

Straightforward synthesis of unnatural poly-oxygenated steroid saponinins

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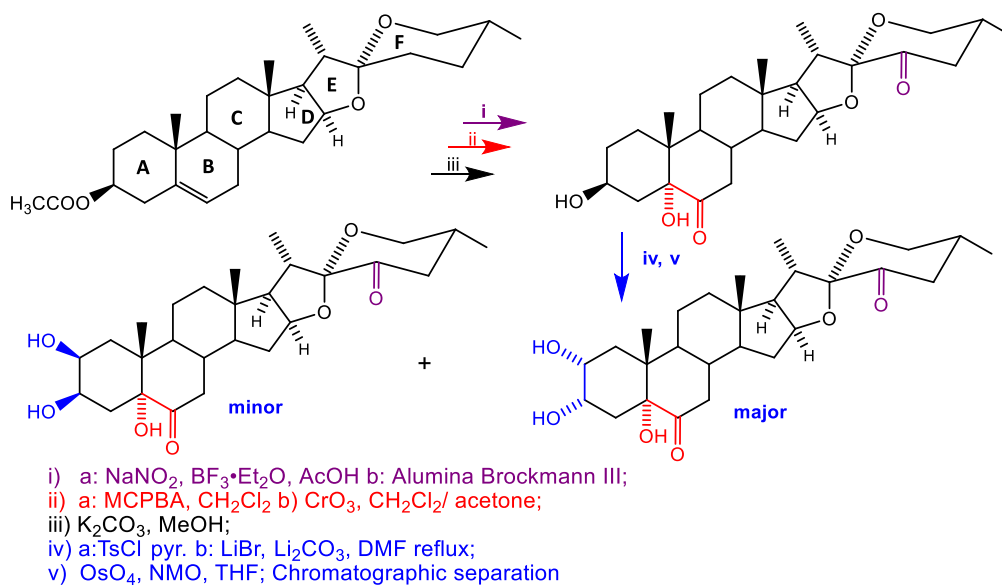
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Abstract

Saponins and their biosynthetic intermediates, sapogenins, display a variety of biological activities of interest to the pharmaceutical, cosmetic and food sectors. Three unnatural steroid sapogenins bearing oxygenated functions in rings A, B and F were prepared following a straightforward synthetic protocol that comprises the installation of a carbonyl function in ring F, a two-step, one-pot generation of a ketol in A,B rings, and the addition of a *cis*-diol in ring A by osmylation. Unambiguous NMR characterization is provided.



Keywords: Steroid sapogenins, 2 α ,3 α -diols, 2 β ,3 β -diols, 5 α -hydroxy-6-oxo steroids, Steroid NMR.

Introduction

Saponins are secondary metabolites found widespread in nature. A large number of such compounds has been isolated from terrestrial plants as well as from some marine organisms.¹⁻³ These kinds of compounds have shown a wide spectrum of properties that include sweet⁴ or bitter taste,⁵ and antimicrobial, insecticidal, and molluscicidal activities⁶ as well as hemolytic⁷ and cytotoxic⁸ properties amongst many others.^{1,9} In addition to the pharmacological and medicinal importance,¹⁰ the usefulness of saponins in the food industry is well recognised.¹¹

Saponins are traditionally classified as triterpene or steroid glycosides according to the aglycone (non-saccharide) part. The wide diversity of these compounds lays in the structural diversity of the less polar aglycone portion that is coupled to one or more units of different carbohydrates.¹²

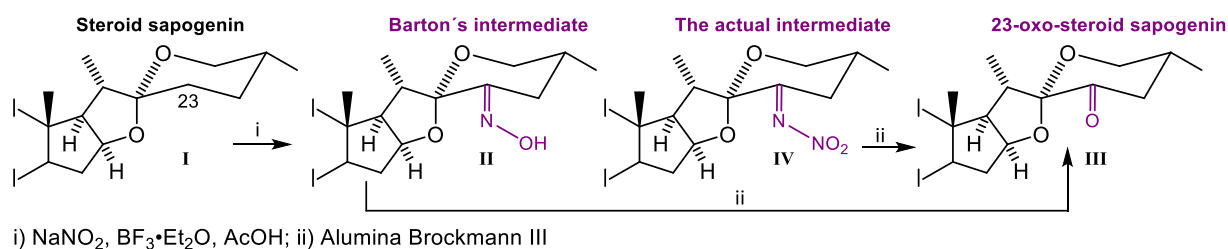
In particular, steroid saponins have attracted significant attention since the mid part of the last century due to their utility as raw materials for the production of steroid sapogenins. The aglycone part, obtained by hydrolysis, serves as the classical starting material for the synthesis of steroid hormones¹³ and other biologically active compounds.¹⁴⁻¹⁰ Additionally, the recognition of biological activity and pharmacological importance of steroid saponins, brought attention of chemists, biochemists and biologists to this family of compounds. Several reviews have covered the isolation, characterization, chemistry, and biological properties of steroid saponins.²¹⁻²³

Consequently, multiple efforts directed towards the synthesis of naturally occurring steroid saponins have been described.^{24,25} Such efforts comprise both the installation of the required functionality in the aglycone part, and synthesis of the carbohydrate building blocks. The last steps of the synthetic sequence are generally the coupling of both units and deprotection of the functional groups.

As a part of our program on the synthesis of biologically active steroids, we have become interested in the synthesis of unnatural steroid sapogenins that could serve as aglycones for the construction of steroid glycosides that may be interesting candidates for biological-activity screening. Herein, we describe the synthesis and characterization of three unnatural steroid sapogenins bearing oxygenated functions in rings A, B and F.

Results and Discussion

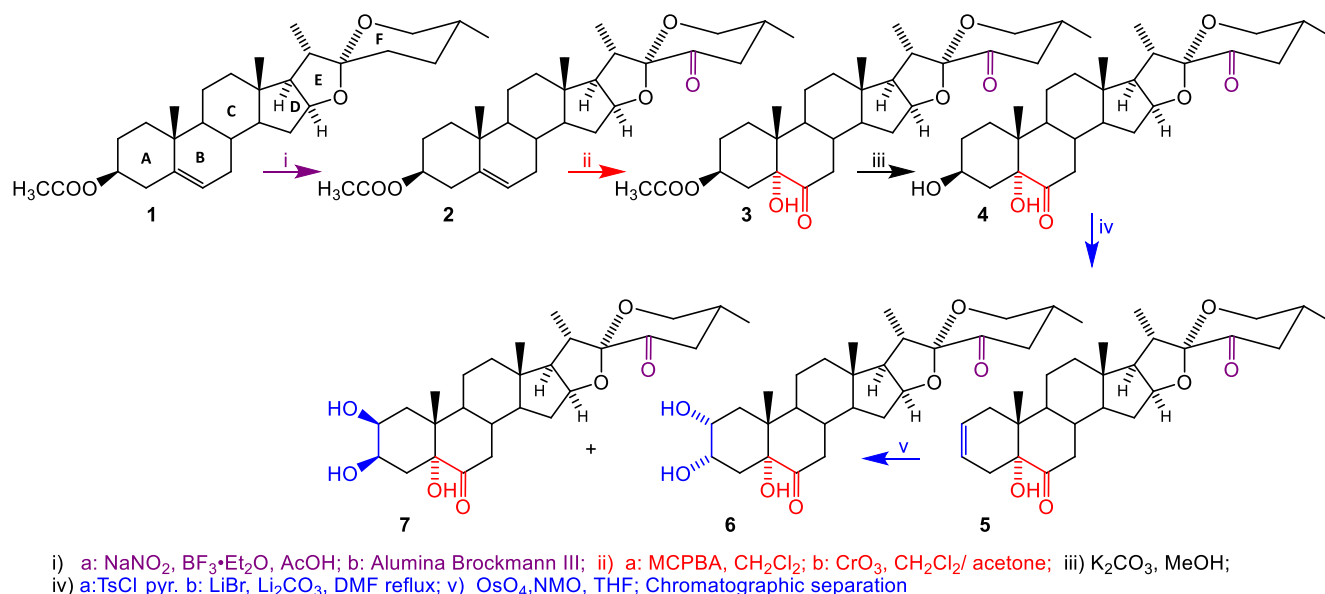
The synthetic protocol started with the introduction of a carbonyl function at position C-23 of the side chain of diosgenin acetate (**1**) employing a methodology described by Barton.²⁶ According to that report, treatment of a steroid sapogenin (**I**) with NaNO_2 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ produces a 23E-oximino sapogenin (**II**) that is hydrolyzed to a 23-keto sapogenin (**III**) by column chromatography in neutral alumina (Brokmann activity III). Our detailed study of this reaction showed that the compound formed by the treatment with NaNO_2 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is the 23E-nitroimino derivative (**IV**) (Scheme 1).²⁷



Scheme 1. Introduction of a carbonyl group at position C-23 of the side chain of steroid sapogenin.

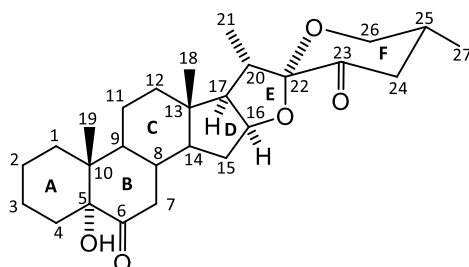
Thus, treatment of diosgenin acetate (**1**) with NaNO_2 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in acetic acid followed by column chromatography in neutral alumina (Brokmann activity III) following Barton's procedure afforded the ketone **2** that was subsequently converted into the acetylated ketol **3** employing our simple one-pot procedure which includes epoxidation with meta-chloroperoxybenzoic acid (mCPBA) followed by oxidative cleavage of the oxirane ring with CrO_3 .²⁸

Hydrolysis of the acetate at position C-3 afforded the target dihydroxylated ketone **4** that was converted into the unsaturated ketol **5** by tosylation in pyridine followed by elimination using treatment with LiBr and Li_2CO_3 in refluxing DMF. Subsequent dihydroxylation employing OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant in THF afforded a mixture of the target trihydroxylated diketone **6** as the major compound, accompanied by its 2 β ,3 β -diastereomer **7** that were separated by column chromatography (Scheme 2).



Scheme 2. Synthesis of the polyoxygenated steroid sapogenins **4**, **6** and **7**.

NMR signals assignments (Tables 1 and 2) were carried out with the aid of a combination of 1D and 2D NMR techniques that included ^1H , ^{13}C , 1H–1H COSY, Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). The observed NOEs allowed the determination of the orientations of the 2 α ,3 α and 2 β ,3 β diols introduced into the A rings of compounds **6** and **7**, respectively (Figure 1).

Table 1. Selected ^1H signals of steroid sapogenins **4**, **6** and **7**. δ (ppm) and multiplicities*

	4	6	7
H-2	n.a.	3.64 m	3.79 – 3.71 m
OH (C-2)	-	4.55 m	4.09 d
H-3	3.96 m	3.92 m	3.79 – 3.71 m
OH (C-3)	n.a.	5.48 d	4.29 d
OH (C-5)	2.95 s	5.65 s	5.38 s
H-16	4.60 dt	4.55 m	4.55 dt
H-18	0.75 s	0.68 s	0.67 s
H-19	0.79 s	0.68 s	0.88 s
H-21	0.93 d	0.86 d	0.86 d
H-26 ax	3.77 dd	3.64 m	3.65 dd
H-26 eq.	3.58 dd	3.64 m	3.59 ddd
H-27	0.93 d	0.87 d	0.88 d

* Solvents: CDCl_3 for **4**; DMSO-d_6 for **6** and **7**. NA not assigned.

Table 2. Selected ^{13}C NMR signals of steroid sapogenins **4**, **6** and **7**. δ (ppm) *

	4	6	7
C-2	30.3	66.5	68.3
C-3	67.2	69.3	67.1
C-5	80.4	79.1	79.3
C-6	212.7	210.2	212.1
C-16	83.0	82.6	82.6
C-18	16.1	15.9	16.0
C-19	14.1	14.5	15.8
C-21	14.3	14.4	14.4
C-22	109.8	109.1	109.1
C-23	201.7	201.4	201.4
C-26	65.7	64.9	64.9
C-27	17.1	16.7	16.7

* Solvents: CDCl_3 for **4**; DMSO-d_6 for **6** and **7**.

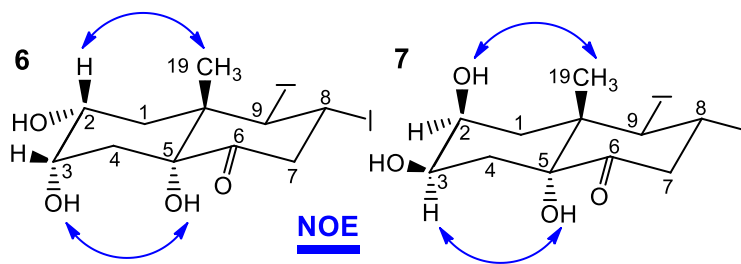


Figure 1. Observed NOEs in compounds **6** and **7**.

Conclusions

We have set up procedures for the synthesis and unambiguous characterization of unnatural steroid sapogenins that will serve as aglycones for the construction of steroid glycosides which may be interesting candidates for biological-activity screening.

Experimental Section

General. Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% HClO₄ and heated until color developed. Melting points were measured on a Melt-Temp II apparatus. NMR spectra were recorded in CDCl₃ or DMSO-d₆ solutions on a Varian INOVA 400 spectrometer using the solvents' signals (CDCl₃; 7.26 ppm for ¹H and 77.00 ppm for ¹³C) or (DMSO-d₆, 2.50 ppm for ¹H and 39.52 ppm for ¹³C) as references. All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer and were processed employing the MestreNova NMR program [See <http://mestrelab.com/>]. Mass spectra (EI) were registered on a Thermo-Electron spectrometer model DFS (Double Focus Sector). HRMS spectra were registered using a PERKIN ELMER Model: AxION-2 TOF MS spectrometer.

(25R)-3β-acetoxyspiros-5-en-23-one (2). NaNO₂ (0.5256 g) was slowly added (45 min) to a solution of diosgenin acetate (**1**) (3g, 6.57 mmol) and BF₃.Et₂O (2.69 mL) glacial in acetic acid (75 mL). After conclusion of this addition, additions of BF₃.Et₂O (2.69 mL) and NaNO₂ (0.5256 g in 45 min.) were repeated, and the resulting mixture was stirred for 1 hour and then poured into ice/water. The resulting solid was filtered off, washed with abundant water, and dissolved in ethyl acetate (200 mL). The organic solution was washed with a 5% aqueous solution of Na₂CO₃ (2 × 50 mL), H₂O (1 × 50 mL) and NaCl (1 × 50 mL), dried (anh. Na₂SO₄) and evaporated. The resulting syrup was dissolved in the smallest amount of a 1/1 benzene/hexane solution and left to stand overnight in a chromatographic column packed with Al₂O₃ (Brockman activity III). Elution with a 10/1 hexane/ethyl acetate mixture afforded 1.093 g (2.32 mmol, 35%) of 23-oxodiosgenin acetate (**2**). Mp. 190–192 °C (from ethyl acetate/hexane). Lit.²⁹ 191–192.5 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.35 (d, *J* 5.1 Hz, 1H, H-6), 4.64 – 4.54 (m, 2H, H-16, H-3), 3.78 (dd, *J* 11.3, 11.3 Hz, 1H, H-26 ax.), 3.58 (ddd, *J* 11.2, 4.6, 1.4 Hz, 1H, H-26 eq.), 2.87 (dd, *J* 13.7, 6.9 Hz, 1H, H-20), 2.49 – 2.38 (m, 2H, H-24), 2.36 – 2.21 (m, 3H, H-4, H-25), 2.02 (s, 3H, CH₃ acetyl), 1.02 (s, 3H, H-19), 0.93 (d, *J* 7.1 Hz, 3H, H-21), 0.93 (d, *J* 6.5 Hz, 3H, H-27), 0.78 (s, 3H, H-18). ¹³C NMR (100.53 MHz) δ ppm 36.9 C-1, 27.7 C-2, 73.8 C-3, 38.1 C-4, 139.8 C-5, 122.2 C-6, 32.0 C-7, 31.4 C-8, 49.9 C-9, 36.7 C-10, 20.7 C-11, 39.5 C-12, 40.7 C-13, 56.5 C-14, 31.8 C-15, 83.3 C-16, 61.7 C-17, 16.0 C-18,

19.3 C-19, 34.8 C-20, 14.4 C-21, 109.8 C-22, 201.8 C-23, 45.3 C-24, 35.8 C-25, 65.6 C-26, 17.1 C-27, 170.5 C=O acetyl, 21.4 CH₃ acetyl.

(25R)-3 β -acetoxy-5-hydroxy-5 α -spirostan-6,23-dione (3). *meta*-Chloroperoxybenzoic acid (mCPBA) (414.5 mg) was added to a solution of the ketone **2** (798.4 mg, 1.70 mmol) in CH₂Cl₂ (10 mL) and the mixture was stirred until the starting material disappeared (1 h, TLC). Acetone (20 mL) was added, and the mixture was cooled to 0° C in an ice bath before the dropwise addition of a solution of CrO₃ (303.4 mg) in water (1 mL). The ice bath was removed, the mixture was stirred at room temperature for 20 min and cooled to 0° C in the ice bath prior to dropwise addition of a solution of CrO₃ (773.6 mg) in water (2.3 mL). The ice bath was removed, and the mixture stirred for 2.5 h, before addition of water (20 mL) and extraction with ethyl acetate (2 × 25 mL). The organic layer was washed sequentially with water (10 × 20 mL), a 10% NaHCO₃ solution (5 × 20 mL), water (2 × 20 mL) and brine (20 mL), then dried (anh. Na₂SO₄) and evaporated to afford 787.6 mg (1.57 mmol, 92 %) of the desired ketol **3**. Mp. 272–274 °C (*from ethyl acetate/hexane*). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.05 – 4.95 (m, 1H, H-3), 4.61 (td, *J* 7.7, 6.0 Hz, 1H, H-16), 3.76 (dd, *J* 11.3, 11.3 Hz, 1H, H-26 ax.), 3.58 (ddd, *J* 11.2, 4.1, 1.2 Hz, 1H, H-26 eq.), 3.01 (s, 1H, OH-5), 2.91 – 2.83 (m, 1H, H-20), 2.76 (t, *J* 12.3 Hz, 1H, H-7ax.), 2.45 – 2.41 (m, 2H, H-24), 2.33 – 2.23 (m, 1H, H-25), 2.10 (dd, *J* 13.0, 4.0 Hz, 1H, H-7 eq.), 1.99 (s, 3H, s, 3H, CH₃ acetyl), 0.93 (d, *J* 7.5 Hz, 3H, H-21), 0.93 (d, *J* 6.4 Hz, 3H, H-27), 0.81 (s, 3H, H-19), 0.75 (s, 3H, H-18). ¹³C NMR (100.53 MHz) δ ppm 29.5 C-1, 26.2 C-2, 70.5 C-3, 32.4 C-4, 80.2 C-5, 211.8 C-6, 41.7 C-7, 36.7 C-8, 44.3 C-9, 42.4 C-10, 21.1 C-11, 39.3 C-12, 41.6 C-13, 56.1 C-14, 31.5 C-15, 83.0 C-16, 61.7 C-17, 16.1 C-18, 14.0 C-19, 34.7 C-20, 14.3 C-21, 109.8 C-22, 201.7 C-23, 45.2 C-24, 35.8 C-25, 65.7 C-26, 17.1 C-27, 171.0 C=O acetyl, 21.3 CH₃ acetyl. MS (IE, 70 e-V): 502 M⁺, 475, 474, 430, 421, 420, 419, 360, 359, 358, 345, 341, 327, 313, 296, 285, 267(100 %), 249, 239, 209, 185, 175, 173, 149, 147, 133, 121, 105, 93, 91, 79, 56. HRMS (EI) observed 502.2897, calculated for C₂₉H₄₂O₇ 502.2925.

(25R)-3 β ,5-dihydroxy-5 α -spirostan-6,23-dione (4). A suspension of the acetylated diketone **3** (699.6 mg, 1.39 mmol) in a saturated solution of K₂CO₃ in methanol (30 mL) was stirred overnight. Half of the solvent was evaporated off and the remaining mixture was poured into ice/water. The obtained solid was filtered off, washed with abundant water, and dried by air to afford 568.5 mg (1.23 mmol, 89 %) of the dihydroxylated diketone **4**. Mp. 296–298 °C (*ethyl acetate/hexane*). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.60 (dt, *J* 7.5, 6.1 Hz, 1H, H-16), 3.96 (m, 1H, H-3), 3.77 (dd, *J* 11.3, 11.3 Hz, 1H, H-26 ax.), 3.58 (dd, *J* 11.1, 4.0 Hz, 1H, H-26 eq.), 2.95 (a, 1H, OH-5), 2.92 – 2.83 (m, 1H, H-20), 2.75 (t, *J* 12.1 Hz, 1H, H-7ax.), 2.51 – 2.41 (m, 2H, H-24), 2.33 – 2.22 (m, 1H, H-25), 2.09 (dd, *J* 13.1, 2.5 Hz, 1H, H-7 eq.), 0.93 (d, *J* 6.7 Hz, 6H, H-21 and H-27), 0.79 (s, 3H, H-19), 0.75 (s, 3H, H-18). ¹³C NMR (100.53 MHz) δ ppm 29.8 C-1, 30.3 C-2, 67.2 C-3, 36.1 C-4, 80.4 C-5, 212.7 C-6, 41.8 C-7, 36.7 C-8, 44.4 C-9, 42.4 C-10, 21.2 C-11, 39.3 C-12, 41.6 C-13, 56.2 C-14, 31.5 C-15, 83.0 C-16, 61.6 C-17, 16.1 C-18, 14.1 C-19, 34.7 C-20, 14.3 C-21, 109.8 C-22, 201.7 C-23, 45.2 C-24, 35.8 C-25, 65.7 C-26, 17.1 C-27. MS (IE, 70 e-V): 460 M⁺, 433, 432, 414, 379, 378, 377, 359, 341, 323, 313, 303, 285, 267 (100%), 249, 239, 225, 199, 185, 175, 173, 165, 147, 121, 107, 93, 91, 81, 67, 56. HRMS (EI): observed 460.2828, calculated for C₂₇H₄₀O₆ 460.2819.

(25R)-5-Hydroxy-5 α -spirost-2-en-6,23-dione (5). Tosyl chloride (672 mg) was added to a solution of the dihydroxylated diketone **4** (638.3 mg, 1.39 mmol) in dry pyridine (8 mL) and the mixture was stirred for 24 h before pouring into a 3% HCl/ice bath. The produced solid was filtered off and dissolved in ethyl acetate (60 mL), and the organic solution was washed with water (2 × 20 mL), dried (anh. Na₂SO₄) and evaporated. The residue was stirred with LiBr (713 mg) and Li₂CO₃ (590 mg) under reflux in dry DMF (12 mL) for 3 h and the mixture was cooled to room temperature. Ethyl acetate (60 mL) was added, the mixture was filtered, the inorganic salts were washed with ethyl acetate (4 × 5 mL) and the organic solution was washed with water (6 × 20 mL) dried (anh. Na₂SO₄) and evaporated. The produced residue was purified in a chromatographic column

packed with silica gel employing hexane-ethyl acetate as eluent to afford 383.6 mg (0.87 mmol, 63 %) of the desired unsaturated ketol **5**. Mp. 258-260 °C (*from hexane/ethyl acetate*). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.69 – 5.57 (m, 2H, H-2 and H-3), 4.65 – 4.57 (m, 1H, H-16), 3.77 (dd, *J* 11.3, 11.3 Hz, 1H, H-26 ax.), 3.57 (ddd, *J* 11.1, 4.4, 1.1 Hz, 1H, H-26 eq.), 2.88 (q, *J* 6.8 Hz, 1H, H-20), 2.69 (t, *J* 12.3 Hz, 1H, H-7ax.), 2.61 (dd, *J* 4.2, 2.1 Hz, 1H, H-1), 2.46 – 2.41 (m, 1H, H-24), 2.34 – 2.21 (m, 1H, H-25), 2.19 (dd, *J* 12.7, 3.6 Hz, 1H, H-7 eq.), 2.12 (dd, *J* 15.9, 2.1 Hz, 1H, H-4), 0.93 (d, *J* 7.3 Hz, 3H, H-21), 0.92 (d, *J* 6.4 Hz, 3H, H-27), 0.75 (s, 3H, H-18), 0.71 (s, 3H, H-19). ¹³C NMR (100.53 MHz) δ ppm 30.1 C-1, 125.4 C-2, 122.3 C-3, 34.5 C-4, 77.9 C-5, 210.7 C-6, 42.6 C-7, 36.8 C-8, 45.1 C-9, 42.2 C-10, 20.7 C-11, 39.3 C-12, 41.3 C-13, 56.2 C-14, 31.4 C-15, 82.9 C-16, 61.6 C-17, 16.0 C-18, 14.6 C-19, 34.7 C-20, 14.3 C-21, 109.8 C-22, 201.7 C-23, 45.2 C-24, 35.8 C-25, 65.7 C-26, 17.0 C-27. MS (FAB): 443 [MH]⁺, 359, 341, 285, 259, 207, 159, 149, 133, 105, 91, 83, 57. HRMS (FAB): Found 443.2811, calculated for C₂₇H₃₉O₅ 443.2792 [MH]⁺.

(25R)-2α,3α,5-Trihydroxy-5α-spirostan-6,23-dione (6) and **(25R)-2β,3β,5-trihydroxy-5α-spirostan-6,23-dione (7)**. *N*-methylmorpholine *N*-oxide (544 mg) and a 12.5 mg/mL solution of OsO₄ (3.26 mL) in tert-butyl alcohol were added to a solution of the unsaturated ketol **5** (301.0 mg, 0.68 mmol) in THF (7 mL) and the mixture was stirred under N₂ for 24 h before addition of a solution of Na₂SO₃ (246 mg) in water (2 mL). The resulting mixture was stirred for 90 min, ethyl acetate (80 mL) was added, the organic solution was washed with brine (5 × 15 mL), dried (anh. Na₂SO₄) and evaporated. The produced residue was purified in a chromatographic column packed with silica gel, employing 1/1 hexane/ethyl acetate mixture to afford the epimeric trihydroxylated diketones **6** and **7**.

(25R)-2α,3α,5-Trihydroxy-5α-spirostan-6,23-dione (6). Yield 132.7 mg (0.28 mmol, 41 %). Mp. 286-288 °C (*from acetone*). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.65 (s, 1H, OH-5), 5.48 (d, *J* 3.2 Hz, 1H, OH-3), 4.55 (m, 2H, H-16, OH-2), 3.92 (a, 1H, H-3), 3.64 (m, 3H, H-2, H-26 ax., eq.), 2.56 (t, *J* 12.3 Hz, 1H, H-7ax.), 0.87 (d, *J* 6.2 Hz, 3H, H-27), 0.86 (d, *J* 6.8 Hz, 3H, H-21), 0.68 (s, 3H, H-19), 0.68 (s, 3H, H-18). ¹³C NMR (100.53 MHz) δ ppm 30.5 C-1, 66.5 C-2, 69.3 C-3, 34.5 C-4, 79.1 C-5, 210.2 C-6, 41.0 C-7, 35.9 C-8, 44.2 C-9, 44.7 C-10, 20.5 C-11, 38.9 C-12, 41.0 C-13, 55.5 C-14, 31.0 C-15, 82.6 C-16, 60.8 C-17, 15.9 C-18, 14.5 C-19, 34.3 C-20, 14.4 C-21, 109.1 C-22, 201.4 C-23, 44.7 C-24, 35.3 C-25, 64.9 C-26, 16.7 C-27. MS (FAB): 477 [M+1]⁺, 459, 385, 341, 327, 281, 267, 221, 207, 165, 147, 136, 97, 91, 73, 69, 57 (100%). HRMS (FAB): Found 477.2872, calculated for C₂₇H₄₁O₇ 477.2847 [MH]⁺.

(25R)-2β,3β,5-Trihydroxy-5α-spirostan-6,23-dione (7). Yield 64.5 mg (0.14 mmol, 21 %). Mp. 288-290 °C (*from acetone/water*). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.38 (s, 1H, OH-5), 4.55 (dt, *J* 7.6, 6.4 Hz, 1H, 1H, H-16), 4.29 (d, *J* 6.4 Hz, 1H, OH-3), 4.09 (d, *J* 2.2 Hz, 1H, OH-2), 3.79 – 3.71 (m, 2H, H-2 and H-3), 3.65 (dd, *J* 11.1, 11.1 Hz, 1H, H-26 ax.), 3.59 (ddd, *J* 11.1, 5.0, 1.2 Hz, 1H, H-26 eq.), 2.75 (q, *J* 6.9 Hz, 1H, H-20), 2.67 (t, *J* 12.3 Hz, 1H, H-7ax.), 2.43 – 2.30 (m, 2H, H-24), 2.18 (qd, *J* 11.6, 5.4 Hz, 1H, H-8), 0.88 (s, 3H, H-19), 0.88 (d, *J* 6.5 Hz, 3H, H-27), 0.86 (d, *J* 7.1 Hz, 3H, H-21), 0.67 (s, 3H, H-18). ¹³C NMR (100.53 MHz) δ ppm 30.5 C-1, 68.3 C-2, 67.1 C-3, 36.6 C-4, 79.3 C-5, 212.1 C-6, 41.2 C-7, 35.3 C-8, 44.1 C-9, 41.5 C-10, 20.8 C-11, 39.0 C-12, 41.1 C-13, 55.5 C-14, 31.1 C-15, 82.6 C-16, 60.9 C-17, 16.0 C-18, 15.8 C-19, 34.2 C-20, 14.4 C-21, 109.1 C-22, 201.4 C-23, 44.7 C-24, 35.4 C-25, 64.9 C-26, 16.7 C-27. Elemental analysis: Found C 68.34 % H 8.54 %, calculated for C₂₇H₄₀O₇ C 68.04 % H 8.46 %.

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Supplementary Material

Copies of the ^1H NMR and ^{13}C NMR spectra of compounds **2-7** are provided in the online edition of the text.

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