A Concise, Biomimetic Total Synthesis of (+)-Davanone

Karen C. Morrison, Jonathan P. Litz, Kathryn P. Scherpelz, Paul D. Dossa, and David A. Vosburg*

Department of Chemistry, Harvey Mudd College, 301 Platt Boulevard, Claremont, California 91711

david_vosburg@hmc.edu

Received April 2, 2009



A concise, biomimetic synthesis of the antifungal and antispasmodic natural product (+)-davanone is described. The key stereoselective reactions are a Sharpless asymmetric epoxidation, a thiazolium-catalyzed esterification, and a palladium-mediated cyclization. All carbons are derived from isoprene units and no protecting groups are used, permitting an atom- and redox-economical synthesis.

Davanone, a sesquiterpene first isolated from *Artemisia pallens* in 1968,¹ is the principle component of davana oil and exhibits both antifungal² and antispasmodic³ properties. The core of its structure is shared with several other secondary metabolites present in davana oil, some of which are shown in Figure 1.⁴ Davanone has attracted significant synthetic interest over the years,⁵ with noteworthy racemic syntheses by Bartlett^{5d} and Molander.^{5f} Fully aware that the only enantioselective synthesis exceeds 20 steps and generates a mixture of davanone and artemone,^{5e} we sought a novel, concise, and enantioselective route to this natural product.

Our synthetic planning was guided by the proposed biosynthesis of davanone shown in Scheme 1. Feeding studies have confirmed that davanone and artemone derive





from farnesyl diphosphate,⁶ and we hypothesized that allylic oxidation and alkene hydration could generate hydroxyketone **1**. Cyclization of such a substrate, with loss of diphosphate, would then directly produce davanone.⁷

Our synthesis began with the known epoxyalcohol **2**,⁸ available in two steps from geranyl acetate via allylic hydroxylation⁹ and Sharpless asymmetric epoxidation.⁸ Oxidation to epoxyaldehyde **3** proceeded smoothly with DMSO/SO₃/pyridine; however, generating *anti*-hydroxyester

⁽¹⁾ Sipma, G.; Van der Wal, B. Recl. Trav. Chim. Pays-Bas. 1968, 87, 715–720.

⁽²⁾ Vajs, V.; Trifunovic, S.; Janackovic, P.; Sokovic, M.; Milosavljevic, S.; Tesevic, V. J. Serb. Chem. Soc. 2004, 69, 969–972.

⁽³⁾ Perfumi, M.; Paparelli, F.; Cingolani, M. L. J. Essent. Oil Res. 1995, 7, 387–392.

⁽⁴⁾ Misra, L. N.; Chandra, A.; Thakur, R. S. Phytochemistry 1991, 30, 549–552.

^{(5) (}a) Naegeli, P.; Weber, G. Tetrahedron Lett. 1970, 959–962. (b)
Ohloff, G.; Giersch, W. Helv. Chim. Acta 1970, 53, 841–843. (c) Birch,
A. J.; Corrie, J. E. T.; Subba Rao, G. S. R. Aust. J. Chem. 1970, 23, 1811–1817. (d) Bartlett, P. A.; Holmes, C. P. Tetrahedron Lett. 1983, 24, 1365–1368. (e) Honda, Y.; Ori, A.; Tsuchihashi, G. Chem. Lett. 1987, 1259–1262. (f) Molander, G. A.; Haas, J. Tetrahedron 1999, 55, 617–624.

⁽⁶⁾ Akhila, A.; Sharma, P. K.; Thakur, R. S. Tetrahedron Lett. 1986, 27, 5885–5888.

⁽⁷⁾ Most likely via an allylic cation as in linalool synthase and methylbutenol synthase; see: Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181–222.





5 was more difficult. While other methods were unsatisfactory, Bode's thiazolium salt 4^{10} was quite effective at providing **5** using a non-aldol approach. To the best of our knowledge, this is the first use of Bode's carbene-catalyzed epoxide-opening reaction in a total synthesis.

Our next concern was the formation of the final stereocenter, as there are few examples of stereoselective allylic *O*-alkylations at tertiary centers with aliphatic alcohols.¹¹ We anticipated that the inherent diastereofacial preference of **5** would be to form *trans*-**6** rather than the desired *cis* product.¹² After screening a range of chiral catalysts and reaction conditions, we found that Pd₂dba₃ with (*S*)-C₃-TunePhos¹³ enabled us to overcome the substrate's diastereofacial bias and favor *cis*-davana acid ethyl ester (**6**), itself a trace natural component of davana oil.^{4,14} (*R*)-C₃-TunePhos gave substantial (>12:1) selectivity for the undesired *trans* product.

Our route converged with the racemic synthesis of Haas and Molander^{5f} at *anti,cis*-Weinreb amide **7**, which we prepared with a three-step isolated yield of 31% from aldehyde **3**. Other than optical rotation, the physical properties of (+)-**7** matched those reported for (\pm)-**7**,^{5f} and reaction of this Weinreb amide with prenylmagnesium chloride proceeded smoothly to produce (+)-davanone and complete the synthesis.

(14) Dibenzylideneacetone co-elutes with $\mathbf{6}$ but can be chemoselectively reduced with sodium borohydride or removed after the following step.

In summary, we have achieved the shortest enantioselective synthesis of davanone to date, requiring merely seven steps from geranyl acetate and proceeding with a yield of 18% over five steps from epoxyalcohol **2**. The atom



economy¹⁵ and redox economy¹⁶ are considerable, as each carbon in the final product derives from an isoprene unit, no protecting groups are used, and superfluous redox manipulations are avoided. Our route parallels the biosynthetic proposal in Scheme 1 and features the first use of a thiazolium-catalyzed epoxide opening in the synthesis of a natural product.

Acknowledgment. This work was supported by a Camille and Henry Dreyfus Foundation Faculty Startup Award, National Science Foundation REU grant CHE-0353662, the Beckman Foundation, the Harvey Mudd College (HMC) and Pomona College Chemistry Departments, the Christian Scholars Foundation, and Pfizer Summer Undergraduate Research Fellowships (to K.C.M. and J.P.L.). We thank Ryan J. Pakula and Kanny K. Wan from HMC for their contributions to this project.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900697W

⁽⁸⁾ Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. 1980, 102, 5974–5976.

^{(9) (}a) Umbreit, M. A.; Sharpless, K. B. J. Am. Chem. Soc. **1977**, 99, 5526–5528. (b) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. J. Org. Chem. **1988**, 53, 4929–4938.

⁽¹⁰⁾ Chow, K.Y.-K.; Bode, J. W. J. Am. Chem. Soc. 2004, 126, 8126-8127.

^{(11) (}a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353–4362. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (c) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. J. Org. Chem. **2003**, *68*, 8092–8096.

⁽¹²⁾ For related cyclizations with achiral catalysts, see ref.11a

^{(13) (}a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. J. Org. Chem. **2000**, 65, 6223–6226. (b) Raghunath, M.; Zhang, X. Tetrahedron Lett. **2005**, 46, 8213–8216.

⁽¹⁵⁾ Trost, B. M. Science 1991, 254, 1471-1477.

^{(16) (}a) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.;
Llamas, T.; Pohjakallio, A.; Baran, P. S. J. Am. Chem. Soc. 2008, 130,
17938–17954. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Angew.
Chem., Int. Ed. 2009, 48, 2854–2867.