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The convergent synthesis of novel cytotoxic certonardosterol D_2 from diosgenin

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Abstract

Certonardosterol D_2, a polyhydroxysterol isolated from starfish *Certonardoa semiregularis* with exceptionally potent antitumor activity, was stereoselectively synthesized from natural rich diosgenin via the protocol of Julia olefination and Evans aldol reaction.

Keywords: Polyhydroxysterol; Certonardosterol; Julia olefination; Evans aldol reaction

1. Introduction

Global research aimed at the discovery of novel and clinically useful antitumor agents from marine organisms continues at a remarkably active pace. Search for the natural products in marine life has led to the discovery of a number of biologically active polyhydroxysterols. These compounds have shown promise as leading agents for the development of novel therapeutics.[1] Starfish are known to be a rich source of structurally unique and biologically active steroids, most of which do not have any counterpart within the entire animal kingdom.[2] A family of novel polyhydroxysterols, certonardosterols, were isolated from the starfish *Certonardoa semiregularis* in 2004. These steroids are always highly oxygenated and often occur in very limited amounts. Among these compounds, certonardosterol D_2 (**1**) was found to be the most cytotoxic for the target human cancer cells with ED_{50} of 0.01−0.15 μg/mL, which was comparable to that of doxorubicin.[3] Herein, we report the first synthesis of this 3β,6α,15β-trihydroxy steroid.

Certonardosterol D_2 (**1**) was established as (22*E*,24*R*)-24-methyl-5α-cholest-22-ene-3β,6α,15β,24[1]-tetrol (Fig. 1). During the last century, the chemistry of spirostanes was intensively studied.[4] Natural rich plant sapogenins are relatively cheap raw materials for the synthesis of a number of medicinally important steroids.[5] One of the major challenges for steroid chemists was to elaborate an efficient degradation route from spirostanol to the C19, C21 and C22 steroids.[6] Especially, C22 carbonyl steroids proved to be useful precursors for the synthesis of continental and marine steroids, such as brassinolide,[6b] squalamine,[7] and other marine steroids. Little progress was reported for the degradation of spirostanes to C22 steroids, which were usually obtained as byproducts in different reactions of sapogenins. Only recently, Iglesias-Arteaga obtained the C22-steroid bisnorcholanic lactone by the Beckmann rearrangement of 23-hydroxyimino-sapogenins promoted by $BF_3 \cdot Et_2O$ in acetic acid.[8] In an intensive study, it was found that direct cleavage of C22−C23 bond of sapogenins was achieved by a simple reaction of sapogenins with

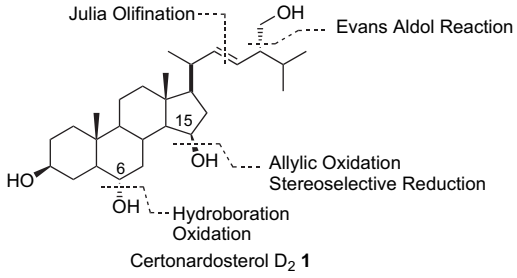

Fig. 1. Synthesis of certonardosterol D_2 from diosgenin.

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peroxyacetic acid, in the presence of catalytic amount of H_2SO_4 and iodine,[9] which provided the skeleton of D_2. Despite the fact that the Claisen or Ireland–Claisen rearrangement has been widely reported for synthesis of the (22*E*)-steroids bearing an *R* or *S* alkyl constituent at C-24 based on the stereochemical transformation of C-22 allylic hydroxyl configuration of steroidal side chain, the stereoselectivity did not offer satisfactory results.[10] With the intent to search for a universal methodology for the stereoselective synthesis of side chains of the family of certonardosterols, we exploited a convergent synthesis strategy via the Julia olefination[11] of steroidal aldehyde with a chiral alkyl sulfone. The 24*R*-hydroxyl methyl group was introduced stereoselectively by Evans aldol reaction.[12] It was observed that C-15β hydroxyl could be transferred from C-16-oxo in sapogenins[13] (Fig. 1).

2. Results and discussion

By using the practical method,[9] chlorogenin (**3**), which was obtained from natural rich diosgenin (**2**) via hydroboration (BH_3/THF, 0 °C) and oxidation with hydrogen peroxide, was degraded to lactone **4** in 85% yield (Scheme 1).

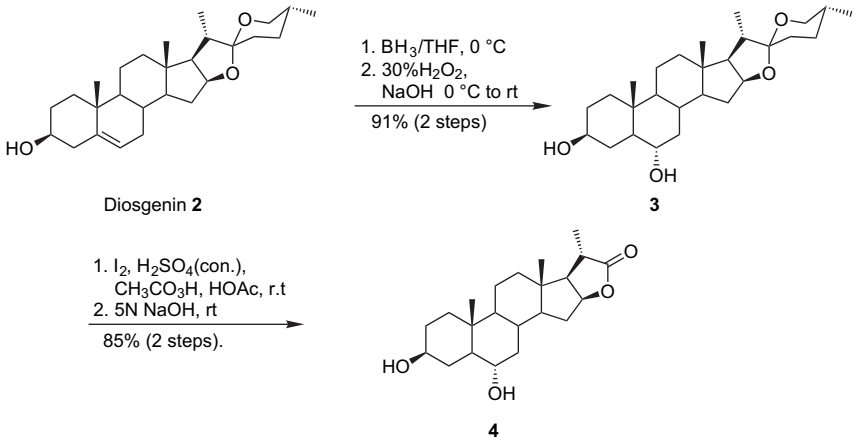
Next, attention was directed toward the transposition of the C-16-oxy in D-ring to the C-15β hydroxyl. Riccards found that the stereochemical outcome of the C-15 carbonyl reduction was strongly dependent on the C-16 and C-17 hybridization. C-15β hydroxyl could be established by the reduction of the C-15 ketone stereoselectively.[13b] Thus, after switching the hydroxyl groups of lactone **4** to methoxy methyl ethers, the lactone **5** on being reduced with $LiAlH_4$ gave the diol **6** in 99% yield. The C22-primary hydroxyl group in the side chain was chemoselectively protected as its acetate (Ac_2O/DMAP/Et_3N). Dehydration of the 16β-alcohol **7** with phosphorous oxychloride in pyridine according to the report of Williams[13a] afforded a mixture of 16-chloro steroid **8** and the desired olefin **9** (in the ratio of 2:1) in 89% yield. Compound **8** could be easily converted into olefin **9** by treatment with Li_2CO_3/LiCl in DMF at 120 °C. C-15 ketone in D-ring was generated by the allylic oxidation using $Na_2Cr_2O_7 \cdot 2H_2O$ and *N*-hydroxy succinimide in 76% yield. Hydrogenation of **10** over 20 wt % $Pd(OH)_2$/C and subsequent reduction by $NaBH_4$ afforded the C-15 alcohol **11** in 89% yield. The chemical shift for the D-ring 15β-hydroxyl C–H in **11** gave a triplet (J=6.0 Hz) at 4.20 ppm, which implies a 15β-hydroxy configuration[13b] in both chemical shift and coupling constant. After masking C-15β hydroxyl in **11** with methoxy methyl chloride and hydrolysis of C-22 acetyl in **12**, Dess–Martin oxidation of the free alcohol afforded C-22 aldehyde **14** quantitatively (Scheme 2).

The construction of steroidal fragment was followed by focusing the attention on the synthesis of chiral C6 piece of steroidal side chain. The (2*S*)-butyl sulfone **19** was obtained with high enantiomeric purity in five steps as shown in Scheme 3. After the generation of the titanium enolate from (*R*)-**15** by treatment with $TiCl_4$ in the presence of Hunig's base according to the protocol of Evans,[14] the subsequent reaction with *s*-trioxane afforded the aldol adduct, which was transferred into methoxy methyl ether directly. Purification by silica gel chromatography afforded the desired (2*R*′,2*S*)-**16** in 81% yield (two steps) with >99% de. Removal of the chiral auxiliary with $LiBH_4$ gave alcohol **17** in 78% yield. Alcohol **17** was subjected to a Mitsunobu reaction with 2-mercaptobenzothiazole affording (2*S*)-butyl sulfide **18** quantitatively, which was further oxidized into sulfone **19** by hydrogen peroxide and ammonium molybdate tetrahydrate in 80% yield.

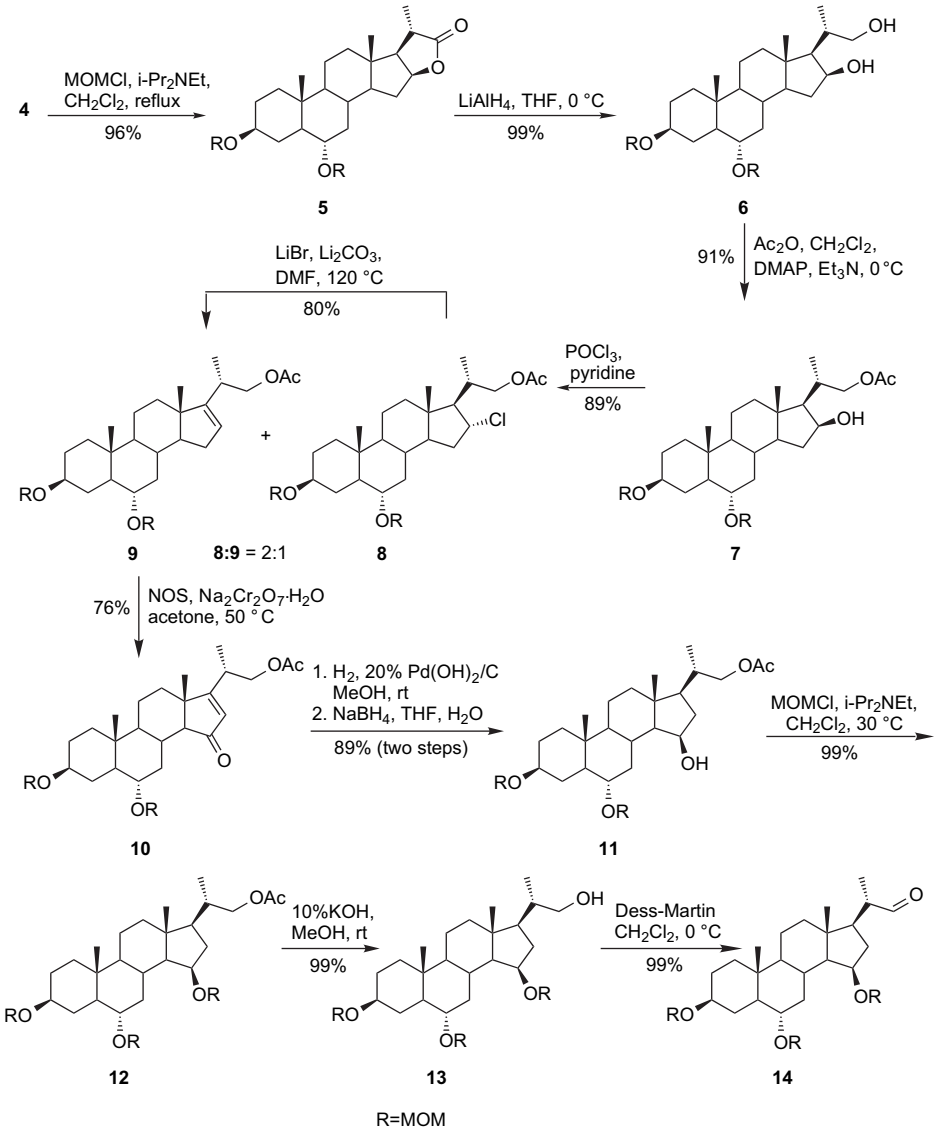
With the C22 steroidal aldehyde **14** and (2*S*)-butyl sulfone **19** fragments in hand, their assembly was finally undertaken. A Julia olefination between aldehyde **14** and butyl sulfone **19** was performed with the LiHMDS at −78 °C, which provided *E*-olefin **20** exclusively in 57% yield. Global removal of the four methoxy methyl ether protection groups in **20** gave certonardosterol D_2 (**1**) in 98% yield. The spectral data of synthetic certonardosterol D_2 were consistent in all respects with that reported for the natural product[3] (Scheme 4).

3. Conclusions

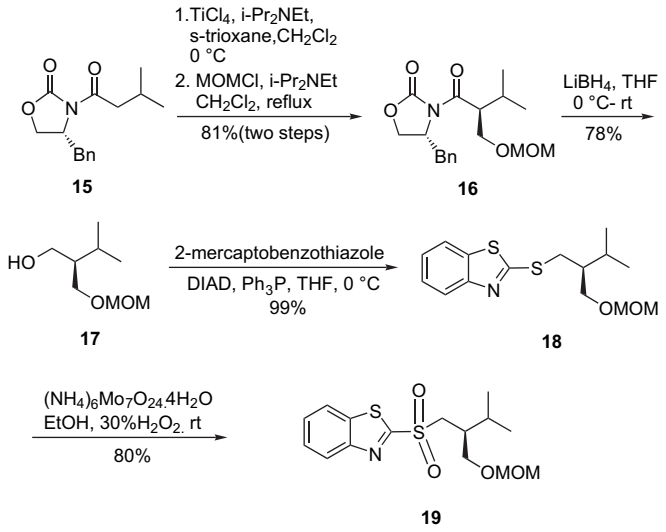
We accomplished the first synthesis of certonardosterol D_2 in 18 steps in an 18% overall yield from the commercially available diosgenin. The strategy for obtaining the C-15β hydroxy steroid from a C-16β hydroxy steroid was shown to be



Scheme 1. Synthesis of bisnorcholanic lactone **4**.



Scheme 2. Synthesis of 15β,C-22 steroidal aldehyde **14**.



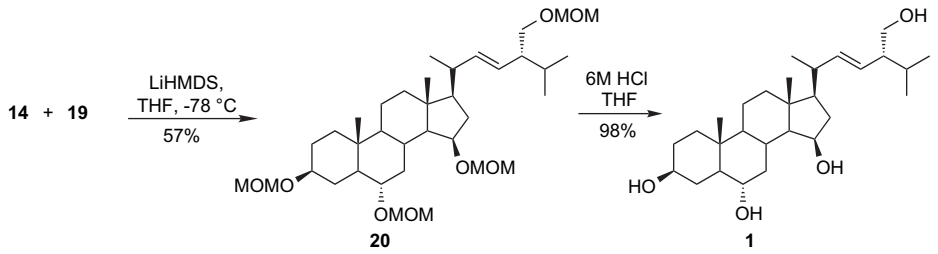
Scheme 3. Synthesis of (2*S*)-butyl sulfone **19**.

effective. Julia olefination was used to assemble the high steric side chain for steroid stereoselectivity. This methodology provided a convenient strategy for diversity-originated synthesis of steroids.

4. Experimental section

4.1. General remarks

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 500 MHz using a Varian EM-360A spectrometer with TMS as the internal standard. Chemical shift (δ) values were given in parts per million. MS were recorded with HP-5989A spectrometer using the ESI method. The melting points were determined on an SGW X-4 melting point apparatus and were uncorrected. Optical rotations were obtained with Perkin–Elmer Polarimeter 341 apparatus.



Scheme 4. Synthesis of certonardosterol D_2.

4.1.1. Chlorogenin (3)[15]

To a solution of diosgenin (**2**) (1.0 g, 2.4 mmol) in dry THF (100 mL) under an argon atmosphere at 0 °C, 1 M BH_3 in THF (7.2 mL, 7.2 mmol) was added slowly. The mixture was allowed to stir overnight at room temperature. NaOH (10 N, 1.5 mL, 15 mmol) was added over 30 min at 0 °C. Subsequently, 30% hydrogen peroxide (1.5 mL, 13 mmol) was added and vigorous stirring was continued at room temperature for 2 h. Extraction with CH_2Cl_2 (20 mL×3) and the combined extracts were washed successively with 1 N HCl, saturated $NaHCO_3$, and brine, dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (Hexane/EtOAc=1:3) gave **3** as a white solid (950 mg, 91% yield). ^{1}H NMR (300 MHz, pyridine-d_5): δ 4.54 (q, 1H, J=7.5 Hz), 3.96–3.89 (m, 1H), 3.66 (dt, 1H, J=10.8, 4.5 Hz), 3.59–3.55 (m, 1H), 3.51–3.44 (m, 1H), 3.01 (1H, br d, J=12.0 Hz), 2.24 (dt, 1H, J=7.8, 3.9 Hz), 1.14 (d, 3H, J=6.6 Hz), 0.87 (s, 3H), 0.85 (s, 3H), 0.67 (d, 3H, J=5.4 Hz).

4.1.2. 3β,6α,16β-Trihydroxy-23,24-dinor-5α-cholan-22-oic acid-16-lactone (4)[16]

To a mixture of HOAc (60 mL) and H_2SO_4 (concd) (0.9 mL), I_2 (0.49 g, 1.9 mmol) was added and stirred for 30 min at room temperature. Then compound **3** (8.4 g, 19.4 mmol) was added and the mixture was further stirred for 10 min. CH_3CO_3H (118.4 mL, 118 mmol, 1 M in HOAc) was added dropwise. After 4 h, the reaction was saponified with 5 N NaOH to pH=13 at room temperature overnight. The crude product was filtered and dried in vacuo. Flash chromatography (CH_2Cl_2/MeOH=10:1) provided **4** (6.0 g, 85%) as a white solid. Mp 252–253 °C. ^{1}H NMR (300 MHz, pyridine-d_5): δ 4.88 (br s, 1H), 3.89 (br s, 1H), 3.64 (br s, 1H), 2.97 (d, 1H, J=11.4 Hz,), 2.65 (d, 1H, J=4.5 Hz), 2.17–2.13 (m, 2H), 2.07–2.03 (m, 1H), 1.23 (d, 3H, J=7.2 Hz), 0.82 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (75 MHz, pyridine-d_5): δ 181.0, 82.5, 70.7, 68.1, 58.8, 54.2, 54.0, 52.4, 42.4, 41.6, 38.0, 37.7, 36.5, 36.1, 33.8, 33.4, 33.1, 32.1, 20.6, 17.7, 13.6, 13.5.

4.1.3. 3β,6α-Dimethoxymethyl-16β-hydroxy-23,24-bisnor-5α-cholan-22-oic acid-lactone (5)

Lactone **4** (6.0 g, 16.6 mmol) was dissolved in dry CH_2Cl_2 (80 mL), DIPEA (24 mL, 145 mmol) and MOMCl (6.9 mL, 90 mmol) were added slowly by syringe. The brown reaction mixture was allowed to stir overnight under reflux. HCl (1 N) was added to neutralize the excessive base. The mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed with brine (30 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc=3:1) provided **5** (7.2 g, 96%) as a white solid. Mp 136–137 °C. $[\alpha]_D^{20}$ −16.1 (c 1.20, $CHCl_3$). IR (KBr): 2939, 1760, 1183, 1146, 1103, 1037, 912 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96–4.89 (m, 1H), 4.70, 4.53 (AB, 2H, J_{AB}=6.9 Hz), 4.66 (s, 2H), 3.47–3.41 (m, 1H,), 3.34 (s, 3H), 3.33 (s, 3H), 3.30–3.28 (m, 1H), 2.55 (q, 1H, J=7.5 Hz), 2.29–2.22 (m, 2H), 2.06 (dt, 1H, J=12.0 Hz, 4.2 Hz), 1.28 (d, 3H, J=4.5 Hz), 0.82 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.2, 95.3, 94.4, 82.5, 75.9, 74.6, 58.9, 55.4, 55.1, 54.3, 53.6, 50.0, 41.7, 38.4, 38.1, 37.1, 36.5, 36.0, 33.5, 32.9, 29.4, 28.2, 20.4, 17.9, 13.7, 13.4. ESI-MS: 468.4 (M+NH_4^+). HRMS calcd for $C_{26}H_{42}O_6Na^+$: 473.2862; found: 473.2874.

4.1.4. 3β,6α-Dimethoxymethyl-23,24-bisnor-5α-cholan-16β,22-diol (6)

Compound **5** (1.0 g, 2.2 mmol) in dry THF (15 mL) was reduced with $LiAlH_4$ (0.15 g, 3.9 mmol) at room temperature for 10 h. The reaction was quenched with wet Na_2SO_4 with caution. The gray precipitate was filtered and washed with THF (10 mL×3). The filtrate was partitioned between water and THF. The aqueous layer was extracted with THF (10 mL×3). The combined organic extracts were washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated to give pure compound **6** (1.0 g, 99%) as a white solid. $[\alpha]_D^{20}$ −29.3 (c 1.30, $CHCl_3$). IR (KBr): 2945, 2852, 1145, 1103, 1039 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72, 4.54 (AB, 2H, J_{AB}=6.9 Hz), 4.67 (s, 2H), 4.38–4.36 (m, 1H), 3.56–3.54 (m, 1H), 3.48 (br, 3H), 3.35 (s, 6H), 2.24–2.17 (m, 3H), 0.94 (d, 3H, J=6.9 Hz,), 0.87 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.2, 94.4, 76.1, 74.9, 72.4, 70.6, 62.2, 55.4, 55.1, 54.0, 53.6, 50.0, 42.9, 40.0, 38.2, 37.1, 36.5, 35.4, 33.7, 32.4, 29.4, 28.2, 20.8, 16.9, 13.4, 13.2. ESI-MS: 572.4 (M+NH_4^+). HRMS calcd for $C_{26}H_{46}O_6Na^+$: 477.3185; found: 477.3187.

4.1.5. 22-Acetoxy-3β,6α-dimethoxymethyl-23,24-bisnor-5α-cholan-16β-ol (7)

To a solution of compound **6** (0.8 g, 1.78 mmol), DMAP (7 mg, 0.04 mmol) in CH_2Cl_2 (40 mL), triethylamine (0.5 mL, 3.2 mmol) was added a solution of Ac_2O (0.18 mL, 2.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 3 h, the reaction was quenched with saturated ammonium chloride (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (15 mL×2). The

combined organic extracts were washed with saturated $NaHCO_3$ (20 mL×2), brine (20 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (Hexane/EtOAc, 3:1 to 1:1) provided **7** (0.80 g, 91%) as a white solid. Mp 89–90 °C. $[\alpha]_D^{20}$ −38.3 (*c* 0.40, $CHCl_3$). IR (KBr): 3528, 2885, 1722, 1257, 1030, 908 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.70, 4.53 (AB, 2H, J_{AB}=6.9 Hz), 4.67 (s, 2H), 4.32 (dd, 2H, *J*=10.8, 3.3 Hz), 3.63 (dd, 1H, *J*=11.1, 7.8 Hz), 3.36–3.34 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.33–3.32 (m, 1H), 2.82 (d, 1H, *J*=3.3 Hz), 2.06 (s, 3H), 1.05 (d, 3H, *J*=6.9 Hz), 0.84 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 95.2, 94.5, 76.0, 74.8, 71.8, 70.1, 58.1, 55.4, 55.1, 53.9, 53.6, 50.0, 42.5, 39.6, 38.2, 37.1, 36.5, 35.9, 33.7, 30.6, 29.5, 28.2, 21.0, 20.7, 16.9, 13.4, 13.1. ESI-MS: 519.4 ($M+Na^+$). HRMS calcd for $C_{28}H_{48}O_7Na^+$: 519.3319; found: 519.3292.

*4.1.6. 22-Acetoxy-16-chlor-3β,6α-dimethoxymethyl-23,24-bisnor-5α-cholane (**8**) and 22-acetoxy-3β,6α-dimethoxymethyl-23,24-bisnor-5α-chol-16-ene (**9**)*

$POCl_3$ (0.19 mL, 2.0 mmol) was slowly added to a solution of compound **7** (100 mg, 0.20 mmol) in dry pyridine (5 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight. The reaction was then quenched with water (10 mL) and diluted with EtOAc. The mixture was acidified to pH 4 with 2 M HCl. The aqueous layer was extracted with EtOAc (15 mL×2). The combined organic extracts were washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc=7:1) provided **8** (63 mg, 61%) and **9** (27 mg 28%) as colorless oil. Compound **8**: IR (KBr): 2936, 1738, 1238, 1039 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62, 4.45 (AB, 2H, J_{AB}=6.9 Hz), 4.59 (s, 2H), 4.21 (dd, 1H, *J*=11.8, 4.2 Hz), 4.02–3.97 (m, 1H), 3.85 (dd, 1H, *J*=11.8, 7.2 Hz), 3.42–3.35 (m, 1H), 3.26 (s, 6H), 3.22–3.19 (m, 1H), 2.20–2.16 (m, 1H), 1.96 (s, 3H), 0.94 (d, 3H, *J*=6.6 Hz), 0.73 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 95.1, 94.4, 75.9, 74.6, 68.7, 64.7, 62.0, 55.4, 55.0, 53.1, 52.5, 49.9, 44.8, 39.3, 38.1, 38.0, 37.0, 36.3, 34.0, 33.0, 29.6, 29.3, 28.1, 20.9, 17.3, 13.2, 13.0. ESI-MS: 532.3 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{46}O_6Na^+$−HCl: 501.3185; found: 501.3187. Compound **9**: $[\alpha]_D^{20}$ −30.6 (*c* 1.1, $CHCl_3$). IR (KBr): 2966, 2934, 1739, 1041, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.74, 4.55 (AB, 2H, J_{AB}=6.9 Hz), 4.68 (s, 2H), 4.13–4.07 (m, 1H), 3.96–3.89 (m, 1H), 3.47–3.36 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.35–3.32 (m, 1H), 2.44–2.38 (m, 1H), 2.27–2.24 (m, 1H), 2.03 (s, 3H), 1.04 (d, 3H, *J*=6.6 Hz), 0.86 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 156.8, 122.5, 95.2, 96.5, 76.0, 74.8, 68.5, 56.6, 55.4, 55.1, 54.3, 50.3, 47.2, 38.1, 37.0, 36.7, 34.6, 32.7, 31.4, 31.1, 29.7, 28.3, 21.0, 20.9, 18.7, 16.1, 13.4. ESI-MS: 496.4 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{46}O_6Na^+$: 501.3188; found: 501.3187.

*4.1.7. Conversion of compound **8** to **9***

To a solution of compound **8** (412 mg, 0.80 mmol) in freshly distilled DMF (4 mL), $LiBr\cdot H_2O$ (210 mg, 2.0 mmol) and Li_2CO_3 (205 mg, 2.8 mmol) were added. The mixture was heated at 120 °C and monitored by TLC. After reaction was completed, water (2 mL) and 1 M HCl (4 mL) were added to the mixture. The solution was extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc=7:1) provided **9** (305 mg, 80%) as a colorless oil.

*4.1.8. 22-Acetoxy-3β,6α-dimethoxymethyl-23,24-bisnor-5α-chol-16-ene-15-one (**10**)*

A solution of compound **9** (10 mg, 0.02 mmol), *N*-hydroxy succinimide (5 mg, 0.04 mmol), and $Na_2Cr_2O_7\cdot 2H_2O$ (10 mg, 0.03 mmol) in acetone (2 mL) was heated at 50 °C. After 4 h, additional *N*-hydroxy succinimide (5 mg, 0.04 mmol) was added and the reaction was kept overnight. Saturated sodium sulfite (10 mL) was added. The solution was extracted with EtOAc (15 mL×3). The combined organic extracts were washed with brine (15 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc=3:1) to afford **10** (7 mg, 76%, 1 mg **9** was recovered) as a colorless oil. $[\alpha]_D^{20}$ 40.2 (*c* 2.00, $CHCl_3$). IR (KBr): 2933, 2887, 1743, 1710, 1230, 1041, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.68 (s, 1H,), 4.80, 4.54 (AB, 2H, J_{AB}=6.9 Hz), 4.67 (s, 2H), 4.13–4.07 (m, 2H), 3.39–3.36 (m, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 3.34–3.32 (m, 1H), 3.11 (dt, *J*=12.6, 3.9 Hz), 2.80–2.74 (m, 1H), 2.01 (s, 3H), 1.14 (d, 3H, *J*=7.2 Hz), 0.97 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 183.5, 170.8, 125.5, 94.8, 94.4, 75.8, 73.7, 66.9, 63.2, 55.5, 55.1, 54.3, 50.1, 46.8, 37.0, 36.5, 32.3, 32.1, 30.9, 29.6, 29.4, 28.2, 23.3, 20.8, 20.3, 17.8, 13.4. ESI-MS: 510.3 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{44}O_7Na^+$: 515.3001; found: 515.2979.

*4.1.9. 22-Acetoxy-3β,6α-dimethoxymethyl-23,24-bisnor-5α-cholan-15β-ol (**11**)*

Compound **10** (100 mg, 0.20 mmol) in MeOH (1 mL) was subjected to hydrogenation over 20 wt % Pd $(OH)_2$ on carbon (30 mg) for 5 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated. The residue oil in MeOH (2 mL) and THF (6 mL) was treated with $NaBH_4$ (30 mg, 0.8 mmol) at 0 °C for 2 h. HCl (1 M, 3 mL) was added. The solution was extracted with THF (8 mL×3). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL×2), brine (15 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc, 1:1) provided **11** (90 mg, 89%) as a colorless oil. $[\alpha]_D^{20}$ 11.8 (*c* 1.15, $CHCl_3$). IR (KBr): 3483, 2935, 1739, 1243, 1045, 915 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.73, 4.54 (AB, 2H, J_{AB}=6.9 Hz), 4.68 (s, 2H), 4.20 (t, 1H, *J*=6.0 Hz), 4.04 (dd, 1H, *J*=10.8, 3.3 Hz), 3.80 (dd, 1H, *J*=10.5, 6.9 Hz), 3.47–3.45 (m, 1H), 3.41–3.37 (m, 1H), 3.35 (s, 6H), 2.34–2.27 (m, 3H), 2.04 (s, 3H), 1.00 (d, 1H, *J*=6.6 Hz), 0.94 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 95.2, 94.4, 76.0, 74.9, 69.3, 60.3, 55.5, 55.1, 54.0, 52.9, 50.1, 42.4, 40.9, 40.6, 37.5, 37.3, 36.5, 35.4, 31.4, 30.1, 29.7, 29.5, 28.3, 21.0, 17.2, 14.6, 13.3. ESI-MS: 514.4 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{48}O_7Na^+$: 519.3311; found: 519.3292.

*4.1.10. 22-Acetoxy-3β,6α,15β-trimethoxymethyl-23,24-bisnor-5α-cholane (**12**)*

To a solution of compound **11** (309 mg, 0.62 mmol) in freshly distilled CH_2Cl_2 (20 mL), MOMCl (0.25 mL, 3.1 mmol) and DIPEA (0.80 mL, 4.3 mmol) were added separately by syringe. The reaction was kept at 30 °C overnight and neutralized with 1 N HCl (5 mL). The mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (15 mL×3). The combined organic extracts were washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc, 1:1) provided **12** (335 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ −4.7 (*c* 0.75, $CHCl_3$). IR (KBr): 2936, 2853, 1740, 1239, 1046, 916, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.70, 4.50 (AB, 2H, J_{AB}=6.9 Hz), 4.68 (s, 2H), 4.63, 4.51 (AB, 2H, J_{AB}=6.9 Hz), 4.04 (d, 1H, *J*=10.2 Hz), 3.98 (t, 1H, *J*=5.7 Hz), 3.78 (dd, 1H, *J*=10.5, 6.9 Hz), 3.47−3.44 (m, 1H), 3.37 (s, 3H), 3.37−3.35 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.31−2.24 (m, 3H), 2.04 (s, 3H), 1.01 (d, 1H, *J*=6.6 Hz), 0.90 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 96.2, 95.2, 94.5, 76.3, 76.1, 74.8, 69.3, 59.9, 56.1, 55.4, 55.1, 54.0, 52.9, 50.2, 42.6, 40.7, 38.0, 37.4, 37.2, 36.6, 35.5, 30.3, 29.5, 28.3, 21.0, 20.9, 17.2, 14.3, 13.4. ESI-MS: 558.3 ($M+NH_4^+$). HRMS calcd for $C_{30}H_{52}O_8Na^+$: 563.3551; found: 563.3554.

*4.1.11. 3β,6α,15β-Trimethoxymethyl-23,24-bisnor-5α-cholan-22-ol (**13**)*

Compound **12** (70 mg, 0.13 mmol) in MeOH (10 mL) was treated with a solution of 10% KOH in MeOH (4 mL) at room temperature for 6 h. The mixture was extracted with EtOAc (20 mL×3). The combined organic extracts were washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated to give compound **13** (276 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ −11.1 (*c* 1.15, $CHCl_3$). IR (KBr): 2964, 1261, 1095, 1027, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.71, 4.51 (AB, 2H, J_{AB}=6.9 Hz), 4.69 (s, 2H), 4.65, 4.53 (AB, 2H, J_{AB}=6.9 Hz), 3.98 (t, 1H, *J*=6.0 Hz), 3.61 (dd, 1H, *J*=10.8, 3.0 Hz), 3.52−3.44 (m, 1H), 3.42−3.38 (m, 1H), 3.38 (s, 3H), 3.38−3.36 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.31−2.24 (m, 3H), 1.04 (d, 1H, *J*=6.6 Hz), 0.90 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.2, 95.1, 94.5, 76.4, 76.1, 74.8, 67.7, 60.0, 56.1, 55.4, 55.1, 54.0, 52.5, 50.2, 42.5, 40.7, 38.4, 38.0, 37.3, 37.2, 36.6, 30.2, 29.5, 28.3, 20.9, 16.8, 14.3, 13.4. ESI-MS: 516.4 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{50}O_7Na^+$: 521.3447; found: 521.3449.

*4.1.12. 3β,6α,15β-Trimethoxymethyl-23,24-bisnor-5α-cholan-22-al (**14**)*

To a solution of alcohol **13** (322 mg, 0.65 mmol) in CH_2Cl_2 (10 mL), Dess−Martin periodinane (1.05 g, 2.4 mmol) was added at 0 °C for 30 min. Saturated $Na_2S_2O_3$ (3 mL) and saturated $NaHCO_3$ (9 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 1:1) gave aldehyde **14** (320 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ −13.6 (*c* 1.30, $CHCl_3$). IR (KBr): 2933, 2852, 1725, 1449, 1148, 1041, 916 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (d, 1H, *J*=3.3 Hz) 4.70, 4.53 (AB, 2H, J_{AB}=6.9 Hz), 4.68 (s, 2H), 4.61, 4.49 (AB, 2H, J_{AB}=6.9 Hz), 4.01 (t, 1H, *J*=6.0 Hz), 3.51−3.42 (m, 1H), 3.37−3.36 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 2.49−2.40 (m, 1H), 2.31−2.24 (m, 3H), 1.12 (d, 1H, *J*=6.9 Hz), 0.91 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 96.1, 95.1, 94.4, 76.3, 76.0, 74.7, 59.5, 56.1, 55.4, 55.1, 54.0, 51.0, 50.2, 49.3, 43.0, 40.6, 37.4, 37.3, 37.1, 36.6, 30.2, 29.5, 28.3, 20.8, 14.6, 13.4, 13.3. ESI-MS: 514.4 ($M+NH_4^+$). HRMS calcd for $C_{28}H_{48}O_7Na^+$: 519.3293; found: 519.3292.

*4.1.13. (R)-4-Benzyl-3-((S)-2-((methoxymethoxy)methyl)-3-methylbutanoyl)oxazolidin-2-one (**16**)*

To a solution of compound **15** (5.0 g, 19 mmol) in freshly distilled CH_2Cl_2 (50 mL), $TiCl_4$ (2.2 mL, 20 mmol) was added dropwise at 0 °C for 10 min under nitrogen. Then DIPEA (3.7 mL, 21 mmol) was added for 1 h, following addition of *s*-trioxane (2.0 g, 22 mmol) in 10 mL CH_2Cl_2. An additional amount of $TiCl_4$ (2.2 mL, 20 mmol) was added. The reaction mixture was stirred for 4 h at 0 °C and quenched by saturated NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL×2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The yellow residue in freshly distilled CH_2Cl_2 (60 mL) was treated with MOMCl (7.5 mL, 95 mmol) and DIPEA (24 mL, 133 mmol) overnight under reflux. Water (20 mL) was added to quench the reaction. The mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed successively by 1 N HCl (20 mL×2), saturated $NaHCO_3$ (25 mL×3), brine (30 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 7:1) provided compound **16** (5.16 g, 81%) as a white solid. $[\alpha]_D^{20}$ −62.7 (*c* 1.00, $CHCl_3$). IR (KBr): 1763, 1696, 1392, 1114, 1062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35−7.24 (m, 5H), 4.75−4.73 (m, 1H), 4.62 (s, 2H), 4.18−4.09 (m, 3H), 3.93 (t, 1H, *J*=9.3 Hz), 3.75 (dd, 1H, *J*=9.3, 3.9 Hz), 3.35 (s, 3H), 3.25 (dd, 1H, *J*=13.5, 3.0 Hz), 2.81 (dd, 1H, *J*=13.5, 6.0 Hz), 2.06−2.00 (m, 1H), 0.99 (d, 3H, *J*=6.6 Hz), 0.97 (d, 3H, *J*=6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 153.1, 135.2, 129.5, 128.8, 127.2, 96.3, 67.0, 65.5, 55.2, 48.8, 37.5, 28.5, 20.9, 19.4. ESI-MS: 353.2 ($M+Na^+$). HRMS calcd for $C_{18}H_{25}NO_5Na^+$: 358.1628; found: 358.1625.

*4.1.14. (R)-2-((Methoxymethoxy)methyl)-3-methylbutan-1-ol (**17**)*

To a solution of compound **15** (4.86 g, 14.5 mmol) in Et_2O (30 mL) and THF (30 mL), a drop of water and $LiBH_4$ (28 mL, 1 M in THF, 28 mmol) were added at 0 °C. The reaction mixture was allowed to stir overnight at room temperature. HCl (1 N, 30 mL) was added with caution to quench the reaction. The solution was extracted with EtOAc (30 mL×2) and the combined organic extracts were washed successively by saturated $NaHCO_3$ (20 mL×3), brine (30 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash

chromatography (hexane/EtOAc, 3:1) provided alcohol **17** (1.83 g, 78%) as a colorless oil. $[\alpha]_D^{20}$ 7.6 (*c* 0.50, $CHCl_3$). IR (KBr): 3443, 2960, 2885, 1151, 1112, 1047, 920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.59 (s, 2H), 3.71–3.58 (m, 4H), 3.34 (s, 3H), 2.62 (br s, 1H), 1.78–1.72 (m, 1H), 1.59–1.55 (m, 1H), 0.91 (d, 3H, *J*=2.7 Hz), 0.89 (d, 3H, *J*=2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.6, 69.3, 64.0, 55.3, 46.4, 26.4, 20.2, 20.0. ESI-MS: 185.1 ($M+Na^+$). HRMS calcd for $C_8H_{18}O_3Na^+$: 185.1150; found: 185.1148.

*4.1.15. (S)-2-(2-((Methoxymethoxy)methyl)-3-methylbutylthio)benzo[d]thiazole (**18**)*

To a solution of alcohol **17** (441 mg, 2.7 mmol) in THF (25 mL) under an argon atmosphere, Ph_3P (1.07 g, 4.0 mmol), 2-mercaptobenzothiazole (683 mg, 4.0 mmol), and DIAD (0.79 mL, 4.0 mmol) were added at 0 °C. After 2 h, water (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL×2). The combined organic extracts were washed by brine (15 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 10:1) provided thioether **18** (845 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ −45.1 (*c* 2.50, $CHCl_3$). IR (KBr): 2916, 1459, 1429, 1041, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, 1H, *J*=8.1 Hz), 7.74 (d, 1H, *J*=7.8 Hz), 7.40 (t, 1H, *J*=7.5 Hz), 7.27 (t, 1H, *J*=7.5 Hz), 4.62 (s, 2H), 3.70 (dd, 1H, *J*=9.9, 4.8 Hz), 3.64–3.58 (m, 1H), 3.42–3.37 (m, 1H), 3.37 (s, 3H), 1.99–1.89 (m, 2H), 1.03 (d, 3H, *J*=6.3 Hz), 1.01 (d, 3H, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 153.2, 135.0, 125.9, 124.0, 121.3, 120.8, 96.6, 67.2, 55.3, 44.5, 33.4, 28.5, 20.0, 19.7. ESI-MS: 312.1 ($M+H^+$). HRMS calcd for $C_{15}H_{22}NO_2S_2^+$: 312.1104; found: 312.1087.

*4.1.16. (S)-2-(2-((Methoxymethoxy)methyl)-3-methylbutylsulfonyl)benzo[d]thiazole (**19**)*

Compound **18** (424 mg, 1.36 mmol) in absolute EtOH (15 mL) was oxidized with ammonium molybdate tetrahydrate (3.36 g, 2.72 mmol) and H_2O_2 30% (4.6 mL, 40 mmol) at 0 °C for 2 h. The mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 10:1 and 5:1) afforded sulfone **19** (375 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ −6.3 (*c* 3.90, $CHCl_3$). IR (KBr): 2961, 2887, 1473, 1328, 1147, 1041, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J*=7.8 Hz), 8.01 (d, 1H, *J*=7.8 Hz), 7.66–7.58 (m, 2H), 4.49 (s, 2H), 3.68–3.60 (m, 3H), 3.53 (dd, 1H, *J*=14.7, 3.9 Hz), 3.28 (s, 3H), 2.29–2.23 (m, 1H), 2.03–1.96 (m, 1H), 0.91 (d, 6H, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 152.6, 136.7, 128.0, 127.6, 125.4, 122.3, 96.6, 66.7, 55.3, 53.7, 39.5, 28.7, 19.3, 19.2. ESI-MS: 366.1 ($M+Na^+$). HRMS calcd for $C_{15}H_{21}NO_4S_2Na^+$: 366.0820; found: 366.0804.

*4.1.17. (E)-(24R)-24-Methyl-3β,6α,15β,24′-tetramethoxymethyl-5α-cholest-22-ene (**20**)*

To a solution of aldehyde **14** (57 mg, 0.11 mmol) and sulfone **19** (47 mg, 0.14 mmol) in THF (1.5 mL) at −78 °C, LiHMDS (0.22 mL, 20% in THF, 0.22 mmol) was added and the resultant mixture was stirred for 5 h at room temperature. The light yellow solution was quenched by saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic extracts were washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 3:1) provided **20** (41 mg, 57%) as a colorless oil. $[\alpha]_D^{20}$ −17.9 (*c* 1.05, $CHCl_3$). IR (KBr): 2936, 2823, 1465, 1448, 1148, 1103, 1045, 917 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (dd, 1H, *J*=15.3, 7.8 Hz), 5.19 (dd, 1H, *J*=15.5, 8.4 Hz), 4.71, 4.54 (AB, 2H, J_{AB}=6.9 Hz), 4.69 (s, 2H), 4.62, 4.49 (AB, 2H, J_{AB}=6.9 Hz), 4.60 (s, 2H), 3.95 (t, 1H, *J*=6.0 Hz), 3.52–3.43 (m, 3H), 3.39–3.37 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.33–2.25 (m, 2H), 1.03 (d, 3H, *J*=6.6 Hz), 0.90 (s, 3H), 0.87 (d, 3H, *J*=6.9 Hz), 0.86 (s, 3H), 0.82 (d, 3H, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 126.4, 96.5, 95.8, 95.1, 94.5, 76.1, 76.0, 74.9, 69.8, 60.2, 56.0, 55.4, 55.1, 54.1, 50.2, 48.7, 42.3, 40.8, 40.1, 38.8, 37.4, 37.2, 36.6, 30.2, 29.7, 29.5, 28.4, 28.3, 20.9, 20.7, 18.3, 14.4, 13.4. ESI-MS: 642.5 ($M+NH_4^+$). HRMS calcd for $C_{36}H_{64}O_8Na^+$: 647.4494; found: 647.4493.

4.1.18. (E)-(24R)-24-Methyl-5α-cholest-22-ene-3β,6α,15β,24[1]-tetrol (certonardosterol D$_2$)

Compound **20** (20 mg, 0.032 mmol) in THF (4 mL) and H_2O (2 mL) was treated with 6 N HCl (2.5 mL) for 3 h at room temperature. The mixture was extracted with EtOAc (20 mL×3). The combined organic extracts were washed successively by saturated $NaHCO_3$ (10 mL×2), brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 8:1) to afford certonardosterol D_2 (14 mg, 98%) as a white solid. $[\alpha]_D^{20}$ −3.9 (*c* 0.5, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 5.30 (dd, 1H, *J*=15.3, 8.5 Hz), 5.19 (dd, 1H, *J*=15.3, 8.9 Hz), 4.12 (t, 1H, *J*=5.7 Hz), 3.56–3.46 (m, 3H), 3.38 (td, 1H, *J*=10.8, 4.5 Hz), 2.28–2.17 (m, 4H), 1.04 (d, 3H, *J*=6.6 Hz), 0.95 (s, 3H), 0.90 (d, 3H, *J*=6.8 Hz), 0.86 (s, 3H), 0.83 (d, 3H, *J*=6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 140.6, 127.7, 72.0, 70.6, 70.0, 65.0, 62.2, 57.5, 55.7, 53.1, 52.8, 43.3, 42.8, 42.5, 41.8, 41.5, 38.6, 37.5, 33.0, 32.0, 31.6, 29.1, 22.2, 21.5, 21.4, 18.7, 15.3, 13.8. ESI-MS: 471.4 ($M+Na^+$). HRMS calcd for $C_{28}H_{48}O_4Na^+$: 471.3458; found: 471.3445.

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