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# First Total Synthesis of Xestobergsterol A and Active Structural Analogues of the Xestobergsterols[1]

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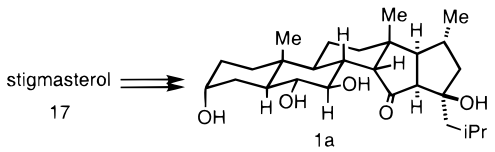
## ABSTRACT




**A novel pentacyclic polyhydroxylated sterol, xestobergsterol A (1a), has been synthesized in 24 steps and in good overall yield from stigmasterol 17. The key steps of the synthesis are the Breslow remote functionalization of the polyoxygenated steroid derived from 25 and the base-catalyzed epimerization–aldol condensation of the dione derived from 27.**

The xestobergsterols are a class of novel pentacyclic polyhydroxylated 14$\beta$ 15-keto steroids which are strong inhibitors of the release of histamines from rat mast cells.[3] Three such compounds have been isolated, xestobergsterols A−C (**1a**−**c**), and their structures determined[4] (Figure 1). Three other steroidal compounds, contignasterol (**2**),[5] haliclostanone (**3**),[6] and 15-dehydro-14$\beta$-anosmagenin,[7] have also been isolated, all of which have similar structures but are missing the additional carbocyclic E ring. Of these, only contignasterol has been shown to have histamine release inhibitory properties, being 16 times less active than xestobergsterol A ($IC_{50}$: **1a**, 50 nM; **1b**, 100 nM; **2**, 800 nM).[3,8] Recently we published the first total synthesis[9] of a member of this class, namely 7-deoxyxestobergsterol A (**1d**), by a route that used an application of Breslow's remote functionalization process[10] (to produce the 14,15-alkene) and a novel epimerization−aldol condensation process to form the DE ring system with the correct stereochemistry at C14, C16, and C23. Since our work, the Krafft group[11] has reported an approach to analogues of **1** using the same final aldol condensation sequence. We report herein the first total synthesis of the most potent member of this structural class, xestobergsterol A (**1a**), as well as two analogues and the biological activity of these compounds.

Before beginning the total synthesis itself, we first tested our route on a simpler model having the unfunctionalized cholesterol side chain (Scheme 1). Of the possible methods[12] for the oxidation of cholesteryl acetate **4** to the enone **5** we

(1) Presented at the 76th Japan Chemical Society meeting, Tokyo, March 1999.

(2) Saul Winstein Fellow; UCLA Graduate Division Fellow, 1998−1999.

(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) Crews, P.; Sperry, S. *J. Org. Chem.* **1997**, *60*, 229.

(7) Gonzalez, A. G.; Freire-barreira, R.; Garcia-Francisco, C.; Salazar-Rocio, J. A.; Suarez-Lopez, E. *An. Quim.* **1974**, *70*, 250.

(8) (a) Takei, M.; Umeyama, A.; Shoji, N.; Arihara, S.; Endo, K. *Experientia* **1993**, *49*, 145. (b) Takei, M.; Burgoyne, D. L.; Andersen, R. J. *J. Pharm. Sci.* **1994**, *83*, 1234. (c) Bramley, A. M.; Langlands, J. M.; Jones, A. K.; Burgoyne, D. L.; Li, Y.; Andersen, R. J.; Salari, H. *Brit. J. Pharmacol.* **1995**, *115*, 1433. (d) These compounds are significantly more active inhibitors than is the antiallergy drug disodium cromoglycate, which has an $IC_{50}$ of 262 $\mu$M for histamine release.

(9) Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412.

(10) (a) Breslow, R. *Chemtracts: Org. Chem.* **1988**, *1*, 333. (b) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.

(11) (a) Krafft, M. E.; Dasse, O. A.; Fu, Z. *J. Org. Chem.* **1999**, *64*, 2475. For earlier work by this group, see: b) Krafft, M. E.; Dasse, O. A.; Shao, B. *Tetrahedron* **1998**, *54*, 7033. (c) Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511.

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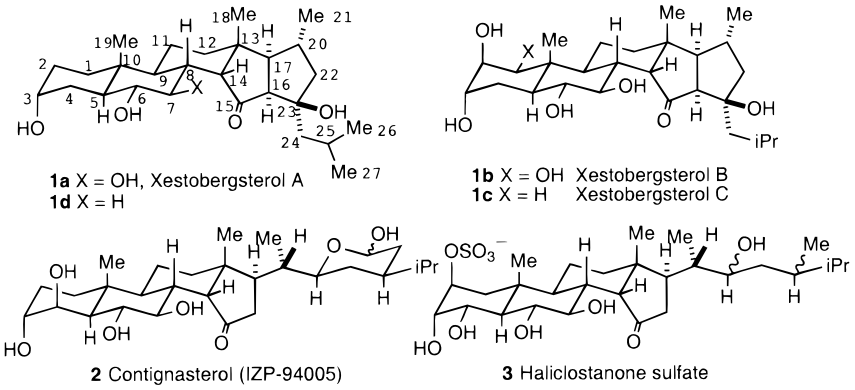
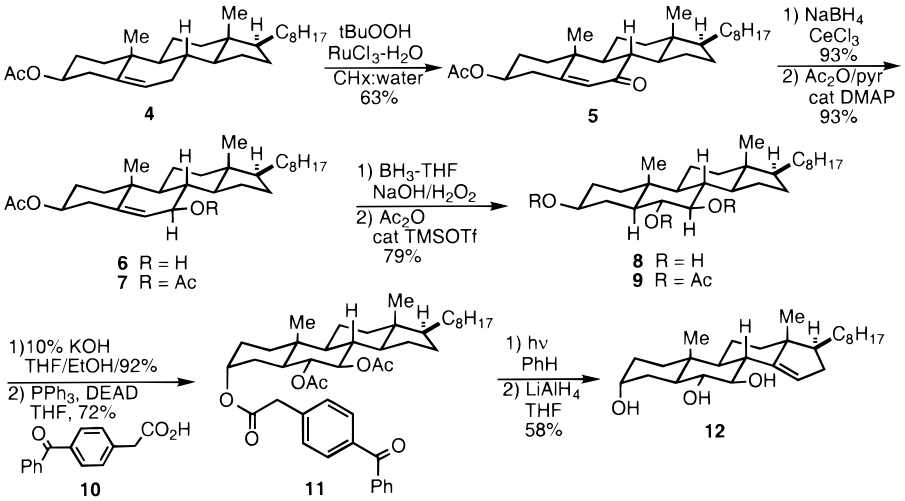



**Figure 1.**

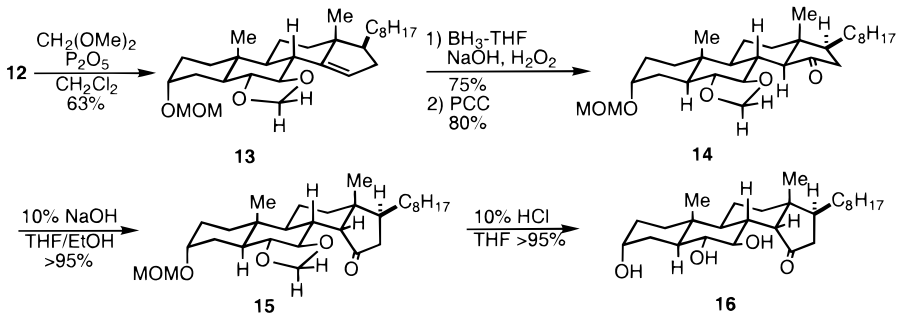
chose a catalytic ruthenium-based oxidation which gave **5** in 63% yield. Although other oxidants, e.g. chromium, gave higher yields, this proved the best method for efficient preparation of **5**. Luche reduction gave the equatorial allylic alcohol **6**, which was acetylated to give the diacetate **7** in good yield. Hydroboration−oxidation of **7** followed by peracetylation afforded the triacetate **9** in 79% yield from **7**. Selective hydrolysis of the least hindered 3α-acetate gave in excellent yield the monoalcohol, which was coupled with the acid **10**[13] using Mitsunobu conditions to give the photolysis substrate **11**. Photolysis and cleavage of all of the esters furnished the desired $\Delta^{14}$-alkene triol **12** in good yield. Thus, the additional acetate at C7 causes no problems with the Breslow remote functionalization process. The completion of the synthesis of the xestobergsterol A model **16** (Scheme 2) required protection of the triol, which proved to be very difficult, since the 7$\beta$-alcohol is quite hindered.[14] We solved this problem by treating the triol **12** with methylal and $P_2O_5$[15] to give the MOM ether cyclic methylene acetal **13** in good yield. Hydroboration−oxidation of **13** gave 75% of the 14α-H 15α-alcohol,[16] which was oxidized to the 14α-H 15-ketone **14** in good yield. We carried out molecular mechanics (MM2) strain energy calculations on **14** and its 14-epimer **15** which predict the energy difference to be about 1.6 kcal/mol in favor of **15**. This is in direct contrast to the 7-deoxy series, where the trans CD ring juncture was significantly more stable than the corresponding cis CD ring juncture.[9] The difference is presumably due to the steric interaction of the 7-alkoxy group with the C14−C15 bond since they are in a pseudo syn-pentane arrangement. In agreement with the calculations, treatment of **14** with base under mild conditions gave completely the isomeric ketone **15**.[17] Acidic hydrolysis of the acetal protecting groups in **15** gave the xestobergsterol A analogue **16** having the simple cholesterol side chain, which is available from **4** in 14 steps and 6% overall yield.

The successful completion of the synthesis of the tetracyclic analogue of xestobergsterol A **16** led us to complete the synthesis of the natural product. Commercially available stigmasterol **17** was converted into the alcohol **18** in four steps, as described previously (Scheme 3).[9] Acetylation and opening of the cyclopropylcarbinyl ether with acetic acid

**Scheme 1**

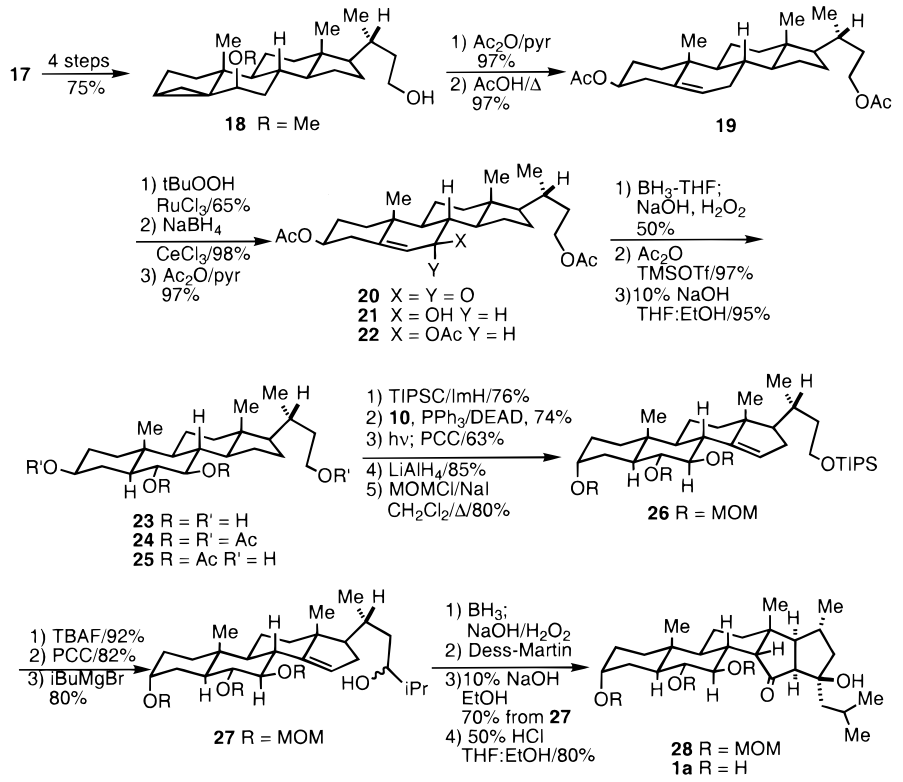


**Scheme 2**




gave the diacetate **19** in excellent yield. Allylic oxidation of **19** using catalytic ruthenium furnished the enone **20** which was reduced to the 7$\beta$-alcohol **21** and then acetylated to give the triacetate **22**. Hydroboration−oxidation of **22** afforded the tetrol **23**, which was converted via the tetraacetate **24** into the diol diacetate **25** in good yield. Selective protection of the primary alcohol in the presence of the secondary alcohol gave the TIPS ether, which was converted into the required benzophenone ester by a Mitsunobu coupling with the acid **10** to give the 3α-ester. Photolysis as before and PCC oxidation (to remove the 1:1 mixture of diastereomers at the new benzhydryl center to facilitate purification) gave the desired 14-alkene in 63% yield. Hydride reduction gave the triol, which was converted into the tris-MOM ether **26** by reaction with MOM iodide (prepared from the chloride in situ).[18] The final stages of the synthesis were modeled on our earlier synthesis of the 7-deoxy analogue.[9] Desilylation of **26** followed by oxidation and addition of isobutyl Grignard reagent afforded the alcohols **27** as a 1:1 diastereomeric mixture in good yield. Hydroboration−oxidation of the alkene gave mainly the 14$\beta$-H 15$\beta$-alcohol, which was oxidized under Dess−Martin conditions[19] to give the 15,-23-dione; this compound was then epimerized and cyclized under basic conditions to afford the desired protected xestobergsterol A **28** in 70% overall yield from **27**.[20] The final step is the acidic hydrolysis of the MOM ethers to give xestobergsterol A (**1a**) in 80% yield, thus ending a relatively short synthesis of **1a** from stigmasterol **17**.[21] The structure was assigned by comparison (spectral data, TLC, optical rotation)[22] to those reported for xestobergsterol A.[4,23]

**Scheme 3**



We have had two analogues of xestobergsterol A tested for inhibition of histamine release from rat mast cells, namely 7-deoxyxestobergsterol A (**1d**)[9] and the tetracyclic analogue with the simple cholesterol side chain, **16**. Both compounds were very effective inhibitors in this assay ($IC_{50}$: **1d**, 500 nM; **16**, 750 nM),[24] indicating that both the E ring and the oxidized side chain are not required for potent activity.

In summary, we have achieved the first total synthesis of xestobergsterol A by an efficient route, which utilizes the Breslow remote functionalization process. Two analogues prepared by this route have good activities in the standard histamine release assay and may prove to be useful leads in the search for new compounds for the treatment of allergic diseases. Further work on the synthesis of the other members of this class is in progress.

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**Supporting Information Available:** Spectroscopic data (proton and carbon NMR and IR) for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Parish, E. J.; Wei, T.-Y.; Livant, P. *Lipids* **1987**, *22*, 760. (b) Miller, R. A.; Li, W. W.; Humphrey, G. R. *Tetrahedron Lett.* **1996**, *37*, 3429. (c) Selinsky, B. S.; Jones, S. R.; Kinney, W. A.; Rao, M. N.; Zhang, X.; Tham, F. S. *J. Org. Chem.* **1998**, *63*, 3786. (d) Pearson, A. J.; Chen, Y.-S.; Han, G. R.; Hsu, S.-Y.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 269. (e) Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. C. *Tetrahedron Lett.* **1997**, *38*, 119.

(13) Zderic, J. A.; Kubitschek, M. J.; Bonner, W. A. *J. Org. Chem.* **1961**, *26*, 1635.

(14) For example, treatment of the triol **12** with various silyl protecting groups afforded mainly the disilyl ether. The triacetate could be prepared but was unstable to the basic oxidation conditions of the next step.

(15) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

(16) In this reaction, we also isolated 13% of the 14$\beta$-H 15$\beta$-alcohol which was oxidized to the ketone **15**.

(17) The stereochemistry of the 14-hydrogen was easily established by proton NMR, since the methyl group at C-13 resonates at higher field ($\delta$ ~0.7−1.0) in the trans CD ring compounds and at lower field ($\delta$ ~1.1−1.3) in the cis CD ring compounds, e.g., at $\delta$ 0.78 in **14** and at $\delta$ 1.16 in **15**. For additional examples, see: Johnson, T. W. Ph.D. Thesis, UCLA, 1999.

(18) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

(19) Martin, J. C.; Dess, D. B. *J. Org. Chem.* **1983**, *48*, 4156.

(20) Since the epimerization of **14** to give **15** is quite fast under these conditions, we believe that epimerization precedes the aldol condensation in this system.

(21) 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. This is especially true of the only very low yielding step, namely the hydroboration−oxidation of **22**, which usually proceeds in much higher yield, e.g., **7** → **9** in 79% yield.

(22) The optical rotation—$[\alpha]_D^{25} = -37.7°$, $c = 2.8$ ($CHCl_3$)—is identical with that reported for xestobergsterol A.[23]

(23) We thank Dr. Akemi Umeyama for providing us with a sample of natural xestobergsterol A and Dr. Maseo Takei for informing us of the optical rotation.

(24) We thank Dr. Takei for performing these assays.