J|A|C|S
ARTICLES
Published on Web 09/03/2004

Biomimetic Enantioselective Total Synthesis of (−)-Siccanin via the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA) and Sequential Radical Cyclizations

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

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

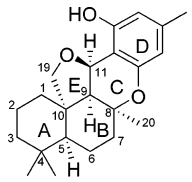
Received April 2, 2004; E-mail: bmtrost@stanford.edu

Abstract: (−)-Siccanin (**1**), a natural product possessing significant antifungal properties, was synthesized enantioselectively via a biomimetic route. This synthetic route features two sequential radical cyclizations: a Ti(III)-mediated radical cyclization of epoxyolefin **48** to construct the B-ring, and a Suarez reaction to establish the tetrahyrofuran ring. Chiral chroman moiety of siccanin was prepared based on our recent development of the Pd-catalyzed asymmetric allylic alkylation (AAA) of phenol trisubstituted allyl carbonates. Several other members of the siccanin family were also synthesized including siccanochromenes A (**2**), B (**3**), E (**6**), F (**7**), and the methyl ether of siccanochromene C (**55**). These studies may shed light on the biosynthesis of this novel family of compounds.

1. Introduction

Siccanin (**1**) (Figure 1) is a mold metabolite first isolated from the culture broth of *Helminthosposium siccans* by Ishibashi in 1962.[1] The structure and absolute stereochemistry of siccanin (**1**) were subsequently established by X-ray crystallographic analysis of its *p*-bromosulfonate ester.[2] As depicted, siccanin (**1**) possesses an unusual cis, syn, cis-fused alicyclic ring system. It can be regarded as derived from a *cis*-fused drimane condensed with orcinol. This compound exhibits potent antifungal activity, particularly against the pathogenic fungi *Trichophyton interdigitale* and *Trichophyton asteroids* as well as *Epidermophyton* and *Mycosporum*.[3] Further studies have demonstrated that siccanin shows a 50% growth inhibition of *Trichophyton menatgraphytes* at a concentration of 0.3 μg/mL, and that its biological activity is repression of respiration by inhibition of succinate dehydrogenase.[4] The clinical effectiveness of siccanin against surface mycosis has also been established.[5]

After extensive scrutiny of the culture broth, siccanochromenes A−H (Figure 2), several congeners related to siccanin, were also isolated by Hirai, et al.[2] The drimanes are an important terpenoid class whose members exhibit broad biological activities including potent antifungal, antibacterial, cytotoxic, insecticidal, etc.[6]



1

Figure 1. (−)-Siccanin (**1**).

The comparison of the structures of minor metabolites of *H. siccans*, such as trans-γ-monocyclofarnesol, siccanochromene A (**2**) and siccanochromene B (**3**) with siccanin (**1**) made it possible to propose a biogenetic pathway leading to siccanin (**1**). Experiments with both cell free and intact cell systems of *Helminthosporium siccans* Drechsler have been used to support this proposed biosynthetic pathway for the formation of siccanin, which begins with farnesyl pyrophosphate **10** and consists of at least six steps (Scheme 1).[7]

As depicted in Scheme 1, the biosynthesis is believed to proceed by cyclization of *trans*,*trans*-farnesyl pyrophosphate **10** to *trans*-γ-monocyclofarnesyl pyrophoshate **11** (Step A) which undergoes condensation with orsellinic acid **12** to yield presiccanochromenic acid **13** (Step B). Oxidative cyclization of presiccanochromenic acid forms siccanochromenic acid **14** (Step C) and the chromene functionality of siccanin. The sequence then continues with decarboxylation to give siccanochromene A (**2**) (Step D). Epoxidation of the exocyclic methylene group of siccanochromene A (**2**) provides siccanochromene B (**3**) (Step E). Epoxyolefin cyclization[8] of siccano-

(1) Ishibashi, K. J. *J. Antibiot. Ser. A.* **1962**, *15*, 161−167.
(2) (a) Hirai, K.; Nozoe, S.; Tsuda, K.; Iitaka, Y.; Shirasawa, M. *Tetrahedron Lett.* **1967**, *8*, 2177−2179. (b) Hirai, K.; Suzuki, K. T.; Nozoe, S. *Tetrahedron* **1971**, *27*, 6057−6061. (c) Nozoe, S.; Suzuki, K. T. *Tetrahedron*, **1971**, *27*, 6063−6071. (d) Nozoe, S.; Hirai, K.; Snatzke, F.; Snatzke, G. *Tetrahedron*, **1974**, *30*, 2773−2776.
(3) Belloti, M. G.; Riviera, L. *Chemioterapia* **1985**, *4*, 431−433.
(4) Nose, K.; Endo, A. *J. Bacteriology* **1971**, *105*, 171−172.
(5) (a) Crippa, D.; Albanese, C. G.; Sala, G. P. *G. Ital. Dermatol. Venereol.* **1985**, *120*, LVII, and references therein. (b) Arai, M.; Ishibashi, K.; Okazaki, H. *Antimicrob. Agents Chemother.* **1969**, 9247−9252. c. Sugawara, S. *Antimicrob. Agents Chemother.* **1969**, 9253−9256.
(6) (a) Jansen, B. M. M.; de Groot, A. *Nat. Prod. Rep.* **1991**, *8*, 309−318. (b) Jansen, B. M. M.; de Groot, A. *Nat. Prod. Rep.* **1991**, *8*, 319−337.
(7) (a) Suzuki, K. T.; Nozoe, S. *Bioorganic Chem.* **1974**, *3*, 72−80. (b) Suzuki, K. T.; Nozoe, S. *J. Chem. Soc., Chem. Commun.* **1971**, 527−528.
(8) (a) Goldsmith, D. J.; Philips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862−5870. (b) Goldsmith, D. J.; Clark, B. C. *Tetrahedron Lett.* **1967**, *8*, 1215−1217.

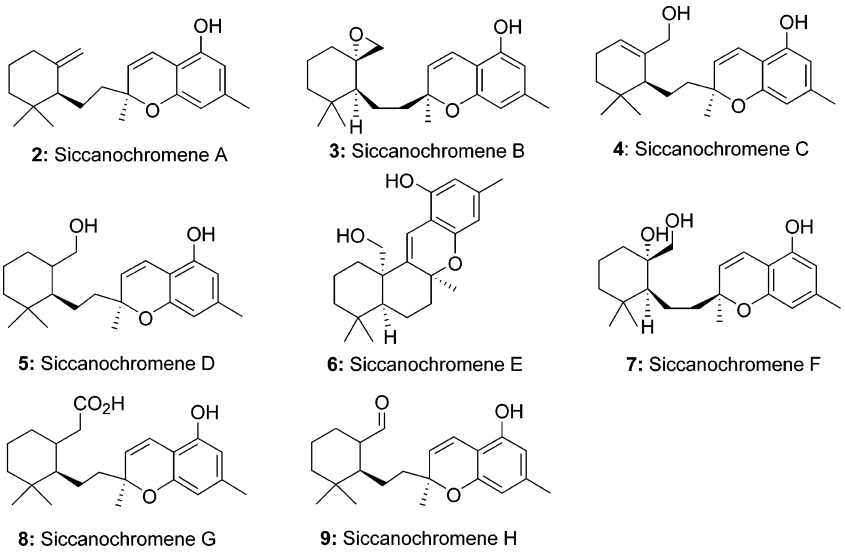
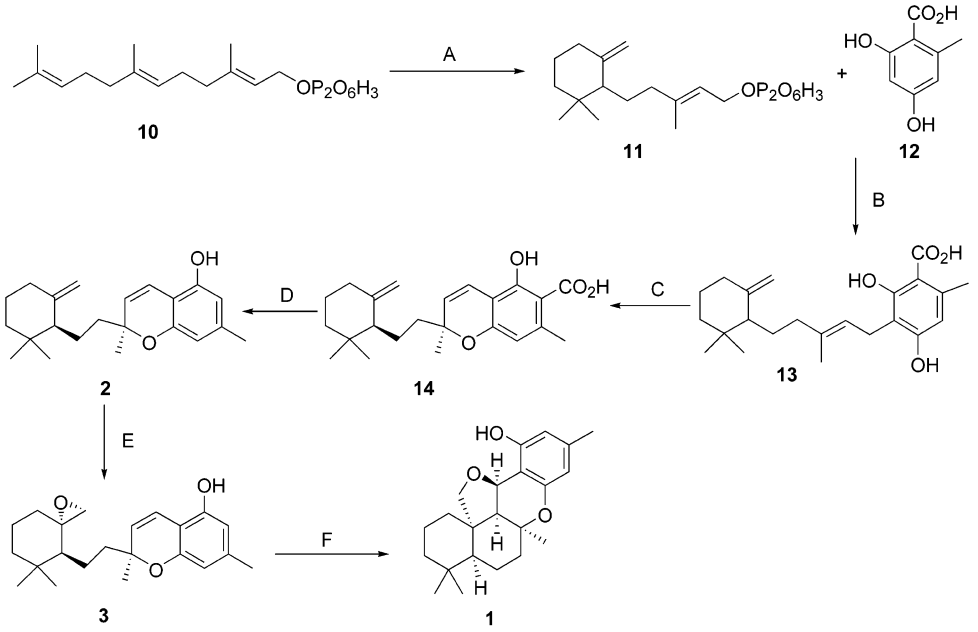


Figure 2. Representative compounds of siccanochromene family.

Scheme 1. Proposed Biosynthesis of Sicannin (1)



chromene B (**3**) then completes the biosynthesic pathway to afford siccanin (**1**) (Step F).

Due to its interesting biological activity, siccanin (**1**) has been the subject of a number of synthetic efforts.[9] Prior to this work, two successful racemic total syntheses of this natural product have been reported. The synthesis of siccanin (**1**) by the Yoshikoshi group proceeded in a linear fashion,[10] in which the A, B, C, and D rings were introduced consecutively. The highlight of our own previous racemic synthesis is the Pd-catalyzed diyne reductive cycloisomerization to construct the B-ring.[11]

Herein we report the first biomimetic enantioselective total synthesis of (−)-siccanin (**1**) via a highly convergent route, featuring a Pd-catalyzed asymmetric allylic alkylation (AAA) and two novel sequential stereoselective radical cyclizations.[12] As a result of its biomimetic premise, the synthesis of siccanochromenes A, B, E, F, and the methyl ether of siccanochromene C were also synthesized.

2. Enantioselective Total Synthesis of (−)-Siccanin

The retrosynthetic plan is illustrated in Scheme 2. The tetrahydrofuran ring and B-ring of siccanin (**1**) can presumably be formed via an epoxyolefin cyclization reaction of siccanochromen B (**3**), the proposed biosynthetic precursor of siccanin (**1**). Siccanochromen B (**3**) can be derived from **15**, prepared from the coupling of chiral sulfone **17** and chiral vinyl chroman **16a**.

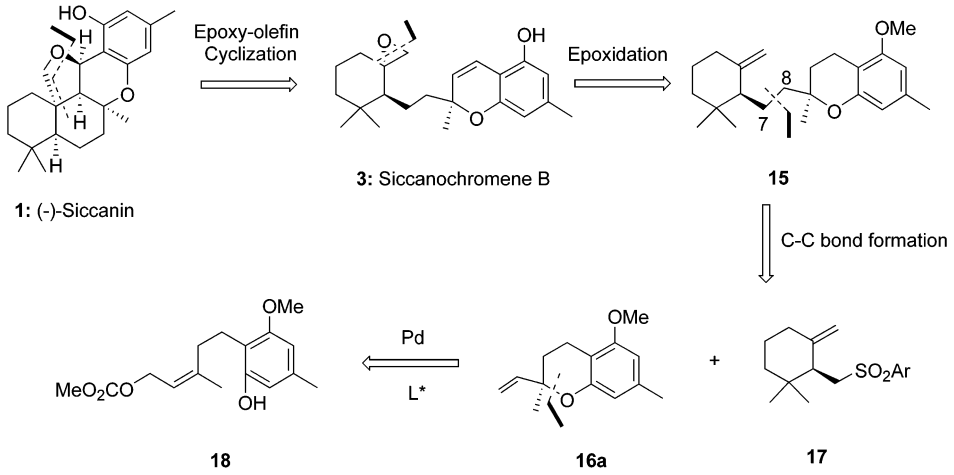
(9) (a) Nozoe, S.; Hirai, K. *Tetrahedron* **1971**, *27*, 6073−6081. (b) Oida, S.; Ohashi, Y.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1972**, *20*, 2634−2641. (c) Yoshida, A.; Oida, S.; Ohashi, Y.; Tamura, C.; Ohki, E. *Chem. Pharm. Bull.* **1972**, *20*, 2642−2650. (d) Oida, S.; Ohashi, Y.; Ohki, E. *Chem. Pharm. Bull.* **1973**, *21*, 528−537. (e) Liu, H.; Ramani, B. *Tetrahedron Lett.* **1988**, *29*, 6721−6724. (f) Kato, M.; Matsuma, Y.; Heima, K.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn* **1988**, *61*, 1991−1998.

(10) (a) Kato, M.; Matsumura, Y.; Heima, K.; Fukamiya, N.; Kabuto, C.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 711−722. (b) Kato, M.; Heima, K.; Matsumura, Y.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1981**, *103*, 2434−2435.

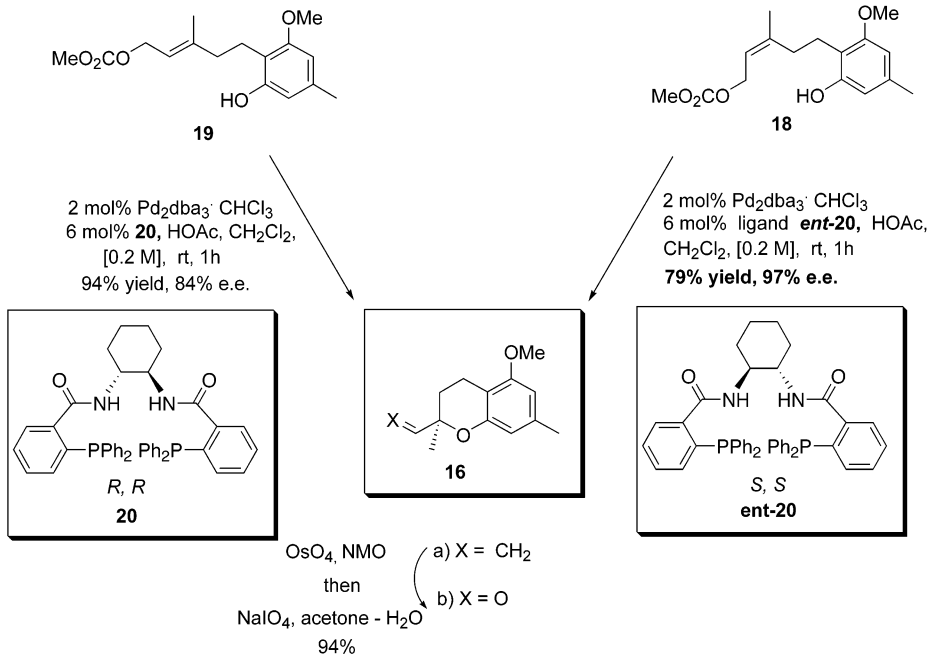
(11) Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146−5147.

(12) For the communication of this work, see: Trost, B. M.; Shen, H. C.; Surivet, J. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3943−3947.

Scheme 2. Retrosynthetic Analysis of (−)-siccanin (1)

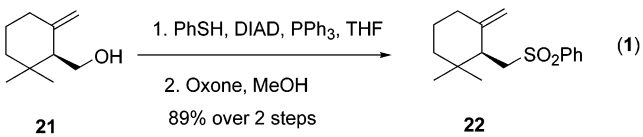


Scheme 3. Synthesis of Chiral Vinyl Chroman 16



Synthesis of Building Blocks. Chroman **16a** is derived form allyl carbonate **18** or **19** via a Pd-catalyzed asymmetric allylic alkylation (AAA) reaction recently developed by our group.[13] In the preceding paper, the syntheses and asymmetric cyclizations of the **Z** and **E** allyl carbonates **18** and **19** (Scheme 3) were described. The absolute configuration was established by the phenylglycine methyl ester (PGME) derivative method developed by Kusumi and Yabuuchi.[14]

Chiral alcohol **21** was readily available in large scale following a literature protocol,[15] which was then transformed to the corresponding phenyl sulfide. The subsequent chemoselective oxidation by oxone gave phenyl sulfone **22**[16] (eq 1). To test the modified Julia olefination, which could save steps compared to the standard Julia reaction, phenyltetrazole sulfone **25** was prepared by the Mitsunobu reaction followed by oxidation, as depicted in Scheme 4. Since the initial molybdenum catalyzed oxidation gave a mixture of the fully oxidized sulfone and partially oxidized sulfoxide, the later was resubjected to the oxidation conditions to provide the desired sulfone in 98% overall yield including the recycle. As shown in Scheme 5, chiral carboxylic acid **27**, the precursor of pyridinyl sulfone **31**, is available via a protocol developed by Kurth's group.[17] The Barton's decarboxylative rearrangement of *O*-acyl thiohydroxamate **29**[18] led to the formation of sulfide **30**, which was further oxidized to pyridinyl sulfone **31** following Charette's procedure.[19]

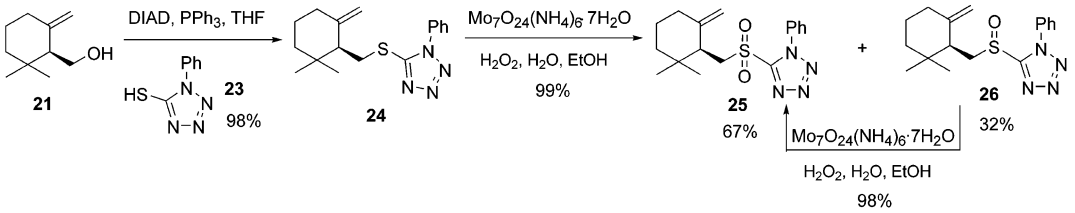


(1)

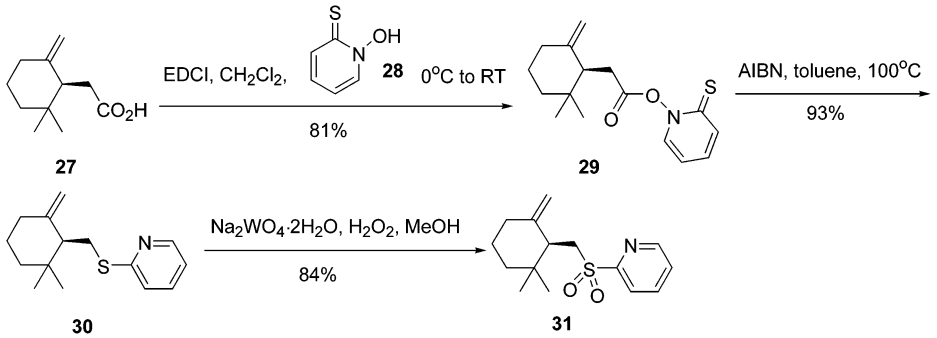
Synthesis of Cyclization Substrates. Two strategies have been examined for the C_6-C_7 bond formation in siccanin. To

(13) Trost, B. M.; Shen, H. C.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276−9277.
(14) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404.
(15) Tanimoto, H.; Oritani, T. *Tetrahedron* **1997**, *53*, 3527−3536.
(16) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287−1290.
(17) (a) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443−448. (b) Kurth, M. J.; Soares, C. J. *Tetrahedron Lett.* **1987**, *28*, 1031−1034.

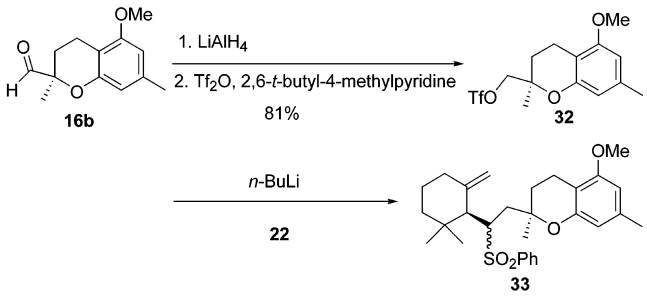
Scheme 4. Synthesis of Tetrazole Sulfone 25



Scheme 5. Synthesis of Pyridinyl Sulfone 31

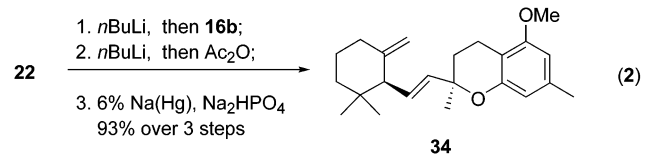


Scheme 6. First Approach for the C_6-C_7 Bond Formation



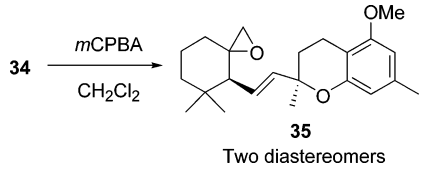
minimize chemoselectivity issues, the critical approach envisioned an alkylation of a sulfone stabilized anion followed by reductive desulfonylation. The electrophilic triflate **32** prepared from reduction of aldehyde **16b** followed by triflate formation,[20] gave only low conversions to the alkylation product **33** presumably due to the neopentyl character of the electrophile (Scheme 6).

To circumvent this problem, Julia olefination was utilized to couple chiral sulfone **22** with chiral chroman aldehyde **16b**.[21] As shown in eq 2, reaction proceeded in high yield to form diene **34**. Unfortunately, the attempts for the modified Julia olefination employing either **25** or **31** failed.



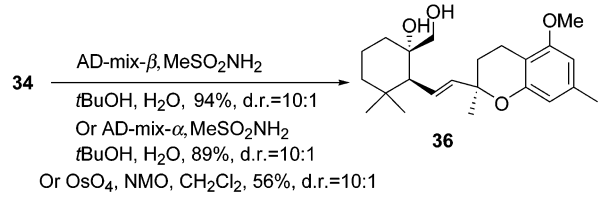
(2)

Epoxidation of diene **34** gave two diastereomers of epoxide **35** and oxidation products of the aromatic ring (eq 3). The reaction was very messy and the impurities were likely phenols resulting from oxidation of the electron-rich aromatic ring of **34**.



(3)

Observing no side reaction occurring with respect to the trans-double bond, we envisioned that catalytic dihydroxylation might avoid the undesired oxidation of the aromatic ring. It has been widely demonstrated that the rate of the dihydroxylation of isolated double bonds are much faster with trans-1,2-disubstituted and trisubstituted olefins than with cis-1,2-disubstituted and terminal alkenes. On the other hand, steric effects may play a decisive role in systems with electronically very similar double bonds, and generally the sterically more accessible site is osmylated preferentially.[22] The chemo- and diastereoselective dihydroxylation of diene **34** with AD-mix-β employing the Sharpless protocol generated diol **36** with 10:1 diastereoselectivity (eq 4). The NMR data showed that the terminal methylene

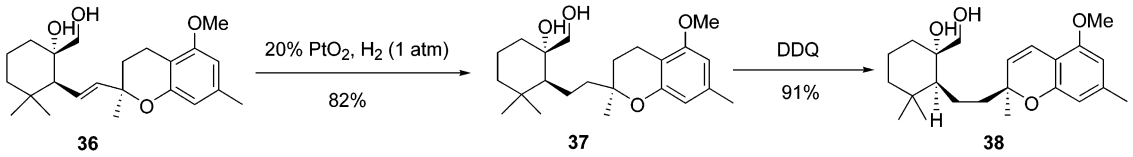


(4)

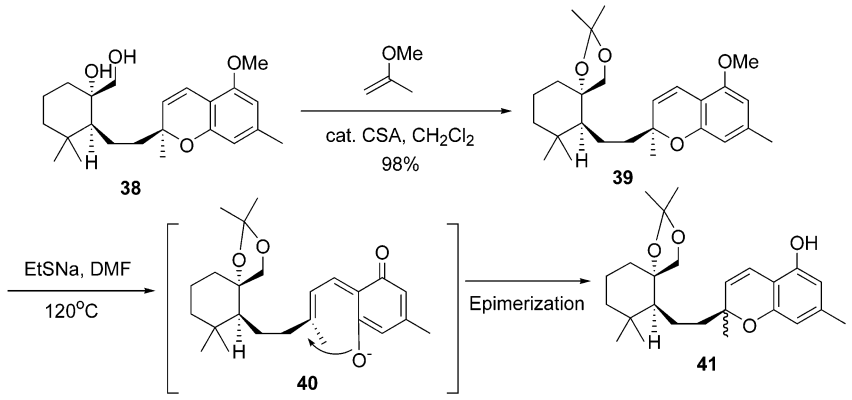
protons (δ 4.59 and 4.14 ppm as two singlets) present in diene **34** have disappeared, and the two olefinic protons of the 1,2-disubstituted double bond (d, 5.54 ppm and dd, 5.48 ppm) remained. The use of AD-mix-α gave similar results in terms of yield and diastereoselectivity. The dihydroxylation protocol using osmium tetraoxide and NMO also gave

(18) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.
(19) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149−5153.
(20) Surivet, J. P.; Vatele, J. M. *Tetrahedron* **1999**, *55*, 13 011−13 028.
(21) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836. (b) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97−127.
(22) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

Scheme 7. Synthesis of Chromen Diol 38



Scheme 8. Demethylation of Chromen Methyl Ether



the desired diastereomer **36** with lower yield presumably resulting from the dihydroxylation of the trans double bond as a side reaction. Apparently, the less sterically hindered terminal olefin is preferably dihydroxylated in the presence of a 1,2-disubstituted trans olefin which is adjacent to a quaternary center. The chiral ligand is unnecessary for the diastereoselectivity in the dihydroxylation reaction due to the substrate control, yet seems to be important to achieve a better chemoselectivity. Presumably, the increased steric bulk of the ligand of the osmium complex will favor the reaction to occur with the sterically more accessible 1,1-disubstituted double bond. On the basis of the lowest energy conformation of **34** calculated by MM2 (Chem 3D), presumably the osmium reagent prefers to approach the 1,1-disubstituted olefin from the less hindered bottom face to give diastereomer **36** (Figure 3). The

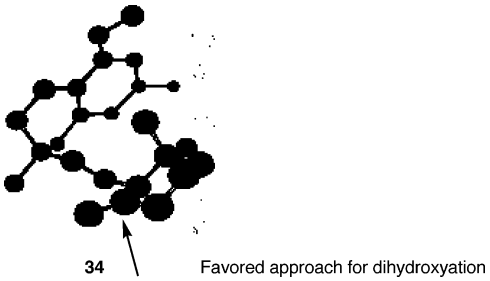


Figure 3. Rationale for diastereoselectivity of dihydroxylation of **34**.

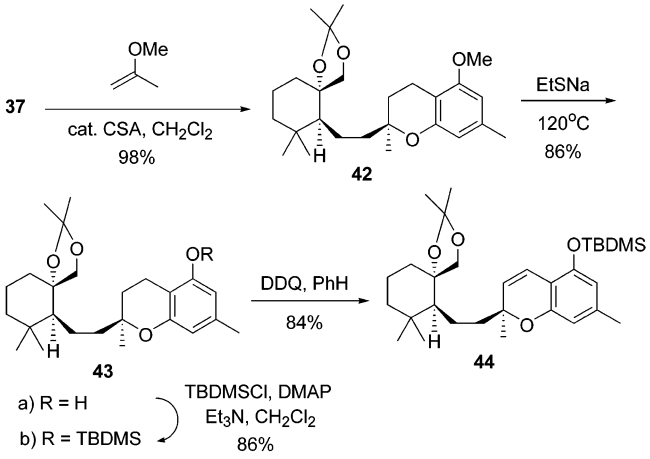
top face is blocked by the chroman moiety as well as the axial methyl group of the cyclohexane. The assigned stereochemistry is later confirmed by the derivatization of **36** into siccanochromene B (**3**) and siccanin (**1**) over several steps. The approximately 10:1 diastereomeric mixtures were inseparable by flash chromatography and were carried on for the subsequent synthesis. Consequently, compounds **37**−**39**, **47**−**48**, and **3** were all accompanied by minor amounts of their diastereomers. However, the stereochemical integrity of C-10 of these intermediates was irrelevant to the synthesis of siccanin, due to the nature of the epoxy-olefin radical cyclization as illustrated later.

The hydrogenation of **36** smoothly afforded chroman diol **37**, which was oxidized by DDQ[23] to generate chromen diol **38** in 91% yield (Scheme 7).

The subsequent demethylation of **38** was problematic. Typical ethyl thiolate demethylation only led to degradation. By protecting the diol as the acetonide, demethylation proceeded smoothly to afford the corresponding phenol **41**. However, under the reaction conditions, a ring-opening and closure led to the complete epimerization of the chromen moiety of phenol **41** (Scheme 8). This result suggests that the demethylation should be executed prior to the oxidation of the chroman to the chromen. As shown in Scheme 9, the acetonide chroman **42** was successfully demethylated to phenol **43a** in good yield.

DDQ oxidation of chroman **43a** as an unprotected phenol only decomposed the starting material. Presumably, the phenol

Scheme 9. Synthesis of Chromen 44

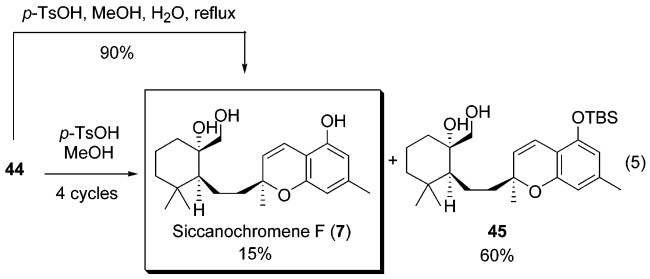


ring is oxidized by DDQ. The acetate derivative of **43a** did not react under the typical DDQ oxidation conditions, likely due

(23) (a) Starratt, A. N.; Stoesl, A. *Can. J. Chem.* **1977**, *55*, 2360−2362. (b) Ahluwalia, V. K.; Jolly, R. S. *Synthesis* **1982**, 74−75. (c) Buckle, D. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 3, p 1699.

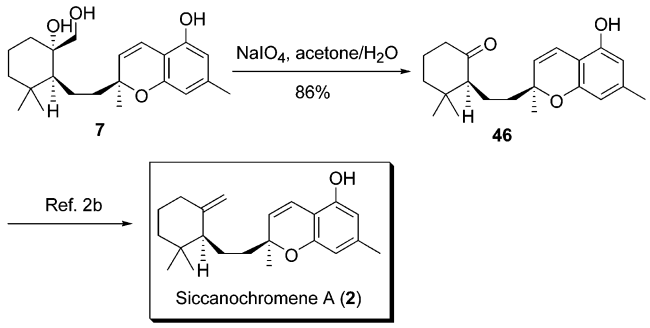
to the electron withdrawing property of the acetate, thus disfavoring the formation of the benzylic cation intermediate initially generated. On the other hand, the TBS ether **43b** was smoothly oxidized to the desired chromen **44** in 84% yield. The ^{1}H NMR spectrum of chromen **44** has two doublets at 6.61 and 5.46 ppm, both of which have a coupling constant of 10.0 Hz, which corresponds to the two olefinic protons of the chromen ring.

The subsequent deprotection of **44** using *p*-TsOH afforded triol **7**, known as siccanochromene F (**7**), in 15% yield and diol **45** in 60% yield (eq 5) after 3 recycles. By using a mixture of water and methanol under reflux, *p*-TsOH removed both the acetonide and TBDMS group to form siccanochromene F (**7**) exclusively.



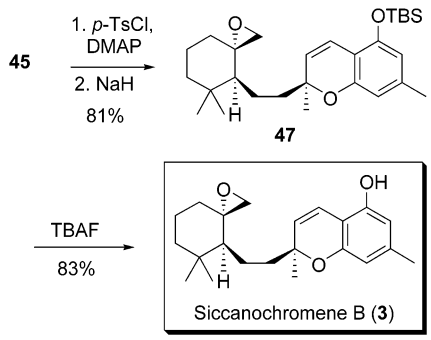
In the natural product isolation paper[2b], the authors reported that siccanochromene F (**7**) existed as a mixture of two epimers at the quaternary center C-10. They also described their diacetate derivatives. Our recorded data for siccanochromene F (**7**) and its diacetylated derivative (**7′**) matched those reported in the literature for one epimeric series. Triol **7** underwent an oxidative cleavage to afford ketone **46** (Scheme 10). It is known in the

Scheme 10. Synthesis of Siccanochromene A (2)

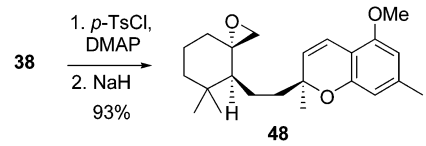


literature that siccanochromene A (**2**) could be prepared from **46** by Wittig olefination.[2b]

Scheme 11. Synthesis of Siccanochromene B (3)

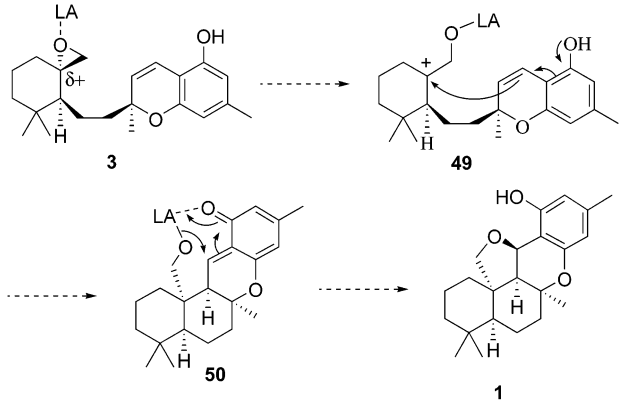


Tosylation of the primary alcohol of **45** was followed by treatment with sodium hydride to give epoxide **47**. Subsequent desilylation yielded siccanochromene B (**3**), the proposed biosynthetic precursor of siccanin (**1**) (Scheme 11). Similarly, the methyl ether of chromen **38** was also converted to epoxide **48** over two steps in 93% yield (**eq 6**).

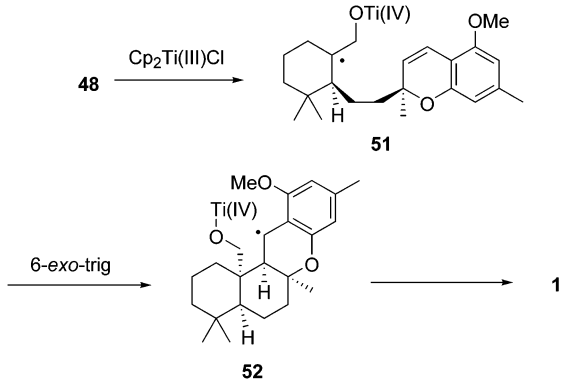


Biomimetic Cyclization and Completion. Now the synthesis reached a pivotal point to test our biomimetic proposal. The proposed cationic cyclization is shown in Scheme 12. A Lewis acid will likely open epoxide **3** to generate a tertiary cation **49**, which is then trapped by an electron-rich olefin to form the B-ring. The resulting oxygen nucleophile can undergo a Lewis acid-promoted 1,4-addition to the pendant enone as in **50** to construct the tetrahydrofuran ring. This novel proposal involves one C−O bond cleavage, followed by a C−C and C−O bond formation, to create the natural product in one step.

Scheme 12. Biomimetic Cationic Cyclization of Siccanochromene B (3) to Form Sicannin (1)

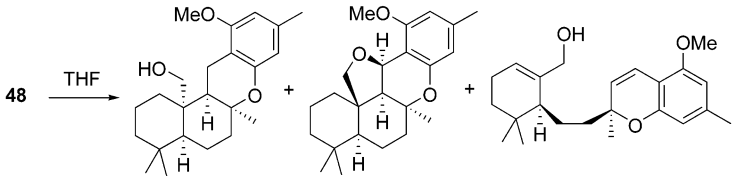


Scheme 13. Proposed Radical Cyclization of Siccanochromene B Methyl Ether 48

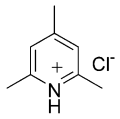


In the event, the treatment of siccanochromene B (**3**) or siccanochromene B methyl ether **48** with a variety of Lewis acids (BF_3·OEt, $SnCl_2$, $SnCl_4$, $TiCl_2(OiPr)_2$, $Yb(OTf)_3$, $FeCl_3$) in various solvents (CH_2Cl_2, dioxanne, nitromethane) gave no reaction, decomposition, or some evidence for aldehydes that would arise by ring opening to an epoxide followed by hydride shift.

Table 1. Ti-mediated Radical Cyclization of Epoxide 48[a]



53 **54** **55**

Entry	Cp_2TiCl_2 (eq.)	Mn (eq.)	Additives (eq.)	Temp.	Time (h)	Yields(%) **53** : **54** : **55** : **48**
1	1	2	None	rt	16	~30 : 10: 0 : 60
2	2	4	$InCl_3$ (2)	rt	12	0 : 0 : 0 : >80
3	3	6	I_2 (1.2)	rt	10	44: ~5: 0 : 0
4	3	6	 (1.5)	rt	10	10 : ~5: 0 : ~80
5	3	6	None	rt	10	60 : 21 : 0 : 0
6	4	8	I_2 (2)	50°C	1	0 : 0 : 68 : 0
7	3	6	None	50°C	6	0 : 0 : 45 : 0
8	3	6	None	0°C	12	<5 : 0 : 0 : 90

[a] All reactions were performed in freshly distilled and degassed THF (THF has to be air and water free by distillation over sodium).

In contrast to cationic intermediate **49**, tertiary radical **51** should not undergo the hydride shift or other cationic decomposition pathways. Inspired by the work of RajanBabu and Nugent,[24] the opening of epoxide **48** may form tertiary radical **51** in the presence of $Cp_2Ti(III)Cl$, and undergo a *6-exo-trig* cyclization to afford benzylic radical **52** (Scheme 13). The stability of the benzylic radical potentially serves as a driving force for the ring formation. Collapse to siccanin expels Ti(+3) and the result is the reaction becomes catalytic in Ti(+3). At this stage, **48** and its diastereomer were presumably both converted to radical **51**. The subsequent cyclization will then establish the stereogenic center C-10.

Table 1 summarized the experimentations of the Ti-mediated radical cyclization of epoxide **48**. With 1 equiv of titanocene dichloride and 2 equiv of manganese (entry 1), the reaction gave about 40% yield of **53**, with the desired stereochemistry, and **54**, a pentacyclic compound, in 3:1 ratio. The pentacyclic compound is the methyl ether of 10-*epi*-siccanin. The rest of the starting material was recovered. The addition of indium trichloride led to no cyclization products (entry 2). Presumably, the redox reaction between indium trichloride and Ti(III) and/or manganese occurred. The addition of iodine was intended to quench the benzylic radical **52**, which could presumably lead to a further cyclization. However, only 44% of tetracyclic product **53** was obtained (entry 3) accompanied with trace amount of **54** (~5%) and decomposition. Gansäuer and coworkers found that pyridinium chloride could protonate alkoxy species to regenerate Ti(IV) species.[25] Their reaction conditions could potentially lead to a Ti-catalyzed radical cyclization of epoxyolefin **48**. However, under their conditions, only 10% yield of tetracyclic product **53** was isolated with about 80% recovery of the starting material (entry 4). The best result is shown in entry 5. Using 3 equiv of titanocene and 6 equivalents of manganese, the Ti(III)-mediated cyclization of **48** gave full conversion of the starting material, to yield the tetracyclic compound **53**, accompanied with the methyl ether of 10-*epi*-siccanin **54**, in 3:1 ratio and 81% overall yield. Compared with entry 1, the reason excessive amount of titanocene and manganese is important for the completion of the reaction is likely due to the Lewis basic sites present in the substrate, which may coordinate with titanium or manganese species. Interestingly, at elevated temperature or in the presence of iodine at elevated temperature (entries 6 and 7), we observed no cyclization products. Instead, the elimination product allylic alcohol **55**, which is the methyl ether of siccanochromene C (**4**), was obtained in modest yield. It seems that temperature is a critical factor in this reaction. Higher temperature favors the elimination product **55**, not the cyclization products, and low temperature (0 °C) gave very slow reaction and low conversion (entry 8).

To understand the intriguing stereoselective formation of **53** and **54**, a mechanism is proposed as shown in Scheme 14. The green-colored Ti(III) species is generated by the reduction of titanocene dichloride using manganese. The ring-opening of epoxide **48** in the presence of Ti(III) species results in the formation of tertiary radical **51**, which then undergoes a *6-exo-trig* cyclization to form benzylic radical **56**. The further reaction

(24) (a) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408−6409. (b) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis*, **2001**, 2500−2520. (c) RajanBabu, T. V.; Nugent, W. A.; *J. Am. Chem. Soc.* **1994**, *116*, 986−997. (d) Roy, S. C.; Rana, K. K.; Guin, C. *J. Org. Chem.* **2002**, *67*, 3242−3248.

(25) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12 849−12 859.

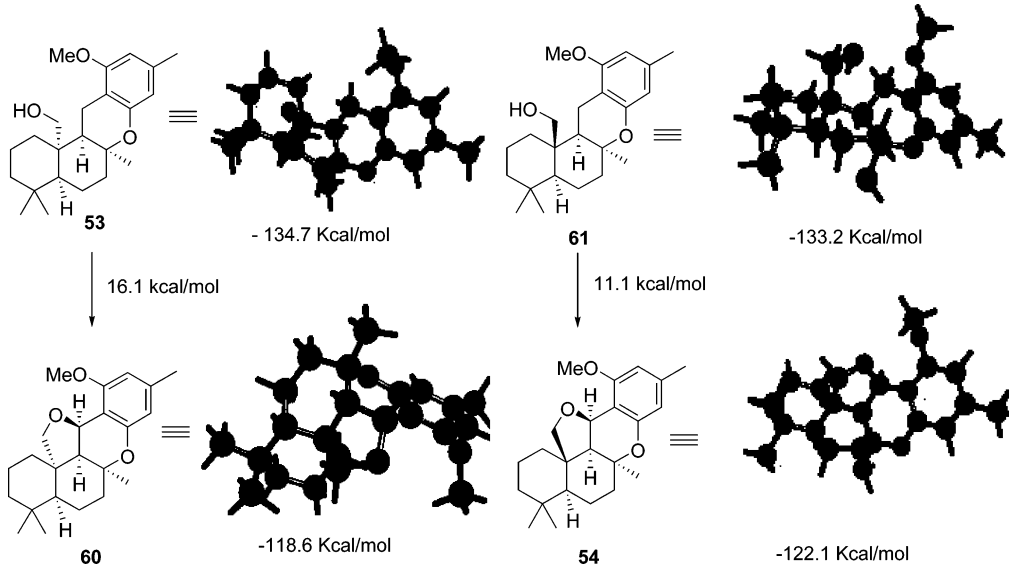
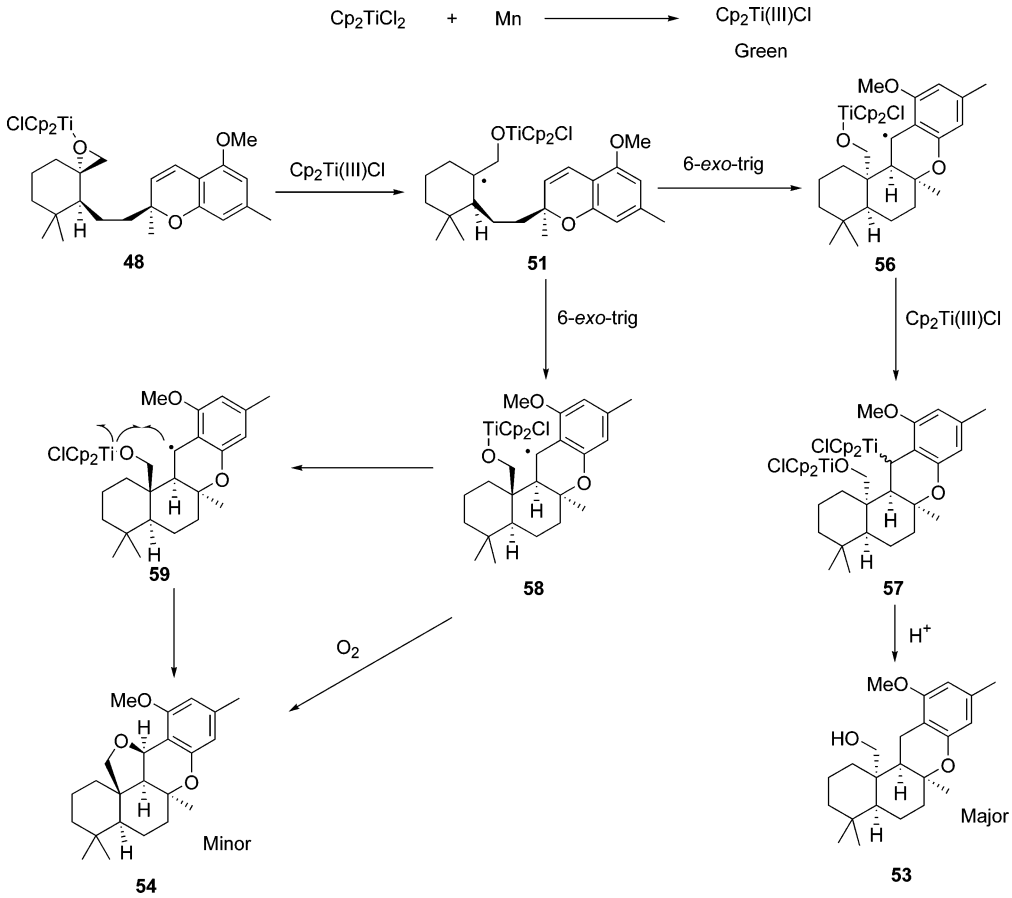


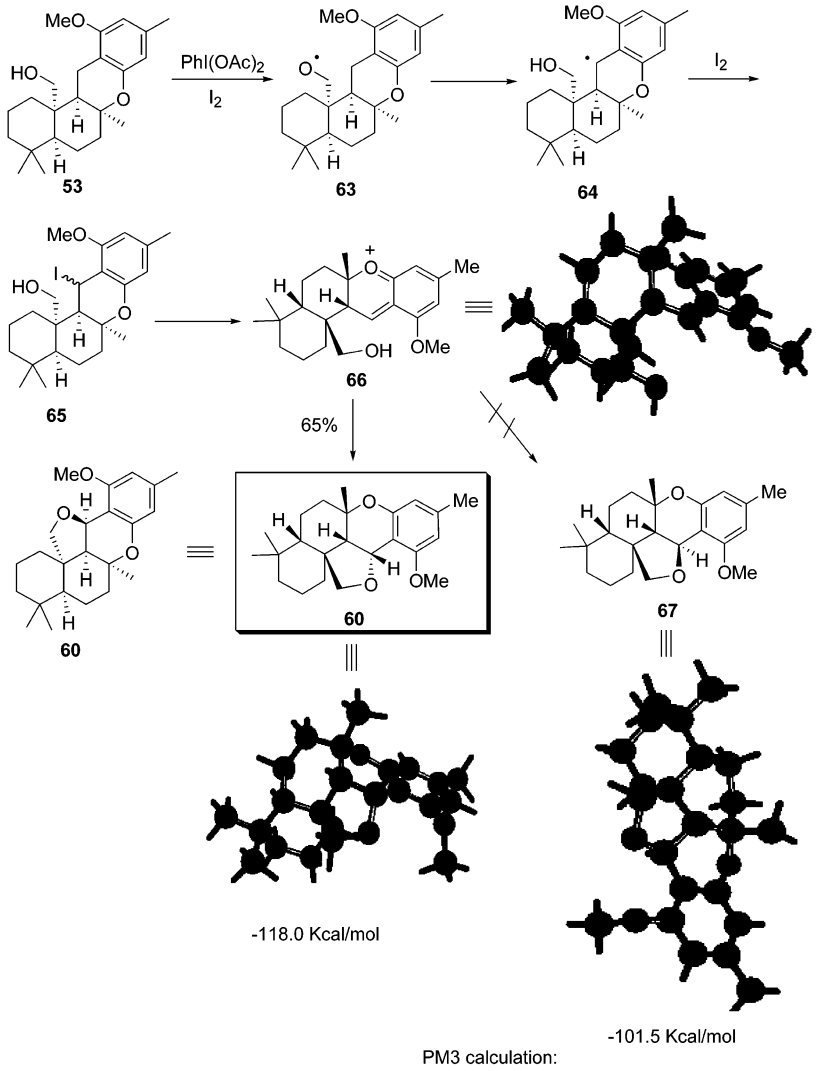
Figure 4. Calculated energy for natural and 10-*epi*-tetracyclic/pentacyclic compounds.

Scheme 14. Proposed Mechanism for the Radical Cyclization

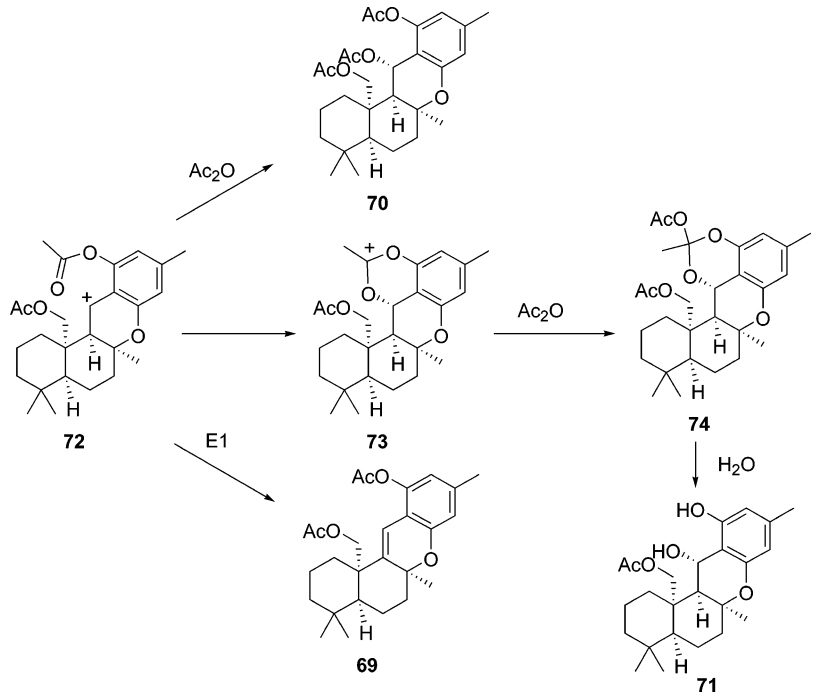


with another equivalent of Ti(III) species forms a C−Ti bond. Subsequent hydrolysis leads to the formation of the desired tetracyclic product **53**. Alternatively, the diastereomeric benzylic radical **58** can be formed. At this stage, it could be oxidized by air during workup to give benzylic cation, which could then react with the oxygen nucleophile intramolecularly to form the tetrahydrofuran ring. However, carefully quenching the reaction mixture under argon also gave the pentacyclic product in almost the same yield, which indicates that the oxidation of benzylic radical to cation is not the case. Another plausible mechanism proposed that intermediate **59** could undergo a further tetrahydrofuran ring formation due to the proximity of the oxygen atom with the benzylic carbon radical. Our original proposal is rather bold and counterintuitive. It involves a homolytic cleavage of a Ti−O bond, although it is well-known that Ti−O bond is quite strong. This conceptually novel reaction can be deemed as a homolytic substitution of Cp_2TiCl radical with a benzylic radical. Coincidentally, in a similar scenario reported very re-

Scheme 15. Formation of Tetrahydrofuran Ring in Pentacyclic Compound 60



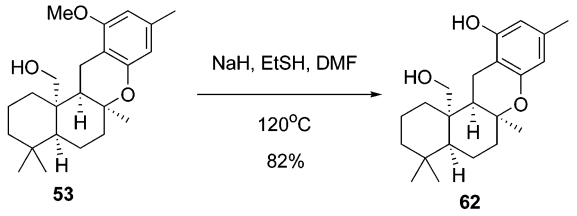
Scheme 16. Proposed Mechanism for the Formation of 69−71



cently by Gansäuer,[26] the counterintuitive cleavage of a strong Ti−O bond was justified both by experiments and DFT calculation. It is very likely that the transformation from **58** to **54** is exothermic given that the Cp_2TiCl species may still bind to oxygen of the tetrahydro furan ring.

To understand why intermediate **58** is more prone to a further cyclization than its diastereomer **56**, we performed PM3 calculations in Spartan 2002 (Figure 4). The results show that the energy difference between tetracyclic compound **53** and pentacyclic compound **60** is 16.1 kcal/mol, which is 5 kcal/mol higher than the energy difference between **61** and **54**. This calculation suggests that it is much easier for intermediate **58** to cyclize than **56**.

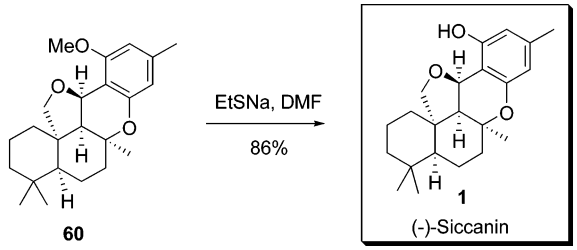
The demethylation of **53** yielded diol **62** (eq 7), whose proton NMR data matches siccanochroman diol, a known derivative of siccanin (**1**),[2b] and therefore ensures our assignment of stereochemistry of **53**.



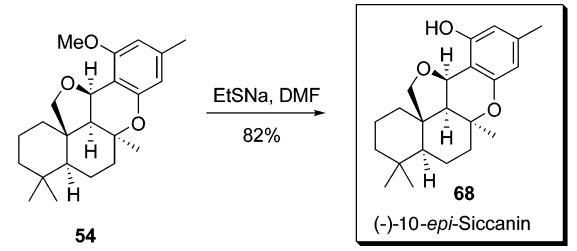
(7)

The end game of the synthesis is to form the tetrahydrofuran ring of siccanin. The attempted cyclization of **53** to **60** by the treatment with DDQ failed with the full recovery of starting material, likely due to the steric hindrance of the benzylic hydrogen atom. This strategy assumed that benzylic cation generated in situ could be trapped by the alcohol nucleophile to form the tetrahydrofuran ring.

Successful realization of formation of the tetrahydrofuran ring of siccanin employed a free-radical remote functionalization via a Barton type reaction under the Suarez conditions.[27] As shown in Scheme 15, the use of iodobenzene diacetate generates oxygen radical **63**, which can abstract a benzylic hydrogen atom to form benzylic radical **64**. This radical is quenched by iodine to form benzyl iodide **65**. The electron-rich aromatic ring may then promote the elimination of benzyl iodide to generate oxonium **66**, which is subsequently attacked by the pendant oxygen nucleophile to form the tetrahydrofuran ring of **60**. Intuitively, the oxygen nucleophile should approach the benzylic carbon in **66** from the top face to form 11-*epi*-siccanin methyl ether **67**. However, PM3 calculations in Spartan 2002 showed that the natural siccanin methyl ether **60** is 16.5 kcal/mol more stable than 11-*epi*-siccanin methyl ether **67**. Presumably, the energy of the transition states that lead to **60** or **67** should reflect the strain energy of the product. Hence, the formation of the product with significantly lower energy is preferred. Consistent with these calculations is an examination of a model of **66** which reveals that the all *cis*-fused ring junction only allows the hydroxyl nucleophile to attack from the bottom face to form the desired pentacyclic compound **60**. Finally, the pentacyclic compounds **60** and **54** were demethylated to afford (−)-siccanin **1** (eq 8) and (−)-10-*epi*-siccanin **68** (eq 9) to constitute the first enantioselective total syntheses.



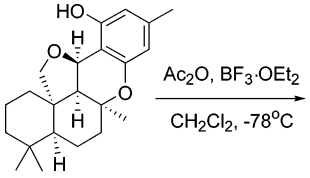
(8)

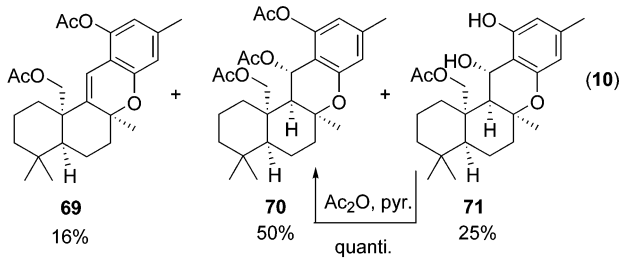


(9)

The availability of siccanin may also provide an access to siccanochromene E (**6**) by a selective cleavage of the benzylic C−O bond and a subsequent elimination. The attempt to convert (−)-siccanin (**1**) to siccanochromene E (**6**) in one step by the treatment of boron trifluoride etherate in dichloromethane, or 1 equivalent of BSA and catalytic amount of TMSOTf only returned starting material. The treatment with excess BSA and 2 equiv of TMSOTf overnight only led to decomposition.

Despite the failure of the reaction of (−)-siccanin with boron trifluoride etherate in dichloromethane, the treatment of (−)-siccanin with acetic anhydride and boron trifluoride etherate at −78 °C, following a protocol developed by Hirai[2b], gave three separable products, siccanochromene E diacetate **69**, triacetate **70** and monoacetate **71** (eq 10). The assignment of stereochemistry of the benzylic acetate **69** and the benzylic alcohol **71** was based on the observation that the benzylic proton in the NMR spectra of both compounds was a singlet. The computational modeling (Spartan 2003, PM3) shows that the dihedral angle $H-C_9-C_{11}-H$ in the α-acetate is 94°, which is much closer to 90°, than the *β*-acetate with the corresponding dihedral angle around −51°. Furthermore, **70** (−289.6 kcal/mol) is considerably more stable than the corresponding *β*-acetate (−280.0 kcal/mol). Therefore, **70** and **71** should most likely bear α-benzylic acetate and hydroxyl group, respectively.

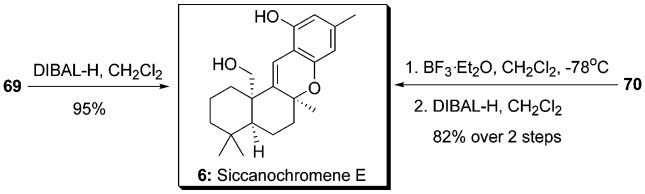




(10)

(26) Gansäuer, A.; Rinker, B.; Pierobon, M.; Gimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687−3690.
(27) Concepcion, J. T.; Francisco, C. G.; Hernandez, R.; Salaza, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953−1956.

Scheme 17. Synthesis of Siccanochromene E (6)



As shown in Scheme 16, the benzylic C−O bond is presumably selectively cleaved by the Lewis acid. The resulting benzylic cation can either be trapped with acetic anhydride, or undergo an E1 type of elimination, with the simultaneous esterification of phenol and primary alcohol to afford **70** and **69**, respectively. It is interesting to observe the formation of monoacetate **71**, which implies the formation of intermediate **72**, followed by the trapping with acetic anhydride to form ortho ester **74**. The subsequent hydrolysis upon aqueous workup leads to **71**. The treatment of monoacetate **71** with acetic anhydride and pyridine gave triacetate **70** in quantitative yield.

Diacetate **69** could be reduced by DIBAL-H to afford (−)-siccanochromene E (**6**) (Scheme 17). The spectroscopic data (^{1}H NMR, IR, MS, mp, and optical rotation) are all in agreement with the data disclosed by the isolation paper.[2b] Conversion of triacetate **70** to siccanochromene E with base either DBU or lithium trifluoroethoxide failed. The use of boron trifluoride etherate, successfully triggered the elimination of benzyl acetate, followed by a DIBAL-H reduction to give cleanly the desired product, siccanochromene E (**6**), in 82% yield over two steps. Therefore, all three products from siccanin, **69**, **70**, and **71**, were directly or indirectly converted to siccanonchromene E (**6**).

Experimental Section

(*R*)-5-Methoxy-2,7-dimethyl-2-vinyl-chroman (16a): To a solution of *Z*-3-methyl-5′-(6′-hydroxy-2′-methoxyphenyl)-2-pentene (1.15 g, 4.92 mmol) in dichloromethane (20 mL) was added pyridine (1.23 mL, 15.2 mmol). The solution was cooled to 0 °C. To this solution was added dropwise methyl chloroformate (0.45 mL, 5.81 mmol). After 15 min, water (20 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with a saturated solution of $CuSO_4$ (3 × 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate and concentrated to dryness to afford *Z*-carbonate **18** (1.45 g, 4.92 mmol, 100%). To a degassed mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.100 g, 0.1 mmol) and chiral ligand ***ent*-20** (*S, S*) (0.200 g, 0.3 mmol), was added dichloromethane (20 mL). The solution was stirred for 10 min, then acetic acid (0.210 mL, 5.57 mmol) was added. After 5 min, a solution of *Z*-carbonate **18** (1.45 g, 4.92 mmol) in dichloromethane (4 mL + 1 mL rinse) was added. The reaction mixture was stirred at room temperature for 1h. The volatiles were removed under reduced pressure and the residue was purified directly over silica gel eluting with 1:11 of diethyl ether in petroleum ether to afford (*R*)-5-methoxy-2.7-dimethyl-2-vinylchroman **16a** (0.852 g, 3.90 mmol, 79%) as a colorless oil.

$[\alpha] = +54.0$ (c 2.18, $CHCl_3$), 97% ee; IR (neat): 2936, 1618, 1586, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (s, 1H), 6.25 (s, 1H), 5.85 (dd, J = 10.7, 17.3 Hz, 1H), 5.20 (dd, J = 1.2, 17.3 Hz, 1H), 5.07 (dd, J = 1.2, 10.7 Hz, 1H), 3.81 (s, 3H), 2.68 (td, J = 5.6, 16.8 Hz, 1H), 2.47 (ddd, J = 6.1, 9.8, 16.8 Hz, 1H), 2.31 (s, 3H), 1.93 (dd, J = 4.8, 5.8, 13.4 Hz, 1H), 1.79 (ddd, J = 5.6, 9.8, 13.4 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 154.3, 141.3, 136.9, 113.6, 110.0, 107.2, 102.6,76.1, 55.2, 31.0, 26.7, 21.6, 16.7. HRMS: Calc'd for $C_{14}H_{18}O_2$ [M$^+$]: 218.1307. Found: 218.1303. Chromatographic separation (GC, Cyclosil B): T oven = 160 °C, t_R (*S*, minor) = 18.5 min, t_R (*R*, major) = 18.9 min.

(*R*)-5-Methoxy-2,7-dimethyl-chroman-2-carboxyaldehyde (16b): To a solution of (*R*)-5-methoxy-2.7-dimethyl-2-vinyl-chroman **16a** (0.20 g, 0.92 mmol) in 3.5 mL of dichloromethane was added *N*-methyl-morphonline-*N*-oxide (0.3 g, 2.56 mmol) and aqueous osmium tetraoxide (0.27 mL, 4% in water, 0.043 mmol). The solution was stirred for 5 h at room temperature and diluted with water (10 mL) and dichloromethane (20 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed with 1:1 to 1:5 of petroleum ether in diethyl ether. The resulting brown oil (contaminated with osmium residue) was resuspended in acetone (4 mL) and a solution of sodium periodate (0.4 g, 1.87 mmol) in water (1 mL) was added. After a white precipitate was formed the reaction mixture was stirred at room temperature for additional 20 min. The mixture was filtered through a pad of diatomaceous earth and the filtrate was partitioned between water (5 mL) and dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried over magnesium sulfate. The residue was separated by flash chromatography eluting with 5% to 25% diethyl ether in petroleum ether to afford aldehyde **16b** as a colorless oil (0.19 g, 0.86 mmol, 94%).

$[\alpha]_D = +16.3$ (*c* 0.47, Et_2O); IR (film): 2935, 1738, 1619, 1587, 1463, 1146, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 6.44 (s, 1H), 6.27 (s, 1H), 3.78 (s, 3H), 2.64 (td, J = 6.4, 17.3 Hz, 1H), 2.47 (ddd, J = 6.6, 9.2, 16.1 Hz, 1H), 2.30 (s, 3H), 2.22 (m, 1H), 1.77 (ddd, J = 6.6, 9.5, 15.8 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 157.5, 153.5, 137.4, 110.0, 107.1, 103.4, 80.0, 55.3, 27.2, 21.5, 21.2, 16.1. HRMS: Calc'd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1093.

***(1S)*-(2,2-Dimethyl-6-methylene cyclohexylmethanesulfonyl)-benzene (22):** To a solution of alcohol **21** (230 mg, 1.49 mmol) in THF (5 mL) were added triphenylphosphine (470 mg, 1.79 mmol) and benzenethiol (197 mg, 0.18 mL, 1.79 mmol). To this solution at 0 °C was added diisopropylazodicarboxylate (362 mg, 0.35 mL, 1.79 mmol). The resulting yellow solution was warmed to room temperature and stirred for 5h. The solution was concentrated in vacuo and the residue was purified by flash chromatography eluting with 5% to 10% diethyl ether in petroleum ether to afford sulfide as a colorless oil (369 mg, 1.50 mmol). The sulfide was dissolved in 5 mL of methanol. To this solution was added a solution of oxone (0.7 g) in 5 mL of water at 0 °C, and the solution was stirred at room temperature overnight. The mixture was then filtered through diatomaceous earth and washed with diethyl ether. The filtrate was concentrated in vacuo. The residue was diluted with 20 mL of dichloromethane and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified on silica gel eluting with diethyl ether in petroleum ether (5%−10%) to afford sulfone **22** (369 mg, 1.33 mmol, 89%) as a colorless oil.

$[\alpha]_D = +10.1$ (*c* 1.06, $CHCl_3$); IR (neat): 3069, 2934, 1470, 1447, 1306, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (dd, J = 1.2, 8.3 Hz, 2H), 7.63 (tt, J = 1.2, 7.3 Hz, 1H), 7.53 (tdd, J = 1.2, 7.3, 8.3 Hz, 2H), 4.74 (s, 1H), 4.56 (s, 1H), 3.36 (dd, J = 9.2, 14.9 Hz, 1H), 3.24 (dd, J = 2.2, 14.9 Hz, 1H), 2.44 (dd, J = 2.2, 9.2 Hz, 1H), 1.99 (m, 2H), 1.49 (m, 2H), 1.30 (m, 2H), 0.89 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.4, 139.8, 133.3, 128.9, 128.0, 110.8, 54.3, 47.6, 37.0, 35.2, 32.8, 27.7, 24.8, 23.1. HRMS: Calc'd for $C_{16}H_{23}O_2S$ [M + H$^+$]: 279.1418. Found: 279.1414.

(1*S*)-2-[2-(2,2-Dimethyl-6-methylene-cyclohexyl)-vinyl]-(2*R*)-5-methoxy-2,7-dimeth-yl-chroman (34): To a solution of phenyl sulfone **22** (0.880 g, 3.16 mmol) in THF (13 mL) was added at −78 °C *n*-butyllthium (1.4 mL, 3.16 mmol, 2.25 M in hexanes, freshly titrated with *N*-benzylbenzamide). The pale yellow solution was stirred at −78 °C for 40 min. To this solution was added a solution of aldehyde **16b** (0.536 g, 2.43 mmol) in THF (5 mL + 2 mL rinse). The reaction was stirred for 2 h at −78 °C and warmed gradually to room temperature

over 1 h. At this point, water (10 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate. After concentration under reduced pressure, the residue was chromatographed eluting with 20% diethyl ether in petroleum ether to afford intermediate sulfone secondary alcohol. This material was taken up in THF (18 mL), and 1,10-phenantroline (a few seeds) was added. The mixture was cooled to −78 °C, and *n*-butyllithium (2.25 N in hexanes) was added until an intense brown color appeared. At this point, a few more drops were added, and the solution was stirred for 10 min. Acetic anhydride (2 mL) was added dropwise, and the reaction mixture turned yellow. The reaction was stirred 10 h at room temperature, diluted with water (10 mL) and diethyl ether (20 mL). The aqueous layer was then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over magnesium sulfate. After evaporation to dryness, the residue was diluted in methanol (30 mL) and sodium phosphate dibasic Na_2HPO_4 (3 g, 21.1 mmol) were added. The reaction was cooled to 0 °C, and to the reaction mixture was added the freshly prepared sodium amalgam (5 g, 13 mmol) in one portion. The reaction was stirred at 0 °C for 30 min, and more sodium amalgan was added (3 g, 8 mmol). After 20 min, the reaction mixture was filtered through a pad of diatomaceous earth washing with diethyl ether. The remaining amalgam was destroyed with 2N of HCl, and disposed in an appropriate way. The filtrate was evaporated under reduced pressure and diluted with 1N HCl (10 mL), water (20 mL) and dichloromethane (30 mL). The aqueous laayer was extracted with dichloromethane (3 × 30 mL), and the combined organic layer were washed with brine (50 mL) and dried over magnesium sulfate. After concentration in vacuo, the residue was purified on silica gel eluting with 10% diethyl ether in petroleum ether to afford 1,4-diene **34** (0.775 g, 2.27 mmol) as a colorless oil.

$[\alpha]_D = +14.8$ (*c* 1.08, $CDCl_3$); IR (neat): 3076, 2928, 1619, 1586, 1352, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.37 (s, 1H), 6.23 (s, 1H), 5.67 (dd, J = 9.8, 15.6 Hz, 1H), 5.47 (d, J = 15.6 Hz, 1H), 4.57 (s, 1H), 4.14 (s, 1H), 3.78 (s, 3H), 2.63 (td, J = 5.3, 16.8 Hz, 1H), 2.45 (ddd, J = 6.3, 10.2, 16.6 Hz, 1H), 2.35 (d, J = 9.8 Hz, 1H), 2.29 (s, 3H), 2.19 (td, J = 4.6, 13.4 Hz, 1H), 1.98−1.88 (m, 2H), 1.78 (ddd, J = 5.8, 10.0, 13.4 Hz, 1H), 1.58−1.46 (m, 2H), 1.44 (s, 3H), 1.42 (m, 1H), 1.29 (m, 1H), 0.87 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.5, 154.4, 150.0, 136.8, 135.0, 128.3, 110.1, 108.1, 107.5, 102.6, 76.0, 56.9, 55.3, 39.8, 35.2, 35.0, 32.0, 29.7, 27.2, 23.3, 22.2, 21.6, 17.0. HMRS: Calc'd for $C_{23}H_{32}O_2$ [M^+]: 340.2402. Found: 340.2402.

(*1S,2S*)-1-Hydroxymethyl-2-[(*2R*)-2-(5-methoxy-2,7-dimethyl-chroman-2-yl)-vinyl]-3,3-dimethyl-cyclohexanol (36): To a solution of 1,4-diene **34** (0.5 g, 1.4 mmol) in *tert*-butyl alcohol (7 mL) was added water (7 mL), AD-mix β (3.5 g) and methanesulfonamide (0.3 g, 3.15 mmol). After 5 min, the solution turned clear, and the reaction was stirred under vigorous stirring for 20 h. Sodium metabisulfite (4 g) was added carefully. After the reaction mixture was stirred for 10 min, to this mixture was added water (10 mL) and diethyl ether (20 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate. After concentration in vacuo, the residue was chromatographed eluting with a mixture of diethyl ether and petroleum ether (3:2) to afford diol **36** (0.494 g, 1.31 mmol) as a sticky slightly brown oil.

$[\alpha]_D = +38.5$ (*c* 1.08, $CDCl_3$); IR (neat): 3440, 2932, 1618, 1585, 1462, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.37 (s, 1H), 6.24 (s, 1H), 5.54 (d, J = 15.4 Hz, 1H), 5.48 (dd, J = 10.2, 15.4 Hz, 1H), 3.79 (s, 3H), 3.11 (m, 1H), 2.81 (d, J = 11.3 Hz, 1H), 2.68 (ddd, J = 3.4, 5.8, 17.3 Hz, 1H), 2.39 (ddd, J = 6.6, 11.0, 17.5 Hz, 1H), 2.30 (s, 3H), 1.91 (ddd, J = 3.1, 6.3, 13.4 Hz, 1H), 1.86 (m, 1H), 1.79 (ddd, J = 5.8, 11.0, 13.4 Hz, 1H), 1.64 (m, 2H), 1.56 (m, 1H), 1.45 (s, 3H), 1.40 (m, 1H), 1.22 (m, 4H), 1.01 (m, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.6, 154.4, 137.3, 136.5, 127.6, 110.0, 107.3, 102.8, 75.9, 73.9, 66.9, 58.0, 55.4, 38.2, 33.4, 31.9, 31.7, 31.1, 30.2, 27.6, 21.6, 18.5, 17.2; HMRS: Calc'd for $C_{23}H_{34}O_4$ [M^+]: 374.2457. Found: 374.2454.

(*1S,2S*)-1-Hydroxymethyl-2-[(*2S*)-2-(5-methoxy-2,7-dimethyl-chroman-2-yl)-ethyl]-3,3-dimethyl-cyclohexanol (37): A solution of diol **36** (0.5 g, 1.33 mmol) and platinum oxide (0.06 g, 0.266 mmol) in ethyl acetate (HPLC grade, 15 mL) was purged thoroughly with argon and the mixture was heated to 70 °C. The reaction flask was then purged with hydrogen (balloon), and the reaction was stirred under H_2 atmosphere at 70 °C for 5 h. The reaction flask was then purged with argon, and the reaction mixture was filtered through a pad of silica gel washing with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified over silica gel (1/1 to 3/1 diethyl ether in petroleum ether) to afford **37** (0.415 g, 1.10 mmol) as a colorless oil containing an inseparable mixture of two diastereomers and starting material **36** (0.042 g, 0.112 mmol).

IR (neat): 3426, 2934, 16117, 1585, 1462, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.32 (s, 1H), 6.25 (s, 1H), 3.82 (s, 3H), 3.63 (dd, J = 6.6, 10.5 Hz, 1H), 3.58 (d, J = 10.5 Hz, 1H), 2.66 (td, J = 6.1, 17.3 Hz, 1H), 2.59 (td, J = 6.9, 17.3 Hz, 1H), 2.49 (s, 1H), 2.45 (m, 1H), 2.30 (s, 3H), 2.04 (m, 1H), 1.91−1.56 (m, 6H), 1.49−1.38 (m, 3H), 1.31 (app t, J = 4.4 Hz, 1H), 1.28 (s, 3H), 1.22 (m, 1H), 1.15 (td, J = 3.4, 12.9 Hz, 1H), 1.00 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.5, 154.0, 136.9, 110.2, 107.1, 102.5, 76.2, 75.6, 63.5, 55.7, 55.2, 42.5, 40.5, 35.7, 35.3, 32.3, 30.4, 23.2, 22.8, 21.5, 19.6, 19.0, 16.4. HMRS: Calc'd for $C_{23}H_{36}O_4$ [M^+]: 376.2613. Found: 376.2607.

(*1S,2S*)-1-Hydroxymethyl-2-[(*2S*)-2-(5-methoxy-2,7-dimethyl-2*H*-chromen-2-yl)-ethyl]-3,3-dimethyl-cyclohexanol (38): To a solution of diol **37** (0.243 g, 0.645 mmol) in benzene (20 mL) was added DDQ (0.250 g, 1.1 mmol). The solution was heated at 80 °C for 45 min and then cooled to room temperature. The reaction mixture was filtered through a pad of silica washing with diethyl ether, and thoroughly washed with diethyl ether. The filtrate was concentrated in vacuo, and the residue was chromatographed eluting with 1/1 to 3/1 diethyl ether in petroleum ether to afford chromene **38** (0.220 g, 0.587 mmol) as a sticky pale yellow oil.

IR (neat): 3418, 2932, 1614, 1573, 1463, 1115 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.67 (d, J = 10.0 Hz, 1H), 6.30 (s, 1H), 6.24 (s, 1H), 5.49 (d, J = 10.0 Hz, 1H), 3.81 (s, 3H), 3.63 (d, J = 10.7 Hz, 1H), 3.56 (d, J = 10.7 Hz, 1H), 2.29 (s, 3H), 2.27 (br s, 1H), 2.17 (br s, 1H), 2.04 (br d, J = 12.9 Hz, 1H), 1.90 (ddd, J = 5.4, 11.7, 13.9 Hz, 1H), 1.81 (ddd, J = 5.4, 11.4, 13.9 Hz, 1H), 1.58 (m, 2H), 1.50−1.38 (m, 3H), 1.36 (s, 3H), 1.30 (t, J = 4.7 Hz, 1H), 1.22 (td, J = 3.4, 12.9 Hz, 1H), 1.13 (td, J = 3.2, 12.9 Hz, 1H), 0.98 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.0, 153.5, 139.3, 126.9, 117.2, 109.7, 107.8, 103.8, 78.6, 75.7, 63.4, 55.6, 55.5, 43.7, 40.6, 36.0, 35.4, 32.3, 26.0, 22.7, 21.9, 19.9, 19.6. HMRS: Calc'd for $C_{23}H_{34}O_4$ [M^+]: 374.2457. Found: 374.2458.

(*3S,4S*)-2-[2-(5,5-Dimethyl-1-oxa-spiro[2.5]oct-4-yl)-ethyl]-(*2S*)-5-methoxy-2,7-dimeth-yl-2H-chroman (48): To a solution of diol **38** (0.220 g, 0.588 mmol) in 5 mL of dichloromethane was added successively at room temperature triethylamine (0.170 mL, 1.21 mmol), DMAP (0.15 g, 1.22 mmol) and *p*-TsCl(0.168 g, 0.88 mmol). The reaction was stirred at room temperature for 3 h. Without workup, the mixture was directly purified by preparative TLC (first eluting with diethyl ether in petroleum ether (1:1), second elution if necessary using diethyl ether in petroleum ether (2:1)) to afford pure tosylate (0.277 g, 0.524 mmol). The material was dissolved in THF (10 mL) and DMSO (15 drops). Sodium hydride (excess) was added, and the reaction mixture was stirred at room temperature for 10 min. The mixture was directly filtered through a pad of silica gel washing with diethyl ether. The filtrate was concentracted in vacuo, and the oil material was purified on silica gel eluting with diethyl ether in petroleum ether (1/9 to 2/3) to afford epoxide **48** (0.195 g, 0.546 mmol, 93%) as a colorless oil.

IR (neat): 2937, 1614, 1573, 1463, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.67 (d, J = 10.0 Hz, 1H), 6.29 (s, 1H), 6.24 (s, 1H), 5.45

(d, J = 10.0 Hz, 1H), 3.82 (s, 3H), 2.63 (d, J = 4.7 Hz, 1H), 2.49 (dd, J = 1.2, 4.6 Hz, 1H), 2.29 (s, 3H), 1.78−1.56 (m, 6H), 1.46 (m, 1H), 1.34 (s, 3H), 1.34 (m, overlapped, 1H), 1.24 (m, 2H), 1.09 (m, 1H), 1.01 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 154.4, 140.1, 127.3, 118.1, 110.6, 108.5, 104.5, 79.0, 60.0, 55.5, 51.3, 50.2, 41.4, 36.9, 35.7, 31.9, 30.3, 28.8, 26.3, 22.0, 21.0, 20.6. HRMS: Calc'd for $C_{23}H_{32}O_3$: 356.2351. Found: 356.2360.

(*2S*)-5-Methoxy-2,7-dimethyl-2-[(*5S,6S*)-2-(2,2,7,7-tetramethyl-1,3-dioxa-spiro[4.5] dec-6-yl)-ethyl]-chroman (42): To a solution of diol **37** (0.577 g, 1.54 mmol) and CSA (0.005 g) in dichloromethane (12 mL) was added dropwise 2-methoxypropene (0.3 mL) (CAUTION: the end of the needle has to be immersed in the solution during the addition). The solution was stirred for 5 min and to this solution was added a saturated aqueous solution of sodium bicarbonate (5 mL). After separation, the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified over silica gel eluting with 1/10 diethyl ether in petroleum ether to afford acetonide **42** (0.629 g, 1.51 mmol, 98%) as a colorless oil.

IR (neat): 2936, 1618, 1585, 1462, 1231 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.29 (s, 1H), 6.22 (s, 1H), 3.83 (d, J = 8.3 Hz, 1H), 3.81 (s, 3H), 3.71 (d, J = 8.3 Hz, 1H), 2.66 (td, J = 6.1, 17.1 Hz, 1H), 2.55 (td, J = 8.5, 17.1 Hz, 1H), 2.28 (s, 3H), 1.95 (m, 2H), 1.84 (ddd, J = 6.3, 8.5, 13.4 Hz, 1H), 1.74 (td, J = 6.1, 13.4 Hz, 1H), 1.60 (m, 3H), 1.48−1.22 (m, 6H), 1.43 (s, 3H), 1.29 (s, 6H), 1.01 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.5, 154.3, 136.7, 110.4, 106.98, 106.91, 102.2, 85.4, 75.7, 68.4, 55.2, 53.1, 43.3, 38.1, 35.9, 31.3, 30.4, 28.7, 28.6, 26.6, 23.67, 23.62, 21.5, 20.3, 19.6, 16.4. HRMS: Calc'd for $C_{26}H_{40}O_4$: 416.2926. Found: 416.2926.

(*2S*)-2,7-Dimethyl-2-[(*5S,6S*)-2-(2,2,7,7-tetramethyl-1,3-dioxa-spiro[4.5]dec-6-yl)-ethyl]-chroman-5-ol (43a): To a solution of acetonide **42** (0.652 g, 1.56 mmol) in DMF (10 mL) were added at room temperature sodium hydride (0.5 g, 12.5 mmol, 60% dispersion in oil, unwashed) and dropwise ethanethiol (1 mL, 13.5 mmol). After 10 min, the mixture was heated at 120 °C for 24 h. After cooling to room temperature, to the reaction mixture was added water (20 mL). The mixture was extracted with diethyl ether (4 × 50 mL). The combined ethereal extracts were washed with brine (20 mL) and dried over magnesium sulfate. After concentration in vacuo, the residue was purified by flash chromatography eluting with 1/5 diethyl ether in petroleum ether to afford first remaining **42** (0.051 g, 0.123 mmol), and desired phenol **43a** (0.540 g, 1.34 mmol) as a colorless oil.

IR (neat): 3388, 2935, 1626, 1586, 1456, 1368, 1215 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (s, 1H), 6.15 (s, 1H), 5.29 (br s, 1H), 3.84 (d, J = 8.3 Hz, 1H), 3.71 (d, J = 8.3 Hz, 1H), 2.66 (td, J = 6.1, 16.6 Hz, 1H), 2.57 (td, 6.1, 16.6 Hz, 1H), 2.20 (s, 3H), 1.97 (m, 2H), 1.86 (ddd, J = 6.6, 8.3, 13.1 Hz, 1H), 1.76 (dt, J = 6.1, 13.4 Hz, 1H), 1.60 (m, 3H), 1.48−1.26 (m, 6H), 1.43 (s, 3H), 1.29 (s, 6H), 1.00 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.7, 153.7, 137.1, 110.1, 107.1, 106.7, 105.4, 85.5, 75.8, 68.4, 53.1, 43.2, 38.1, 35.9, 31.3, 30.3, 28.67, 28.62, 26.6, 23.7, 23.6, 21.1, 20.3, 19.6, 16.3. HRMS: Calc'd for $C_{25}H_{38}O_4$: 402.2770. Found: 402.2774.

***tert*-Butyl-{(*2S*)-2,7-dimethyl-2-[(*5S,6S*)-2-(2,2,7,7-tetramethyl-1,3-dioxa-spiro[4.5] dec-6-yl)-ethyl]-chroman-5-yloxy}-dimethylsilane (43b):** To a solution of phenol **43a** (0.390 g, 0.968 mmol) in dichloromethane (5 mL) were added successively triethylamine (0.200 mL, 1.43 mmol), DMAP (0.190 g, 1.55 mmol) and *tert*-butyldimethylsilyl chloride (0.190 g, 1.25 mmol). The resulting mixture was stirred for 24 h art room temperature. The reaction mixture was then partitioned between water (20 mL) and dichloromethane (20 mL). The aqueous layer was then extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dired over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by chromatography over silica gel eluting with 1/10 diethyl ether in petroleum ether to afford silyl ether **43b** (0.430 g, 0.832 mmol) as a clear oil.

IR (neat): 2934, 1615, 1574, 1455, 1417, 1367, 1252 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.28 (s, 1H), 6.17 (s, 1H), 3.83 (d, J = 8.3 Hz, 1H), 3.71 (d, J = 8.3 Hz, 1H), 2.66 (td, J = 6.1, 17.1 Hz, 1H), 2.58 (td, J = 8.5, 17.1 Hz, 1H), 2.22 (s, 3H), 1.96 (m, 2H); 1.84 (td, J = 7.6, 13.4 Hz, 1H), 1.73 (td, J = 6.4, 13.4 Hz, 1H), 1.60 (m, 3H), 1.48−1.26 (m, 3H), 1.43 (s, 3H), 1.29 (s, 6H), 1.04 (s, 9H), 1.01 (s, 3H), 0.74 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.7, 153.6, 136.5, 110.6, 1110.3, 109.6, 106.9, 85.3, 75.6, 68.4, 53.1, 43.2, 38.1, 35.9, 31.3, 30.4, 28.68, 28.63, 26.8, 26.6, 25.7, 23.8, 21.2, 20.3, 19.7, 18.1, 17.4, −4.1, −4.2. HRMS: Calc'd for $C_{31}H_{52}O_4Si$: 516.3635. Found: 516.3637.

***tert*-Butyl-{(*2S*)-2,7-dimethyl-2-[(*5S,6S*)-2-(2,2,7,7-tetramethyl-1,3-dioxa-spiro[4.5] dec-6-yl)-ethyl]-2H-chromen-5-yloxy}-dimethylsilane (44):** To a solution of chromane **43c** (0.5 g, 0.967 mmol) in benzene (55 mL) was added at 80 °C in one portion DDQ (0.55 g, 2.42 mmol). The mixture was refluxed for 8 h. Without workup, the reaction mixture was directly purified by chromatography over silica gel eluting with 1/8 diethyl ether in petroleum ether to afford chromene **44** (0.42 g, 0.815 mmol) as a colorless oil.

IR (neat): 2931, 1614, 1566, 1461, 1387, 1214 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.61 (d, J = 10.0 Hz, 1H), 6.27 (s, 1H), 6.15 (s, 1H), 5.46 (d, J = 10.0 Hz, 1H), 3.80 (d, J = 8.5 Hz, 1H), 3.65 (d, J = 8.2 Hz, 1H), 2.22 (s, 3H), 1.99 (m, 1H), 1.88 (dd, J = 5.4, 13.4 Hz, 1H), 1.78 (td, J = 4.4, 13.4 Hz, 1H), 1.62−1.20 (m, 8H), 1.44 (s, 3H), 11.36 (s, 6H), 1.02 (s, 9H), 0.98 (s, 3H), 0.67 (s, 3H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.2, 151.2, 138.9, 126.8, 118.1, 112.1, 110.5, 110.3, 106.9, 85.5, 78.4, 68.4, 53.2, 45.0, 38.1, 36.0, 31.4, 30.3, 28.8, 26.9, 26.8, 26.7, 25.8, 21.7, 20.5, 20.4, 18.3, −4.2, −4.3. HRMS: Calc'd for $C_{31}H_{50}O_4Si$: 514.3478. Found: 514.3468.

2-{2-[5-(*tert*-Butyldimethylsilanyloxy)−(*2S*)-2,7-dimethyl-2H-chromen-2-yl]-ethyl}-(*1S,2S*)-1-hydroxymethyl-3,3-dimethyl-cyclohexanol (45) and **(+)-siccanochromene F (7):** Method A: A solution of chromene **44** (0.400 g, 0.777 mmol) and *p*-TsOH (0.035 g, 0.183 mmol) in MeOH (40 mL) was refluxed for 1h. To this mixture was then added a saturated solution of sodium bicarbonate (10 mL), and the mixture was evaporated to dryness in vacuo. The solid residue was diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative TLC (petroleum ether/diethyl ether 4/1 v/v double elution) to afford first starting material (0.310 g, 0.602 mmol), then diol **45** and siccanochromene F (**7**). The remaining starting material has been submitted again three times, adjusting the relative amount of reagent and solvent for each run. In total, we have obtained diol **45** (0.221 g, 0.465 mmol), siccanochromene F (**7**) (0.043 g, 0.119 mmol) and starting chromene **44** (0.021 g, 0.04 mmol) has been discarded.

Method B: To a solution of compound **44** (25 mg, 0.049 mmol) in 2 mL of aqueous methanol (MeOH:water = 4:1) was added toluenesulfonic acid monohydrate (5 mg, 0.026 mmol). The resulting mixture was under reflux for 4 h. The mixture was directly purified by flash chromatography eluting with 50% ethyl acetate in petroleum ether to afford siccanochromene F (**7**) (21 mg, 0.044 mmol, 90%) as a colorless oil.

45: IR (neat): 2931, 1614, 1566, 1461, 1387, 1214 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.62 (d, J = 10.0 Hz, 1H), 6.29 (s, 1H), 6.17 (s, 1H), 5.49 (d, J = 10.0 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 2.23 (s, 3H), 2.23 (m, overlapped, 1H), 2.10 (br s, 1H), 2.05 (m, 1H), 1.90 (m, 2H), 1.60 (m, 2H), 1.50−1.38 (m, 3H), 1.36 (s, 3H), 1.31 (m, 1H), 1.23 (m, 1H), 1.11 (m, 1H), 1.02 (s, 9H), 0.97 (s, 3H), 0.76 (s, 3H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.8, 151.2, 139.0, 127.0, 118.1, 112.3, 110.7, 110.2, 78.5, 75.7, 63.5, 55.5, 43.7, 40.6, 36.0, 35.4, 32.3, 26.1, 25.7, 22.7, 21.6, 19.9, 19.7, 18.2, −4.2, −4.3. HRMS: Calc'd for $C_{28}H_{46}O_4Si$: 474.3165. Found: 474.3159.

7: IR (neat): 3381, 2931, 1624, 1579, 1454, 1062 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.64 (d, J = 10.0 Hz, 1H), 6.25 (s, 1H), 6.14 (s,

1H), 5.66 (br s, 1H), 5.51 (d, J = 10.0 Hz, 1H), 3.65 (d, J = 10.7 Hz, 1H), 3.57 (d, J = 10.7 Hz, 1H), 2.35 (br s, 1H), 2.29 (br s, 1H), 2.21 (s, 3H), 2.05 (br d, J = 12.9 Hz, 1H), 1.90 (ddd, J = 5.1, 11.4, 13.6 Hz, 1H), 1.80 (m, 2H), 1.60 (m, 2H), 1.50−1.38 (m, 3H), 1.30 (m, 1H), 1.24 (m, 1H), 1.15 (td, J = 4.1, 12.7 Hz, 1H), 0.98 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.9, 151.3, 139.5, 127.2, 117.0, 109.5, 108.5, 106.9, 78.7, 75.9, 63.5, 55.6, 43.7, 40.7, 36.0, 35.5, 32.4, 26.1, 22.7, 21.6, 19.9, 19.7. HRMS: Calc'd for $C_{22}H_{32}O_4$: 360.2301. Found: 360.2302.

2-[2-(5-Hydroxy-2,7-dimethyl-*2H*-chromen-2-yl)-ethyl]-3,3-dimethylcyclohexanone (46): To diol **7** (19 mg, 0.039 mmol) in 1 mL of acetone was added sodium periodate (33 mg, 0.156 mmol) at room temperature. After 5 h, the reaction mixture was directly purified by flash chromatography eluting with 50% diethyl ether in petroleum ether to afford ketone **46** (11 mg, 0.034 mmol, 86%) as a colorless oil.

$[\alpha]_D$ = +42 (*c* 1.1, $CDCl_3$); IR (neat): 3620, 3385, 1710, 1638, 1580, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (d, J = 11.1 Hz, 1H), 6.08 (s, 1H), 6.03 (s, 1H), 5.45 (d, J = 11.1 Hz, 1H), 2.16 (s, 3H), 2.15−2.05 (m, 3H), 1.80−1.55 (m, 4H), 1.50−1.25 (m, 4H), 1.27 (s, 3H), 1.01 (s, 3H), 0.75 (s, 3H); HRMS: Calc'd for $C_{21}H_{28}O_3$: 328.2038. Found: 328.2040.

***tert*-Butyl-{2-[(*1S,2S*)-2-(5,5-dimethyl-1-oxa-spiro[2.5]oct-4-yl)-ethyl]-(*2S*)-2,7-dimethyl-2*H*-chromen-5-yloxy}-dimethylsilane (47):** To a solution of diol **45** (0.180 g, 0.379 mmol) in dichloromethane (4 mL) at room temperature were added DMAP (0.110 g, 0.9 mmol) and *p*-TsCl (0.121 g, 0.633 mmol). The solution was stirred for 4 h. Without workup, the mixture was then directly purified by preparative TLC (one elution, petroleum ether/diethyl ether = 4/1) to afford intermediate tosylate (0.230 g). This material was resuspended in 5 mL of THF and sodium hydride (48 mg, 1.2 mmol, 60%) was added in one portion. After gas evolution ceased, the solution was stirred for 5 more min and the solution directly filtered through silica gel washing with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC (one elution, petroleum ether/diethyl ether = 10/1) to afford epoxide **47** (0.141 g, 0.308 mmol) as a colorless oil.

IR (neat): 2930, 1614, 1565, 1461, 1387, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.62 (d, J = 10.0 Hz, 1H), 6.28 (s, 1H), 6.17 (s, 1H), 5.45 (d, J = 10.0 Hz, 1H), 2.62 (d, J = 4.7 Hz, 1H), 2.48 (d, J = 4.7 Hz, 1H), 2.23 (s, 3H), 1.78−1.59 (m, 6H), 1.44 (ddd, J = 3.9, 8.8, 13.1 Hz, 1H), 1.34 (s, 3H), 1.34 (m, overlapped, 1H), 1.29−1.24 (m, 2H), 1.09 (m, 1H), 1.06 (s, 3H), 1.02 (s, 9H), 0.83 (s, 3H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.9, 151.1, 139.0, 126.8, 118.2, 112.3, 110.6, 110.2, 78.1, 59.9, 51.2, 50.1, 41.3, 36.9, 35.7, 31.9, 28.8, 26.3, 26.1, 25.7, 21.6, 20.8, 20.6, 18.2, −4.2. HRMS: Calc'd for $C_{28}H_{44}O_3Si$: 456.3060. Found: 456.3065.

(+)-Siccanochromene B (3): To a solution of epoxide **47** (130 mg, 0.285 mmol) in THF (5 mL) at 0 °C was added TBAF (0.5 mL, 0.5 mmol, 1M in THF). The solution was stirred for 10 min at 0 °C, and was then filtrate through silica gel washing with diethyl ether. The residue was purified by preparative TLC (one elution, petroleum ether/diethyl ether = 5/1) to afford siccanochromene B (**3**) (81 mg, 0.236 mmol) as a colorless oil.

IR (neat): 3375, 2939, 1624, 1579, 1453, 1065 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.63 (d, J = 10.0 Hz, 1H), 6.21 (s, 1H), 6.12 (s, 1H), 5.44 (d, J = 10.0 Hz, 1H), 5.02 (br s, 1H), 2.65 (d, J = 4.4 Hz, 1H), 2.50 (d, J = 4.4 Hz, 1H), 2.18 (s, 3H), 1.76−1.50 (m, 6H), 1.42 (ddd, J = 4.2, 8.8, 13.4 Hz, 1H), 1.38−1.16 (m, 4H), 1.32 (s, 3H), 1.04 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.9, 151.4, 139.3, 126.7, 117.2, 117.1, 109.4, 108.4, 106.7, 78.3, 60.6, 51.4, 50.1, 41.3, 35.7, 28.7, 26.2, 25.9, 21.5, 20.7, 20.5, 20.4. HRMS: Calc'd for $C_{22}H_{30}O_3$: 342.2195. Found: 342.2198.

(−)-Siccanochromene Methyl Ether (53) and (−)-5-*epi*-Siccanin Methyl Ether (54): To titanocene dichloride (58 mg, 0.224 mmol) and manganese (25 mg, 0.448 mmol) under argon was added 1 mL of distilled THF. The resulting red mixture was stirred for 30 min at room temperature and the color of the solution turned green. To this solution was then added a solution of epoxide **48** (20 mg, 0.056 mmol) in 0.5 mL of distilled THF under argon. The resulting solution was still green and this solution was stirred at room temperature for 12 h. The solution was filtered through diatomaceous earth, washed with ethyl acetate and the mixture was concentrated to 2 mL. The residue was chromatographed eluting with 5% to 30% diethyl ether in petroleum ether to afford the tetracyclic compound **53** (12 mg, 0.034 mmol, 61%) and pentacyclic compound **54** (4 mg, 0.011 mmol, 20%) as a colorless oil.

53: $[\alpha]_D$ = -83.8 (*c* 1.8, $CDCl_3$); IR (neat): 3453b, 2922s, 2872m, 1618m, 1587s, 1462m, 1352m, 1224m, 1166m, 1112s, 1040m, 900w, 812w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (s, 1H), 6.21 (s, 1H), 4.05 (d, J = 12.0 Hz, 1H), 3.79 (s, 3H), 3.63 (d, J = 12.0 Hz, 1H), 2.79 (d, J = 18.5 Hz, 1H), 2.59 (dd, J = 8.5, 18.0 Hz, 1H), 2.27 (s, 3H), 2.00 (dt, J = 3.0, 14.0 Hz, 1H), 1.92 (d, J = 8.5 Hz, 1H), 1.80 (td, J = 3.0, 13.5 Hz, 1H), 1.64 (m, 1H), 1.49 (dd, J = 3.0, 13.5 Hz, 1H), 1.22−1.43 (m, 5H), 1.19 (s, 3H), 1.18 (s, 3H), 0.93 (s, 3H), 1.10 (d, J = 9.5 Hz, 1H), 0.72 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 154.8, 136.3, 110.2, 107.8, 102.6, 75.2, 64.5, 55.3, 43.4, 42.9, 39.1, 38.3, 34.7, 33.8, 33.6, 30.0, 27.1, 23.9, 21.6, 19.7, 18.6, 17.5. HRMS: Calc'd for $C_{23}H_{34}O_3$: 358.2508. Found: 358.2490.

54: $[\alpha]_D$ = -118.6 (*c* 1.4, Et_2O); IR (neat): 2925s, 2850m, 1618m, 1592m, 1463m, 1356w, 1230w, 1209w, 1163w, 1134w, 1110s, 1053w, 1102w, 950w, 895w, 817w, 733w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 (s, 1H), 6.33 (s, 1H), 5.48 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.85 (d, J = 8.5 Hz, 1H), 3.76 (d, J = 8.5 Hz, 1H), 2.30 (s, 3H), 2.27 (m, 1H), 2.13 (d, J = 12.5 Hz, 1H), 2.05 (d, J = 8.0 Hz, 1H), 1.43−1.64 (m, 6H), 1.20−1.34 (m, 3H), 1.08 (s, 3H), 1.01 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 156.0, 139.4, 112.5, 111.8, 104.8, 68.8, 65.6, 56.3, 55.5, 51.7, 48.7, 41.9, 40.7, 38.0, 33.7, 32.4, 29.7, 29.0, 21.9, 21.2, 19.4, 17.0. HRMS: Calc'd for $C_{23}H_{32}O_3$: 356.2351. Found: 356.2352.

(−)-Siccanochromene C methyl ether (55): To manganese (25 mg, 0.45 mmol) and titanocene dichloride (58 mg, 0.22 mmol) was added THF under argon. The resulting red mixture was stirred for 30 min to give a green solution. To the solution was added a solution of epoxide **48** (20 mg, 0.056 mmol) in 0.5 mL of THF followed by iodine (30 mg, 0.11 mmol) in 0.5 mL of THF. The red solution was heated for 1 h before the addition of aqueous sodium thiosulfate (10%). The mixture was chromatographed eluting with 5% to 40% diethyl ether in petroleum ether to afford the allylic alcohol **55** (13.5 mg, 0.038 mmol, 68%) as pale yellow oil.

$[\alpha]_D$ = −16.7 (*c* 0.8, Et_2O); IR (neat): 3418b, 2983s, 2853s, 1614m, 1574m, 1456m, 1386w, 1230w, 1211w, 1115s, 1017m, 814m, 772w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, J = 9.5 Hz, 1H), 6.28 (s, 1H), 6.23 (s, 1H), 5.65 (s, 1H), 5.44 (d, J = 9.5 Hz, 1H), 4.03 (bs, 2H), 3.82 (s, 3H), 2.29 (s, 3H), 2.03 (d, J = 4.0 Hz, 2H), 1.70−1.26 (m, 11H), 1.26 (s, 3H); 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0, 140.3, 139.4, 126.6, 122.5, 117.3, 109.8, 103.8, 78.4, 66.6, 55.5, 45.0, 41.0, 32.3, 31.5, 29.7, 27.7, 27.4, 26.3, 25.2, 22.7, 22.0, 14.1. HRMS: Calc'd for $C_{23}H_{32}O_3$: 356.2352. Found: 356.2350.

(−)-Siccanin Methyl Ether (60): To a solution of alcohol **53** (28 mg, 0.078 mmol) in 1.0 mL of cyclohexane was added iodobenzene diacetate (28 mg, 0.088 mmol) and iodine (5.0 mg, 0.02 mmol) at room temperature. The red mixture was irradiated with 150 w filament tungsten lamp for 1.5 h. To the mixture was added saturated sodium thiosulfate (1.0 mL). After this mixture turned colorless, the mixture was chromatographed eluting with 5% to 20% diethyl ether in petroleum ether to afford **60** (18 mg, 0.051 mmol, 65%) as a pale yellow oil.

$[\alpha]_D$ = −107 (*c* 1.8, Et_2O); IR (neat): 2930s, 2866s, 1617s, 1578s, 1463s, 1416m, 1361s, 1308w, 1287w, 1273w, 1232m, 1219m, 1188m, 1170s, 1138m, 1106s, 1055w, 1022m, 990w, 972w, 954w, 926m, 905w, 876w, 855w, 817w, 805w, 732s, 670w, 644w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (s, 1H), 6.20 (s, 1H), 5.12 (d, J = 9.2 Hz, 1H), 4.24 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 3.40 (dd, J = 2.0, 7.6 Hz, 1H), 2.25 (s, 3H), 2.13 (dd, J = 4.0, 14.8 Hz, 1H), 1.95 (d, J = 9.2 Hz, 1H), 1.90 (m, 2H), 1.65 (m, 1H), 1.54 (dd, J = 6.4, 14.4 Hz, 1H), 1.46

(m, 2H), 1.33 (m, 2H), 1.20 (s, 3H), 1.14 (dd, J = 2.8, 12.0 Hz, 1H), 1.08 (d, J = 8.8 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 154.7, 139.1, 110.6, 110.2, 104.2, 78.5, 75.2, 66.9, 55.9, 54.2, 50.3, 46.0, 37.4, 33.9, 33.7, 30.3, 28.2, 26.1, 23.2, 21.7, 21.2, 20.0. HRMS: Calc'd for $C_{23}H_{32}O_3$: 356.2351. Found: 356.2351.

(−)-Siccanin (1): To a slurry of sodium hydride (12 mg, 0.46 mmol) in 1 mL of DMF was added ethanethiol (26 mg, 31 uL, 0.42 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 40 min before the addition of methyl ether **60** (15 mg, 0.042 mmol) in 1 mL of DMF. The mixture was heated at 120 °C for 12 h. Without workup, the mixture was directly chromatographed eluting with 10% to 30% diethyl ether in petroleum ether to afford sicannin (**1**) as a white solid (12.4 mg, 0.036 mmol, 86%).

$[\alpha]_D$ = −132.3 (*c* 1.28, $CDCl_3$); mp = 125−130 °C; $[\alpha]_D$[2a] = −150 (*c* 7.75, $CDCl_3$); mp[2a] = 138 °C; IR (neat): 3465b, 2960s, 2929s, 2866s, 1634s, 1576s, 1456m, 1361s, 1304w, 1279w, 1197m, 1175s, 1134m, 1064s, 1012s, 985m, 971w, 953w, 906m, 806w, 766w, 734m, 702w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.31 (s, 1H), 6.14 (s, 1H), 5.16 (d, J = 8.8 Hz, 1H), 4.24 (d, J = 7.6 Hz, 1H), 3.48 (dd, J = 2.0, 7.6 Hz), 2.21 (s, 3H), 2.18 (dd, J = 1.6, 5.2 Hz, 1H), 1.96 (d, J = 8.4 Hz, 1H), 1.90 (td, J = 5.2, 13.6 Hz, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.54 (ddd, J = 6.0, 7.1, 12.2 Hz, 1H), 1.37 (m, 3H), 1.26 (s, 3H), 1.18−1.07 (m, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 154.7, 139.6, 109.9, 109.5, 108.3, 79.4, 74.8, 68.1, 53.5, 50.5, 45.9, 37.3, 33.6, 30.2, 28.1, 27.1, 23.5, 21.4, 21.2, 19.9. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.31 (s, 1H), 6.14 (s, 1H), 5.16 (d, J = 8.8 Hz, 1H), 4.24 (d, J = 7.6 Hz, 1H), 3.48 (dd, J = 2.0, 7.6 Hz), 2.21 (s, 3H), 2.18 (ddd, J = 1.6, 5.2, 14.8 Hz, 1H), 1.96 (d, J = 8.4 Hz, 1H), 1.90 (td, J = 5.2, 13.6 Hz, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.54 (ddd, J = 6.0, 7.1, 12.2 Hz, 1H), 1.37 (m, 3H), 1.26 (s, 3H), 1.18−1.07 (m, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 154.7, 139.6, 109.9, 109.5, 108.3, 79.4, 74.8, 68.1, 53.5, 50.5, 45.9, 37.3, 33.6, 33.5, 30.2, 28.1, 27.1, 23.5, 21.4, 21.2, 19.9. (^{1}H NMR (300 MHz, $CDCl_3$) in the literature:[11] δ 6.58 (s, 1H), 6.31 (s, 1H), 6.15 (s, 1H), 5.16 (d, J = 8.8 Hz, 1H), 4.24 (d, J = 7.6 Hz, 1H), 3.48 (dd, J = 2.4, 7.6 Hz), 2.21 (s, 3H), 2.16 (ddd, J = 1.5, 5.1, 14.7 Hz, 1H), 1.96 (d, J = 8.7 Hz, 1H), 1.94−1.62 (m, 3H), 1.60−1.46 (m, 1H), 1.45−1.29 (m, 3H), 1.26 (s, 3H), 1.20−1.02 (m, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) in the literature:[11] δ 155.8, 153.8, 139.7, 109.9, 109.5, 108.4, 79.4, 74.8, 68.1, 53.5, 50.5, 45.8, 37.2, 33.6, 33.5, 30.1, 28.0, 27.0, 23.4, 21.3, 21.1, 19.8.) HRMS: Calc'd for $C_{22}H_{30}O_3$: 342.2195. Found: 342.2212.

5-*epi*-(−)-Siccanin (68): To a slurry of sodium hydride (20 mg, 60% in mineral oil, 0.51 mmol) in 1.0 mL of DMF at 0 °C was added ethane thiol (29 mg, 35 uL, 0.47 mmol). After 10 min, the mixture was warmed to room temperature and stirred for 0.5 h. To the mixture was added *epi*-siccanin methyl ether **54** (14 mg, 0.039 mmol) in 1 mL of DMF. The mixture was heated at 120 °C for 28 h. Without workup, the mixture was purified by flash chromatography twice eluting with 10% to 50% ethyl ether in petroleum ether to afford phenol **68** as a pale yellow oil (11 mg, 0.032 mmol, 82%).

$[\alpha]_D$ = -76.8 (*c* 0.7, $CDCl_3$); IR (neat): 3283b, 2925s, 2853s, 1626m, 1597m, 1466m, 1366m, 1268w, 1208w, 1165w, 1133m, 1066m, 1048m, 1010m, 896w, 826w, 757w, 724w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.16 (s, 1H), 5.29 (d, J = 8.5 Hz, 1H), 3.88 (d, J = 9.0 Hz, 1H), 3.66 (d, J = 9.0 Hz, 1H), 2.17 (s, 3H), 2.02 (m, 3H), 1.45−1.70 (m, 9H), 1.35 (s, 3H), 0.90 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 154.0, 139.7, 110.5, 109.9, 109.1, 75.9, 69.6, 69.2, 56.5, 49.1, 46.6, 42.0, 39.3, 33.8, 33.0, 31.9, 29.7, 21.4, 20.7, 19.6, 17.5. HRMS: Calc'd for $C_{22}H_{30}O_3$: 342.2195. Found: 342.2182.

12b-Hydroxymethyl-4,4,6a,9-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-ben-zo[*a*]xanthen-11-ol (62): To a slurry of sodium hydride (40 mg, 60% in mineral oil, 1.01 mmol) in 0.5 mL of DMF at 0 °C was added ethanethiol (58 mg, 69 uL, 0.94 mmol). After 10 min, the mixture was warmed to room temperature and stirred for half an hour. To the mixture was added a solution of **53** (28 mg, 0.078 mmol) in 1.5 mL of DMF. The mixture was heated at 120 °C for 48 h. The mixture was purified by flash chromatography eluting with 10% to 50% ethyl acetate in petroleum ether to afford phenol **62** as a dark brown oil without any contamination of DMF (22 mg, 0.064 mmol, 82%).

$[\alpha]_D$ = −68.1 (*c* 1.8, $CDCl_3$); IR (neat): 3419b, 2924s, 2855s, 1716w, 1623m, 1589s, 1456s, 1415m, 1349m, 1320m, 1261w, 1167s, 1075m, 1037m, 903w, 821w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (s, 1H), 6.17 (s, 1H), 4.10 (d, J = 12.0 Hz, 1H), 3.66 (d, J = 12.0 Hz, 1H), 2.78 (d, J = 18.0 Hz, 1H), 2.67 (dd, J = 8.0, 18.0 Hz, 1H), 2.22 (s, 3H), 2.02 (dt, J = 3.5, 14.0 Hz, 1H), 1.98 (d, J = 8.0 Hz, 1H), 1.85 (dd, J = 3.0, 13.0 Hz, 1H), 1.80 (dd, J = 3.0, 13.5 Hz, 1H), 1.68 (m, 2H), 1.32−1.53 (m, 6H), 1.21 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 153.1, 136.7, 110.0, 107.2, 106.4, 75.3, 64.6, 43.4, 42.9, 39.1, 38.3, 34.6, 33.8, 33.6, 30.0, 27.1, 24.0, 21.2, 19.7, 18.6, 17.3. HRMS: Calc'd for $C_{22}H_{32}O_3$ [M^+]: 344.2351. Found: 344.2352.

Conclusion

In conclusion, we have achieved the first enantioselective total synthesis of (−)-siccanin (**1**) based on the development of the Pd-catalyzed asymmetric allylic alkylation (AAA) of phenol allyl carbonate **18** and two sequential radical cyclizations. The failure of siccanochromene B to cyclize under acid conditions may provide insight into the biosynthesis. Presuming it is indeed an enzyme catalyzed event, the enzyme must suppress the intrinsic bias of the system to undergo a 1,2-hydride shift faster than cyclization. Alternatively, the success of a radical based cyclization opens the question of whether a similar mechanism may be involved. This reaction is by far the most complicated application of the Ti(III)-mediated epoxyolefin cyclization reported to date and poses interesting mechanistic questions. The second stereoselective radical cyclization to form the tetrahydrofuran moiety is quite efficient and involves multiple steps including oxygen radical formation, selective hydrogen atom abstraction, benzyl iodide formation, elimination and oxygen nucleophile cyclization. During the course of the synthesis, other members of the siccanin family were also prepared including siccanochromenes A, B, E, F, and the methyl ether of siccanochromene C.

Acknowledgment. We thank the National Institutes of Health (GM-13598) and the National Science Foundation for their generous support of our programs. We thank Professor Dan Yang for helpful discussions. H.C.S. was a Stanford Graduate Fellow. 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 Available: Experimental procedures for the preparation of **24**−**26**, **29**−**32**, **39**, **48**, **69**−**71**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA048084P