Synthesis of Helically Chiral Molecules: Stereoselective Total Synthesis of the Perylenequinones Phleichrome and Calphostin A

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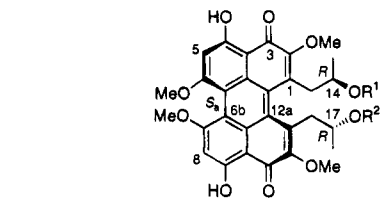
Abstract: The total syntheses of the perylenequinone natural products phleichrome and calphostin A are detailed. The syntheses were based on (1) the *de novo* construction of regiospecifically oxygenated and selectively protected naphthalene subunits, (2) the enantiospecific introduction of the stereogenic side chains using a chiral (α-alkoxyalkyl)-lithium reagent, and (3) a highly atropdiastereoselective Cu(I)-promoted biaryl synthesis for the stereoselective introduction of the helical axis of the calphostins. The total syntheses were achieved in 13 or 14 steps, respectively, with excellent control of absolute stereochemistry.

Introduction

In the course of screening for inhibitors of the enzyme protein kinase C (PKC), a ubiquitous regulatory enzyme important in controlling cellular differentiation and proliferation,[1] Kobayashi and co-workers[2] isolated the calphostin family of natural products from fermentation broths of the phytoparasitic mold *Cladosporium cladosporioides*.[3] The calphostins were demonstrated to be selective inhibitors of PKC,[4] and were found to bind in the regulatory site of the enzyme. Inhibition by calphostin C remains competitive in the presence of excess amounts of enzyme activators, *i.e.*, Ca^{2+} or phospholipids. Specificity is a significant issue in the development of therapeutic agents that inhibit PKC, as most inhibitors of this enzyme show cross-inhibition with other classes of kinases. In contrast, calphostin C (**1c**) has been shown to exhibit greater than 10^3-fold selectivity in the inhibition of protein kinase C when compared with a cAMP-dependent protein kinase or a tyrosine-specific kinase, and therefore represents an exciting new lead in the development of therapeutic agents specifically targeted toward protein kinase C.

Of particular importance to oncology and acquired immunodeficiency syndrome (AIDS) research is the failure of the regulatory site to distinguish between extracellular diacyl glycerol and tumor-promoting agents such as phorbol esters. Activation of PKC has been shown to be the principle mode of action of the tumor-promoting phorbol esters, resulting in unregulated cell growth and gene expression. In addition, researchers have shown that HIV-infected cells will undergo phenotypic changes associated with AIDS upon prolonged activation of PKC, where the enzyme has been demonstrated to play a specific role in the transactivation event in human immunodeficiency virus (HIV) infected T-lymphocytes.[5]



R^1 = COPh, R^2 = COPh — calphostin A **1a**

R^1 = COPh, R^2 = H — calphostin B **1b**

R^1 = COPh, R^2 = CO–⟨⟩–OH — calphostin C **1c**

R^1 = H, R^2 = H — calphostin D **1d**

R^1 = C(=O)–⟨⟩–OH, R^2 = CO–⟨⟩–OH — calphostin I **1e**

The calphostins are members of a family of natural products known as the 4,9-dihydroxy-3,10-perylenequinones, an antibiotic family first established with the isolation of cercosporin (**3**) in 1957.[6] Since then, additional perylenequinones have been isolated (*e.g.*, phleichrome (**2**) from *Cladosporium phlei*),[7] with the latest members being the calphostins. Most examples in this family are mold metabolites, with the exception of the erythroaphins (*e.g.*, **4**), which are isolated from aphids.[8]

The inhibition of PKC by calphostin C is light-dependent and occurs in the presence or absence of oxygen and radical scavengers.[9] The pentacyclic aromatic dione core of perylene-

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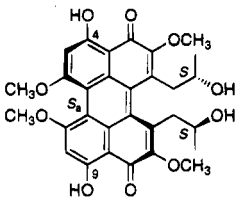
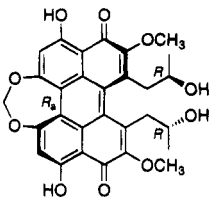
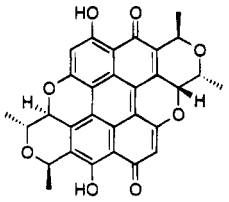


phleichrome (2)

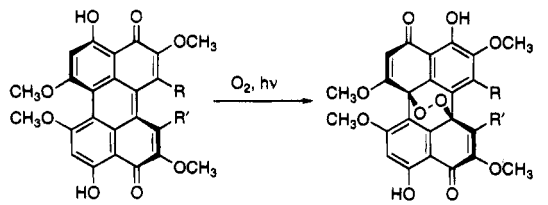


cercosporin (3)



erythroaphin *fb* (4)

quinones generates singlet oxygen upon irradiation in the presence of oxygen. Perylenequinones are among the best $^1O_2$ generators found in nature, with quantum yields as high as 81%.[10] Photoactivation of perylenequinones following their release into plant cells by the producing phytopathogenic mold initiates destruction of various cellular components, either through a reactive perylenequinone-based intermediate or by the action of singlet oxygen.[11] The exact nature of the reactive species is currently unknown,[12] although these pigments are transformed into the corresponding endoperoxides **5** in the presence of light and molecular oxygen.[13] Cytotoxic effects may result when this peroxide collapses to generate singlet oxygen ($^1O_2$). Perylenequinones are being examined as antitumor agents for use in photodynamic therapy (PDT).[14]



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The properties of perylenequinones have been detailed in a review by Weiss *et al.*[11] Many naturally occurring 4,9-dihydroxy-3,10-perylenequinones contain three chirotopic elements.[7] A stereogenic center is typically present in each of the two side chains (both side chains have the same absolute configuration, leading to a C2-axis of symmetry). The corresponding *meso*-perylenequinone—a perylenequinone with an *R*-stereocenter in one side chain and an *S*-stereocenter in the other—has not been reported as a natural product. The third chirotopic element of naturally occurring perylenequinones exists because of a sterically induced twist along the quinoid axis that makes the pentacyclic dione system nonplanar, and hence helically chiral. The twist is induced by steric repulsions between the 1- and 12-side chains and the 6- and 7-methoxy groups, and is approximately 10° as determined by X-ray crystallography.[15] These atropisomers, with axial chirality designated R_a or S_a herein, are noninterconverting at room temperature. The axial configuration of phleichrome (**2**) is S_a, the same as the calphostins, whereas that of cercosporin (**3**) is R_a.

Attainment of atropselection in biaryl systems is a relatively unexplored area of synthesis. Early investigations into atropdiastereoselection by Wynberg with phenoxy radical dimerization of (*S*)-(+)-2-hydroxy-3,4,8-trimethyl-5,6,7,8-tetrahydronaphthalene have demonstrated the elements responsible for atropdiastereoselection.[16] Recent efforts in this area[17,18] have been reviewed.[19]

Earlier synthetic strategies toward perylenequinones centered on the modification of an existing biaryl skeleton. Of particular interest is the work of Dallacker and Leidig,[20] who reported the construction of an oxygenated pentacyclic system from 3,5-dimethoxy-2-iodobenzaldehyde via an Ullmann coupling and a Friedel–Crafts acylation. Later efforts by Chao and Zhang[21] described a remarkable oxidative dimerization where perylenequinone formation occurred directly from the appropriate naphthalene precursor. This protocol was improved by Lown and Diwu[22] and provided the perylenequinone system in greater than 91% yield. The first reported synthesis of the naturally occurring perylenequinones phleichrome and calphostins A and D was achieved in 24 steps by Broka in 1991.[23] In this study, the relative configuration of an axially chiral binaphthalene could be introduced with useful diastereoselectivity (3:1) based on the starting configuration of the bromonaphthalene.[24] More recently, a nonstereocontrolled (stereorandom) 14-step synthesis of calphostin D was reported by Hauser and co-workers.[25]

We have communicated a preliminary account of 13- and 14-step syntheses of phleichrome and calphostin A, respectively, both enantioselective and atropdiastereoselective.[26] Our synthetic strategy was based on (1) the *de novo* construction of regiospecifically oxygenated and selectively protected naphthalene subunits,[27] (2) the enantiospecific introduction of the stereogenic side chains using a chiral (α-alkoxyalkyl)lithium reagent, (3) a highly atropdiastereoselective Cu(I)-promoted biaryl synthesis[28] for introduction of the chiral axis of the

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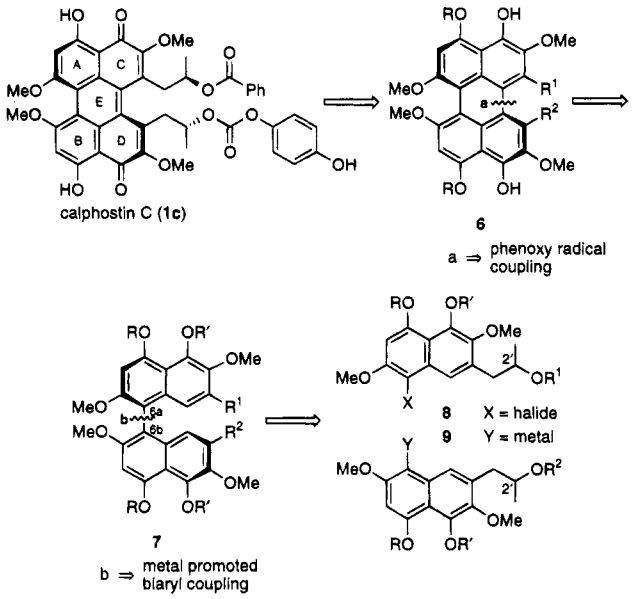
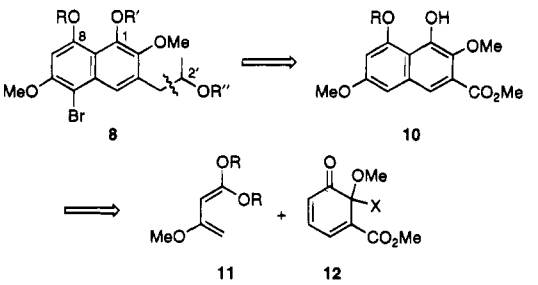
calphostins, and (4) a low-temperature variant of the Mitsunobu inversion reaction[29] for installation of the (2*R*)-2-acyloxy group of the side chains. Herein, we provide full details of our studies on perylenequinone natural products and on the total syntheses of phleichrome (**2**) and calphostin A (**1a**).

Analysis

Typical 4,9-dihydro-3,10-perylenequinone antibiotics such as the calphostins **1** and phleichrome (**2**) contain a C_2-symmetric pentacyclic core suited for development of a highly convergent synthetic strategy. The calphostin family has members that are unsymmetrically substituted, so that a general strategy for the construction of relevant 4,9-dihydroxy-3,10-perylenequinones must address the synthesis of symmetric and unsymmetric systems. In a retrosynthetic analysis of calphostin C (**1c**), reduction affords the perylene **6**. Cleavage of bond **a** will afford the unsymmetric 1,1′-binaphthalene **7**, which can be cyclized to the perylene by an intramolecular *p*-phenoxy radical coupling reaction. Bond **b** of intermediate **7** will be formed by a transition metal-promoted coupling of bromonaphthalene **8** and metallonaphthalene **9**. Thus, bromonaphthalene **8** becomes the key subtarget for the entire synthetic scheme, since metallonaphthalene **9** can be derived directly from **8**.



The 2′-stereogenic center of bromonaphthalene subtarget **8** is the essential stereocontrol element for asymmetric formation of the 6a−6b bond of binaphthalene **7**. Differentiation of the top and bottom halves ($R^1 \neq R^2$) becomes possible through transition metal-promoted *cross*-coupling of the naphthalene subunits. Subtarget **8** will be prepared in a *de novo* manner from napthalenecarboxylate **10** by a two-carbon homologation concomitant with introduction of the remote stereogenic center. The parent naphthalene system will be constructed in a *de novo* manner using a Diels−Alder reaction of 1,3-butadiene **11** and cyclohexadiene **12**,[30] as previously detailed.[27,31] The cornerstones of our synthetic strategy are (1) the preparation of naphthalene **10** using an innovative cyclocondensation between the benzyne equivalent **12** and 1,3-butadiene **11** that is anticipated to occur with complete control of regiochemistry, (2) the cross-coupling of electron-rich, *ortho*-substituted naphthalenes to afford an unsymmetrical 1,1′-binaphthalene, and (3) the introduction of a remote stereogenic center within the aliphatic side chain.



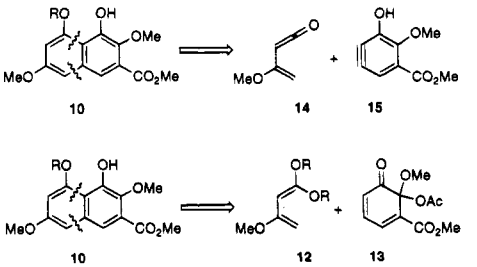
Crucial to our strategy was the choice of the protecting groups, in order that the C1-, C8-, and C2′-hydroxyl groups are orthogonally protected. In particular, the side chain C2′-protecting group must be removable in the presence of both phenol protecting groups, and the C1-hydroxyl group must be unmasked without affecting the C8-hydroxyl group. In the presence of this collection of hydroxyl groups, carefully designed strategies for introduction of protecting groups are essential to maintain synthetic efficiency.

The proposed *de novo* strategy for naphthalene construction centered on an orchestrated aromatization reaction sequence following [4 + 2] cycloaddition reaction between *o*-quinol acetate **13** and 1,3-butadiene **12**. Significant electronic differences between the terminal carbons of the 1,3-butadiene system, combined with the polarization of the enone of the cyclohexadienone, were expected to effect regiochemical control in the Diels−Alder reaction. Cycloaddition of **12** with **13** will afford the hydronaphthalene system **16**. Aromatization of this intermediate will occur by 1,4-elimination of one of the ketal alcohols of **16** to provide **17** and a second 1,4-elimination of acetic acid to afford unstable ketone **18**; a final keto−enol tautomerization of **18** will provide naphthalene **10**.

Cyclohexadienone **13** is a member of a synthetically underutilized quinone monoketal family known as *o*-quinol acetates.[32] Prior use of these *o*-quinone derivatives in cycloadditions has been exclusively as the 4π participant in [4_π + 2_π] reactions.[33] These cyclohexadienones polymerize spontaneously unless the system is substituted at the 3- or 5-position.[34] The

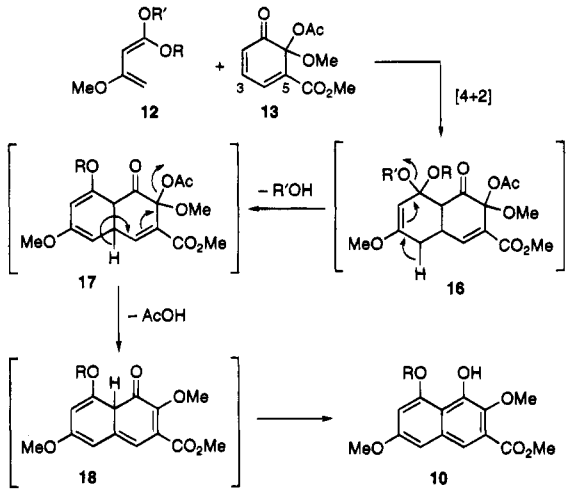
(29) Coleman, R. S., Grant, E. B. *Tetrahedron Lett.* **1994**, *35*, 8341.
(30) Brassard, P.; Savard, J. *Tetrahedron Lett.* **1979**, *20*, 4911.

(31) Formal retrosynthetic disconnection of naphthalene **10** afforded vinyl ketene **14** and benzyne **15**. These reactive intermediates would be difficult to prepare concurrently, and would likely afford regioisomeric mixtures upon cycloaddition. However, this disconnection was reformulated to the stable synthetic equivalents trioxygenated 1,3-butadiene **11** and cyclohexadienone **13**.



(32) To our knowledge, *o*-quinol acetates had not been shown previously to participate as the 2π partner in Diels−Alder reactions. For studies on the participation of *o*-quinones as the 2π partner in [4 + 2] cycloadditions, see: Mazza, S.; Danishefsky, S.; McCurry, P. *J. Org. Chem.* **1974**, *39*, 3610 and references therein.

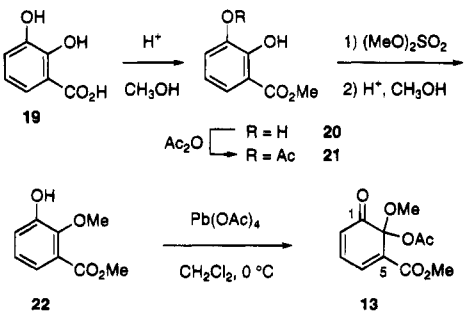
(33) For studies on the participation of 2,4-cyclohexadienones (obtained by Wesseley oxidation of the corresponding phenols) as the 4π partner in [4 + 2] cycloadditions, see: (a) Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1. (b) Carman, R. M.; Owsia, S.; Van Dongen, J. M. A. M. *Aust. J. Chem.* **1987**, *40*, 333. (c) Bichan, D. J.; Yates, P. *Can. J. Chem.* **1975**, *53*, 2054.



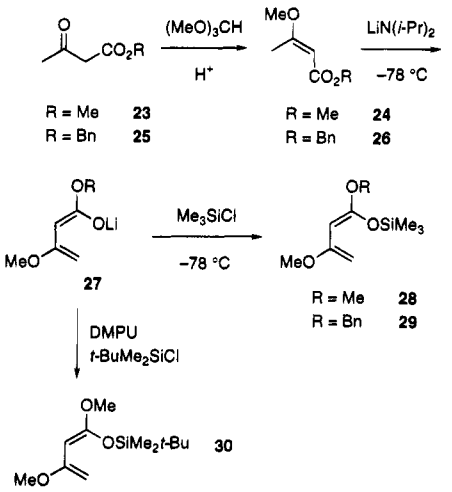
potential for this quinone to participate as the 2π partner in [$4_\pi + 2_\pi$] cycloaddition reactions had not been explored at the time of our studies. Both double bonds of **13** are potential Michael acceptors, although the less sterically crowded 2,3-enone double bond was anticipated to react faster than the 4,5-enoate double bond. The crucial feature in choosing **13** was the C5-ester: (1) it should inhibit polymerization; (2) it is proposed to effect chemoselectivity in the Diels–Alder reaction; (3) it will act as a handle for elaboration of the stereogenic side chains.

De Novo Naphthalene Construction

Cyclohexadienone **13** was prepared from commercially available 2,3-dihydroxybenzoic acid (**19**). Esterification of **19** with acidic methanol, selective acetylation of the less-hindered, more nucleophilic phenol of **20**, O-methylation of the remaining C2-phenol, and deprotection of the *O*-acetate using acidic methanolysis generated the desired monomethyl catechol **22** in 52% overall yield. Wesseley oxidation of **22** with lead tetraacetate afforded methyl 6-acetoxy-6-methoxy-1-oxo-2,4-cyclohexadiene-5-carboxylate (**13**) in 86% yield.[35] Overall, this reaction sequence proceeded in ~50% yield on a multigram scale with a single chromatographic purification.



Brassard and co-workers have used diene **28** in the synthesis of a variety of natural products.[36] Dienes used in our studies were prepared by conversion of methyl acetoacetate (**23**) to the corresponding methyl enol ether **24** with trimethyl orthoformate; metalation with lithium diisopropylamide (LDA) at −78 °C afforded the lithium dienolate **27** (R = Me). Brassard's diene (**28**) was synthesized by trapping dienolate **27** with a chlorotrimethylsilane at −78 °C. Alternatively, the more stable (*tert*-butyldimethylsilyl)oxy diene **30** was prepared by adding 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or hexamethylphosphoramide (HMPA) to dienolate **27** (R = Me) followed by O-silylation with *tert*-butyldimethylsilyl chloride at 0 °C.[37] In a similar manner, starting with benzyl acetoacetate (**25**) and proceeding through the corresponding methyl enol ether **26**, we prepared the benzyl trimethylsilyl diene **29**.



Success in forming the naphthalene ring system was achieved initially by mixing *o*-quinol acetate **13** and butadiene **28** in $CDCl_3$ and monitoring the reaction by ^1H NMR. After extended reaction times (5–7 d), naphthalene **33** was observed as the major adduct. After extensive experimentation,[38] the preparation of naphthalene **33** was optimized by dissolving *o*-quinol acetate **13** in *neat* Brassard's diene (**28**) and allowing the reaction mixture to stand at room temperature for several days. Subsequent treatment of the intermediate cycloadduct that was formed with mild acid (*e.g.*, pyridinium *p*-toluenesulfonate, silica gel) effected aromatization to naphthalene **33**. This cycloaddition/elimination sequence afforded a mixture of the 8-methyl ether **33** and 1,8-dihydroxynaphthalene **32**, where **33** was the major product, indicating that selective elimination of silanol was occurring from intermediate **16**. A systematic study was made by comparing trimethylsilyl and *tert*-butyldimethylsilyl groups and methyl and benzyl esters of the butadiene in reactions with *o*-quinol acetate **13**. The benzyl diene **29** afforded the 8-alkoxynaphthalene **34** in only modest yields, as an unsuitable mixture with **32**. The *tert*-butyldimethylsilyl diene **30** afforded the most useful ratio of **33** to **32**. Naphthalene **33** could be produced as the exclusive product of the reaction of **13** with diene **30** when adventitious water was removed by running the reaction in the presence of 4 Å molecular sieves. Treatment of

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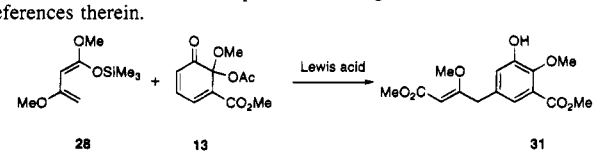
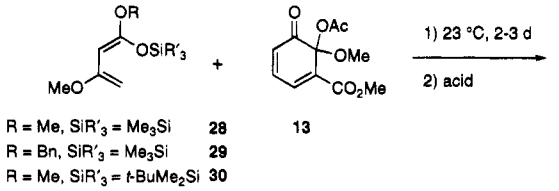
(36) Blouin, M.; Béland, M.-C.; Brassard, P. *J. Org. Chem.* **1990**, *55*, 1466 and references therein.

(37) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

(38) Attempts to promote the cyclocondensation of **28** and **13** using the Lewis acids Et_2AlCl, $BF_3{\cdot}Et_2O$ and $TiCl_4$ in CH_2Cl_2 at −78 °C afforded Michael adduct **31** in high yields. The same product was obtained when **28** and **13** were mixed in THF, acetone, or DMF solution in the absence of Lewis acids at room temperature. Forcing the cyclocondensation by heating a solution of **28** and **13** in toluene effected only rearrangement of the 1,3-butadiene to the corresponding *C*-silyl compound, which was formed in a [1,5]-sigmatopic rearrangement. Diene **28** rearranged upon warming above 50 °C. Midlands, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058 and references therein.

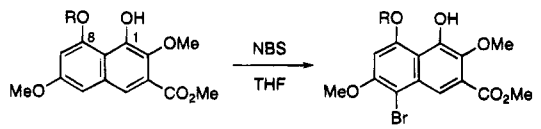


the reaction mixture with silica gel promoted aromatization.[39] After optimization, this protocol allowed for the production of naphthalene with a methyl ether (**33**; $SiR'_3 = SiMe_2t\text{-Bu}$) or benzyl ether (**34**; $SiR'_3 = SiMe_3$) at the 8-position, in modest to good yields. By changing to a 5% aqueous HCl workup, the 1,8-dihydroxynaphthalene **32** could be formed selectively from the Diels–Alder cycloadduct. These results provided a superior simple solution to the problem of selective protection of the 1,8-dihydroxynaphthalene system, as it permitted the incorporation of the alkyl ether from the ketene acetal into the C8-phenol of naphthalene products.



R = Me, $SiR'_3 = Me_3Si$ **28**
R = Bn, $SiR'_3 = Me_3Si$ **29**
R = Me, $SiR'_3 = t\text{-}BuMe_2Si$ **30**

13

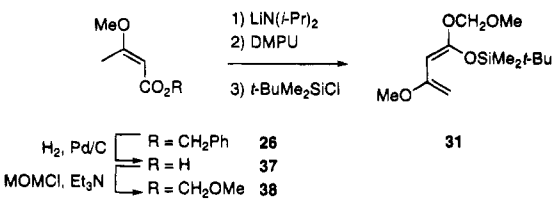


R = H **32**
R = Me **33**
R = Bn **34**

R = Me **36**
R = Bn **37**

Regioselective bromination of **33** and **34** occurred upon treatment with *N*-bromosuccinimide in THF at 0–25 °C, to afford the C5-bromides **36** and **37** in excellent yields. The regiochemistry of the bromination of **33** was clearly evident by the absence of a resonance attributable to C5-H in the ^1H NMR spectrum of bromide **36**.[40]

In a strategy designed to make use of selective elimination of silanol from the intermediate [4 + 2] cycloadduct, a synthesis of naphthalene **35**, protected as the methoxymethyl (MOM) ether at the 8-position, was developed. The necessary methoxymethoxy diene **31** was prepared from benzyl acetoacetate. Hydrogenolysis of the benzyl ester of **26** using a hydrogen over Pd/C catalyst afforded acetoacetic acid derivative **37**. O-Alkylation of the acid **37** with chloromethyl methyl ether in the presence of triethylamine afforded the desired ester **38**. Conversion to the ketene silyl acetal with lithium diisopropylamide and *tert*-butyldimethylsilyl chloride in the presence of DMPU afforded the desired butadiene **31**.



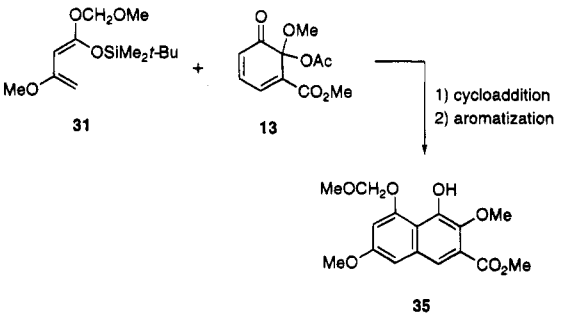
26 **37** **38**

31

(39) Special care needed to be exercised in order to maximize the yield using this workup. Gradient elution chromatography was required since silica gel initiated elimination of the cycloadduct on contact, and the elimination continued as the adduct moved down the column. If the elution strength of the mobile phase was too great or the column had been deactivated (Et_3N), the unaromatized cycloadduct eluted with the solvent front and no elimination occurred. A long elution time was equally detrimental to naphthalene production, as extended exposure to silica gel promoted the destruction of the naphthalene and yields consequently plummeted.

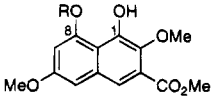
(40) The C5-H resonance of naphthalene **33** was assigned by nuclear Overhauser effect experiments that showed a strong reciprocal enhancement between C4-H (δ 7.77, s) and C5-H (δ 6.42, d, J = 2.2 Hz) of **33** (benzene-d_6, 25 °C). In either experiment, no enhancement of C7-H occurred (δ 6.21, d, J = 2.2 Hz).

Cyclocondensation of diene **31** and acetate **13** was less effective than previous studies with Brassard's diene, and a low yield of naphthalene **35** was obtained. A nuclear magnetic resonance (NMR) study revealed that **31** rearranged to a C-silylated compound over 2 d at 25 °C. The rate of this rearrangement could be effectively decreased if the reaction mixture was cooled to 0 °C, allowing the cyclocondensation to compete with the rearrangement. Cyclocondensation was best accomplished by mixing **13** and **31** (4 equiv) in the presence of 4 Å sieves and anhydrous K_2CO_3 at 0 °C. Silica impregnated with K_2HPO_4 was found to promote aromatization of the intermediate cycloadduct to **35** in 47–51% optimized yield.



31 **13** **35**

In these one-pot reaction sequences, selectively protected naphthalenes **33**–**35** have been prepared in a *de novo* manner from readily available starting materials using a novel Diels–Alder cyclocondensation. This efficient tactic of polyoxygenated naphthalene synthesis is suitable for the preparation of naphthalenes wherein the phenolic C8- and C1-hydroxyl groups are selectively protected, and which are ideally suited for elaboration to perylenequinone systems of interest. The problem of phenol protecting groups had a number of possible solutions, all of which had to meet the requirements of orthogonality, in addition to ease of introduction. For this reason, we chose to examine a range of possibilities in subsequent studies, including benzyl, methoxymethyl, and, less obviously, methyl.



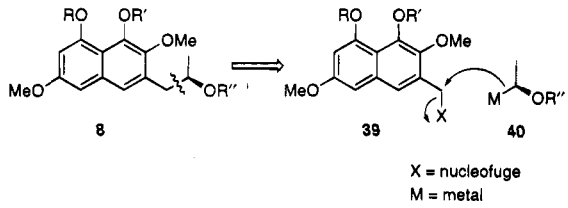
R = CH_3 **33**
R = CH_2Ph **34**
R = CH_2OCH_3 **35**

Installation of the Stereogenic Side Chains

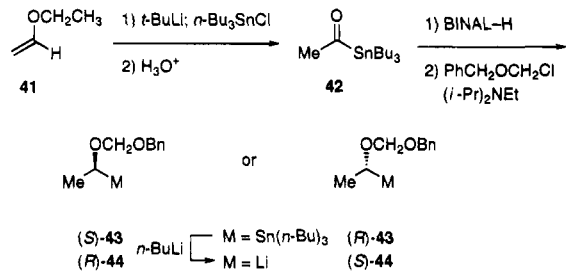
The second major synthetic objective was the conversion of the naphthalene C3-carboxylic ester to the appropriate stereogenic 2-hydroxypropyl side chain. Ideally, this introduction will be executed in a convergent manner, with effective levels of enantioselectivity, to produce either absolute configuration at the stereogenic center. Few methods exist for the enantioselective introduction of a β-aryl alcohol,[41] and most techniques have focused on the asymmetric transformation of a prochiral substrate with an optically active reagent.[42] While methods exist for the enantioselective reduction of prochiral ketones, a majority of these protocols are limited to the reduction of aryl alkyl ketones such as acetophenones or to the asymmetric alkylation of an arenealdehyde to achieve effective levels of enantioselectivity. In accord with this prognosis, Seebach's dialkylzinc asymmetric alkylation[43] was less than effective with phenylacetaldehyde model systems.

(41) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, 1984; Vol. 3, p 411 and references therein.
(42) Evans, D. A. *Science* **1988**, *240*, 240.
(43) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *30*, 1008.

A general and efficient scheme for installation of the stereogenic side chains was developed that was based on the addition of a chiral, enantiomerically pure α-alkoxyalkyl organometallic reagent, **40**, to a benzylic nucleofuge, **39**, to afford **8** directly. (α-Alkoxyalkyl)stannanes provided the elements necessary to execute this strategy. Nonracemic (α-alkoxyalkyl)-stannanes have been prepared by asymmetric reduction of a prochiral acylstannane precursor using the Noroyi BINAL-H reagents.[44] Furthermore, these organostannane reagents can be readily converted to the corresponding organolithium reagents via transmetalation, and chiral (α-alkoxyalkyl)lithium reagents have been demonstrated to undergo addition of electrophiles with retention of stereochemistry.

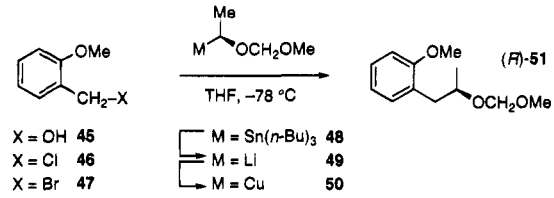


The nonracemic (α-alkoxyalkyl)stannanes (*S*)-**43** and (*R*)-**43** were prepared by a four-step sequence. The prochiral acylstannane **42** was prepared by addition of the anion of ethyl vinyl ether (**41**) to tributyltin chloride, followed by acid-promoted hydrolysis of the enol ether to afford air-sensitive acylstannane **42**. Asymmetric reduction of **42** with (*R*)-BINAL-H or (*S*)-BINAL-H followed by protection of the hydroxy group as the (benzyloxy)methyl (BOM) ether afforded (*S*)-**43** and (*R*)-**43**, respectively, in a greater than 95:5 ratio of enantiomers, as determined by analysis of the corresponding *O*-methylmandelate esters by ^{1}H NMR.[45] The corresponding (*S*)-methoxymethyl (MOM) ether was prepared similarly. Tin−lithium exchange provided the enantiomerically pure organolithium reagents (*R*)-**44** and (*S*)-**44**, respectively. These organometallic reagents maintain the integrity of the stereogenic center at −78 °C and can be converted to higher order cuprate or organocopper reagents.[46]

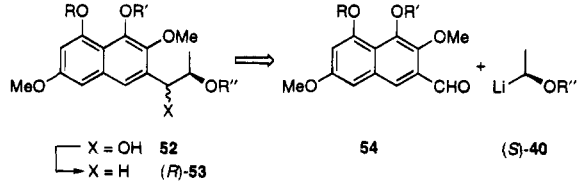


Homologation was examined using the model benzylic electrophiles **46** and **47**, which were prepared from *o*-methoxybenzyl alcohol (**45**). These reagents were treated with alkyllithium reagent (*S*)-**49** (M = Li). Direct alkylation of **46** and **47** with enantiomerically enriched organolithium (*S*)-**49** provided propanol **51** in low yield (10−20%), where the major product was the reduced 2-methoxytoluene. Determination of the optical purity of the alkylated product **51** by removing the alcohol protecting group (HCl, MeOH) and preparing the *O*-methylmandelate ester (DCC, CH_2Cl_2) revealed that the optical purity of **51** was within 5% of that of the starting stannane (by ^{1}H NMR). Even though organolithium **49** underwent substitution with benzylic electrophiles with retention of the stereogenic center, the low yields made this strategy unacceptable.

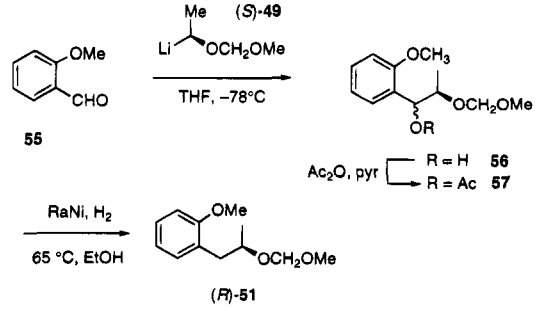
One alternative involved formation of the corresponding organocuprate or organocopper reagent **50**, with the expectation that copper would more effectively participate in the displacement reactions. Alkylation of **47** with the organocopper (1 equiv of CuI, THF, −78 °C) or higher-order cuprate (0.5 equiv of CuCN, THF, −78 °C) of **50** provided the alkylated product **51** as the major product, but as a racemic mixture. In short, these studies determined that the replacement of the benzyl halogen by **46** or **47** was possible, but only in low yields (M = Li) or with complete racemization of the stereogenic center (M = Cu).



The alkylation of aldehydes and carbon dioxide with nonracemic (α-alkoxyalkyl)lithium reagents was demonstrated by Chong and co-workers to occur with retention at the stereogenic center.[47] If naphthaldehyde **54** could be alkylated with enantiomerically pure organolithium reagent (*S*)-**40**, with retention of configuration to afford alcohol **52**, then it should be possible to selectively remove the unnecessary benzylic oxygen[48] to afford (*R*)-**53**.



Anisaldehyde (**55**) was readily alkylated with (*S*)-**49** to afford **56** in good yields. Selective deoxygenation of the benzylic position by Raney nickel-promoted hydrogenolysis of acetate **57**[49] produced (*R*)-**51** in modest yields. The stereogenic center of (*R*)-**51** emerged from this sequence intact.



(44) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *101*, 1481. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584. (c) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647. (d) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830.

(45) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

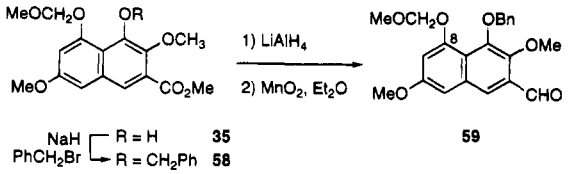
(46) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1990**, *55*, 5428 and references within.

(47) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981. Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985.

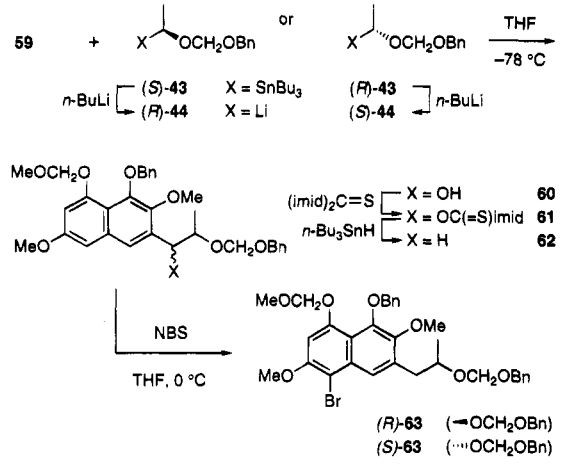
(48) Olah, G. A.; Surya-Prakash, G. K. *Synthesis* **1978**, 397.

(49) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 543.

Application of this homologation methodology to relevant naphthalene systems began with protection of the C1-phenol of **35** with benzyl bromide to give **58**. Conversion of the carboxylic ester of **58** to the corresponding aldehyde by reduction with $LiAlH_4$ and oxidation with MnO_2 afforded **59** in 71% yield.



Both bromonaphthalene enantiomers (*R*)-**63** and (*S*)-**63** were prepared from the corresponding enantiomerically pure stannanes (*S*)-**43** and (*R*)-**43**, respectively, and naphthaldehyde **59**. Alkylation of **59** with the appropriate organolithium (*R*)-**44** or (*S*)-**44** afforded the corresponding benzylic alcohol **60**. Reductive cleavage of the benzylic C−O bond was accomplished using a Barton deoxygenation on the derived thioimidazolide **61**, and provided homologated naphthalene enantiomers (*R*)-**62** and (*S*)-**62**. Determination of the optical purity of **62** by removing the alcohol protecting group (HCl, MeOH) and preparing the *O*-methylmandelate ester (DCC, CH_2Cl_2) revealed that the optical purity of **62** was within 5% of that of the starting stannane (by ^1H NMR). Regioselective bromination with *N*-bromosuccinimide at 0 °C afforded (*R*)-**63** and (*S*)-**63**.

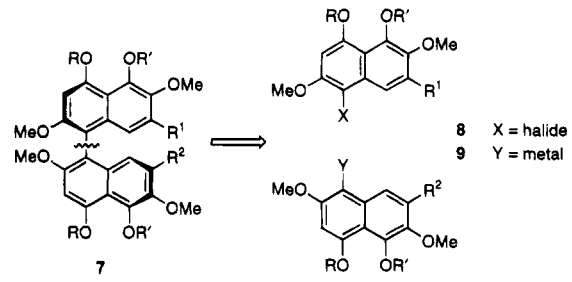


Asymmetric Biaryl Formation

After realization of a *de novo* method for rapid construction of polyoxygenated naphthalenes and a stereospecific method for 2-hydroxypropyl side chain installation, attention was turned to the cross-coupling of halonaphthalene **8** with the corresponding metallonaphthalene **9** for formation of the biaryl bond of 1,1′-binaphthalene **7**. Although this transformation appears late in the overall synthetic strategy, it was recognized as an extremely critical conversion. Biaryl synthesis has become almost routine with the advent of transition metal-promoted cross-coupling methods, but most protocols are limited to the addition of a nucleophilic aryl system to an electrophilic aryl system. Transition metals such as Pd(0) or Ni(0) resist oxidative insertion processes when electron-rich aromatic systems are used.[50] Limitations of transition metal-promoted cross-coupling reactions have been summarized in a review by Bringmann.[19]

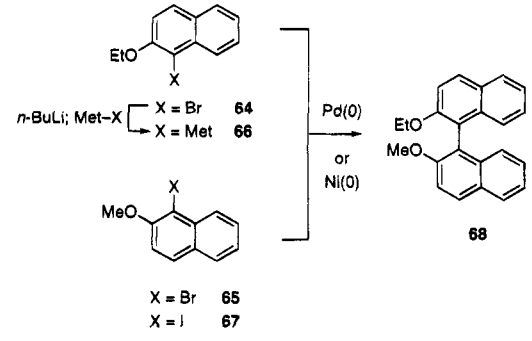
(50) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349 and references therein.

Fe(III)-mediated coupling of lithionaphthalenes related to **9** was achieved by Broka in his synthesis of calphostins A and D.[23]



Perhaps the most important aspect of the Broka study was his demonstration of significant atropdiastereoselectivity in a biaryl coupling reaction of chiral naphthalene systems. This fact provided a potential solution to our goal of stereoselective construction of helically chiral perylenequinones. We anticipated that the stereogenic center in the side chains R^1 and R^2 would effect atropselection in the cross-coupling of naphthalenes **8** and **9**, although the level and absolute sense of stereoinduction was far from predetermined. Before embarking on more complicated systems, we set out to develop methods for cross-coupling of electron-rich naphthalene systems using simple models.

A study of cross-coupling techniques was performed with simple commercially available oxygenated naphthalenes. 1-Bromo-2-hydroxynaphthalene was chosen as the model for these coupling studies, and was converted to its ethyl or methyl ethers **64** and **65**, respectively. Cross-coupling was attempted using metallonaphthalenes **66** such as the corresponding stannane (X = $Sn(n\text{-}Bu)_3$), boronic acid (X = $B(OH)_2$), zinc (X = ZnCl), or magnesium (X = MgBr) reagents with bromonaphthalene **65** or iodonaphthalene **67**. The metallonaphthalenes **66** were prepared by lithiation of **64** via by a lithium−halogen exchange at −78 °C, followed by treatment of the lithionaphthalene with an appropriate metal salt. In this manner, the stannane (X = $Sn(n\text{-}Bu)_3$), boronic acid (X = $B(OH)_2$), and zinc (X = ZnCl) reagents of **66** were prepared. In all cases, palladium(0)- or nickel(0)-promoted cross-coupling of these metallonaphthalenes with halonaphthalene **65** or **67** failed to effect biaryl formation.



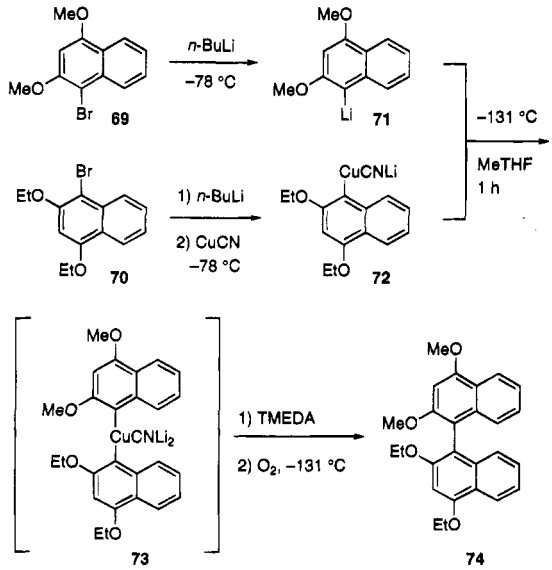
Suzuki's boronic acid protocol[51] with **66** (Met = $B(OH)_2$) with iodonaphthalene **67** in the presence of catalytic palladium(0) and K_3PO_4 in dry dimethyl sulfoxide (DMSO) at 85 °C afforded **68** in a modest 39% yield. The Suzuki protocol, however, was unsuccesful in effecting the proposed cross-coupling with more highly oxygenated aromatic systems (*e.g.*, 2,4-dialkoxy-1-halonaphthalenes), due to competing protodeboration of the intermediate boronic acids caused by increased

(51) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.

electron density from the additional alkoxy group(s). Coupling of the organozinc reagent **66** (Met = ZnCl) and **67** occurred in the presence of hexamethylphosphoramide (HMPA): the slow addition of HMPA to a solution of iodonaphthalene **67** and organozinc reagent **66** in the presence of a Pd(0) catalyst provided binaphthalene **68** in 35−36% yield.

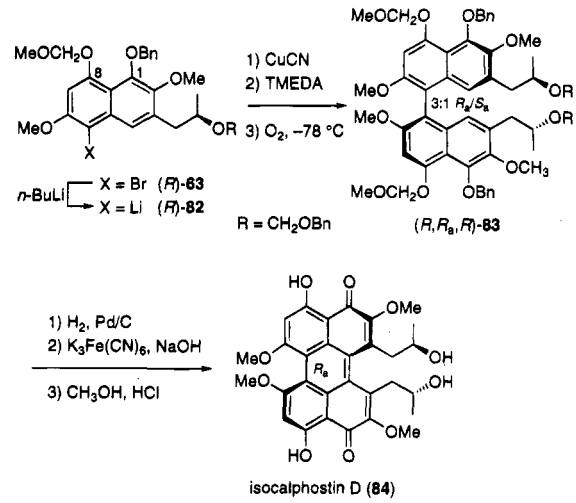
During the course of our investigations on this matter, Lipshutz and co-workers[52] disclosed a Cu(I)-promoted biaryl cross-coupling procedure that proved ideal in our hands[28] when applied to highly functionalized, electron-rich naphthalenes. These researchers reported the low-temperature Cu(I)-promoted cross-coupling reaction where unsymmetrical biaryl compounds could be prepared by the oxidation of a kinetically formed higher-order biaryl cuprate. At low temperature (−125 °C), ligand exchange on copper does not occur and unsymmetrically substituted higher order cyanocuprates can be formed by sequential addition of dissimilar organolithium reagents to CuCN.[53]

Lithiation of bromonaphthalenes **69** and **70** with *n*-BuLi was achieved at −78 °C in 2-methyltetrahydrofuran (MeTHF). The lithionaphthalene of **70** was transferred to a slurry of copper cyanide (1 equiv) in MeTHF to form the cuprate **72**. The reaction mixture was allowed to warm until the solution became homogeneous, and the reaction mixture was cooled to −131 °C ($N_{2(l)}$/ethanol). After several minutes at this temperature, a solution of lithionaphthalene **71** was added and the resulting light yellow solution was allowed to stir for 1 h to form cuprate **73**. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA; 3 equiv) was added, and the reaction mixture was allowed to warm to −100 °C over a 30 min period. The solution of the higher-order cyanocuprate **73** was recooled to −131 °C and was treated with a stream of precooled, dry oxygen. After 1.5 h, the reaction was quenched (NH_4Cl/NH_4OH, 9:1) to afford binaphthalene **74** in 67% yield.



At this point, the question of atropdiastereoselection in the coupling reaction with optically active naphthalenes had not been addressed. Wynberg's study involving tetrahydronaphthalenes and Broka's synthesis of **1a** and **1d** led us to anticipate being able to achieve atropdiastereoselection in our biaryl coupling reaction, although the absolute sense of stereoselection, R_a or S_a, could not be predicted *a priori*. However, since we had easy access to either enantiomer at the side chain stereogenic center, in principle we should be able to access either stereoisomer about the newly created stereogenic biaryl axis. Furthermore, with an effective method for naphthalene cross-coupling in hand, this issue was reduced to the determination of reaction parameters that would provide useful levels of stereocontrol.

Lithiation of (*R*)-**63** with *n*-BuLi at −78 °C via lithium−halogen exchange and addition of the resulting lithionaphthalene (*R*)-**82** to a slurry of CuCN at 0 °C provided the higher-order cyanocuprate. The reaction mixture was recooled to −78 °C and stirred for 1 h, and the cuprate was treated with dry oxygen at −78 °C to promote oxidation and coupling. After purification, a 3:1 ratio of binaphthalene **83** diastereomers was obtained, with the R_a-diastereomer unfortunately the predominate isomer. Confirmation of the R_a-stereoaxis was achieved when **83** was converted to isocalphostin D (**84**) in 25% overall yield by the sequence (1) benzyl and (benzyloxy)methyl protecting group hydrogenolysis, (2) oxidative cyclization with ferricyanide and base, and (3) acetal cleavage with acidic methanol. Although the observed atropdiastereoselectivity about the stereogenic axis obtained with (*R*)-**83** was opposite to that required for synthesis of the calphostins, in theory this problem can be solved by inverting the side chain stereogenic center in the coupling partner, which would necessarily effect diastereoinduction in the desired sense.



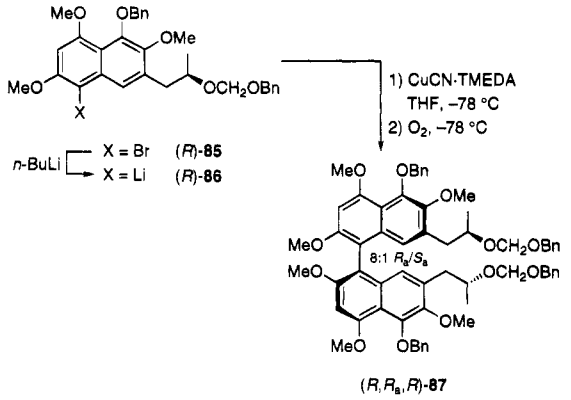
It is necessary to digress from a discussion of biaryl construction to deal with the issue of phenolic protecting groups. In practice, the preparation of the C8 methoxymethyl-protected naphthalene proved difficult to scale-up, and the yields of the cycloaddition reaction with methoxymethoxy diene **31** and cyclohexadiene **13** were at best 45%. The option of using a synthetically more accessible C8-*O*-methyl ether, normally not a readily removable protecting group, seemed to be worth examining because the final perylenequinone product presents the phenolic C8-oxygen as a vinylogous ester. Thus, the normally vigorous conditions needed for removal of methyl ethers potentially would be attenuated.

A modification of the original cuprate coupling reaction conditions was made to simplify the *homo*coupling of bromonaphthalene (*R*)-**85**. The extremely low reaction temperature (−130 °C) necessary to prevent ligand exchange on an intermediate *mixed* biaryl cuprate was no longer necessary, and a solubilized source of CuCN complexed with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was found to signifi-

(52) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161.

(53) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815. Lipshutz, B. H.; Siegmann, K.; Garcia, E. *Tetrahedron* **1992**, *28*, 2579.

cantly increase the coupling yield. After lithiation of (*R*)-**85** via halogen−metal exchange at −78 °C to form (*R*)-**86**, a solution of a preformed CuCN·TMEDA complex (3:1 TMEDA/CuCN) in THF was added to the solution of lithionaphthalene at −78 °C via a cannula. After 1 h, the cuprate was treated with a stream of dry oxygen for 30 min and gave the cercosporin-like (R_a)-binaphthlene **87** in 65% yield as an improved 8:1 ratio of diastereomers. The atropdiastereoselective ratio and coupling yield had been notably increased to useful levels, although the sense of stereoselection remained opposite to that needed for synthesis of phleichrome and the calphostins.

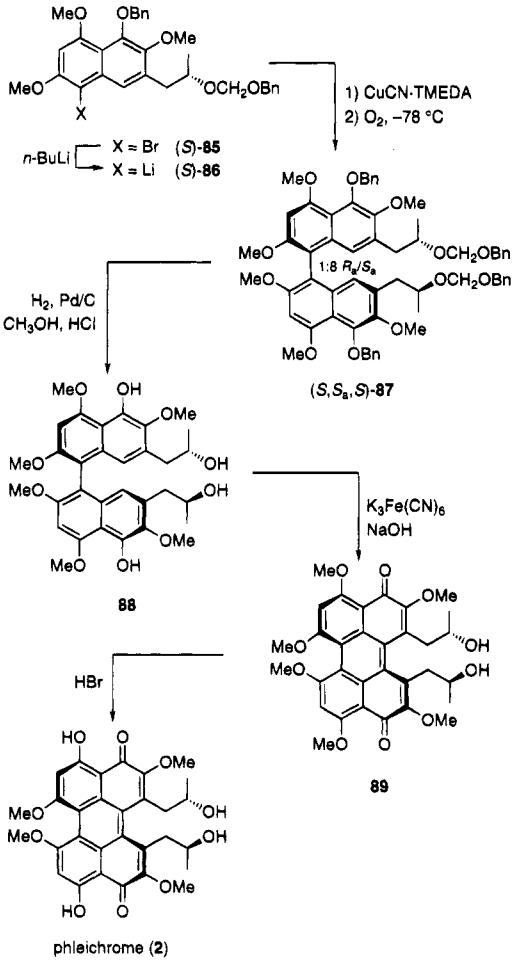


Total Synthesis of Phleichrome

With the establishment of the sense of atropdiastereoselection of the cuprate coupling at useful levels, changing the (*R*)-stereogenic center in the side chain to the (*S*)-stereocenter will necessarily provide the correct atropisomer (S_a) upon coupling, suitable for the synthesis of both phleichrome and the calphostins. However, the side chains will be the wrong configuration for conversion to the calphostins. Clearly, inversion of configuration must occur after biaryl formation since the side chain stereogenic centers control the absolute sense of axial chirality. Furthermore, if the inversion were thoughtfully executed, it could also serve to introduce the acyl appendages of the calphostins. Mitsunobu esterification of an (*R*)-alcohol with the appropriate carboxylic acid via a Walden inversion would afford the corresponding (*S*)-ester, solving the problems of both absolute configuration of the side chain stereocenters and installation of the acyl groups of the natural products.

Bromonaphthalene (*S*)-**85** was converted to the desired (S_a)-binaphthalene **87** in 70% yield as an 8:1 ratio of diastereomers using the solubilized low-temperature cuprate technique detailed previously. Simultaneous deprotection of 1,1′-benzyl ethers and the side chain (benzyloxy)methyl protecting groups of **87** by hydrogenolysis in the presence of acid afforded tetrol **88**. Oxidative cyclization of **88** with potassium ferricyanide afforded the methyl ether **89** of phleichrome in a modest, unoptimized 32% yield. Selective demethylation in perylenequinone systems has been achieved using MgI_2 by Hauser[25] and with HBr by Zhao.[54] In the Zhao procedure, bromine is added to acetone at 25 °C and stirred until the solution becomes colorless. This freshly prepared solution of bromoacetone and HBr was added to a solution of **89** in chloroform. After 16 h, the solvent was removed and phleichrome (**2**)[55] was isolated. This provided unequivocal confirmation of the atropdiastereoselection in the key cuprate coupling.

(54) Zhao, C.; Zhang, X.; Zhang, P. *Liebigs Ann. Chim.* **1993**, *35*, 1.
(55) Arnone, A.; Camarda, L.; Nasini, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1387.

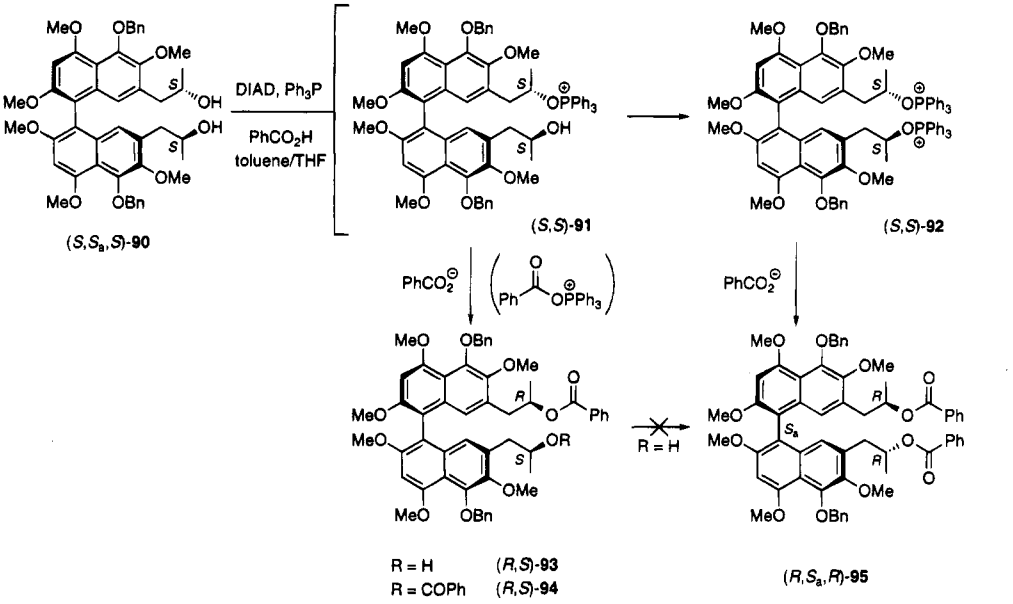


Total Synthesis of Calphostin A

Ideally, double inversion of the side chain diols of phleichrome (**2**) could be achieved with *concomitant introduction* of the benzoyl appendages of calphostin A using a Mitsunobu reaction[56] or by S_N2 displacement of the corresponding methanesulfonate or trifluoromethanesulfonate esters with benzoate anion. Under the standard Mitsunobu conditions [benzoic acid, Ph_3P, *i*-$PrO_2CN{=}NCO_2i$-Pr (DIAD), 25 °C], the starting diol was recovered unchanged.[57] Similarly, treatment of the methanesulfonate or trifluoromethanesulfonate with potassium benzoate was unsuccessful. Warming these reaction mixtures above 80 °C led to isomerization about the stereogenic axis. Failure to effect diol inversion within the perylenequinone framework was postulated to arise from side chain conformational preferences that severely hindered the approach of nucleophiles.[58]

1,1′-Binaphthalenediol **90**, prepared from **87** (HCl, MeOH), appeared to be a better candidate for double inversion of the (2*S*)-hydroxypropyl side chains. Compared to perylenequinones such as **1** or **2**, the side chains of **90** are more accessible, being able to rotate independently. Furthermore, **90** was not prone to thermally induced isomerization about the stereogenic axis.

(56) Mitsunobu, O. *Synthesis* **1981**, 1. Castro, B. R. *Org. React.* **1983**, *29*, 1. Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(57) The prerequisite of direct introduction of the benzoate esters of calphostin A concomitant with inversion of the stereogenic centers ruled out the use of more acidic carboxylic acids that have been shown to participate with greater efficacy in Mitsunobu reactions of hindered secondary alcohols. For these modifications, see: (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(58) The side chains of substituted perylenequinones are substantially restricted in their ability to rotate independent of one another because of the helical twist of the rigid perylene ring system.

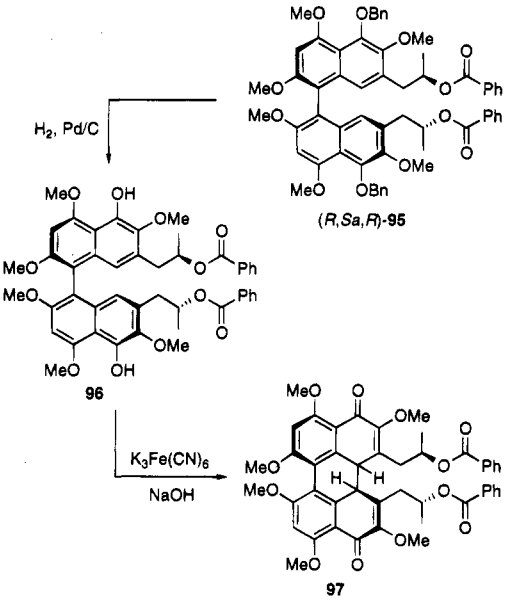


Diol **90** was also the earliest intermediate from which *both* phleichrome (**2**) and calphostin A (**1a**) could be prepared, being the first compounds in the synthetic pathway that possessed the correct (S_a)-stereogenic axis.

Subjecting diol **90** to standard Mitsunobu conditions at 25 °C failed to provide the doubly inverted binaphthalene diester **95** but instead afforded the monoinverted ester **93**. The failure to form **95** was attributed to steric hindrance by the inverted, esterified alcohol in **93**, where the ester either prevented formation of the second oxyphosphonium salt, thereby stopping the reaction at intermediate **93**, or prevented attack of the benzoate nucleophile on the already formed oxyphosphonium salt of **93** (R = P^+Ph_3), which underwent hydrolysis back to the alcohol **93** upon workup. Resubjection of **93** to the above conditions did not provide the doubly inverted diester **95**.

The mechanism and kinetics of the Mitsunobu reaction have been studied in detail by Hughes *et al.*,[59] who found that the rate of S_N2 displacement versus alcohol activation varied with the concentration of protonated and deprotonated carboxylic acid (RCO_2H/RCO_2^-). When the ratio of RCO_2H/RCO_2^- was ≤ 1:1, S_N2 displacement was rate determining, and when the ratio was ≥ 3:1, alcohol activation became rate determining. On the basis of our results and the work of Hughes *et al.*, we felt that if the bis(oxyphosphonium salt) **92** could be formed quantitatively prior to S_N2 displacement on **91**, then the subsequent double inversion could be achieved.

A solution of 1,1′-binaphthalene **90**, Ph_3P (2.5 equiv per equiv of hydroxyl), and benzoic acid (3 equiv per equiv of hydroxyl) in a mixture of toluene/THF (10:1) at −23 °C ($CO_{2(s)}/CCl_4$) was treated with DIAD, and the reaction was allowed to stir for 1 h at −23 °C and then at 25 °C. This procedure provided a 2:1 ratio of doubly inverted diester **95** to singly inverted diester **93**, after careful chromatographic purification.[60] Upon variation of the reaction conditions, the formation of **95** was found to depend principally upon two variables: the time the reaction mixture spent at −23 °C and the polarity of the solvent.[61] Increasing the time the reaction was maintained at −23 °C from 1 to 3 h and increasing the proportion of THF from 10% to 50% proved to be optimal for the formation of **95**. Under these conditions, 1,1′-binaphthalene diester **95** was isolated in a synthetically useful 46% yield, with much of the remainder of the material isolated consisting of elimination byproducts.[62]



The synthesis of **1a** proceeded from binaphthalene **95** by selective deprotection of the 1,1′-positions by hydrogenolysis of the benzyl ethers to provide unstable bisphenol **96**. Oxidation of **96** with potassium ferricyanide afforded *dihydro*perylenequinone **97** in 77% yield.[63] Excess oxidant failed to completely oxidize diphenol **97** to the quinone. The same phenomenon was observed by Broka in his synthesis of **1d**, when the oxidation was attempted with side chains protected as silyl ethers. In this case, removal of the silyl ether was required for complete oxidation, an option not available to us. A superior oxidation method was sought.

Manganese(IV) oxide (MnO_2) proved superior to the standard iron-based oxidants ferricyanide or ferric chloride, and it

(59) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

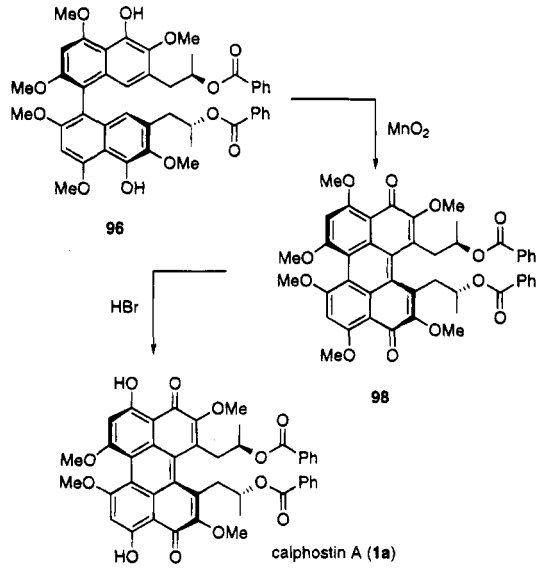
(60) Diester **94** presumably arises by formation of mono(oxyphosphonium salt) **91** and displacement to afford **93**, followed by acylation via a phosphonium-activated carboxylate.

(61) At −23 °C, toluene was found to cause solubility problems (*i.e.*, precipitation of **91** or **92** occurred) during attempted formation of bis(oxyphosphonium salt) **92**.

(62) Olefinic byproducts were formed in significant amounts in all displacement reactions of these homobenzylic alcohols.

(63) Taylor, W. I., Batersby, A. R. *Oxidative Coupling Of Phenols*; Marcel Dekker: New York, 1967.

oxidized diphenol **96** to quinone **98** in 67% yield over 24 h. Crucial to the oxidation was the preparation of the MnO_2, which was most effective when heated for 24 h at 140 °C prior to use and when added portionwise over 24 h to an ethereal solution of **96**. This procedure provided perylenequinone **98** as a red-orange amorphous solid. Regioselective demethylation using the conditions of Zhao with *in situ* formation of HBr afforded calphostin A (**1a**) in 45% yield as a dark red powder after flash chromatography. Spectral data of **1a** proved identical with those published.[64]



Experimental Section

Methyl 6-Acetoxy-6-methoxy-1-oxo-2,4-cyclohexadiene-5-carboxylate (13). A solution of **22** (5.00 g, 27.5 mmol) in CH_2Cl_2 (50 mL) was added to a solution of lead tetraacetate (13.4 g, 30.0 mmol, 1.1 equiv) in CH_2Cl_2 (300 mL) via a syringe pump at 0 °C under argon. After 1 h at 0 °C, ethylene glycol (5 mL) was added to destroy any remaining oxidant. The reaction mixture was diluted with CH_2Cl_2 (250 mL), washed with 5% aqueous HCl (150 mL), saturated aqueous $NaHCO_3$, and NaCl (200 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (silica, 5 × 15 cm, 20% Et_2O/CH_2Cl_2) to afford **13** (4.19 g, 63%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 6.3, 1.1 Hz, 1 H, C2-H), 6.98 (dd, J = 9.8, 6.3 Hz, 1 H, C3-H), 6.29 (dd, J = 9.8, 1.1 Hz, 1 H, C4-H), 3.77 (s, 3 H, CO_2CH_3), 3.41 (s, 3 H, OCH_3), 2.11 (s, 3 H, $C(O)CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 170.6, 163.3, 137.8, 136.6, 133.6, 129.7, 93.7, 52.6, 52.0, 20.9; IR (neat) ν_{max} 1738, 1691, 1436, 1371, 1252, 1107, 1013, 819 cm^{-1}; EIMS, *m/z* (relative intensity) 240 (M^+, 5), 225 (5), 209 (10), 198 (60), 181 (20), 166 (base), 149 (20), 138 (27), 123 (15), 107 (65), 95 (20), 79 (26), 59 (25); HRMS, *m/z* calcd for $C_{11}H_{12}O_6$ 240.0633, found 240.0634. Anal. Calcd for $C_{11}H_{12}O_6$: C, 54.99; H, 5.04. Found: C, 54.94; H, 5.07.

1-Benzoxy-3-methoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (29). Dry tetrahydrofuran (50 mL) was cooled to −78 °C, and *n*-BuLi (2.01 M in hexane, 6.5 mL, 13.1 mmol) was added with a syringe. Diisopropylamine (2.0 mL, 14.3 mmol) was added dropwise over 5 min. The solution was stirred for 5 min at −78 °C and then warmed to 0 °C for 15 min. The light yellow solution was cooled to −78 °C, and **26** (2 g, 76.9 mmol) was slowly added with a syringe. This red solution was stirred for 1 h at −78 °C. The reaction mixture was treated with chlorotrimethylsilane (2.0 mL, 15 mmol) at −78 °C and stirred for 45 min at −78 °C. The solution was diluted with hexane (50 mL) and allowed to warm to 25 °C. The mixture was filtered through dry Celite 505 under nitrogen, washed with hexane, and concentrated *in vacuo* to afford **29** (2.74 g, 100%) as a orange liquid. The purity was determined to be greater 90% by NMR: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5 H, ArH), 4.77 (s, 2 H, OCH_2Ph), 4.36 (d, J = 1.9 Hz, 1 H, C2-H), 4.14 (d, J = 1.5 Hz, 1 H, C4-H), 3.99 (d, J = 1.6 Hz, 1 H, C4-H), 3.55 (s, 3 H, OCH_3), 0.223 (s, 9 H, $Si(CH_3)_3$).

1-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dimethoxy-1,3-butadiene (30). A solution of diisopropylamine (16.0 mL, 115 mmol) in THF (175 mL) at 0 °C under argon was treated with a solution of *n*-BuLi (64 mL, 115 mmol, 1.6 M in hexane) via syringe. The reaction mixture was stirred for 15 min at 0 °C and cooled to −78 °C, and **24** (15 g, 115 mmol) was added via syringe. After 1 h the reaction mixture was treated with DMPU (50 mL, 460 mmol, 4 equiv) via syringe. After 30 min the reaction mixture was treated with a solution of *tert*-butyldimethylsilyl chloride (30 g, 200 mmol) in THF (100 mL) at −78 °C, and the reaction was allowed to warm to 0 °C over 45 min. The mixture was diluted with Et_2O (200 mL), washed with saturated aqueous NaH_2PO_4 (6 × 150 mL), and dried (K_2CO_3). The light orange solution filtrate was concentrated *in vacuo* to afford **30** (21.2 g, 100%) as an orange liquid that was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (d, J = 1.7 Hz, 1 H, C2-H), 3.99 (apparent d, J = 4.3 Hz, 2 H, C4-H), 3.54 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 6 H, $Si(CH_3)_2$).

Methyl 2,6,8-trimethoxy-1-hydroxynaphthalene-3-carboxylate (33). A mixture of cyclohexadienone **13** (1.98 g, 8.25 mmol), neat **30** (5.03 g, 20.6 mmol, 2.5 equiv), and solid $NaHCO_3$ (250 mg) was briefly stirred and allowed to stand for 2 days at 23 °C. Direct purification of the mixture by flash chromatography (3 × 28 cm, silica, 5−30% EtOAc/hexane) afforded **33** (1.57 g, 65%) as a yellow solid: mp 108−110 °C (Et_2O/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1 H, OH), 7.60 (s, 1 H, C4-H), 6.68 (d, J = 2.2 Hz, 1 H, C5-H), 6.50 (d, J = 2.2 Hz, 1 H, C7-H), 4.02 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 157.4, 156.5, 147.6, 140.1, 132.4, 126.7, 119.9, 113.3, 99.8, 99.6, 61.3, 56.3, 55.4, 52.3, 29.7; IR (neat) ν_{max} 3389, 2926, 1728, 1619, 1450, 1369, 1279, 1279, 1163, 1108, 1038, 1007 cm^{-1}; EIMS, *m/z* (relative intensity) 292 (M^+, base), 277 (33), 261 (20), 245 (75), 217 (83), 203 (10), 189 (25), 157 (25), 123 (10), 107 (10), 89 (9), 73 (14), 59 (5); HRMS, *m/z* calcd for $C_{15}H_{16}O_6$ 292.0934, found 292.0947. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.62; H, 5.54.

1-(Methoxymethoxy)-3-methoxy-1-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene (31). Following the procedure for the preparation of **30**, ester **38** (12.4 g, 77 mmol) was converted to **31** (21.2 g, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 2 H, OCH_2O), 4.32 (d, J = 1.7 Hz, 1 H, C2-H), 3.99 (apparent d, J = 4.3 Hz, 2 H, C4-H), 3.52 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 6 H, $Si(CH_3)_2$).

Methyl 2,6-Dimethoxy-1-hydroxy-8-(methoxymethoxy)naphthalene-3-carboxylate (38). *o*-Quinol acetate **13** (4.19 g, 17.5 mmol) and diene **31** (12 g, 44 mmol, 2.5 equiv) were mixed at 23 °C and allowed to stand at 0 °C for 2 d under argon. Aromatization of the crude cycloadduct is accomplished by stirring a solution of the reaction mixture in EtOAc (100 mL) over 7.5% K_2HPO_4-deactivated silica gel (40 g) for 1 h, filtering the resulting brown solution, concentrating the filtrate *in vacuo*, and passing the reaction mixture slowly through a column of 7.5% K_2HPO_4-deactivated silica (40 g silica, 5−20% EtOAc/hexane, 0.5 cm/min). Purification of the effluent by flash chromatography (Et_3N-deactivated silica, 3.0 × 28 cm, 5−20% EtOAc/hexane) afforded **38** (3.39 g, 60%) as a green-yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1 H, OH), 7.63 (s, 1 H, C4-H), 6.80 (d, J = 2.2 Hz, 1 H, C5-H), 6.75 (d, J = 2.2 Hz, 1 H, C7-H), 5.40 (s, 2 H, OCH_2O), 3.96 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 157.3, 153.9, 147.3, 140.1, 132.3, 126.7, 120.2, 106.1, 103.2, 101.1, 95.9, 61.3, 57.0, 55.5, 52.3; IR (neat) ν_{max} 3398, 2932, 1731, 1617, 1441, 1368, 1279, 1219, 1162, 1070, 1007, 943 cm^{-1}; EIMS, *m/z* (relative intensity) 322 (M^+, base), 291 (40), 277 (85), 261 (40), 246 (60), 203 (40), 99 (28), 75 (35); HRMS, *m/z* calcd for $C_{16}H_{18}O_7$ 322.1053, found 322.1049.

(1*R*)-[1-(Benzoxymethoxy)ethyl]tri-*n*-butylstannane [(*R*)-43]. A solution of ethyl vinyl ether (**41**) (10 mL, 100 mmol, 1.7 equiv) in THF (42 mL) at −78 °C under argon was treated with a solution of *tert*-butyllithium (36 mL, 90 mmol, 2.5 M in hexane, 1.5 equiv) dropwise via a cannula over 1 h. The reaction mixture was allowed to slowly warm to 23 °C (**CAUTION**: a rapid exotherm is possible if

(64) Kobayshi, E.; Ando, K.; Nakano, H.; Tamaoki, T. *J. Antibiot.* **1989**, *42*, 153.

the reaction mixture is warmed too rapidly) and stir for 3 h. The reaction mixture was recooled to 0 °C, treated with (n-Bu)$_3$SnCl (20 mL, 75 mmol, 1.3 equiv) via a syringe, and allowed to stir for 2 h at 0 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1 mL) and treated with a degassed 8 M solution of H_2SO_4 in acetone/H_2O (3:1, 100 mL). The reaction mixture was allowed to stir for 3 h diluted with Et_2O (100 mL), the layers were separated, and the organic layer was concentrated *in vacuo*. Purification of the residue by flash chromatography (5 × 8 cm, silica, 0−5% Et_2O/hexane) afforded (tri-*n*-butylstannyl)ethanone (**42**) (20 g, 80%) as a yellow oil that was used immediately in the subsequent reduction.[47]

Methyl 1-Benzoxy-2,6-dimethoxy-8-(methoxymethoxy)naphthalene-3-carboxylate (58). A solution of **35** (3.39 g, 10.5 mmol), benzyl bromide (5 mL, 42.1 mmol, 4 equiv), K_2CO_3 (7 g, 50 mmol, 4.8 equiv), and catalytic n-Bu_4NI (1.56 g, 4.2 mmol, 0.4 equiv) in dimethyl sulfoxide (DMSO, 50 mL) at 28 °C was allowed to stir for 3 d. The reaction mixture was diluted with Et_2O (50 mL), washed with saturated aqueous NH_4Cl (3 × 25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica, 1 × 20 cm, 0−20% EtOAc/hexane) afforded **58** (2.02 g, 47%) as a yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1 H, C4-H), 7.57 (d, J = 6.9 Hz, 2 H, ArH), 7.43−7.33 (m, 3 H, ArH), 6.90 (d, J = 2.4 Hz, 1 H, C5-H), 6.81 (d, J = 2.4 Hz, 1 H, C7-H), 5.17 (s, 2 H, OCH_2O), 5.06 (s, 2 H, $ArCH_2$), 3.97 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3); IR (neat) ν_{max} 2949, 2360, 1731, 1625, 1598, 1341, 1275, 1075, 1008 cm^{-1}; EIMS, *m/z* 412 (M^+, 67), 321 (base), 289 (98), 277 (50), 261 (38), 249 (20), 233 (20), 217 (30), 203 (42), 189 (20), 91 (85).

1-Benzoxy-2,6-dimethoxy-3-(hydroxymethyl)-8-(methoxymethoxy)naphthalene. A solution of **58** (2.0 g, 4.8 mmol) in toluene (5 mL) at −78 °C under argon was treated with a solution of i-Bu_2AlH (7.1 mL, 1.5 M in toluene, 10.7 mmol, 2.2 equiv, Aldrich) via syringe. After 30 min, the reaction mixture was treated with wet acetone (1 mL) via a syringe at −78 °C, and the reaction mixture was allowed to warm to 23 °C. The reaction mixture was diluted with EtOAc (25 mL), washed with 5% aqueous HCl (2 × 15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (Et_3N-deactivated silica, 0.5 cm × 10 cm, 10−20% EtOAc/hexane) afforded the title compound (1.76 g, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 6.9 Hz, 2 H, ArH), 7.43−7.33 (m, 4 H, ArH and C4-H), 6.83 (d, J = 2.4 Hz, 1 H, C5-H), 6.75 (d, J = 2.4 Hz, 1 H, C7-H), 5.17 (s, 2 H, OCH_2O), 5.03 (s, 2 H, $ArCH_2$), 4.78 (s, 2 H, $ArCH_2$), 3.97 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 154.2, 147.8, 147.1, 138.2, 135.1, 134.1, 128.4, 127.9, 127.7, 122.1, 117.1, 104.1, 100.5, 95.77, 76.1, 62.1, 61.6, 56.3, 55.3; IR (neat) ν_{max} 3417, 2937, 1609, 1580, 1454, 1338, 1254, 1149, 1056, 933 cm^{-1}; EIMS, *m/z* (relative intensity) 384 (M^+, 65), 293 (base), 262 (20), 231 (60), 215 (50), 203 (40), 175 (20), 111 (50), 91 (75); HRMS, *m/z* calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1567.

1-Benzoxy-2,6-dimethoxy-8-(methoxymethoxy)naphthalene-3-carboxaldehyde (59). A solution of 1-benzoxy-2,6-dimethoxy-3-(hydroxymethyl)-8-(methoxymethoxy)naphthalene (1.76 g, 4.6 mmol) in diethyl ether (20 mL) was treated with activated MnO_2 (8.3 g, 97 mmol, 21 equiv) at 23 °C. After 1 h, the reaction mixture was filtered through a pad of Celite, repeatedly washed with EtOAc (3 × 20 mL), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 18 cm silica, 10−20% EtOAc/hexane) afforded **59** (1.43 g, 81%) as a green-yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1 H, CHO), 8.00 (s, 1 H, C4-H), 7.58 (d, J = 6.9 Hz, 2 H, ArH), 7.44−7.34 (m, 3 H, ArH), 6.93 (d, J = 2.4 Hz, 1 H, C5-H), 6.87 (d, J = 2.4 Hz, 1 H, C7-H), 5.17 (s, 2 H, OCH_2O), 5.08 (s, 2 H, $ArCH_2$), 4.03 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 157.7, 154.2, 150.0, 148.2, 137.9, 133.3, 128.4, 127.9, 127.8, 124.6, 121.1, 107.8, 102.4, 95.7, 76.4, 62.8, 56.4, 55.4; IR (neat) ν_{max} 2938, 1692, 1621, 1596, 1378, 1338, 1152, 1054, 1006 cm^{-1}; EIMS, *m/z* (relative intensity) 382 (M^+, 68), 291 (92), 272 (50), 260 (35), 231 (40), 203 (35), 160 (18), 91 (base), 65 (30); HRMS, *m/z* calcd for $C_{22}H_{22}O_6$ 382.1416, found 382.1413.

(2′*R*,1′*R)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-hydroxy-1-propyl]-2,6-dimethoxy-4-(methoxymethoxy)naphthalene (60).** A solution of stannane (*S*)-**43** (3.73 g, 8.2 mmol, 2 equiv) in THF (10 mL) at −78 °C under argon was treated with a solution of n-BuLi (3.3 mL, 2.5 M in hexane, 8.2 mmol, 2.05 equiv) via syringe. After 30 min, the reaction mixture was treated with a solution of **59** (1.58 g, 4.13 mmol) in THF (3 mL) and allowed to stir for 30 min at −78 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1 mL), allowed to warm to 27 °C, and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica, 1 × 8 cm, 0−30% EtOAc/hexane) afforded **60** (1.28 g, 54%) as a 1:1 mixture of diastereomers, which were characterized as the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1 H, C4-H), 7.55−7.52 (m, 5 H, ArH and C4-H), 7.42−7.20 (m, 6 H, ArH), 6.81 (d, J = 2.6 Hz, 2 H, C5-H), 6.79 (d, J = 2.6 Hz, 2 H, C7-H), 5.25−5.12 (m, 6 H, OCH_2O and $ArCH_2$), 5.08−4.75 (m, 10 H, OCH_2O and $ArCH_2$), 4.55 (s, 1 H, ArC*H*CH), 4.45 (d, J = 3.3 Hz, 1 H, ArC*H*CH), 4.22 (dd, J = 6.4, 3.88 Hz, 1 H, ArCHC*H*), 4.06 (apparent t, J = 6.4 Hz, 1 H, ArCHC*H*), 3.94 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.41 (s, 6 H, OCH_3), 1.20 (d, J = 6.4 Hz, 3 H, CH_3), 1.11 (d, J = 6.37 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.2, 147.6, 147.1, 146.8, 138.2, 137.6, 135.6, 134.6, 133.9, 128.4, 127.8, 121.8, 121.5, 117.1, 116.8, 104.0, 100.7, 100.5, 95.7, 93.9, 93.0, 78.2, 75.8, 73.5, 72.0, 69.6, 61.5, 56.3, 55.3, 17.3, 13.8; IR (neat) ν_{max} 3476, 2937, 1625, 1605, 1578, 1340, 1150, 1053 cm^{-1}; EIMS, *m/z* (relative intensity) 548 (M^+, 30), 351 (10), 305 (70), 261 (20), 91 (base); HRMS, *m/z* calcd for $C_{32}H_{36}O_8$ 548.2410, found 548.2408.

(2′*R*,1′*R)-1-Benzoxy-3-[2-benzoxymethoxy)-1-[[imidazol-1-yl(thiocarbonyl)]oxy]-1-propyl]-2,6-dimethoxy-8-(methoxymethoxy)-naphthalene (61).** A solution of **60** (1.16 g, 2.0 mmol) and 1,1′-(thiocarbonyl)diimidazole (1.07 g, 6.0 mmol, 2 equiv) in THF (1 mL) was warmed at reflux under argon. After 18 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (Et_3N-deactivated silica, 1 × 10 cm, 0−35% EtOAc/hexane) to afford **61** (657 mg, 47%) as a 1:1 mixture of diastereomers, which were characterized as the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (apparent d, J = 5.0 Hz, 2 H, C2″-H), 7.76 (apparent d, J = 5.7 Hz, 2 H, C5″-H), 7.52 (apparent dd, J = 17.8, 7.0 Hz, 4 H, ArH), 7.40−7.20 (m, 16 H, ArH, C4-H and C4″-H), 7.10−7.05 (m, 4 H, ArH), 6.97 (d, J = 3.3 Hz, 1 H, ArC*H*CH), 6.82 (s, 2 H, ArC*H*CH and C5-H), 6.77 (d, J = 2.3 Hz, 1 H, C5-H), 6.74 (d, J = 2.3 Hz, 1 H, C7-H), 6.70 (d, J = 2.3 Hz, 1 H, C7-H), 5.20−5.10 (m, 4 H, OCH_2O), 5.05−4.60 (m, 8 H, OCH_2O and $ArCH_2O$), 4.52 (s, 2 H, $ArCH_2$), 4.43 (apparent t, J = 5.6 Hz, 1 H, ArCHC*H*), 4.36 (m, 2 H, $ArCH_2$ and ArCHC*H*), 4.25 (d, J = 12 Hz, 1 H, $ArCH_2$), 4.05 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.40 (s, 6 H, OCH_3), 1.31 (d, J = 6.5 Hz, 3 H, CH_3), 1.26 (d, J = 6.5 Hz, 3 H, CH_3); IR (neat) ν_{max} 2939, 1606, 1463, 1388, 1340, 1286, 1228, 1150, 1055 cm^{-1}; EIMS, *m/z* (relative intensity) 658 (M^+, 10), 598 (5), 530 (10), 415 (10), 305 (30), 245 (20), 91 (base).

(2′*R*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-propyl]-2,6-dimethoxy-8-(methoxymethoxy)naphthalene [(*R*)-62]. A solution of **61** (639 mg, 0.94 mmol) in toluene (5 mL) was added dropwise via syringe over 1 h to a refluxing solution of (n-Bu)$_3$SnH (0.75 mL, 2.8 mmol, 3 equiv) in toluene (10 mL) under argon. After an additional 30 min, the reaction mixture was allowed to cool to 26 °C, diluted with Et_2O (10 mL), washed with saturated aqueous NH_4Cl (3 × 5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica, 0.5 × 8 cm, 0−20% CH_2Cl_2/hexane) afforded (*R*)-**62** (335 mg, 67%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 6.7 Hz, 2 H, ArH), 7.44−7.30 (m, 4 H, ArH), 7.23−7.20 (m, 3 H, ArH and C4-H), 7.15−7.05 (m, 2 H, ArH), 6.78 (d, J = 2.3 Hz, 1 H, C5-H), 6.71 (d, J = 2.3 Hz, 1 H, C7-H), 5.16 (s, 2 H, OCH_2O), 4.97 (apparent d, J = 2.1 Hz, 2 H, $ArCH_2$), 4.73 (ABq, J = 7.0, $\Delta\nu$ = 29.3 Hz, 2 H, OCH_2O), 4.31 (dd, J = 24.4, 11.7 Hz, 2 H, $ArCH_2$), 4.17 (ddd, J = 19.1, 12.7, 6.3 Hz, 1 H, $ArCH_2CH$), 3.93 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 2.95 (ABX, J = 13.2, 6.3, $\Delta\nu$ = 53 Hz, 2 H, $ArCH_2CH$), 1.26 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.2, 148.8, 147.1, 138.4, 137.9, 133.9, 133.7, 128.3, 127.9, 127.6, 127.4, 124.7, 116.6, 103.6, 99.9, 95.7, 92.7, 75.8, 73.1, 69.1, 61.3, 56.3, 55.3, 38.5, 20.4; IR (neat) ν_{max} 2932, 1605, 1455, 1339, 1213, 1150, 1053 cm^{-1}; EIMS, *m/z* (relative intensity) 532 (M^+, 40), 438 (20), 335 (30), 289 (90), 229 (35), 91 (base); HRMS, *m/z* calcd for $C_{32}H_{36}O_7$ 532.2465, found 532.2461.

(2′*R*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-propyl]-5-bromo-2,6-dimethoxy-4-(methoxymethoxy)naphthalene [(*R*)-63]. A solution of (*R*)-**62** (345 mg, 0.65 mmol) in THF (1 mL) at −78 °C was treated with *N*-bromosuccinimide (121 mg, 0.68 mmol, 1.05 equiv) under argon. After 1 h, the reaction mixture was treated with sodium thiosulfate (10 mg), allowed to warm to 26 °C, and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica, 0.5 × 4 cm, 0−100% CH_2Cl_2/hexane) afforded (*R*)-**63** (263 mg, 66%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1 H, C4-H), 7.56 (d, J = 6.7 Hz, 2 H, ArH), 7.44−7.30 (m, 4 H, ArH), 7.25−7.18 (m, 3 H, ArH), 7.15−7.05 (m, 2 H, ArH), 6.99 (s, 1 H, C7-H), 5.17 (s, 2 H, OCH_2O), 4.98 (apparent d, J = 2.1 Hz, 2 H, $ArCH_2$), 4.80 (ABq, J = 7.0 Hz, $\Delta\nu$ = 29.3 Hz, 2 H, OCH_2O), 4.31 (dd, J = 24.4, 11.7 Hz, 2 H, $ArCH_2$), 4.19 (ddd, J = 19.1, 12.7, 6.3 Hz, 1 H, $ArCH_2CH$), 3.97 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.02 (ABX, J = 13.2 Hz, 6.3, $\Delta\nu$ = 53 Hz, 2 H, $ArCH_2CH$), 1.30 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.2, 149.3, 146.8, 138.2, 137.9, 135.3, 131.4, 128.4, 127.8, 127.4, 126.9, 124.2, 117.5, 101.4, 100.4, 96.3, 92.6, 75.9, 73.2, 69.0, 61.3, 57.0, 56.4, 38.8, 31.6, 22.7, 20.4; IR (neat) ν_{max} 2934, 1598, 1455, 1337, 1036 cm^{-1}; EIMS, *m/z* (relative intensity) 612 /610 (M^+ + 2 and M^+, 23/25), 369/367 (50/50), 309/307 (20/20), 228 (20), 91 (base); HRMS, *m/z* calcd for $C_{32}H_{35}O_7Br$ 610.1566, found 610.1563.

2,4-Diethoxy-2′,4′-dimethoxy-1,1′-binaphthalene (74). A solution of **70** (348 mg, 1.18 mmol, 1.1 equiv) in MeTHF (15 mL) was treated with *n*-BuLi (0.8 mL, 1.18 mmol, 1.5 M in hexane, 1.18 equiv) at −78 °C under argon. After 1 h, the reaction mixture was transferred with a cannula to a flask containing CuCN (95.1 mg, 1.06 mmol) at −78 °C under argon. The reaction mixture was allowed to warm to 0 °C over 10 min and stirred until homogeneous. The resulting solution was cooled to −131 °C ($N_{2(l)}$/EtOH). A solution of **69** (315 mg, 1.18 mmol) in MeTHF (5 mL) was treated with *n*-BuLi (0.5 mL, 1.0 mmol, 1.5 M in hexane, 1.0 equiv) at −78 °C under argon for 1 h. The reaction mixture was added to the previously prepared aryl cuprate using a cannula at −131 °C, and the resulting mixture was stirred at this temperature. After 5 min, TMEDA (0.4 mL, 2.4 mmol, 2.0 equiv) was added with a syringe at −131 °C, and the reaction mixture was allowed to warm to −100 °C over 1 h. The reaction mixture was cooled to −131 °C and allowed to stir for 10 min. Dry oxygen gas was introduced via a fine-fritted gas dispersion tube at −131 °C as the solution became red. The reaction mixture was allowed to stir for 30 min under an oxygen atmosphere at −131 °C, and the solution was allowed to warm to −100 °C over 1 h. The oxygen was removed *in vacuo*, and the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) at −100 °C. The reaction mixture was allowed to warm to 23 °C, diluted with CH_2Cl_2 (40 mL), washed with saturated aqueous NH_4Cl (2 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica gel, 1 × 5 cm, CH_2Cl_2) followed by trituration with hexane afforded **74** (287 mg, 67%) as a white solid: mp 105−107 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.5 Hz, 1 H, C8-H), 8.22 (d, J = 7.7 Hz, 1 H, C8′-H), 7.26 (m, 2 H, C5-H and C5′-H), 7.18 (m, 2 H, C7-H and C7′-H), 7.10 (m, 2 H, C6-H and C6′-H), 6.79 (s, 1 H, C3-H), 6.76 (s, 1 H, C3′-H), 4.27 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 4.09 (s, 3 H, OCH_3), 3.94 (m, 2 H, OCH_2CH_3), 3.73 (s, 3 H, OCH_3), 1.59 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.01 (t, J = 7.0 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 156.8, 155.9, 155.3, 135.3, 135.1, 127.3, 127.2, 127.1, 125.8, 125.7, 123.3, 123.2, 122.5, 122.4, 122.3, 122.2, 122.2, 122.0, 121.9, 113.4, 112.7, 97.7, 95.0, 66.2, 66.1, 57.6, 56.0, 15.6, 15.3; IR (neat) ν_{max} 2979, 1620, 1344, 1108, 764.4 cm^{-1}; EIMS *m/z* (relative intensity) 402 (M^+, base), 373 (25), 342 (25), 313 (35), 241 (30), 185 (43).

(2″*R*,2‴*R*)-1,1′-Dibenzoxy-3,3′-bis[2-(benzoxymethoxy)-1-propyl]-2,2′,6,6′-tetramethoxy-4,4′-bis(methoxymethoxy)-5,5′-binaphthalene [(*R*,R_a,*R*)-83]. A solution of (*R*)-**63** (283 mg, 0.46 mmol) in THF (6 mL) was treated with *n*-BuLi (0.18 mL, 2.5 M in hexane, 0.46 mmol, 1.0 equiv) at −78 °C under argon. After 1 h the reaction mixture was transferred using a cannula to a flask containing CuCN (20 mg, 0.23 mmol, 0.5 equiv) at −78 °C under argon. The reaction mixture was stirred for 5 min, allowed to slowly warm to 0 °C until homogeneous, and then cooled to −78 °C. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA, 0.1 mL, 0.66 mmol, 3.3 equiv) was added with a syringe, and the reaction mixture was allowed to stir for 1 h at −78 °C. Oxygen gas was bubbled through the solution at −78 °C for 1.2 h. The oxygen was removed *in vacuo*, and the reaction mixture was treated with 20% NH_4OH in saturated aqueous NH_4Cl (5 mL) and allowed to warm to 25 °C. The reaction mixture was diluted with EtOAc (20 mL), washed with 20% NH_4OH in saturated aqueous NH_4Cl (5 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (0.5 × 8 cm silica, 0−20% EtOAc/hexane) to afford the major diastereomer (*R*,R_a,*R*)-**83** (131 mg, 62%) as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 6.7 Hz, 4 H, ArH), 7.44−7.30 (m, 8 H, ArH), 7.23−7.20 (m, 6 H, ArH and C4-H), 7.10−7.05 (m, 4 H, ArH), 6.78 (s, 2 H, C7-H), 5.16 (s, 4 H, OCH_2O), 5.03 (apparent dd, J = 7.5, 10.5 Hz, 4 H, $ArCH_2$), 4.54 (ABq, J = 7.0 Hz, $\Delta\nu$ = 29.3 Hz, 4 H, OCH_2O), 4.25 (dd, J = 24.4, 11.7 Hz, 4 H, $ArCH_2$), 3.89 (m, 8 H, OCH_3 and $ArCH_2CH$), 3.65 (s, 6 H, OCH_3), 3.49 (s, 6 H, OCH_3), 2.65 (ABX, J = 13.1, 6.4 Hz, $\Delta\nu$ = 151 Hz, 4 H, $ArCH_2CH$), 1.03 (d, J = 6.3 Hz, 6 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 149.0, 147.1, 139.1, 138.4, 133.6, 128.6, 128.3, 128.0, 127.6, 123.5, 117.4, 113.8, 100.9, 96.7, 93.4, 75.9, 74.0, 69.5, 61.6, 57.1, 56.8, 38.9, 37.0, 25.0, 23.7, 20.6; IR (neat) ν_{max} 2933, 1584, 1451, 1339, 1148, 1107, 1041 cm^{-1}; EIMS, *m/z* (relative intensity) 1062 (M^+, base), 972 (20), 819 (60), 743 (20), 667 (30), 607 (25), 545 (15).

(2′*R*,R_a,2″*R*)-4,9-Dihydroxy-1,12-bis(2-hydroxy-1-propyl)-2,6,7,-11-tetramethoxy-3,10-perylenequinone (Isocalphostin D, 84). A solution of debenzylated **83** (8.2 mg, 9.3 μmol) and NaOH (2.2 mg, 56 μmol, 6 equiv) in THF/EtOH/H_2O (5:5:2, 1 mL) at 23 °C under argon was treated with $K_3Fe(CN)_6$ (40 mg, 0.12 mmol, 13 equiv). After 1 h, the reaction mixture was diluted with $CHCl_3$ (6 mL), washed with 5% aqueous HCl (3 × 3 mL), and dried ($MgSO_4$). The red solution was treated with 10% methanolic HCl (3 mL). After 10 min, the red solution was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 4 cm, 0−5% MeOH/$CHCl_3$) afforded **84** (3.8 mg, 71%) as a red-orange oil: ^1H NMR (300 MHz, $CDCl_3$) δ 15.79 (s, 2 H, OH), 6.58 (s, 2 H, C5-H and C8-H), 4.20 (s, 6 H, OCH_3), 4.06 (s, 6 H, OCH_3), 3.60 (dd, J = 12.9, 6.6 Hz, 2 H, C13-H, C16-H), 3.41 (m, 2 H, C14-H and C17-H), 2.95 (dd, J = 12.9, 6.6 Hz, 2 H, C13-H and C16-H), 0.53 (d, J = 6.1 Hz, 6 H, C15-H and C18-H).

Methyl 1-Benzoxy-2,6,8-trimethoxynaphthalene-3-carboxylate. A slurry of NaH (7 g, 50 mmol, 4.8 equiv), benzyl bromide (5 mL, 42.1 mmol, 4 equiv), and *n*-Bu_4NI (1.56 g, 4.2 mmol, 0.4 equiv) in DMF (50 mL) at 0 °C under argon was treated with a solution of **33** (3.3 g, 11.3 mmol) via a cannula. After 12 h at 25 °C, the reaction mixture was diluted with Et_2O (150 mL), washed with 5% aqueous HCl (3 × 75 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 20 cm, silica, 0−20% EtOAc/hexane) afforded the title compound (2.02 g, 47%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1 H, C4-H), 7.57 (d, J = 6.9 Hz, 2 H, ArH), 7.43−7.33 (m, 3 H, ArH), 6.90 (d, J = 2.4 Hz, 1 H, C5-H), 6.81 (d, J = 2.4 Hz, 1 H, C7-H), 5.06 (s, 2 H, $ArCH_2$), 3.97 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3); IR (neat) ν_{max} 2938, 1730, 1624, 1597, 1453, 1342, 1259, 1212, 1165, 1043, 1009 cm^{-1}; EIMS, *m/z* (relative intensity) 382 (M^+, 50), 291 (base), 263 (90), 258 (40), 217 (30), 203 (22), 186 (15), 91 (65).

1-Benzoxy-3-(hydroxymethyl)-2,6,8-trimethoxynaphthalene. A solution of the above ester (1.0 g, 2.7 mmol) in THF (5 mL) at 0 °C under argon was treated with a solution of $LiAlH_4$ (2.6 mL, 1.0 M in THF, 2.6 mmol, 2.2 equiv, Aldrich) via syringe. After 30 min, the reaction mixture was treated with wet acetone (1 mL) via a syringe at 0 °C and allowed to warm to 23 °C. The mixture was diluted with EtOAc (25 mL), washed with 5% aqueous HCl (2 × 15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (0.5 × 10 cm, Et_3N-deactivated silica, 10−20% EtOAc/hexane) afforded 1-benzoxy-3-(hydroxymethyl)-2,6,8-trimethoxynaphthalene (671 mg, 70%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 6.9 Hz, 2 H, ArH), 7.43−7.26 (m, 4 H, ArH and C4-H), 6.66 (d, J = 2.4 Hz, 1 H, C5-H), 6.48 (d, J = 2.4 Hz, 1 H, C7-H), 4.89 (s, 2 H, $ArCH_2$), 4.79 (s, 2 H, $ArCH_2$), 3.97 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 2.30 (br s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 157.0, 147.7, 147.4, 137.9, 135.1, 134.1, 128.5, 127.9, 122.0, 116.7, 98.9, 98.7, 76.4, 62.1, 61.5, 55.7, 55.3; IR (neat) ν_{max} 3424, 2936, 1607, 1580, 1452, 1340, 1258, 1205, 1162, 1110, 1027, 880 cm^{-1};

EIMS, *m/z* (relative intensity) 354 (M^+, 30), 263 (base), 235 (70), 191 (25), 107 (20), 91 (55), 62 (25); HRMS, *m/z* calcd for $C_{21}H_{22}O_5$ 354.1467, found 354.1466.

1-Benzoxy-2,6,8-trimethoxynaphthalene-3-carbaldehyde. A solution of 1-benzoxy-3-(hydroxymethyl)-2,6,8-trimethoxynaphthalene (3.52 g, 9.94 mmol) in diethyl ether (50 mL) was treated with activated MnO_2 (17.1 g, 198 mmol, 20 equiv) at 23 °C. After 1 h, the reaction mixture was filtered through a pad of Celite and repeatedly washed with EtOAc (3 × 20 mL), and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (2.5 × 8 cm silica, 10−20% EtOAc/hexane) afforded the title compound (2.48 g, 71%) as a green-yellow solid: mp 120−122 °C (Et_2O/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1 H, CHO), 7.98 (s, 1 H, C4-H), 7.56 (d, J = 6.9 Hz, 2 H, ArH), 7.44−7.35 (m, 3 H, ArH), 6.78 (d, J = 2.4 Hz, 1 H, C5-H), 6.59 (d, J = 2.4 Hz, 1 H, C7-H), 5.03 (s, 2 H, $ArCH_2$), 4.04 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 157.8, 156.9, 150.0, 137.7, 133.4, 129.4, 128.5, 128.0, 124.4, 120.8, 101.6, 100.0, 76.6, 62.8, 55.9, 55.4; IR (neat) ν_{max} 2933, 2851, 1692, 1594, 1451, 1379, 1338, 1261, 1200, 1159, 1107, 1046, 1005 cm^{-1}; EIMS, *m/z* (relative intensity) 352 (M^+, 51), 261 (base), 248 (40), 233 (74), 190 (25), 91 (75), 65 (26); HRMS, *m/z* calcd for $C_{21}H_{20}O_5$ 352.1311, found 352.1302. Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H,5.72. Found: C, 71.56; H, 5.78.

(1′*R,2′*S*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-hydroxy1-propyl]-2,6,8-trimethoxynaphthalene.** A solution of stannane (*R*)-**43** (8.65 g, 19 mmol, 2.1 equiv) in THF (25 mL) at −78 °C under argon was treated with a solution of *n*-BuLi (11 mL, 18.5 mmol, 2.5 M in hexane, 2.0 equiv) via syringe. After 30 min, the reaction mixture was treated with a solution of the above aldehyde (3.08 g, 8.75 mmol) in THF (25 mL) and allowed to stir for 30 min at −78 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1 mL), allowed to warm to 27 °C, and concentrated *in vacuo*. Purification by flash chromatography (Et_3N-deactivated silica, 1 × 8 cm, 0−30% EtOAc/hexane) afforded the title compound (3.84 g, 85%) as a 1:1 mixture of diastereomers, which were characterized as the mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1 H, C4-H), 7.54−7.52 (m, 5 H, ArH and C4-H), 7.42−7.20 (m, 16 H, ArH), 6.69 (d, J = 2.6 Hz, 2 H, C5-H), 6.48 (d, J = 2.6 Hz, 2 H, C7-H), 5.21 (m, 1 H, OH), 4.96−4.76 (m, 8 H, OCH_2O and $ArCH_2$), 4.54 (s, 2 H, $ArCH_2$), 4.45 (apparent d, J = 2.3 Hz, 2 H, $ArCH_2$), 4.23 (dd, J = 6.4, 3.8 Hz, 1 H, ArCHC*H*), 4.07 (apparent t, J = 6.4 Hz, 1 H, ArCHC*H*), 3.96 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 3.36 (d, J = 5.2 Hz, 1 H, ArC*H*CH), 2.85 (d, J = 3.6 Hz, 1 H, ArC*H*CH), 1.20 (d, J = 6.4 Hz, 3 H, CH_3), 1.12 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.9, 147.5, 147.4, 137.9, 137.5, 135.6, 134.7, 133.9, 128.4, 127.8, 121.7, 121.3, 98.9, 98.6, 93.8, 93.0, 78.3, 76.3, 75.6, 73.6, 72.0, 69.6, 61.5, 61.4, 55.7, 55.3, 17.3, 13.8; IR (neat) ν_{max} 3465, 2933, 1605, 1574, 1446, 1338, 1164, 1102, 1025 cm^{-1}; EIMS, *m/z* (relative intensity) 518 (15, M^+), 275 (39), 91 (base); HRMS, *m/z* calcd for $C_{31}H_{34}O_7$ 518.2305, found 518.2300.

(1′*R,2′*R*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-hydroxy-1-propyl]-2,6,8-trimethoxynaphthalene:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1 H, C4-H), 7.54−7.52 (m, 5 H, ArH and C4-H), 7.42−7.20 (m, 16 H, ArH), 6.69 (d, J = 2.6 Hz, 2 H, C5-H), 6.48 (d, J = 2.6 Hz, 2 H, C7-H), 5.21 (m, 1 H, OH), 4.96−4.76 (m, 8 H, OCH_2O and $ArCH_2$), 4.54 (s, 2 H, $ArCH_2$), 4.45 (apparent d, J = 2.3 Hz, 2 H, $ArCH_2$), 4.23 (dd, J = 6.4, 3.8 Hz, 1 H, ArCHC*H*), 4.07 (apparent t, J = 6.4 Hz, 1 H, ArCHC*H*), 3.96 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 3.36 (d, J = 5.2 Hz, 1 H, ArC*H*CH), 2.85 (d, J = 3.6 Hz, 1 H, ArC*H*CH), 1.20 (d, J = 6.4 Hz, 3 H, CH_3), 1.12 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.9, 147.5, 147.4, 137.9, 137.5, 135.6, 134.7, 133.9, 128.4, 127.8, 121.7, 121.3, 98.9, 98.6, 93.8, 93.0, 78.3, 76.3, 75.6, 73.6, 72.0, 69.6, 61.5, 61.4, 55.7, 55.3, 17.3, 13.8.

(1′*R,2′*S*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-[[imidazol-1-yl(thiocarbonyl)]oxy]-1-propyl]-2,6,8-trimethoxynaphthalene.** A solution of the corresponding alcohol (3.84 g, 7.4 mmol) and 1,1′-(thiocarbonyl)-diimidazole (3.95 g, 22 mmol, 3 equiv) in THF (10 mL) was warmed at reflux under argon. After 18 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (Et_3N-deactivated silica, 1 × 10 cm, 0−35% EtOAc/hexane) to afford the title compound (3.57 g, 78%) as a 1:1 mixture of diastereomers, which were characterized as the mixture: ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (apparent d, J = 5.0 Hz, 2 H, C2″-H), 7.76 (d, J = 5.7 Hz, 2 H, C5″-H), 7.51−7.48 (m, 4 H, ArH), 7.40−7.20 (m, 18 H, ArH and C4-H), 7.10−6.97 (m, 2 H, C4″-H), 6.98 (d, J = 3.3 Hz, 1 H, ArC*H*CH), 6.78 (d, J = 5.5 Hz, 1 H, ArC*H*CH), 6.66 (d, J = 2.3 Hz, 1 H, C5-H), 6.62 (d, J = 2.3 Hz, 1 H, C5-H), 6.48 (m, 2 H, C7-H), 5.05−4.76 (m, 7 H, OCH_2OBn and $ArCH_2$), 4.63 (d, J = 7.2 Hz, 1 H, OCH_2OBn), 4.51 (s, 2 H, $ArCH_2$), 4.38−4.25 (m, 2 H, ArCHC*H*), 4.06 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 3.86−3.84 (m, 6 H, OCH_3), 1.31 (d, J = 6.5 Hz, 3 H, CH_3), 1.26 (d, J = 6.5 Hz, 3 H, CH_3); IR (neat) ν_{max} 2940, 1605, 1580, 1453, 1389, 1342, 1286, 1228, 1164, 1110, 1026 cm^{-1}; EIMS, *m/z* (relative intensity) 628 (30, M^+), 568 (20), 500 (20), 385 (70), 319 (10), 257 (35), 91 (base).

(1′*R,2′*R*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-[[imidazol-q-yl-(thiocarbonyl)]oxy]propyl]-2,6,8-trimethoxynaphthalene:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (apparent d, J = 5.0 Hz, 2 H, C2″-H), 7.76 (d, J = 5.7 Hz, 2 H, C5″-H), 7.51−7.48 (m, 4 H, ArH), 7.40−7.20 (m, 18 H, ArH and C4-H), 7.10−6.97 (m, 2 H, C4″-H), 6.98 (d, J = 3.3 Hz, 1 H, ArC*H*CH), 6.78 (d, J = 5.5 Hz, 1 H, ArC*H*CH), 6.66 (d, J = 2.3 Hz, 1 H, C5-H), 6.62 (d, J = 2.3 Hz, 1 H, C5-H), 6.48 (m, 2 H, C7-H), 5.05−4.76 (m, 7 H, OCH_2OBn and $ArCH_2$), 4.63 (d, J = 7.2 Hz, 1 H, OCH_2O), 4.51 (s, 2 H, $ArCH_2$), 4.38−4.25 (m, 2 H, ArCHC*H*), 4.06 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 3.86−3.84 (m, 6 H, OCH_3), 1.31 (d, J = 6.5 Hz, 3 H, CH_3), 1.26 (d, J = 6.5 Hz, 3 H, CH_3).

(2′*S*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-propyl]-2,6,8-trimethoxynaphthalene. A solution of the corresponding thioimidazolide (3.57 g, 5.8 mmol) in toluene (15 mL) was added dropwise via syringe over 1 h to a refluxing solution of $(n\text{-}Bu)_3SnH$ (5.38 mL, 22 mmol, 3.7 equiv) in toluene (20 mL) under argon. After an additional 30 min, the reaction mixture was allowed to cool to 26 °C, diluted with Et_2O (10 mL), washed with saturated aqueous NH_4Cl (3 × 5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (0.5 × 8 cm, Et_3N-deactivated silica, 0−20% EtOAc/hexane) afforded the title compound (2.02 g, 54%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 6.7 Hz, 2 H, ArH), 7.44−7.30 (m, 4 H, ArH), 7.25−7.23 (m, 3 H, ArH and C4-H), 7.12−7.10 (m, 2 H, ArH), 6.64 (d, J = 2.3 Hz, 1 H, C5-H), 6.46 (d, J = 2.3 Hz, 1 H, C7-H), 4.93 (apparent d, J = 2.1 Hz, 2 H, $ArCH_2$), 4.68 (ABq, J = 7.0, $\Delta\nu$ =29.3 Hz, 2 H, OCH_2O), 4.28 (ABq, J = 11.7 Hz, $\Delta\nu$ = 24.4 Hz, 2 H, OCH_2Ph), 4.19 (ddd, J = 19.1, 12.7, 6.3 Hz, 1 H, $ArCH_2CH$), 3.96 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 2.96 (ABX, J = 13.2, 6.3, $\Delta\nu$ = 53 Hz, 2 H, $ArCH_2CH$), 1.27 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 157.0, 148.8, 147.4, 138.2, 137.9, 133.8, 128.5, 128.3, 127.7, 127.5, 124.6, 116.3, 98.4, 98.2, 92.6, 76.2, 73.2, 69.0, 61.3, 55.7, 55.3, 38.5, 20.3; IR (neat) ν_{max} 2934, 1624, 1604, 1578, 1452, 1342, 1205, 1163, 1111, 1053, 824 cm^{-1}; EIMS, *m/z* (relative intensity) 502 (20, M^+), 412 (10), 259 (90), 91 (base); HRMS, *m/z* calcd for $C_{31}H_{34}O_6$ 502.2355, found 502.2354.

(2′*R*)-1-Benzoxy-3-[2-(benzoxymethoxy)-1-propyl]-5-bromo-2,6,8-trimethoxynaphthalene [(*R*)-85]. A solution of the corresponding naphthalene (388 mg, 0.77 mmol) in THF (10 mL) at 0 °C was treated with *N*-bromosuccinimide (151 mg, 0.85 mmol, 1.05 equiv) under argon. After 30 min, the reaction mixture was treated with sodium thiosulfate (10 mg), allowed to warm to 26 °C, and concentrated *in vacuo*. Purification of the residue by flash chromatography (Et_3N-deactivated silica, 0.5 × 4 cm, 0−100% CH_2Cl_2/hexane) afforded (*R*)-**85** (350 mg, 78%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1 H, C4-H), 7.53 (d, J = 16.7 Hz, 2 H, ArH), 7.44−7.30 (m, 3 H, ArH), 7.25−7.18 (m, 3 H, ArH), 7.10−7.05 (m, 2 H, ArH), 6.59 (s, 1 H, C7-H), 4.91 (apparent d, J = 2.1 Hz, 2 H, $ArCH_2$), 4.71 (ABq, J = 7.0, $\Delta\nu$ = 29.3 Hz, 2 H, OCH_2OBn), 4.28 (dd, J = 24.4, 11.7 Hz, 2 H, OCH_2Ph), 4.19 (ddd, J = 19.1, 12.7, 6.3 Hz, 1 H, $ArCH_2CH$), 3.99 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 2.99 (ABX, J = 13.2, 6.3, $\Delta\nu$ = 53 Hz, 2 H, $ArCH_2CH$), 1.29 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 153.3, 149.3, 147.1, 137.8, 135.3, 131.2, 128.4, 127.8, 127.4, 124.0, 117.0, 99.7, 95.0, 92.5, 76.2, 73.2, 68.9, 61.3, 57.2, 56.0, 38.7, 20.4; IR (neat) ν_{max} 2934, 1597, 1453, 1343, 1205, 1026 cm^{-1}; EIMS, *m/z* (relative intensity) 582/580 (10/10, M^+), 339/337 (50/50), 259 (35), 91 (base); HRMS, *m/z* calcd for $C_{31}H_{33}O_6{}^{79}Br$ 580.1461, found 580.1458.

(+)-(2″*R*,*R*$_a$,2‴*R*)-1,1′-Dibenzoxy-3,3′-bis[2-(benzoxymethoxy)-1-propyl]-2,2′,6,6′,8,8′-hexamethoxy-5,5′-binaphthalene [(*R*,*R*$_a$,*R*)-87]. A solution of (*R*)-**85** (337 mg, 0.58 mmol, 2.2 equiv) in THF (7 mL) was treated with *n*-BuLi (0.22 mL, 0.58 mmol, 1.7 M in hexane, 2.2 equiv) at −78 °C under argon. After 1 h, a second flask containing a slurry of dry CuCN (25 mg, 0.28 mmol) in THF (0.5 mL) under argon at 23 °C was treated with TMEDA (0.13 mL, 0.84 mmol, 3.0 equiv) via a syringe, and the reaction mixture was allowed to stir until homogeneous. The organolithium solution at −78 °C was treated with the freshly prepared colorless solution of the CuCN·TMEDA complex via cannula, and the reaction mixture was allowed to stir for 1 h at −78 °C. Oxygen gas was bubbled through the solution at −78 °C for 1.2 h. The oxygen was removed *in vacuo*, and the reaction mixture was treated with 20% concentrated NH_4OH in saturated aqueous NH_4Cl (5 mL) and allowed to warm to 25 °C. The reaction mixture was diluted with EtOAc (20 mL), washed with 20% NH_4OH in saturated aqueous NH_4Cl (5 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (0.5 × 8 cm silica, 0−20% EtOAc/hexane) to afford (*R*,*R*$_a$,*R*)-**87** (183 mg, 65%) as an 8:1 mixture of atropisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.55 (m, 4 H, ArH), 7.44−7.40 (m, 4 H, ArH), 7.36−7.33 (m, 2 H, C4-H), 7.25−7.17 (m, 8 H, ArH), 7.12−7.00 (m, 4 H, ArH), 6.75[a] (s, 2 H, C7-H), 6.68[b] (s, 1 H, C7-H), 5.03 (m, 3 H, $ArCH_2$), 4.88 (m, 1 H, $ArCH_2$), 4.60−4.45 (m, 4 H, OCH_2OBn), 4.38−4.15 (m, 4 H, $ArCH_2$), 3.97 (s, 6 H, OCH_3), 3.90−3.85 (m, 8 H, OCH_3 and CH_2CH), 3.67 (s, 6 H, OCH_3), 2.65[a] (ABX, *J* = 3.1, 6.37, Δν = 151 Hz, 4 H, CH_2CH), 2.64[b] (m, 1 H, CH_2CH), 2.56[b] (m, 1 H, CH_2CH), 1.03[a] (d, *J* = 6.3 Hz, 6 H, CH_3), 0.98[b] (d, *J* = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 155.1, 149.0, 147.4, 138.8, 138.4, 133.6, 128.7, 128.2, 127.9, 128.7, 123.6, 117.0, 112.3, 95.9, 93.4, 76.3, 74.0, 69.3, 61.5, 57.3, 56.2, 38.8, 20.6. (Notation: (a) major diastereomer; (b) minor diastereomer).

(−)-(2″*S*,*S*$_a$,2‴*S*)-1,1′-Dibenzoxy-3,3′-bis[2-(benzoxymethoxy)-1-propyl]-2,2′,6,6′,8,8′-hexamethoxy-5,5′-binaphthalene [(*S*,*S*$_a$,*S*)-87]. A solution of (*S*)-**85** (450 mg, 0.77 mmol, 2.2 equiv) in THF (7 mL) was treated with *n*-BuLi (0.44 mL, 0.77 mmol, 1.7 M in hexane, 2.2 equiv) at −78 °C under argon. After 1 h, a second flask containing a slurry of dry CuCN (31 mg, 0.35 mmol) in THF (0.5 mL) under argon at 23 °C was treated with TMEDA (0.16 mL, 1.05 mmol, 3.0 equiv) via a syringe, and the reaction mixture was allowed to stir until homogeneous. The organolithium solution at −78 °C was treated with the freshly prepared colorless solution of the CuCN·TMEDA complex via cannula, and the reaction mixture was allowed to stir for 1 h at −78 °C. Oxygen gas was bubbled through the solution at −78 °C for 1.2 h. The oxygen was removed *in vacuo*, and the reaction mixture was treated with 20% concentrated NH_4OH in saturated aqueous NH_4Cl (5 mL) and allowed to warm to 25 °C. The reaction mixture was diluted with EtOAc (20 mL), washed with 20% NH_4OH in saturated aqueous NH_4Cl (5 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (0.5 × 8 cm silica, 0−20% EtOAc/hexane) to afford (*S*,*S*$_a$,*S*)-**87** (238 mg, 68%) as an 8:1 mixture of atropisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.55 (m, 4 H, ArH), 7.44−7.40 (m, 4 H, ArH), 7.36−7.33 (m, 2 H, C4-H), 7.25−7.17 (m, 8 H, ArH), 7.12−7.00 (m, 4 H, ArH), 6.75[a] (s, 2 H, C7-H), 6.68[b] (s, 1 H, C7-H), 5.03 (m, 3 H, $ArCH_2$), 4.88 (m, 1 H, $ArCH_2$), 4.60−4.45 (m, 4 H, OCH_2OBn), 4.38−4.15 (m, 4 H, $ArCH_2$), 3.97 (s, 6 H, OCH_3), 3.90−3.85 (m, 8 H, OCH_3 and CH_2CH), 3.67 (s, 6 H, OCH_3), 2.65[a] (ABX, *J* = 3.1, 6.37, Δν = 151 Hz, 4 H, CH_2CH), 2.64[b] (m, 1 H, CH_2CH), 2.56[b] (m, 1 H, CH_2CH), 1.03[a] (d, *J* = 3 Hz, 6 H, CH_3), 0.98[b] (d, *J* = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 155.1, 149.0, 147.4, 138.8, 138.4, 133.6, 128.7, 128.2, 127.9, 128.7, 123.6, 117.0, 112.3, 95.9, 93.4, 76.3, 74.0, 69.3, 61.5, 57.3, 56.2, 38.8, 20.6; IR (neat) ν_{max} 2933, 1588, 1566, 1442, 1326, 1123, 1028 cm^{-1}; FABMS (NBA), *m/z* (relative intensity) 1002 (70, M^+), 895 (20), 683 (10), 547 (30), 307 (20), 154 (base). (Notation: (a) major diastereomer; (b) minor diastereomer).

(2″*S*,*S*$_a$,2‴*S*)-1,1′-Dihydroxy-3,3′-bis(2-hydroxy-1-propyl)-2,2′,6,6′-hexamethoxy-5,5′-binaphthalene [(*S*,*S*$_a$,*S*)-88]. A slurry of (*S*,*S*$_a$,*S*)-**87** (33 mg, 43 μmol) and 10% Pd/C (10 mg) in THF/MeOH (1:1, 1 mL) at 23 °C was placed under a hydrogen atmosphere using a balloon. After 3 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 6 cm, Et_3N-deactivated silica, 0−75% EtOAc/hexane) afforded the (*S*,*S*$_a$,*S*)-**88** (20 mg, 78%) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 2 H, ArOH), 6.71 (s, 2 H, C4-H), 6.33 (s, 2 H, C7-H), 4.15 (s, 6 H, OCH_3), 3.88 (s, 6 H, OCH_3), 3.82 (m, 2 H, $ArCH_2CH$), 3.69 (s, 6 H, OCH_3), 2.83−2.74 (m, 2 H, $ArCH_2CH$), 2.55−2.38 (m, 2 H, $ArCH_2CH$), 1.05 (d, *J* = 6.2 Hz, 6 H, CH_3); IR (neat) ν_{max} 3384, 2923, 1717, 1605, 1456, 1374, 1317, 1117 cm^{-1}; EIMS, *m/z* (relative intensity) 582 (M^+, base), 550 (20).

(2′*S*,*S*$_a$,2″*S*)-1,12-Bis(2-hydroxy-1-propyl)-2,4,6,7,9,11-hexamethoxy-3,10-perylenequinone [(*S*,*S*$_a$,*S*)-89]. A solution of (*S*,*S*$_a$,*S*)-**88** (14 mg, 24 μmol) and NaOH (2 mg, 53 μmol, 2.2 equiv) in THF/EtOH/H_2O (5:5:2, 1 mL) at 23 °C under argon was treated with $K_3Fe(CN)_6$ (114 mg, 0.31 mmol, 13 equiv). After 1 h, the reaction mixture was diluted with $CHCl_3$ (6 mL), washed with 5% aqueous HCl (3 × 3 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 4 cm, 0−5% MeOH/$CHCl_3$) afforded (*S*,*S*$_a$,*S*)-**89** (6.5 mg, 47%) as a red-orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 2 H, C5-H and C8-H), 4.15 (s, 6 H, OCH_3), 4.11−4.03 (m, 14 H, C14-H, C17-H, and OCH_3), 3.38−3.30 (m, 2 H, C13-H and C16-H), 2.64 (dd, *J* = 11.7, 4.8 Hz, 2 H, C13-H and C16-H), 0.64 (d, *J* = 5.7 Hz, 6 H, C15-H and C18-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 163.9, 163, 154, 131.4, 131.2, 130.8, 110.9, 108.5, 94.9, 76.6, 68.2, 60.8, 56.5, 56.1, 40.8, 23.3; IR (neat) ν_{max} 3404, 2932, 1609, 1457, 1210, 1144 cm^{-1}.

(2′*S*,*S*$_a$,2″*S*)-4,9-Dihydroxy-1,12-bis(2-hydroxy-1-propyl)-2,6,7,-11-tetramethoxy-3,10-perylenequinone (2, Phleichrome). Bromine (153 mg, 1.9 mmol) was carefully added to acetone (1 mL) at 23 °C, and the mixture was allowed to stir until colorless. A portion of this solution (43 μL) was added to a solution of (*S*,*S*$_a$,*S*)-**89** (6.5 mg, 1.1 μmol) in $CHCl_3$ (2 mL) at 23 °C. After 24 h, the reaction mixture was diluted with $CHCl_3$ (5 mL), washed with saturated aqueous $NaHCO_3$ (2 × 2.5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 6 cm, silica, 0−5% MeOH/$CHCl_3$) afforded **2** (1 mg, 17%) as red oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.79 (s, 2 H, OH), 6.56 (s, 2 H, C5-H and C8-H), 4.18 (s, 6 H, OCH_3), 4.04 (s, 6 H, OCH_3), 3.60 (dd, *J* = 12.9, 6.4 Hz, 2 H, C13-H and C16-H), 3.42 (ddq, *J* = 6.6, 6.4, 6.2 Hz, 2 H, C14-H and C17-H), 2.95 (dd, *J* = 12.9, 6.4 Hz, 2 H, C13-H and C16-H), 0.51 (d, *J* = 6.1 Hz, 6 H, C15-H and C18-H); IR (neat) ν_{max} 3405, 2927, 1605, 1452, 1212, 1158 cm^{-1}.

(2″*S*,*S*$_a$,2‴*S*)-1,1′-Dibenzoxy-3,3′-bis(2-hydroxy-1-propyl)-2,2′,6,6′-hexamethoxy-5,5′-binaphthalene [(*S*,*S*$_a$,*S*)-90]. A solution of (*S*,*S*$_a$,*S*)-**87** (238 mg, 0.24 mmol) in THF/MeOH (1:1, 1 mL) at 23 °C under argon was treated with acetyl chloride (0.2 mL) via a syringe. After 3 h, the reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (1 × 6 cm, Et_3N-deactivated silica, 0−45% EtOAc/hexane) afforded (*S*,*S*$_a$,*S*)-**90** (135 mg, 75%) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.1 Hz, 4 H, ArH), 7.45−7.35 (m, 6 H, ArH), 6.77 (s, 2 H, C7-H), 6.65 (m, 2 H, C4-H), 5.08 (s, 4 H, $ArCH_2$), 3.99 (s, 6 H, OCH_3), 3.92 (s, 6 H, OCH_3), 3.88−3.75 (m, 2 H, $ArCH_2CH$), 3.73 (s, 6 H, OCH_3), 2.80−2.65 (m, 2 H, $ArCH_2CH$), 2.54−2.40 (m, 2 H, $ArCH_2CH$), 1.04 (d, *J* = 6.1 Hz, 6 H, CH_3); IR (neat) ν_{max} 3425, 2932, 1587, 1458, 1338, 1209, 1120 cm^{-1}; EIMS, *m/z* (relative intensity) 762 (M^+, base), 639 (90), 548 (85), 516 (55), 489 (40), 415 (10), 357 (10), 267 (10).

(2″*R*,*S*$_a$,2‴*R*)-1,1′-Dibenzoxy-3,3′-bis[2-(benzoyloxy)-1-propyl]-2,2′,6,6′-hexamethoxy-5,5′-binaphthalene [(*R*,*S*$_a$,*R*)-95]. A solution of (*S*,*S*$_a$,*S*)-**90** (25.5 mg, 33 μmol), PPh_3 (42 mg, 0.16 mmol, 4.8 equiv), and benzoic acid (22 mg, 0.18 mmol, 5 equiv) in toluene/THF (4:1, 2.5 mL) at −23 °C under argon was treated with diisopropyl azodicarboxylate (32 μL, 0.16 mmol, 4.8 mmol) via a syringe. After 2.5 h, the reaction mixture was allowed to warm to 25 °C and stirred for an additional 2 h. The reaction mixture was diluted with Et_2O (5 mL), washed with saturated aqueous $NaHCO_3$ (2 × 3mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 6 cm, Et_3N-deactivated silica, 0−30% EtOAc/hexane) afforded (*R*,*S*$_a$,*R*)-**95** (14.7 mg, 46%) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 4 H, ArH), 7.56 (d, *J* = 7.2 Hz, 4 H, ArH), 7.47−7.30 (m, 12 H, ArH), 6.71 (s, 2 H, C4-H), 6.66 (s, 2 H, C7-H), 5.21 (apparent q, *J* = 6.7 Hz, 2 H,

$ArCH_2CH$), 5.04 (s, 4 H, $ArCH_2$), 3.98 (s, 6 H, OCH_3), 3.92 (s, 6 H, OCH_3), 3.57 (s, 6 H, OCH_3), 2.82 (d, J = 6.7 Hz, 4 H, $ArCH_2CH$), 1.08 (d, J = 6.2 Hz, 6 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 157.2, 155.1, 148.9, 147.5, 138.8, 133.6, 132.6, 131.2, 129.9, 128.6, 128.0, 123.6, 123.3, 117.2, 112.3, 96.3, 76.4, 71.9, 61.5, 57.4, 57.3, 56.2, 37.5, 19.7; IR (neat) ν_{max} 2932, 1714, 1590, 1454, 1337, 1273, 1119, 911, 714 cm^{-1}; EIMS, *m/z* (relative intensity) 970 (M^+, 60), 879 (45), 788 (65), 666 (20), 503 (base).

(2″*R*,S_a,2‴*R*)-1,1′-Dihydroxy-3,3′-bis[2-(benzoyloxy)-1-propyl]-2,2′,6,6′-hexamethoxy-5,5′-binaphthalene [(*R*,S_a,*R*)-96]. A slurry of (*R*,S_a,*R*)-**95** (14.7 mg, 15.2 μmol) and 10% Pd/C (3 mg) in THF/MeOH (1:1, 1 mL) at 23 °C was placed under a hydrogen atmosphere using a balloon. After 3 h, the reaction mixture was diluted with EtOAc (5 mL), filtered through a pad of Celite, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 6 cm, Et_3N-deactivated silica, 0−60% EtOAc/hexane) afforded (*R*,S_a,*R*)-**96** (6.3 mg, 53%) as a light brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 2 H, OH), 7.83 (d, J =7.1 Hz, 4 H, ArH), 7.46 (m, 2 H, ArH), 7.32 (apparent t, J = 7.7 Hz, 4 H, ArH), 6.61 (s, 2 H, C7-H), 6.40 (s, 2 H, C4-H), 5.23 (apparent q, J = 6.5 Hz, 2 H, $ArCH_2CH$), 3.92 (s, 6 H, OCH_3), 3.53 (s, 6 H, OCH_3), 3.47 (s, 6 H, OCH_3), 2.84 (dd, J = 9.8, 6.7 Hz, 4 H, $ArCH_2CH$), 1.11 (d, J = 6.2 Hz, 6 H, CH_3); IR (neat) ν_{max} 3386, 2933, 1714, 1605, 1450, 1274, 1116, 713 cm^{-1}.

(2′*R*,S_a,2″*R*)-1,12-Bis[2-(benzoyloxy)-1-propyl]-2,4,6,7,9,11-hexamethoxy-3,10-perylenequinone [(*R*,S_a,*R*)-98]. A solution of (*R*,S_a,*R*)-**96** (4.2 mg, 8.0 μmol) in diethyl ether (1 mL) was treated with activated MnO_2 (43 mg, 3.69 mmol, 10 wt equiv) at 23 °C. After 24 h, the reaction mixture was filtered through a pad of Celite and washed with 5% MeOH/$CHCl_3$ (3 × 3 mL), and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (0.25 × 2 cm silica, 0−5% MeOH/$CHCl_3$) afforded the title compound (4.2 mg, 67%) as a 5:1 inseparable mixture of (*R*,S_a,*R*)-**98** and dihydroperylenequinone. Perylenequinone was characterized: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (apparent t, J = 7.2 Hz, 4 H, ArH), 6.95−6.86 (m, 6 H, ArH), 6.42 (s, 2 H, C5-H and C8-H), 5.09 (m, 2 H, C14-H and C17-H), 4.18 (s, 6 H, OCH_3), 4.09 (s, 6 H, OCH_3), 3.84 (s, 6 H, OCH_3), 3.37 (d, J = 13.4 Hz, 2 H, C13-H and C16-H), 2.96 (apparent t, J = 10.2 Hz, 2 H, C13-H and C16-H), 1.22 (d, J = 6.2 Hz, 6 H, C15-H and C-18-H); IR (neat) ν_{max} 2933, 1714, 1620, 1574, 1538, 1460, 1271, 1213 cm^{-1}.

(2′*R*,S_a,2″*R*)-4,9-Dihydroxy-1,12-bis[2-(benzoyloxy)-1-propyl]-2,6,7,11-tetramethoxy-3,10-perylenequinone (Calphostin A, 1a). Bromine (100 mg, 1.25 mmol) was carefully added to acetone (1 mL) at 23 °C via a pipet, and the mixture was allowed to stir until colorless. An aliquot of this solution (0.6 mL) was added to a solution of (*R*,S_a,*R*)-**98** (3 mg, 3.8 μmol) in $CHCl_3$ (0.5 mL) at 23 °C. After 24 h, the solvent was removed, and the residue was purified by flash chromatography (0.25 × 2 cm silica, 0−1% MeOH/$CHCl_3$) to afford **1a** (1.3 mg, 45%) as a red oil: ^1H NMR (300 MHz, $CDCl_3$) δ 15.82 (s, 2 H, OH), 7.22 (t, J = 7.2 Hz, 4 H, ArH), 6.90 (apparent t, J = 7.8 Hz, 4 H, ArH), 6.84 (dd, J = 7.8, 1.3 Hz, 4 H, ArH), 6.22 (s, 2 H, C5-H and C8-H), 5.03 (m, 2 H, C14-H and C17-H), 4.32 (s, 6 H, OCH_3), 3.88 (s, 6 H, OCH_3), 3.60 (dd, J = 13.4, 2.2 Hz, 2 H, C13-H and C16-H), 3.18 (dd, J = 13.4, 10.2 Hz, 2 H, C13-H and C16-H), 1.29 (d, J = 6.2 Hz, 6 H, C15-H and C-18-H).

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Supporting Information Available: Text giving detailed experimental procedures and full characterization of intermediates (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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