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Perylenequinone Natural Products: Total Synthesis of Hypocrellin A

Erin M. O'Brien, Barbara J. Morgan, Carol A. Mulrooney, Patrick J. Carroll, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

marisa@sas.upenn.edu

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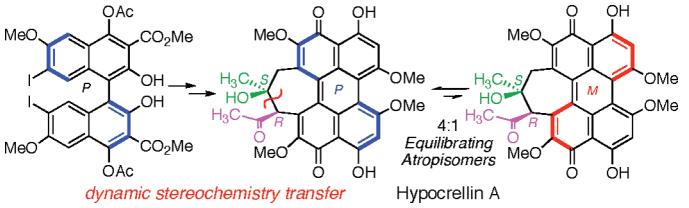

An efficient and stereoselective total synthesis of the perylenequinone natural product hypocrellin A (**1**) is described. The key features include a potentially biomimetic 1,8-diketone aldol cyclization to set the centrochiral C7,C7′-stereochemistry, bis(trifluoroacetoxy)iodobenzene mediated oxygenation, a palladium-catalyzed decarboxylation, and an enantioselective catalytic oxidative 2-naphthol coupling to establish the biaryl axial chirality. The helical stereochemistry is formed from an axial chiral intermediate and is then utilized in a *dynamic stereochemical transfer* to dictate the stereochemistry of the C7,C7′-seven membered ring formed during the aldol cyclization.

Introduction

The hypocrellin family **1**-**3** (Figure 1) are members of the naturally occurring mold perylenequinones.[1] Similar to many other natural perylenequinones, the hypocrellins are characterized by a helical chiral pentacyclic conjugated core combined with C7,C7′-substitution containing centrochiral stereochemistry. However, pigments **1**-**3** are distinct from other perylenequinones due to the unsymmetrical seven-membered carbocyclic ring, which except for **2**, contains two stereogenic centers, one of which is quaternary. As a result, these natural products lack the characteristic C_2 symmetry which is present in most of the other members of this class.[2]

The parent members of this family are the enantiomers hypocrellin A (**1**) and hypocrellin (*ent*-**1**). Interestingly, **1** and *ent*-**1** arise from different fungal species (Figure 1). The first member to be isolated and characterized was hypocrellin

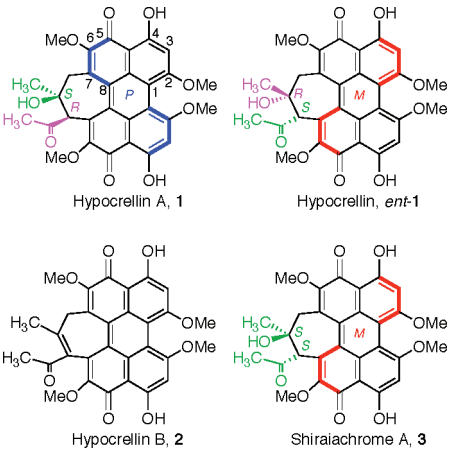

FIGURE 1. Hypocrellin natural product family.

(*ent*-**1**) from *Hypocrella bambusae*.[3] In subsequent seminal publications from Wu[4] and Kishi,[5] **1**, **2**, and **3**, but not *ent*-**1**, were isolated from *Shiraia bambusicola*. There has been

(1) For reviews, see: (a) Weiss, U.; Merlini, L.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1–71. (b) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1–249.

(2) For example, the perylenequinones (+)-phleichrome, (+)-calphostin D, and cercosporin detailed in the previous papers in this series (DOIs: 10.1021/jo9012832, 10.1021/jo901384h, and 10.1021/jo9013854) are C_2-symmetric due to the same identity of the C7,C7′-positions.

(3) Chen, W. S.; Chen, Y. T.; Wang, X. Y.; Friedrichs, E.; Puff, H.; Breitmaier, E. *Liebigs Ann. Chem.* **1981**, 1880–1885.

(4) Wu, H; Lao, X. F.; Wang, Q. W.; Lu, R. R. *J. Nat. Prod.* **1989**, *52*, 948–951. (hypocrellin A is called shiraiachrome B here).

(5) Kishi, T.; Tahara, S.; Tsuda, M.; Tanaka, C.; Takahashi, S. *Planta Med.* **1991**, *57*, 376–379. (shiraiachrome A is called hypocrellin B here).

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considerable variation and confusion in the naming of these perylenequinones. For example, hypocrellin A (**1**) has been referred to as shiraiachrome B.[4] Furthermore, hypocrellin (*ent*-**1**) has been referred to as hypocrellin A in several reported studies on the biological and photodynamic properties of this family.[6] Although attempts have been made to systematize the nomenclature, irregularities still exist and for **1** and *ent*-**1** the best way to determine the enantiomer utilized is by its fungal species, *Shiraia bambusicola* and *Hypocrella bambusae*, respectively. Here, we employ the names and structural assignments suggested by Mondelli et al.[7]

Although misunderstandings did originate from the varied nomenclature of **1**-**3**, further confusion is present due to the unusual architectural aspects of the hypocrellins, namely keto−enol tautomerism and rapid atropisomerization of the helical perylene core (Figure 2). In particular, hypocrellin A exists as an equilibrium mixture of four forms (Figure 2) and no single structure is uniformly utilized in the literature. The keto−enol tautomeric process (**1** to **1·taut**) is fast with respect to the NMR time scale resulting in a single set of sharp peaks at ambient temperature.[8] The important factors governing the position of the tautomerization equilibria are substituent effects, strength of the intramolecular phenol-quinone hydrogen bonds, and distortion of the planarity of the naphthalene core. For the hypocrellins, including **1**, *ent*-**1** and **3**, the two tautomers represented by **1** and **1·taut** in Figure 2 are present in almost equal amounts.[7,8]

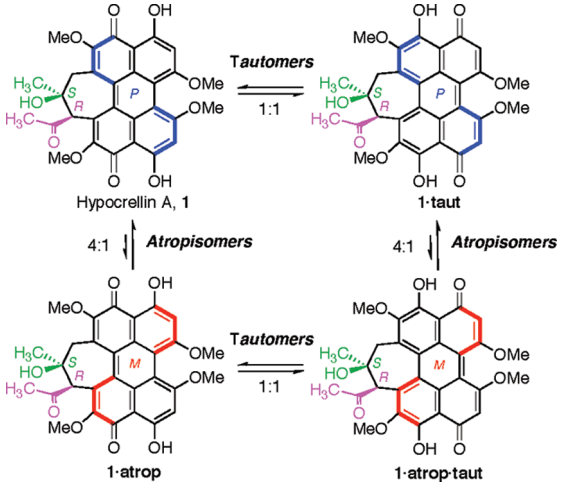


FIGURE 2. Tautomeric and atropisomeric forms of hypocrellin A.

The barrier to atropisomerization of the helical configuration varies substantially for the perylenequinones. Whereas most are atropisomerically stable at ambient temperature, the additional seven-membered ring in the hypocrellins lowers the barrier, making them particularly challenging synthetic targets. Spectroscopic studies showed that both **1** and *ent*-**1** atropisomerize rapidly at ambient temperature presenting two sets of sharp peaks in the NMR spectrum for the resultant diastereomers.[8] Thus, hypocrellin A (Figure 2) exists as an equilibrium mixture of atropisomers (**1**, **1·atrop**) favoring the more stable atrop-diastereomer **1**. In support of this assertion, **1**, *ent*-**1**, and **3** exhibit CD spectra characteristic of helical stereochemistry. Notably, the CD spectra of *ent*-**1** and **3** are quite similar indicating that the main contributor to the CD is the helical stereochemistry vs the centrochiral stereochemistry. On the other hand, hypocrellin B (**2**), which would form by elimination of water from hypocrellin A, exhibits no peaks in the CD spectrum.[5] The presence of a double bond in the seven-membered ring of hypocrellin B could lead to a planar structure accounting for this phenomenon. However, we have performed calculations which indicate that the ground state of **2** contains a similar stereogenic helix as the related congeners **1**, *ent*-**1**, and **3**. Apparently, for **2**, the CD signals from the atropisomeric enantiomers (Figure 3) cancel each other.

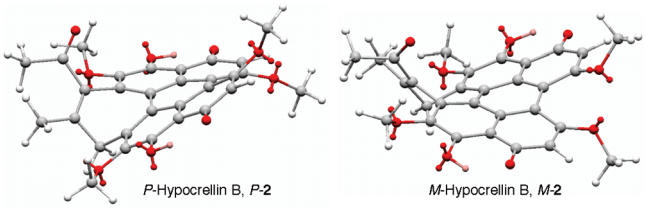


FIGURE 3. Atropisomers of hypocrellin B.

Prior to our efforts, the syntheses of the calphostins and phleichrome had been reported.[9] However, the more architecturally complex perylenequinones, including **1**, *ent*-**1**, and **3**, had not succumbed to total synthesis. Given the exciting biological activity, one of the parent members of the hypocrellins, hypocrellin A (**1**), was selected as a synthetic target. Here, we disclose a full description of the development of this synthesis.[10]

Given the facile atropisomerization of **1**, it is unclear which stereochemical elements are established first in the biosynthesis, the helical axis or the 7-membered ring stereocenters. Establishing the centrochiral stereochemistry first would require a regio-, diastereo-, and enantioselective intermolecular aldol reaction between two ketones to provide **4a** (path *a*, Scheme 1), a conceptually simple but practically difficult transformation. Furthermore, the centrochiral elements of **4a** would then need to direct the diastereoselection in the coupling to form the binaphthalene/perylenequinone. Alternately, the helical stereochemistry could be formed first (path *b*, Scheme 1), which would in turn be used to the direct the centrochiral stereochemistry via a diastereoselective aldol reaction. The observation that certain enzymes can catalyze enantioselective coupling of 2-naphthol provides considerable confidence that the enantioselective coupling of an intermediate similar to **5** is accessible biosynthetically. Furthermore, intermediate **4b** is a plausible biosynthetic intermediate in the genesis of all the mold perylenequinone

(6) SciFinder indexes hypocrellin and hypocrellin A as the identical compound.

(7) For the correct structural assignment of shiraiachrome A, see: (a) Mazzini, S.; Merlini, L.; Mondelli, R.; Scagloni, L. *J. Chem. Soc., Perkin Trans. 2* **2001**, 409–416. Which corrects: (b) Smirnov, A.; Fulton, D. B.; Andreotti, A.; Petrich, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 7979–7988.

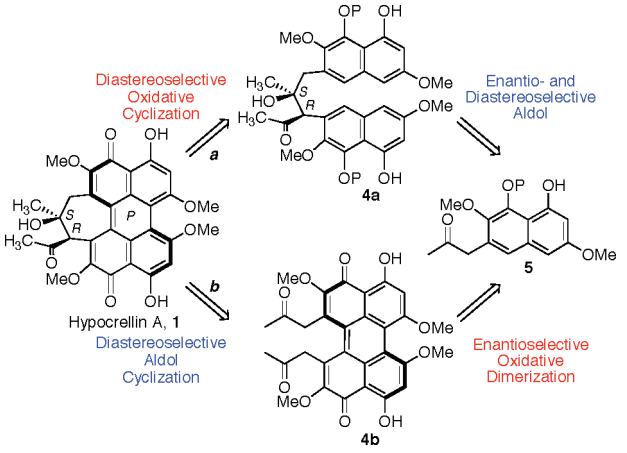
(8) Arnone, A.; Merlini, L.; Mondelli, R.; Nasini, G.; Ragg, E.; Scaglioni, L.; Weiss, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1447–1454.

(9) (a) Broka, C. A. *Tetrahedron Lett.* **1991**, *32*, 859–862. (b) Hauser, F. M.; Sengupta, D.; Corlett, S. A. *J. Org. Chem.* **1994**, *59*, 1967–1969. (c) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1994**, *116*, 8795–8796. (d) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889–10904. (e) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A. *J. Am. Chem. Soc.* **2000**, *122*, 3224–3225. (f) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297–1309.

(10) For an initial communication of this work, see: O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6877–6880.

natural products with ketone reduction giving rise to the calphostins/phleichromes/cercosporin, aldol cyclization giving rise to the hypocrellins/shiraiachromes, and oxidative enol coupling giving rise to the elsinochromes as outlined in the first paper of this series. For these reasons, we believe that path *b* reflects the biosynthesis and were inspired to use it as the basis of our synthetic approach.

SCHEME 1. Retrosynthetic Analysis of Hypocrellin A

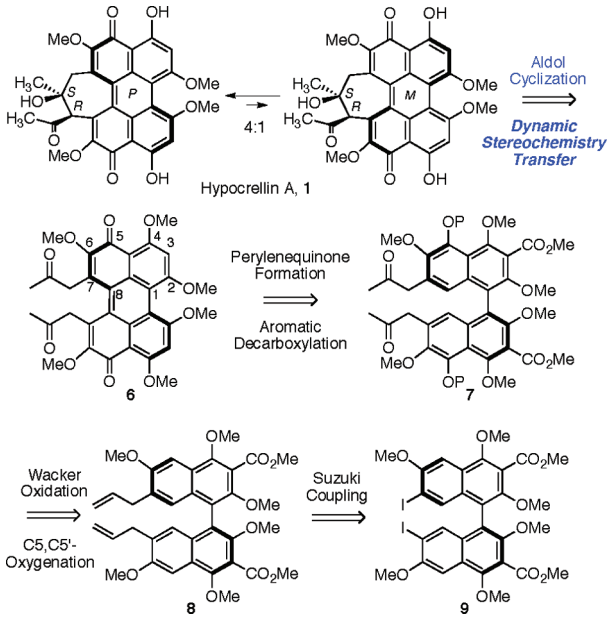


In implementing such a biomimetic approach, the viability of the aldol cyclization needed to be reconciled with the rapid atropisomeric interconversion of the product **1**. In the retrosynthetic analysis of this biomimetic approach (Scheme 2), the helical stereochemistry of **6** is proposed to control the C7, C7′-stereochemistry *prior* to any atropisomerization of the product **1**. Such a *dynamic stereochemistry transfer* (*DST*) *reaction* fulfilling the following criteria is rare:[11] 1) a directing stereocenter that is not involved in any bond-forming or bond-breaking processes, 2) diastereocontrol from this directing stereocenter in the formation of a new stereocenter, and 3) loss of the integrity of the original directing stereocenter subsequent to the transformation. To implement this strategy, the helical axis as found in enantiomerically pure perylenequinone **6** would be synthesized *first*. This helical chiral perylenenquinone **6** would, in turn, be generated with complete stereocontrol from axial chiral **7**. The intermediate **7** would be generated from **8** via a Wacker oxidation and C5,C5′-oxidation. A Suzuki coupling of the enantiopure intermediate **9** would provide the C7,C7′-allyl substituents seen in **8**.

This strategy permits a flexible approach to all of the perylenequinone natural products. Either the helical stereochemistry of **6** (Scheme 2), arising from axial diketone **16** (Scheme 3) can be used to control formation of C7,C7′-stereochemistry or it can be introduced from an external source in conjunction with bisiodide **14** (Scheme 3). In contrast, other reported perylenequinone syntheses involved the diastereoselective coupling of chiral napthalenes.[9] To adapt such syntheses to the hypocrellins would involve an oxidation of the C7,C7′-substitutents (i.e., **13** to **16**, Scheme 3) thereby negating the centrochiral stereochemistry which had required much effort to generate. In two of the

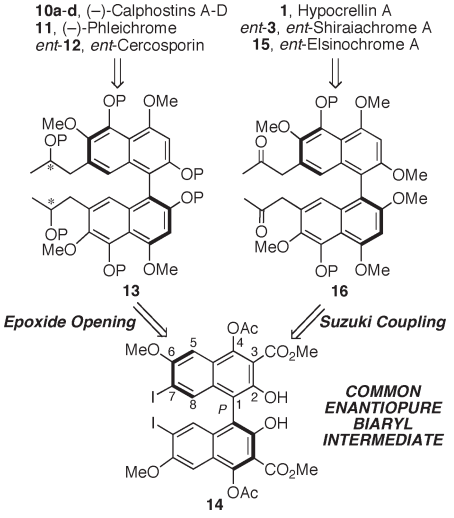
(11) Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226–1229.

SCHEME 2. Retrosynthesis of Hypocrellin A via Path *b*



preceding papers of this series, we described the total syntheses of the perylenequinones (+)-calphostin D (*ent*-**10d**), (+)-phleichrome (*ent*-**11**) and cercosporin (**12**) utilizing an epoxide opening to introduce the C7,C7′-stereochemistry. Each of the syntheses evolved from a common late-stage intermediate, enantiopure **14** (Scheme 3). In the synthesis of **1**, this intermediate is again employed, but in this case, as the *P*-antipode. Notably, access to both enantiomers of the common intermediate **14** permits the synthesis of all the perylenequinones, including the unnatural epimers of the natural products. In addition, bisiodide **14** is readily coupled to different fragments providing considerable versatility (Scheme 3).

SCHEME 3. Enantiopure Common Intermediate to the Perylenequinone Natural Products

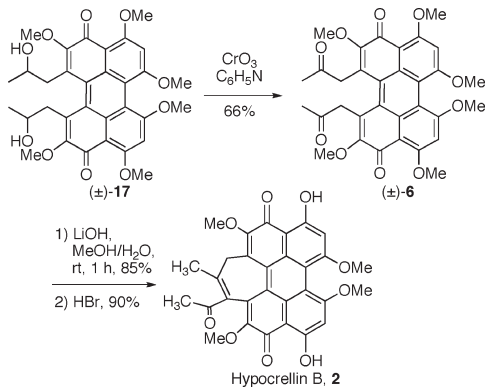


Results and Discussion

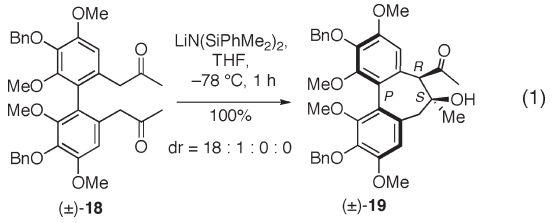
Model System for a 1,8-Diketone Aldol Reaction. The investigation of hypocrellin A (**1**) commenced with an

assessment of the key transannular 1,8-diketone aldol reaction. Lown had reported the use of a 1,8-diketone aldol condensation in a synthesis of hypocrellin B (**2**, Scheme 4), which lacks optical activity (see Figure 3 and accompanying discussion above).[12] Notably, a stereoselective synthesis of hypocrellin A relying on the route in Scheme 4 would require oxidation of the initially formed alcohol stereocenters (i.e., those in **17**) resulting in loss of this stereochemical information. With the racemic diketone **6**, the aldol addition *and* the elimination reaction proceeded very readily raising concerns that suppressing elimination to doubly conjugated alkene **2** would be difficult. Furthermore, this system does not address whether the necessary stereochemical array can be established in such a process.

SCHEME 4. Hypocrellin B Synthesis



To shed light on these concerns, racemic model system **18** was selected to evaluate the regio- and diastereoselectivity of the process, including the effect of the biaryl axis, as well as the propensity for elimination. In principle, four diastereomers are possible in the aldol reaction, provided that no elimination products form. As described in the preceding paper in this series,[13] silazide bases were found to provide the *syn* aldol diastereomer (**19**) corresponding to that required for the synthesis of hypocrellin A (**1**) in high yields by means of a (*Z*) enolate (eq 1).



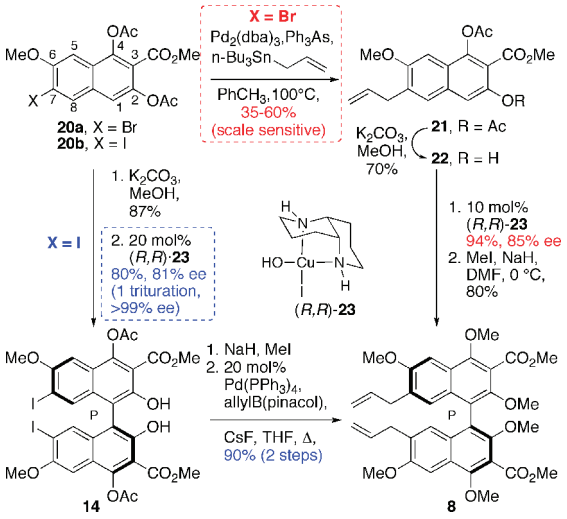
(1)

The high yield observed in the 1,8-diketone aldol reaction of **18** was remarkable in light of past precedent.[13–15]

Presumably, the conformational restriction afforded by the biaryl bond and the four sp^2 centers in the forming ring permits an efficient aldol reaction between ketone centers in a 1,8-relationship. These results were highly encouraging with respect to the desired aldol reaction of hypocrellin A (Scheme 2). However, it remained unclear how well these results would translate to the natural product substrate **6** (Scheme 2), which possesses a 20° dihedral angle between the upper and lower rings of the perylenequinone vs the 70° dihedral angle in model **18**. Presumably, the closer proximity between the reacting centers caused by the smaller dihedral angle would facilitate the aldol reaction. However, the lower dihedral angle might also facilitate elimination to hypocrellin B (**2**, Scheme 4) since there would be less strain in the seven-membered ring. A further complication is the perylenequinone itself, which is highly electron-withdrawing and would be expected to acidify the enolic positions in **6** (Scheme 2) similar to a 1,3-dicarbonyl. This effect would facilitate enolate formation but also render the enolate less reactive.

Helical Chiral Perylenequinone Formation. With the knowledge that the required stereochemical array is accessible in the intramolecular 1,8-diketone aldol reaction of a model system, investigations began to generate of helical axis of **6** (Scheme 2). To this end, we examined the applicable routes to axial chiral **8** (Scheme 5).

SCHEME 5. Synthesis of C7,C7′-Allyl Intermediate 8



As previously seen in this series, a cationic cyclization readily provided the desired halo-naphthalenes **20a** and **20b** (Scheme 5), though iodonaphthalene **20b** was somewhat more difficult to purify than bromo analog **20a**. This particular substitution pattern was selected in order to achieve high selectivity in the subsequent asymmetric oxidative coupling.[16] While some refunctionalization of the naphthalene portion will be required to complete hypocrellin A, the

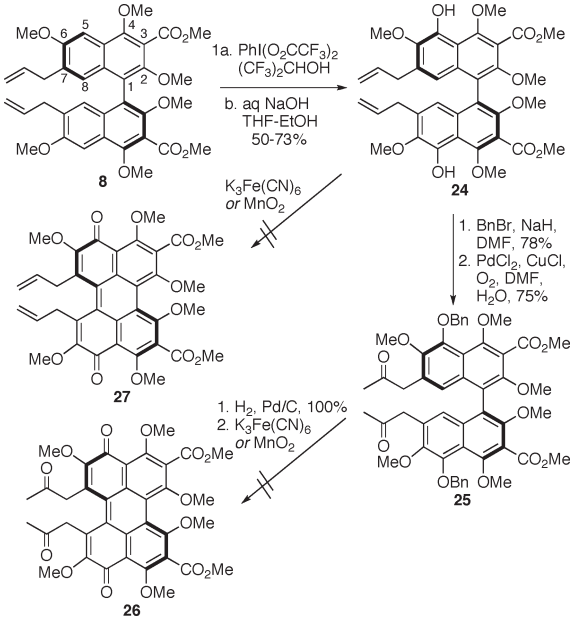
(12) Lown, J. W. *Can. J. Chem.* **1997**, *75*, 99–119.
(13) O'Brien, E. M.; Li, J.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, DOI: 10.1021/jo9018914.
(14) For selected examples, see: (a) Miyahara, Y. *J. Org. Chem.* **2006**, *71*, 6516–6521. (b) Davies, S.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802–3804. (c) Piers, E.; Skupinska, K. A.; Wallace, D. J. *Synlett* **1999**, *12*, 1867–1870. (d) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420. (e) Shizuri, Y.; Ohtsuka, J.; Kosemura, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 5547–5550.
(15) Baik, T. G.; Luis, A. L.; Wang, L. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113.
(16) (a) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137–1140. (b) Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513–4522. (c) Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2168–2170. (d) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856–6857. (e) Li, X.; Hewgley, J. B.; Mulrooney, C.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500–5511. (f) Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 12232–12233.

scalability of these intermediates and the functionality needed to access novel analogs outweighed these concerns.

As outlined in Scheme 5 the C7,C7′-allyl substitution could be installed either before or after the enantioselective coupling. Addition of the allyl group prior to oxidative dimerization was best accomplished with a Stille reaction. With trifuryl phosphine as the palladium ligand, a significant amount of butyl transfer (20%) was observed. As the allyl and butyl products have the same R_f value, purification was problematic. Fortunately, no butyl transfer was observed with triphenyl arsine as the ligand,[17] ameliorating this problem. While the dimerization of the allyl substrate was superior, the Stille coupling and removal of the tin byproducts to provide the requisite precursor proved problematic on preparative scale (> 10.0 mmol, ~35% yield). Furthermore, generation of enantiopure **8** (≥99% ee) from **22** required multiple triturations (5−10) contributing to a poor mass recovery. Unfortunately, the Stille reaction was the only coupling procedure compatible with the acetate protecting groups in **20a**.

For these reasons, a different sequence to **8** was investigated culminating in allylation after biaryl coupling (Scheme 5). This route utilized **14**, an antipode of the intermediate utilized in our investigation of (+)-phleichrome (see Scheme 3) as detailed in the second paper in this series. This route permitted allylation after removal of the labile acetate protecting groups of **14**. In the absence of acetates, the less toxic, more efficient Suzuki reaction could now be employed, supplying enantiopure **8** in high yield on a preparative scale (90%, 2 steps).[18]

SCHEME 6. Attempted Formation of Perylenequinones 26 and 27



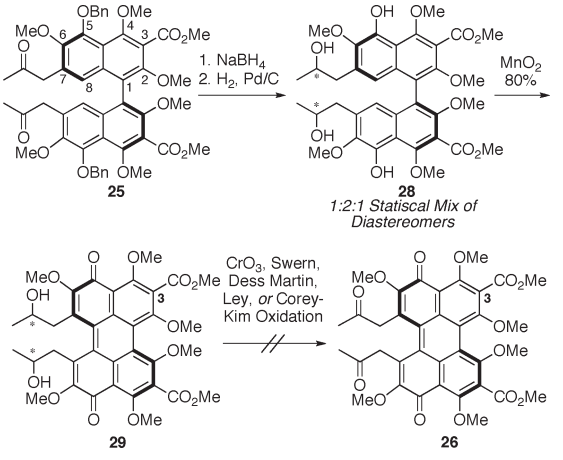
The reported calphostin syntheses demonstrated that formation of the perylenequinone core was possible with a variety of functionalized C7,C7′-substituents.[9] Additionally, we previously reported that C7,C7′-propyls are also compatible with these conditions.[16d] However, we could find no reported examples with a C7,C7′-keto-derivative. Thus, the transformation was examined with **25** (Scheme 6), which varies from the required substrate **16** (Scheme 3) by addition of the C3,C3′-esters.

We commenced these efforts with the C5,C5′-oxygenation of **8** (Scheme 6) via a nucleophilic substitution reaction induced by a hypervalent iodine reagent as has been discussed in the earlier papers of this series. Accordingly, treatment of bisallyl **8** with bis(trifluoroacetoxy)iodobenzene (PIFA) in $(CF_3)_2CHOH$ afforded the desired compound in yields ranging from 50% to 73%. Protection of the bisphenol with a benzyl group proceeded smoothly with benzyl bromide and NaH in 78% yield. Finally, the Wacker oxidation afforded the desired diketone **25** without the formation of any regioisomeric aldehyde.

Following C5,C5′-debenzylation of **25** to generate the required bisphenol, perylenequinone formation was examined (Scheme 6). Unfortunately, treatment with MnO_2[9c,d] or alternatively, $K_3Fe(CN)_6$[9a] did not provide the desired **26** and resulted in only decomposed starting material. The same result was observed with diallyl biaryl **24**. Since the use of MnO_2 with the corresponding C7,C7′-propyl[16d] or C7,C7′-2-hydroxypropyl[9c,d] derivatives proceeded smoothly to perylenequinone, it appears that substitution of the benzylic centers in **24** and **25** can dramatically change the outcome of this reaction. Apparently, the addition of acidifying groups to this position (ketones or alkenes) allows alternate reaction pathways.

Since the secondary alcohols at the C7,C7′-positions are stable to the MnO_2 oxidation protocol[9c,d] and oxidation of bisalcohol **17** to diketone **6** has been reported (Scheme 4),[12] a route using reduction to "protect" the ketone was examined (Scheme 7). Distinct from prior efforts involving the diastereoselective dimerizations of chiral naphthalenes,[9] this route would not rely on the C7,C7′-alcohol stereochemistry to form the axial stereochemistry. As such, the diketone could be reduced with no regard to selectivity. As was seen in similar reductions examined in the second paper in this series, treatment of diketone **29** with $NaBH_4$ and subsequent hydrogenation provided **28** as a statistical mixture of three diastereomers (Scheme 7). Oxidation of **28** with MnO_2 to the perylenequinone supplied **29** as the sole product. To our dismay, applying Lown's conditions (Scheme 4)[12] to **29** provided none of the oxidized product **26** (Scheme 7) with

SCHEME 7. Attempted Formation of Diketone Intermediate 26



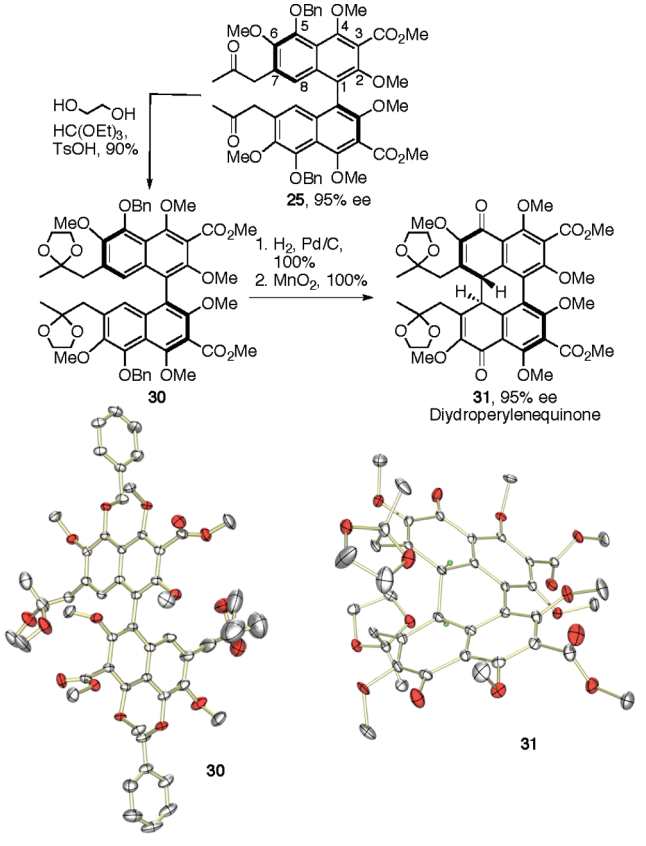
(17) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9587.

(18) For a simple synthetic approach to allylated aromatics via the Suzuki−Miyaura cross-coupling reaction, see: Kotha, S.; Behera, M.; Shah, V. *Synlett* **2005**, 1877–1880.

only rapid decomposition being observed even when a rapid quench was employed. Presumably, the electron-withdrawing C3,C3′-esters acidify the benzylic protons of **29** resulting in a more rapid decomposition pathway. All attempts to oxidize the secondary alcohols with mild oxidation protocols, such as Dess-Martin periodinane or the Swern oxidation, resulted in unreacted starting material. It was reasoned that the congested steric environment of the hydroxyl groups accounted these results. As seen with CrO_3, stronger oxidants resulted in decomposition.

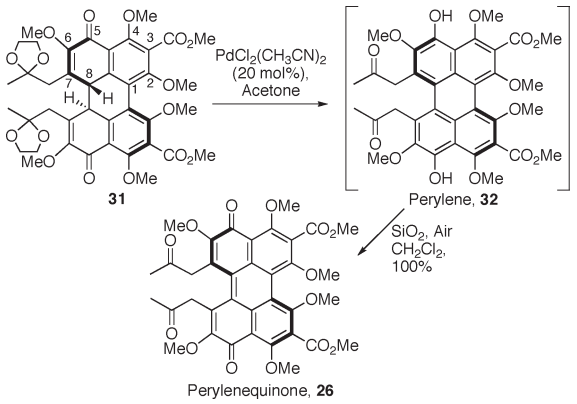
The results of Scheme 6 and Scheme 7 led us to use a ketal protection group that would be stable to the oxidative cyclization and would be readily removed following perylenequinone formation. To this end, bisketone **25** was treated with acidic ethylene glycol to yield bisketal **30** (Scheme 8). Hydrogenolysis of **30**, followed by reaction with MnO_2 resulted in clean conversion to the unexpected dihydroperylenequinone **31**, which was confirmed with a crystal structure. Remarkably, the enantiopurity was conserved during this process as judged by chiral HPLC (95% ee). Apparently, the increased steric congestion caused by ketal substitution, compared to the propyl side chains, distorts the molecule such that formation of the more planar perylenequinone (20° vs 70° biaryl dihedral) is disfavored.[19]

SCHEME 8. Formation of an Unexpected Hydroperylenequinone (31) (ORTEPs Shown with 30% Probability Thermal Ellipsoids)



Initial attempts to hydrolyze the ketals of **31** with standard acidic conditions were unsuccessful. Fortunately, a palladium dichloride acetonitrile complex was found to remove the ketal[20] as well as tautomerize the dihydroperylenequinone to the perylene **32** (Scheme 9). The desired diketone perylenequinone **26** was obtained after oxidation of perylene **32** with air in the presence of silica. With a viable route to synthesizing the key diketone perylenequinone structure in hand, efforts turned to removal of the C3,C3′-methyl esters.

SCHEME 9. Synthesis of Model Diketone Perylenequinone 26



First Total Synthesis of Hypocrellin A. Returning to the synthesis of hypocrellin A, we investigated the removal of the C3,C3′-methyl esters via decarboxylation of the respective C3,C3′-diacid. As outlined in the previous papers in this series, the ineffectiveness of standard decarboxylation protocols[21] led us to develop a palladium-catalyzed decarboxylation protocol,[22] which worked well with biaryl systems. The standard three-step protocol that we had used previously to form the required calphostin and cercosporin diacid intermediates, provided the requisite diacid **33** here in high yield (entry 1, Table 1). However, in an attempt to form **33** directly from **30** we evaluated other procedures. Due to steric hindrance, an efficient saponification of **30** was only observed at temperatures greater than 130 °C, at which atropisomerization is also observed (entries 2−4). Anionic displacement was investigated next, but iodide nucleophiles proved ineffective (entries 5−6, Table 1). Application of the Krapcho conditions used to decarboxylate esters via the corresponding carboxylate (excess NaCN in DMSO and H_2O at 100−110 °C) afforded the diacid **33** quantitatively after neutralization (entry 7).[23] Not unexpectedly, these conditions did not cause decarboxylation since the resultant aromatic anion is not stabilized.

The palladium-catalyzed decarboxylation[20] that was applied in the previous two papers of this series was optimized originally with **33** because it proved to be the most recalcitrant of all the substrates. By virtue of the ketal protecting groups, **33** possesses the largest C7,C7′- substituents which cause steric gearing leading to considerable congestion of the

(19) See ref 9a for another report of a dihydroperylenequinone.

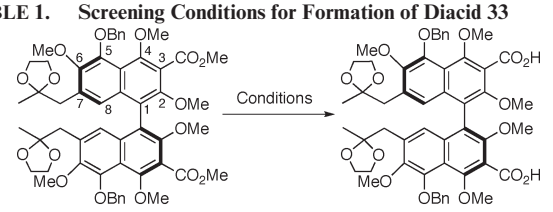
(20) For the use of $PdCl_2(CH_3CN)_2$ as a catalyst for deacetalization, see: Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705–708.

(21) Protic acid protocol: Horper, W.; Marner, F.-J. *Phytochemistry* **1996**, *41*, 451. Copper/quinoline protocol: Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189.

(22) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441–2444.

(23) For synthetic applications of NaCN in dealkoxycarbonylations, see: (a) Krapcho, A. P. *Synthesis* **1982**, 805–822. (b) Krapcho, A. P. *Synthesis* **1982**, 893–914.

TABLE 1. Screening Conditions for Formation of Diacid 33

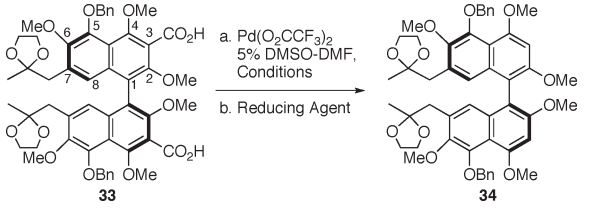


entry	conditions	yield (%)
1	(1) DIBALH, $PhCH_3$; (2) *o*-iodoxybenzoic acid; (3) $NaClO_2$, NaH_2PO_4, 2-butene, THF, H_2O, *t*-BuOH	90
2	LiOH, 10%H_2O−dioxane, 100 °C	0[a]
3	$Ba(OH)_2$ 10% H_2O−DMSO, 100 °C	< 50
4	KOH, ethylene glycol, 130 °C	100[b]
5	NaI, 10% H_2O−DMSO, 100 °C	0[a]
6	LiI, DMF, 100 °C	0[a]
7	NaCN,10% H_2O−DMSO, 105 °C	100

[a]Starting material recovered. [b]Atropisomerization observed.

C3,C3′-positions and thereby slowing the decarboxylative palladation[22] necessary for decarboxylation. Utilizing the previously successful conditions for the corresponding C7, C7′-propyl derivative seen in the first paper in this series provided decarboxylated **34** in a disappointing 30% yield (Table 2, entry 1). A screen of reductants (entries 2−5) provided only a modest improvement. Performing the decarboxylation under basic conditions with Ag_2CO_3 proved beneficial providing **34** in 60% yield (entry 6).

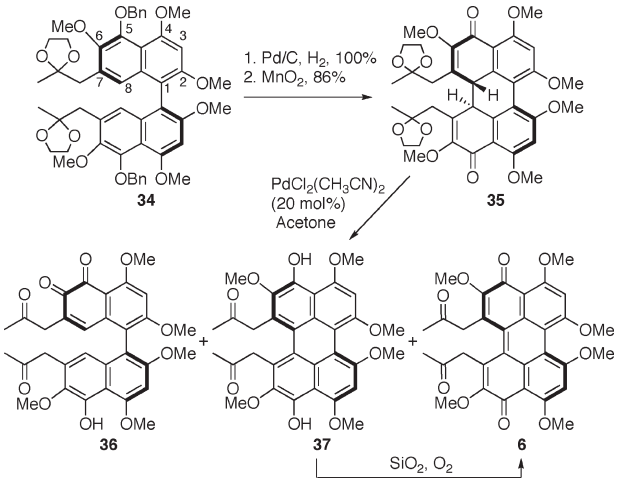
TABLE 2. Optimization of the Palladium-Catalyzed Decarboxylation of 33



entry	$Pd(O_2CCF_3)_2$ (mol %)	(a) conditions	(b) reductant	yield (%)
1	300	90 °C, 1.5 h	H_2, THF	30
2	220	70 °C, 1.5 h	$HSi(Oi\text{-}Pr)_3$	37
3	220	70 °C, 1 h	KF, H_2O PHMS	25
4	220	70 °C, 1.5 h	$NaBH_4$	44
5	220	70 °C, 3 h	$NaBH_4$	28
6	220	Ag_2CO_3, 70 °C, 1 h	$NaBH_4$	60

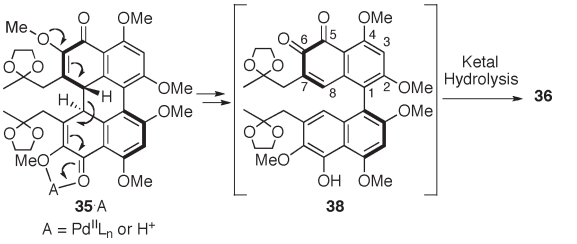
With a viable route to **34** established, investigations centered on forming diketone perylenequinone **6** to complete the synthesis. Thus, **34** was subjected to hydrogenolysis conditions (Scheme 10) and oxidized to dihydroperylenequinone **35** (86% yield over two steps). Akin to the C3,C3′-ester model system **31** (Scheme 8), the fully oxidized perylenequinone was not observed under these conditions (Scheme 10). Ketal deprotection of **35** with catalytic $PdCl_2(CH_3CN)_2$ in acetone provided a mixture of perylene **37** and desired perylenequinone **6**; however, the yield was inconsistent due to a significant amount of *ortho*-quinone (**36**) formation.

SCHEME 10. Attempted Synthesis of Perylenequinone 6



The generation of unsymmetrical *ortho*-quinone **36** (Scheme 10) was perplexing considering no such product was observed for the C3,C3′-ester model system (**26**, Scheme 9). The proposed mechanism for the formation of **36** is shown in Scheme 11. Coordination of either palladium or trace HCl (formed from $PdCl_2(CH_3CN)_2$ by exposure to trace water) sets the stage for ring cleavage which, presumably, is driven by the release of ring strain. The absence of the ester provides a more electron rich ring which facilitates this cleavage by providing a superior coordinating agent for the acid and by better stabilizing the positive charge build up in the upper ring. The subsequent cascade would result in cleavage of the hydroperylenequinone bond. Ketal removal before or after *ortho*-quinone formation would supply the observed product **36**.

SCHEME 11. Possible Mechanism for Formation of Unsymmetrical *o*-Quinone 36

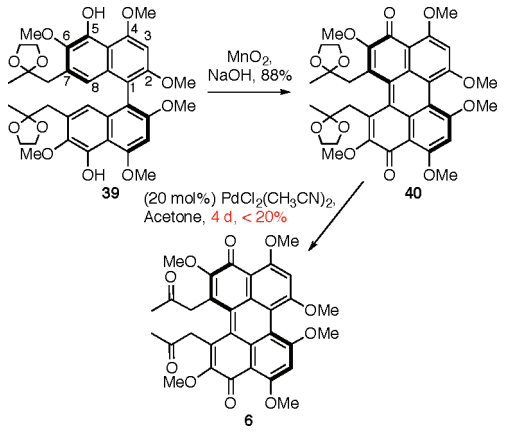


A mechanism such as the one shown in Scheme 11 would not be possible for the fully oxidized perylenequinone; hence, we reexamined the oxidation of **39** (Scheme 12). Addition of base during the oxidation step was proposed to facilitate tautomerization of dihydroperylenequinone **35** to perylene **37** which should, in turn, readily oxidize to perylenequinone **6** (Scheme 10). Pleasingly, reaction of **39** with MnO_2 and NaOH in a mixture of EtOH and THF afforded the desired perylenequinone **40** (Scheme 12). Unfortunately, ketal removal from **40** was again problematic. In contrast to **31** (Scheme 9), the $PdCl_2(CH_3CN)_2$ reaction was sluggish with **40** providing less than 20% product after 4 d. Stoichiometric palladium did not to facilitate the reaction and conventional acidic ketal hydrolysis resulted in decomposition.

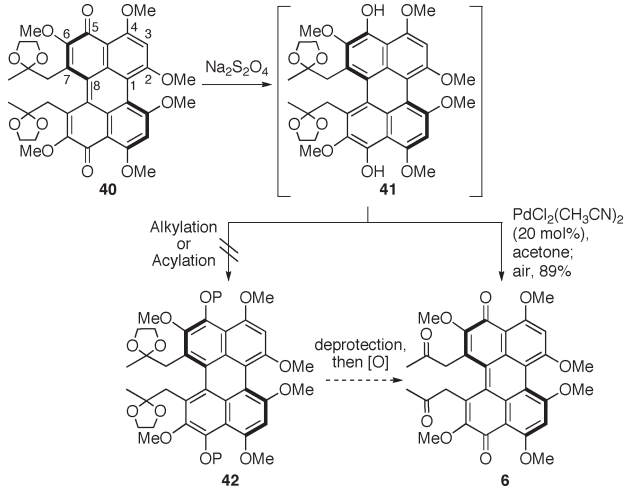
From the above results, it appears that neither the dihydroperylenequinone (**35**) or the perylenequinone (**40**) can

withstand conditions need for deketalization. Reasoning that the acidic species (Pd^{II} or H^+) were activating the carbonyls of these compounds and promoting undesired reactions, the use of a reduced perylene such as **41** (Scheme 13) that should bypass such a manifold was considered. Pleasingly, perylene, **41** was readily formed by reduction of **40** with $Na_2S_2O_4$ in benzene. Frustratingly, all attempts to alkylate or acylate perylene **41** to provide **42** resulted in reversion to the fully oxidized perylenequinone **40**, even though **41** was sufficiently stable to be observed quantitatively by ^1H NMR. To our delight, perylene **41** itself was sufficient to alleviate the undesirable properties of perylenequinone **40** and treatment of in situ generated perylene **41** with $PdCl_2(CH_3CN)_2$ provided a facile hydrolysis of the ketal protecting group. Exposure to air during isolation resulted in reoxidation to the desired perylenequinone **6** in very good yield.

SCHEME 12. Attempted Formation of Diketone Aldol Substrate 6



SCHEME 13. Formation of Diketone Aldol Substrate 6



With a practical route to the diketone **6** in hand, the stage was set to investigate the key intramolecular diketone aldol cyclization. Although we proposed such an aldol reaction for the biosynthesis of the hypocrellins, precedent for this type of 1,8-diketone aldol reaction, with the exception of our model system **18**, is uncommon. To predict if the stereochemical outcome would be the same as in the model system[13] we again turned to molecular modeling (Scheme 14). With **6**, a *Z*-enolate geometry would give rise to the *syn* aldol product corresponding to hypocrellin A via closed chairlike transition states, while the *E*-enolate would produce the *anti* product corresponding to shiraiachrome A.[24] An analysis of the relevant transition states revealed that the helical stereochemistry of **6** would expose one diastereoface of the ketone, resulting in the required (*S*) tertiary alcohol stereochemistry of both hypocrellin A (**1**) and shiraiachrome A (**3**). MM2 calculations found that of the two possible *Z*-enolate transition states, transition state A, corresponding to the configuration of the target hypocrellin A, was lower in energy (Scheme 14). Interestingly, if the reaction were to progress via transition state B, the cyclization of **6** with *P*-helical stereochemistry would lead to the enantiomer hypocrellin (*ent*-**1**), which would equilibrate after cyclization to predominantly the opposite *M*-atropisomer. Significantly, this approach requires that the helical stereochemistry be sufficiently stable during the aldol reaction, even though it atropisomerizes freely thereafter. To undertake this proposal, the previously evaluated silazide bases

SCHEME 14. *Z*-Enolate Transition States and Correlation to Natural Products

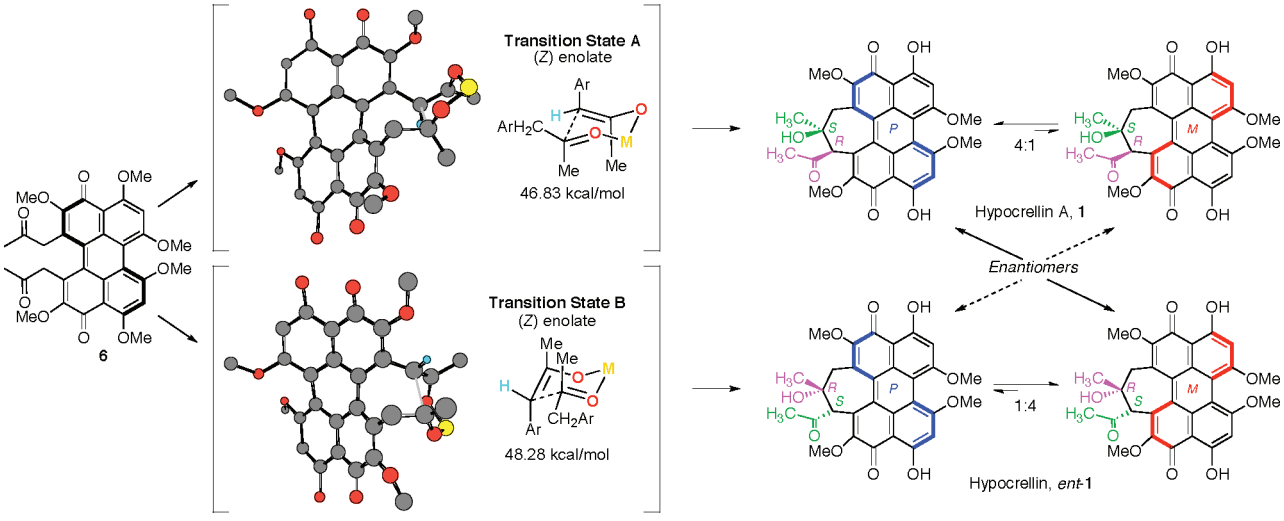
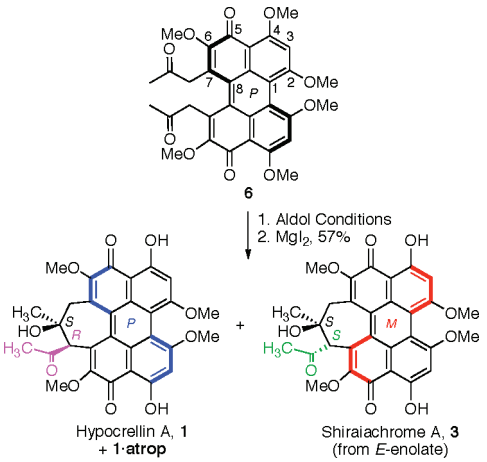


TABLE 3. Transannular 1,8-Diketone Aldol Cyclization in the Synthesis of Hypocrellin A, 1



entry	base	T (°C)	dr (**1**:**3**)	ee (%)
1	LiHMDS	−15		55
2	LiHMDS	−78		70
3	LiHMDS	−105	4:1	79
4	$LiN(SiPhMe_2)_2$	−78	10:1	70
5	$LiN(SiPhMe_2)_2$	−105	10:1	(92 after trituration) 74% yield

were chosen to effect deprotonation as their use with model system **18** (eq 1) gave predominantly *Z*-enolates.

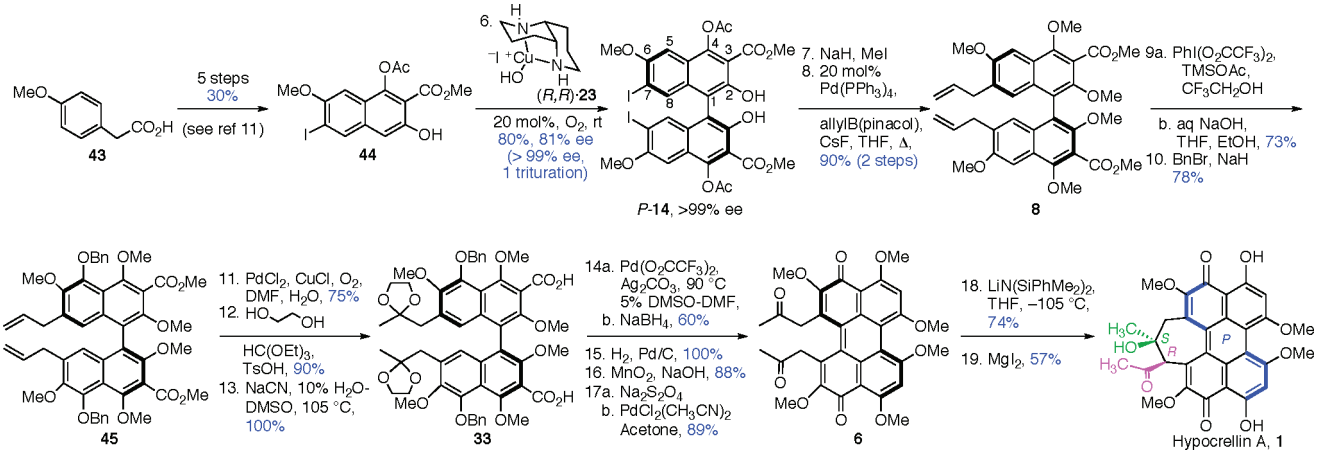
In an examination of the crucial aldol reaction, the *diastereomeric ratios* reflect the formation of the *syn* vs *anti* aldol product, which presumably reflects the ratio of the *Z*-enolate to the *E*-enolate, while the *enantioselectivity* is a measure of the predilection for transition state A over B as seen in Scheme 14. Since the diastereomeric mixture from the cyclization was difficult to analyze, a selective removal of the C4,C4′-methyl ethers with MgI_2 was undertaken to yield hypocrellin A (**1**) and shiraiachrome A (**3**) (both isolated from *Shiraia bambusicola*) as a distinguishable mixture. To examine the effect of temperature on the aldol transformation (entry 1−3, Table 3), LiHMDS was chosen to achieve deprotonation. As expected, the cyclization was much more facile than the model system, accompanied with lower diastereoselectivity of the desired *syn* aldol product (*dr* 4:1, entry 3). However, it was surprising that even at very low temperatures (−105 °C) the less favored transition state B of the *Z*-enolate was accessible, leading to lower enantioselectivities than expected (79% ee, entry 3). Use of the bulkier $LiN(SiPhMe_2)_2$ enhanced the diastereoselective formation of **1** (*dr* 10:1) though it did not effect the enantioselectivity (entries 4−5). Fortunately, a single trituration afforded **1** with 92% ee (entry 5). Spectroscopic data from our synthetic **1**:**1**·**atrop** was identical to the data from hypocrellin (*ent*-**1**) from natural sources, with the exception of the absolute stereochemistry, as determined by direct comparison. As expected, the minor diastereomer, **3**, resulting from the *anti*-aldol product was confirmed by ^1H NMR spectroscopy to be shiraiachrome A. Significantly, in the case of shiraiachrome A (**3**), the atropisomeric equilibrium after the aldol reaction favors the opposite (*M*) helical configuration even though both hypocrellin A (**1**) and **3** originally arose from the same (*P*) configuration of **6** (Scheme 14).

Conclusions

As seen in Scheme 15 we have completed the first total synthesis of the hypocrellin A in 19 steps (1.6% overall yield; average 82% per step). Key points of our enantioselective synthesis include: **1**) an enantioselective oxidative coupling to provide the *P*-antipode of the common enantiopure intermediate; **2**) a mild aromatic decarboxylation; and **3**) a biomimetic 1,8-diketone aldol reaction to establish the 7-membered ring of hypocrellin A. In the aldol reaction, the two newly formed centrochiral stereocenters in the 7-membered ring are dictated by the stable perylenequinone helical stereochemistry[16d] and the enolate geometry. After the aldol reaction, however, the helical stereochemistry is labile as observed in the natural product (4:1 mixture of atropisomers). As such, we have shown that a *dynamic stereochemical transfer* is viable for the construction of hypocrellin. Significantly, our approach to hypocrellin A also provides an avenue to shiraiachrome A by formation of the *anti* aldol product.

As seen in the first paper of this series, we established that helical chiral perylenequinones can be configurationally stable even if no other stereocenters are present. This key

SCHEME 15. Total Synthesis of Hypocrellin A (1)



discovery enabled the biomimetic synthesis of hypocrellin A (**1**) via a dynamic stereochemistry transfer, as described in this paper, via intermediate **6**. The additional discovery of an efficient double epoxide alkylation with the complex biaryl biscuprate derived from **14**, enabled the synthesis of the diastereomeric (+)-calphostin D and (+)-phleichrome as well as the atropisomerically labile cercosporin as detailed in the second and third papers of this series, respectively. Thus, all of the stereoisomeric mold perylenequinone natural products, as well as a number of analogs,[25] can be generated in stereosiomerically pure form from common intermediates *M*-**14** and *P*-**14** which are readily generated via a catalytic, enantioselective naphthol coupling.

Experimental Section

(*P*)-Dimethyl 4,4′-diacetoxy-2,2′-dihydroxy-7,7′-diiodo-6,6′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (14). Bisacetate (*P*)-**14** was synthesized as a white foam (1.3 g, 80%) following our previously reported procedure for the enantiomer.[26] Spectral data agreed with those reported previously for the enantiomer with the exception of the optical rotation: $[\alpha]_D^{20}$ −26.5 (c 0.5, CH_2Cl_2, >99% ee).

(*P*)-Dimethyl 7,7′-diallyl-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (8). To a solution of **14** (725 mg, 0.87 mmol) in DMF (25 mL) was added NaH (60% in oil, 1 g, 26.2 mmol), and MeI (1.6 mL, 26.2 mmol). After stirring for 4 h at room temperature under argon, the mixture was quenched with 1 N HCl. The aqueous phase was extracted with EtOAc and the combined organics were washed with 1 N HCl (3 × 20 mL) and brine (2 × 20 mL). The organics were dried (Na_2SO_4), and after the solvent was evaporated, the residue was chromatographed (25% EtOAc/hexanes) to yield the bismethyl ether as a white solid (660 mg, 94%): $[\alpha]_D^{20}$+57.4 (c 0.5, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2945, 1733, 1579, 1463, 1436 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.36 (s, 6H), 4.00 (s, 6H), 4.02 (s, 6H), 4.14 (s, 6H), 7.42 (s, 2H), 7.63 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.7, 56.5, 61.9, 62.6, 91.9, 100.7, 118.3, 120.9, 125.9, 131.4, 136.9, 152.0, 153.3, 155.2, 166.9; HRMS (ESI) calcd for $C_{30}H_{28}I_2O_{10}Na$ (MNa^+) 824.9669, found 824.9638.

To a solution of the bismethyl ether (1.41 g, 1.75 mmol) in anhydrous THF (20 mL) was added $Pd(PPh_3)_4$ (303 mg, 0.26 mmol) and CsF (2.13 g, 0.014 mol). The mixture was stirred at 25 °C for 0.5 h. Allylpinacol borane (1.4 mL, 7.1 mmol) was added neat and the reaction mixture heated to reflux. After removing from the oil bath, the reaction was quenched with H_2O. The mixture was diluted with EtOAc, and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), and the solvent evaporated. Purification was accomplished via chromatography (20−30% EtOAc/hexanes) to yield **8** (1.1 g, 96%) as a resin: $[\alpha]_D^{20}$+102.2 (c 0.85, CH_2Cl_2, >99% ee); IR (thin film) 2945, 2845, 1733, 1590, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.22−3.33 (m, 4H), 3.33 (s, 6H), 3.96 (s, 6H), 3.98 (s, 6H), 4.13 (s, 6H), 4.78−4.85 (m, 4H), 5.74−5.82 (m, 2H), 6.95 (s, 2H), 7.43 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9, 52.7, 55.7, 62.1, 62.9, 100.3, 115.7, 120.1, 120.4, 125.1, 127.2, 130.6, 132.9, 136.5, 151.7, 153.5, 156.3, 167.6; HRMS (ESI) calcd for $C_{36}H_{38}O_{10}Na$ (MNa^+) 653.2363, found 653.2377.

(*P*)-Dimethyl 7,7′-diallyl-5,5′-dihydroxy-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (24). Biaryl **8** (1.96 g, 3.10 mmol) and [bis(trifluoroacetoxy)-iodo]benzene (3.3 g, 7.67 mmol) were dissolved in 2,2,2-trifluoroethanol (50 mL) and stirred at 25 °C under argon. After 2.5 h, the purple reaction mixture was quenched with NaOAc (1.40 g). After stirring for 5 min, the resulting red solution was diluted with EtOAc, and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), and the solvent evaporated. The red residue was diluted with H_2O/THF/EtOH (1:3:3, 35 mL) and 10% aq. NaOH (10 mL) was added. After stirring for 5 h at room temperature under argon, the mixture was quenched with 1 N HCl. The aqueous phase was extracted with EtOAc, the organics were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The concentrate was purified by column chromatography (30% EtOAc/hexanes) to afford **24** as a red resin (1.5 g, 73%): $[\alpha]_D^{20}$+53.3 (c 0.75, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 3365, 2948, 2360, 1734, 1595, 1568 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.24−3.36 (m, 4H), 3.31 (s, 6H), 3.89 (s, 6H), 3.98 (s, 6H), 4.15 (s, 6H), 4.78 (d, J = 1.6, 17.1 Hz, 2H), 4.84 (dd, J = 1.3, 10.1 Hz, 2H), 5.71−5.78 (m, 2H), 6.44 (s, 2H), 9.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9, 53.1, 60.7, 62.2, 64.5, 114.3, 115.8, 117.7, 119.3, 120.6, 132.7, 136.9, 137.1, 142.2, 146.0, 152.5, 154.3, 166.8; HRMS (ESI) calcd for $C_{36}H_{38}O_{12}Na$ (MNa^+) 685.2261, found 685.2242.

(*P*)-Dimethyl 5,5′-bis(benzyloxy)-2,2′,4,4′,6,6′-hexamethoxy-7,7′-bis(2-oxopropyl)-1,1′-binaphthyl-3,3′-dicarboxylate (25). A solution of **24** (215 mg, 0.32 mmol) in DMF (8 mL) was cooled to 0 °C. NaH (60% in oil, 31 mg, 0.77 mmol) was added and stirred for 15 min. Benzyl bromide (0.91 mL, 0.77 mmol) and Bu_4NI (19 mg, 0.051 mmol) were added at 25 °C. After completion as judged by TLC, the mixture was acidified with 1 M HCl, diluted with EtOAc, washed with H_2O (6X) and brine, and dried (Na_2SO_4). The concentrate was purified by column chromatography (20% EtOAc/hexanes) to afford the bisbenzyl ether as a yellow resin (212 mg, 78%): $[\alpha]_D^{20}$+40.0 (c 0.45, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2942, 1736, 1587, 1562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.22−3.34 (m, 4H), 2.97 (s, 6H), 3.90 (s, 6H), 3.93 (s, 6H), 3.95 (s, 6H), 4.74−4.77 (m, 2H), 4.82−4.84 (m, 2H), 5.02 (d, J = 9.8 Hz, 2H), 5.05 (d, J = 9.8 Hz, 2H), 5.69−5.77 (m, 2H), 6.75 (s, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.2 Hz, 4H), 7.59 (d, J = 7.1, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 35.1, 52.1, 61.9, 64.4, 64.9, 76.9, 115.7, 120.4, 120.5, 123.1, 123.2, 128.1, 128.6, 129.1, 133.6, 136.2, 136.9, 138.1, 146.8, 150.2, 152.5, 154.3, 167.5; HRMS (ESI) calcd for $C_{50}H_{50}O_{12}Na$ (MNa^+) 865.3199, found 865.3182.

$PdCl_2$ (76 mg, 0.43 mmol) and CuCl (212 mg, 2.14 mmol) were stirred in a DMF/H_2O mixture (7:1, 1 mL) at room temperature for 30 min. The bisbenzyl ether (87 mg, 0.10 mmol) was added and the mixture stirred under oxygen for 18 h. The mixture was acidified with 1 M HCl, diluted with EtOAc, washed with H_2O (6X), brine, and dried (Na_2SO_4). The concentrate was purified by column chromatography (40% EtOAc/hexanes) to afford **25** as a yellow resin (68 mg, 75%): $[\alpha]_D^{20}$+2.0 (c 0.5, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2944, 1732, 1588, 1563 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 6H), 3.41 (s, 6H), 3.61−3.67 (m, 4H), 3.96 (s, 6H), 3.97 (s, 6H), 4.01 (s, 6H), 5.08 (s, 4H), 6.82 (s, 2H), 7.37 (t, J = 7.1 Hz, 2H), 7.43 (t, J = 7.6 Hz, 4H), 7.62 (d, J = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 46.6, 52.8, 61.3, 62.0, 64.6, 76.9, 120.6, 121.1, 123.6, 124.2, 128.2, 128.6, 129.1, 131.7, 133.4, 137.8, 146.6, 150.0, 152.6, 154.3, 167.4, 205.7; HRMS (ESI) calcd for $C_{50}H_{50}O_{14}Na$ (MNa^+) 897.3098, found 897.3088.

(*P*)-Dimethyl 5,5′-bis(benzyloxy)-2,2′,4,4′,6,6′-hexamethoxy-7,7′-bis((2-methyl-1,3-dioxolan-2-yl)methyl)-1,1′-binaphthyl-3,3′-dicarboxylate (30). Ketone **25** (145 mg, 0.219 mmol), triethyl orthoformate (972 mg, 6.57 mmol), ethylene glycol (394 mg, 6.57 mmol), and *p*-toluenesulfonic acid (4.0 mg,

(24) Still, W. C. *MacroModel*, V4.0, V5.0, V6.0, V6.5; Columbia University.

(25) Morgan, B. J.; Dey, S.; Johnson, S. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 9413–9425.

(26) See theexperimental description in the second paper of this series (DOI: 10.1021/jo901384h).

0.0219 mmol) were refluxed in CH_2Cl_2 (5 mL) under Ar for 24 h. The mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%) and brine, and dried (Na_2SO_4). The concentrate was purified by column chromatography (30% EtOAc/hexanes) to afford **30** as a white solid (148 mg, 90%): $[\alpha]_D^{20}$+10.1 (c 0.82, CH_2Cl_2, >99% ee (*S*)); mp 158−162 °C; IR (thin film) 2942, 2880, 1735, 1588, 1560 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.85 (d, J = 13.8, 2H), 2.98 (d, J = 13.8 Hz, 2H), 3.39−3.50 (m, 4H), 3.45 (s, 6H), 3.67−3.71 (m, 4H) 3.95 (s, 6H), 3.99 (s, 6H), 2.40 (s, 6H), 5.06 (d, J = 9.8 Hz, 2H), 5.10 (d, J = 9.8 Hz, 2H), 6.94 (s, 2H), 7.36 (t, J = 7.3 Hz, 2H), 7.44 (t, J = 7.6 Hz, 4H), 7.65 (d, J = 8.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.4, 40.0, 54.5, 63.3, 63.7, 66.2, 66.5, 66.6, 78.8, 111.6, 122.3, 122.9, 125.1, 127.4, 130.0, 130.5, 130.9, 135.0, 135.2, 140.1, 148.4, 152.9, 154.0, 169.2; HRMS (ESI) calcd for $C_{54}H_{58}O_{16}Na$ (MNa^+) 985.3622, found 985.3646. The structure was further confirmed by crystallography, the data for the X-ray structure is supplied in the Supporting Information.

(*P*)-5,5′-bis(benzyloxy)-2,2′,4,4′,6,6′-hexamethoxy-7,7′-bis-((2-methyl-1,3-dioxolan-2-yl)methyl)-1,1′-binaphthyl-3,3′-dicarboxylic acid (33). To a solution of **30** (25 mg, 0.026 mmol) in 5% H_2O−DMSO (1 mL) was added NaCN (10 mg, 0.21 mmol). The mixture was heated in an oil bath (100−110 °C) oil bath for 24 h. The mixture was diluted with EtOAc, and the organic phase washed with 1N HCl and brine, dried (Na_2SO_4), and the solvent was evaporated to yield diacid **33** as a white resin (24 mg, 100%): $[\alpha]_D^{20}$+34.0 (c 0.85, CH_2Cl_2, >99% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 6H), 2.85 (d, J = 13.8 Hz, 2H); 3.03 (d, J = 13.8 Hz, 2H), 3.42 (m, 2H), 3.52 (m, 2H), 3.52 (s, 6H), 3.71 (m, 4H), 4.02 (s, 6H), 4.05 (s, 6H), 5.08 (d, J = 9.8 Hz, 2H), 5.12 (d, J = 9.7 Hz, 2H), 6.99 (s, 2H), 7.37 (m, 2H), 7.44 (t, J = 7.2 Hz, 4H), 7.65 (d, J = 7.8 Hz, 4H); HRMS (ESI) calcd for $C_{52}H_{54}O_{16}Na$ (MNa^+) 957.3310, found 957.3277.

(*P*)-2,2′-(5,5′-Bis(benzyloxy)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-7,7′-diyl)bis-(methylene)bis(2-methyl-1,3-dioxolane) (34). To a solution of the diacid **33** (100 mg, 0.11 mmol) in 5% DMSO−DMF (4 mL) was added $Pd(OC(O)CF_3)_2$ (89 mg, 0.27 mmol) and Ag_2CO_3 (177 mg, 0.64 mmol). After heating in a 75 °C oil bath for 1 h, the mixture was removed from the oil bath and quenched with $NaBH_4$ (28 mg, 0.428 mmol). The resultant black mixture was diluted with EtOAc, and the organic phase washed with 1N HCl and brine, dried (Na_2SO_4), and the solvent was evaporated. Purification was accomplished via chromatography (50% EtOAc/hexanes) to yield **34** (50 mg, 60%) as an oil: $[\alpha]_D^{20}$−27.7 (c 1.0, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2937, 1590, 1575, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.79 (d, J = 13.7 Hz, 2H); 2.94 (d, J = 13.7 Hz, 2H), 3.32 (dd, J = 5.1, 11.5 Hz, 2H), 3.43 (dd, J = 7.2, 13.1 Hz, 2H), 3.61−3.69 (m, 4H), 3.75 (s, 6H), 3.95 (s, 6H), 4.01 (s, 6H), 5.08 (d, J = 10.1 Hz, 2H), 5.13 (d, J = 10.1 Hz, 2H), 6.79 (s, 2H), 6.83 (s, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.46 (t, J = 7.2 Hz, 4H), 7.64 (d, J = 7.0 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 25.1, 38.5, 56.1, 57.4, 61.4, 64.7, 64.9, 76.3, 96.1, 110.1, 112.6, 116.9, 124.6, 127.9, 128.5, 128.6, 131.3, 133.4, 138.8, 147.1, 149.3, 154.8, 157.1; HRMS (ESI) calcd for $C_{50}H_{54}O_{12}Na$ (MNa^+) 869.3513, found 869.3505.

(*P*)-2,2′,4,4′,6,6′-hexamethoxy-7,7′-bis((2-methyl-1,3-dioxolan-2-yl)methyl)-1,1′-binaphthyl-5,5′-diol (39). Biaryl **34** (19 mg, 0.021 mmol) was dissolved in MeOH/THF mixture (1:1 v:v, 4 mL) with 10% Pd/C (22 mg, 0.021 mmol). A hydrogen balloon was added. After stirring for 1 h, the mixture was filtered through silica (2.5% MeOH/CH_2Cl_2) to afford **39** as a colorless oil (14 mg, 100%): $[\alpha]_D^{20}$−35.8 (c 0.60, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 3401, 2841,1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.76 (d, J = 13.6 Hz, 2H), 2.94 (d, J = 13.6 Hz, 2H), 3.39 (dd, J = 5.3, 11.9 Hz, 2H), 3.48 (dd, J = 7.2, 13.2 Hz, 2H), 3.63−3.74 (m, 4H), 3.71 (s, 6H), 3.91 (s, 6H), 4.16 (s, 6H), 6.53 (s, 2H), 6.72 (s, 2H), 9.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 38.3, 56.4, 57.5, 60.4, 64.7, 64.9, 94.8, 110.2, 111.6, 113.4, 118.9, 132.1, 132.5, 141.5, 145.9, 154.3, 156.8; HRMS (ESI) calcd for $C_{36}H_{42}O_{12}Na$ (MNa^+) 689.2574, found 689.2571; CSP HPLC (Chiralpak AD, 1.0 mL/min, 80:20 hexanes:*i*-PrOH): $t_R(R)$ = 15.7 min, $t_R(S)$ = 17.6 min.

(*P*)-2,4,6,7,9,11-hexamethoxy-1,12-bis((2-methyl-1,3-dioxolan-2-yl)methyl)perylene-3,10-dione (40). Substrate **39** (40 mg, 0.060 mmol) was dissolved in THF (4 mL) under argon. MnO_2 (157 mg, 1.80 mmol) was added and the mixture stirred for 1 h. NaOH (116 mg, 2.89 mmol) in EtOH/H_2O (1:1 v:v, 5 mL) was added and the reaction stirred for an additional 1 h. The mixture was filtered through Celite (EtOAc). The organic phase was washed with 1 N HCl, dried (Na_2SO_4), and the solvent evaporated. Purification was accomplished via chromatography (10% MeOH/CH_2Cl_2) to yield **40** as a red oil (35 mg, 88%): $[\alpha]_D^{20}$−780.0 (c 0.05, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2941, 1617, 1575, 1544 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 6H), 2.86 (d, J = 13.3 Hz, 2H); 3.31−3.33 (m, 4H), 3.46−3.53 (m, 4H), 3.55 (d, J = 13.4 Hz, 2H), 4.08 (s, 6H), 4.11 (s, 6H), 4.16 (s, 6H), 6.78 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 39.1, 56.3, 56.7, 60.5, 64.5, 65.1, 94.9, 109.1, 109.9, 110.8, 128.9, 131.7, 132.9, 155.1, 163.1, 163.8, 178.9; HRMS (ESI) calcd for $C_{36}H_{39}O_{12}$ (MH^+) 663.2441, found 663.2421.

(*P*)-2,4,6,7,9,11-hexamethoxy-1,12-bis(2-oxopropyl)perylene-3,10-dione (6). Substrate **40** (26 mg, 0.039 mmol) was dissolved in benzene (2 mL) and a saturated solution of $Na_2S_2O_4$ was added (2 mL). After stirring vigorously for 30 min, the orange organic layer was separated and concentrated using standard rotary evaporation without special measures to exclude air. The perylene (**41**) was dissolved in acetone (2 mL) under argon. $PdCl_2(CH_3CN)_2$ (2.0 mg, 0.0080 mmol) was added and the mixture stirred for 12 h under argon. The reaction mixture was filtered through silica (5% MeOH/CH_2Cl_2) to afford **6** as a red oil (20 mg, 89%): $[\alpha]_D^{20}$ + 908.0 (c 0.025, CH_2Cl_2, >99% ee (*S*)); IR (thin film) 2926, 2853, 1722, 1617, 1579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.07 (s, 6H), 3.52 (d, J = 16.7 Hz, 2H), 3.99 (s, 6H), 4.09 (s, 6H), 4.11 (d, J = 14.5 Hz, 2H), 4.18 (s, 6H), 6.77 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.2, 45.7, 56.4, 56.8, 60.1, 95.2, 111.8, 125.6, 129.1, 131.3, 131.5, 154.4, 163.5, 164.3, 178.1, 204.1; HRMS (ESI) calcd for $C_{32}H_{31}O_{10}$ (MH^+) 575.1917, found 575.1924.

Hypocrellin A (1). A solution of **6** (5.0 mg, 0.0087 mmol) in anhydrous THF (3 mL) was cooled to −105 °C under argon. $LiN(SiMe_2Ph)_2$ (57 μL, 0.0218 mmol, 0.38 M in THF) was added. After the solution stirred for 15 min, it was quenched with saturated NH_4Cl (aq), making sure the solution temperature was still at −105 °C when quenched. The frozen mixture was diluted with EtOAc, and the organics were separated upon melting, washed with brine, and dried (Na_2SO_4). The concentrate was purified by column chromatography (2.5% MeOH/CH_2Cl_2) to afford the cyclized product as a mixture of two diastereomers red oil (3.7 mg, 74%): $[\alpha]_D^{20}$−825 (c 0.025, CH_2Cl_2, >99% ee); IR (thin film) 3416, 2922, 2853, 1702, 1613, 1579, 1540, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.95 (s, 3H), 2.54 (d, J = 12.2 Hz, 1H), 3.28 (s, 1H), 3.38 (d, J = 12.0 Hz, 1H), 4.06 (s, 3H), 4.08 (s, 3H), 4.14 (s, 3H), 4.15 (s, 3H), 4.20 (s, 3H), 4.21 (s, 3H), 4.63 (s, 1H), 6.84 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2, 29.9, 41.6, 56.4, 56.5, 56.8, 56.9, 60.6, 61.6, 61.7, 76.8, 95.3, 95.4, 109.0, 109.5, 111.5, 111.6, 129.1, 130.1, 130.2, 130.3, 132.7, 133.1, 153.1, 154.1, 163.5, 163.6, 164.5, 164.6, 178.3, 178.9, 207.7; HRMS (ESI) calcd for $C_{32}H_{31}O_{10}$ (MH^+) 575.1917, found 575.1939.

A 0.076 M solution of MgI_2 was prepared by stirring Mg turnings (10.2 mg, 0.42 mmol) and I_2 (55 mg, 0.21 mmol) in anhydrous Et_2O (2.75 mL) for 3 h, during which the solution

turns from red/brown to clear. To a solution of perylenequinone (3.5 mg, 0.0061 mmol) in dry THF (1 mL) under an argon atmosphere was added a solution of MgI_2 in Et_2O (0.16 mL, 0.076 M, 0.0122 mmol). The dark green solution was stirred for 15 min, diluted with EtOAc, washed with saturated NH_4Cl (aq) and brine, dried (Na_2SO_4), and the solvent evaporated to yield a 10:1 mixture of diastereomers (hypocrellin A and shiraichrome A, respectively), which was determined by crude ^1H NMR. The diastereomers were separated by preparatory thin layer chromatography. The plate was treated with a 3% oxalic acid solution in EtOH and dried before elution (1% EtOH/$CHCl_3$). The top fraction was concentrated and triturated (hexanes: *n*-pentane:*i*-PrOH) to yield hypocrellin A (**1**) as a red resin (57%, 92% ee): See CD spectra in spectral section of Supporting Information; IR (thin film) 3505, 2941, 1702, 1610, 1540, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.89 (s, 3H), 4.07 (s, 6H), 4.12 (s, 6H), 6.56 (s, 1H), 6.57 (s, 1H), 15.91 (s, 1H), 15.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 30.1, 41.9, 56.5, 56.6, 60.8, 61.7, 62.1, 78.8, 102.0, 102.1, 106.7, 106.9, 117.7, 118.2, 125.0, 125.0, 127.6, 128.5, 133.2, 134.0, 150.6, 150.9, 167.5, 167.5, 170.9, 171.8, 179.9, 180.4, 207.4; MALDI-TOF: *m*/*z* 546.46 (calculated for $C_{30}H_{26}O_{10}$ $(M)^+$ 546.15).

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Supporting Information Available: Additional experimental descriptions and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.