (CH_3); ESI-MS, *m*/*z*: 479 [$(M+Na)^+$, 100%]; HRMS calcd for $C_{29}H_{44}NaO_4$: 479.3137, found: 479.3153.

4.3. Reaction of tigogenin acetate (1) with BSA in the presence of $BF_3 \cdot Et_2O$

To a solution of tigogenin acetate (**1**, 50 mg, 0.1 mmol) in dry toluene (10 mL) BSA (41 mg, 1.2 equiv) and $BF_3 \cdot Et_2O$ (0.082 mL, 6 equiv) were added. The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. After 1 h the reaction mixture was poured into brine and extracted exhaustively with dichloromethane. Combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. Column chromatography with ethyl acetate/hexane 5:95 elution gave pure (22*R*,25*R*)-23-phenylseleno-5α-spirostan-3β-ol acetate (**6**, 20 mg, 30%) followed by (25*R*)-3β-acetoxy-5α-spirostan-23-one (**7**, 16 mg, 31%). Further elution with acetate/hexane 15:85 afforded (23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxy-5α-cholestan-22-one (**8**, 13 mg, 25%).

*4.3.1. (22R,25R)-23-Phenylseleno-5α-spirostan-3β-ol acetate (**6**).* Mp 168–170 °C (CH_2Cl_2-hexane); R_f (15% AcOEt/hexane) 0.35; $[\alpha]_D^{20}$ −20.1 (*c* 1.0, $CHCl_3$); IR ν_{max} (cm^{-1}): 1724, 1579, 1262, 1024, 943; ^1H NMR δ (ppm): 7.55 (m, 2H), 7.27 (t, m, 3H), 4.69 (m, 1H), 4.39 (m, 1H), 3.48 (dd, J_1=10.8, J_2=4.6 Hz, 1H), 3.41 (t, J=10.9 Hz, 1H), 3.28 (dd, J_1=12.6, J_2=4.8 Hz, 1H), 2.84 (m, 1H), 2.03 (s, 1H), 0.93 (d, J=6.8 Hz, 3H), 0.92 (s, 3H), 0.85 (s, 3H), 0.77 (d, J=6.5 Hz, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 133.9 (CH×2), 130.5 (C), 129.0 (CH×2), 127.1 (CH×2), 110.6 (C), 81.4 (CH), 73.6 (CH), 66.1 (CH_2), 61.4 (CH), 56.0 (CH), 54.2 (CH), 45.6 (CH), 44.6 (CH), 41.2 (C), 40.3 (CH_2), 38.84 (CH_2), 38.76 (CH), 36.7 (CH_2), 35.6 (C), 34.8 (CH), 34.0 (CH_2), 32.7 (CH), 32.2 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 21.4 (CH_3), 21.0 (CH_2), 17.1 (CH_3), 16.6 (CH_3), 14.2 (CH_3), 12.2 (CH_3); ESI-MS, *m*/*z*: 457 $(M-C_6H_5SeH)^+$, 615 $[M(^{80}Se)+H]^+$. Elemental analysis, found C, 68.15; H, 8.15. $C_{35}H_{50}O_4Se$ requires C, 68.50; H, 8.21%.

Compounds **7**[7d,22] and **8**[20] proved identical in all respects with the same compounds described in the literature.

4.4. Reaction of sarsasapogenin acetate (3) with BSA in the presence of $BF_3 \cdot Et_2O$

To a solution of sarsasapogenin acetate (**3**, 50 mg, 0.1 mmol) in dry toluene (10 mL) BSA (41 mg, 1.2 equiv) and $BF_3 \cdot Et_2O$ (0.082 mL, 6 equiv) were added. The reaction mixture was stirred one hour at room temperature, poured into brine and extracted exhaustively with dichloromethane. Combined organic extracts were dried over Na_2SO_4, evaporated in vacuo and the products were separated by silica gel column chromatography. Elution with ethyl acetate/hexane 10:90 gave consecutively: (22*R*,25*S*)-23-phenylseleno-5β-spirostan-3β-ol acetate (**9**, 5.5 mg, 5%), (25*S*)-3α-acetoxy-5α-spirostan-23-one (**10**, 13 mg, 15%), and (23*R*,25*S*)-3α-acetoxy-16β,23:23,26-diepoxy-5α-cholestan-22-one (**11**, 57 mg, 69%).

*4.4.1. (22R,25S)-23-Phenylseleno-5β-spirostan-3β-ol acetate (**9**).* An oil; R_f (15% AcOEt/hexane) 0.35; $[\alpha]_D^{20}$ −32.2 (*c* 0.5, $CHCl_3$); IR, ν_{max} (cm^{-1}): 1724, 1264, 1024, 948; ^1H NMR ($CDCl_3$) δ (ppm): 7.52 (m, 2H), 7.26 (m, 3H), 5.08 (br s, 1H), 4.42 (m, 1H), 3.99 (dd, J_1=11.0 Hz, J_2=2.6 Hz, 1H), 3.51 (dd, J_1=13.1 Hz, J_2=5.0 Hz, 1H), 3.31

(d, J=11.0 Hz, 1H), 2.78 (m, 1H), 2.37 (m, 1H), 2.06 (s, 3H), 1.07 (d, J=7.1 Hz, 3H), 1.00 (s, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C), 133.5 (CH×2), 130.6 (C), 129.0 (CH×2), 127.0 (CH), 111.2 (C), 81.6 (CH), 70.7 (CH), 64.5 (CH_2), 61.4 (CH), 56.2 (CH), 41.5 (CH), 41.3 (C), 40.5 (CH_2), 40.0 (CH), 39.2 (CH), 37.3 (CH_2), 36.3 (CH_2), 35.1 (CH), 35.0 (C), 31.5 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.0 (CH), 26.5 (CH_2), 26.4 (CH_2), 25.0 (CH_2), 23.8 (CH_3), 21.5 (CH_3), 20.9 (CH_2), 17.0 (CH_3), 16.1 (CH_3), 14.1 (CH_3); ESI-MS, m/z: 637 [M(^{80}Se)+Na]$^+$; HRMS (ESI): [M(^{80}Se)+Na]$^+$, found 637.2797. $C_{35}H_{50}NaO_4Se$ requires 637.2772.

Compounds **10**[20c,22] and **11**[20] proved identical in all respects with the same compounds described in the literature.

4.5. Reaction of tigogenin acetate (1) with BSA in the presence of $TiCl_4$

To a solution of tigogenin acetate (**1**, 154 mg, 0.3 mmol) in dry toluene (8 mL) BSA (121 mg, 1 equiv) and $TiCl_4$ (0.11 mL, 3 equiv) were added. The reaction mixture was stirred for 24 h at room temperature, poured into saturated aqueous solution of NaCl and extracted exhaustively with dichloromethane. Combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. Column chromatography gave pure 23,23-dichlorotigogenin acetate (**14**, 74 mg, 42%), (23*R*)-23-chlorotigogenin acetate (**13**, 34 mg, 20%), and (23*S*)-23-chlorotigogenin acetate (**12**, 42 mg, 25%) eluted consecutively with ethyl acetate/benzene 0.1:99.9.

*4.5.1. 23,23-Dichlorotigogenin acetate (**14**).* Mp 175–177 °C (CH_2Cl_2-hexane); R_f (1.5% AcOEt/benzene) 0.33; $[\alpha]_D^{20}$ −68.2 (c 1.0, $CHCl_3$); IR ν_{max} (cm^{-1}): 1723, 1264, 1027, 906, 811; ^{1}H NMR δ (ppm): 4.69 (m, 1H), 4.4 (q, J=7.4 Hz, 1H), 3.54 (dd, J_1=11.1 Hz, J_2=4.9 Hz, 1H), 3.47 (t, J=11.1 Hz, 1H), 2.78 (m, 1H), 2.39 (m, 2H), 2.32 (m, 1H), 2.03 (s, 3H), 1.22 (d, J=6.8 Hz, 3H), 0.94 (s, 3H), 0.85 (s, 3H), 0.84 (d, J=6.2 Hz, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 109.8 (C), 90.3 (C), 81.3 (CH), 73.6 (CH), 65.4 (CH_2), 63.7 (CH), 56.1 (CH), 54.2 (CH), 49.5 (CH_2), 44.6 (CH), 41.7 (C), 39.9 (CH_2), 37.9 (CH), 36.7 (CH_2), 35.5 (C), 34.9 (CH), 34.0 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 29.2 (CH), 28.4 (CH_2), 27.4 (CH_2), 21.4 (CH_3), 20.9 (CH_2), 17.5 (CH_3), 16.4 (CH_3), 15.6 (CH_3), 12.2 (CH_3); ESI-MS, m/z: 549 [M(^{35}Cl)+Na]$^+$; HRMS (ESI): [M(^{35}Cl)+Na]$^+$, found 549.2527. $C_{29}H_{44}Cl_2NaO_4$ requires 549.2514.

*4.5.2. (23R)-23-Chlorotigogenin acetate (**13**).* Mp 160–164 °C (CH_2Cl_2-hexane); *Rf* (1.5% AcOEt/benzene) 0.31; $[\alpha]_D^{20}$ −52.3 (c 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 1723, 1263, 1022, 983; ^{1}H NMR δ (ppm): 4.69 (m, 1H), 4.48 (m,1H), 4.01 (t, J=2.9 Hz, 1H), 3.57 (m, 1H), 3.46 (t, J=11.4 Hz, 1H), 2.22 (m,1H), 2.03 (s, 3H), 1.17 (d, J=6.9 Hz, 3H), 0.85 (s, 3H), 0.81 (d, J=6.7 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 107.6 (C), 81.7 (CH), 73.6 (CH), 66.6 (CH2), 64.7 (CH), 60.5 (CH), 56.3 (CH), 54.2 (CH), 44.6 (CH), 41.7 (CH), 41.1 (C), 39.4 (CH_2), 37.4 (CH_2), 36.7 (CH_2), 35.6 (C), 35.3 (CH), 34.0 (CH_2), 32.08 (CH_2), 32.06 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 23.8 (CH), 21.4 (CH_3), 20.8 (CH_2), 17.1 (CH_3), 16.3 (CH_3), 16.1 (CH_3), 12.2 (CH_3); ESI-MS, m/z: 515 [M(^{35}Cl)+Na]$^+$, 1007 [2M(^{35}Cl)+Na]$^+$; HRMS (ESI): [M(^{35}Cl)+Na]$^+$, found 515.2921. $C_{29}H_{45}ClNaO_4$ requires 515.2904.

*4.5.3. (23S)-23-Chlorotigogenin acetate (**12**).* Mp 235–238 °C (CH_2Cl_2/hexane); R_f (1.5% AcOEt/benzene) 0.29; $[\alpha]_D^{20}$ −48.1 (c 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 1723, 1262, 1054, 919, 870; ^{1}H NMR δ (ppm): 4.69 (m, 1H), 4.41 (m, 1H), 3.93 (m, 1H), 3.44 (m, 2H), 2.59 (m, 1H), 2.03 (s, 3H), 0.95 (d, J=7.0 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.84 (d, J=6.3 Hz, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 109.3 (C), 81.4 (CH), 73.7 (CH), 65.6 (CH_2), 61.4 (CH), 56.9 (CH), 56.1 (CH), 54.2 (CH), 44.6 (CH), 41.2 (C), 40.2 (CH_2), 39.3 (CH_2), 36.8 (CH), 36.7 (CH_2), 35.6 (C), 34.9 (CH), 34.0 (CH_2), 32.5 (CH), 32.2 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 21.4 (CH_3), 21.0 (CH_2), 16.5 (CH_3), 16.3 (CH_3), 14.0 (CH_3), 12.2 (CH_3); ESI-MS, m/z: 515 [M(^{35}Cl)+Na]$^+$; HRMS (ESI): [M(^{35}Cl)+Na]$^+$, found 515.2920. $C_{29}H_{45}ClNaO_4$ requires 515.2904.

4.6. Reaction of sarsasapogenin acetate (3) with BSA in the presence of $TiCl_4$

To a solution of sarsasapogenin acetate (**3**, 110 mg, 0.24 mmol) in dry toluene (8 mL) BSA (86 mg, 1 equiv) and $TiCl_4$ (0.03 mL, 1.1 equiv) were added. The reaction mixture was stirred 20 h at room temperature, poured into saturated aqueous solution of NaCl and extracted exhaustively with dichloromethane. Combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. Column chromatography with ethyl acetate/hexane 5:95 elution afforded pure 23,23-dichlorosarsasapogenin acetate (**15**, 75 mg, 70%).

*4.6.1. 23,23-Dichlorosarsasapogenin acetate (**15**).* Mp 282–284 °C (CH_2Cl_2-hexane); R_f (15% AcOEt/hexane) 0.40; $[\alpha]_D^{20}$ −152.1 (c 1.0, $CHCl_3$); IR ν_{max} (cm^{-1}): 1724, 1263, 1026, 988, 924, 845; ^{1}H NMR δ (ppm): 5.07 (m, 1H), 4.43 (m,1H), 4.24 (dd, J_1=11.3, J_2=3.8 Hz, 1H), 3.39 (dd, J_1=11.2, J_2=1.4 Hz, 1H), 2.91 (dd, J_1=14.5, J_2=6.3 Hz, 1H), 2.79 (m, 1H), 2.39 (dt, J_1=14.4, J_2=1.8 Hz, 1H), 2.06 (s, 3H), 1.35 (d, J=7.5 Hz, 3H), 1.26 (d, J=6.8 Hz, 3H), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR δ (ppm): 170.7 (C), 110.2 (C), 89.2 (C), 81.5 (CH), 70.7 (CH), 63.79 (CH), 63.77 (CH_2), 56.3 (CH), 47.0 (CH_2), 41.8 (C), 40.2 (CH_2), 40.0 (CH), 38.5 (CH), 37.3 (CH), 35.2 (CH), 35.0 (C), 31.7 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 29.7 (CH), 26.43 (CH_2), 26.39 (CH_2), 25.0 (CH_2), 23.8 (CH_3), 21.5 (CH_3), 20.8 (CH_2), 19.4 (CH_3), 17.6 (CH_3), 16.3 (CH_3); ESI-MS, m/z: 549 [M(^{35}Cl)+Na]$^+$; HRMS (ESI): [M(^{35}Cl)+Na]$^+$, found 549.2528. $C_{29}H_{44}Cl_2NaO_4$ requires 549.2514.

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