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Divergent Approach to the Bisanthraquinone Natural Products: Total Synthesis of (*S*)-Bisoranjidiol and Derivatives from Binaphtho-*para*-quinones

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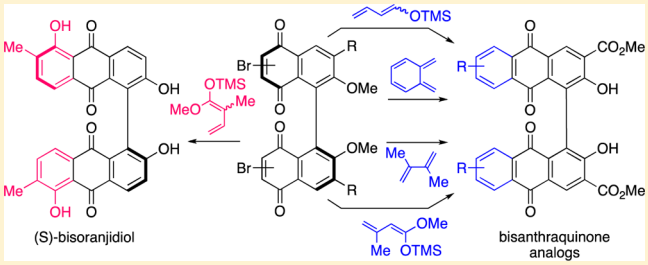
Supporting Information

ABSTRACT: The development of the first asymmetric synthesis of a chiral anthraquinone dimer is outlined, resulting in the first total synthesis of (*S*)-bisoranjidiol. Rather than a biomimetic dimerization retrosynthetic disconnection, the anthracenyl ring systems are generated after formation of the axially chiral binaphthalene framework. This synthetic strategy has enabled the synthesis of several analogues. Key features of the synthesis include the enantioselective coupling of a hindered 2-naphthol containing substitution *peri* to the site of C−C bond formation, the regioselective oxidation of 8,8′-hydroxylated binaphthols to binaphtho-*para*-quinones, and a tandem regioselective Diels−Alder/aromatization reaction.



INTRODUCTION

Over the last several decades, many natural bisanthraquinones and related polyoxygenated biaryl aromatic systems have been isolated and identified.[1] The bisanthraquinone family of natural products is partly composed of a collection of axially chiral symmetrical anthraquinone dimers possessing a 1,1′-biaryl linkage (Figure 1). With one exception, all of these bisanthraquinones have a *meta*-substitution pattern on the distal rings, as well as 2,2′-, 4,4′-, and 5,5′-hydroxyl groups. Examples include skyrin (**1a**),[2] bislunatin (**1d**),[3] disolorinic acid (**1e**),[4] trachypone (**1h**),[5] etc. The exception to this general pattern is (*S*)-bisoranjidiol [(*S*)-**2**, Figure 1]. Unlike disolorinic acid (**1e**) and the other members, (*S*)-bisoranjidiol lacks the 4,4′-hydroxyl groups and contains an *ortho*-substitution pattern on the distal rings. In 2006, the dimer was isolated from the leaves of the South American shrub, *Heterophyllaea pustulata*.[6] Useful properties of the compound include its ability to generate singlet oxygen and the ground-state radical anion upon exposure to light,[7] which contributes to the photodynamic activity of the compound against bacteria[8] and cancer cells,[9] leading to potential applications in photodynamic therapy.[10−13] Other bisanthraquinones are also active against cancer[14] and have shown potential for the treatment of diabetes,[15] depression,[16] etc. Despite the interesting biological activity of bisoranjidiol and related bisanthraquinones, no stereoselective syntheses of a 1,1′-linked bisanthraquinone had been achieved until recently, when we reported the first total synthesis of (*S*)-bisoranjidiol.[17] Herein we disclose a full description of the development of the synthesis of (*S*)-bisoranjidiol as well as the synthesis of a number of potentially bioactive analogues.

RESULTS AND DISCUSSION

Previous approaches toward the synthesis of 1,1′-bisanthraquinones have generally concentrated on biomimetic pathways, such as the oxidative coupling of anthraquinones or anthrones (low yields)[18−20] and Ullman couplings of brominated anthraquinones. Good yields have been achieved with the Ullman reaction, but harsh conditions were required that are incompatible with highly functionalized substrates.[21−24] We initially proposed a biomimetic synthesis involving late-stage oxidative asymmetric coupling of an anthraquinone. Enantioselective binaphthol couplings have been a vital part of many syntheses of biaryl natural products containing axial or helical chirality, both by our group and others.[25−27] However, preliminary results revealed that a biomimetic approach was not feasible because of the high oxidation potential of anthraquinones. For example, the coupling of **3** using copper catalyst **4** did not proceed (Scheme 1).

We therefore considered a nonbiomimetic approach, which would allow for the enantioselective synthesis of both (*S*)-bisoranjidiol and a variety of derivatives via three major retrosynthetic steps (Scheme 2). The first key disconnection of bisoranjidiol or analogues is a regioselective tandem Diels−Alder/aromatization reaction between an alkyl trimethylsilylvinyl ketene acetal or other diene and a binaphtho-*para*-quinone (**7**). This chiral *p*-quinone intermediate could be formed via a selective oxidation of an 8,8′-dihydroxylated binaphthol (**8**). The binaphthol could in turn be generated via an enantioselective biaryl coupling reaction of a hindered 8-

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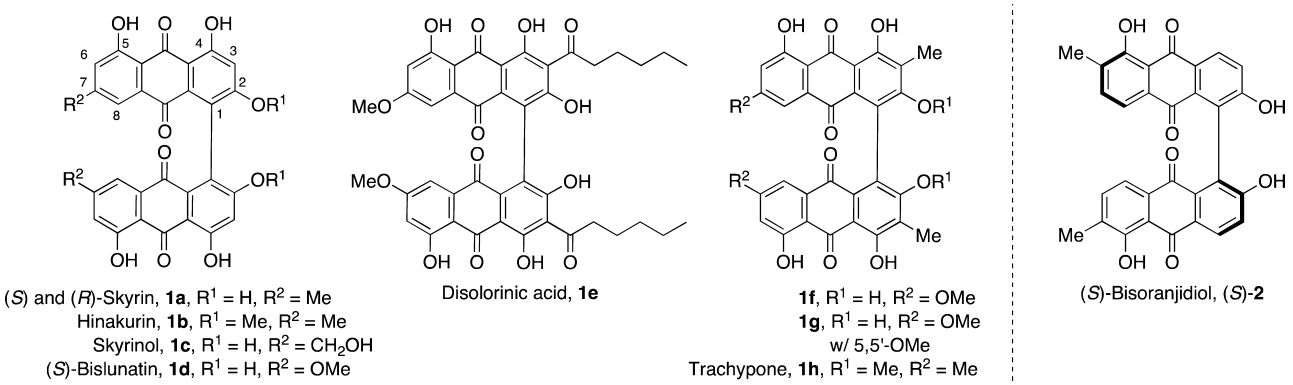
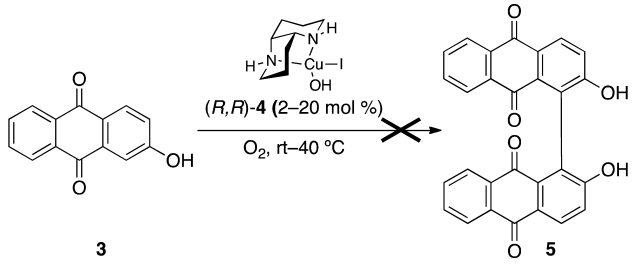
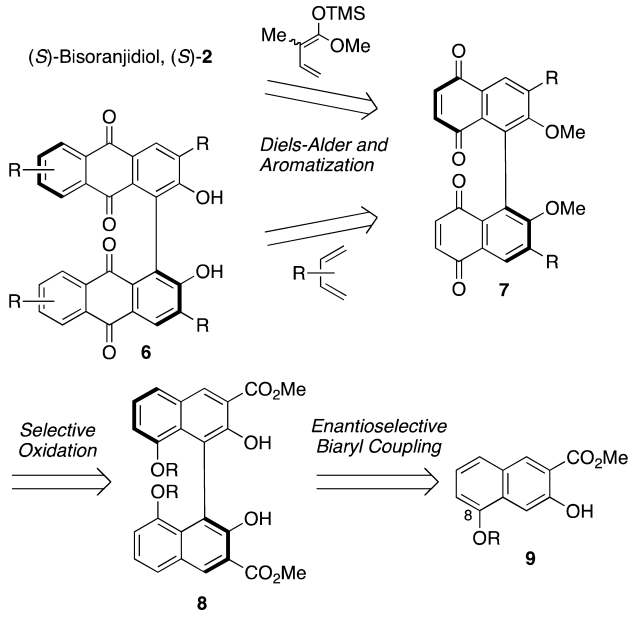


Figure 1. Examples of bisanthraquinone natural products.

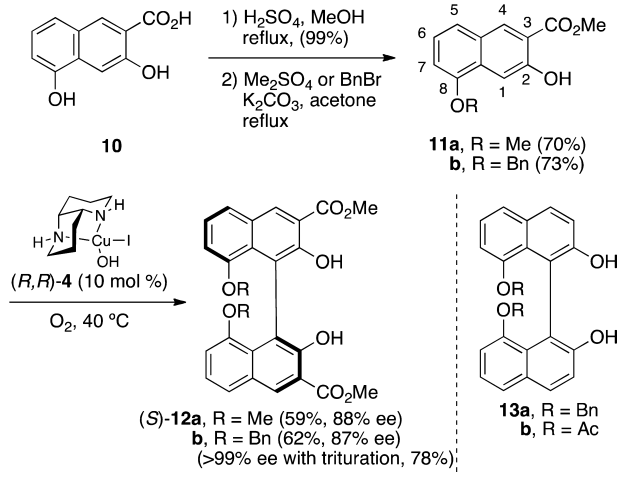
Scheme 1. Attempted Biomimetic Coupling of Anthraquinones



Scheme 2. Retrosynthesis



Scheme 3. Enantioselective Biaryl Coupling of an 8-Substituted 2-Naphthol



substituted 2-naphthol. The formation of hindered biaryls have been demonstrated recently with Suzuki–Miyaura cross-coupling,[28−31] Ullmann–Ziegler coupling,[32] C–H arylation,[33] and other approaches, such as the domino reaction with alkynes.[34]

In choosing the appropriate catalyst for the biaryl coupling reaction, both chiral vanadium and copper catalysts were examined. A brief screen of vanadium-catalyzed couplings[35,36] to form either biaryl **13a** or **13b** (Scheme 3) from their corresponding monomers was investigated. The monomer of **13a** was prepared by monobenzylation of naphthalene-1,7-diol, and the monomer of **13b** was prepared by diacetylation of naphthalene-1,7-diol, followed by monodeprotection of the 2-acetoxy group. The chiral vanadium-catalyzed couplings of either monomer, however, produced only low conversions and selectivities. Apparently, substitution at the C8-position of the substrate greatly slows coupling at the C1-position and lowers selectivity. On the other hand, the copper-catalyzed reactions were more promising. The 8-substituted 2-naphthol **11a**, prepared via a Fischer esterification and selective methylation, was selectively coupled in 59% yield and 88% ee with a 1,5-diaza-*cis*-decalin copper catalyst[37−40] (Scheme 3). To the best of our knowledge, this represents the first catalyzed enantioselective coupling reaction of a 2-naphthol with considerable steric hindrance *peri* to the site of C–C bond formation. One other enantioselective reaction of an 8-substituted 2-naphthol was reported in the literature with good yield and selectivity (50% yield, 75% ee), but required superstoichiometric copper.[41]

Although the coupling of **11a** proved proof of concept, the methoxy-protected phenols at the 8,8′-positions were not suitable for the synthesis of (*S*)-bisoranjidiol because they could not be easily removed without affecting the methyl ester or protecting groups on the 2,2′-hydroxyl groups. Thus, the synthesis was adjusted to incorporate an 8-benzyloxy substituent (**11b**, Scheme 3). The synthesis of this substrate was accomplished via selective benzylation to afford the coupling substrate in 73% yield. The enantioselective biaryl

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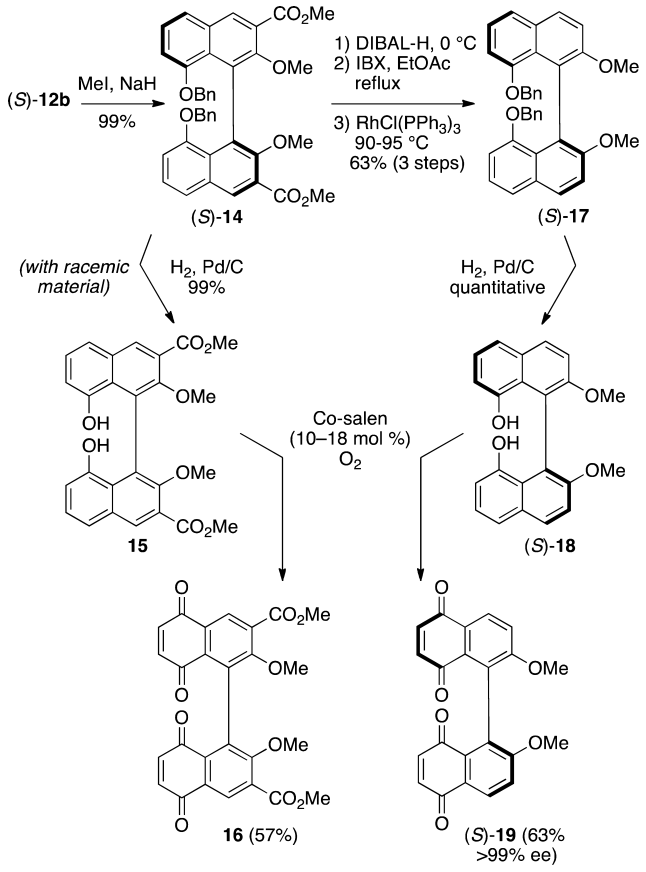
coupling reaction worked well with this substrate, providing (*S*)-**12b** in 62% yield and 87% ee [61% yield, 92% ee with (*S*,*S*)-**4**].[42] The enantiopurity could readily be enhanced to >99% ee with one trituration. The racemate of **12b** could also be generated in 91% yield using CuCl(OH)TMEDA as the catalyst.

With a successful synthesis of biaryl (*S*)-**12b** in hand, we chose to examine the regioselective oxidation and Diels–Alder/aromatization reaction with a racemic model substrate that retained the 3,3′-methyl esters. Methylation, followed by hydrogenolysis of *rac*-**12b**, yielded 8,8′-hydroxylated binaphthol **15** (Scheme 4). Selective oxidation to the binaphtho-*para*-quinone[43] via a Co-salen catalyzed oxidation proceeded well, as compound **15** was transformed into model Diels–Alder substrate **16** in 57% yield. Since the selective oxidation was successful, the binaphtho-*para*-quinone intermediate [(*S*)-**19**] to bisoranjidiol was synthesized in a similar manner from (*S*)-**14**, following removal of the ester groups. The ester groups were efficiently removed via a three-step sequence involving transformation of the esters to aldehydes and decarbonylation. Notably, oxidation of (*S*)-**18** provided quinone (*S*)-**19** without loss of enantiopurity.

Scheme 4. Synthesis of Binaphtho-*para*-quinones



The next major challenge following the synthesis of binaphtho-*para*-quinones was the regioselective Diels–Alder reaction. Use of a tandem Diels–Alder/aromatization reaction to form hydroxylated anthraquinones, particularly with a hydroxyl group *peri* to one of the anthraquinone carbonyls, is well-known. Many different types of alkyl- and silyloxy dienes have been reported for this transformation, including 2-pyrones or cyclohexadiene derivatives,[44] which lose carbon dioxide or ethylene during the aromatization step. Noncyclic dienes, such as Danishefsky's diene or Brassard-type dienes (alkyl silylvinyl ketene acetals), have also been employed.[45−48] For alkyl silylvinyl ketene acetals, in general, formation of the hydroxylated anthraquinone involves a [4 + 2] cycloaddition reaction with the *p*-naphthoquinone, followed by acid- or base-mediated aromatization. Aromatization involves loss of the silyl groups, elimination of the alkoxy group, tautomerization, and air oxidation to yield the aromatic ring. An imposing challenge of this Diels–Alder/aromatization strategy is control over the regioselectivity of the cycloaddition reaction when an unsymmetrically substituted *p*-naphthoquinone is the electrophile. For example, with a 2-alkoxy-*p*-naphthoquinone, as shown in Figure 2, or as proposed in our retrosynthetic scheme (**7**, Scheme 2),

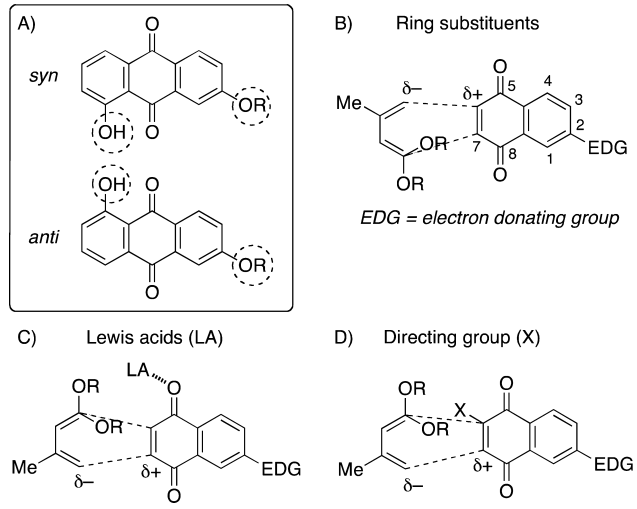


Figure 2. Diels–Alder regioselectivity.

two possible regioisomers could result in which the newly formed *peri*-hydroxyl group is either *syn* or *anti* to the 2-alkoxy (Figure 2A).

It has been suggested with juglone (5-hydroxynaphthalene-1,4-dione) derivatives that the polarization of the diene imparts a larger influence on the regiochemical outcome than the substituent effects of the dienophile, except for strongly polarized dienes.[49] As alkyl silylvinyl ketene acetals are strongly polarized dienes, prediction of the regiochemical outcome of the cycloaddition can be rationalized through charge affinity patterns. Influences, such as hydrogen bonding and resonance of substituents on the naphthoquinone, can affect the regioselectivity. For example, with a 2-methoxy-*p*-naphthoquinone or similar quinone with an electron-donating group (EDG) at the 2-position, donation of electron density into the 5-carbonyl polarizes the dienophile (Figure 2B). In this case, the 8-carbonyl is more electrophilic and will exert greater control over the regioselectivity, so that the *syn* isomer predominates. Extrapolation of this analysis to the retrosynthesis of bisoranjidiol (Scheme 2) reveals an unfavorable outcome in which the bis-*syn*-adduct (*in-in*-isomer) is the major product. However, formation of the bis-*anti*-adduct (*out-out*-isomer) is necessary for the natural product. Two methods for controlling the regioselectivity beyond substituent effects are to use Lewis acids (LA)[49,50] or directing groups.[46−48,51] The LA will coordinate to the more basic carbonyl, resulting in a more electrophilic 7-carbon and leading to the *anti*-isomer in this example (Figure 2C). Alternatively, directing groups such as

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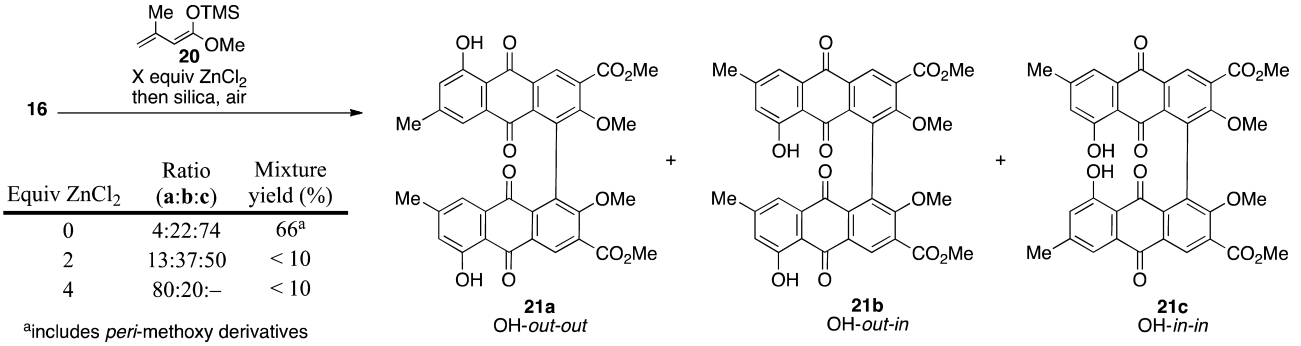
Scheme 5. Synthesis of Bisanthraquinones and Effect of LA on Regioselectivity on Model Binaphtho-*para*-quinone



Equiv $ZnCl_2$	Ratio (a:b:c)	Mixture yield (%)
0	4:22:74	66[a]
2	13:37:50	< 10
4	80:20:–	< 10

[a]includes *peri*-methoxy derivatives

halogens, sulfoxides, and acetoxy groups on the quinone can provide a similar outcome (Figure 2D).

Initial evaluation of the Diels–Alder reaction was pursued between the model substrate **16** and diene **20** (Scheme 5). Diene **20**, with *meta*-substitution, was chosen over the *ortho*-substituted diene necessary for bisoranjidiol because it is more stable than many of the other vinyl ketene acetals.[47] Based on the charge affinity patterns of binaphtho-*para*-quinone **16**, the *in-in*-isomer, **21c**, was expected to be favored. A LA or directing group would be necessary to achieve selectivity for the required *out-out*-isomer. This hypothesis was supported by the results of the control reaction. Without a LA, the cycloaddition reaction highly favored **21c** (4:22:74 ratio for **21a**:**21b**:**21c**), providing the bisanthraquinone mixture in 56–66% yield. When 2 equiv of $ZnCl_2$ were added, improvement in the selectivity was observed. With 4 equiv of the LA, **21a** was obtained as the major isomer and none of **21c** was observed.[52] Unfortunately, the yields were consistently poor (<10%) when a LA was added due to the formation of numerous byproducts and decomposition.

Since the yields were poor with the dimer, we decided to optimize conditions on the monomer and explore directing groups. The monomer, **23**, was synthesized from **22** in 52% yield (Scheme 6). Methylation under mild conditions, using MeI and Ag_2O, provided **24** in 79% yield.

For the thermal Diels–Alder reaction, like the dimer, preferential formation of the *syn*-isomer (**27b**, **28b**) and good anthraquinone yields were observed (62–78%, entries 1–3, Table 1). The substrate lacking the 3-methyl ester was reported to give better selectivity[51c] (24:76, entry 3) than either of the ester substrates. For both the monomer and dimer,

Scheme 6. Synthesis of *p*-Naphthoquinone Monomers

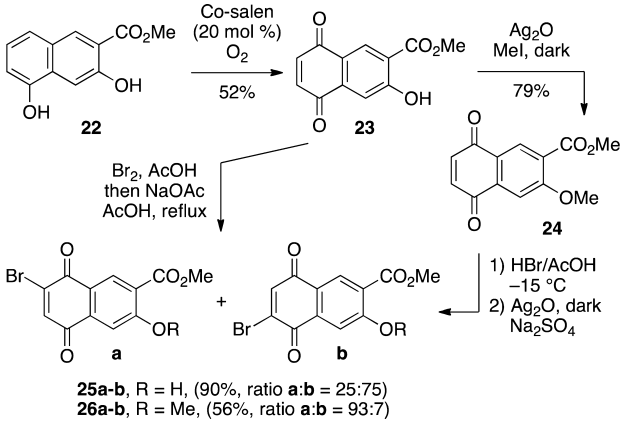
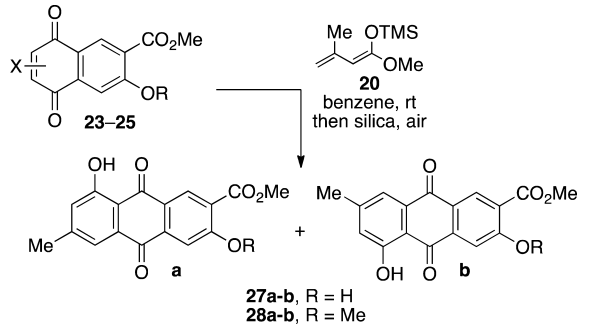


Table 1. Diels–Alder Regioselectivity on a Monomeric System



entry	R	X	additive	mixture yield (%)	ratio (a:b)
1	H	H	-	65[a]	9:91
2	Me	H	-	62[a]	13:87
3[b]	Me (no ester)	H	-	78	24:76
4	H	H	$ZnCl_2$ (2 equiv)	17	19:81
5[c]	H	H	$Ti(OMe)_4$(2 equiv)	38	12:88
6[d]	H	Br	-	84	24:76

[a]Includes *peri*-methoxys. [b]Benzene reflux then O_2, 5% aq NaOH; ref 51c. [c]In toluene. [d]25:75 ratio of bromoquinone regioisomers.

regioisomeric ratios could be determined by analysis of the ^{1}H NMR spectrum. The chemical shifts of the newly formed *peri*-hydroxyl groups differ by at least 0.2 ppm between the *syn* and *anti* isomers. The *peri*-hydroxyl group for the *anti*-isomer, **27a**, is shifted downfield relative to **27b** because it is hydrogen-bonded to the more basic carbonyl. This analysis also extended to the dimers. A crystal structure of **27b** confirmed that the correct regioisomeric assignments were being made.

Interestingly, significant amounts of *peri*-methoxyanthraquinones (Figure 3) were also isolated from the reactions in entries 1 and 2 (Table 1). This material arises from elimination of the trimethylsiloxy group instead of the methoxy group on

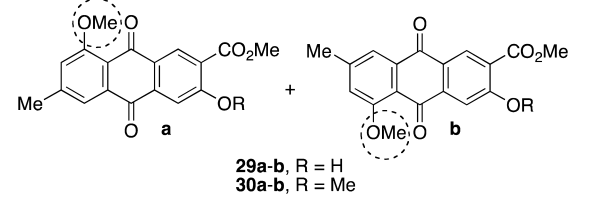


Figure 3. Anthraquinones with *peri*-methoxy substituents.

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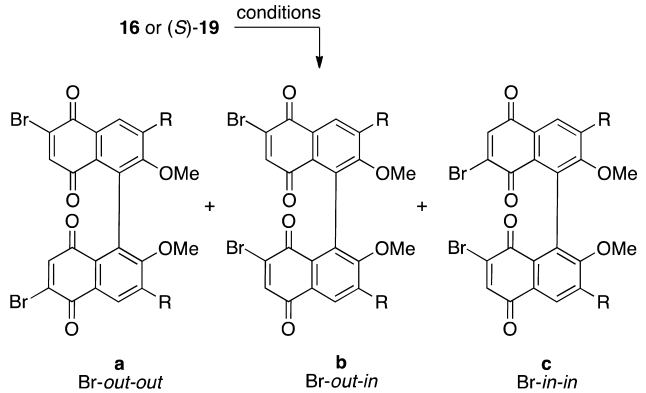
the cyclohexene ring of the cycloadduct during the aromatization portion of the transformation. The mixture yields for these entries include the *peri*-methoxyanthraquinone isomers. To confirm that the ratios of *peri*-hydroxy- and *peri*-methoxyanthraquinones were the same, it was necessary to deprotect the methoxy groups, since the regioisomeric ratio could not be determined from the ^{1}H NMR spectrum of the mixture. Following BCl_3 deprotection, analysis confirmed that the regioisomeric ratios were identical. Thus, measurement of the *peri*-hydroxyanthraquinone isomer ratio was sufficient to determine the overall selectivity. No formation of the *peri*-methoxy products **29a,b** (Figure 3) was observed for the other entries in Table 1.

When Lewis acids were screened, yields were low due to decomposition and side reactions (entries 4 and 5, Table 1). In particular, $ZnCl_2$ led to 33% of a side product resulting from Michael addition of the diene. In addition, the undesired *syn* product (**27b**) was still predominant. Other Lewis acids, such as $Ti(OMe)_4$, $BF_3{\cdot}Et_2O$, and $Ti(Oi\text{-}Pr)_4$, were also unsuccessful. Because of the low yields and undesired selectivity observed with Lewis acids, directing groups were explored, particularly a bromine group which could easily be added to the quinone. Formation of bromoquinones **25a,b** was accomplished by bromination followed by dehydrobromination (Scheme 6). The bromoquinones were obtained in 90% yield as an inseparable 25:75 mixture of **25a** and **25b**. Alternatively, hydrobromination of **24**, followed by oxidation of the ensuing hydroquinone, provided a promising bromoquinone ratio of 93:7 (**26a**:**26b**) in a 56% yield. For the Diels–Alder reaction, bromine-directing groups looked promising (entry 6, Table 1). Anthraquinones **27a** and **27b** were obtained in high yields (84%), and the ratio of regioisomers of the starting material was reflected in the products. This result prompted us to explore bromine as a directing group for the dimeric compounds.

Unfortunately, the success of the hydrobromination/reoxidation reaction of naphthoquinone monomer **24** to form **26** (Scheme 6) could not be extended to the biaryl system (Table 2). While the desired *out-out*-regioisomer was favored in the reaction, the majority of the isolated material was the monobrominated species. More vigorous reaction conditions led to demethylation of the methoxy groups and a complex mixture rather than dibromination. Bromination of **16** or (*S*)-**19**, followed by dehydrohalogenation, proved more promising. The ester substrate could be brominated in 87% yield, providing **31a–c** in a 37:50:13 ratio. As with the monomer (entry 6, Table 1), we were encouraged that the isomer ratio of dibrominated quinones **31a–c** (37:50:13) was reflected in the bisanthraquinone products **21a–c** (39:47:14), following the Diels–Alder/aromatization reaction.

With these results in hand, we turned to the synthesis of (*S*)-bisoranjidiol. Bromination of (*S*)-**19** provided a mixture of bromoquinone regioisomers (*S*)-**32** in 95% yield and a ratio of 43:47:10 (Table 2). This material could be used to synthesize a significant amount of the natural product as well as an unnatural regioisomer. On the basis of the results observed with diene **20** and binaphtho-*para*-quinones **31a–c**, it was anticipated that the regioisomer ratio of the starting quinones would be reflected in the product bisanthraquinones (see Table 1, entry 6). However, when binaphtho-*para*-quinone *rac*-**32a–c** was treated with *ortho*-substituted diene **33**,[53] followed by aromatization using silica as the Lewis acid, almost no product was observed. It appeared that the aromatization process was much slower for this diene. The silica source proved key to success in this transformation, with silica from TLC plates (Silicycle) proving more efficient than the bulk silica gel (Silicycle, 40–63 μm) used previously. Even so, the ratio of bisanthraquinone products did not reflect the starting material (Scheme 7) as had consistently been the case with diene **20**.

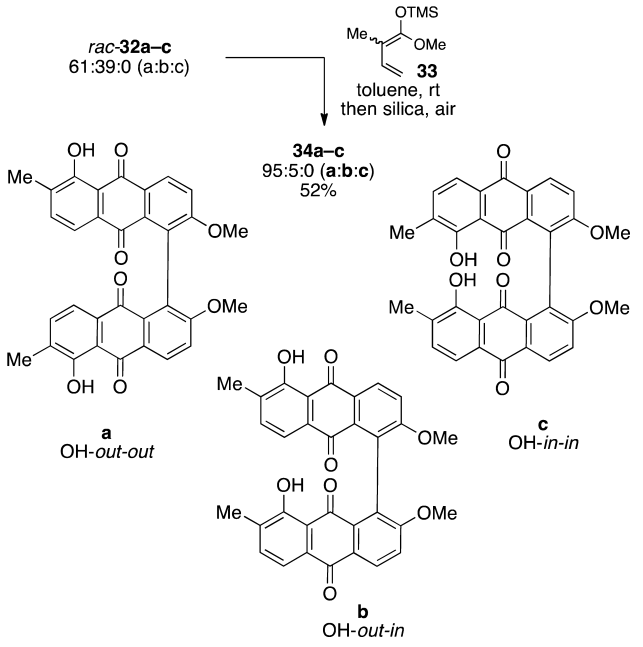
Table 2. Bromination of Binaphtho-*para*-quinones[a]



product	R	conditions	mixture yield (%)	ratio (**a**:**b**:**c**)
31	CO_2Me	A	30[b]	66:33:<1
31	CO_2Me	B	87	37:50:13
(*S*)-**32**	H	B	95 (75)[c]	43:47:10

[a]Conditions: A = (1) HBr/AcOH, −15 °C, (2) Ag_2O, Na_2SO_4, dark; B = Br_2, AcOH then NaOAc, AcOH, reflux. [b]Incomplete reaction; longer times result in demethylation. [c]After semipreparative HPLC.

Scheme 7. Reactivity Differences in the Diels–Alder Reaction



The same problem was also encountered when dienophile **31a–c** was combined with diene **33**, indicating that the change in product distribution was not due to the binaphtho-*para*-quinone structure. The ^{1}H NMR spectrum of the reaction mixture showed predominantly the *out-out*-bisanthraquinone regioisomer, **34a**. The yield (52%) suggested that the other bromoquinone regioisomers or monocycloadducts were either

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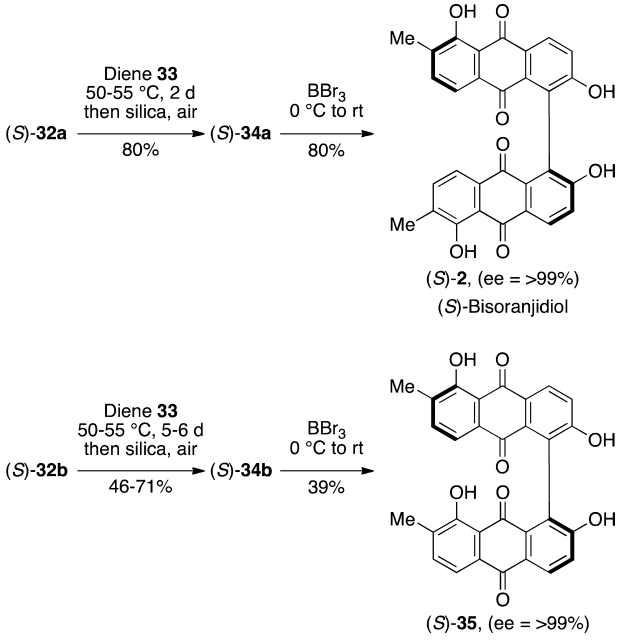
not reacting well with diene **33** and/or were decomposing in the Diels–Alder reaction.

To investigate the observed reactivity difference, each of the bromoquinone regioisomers (*S*)-**32a–c** were separated via semipreparative HPLC and reacted individually with diene **33** (Scheme 8). Formation of (*S*)-**34a** from (*S*)-**32a** proceeded

Scheme 8. Synthesis of (*S*)-Bisoranjidiol and Regioisomer



well (80% yield), which was consistent with observations from reaction of the bromoquinone mixture. Notably, the two reaction sequences, cycloaddition and aromatization, on both quinones of the dimer must proceed with high efficiency (~95% per transformation) to generate the observed overall 80% yield. The unsymmetrical dibromoquinone, (*S*)-**32b**, required nearly three times longer for the cycloaddition reaction to reach completion because it stalled at the monocycloadduct stage. More decomposition was also observed compared to formation of (*S*)-**34a**, resulting in lower yields of (*S*)-**34b** (46–71% yield). The more sterically congested product (*S*)-**34c** did not form readily; primarily, decomposition was observed.

To complete the synthesis of bisoranjidiol, and its unnatural regioisomer, both (*S*)-**34a** and (*S*)-**34b** were deprotected with BBr_3 to yield the natural product (*S*)-**2** and the regioisomer (*S*)-**35** with no erosion of the enantiomeric excess (Scheme 8).

The NMR spectroscopic data of synthetic-(*S*)-**2** corresponded well with the literature.[6] Using an authentic sample of bisoranjidiol kindly provided by Dr. Cabrera,[6] the configuration of the natural product isolate was analyzed using HPLC with a chiral stationary phase. This analysis revealed that the natural product isolate was 5% ee (*S*). Evaluation of the atropisomeric stability of (*S*)-**2** revealed that the enantiopurity of bisoranjidiol degrades in MeOH (25 °C, $t_{1/2}$ = 3.8 months; 80 °C, $t_{1/2}$ = 1.8 h, $\Delta G^{\ddagger}$ (rt) = 27.20 kcal/mol), eroding from >99% ee to 71% ee after 26 days (Figure 4). Notably, over the same period of time a sample of the solid did not show any degradation. In view of the observed racemization, it is possible that any naturally occurring enantiopurity of bisoranjidiol could have been significantly

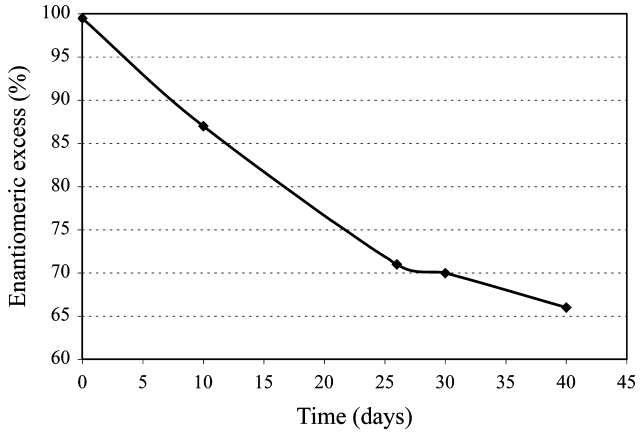


Figure 4. Racemization of (*S*)-**2** in MeOH (25 °C).

eroded during isolation, which involved heating to 80 °C as well as exposure to acid and base.

A pathway for racemization may arise through formation of enone **36** (Scheme 9, path A). Although the enone is highly strained, structurally similar compounds, such as binaphthone **41** (Figure 5) with an extended quinone, have been isolated.[54] In addition, binaphthone **41** was atropisomerically unstable due to equilibration between twisted and stacked conformations.[54] It is conceivable that enone **36** may proceed through an analogous equilibration toward conformation **38** and ultimately (*R*)-**2**. An alternate pathway for racemization is also possible through bishemiketal intermediate **39** (Scheme 9, path B). Formation of this type of structure has been observed with a binaptho-*p*-quinone under neutral conditions[43] as well as an anthraquinone upon treatment with sulfuric acid.[23] Formation of the bishemiketal introduces a bridged biaryl bond, which is known to lower the barrier for atropisomerization.[55] Ring flip of the pyrans lead to intermediate **40**, which forms the opposite enantiomer of bisoranjidiol, (*R*)-**2**, upon ring-opening.

Because of the interesting biological properties of bisoranjidiol and bisanthraquinones in general, several analogues were synthesized by varying the diene for the Diels–Alder reaction (Scheme 10). A mixture of dibromoquinones **31a–c** was treated with either 2,3-dimethyl-1,3-butadiene or 1-(trimethylsiloxy)-1,3-butadiene, followed by NEt_3 to generate bisanthraquinones **44** and **46** in 71% and 65% yield, respectively. Sultine **43**,[56] which degrades above 80 °C to the exocyclic diene, and SO_2 could also be used to generate a bisanthraquinone with an extended ring system. All three of these compounds were deprotected with BCl_3 to yield analogues **42**, **45**, and **47** in good overall yields.

■ CONCLUSION

In summary, chiral binaphtho-*para*-quinones, generated via enantioselective oxidative naphthol coupling followed by regioselective oxidation, were used effectively to complete the first enantioselective synthesis of a 1,1′-linked bisanthraquinone and the first synthesis of bisoranjidiol. The Diels–Alder/aromatization cascades of binaphthoquinones are highly efficient (~95% per transformation). Overall, bromines were found to be superior activators and directing groups in quinone Diels–Alder reactions relative to Lewis acids or electron-donating substituents. This approach described herein also permitted the generation of several analogues, including the

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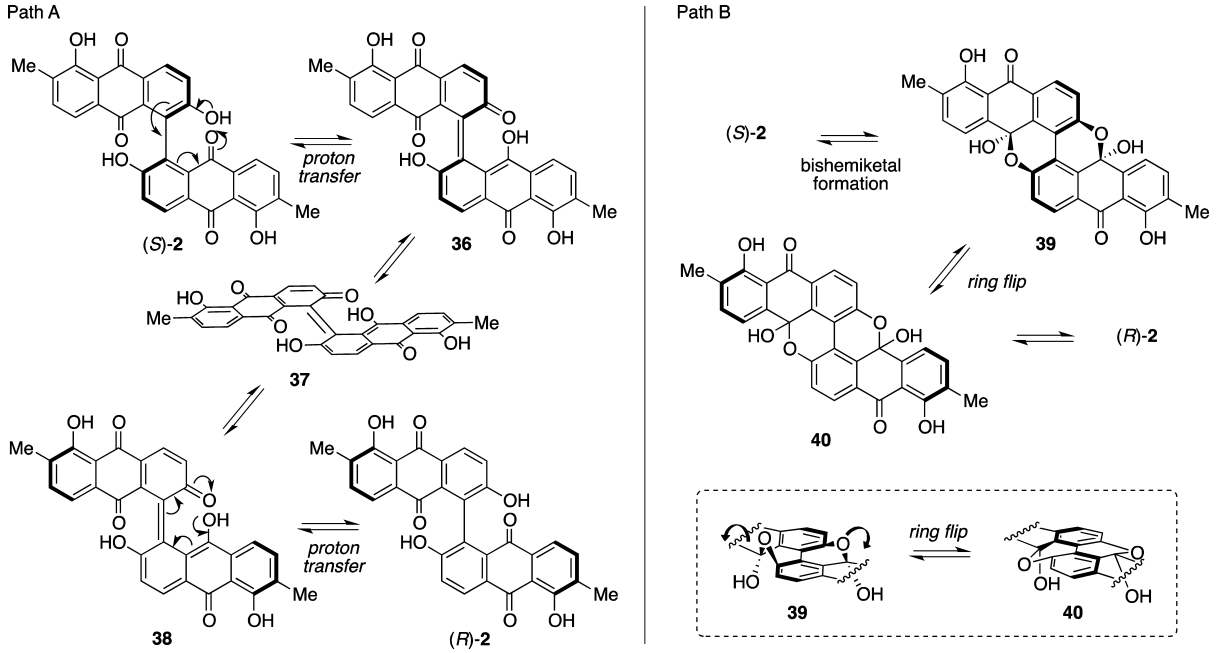
Scheme 9. Proposed Pathways for Racemization



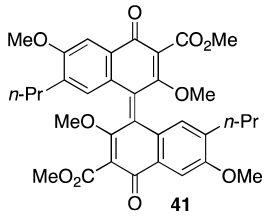


Figure 5. Known binaphthone compound.

regioisomer of bisoranjidiol and four other bisanthraquinones for further study (**21**, **42**, **45**, and **47**).

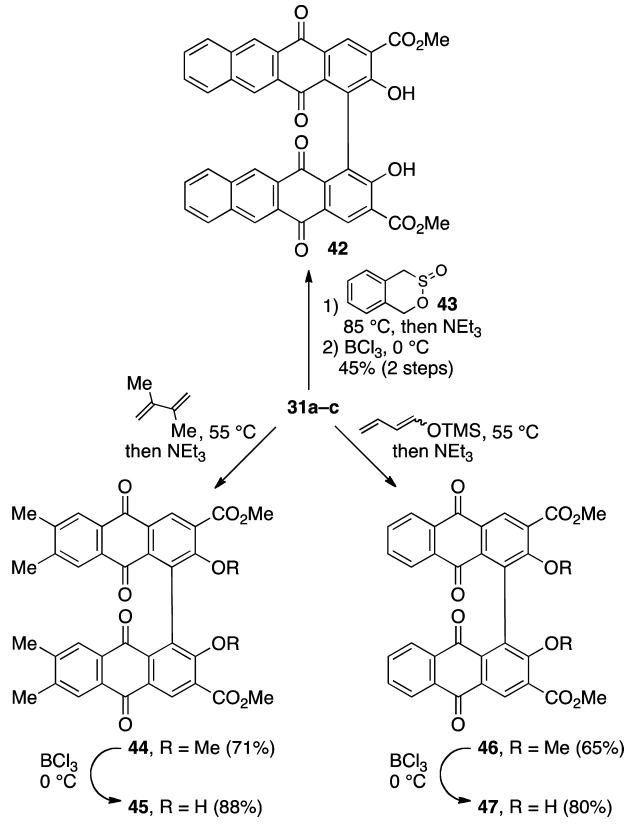
EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an atmosphere of dry argon, unless otherwise noted. Dienes **20** and **33** were prepared according to reported procedures,[57,53] distilled under reduced pressure, and stored at −20 °C under argon. Diene **33** was used within two weeks of preparation, and diene **20** was used within a month. Compounds **2**, **11b**, **12b**, **14**−**19**, **22**, **32**, **34**, and **35** were reported previously.[17,43]

Multiplicity for ^{1}H NMR data are reported as follows: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. ^{1}H NMR spectra were referenced to the residual solvent peaks: $CDCl_3$ (7.26 ppm), acetone-d_6 (2.05 ppm), and C_6D_6 (7.16 ppm). ^{13}C NMR spectra were referenced to $CDCl_3$ (77.16 ppm) and acetone-d_6 (29.84 ppm). High-resolution mass spectra were measured on a LC-TOF mass spectrometer (ionization mode: ESI+ or ESI−). Enantiomeric excesses were determined using analytical HPLC with UV detection at 254 nm and analytical Chiralpak AD column (4.6 mm × 250 mm, 10 μm). Reactions were monitored via analytical thin layer chromatography (TLC) and visualization was accomplished with UV light and/or ceric ammonium molybdate stain. Column chromatography was performed with silica gel (40−63 μm particle size).

Methyl 3-Hydroxy-5-methoxy-2-naphthoate (11a). In a modified procedure,[58] anhydrous K_2CO_3 (4.59 g, 33.2 mmol) was added to a solution of **22** (5.00 g, 22.9 mmol) in acetone (78 mL). Following dropwise addition of Me_2SO_4 (2.4 mL, 25.4 mmol), the reaction was heated at reflux. After 4 h, water was added and the aqueous layer extracted with CH_2Cl_2. The organic extract was washed with brine and dried over Na_2SO_4. Following filtration and concentration, the crude solid was combined with crude solid from two 15.00 g scale reactions and recrystallized from MeOH to afford **11a** as a yellow solid (26.2 g, 70% yield): mp 145−148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.44 (s, 1H), 7.72 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 156.5, 154.4, 132.0, 130.7, 128.2, 124.0, 121.4, 114.6, 107.1, 106.4,

Scheme 10. Synthesis of Bisanthraquinone Analogues



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55.8, 52.7; IR (film) 3159, 3024, 2962, 1686, 1284, 1198 cm^{-1}; HRMS (ESI) m/z 233.0815 $[M + H]^+$ (calcd for $C_{13}H_{13}O_4$, 233.0814).

(*S*)-Dimethyl 2,2′-Dihydroxy-8,8′-dimethoxy-1,1′-binaphthyl-3,3′-dicarboxylate [(*S*)-12a]. To a solution of **11a** (40 mg, 0.17 mmol) in $ClCH_2CH_2Cl$ (2 mL) was added (*R*,*R*)-**4** (6.3 mg, 10 mol %). Following sonication, the solution was placed under an oxygen atmosphere and heated in a 40 °C oil bath. After 20 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed (30% EtOAc/hexanes) to afford (*S*)-**12a** as a yellow solid (47 mg, 59% yield, 88% ee): mp >250 °C; $[\alpha]^{26}_D$ −80 (*c* 0.061, 88% ee, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 2H), 8.50 (s, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.19 (t, *J* = 7.9 Hz, 2H), 6.70 (d, *J* = 7.2 Hz, 2H), 4.02 (s, 6H), 3.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 156.6, 152.9, 131.1, 129.8, 128.7, 123.4, 122.8, 120.9, 113.5, 108.9, 56.2, 52.7; IR (film) 3175, 3013, 2949, 1676, 1260, 1127 cm^{-1}; HRMS (ESI) m/z 463.1391 $[M + H]^+$ (calcd for $C_{26}H_{23}O_8$ 463.1393).

Racemate (*rac*-12a). To a solution of **11a** (5.00 g, 21.5 mmol) in 2:1 MeCN/$ClCH_2CH_2Cl$ (375 mL) was added CuCl(OH)TMEDA (0.500 g, 10 mol %). The reaction mixture was warmed in a 35 °C oil bath and stirred under an oxygen atmosphere. After 10 h, the mixture was cooled and diluted with CH_2Cl_2. The organic layer was washed with 0.5 M HCl, followed by water and brine. After the organic layer over was dried over Na_2SO_4, the mixture was filtered and concentrated. The residue was triturated with cold 1:1 EtOAc/hexanes to afford *rac*-**12a** as a yellow solid (4.44 g, 87% yield): CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:*i*-PrOH): $t_R(S)$ = 12.0 min, $t_R(R)$ = 23.1 min.

8,8′-Bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol (13a). To a solution of commercially available naphthalene-1,7-diol (1.00 g, 6.24 mmol) in acetone (25 mL) were added anhydrous K_2CO_3 (1.25 g, 9.05 mmol) and BnBr (0.89 mL, 7.5 mmol). After the reaction mixture was heated to reflux for approximately 8 h, the solids were removed via vacuum filtration and washed with acetone. The filtrate was concentrated and the residue chromatographed (5% EtOAc/hexanes) to yield 8-(benzyloxy)naphthalen-2-ol as a light brown oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 6.7 Hz, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.40−7.36 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.12 (dd, *J* = 8.8 Hz, 2.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.23 (s, 2H), 4.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 153.3, 137.3, 130.1, 129.7, 128.8, 128.1, 127.7, 127.0, 123.6, 120.6, 118.1, 105.9, 104.6, 70.3.

$VO(acac)_2$ (9 mol %, 8.0 mg) was added to a solution of 8-(benzyloxy)naphthalen-2-ol (83 mg, 0.33 mmol) in CH_2Cl_2 (3.3 mL) and the reaction mixture stirred under an oxygen atmosphere. After 3 h, the mixture was concentrated. The residue was chromatographed (15% EtOAc/hexanes) to yield **13a** as an off-white solid (30 mg, 36%, 68% based on recovered starting material): mp 188−190 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 6.7 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 4H), 6.73 (d, *J* = 7.2 Hz, 2H), 6.57 (d, *J* = 7.2 Hz, 4H), 5.00 (s, 2H), 4.55 (d, *J* = 11.4 Hz, 2H), 4.51 (d, *J* = 11.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 151.5, 136.2, 131.3, 130.3, 128.2, 127.6, 127.4, 125.4, 123.3, 121.7, 117.2, 113.4, 107.3, 70.5; IR (film) 3483, 3059, 2920, 2873, 1583, 1514, 1452, 1259 cm^{-1}; HRMS (ESI) m/z 521.1711 $[M + Na]^+$ (calcd for $C_{34}H_{26}O_4Na$, 521.1729).

2,2′-Dihydroxy-1,1′-binaphthalene-8,8′-diyl Diacetate (13b). A solution of naphthalene-1,7-diol (500 mg, 3.12 mmol) in pyridine (3.1 mL) was cooled to 0 °C before addition of Ac_2O (1.2 mL, 12.5 mmol). After being stirred for 3 h, the reaction mixture was diluted with EtOAc and washed with 1 M HCl, followed by brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (10−20% EtOAc/hexanes) to yield the diacetate as a white solid (652 mg, 86%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.31−7.27 (m, 2H), 2.46 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.4, 149.1, 146.5, 132.8, 129.8, 127.4, 125.9, 125.4, 122.0, 118.9, 112.5, 21.3, 21.2.

To a solution of the diacetate (652 mg, 2.67 mmol) in CH_2Cl_2/MeOH (13 mL/13 mL) at 0 °C was added anhydrous K_2CO_3 (462 mg, 3.34 mmol). After the solution was stirred for 1 h, the reaction was quenched with 1 M HCl and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4, followed by filtration and concentration. The residue was chromatographed (10−20% EtOAc/hexanes) to yield 7-hydroxynaphthalen-1-yl acetate as a yellow solid (226 mg, 42% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.5, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 2.44 (s, 3H).

CuCl(OH)TMEDA (27 mg, 10 mol %) was added to a solution of the monoacetate (237 mg, 1.17 mmol) in $ClCH_2CH_2Cl$ (11.7 mL) and the reaction mixture stirred under an oxygen atmosphere. After 2 h, the mixture was concentrated and suspended in hexanes. Following sonication, the solids were collected via vacuum filtration and washed thoroughly with 1 M HCl, followed by water. Then the solid was washed carefully with cold EtOAc and a minimal amount of acetone to remove pinkish color, leaving **13b** as a white solid (140.5 mg, 59%): mp >200 °C dec; ^1H NMR (500 MHz, acetone-d_6) δ 7.88 (d, *J* = 8.9 Hz, 2H), 7.78 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.61 (bs, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.9, 2H), 6.99 (dd, *J* = 7.5, 1.2 Hz, 2H), 0.93 (s, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.1, 154.4, 147.6, 132.3, 130.7, 129.0, 127.1, 123.1, 121.7, 119.9, 114.7, 19.6; IR (film) 3344, 1730, 1514, 1220 cm^{-1}; HRMS (ESI) m/z 425.1007 $[M + Na]^+$ (calcd for $C_{24}H_{18}O_6Na$, 425.1001).

Bisanthraquinones [21a, 21b, 21c (Major)]. To a suspension of **16** (30 mg, 0.062 mmol) in dry benzene (1.0 mL) was added diene **20** (46 μL, 4 equiv). Additional diene (4 equiv) was added after 6 and 24 h. After a total of 32 h, the reaction mixture was diluted with CH_2Cl_2 and poured over silica (1200 mg). The solvent was allowed to evaporate open to air. More silica was added as needed. When complete, the silica was loaded directly onto a column and chromatographed (CH_2Cl_2−2.5% EtOAc/CH_2Cl_2) to afford **21** as a mixture of regioisomers in a 4:22:74 ratio (**a**, **b**, **c**; 56%, 10% mono-*peri*-methyl ether also isolated): ^1H NMR (500 MHz, $CDCl_3$) **21a** (*out-out*-OH): δ 12.51 (s, 2H), 8.91 (s, 2H), 7.30 (s, 2H), 7.07 (s, 2H), 4.00 (s, 6H), 3.59 (s, 6H), 2.33 (s, 6H). **21b** (*out-in*-OH): δ 12.52 (s, 1H), 11.99 (s, 1H), 8.90 (s, 1H), 8.88 (s, 1H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); **21c** (*in-in*-OH): δ 12.01 (s, 2H), 8.87 (s, 2H), 7.67 (d, *J* = 1.0 Hz, 2H), 7.01 (s, 2H), 4.00 (s, 6H), 3.59 (s, 6H), 2.44 (s, 6H). Major isomer **21c** (*in-in*-OH): ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 181.6, 165.4, 163.1, 161.8, 149.1, 134.7, 134.1, 132.8, 131.6, 129.9, 128.7, 124.4, 120.9, 114.8, 62.8, 53.0, 22.4; HRMS (ESI) m/z 673.1355 $[M + Na]^+$ (calcd for $C_{36}H_{26}O_{12}Na$, 673.1322).

Methyl 3-Hydroxy-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (23). To a solution of **22** (100 mg, 0.458 mmol) in DMF (9 mL) was added Co-salen (30 mg, 20 mol %). After being stirred under an oxygen atmosphere for 3 h, the mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude solid was chromatographed (30−60% EtOAc/hexanes) to afford **23** as a yellow solid (55.3 mg, 52%): mp 218−220 °C dec; ^1H NMR (500 MHz, $CDCl_3$) δ 11.37 (s, 1H), 8.64 (s, 1H), 7.62 (s, 1H), 6.99 (s, 2H), 4.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 183.3, 169.8, 165.8, 139.8, 138.9, 137.3, 130.7, 124.0, 116.5, 115.9, 53.3; IR (film) 3159, 3082, 2966, 2927, 1668, 1568, 1452, 1313, 1244 cm^{-1}; HRMS (ESI) m/z 233.0440 $[M + H]^+$ (calcd for $C_{12}H_9O_5$, 233.0450).

Methyl 3-Methoxy-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (24). To a suspension of **23** (35.7 mg, 0.154 mmol) in CH_2Cl_2 (1 mL) was added Ag_2O (30 mg, 0.8 equiv), followed by MeI (20 μL, 2 equiv). After the mixture was stirred for 21.5 h in the dark, additional Ag_2O (30 mg, 0.8 equiv) and MeI (20 μL, 2 equiv) were added. When the reaction was complete, the mixture was filtered through Celite with CH_2Cl_2 and concentrated. The residue was chromatographed (15−30% EtOAc/hexanes) to afford **24** as a yellow

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solid (30 mg, 79%): mp 163−164 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.59 (s, 1H), 6.98 (s, 1H), 6.97 (s, 1H), 4.06 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 183.4, 165.2, 163.0, 139.5, 138.5, 135.7, 130.9, 125.6, 124.9, 109.0, 57.0, 52.7; IR (film) 3066, 2958, 2858, 1730, 1668, 1599, 1321, 1236 cm^{-1}; HRMS (ESI) m/z 247.0609 [M + H]$^+$ (calcd for $C_{13}H_{11}O_5$, 247.0606).

Bromoquinone Monomers (26a and 26b). Naphthoquinone **24** (5.0 mg, 0.020 mmol) was dissolved in propionic acid (1 mL) flushed with Ar and cooled to −10 °C. The addition of HBr/AcOH (33 wt %, 50 μL) turned the solution green. After 10 min, the reaction mixture was diluted with water, extracted with EtOAc, and washed several times with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was reconstituted in THF (0.7 mL), followed by the addition of Na_2SO_4 (44 mg) and Ag_2O (7.7 mg, 0.033 mmol). After the mixture was stirred in the dark for 12.5 h, it was filtered through Celite and chromatographed on a short column of silica (CH_2Cl_2) to afford **26** as an inseparable 93:7 mixture of bromoquinones **26a** and **26b** (3.7 mg, 56% yield): ^{1}H NMR (300 MHz, $CDCl_3$) **26a** (*anti*-Br) δ 8.53 (s, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 4.07 (s, 3H), 3.95 (s, 3H). **26b** (*syn*-Br) δ 8.46 (s, 1H), 7.68 (s, 1H), 7.52 (s, 1H), 4.08 (s, 3H), 3.94 (s, 3H); major isomer **26a** (*anti*-Br) ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 176.3, 165.0, 163.3, 141.5, 140.2, 135.6, 132.2, 125.0, 123.6, 109.4, 57.1, 52.9; HRMS (ESI) m/z 324.9723 [M + H]$^+$ (calcd for $C_{13}H_{10}O_5Br$, 324.9712).

Anthraquinone Monomers 27a and 27b (Entry 6, Table 1). Naphthoquinone **23** (20 mg, 0.081 mmol) was suspended in glacial acetic acid (0.2 mL), and a solution of Br_2 in AcOH was added dropwise (1 equiv). When the reaction was complete as determined by TLC, it was diluted with cold water and quenched with $NaHSO_3$. The mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The residue was chromatographed (15% EtOAc/hexanes) to remove any over brominated material and dissolved in AcOH (5 mL). Following the addition of NaOAc (100 mg), the solution was heated to reflux for 5 min. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, followed by drying over Na_2SO_4. The product was obtained as an inseparable mixture of bromoquinones **25a** and **25b** (25:75 ratio) and used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) **25a** (*anti*-Br) δ 11.42 (bs, 1H), 8.71 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 4.06 (s, 3H). **25b** (*syn*-Br) δ 11.42 (bs, 1H), 8.63 (s, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 4.04 (s, 3H).

To a 0 °C solution of a 25:75 mixture of bromoquinones **25a** and **25b** (5.4 mg, 0.016 mmol) in dry toluene (2 mL) was added diene **20** (8 μL, 2.6 equiv). After 1 h, the reaction mixture was concentrated, diluted with CH_2Cl_2, and poured over silica (50 mg). The solvent was allowed to evaporate open to air. After overnight, the silica was filtered to afford **27** as a 24:76 mixture of anthraquinones **27a** and **27b** (4.2 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) **27a** (*anti*-OH): δ 12.65 (s, 1H), 11.40 (s, 1H), 8.84 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 7.11 (s, 1H), 4.06 (s, 3H), 2.47 (s, 3H). **27b** (*syn*−OH): δ 12.43 (s, 1H), 11.38 (s, 1H), 8.83 (s, 1H), 7.83 (s, 1H), 7.67 (d, J = 1.3 Hz, 1H), 7.11 (d, J = 0.7 Hz, 1H), 4.06 (s, 3H), 2.47 (s, 3H).

Isomer **27b** (*syn*-OH) was purified via chromatography (8% EtOAc/hexanes): mp 224−226 °C; ^{13}C NMR (500 MHz, $CDCl_3$) δ 187.1, 181.0, 169.8, 165.8, 163.2, 149.5, 139.0, 133.5, 131.6, 125.5, 124.1, 121.2, 117.0, 116.0, 114.7, 53.3, 22.5; IR (film) 3128, 3082, 2927, 2858, 1692, 1645, 1568, 1444, 1298, 1251 cm^{-1}; HRMS (ESI) m/z 313.0713 [M + H]$^+$ (calcd for $C_{17}H_{13}O_6$, 313.0712). X-ray quality crystals were obtained by suspending **27b** in 1:1 EtOAc/hexanes and adding a minimal amount of CH_2Cl_2 until fully dissolved, followed by slow evaporation. The crystallographic data for **27b** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number 914772. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(0)-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Anthraquinone Monomers 28a and 28b (Entry 2, Table 1). A solution of **24** (20 mg, 0.081 mmol) in benzene (1 mL) was cooled to 5 °C before addition of diene **20** (2 equiv). When complete, as determined by TLC, the reaction mixture was poured over silica (200 mg) and allowed to evaporate open to air. After 1 day, the silica was filtered with CH_2Cl_2−2.5% MeOH/CH_2Cl_2 and the residue chromatographed (30−50% EtOAc/hexanes) to afford the anthraquinone as a 13:87 mixture of regioisomers **28a** (*anti*-OH) and **28b** (*syn*-OH). Isomers containing *peri*-methyl ethers instead of hydroxyl groups were also isolated (62% combined anthraquinone yield): ^{1}H NMR (500 MHz, $CDCl_3$) **28a** (*anti*-OH) δ 12.58 (s, 1H), 8.65 (s, 1H), 7.79 (s, 1H), 7.63 (d, J = 1.2 Hz, 1H), 7.12 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 2.47 (s, 3H). **28b** (*syn*-OH) δ 12.38 (s, 1H), 8.63 (s, 1H), 7.80 (s, 1H), 7.65 (d, J = 1.4 Hz, 1H), 7.10 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) **28b** (*syn*-OH) δ 187.3, 181.1, 165.2, 163.1, 149.5, 148.5, 137.3, 133.3, 131.8, 126.4, 125.8, 124.0, 121.2, 114.4, 109.0, 57.0, 52.7, 22.5; HRMS (ESI) m/z 327.0865 [M + H$^+$] (calcd for $C_{18}H_{15}O_6$, 327.0869).

Bishaloquinones (31a−c). To a suspension of **16** (250 mg, 0.509 mmol) in glacial AcOH (2.5 mL) was added bromine (2 mL, 0.5 M in AcOH). After the mixture was stirred for 10 min, ice/water was added and the mixture extracted with EtOAc. The organic layer was washed with saturated aqueous sodium thiosulfate, followed by water and brine. After concentrating, the residue was reconstituted in AcOH (10 mL). Anhydrous NaOAc (417 mg, 5.09 mmol) was added and the mixture heated to reflux for 3 min. After the mixture was cooled to 0 °C, the solid was collected via vacuum filtration and washed well with water. The crude solid was chromatographed (CH_2Cl_2−5% EtOAc/CH_2Cl_2) to afford a yellow solid as an inseparable 37:50:13 mixture of **31a**, **31b**, and **31c** (287 mg, 87%): ^{1}H NMR (500 MHz, C_6D_6) **31a** (*out-out*-Br) δ 8.78 (s, 2H), 6.68 (s, 2H), 3.41 (s, 6H), 3.35 (s, 6H). **31b** (*out-in*-Br) δ 8.80 (s, 1H), 8.78 (s, 1H), 6.83 (s, 1H), 6.61 (s, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H); **31c** (*in-in*-Br) δ 8.81 (s, 2H), 6.79 (s, 2H), 3.39 (s, 6H), 3.35 (s, 6H); ^{13}C NMR (500 MHz, acetone-d_6) **31a** (*out-out*-Br) δ 183.1, 177.5, 165.8 (overlap with b and c), 162.8, 142.2, 140.0, 133.8, 133.2, 131.9, 129.1, 127.9, 63.1 (overlap with b and c), 53.3 (overlap with b and c); **31b** (*out-in*-Br) δ 183.2, 181.7, 178.6, 177.4, 165.8 (2 peaks, overlap with a and c), 162.7, 162.4, 142.2, 141.1, 140.9, 140.1, 134.6, 133.9, 133.2, 132.3, 131.9, 130.9, 129.6, 129.1, 128.8, 128.0, 63.1 (2 peaks, overlap with a and c), 53.3 (2 peaks, overlap with a and c); **31c** (*in-in*-Br) δ 181.7, 178.6, 165.8 (overlap with a and b), 162.4, 141.2, 140.8, 134.6, 132.3, 131.0, 129.5, 128.9, 63.1 (overlap with a and b), 53.3 (overlap with a and b); HRMS (ESI) m/z 646.9209 [M + H]$^+$ (calcd for $C_{26}H_{17}O_{10}Br_2$, 646.9188).

Dimethyl 2,2′-Dihydroxy-5,5′,12,12′-tetraoxo-5,5′,12,12′-tetrahydro-1,1′-bitetracene-3,3′-dicarboxylate (42). A solution of **31a−c** (20 mg, 0.031 mmol) and sultine **43**[56] (15 mg, 0.089 mmol) in toluene (0.5 mL) was heated to 85−90 °C. Additional **43** (30 mg, 0.178 mmol) was added after 16 h. After 25 h total, the reaction mixture was concentrated and reconstituted in toluene, and NEt_3 (200 μL) was added with the flask open to air. When the reaction was complete as judged by TLC, the mixture was diluted with CH_2Cl_2 and washed with 1 M HCl. The organic layer was passed through Na_2SO_4 and used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 2H), 8.90 (s, 2H), 8.54 (s, 2H), 8.11 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 8.1 Hz, 2H), 7.72−7.61 (m, 4H), 4.04 (s, 6H), 3.65 (s, 6H); HRMS (ESI) m/z 713.1420 [M + Na]$^+$ (calcd for $C_{42}H_{26}O_{10}Na$, 713.1424).

The crude anthraquinone was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C, followed by the dropwise addition of BCl_3 (1 M in hexanes, 90 μL). After 40 min the reaction was quenched with cold water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (30% EtOAc/hexanes) to yield **42** as a yellow solid (9.3 mg, 45%, two steps): mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (s, 2H), 9.18 (s, 2H), 8.88 (s, 2H), 8.56 (s, 2H), 8.09 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.68−7.65 (m, 2H), 7.63−7.59 (m, 2H), 4.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 181.8, 170.3, 163.4, 136.6, 135.4, 135.2, 131.2, 130.5, 130.2 (overlapped peaks), 130.1, 129.71, 129.68, 129.5, 129.4, 128.2, 127.5, 116.2, 53.3; IR (film) 2923, 2852, 1725, 1676, 1444, 1287, 1252 cm^{-1};

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HRMS (ESI) m/z 661.1119 [M − H$^-$] (calcd for $C_{40}H_{21}O_{10}$, 661.1135).

Dimethyl 2,2′-Dimethoxy-6,6′,7,7′-tetramethyl-9,9′,10,10′-tetraoxo-9,9′,10,10′-tetrahydro-1,1′-bianthracene-3,3′-dicarboxylate (44). To a suspension of **31a−c** (20 mg, 0.031 mmol) in toluene (0.5 mL) was added 2,3-dimethyl-1,3-butadiene (4 equiv). The reaction mixture was heated to 50 °C. Additional diene was added as needed in three portions (12 equiv total) over 44 h. After 44 h, the solution was cooled to 0 °C, and NEt_3 (>20 equiv) was added while exposed to air. When the reaction was complete, the mixture was concentrated and chromatographed (30% EtOAc/hexanes) to yield **44** as a yellow solid (14 mg, 71%): mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 2H), 8.05 (s, 2H), 7.71 (s, 2H), 3.99 (s, 6H), 3.57 (s, 6H), 2.40 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 182.2, 165.6, 161.8, 144.4, 144.2, 134.7, 134.5, 132.2, 131.4, 131.2, 130.1, 128.5, 128.4, 128.1, 62.7, 52.9, 20.31, 20.26; IR (film) 2950, 1733, 1673, 1602, 1585, 1281, 1251 cm^{-1}; HRMS (ESI) m/z 647.1932 [M + H]$^+$ (calcd for $C_{38}H_{31}O_{10}$, 647.1917).

Dimethyl 2,2′-Dihydroxy-6,6′,7,7′-tetramethyl-9,9′,10,10′-tetraoxo-9,9′,10,10′-tetrahydro-1,1′-bianthracene-3,3′-dicarboxylate (45). BCl_3 (1 M in hexanes, 3.2 equiv) was added dropwise to a solution of **44** (10 mg, 0.016 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After 15 min, the reaction was quenched with cold water, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed ($CHCl_3$) on a short column to afford **45** as a yellow solid (8.4 mg, 88%): mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.55 (s, 2H), 9.03 (s, 2H), 8.06 (s, 2H), 7.74 (s, 2H), 4.05 (s, 6H), 2.41 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.6, 182.0, 170.3, 163.3, 144.4, 143.9, 135.8, 132.3, 131.5, 130.7, 128.5, 128.1, 127.8, 126.6, 115.7, 53.2, 20.3, 20.2; IR (film) 3418, 1669, 1291 cm^{-1}; HRMS (ESI) m/z 619.1594 [M + H]$^+$ (calcd for $C_{36}H_{27}O_{10}$, 619.1604).

Dimethyl 2,2′-Dimethoxy-9,9′,10,10′-tetraoxo-9,9′,10,10′-tetrahydro-1,1′-bianthracene-3,3′-dicarboxylate (46). Compound **31a−c** (20.0 mg, 0.0309) was partially dissolved in toluene (0.5 mL). After the addition of 1-(trimethylsiloxy)-1,3-butadiene (22 μL, 0.123 mmol), the mixture was heated to 50 °C. Additional diene was added as necessary in three portions (12 equiv total) over 2 d. After 2 d, the reaction mixture was concentrated and reconstituted in CH_2Cl_2. Once the mixture was cooled to 0 °C, NEt_3 (10 equiv) was added while exposed to air. After 40 min, the mixture was washed with 1 M HCl and passed through Na_2SO_4. The residue was chromatographed (CH_2Cl_2−5% EtOAc/CH_2Cl_2) to afford **46** as a yellow solid (11.8 mg, 65%): mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 2H), 8.32 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 7.6 Hz, 2H), 7.77 (t, J = 7.5 Hz, 2H), 7.68 (t, J = 7.5 Hz, 2H), 4.00 (s, 6H), 3.59 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 182.0, 165.5, 161.9, 134.7, 134.4, 134.3 (overlapped peaks), 134.2, 133.2, 131.7, 129.9, 128.7, 127.6, 127.3, 62.7, 53.0; IR (film) 1729, 1676, 1267, 1240 cm^{-1}; HRMS (ESI) m/z 591.1292 [M + H]$^+$ (calcd for $C_{34}H_{23}O_{10}$, 591.1291).

Dimethyl 2,2′-Dihydroxy-9,9′,10,10′-tetraoxo-9,9′,10,10′-tetrahydro-1,1′-bianthracene-3,3′-dicarboxylate (47). A solution of **46** (9.1 mg, 0.016 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C, followed by the dropwise addition of BCl_3 (1 M in hexanes, 3.2 equiv). After 15 min, the reaction was quenched with cold water, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (CH_2Cl_2) to afford **47** as a yellow solid (6.9 mg, 80%): mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.59 (s, 2H), 9.08 (s, 2H), 8.33 (dd, J = 7.8 Hz, 0.9 Hz, 2H), 7.99 (dd, J = 7.5 Hz, 0.9 Hz, 2H), 7.76 (dt, J = 7.5 Hz, 1.3 Hz, 2H), 7.67 (dt, J = 7.5 Hz, 1.3 Hz 2H), 4.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 181.8, 170.2, 163.4, 135.7, 134.3 (overlapped peaks), 134.0, 133.5, 131.0, 127.8, 127.5, 127.3, 126.5, 116.0, 53.3; IR (film) 2918, 1663, 1283, 1252 cm^{-1}; HRMS (ESI) m/z 563.0979 [M + H]$^+$ (calcd for $C_{32}H_{19}O_{10}$, 563.0978).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for new products; crystallographic data for **27b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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