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Sapogenins and Dimethyldioxirane: a New Entry to Cholestanes Functionalized at the Side Chain.

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Abstract: *A new and simple opening of the sapogenin spiroketal side chain by DMDO as oxyfunctionalizing agent, with the aim to get an easy approach to steroidal functionalized side chains from natural compounds available in large amounts, is reported.*

Dioxiranes, new and powerful oxidants, have shown a great effectiveness and utility in the selective oxyfunctionalization of steroids, as reported for the hydroxylation at the benzylic C_9 of estrone[1], at C_{25} of cholestane derivatives[2], at C_5 of cholanic acids[3], and at C_{14} and C_{17} of pregnane and androstane steroids[4].

Continuing our study on the site-selective oxyfunctionalization of steroids by dioxiranes we tested the chemical behaviour of other natural compounds, sapogenins. These last are in fact available in large amounts in nature, and for this reason they are well used as starting material in a number of industrial process for the synthesis of bioactive steroids such as cortisone[5].

We report here a new and simple opening of the spiroketal side chain of sapogenins in high yields and mild reaction conditions by oxyfunctionalization of the activated ethereal carbon[6] with DMDO.

Tigogenin acetate **1** (scheme 1) was selectively oxyfunctionalized at C_{16}-H bond to give the corresponding C_{16} hemiketal **4** as the only product (r.t., 2 h, 95% yield).

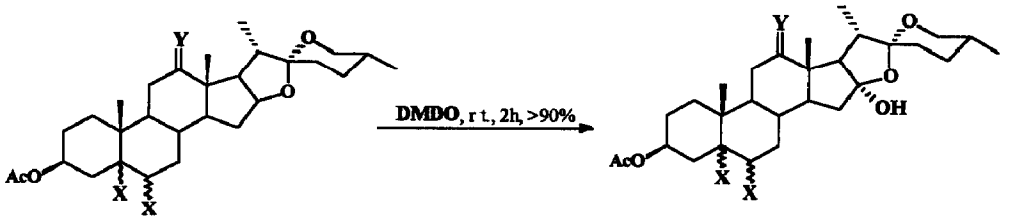
In the same way hecogenin **2** and 5,6-dibromodiosgenin **3** were converted into the corresponding C_{16} hemiketals **5** and **6** (r.t., 2 h, >90% yield). Subsequent treatment in very mild conditions (40°C) with acetic anhydride in acetic acid of the formed C_{22}, and C_{16} hemiketals gave the corresponding 16,22-dioxo-27-acetoxycholestane derivatives **7**, **8** and **9** in quantitative yields.

In the case of diosgenin acetate **10**, having the C_5-C_6 double bond, the oxidation with 1 mole of DMDO led exclusively to the 5,6-epoxides. The addition of a second mole of the reagent led to the oxyfunctionalization at C_{16} to give the epoxyhemiketal **11**. The acetolysis of **11** in very mild condition, led to **12** as the only product, the oxirane ring been untouched.

To investigate the selectivity of DMDO toward different-activated C-H bonds, we prepared **13**, which has two different C-H ethereal bonds at C_{16} and C_{22}, by hydrogenolysis of diosgenin (scheme 2). **13** was

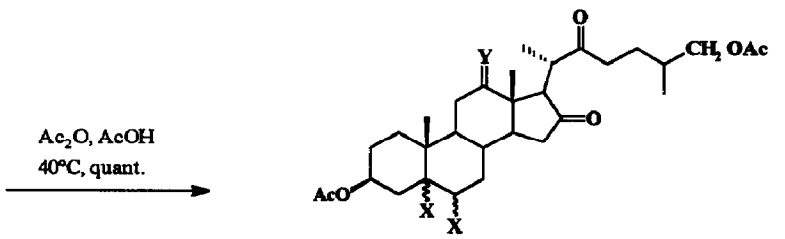
selectively oxyfunctionalized at C_{16}-H bond by a molar amount of DMDO to give the hemiketal 14 (0°C, 4 h, 84% yield).

Scheme1

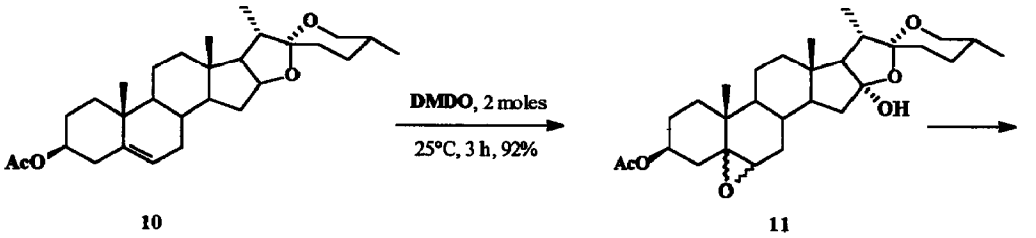


1 X=α-H; Y=H_2
2 X=α-H; Y=O
3 X=Br (*trans* diastereoisomers); Y=H_2

4 X=α-H; Y=H_2
5 X=α-H; Y=O
6 X=Br (*trans* diast.); Y=H_2

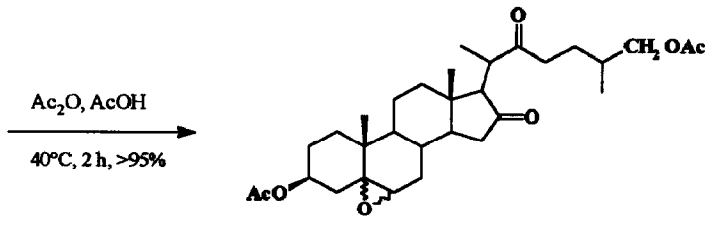


7 X=α-H; Y=H_2
8 X=α-H; Y=O
9 X=Br (*trans* diast.); Y=H_2



10

11

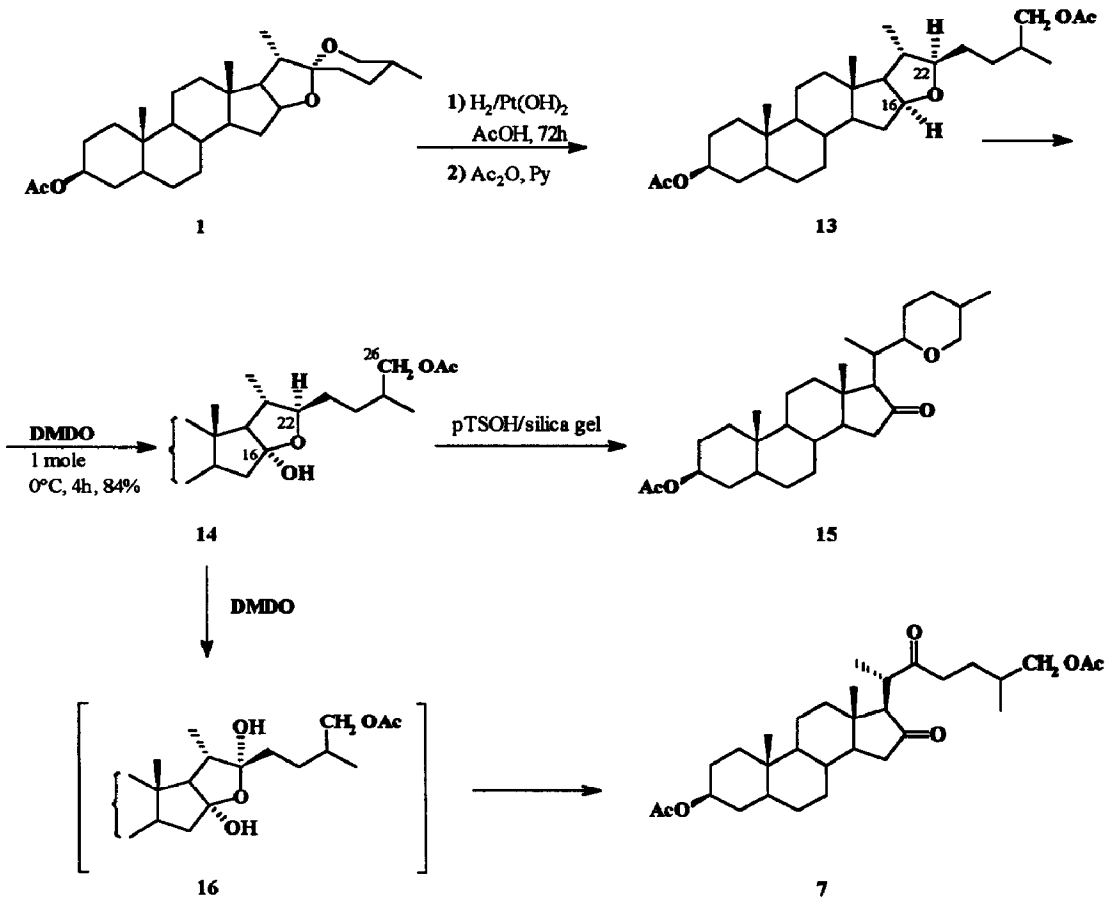


12

This is probably due to a less hindered steric enviroment at C_{16} position compared to the C_{22} one. **14** showed to be stable in mild acidic conditions (dil. HCl), but gave a mixture of products in the presence of strong acids such as conc. H_2SO_4. Nevertheless we obtained an interesting opening of the hemiketalic moiety by reaction with p-toluenesulphonic acid supported on silica gel[7] which yielded **15** via initial hydrolysis of the acetate at C_{26}.

Otherwise, treatment of **14** with DMDO led directly to the dioxoderivative **7**, probably via the dihydroxylated intermediate **16**.

Scheme 2



Since the operative conditions of other degradations of sapogenins, like that reported from Marker[8], are very harsh (240°C, Ac_2O, AcOH), we claim that our method, via DMDO, is an approach to alternative oxidative degradations in two synthetic steps to give steroidal-functionalized side chains.

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References and Notes

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6. Recent reports showed that simple ethers were easily oxidized by DMDO, so that, for example, methyl ethers gave the corresponding ketones. Van Heerden, F.R.; Dixon, J.T.; Holzapfel, C.W.; *Tetrahedron Lett.*, **1992**, *33*, 7399-7402.
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9. Significant nmr signals of main products:
   4. ^{1}H-nmr, δ (ppm): 0.69 (3H, s, C_{18}-H), 0.79 (3H, s, C_{19}-H), 0.78 (3H, d, J=6.2 Hz, C_{27}-H), 0.97 (3H, d, J=7.5 Hz, C_{26}-H), 4.63 (1H, m, C_3-H). ^{13}C-nmr δ (ppm): 116.1 (C_{16}), 110.9 (C_{22}). **5.** ^{1}H-nmr, δ (ppm): 0.77 (3H, d, J=6.2 Hz, C_{27}-H), 0.86 (3H, s, C_{19}-H), 0.96 (3H, s, C_{18}-H), 1.04 (3H, d, J=6.9 Hz, C_{21}-H), 3.5 (2H, d, J=8 Hz, C_{26}-H), 4.62 (1H, m, C_3-H). ^{13}C-nmr δ (ppm): 213 (C_{12}), 170.7 (COO-), 114.4 (C_{16}), 110.9 (C_{22}). **7.** ^{1}H-nmr, δ (ppm): 0.74 (3H, s, C_{18}-H), 0.8 (3H, s, C_{19}-H), 0.94 (3H, d, J=6.64 Hz, C_{27}-H), 0.99 (3H, d, J=7.5 Hz, C_{21}-H), 2.0 (3H, s, AcO), 2.03 (3H, s, AcO), 3.91 (2H, d, J=6.25, C_{26}-H), 4.7 (1H, m, C_3-H). ^{13}C-nmr δ (ppm): 171.2, 171.9 (COO-) 214.0, 218.8 (C=O). **8.** ^{1}H-nmr, δ (ppm): 0.9 (3H, d, J=6.6 Hz, C_{27}-H), 0.9 (3H, s, C_{19}-H), 0.99 (3H, d, J=7.2 Hz, C_{21}-H), 1.06 (3H, s, C_{18}-H), 1.97 (3H, s, AcO), 2.0 (3H, s, AcO), 3.88 (2H, d, J=6.2 Hz, C_{26}-H), 4.64 (1H, m, C_3-H). **11.** Mixture of α and β-epoxides. ^{1}H-nmr, δ (ppm): 0.62, 0.65 (3H, 2s, C_{18}-H), 0.76 (3H, d, J=6.5 Hz, C_{27}-H), 0.92 (3H, d, J=6.5 Hz, C_{21}-H), 0.96, 1.20 (3H, 2s, C_{19}-H), 1.96, 1.98 (3H, 2s, AcO), 2.83 (0.5H, d, J=4.4 Hz, C_6-H, α-epoxide), 3.02 (0.5 Hz, d, J=2.4 Hz, C_6-H, β-epoxide), 3.5 (2H, broad d, J=7.5 Hz, C_{26}-H), 4.70 (0.5 H, m, C_3-H, β-epoxide), 4.88 (0.5 H, m, C_3-H, α-epoxide). ^{13}C-nmr δ (ppm): 171.0, 170.9 (COO), 129.3, 128.5 (C_{16}), 116.5, 11.4 (C_{22}). **12.** Mixture of α and β-epoxides. 0.73, 0.76 (3H, 2s, C_{18}-H), 0.95 (3H, d, J=6.6 Hz, C_{27}-H), 1.02 (3H, d, J=5.9 Hz, C_{21}-H), 1.03, 1.10 (3H, 2s, C_{19}-H), 2.01, 2.03 (3H, 2s, $\underline{CH_3}$COO at C_3), 2.05 (3H, s, $\underline{CH_3}$COO at C_{26}), 2.91 (0.5, d J=4.2 Hz, C_6-H, α-epoxide), 3.11 (0.5, d, J=2.2 Hz, β-epoxide), 3.90 (2H, d, J=6 Hz, C_{26}-H), 4.38, 4.95 (1H, 2m, C_3-H). **14.** ^{13}C-nmr δ (ppm): 0.72 (3H, s, C_{18}-H), 0.72 (3H, s, C_{19}-H), 0.91 (3H, d, J=6.7 Hz, C_{27}-H), 0.99 (3H, d, J=6.5 Hz, C_{21}-H), 1.98. 2.02 (6H, 2s, AcO at C_3 an at C_{26}), 3.85 (3H, m, C_{26}-H and C_{22}-H), 4.65 (1H, m, C_3-H). ^{13}C-nmr δ (ppm): 170.9, 171.4 (2 COO), 115.0 (C_{16}), 89.0 (C_{22}). **15.** ^{1}H-nmr, δ (ppm): 0.72 (3H, d, J=6.62 Hz, C_{27}-H), 0.75 (3H, s, C_{18}-H), 0.81 (3H, s, C_{19}-H), 0.90 (3H, d, 7.1 Hz, C_{21}-H), 2.0 (3H, s, AcO), 2.88 (1H, bdt, J=10.9 Hz, C_{22}-H), 3.75 (2H, m, C_{26}-H), 4.65 (1H, m, C_3-H). ^{13}C-nmr δ (ppm): 220 (C_{16}), 170.9 (COO), 78.6 (C_{22}), 75.1 (C_{26}), 73.6 (C_3), 64.1 (C_{17}).

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