DOI: 10.1002/ejoc.201100390

Androstanes with Modified Carbon Skeletons

Sascha Norden,[a,b] Matthias Bender,[a] Jürgen Rullkötter,[b] and Jens Christoffers*[a]

Keywords: Estranes / Androstanes / A-*nor*-steranes / Ring contraction / Hydrocarbons / Fossil biomarkers

Four sterane hydrocarbons were prepared for comparison with fossil organic biomarkers in geological samples from Oman. 17β-Methylestrane was prepared in six steps (36 % overall yield) from estrone methyl ether. Key steps of this sequence were a Wittig olefination and Birch reduction of the A-ring. 17β-Methylandrostane was obtained in four steps (85 % overall yield) from *trans*-androsterone by four functional group interconverting reactions, including a Wittig olefination. 17β-Methyl- and 2α-methyl-A-*nor*-5α-androstanes (14 and 15 % overall yields, respectively) were also prepared from *trans*-androsterone. Key steps were the thallium trinitrate mediated ring contractions of A-ring ketones to A-*nor*-2-carboxylic acids. Defunctionalization in the four syntheses was achieved by catalytic hydrogenation, Huang-Minlon reduction, Barton decarboxylation, and Bu_3SnH-mediated reduction of a chloromethyl group, respectively.

Introduction

Molecular fossils (fossil biomarkers) are an important tool in modern organic geochemistry for unraveling geological and oceanographic developments and processes. Their structures, distribution patterns, and reaction pathways reveal deep insight into geological history. In the course of a recent project, mass spectra provided evidence that Early Paleozoic crude oils and sedimentary rocks from the Oman Salt Basin contained three clearly separated isomers (gas chromatography) of putative C_{19} and C_{20} steranes with modified carbon skeletons and unknown constitutions in addition to the known suite of regular steranes and rearranged diasteranes;[1] probably the widest and best studied class of fossil biomarkers.[2] Since there is empirical evidence that the occurrence and isomer distribution of the unknown biomarkers correlate with the salinity of the waters during sediment formation, there is considerable interest in revealing the precise structures of the unknown compounds to be able to trace them back to potential biogenic ancestors in specific precursor organisms.

The concentrations of the unknown biomarkers in the Oman samples are too low for them to be readily isolated as pure compounds for rigorous spectroscopic structural identification. Thus, based on the mass spectrometry data, a strategy was developed to synthesize several possible C_{19} reference standards (androstane derivatives **1**, **3**, and **4**; Figure 1) for identification based on mass spectra and gas chromatographic retention times by GC–MS coinjection on columns of different lengths. Compound **2** (Figure 1) was synthesized for a systematic study of the effects of changes in the carbon skeleton of androstane on mass spectral fragmentation patterns. The results of this mass spectrometric study will be reported in a separate communication. Herein, we wish to disclose our synthetic efforts towards compounds **1**–**4**.

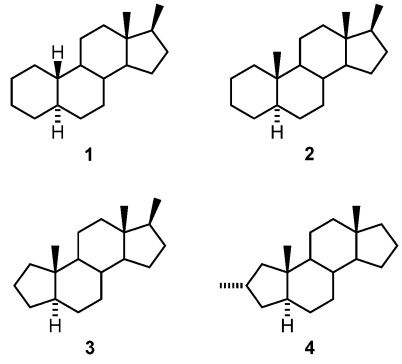


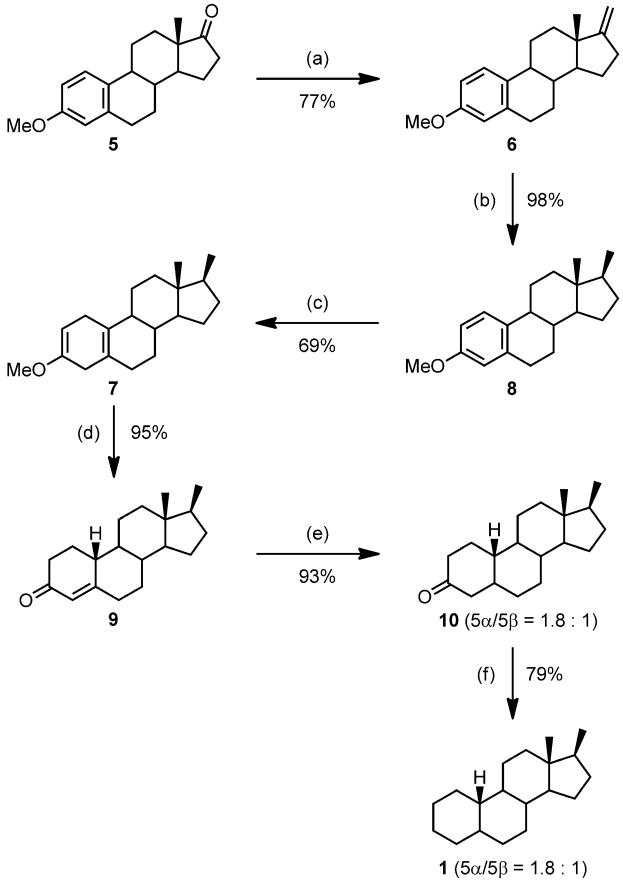
Figure 1. Target compounds of this synthetic study: 17β-methylestrane (**1**), 17β-methyl-5α-androstane (**2**), 17β-methyl-A-*nor*-5α-androstane (**3**), and 2α-methyl-A-*nor*-5α-androstane (**4**).

Results and Discussion

Synthesis of 17β-methylestrane (**1**) started with estrone methyl ether **5**, which was prepared according to literature protocols from estrone.[3] A Wittig reaction[4] gave 17-methylene derivative **6**[5] in 77% yield (Scheme 1). Subsequent catalytic hydrogenation gave product **8**[6] (98% yield) as a single diastereomer [by gas-liquid chromatography (GLC)]. We assumed that the 17-methyl group was in the β-configuration, as described in the literature for similar hydrogenations.[7] Birch reduction of the A-ring[8] afforded diene **7**

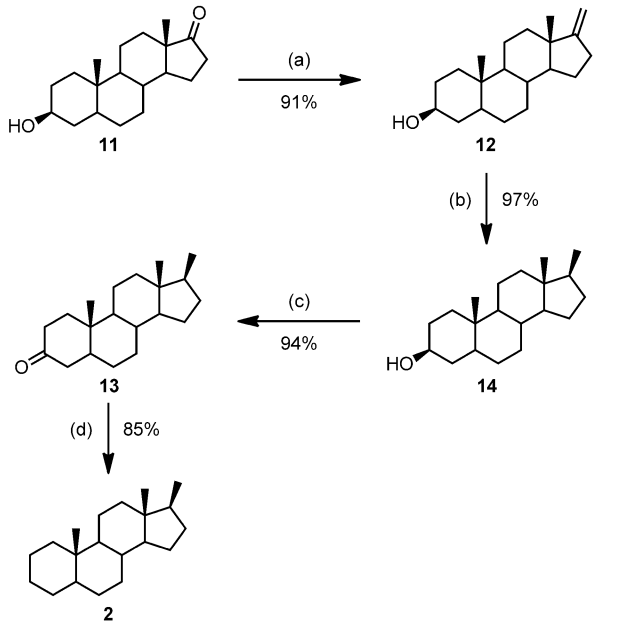
[a] Institut für Reine und Angewandte Chemie (IRAC), Carl von Ossietzky-Universität Oldenburg,
26111 Oldenburg, Germany
Fax: +49-441-798-3873
E-mail: jens.christoffers@uni-oldenburg.de
[b] Institut für Chemie und Biologie des Meeres (ICBM), Carl von Ossietzky-Universität Oldenburg,
26111 Oldenburg, Germany

(69% yield), which was subsequently hydrolyzed and isomerized with Brønsted acid to give enone **9** (95% yield) as a single diastereomer with 10-H in the β-configuration. Catalytic hydrogenation of enone **9** yielded ketone **10** as a mixture of 5α- and 5β-diastereomers in a 1.8:1 ratio (by GLC). This mixture was submitted to the Huang-Minlon version[9] of the Wolff–Kishner reduction in diethylene glycol (DEG). Chromatographic separation of this reaction mixture gave the sterane hydrocarbon **1**, again as a mixture of 5α- and 5β-epimers in a 1.8:1 ratio (by GLC). Overall yield of the six-step sequence from starting material **5** to hydrocarbon **1** was 36%.



Scheme 1. Synthesis of 17β-methylestrane (**1**). Reagents and conditions: (a) $[Ph_3PMe]Br$, *n*BuLi, THF, 66 °C, 12 h; (b) H_2 (1 bar), cat. Pd/C, EtOAc, 23 °C, 3 d; (c) Li, NH_3(l), –60 °C, 3 h, then *i*PrOH, –60 °C, 3 h; (d) HCl, H_2O, MeOH, 23 °C, 1 h; (e) H_2 (1 bar), cat. Pd/C, EtOAc, 23 °C, 4 d; (f) $H_2NNH_2{\cdot}H_2O$, KOH, diethylene glycol (DEG), 200 °C, 2 h.

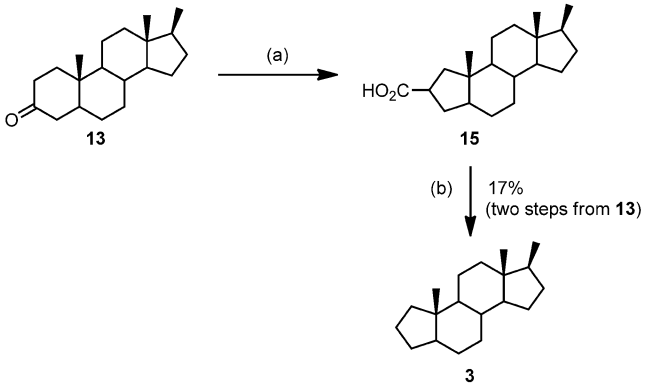
Synthesis of 17β-methylandrostane **2** was accomplished in four steps with 70% overall yield from commercially available *trans*-androsterone **11** as follows (Scheme 2): Wittig olefination gave 17-methylene compound **12**[10] (91% yield). Subsequent hydrogenation afforded 17β-methyl compound **14**[11] in 97% yield as a single diastereomer (by GLC), which was submitted to PCC oxidation[12] (94% yield) to give ketone **13**.[11] Huang-Minlon reduction gave hydrocarbon **2**[13] in 85% yield.



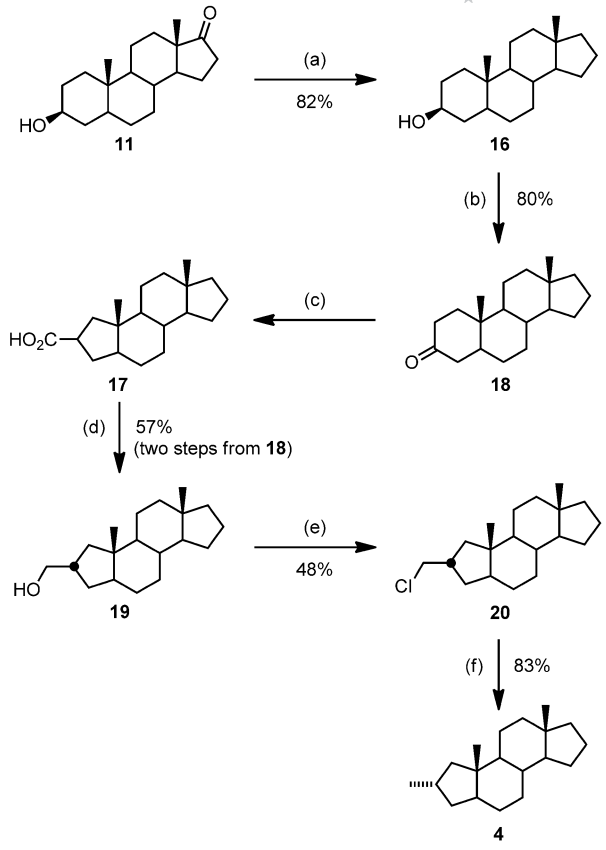
Scheme 2. Synthesis of 17β-methyl-5α-androstane (**2**). Reagents and conditions: (a) $[Ph_3PMe]Br$, NaH, THF, 70 °C, 16 h; (b) H_2 (3 bar), cat. Pd/C, *i*PrOH, 65 °C, 16 h; (c) pyridinium chlorochromate (PCC), CH_2Cl_2, 23 °C, 2 h; (d) $H_2NNH_2{\cdot}H_2O$, KOH, DEG, 200–220 °C, 16 h.

A-ring-contracted steroids, specifically A-*nor*-steranes, were reported to be constituents of sedimentary hydrocarbon mixtures.[14] The preparation of A-*nor*-steranes was achieved from steran-3-ones by either oxidative cleavage of the A-ring with CrO_3 followed by Dieckmann condensation[15] or Favorskii rearrangement.[16] We investigated both strategies on ketone **13**, but failed to isolate a respective A-*nor*-androstane derivative. For this reason, we decided to apply a rather unusual, although very effective, ring-contraction method using thallium trinitate trihydrate (TTN).[17] Reaction of ketone **13** with an excess of TTN in CH_2Cl_2 at ambient temperature resulted in full conversion of starting material **13** after a few hours (Scheme 3). Filtration of the reaction mixture through SiO_2 gave a material that contained carboxylic acid **15** together with other unspecified components. This material was esterified with 1-hydroxy-2-thiopyridone by using DCC and then submitted to Barton decarboxylation.[18] After chromatography, A-*nor*-sterane **3** was isolated in low yield (17% from compound **13**, 14% from compound **11**) but high purity as a single diastereomer (by GLC).

Preparation of A-*nor*-androstane derivative **4**, with a 2α-methyl group instead of a 17β-methyl group (as in compound **3**), started with Huang-Minlon reduction of androsterone **11** to yield alcohol **16** (82%),[19] which was then oxidized with PCC (80% yield) to give ketone **18**.[20] Application of TTN-mediated ring contraction gave a material containing carboxylic acid **17**, which was not purified, but directly submitted to $LiAlH_4$ reduction. Alcohol **19** was obtained in 57% yield (from ketone **18**) and unexpectedly as a single diastereomer (by ^{13}C NMR spectroscopy and GLC). The constitution of compound **19**, that is, the hy-



Scheme 3. Synthesis of 17β-methyl-A-*nor*-5α-androstane (**3**). Reagents and conditions: (a) $Tl(NO_3)_3{\cdot}3H_2O$, CH_2Cl_2, 23 °C, 16 h; (b) 1. dicyclohexylcarbodiimide (DCC), cat. 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 23 °C, 5 min; 2. 1-hydroxy-2-thiopyridone, 23 °C, 2.5 h (exclusion of light); 3. Bu_3SnH, cat. 2,2′-azobis(isobutyronitrile) (AIBN), C_6H_6, 85 °C, 16 h; 4. KOH, H_2O, 23 °C, 0.5 h; 5. HCl, H_2O, 23 °C, 2 h.



Scheme 4. Synthesis of 2α-methyl-A-*nor*-5α-androstane (**4**). Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, KOH, DEG, 200–220 °C, 16 h; (b) PCC, CH_2Cl_2, 23 °C, 16 h; (c) $Tl(NO_3)_3{\cdot}3H_2O$, CH_2Cl_2, 23 °C, 16 h; (d) $LiAlH_4$, THF, 50 °C, 16 h; (e) $MeSO_2Cl$, pyridine, 90 °C, 2 h; (f) Bu_3SnH, cat. AIBN, C_6H_6, 85 °C, 16 h.

droxymethyl group at position 2 of the A-*nor*-ring, was established by 2D NMR spectroscopy: In the HMBC spectrum, the 2-CH_2 protons showed a $^3J(^1H,^{13}C)$ correlation to C-1 and C-3, which were both identified to be methylene groups by a DEPT135 experiment. Our synthetic plan was then to eliminate the hydroxy group after activation and then hydrogenate the corresponding exocyclic olefin. However, treatment of alcohol **19** with $MeSO_2Cl$ and pyridine gave neither the mesylate nor the olefin, but S_N2 reaction occurred and led to the chloro compound **20** as a single isomer (48% yield). The relative configuration at C-2 was established by 1D-NOE experiments: Irradiation of 2β-H (δ =2.45 ppm) showed strong NOEs at δ = 3.5 (s, 2α-CH_2Cl), 1.81 (d, ^2J = 12 Hz, 1β-H), 1.61 (t, J = 12.8 Hz, 3β-H) ppm and most importantly at δ = 0.76 ppm [H_3C-19β, which was assigned by $^3J(^1H,^{13}C)$ to C-5 at δ = 35.80 ppm in the HMBC spectrum, see below]. The last signal certainly proved that 2-CH_2Cl was on the α-side. Weak NOEs were observed at δ = 1.50 (m, 3α-H) and 0.96 (d, ^2J = 12 Hz, 1α-H) ppm. Irradiation of the 2α-CH_2Cl group (δ =3.5 ppm) showed strong NOEs at δ = 2.45 (m, 2β-H), 1.50 (ddd, ^2J = 12.8 Hz, ^3J = 7.5 Hz, ^3J = 3.0 Hz, 3α-H), and 0.96 (dd, ^2J = 12 Hz, ^3J = 8.9 Hz, 1α-H) ppm. Weak NOEs were observed with δ = 1.81 (dd, ^2J = 12 Hz, ^3J = 7.7 Hz, 1β-H), 1.61 (dd, ^2J = 12.8 Hz, ^3J = 10.4 Hz, 3β-H), and 1.32 (m, 5α-H) ppm. In the HMQC spectrum, the signal at δ = 1.32 ppm (m, 5α-H) showed $^1J(^1H,^{13}C)$ with the carbon signal at δ = 35.80 (C-5) ppm, which was identified as a CH signal by a DEPT135 experiment. Finally, compound **4** was obtained by reductive dehalogenation with Bu_3SnH (83%).[21] The crude material contained Bu_3Sn–$SnBu_3$, which was identified by comparing its NMR spectroscopic data with that reported in the literature.[22] This impurity was almost completely removed (residual amount 2% by GLC integral) by stirring the product mixture with hydrochloric acid overnight. Overall yield (six steps) from **11** to **4** was 15%. (Scheme 4).

Conclusions

The mass spectra and gas chromatographic retention times of the synthetic androstane derivatives **1**, **2**, and **4** were compared with those of the putative unknown C_{19} steranes in sediments and crude oils from the Oman Salt Basin. Neither the spectral nor GC data matched closely enough to infer the structural identity of the natural hydrocarbons from any of the synthetic standards. Further investigation will focus on both the conceptualization of alternative target compounds for synthesis and the preparation of all-isomer mixtures of the synthesis products to account for eventual geochemical epimerization reactions during diagenesis or catagenesis in the course of geological history.

Experimental Section

General Methods: Preparative column chromatography was carried out by using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane, ethyl acetate, or *tert*-butyl methyl ether (MTBE) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminum sheets. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance

DRX 500 spectrometer. Multiplicities of ^{13}C signals were determined with DEPT experiments. Mass spectra and HR mass spectra were obtained with a Finnigan MAT 95 (EI) and a Waters Q-TOF Premier (ESI, negative mode) spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. Optical rotations were measured with a Perkin–Elmer polarimeter 343 instrument. All starting materials were commercially available.

3-Methoxy-17-methyleneestra-1,3,5(10)-triene (6): A solution of *n*BuLi (26.4 mmol, 16.5 mL, 1.6 mol/L in hexane) was slowly added to a suspension of $[Ph_3PMe]Br$ (9.43 g, 26.4 mmol) in abs. THF (90 mL) under N_2 at –5 °C. The reaction mixture was stirred for 30 min. Then, a solution of **5** (1.50 g, 5.27 mmol) in abs. THF (100 mL) was added slowly at –5 °C. After heating of the mixture to 66 °C for 12 h, water was added (100 mL). The layers were separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude product was purified by column chromatography (SiO_2, hexane/MTBE = 4:1, R_f = 0.62) to yield **6** (1.14 g, 4.04 mmol, 77%) as colorless crystals. M.p. 81 °C. $[\alpha]_D^{21}$ = +58.3 (*c* = 15.2 g/L, in CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.74 (s, 3 H), 1.11–1.23 (m, 2 H), 1.26–1.41 (m, 3 H), 1.46 (qd, *J* = 12.8, *J* = 3.5 Hz, 1 H), 1.70–1.76 (m, 1 H), 1.87 (tt, *J* = 11.8, *J* = 3.1 Hz, 2 H), 2.14 (dt, *J* = 10.8, *J* = 4.1 Hz, 1 H), 2.20 (pt, *J* = 8.6, *J* = 1.7 Hz, 1 H), 2.28 (dq, *J* = 12.5, *J* = 3.2 Hz, 1 H), 2.43–2.49 (m, 1 H), 2.74–2.85 (m, 2 H), 3.70 (s, 3 H), 4.60 (s, 2 H), 6.56 (d, *J* = 2.6 Hz, 1 H), 6.64 (dd, *J* = 2.7, *J* = 8.6 Hz, 1 H), 7.15 (d, *J* = 8.9 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 18.56 (CH_3), 23.92 (CH_2), 26.65 (CH_2), 27.63 (CH_2), 29.47 (CH_2), 29.89 (CH_2), 35.77 (CH_2), 38.83 (CH), 44.05 (CH), 44.38 (C), 53.52 (CH), 55.21 (CH_3), 100.81 (CH_2), 111.47 (CH), 113.84 (CH), 126.30 (CH), 132.86 (C), 138.03 (C), 157.48 (C), 161.78 (CO) ppm. IR (ATR): $\tilde{\nu}$ = 3062 (w), 3010 (w), 2954 (m), 2924 (m), 2905 (m), 2871 (m), 2847 (m), 2814 (w), 1650 (m), 1607 (m), 1582 (w), 1499 (s), 1460 (m), 1443 (m), 1368 (m), 1355 (w), 1311 (m), 1233 (s), 1189 (w), 1160 (m), 1047 (m), 904 (m), 863 (s), 846 (m), 816 (m), 786 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 282 (100) $[M]^+$, 254 (3), 225 (15), 211 (4), 186 (15), 173 (21), 147 (51), 107 (8). HRMS (EI): calcd. for $C_{20}H_{26}O$ $[M]^+$ 282.1984; found 282.1980.

3-Methoxy-17β-methylestra-1,3,5(10)-triene (8): A degassed suspension of olefin **6** (1.00 g, 3.54 mmol) and Pd/C (188 mg, 10% w/w Pd) in EtOAc (30 mL) was stirred under H_2 (1 atm) at 23 °C for 3 d. After filtration through a short pad of SiO_2, the crude product was purified by column chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.54) to obtain **8** (994 mg, 3.49 mmol, 98%) as colorless crystals. M.p. 87 °C. $[\alpha]_D^{21}$ = +73.6 (*c* = 14.3 g/L, in CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.51 (s, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 1.07–1.45 (m, 11 H), 1.74–1.83 (m, 1 H), 2.12 (td, *J* = 10.8, *J* = 3.9 Hz, 1 H), 2.19 (dq, *J* = 13.2, *J* = 3.7 Hz, 1 H), 2.72–2.83 (m, 2 H), 3.69 (s, 3 H), 6.65 (d, *J* = 2.4 Hz, 1 H), 6.62 (dd, *J* = 8.5, *J* = 2.4 Hz, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 11.99 (CH_3), 13.89 (CH_3), 24.46 (CH_2), 26.53 (CH_2), 27.93 (CH_2), 29.96 (CH_2), 30.25 (CH_2), 37.56 (CH_2), 39.07 (CH), 42.37 (C), 44.17 (CH), 45.21 (CH), 54.86 (CH), 55.18 (CH_3), 111.39 (CH), 113.82 (CH), 126.27 (CH), 133.15 (C), 138.12 (C), 157.41 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2961 (m), 2921 (s), 2866 (m), 2846 (m), 1739 (w), 1608 (m), 1501 (s), 1453 (s), 1453 (m), 1315 (m), 1282 (w), 1250 (m), 1236 (s), 1178 (w), 1161 (m), 1100 (w), 1038 (s), 901 (m), 862 (m), 818 (m), 786 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 284 (100) $[M^+]$, 256 (3), 228 (2), 199 (27), 173 (22), 160 (13), 147 (11), 109 (9), 84 (8). HRMS (EI): calcd. for $C_{20}H_{28}O$ $[M]^+$ 284.2140; found 284.2137.

3-Methoxy-17β-methylestra-2,5(10)-diene (7): A solution of aromatic compound **8** (500 mg, 1.76 mmol) in abs. THF (20 mL) was added to a solution of lithium (364 mg, 52.8 mmol) in liquid ammonia (25 mL) at –60 °C. The mixture was stirred at –60 °C for 3 h. Then, abs. *i*PrOH (1 mL) was added, and the mixture was stirred again at –60 °C for 3 h. By warming the mixture to 23 °C, the ammonia was evaporated. Addition of *i*PrOH (10 mL) removed traces of lithium. After NH_4OAc (150 mg), a saturated solution of NaCl (25 mL), and MTBE (20 mL) were added, the layers were separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents were evaporated. After column chromatography (SiO_2, hexane/toluene/NEt_3 = 20:1:2, R_f = 0.14), compound **7** (350 mg, 1.22 mmol, 69%) was obtained as colorless crystals. M.p. 93 °C. $[\alpha]_D^{21}$ = +102 (*c* = 11.1 g/L, in CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.58 (s, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 1.04 (td, *J* = 12.8, *J* = 3.9 Hz, 1 H), 1.08–1.29 (m, 5 H), 1.31–1.47 (m, 2 H), 1.62–1.67 (m, 2 H), 1.72 (dt, *J* = 12.5, *J* = 3.2 Hz, 2 H), 1.78–1.90 (m, 3 H), 2.05–2.10 (m, 1 H), 2.49–2.70 (m, 3 H), 2.85–2.93 (m, 1 H), 3.55 (s, 3 H), 4.65 (t, *J* = 3.4 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 12.18 (CH_3), 13.93 (CH_3), 24.32 (CH_2), 25.62 (CH_2), 27.44 (CH_2), 28.40 (CH_2), 30.32 (CH_2), 30.72 (CH_2), 34.21 (CH_2), 37.90 (CH_2), 39.22 (CH), 42.47 (C), 45.19 (CH), 45.78 (CH), 53.80 (CH), 54.77 (CH_3), 90.72 (CH), 124.85 (C), 128.23 (C), 152.74 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3011 (w), 2924 (m), 2870 (m), 2826 (m), 1697 (m), 1667 (m), 1465 (m), 1451 (m), 1437 (m), 1222 (s), 1206 (m), 1174 (m), 1152 (m), 1125 (m), 1099 (m), 1019 (m), 792 (s), 765 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 286 (81) $[M^+]$, 201 (3), 175 (2), 147 (4), 134 (18), 122 (100), 109 (18). HRMS (EI): calcd. for $C_{20}H_{30}O$ $[M]^+$ 286.2297; found 286.2293.

17β-Methylestr-4-ene-3-one (9): Concentrated hydrochloric acid (317 mg, 3.14 mmol) and H_2O (5 mL) were added to a solution of enol ether **7** (200 mg, 0.70 mmol) in MeOH (20 mL). The mixture was stirred under reflux for 1 h and then cooled to 23 °C. After addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents evaporated. The crude product was purified by chromatography (SiO_2, hexane/MTBE = 4:1, R_f = 0.28) to give **9** (180 mg, 0.66 mmol, 95%) as colorless crystals. M.p. 111 °C. $[\alpha]_D^{21}$ = +48.0 (*c* = 12.5 g/L, in CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.61 (s, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 0.98–1.38 (m, 8 H), 1.41 (ddd, *J* = 16.5, *J* = 6.9, *J* = 1.9 Hz, 1 H), 1.54–1.65 (m, 2 H), 1.73 (dt, *J* = 12.7, *J* = 3.3 Hz, 1 H), 1.78–1.87 (m, 3 H), 2.10 (td, *J* = 10.0, *J* = 4.4 Hz, 1 H), 2.22–2.29 (m, 3 H), 2.38–2.43 (m, 1 H), 2.47 (dt, *J* = 14.6, *J* = 2.9 Hz, 1 H), 5.82 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 11.96 (CH_3), 13.81 (CH_3), 24.51 (CH_2), 26.35 (CH_2), 26.62 (CH_2), 30.07 (CH_2), 31.34 (CH_2), 35.67 (CH_2), 36.54 (CH_2), 37.22 (CH_2), 40.76 (CH), 42.11 (C), 42.75 (CH), 45.07 (CH), 49.85 (CH), 54.46 (CH), 124.46 (CH), 167.04 (C), 199.92 (CO) ppm. IR (ATR): $\tilde{\nu}$ = 2943 (m), 2912 (s), 2866 (w), 2846 (m), 2362 (w), 1664 (s), 1612 (m), 1448 (w), 1419 (w), 1382 (w), 1360 (w), 1330 (w), 1257 (m), 1204 (m), 1179 (w), 1106 (w), 965 (m), 881 (m), 854 (w), 758 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 272 (100) $[M^+]$, 257 (17), 244 (13), 215 (28), 163 (51), 149 (29), 147 (27), 110 (83). HRMS (EI): calcd. for $C_{19}H_{28}O$ $[M]^+$ 272.2140; found 272.2143.

17β-Methylestr-3-one (10): A degassed suspension of enone **9** (80 mg, 0.29 mmol) and Pd/C (16 mg, 10% w/w Pd) in EtOAc (4 mL) was stirred under H_2 (1 atm) at 23 °C for 4 d. After filtration through a short pad of SiO_2, the crude product was purified by column chromatography (SiO_2, hexane/MTBE = 4:1, R_f = 0.32) to give a mixture of two epimers (ratio 5α/5β = 1.8:1 by GLC) of **10** (84 mg, 0.31 mmol, 93%) as colorless crystals. M.p. 105 °C.

$[\alpha]_D^{21}$ = +41 (*c* = 8.3 g/L, in CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): both epimers: δ = 0.58 (s, 3 H), 0.59 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.94–1.26 (m, 17 H), 1.31–1.34 (m, 7 H), 1.59–1.81 (m, 13 H), 2.06–2.40 (m, 10 H), 2.61 (t, *J* = 14.1 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 5β-epimer: δ = 12.01 (CH_3), 13.81 (CH_3), 24.56 (CH_2), 26.02 (CH_2), 30.21 (CH_2), 30.68 (CH_2), 30.89 (CH_2), 34.14 (CH_2), 37.48 (CH_2), 41.39 (CH), 41.41 (CH_2), 42.22 (C), 43.86 (CH), 45.24 (CH), 46.01 (CH), 48.14 (CH), 48.78 (CH_2), 54.80 (CH), 211.83 (CO); 5α-epimer: δ = 12.06 (CH_3), 13.81 (CH_3), 24.56 (CH_2), 25.70 (CH_2), 25.76 (CH_2), 27.85 (CH_2), 30.21 (CH_2), 30.76 (CH_2), 36.50 (CH_2), 37.56 (CH_2), 38.51 (CH), 38.72 (CH), 39.95 (CH), 41.84 (CH), 42.36 (C), 43.03 (CH_2), 45.30 (CH), 54.86 (CH), 212.95 (CO) ppm. IR (ATR): both epimers: $\tilde{\nu}$ = 2936 (m), 2909 (m), 2867 (m), 2845 (m), 1707 (s), 1468 (w), 1451 (w), 1373 (w), 1314 (w), 1266 (w), 1244 (w), 1232 (w), 1176 (w), 1102 (w), 1065 (w), 976 (w), 960 (w), 859 (w), 750 (w) cm^{-1}. GC–MS (EI, 70 eV): 5β-epimer: *m*/*z* (%) = 274 (22) [M^+], 232 (18), 218 (100), 217 (94), 203 (27), 199 (19), 175 (30), 162 (64), 147 (26), 135 (19), 107(38); 5α-epimer: *m*/*z* (%) = 274 (33) [M^+], 232 (17), 218 (100), 217 (84), 203 (35), 199 (57), 175 (27), 162 (47), 147 (49), 120 (30), 107 (55). HRMS (EI): calcd. for $C_{19}H_{30}O$ [M^+] 274.2297; found 274.2290.

17β-Methylestrane (1): A suspension of ketone **10** (80 mg, 0.29 mmol, 5α/5β = 1.8:1), $H_2NNH_2{\cdot}H_2O$ (43.5 mg, 0.87 mmol) and KOH (31 mg, 0.87 mmol) in DEG (3 mL) and toluene (0.5 mL) was heated under reflux for 1 h. Toluene and H_2O were removed by distillation, and the residue was subsequently heated to 200 °C for 2 h. After cooling to 23 °C, the solution was neutralized with hydrochloric acid (1 mL, 1 mol/ L), diluted with H_2O (5 mL) and extracted with MTBE (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvents evaporated. The crude product was purified by column chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.73) to give two epimers (ratio 5α/5β = 1.8:1 by GLC) of the title compound **1** (60 mg, 0.23 mmol, 79%) as a colorless oil. $[\alpha]_D^{21}$ = +20 (*c* = 8.2 g/L, in CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): both epimers: δ = 0.48 (s, 6 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H), 0.81–1.74 (m, 50 H), 1.81–1.84 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 5β-epimer: δ = 13.84 (CH_3), 12.03 (CH_3), 24.57 (CH_2), 25.55 (CH_2), 26.51 (CH_2), 26.93 (CH_2), 30.23 (CH_2), 30.39 (CH_2), 31.32 (CH_2), 34.18 (CH_2), 34.63 (CH_2), 37.67 (CH_2), 41.71 (CH), 42.19 (C), 43.39 (CH), 45.27 (CH), 47.59 (CH), 48.87 (CH), 55.16 (CH); 5α-epimer: δ = 13.84 (CH_3), 12.39 (CH_3), 20.39 (CH_2), 24.65 (CH_2), 25.62 (CH_2), 26.61 (CH_2), 26.97 (CH_2), 27.01 (CH_2), 28.64 (CH_2), 30.29 (CH_2), 32.52 (CH_2), 37.45 (CH), 37.75 (CH_2), 38.96 (CH), 41.50 (CH), 42.32 (C), 42.36 (CH), 45.35 (CH), 55.03 (CH) ppm. IR (ATR): both epimers: $\tilde{\nu}$ = 2912 (s), 2864 (m), 1446 (m), 1378 (m), 1334 (w), 1257 (w), 1098 (w), 1057 (w), 970 (w) cm^{-1}. GC–MS (EI, 70 eV): 5β-epimer: *m*/*z* (%) = 260 (21), 245 (6), 218 (19), 204 (83), 203 (100), 189 (26), 148 (24), 135 (20), 121 (14), 67 (17); 5α-epimer: *m*/*z* (%) = 260 (20), 245 (5), 218 (16), 204 (83), 203 (100), 189 (24), 148 (22), 135 (218), 121 (16), 67 (17). HRMS (EI): calcd. for $C_{19}H_{32}$ [M^+] 260.2504; found 260.2499.

3β-Hydroxy-17-methylene-5α-androstane (12): A suspension of $[Ph_3PMe]Br$ (939 mg, 2.63 mmol) and NaH (350 mg of a 60% dispersion in mineral oil, 8.76 mmol) in abs. THF (20 mL) under an inert gas was stirred at 70 °C for 15 min. A solution of **11** (509 mg, 1.75 mmol) in abs. THF (10 mL) was added dropwise, and the resulting mixture was further stirred at 70 °C for 16 h. After cooling to ambient temperature, some water was added dropwise, and then the mixture was diluted with water (75 mL) and MTBE (75 mL). The layers were separated, and the aqueous layer was extracted with MTBE (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), and, after filtration, the solvent was evaporated and the residue submitted to column chromatography (SiO_2, hexane/MTBE = 1:1 → 1:5) to yield **12** (458 mg, 1.58 mmol, 91%) in the main fraction [R_f(hexane/MTBE = 1:2) = 0.35] as a colorless solid. M.p. 131 °C. $[\alpha]_D^{20}$ = +11.6 (*c* = 8.35 g/L, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.66–0.72 (m, 1 H), 0.81 (s, 3 H), 0.86 (s, 3 H), 0.91–0.94 (m, 3 H), 1.11–1.17 (m, 1 H), 1.19–1.49 (m, 8 H), 1.58–1.68 (m, 3 H), 1.70–1.78 (m, 3 H), 1.81–1.85 (m, 2 H), 2.25 (dt, *J* = 17.3, *J* = 8.7 Hz, 1 H, 16-H), 2.51 (ddd, *J* = 17.3, *J* = 10.1, *J* = 1.7 Hz, 1 H, 16-H), 3.62 (tt, *J* = 11.1, *J* = 4.8 Hz, 1 H, 3-H), 4.64 (s, 1 H, 20-H), 4.65 (s, 1 H, 20-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 12.25 (CH_3), 18.44 (CH_3), 21.07 (CH_2), 24.05 (CH_2), 28.59 (CH_2), 29.30 (CH_2), 31.36 (CH_2), 31.84 (CH_2), 35.39 (CH), 35.51 (C), 35.65 (CH_2), 36.98 (CH_2), 38.06 (CH_2), 44.01 (C), 44.86 (CH), 54.37 (CH), 54.53 (CH), 71.01 (CH), 100.57 (C), 161.72 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3327 (s, br), 3062 (w), 2925 (vs), 2846 (s), 1653 (m), 1467 (m), 1447 (m), 1368 (m), 1141 (m), 1077 (m), 1036 (vs), 873 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 288 (12) [M^+], 273 (49), 255 (48), 232 (18), 231 (13), 214 (5), 199 (7), 189 (7), 188 (13), 176 (5), 173 (5), 163 (48), 162 (68), 149 (14), 147 (38), 135 (16), 133 (27), 121 (27), 120 (26), 119 (30), 108 (74), 107 (100), 105 (59), 95 (44), 93 (88), 91 (93). HRMS (EI): calcd. for $C_{20}H_{32}O$ [M^+] 288.2453; found 288.2445.

3β-Hydroxy-17β-methyl-5α-androstane (14): A suspension of olefin **12** (458 mg, 1.58 mmol) and Pd/C (50 mg, 10% w/w Pd) in *i*PrOH (11 mL) was hydrogenated with H_2 (3 bar) at 65 °C for 16 h. The mixture was filtered through SiO_2 (5 cm, hexane/MTBE = 1:2, R_f = 0.41), and the solvent was evaporated to yield **14** (446 mg, 1.53 mmol, 97%) as a colorless solid. M.p. 127 °C. $[\alpha]_D^{20}$ = +6.5 (*c* = 10.4 g/L, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.56 (s, 3 H), 0.64–0.69 (m, 1 H), 0.84 (s, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H, 17-CH_3), 0.88–1.03 (m, 4 H), 1.02–1.84 (m, 19 H), 3.61 (tt, *J* = 11.1, *J* = 4.8 Hz, 1 H, 3-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 11.97 (CH_3), 12.29 (CH_3), 13.75 (CH_3), 20.97 (CH_2), 24.65 (CH_2), 28.71 (CH_2), 30.11 (CH_2), 31.41 (CH_2), 32.17 (CH_2), 35.51 (C), 35.67 (CH), 37.06 (CH_2), 37.53 (CH_2), 38.13 (CH_2), 42.00 (C), 44.96 (CH), 45.03 (CH), 54.73 (CH), 55.76 (CH), 71.10 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3299 (br. s), 2931 (vs), 2865 (s), 2846 (s), 1469 (m), 1447 (m), 1369 (m), 1343 (m), 1133 (m), 1083 (m), 1039 (vs), 731 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 290 (29) [M^+], 275 (34), 257 (32), 248 (14), 234 (78), 233 (65), 215 (29), 216 (42), 215 (84), 165 (57). HRMS (EI): calcd. for $C_{20}H_{34}O$ for $C_{20}H_{34}O$ [M^+] 290.2610; found 290.2604.

17β-Methyl-5α-androstan-3-one (13): PCC (851 mg, 3.95 mmol) was added to a solution of alcohol **14** (446 mg, 1.53 mmol) in CH_2Cl_2 (40 mL). The resulting mixture was stirred at 23 °C for 2 h and then diluted with MTBE (40 mL). Filtration through SiO_2 (5 cm, hexane/MTBE = 1:2, R_f = 0.57) and evaporation of the solvent yielded **13** (415 mg, 1.44 mmol, 94%) as a colorless solid. M.p. 137 °C. $[\alpha]_D^{20}$ = +29 (*c* = 9.4 g/L, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.47 (s, 3 H), 0.64–0.71 (m, 1 H), 0.74 (d, *J* = 6.8 Hz, 3 H, 17-CH_3), 0.79–0.90 (m, 3 H), 0.93 (s, 3 H), 0.99–1.72 (m, 14 H), 2.01 (dt, *J* = 15.0, *J* = 2.9 Hz, 1 H), 1.95 (ddd, *J* = 13.1, *J* = 6.5, *J* = 2.0 Hz, 1 H), 2.18 (d, *J* = 14.3 Hz, 1 H), 2.20–2.24 (m, 1 H), 2.31 (dt, *J* = 6.6, *J* = 14.3 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 11.20 (CH_3), 11.78 (CH_3), 13.56 (CH_3), 20.98 (CH_2), 24.46 (CH_2), 28.75 (CH_2), 29.89 (CH_2), 31.61 (CH_2), 35.35 (CH), 35.49 (C), 37.22 (CH_2), 37.83 (CH_2), 38.39 (CH_2), 41.80 (C), 44.40 (CH_2), 44.80 (CH), 46.55 (CH), 53.97 (CH), 55.34 (CH), 211.07 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2930 (s), 2865 (s), 2843 (m), 1712 (vs), 1442 (m), 1431 (m), 1367 (m), 1228 (m), 965 (m), 879 (m), 683 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 288 (84) [M^+], 273 (24), 255

(5), 246 (22), 232 (95), 231 (100), 217 (35), 163 (38). HRMS (EI): calcd. for $C_{20}H_{32}O$ $[M]^+$ 288.2453; found 288.2445.

17β-Methyl-5α-androstane (2): A suspension of ketone **13** (338 mg, 1.17 mmol), KOH (164 mg, 2.93 mmol), $H_2NNH_2{\cdot}H_2O$ (585 mg, 11.7 mmol) in DEG (8 mL) was heated to 200–220 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with brine (30 mL) and extracted with hexane (3 × 30 mL). The combined hexane layers were dried (Na_2SO_4) and concentrated after filtration. The residue was purified by chromatography (SiO_2, hexane, R_f = 0.70) to yield **2** (270 mg, 0.99 mmol, 85%) as a colorless wax. M.p. 86.9–90.5 °C. $[\alpha]_D^{20}$ = +6.5 (*c* = 9.9 g/L, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.51 (s, 3 H), 0.62–0.67 (m, 1 H), 0.76 (s, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.83–1.65 (m, 23 H), 1.69–1.77 (m, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 12.09 (CH_3), 12.31 (CH_3), 13.88 (CH_3), 20.68 (CH_2), 22.31 (CH_2), 24.77 (CH_2), 26.94 (CH_2), 29.20 (CH_2), 29.22 (CH_2), 30.27 (CH_2), 32.42 (CH_2), 35.85 (CH), 36.43 (C), 37.75 (CH_2), 38.88 (CH_2), 42.14 (C), 45.20 (CH_2), 47.29 (CH_2), 55.29 (CH_2), 56.05 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 2921 (vs), 2863 (s), 1468 (m), 1446 (m), 1376 (m), 1334 (w), 1103 (w), 966 (w), 831 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 274 (29) $[M^+]$, 259 (59), 232 (12), 218 (83), 217 (100), 203 (24), 149 (53). HRMS (EI): calcd. for $C_{20}H_{34}$ $[M]^+$ 274.2661; found 274.2655.

17β-Methyl-A-*nor*-androstane (3): $Tl(NO_3)_3{\cdot}3H_2O$ (1.35 g, 3.04 mmol) was added to a solution of ketone **13** (399 mg, 1.38 mmol) in CH_2Cl_2 (23 mL). The resulting heterogeneous mixture was vigorously stirred at 23 °C for 16 h. The solvent was evaporated, and the residue was suspended in MTBE (4 mL). Filtration through SiO_2 (5 cm, hexane/MTBE = 1:2, R_f = 0.89–0.44) yielded a crude mixture of carboxylic acids **15** (453 mg) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.46 (s, 3 H), 0.64 (s, 3 H), 0.74 (d, *J* = 6.9 Hz, 3 H), 0.63–1.73 (m, 21 H), 2.77–2.88 (m, 1 H), 7.10 (br. s, 1 H) ppm. MS (ESI, neg. mode): *m*/*z* 303 $[M - H^+]$. The material was redissolved in C_6H_6 (25 mL). DCC (432 mg, 2.09 mmol) and DMAP (5 mg) were added, and the mixture was stirred at 23 °C for 5 min. Subsequently, 1-hydroxy-2-thiopyridone (320 mg, 2.52 mmol) was added, and the mixture was further stirred under exclusion of light at 23 °C for 2.5 h. Bu_3SnH (2.5 mL, 2.7 g, 9.4 mmol) and AIBN (10 mg) were then added, and the mixture was heated to reflux for 16 h. After cooling to ambient temperature, a solution of KOH (26 g) in water (60 mL) was added, and the resulting mixture was stirred at 23 °C for 0.5 h and then extracted with hexane (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvents were evaporated. The residue was purified by chromatography (SiO_2, hexane, R_f = 0.70–0.65) to yield a nonpolar fraction. After evaporation of the solvent (1.42 g, colorless liquid), it was treated with concentrated hydrochloric acid (10 mL). The resulting mixture was stirred at 23 °C for 2 h and then extracted three times with hexane (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvents were evaporated. The residue was purified by chromatography (SiO_2, hexane, R_f = 0.69) to yield **3** (60 mg, 0.23 mmol, 17%) as a colorless solid. M.p. 47.3–47.5 °C. $[\alpha]_D^{20}$ = +1.6 (*c* = 8.6 g/L, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.48 (s, 3 H), 0.59 (s, 3 H), 0.75 (d, *J* = 6.9 Hz, 3 H, 17-CH_3), 0.63–1.73 (m, 23 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 12.19 (CH_3), 13.00 (CH_3), 13.84 (CH_3), 20.50 (CH_2), 23.32 (CH_2), 25.01 (CH_2), 25.57 (CH_2), 27.69 (CH_2), 30.20 (CH_2), 32.50 (CH_2), 35.93 (CH), 37.62 (CH_2), 38.82 (CH_2), 42.48 (C), 43.60 (C), 45.13 (CH), 50.76 (CH), 55.37 (CH), 55.67 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 2922 (vs), 2866 (s), 1468 (m), 1448 (m), 1376 (m), 1332 (w), 1107 (w), 937 (w), 888 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 260 (9) $[M^+]$, 245 (42), 218 (17), 217 (11), 204 (66), 203 (100), 189 (41), 175 (16), 164 (19), 161 (20), 149 (28), 136 (32), 135 (85), 121 (31),109 (43), 107 (39), 95 (63), 93 (38), 91 (28). HRMS (EI): calcd. for $C_{19}H_{32}$ $[M]^+$ 260.2504; found 260.2499.

3β-Hydroxy-5α-androstane (16): A suspension of ketone **11** (1.05 g, 3.63 mmol), KOH (508 mg, 9.05 mmol), and $H_2NNH_2{\cdot}H_2O$ (1.8 g, 36 mmol) in DEG (24 mL) was heated to 200–220 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with brine (250 mL) and extracted with MTBE (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated after filtration. The residue was purified by chromatography (SiO_2, hexane/MTBE = 1:2, R_f = 0.32) to yield **16** (817 mg, 2.96 mmol, 82%) as a colorless solid. M.p. 134 °C. $[\alpha]_D^{20}$ = +2.2 (*c* = 9.0 g/L, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.60–0.64 (m, 1 H), 0.66 (s, 3 H), 0.78 (s, 3 H), 0.81–1.78 (m, 24 H), 3.55 (tt, *J* = 11.1, *J* = 4.7 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 12.29 (CH_3), 17.47 (CH_3), 20.43 (CH_2), 21.20 (CH_2), 25.45 (CH_2), 28.69 (CH_2), 31.38 (CH_2), 32.38 (CH_2), 35.51 (C), 35.79 (CH), 37.02 (CH_2), 38.07 (CH_2), 38.84 (CH_2), 40.36 (CH_2), 40.75 (C), 44.80 (CH), 54.46 (CH), 54.56 (CH), 71.20 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3339 (m), 2929 (vs), 2843 (s), 1447 (m), 1376 (m), 1132 (m), 1080 (m), 1044 (s), 754 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 276 (93) $[M^+]$, 261 (22), 258 (28), 243 (100), 218 (18), 215 (24), 203 (44), 190 (22), 161 (19), 149 (24), 147 (25), 135 (33), 107 (47), 95 (64), 81 (53). HRMS (EI): calcd. for $C_{19}H_{32}O$ $[M]^+$ 276.2453; found 276.2461.

5α-Androstan-3-one (18): PCC (1.60 g, 7.40 mmol) was added to a solution of alcohol **16** (817 mg, 2.96 mmol) in CH_2Cl_2 (80 mL). The resulting mixture was stirred at 23 °C for 16 h and then diluted with MTBE (80 mL). Filtration through SiO_2 (10 cm, hexane/MTBE = 1:2, R_f = 0.66) and evaporation of the solvent yielded **18** (647 mg, 2.34 mmol, 80%) as a colorless solid. M.p. 87–88 °C. $[\alpha]_D^{20}$ = +20 (*c* = 9.1 g/L, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.69 (s, 3 H), 0.70–0.75 (m, 1 H), 0.86–0.93 (m, 2 H), 0.98 (s, 3 H), 1.09–1.16 (m, 3 H), 1.23–1.43 (m, 6 H), 1.47–1.72 (m, 7 H), 1.99 (dd, *J* = 13.1, *J* = 6.4 Hz, 1 H), 2.05 (dt, *J* = 14.9, *J* = 1.8 Hz, 1 H), 2.21 (d, *J* = 14.4 Hz, 1 H), 2.23–2.28 (m, 1 H), 2.35 (td, *J* = 14.6, *J* = 6.6 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 11.43 (CH_3), 17.47 (CH_3), 20.46 (CH_2), 21.44 (CH_2), 25.48 (CH_2), 28.97 (CH_2), 32.05 (CH_2), 35.74 (CH and C), 38.12 (CH_2), 38.62 (CH_2), 38.76 (CH_2), 40.35 (CH_2), 40.79 (C), 44.67 (CH_2), 46.71 (C), 54.09 (CH), 54.34 (CH), 211.89 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2931 (s), 2894 (m), 2868 (m) 2843 (m), 1711 (vs), 1444 (m), 1376 (m), 1240 (m), 944 (m), 730 (m), 685 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 274 (30) $[M^+]$, 259 (12), 241 (14), 231 (19), 217 (10), 207 (11), 204 (75), 203 (100), 189 (13), 187 (37). HRMS (EI): calcd. for $C_{19}H_{30}O$ $[M]^+$ 274.2297; found 274.2290.

2α-(Hydroxymethyl)-A-*nor*-androstane (19): $Tl(NO_3)_3{\cdot}3H_2O$ (2.59 g, 5.85 mmol) was added to a solution of ketone **18** (647 mg, 2.34 mmol) in CH_2Cl_2 (40 mL). The resulting heterogeneous mixture was vigorously stirred at 23 °C for 16 h. The solvent was evaporated, and the residue was suspended in MTBE (4 mL). Filtration through SiO_2 (5 cm, hexane/MTBE = 1:2, R_f = 0.70–0.35) yielded a crude mixture of carboxylic acids **17** (761 mg) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.72 (s, 3 H), 0.73 (s, 3 H), 0.83–0.97 (m, 3 H), 1.11–1.32 (m, 5 H), 1.38–1.52 (m, 5 H), 1.56–1.76 (m, 7 H), 1.91–2.02 (m, 2 H), 2.89–2.99 (m, 1 H) ppm; the signal of the carboxylate proton was not observed. The material was redissolved in abs. THF (20 mL), then $LiAlH_4$ (994 mg, 26.2 mmol) was added, and the resulting mixture was stirred under an inert gas at 50 °C for 16 h. The mixture was diluted with a saturated aqueous solution of NH_4Cl (200 mL) and concentrated hydrochloric acid (4 mL) and then extracted with CH_2Cl_2 (3 × 100 mL). The organic extract was dried ($MgSO_4$), the solvent was evaporated, and the

residue was purified by chromatography (SiO_2, hexane/MTBE, 1:2, R_f = 0.44) to give **19** (441 mg, 1.48 mmol, 57%) as a colorless oil, which slowly solidified upon storage at –5 °C. M.p. 69 °C. $[\alpha]_D^{20}$ = +11 (c = 3.0 g/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.67 (s, 3 H), 0.69 (s, 3 H), 0.71–0.93 (m, 5 H), 1.08–1.26 (m, 5 H), 1.34–1.70 (m, 13 H), 2.20–2.25 (m, 1 H), 3.44–3.49 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.71 (CH_3), 17.68 (CH_3), 20.44 (CH_2), 23.46 (CH_2), 25.36 (CH_2), 25.74 (CH_2), 31.36 (CH_2), 32.58 (CH_2), 35.89 (CH), 37.92 (CH), 38.90 (CH_2), 40.48 (CH_2), 41.20 (C), 43.06 (CH_2), 44.14 (C), 49.33 (CH), 54.32 (CH), 55.29 (CH), 68.23 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3299 (m), 2920 (vs), 2860 (s), 2847 (s), 1454 (m), 1378 (m), 1334 (w), 1170 (w), 1066 (m), 1041 (s), 1023 (m), 986 (m), 896 (w) cm^{-1}. MS (EI, 70 eV): m/z (%) = 276 (36) [M$^+$], 261 (64), 258 (24), 243 (100), 233 (16), 218 (21), 203 (76), 189 (20), 176 (18), 175 (20), 165 (20), 161 (21), 149 (33), 147 (31), 135 (32), 133 (17), 121 (23), 119 (13), 109 (23), 108 (25), 107 (44), 105 (20), 95 (73), 93 (42), 91 (24), 81 (55), 79 (38), 67 (42). HRMS (EI): calcd. for $C_{19}H_{32}O$ [M]$^+$ 276.2453; found 276.2450.

2α-(Chloromethyl)-A-*nor*-androstane (20): A mixture of alcohol **19** (335 mg, 1.21 mmol), pyridine (2.0 mL, 24 mmol), and methanesulfonyl chloride (0.9 mL, 12 mmol) was stirred at 90 °C for 1.5 h. The mixture was diluted with hexane (20 mL), water (20 mL), and concentrated hydrochloric acid (2 mL) and then extracted with MTBE (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents were evaporated. The residue was purified by chromatography (SiO_2, hexane, R_f = 0.41) to yield **20** (172 mg, 0.583 mmol, 48%) as a colorless oil. $[\alpha]_D^{20}$ = +12 (c = 5.7 g/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.74 (s, 3 H, C-18), 0.76 (s, 3 H, C-19), 0.83 (ddd, J = 12.3, J = 10.6, J = 4.3 Hz, 1 H), 0.88–0.99 (m, 3 H), 1.15–1.77 (m, 17 H), 1.81 (dd, J = 12.0, J = 7.8 Hz, 1 H, 1β-H), 2.44–2.53 (m, 1 H, 2β-H), 3.50 (d, J = 6.9 Hz, 2 H, 2α-CH_2Cl) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.65 (CH_3; C-19), 17.67 (CH_3; C-18), 20.43 (CH_2), 23.44 (CH_2), 25.22 (CH_2), 25.71 (CH_2), 32.49 (CH_2), 32.74 (CH_2), 35.80 (CH; C-5), 38.06 (CH; C-2), 38.83 (CH_2), 40.45 (CH_2), 41.16 (C), 44.58 (C), 44.72 (CH_2; C-1), 49.31 (CH), 51.02 (CH_2; 2-CH_2Cl), 54.25 (CH), 55.12 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 2922 (vs), 2858 (s), 2845 (s), 1451 (m), 1377 (m), 1297 (w), 1284 (w), 1254 (w), 722 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 294 (2) [M$^+$], 279 (25), 251 (19), 204 (18), 203 (23), 189 (16), 183 (23). HRMS (EI): calcd. for $C_{19}H_{31}Cl$ [M]$^+$ 294.2114; found 294.2121.

2α-Methyl-A-*nor*-androstane (4): A solution of **20** (134 mg, 0.454 mmol), nBu$_3$SnH (720 mg, 2.47 mmol), and AIBN (24 mg, 0.15 mmol) in C_6H_6 (10 mL) was degassed and heated to reflux under N_2 for 16 h. Subsequently, all volatile materials were removed in vacuo, and the residue was purified by chromatography (SiO_2, hexane, R_f = 0.70–0.65) to yield a mixture of Bu$_3$SnH, compound **4** and Bu$_3$SnSnBu$_3$ (531 mg; 6:3:1 according to GLC). This mixture was stirred with concentrated hydrochloric acid (5 mL) at 23 °C for 16 h. The mixture was extracted with hexane (3 × 25 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the solvents were evaporated. The residue was purified by chromatography (SiO_2, hexane, R_f = 0.68) to give **4** (98 mg, 0.376 mmol, 83%) as a colorless oil. According to GLC integration, the material contained about 2% Bu$_3$SnSnBu$_3$. $[\alpha]_D^{20}$ = +3.3 (c = 2.0 g/L, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69 (s, 3 H), 0.70 (s, 3 H), 0.72–0.80 (m, 1 H), 0.97 (d, J = 6.9 Hz, 3 H), 1.11–1.76 (m, 21 H), 2.08–2.15 (m, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.67 (CH_3), 17.69 (CH_3), 20.45 (CH_2), 23.34 (CH_3), 23.48 (CH_2), 25.44 (CH_2), 25.75 (CH_2), 29.16 (CH), 32.72 (CH_2), 35.88 (CH), 36.65 (CH_2), 38.96 (CH_2), 40.50 (CH_2), 41.21 (C), 45.04 (C), 49.11 (CH), 49.14 (CH_2), 54.37 (CH), 55.42 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 2946 (s), 2923 (vs), 2859 (s), 1452 (m), 1376 (m), 941 (w), 891 (w) cm^{-1}. MS (EI, 70 eV): m/z (%) = 260 (25) [M$^+$], 245 (100), 218 (17), 217 (32), 204 (60), 203 (90), 189 (79), 176 (22), 175 (34), 163 (27), 161 (33), 149 (90), 135 (69), 133 (24), 121 (44), 109 (54), 107 (62), 95 (99), 93 (56), 91 (33). HRMS (EI): calcd. for $C_{19}H_{32}$ [M]$^+$ 260.2504; found 260.2500.

Acknowledgments

We are indebted to Prof. Roger E. Summons (MIT, Cambridge) for stimulating this study, for information on the natural occurrence of the unknown putative C_{19} steranes, and for discussions on the strategies for selecting target compounds for organic synthesis. We thank Dr. Herbert Frey (IRAC) and Bernd Kopke (ICBM) for their support in synthesis and comparative GC–MS analysis of synthetic and fossil steranes, respectively. We are moreover grateful to Dr. Amy E. Kelly, Arizona State University, for supplying saturated hydrocarbon fractions of crude oils for coinjections.

[1] E. Grosjean, G. D. Love, C. Stalvies, D. A. Fike, R. E. Summons, *Org. Geochem.* **2009**, *40*, 87–100.

[2] For overviews, see: a) S. M. Gaines, G. Eglinton, J. Rullkötter, *Echoes of Live: What Fossil Molecules Reveal About Earth History*, Oxford University Press, New York, **2008**; b) K. E. Peters, C. C. Walters, J. M. Moldowan, *The Biomarker Guide*, Cambridge University Press, Cambridge, **2005**; c) S. C. Brassell, G. Eglinton, J. R. Maxwell, *Biochem. Soc. Trans.* **1983**, *11*, 575–586.

[3] a) W. Xie, H. Peng, D.-I. Kim, M. Kunkel, G. Powis, L. H. Zalkow, *Bioorg. Med. Chem.* **2001**, *9*, 1073–1083; b) D. Klomp, K. Djanashvili, N. C. Svennum, N. Chantapariyavat, C.-S. Wong, F. Vilela, T. Maschmeyer, J. A. Peters, U. Hanefeld, *Org. Biomol. Chem.* **2005**, *3*, 483–489.

[4] For a review, see: B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.

[5] A. Kuhl, W. Kreiser, *Helv. Chim. Acta* **1998**, *81*, 2264–2269.

[6] H. J. Nicholas, *J. Org. Chem.* **1958**, *23*, 1747–1749.

[7] a) N. G. Aher, R. G. Gonnade, V. S. Pore, *Synlett* **2009**, 2005–2009; b) R. Jogireddy, J. Rullkötter, J. Christoffers, *Synlett* **2007**, 2847–2850.

[8] a) A. L. Wilds, N. A. Nelson, *J. Am. Chem. Soc.* **1953**, *75*, 5360–5365; b) C. Djerassi, P. A. Hart, C. Beard, *J. Am. Chem. Soc.* **1965**, *87*, 85–90; c) for a review, see: H. Pellissier, M. Santelli, *Org. Prep. Proced. Int.* **2002**, *34*, 609–642.

[9] a) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488; b) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301–3303.

[10] M. Pelecanou, S. Nicolaropoulos, *Z. Naturforsch., Teil B* **1993**, *48*, 1305–1306.

[11] a) K. Ueno, *Chem. Pharm. Bull.* **1964**, *12*, 92–100; b) S. A. Julia, H. Heusser, *Helv. Chim. Acta* **1952**, *35*, 2080–2089; c) L. Ruzicka, P. Meister, V. Prelog, *Helv. Chim. Acta* **1947**, *30*, 867–878.

[12] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647–2650.

[13] A. K. Bose, P. Mangiaracina, *Tetrahedron Lett.* **1987**, *28*, 2503–2506.

[14] G. van Graas, F. de Lange, J. W. de Leeuw, P. A. Schenck, *Nature* **1982**, *296*, 59–61.

[15] L. Ruzicka, V. Prelog, P. Meister, *Helv. Chim. Acta* **1945**, *28*, 1651–1660.

[16] N. Pappas, H. R. Nace, *J. Am. Chem. Soc.* **1959**, *81*, 4556–4561.

[17] a) H. M. C. Ferraz, L. F. Silva Jr., *J. Org. Chem.* **1998**, *63*, 1716–1718; b) H. M. C. Ferraz, L. F. Silva Jr., *J. Braz. Chem.*

Soc. **2001**, *12*, 548–551; c) for a review, see: L. F. Silva Jr., V. M. T. Carneiro, *Synthesis* **2010**, 1059–1074.
[18] M.-L. Bennasar, B. Vidal, R. Kumar, A. Lazaro, J. Bosch, *Eur. J. Org. Chem.* **2000**, 3919–3925.
[19] J. Fishman, *J. Org. Chem.* **1962**, *27*, 1745–1749.
[20] H.-J. Schneider, U. Buchheit, N. Becker, G. Schmidt, U. Siehl, *J. Am. Chem. Soc.* **1985**, *107*, 7027–7039.
[21] S. Sarkar, S. Gosh, *Tetrahedron* **1994**, *50*, 921–930.
[22] M. Ratier, B. Jousseaume, N. Noiret, N. Petit, J.-C. Lartigue, M. Petraud, *Magn. Reson. Chem.* **1993**, *31*, 176–181.
Received: March 21, 2011
Published Online: June 17, 2011

