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Perylenequinone Natural Products: Evolution of the Total Synthesis of Cercosporin

Barbara J. Morgan, Carol A. Mulrooney, 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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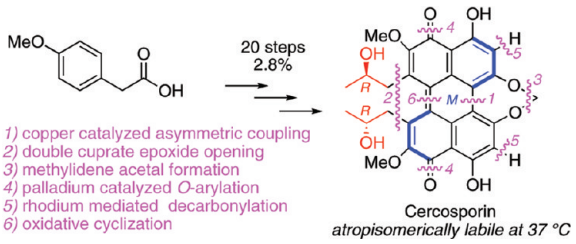

The evolution of the first total synthesis of perylenequinone cercosporin is described. The key features developed during these efforts include a biscuprate epoxide alkylation, installation of the methylidene acetal, palladium-catalyzed *O*-arylation, and C3,C3′-decarbonylation. Due to the rapid atropisomerization of the helical axis of cercosporin (at 37 °C), the sequencing of these transformations was critical. To this end, the developed protocol enabled the formation of a key advanced intermediate on preparative scale absent any atropisomerization. Furthermore, the *O*-arylation proved to be general, and the strategy was used in an improved synthesis of a helical chiral perylenequinone structure.

Introduction

The perylenequinone cercosporin (**1**, Figure 1) was first isolated by Kuyama and Tamura from the pathogenic soybean fungus *Cercospora kikuchii*.[1] Following this discovery, it was found to be prevalent in nature and was isolated from multiple members of the genus *Cercospora*. The destructive *Cercospora* species is responsible for causing disease worldwide on a variety of crop plants, including corn, sugar, beet, bananas, tobacco, coffee, and soybean.[2] Prior to an understanding of the pathogen toxicity, it was observed that intense light was required for symptom development of infected plants.[3] Though **1** was isolated in 1957 and conjectured to be photodynamic, it was not until the 1970s that the structure was elucidated and it was confirmed to be the phototoxin produced by the respective fungi.[4] Largely due to the pathogenic nature of the *Cercospora* species, cercosporin has become one of the most widely studied perylenequinones.[5]

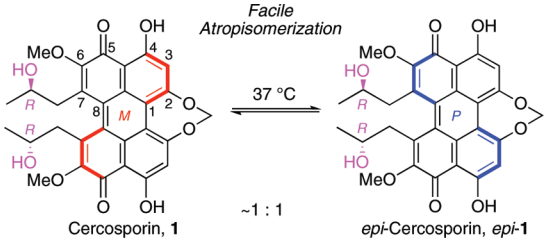

FIGURE 1. Cercosporin atropisomerization.

As represented by cercosporin (**1**) in Figure 1, the perylenequinone natural products are characterized by a chiral helical oxidized core and stereogenic C7,C7′-substitution.[6] Interestingly, the helicity of cercosporin, which is *M*, differs

(1) Kuyama, S.; Tamura, T. *J. Am. Chem. Soc.* **1957**, *79*, 5725–5726.
(2) For a review, see: Daub, M. E.; Ehrenshaft, M. *Annu. Rev. Phytopath.* **2000**, *38*, 461–490.
(3) Calpouzos, L.; Stalknecht, G. F. *Phytopathology* **1967**, *57*, 799–800.
(4) (a) Lousberg, R. J. J.; Weiss, U.; Salemink, C. A.; Arnone, A.; Merlini, L.; Nasini, G. *Chem. Commun.* **1971**, 1463–1464. (b) Yamazaki, S.; Ogawa, T. *Agric. Biol. Chem.* **1972**, *36*, 1707–1718. (c) Yamazaki, S.; Okube, A.; Akiyama, Y.; Fuwa, K. *Agric. Biol. Chem.* **1975**, *39*, 287–288.
(5) Daub, M. E.; Herrero, S.; Chung, K.-R. *FEMS Microbiol. Lett.* **2005**, *252*, 197–206. and references cited therein.
(6) The entire mold perylenequinone family can be seen in Figure 2 of the first paper in this series: Mulrooney, C. A.; Morgan, B. J.; Li, X.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75* (DOI 10.1021/jo9013832).

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from that of the calphostins (**2**) and phleichrome (**3**), which are *P* (Figure 2). Furthermore, cercosporin is distinguished from the structurally similar perylenequinones, calphostins, and phleichrome by a seven-membered ring spanning the C2, C2′-positions. This seven-membered ring lowers the atropisomerization barrier, allowing **1** to readily atropisomerize at 37 °C (Figure 1).[7] The formation of a ~1:1 mixture of **1**/*epi*-**1** under thermodynamic conditions[7,8] contraindicates a simple thermodynamic equilibration following biosynthesis of the dioxepane ring as the source of the *M*-stereochemistry; rather, it appears that the formation of the helical stereochemistry itself occurs differently in the *Cercospora* species vs the *Cladosporium* fungi. This facile atropisomerization of cercosporin presents significant synthetic challenges; while atropisomerically stable **2** and **3** had been synthesized (Figure 2),[9] the labile cercosporin remained a challenging synthetic target.[8]

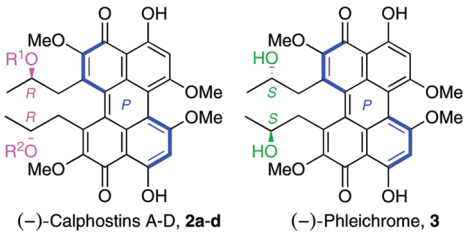


FIGURE 2. Perylenequinones, (−)-calphostins (**2**), and (−)-phleichrome (**3**).

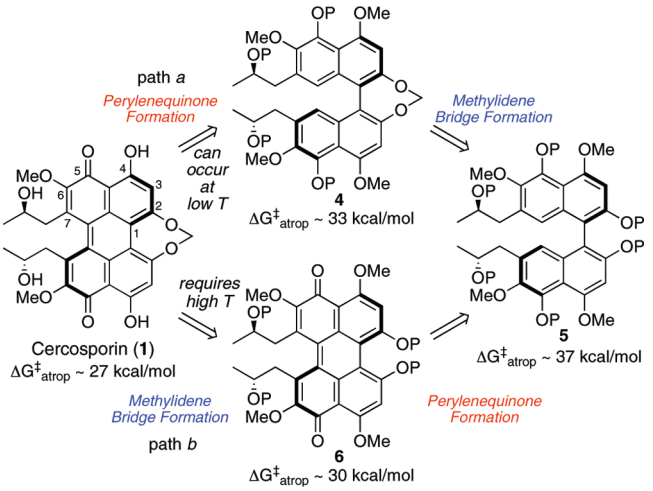
The common theme of the previously reported syntheses of **2** and **3** centered on a diastereoselective coupling of a chiral naphthalene, affording the biaryl with modest diastereoselectivity.[9] Distinct from these approaches, our synthetic strategy involved the use of an enantioselective coupling to set the biaryl axis followed by installation of the C7,C7′-stereochemistry. In the preceding papers of this series (DOIs 10.1021/jo9013832 and 10.1021/jo901384h), we detailed these aspects in the context of total syntheses of (+)-calphostin D (*ent*-**2d**) and (+)-phleichrome (*ent*-**3**). In this paper, we provide a complete account of our strategy to accomplish the total synthesis of atropisomerically sensitive cercosporin (**1**), with a focus on the sequence of transformations needed to form a key advanced intermediate (**4**) containing the methylidene acetal.

Results and Discussion

Retrosynthetic Analysis. In our strategy toward cercosporin (**1**), the central concern was the installation of the methylidene acetal, which lowers the atropisomerization barrier relative to the calphostins (**2a**−**d**) and phleichrome (**3**). In a previous publication, we explored the combined effects of the perylenequinone, the methylidene acetal, and the C7,C7′-2-hydroxypropyl groups on atropisomerization.[8]

In examining these measurements, it was clear that the combination of the perylenequinone and the methylidene acetal must be reserved to occur as late as possible. Furthermore, it became clear that the perylenequinone was a greater contributor to the atropisomerization barrier than the methylidene acetal (Scheme 1). In addition, the methods for forming the methylidene acetal require higher temperatures than those for forming the perylenequinone. For these reasons, we determined that path *a* in Scheme 1 was far more viable than path *b*.

SCHEME 1. Atropisomerization in the Retrosynthetic Routes to Cercosporin

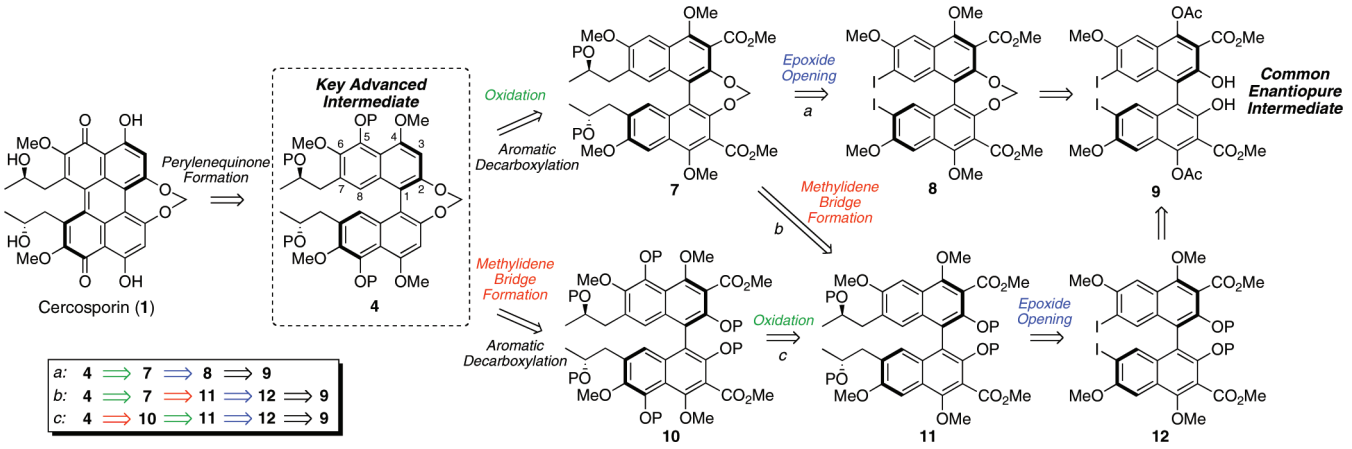


As such, our synthetic efforts rapidly focused on **4** (Scheme 2) with the 7-membered methylidene acetal as a late-stage intermediate, which would be less prone to atropisomerization than early intermediates with the perylenequinone core. From this key intermediate, paths *a*−*c* (Scheme 2) were identified, varying in the sequence of three transformations: C5,C5′-oxygenation, biscuprate epoxide opening, and methylidene acetal formation. All of these paths converge on common enantiopure intermediate **9**, congruent with our goal of synthesizing all the perylenequinone natural products from this compound.

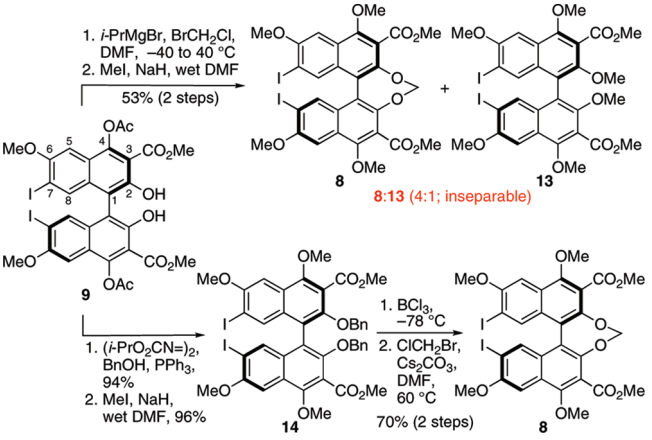
Thus, helical chiral **1** would arise from axial chiral **4** (Scheme 2). At this branchpoint, retrosynthetic installation of the C3,C3′-methyl esters and C5,C5′-deoxygenation leads to intermediate **7**. The C3,C3′-esters are necessary to achieve a highly selective biaryl coupling and also serve to protect the C3,C3′-positions during the C5,C5′-oxygenation. In path *a*, the epoxide opening disconnection is applied to **7** and is followed by removal of the methylidene acetal to generate the common enantiopure intermediate **9**. By installing the methylidene acetal prior to epoxide opening, path *a* offers the most direct route by avoiding unnecessary C2,C2′-protecting groups. Intercepting the intermediate **7** from path *a*, path *b* diverges with the cleavage of the methylidene acetal to afford **11** (Scheme 2). Following the epoxide opening disconnection to provide **12**, removal of protecting groups yields common intermediate **9**. Path *b* would be necessary if the methylidene acetal is not stable to the epoxide opening conditions needed to add the C7,C7′-substitution (i.e., **8** to **7** in path *a*). However, by reserving the oxygenation until after methylidene acetal installation in path *b*, the three sets of orthogonal protecting groups in intermediate **10** of path *c*

(7) Nasini, G.; Merlini, L.; Andreetti, G. D.; Bocelli, G.; Sgarabotto, P. *Tetrahedron* **1982**, *38*, 2787–2796.
(8) For a preliminary account of this work, see: Morgan, B. J.; Dey, S.; Johnson, S. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 9413–9425.
(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.

SCHEME 2. Retrosynthetic Sequencing for Cercosporin from Key Advanced Intermediate 4



SCHEME 3. Formation of Iodonaphthalene 8

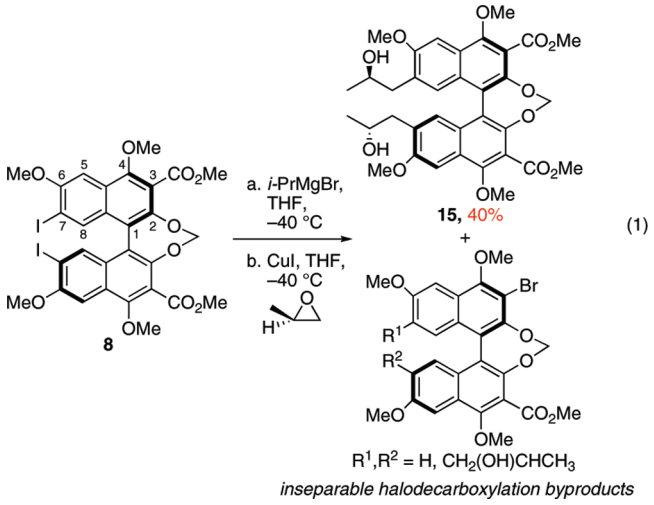


acetal may be avoided. Path *c* moves methylidene acetal formation to after C5,C5′-oxygenation and epoxide opening and intercepts intermediate **11** from path *b*. Even though path *c* involves the greatest number of protecting group manipulations, it is the most conservative route since the sensitive methylidene acetal is installed after the most demanding transformations. Due to its efficiency, we began with the most speculative route, path *a,* even though the methylidene acetal may not be orthogonal to all the reaction conditions.

Path *a*: Biscuprate Containing a Methylidene Acetal. As outlined in path *a* (Scheme 2), a direct installation of the methylidene acetal was to be attempted using enantiopure **9**. The synthesis of the common enantiopure intermediate **9**, involving an enantioselective naphthol dimerization, is detailed in the preceding paper of this series. In the initial formation of **8** (Scheme 3), the base *i*-PrMgBr was used in conjunction with $BrCH_2Cl$ to install the methylidene acetal. As described below, these conditions were optimal (see Table 2). Even so, cleavage of the labile C4,C4′-acetates was competitive and conditions that drove the C2,C2′-alkylation with $BrCH_2Cl$ to completion resulted in undesired alkylation of the C4,C4′-positions. Milder reaction conditions led to incomplete reaction resulting in an inseparable mixture of **8** and **13** after one-pot deacylation/methylation with NaH and MeI in wet DMF.

Before optimizing this difficult transformation further, the viability of the epoxide alkylation with **8** was tested. To afford a pure sample of **8**, a longer alternate route was employed. Specifically, the C2,C2′-phenols were masked as benzyl ethers via a Mitsunobu reaction (Scheme 3). Following a one-pot deacylation/methylation of the C4,C4′-phenols, the orthogonally protected **14** was generated in high yield. Selective deprotection of the C2,C2′-benzyl ethers was achieved with BCl_3. Treatment of the resulting bisphenol with $BrCH_2Cl$ and Cs_2CO_3 provided the desired **8** as the only product. With pure **8** in hand, the biscuprate epoxide opening was investigated.

In the preceding paper of this series (DOI 10.1021/jo901384h), we investigated the dianionic cuprate formation of a biaryl system similar to **8** in a double-epoxide alkylation. Pleasingly, the resulting complex biscuprate was well-behaved with no evidence of deleterious interactions between the two reacting centers. However, use of these optimized conditions with **8** provided the desired product **15** (eq 1) in only moderate

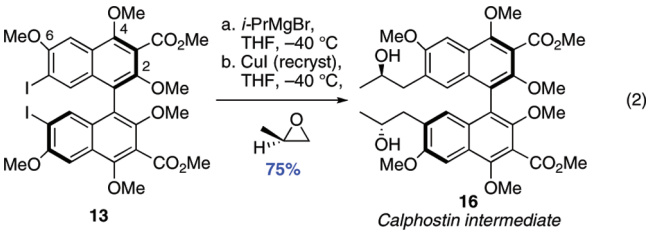


(1)

yield (40%). One of the challenges of these structures is that every step involves reaction at two separate sites on the same molecule. In this case, yet another reaction was competitive. In particular, the less hindered C2,C2′-methylidene acetal permitted reaction at the C3,C3′-esters resulting in a halodecarboxylation product that was inseparable from **15**. Due to the difficulties encountered in this route (Scheme 3, eq 1), our efforts shifted to path *b* (Scheme 2) where the

methylidene acetal would be generated after the epoxide alkylation.

Path *b*: C5,C5′-Oxygenation with the Methylidene Acetal. As seen in the previous paper of this series, the epoxide alkylation proceeded smoothly with bisiodonaphthalene **13** containing C2,C2′,C4,C4′-methyl ethers (eq 2). Thus, we desired to intercept the calphostin intermediate **16** in the synthesis of **1**. In order to utilize this path *b* strategy (Scheme 2), a selective cleavage of the C2,C2′-methyl ethers vs the C4,C4′,C6,C6′-methyl ethers was required to permit formation of the methylidene acetal. Encouragingly, aryl methyl ethers *ortho* to carbonyls (such as, the C2,C2′,C4,C4′-methyl ethers of **16**) can be selectively demethylated with relatively mild Lewis acids in the presence of unactivated aryl methyl ethers (such as the C6,C6′-methyl ethers of **16**).[10]



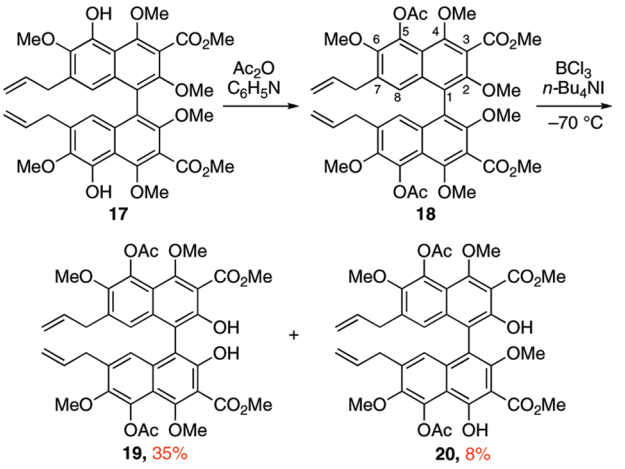
(2)

In order to distinguish between the C2,C2′- and C4,C4′-methyl ethers, model system **18** was examined which was available from our hypocrellin A synthesis (Scheme 4).[11] Due to substitution at the C5,C5′-*peri* positions, it was expected that the C4,C4′-methyl ethers would be more hindered than the C2,C2′-methyl ethers resulting in selective cleavage of the latter. Screening of reagents to demethylate phenols revealed that BCl_3 in combination with *n*-Bu_4NI[10b] was the most selective. Unfortunately, a complex mixture of C2,C2′,C4,C4′-demethylated products was produced, and the C2,C2′-bisphenol **19** was obtained in only a modest 35% yield. With such a nonselective process, the C2,C2′-demethylation of a calphostin intermediate was eliminated as a route to cercosporin (**1**).

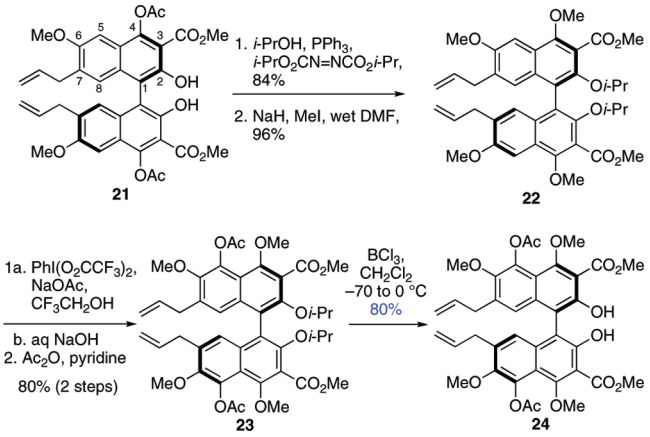
Although the selective demethylation was disappointing, the observation of some intrinsic selectivity provided an impetus to consider other alkyl groups for protection of the C2,C2′-phenols. Choices include the less hindered, more stable isopropyl ether and the bulkier, more labile *tert*-butyl ether. Precedent for the selective removal of isopropyl aryl ethers in the presence of methyl aryl ethers,[12] in conjunction with the stability and more facile installation, led to selection of the isopropyl group.

To examine the selectivity for cleavage of C2,C2′-isopropyl ethers, model **23** was generated (Scheme 5). Bis-isopropoxy compound **33** was synthesized from the allyl biaryl coupling product **21**.[13] Mitsunobu reaction of **21** with 2-propanol followed by the deacylation/methylation afforded

SCHEME 4. Attempted Selective Demethylation on Model Substrate 18



SCHEME 5. Selective Cleavage of C2,C2′-Isopropyl Ethers



22 in high yield. As will become apparent in subsequent discussion, the $PhI(OCOCF_3)_2$-induced[14] C5,C5′-oxygenation was sensitive to most ether functionality. Pleasingly, the isopropyl ethers departed from this trend and $PhI(OCOCF_3)_2$ treatment followed by bisacetylation furnished bisacetate **23** in 80% yield, with no erosion of the enantiopurity. Selective removal of the C2,C2′-isopropyl ethers proceeded smoothly upon treatment of **23** with BCl_3 at low temperatures to yield the desired C2,C2′-bisphenol **24**. While these results were encouraging, the ultimate test would be if the isopropoxy groups could withstand the biscuprate epoxide opening.

To this end, the biscuprate epoxide opening was examined with the bis-isopropyl ether **25** (Scheme 6). Using the same method as before (Scheme 5), Mitsunobu reaction of **9** followed by deacylation/methylation provided the required bisiodide **25**. This route was readily scalable allowing the generation of over 15 g of enantiopure **25**. Furthermore, using the developed conditions,[13] the epoxide openings of (*R*)-propylene oxide with the biscuprate of **25** afforded **26** in high yield supplying two new stereocenters (two couplings,

(10) (a) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, 4153–4159. (b) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719–9721.

(11) O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6877–6880.

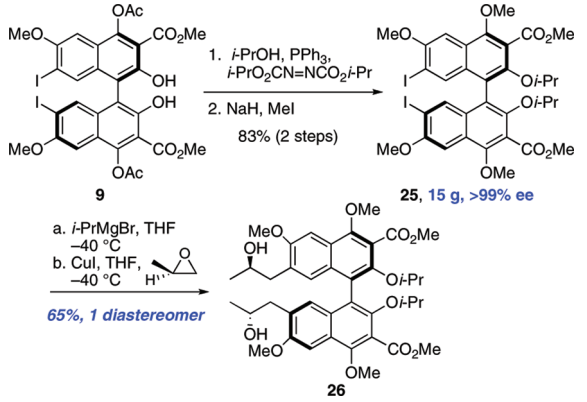
(12) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593–2598.

(13) See the preceding paper in this series. Morgan, B. J.; Mulrooney, C. A.; O'Brien, E. M.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75* (DOI 10.1021/jo901384h).

(14) (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691. (b) Arisawa, M.; Ramesh, N. G.; Nakajima, M.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 59–65.

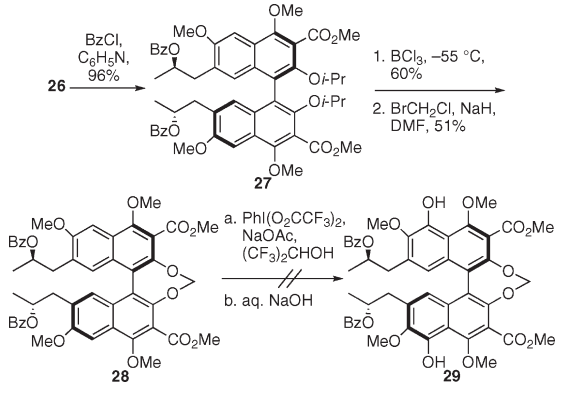
81% yield each). With establishment of the C7,C7′-stereochemistry, the next transformation to address in path *b* (Scheme 2) is installation of the methylidene acetal.

SCHEME 6. Dianion Epoxide Opening with 25



As outlined in the preceding paper in this series (DOI 10.1021/jo901384h), the benzoyl group was the only substitution compatible with the PIFA conditions. Thus, the newly formed alcohol stereocenters of **26** were protected as benzoates providing **27** in 96% yield (Scheme 7). As seen with **23** (Scheme 5), the C2,C2′-isopropyls of **27** (Scheme 7) were selectively cleaved using BCl_3 to afford the desired bisphenol. Methylidene ketal **28** was generated upon exposure to $BrCH_2Cl$ and NaH. Unfortunately, the PIFA oxygenation conditions with the C2,C2′-methylidene acetal resulted in decomposition and provided none of the desired product **29**. Apparently, PIFA is sufficiently oxidizing to react with the activated methylidene. The low functional group tolerance of the PIFA reagent compelled us to turn from path *b* to path *c* (Scheme 2) to generate intermediate **4**.

SCHEME 7. Attempted PIFA Oxygenation on Methylidene Acetal 28



Though not following one of the paths outlined in Scheme 2, the above success with the C2,C2′-isopropoxy protecting groups stimulated us to evaluate PIFA oxygenation and subsequent epoxide opening of the readily available **25** (Scheme 8). Advantages of this plan include avoidance of the three sets of orthogonal protecting groups necessary in path *c* and late stage introduction of the C7,C7′-subsitution which would facilitate synthesis of analogs. The PIFA oxygenation was sensitive to most ethers (see Scheme 7, Table 1), but tolerated a small subset of other functionalities including halogens.[15] Thus, oxygenation of **25** successfully yielded **30**. Unfortunately, the attempted epoxide alkylation on **30** was unsuccessful; the additional C5,C5′-substituents cause steric gearing with the C6,C6′-methoxy groups which in turn hindered the C7,C7′-metalated species. As a consequence, only the arene from protodemetalation was obtained with the C5,C5′-acetates intact.[8]

SCHEME 8. PIFA Oxygenation of Iodonaphthalene 25

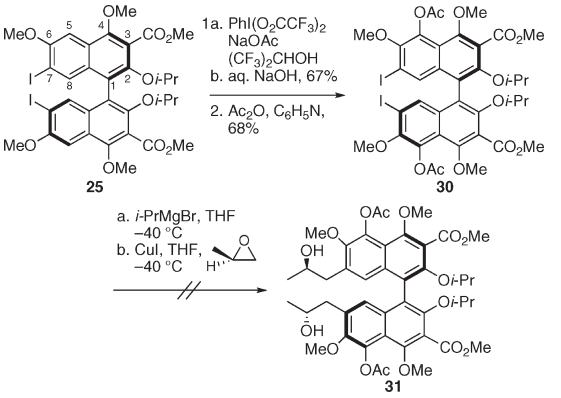
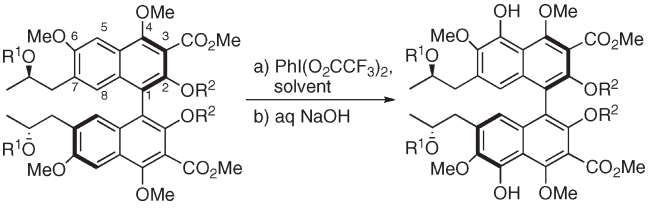


TABLE 1. Screening Substrates and Conditions for PIFA Oxygenation



entry	R^1	R^2	solvent[a]	product	yield (%)
1	Bz	Me	TFE/HFIP(1:1)	**32**	59
2	Bz	*i*-Pr	TFE/HFIP(1:1)	**33**	25
3	Piv	*i*-Pr	TFE/HFIP(1:1)	**34**	< 20
4	Bz	Bn	TFE/HFIP(1:1)	**35**	0
5	Bz	*i*-Pr	HFIP	**33**	55

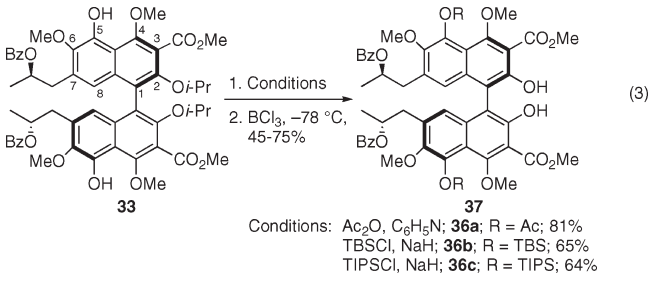
[a]TFE = CF_3CH_2OH; HFIP = $(CF_3)_2CHOH$.

Path *c*: Late-Stage Methylidene Acetal Installation. With the elimination of path *a* and path *b*, attention turned to path *c* (Scheme 2). Path *c* diverges from path *b* by reserving formation of the methylidene acetal to after C5,C5′-oxygenation. As seen in Scheme 8, the C2,C2′-isopropyl ethers are compatible with the PIFA oxygenation condition providing promise that **27** would be successful as well. Unfortunately, the same conditions that had been successfully employed to provide the calphostin intermediate **32** (entry 1, Table 1), generated **33** in only 25% yield (entry 2). With the more robust pivaloyl esters of the C7,C7′-hydroxypropyl groups (**34**) or with the orthogonal C2,C2′-benzyl ethers (**35**) even more unsatisfactory results were obtained (entries 3 and 4). The use of neat 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) compared to a 1:1 mixture of HFIP/2,2,2-trifluoroethanol proved essential and afforded the desired product **33** in

(15) The other functionalities include C2,C2′-isopropoxy and C7,C7′-propyls and -allyls, as can be seen in the other papers of this series (DOIs 10.1021/jo9013832 and 10.1021/jo901384h) and in Scheme 5 and Table1.

55% yield (entry 5). The more polar HFIP provided faster reaction times, which allowed less time for concurrent product decomposition as was seen with entry 2. Even with these harsher reaction conditions, no atropisomerization was observed in contrast to the case when C7,C7′-propyl groups were employed as described in the first paper of this series (DOI 10.1021/jo9013832)". With the C5,C5′-oxygenation in place, selective removal of the C2,C2′-isopropyl ethers was assessed to set the stage for methylidene acetal installation.

As seen in the discussions above, the installation and presence of the methylidene acetal has provided many challenges. Thus, it has been the central focus of our work toward cercosporin. To optimize the success in methylidene acetal installation, a variety of orthogonal C5,C5′-protecting groups were assessed during the selective removal of the C2,C2′-isopropyl ethers and the subsequent formation of the methylidene acetal. Happily, C5,C5′-acetates and silyl ethers (TBS and TIPS) were compatible with the BCl_3-mediated deprotection of the C2,C2′-isopropyl ethers supplying bisphenols **37a**−**c** (eq 3). Unfortunately, these transformations proved to be sensitive to scale and attempts to perform them on more than 0.06 mmol were unsuccessful, providing mixtures of C2,C2′,C4,C4′-dealkylation. Prior to further optimization of these reactions, the installation of the methylidene acetal was examined.

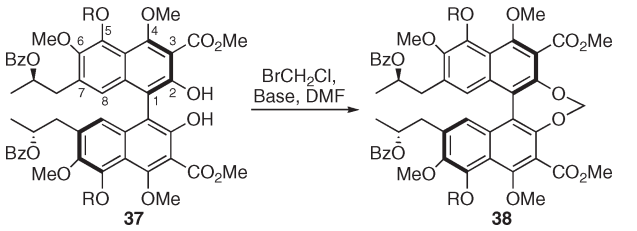


(3)

Although formation of the methylidene acetal is presented above (Schemes 3 and 7), this transformation was not trivial and required considerable optimization. Presumably, the disfavorable entropy in forming the seven-membered ring combined with ring strain slows this process. Use of formaldehyde equivalents under acidic conditions failed. Of all the potential methylidene equivalents, ring formation was most facile via S_N2 displacements with $BrCH_2Cl$ vs $BrCH_2Br$, $BrCH_2I$, ICH_2Cl, and $ClCH_2Cl$. Clearly, there is a necessary balance between leaving group ability and halide size. For example, $BrCH_2Br$ or ICH_2Cl with superior leaving groups would be expected to supersede $BrCH_2Cl$; however, the larger bromo/iodo group appears to hinder the first alkylation event. On the other hand, $ClCH_2Cl$ performed poorly since the chloride is an inferior leaving group in the crucial first alkylation. Furthermore, DMF provides substantial acceleration of the S_N2 displacements and was the only acceptable solvent.

With substrates **37a**−**c**, the lability of the C5,C5′-phenolic protecting groups presented a serious challenge (Table 2). For example, the use a hydride base (NaH or LiH) and $BrCH_2Cl$ failed to provide significant amounts of **38a**,**b** due to cleavage of C5,C5′-acetates or -silyls (entries 1−3). After a survey of both the more robust TIPS group and other nonnucleophilic bases (entries 3−5), we attributed the C5,C5′-cleavage to hydroxide formed from small amounts of water present during the reaction. To circumvent this problem, the self-desiccating base *i*-PrMgBr was employed, which would form polymeric $MgO/Mg(OH)_2$. Under these conditions, methylidene acetal **38c** formed smoothly with no loss of the C5,C5′-silyl groups (entries 6 and 7). Furthermore, no atropisomerization was observed. With the methylidene acetal achieved, our efforts focused on removal of the C3, C3′-methyl esters.

TABLE 2. Screening Substrates and Conditions for Methylidene Acetal Installation



entry	R	base	temp (°C)	product	yield (%)
1	Ac	NaH	65	**a**	$< 5^{a,b}$
2	TBS	NaH	65	**b**	$< 5^{a,b}$
3	TBS	LiH	rt	**b**	$< 5^{a,b}$
4	TBS	LHMDS	rt	**b**	$< 10^{a,b}$
5	TIPS	LHMDS	rt	**c**	$< 10^{a,b}$
6	TIPS	*i*-PrMgBr	rt	**c**	40 (85% brsm)
7	TIPS	*i*-PrMgBr	45	**c**	73

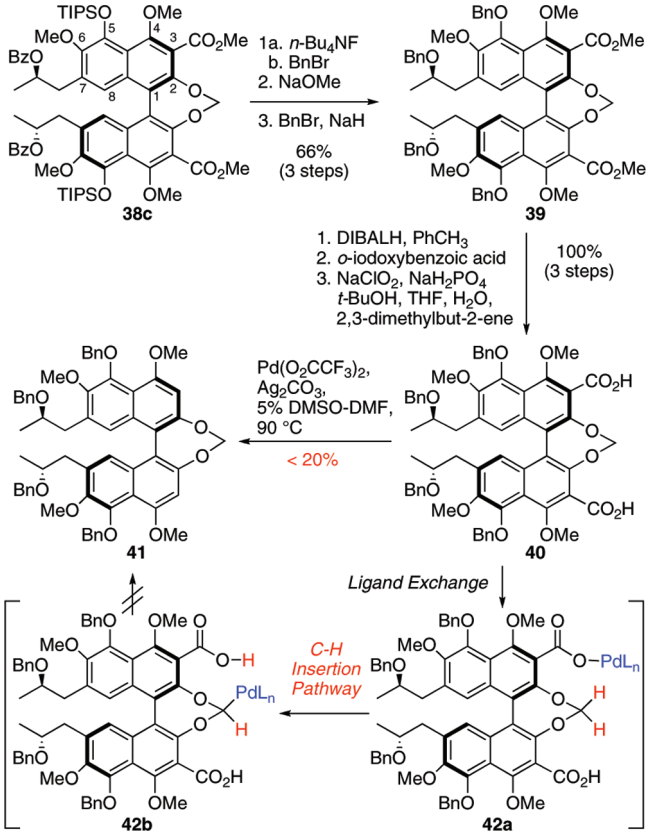
[a]Conversion by NMR. [b]C5,C5′-protecting groups cleaved.

Decarboxylation vs Decarbonylation (Path *c*). Upon removal of the C3,C3′-esters, the key advanced intermediate **4** (Scheme 2) would be obtained. Based upon the success with a similar calphostin intermediate described in the previous paper of this series, a palladium-catalyzed decarboxylation[16] was employed here. To apply this transformation, the incompatible benozyl and silyl of **38c** need to be converted to more robust protecting groups (Scheme 9). Removal of the silyl ethers with TBAF and quenching with benzyl bromide afforded the C5,C5′-bisbenzyl ether. Following hydrolysis of the benzoates with NaOMe, benzylation yielded tetrabenzyl ether **39**. Due to the steric hindrance of the C3,C3-esters, a three-step sequence was used to furnish diacid **40** in a higher overall yield and no atropisomerization compared to a base mediated hydrolysis. Surprisingly, application of the decarboxylation procedure to **40** furnished less than 20% of the key intermediate **41**. Molecular models indicated that the protons of the 7-membered ring in **42a** are in close proximity to the palladium of the intermediate palladium carboxylate causing a competing C−H insertion into the methylidene ring as seen in **42b**.

In the hope of avoiding this unproductive pathway, the C3,C3′-decarboxylation was evaluated with the bis-isopropoxy **44**. After hydroxylation, the C5,C5′-phenols of **33** were benzylated (Scheme 10). Hydrolysis of the benzoate groups and replacement with the benzyl ethers afforded the desired product **43** in high yield. The three-step reduction/oxidation/oxidation sequence was used to provide the bisacid **44**. The yield of this sequence was slightly lower due to greater steric

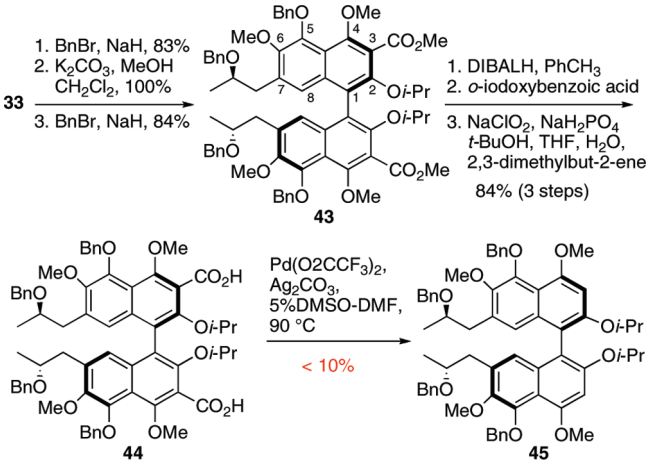
(16) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441–2444.

SCHEME 9. Attempted Palladium-Mediated Decarboxylation of Methylidene Substrate 40

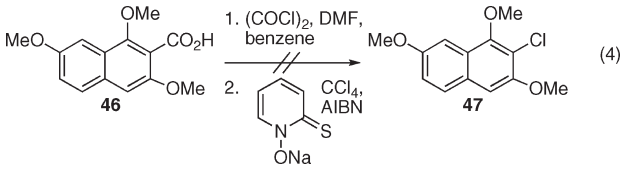


hindrance at the C3,C3′-esters due to the larger C2,C2′-isopropoxy groups. Unfortunately, the sterically large C2,C2′-isopropoxys also effected the decarboxylation, and less than a 10% yield of the desired **45** was isolated. The sluggish reaction primarily afforded monodecarboxylated product along with unreacted starting material.

SCHEME 10. Attempted Palladium-Mediated Decarboxylation on Bis-isopropoxy 44

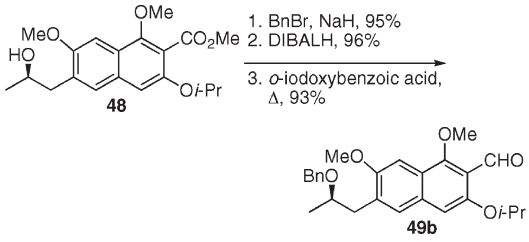


At this point, a Barton decarboxylation protocol was assessed on the naphthalene model system **46** (eq 4). The required acid chloride of **46** was readily formed, but none of the corresponding thiohydroxamate ester could be generated.[17] It has been reported that Barton ester formation can be stalled by hindered reaction sites.[18] As such, an alternate method was sought.



(4)

The decarbonylation of aldehydes by rhodium complexes represents an important method for total synthesis in that it permits the removal of a sensitive functional group under mild and neutral conditions.[19] Though there have been some descriptions of catalytic processes,[20] most applications require stoichiometric rhodium. Utilizing the epoxide alkylation product **48** formed during optimization of the cuprate procedure described in the preceding paper of this series, model aldehyde **49b** was generated to investigate the potential of the rhodium-mediated decarbonylation in a hindered system (eq 5).



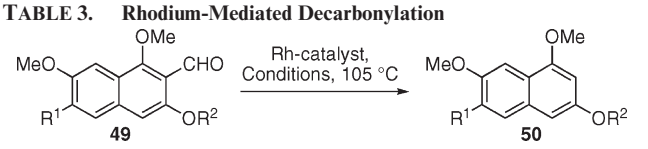
(5)

Studies began with the simple aldehyde **49a** using $RhCl_3 \cdot H_2O$ with 1,3-bis(diphenylphosphino)propane (dppp)[21] (entry 1, Table 3) as an alternative to the more air-sensitive system of $[RhCl(COD)_2]_2$ and dppp. Due to the atropisomerically labile cercosporin system (cf. **39**, Scheme 9), a lower temperature (105 vs 162 °C) was employed, but none of the desired product **50a** was observed. Apparently, the higher temperatures are vital to the in situ formation of $Rh(dppp)_2Cl$ from this rhodium(III) source. On the other hand, the active catalyst readily forms from $[RhCl(COD)_2]_2$, and the decarbonylated **50a** was generated in good yields (entries 2 and 3). Using Wilkinson's catalyst $[RhCl(PPh_3)_3]$ was superior (entries 4 and 5) with the best results observed using diglyme as the solvent (90%). Notably, the reactions involving $[RhCl(COD)_2]_2$ and $RhCl(PPh_3)_3$ were extremely sensitive to air, and rigorously air-free conditions were required to obtain satisfactory results. With these optimized conditions, more complex naphthalene **49b** supplied the desired arene **50b** in excellent yield (80−96%, entries 6 and 7).

To obtain the dialdehyde (**51**) needed for the double decarbonylation, bisester **39** was reduced with DIBALH and then oxidized with *o*-iodoxybenzoic acid (IBX) (Scheme 11). To our

(17) For a review, see: Chimiak, A.; Przychodzen, W.; Rachon, J. *Heteroatom Chem.* **2002**, *13*, 169–194.
(18) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732–5733.
(19) For a review, see: Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566–1591.
(20) Catalytic decarbonylations: (a) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083–7085. (b) Meier, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195–3199. (c) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Liable-Sands, L. M.; Rheingold, A. L. *Organometallics* **1999**, *18*, 5311–5317.
(21) Kreis, M.; Palmelund, A.; Bunch, L.; Madsena, R. *Adv. Synth. Catal.* **2006**, *348*, 2148–2154.

TABLE 3. Rhodium-Mediated Decarbonylation

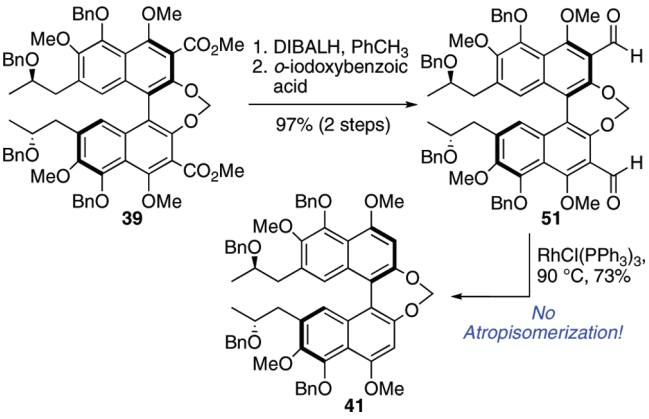


entry	substrate	R^1	R^2	Rh-catalyst	conditions[a]	product	yield
1	**a**	H	Me	$RhCl_3 \cdot 3\ H_2O$	dppp, diglyme	**a**	0 %[b]
2	**a**	H	Me	$[RhCl(COD)_2]_2$	dppp, toluene	**a**	85%
3	**a**	H	Me	$[RhCl(COD)_2]_2$	dppp, diglyme	**a**	68%
4	**a**	H	Me	$RhCl(PPh_3)_3$	toluene	**a**	73%
5	**a**	H	Me	$RhCl(PPh_3)_3$	diglyme	**a**	90%
6	**b**		*i*-Pr	$RhCl(PPh_3)_3$	toluene	**b**	80%
7	**b**		*i*-Pr	$RhCl(PPh_3)_3$	diglyme	**b**	96%

[a]dppp = diphenylphosphinopropane. [b]Starting material recovered.

delight, decarbonylation of the dialdehyde with $RhCl(PPh_3)_3$ proceeded well. Furthermore, the moderate temperatures (90 °C in diglyme) required for this process were well tolerated, and no atropisomerization of the biaryl was observed. With this result, a reliable route (via path *c*, Scheme 2) to the key advanced intermediate **41** (cf. **4**, Scheme 2) was secured.

SCHEME 11. Formation of Key Advanced Intermediate 41 via Decarbonylation

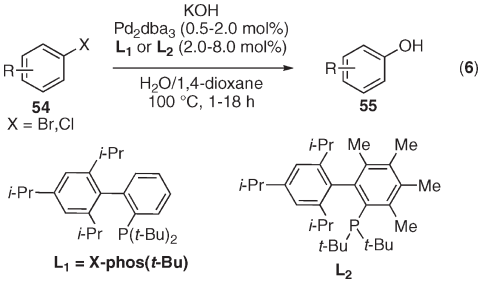


First Total Synthesis of Cercosporin. To complete the synthesis of **1**, we employed the same steps used in the conclusion of the calphostin synthesis as described in the previous paper of this series (DOI 10.1021/jo901384h). After a global debenzylation of **41**, the bisphenol was oxidized by MnO_2 to afford perylenequinone (Scheme 12).[9c,d] This final cyclization step was held until this stage because formation of the perylenequinone reduces the dihedral angle from 50° in axial chiral **41** to 20° in helical chiral **1**, further facilitating atropisomerization. The selective removal of the C4,C4′-methyl ethers was accomplished under mild conditions with MgI_2,[9b,e,f] completing the first total synthesis of cercosporin (**1**) in 23 steps and 0.4% overall yield (82% average yield per step).

To summarize, the complete route to cercosporin is outlined in Scheme 12 (problematic steps shown in boxes). This synthesis established methods for several key steps including biscuprate epoxide alkylation, methylidene acetal formation, and C3,C3′-decarbonylation. Due to functional group incompatibilities, the synthesis required the most conservative of the proposed routes (path *c*) from Scheme 2. Though alternative, more direct routes were examined, the installation of the methylidene acetal (path *a*) and the sensitive nature of the PIFA-induced C5,C5′-oxygenation (path *b*) proved to be impediments. The primary culprit contributing to the length of path *c* was the PIFA oxygenation (Scheme 12). Since the C7,C7′-benzoate substitution and C2,C2′-isopropoxys were the only protecting groups tolerated in the reaction, deprotection/reprotection sequences resulted. In addition, the selective removal of the C2,C2′-isopropyl ethers with BCl_3 was scale-sensitive, inhibiting generation of scalable amounts of the bisphenol needed for methylidene acetal installation. Due to these limiting factors, we revised our synthetic strategy by pursuing a different C5,C5′-oxygenation protocol to streamline the synthesis.

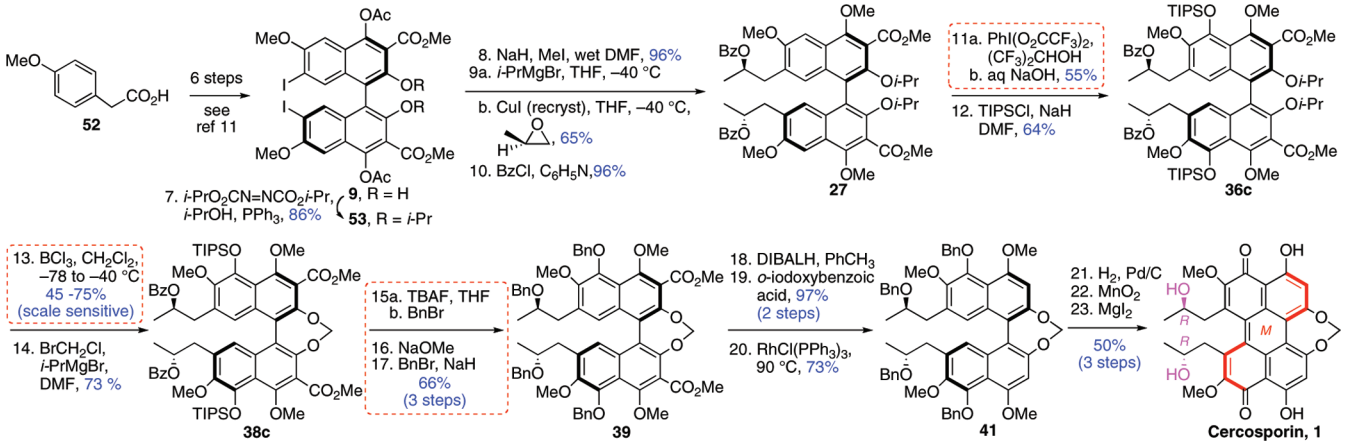
Second-Generation Strategy: Palladium-Catalyzed *O*-Arylation. As seen in the preceding paper of this series (DOI 10.1021/jo901384h), the palladium-catalyzed *O*-arylation was investigated in order to avoid the cumbersome PIFA reaction. In addition to providing a more efficient synthesis of **1**, a less sensitive transformation was sought to provide strategic flexibility, permitting derivatization to different analogs at many points in the pathway.[8] Here, we provide a complete account of the palladium-catalyzed *O*-arylation, which was investigated as a result of the limitations encountered in the first total synthesis of **1**.

While arylations of alcohols have been reported for a host of systems,[22] we could locate no *O*-arylations of highly functionalized, hindered, electron-rich systems. Furthermore, the arylation of aliphatic alcohols, such as benzyl alcohol, is particularly challenging due to a competitive β-hydride elimination of the coordinated alcohol. While early reports centered on couplings with 2-methyl-2-propanol, which contains no hydrogens that can undergo β-hydride elimination,[23] Buchwald later described the arylation of primary and secondary alcohols containing α-hydrogens.[24] A further report of phenol formation by palladium-catalyzed coupling of KOH with aryl chlorides and bromides (eq 6), including several hindered aryl halides,[25] provided the impetus for us to examine this method.



(22) Reviews: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (c) Carril, M.; SanMartin, R.; Dominguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639–647.

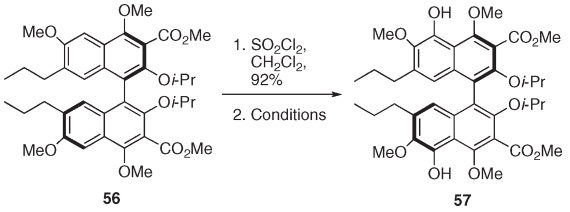
SCHEME 12. Summary of the First Total Synthesis of Cercosporin (1)



Studies commenced with the C7,C7′-propyl substrate **56** (Table 4), an intermediate utilized in the synthesis of perylenequinone analogues.[8] Due to the steric crowding of the C5,C5′-positions, we elected to use the smaller chlorides. An evaluation of chloride electrophiles (NCS, $SOCl_2$, SO_2Cl_2) revealed that sulfuryl chloride (SO_2Cl_2) effected chlorination with the highest yield (92%). Since the X-phos(*t*-Bu) (L_1) ligand was reported as the most effective for phenyl halides bearing two *ortho*-substituents, it was employed with our sterically demanding aryl chloride. Using the reported conditions, involving the catalyst system derived from Pd_2dba_3 and L_1,[25] provided the monophenol and arene products but none of the desired bisphenol **57** (entry 1, Table 4). Distinct from other systems, the biaryls here require two couplings per reacting structure to obtain the desired product. Encouragingly, this preliminary result indicated that the oxidative addition and reductive elimination are feasible. Though the more hindered L_2 ligand was reported be more stable (Pd-black was observed with L_1), none of the desired product was observed with our sterically demanding system (entry 2). Since the starting material was recovered, the bulky L_2 appeared to prevent oxidative addition. Utilizing a higher catalyst loading and rigorously air-free conditions with the less stable L_1 were paramount to an effective C−O coupling, supplying **57** in 90% yield (entry 3).

The success of the C5,C5′-*O*-arylation in the model system led us to evaluate the C−O coupling with cercosporin intermediate **59** (Scheme 13). Starting from the same common intermediate **9** employed in the first-generation synthesis (Scheme 12), Mitsunobu reaction with benzyl alcohol and one-step deacetylation/methylation provided **14**. The C2,C2′-bisbenzyl ether **14** was employed since the methylidene acetal led to the formation of undesired halodecarboxylation products in the epoxide alkylation (eq 1). Furthermore, it would not be possible to remove C2,C2′-bis-isopropoxy ethers (cf. **27**, Scheme 12) in the presence of aliphatic benzyl ethers on the C7,C7′-hydroxypropyl groups

TABLE 4. Screening Buchwald Cross-Coupling Conditions for Formation of 57



entry	ligand[a]	conditions[b]	yield (%)
1	L_1	Pd_2dba_3, KOH, H_2O/1,4-dioxane, 80 °C, 2 h	0[c]
2	L_2	Pd_2dba_3, KOH, H_2O/1,4-dioxane, 80 °C, 17 h	0[d]
3	L_1	Pd_2dba_3, KOH, H_2O/1,4-dioxane, 95 °C, 5 h	90[e]

[a]For L_1 and L_2, see eq 6. [b]4 mol % of Pd_2dba_3, 8 mol % of ligand, 6 equiv of KOH, H_2O/1,4-dioxane (1:1). [c]Isolated 48% arene and 47% mono-oxidation product. [d]Starting material recovered. [e]20 mol % of Pd_2dba_3, 40 mol % of ligand, 8 equiv of KOH.

(see below). Pleasingly, the double alkylation of the biscuprate of **14** with (*R*)-propylene oxide furnished the desired alkylated product in 65% yield as a single diastereomer (Scheme 13). The newly installed aliphatic alcohol stereocenters were directly benzylated, and subsequent debenzylation of the C2,C2′-phenolic benzyl ethers to provide **58** was accomplished using pyridine to attenuate the activity of the Pd/C.[26] As previously detailed (see Table 2 and corresponding discussion), generation of the methylidene acetal was not trivial. In this system, however, the use of a self-desiccating base was unnecessary since no other labile functional groups were present. Thus, treatment of the bisphenol **58** with $BrCH_2Cl$ and Cs_2CO_3 supplied the desired methylidene acetal. Finally, the necessary aryl chloride **59** was synthesized efficiently using sulfuryl chloride.

Disappointingly, direct *O*-arylation of bischloride **59** with benzyl alcohol (entries 1 and 2, Table 5) to generate a protected bisphenol directly was unsuccessful. In these reactions, the oxidative addition of aryl chloride **59** proceeded smoothly, but as previously discussed, β-hydride elimination was favored over reductive elimination resulting in arene

(23) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.
(24) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396. (b) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771. (c) Vorogushi, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149.
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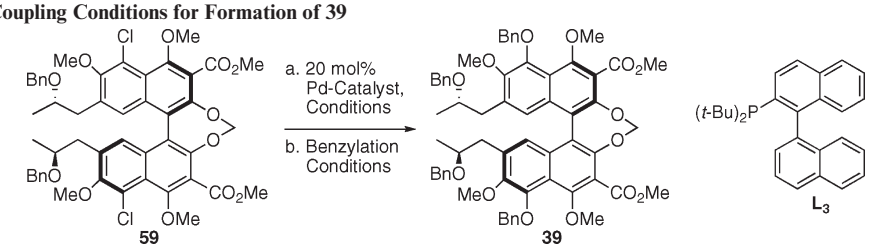
(26) (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468. (b) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399–402.

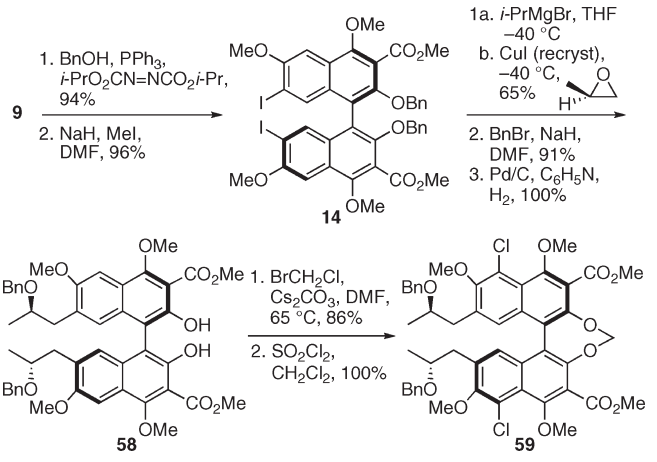
TABLE 5. Screening Coupling Conditions for Formation of 39



entry	Pd catalyst	ligand[a]	coupling conditions	benzylation conditions	yield (%)
1	Pd_2dba_3	L_1	BnOH, Cs_2CO_3, toluene, 80 °C		0[b]
2	Pd_2OAc_2	L_3	BnOH, Cs_2CO_3, toluene, 80 °C		0[b]
3	Pd_2dba_3[c]	L_1[c]	KOH, 1,4-dioxane/H_2O (5:3), 80 °C		40[d]
4	Pd_2dba_3	L_1	KOH, 1,4-dioxane: H_2O (5:3), 80 °C	$Me_3NC_{16}H_{33}Br$, BnBr, KOH, 90 °C	0[e]
5	Pd_2dba_3[c]	L_1[c]	KOH, 1,4-dioxane/H_2O (5:3), 80 °C	$Me_3NC_{16}H_{33}Br$, BnBr, KOH, rt	0[e]
6	Pd_2dba_3[c]	L_1[c]	KOH, 1,4-dioxane/H_2O (5:3), 80 °C	BnBr, NaH, DMF	70[f]

[a]L1 = X-phos(*t*-Bu); see eq 6. [b]Arene recovered. [c]Ligand and Pd_2dba_3 stored and dispensed in an inert atmosphere box. [d]Isolated yield of diphenol; diphenol decomposes on SiO_2 column. [e]Diphenol formed, but benzylation conditions afforded decomposition. [f]Reaction mixture was quenched at 0 °C with 0.5 M HCl after phenol formation and immediately subjected to benzylation conditions.

SCHEME 13. Formation of Aryl Chloride Substrate



formation. Thus, attempts were made to use Buchwald's two-step, one-pot protocol for formation of benzyl ether **39**. The catalyst identified above (Table 4) derived from Pd_2dba_3 and Buchwald's X-phos(*t*-Bu) ligand (L_1) again proved effective in the coupling with KOH to provide the desired bisphenol (entry 3, Table 5). Due to the lower atropisomerization barrier of **59** containing a seven-membered ring (see Scheme 1), lower temperatures (80 vs 95 °C) were employed here compared to the reaction of the system lacking the methylidene bridge (Table 4). Pleasingly, no atropisomerization was observed under these conditions. However, the resulting bisphenol was highly unstable (40% isolated yield) and could not withstand the typical one-pot benzylation protocols (entries 4−5). To solve this problem, the C−O coupling reaction was quenched at low temperature (0 °C) with dilute HCl to supply the bisphenol. After immediate concentration and exposure to standard benzylation procedures (BnBr, NaH, and DMF), the advanced intermediate **39** was isolated in 70% yield (entry 6).

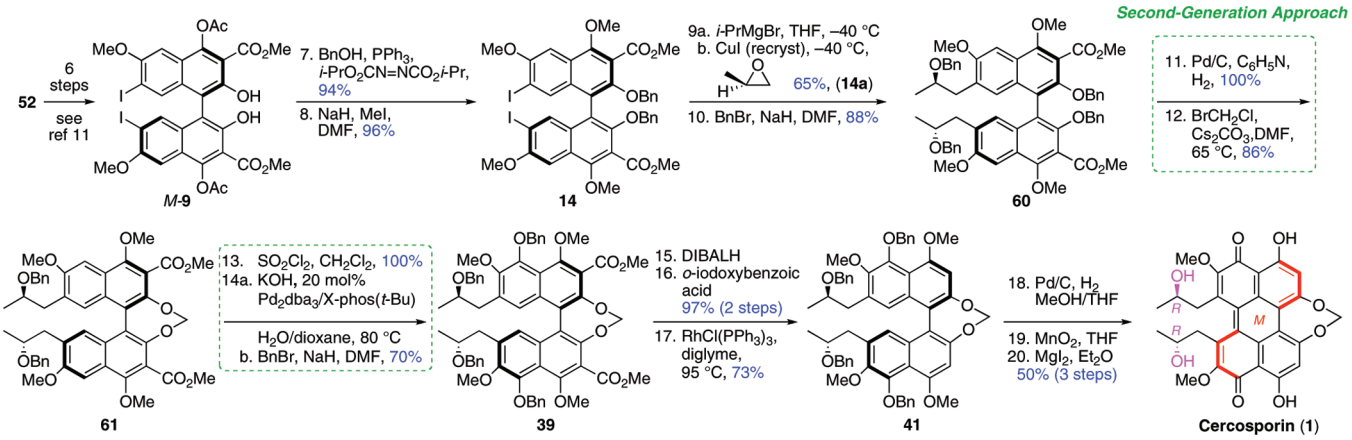
Notably, the first- and second-generation approaches diverged at the common enantiopure intermediate **9** and then intersected in the formation of **39** (Scheme 12). The synthesis of **39**, therefore, concludes the second-generation approach. After decarbonylation and perylenequinone formation, the second-generation synthesis of **1** (Scheme 14) was completed in 20 steps and a 2.8% overall yield (86% average yield per step).

Use of the mild *O*-arylation protocol (**61** → **39**, Scheme 14) allowed C5,C5′-oxygenation in the presence of the methylidene acetal, thereby permitting a shift to the more efficient path *b* (Scheme 2) which was not possible with the PIFA method due to reaction at the methylidene acetal (Scheme 7). In addition, the milder C5,C5′-oxygenation allowed the use of benzyl ether protection at the C7,C7′-substitution and the C5,C5′-centers which eliminated two protecting group exchanges needed in the first-generation approach (Scheme 12) via path *c* (Scheme 2). The second-generation approach required three fewer steps and improved the efficiency dramatically providing a 7-fold increase in the overall yield (2.8%, Scheme 14 vs 0.4%, Scheme 12). The greater functional group tolerance and generality of the palladium-catalyzed *O*-arylation also provided synthetic flexibility permitting the synthesis of analogs.[8] For example, the *O*-arylation protocol was viable with a variety of C2,C2′-substitution (−CH_2−, Me, *i*-Pr, *n*-Pr, and Bn) affording high yields of the desired products.

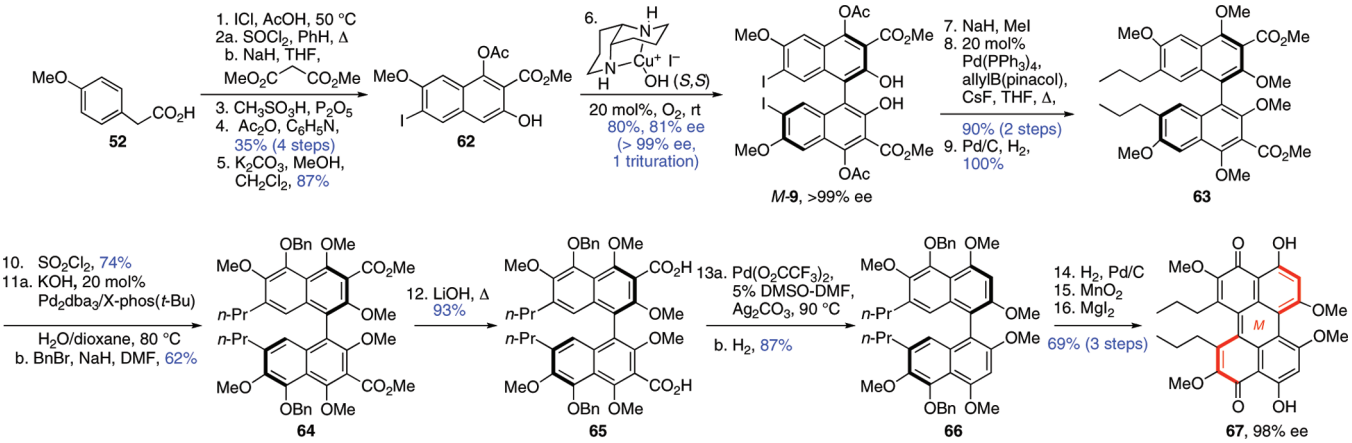
Conclusions

The first total synthesis of cercosporin has been completed comprising 20 steps from commercially available **52** and proceeding with 2.8% overall yield (86% average yield per step). The synthetic work encompassed two generations. In the first synthesis, the methylidene acetal installation and C3, C3′-decarbonylation problems were solved resulting in the completion of the atropisomerically sensitive cercosporin without any accompanying atropisomerization. However, the PIFA C5,C5′-oxygenation was identified as a major limitation of the synthesis due to high cross reactivity with other functional groups and low generality. In the second generation synthesis, an alternate C5,C5′-oxygenation was identified relying on a palladium-catalyzed *O*-arylation. This protocol enabled the formation of the key advanced intermediate **41** on preparative scale with enhanced yields and no

SCHEME 14. Second-Generation Synthesis of Cercosporin (1)



SCHEME 15. Second-Generation Synthesis of Enantiopure Perylenequinone 67



loss of enantioenrichment. Furthermore, the *O*-arylation proved to be general, and the strategy was used in an improved synthesis of helical chiral perylenequinone **67** (Scheme 15). In the first paper of this series, we focused on the generation of the perylenequinone helical chirality, culminating in the synthesis of **67**. In the synthesis seen in Scheme 15 employing the palladium-catalyzed *O*-arylation for C5,C5′-oxygenation, **67** is provided in fewer steps, higher overall yield, and increased optical purity: 16 steps, 5.6% overall yield (average of 86% per step), 98% ee. Though the new C5,C5′-oxygenation protocol enabled higher yields of **64**, the shortened synthesis and increased enantioenrichment of **67** also arose from the use of the common enantiopure intermediate **9**. As seen here and in the syntheses of **2** and **3**, detailed in the previous paper of this series (DOI 10.1021/jo901384h), we desired to utilize this common intermediate in the syntheses of all the perylenequinone natural products. To this end, its use in the total synthesis of hypocrellin A is detailed in the fifth paper in this series (DOI 10.1021/jo901386d).

Experimental Section

(*M*)-Dimethyl 2,2′-bis(benzyloxy)-7,7′-diiodo-4,4′,6,6′-tetramethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (14). To a solution of **9** (750 mg, 0.90 mmol) in THF (20 mL) were added benzyl alcohol (0.94 mL, 9.0 mmol) and PPh_3 (830 mg, 3.2 mmol) under an argon atmosphere. The resulting solution was cooled to 0 °C, at which time a diisopropyl azodicarboxylate (0.63 mL, 3.2 mmol) solution in THF (5 mL) was added dropwise. After the mixture was stirred for 1.5 h, the reaction was quenched with 1 M HCl. The aqueous phase was extracted with EtOAc, and the organic portions were washed with brine and dried (Na_2SO_4). After concentration, the residue was chromatographed (30% EtOAc/hexanes) to yield the bisacetate as a yellow solid (860 mg, 94%): [α] −91.3 (*c* 0.7, CH_2Cl_2, >99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 6H), 3.88 (s, 6H), 3.99 (s, 6H), 4.40 (d, *J* = 10.0 Hz, 2H), 4.82 (d, *J* = 10.0 Hz, 2H), 6.77 (m, 4H), 7.06 (s, 2H), 7.12 (m, 6H), 7.66 (s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 20.2, 52.7, 56.6, 76.9, 93.1, 101.0, 122.1, 122.7, 126.4, 128.2, 128.5, 128.6, 131.3, 136.8, 137.2, 145.9, 151.3, 156.4, 165.4, 168.6; IR (film) 2950, 1730, 1583, 1468, 1236 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{36}I_2O_{12}Na$ (MNa^+) 1033.0194, found 1033.0234.

To a solution of the bisacetate (585 mg, 0.58 mmol) in DMF (7 mL) were added NaH (60% in oil, 350 mg, 8.8 mmol) and MeI (0.7 mL, 11 mmol). After being stirred for 1 h at room temperature under argon, the mixture was quenched with 1 M HCl. The aqueous phase was extracted with EtOAc (2×), and the combined organics were washed with aq NH_4Cl (2×). The organic portions were dried (Na_2SO_4) and concentrated. Chromatography (15% EtOAc/hexanes) yielded **14** as a white foam (530 mg, 96%): [α] −94.0 (*c* 0.35, CH_2Cl_2, >99% ee); ^{1}H NMR (360 MHz, $(CD_3)_2CO$) δ 3.94 (s, 6H), 4.04 (s, 6H), 4.15 (s, 6H), 4.45 (d, *J* = 10.5 Hz, 2H), 4.84 (d, *J* = 10.5 Hz, 2H), 6.80 (m, 4H), 7.12 (m, 6H), 7.54 (s, 2H), 7.80 (s, 2H); ^{13}C NMR (75 MHz,

$(CD_3)_2CO$) δ 52.5, 56.5, 62.9, 76.7, 92.1, 101.3, 119.5, 122.7, 126.7, 128.1, 128.1, 128.4, 131.7, 137.2, 137.3, 151.6, 154.2, 155.9, 166.7; IR (film) 2943, 1730, 1576, 1468, 1236 cm^{-1}; HRMS (ES) calcd for $C_{42}H_{36}I_2O_{10}Na$ (MNa^+) 977.0296, found 977.0283.

General Procedure for the Copper-Mediated Epoxide-Opening. A flame-dried Schlenk flask was charged with the aryl iodide, and the system was vacuum purged with argon (3×). After dissolution in anhydrous THF, the solution was cooled to −40 °C, and *i*-PrMgBr (1 M in THF, 1.25 equiv) was added dropwise along the sides of the flask. The reaction mixture was stirred at −40 °C for 40 min under argon. CuI (recrystallized from aqueous NaI and stored in an inert atmosphere box, 0.5 equiv) was introduced to a separate flame-dried Schlenk flask, and the system was vacuum purged with argon (3×). After addition of anhydrous THF, the mixture was cooled to −40 °C. The contents of the first flask (Grignard solution) were added dropwise to the second flask (CuI mixture) via cannula. After the mixture was stirred for 30 min at −40 °C under argon, a solution of (*R*)-propylene oxide (2.5 equiv) was added dropwise over 5 min. The mixture was stirred at −40 °C for 30 min and was then allowed to slowly warm to 0 °C over 1 h. The reaction was quenched with 1 N HCl and then extracted with EtOAc. The combined organic fractions were washed with 1 N HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification was then accomplished by SiO_2 chromatography.

(*M*)-Dimethyl 2,2′-Bis(benzyloxy)-7,7′-bis((*R*)-2-hydroxypropyl)-4,4′,6,6′-tetramethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (14a). The epoxide-opening was carried out according to the general procedure with iodo substrate **14** (260 mg, 0.27 mmol) and *i*-PrMgBr (1 M in THF, 820 μL, 0.82 mmol) in THF (3.5 mL) at −78 °C and CuI (52 mg, 0.27 mmol) in THF (2 mL) and (*R*)-propylene oxide (76 μL, 1.1 mmol). The crude material was chromatographed (SiO_2, 50% EtOAc/hexanes). Product **14a** was obtained diastereomerically pure as a white foam (145 mg, 65%): [α] −62.0 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.2 Hz, 6H), 1.99 (br s, 2H), 2.38 (dd, *J* = 8.7, 13.3 Hz, 2H), 2.89 (dd, *J* = 3.2, 13.3 Hz, 2H), 3.89 (s, 6H), 3.91 (m, 2H), 3.96 (s, 6H), 4.14 (s, 6H), 4.36 (d, *J* = 10.4 Hz, 2H), 4.72 (d, *J* = 10.4 Hz, 2H), 6.79 (m, 4H), 7.06 (s, 2H), 7.12 (m, 6H), 7.43 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 23.6, 41.2, 52.7, 55.8, 63.2, 67.2, 77.0, 100.8, 121.6, 122.1, 125.9, 128.4, 128.7, 128.8, 129.4, 131.0, 132.9, 138.0, 151.3, 154.2, 157.4, 167.7; IR (film) 3321, 2958, 1730, 1591, 1498, 1444 cm^{-1}; HRMS (ES) calcd for $C_{48}H_{51}O_{12}$ (MH^+) 819.3381, found 819.3408.

(*M*)-Dimethyl 2,2′-Bis(benzyloxy)-7,7′-bis((*R*)-2-(benzyloxy)propyl)-4,4′,6,6′-tetramethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (60). To a solution of **14a** (277 mg, 0.338 mmol) in DMF (8.9 mL) were added benzyl bromide (0.810 mL, 6.63 mmol) and *n*-Bu_4NI (25 mg, 0.119 mmol). NaH (60% in oil, 202 mg, 5.09 mmol) was added and the reaction stirred under argon. After completion as judged by TLC, the mixture was acidified with 1 M HCl, diluted, and washed with EtOAc (2×). The combined organic portions were washed with NH_4Cl (aq, 2×), dried (Na_2SO_4), and concentrated. Purification by column chromatography (10−50% EtOAc/hexanes) afforded tetrabenzyl ether 60 as a white resin (309 mg, 91%): [α] −84.5 (*c* 0.2, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 0.93 (d, *J* = 6.1 Hz, 6H), 2.51 (dd, *J* = 6.3, 13.6 Hz, 2H), 2.93 (dd, *J* = 6.1, 13.6 Hz, 2H), 3.63 (m, 2H), 3.89 (s, 6H), 3.92 (s, 6H), 4.11 (s, 6H), 4.24 (d, *J* = 12.3 Hz, 2H), 4.31 (d, *J* = 12.3 Hz, 2H), 4.43 (d, *J* = 10.3 Hz, 2H), 4.78 (d, *J* = 10.3 Hz, 2H), 6.79 (m, 4H), 7.07 (m, 4H), 7.13 (m, 6H), 7.20 (m, 6H), 7.29 (s, 2H), 7.52 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 19.9, 38.3, 52.6, 55.8, 63.2, 70.5, 74.5, 77.0, 100.9, 121.5, 122.2, 126.0, 127.8, 128.0, 128.4, 128.6, 128.8, 128.8, 128.9, 131.0, 132.6, 138.0, 140.3, 151.4, 154.3, 157.4, 167.6; IR (film) 2943, 1730, 1591, 1498, 1452 cm^{-1}; HRMS (ES) calcd for $C_{62}H_{63}O_{12}$ (MH^+) 999.4320, found 999.4315.

(*M*)-Dimethyl 7,7′-Bis((*R*)-2-(benzyloxy)propyl)-2,2′-dihydroxy-4,4′,6,6′-tetramethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (58). Upon dissolution of **60** (135 mg, 0.14 mmol) in a pyridine solution (0.037 M in 1,4-dioxane, 2.25 mL; too much pyridine significantly hinders the reaction), MeOH (2.25 mL) was added and argon was bubbled through the solution for 5 min. Pd/C (120 mg) was added to the solution, and argon was bubbled through for 5 min. Hydrogen (balloon) was bubbled through the solution until the reaction was complete, as judged by TLC. The mixture was purged with argon and then filtered through Celite, washing with EtOAc. After concentration, the residue was chromatographed (25% EtOAc/hexanes) to yield **58** as a yellow solid (110 mg, 100%): [α]−54.2 (*c* 0.2, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.1 Hz, 6H), 2.53 (dd, *J* = 6.9, 13.3 Hz, 2H), 3.02 (dd, *J* = 6.0, 13.3 Hz, 2H), 3.68 (m, 2H), 3.89 (s, 6H), 4.07 (s, 6H), 4.10 (s, 6H), 4.30 (d, *J* = 11.9 Hz, 2H), 4.35 (d, *J* = 11.9 Hz, 2H), 7.04 (s, 2H), 7.10 (m, 4H), 7.19 (m, 6H), 7.42 (s, 2H), 10.6 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 19.9, 38.7, 52.9, 55.7, 63.3, 70.5, 74.5, 101.3, 112.1, 112.4, 123.6, 127.7, 127.8, 128.0, 128.7, 132.7, 133.4, 140.3, 152.3, 156.0, 157.4, 170.1; IR (film) 3429, 2935, 1730, 1668, 1498, 1444 cm^{-1}; HRMS (ES) calcd for $C_{48}H_{51}O_{12}$ (MH^+) 819.3381, found 819.3408.

(*M*)-Dimethyl 10,13-Bis((*R*)-2-(benzyloxy)propyl)-1,7,9,14-tetramethoxydinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepine-2,6-dicarboxylate (61). To a solution of **58** (107 mg, 0.13 mmol) and anhydrous $ClCH_2Br$ (40 μL, 0.39 mmol) in anhydrous DMF (3 mL) under argon was added Cs_2CO_3 (383 mg, 1.2 mmol). The yellow mixture was heated to 60 °C. After the mixture was stirred for 1 h, additional $ClCH_2Br$ (40 μL, 0.392 mmol) was added; a further aliquot was added after 2 h. After being stirred for a total of 3 h under argon, the mixture was cooled, quenched with NH_4Cl (aq), and washed with EtOAc (2×). The organic phase was washed with aq NH_4Cl (2×), dried (Na_2SO_4), and concentrated to yield an orange oil. Purification was accomplished by chromatography (10−25% EtOAc/hexanes) to yield **61** as a yellow resin (82 mg, 76%, 86% based on recovered starting material): [α] −202.0 (*c* 0.25, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.1 Hz, 6H), 2.52 (dd, *J* = 7.6, 13.8 Hz, 2H), 3.08 (dd, *J* = 5.5, 13.8 Hz, 2H), 3.65 (m, 2H), 3.94 (s, 6H), 4.02 (s, 6H), 4.07 (s, 6H), 4.21 (d, *J* = 11.7 Hz, 2H), 4.39 (d, *J* = 11.7 Hz, 2H), 5.73 (s, 2H), 7.12 (m, 4H), 7.24 (m, 6H), 7.29 (s, 2H), 7.43 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 37.6, 52.8, 55.6, 62.8, 70.5, 74.8, 100.3, 104.4, 118.8, 121.9, 126.2, 127.5, 127.7, 128.4, 128.5, 129.0, 131.5, 139.0, 146.2, 153.6, 156.7, 166.8; IR (film) 2927, 1730, 1583, 1498, 1460 cm^{-1}; HRMS (ES) calcd for $C_{49}H_{50}O_{12}Na$ (MNa^+) 853.3200, found 853.3237.

(*M*)-Dimethyl 10,13-Bis((*R*)-2-(benzyloxy)propyl)-8,15-dichloro-1,7,9,14-tetramethoxydinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepine-2,6-dicarboxylate (59). Methylidene acetal **61** (30 mg, 0.036 mmol) in anhydrous CH_2Cl_2 (0.4 mL) was treated with SO_2Cl_2 (8.0 μL, 0.090 mmol) and was allowed to stir at room temperature under argon until the reaction was complete, as determined by TLC. The mixture was quenched with H_2O, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. Purification was accomplished by chromatography (35% EtOAc/hexanes) to yield bischloride **59** as a yellow resin (33 mg, 100%): [α] −46.2 (*c* 0.25, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.1 Hz, 6H), 2.56 (dd, *J* = 6.7, 14.4 Hz, 2H), 3.00 (dd, *J* = 6.4, 14.4 Hz, 2H), 3.50 (m, 2H), 3.89 (s, 6H), 3.95 (s, 6H), 4.03 (s, 6H), 4.05 (d, *J* = 11.6 Hz, 2H), 4.34 (d, *J* = 11.6 Hz, 2H), 5.71 (s, 2H), 7.02 (m, 4H), 7.16 (s, 2H), 7.22 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.5, 37.5, 52.8, 60.6, 64.5, 70.4, 74.6, 103.8, 122.1, 122.5, 122.7, 123.4, 127.1, 127.4, 127.5, 128.3, 131.7, 134.8, 138.1, 147.5, 154.4, 154.7, 165.8; IR (film) 2927, 1738, 1591, 1552, 1452 cm^{-1};

HRMS (ES) calcd for $C_{49}H_{49}O_{12}Cl_2$ (MH^+) 899.2601, found 899.2637.

(*M*)-Dimethyl 8,15-Bis(benzyloxy)-10,13-bis((*R*)-2-(benzyloxy)-propyl)-1,7,9,14-tetramethoxydinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepine-2,6-dicarboxylate (39). An oven-dried microwave tube with a crimp top and Teflon septa containing a stirbar was charged with aryl halide **59** (28 mg, 0.031 mmol) and KOH (14 mg, 0.25 mmol). In an inert atmosphere box, the substrate-containing microwave tube was charged with Pd_2dba_3 (5.7 mg, 0.0062 mmol) and X-phos(*t*-Bu) ligand (11 mg, 0.025 mmol), and the reaction tube was crimped in the inert atmosphere box to avoid exposure to oxygen. The tube was further evacuated and backfilled with argon (2×). A solution of 1,4-dioxane (0.70 mL) and deionized water (0.40 mL) was vigorously purged with argon for 1 h prior to use. At this time, the solvent mixture was added to the reaction tube, and the mixture was stirred in a preheated oil bath (80 °C) until the aryl halide was consumed as judged by TLC. The reaction mixture was cooled to 0 °C and carefully acidified with aqueous HCl (0.5 N), and the resulting mixture was extracted with EtOAc (2×). The organic layer was dried (Na_2SO_4) and concentrated to yield an orange oil. This unstable oil was immediately dissolved in anhydrous DMF (2.0 mL) and treated with BnBr (60 μL, 0.52 mmol) and NaH (95%, 15 mg, 0.56 mmol) under argon and allowed to stir at room temperature for 1 h. The reaction was quenched with NH_4Cl (aq) and washed with EtOAc (2×). The organic phase was washed with NH_4Cl (aq, 2×) and dried (Na_2SO_4), and the solvent was evaporated. Purification was accomplished by chromatography (25% EtOAc/hexanes) to yield tetrabenzyl ether **39** as a yellow resin (23 mg, 70%): [α] −68.0 (*c* 0.2, CH_2Cl_2, >99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.1 Hz, 6H), 2.56 (dd, *J* = 7.0, 13.9 Hz, 2H), 3.06 (dd, *J* = 6.0, 13.9 Hz, 2H), 3.59 (m, 2H), 3.88 (s, 6H), 3.96 (s, 6H), 4.03 (s, 6H), 4.15 (d, *J* = 11.2 Hz, 2H), 4.37 (d, *J* = 11.2 Hz, 2H), 4.89 (m, 4H), 5.72 (s, 2H), 7.07 (m, 4H), 7.13 (s, 2H), 7.22 (m, 6H), 7.42 (m, 6H), 7.60 (m, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 19.9, 37.5, 52.7, 61.6, 64.6, 70.8, 75.5, 77.4, 104.8, 122.0, 122.8, 123.1, 125.0, 128.0, 128.3, 128.7, 129.0, 129.2, 129.4, 132.0, 136.2, 138.6, 139.7, 147.5, 147.9, 151.6, 154.9, 166.5; IR (film) 2927, 1738, 1568, 1452 cm^{-1}; HRMS (ES) calcd for $C_{63}H_{62}O_{14}Na$ (MNa^+) 1065.4037, found 1065.4017.

(*M*)-8,15-Bis(benzyloxy)-10,13-bis((*R*)-2-(benzyloxy)propyl)-1,7,9,14-tetramethoxydinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepine (41). To a chilled (0 °C) solution of **39** (38 mg, 0.0364 mmol) in toluene (2.5 mL) under argon was added DIBALH (1 M in hexanes, 250 μL). The solution was stirred for 30 min and then was quenched with deionized H_2O and extracted with EtOAc. The organic phases were washed with aq NH_4Cl, dried (Na_2SO_4), and the solvent was evaporated to yield a yellow resin, which was carried on to the next step without further purification.

To a solution of the bisbenzyl alcohol in EtOAc (2 mL) was added 2-iodoxybenzoic acid (72 mg, 0.255 mmol). The mixture was heated at reflux under argon until the alcohol was consumed as judged by TLC. The mixture was diluted with EtOAc and filtered through Celite. The solvent was evaporated in vacuo to yield the bisaldehyde as a yellow oil, which was carried on to the next step without further purification.

The bisaldehyde (15 mg, 0.0152 mmol) in diglyme (1.2 mL) was vigorously purged with argon for 30 min. In an inert atmosphere box, an oven-dried microwave tube with a crimp top and Teflon septa was charged with $ClRh(PPh_3)_3$ (30 mg, 0.0320 mmol). The aldehyde solution was added dropwise via cannula to the argon-purged microwave tube containing $ClRh(PPh_3)_3$. The mixture was vigorously purged with argon for 20 min and then was heated at 90 °C for 17 h. The mixture was cooled, diluted with EtOAc, and washed with saturated aq NH_4Cl. The organic phases were dried (Na_2SO_4), and the solvent was evaporated to yield a yellow resin. Purification was accomplished by chromatography (10−25% EtOAc/hexanes) to yield **41** as a yellow resin (11 mg, 71%): [α] −221.7 (*c* 0.3, CH_2Cl_2, >99% ee); IR (thin film) 2927, 1738, 1583, 1460 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.1 Hz, 6H), 2.59 (dd, *J* = 7.1, 14.2 Hz, 2H), 3.02 (dd, *J* = 5.8, 14.2 Hz, 2H), 3.55 (m, 2H), 3.93 (s, 6H), 3.93 (s, 6H), 4.09 (d, *J* = 11.4 Hz, 2H), 4.35 (d, *J* = 11.4 Hz, 2H), 5.01 (m, 4H), 5.70 (s, 2H), 6.79 (s, 2H), 7.08 (m, 4H), 7.13 (s, 2H), 7.22 (m, 6H), 7.38 (m, 2H), 7.44 (m, 4H), 7.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 37.3, 56.1, 61.4, 70.7, 75.7, 76.5, 101.0, 102.9, 118.1, 119.2, 124.3, 127.5, 127.8, 128.0, 128.4, 128.6, 128.6, 131.4, 133.6, 138.4, 138.8, 147.6, 149.8, 151.0, 157.3; HRMS (ESI) calcd for $C_{59}H_{59}O_{10}$ (MH^+) 927.4108, found 927.4069.

Cercosporin (1). To a solution of **41** (5 mg, 0.0054 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added 10% Pd/C (6 mg). The mixture was stirred while purging with H_2 (H_2 balloon). After completion as judged by TLC, the mixture was filtered through Celite, rinsing with EtOAc and CH_2Cl_2. Concentration yielded an unstable bisnaphthol as a brown oil which was used directly in the next reaction.

To a solution of the bisnaphthol in anhydrous THF (1 mL) was added MnO_2 (10 mg, 0.13 mmol). After completion as judged by TLC, the mixture was diluted with EtOAc, filtered through Celite, and concentrated to yield the perylenequinone. Purification was accomplished by chromatography (2.5% $MeOH/CH_2Cl_2$) to yield the perylenequinone as a red resin (3 mg, 100%).

To a solution of the above perylenequinone product (3 mg, 0.00534 mmol) in anhydrous THF (0.5 mL) under an argon atmosphere was added a solution of MgI_2 in Et_2O (0.07 M, 130 μL, 0.0112 mmol). The dark purple mixture was stirred 10 min (until the mixture turned from purple to black), diluted with EtOAc, washed with saturated aq NH_4Cl, and dried (Na_2SO_4). Concentration yielded a red residue, which was chromatographed (1% $MeOH/CH_2Cl_2$) to yield product **1** as a red resin (1.5 mg, 50%): see the Supporting Information for the CD spectrum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.1 Hz, 6H), 2.91 (dd, *J* = 6.1, 13.0 Hz, 2H), 3.39 (m, 2H), 3.54 (dd, *J* = 6.9, 13.0 Hz, 2H), 4.22 (s, 6H), 5.75 (s, 2H), 7.09 (s, 2H), 14.8 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 42.4, 61.4, 68.3, 92.9, 108.5, 109.6, 113.1, 128.2, 130.8, 135.4, 153.1, 163.6, 167.7, 182.0; IR (film) 3398, 2966, 1622, 1583, 1460, 1267 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{27}O_{10}$ (MH^+) 535.1604, found 535.1596.

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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.