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# Preparation of 22,26-epoxycholest-22-ene steroids. Novel transformation of the side chain in sapogenins

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**Abstract**

The one step conversion of the side chain in sapogenins into the 22,26-epoxycholest-22-ene framework was achieved in yields >85% using $BF_3 \cdot OEt_2$. The new structures maintain the natural chirality at C20 and C25, as shown by X-ray diffraction analyses. 

Sapogenins are present as glycosides in a great variety of plants, they contain 27 carbons in six rings presenting a spiroketal between rings E and F. Sapogenins achieved economical importance in the 40s due to the discovery by R. E. Marker[1] of their transformation into steroids having a pregnane skeleton. This methodology allowed one to produce large quantities of progesterone[2] from diosgenin **1** and to obtain economically important compounds related to cortisone[3] from hecogenin **2**. In the process developed by Marker, sapogenins were transformed into furostene skeletons (the pseudosapogenins) and the oxidation of their C20=C22 double bond afforded pregnane steroids (Scheme 1, route a). Subsequent studies were directed mainly to improve the yields of pseudosapogenins[4] while other authors[5] carried out the preparation of different structures, such as pregnane, furostane or cholestane skeletons (Scheme 1, route b).

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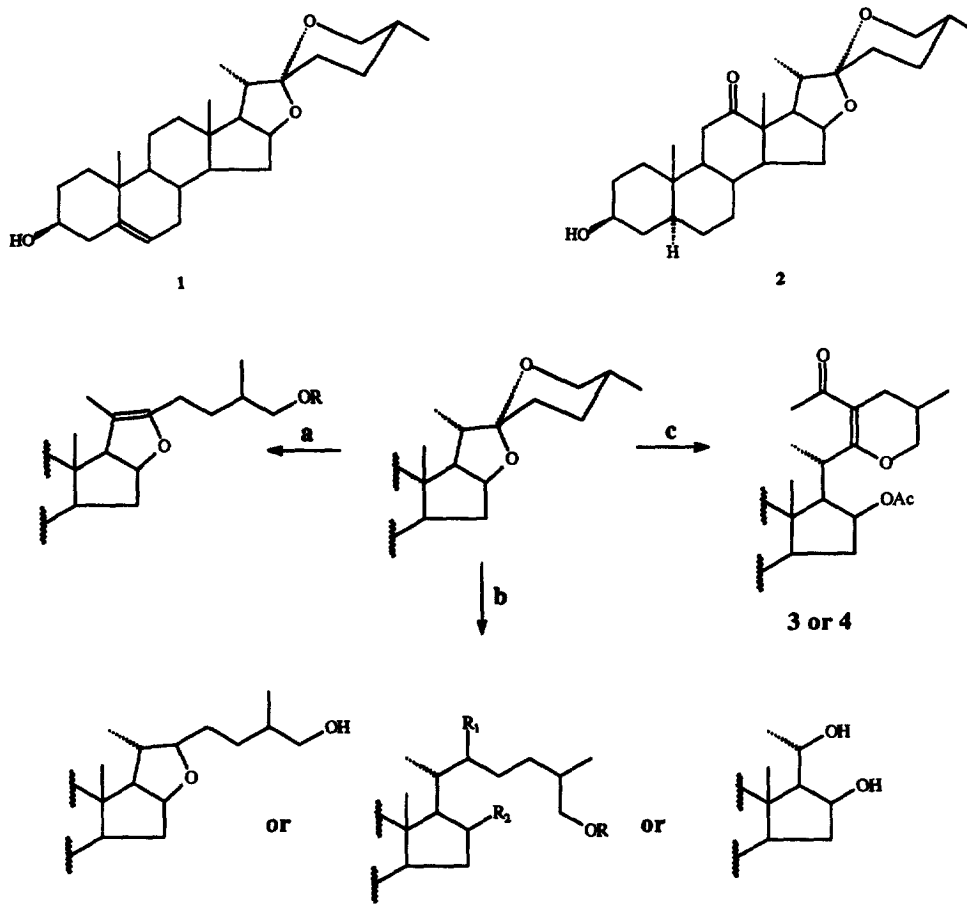



Scheme 1.

The transformation of the side chain present in sapogenins **1** and **2** into the 22,26-epoxycholest-22-ene steroids (**3** and **4**, Scheme 1, route c) is described in this paper. These new steroidal derivatives constitute useful starting materials for the preparation of many structures of biological importance. Thus, oxidation of this type of product could provide access to 16β-hydroxy-23,24-bisnorcholanic acid derivatives while catalytic hydrogenation of the C22 double bond could yield analogues with the skeleton present in withanolides. It is worth noting that this novel method permits oxidiation of the spiroketal function without affecting the configuration of the stereogenic centers at C20 and C25. Moreover, under the reaction conditions, protection of the double bonds in **1** or the carbonyl group in **2** is not required.

The behavior of Lewis acids such as titanium tetrachloride, aluminum trichloride and boron trifluoride, was reinvestigated[6] in diosgenin **1** and hecogenin **2**. It was found that when $BF_3$ was used with acetic anhydride, a new product was obtained in high yields (Scheme 1, route c). Typically, 0.5 g of **1** was dissolved in 5.0 ml of $Ac_2O$ followed and 1.5 ml of $BF_3 \cdot OEt_2$ was added at room temperature. The mixture was stirred 50 minutes and the resulting syrup (0.65 g) was submitted to flash chromatography to yield as (25*R*)-23-acetyl-3β,16β-diacetoxy-22,26-epoxycholest-5,22-diene, (**3**) in 85% yield, mp 95–96°C, $[\alpha]_D^{25}$ –24.0 (*c* 0.65, $CHCl_3$). The UV spectrum of **3** presented an absorption at $\lambda_{max}$ 275 nm, (ε 10300), the IR spectrum showed carbonyls at 1732 and 1660 $cm^{-1}$, the mass spectrum exhibited the molecular ion *m/z* 540. The $^1H$ spectrum displayed the characteristic singlets for Me-18 (0.89 ppm), Me-19 (1.01 ppm) and doublets (J=6 Hz) for Me-21 (0.94 ppm) and for Me-27 (1.15 ppm). The $^{13}C$

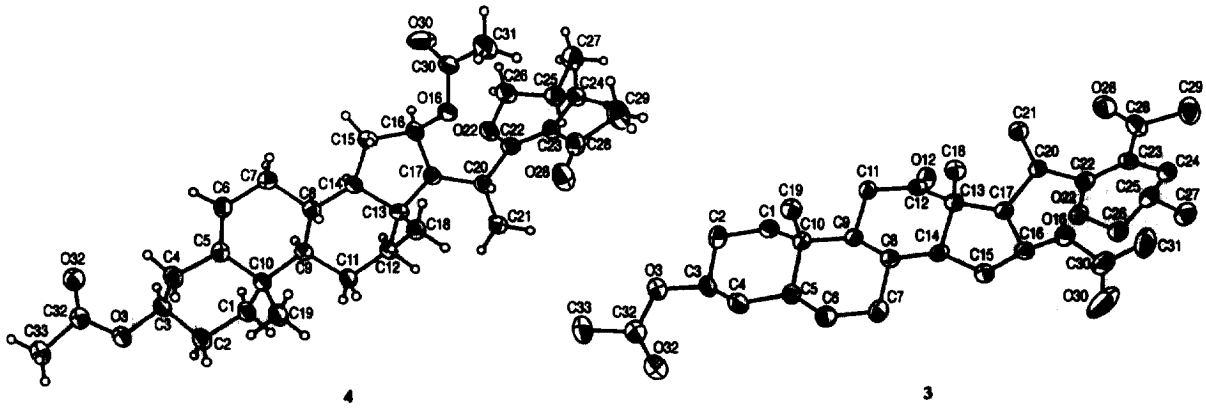
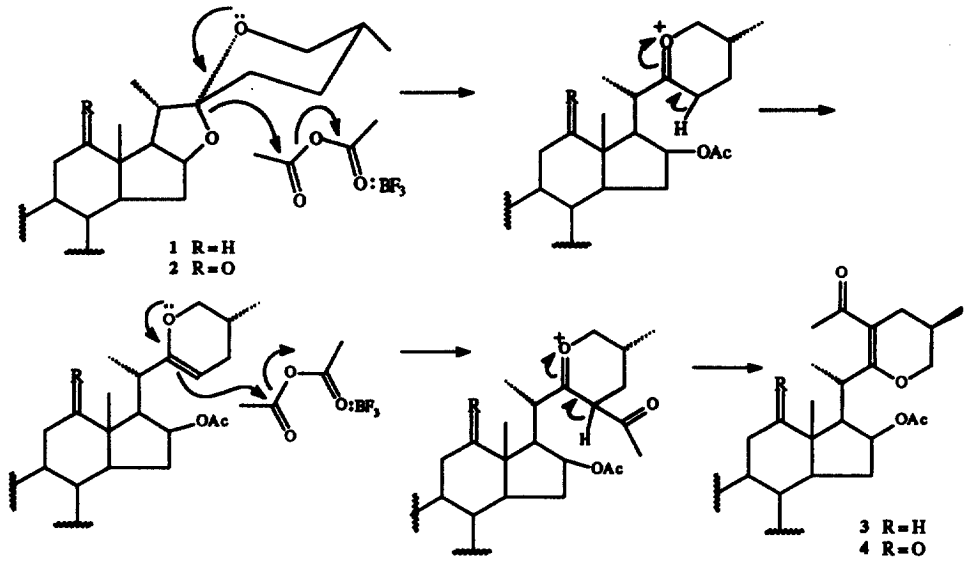


Figure 1. Perspective view of the molecular structures of **3** and **4**

NMR spectrum showed 33 signals, the one at 198.2 ppm was asigned to the acetyl group at C23 while the acetates at 3β and 16β appeared at 170.7 and 170.6 ppm. Microanalysis of **3** gave calcd values for $C_{33}H_{48}O_6$: C, 73.30, H, 8.95; found C, 73.29, H, 9.28. Furthermore, the stereochemistry at C20 and C25 in both compounds was established by single crystal X-ray diffraction analysis[7] (see Fig. 1).

To explain this interesting conversion of the sapogenin side chain we propose the reaction mechanism depicted in Scheme 2.




Scheme 2.

Under similar conditions, hecogenin (**2**) yielded (25*R*)-23-acetyl-3β,16β-diacetoxy-22,26-epoxy-5α-cholest-22-en-12-one (**4**).[8]

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7. X-Ray analyses of **3** and **4** were performed on an Enraf–Nonius CAD4. Compound **3**: colorless crystals, $C_{33}H_{48}O_6 \cdot C_6H_6$, M=618.82 gmol$^{-1}$, $P2_12_12_1$, $a$=1.685(2), $b$=12.250(2), $c$=25.393(5) Å, $V$=3634.8(11) Å$^3$, $Z$=4, $\rho$=1.128 gcm$^{-3}$. Total reflections 5156 of which 4838 were independent. Refinements were based on $F^2$ with values $R$=0.0468, $R_w$=0.1224 from 2556 reflections with $F>4\sigma(F)$ for 405 parameters, $s$=1.978, largest residual electron density peak/hole in the final difference map $\rho_{max}$=0.134, $\rho_{min}$=0.175 e Å$^3$. Compound **4**, colorless crystals $C_{33}H_{48}O_7 \cdot (C_2H_5)_2O$ M=630.83 gmol$^{-1}$, $P2_12_12_1$, $a$=11.797(2), $b$=12.244(2), $c$=25.720(5) Å, $V$=3634.8(11) Å$^3$, $Z$=4, $\rho$=1.128 gcm$^{-3}$, 5031 total reflections of which 4524 were independent. Refinements were based on $F^2$ with values $R$=0.0604, $R_w$=0.1622 from 2343 reflections with $F>4\sigma(F)$ for 386 parameters, $s$=1.020, largest residual electron density peak/hole in the final difference map $\rho_{max}$=0.267, $\rho_{min}$=0.349 e Å$^3$.
8. Compound **4** was obtained in 87% yield as colorless crystals, mp 195°C (crystallized from MeOH); $[\alpha]_D^{25}$ +37.6 (*c* 0.62, $CHCl_3$). UV: $\lambda_{max}$ 274 (9620). IR: 1732, 1708, 1665 cm$^{-1}$. MS: 556 [M$^{+\cdot}$]. $^1$H NMR: 0.93 and 1.24 ppm (Me-19 and Me-18); 0.97 and 1.08 ppm (Me-27 and Me-21). $^{13}$C NMR: 33 signals, among them 6 at low field: 106.8, 170.4, 170.6, 171.3, 198.1 and 213.6 for C22 double bond, acetyls and acetates. Microanalysis for $C_{33}H_{48}O_7$: calculated: C 71.19, H 8.69, found: C 71.03, H 8.69.