Biomimetic Total Synthesis

An Enantioselective Biomimetic Total Synthesis of (−)-Siccanin**

Barry M. Trost, Hong C. Shen, and Jean-Philippe Surivet*

Siccanin (**1**), a mold metabolite isolated from the culture broth of *Helminthosposium siccans* by Ishibashi in 1962,[1] possesses an unusual *cis*,*syn*,*cis*-fused alicyclic ring system. Siccanin exhibits potent antifungal activity, in particular against several pathogenic fungi,[2] and its clinical effectiveness against surface mycosis has also been established.[3]

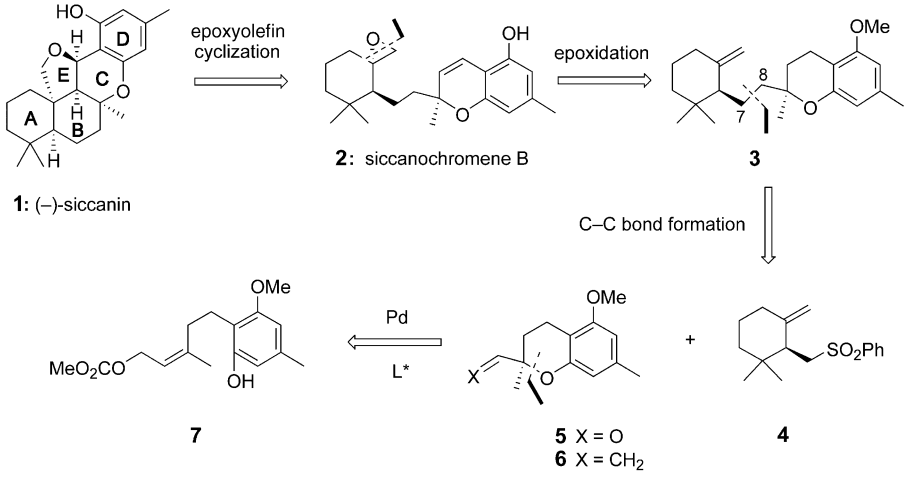
As a result of its interesting biological activity, siccanin has been the subject of a number of synthetic efforts.[4] However, only two successful racemic syntheses of this natural product have been reported to date.[4g–i] Herein we

[*] Prof. B. M. Trost, H. C. Shen, J.-P. Surivet
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

[**] We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences (GM-13598) for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California, San Francisco, supported by the NIH Division of Research Resources.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200351868



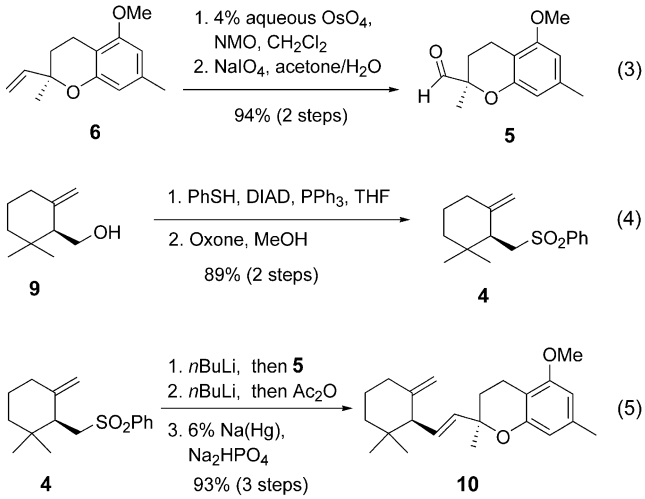
Scheme 1. Retrosynthetic analysis of (−)-siccanin (**1**). L = ligand.

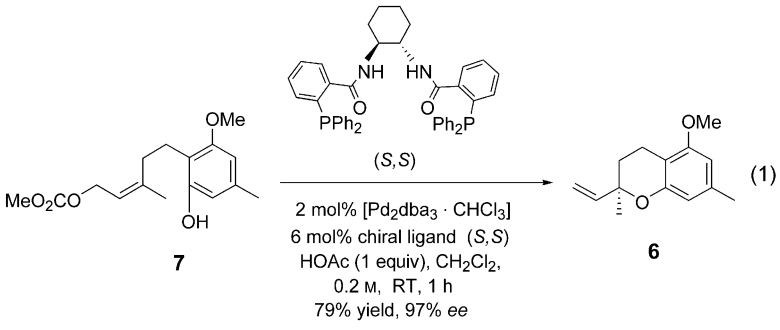
report the first enantioselective biomimetic total synthesis of (−)-siccanin (**1**), which has a Pd-catalyzed asymmetric allylic alkylation and an epoxyolefin radical cyclization as key steps (Scheme 1).

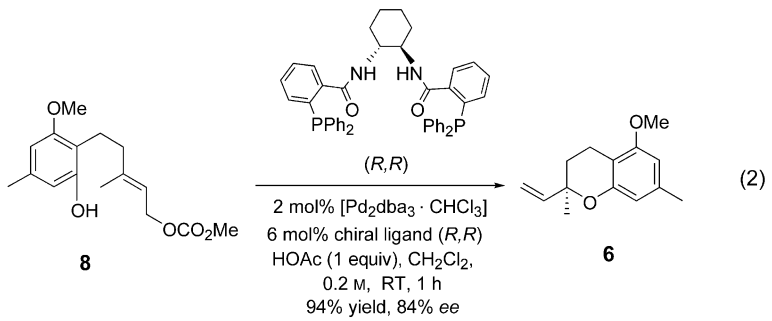
Inspired by the biosynthetic pathway of **1**,[5] we envisaged that its B and E rings could be formed through an epoxyolefin cyclization reaction of siccanochromene B (**2**), a proposed biosynthetic precursor of **1**. Siccanochromene B (**2**) can be seen to be derived from **3**, which itself could be prepared from a coupling reaction of chiral sulfone **4** with chiral chroman **5**. Chroman **6**, the precursor of **5**, is in turn available through a Pd-catalyzed asymmetric allylic alkylation reaction that has been developed recently by our group [Eq. (1) and (2)] (dba = dibenzylideneacetone).

Both the *Z* and the *E* allylic carbonates **7** and **8**, readily available through literature procedures,[6] can be used to prepare the same chiral chroman **6** by using ligands of opposite chirality [Eq. (1) and (2)]. Use of the *Z* allylic carbonate **7** afforded chiral chroman **6** with a substantially higher *ee* value (97%) than did use of its *E* counterpart **8** (84%). The resulting chiral chroman **6** underwent a dihydroxylation followed by oxidative cleavage to afford aldehyde **5** [Eq. (3)] (NMO = *N*-methylmorpholine *N*-oxide).

As shown in Equation (4), sulfone **4** can be prepared from the readily available chiral alcohol **9** in two steps (DIAD = diisopropyl azodicarboxylate.)[7] The subsequent Julia olefination[8] of chiral sulfone **4** with chiral chroman aldehyde **5** proceeded in high yield to give diene **10** [Eq. (5)].

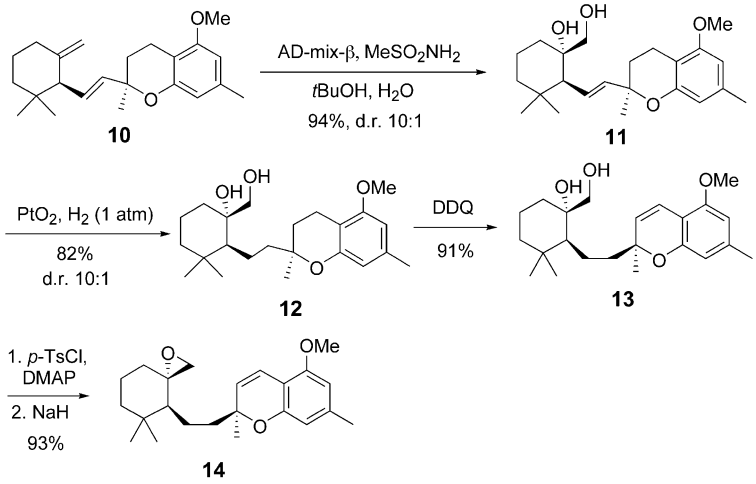




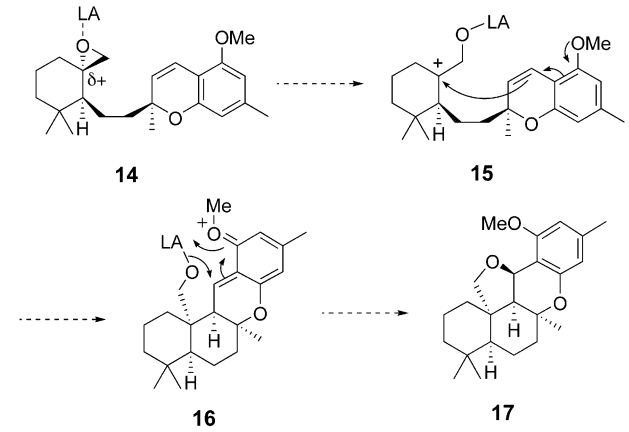


The epoxidation of diene **10** with *m*CPBA gave a complex mixture of products. In contrast, the dihydroxylation of **10** under the conditions of Sharpless and coworkers[9] took place chemo- and diastereoselectively to generate diol **11** (d.r. 10:1). The subsequent hydrogenation smoothly afforded chroman diol **12** (Scheme 2). DDQ oxidation[10] of diol **12** afforded chromene diol **13**, which was readily converted into epoxide **14**, the methyl ether of **2**.

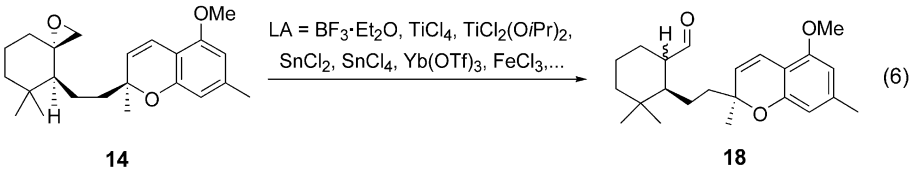
Our first approach to the biomimetic synthesis of **1** involved a proposed novel cationic cyclization (Scheme 3). A Lewis acid should open epoxide **14** to generate a tertiary cation **15**, which could then be trapped by the electron-rich olefin to form the B ring of siccanin, as in **16**. The resulting oxygen nucleophile could undergo a 1,4-addition to the adjacent enone, facilitated by the Lewis acid (LA), to construct the tetrahydrofuran ring and form the siccanin methyl ether (**17**). This proposal would allow **17** to be built up in one pot, with the cleavage of one C–O bond and the formation of one C–C bond and one C–O bond. However, when **14** was treated with a variety of Lewis acids, only decomposition or formation of 1,2-hydride-shift product **18** were observed, and no cyclization products were isolated [Eq. (6)].



Scheme 2. Synthesis of epoxide **14**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP = 4-(dimethylamino)pyridine; Ts = toluenesulfonyl.



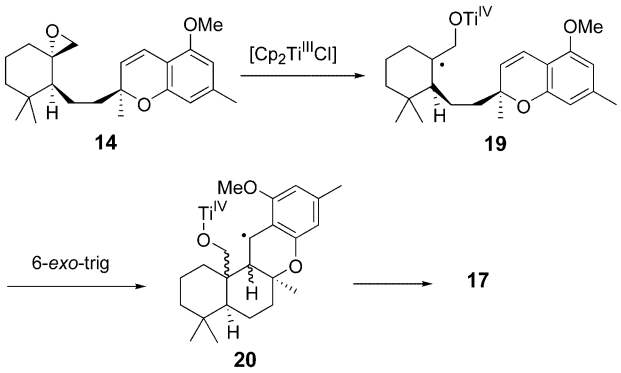
Scheme 3. Proposed biomimetic cationic cyclization.



(6)

To overcome this problem, we proposed a radical cyclization of epoxide **14** in the presence of $Cp_2Ti^{III}Cl$.[11] The resulting tertiary radical **19** should undergo a 6-*exo*-trig cyclization to form benzylic radical **20** (Scheme 4). After considerable experimentation, we were pleased to observe that the Ti^{III}-mediated cyclization of **14** afforded the desired tetracyclic compound **21**, and the 5-*epi*-siccanin methyl ether (**22**) as a side product, in a 3:1 ratio and 81% combined yield [Eq. (7)].

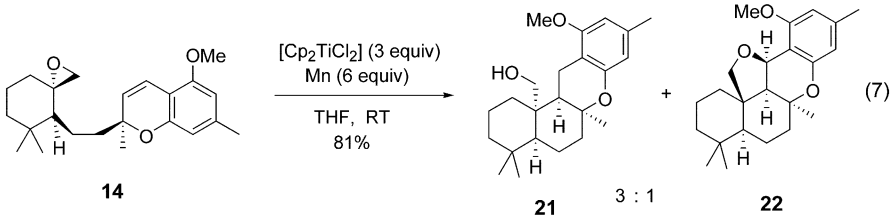
A mechanistic rationale for the formation of **21** and **22** is proposed in Scheme 5. The Ti^{III} species, generated in situ by the reduction of titanocene dichloride with manganese, opens epoxide **14** to form a tertiary radical **19**. Intermediate **19** then cyclizes in a 6-*exo*-trig fashion to form benzylic radical **23**, which reacts further with a second equivalent of the Ti^{III} species to form a C–Ti^{IV} bond. Subsequent hydrolysis leads to the formation of tetracyclic product **21** with the desired stereochemistry. Alternatively, **19** may undergo cyclization to benzylic radical **25**, which is diastereomeric with respect to **23**. It appears that the proximity of the Ti^{IV}-bonded oxygen atom to the benzylic carbon radical in **25** leads to a further cyclization. Radical recombination as illustrated liberates Ti^{III} and produces **22**.



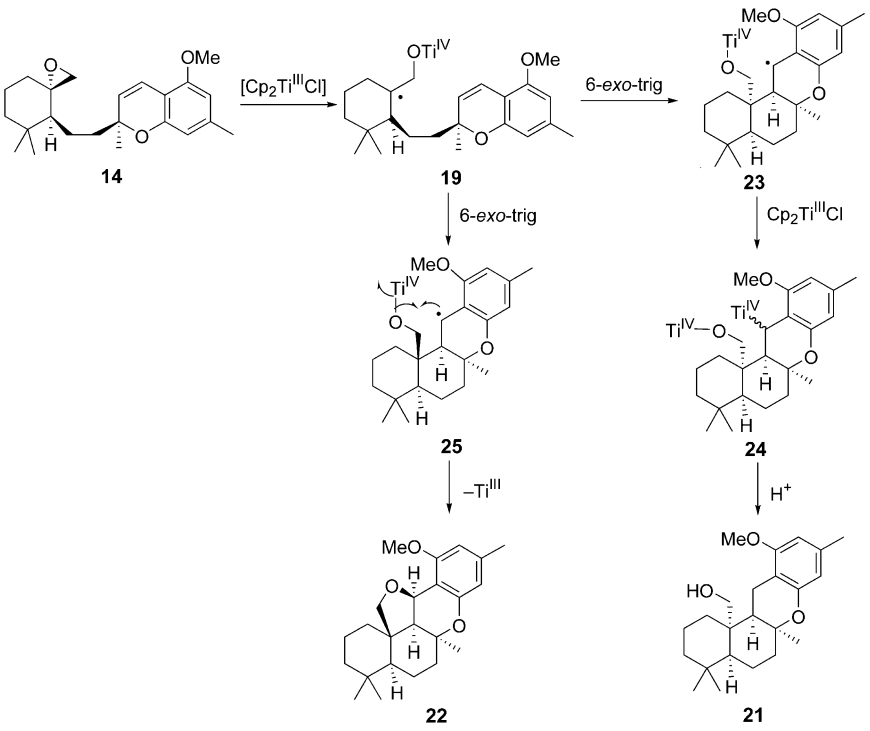
Scheme 4. Proposed biomimetic radical cyclization. Cp = cyclopentadienyl.

The final key step in the synthesis of siccanin involves a free-radical remote functionalization of **21** under conditions reported by Suarez and co-workers[12] to provide pentacyclic compound **28**, presumably via iodide **26** and oxonium ion **27**(Scheme 6). PM3 calculations showed that the energy of natural siccanin methyl ether (**28**) is 16.5 kcal mol^{-1} lower than that of 11-*epi*-siccanin methyl ether (**29**). The energy of the transition states that lead to **28** or **29** should reflect the strain energy of the product. Therefore, the product with significantly lower energy is formed preferentially. Furthermore, the preferred conformation of intermediate **27** acts as a constraint on the hydroxy nucleophile to attack **27** from the face that leads to the *cis*-fused ring system of the desired pentacyclic compound **28** (Scheme 6).

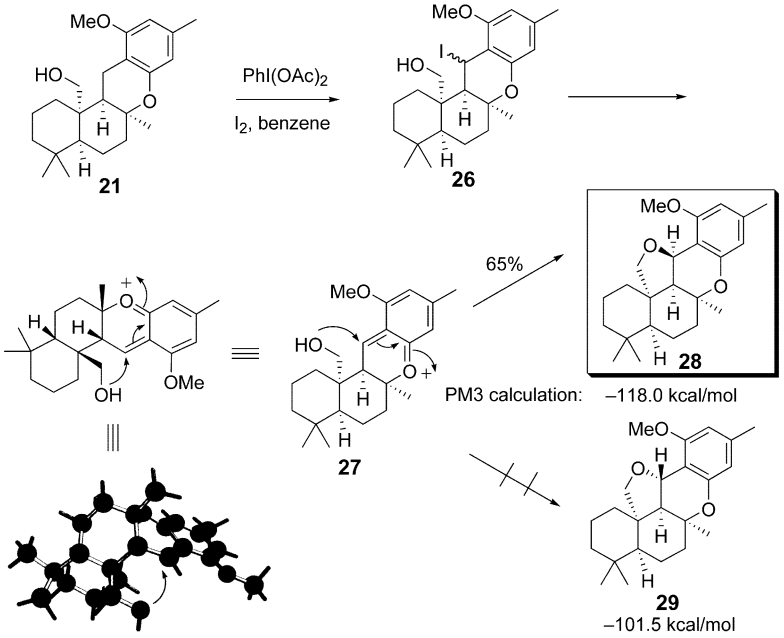
Finally, the pentacyclic compounds **28** and **22** were demethylated to afford (−)-siccanin (**1**) and (−)-5-*epi*-sicca-



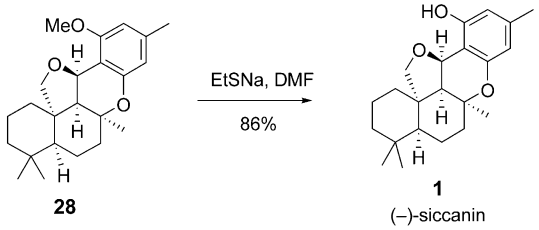
(7)



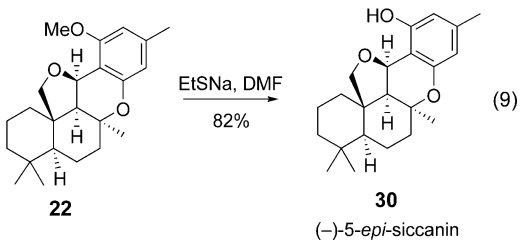
Scheme 5. Proposed mechanism for the radical cyclization.



Scheme 6. The synthesis of pentacyclic compound **28**.



(8)



(9)

nin (**30**), respectively [Eq. (8) and (9)] (DMF = *N*,*N*-dimethylformamide).

In summary, we have carried out the first enantioselective total synthesis of (−)-siccanin (**1**), inspired by the biosynthetic route and based on our development of the Pd-catalyzed asymmetric allylic alkylation and a novel radical epoxide cyclization. Our synthesis consists of 13 linear steps from allyl carbonate **7** or **8.** These results may have implications for the understanding of the biosynthetic pathway—that is, whether the corresponding biocyclization is cationic or radical in nature.

Received: May 12, 2003 [Z51868]

Keywords: asymmetric synthesis · biomimetic synthesis · cyclization · natural products · radical reactions

[1] K. J. Ishibashi, *J. Antibiot. Ser. A* **1962**, *15*, 161.
[2] a) K. Ishibashi, K. Hirai, M. Arai, S. Sugasawa, A. Endo, A. Yasumura, H. Matsuda, T. Muramatsu, *Annu. Rep. Sankyo Res. Lab.* **1970**, *22*, 1; b) M. G. Belloti, L. Riviera, *Chemioterapia* **1985**, *4*, 431.
[3] a) D. Crippa, C. G. Albanese, G. P. Sala, *G. Ital. Dermatol. Venereol.* **1985**, *120*, LVII and references therein; b) M. Arai, K. Ishibashi, H. Okazaki, *Antimicrob. Agents Chemother.* **1969**, 247; c) S. Sugawara, *Antimicrob. Agents Chemother.* **1969**, 253.
[4] a) S. Nozoe, K. Hirai, *Tetrahedron* **1971**, *27*, 6073; b) S. Oida, Y. Ohashi, A. Yoshida, E. Ohki, *Chem. Pharm. Bull.* **1972**, *20*, 2634; c) A. Yoshida, S. Oida, Y. Ohashi, C. Tamura, E. Ohki, *Chem. Pharm. Bull.* **1972**, *20*, 2642; d) S. Oida, Y. Ohashi, E. Ohki, *Chem. Pharm. Bull.* **1973**, *21*, 528; e) H. Liu, B. Ramani, *Tetrahedron Lett.* **1988**, *29*, 6721; f) M. Kato, Y. Matsuma, K. Heima, A. Yoshikoshi, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1991; g) M. Kato, K. Heima, Y. Matsuma, A. Yoshikoshi, *J. Am. Chem. Soc.* **1981**, *103*, 2434; h) M. Kato, Y. Matsuma, K. Heima, N. Fukamiya, C. Kabuto, A. Yoshikoshi, *Tetrahedron* **1987**, *43*, 711; i) B. M. Trost, F. J. Fleitz, W. J. Watkins, *J. Am. Chem. Soc.* **1996**, *118*, 5146.
[5] a) S. Nozoe, K. T. Suzuki, *Tetrahedron* **1971**, *27*, 6063; b) K. T. Suzuki, S. Nozoe, *Bioorg. Chem.* **1974**, *3*, 72; c) K. T. Suzuki, S. Nozoe, *J. Chem. Soc. Chem. Commun.* **1971**, 527; d) D. J. Goldsmith, C. F. Philips, *J. Am. Chem. Soc.* **1969**, *91*, 5862; e) D. J. Goldsmith, B. C. Clark, *Tetrahedron Lett.* **1967**, *8*, 1215.
[6] B. M. Trost, N. Asakawa, *Synthesis* **1999**, 1491.

[7] H. Tanimoto, T. Oritani, *Tetrahedron* **1997**, *53*, 3527.
[8] a) M. Julia, J. M. Paris, *Tetrahedron Lett.* **1973**, 4833; b) P. Kocienski, *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 97.
[9] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[10] a) A. N. Starrat, A. Stoesl, *Can. J. Chem.* **1977**, *55*, 2360; b) V. K. Ahluwalia, R. S. Jolly, *Synthesis* **1982**, 74; c) D. R. Buckle, in *Encyclopedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. A. Paquette), Wiley, New York, **1995**, p. 1699.
[11] a) T. V. RajanBabu, W. A. Nugent, M. S. Beattie, *J. Am. Chem. Soc.* **1990**, *112*, 6408; b) A. Gansauer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500; c) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986; d) S. C. Roy, K. K. Rana, C. Guin, *J. Org. Chem.* **2002**, *67*, 3242.
[12] J. T. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salaza, E. Suarez, *Tetrahedron Lett.* **1984**, *25*, 1953.

