

Synthesis of Hoodigogenin A, the Aglycone of Hoodigosides Extracted from *Hoodia gordonii*

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Introduction

Hoodia gordonii is a succulent plant (asclepiadaceae family) which grows in the Kalahari desert in South Africa. On a historical point of view, it was claimed that the San people, a Bushmen tribe leaving in the Kalahari desert, were able to make long hunting trips without feeling thirsty and hungry after chewing fresh sap from *H. gordonii*. Therefore, it was claimed that *H. gordonii* could represent a new help for fighting obesity, which is one of the major health problems in the 21st century. Indeed, in 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese [1].

In 2007, Van Herdeen et al. reported for the first time the appetite suppressant properties of *H. gordonii* [2,3]. According to these authors, the compound responsible for that, is the pregnane glycoside P57AS3. Later on, Shukla et al. reported that more than 40 different pregnane glycosides (Hoodigosides) were isolated from *H. gordonii* [4,5]. The common aglycone of all these compounds is Hoodigogenin A (or Gordonoside A) (Figure 1).

The yield of extraction of the Hoodigosides from *Hoodia gordonii* lies between 0.003% and 0.02%. On the other hand, the isolation of analytically pure compounds proved to be highly time consuming and tedious. Therefore, in the frame of a collaborative study concerning the synthesis, the extraction and the biological evaluation of Hoodigogenin A, we developed an original synthesis of Hoodigogenin A starting from commercially available reagents. Indeed, Hoodigogenin A could provide different Hoodigosides after running a glycosylation reaction with the required sugar moiety. We report herein the synthesis of Hoodigogenin A, the key step being a Norrish type I-Prins reaction.

Synthesis of Hoodigogenin A

The synthesis started from the commercially available compound **1**. After a regioselective deprotection of the 3 α -acetoxy group and oxidation of the resulting hydroxy group, a regioselective α -bromination of the diketo derivative **2** yielded stereospecifically the β -bromoketo derivative **3**. A dehydrobromination reaction led to the α,β -unsaturated keto derivative **4** [6]. The latter was treated with acetic anhydride and acetyl chloride to give readily the dienol acetate **5** [7]. After protection of the carbonyl group with ethyleneglycol, the dienol acetate was reduced in the presence of NaBH₄ [8,9] followed by a KOH promoted deprotection of the 12 α -acetate group, allowing the introduction of the double bond in the B ring and yielding the unstable diol **6**. A regioselective protection of the 3 β -hydroxyl group gave compound **7**, which was subjected to a Dess Martin periodane oxidation [10] to afford the keto derivative **8** (Figure 2).

Compound **8** was then suitable to undergo a Norrish type I reaction [11-15]. It has to be noted that the photochemical ring opening of pregnenolone derivatives was never reported in the literature. We were pleased to see that the photolysis of compound **8**, which was carried out in a quartz apparatus with a 125 W high pressure mercury lamp, led readily to the formation of aldehyde **9**. The latter proved to be instable. Therefore the subsequent Prins reaction was directly carried out on the crude photolysis reaction mixture. Under these reactions conditions,

three compounds were isolated: compound **10** that resulted from a deprotection of the dioxolane **8**, the spiro derivative **11** and the desired compound **12**, which was isolated in 25% yield (Figure 3) [16].

Finally, the protection of the 12 β -hydroxy group with tigloyl chloride in the presence of pyridine and DMAP afforded compound **13**. Deprotection of the 3 β -acetate group gave Hoodigogenin A, whose structure was confirmed by ¹H and ¹³C NMR analysis and by X-ray analysis (Figures 4 and 5) [17].

Conclusion

To overcome the limited availability of Hoodigogenin A, we have disclosed an original synthetic route that affords the latter in 3% overall yield. This synthesis represents a very interesting alternative to the extraction methods for which the yields are 100 times lower. Moreover, analogs of Hoodigogenin A are now accessible by our method [18]. Concerning the biological activities, Smith et al. reported recently a summary of the current knowledge concerning the efficiency of *H. gordonii* as an appetite suppressant drug. Many contradictory results were obtained and it clearly came out that more studies are absolutely necessary to elucidate the mode of action of hoodigosides [19].

Experimental section

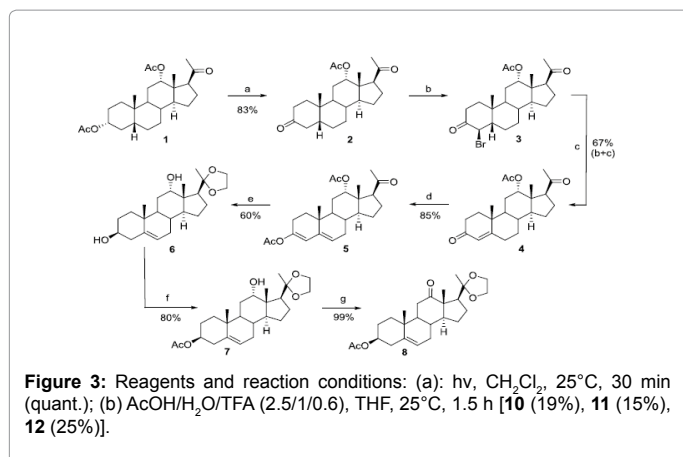
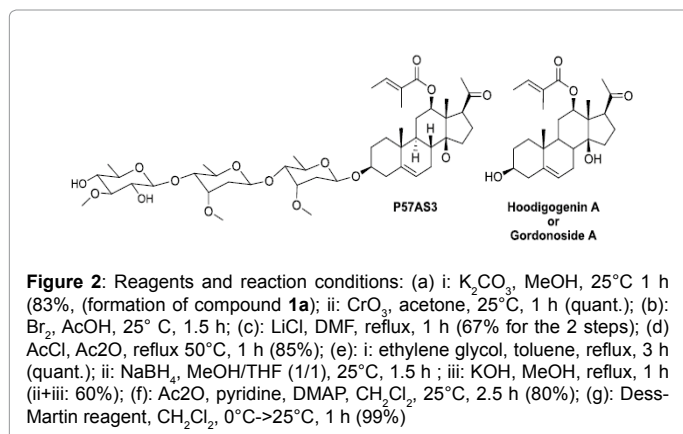
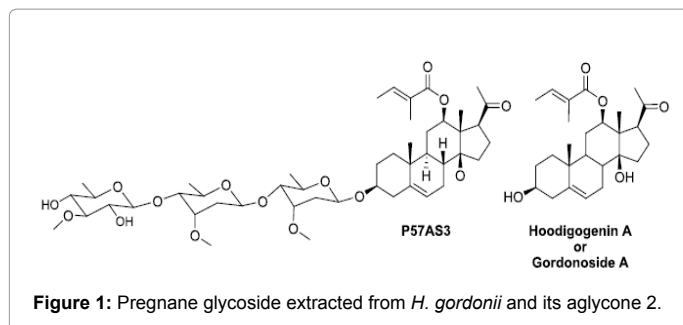
Melting points were measured on a Stuart Scientific melting point apparatus (SMP 3) and are uncorrected. Reactions were carried out under argon with magnetic stirring and degassed solvents. Et₂O and THF were distilled from Na/benzophenone. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck 60F254) and the spots were visualized under UV lamp (254 or 365 nm) and sprayed with phosphomolybdic acid solution (25 g phosphomolybdic acid, 10 g cerium sulfate, 60 mL H₂SO₄, 940 mL H₂O) followed by heating on a hot plate. For column chromatography, silica gel (Merck Si 60 40-60 μ m) was used. IR spectra were recorded on Bruker Alpha (ATR) spectrophotometer. ¹H NMR spectra were recorded at 300 MHz (Bruker AC-300) and ¹³C NMR spectra at 75 MHz (Bruker AC-300) using the signal of the residual nondeuterated solvent as internal reference. Significant ¹H NMR data are tabulated in the following order: chemical shift (δ) expressed in ppm, 6 multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants in hertz, number

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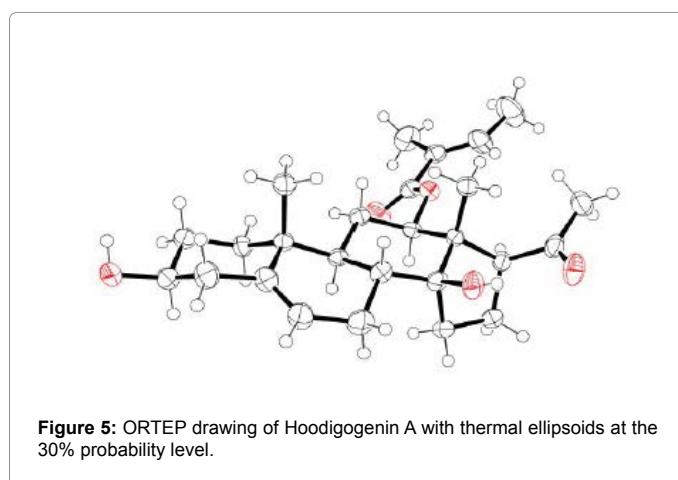
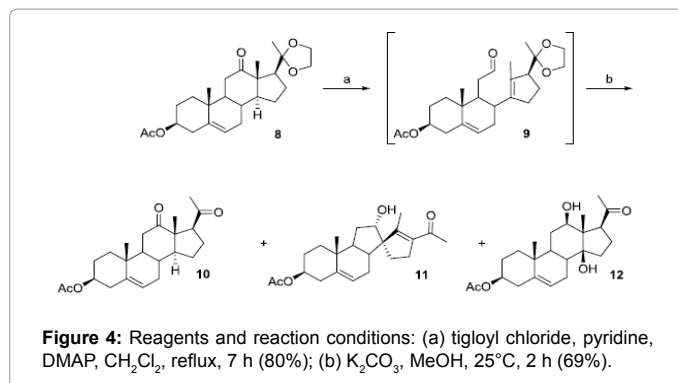
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of protons. High-resolution mass spectra (HRMS) were performed on a Agilent 6520 Accurate Mass Q-TOF.

3 α -hydroxy,12 α -acetoxy-5H β -pregnan-20-one (**1a**)

To a solution of compound **1** (3.37 g, 8.05 mmol) in MeOH (80 mL) was added K_2CO_3 (1.00 g, 7.24 mmol). The reaction mixture was stirred for 1 h at r.t. and treated with water (50 mL). The aqueous layer was extracted with Et₂O (3 × 60 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The white residue was purified by column chromatography (30 g silica gel, petroleum ether-ethyl acetate, 3:7), to afford compound **1a** as a white solid (2.48 g, 83%, mp 201.5-203.8°C). IR (ATR, cm^{-1}): 3472, 1714, 1696. ¹H NMR ($CDCl_3$) δ : 5.12 (t, ¹H, J=2.7 Hz, H-12 β); 3.63 (tt, ¹H, J=10.9-4.6 Hz, H-3 β); 2.95 (t, ¹H, J=9.3 Hz, H-17 α); 2.20-2.05 (¹H, m); 2.14 (s, 3H, H-21); 2.01



(s, 3H, CH₃, Ac); 1.95-0.85 (m, 20H); 0.89 (s, 3H, CH₃); 0.67 (3H, s, CH₃). ¹³C NMR ($CDCl_3$) δ : 208.9 (C=O, C-20); 170.5 (C=O, OAc); 74.5 (CH, C-3); 71.6 (CH, C-12); 55.6 (CH); 49.6 (CH); 46.7 (C); 41.9 (CH); 36.2 (CH₂); 35.6 (CH); 35.0 (CH₂); 34.5 (CH); 34.1 (C); 31.1 (CH₃); 30.4 (CH₂); 27.0 (CH₂); 26.0 (CH₂); 25.6 (CH₂); 23.7 (CH); 23.0 (CH₃); 22.3 (CH₂); 21.4 (CH₃); 13.8 (CH₃). HRMS (ESI) m/z: C₂₃H₃₆NaO₄ [M+Na]⁺ calcd. 399.2506, found 399.2518; [α]_D²⁰: +154 (c 0.01, $CHCl_3$).

12 α -acetoxy-5H β -pregnan-3,20-dione (**2**)

A solution of compound **1a** (1.00 g, 2.66 mmol) in acetone (60 mL) at 0°C was treated dropwise with Jones reagent (2.7 mL). The orange solution was stirred for 1 h at r.t. and treated with water (50 mL). The aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (1 × 50 mL) and then with brine (1 × 50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford compound **2** as a white solid (1.034 g, quant., mp 124-125.7°C) which was used directly for the next step. IR (ATR, cm^{-1}): 1714-1699. ¹H NMR ($CDCl_3$) δ : 5.16 (t, ¹H, J=2.7 Hz, H-12 β); 2.93 (t, ¹H, J=9 Hz, H-17 α); 2.63 (dd, ¹H, J=13.5-15.3 Hz); 2.30-1.05 (m, 19H); 2.11 (s, 3H, CH₃, H-21); 2.00 (s, 3H, CH₃, Ac); 0.98 (3H, s, CH₃); 0.70 (3H, s, CH₃). ¹³C NMR ($CDCl_3$) δ : 212.6 (C=O, C-3); 208.6 (C=O, C-20); 170.3 (C=O, OAc); 74.3 (CH, C-12); 55.5 (CH); 49.5 (CH); 46.7 (C); 43.8 (CH); 42.1 (CH₂); 36.8 (CH₂); 36.5 (CH₂); 35.3 (CH); 34.7 (CH); 34.3 (C); 31.1 (CH₃); 26.3 (CH₂); 25.9 (CH₂); 25.7 (CH₂); 23.6 (CH₂); 22.3 (CH₂); 22.3 (CH₃); 21.3 (CH₃); 13.9 (CH₃). HRMS (ESI) m/z: C₂₃H₃₄NaO₄ [M+Na]⁺ calcd. 397.2349, found 397.2357. [α]_D²⁰: +146 (c 0.01, $CHCl_3$).

4 β -bromo,12 α -acetoxy-5H β -pregnan-3,20-dione (**3**)

To a solution of compound 2 (2.14 g, 5.71 mmol) in AcOH (60 mL), was added dropwise over 45 min a solution of Br₂ (0.29 mL, 5.65 mmol) in AcOH (25 mL). The solution was stirred for an additional 30 min and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 30 mL). The combined aqueous layers were extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with sat. NaHCO₃ (3 × 30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield compound 3 as a white solid (2.89 g, quant., mp 167.4-169.9°C) which was used directly for the next step. IR (ATR, cm⁻¹): 1726, 1698. ¹H NMR (CDCl₃) δ: 5.16 (t, ¹H, J=2.4 Hz, H-12β); 4.92 (d, ¹H, J=11.7 Hz, H-4α); 2.92 (t, ¹H, J=9.3 Hz, H-17α); 2.47 (dt, ¹H, J=3.9-14.4 Hz); 2.35-0.60 (17H, m); 2.11 (s, 3H, CH₃, H-21); 2.00 (s, 3H, CH₃, Ac); 0.88 (s, 3H, CH₃); 0.71 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 208.5 (C=O); 201.8 (C=O); 170.2 (C=O, OAc); 74.1 (CH, C-12); 59.5 (CH); 55.4 (CH); 53.9 (CH); 49.4 (CH); 46.6 (C); 37.6 (C); 36.3 (CH₂); 36.2 (CH₂); 35.8 (CH); 35.4 (CH); 31.1 (CH); 26.0 (CH₂); 25.4 (CH₂); 24.7 (CH₂); 23.6 (CH₂); 2.9 (CH₃); 2.2.4 (CH₂); 21.3 (CH₃); 13.9 (CH₃). HRMS (ESI) m/z: C₂₃H₃₃BrNaO₄ [M+Na]⁺ calcd. 477.1437, found 477.1445. [α]_D²⁰: +151 (c 0.01, CHCl₃).

12α-acetoxy-pregna-4-ene-3,20-dione (4)

To a solution of the crude compound 3 (2.60 g, 5.73 mmol) in DMF (65 mL), was added LiCl (1.20 g, 28.24 mmol). The reaction mixture was refluxed for 1 h and the medium was concentrated under reduced pressure. The orange residue was dissolved in AcOEt (50 mL) and washed with water (3 × 30 mL). The combined aqueous layers were extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine (1 × 30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (60 g silica gel, petroleum ether-ethyl acetate, 8:2) to afford compound 4 as a slightly yellow solid (1.43 g, 67%, mp 147.4-151°C). IR (ATR, cm⁻¹): 1729, 1700, 1665, 1618. ¹H NMR (CDCl₃) δ: 5.71 (s, ¹H, H-4); 5.15 (t, ¹H, J=2.7 Hz, H-12β); 2.91 (t, ¹H, J=9 Hz, H-17α); 2.40-0.60 (m, 17H); 2.16 (s, 3H, CH₃, H-21); 2.00 (s, 3H, CH₃, Ac); 1.14 (s, 3H, CH₃); 0.72 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 208.5 (C=O, C-20); 199.1 (C=O, C-3); 170.2 (C=C, C-5); 170.0 (C=O, OAc); 124.1 (CH, C-4); 74.3 (CH, C-12); 55.3 (CH, C-17); 48.7 (CH); 47.9 (CH); 46.4 (C); 38.0 (C); 35.7 (CH); 35.6 (CH₂); 33.8 (CH₂); 32.6 (CH₂); 31.6 (CH₂); 31.1 (CH₃); 25.6 (CH₂); 23.6 (CH₂); 22.2 (CH₂); 21.2 (CH₃); 17.1 (CH₃); 13.7 (CH₃). HRMS (ESI) m/z: C₂₃H₃₂NaO₄ [M+Na]⁺ calcd. 395.2193, found 395.2202. [α]_D²⁰: +217 (c 0.01, CHCl₃).

3,12α-diacetoxy-pregna-3,5-diene-20-one (5)

A solution of compound 4 (2.80 g, 3.73 mmol) in Ac₂O (18 mL) was treated with AcCl (30 mL) and heated under reflux for 1 h. After cooling to r.t., the reaction mixture was concentrated under reduced pressure without heating (25°C, 10-2 mbar). The orange material was purified by column chromatography (100 g silica gel, petroleum ether-ethyl acetate, 9:1), to afford compound 5 as a white solid (2.69 g, 85%, mp 134.7-137.5°C). IR (ATR, cm⁻¹): 1745, 1726, 1700, 1667. ¹H NMR (CDCl₃) δ: 5.69 (d, ¹H, J=1.8 Hz, H-4); 5.39 (d, ¹H, J=3.6 Hz, H-6); 5.18 (t, ¹H, J=3, H-12β); 2.94 (t, ¹H, J=8.7, H-17α); 2.50-1.45 (m, 1¹H); 2.13 (s, 3H, CH₃, H-21); 2.11 (s, 3H, CH₃, Ac); 2.03 (s, 3H, CH₃, Ac); 1.45-0.80 (m, 4H); 0.98 (s, 3H, CH₃); 0.74 (3H, s, Me). ¹³C NMR (CDCl₃) δ: 208.7 (C=O, C-20); 170.4 (C=O, OAc); 169.4 (C=O, OAc); 147.1 (C=C); 139.2 (C=C); 132.4 (CH, C=CH); 116.8 (CH, C=CH); 74.3 (CH, C-12); 55.4 (CH); 49.5 (CH); 46.5 (C); 42.4 (CH); 34.4 (CH₂); 33.7 (C); 31.5 (CH); 31.4 (CH₂); 31.1 (CH₃); 25.7 (CH₂); 24.6 (CH₂); 23.6 (CH₂); 22.9 (CH₂); 21.3 (CH₃); 21.1 (CH₃); 18.6 (CH₃); 13.8 (CH₃). HRMS (ESI)

m/z: C₂₅H₃₄NaO₅ [M+Na]⁺ calcd. 437.2298, found 437.2302. [α]_D²⁰: +2 (c 0.01, CHCl₃).

3,12α-diacetoxy, cyclic 20-(ethylene acetal)-pregna-3,5-diene (5a)

To a solution of compound 5 (635 mg, 1.53 mmol) in toluene (25 mL), were added ethylene glycol (1.10 mL, 20.03 mmol) and PPTS (catalytic amount). The reaction mixture was refluxed (Dean Stark trap) for 3.5 h. The solvent was evaporated under reduced pressure and the residue dissolved in CH₂Cl₂ (20 mL) was washed with water (2 × 20 mL). The combined aqueous layers were extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with sat. NaHCO₃ (1 × 20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (30 g silica gel, petroleum ether-ethyl acetate, 9:1) to afford compound 5a as a yellow solid (700 mg, quant., mp 68-69°C). IR (ATR, cm⁻¹): 1733-1680. ¹H NMR (CDCl₃) δ: 5.69 (s, ¹H, H-6); 5.40 (d, ¹H, J=3.0 Hz, H-4); 5.14 (t, ¹H, J=2.4 Hz, H-12β); 4.00-3.80 (m, 4H, OCH₂); 2.50-1.90 (m, 4H); 2.13 (s, 3H, CH₃, Ac); 2.04 (s, 3H, CH₃, Ac); 1.90-1.40 (m, 10H); 1.40-0.90 (m, 2H); 1.22 (s, 3H, CH₃, H-21); 0.99 (s, 3H, CH₃); 0.88 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 170.6 (C=O, OAc); 169.4 (C=O, OAc); 147.0 (C=C); 139.3 (C=C); 123.7 (C=CH); 116.7 (C=CH); 111.4 (C, C-2); 75.3 (CH, C-12); 64.9 (OCH₂); 63.3 (OCH₂); 49.7 (CH); 49.2 (CH); 44.3 (C, 13-C); 42.5 (CH); 34.4 (CH₂); 33.7 (10-C); 31.4 (CH₂); 31.0 (CH); 25.4 (CH₂); 24.7 (CH₂); 24.0 (CH); 23.1 (CH₂); 22.3 (CH₂); 21.4 (CH₃); 21.1 (CH₃); 18.6 (CH₃); 13.5 (CH₃). HRMS (ESI) m/z: C₂₇H₃₈NaO₆ [M+Na]⁺ calcd. 481.2561, found 481.2569. [α]_D²⁰: +61 (c 0.02, MeOH).

3β hydroxy, 12α-acetoxy, cyclic 20-(ethylene acetal) pregn-5-ene (5b)

To a suspension of NaBH₄ (860 mg, 22.7 mmol) in a mixture of MeOH (6 mL) and THF (6 mL), was added a solution of compound 5a (540 mg, 1.18 mmol) in THF (5 mL). The reaction mixture was stirred for 1.5 h at r.t. and treated with 10% HCl until neutral pH. CH₂Cl₂ (15 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phase were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (30 g silica gel, petroleum ether-ethyl acetate, 7:3), to afford compound 5b as a white solid (333 mg, 70%, mp 166-167°C). IR (ATR, cm⁻¹): 3446, 1699; ¹H NMR (CDCl₃) δ: 5.55 (s, ¹H, H-6); 5.11 (t, ¹H, J=2.7 Hz, H-12β); 4.24 (t, ¹H, J=2.4 Hz, H-3α); 4.00-3.70 (m, 4H, OCH₂); 2.28 (t, ¹H, J=9.9 Hz, H-17α); 2.10-1.90 (m, 3H); 2.04 (s, 3H, CH₃, Ac); 1.90-0.70 (m, 15H); 1.23 (s, 3H, CH₃, H-21); 1.20 (s, 3H, CH₃); 0.88 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 170.5 (C=O, OAc); 147.1 (C=C, C-5); 129.0 (C=CH, C-6); 111.4 (C, C-20); 75.2 (CH, C-3); 74.0 (CH, C-12); 67.8 (CH); 64.9 (OCH₂); 63.3 (OCH₂); 49.7 (CH); 48.5 (CH); 48.4 (C); 44.4 (CH₂); 38.6 (CH₂); 36.8 (C); 36.2 (CH₂); 29.6 (CH); 29.1 (CH₂); 25.2 (CH₂); 24.0 (CH₃); 23.0 (CH₂); 22.3 (CH₂); 21.4 (CH₃); 21.2 (CH₃); 13.5 (CH₃). HRMS (ESI) m/z: C₂₅H₃₀O₅ [M+H]⁺ calcd. 419.2680, found 419.2745. [α]_D²⁰: +58 (c 0.01, CHCl₃).

3β,12α-dihydroxy, cyclic 20-(ethylene acetal) pregn-5-ene (6)

A solution of compound 5b (330 mg, 1.15 mmol) in MeOH (15 mL) was treated with KOH (83 mg, 1.48 mmol) and refluxed for 1 h. After cooling to r.t., water (20 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford compound 6 as a white solid (266 mg, 85 %, mp 133.0-135.2°C)

which was used directly for the next step. IR (ATR, cm^{-1}): 3460, 1733. ^1H NMR (C_6D_6) δ : 5.34 (m, ^1H , H-6); 4.01 (t, ^1H , $J=3$ Hz, H-12 β); 3.55-3.25 (m, 5H, OCH_2 + H-3 α); 2.37 (t, ^1H , $J=9.96$ Hz, H-17 α); 2.30-2.20 (m, 3H); 2.05-0.80 (m, 16H); 1.021 (s, 3H, CH_3 , H-21); 0.92 (s, 3H, CH_3); 0.87 (s, 3H, CH_3). ^{13}C NMR (C_6D_6) δ : 140.6 (C=C, C-5); 121.6 (C=CH, C-6); 112.2 (C, C-20); 72.7 (CH, C-12); 71.7 (CH, C-3); 64.0 (OCH_2); 63.7 (OCH_2); 49.7 (CH); 48.0 (CH); 45.8 (C); 44.2 (CH); 42.3 (CH_2); 37.0 (CH_2); 36.1 (C); 31.6 (CH); 31.3 (CH_2); 31.2 (CH_2); 27.6 (CH_2); 23.8 (CH_3); 23.1 (CH_2); 22.9 (CH_2); 19.2 (CH_3); 13.9 (CH_3). HRMS (ESI) m/z : $\text{C}_{23}\text{H}_{36}\text{NaO}_4$ [M+Na] $^+$ calcd. 399.2506, found 399.2518, $[\alpha]_{20\text{D}}$: -25 (c 0.0075, CHCl_3).

3 β -acetoxy,12 α -hydroxy, cyclic 20-(ethylene acetal) pregn-5-ene (7)

To a solution of compound 6 (564 mg, 1.51 mmol) in CH_2Cl_2 (25 mL), were added Ac_2O (0.17 mL, 1.81 mmol), pyridine (0.24 mL, 3.02 mmol) and DMAP (catalytic amount). The reaction mixture was stirred at r.t. for 3 h and treated with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 20 mL). The combined organic layers were washed with 10% HCl (1 \times 20 mL), with sat. NaHCO_3 (1 \times 20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (30 g silica gel, petroleum ether-ethyl acetate, 9:1) to afford compound 7 as a white solid (505 mg, 80%, mp 158.8-160.6 $^\circ\text{C}$). IR (ATR, cm^{-1}): 3417, 1733. ^1H NMR (C_6D_6) δ : 5.40-5.33 (m, ^1H , H-6); 4.81 (tt, ^1H , $J=4.8$ -11.3 Hz, H-3 α); 4.01 (t, ^1H , $J=2.4$ Hz, H-12 β); 3.48 (s, 4H, OCH_2); 2.60-2.30 (m, 3H); 2.00-0.80 (m, 16H); 1.75 (s, 3H, CH_3 , Ac); 1.22 (s, 3H, CH_3 , H-21); 0.89 (s, 3H, CH_3); 0.86 (s, 3H, CH_3). ^{13}C NMR (C_6D_6) δ : 169.3 (C=O, OAc); 139.5 (C=C, C-5); 122.5 (C=CH, C-6); 111.9 (C, C-20); 73.6 (CH, C-12); 72.2 (CH, C-3); 64.0 (OCH_2); 63.2 (OCH_2); 49.6 (CH); 47.8 (CH); 45.8 (C, 13-C); 43.9 (CH); 38.3 (CH_2); 36.7 (CH_2); 36.1 (C, 10-C); 31.5 (CH_2); 31.2 (CH); 27.8 (CH_2); 23.6 (CH_3); 23.1 (CH_2); 22.7 (CH_2); 20.7 (CH_3); 18.8 (CH_3); 13.8 (CH_3). HRMS (ESI) m/z : $\text{C}_{25}\text{H}_{38}\text{NaO}_5$ [M+Na] $^+$ calcd. 441.2611, found 441.2608, $[\alpha]_{20\text{D}}$: -31 (c 0.006, CHCl_3).

3 β -acetoxy,12-keto, cyclic 20-(ethylene acetal) pregn-5-ene (8)

To a solution of compound 7 (143 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) at 0°C , was added the Dess Martin reagent (174 mg, 0.41 mmol). The reaction mixture was stirred for 1 h at r.t., then was treated with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (8 mL) and the reaction mixture was stirred for 5 min. To the medium was added sat. NaHCO_3 (8 mL) and the reaction mixture was stirred for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (5 g silica gel, cyclohexane-ethyl acetate, 7:3) to afford compound 8 as a white solid (140 mg, 99 %, mp 150-151 $^\circ\text{C}$). IR (ATR, cm^{-1}): 1722, 1700. ^1H NMR (CDCl_3) δ : 5.40 (m, ^1H , H-6); 4.58 (tt, ^1H , $J=4.6$ -1.4 Hz, H-3 α); 4.05-3.65 (m, 4H, OCH_2); 2.80-2.55 (m, 2H); 2.45-1.95 (m, 4H); 2.3 (s, 3H, CH_3 , Ac); 1.95-1.10 (m, 12H); 1.25 (s, 3H, CH_3 , H-21); 1.15 (s, 3H, CH_3); 1.12 (s, 3H, CH_3). ^{13}C NMR (CDCl_3) δ : 214.0 (C=O, C-12); 170.4 (C=O, OAc); 139.4 (C=C, C-5); 122.3 (C=CH, C-6); 111.2 (C, C-20); 73.5 (CH, C-3); 65.5 (OCH_2); 62.9 (OCH_2); 58.3 (CH); 56.6 (C, C-13); 53.6 (CH); 49.1 (CH); 37.9 (CH_2); 37.7 (CH_2); 37.5 (C, C-10); 36.7 (CH_2); 31.4 (CH); 31.3 (CH_2); 27.5 (CH_2); 4.4 (CH_3); 24.0 (CH_2); 22.0 (CH_2); 21.4 (CH_3); 18.9 (CH_3); 12.9 (CH_3). HRMS (ESI) m/z : $\text{C}_{25}\text{H}_{36}\text{NaO}_5$ [M+Na] $^+$ calcd. 439.2455, found 439.2496, $[\alpha]_{20\text{D}}$: +12 (c 0.01, CHCl_3).

Synthesis of compounds 10, 11 and 12

A solution of compound 8 (895 mg, 2.15 mmol) in CH_2Cl_2 (280 mL) was degassed with argon for 15 min and then was irradiated with a high pressure mercury lamp Philips HPK 125 for 15 min in a quartz vessel. The solvent was then evaporated under reduced pressure, to afford the crude seco aldehyde 9 (931 mg, 100%).

To a solution of crude seco aldehyde (931 mg, max. 2.15 mmol) in THF (4.0 mL), was added a solution of $\text{AcOH}/\text{H}_2\text{O}/\text{CF}_3\text{COOH}$ (2/1/0.6, 20.0 mL). The reaction mixture was stirred 1.5 h at r. t.. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (2 \times 30 mL), with sat. NaHCO_3 (3 \times 30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (30 g, silica gel, petroleum ether-ethyl acetate, 8:2 to 6:4) affording compound 10 (153 mg, 19%, mp 192-194 $^\circ\text{C}$), compound 11 (118 mg, 15%, mp 116-117 $^\circ\text{C}$) and compound 12 (210 mg, 25%, mp 140-142 $^\circ\text{C}$).

3 β -acetoxy, pregn-5-ene-12,20-dione (10)

IR (ATR, cm^{-1}): 1729, 1703. ^1H NMR (CDCl_3): 5.42-5.40 (m, ^1H , H-6); 4.59 (tt, ^1H , $J=4.6$ -11.4 Hz, H-3 α); 3.34 (t, ^1H , $J=9.6$ Hz, H-17 α); 2.62 (t, ^1H , $J=13.2$ Hz, H-11); 2.50-2.00 (m, 4H); 2.26 (s, 3H, CH_3 , H-21); 2.03 (s, 3H, CH_3 , Ac); 2.00-0.80 (m, 12H); 1.12 (s, 3H, CH_3); 0.98 (s, 3H, CH_3). ^{13}C NMR (CDCl_3): 213.0 (C=O); 209.4 (C=O); 170.2 (C=O, OAc); 139.2 (C=C, C-5); 121.9 (C=CH, C-6); 73.1 (CH, C-3); 57.6 (C, C-13); 57.4 (CH); 54.0 (CH); 52.7 (CH); 52.7 (CH); 37.6 (CH_2); 37.4 (CH_2); 37.2 (C, C-10); 36.4 (CH_2); 31.1 (2CH + CH_2); 27.3 (CH_2); 24.0 (CH_2); 22.4 (CH_2); 21.2 (CH_3); 18.7 (CH_3); 13.2 (CH_3). $[\alpha]_{20\text{D}}$: +55 (c 0.009, CHCl_3).

3 β -acetoxy,12 α -hydroxy-12,14 α -cyclo-12,13-secopregna-5,13(17)-diene-20-one (11)

IR (ATR, cm^{-1}): 3430, 1729, 1666, 1608. ^1H NMR (CDCl_3): 5.36 (d, ^1H , $J=4.8$ Hz, H-6); 4.58 (tt, ^1H , $J=4.8$ -11.4 Hz, H-3 α); 4.14 (dt, ^1H , $J=8.2$ -9.7 Hz, H-12 β); 2.80-0.80 (m, 17H); 2.22 (s, 3H, CH_3 , H-21); 2.02 (s, 3H, CH_3 , Ac); 1.96 (t, 3H, $J=2.1$ Hz, CH_3 , H-18); 1.04 (s, 3H, CH_3 , H-19). ^{13}C NMR (CDCl_3): 198.7 (C=O, C-20); 170.5 (C=O, OAc); 153.7 (C=C); 140.5 (C=C); 137.9 (C=C); 122.6 (C=CH); 76.5 (CH, C-12); 73.7 (CH, C-3); 65.7 (C, C-14); 48.3 (CH); 39.9 (CH); 37.9 (CH_2); 37.7 (CH_2); 37.2 (C, C-10); 32.4 (CH_2); 30.5 (CH); 30.3 (CH_2); 27.4 (CH_2); 25.9 (CH_2); 21.8 (CH_2); 21.4 (CH_3); 18.0 (CH_3); 12.1 (CH_3). $[\alpha]_{20\text{D}}$: -12 (c 0.006, CHCl_3).

3 β -acetoxy,12 β ,14 β -dihydroxy pregn-5-ene-20-one (12)

IR (ATR, cm^{-1}): 3399, 1730, 1686; ^1H NMR (CDCl_3) δ : 5.42 (m, ^1H , H-6); 4.65-4.50 (m, ^1H , H-3 α); 4.37 (s, ^1H OH); 3.61 (t, ^1H , $J=6.3$ Hz, H-17 α); 3.35 (dd, ^1H , $J=4.2$ -11.7 Hz, H-12 α); 2.40-2.15 (m, 3H); 2.27 (s, 3H, CH_3 , H-21); 2.10-0.80 (m, 16H); 2.03 (s, 3H, CH_3 , Ac); 1.01 (s, 3H, CH_3 , H-18); 0.92 (s, 3H, CH_3 , H-19). ^{13}C NMR (CDCl_3) δ : ^{13}C NMR (CDCl_3): 218.0 (C=O, C-20); 170.6 (C=O, OAc); 137.8 (C=C, C-5); 123.1 (C=CH, C-6); 85.5 (C, C-14); 73.6 (CH, C-12); 73.4 (CH, C-3); 56.9 (CH, C-17); 55.0 (C, C-13); 43.3 (CH, C-9); 37.8 (CH_2 , C-1); 37.0 (CH_2 , C-4); 36.8 (C, C-10); 35.6 (CH_3 , C-21); 34.5 (CH_2 , C-15); 33.1 (CH, C-8); 29.9 (CH_2 , C-11); 27.6 (CH_2 , C-2); 27. (CH_2 , C-7); 24.4 (CH_2 , C-16); 21.4 (CH_3 , Ac); 19.3 (CH_3 , C-19); 8.3 (CH_3 , C-18). HRMS (ESI) m/z : $\text{C}_{23}\text{H}_{34}\text{NaO}_5$ [M+Na] $^+$ calcd. 413.2298, found 413.2308, $[\alpha]_{20\text{D}}$: +14 (c 0.01, CHCl_3).

12-O- β -tigloyl-3 β -acetoxy, 14 β -hydroxy-pregn-5-ene-20-one (13)

To a solution of compound 12 (40 mg, 0.10 mmol) in CH_2Cl_2 (5 mL), were added tigloyl chloride (0.12 mL, 1.09 mmol), pyridine (0.14 mL, 1.74 mmol) and DMAP (catalytic amount). The reaction mixture was heated under reflux for 7 h and stirred for 15 h at r.t. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 10% HCl (1 × 10 mL), with sat. NaHCO_3 (1 × 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (5 g silica gel, cyclohexane-ethyl acetate, (95:5) to afford compound 13 as a white solid (38 mg, 80%, mp 70-72°C). IR (ATR, cm^{-1}): 3434, 1730, 1696, 1650; ^1H NMR (CDCl_3) δ : 6.93 (dq, ^1H , J=1.5-7.2 Hz, H-tig); 5.44 (m, ^1H , H-6); 4.65 (dd, ^1H , J=4.5-11.7 Hz, H-12 α); 4.65-4.55 (m, ^1H , H-3 α); 4.29 (s, ^1H , OH); 3.15 (m, ^1H , H-17 α); 2.50-2.05 (m, 3H); 2.21 (s, 3H, CH_3 , H-21); 2.05-0.90 (m, 13H); 2.03 (s, 3H, CH_3 , Ac); 1.89 (s, 3H, CH_3 , H-tig); 1.84 (dd, 3H, CH_3 , J=0.9-6.3 Hz, H-tig); 1.07 (s, 3H, CH_3 , H-18); 1.02 (s, 3H, CH_3 , H-19). ^{13}C NMR (CDCl_3) δ : 217.0 (C=O, C-20); 170.5 (C=O, OAc); 167.7 (C=O, C-tig); 137.8 (C=CH, C-tig); 123.0 (C=CH, C-6); 85.7 (C, C-14); 75.9 (CH, C-3); 73.9 (CH, C-12); 57.2 (CH, C-17); 53.7 (C, C-13); 42.9 (CH, C-9); 37.8 (CH_2 , C-1); 36.9 (CH_2 , C-4); 36.9 (C, C-10); 35.6 (CH_3 , C-21); 34.4 (CH_2 , C-15); 33.2 (CH, C-8); 27.6 (CH_2 , C-2); 27.3 (CH_2 , C-7); 26.0 (CH_2 , C-11); 24.4 (CH_2 , C-16); 21.4 (CH_3 , Ac); 19.3 (CH_3 , C-19); 14.5 (CH_3 , C-tig); 12.2 (CH_3 , C-tig); 9.9 (CH_3 , C-18). HRMS (ESI) m/z: $\text{C}_{28}\text{H}_{40}\text{NaO}_6$ [M+Na] $^+$ calcd. 495.2717, found 495.2693, $[\alpha]_{20\text{D}}$: +5 (c 0.01, CHCl_3).

12-O- β -tigloyl-3 β ,14 β -dihydroxy-pregn-5-ene-20-one (Hoodigogenin A)

A solution of compound 13 (42 mg, 0.09 mmol) in MeOH (5 mL) was treated with K_2CO_3 (33 mg, 0.24 mmol). The reaction mixture was stirred for 2 h at r.t. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5 g silica gel, cyclohexane-ethyl acetate, 6:4) to afford Hoodigogenin A as a white solid (26 mg, 69%, mp 151-153°C). IR (ATR, cm^{-1}) 3535, 3471 1698, 1682, 1651 ^1H NMR (CDCl_3) δ : 6.91 (dq, ^1H , J=1.6-7.2 Hz, H-tig); 5.40 (m, ^1H , H-6); 4.63 (dd, ^1H , J=4.4-12.0 Hz, H-12 α); 4.26 (s, ^1H , OH); 3.51 (tt, ^1H , J=4.6-11.2 Hz, H-3 α); 3.12 (m, ^1H , H-17 α); 2.40-2.15 (m, 3H); 2.10 (s, 3H, CH_3 , H-21); 2.10-0.90 (m, 14H); 1.88 (s, 3H, CH_3 , H-tig); 1.83 (dd, 3H, CH_3 , J=0.8-6.8 Hz, H-tig); 1.06 (s, 3H, CH_3 , H-18); 0.99 (s, 3H, CH_3 , H-19). ^{13}C NMR (CDCl_3) δ : 217.1 (C=O, C-20); 167.7 (C=O, C-tig); 139.0 (C=C, C-5); 137.8 (C=C, C-tig); 128.7 (C=CH, C-tig); 122.0 (C=CH, C-6); 85.7 (C, C-14); 75.9 (CH, C-3); 71.5 (CH, C-12); 57.2 (CH, C-17); 53.8 (C, C-13); 43.1 (CH, C-9); 42.0 (CH_2 , C-4); 37.2 (CH_2 , C-1); 36.9 (C, C-10); 35.8 (CH, C-8); 34.5 (CH_2 , C-15); 33.2 (CH_3 , C-21); 31.4 (CH_2 , C-2); 27.4 (CH_2 , C-7); 26.1 (CH_2 , C-11); 24.4 (CH_2 , C-16); 19.4 (CH_3 , C-19); 14.5 (CH_3 , C-tig); 12.2 (CH_3 , C-tig); 9.9 (CH_3 , C-18). HRMS (ESI) m/z: $\text{C}_{26}\text{H}_{38}\text{NaO}_5$ [M+Na] $^+$ calcd. 453.2611, found 453.2576, $[\alpha]_{20\text{D}}$: +1.13 (c 0.006, CHCl_3).

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