Synthesis of 7-Deoxyxestobergsterol A, a Novel Pentacyclic Steroid of the Xestobergsterol Class[1]

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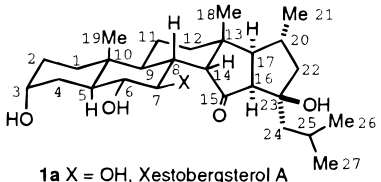
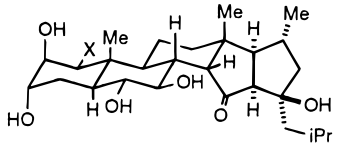
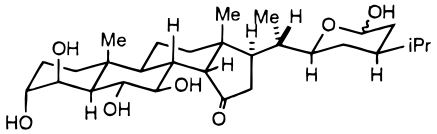
In 1992, Umeyama and co-workers reported the isolation of xestobergsterols A and B, **1ab**, novel pentacyclic steroids with a cis C/D ring junction which are powerful inhibitors of histamine release.[3] Three years later, another member of this novel class, xestobergsterol C, **1c**, was isolated and the original stereochemistry proposed for C23 was corrected.[4] Another inhibitor of histamine release is contignasterol, **2**, which has a similar structure but is missing the additional E ring.[5] To date,



1a X = OH, Xestobergsterol A
1d X = H



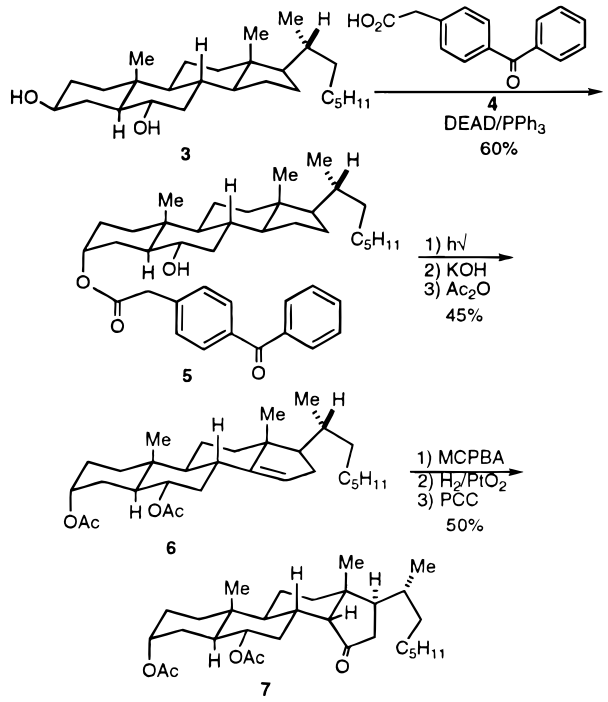
1b X = OH Xestobergsterol B
1c X = H Xestobergsterol C



2 Contignasterol (IZP-94005)

very little has been published on routes to these molecules.[6] All of these compounds strongly inhibited histamine release from rat mast cells induced by anti-IgE in a dose-dependent manner (**1a** IC_{50} 0.05 μM; **1b** 0.10 μM; and **2** 0.8 μM).[3,7] Since the well-known antiallergy drug disodium cromoglycate has an IC_{50} of 262 μM, these compounds are much more potent inhibitors of histamine release, being up to 5000 times more active inhibitors. Contignasterol is also very potent in both in vivo and in vitro models of allergen-induced bronchoconstriction and airway smooth muscle contraction and therefore is extremely effective as an antiasthma agent.[8] Recently it has been shown that the mechanism of action of xestobergsterol A is through strong inhibition of phosphatidylinositol phospholipase C (PI-PLC).[9] We report herein the first total synthesis of this structural

Scheme 1



class, the nonnatural analogue 7-deoxyxestobergsterol A (**1d**) by a route which should be applicable to the natural products.

Breslow has reported a very useful technique for "remote functionalization" of steroids that involves the abstraction of a tertiary hydrogen atom by a radical species generated by photolysis of an appropriate precursor which is attached to the steroid backbone so that it sits preferentially under one of the several abstractable tertiary hydrogens in a steroid.[10] We first tested this process for the synthesis of the steroid skeleton necessary for the xestobergsterols (Scheme 1). The diol **3**, prepared in 78% yield by hydroboration−oxidation of cholesteryl acetate, was treated with the known acid **4**[11] and excess DEAD and triphenylphosphine to produce the monoester **5** in 60% yield. This selective Mitsunobu reaction proceeds well due to the severe steric hindrance in the inversion of the 6α-alcohol. Photolysis and cleavage with hydroxide followed by protection gave the desired Δ^{14}-alkene diacetate **6** in 45% isolated yield along with 35% of the saturated 3α,6α-diacetate, which could be recycled. Conversion of the alkene to the desired 14β-H 15-ketone **7** was quite difficult. Simple hydroboration−oxidation gave mainly the 14α-H 15α-alcohol[12] which could be oxidized to the 14α-H 15-ketone, but this compound was not epimerized to the desired epimer. Therefore a stereoselective route was developed. Epoxidation[13] of **6** gave the α-epoxide which was opened with hydrogen over platinum oxide in acetic acid to give the 14β-H 15α-alcohol which was then oxidized with PCC to the desired ketone **7**. Treatment of **7** with either strong base or strong acid caused epimerization to the more stable 14α-H 15-ketone.

To determine the strategy necessary for final production of the cis C/D ring junction as well as the final E ring, we carried out a series of molecular mechanics calculations on a tricyclic

(1) Presented at the 213th National American Chemical Society meeting, San Francisco, CA, April 1997, ORGN 118.
(2) American Chemical Society Arthur C. Cope Scholar, 1995.
(3) Shoji, N.; Umeyama, A.; Shin, K.; Takeda, K.; Arihara, S.; Kobayashi, J.; Takei, M. *J. Org. Chem.* **1992**, *57*, 2996.
(4) Kobayashi, J.; Shinonaga, H.; Shigemori, H.; Umeyama, A.; Shoji, N.; Arihara, S. *J. Nat. Prod.* **1995**, *58*, 312.
(5) Burgoyne, D. L.; Andersen, R. J.; Allen, T. M. *J. Org. Chem.* **1992**, *57*, 525.
(6) Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511.
(7) Bramley, A. M.; Langlands, J. M.; Jones, A. K.; Burgoyne, D. L.; Li, Y.; Andersen, R. J.; Salari, H. *Br. J. Pharmacol.* **1995**, *115*, 1433.
(8) Takei, M.; Burgoyne, D. L.; Andersen, R. J. *J. Pharm. Sci.* **1994**, *83*, 1234.
(9) Takei, M.; Umeyama, A.; Shoji, N.; Arihara, S.; Endo, K. *Experientia* **1993**, *49*, 145.
(10) (a) Breslow, R. *Chemtracts* **1988**, *1*, 333. (b) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.
(11) Zderic, J. A.; Kubitschek, M. J.; Bonner, W. A. *J. Org. Chem.* **1961**, *26*, 1635.
(12) In addition to the major product, a small amount of the desired 14β-H 15β-alcohol was also isolated (an approximate 10:1 ratio), which could be taken on to **7** by simple oxidation.
(13) Lardon, A.; Sigg, H. P.; Reichstein, T. *Helv. Chim. Acta* **1959**, *42*, 1457.

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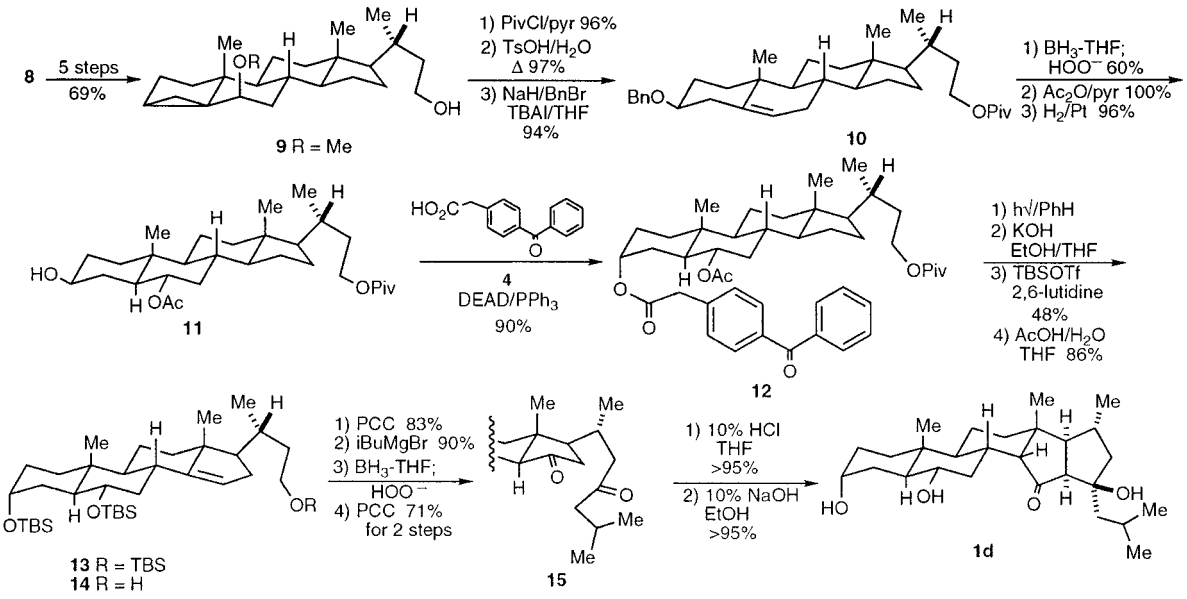
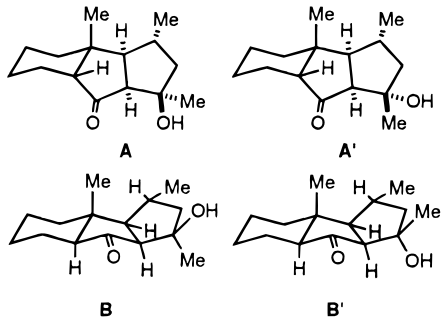
Scheme 2



model system which indicated that the desired final aldol product, **A**, was much more stable than any of the other possible aldols, **A′**, **B**, or **B′**.[14] Thus we theorized that one could carry out the desired aldol on the more easily accessible 14α-H 15-ketone to generate the desired 14β-H 15-ketone structure.



MM2 Strain Energy Calculations (kcal/mol):
A: 27.97; **A'**: 31.25; **B**: 32.31; **B'**: 36.37

The synthesis of 7-deoxyxestobergsterol A (**1d**) began with the known alcohol **9**, prepared in 5 steps and 69% yield from stigmasterol (**8**)[15] (Scheme 2). Protection as the pivalate, opening of the cyclopropylmethyl methyl ether, and protection of the alcohol gave the 3β-benzyl ether **10** in excellent yield. Hydroboration−oxidation of the alkene, followed by acetylation, and debenzylation gave the 6α-acetoxy 3β-alcohol **11**. Mitsunobu reaction with the acid **4** afforded the diester **12** which was photolyzed, treated with base as above, and then protected to give the desired Δ^{14}-alkene trisilyl ether **13** in 48% yield along with 32% of the saturated triether which could be recycled. Monodeprotection of the primary silyl ether with aqueous acetic acid gave the alcohol **14**. Oxidation to the aldehyde and addition of isobutylmagnesium bromide gave the secondary alcohol. Hydroboration−oxidation of the alkene gave the 15α,23-diol[16] which on oxidation with PCC gave the diketone **15**. Acidic removal of the TBS groups and final aldol condensation−epimerization afforded 7-deoxyxestobergsterol A (**1d**) in nearly quantitative yield.[17] Thus the calculations in the model system were borne out in the full steroidal skeleton. The structure was assigned by comparison of the chemical shifts and coupling constants to those reported for xestobergsterol A[4] and by a NOESY experiment which showed correlation between the angular 16-H and the hydrogens at C24 and C25, thus establishing the stereochemistry at C23.[18]

In summary, we have achieved the first total synthesis of a pentacyclic steroid of the xestobergsterol class by an efficient route, which utilizes the Breslow remote functionalization process. In this way, 7-deoxyxestobergsterol A (**1d**) is available in 17 steps and 10% overall yield from the known alcohol **9** (22 steps and 7% overall yield from stigmasterol (**8**)).[19] Further work on the synthesis of the other members of this class is in progress.

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Supporting Information Available: Experimental procedures for compounds **12** and **13** and characterization data for compounds **10**−**15** and **1d** (3 pages). See any current masthead page for ordering and Internet access instructions.

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(14) The eight additional possible aldol products, all bridged systems, had energies much higher than any of these four.

(15) Cho, J.-H.; Djerassi, C. *J. Org. Chem.* **1987**, *52*, 4517.

(16) Again a small amount of the 14β-H 15β-alcohol was also isolated (an approximate 10:1 ratio) in this hydroboration−oxidation, which could be oxidized to the 14β-H epimer of **15**.

(17) No intermediates are observed in this reaction so we have no evidence for whether aldol condensation precedes epimerization at C-14 or vice versa.

(18) The stereochemistry of the 14-hydrogen is easily established by the chemical shift of the 7-hydrogens. In the ketone **15**, the 7β-H resonates at low field (δ 2.87) as a double of triplets (J = 12.6, 3.2 Hz), whereas in compound **7** or **1d**, the 7α-H resonates at low field as a pseudo quartet (**7**, δ 2.55, J = 12.8 Hz; **1d**, δ 2.51, J = 11.7 Hz). The low-field resonance is due to the deshielding effect of the 15-ketone which has a pseudo 1,3-diaxial interaction with the 7α- or 7β-H, depending on the C-14 stereochemistry.

(19) No serious attempts have been made to optimize the yields at each step, so it is likely that the overall yield and efficiency of this process can be increased.