Synthesis of 3-Epi-6,7-dideoxyxestobergsterol A

Yuko KAJI, Takeshi KOAMI, Atsuko NAKAMURA, and Yoshinori FUJIMOTO*

Department of Chemistry and Materials Science, Tokyo Institute of Technology, Meguro, Tokyo 152–8551, Japan.
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3-Epi-6,7-dideoxyxestobergsterol A (2), an analogue of xestobergsterol A, has been synthesized from dehydroepiandrosterone (3) in 15 steps. The key synthetic intermediate, 15β,16α-dioxypregn-17(20)*E*-ene derivative 8, was prepared from the corresponding 15β,16β-epoxide 6 by treating with acetic acid and titanium tetraisopropoxide. The 23-oxo side chain was constructed stereoselectively by orthoester Claisen rearrangement of 8 followed by introduction of an isobutyl group. Basic treatment of the 15,23-diketone 12 followed by deprotection gave the title compound 2.

Key words xestobergsterol A; steroid; synthesis; epoxide; orthoester Claisen rearrangement

Xestobergsterols A (**1a**) and B (**1b**) were isolated in 1992 from the sponge *Xestospongia bergquistia*, as unique steroids having a *cis* C/D ring junction and an additional carbocyclic E-ring.[1] Subsequently, xestobergsterol C (**1c**) was isolated, and the full structures of these xestobergsterols were established (Fig. 1).[2] Xestobergsterols are strong inhibitors of the release of histamine from rat mast cells induced by anti-immunogloblin E (anti-IgE).[1] It has been reported that the mechanism of action of xestobergsterol A is through strong inhibition of phosphatidylinositol phospholipase C.[3] Several structurally related steroidal compounds, but devoid of the E-ring, *i.e.*, contignasterol, have been isolated from marine sources.[4] Synthetic approaches toward xestobergsterol A have been reported by Krafft's[5] and Jung's[6] groups, and recently the first synthesis of **1a** has been completed by the latter group using Breslow's remote functionalization for the introduction of C-15 functionality.[7] We report herein our approach to the 15-oxo functionalization and the side chain construction starting from dehydroepiandrosterone (**3**) which led to the synthesis of 3-epi-6,7-dideoxyxestobergsterol A (**2**), an analogue of xestobergsterol. The route described herein can be applied to the synthesis of xestobergsterols by employing a 17-oxoandrostane derivative having the requisite hydroxy groups in the A,B-ring.

Our retrosynthetic analysis is outlined in Chart 1. Since we decided to use commercially available dehydroepiandrosterone (**3**) as a starting material for the synthesis of all xestobergsterols, the inversion of 14α-H to 14β-H is required at a certain stage of the synthesis. Based on a series of molecular mechanics (MM2) calculations on various candidates, this inversion appeared possible either at a very early stage, *i.e.*, a 15-en-17-one compound or at the last stage, *i.e.*, an E-ring containing compound.[8] The C-14 epimerization was indeed embodied by Jung's group, on the basis of a similar consideration of the stability of E-ring containing compounds.[6] They demonstrated that a basic treatment of a 14α-H-15,23-dioxo compound effected epimerization–aldol condensation to yield a cyclized product having the thermodynamically favorable and correct configurations at C-14, C-16 and C-23. Thus, a 15,23-diketone **A** was confidently chosen as a precursor of **2**. Intentional addition of Δ^{16} to the structure **A** gave a synthetic precursor, structure **B**. Hydrogenation of the steroidal Δ^{16} is known to occur from the α-face to yield the requisite 17β-orientation of the side chain.[9—12] The 16-ene **B** was expected to be available from a 15-oxygenated allylic alcohol (16-hydroxy-17(20)-ene) **C** through a 3,3-sigmatropic reaction, since such an alcohol without 15-oxygen function, was reported to undergo Carroll[11] rearrangement to the product with the correct C-20 configuration. It is known that the stereochemistries, 16α-alcohol and *E* configuration of $\Delta^{17(20)}$, are essential to obtain the rearranged product **B** with the correct C-20 configuration. It is clear from the foregoing analysis that a simple preparation of the key intermediate **C** is crucial for the success of this retrosynthesis. Fortunately, the corresponding epoxide **D**, a possible precursor of **C**, is known and its synthesis from **3** is well documented.[9,10,12] It should be noted the 15-oxy function originates from the epoxide oxygen.

The synthesis of **2** was carried out according to Chart 2. Dehydroepiandrosterone was protected as methoxymethyl ether **4** and the resulting ether was converted to the conjugated enone **5** in a two-step sequence *via* the enol silyl ether by the Saegusa method.[13] Epoxidation of the enone with *tert*-butyl hydroperoxide (TBHP) and benzyltrimethylammonium hydroxide (Triton-B) afforded, as reported previously, the 15β,16β-epoxide stereoselectively.[10] Wittig olefination of the epoxide using ethyl triphenylphosphonium iodide and *n*-BuLi gave a *ca*. 9 : 1 mixture of $\Delta^{17(20)}$-olefin favoring the *E*-isomer as reported previously.[5c] Change of the base from *n*-BuLi to potassium hexamethyldisilazide (KHMDS) gave $\Delta^{17(20)E}$-olefin **6** free of the *Z*-isomer. We attempted to open the epoxide ring by attack of a hydroxyl or acetoxy group to obtain a 15,16-dioxy derivative. Although acidic reaction conditions afforded more than several products, treatment of **6** with CsOAc in hexamethylphosphoric triamide (HMPA)[14] afforded a mixture of the desired 15β-hydroxy-16α-acetoxy product **7** and its C-16 epimer (*ca*. 40%). A slightly better

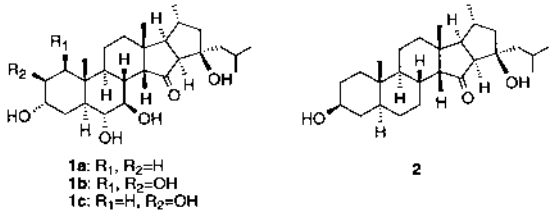


Fig. 1. Structures of Xestobergsterols (**1a—c**) and 3-Epi-6,7-dideoxyxestobergsterol A (**2**)

* To whom correspondence should be addressed. e-mail: fujimoto@cms.titech.ac.jp
Dedicated to the memory of Dr. Kyosuke Tsuda.

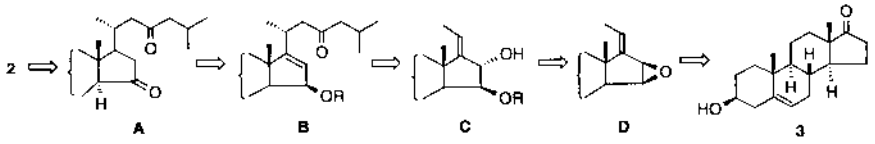
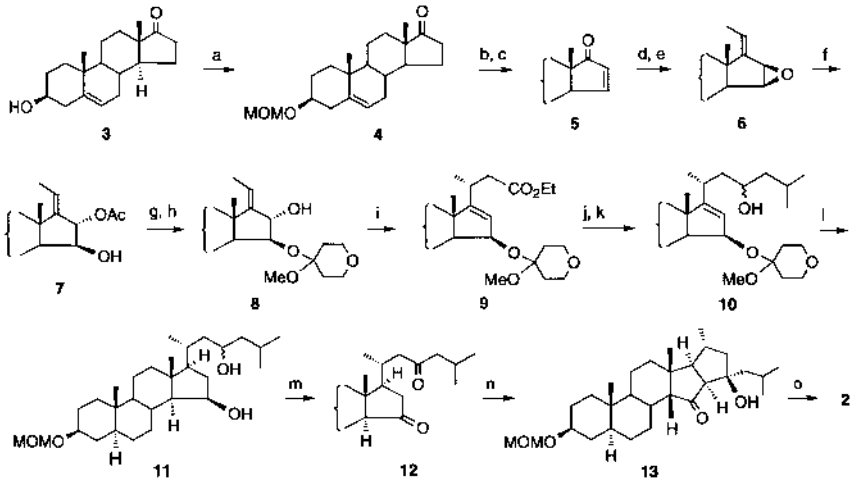


Chart 1. Retrosynthetic Analysis of 3-Epi-6,7-dideoxyxestobergsterol (**2**)



Reagents and conditions: a) MOMCl, iPr$_2$NEt, 99%, b) LDA, TMSCl, c) Pd(OAc)$_2$, 92% from **4**, d) TBHP, Triton-B, 87%, e) Ph$_3$PEtI, KHMDS, 95%, f) AcOH, Ti(OiPr)$_4$, 56%, g) MDHP, PPTS, h) LiAlH$_4$, 82% from **7**, i) (EtO)$_3$CMe, EtCO$_2$H, 98%, j) DIBAL, k) iBuMgBr, 56% from **9**, l) H$_2$, Pd/C, 83%, m) PCC, 94%, n) NaOH, EtOH, 88%, o) 6N HCl, 78%.

Chart 2. Synthesis of 3-Epi-6,7-dideoxyxestobergsterol (**2**)

result was obtained by the use of ammonium acetate (NH_4OAc) and titanium tetraisopropoxide [Ti(OiPr)$_4$][15]) to give compound **7** (42%) and 15β-hydroxy-16α-isopropoxy by-product. Further optimization of conditions allowed us to find the use of acetic acid (3 eq) and Ti(OiPr)$_4$ (1.5 eq) in tetrahydrofuran (THF) to reproducibly afford the desired **7** in 55—60% yield from **6**. The α-orientation of the 16-acetoxy group in **7** was determined on the basis of nuclear Overhauser effect (NOE) studies in which irradiation of 18-H$_3$ (δ 1.21) caused enhancement of the 16β-H (δ 5.23) signal intensity while the β-orientation of the 15-OH group was assigned from a mechanistic consideration of an epoxide ring-opening reaction. Protection of the 15-hydroxyl group of **7** as 4-methoxytetrahydropyran-4-yl (MTHP) ether followed by removal of the 16-acetyl group gave the key intermediate **8** desired for the side chain introduction. The 15β-hydroxyl group appeared to be substantially sterically hindered since an attempted conversion to *tert*-butyldimethylsilyl (TBS) ether under standard conditions (TBSCl/imidazole or *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/lutidine) failed and gave only recovered starting material.

Encouraged by a known example of a 3,3-sigmatropic reaction of a steroidal 16α-hydroxy-$\Delta^{17(20)E}$ system,[11]) the allylic alcohol **8** was subjected to the conditions of orthoester Claisen rearrangement (triethyl orthoacetate, propionic acid, heating in xylene), which gave rise to the rearranged ester **9** as a single isomer in quantitative yield. Carroll rearrangement of **8** using 5-isovaleryl Meldrum's acid[11]) did not succeed, although the 16-(β-keto) ester was obtained in good yield. The side chain of **9** was extended *via* the aldehyde to yield 23-ol **10** as a *ca.* 1 : 1 epimeric mixture at the C-23 position. Hydrogenation of **10** proceeded stereoselectively to yield the saturated product **11** with β-orientation of the side-chain. It should be noted that the MTHP protecting group was cleaved under the hydrogenation conditions (H_2/10% Pd–C). Similar cleavage of the MTHP group under the same hydrogenation condition was also observed for compound **9**. PCC oxidation of the diol **11** furnished the diketone **12**, whose structure including 14α-H, 17α-H and 20R stereochemistry was established from comparison of the NMR data with those reported for the corresponding 3-TBS ether.[5c]) As expected from earlier work by Jung's[6,7]) and Krafft's[5c]) groups, treatment of the diketone **12** with NaOH/ethanol (EtOH) afforded the pentacyclic compound **13** in good yield without formation of any other stereoisomers. The ^{1}H- and ^{13}C-NMR data of **13** were essentially identical with those reported for the corresponding 3-TBS ether[5c]) except for the signals around the C-3 positions. Final deprotection of **13** under acidic conditions completed the synthesis of the target compound **2**. The ^{1}H- and ^{13}C-NMR data for **2**, in comparison with those reported for 7-deoxyxestobergsterol A[6]) and xestobergsterol A,[2]) confirmed the synthetic analogue to have the natural C-14,C-16 C-17 and C-23 configurations.

In conclusion, we have developed a relatively simple synthetic route leading to the construction of the E-ring found in xestobergsterols, which is characterized by an appropriate use of compound **8** readily available from the corresponding epoxide **6**. We previously developed a method of preparation of 3α,6α,7β-trihydroxyandrostan-17-one.[8]) The synthesis of xestobergsterol A by combining the latter method with the present approach is in progress in our laboratory.

Experimental

General Methods Melting points were determined on a Yazawa hot-stage melting point apparatus and were uncorrected. NMR spectra were obtained on a JEOL JNM-LA300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or JEOL JNM-LA400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$ solutions, unless otherwise noted. ^{1}H chemical shifts are given in ppm relative to tetramethylsilane δ 0.00) and ^{13}C chemical shifts are shown relative to the solvent (δ 77.00). Merck Kieselgel 60 was used for column chromatography.

3β-(Methoxymethoxy)androst-5-en-17-one (4) *i*-Pr_2NEt (10.6 ml, 60.8 mmol) and chloromethyl methyl ether (3.95 ml, 52.0 mmol) were added to a solution of **3** (5.00 g, 17.3 mmol) in dry CH_2Cl_2 (40 ml) at 0 °C under N_2, and the mixture was stirred at the same temperature for 30 min and then at room temperature for 3 h. CH_2Cl_2 and 2 N HCl were added to the mixture, and the separated CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (7 : 1) to give **4** (5.70 g, 99%) as white needles, mp 131—132 °C (from hexane–AcOEt). ^{1}H-NMR δ: 0.89 (s, 18-H_3), 1.04 (s, 19-H_3), 3.38 (s, OCH_3), 3.43 (m, 3α-H), 4.69 (s, OCH_2O), 5.39 (m, 6-H). ^{13}C-NMR δ: 13.48, 19.33, 20.29, 21.82, 28.81, 30.75, 31.40, 31.45, 35.77, 36.81, 37.13, 39.48, 47.46, 50.24, 51.72, 55.11, 76.71, 94.66, 120.89, 140.95, 220.90. *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.03; H, 9.90.

3β-(Methoxymethoxy)androsta-5,15-dien-17-one (5) A solution of **4** (5.70 g, 17.1 mmol) in dry THF (35 ml) was added at −78 °C under N_2 to a solution of LDA [prepared from diisopropylamine (3.84 ml, 27.4 mmol) in dry THF (20 ml) and *n*-BuLi (1.50 N solution in hexane, 17.1 ml, 25.7 mol)]. The mixture was stirred at the same temperature for 1 h, then chlorotrimethylsilane (4.35 ml, 34.3 mmol) was added. The mixture was warmed up to room temperature over a period of 20 min with stirring. Ether and saturated aqueous NH_4Cl were added. The separated organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give the crude enol TMS ether (7.4 g) as a yellow solid.

Palladium (II) acetate (3.85 g, 17.1 mmol) was added to a solution of the enol ether in CH_3CN (60 ml) and the mixture was stirred for 14 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated to give a crude product which was chromatographed on silica gel with hexane–AcOEt (7 : 1) to afford **5** (5.20 g, 92%) as white needles, mp 130—132 °C (from hexane–AcOEt). ^{1}H-NMR δ: 1.09 (s, 18-H_3, 19-H_3), 3.38 (s, OCH_3), 3.44 (m, 3α-H), 4.70 (s, OCH_2O), 5.41 (m, 6-H), 6.05 (dd, J=5.9, 3.2 Hz, 16-H), 7.50 (dd, J=5.2, 1.2 Hz, 15-H). ^{13}C-NMR δ: 19.30, 19.93, 20.08, 28.76 (×2), 28.99, 30.58, 36.92, 37.00, 39.48, 50.66, 51.24, 55.16, 57.23, 76.58, 94.66, 120.37, 131.83, 141.44, 158.53, 213.08. *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.39; H, 9.32.

15β,16β-Epoxy-3β-(methoxymethoxy)androst-5,17(20)*E*-diene (6) Triton B (40% aqueous solution, 8.36 ml, 21.2 mmol) and TBHP (90% aqueous solution, 4.66 ml, 41.9 mmol) were added to a solution of **5** (4.84 g, 14.7 mmol) in THF (44 ml) at −20 °C, and the mixture was stirred for 15 min at the same temperature. Ether and aq. $Na_2S_2O_3$ were added, and the separated ether layer was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (7 : 1) to give the epoxide (4.41 g, 87%) as white crystals, mp 131—133 °C (from hexane–AcOEt). ^{1}H-NMR δ: 1.07 (s, 18-H_3), 1.17 (s, 19-H_3), 3.31 (d, J=2.9 Hz, 15α-H), 3.38 (s, OCH_3), 3.44 (m, 3α-H), 3.82 (d, J=2.9 Hz, 16α-H), 4.70 (s, OCH_2O), 5.42 (m, 6-H). ^{13}C-NMR δ: 18.91, 19.17, 19.90, 28.51, 28.75, 30.15, 32.74, 36.94, 36.99, 39.45, 41.88, 51.07, 52.93, 53.39, 55.20, 55.66, 76.58, 94.68, 120.25, 141.48, 213.23. *Anal.* Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.85; H, 9.03.

To a suspension of ethyltriphenylphosphonium iodide (11.4 g, 27.3 mmol) in THF (10 ml) was added potassium hexamethyldisilylazide (0.52 M toluene solution, 45.6 ml, 15.4 mmol) at 0 °C under N_2, and the mixture was stirred at the same temperature for 30 min. The mixture was cooled to −20 °C, and a solution of the epoxide **12** (3.81 g, 11.0 mmol) in THF (3.0 ml) was added and stirring was continued for 15 min. Ether and brine were added and the ether layer was dried over Na_2SO_4 and concentrated to give a yellow solid. This was suspended in hexane, and the insoluble portion was removed and concentrated to give **6** (3.74 g, 95%) as a white solid, mp 149—152 °C. ^{1}H-NMR δ: 1.06 (s, 18-H_3), 1.15 (s, 19-H_3), 1.75 (d, J=7.3 Hz, 21-H_3), 3.38 (s, OCH_3), 3.43 (m, 3α-H), 3.48 (d, J=3.2 Hz, 15α-H), 3.61 (d, J=3.2 Hz, 16α-H), 4.70 (s, OCH_2O), 5.41 (m, 6-H), 5.71 (q, J=7.1 Hz, 20-H). ^{13}C-NMR δ: 13.45, 19.11, 20.86, 22.38, 28.16, 28.83, 31.26, 36.96, 37.05, 37.98, 39.39, 39.51, 51.12, 55.13, 57.10, 57.75, 58.94, 76.79, 94.67, 120.87, 121.80, 141.24, 146.24. *Anal.* Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.11; H, 9.85.

16α-Acetoxy-15β-Hydroxy-3β-(methoxymethoxy)androst-17(20)*E*-ene (7) $Ti(OiPr)_4$ (4.86 ml, 16.5 mmol) and acetic acid (1.88 ml, 32.8 mmol) were added to a solution of **6** (3.60 g, 10.0 mmol) and the mixture was stirred for 2 h. Ether and saturated aqueous $NaHCO_3$ were added, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (7 : 1) to give **7** (2.34 g, 56%) as white plates, mp 148—150 °C (from hexane–AcOEt). ^{1}H-NMR δ: 1.05 (s, 19-H_3), 1.21 (s, 18-H_3), 1.77 (d, J=7.3 Hz, 21-H_3), 2.11 (s, OAc), 3.37 (s, CH_3O), 3.45 (m, 3α-H), 3.97 (d, J=5.6 Hz, 15β-H), 4.69 (s, OCH_2O), 5.23 (s, 16α-H), 5.37 (m, 6-H), 5.49 (dq, J=7.1 Hz, 20-H). ^{13}C-NMR δ: 13.14, 19.09, 20.29, 20.89, 21.23, 27.27, 28.86, 30.69, 36.78, 37.15, 38.22, 39.46, 44.03, 50.35, 55.12, 57.38, 76.28, 76.84, 85.09, 94.64, 119.47, 121.20, 140.65, 147.31, 171.80. *Anal.* Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.59; H, 9.24.

16α-Hydroxy-15β-(4-methoxytetrahydropyran-4-yloxy)-3β-(methoxymethoxy)-androsta-5,17(20)*E*-diene (8) 5,6-Dihydro-4-methoxy-2*H*-pyran (855 μl, 7.65 mmol) and pyridinium *p*-toluenesulfonate (48 mg, 0.19 mmol) were added to a solution of **7** (1.60 g, 3.82 mmol) in dry CH_2Cl_2 (16 ml) and the mixture was stirred for 13 h. AcOEt and saturated aqueous $NaHCO_3$ were added, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (5 : 1) to give the ether (1.9 g, 93%) as an oil. ^{1}H-NMR δ: 1.07 (s, 19-H_3), 1.25 (s, 18-H_3), 1.75 (dd, J=9.4 Hz, 21-H_3), 2.04 (s, OAc), 3.21(s, CH_3O), 3.38 (s, CH_3O), 3.44 (m, 3α-H), 3.35—3.82 (m, 3α-H, 2,4-H_4 of MTHP), 4.00 (d, J=5.5 Hz, 15α-H), 4.70 (s, OCH_2O), 5.38 (m, 6-H), 5.61 (m, 16β-H, 20-H). ^{13}C-NMR δ: 13.73, 19.16, 20.31, 20.92, 21.44, 27.15, 28.84, 31.24, 34.35, 34.46, 36.99, 37.18, 38.62, 39.46, 43.37, 48.47, 50.48, 55.16, 57.38, 64.98, 65.12, 74.40, 76.83, 81.19, 94.65, 98.77, 121.14, 123.65, 140.98, 149.23, 170.34. *Anal.* Calcd for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08. Found: C, 69.76; H, 8.95.

$LiAlH_4$ (203 mg, 5.35 mmol) was added to a solution of the ether (1.90 g, 3.57 mmol) in ether (19 ml) at 0 °C under N_2 and the mixture was stirred for 10 min. Ether and 2 N HCl were added, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (2 : 1) to give **8** (1.54 g, 88%) as a colorless amorphous solid. ^{1}H-NMR δ: 1.06 (s, 19-H_3), 1.20 (s, 18-H_3), 1.77 (d, J=7.2 Hz, 21-H_3), 3.18 (s, CH_3O), 3.38 (s, CH_3O), 3.35—3.82 (m, 3α-H, 2,4-H_4 of MTHP), 4.02 (d, J=5.6 Hz, 15α-H), 4.45 (brs, 16β-H), 4.69 (s, OCH_2O), 5.37 (m, 6-H), 5.60 (q, J=7.2 Hz, 20-H). ^{13}C-NMR δ: 13.45, 19.15, 20.18, 20.87, 27.19, 28.82, 31.13, 34.57 (×2), 36.91, 37.13, 38.67, 39.45, 43.71, 48.33, 50.49, 55.13, 56.57, 64.90, 65.07, 76.80, 76.86, 79.92, 94.61, 98.63, 120.12, 121.33, 140.77, 153.96. *Anal.* Calcd for $C_{29}H_{46}O_6$: C, 70.99; H, 9.45. Found: C, 70.86; H, 9.68.

Ethyl 15β-(4-Methoxytetrahydropyran-4-yloxy)-3β-(methoxymethoxy)-24-norchola-5,16-dien-23-oate (9) Ethyl orthoacetate (2.86 ml, 15.6 mmol) and propionic acid (140 μl, 1.88 mmol) were added to a solution of **8** (1.53 g, 3.12 mmol) in xylene (15 ml). After the mixture was stirred at 130 °C for 30 min, it was concentrated under reduced pressure. Purification of the crude product on silica gel with hexane–AcOEt (7 : 1) afforded **9** (1.71 g, 98%) as an oil. ^{1}H-NMR δ: 1.04 (d, J=6.8 Hz, 21-H_3), 1.09 (s, 19-H_3), 1.15 (s, 18-H_3), 1.26 (t, J=7.1, 7.2 Hz, 21-H_3), 2.76 (m, 20-H), 3.11 (s, CH_3O), 3.38 (s, CH_3O), 3.35—3.82 (m, 3α-H, 2,4-H_4 of MTHP), 4.10 (q, J=7.2 Hz, OEt), 4.11 (q, J=7.2 Hz, OEt), 4.40 (dd, J=5.4, 2.9 Hz, 15α-H), 4.70 (s, OCH_2O), 5.38 (m, 6-H), 5.57 (d, J=1.7 Hz, 16-H). ^{13}C-NMR δ: 14.20, 19.18, 20.53, 21.11, 21.47, 27.61, 28.68, 28.85, 30.96, 34.55, 34.76, 35.05, 37.02, 37.15, 39.50, 41.56, 47.34, 48.35, 51.05, 55.15, 59.80, 60.23, 64.90, 65.16, 71.52, 76.78, 94.63, 97.89, 121.49, 124.24, 140.97, 163.45, 172.49. *Anal.* Calcd for $C_{33}H_{52}O_7$: C, C, 70.68; H, 9.35. Found: C, 70.88; H, 9.10.

(23*RS*)-15β-(4-Methoxytetrahydropyran-4-yloxy)-3β-(methoxymethoxy)cholesta-5,16-dien-23-ol (10) DIBAL (1.01 N solution in toluene, 2.39 ml, 2.41 mmol) was added to a solution of **9** (1.50 g, 2.67 mmol) in dry toluene (15 ml) at −78 °C under N_2 and the mixture was stirred for 30 min at the same temperature. Ether and saturated aqueous NH_4Cl were added, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give a crude aldehyde (1.28 g) as an oil. ^{1}H-NMR δ: 1.08 (d, J=6.8 Hz, 21-H_3), 1.09 (s, 19-H_3), 1.16 (s, 18-H_3), 2.51 (ddd, J=16.2, 7.7, 1.9 Hz, 22-Ha), 2.67 (ddd, J=16.2, 7.0, 1.9 Hz, 22-Hb), 2.82 (m, 20-H), 3.09 (s, CH_3O), 3.38 (s, CH_3O), 3.36—3.82 (m, 3α-H, 2,4-H_4 of MTHP), 4.41 (dd, J=5.2, 2.8 Hz, 15α-H), 4.70 (s, OCH_2O), 5.38 (m, 6-H), 5.58 (d, J=2.0 Hz, 16-H), 9.73 (t, J=1.9 Hz, CHO). ^{13}C-NMR δ: 19.17, 20.55, 21.33, 21.76, 26.63, 27.60, 28.86, 30.90, 34.47, 34.77, 35.09, 37.01, 37.16, 39.48, 47.36, 48.43, 50.20, 51.02, 55.14, 59.81,

64.87, 65.15, 71.47, 76.76, 94.62, 97.97, 121.44, 124.96, 140.96, 163.04, 202.09.

Isobutylmagnesium bromide solution, prepared from Mg (130 mg, 5.35 mmol) and isobutyl bromide (582 μl, 5.35 mmol) in THF (8 ml), was added to a solution of the aldehyde (1.28 g) in THF (10 ml) under N_2 and the mixture was stirred for 40 min. Ether and 2 N HCl were added, and the aqueous layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **10** (861 mg, 56% from **9**) as an oil. ^{1}H-NMR δ: 0.86—0.94 (m, 26-H_3, 27-H_3), 1.01 (d, J=6.8 Hz, 21-H_3), 1.09 (s, 19-H_3), 1.149, 1.154 (s, 18-H_3), 3.13, 3.14 (s each, CH_3O), 3.38 (s, CH_3O), 3.38—3.82 (m, 3α-H, 2,4-H_4 of MTHP, 23-H), 4.42 (br s, 15α-H), 4.70 (s, OCH_2O), 5.39 (m, 6-H), 5.53, 5.58 (d each, J=1.7 Hz, 16-H). ^{13}C-NMR δ: 51.06, 51.12, 55.12, 64.88, 64.90, 65.13, 65.16, 71.64, 71.68, 76.78, 94.59, 97.88, 120.51, 123.83, 123.96, 140.93, 164.76, 165.20. *Anal*. Calcd for $C_{35}H_{58}O_6$: C, 73.13; H, 10.17. Found: C, 73.00; H, 10.32.

(23*RS*)-3β-(Methoxymethoxy)cholestane-15β,23-diol (11) A solution of **10** (690 mg, 1.20 mmol) in AcOEt (7 ml) containing 10% Pd/C (Kojima Chemicals Co. Ltd., 200 mg) was stirred under an atmospheric pressure of H_2 for 40 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **11** (462 mg, 83%) as amorphous solid. ^{1}H-NMR δ: 0.84 (s, 19-H_3), 0.91 (d each, J=6.7 Hz, 26, 27-H_3), 0.95 (s, 18-H_3), 0.96 (d, J=6.7 Hz, 21-H_3), 2.41 (m, 20-H), 3.37 (s, CH_3O), 3.50 (m, 3α-H), 3.76 (m, 23-H), 4.17 (m, 15α-H), 4.68 (s, OCH_2O). ^{13}C-NMR δ: 12.15, 14.63, 14.76, 18.58, 19.20, 21.00, 21.54, 22.24, 23.20, 23.96, 24.32, 24.58, 28.54, 28.59, 31.26, 31.30, 31.34, 31.37, 32.08, 33.46, 35.09, 35.65, 36.90 41.12, 41.17, 41.33, 41.36, 42.23, 42.32, 44.32, 44.87, 44.89, 44.98, 46.26, 47.91, 54.66, 54.69, 55.04, 57.07, 60.86, 60.93, 66.73, 68.29, 70.11, 70.12, 76.18, 94.37. *Anal.* Calcd for $C_{29}H_{52}O_4$: C, 74.95; H, 11.28. Found: C, 74.75; H, 11.43.

3β-(Methoxymethoxy)cholestane-15,23-dione (12) PCC (820 mg, 3.81 mmol) and Celite (1.0 g) were added to a solution of **11** (442 mg, 0.951 mmol) in dry CH_2Cl_2 (11 ml) and the mixture was stirred for 2 h. Dry ether (55 ml) was added and the suspension was filtered through a pad of Celite. Concentration of the filtrate gave a crude product which was chromatographed on silica gel with hexane–AcOEt (7 : 1) to give **12** (411 mg, 94%) as white crystals, mp 134—136 °C (from hexane–AcOEt). ^{1}H-NMR δ: 0.78 (s, 18-H_3), 0.81 (s, 19-H_3), 0.90 (d, J=6.6 Hz, 26-H_3), 0.91 (d, J=6.6 Hz, 27-H_3), 0.99 (d, J=6.6 Hz, 21-H_3), 2.65 (m, 7β-H), 3.36 (s, CH_3O), 3.49 (m, 3-H), 4.67 (s, OCH_2O). ^{13}C-NMR δ: 12.06, 12.96, 20.10, 20.64, 22.44, 22.55, 24.46, 28.20, 28.55, 30.53, 31.64, 31.80, 35.00, 35.62, 36.87, 39.65, 41.65, 42.34, 44.72, 49.76, 51.04, 52.52, 53.80, 55.04, 65.81, 76.01, 94.42, 210.06, 214.97. *Anal.* Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.38; H, 10.73.

3β-(Methoxymethoxy)-3-Epi-6,7-dideoxyxestobergsterol (13) 2 N NaOH (0.38 ml) was added to a solution of **12** (200 mg, 0.434 mmol) in EtOH (6.6 ml) and THF (2.8 ml) and the mixture was stirred for 37 h. Ether and saturated aqueous NH_4Cl were added. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (10 : 1) to give **13** (175 mg, 88%) as white needles, mp 116—117 °C (from MeOH) ^{1}H-NMR δ: 0.76 (s, 19-H_3), 0.95 (d, J=6.8 Hz, 26-H_3), 0.97 (d, J=6.8 Hz, 27-H_3), 1.10 (d, J=6.4 Hz, 21-H_3), 1.13 (s, 18-H_3), 2.11 (t, J=3.1 Hz, 14β-H), 2.28 (m, 20-H), 2.49 (td, J=9.1, 4.9 Hz, 7α-H), 2.61 (d, J=9.8 Hz, 16α-H), 3.36 (s, CH_3O), 3.49 (m, 3-H), 4.68 (s, OCH_2O). ^{13}C-NMR δ: 12.04, 19.79, 20.41 (C-21), 21.09 (C-11), 24.44 (C-26), 24.56 (C-25), 24.65 (C-27), 28.42, 28.86, 28.90, 32.72, 34.35, 35.25 (C-20), 33.54 (C-10), 36.38, 38.05, 38.78 (C-13), 43.90, 47.38 (C-9), 50.67 (C-22), 51.89 (C-24), 55.04, 56.79 (C-14), 57.38 (C-17), 62.94 (C-16), 76.26 (C-3), 81.91 (C-23), 94.51, 220.16 (C-15). *Anal.* Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.46; H, 10.74.

3-Epi-6,7-dideoxyxestobergsterol (2) 6 N-HCl (0.2 ml) was added to a solution of **13** (124 mg, 0.269 mmol) in THF (2.0 ml) and the mixture was stirred for 48 h. Ether and saturated aqueous $NaHCO_3$ were added, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **2** (78 mg, 78%) as white needles, mp 97—98 °C (from MeOH). ^{1}H-NMR (pyridine-d_5, chemical shifts are given relative to H-2 of the residual solvent, δ=7.19) δ: 0.74 (s, 19-H_3), 0.95 (d, J=6.5 Hz, 27-H_3), 1.00 (d, J=6.5 Hz, 26-H_3), 1.12 (d, J=6.5 Hz, 21-H_3), 1.14 (s, 18-H_3), 2.49 (brs, H-14), 2.61 (m, 20-H), 2.67 (d, J=10.0 Hz, 16α-H), 2.78 (m, 7α-H), 3.77 (m, 3α-H). ^{13}C-NMR (pyridine-d_5, chemical shifts are given relative to C-3 of the solvent, δ=123.50) δ: 12.22 (C-19), 19.81 (C-21), 20.87 (C-18), 21.62 (C-11), 24.66 (C-26), 24.82 (C-25), 25.12 (C-27), 29.45 (C-6), 29.45 (C-7), 32.20 (C-2), 32.91 (C-12), 34.98 (C-20), 35.78 (C-10), 37.35 (C-1), 38.63 (C-4), 38.67 (C-8), 39.33 (C-13), 44.42 (C-5), 47.45 (C-9), 51.63 (C-22), 51.92 (C-24), 56.64 (C-14), 57.63 (C-17), 62.90 (C-16), 70.47 (C-3), 82.01 (C-23), 217.20 (C-15). *Anal.* Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.64. Found: C, 77.61; H, 10.90.

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