

Biomimetic Total Synthesis

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

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Siccanin (**1**), a mold metabolite isolated from the culture broth of *Helminthosporium 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]

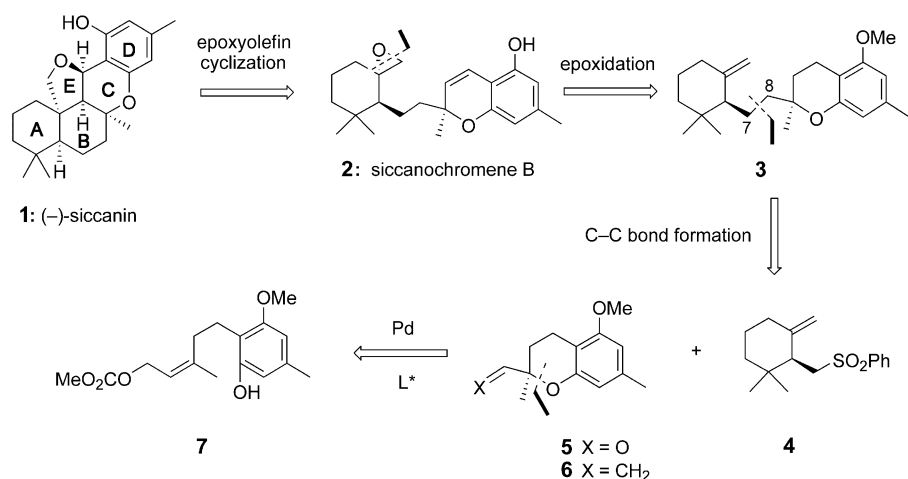
As a result of its interesting biological activity, siccanin has been the subject of a number of synthetic efforts.^[4] However, only two successful racemic syntheses of this natural product have been reported to date.^[4g–i] Herein we

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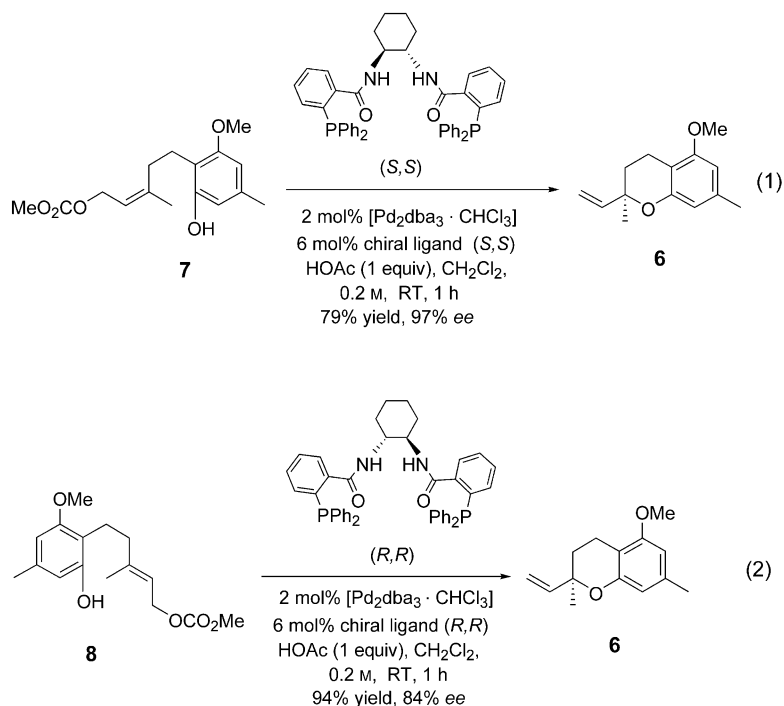


Scheme 1. Retrosynthetic analysis of (-)-siccanin (**1**). L = ligand.

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).

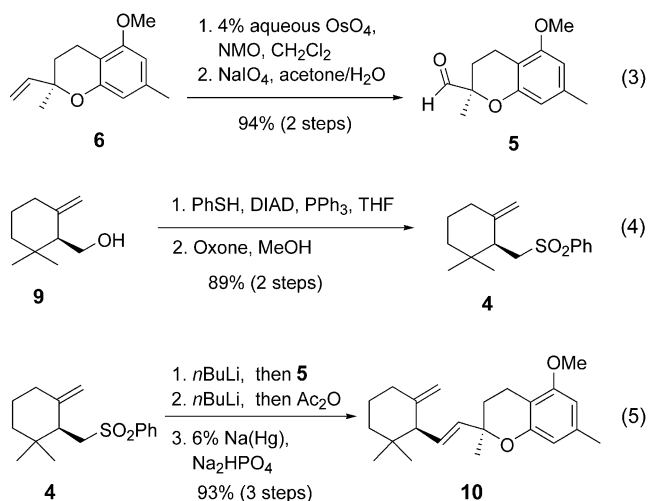
Inspired by the biosynthetic pathway of **1**,^[5] we envisaged that its B and E rings could be formed through an epoxyolefin cyclization reaction of siccanochromene B (**2**), a proposed biosynthetic precursor of **1**. Siccanochromene B (**2**) can be seen to be derived from **3**, which itself could 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



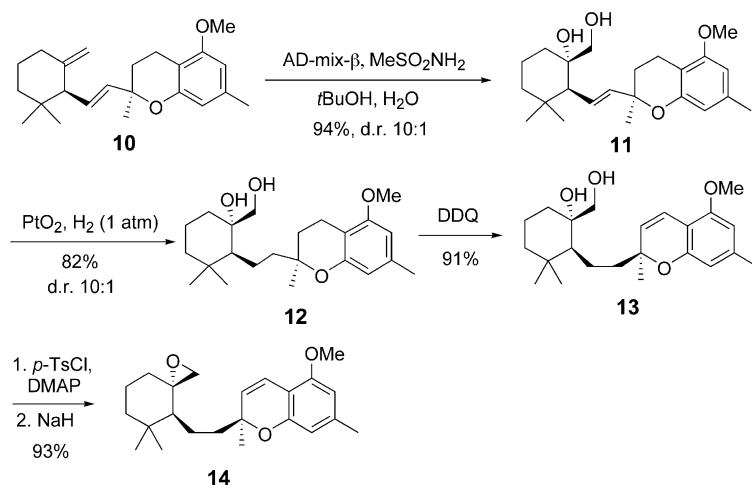
prepare the same chiral chroman **6** by using ligands of opposite chirality [Eq. (1) and (2)]. Use of the *Z* allylic carbonate **7** afforded chiral chroman **6** with a substantially higher *ee* value (97%) than did use of its *E* counterpart **8** (84%). The resulting chiral chroman **6** underwent 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)].

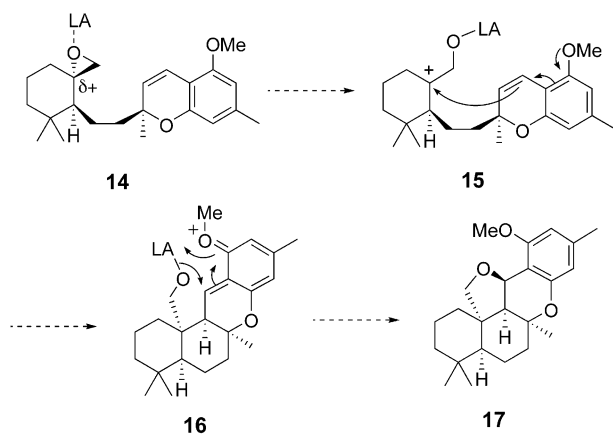


The epoxidation of diene **10** with *m*CPBA gave a complex mixture of products. In contrast, the dihydroxylation of **10** under the conditions of Sharpless and co-workers^[9] took place chemo- and diastereoselectively to generate diol **11** (d.r. 10:1). The subsequent hydrogenation smoothly afforded 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**.

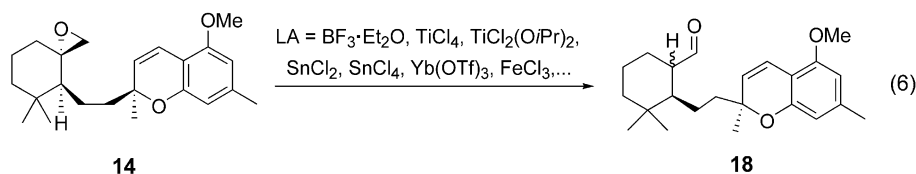
Our first approach to the biomimetic synthesis of **1** involved a proposed novel cationic cyclization (Scheme 3). A Lewis acid should open epoxide **14** to generate a tertiary cation **15**, which could then be trapped by the electron-rich olefin to form the B ring of siccanin, as in **16**. The resulting 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.



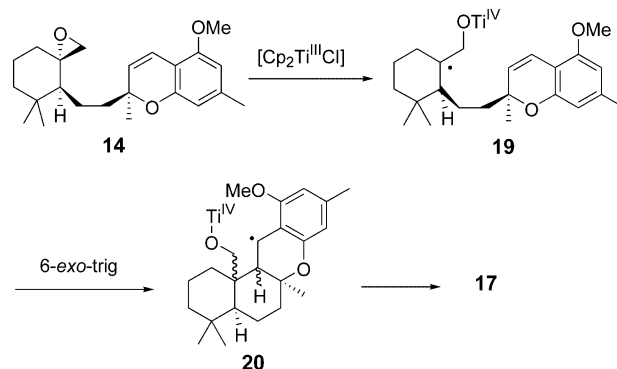
Scheme 3. Proposed biomimetic cationic cyclization.



To overcome this problem, we proposed a radical cyclization of epoxide **14** in the presence of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.^[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**.

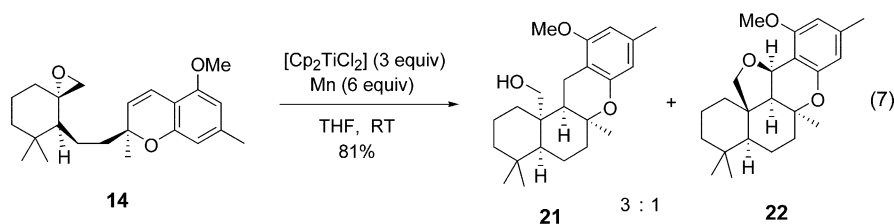


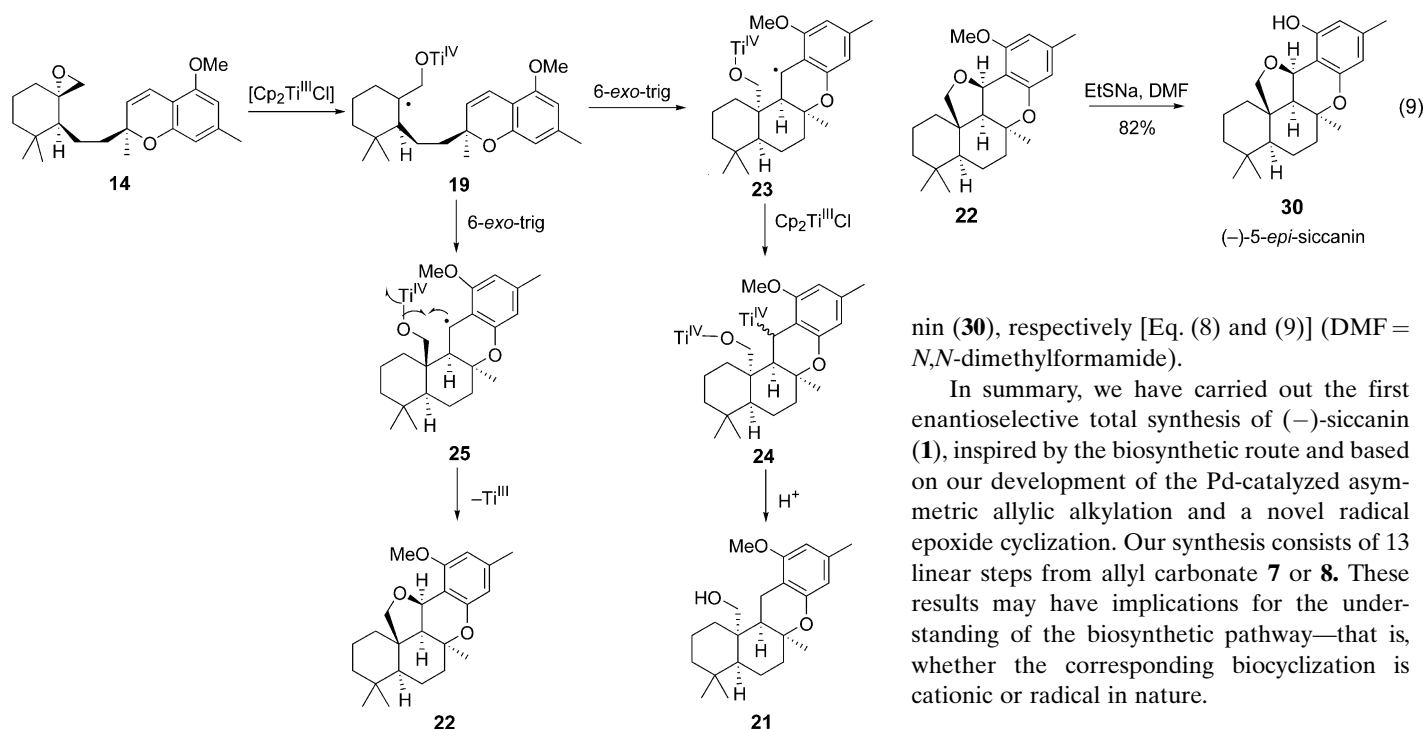
Scheme 4. Proposed biomimetic radical cyclization. Cp = cyclopentadienyl.

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

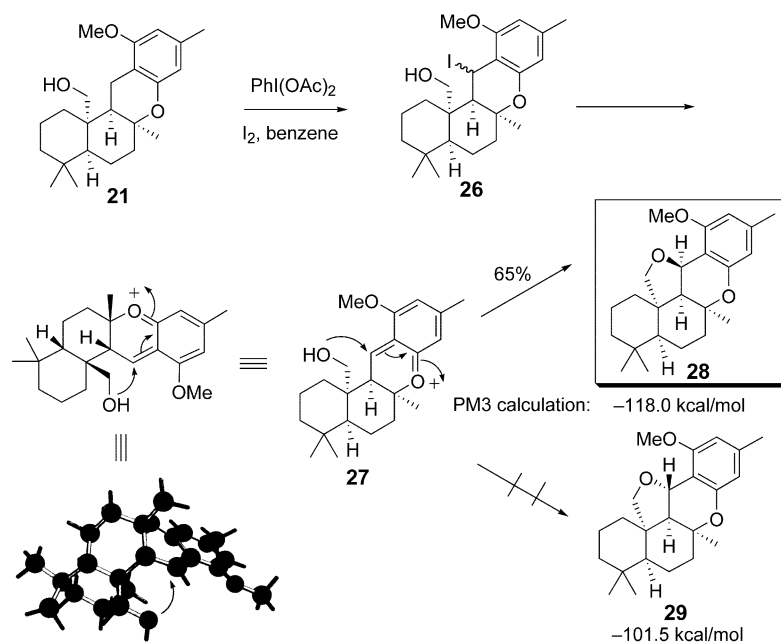
of intermediate **27** acts as a constraint on the hydroxy nucleophile to attack **27** from the face that leads to the *cis*-fused ring system of the desired pentacyclic compound **28** (Scheme 6).

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

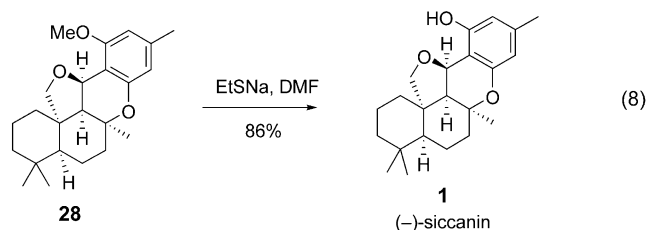




Scheme 5. Proposed mechanism for the radical cyclization.



Scheme 6. The synthesis of pentacyclic compound 28.



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.

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