Total Synthesis of the Calphostins: Application of Fischer Carbene Complexes and Thermodynamic Control of Atropisomers

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The total syntheses of the potent protein kinase C inhibitors calphostins A, B, C, and D as well as a variety of structural analogues are reported. An aminobenzannulation reaction of an enantiopure chromium Fischer carbene complex is utilized to prepare a pentasubstituted naphthylamine. After optimization of side-chain substituents, conversion of the naphthylamine to an *o*-naphthoquinone was followed by biomimetic oxidative dimerization using trifluoroacetic acid and air yielding a 1:2 P/M mixture of atropisomeric perylenequinones. Thermal equilibration to a 3:1 P:M atropisomeric ratio and separation of the perylenequinones followed by side chain desymmetrization and functionalization led to the total synthesis of enantio- and diastereomerically pure calphostin C in only twelve steps from commercially available starting materials. In addition, calphostins A, B, D, and several structural analogues were prepared to evaluate biological activities.

Introduction

Calphostins A, B, C, and D (**1**−**4**) are architecturally interesting and biologically significant perylenequinones that were isolated by Tamaoki et al. in 1989 from *Cladosporium cladosporioides* (Figure 1).[1,2] The calphostins, and calphostin C in particular, were found to be potent and selective inhibitors[3] of protein kinase C (PKC), a phosphorylation enzyme that plays a central role in signal transduction.[4,5] PKC represents one arm of the intracellular signaling pathway, and its overstimulation is thought to underlie not only developmental and proliferative diseases such as cancer and psoriasis but also inflammatory diseases, diabetes, and central nervous system disorders.[6,7] PKC exists as a family of 11 related isozymes,[8] and the differential expression of these across different cell types has led to the search for isozyme selective inhibitors.[9,10] PKC contains two domains, a highly conserved *C*-terminal catalytic domain[11] and a *N*-terminal regulatory domain.[8] The vast majority of PKC inhibitors which have been investigated bind to the less desirable catalytic domain; however, the calphostins are unique in that they bind to the regulatory domain, making them potentially more suitable as isozyme selective inhibitors.[12] The calphostins have generated considerable attention as potential agents for anticancer therapy and have been investigated in a variety of cancers showing excellent results against bladder,[13] brain,[14] prostate,[15] and leukemia cell lines[16] where PKC activity is high. Calphostin C was ineffective against a colorectal cell line in accord with the low activity of PKC found in

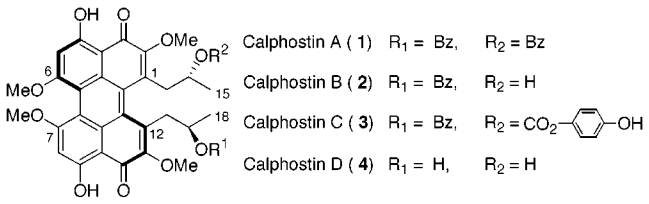

Figure 1. Structures of the calphostins.

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colorectal cells.[17] Explorations into the downstream effects of PKC using calphostin C have uncovered several interesting physiological activities including inhibition of angiogenesis,[18] multidrug resistance (MDR),[19] and Bcl-2.[20] One of the key disadvantages of the calphostins that has hampered their development as therapeutic agents is their requirement of light for activity; although this feature has been exploited in their development as substrates for photodynamic therapy.[21,22]

Our interest in the calphostins arises from not only their remarkable biological activity but also their unique topological features. The defining characteristic of the calphostins is their central highly substituted perylenequinone core, which is not flat, but canted at an angle of 10° out of planarity due to eclipsing interactions of the side chains at C1 and C12 as well as the methoxy substituents at C6 and C7.[23] The result is that the central core is axial chiral and can exist as two atropisomers.[24] Atropisomerism has recently emerged as a subject of great interest in organic synthesis.[25] Many beautiful strategies have been developed to address issues in atropselective synthesis such as Bringmann's lactone concept,[26] Uemura's tricarbonyl(arene) chromium complex template,[27] Lipshutz's chiral tether,[28] or Meyer's oxazoline auxiliary method;[29] however, none offer a general solution or are readily applicable to the synthesis of the calphostins.

Three total syntheses of the simplest, and least biologically active, members of this group have been reported which all take advantage of the inherent symmetry in the calphostins. Broka reported the first synthesis of a naturally occurring perylenequinone; however, his synthesis required 18 steps alone to arrive at an appropriately functionalized naphthalene core. This naphthalene was dimerized to a perylenequinone and then further elaborated to calphostins A and D.[30] Coleman and Grant designed innovative new chemistry for the fabrication of a naphthalene precursor, but their synthesis suffered from poor atropselective control in the naphthalene dimerization and required ninteen steps to produce calphostin A.[31] Both of the aforementioned syntheses built the perylenequinone core stepwise from naphthalene derivatives, constructing each biaryl bond separately. Diwu and Lown, who were interested in perylenequinones for their use as singlet oxygen sensitizers in photodynamic therapy, developed the most efficient synthesis of the perylenequinone core.[32] Building on the work of Chao and Zhang,[33] they found that *o*-naphthoquinones underwent oxidative dimerization to afford perylenequinones in a single step. This new protocol greatly simplifies perylenequinone synthesis and was employed by Hauser in a total synthesis of calphostin D, the simplest member of the calphostins.[34] Hauser's synthesis is the most efficient synthesis of the three reported, requiring only 14 steps, but it suffers from lack of diastereocontrol in the key dimerization process. We provide herein a detailed report on our synthetic endeavors toward the calphostins culminating in the concise and enantioselective total syntheses of calphostins A−D, as well as the synthesis of a number of structural analogues, featuring a benzannulation of an enantiopure Fischer carbene complex and an atropselective thermal isomerization to control axial chirality.[35]

Retrosynthetically, we sought to assemble the perylenequinone core through a biomimetic oxidative dimerization of two *o*-naphthoquinone moieties to provide the fully functionalized perylenequinone nucleus following the precedent of Diwu and Lown[32] as well as Hauser[34] (Scheme 1). In this single step, two new biaryl carbon−carbon bonds are formed with the simultaneous creation of the chiral axis. This coupling proceeds through a binaphthalene intermediate; thus, it was envisioned, at least as a first approach, that relay of the remote side chain chirality to the incipient biaryl axis would provide a mechanism for stereocontrol. Elaboration of the side chain appendages allows access to all of the naturally occurring calphostins. The most important target, calphos-

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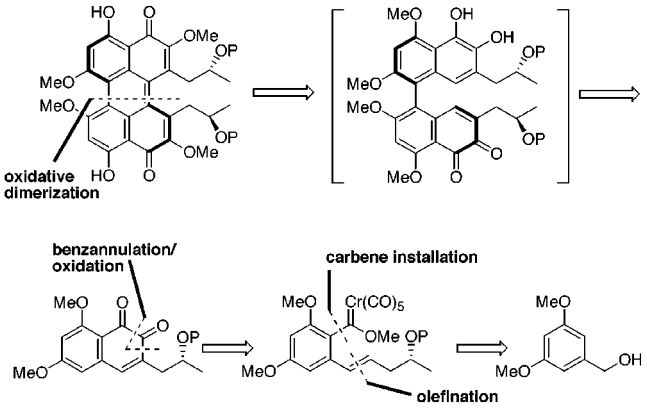
Scheme 1. Retrosynthetic Disconnections for the Calphostins



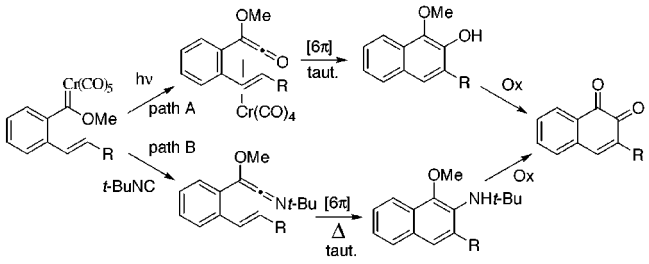
tin C, has different side-chain substituents, so we planned on effecting a desymmetrization of a symmetric perylenequinone rather than the cross-coupling of two naphthalene subunits as initially proposed by Coleman and Grant.[31]

This analysis targets a highly functionalized *o*-naphthoquinone as a critical intermediate. The requisite *o*-naphthoquinone precursors can be prepared by either of two benzannulation strategies developed in these laboratories utilizing chromium carbene complexes. In the first, photolysis of a formally dienyl chromium carbene complex leads, via electrocyclization of a chromium complexed ketene intermediate, to an *o*-alkoxy phenol product (path A, Scheme 2).[36] The second annulation method involves an isonitrile thermal addition reaction forming a chromium complexed ketenimine intermediate, which undergoes an electrocyclization leading to an *o*-alkoxy aromatic amine product (path B, Scheme 2).[37] Oxidation of either of these products yields the same *o*-naphthoquinone required for perylenequinone synthesis. The carbene complexes are prepared from the corresponding aryl bromides which are in turn accessible by a variety of procedures. Moreover, our antithetic disconnections allow us to easily introduce different side-chain appendages to prepare a variety of modified side-chain analogues, which is important for our mapping of structure−activity relationships.

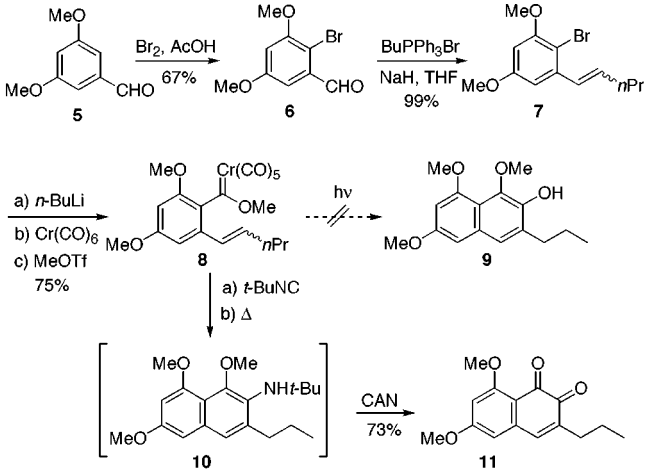
Results and Discussion

Model System. Our initial foray into the synthesis of the calphostins involved preparation of a model system that retained the essential features of the real system. To this end, we chose to prepare the *n*-propyl side chain derivative, which lacked the alcohol functionality of the natural products, thus simplifying the structure and making the issue of atropselectivity moot. Regioselective monobromination of 3,5-dimethoxybenzaldehyde with bromine in cold acetic acid provided bromoaldehyde **6**[38] (Scheme 3). Wittig olefination with *n*-butyltriphenylphosphonium bromide furnished an approximately 1:1 mixture of isomeric olefins **7**. Treatment of the aryl bromide with *n*-BuLi to effect metal−halogen exchange, addition

Scheme 2. Photochemical and Thermal Benzannulation Reactions of an Aryl−Alkenyl Carbene Complex

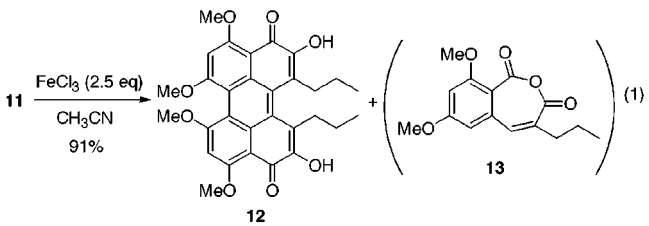


Scheme 3. Preparation of Model *o*-Naphthoquinone 11



of chromium hexacarbonyl, and methylation employing methyl triflate afforded the methoxy carbene complex **8**. Attempts to achieve the desired photocyclization[36] to the *o*-alkoxynaphthol derivative **9** were impeded by the very electron-rich aryl ring, which may inhibit carbonyl insertion in the carbene moiety. Fortunately, the alternative thermal isonitrile reaction[37] proved more productive. Addition of *tert*-butyl isonitrile to carbene complex **8** at room temperature provided the chromium complexed ketenimine. This step was conveniently monitored by observing loss of the deep red color of the carbene complex. Subsequent heating at reflux in THF effected electrocyclization to give the *o*-alkoxynaphthylamine derivative **10** which could be isolated, but was more conveniently oxidized in situ with ceric ammonium nitrate (CAN) to afford the desired *o*-naphthoquinone **11**.

With the key *o*-naphthoquinone in hand, we began to explore dimerization conditions. Following the work of Diwu and Lown, we found that, through the agency of iron(III) chloride in acetonitrile, dimerization proceeded smoothly to afford 91% of the perylenequinone **12** (eq 1)![32a] Interestingly, if this oxidative dimerization was not



conducted under strictly anaerobic conditions, varying amounts (5−10%) of the novel anhydride byproduct **13**

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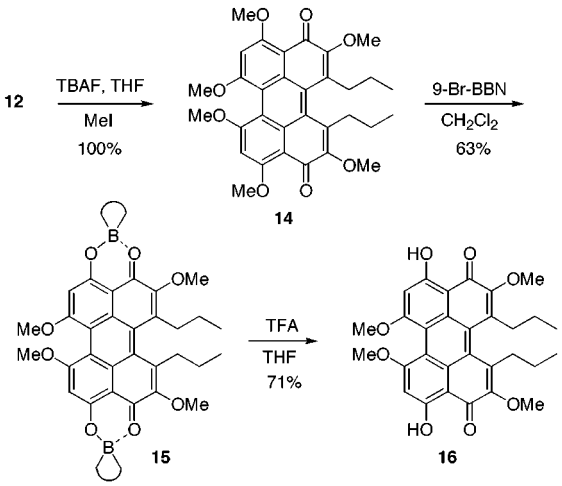
Scheme 4. Methylation−Demethylation Sequence



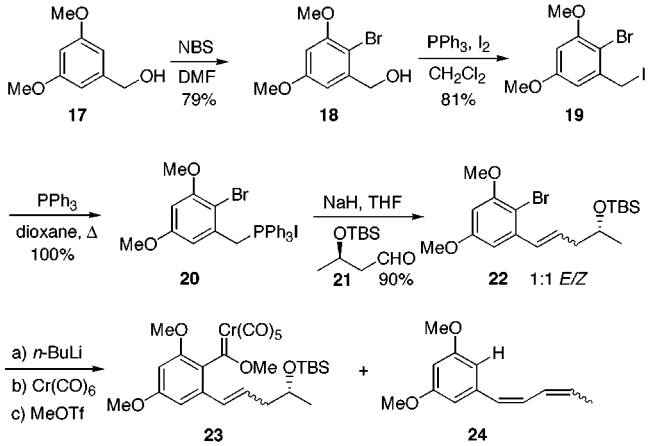
were isolated. This impressive transformation bears close resemblance to that carried out by a class of enzymes known as the catechol dioxygenases. These are non-heme iron enzymes that catalyze oxidation of catechols to the corresponding bis-carboxylic acids via intermediate anhydrides.[39]

Adjustment of the methylation pattern to reflect the natural methylation pattern found in the calphostins was readily accomplished (Scheme 4). Treatment of perylenequinone **12** with methyl iodide using tetrabutylammonium fluoride (TBAF) as base provided hexamethoxyperylenequinone **14** in quantitative yield.[40] Regioselective demethylation was achieved using 9-bromo-9-borabicyclo-[3.3.1]nonane (9-Br-BBN), which afforded the chromatographically isolable bis-cyclic borane adduct **15**. Subsequent exposure to trifluoroacetic acid (TFA) liberated the product perylenequinone **16**.[41] This route to dideoxycalphostin D proved to be extremely efficient, highlighted by an innovative *o*-naphthoquinone synthesis, an outstanding oxidative dimerization process, and new conditions for regioselective demethylation.

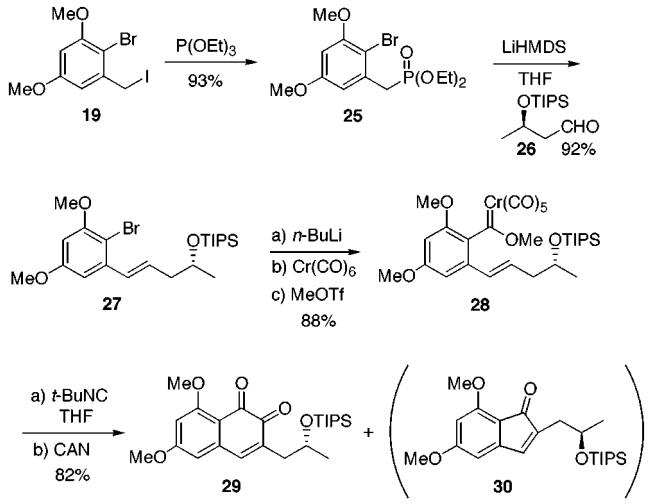
Toward the Calphostins. With an efficient route to the perylenequinone core established, we set out to explore the real system, which differed from the model solely by the alcohol functionality at the 2′ positions of the side chains. With the resulting introduction of stereocenters, the issue of atropselectivity became central and guided many of the modifications to the model route. The synthesis of aryl bromide **22** followed a similar synthetic sequence outlined for the model system except that the umpolung coupling arrangement of aldehyde **21** and phosphonium salt **20** proved more successful (Scheme 5). Unfortunately, only low yields of the desired carbene complex **23** were obtained with attendant formation of diene **24**. Generation of this side product is reconciled by E2 elimination of the lithiated *cis*-alkene, which positions the allylic hydrogens in close proximity to the aryl anion.

Previously, we were satisfied with a nonstereoselective olefin synthesis since the geometry of the olefin is lost

Scheme 5. Attempted Formation of Carbene Complex 23



Scheme 6. Synthesis of Substituted *o*-Naphthoquinone 29



in the benzannulation reaction; however, we now needed an olefination approach that exclusively delivered the *trans*-olefin.[42] This was easily achieved employing benzyl phosphonate **25** and (*R*)-3-triisopropylsiloxybutyraldehyde **26** to provide solely the desired *E*-bromoarylalkene **27** (Scheme 6). The triisopropylsilyl protecting group was required to avoid silyl migration in the intermediate alkoxide of the olefination reaction.[43] Carbene formation from *E*-olefin **27** now proceeded without incident to furnish **28** in 88% yield. Conversion of the pivotal carbene complex to the *o*-naphthoquinone using the isonitrile method[37] proceeded smoothly to afford **29** in 82% yield. However, small amounts of an indenone side product **30** were isolated, presumably arising from direct electrocyclization of the carbene complex.[44] This side reaction was overridden by conducting the reaction at high concentrations (∼1 M) to favor reaction with the isonitrile. Surprisingly, photocyclization of carbene complex **28** fur-

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(42) Alkene **22** could be isomerized to a 6:1 *E*/*Z* mixture of isomers employing iodine; however, the moderate selectivity coupled with the additional synthetic step favored the Horner−Wadsworth−Emmons olefination.

(43) The bulkier TIPS group has a reduced propensity to migrate as compared to the smaller TBS group. For an encyclopedic review of the TIPS protecting group, see: Rücker, C. *Chem. Rev.* **1995**, *95*, 1009−1064.

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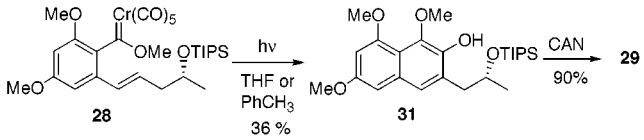
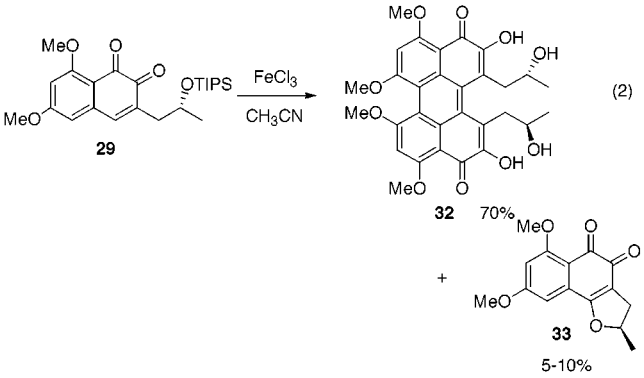
Scheme 7. Photocyclization of Carbene Complex 28



nished naphthol **31** in 36% yield in contrast to the model system, which never provided more than a few percent of the benzannulated product (Scheme 7). The bulky triisopropylsiloxy group may contribute to the improved photocyclization by not allowing the carbene to remain in coplanar conjugation with the electron-rich aromatic core. Nevertheless, the photocyclization efficiency could not be further improved, as a result the isonitrile route continued to be employed.

We were now ready to explore dimerization of the *o*-naphthoquinone **29** employing iron(III) chloride in acetonitrile. Dimerization, with concomitant deprotection of the TIPS groups, afforded 70% of the desired perylenequinone **32** as an approximately 1.1:1 P/M mixture of atropisomers along with small amounts of the dihydrofuranyl fused tricycle **33** (eq 2). The interesting



tricyclic *o*-quinone **33** side product was always isolated in 5−10% yields and resulted from Michael addition of the side chain alcohol into the quinone followed by oxidation. Product **32** only varies from calphostin D in the methylation pattern; consequently, we attempted to convert this inseparable mixture of atropisomers to calphostin D by a methylation−demethylation sequence. Regrettably, the obstinate side-chain alcohols or the enols evaded all attempts at methylation or further functionalization. Mild conditions failed to induce reaction, while more forcing conditions led to demethylation and decomposition of **32**.[45] Some of this difficulty may be attributed to an extended hydrogen-bonding network that is formed between the carbonyl, enol, and side-chain alcohol functions. Evidence for this is provided in the ^{1}H NMR spectrum, which shows very broad signals at room

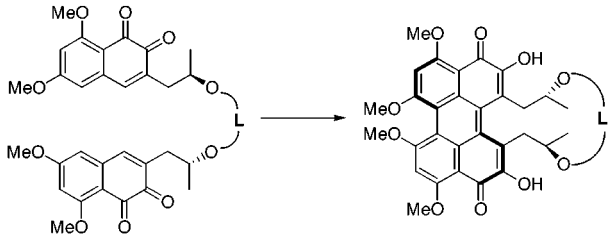


Figure 2. Tether design.

temperature of all the side-chain hydrogens, suggestive of hindered rotation of the side chains. Although we had gained rapid entry into a functionalized perylenequinone, the dimerization was rather discouraging since the process was not atropselective and the recalcitrant perylenequinone could not be coerced into any useful reaction manifold, despite great efforts.

Atropselective Synthesis. Provision for control of atropselectivty was not properly addressed in the original synthetic design, a most crucial issue for synthesis of the calphostins. At this point in the synthesis, much effort had already been expended, so an approach that maintained as much continuity in our synthetic scheme was desired. Employing a tether would be synthetically minimally disruptive and potentially favor the formation of a single diastereomer in addition to facilitating the dimerization process by bringing the two quinone moieties in close proximity.[46] The tether could be achiral and utilize the side-chain chirality to control atropisomer formation or the tether could be chiral with the resultant possibility of double diastereoselection for control of atropisomerism. Attachment could be achieved at several positions on the quinone precursor, clearly the most synthetically accessible position was the side-chain alcohol (Figure 2).

Before proceeding synthetically, several achiral tethers were first examined computationally by a molecular mechanics conformational search of perylenequinone products with tethers linking the side-chain alcohols using Spartan.[47] The product geometries were minimized for each atropisomer and all tethers uniformly favored the undesired M atropisomer. To verify the computational results, several tethered bis-naphthoquinones were prepared, but only the *o*-phthaloyl-tethered bis-naphthoquinone **35** underwent dimerization to afford a single diastereomeric product **36** (Scheme 8). Bis-naphthoquinone **35** was prepared from carbene complex **28** in the sequence outlined in Scheme 8. Conversion of **36** to derivative **38M** by methylation of the enols and cleavage of the tether with NaOMe (Scheme 9) secured the absolute configuration by comparison to the CD spectra of **38P** (prepared independently), which indicated that **36** was the M atropisomer as predicted by computations.

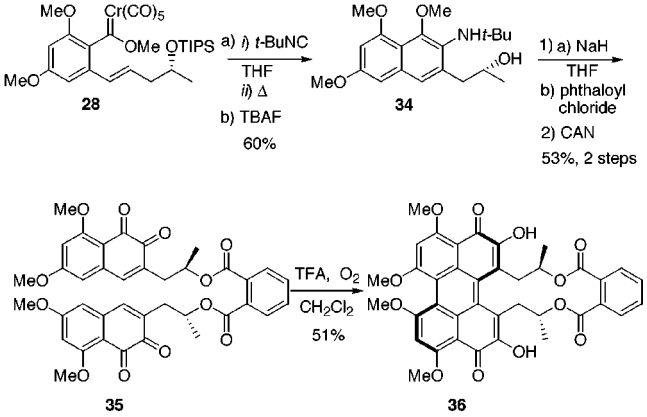
While our synthetic options had been severely limited, we realized that a simple protecting group change might

(45) A brief list of some methylation conditions surveyed: (a) CH_2N_2: see ref 32b. (b) K_2CO_3, MeI: Adams, S. P.; Whitlock, H. W., Jr. *J. Org. Chem.* **1981**, *46*, 3474−3478. (c) Ag_2O, MeI: Arnone, A.; Camarda, L.; Nasini, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1387. (d) AgOTf, MeI: Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett.* **1994**, 8111−8112. (e) CsF, MeI: Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230−4234. (f) $Bu_2Sn(OMe)_2$, MeI: Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913−914. (g) Me_2SO_4, EtOH, NaOH: *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. VI, pp 800−803. (h) For H-bonded alcohols: TBAF, DMF, MeI: see, ref 40. (i) For a recent paper with excellent references for the chemoselective O-methylation of phenols under nonaqueous conditions, see: Basak, A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1998**, *39*, 4883−4886.

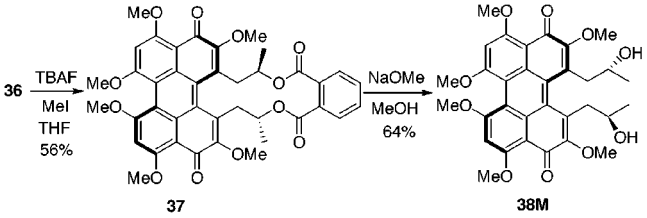
(46) Several tethering strategies have been developed using a chiral auxiliary to control the sense of atropselection. (a) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357−3366. For an application in synthesis, see: Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606−2612. (c) Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249−3254. (d) See ref 28.

(47) *Spartan, SGI Version 5.0*; Wavefunction Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612. http://www.wavefun.com/.

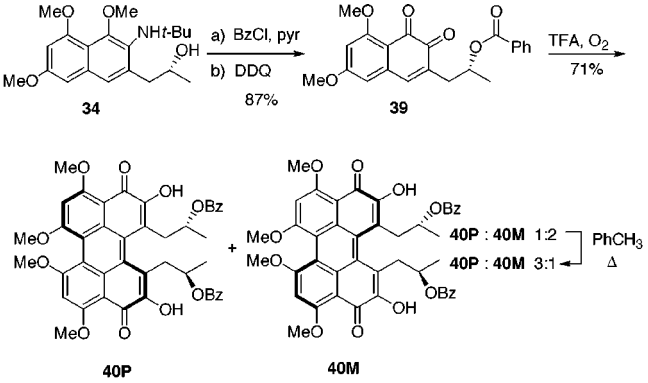
Scheme 8. Preparation of a Tethered Perylenequinone



Scheme 9. Securing the Stereochemistry of 36 by Conversion to Derivative 38M



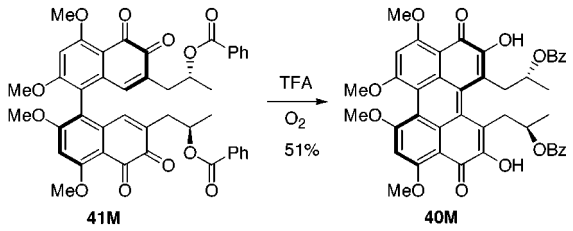
Scheme 10. Preparation of Benzoylated Perylenequinone



greatly alleviate our difficulties.[48] Since the TIPS protecting group was incompatible under the dimerization conditions, it was anticipated that the benzoate protecting group, which also happens to conveniently be the side-chain functional group in some of the calphostins, should be stable.[49] Deprotection of *o*-naphthoquinone **29** proved to be problematic, due to the propensity for the side-chain alcohol to undergo an internal Michael addition into the quinone; however, installation of the benzoate at an earlier stage was readily accomplished. Protection of naphthalene **34** as the benzoate ester and oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) provided the benzoylated naphthoquinone **39** (Scheme 10).

We were delighted to find that dimerization proceeded smoothly using modified conditions of Diwu and Lown employing trifluoroacetic acid (TFA) and air as the oxidant to provide perylenequinone **40** in 71% yield with the benzoate intact (Scheme 10).[32b,50] Disappointingly, a 2:1 mixture of atropisomers favoring the undesired M isomer was obtained.[51] We were aware that the chiral axis was not configurationally stable at high temperatures as the isomerization barrier was measured for a related perylenequinone to be 21 kcal/mol, and we had accordingly taken precautions to avoid reactions at elevated temperatures.[23] Now, we considered turning this apparent limitation to our advantage. After carefully sparging with argon, the perylenequinone was found to smoothly epimerize in refluxing toluene over 36 h. We were elated to discover that the 1:2 P/M ratio of atropisomers thermally equilibrated to a 3:1 separable mixture favoring the desired P atropisomer! Recycling **40M** led to an overall yield of 56% for **40P** from **39**. From molecular modeling, as well as NMR data, the observed selectivity can be explained as arising from a stabilizing π interaction[52] of the side chain benzoate with the perylenequinone core, which is favorable for the P isomer, but conformationally inaccessible for the M isomer.[53] The ^{1}H NMR beautifully illustrates this, as the ortho protons of the side chain benzoate groups of the P isomer are shielded by 0.7 ppm relative to the M isomer.

The binaphthoquinone **41** could also be isolated as a 1:1 mixture of atropisomers, if the reaction was stopped prematurely (Scheme 11).[54] Since the biaryl bond that is remote from the side chain stereogenic centers is generated first, the lack of significant stereoinduction is understandable. Formation of the remote bond is the stereodefining step as the biaryl axis is configurationally stable at room temperature. To verify that the binaphthoquinone chirality was preserved in conversion to the perylenequinone, atropisomerically pure binaphthoquinone **41M** was oxidatively closed to perylenequinone **40M** with retention of configuration in accord with a related binaphthalene system observed by Broka (eq 3).[30]



(3)

Hauser proposed a very tenable mechanism for acid-catalyzed dimerization of *o*-naphthoquinones via intermediates such as **42** (Scheme 11).[34] Two mechanistic

(48) For an excellent review on the importance of protecting group strategies, see: Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056−2083.

(49) The acetate protecting group was stable to TFA in Hauser's synthesis (ref 34) of Calphostin D and the more stable benzoate was anticipated to also be stable under the reaction conditions.

(50) Conditions employing $FeCl_3/CH_3CN$ also provided useful yields of the product perylenequinone, typically 40−50%; however, the experimentally simpler conditions utilizing TFA and oxygen were cleaner and afforded higher overall yields.

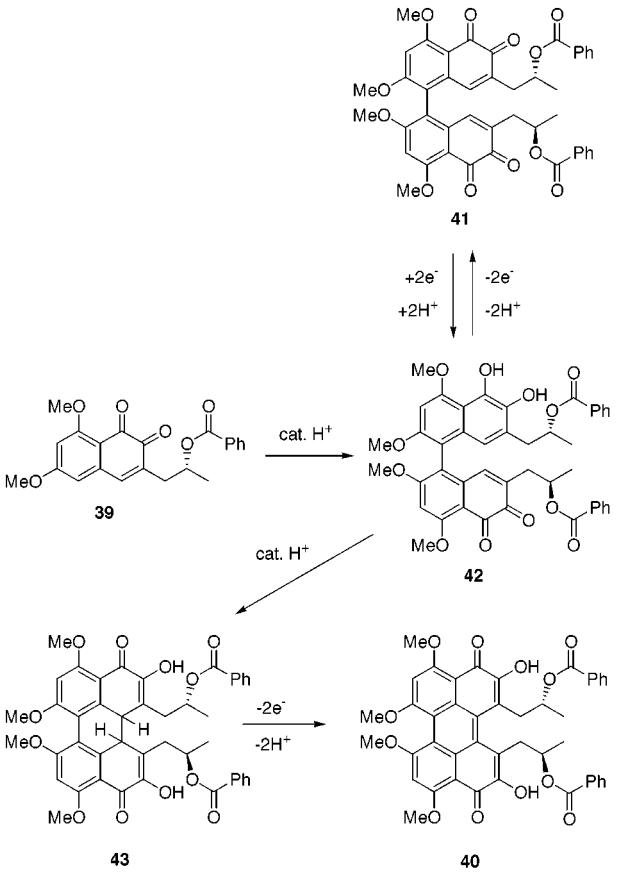
(51) The stereochemistry was confirmed by elaborating the minor diastereomer to Calphostin A by a methylation/demethylation sequence which indicated that this was indeed the P atropisomer by comparison to the literature data in ref 1b. Similarly, the major diastereomer was elaborated to the M-atropisomer of Calphostin A as determined by comparison of its CD spectra to that of Calphostin A.

(52) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330−5331.

(53) The hexamethoxyperylenquinone **44** with only side chain alcohols isomerized to a 1:1 mixture of atropisomers demonstrating the importance of the benzoate function. See ref 23 for a similar finding with cercosporin.

(54) A related binaphthoquinone was isolated by Hauser; see ref 34. Diwu and Lown also isolated a regioisomeric binaphthoquinone; see ref 32a.

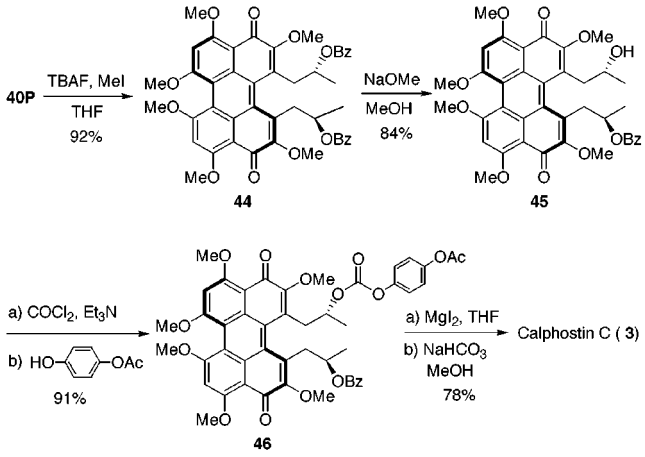
Scheme 11. Dimerization Mechanism



manifolds diverge from this common intermediate. The first involves closure to dihydroperylenequinone **43** where subsequent oxidation leads to perylenequinone **40**. The second, less fruitful, pathway for **42** is direct oxidation to binaphthoquinone **41**. Hauser found that this second pathway was unproductive as the binaphthoquinone did not undergo closure to the perylenequinone; consequently, he attempted to avoid this pathway by slow addition of an oxidant. In contrast, we found that binaphthoquinone **41** closed to perylenequinone **40**, albeit much more slowly. Thus, 50% yields of perylenequinone **40** could be isolated from **39** after only a few hours reaction along with 20−30% of binaphthoquinone **41**. Since the binaphthoquinone closed slowly, the naphthoquinone dimerization reaction was routinely run for 24−36 h until complete consumption of intermediate binaphthoquinone was observed by TLC. The reluctance to closure of the binaphthoquinone can be readily understood by examining the reaction mechanism. Reduction to intermediate **42** would formally allow a pathway whereby binaphthoquinone could reenter a productive pathway to perylenequinone; however, considering the reaction conditions (TFA, O_2), this seems unlikely, but would account for the sluggishness of the reaction. One possible reducing agent is of course dihydroperylenequinone **43**.

Completion of the Synthesis. With a successful route to enantiomerically and atropisomerically pure perylenequinone **40P**, completion of the calphostin C synthesis was undertaken (Scheme 12). Methylation of **40P** provided hexamethoxyperylenequinone **44** which was utilized as a common intermediate for the synthesis of all four calphostin targets. This reaction was conveniently followed colorimetrically as the blood-red perylenequinone solution turned dark green upon addition of TBAF indicating formation of the anion and the sanguine color returned within minutes upon completion of methylation. Desymmetrization of the calphostin side chains was performed by a carefully controlled methanolysis of **44**, which provided an astonishing 84% yield of the monobenzoate **45** based on a 58% conversion. This was indeed noteworthy since we expected a statistical mixture of products. One rationale is a steric activation for loss of the first benzoyl group. A second, and more intriguing explanation, would be mono debenzoylation followed by hemiortho ester formation under the basic conditions that protects the second benzoate.

Scheme 12. Completion of Calphostin C Synthesis



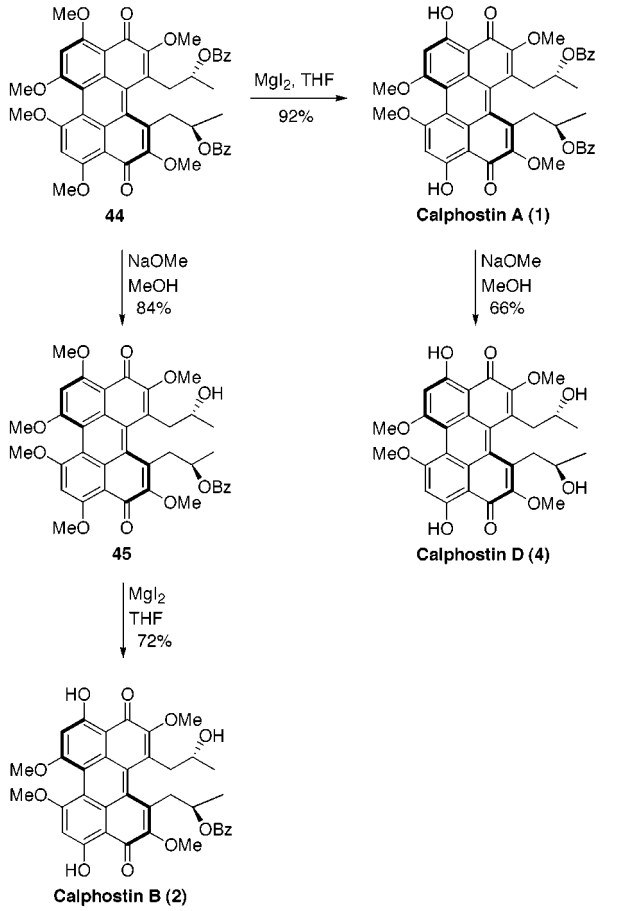
The final task remaining was installation of the mixed carbonate linkage, which was fashioned by reacting the secondary alcohol on **45** with phosgene to afford the chloroformate ester that was not isolated, but reacted in situ with 4-acetoxyphenol providing the mixed carbonate **46**.[55] A monoprotected hydroquinone had to be employed due to the preference of dihydroquinone to react on both hydroxy groups. Careful choice of the protecting group was made such that it could be removed under extremely mild conditions, provide favorable solubility properties to the hydroquinone, and enhance the reactivity of the *p*-hydroxyl group. Illustrating this final point, the mono-TBS protected dihydroquinone failed to react, but the monoacetate-protected dihydroquinone reacted rapidly.

Regioselective demethylation using freshly prepared MgI_2[34,56] followed by chemoselective methanolysis of the acetate in the presence of the benzoate and carbonate linkages provided calphostin C (**3**). While our 9-Br-BBN/TFA protocol developed in the model system for the regioselective demethylation proved satisfactory, the simple one-step procedure used initially by Hauser employing MgI_2 provided higher overall yields on the more highly functionalized calphostin C. Analogously, the other calphostins were efficiently prepared from the common hexamethoxyperylenequinone intermediate **44** (Scheme 13). Regioselective demethylation of **44** with MgI_2 yielded calphostin A (**1**). Initial attempts to prepare calphostin D by hydrolysis of the benzoates followed by

(55) Petersen, U. In *Houben-Weyl Methoden der Organischen Chemie*; Hagemann, H., Ed.; Georg Thieme Verlag: 4. Auflage, Stuttgart, 1983; *Bd E4*, 66−77.

(56) Yamaguchi, S.; Nedachi, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **1999**, *40*, 7363−7365.

Scheme 13. Synthesis of Calphostins A, B, and D



demethylation of the *peri*-methoxy groups were unrewarding, providing only trace amounts of product. However, the reversed sequence of demethylation followed by methanolysis was more productive. Thus, methanolysis of calphostin A provided calphostin D (**4**). Calphostin B (**2**) was in turn prepared by demethylation of **45**. Synthetic calphostins A, B, C, and D were identical to natural samples by comparison of ^{1}H NMR, ^{13}C NMR, CD, UV, IR, and HRMS spectral data.[1c]

Synthesis of Analogues. Our flexible and efficient synthetic route allowed us to prepare a number of calphostin analogues that kept the central perylenequinone pharmacophore intact while varying the functionality around the periphery of this core. Additionally, we explored structures of key intermediates and side products that we obtained during the total synthesis of the calphostins. Together, these approaches afforded more than twenty structurally unique compounds that will provide a preliminary examination of the SAR of the calphostins. The structural features that we addressed were as follows: (1) the axial chirality of the perylenequinone; (2) the methylation pattern; (3) the appendage length; and (4) the appendage oxygenation pattern (Figure 3). Although much effort was spent in controlling the axial chirality, we were also interested in the bioactivity of the unnatural M-atropisomer. Adjustments to the methylation pattern are worth investigating since the methylation of the C-2 and C-11 enols leads to compounds that possess a significant red-shift in the UV spectrum making these derivatives more suitable as agents for photodynamic therapy.[57] Moreover, the change in hydrogen-bonding capabilites would be expected to modulate calphostin binding. We planned at the outset to explore most extensively modifications on the side chains as slight structural perturbations within the natural series have significant effects on the bioactivity.[1b]

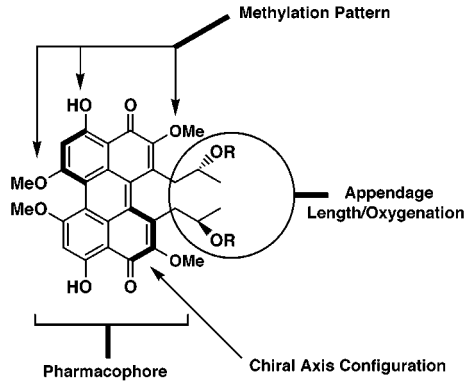


Figure 3. SAR analysis.

It will be interesting investigating the activity of model perylenequinone **16** since it will provide insight into whether side chain oxygenation is required. The truncated des-methyl analogue **47** reduces the stereochemical elements present in the calphostins by removing the stereogenic center of the side chain (Figure 4). In analogue **48**, the appendage oxygenation has been shifted to the terminal position of the side chain, which probes the positional requirements of the side-chain oxygenation. The methylation patterns of all three series of compounds will also be examined to determine how alteration of these important functionalities affects the biological activity. The interesting cyclized perylenequinone **50** was isolated during the synthesis of analogue **48**. The novel structure will be investigated as the side chains are now completely folded back onto the perylenequinone core and the resulting drastic conformational change should affect the biological profile. The phthaloyl-tethered perylenequinone **49** will be investigated because the side-chain sector is also fairly restricted as in **50**, but has an aromatic residue which appears to be important for activity. Additionally, **49** possesses the opposite M axial chirality. To more appropriately address the axial chirality issue, we prepared analogue **51** from **40M** which is the M-axial diastereomer of calphostin A. Last, we hypothesize that the calphostins bind edge-on in the binding pocket, whereby only half of the molecule strongly interacts, while the other half resides outside the binding pocket. Thus, the greater activity of calphostin C versus calphostin A may be due to the presence of the *p*-hydroxyphenyl carbonate moiety versus the benzoate function. Therefore, the C_2 symmetric analogue **52** was prepared from **44** via a route analogous to that for calphostin C. Future studies may explore replacement of the carbonate moiety with a more stable isostere since a pilot pharmokinetics study has shown that calphostin C is hydrolyzed to the less active calphostin B by loss of the carbonate moiety.[58]

(57) Henderson, B. W.; Dougherty, T. J. *Photochem. Photobiol.* **1992**, *55*, 145−157.

(58) Chen, C.-L.; Tai, H.-L.; Zhu, D.-M.; Uckun, F. M. *Pharm. Res.* **1999**, *16*, 1003−1009.

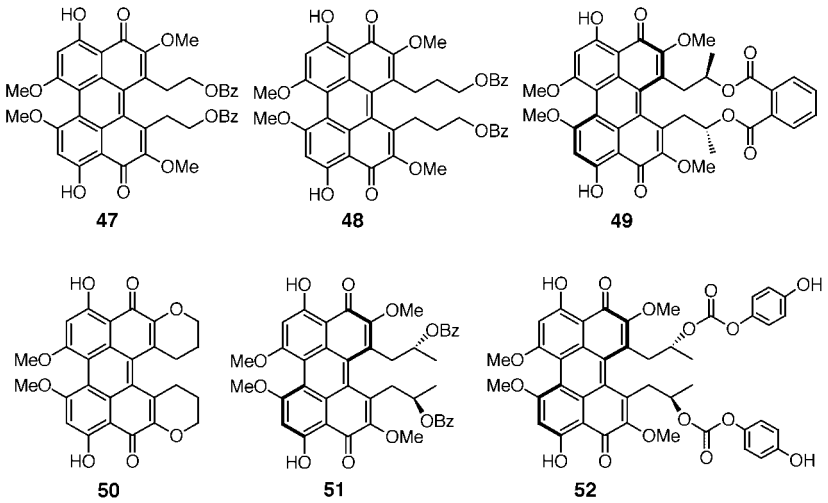


Figure 4. Analogue structures.

Conclusion

The final route to calphostin C proceeded in only 12 steps from commercially available starting materials. The synthesis hinged on a rapid and efficient construction of an *o*-naphthoquinone using benzannulation of a chromium carbene complex. The atropselectivity was in turn controlled by thermal epimerization of the chiral axis to provide the desired P-atropisomer. The use of a tether to provide stereochemical induction followed by removal represents a general strategy for challenging stereochemical issues found in the calphostins, albeit with poor atom economy. Nevertheless, for stereochemically complex and rare situations, as found with axial chirality, case by case studies need to be done.[59] Calphostin C likely represents the most complex natural product yet prepared using Fischer carbene complexes.[60] Furthermore, the brevity and versatility of our synthetic route allowed preparation of analogues which will provide a mapping of the structural requirements for the biological activity of the calphostins. Biological testing of these analogues will be reported in due course and the results will provide the first SAR for the calphostins. The calphostins are fascinating structures and their unparalleled potent and selective inhibition of PKC warrants further exploration.

Experimental Section

Apparatus and Reagents. Infrared (IR) spectra were recorded on a Nicolet 510P FT-IR spectrophotometer and selected absorption maxima are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were obtained with a Bruker AM 360 instrument or ARX 400 instrument in deuteriochloroform and/or deuteriobenzene solutions, unless otherwise specified. Chemical shifts are reported in parts per million downfield from tetramethylsilane, and coupling constants are reported in Hertz. EI mass spectra were recorded on a Micromass Autospec instrument. FAB mass spectra were recorded on a (VG) ZAB-SE instrument. Specific rotations $[\alpha]^{22}_D$ were determined on a Perkin-Elmer 241MC polarimeter at the sodium D line at 22 °C. Precoated silica gel plates (Macherey-Nagel) were used for analytical thin-layer chromatography (TLC). ICN Silitech silica gel 60 (230−400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium−benzophenone ketyl; dichloromethane, acetonitrile, and hexanes were distilled from calcium hydride. Reagents were obtained commercially and used as received unless otherwise specified. All moisture- or air-sensitive reactions were carried out under a static argon atmosphere.

2-Bromo-3,5-dimethoxybenzyl alcohol (18). NBS (21.8 g, 122 mmol) was added in one portion to a solution of 3,5-dimethoxybenzyl alcohol (20.5 g, 122 mmol) in DMF (100 mL) at room temperature in the dark and then stirred for 60 h. The reaction was poured onto H_2O (500 mL), and the white precipitate was collected by vacuum filtration and air-dried. The crude product was recrystallized from 2:1 CH_2Cl_2/hexanes (120 mL) to afford 23.8 g (79%) of the product as white needles: $R_f = 0.18$ (70:30 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.03 (t, $J = 6.5$ Hz, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 4.74 (d, $J = 6.5$ Hz, 2H), 6.44 (d, $J = 2.7$ Hz, 1H), 6.70 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 55.6, 56.3, 65.3, 98.9, 102.2, 104.7, 141.7, 156.5, 160.0; IR (film) 3283, 3005, 2934, 2841, 1586, 1491, 1421, 1329, 1290, 1201, 1041, 1020 cm^{-1}; HRMS (EI) calcd M^+ ($C_9H_{11}{}^{79}BrO_3$) 247.9871, found 247.9867; LRMS (EI) 248 (85), 246 (100), 215 (10), 137 (27), 124 (25).

2-Bromo-3,5-dimethoxybenzyl Iodide (19). Iodine (41.1 g, 162 mmol) was added in portions to a solution of triphenylphosphine (42.5 g, 162 mmol) in CH_2Cl_2 (300 mL) at 0 °C and allowed stir for 5 min. To the resulting yellow slurry was added dropwise via an addition funnel over 10 min a solution of **18** (26.7 g, 108 mmol) and imidazole (22.0 g, 324 mmol) in CH_2Cl_2 (200 mL). After being stirred for 1 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed successively with 5% $NaHSO_3$ (300 mL), H_2O (300 mL), and brine (300 mL), dried with $MgSO_4$, and filtered through a 1 in. plug of silica gel, washing with an additional 500 mL of CH_2Cl_2. The filtrate was concentrated to a white solid and recrystallized from 1:1 CH_2Cl_2/hexanes (500 mL) to provide 22.4 g of white needles from the first crop and an additional 9.0 g from the second crop for a total yield of 31.4 g (81%): $R_f = 0.35$ (90:10 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3 H), 4.53 (s, 2 H), 6.39 (d, $J =$

(59) For examples where substrate control has been successfully applied to direct the sense of atropselection, see: (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704. (b) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2704−2708. (c) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226−3227. (d) Boger, D. L.; Castle, S. L.; Miyazaki, S.; Wu, J. H.; Beresis, R. T.; Loiseleur, O. *J. Org. Chem.* **1999**, *64*, 70−80. (e) Yoshimura, F.; Kawata, S.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 8281−8285. (f) Lipshutz, B. H.; Keith, J. M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3530−3533. (g) Landais, Y.; Robin, J.-P. *Tetrahedron Lett.* **1986**, *27*, 1785−1788.

(60) For a review of syntheses employing benzannulation of Fischer carbene complexes in natural product synthesis, see: (a) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: 1995; Vol. 12, pp 491−497. (b) For the synthesis of amino acids and peptides utilizing chromium complex photochemistry, see: Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105−4128.

2.7 Hz, 1H), 6.59 (d, J = 2.7 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 6.3, 55.5, 56.3, 99.4, 104.5, 106.2, 139.8, 157.1, 159.5; IR (film) 2977, 2940, 2840, 1591, 1458, 1427, 1329, 1205, 1155, 1078, 1020, 936, 820, 650 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_9H_{10}{}^{79}BrIO_2$) 355.8909, found 355.8916; LRMS (EI) 357 (25), 355 (25), 229 (100), 135 (45).

Diethyl 2-Bromo-3,5-dimethoxybenzyl Phosphonate (25). A slurry of **19** (11.6 g, 32.5 mmol) in neat triethyl phosphite (20 mL) was heated until all the solids went into solution and a gentle reflux began (~60−70 °C evolution of ethyl iodide). Heating was stopped when reflux was noted to stop (2 h). Excess triethyl phosphite was removed by vacuum distillation, and the oily residue was recrystallized from 2:3 Et_2O/hexanes (125 mL) to afford 11.2 g (93%) of white needles: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 6H), 3.40 (d, J = 22.1 Hz, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 4.03 (pent, J = 7.2 Hz, 4H), 6.37 (t, J = 2.4 Hz, 1H), 6.63 (t, J = 2.7 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 16.3 (d, J = 6.1 Hz), 33.7 (d, J = 139 Hz), 55.5, 56.2, 62.2 (d, J = 6.5 Hz), 98.7 (d, J = 3.3 Hz), 105.6 (d, J = 9.1 Hz), 107.3 (d, J = 4.8 Hz), 133.5 (d, J = 8.7 Hz), 156.8 (d, J = 2.8 Hz), 159.2 (d, J = 3.4 Hz); IR (film) 2930, 2857, 1612, 1514, 1464, 1250, 1096, 835 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{13}H_{20}{}^{79}BrO_5P$) 368.0211, found 368.0218; LRMS (EI) 368 (50), 366 (50), 287 (100), 259 (30).

(*E*)-2-Bromo-3,5-dimethoxy-1-(4′(*R*)-(triisopropylsilyloxy)pent-1′-enyl)benzene (27). A 2.0 M solution of *n*-butyllithium (1.35 mL, 2.71 mmol) was added to a solution of hexamethyldisilazane (574 μL, 2.72 mmol) in THF (5 mL) at 0 °C, turning the solution pale yellow over 15 min. A solution of phosphonate **25** (903 mg, 2.46 mmol) in THF (10 mL) was slowly added and the reaction allowed to stir for 30 min until it became orange-yellow. A solution of aldehyde **26** (680 mg, 2.96 mmol) in THF (5 mL) was added and the reaction mixture allowed to warm slowly to room temperature with stirring for 16 h. The reaction mixture was diluted with water and extracted with ether, dried with $MgSO_4$, filtered, and concentrated to a yellow oil. Chromatography with 97:3 hexanes/EtOAc afforded 966 mg (92%) of a colorless oil: R_f = 0.28 (95:5 hexanes/EtOAc); ^{1}H NMR 360 MHz ($CDCl_3$) δ 1.03−1.09 (m, 21H), 1.22 (d, J = 6.1 Hz, 3H), 2.37−2.51 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 4.09 (sext, J = 5.9 Hz, 1H), 6.22 (dt, J = 15.7, 7.3 Hz, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 6.80 (d, J = 15.7, 1 H); ^{13}C NMR 90 MHz ($CDCl_3$) δ 12.4, 18.1, 23.6, 43.5, 55.4, 56.3, 68.4, 98.6, 102.6, 104.1, 130.7, 131.0, 139.2, 156.7, 159.4; IR (film) 2942, 2866, 1734, 1581, 1464, 1415, 1204, 1163, 1134, 1088, 883, 679 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{22}H_{37}{}^{79}BrO_3Si$) 456.1695, found 456.1687; LRMS (EI) 458 (8), 456 (7), 413 (20), 371 (27), 201 (100), 157 (35), 131 (29), 103 (22); $[\alpha]^{22}_D$ = 0.050 (c = 0.10, Et_2O).

[(2,4-Dimethoxy-6-((*E*)-4′(*R*)-(triisopropylsilyloxypent-1′-enyl)phenyl)(methoxy)methylene]pentacarbonylchromium (28). A 1.5 M solution of *t*-BuLi (5.3 mL, 7.92 mmol) was added to a stirred slurry of $Cr(CO)_6$ (924 mg, 4.20 mmol) and aryl bromide **27** (1.70 g, 3.96 mmol) in ether (40 mL) at 0 °C. The reaction turned yellow then orange-brown over 10 min when all solids were noted to go into solution. Neat methyl triflate (1.34 mL, 11.88 mmol) was added and the reaction stirred for 30 min before becoming orange-red. The reaction was quenched at 0 °C with 500 μL of saturated aqueous $NaHCO_3$ solution, followed by dilution with ether (50 mL) and addition of $MgSO_4$. The reaction mixture was passed through a pad of silica gel (1/4 in.), and the filtrate was concentrated to a red oil. Chromatography with 95:5 hexanes/EtOAc afforded 2.12 g (88%) of a dark orange-red oil. The product is unstable and was used immediately in the subsequent cyclization reaction: R_f = 0.20 (95:5 hexanes/EtOAc); ^{1}H NMR (360 MHz, C_6D_6) δ 1.16 (br s, 24H), 2.45 (br s, 2H), 3.23 (br s, 3H), 3.40 (br s, 3H), 3.54 (br s, 3H), 4.05 (br s, 1H), 6.25 (br s, 1H), 6.35 (br s, 1H), 6.74 (br s, 1H), 7.20 (br s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.8, 18.4, 23.7, 44.0, 54.9 (2C), 64.6, 68.7, 97.9, 101.3, 130.3, 131.1, 131.4, 132.0, 150.9, 161.3, 217.0, 225.5, 360.0; IR (film) 2946, 2868, 2062, 1935, 1599, 1570, 1462, 1254, 1134, 937, 881, 650 cm^{-1}; HRMS (CI) calcd M$^+$ ($C_{29}H_{40}{}^{52}CrO_9Si$) 612.1847, found 612.1814; LRMS (CI) 612 (0.2), 556 (13), 472 (19), 470 (15), 420 (65), 363 (42), 219 (100).

6,8-Dimethoxy-3-(2′(*R*)-(triisopropylsilyloxypropyl)-1,2-naphthoquinone (29). Neat *tert*-butylisonitrile (50 μL, 0.44 mmol) was added to a stirring orange solution of carbene complex **28** (120 mg, 0.20 mmol) in THF (0.5 mL) and the mixture allowed to stir for 10 h at room temperature. The reaction was diluted with an additional 10 mL of THF, and the resulting yellow solution was heated at gentle reflux for 16 h before becoming transparent green. After cooling, a solution of CAN (548 mg, 1.0 mmol) in H_2O (2 mL) was added, and the resulting deep orange solution was stirred for 15 min. The reaction was poured into aqueous saturated $NaHCO_3$ and extracted with chloroform. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated to an orange oil. Chromatography with chloroform afforded 94 mg (82% yield) of the *o*-naphthoquinone **29** as an orange oil. When the initial reaction was run more dilute (0.1 M) then the indenone **30** was isolated in 20−25% yields with a corresponding decrease in the yield of the desired *o*-naphthoquinone **29**.

Data for 29: R_f = 0.33 (98:2 CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.03 (d, J = 6.4 Hz, 18H), 1.00−1.10 (m, 6H), 2.52 (dd, J = 13.2, 5.7 Hz, 1H), 2.58 (dd, J = 13.3, 6.3 Hz, 1H), 3.91 (s, 3H), 3.96 (s, 3H), 4.20 (sext, J = 6.0 Hz, 1H), 6.38 (d, J = 2.2, 1H), 6.41 (d, J = 2.2 Hz, 1H), 7.12 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.4, 18.1, 23.8, 40.0, 55.8, 56.3, 67.1, 98.4, 109.1, 112.9, 137.8, 138.8, 143.3, 165.4, 166.4, 176.1, 181.8; IR (film) 2944, 2867, 1655, 1565, 1462, 1354, 1235, 1121 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{24}H_{36}O_5Si$) 432.2332, found 432.2324; LRMS (EI) 434 (53), 433 (37), 432 (38), 389 (100), 361 (70), 343 (43), 260 (58), 157 (25); $[\alpha]^{22}_D$ = 1.3 (c = 0.0020, Et_2O).

Data for 30: R_f = 0.6 (70:30 hexanes/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01−1.11 (m, 21H), 1.12 (d, J = 6.0 Hz, 3H), 2.32 (dd, J = 13.9, 7.5 Hz, 1H), 2.54 (dd, J = 14.0, 4.8 Hz, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 4.16 (sext, J = 6.0 Hz, 1H), 6.11 (d, J = 1.7 Hz, 1H), 6.20 (d, J = 1.8 Hz, 1H), 6.92 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.3, 18.0 (2C), 23.3, 35.3, 55.6, 55.8, 67.2, 96.1, 103.5, 108.6, 139.0, 140.3, 149.2, 158.1, 166.7, 194.8; IR (film) 2961, 2866, 1698, 1624, 1601, 1464, 1377, 1209, 1159, 1122, 1096, 1003 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{23}H_{37}O_4Si$) 405.2461, found 405.2455; $[\alpha]^{22}_D$ = 83.6 (c = 1.74, CH_2Cl_2).

2-Hydroxy-3-(2′(*R*)-triisopropylsilyloxypropyl)-1,6,8-trimethoxynaphthalene (31). A solution of freshly prepared carbene **28** (308 mg, 0.50 mmol) in THF (18 mL) was degassed by sparging with argon for 20 min and then pressurized to 40 psi with CO in a Pyrex pressure tube. The red carbene solution was irradiated using a 450 W medium-pressure mercury lamp fitted with a quartz filter. The color of the solution faded and turned yellow after 1 h. The contents were concentrated to a yellow-green film and chromatographed with 90:10 hexanes/EtOAc to provide 80 mg (36%) of a colorless oil: R_f = 0.1 (95:5 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.03−1.10 (m, 21H), 1.15 (d, J = 6.0 Hz, 3H), 2.87 (dd, J = 13.2, 6.6 Hz, 1H), 3.04 (dd, J = 13.2, 5.7 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.38 (sext, J = 6.0 Hz, 1H), 6.47−6.49 (m, 2H), 6.61 (d, J = 2.2 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.4, 18.0, 18.1, 23.3, 41.7, 55.2, 56.0, 62.2, 68.5, 98.5, 98.7, 114.7, 125.1, 128.4, 131.0, 140.6, 144.4, 155.7, 156.0; IR (film) 2959, 2943, 2867, 1613, 1585, 1452, 1371, 1348. 1265, 1205, 1159, 1109, 1055 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{25}H_{40}O_5Si$) 448.2645, found 448.2639; LRMS (EI) 448 (97), 390 (75), 274 (100), 259 (25), 157 (23); $[\alpha]^{22}_D$ = −12 (c = 0.93, CH_2Cl_2).

(2′*R*)-2,11-Dihydroxy-4,6,7,9-tetramethoxy-1,12-bis(2′-hydroxypropyl)-3,10-perylenequinone (32). Solid iron trichloride (54 mg, 0.34 mmol) was added to a degassed solution (freeze−pump−thaw) of quinone **29** (58 mg, 0.134 mmol) in acetonitrile (2 mL) to provide a deep red solution that was stirred 16 h at room temperature before turning brown. After 48 h, the solution was dark blue. The reaction was diluted with chloroform, washed with an aqueous 0.5 N HCl, and dried with $CaCl_2$. Charcoal was added to the solution, which was then filtered and concentrated to a red oil. Chromatography with $CHCl_3$ → 98:2 $CHCl_3$/MeOH afforded 26 mg (70%) of perylenequinone **32** as a red oil as a 0.55 P/0.45 M

mixture of diastereomers and 4 mg (10%) of tricyclic *o*-naphthoquinone **33** as a yellow oil.

Data for 32: $R_f = 0.16$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, CD_2Cl_2, 235 K) δ 1.31 (d, $J = 6.1$ Hz, 3H), 1.63 (d, $J = 6.2$ Hz, 3H), 2.68 (dd, $J = 15.9$, 10.5 Hz, 1H), 3.09 (dd, $J = 15.3$, 8.2 Hz, 1H), 3.28 (dd, $J = 15.2$, 9.5 Hz, 1H), 3.65 (dd, $J = 16.0$, 8.4 Hz, 1H), 4.07 (s, 3H), 4.10 (s, 3H), 4.13 (s, 3H), 4.14 (s, 3H), 4.75−4.85 (m, 1H), 5.02−5.12 (m, 1H), 6.74 (s, 1H), 6.75 (s, 1H); ^{1}H NMR (200 MHz, DMSO-d_6, 298 K) new signals appear at δ 5.75 (s, 2H, O*H*) and δ 8.31 (s, 2H, O*H*); ^{13}C NMR (100 MHz, CD_2Cl_2, 235 K) δ 20.4, 20.5, 41.0, 41.5, 56.4, 56.6, 81.1, 81.2, 94.0 (2C), 108.4, 108.5, 111.0, 111.1, 121.4, 122.3, 126.8, 127.0, 130.7, 131.3, 154.3, 154.7, 163.1, 163.2, 164.1, 164.2, 174.0, 174.3, (2 O*C*H$_3$ peaks under CD_2Cl_2 signal); IR (film) 3443, 2925, 1618, 1541, 1209 cm^{-1}; FABMS 551.1 M + H (weak), 515.3 (strong) (loss of 2 H_2O from M + H); UV−vis (MeOH) λ_{max} nm (ϵ) 437 (5300), 510 (7400); CD (MeOH) nm ($\Delta\epsilon$) 307 (+3.9), 348 (−1.1), 440 (+1.9), 571 (−1.3).

Data for 33: $R_f = 0.27$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, $J = 6.3$ Hz, 3 H), 2.74 (dd, $J = 16.3$, 7.6 Hz, 1 H), 3.28 (dd, $J = 16.3$, 10.1 Hz, 1 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 5.15 (ddq, $J = 16.5$, 7.5, 6.4 Hz, 1 H), 6.64 (d, $J = 2.4$ Hz, 1 H), 7.28 (d, $J = 2.5$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 34.1, 56.0, 56.4, 83.0, 102.8, 104.1, 113.5, 120.5, 137.8, 161.4, 162.5, 165.2, 175.9, 181.7; IR (film) 2925, 2851, 1653, 1631, 1589, 1456, 1370, 1316, 1224, 1157 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{15}H_{14}O_5$) 274.0841, found 274.0835; LRMS (EI) 275 (49), 274 (100), 259 (28), 257 (26), 227 (15).

2-*tert*-Butylamino-3-(2′(*R*)-hydroxypropyl)-1,6,8-trimethoxynaphthalene (34). *tert*-Butylisonitrile (0.38 mL, 3.3 mmol) was added to carbene **28** (929 mg, 1.51 mmol) in THF (2 mL) at room temperature and the mixture allowed to stir for 20 h. The solution faded from a deep red to a light brown with formation of a white precipitate ($Cr(CO)_5CN$-*t*-Bu). The solution of ketenimine was then diluted with THF (15 mL) and heated at reflux for 24 h. The reaction was allowed to cool to room temperature, and then a 1.0 M solution of tetrabutylammonium fluoride in THF (4.8 mL, 4.8 mmol) was added. After 4 h, the resulting green solution was diluted with Et_2O (50 mL), washed with brine, dried over $MgSO_4$, and concentrated to a yellow-brown oil. Chromatography with 60:40 hexanes/EtOAc afforded 317 mg (60%) of a yellow oil: R_f = 0.2 (60:40 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.15 (d, $J = 6.2$ Hz, 3H), 1.25 (s, 9H), 2.99 (dd, $J = 14$, 1.9 Hz, 1H), 3.17 (dd, $J = 14$, 7.4 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 3.95 (s, 3H), 3.95−4.05 (m, 1H), 6.48 (d, $J = 2.2$ Hz, 1H), 6.62 (d, $J = 2.2$ Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.0, 30.4, 44.2, 55.2, 56.1 (2C), 61.9, 69.9, 98.3, 98.7, 114.7, 124.8, 132.4, 135.2, 138.8, 152.2, 156.4, 157.6; IR (film) 3360 (br), 2965, 2930, 1624, 1578, 1450, 1391, 1338, 1261, 1205, 1157, 1111, 1057, 910, 733 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{20}H_{29}NO_4$) 347.2097, found 347.2095; LRMS (EI) 347.2 (100), 332.2 (16), 291.1 (12), 276.1 (10), 259.1 (36), 219.1 (10), 213.1 (6); $[\alpha]^{22}_D = -87.3$ ($c = 1.28$, CH_2Cl_2).

Preparation of Phthaloyl-Tethered Naphthylamine. Sodium hydride (55 mg, 1.50 mmol, 65% dispersion in oil, hexanes−washed) was added to a stirring solution of alcohol **34** (175 mg, 0.50 mmol) (azeotroped 3 × 5 mL, benzene) in THF (5 mL) at room temperature and the mixture allowed to stir 1 h. Phthaloyl chloride (36 μL, 0.25 mmol) was added to the sodium alkoxide and the reaction stirred for 12 h when TLC showed completion. The reaction was diluted with Et_2O (30 mL), washed with brine, dried with $MgSO_4$, and concentrated to a brown oil. Chromatography with 80:20 hexanes/EtOAc afforded 136 mg (66%) of a colorless oil: TLC $R_f = 0.47$ (80:20 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 18H), 1.30 (d, $J = 6.2$ Hz, 6H), 3.17 (dd, $J = 13.1$, 7.0 Hz, 2H), 3.30 (dd, $J = 13.3$, 6.1 Hz, 2H), 3.76 (s, 6H), 3.86 (s, 6H), 3.96 (s, 6H), 5.46 (hext, $J = 6.6$ Hz, 2H), 6.47 (d, $J = 2.2$ Hz, 2H), 6.62 (d, $J = 2.2$ Hz, 2H), 7.34 (s, 2H), 7.41 (dd, $J = 5.7$, 3.3 Hz, 2H), 7.52 (dd, $J = 5.7$, 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 30.8, 38.9, 55.1, 55.2, 56.2, 61.2, 73.0, 98.2, 98.6, 115.3, 123.9, 128.7, 130.6, 132.6, 133.9, 134.8, 136.0, 151.4, 156.5, 157.0, 167.0; IR (film) 2963, 1720, 1624, 1577, 1339, 1263, 1205, 1159, 1113, 1055 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{48}H_{61}N_2O_{10}$) 825.4326, found 825.4307; $[\alpha]^{22}_D = -21$ ($c = 0.40$, CH_2Cl_2).

Preparation of Phthaloyl-Tethered Bis-*o*-naphthoquinone (35). CAN (46 mg, 0.08 mmol) in H_2O (0.3 mL) was added to a solution of phthaloyl-tethered naphthylamine (15.8 mg, 0.019 mmol) in THF (2 mL) at room temperature. TLC showed completion after 30 min. The reaction mixture was diluted with $CHCl_3$ (5 mL) and washed successively with H_2O and brine. The organic layer was dried with Na_2SO_4 and concentrated to an orange oil. Chromatography with 98:2 CH_2Cl_2/MeOH afforded 12.2 mg (80%) of the title compound as an orange oil: $R_f = 0.24$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, $J = 6.3$ Hz, 6H), 2.67 (dd, $J = 14.7$, 8.0 Hz, 2H), 2.77 (dd, $J = 14.7$, 4.6 Hz, 2H), 3.91 (s, 12H), 5.25−5.30 (m, 2H), 6.39 (d, $J = 2.0$ Hz, 2H), 6.48 (d, $J = 2.0$ Hz, 2H), 7.16 (s, 2H), 7.47 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.59 (dd, $J = 5.7$, 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 34.9, 55.9, 56.2, 70.9, 98.8, 109.6, 113.0, 128.7, 130.9, 132.3, 136.3, 138.7, 143.0, 165.3, 166.5, 166.8, 175.9, 181.6; IR (film) 2936, 1716, 1653, 1591, 1456, 1327, 1263, 1165 cm^{-1}; HRMS (EI) calcd (M + H)$^+$ ($C_{38}H_{35}O_{12}$) 683.2129, found 683.2105; LRMS (EI) 683 (3), 279 (76), 246 (100), 204 (75), 148 (82); $[\alpha]^{22}_D = -75$ ($c = 0.42$, CH_2Cl_2).

Preparation of Phthaloyl-Tethered Perylenequinone (36). A solution of bis-*o*-naphthoquinone **35** (31.6 mg, 0.046 mmol) in CH_2Cl_2 (10 mL) was added via syringe pump over 7 h to neat trifluoroacetic acid (10 mL) at room temperature under an oxygen atmosphere and then stirred for an additional 15 h. The dark blue reaction was diluted with $CHCl_3$ (20 mL) and then quenched by the slow addition of an aqueous saturated $NaHCO_3$ solution. The deep red organic layer was washed with brine, dried over Na_2SO_4, and concentrated to a red oil. Chromatography with 95:5 EtOAc/MeOH affored 16.2 mg (51%) of a single diastereomeric product as a red oil: R_f = 0.28 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.15 (d, $J = 6.3$ Hz, 6H), 2.93 (dd, $J = 15.7$, 7.0 Hz, 2H), 3.79 (dd, $J = 15.7$, 9.2 Hz, 2H), 4.12 (s, 6H), 4.20 (s, 6H), 6.05−6.10 (m, 2H), 6.74 (s, 2H), 7.49 (dd, $J = 5.7$, 3.3 Hz, 2H), 7.73 (dd, $J = 5.8$, 3.3 Hz, 2H), 8.08 (br s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.0, 38.5, 56.2, 56.6, 71.6, 93.9, 105.2, 106.0, 111.4, 117.6, 128.8, 130.6, 131.4, 131.8, 149.7, 164.2, 164.9, 167.6, 175.7; IR (film) 3279 (br), 2934, 2851, 1714, 1591, 1296, 1217 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{38}H_{33}O_{12}$) 681.1972, found 681.1986; UV−vis (MeOH) λ_{max} nm (ϵ) 229 (32 000), 273 (22 300), 344 (13 900), 520 (3300); $[\alpha]^{22}_D = 2.3 \times 10^3$ (c = 0.0032, MeOH).

3-(2′(*R*)-(Benzoyloxy)propyl)-6,8-dimethoxy-1,2-naphthoquinone (39). Pyridine (19 μL, 0.19 mmol), benzoyl chloride (19 μL, 0.16 mmol), and catalytic 4-(dimethylamino)-pyridine were added consecutively to a stirring solution of naphthylamine **34** (43 mg, 0.125 mmol) in CH_2Cl_2 (6 mL) at room temperature. The reaction was stirred for 3 h, and then DDQ (86 mg, 0.38 mmol) was added in one portion. The solution immediately turned deep brown. After 1 h, the solution was diluted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, and concentrated to an orange oil. Chromatography with 99:1 CH_2Cl_2/MeOH afforded 41 mg (87%) of an orange solid: $R_f = 0.40$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.39 (d, $J = 6.2$ Hz, 3H), 2.70−2.85 (m, 2H), 3.86 (s, 3H), 3.92 (s, 3H), 5.33 (sext, $J = 6.2$ Hz, 1H), 6.29 (d, $J = 1.9$ Hz, 1H), 6.38 (d, $J = 1.9$ Hz, 1H), 7.10 (s, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.97 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.3, 35.3, 56.0, 56.5, 70.4, 98.9, 109.5, 113.1, 128.5, 129.7, 130.5, 133.1, 136.8, 138.5, 143.0, 165.6, 166.1, 166.6, 175.9, 181.6; IR (film) 3065, 2980, 2939, 1713, 1657, 1591, 1562, 1327, 1273, 1165, 1113, 713 cm^{-1}; HRMS (EI) calcd M$^+$ ($C_{22}H_{20}O_6$) 380.1260, found 380.1263; LRMS (EI) 380.1 (23), 336.1 (5), 259.1 (15), 230.1 (42), 105.0 (100); $[\alpha]^{22}_D = -154$ ($c = 1.28$, CH_2Cl_2).

(2′*R*)-1,12-Bis(2′-benzoyloxypropyl)-2,11-dihydroxy-4,6,7,9-tetramethoxy-3,10-perylenequinone (40). Neat trifluoroacetic acid (4 mL) was added to *o*-naphthoquinone **39** (248 mg, 0.65 mmol) at 0 °C. The solution instantly turned green and then dark blue over a few minutes. A stream of

oxygen was passed through the solution for 3 h at 0 °C, and then the reaction was stirred for another 30 h at room temperature under a static oxygen atmosphere until TLC indicated completion. The reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ (30 mL), and then the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to a deep red oil. Chromatography with 95:5 EtOAc/MeOH provided 175 mg (71%) of a deep red oil as an approximately 1:2 (**40P**/**40M**) mixture of diastereomers.

Data for 40P: $R_f = 0.13$ (98:2 $CHCl_3$/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (d, $J = 6.2$ Hz, 6H), 3.15 (dd, $J = 13.7$, 9.7 Hz, 2H), 3.46 (dd, $J = 13.8$, 2.4 Hz, 2H), 3.92 (s, 6H), 4.16 (s, 6H), 5.15−5.25 (m, 2H), 6.48 (s, 2H), 6.88 (t, $J = 7.5$ Hz, 4H), 6.99 (d, $J = 7.1$ Hz, 4H), 7.19 (t, $J = 7.4$ Hz, 2H), 8.11 (br s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.0, 37.5, 55.9, 56.6, 71.8, 94.0, 106.3, 111.2, 119.8, 127.6, 128.9, 130.0, 130.9, 131.1, 131.7, 149.8, 164.1, 164.8, 165.2, 176.3; IR (film) 2934, 1717, 1593, 1547, 1435, 1368, 1273, 1215, 1053, 711 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{44}H_{39}O_{12}$) 759.2442, found 759.2454; $[\alpha]^{22}_D = -2.1 \times 10^3$ ($c = 0.0030$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 271 (29 000), 344 (4100), 517 (22 000).

Data for 40M: $R_f = 0.17$ (98:2 $CHCl_3$/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.76 (d, $J = 6.3$ Hz, 6H), 3.19 (dd, $J = 13.4$, 7.4 Hz, 2H), 3.62 (dd, $J = 13.4$, 4.8 Hz, 2H), 4.10 (s, 6H), 4.16 (s, 6H), 5.05 (sext, $J = 6.7$ Hz, 2H), 6.60 (s, 2H), 7.26 (t, $J = 8.2$ Hz, 4H), 7.42 (t, $J = 7.4$ Hz, 2H), 7.69 (d, $J = 7.2$ Hz, 4H), 8.14 (br s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.3, 36.2, 56.3, 56.6, 70.9, 94.3, 106.2, 111.4, 117.8, 128.2, 129.5, 130.5, 131.0, 131.1, 132.5, 150.5, 164.4, 164.9, 165.7, 176.1; IR (film) 2938, 1711, 1593, 1547, 1466, 1435, 1367, 1298, 1273, 1215, 1178, 1161, 1053, 819, 754, 711 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{44}H_{39}O_{12}$) 759.2442, found 759.2447; $[\alpha]^{22}_D = +8.0 \times 10^2$ ($c = 0.0042$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 226 (54 000), 273 (31 000), 345 (4200), 511 (23 000).

Isomerization to 40P. A solution of **40** (1:2, **40P**/**40M**, 726 mg, 0.96 mmol) in toluene (100 mL) was sparged with argon for 20 min and then heated at reflux for 36 h. The solvent was removed and the red oil chromatographed with 99:1 $CHCl_3$/MeOH. The diastereomers were difficult to separate, but after repeated chromatography of the overlap region 472 mg (65%) of **40P** and 153 mg (21%) of **40M** were isolated as a red solids. Thermal equilibration of **40M** provided another 100 mg (14%) of **40P**.

***(2′R,P)*-1,12-Bis(2′-benzoyloxypropyl)-2,4,6,7,9,11-hexamethoxy-3,10-perylenequinone (44).** Tetrabutylammonium fluoride (0.32 mL, 1.0 M THF) was added to a stirring solution of **40P** (55 mg, 0.073 mmol) in THF (10 mL) and MeI (3 mL) to provide a dark green solution, which turned deep red within 3 min. The solution was allowed to stir for an additional 20 min and then diluted with chloroform (20 mL) and poured onto H_2O (20 mL). The organic layer was separated and dried with Na_2SO_4. Chromatography with 99:1 $CHCl_3$/MeOH afforded 53 mg (92%) of a deep red oil: $R_f = 0.26$ (95:5, CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (d, $J = 6.2$ Hz, 6H), 2.93 (dd, $J = 13.4$, 10.0 Hz, 2H), 3.40 (dd, $J = 13.4$, 1.9 Hz, 2H), 3.85 (s, 6H), 4.10 (s, 6H), 4.20 (s, 6H), 5.05−5.15 (m, 2H), 6.44 (s, 2H), 6.87 (t, $J = 8.1$ Hz, 4H), 6.95 (d, $J = 7.0$ Hz, 4H), 7.18 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.0, 37.5, 55.5, 56.3, 60.3, 72.4, 94.5, 108.7, 110.5, 127.4, 128.6, 129.4, 130.3, 130.6, 131.4, 131.7, 153.8, 162.4, 163.4, 165.0, 178.1; IR (film) 3000, 2978, 2940, 2883, 2847, 1715, 1618, 1576, 1543, 1367, 1285, 1213, 1159, 983, 711 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{46}H_{43}O_{12}$) 787.2754, found 787.2769; $[\alpha]^{22}_D = -2.9 \times 10^3$ ($c = 0.0032$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 340 (4200), 472 (20 000), 572 (6200).

***(2′R,2″R,P)*-1-(2′-Benzoyloxypropyl)-2,4,6,7,9,11-hexamethoxy-12-(2″-hydroxypropyl)-3,10-perylenequinone (45).** A solution of NaOMe (30 mL, 13 mmol, 0.43 M NaOMe/MeOH) was added to a stirring solution **44** (117 mg, 0.15 mmol) in MeOH (20 mL) at room temperature. The progress of the reaction was monitored by TLC. After 3.15 h, the reaction was diluted with chloroform (50 mL), washed successively with aqueous saturated $NaHCO_3$, brine, and dried with Na_2SO_4. Chromatography with 98:2→96:4 CH_2Cl_2/MeOH provided three fractions. Recovered starting material **44** was isolated from the first fraction 49 mg (42%). The desired product **45** eluted next affording 50 mg (49%) of a deep red oil. Finally, the bis-debenzoylated product **38P** (see characterization and independent preparation of **38P** in supporting info) was isolated as the third fraction 3.8 mg (4%).

Data for 45: $R_f = 0.15$ (95:5, CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.90 (d, $J = 6.2$ Hz, 3H), 1.24 (d, $J = 6.2$ Hz, 3H), 2.69 (dd, $J = 13.2$, 7.7 Hz, 1H), 2.95 (dd, $J = 13.4$, 9.9 Hz, 1H), 3.30−3.40 (m, 2H), 3.65−3.75 (m, 1H) 3.94 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.14 (s, 3H), 4.16 (s, 3H), 4.18 (s, 3H), 5.02−5.12 (m, 1H), 6.54 (s, 1H), 6.62 (s, 1H), 6.92 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.4$ Hz, 2H), 7.22 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.0, 23.2, 37.7, 40.6, 55.7, 56.0, 56.3, 56.4, 60.4, 60.5, 68.9, 72.4, 94.6, 94.8, 108.8, 110.8, 127.5, 128.7, 129.6, 130.2, 130.7, 131.0, 131.5, 131.7, 132.4, 153.7, 153.9, 162.6, 162.7, 163.6 (2C), 165.0, 178.1, 178.4 (3 aryl C's not observed); IR (film) 3426, 3000, 2975, 2938, 2883, 2845, 1715, 1614, 1576, 1543, 1464, 1367, 1287, 1214, 1154, 983, 752, 711 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{39}H_{39}O_{11}$) 683.2493, found 683.2489; $[\alpha]^{22}_D = -3.3 \times 10^3$ ($c = 0.0038$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 221 (42 000), 268 (27 000), 338 (4800), 471 (21 000), 657 sh (6200).

***(2′R,2″R,P)*-1-(2′-(Benzoyloxypropyl)-2,4,6,7,9,11-hexamethoxy-12-(2″-(4‴-acetoxy)phenoxycarbonyloxypropyl)-3,10-perylenequinone (46).** Triethylamine (20 μL, 0.13 mmol) and phosgene (78 μL, 0.13 mmol, 1.9 M/toluene) were added consecutively to a solution of **45** (29.7 mg, 0.0435 mmol) in THF (5 mL) at 0 °C. After 15 min of stirring, when TLC indicated complete conversion to the chloroformate ester, the solvent and excess phosgene were removed in vacuo. The residue was redissolved in THF (5 mL), then triethylamine (60 μL, 0.39 mmol), *p*-acetoxyphenol (66 mg, 0.435 mmol), and catalytic 4-(dimethylamino)pyridine were added. After 1.5 h, the reaction was diluted with chloroform (30 mL), washed with aqueous 1 N HCl and brine, dried with Na_2SO_4, and concentrated to a red oil. Chromatography with 99:1 → 98:2 CH_2Cl_2/MeOH afforded 34.1 mg (91%) of a deep red oil.

Data for intermediate chloroformate ester: $R_f = 0.29$ (95:5 CH_2Cl_2/MeOH).

Data for 46: $R_f = 0.29$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.17 (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 6.2$ Hz, 3H), 2.26 (s, 3H), 2.83 (dd, $J = 13.5$, 9.6 Hz, 1H), 2.92 (dd, $J = 13.4$, 10.0 Hz, 1H), 3.32−3.42 (m, 2H), 3.69 (s, 3H), 3.91 (s, 3H), 4.04 (s, 3H), 4.16 (s, 3H), 4.18 (s, 3H), 4.19 (s, 3H), 4.72−4.80 (m, 1H), 5.05−5.15 (m, 1H), 6.23−6.30 (m, 2H), 6.47 (s, 1H), 6.54 (s, 1H), 6.72−6.79 (m, 2H), 6.91 (t, $J = 8.0$ Hz, 2H), 6.98 (dd, $J = 8.2$, 1.2 Hz, 2H), 7.20 (tt, $J = 7.4$, 1.2 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.5, 21.0 (2C), 37.1, 37.4, 55.6, 55.7, 56.3, 56.4, 60.3, 60.4, 72.4, 76.6, 94.4, 94.7, 108.9 (2C), 110.8 (2C), 121.3, 121.6, 127.5, 128.7, 129.0, 129.6, 129.8, 130.6, 131.1, 131.2, 131.5, 132.4, 147.5, 147.9, 152.3, 154.0 (2C), 162.6, 162.9, 163.5, 163.8, 165.0, 169.3, 178.2 (1 aryl C not observed); IR (film) 3000, 2980, 2937, 1753, 1716, 1618, 1576, 1541, 1458, 1369, 1284, 1213, 1180, 1161, 983, 752, 713 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{48}H_{45}O_{15}$) 861.2758, found 861.2767; $[\alpha]^{22}_D = -2.1 \times 10^3$ ($c = 0.0070$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 220 (43 000), 269 (27 000), 334 (4600), 473 (21 000), 570 sh (6200).

Calphostin C (3). A freshly prepared MgI_2 solution[61] (0.64 mL, 0.064 mmol, 0.10 M/Et_2O) was added to a solution of **46** (22 mg, 0.026 mmol) in THF (10 mL) at room temperature. The solution gradually changed from deep red to green over 30 min. After 2 h, the reaction was diluted with chloroform (20 mL), washed successively with aqueous 1 N HCl and brine, dried with Na_2SO_4, treated with EDTA to remove any residual magnesium, and concentrated to a purple oil. The intermediate acetyl calphostin C was chromatographed on a short column of silica gel eluting with CH_2Cl_2 → 99:1 CH_2Cl_2/MeOH to afford a red oil that was treated with methanol (5 mL) and solid $NaHCO_3$ (40 mg). The solution was stirred for 2 h under argon and then diluted with $CHCl_3$ (20 mL), washed with aqueous 1

(61) See the Supporting Information.

N HCl and brine, dried with Na_2SO_4, and concentrated to a deep red oil. Chromatography with 198:2 → 197:3 CH_2Cl_2/MeOH afforded 15.5 mg (78%) of a deep red solid.

Data for intermediate acetyl calphostin C: $R_f = 0.53$ (95:5 CH_2Cl_2/MeOH).

Data for calphostin C: $R_f = 0.31$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, $J = 6.2$ Hz, 3H), 1.29 (d, $J = 6.2$ Hz, 3H), 3.10 (dd, $J = 13.3$, 10.2 Hz, 1H), 3.17 (dd, $J = 13.4$, 10.0 Hz, 1H), 3.60−3.67 (m, 2H), 3.67 (s, 3H), 3.85 (s, 3H), 4.30 (s, 6H), 4.67−4.75 (m, 1H), 5.00−5.10 (m, 1H), 5.59 (br s, 1H), 6.13 (d, $J = 8.7$ Hz, 2H), 6.28 (s, 1H), 6.30 (s, 1H), 6.49 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 7.6$ Hz, 2H), 6.94 (t, $J = 7.5$ Hz, 2H), 7.23−7.25 (m, 1H), 15.81 (br s, 1H), 15.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 21.2, 38.7, 38.9, 53.4, 56.0 (2C), 61.2, 72.3, 76.3, 101.2 (2C), 106.4, 106.5, 115.4, 116.8, 117.3, 121.3, 125.3, 125.8, 127.1, 127.5, 127.6, 128.4, 129.1, 132.1, 133.6, 134.3, 143.8, 151.5, 151.6, 152.6, 153.2, 164.6, 166.6, 166.7, 172.1 (2C), 178.2, 178.6; IR (film) 2964, 2936, 1755, 1717, 1605, 1508, 1450, 1269, 1207, 1159, 752, 711 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{44}H_{39}O_{14}$) 791.2340, found 791.2352; $[\alpha]^{22}_D = -8.7 \times 10^2$ ($c = 0.0062$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 223 (36 000), 271 (18 000), 349 (2900), 477 (15 000), 543 (7400), 587 (7100); CD (MeOH) nm ($\Delta\epsilon$) 232 (−64.5), 292 (+52.3), 359 (−14.9), 448 (+22.2), 584 (−12.2).

Calphostin A (1). A freshly prepared MgI_2 solution[61] (2.63 mL, 0.095 mmol, 0.036 M/Et_2O) was added to a stirring solution of **44** (29 mg, 0.038 mmol) in THF (40 mL) at room temperature under argon. The solution gradually changed from deep red to green. After 6 h, TLC showed complete reaction. The solution was diluted with chloroform (60 mL), washed with aqueous 1 N Hcl (20 mL), dried with Na_2SO_4, treated with EDTA to remove any residual magnesium, and concentrated to a deep purple oil. Chromatography with 200:1 $CHCl_3$/MeOH afforded 26 mg (92%) of a deep red solid: $R_f =$ 0.75 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.28 (d, $J = 6.3$ Hz, 6H), 3.16 (dd, $J = 13.2$, 10.0 Hz, 2H), 3.67 (dd, $J = 13.4$, 1.2 Hz, 2H), 3.79 (s, 6H), 4.33 (s, 6H), 5.00−5.10 (m, 2H), 6.21 (s, 2H), 6.82 (d, $J = 8.0$ Hz, 4H), 6.90 (t, $J = 7.6$, 4H), 7.22 (t, $J = 7.2$ Hz, 2H), 15.85 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 39.0, 55.8, 61.2, 72.3, 101.2, 106.3, 116.6, 125.5, 127.3, 127.5, 128.4, 129.0, 131.9, 134.6, 151.4, 164.6, 166.2, 172.4, 177.9; IR (film) 3010, 2980, 2940, 2875, 2847, 1717, 1607, 1541, 1456, 1271, 1211, 1159, 1109, 756, 709 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{44}H_{39}O_{12}$) 759.2442, found 759.2422; $[\alpha]^{22}_D = -1.4 \times 10^3$ ($c = 0.0036$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 225 (53 000), 270 (23 000), 350 (4000), 477 (19 000), 543 (9800), 587 (9400); CD (MeOH) nm ($\Delta\epsilon$) 232 (−96.4), 291 (+46.7), 360 (−14.6), 451 (+20.9), 588 (−12.8).

Calphostin B (2). A freshly prepared MgI_2 solution[61] (0.90 mL, 0.090 mmol, 0.10 M/Et_2O) was added to a solution of **45** (23.5 mg, 0.034 mmol) in THF (30 mL) at room temperature. The solution gradually changed from deep red to green over 2 h. The reaction was diluted with chloroform (75 mL), washed successively with aqueous 1 N HCl and brine, dried with Na_2SO_4, treated with EDTA to remove any residual magnesium, and concentrated to a deep purple oil. Chromatography with 200:1 CH_2Cl_2/MeOH afforded 16.2 mg (72%) of a deep red solid: $R_f = 0.42$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.99 (d, $J = 6.1$ Hz, 3H), 1.27 (d, $J = 6.3$ Hz, 3H), 2.91 (dd, $J = 13.2$, 8.8 Hz, 1H), 3.22 (dd, $J = 13.3$, 9.7 Hz, 1H), 3.55−3.68 (m, 2H), 3.69−3.77 (m, 1H) 3.80 (s, 3H), 3.84 (s, 3H), 4.26 (s, 3H), 4.31 (s, 3H), 4.95−5.08 (m, 1H), 6.11 (s, 1H), 6.27 (s, 1H), 6.86 (d, $J = 7.1$ Hz, 2H), 6.92 (t, $J = 7.4$ Hz, 2H), 7.26 (t, $J = 7.5$ Hz, 1H), 15.75 (br s, 1H), 15.93 (br s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 23.8, 39.0, 42.5, 55.9, 56.1, 61.2 (2C), 69.0, 72.2, 101.2, 101.4, 106.2, 106.4, 117.2, 117.5, 125.3, 125.5, 127.4, 127.5, 128.3, 128.4, 129.1, 132.0, 134.7, 136.5, 151.1, 151.2, 164.5, 166.5, 166.8, 171.1, 171.8, 178.9, 179.2; IR (film) 3387, 2967, 2934, 2852, 1717, 1605, 1540, 1450, 1271, 1214, 1157, 1113, 760, 712 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{37}H_{35}O_{11}$) 655.2179, found 655.2188; $[\alpha]^{22}_D = -2.3 \times 10^3$ ($c = 0.0032$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 225 (45 000), 269 (24 000), 348 (3700), 476 (19 000), 541 (9900), 586 (9700); CD (MeOH) nm ($\Delta\epsilon$) 233 (−68.5), 291 (+43.4), 360 (−14.3), 448 (+19.1), 584 (−13.5).

Calphostin D (4). A solution of NaOMe (15 mL, 5.6 mmol, 0.37 M/MeOH) was added to **1** (22.0 mg, 0.028 mmol) at room temperature to provide a green solution. After 72 h, the reaction was diluted with chloroform (30 mL) and washed successively with aqueous 1 N HCl and brine, dried with Na_2SO_4, and concentrated to a deep purple oil. Chromatography with 98:2 CH_2Cl_2/MeOH afforded 10.1 mg (66%) of a red oil: $R_f = 0.31$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, $J = 6.1$ Hz, 6H), 2.95 (dd, $J = 13.2$, 8.7 Hz, 2H), 3.56 (dd, $J = 13.2$, 2.8 Hz, 2H), 3.70−3.80 (m, 2H), 3.92 (s, 6H), 4.24 (s, 6H), 6.31 (s, 2H), 15.83 (br s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.1, 43.8, 57.3, 61.5, 69.7, 101.8, 107.1, 118.2, 127.5, 130.2, 139.0, 152.8, 168.6, 175.3, 178.1; IR (film) 3387, 2968, 2927, 2854, 1604, 1541, 1456, 1277, 1157 cm^{-1}; HRMS (FAB) calcd (M + H)$^+$ ($C_{30}H_{31}O_{10}$) 551.1917, found 551.1937; $[\alpha]^{22}_D = -3.6 \times 10^3$ ($c = 0.0031$, MeOH); UV−vis (MeOH) λ_{max} nm (ϵ) 224 (48 000), 268 (32 000), 345 (4700), 476 (24 000), 538 (13 000), 583 (12 000); CD (MeOH) nm ($\Delta\epsilon$) 225 (−56.1), 291 (+ 44.4), 358 (−14.2), 442 (+18.7), 586 (−11.5).

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Supporting Information Available: Description of the experimentals and characterization data for compounds **6**−**8**, **11**−**16**, **20**, **22**, **26**, **37**. Description of the complete syntheses of analogues **47**−**52** starting from commercially available starting materials. ^{1}H NMR and ^{13}C NMR for compounds **1**−**22**, **25**−**37**, **38M**, **38P**, **39**, **40M**, **40P**, **41M**, **41P**, **44**−**46**. Additionally, complete ^{1}H NMR and ^{13}C NMR spectra for analogues **47**−**52**, including all intermediates in their synthesis**.** CD spectra for **1**−**4**, **32**, **38M**, **38P**, **41M**, and **41P** This material is available free of charge via the Internet at http://pubs.acs.org.

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