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# Stereoselective synthesis of selenosteroids

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ABSTRACT

A stereoselective synthesis of selenosteroids **4** and **5** has been achieved. Starting from commercial available cholesterol **1**, followed by asymmetric epoxidation, and subsequently, by stereoselective epoxide ring opening, employing a selenium nucleophilic species, the correspondent products were afforded in high yields. The compounds were being evaluated for their biological activity and as a chiral pool for asymmetric transformations.



## 1. Introduction

Oxygenated derivatives of cholesterol, known as oxysterols, represent a group of biomolecules receiving much attention in recent years due to their relevant bioactivities.[1] Oxysterols have been detected in appreciable quantities in human tissues and fluids and have been implicated in a number of important biological processes such as regulation of cholesterol homeostasis, atherosclerosis, cytotoxicity[2], and have found use as antitumoral and antileukemic compounds for inducing apoptosis.[3] Likewise, compounds containing selenium can possess biological properties and have been used as antiviral, antihypertensive, antibacterial, or chemopreventive anticancer agents.[4] There are several reports in the literature describing the antitumoral activity of selenium compounds via apoptosis in cancer cells induced by the generation of ROS in a pro-oxidant fashion.[5] The combination of oxysterols and selenium is quite rare and only a few examples are described in the literature with a very limited selenium moiety.[6] The designed synthesis of new pro-oxidant biomolecules combining oxysterol and selenium-containing compounds has a great potential for the creation of a new library of molecules important for biological applications.

This field has been explored by our research group and in this context, we report herein the stereoselective synthesis of selenosteroids **4** and **5** derived from cholesterol **1** (Fig. 1). Firstly, the hydroxyl protection in $C_3$ position in cholesterol **1** was introduced using sodium hydride and methyl iodide to afford the respective methyl-ether **2**. Next, an asymmetric epoxidation in the cholesterol double bond ($C_5$=$C_6$) was performed to introduce the desired epoxide functional group in the steroidal nucleus, using the protocol employed by Marson and co-workers with MCPBA as the oxidant agent to give the epoxide ring with high selectivity in the least hindered face of steroid.[7] The introduction of selenium in the steroid moiety was performed using a selective epoxide ring opening with nucleophilic selenolates. For compounds **4a**–**i**, the anionic species were generated from the respective diselenides. To optimize the selenium insertion, a standard condition was employed and the epoxide **3** was treated with diphenyl diselenide using two methodologies. In the first protocol, the selenolates were generated from the appropriate diselenide, followed by the reductive cleavage of dichalcogenide bond using sodium borohydride in EtOH/THF (Method A). In the second methodology, the selenolate species were obtained by reductive cleavage of the Se–Se bond of diselenide using Zn and HCl (Method B), as depicted in Scheme 1. Since we found that Method B gave better yields than Method A (90% vs 63% for the compound **4a**, respectively), Method B was used as the standard protocol for the synthesis of selenides **4**. For the diselenide **5**, the nucleophilic species was formed using elemental selenium and lithium triethylborohydride to give $Li_2Se_2$, as shown in Scheme 1 (for detailed procedures, see Section 2). The yields of the respective seleno-oxysterols **4** and **5** are depicted in Table 1.

The stereo- and regioselectivity in the epoxide **3** ring opening can be rationalized as shown in Figure 2.

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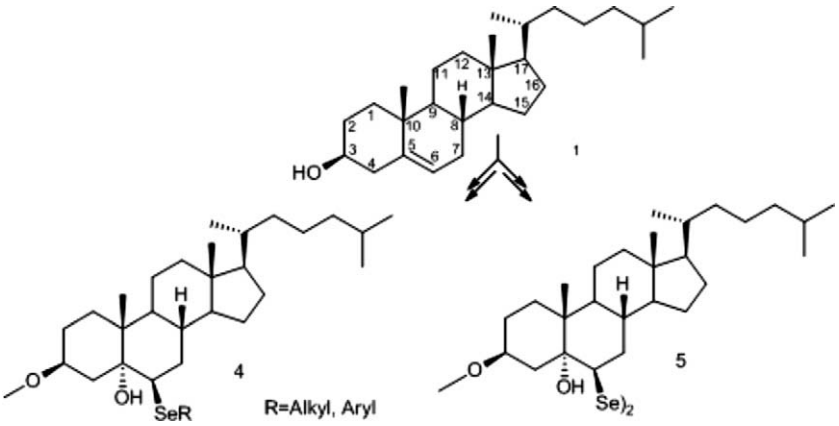
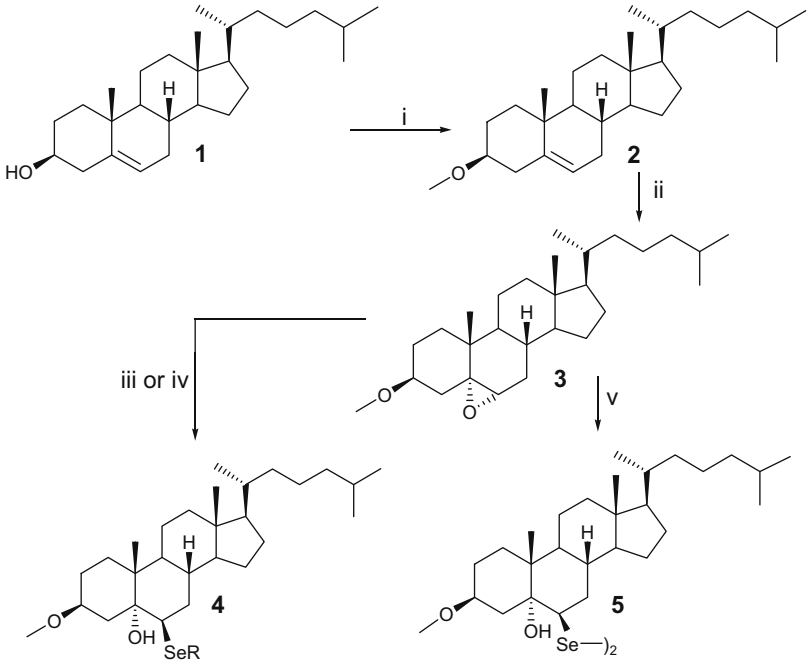



**Figure 1.** Selenosteroids **4** and **5**.




**Scheme 1.** Synthesis of steroids containing selenium. Reagents and conditions: (i) (a) THF, NaH; (b) $CH_3I$, rt; (ii) $CHCl_3$, MCPBA, rt; (iii) (a) EtOH/THF, $(RSe)_2$, $NaBH_4$; (b) epoxide **3**, reflux; (iv) (a) THF, ZnO, HCl, $(RSe)_2$, ultrasound; (b) epoxide **3**, ultrasound; (v) (a) THF, SeO, lithium triethylborohydride; (b) epoxide **3**, reflux.

The nucleophilic attack in the epoxide ring opening would be made exclusively on the least sterically hindered carbon of the epoxide ($C_6$), due to the $SN_2$ mechanism employed in this methodology. In stereochemical terms, the classical and much stabilized *anti* approximation of selenium nucleophiles species with the α-epoxide[8] produces the respective *trans*-hydroxy selenides **4** and **5**. To prove the regio- and stereochemistry we attempted the single crystal X-ray analysis of the selenosteroids. Unfortunately none of the compounds was suitable for this analysis. As proof of the stereochemistry, the single crystal X-ray structure of the chloride **6** (Fig. 3), synthesized by epoxide ring opening via a $SN_2$ mechanism, was performed.

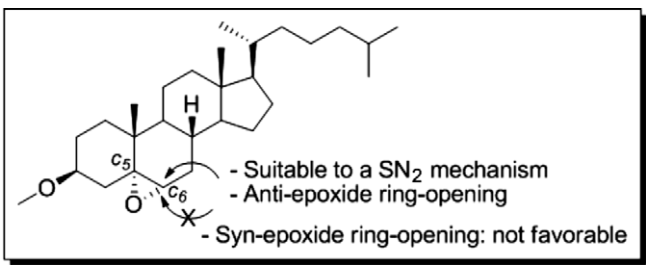



**Figure 2.** Proposed mechanism of epoxide ring opening.

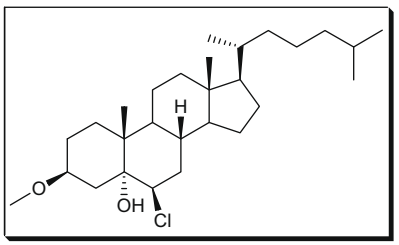
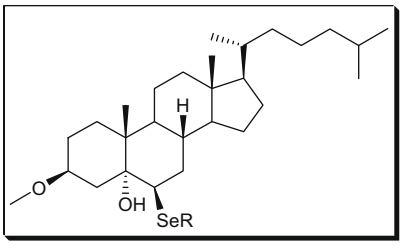
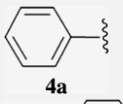
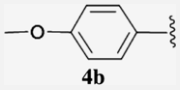
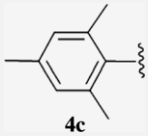
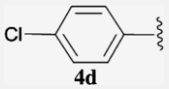
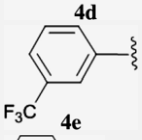
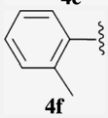
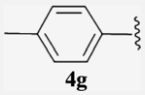
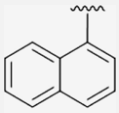
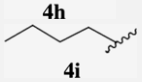
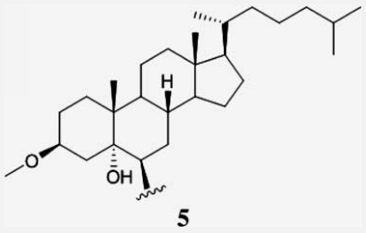



**Figure 3.** 6β-Chloro-5α-hydroxy-3β-methoxycholestane, **6**.

**Table 1**
Selenosteroids compounds **4a–i** and **5**




| Entry | R | Yield[a] (%) |
|---|---|---|
| 1 |  **4a** | 90 |
| 2 |  **4b** | 92 |
| 3 |  **4c** | 95 |
| 4 |  **4d** | 91 |
| 5 |  **4e** | 87 |
| 6 |  **4f** | 87 |
| 7 |  **4g** | 88 |
| 8 |  **4h** | 94 |
| 9 |  **4i** | 85 |
| 10 |  **5** | 82 |

[a] Yields are given for isolated products.

The structure[9] of **6**, 6β-chloro-5α-hydroxy-3β-methoxycholestane ($C_{28}H_{49}ClO_2$), determined in the noncentrosymmetric space group $P2_12_12_1$, is that of a single stereoisomer with the stereocenters C3 = *R*, C5 = *R*, C6 = *R*, C8 = *S*, C9 = *S*, C10 = *R*, C13 = *R*, C14 = *S*, C17 = *R* and C20 = *R* (using the standard chlorestane numbering scheme)[10] resolved absolutely by the anomalous dispersion effects of the chlorine atom (Fig. 4). The molecule has the same conformation as the core of the cholestane parent compound[11] (see Supplementary data for an overlay diagram) possessing three fused six-membered ring systems, all in the chair configuration to which a five-membered ring system is fused. The three substitutions have an effect only on the molecular packing. In **6**, the individual molecules are joined into chains along the crystallographic *a* axis by hydrogen-bonded interactions between the hydrogen atom of O1 and O2 [$d(O1\cdots O2^a) = 2.8266(13)$ Å; $d(H1\cdots O2^a) = 1.99$ Å; $\angle O1–H1\cdots O2^a = 170.5°$;[a]: $x + 1/2, -y + 3/2, -z$].

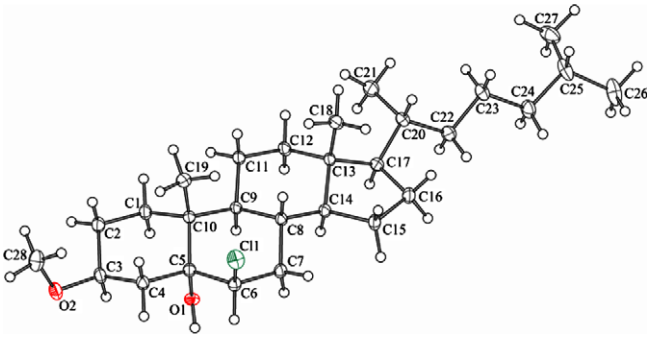



**Figure 4.** Molecule structure and numbering scheme for **6**.

The respective steroid **6** obtained via a similar reactional pathway as the selenosteroids **4** and **5**, allowed the confirmation of the regio- and stereochemistry of the respective compounds, as depicted in Figure 2**.**

The yields of the respective selenosteroids are depicted in Table 1.

By analyzing Table 1, it is possible to verify that the epoxide ring opening is not sensitive to electronic effects of the aromatic moiety in the selenium nucleophiles. For instance, for compound **4g** (Table 1, entry 7), made from a selenium nucleophile with an activating R group, the yield was 88%, while compound **4e** (Table 1, entry 5), made with a deactivating R group on the selenium nucleophile, had a similar yield of 87%. Also, these reactions are not sensitive to steric effects as shown by the diselenides containing mesityl and naphthyl groups which gave the corresponding products **4c** and **4h** in excellent yields (Table 1, entries 3 and 8).

As noted earlier, both oxysterol and selenium-containing compounds show very interesting biological applications related to the pro-oxidant activity inducing apoptosis. The selenosteroid **5** should show this behavior. Indeed, **5** shows a pro-oxidant effect leading to the formation of reactive oxygen species.[12]

In summary, we describe a versatile stereoselective synthesis of a new class of selenosteroids. Organoselenium compounds have been documented as promising pharmacological agents against a number of diseases. Tests to check the biological activity of selenosteroids were performed and the compound **5** showed a pro-oxidant activity. Tests to check the biological activity of the steroids **4**, antitumoral activity of compound **5**, and the asymmetric application of the related compounds in chiral transformations are being conducted by our group.

## 2. Experimental

Experimental data of the steroids **4**–**6** and general procedures to the synthesis of the respective compounds are detailed in Supplementary data.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.090.

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9. *Crystal data for* **6**: Colorless block, $0.19 \times 0.28 \times 0.40\ mm^3$, $C_{28}H_{49}ClO_2$, $M = 453.12$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 7.5811(2)$ Å, $b = 15.1268(5)$ Å, $c = 22.4198(8)$ Å, $V = 2571.05(17)$ Å$^3$, $T = 100(2)$ K, $Z = 4$, $D_{calcd} = 1.171\ g/cm^{-3}$, $\mu = 0.170\ mm^{-1}$, $2.69° < \theta < 30.64°$, $F(0\,0\,0) = 1000$; 53,592 reflections measured, 7910 unique ($R_{int} = 5.55\%$, $R_{sig} = 4.08\%$). The final $wR_2 = 10.03\%$ (all data), $R_1$ [$I > \sigma(I)$] = 3.78%, 288 parameters, GoF = 1.064, $\rho_{max} = 0.608\ e^-/Å^3$, $\rho_{min} = -0.366\ e^-/Å^3$. CCDC No. 759891. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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