Supporting Information
for
C–H-Functionalization logic guides the synthesis of a carbacyclo pa mine analog
Sebastian Rabe¹, Johann Moschner¹, Marina Bantzi¹, Philipp Heretsch*² and Athanassios Giannis*¹

Address: ¹Universität Leipzig, Institut für Organische Chemie, Johannisallee 29, D-04103 Leipzig, Germany and ²Rice University, Department of Chemistry, BioScience Research Collaborative, 6100 Main St., Houston, Texas 77005, United States

*Corresponding author
Email: Philipp Heretsch - heretsch@rice.edu; Athanassios Giannis - giannis@uni-leipzig.de

Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra for new compounds

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1. General Information

General procedures. All reactions were run under an atmosphere of argon unless otherwise indicated. Room temperature refers to 22 °C, ambient pressure to 1013 hPa. Reagents and anhydrous solvents were transferred via oven-dried syringes and cannulae. Flasks were flame-dried under vacuum and cooled under a constant stream of argon. Tetrahydrofuran was distilled from potassium under argon, dichloromethane from SICAPENT (phosphorus pentoxide on solid support with indicator), ethanol from magnesium ethoxide and triethylamine from calcium hydride. Methanol, toluene, acetone, dimethylformamide,
acetonitrile and pyridine were purchased from Acros or Sigma-Aldrich (anhydrous over molecular sieves).
All other chemicals were purchased from ABCR, Acros, Sigma-Aldrich, Alfa Aesar, Fluorochem, Merck and TCI Europe at the highest commercially available purity and used as such.
Reactions were monitored by thin-layer chromatography using Merck silica gel 60 F254 TLC aluminium sheets and visualized with ceric ammonium molybdate, potassium permanganate or vanillin staining solution. Chromatographic purification was performed as flash chromatography on Merck silica gel 40–63 μm, 60 Å, using a forced flow of eluent (method of Still). Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure.
Yields refer to chromatographically purified and spectroscopically pure compounds.
NMR spectra were recorded on a Bruker Avance 700 (operating at 700 MHz for 1H and 176 MHz for 13C), Varian Mercury plus 400 (operating at 400 MHz for 1H and 100 MHz for 13C) and a Varian Mercury plus 300 (operating at 300 MHz for 1H and 75 MHz for 13C acquisitions). Chemical shifts δ are reported in ppm with the solvent resonance as the internal standard (d1-chloroform: 7.26 (1H-NMR), 77.16 (13C-NMR); d6-benzene: 7.16 (1H-NMR), 128.06 (13C-NMR); d4-methanol: 3.31 (1H-NMR), 49.00 (13C-NMR). Coupling constants J are reported in Hertz (Hz). Multiplicities are classified by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, and combinations thereof, or m = multiplet, or br = broad signal.
Where 2D-spectra were recorded and allowed complete assignment of all hydrogen and carbon-atoms of a compound, spectral data include this assignment using common steroid numbering. Where this is not the case, all hydrogen signals below 2 ppm are omitted and only methyl groups and isolated signals in this range are listed. All spectra can be found as copies at the end of the experimental section.
High resolution mass spectra were obtained on a Bruker Daltonics ESI-FT-ICR-MS APEX II. IR spectra were obtained on an ATI/MATTSON Genesis FT-IR and JASCO FT/IR-4100typeA as thin film (in CCl4) or KBr disk. Absorbance frequencies are reported in reciprocal centimeters (cm⁻¹).
Melting points were measured on a Boetius-micro hot stage and are uncorrected.
Optical rotations were obtained on a Schmidt+Haensch Polartronic MHZ-8 at the sodium-D line (589 nm) using a 50 mm path-length cell and solvent and concentration as indicated.
2. Synthetic Route
3. Experimental Procedures

3.1 3β-O-Tetrahydropyranyl-5-androstene-17-one (15):
To a solution of dehydroepiandrosterone (5) (80.0 g, 277.0 mmol, 1.0 equiv.) in CH₂Cl₂ (1.1 L) at room temperature was sequentially added 3,4-dihydro-2H-pyran (55.0 mL, 604.0 mmol, 2.7 equiv.) and pyridinium para-toluensulfonate (3.48 g, 13.9 mmol, 0.05 equiv.). After stirring for 2.5 h the mixture was quenched with water (400 mL). The phases were separated, the aqueous layer was extracted with CH₂Cl₂ (2 x 300 mL) and the combined organic phases were dried (MgSO₄). All volatiles were removed under reduced pressure to give crude title compound (84.5 g, 227.0 mmol, quant.; mixture of diastereoisomers) as a colorless solid which was used in the next step without further purification.

15: mp.: 166-169 °C; Rf: 0.33 (n-hexane/EtOAc, 5:1); IR (KBr): νmax 2940, 1731, 1112, 1057, 1028, 975 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 5.37 (m, 1 H), 4.71 (m, 1 H), 3.90 (m, 1 H), 3.52 (m, 1 H), 3.49 (m, 1 H), 2.45 (m, 1 H), 2.37 (m, 1 H), 1.03 (s, 3 H), 0.87 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 221.1, 170.6, 140.1, 122.0, 73.9, 51.8, 50.3, 47.7, 38.2, 37.1, 36.9, 35.9, 31.6, 31.5, 30.9, 27.8, 22.0, 21.6, 20.5, 19.5, 13.7; HRMS (m/z): [M+Na]⁺ calculated for C₃₀H₅₆O₃Na: 395.25567, found: 395.25532; calculated for C₄₈H₇₂O₆Na: 767.52211, found: 767.52123.

3.2 17-(N-2-Pyridylmethyl)imino-3β-O-tetrahydropyranyl-androst-5-ene (16):
To a solution of 15 (26.3 g, 70.7 mmol, 1.0 equiv.) in toluene (600 mL) was sequentially added para-toluensulfonic acid monohydrate (336 mg, 1.80 mmol, 0.025 equiv.) and 2-picolylamine (38.2 g, 353.5 mmol, 5.0 equiv.). The mixture was heated to 110 °C for 3.5 h with a Dean-Stark trap and then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (950 mL) and washed sequentially with saturated aqueous NaHCO₃-solution (2 x 500 mL) and saturated brine (500 mL). The combined organic phases were dried (Na₂SO₄), the crude was concentrated under reduced pressure and the residue was recrystallized from a mixture of boiling EtOAc:Et₂O (2:1, 620 mL) to give pure title compound (30.1 g, 65.1 mmol, 92%, mixture of diastereoisomers) as colorless needles.

16: mp.: 158-160 °C; IR (KBr): νmax 2944, 2849, 1672, 1591, 1438, 1136, 1074, 1031, 765 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 8.52 (m, 1 H), 7.65 (m, 1 H), 7.42 (m, 1 H), 7.12 (m, 1 H) 5.37 (m, 1 H), 4.72 (m, 1 H), 4.63 (d, J = 16.5 Hz, 1 H), 4.55 (d, J = 16.5 Hz, 1 H), 3.91 (m, 1 H)
3.3 (-)-3β,12β-Dihydroxyandrost-5-ene-17-one (6):
To a suspension of imine 16 (30.8 g, 66.7 mmol, 1.0 equiv.) in acetone (600 mL) was added copper(I) tetra(acetonitrilo) hexafluorophosphat (29.8 g, 80.1 mmol, 1.2 equiv.) in one portion. The brownish suspension was stirred for 1 h after which dry oxygen was bubbled through the suspension for 30 min and the resulting dark-green solution was stirred under an atmosphere of oxygen for 24 h. The solvent was removed under reduced pressure, the resulting green solid was taken up in EtOAc/Et₂O/NH₃ (aq, 25%) (2.0 L, 1:2:1), the layers were separated and the organic layer was washed with aqueous ammonia (25%, 2 x 300 mL) and saturated brine (150 mL), dried (Na₂SO₄) and the solvents were removed under reduced pressure. The residue was redissolved in MeOH/AcOH (600 mL, 1:1) and heated to 90°C for 6 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (1.3 L) and saturated brine (200 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (SiO₂; n-hexane/EtOAc, 1:2, ν/ν) to give pure title compound (9.36 g, 30.7 mmol, 46%) as a yellowish solid.

6: mp.: 190-194 °C; Rₒ: 0.38 (n-hexane/EtOAc, 1:2); [α]D⁰₂₂: −22.3 (deg cm³ g⁻¹ dm⁻¹, c = 0.99, CHCl₃); IR (KBr): νmax 3429, 2931, 1730, 1466, 1437, 1383, 1047, 846 cm⁻¹; ¹H-NMR (400 MHz, MeOH-d₄) δ 5.39 (m, 1 H), 3.74 (dd, J = 11.2, 4.8 Hz, 1 H), 3.40 (m, 1 H), 2.44 (m, 1 H), 1.06 (s, 3 H), 0.94 (s, 3 H); ¹³C-NMR (100 MHz, MeOH-d₄) δ 223.0, 142.3, 121.9, 73.1, 72.2, 52.8, 51.0, 50.6, 42.9, 38.4, 37.8, 36.5, 32.2, 31.7, 31.4, 30.4, 22.4, 19.8, 8.4; HRMS (m/z): [M+Na]⁺ calculated for C₃₆H₅₆O₃Na: 327.19307, found: 327.19359; [2M+Na]⁺ calculated for C₆₈H₆₆O₆Na: 631.39691, found: 631.39730.

3.4 (-)-3β,12β-bis(Triethylsilyloxy)-androst-5-ene-17-one (17):
To a solution of diol 6 (6.00 g, 19.7 mmol, 1.0 equiv.) and 2,6-lutidine (9.2 mL, 78.8 mmol, 4.0 equiv.) in CH₂Cl₂ (800 mL) at 0 °C was added dropwise triethylsilyl trifluoromethanesulfonate (9.8 mL, 43.4 mmol, 2.2 equiv.) over a period of 45 min. After 3 h at the same temperature another portion of triethylsilyl trifluoromethanesulfonate (2.3 mL, 10.0
mmol, 0.5 equiv.) was added and the mixture was stirred for an additional 1 h. The reaction was then quenched with saturated aqueous NaHCO₃-solution (200 mL), the phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 200 mL). The combined organic phases were dried (MgSO₄), all volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 20:1, v/v) to give pure title compound (8.30 g, 15.6 mmol, 79%) as a colorless oil.

17: Rᵣ: 0.63 (n-hexane/EtOAc, 10:1); [α]D²²: −17.3 (deg cm³ g⁻¹ dm⁻¹, c = 1.05, CHCl₃); IR (KBr): v max 2953, 2875, 1744, 1459, 1093, 1012, 825, 741 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.34 (m, 1 H), 3.72 (dd, J = 10.8, 4.9 Hz, 1 H), 3.47 (m, 1 H), 2.41 (m, 1 H), 1.02 (s, 3 H), 0.96 (s, 3 H); ¹³C-NMR (75 MHz, CDCl₃) δ 218.2, 141.8, 120.6, 72.3, 72.2, 52.0, 50.4, 49.4, 42.9, 37.5, 36.8, 35.8, 32.2, 31.7, 30.6, 30.5, 21.2, 19.5, 8.4, 7.2, 7.0, 6.9, 6.6, 5.7, 5.4, 5.0; HRMS (m/z): [M+Na]⁺ calculated for C₃₁H₅₆O₃Si₂Na: 555.36602, found: 555.36555; [2M+Na]⁺ calculated for C₆₂H₁₁₂O₆Si₄Na: 1087.74282, found: 1087.74281.

3.5 (-)-3β-Hydroxy-12β-(triethysilyloxy)androst-5-ene-17-one (7):
To a solution of HF•pyridine complex (70% HF, 30% pyridine, 3.6 mL) in pyridine (22 mL) and THF (110 mL) at 0 °C was added dropwise a solution of bis-silylether 17 (8.62 g; 16.2 mmol, 1.0 equiv.) in THF (20 mL). After 2 h at the same temperature the reaction mixture was diluted with Et₂O (400 mL) and neutralized with saturated NaHCO₃-solution (200 mL). The phases were separated and the aqueous layer was extracted with Et₂O (3 x 300 mL). The combined organic layers were dried (MgSO₄), all volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 3:1, v/v) to give pure title compound (5.64 g, 13.8 mmol, 85%) as a colorless foam.

7: Rᵣ: 0.30 (n-hexane/EtOAc, 3:1); [α]D²²: −40.9 (deg cm³ g⁻¹ dm⁻¹, c = 0.63, CHCl₃); IR (KBr): v max 3435, 2955, 2875, 1742, 1458, 1240, 1102, 1054, 825, 742 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 5.36 (m, 1 H), 3.72 (dd, J = 10.8, 4.9 Hz, 1 H), 3.51 (m, 1 H), 2.41 (m, 1 H), 2.31 (m, 1 H), 2.23 (m, 1 H), 1.02 (s, 3 H), 0.96 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 218.3, 141.0, 121.0, 72.1, 71.7, 51.9, 50.4, 49.2, 42.3, 37.3, 36.7, 35.8, 31.7, 31.7, 30.6, 30.5, 21.2, 19.5, 8.4, 7.1, 5.3; HRMS (m/z): [M+Na]⁺ calculated for C₂₅H₄₂O₃Si₂Na: 441.27954, found: 441.27933; [2M+Na]⁺ calculated for C₅₀H₆₀O₅Si₂Na: 859.56986, found: 859.56940.
3.6 (−)-3β-Tosyloxy-12β-(triethylsilyloxy)androst-5-ene-17-one (18):
To a solution of the alcohol 7 (5.70 g, 13.6 mmol, 1.0 equiv.) in pyridine (50 mL) at 0 °C was added para-toluenesulfonyl chloride (6.40 g, 34.0 mmol, 2.5 equiv.) and the reaction mixture was stirred for 16 h at room temperature. The mixture was then cooled to 0 °C and quenched with water (25 mL). The reaction mixture was extracted with EtOAc (3 x 60 mL), the combined organic layers were washed with saturated brine (50 mL) and dried (MgSO₄). All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 10:1, v/v) to give pure title compound (7.32 g, 12.8 mmol, 94%) as a colorless foam.

18: Rₜ: 0.20 (n-hexane/EtOAc, 10:1); [α]D₂²²: −29.3 (deg cm⁻¹ g⁻¹ dm⁻¹, c = 0.90, CHCl₃); IR (KBr): νmax 2953, 1741, 1364, 1176, 1095, 940, 865, 739 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 5.34 (m, 1 H), 4.32 (m, 1 H), 3.70 (dd, J = 10.8, 4.8 Hz, 1 H), 2.44 (s, 3 H), 2.36 (m, 3 H), 0.95 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 218.0, 144.6, 139.1, 134.8, 129.9, 127.8, 122.9, 82.0, 72.0, 51.9, 50.2, 49.0, 38.9, 36.9, 36.5, 35.7, 31.6, 30.5, 30.4, 28.6, 21.8, 21.1, 19.2, 8.4, 7.1, 5.3; HRMS (m/z): [M+Na]⁺ calculated for C₃₂H₄₉O₃SiNa: 595.28839, found: 595.28787; [2M+Na]⁺ calculated for C₆₄H₉₀O₁₀Si₂Na: 1167.58765, found: 1167.58798.

3.7 (+)-3β,5-Cyclo-5β-6β-methoxy-12β-triethylsilyloxy-androstane-17-one (8):
A flask containing potassium acetate (8.50 g, 86.8 mmol, 7.0 equiv.) was dried under vacuum (0.7 mbar) at 120 °C for 24 h. It was allowed to cool to room temperature and a solution of tosylate 18 (7.10 g, 12.4 mmol, 1.0 equiv.) in MeOH (230 mL) was added. The reaction mixture was heated to 64 °C for 1.5 h. The mixture was allowed to cool to room temperature, water (100 mL) was added and the mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with saturated brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 20:1, v/v) to give pure title compound (7.83 g, 12.8 mmol, 90%) as a colorless foam.

8: Rₜ: 0.28 (n-hexane/EtOAc, 10:1), [α]D₂²²: +54.4 (deg cm⁻¹ g⁻¹ dm⁻¹, c = 1.60, CHCl₃); IR (KBr): νmax 2953, 2874, 1743, 1457, 1092, 1016, 853, 741 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 3.77 (dd, J = 11.2, 4.8 Hz, 1 H), 3.34 (s, 3 H) 2.81 (m, 1 H) 2.41 (m, 1 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.48 (dd, J = 7.9, 5.3 Hz, 1 H); ¹³C-NMR (75 MHz, CDCl₃) δ 218.3, 82.0, 72.6, 56.8, 52.5, 50.1, 46.6, 43.5, 35.8, 35.0, 33.9, 33.5, 33.1, 29.4, 25.0, 21.3, 21.0, 19.3, 13.3, 8.7, 7.1, 5.3; HRMS (m/z): [M+Na]⁺ calculated for C₃₂H₄₉O₃SiNa: 455.29519, found: 455.29541; [2M+Na]⁺ calculated for C₆₄H₉₀O₁₀Si₂Na: 887.60116, found: 887.60202.
3.8 (+)-3β,5-Cyclo-5β-6β-methoxy-12β-triethylsilyloxy-17-trifluoromethane-sulfonyl oxyandrost-16-ene (19):

To a solution of i-steroid 8 (10.30 g, 23.9 mmol, 1.0 equiv.) in THF (250 mL) at −20 °C was added potassium hexamethyldisilazide (0.5 M in toluene, 134.0 mL, 67.0 mmol, 2.8 equiv.) and the reaction mixture was stirred for 1 h. The cooling bath was removed and the mixture was stirred for 15 min while warming to room temperature. Afterwards, the reaction mixture was cooled to −10 °C and a solution of N-phenyl-bis-(trifluoromethane sulfonimide) (14.50 g, 40.6 mmol, 1.7 equiv.) in THF (50 mL) was added dropwise. The reaction mixture was stirred for 20 min at −10 °C at which time it was partitioned between water (50 mL) and EtOAc (250 mL). The aqueous layer was separated and extracted with EtOAc (3 x 300 mL), the combined organic layers were washed with saturated brine (250 mL), dried (MgSO₄) and all volatiles were removed under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 30:1, v/v) to give pure title compound (11.50 g, 20.3 mmol, 85%) as a colorless solid.

19: mp.: 125-128 °C; Rf: 0.48 (n-hexane/EtOAc, 10:1); [α]D⁺²²: +21.7 (deg cm³ g⁻¹ dm⁻¹, c = 0.90, CHCl₃); IR (KBr): νmax 2956, 1626, 1423, 1212, 1144, 1090, 894, 816, 733 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 5.34 (m, 1 H), 3.85 (m, 1 H), 3.13 (s, 3 H), 2.49 (m, 1 H), 1.88 (m, 1 H), 0.52 (m, 1 H), 0.33 (dd, J = 8.0, 5.2 Hz, 1 H); ¹³C-NMR (75 MHz, CDCl₃) δ 159.6, 115.0, 82.0, 75.1, 56.7, 51.8, 50.8, 47.4, 43.8, 35.4, 34.1, 33.5, 32.9, 27.9, 27.8, 25.1, 21.3, 19.3, 13.4, 11.3, 7.3, 6.0; ¹⁹F-NMR (376 MHz, CDCl₃) δ −73.8; HRMS (m/z): [M+Na]⁺ calculated for C₃₇H₄₃F₅O₅SiNa: 587.2448, found: 587.24411.

3.9 (−)-Methyl 3β,5-cyclo-5β-6β-methoxy-12β-triethylsilyloxypregna-16,20-diene-21-carboxylate (4):

To a stirred solution of enoltriflate 19 (3.70 g, 6.56 mmol, 1.0 equiv.) in DMF (75 mL) at room temperature was added triethylamine (2.8 mL, 19.7 mmol, 3.0 equiv.), methyl acrylate (1.50 mL, 16.4 mmol, 2.5 equiv.), triphenylphosphine (172 mg, 0.66 mmol, 0.1 equiv.) and palladium(II) acetate (74 mg, 0.33 mmol, 0.05 equiv.). The reaction mixture was heated to 70 °C for 75 min and then allowed to cool to room temperature. It was partitioned between water (25 mL) and EtOAc (150 mL) and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with saturated brine,
dried (MgSO₄) and all volatiles were removed under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 20:1, v/v) to give pure title compound (2.10 g, 4.20 mmol, 64%) as a colorless oil.

4: Rí; 0.25 (n-hexane/EtOAc, 10:1); [α]D²² = −29.8 (deg cm⁻³ g⁻¹ dm⁻¹, c = 0.93, CHCl₃); IR (CCl₄): v max 2953, 2875, 1651, 1084, 1016, 788, 743 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.51 (d, J = 16.0 Hz, 1 H), 6.18 (d, J = 16.0 Hz, 1 H), 6.10 (m, 1 H), 3.73 (s, 3 H), 3.72 (m, 1 H), 3.34 (s, 3 H) 2.79 (m, 1 H), 2.6 (ddd, J = 16.6, 7.0, 3.2 Hz, 1 H), 1.05 (s, 3 H), 0.95 (s, 3 H), 0.48 (dd, J = 8.0, 5.3 Hz, 1 H); ¹³C-NMR (75 MHz, CDCl₃) δ 167.7, 151.8, 141.3, 132.6, 118.0, 82.3, 76.6, 56.8, 54.2, 52.2, 51.4, 47.5, 43.7, 35.3, 35.0, 33.3, 32.9, 28.2, 25.0, 21.4, 19.2, 13.2, 12.4, 7.1, 5.6; HRMS (m/z): [M+Na]⁺ calculated for C₃₀H₄₆O₅SiNa: 523.32141, found: 523.32145; [2M+Na]⁺ calculated for C₆₀H₉₆O₁₀Si₂Na: 1023.65359, found: 1023.65675.

3.10 (+)-Methyl 3β,5-cyclo-5β:12β-hydroxy-6β-methoxypregnan-21-carboxylate (9):
To a stirred solution of diene 4 (2.09 g, 4.17 mmol, 1.0 equiv.) in MeOH (100 mL) was added palladium on charcoal (10%), 340 mg, 0.32 mmol, 0.08 equiv.). The reaction mixture was flushed five times with H₂ and stirred under an H₂-atmosphere for 2 h. The suspension was filtered through Celite and concentrated under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 5:1, v/v) to give pure title compound (1.34 g, 3.42 mmol, 82%) as a colorless oil.

9: Rí; 0.63 (n-hexane/EtOAc, 2:1); [α]D²² = +50.4 (deg cm⁻³ g⁻¹ dm⁻¹, c = 1.00, CHCl₃); IR (CCl₄): v max 3470, 2950, 2870, 1737, 1083, 787, 713 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 3.73 (s, 3 H, -COOCH₃), 2.76 (m, 1 H, H-6), 2.33 (m, 1 H, H-21), 2.30 (m, 1 H, H-21), 1.91 (m, 1 H, H-7), 1.86 (m, 1 H, H-16), 1.71 (m, 1 H, H-2), 1.69 (m, 1 H, H-8), 1.65 (m, 1 H, H-15), 1.57 (m, 1 H, H-11), 1.52 (m, 1 H, H-2), 1.50 (m, 1 H, H-1), 1.43 (m, 2 H, H-20), 1.43 (m, 1 H, H-17), 1.41 (m, 1 H, H-11), 1.28 (m, 1 H, H-15), 1.22 (m, 1 H, H-16), 1.03 (s, 3 H, H-19), 1.02 (m, 1 H, H-7), 0.94 (m, 1 H, H-14), 0.87 (m, 1 H, H-3), 0.86 (m, 1 H, H-1), 0.71 (s, 3 H, H-18), 0.65 (m, 1 H, H-4), 0.44 (dd, J = 8.0, 5.2 Hz, 1 H, H-4); ¹³C-NMR (100 MHz, CDCl₃) δ 175.1 (C-21), 82.4 (C-6), 80.2 (C-12), 56.7 (-OCH₃), 54.4 (C-14), 51.7 (-COOCH₃), 50.6 (C-17), 47.4 (C-13), 47.1 (C-9), 43.5 (C-10), 35.3 (C-5), 35.0 (C-7), 33.6 (C-21), 33.4 (C-1), 32.3 (C-11), 29.6 (C-8), 29.0 (C-16), 27.7 (C-20), 25.0 (C-2), 24.5 (C-15), 21.5 (C-3), 19.3 (C-19), 13.2 (C-4), 7.4 (C-18); HRMS (m/z): [M+Na]⁺ calculated for C₂₄H₃₂O₁₀Na: 413.26623, found: 413.26650; [2M+Na]⁺ calculated for C₄₈H₇₆O₁₆Na: 803.54324, found: 803.53868.
3.11 (−)-Methyl 3β,12β-dihydroxy pregn-5-ene-21-carboxylate (20):
To a solution of methylester 9 (1.33 g, 3.40 mmol, 1.0 equiv.) in 1,4-dioxane (60 mL) and water (6 mL) was added para-toluenesulfonic acid monohydrate (108 mg, 0.57 mmol, 0.17 equiv.) and the mixture was heated to 64 °C for 5 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The so-obtained residue was partitioned between EtOAc (80 mL) and water (15 mL) and the phases were separated. The organic phase was washed with saturated brine (30 mL), dried (MgSO₄), and all volatiles were removed under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 1:1, v/v) to give pure title compound (960 mg, 2.55 mmol, 75%) as a colorless solid. 20: mp.: 122-125 °C; Rᵢ: 0.23 (n-hexane/EtOAc, 1:1); [α]D²²: −31.7 (deg cm⁻¹ g⁻¹ dm⁻¹, c = 0.73, CHCl₃); IR (KBr): vₘₐₓ 3423, 2942, 2867, 2360, 1737, 1437, 1049, 1002, 953 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 3.54 (s, 3 H), 2.09 (s, 3 H), 1.02 (s, 3 H); ¹³C-NMR (75 MHz, CDCl₃) δ 175.8, 140.9, 121.6, 80.0, 71.8, 54.6, 51.8, 50.3, 49.9, 47.0, 43.3, 37.4, 36.8, 33.5, 31.7, 31.1, 30.6, 29.0, 27.7, 24.6, 19.5, 7.2; HRMS (m/z): [M+Na]⁺ calculated for C₃₈H₇₂O₈Na: 775.51203, found: 775.51203.

3.12 (−)-3β,12β-Dihydroxy pregn-5-ene-21-carboxylic acid (21):
To a solution of methyl ester 20 (960 mg, 2.55 mmol, 1.0 equiv.) in THF (50 mL) was added aqueous LiOH-solution (1.0 M, 50.0 mL, 50.0 mmol, 20 equiv.). The mixture was stirred at 30 °C for 4 h, allowed to cool to room temperature and neutralized with aqueous HCl (1.0 M, 50.0 mL, 50.0 mmol, 20 equiv.). The organic solvent was removed under reduced pressure and the remaining aqueous phase was extracted with EtOAc (5 x 150 mL). The combined organic layers were dried (MgSO₄), all volatiles were removed under reduced pressure and the so-obtained crude was purified by column chromatography (SiO₂, n-hexane/EtOAc; 1:1, v/v) to give pure title compound (831 mg, 2.30 mmol, 90%) as a colorless solid. 21: mp.: 205-208 °C; Rᵢ: 0.30 (EtOAc); [α]D²²: −17.8 (deg cm⁻¹ g⁻¹ dm⁻¹, c = 0.90, MeOH); IR (KBr): vₘₐₓ 3428, 2942, 2820, 2360, 1683, 1271, 1049, 1017, 950 cm⁻¹; ¹H-NMR (300 MHz, MeOH-d₄) δ 5.34 (m, 1 H), 3.39 (m, 1 H), 3.30 (m, 1 H), 1.04 (s, 3 H), 0.69 (s, 3 H); ¹³C-NMR (100 MHz, MeOH-d₄) δ 178.3, 142.2, 122.4, 80.7, 72.4, 55.9, 51.8, 50.3, 48.0, 42.9, 38.6,
3.13 (-)-3β,12β-Diformyloxypregn-5-ene-21-carboxylic acid (10):
A suspension of dihydroxycarboxylic acid 21 (831 mg, 2.30 mmol, 1.0 equiv.) in formic acid (98%, 16 mL) was heated to 50 °C for 30 min. The reaction mixture was allowed to cool to room temperature and under reduced pressure to give the crude product which was purified by column chromatography (SiO₂, n-hexane/EtOAc; 1:1, v/v) to give pure title compound (818 mg, 1.96 mmol, 85%) as a colorless solid.

10: mp.: 64-65 °C; Rf: 0.50 (n-hexane/EtOAc, 1:1); [α]D₂₂: -52.4 (deg cm³ g⁻¹ dm⁻¹, c = 0.84, CHCl₃); IR (KBr): νmax 3341, 2932, 1722, 1453, 1384, 1184, 932 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 8.10 (s, 1 H), 8.03 (s, 1 H), 5.40 (m, 1 H), 4.82 (dd, J = 11.3, 4.6 Hz, 1 H), 4.73 (m, 1 H), 2.37 (m, 1 H), 2.33 (m, 2 H), 2.23 (m, 1 H), 1.04 (s, 3 H), 0.79 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 179.4, 161.2, 160.7, 139.3, 122.8, 81.6, 73.8, 54.6, 49.7, 49.4, 45.4, 38.0, 37.0, 36.9, 33.2, 31.5, 31.0, 28.4, 27.7, 27.2, 27.1, 24.3, 19.3, 8.3; HRMS (m/z): [M-H⁺] calculated for C₂₄H₃₃O₆: 417.22816, found: 417.22800; [2M-H⁺] calculated for C₄₈H₆₇O₁₂: 835.46380, found: 835.46334.

3.14 (-)-3β-Acetoxypregn-5-ene-21,12β-carbolactone (25):
To a solution of the dihydroxy carboxylic acid 21 (250 mg, 0.69 mmol) in pyridine (8 mL) acetic anhydride (0.40 mL, 4.2 mmol, 6.0 equiv.) and 4-dimethylaminopyridine (21 mg, 0.17 mmol, 0.25 equiv.) were added at room temperature. The reaction mixture was stirred for 1.5 h and then concentrated to half the volume. The resulting solution was diluted with EtOAc (20 mL), washed with water (2 x 10 mL) and brine (10 mL), dried (MgSO₄) and evaporated to dryness under reduced pressure. Purification by column chromatography (SiO₂, n-hexane/EtOAc; 1:1, v/v) gave pure title compound (195 mg, 0.53 mmol, 77%) as colorless needles.

25: mp.: 65-68 °C; Rf: 0.40 (n-hexane/EtOAc, 2:1) [α]D₂₂: -16.2 (deg cm³ g⁻¹ dm⁻¹, c = 0.52, CHCl₃); IR (KBr): νmax 2945, 1773, 1723, 1606, 1467, 1440, 1366, 1248, 1194, 1168, 1034, 788, 763 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 5.38 (m, 1 H), 4.58 (m, 1 H), 4.11 (m, 1 H), 2.77 (dd, J = 12.9, 5.6 Hz, 1 H), 2.33 (m, 1 H), 2.02 (s, 3 H), 1.03 (s, 3 H), 0.63 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 175.4, 170.7, 139.7, 122.2, 84.5, 73.7, 54.5, 54.0, 49.4, 45.3, 38.1, 37.1,
36.8, 31.1, 30.4, 27.8, 27.5, 26.7, 23.8, 23.1, 21.6, 21.5, 19.4, 7.0; HRMS (m/z): [M+Na]^+ calculated for C_{24}H_{34}O_4Na: 409.23493, found: 409.23476.

3.15 (–)-21-nor-24-Diazo-3β,12β-diformyloxy-chol-5-ene-23-one (3):
To a solution of carboxylic acid 10 (200 mg, 0.48 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added oxalyl chloride (87 µL, 0.96 mmol, 2.0 equiv.) and DMF (1 drop) sequentially and the reaction mixture was stirred for 2 h. The so-obtained solution of the acid chloride was concentrated under reduced pressure and redisolved in THF (6 mL). To this solution at 0 °C was added a freshly prepared solution of diazomethane in Et_2O (ca. 0.2 M, 8.0 mL, ca. 1.6 mmol, ca. 3.3 equiv.) and the reaction mixture was kept at this temperature for 1 h. The resulting yellowish solution was allowed to warm to room temperature and stirred for another 1 h. The reaction mixture was quenched carefully with acetic acid (80 µL, 1.40 mmol, 2.9 equiv.) and all volatiles were removed under reduced pressure. The so-obtained crude product was purified by column chromatography (SiO_2, n-hexane/EtOAc; 3:1, v/v) to give pure title compound (180 mg, 0.406 mmol, 85%) as a yellow solid.

3: mp.: 68-70 °C; R_f: 0.50 (n-hexane/EtOAc, 1:1); [α]_D^{22}: −26.4 (deg cm^3 g⁻¹ dm⁻¹, c = 1.21, CHCl_3); IR (KBr): νmax 2932, 2103, 1720, 1642, 1363, 1184, 930, 788, 763 cm⁻¹; ¹H-NMR (300 MHz, CDCl_3) δ 8.10 (s, 1 H), 8.03 (s, 1 H), 5.39 (m, 1 H), 5.19 (s (br), 1 H), 4.82 (dd, J = 11.4, 4.5 Hz, 1 H), 4.71 (m, 1 H), 2.36 (m, 1 H), 2.25 (m, 2 H), 1.04 (s, 3 H), 0.77 (s, 3 H); ¹³C-NMR (100 MHz, CDCl_3) δ 195.2, 161.1, 160.7, 139.3, 122.8, 81.5, 73.7, 54.6, 49.9, 49.4, 45.5, 38.0, 37.0, 36.9, 31.5, 30.9, 28.5, 27.7, 27.6, 27.3, 24.3 (2 x C), 19.3, 8.3;¹¹ HRMS (m/z): [M+Na]^+ calculated for C_{25}H_{34}N_2O_3Na: 465.23599, found: 465.23613.

3.16 (–)-21,26,27-tri-nor-24-Diazo-3β,12β-diformyloxycholest-5-ene-23-one (24):
To a solution of carboxylic acid 10 (28.0 mg, 70.0 µmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at room temperature was added oxalyl chloride (13 µL, 140 µmol, 2.0 equiv.) and DMF (1 drop) sequentially and the reaction mixture was stirred for 2 h. The so-obtained solution of the acid chloride was concentrated under reduced pressure and

¹ One signal is hidden by doubling. NMR shift values of hidden signals were assigned by comparison with an assigned 2D-NMR of an analogous compound. The C24-signal is missing due to low concentration of the NMR sample and the quadrupolar coupling with N.
redissolved in THF (1 mL). To this solution at 0 °C was added a freshly prepared solution of diazoethane in Et₂O (ca. 0.2 M, 2.0 mL, ca. 0.4 mmol, ca. 5.7 equiv.) and the reaction mixture was kept at this temperature for 1 h. The resulting yellowish solution was allowed to warm to room temperature and kept at this temperature for another 3 h. All volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 3:1, v/v) to give pure title compound (14.7 mg, 32.0 µmol, 46%) as a yellow solid.

**24**: mp.: 50-51 °C; Rf: 0.40 (n-hexane/EtOAc, 2:1); [α]²⁰D = -43.3° (deg cm³ g⁻¹ dm⁻¹, c = 0.49, CHCl₃); IR (KBr): νmax 2942, 2069, 1721, 1635, 1384, 1184, 932, 788 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 8.09 (s, 1 H), 8.01 (s, 1 H), 5.39 (m, 1 H), 5.04 (dd, J = 11.0, 4.8 Hz, 1 H), 4.76 (m, 1 H), 1.05 (s, 3 H), 0.98 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 198.5, 160.6, 160.6, 139.2, 122.7, 76.7, 73.6, 53.6, 52.4, 48.9, 47.5, 47.1, 38.0, 37.3, 37.0, 36.8, 36.3, 32.8, 31.6, 31.5, 27.6, 27.1, 24.3, 19.3, 10.3; HRMS (m/z): [M+Na]⁺ calculated for C₂₈H₃₅N₂O₅: 457.26970, found: 457.26987; [M+Na]⁺ calculated for C₂₈H₃₆N₂O₅Na: 479.25164, found: 479.25188; [2M+Na]⁺ calculated for C₅₂H₇₂N₄O₁₀Na: 935.51407, found: 935.51462.

3.17 (−)-(17R)-spiro[3β,12β-Diformyloxyandrost-5-ene-17,3'-cyclopenta-1'-one] (11): A suspension of rhodium(II) acetate dimer (6.2 mg, 14 µmol, 0.07 equiv.) in CH₂Cl₂ (3 mL) was degassed three times using freeze-and-thaw cycles. The resulting green suspension was heated to 41 °C and a solution of diazoketone 3 (88 mg, 0.20 mmol, 1.0 equiv.) in degassed CH₂Cl₂ (2.5 mL) was added dropwise. The mixture was kept at this temperature for 2 h, allowed to cool to room temperature, and all volatiles were removed under reduced pressure to obtain the crude product which was purified by column chromatography (SiO₂, n-hexane/EtOAc; 5:1, v/v) to give pure title compound (43 mg, 0.104 mmol, 52%) as colorless crystals.

**11**: mp.: 122-126 °C; Rf: 0.20 (n-hexane/EtOAc, 5:1); [α]²⁰D = -33.4° (deg cm³ g⁻¹ dm⁻¹, c = 1.09, CHCl₃); IR (KBr): νmax 2965, 1741, 1715, 1466, 1387, 1185, 931 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 8.05 (s, 1 H), 8.01 (s, 1 H), 5.39 (m, 1 H), 5.04 (dd, J = 11.0, 4.8 Hz, 1 H), 4.76 (m, 1 H), 1.05 (s, 3 H), 0.98 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 218.5, 160.6, 160.6, 139.2, 122.7, 76.7, 73.6, 53.6, 52.4, 48.9, 47.5, 47.1, 38.0, 37.3, 37.0, 36.8, 36.3, 32.8, 31.6, 31.5, 27.6, 27.1, 24.3, 19.3, 10.3; HRMS (m/z): [M+Na]⁺ calculated for C₂₅H₃₄O₅Na: 437.22985, found: 437.22957; [2M+Na]⁺ calculated for C₅₀H₆₈O₁₀Na: 851.47047, found: 851.46981.
3.18 (−)-(17R)-spiro[3β,12β-Dihydroxyandrost-5-ene-17,3'-cyclopenta-1'-one] (22): To a solution of cyclopentanone 11 (82 mg, 0.20 mmol, 1.0 equiv.) in THF (4 mL) was added aqueous LiOH-solution (1.0 M, 4.0 mL, 4.0 mmol, 20 equiv.) and the resulting mixture was heated to 30 °C for 2 h. The reaction mixture was allowed to cool to room temperature, acidified with aqueous HCl (1.0 M, 4.2 mL, 4.2 mmol, 21 equiv.) and extracted with EtOAc (5 x 10 mL). The combined organic phases were dried (MgSO₄), all volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 1:1, v/v) to give pure title compound (67 mg, 0.186 mmol, 94%) as a colorless solid.

22: mp.: 123–125 °C; Rf: 0.23 (n-hexane/EtOAc, 1:1); [α]D₂²⁵: −26.1 (deg cm³ g⁻¹ dm⁻¹, c = 1.16, CHCl₃); IR (KBr): νmax 3435, 2933, 1731, 1633, 1403, 1278, 1171, 1049, 1013, 956 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.34 (m, 1 H), 3.68 (dd, J = 10.8, 4.5 Hz, 1 H), 3.50 (m, 1 H), 1.02 (s, 3 H), 0.86 (s, 3 H); ¹³C-NMR (75 MHz, CDCl₃) δ 195.5, 9.2; HRMS (m/z): [M+Na]⁺ calculated for C₂₃H₃₅O₃Na: 381.24005; [2M+Na]⁺ calculated for C₄₆H₆₆O₆Na: 739.49081, found: 739.49165.

3.19 (−)-(17R)-spiro[3β-tert-Butyldimethylsilyloxy-12β-hydroxyandrost-5-ene-17,3'-cyclopenta-1'-one] (12): To a solution of diol 22 (66.0 mg, 0.180 mmol, 1.0 equiv.) in DMF (2 mL) at room temperature was added sequentially imidazole (50 mg, 0.72 mmol, 4.0 equiv.) and tert-butyldimethylsilyl chloride (68 mg, 0.45 mmol, 2.5 equiv.). After 1.5 h at this temperature, water (3 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄), all volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 4:1, v/v) to give pure title compound (83.0 mg, 0.176 mmol, 95%) as a colorless solid.

12: mp.: 193–195 °C; Rf: 0.23 (n-hexane/EtOAc, 1:1); [α]D₂²⁵: −10.6 (deg cm³ g⁻¹ dm⁻¹, c = 1.28, CHCl₃); IR (KBr): νmax 3435, 2932, 2901, 2857, 1731, 1634, 1472, 1254, 1095, 888, 872, 837, 775 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.30 (m, 1 H), 3.69 (dd, J = 10.9, 4.8 Hz, 1 H), 3.46 (m, 1 H), 2.41 (d, J = 16.8 Hz, 1 H), 2.34 (m, 1 H), 2.31 (d, J = 13.8 Hz, 1 H), 2.02 (d, J = 16.5 Hz, 1 H), 1.02 (s, 3 H), 0.88 (s, 9 H), 0.86 (s, 3 H), 0.05 (s, 6 H); ¹³C-NMR (75 MHz, CDCl₃) δ 220.3, 141.4, 121.0, 74.7, 72.6, 53.7, 52.5, 49.5, 48.2, 48.0, 42.8, 37.5, 37.5,
36.8, 36.4, 33.2, 32.1, 31.7, 31.6, 31.5, 26.0, 24.8, 19.5, 18.4, 9.2, −4.5; HRMS (m/z): [M+Na]⁺ calculated for C₃₉H₄₆O₅SiNa: 495.32649, found: 495.32598; [2M+Na]⁺ calculated for C₅₅H₇₅O₆Si₂Na: 967.66376, found: 967.66378.

3.20 (+)-(17R)-spiro[14(13→12)abedo-3β-tert-Butyldimethylsilyloxyandrosta-5,12-dien-17,3'-cyclopenta-1'-one] (13):
To a solution of hydroxysteroid 12 (83 mg, 0.18 mmol, 1.0 equiv.) in toluene (12 mL) was added 4-dimethylaminopyridine (131 mg, 1.08 mmol, 6.0 equiv.) and N-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (211 mg, 0.54 mmol, 3.0 equiv.) in one portion. The flask was immersed into an oil bath at a temperature of 130 °C and the reaction mixture kept at this temperature for 1 h. The suspension was allowed to cool to room temperature and was filtered through Celite washing several times with toluene. All volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 20:1, v/v) to give the title compound (71 mg, 0.16 mmol, 89%) as an inseparable mixture of endo- and exo alkene (endo:exo, 4:1, ratio determined by the ¹H-NMR integrals of the signals at 5.34 ppm (endo) and 4.89 ppm (exo)). To remove the minor isomer, the mixture was dissolved in EtOAc (4 mL) and rhodium on carbon (10%, 12 mg, 12 μmol, 0.07 equiv.) was added. The reaction mixture was flushed five times with H₂ and stirred for 1 h at room temperature under an H₂-atmosphere. The suspension was then filtered through Celite, washing several times with CH₂Cl₂, and concentrated under reduced pressure. The so-obtained residue was purified by column chromatography (SiO₂, n-hexane/EtOAc; 30:1, v/v) to yield pure title compound (56 mg, 0.12 mmol, 70%) as a colorless solid.

¹H-NMR of the mixture (300 MHz, CDCl₃) δ 5.34 (m, 1H, exo+endo), 4.89 (d, J = 1.8 Hz, 1H, exo), 4.87 (d, J = 1.6 Hz, 1H, exo), 3.50 (m, 1H, exo+endo), 2.57 (d, J = 18.0 Hz, 1H, endo), 1.59 (s, 3H, endo), 1.00 (s, 3H, exo), 0.98 (s, 3H, endo), 0.89 (s, 9H, exo+endo), 0.06 (s, 6H, exo+endo);

13: mp.: 180-184 °C; Rₛ: 0.25 (n-hexane/EtOAc, 20:1); [α]D²²: +19.6 (deg cm² g⁻¹ dm⁻¹), c = 0.92, CHCl₃; IR (KBr): νmax 2929, 2856, 1746, 1636, 1462, 1379, 1252, 1095, 877, 836, 775 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.34 (m, 1H), 3.48 (m, 1H), 2.41 (d, J = 18.0 Hz, 1H), 1.59 (s, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 220.5, 142.6, 140.9, 126.7, 121.5, 72.8, 52.5, 51.1, 49.4, 44.4, 42.5, 42.4, 38.5, 36.8, 36.2, 35.7, 32.0, 31.7, 31.1, 29.0, 26.1, 24.4, 19.8, 18.4, 13.9, −4.4; HRMS (m/z): [M+Na]⁺ calculated for C₃₉H₄₆O₅SiNa: 477.31593, found: 477.31591; [2M+Na]⁺ calculated for C₅₅H₇₅O₆Si₂Na: 931.64264, found: 931.64341.
3.21 (−)-(17R)-spiro[14(13→12)abeo-3β-tert-Butyldimethylsilyloxyandrosta-5,12-dien-17,6′-pyrindan] (23):
A solution of C-nor-D-homo steroid 13 (36.0 mg, 80.0 µmol, 1.0 equiv.), propargylamine (10 µL, 0.16 mmol, 2.0 equiv.) and sodium[tetrachloroaurat(III)] dihydrate (2.9 mg, 8.0 µmol, 0.1 equiv.) in EtOH (3 mL) was prepared in a microwave vial. The vial was sealed and heated to 100 °C for 10 h. The reaction mixture was allowed to cool to room temperature and the so-obtained suspension was filtered through Celite, washing several times with CH₂Cl₂. All volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, n-hexane/EtOAc; 10:1, v/v) to give pure title compound (17.4 mg, 36.0 µmol, 45%) as a colorless solid.

23: mp.: 135-138 °C; Rₓ: 0.25 (n-hexane/EtOAc, 10:1); [α]₂₂°: −57.1 (deg cm⁻³ g⁻¹ dm⁻¹, c = 0.07, CHCl₃); IR (KBr): ν_max 2926, 2854, 1734, 1716, 1383, 1255, 1092, 836, 775 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 8.34 (d, J = 5.0 Hz, 1 H), 7.43 (d, J = 7.4 Hz, 1 H), 7.03 (dd, J = 7.4, 5.0 Hz, 1 H), 5.35 (m, 1 H), 3.35 (m, 1 H), 3.42 (d, J = 16.8 Hz, 1 H), 1.55 (s, 3 H), 1.51 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ¹³C-NMR (75 MHz, CDCl₃) δ 164.8, 147.5, 142.6, 139.7, 136.3, 128.0, 121.5, 121.3, 72.8, 52.6, 49.5, 46.8, 43.2, 42.6, 42.5, 38.5, 38.5, 36.8, 32.0, 31.2, 28.8, 26.1, 24.9, 18.9, 18.4, 14.7, −4.4; HRMS (m/z): [M+H]+ calculated for C₃₂H₄₈NOSi: 490.34997, found: 490.34987; [M+Na]+ calculated for C₃₂H₄₇NOSiNa: 512.33191, found: 512.33188.

3.22 Carbacyclopamine analog 2:
To a solution of silyl ether 23 (6.0 mg, 12.0 µmol, 1.0 equiv.) in THF (0.5 mL) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 36 µL, 36 µmol, 3.0 equiv.) and the reaction mixture was stirred for 10 h. After this time water (3 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried (MgSO₄), all volatiles were removed under reduced pressure and the so-obtained crude product was purified by column chromatography (SiO₂, CHCl₃ + 3% MeOH) to give the title compound in ca. 90% purity judged by ¹H-NMR (3.6 mg, 9.9 µmol, 79%) as a colorless solid.

2: mp.: 170-175 °C; Rₓ: 0.53 (CHCl₃/MeOH, 95:5); [α]₂₂°: −33.0 (deg cm⁻³ g⁻¹ dm⁻¹, c = 0.12, CHCl₃); IR (CCl₄): ν_max 3420, 2929, 2875, 2854, 1733, 1716, 1457, 1436, 1384, 1260, 1092,
1072, 786, 763 cm⁻¹; ¹H-NMR (700 MHz, CDCl₃) δ 8.34 (d, J = 4.9 Hz, 1 H, H-2'), 7.43 (d, J = 7.4 Hz, 1 H, H-4'), 7.03 (dd, J = 7.4, 4.9 Hz, 1 H, H-3'), 5.39 (m, 1 H, H-6), 3.56 (m, 1 H, H-3), 3.42 (d, J = 17.1 Hz, 1 H, H-7'), 3.01 (d, J = 16.5 Hz, 1 H, H-5'), 2.69 (d, J = 17.1 Hz, 1 H, H-7'), 2.60 (d, J = 16.5 Hz, 1 H, H-5'), 2.39 (ddd, J = 2.1, 4.6, 12.6 Hz, 1 H, H-4), 2.27 (m, 1 H, H-4), 2.24 (m, 2 H, H-7 + H-11), 2.08 (m, 1 H, H-11), 1.87 (m, 1 H, H-14), 1.86 (m, 1 H, H-16), 1.83 (m, 2 H, H-2 + H-15), 1.78 (m, 1 H, H-7), 1.74 (m, 1 H, H-1), 1.56 (s, 3 H, H-18), 1.53 (m, 1 H, H-2), 1.47 (dt, J = 9.1, 11.6 Hz, 1 H, H-9), 1.22 (m, 1 H, H-8), 1.20 (m, 1 H, H-1), 1.14 (m, 1 H, H-15), 1.00 (s, 3 H, H-3); ¹³C-NMR (176 MHz, CDCl₃) δ 164.9 (C-7a'), 147.6 (C-2'), 141.8 (C-5), 139.6 (C-12), 136.4 (C-4a'), 132.6 (C-4'), 128.0 (C-13), 122.1 (C-6), 121.3 (C-3'), 72.1 (C-3), 52.4 (C-9), 49.5 (C-14), 46.9 (C-7'), 45.8 (C-17), 43.2 (C-5'), 42.4 (C-8), 38.5 (C-16), 38.3 (C-1), 36.7 (C-10), 31.5 (C-2), 31.1 (C-7), 28.7 (C-11), 24.9 (C-16), 18.8 (C-18), 14.7 (C-19); HRMS (m/z): [M+H]+ calculated for C₂₆H₃₄NOSi: 376.2634, found: 376.26386; [M+Na]+ calculated for C₂₆H₃₃NOSiNa: 398.24544, found: 398.24593.

### 4. Acid Stability

To a solution of carbacyclopamine analog 2 (2.0 mg, 5.5 µmol) in THF (0.5 mL) was dropwise added aqueous HCl (2.0 M) until a pH value of approx. 0.3 was reached. The mixture was stirred for 1 h at room temperature after which the solution was neutralized with saturated NaHCO₃-solution, extracted with CH₂Cl₂ (3 x 5 mL), dried (MgSO₄) and filtered. All volatiles were removed under reduced pressure and the so-obtained white solid (2.0 mg, 5.5 µmol) was used directly for H-NMR measurements. The ¹H-NMR spectra recorded before and after treatment with acid are shown in Figure 1.

![Figure S1](image_url): ¹H-NMR spectra of carbacyclopamine analog 2 in CDCl₃ before (700 MHz, blue) and after treatment with hydrochloric acid at pH 0.3 (400 MHz, maroon).
5. Biochemistry

The interference of the carbacyclopamine analog 2 with the hedgehog signaling pathway was tested in an established reporter gene assay [1] based on the inhibition of the target gene Gli1. Shh-LIGHTII cells (ATCC CRL-2795, LGC, Wesel, Germany) represent a clonal mouse fibroblast cell line (NIH 3T3), which stably incorporates a Gli-dependent firefly luciferase reporter and a constitutive Renilla luciferase reporter. They were grown in 75 cm² cell culture flasks at 37°C in a humid atmosphere with 5% CO₂. Cell growth medium DIMETHOXYETHANEM (Dulbecco’s Modified Eagle’s Medium, high glucose, sodium pyruvate, w/o glutamine), ZeocinTM Selection Reagent and Geneticin® Selection Antibiotic (G418 sulfate) were obtained from Invitrogen. Additive L-glutamin and trypsin were obtained from PAA. VerseneTM chelating agent was obtained from Gibco, bovine fetal serum (FBS) from Sigma. The cell freeze medium contained 5% DMSO in complete growth medium. The cell number was counted using a Neubauer-Zählkammer (Hemocytometer). DIMETHOXYETHANEM (high glucose, sodium pyruvate, w/o glutamine) supplemented with 0.5% FBS, 4 mM L-glutamin and 50 mM HEPES buffer (4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid) (pH 7.4) was used as incubation medium. The measurement of reporter gene and constitutive Renilla luminescence was performed with the Dual Luciferase® reporter system according to the manufacturer’s instructions (Promega, Mannheim, Germany) using a GENios reader (TECAN, Crailsheim, Germany).

5.1 Luciferase reporter assay

Incubation of cells. For performing the assay, Shh-LIGHTII cells were grown to reach 80% confluence, washed twice with Versene, detached with 2 mL trypsin for not longer than 2 min and resuspended in 8 mL of growth medium. After centrifugation for 3 min, the supernatant was removed and the cell pellet dissolved in approximately 10 mL of growth medium. Finally, 20,000 to 100,000 cells per well were cultured in a 24-well plate for 48 h. For exposure to the analog the growth medium was removed and the cells were exposed to the compound in 500 μL/well incubation medium for 48 h. Stock solutions were prepared in EtOH and introduced in different concentrations into the incubation medium to reach a final solvent concentration of 0.05%. Due to the assay principle, Shh-LIGHTII cells had to be co-exposed to 100 nM of SAG (Smoothened agonist) for determining the inhibitory activity of the compounds. A SAG stock solution was prepared in EtOH and introduced into the medium. The final EtOH-concentration – introduced by SAG and the test compound – was 0.1%. As a positive control a 100 nM SAG solution in incubation medium (0.1% EtOH) was used, negative controls were treated with EtOH only.
Performing the luciferase measurement. After 48 h of incubation cells were washed with 500 μL PBS (phosphate buffered saline, w Mg/Ca, Invitrogen) and afterwards incubated for 15 min with 100 μL 1x passive lysis buffer on a shaker. The lysed cells together with lysis solution were transferred into 1.5 mL reaction tubes, centrifuged for 1 min at 4°C and kept on ice until further use. At first, the blank of luminescence of a 96-well plate (flat bottom, white, Greiner bio-one) was recorded. Then, 100 μL luciferase assay reagent and 10 μL cell supernatant were mixed per well and the luminescence of firefly luciferase was recorded. Addition of 100 μL Stop&Glo® reagent permitted the recording of Renilla luminescence. The measurement was performed per row of a well, i.e. assay reagent was added to 8 wells and luminescence recorded, before the next row was processed. Analysis of constitutive Renilla luminescence was used to normalize for any potential unspecific Gli1-reporter gene luminescence.
6. NMR Spectra

^{1}H-NMR (400 MHz, CDCl\textsubscript{3})

\textbf{Sample: SH-139}

Pulse sequence: zfpul

Date: Jul 23 2010

Solvent: CDCl\textsubscript{3}

Temp: 298.1 K

Operator: walgup



^{13}C-NMR (100 MHz, CDCl\textsubscript{3})

\textbf{Sample: SH-139}

Pulse sequence: zfpul

Date: Jul 23 2010

Solvent: CDCl\textsubscript{3}

Temp: 298.1 K

Operator: walgup




**1H-NMR (300 MHz, CDCl<sub>3</sub>)**

- **Sample:** 90-1417
- **Pulse Sequence:** sslpul
- **Date:** Jul 29 2010
- **Solvent:** cdcl3
- **Temp.:** 24.6 °C / 259.1 K
- **Operator:** wakug
- **Mercury-500BB "Jupiter"**

- **Relax. delay:** 1.000 sec
- **Pulsel. decay:** 33.0 deg/sec
- **Acq. time:** 1.500 sec
- **Width:** 40.0 kHz

**13C-NMR (100 MHz, CDCl<sub>3</sub>)**

- **Sample:** 90-1417
- **Pulse Sequence:** sslpul
- **Date:** Jul 29 2010
- **Solvent:** cdcl3
- **Temp.:** 24.6 °C / 259.1 K
- **Operator:** wakug
- **Mercury-500BB "Jupiter"**

- **Relax. delay:** 1.000 sec
- **Pulsel. decay:** 33.0 deg/sec
- **Acq. time:** 1.500 sec
- **Width:** 101.25 kHz

**Notes:**
- Data processing
- Line broadening 0.5 Hz
- FT size 16384
- Total time 1 hr, 24 min, 1 sec
$^1$H-NMR (400 MHz, CD$_3$OD)

Sample: SR-144
Pulse sequence: opti-pul
Date: Aug 23 2010
Solvent: cdod
Temp: 24.0 °C / 295.1 K
Remark: 24.0 °C

$^{13}$C-NMR (100 MHz, CD$_3$OD)

Sample: SR-144
Pulse sequence: opti-pul
Date: Aug 23 2010
Solvent: cdod
Temp: 24.0 °C / 295.1 K
Operator: walkup
Mercury-400A "Felix"

Delay: delay 1.000 sec
Pulse: 20.0 degrees
Acq. time: 1.200 sec
Width: 24154.8 Hz
352 repetitions

Measuring C13, 100.580564 MHz
DECODED: F1 400.044437 MHz
Power: 35 dB
continuously on

DATA PROCESSING
Line broadening: 1.0 Hz
FT size: 65536
Total time: 1 hr, 25 min, 53 sec
$^1$H-NMR (300 MHz, CDCl$_3$)

$^{13}$C-NMR (75 MHz, CDCl$_3$)
\(^1\)H-NMR (400 MHz, CDCl\(_3\))

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\))
$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
$^1$H-NMR (400 MHz, C$_6$D$_6$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
$^1$H-NMR (300 MHz, CDCl$_3$)

$^{13}$C-NMR (75 MHz, CDCl$_3$)
$^{1}H$-NMR (300 MHz, CDCl$_3$)

$^{13}C$-NMR (75 MHz, CDCl$_3$)
$^1$H-NMR (300 MHz, CDCl$_3$)

Sample: 88-888-III
Pulse Sequence: zgpgp
Solvent: ocd13
Temp. 26.3°C / 293.1 K
Operator: wavel
Mercury-2038B "gtsix"

FID: 0.5 sec
Pulse delay: 5.0 sec
Acq. 50.0 sec
Data: 2048 points
2000 Hz spectral width
Centered at 0.0 ppm

Data Processing
Line-broadening 0.8 Hz
FT size 32768
Total time 7 min, 12 sec

$^{13}$C-NMR (75 MHz, CDCl$_3$)

Sample: 88-888-III
Pulse Sequence: zgpgp
Solvent: ocd13
Temp. 26.3°C / 293.1 K
Operator: wavel
Mercury-2038B "gtsix"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. 1.062 sec
Width 1411.9 Hz
65536 repetitions

Data Processing
Line-broadening 1.0 Hz
FT size 65536
Total time 43 min, 2 sec
$^1$H-NMR (300 MHz, CD$_3$OD)

Sample: Ethanol
Pulse Sequence: a100
Solvent: methanol
Temp: 298.0 K / 24.0 °C
Operator: veron
Memory: 1024 KB

Delay: 1.000 sec
Pulse 1.093 sec
Acq. time: 1.000 sec
No. of scans: 1
256 FIDs per scan

$^{13}$C-NMR (75 MHz, CD$_3$OD)

Sample: Ethanol
Pulse Sequence: 1D
Data: 2D-1A
Solvent: methanol
Temp: 298.0 K / 24.0 °C
Operator: veron
Memory: 1024 KB

Delay: 1.000 sec
Pulse 1.093 sec
Acq. time: 1.000 sec
No. of scans: 1
256 FIDs per scan

S32
$^{1}$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)

S. Name

Sample: S-1462

Pulse Sequence: sdpul

Data: Mar 17 2013

Solvent: cdcl$_3$

Temp: 29.8 C / 398.1 K

Operator: gsehp

Memory-400M "refine"

Pulse: delay 1.000 sec

Pulse 90.0 degrees

Avg. time 1.500 sec

Widths 432.5 Hz

32 repetitions

RESONANCE 65.45 Hz (6545 ppm)

DATA PROCESSING: 0

Line broadening: PA Hz

PT size 62436

Total time 42 min. 58 sec
$\^{1}H$-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)

| Parameter          | Value          |
|--------------------|----------------|
| Title              | S362C          |
| Comment            | S. Hame        |
| Origin             | Varan          |
| Author             |                |
| Solvent            | CDCl$_3$       |
| Temperature        | 253            |
| Pulse Sequence     | $\pi/2$        |
| Acquisition Time   | 1.3005         |
| Acquisition Date   | 2019-11-07     |
| Spectrometer       | Perkin-Elmer   |
| Spectrometer Frequency | 100.39  |
| Spectrometer Width | 34154.6       |
| Lowest Frequency   | 15284.6        |
| Noiseout           | 130            |
| Ac quis Band       | 31413          |
| Spectral Size      | 32768          |

S36
$^{1}H$-NMR (400 MHz, CDCl$_3$)

Sample: SN-169-2
Pulse Sequence: zpul
Date: May 30 2011
Solvent: cdc13
Temp: 26.0 °C / 299.1 K
Operator: walkup
Memory: 4096000 “failis”

Pulse delay 1.000 sec
Pulse 30.2 degree
Acq. time 1.996 sec
Width 6422.0 Hz
200 repetitions
OVERLAP ML, 400.007956 MHz
DATA PROCESSING
Line broadening 3.2 Hz
FT size 32768
Total time 1 min, 50 sec

$^{13}$C-NMR (100 MHz, CDCl$_3$)

Sample: SN-169-2
Pulse Sequence: zpul
Date: May 30 2011
Solvent: cdc13
Temp: 26.0 °C / 299.1 K
Operator: walkup
Memory: 4096000 “failis”

Pulse delay 1.000 sec
Pulse 48.9 degree
Acq. time 1.996 sec
Width 24134.6 Hz
200 repetitions
OVERLAP ML, 100.002671 MHz
DECOUPLING ml, 400.002820 MHz
Power 35 dB
continuously on
WATSON-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 25 min, 59 sec
$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
$^{1}H$-NMR (400 MHz, CDCl$_{3}$)

$^{13}C$-NMR (100 MHz, CDCl$_{3}$)
$^1$H-NMR (400 MHz, CDCl$_3$)

Parameter | Value
---|---
Title | SR124H
Comment | S. Nabe
Origin | Varian
Owner | 
Site | 
Spectrometer | mercury
Author | 
Solvent | cdcl3
Temperature | 26.0
Pulse Sequence | 2D
Experiment | 3D
Number of Scans | 16
Receiver Gain | 16
Relaxation Delay | 1.0000
Pulse Width | 0.0000
Acquisition Time | 1.9511
Acquisition Date | 2011-06-09T09:15:14
Spectrometer Frequency | 400.11
Spectral Width | 6D12.0
Lowest Frequency | -401.1
Nucleus | 1H
Acquired Size | 12779
Spectral Size | 1024

S40
$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
\[ ^1H-\text{NMR (300 MHz, CDCl}_3 \] 

\[ ^{13}C-\text{NMR (75 MHz, CDCl}_3 \]
$^1$H-NMR (700 MHz, CDCl$_3$)

Parameter | Value
--- | ---
Title | Rate, pH 7.4
Comment | 700 MHz
Origin | Bruker BioSpin GmbH
User | Frey
Site | 6
Spectrometer | dmx100
Author | 
Solvent | CDCl$_3$
Temperature | 300.0
Pulse Sequence | 
Experiment | 10
Number of Scans | 64
Receiver Gain | 30
Relaxation Delay | 4.0000
Pulse Width | 8.8579
Acquisition Time | 3.2800
Acquisition Date | 2011-11-27T00:51:13
Modification Date | 2011-11-27T00:51:13
Spectrometer Frequency | 700.18
Spectral Width | 999.13
Lowest Frequency | -5671.0
Nucleus | 1H
Acquired Size | 32768
Spectral Size | 65536

$^{13}$C-NMR (176 MHz, CDCl$_3$)

Parameter | Value
--- | ---
Title | Rate, pH 7.4
Comment | 700 MHz
Origin | Bruker BioSpin GmbH
User | Frey
Site | 6
Spectrometer | dmx100
Author | 
Solvent | CDCl$_3$
Temperature | 300.0
Pulse Sequence | 
Experiment | 10
Number of Scans | 64
Receiver Gain | 30
Relaxation Delay | 4.0000
Pulse Width | 11.5000
Acquisition Time | 1.0896
Acquisition Date | 2011-11-27T00:51:13
Modification Date | 2011-11-27T00:51:13
Spectrometer Frequency | 176.08
Spectral Width | 38799.7
Lowest Frequency | -57945.6
Nucleus | 13C
Acquired Size | 32768
Spectral Size | 13277
7. Reference

1. Taipale, J.; Chen, J. K.; Cooper, M. K.; Wang, B.; Mann, R. K.; Milenkovic, L.; Scott M. P.; Beachy, P. A. Nature, 2000, 406, 1005–1009. doi:10.1038/35023008