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Stereoselective synthesis of Certonardolsterol D_3

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ABSTRACT

The first stereoselective synthesis of Certonardolsterol D_3 was described. Ene reaction and improved allylic oxidation were employed as key steps for efficient construction of the desired 3β,6α,15β-triol steroidal framework. The chiral side chain in Certonardolsterol D_3 was finally introduced by Julia olefination.

1. Introduction

In recent years, the discovery of interesting polyhydroxy steroids, mainly isolated from marine sources, has gained considerable attention.[1] These compounds have shown promising pharmaceutical activities as leading agents for the development of novel therapeutics.[2] Starfish appears to be the richest source of polyhydroxy steroids. Almost 44 polyhydroxysterols were isolated from starfish *Certonardoa semiregularis* collected from Korean waters, which showed remarkably stronger cytotoxicity than those saponins in it.[3] The vast majority of them bears hydroxyl group mainly in positions 3β, 4α (or 4β), 6α (or 6β), 15α (or 15β), and 16α, and hydroxyl methyl or hydroxyl ethyl group in the position of C-24 or C-25 of side chain, for example, Certonardolsterol D_2 (**1**) and Certonardolsterol D_3 (**2**). These highly oxygenated steroids often occur as complex mixtures that are very difficult to separate into individual components with limited amounts. The purpose of biological activity investigation has stimulated the request for a universal methodology for the stereoselective synthesis of the class of polyhydroxy steroids practically. In our previous report, we accomplished the first synthesis of Certonardolsterol D_2 (**1**) from the natural diosgenin (**3**)[4] via the C22-steroid, 23,24-bisnorcholanic lactone **4**, which was derived from sapogenins with peroxyacetic acid in the presence of catalytic concentration of H_2SO_4 and iodine.[5] The side chain was facilely stereoselective installed via Julia olefination with a chiral alkyl sulfone (Fig. 1).

Certonardolsterol D_3 **2**, a member of the novel certonardolsterols, was isolated as colorless needles and was defined as (24*R*) 24-ethyl-5*R*-cholestane-3β,6α,15β,24[2]-tetrol.[3] Its toxicity was briefly studied for its minute amounts in appearance (1.3 mg/9 kg). A small panel of human solid tumor cell lines were selected for the test of the toxicity and the performance of certonadosterol D_3 (ED_{50}=0.68–2.48 μg/mL) was noticeable. In our continuing interest in biological activity studies of marine natural products, we endeavoured to develop efficient methodology for synthesizing this class of sterols. Herein, we reported an efficient method for stereocontrolled synthesis of C22 steroidal aldehyde **6** from common source of C17 steroid dehydroepiandrosterone (**5**), which was subsequently converted into Certonardolsterol D_3 stereoselectively in high yield.

2. Results and discussion

Taking into account the report of an efficient stereocontrolled access to 15- and 16-hydroxy steroids by Riccardis et al.,[6] we designed a novel synthesis pathway of 3β,6α,15β-triol steroidal aldehyde **6** as outlined in Scheme 1. Commercially available dehydroepiandrosterone **5** was first protected with ethylene glycol in 94% yield. 6α-Hydroxyl was formed by hydroboration (BH_3·THF, 0 °C) and oxidation (30% H_2O_2, 0 °C) of B-ring double bond to afford 3β,6α-diol **7** in 75% yield. After releasing the protecting group of the C-17 ketone with concentrated hydrochloride in methanol, the resulted crude 3,6-diol was masked as silyl ether with (*t*-Bu)Me_2SiOTf/2,6-lutidine in dichloromethane to give the C-17 ketone **9** in 79% yield for two steps. The C-17 ketone **9** was then converted to *Z* olefin with trace of its *E* isomer

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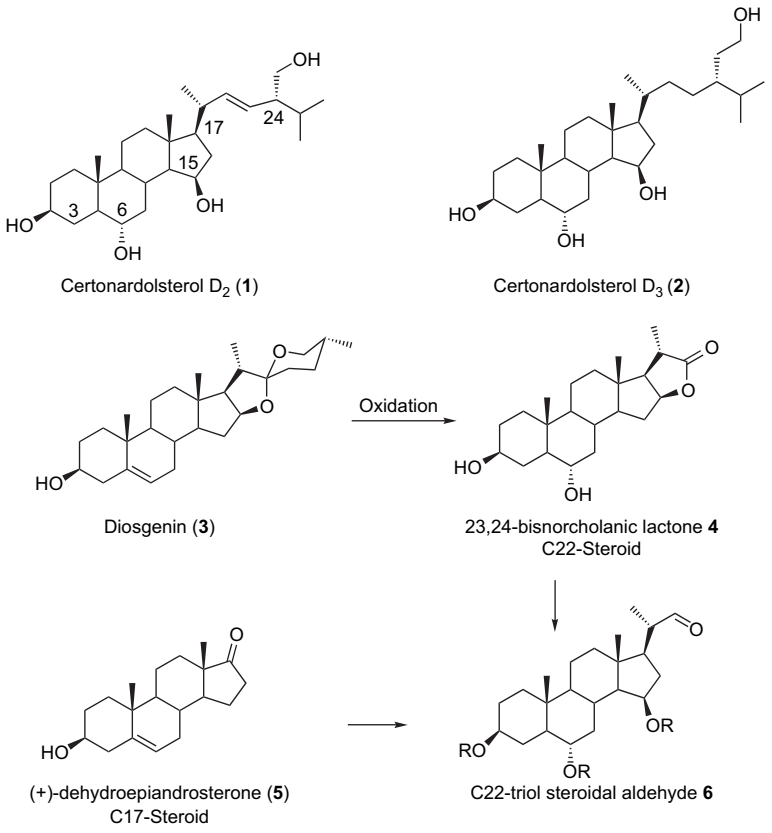


Figure 1. Certonardolsterol D_2, Certonardolsterol D_3 and conversion of steroids.

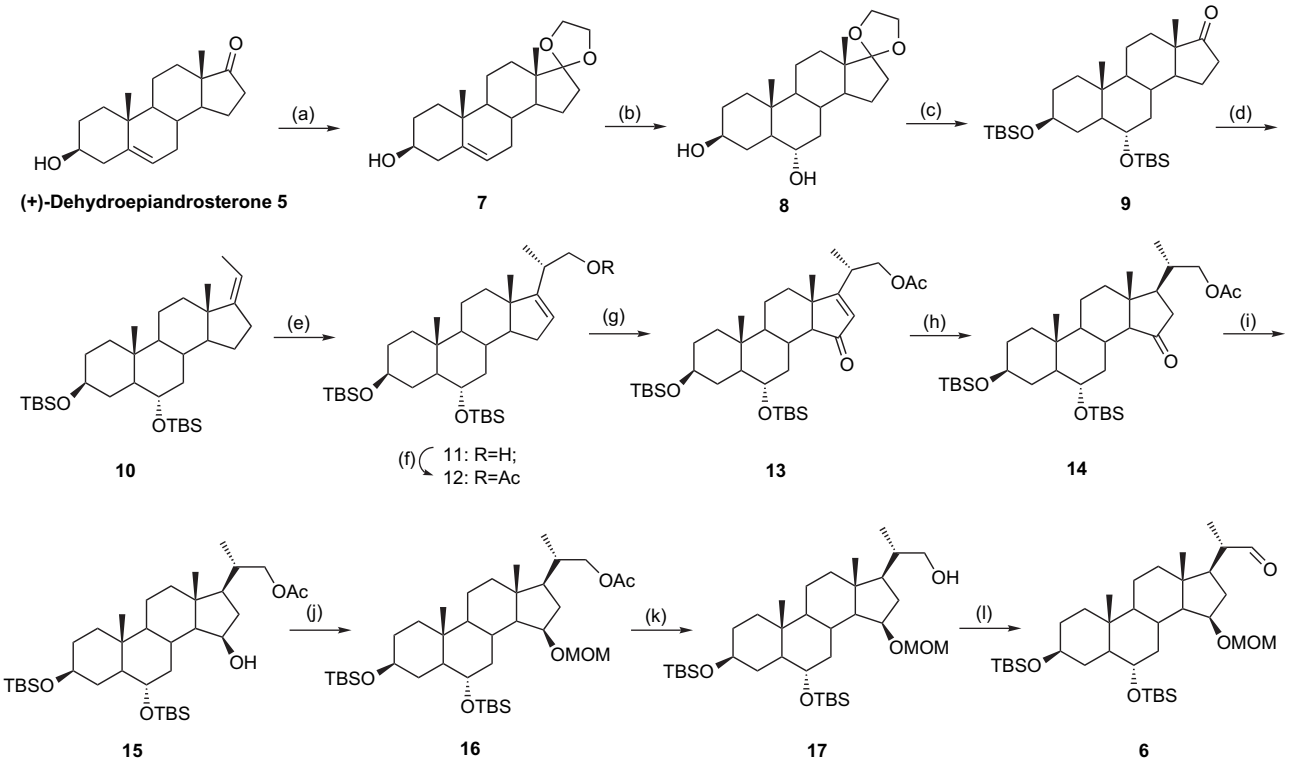
(<5%) by Wittig reaction. C-17 ketone **9** was heated with (ethyl)triphenylphosphonium bromide and *t*-BuOK in dry THF to afford compound **10** in 92% yield. An ene reaction of **10** with paraformaldehyde in the presence of a catalytic amount of borontrifluoride etherate was performed to afford the alcohol **11** stereospecifically in 76% yield, which was subsequently protected as its acetate **12**. By using an improved allylic oxidation,[7] C-15 ketone group in steroidal frame was introduced by oxidation of **12** with *N*-hydroxy phthalimide and $Na_2Cr_2O_7{\cdot}2H_2O$ in acetone at 40 °C to afford α,β-unsaturated ketone **13** in 74% yield. Hydrogenation of **13** over 20% Pd/C and subsequent reduction by $NaBH_4$ afforded the desired 15β-hydroxyl steroid **15** in 94% yield. ^{1}H NMR spectra shows a triplet (J=6.0 Hz) at 4.22 ppm for the 15-hydroxyl C–H in **15**, which implies 15-hydroxyl group has the expected β-configuration.[4,6] After masking 15β hydroxyl with methoxymethyl chloride and hydrolysis of the C-22 acetyl, C17 3β,6α,15β-triol steroidal aldehyde **6** was obtained in 99% yield by Dess–Martin oxidation.

In parallel, a nine-step route was launched to construct the chiral piece of steroidal side chain (Scheme 3). Initially, we tried to introduce the hydroxyl ethyl group by reaction of oxirane with titanium enolate derived from (*R*)-oxazolidinone **18** with $TiCl_4$ in the presence of Hunig's base.[8] The reaction gave fruitless results without the isolation of **19** (Scheme 2). Switching into alkylation of the lithium enolate (LDA, −78 °C) with *tert*-butylbromoacetate afforded (2*R*′,*R*)-**20** in 93% yield. Removal of oxazolidinone auxiliary with LiOH in the presence of 30% H_2O_2 gave (2*R*)-acid ester **21** in 87% yield. The acid moiety of **21** was selectively reduced with $BH_3{\cdot}Me_2S$ in THF at room temperature for 24 h to afford alcohol **22** quantitatively. After protection of the hydroxyl group with (*t*-Bu)Me_2SiOTf/2,6-lutidine, the ester part was converted into alcohol by reduction with DIBAL-H at −78 °C for 1 h to give (*R*)-alcohol **23** in 91% yield for two steps. Subsequently, conversion of the free hydroxyl in **23** into its benzyl ether (BnBr/NaH) and removal of the silyl protection group with hydrogen chloride in methanol gave the (*R*)-alcohol **24** with 85% yield. (*R*)-Alcohol **24** was subjected to a Mitsunobu reaction using 2-mercaptobenzothiazole as nucleophile affording high yield of (2*R*)-butyl sulphide **25**. Oxidation under hydrogen peroxide and ammonium molybdate tetrahydrate at 0 °C provided (*R*)-butyl sulphone **26** in 84% yield.

With the C22 3β,6α,15β-triol steroidal aldehyde **6** steroid frame and C7 (*R*)-butyl sulphone **26** in hand, their assembling to obtain Certonardolsterol D_3 was accomplished by Julia olefination. A Julia olefination between aldehyde **6** and (*R*)-butyl sulphone **26** was performed with the LiHMDS at −78 °C, which provided 22*E*-olefin **27** exclusively in 93% yield (Scheme 4). 22*E*-Olefin **27** contained all structure features of Certonardolsterol D_3. Simultaneous saturation of C-22-*E* double bond and cleavage of the benzyl ether gave sterol **28** in excellent yield when hydrogenation of **27** over $Pd(OH)_2$ in ethanol. Finally, deprotection of the three hydroxyls in the sterol nucleus with 6 M HCl completed the synthesis of Certonardolsterol D_3 in 99% for two steps. The spectroscopic data was in agreement with the published values for natural Certonardolsterol D_3.[3]

3. Conclusion

In summary, an efficient and highly stereoselective convergent synthesis of Certonardolsterol D_3 has been achieved from commercially available (+)-dehydroepiandrosterone **5**. The combination of an ene reaction and improved allylic oxidation was proved to be efficient to construct the C15 functional group in sterol skeleton. The highly selective Julia olefination was used to couple the chiral side chain for steroid.



Scheme 1. Synthesis of 3β,6α,15β-triol C-22 steroidal aldehyde **6**; (a) ethylene glycol, *p*-TsOH, benzene, reflux, 94%; (b) (i) $BH_3 \cdot THF$, THF, 0 °C to rt; (ii) 10 M NaOH, 30% H_2O_2, 0 °C to rt, 74%; (c) (i) HCl/MeOH, reflux; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 94% for two steps; (d) Ph_3PEtBr, *t*-BuOK, THF, reflux, 92%; (e) $BF_3 \cdot Et_2O$, $(HCHO)_n$, CH_2Cl_2, 0 °C, 77%; (f) Ac_2O, cat. DMAP, CH_2Cl_2, rt, 97%; (g) *N*-hydroxy phthalimide, $NaCr_2O_7 \cdot 2H_2O$, acetone, 40 °C, 49% (74% based on recovery of **12**); (h) 10% Pd/C, H_2, EtOAc, rt, 99%; (i) $NaBH_4$, THF/MeOH, 0 °C, 94%; (j) MOMCl, DIPEA, CH_2Cl_2, rt to reflux, 94%; (k) 10% KOH, MeOH, 0 °C to rt, 99%; (l) Dess–Martin periodinane, Py, CH_2Cl_2, 0 °C to rt, 99%.

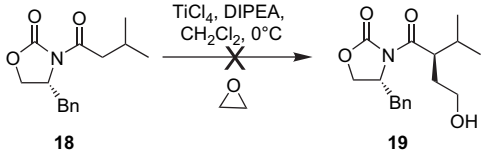
4. Experimental section

4.1. General remarks

^1H 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.

*4.1.1. 17,17-Ethylenedioxy-androst-5-en-3β-ol (**7**)*[9]

To a solution of (+)-dehydroepiandrosterone **5** (5.0 g, 17.3 mmol) and *p*-TsOH·H_2O (132 mg, 0.69 mmol) in benzene (50 mL), ethylene glycol (5.0 mL, 90 mmol) was added dropwise. The mixture was refluxed under a Dean–Stark trap for 5 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ solution (30 mL×3) and brine (25 mL×3). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 3:1) provided **7** (5.4 g, 94%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 5.36–5.34 (m, 1H), 3.95–3.84 (m, 4H), 3.49–3.54 (m, 1H), 1.01 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 121.4, 119.5, 71.6, 65.1, 64.5, 50.5, 49.9, 45.7, 42.2, 37.2, 36.5, 34.1, 32.1, 31.5, 31.2, 30.5, 22.7, 20.4, 19.4, 14.2.



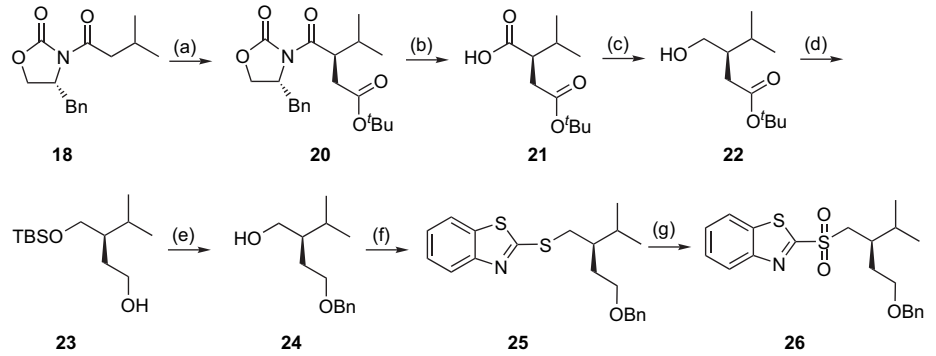
Scheme 2. Synthetic attempt for compound **19**.

*4.1.2. 17,17-Ethylenedioxy-5α-androstan-3β,6α-diol (**8**)*

To a solution of compound **7** (2.3 g, 6.9 mmol) in dry THF (30 mL) under an argon atmosphere at 0 °C, was added BH_3 (21.0 mL, 21.0 mmol, 1 M in THF) slowly. The mixture was allowed to stir for 6 h at room temperature. NaOH (10 N, 5.0 mL, 50.0 mmol) was added over 30 min at 0 °C. Subsequently, 30% hydrogen peroxide (5.0 mL, 44.0 mmol) was added and vigorous stirring continued at room temperature for 2 h. The reaction mixture was poured into ice water and filtered to give the crude product. Purification by column chromatography (CH_2Cl_2/MeOH, 10:1) gave compound **8** (1.8 g, 74%) as a white solid. IR (KBr): 3333, 2934, 1049, 1037 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 3.83–3.74 (m, 4H), 3.44–3.34 (m, 1H), 3.28–3.26 (m, 1H), 2.11–2.07 (m, 1H), 1.91–1.83 (m, 2H), 0.75 (s, 3H), 0.74 (s, 3H), 0.60–0.58 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 120.5, 72.0, 70.0, 66.2, 65.6, 553, 52.9, 51.5, 47.2, 42.0, 38.7, 37.5, 36.0, 35.1, 33.0, 31.9, 31.8, 23.7, 21.7, 14.9, 13.9; ESI-MS: 351.2 ($M+H^+$); HRMS calcd for $C_{21}H_{35}O_4^+$:351.2530; found: 351.2530.

*4.1.3. 3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-5α-andostan-17-one (**9**)*

HCl (20 mL, 36%) was added dropwise to a solution of compound **8** (500 mg, 1.43 mmol) in MeOH (50 mL). The mixture was refluxed for 4 h and cooled to room temperature. The solution was concentrated to give the crude product, which was used for the next step without further purification. To a solution of crude product in CH_2Cl_2 (10 mL), 2,6-lutidine (1.7 mL, 14.7 mmol) and TBSOTf (2.1 mL, 9.2 mmol) were added sequentially. The solution was stirred for 30 min at room temperature and was then quenched by water. The aqueous layer was extracted with CH_2Cl_2



Scheme 3. Synthesis of (*R*)-butyl sulfone **26**; (a) LDA, $BrCH_2CO_2t$-Bu, THF, −78 °C to rt, 93%; (b) LiOH, H_2O_2, THF/H_2O, 0 °C, 87%; (c) $BH_3.Me_2S$, THF, 0 °C to rt, 99%; (d) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 91% for two steps; (e) (i) NaH, BnBr, cat. TBAI, THF, rt to reflux; (ii) 3.3 M HCl, THF/H_2O, rt, 84% for two steps; (f) 2-mercaptobenzothiazole, PPh_3, DIAD, THF, 0 °C, 92%; (h) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH, 0 °C, 83%.

(10 mL×2).The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 20:1) afforded ketone **9** (718 mg, 94%) as a white solid. Mp 115–116 °C. $[\alpha]_D^{20}$ 74.7 (*c* 1.00, $CHCl_3$); IR (KBr): 2956, 1742, 1084, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.51–3.48 (m, 1H), 3.39–3.37 (m, 1H), 2.43 (dd, 1H, *J*=18.6, 9.0 Hz), 0.87 (s, 18H), 0.84 (s, 3H), 0.82 (s, 3H), 0.03 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.0, 72.1, 69.9, 53.9, 51.7, 51.1, 47.8, 40.6, 37.5, 36.3, 35.7, 33.8, 33.1, 31.6, 31.4, 25.88, 25.86, 21.7, 20.3, 18.3, 18.0, 13.8, 13.5, −4.1, −4.7, −4.8; EIMS: 519 (M^+−Me), 477 (M^+−*t*-Bu); HRMS (MALD) calcd for $C_{31}H_{58}O_3Si_2Na^+$: 557.3840; found: 557.3817.

4.1.4. (17Z)-Ethylidene-3β,6α-bis[(tert-butyldimethylsilyl)oxy]-5α-andostane (**10**)

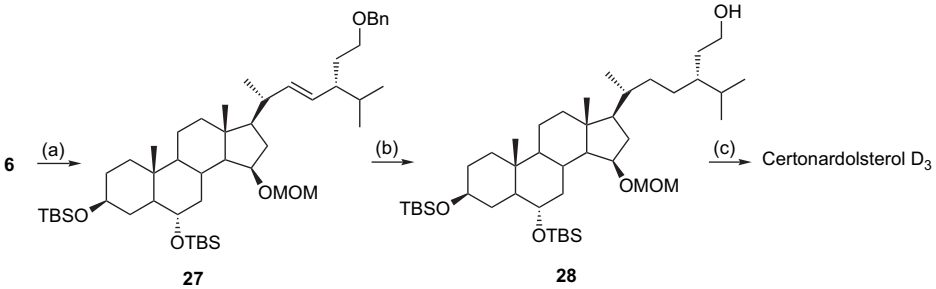
A mixture of ketone **9** (0.71 g, 1.33 mmol), (ethyl)-triphenylphosphonium bromide (1.5 g, 4.0 mmol) and *t*-BuOK (0.42 g, 3.75 mmol) in dry THF (11 mL) was allowed to reflux under argon for 4 h. After being cooled, the mixture was diluted with petroleum ether (20 mL) and filtered. The filtrate was concentrated and purified by flash chromatography (hexane/EtOAc, 100:1) to afford **10** (0.67 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ 37.7 (*c* 0.95, $CHCl_3$); IR (KBr): 2962, 1261, 1088, 1062, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.11 (q, 1H, *J*=7.5 Hz), 3.56–3.46 (m, 1H), 3.38 (dt, 1H, *J*=10.2, 4.5 Hz), 2.37 (dd, 1H, *J*=16.8, 7.2 Hz), 1.89 (td, 1H, *J*=12.6, 3.9 Hz), 1.64 (d, 3H, *J*=6.9 Hz), 0.88 (s, 18H), 0.86 (s, 3H), 0.81 (s, 3H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2, 113.4, 72.3, 70.3, 55.9, 53.8, 51.7, 44.3, 41.8, 37.6, 37.0, 36.3, 33.8, 33.2, 31.7, 31.3, 25.9, 24.3, 21.3, 18.3, 18.1, 16.9, 13.5, 13.1, −4.1, −4.6, −4.7, −4.8; EIMS: 531 (M^+−Me), 489 (M^+−*t*-Bu); HRMS calcd for $C_{33}H_{62}O_2Si_2^+$: 546.4288; found: 546.4286.

4.1.5. 3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-5α-23,24-bisnorchol-16-en-22-ol (**11**)

To a suspension of **10** (100 mg, 0.18 mmol) and paraformaldehyde (0.032 g, 0.9 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of $BF_3\cdot Et_2O$ (23 μL, 0.027 mmol) in CH_2Cl_2 (10 mL) slowly by syringe under argon at 0 °C. The reaction mixture was allowed to stir at the same temperature for 25 min. The reaction was then quenched by ice water, diluted by CH_2Cl_2 (10 mL) and filtered. The filtrate was washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 15:1) afforded alcohol **11** (80 mg, 77%) as a white solid. Mp 60–61 °C; $[\alpha]_D^{20}$ 18.7 (*c* 0.50, $CHCl_3$); IR (KBr): 2931, 1253, 1089, 836, 773, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.42 (s, 1H), 3.58–3.50 (m, 3H), 3.40 (dt, 1H, *J*=10.2, 4.2 Hz), 2.37 (q, 1H, *J*=7.2 Hz), 1.02 (d, 3H, *J*=6.9 Hz), 0.88 (s, 9H), 0.87 (s, 9H), 0.83 (s, 3H), 0.77 (s, 3H), 0.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 122.8, 72.2, 70.2, 66.5, 56.9, 54.4, 52.0, 47.1, 41.7, 37.4, 36.4, 35.3, 34.7, 33.2, 32.9, 31.7, 31.1, 25.9, 21.0, 18.3, 18.1, 16.3, 13.5, −4.0, −4.6, −4.7; EIMS: 561 (M^+−Me), 519 (M^+−*t*-Bu), 489 (M^+−*t*-Bu−2Me); HRMS calcd for $C_{33}H_{61}O_3Si_2^+$: 561.4159; found: 561.4166.

4.1.6. 3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-5α-23,24-bisnorchol-16-en-22-acetate (**12**)

To a solution of alcohol **11** (1.94 g, 3.36 mmol) and DMAP (40 mg, 0.33 mmol) in dry CH_2Cl_2 (110 mL) were added freshly distilled triethylamine (0.97 mL, 6.96 mmol) and Ac_2O (0.65 mL, 7.58 mmol) sequentially by syringe. The solution was stirred for 1.5 h at room temperature and quenched by saturated ammonium chloride (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The combined organic extracts were washed with saturated $NaHCO_3$ (30 mL×2), brine (30 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 10:1) afforded **12** (2.02 g, 97%) as a white solid. Mp 103–104 °C; $[\alpha]_D^{20}$ 34.7 (*c* 1.00, $CHCl_3$). IR (KBr): 2931, 1737, 1228, 1091, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.13–4.08 (m, 1H), 3.95–3.89 (m, 1H), 3.53–3.48 (m, 1H), 3.40 (dt, 1H, *J*=10.2, 4.2 Hz), 2.43 (q, 1H, *J*=6.9 Hz), 2.03 (s, 3H), 1.04 (d, 3H, *J*=7.2 Hz), 0.88 (s, 18H), 0.82 (s, 3H), 0.74 (s, 3H), 0.040 (s, 6H), 0.037 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 156.9, 122.5, 72.3, 70.2, 68.6, 56.6,



Scheme 4. Synthesis of Certonardolsterol D_3; (a) **26**, LiHMDS (1.0 M in hexane), THF, −78 °C to rt, 93%; (b) $Pd(OH)_2$, H_2, EtOH/EtOAc, rt; (c) 6 M HCl, THF/H_2O, rt, 99% for two steps.

54.4, 52.0, 47.2, 41.7, 37.4, 36.4, 34.7, 33.2, 32.9, 31.7, 31.4, 31.1, 25.9, 21.0, 20.9, 18.7, 18.3, 18.1, 16.2, 13.5, −4.1, −4.6, −4.7; EIMS: 561 (M^+-t-Bu), 501 (M^+-2t-Bu); HRMS calcd for $C_{32}H_{57}O_4Si_2^+$: 561.3795; found: 561.3796.

4.1.7. 22-Acetoxy-3β,6α-bis[(tert-butyldimethylsilyl)oxy]-5α-23,24-bisnorchol-16-ene-15-one (**13**)

A mixture of **12** (30 mg, 0.048 mmol), *N*-hydroxy phthalimide (32 mg, 0.20 mmol) and $Na_2Cr_2O_7\cdot 2H_2O$ (30 mg, 0.10 mmol) in freshly distilled acetone (1.5 mL) was stirred at 40 °C for 3 h. Additional *N*-hydroxy phthalimide (32 mg, 0.20 mmol) and $Na_2Cr_2O_7\cdot 2H_2O$ (30 mg, 0.10 mmol) were added and the reaction mixture was allowed to keep overnight at the same temperature. Saturated sodium sulfite (2 mL) was added to remove the oxidant. After the reaction mixture was filtered, the filtrate was extracted with EtOAc (15 mL×2). The combined organic extracts were washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 8:1) afforded **13** (15 mg, 74%, 10 mg of **12** was recovered) as a light yellow oil. $[\alpha]_D^{20}$ 22.7 (*c* 1.60, $CHCl_3$); IR (KBr): 2930, 1743, 1712, 1471, 1097, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 (s, 1H), 4.15–4.04 (m, 2H), 3.53–3.49 (m, 1H), 3.46–3.42 (m, 1H), 2.97–2.93 (m, 1H), 2.79 (q, 1H, *J*=7.2 Hz), 0.99 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 3H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.7, 183.3, 170.8, 125.6, 72.0, 69.7, 67.0, 63.3, 54.3, 51.9, 46.9, 39.8, 37.3, 36.3, 33.0, 32.3, 32.2, 31.6, 30.9, 25.92, 25.88, 23.4, 20.8, 18.3, 18.1, 17.8, 13.5, −4.0, −4.68. −4.75, −4.8; ESI-MS: 575 (M^+-t-Bu), 515 (M^+−4Me); HRMS calcd for $C_{32}H_{55}O_5Si_2^+$: 575.3588; found: 575.3583.

4.1.8. 22-Acetoxy-3β,6α-bis[(tert-butyldimethylsilyl)oxy]-5α-23,24-bisnorcholan-15-one (**14**)

Ketone **13** (64 mg, 0.1 mmol) in EtOAc (2.5 mL) was hydrogenated over 10 wt % Pd/C (8 mg) for 2 days. After the reaction mixture was diluted by EtOAc (10 mL), the catalyst was removed by filtration through Celite. The filtrate was concentrated. Flash chromatography (hexane/EtOAc, 8:1) afforded **14** (64 mg, 99%) as a white solid. Mp 72–73 °C; $[\alpha]_D^{20}$ 27.9 (*c* 1.00, $CHCl_3$); IR (KBr): 2955, 1743, 1251, 1082, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.01 (dd, 1H, *J*=10.8, 3.3 Hz), 3.81 (dd, 1H, *J*=10.8, 6.6 Hz), 3.53–3.46 (m, 1H), 3.39 (dt, 1H, *J*=9.6, 4.2 Hz), 2.92–2.88 (m, 1H), 2.42 (dd, 1H, *J*=18.3, 8.4 Hz), 2.10–2.08 (m, 2H), 2.05 (s, 3H), 1.08 (d, 3H, *J*=6.6 Hz), 0.873 (s, 9H), 0.866 (s, 9H), 0.79 (s, 3H), 0.74 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.44, 171.2, 72.1, 69.7, 68.9, 65.0, 53.3, 51.7, 48.1, 42.2, 41.1, 40.1, 39.5, 37.5, 36.2, 35.3, 33.0, 31.6, 30.5, 25.9, 20.9, 20.6, 18.3, 18.1, 17.5, 13.4, 12.9, −4.1, −4.67, −4.72, −4.9; ESI-MS: 635.5 ($M+H^+$); HRMS calcd for $C_{36}H_{66}O_5Si_2Na^+$: 657.4359; found: 657.4341.

4.1.9. 22-Acetoxy-3β,6α-bis[(tert-butyldimethylsilyl)oxy]-5α-23,24-bisnorcholan-15β-ol (**15**)

To a solution of **14** (19 mg, 0.03 mmol) in THF (3 mL) and MeOH (1 mL) was added $NaBH_4$ (6 mg, 0.15 mmol) at 0 °C. The mixture was allowed to stir at the same temperature for 30 min and quenched by water. The aqueous layer was extracted with CH_2Cl_2 (5 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, 9:1) afforded **15** (18 mg, 94%) as a white solid. Mp 114–115 °C; $[\alpha]_D^{20}$ 4.9 (*c* 0.9, $CHCl_3$); IR (KBr): 2930, 1730, 1259, 1089, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.22 (t, 1H, *J*=6.0 Hz), 4.05 (dd, 1H, *J*=10.5, 3.0 Hz), 3.78 (dd, 1H, *J*=10.5, 7.2 Hz), 3.52–3.49 (m, 1H),3.42 (dt, 1H, *J*=10.2, 4.5 Hz), 2.39–2.34 (m, 1H), 2.14–2.08 (m, 2H), 2.05 (s, 3H), 1.00 (d, 3H, *J*=6.3 Hz), 0.95 (s, 3H), 0.87 (s, 18H), 0.83 (s, 3H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 76.6, 72.2, 70.2, 70.0, 69.3, 60.2, 54.1, 53.0, 51.9, 42.4, 41.0, 40.7, 37.6, 36.3, 35.4, 33.1, 31.7, 30.2, 25.9, 25.8, 21.0, 18.3, 18.0, 17.2, 14.6, 13.4, −4.1, −4.6, −4.7, −4.8; ESI-MS: 659.2 ($M+Na^+$); HRMS calcd for $C_{36}H_{68}O_5Si_2Na^+$: 659.4504; found: 659.4498.

4.1.10. 22-Acetoxy-3β,6α-bis[(tert-butyldimethylsilyl)oxy]-15β-methoxymethyl-5α-23,24-bisnorcholane (**16**)

To a solution of **15** (50 mg, 0.08 mmol) and *N*,*N*-diisopropylethylamine (0.15 mL, 0.86 mmol) in freshly distilled CH_2Cl_2 (7 mL), MOMCl (45 μL) was added slowly by syringe. The solution was allowed to reflux overnight. After being cooled to room temperature, the reaction was quenched by water. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The combined organic extracts were washed with 0.1 M HCl (5 mL×2), saturated $NaHCO_3$ (8 mL×2) and brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 20:1) afforded **16** (50 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ 16.2 (*c* 4.2, $CHCl_3$); IR (KBr): 2856, 1743, 1249, 1083, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.61, 4.53 (AB, 2H, J_{AB}=6.3 Hz), 4.04 (dd, 1H, *J*=10.8, 3.3 Hz), 3.87 (t, 1H, *J*=6.0 Hz), 3.77 (dd, 1H, *J*=10.5, 7.5 Hz), 3.51–3.47 (m, 1H), 3.42–3.38 (m, 1H), 3.34 (s, 3H), 2.31–2.27 (m, 1H), 2.03 (s, 3H), 1.00 (d, 3H, *J*=6.6 Hz), 0.89 (s, 3H), 0.86 (s, 18H), 0.82 (s, 3H), 0.02 (s, 6H), 0.01 (s, 3H), −0.004 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 97.5, 78.0, 72.2, 70.1, 69.3, 60.1, 55.9, 54.1, 52.9, 51.8, 42.6, 41.0, 40.7, 38.4, 37.6, 36.3, 35.4, 33.1, 31.7, 30.4, 25.89, 25.88, 20.94, 20.92, 18.3, 18.1, 17.2, 14.2, 13.5, −4.2, −4.66, −4.75, −4.8; ESI-MS: 703.3 ($M+Na^+$); HRMS calcd for $C_{38}H_{72}O_6Si_2Na^+$: 703.4752; found: 703.4760.

4.1.11. 3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-15β-methoxymethyl-5α-23,24-bisnorcholan-22-ol (**17**)

Compound **16** (84 mg, 0.12 mmol) in MeOH (13 mL) was treated with KOH solution (4.8 mL, 10 wt % in MeOH) under ice-salt bath. The reaction mixture was warmed to room temperature and stirred for 1 h. The solution was diluted with EtOAc, acidified with 0.3 M HCl (3 mL×2), washed with saturated $NaHCO_3$ (5 mL×2) and brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 10:1 to 4:1) afforded **17** (78 mg, 99%) as a white solid. Mp 123–124 °C; $[\alpha]_D^{20}$ 12.5 (*c* 2.85, $CHCl_3$); IR (KBr): 2932, 1251, 1093, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.62, 4.54 (AB, 2H, J_{AB}=6.3 Hz), 3.87 (t, 1H, *J*=6.0 Hz), 3.64–3.61 (m, 1H), 3.53–3.46 (m, 1H), 3.43–3.39 (m, 2H), 3.35 (s, 3H), 2.36–2.26 (m, 1H), 1.03 (d, 3H, *J*=5.7 Hz), 0.90 (s, 3H), 0.87 (s, 18H), 0.82 (s, 3H), 0.03 (s, 6H), 0.01 (s, 3H), −0.001 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.6, 78.3, 72.3, 70.1, 67.7, 60.2, 55.9, 54.2, 52.6, 51.9, 42.5, 41.0, 40.7, 38.5, 38.4, 37.6, 36.3, 35.4, 33.1, 31.7, 30.4, 25.9, 20.9, 18.3, 18.1, 16.7, 14.2, 13.5, −4.2, −4.65, −4.75, −4.8; ESI-MS: 661.2 ($M+Na^+$); HRMS calcd for $C_{36}H_{70}O_5Si_2Na^+$: 661.4663; found: 661.4654.

4.1.12. 3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-15β-methoxymethyl-5α-23,24-bisnorcholan-22-al (**6**)

Preparation of pyridine-buffered Dess–Martin periodinane stock solution: to a suspension of Dess–Martin periodinane (52 mg, 0.12 mmol) in freshly distilled CH_2Cl_2 (2 mL) under argon, pyridine (60 μL, 0.5 mmol) was added at 0 °C. The clear solution was used within 20 min.

To a solution of alcohol **17** (20 mg, 0.03 mmol) in freshly distilled CH_2Cl_2 (1.5 mL) under argon, the freshly prepared pyridine-buffered Dess–Martin periodinane (2 mL, 0.12 mmol) was added by syringe under ice bath. The solution was warmed to room temperature and stirred for 1 h. The reaction was quenched by 1:1 saturated $NaHCO_3$/sodium bisulfite (5 mL) and stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL×2) and brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/

EtOAc, 10:1) afforded aldehyde **6** (20 mg, 99%) as a white solid. Mp 104–105 °C; $[\alpha]_D^{20}$ 6.4 (*c* 2.75, $CHCl_3$); IR (KBr): 2938, 1732, 1259, 1095, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 9.56 (d, 1H, *J*=3.3 Hz), 4.61, 4.53 (AB, 2H, J_{AB}=6.6 Hz), 3.92 (t, 1H, *J*=6.0 Hz), 3.54–3.47 (m, 1H), 3.44–3.39 (m, 1H), 3.34 (s, 3H), 1.12 (d, 3H, *J*=7.2 Hz), 0.93 (s, 3H), 0.87 (s, 18H), 0.83 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.002 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 204.6, 97.5, 78.1, 72.2, 70.0, 59.7, 56.0, 54.2, 51.8, 51.1, 49.3, 43.0, 40.9, 40.6, 37.8, 37.6, 36.4, 33.1, 31.7, 30.4, 25.91, 25.89, 20.9, 18.3, 18.1, 14.5, 13.5, 13.4, −4.2, −4.6, −4.7, −4.8; ESI-MS: 659.2 ($M+Na^+$); HRMS calcd for $C_{36}H_{68}O_5Si_2Na^+$: 659.4496; found: 659.4498.

4.1.13. (4R)-3-[(2R)-4-(tert-Butoxy)-2-(1-methylethyl)-4-oxobutanoyl]-4-(phenylmethyl)-1,3-oxazolidine-2-one (**20**)

To a solution of **18** (3.0 g, 11.5 mmol) in freshly distilled THF (60 mL) were added LDA (7.5 mL, 15 mmol, 2 M in THF) and *tert*-butylbromoacetate (8.3 mL, 53.0 mmol) sequentially by syringe at −78 °C under argon. The solution was warmed to room temperature and stirred for 12 h. The reaction was quenched by saturated ammonium chloride (50 mL). The aqueous layer was extracted with EtOAc (30 mL×2). The combined organic extracts were washed with 1 M HCl (10 mL×2), saturated $NaHCO_3$ (15 mL×2), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 40:1 to 20:1) afforded **20** (4.02 g, 93%) as a white solid. Mp 135–136 °C; $[\alpha]_D^{20}$ −52.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.26 (m, 5H), 4.67–4.65 (m, 1H), 4.18–4.14 (m, 3H), 3.35 (dd, 1H, *J*=13.5, 3.0 Hz), 2.88–2.70 (m, 2H), 2.45 (dd, 1H, *J*=16.5, 3.6 Hz), 1.99 (q, 1H, *J*=6.6 Hz), 1.42 (s, 9H), 1.01 (d, 3H, *J*=6.6 Hz), 0.91 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 171.8, 153.1, 135.8, 129.5, 128.8, 127.1, 80.6, 65.7, 55.6, 44.3, 37.3, 33.4, 29.7, 28.0, 20.7, 18.3; ESI-MS: 3981.1 ($M+Na^+$); HRMS calcd for $C_{21}H_{29}NO_5Na^+$: 398.1937; found: 398.1938.

4.1.14. (R)-4-(tert-Butoxy)-2-(1-methylethyl)-4-oxobutanoic acid (**21**)[8a]

To a solution of **20** (200 mg, 0.53 mmol) in THF (8.0 mL) and H_2O (2.7 mL) was added 30% H_2O_2 (0.26 mL, 2.3 mmol) dropwise under ice-salt bath. $LiOH·H_2O$ (36 mg, 0.86 mmol) was added in three portions and the hydrolysis was allowed to proceed for 3 h at 0 °C. The reaction was quenched by saturated sodium sulphite (5 mL). After stirring for 10 min, the solution was extracted with Et_2O. The aqueous layer was acidified by 1 M HCl to pH=2–3 and extracted with CH_2Cl_2 (15 mL×3). The combined CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 1:1) afforded chiral acid **21** (100 mg, 87%) as a colorless liquid. $[\alpha]_D^{20}$ −7.8 (*c* 4.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 11.33 (br, 1H), 2.71–2.65 (m, 1H), 2.63–2.54 (m, 1H), 2.32 (dd, 1H, *J*=15.9, 3.3 Hz), 2.02–1.96 (m, 1H), 1.40 (s, 9H), 0.95 (d, 3H, *J*=7.2 Hz), 0.92 (d, 3H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 171.5, 80.9, 47.5, 33.9, 29.8, 27.9, 20.1, 19.4.

4.1.15. (R)-tert-Butyl-3-hydroxymethyl-4-methyl-pentanoate (**22**)

A solution of acid **21** (85 mg, 0.39 mmol) in freshly distilled THF, BH_3–Me_2S complex (45 μL, 0.45 mmol) was added by syringe under ice-salt bath. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by water (0.3 mL) with caution at 0 °C. Solid K_2CO_3 (55 mg) was added and the mixture was stirred for 2 min. The aqueous layer was extracted with Et_2O (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, 10:1) afforded **22** (80 mg, 99%) as a colorless liquid. $[\alpha]_D^{20}$ 7.7 (*c* 0.9, $CHCl_3$); IR (KBr): 2964, 1731, 1396, 1155, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (dd, 1H, *J*=11.1, 4.5 Hz), 3.51 (dd, 1H, *J*=10.2, 7.2 Hz), 2.54 (br, 1H), 2.26 (m, 2H), 1.83–1.77 (m, 1H), 1.75–1.71 (m, 1H), 1.42 (s, 9H), 0.88 (d, 3H, *J*=6.6 Hz), 0.86 (d, 3H, *J*=10.2, 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 80.6, 64.3, 43.6, 35.5, 28.5, 28.0, 19.9, 19.2; ESI-MS: 225.2 ($M+Na^+$); HRMS calcd for $C_{11}H_{22}O_3Na^+$: 225.1465; found: 225.1461.

4.1.16. (R)-3-[(tert-Butyldimethylsilyloxy)methyl]-4-methyl-pentan-1-ol (**23**)

To a solution of **22** (275 mg, 1.36 mmol) in dry CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.87 mL, 7.5 mmol) and TBSOTf (0.94 mL, 4.1 mmol) at 0 °C. The solution was then warmed to room temperature and stirred for further 30 min. The reaction was quenched by water and excess 2,6-lutidine was removed by 1 N HCl (1.0 mL). The aqueous layer was extracted with Et_2O (10 mL×3). The combined organic extracts were washed with brine (15 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was used for the next step without further purification.

To a solution of crude product in dry CH_2Cl_2 (8 mL) was added DIBAL-H (8.2 mL, 8.2 mmol, 1 M in toluene) at −78 °C under argon. The reaction was stirred for 1 h at the same temperature. The reaction was quenched by saturated potassium sodium tartrate (2 mL). The aqueous layer was extracted with Et_2O (15 mL×3). The combined organic extracts were washed with brine (15 mL×2), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 15:1 to 10:1) afforded alcohol **23** (390 mg, 91%) as a colorless liquid. $[\alpha]_D^{20}$ −7.2 (*c* 1.70, $CHCl_3$); IR (KBr): 2958, 1472, 1257, 1089, 1055, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69–3.61 (m, 2H), 3.52 (dd, 2H, *J*=9.9, 8.1 Hz), 3.32 (br, 1H), 1.73–1.66 (m, 2H), 1.54–1.51 (m, 1H), 1.48–1.44 (m, 1H), 0.90 (s, 9H), 0.87 (d, 3H, *J*=6.9 Hz), 0.85 (d, 3H, *J*=6.6 Hz), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.9, 61.9, 45.2, 33.3, 29.7, 25.8, 19.9, 19.2, 18.2, 0.99, −5.51, −5.55; ESI-MS: 247.3 ($M+H^+$); HRMS calcd for $C_{13}H_{30}O_2SiNa^+$: 269.1905; found: 269.1907.

4.1.17. (R)-2-[2-(Benzyloxy)ethyl]-3-methylbutan-1-ol (**24**)

To a mixture of **23** (56 mg, 0.23 mmol) and TBAI (21 mg, 0.06 mmol) in freshly distilled THF (2 mL) was added NaH (60% in mineral oil, 46 mg, 1.15 mmol) and the suspension was allowed to stir for 15 min. BnBr (70 μL, 0.58 mmol) was added dropwise and the mixture was allowed to reflux overnight. The reaction was quenched by water. 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. The crude product was used for the next step without further purification.

HCl (3.3 M, 1 mL) was added to the solution of crude product in THF (2 mL) and the mixture was allowed to stir at room temperature for 1 h. The solution was diluted with water (5 mL) and extracted with EtOAc (10 mL×3). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL×3), brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 20:1 to 10:1) afforded alcohol **24** (43 mg, 84%) as a colorless liquid. $[\alpha]_D^{20}$ −6.7 (*c* 0.9, $CHCl_3$); IR (KBr): 2960, 1455, 1261, 1094, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 4.53 (s, 2H), 3.64–3.55 (m, 2H), 3.53–3.48 (m, 2H), 3.05 (br, 1H), 1.80–1.68 (m, 2H), 1.67–1.62 (m, 1H), 1.45–1.42 (m, 1H), 0.89 (d, 3H, *J*=7.2 Hz), 0.87 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 128.5, 127.8, 73.2, 69.7, 64.7, 45.6, 29.7, 29.4, 20.0, 19.4; ESI-MS: 245.2 ($M+Na^+$); HRMS calcd for $C_{14}H_{22}O_2Na^+$: 245.1515; found: 245.1512.

4.1.18. (R)-2-[4-(Benzyloxy)-2-isopropylbutylthio]benzo[d]thiazole (**25**)

To a mixture of **24** (60 mg, 0.27 mmol), 2-mercaptobenzothiazole (68 mg, 0.40 mmol) and PPh_3 (106 mg, 0.40 mmol) in freshly distilled THF (4 mL) was added DIAD (80 μL, 0.40 mmol) dropwise at 0 °C under argon. After being stirred for 3 h at the same temperature, the reaction was quenched by water. The aqueous layer

was extracted with EtOAc (15 mL×3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 60:1) afforded thioether **25** (92 mg, 92%) as a light yellow oil. $[\alpha]_D^{20}$ −0.3 (*c* 2.40, $CHCl_3$); IR (KBr): 2959, 1457, 1428, 1101, 996, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, 1H, *J*=7.8 Hz), 7.75 (d, 1H, *J*=7.8 Hz), 7.41 (t, 1H, *J*=7.5 Hz), 7.35–7.26 (m, 6H), 4.53 (s, 2H), 3.61 (q, 2H, *J*=5.7 Hz), 3.41 (t, 2H, *J*=5.1 Hz), 1.92–1.86 (m, 1H), 1.85–1.77 (m, 2H), 1.77–1.68 (m, 1H), 0.96 (d, 6H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 153.2, 138.3, 135.1, 128.3, 127.6, 127.5, 125.9, 124.0, 121.3, 120.9, 72.9, 68.8, 40.9, 35.7, 29.9, 29.7, 19.5, 18.6; ESI-MS: 372.2 ($M+H^+$); HRMS calcd for $C_{21}H_{26}NOS_2^+$: 372.1459; found: 372.1450.

4.1.19. *(R)-2-(4-(Benzyloxy)-2-isopropylbutylsulfonyl) benzo[d]thiazole (**26**)*

A solution of **25** (44 mg, 0.12 mmol) in EtOH (1.5 mL) was oxidized with molybdate tetrahydrate (297 mg, 0.24 mmol) and 30% H_2O_2 (0.41 mL, 3.6 mmol) at 0 °C for 2 h. The mixture was extracted with EtOAc (10 mL×3). The combined organic extracts were washed with brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 15:1–5:1) afforded sulfone **26** (40 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ −1.3 (*c* 1.55, $CHCl_3$); IR (KBr): 2962, 1473, 1328, 1146, 1098, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J*=8.4 Hz), 7.98 (d, 1H, *J*=8.4 Hz), 7.65–7.55 (m, 2H), 7.31–7.22 (m, 5H), 4.40 (s, 2H), 3.55–3.50 (m, 4H), 2.29–2.24 (m, 1H), 2.06–2.00 (m, 1H), 1.77 (q, 2H, *J*=6.6 Hz), 0.87 (d, 3H, *J*=6.9 Hz), 0.85 (d, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 152.6, 138.2, 136.7, 128.2, 127.9, 127.6, 127.5, 127.4, 125.3, 122.3, 72.8, 68.3, 56.1, 36.3, 30.0, 29.5, 18.5, 18.2; ESI-MS: 426.2 ($M+Na^+$); HRMS calcd for $C_{21}H_{26}NO_3S_2^+$: 404.1362; found: 404.1349.

4.1.20. *(E)-(24R)-3β,6α-Bis[(tert-butyldimethylsilyl)oxy]-15β-methoxymethyl-24-ethyl-24² benzyloxy-5α-cholest-22-ene (**27**)*

To a mixture of aldehyde **6** (50 mg, 0.078 mmol) and sulfone **26** (14 mg, 0.15 mmol) in freshly distilled THF (3.6 mL) was added LiHMDS (0.31 mL, 0.31 mmol, 1.0 M in hexane) at −78 °C under argon. After being stirred for 1 h at −78 °C, the solution was warmed to room temperature and stirred overnight. The reaction was quenched by water. The aqueous layer was extracted with EtOAc (15 mL×3). The combined organic extracts were washed with brine (10 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 40:1 to 20:1) afforded **27** (60 mg, 93%) as a yellow solid. $[\alpha]_D^{20}$ 16.6 (*c* 2.0, $CHCl_3$); IR (KBr): 2962, 1261, 1093, 1046, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.28–7.35 (m, 5H), 5.17 (dd, 1H, *J*=15.3, 8.1 Hz), 5.06 (dd, 1H, *J*=15.3, 8.4 Hz), 4.62, 4.53 (AB, 2H, J_{AB}=6.3 Hz), 4.45 (d, 2H, *J*=12.0 Hz), 3.82 (t, 1H, *J*=6.0 Hz), 3.52–3.47 (m, 2H), 3.46–3.38 (m, 2H), 3.35 (s, 3H), 1.00 (d, 3H, *J*=6.3 Hz), 0.88 (s, 18H), 0.843 (d, 3H, *J*=7.8 Hz), 0.835 (s, 3H), 0.81 (d, 3H, *J*=6.9 Hz), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.3, 129.0, 128.3, 127.7, 127.4, 97.3, 78.0, 72.9, 72.3, 70.2, 69.2, 60.5, 56.0, 55.8, 54.3, 51.9, 45.6, 42.3, 41.1, 40.8, 40.2, 39.7, 37.6, 36.4, 33.2, 32.6, 32.2, 31.7, 30.4, 29.7, 25.9, 21.0, 20.7, 18.8, 18.3, 18.1, 14.4, 13.5, −4.1, −4.6, −4.7, −4.8; ESI-MS: 842.5 ($M+NH_4^+$); HRMS calcd for $C_{50}H_{88}Si_2O_3Na^+$: 847.6079; found: 847.6063.

4.1.21. *(24R)-24-Ethyl-5a-cholestane-3β,6α,15β,24²-terol (**2**) (Certonardolsterol D₃)*

A solution of **27** (10 mg, 0.012 mmol) in EtOAc (1 mL) and absolute EtOH (2 mL) was hydrogenated over 20 wt% $Pd(OH)_2$ on carbon (4 mg) for 2 days. The suspension was filtered through Celite. The resulted clear solution was concentrated in vacuo and gave the crude saturated steroid. The crude product **28** was used for the next step without further purification.

To a solution of crude product **28** in THF (2 mL) and H_2O (1 mL) was added 6 M HCl (1 mL). The reaction was monitored by TLC. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (hexane/EtOAc, 10:1 to 3:1) afforded Certonardolsterol D_3 **2** (6 mg, 99%) as a yellow solid. Mp 115–116 °C; $[\alpha]_D^{20}$ 9.8 (*c* 0.2, $CHCl_3$); IR (KBr): 2964, 1262, 1097, 1021, 801 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): 4.16 (t, 1H, *J*=5.8 Hz), 3.61–3.50 (m, 2H), 3.49–3.45 (m, 1H), 3.38 (td, 1H, *J*=10.8, 4.7 Hz), 2.38 (dt, 1H, *J*=14.5, 8.4 Hz), 2.27 (dt, 1H, *J*=12.0, 3.9 Hz), 0.94 (d, 3H, *J*=7.2 Hz), 0.93 (s, 3H), 0.87 (d, 3H, *J*=6.9 Hz), 0.86 (s, 3H), 0.84 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 72.0, 70.6, 70.0, 62.2, 62.0, 57.7, 55.7, 53.2, 43.4, 42.7, 42.3, 41.9, 41.8, 38.6, 37.5, 37.2, 34.9, 34.6, 33.1, 32.0, 31.6, 30.5, 28.3, 22.2, 20.0, 19.4, 18.9, 15.2, 13.8; ESI-MS: 487.4 ($M+Na^+$); HRMS calcd for $C_{29}H_{52}O_4Na^+$: 487.3764; found: 487.3758.

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