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Synthesis of xestobergsterol A from dehydroepiandrosterone

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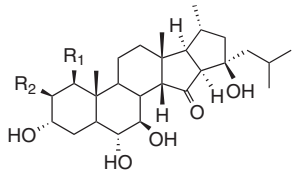
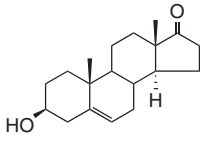
Abstract—Xestobergsterol A, a potent inhibitor of histamine release, has been synthesized from dehydroepiandrosterone in a route that used introduction of a novel 15-oxygen functionality, side-chain construction via the orthoester Claisen rearrangement and TBAF-promoted epimerization–aldol condensation.

Xestobergsterols A (**1**) and B (**2**) were isolated in 1992 from the Okinawan marine sponge *Xestospongia bergquistia*, as unique polyhydroxy-steroids having a cis C/D-ring junction and an additional carbocyclic E-ring.[1] Subsequently, xestobergsterol C (**3**) was isolated from the Okinawan sponge, *Ircinia* sp., and the full structures, including the C-23 configuration, of these sterols were established.[2] Xestobergsterols A and B are strong inhibitors of histamine release from rat mast cells induced by anti-immunoglobulin E.[1] It was further shown that xestobergsterol A exerts its action by inhibiting phosphatidylinositol phospholipase C.[3] In addition, xestobergsterols A and C were shown to exhibit cytotoxicity against L-1210 murine leukemia cells.[2] The unique structures and potent biological activities of xestobergsterols prompted our and other groups to study the synthesis of xestobergsterols.[4–6] In the previous paper, we reported a model synthesis of 3-*epi*-6,7-dideoxyxestobergsterol A from dehydroepiandrosterone (**4**) in a route that used a novel C-15 functionalization followed by a side-chain construction via an orthoester Claisen rearrangement.[7] Herein, we report the synthesis of naturally occurring xestobergsterol A by applying this methodology. The first synthesis of **1** has been described by Jung and Johnson[8] who employed Breslow et al.'s remote oxidation for the C-15 functionalization.[9]



1: R_1, R_2 = H
2: R_1, R_2 = OH
3: R_1 = H, R_2 = OH



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Before beginning the total synthesis of **1** itself, we first examined the feasibility of the order of introduction of the C-6/C-7 glycol and the C-15 oxygen functions. The study suggested that the C-15 oxygen functionality (and the side-chain construction) should be introduced before the C-6/C-7 glycol formation, since epoxidation of an androst-15-en-17-one derivative having a protected C-6/C-7 glycol moiety failed to proceed. Thus, we chose a compound that bears a protected 3β-ol function and the Δ^5-double bond as well as C-15 and C-23 oxygen functions as a key intermediate. Retrosynthesis of **1** along this line is shown in Scheme 1. The E-ring of **1** could be formed from the diketone A according to the base-catalyzed epimerization–aldol condensation originally developed by Jung and Johnson.[6] The suitably protected pentanol B, in which the R_1 protecting group needs to be removed in the presence of the R_3 and R_4 protecting groups, could be a precursor of the diketone A. We anticipated a possible use of compound B for the synthesis of **2** and **3**, since the introduction of the A-ring functionalities in **2** and **3** might be possible from it. The Δ^5-double bond of compound C is a good clue for the introduction of the C-6/C-7 glycol moiety. In the

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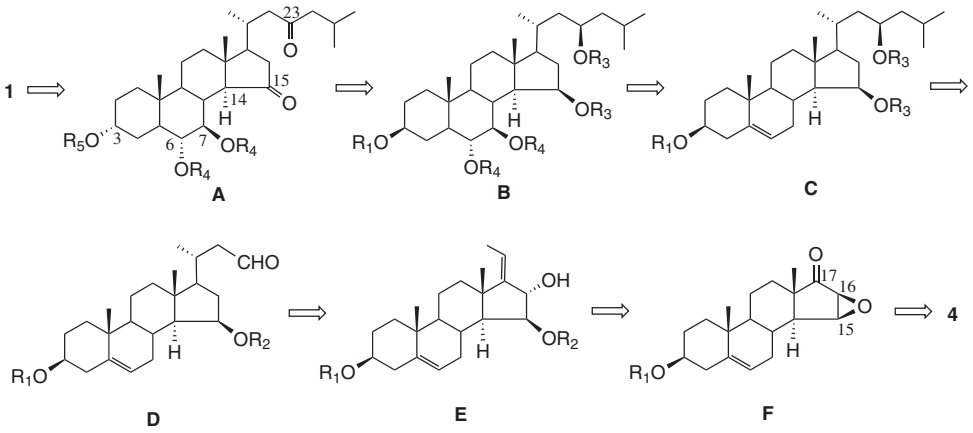
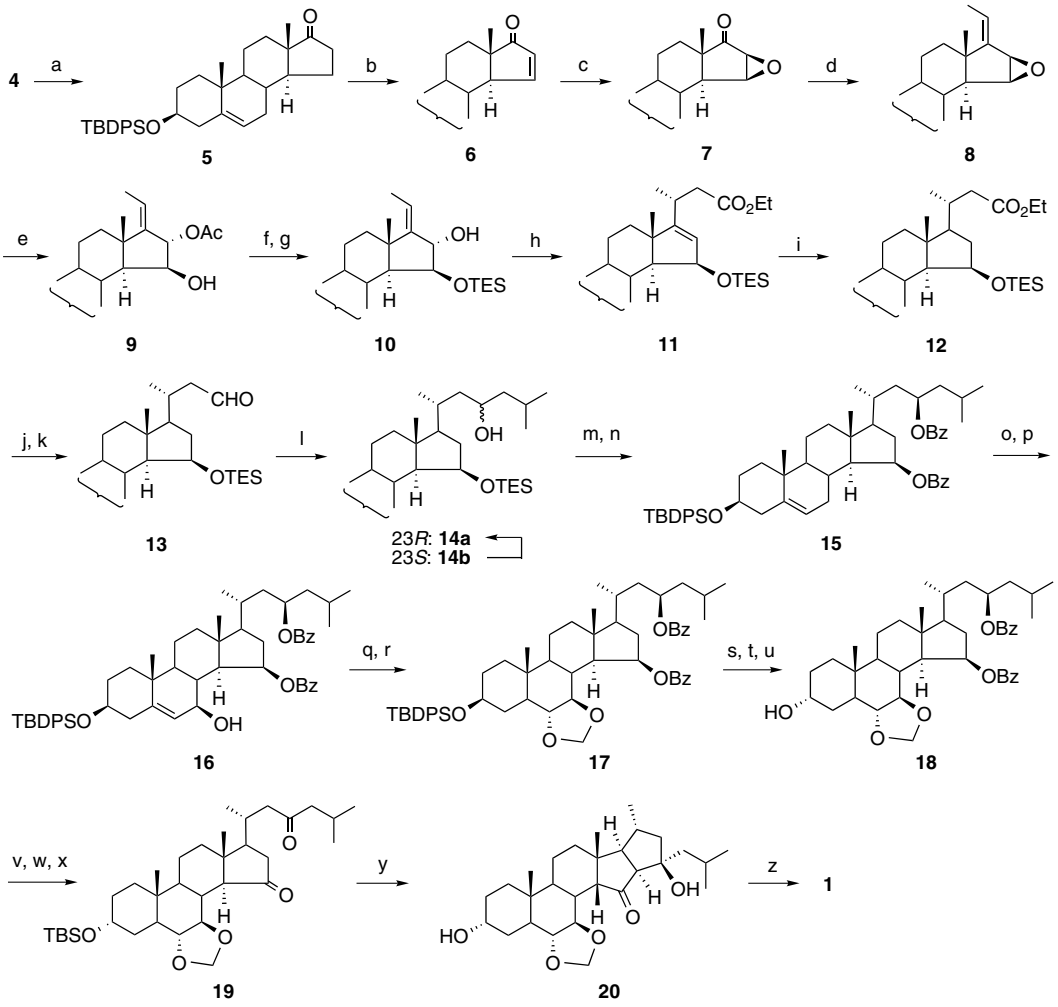


Scheme 1. Retrosynthesis of **1**.

intermediate C, the C-15 and C-23 alcohol groups were intentionally protected with the same group (R_3). This required a selective removal of the C-15 hydroxy protecting group (R_2) in the presence of the C-3 alcohol-protecting group (R_1). Use of a single C-23 epimer would be convenient from the viewpoint of synthetic simplicity, although the C-23 chiral center in compound C disappears at a later stage. The full side-chain structure in compound C can be readily prepared from the C-23 aldehyde D, which can be obtained in reactions involving the orthoester Claisen rearrangement of the allylic alcohol E with a suitably protected (R_2) C-15 alcohol group. At the outset of this study, we developed a method to attain such an allylic alcohol by titanium tetraisopropoxide-mediated ring-opening of a 15,16-epoxy-17(20)-ene,[7] which is available from the epoxy-ketone F. The synthesis of the epoxide F from dehydroepiandrosterone appeared to be straightforward according to the known procedure.[10,11]

The TBDPS ether was selected as the R_1 protecting group of **4** in the hope of a selective removal of the C-15 protecting group. The ether **5** was converted to the enol TMS ether, which was then gently heated in $CHCl_3$–DMSO in the presence of 0.1 equiv of $Pd(OAc)_2$ under oxygen atmosphere to yield the enone **6**.[12] Epoxidation of **6** with TBHP/triton B afforded the β-epoxide **7** stereoselectively.[10] Wittig reaction of **7** gave exclusively the (*E*)-olefin **8** [(*E*):(*Z*) = 10:1].[5] The epoxide-ring-opening of **8** with acetic acid (3 equiv) and $Ti(OiPr)_4$ (1.5 equiv) gave 15β-hydroxy-16α-acetate **9** in 84% yield, as we reported previously.[7] Protection of the C-15 hydroxyl group as TES ether followed by deacetylation afforded the protected allylic alcohol **10**, a substrate for the side-chain introduction. Compound **10** was subjected to the standard conditions of the orthoester Claisen rearrangement using triethyl orthopropionate to give the rearranged ester **11** as a single isomer in 88% yield. The Δ^{16}-olefinic bond in **11** was selectively hydrogenated with Pt–C as a catalyst to give the ester **12** with the correct C-17 configuration.[11] Compound **12** was converted to the aldehyde **13** via the corresponding C-23 alcohol. Reaction of **13** with isobutylmagnesium bromide gave the C-23 epimeric alcohols, the less polar (23*S*)-ol **14b** (30%) and the more polar (23*R*)-ol **14a** (36%) together with the reduced C-23 primary alcohol (17%). Reaction of **13** with isobutyllithium at −78 °C gave an improved result, yielding **14b** (25%) and **14a** (58%) together with the C-23-alcohol (6%). The (23*S*)-ol **14b** was found to be readily converted to (23*R*)-ol **14a** in 83% yield via a protocol reported by Corey et al., that is, mesylation followed by KO_2 treatment (80% combined yield from **13** to **14a**).[13] The configuration at the C-23 stereocenter for **14a** and **b** was determined by application of the modified Mosher's ester method.[14] Chemoseletive desilylation of the C-15 TES group in **14a** was achieved by a brief treatment of **14a** with $BF_3{\cdot}Et_2O$ (2 equiv) in CH_2Cl_2 at 0 °C, although TBAF or acidic treatment deprotected the two silyl groups without selectivity. The 15,23-diol thus obtained was now protected as the dibenzoate **15**.

The stage was now set for the B-ring modification. It was found that *N*-hydroxyphthalimide-catalyzed air oxidation[15] of **15** in the presence of dibenzoyl peroxide followed by decomposition of the resulting peroxy product with $CuCl_2$ in pyridine afforded the corresponding 5-ene-7-one in a better yield than other oxidation methods such as $RuCl_3$/TBHP and PCC. Luche reduction of the C-7 ketone with $NaBH_4$ gave the 7β-ol **16** stereoselectively.[16] Hydroboration–oxidation of **16** gave the 6α,7β-diol which was protected as the methylenedioxy compound **17** (corresponding to compound B). The modest yield (51%) of this step was mainly due to partial removal of the C-15 benzoate group. The C-3 silyl group was removed with TBAF, and the orientation of the C-3 alcohol was inverted via an oxidation–reduction sequence using L-Selectride as a reducing agent[5] to yield the 3α-alcohol **18**. Protection of the hydroxyl group of **18** as *tert*-butyldimethylsilyl ether and reductive removal of the benzoyl group gave the C-15,C-23-diol. This diol was smoothly oxidized to the corresponding diketone **19** with Dess–Martin periodinane. We found that TBAF treatment of the diketone **19** effected deprotection of the TBS group as well as epimerization–aldol condensation to furnish the 6,7-methylal derivative **20** of xestobergsterol A in good yield. The new epimerization–aldol condensation method could be used as an alterna-



Scheme 2. Synthetic route to **1**. Reagents and conditions: (a) TBDPSCl, Im, 99%; (b) LDA, TMSC1; O_2, $Pd(OAc)_2$, 84%; (c) TBHP, Triton B, 83%; (d) $EtPPh_3I$, KHMDS, 83%; (e) AcOH, $Ti(OiPr)_4$, 84%; (f) TESOTf, lutidine; (g) $LiAlH_4$, 70% (two steps); (h) $EtC(OEt)_3$, $EtCO_2H$, 88%; (i) H_2, Pt–C, 96%; (j) $LiAlH_4$; (k) TPAP, NMO, 83% (two steps); (l) isobutyllithium; (m) $BF_3{\cdot}Et_2O$, 90%; (n) BzCl, Py, 91%; (o) *N*-hydroxyphthalimide, O_2, Bz_2O_2; $CuCl_2$, Py, 75%; (p) $NaBH_4$, $CeCl_3$, 89%; (q) $BH_3{\cdot}THF$; H_2O_2, NaOH, 51%; (r) $CH_2(OMe)_2$, P_2O_5, 85%; (s) TBAF, 95%; (t) Dess–Martin, 91%; (u) L-Selectride, 90%; (v) TBSOTf, lutidine, 63%; (w) $LiAlH_4$, 90%; (x) Dess–Martin, 60%; (y) TBAF; (z) 6 N HCl/THF, 60% (two steps).

tive to the known base-catalyzed one in the synthesis of the other xestobergsterols. Final deprotection of the methylal group under acidic conditions furnished **1** (Scheme 2). The spectroscopic data of synthetic **1** were in complete accord with those of natural xestobergsterol A.

In summary, we have achieved the synthesis of xestobergsterol A from dehydroepiandrosterone in a route that used introduction of a novel 15-oxygen functionality, side-chain construction via the orthoester Claisen rearrangement, and TBAF-promoted epimerization–aldol condensation. This paper constitutes the second synthesis of xestobergsterol A. As an extension of this work, the synthesis of xestobergsterols B and C is in progress utilizing the intermediate **17**.

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