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A Simple Enantioselective Synthesis of Serratenediol

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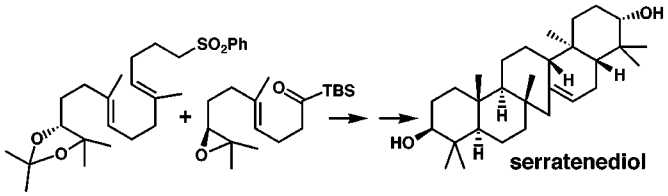
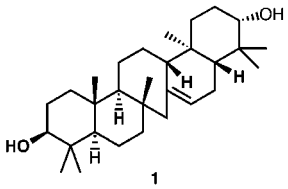
ABSTRACT

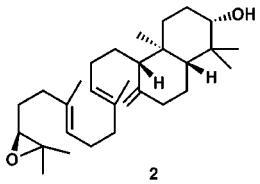


A short synthesis of serratenediol is described, which involves a number of powerful key steps including (1) catalytic enantioselective syntheses of the phenyl sulfone and acylsilane shown above, (2) their coupling, and (3) further stereoselective cationic cyclizations.

Serratenediol (**1**),[1] a pentacyclic triterpenoid containing a unique seven-membered central ring, is the parent member of a skeletal class of more than 30 natural products.[2] Although the biosynthesis of **1** probably involves the (*S*,*S*)-2,3,22,23-bisepoxide of squalene, it is not clear whether the final cyclization involves tricyclization of the bicyclic epoxide **2** or monocyclization of onocerin (**3**).[3] In this paper we describe the first enantioselective synthesis of **1** by a short, biomimetic pathway involving a tricyclization of the *N*-phenylcarbamate **13** (Scheme 1).[4]



1



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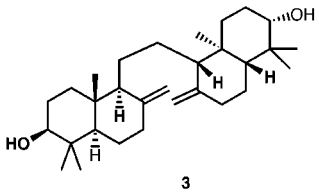

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The control of absolute stereochemistry in the synthesis was achieved using a transition structure designed catalyst (**4**) for enantio- and position-selective terminal dihydroxylation of polyprenoids that has recently been described.[5] Thus, reaction of (*E*,*E*)-farnesyl acetate with 1 mol % of **4**, 0.5 mol % of $K_2OsO_4 \cdot 2H_2O$, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, and 1 equiv of $CH_3SO_2NH_2$ in 1:1 *t*-BuOH/H_2O at 0 °C for 4 h produced the triol monoacetate **5**[5,6] of 97% ee in 72% yield (84% based on recovered farnesyl acetate). Transformation of **5** to the bromo acetonide **6** was effected by acetonide formation, deacetylation, and allylic bromide formation, as shown in Scheme 1. Displacement of bromide in **6** by $CuCH_2COOEt$[7] afforded the bishomologated ester **7**, which was sequentially transformed into the corresponding alcohol, primary iodide, and phenyl sulfone **8**, as outlined. Reaction of the α-lithio derivative of **8** with the acylsilane **9**[8] provided stereoselectively the *Z*-coupled silyl enol ether

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(4) For an earlier synthesis of racemic **1** (in less than 0.01% yield), see: Prestwich, G. D.; Labovitz, J. N. *J. Am. Chem. Soc.* **1974**, *96*, 7103.

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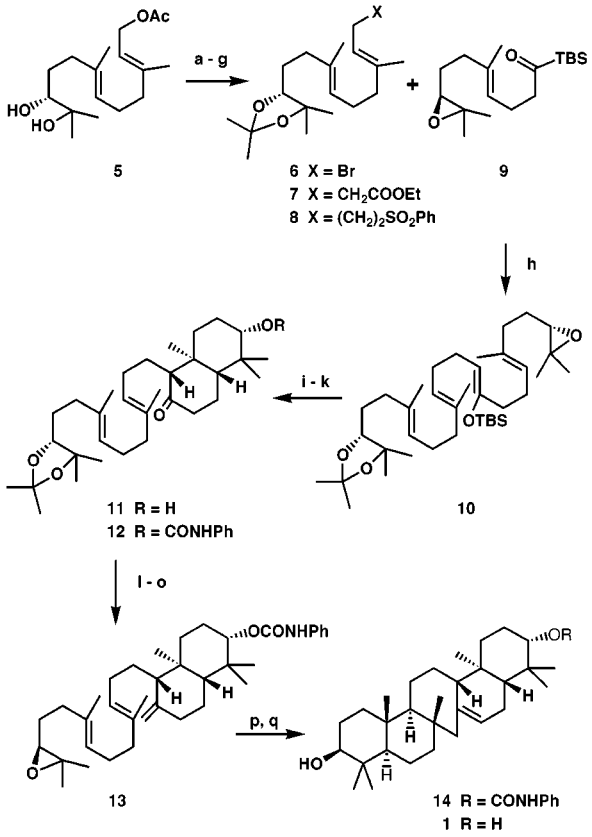
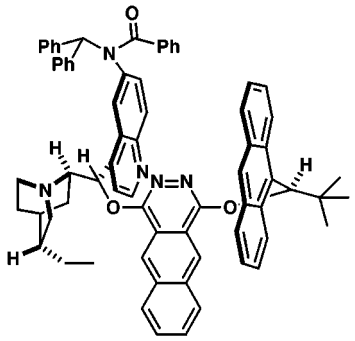
Scheme 1[a]



[a] (a) $(MeO)_2$ CMe_2, cat. *p*-TsOH, 0.5 h, 23 °C. (b) K_2CO_3, MeOH, 1 h, 23 °C. (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 1 h, −42 °C, then 0.5 h, 0 °C; then LiBr, THF, 1 h, 0 °C (91% of **6** from **5**). (d) 2 equiv of LDA, 2 equiv of EtOAc, 4 equiv of CuI, THF at −110 °C, then −110 to −30 °C and 1 h at −30 °C (92% of **7** from **6**). (e) $LiAlH_4$, Et_2O, 1 h at 23 °C, then 0.5 h at 40 °C. (f) Ph_3P, imidazole, I_2, CH_2Cl_2, 0.5 h, 23 °C. (g) 2 equiv of $PhSO_2Na$, DMF, 24 h, 23 °C (78% of **8** from **7**). (h) **8** + BuLi in 1:1 THF/Et_2O for 0.5 h at −78 °C, then **9** for 0.5 h at 0 °C (89% of **10**). (i) 1.2 equiv of $MeAlCl_2$, CH_2Cl_2, 0.3 h at −94 °C. (j) Bu_4NF, THF then 10% KOH in CH_3OH for 3 h at reflux (75% of **11** from **10**). (k) PhNCO, py, 12 h at 23 °C. (l) CH_3PPh_3Br, KO*t*Bu, C_6H_6, 2 h at 80 °C (68% of **12** from **11**). (m) 3:1 HOAc/H_2O, 5 h at 50 °C. (n) CH_3SO_2Cl, py, 12 h at 23 °C. (o) K_2CO_3/MeOH, 5 h at 23 °C (80% of **13** from **12**). (p) 1.3 equiv of $MeAlCl_2$, CH_2Cl_2, 1 h at −78 °C. (q) 40% KOH, MeOH, 1.5 h at 100 °C, then silica gel chromatography (21% of **1** from **13**).

10, in a second key step in the synthesis of **1**. Conversion of **10** to the bicyclic hydroxy ketone **11** was effected by $MeAlCl_2$-catalyzed, epoxide-initiated cationic cyclization followed by treatment of the product with Bu_4NF to cleave silyl ethers formed during this conversion and then methanolic base to convert any C(α) axial diastereomer to the more stable equatorial form **11**. The hydroxyl group of **11** was protected as the phenylcarbamate, and the acetonide unit was transformed in the usual way to the epoxide subunit of **13**. Finally, $MeAlCl_2$-catalyzed tricyclization of **13** followed by deprotection and silica gel chromatography gave levorotatory serratenediol corresponding to the natural product by comparison of ^1H and ^{13}C NMR spectra, infrared spectrum, optical rotation, and melting point.[1,2,9]



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The success of the short and simple synthesis of the complex serratenediol structure **1** by the pathway shown in Scheme 1 depended on several crucial steps, including the application of catalyst **4** to the construction of chiral glycol **5**, the stereoselective coupling of **8** and **9** to form **10**, and the cationic cyclizations used to generate **11** and **14**. The power of these epoxide-initiated, stereoselective cationic cyclizations, nonenzymic mimics of biosynthetic processes, is clearly demonstrated here, as it has been in other recent syntheses.[10]

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Supporting Information Available: Full experimental procedures for the synthesis of **1** from geranyl and farnesyl acetate. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See, for example: (a) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999. (b) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (c) Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (d) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (e) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149.