Steroids 118 (2017) 68–75

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Synthesis of 23-deoxy-25-*epi* north unit of cephalostatin 1 via reductive and oxidative modifications of hecogenin acetate

Rayala Naveen Kumar, Seongmin Lee *

The Division of Chemical Biology and Medicinal Chemistry, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA

ARTICLE INFO

Article history:
Received 26 June 2016
Received in revised form 29 November 2016
Accepted 20 December 2016
Available online 29 December 2016

Keywords:
Cephalostatin
Ritterazine
Steroidal alkaloids
Anticancer steroids

ABSTRACT

An efficient synthesis of the 23-deoxy-25-*epi* north unit of cephalostatin 1 has been achieved in 17 steps via reductive and oxidative functionalizations of hecogenin acetate with an overall yield of 3.8%. This synthesis features transetherification-mediated E-ring opening, D-ring oxidation, hemiketalization-mediated E-ring closure, and stereoselective 5/5-spiroketalization.

1. Introduction

Marine natural products cephalostatins and ritterazines are composed of growing number of bis-steroidal pyrazines that contain two C_{27} steroidal units and a central pyrazine. The cephalostatin/ritterazine family is composed of twenty cephalostatins (1–20) from the marine tube worm *Cephalodiscus gilchristi* and twenty-six ritterazines (A–Z) from the tunicate *Ritterella tokioka* [1–6]. These bissteroidal pyrazine natural products display potent antiproliferative activities against various cancer cell lines. In particular, cephalostatin 1 is among the most powerful anticancer agents ever tested by the National Cancer Institute (NCI), displaying average GI_{50} value of 1.8 nM in the NCI 60-cell line panel [3]. The cytotoxicity profiles of these anticancer agents, which induce apoptosis via mitochondrial-dependent pathway, did not correlate with any molecule of known mechanism of action [7–11]. The bissteroidal pyrazine anticancer agents and structurally unrelated monosteroidal glycoside OSW-1 have been suggested to kill cancer cells by targeting oxysterol-binding proteins (OSBP) and OSBP-related protein 4L and to reduce the cellular level of these proteins in proteasome-dependent manner [12–14].

Due to the medical significance of the bisteroidal pyrazine antineoplastics, several research groups have reported the synthesis of natural cephalostatins and ritterazines [15–23]. Development of a cephalostatin-based anticancer drug, however, has been significantly hampered due to lengthy (>60 steps) synthetic steps that were required to construct the north and south units of the natural cephalostatins and ritterazines [18,19,23]. In order to develop structurally less complex yet extremely potent cephalostatin/ritterazine analogs, a number of research groups have synthesized cephalostatin/ritterazine analogs including hybrid of cephalostatins and ritterazines (hereafter called ritterostatins) [17,23]. In particular, 25-*epi* ritterostatin G_N1_N, which contains the north unit of ritterazine G and the 25-*epi* north unit of cephalostatin 1, was ~30- and 2-fold more cytotoxic than ritterostatin G_N1_N and cephalostatin 1, respectively. The results revealed that structurally complex south 1 unit can be replaced by the readily accessible north G unit without significantly compromising the potency and the stereochemistry at C25 of the north 1 unit is important for bioactivity (Fig. 1) [23].

In conjunction with our on-going efforts to develop cephalostatin analogs that are potent yet structurally less complex than cephalostatin 1 [15,20], herein we report the synthesis of 23-deoxy-25-*epi* north 1 unit **4** via multiple reductions and oxidations of key intermediate **5**, which is readily accessible from commercially available hecogenin acetate **6** (Scheme 1). The synthesis of the 23-deoxy-25-*epi* north 1 unit was accomplished in 17 synthetic steps starting from hecogenin acetate with an overall yield of 3.8%. This synthesis features transetherification-mediated E-ring opening, D-ring oxidation, hemiketalization-induced E-ring closure, and stereoselective 5/5 spiroketalization.

* Corresponding author.
E-mail address: SeongminLee@austin.utexas.edu (S. Lee).

http://dx.doi.org/10.1016/j.steroids.2016.12.012
0039-128X/

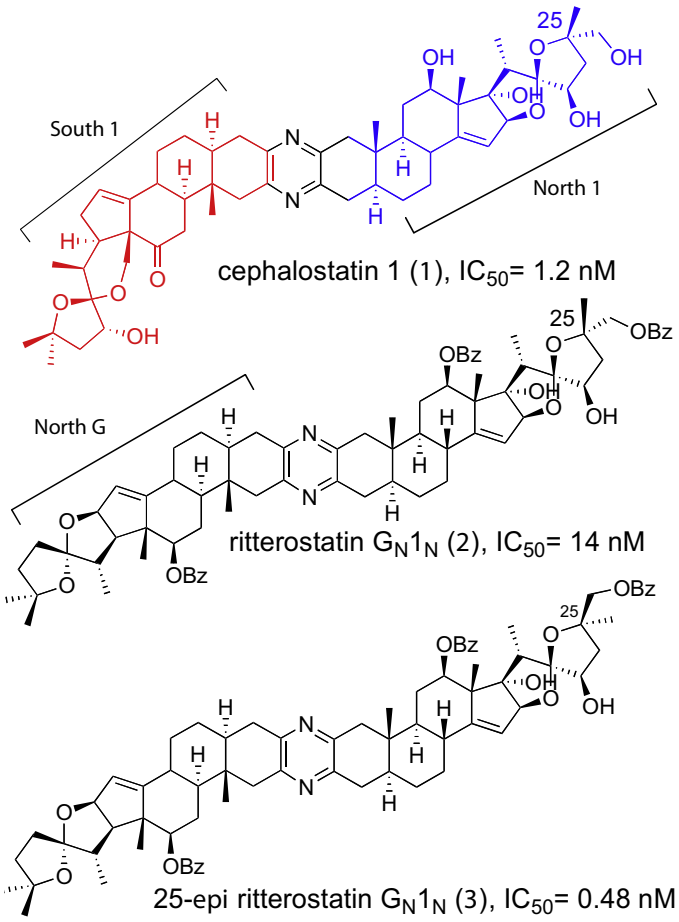


Fig. 1. Structures of cephalostatin 1 **1**, ritterostatin G_N1_N **2** and 25-*epi* ritterostatin G_N1_N **3** and their IC_{50} values in the NCI-60 cancer cell lines.

2. Experimental

2.1. General methods

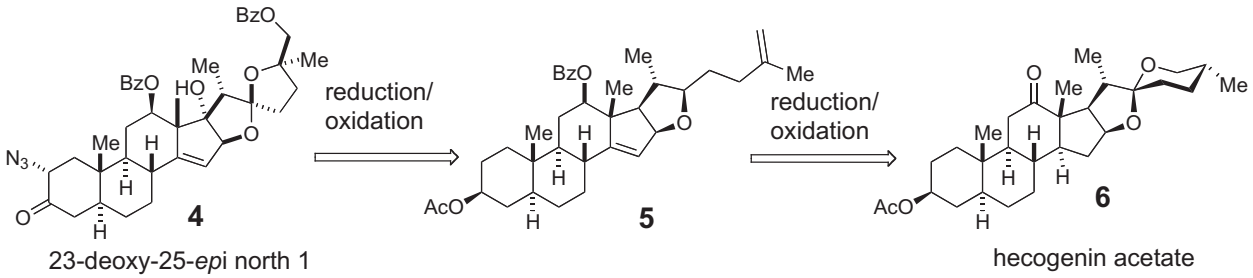
Boron trifluoride etherate (BF_3OEt_2), triethylsilane (Et_3SiH), imidazole, iodine, iodobenzene diacetate ($PhI(OAc)_2$), potassium carbonate, and *N*,*N*-dimethyl formamide (DMF) were purchased from Acros Organics (Geel, Belgium). Methylene chloride (dichloromethane or DCM), tetrahydrofuran (THF), and methanol were purchased from Fisher Chemical (Farlawn, NJ). Triphenylphosphine (PPh_3) was purchased from Alfa Aesar (Ward Hill, MA). Sodium azide was purchase from MP Biomedicals, LLC (Solon, OH). All reactions were performed under positive pressure of argon in anhydrous solvents. Each reaction progress was monitored by thin layer chromatography (TLC). TLC Silica gel 60 F_{254} glass plates from EMD Chemicals Inc. (Darmstadt, Germany) and appropriate solvent systems were used for TLC development. TLC plates were visualized by ultraviolet illumination (254 nm) and *p*-Anisaldehyde solution (4 mL of concentrated sulfuric acid, 800 mL of ethanol, 1.2 mL of acetic acid, and 1.6 mL of *p*-anisaldehyde). Analytical samples were prepared via flash silica gel chromatography. 60 Å silica from Bonna-Agela technologies (Wilmington, DE) was used to purify the products. ^1H and ^{13}C NMR spectra were generated by Varian MERCURY 400 (400 MHz). $CDCl_3$ was used as the NMR standard. Peak multiplicates in ^1H NMR spectra, when reported, were abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), ap (apparent), and br (broad). High-resolution mass spectrometry data were generated by Agilent 6530 Accurate-Mass Q-TOF LC/MS.

2.2. Chemical synthesis

2.2.1. 3β-Acetoxy-12β-benzyloxy-22-hydroxy-5α-furostan-14,16-diene (**8**)

To a solution of the iodide **7a** (6 g, 8.75 mmol) in 100 mL of ethanol was added zinc powder (5.6 g, 87.5 mmol) followed by AcOH (5.6 mL, 94 mmol). The reaction mixture was heated to 95 °C and stirred for 3 h at this temperature. Check TLC for the completion of reaction, then the reaction mixture was diluted with 50 mL of EtOAc and filtered. The filtrate was concentrated to remove excess acetic acid, then the residue was diluted with EtOAc (100 mL). It was washed with 50 mL of saturated aqueous $NaHCO_3$, brine (50 mL), dried ($MgSO_4$), and concentrated in vacuum. The resulting product was purification by flash chromatography (petroleum ether–EtOAc, 7:3) afforded **8** as white solid. (4.4 g, 89%; m.p. 171–172 °C).

R_f = 0.5 (petroleum ether–EtOAc, 4:1); ^1H NMR (400 MHz, $CDCl_3$): 8.08 (dd, *J* = 8.6, 1.6, 2H), 7.59 (td, *J* = 7.3, 1.7 Hz, 1H), 7.47 (td, *J* = 7.3, 1.7 Hz, 2H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.97 (t, *J* = 2.0 Hz, 1H), 4.75 (m, 1H), 4.68 (m, 1H), 4.64 (m, 9H), 4.46 (dd, *J* = 11.3, 4.3, 1H), 3.56 (tt, *J* = 8.6, 2.0, 1H), 2.58 (dq, *J* = 8.6, 7.0, 1H), 2.27–2.18 (m, 1H), 2.18–2.11 (m, 1H), 2.11–2.05 (m, 1H), 2.05–1.97 (m, 1H), 2.02 (s, 3H), 1.85–1.76 (m, 2H), 1.76–1.65 (m, 2H), 1.57–1.50 (m, 1H), 1.52–1.45 (m, 2H), 1.45–1.40 (m, 2H), 1.42–1.32 (m, 2H), 1.28 (m, 3H), 1.28–1.19 (m, 2H), 1.10 (td, *J* = 13.7, 3.5, 1H), 0.93 (s, 3H), 0.88–0.82 (m, 1H), 0.80 (d, *J* = 6.7 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6 (—C=O—, OAc), 165.6 (—C=O, Bz), 160.1 (—C14—), 156.1 (—C17—), 146.0 (—C25—), 133.1 (—CH—, Bz), 130.5 (—CH—, Bz), 129.4 (—C15H—), 128.5 (—CH—, Bz), 124.9 (—C16H—), 120.8 (—CH—, Bz), 109.8 (—C26H—), 79.2 (—C12H—), 75.4 (—C22H—), 73.3 (—C3H—), 57.0 (—C13—), 53.1 (—C10—), 44.3 (—C20H—), 39.2 (—C5H—), 37.0 (—C8H—), 35.8 (—C9H—), 34.8 ($—C4H_2—$), 33.8 ($—C23H_2—$), 33.5 ($—C1H_2—$), 31.9 ($—C24H_2—$), 29.2 ($—C2H_2—$), 28.1 ($—C6H_2—$), 27.4 ($—C18H_3—$), 27.2 ($—C11H_2—$), 22.5 ($—C7H_2$), 21.4 ($—C27H_3—$), 19.7 ($—CH_3—$, OAc), 14.3 ($—C21H_3—$), 12.2 ($—C19H_3—$); MS (ESI): *m*/*z* = 583 [M+Na]$^+$. HRMS: calcd. for $C_{36}H_{48}O_5Na$ [M+Na]$^+$: 583.3399: found: 583.3401.8.



Scheme 1. Retrosynthetic analysis of the 23-deoxy-25-*epi* north 1 unit.

*2.2.2. 12β-Benzyloxy-3,22-dihydroxy-5α-furostan-14,16-diene (**9**)*

Potassium carbonate (2.2 g, 15.7 mmol) was added to the stirred solution of olefin **8** (4.4 g, 7.85 mmol) in methanol (50 mL) and stir the reaction mixture at rt for 2 h. After the completion of the reaction, analyzed by TLC, the methanol was evaporated, the product was extracted with dichloromethane (100 mL) and washed with a saturated solution of ammonium chloride (30 mL). The organic phase was dried with sodium sulfate, filtered and evaporated. The crude product was subjected to silica gel chromatography using hexane–ethyl acetate (1:1) to give diol **9** (7.23 mmol, 3.74 g. 92%) as white solid (m.p. 78–80 °C).

R_f = 0.5 (petroleum ether–EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): 8.08 (ABq, *J* = 8.6 Hz, 2H), 7.59 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.47 (tt, *J* = 7.4, 1.6 Hz, 2H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.96 (t, *J* = 2.0 Hz, 1H), 4.69–4.66 (m, 1H), 4.65–4.62 (m, 1H), 4.44 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.60 (d, *J* = 5.1 Hz, 1H), 3.56 (td, *J* = 8.6, 2.3 Hz, 1H), 2.57 (dq, *J* = 8.6, 7.0 Hz, 1H), 2.27–2.18 (m, 1H), 2.18–2.11 (m, 1H), 2.10–2.04 (m, 1H), 2.04–1.97 (m, 1H), 1.85–1.75 (m, 2H), 1.75–1.69 (m, 2H), 1.69 (s, 3H), 1.63 (dquin, *J* = 12.5, 2.3 Hz, 2H), 1.56–1.45 (m, 1H), 1.46–1.39 (m, 3H), 1.39–1.31 (m, 2H), 1.27 (s, 3H), 1.22–1.12 (m, 1H), 1.06 (td, *J* = 13.3, 3.5 Hz, 1H), 0.91 (s, 3H), 0.88–0.81 (m, 1H), 0.80 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.2 (—C=O, Bz), 160.0 (—C14—), 156.3 (—C17—), 146.0 (—C25—), 133.1 (—CH—, Bz), 130.5 (—CH—, Bz), 129.4 (—C15H—), 128.5 (—CH—, Bz), 124.9 (—C16H—), 120.7 (—CH—, Bz), 109.8 (—C26H—), 79.3 (—C12H—), 75.4 (—C22H—), 71.0 (—C3H—), 57.1 (—C13—), 53.3 (—C10—), 44.5 (—C20H—), 39.2 (—C5H—), 37.9 (—C8H—), 35.8 (—C9H—), 34.8 (—C_4H_2—), 33.5 (—$C_{23}H_2$—), 31.9 (—C_1H_2—), 31.3 (—$C_{24}H_2$—), 29.2 (—C_2H_2—), 28.2 (—C_6H_2—), 27.4 (—$C_{18}H_3$—), 27.2 (—$C_{11}H_2$—), 22.5 (—C_7H_2), 21.3 (—$C_{27}H_3$—), 14.3 (—$C_{21}H_3$—), 12.3 (—$C_{19}H_3$—); MS (ESI): *m*/*z* = 541 [M+Na]$^+$. HRMS: calcd. for $C_{34}H_{46}O_4Na$ [M+Na]$^+$: 541.3294: found: 541.3297.

*2.2.3. 12β-Benzyloxy-3,22-diketo-5α-furostan-14,16-diene (**10**)*

Add IBX (4.86 g, 17.4 mmol) to the stirred solution of diol **9** (3.74 g, 7.23 mmol) in EtOAc (80 mL) at rt, then reflux the reaction mixture at 94 °C for 5 h and check TLC for the completion of reaction. After completion of reaction, quench with saturated aqueous $NaHCO_3$ (50 mL) and the mixture stirred for another 30 min. The organic layer was extracted with EtOAc (3 × 100 mL), and the combined extracts were dried over $MgSO_4$ and rotary evaporated to give the corresponding crude diketo **10**. Purification of the crude product by column chromatography using 5:1 petroleum ether–EtOAc as an eluent gave **10** (3.46 g, 6.72 mmol, 93%) as white solid (m.p. 83–84 °C).

R_f = 0.4 (petroleum ether–EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): 8.08 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.58 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 2H), 6.11 (d, *J* = 2.0 Hz, 1H), 5.95 (t, *J* = 2.0 Hz, 1H), 4.67–4.63 (m, 1H), 4.58–4.55 (m, 1H), 4.44 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.50 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.62–2.51 (m, 1H), 2.51–2.42 (m, 1H), 2.39–2.13 (m, 7H), 2.13–1.93 (m, 3H), 1.66 (s, 3H), 1.64–1.52 (m, 2H), 1.51–1.34 (m, 4H), 1.31 (s, 3H), 1.09 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 210.9 (—C3=O—), 209.5 (—C22=O—), 165.5 (—C=O, Bz), 156.0 (—C14—), 154.6 (—C17—), 144.6 (—C25—), 133.2 (—CH—, Bz), 130.3 (—CH—, Bz), 129.4 (—C15H—), 128.6 (—CH—, Bz), 127.6 (—C16H—), 121.5 (—CH—, Bz), 110.0 (—C26H—), 78.8 (—C12H—), 56.9 (—C20H—), 52.5 (—C13—), 46.0 (—C10—), 44.4 (—C_4H_2—), 38.5 (—C5H—), 38.4 (—C13H—), 37.8 (—C9H—), 35.9 (—C_2H_2—), 34.7 (—C_1H_2—), 31.8 (—$C_{23}H_2$—), 28.8 (—C8H—), 28.4 (C24H_2—), 27.5 (—C_7H_2—), 22.6 (—C_6H_2—), 18.0 (—$C_{11}H_2$—), 14.4 (—$C_{18}H_3$—, —$C_{27}H_3$—), 11.5 (—$C_{19}H_3$—, —$C_{18}H_3$—); MS (ESI): *m*/*z* = 537 [M+Na]$^+$. HRMS: calcd. for $C_{34}H_{42}NaO_4$ [M+Na]$^+$: 537.2981: found: 537.2978.

*2.2.4. 12β-Benzyloxy-3,22-diketo-14,17-peroxo-5α-furostan-15-ene (**11**)*

Diene **10** (3.46 g, 6.72 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C. Tetraphenylporphine (5 mg, 0.1 mol%) was added to the solution and then oxygen was bubbled into the solution via a balloon with photoactivation (GE Sunlamp 300 W) at a distance of approximately 8–9 in. from the reaction flask. The reaction was stirred under sunlamp irradiation at −78 °C for 2 h. The reaction solvent was evaporated and the crude peroxides (**11a** and **11b**) were directly used in the next step without further purification.

R_f = 0.35 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.02 (Abq, *J* = 7.0 Hz, 2H), 7.57 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.44 (td, *J* = 7.4, 1.6 Hz, 1H), 6.76 (d, *J* = 5.9 Hz, 1H), 6.39 (d, *J* = 6.3 Hz, 1H), 5.69 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.54–4.51 (m, 1H), 4.29–4.25 (m, 1H), 3.03 (q, *J* = 8.2 Hz, 1H), 2.48–2.37 (m, 2H), 2.37–2.28 (m, 2H), 2.28–2.22 (m, 2H), 2.17–2.10 (m, 2H), 2.10–2.04 (m, 2H), 2.00–1.90 (m, 2H), 1.88–1.82 (m, 1H), 1.68–1.57 (m, 1H), 1.53–1.48 (m, 1H), 1.47 (s, 3H), 1.45–1.36 (m, 2H), 1.30–1.23 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 210.9 (—C3=O—), 209.8 (—C22=O—), 165.3 (—C=O, Bz), 135.3 (—C25—), 133.3 (—CH—, Bz), 131.6 (—CH—, Bz), 129.5 (—C16H—), 128.7 (—C15H—), 110.1 (—C26H—), 98.2 (—C17—), 96.7 (—C14—), 71.0 (—C12H—), 63.8 (—C20H—), 45.5 (—C13—), 45.0 (—C10—), 44.2 (—C_4H_2—), 43.0 (—C5H—), 41.1 (—C9H—), 38.0 (—C_2H_2—), 37.7 (—C_1H_2—), 35.7 (—$C_{23}H_2$—), 33.4 (—C8H—), 30.5 (C24H_2—), 28.7 (—C_7H_2—), 26.9 (—C_6H_2—), 26.7 (—$C_{11}H_2$—), 22.5 (—$C_{18}H_3$—), 15.1 (—$C_{27}H_3$—), 13.1(—$C_{19}H_3$—), 10.8 (—$C_{18}H_3$—); MS (ESI): *m*/*z* = 569 [M+Na]$^+$. HRMS: calcd. for $C_{34}H_{42}NaO_6$ [M+Na]$^+$: 569.2879: found: 569.2882.

*2.2.5. 12β-Benzyloxy-3,22-diketo-14,17-dihydroxy-5α-furostan-15-ene (**12**)*

To the crude peroxides (**11a** and **11b**) in CH_2Cl_2 (40 mL) was added activated Zn powder (4.3 g, 67.2 mmol) and AcOH (4.3 mL). The mixture was stirred at rt for 2 h. Aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel to provide **12a** and **12b** as white solid (α isomer, 1.99 g, 54%, m.p. 188–189 °C) and β isomer (1.36 g, 37%).

12a (α isomer): R_f = 0.3 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.06, 8.04 (Abq, *J* = 1.6 Hz, 2H), 7.57 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.45 (tt, *J* = 7.4, 1.6 Hz, 2H), 6.31 (d, *J* = 5.9 Hz, 1H), 6.11 (dd, *J* = 10.2, 5.9 Hz, 1H), 5.79 (d, *J* = 5.9 Hz, 1H), 5.01 (s, 1H), 4.73–4.70 (m, 1H), 4.62–4.59 (m, 1H), 3.88 (s, 1H), 2.84 (q, *J* = 7.0 Hz, 1H), 2.73–2.63 (m, 1H), 2.58–2.48 (m, 1H), 2.36–2.26 (m, 2H), 2.26–2.17 (m, 3H), 2.15–2.06 (m, 2H), 1.96–1.87 (m, 3H), 1.76–1.70 (m, 1H), 1.70 (s, 3H), 1.67–1.61 (m, 1H), 1.60–1.53 (m, 2H), 1.51–1.41 (m, 2H), 1.36 (td, *J* = 12.9, 3.9 Hz, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 216.7 (—C3=O—), 211.4 (—C22=O—), 165.7 (—C=O, Bz), 138.1 (—C25—), 137.8 (—CH—, Bz), 133.0 (—CH—, Bz), 130.7 (—C16H—), 129.6 (—C15H—), 128.4 (—CH—, Bz), 110.4 (—C26H—), 88.6 (—C17—), 87.3 (—C14—), 71.3 (—C12H—), 54.6 (—C20H—), 47.9 (—C13—), 46.0 (—C10—), 45.2 (—C_4H_2—), 44.5 (—C5H—), 41.1 (—C9H—), 37.9 (—C_2H_2—), 34.7(—C_1H_2—), 30.9 (—$C_{23}H_2$—), 28.8 (—C8H—), 26.9 (—$C_{24}H_2$—), 26.0 (—C_7H_2—), 22.7 (—C_6H_2—), 14.8 (—$C_{11}H_2$—), 12.3 (—$C_{18}H_3$—, —$C_{27}H_3$—), 10.8 (—$C_{19}H_3$—, —$C_{18}H_3$—); MS (ESI): *m*/*z* = 571 [M+Na]$^+$. HRMS: calcd. for $C_{34}H_{44}NaO_6$ [M+Na]$^+$: 571.3036: found: 571.3024.

12b (β isomer): R_f = 0.3 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.01, 7.99 (Abq, *J* = 1.6 Hz, 2H), 7.59 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.46 (tt, *J* = 7.4, 1.6 Hz, 2H), 6.44 (d, *J* = 6.3 Hz, 1H), 6.12 (d, *J* = 6.3 Hz, 1H), 5.74 (s, 1H), 4.88 (dd, *J* = 11.3, 4.7 Hz, 1H), 4.39–4.35 (m, 1H), 4.02–3.98 (m, 1H), 3.68 (s, 1H), 2.75 (q,

J = 7.0 Hz, 1H), 2.36–2.24 (m, 4H), 2.20–2.11 (m, 2H), 1.99–1.89 (m, 3H), 1.89–1.74 (m, 4H), 1.66–1.61 (m, 1H), 1.59–1.49 (m, 1H), 1.47–1.37 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 0.97 (s, 3H), 0.93–0.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 217.1 (—C3═O—), 210.7 (—C22—), 165.9 (—C═O, Bz), 143.4 (—C25—), 139.8 (—CH—, Bz), 135.9 (—CH—, Bz), 133.6 (—C16H—), 130.5 (—CH—, Bz), 129.6 (—C15H—), 109.6 (—C26H—), 89.4 (—C17—), 88.1 (—C14—), 76.5 (—C12H—), 55.9 (—C20H—), 45.3 (—C13—), 44.4 (—C10—), 41.8 (—C4H_2—), 39.7 (—C5H—), 38.4 (—C9H—), 35.6 (—C2H_2—), 35.4 (—C1H_2—), 34.9 (—C23H_2—), 30.7 (—C8H—), 28.2 (—C24H_2—), 27.6 (—C7H_2—), 26.7 (—C6H_2—), 22.2 (—C11H_2—), 14.1(—C18H_3—), 11.3 (—C27H_3—), 9.4 (—C19H_3—, —C18H_3—); MS (ESI): m/z = 571 $[M+Na]^+$. HRMS: calcd. for $C_{34}H_{44}NaO_6$ $[M+Na]^+$: 571.3036: found: 571.3047.

2.2.6. 12β-Benzyloxy-3,22-trimethoxy-5α-furostan-17-hyroxy-14,26-diene (**13**)

Pyridinium *p*-toluenesulfonate (PPTS) (182 mg, 20 mol%) was added to the stirred solution of diol **12** (1.99 g, 3.63 mmol) in CH_2Cl_2:MeOH (1:1, 20 mL) and the reaction was stirred for 3 h at rt. After the disappearance of starting material was ensured by TLC, the solvent was evaporated under reduced pressure and then CH_2Cl_2 (100 mL) was added to the reaction. The reaction mixture was washed with saturated $NaHCO_3$ solution (60 mL) and brine (60 mL), dried over Na_2SO_4, and concentrated. The crude product was subjected to chromatography (petroleum ether–EtOAc, 7:3) on silica gel to provide **13** (1.74 g, 79%) as white solid (m.p. 74–75 °C).

R_f = 0.6 (petroleum ether–EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): 8.05, 8.03 (ABq, J = 1.6 Hz, 2H), 7.53 (tt, J = 7.4, 1.6 Hz, 1H), 7.43 (dd, J = 7.4, 1.6 Hz, 2H), 5.39 (t, J = 1.6 Hz, 1H), 5.31 (dd, J = 11.3, 5.1 Hz, 1H), 3.19 (s, 3H), 3.17 (s, 3H), 3.13 (s, 3H), 2.19–2.09 (m, 2H), 2.05–1.96 (m, 2H), 1.96–1.90 (m, 2H), 1.90–1.78 (m, 2H), 1.73 (s, 3H), 1.72–1.64 (m, 2H), 1.55–1.48 (m, 2H), 1.47–1.35 (m, 3H), 1.34 (s, 3H), 1.33–1.19 (m, 4H), 1.18–1.07 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.8 (—C═O, Bz), 154.3 (—C14—), 153.5 (—C25—), 145.8 (—CH—, Bz), 132.9 (—CH—, Bz), 132.4, 130.8 (—CH—, Bz), 128.2 (—C15H—), 119.1(—C3—), 111.0 (—C22—), 109.9 (—C26—), 94.1 (—C16H—), 93.1 (—C17—), 75.9 (—C12H—), 53.9 (—C13—), 52.1 (—C20—), 47.5 (—C3, OMe), 46.0 (—C3, OMe), 44.9 (—C22, OMe), 42.0 (—C10—), 36.2 (—C4H_2—), 35.4 (—C5H—), 34.9 (—C9H—), 34.7 (—C2H_2—), 34.0 (—C1H_2—), 32.2 (—C23H_2—), 31.4 (—C8H—), 29.7 (—C24H_2—), 28.9 (—C7H_2—), 28.2 (—C6H_2—), 22.6 (—C11H_2—), 16.2 (—C18H_3—), 14.5 (—C27H_3—), 13.2 (—C19H_3—), 10.6 (—C18H_3—); MS (ESI): m/z = 631 $[M+Na]^+$. HRMS: calcd. for $C_{37}H_{52}NaO_7$ $[M+Na]^+$: 631.3611: found: 631.3599.

2.2.7. 12β-Benzyloxy-3,22-trimethoxy-5α-furostan-17,25,26-trihyroxy-14-ene (**14**)

Potassium carbonate (822 mg, 6 mmol) and potassium hexacyanoferrate(III) (1.98 g, 6 mmol) were dissolved in a mixture of 10 mL of *t*-butanol and 10 mL of water. Potassium osmate (13 mg, 0.04 mmol) and hydroquinidine-1,4-phthalazinediyl diether $(DHQD)_2PHAL$ (155 mg, 0.2 mmol) were added to this reaction mixture at 0 °C and stirred for 10 min. Terminal olefin **13** (1.2 g, 2 mmol) was added to the reaction mixture, and was stirred overnight at 0 °C. After completion of the reaction, the reaction was quenched with aq. $Na_2S_2O_3$ and extracted with EtOAc (3 × 100 mL) and the combined extracts were dried over sodium sulfate and concentrated. The crude product was subjected to chromatography (petroleum ether–EtOAc, 3:7) on silica gel to provide diol **14** (1.05 g, 82%).

R_f = 0.3 (petroleum ether–EtOAc, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.03, 8.01 (ABq, J = 1.6 Hz, 2H), 7.51 (tt, J = 7.4, 1.2 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 5.36 (t, J = 1.6 Hz, 1H), 5.28 (dd, J = 11.3, 5.1 Hz, 1H), 4.69–4.64 (m, 1H), 3.43–3.35 (m, 2H), 3.17 (s, 3H), 3.16 (s, 3H), 3.11 (s, 3H), 2.77–2.62 (br, 1H), 2.48–2.35 (br, 1H), 2.16–2.05 (m, 2H), 2.03–1.90 (m, 2H), 1.90–1.75 (m, 2H), 1.71–1.61 (m, 1H), 1.61–1.53 (m, 2H), 1.53–1.45 (m, 2H), 1.44–1.36 (m, 2H), 1.36–1.29 (m, 4H), 1.33 (s, 3H), 1.29–1.23 (m, 1H), 1.16–1.07 (m, 1H), 1.14 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.8 (—C═O, Bz), 154.9 (—C14—), 132.5 (—CH—, Bz), 131.3 (—CH—, Bz), 129.5 (—C15H—), 128.2 (—CH—, Bz), 118.6 (—C3—), 111.3 (—C22—), 100.1 (—C16H—), 94.3 (—C17—), 75.3 (—C25—), 72.2 (—C26H_2—), 70.0 (—C12H—), 53.9 (—C13—), 52.1 (—C20—), 47.6 (—C3, OMe), 47.5 (—C3, OMe), 47.4 (—C22, OMe), 42.0 (—C10—), 36.2 (—C4H_2—), 35.3 (—C5H—), 34.7 (—C9H—), 34.1 (—C2H_2—), 32.2 (—C1H_2—), 29.0 (—C23H_2—), 28.2 (—C8H—), 27.8 (—C24H_2—), 27.3 (—C7H_2—), 24.8 (—C6H_2—), 23.3 (—C11H_2—), 15.0 (—C18H_3—), 11.4 (—C27H_3—, —C19H_3—), 7.5 (—C18H_3—); MS (ESI): m/z = 665 $[M+Na]^+$. HRMS: calcd. for $C_{37}H_{54}NaO_9$ $[M+Na]^+$: 665.3666: found: 665.3648.

2.2.8. 3-Dimethoxy-12β,25-dibenzyloxy-17-hydroxy-5α-spirostan-14-ene (**15**)

Diol **12** (963 mg, 1.5 mmol) was dissolved in pyridine (10 mL) and the solution was cooled to below 10° C, in an ice-water bath. Benzoyl chloride (90.15 ml, 0.076 mol) was slowly added dropwise maintaining the inside temperature below 10 °C. It was warmed to rt after the addition was completed, and was stirred for overnight. After the reaction was completed, the reaction mixture was washed with water (100 mL), and extracted with dichloromethane (3 × 100 mL). After drying the combined extracts with anhydrous magnesium sulfate, the solvent was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether–EtOAc, 3:2) to provide **15** and **15a**. The resulting uncyclized **15a** was subjected to 5/5 spiroketalization using PPTS (Cat.) in methanol 10 mL at 25 °C for 1 h to give **15** (771 mg, 72% overall yield) as a foam.

R_f = 0.5 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.14, 8.12 (ABq, J = 1.6 Hz, 2H), 8.07 (ddd, J = 8.2, 12.9, 1.2 Hz, 2H), 7.62 (tt, J = 7.4, 1.2 Hz, 1H), 7.59–7.51 (m, 1H), 7.51–7.47 (m, 2H), 7.44 (dd, J = 7.4, 2.3 Hz, 2H), 5.31 (t, J = 2.0 Hz, 1H), 4.66 (d, J = 1.2 Hz, 1H), 4.33 (d, J = 11.3 Hz, 1H), 4.19 (d, J = 10.9 Hz, 1H), 3.19 (s, 3H), 3.13 (s, 3H), 2.28 (dt, J = 12.1, 11.7 Hz, 1H), 2.18 (q, J = 6.7 Hz, 1H), 2.13–1.98 (m, 5H), 1.87 (dq, J = 13.7, 3.1 Hz, 1H), 1.82–1.75 (m, 1H), 1.75–1.65 (m, 2H), 1.59–1.47 (m, 2H), 1.46–1.39 (m, 2H), 1.38–1.30 (m, 2H), 1.35 (s, 3H), 1.30–1.24 (m, 1H), 1.19 (s, 3H), 1.13 (td, J = 13.3, 3.5 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.7 (—C═O, Bz), 164.8 (—C═O, Bz), 155.0 (—C14—), 133.7 (—CH—, Bz), 132.9 (—CH—, Bz), 132.5 (—CH—, Bz), 131.4 (—CH—, Bz), 129.6 (—CH—, Bz), 128.5 (—CH—, Bz), 128.2 (—C15H—), 118.9 (—C3—), 117.8 (—C22—), 100.2 (—C16H—), 93.7 (—C17—), 83.1 (—C25—), 75.2 (—C26H_2—), 70.1 (—C12H—), 53.8 (—C13—), 51.8 (—C20—), 47.5 (—C3, OMe), 47.4 (—C3, OMe), 42.0 (—C10—), 36.2 (—C4H_2—), 35.3 (—C5H—), 34.7 (—C9H—), 34.1 (—C2H_2—), 32.7 (—C1H_2—), 31.9 (—C23H_2—), 28.2 (—C8H—), 27.8 (—C24H_2—), 27.3 (—C7H_2—), 23.9 (—C6H_2—), 22.2 (—C11H_2—), 15.5 (—C18H_3—), 11.4 (—C27H_3—, —C19H_3—), 7.7 (—C18H_3—); MS (ESI): m/z = 737 $[M+Na]^+$. HRMS: calcd. for $C_{43}H_{54}NaO_9$ $[M+Na]^+$: 737.3666: found: 737.3666.

2.2.9. 3-Keto-12β,25-dibenzyloxy-17-hydroxy-5α-spirostan-14-ene (**16**)

A reaction mixture of ketal **15** (714 mg, 1 mmol) and iodine (25.4 mg, 0.1 mmol) in acetone (10 mL) was stirred at room temperature for 5 min. After completion of reaction, acetone solvent was removed under vacuum, and the residue was diluted with dichloromethane (50 mL). The mixture was washed successively with 5% aqueous $Na_2S_2O_3$ (20 mL), H_2O (30 mL), and brine

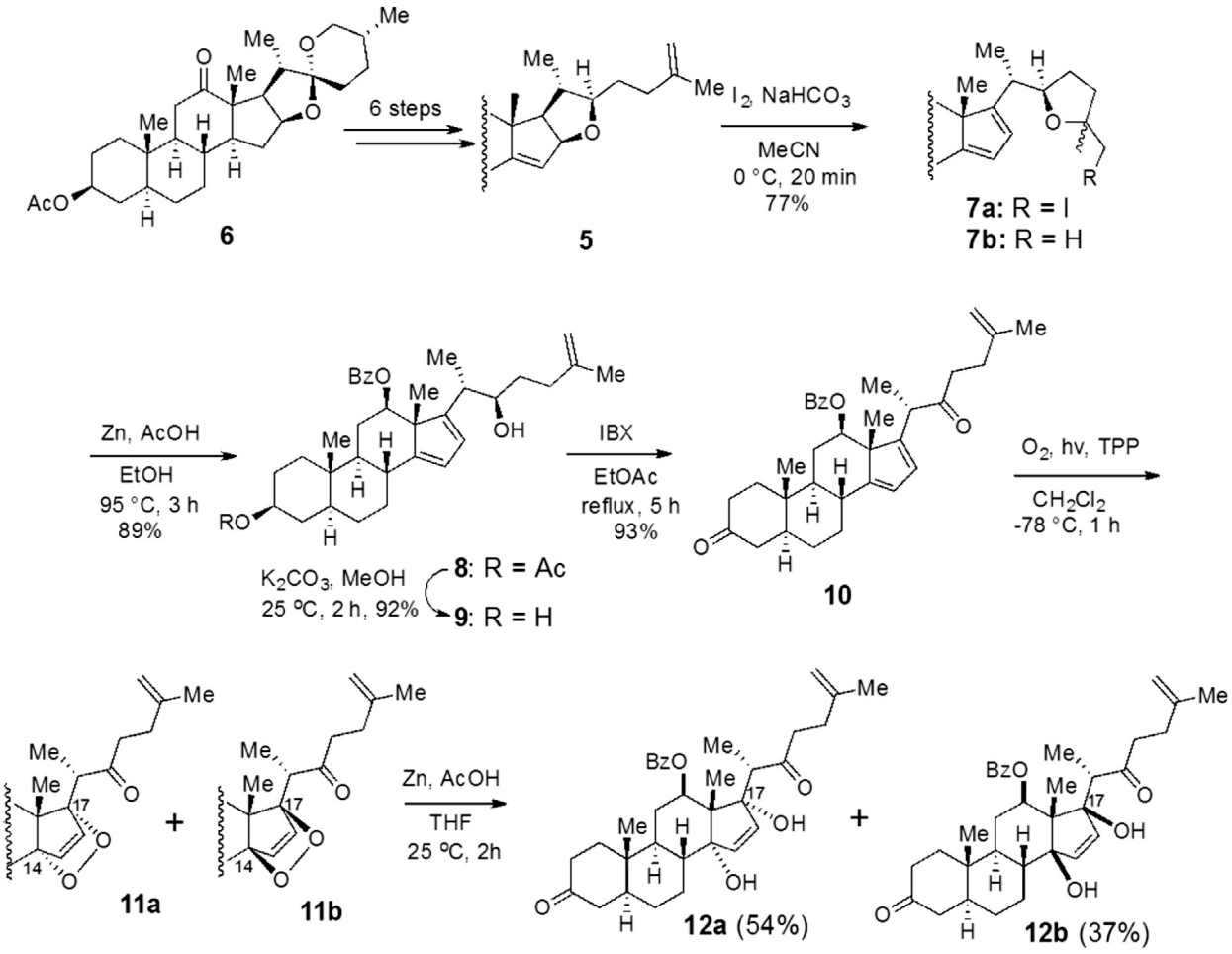
(50 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by short column chromatography to provide **16** (641 mg, 96%) as white solids (m. p. 106–108 °C).

R_f = 0.4 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.14–8.03 (m, 4H), 7.61 (ddt, *J* = 12.1, 8.6, 1.6 Hz, 1H), 7.54 (ddt, *J* = 7.4, 4.3, 1.2 Hz, 1H), 7.51–7.41 (m, 4H), 5.36–5.30 (m, 1H), 4.66 (dd, *J* = 2.3, 1.2 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 10.9 Hz, 1H), 2.66–2.58 (br, 1H), 2.40–2.22 (m, 4H), 2.22–2.10 (m, 3H), 2.10–2.01 (m, 2H), 1.97 (ddd, *J* = 12.9, 6.2, 2.3 Hz, 1H), 1.88–1.80 (m, 1H), 1.71 (ddd, *J* = 11.3, 7.0, 3.9 Hz, 1H), 1.67–1.51 (m, 2H), 1.49–1.32 (m, 4H), 1.37 (s, 3H), 1.29–1.23 (m, 1H), 1.20 (s, 3H), 1.06 (s, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 211.1 (—C3═O—), 166.3 (—C═O, Bz), 165.6 (—C═O, Bz), 154.2 (—C14—), 132.9 (—CH—, Bz), 132.5 (—CH—, Bz), 129.7 (—CH—, Bz), 129.5 (—CH—, Bz), 128.3 (—CH—, Bz), 128.2 (—C15H—), 119.5 (—C22—), 117.8 (—C16H—), 93.6 (—C17—), 90.5 (—C25—), 83.2 (—C26H_2—), 74.9 (—C12H—), 53.7 (—C13—), 51.5 (—C20—), 45.9 (—C10—), 38.0 (—C4H_2—), 37.9 (—C5H—), 36.0 (—C9H—), 34.0 (—C2H_2—), 32.7 (—C1H_2—), 31.9 (—C23H_2—), 30.9 (—C8H—), 28.7 (—C24H_2—), 28.3 (—C7H_2—), 27.4 (—C6H_2—), 23.9 (—C11H_2—), 15.5 (—C18H_3—), 11.2 (—C27H_3—, —C19H_3—), 7.7 (—C18H_3—); MS (ESI): *m*/*z* = 691 [M+Na]$^+$. HRMS: calcd. for $C_{41}H_{48}NaO_8$ [M+Na]$^+$: 691.3247: found: 691.3249.

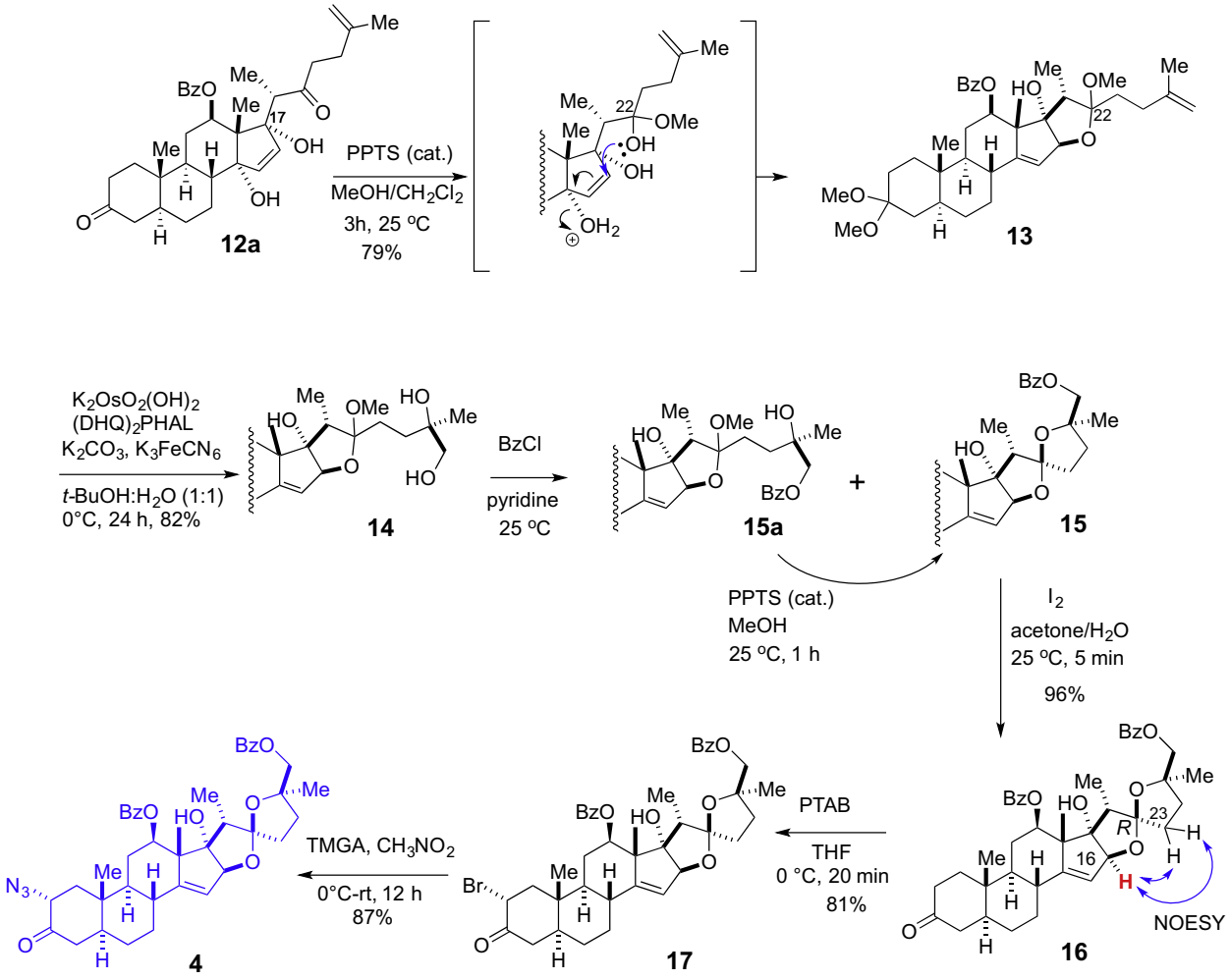
*2.2.10. 2α-Bromo-3-keto-12β,25-dibenzyloxy-17-hydroxy-5α-spirostan-14-ene (**17**)*

To a solution of ketone **16** (600 mg, 0.9 mmol) in THF (10 mL) was added Phenyltrimethylammonium tribromide (PTAB, 376 mg, 1 mmol) at 0 °C in one portion. After 20 min check TLC for completion of reaction, and then quenched with aq. NaS_2O_3. The reaction was diluted with water (50 mL) and extracted with Dichloromethane (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was chromatographed on silica gel using petroleum ether–EtOAc, 3:2 to provide bromide **17** (540 mg, 81%) as white solid (m.p. 132–133 °C).

R_f = 0.4 (petroleum ether–EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): 8.10–8.02 (m, 4H), 7.59–7.52 (m, 2H), 7.48–7.40 (m, 4H), 5.34 (dq, *J* = 9.0, 5.5 Hz, 1H), 4.69 (dd, *J* = 13.3, 6.3 Hz, 1H), 4.67–4.64 (m, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 11.0 Hz, 1H), 2.57 (dd, *J* = 12.9, 6.3 Hz, 1H), 2.50–2.38 (m, 2H), 2.32–2.22 (m, 1H), 2.21–2.13 (m, 2H), 2.12–2.00 (m, 4H), 1.89–1.79 (m, 2H), 1.76–1.66 (m, 1H), 1.66–1.59 (m, 2H), 1.58 (s, 3H), 1.53–1.47 (m, 1H), 1.43–1.35 (m, 2H), 1.37 (s, 3H), 1.31–1.23 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 1.00 (d, *J* = 12.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.4 (—C3═O—), 166.4 (—C═O, Bz), 165.6 (—C═O, Bz), 153.6 (—C14—), 134.2 (—CH—, Bz), 132.9 (—CH—, Bz), 132.6 (—CH—, Bz), 131.1 (—CH—, Bz), 130.1 (—CH—, Bz), 129.7 (—CH—, Bz), 128.3 (—C15H—), 119.8 (—C22—), 117.8 (—C16H—), 93.5 (—C17—), 90.4 (—C25—), 83.2 (—C26H_2—), 74.5 (—C12H—), 67.7 (—C2H—), 53.7 (—C13—), 53.5 (—C20—), 51.1 (—C1H_2—), 46.7 (—C10—), 44.4 (—C4H_2—), 43.6 (—C5H—), 38.9 (—C9H—), 33.5 (—C23H_2—), 32.6v (—C8H—), 31.9 (—C24H_2—), 29.7 (—C7H_2—), 27.5 (—C6H_2—), 23.9 (—C11H_2—), 15.5 (—C18H_3—), 14.0 (—C2—) 7H_3—), 11.9 (—C19H_3—), 7.7 (—C18H_3—); MS (ESI): *m*/*z* = 769 [M+Na]$^+$. HRMS: calcd. for $C_{41}H_{47}BrNaO_8$ [M+Na]$^+$: 769.2352: found: 769.2347.



Scheme 2. Synthesis of C14,17-dihydroxy compounds **12a** and **12b** starting from hecogenin acetate.



Scheme 3. Final stage of the 23-deoxy-25-*epi* north 1 unit synthesis.

*2.2.11. 2α-Azido-3-keto-12β,25-dibenzyloxy-17-hydroxy-5α-spirostan-14-ene (**4**)*

To the bromo ketone **17** (347 mg, 0.5 mmol) in 10 mL of nitromethane was added *N,N,N′,N′*-tetramethylguanidinium azide ($TMGN_3$) at 0 °C. The mixture was stirred overnight, then quenched with H_2O (30 mL), and extracted with Dichloromethane (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using petroleum ether–EtOAc (7:3) to provide azide **4** (308 mg, 87%) as white solid (m.p. 127–129 °C).

R_f = 0.4 (petroleum ether–EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): 8.11–8.03 (m, 4H), 7.59–7.52 (m, 2H), 7.48–7.41 (m, 4H), 5.35 (dd, *J* = 11.3, 5.5 Hz, 1H), 5.33 (t, *J* = 1.6 Hz, 1H), 4.66 (d, *J* = 1.6 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 10.9 Hz, 1H), 3.45 (dd, *J* = 12.1, 4.7 Hz, 1H), 2.73–2.69 (br, 1H), 2.62 (s, 1H), 2.33–2.22 (m, 1H), 2.21–2.13 (m, 1H), 2.12–1.99 (m, 4H), 1.87 (dd, *J* = 12.5, 4.7 Hz, 1H), 1.85–1.77 (m, 1H), 1.76–1.66 (m, 2H), 1.66–1.60 (m, 1H), 1.59 (s, 3H), 1.59–1.49 (m, 2H), 1.44–1.37 (m, 2H), 1.35 (s, 3H), 1.30–1.22 (m, 2H), 1.20 (s, 3H), 1.15–1.03 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 205.2 (—C3=O—), 166.4 (—C=O, Bz), 165.6 (—C=O, Bz), 154.0 (—C14—), 132.9 (—CH—, Bz), 132.6 (—CH—, Bz), 131.2 (—CH—, Bz), 130.2 (—CH—, Bz), 129.7 (—CH—, Bz), 129.6 (—CH—, Bz), 128.3 (—C15H—), 119.6 (—C22—), 117.8 (—C16H—), 93.6 (—C17—), 90.4 (—C25—), 83.2 (—$C26H_2$—), 74.7 (—C12H—), 60.3 (—C2H—), 53.7 (—C13—), 51.4 (—C20—), 44.4 (—$C1H_2$—), 42.2 (—C10—), 39.7 (—$C4H_2$—), 39.1 (—C5H—), 35.8 (—C9H—), 33.5 (—$C23H_2$—), 32.7 (—C8H—), 31.9 (—$C24H_2$—), 28.7 (—$C7H_2$—), 27.2 (—$C6H_2$—), 26.8 (—$C11H_2$—), 15.5 (—$C18H_3$—), 14.2 (—$C27H_3$—), 12.0 (—$C19H_3$—), 7.7 (—$C18H_3$—); MS (ESI): *m*/*z* = 732 $[M+Na]^+$. HRMS: calcd. for $C_{41}H_{47}N_3NaO_8$ $[M+Na]^+$: 732.3261: found: 732.3264.

3. Results and discussion

The 23-deoxy-25-*epi* north 1 **4** synthesis commenced with the transformation of hecogenin acetate **6** into 14,25-diene **5** according to published procedures [20]. When allyl cyclic ether **5** was treated with iodine and sodium bicarbonate in acetonitrile, iodoetherification-mediated E-ring opening occurred to give F-ring-containing C14,16-diene **7a** in 77% yield. For the transetherification, the use of acetonitrile was crucial; the use of other solvents such as ethyl acetate and dichloromethane resulted in the formation of C14,16-diene lacking iodine moiety (**7b**, Scheme 2). The nonhalogenated cyclic ether **7b** was also formed in the absence of sodium bicarbonate, indicating that the formation of **7b** involves the acid-catalyzed transetherification. Subjection of β-iodoether **7a** to zinc in acetic acid at 95 °C triggered a reductive opening of F-ring to give C22-OH **8** in 89% yield [24]. The acetyl protective group in C3-OAc **8** was removed with methanolic potassium carbonate to render C3,22-dialcohol **9**, which was then subjected to IBX oxidation under refluxing EtOH to give C3,22-diketone **10** in 93% yield. Treatment of D-ring diene **10** with singlet oxygen, which was generated by tetraphenylporphine (TPP) photosensitization, induced

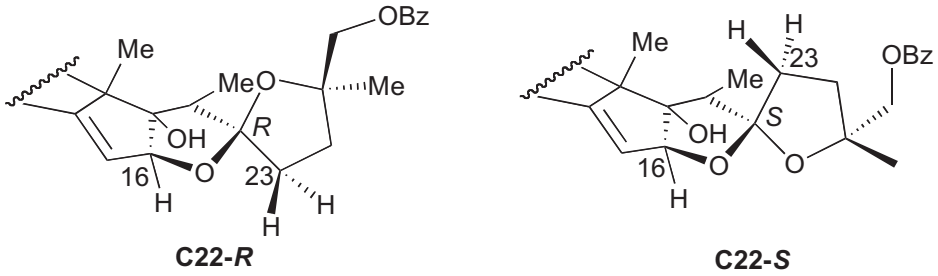


Fig. 2. Structures of C22-*R* spiroketal **15** and its C22-*S* isomer. The distance between C16 proton and C23 protons in C22-*R* spiroketal **15** is shorter than that in C22-*S* spiroketal.

[4+2] cycloaddition reaction to give an inseparable mixture of C14,17-peroxo compounds **11a** and **11b** [25–27]. Singlet oxygen reaction of C22-hydroxy-14,16-diene **8** was also attempted but the resulting adducts were unstable in the presence of C22-OH to give complex mixtures of products. Reductive cleavage of peroxides **11a** and **11b** with activated zinc in acetic acid afforded C14,17 dialcohol **12a** (54%) and **12b** (37%), which were separated by silica gel column chromatography [24].

Under the influence of *p*-TsOH in methanol, acid-catalyzed cyclization of C14 α alcohol **12a** smoothly occurred to give Δ^{14}-alkene **13** as a single stereoisomer (Scheme 3). It is noteworthy that C14 β alcohol **12b** was inert under the same reaction conditions, highlighting the importance of the C14 alcohol stereochemistry in the acid-catalyzed E-ring formation. One possible mechanism for the formation of C22 ketal **13** involves C22-hemiketalization followed by the attack of the hemiketal hydroxyl group on C16 (Scheme 3). Sharpless asymmetric dihydroxylation of terminal olefin **13** in the presence of potassium osmate and hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) preferentially afforded (*R*)-C25 alcohol **14** in 82% yield. Treatment of vicinal diol **14** with benzoyl chloride in the presence of pyridine triggered a tandem benzoylation and spiroketalization to give a mixture of 5/5-spiroketal **15** and C25 alcohol **15a**. The C25 tertiary alcohol **15a** was converted to 5/5-spiroketal **15** by PPTS-catalyzed cyclization. Treatment of ketal **15** with I_2 in acetone and H_2O unmasked the C3 ketal moiety to produce C3 ketone **16**. The stereochemistry of C22 spiroketal **16** was determined by NOESY, which showed interaction of the C16 proton with the C23 protons (Fig. 2). Phenyltrimethylammonium tribromide (PTAB)-mediated bromination of C23 ketone **16** gave C2-α-bromo-C3 ketone **17**. Treatment of C2-α-bromo-C3 ketone **17** with tetramethyl guanidinium azide (TMGA) triggered S_N2 reaction between alkyl bromide and azide followed by epimerization at C2 to afford the desired C3-α-azido-C23-deoxy-C25-*epi* north 1 unit **4**.

In summary, using 'reduction-oxidation' strategy, we have synthesized 23-deoxy-25-*epi* north 1 **4** in 17 steps starting from hecogenin acetate with 3.8% overall yield. Our synthesis, which is >13 steps shorter than the previously reported north 1 synthesis, yielded 0.3 g of 23-deoxy-25-*epi* north 1 **4**. This synthetic approach can be used in efficient synthesis of various bissteroidal pyrazines, thereby facilitating development of cephalostatin-based anticancer drugs. Synthesis and bioactivity evaluation of cephalostatin analogs that contain the 23-deoxy-25-*epi* north 1 unit is under progress in our laboratory and the results will be reported elsewhere in due course.

Acknowledgements

This research was supported by Cancer Prevention Research Institute of Texas (RP130219).

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