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Neighboring group participation in epoxide ring cleavage in reactions of some 16α,17α-oxidosteroids with lithium hydroperoxide

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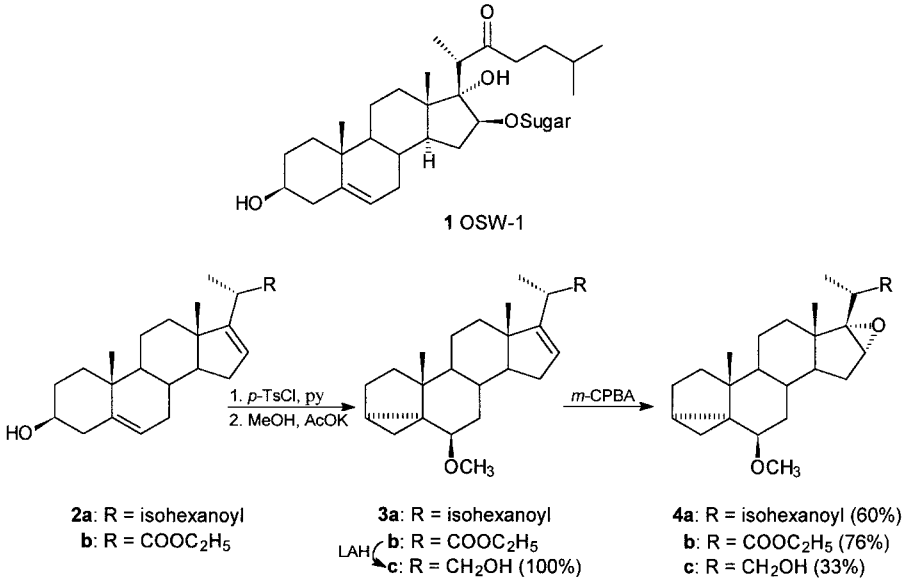
Abstract—In order to work out a new approach to the synthesis of the potent anti-tumor saponin OSW-1 aglycone, 16α,17α-oxidosteroids were treated with acids, bases and lithium hydroperoxide. Acids caused Wagner–Meerwein type rearrangements irrespective of the side-chain structure. 16α,17α-Epoxides proved resistant to bases unless a 22-carbonyl group was present; in the case of 22-esters or 22-ketones the epoxide rings were cleaved with base and the corresponding allylic alcohols were formed. The epoxide ring cleavage of 16α,17α-oxido-22-ester with lithium hydroperoxide was followed by lactonization of the intermediate 16β,17α-dihydroxy acid. The saponin OSW-1 aglycone was obtained by reaction of the lactone with isoamyllithium. © 2001 Published by Elsevier Science Ltd.

1. Introduction

A family of cholestane saponins was isolated from bulbs of *Ornithogalum saundersiae* and identified by Sashida et al.[1,2] The saponins, especially a major component of the mixture, OSW-1 (**1**), were strongly cytostatic.[2,3] OSW-1 selectively attacks cancer cells and is more potent than the commonly used chemoterapeutics, such as taxol, adriamycin, *cis*-platin, etc. The cytotoxity profile of OSW-1 is similar[2–4] to that of cephalostatins[5–7] suggesting the same, as yet unidentified, mechanism of action. Speculation involves the concept of a 'cocked gun' release of energy by a sudden



Scheme 1.

Keywords: steroids; neighboring group effects; epoxides; lithium compounds.

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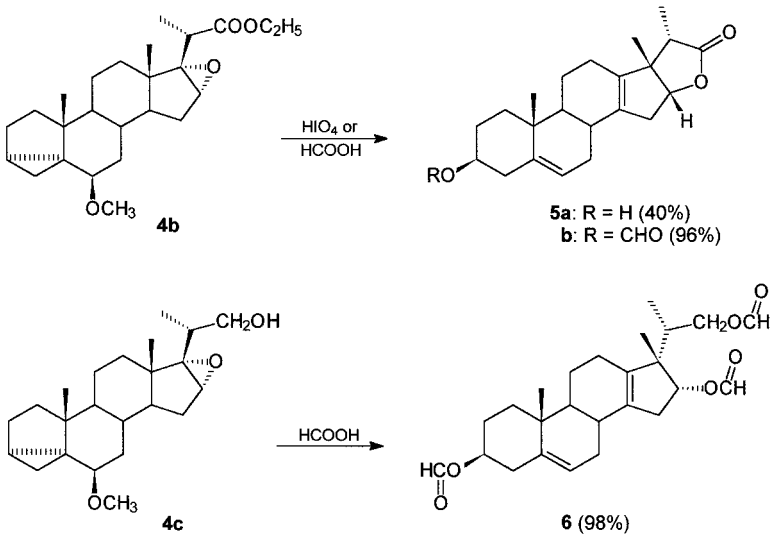
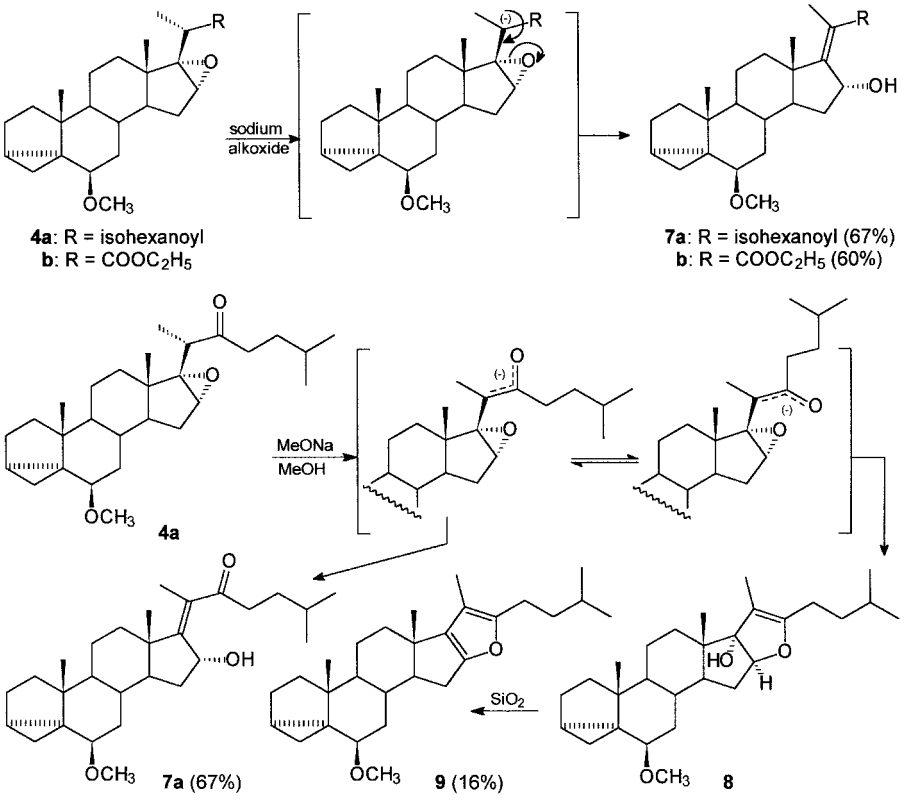
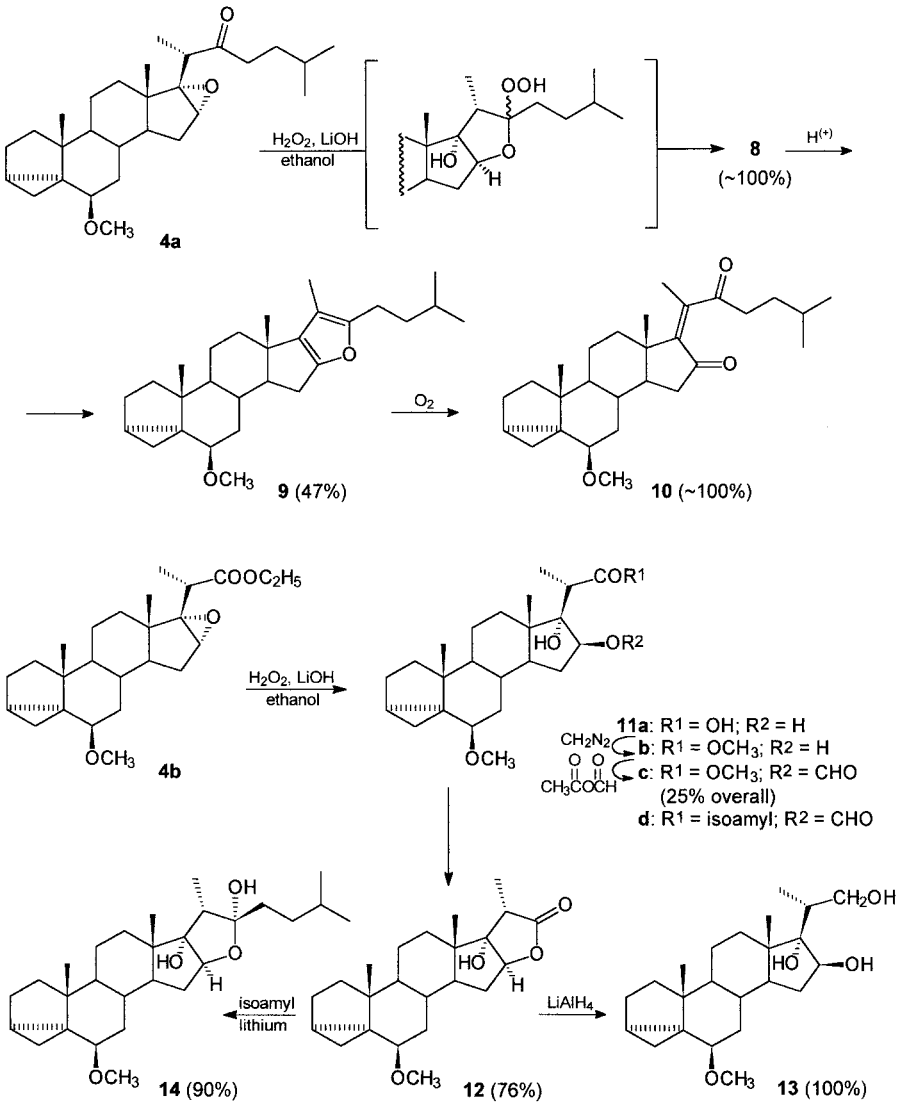


Scheme 2.

change in molecular arrangement, e.g. on removal of a sugar part from the *O. saundersiae* saponins or during spiroketal isomerization in cephalostatins.[7] Recent studies show that an oxocarbenium ion, that can be generated from both types of compounds, is the likely intermediate responsible for cytotoxicity.[4] The aim of this work was to elaborate a simple method of synthesis of 16β,17α-dihydroxy-22-carbonyl steroids. The importance of the presence of the 17α-hydroxy group to tumor inhibition has been documented in cephalostatins and in angiostatic steroids such as 17α-hydroxyprogesterone and analogs.[7,8] In both groups of cytostatic compounds, cephalostatins and *O. saundersiae* saponins, a 16β-oxygen functionality is present. A new group of natural 16β-hydroxycholestanes lacking a 17α-OH has been recently discovered. However, their cytostatic activity is three orders of magnitude less than that of OSW-1.[9] The most direct approach to the 16β,17α-diol systems involves ring opening of 16α,17α-epoxides with oxygen nucleophiles. This approach, however, proved difficult since 16α,17α-epoxides are rather unreactive. Therefore, 16β,17α-diols have been synthesized from the Δ^{16}-steroids by osmium tetroxide hydroxylation, oxidation of the



Scheme 3.

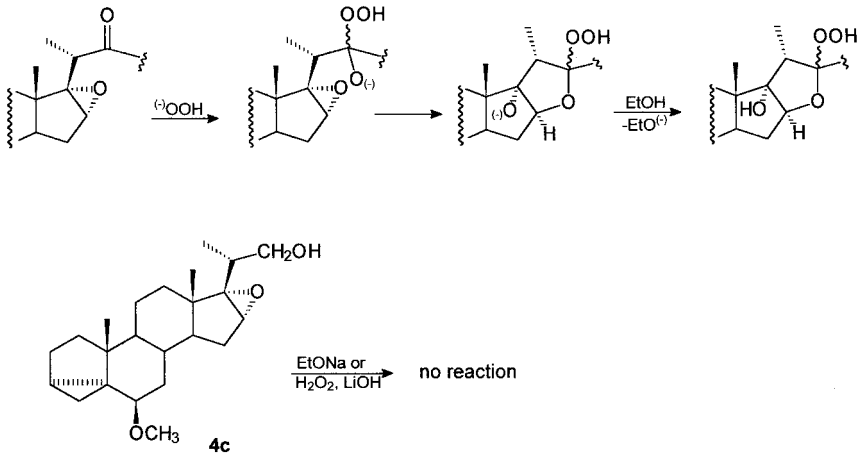


Scheme 4.

resulting 16α,17α-diol to 17α-hydroxy-16-ketone and its stereoselective reduction to the desired *trans*-system.[3,10] However, this approach is unsatisfactory since it is long and expensive.

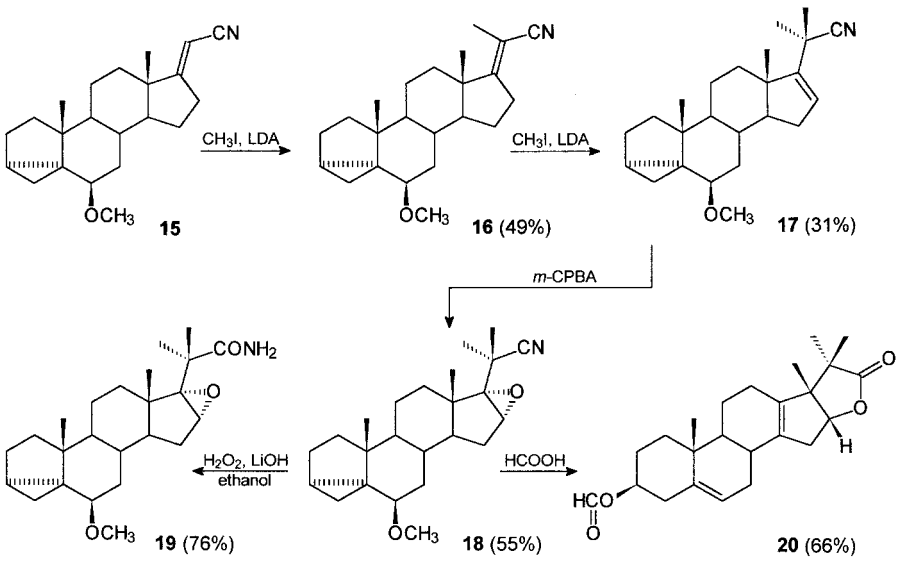
2. Results and discussion

Czech chemists some years ago[11] found that 16α,17α-oxido-5α-cholestane derivatives undergo Wagner–Meerwein rearrangement on acid treatment. The rearrangement is similar to that of 17α-hydroxysteroids – the angular methyl group migrates from C-13 to the cationic center at C-17 and a double bond is formed by 14α-proton abstraction. Hydrides attack 16α,17α-oxido-5α-cholestane derivatives at C-16 yielding the corresponding 17α-hydroxysteroids. However, the 16α,17α-epoxides were reported to be resistant to other nucleophiles. Having in mind the synthesis of cytostatic glycosides related to OSW-1, we studied the ring-opening of three steroidal 16α,17α-epoxides **4a**, **4b** and **4c**.[12] These compounds were conveniently prepared from the corresponding 3β-hydroxy-5,16-dienes (**2a** and **2b**)[13,14] by epoxidation with *m*-CPBA preceded by selective protection of the B-ring double bond as 3α,5α-cyclo-6β-methoxy derivatives (Scheme 1). Cleavage experiments were performed with these epoxides under acid conditions. In the case of **4b**, irrespective of the reagent used (periodic acid, formic acid, silica gel impregnated with sulfuric acid), a rearrangement to **5** (**a** or **b**) was observed with formation of a γ-lactone and simultaneous deprotection of the functional groups in rings A and B. Compound **4c**, when treated with formic acid, afforded triformate **6** (Scheme 2). Attempts to cleave 16α,17α-epoxides under neutral or alkaline conditions were unsuccessful. There was no reaction with nucleophiles, such as iodides or sulfides; whereas strong bases (potassium hydroxide or sodium ethoxide) caused isomerization of epoxides possessing the 22-carbonyl group (**4a** or **4b**) to the corresponding allylic alcohols **7a** or **7b** via a well-known mechanism (Scheme 3). Alternatively, a competitive intramolecular attack of the enolate oxygen atom on C16 from the β-side may also occur. This reaction pathway dominated when the 20*R* epimer of the starting compound was used. The primary cyclization product **8** appeared to be very unstable and its structure was only



Scheme 5.

proved by analysis of the crude reaction products by ^{1}H NMR spectroscopy (pure **8** from a subsequent reaction was used for comparison). In spite of a 17α-OH configuration unfavorable for dehydration, the intermediate **8** readily loses water during silica gel column chromatography affording furan derivative **9** (probably via Ferrier type rearrangement). Of course, compound **4c** lacking the 22-carbonyl group did not react with sodium ethoxide. Several reactions were also attempted with oxidizing agents. There was no reaction of compounds **4a** and **b** with pyridinium chlorochromate or Sarrett's reagent. In contrast, both compounds reacted smoothly with hydrogen peroxide/LiOH.[15] However, the hydroxy-epoxide **4c** and the 22-ketal derivative of **4a** were unreactive. These results suggest that a carbonyl group at C-22 is necessary for successful 16α,17α-epoxide cleavage. The presumed hydroperoxy product of compound **4a** reaction with H_2O_2/LiOH could not be isolated from the reaction mixture (Scheme 4). Instead, the unsaturated product **8** was obtained nearly quantitatively upon neutral work-up. Its purification on a silica gel column caused dehydration to the furan derivative **9**. Compound **9** in turn, when allowed to stand (neat) for several days in an open flask underwent air oxidation to the dione **10**. The hemiketal structure of the intermediate from the reaction of **4a** and H_2O_2/LiOH was supported by trapping its open-chain form with acetic formic anhydride/pyridine. The corresponding 16β-formyl derivative **11d** was formed, but in a very poor yield (11%). Epoxy-ester **4b**, when subjected to lithium hydroperoxide, afforded dihydroxy-acid **11a**. Compound **11a** was isolated from the reaction mixture by column chromatography, but it is stable only in solution. Upon removal of solvent, it underwent spontaneous cyclization to the hydroxy-lactone **12**. In order to protect against lactonization, the combined chromatographic fractions containing dihydroxy-acid **11a** were treated with diazomethane. Although methyl ester **11b** still showed some tendency to lactonize via transesterification, its derivatization was possible, e.g. 16-formate **11c** was prepared in the usual way. $LiAlH_4$ reduction of hydroxy-ester **11b** or hydroxylactone **12** yielded the same triol **13**. It is most likely that the epoxide ring cleavage in **4a** and **b** proceeds via an intramolecular nucleophilic reaction of an intermediate formed upon hydroperoxide addition to the 22-carbonyl group (Scheme 5). However, if the reaction



Scheme 6.

proceeds by attack of the intermediate anion from the β-face of a steroid molecule on carbon atom C-16, it is difficult to explain why the analogous alkoxide deriving from the hydroxy-epoxide **4c** did not undergo similar transformation. Its conformation may not be suitable for the intramolecular reaction.

Lactone **12** treated with isoamyllithium afforded compound **14** (a single diastereomer, probably the more stable 22*R* epimer)[4] in 90% yield. It can be considered as the hemiketal form of the saponin OSW-1 aglycone. However, all attempts of compound **14** glycosylation failed due to its fast decomposition to the furan derivative **9** under weakly acidic conditions.[3] A reaction of the 16α,17α-epoxy-nitrile with lithium hydroperoxide was also studied. However, during methylation of α,β-unsaturated nitrile **15**,[16] a double bond was not shifted to the desired $C_{(16)}$–$C_{(17)}$ position. Only further methylation of monomethyl derivative **16** yielded the $C_{(16)}$–$C_{(17)}$ olefin **17**, that was epoxidized with *m*-CPBA (Scheme 6). Epoxy-nitrile **18** was subjected to reaction with lithium hydroperoxide. However, the epoxide ring of **18** proved resistant to the reagent in contrast to the nitrile group. The reaction product was the epoxy-amide **19**. Hydrolysis of nitriles to amides with highly nucleophilic hydroperoxides is well known.[17] The reactions of **18** with formic acid proceeded with a Wagner–Meerwein rearrangement to give the lactone **20**. The reaction is similar to the previously described reactions of epoxides **4b** or **c** with the same reagent. Presumably, an intermediate 17α-hydroxy-nitrile underwent immediately intramolecular reaction to afford lactone **20**. Cyclization proved faster than formylation as was observed in the case of **4c** under the same conditions.

3. Conclusions

Since it is not easy to prepare the aglycone directly from the saponin OSW-1,[1] synthesis of this compound from readily available steroids is important. The shortest way to the steroidal 16β,17α-diols (such as OSW-1 aglycone) is epoxide ring cleavage in 16α,17α-oxidosteroids. It was proved that 16α,17α-epoxides with a 22-carbonyl group (e.g. **4a** or **b**) undergo the desired ring opening with H_2O_2/LiOH via an intramolecular mechanism. Lactone **12** and 16β,17α-dihydroxy compounds such as **11** or **13** should serve as key precursors for the synthesis of the saponin OSW-1 aglycone and its analogs with different side chains. For example, compound **12**, treated with isoamyllithium afforded the hemiketal form of the aglycone **14**. However, this compound proved to be very sensitive to acids and therefore cannot be used for glycosylation. Further studies in this area are under way.

4. Experimental

4.1. General methods

Melting points were determined on a Kofler apparatus of the Boetius type. NMR spectra were recorded with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with TMS as the internal standard (only selected signals in the ^{1}H NMR spectra are reported). Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer as chloroform solutions unless otherwise stated. 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 (J. T. Baker).

4.1.1. 6β-Methoxy-16α,17α-oxido-3α,5α-cyclocholestan-22-one (4a). 6β-Methoxy-3α,5α-cyclocholest-16-en-22-one (**3a**) (50 mg, 0.12 mmol) was dissolved in dichloromethane (2 mL) and a solution of *m*-CPBA (23 mg, 0.13 mmol) in dichloromethane (2 mL) was added. The reaction mixture was stirred for 4 h at room temperature, excess *m*-CPBA was reduced with aqueous sodium sulfide and the product was extracted with chloroform. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. Purification of the crude product by silica gel column chromatography (7% ethyl acetate/hexane) gave compound **4a** as a colorless oil (31.2 mg, 60%), IR, ν_{max}: 1713, 1090 cm^{-1}, ^{1}H NMR, δ (ppm): 3.32 (s, 3H), 3.15 (s, 1H), 3.11 (q, *J*=7.0 Hz, 1H), 2.77 (m, 1H), 2.45 (m, 2H), 1.18 (d, *J*=7.0 Hz, 3H), 1.03 (s, 3H), 0.91 (s, 3H), 0.88 (d, *J*=6.3 Hz, 6H), 0.65 (m, 1H), 0.44 (dd, *J*=8.0, 5.5 Hz, 1H), ^{13}C NMR, δ (ppm): 210.0 (C), 82.0 (CH), 69.9 (C), 59.9 (CH), 56.6 (CH_3), 48.3 (CH), 44.9 (CH), 43.6 (C), 43.4 (C), 42.9 (CH), 39.7 (CH_2), 35.09 (CH_2), 35.00 (C), 33.2 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 28.8 (CH), 27.6 (CH), 27.2 (CH_2), 24.8 (CH_2), 22.36 (CH_3), 22.29 (CH_3), 22.18 (CH_3), 21.2 (CH), 19.1 (CH_3), 16.3 (CH_3), 13.0 (CH_2), 12.9 (CH_3), EI-MS, *m/z* (%): 428 (M+, 3), 396 (28), 329 (100), 297 (7). For $C_{28}H_{44}O_3$, calculated: 428.3290; found: 428.3276. Anal. calcd for $C_{28}H_{44}O_3$: C, 78.46; H, 10.35. Found: C, 78.59; H, 10.36.

4.1.2. Ethyl (20*S*)-6β-methoxy-16α,17α-oxido-3α,5α-cyclopregnane-20-carboxylate (4b). To a solution of ethyl (20*S*)-6β-methoxy-3α,5α-cyclopregn-16-ene-20-carboxylate (**3b**) (400 mg, 1 mmol) in dichloromethane (2 mL), a solution of *m*-CPBA (200 mg, 1.1 mmol) in dichloromethane (1.2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. After completion of the reaction, the excess *m*-CPBA was quenched by aqueous solution of sodium sulfide and the product was extracted with chloroform. The extract was washed with 10% aqueous sodium bicarbonate and water, dried over magnesium sulfate, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel. The title compound **4b** (280 mg, 76%) was eluted with 8% ethyl acetate/hexane as an oil, IR, ν_{max}: 1729, 1187, 1091 cm^{-1}, ^{1}H NMR, δ (ppm): 4.07 (q, *J*=7.1 Hz, 2H), 3.28 (s, 4H), 3.04 (q, *J*=7.1 Hz, 1H), 2.73 (m, 1H), 1.20 (t, *J*=7.1 Hz, 3H), 1.15 (d, *J*= 7.2 Hz, 3H), 0.98 (s, 3H), 0.86 (s, 3H), 0.61 (m, 1H), 0.40 (dd, *J*=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 173.5 (C), 81.8 (CH), 70.0 (C), 60.1 (CH_2), 59.7 (CH), 56.3 (CH_3), 48.1 (CH), 44.8 (CH), 43.2 (C), 43.1 (C), 36.3 (CH), 34.8 (C), 34.7 (CH_2), 32.9 (CH_2), 32.1 (CH_2), 28.5 (CH), 27.0 (CH_2), 24.6 (CH_2), 21.9 (CH_2), 21.0 (CH), 18.9 (CH_3), 15.6 (CH_3), 13.9 (CH_3), 13.2 (CH_3), 12.8 (CH_2), EI-MS, *m/z* (%): 402 (M+, 10), 387 (5), 370 (100), 301 (12). For $C_{25}H_{38}O_4$, calculated: 402.2770; found: 402.2765. Anal. calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.39; H, 9.42.

4.1.3. (20*S*)-20-Hydroxymethyl-6β-methoxy-3α,5α-cyclopregn-16-ene (3c). To a solution of **3b** (150 mg, 0,38 mmol) in anhydrous ether (10 mL), a reducing agent was added. The reagent was prepared from lithium aluminum hydride (100 mg) in diethyl ether (7.5 mL) by adding 0.075 mL of absolute ethanol. The reaction mixture was stirred at room temperature for 5 h. An excess of hydride was carefully quenched with water. The product **3c** was extracted with ether and used to the next step without any further purification, ^{1}H NMR, δ (ppm): 5.44 (m, 1H), 3.59 (m, 2H), 3.36 (s, 3H), 2.81 (m, 1H), 1.07 (s, 3H), 1.05 (d, J=7.0 Hz, 3H), 0.86 (s, 3H), 0.68 (m, 1H), 0.46 (dd, J=8.0, 5.1 Hz, 1H).

4.1.4. 6β-Methoxy-16α,17α-oxido-20-hydroxymethyl-3α,5α-cyclopregnane (4c). The reaction of **3c** (170 mg, 0.5 mmol) with *m*-CPBA (95.5 mg, 0.55 mmol) was performed in the same way as described above for compound **3b**. Epoxide **4c** was obtained in 33% yield (63 mg) as prisms, mp 97–99°C (hexane/dichloromethane), IR, ν_{max}: 3630, 3472, 1456, 1380, 1083 cm^{-1}, ^{1}H NMR, δ (ppm): 3.49 (s, 1H), 3.41 (m, 2H), 3.32 (s, 3H), 2.78 (m, 1H), 1.09 (d, J=6.7 Hz, 3H), 1.01 (s, 3H), 0.88 (s, 3H), 0.64 (t, J=5.0 Hz, 1H), 0.43 (dd, J=8.0, 5.0 Hz, 1H), ^{13}C NMR, δ (ppm): 82.1 (CH), 72.8 (C), 65.5 (CH_2), 60.2 (CH), 56.6 (CH_3), 48.2 (CH), 44.9 (CH), 43.4 (C), 43.0 (C), 35.0 (CH_2 and C), 33.6 (CH_2), 33.2 (CH_2), 31.8 (CH), 28.8 (CH), 27.3 (CH_2), 24.8 (CH_2), 22.4 (CH_2), 21.2 (CH), 19.1 (CH_3), 16.6 (CH_3), 13.7 (CH_3), 13.1 (CH_2). EI-MS, *m/z* (%): 360 (M+, 15), 345 (5), 328 (42), 301 (100), 269 (53). For $C_{23}H_{36}O_3$, calculated: 360.2665; found: 360.2681.

4.1.5. (20*S*)-3β-Hydroxy-18-nor-17β-methylpregna-5,13-diene-20,16α-carbolactone (5a). Ethyl (20*S*)-6β-methoxy-16α,17α-oxido-3α,5α-cyclopregnane-20-carboxylate (**4b**) (500 mg, 1.2 mmol) was dissolved in hot acetone (12 mL). To this solution 275 mg (1.5 mmol) of HIO_4×$2H_2O$ in water/acetone (8 mL) was added. The reaction mixture was stirred at room temperature for 15 min and then heated for 30 min at reflux. When the reaction was completed, it was poured into water and the product was extracted with chloroform. The solvent was removed under vacuum from the dried (over anhydrous $MgSO_4$) extract and the residue was purified by column chromatography on silica gel. Elution with 23% ethyl acetate/hexane afforded **5a** (180 mg, 40%) as white crystals, mp 155–159°C (hexane/methylene chloride). IR, ν_{max}: 3603, 3458, 1760, 1275 cm^{-1}, CD (acetonitrile), [ϕ]: 251 nm (−0.03), 231 nm (+0.36), 196 nm (−24.99), ^{1}H NMR, δ (ppm): 5.42 (m, 1H), 4.58 (dd, J=4.7, 2.2 Hz, 1H), 3.54 (m, 1H), 1.24 (s, 3H), 1.23 (d, J=7.1 Hz, 3H), 0.98 (s, 3H), ^{13}C NMR, δ (ppm): 179.1 (C), 141.2 (C), 137.8 (C), 135.3 (C), 121.4 (CH), 87.3 (CH), 71.7 (CH), 57.6 (C), 48.5 (CH), 45.4 (CH), 42.0 (CH_2), 37.2 (C), 36.9 (CH_2), 36.7 (CH_2), 33.2 (CH), 31.3 (CH_2), 31.1 (CH_2), 25.3 (CH_2), 23.7 (CH_2), 22.2 (CH_3), 18.6 (CH_3), 11.4 (CH_3), EI-MS, *m/z* (%): 342 (M+, 100), 324 (34), 309 (49), 269 (78). For $C_{22}H_{30}O_3$, calculated: 342.2195; found: 342.2171. Anal. calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.07; H, 8.70.

The same compound **5a** was obtained in 77% yield from ethyl (20*S*)-6β-methoxy-16α,17α-oxido-3α,5α-cyclopregnane-20-carboxylate (**4b**) by column chromatography on specially prepared silica gel, impregnated with 50% sulfuric acid (7% weight). The compound **5a** was eluted from the column with 20% ethyl acetate/hexane.

4.1.6. (20*S*)-3β-Carbonyloxy-18-nor-17β-methylpregna-5,13-diene-20,16α-carbolactone (5b). Compound **4b** (80 mg, 0.2 mmol) was dissolved in 99% formic acid (5 mL). The solution was stirred at room temperature for 2.5 h. The reaction mixture was then poured into water and extracted with chloroform. The extract was washed with aqueous sodium bicarbonate, water and the solvent was evaporated in vacuo from the dried (over anhydrous $MgSO_4$) extract. The crude product **5b** (69 mg, 96%); ^{1}H NMR, δ (ppm): 8.05 (s, 1H), 5.45 (m, 1H), 4.79 (m, 1H), 4.57 (dd, J=4.5, 2.0 Hz, 1H) was dissolved in methanol and aqueous sodium hydroxide was added. The mixture was stirred for 1 h at room temperature. The product of hydrolysis isolated by extraction with chloroform was identical in all respects with compound **5a** described above.

4.1.7. (20*S*)-20-Carbonyloxymethyl-18-nor,17β-methylpregna-5,13-diene-3β,16α-diol diformate (6). Compound **4c** (100 mg, 0.27 mmol) was dissolved in 90% formic acid (6 mL). The reaction mixture was stirred at room temperature for 2 h, then it was poured into water, and extracted with chloroform. The extract was washed with aqueous sodium bicarbonate, water and dried over magnesium sulfate. The solvent was evaporated in vacuo and the product **6** (118 mg, 98%) crystallized from dichloromethane/hexane as needles, mp 99–102°C, IR, ν_{max}: 2936, 2857, 1720, 1456, 1187 cm^{-1}, ^{1}H NMR, δ (ppm): 8.14 (s, 1H), 8.08 (s, 1H), 8.05 (s, 1H), 5.46 (m, 1H), 5.17 (t, J=7.7 Hz, 1H), 4.76 (m, 1H), 4.41 (dd, J=10.4, 3.4 Hz, 1H), 4.07 (t, J=10.4 Hz), 1.18 (s, 3H), 1.05 (d, J=7.0 Hz, 3H), 1.01 (s, 3H), ^{13}C NMR, δ (ppm): 161.2 (CH), 160.8 (CH), 160.6 (CH), 140.1 (C), 137.5 (C), 135.2 (C), 122.7 (CH), 82.1 (CH), 73.9 (CH), 66.7 (CH_2), 52.6 (C), 48.8 (CH), 38.5 (CH_2), 38.1 (CH), 37.8 (CH_2), 36.9 (C), 36.5 (CH_2), 32.9 (CH), 30.9 (CH_2), 27.5 (CH_2), 24.2 (CH_3), 23.6 (CH_2), 22.8 (CH_2), 18.5 (CH_3), 13.8 (CH_3).

4.1.8. 16α-Hydroxy-6β-methoxy-3α,5α-cyclocholest-17(20)-en-22-one (7a). 6β-Methoxy-16α,17α-oxido-3α,5α-cyclocholestan-22-one (**4a**) (75 mg, 0.175 mmol) was dissolved in methanol (8 mL) and treated with sodium methoxide (100 mg, 1.85 mmol). The reaction mixture was stirred 15 h at room temperature, poured into water and extracted with ethyl acetate. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. Silica gel column chromatography afforded furan derivative **9** (12 mg, 16%, its analytical data are given later) eluted with 7% ethyl acetate/hexane followed by **7a**. An oily product **7a** (50 mg, 67%) was eluted with 14% ethyl acetate/hexane, IR, ν_{max}: 3600, 3423, 1690, 1091, 1078 cm^{-1}, ^{1}H NMR, δ (ppm): 4.74 (d, J=3.9 Hz, 1H), 3.34 (s, 3H), 2.81 (m, 1H), 1.97 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.91 (d, J=6.1 Hz, 6H), 0.67 (m, 1H), 0.46 (dd, J=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 209.5 (C), 151.0 (C), 133.6 (C), 81.9 (CH), 72.3 (CH), 56.4 (CH_3), 52.5 (CH), 47.6 (CH), 44.8 (C), 43.2 (C), 39.8 (CH_2), 35.9 (CH_2), 35.1 (CH_2), 35.0 (CH_2), 34.8 (C), 33.0 (CH_2), 31.9 (CH_2), 29.2 (CH), 27.4 (CH), 24.6 (CH_2), 22.4 (CH_2), 22.2 (CH_3), 22.1 (CH_3), 21.0 (CH), 19.1 (CH_3), 18.9 (CH_3), 17.1 (CH_3), 12.9

(CH_2), EI-MS, *m/z* (%): 428 (M+, 4), 413 (5), 396 (37), 381 (24), 221 (44), 192 (79), 179 (100). For $C_{28}H_{44}O_3$, calculated: 428.3291; found: 428.3285. Anal. calcd for $C_{28}H_{44}O_3$: C, 78.46; H, 10.35. Found: C, 78.62; H, 10.46.

4.1.9. Ethyl 16α-hydroxy-6β-methoxy-3α,5α-cyclopregn-17(20)-ene-20-carboxylate (7b). To a solution of **4b** (100 mg, 0.2 mmol) in ethanol (3 mL), a solution of sodium ethoxide (prepared by dissolving 20 mg of sodium in 1 mL of absolute ethanol) was added. The reaction mixture was stirred at room temperature for 24 h. Acetic acid (0.06 mL) was then added, and the reaction mixture was poured into water. The product was extracted with chloroform. The extract was dried over magnesium sulfate and evaporated in vacuo. The crude product was purified by column chromatography on silica gel. Compound **7b** was eluted with 20% ethyl acetate/hexane. Yield 60 mg (60%), an oil, IR, ν_{max}: 3601, 3434, 1716, 1454, 1375, 1295 cm^{-1}, ^1H NMR, δ (ppm): 4.74 (brd, *J*=4.2 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.34 (s, 3H), 2.81 (m, 1H), 2.01 (s, 3H), 1.31 (t, *J*=7.1 Hz, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.66 (m, 1H), 0.45 (dd, *J*=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 170.6 (C), 154.3 (C), 125.1 (C), 82.1 (CH), 72.6 (CH), 60.5 (CH_2), 56.6 (CH_3), 52.7 (CH), 47.8 (CH), 45.2 (C), 43.4 (C), 35.3 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 35.0 (C), 33.2 (CH_2), 29.4 (CH), 24.9 (CH_2), 22.6 (CH_2), 21.2 (CH), 19.1 (CH_3), 13.1 (CH_3), 17.8 (CH_3), 14.2 (CH_3), 13.1 (CH_2), EI-MS, *m/z* (%): 402 (M+, 100), 387 (17), 384 (31), 356 (46). For $C_{25}H_{38}O_4$, calculated: 402.2770; found: 402.2758.

4.1.10. 17α-Hydroxy-6β-methoxy-3α,5α-cyclofurost-20(22)-ene (8). 6β-Methoxy-16α,17α-oxido-3α,5α-cyclocholestan-22-one (**4a**, 90 mg, 0.2 mmol) was dissolved in 4 mL of ethanol. A suspension of lithium hydroxide (100 mg, 4 mmol) in ethanol (3 mL) and 30% hydrogen peroxide (1.6 mL) was added to this solution. The reaction mixture was stirred at 40°C overnight, insoluble inorganic material was filtered off and the solvent was removed in vacuo. The residue was dissolved in ether, washed with water, dried ($MgSO_4$) and evaporated. The crude **8** was pure enough for analytical purpose, ^1H NMR, δ (ppm): 4.36 (bs, 1H, OH), 4.29 (d, *J*=5.3 Hz, 1H), 3.35 (s, 3H), 2.82 (m, 1H), 2.56 (m, 2H), 2.05 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.91 (d, *J*=6.2 Hz, 6H), 0.67 (m, 1H), 0.46 (dd, *J*=8.0, 5.1 Hz, 1H).

4.1.11. 6β-Methoxy-3α,5α-cyclofurosta-16,20(22)-diene (9). 6β-Methoxy-16α,17α-oxido-3α,5α-cyclocholestan-22-one (**4a**, 67 mg, 0.15 mmol) was dissolved in 4 mL of *n*-propyl alcohol. To this solution the earlier prepared suspension of lithium hydroxide (75 mg, 3.0 mmol) in 4 mL of *n*-propyl alcohol and 1 mL of 30% hydrogen peroxide was added. The reaction mixture was stirred 2 h at 90°C, poured into water and extracted with chloroform. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. Pure **9** (31 mg, 47%) was obtained by column chromatography on silica gel with 7% ethyl acetate/hexane elution as an oil, IR, ν_{max}: 1569, 1090, 1078 cm^{-1}, ^1H NMR, δ (ppm): 3.37 (s, 3H), 2.82 (t, *J*=2.8 Hz, 1H), 1.91 (s, 3H), 1.09 (s, 3H), 0.95 (s, 3H), 0.92 (d, *J*=6.2, 6H), 0.69 (m, 1H), 0.47 (dd, *J*=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 154.9 (C), 153.6 (C), 136.8 (C), 111.2 (C), 82.2 (CH), 60.5 (CH), 56.7 (CH_3), 48.8 (CH), 43.8 (C), 41.5 (C), 37.9 (CH_2), 35.8 (CH_2), 35.4 (CH_2), 35.3 (C), 33.1 (CH_2), 29.0 (CH), 27.7 (CH), 26.7 (CH_2), 24.9 (CH_2), 24.5 (CH_2), 22.4 (2×CH_3), 22.1 (CH_2), 21.4 (CH), 19.3 (CH_3), 18.5 (CH_3), 13.1 (CH_2), 8.8 (CH_3), EI-MS, *m/z* (%): 410 (M+, 75), 395 (100), 363 (12), 353 (33). For $C_{28}H_{42}O_2$, calculated: 410.3185; found: 410.3181. Anal. calcd for $C_{28}H_{42}O$: C, 81.99; H, 10.31. Found: C, 81.75; H, 10.15.

4.1.12. 6β-Methoxy-3α,5α-cyclocholest-17(20)-en-16,22-dione (10). Compound **9** was allowed to stand in an open flask for several days. It was quantitatively transformed into the oily compound **10**, IR, ν_{max} (CCl_4): 1760, 1714, 1695, 1631, 1091 cm^{-1}, ^1H NMR, δ (ppm): 3.35 (s, 3H), 2.82 (m, 1H), 1.94 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 0.90 (d, *J*=6.2, 6H), 0.69 (m, 1H), 0.48 (dd, *J*=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 211.4 (C), 205.7 (C), 144.9 (C), 142.5 (C), 81.9 (CH), 56.7 (CH_3), 50.5 (CH), 47.7 (CH), 43.8 (C), 43.5 (C), 39.0 (CH_2), 37.8 (CH_2), 36.6 (CH), 35.3 (CH_2), 34.9 (C), 33.1 (CH_2), 32.3 (CH_2), 29.6 (CH), 27.7 (CH), 24.9 (CH_2), 22.42 (2×CH_3), 22.39 (CH_2), 21.2 (CH), 19.1 (CH_3), 17.5 (CH_3), 15.7 (CH_3), 13.2 (CH_3), EI-MS, *m/z* (%): 426 (M+, 100), 411 (82), 370 (32), 355 (99), 323 (26). For $C_{28}H_{42}O_3$, calculated: 426.3134; found 426.3134.

4.1.13. Methyl (20*S*)-16β,17α-dihydroxy-6β-methoxy-3α,5α-cyclopregnane-20-carboxylate (11b) and its 16 formyl derivative (11c). A solution of **4b** (100 mg, 0.25 mmol) in 3 mL of ethanol was added to the earlier prepared suspension of lithium hydroxide in 10 mL of ethanol and 1 mL of 30% hydrogen peroxide. The reaction mixture was stirred for 16 h at 80°C. Then insoluble inorganic material was filtered off and the solvent was evaporated in vacuo. The crude polar product was purified by column chromatography on silica gel. It was eluted with 5% methanol/chloroform. To the combined chromatographic fractions (without evaporation of solvent) etheral solution of diazomethane was added and the mixture was allowed to stand for 1 h at room temperature. Evaporation of the solvent in vacuo at room temperature yielded the oily methyl ester **11b** which was only briefly characterized due to its tendency to lactonization, ^1H NMR, δ (ppm): 4.08 (dd, *J*=8.1, 5.4 Hz, 1H), 3.70 (s, 3H), 3.31 (s, 3H), 3.08 (q, *J*=7.1 Hz, 1H), 2.76 (m, 1H), 2.29 (m, 1H), 1.26 (d, *J*=7.1 Hz, 3H), 1.01 (s, 3H), 0.92 (s, 3H), 0.63 (m, 1H), 0.42 (dd, *J*=8.0, 5.1 Hz, 1H). Crude **11b** was dissolved in 5 mL of pyridine and acetic–formic anhydride (prepared from 15 mL of acetic anhydride and 6.5 mL of 86% formic acid) was added dropwise. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into aqueous solution of potassium carbonate. The product was extracted with chloroform, dried over magnesium sulfate, and the solvent was removed in vacuo. Pure compound **11c** (26 mg, 25%) was eluted from silica gel column with 16% ethyl acetate/hexane as an oil, IR, ν_{max}: 3500, 1723, 1181 cm^{-1}, ^1H NMR, δ (ppm): 7.93 (s, 1H), 4.96 (dd, *J*=7.7, 5.3 Hz, 1H), 4.05 (s, 1H, OH), 3.65 (s, 3H), 3.31 (s, 3H), 3.03 (q, *J*=7.3 Hz, 1H), 2.76 (m, 1H), 2.49 (m, 1H),1.29 (d, *J*=7.3 Hz, 3H), 1.02 (s, 3H), 0.91 (s, 3H), 0.65 (m, 1H), 0.42 (dd, *J*=8.0, 5.1 Hz, 1H), ^{13}C NMR, δ (ppm): 178.6 (C), 159.1 (CH), 83.8 (C), 82.8 (CH), 82.2 (CH), 56.6 (CH_3), 51.9 (CH_3), 48.1 (CH), 47.4 (CH), 46.8 (C), 43.3 (C), 40.4 (CH), 35.2 (C), 34.9 (CH_2), 33.7 (CH_2), 33.4 (CH_2), 32.6 (CH_2), 30.3 (CH), 24.9 (CH_2), 22.2 (CH_2),

21.5 (CH), 19.2 (CH_3), 13.8 (CH_3), 13.1 (CH_2), 12.6 (CH_3), EI-MS, *m/z* (%): 434 (M+, 19), 419 (51), 402 (49), 388 (45), 379 (100). For $C_{25}H_{38}O_6$, calculated: 434.2668; found: 434.2670.

4.1.14. (20*S*)-6β-Methoxy-17α-hydroxy-3α,5α-cyclopregnane-20,16β-carbolactone (12). The solution of **4b** (50 mg, 0.12 mmol) in 1 mL of ethanol was added to the earlier prepared suspension of lithium hydroxide (69 mg, 10 mmol) in 5 mL of ethanol and 0.5 mL of 30% hydrogen peroxide. The reaction mixture was stirred and heated at 80°C for 16 h. The insoluble inorganic material was filtered off and the filtrate was evaporated in vacuo. The crude product was purified by column chromatography on silica gel to give compound **11a** eluted with 5% methanol/chloroform. Evaporation of the combined chromatographic fractions afforded lactone **12** as an amorphous solid (38 mg, 76%), IR, ν_{max}: 3604, 3408, 1763, 1107, 1041 cm^{-1}, CD (acetonitrile), [ϕ]: 186 nm (+12.48), 219 nm (−3.12), ^{1}H NMR, δ (ppm): 4.49 (dd, *J*=8.0, 4.6 Hz, 1H), 3.32 (s, 3H), 2.79 (m, 1H), 2.75 (q, *J*=7.7 Hz), 2.33 (m, 1H), 1.28 (d, *J*=7.7 Hz, 3H), 1.03 (s, 3H), 0.83 (s, 3H), 0.66 (m, 1H), 0.45 (dd, *J*=8.0, 5.2 Hz, 1H), ^{13}C NMR, δ (ppm): 179.9 (C), 88.4 (CH), 86.4 (C), 81.9 (CH), 56.6 (CH_3), 50.4 (CH), 47.7 (CH), 46.5 (C), 43.4 (C), 40.0 (CH), 35.2 (CH_2), 35.0 (C), 33.3 (CH_2), 32.2 (CH_2), 30.6 (CH_2), 30.3 (CH), 24.8 (CH_2), 21.7 (CH_2), 21.3 (CH), 19.2 (CH_3), 14.5 (CH_3), 13.1 (CH_2), 12.9 (CH_3), EI-MS, *m/z* (%): 374 (M+, 13), 359 (49), 342 (45), 319 (100), 301 (4). For $C_{23}H_{34}O_4$, calculated: 374.2457; found: 374.2458.

4.1.15. (20*S*)-20-Hydroxymethyl-6β-methoxy-3α,5α-cyclopregnane-16β,17α-diol (13). To the solution of compound **12** (84 mg, 0.24 mmol) in 1 mL THF, a suspension of $LiAlH_4$ (20 mg, 0.5 mmol) in 1 mL THF was added and the reaction mixture was stirred for 20 min at room temperature. After completion of the reaction, excess $LiAlH_4$ was quenched carefully with water and the product was extracted with chloroform. The organic extract was washed with water, dried over magnesium sulfate and evaporated. An oily product **13** was pure enough for analytical purpose, IR, ν_{max}: 3604, 3426, 1090, 1077 cm^{-1}, ^{1}H NMR, δ (ppm): 3.99 (dd, *J*=8.2, 5.0 Hz, 1H), 3.88 (dd, *J*=10.4, 8.3 Hz, 1H), 3.71 (dd, *J*=10.4, 3.5 Hz, 1H), 3.33 (s, 3H), 2.76 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 0.96 (d, *J*=7.1 Hz, 3H), 0.66 (m, 1H), 0.44 (dd, *J*=8.0, 5.1 Hz), ^{13}C NMR, δ (ppm): 86.1 (C), 82.3 (CH), 80.8 (CH), 66.4 (CH_2), 56.5 (CH_3), 48.3 (CH), 47.6 (CH), 47.5 (C), 43.3 (C), 35.6 (CH), 35.4 (C), 34.9 (CH_2), 34.8 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 30.4 (CH), 25.0 (CH_2), 22.2 (CH_2), 21.6 (CH), 19.3 (CH_3), 13.5 (CH_3), 13.0 (CH_2), 12.5 (CH_3), EI-MS, *m/z* (%): 378 (M+, 3), 360 (8), 346 (44), 328 (28), 269 (47), 259 (59), 214 (100). For $C_{23}H_{38}O_4$, calculated: 378.2770; found: 378.2788. Anal. calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 72.75; H, 9.99.

4.1.16. (22*R*)-6β-Methoxy-3α,5α-cyclofurostane-17α,22-diol (14). A solution of isoamyllithium in anhydrous ether was prepared from lithium (100 mg, 13 mmol) and isoamyl bromide (1.6 mL, 13 mmol). This reagent was added dropwise during 1 h to a stirred solution of lactone **12** (500 mg, 1.3 mmol) in 100 mL of anhydrous ether at room temperature under argon. The reaction mixture was quenched with saturated aqueous NH_4Cl and the product was extracted with ether. Evaporation of the solvent from the dried (anhydrous $MgSO_4$) extract afforded compound **14**, which was purified by silica gel column chromatography. Elution with 17.5% ethyl acetate/hexane yielded 540 mg of unstable crystalline material, ^{1}H NMR, δ (ppm): 4.17 (t, *J*=7.6 Hz, 1H), 3.33 (s, 3H), 2.78 (m, 1H), 2.69 (bs, 1H), 2.23 (q, *J*=7.1 Hz, 1H), 1.04 (s, 3H), 0.95 (d, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H), 0.89 (s, 3H), 0.66 (m, 1H), 0.44 (dd, *J*=7.9, 5.1 Hz), ^{13}C NMR, δ (ppm): 111.3 (C), 90.5 (CH), 90.4 (C), 82.1 (CH), 56.4 (CH_3), 52.3 (CH), 47.5 (CH), 44.5 (C), 43.3 (C), 42.3 (CH), 35.6 (CH_2), 35.1 (C), 35.0 (CH_2), 33.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 30.8 (CH_2), 29.9 (CH), 28.2 (CH), 24.8 (CH_2), 22.4 (2×CH_3), 22.2 (CH_2), 21.3 (CH), 19.2 (CH_3), 17.3 (CH_3), 13.0 (CH_2), 8.4 (CH_3).

4.1.17. 6β-Methoxy-3α,5α-cyclopregn-17-ene-21-nitrile (15). To a stirred solution of 6β-methoxy-3α,5α-cycloandrostan-17-one (200 mg, 0.64 mmol) and diethylophosfonitrile (1.92 mmol, 0.3 mL), a sodium ethoxide solution prepared from 100 mg (4.3 mmol) of sodium and 1.5 mL of ethanol was added dropwise under argon at room temperature. The reaction mixture was refluxed for 12 h and evaporated. The residue was diluted with water, acidified with acetic acid and extracted with diethyl ether. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. The product was purified by silica gel column chromatography. Elution with 6% ethyl acetate/hexane yielded compound **15** as a colorless oil (67.5%, 145 mg). IR, ν_{max}: 2217, 1637, 1470, 1455, 1091, 1076 cm^{-1}, ^{1}H NMR, δ (ppm): 4.98 (s, 1H), 3.32 (s, 3H), 2.71 (m, 1H), 1.02 (s, 3H), 0.87 (s, 3H), 0.65 (t, *J*=5.2 Hz, 1H), 0.45 (dd, *J*=5.2, 1.7 Hz, 1H), ^{13}C NMR, δ (ppm): 181.1 (C), 140.9 (C), 117.5 (C), 87.5 (CH), 81.9 (CH), 56.6 (CH_3), 53.9 (CH), 47.9 (CH), 46.3 (C), 34.98 (C), 34.94 (CH_2), 34.91 (CH_2), 33.3 (CH_2), 30.2 (CH_2), 30.1 (CH), 24.8 (CH_2), 23.7 (CH_2), 22.4 (CH_2), 21.2 (CH), 19.2 (CH_3), 18.2 (CH_3), 13.1 (CH_2). EI-MS, *m/z* (%): 325 (M+, 27), 310 (60), 293 (63), 278 (29), 270 (100). For $C_{22}H_{31}ON$, calculated: 325.2406; found: 325.2399.

4.1.18. 6β-Methoxy-20-methyl-3α,5α-cyclopregn-17-ene-21-nitrile and (16) 6β-methoxy-20,20-dimethyl-3α,5α-cyclopregn-16-ene-21-nitrile (17). Compound **15** (200 mg, 0.57 mmol) dissolved in THF (2 mL) was treated with 2 M solution of LDA in heptane/THF/ethylbenzene (0.8 mL) under argon at −78°C and stirred for 1 h, then methyl iodide (0.11 mL) and HMPA (0.6 mL) were added by syringe. The reaction mixture was maintained at −78°C for 3 h and then the temperature was allowed to rise to −40°C. After 1 h stirring at this temperature, a saturated ammonium chloride solution was slowly added by syringe. The mixture was extracted with ether, the extract was washed with 5% hydrochloric acid, 5% sodium bicarbonate, water, then dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography to give **17** (68.7 mg, 31%) eluted with 6% ethyl acetate/hexane followed by **16** (10.3 mg, 49%). Compound **17** – colorless prisms, mp 51–52°C (hexane), IR, ν_{max}: 2234, 1469, 1457, 1376 cm^{-1}, ^{1}H NMR, δ (ppm): 5.65 (m, 1H), 3.31 (s,

3H), 2.76 (m, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.01 (s, 6H), 0.62 (m, J=5.0 Hz, 1H), 0.41 (dd, J=8.0, 5.0 Hz, 1H), ^{13}C NMR, δ (ppm): 153.9 (C), 125.9 (CH), 123.9 (C), 81.7 (CH), 58.1 (CH), 56.3 (CH_3), 47.8 (CH), 47.4 (C), 43.2 (C), 35.4 (CH_2), 34.9 (C), 34.7 (CH_2), 33.1 (C), 32.8 (CH_2), 30.4 (CH_2), 28.7 (CH), 28.0 (CH_3), 27.5 (CH_3), 24.6 (CH_2), 22.1 (CH_2), 20.9 (CH), 18.9 (CH_3), 17.2 (CH_3), 12.9 (CH_2), MS, *m/e* (%): 353 (M+, 20), 338 (57), 321 (37), 298 (100), 285 (14). For $C_{24}H_{35}ON$, calculated: 353.2719; found: 353.2720. Compound **16** (colorless prisms), mp 152–153°C (hexane), IR, ν_{max}: 2210, 1469, 1455, 1376, 1091, 1077 cm^{-1}, ^{1}H NMR, δ (ppm): 3.34 (s, 3H), 2.79 (m, 1H), 1.04 (s, 3H), 1.00 (s, 3H), 0.68 (m, 1H), 0.46 (dd, J=8.1, 5.2 Hz, 1H), ^{13}C NMR, δ (ppm): 170.9 (C), 119.4 (C), 96.3 (C), 82.0 (CH), 55.8 (CH), 55.4 (CH_3), 47.7 (CH), 46.2 (C), 43.3 (C), 35.2 (CH_2), 34.9 (C), 33.2 (CH_2), 30.9 (CH_2), 30.0 (CH), 29.6 (CH_2), 24.8 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 21.2 (CH), 19.1 (CH_3), 17.9 (CH_3), 17.1 (CH_3), 13.1 (CH_2). Anal. calcd for $C_{24}H_{35}ON$: C, 81.54; H, 9.98; N, 3.96. Found: C, 81.35; H, 9.92; N, 3.97.

4.1.19. 6β-Methoxy-16α,17α-oxido-20,20-dimethyl-3α,5α-cyclopregnane-21-nitrile (18). Compound **18** (114 mg, 55%) was prepared similarly to **4b**. The reaction was carried out starting from 200 mg (0.57 mmol) of **17** and 117 mg (0.68 mmol) of *m*-CPBA. An oil, IR, ν_{max}: 2237, 1471, 1457, 1384, 1082 cm^{-1}, ^{1}H NMR, δ (ppm): 3.38 (s, 1H), 3.31 (s, 3H), 2.77 (m, 1H), 1.49 (s, 3H), 1.33 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H), 0.63 (t, J=5.0 Hz, 1H), 0.42 (dd, J=8.0, 5.0 Hz, 1H), ^{13}C NMR, δ (ppm): 124.2 (C), 81.9 (CH), 70.1 (C), 58.9 (CH), 56.5 (CH_3), 47.9 (CH), 46.2 (CH), 44.1 (C), 43.3 (C), 34.9 (C), 34.8 (CH_2), 33.4 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 28.2 (CH), 26.6 (CH_3), 25.7 (CH_3), 25.3 (C), 24.7 (CH_2), 22.0 (CH_2), 21.1 (CH), 19,0 (CH_3), 16.9 (CH_3), 13.00 (CH_2).

4.1.20. 6β-Methoxy-16α,17α-oxido-20-methyl-3α,5α-cyclopregnane-20-carboxamide (19). A solution of 6β-methoxy-16α,17α-oxido-20,20-dimethyl-3α,5α-cyclopregnane-21-nitrile (**18**, 140 mg, 0.4 mmol) in ethanol (12 mL) was treated with lithium hydroxide (200 mg, 8 mmol) and 30% hydrogen peroxide (3.25 mL). The reaction conditions and work-up were similar to those previously described for the other reactions with the same reagent. Compound **19** was obtained in 76% yield as colorless needles, mp 186–189°C (hexane/dichlomethane), IR, ν_{max} (CCl_4): 3520, 3402, 1580, 1112, 1096 cm^{-1}, ^{1}H NMR, δ (ppm): 6.21 (bs, 1H), 6.01 (bs, 1H), 3.47 (s, 1H), 3.30 (s, 3H), 2.76 (m, 1H), 1.28 (s, 3H), 1.17 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.62 (m, 1H), 0.41 (dd, 1H, J=8.0, 5.2 Hz), ^{13}C NMR, δ (ppm): 179.0 (C), 82.0 (CH), 72.0 (C), 58.6 (CH), 56.5 (CH_3), 48.1 (CH), 46.2 (CH), 44.1 (C), 43.8 (C), 43.3 (C), 34.9 (CH_2 and C), 33.1 (CH_2), 33.06 (CH_2), 28.2 (CH), 26.7 (CH_2), 24.8 (CH_3), 24.7 (CH_2), 24.6 (CH_3), 22.0 (CH_2), 21.1 (CH), 19.1 (CH_3), 17.5 (CH_3), 13.0 (CH_2), EI-MS, *m/z* (%): 387 (M+, 2), 372 (17), 355 (100), 342 (9), 332 (17), 301 (8). For $C_{24}H_{37}NO_3$, calculated: 387.2773; found: 387.2791. Anal. calcd for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62; N, 3.61. Found: C, 74.17; H, 9.63; N, 3.52.

4.1.21. 3β-Carbonyloxy-18-nor-17β,20-dimethylpregna-5,13-diene-20,16α-carbolactone (20). Compound **18** (100 mg, 0.27 mmol) was dissolved in 98–99% formic acid (5 mL) and the solution was stirred at room temperature. After 1 h the reaction was completed. The work-up of the reaction mixture was the same as in the case of compound **5b**. The reaction product **20** was obtained in 66% yield as colorless prisms, mp 116–120°C (hexane), IR, ν_{max}: 2855, 1754, 1719, 1466, 1456, 1391, 1371, 1342 cm^{-1}, ^{1}H NMR, δ (ppm): 8.05 (s, 1H), 5.48 (m, 1H), 5.04 (m, 1H), 4.59 (dd, J=5.2, 1.8 Hz), 1.19 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 0.98 (s, 3H), ^{13}C NMR, δ (ppm): 182.3 (C), 160.5 (CH), 139.8 (C), 137.24 (C), 137.21 (C), 122.8 (CH), 86.0 (CH), 73.8 (CH), 59.8 (C), 48.4 (CH), 45.3 (C), 37.8 (CH_2), 37.1 (CH_2), 36.8 (C), 36.6 (CH_2), 33.3 (CH), 31.0 (CH_2), 27.5 (CH_2), 25.5 (CH_2), 23.9 (CH_2), 23.5 (CH_3), 21.3 (CH_3), 18.4 (CH_3), 17.3 (CH_3).

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