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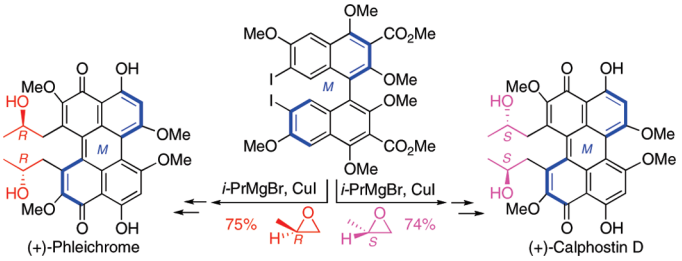
Perylenequinone Natural Products: Total Syntheses of the Diastereomers (+)-Phleichrome and (+)-Calphostin D by Assembly of Centrochiral and Axial Chiral Fragments

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

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

marisa@sas.upenn.edu

Received June 30, 2009



The first total synthesis of (+)-calphostin D and the total synthesis of (+)-phleichrome are outlined. The convergent syntheses utilize an enantiopure biaryl common intermediate, which is formed via an enantioselective catalytic biaryl coupling. The established axial chirality is transferred to the perylenequinone helical stereochemistry with good fidelity. Additionally, efforts focused on the installation of the stereogenic C7,C7′-2-hydroxypropyl groups. Three routes were evaluated to establish the C7,C7′-stereochemistry, in which the successful route involved a double epoxide alkylation with a complex axial chiral biscuprate. This strategy not only allowed the synthesis of the unnatural isomers of calphostin D and phleichrome for assessment in biological systems but also provided valuable information for the syntheses of the more complex cercosporin and hypocrellin A.

Introduction

The natural products **1**−**4** (Figure 1) are representative members of the mold perylenequinones, one of the three major classes of naturally occurring perylenequinones.[1] They are characterized by a helical chiral oxidized pentacyclic core in conjunction with C7,C7′-substitution containing centrochiral stereocenters. Calphostin D ($R^1 = R^2 = H$, **1d**) and phleichrome (**2**) are the simplest of this growing class of natural products. Calphostin D (**1d**) is accompanied in nature by its substituted counterparts: calphostin A ($R^1 = R^2 = COPh$, **1a**), calphostin B ($R^1 = H$, $R^2 = COPh$; **1b**), and calphostin C ($R^1 = COPh$, $R^2 = CO_2$(*p*-OH-Ph); **1c**). The pigments **1a**−**d** and **2** are isolates of the *Cladosporium fungi*, specifically *Cladosporium cladosporioides* (**1a**−**d**) and *Cladosporium phlei* (**2**).[2,3] The more architecturally complex perylenequinones cercosporin (**3**)[4] and hypocrellin A (**4**)[5] have also been isolated from different fungi.

From a synthetic viewpoint, **1**−**3** contain the same stereochemical elements − helical chirality and stereogenic C7, C7′-2-hydroxypropyl groups. Prior to our investigations, the total syntheses of the calphostins and phleichrome were reported involving diastereoselective biaryl couplings.[6] Unfortunately, the chiral naphthalenes provided only modest

(1) Perylenequinone reviews: (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) (a) Kobayashi, E.; Ando, K.; Nakano, H.; Iida, T.; Ohno, H.; Morimoto, M.; Tamaoki, T. *J. Antibiot.* **1989**, *42*, 1470–1474. (b) Iida, T.; Kobayashi, E.; Yoshida, M.; Sano, H. *J. Antibiot.* **1989**, *42*, 1475–1481.

(3) Yoshihara, T.; Shimanuki, T.; Araki, T.; Saramura, S. *Agric. Biol. Chem.* **1975**, *39*, 1683–1684.

(4) (a) Kuyama, S.; Tamura, T. *J. Am. Chem. Soc.* **1957**, *79*, 5725–5726. (b) Kuyama, S.; Tamura, T. *J. Am. Chem. Soc.* **1957**, *79*, 5726–5729.

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

(6) (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.

Published on Web 11/09/2009 DOI: 10.1021/jo901384h

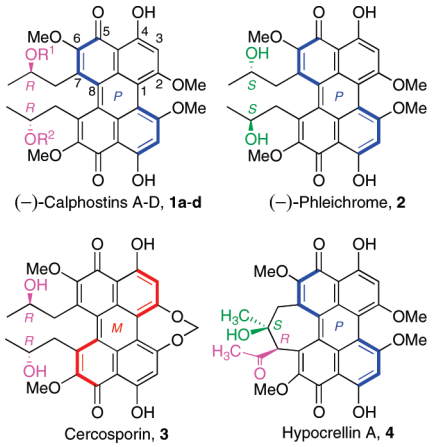
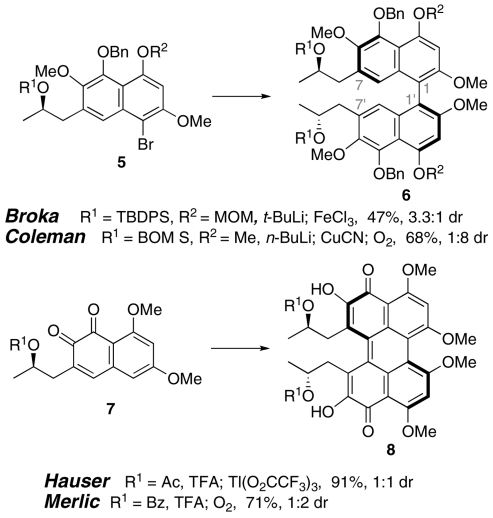


FIGURE 1. Representatives of the naturally occurring mold perylenequinones.

stereocontrol during the dimerizations (Scheme 1).[7] Furthermore, **3** with the opposite helical chirality and an additional seven-membered ring remained a target that would be difficult to access via the reported approaches. The synthetic challenge of **3** centers on the bridging seven-membered ring, which lowers the atropisomerization barrier such that significant atropisomerization occurs at 37 °C.[8]

SCHEME 1. Diastereoselective Dimerization to the Calphostins



As such, we pursued a flexible strategy that would permit stereoselective synthesis of any stereoisomer of the calphostin/phleichrome framework for biological evaluation and provide an entry into the more complex **3**. In this paper, we describe the evolution of the total synthesis of *ent*-**2** and *ent*-**1**, with the main focus being the stereoselective installation of the C7,C7′-2-hydroxypropyl groups.

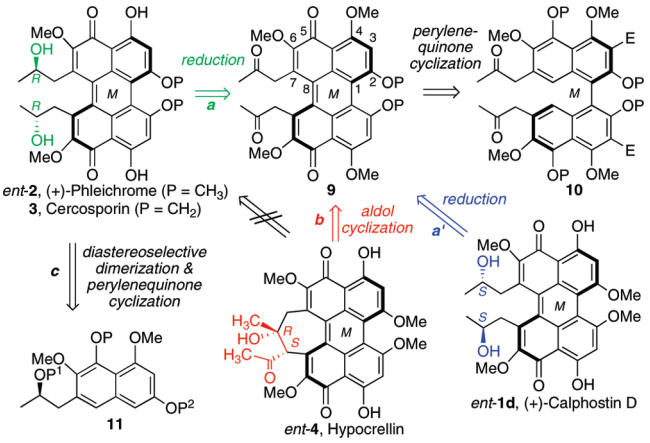
(7) In all of the prior approaches the C7-stereochemistry was generated first and was followed by a diastereoselective coupling (moderate selectivity) of the chiral naphthalene. Additionally, the predominant diastereomer does not generally correspond to the expected calphostin array, although it does match that needed for phleichrome.

(8) Nasini, G.; Merlini, L.; Andreetti, G. D.; Bocelli, G.; Sgarabotto, P. *Tetrahedron* **1982**, *38*, 2787–2796.

Results and Discussion

Retrosynthetic Analysis. We sought a synthetic strategy to permit a flexible approach to all the perylenequinone natural products **1**−**4** (Figure 1). In the previous installment of this series (DOI 10.1021/jo9013832), we described the synthesis of helical chiral perylenequinones absent any centrochiral stereocenters. The synthesis employed an enantioselective biaryl coupling to establish the axial chirality from which the corresponding helical stereochemistry was generated with complete stereocontrol. Having shown with this work that compounds such as helical chiral **9** are configurationally stable, we proposed that such an intermediate could be employed in a biomimetic synthesis of *ent*-**1**, *ent*-**2**, **3**, and **4**. Specifically, reduction of intermediate **9** directed by the helical axis would furnish *ent*-**2** and **3** (path *a*) while chelate-controlled reduction would provide *ent*-**1d** (path *a*′). Furthermore, a transannular aldol reaction would access hypocrellin *ent*-**4** (path *b*). This proposal would circumvent the moderate selectivities encountered in the establishing the axial/helical stereochemistry in prior approaches (Scheme 1, Scheme 2, path *c*).[9] Furthermore, there is no direct means to generate hypocrellin (*ent*-**4**) via the strategy in path *c*; oxidation of the alcohols would be required resulting in loss of their stereochemical information.

SCHEME 2. Retrosynthetic Analysis of Calphostins

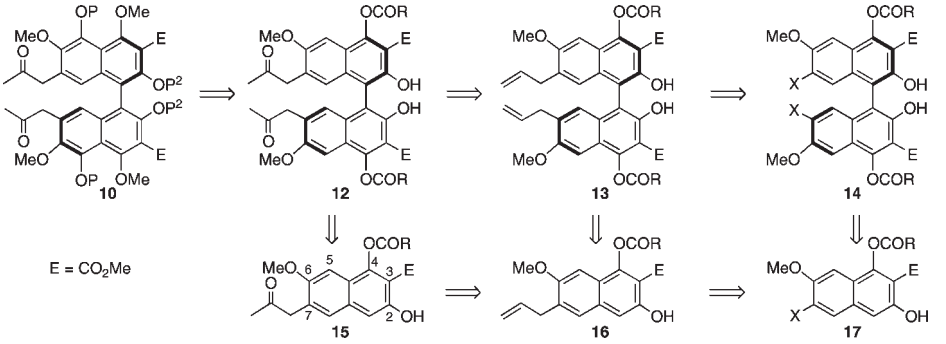


Catalytic Enantioselective Oxidative Binaphthol Coupling. Thus, we began our efforts toward (+)-calphostin D (*ent*-**1d**) and (+)-phleichrome (*ent*-**2**) by devising a synthesis of chiral binaphthalene **10** in order to prepare **9** (Scheme 2). Previously, we had discovered that diaza-*cis*-decalin catalyst **28** (Table 1) was effective in the coupling of functionalized 2-naphthols and determined the optimal substitution patterns to generate products with high yield and selectivity.[10] With these constraints in mind, **15**−**17** illustrated in Scheme 3 were anticipated to be suitable substrates. Binaphthol coupling as

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

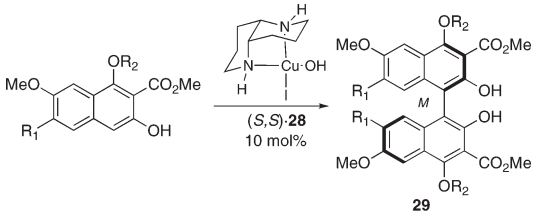
(10) (a) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137–1140. (b) Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513–4522. (c) Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2168–2170. (d) Mulrooney, C. A.; Li, 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.

SCHEME 3. Potential Binaphthol Coupling Substrates



late as possible (i.e., **15**) was desirable as the monomers were simpler to manipulate than the corresponding dimers. To determine the optimal pathway in Scheme 3, a series of substrates was synthesized and examined in the asymmetric catalytic naphthol coupling.

TABLE 1. Biaryl Coupling with Diaza-*cis*-decalin Catalyst Complex 28 under O_2

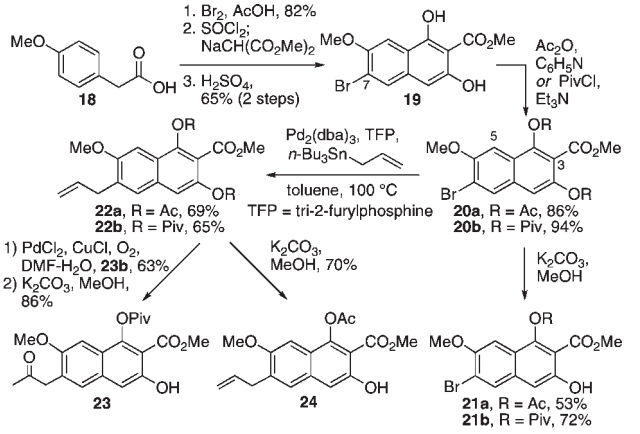


Entry	R_1	R_2	Conditions	Product	Yield, ee
1	H	Ac	$ClCH_2CH_2Cl$, 40 °C, O_2, 48 h	**a**	71%, 86% ee
2	Br	Ac	MeCN, 40 °C, O_2, 18 h	**b**	67%, 81% ee
3	Br	Piv	MeCN, 40 °C, O_2, 48 h	**c**	60%, 71% ee
4	I	Ac	$ClCH_2CH_2Cl$, 40 °C, O_2, 48 h	**d**	<10% (conv)
5	I	Ac	$ClCH_2CH_2Cl$:MeCN (1:1), rt, O_2, 48 h	**d**	<20%, 80% ee
6	I	Ac	MeCN, rt, O_2, 48 h	**d**	81%, 80% ee (1 trituration, >99% ee)
7		Ac	MeCN, rt, O_2, 48 h	**e**	94%, 85% ee
8		Ac	MeCN, rt, O_2, 24 h	**f**	<25%

Commercially available *p*-methoxyphenylacetic acid (**18**) was subjected to regioselective bromination, acid chloride formation, condensation with dimethyl malonate, and Friedel−Crafts cyclization to afford **19** (Scheme 4).[11] The bromonaphthalenediol **19** was protected as the bisacetate **20a**, using acetic anhydride and pyridine, and as the bispivalate **20b**, using pivaloyl chloride and triethylamine. In the first branch point of the naphthol syntheses, selective removal of the less sterically encumbered C2-acyl groups supplied the coupling substrates **21a** and **21b**.

In the previous paper of this series (DOI 10.1021/jo9013832), the failed synthesis of **22a** via cyclization of C3-allylated-**18** was attributed to the instability of the allyl

SCHEME 4. Synthesis of Naphthol Coupling Substrates



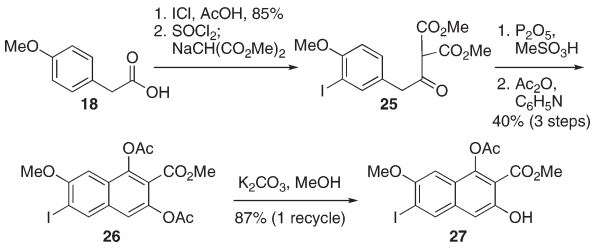
group to the Friedel−Crafts cyclization conditions. However, installation of the allyl group after formation of the naphthalene proceeded readily. While the bromo-substrates **20a**,**b** performed poorly in Suzuki couplings, Stille coupling with allyl tri*n*-butyltin provided the desired C7-allyl naphthalenes **22a** and **22b** in suitable yields (Scheme 4). An efficient selective deprotection of the C2-acetate yielded the allyl coupling monomer **24**. A Wacker oxidation of **22b** afforded the ketone in 63% yield, and after removal of the C2-pivalate, the crucial ketone naphthol **23** was provided.

Because substrates with C7,C7′-halogens provide a readily convertible scaffold, the C7-iodonaphthol[12] was examined in addition to the C7-bromo variant. Beginning with the use of iodine monochloride as the halogen source (Scheme 5), the route mirrors that of bromonaphthol **20a** (Scheme 4). Though the syntheses are comparable, significant differences were noted in the Friedel−Crafts cyclization step. The use of sulfuric acid with the iodo analogue **25** provided none of the desired product, whereas these conditions efficiently afforded bromo analogue **19**. For the more sensitive iodo analogue, P_2O_5 in methanesulfonic acid proved essential in the cyclization, although small amounts of byproduct were still observed. The overall yields to the diacetates are slightly less for the iodo (40%) vs the bromo (53%) series; however, the iodo substrate provided advantages at later stages (see below).

(11) Morgan, B. J.; Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem.* **2007**, *72*, 6171–6182.

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

SCHEME 5. Synthesis of Iodonaphthol Biaryl Coupling Monomer



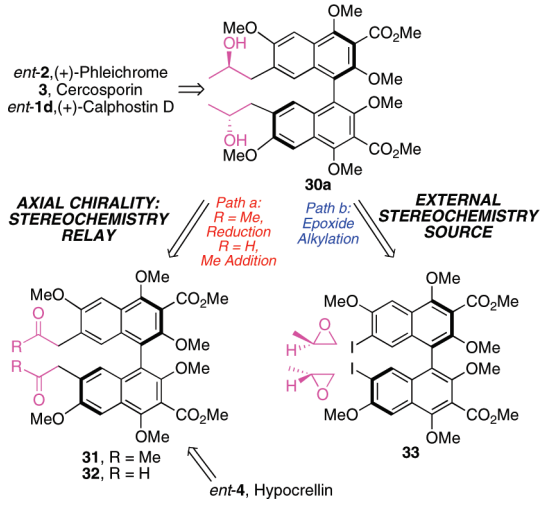
Employing the optimized conditions (40 °C under oxygen for 48 h), the biaryl coupling screening results for the above substrates are collected in Table 1. As expected, substrates with the electron-withdrawing bromo substituent reacted more slowly compared to reported substrate **29a** (entry 1).[10d] Rates improved with acetonitrile as a solvent in place of dichloroethane such that bromo analogue **29b** was obtained with good yield (67%) and selectivity (81% ee) (entry 2). Replacement of the C4-acetoxy group with the more stable pivaloyl group was promising but would require further optimization due to lower yield and selectivity (entry 3). With iodo substrate **27**, the standard coupling conditions again provided low conversion (entry 4). Use of a mixed solvent system (1:1 dichloroethane/acetonitrile) resulted in some improvement in yield and good enantioselection (entry 5). Due to substrate solubility, acetonitrile alone was initially not considered, but reaction at lower concentrations for a longer period of time (2 days) afforded **29d** in 81% yield and 80% enantioselectivity (entry 6). Further attempts to increase selectivity were halted when it was discovered that the high crystallinity of **29d** could provide >99% ee material in one trituration with excellent mass recovery. In a final comparison of the bromo and iodo derivatives, this property rendered the synthesis of highly enantioenriched material with iodobiaryl **29d** more efficient even though the yields in the synthesis of iodonaphthol substrate **27** were somewhat lower than that of the corresponding bromonaphthol **21a**.

The best results for the asymmetric biaryl coupling were obtained with the allylated naphthol **24** to provide **29e** in good yield (94%) and enantioselectivity (85%) (entry 7, Table 1). Enantiopure material could be obtained, but unlike the iodo analogue **29d**, multiple triturations had to be employed. The survival of the oxidatively sensitive allyl group speaks to the compatibility of the coupling conditions with most functionality. Unfortunately, this generalization did not hold true with the corresponding ketone (2-oxopropyl) substrate (entry 8), where formation of **29f** was slow and accompanied by significant decomposition. Both enol formation and oxidative enol coupling could compete with the coupling reaction, accounting for these observations.

Stereoselective Generation of the C7,C7′ 2-Hydroxypropyl Groups (Parts I−III). To install the C7,C7′-stereochemistry we desired a synthetic strategy that was both direct and flexible, utilizing intermediates that could lead to all of the natural products **1**−**4**. In the prior syntheses of the calphostins and phleichrome, formation of the stereogenic C7,C7′ 2-hydroxypropyl groups preceded dimerization (see Scheme 1). Since our strategy (Scheme 2) introduces this stereochemical array after coupling, maximum diversity is possible permitting the synthesis of multiple natural products.

Two distinct paths were envisioned (Scheme 6). In path *a*, the axial stereochemistry could be utilized as a relay to control the C7,C7′-stereochemistry. We demonstrated the fidelity of this approach in our synthesis of hypocrellin A,[12] which is detailed in the fifth paper in this series (DOI 10.1021/jo901386d). In applying the strategy to phleichrome, the alcohol stereocenters could be generated in a diastereoselective fashion by either the reduction of diketone **31** (path *a*, R = Me) or the methyl addition to dialdehyde **32** (path *a*, R = H). Alternatively, the stereogenic C7,C7′-substitution could be introduced from an external source, as seen in the epoxide opening of path *b*. The latter approach is attractive in that independent introduction of the C7,C7′-stereochemistry would permit a more facile synthesis of the complete diastereomeric series of **1**, **2**, and **3**. Though the flexibility of path *b* was attractive, we initially investigated the likely biomimetic path *a* (R = Me). Specifically, the breadth of precedent for stereoselective ketone reduction and the interception of a late-stage intermediate (**9**) from the hypocrellin A synthesis led us to investigate the diastereoselective reduction of **31**.

SCHEME 6. Retrosynthetic Paths for Stereogenic C7,C7′-2-Hydroxypropyl Groups



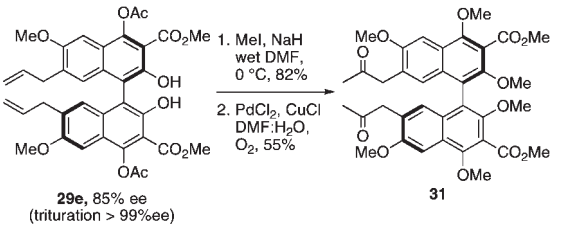
I. Stereoselective Ketone Reductions. The asymmetric reduction of ketones to form chiral secondary alcohols[13] is a common transformation in synthesis that is widely regarded as a "solved problem". However, consideration of the reduction of a diketone **31** to form **30a** reveals problematic aspects still encountered in this methodology. First, the groups flanking the ketone, methyl, and benzyl are sterically similar such that facial bias in asymmetric reductions is difficult. Second, the enolization of benzylic ketones results in low yields. The challenges of the motif can be seen in the approaches to these centers in the prior calphostins syntheses.[6]

To test the viability of the ketone reduction approach, bisketone **31** was employed initially. The allyl biaryl **29e**

(13) For reviews, see: (a) Singh, V. K. *Synthesis* **1991**, 605–617. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (c) Daverio, P.; Zanda, M. *Tetrahedron: Asymm.* **2001**, *12*, 2225–2259.

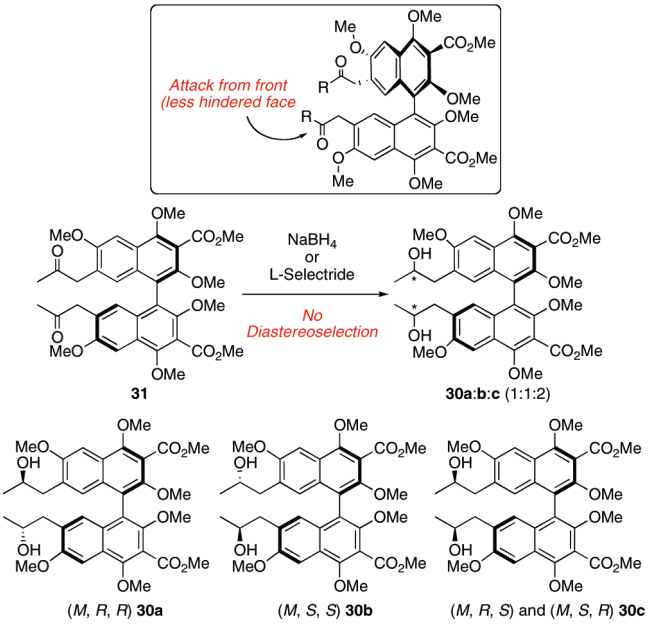
offered the most direct means to the desired bisketone **31**. Following a one-pot deacetylation/methylation, a Wacker reaction provided substrate **31** (Scheme 7).

SCHEME 7. Formation of Diketone Intermediate 31



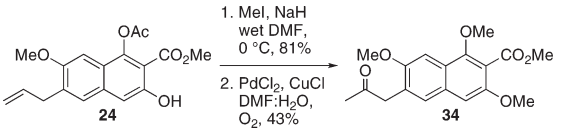
Molecular models (Scheme 8) suggested that the axial biaryl stereochemistry would block one prochiral face of the ketone to allow for a stereoselective approach of an achiral reducing agent. The reductions could provide three diastereomers: (*M*,*R*,*R*)-diastereomer **30a**, (*M*,*S*,*S*)-diastereomer **30b**, and *meso*-(*M*,*R*,*S*)-diastereomer **30c**. Unfortunately, statistical mixtures of the isomers (dr = 1:1:2, **30a**/**b**/**c**; Scheme 8) were obtained using $NaBH_4$ or the larger L-Selectride. Apparently, the biaryl axis is too distant to provide any stereocontrol over approach to the C7,C7′-ketone functionality. This outcome is reminiscent of the prior perylenequinone syntheses,[6] where poor diastereoselectivity was observed due to the distance of the C7,C7′-stereochemistry from the forming biaryl bond (Scheme 1). Furthermore, the free rotation about the aryl−methylene bond would result in conformers where the opposite faces are blocked by the axial chiral biaryl.

SCHEME 8. Attempted Diastereoselective Reductions of 31

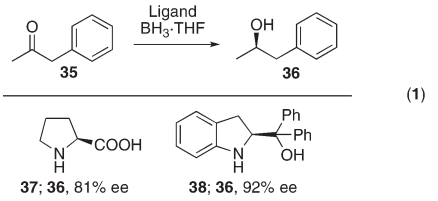


At this point, external asymmetric reducing agents were examined since internal diastereocontrol was absent. In a parallel synthesis to the biaryl counterpart, a deacetylation/methylation followed by a Wacker reaction yielded model naphthalene **34** (Scheme 9) for this study. Due to the similar

SCHEME 9. Synthesis of Ketone Model System 34



steric demands of the methyl and benzyl ketone substituents, the development of asymmetric reductions of arylacetones has been limited. Although **37**[14] and **38**[15] were well precedented for this transformation (eq 1), they were ineffectual with naphthalene **34** (17% and 36% ee), respectively (entries 1 and 2; Table 2). Even the reliable CBS catalyst[16] only provided a modest 50% ee (entry 3). Commercially available amino alcohol **41** was also evaluated but with no improvement to selectivity (entry 4).

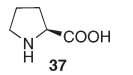
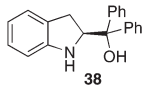
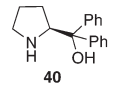
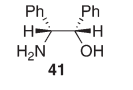
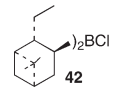
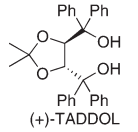
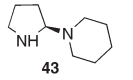
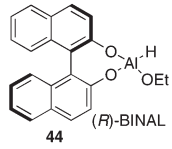
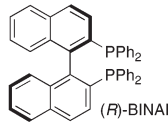
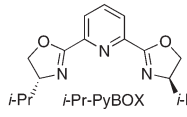


(1)

Other reduction methods including α-pinene borane reagent **42**,[17] (+)-TADDOL/Ti(Oi-Pr)$_4$/catecholborane,[18] pyrrolidinylproline **43**/DIBAL/$SnCl_2$,[19] BINAL **44**,[20] and $RuCl_2$(BINAP)/diphenylethylenediamine/1000 psi H_2[21] provided little or no enantioselectivity with **34** (entries 5−9, Table 2) in spite of strong precedents with related systems. Most surprising was the complete absence of hydrosilylation of ketone **34** with a rhodium−pybox catalyst (entry 10), even though the same catalyst performed well in our hands with the closely related 2-methoxyphenylacetone (82% ee).[22] Both immobilized *Geotrichum candidum* and baker's yeast have been known to reduce phenylacetone in >99% ee.[23,24] Unfortunately, baker's yeast had no effect on our model ketone **34** (entry 11, Table 2), although we successfully reduced acetophenone under the

(14) Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255–2260.
(15) Kim, Y. H.; Park, D. H.; Byun, Y. S.; Yoon, I. K.; Park, C. S. *J. Org. Chem.* **1993**, *58*, 4511–4512.
(16) Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **2002**, *58*, 183–189.
(17) (a) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16–24. (b) Brown, H. C.; Ramachandran, P. V.; Teodorovic', A. V.; Swaminathan, S. *Tetrahedron Lett.* **1991**, *32*, 6691–6694. (c) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Weissman, S. A.; Jadhav, P. K.; Perumal, P. T. *J. Org. Chem.* **1988**, *53*, 5513–5518.
(18) (a) Lindsley, C. W.; DiMare, M. *Tetrahedron Lett.* **1994**, *35*, 5141–5144. (b) Giffels, G.; Dreisbach, C.; Kragl, U.; Weigerding, M.; Waldmann, H.; Wandrey, C. *Angew. Chem., Int. Ed.* **1995**, *34*, 2005–2006.
(19) Mukaiyama, T.; Tomimori, K.; Oriyama, T. *Chem. Lett.* **1985**, 1359–1362.
(20) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716.
(21) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73. and references cited therein.
(22) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500–508.
(23) Enzymatic reduction review: Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, *40*, 1412–1419.
(24) (a) Fronza, G.; Fuganti, C.; Grasselli, P.; Mele, A. *J. Org. Chem.* **1991**, *56*, 6019–6023. (b) Nakamura, K.; Inoue, Y.; Matsuda, T.; Misawa, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2397–2402. (c) Servi, S. *Synthesis* **1990**, 1–25.

TABLE 2. Attempted Enantioselective Formation of 39

Entry	Chiral Ligand/Catalyst	Reaction Conditions	ee
1	 **37**	1 equiv **37** excess BH_3-SMe_2, rt	17% ee
2	 **38**	1 equiv **38** 2 equiv BH_3-SMe_2 toluene, Δ	36% ee
3	 **40**	2 equiv **40** 2 equiv BH_3-SMe_2 THF, rt	50% ee
4	 **41**	2.2 equiv **41** excess BH_3-SMe_2, rt	20% ee
5	 **42**	1 equiv **42** Et_2O, -25 °C-rt	no reduction observed
6	 (+)-TADDOL	(+)-TADDOL, Ti(O*i*-Pr)$_4$, catecholborane	22% ee
7	 **43**	1 equiv **43**, $SnCl_2$,DIBALH	0% ee
8	 **44**	1 equiv **44**	34% ee
9	 (*R*)-BINAP	1 equiv $RuCl_2$(BINAP), diphenylethylenediamine, MeOH, 1000 psi H_2	no reduction observed
10	 *i*-Pr *i*-Pr-PyBOX *i*-Pr	$RhCl_3$(*i*-Pr-PyBOX) $AgBF_4$, Ph_2SiH_2	no reduction observed
11	----------	*Geotrichum candidum* Baker's yeast	no reduction observed

same conditions. Apparently, the additional steric hindrance from the *o*-methoxy group has a profound effect on reactivity with enzymatic catalysts.

Since the best result was obtained with the CBS catalyst **40** (entry 3, Table 2), these conditions were applied to the chiral biaryl **31** (Scheme 8). Unfortunately, only moderate selectivity (dr = 1.3:1.0:2.0, **30a**/**b**/**c**) was observed regardless of which axial antipode (*M* or *P*) was used. These results highlight that benzyl methyl ketone substrates remain a problematic asymmetric reduction class compared to aryl alkyl ketones or even many dialkyl ketones.[13,16,23] At this point, attention was turned to the second strategy in path *a*: stereoselective methyl addition to bisaldehyde **32** (Scheme 6).

II. Asymmetric Aldehyde Alkylation. We initially proposed to use the biaryl axis to direct a diastereoselective methyl addition to **32** (path *a* R = H, Scheme 6), but the lack of stereocontrol observed in the reduction of **31** would likely be problematic in this route as well. Thus, chiral catalysts were surveyed in the enantioselective addition of Me_2Zn to model phenylacetaldehyde **45**. Although the asymmetric addition of dialkylzinc reagents to aldehydes is quite common,[25] few examples have been reported with α-arylacetaldehydes and Me_2Zn,[26] likely due to the challenges surrounding the reaction: (1) the acidity of the aldehyde **45**, making aldol byproduct likely, and (2) the use of the less reactive, more basic $ZnMe_2$ relative to the more common $ZnEt_2$. A survey of several promising catalyst systems from the literature including MIB,[27] more reactive amino alcohol **47**,[28] BINOL titanium complexes,[29] and titanium salen complexes[30,31] (entries 1−4, Table 3) was not promising as aldol byproducts predominated.[32]

Since substrate activation seemed to be crucial, the highly reactive bis(sulfonamide) catalysts,[25,33] which catalyze additions even to less reactive ketones,[34] were assessed. Encouragingly, the bis(sulfonamides) **49a** and **49b** were capable of catalyzing the methyl addition to generate the desired alcohol **46** (41−65% yield, 10−24% ee; entry 5, Table 3). Reducing the amount of Ti(O-*i*-Pr)$_4$ and $ZnMe_2$ did increase the selectivity up to 70% ee but also increased the aldol byadducts. Prior to further optimization, the bis(sulfonamide) catalysts were applied to model naphthalene **52**.

(25) Reviews of organometal additions to carbonyls: (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127–157. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.

(26) Asymmetric examples of alkyl additions to phenylacetaldehyde: (a) Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1733–1738. (b) Dreisbach, C.; Kragl, U.; Wandrey, C. *Synthesis* **1994**, 911–912. (c) Qiu, J.; Guo, C.; Zhange, X. *J. Org. Chem.* **1997**, *62*, 2665–2668. (d) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467.

(27) (a) Nugent, W. A. *Chem. Commun.* **1999**, 1369–1370. (b) Rosner, T.; Seras, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511–2513. (c) Chen, Y. K.; Costa, A. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 5378–5379.

(28) Ianni, J. C.; Annamalai, V.; Phuan, P.-W.; Panda, M.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 5502–5505.

(29) (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236. (b) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651–3655. (d) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699–702.

(30) For reviews, see: (a) Gupta, K. C.; Sutar, A. K. *Coord. Chem. Rev.* **2008**, *252*, 1420–1450. (b) Baleizao, C.; Garcia, H. *Chem. Rev.* **2006**, *106*, 3987–4043. (c) Katsuki, T. *Adv. Synth. Catal.* **2003**, *344*, 133–147. (d) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603–619. (e) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85–93.

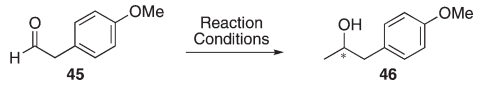
(31) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249–6265.

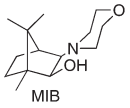
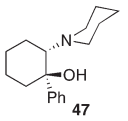
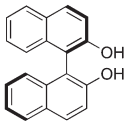
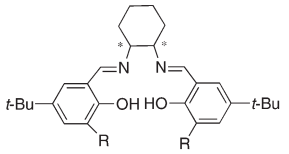
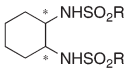
(32) For comparison, the reaction was also run with (±)-MIB and $ZnEt_2$ as the alkylating agent, which provided complete conversion to the alkylated product, pointing to the less reactive, more basic $ZnMe_2$ as the problem.

(33) (a) Takahashi, H; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095–7098. (b) Takahashi, H; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700. For reviews, see: (c) Knochel, P. *Synlett* **1995**, 393–403. (d) Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319. (e) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749.

(34) (a) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971. (b) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544–9545.

TABLE 3. Screening of Catalysts for Me_2Zn Addition to Model Substrate 45

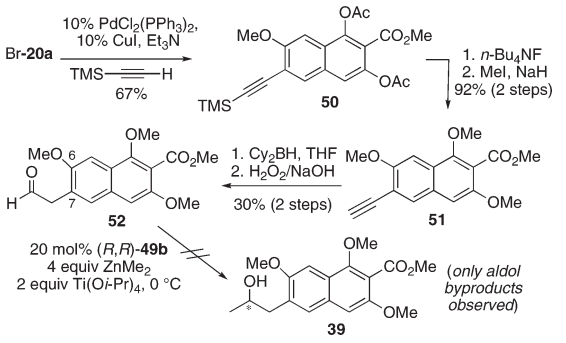


Entry	Chiral Ligand/Catalyst	Reaction Conditions	Yield
1	 MIB	25 mol% (±)-MIB, 2 equiv $ZnMe_2$, 0 °C	0%[a]
2	 **47**	20 mol% **47**, 2 equiv $ZnMe_2$, -40 °C	0%[a]
3	 (*R*)-BINOL	20 mol% (*R*)-BINOL, 2 equiv $ZnMe_2$, 1.2 equiv Ti(O*i*-Pr)$_4$, 0 °C	0%[a]
4	 **48a**, R = *t*-Bu **48b**, R = 	20 mol% (±)-**48a** 2 equiv $ZnMe_2$ 0-1 equiv Ti(O*i*-Pr)$_4$ 0 °C	0%[a]
		20 mol% (±)-**48b** 2 equiv $ZnMe_2$ 0-1 equiv Ti(O*i*-Pr)$_4$ 0 °C	0%[a]
5	 **49a**, R = *p*-Tol **49b**, R = CF_3	10 mol% (±)-**49a** 4 equiv $ZnMe_2$ 2 equiv Ti(O*i*-Pr)$_4$ 0 °C	65%
		10 mol% (*R,R*)-**49b** 2-4 equiv $ZnMe_2$ 1-2 equiv Ti(O*i*-Pr)$_4$ 0 °C	41-65% (10-24% ee)

[a]Complex mixture resulting from aldol byproducts.

Synthesis of naphthalene aldehyde **52** commenced from intermediate **20a**, which was subjected to a Sonagashira coupling to install generate alkyne **50** (Scheme 10). Subsequent tetra-*n*-butylammonium fluoride treatment furnished the terminal alkyne. A one-pot deacetylation/methylation of the C2,C4 phenols was achieved using NaH (60%) and MeI in wet DMF to supply **51** with in high yield. Upon screening a range of hydroboration reagents [bis-*sec*-isoamylborane (Sia_2BH), $BH_3 \cdot THF$, catecholborane, and Cy_2BH], Cy_2BH was found to be the most successful providing **52** after hydrogen peroxide oxidation in low yield (30%). Before further optimization, the alkylation conditions were examined on this substrate. Unfortunately, when the methyl addition with **49b** was attempted only a mixture of aldol adducts were produced. Steric interactions from the C6-methyl ether that is not present in model **45** could account for the inability of the catalyst to activate the substrate, allowing deprotonation of the α-center as the only viable pathway. At this juncture, the difficulties encountered in both routes of path *a* from Scheme 6 stimulated us to investigate the alternate path *b* utilizing an external chiral reagent as a source for the C7,C7′-stereochemical array.

SCHEME 10. Synthesis of Naphthalene Aldehyde 52 and Attempted Asymmetric Alkylation



III. Organocopper Epoxide-Opening. Although we had initially examined biomimetic diastereoselective approaches, the introduction of an independent chiral fragment (path *b*, Scheme 6) presents distinct advantages with respect to convergency. As discussed previously, the use of separate fragments allows facile entry to all diastereomeric combinations of the natural products **1**−**3** including the unnatural isomers. We elected to investigate copper-mediated epoxide openings to achieve this goal. Since the biaryl axis seems to exert minimal stereocontrol over reactions at the C7,C7′-position, the epoxide opening should not be limited to a *matched* case (double diastereocontrol), meaning both the (*R*)- and (*S*)-epoxide can be utilized with equal facility. Prior to this series of papers, we published an overview of this work;[9] Table 4 and the discussion below provide a full report of this chemistry in the calphostin/phleichrome system.[35]

While Grignard-derived cuprates enjoy considerable precedent in epoxide openings,[36] there are few examples of biscuprates being employed in this alkylation. While complex cuprates have been used successfully (eq 2)[37] and simple biscuprates have been employed in epoxide alkylation (eq 3),[38] we could locate no reports of a highly functionalized dianion effecting two ring-openings. Our primary concerns were (1) the metal−halogen exchange on an electron-rich system and in the presence of the C3-methyl esters, (2) the stability of the electron-rich bisarylcuprate, and (3) the use of stoichiometric biscuprate rather than the excess that is typical for cuprate additions. These concerns were assessed by means of several naphthalene

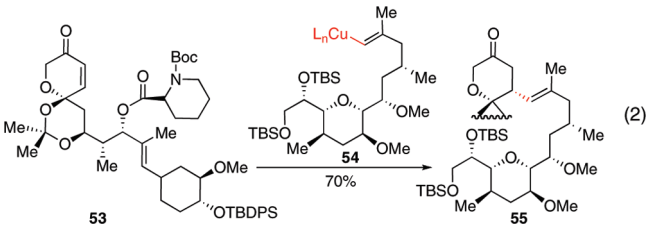
(35) The next paper in this series describes the further evolution of the biscuprates for the cercosporin synthesis. Morgan, B. J.; Mulrooney, C.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75* (DOI: 10.1021/jo9013854).

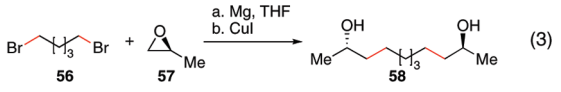
(36) (a) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305–2307. (b) Smith, J. G. *Synthesis* **1984**, 629–656. (c) Sheperd, T.; Aikins, J.; Bleakman, D.; Cantrell, B.; Rearick, J.; Simon, R.; Smith, E.; Stephenson, G.; Zimmerman, D. *J. Med. Chem.* **2002**, *45*, 2101–2111. (d) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711–7714. (e) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3751–3771. (f) Review of organocopper reagents: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(37) (a) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856–6872. (b) Ireland, R. E.; Liu, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221–13256.

(38) (a) Cahill, S.; Evans, L. A.; O'Brien, M. *Tetrahedron Lett.* **2007**, *48*, 5683–5686. For simple bis-Grignard and bis-lithium reagents in epoxide opening, see: (b) Bianchetti, G. *Farm. Ed. Sci.* **1957**, *12*, 441–448. (c) Ghorai, P.; Dussault, P. H.; Hu, C. *Org. Lett.* **2008**, *10*, 2401–2404. (d) Gordon, B. III; Blumenthal, M.; Mera, A. E.; Kumpf, R. J. *J. Org. Chem.* **1985**, *50*, 1540–1542.

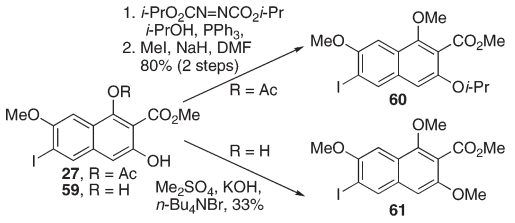
systems, including bismethyl ether **61** and isopropyl ether **60**.[39]





Starting from iodo intermediates, the two naphthalene substrates were synthesized as shown in Scheme 11. Mitsunobu reaction with **27** was used to install the C2-isopropyl ether and was followed by a one-pot deacetylation/methylation to generate **60** in high yield. Methylation of the bisnaphthol **59** with dimethyl sulfate and potassium hydroxide provided the bismethyl ether **61** directly. The low yield (33%) was attributed to a byproduct resulting from the electrophilic methylation of the C1-position.

SCHEME 11. Synthesis of Iodo Substrates



To examine the functional group compatibility of the epoxide-opening reaction, a variety of substrates were evaluated. Bromonaphthalene **20a** formed the Grignard reagent, but only at elevated temperatures, which caused removal of the C2,C4-acetate groups (entry 1, Table 4). While organolithium formation from the iodonaphthalene **26** with *t*-BuLi was unsuccessful due to addition to the C3-ester, the corresponding Grignard reagent was formed readily at low temperatures (−40 °C) using *i*-PrMgBr[40] (entry 2). The attempted cuprate formation and epoxide-opening from this Grignard only resulted in cleavage of the C2,C4-acetates (entry 3). Pleasingly, when the C2,C4-hydroxyl groups were masked as methyl ethers in **61**, the epoxide-opening could be completed in 65% yield with complete regioselection (entry 4).

Since we plan to undertake this same transformation twice on one substrate (65% yield with the monomer would correspond to 43% yield with the dimer), the conditions were optimized further with iodonaphthalene **60**. The initial epoxide-opening with **60** yielded modest amounts of the desired product (40%). Fortunately, the use of rigorously oxygen- and water-free conditions drastically decreased the amount of arene formed, improving the yield of **64** to 77% (entry 5a, Table 4). The use of Et_2O as a solvent (entry 5b) had no effect on the reaction. The use of other copper reagents (CuCN, entry 5c; CuBr, entry 5d) and additives such as TMSCl or HMPA (entries 5e and f) provided lower yields of the desired **64** due to more protodemetalation of the organocopper reagent. Ultimately, careful purification of the CuI by recrystallization proved to be the most important finding, providing **64** in 87% yield (entry 5g). Interestingly, the use of lower temperatures (−78 °C) did not improve the outcome (entry 5h), indicating that the cuprate and product are fairly robust. With isolated yields in the 85% range (entry 5g), acceptable yields (85% × 85% = 72%) were anticipated in the dimeric systems.

The fact that acetate protecting groups were unacceptable in the epoxide opening (entry 3, Table 4) indicated that this key transformation must be conducted after biaryl formation (a C4-acetate is necessary for high selectivity in the biaryl coupling)[10d] in order to reduce the number of protecting group steps. Conveniently, this sequence permits more flexibility in the strategy, allowing the syntheses of **1**−**3** to diverge at a late biaryl intermediate (**33**, Scheme 6). In spite of these advantages, the formation of a functionalized dianionic organocuprate and two epoxide alkylations remained speculative. The success of the transformation relies on the derived biscuprate behaving as two independent cuprates (Scheme 12). If the two entities interact significantly, side products resulting from an intramolecular reaction of intermediate **66** would occur. In spite of these reservations, enantiopure *M*-**29d** was deacetylated and methylated in a one-pot protocol using the previously described conditions (Schemes 7,9) to yield **33** in 94% yield (Scheme 12). With the optimized epoxide-opening conditions, we discovered that (*R*)-propylene oxide reacted smoothly with the biscuprate of **33** providing the target structure **30a** with two new stereocenters in 75% yield as a single diastereomer (two couplings, 81% yield each). Interestingly, the cuprates formed from **65** do appear to act independently since the only byproduct isolated arose from protodemetalation.

First-Generation Approach: Radical Cation C5,C5′-Oxidation and Palladium-Mediated C3,C3′-Decarboxylation. With the stereochemical issue resolved, synthesis of one of the simplest mold perylenequinone natural products, (+)-phleichrome (*ent*-**2**), was undertaken. Our studies commenced with application of the $PhI(OCOCF_3)_2$-induced oxidation[41] of the C5,C5′-positions described in the previous paper of this series (DOI 10.1021/jo9013832) to epoxide-opening product **30a** (Scheme 12). A survey of protecting groups (Me, TBS, Ac, and Bz) on the newly installed C7,C7′-hydroxyl stereocenters revealed that only the benzoate group was able to withstand the reaction conditions to provide **68d** without substantial decomposition (Scheme 13).

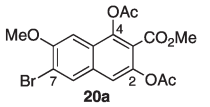
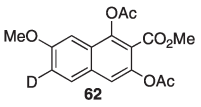
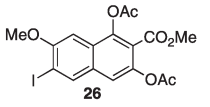
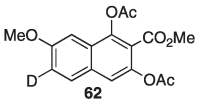
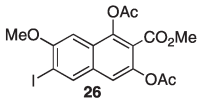
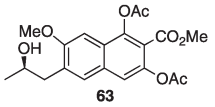
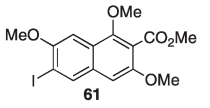
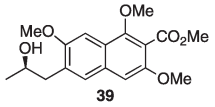
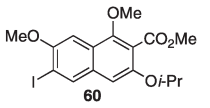
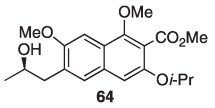
With the necessary oxygenation pattern established, our next task was removal of the C3,C3′-ester groups via decarboxylation of the respective C3,C3′-diacid. Significantly,

(39) A C2,C2′-bis-isopropyl ether was utilized in the epoxide opening in the first-generation synthesis of cercosporin **3**, which is detailed in the next paper of this series (DOI: 10.1021/jo9013854).

(40) For a review, see: Knochel, P.; Wolfgang, D.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Anh Vu, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.

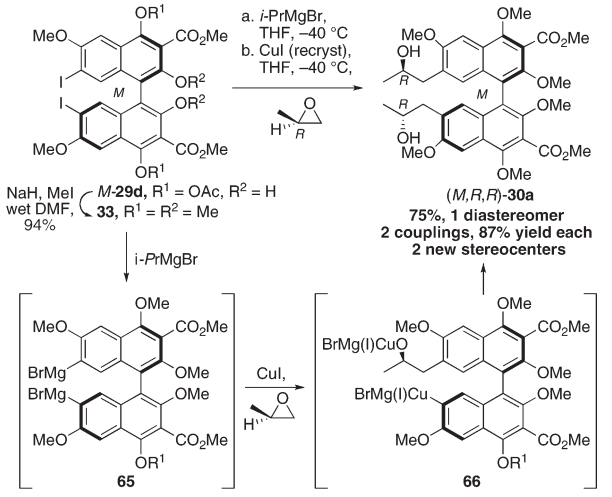
(41) (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691. (b) Arisawa, M.; Ramesh, N. G.; Nakajima, M.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 59–65.

TABLE 4. Screening of Epoxide-Opening Conditions on Naphthalene Substrates

Entry	Substrate	Conditions[a]	Product	Yield
1	 **20a**	*i*-PrMgBr, THF, –40 to 0 °C; MeOD	 **62**	0%[b,c]
2	 **26**	a. *t*-BuLi, THF, –40 °C; MeOD b. *i*-PrMgBr, THF, –40 °C; MeOD	 **62**	a. 0%[b,c] b. >99%[b]
3	 **26**	*i*-PrMgBr, THF, –40 °C; CuI, 	 **63**	0%[b,c]
4	 **61**	*i*-PrMgBr, THF, –40 °C; CuI, 	 **39**	65%[b,c]
5	 **60**	a. *i*-PrMgBr, THF, –40 °C; CuI,  b. *i*-PrMgBr, Et_2O, –40 °C; CuI,  c. *i*-PrMgBr, THF, –40 °C; CuCN,  d. *i*-PrMgBr, THF, –40 °C; CuBr,  e. *i*-PrMgBr, THF, –40 °C; CuI, TMSCl  f. *i*-PrMgBr, THF, –40 °C; CuI, TMSCl/HMPA  g. *i*-PrMgBr, THF, –40 °C; CuI (recryst),  h. *i*-PrMgBr, THF, –78 °C; CuI (recryst), 	 **64**	a. 77%[b] b. 77%[b] c. 50%[b] d. 71%[b] e. 33%[b,c] f. 0%[b,c] g. 87%[b] (85%)[d] h. 87%[b]

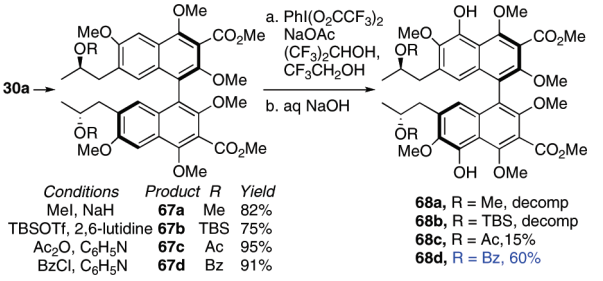
[a]1.25 equiv of *i*-PrMgBr; 0.5 equiv of CuX. [b]Conversion. [c]Remaining yield attributed to dehalogenated arene. [d]Isolated yield in parentheses.

SCHEME 12. Biscuprate Epoxide Opening



the C3,C3′-ester groups served four distinct purposes: (1) coordination to the catalyst during biaryl coupling (Table 1) to enable a highly enantioselective process, (2) stabilization of the highly electron-rich biaryl in the biscuprate epoxide alkylations (Scheme 12), (3) blocking the C3,C3′-position during the C5,C5′-oxidation (Scheme 13), and (4) providing an avenue for C3,C3′-derivatization.[9] As outlined in the previous paper of this series (DOI 10.1021/jo9013832), the lack of success of conventional decarboxylation protocols[42]

SCHEME 13. Screening of Protecting Groups for PIFA Oxidation

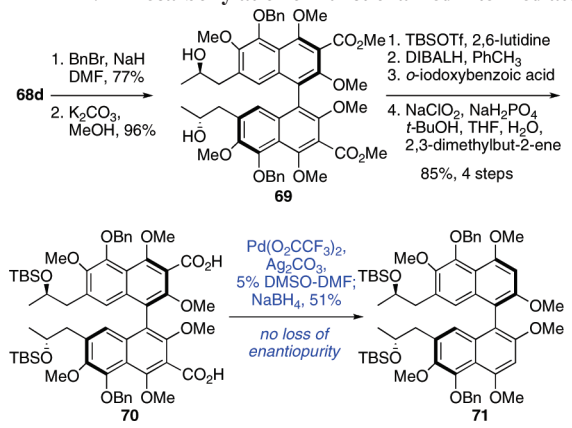


led us to develop a palladium-catalyzed decarboxylation protocol.[12,43] Following benzylation of the bisphenol **68d**, a deprotection/reprotection sequence of the C7,C7′-hydroxypropyl groups was needed to withstand the decarboxylation protocol. Thus, the bisbenzoate was cleaved with K_2CO_3 and MeOH to afford **69**, which was subjected to TBSOTf and 2,6-lutidine to provide the bissilyl ether (Scheme 14). The high temperatures that were needed to saponify the sterically encumbered C3,C3′-ester groups resulted in atropisomerization of the biaryl axis. Consequently, a three-step (reduction/oxidation/oxidation) protocol was used to synthesize diacid **70** in high yield (85% over three steps). The novel palladium-mediated decarboxylation of **70** proceeded smoothly to provide the key intermediate **71** in moderate yield and with no loss of enantioenrichment.[43]

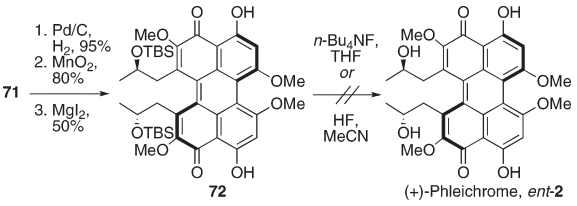
(42) Protic acid protocol: (a) Horper, W.; Marner, F.-J. *Phytochemistry* **1996**, *41*, 451. Copper/quinoline protocol: (b) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189.

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

SCHEME 14. Decarboxylation of Functionalized Intermediate 70



SCHEME 15. Attempted Formation of (+)-Phleichrome



After cleavage of the benzyl ethers, the bisphenol was oxidized by MnO_2 to afford perylenequinone (Scheme 15).[6c,d] The use of MgI_2 allowed for the selective removal of the C4, C4′-methyl ethers yielding **72**.[6b,e,f] However, all attempts to remove the C7,C7′-silyl groups resulted in no reaction or significant decomposition, providing none of the desired *ent*-**2**.[44] Analysis of our initial foray revealed many protection/deprotection steps in addition to the final protecting group problem. Central to these problems was the PhI(OCOCF$_3$)$_2$ (PIFA) oxidation. While the method enabled phenol formation, its incompatibility with most protecting groups (Scheme 13) ultimately restricted and lengthened the synthesis.

Second Generation Approach: Palladium-Catalyzed C5, C5′-O-Arylation and C3,C3′-Decarbonylation in the Total Syntheses of (+)-Phleichrome and (+)-Calphostin D. Though our initial goal was the synthesis of (+)-phleichrome (*ent*-**2**), the use of an external chiral source in the epoxide alkylations (Scheme 12) made a convergent synthesis of the epimers, *ent*-**1** and *ent*-**2**,[9] straightforward (Scheme 16). For the purposes of this discussion, the total syntheses illustrated in Scheme 16 represent the culmination of our synthetic studies and will be used to draw a comparison between the first and second approaches.[45]

The first- and second-generation strategies diverge after the epoxide alkylation of intermediate **33** (Scheme 16). Notably, both (*R*)- and (*S*)-propylene oxide were used to provide the diastereomers (*M*,*R*,*R*)-**73** and (*M*,*S*,*S*)-**73**, respectively, after benzylation of the newly formed alcohol stereocenters. While different rates might be expected due to double diastereodifferentiation (*matched* and *mismatched* cases), no difference in the reaction rate was seen here. The benzyl protection was chosen to minimize protecting group manipulations, since a global debenzylation would be undertaken prior to perylenequinone formation. While such benzyl ethers are compatible with the latter stages of chemistry described above (Scheme 14-Scheme 15), they are not compatible with the key PIFA oxidation (Scheme 13).[46] The only suitable protecting group of the C7,C7′-hydroxypropyl groups for the PIFA oxidation was benzoate which was not viable in the remainder of the synthesis, requiring protecting group exchanges. For these reasons, a new C5, C5′-oxidation route was investigated with benzyl ethers (*M*, *R*,*R*)-**73** and (*M*,*S*,*S*)-**73** (Scheme 16).

In initial work, we had shown that halogenation and lithiation of the C5-position was facile; however, oxygenation did not proceed.[47] In the intervening time, important advances were made in the palladium-catalyzed couplings of aryl halides with oxygen nucleophiles.[48,49] Even though these methods had not been utilized in highly hindered systems as encountered here, we aimed to test their feasibility with our challenging highly functionalized, electron-rich system. To this end, chlorination using sulfuryl chloride readily afforded the aryl chloride substrate (Scheme 16).[45] Optimization of Buchwald's protocol,[48c] involving the catalyst system derived from Pd_2dba_3 and the X-phos(*t*-Bu) ligand, enabled the coupling of the bisaryl chloride with KOH to provide the desired bisphenols. Unfortunately, the same reactions with alkoxides such as benzyl alkoxide were poor. Presumably, the steric hindrance of the reacting position combined with that of the alkoxide disfavors *O*-arylation. However, immediate protection of the unstable bisphenols with benzyl bromide supplied the tetrabenzyl ethers (*M*,*R*,*R*)-**74** and (*M*, *S*,*S*)-**74** in high yield. In comparison to the first generation approach, the new oxidation procedure allowed a more direct and higher yielding route to **74** (Scheme 16). Whereas the electronics of the naphthalenes played a large role in the PIFA oxidation chemistry such that each substrate required optimization, the palladium-catalyzed coupling was surprising general.

The final improvement in the second-generation strategy was the rhodium-mediated decarbonylation protocol utilized in the removal of the C3,C3′-ester groups of (*M*,*R*,*R*)-**74** and (*M*,*S*,*S*)-**74** (Scheme 16). Though the palladium-mediated decarboxylation[43] of diacid **70** (Scheme 14) was an important contribution employed in the synthesis of perylenequinone analogues,[9] an unexpected reaction occurred in this transformation during the cercosporin synthesis.[45] As such, a rhodium-mediated decarbonylation

(44) Broka in ref 6a reported long reaction times (3 d) in cleaving TBDPS ethers (present in the C7,C7′-substitution) of a biaryl similar to **71**. In addition, the oxidative cyclization to the perylenequinone stalled at the hydroperylenequinone when the TBDPS groups were present.

(45) For further details on the optimization of the palladium-catalyzed *O*-arylation and the rhodium-mediated decarbonylation, see the next paper in this series (DOI: 10.1021/jo9013854).

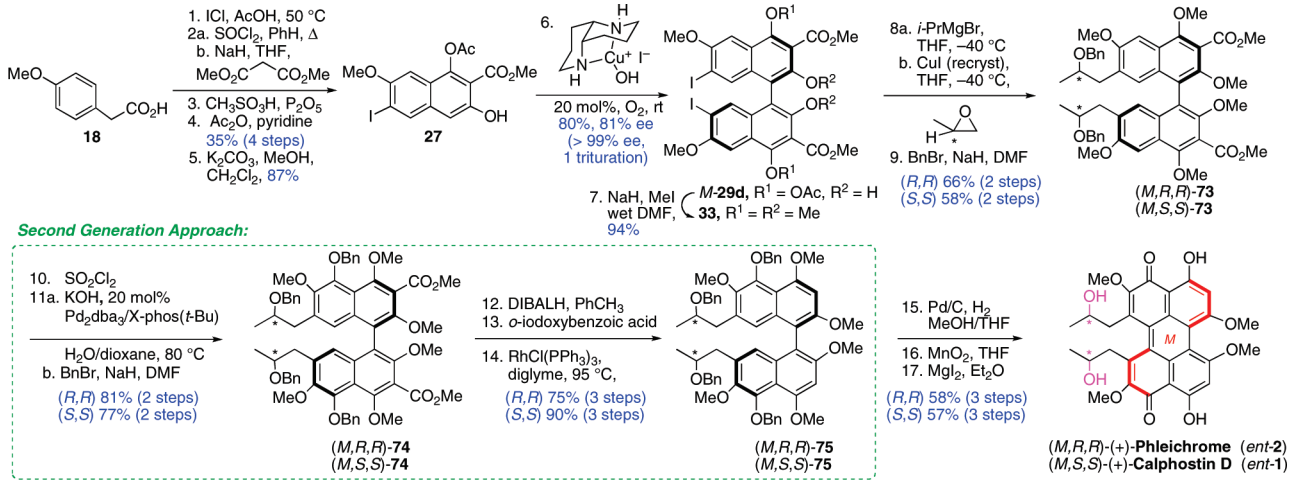
(46) For further details on the sensitivity of different functional groups to PIFA, see the next paper in this series (DOI: 10.1021/jo9013854).

(47) See Scheme 16 in the preceding paper of this series: Mulrooney, C.; Morgan, B. J.; Li, X.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75* (DOI: 10.1021/jo9013832).

(48) 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.

(49) (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110. (b) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771. (c) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566. (d) Vorogushi, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149. (e) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

SCHEME 16. Total Syntheses of (+)-Phleichrome and (+)-Calphostin D



approach was examined. After optimization on several model systems,[45] the (+)-calphostin D (*ent*-**1d**) and (+)-phleichrome (*ent*-**2**) syntheses were used as the penultimate test of the decarbonylation protocol.

The requisite bisaldehydes were generated by reduction to the alcohol using DIBALH and then oxidation with *o*-iodoxybenzoic acid (IBX) (Scheme 16). Pleasingly, treatment with $RhCl(PPh_3)_3$ in diglyme at 95 °C supplied a smooth decarbonylation provided that rigorously oxygen-free conditions were employed. The desired (*M*,*R*,*R*)-**75** and (*M*,*S*,*S*)-**75** were provided with no loss in enantioenrichment and with increased yields of 75% and 90% (cf. **71**, Scheme 14). After global removal of all four benzyl ethers of **75**, the total syntheses of *ent*-**2** and *ent*-**1** culminated with perylenequinone formation and a selective cleavage of the C4,C4′-methyl ethers.

Conclusions

The first total synthesis of (+)-calphostin D and the total synthesis of (+)-phleichrome from commercially available **18** have been developed. The products were generated in 17 steps with overall yields of 5.3% (average of 87% per step) for *ent*-**2** and 5.2% (average of 87% per step) for *ent*-**1**. The syntheses diverge after the first seven steps from enantiopure biaryl (*M*)-**29d**, which is formed via an enantioselective catalytic biaryl coupling. While our initial biomimetic route to the stereogenic C7,C7′-2-hydroxypropyl groups was unsuccessful, invaluable information was gained concerning the challenges surrounding this substitution pattern. Furthermore, weaknesses in current asymmetric ketone reduction and aldehyde alkylation methods have been highlighted providing impetus for further study. Ultimately, a three-component coupling reaction was developed involving the union of a complex axial chiral biscuprate with two equivalents of a centrochiral epoxide. This strategy permitted stereoselective access to both *ent*-**2** and *ent*-**1**. With the centrochiral centers established, the C5,C5′-oxidation evolved from a capricious PIFA reaction to a remarkably robust palladium-catalyzed *O*-arylation. Two strategies, a palladium-catalyzed decarboxylation and rhodium-mediated decarbonylation, were found viable for removal of the C3, C3′-ester functionality to establish the perylenequinone substitution pattern. This investigation not only provided the unnatural isomers of calphostin D (**1**) and phleichrome (**2**) for assessment in biological systems, but also provided valuable information for the syntheses of the more complex cercosporin (**3**)[9] and hypocrellin (*ent*-**4**)[12] which are detailed in the subsequent papers in this series.

Experimental Section

Methyl 1-Acetoxy-3-hydroxy-6-iodo-7-methoxy-2-naphthoate (27). A MeOH (275 mL × 2) and K_2CO_3 (1.4 g × 2, 10.5 mmol) mixture is heated and sonicated to promote salt dissolution and then cooled to 0 °C. To a chilled (0 °C/ice bath) solution of diacetate **26** (6.0 g × 2, 13.1 mmol) in CH_2Cl_2 (110 mL × 2) was added the MeOH/K_2CO_3 mixture. The mixture was stirred at 0 °C for 0.5 h under argon. After being quenched with 1 N HCl, the aqueous phase was extracted with CH_2Cl_2. The organics were washed with brine and dried (Na_2SO_4). After the solvent was evaporated, the residue was recrystallized from hexanes/CH_2Cl_2 to yield **27**. Subsequent reacylation of the filtrate (containing C4-naphthol and C2,C4-diol) and application of the above procedure afforded 9.5 g of **27** in an 84% overall yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.49 (s, 6H), 3.96 (s, 6H), 4.04 (s, 6H), 7.03 (s, 2H), 7.15 (s, 2H), 8.22 (s, 2H), 10.50 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 53.1, 56.2, 94.8, 99.5, 108.2, 109.1, 122.3, 134.1, 137.9, 154.4, 155.3, 168.9; IR (thin film) 2926, 1772, 1729, 1440 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}IO_6$Na (MNa^+) 438.9654, found 438.9643.

(*M*)-Dimethyl-4,4′-diacetoxy-2,2′-dihydroxy-7,7′diiodo-6,6′-dimethoxy[1,1′]binaphthalenyl-3,3′-dicarboxylate (29d). To a solution of **27** (1.7 g, 4.1 mmol) in MeCN (550 mL) was added 20 mol % of CuI·(*S*,*S*)-1,5-diaza-*cis*-decalin catalyst **28** (292 mg, 0.84 mmol). After being stirred for 3 d under oxygen, the solution was quenched with 1 N HCl. The aqueous phase was extracted with EtOAc, and the organics were washed with brine, dried (Na_2SO_4), and concentrated. The resultant resin was chromatographed (50% EtOAc/hexanes) to give **29d** in 81% ee. Trituration from CH_2Cl_2 and hexane (1:5) afforded **29d** in >99% ee as a yellow solid (1.3 g, 80%): $[\alpha]_D^{20}$ +26.5 (*c* 0.5, CH_2Cl_2, >99% ee (*M*)); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.54 (s, 6H), 3.98 (s, 6H), 4.04 (s, 6H), 7.07 (s, 2H), 7.65 (s, 2H), 10.72 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 53.6, 56.6, 96.2, 100.5, 108.7, 113.9, 122.9, 133.8, 136.3, 148.2, 153.3, 154.8, 169.1, 169.6; IR (film) 3096, 2957, 1768, 1671, 1613, 1563, 1478, 1440 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{24}I_2O_{12}$Na (MNa^+) 852.9300, found 852.9250; CSP HPLC (Chiralpak AD, 1.0 mL/min, 80:20 hexanes/*i*-PrOH) t_R (*M*) = 22.0 min, t_R (*P*) = 30.2 min.

(*M*)-Dimethyl 7,7′-Diiodo-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (33). To a solution of **29d** (725 mg, 0.87 mmol) in DMF (25 mL) were added NaH (60% in oil, 1.0 g, 26 mmol) and MeI (1.6 mL, 26 mmol). After being stirred 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 organic fractions were washed with 1 N HCl (3×) and brine (2×). After drying (Na_2SO_4) and concentration, the residue was chromatographed (25% EtOAc/hexanes) to yield **33** as a white foam (660 mg, 94%): $[\alpha]_D^{20}$ −57.4 (*c* 0.5, CH_2Cl_2, >99% ee (*M*)); ^{1}H 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; IR (film) 2945, 1733, 1579, 1463, 1436 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{28}I_2O_{10}Na$ (MNa^+) 824.9669, found 824.9638.

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 being 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 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 7,7′-Bis((*R*)-2-hydroxypropyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (30a). The epoxide-opening was carried out according to the general procedure with **33** (500 mg, 0.623 mmol) and *i*-PrMgBr (1 M in THF, 1.87 mL, 1.87 mmol) in THF (7.0 mL) and CuI (119 mg, 0.623 mmol) in THF (4 mL) and (*R*)-propylene oxide (175 μL, 2.49 mmol). The material was chromatographed (SiO_2, 50% EtOAc/hexanes), and the product **30a** was obtained diastereomerically pure as a white foam (312 mg, 75%): $[\alpha]_D^{20}$ −120.2 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, J = 6.2 Hz, 6H), 1.99 (br s, 2H), 2.37 (dd, J = 8.7, 13.2 Hz, 2H), 2.89 (dd, J = 3.1, 13.2 Hz, 2H), 3.32 (s, 6H), 3.95 (m, 2H), 3.96 (s, 6H), 3.98 (s, 6H), 4.14 (s, 6H), 6.95 (s, 2H), 7.44 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 41.2, 52.8, 55.7, 62.1, 62.9, 67.4, 100.6, 119.9, 120.5, 125.2, 128.5, 130.4, 131.6, 151.7, 153.5, 156.3, 167.6; IR (film) 3313, 2950, 1730, 1591, 1498, 1444 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{42}O_{12}Na$ (MNa^+) 689.2572, found 689.2563.

(*M*)-Dimethyl 7,7′-Bis((*S*)-2-hydroxypropyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate (30b). The epoxide-opening was carried out according to the general procedure with iodo substrate **33** (475 mg, 0.592 mmol) and *i*-PrMgBr (1 M in THF, 1.8 mL, 1.8 mmol) in THF (7.0 mL) at −78 °C and CuI (113 mg, 0.592 mmol) in THF (4.0 mL) and (*S*)-propylene oxide (166 μL, 2.37 mmol). The material was chromatographed (SiO_2, 50% EtOAc/hexanes). Product **30b** was obtained diastereomerically pure as a white foam (292 mg, 74%): $[\alpha]_D^{20}$ −61.4 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 6.2 Hz, 6H), 2.04 (br s, 2H), 2.66 (dd, J = 7.5, 13.5 Hz, 2H), 2.71 (dd, J = 4.6, 13.5 Hz, 2H), 3.32 (s, 6H), 3.88 (m, 2H), 3.97 (s, 6H), 3.98 (s, 6H), 4.13 (s, 6H), 6.97 (s, 2H), 7.45 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 40.4, 52.8, 55.7, 62.1, 62.9, 67.8, 100.6, 119.8, 120.6, 125.2, 128.4, 130.4, 131.3, 151.9, 153.5, 156.3, 167.5; IR (film) 3414, 2950, 1730, 1591, 1498, 1444 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{42}O_{12}Na$ (MNa^+) 689.2572, found 689.2565.

(*M*)-Dimethyl 7,7′-Bis((*R*)-2-(benzyloxy)propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate ((*M,R,R*)-73). To a solution of **30a** (300 mg, 0.45 mmol) in DMF (12 mL) were added benzyl bromide (1.1 mL, 9.0 mmol) and *n*-Bu_4NI (33 mg, 0.090 mmol). NaH (60% in oil, 270 mg, 6.8 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 (*M,R,R*)-**73** as a yellow resin (337 mg, 88%): $[\alpha]_D^{20}$ −103.3 (*c* 0.3, CH_2Cl_2, >99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.1 Hz, 6H), 2.48 (dd, J = 7.1, 13.2 Hz, 2H), 3.00 (dd, J = 5.7, 13.2 Hz, 2H), 3.33 (s, 6H), 3.64 (m, 2H), 3.91 (s, 6H), 3.97 (s, 6H), 4.13 (s, 6H), 4.34 (br m, 4H), 7.03 (s, 2H), 7.11 (m, 4H), 7.22 (m, 6H), 7.40 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 19.9, 38.4, 52.6, 55.8, 61.9, 63.0, 70.5, 74.5, 100.8, 120.7, 121.5, 125.7, 127.7, 128.0, 128.8, 128.9, 130.9, 132.3, 140.3, 152.2, 154.1, 157.3, 167.5; IR (film) 2943, 1738, 1591, 1498, 1452 cm^{-1}; HRMS (ES) calcd for $C_{50}H_{54}O_{12}Na$ (MNa^+) 869.3513, found 869.3480.

(*M*)-Dimethyl 7,7′-Bis((*S*)-2-(benzyloxy)propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate ((*M,S,S*)-73). Bisbenzyl ether (*M,S,S*)-**73** was prepared in the same manner as (*M,R,R*)-**73** and was obtained as a yellow resin (285 mg, 79%): $[\alpha]_D^{20}$ −68.1 (*c* 0.3, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 0.96 (d, J = 6.1 Hz, 6H), 2.61 (dd, J = 5.6, 13.6 Hz, 2H), 2.76 (dd, J = 7.0, 13.6 Hz, 2H), 3.30 (s, 6H), 3.71 (m, 2H), 3.93 (s, 6H), 3.94 (s, 6H), 4.09 (s, 6H), 4.19 (d, J = 12.2 Hz, 2H), 4.32 (d, J = 12.2 Hz, 2H), 7.00 (m, 4H), 7.06 (s, 2H), 7.16 (m, 6H), 7.46 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.0, 39.0, 52.6, 55.8, 61.9, 63.0, 70.6, 74.3, 100.8, 120.7, 121.5, 125.7, 127.7, 127.9, 128.7, 128.9, 130.9, 132.4, 140.2, 152.3, 154.0, 157.2, 167.5; IR (film) 2943, 1738, 1591, 1498, 1452 cm^{-1}; HRMS (ES) calcd for $C_{50}H_{54}O_{12}Na$ (MNa^+) 869.3513, found 869.3517.

(*M*)-Dimethyl 5,5′-Bis(benzyloxy)-7,7′-bis((*R*)-2-(benzyloxy)propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate ((*M,R,R*)-74). Bisbenzyl ether (*M,R,R*)-**73** (30 mg, 0.036 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was treated with SO_2Cl_2 (7.0 μL, 0.089 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 (25% EtOAc/hexanes) to yield (*M,R,R*)-bischloride as a yellow resin (30 mg, 94%): $[\alpha]_D^{20}$ −49.0 (*c* 0.15, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, J = 6.1 Hz, 6H), 2.50 (dd, J = 6.6, 13.6 Hz, 2H), 2.97 (dd, J = 6.4, 13.6 Hz, 2H), 3.35 (s, 6H), 3.59 (m, 2H), 3.84 (s, 6H), 3.97 (s, 6H), 4.01 (s, 6H), 4.25 (d, J = 12.1 Hz, 2H), 4.34 (d, J = 12.1 Hz, 2H), 7.02 (s, 2H), 7.06 (m, 4H), 7.20 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 38.3, 52.9, 60.9, 61.9, 64.8, 70.7, 75.0, 120.7, 122.5, 122.7, 124.4, 127.2, 127.5, 127.6, 128.4, 133.7, 135.2, 138.9, 152.9, 154.6, 154.8, 167.0; IR (film) 2935, 1738, 1591, 1552, 1452 cm^{-1}; HRMS (ESI) calcd for $C_{50}H_{52}Cl_2O_{12}Na$ (MNa^+) 937.2734, found 937.2750.

An oven-dried microwave tube with a crimp top and Teflon septum containing a stirbar was charged with aryl halide (*M,R,R*)-bischloride (120 mg, 0.13 mmol) and KOH (44 mg, 0.79 mmol). In an inert atmosphere box, the substrate-containing microwave tube was charged with Pd_2dba_3 (18 mg, 0.020 mmol) and

Xphos(*t*-Bu) ligand (33 mg, 0.79 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 (1.7 mL) and deionized water (1.2 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 (90 °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 (2.5 mL) and treated with BnBr (300 μL, 2.6 mmol) and NaH (95%, 70 mg, 2.6 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 (*M,R,R*)-**74** as a yellow resin (120 mg, 86% yield): $[\alpha]_D^{20}$ −29.5 (*c* 0.3, CH_2Cl_2, >99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.1 Hz, 6H), 2.50 (dd, J = 6.6, 13.3 Hz, 2H), 2.99 (dd, J = 6.4, 13.2 Hz, 2H), 3.37 (s, 6H), 3.60 (m, 2H), 3.85 (s, 6H), 3.96 (s, 6H), 3.99 (s, 6H), 4.27 (d, J = 12.1 Hz, 2H), 4.36 (d, J = 12.1 Hz, 2H), 5.02 (d, J = 10.0 Hz, 2H), 5.06 (d, J = 10.0 Hz, 2H), 6.93 (s, 2H), 7.07 (m, 4H), 7.18 (m, 6H), 7.40 (m, 6H), 7.61 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 38.2, 52.7, 61.4, 61.9, 64.5, 70.7, 75.4, 76.9, 120.5, 120.6, 123.1, 124.0, 127.5, 127.6, 128.1, 128.4, 128.6, 129.0, 133.4, 135.4, 138.0, 139.1, 146.6, 150.5, 152.3, 154.3, 167.5; IR (film) 2935, 1738, 1591, 1452 cm^{-1}; HRMS (ESI) calcd for $C_{64}H_{66}O_{14}Na$ (MNa^+) 1081.4350, found 1081.4380.

(*M*)-Dimethyl 5,5′-Bis(benzyloxy)-7,7′-bis((*S*)-2-(benzyloxy)-propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl-3,3′-dicarboxylate ((*M,S,S*)-74). (*M,S,S*)-Bischloride was prepared in the same manner as diastereomer (*M,R,R*)-bischloride and was obtained as a yellow resin (215 mg, 99%): $[\alpha]_D^{20}$ −20.0 (*c* 0.15, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.1 Hz, 6H), 2.57 (dd, J = 6.3, 13.6 Hz, 2H), 2.81 (dd, J = 6.8, 13.6 Hz, 2H), 3.31 (s, 6H), 3.68 (m, 2H), 3.84 (s, 6H), 3.98 (s, 6H), 4.02 (s, 6H), 4.22 (d, J = 12.0 Hz, 2H), 4.35 (d, J = 12.0 Hz, 2H), 6.95 (s, 2H), 7.03 (m, 4H), 7.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 38.9, 52.9, 60.9, 61.9, 64.7, 70.7, 74.7, 120.6, 122.5, 122.7, 124.5, 127.4, 127.5, 127.6, 128.4, 133.8, 135.1, 138.8, 153.1, 154.4, 154.8, 166.9; IR (film) 2935, 1738, 1591, 1552, 1452 cm^{-1}; HRMS (ESI) calcd for $C_{50}H_{52}Cl_2O_{12}Na$ (MNa^+) 937.2734, found 937.2726.

Bisbenzyl ether (*M,S,S*)-**74** was prepared in the same manner as diastereomer (*M,R,R*)-**74** and was obtained as a yellow resin (182 mg, 77%): $[\alpha]_D^{20}$ −22.0 (*c* 0.25, CH_2Cl_2, >99% ee); ^{1}H NMR (360 MHz, $CDCl_3$ δ 0.96 (d, J = 6.1 Hz, 6H), 2.56 (dd, J = 6.3, 13.3 Hz, 2H), 2.85 (dd, J = 6.7, 13.3 Hz, 2H), 3.35 (s, 6H), 3.67 (m, 2H), 3.89 (s, 6H), 3.99 (s, 6H), 4.03 (s, 6H), 4.28 (d, J = 12.1 Hz, 2H), 4.38 (d, J = 12.1 Hz, 2H), 5.01 (d, J = 9.9 Hz, 2H), 5.05 (d, J = 9.9 Hz, 2H), 6.86 (s, 2H), 7.05 (m, 4H), 7.19 (m, 6H), 7.37 (m, 2H), 7.44 (m, 4H), 7.61 (m, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.0, 39.1, 52.6, 61.5, 61.8, 64.5, 70.7, 75.0, 77.3, 120.8, 121.4, 124.1, 124.8, 127.8, 128.1, 128.7, 128.8, 129.2, 129.4, 134.0, 136.1, 138.7, 140.2, 147.0, 151.2, 153.1, 154.6, 167.3; IR (film) 2943, 1738, 1591, 1452 cm^{-1}; HRMS (ESI) calcd for $C_{64}H_{67}O_{14}$ (MH^+) 1059.4531, found 1059.4524.

(*M*)-5,5′-Bis(benzyloxy)-7,7′-bis((*R*)-2-(benzyloxy)propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl ((*M,R,R*)-75). To a chilled (0 °C) solution of (*M,R,R*)-**74** (50 mg, 0.047 mmol) in toluene (4 mL) under argon was added DIBALH (1 M in hexanes, 0.4 mL, 0.40 mmol). 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 and 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 (2.5 mL) was added 2-iodoxybenzoic acid (112 mg, 0.40 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 a yellow oil, which was carried on to the next step without further purification.

The bisaldehyde in diglyme (3 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 $ClRh(PPh_3)_3$ (92 mg, 0.0992 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 (*M,R,R*)-**75** as a yellow resin (33 mg, 75%): $[\alpha]_D^{20}$ −10 (*c* 0.25, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, J = 6.1 Hz, 6H), 2.41 (dd, J = 7.3, 13.4 Hz, 2H), 3.06 (dd, J = 5.8, 13.3 Hz, 2H), 3.64 (m, 2H), 3.67 (s, 6H), 3.89 (s, 6H), 3.99 (s, 6H), 4.33 (d, J = 12.0 Hz, 2H), 4.39 (d, J = 12.0 Hz, 2H), 5.06 (d, J = 10.1 Hz, 2H), 5.09 (d, J = 10.1 Hz, 2H), 6.75 (s, 2H), 6.80 (s, 2H), 7.17 (m, 4H), 7.21 (m, 6H), 7.37 (m, 2H), 7.45 (m, 4H), 7.62 (m, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.0, 38.7, 56.3, 56.7, 61.3, 70.8, 75.7, 76.4, 96.5, 112.7, 117.2, 123.7, 127.8, 128.1, 128.2, 128.8, 128.9, 129.0, 134.1, 134.4, 139.8, 140.6, 148.1, 149.2, 155.8, 157.9; IR (film) 2927, 2858, 1645, 1591, 1460, 1336, 1259, 1205 cm^{-1}; HRMS (ES) calcd for $C_{60}H_{63}O_{10}$ (MH^+) 943.4421, found 943.4413.

(*M*)-5,5′-Bis(benzyloxy)-7,7′-bis((*S*)-2-(benzyloxy)propyl)-2,2′,4,4′,6,6′-hexamethoxy-1,1′-binaphthyl ((*M,S,S*)-75). Compound (*M,S,S*)-**75** was prepared in the same manner as diastereomer (*M,R,R*)-**75** and was obtained as a yellow resin (80 mg, 90%): $[\alpha]_D^{20}$ −6.0 (*c* 0.25, CH_2Cl_2, >99% ee); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 0.96 (d, J = 6.1 Hz, 6H), 2.56 (dd, J = 6.0, 13.5 Hz, 2H), 2.76 (dd, J = 6.7, 13.5 Hz, 2H), 3.64 (m, 2H), 3.67 (s, 6H), 3.83 (s, 6H), 4.02 (s, 6H), 4.26 (d, J = 12.2 Hz, 2H), 4.35 (d, J = 12.2 Hz, 2H), 4.99 (d, J = 10.1 Hz, 2H), 5.03 (d, J = 10.1 Hz, 2H), 6.82 (s, 2H), 6.97 (s, 2H), 7.09 (m, 4H), 7.18 (m, 6H), 7.36 (m, 2H), 7.45 (m, 4H), 7.64 (m, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.1, 38.9, 56.3, 56.8, 61.2, 70.8, 75.6, 76.4, 96.7, 112.8, 117.2, 123.7, 127.7, 128.2, 128.3, 128.8, 128.9, 129.0, 134.1, 134.4, 139.8, 140.4, 18.1, 149.2, 155.9, 157.8; IR (film) 2927, 2858, 1730, 1591, 1460, 1336, 1259, 1205 cm^{-1}; HRMS (ES) calcd for $C_{60}H_{63}O_{10}$ (MH^+) 943.4421, found 943.4431.

(+)-Phleichrome (*ent*-2). To a solution of (*M,R,R*)-**75** (10 mg, 0.011 mmol) in THF (0.7 mL) and MeOH (0.7 mL) was added 10% Pd/C (15 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 brown oil which was used directly in the next reaction.

To a solution of the binaphthol in anhydrous THF (1 mL) was added MnO_2 (20 mg, 0.23 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 (5% MeOH/CH_2Cl_2) to yield the perylenequinone as red resin (5 mg, 82%).

To a solution of the above perylenequinone product (1.5 mg, 0.0026 mmol) in THF (1 mL) under an argon atmosphere was added a solution of MgI_2 in Et_2O (0.07 M, 80 μL, 0.0055 mmol). The dark purple mixture was stirred for 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 (5% MeOH/CH_2Cl_2) to yield product *ent*-**2** as a red resin (1 mg, 70%): see the Supporting Information for the CD spectrum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.54 (d, J = 6.1 Hz, 6H), 2.96 (dd, J = 6.3, 12.7 Hz, 2H), 3.42 (m, 2H), 3.61 (dd, J = 6.6, 12.7 Hz, 2H), 4.07 (s, 6H), 4.22 (s, 6H), 6.59 (s, 2H), 15.8 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 42.4, 56.7, 61.7, 68.7, 101.7, 106.1, 117.3, 126.4, 127.3, 135.5, 152.0, 167.0, 173.7, 177.8; IR (film) 3298, 2927, 2858, 1730, 1607, 1452, 1413, 1375, 1267, 1220 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{29}O_{10}$ (MH^-) 549.1761, found 549.1776.

(+)-Calphostin D (*ent*-1d). The perylenequinone *ent*-**1d** was prepared in the same manner as diastereomer *ent*-**2** and was obtained as a red resin (1.3 mg, 57%): see the Supporting Information for the CD spectrum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 6.1 Hz, 6H), 2.92 (dd, J = 8.1 Hz, 13.3 Hz, 2H), 3.54 (dd, J = 3.3 Hz, 13.4 Hz, 2H), 3.74 (m, 2H), 4.05 (s, 6H), 4.22 (s, 6H), 6.54 (s, 2H), 15.9 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 42.5, 56.6, 61.5, 69.3, 101.8, 106.5, 117.9, 125.8, 127.9, 136.3, 151.4, 167.2, 172.4, 179.1; IR (film) 3375, 2927, 2858, 1607, 1522, 1452, 1413, 1282, 1244 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{30}O_{10}Na$ (MNa^+) 573.1737, found 573.1757.

Acknowledgment. We are grateful to the NIH (CA-109164) for financial support. Partial instrumentation support was provided by the NIH for MS (1S10RR023444) and NMR (1S10RR022442). We thank 3D Pharmaceuticals (C. A.M.), Novartis (B.J.M.), Eli Lilly (E.O.B.), and the Division of Organic Chemistry of the American Chemical Society (C.A.M., B.J.M.) for graduate fellowships. We thank Dr. Joseph Kozlowski for helpful discussions regarding the epoxide alkylation chemistry. We acknowledge the work of Michelle Clasquin in the synthesis of starting materials. We thank Virgil Percec for assistance with CD measurements.

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