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An Efficient, Stereocontrolled Synthesis of the 25-(*R*)-Diastereomer of Dafachronic Acid A from β-Ergosterol

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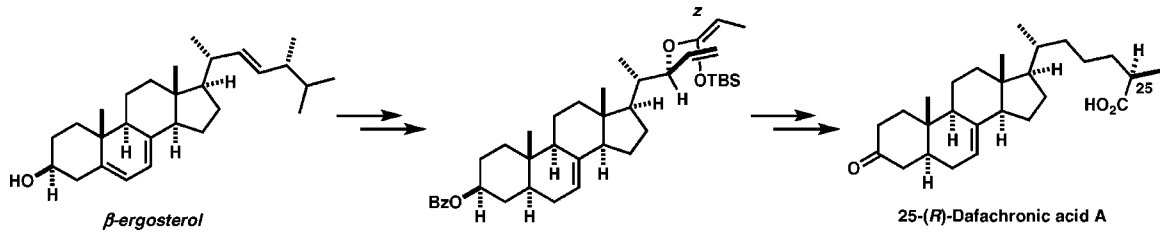
ABSTRACT



A direct and stereocontrolled synthesis of the 25-(*R*)-diastereomer of dafachronic acid A from β-ergosterol has been developed.

The lifespan of *C. elegans* can be increased from 2 weeks to ca. 12 weeks by loss-of-function mutations in two genes, daf-2 and daf-9,[1] the daf-9 gene codes for a protein (DAF-9) of the cytochrome P450 class of steroid oxidases. A product of the DAF-9 pathway serves as a ligand for another protein, DAF-12, that activates the daf-12 gene and restores the normal wild-type state of *C. elegans*. Mangelsdorf, Antebi, and their colleagues screened a large number of steroids and compared their activity on *C. elegans* to the natural ligand, which was only available in trace amounts. They found that the most active of the steroids tested contained a 3-keto group, a Δ^7 olefinic linkage, or a 26-carboxylic function.[2] From these observations, they surmised that the natural regulator might be the steroidal acid **1** (Figure 1), which they named dafachronic acid. We recently synthesized **1** stereoselectively from β-stigmasterol.[3] The activity of synthetic **1** (specifically the 25-(*S*)-diastereomer, which we have termed dafachronic acid A) was found to correspond to that of the natural DAF-12 ligand. At subnanomolar concentrations synthetic **1** rescued mutant *C. elegans* from the diapausal (i.e., low metabolism, quiescent) state displaying a potency equal to that of the natural DAF-12 ligand.

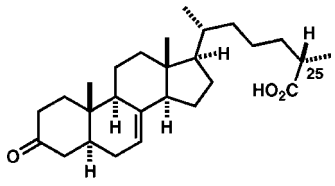


Figure 1. Chemical structure of dafachronic acid A (**1**).

In this paper we report the stereocontrolled and efficient synthesis of **2**, the 25-(*R*)-diastereomer of **1**, starting from the abundant β-ergosterol by the route summarized in Scheme 1. We chose β-ergosterol as the starting point not only because of its abundance but because the Δ^7 olefinic linkage is already in place. In addition, there is some evidence

(1) (a) Motola, D. L.; Cummins, C. L.; Rottiers, V.; Sharma, K. K.; Li, T.; Li, Y.; Suino-Powell, K.; Xu, H. E.; Auchus, R. J.; Antebi, A.; Mangelsdorf, D. J. *Cell* **2006**, *124*, 1209−1223. (b) Gerisch, B.; Rottiers, V.; Li, D.; Motola, D. L.; Cummins, C. L.; Lehrach, H.; Mangelsdorf, D. J.; Antebi, A. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 5014−5019. (c) For an online resource on *C. elegans*, see: http://www.wormbook.org.

(2) Rottiers, V.; Motola, D. L.; Gerisch, B.; Cummins, C. L.; Nishiwaki, K.; Mangelsdorf, D. J.; Antebi, A. *Dev. Cell* **2006**, *10*, 473−482.

(3) Giroux, S.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 9866−9867.

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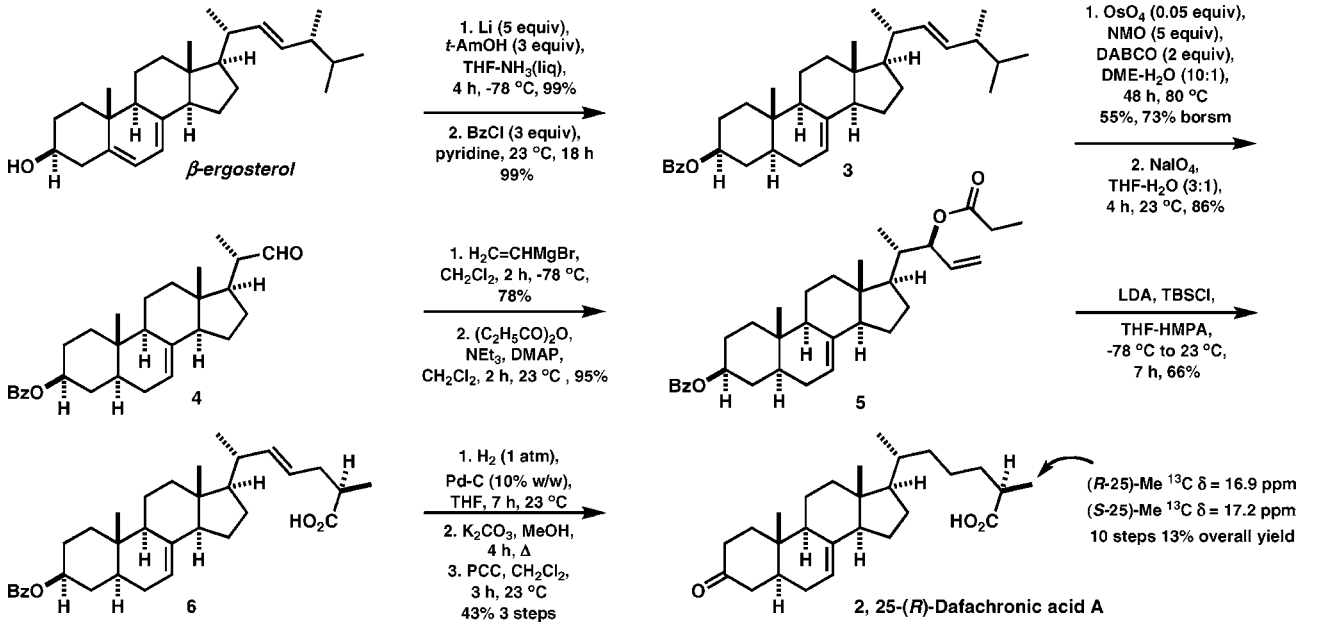
Scheme 1. Synthesis of **2** from β-Ergosterol



that the same $\Delta^{5,7}$-diene subunit might be present in a biosynthetic precursor of **1**. Specifically, a protein on the pathway to **1**, DAF-36, is homologous to a known oxidase that produces the $\Delta^{5,7}$-diene system (personal communication from Dr. Antebi).

A key step in the realization of the synthesis of **2** was our discovery that β-ergosterol could be selectively reduced at the Δ^5 linkage by a slow addition of a THF solution containing 3 equiv of *tert*-amyl alcohol to a solution of 5 equiv of Li in liquid NH_3 at −78 °C. Benzoylation of the reduction product (BzCl, pyridine) afforded the benzoate **3** in nearly quantitative overall yield. Selective oxidation of the Δ^{22} double bond was effected by using OsO_4(catalytic) and *N*-methylmorpholine *N*-oxide (NMO) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv) in a mixture of 1,2-dimethoxyethane and H_2O (10:1) at 80 °C for 48 h, which afforded the 22,23-diol in 55% yield along with recovered **3** (18%) after flash chromatography on silica gel. Oxidative cleavage ($NaIO_4$, THF−H_2O) of the diol afforded aldehyde **4** in 86% yield. Addition of vinylmagnesium bromide to aldehyde **4** in CH_2Cl_2 at −78 °C led to the desired Felkin product in 78% yield, which was acylated by using propionic anhydride, NEt_3, and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to give the propionate **5**. This was then subjected to Claisen rearrangement.[4] Deprotonation of **5** with LDA in a mixture of THF−HMPA (4:1) for 45 min at −78 °C and trapping of the resulting enolate with *tert*-butyldimethylsilyl chloride (TBSCl) led to the *Z*-silylketene acetal, which rearranged upon heating to room temperature to the desired δ,γ-unsaturated acid **6** as a single diastereomer (25*R*/25*S* > 20:1) in 66% yield. The acid **6** was then converted to **2** by using the following sequence: (1) selective reduction of the Δ^{22} olefinic linkage in the presence of the more hindered Δ^7 double bond, using H_2−Pd/C in THF; (2) saponification of the 3-*O*-benzoate with K_2CO_3 in MeOH; and (3) oxidation of the resulting alcohol with 1.5 equiv of pyridinium chlorochromate (PCC) in CH_2Cl_2. The synthesis of **2** described herein is short (10 steps with an overall yield of 13%) and uses β-ergosterol, a cheap starting material. A detailed biological comparison of synthetic **1** and **2** is now underway in the laboratory of Dr. Adam Antebi.

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Supporting Information Available: Experimental protocols and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452.