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

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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-oxide side chain was constructed stereoselectively by orthoester Claissen rearrangement of the epoxide using ethyl triphenylphosphonium iodide and 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 9:1 mixture of 17(20)-ene favoring the C-epimer. 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-oxo 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 17(20)-ene favoring the C-epimer as reported previously.5) Change of the base from n-BuLi to potassium hexamethyldisilazide (KHMDMS) gave 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 hexamethylyphosphoric triamide (HMPA) 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-dideoxy-xestobergsterol A (2)](image)

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Dedicated to the memory of Dr. Kyousuke Tsuda.
result was obtained by the use of ammonium acetate (NH₄OAc) and titanium tetraisopropoxide [Ti(OiPr)₄] 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-D₁7(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 acid11) 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 (H₂/10% 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’s6,7) and Krafft’s5c) 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 1H- and 13C-NMR data of 13 were essentially identical with those reported for the corresponding 3-TBS ether5c) 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 1H- and 13C-NMR data for 2, in comparison with those reported for 7-deoxyxestobergsterol A5b) and xestobergsterol A2), 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-trihydroxyandrost-17-one8) 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 Yawaz anhot stage melting point apparatus and were uncorrected. NMR spectra were obtained on a JEOL JNM-LA300 (300 MHz for H and 75 MHz for 13C) or JEOL JNM-LA400 (400 MHz for H and 100 MHz for 13C) spectrometer in CDCl3 solutions, unless otherwise noted. 1H chemical shifts are given in ppm (ppm = delta (δ)) relative to the solvent (δ 7.00). Merck Kieselgel 60 was used for column chromatography.

3β-(Methoxymethoxy)androsten-5β-ene-17-one (4) 1H-NMR (400 MHz for 1H and 100 MHz for 13C) in CDCl3: 1.07 (s, 19-H3), 1.25 (s, 18-H3), 1.77 (J = 5.5 Hz, 15-H), 4.69 (s, OCH3), 5.23 (s, 16β-H), 5.67 (m, 6-H), 5.49 (d, J = 7.1 Hz, 20-H). 13C-NMR: Δ 13.1, 19.0, 20.29, 20.89, 21.21, 27.27, 30.69, 36.78, 37.15, 38.22, 49.46, 50.33, 50.52, 51.37, 57.28, 76.28, 76.84, 85.09, 94.64, 91.17, 120.61, 145.71, 171.80. Anal. Calcd for C21H32O3: C, 75.86; H, 9.08. Found: C, 76.32; H, 9.18.

16β-Hydroxy-15β-(4-methoxymethoxy)propan-2-ol (5) 1H-NMR (400 MHz for 1H and 100 MHz for 13C) in CDCl3: 1.07 (s, 19-H3), 1.25 (s, 18-H3), 1.74 (d, J = 5.6 Hz, 15-H), 4.69 (s, OCH3), 5.34 (m, 6-H), 5.67 (m, 20-H). 13C-NMR: Δ 13.1, 19.09, 20.29, 20.89, 21.21, 27.27, 30.69, 36.78, 37.15, 38.22, 49.46, 50.33, 50.52, 51.37, 57.28, 76.28, 76.84, 85.09, 94.64, 91.17, 120.61, 145.71, 171.80. Anal. Calcd for C21H32O3: C, 75.86; H, 9.08. Found: C, 76.32; H, 9.18.

Ethyl 15β-(4-methoxymethoxy)propan-2-yl 3β-(3-methoxymethoxy)-cholestanoate (6) 1H-NMR (400 MHz for 1H and 100 MHz for 13C) in CDCl3: 1.07 (s, 19-H3), 1.18 (s, 18-H3), 1.74 (d, J = 5.6 Hz, 15-H), 4.49 (s, OCH3), 5.35 (m, 6-H), 5.59 (d, J = 7.1 Hz, 20-H). 13C-NMR: Δ 13.1, 19.09, 20.29, 20.89, 21.21, 27.27, 30.69, 36.78, 37.15, 38.22, 49.46, 50.33, 50.52, 51.37, 57.28, 76.28, 76.84, 85.09, 94.64, 91.17, 120.61, 145.71, 171.80. Anal. Calcd for C22H34O5: C, 76.56; H, 9.08. Found: C, 76.32; H, 9.18.

16β-Hydroxy-15β-(4-methoxymethoxy)propan-2-yl 3β-(3-methoxymethoxy)-cholesta-5,14-dien-3β-ol (7) 1H-NMR (400 MHz for 1H and 100 MHz for 13C) in CDCl3: 1.07 (s, 19-H3), 1.25 (s, 18-H3), 1.77 (d, J = 7.3 Hz, 21-H), 2.11 (s, OAc), 3.37 (s, CH2O), 3.45 (m, 3-H), 3.97 (d, J = 5.6 Hz, 15-H), 4.69 (s, OCH3), 5.23 (s, 16α-H), 5.67 (m, 6-H), 5.49 (d, J = 7.1 Hz, 20-H). 13C-NMR: Δ 13.1, 19.09, 20.29, 20.89, 21.21, 27.27, 30.69, 36.78, 37.15, 38.22, 49.46, 50.33, 50.52, 51.37, 57.28, 76.28, 76.84, 85.09, 94.64, 91.17, 120.61, 145.71, 171.80. Anal. Calcd for C21H32O3: C, 75.86; H, 9.08. Found: C, 76.32; H, 9.18.

The residue was chromatographed on silica gel with hexane–AcOEt (7:1) to give 7 (2.34g, 56%) as white plates, mp 148–150°C (from hexane–AcOEt).

C77.11; H, 9.85.

16α-Acetoxy-15β-Hydroxy-3β-(methoxymethoxy)androstan-17β-ol (8) (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 (3.69 g, 10.0 mmol) and the mixture was stirred for 2h. Ether and saturated aqueous NaHCO3 were added, and the organic layer was washed with brine, dried over Na2SO4 and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (7:1) to give 8 (2.43g, 56%) as white plates, mp 148–150°C (from hexane–AcOEt).

1H-NMR: Δ 1.05 (s, 19-H), 1.21 (s, 18-H), 1.77 (d, J = 7.3 Hz, 21-H), 2.11 (s, OAc), 3.37 (s, CH2O), 3.45 (m, 3-H), 3.97 (d, J = 5.6 Hz, 15-H), 4.69 (s, OCH3), 5.23 (s, 16α-H), 5.67 (m, 6-H), 5.49 (d, J = 7.1 Hz, 20-H). 13C-NMR: Δ 13.1, 19.09, 20.29, 20.89, 21.21, 27.27, 30.69, 36.78, 37.15, 38.22, 49.46, 50.33, 50.52, 51.37, 57.28, 76.28, 76.84, 85.09, 94.64, 91.17, 120.61, 145.71, 171.80. Anal. Calcd for C22H34O5: C, 76.56; H, 9.08. Found: C, 76.32; H, 9.18.
to a solution of the aldehyde (1.28 g) in THF (10 ml) under N₂ and the mixture was stirred for 40 min. Ether and 2 N HCl were added and the mixture was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ 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 white needles, mp 116—117 °C (from MeOH). 1H-NMR (400 MHz, CDCl₃) δ: 1.99 (s, 3-H), 2.49 (td, J = 9.1, 4.9 Hz, 7α-H), 2.61 (d, J = 9.8 Hz, 16α-H), 3.36 (s, CH₃O), 3.49 (m, 3-H), 4.68 (s, OCH₂O). 13C-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 (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, 210.16 (15). Anal. Calcd for C₃₅H₅₈O₆: C, 73.13; H, 10.17. Found: C, 73.00; H, 10.32.

3-Epi-6,7-dideoxyxestobergsterol (12) 6-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 NaHCO₃ were added, and the organic layer was washed with brine, dried over Na₂SO₄ and concentrated to dryness. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give 12 (78 mg, 78%) as white needles, mp 97—98 °C (from MeOH). 1H-NMR (pyridine-d₅) chemical shifts are given relative to H-2 of the residual solvent, δ = 7.19 δ: 0.74 (s, 19-H), 0.95 (d, J = 6.5 Hz, 27-H), 1.00 (d, J = 6.5 Hz, 26-H), 1.12 (d, J = 6.5 Hz, 21-H), 1.14 (s, 18-H), 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). 13C-NMR (pyridine-d₅) 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 C₃₅H₅₈O₆: C, 77.84; H, 10.64. Found: C, 77.61; H, 10.90.

References and Notes