Supporting Information

Stereoselective Semisynthesis of Uzarigenin and *allo*-Uzarigenin

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Contents

1. General remarks

NMR spectra were recorded on a *Bruker* Avance 400, *Bruker* Avance 500 DRX or *Bruker* Avance 600 spectrometer from dissolved samples at room temperature. Chemical shifts δ are expressed in parts per million (ppm) and referenced to the residual solvent peaks of chloroform (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.16 ppm) and DMSO-d_6 (^{1}H: δ = 2.50 ppm; ^{13}C: δ = 39.52 ppm), respectively. The measured coupling constants (*J*) are absolute values expressed in Hertz (Hz). The description of signals includes: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets and so forth. The spectra were analysed according to first order. The assignments of the signal structure in ^{1}H NMR were made based on the multiplicity and chemical shifts including the usage of 2D-experiments such as COSY (correlation spectroscopy), HSQC (Heteronuclear Single-Quantum Correlation Spectroscopy), HMBC (Heteronuclear Multiple-Bond Correlation Spectroscopy) and NOESY (Nuclear Overhauser Effect Spectroscopy). Additionally, the assignments for ^{13}C NMR were based on the evaluation of DEPT 90- and DEPT 135-spectra (DEPT = Distortionless Enhancement by Polarization Transfer) or edited HSQC experiments and are described as follows: + = primary or tertiary C-atom (positive signal), – = secondary C-atom (negative signal) and C_q = quaternary C-atom (no signal). For the synthesized organotin compounds, couplings to the tin isotopes ^{119}Sn and ^{117}Sn were observed in the ^{1}H NMR and ^{13}C NMR spectra. If their coupling was clearly evident, it was stated with a "+" (for example as s+d+d for a ^{1}H or ^{13}C singlet showing ^{119}Sn- and ^{117}Sn-coupling or as s+d for a ^{1}H or ^{13}C singlet for which the different couplings could not be resolved). The greater coupling constant indicates the ^{119}Sn-coupling with the coupling constant stated as $^{n}J_{119Sn\text{-}H/C}$, whereas the smaller coupling constant indicates the ^{117}Sn-coupling with the coupling constant stated as $^{n}J_{117Sn\text{-}H/C}$. If the different ^{119}Sn- and ^{117}Sn-couplings could not be resolved, the coupling constant was stated as $^{n}J_{119/117Sn\text{-}H/C}$.

Common solvent impurity signals as followed were not explicitly listed: ^{1}H NMR ($CDCl_3$): 1.56 (H_2O), 1.26 (H grease), 0.84 – 0.87 (H grease), 0.07 (silicon grease) ppm; ^{13}C NMR ($CDCl_3$): 29.8 (H grease), 1.0 (silicon grease) ppm; ^{1}H NMR (DMSO-d_6): 3.33 (H_2O) ppm; ^{13}C NMR (DMSO-d_6): 29.2 (H grease) ppm.

IR spectra were recorded on an FT-IR *Bruker* IFS 88 spectrometer. The compounds were measured as pure substances by ATR technique (ATR = attenuated total reflection). The positions of the absorption bands are given in wavenumbers $\tilde{\nu}$ in cm^{-1}. The intensities of the bands were characterized as follows: vs = very strong (0 – 9% T), s = strong (10 – 39% T), m = medium (40 – 69% T), w = weak (70 – 89% T), vw = very weak (90 – 100% T).

Mass spectra were measured by EI-MS (electron ionization mass spectrometry) and FAB-MS (fast atom bombardment mass spectrometry) and were recorded on a *Finnigan* MAT 95. The peaks are given as mass-to-charge ratio (*m*/*z*). Furthermore, ESI experiments were recorded on a Q-Exactive (Orbitrap) mass spectrometer (*Thermo Fisher Scientific*, San José, CA, USA) equipped with a HESI II probe to record high resolution. The molecule peak is given as $[M]^+$, $[M+H]^+$ or $[M–H]^+$ and characteristic fragment peaks are given as $[M–fragment]^+$ or $[fragment]^+$. The signal intensities are given in percent, relatively to the intensity of the base signal (100%). For the high resolution mass, the following abbre*via*tions were used: calc. = calculated data, found = measured data.

Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel coated aluminium plates (silica gel 60, F254). The detection was conducted under UV-light at 254 nm or stained with "Seebach staining solution" (mixture of molybdato phosphoric acid, cerium(IV)-sulfate tetrahydrate, sulfuric acid and water). Solvent mixtures are understood as volume/volume. Solvents, reagents, and chemicals were purchased from *Sigma-Aldrich*, *abcr, Thermo Fisher Scientific, TCI, ChemPur, Carbosynth* and *Acros Organics*. All solvents, reagents, and chemicals were used as purchased unless stated otherwise. Palladium on carbon (10 wt.% loading) was purchased from *Sigma-Aldrich*. The Co(II) catalysts $Co(dpm)_2$[1], $Co(bzac)_2$[2], $Co(tfa)_2$[3,4] and the Co(III) catalyst [*N*-salicylidene-2-amino-isobutyrato]-[2-amino-isobutyrato]-cobalt (III) (**SI-01**)[5] were synthesized according to the literature.

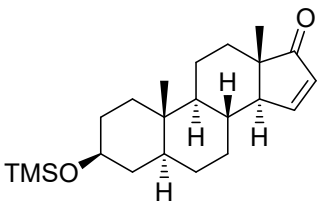
Air- or moisture-sensitive reactions were carried out under argon atmosphere in oven-dried and previously evacuated glassware. Liquids were transferred with plastic syringes and steel cannula. Reaction control was performed by thin-layer chromatography. If not stated otherwise, crude products were purified by flash chromatography by the procedure of *Still*.[6] Silica gel 60 (0.040 × 0.063 mm, *Merck*) was used as stationary phase and as mobile phase, solvents of *p.a.* quality were used.

2. Experimental procedures and analytical data

2.1. *Saegusa-Ito* oxidation

2.1.1. Experimental procedures and analytical data of the precursors and products

3β-Trimethylsilyloxy-5α-androst-15-en-17-one (**8**)



In a flame dried Schlenk flask under argon atmosphere, *epi*-androsterone (**5**) (5.00 g, 17.2 mmol, 1.00 equiv.) was dissolved in absolute tetrahydrofuran (250 mL) and cooled to –78 °C. Then 2 M lithium diisopropylamide solution in tetrahydrofuran/*n*-heptane/ethylbenzene (26 mL, 51.6 mmol, 3.00 equiv.) was added dropwise over 1.5 h. The suspension was stirred at this temperature for 1 h before absolute triethylamine (14 mL, 10.5 g, 103 mmol, 6.00 equiv.) and trimethylsilyl chloride (6.6 mL, 5.61 g, 51.6 mmol, 3.00 equiv.) were added and the reaction mixture was slowly warmed up to room temperature. The mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine (200 mL) and after phase separation, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The obtained crude product was dissolved in a mixture of absolute dichloromethane and absolute *N*,*N*-dimethylformamide (3:2, 70 mL) under oxygen atmosphere and palladium(II) acetate (772 mg, 3.44 mmol, 20 mol%) and copper(II) acetate (1.25 g, 6.88 mmol, 40 mol%) were added. Oxygen was bubbled through the solution for 1 h and the reaction mixture was stirred at room temperature for 24 h. The suspension was filtered through a pad of silica gel (cHex/EtOAc, 1:1 as eluent) and the solvents were removed under reduced pressure. The crude product was taken up in dichloromethane (200 mL) and washed with water (300 mL). The aqueous phase was extracted with dichloromethane (2 × 200 mL) and the combined organic phases were washed with water (200 mL), saturated aqueous NH_4Cl solution (200 mL) and brine (200 mL). After phase separation, the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (cHex/EtOAc, 4:1) afforded the title compound as a colorless solid (4.09 g, 11.4 mmol, 66%).

***R*$_f$** = 0.36 (cHex/EtOAc, 6:1). – **^{1}H NMR** (400 MHz, $CDCl_3$)*: δ = 7.54 – 7.48 (m, 1H, 16-C*H*), 6.01 (dd, *J* = 6.0, 3.1 Hz, 1H, 15-C*H*), 3.55 (tt, *J* = 11.1, 4.8 Hz, 1H, 3-C*H*), 2.26 (dt, *J* = 11.4, 2.6 Hz, 1H, 14-C*H*), 1.97 (dq, *J* = 12.6, 3.5 Hz, 1H, CH_2), 1.90 – 1.82 (m, 1H, CH_2), 1.83 – 1.72 (m, 1H, 8-C*H*), 1.75 – 1.59 (m, 3H, 3 different CH_2), 1.57 – 1.25 (m, 7H, 5 different CH_2), 1.19 – 1.10 (m, 1H, 5-C*H*), 1.10 – 1.04 (m, 1H, CH_2), 1.05 (s, 3H, 18-CH_3), 0.97 (td, *J* = 13.6, 4.3 Hz, 1H, CH_2), 0.86 (s, 3H, 19-CH_3), 0.84 – 0.68 (m, 1H, 9-C*H*), 0.11 (s, 9H,

3 × Si*C*H_3) ppm. – **^{13}C NMR** (101 MHz, $CDCl_3$)*: δ = 213.5 (C_q, *C*O), 158.8 (+, 15-*C*H), 131.8 (+, 16-*C*H), 71.8 (+, 3-*C*H), 57.1 (+, 14-*C*H), 56.0 (+, 9-*C*H), 51.3 (C_q, 13-*C*), 45.5 (+, 5-*C*H), 38.6 (–, *C*H_2), 37.0 (–, *C*H_2), 36.1 (C_q, 10-*C*), 32.5 (+, 8-*C*H), 31.9 (–, *C*H_2), 31.0 (–, *C*H_2), 29.3 (–, *C*H_2), 28.4 (–, *C*H_2), 20.9 (+, 18-*C*H_3), 20.4 (–, *C*H_2), 12.5 (+, 19-*C*H_3), 0.4 (+, 3 × Si*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2924 (w), 2856 (vw), 1708 (w), 1450 (vw), 1246 (w), 1082 (w), 1064 (w), 1035 (w), 880 (w), 837 (w), 814 (w), 750 (w), 707 (w), 692 (w), 617 (vw), 599 (vw), 576 (vw), 528 (vw), 391 (vw) cm^{-1}. – **MS** (EI, 70 eV, 100 °C): *m/z* (%) = 360 (46) $[M]^+$, 345 (100) $[M–CH_3]^+$, 270 (25) $[M–OTMS]^+$, 255 (13), 181 (14), 131 (13), 108 (22), 80 (12), 75 (11), 69 (13). – **HRMS** ($[M]^+$, $C_{22}H_{36}O_2{}^{28}Si^+$): calc. = 360.2479; found = 360.2481.

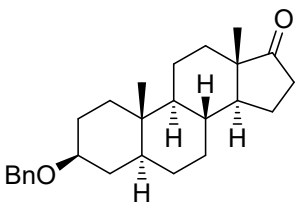
* The NMR spectra contain traces of cyclohexane (3%).

The analytical data are in accordance with the literature.[7]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-UFFYXOGYLH-UHFFFADPSC-NUHFF-NUKRR-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/UFFYXOGYLHHFHS-UMWWKMARSA-N.1

3β-Benzyloxy-5α-androst-17-one (**SI-02**)



Under argon atmosphere, *epi*-androsterone (**5**) (3.00 g, 10.3 mmol, 1.00 equiv.) was dissolved in absolute 1,4-dioxane (70 mL) and the reaction mixture was cooled to 0 °C. Subsequently, benzyl 2,2,2-trichloroacetimidate (2.9 mL, 3.91 g, 15.5 mmol, 1.50 equiv.) and trifluoromethanesulfonic acid (0.30 mL) were added. The reaction mixture was warmed up to room temperature and stirred for 16 h at room temperature. Afterwards, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (cHex/EtOAc, 10:1) to afford the title compound as a colorless solid (2.43 g, 6.39 mmol, 62%).

***R*$_f$** = 0.27 (cHex/EtOAc, 10:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 – 7.32 (m, 4H, 4 × CH_{Ar}), 7.29 – 7.24 (m, 1H, CH_{Ar}), 4.55 (s, 2H, OCH_2Ph), 3.34 (tt, *J* = 11.1, 4.7 Hz, 1H, 3-C*H*), 2.43 (dd, *J* = 19.2, 8.5 Hz, 1H, 16-C$H_2{}^a$), 2.12 – 2.00 (m, 1H, 16-C$H_2{}^b$), 1.97 – 1.88 (m, 2H, 15-C$H_2{}^a$ + CH_2), 1.83 – 1.62 (m, 5H, 1-C$H_2{}^a$ + 12-C$H_2{}^a$ + 2 different CH_2), 1.59 – 1.40 (m, 3H, 8-C*H* + 15-C$H_2{}^b$ + CH_2), 1.38 – 1.18 (m, 6H, 14-C*H* + 4 different CH_2),

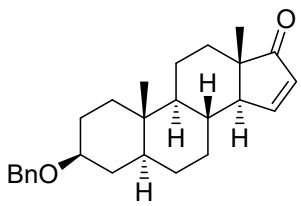
1.14 – 1.04 (m, 1H, 5-C*H*), 1.02 – 0.90 (m, 2H, 1-CH_2^b + 12-CH_2^b), 0.86 (s, 3H, 18-CH_3), 0.84 (s, 3H, 19-CH_3), 0.72 – 0.63 (m, 1H, 9-C*H*) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 221.5 (C_q, *C*O), 139.3 (C_q, C_{Ar}), 128.5 (+, 2 × C_{Ar}H), 127.7 (+, 2 × C_{Ar}H), 127.5 (+, C_{Ar}H), 78.0 (+, 3-*C*H), 70.0 (–, O*C*H_2Ph), 54.6 (+, 9-*C*H), 51.6 (+, 14-*C*H), 48.0 (C_q, 13-*C*), 45.0 (+, 5-*C*H), 37.1 (–, 1-*C*H_2), 36.1 (C_q, 10-*C*), 36.0 (–, 16-*C*H_2), 35.2 (+, 8-*C*H), 34.9 (–, *C*H_2), 31.7 (–, 12-*C*H_2), 31.1 (–, *C*H_2), 28.7 (–, *C*H_2), 28.4 (–, 15-*C*H_2), 21.9 (–, *C*H_2), 20.6 (–, *C*H_2), 14.0 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2919 (m), 2852 (m), 1730 (m), 1496 (w), 1449 (w), 1405 (vw), 1354 (w), 1303 (w), 1248 (w), 1203 (w), 1091 (m), 1070 (m), 1019 (m), 949 (w), 827 (w), 741 (m), 700 (m), 630 (w), 584 (w), 458 (w), 387 (vw) cm^{-1}. – **MS** (EI, 70 eV, 110 °C), m/z (%): 380 (3) $[M]^+$, 290 (17), 289 (74) $[M–Bn]^+$, 288 (34), 107 (12) $[C_7H_7O]^+$, 95 (11), 93 (14), 92 (44), 91 (100) $[C_7H_7]^+$, 81 (13), 79 (10), 67 (10), 55 (13). – **HRMS** ($[M]^+$, $C_{26}H_{36}O_2^+$): calc. = 380.2715; found = 380.2716.

The analytical data are in accordance with the literature.[8]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-UNVMFWARNI-UHFFFADPSC-NUHFF-NROVA-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/UNVMFWARNISDCV-DRKCKIEBSA-N.2

3β-Benzyloxy-5α-androst-15-en-17-one (**SI-03**)



In a baked out Schlenk flask under argon atmosphere, 3β-benzyloxy-5α-androst-17-one (**SI-02**) (1.69 g, 4.44 mmol, 1.00 equiv.) was dissolved in absolute tetrahydrofuran (60 mL) and cooled down to –78 °C. Subsequently, 2 M lithium diisopropylamide solution in tetrahydrofuran/ *n*-heptane/ ethylbenzene (3.3 mL, 710 mg, 6.66 mmol, 1.50 equiv.) was added dropwise over the course of 45 min *via* a syringe pump and the reaction mixture was further stirred at –78 °C for 1 h. Then, absolute triethylamine (1.9 mL, 1.35 g, 13.3 mmol, 3.00 equiv.) and trimethylsilyl chloride (0.90 mL, 770 mg, 7.10 mmol, 1.60 equiv.) were added to the reaction mixture. It was slowly warmed to room temperature and stirred at room temperature for 1 h. After adding saturated aqueous $NaHCO_3$ solution (60 mL), the aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (125 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue obtained was dissolved in a mixture of absolute dichloromethane and absolute *N*,*N*-dimethylformamide (3:2, 20 mL) under oxygen atmosphere. $Pd(OAc)_2$ (200 mg, 890 µmol, 20 mol%) and $CuSO_4$ (280 mg, 1.78 mmol, 40 mol%) were added. Oxygen was passed through the solution for 1 h

and the reaction mixture was stirred at room temperature for 3 days. The reaction solution was filtered through a pad of Celite® and silica gel (cHex/EtOAc, 1:1 as eluent) and concentrated under reduced pressure. The residue obtained was dissolved in dichloromethane (200 mL) and washed with water (300 mL). The aqueous phase was extracted with dichloromethane (2 × 200 mL) and the combined organic phases were washed successively with water (200 mL), saturated aqueous NH_4Cl solution (200 mL) and brine (200 mL). It was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (cHex/EtOAc, 10:1) afforded the title compound as a colorless solid (970 mg, 2.56 mmol, 58%).

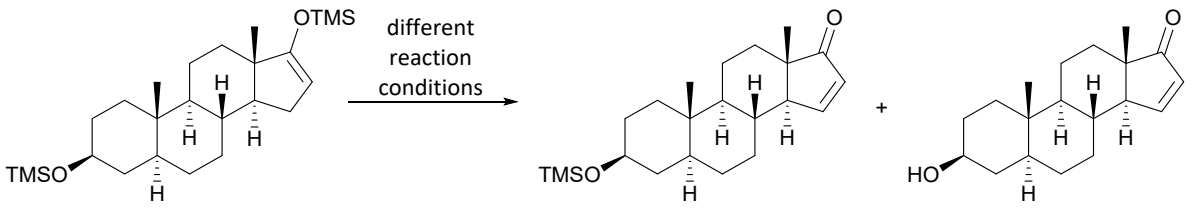
***R*$_f$** = 0.17 (cHex/EtOAc, 10:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 6.2, 1.9 Hz, 1H, 16-C*H*), 7.36 – 7.32 (m, 4H, 4 × CH_{Ar}), 7.29 – 7.24 (m, 1H, CH_{Ar}), 6.01 (dd, *J* = 6.0, 3.1 Hz, 1H, 15-C*H*), 4.56 (s, 2H, OCH_2Ph), 3.35 (tt, *J* = 11.2, 4.7 Hz, 1H, 3-C*H*), 2.29 – 2.22 (m, 1H, 14-C*H*), 2.02 – 1.91 (m, 2H, 2 different CH_2), 1.89 – 1.82 (m, 1H, CH_2), 1.77 – 1.65 (m, 4H, 8-C*H* + 1-CH_2[a] + 2 different CH_2), 1.56 – 1.43 (m, 3H, 3 different CH_2), 1.43 – 1.28 (m, 3H, 3 different CH_2), 1.17 – 1.07 (m, 2H, 5-C*H* + CH_2), 1.05 (s, 3H, 18-CH_3), 0.96 (td, *J* = 13.5, 3.9 Hz, 1H, 1-CH_2[b]), 0.88 (s, 3H, 19-CH_3), 0.82 – 0.73 (m, 1H, 9-C*H*) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 213.4 (C_q, *C*O), 158.8 (+, 16-*C*H), 139.2 (C_q, C_{Ar}), 131.8 (+, 15-*C*H), 128.5 (+, 2 × C_{Ar}H), 127.7 (+, 2 × C_{Ar}H), 127.5 (+, C_{Ar}H), 77.8 (+, 3-*C*H), 70.0 (–, O*C*H_2Ph), 57.1 (+, 14-*C*H), 55.9 (+, 9-*C*H), 51.3 (C_q, 13-*C*), 45.2 (+, 5-*C*H), 36.8 (–, 1-*C*H_2), 36.3 (C_q, 10-*C*), 34.9 (–, *C*H_2), 32.5 (+, 8-*C*H), 31.0 (–, *C*H_2), 29.3 (–, *C*H_2), 28.5 (–, *C*H_2), 28.3 (–, *C*H_2), 20.9 (+, 18-*C*H_3), 20.4 (–, *C*H_2), 12.5 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2927 (w), 2851 (w), 1713 (w), 1558 (vw), 1494 (vw), 1448 (w), 1366 (w), 1328 (vw), 1243 (vw), 1206 (wv), 1131 (w), 1094 (w), 1065 (w), 1026 (w), 973 (w), 943 (vw), 907 (w), 818 (w), 740 (w), 710 (w), 695 (w), 652 (w), 597 (vw), 577 (vw), 459 (w) cm^{-1}. – **MS** (EI, 70 eV, 100 °C), m/z (%): 378 (22) $[M]^+$, 364 (20), 363 (76) $[M–CH_3]^+$, 288 (25), 287 (100) $[M–Bn]^+$, 286 (19), 179 (16), 149 (25), 131 (14), 108 (24), 105 (14), 92 (22), 91 (90) $[C_7H_7]^+$, 80 (16), 69 (23), 58 (19). – **HRMS** ($[M]^+$, $C_{26}H_{34}O_2^+$): calc. = 378.2559; found = 378.2558.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-OQADXBDIJG-UHFFFADPSC-NUHFF-NROVA-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/OQADXBDIJGWCKW-DRKCKIEBSA-N.1

2.1.2. Additional screening of the reaction conditions

Table SI-1: Additional reaction conditions screened for the *Saegusa-Ito* oxidation of **7**.



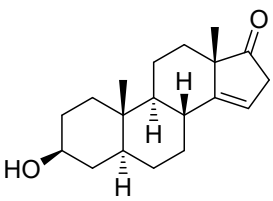
7 **8** **10**

entry	reagents[a]	reaction conditions	Isolated yield of **8** (**10**) [%]
1	$Pd(OAc)_2$, $Cu(OAc)_2$	CH_2Cl_2/DMSO (2:3), r.t., 48 h	40
2	$Pd(OAc)_2$, CuCl	CH_2Cl_2/DMSO (2:3), r.t., 24 h	0 (11)
3	$Pd(OAc)_2$, $Cu(OAc)_2$ + NaOAc	CH_2Cl_2/DMSO (2:3), r.t., 24 h	9.8 (11)
4	$Pd(OAc)_2$, $Cu(OAc)_2$ + Na_2CO_3	CH_2Cl_2/DMSO (2:3), r.t., 24 h	20 (26)
5	$Pd(OAc)_2$, $Cu(OAc)_2$	DMSO, 60 °C, 24 h	38
6	$Pd(OAc)_2$, $Cu(OAc)_2$	$CHCl_3$/DMSO (2:3), r.t., 24 h	0 (54)
7	$Pd(OAc)_2$, $Cu(OAc)_2$	$CHCl_3$/DMSO (2:3), 60 °C, 24 h	0 (26)
8	$Pd(OAc)_2$, 1,4-benzoquinone	CH_2Cl_2/DMSO (2:3), r.t., 24 h	traces
9	$Pd(OAc)_2$, 1,4-benzoquinone[b]	CH_2Cl_2/MeCN (3:2), r.t., 44 h	62
10	$Pd(OAc)_2$, Oxone®, Na_2HPO_4	CH_2Cl_2/DMSO (2:3), r.t., 24 h	0 (traces)
11	$Pd(OAc)_2$, Oxone®, Na_2HPO_4	MeCN, 45 °C, 24 h	0 (32)

a) 20 mol% $Pd(OAc)_2$ were used if not stated otherwise. b) 60 mol% $Pd(OAc)_2$ were used. *Michael* system **10** is also literature known.[9]

2.2. Rearrangement reaction

3β-Hydroxy-5α-androst-14-en-17-one (**9**)



In a round bottom flask, 3β-trimethylsilyloxy-5α-androst-15-en-17-one (**8**) (2.20 g, 6.10 mmol, 1.00 equiv.) and *p*-toluenesulfonic acid monohydrate (1.25 g, 6.55 mmol, 1.05 equiv.) were dissolved in toluene (80 mL) and refluxed for 20 minutes. The solution was treated with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (2 × 150 mL). The combined organic phases were washed with brine (100 mL) and after phase separation, dried over Na_2SO_4, filtered and the solvent was

removed under reduced pressure. Flash column chromatography on silica gel (cHex/EtOAc, 4:1) afforded the title compound as a colorless solid (1.07 g, 3.71 mmol, 61%). 3β-Hydroxy-5α,14β-androst-15-en-17-one (**11**) could be identified as a side product. The respective structure was elucidated by single crystal X-ray analysis. This molecule is also literature known.[10]

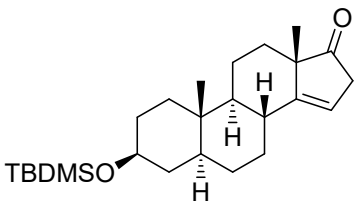
***R**$_f$* = 0.59 (cHex/EtOAc, 1:2). – **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 5.49 – 5.46 (m, 1H, 15-C*H*), 3.58 (tt, *J* = 10.7, 4.8 Hz, 1H, 3-C*H*), 2.98 (ddd, ^2J = 23.1 Hz, ^3J = 4.1, 2.1 Hz, 1H, 16-CH_2^a), 2.85 – 2.78 (m, 1H, 16-CH_2^b), 2.19 – 2.11 (m, 1H, 8-C*H*), 1.89 – 1.83 (m, 1H, CH_2), 1.82 – 1.78 (m, 1H, CH_2), 1.79 – 1.71 (m, 2H, 2 different CH_2), 1.72 – 1.65 (m, 1H, CH_2), 1.63 – 1.58 (m, 1H, CH_2), 1.43 – 1.29 (m, 6H, 5 different CH_2), 1.20 (td, *J* = 13.2, 3.9 Hz, 1H, CH_2), 1.14 – 1.05 (m, 1H, 5-C*H*), 1.10 (s, 3H, 18-CH_3), 0.95 (td, *J* = 13.5, 3.8 Hz, 1H, CH_2), 0.86 (s, 3H, 19-CH_3), 0.70 (td, *J* = 11.7, 3.3 Hz, 1H, 9-C*H*) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$. – **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 222.9 (C_q, *C*O), 153.7 (C_q, 14-*C*), 113.0 (+, 15-*C*H), 71.2 (+, 3-*C*H), 54.9 (+, 9-*C*H), 51.1 (C_q, 13-*C*), 44.6 (+, 5-*C*H), 41.5 (–, 16-*C*H_2), 38.1 (–, *C*H_2), 36.9 (–, *C*H_2), 36.1 (C_q, 10-*C*), 35.6 (+, 8-*C*H), 33.4 (–, *C*H_2), 31.5 (–, *C*H_2), 29.0 (–, *C*H_2), 28.2 (–, *C*H_2), 20.9 (–, *C*H_2), 20.1 (+, 18-*C*H_3), 12.2 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3435 (w), 2924 (w), 2850 (w), 1728 (m), 1638 (vw), 1445 (w), 1402 (w), 1370 (w), 1297 (vw), 1278 (w), 1228 (vw), 1195 (w), 1138 (vw), 1073 (w), 1044 (w), 980 (w), 960 (w), 941 (vw), 899 (vw), 842 (vw), 819 (vw), 792 (vw), 754 (vw), 648 (vw), 623 (w), 591 (w), 497 (w), 406 (vw) cm^{-1}. – **MS** (EI, 70 eV, 120 °C): *m/z* (%) = 288 (59) $[M]^+$, 260 (100), 245 (15), 227 (13), 134 (49), 119 (14), 107 (21), 105 (17), 96 (23), 93 (13), 91 (17), 79 (15). – **HRMS** ($[M]^+$, $C_{19}H_{28}O_2^+$): calc. = 288.2084; found = 288.2083.

The analytical data are in accordance with the literature.[11]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-XKQCWEVZYH-UHFFFADPSC-NUHFF-NZOJN-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/XKQCWEVZYHANOT-HDOZPKFNSA-N.1

3β-*tert*-Butyldimethylsilyloxy-5α-androst-14-en-17-one (**12**)



Under argon atmosphere, 3β-hydroxy-5α-androst-14-en-17-one (**9**) (538 mg, 1.86 mmol, 1.00 equiv.) was dissolved in absolute dichloromethane (20 mL) and imidazole (177 mg, 2.60 mmol, 1.40 equiv.) and *tert*-butyldimethylsilyl chloride (308 mg, 2.05 mmol, 1.10 equiv.) were added. The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (cHex/EtOAc, 10:1) afforded the title compound as a colorless solid (596 mg, 1.48 mmol, 80%).

***R**$_f$* = 0.83 (cHex/EtOAc, 3:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 5.50 – 5.43 (m, 1H, 15-C*H*), 3.53 (tt, *J* = 10.7, 4.7 Hz, 1H, 3-C*H*), 2.98 (d, ^2J = 23.1 Hz, 1H, 16-CH_2^a), 2.82 (d, ^2J = 23.0 Hz, 1H, 16-CH_2^b), 2.21 – 2.08 (m, 1H, 8-C*H*), 1.88 – 1.83 (m, 1H, CH_2), 1.81 – 1.72 (m, 1H, CH_2), 1.72 – 1.63 (m, 3H, 3 different CH_2), 1.52 – 1.16 (m, 8H, 6 different CH_2), 1.10 (s, 3H, 18-CH_3), 1.09 – 1.02 (m, 1H, 5-C*H*), 1.00 – 0.88 (m, 1H, CH_2), 0.87 (s, 9H, 3 × SiCCH_3), 0.85 (s, 3H, 19-CH_3), 0.68 (ddd, *J* = 14.6, 10.4, 3.1 Hz, 1H, 9-C*H*), 0.04 (s, 6H, 2 × SiCH_3) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$)*: δ = 223.0 (C_q, *C*O), 153.8 (C_q, 14-*C*), 112.9 (+, 15-*C*H), 72.1 (+, 3-*C*H), 55.0 (+, 9-*C*H), 51.1 (C_q, 13-*C*), 44.8 (+, 5-*C*H), 41.6 (–, 16-*C*H_2), 38.6 (–, *C*H_2), 37.1 (–, *C*H_2), 36.1 (C_q, 10-*C*), 35.6 (+, 8-*C*H), 33.4 (–, *C*H_2), 31.9 (–, *C*H_2), 29.0 (–, *C*H_2), 28.3 (–, *C*H_2), 26.1 (+, 3 × SiC*C*H_3), 20.9 (–, *C*H_2), 20.1 (+, 18-*C*H_3), 18.4 (C_q, Si*C*$(CH_3)_3$), 12.3 (+, 19-*C*H_3), –4.4 (+, 2 × Si*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2927 (m), 2855 (w), 1743 (m), 1448 (w), 1375 (w), 1359 (w), 1250 (w), 1130 (w), 1082 (m), 1059 (m), 1009 (w), 979 (w), 961 (w), 941 (w), 905 (w), 870 (m), 835 (m), 775 (m), 671 (w), 571 (vw), 533 (vw), 397 (vw) cm^{-1}. – **MS** (EI, 70 eV, 70 °C): *m/z* (%) = 402 (8) $[M]^+$, 345 (100) [M–*tert*-butyl]$^+$, 181 (11), 131 (13), 75 (33), 73 (10), 69 (22). – **HRMS** ($[M]^+$, $C_{25}H_{42}O_2{}^{28}Si^+$): calc. = 402.2954; found = 402.2955.

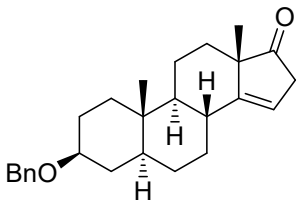
* The NMR spectra contain an unknown impurity.

Although literature known, no analytical data for comparison have been published.[12]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-KZLZBBZTIC-UHFFFADPSC-NUHFF-NIVXU-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/KZLZBBZTICQZFV-CMPHSYMRSA-N.3

3β-Benzyloxy-5α-androst-14-en-17-one (**13**)



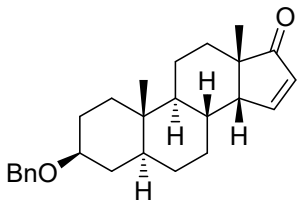
In a round bottom flask, 3β-benzyloxy-5α-androst-15-en-17-one (**SI-03**) (2.40 g, 6.34 mmol, 1.00 equiv.) and *p*-toluenesulfonic acid monohydrate (1.27 g, 6.66 mmol, 1.05 equiv.) were dissolved in toluene (150 mL) and refluxed for 20 minutes. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (2 × 150 mL). The combined organic phases were washed with brine (200 mL) and after phase separation, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (cHex/EtOAc, 10:1) afforded the title compound as a colorless solid (1.26 g, 3.33 mmol, 52%). The respective structure was elucidated by single crystal X-ray analysis. In addition, 3β-benzyloxy-5α,14β-androst-15-en-17-one (**SI-04**) (725 mg, 1.92 mmol, 30%) could be isolated as a side product, which can be reused as starting material for this isomerization.

***R**$_f$* = 0.22 (cHex/EtOAc, 10:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 – 7.32 (m, 4H, 4 × C*H*$_{Ar}$), 7.30 – 7.24 (m, 1H, C*H*$_{Ar}$), 5.49 – 5.46 (m, 1H, 15-C*H*), 4.56 (s, 2H, OC*H*$_2$Ph), 3.35 (tt, *J* = 11.0, 4.7 Hz, 1H, 3-C*H*), 2.99 (ddd, ^2J = 23.1 Hz, ^3J = 3.90 Hz, ^5J = 1.8 Hz, 1H, 16-C*H*$_2^a$), 2.82 (ddd, ^2J = 23.1 Hz, ^3J = 2.3 Hz, ^5J = 2.3 Hz, 1H, 16-C*H*$_2^b$), 2.23 – 2.10 (m, 1H, 8-C*H*), 1.97 – 1.91 (m, 1H, C*H*$_2$), 1.90 – 1.85 (m, 1H, C*H*$_2$), 1.80 – 1.64 (m, 4H, 4 different C*H*$_2$), 1.53 – 1.29 (m, 6H, 5 different C*H*$_2$), 1.21 (td, *J* = 13.2, 3.8 Hz, 1H, C*H*$_2$), 1.11 (s, 3H, 18-C*H*$_3$), 1.08 – 0.98 (m, 1H, 5-C*H*), 0.95 – 0.89 (m, 1H, C*H*$_2$), 0.87 (s, 3H, 19-C*H*$_3$), 0.70 (td, *J* = 11.7, 3.3 Hz, 1H, 9-C*H*) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 222.9 (C$_q$, *C*O), 153.7 (C$_q$, 14-*C*), 139.2 (C$_q$, *C*$_{Ar}$), 128.5 (+, 2 × *C*$_{Ar}$H), 127.7 (+, 2 × *C*$_{Ar}$H), 127.5 (+, *C*$_{Ar}$H), 113.0 (+, 15-*C*H), 77.9 (+, 3-*C*H), 70.0 (–, O*C*H$_2$Ph), 55.0 (+, 9-*C*H), 51.1 (C$_q$, 13-*C*), 44.7 (+, 5-*C*H), 41.4 (–, 16-*C*H$_2$), 37.0 (–, *C*H$_2$), 36.4 (C$_q$, 10-*C*), 35.6 (+, 8-*C*H), 34.9 (–, *C*H$_2$), 33.4 (–, *C*H$_2$), 29.0 (–, *C*H$_2$), 28.4 (–, *C*H$_2$), 28.3 (–, *C*H$_2$), 20.9 (–, *C*H$_2$), 20.1 (+, 18-*C*H$_3$), 12.2 (+, 19-*C*H$_3$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2930 (w), 2854 (w), 1733 (m), 1632 (vw), 1496 (vw), 1447 (w), 1398 (w), 1356 (w), 1314 (w), 1267 (vw), 1199 (w), 1092 (m), 1065 (m), 1049 (m), 1027 (w), 974 (w), 940 (w), 901 (w), 834 (w), 817 (w), 796 (w), 748 (m), 699 (m), 647 (w), 628 (w), 594 (w), 447 (vw) cm^{-1}. – **MS** (EI, 70 eV, 100 °C), m/z (%): 378 (100) [M]$^+$, 350 (15), 287 (26) [M–Bn]$^+$, 271 (16), 270 (62), 257 (15), 255 (51), 216 (17), 204 (36), 178 (25), 139 (22), 105 (20), 93 (14), 92 (14), 91 (70) [C_7H_7]$^+$, 79 (16), 77 (23). – **HRMS** ([M]$^+$, $C_{26}H_{34}O_2^+$): calc. = 378.2559; found = 378.2558.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-OSKZMBIIHJ-UHFFFADPSC-NUHFF-NBUMY-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/SMZAQGMUMIUEJN-RNGXFJMISA-N.1

3β-Benzyloxy-5α,14β-androst-15-en-17-one (**SI-04**)



***R*$_f$** = 0.12 (cHex/EtOAc, 10:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 5.9, 2.3 Hz, 1H, 16-C*H*), 7.35 – 7.31 (m, 4H, 4 × CH_{Ar}), 7.29 – 7.24 (m, 1H, CH_{Ar}), 6.19 (dd, *J* = 5.9, 2.4 Hz, 1H, 15-C*H*), 4.54 (s, 2H, OCH_2Ph), 3.31 (tt, *J* = 11.1, 4.7 Hz, 1H, 3-C*H*), 2.57 (dt, *J* = 4.9, 2.3 Hz, 1H, 14-C*H*), 1.97 – 1.86 (m, 2H, 8-C*H* + CH_2), 1.78 – 1.58 (m, 4H, 4 different CH_2), 1.49 – 1.34 (m, 5H, 4 different CH_2), 1.34 – 1.29 (m, 1H, CH_2), 1.29 – 1.20 (m, 2H, CH_2), 1.08 (s, 3H, 18-CH_3), 1.06 – 0.98 (m, 1H, 5-C*H*), 0.82 (dd, *J* = 13.5, 3.8 Hz, 1H, CH_2), 0.78 (s, 3H, 19-CH_3), 0.70 (dt, *J* = 12.4, 7.3 Hz, 1H, 9-C*H*) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 215.9 (C_q, *C*O), 164.4 (+, 16-*C*H), 139.2 (C_q, C_{Ar}), 133.2 (+, 15-*C*H), 128.5 (+, 2 × C_{Ar}H), 127.7 (+, 2 × C_{Ar}H), 127.5 (+, C_{Ar}H), 77.9 (+, 3-*C*H), 70.0 (–, O*C*H_2Ph), 54.8 (+, 14-*C*H), 47.7 (C_q, 13-*C*), 45.7 (+, 9-*C*H), 44.7 (+, 5-*C*H), 37.0 (C_q, 10-*C*), 36.4 (–, *C*H_2), 34.8 (–, *C*H_2), 34.2 (+, 8-*C*H), 33.0 (–, *C*H_2), 31.0 (–, *C*H_2), 28.9 (–, *C*H_2), 27.9 (–, *C*H_2), 22.3 (+, 18-*C*H_3), 20.1 (–, *C*H_2), 11.4 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2922 (m), 2855 (m), 1697 (s), 1585 (w), 1496 (w), 1449 (m), 1349 (w), 1244 (w), 1148 (w), 1107 (m), 1071 (m), 1029 (m), 1003 (w), 884 (m), 851 (w), 816 (m), 732 (m), 695 (m), 632 (w), 520 (w), 461 (w) cm^{-1}. – **MS** (EI, 70 eV, 130 °C), m/z (%): 378 (1) $[M]^+$, 288 (24), 287 (100) $[M–Bn]^+$, 92 (27), 91 (66) $[C_7H_7]^+$. – **HRMS** ($[M]^+$, $C_{26}H_{34}O_2^+$): calc. = 378.2559; found = 378.2560.

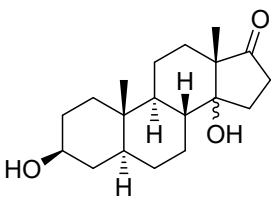
Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-OSKZMBIIHJ-UHFFFADPSC-NUHFF-NBUMY-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/OQADXBDIJGWCKW-FYXWGFNCSA-N.2

2.3. *Mukaiyama* oxidation

2.3.1. Experimental procedures and analytical data of the precursors and products

(3β,14)-Dihydroxy-5α-androstan-17-one (**14**)



In a Schlenk flask, 3β-hydroxy-5α-androst-14-en-17-one (**9**) (100 mg, 347 µmol, 1.00 equiv.) was dissolved in absolute 1,4-dioxane (6.5 mL) and saturated with oxygen for 15 minutes. Thereafter, cobalt(II) acetylacetonate (27.0 mg, 105 µmol, 30 mol%) was added and phenylsilane (0.19 mL, 169 mg, 1.56 mmol, 4.50 equiv.) was dissolved in absolute 1,4-dioxane (1.0 mL) and added dropwise over the course of 2 h *via* a syringe pump, oxygen being continuously passed through the solution. The solution turned from pink to green as the reaction progressed. It was stirred at room temperature for 20 h and then quenched with dilute aqueous $Na_2S_2O_3$ solution (5 mL). After addition of saturated aqueous $NaHCO_3$ solution (30 mL), it was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography on silica gel (cHex/EtOAc, 2:1) to afford the title compound as a colorless solid (56.0 mg, 184 µmol, 53%). The material obtained contained a 2:1 mixture of the two 14-epimers A and B, which were indistinguishable from each other in the ^{1}H NMR spectrum with the exception of the angular methyl groups. However, a correct assignment of the two sets of signals was achieved in the ^{13}C NMR spectrum.

***R**$_f$* = 0.66 (cHex/EtOAc, 3:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 3.59 (tt, *J* = 11.0, 5.0 Hz, 1H, 3-C*H*), 2.45 – 2.29 (m, 2H, CH_2), 2.16 – 2.07 (m, 1H, CH_2), 1.97 (dd, *J* = 12.5, 3.3 Hz, 1H, CH_2), 1.87 – 1.07 (m, 17H, 5-C*H* + 8-C*H* + different CH_2), 1.03 (s, 3H, CH_3^A) and 0.98 (s, 3H, CH_3^B), 1.02 – 0.91 (m, 2H, 9-C*H* + CH_2), 0.83 (s, 3H, CH_3^B) and 0.80 (s, 3H, CH_3^A) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$.

14-epimer A (main isomer):

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 221.8 (C_q, 17-*C*O), 82.6 (C_q, 14-*C*), 71.2 (+, 3-*C*H), 53.7 (C_q, 13-*C*), 50.0 (+, 9-*C*H), 44.4 (+, 5-*C*H), 41.3 (+, 8-*C*H), 37.9 (–, 4-*C*H_2), 37.1 (–, 1-*C*H_2), 35.8 (C_q, 10-*C*), 33.1 (–, 16-*C*H_2), 31.9 (–, 2-*C*H_2), 31.3 (–, 6-*C*H_2), 28.3 (–, 12-*C*H_2), 27.4 (–, 15-*C*H_2), 25.6 (–, 7-*C*H_2), 19.9 (–, 11-*C*H_2), 12.9 (+, 18-*C*H_3), 12.3 (+, 19-*C*H_3) ppm.

14-epimer B (minor isomer):

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 219.4 (C_q, 17-*C*O), 81.4 (C_q, 14-*C*), 71.2 (+, 3-*C*H), 52.8 (C_q, 13-*C*), 47.5 (+, 9-*C*H), 44.6 (+, 5-*C*H), 38.0 (–, 4-*C*H_2), 37.8 (+, 8-*C*H), 37.1 (–, 1-*C*H_2), 35.8 (C_q, 10-*C*), 33.3 (–, 16-*C*H_2), 31.5 (–,

2-CH_2), 30.2 (–, 6-CH_2), 28.2 (–, 12-CH_2), 25.5 (–, 15-CH_2), 24.9 (–, 7-CH_2), 19.3 (–, 11-CH_2), 18.1 (+, 18-CH_3), 12.3 (+, 19-CH_3) ppm.

– **IR** (ATR, $\tilde{\nu}$) = 3406 (w), 2923 (w), 2856 (w), 1725 (w), 1447 (vw), 1371 (vw), 1263 (vw), 1198 (vw), 1127 (vw), 1084 (vw), 1061 (w), 1039 (w), 996 (vw), 952 (w), 897 (vw), 874 (vw), 635 (vw), 578 (vw), 502 (vw) cm^{-1}. – **MS** (EI, 70 eV, 130 °C): *m/z* (%) = 306 (100) $[M]^+$, 291 (39) $[M–CH_3]^+$, 250 (43), 215 (56), 180 (70), 147 (40), 121 (50), 107 (79), 93 (57). – **HRMS** ($[M]^+$, $C_{19}H_{30}O_3^+$): calc. = 306.2189; found = 306.2188.

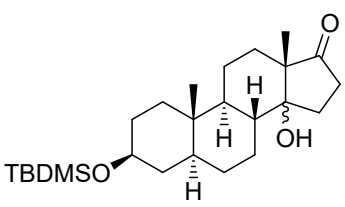
Both epimers are literature known.[13–15]

* The NMR spectra contain an unknown impurity.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-JBLSYSNVWG-UHFFFADPSC-NUHFF-NXMGP-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/JBLSYSNVWGGVRJ-WLNAVQFHSA-N.1

3β-*tert*-Butyldimethylsilyloxy-14-hydroxy-5α-androstan-17-one (**15**)



In a Schlenk flask, 3β-*tert*-butyldimethylsilyloxy-5α-androst-14-en-17-one (**12**) (100 mg, 248 µmol, 1.00 equiv.) was dissolved in absolute 1,4-dioxane (6.5 mL) and saturated with oxygen for 15 minutes. Thereafter, cobalt(II) acetylacetonate (18.0 mg, 70.0 µmol, 28 mol%) was added and phenylsilane (0.13 mL, 114 mg, 1.05 mmol, 4.24 equiv.), dissolved in absolute 1,4-dioxane (1.0 mL), was added dropwise over the course of 2 h *via* a syringe pump, oxygen being continuously passed through the solution. The solution turned from pink to green as the reaction progressed. It was stirred at room temperature for 20 h and then quenched with dilute aqueous $Na_2S_2O_3$ solution (5 mL). After addition of saturated aqueous $NaHCO_3$ solution (30 mL), it was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (30 mL) before being dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (cHex/EtOAc, 2:1) to afford the title compound as a colorless solid (67.0 mg, 159 µmol, 64%). The material obtained contained a 2:1 mixture of the two 14-epimers A and B, which were indistinguishable from each other in the ^1H NMR spectrum with the exception of the angular methyl groups. However, a correct assignment of the two sets of signals was achieved in the ^{13}C NMR spectrum.

***R*$_f$** = 0.49 (cHex/EtOAc, 3:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 3.54 (tq, *J* = 10.0, 4.8 Hz, 1H, 3-C*H*), 2.41 – 2.31 (m, 2H, CH_2), 2.16 – 1.03 (m, 17H, 5-C*H* + 8-C*H* + different CH_2), 1.02 (s, 3H, 18-CH_3^A) and 0.97 (s, 3H, 18-CH_3^B), 0.97 – 0.87 (m, 2H, 9-C*H* + CH_2), 0.87 (s, 9H, 3 × SiCCH_3), 0.82 (s, 3H, 19-CH_3^B) and 0.79 (s, 3H, 19-CH_3^A), 0.04 (s, 6H, 2 × SiCH_3) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$.

<u>14-epimer A (main isomer):</u>

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 221.7 (C_q, *C*O), 82.6 (C_q, 14-*C*), 72.0 (+, 3-*C*H), 53.7 (C_q, 13-*C*), 50.1 (+, 9-*C*H), 44.6 (+, 5-*C*H), 41.3 (+, 8-*C*H), 38.5 (–, 4-*C*H_2), 37.3 (–, 1-*C*H_2), 35.8 (C_q, 10-*C*), 33.1 (–, 16-*C*H_2), 32.0 (–, 2-*C*H_2), 31.8 (–, 6-*C*H_2), 28.3 (–, 12-*C*H_2), 27.3 (–, 15-*C*H_2), 26.0 (+, 3 × SiC*C*H_3), 25.7 (–, 7-*C*H_2), 19.9 (–, 11-*C*H_2), 18.4 (C_q, Si*C*$(CH_3)_3$), 12.9 (+, 18-*C*H_3), 12.3 (+, 19-*C*H_3), –4.5 (+, 2 × Si*C*H_3) ppm.

<u>14-epimer B (minor isomer):</u>

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 219.3 (C_q, *C*O), 81.4 (C_q, 14-*C*), 71.7 (+, 3-*C*H), 52.8 (C_q, 13-*C*), 47.6 (+, 9-*C*H), 44.7 (+, 5-*C*H), 38.6 (–, 4-*C*H_2), 37.8 (+, 8-*C*H), 37.3 (–, 1-*C*H_2), 35.9 (C_q, 10-*C*), 33.3 (–, 16-*C*H_2), 31.9 (–, 2-*C*H_2), 30.2 (–, 6-*C*H_2), 28.2 (–, 12-*C*H_2), 26.0 (+, 3 × SiC*C*H_3), 25.5 (–, 15-*C*H_2), 24.9 (–, 7-*C*H_2), 19.3 (–, 11-*C*H_2), 18.4 (C_q, Si*C*$(CH_3)_3$), 18.1 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3), –4.5 (+, 2 × Si*C*H_3) ppm.

– **IR** (ATR, ṽ) = 3486 (w), 2928 (vs), 2884 (m), 2857 (s), 1728 (vs), 1463 (m), 1445 (w), 1380 (w), 1363 (w), 1251 (m), 1184 (w), 1130 (s), 1094 (vs), 1082 (vs), 1065 (vs), 1006 (m), 980 (w), 956 (m), 942 (w), 909 (w), 899 (m), 868 (vs), 836 (vs), 798 (w), 772 (vs), 738 (w), 697 (m), 670 (m), 579 (w), 486 (w) cm^{-1}. – **MS** (FAB, 3-NBA): *m/z* (%) = 419 (26) $[M–H]^+$, 403 (14) $[M–OH]^+$, 363 (30) [M–*tert*-Butyl]$^+$, 287 (19), 272 (22), 271 (100), 269 (22), 260 (16), 259 (58), 183 (74), 136 (44), 107 (58), 105 (48), 95 (52), 93 (51), 91 (57). – **HRMS** ($[M–H]^+$, $C_{25}H_{43}O_3{}^{28}Si^+$): calc. = 419.2976; found = 419.2978.

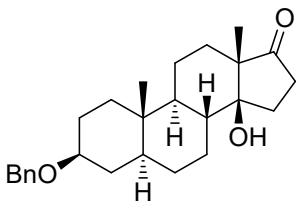
* The NMR spectra contain an unknown impurity.

Although literature known, no analytical data for comparison have been published.[12]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-NZLOPGJDGN-UHFFFADPSC-NUHFF-NWYQK-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/NZLOPGJDGNDESQ-OUDGWNFDSA-N.2

3β-Benzyloxy-14β-hydroxy-5α-androst-17-one (**16**)



Under oxygen atmosphere, 3β-benzyloxy-5α-androst-14-en-17-one (**13**) (50.0 mg, 132 µmol, 1.00 equiv.) was dissolved in absolute ethanol (6.0 mL). The solution was saturated with oxygen for 15 minutes. Then cobalt(II) acetylacetonate (10.2 mg, 39.7 µmol, 30 mol%) was added and oxygen was bubbled through the solution for 5 minutes. Phenylsilane (73 µL, 64.3 mg, 594 µmol, 4.50 equiv.) was dissolved in absolute acetonitrile (1.0 mL) and added dropwise over the course of 2 h *via* a syringe pump, oxygen being continuously passed through the solution. The mixture was stirred at room temperature for 20 h and then quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL). Saturated aqueous $NaHCO_3$ solution (10 mL) was added and it was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (toluene/EtOAc, 4:1) afforded the title compound as a colorless solid (34.2 mg, 86.3 µmol, 65%). In addition, the 14α-epimer 3β-benzyloxy-14α-hydroxy-5α-androst-17-one (**17**) (3.64 mg, 9.18 µmol, 6.9%) could be isolated as a side product.

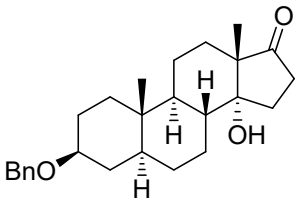
***R*$_f$** = 0.25 (toluene/EtOAc, 4:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 7.36 – 7.31 (m, 4H, 4 × CH_{Ar}), 7.30 – 7.24 (m, 1H, CH_{Ar}), 4.56 (s, 2H, OCH_2Ph), 3.39 – 3.30 (m, 1H, 3-C*H*), 2.43 – 2.36 (m, 2H, 15-CH_2), 2.17 – 2.08 (m, 1H, 16-CH_2^a), 2.02 – 1.91 (m, 2H, 2 different CH_2), 1.84 – 1.71 (m, 3H, 1-CH_2^a + 16-CH_2^b + CH_2), 1.63 – 1.53 (m, 2H, 8-C*H* + CH_2), 1.52 – 1.32 (m, 4H, 4 different CH_2), 1.32 – 1.23 (m, 2H, 2 different CH_2), 1.23 – 1.07 (m, 3H, 5-C*H* + 2 different CH_2), 1.05 (s, 3H, 18-CH_3), 1.00 – 0.91 (m, 2H, 9-C*H* + 1-CH_2^b), 0.82 (s, 3H, 19-CH_3) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$. – **^{13}C NMR** (126 MHz, $CDCl_3$)*: δ = 221.5 (C_q, *C*O), 139.2 (C_q, *C*$_{Ar}$), 128.5 (+, 2 × *C*$_{Ar}$H), 127.7 (+, 2 × *C*$_{Ar}$H), 127.6 (+, *C*$_{Ar}$H), 82.7 (C_q, 14-*C*), 77.8 (+, 3-*C*H), 70.0 (–, O*C*H$_2$Ph), 53.7 (C_q, 13-*C*), 50.2 (+, 9-*C*H), 44.5 (+, 5-*C*H), 41.5 (+, 8-*C*H), 37.2 (–, 1-*C*H$_2$), 36.2 (C_q, 10-*C*), 34.8 (–, *C*H$_2$), 33.1 (–, 15-*C*H$_2$), 32.0 (–, *C*H$_2$), 28.5 (–, *C*H$_2$), 28.2 (–, *C*H$_2$), 27.4 (–, 16-*C*H$_2$), 25.7 (–, *C*H$_2$), 20.0 (–, *C*H$_2$), 13.0 (+, 18-*C*H$_3$), 12.3 (+, 19-*C*H$_3$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3519 (vw), 2917 (w), 2853 (w), 1718 (w), 1451 (vw), 1357 (vw), 1273 (vw), 1177 (vw), 1133 (w), 1097 (w), 1072 (w), 1027 (w), 970 (vw), 949 (w), 899 (vw), 873 (vw), 751 (w), 701 (w), 604 (vw), 571 (vw), 488 (vw) cm^{-1}. – **MS** (EI, 70 eV, 150 °C), m/z (%): 396 (9) [M]$^+$, 384 (16), 305 (43) [M–Bn]$^+$, 304 (13), 107 (15) [C_7H_7O]$^+$, 92 (25), 91 (100) [C_7H_7]$^+$, 69 (19), 57 (13), 55 (14). – **HRMS** ([M]$^+$, $C_{26}H_{36}O_3^+$): calc. = 396.2664; found = 396.2666.

* The NMR spectra contain an unknown impurity that was present in all benzyl protected Mukaiyama products and presumably originated from the catalyst.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-YMCYXAXPFM-UHFFFADPSC-NUHFF-NAFBC-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/RWAJZRJQGGJQFL-SIGVLJBRSA-N.2

3β-Benzyloxy-14α-hydroxy-5α-androst-17-one (**17**)



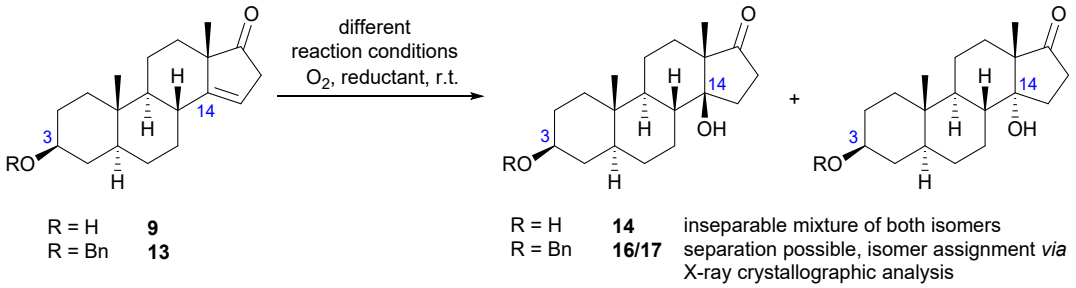
***R*$_f$** = 0.32 (toluene/EtOAc, 4:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 – 7.31 (m, 4H, 4 × C*H*$_{Ar}$), 7.29 – 7.24 (m, 1H, C*H*$_{Ar}$), 4.55 (s, 2H, OC*H*$_2$Ph), 3.34 (tt, *J* = 11.2, 4.7 Hz, 1H, 3-C*H*), 2.48 – 2.28 (m, 2H, 15-C*H*$_2$), 1.98 – 1.91 (m, 1H, C*H*$_2$), 1.91 – 1.85 (m, 2H, 16-C*H*$_2$), 1.79 – 1.69 (m, 4H, 8-C*H* + 1-C*H*$_2^a$ + 2 different C*H*$_2$), 1.69 – 1.58 (m, 2H, 2 different C*H*$_2$), 1.57 – 1.51 (m, 1H, C*H*$_2$), 1.51 – 1.22 (m, 6H, 5 different C*H*$_2$), 1.22 – 1.04 (m, 2H, 5-C*H* + 9-C*H*), 1.04 – 0.95 (m, 1H, 1-C*H*$_2^b$), 0.99 (s, 3H, 18-C*H*$_3$), 0.85 (s, 3H, 19-C*H*$_3$) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 219.0 (C_q, *C*O), 139.2 (C_q, *C*$_{Ar}$), 128.5 (+, 2 × *C*$_{Ar}$H), 127.7 (+, 2 × *C*$_{Ar}$H), 127.5 (+, *C*$_{Ar}$H), 81.5 (C_q, 14-*C*), 77.9 (+, 3-*C*H), 70.0 (–, O*C*H$_2$Ph), 52.8 (C_q, 13-*C*), 47.6 (+, 9-*C*H), 44.7 (+, 5-*C*H), 37.8 (+, 8-*C*H), 37.2 (–, 1-*C*H$_2$), 36.2 (C_q, 10-*C*), 34.9 (–, *C*H$_2$), 33.3 (–, 15-*C*H$_2$), 30.2 (–, 16-*C*H$_2$), 28.4 (–, *C*H$_2$), 28.3 (–, *C*H$_2$), 25.5 (–, *C*H$_2$), 25.0 (–, *C*H$_2$), 19.3 (–, *C*H$_2$), 18.2 (+, 18-*C*H$_3$), 12.3 (+, 19-*C*H$_3$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3524 (vw), 2921 (w), 2855 (w), 1724 (w), 1451 (w), 1350 (w), 1267 (vw), 1069 (m), 1021 (w), 952 (w), 894 (w), 738 (w), 698 (w), 643 (vw), 603 (vw), 486 (w), 402 (vw) cm^{-1}. – **MS** (EI, 70 eV, 130 °C), m/z (%): 396 (10) [M]$^+$, 305 (19) [M–Bn]$^+$, 181 (30), 131 (35), 107 (13) [C_7H_7O]$^+$, 93 (16), 92 (20), 91 (100) [C_7H_7]$^+$, 69 (52). – **HRMS** ([M]$^+$, $C_{26}H_{36}O_3^+$): calc. = 396.2664; found = 396.2662.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-YMCYXAXPFM-UHFFFADPSC-NUHFF-NAFBC-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/RWAJZRJQGGJQFL-VRESFZDRSA-N.2

2.3.2. Additional screening of the reaction conditions

Table SI-2: Additional reaction conditions screened for the *Mukaiyama* oxidation of **9** and **13**.

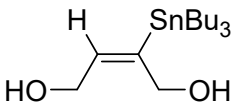


entry	R	reductant (equiv., a.r.)	catalyst	solvent	additive	reaction time	yield [%], dr (β-OH: α-OH)
1	H	$PhSiH_3$ (3.0, 1 h)	$Co(acac)_2$	1,4-dioxane	-	8 h	46
2	H	$PhSiH_3$ (4.5, 1 h)	$Co(acac)_2$	1,4-dioxane	4 Å MS	20 h	49
3	H	$PhSiH_3$ (3.0, 1 h)	$Co(acac)_2$	THF	4 Å MS	20 h	38
4	H	$PhSiH_3$ (4.5, 2 h)	$Co(acac)_2$	1,4-dioxane + THF	4 Å MS	3 h	47
5	Bn	$PhSiH_3$ (4.5, 2 h)	$Co(bzac)_2$	1,4-dioxane	4 Å MS	20 h	62 (2.0:1)
6	Bn	$PhSiH_3$ (4.5, 2 h)	$Co(tfa)_2$	1,4-dioxane	4 Å MS	20 h	0
7	Bn	$PhSiH_3$ (4.5, 2 h)	$Co(acac)_2$	1,2-dichloroethane	4 Å MS	20 h	65 (2.8:1)
8	Bn	$PhSiH_3$ (4.5, 2 h)	$Co(acac)_3$	1,4-dioxane	4 Å MS	20 h	0
9	Bn	$PhSiH_3$ (4.5, 2 h)	$Mn(acac)_3$	1,4-dioxane	4 Å MS	20 h	0
10	Bn	$PhSiH_3$ (4.5, 2 h)	**SI-01**	1,4-dioxane	4 Å MS	20 h	0
11	Bz	$NaBH_4$ (1.5, -)	Co-TPP	THF	4 Å MS	20 h	0
12	Bz	$NaBH_4$ (1.5, -)	CoPc	THF	4 Å MS	20 h	0

Reaction conditions: catalyst (30 mol%); yields refer to the isolated mixture; diastereomeric ratio was determined by integration of the resonance of the angular methyl group C-18 in the ^{13}C NMR spectra of the product mixture after prolonged relaxation delay (d1 = 10 sec.). a.r. = addition rate; **SI-01** = [*N*-salicylidene-2-amino-isobutyrato]-[2-amino-isobutyrato]-cobalt (III); Co-TPP = 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphin-Cobalt(II); CoPc = Cobalt(II) phthalocyanine.

2.4. Synthesis of the γ-lactone moiety

(*E*)-2-Tributylstannylbut-2-en-1,4-diol (**SI-05**)[16,17]



In a Schlenk flask under argon atmosphere, 2-butyne-1,4-diol (1.00 g, 11.6 mmol, 1.00 equiv.) and bis(triphenylphosphine)palladium(II) dichloride (163 mg, 232 µmol, 2.00 mol%) were suspended in absolute tetrahydrofuran (10 mL) and tributyltin hydride (3.7 mL, 4.06 g, 13.9 mmol, 1.20 equiv.) was slowly added dropwise. While stirring at room temperature, the solution first became clear and then turned dark red. After further 20 minutes, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (cHex/EtOAc, 4:1 → 3:1) to afford the title compound as a light yellow oil (4.01 g, 10.6 mmol, 92%), which was stored in a refrigerator under argon atmosphere.

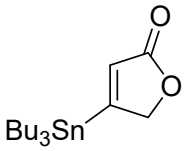
R_f = 0.25 (cHex/EtOAc, 4:1). – **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.77 (tt, J = 6.0, 1.9 Hz, 1H, =C*H*), 4.42 – 4.26 (m, 2H, C_qCH_2OH), 4.19 – 4.10 (m, 2H, $CHCH_2OH$), 2.96 – 2.33 (m, 2H, 2 × O*H*), 1.59 – 1.39 (m, 6H, 3 × $SnCH_2CH_2$), 1.36 – 1.21 (m, 6H, 3 × CH_2CH_3), 0.95 – 0.83 (m, 15H, 3 × $SnCH_2$ + 3 × CH_3) ppm. – **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.3 (C_q, s+d+d, $^1J_{119Sn-C}$ = 369.5 Hz, $^1J_{117Sn-C}$ = 352.8 Hz, *C*Sn), 138.1 (+, s+d, $^2J_{119/117Sn-C}$ = 19.0 Hz, =*C*H), 63.4 (–, C_qCH_2OH), 59.6 (–, s+d, $^3J_{119/117Sn-C}$ = 57.1 Hz, $CHCH_2OH$), 29.2 (–, s+d, $^2J_{119/117Sn-C}$ = 19.4 Hz, 3 × $SnCH_2CH_2$), 27.5 (–, s+d+d, $^3J_{119Sn-C}$ = 59.0 Hz, $^3J_{117Sn-C}$ = 56.7 Hz, 3 × CH_2CH_3), 13.8 (+, 3 × CH_2CH_3), 10.1 (–, s+d+d, $^1J_{119Sn-C}$ = 339.9 Hz, $^1J_{117Sn-C}$ = 325.0 Hz, 3 × $SnCH_2$) ppm.

The analytical data are in accordance with the literature.[16,17]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-OPJCQQUNAS-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/OPJCQQUNASDODS-UHFFFAOYSA-N.1

4-Tributylstannyl-2(5*H*)-furanone (**19**)[18]



Under argon atmosphere, (*E*)-2-tributylstannylbut-2-en-1,4-diol (**SI-05**) (2.07 g, 5.50 mmol, 1.00 equiv.) and 4-methylmorpholine-*N*-oxide (1.61 g, 13.7 mmol, 2.50 equiv.) were dissolved in absolute dichloromethane (30 mL) and 4 Å molecular sieves were added. The mixture was cooled to –78 °C and tetrapropylammonium perruthenate (135 mg, 384 µmol, 7.00 mol%) was added. The mixture was slowly warmed to room temperature in a flat *Dewar* flask overnight and then filtered through a pad of Celite® and silica gel (EtOAc

as eluent). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (cHex/EtOAc, 15:1) to afford the title compound as a yellow oil (582 mg, 1.56 mmol, 28%).

***R*$_f$** = 0.57 (cHex/EtOAc, 5:1). – **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.18 (t+d, $J_{H\text{-}H}$ = 2.2 Hz, $^3J_{119/117Sn\text{-}C}$ = 23.4 Hz 1H, =C*H*), 4.96 (d, *J* = 2.1 Hz, 2H, CH_2OCO), 1.58 − 1.47 (m, 6H, 3 × SnCH$_2$CH_2), 1.37 − 1.26 (m, 6H, 3 × CH_2CH$_3$), 1.11 – 1.04 (m, 6H, 3 × SnCH_2), 0.91 (t, *J* = 7.3 Hz, 9H, 3 × CH$_2$CH_3) ppm. – **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.3 (C_q, *C*Sn), 173.9 (C_q, *C*O), 129.5 (+, =*C*H), 78.7 (–, *C*H$_2$OCO), 29.1 (–, s+d, $^2J_{119/117Sn\text{-}C}$ = 21.9 Hz, 3 × SnCH$_2$*C*H$_2$), 27.3 (–, s+d+d, $^3J_{119Sn\text{-}C}$ = 59.4 Hz, $^3J_{117Sn\text{-}C}$ = 56.9 Hz, 3 × *C*H$_2$CH$_3$), 13.7 (+, 3 × CH$_2$*C*H$_3$), 10.1 (–, s+d+d, $^1J_{119Sn\text{-}C}$ = 356.9 Hz, $^1J_{117Sn\text{-}C}$ = 341.6 Hz, 3 × Sn*C*H$_2$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2955 (w), 2921 (m), 2852 (w), 1774 (m), 1742 (s), 1462 (w), 1377 (w), 1336 (w), 1159 (m), 1074 (w), 1035 (m), 986 (m), 882 (m), 857 (w), 697 (w), 600 (w), 510 (w), 412 (m) cm^{-1}. – **MS** (EI, 70 eV, 80 °C): *m/z* (%) = 374 (2) [M]$^+$, 317 (100) [M–Bu]$^+$, 261 (48) [M–2 × Bu]$^+$, 203 (37) [M–3 × Bu]$^+$. – **HRMS** ([M]$^+$, $C_{16}H_{30}O_2{}^{120}Sn^+$): calc. = 374.1268; found = 374.1266.

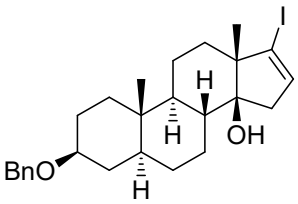
The analytical data are in accordance with the literature.[19]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-SFOGKNHRVG-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/SFOGKNHRVGTLCF-UHFFFAOYSA-N.1

2.5. Finalization of the semisynthesis of uzarigenin

3β-Benzyloxy-17-iodo-5α-androst-16-en-14β-ol (**18**)



Under argon atmosphere, 3β-benzyloxy-14β-hydroxy-5α-androstan-17-one (**16**) (369 mg, 931 µmol, 1.00 equiv.) was dissolved in absolute ethanol (10 mL), before absolute triethylamine (2.58 mL, 1.88 g, 18.6 mmol, 20.0 equiv.) and hydrazine monohydrate (64%, 0.65 mL, 932 mg, 18.6 mmol, 20.0 equiv.) were added. The reaction mixture was heated to 50 °C for 16 h. It was allowed to reach room temperature, the solvent was removed under reduced pressure and the residue was dissolved in a mixture of absolute tetrahydrofuran (10 mL) and absolute triethylamine (5 mL). The mixture was cooled to 0 °C and a solution of iodine (472 mg, 1.86 mmol, 2.00 equiv.) in absolute tetrahydrofuran (5 mL) was added

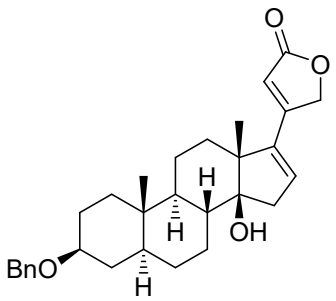
dropwise. It was stirred for 3 days at room temperature, before saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (25 mL) were added. It was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with brine (100 mL). It was dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (cHex/EtOAc, 10:1) to afford the title compound as a colorless solid (242 mg, 477 µmol, 51%).

***R*$_f$** = 0.08 (cHex/EtOAc, 10:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.39 – 7.30 (m, 4H, 4 × C*H*$_{Ar}$), 7.29 – 7.24 (m, 1H, C*H*$_{Ar}$), 6.10 (s, 1H, 16-C*H*), 4.60 – 4.52 (m, 2H, OC*H*$_2$Ph), 3.34 (tt, *J* = 10.7, 4.8 Hz, 1H, 3-C*H*), 2.51 (dd, *J* = 16.5 Hz, 1H, 15-C*H*$_2^a$), 2.18 (dd, *J* = 16.5, 3.2 Hz, 1H, 15-C*H*$_2^b$), 2.07 (dd, *J* = 12.9, 3.6 Hz, 1H, C*H*$_2$), 1.92 (d, *J* = 13.1 Hz, 1H, C*H*$_2$), 1.84 – 1.69 (m, 3H, 3 different C*H*$_2$), 1.68 – 1.58 (m, 2H, 8-C*H* + O*H*), 1.58 – 1.41 (m, 2H, 2 different C*H*$_2$), 1.39 – 1.23 (m, 3H, 2 different C*H*$_2$), 1.12 – 1.02 (m, 3H, 5-C*H* + 2 different C*H*$_2$), 1.04 (s, 3H, 18-C*H*$_3$), 0.99 – 0.90 (m, 2H, 2 different C*H*$_2$), 0.82 (s, 3H, 19-C*H*$_3$), 0.82 – 0.74 (m, 1H, 9-C*H*) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 139.3 (C_q, *C*$_{Ar}$), 133.8 (+, 16-*C*H), 128.5 (+, 2 × *C*H$_{Ar}$), 127.7 (+, 2 × *C*H$_{Ar}$), 127.5 (+, *C*H$_{Ar}$), 111.5 (C_q, 17-*C*), 82.6 (C_q, 14-*C*), 77.9 (+, 3-*C*H), 70.0 (–, O*C*H$_2$Ph), 54.9 (C_q, 13-*C*), 50.7 (+, 9-*C*H), 44.5 (+, 5-*C*H), 42.7 (–, 15-*C*H$_2$), 41.2 (+, 8-*C*H), 37.3 (–, 2 × *C*H$_2$), 36.2 (C_q, 10-*C*), 34.8 (–, *C*H$_2$), 28.6 (–, *C*H$_2$), 28.3 (–, *C*H$_2$), 27.4 (–, *C*H$_2$), 19.8 (–, *C*H$_2$), 18.0 (+, 18-*C*H$_3$), 12.5 (+, 19-*C*H$_3$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3502 (w), 2924 (s), 2853 (m), 1451 (m), 1383 (w), 1358 (m), 1255 (m), 1188 (w), 1147 (w), 1133 (w), 1089 (s), 1067 (vs), 1054 (vs), 1027 (s), 973 (m), 953 (m), 926 (m), 898 (vs), 861 (m), 837 (m), 803 (w), 754 (s), 738 (vs), 697 (vs), 650 (w), 633 (w), 606 (w), 589 (w), 562 (w), 458 (m), 438 (m), 402 (m) cm^{-1}. – **MS** (FAB, 3-NBA), m/z (%): 506 (2) $[M]^+$, 489 (5), 460 (4), 381 (10), 307 (31), 289 (16), 195 (13), 155 (30), 154 (100), 137 (65), 136 (64), 107 (21), 91 (43). – **HRMS** ($[M]^+$, $C_{26}H_{35}{}^{127}IO_2{}^+$): calc. = 506.1676; found = 506.1677.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-ZQYIAZUUTS-UHFFFADPSC-NUHFF-NVJIX-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/ZQYIAZUUTSEOHI-SIGVLJBRSA-N.1

3β-Benzyloxy-14β-hydroxy-5α-carda(16,20)-dienolide (**20**)



In a flame-dried Schlenk flask under argon atmosphere, 3β-benzyloxy-17-iodo-5α-androstan-16-en-14β-ol (**18**) (200 mg, 395 µmol, 1.00 equiv.), 4-tributylstannyl-2(5*H*)-furanone (**19**) (442 mg, 1.18 mmol, 3.00 equiv.), lithium chloride (167 mg, 3.95 mmol, 10.0 equiv.) and copper(I) chloride (391 mg, 3.95 mmol, 10.0 equiv.) were dissolved in absolute *N*,*N*-dimethylformamide (10.0 mL). The reaction mixture was degassed with three freeze-pump-thaw cycles and then $Pd(PPh_3)_4$ (91.3 mg, 79.0 µmol, 20 mol%) was added. The reaction mixture was heated to 60 °C for 24 h. After cooling to room temperature, 3 M aqueous potassium fluoride solution (0.530 mL, 91.8 mg, 1.58 mmol, 4.00 equiv.) was added, and it was stirred at room temperature for 30 minutes, filtered through a pad of Celite® and silica gel (EtOAc as eluent) and concentrated under reduced pressure. It was then washed with saturated aqueous NH_4Cl solution (100 mL) and the aqueous phase was extracted with dichloromethane (3 × 80 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and filtered. After removing the solvent under reduced pressure, the crude product was purified *via* flash column chromatography on silica gel (cHex/EtOAc, 2:1 → 1:1) to afford the title compound as a beige solid (122 mg, 264 µmol, 67%).

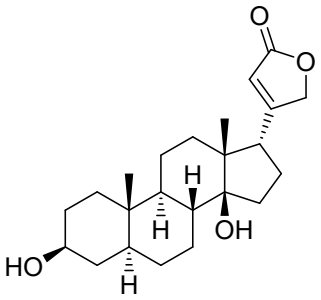
***R*$_f$** = 0.23 (cHex/EtOAc, 1:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.37 – 7.31 (m, 4H, 4 × C*H*$_{Ar}$), 7.29 – 7.24 (m, 1H, C*H*$_{Ar}$), 6.12 – 6.06 (m, 1H, 16-C*H*), 5.95 (s, 1H, 22-C*H*), 4.99 (dd, *J* = 16.2, 1.7 Hz, 1H, 21-CH_2^a), 4.93 (dd, *J* = 16.3, 1.6 Hz, 1H, 21-CH_2^b), 4.60 – 4.51 (m, 2H, OCH_2Ph), 3.34 (tt, *J* = 11.2, 4.7 Hz, 1H, 3-C*H*), 2.65 (dd, *J* = 18.6, 2.3 Hz, 1H, 15-CH_2^a), 2.33 (dd, *J* = 18.5, 3.5 Hz, 1H, 15-CH_2^b), 2.07 (dt, *J* = 10.4, 3.4 Hz, 1H, CH_2), 2.01 – 1.90 (m, 2H, 2 different CH_2), 1.80 (dt, *J* = 13.3, 3.7 Hz, 1H, CH_2), 1.77 – 1.70 (m, 1H, CH_2), 1.65 (td, *J* = 11.9, 3.6 Hz, 1H, 8-C*H*), 1.56 – 1.42 (m, 3H, O*H* + 2 different CH_2), 1.41 – 1.32 (m, 2H, 2 different CH_2), 1.32 – 1.24 (m, 1H, CH_2), 1.28 (s, 3H, 18-CH_3), 1.19 – 1.03 (m, 4H, 5-C*H* + 3 different CH_2), 0.95 (td, *J* = 13.9, 4.2 Hz, 1H, CH_2), 0.86 – 0.78 (m, 1H, 9-C*H*), 0.84 (s, 3H, 19-CH_3) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 174.5 (C$_q$, *C*O), 158.5 (C$_q$, 20-*C*), 144.0 (C$_q$, 17-*C*), 139.2 (C$_q$, *C*$_{Ar}$), 132.4 (+, 16-*C*H), 128.5 (+, 2 × *C*H$_{Ar}$), 127.7 (+, 2 × *C*H$_{Ar}$), 127.5 (+, *C*H$_{Ar}$), 112.5 (+, 22-*C*H), 85.7 (C$_q$, 14-*C*), 77.9 (+, 3-*C*H), 71.8 (–, 21-*C*H$_2$), 70.0 (–, O*C*H$_2$Ph), 52.2 (C$_q$, 13-*C*), 50.6 (+, 9-*C*H), 44.4 (+, 5-*C*H), 40.9 (+, 8-*C*H), 40.5 (–, 15-*C*H$_2$), 38.3 (–, *C*H$_2$), 37.3 (–, *C*H$_2$), 36.2 (C$_q$, 10-*C*), 34.8 (–, *C*H$_2$), 28.6 (–, *C*H$_2$), 28.2 (–, *C*H$_2$), 27.5 (–, *C*H$_2$), 19.9 (–, *C*H$_2$), 16.7 (+, 18-*C*H$_3$), 12.5 (+, 19-*C*H$_3$) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3507 (w), 2941 (m), 2919 (m), 2885 (m), 2853 (m), 2837 (m), 1789 (w), 1741 (vs), 1697 (w), 1613 (vs), 1452 (m), 1384 (w), 1357 (m), 1336 (s), 1316 (w), 1273 (w), 1248 (w), 1198 (w), 1187 (w), 1159 (s), 1129 (w), 1094 (vs), 1074 (vs), 1048 (vs), 1034 (s), 1026 (m), 1003 (s), 987 (m), 973

(m), 952 (m), 894 (vs), 885 (s), 840 (s), 802 (s), 754 (vs), 701 (vs), 637 (w), 608 (w), 535 (m), 490 (s), 462 (s), 435 (m) cm^{-1}. – **HRMS** (ESI, $[M+H]^+$, $C_{30}H_{39}O_4^+$): calc. = 463.2843; found = 463.2842.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-RPSOUIUISV-UHFFFADPSC-NUHFF-NPSBK-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/RPSOUIUISVVWAN-ZKJSLFQJSA-N.1

<u>*allo*-Uzarigenin (**21**)</u>



Under argon atmosphere, 3β-benzyloxy-14β-hydroxy-5α-carda(16,20)-dienolide (**20**) (50.0 mg, 108 µmol, 1.00 equiv.) was dissolved in EtOAc (7.0 mL), before 10 wt.% Pd/C (80.0 mg) was added. After exchanging the argon atmosphere with hydrogen, hydrogen was bubbled through the solution for 5 minutes. Subsequently, the reaction mixture was stirred at room temperature for 20 minutes. It was filtered through a pad of Celite® (EtOAc as eluent) and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica gel (dichloromethane/MeOH, 20:1) to afford the title compound as a colorless solid (30.2 mg, 80.6 µmol, 76%).

***R*$_f$** = 0.36 (dichloromethane/MeOH, 20:1). – **^{1}H NMR** (500 MHz, **$CDCl_3$**): δ = 5.87 (s, 1H, 22-C*H*), 4.81 (d, ^2J = 17.5 Hz, 1H, 21-CH_2^a), 4.71 (d, ^2J = 17.5 Hz, 1H, 21-CH_2^b), 3.59 (tt, *J* = 10.5, 4.6 Hz, 1H, 3-C*H*), 3.18 (t, *J* = 9.5 Hz, 1H, 17-C*H*), 2.14 – 2.00 (m, 2H, 16-CH_2^a + CH_2), 2.00 – 1.93 (m, 1H, CH_2), 1.85 – 1.69 (m, 3H, 16-CH_2^b + 2 different CH_2), 1.64 – 1.49 (m, 5H, 8-C*H* + 3 different CH_2 + O*H*), 1.44 – 1.32 (m, 2H, 2 different CH_2), 1.32 – 1.20 (m, 3H, 2 different CH_2 + O*H*), 1.18 – 1.05 (m, 5H, 5-C*H* + 3 different CH_2), 1.03 (s, 3H, 18-CH_3), 0.97 (td, *J* = 13.6, 3.9 Hz, 1H, CH_2), 0.89 – 0.82 (m, 1H, 9-C*H*), 0.80 (s, 3H, 19-CH_3) ppm. – **^{13}C NMR** (126 MHz, **$CDCl_3$**): δ = 174.1 (C_q, *C*O), 171.4 (C_q, 20-*C*), 116.9 (+, 22-*C*H), 86.2 (C_q, 14-*C*), 73.9 (–, 21-*C*H_2), 71.3 (+, 3-*C*H), 50.1 (+, 9-*C*H), 48.9 (C_q, 13-*C*), 48.5 (+, 17-*C*H), 44.5 (+, 5-*C*H), 41.7 (+, 8-*C*H), 38.0 (–, *C*H_2), 37.2 (–, *C*H_2), 35.8 (C_q, 10-*C*), 31.5 (–, 2 × *C*H_2), 30.9 (–, *C*H_2), 28.5 (–, *C*H_2), 27.1 (–, *C*H_2), 24.6 (–, 16-*C*H_2), 20.3 (–, *C*H_2), 18.3 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm. – **^{1}H NMR** (500 MHz, **DMSO-d_6**): δ = 5.98 (s, 1H, 22-C*H*), 4.89 (dd, *J* = 18.0, 1.8 Hz, 1H, 21-CH_2^a), 4.82 (dd, *J* = 18.0, 1.8 Hz, 1H, 21-CH_2^b), 4.42 (d, *J* = 4.7 Hz, 1H, 3-O*H*), 4.06 (s, 1H, 14-O*H*), 3.39 – 3.26 (m, 1H, 3-C*H*, concealed under the H_2O-signal), 3.07 (t, *J* = 9.6 Hz, 1H, 17-C*H*), 2.01 – 1.89 (m, 2H, 15-CH_2^a + CH_2), 1.88 – 1.80 (m, 1H, 16-CH_2^a), 1.80 – 1.71 (m, 1H,

16-CH_2^b), 1.66 – 1.59 (m, 2H, 2 different CH_2), 1.51 – 1.38 (m, 4H, 8-C*H* + 15-CH_2^b + 2 different CH_2), 1.30 – 1.19 (m, 2H, 2 different CH_2), 1.19 – 1.08 (m, 2H, 2 different CH_2), 1.08 – 0.96 (m, 4H, 5-C*H* + 2 different CH_2), 0.96 – 0.84 (m, 2H, 2 different CH_2), 0.92 (s, 3H, 18-CH_3), 0.79 (td, *J* = 11.9, 3.9 Hz, 1H, 9-C*H*), 0.72 (s, 3H, 19-CH_3) ppm. – **^{13}C NMR** (126 MHz, **DMSO-d$_6$**): δ = 173.7 (C_q, *C*O or 20-*C*), 173.5 (C_q, *C*O or 20-*C*), 115.3 (+, 22-*C*H), 84.2 (C_q, 14-*C*), 73.6 (–, 21-*C*H_2), 69.3 (+, 3-*C*H), 49.3 (+, 9-*C*H), 48.3 (C_q, 13-*C*), 48.1 (+, 17-*C*H), 44.0 (+, 5-*C*H), 40.4 (+, 8-*C*H), 38.1 (–, 2- or 4-*C*H_2), 36.7 (–, *C*H_2), 35.3 (C_q, 10-*C*), 31.3 (–, 2- or 4-*C*H_2), 30.6 (–, 15-*C*H_2), 30.0 (–, *C*H_2), 28.4 (–, *C*H_2), 26.8 (–, *C*H_2), 23.9 (–, 16-*C*H_2), 19.9 (–, *C*H_2), 18.2 (+, 18-*C*H_3), 12.1 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3438 (w), 2928 (m), 2860 (w), 1708 (vs), 1618 (m), 1470 (w), 1446 (w), 1361 (w), 1261 (w), 1184 (w), 1111 (w), 1069 (w), 1037 (s), 1016 (m), 982 (w), 955 (w), 907 (s), 885 (m), 861 (m), 731 (vs), 711 (m), 647 (w), 564 (w), 535 (w), 516 (m), 486 (w), 445 (m) cm^{-1}. – **HRMS** (ESI, $[M+H]^+$, $C_{23}H_{35}O_4^+$): calc. = 375.2529; found = 375.2527.

The analytical data are in accordance with the literature.[20]

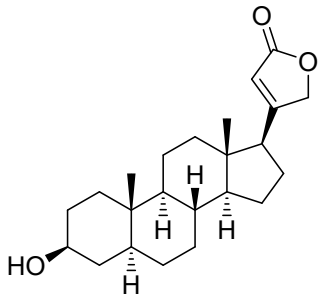
Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-XZTUSOXSLK-UHFFFADPSC-NUHFF-NLDNR-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/XZTUSOXSLKTKJQ-APYKUEBJSA-N.1

Table SI-3: ^{1}H NMR shifts (DMSO-d$_6$) comparison of the relevant proton resonances of *allo*-uzarigenin (**21**) synthesized in this work with reported data from the literature.

^{1}H NMR shifts in DMSO-d$_6$	**14-O*H***	**17-C*H***	**18-CH_3**	**19-CH_3**	**21-CH_2**	**22-C*H***
***allo*-Uzarigenin (this work)**	4.06 (s)	3.07 (t, *J* = 9.6 Hz)	0.92 (s)	0.72 (s)	4.89 (dd) 4.82 (dd)	5.98 (s)
***allo*-Uzarigenin (Ghorbani *et al.*)[20]**	4.08 (s)	3.07 (t, *J* = 9.5 Hz)	0.93 (s)	0.74 (s)	4.91 (d) 4.81 (d)	5.99 (s)

For comparison: Hydrogenation of 3β-hydroxy-5α,14α-carda-(16,20)-dienolide yielded exclusively the desired 17β-product 3β-hydroxy-5α,14α-card-(20,22)-enolide (**SI-06**)



Under argon atmosphere, 3β-hydroxy-5α,14α-carda-(16,20)-dienolide (50.0 mg, 140 µmol, 1.00 equiv.) was dissolved in EtOAc (6.0 mL), before 10 wt.% Pd/C (100 mg) was added. After exchanging the argon atmosphere with hydrogen, hydrogen was bubbled through the solution for 10 minutes. Subsequently, the reaction mixture was stirred at room temperature for 2 h. It was filtered through a pad of Celite® (EtOAc as eluent) and concentrated under reduced pressure to afford the title compound as a colorless solid (48.2 mg, 134 µmol, 96%). The absolute configuration could be determined by single crystal X-ray analysis. With prolonged reaction times only the diastereomeric mixture 3β-hydroxy-5α,14α,20α/β-cardanolide (**SI-07**) could be obtained as a colorless solid. The assignment of the epimers was not possible, but the ratio of the two epimers could be determined to be 1:0.9 by integration of the resonances of the 21-CH_2 group in the ^{1}H NMR spectrum.

***R**$_f$* = 0.31 (cHex/EtOAc, 1:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 5.83 – 5.77 (m, 1H, 22-C*H*), 4.79 (dd, *J* = 17.4, 1.8 Hz, 1H, 21-CH_2^a), 4.66 (dd, *J* = 17.5, 1.9 Hz, 1H, 21-CH_2^b), 3.57 (tt, *J* = 11.0, 4.8 Hz, 1H, 3-C*H*), 2.33 (t, *J* = 9.5 Hz, 1H, 17-C*H*), 2.00 – 1.92 (m 1H, 16-CH_2^a), 1.83 – 1.64 (m, 6H, 16-CH_2^b + 5 different CH_2), 1.61 – 1.53 (m, 2H, 2 different CH_2), 1.44 – 1.32 (m, 2H, 8-C*H* + CH_2), 1.32 – 1.06 (m, 8H, 5-C*H* + 14-C*H* + 5 different CH_2), 1.01 – 0.85 (m, 2H, 2 different CH_2), 0.79 (s, 3H, 19-CH_3), 0.67 (ddd, *J* = 12.3, 10.5, 4.2 Hz, 1H, 9-C*H*), 0.59 (s, 3H, 18-CH_3) ppm. One missing signal (1H, OH) due to H/D exchange in $CDCl_3$. – **^{13}C NMR** (126 MHz, $CDCl_3$)*: δ = 174.3 (C_q, *C*O), 171.6 (C_q, 20-*C*), 116.0 (+, 22-*C*H), 73.6 (–, 21-*C*H_2), 71.2 (+, 3-*C*H), 56.4 (+, 14-*C*H), 54.3 (+, 9-*C*H), 51.0 (+, 17-*C*H), 44.9 (+, 5-*C*H), 44.7 (C_q, 13-*C*), 38.3 (–, *C*H_2), 38.2 (–, *C*H_2), 37.1 (–, *C*H_2), 35.9 (+, 8-*C*H), 35.6 (C_q, 10-*C*), 32.0 (–, *C*H_2), 31.5 (–, *C*H_2), 28.6 (–, *C*H_2), 26.0 (–, 16-*C*H_2), 24.4 (–, *C*H_2), 21.1 (–, *C*H_2), 13.4 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 3441 (vw), 2924 (w), 2837 (w), 1729 (w), 1619 (w), 1449 (vw), 1380 (vw), 1262 (vw), 1165 (vw), 1136 (vw), 1108 (vw), 1079 (vw), 1040 (w), 1009 (w), 953 (vw), 900 (w), 864 (w), 706 (vw), 665 (vw), 591 (vw), 555 (vw), 470 (vw), 451 (vw) cm^{-1}. – **HRMS** (ESI, $[M+H]^+$, $C_{23}H_{35}O_3^+$): calc. = 359.2581; found = 359.2574.

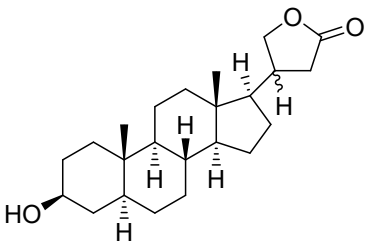
The analytical data are in accordance with the literature.[21]

* The NMR spectra contain an unknown impurity.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-SNNJOYYRZH-UHFFFADPSC-NUHFF-NXKBZ-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/SNNJOYYRZHOKFM-PQHHJXOYSA-N.1

3β-Hydroxy-5α,14α,20-cardanolide (**SI-07**)



***R**$_f$* = 0.41 (cHex/EtOAc, 1:1). – **^{1}H NMR** (500 MHz, $CDCl_3$, main isomer A, minor isomer B)*: δ = 4.49 – 4.40 (m, 1H, 21^B-CH_2^a) and 4.35 (t, *J* = 8.2 Hz, 1H, 21^A-CH_2^a), 3.90 (t, *J* = 9.3 Hz, 1H, 21^B-CH_2^b) and 3.81 (dd, *J* = 9.9, 8.8 Hz, 1H, 21^A-CH_2^b), 3.58 (tt, *J* = 10.8, 4.8 Hz, 1H, 3-C*H*), 2.58 (dd, *J* = 16.9, 7.9 Hz, 1H, 22^A-CH_2^a), 2.56 – 2.41 (m, 1H, 20^A-C*H*) and 2.56 – 2.41 (m, 2H, 20^B-C*H* + 22^B-CH_2^a), 2.25 – 2.13 (m, 1H, 22^A-CH_2^b) and 2.25 – 2.13 (m, 1H, 22^B-CH_2^b), 1.94 (bs, 1H, O*H*), 1.83 – 1.75 (m, 1H, ^{B}CH_2^a) and 1.83 – 1.75 (m, 1H, CH_2), 1.73 – 1.62 (m, 1H, ^{A}CH_2^a) and 1.73 – 1.62 (m, 4H, 4 different CH_2), 1.60 – 1.48 (m, 2H, 2 different CH_2), 1.44 – 1.21 (m, 2H, 17^A-C*H* + ^{A}CH_2^b) and 1.44 – 1.21 (m, 2H, 17^B-C*H* + ^{B}CH_2^b) and 1.44 – 1.21 (m, 6H, 8-C*H* + 4 different CH_2), 1.21 – 1.05 (m, 3H, 5-C*H* + 2 different CH_2), 1.05 – 0.95 (m, 2H, 14-C*H* + CH_2), 0.95 – 0.81 (m, 1H, CH_2), 0.80 (s, 3H, 19^A-CH_3) and 0.80 (s, 3H, 19^B-CH_3), 0.67 (s, 3H, 18^B-CH_3) and 0.65 (s, 3H, 18^A-CH_3), 0.64 – 0.60 (m, 1H, 9-C*H*) ppm.

20-epimer A (main isomer):

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 177.7 (C_q, *C*O), 73.3 (–, 21-*C*H_2), 71.4 (+, 3-*C*H), 55.6 (+, 14-*C*H), 54.5 (+, 17-*C*H), 54.5 (+, 9-*C*H), 44.9 (+, 5-*C*H), 43.0 (C_q, 13-*C*), 39.0 (–, *C*H_2), 38.3 (+, 20-*C*H), 38.2 (–, *C*H_2), 37.1 (–, *C*H_2), 35.6 (C_q, 10-*C*), 35.5 (+, 8-*C*H), 34.3 (–, 22-*C*H_2), 32.2 (–, *C*H_2), 31.6 (–, *C*H_2), 28.7 (–, *C*H_2), 26.3 (–, *C*H_2), 24.6 (–, *C*H_2), 21.1 (–, *C*H_2), 13.1 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm.

20-epimer B (minor isomer):

^{13}C NMR (126 MHz, $CDCl_3$)*: δ = 177.1 (C_q, *C*O), 72.9 (–, 21-*C*H_2), 71.4 (+, 3-*C*H), 55.8 (+, 14-*C*H), 54.7 (+, 17-*C*H), 54.4 (+, 9-*C*H), 44.9 (+, 5-*C*H), 42.7 (C_q, 13-*C*), 39.0 (–, *C*H_2), 38.8 (+, 20-*C*H), 38.2 (–, *C*H_2), 37.1 (–, *C*H_2), 35.6 (C_q, 10-*C*), 35.5 (+, 8-*C*H), 34.5 (–, 22-*C*H_2), 32.1 (–, *C*H_2), 31.6 (–, *C*H_2), 28.7 (–, *C*H_2), 27.5 (–, *C*H_2), 24.5 (–, *C*H_2), 21.1 (–, *C*H_2), 13.1 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm.

– **IR** (ATR, $\tilde{\nu}$) = 2918 (vs), 2849 (vs), 1778 (vs), 1468 (m), 1443 (s), 1414 (w), 1380 (m), 1350 (w), 1306 (w), 1264 (w), 1249 (w), 1232 (w), 1173 (vs), 1137 (m), 1108 (m), 1078 (s), 1030 (vs), 1000 (vs), 952 (m), 935 (m), 905 (w), 882 (w), 850 (m), 836 (w), 798 (w), 731 (w), 718 (w), 688 (m), 664 (m), 630 (m), 605 (m), 547 (m), 506 (m), 493 (m), 469 (m), 439 (m) cm^{-1}. – **MS** (FAB, 3-NBA), m/z (%): 361 (31) $[M+H]^+$, 284 (49), 155

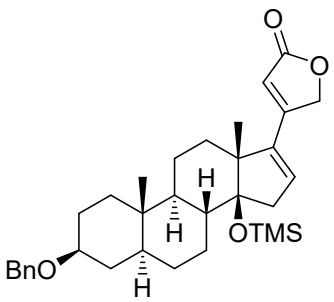
(46), 154 (68), 137 (83), 136 (64), 95 (100). – **HRMS** ([M+H]$^+$, $C_{23}H_{37}O_3^+$): calc. = 361.2737; found = 361.2736.

* The NMR spectra contain an unknown impurity.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-PNJRWCQUQC-UHFFFADPSC-NUHFF-NGPIL-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/PNJRWCQUQCUHAW-JMKKDLITSA-N.1

3β-Benzyloxy-14β-trimethylsilyloxy-5α-carda(16,20)-dienolide (**22**)



Under argon atmosphere, 3β-benzyloxy-14β-hydroxy-5α-carda(16,20)-dienolide (**16**) (50.9 mg, 110 µmol, 1.00 equiv.) was dissolved in absolute *N*,*N*-dimethylformamide (5.0 mL). 1*H*-Imidazol (74.9 mg, 1.10 mmol, 10.0 equiv.) was added and the reaction mixture was stirred for 10 min at room temperature. Subsequently, trimethylsilyl chloride (70.0 µL, 59.8 mg, 550 µmol, 5.00 equiv.) was added dropwise and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (5 mL) and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and filtered. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (cHex/EtOAc, 10:1 → 5:1) to afford the title compound as a colorless solid (55.1 mg, 103 µmol, 94%).

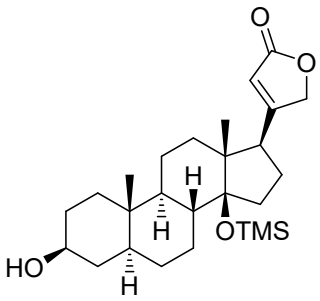
***R*$_f$** = 0.16 (cHex/EtOAc, 5:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.37 – 7.31 (m, 4H, 4 × C*H*$_{Ar}$), 7.29 – 7.25 (m, 1H, C*H*$_{Ar}$), 6.02 (t, *J* = 2.8 Hz, 1H, 16-C*H*), 5.95 (s, 1H, 22-C*H*), 5.00 (dd, ^2J = 16.2 Hz, ^4J = 1.7 Hz, 1H, 21-C*H*$_2^a$), 4.90 (dd, ^2J = 16.2 Hz, ^4J = 1.6 Hz, 1H, 21-C*H*$_2^b$), 4.56 (s, 2H, OC*H*$_2$Ph), 3.34 (tt, *J* = 11.1, 4.7 Hz, 1H, 3-C*H*), 2.55 (d, ^2J = 18.4 Hz, 1H, 15-C*H*$_2^a$), 2.37 (dd, ^2J = 18.6 Hz, *J* = 3.4 Hz, 1H, 15-C*H*$_2^b$), 2.00 – 1.89 (m, 3H, 3 different C*H*$_2$), 1.79 (dt, *J* = 13.2, 3.6 Hz, 1H, C*H*$_2$), 1.76 – 1.70 (m, 1H, C*H*$_2$), 1.63 (td, *J* = 12.0, 3.7 Hz, 1H, 8-C*H*), 1.53 – 1.42 (m, 2H, 2 different C*H*$_2$), 1.40 – 1.24 (m, 3H, 3 different C*H*$_2$), 1.20 (s, 3H, 18-C*H*$_3$), 1.17 – 0.98 (m, 4H, 5-C*H* + 3 different C*H*$_2$), 0.98 – 0.90 (m, 1H, C*H*$_2$), 0.83 (s, 3H, 19-C*H*$_3$), 0.75 (td, *J* = 11.8, 3.2 Hz, 1H, 9-C*H*), 0.00 (s, 9H, 3 × SiC*H*$_3$) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 174.7 (C$_q$, *C*O), 158.7 (C$_q$, 20-*C*), 145.0 (C$_q$, 17-*C*), 139.3 (C$_q$, *C*$_{Ar}$), 132.3 (+, 16-*C*H), 128.5 (+, 2 × *C*H$_{Ar}$), 127.7 (+, 2 × *C*H$_{Ar}$), 127.5 (+, *C*H$_{Ar}$),

112.4 (+, 22-*C*H), 90.0 (C_q, 14-*C*), 77.9 (+, 3-*C*H), 71.7 (–, 21-*C*H_2), 70.0 (–, O*C*H_2Ph), 53.0 (C_q, 13-*C*), 50.7 (+, 9-*C*H), 44.5 (+, 5-*C*H), 42.0 (+, 8-*C*H), 39.5 (–, 15-*C*H_2), 38.6 (–, *C*H_2), 37.4 (–, *C*H_2), 36.2 (C_q, 10-*C*), 34.8 (–, *C*H_2), 28.8 (–, *C*H_2), 28.3 (–, *C*H_2), 27.8 (–, *C*H_2), 19.9 (–, *C*H_2), 17.3 (+, 18-*C*H_3), 12.6 (+, 19-*C*H_3), 2.8 (+, 3 × Si*C*H_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2931 (m), 2856 (w), 1781 (m), 1748 (vs), 1621 (m), 1452 (w), 1361 (w), 1337 (w), 1248 (s), 1203 (w), 1153 (s), 1133 (w), 1085 (vs), 1038 (s), 1010 (m), 969 (s), 911 (w), 890 (m), 863 (s), 829 (vs), 749 (s), 734 (vs), 697 (vs), 649 (w), 598 (w), 460 (m) cm^{-1}. – **HRMS** (ESI, $[M+H]^+$, $C_{33}H_{47}O_4Si^+$): calc. = 535.3238; found = 535.3237.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-OKOKTQABRM-UHFFFADPSC-NUHFF-NARSA-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/OKOKTQABRMFVHZ-IUQDNMFSSA-N.1

14β-Trimethylsilyluzarigenin (**23**)



Under argon atmosphere, 3β-benzyloxy-14β-trimethylsilyloxy-5α-carda(16,20)-dienolide (**22**) (39.0 mg, 72.5 µmol, 1.00 equiv.) was dissolved in EtOAc (5.0 mL), before 10 wt.% Pd/C (53.0 mg) was added. After exchanging the argon atmosphere with hydrogen, hydrogen was bubbled through the solution for 5 minutes. Subsequently, the reaction mixture was stirred at room temperature for 20 minutes. It was filtered through a pad of Celite® (EtOAc as eluent) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (dichloromethane/MeOH, 20:1) to afford the title compound as a colorless solid (20.1 mg, 45.0 µmol, 62%).

***R**$_f$* = 0.44 (dichloromethane/MeOH, 20:1). – **^{1}H NMR** (500 MHz, $CDCl_3$)*: δ = 5.83 (s, 1H, 22-C*H*), 4.75 (dd, *J* = 5.7, 1.8 Hz, 2H, 21-C*H*$_2$), 3.60 (tt, *J* = 10.8, 4.9 Hz, 1H, 3-C*H*), 2.56 (dd, *J* = 9.0, 6.4 Hz, 1H, 17-C*H*), 2.09 – 1.94 (m, 2H, 2 different C*H*$_2$), 1.92 – 1.78 (m, 3H, 3 different C*H*$_2$), 1.75 – 1.67 (m, 2H, 2 different C*H*$_2$), 1.67 – 1.52 (m, 3H, 8-C*H* + 2 different C*H*$_2$), 1.49 – 1.34 (m, 3H, 3 different C*H*$_2$), 1.34 – 1.09 (m, 7H, C*H* + 5 different C*H*$_2$ + O*H*), 0.99 (td, *J* = 13.5, 4.0 Hz, 1H, C*H*$_2$), 0.87 (s, 3H, 18-C*H*$_3$), 0.87 – 0.79 (m, 1H, C*H*), 0.79 (s, 3H, 19-C*H*$_3$), 0.12 (s, 9H, 3 × SiC*H*$_3$) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$)*: δ = 174.5 (C_q, 20-*C* or *C*O), 174.2 (C_q, 20-*C* or *C*O), 117.2 (+, 22-*C*H), 91.4 (C_q, 14-*C*), 74.1 (–, 21-*C*H_2), 71.3 (+, 3-*C*H), 51.0 (C_q, 13-*C*), 50.9 (+, *C*H), 50.7 (+, 17-*C*H), 44.8 (+, *C*H), 41.5 (–, *C*H_2), 40.6 (+, 8-*C*H), 38.0 (–, *C*H_2), 37.2 (–, *C*H_2), 36.2 (C_q, 10-*C*),

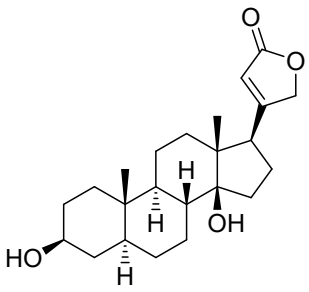
34.0 (–, CH_2), 31.5 (–, CH_2), 29.6 (–, CH_2), 28.6 (–, CH_2), 27.4 (–, 16-CH_2), 21.0 (–, CH_2), 18.3 (+, 18-CH_3), 12.3 (+, 19-CH_3), 3.1 (+, 3 × SiCH_3) ppm. – **IR** (ATR, $\tilde{\nu}$) = 2927 (m), 2859 (w), 2850 (w), 2198 (w), 2050 (w), 2044 (w), 1781 (w), 1747 (s), 1731 (vs), 1629 (m), 1448 (m), 1381 (m), 1249 (s), 1089 (vs), 1068 (vs), 1040 (vs), 1018 (vs), 899 (s), 875 (s), 832 (vs), 752 (s), 683 (s), 671 (s), 642 (s), 628 (s), 606 (s), 575 (s), 557 (s), 531 (s), 516 (s), 501 (s), 466 (s), 443 (s), 422 (m) cm^{-1}. – **MS** (EI, 70 eV, 170 °C), m/z (%): 447 (22) $[M+H]^+$, 446 (66) $[M]^+$, 431 (10), 356 (13), 253 (27), 252 (100), 251 (91), 237 (12), 183 (25), 181 (10), 169 (10), 158 (13), 157 (88), 119 (11), 107 (12), 93 (11), 75 (24), 73 (50), 69 (15). – **HRMS** ($[M]^+$, $C_{26}H_{42}O_4Si^+$): calc. = 446.2847; found = 446.2845.

* The NMR spectra contain 3β-hydroxy-5α-carda-14(15),20(22)-dienolide (14-dehydrouzarigenin) as impurity, which could be removed by flash column chromatography after the following reaction.

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-BFEUCRVIZQ-UHFFFADPSC-NUHFF-NCFCK-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/BFEUCRVIZQSZLP-ZEZUZNRDSA-N.1

Uzarigenin (**2**)



To a solution of 14β-trimethylsilyluzarigenin (**23**) (13.2 mg, 29.6 µmol, 1.00 equiv.) in methanol (3.0 mL), a 3 M aqueous HCl solution (400 µL) was added and it was stirred for 4 h at room temperature. Subsequently, saturated aqueous $NaHCO_3$ solution (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and filtered. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (dichlormethane/MeOH, 20:1) to afford the title compound as a colorless solid (8.8 mg, 23.5 µmol, 79%).

R_f = 0.12 (dichloromethane/MeOH, 20:1). – **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 5.87 (s, 1H, 22-C*H*), 4.98 (d, ^2J = 17.9 Hz, 1H, 21-CH_2^a), 4.80 (d, ^2J = 17.8 Hz, 1H, 21-CH_2^b), 3.64 – 3.55 (m, 1H, 3-C*H*), 2.77 (dd, *J* = 8.8, 5.6 Hz, 1H, 17-C*H*), 2.19 – 1.99 (m, 2H, 16-CH_2^a + CH_2), 1.97 – 1.90 (m, 1H, CH_2), 1.90 – 1.77 (m, 2H, 16-CH_2^b + CH_2), 1.76 – 1.70 (m, 1H, CH_2), 1.70 – 1.63 (m, 1H, CH_2), 1.63 – 1.56 (m, 1H, CH_2), 1.55 – 1.46 (m, 4H, C*H* + 3 different CH_2), 1.46 – 1.18 (m, 7H, 4 different CH_2 + 2 × O*H*), 1.15 – 1.05 (m, 2H, C*H* + CH_2), 1.02 – 0.90 (m, 2H, 9-C*H* + CH_2), 0.87 (s, 3H, 18-CH_3), 0.80 (s, 3H, 19-CH_3) ppm. – **^{13}C NMR** (126 MHz, $CDCl_3$): δ

= 174.6 (C_q, *C*O), 174.6 (C_q, 20-*C*), 117.9 (+, 22-*C*H), 85.7 (C_q, 14-*C*), 73.6 (–, 21-*C*H_2), 71.3 (+, 3-*C*H), 51.0 (+, 17-*C*H), 49.9 (+, 9-*C*H), 49.6 (C_q, 13-*C*), 44.5 (+, 5-*C*H or 8-*C*H), 41.8 (+, 5-*C*H or 8-*C*H), 40.0 (–, *C*H_2), 38.0 (–, *C*H_2), 37.2 (–, *C*H_2), 35.9 (C_q, 10-*C*), 33.2 (–, *C*H_2), 31.5 (–, *C*H_2), 28.6 (–, *C*H_2), 27.5 (–, *C*H_2), 27.0 (–, 16-*C*H_2), 21.3 (–, *C*H_2), 15.9 (+, 18-*C*H_3), 12.4 (+, 19-*C*H_3) ppm. – **IR** (ATR, ṽ) = 3568 (w), 3493 (w), 2935 (m), 2918 (w), 2883 (w), 2856 (w), 1793 (w), 1734 (vs), 1621 (m), 1469 (w), 1446 (w), 1375 (w), 1303 (w), 1288 (w), 1190 (m), 1174 (m), 1159 (m), 1136 (m), 1094 (s), 1071 (vs), 1048 (vs), 1017 (vs), 980 (s), 952 (vs), 939 (s), 897 (vs), 851 (s), 843 (s), 819 (m), 735 (m), 710 (m), 698 (m), 628 (w), 612 (w), 547 (s), 524 (s), 497 (s), 473 (vs), 453 (vs), 441 (vs), 422 (vs), 416 (vs), 402 (vs), 394 (vs) cm^{-1}. – **HRMS** (ESI, $[M+Cl]^-$, $C_{23}H_{34}O_4Cl^-$): calc. = 409.2151; found = 409.2154.

The analytical data are in accordance with the literature.[22,23]

Additional information on the chemical synthesis is available *via* Chemotion repository: https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-XZTUSOXSLK-UHFFFADPSC-NUHFF-NZDRL-NUHFF-ZZZ

Additional information on the analysis of the target compound is available *via* Chemotion repository: https://dx.doi.org/10.14272/XZTUSOXSLKTKJQ-CIXPXFMPSA-N.1

Table SI-4: ^{1}H NMR shifts ($CDCl_3$) comparison of the relevant proton resonances of *allo*-uzarigenin (**21**) and uzarigenin (**1**) synthesized in this work with reported data from the literature.

^{1}H NMR shifts in $CDCl_3$	**17-C*H***	**18-CH_3**	**19-CH_3**	**21-CH_2**	**22-C*H***
***allo*-Uzarigenin (this work)**	3.18 (t, *J* = 9.5 Hz)	1.03 (s)	0.80 (s)	4.81 (d) 4.71 (d)	5.87 (s)
Uzarigenin (this work)	2.77 (dd, *J* = 8.8, 5.6 Hz)	0.87 (s)	0.80 (s)	4.98 (d) 4.80 (d)	5.87 (s)
Uzarigenin (El-Askary *et al.*)[22]	2.78 (dd, *J* = 9.0, 5.5 Hz)	0.93 (s)	1.02 (s)	4.98 (dd) 4.81 (dd)	5.87 (s)

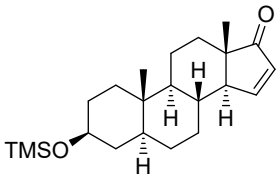
Table SI-5: ^{13}C NMR shifts ($CDCl_3$) comparison of the relevant carbon resonances of *allo*-uzarigenin (**21**) and uzarigenin (**1**) synthesized in this work with reported data from the literature.

^{13}C NMR shifts in $CDCl_3$	**17-*C*H**	**18-*C*H_3**	**20-C_q**	**21-*C*H_2**	**22-*C*H**	**23-C_q**
***allo*-Uzarigenin (this work)**	48.5	18.3	171.4	73.9	116.9	174.1
Uzarigenin (this work)	51.0	15.9	174.6	73.6	117.9	174.6
Uzarigenin (El-Askary *et al.*)[22]	50.9	15.8	174.5	73.4	117.7	174.5
Uzarigenin (Yang *et al.*)[23]	51.1	16.0	174.7	73.6	117.9	174.6

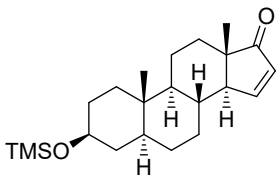
3. NMR spectra of the synthesized compounds

3.1. *Saegusa-Ito* oxidation

3β-Trimethylsilyloxy-5α-androst-15-en-17-one (**8**)



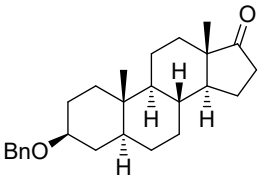
^{1}H NMR: 400 MHz, $CDCl_3$



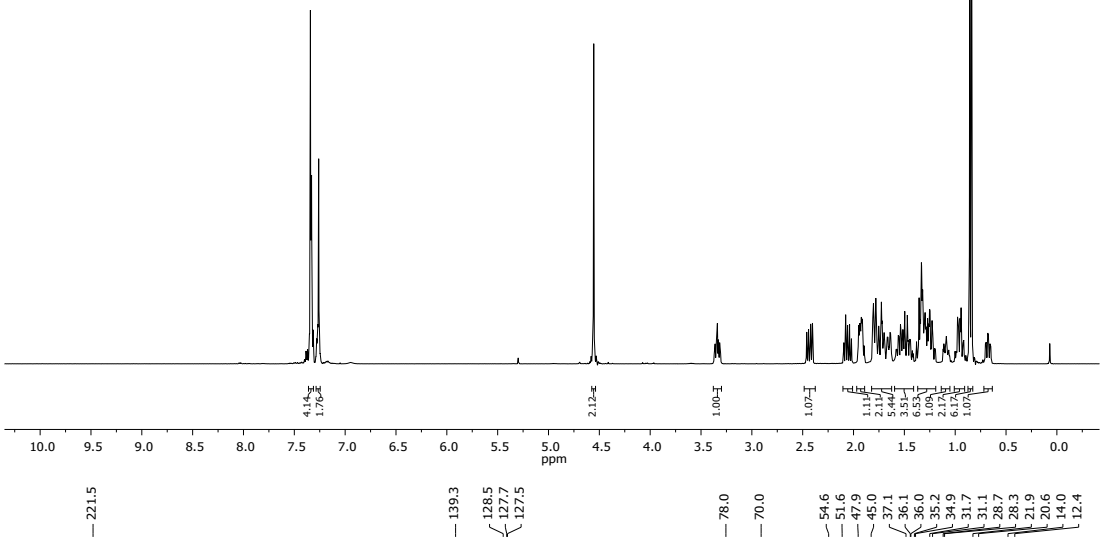
^{13}C NMR: 101 MHz, $CDCl_3$

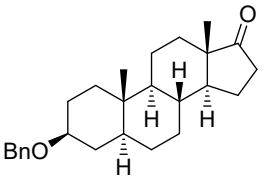
The NMR spectra contain traces of cyclohexane (3%).

3β-Benzyloxy-5α-androst-17-one (**SI-02**)



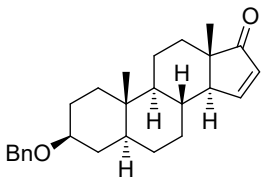
^{1}H NMR: 500 MHz, $CDCl_3$



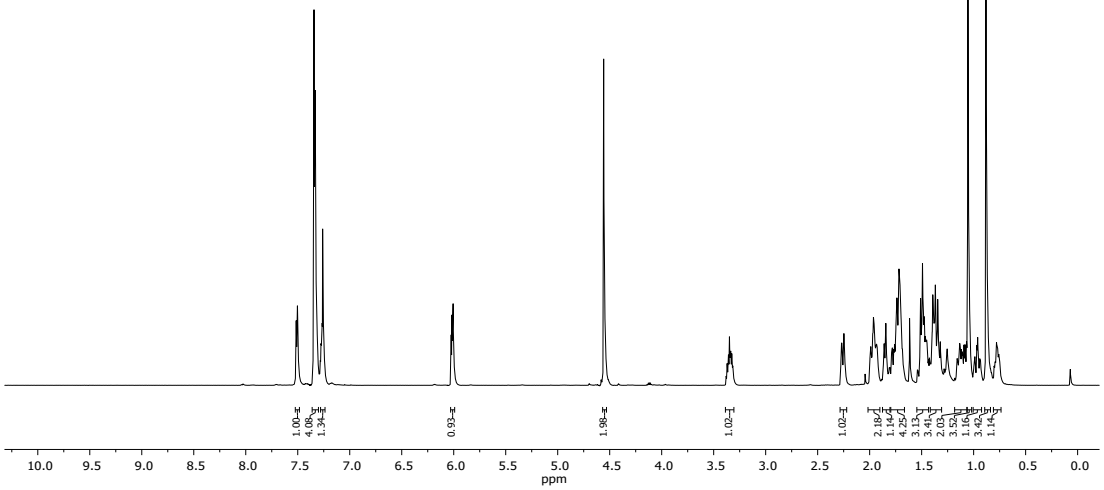


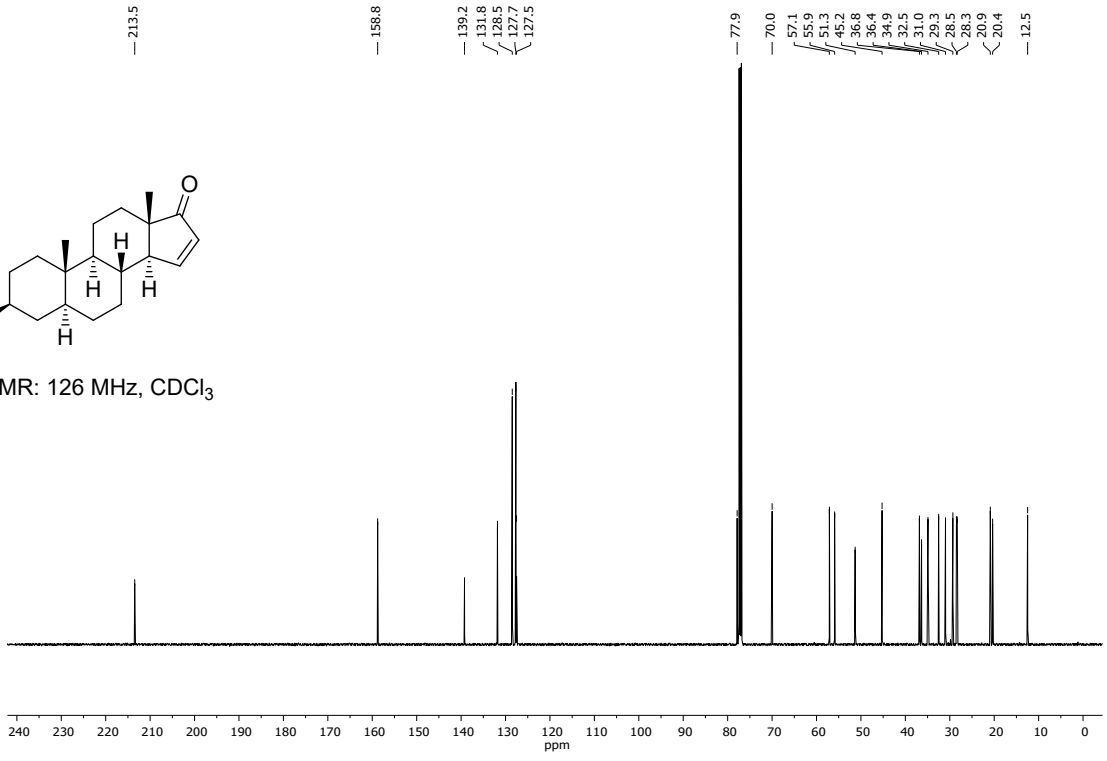
^{13}C NMR: 126 MHz, $CDCl_3$

3β-Benzyloxy-5α-androst-15-en-17-one (**SI-03**)



^{1}H NMR: 500 MHz, $CDCl_3$

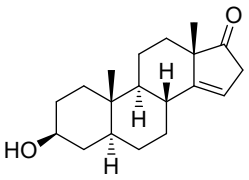




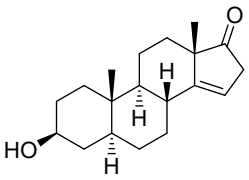
^{13}C NMR: 126 MHz, $CDCl_3$

3.2. Rearrangement reaction

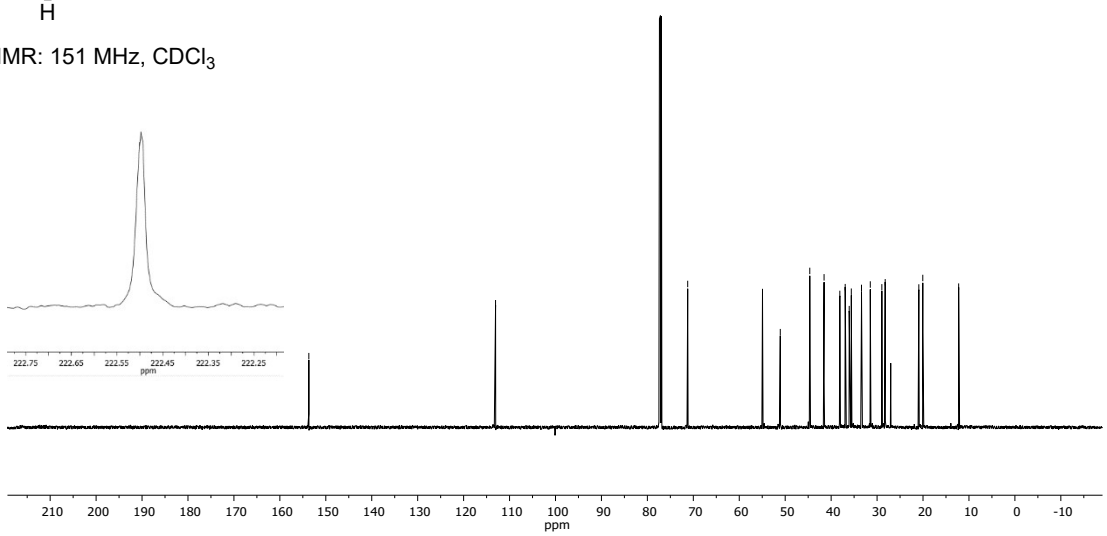
3β-Hydroxy-5α-androst-14-en-17-one (**9**)



^{1}H NMR: 600 MHz, $CDCl_3$

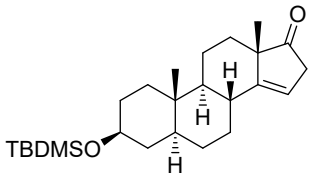


^{13}C NMR: 151 MHz, $CDCl_3$

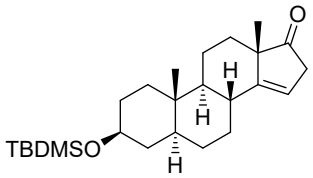


To prove the carbonylic carbon, a broader range spectrum was recorded. For the above spectra it can be assumed that the carbonylic carbon is present.

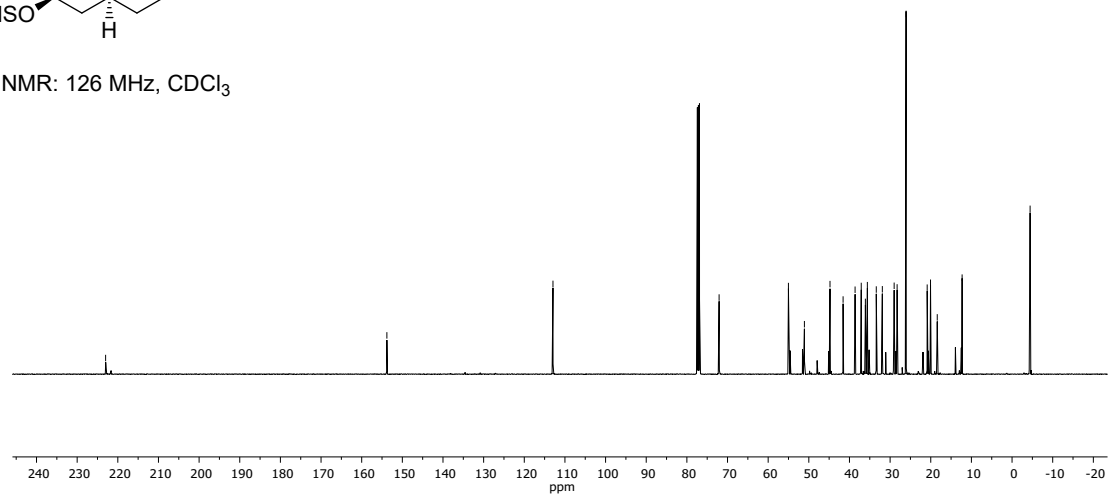
3β-*tert*-Butyldimethylsilyloxy-5α-androst-14-en-17-one (**12**)



^{1}H NMR: 500 MHz, $CDCl_3$

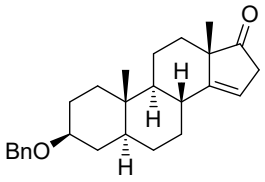


^{13}C NMR: 126 MHz, $CDCl_3$

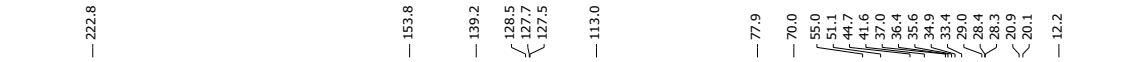


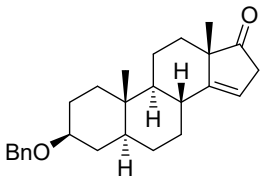
The NMR spectra contain an unknown impurity.

3β-Benzyloxy-5α-androst-14-en-17-one (**13**)



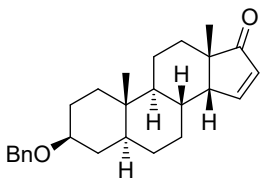
^{1}H NMR: 500 MHz, $CDCl_3$



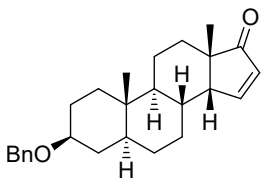


^{13}C NMR: 126 MHz, $CDCl_3$

3β-Benzyloxy-5α,14β-androst-15-en-17-one (**SI-04**)



^{1}H NMR: 500 MHz, $CDCl_3$

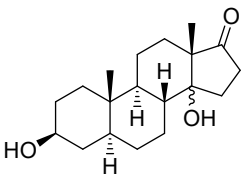


^{13}C NMR: 126 MHz, $CDCl_3$

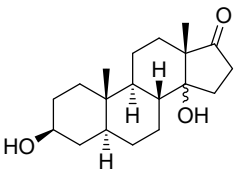
3.3. *Mukaiyama* oxidation

(3β,14)-Dihydroxy-5α-androstan-17-one (**14**)

Isomeric mixture of the 14-epimer A and B in the ratio of 2:1.



^{1}H NMR: 500 MHz, $CDCl_3$

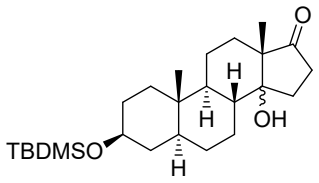


^{13}C NMR: 126 MHz, $CDCl_3$

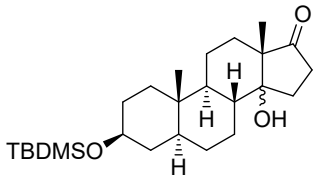
The NMR spectra contain an unknown impurity.

3β-*tert*-Butyldimethylsilyloxy-14-hydroxy-5α-androstan-17-one (**15**)

Isomeric mixture of the 14-epimer A and B in the ratio of 2:1.



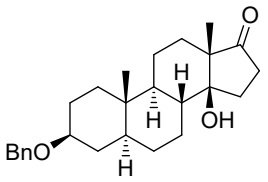
^{1}H NMR: 500 MHz, $CDCl_3$



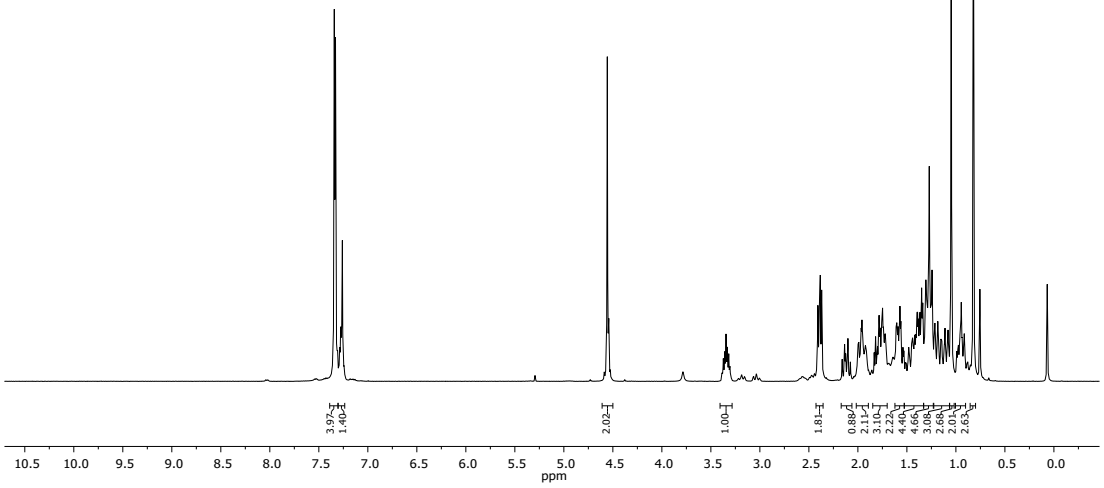
^{13}C NMR: 126 MHz, $CDCl_3$

The NMR spectra contain an unknown impurity.

3β-Benzyloxy-14β-hydroxy-5α-androst-17-one (**16**)



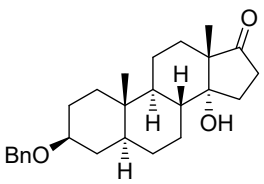
^{1}H NMR: 500 MHz, $CDCl_3$



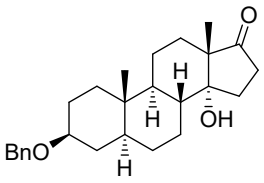
^{13}C NMR: 126 MHz, $CDCl_3$

The NMR spectra contain an unknown impurity that was present in all benzyl protected *Mukaiyama* oxidation products and presumably originated from the catalyst.

3β-Benzyloxy-14α-hydroxy-5α-androst-17-one (**17**)



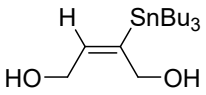
^{1}H NMR: 500 MHz, $CDCl_3$



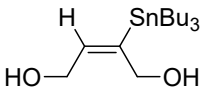
^{13}C NMR: 126 MHz, $CDCl_3$

3.4. γ-lactone moiety

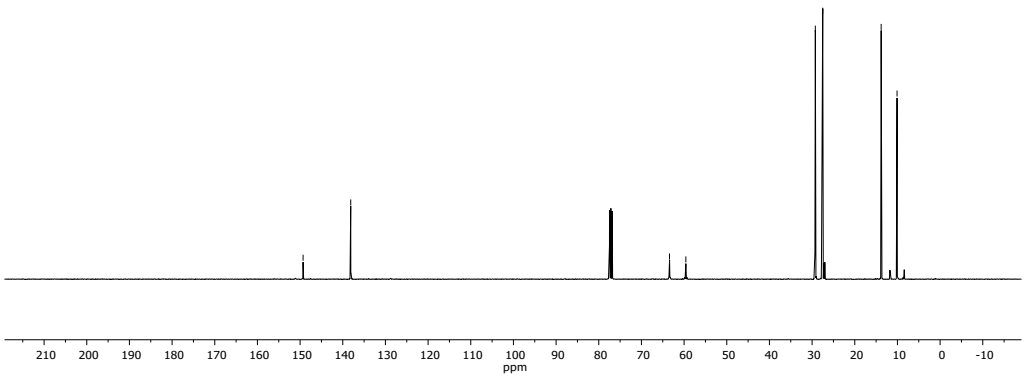
(*E*)-2-Tributylstannylbut-2-en-1,4-diol (**SI-05**)



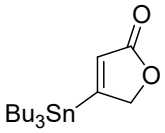
^{1}H NMR: 400 MHz, $CDCl_3$



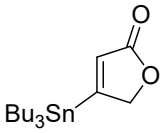
^{13}C NMR: 101 MHz, $CDCl_3$



4-Tributylstannyl-2(5*H*)-furanone (**19**)



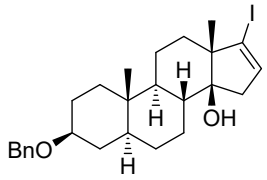
^{1}H NMR: 400 MHz, $CDCl_3$



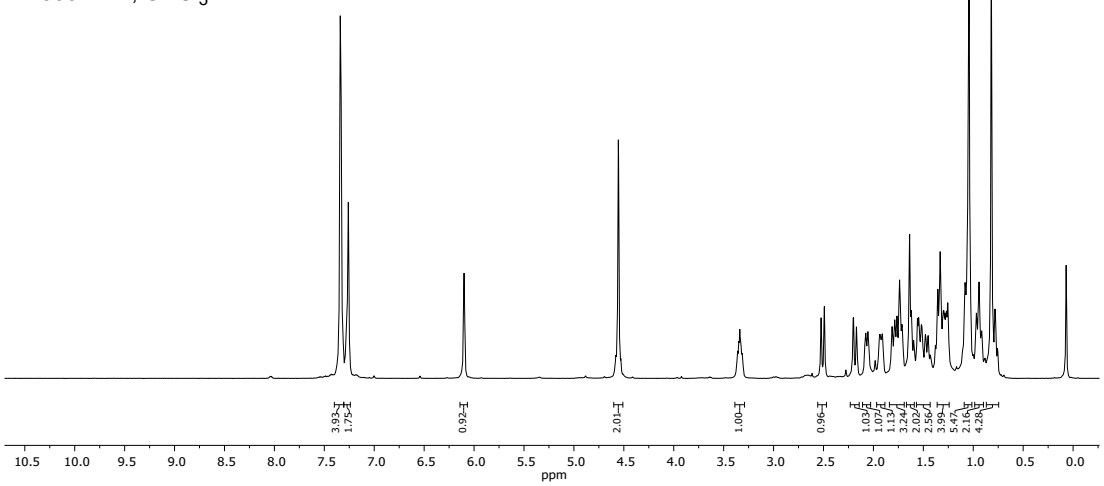
^{13}C NMR: 101 MHz, $CDCl_3$

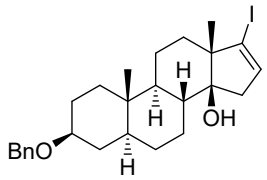
3.5. Finalization of the semisynthesis of uzarigenin

3β-Benzyloxy-17-iodo-5α-androst-16-en-14β-ol (**18**)



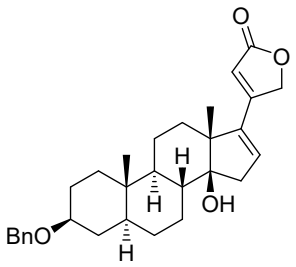
^{1}H NMR: 500 MHz, $CDCl_3$



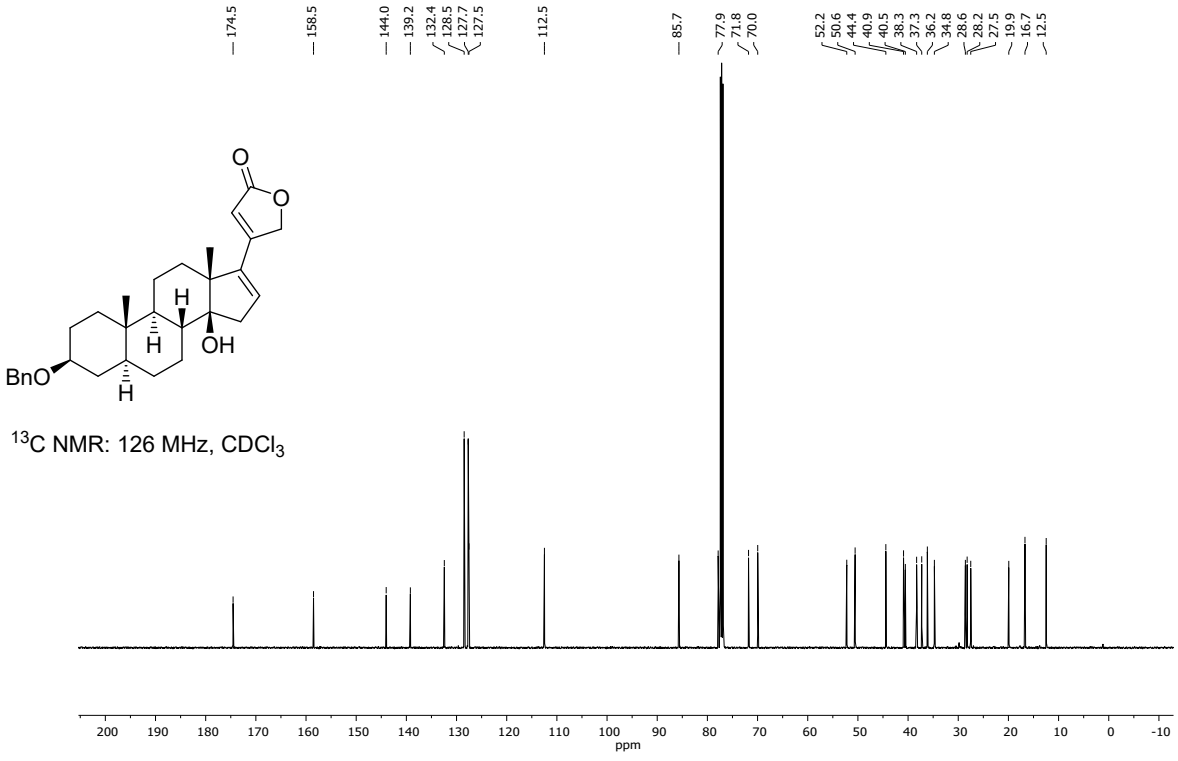


^{13}C NMR: 126 MHz, $CDCl_3$

3β-Benzyloxy-14β-hydroxy-5α-carda(16,20)-dienolide (**20**)

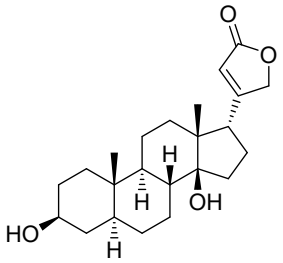


^{1}H NMR: 500 MHz, $CDCl_3$

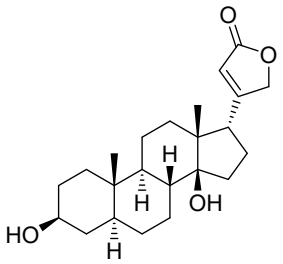


^{13}C NMR: 126 MHz, $CDCl_3$

allo-Uzarigenin (**21**)

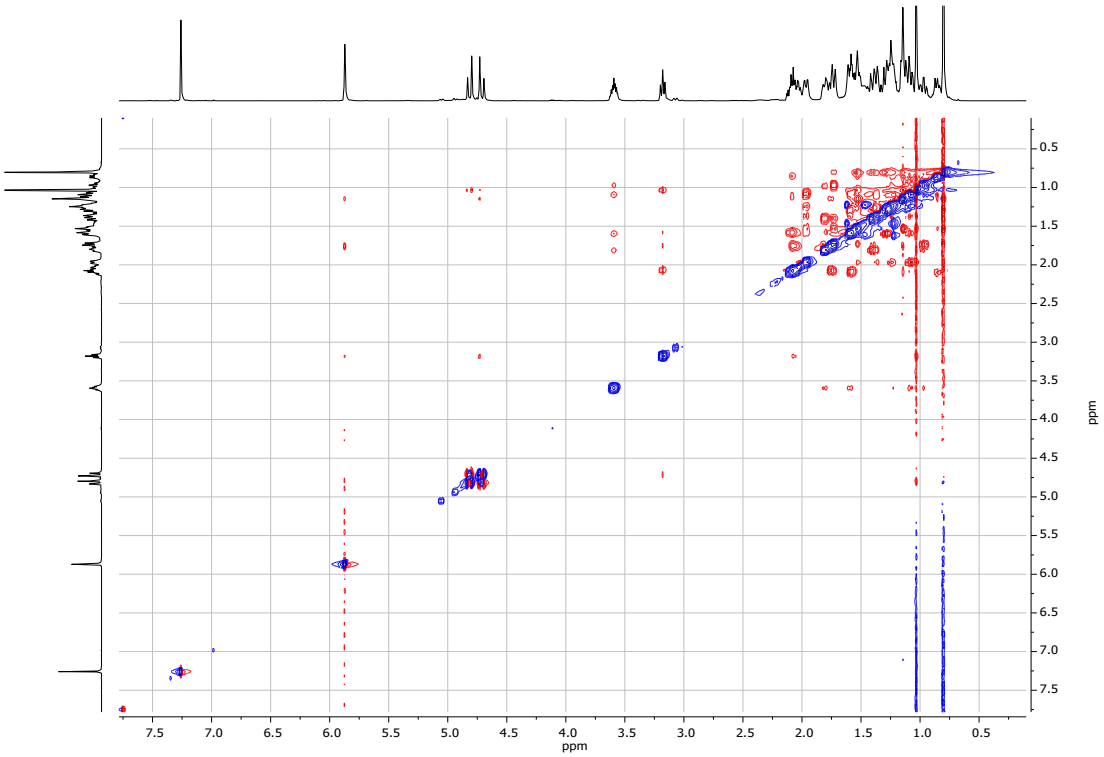


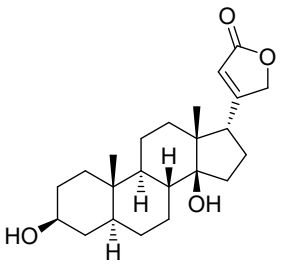
^{1}H NMR: 500 MHz, $CDCl_3$



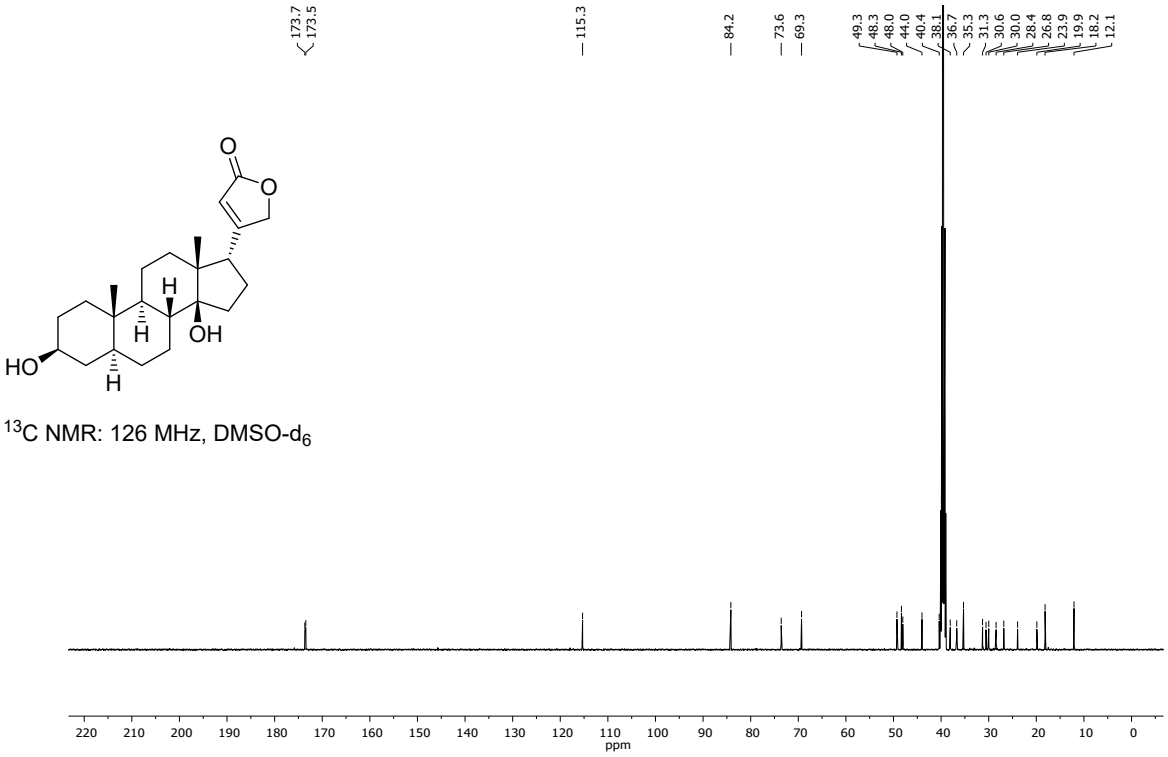
^{13}C NMR: 126 MHz, $CDCl_3$

NOESY spectrum ($CDCl_3$)



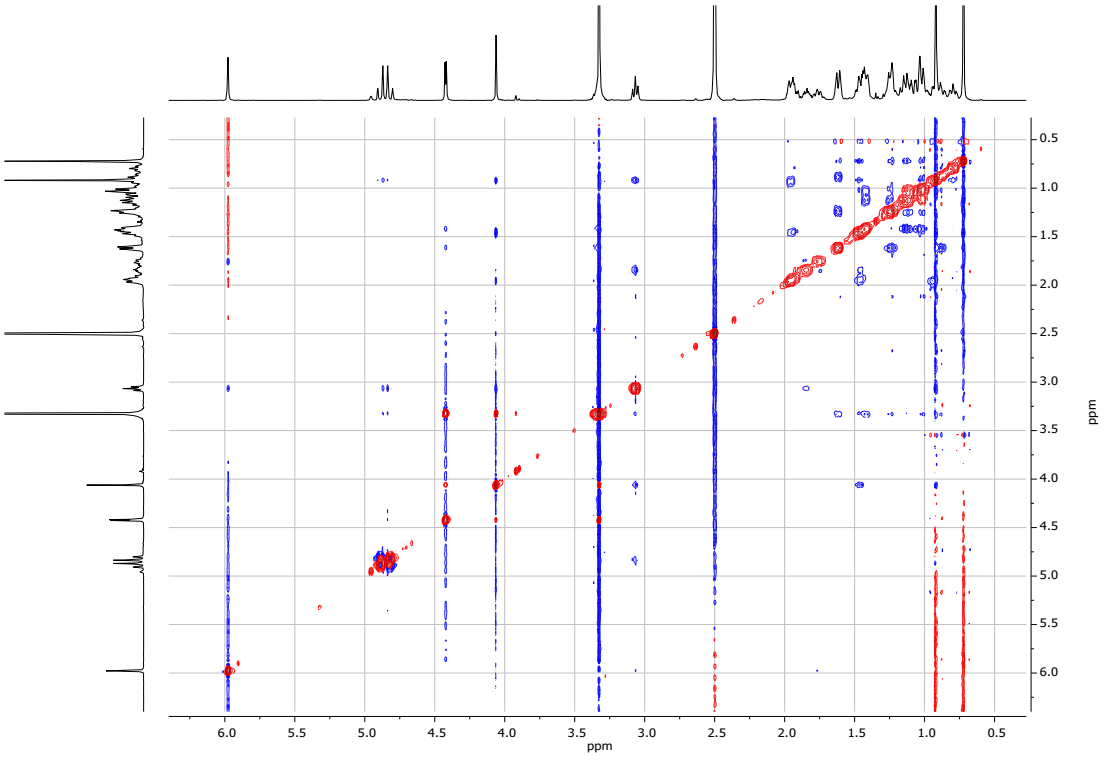


^{1}H NMR: 500 MHz, DMSO-d_6

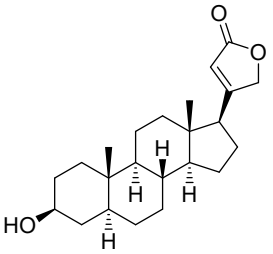


^{13}C NMR: 126 MHz, DMSO-d$_6$

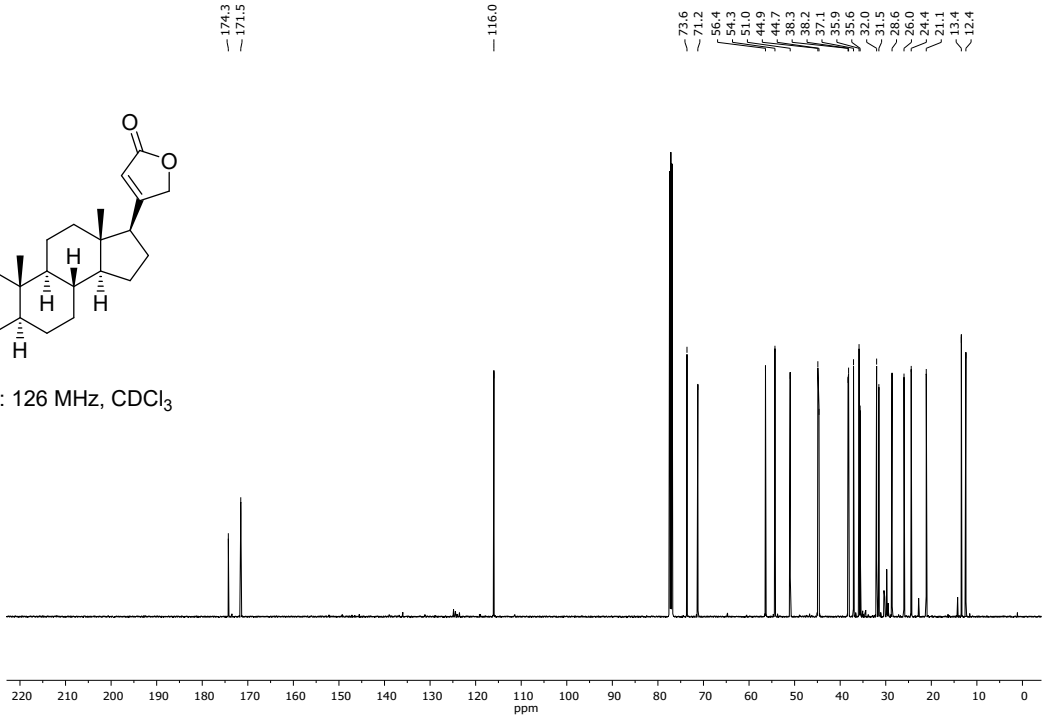
NOESY spectrum (DMSO-d$_6$)



3β-Hydroxy-5α,14α-card-(20,22)-enolide (**SI-06**)



^{1}H NMR: 500 MHz, $CDCl_3$

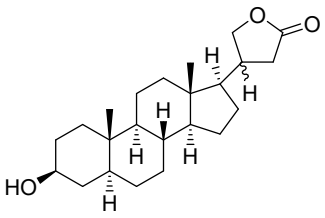


^{13}C NMR: 126 MHz, $CDCl_3$

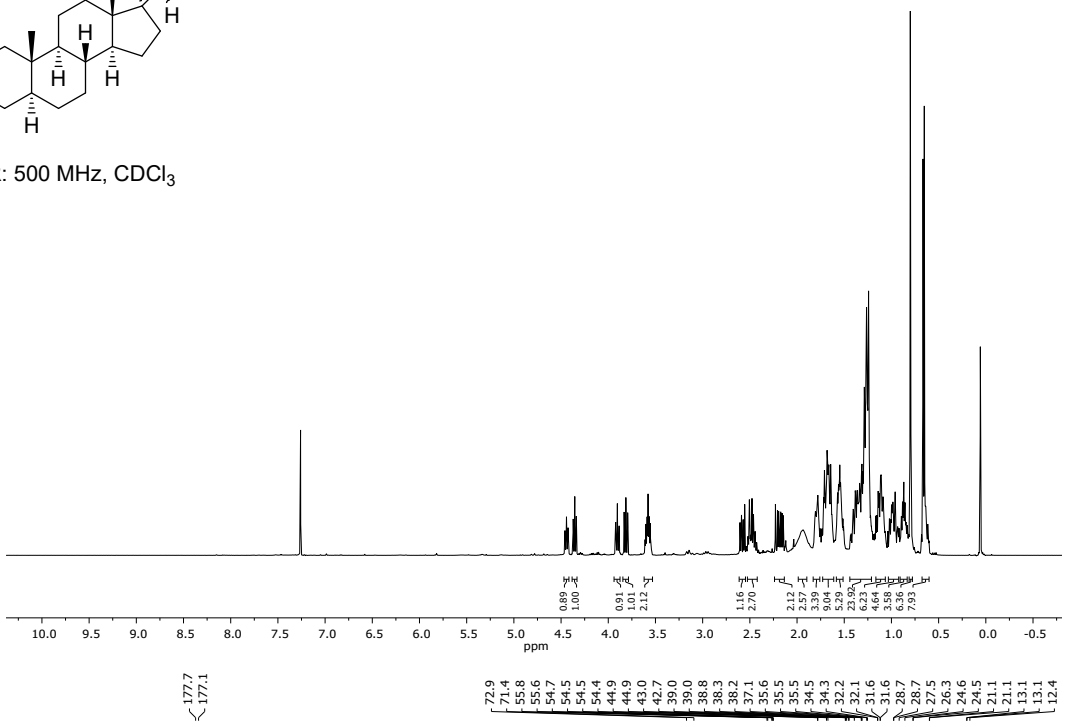
The NMR spectra contain an unknown impurity.

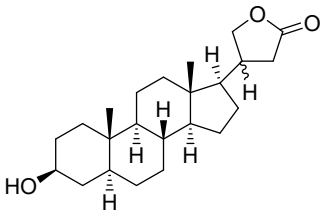
3β-Hydroxy-5α,14α,20α/β-cardanolide (**SI-07**)

Isomeric mixture of the 20-epimer A and B in the ratio of 1:0.9.



^{1}H NMR: 500 MHz, $CDCl_3$

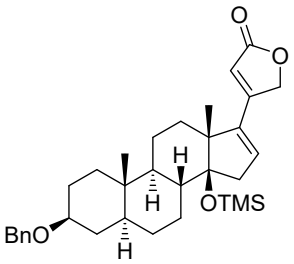




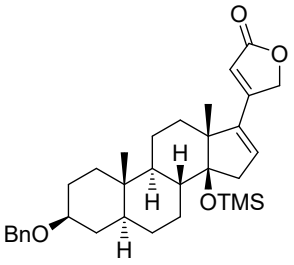
^{13}C NMR: 126 MHz, $CDCl_3$

The NMR spectra contain an unknown impurity.

3β-Benzyloxy-14β-trimethylsilyloxy-5α-carda(16,20)-dienolide (**22**)

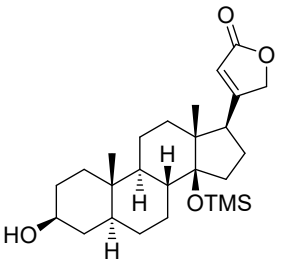


^{1}H NMR: 500 MHz, $CDCl_3$

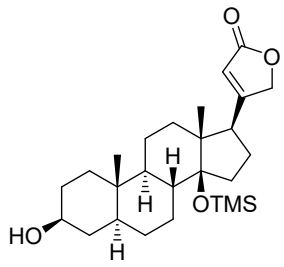


^{13}C NMR: 126 MHz, $CDCl_3$

14β-Trimethylsilyluzarigenin (**23**)



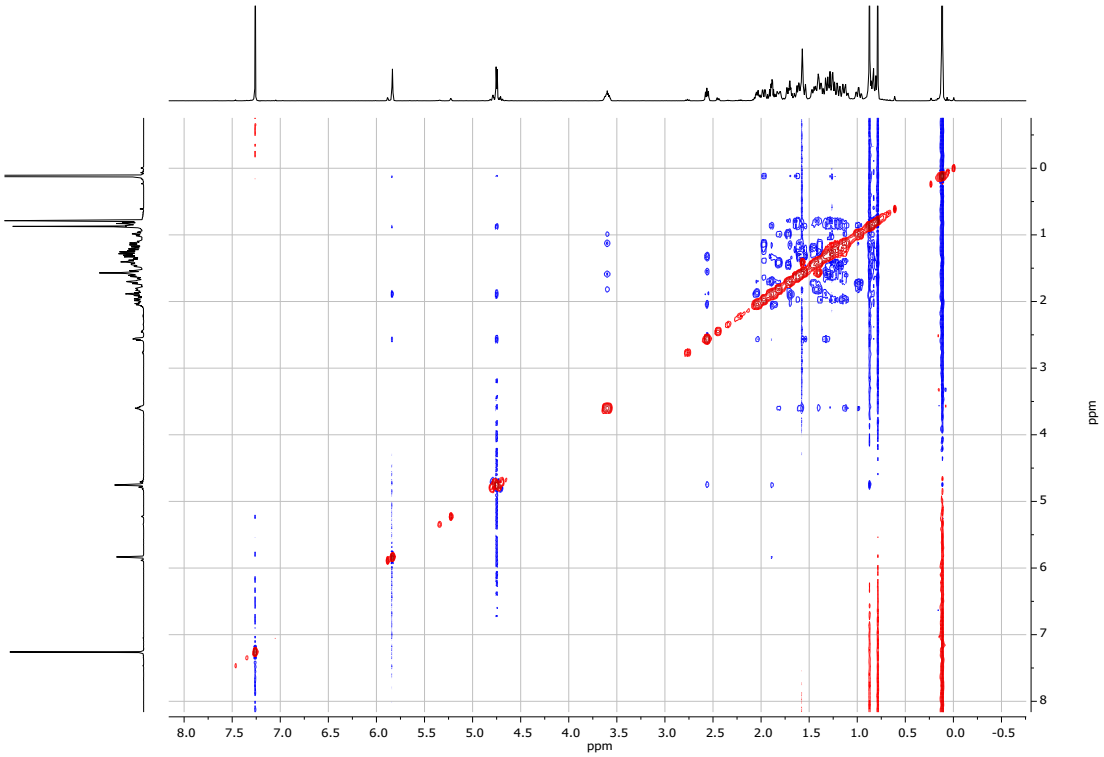
^{1}H NMR: 500 MHz, $CDCl_3$



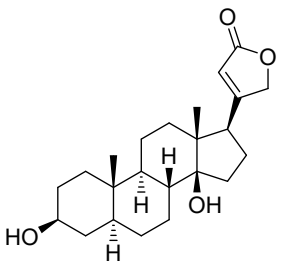
^{13}C NMR: 126 MHz, $CDCl_3$

The NMR spectra contain 3β-hydroxy-5α-carda-14(15),20(22)-dienolide (14-dehydrouzarigenin) as impurity.

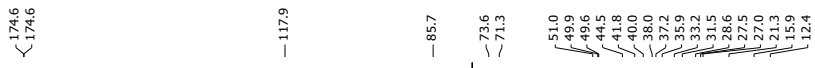
NOESY spectrum ($CDCl_3$)

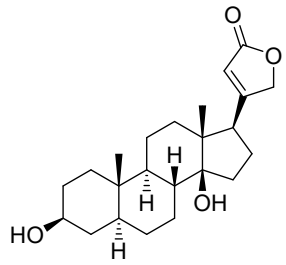


Uzarigenin (**2**)



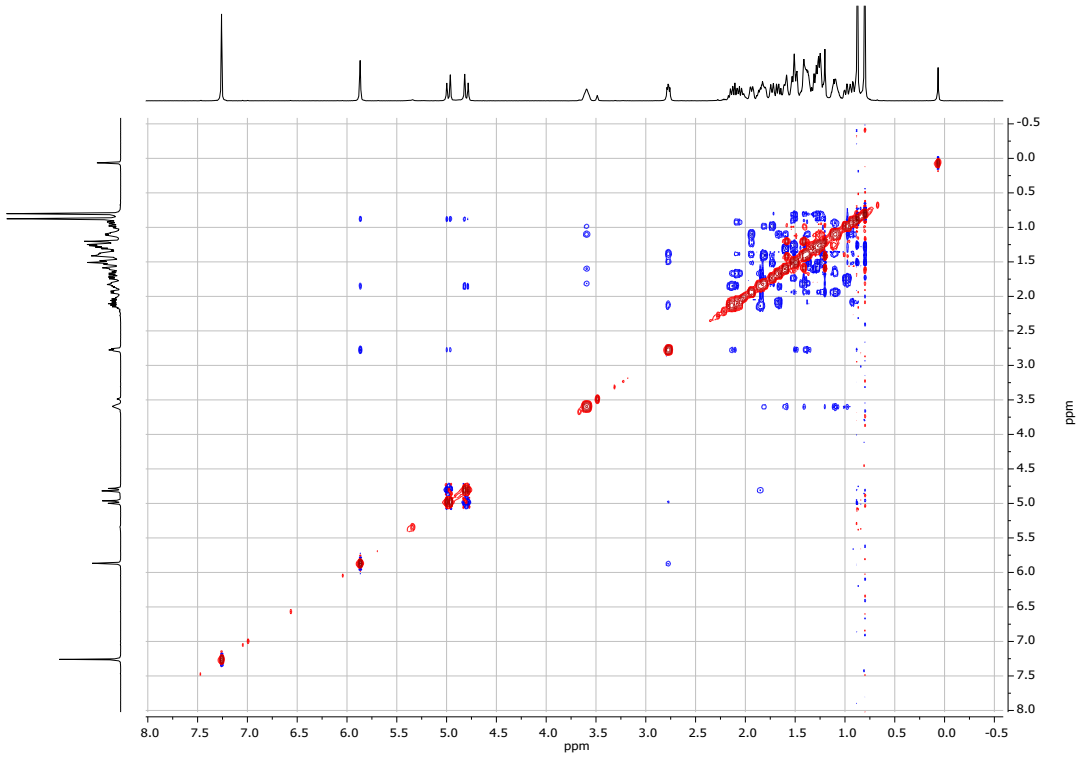
^{1}H NMR: 500 MHz, $CDCl_3$





^{13}C NMR: 126 MHz, $CDCl_3$

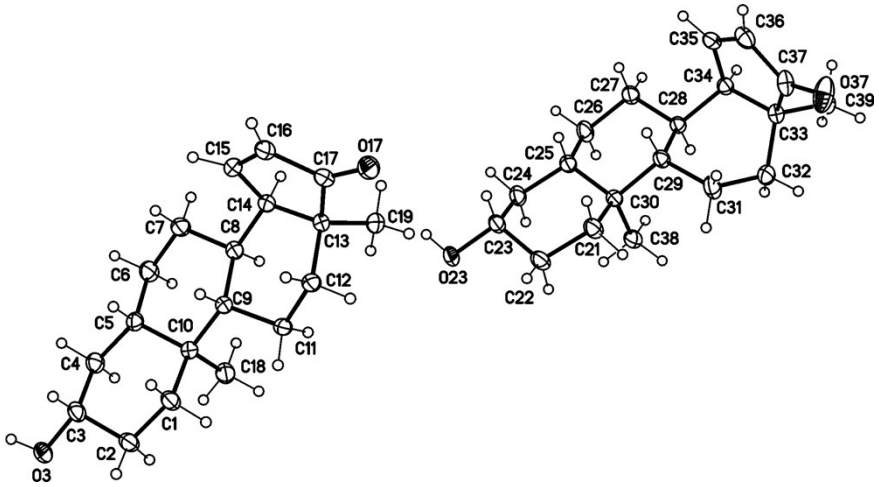
NOESY spectrum ($CDCl_3$)



4. Crystallographic Data

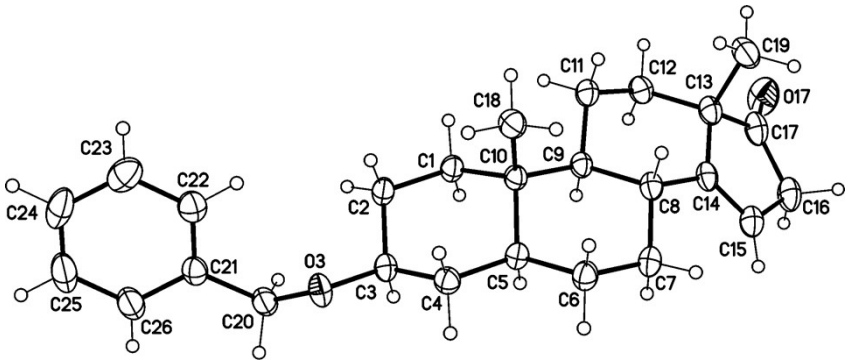
The single-crystal X-ray diffraction study were carried out on a *Bruker* D8 Venture diffractometer with a Photon II detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Direct Methods (SHELXS)[24] or dual space methods (SHELXT)[25] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2)[26]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O) free). Semi-empirical absorption corrections were applied. The absolute configurations were determined by refinement of Parsons' x-parameter[27]. In **11** the absolute configuration could not be established by anomalous dispersion effects in diffraction measurement on the crystal. For **11** Flack's x-parameter was used.[28] For all structures the enantiomer have been assigned by reference to an unchanging chiral center in the synthetic procedure (see cif-file for details).

3β-Hydroxy-5α,14β-androst-15-en-17-one (**11**)



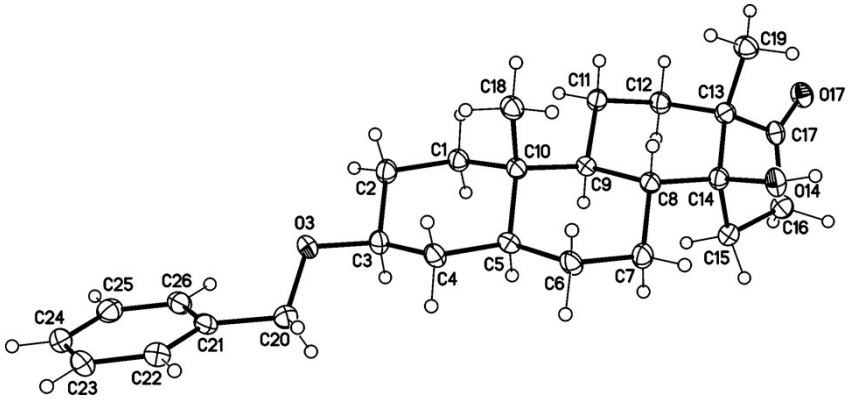
11: colorless crystals, $C_{19}H_{28}O_2$, M_r = 288.41, crystal size 0.32 × 0.12 × 0.06 mm, triclinic, space group *P*1 (No. 1), *a* = 6.1269(3) Å, *b* = 6.8473(3) Å, *c* = 20.2325(9) Å, α = 98.233(2)°, β = 95.708(2)°, γ = 101.625(2)°, *V* = 815.59(7) Å^3, *Z* = 2, ρ = 1.174 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.57 mm^{-1}, *F*(000) = 316, $2\theta_{max}$ = 144.2°, *T* = 123(2) K, 9963 reflections, of which 5361 were independent (R_{int} = 0.026), 385 parameters, 5 restraints, R_1 = 0.043 (for 5197 I > 2σ(I)), wR_2 = 0.115 (all data), *S* = 1.03, largest diff. peak / hole = 0.29 / -0.16 e Å^{-3}. Flack's x = -0.3(2). The absolute configuration could not be established by anomalous dispersion effects in diffraction measurement on the crystal. The enantiomer has been assigned by reference to an unchanging chiral center in the synthetic procedure

3β-Benzyloxy-5α-androst-14-en-17-one (**13**)



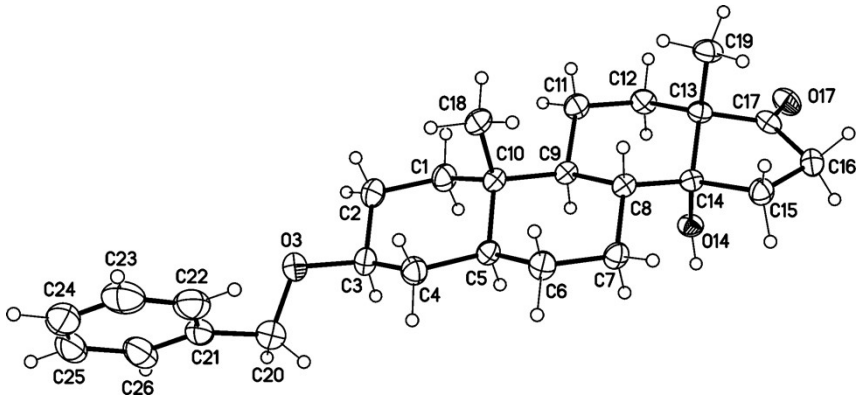
13: colorless crystals, $C_{26}H_{34}O_2$, M_r = 378.53, crystal size 0.12 × 0.08 × 0.04 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.4289(2) Å, b = 12.1170(2) Å, c = 17.9789(3) Å, V = 2047.23(6) Å^3, Z = 4, ρ = 1.228 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.58 mm^{-1}, F(000) = 824, $2\theta_{max}$ = 144.2°, T = 123(2) K, 19971 reflections, of which 4009 were independent (R_{int} = 0.037), 253 parameters, R_1 = 0.034 (for 3782 I > 2σ(I)), wR_2 = 0.084 (all data), S = 1.03, largest diff. peak / hole = 0.20 / -0.17 e Å^{-3}, x = 0.12(11).

3β-Benzyloxy-14β-hydroxy-5α-androst-17-one (**16**)



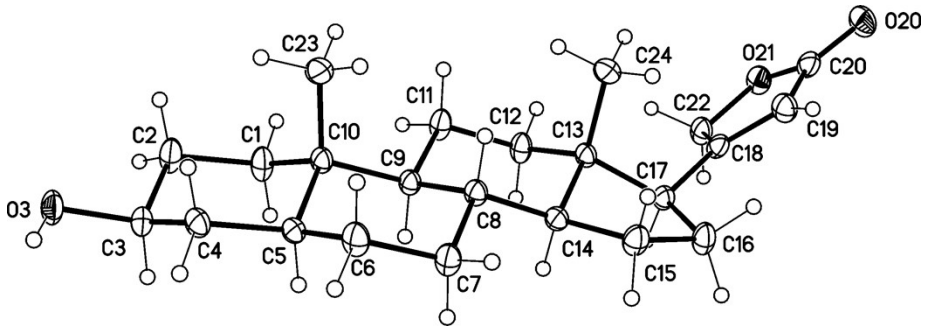
16: colorless crystals, $C_{26}H_{36}O_3$, M_r = 396.55, crystal size 0.22 × 0.06 × 0.02 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.4304(2) Å, b = 10.3893(3) Å, c = 31.1434(9) Å, V = 2080.61(11) Å^3, Z = 4, ρ = 1.266 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.63 mm^{-1}, F(000) = 864, $2\theta_{max}$ = 144.4°, T = 123(2) K, 18135 reflections, of which 4089 were independent (R_{int} = 0.052), 265 parameters, 1 restraint, R_1 = 0.044 (for 3793 I > 2σ(I)), wR_2 = 0.104 (all data), S = 1.04, largest diff. peak / hole = 0.32 / -0.20 e Å^{-3}, x = 0.08(15).

3β-Benzyloxy-14α-hydroxy-5α-androst-17-one (**17**)



17: colourless crystals, $C_{26}H_{36}O_3$, M_r = 396.55, crystal size 0.32 × 0.28 × 0.16 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.1112(1) Å, b = 10.7555(2) Å, c = 32.6186(7) Å, V = 2143.99(7) Å^3, Z = 4, ρ = 1.229 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.61 mm^{-1}, F(000) = 864, $2\theta_{max}$ = 144.2°, T = 123(2) K, 16677 reflections, of which 4202 were independent (R_{int} = 0.026), 265 parameters, 1 restraint, R_1 = 0.039 (for 4125 I > 2σ(I)), wR_2 = 0.105 (all data), S = 1.06, largest diff. peak / hole = 0.46 / -0.15 e Å^{-3}, x = 0.03(6).

3β-Hydroxy-5α,14α-card-(20,22)-enolide (**SI-06**)



SI-06: colourless crystals, $C_{23}H_{34}O_3$, M_r = 358.50, crystal size 0.20 × 0.12 × 0.04 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.3887(2) Å, b = 13.9158(5) Å, c = 18.7736(6) Å, V = 1930.30(11) Å^3, Z = 4, ρ = 1.234 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.62 mm^{-1}, F(000) = 784, $2\theta_{max}$ = 144.2°, T = 123(2) K, 23035 reflections, of which 3799 were independent (R_{int} = 0.026), 239 parameters, 1 restraint, R_1 = 0.029 (for 3724 I > 2σ(I)), wR_2 = 0.077 (all data), S = 1.06, largest diff. peak / hole = 0.27 / -0.12 e Å^{-3}, x = 0.06(4).

CCDC 2207135 (**11**), 2207136 (**13**), 2207137 (**16**), 2207138 (**17**), and 2207139 (**SI-07**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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