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Synthesis of the Potent Antitumor Saponin OSW-1 Aglycone

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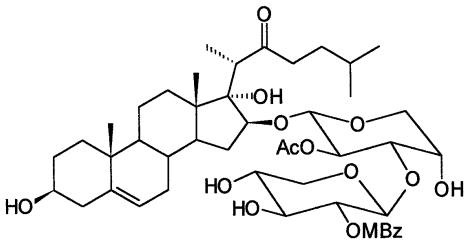
A simple synthesis of the saponin OSW-1 aglycone is described. A key step of the synthesis is the reaction of a recently reported steroidal 17α-hydroxy-22,16-lactone with *iso*amyllithium. The relative reactivity of the hydroxy groups in the 16β-, 17α-, and 22-positions was examined.

Key words: saponin OSW-1, antitumor compounds, steroids

A group of cholestane glycosides isolated a few years ago [1] from the bulbs of plant *Ornithogalum saundersiae* shows extraordinary antitumor activity [2]. The most abundant saponin OSW-1 (Scheme 1) is about 10–100 times more potent against a broad spectrum of malignant tumor cells than the clinically applied anticancer agents, such as adriamycin, cisplatin, taxol, *etc*. The mechanism of cytostatic activity of the saponins is not established yet [3,4], although it seems to be similar to that of cephalostatins, a group of dimeric steroid-pyrazines found in some marine organisms [4–6].

Scheme 1



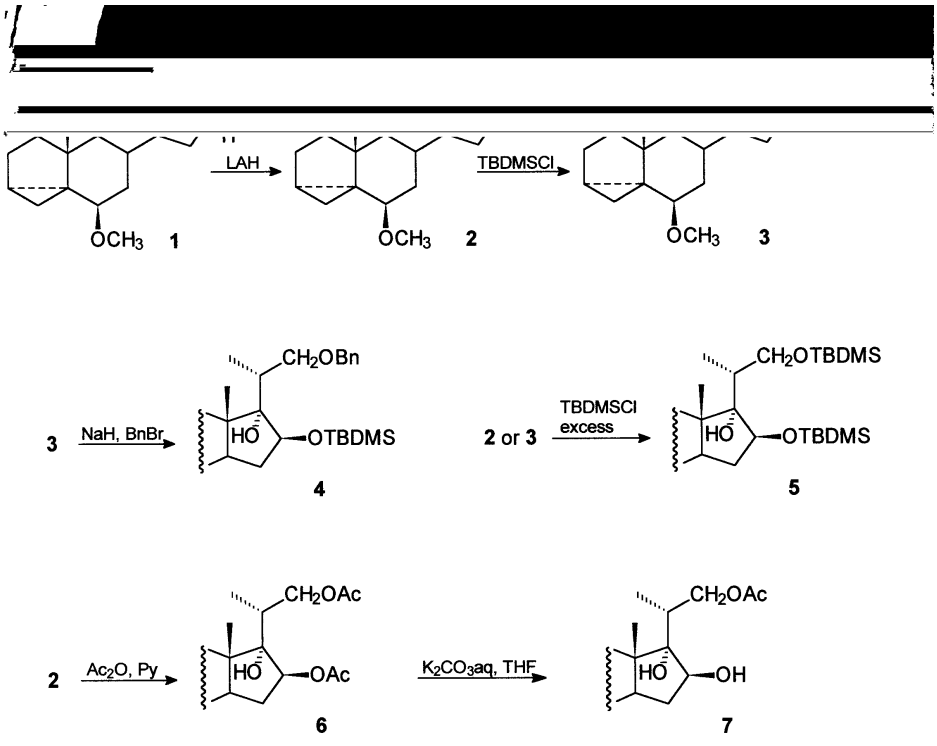
Saponin OSW-1 (MBz = *p*-methoxybenzoyl)

The synthesis of the saponin OSW-1 aglycone [3] and the saponin itself has been recently reported [7]. In both cases, essentially the same synthetic strategy was applied for the steroid part. The strategy needs some improvement since it is long and expensive. In our previous paper [8], we described the six-step synthesis of lactone **1** from 3β-hydroxyandrost-5-en-17-one. Now, the lactone **1** transformation into the saponin OSW-1 aglycone is reported.

RESULTS AND DISCUSSION

In our first synthetic approach, compound **1** was reduced to the triol **2** with lithium aluminum hydride (Scheme 2). Each of the three hydroxy groups of **2** shows different reactivity. The most reactive one, the primary hydroxy group can be selectively protected, *e.g.* as an ether or ester. Controlled silylation (or acetylation) with *tert*-butyldimethylsilyl chloride (or acetic anhydride) yielded the corresponding 22-mono derivatives (**3** or **7**, respectively). 16,22-Disilyl ether **5** or diacetate **6** can also be obtained with an excess of the reagent. The synthetic plan was to prepare the triol **2** derivative with 16β-OH protected and free 22-hydroxy group. Elaboration of the side chain in such a compound would lead to the desired saponin OSW-1 aglycone. Monosilyl ether **3** was benzylated with benzyl bromide. The benzyl derivative thus formed was subjected to desilylation with tetrabutylammonium fluoride followed by PDC oxidation. Surprisingly, the 16-ketone was obtained instead of the 22-aldehyde. This result unequivocally proved that the intermediate benzyl silyl ether had the structure **4**. Such a silyl group migration is rather unusual (there was no precedent to our knowledge) and was additionally proved by partial isomerization of the monosilyl ether **3** on treatment with sodium hydride in THF. The next attempt to obtain the triol **2** derivative with 16β-OH protected was selective desilylation of the disilyl ether

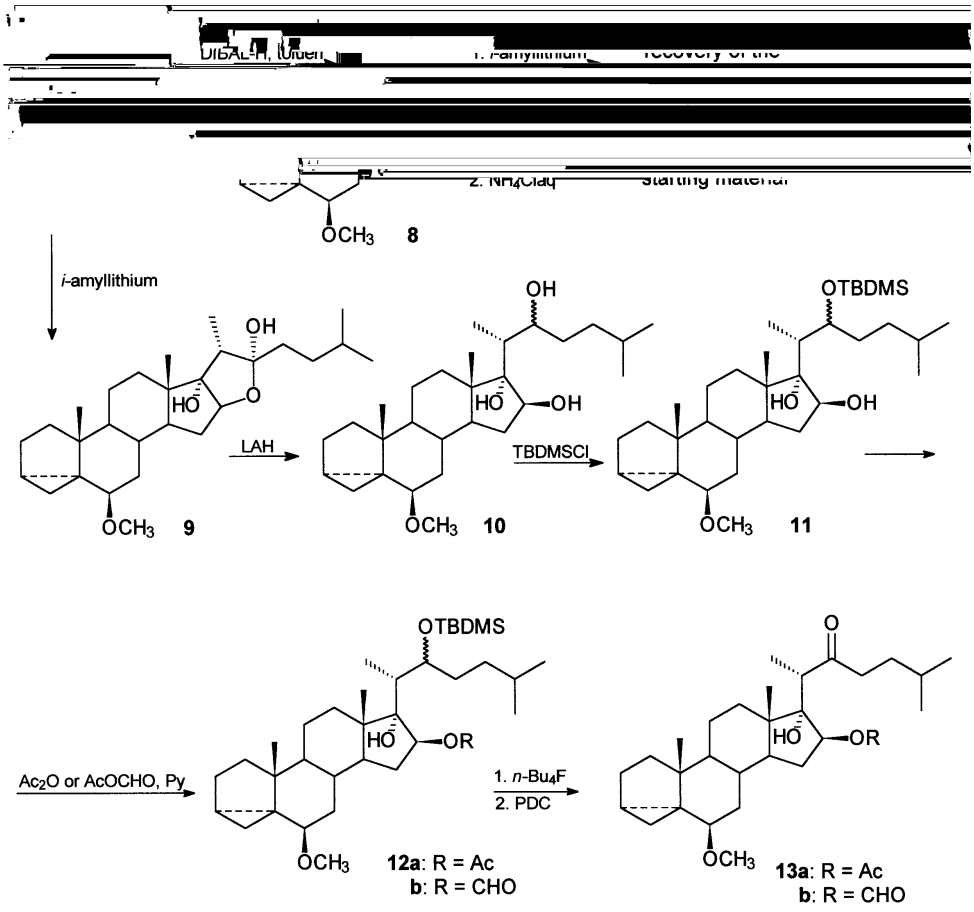
Scheme 2



5, which was, however, unsuccessful. Due to this failure, selective deacetylation of the diacetate **6** was also tried. The reaction was carried out under very mild conditions (K_2CO_3aq, THF, room temperature, several days). Monoacetate obtained was not the one that was expected but had an isomeric structure **7**. Again, this result may be explained assuming that during the reaction, acetyl group migration in the intermediate 16β-monoacetate from O-16 to O-22 took place. It seems that any protective group at O-16 tends to migrate to the less hindered, neighboring primary hydroxy group. It should be added that monobenzylation proceeded at the primary O-22 position, whereas reaction with an excess of benzyl bromide at elevated temperatures failed to afford the dibenzyl ether.

The failure of the above discussed approach compelled us to consider a different synthetic strategy. The lactone **1** was reduced with di*iso*butylaluminum hydride (DIBAL-H®) to the hydroxy aldehyde existing in the form of hemiacetal **8** (Scheme 3).

Scheme 3



This compound, however, was not alkylated with organometallic reagents, such as *iso*amyllithium, and therefore was useless for our purpose. However, the reaction of lactone **1** with *iso*amyllithium proceeded smoothly and afforded compound **9** in almost quantitative yield. Hemiketal **9** can be considered as the protected form of the saponin OSW-1 aglycone. Since compound **9** exists exclusively in a cyclic form (no hydroxy ketone form was detected in its IR spectrum), it is rather useless for the glycosylation purpose. Compound **9** proved stereochemically pure, but its configuration at C-22 cannot be elucidated directly from the spectra. Presumably, the more stable 22*R* epimer of **9** was formed (the 22*R* compound **9** was calculated using the MM^+ force field, to be over 4 kcal/mol more stable than its 22*S* epimer). An attempt of the compound **9** reaction with a glycosyl donor was undertaken, but instead of glycosylation it gave rise to the double dehydration of **9** to the ring E furan derivative [9]. In a separate experiment, it was proved that **9** is very sensitive to acids (including TMSOTf used as a glycosylation promoter). Hemiketal **9** was reduced with lithium aluminum hydride in order to obtain a product with free 16β-OH. The triol **10** was obtained in nearly quantitative yield as a mixture of epimers at C-22. Stereochemistry around C-22 in this compound was not important from the point of view of the saponin OSW-1 aglycone synthesis, since the 22-alcohol had to be oxidized to the ketone in due course. The triol **10** was treated with *tert*-butyldimethylsilyl chloride under the controlled conditions. Regioselectivity of the reaction was satisfactory – 22-monosilyl ether **11** was obtained in over 50% yield. The major reaction product **11** was accompanied by two other silyl derivatives that were not studied in detail (upon desilylation and oxidation they gave the same 16,22-dione). Compound **11** was converted into its 16-acetyl and 16-formyl derivatives (**12a** and **12b**). Both compounds were desilylated with tetrabutylammonium fluoride. The 22-hydroxy products were oxidized to the 22-ketones (**13a** or **13b**). In order to protect the 22-carbonyl group against formation of hemiketal on deprotection of the 16β-hydroxy group, compounds **13a** and **13b** were treated with ethylene glycol. However, there was no ketalization, presumably due to steric hindrance (22-carbonyl compounds devoid of substituents in ring D readily form ketals). The only reaction observed was cycloreversion in rings A and B.

The saponin OSW-1 aglycone described in this paper cannot be successfully glycosylated. However, some intermediate compounds with a free 16β-hydroxy group, *e.g.* **3**, **7**, and **11** can be combined with a sugar moiety. The studies of their glycosylation are currently in progress.

EXPERIMENTAL

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 ^1H 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). Lactone **1** was prepared from the commercially available 3β-hydroxyandrost-5-en-17-one according to the procedure described in [9].

***(20S)-20-Hydroxymethyl-6β-methoxy-3α,5α-cyclopregnane-16β,17α-diol* (2)**. To the solution of lactone **1** (84 mg; 0.24 mmol) in THF (1 mL) a suspension of $LiAlH_4$ (20 mg; 0.5 mmol) in THF (1 mL) was added and the reaction mixture was stirred 20 min at room temperature. After completion of the reaction (TLC control) 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 **2** was pure enough for analytical purpose; IR, ν_{max}: 3604, 3426, 1090, 1077 cm^{-1}; ^1H 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.

***(20S)-20-t-Butyldimethylsilyloxymethyl-6β-methoxy-3α,5α-cyclopregnane-16β,17α-diol* (3)**. The triol (**2**) (40 mg; 0.1 mmol) dissolved in 0.5 ml of dry DMF was treated with imidazole (20 mg; 0.25 mmol) and *tert*-butyldimethylsilyl chloride (38 mg; 0.25 mmol). The reaction mixture was stirred 4 h at 60°C, poured into water and extracted with methylene chloride. The extract was dried over magnesium sulfate and solvent was evaporated *in vacuo*. Compound **3** (38 mg, 73%) was purified by silica gel column chromatography with hexane – ethyl acetate 85:15 elution; m.p. 144–146°C (hexane); IR, ν_{max}: 3605, 3415, 1471, 1259 cm^{-1}; ^1H NMR, δ (ppm): 3.90 (m, 1H), 3.79 (m, 1H), 3.64 (m, 1H), 3.32 (s, 1H), 2.78 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.93 (d, *J* = 4.8 Hz, 3H), 0.92 (s, 9H), 0.64 (m, 1 H), 0.44 (dd, *J* = 8.0, 5.1 Hz, 1H), 0.12 (s, 6H); ^{13}C NMR, δ (ppm): 85.8 (C), 82.3 (CH), 80.6 (CH), 67.1 (CH_2), 56.4 (CH_3), 48.4 (CH), 47.6 (CH), 47.4 (C), 43.3 (C), 35.6 (CH), 35.4 (C), 34.7 (CH_2), 34.6 (CH_2), 33.3 (2 × CH_2), 30.3 (CH), 25.9 (3 × CH_3), 25.0 (CH_2), 22.2 (CH_2), 21.7 (CH), 19.3 (CH_3), 18.2 (C), 13.5 (2 × CH_3), 13.0 (CH_2), 12.7 (2 × CH_3).

***(20S)-16β-Benzyloxy-20-t-butyldimetylsilyloxymethyl-6β-methoxy-3α,5α-cyclopregnan-17α-ol* (4)**. The stirred solution of compound **3** (30 mg, 0.06 mmol) in THF (2 ml) was cooled in an ice-water bath and NaH was added (6 mg of 60% dispersion in mineral oil; 0.15 mmol). Then benzyl bromide (0.018 ml; 0.15 mmol) and $Bu_4N^+I^-$ (5 mg; 0.022 mmol) were added. The reaction mixture was stirred 16 h at reflux, excess NaH was carefully quenched with water, and extracted with ether. The extract was dried over magnesium sulfate and solvent was evaporated *in vacuo*. Pure **4** (29 mg, 83%) was eluted from the silica gel column with hexane – ethyl acetate 97:3, IR, ν_{max}: 3445, 3089, 1471, 1455, 1254 cm^{-1}; ^1H NMR, δ (ppm): 7.33 (m, 5H), 4.49 (m, 2H), 4.06 (s, 1H, OH), 3.95 (m, 1H), 3.92 (m, 1H), 3.43 (m, 1H), 3.36 (s, 3H), 2.79 (m, 1H), 1.17 (d, *J* = 7.3 Hz, 3H), 1.04 (s, 3H), 0.94 (s, 3H), 0.85 (s, 9H), 0.67 (m, 1H), 0.46 (t, *J* = 8.0, 5.1 Hz, 1H), 0.03 (s, 3H), –0.05 (s, 3H); ^{13}C NMR, δ (ppm): 137.8 (C), 128.5 (CH), 127.7 (2 × CH), 127.6 (2 × CH), 87.4 (C), 82.4 (CH), 81.4 (CH), 75.9 (CH_2), 73.7 (CH_2), 56.6 (CH_3), 48.1 (CH), 47.6 (CH), 46.7 (C), 43.3 (C), 36.8 (CH_2), 35.3 (CH_2), 34.9 (C), 33.9 (CH), 33.3 (CH_2), 33.1 (CH_2), 30.6 (CH), 25.8 (3 × CH_3), 24.9 (CH_2), 22.3 (CH_2), 21.1 (CH), 19.1 (CH_3), 17.6 (C), 13.5 (CH_3), 13.4 (CH_3), 13.2 (CH_2), –3.3 (CH_3), –5.7 (CH_3).

***(20S)-16β-t-Butyldimethylsilyloxy-20-t-butyldimethylsilyloxymethyl-6β-methoxy-3α,5α-cyclopregnan-17α-ol* (5)**. Compound **5** was obtained from the triol **2** in 38% yield in a similar way as the compound **3** by using 5 equivalents of the reagent (benzyl bromide/NaH). The work-up of the reaction mixture was identical as described in the previous case. Compound **5** was purified by silica gel column chromatography with hexane – ethyl acetate 95:5 elution; ^1H NMR, δ (ppm): 4.52 (s, 1H), 4.25 (dm, *J* = 9.8 Hz, 1H), 4.02 (m, 1H), 3.53 (dd, *J* = 9.8, 2.8 Hz, 1H), 3.35 (s, 3H), 2.78 (m, 1H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.66 (m, 1H), 0.45 (dd, *J* = 8.1, 5.0 Hz), 0.07 (s, 6H), 0.06 (s, 6H).

***(20S)-16β-Acetoxy-20-acetoxymethyl-6β-methoxy-3α,5α-cyclopregnan-17α-ol* (6)**. The solution of triol **2** (100 mg, 0.26 mmol) in 0.5 ml of pyridine was treated with 0.25 ml of acetic anhydride. The reaction mixture was stirred overnight at room temperature. Standard work-up of the reaction mixture afforded quantitatively crude product **6** which was purified by silica gel column chromatography with

hexane – ethyl acetate 75:25 elution; ^{1}H NMR, δ (ppm): 4.78 (dd, *J* = 8.1, 4.5 Hz, 1H), 4.19 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.86 (dd, *J* = 11.1, 7.0 Hz, 1H), 3.30 (s, 3H), 2.75 (m, 1H), 2.04 (s, 6H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.63 (m, 1H), 0.42 (dd, *J* = 8.0, 5.1 Hz, 1H).

(20S)-20-Acetoxymethyl-6β-methoxy-3α,5α-cyclopregnane-16β,17α-diol **(7)** was obtained by regioselective partial hydrolysis of compound **6** with one equivalent of potassium carbonate in aqueous THF solution. The reaction mixture was maintained at room temperature for several days. Compound **7**: ^{1}H NMR, δ (ppm): 4.53 (dd, *J* = 11.7, 3.0 Hz, 1H), 4.04 (m, 1H), 3.79 (bs, 1H), 3.69 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.29 (s, 3H), 2.74 (m, 1H), 2.06 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 3H), 0.96 (s, 3H), 0.62 (m, 1H), 0.41 (dd, *J* = 8.0, 5.1 Hz, 1H).

(20S)-6β-Methoxy-16β,17α-dihydroxy-3α,5α-cyclo-norcholanaldehyde 23,16-hemiacetal **(8)**. To the stirred solution of lactone **1** (40 mg; 0.11 mmol) in dry toluene cooled to –70°C (dry ice – acetone bath) DIBAL-H (0.21 ml of 1M solution in hexane; 0.21 mmol) was added. The reaction was maintained at –70°C under argon 4 h, then poured into water, and extracted with ether. Pure lactol **8** (0.03 mg) was obtained in 85% yield by silica gel column chromatography with hexane – ethyl acetate 68:32 elution; an oil; IR, ν_{max}: 3603, 3407, 1456, 1080 cm^{-1}; ^{1}H NMR, δ (ppm): 5.46 (m, 1H), 4.30 (t, *J* = 7.6 Hz, 1H), 3.33 (s, 3H), 2.78 (m, 1H), 1.04 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 3H), 0.66 (m, 1H), 0.45 (dd, J_1 = 8.0, 5.1 Hz, 1H); ^{13}C NMR, δ (ppm): 104.4 (CH), 91.5 (CH), 89.4 (C), 82.1 (CH), 56.6 (CH_3), 52.7 (CH), 47.6 (CH), 44.5 (C), 43.4 (C), 43.2 (CH), 35.2 (C and CH_2), 33.3 (CH_2), 32.0 (CH_2), 30.9 (CH_2), 30.1 (CH), 24.9 (CH_2), 22.3 (CH_2), 21.3 (CH), 19.3 (CH_3), 17.4 (CH_3), 13.1 (CH_2), 8.2 (CH_3).

(22R)-6β-Methoxy-3α,5α-cyclofurostane-17α,22-diol **(9)**. A solution of *iso*amyllithium in anhydrous ether was prepared from lithium (100 mg; 13 mmol) and *iso*amyl bromide (1.6 ml; 13 mmol). This reagent was added dropwise during 1 h to a stirred solution of lactone **1** (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 **9**, 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).

6β-Methoxy-3α,5α-cyclocholest-16β,17α,22-triol **(10)**. A solution of lactol **9** in anhydrous ether was obtained again according to the above procedure (no isolation of **9** from the reaction mixture) and treated with excess of LiAH. The reaction was completed in 6 h. The work-up of the reaction mixture was the same as in the case of compound **2**. Triol **10** was obtained as a mixture of epimers around C-22 with 63% yield (from lactone **1**) by silica gel chromatography with hexane:ethyl acetate 73:27 elution. Without further separation and analysis, the mixture of isomers was subjected to the next step.

22-t-Butyldimethylsilyloxy-6β-methoxy-3α,5α-cyclocholestane-16β,17α-diol **(11)**. The monosilyl ether **11** was obtained from the triol **10** in 50% yield in the same way as compound **3**. Product **11** was purified by silica gel column chromatography with hexane – ethyl acetate (5%) elution; an oil; IR, ν_{max}: 3439, 1468, 1384, 1259, 1090 cm^{-1}; ^{1}H NMR, δ (ppm): 4.42 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.24 (s, 1H, OH), 4.08 (m, 1H), 3.34 (s, 3H), 2.77 (m, 1H), 1.03 (s, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 3H), 0.9 (s, 9H), 0.88 (d, *J* = 6.4 Hz, 6H), 0.64 (m, 1H), 0.42 (dd, J = 8.0, 5.1 Hz, 1H), 0.13 (s, 6H); ^{13}C NMR, δ (ppm): 87.1 (C), 82.4 (CH), 81.2 (CH), 76.5 (CH), 56.6 (CH_3), 47.6 (CH), 47.3 (CH), 47.1 (C), 43.3 (C), 37.1 (CH_2), 35.2 (C), 34.9 (CH), 34.8 (2 × CH_2), 33.4 (CH_2), 33.3 (CH_2), 30.5 (CH), 29.7 (2 × CH_2), 28.3 (CH), 26.0 (3 × CH_3), 24.9 (CH_2), 22.7 (CH_3), 22.4 (CH_3), 21.4 (CH), 19.2 (CH_3), 18.1 (C), 13.7 (CH_3), 13.1 (CH_2), 7.0 (CH_3), –2.9 (CH_3); EI-MS, m/z (%): 378 (M^+-MeOH, 8), 381 (17), 215 (100).

16β-Acetoxy-17α–hydroxy-6β-methoxy-3α,5α-cyclocholest-22-one **(13a)**. Acetylation of **11** was carried out quantitatively with acetic anhydride/pyridine in a routine way. The crude product **12a** was treated with 2.5 equivalents of the commercially available (Aldrich) 1 M solution of $Bu_4N^+F^-$ in THF in order to remove the TBDMS protecting group. 22-Alcohol thus obtained was subsequently oxidized with PDC/CH_2Cl_2 to the ketone **13a**; ^{1}H NMR, δ (ppm): 4.69 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.35 (s, 1H, OH), 3.30 (s,

3H), 3.14 (q, *J* = 7.3 Hz, 1H), 2.76 (m, 1H), 1.98 (s, 3H), 1.09 (s, 3H), 0.91 (d, *J* = 4.3 Hz, 3H), 0.9 (s, 3H), 0.88 (d, *J* = 3.6 Hz, 6H), 0.63 (m, 1H), 0.43 (dd, *J* = 8.0, 5.1 Hz, 1H).

16β-Formyloxy-17α–hydroxy-6β-methoxy-3α,5α-cyclocholest-22-one **(13a)**. A similar procedure to the described above (except for using mixed formic-acetic anhydride instead of acetic anhydride) was applied in order to obtain compound **13b**. 7.90 (s, 1H), 4.80 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.39 (s, 1H, OH), 3.31 (s, 3H), 3.14 (q, *J* = 7.4 Hz, 1H), 2.76 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.64 (m, 1H), 0.43 (dd, *J* = 8.0, 5.1 Hz, 1H).

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