Formal Total Synthesis of (+)-Diepoxin σ

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The highly oxygenated antifungal anticancer natural product (±)-diepoxin σ was prepared in 10 steps and in 15% overall yield from *O*-methylnaphthazarin. Highlights of the synthetic work include an Ullmann coupling and a possibly biomimetic oxidative spirocyclization for the introduction of the naphthalene ketal as well as the use of a retro-Diels−Alder reaction to unmask the reactive enone moiety in the naphthoquinone bisepoxide ring system. A novel highly bulky chiral binaphthol ligand was developed for a boron-mediated Diels−Alder reaction that constitutes a formal asymmetric total synthesis of (+)-diepoxin σ.

Introduction

The first natural product with a naphthalenediol spiroketal moiety, the antibiotic MK 3018, was reported in the patent literature in 1989 by Ogishi and co-workers (Figure 1).[1] A second report of an epoxynaphthalenediol spiroketal, bipendensin, appeared in 1990.[2] Bipendensin had been isolated in very small amounts from wood samples of the African tree *Afzelia bipendensis*. A compound with the same constitution was also isolated in 1994 from an unidentified *Coniothyium* fungus collected from forest soil on West Borneo, and was named palmarumycin C_{11} by Krohn and co-workers.[3]

During the investigation of the chemistry associated with interspecies competition among coprophilous fungi, Gloer and co-workers discovered an unusual series of antifungal metabolites, the preussomerins A−F from *Preussia isomera* Cain.[4] Preussomerins were also isolated from the endophytic fungus *Harmonerna dematioides*,[5] as well as from other sources.[6]

A related series of highly oxygenated compounds, the diepoxins, were reported in 1993 by Schlingmann and co-workers from American Cyanamid (Figure 2).[7] Diepoxins were isolated from fermentation broths of a nonsporulating fungus, LL-07F275, collected from a tree trunk found in Panama. Their antimicrobial activities varied

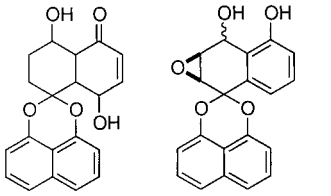

Figure 1. The first naphthalenediol spiroketal natural products.

greatly. Whereas the most oxidized compound, diepoxin σ, had antifungal activity in addition to antibacterial activity with MICs against a panel of selected bacteria in the range of 4−32 μg/mL, the least oxidized compound, diepoxin η, was virtually inactive. Diepoxins α and ζ, which have the same oxidation level, showed about the same antibacterial potency (2−4 times lower than diepoxin σ). The absolute stereochemistry of the diepoxins was determined by exciton-coupled CD in 1996.[8]

The antitumor properties of diepoxin σ were disclosed in 1994 by Chu and co-workers.[9] They isolated the natural product from the fermentation of a fungal culture, SCF-0642, *Nattrassia mangiferae*, collected in Guatemala and named it Sch 49209. Biological evaluation of Sch 49209 (diepoxin σ) and its triepoxide derivative Sch 50674 revealed potent in vitro inhibitory activity against the invasion of HT 1080 human fibrosarcoma cells through a matrigel membrane with IC_{50} values of 0.75 and 0.25 μM, respectively, in the invasion chamber assay. Furthermore, in vivo these compounds demonstrated a significant reduction in the size of primary tumors and the number of metastases. Diepoxins η and ζ were also reported independently as palmarumycins C_{14} and C_{13}, respectively, by Krohn and co-workers,[3] and as Sch 53516 and 53514, respectively, by Chu and co-workers.[10] The latter group isolated these natural prod-

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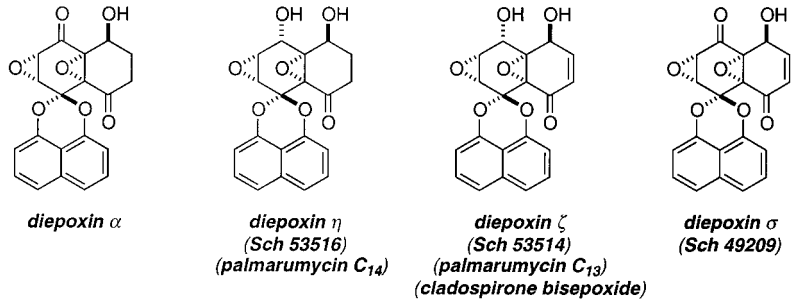

Figure 2. Diepoxins.

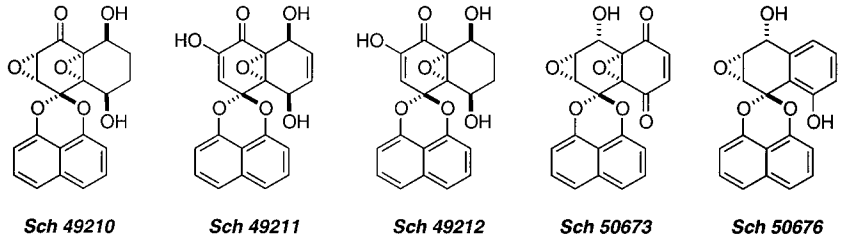

Figure 3. Novel fungal metabolites from *N. mangiferae.*

ucts from the fermentation broth of a culture identified as *N. mangiferae.* Sch 53516 and 53514 exhibited potent in vitro activity in a phospholipase D (PLD) assay, and anti-invasive activity against various tumor cells in the invasion chamber assay. Sch 53514 (diepoxin ζ), which showed an IC_{50} value of 0.2 μM in the PLD assay as well as an IC_{50} of 0.37 μM against HT 1080 human fibrosarcoma in the antitumor invasion assay, was more active than Sch 53516 (diepoxin η).

Diepoxin ζ was further reported as cladospirone bisepoxide by a Ciba-Geigy group in 1994 who isolated the natural product from cultures of a saprophytic fungus originally classified as a *Cladosporium chlorocephalum* strain (later reassigned to the *Sphaeropsidales* group, on the basis of the morphological characteristics).[11]

Other diepoxin-like compounds and related less oxygenated derivatives were isolated from fungal fermentation broths of *N. mangiferae* by Chu and co-workers (Figure 3).[12] Sch 49210, 49211, and 49212 demonstrated potent in vitro acitvity in a phospholipase D (PLD) assay, with IC_{50} values of 1.6, 11, and 12 μM, respectively. Sch 49210, 50673, and 50676 were tested in vitro for inhibitory activity in the tumor cell invasion assay. Their IC_{50} values were found to be 0.26, 6.2, and 2.8 μM, respectively. Chu and co-workers also reported Sch 53823 and 53825, which were isolated from the fermentation broth of an unidentified fungus collected from the dead leaves of *Ruerus virginiana* Miller growing in Tamalupas, Mexico (Figure 4).[13] These compounds also had phospholipase D inhibitory activity with IC_{50} values of 24 and 19 μM, respectively. The recently disclosed spiroxins also display close structural similarity to diepoxins and preussomerins.[14]

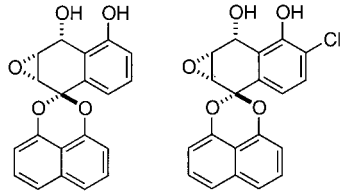

Figure 4. Fungal metabolites with phospholipase D inhibitory activity.

Results and Discussion

Both the palmarumycin and diepoxin families of natural products have attracted vivid synthetic activity.[15−23] After some initial model studies that explored the application of electrostatically controlled chiral auxiliaries to the diepoxin problem,[16] we decided that the construction of the naphthalenediol spiroketal moiety of diepoxin σ was the foremost synthetic challenge posed by this natural compound and that this spiroketal should be constructed before epoxide formation. On the basis of this concept, our synthetic approach targeted *p*-quinone naphthalenediol spiroketal **2**, which would be easily epoxidized by hydrogen peroxide anion to afford 8-dehydroxydiepoxin α(**1**) (Figure 5). Dehydrogenation of **1** and allylic oxidation would complete a route to diepoxin σ. The construction of the naphthalenediol spiroketal function

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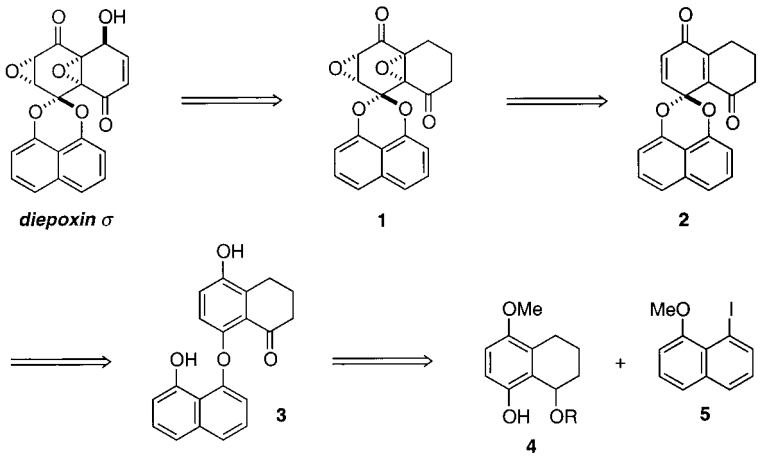
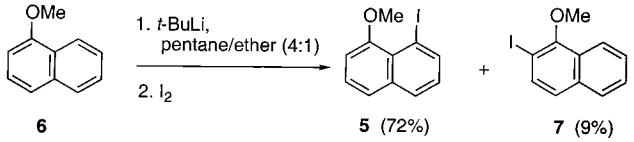


Figure 5. First-generation retrosynthetic approach toward diepoxin σ.

Scheme 1



of compound **2** was envisioned through a putative biomimetic oxidative spirocyclization[15] from naphthyl ether **3**, which would be derived by Ullmann ether coupling reaction of tetralinol derivative **4** with naphthalene **5**.

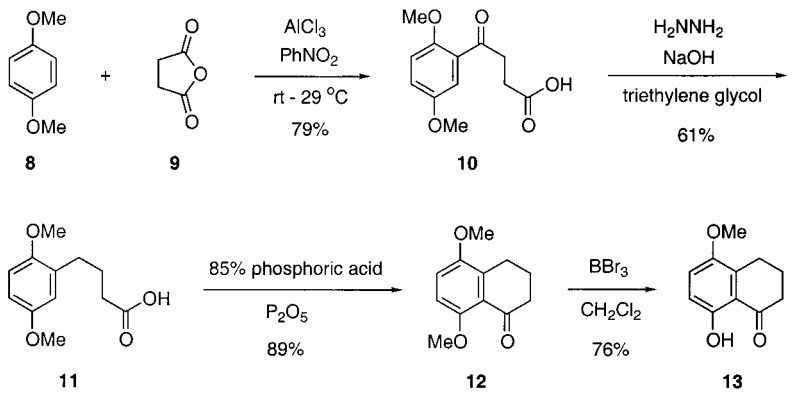
1-Iodo-8-methoxynaphthalene (**5**) was first prepared by Graybill and Shirley in 1966 in low yield and six steps from 8-amino-1-naphthalenesulfonic acid.[24] This group also investigated the C(8)-lithiation of 1-methoxynaphthalene (**6**) by *n*-butyllithium. The best yield of the C(8)-lithiated compound was obtained when *n*-butyllithium was prepared in situ from *n*-butyl bromide and lithium in ether. However, the C(2)-lithiated product was still the major product in a ratio of 65:35. We reinvestigated this reaction and found that treatment of compound **6** with *tert*-butyllithium in pentane/ether (4:1) led to predominant lithiation at C(8) over C(2) in a ratio of 89:11 (Scheme 1). Further increases of the pentane vs ether ratio led to gel formation and reaction failure, whereas reducing the amount of pentane in the reaction mixture resulted in a deterioration of the regioselectivity of the lithiation. 8-Iodo compound **5** could be separated by chromatography from 2-iodo isomer **7** but remained contaminated with remaining starting material **6**; however, **6** was inert to the ensuing Ullmann ether coupling reaction, and crude **5** could thus be used without further purification.

The second building block required for spiroketal formation, 8-hydroxy-5-methoxy-1-tetralone (**13**), was prepared according to a literature procedure (Scheme 2).[25] Friedel−Crafts acylation of *p*-dimethoxybenzene with succinic anhydride led to benzoylpropionic acid **10** in 79% yield. Wolff−Kishner reduction, followed by cyclization of the reduction product **11** in highly acidic media, and regioselective demethylation of **12** with boron tribromide provided **13** in 33% overall yield.

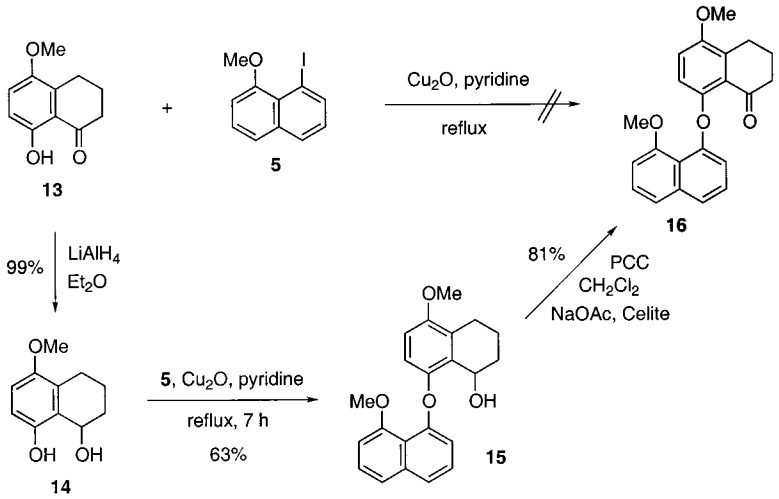
The first attempts for an Ullmann ether coupling[26] between tetralone **13** and 1-iodo-8-methoxynaphthalene failed, possibly due to the lack of nucleophilicity of the deactivated tetralone hydroxy group under the standard Ullmann reaction conditions (Scheme 3). However, diol **14**, which was obtained by reduction of tetralone **13** with $LiAlH_4$, was nicely coupled with 1-iodo-8-methoxynaphthalene under standard Ullmann reaction conditions to result in naphthyl ether **15** in 63% yield. Compound **15** was oxidized to **16** with PCC before demethylation, because the benzylic alcohol function present in **15** was labile under typical demethylation reaction conditions.

Several initial attempts to demethylate naphthyl ether **16** were also unsuccessful. Under acidic conditions (e.g., BBr_3, HBr, or $AlCl_3$/NaI), decomposition products were obtained, and under basic conditions (e.g., NaSEt/DMF, LiI/collidine, or NaCN/DMSO), **16** did not react or the aryl ether linkage adjacent to the carbonyl function was cleaved. However, after protection of the carbonyl group, ketal **17** was smoothly demethylated in almost quantita-

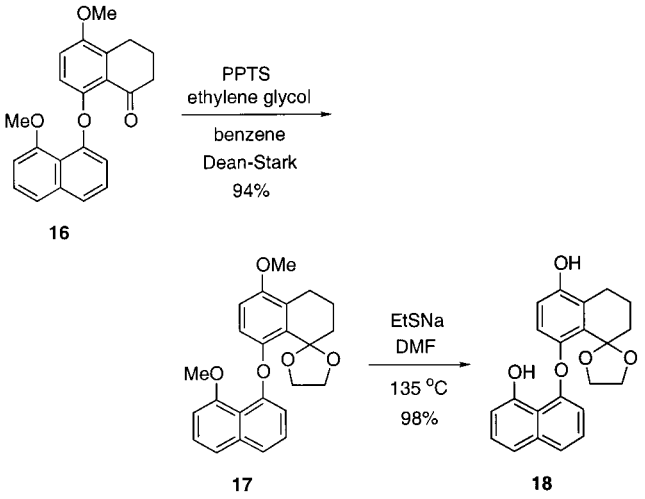
Scheme 2



Scheme 3



Scheme 4



tive yield by NaSEt in DMF (Scheme 4). The demethylated product **18** was hydrolyzed under aqueous acidic conditions to give the cyclization precursor **3** (Scheme 5). The solubility of **3** in trifluoroethanol was so low that the oxidative spirocyclization reaction[16,27,28] was attempted in acetonitrile. Whereas the oxidation of ketone **3** gave the naphthalenediol spiroketal **2** in less than 30% yield, the oxidation of ketal **18** provided the oxidative cyclized product **19** in 82% yield, and the desired naphthospiroketal **2** was obtained almost quantitatively after acidic hydrolysis.

Treatment of **19** with hydrogen peroxide provided exclusively the monoepoxide **20**, which was selectively hydrolyzed to afford **21** in 85% yield (Scheme 6). Further oxidation of **21** with hydrogen peroxide anion gave *anti*-diepoxide **23** as the major product. In contrast, epoxidation of diketone **2** gave the *syn*-diepoxide **1**, e.g., (±)-8-dehydroxydiepoxin α, as the major product. The assignment of the relative configurations of these diepoxides was confirmed by an X-ray analysis of *syn*-diepoxide **1** (Figure 6). The epoxidation of diketone **2** appears to occur first on the more electron-deficient internal double bond, thus leading to the formation of monoepoxide **22**, which was obtained as a mixture with diepoxides after partial reaction had taken place. The formation of terminal monoepoxide **21** was not detected in the epoxidation of diketone **2**. The reversal of *syn*/*anti* selectivity in the second epoxidation step of the terminal monoepoxide **21** vs the internal monoepoxide **22** can be rationalized by considering the stereoviews of minimum-energy conformations of **21** and **22** (Figure 7).[29] Attack of hydrogen peroxide at C(3) of epoxide **22** is likely to occur *syn* to the internal epoxide from the convex face of the spirocycle and *anti* to the pseudoaxial naphthalene ketal oxygen to give **1** as the major product. A more delicate steric bias

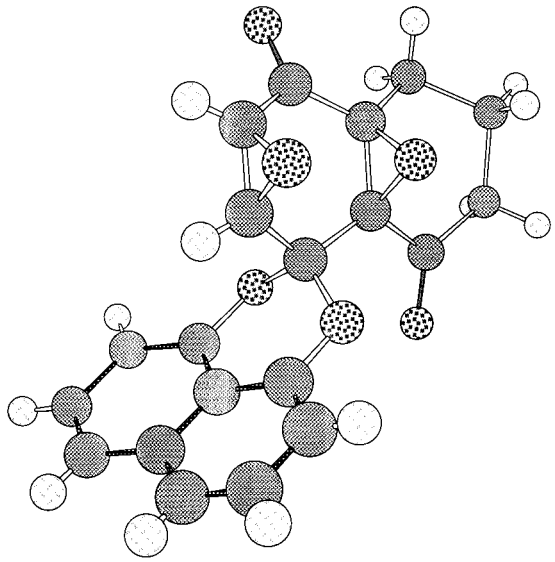


Figure 6. X-ray crystal structure of 8-dehydroxydiepoxin α (**1**).

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(26) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.
(27) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.
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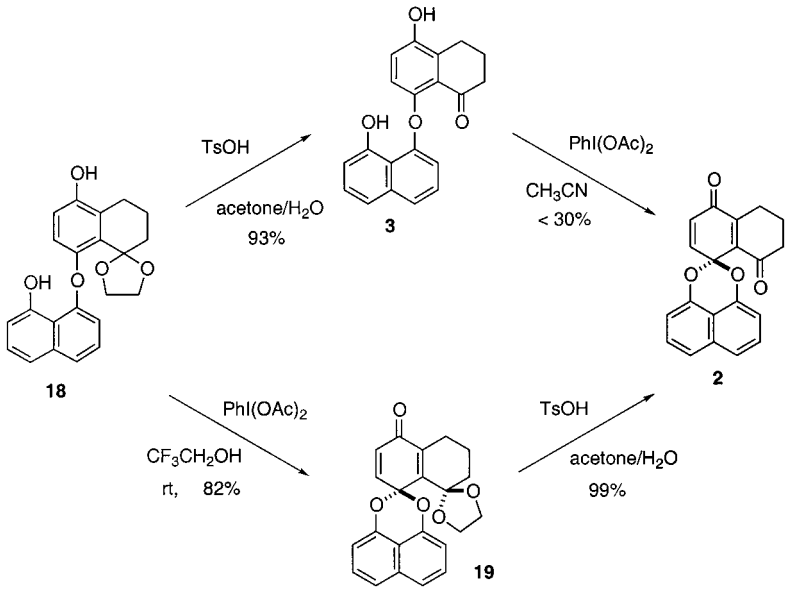
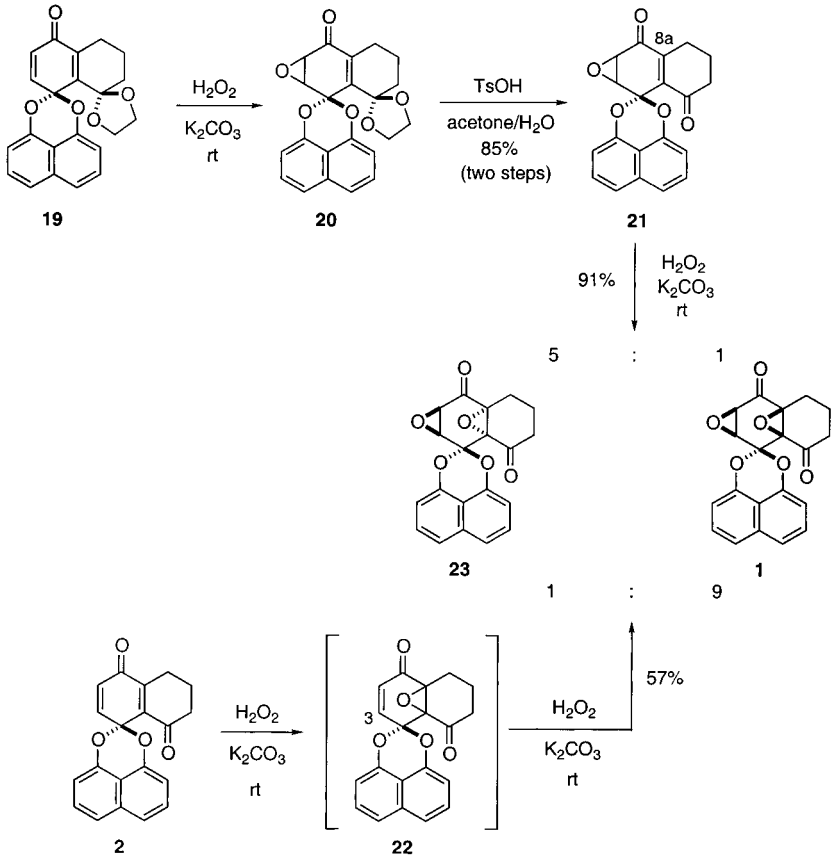
(29) Energy-minimized conformations shown in Figure 7 were obtained by Monte Carlo conformer searching with MacroModel (v. 5.5; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440). The lowest energy conformations were further optimized with Spartan (v. 5.1.1; Wavefunction, Inc., Irvine, CA) at the HF 6-31G* level.

Scheme 5



Scheme 6



presents itself in epoxide **21**, which, in principle, could undergo conjugate addition by hydrogen peroxide at either side of the enedione double bond. However, attack at C(4a) is sterically disfavored, and the less crowded C(8a) position is likely to represent the major site of addition. Due to the steric shielding of the C(7)-methylene group positioned *syn* to the C(2)−C(3)-epoxide in the ab initio minimized lowest-energy conformation of **21**, attack *anti* to both groups is more likely at C(8a) and provides diepoxide **23**. Therefore, we conclude that steric effects due to subtle differences in the conformation of monoepoxides **22** and **21** are mainly involved in directing the facial selectivity of further epoxidation reactions.

With (±)-8-dehydroxydiepoxin α (**1**) in hand, further transformation to (±)-diepoxin σ was investigated. However, various attempted dehydrogenations of **1** gave decomposed products or/and recovered starting material. When **1** was treated with phenylseleninic anhydride,[30] the formation of the desired enone was detected, but the

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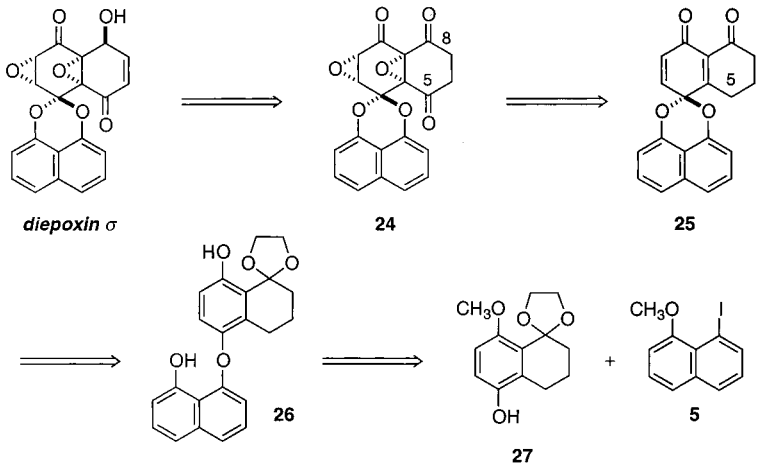
Scheme 7



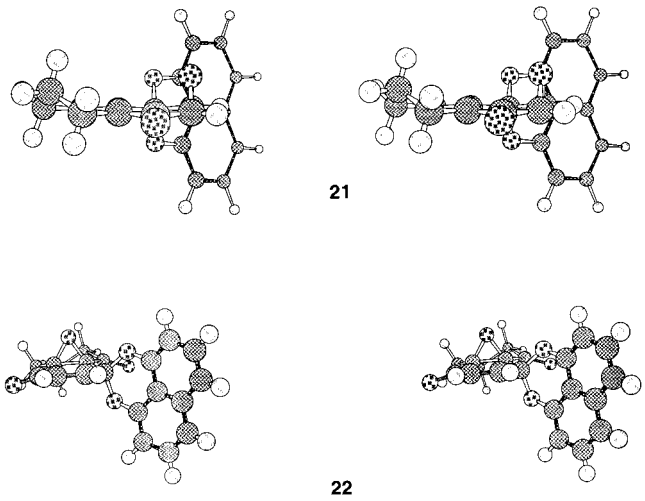


Figure 7. Stereoviews of energy-minimized structures of monoepoxides **21** and **22**.

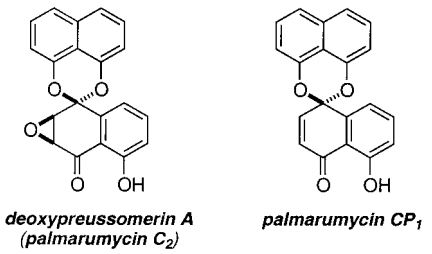


Figure 8. Palmarumycin CP_1 and deoxypreussomerin A.

yield was less than 5%. Accordingly, the retrosynthetic approach toward diepoxin σ was revised, and a new intermediate, naphthalenediol spiroketal diketone **25**, was introduced to facilitate hydroxylation at C(5) (Scheme 7). *syn*-Bisepoxidation and oxidation of a C(5)-alcohol would provide **24**, which was expected to allow an easy dehydrogenation to the enone. Further regioselective reduction of the ketone at C(8) with a bulky reducing agent would afford diepoxin σ. The key intermediate **25** would be derived from naphthyl ether **26** and the Ullmann ether coupling reaction developed earlier for 1-iodo-8-methoxynaphthalene (**5**) and the tetraline derivative **27**.

While this synthetic approach ultimately led to successful total syntheses of the less oxygenated palmarumycin CP_1 and deoxypreussomerin A (Figure 8),[19,31] it failed to provide us with an entry toward diepoxin σ since we were unable to effect the C(5)-oxygenation of **25** or related intermediates.[32] It became clear that a fundamentally different strategy was needed to address the diepoxin problem and that neither the introduction of the carbonyl groups nor the remaining double bond in the naphthoquinone ring could be postponed to the endgame of the synthesis. Our new retrosynthetic plan originated therefore from *O*-methylnaphthazarin (**31**; Scheme 8). Protection of the enone alkene moiety as the Diels−Alder adduct with cyclopentadiene during the entire course of the synthesis was necessary to prevent aromatization or epoxidation at this position. Ullman coupling methodology would provide the cyclization precursor **29**. A biomimetic oxidative cyclization would lead to naphthalenediol spiroketal **28**, in which the enone function of diepoxin σ is still masked. Oxidation of the secondary alcohol at C(5) after regioselective protection of the less hindered alcohol at C(8), followed by *syn*-diepoxidation, and deprotection of the enone alkene and allylic hydroxyl functions were expected to afford the target molecule.

O-Methylnaphthazarin (**31**) was prepared by a literature procedure[33] in 95% yield from C_2-symmetric naphthalenediol **32**, which in turn was prepared from 1,5-dimethoxynaphthalene by a reaction sequence involving bisformylation, Baeyer−Villiger oxidation, and hydrolysis (Scheme 9).[16] The Fe(III)-oxidation of **32** was completed in 10 min, and the reaction mixture had to be quenched immediately with NaOH solution. Any prolonged exposure of the product to the acidic reaction conditions decreased the yield due to demethylation, resulting in naphthazarin. Diels−Alder reaction of red *O*-methylnaphthazarin (**31**) with excess cyclopentadiene in methylene chloride afforded the yellow adduct **33** in quantitative yield. This Diels−Alder adduct was air sensitive and stored under nitrogen at −20 °C.

Compound **33** was reduced to diol **30** before the Ullmann ether coupling reaction because the deactivation of the nucleophilic phenol by the ketone functions retarded the coupling reaction. Whereas the reduction of **33** with $LiAlH_4$ or DIBAL-H gave the desired product **30** in less than 50% yield, the reduction with $NaBH_4$

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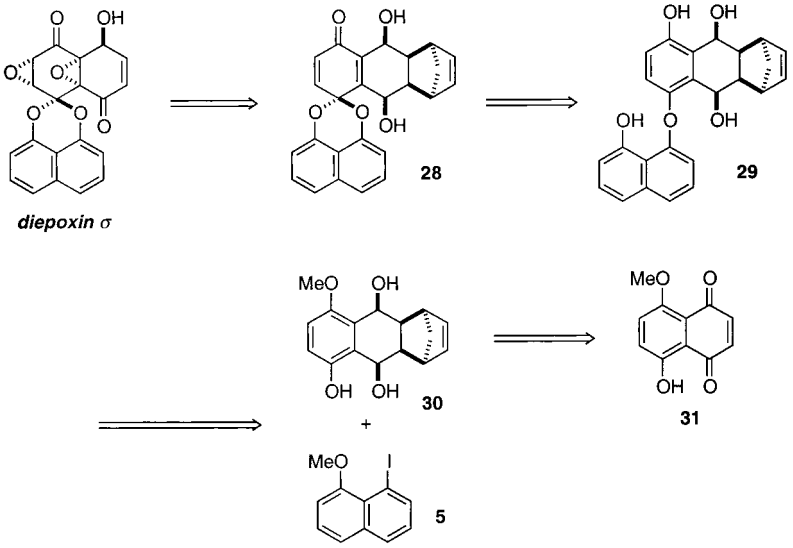
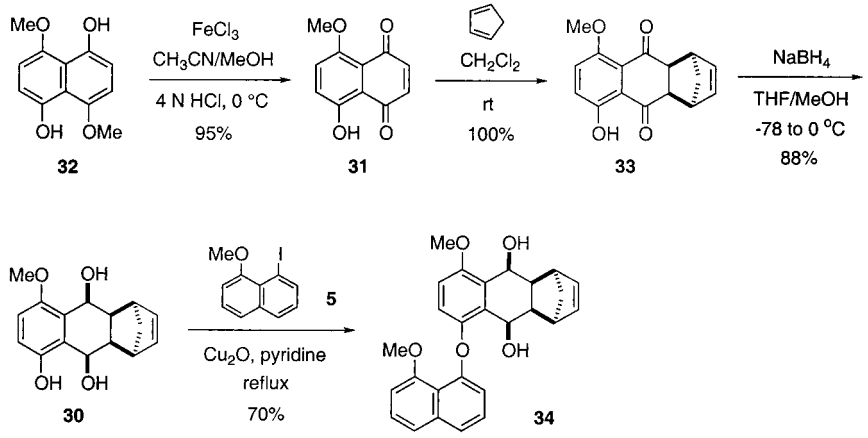
Scheme 8



Scheme 9



increased the yield to 88%. The reduced phenol **30** was readily coupled with 1-iodo-8-methoxynaphthalene (**5**) under standard Ullmann ether coupling conditions to provide naphthyl ether **34** in 70% yield.

Demethylation of **34** proved to be very difficult, because the benzylic alcohols were labile under both acidic and basic conditions. After considerable experimentation with various aryl methyl ether cleavage protocols,[34] we found that lithium diphenylphosphide[35] effected clean chemoselective demethylation. Treatment of **34** with an excess of lithium diphenylphosphide in THF at room temperature for 24 h led to a monodemethylated product which, however, could not be oxidatively cyclized to **28**. In contrast, when **34** was treated with an excess of lithium diphenylphosphide in THF for 7 d at room temperature, bisdemethylated compound **29** was obtained in 95% yield. Oxidative cyclization of **29** in trifluoroethanol with PhI(OAc)$_2$ gave **28** in unexpectedly low yield (25%). A mixed naphthoxy trifluoroethoxy ketal was formed as the major product.[36] Transketalization of this mixed ketal to **28** was unsuccessful. The oxidative cyclization of **29** in methylene chloride with acetonitrile as a cosolvent led mainly to decomposition and gave **28** in only 30% yield. However, when **29** was treated with PhI(OAc)$_2$ in hexafluoro-2-propanol, the yield increased to 61% (Scheme 10).

Regioselective protection of the less hindered C(8)-hydroxy group in **28** with TBDMS−Cl at room temperature gave the desired product **35** and a regioisomer in a 7:2 ratio. However, analogous protection with TBDMS−OTf at −78 °C gave exclusively **35** in 91% yield (Scheme 11). Whereas the oxidation of the remaining hydroxyl group in **35** with MnO_2 or under Swern conditions failed, PDC oxidation of **35** gave diketone **36** in 72% yield. Epoxidation of dienone **36** with hydrogen peroxide under basic conditions at room temperature provided the desired *syn*-diepoxide **37** contaminated with a small amount of a stereoisomer. At 0 °C, however, only a single *syn*-diepoxide, **37**, was obtained in 88% yield.

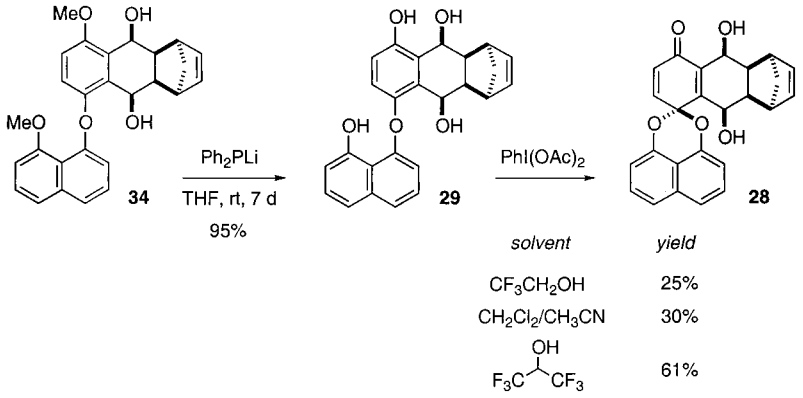
With the protected diepoxin σ in hand, we turned our attention to the unmasking of the enone alkene bond through a retro-Diels−Alder reaction.[37] At first, to avoid decomposition of the epoxy ketone functionality, the retro-Diels−Alder reaction was attempted in relatively

(34) Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 2nd ed.; Wiley: New York, 1991.

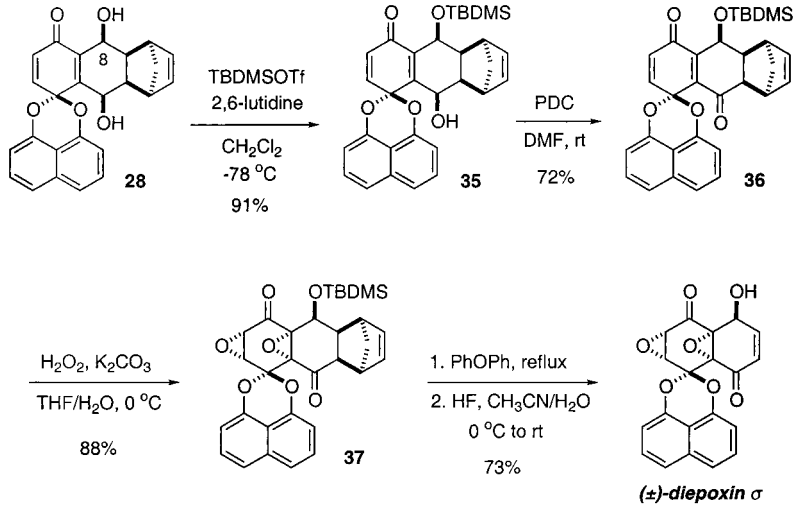
(35) (a) Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4120. (b) Ireland, R. E.; Walba, D. M. *Org. Synth.* **1977**, *56*, 44.

(36) ^{1}H NMR of the mixed ketal: ($CDCl_3$) δ 9.55 (s, 1 H, OH), 7.57−7.41 (m, 4 H), 7.10 (dd, 1 H, J = 7.6, 0.9 Hz), 6.91 (d, 1 H, J = 7.9 Hz), 6.88 (d, 1 H, J = 10.5 Hz), 6.71 (d, 1 H, J = 10.7 Hz), 6.60 (dd, 1 H, J = 10.2, 8.2 Hz), 6.17 (d, 1 H, J = 10.3 Hz), 5.92−5.87 (m, 1 H), 5.50−5.46 (m, 1 H), 4.21−4.07 (m, 2 H), 2.88 (q, 1 H, J = 4.2 Hz), 2.80−2.67 (m, 1 H), 2.47−2.35 (m, 1 H). These data indicate the presence of a trifluoroethoxy group and a phenol moiety, but the structure was not fully assigned.

Scheme 10



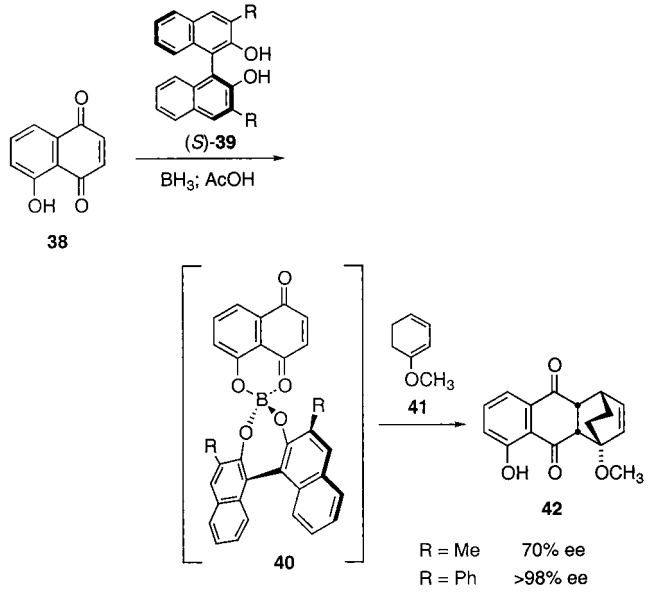
Scheme 11



low boiling solvents.[38] The reactions in refluxing toluene or xylene failed even in a sealed tube. However, the retro-Diels–Alder reaction proceeded successfully at reflux in phenyl ether (250–260 °C)[39] without significant decomposition of the TBDMS-protected natural product. Removal of the TBDMS group with HF/acetonitrile and water afforded (±)-diepoxin *σ* that was spectroscopically identical to the fermented compound. Synthetic material was thus obtained in 15% overall yield in 10 steps from *O*-methylnaphthazarin (**31**).

For the asymmetric total synthesis of (+)-diepoxin *σ*, the enantioselective construction of **33** was required. Accordingly, the asymmetric Diels–Alder reaction of **31** with cyclopentadiene was investigated. A significant level of asymmetric induction was expected from chelation of a chiral reagent to the phenol moiety of *O*-methylnaphthazarin (**31**), since both Kelly[40] and Yamamoto[41] utilized

Scheme 12



boron Lewis acids successfully in their asymmetric Diels–Alder reactions of juglone. In particular, Kelly and co-workers used a chiral boron Lewis acid with the binaphthyl ligand (*S*)-**39** for promoting an asymmetric Diels–Alder reaction of juglone **38** to diene **41**, resulting in anthraquinone derivative **42** (Scheme 12).[40] The substituent on the diene plays an important role in the high chiral induction by interacting with the substituents on

(37) (a) Rickborn, B. *Org. React.* **1998**, *52*, 1. (b) Rickborn, B. *Org. React.* **1998**, *53*, 223. (c) Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S.; Sakai, R. *Tetrahedron* **1979**, *35*, 2861. (d) Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499. (e) Weinmann, H.; Winterfeldt, E. *Synthesis* **1996**, 357. (f) Stork, G.; La Clair, J. J.; Spargo, P.; Nargund, R. P.; Totah, N. *J. Am. Chem. Soc.* **1996**, *118*, 5304. (g) Bunnage, M. E.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1110. (h) Bunnage, M. E.; Nicolaou, K. C. *Eur. J. Chem.* **1997**, *3*, 187.

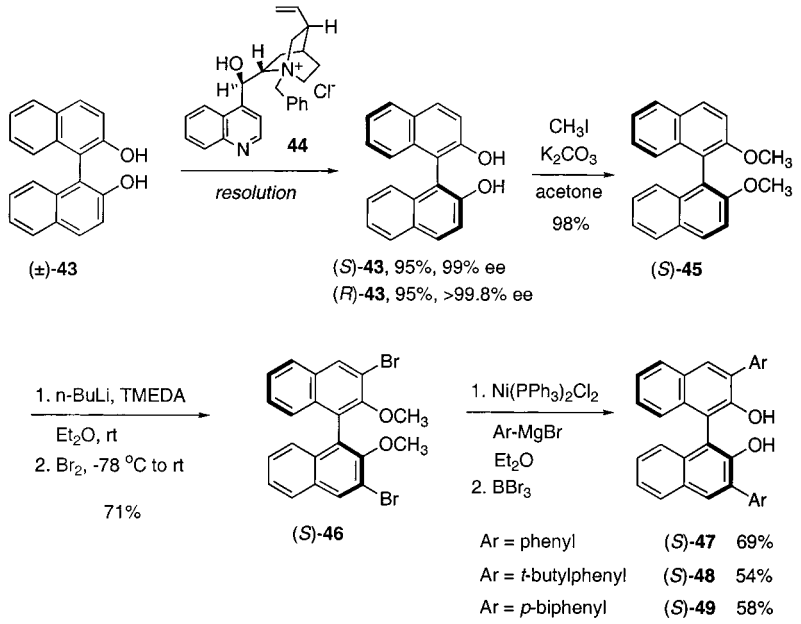
(38) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 4741.

(39) Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679.

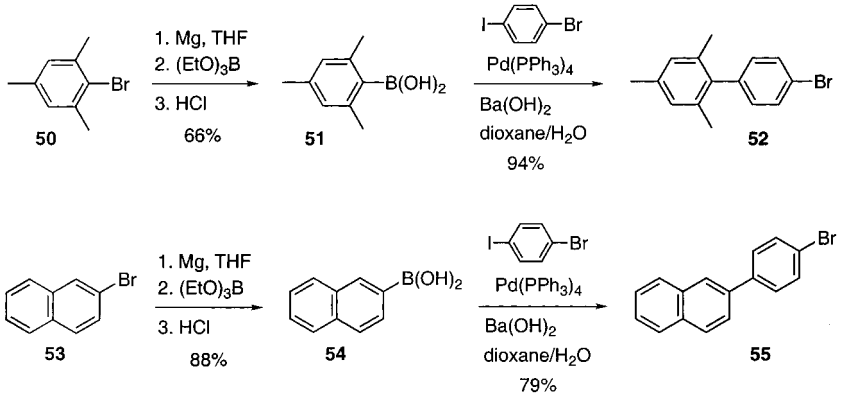
(40) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510.

(41) Maruoka, K.; Sakurai, M.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4895.

Scheme 13



Scheme 14



the binaphthyl ligand. However, cyclopentadiene used in our Diels−Alder reaction with *O*-methylnaphthazarin (**31**) is smaller and symmetrical. To compensate for this lack of a differentiating end group, we hypothesized that chiral binaphthol auxiliaries with very bulky substituents at the *ortho* positions would be required, and several highly substituted analogues of **39** were prepared.

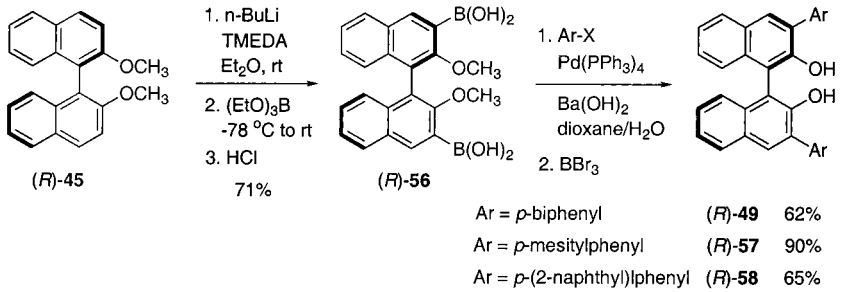
The chiral binaphthol ligands were initially prepared by Cram's method.[42] (*S*)-1,1′-Bi-2-naphthol ((*S*)-**43**) was obtained by resolution using *N*-benzylcinchonidinium chloride (**44**), as recently reported by a Merck group (Scheme 13).[43] Methylation of (*S*)-**43** with methyl iodide gave dimethoxybinaphthyl (*S*)-**45** in 98% yield. (*S*)-**45** was treated with *n*-BuLi and *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) in ether at room temperature to generate the dilithiated compound, which reacted with bromine at −78 °C to afford the dibromide (*S*)-**46** in 71% yield. (*S*)-**46** was coupled with phenylmagnesium bromide in the presence of commercially available dichlorobis(triphenylphosphine)nickel(II)[44] as a catalyst, and the coupling product was demethylated to give phenyl-substituted binaphthol (*S*)-**47** in 69% yield from (*S*)-**46**. The *p*-*tert*-butylphenyl-substituted binaphthol (*S*)-**48** and the *p*-biphenyl-substituted binaphthol (*S*)-**49** were prepared analogously in 54% and 58% yield by the Grignard cross-coupling reaction of dibromide (*S*)-**46** with *p*-*tert*-butylphenylmagnesium bromide and *p*-biphenylmagnesium bromide, respectively, followed by demethylation using BBr_3.

Even larger substituents at the 3- and 3′-positions of binaphthol **39** were prepared from the sterically demanding aromatic bromides **52**[45] and **55**[46] (Scheme 14). *p*-Mesitylphenyl bromide (**52**) was prepared in 94% yield by Suzuki coupling reaction[47] of 1-bromo-4-iodobenzene with mesitylboronic acid (**51**), which was prepared in 66% yield from mesityl bromide (**50**). *p*-(2-Naphthyl)phenyl bromide (**55**) was also obtained analogously from 2-bromonaphthalene (**53**).

The optical rotation ($[\alpha]_D$ +55.1 (*c* 1.0, $CHCl_3$)) for (*S*)-**49** prepared by Cram's method proved to be quite

(42) Lingenfalter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393.
(43) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.
(44) (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1958. (b) Cotton, F. A.; Faut, O. D.; Goodgame, M. L. *J. Am. Chem. Soc.* **1961**, *83*, 344.
(45) Hafelinger, G.; Hack, F.; Westermayer, G. *Chem. Ber.* **1978**, *111*, 1323.
(46) Holloway, H. E.; Nauman, R. V.; Wharton, J. H. *J. Phys. Chem.* **1968**, *72*, 4468.
(47) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

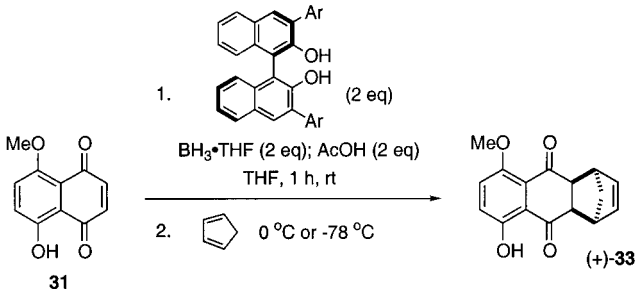
Scheme 15

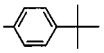
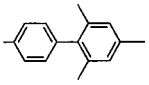
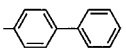
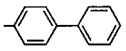
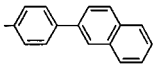
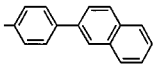


different from the literature value ($[\alpha]_D$ −70.3 (*c* 1.0, $CHCl_3$)) for (*R*)-**49** prepared by a Suzuki coupling method recently reported by Jørgensen and co-workers.[48] Thus, for comparison, (*R*)-**49** was also prepared by Suzuki coupling (Scheme 15). The diboronic acid (*R*)-**56** was obtained by treatment of (*R*)-**45** with *n*-BuLi and TMEDA in ether at room temperature to generate the dilithiated compound, which reacted with triethyl borate at −78 °C. During acidic workup, the borate was hydrolyzed to give (*R*)-**56** in 71% yield. The boronic acid (*R*)-**56** was coupled with *p*-iodobiphenyl bromide under standard Suzuki coupling conditions, and the product was demethylated using BBr_3 to afford (*R*)-**49**, in 62% yield with an optical rotation $[\alpha]_D$ −54.8 (*c* 1.01, $CHCl_3$) that was very similar to the value listed above for (*S*)-**49** prepared by Cram's method. Accordingly, the literature $[\alpha]_D$ value[48] for (*R*)-**49** should be corrected. *p*-Mesitylphenyl-substituted binaphthol (*R*)-**57** and *p*-(2-naphthyl)phenyl-substituted binaphthol (*R*)-**58** were also prepared by Suzuki coupling from the corresponding bromides **52** and **55** in 90% and 65% yield, respectively (Scheme 15).

For the asymmetric Diels−Alder reaction of *O*-methylnaphthazarin with cyclopentadiene, the chiral boron Lewis acid was prepared in situ by addition of 1 equiv of acetic acid to a 1:1 mixture of borane and binaphthol chiral auxiliary in THF (Scheme 16).[40] The complexation of red *O*-methylnaphthazarin with the chiral borane at room temperature promptly changed the color of the solution to a deep violet. Initially the complexation was performed at room temperature for 5 min, then the resulting mixture was cooled to −78 °C, and cyclopentadiene was added. The Diels−Alder reaction did not go to completion at −78 °C; however, when the reaction mixture was warmed to 0 °C, almost complete conversion of *O*-methylnaphthazarin to the yellow adduct **33** occurred. Later, it was found that the incomplete turnover of the Diels−Alder reaction at −78 °C was due to an incomplete complexation of the chiral boron Lewis acid with *O*-methylnaphthazarin. When the complex formation was performed for 1 h at room temperature, *O*-methylnaphthazarin was quantitatively converted to the adduct **33** at −78 °C in 1−2 h. The chiral induction at −78 °C was higher than at 0 °C. As expected, the bulkier the substituents on the chiral ligands, the higher the enantioselectivity of the cycloaddition process. When *p*-(2-naphthyl)phenyl-substituted chiral ligand **58** was used, the reaction provided product in 72% yield and up to 94% ee. The enantiomeric excess was determined by chiral HPLC using a Chiralcel OD column.[49] With the exception of ligand **57**, (*R*)-ligands provided the (+)-adduct and (*S*)-ligands led to the (−)-adduct as the major enantiomer. However, the *o*-methyl substitution in ligand **57** seems to steer the reaction toward an alternative transition state, as indicated by a switch in enantioselectivity. The preparation of Diels−Alder adduct (+)-**33** in a maximum of 94% ee constitutes a formal asymmetric total synthesis of natural (+)-diepoxin *σ*.

Scheme 16



chiral ligand	*Ar*	*ee* 0 °C	*ee* -78 °C	*sign of* $[\alpha]_D$ *for* ***33***
(*S*)-**47**		<30%	–	(-)
(*S*)-**48**		37%	42%	(-)
(*R*)-**57**		52%	54%	(-)
(*S*)-**49**		70%	–	(-)
(*R*)-**49**		–	88%	(+)
(*R*)-**58**		–	93%	(+)
(*S*)-**58**		–	94%	(-)

Conclusions

Diepoxin *σ* is one of the most highly oxygenated compounds among the naphthalenediol spiroketal fungal metabolites and has very promising antitumor as well as potent antimicrobial activity. After considerable optimization of the strategic timing of oxygen and double bond introductions into suitable intermediates, we were able to realize a potentially biomimetic synthetic plan using Ullmann ether coupling and oxidative spirocyclization that afforded the first total synthesis of diepoxin *σ*

(48) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536.

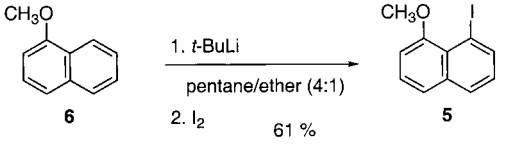
(49) The absolute configuration of **(+)-33** was assigned in accordance with ref 40.

in 10 steps and in 15% overall yield from *O*-methylnaphthazarin. Asymmetric Diels−Alder reaction of *O*-methylnaphthazarin with cyclopentadiene promoted by a chiral boron complex derived from the novel extremely bulky chiral ligand *p*-(2-naphthyl)phenyl-substituted binaphthol **58** afforded the key intermediate **33** in 94% ee. The enantioselective preparation of this chiral Diels−Alder adduct constitutes a formal asymmetric total synthesis of natural (+)-diepoxin σ. The cycloadduct with cyclopentadiene serves thus not only as a protective group for a sensitive moiety of the natural product but also as a reversible stereochemical anchor. The synthetic strategy developed in this work has been applied to the syntheses of other palmarumycin-, diepoxin-, and preussomerin-type natural compounds and their derivatives for structure−activity studies.[19,31]

Experimental Section

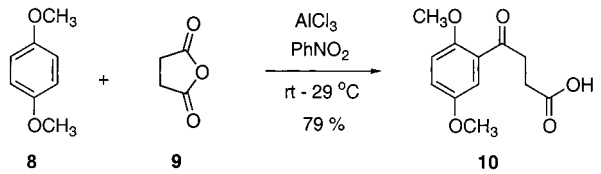
General Procedures. THF and Et_2O were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH_2Cl_2 was obtained by distillation from CaH_2. Dry DMF was obtained by distillation from alumina under reduced pressure. Dry CF_3CH_2OH was obtained by distillation from $CaSO_4$. Unless otherwise stated, solvents or reagents were used without further purification. NMR spectra were recorded at 300 MHz/75 MHz ($^1H/^{13}C$) in $CDCl_3$ unless stated otherwise.

1-Iodo-8-methoxynaphthalene (5).[24] To a solution of **6** (6.33 g, 40.0 mmol) in ether (17 mL) was added 1.7 M *t*-BuLi in pentane (70.6 mL, 120 mmol) in an ice bath to avoid evaporation of pentane. The mixture was mechanically stirred



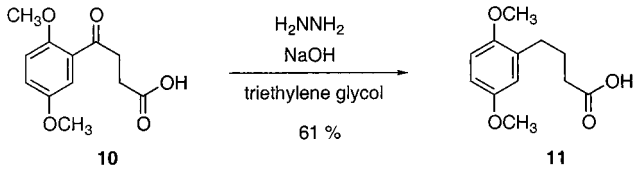
at 0 °C for 2 h and then at room temperature for 21 h. To the resulting orange suspension was added at 0 °C iodine (5.08 g, 20 mmol) in portions to avoid evaporation of pentane. The resulting solution was stirred for 4 h at room temperature, quenched with water (2 mL) in an ice bath, poured into water, and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes) gave 6.9 g (61%) of **5** as a solid with **6** (10%) as an impurity. Data for **5**: ^1H NMR δ 8.18 (dd, 1 H, J = 7.3, 1.1 Hz), 7.75 (dd, 1 H, J = 8.0, 1.1 Hz), 7.41 (t, 2 H, J = 3.0 Hz), 7.04 (t, 1 H, J = 7.8 Hz), 6.92 (q, 1 H, J = 2.9 Hz), 3.95 (s, 3 H).

4-(2′,5′-Dimethoxyphenyl)-4-oxobutyric Acid (10).[25a] To a solution of $AlCl_3$ (80.0 g, 0.60 mol) in nitrophenol (500 mL) were added at 0 °C succinic anhydride (30.02 g, 0.30 mol) and *p*-dimethoxybenzene (37.31 g, 0.27 mol). The mixture was



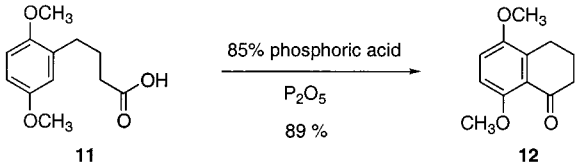
allowed to warm from 5 to 29 °C over a 3.5 h period, and the solution was then promptly poured into ice−water. The organic layer was separated and extracted with 10% $NaHCO_3$ solution. The combined aqueous layers were fitered and acidified to pH 1 by concd HCl solution in an ice bath. The resulting very pale yellow solid was filtered and dried to afford 51 g (79%) of **10**: ^1H NMR δ 7.34 (d, 1 H, J = 3.3 Hz), 7.05 (dd, 1 H, J = 9.0, 3.3 Hz), 6.92 (d, 1 H, J = 9.0 Hz), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.34 (t, 2 H, J = 6.5 Hz), 2.75 (t, 2 H, J = 6.5 Hz).

4-(2′,5′-Dimethoxyphenyl)butyric Acid (11).[25a] A solution of **10** (50.0 g, 0.21 mol) in triethylene glycol (620 mL) containing sodium hydroxide (31.6 g, 0.79 mol), hydrazine hydrate (26.5 g, 0.53 mol), and water (30 mL) was heated at reflux for 3 h and then heated further without a condenser until the temperature rose to 210 °C. After another hour,



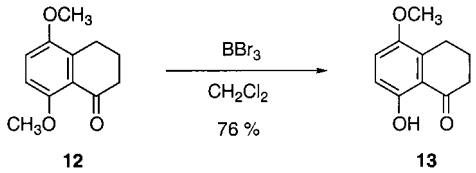
sufficient water was added to lower the temperature to 190 °C, and heating was continued for 4 h. The solution was then cooled, poured into a mixture of concd HCl and ice, and extracted with ether. The combined ether layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1 → 1:1) gave 28.7 g (61%) of **11** as a solid: ^1H NMR δ 6.77 (d, 1 H, J = 9.0 Hz), 6.72 (s, 1 H), 6.70 (d, 1 H, J = 9.0 Hz), 3.77 (s, 3 H), 3.76 (s, 3 H), 2.65 (t, 2 H, J = 7.4 Hz), 2.37 (t, 2 H, J = 7.5 Hz), 1.93 (p, 2 H, J = 7.5 Hz).

5,8-Dimethoxy-3,4-dihydro-2*H*-naphthalen-1-one (12).[25a] To polyphosphoric acid prepared from 85% phosphoric acid (305 g) and P_2O_5 (278 g) was added **11** (14.0 g, 62.4 mmol).



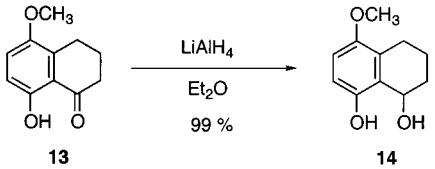
After the reaction mixture was stirred for 0.5 h at 80 °C, the resulting orange solution was poured into ice−water and extracted with ether. The combined ether layers were washed with 1 N NaOH solution, dried (Na_2SO_4), and concentrated in vacuo to afford 11.5 g (89%) of **12** as a pale yellow solid: ^1H NMR δ 6.98 (d, 1 H, J = 9.1 Hz), 6.79 (d, 1 H, J = 9.1 Hz), 3.86 (s, 3 H), 3.81 (s, 3 H), 2.87 (t, 2 H, J = 6.2 Hz), 2.61 (t, 2 H, J = 6.5 Hz), 2.05 (p, 2 H, J = 6.5 Hz).

8-Hydroxy-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (13).[25b] To a solution of **12** (4.12 g, 20 mmol) in CH_2Cl_2 (150 mL) was added 1.0 M BBr_3 in CH_2Cl_2 (10.5 mL, 10.5 mmol) at −78 °C. After 2 h, the reaction mixture was warmed



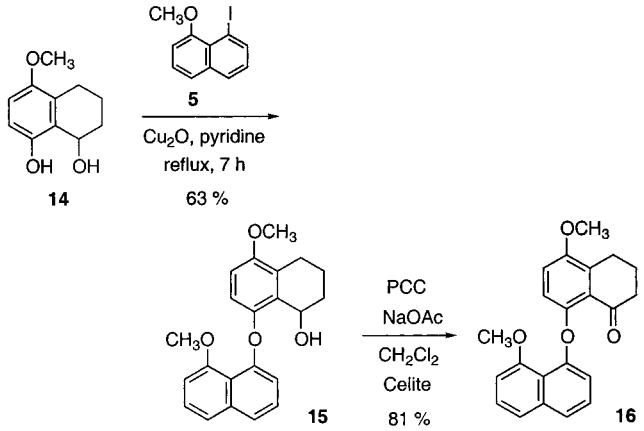
to room temperature, stirred for an additional hour at room temperature, and quenched with water (50 mL) in an ice bath. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 2.9 g (76%) of **13** as a yellow crystalline solid: ^1H NMR δ 11.92 (s, 1 H, OH), 7.07 (d, 1 H, J = 9.0 Hz), 6.78 (d, 1 H, J = 9.0 Hz), 3.80 (s, 3 H), 2.89 (t, 2 H, J = 6.3 Hz), 2.67 (t, 2 H, J = 6.3 Hz), 2.08 (p, 2 H, J = 6.3 Hz).

5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,8-diol (14). To a solution of **13** (1.95 g, 10.1 mmol) in ether (60 mL) was added $LiAlH_4$ (0.76 g, 20 mmol) at 0 °C. The reaction mixture



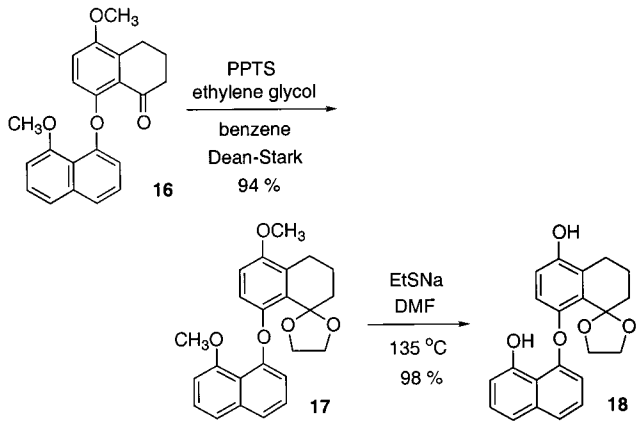
was warmed to room temperature and stirred for 1 h. After being quenched with water (1 mL) in an ice bath, the reaction mixture was diluted with ether and 10% sodium bisulfate solution. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 1.95 g (99%) of **14** as an oil: IR (neat) 3318, 1611 cm^{-1}; ^1H NMR δ 7.27 (s, 1 H, OH), 6.70 (s, 2 H), 5.04 (q, 1 H, J = 6.6 Hz), 3.77 (s, 3 H), 2.70−2.55 (m, 2 H), 2.22−2.10 (m, 1 H), 2.17 (d, 1 H, J = 7.7 Hz, OH), 1.95−1.58 (m, 3 H); ^{13}C NMR δ 150.6, 149.9, 127.3, 125.1, 113.1, 110.4, 67.7, 55.9, 32.5, 23.5, 19.5; MS (EI) m/z (rel intens) 194 (M^+, 5), 176 (100); HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0936.

5-Methoxy-8-(8′-methoxynaphthalen-1′-yloxy)-3,4-dihydro-2*H*-naphthalen-1-one (16). To a solution of **14** (1.95 g, 0.01 mol) and **5** (4.26 g, 0.015 mol) in degassed pyridine (100 mL) was added Cu_2O (2.15 g, 0.015 mol). The reaction



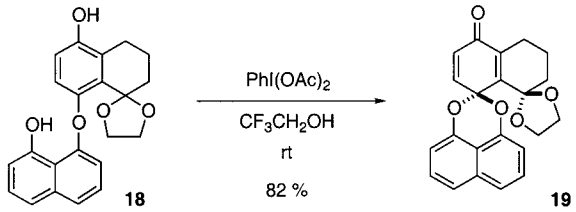
mixture was heated at reflux for 7 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in a mixture of water and ether. The water layer was extracted with additional ether. The combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 5:1) gave 2.21 g (63%) of **15** as an oil. A solution of **15** (2.1 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was added to a solution of PCC (2.6 g, 12 mmol) in CH_2Cl_2 (70 mL) containing sodium acetate (164 mg, 2.0 mmol) and Celite (9.0 g) in a water bath at room temperature. After the resulting solution was stirred for 4 h, additional PCC (1.3 g, 6 mmol) was added, the mixture was stirred overnight and allowed to stand for 1 h, and then the supernatant was decanted. The residue was washed with ether until no product was detected by TLC. The combined supernatant and washings were concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 1.7 g (81%) of **16** as an oil: IR (neat) 3055, 1687, 1578 cm^{-1}; ^1H NMR δ 7.60 (d, 1 H, J = 8.2 Hz), 7.44 (d, 1 H, J = 8.2 Hz), 7.37 (t, 1 H, J = 7.8 Hz), 7.36 (t, 1 H, J = 7.8 Hz), 6.97 (d, 1 H, J = 7.4 Hz), 6.81 (d, 1 H, J = 9.0 Hz), 6.77 (d, 1 H, J = 7.7 Hz), 6.41 (d, 1 H, J = 8.9 Hz), 3.78 (s, 3 H), 3.68 (s, 3 H), 2.95 (t, 2 H, J = 6.2 Hz), 2.68 (t, 2 H, J = 6.2 Hz), 2.14 (q, 2 H, J = 6.5 Hz); ^{13}C NMR δ 196.8, 156.3, 153.2, 152.5, 150.9, 137.5, 134.6, 126.4, 126.3, 124.2, 123.6, 120.7, 119.7, 117.4, 115.4, 115.3, 106.6, 56.4, 55.9, 40.8, 23.7, 22.5; MS (EI) m/z (rel intens) 348 (M^+, 100), 331 (24), 189 (70); HRMS (EI) calcd for $C_{22}H_{20}O_4$ 348.1362, found 348.1364.

5-Hydroxy-8-(8′-hydroxynaphthalen-1′-yloxy)-1,2,3,4-tetrahydronaphthalene-1-spiro-2″-dioxolane (18). To a solution of **16** (1.7 g, 4.88 mmol) and ethylene glycol (12 mL) in benzene (150 mL) was added PPTS (70 mg). This reaction mixture was heated at reflux for 24 h in a flask equipped with a Dean−Stark apparatus and then cooled to room temperature, washed with 5% $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave 1.80 g (94%) of **17** as a colorless solid. To a solution of **17** (830 mg, 2.11 mmol) in degassed DMF (30 mL) was added EtSH (1.56 mL, 21 mmol), and the mixture



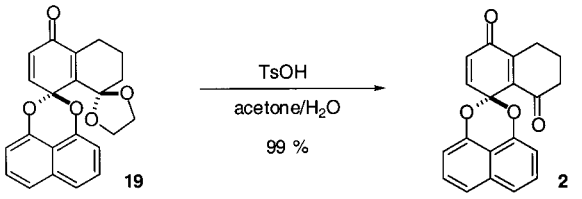
was cooled to 0 °C. The cold solution was carefully treated with NaH (60%, 840 mg, 21 mmol). The reaction mixture was heated to 135 °C, stirred for 3 h at this temperature, and cooled to room temperature. The mixture was poured into ice−water (100 g) containing 7 mL of saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2.4:1) gave 752 mg (98%) of **18** as an oily solid: IR (neat) 3405, 3057. 1633, 1607 cm^{-1}; ^1H NMR δ 9.32 (s, 1 H, OH), 7.49 (d, 1 H, J = 8.2 Hz), 7.41−7.34 (m, 2 H), 7.25 (t, 1 H, J = 8.0 Hz), 6.94 (dd, 1 H, J = 6.0, 2.7 Hz), 6.71 (d, 1 H, J = 7.6 Hz), 6.69 (d, 1 H, J = 8.7 Hz), 6.64 (d, 1 H, J = 8.7 Hz), 5.34 (s, 1 H, OH), 4.34 (td, 1 H, J = 7.4, 4.8 Hz), 4.07 (q, 1 H, J = 7.6 Hz), 3.88 (td, 1 H, J = 7.4, 4.8 Hz), 3.70 (q, 1 H, J = 7.4 Hz), 2.69 (t, 2 H, J = 6.0 Hz), 2.01−1.90 (m, 4 H); ^{13}C NMR δ 154.4, 153.8, 149.8, 147.4, 136.9, 129.1, 128.6, 127.6, 125.9, 122.9, 119.3, 119.0, 115.8, 115. 7, 111.0, 110.8, 107.4, 64.9, 34.5, 23.9, 19.9; MS (EI) m/z (rel intens) 364 (M^+, 100), 320 (99), 303 (21), 160 (99), 149 (15), 131 (25), 121 (11), 115 (43); HRMS (EI) calcd for $C_{22}H_{20}O_5$ 364.1311, found 364.1322.

1-Oxo-1,4,5,6,7,8-hexahydronaphthalene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin-5-spiro-2‴-dioxolane (19). To a suspension of **18** (705 mg, 1.93 mmol) in dry trifluoroethanol (70 mL) was added $PhI(OAc)_2$ (747 mg, 2.32 mmol) at room temperature. The reaction mixture was stirred for 15



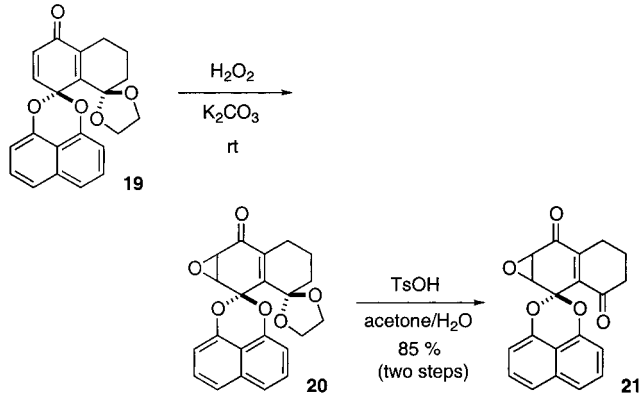
min, treated with $NaHCO_3$ (390 mg, 4.64 mmol), and concentrated in vacuo. The residue was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave 572 mg (82%) of **19** as a yellow solid: mp 184−185 °C (hexanes/EtOAc); IR (neat) 3058, 1677, 1650 cm^{-1}; ^1H NMR δ 7.53 (d, 2 H, J = 8.0 Hz), 7.44 (t, 2 H, J = 7.9 Hz), 7.00 (d, 2 H, J = 7.8 Hz), 6.87 (d, 1 H, J = 10.4 Hz), 6.14 (d, 1 H, J = 10.2 Hz), 4.00−3.95 (m, 4 H), 2.51 (t, 2 H, J = 6.2 Hz), 2.04−1.89 (m, 4 H); ^{13}C NMR δ 185.4, 146.5, 142.5, 140.6, 139.7, 134.1, 127.6, 127.5, 120.9, 112.4, 109.5, 107.4, 93.6, 65.6, 34.9, 22.6, 18.7; MS (EI) m/z (rel intens) 362 (M^+, 100); HRMS (EI) calcd for $C_{22}H_{18}O_5$ 362.1154, found 362.1145.

1,5-Dioxo-1,4,5,6,7,8-hexahydronaphthalene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (2). To a solution of **19** (230 mg, 0.635 mmol) in acetone/water (9 mL, 8:1) was added $TsOH\cdot H_2O$ (170 mg), and the reaction mixture was stirred for 40 h at room tempeature. The resulting mixture was concentrated in vacuo, and the residue was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concen-



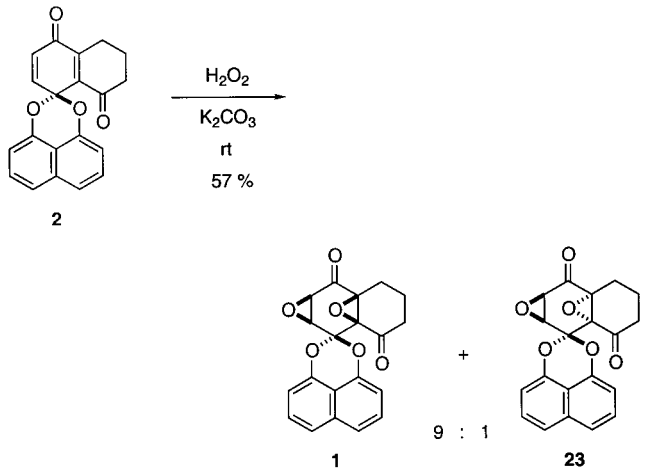
trated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 3:1) gave 199 mg (99%) of **2** as a yellow solid: mp 214−216 °C dec (hexanes/EtOAc); IR (neat) 3060, 1694, 1674, 1645 cm^{-1}; ^1H NMR δ 7.52 (d, 2 H, J = 8.1 Hz), 7.43 (t, 2 H, J = 7.9 Hz), 6.94 (d, 1 H, J = 10.4 Hz), 6.92 (d, 2 H, J = 7.7 Hz), 6.27 (d, 1 H, J = 10.4 Hz), 2.76 (t, 2 H, J = 6.1 Hz), 2.64 (t, 2 H, J = 6.5 Hz), 2.17 (p, 2 H, J = 6.4 Hz); ^{13}C NMR δ 195.8, 185.9, 148.5, 146.2, 139.7, 137.0, 134.2, 127.6, 127.5, 121.1, 112.4, 109.5, 92.1, 39.5, 22.6, 21.2; MS (EI) m/z (rel intens) 318 (M^+, 100), 263 (20); HRMS (EI) calcd for $C_{20}H_{14}O_4$ 318.0892, found 318.0888.

(±)-2,3-Epoxy-1,5-dioxo-1,2,3,4,5,6,7,8-octahydronaphthalene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (21). To a solution of **19** (112 mg, 0.31 mmol) in THF/H_2O (14 mL, 12/1) containing K_2CO_3 (86 mg, 0.62 mmol) was added 3 mL of a 30% H_2O_2 solution. The reaction mixture was stirred for 10 h,



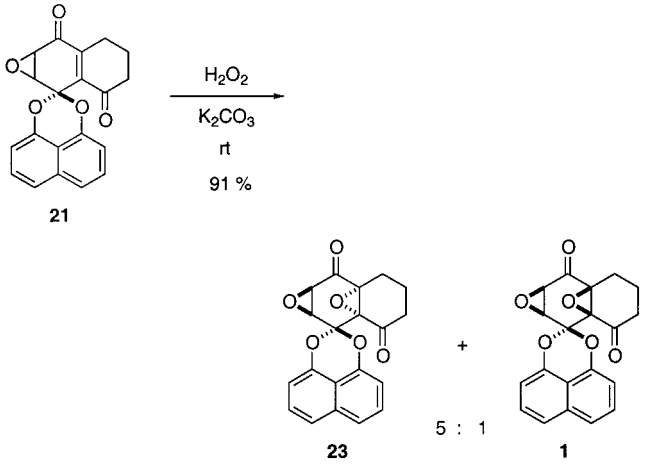
and then additional K_2CO_3 (86 mg, 0.62 mmol) and 30% H_2O_2 solution (2 mL) were added. The mixture was stirred for an additional 20 h and concentrated in vacuo. The residue was dissolved in EtOAc, washed with water, concentrated in vacuo, and dissolved in acetone/water (13 mL, 10:3) containing TsOH·H_2O (170 mg). The reaction mixture was stirred for 4 d at room temperature, concentrated in vacuo, and dissolved in EtOAc (50 mL). The solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave 88 mg (85%) of **21** as a yellow solid: mp 204−205 °C (hexanes/EtOAc); IR (neat) 3060, 1696 cm^{-1}; ^1H NMR δ 7.53 (d, 2 H, J = 8.2 Hz), 7.46 (t, 1 H, J = 7.4 Hz), 7.43 (t, 1 H, J = 7.6 Hz), 7.04 (dd, 1 H, J = 7.2, 0.8 Hz), 6.92 (d, 1 H, J = 7.4 Hz), 3.92 (d, 1 H, J = 4.1 Hz), 3.59 (d, 1 H, J = 4.1 Hz), 2.81 (ddd, 1 H, J = 19.1, 6.7, 6.0 Hz), 2.67 (ddd, 1 H, J = 17.7, 7.0, 5.7 Hz), 2.57−2.45 (m, 2 H), 2.16−2.09 (m, 2 H); ^{13}C NMR δ 195.3, 193.6, 146.9, 146.1, 145.6, 135.7, 134.2, 127.7, 127.4, 121.2, 121.0, 112.2, 109.6, 109.2, 94.4, 54.4, 52.3, 39.3, 23.2, 20.9; MS (EI) m/z (rel intens) 334 (M^+, 100), 318 (7), 278 (8), 250 (9), 222 (8), 208 (10), 171 (8), 114 (28), 77 (6), 63 (10); HRMS (EI) calcd for $C_{20}H_{14}O_5$ 334.0841, found 334.0852.

(±)-2,3;9,10-*syn*-Diepoxy-1,5-dioxoperhydronaphthalene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (1). To a solution of **2** (259 mg, 0.81 mmol) in THF (18 mL) containing K_2CO_3 (424 mg, 3.07 mmol) was added at room temperature 6.4 mL of a 30% H_2O_2 solution. The reaction mixture was stirred for 2 h at room temperature and diluted with water (10 mL) and saturated NH_4Cl solution (3 mL), and THF was removed in vacuo. The residue was extracted with EtOAc. The combined EtOAc layers were washed with brine and dried (Na_2SO_4). The resulting solution was treated with 4 Å molecular sieves (1 g, powder) and stirred for 12 h at room



temperature. Filtration and concentration in vacuo gave 170 mg (57%) of *syn*- and *anti*-diepoxides (9:1). Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 112 mg of **1** as a colorless solid: R_f 0.50 (hexanes/EtOAc, 2:1); mp 245−247 °C dec (hexanes/EtOAc); IR (neat) 3043, 1722, 1610 cm^{-1}; ^1H NMR δ 7.56−7.39 (m, 4 H), 7.17 (dd, 1 H, J = 7.2, 1.0 Hz), 6.92 (dd, 1 H, J = 7.0, 0.6 Hz), 3.79 (d, 1 H, J = 4.0 Hz), 3.50 (d, 1 H, J = 4.0 Hz), 2.61 (dt, 1 H, J = 17.7, 4.4 Hz), 2.49 (dt, 1 H, J = 15.7, 4.7 Hz), 2.44 (ddd, 1 H, J = 16.7, 9.8, 5.8 Hz), 2.19 (ddd, 1 H, J = 16.9, 10.8, 6.5 Hz), 1.89−1.79 (m, 2 H); ^{13}C NMR δ 196.4, 196.1, 145.1, 134.2, 127.9, 127.3, 121.5, 121.2, 112.1, 110.1, 109.0, 94.1, 67.5, 66.4, 57.7, 54.9, 37.8, 21.3, 16.0; MS (EI) m/z (rel intens) 350 (M^+, 100), 211 (15); HRMS (EI) calcd for $C_{20}H_{14}O_6$ 350.0790, found 350.0806.

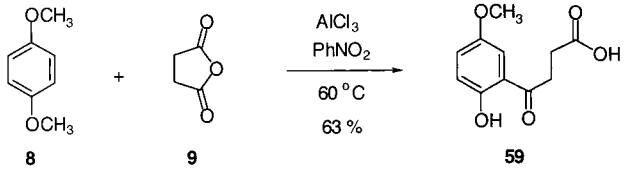
(±)-2,3;9,10-*anti*-Diepoxy-1,5-dioxoperhydronaphthalene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (23). To a solution of **21** (55 mg, 0.164 mmol) in THF/H_2O (5 mL, 4/1) containing K_2CO_3 (23 mg, 0.164 mmol) was added 0.5 mL of a 30% H_2O_2 solution at room temperature. The reaction mixture



was stirred for 10 min and diluted with water (5 mL) and saturated NH_4Cl solution (1 mL), and THF was removed in vacuo. The residue was extracted with EtOAc. The combined EtOAc layers were washed with brine and dried (Na_2SO_4). The resulting solution was treated with 4 Å molecular sieves (0.5 g, powder) and stirred for 12 h at room temperature. Filtration and concentration in vacuo gave 52 mg (91%) of *syn*- and *anti*-diepoxides (1:5). Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 31 mg of **23** as a colorless solid: R_f 0.65 (hexanes/EtOAc, 2:1); mp 173−175 °C (hexanes/EtOAc); IR (neat) 3061, 1726, 1611 cm^{-1}; ^1H NMR δ 7.55 (d, 2 H, J = 8.4 Hz), 7.47 (t, 1 H, J = 7.7 Hz), 7.45 (t, 1 H, J = 8.0 Hz), 7.11 (d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 7.3 Hz), 3.41 (d, 1 H, J = 3.6 Hz), 3.36 (d, 1 H, J = 3.6 Hz), 2.74 (dt, 1 H, J = 15.7, 3.9 Hz), 2.63 (dt, 1 H, J = 16.3, 3.9 Hz), 2.32−2.15 (m, 2 H), 1.92−1.78 (m,

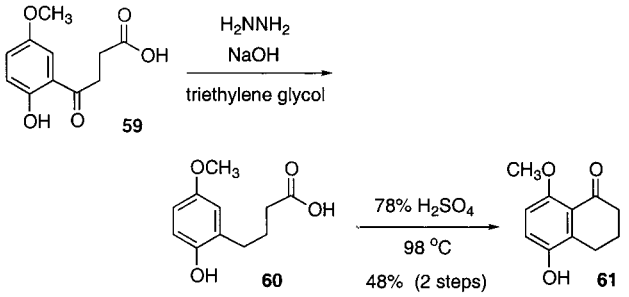
2 H); ^{13}C NMR δ 195.4, 192.6, 145.4, 134.3, 127.6, 127.6, 121.5, 121.4, 113.3, 110.1, 109.6, 95.6, 62.4, 60.6, 52.4, 49.6, 38.8, 20.6, 16.2; MS (EI) *m*/*z* (rel intens) 350 (M^+, 100), 211 (15); HRMS (EI) calcd for $C_{20}H_{14}O_6$ 350.0790, found 350.0781.

4-(2-Hydroxy-5-methoxyphenyl)-4-oxobutyric Acid (59).[50] To a solution of $AlCl_3$ (80.0 g, 0.60 mol) in nitrophenol (480 mL) were added at 0 °C succinic anhydride (30.02 g, 0.30 mol) and *p*-dimethoxybenzene (37.31 g, 0.27 mol). The reaction



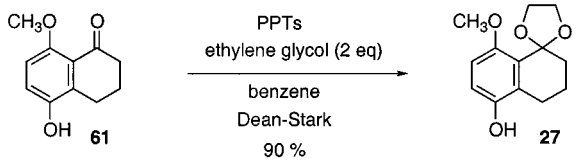
mixture was allowed to warm to 60 °C, stirred at that temperature for 4 h, cooled to room temperature, and then promptly poured into ice−water. The organic layer was extracted with 10% $NaHCO_3$ solution. The combined aqueous layers were filtered and acidified to pH 1 by addition of concentrated HCl solution in an ice bath. The resulting very pale yellow solid was filtered and dried to afford 38 g (63%) of **59** contaminated with ~20% inseparable **10**. Data for **59**: ^{1}H NMR δ 11.66 (s, 1 H, OH), 7.21 (d, 1 H, J = 3.0 Hz), 7.12 (dd, 1 H, J = 9.0, 3.0 Hz), 6.93 (d, 1 H, J = 9.0 Hz), 3.81 (s, 3 H), 3.35 (t, 2 H, J = 6.3 Hz), 2.81 (t, 2 H, J = 6.3 Hz).

5-Hydroxy-8-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (61).[50] A solution of **59** (38.0 g, 0.169 mol) in triethylene glycol (500 mL) containing sodium hydroxide (25.0 g, 0.625 mol), hydrazine hydrate (22 mL, 0.454 mol), and water (25 mL) was heated at reflux for 3 h and then heated further without a condenser until the temperature rose to 210 °C. After

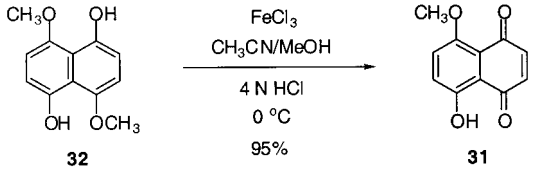


1 h, sufficient water was added to lower the temperature to 190 °C, and heating was continued for 4 h. The solution was then cooled, poured into a mixture of concd HCl (110 mL) and ice (1100 g), and extracted with ether. The combined ether layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1 → 1:1) gave 30.2 g of **60** contaminated with a nonseparable isomer as a solid, which was treated with 130 mL of 75% (v/v) sulfuric acid solution at 98 °C for 1 h. The resulting orange solution was poured into ice−water and extracted with ether. The combined ether layers were washed with 1 N NaOH solution and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 1:1) gave 15.5 g (48%) of **61** as a yellow solid: ^{1}H NMR δ 6.98 (d, 1 H, J = 8.9 Hz), 6.93 (d, 1 H, J = 8.9 Hz), 3.84 (s, 3 H), 2.88 (t, 2 H, J = 6.2 Hz), 2.63 (t, 2 H, J = 6.6 Hz), 2.09 (p, 2 H, J = 6.4 Hz).

5-Hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene-1-spiro-2′-dioxolane (27). To a solution of **61** (4.8 g, 25 mmol) and ethylene glycol (3.1 g, 50 mmol) in benzene (700 mL) was added PPTS (0.3 g). The reaction mixture was heated at reflux for 30 h in a flask equipped with a Dean−Stark apparatus, washed with 5% $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 5.32 g (90%) of **27** as a solid: mp 139−140 °C (hexanes/EtOAc); IR (neat) 3359, 1583 cm^{-1}; ^{1}H NMR δ 6.55 (d, 1 H, J = 8.8 Hz), 6.54 (d, 1 H, J = 8.8 Hz), 5.42 (s, 1 H, OH), 4.25 (t, 2 H, J = 6.6 Hz), 4.07 (t, 2 H, J = 6.6 Hz), 3.75 (s, 3 H), 2.57 (t, 2 H, J = 6.0 Hz), 1.93−1.80 (m, 4 H); ^{13}C NMR δ 152.6, 146.9, 128.3, 125.8, 115.2, 110.7, 108.1, 65.5, 56.6, 35.9, 24.0, 20.1; MS (EI) *m*/*z* (rel intens) 236 (M^+, 94), 208 (100); HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1052.

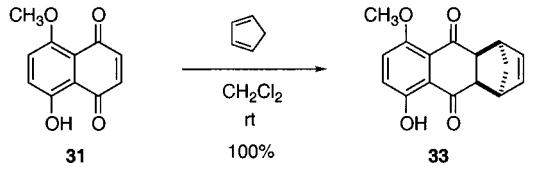


5-Hydroxy-8-methoxy-1,4-naphthoquinone (31).[33] To a partially heterogeneous solution of **32** (3.96 g, 18 mmol) in acetonitrile/methanol (1:1, 340 mL) and 4 N HCl (70 mL) was added $FeCl_3$ (11.68 g, 72 mmol) at 0 °C. The reaction mixture



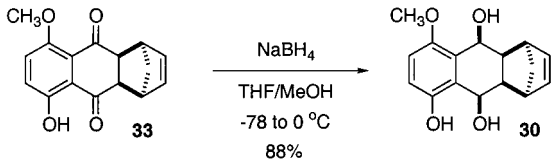
was stirred for 10 min at 0 °C, neutralized with 1 N NaOH solution in an ice bath, and extracted with methylene chloride. The combined methylene chloride solutions were concentrated to 600 mL, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1) gave 3.5 g (95%) of **31** as a red solid: ^{1}H NMR δ 11.45 (s, 1 H, OH), 7.38 (d, 1 H, J = 9.6 Hz), 7.31 (d, 1 H, J = 9.3 Hz), 6.88 (s, 2 H), 3.99 (s, 3 H).

(5*S,8*R**,8a*S**,10a*R**)-4-Hydroxy-1-methoxy-9,10-dioxo-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (33).** To a red solution of **31** (1.43 g, 7 mmol) in CH_2Cl_2 (150 mL) was added cyclopentadiene (1.39 g, 21 mmol) at room temperature. The reaction mixture was stirred for 5 h and concen-



trated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 1.89 g (100%) of **33** as a yellow solid: mp 120−140 °C dec (hexanes/EtOAc); IR (neat) 3584, 1678, 1634 cm^{-1}; ^{1}H NMR δ 12.31 (s, 1 H, OH), 7.26 (d, 1 H, J = 9.3 Hz), 7.14 (d, 1 H, J = 9.3 Hz), 6.05 (dd, 1 H, J = 5.5, 2.8 Hz), 5.97 (dd, 1 H, J = 5.5, 2.7 Hz), 3.86 (s, 3 H), 3.59 (t, 2 H, J = 1.5 Hz), 3.44 (dd, 1 H, J = 9.3, 3.9 Hz), 3.36 (dd, 1 H, J = 9.3, 3.8 Hz), 1.53 (dt, 1 H, J = 8.7, 1.7 Hz), 1.47 (d, 1 H, J = 8.7 Hz); ^{13}C NMR δ 205.1, 196.5, 155.7, 152.1, 136.5, 135.0, 124.4, 123.4, 123.3, 118.8, 57.2, 50.5, 50.0, 49.5, 49.0, 48.9; MS (EI) *m*/*z* (rel intens) 270 (M^+, 10), 204 (100); HRMS (EI) calcd for $C_{16}H_{14}O_4$ 270.0892, found 270.0902.

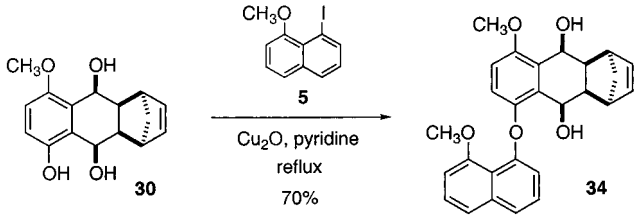
(5*S,8*R**,8a*S**,9*S**,10*R**,10a*R**)-4,9,10-Trihydroxy-1-methoxy-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (30).** To a suspension of $NaBH_4$ (0.38 g, 10 mmol) in THF (100 mL) was added at −78 °C a solution of **33** (1.35 g, 5 mmol) in THF (20 mL), followed by addition of methanol (30 mL).



(50) Newhall, W. F.; Harris, S. A.; Holly, F. W.; Johnston, E. L.; Richter, J. W.; Walton, E.; Wilson, A. N.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *77*, 5646.

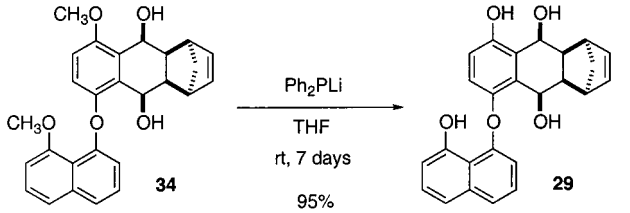
After being stirred for 2 h at −78 °C, the reaction mixture was warmed to 0 °C and stirred for 1 h. The solution was carefully quenched with saturated NH_4Cl (15 mL) in an ice bath and concentrated in vacuo. The resulting residue was diluted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). The solution was filtered through a short SiO_2 column. Concentration of the filtrate gave 1.21 g (88%) of **30** as a colorless solid: mp 148−155 °C dec (hexanes/EtOAc); IR (neat) 3324, 1494 cm^{-1}; ^1H NMR (CD_3OD) δ 6.74 (d, 1 H, J = 8.8 Hz), 6.69 (d, 1 H, J = 8.8 Hz), 6.14 (t, 2 H, J = 1.6 Hz), 5.30 (t, 2 H, J = 3.6 Hz), 3.75 (s, 3 H), 2.89 (s, 2 H), 2.39 (m, 2 H), 1.47 (d, 2 H, J = 1.4 Hz); ^{13}C NMR (CD_3OD) δ 150.9, 149.1, 134.6, 132.7, 130.9, 116.0, 112.9, 64.0, 63.8, 57.0, 53.8, 47.4, 46.9; MS (EI) m/z (rel intens) 274 (M^+, 25), 175 (100); HRMS (EI) calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1208.

(5*R,8*S**,8a*R**,9*R**,10*S**,10a*S**)-4-Methoxy-1-(8′-methoxynaphthalen-1′-yloxy)-8,9-dihydroxy-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (34).** A solution of **30** (1.08 g, 3.94 mmol) and **5** (1.90 g, 6.70 mmol) in pyridine (100 mL) was treated with Cu_2O (572 mg, 4.0 mmol) and heated at reflux for 20 h. After concentration of the reaction mixture in



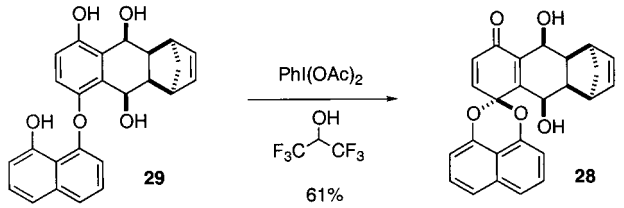
vacuo, the residue was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (CH_2Cl_2/EtOAc, 9:1) gave 1.19 g (70%) of **34** as a colorless solid: mp 167−169 °C (CH_2Cl_2/EtOAc); IR (neat) 3331, 1578 cm^{-1}; ^1H NMR δ 7.56 (dd, 1 H, J = 8.2, 0.9 Hz), 7.46 (dd, 1 H, J = 8.2, 1.1 Hz), 7.40 (t, 1 H, J = 7.9 Hz), 7.33 (t, 1 H, J = 7.8 Hz), 6.86 (dd, 1 H, J = 7.4, 1.0 Hz), 6.84 (dd, 1 H, J = 6.9, 1.0 Hz), 6.70 (d, 1 H, J = 8.9 Hz), 6.56 (d, 1 H, J = 8.8 Hz), 6, 31 (dd, 1 H, J = 5.4, 3.0 Hz), 6.22 (dd, 1 H, J = 5.4, 3.0 Hz), 5.53 (s, 1 H), 5.45 (s, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.03 (s, 1 H), 2.97 (s, 1 H), 2.69 (br s, 2 H, OH), 2.57 (s, 2H), 1.54 (dt, 1 H, J = 7.9, 1.7 Hz), 1.49 (d, 1 H, J = 7.8 Hz); ^{13}C NMR δ 156.6, 153.9, 151.9, 149.3, 137.6, 134.3, 133.9, 132.8, 132.2, 126.7, 126.4, 123.7, 120.9, 119.0, 117.2, 115.6, 111.5, 106.8, 63.6, 63.0, 56.6, 56.3, 53.2, 46.0, 45.7; MS (EI) m/z (rel intens) 430 (M^+, 29), 412 (100); HRMS (EI) calcd for $C_{27}H_{26}O_5$ 430.1780, found 430.1801.

(5*R,8*S**,8a*R**,9*R**,10*S**,10a*S**)-4,9,10-Trihydroxy-1-(8′-hydroxynaphthalene-1′-yloxy)-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (29).** To a colorless solution of Ph_2PH (1.22 mL, 7.0 mmol) in THF (25 mL) was added dropwise at 0 °C a 1.6 M solution of *n*-BuLi in hexanes (6.13 mL, 9.8 mmol). The reaction mixture was warmed to room



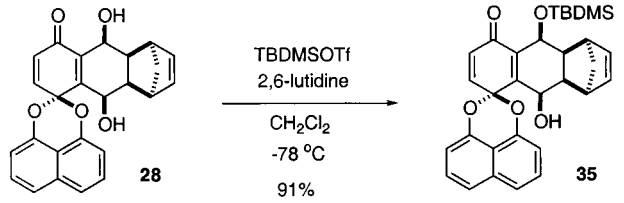
temperature and stirred for 20 min. To the red solution was added **34** (603 mg, 1.4 mmol) as a solid, and the mixture was stirred for 7 d, quenched with saturated NH_4Cl solution (50 mL), extracted with EtOAc, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 1:2) gave 535 mg (95%) of **29** as a colorless solid: mp 169−184 °C dec (hexanes/EtOAc); IR (neat) 3439, 1608, 1583 cm^{-1}; ^1H NMR (acetone-d_6) δ 9.15 (s, 1 H, OH), 8.63 (s, 1 H, OH), 7.49 (d, 1 H, J = 8.1 Hz), 7.43−7.36 (m, 2 H), 7.22 (t, 1 H, J = 8.1 Hz), 6.97 (d, 1 H, J = 8.7 Hz), 6.92 (d, 1 H, J = 8.8 Hz), 6.88 (dd, 1 H, J = 6.0, 2.8 Hz), 6.47 (d, 1 H, J = 7.7 Hz), 6.16 (dd, 1 H, J = 5.3, 3.0 Hz), 6.09 (dd, 1 H, J = 5.3, 3.0 Hz), 5.41 (s, 1 H), 5.09 (s, 1 H), 4.37 (s, 1 H, OH), 4.19 (s, 1 H, OH), 2.93 (s, 1 H), 2.79 (s, 1 H), 2.52 (dt, 1 H, J = 10.7, 3.7 Hz), 2.45 (dt, 1 H, J = 10.9, 3.7 Hz), 1.45 (d, 1 H, J = 7.6 Hz), 1.38 (dt, 1 H, J = 7.7, 1.6 Hz);^{13}C NMR (acetone-d_6) δ 157.5, 155.1, 152.8, 143.8, 138.0, 137.4, 134.3, 134.1, 131.5, 128.5, 126.6, 123.2, 122.5, 119.7, 116.9, 115.8, 111.2, 109.2, 64.1, 63.2, 53.1, 47.0, 46.7, 46.4, 46.3; MS (EI) m/z (rel intens) 402 (M^+, 2), 360 (67), 318 (100); HRMS (EI) calcd for $C_{25}H_{22}O_5$ 402.1467, found 402.1476.

(5*S,8*R**,8a*S**,9*S**,10*R**,10a*R**)-9,10-Dihydroxy-1-oxo-1,4,5,8,8a,9,10,10a-octahydro-5,8-methanoanthracene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (28).** To a solution of **29** (322 mg, 0.80 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (5 mL) in the presence of molecular sieves (4 Å powder, 200 mg) was added $PhI(OAc)_2$ (348 mg, 1.08 mmol) at room temperature. The reaction mixture was stirred for 1 h and



concentrated in vacuo. After dilution of the residue with EtOAc, the solution was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 195 mg (61%) of **28** as a yellow solid: mp 192−195 °C dec (hexanes/EtOAc); IR (neat) 3343, 1679, 1651, 1607 cm^{-1}; ^1H NMR δ 7.56 (d, 2 H, J = 8.4 Hz), 7.45 (td, 2 H, J = 7.9, 1.2 Hz), 6.99 (d, 1 H, J = 7.4 Hz), 6.95 (d, 1 H, J = 7.6 Hz), 6.82 (d, 1 H, J = 10.3 Hz), 6.27 (dd, 1 H, J = 5.3, 2.8 Hz), 6.21 (d, 1 H, J = 10.2 Hz), 6.20 (dd, 1 H, J = 5.3, 2.8 Hz)), 5.14 (d, 1 H, J = 4.9 Hz), 5.04 (d, 1 H, J = 4.7 Hz), 3.01 (s, 1 H), 2.97 (s, 1 H), 2.86 (s, 2 H, OH), 2.69 (ddd, 1 H, J = 10.8, 4.7, 3.4, Hz), 2.55 (ddd, 1 H, J = 10.8, 5.0, 3.4 Hz), 1.54 (s, 2 H);^{13}C NMR δ 183.4, 152.6, 146.6, 146.4, 141.3, 137.4, 134.2, 134.0, 133.8, 129.2, 127.7, 127.6, 121.5, 113.0, 110.2, 109.9, 93.4, 64.7, 61.3, 53.2, 45.6, 45.5, 45.4; MS (EI) m/z (rel intens) 400 (M^+, 100), 382 (15); HRMS (EI) calcd for $C_{25}H_{20}O_5$ 400.1311, found 400.1292.

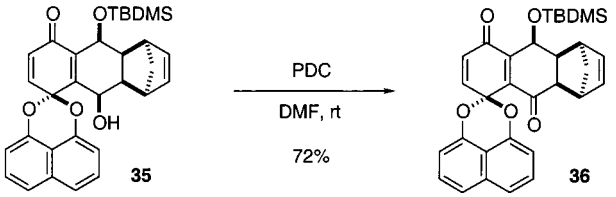
(5*S,8*R**,8a*S**,9*S**,10*R**,10a*R**)-9-*tert*-Butyldimethylsilyloxy-10-hydroxy-1-oxo-1,4,5,8,8a,9,10,10a-octahydro-5,8-methanoanthracene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]-dioxin (35).** To a stirred solution of **28** (137 mg, 0.34 mmol) and 2,6-lutidine (119 μL, 1.02 mmol) in CH_2Cl_2 (5 mL) was added dropwise at −78 °C TBDMSOTf (234 μL, 1.02 mmol).



The reaction mixture was stirred for 1 h, quenched with H_2O (0.1 mL), and warmed to room temperature. After dilution with EtOAc, the reaction mixture was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 160 mg (91%) of **35** as a yellow oil: IR (neat) 3441, 1677, 1650, 1608 cm^{-1}; ^1H NMR δ 7.53 (d, 2 H, J = 8.5 Hz), 7.45 (t, 1 H, J = 7.4 Hz), 7.42 (t, 1 H, J = 7.4 Hz), 7.07 (d, 1 H, J = 7.5 Hz), 6.90 (d, 1 H, J = 7.6 Hz), 6.87 (d, 1 H, J = 10.4 Hz), 6.27 (dd, 1 H, J = 5.3, 2.9 Hz), 6.18 (dd, 1 H, J = 5.3, 2.9 Hz), 6.18 (d, 1 H, J = 10.3 Hz), 5.31 (d, 1 H, J = 4.3 Hz), 4.84 (dd, 1 H, J = 12.4, 4.3 Hz), 3.58 (d, 1 H, J = 12.4 Hz, OH), 2.92 (s, 1 H), 2.89 (s, 1 H), 2.59−2.53 (m, 2 H), 1.55 (s, 2 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR δ 183.3, 156.2, 147.0, 146.7, 140.5, 138.3, 134.1,

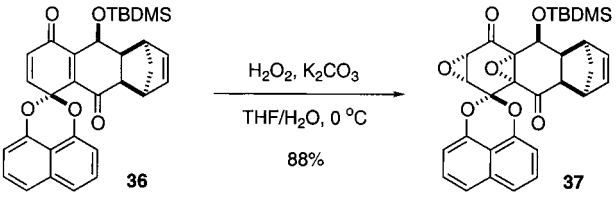
133.8, 133.5, 128.7, 127.7, 127.3, 121.3, 121.1, 113.1, 110.6, 109.4, 93.1, 64.8, 62.2, 53.5, 47.3, 47.0, 45.2, 45.1, 26.2, 18.2, −4.1, −4.5; MS (EI) *m*/*z* (rel intens) 514 (M^+, 26), 457 (91), 115 (100); HRMS (EI) calcd for $C_{31}H_{34}O_5Si$ 514.2176, found 514.2170.

(5*S,8*R**,8a*S**,9*S**,10a*R**)-9-*tert*-Butyldimethylsilyloxy-1,10-dioxo-1,4,5,8,8a,9,10,10a-octahydro-5,8-methanoanthracene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (36).** To a solution of **35** (54 mg, 0.105 mmol) in DMF (3 mL) was added PDC (119 mg, 0.315 mmol) at room temperature. The reaction



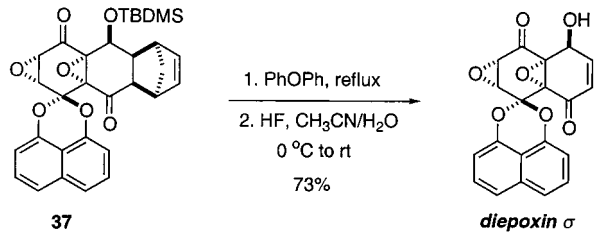
mixture was stirred for 24 h at room temperature, diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 39 mg (72%) of **36** as a yellow oil: IR (neat) 3060, 1713, 1674, 1644, 1608 cm^{-1}; ^1H NMR δ 7.51(d, 2 H, J = 8.8 Hz), 7.42 (t, 1 H, J = 7.9 Hz), 7.40 (t, 1 H, J = 7.9 Hz), 6.95 (dd, 1 H, J = 7.6, 0.8 Hz), 6.89 (dd, 1 H, J = 7.6, 0.7 Hz), 6.86 (d, 1 H, J = 10.4 Hz), 6.24 (dd, 1 H, J = 5.5, 2.9 Hz), 6.20 (d, 1 H, J = 10.4 Hz), 6.10 (dd, 1 H, J = 5.5, 2.9 Hz), 5.28 (d, 1 H, J = 6.1 Hz), 3.26 (s, 1 H), 3.20 (dd, 1 H, J = 10.6, 3.7 Hz), 3.03 (s, 1 H), 2.93 (ddd, 1 H, J = 10.5, 6.2, 3.3 Hz), 1.55 (dt, 1 H, J = 8.4, 1.7 Hz), 1.45 (d, 1 H, J = 8.3 Hz), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR δ 197.9, 184.5, 146.9, 146.2, 146.1, 142.7, 138.7, 136.6, 134.1, 132.6, 128.3, 127.5, 127.3, 121.3, 121.0, 112.6, 110.0, 109.6, 92.5, 60.6, 54.0, 50.3, 45.3, 44.9, 44.2, 26.1, 18.3, −3.8, −4.4; MS (EI) *m*/*z* (rel intens) 512 (M^+, 10), 455 (33), 389 (70); HRMS (EI) calcd for $C_{31}H_{32}O_5Si$ 512.2019, found 512.2010.

(2*S,3*R**,4a*R**,5*S**,8*R**,8a*S**,9*S**,9a*R**,10a*R**)-9-*tert*-Butyldimethylsilyloxy-2,3;4a,9a-diepoxy-1,10-dioxo-1,2,3,4,-4a,5,8,8a,9,9a,10,10a-dodecahydro-5,8-methanoanthracene-4-spiro-2′-naphtho[1″,8″-*de*][1′,3′]dioxin (37).** To a suspension of **36** (48 mg, 0.094 mmol) and K_2CO_3 (104 mg, 0.752 mmol) in THF (8 mL) was added 30% H_2O_2 solution (3 mL) in an ice bath. The reaction mixture was stirred for 9 h



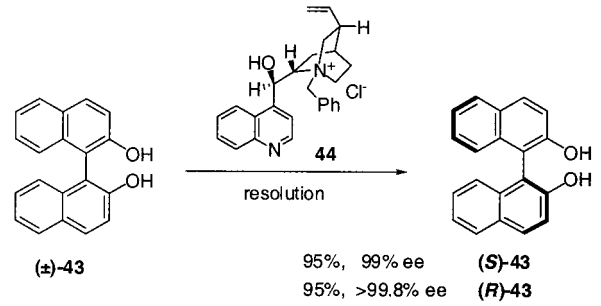
at 0 °C, quenched with saturated NH_4Cl solution (1 mL), and concentrated in vacuo. The residue was diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 45 mg (88%) of **37** as a colorless solid: mp 210−252 °C dec (hexanes/EtOAc); IR (neat) 3060, 1738, 1722, 1609 cm^{-1}; ^1H NMR δ 7.53-(d, 1 H, J = 7.8 Hz), 7.52 (d, 1 H, J = 8.1 Hz), 7.46 (t, 1 H, J = 7.9 Hz), 7.42 (t, 1 H, J = 8.0 Hz), 7.11 (dd, 1 H, J = 7.2, 0.6 Hz), 6.90 (d, 1 H, J = 7.1 Hz), 6.07 (s, 2 H), 5.28 (d, 1 H, J = 4.7 Hz), 3.74 (d, 1 H, J = 3.9 Hz), 3.38 (d, 1 H, J = 3.9 Hz), 3.29 (dd, 1 H, J = 11.2, 3.5 Hz), 2.99 (s, 1 H), 2.89 (s, 1 H), 2.70 (ddd, 1 H, J = 11.2, 4.6, 3.1 Hz), 1.42 (d, 1 H, J = 8.2 Hz), 1.29 (d, 1 H, J = 8.3 Hz), 0.95 (s, 9 H), 0.21 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR δ 198.5, 193.8, 145.4, 145.2, 135.8, 134.2, 133.3, 127.6, 127.5, 121.4, 121.2, 112.0, 109.9, 109.2, 94.0, 68.8, 66.6, 64.8, 56.7, 53.7, 50.7, 50.1, 44.8, 44.5, 42.5, 26.5, 18.8, −2.0, −3.5; MS (EI) *m*/*z* (rel intens) 544 (M^+, 80), 487 (100), 421(77), 393 (77); HRMS (EI) calcd for $C_{31}H_{32}O_7Si$ 544.1917, found 544.1918.

(±)-Diepoxin *σ*. A solution of **37** (35 mg, 0.064 mmol) was heated at reflux in phenyl ether (2 mL) for 1 h. After phenyl



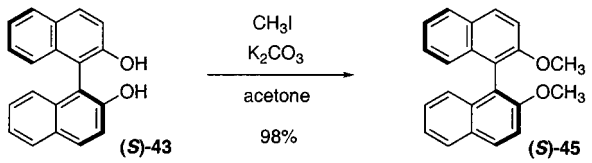
ether was removed under high vacuum, the remaining residue was treated with 48% HF solution (0.5 mL) in CH_3CN (4 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 20 h, and carefully quenched with saturated $NaHCO_3$ solution (2 mL) in an ice bath. After extraction with EtOAc, the organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 1:1) gave 17 mg (73%) of (±)-diepoxin *σ* as a colorless solid: mp 230−235 °C dec (hexanes/EtOAc); IR (neat) 3426, 1726, 1699, 1638 cm^{-1}; ^1H NMR δ 7.57(d, 1 H, J = 8.0 Hz), 7.56 (d, 1 H, J = 8.2 Hz), 7.50 (t, 1 H, J = 7.5 Hz), 7.45 (t, 1 H, J = 7.9 Hz), 7.17 (d, 1 H, J = 7.6 Hz), 6.99 (d, 1 H, J = 7.5 Hz), 6.65 (dd, 1 H, J = 10.6, 5.3 Hz), 6.05 (d, 1 H, J = 10.5 Hz), 5.18 (d, 1 H, J = 5.3 Hz), 3.86 (d, 1 H, J = 3.9 Hz), 3.52 (d, 1 H, J = 3.9 Hz), 3.52 (s, 1 H, OH); ^{13}C NMR δ 197.8, 185.4, 145.0, 139.8, 134.3, 128.0, 127.8, 127.5, 121.5, 121.4, 112.0, 110.0, 109.3, 93.6, 66.5, 65.5, 62.0, 58.1, 54.8; MS (EI) *m*/*z* (rel intens) 364 (M^+, 100), 211 (25); HRMS (EI) calcd for $C_{20}H_{12}O_7$ 364.0583, found 364.0597.

Resolution of (±)-1,1′-Bi-2-naphthol (43).[43] To a solution of (±)-1,1′-bi-2-naphthol (12.03 g, 42 mmol) in acetonitrile (158 mL) was added *N*-benzylcinchonium chloride (9.72 g, 23.1 mmol). The resulting suspension was heated at reflux for 4 h,



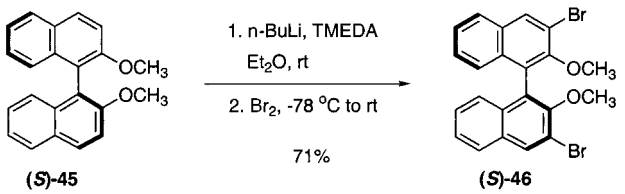
cooled to room temperature, and stirred for 12 h. The mixture was cooled to 0 °C, kept at this temperature for 2 h, and filtered. The filtrate was concentrated to dryness, redissolved in ethyl acetate, and washed with 1 N HCl and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 5.70 g (95%) of (*S*)-1,1′-bi-2-naphthol as a light brown solid: $[\alpha]_D$ −34.0 (*c* 1.0, THF; lit.[43] 99% ee, $[\alpha]_D$ −34.0 (*c* 1.0, THF)). The solid was washed with acetonitrile (30 mL) and heated at reflux in methanol (55 mL) for 24 h. After being cooled to room temperature, the mixture was filtered, and the solid was washed with methanol (10 mL). The resulting solid complex was suspended in a mixture of ethyl acetate (160 mL) and 1 N HCl solution (80 mL) and stirred until it was completely dissolved. The organic layer was washed with 1 N HCl solution and brine, dried (Na_2CO_3), and concentrated in vacuo to afford 5.71 g (95%) of (*R*)-1,1′-bi-2-naphthol as a colorless solid: $[\alpha]_D$ +34.5 (*c* 1.0, THF; lit.[43] >99.8% ee, $[\alpha]_D$ +34.3 (*c* 1.0, THF)).

(*S*)-2,2′-Dimethoxy-1,1′-dinaphthyl ((*S*)-45).[42] A suspension of (*S*)-1,1′-bi-2-naphthol (5.1 g, 17.81 mmol) was heated in acetone to give a homogeneous solution. To this solution were added potassium carbonate (8.3 g, 60 mmol) and methyl iodide (9.94 g, 70 mmol), and the mixture was heated at reflux for 24 h. Additional methyl iodide (4.26 g, 30 mmol) was added,



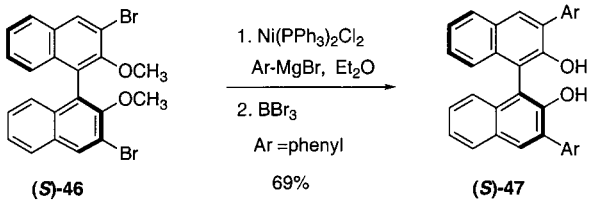
and heating was continued for 12 h. The solvent was evaporated to leave a volume of 30 mL, which was cooled to 25 °C and treated with 160 mL of water. The mixture was stirred for 8 h, and the resulting solid was washed with water and dried to afford 5.47 g (98%) of (*S*)-**45** as a white powder: ^{1}H NMR δ 7.98 (d, 2 H, J = 9.0 Hz), 7.86 (d, 2 H, J = 8.1 Hz), 7.46 (d, 2 H, J = 9.0 Hz), 7.31 (t, 2 H, J = 7.3 Hz), 7.21 (t, 2 H, J = 7.4 Hz), 7.10 (d, 2 H, J = 8.5 Hz), 3.77 (s, 6 H).

(*S*)-3,3′-Dibromo-2,2′-dimethoxy-1,1′-dinaphthyl ((*S*)-46).[42] To a solution of TMEDA (1.92 mL,12.74 mmol) in ether (100 mL) was added at room temperature 1.6 M *n*-BuLi in hexane (10.9 mL, 17.37 mmol). The solution was stirred for



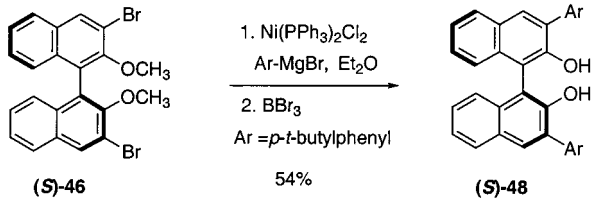
15 min, solid (*S*)-**45** (1.82 g, 5.79 mmol) was added in one portion, and the reaction mixture was stirred for 3 h at room temperature. The resulting light brown suspension was cooled to −78 °C, and bromine (3.6 mL, 70 mmol) was added over a period of 10 min. The mixture was allowed to warm to room temperature, and after 4 h, a saturated Na_2SO_3 solution (60 mL) was added cautiously. The reaction mixture was stirred for an additional 4 h, and diluted with ether and water. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 1.94 g (71%) of (*S*)-**46** as a solid: ^{1}H NMR δ 8.27 (s, 2 H), 7.83 (d, 2 H, J = 8.2 Hz), 7.43 (td, 2 H, J = 7.3, 0.9 Hz), 7.27 (td, 2 H, J = 7.1, 1.0 Hz), 7.08 (d, 2 H, J = 8.6 Hz), 3.51 (s, 6 H).

(*S*)-3,3′-Diphenyl[1,1′]binaphthalenyl-2,2′-diol ((*S*)-47).[48] To a suspension of (*S*)-**46** (236 mg, 0.5 mmol) and $Ni(PPh_3)_2Cl_2$ (26 mg, 0.04 mmol) in ether (10 mL) was added a 3 M solution of PhMgBr in ether (1 mL, 3.0 mmol) over a period of 10 min. The reaction mixture was heated at reflux for 20 h,



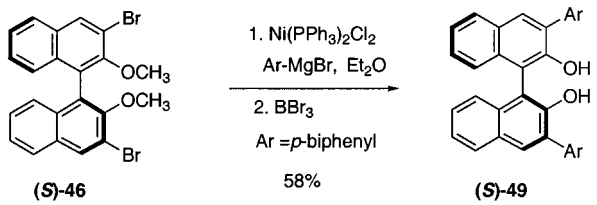
cooled to 0 °C, and quenched with water (1 mL). After addition of 1 N HCl solution (20 mL), the mixture was stirred for 10 min and extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 10:1) gave 170 mg of the coupling product as a colorless solid. To a solution of this solid (170 mg) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (1.5 mL, 1.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, quenched with water (1 mL) in an ice bath, and poured into a stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 151 mg (69%) of (*S*)-**47** as a solid: $[\alpha]_D$ −73.3 (*c* 1.0, $CHCl_3$; lit.[48] for the (*R*)-isomer $[\alpha]_D$ +69.1 (*c* 1.0,$CHCl_3$)); ^{1}H NMR δ 8.05 (s, 2 H), 7.94 (d, 2 H, J = 7.9 Hz), 7.77−7.75 (m, 4 H), 7.54−7.32 (m, 10 H), 7.25 (d, 2 H, J = 8.1 Hz), 5.38 (s, 2 H, OH).

(*S*)-3,3′-Bis(4-*tert*-butylphenyl)[1,1′]binaphthalenyl-2,2′-diol ((*S*)-48). To a suspension of (*S*)-**46** (331 mg, 0.7 mmol) and $Ni(PPh_3)_2Cl_2$ (46 mg, 0.07 mmol) in ether (10 mL) was added a solution of 4-*tert*-butylphenylmagnesium bromide in ether, prepared from 4-*tert*-butylphenyl bromide (949 mg, 4.5 mmol) and magnesium turnings (114 mg, 4.7 mmol) in refluxing ether (10 mL), over a period of 10 min. The reaction



mixture was heated at reflux for 24 h, cooled to 0 °C, and quenched with water (1 mL). The resulting solution was mixed with 1 N HCl (20 mL), stirred for 10 min, and extracted with ether. The combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude coupling products. To a solution of these products in CH_2Cl_2 (15 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (3.5 mL, 3.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, quenched with water (1 mL) in an ice bath, and poured into the stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 10:1) gave 207 mg (54%) of (*S*)-**48** as an oily solid: $[\alpha]_D$ −31.7 (*c* 1.0, $CHCl_3$); IR (neat) 3518, 1621 cm^{-1}; ^{1}H NMR δ 8.04 (s, 2 H), 7.92 (d, 2 H, J = 7.9 Hz), 7.69 (d, 4 H, J = 8.2 Hz), 7.53 (d, 4 H, J = 8.2 Hz), 7.39 (t, 2 H, J = 7.4 Hz), 7.31 (t, 2 H, J = 7.4 Hz), 7.23 (d, 2 H, J = 8.2 Hz), 5.39 (s, 2 H, OH), 1.39 (s, 18 H); ^{13}C NMR δ 150.8, 150.3, 134.5, 132.9, 131.3, 130.6, 129.5, 129.3, 128.4, 127.2, 125.6, 124.4, 124.3, 112,4, 34.7, 31.4; MS (EI) *m*/*z* (rel intens) 550 (M^+, 100), 535 (13), 260 (17); HRMS (EI) calcd for $C_{40}H_{38}O_2$ 550.2872, found 550.2876.

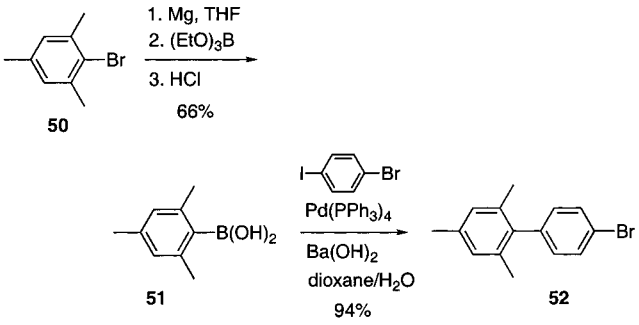
(*S*)-3,3′-Bis(biphenyl-4-yl)[1,1′]binaphthalenyl-2,2′-diol ((*S*)-49).[48] To a suspension of (*S*)-**46** (331 mg, 0.7 mmol) and $Ni(PPh_3)_2Cl_2$ (46 mg, 0.07 mmol) in ether (10 mL) was added a solution of *p*-biphenylmagnesium bromide in ether, prepared from 4-bromobiphenyl (1.05 g, 4.5 mmol) and magnesium turnings (114 mg, 4.7 mmol) in refluxing ether (10 mL), over a period of 10 min. The reaction mixture was heated at



reflux for 20 h, cooled to 0 °C, quenched with water (1 mL), mixed with 1 N HCl solution (20 mL), stirred for 10 min, and extracted with ether. The combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 260 mg of the coupling products as a solid. To a solution of this solid (260 mg) in CH_2Cl_2 (15 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (2.5 mL, 2.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, quenched with water (1 mL) in an ice bath, and poured into a stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 240 mg (58%) of (*S*)-**49** as a solid: $[\alpha]_D$ +55.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.11 (s, 2 H), 7.97 (d, 2 H, J = 7.9 Hz), 7.85 (d, 4 H, J = 8.4

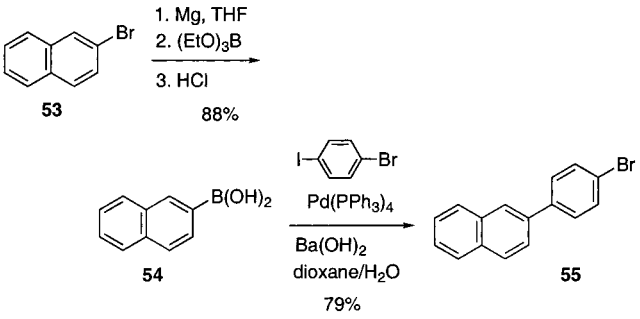
Hz), 7.74 (d, 4 H, J = 8.3 Hz), 7.69 (d, 4 H, J = 7.3 Hz), 7.53−7.26 (m, 12 H), 5.43 (s, 2 H, OH).

4′-Bromo-2,4,6-trimethylbiphenyl (52).[45] To a solution of bromomesitylene (5.97 g, 30 mmol) in THF (40 mL) containing magnesium turnings (972 mg, 40 mmol) was added one crystal of iodine (30 mg) without stirring to initiate the reaction. The



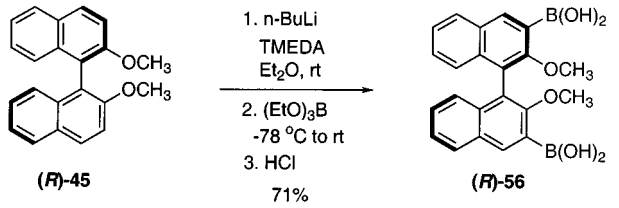
reaction mixture was heated at reflux for 14 h and then cooled to −78 °C. Triethyl borate (10.2 mL, 60 mmol) was added to the solution at −78 °C. The mixture was warmed to room temperature, stirred for 5 h, and cooled to 0 °C, and 1 N HCl (50 mL) was added. The resulting solution was stirred for 2 h at room temperature and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting solid was recrystallized from benzene to afford 3.27 g (66%) of mesitylboronic acid (**51**) as a colorless solid. To a solution of this boronic acid (1.97 g, 12.0 mmol) in degassed dioxane/water (32 mL, 3:1) were added *p*-bromoiodobenzene (3.73 g, 13.2 mmol), $Ba(OH)_2 \cdot 8H_2O$ (7.57 g, 24 mmol), and $Pd(PPh_3)_4$ (277 mg, 0.24 mmol). The reaction mixture was heated at reflux for 24 h and cooled to room temperature. Dioxane was removed, and the resulting residue was redissolved in methylene chloride, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes) gave 3.1 g (94%) of **52** as a colorless solid: ^{1}H NMR δ 7.54 (dd, 2 H, J = 6.5, 1.8 Hz), 7.02 (dd, 2 H, J = 6.6, 1.8 Hz), 6.94 (s, 2 H), 2.32 (s, 3 H), 1.99 (s, 6 H).

2-(4′-Bromophenyl)naphthalene (55).[46] To a solution of 2-bromonaphthalene (8.5 g, 41 mmol) in THF (80 mL) including magnesium turnings (1.04 g, 43 mmol) was added one crystal of iodine (30 mg) without stirring to initiate the reaction. The reaction mixture was heated at reflux for 14 h



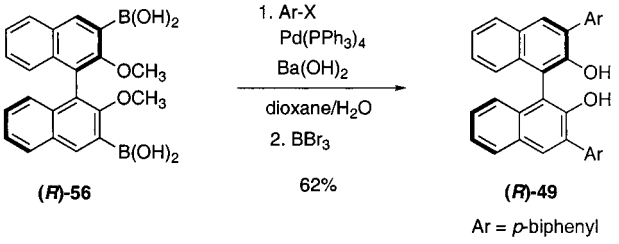
and then cooled to −78 °C. Triethyl borate (10.2 mL, 60 mmol) was added at −78 °C, and the mixture was warmed to room temperature, stirred for 5 h, and cooled to 0 °C, and a 1 N HCl solution (50 mL) was added. The resulting solution was stirred for 2 h at room temperature and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting solid was recrystallized from benzene to afford 6.2 g (88%) of 2-naphthylboronic acid (**54**) as a colorless solid. To a solution of this boronic acid (6.2 g, 36.0 mmol) in degassed dioxane/water (160 mL, 3/1) were added *p*-bromoiodobenzene (12.84 g, 45.4 mmol), $Ba(OH)_2 \cdot 8H_2O$ (35.8 g, 113.4 mmol), and $Pd(PPh_3)_4$ (878 mg, 0.76 mmol). The reaction mixture was heated at reflux for 24 h and cooled to room temperature. Dioxane was removed, and the resulting residue was redissolved in methylene chloride, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 20:1) gave 8.1 g (79%) of **55** as a colorless solid: ^{1}H NMR δ 8.01 (s, 1 H), 7.94−7.85 (m, 3 H), 7.70 (dd, 1 H, J = 8.6, 1.8 Hz), 7.64−7.57 (m, 4 H), 7.56−7.48 (m, 2 H).

(*R*)-3,3′-Bis(dihydroxyborane)-2,2′-dimethoxy-1,1′-dinaphthyl ((*R*)-56).[48] To a solution of TMEDA (5.89 mL, 39 mmol) in ether (200 mL) was added at room temperature 1.6 M *n*-BuLi in hexane (24.4 mL, 39 mmol). The solution was



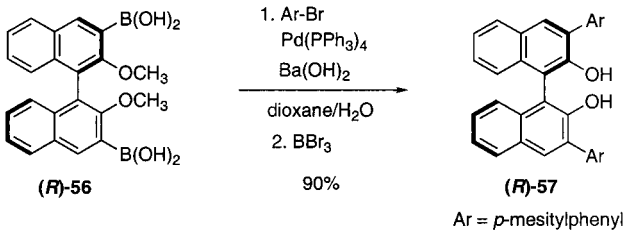
stirred for 30 min, solid (*R*)-2,2′-dimethoxy-1,1′-dinaphthyl (4.07 g, 13 mmol) was added in one portion, and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to −78 °C, and ethyl borate (15.48 mL, 91 mmol) was added over a period of 10 min. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C, 1 M HCl solution (100 mL) was added, and the resulting solution was stirred for 2 h at room temperature. The organic layer was washed with 1 M HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting pale yellow solid was recrystallized from toluene to give 3.7 g (71%) of (*R*)-**56** as colorless crystals: $[\alpha]_D$ −159.0 (*c* 1.05, $CHCl_3$; lit.[48] $[\alpha]_D$ −153.4 (*c* 1.0, $CHCl_3$)); ^{1}H NMR δ 8.62 (s, 2 H), 7.99 (d, 2 H, J = 8.1 Hz), 7.44 (t, 2 H, J = 7.4 Hz), 7.32 (td, 2 H, J = 7.7, 0.8 Hz), 7.16 (d, 2 H, J = 8.4 Hz), 6.10 (s, 4 H, OH), 3.31 (s, 6 H).

(*R*)-3,3′-Bis-biphenyl-4-yl[1,1′]binaphthalenyl-2,2′-diol ((*R*)-49).[48] To a solution of (*R*)-**56** (402 mg, 1.00 mmol) in degassed dioxane/water (8 mL, 3:1) were added 4-iodobiphenyl (840 mg, 3.0 mmol), $Ba(OH)_2 \cdot 8H_2O$ (946 mg, 3.0 mmol), and $Pd(PPh_3)_4$ (46.2 mg, 0.04 mmol). The reaction mixture was



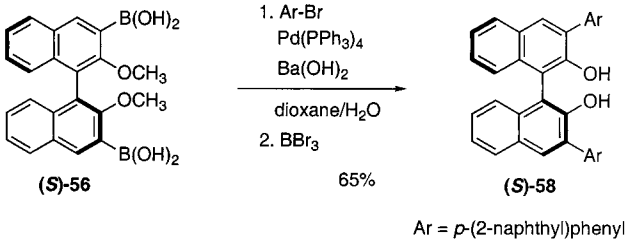
heated at reflux for 24 h and cooled to room temperature. Dioxane was removed, and the resulting residue was redissolved in methylene chloride, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give crude coupling products. To a solution of these crude products in CH_2Cl_2 (50 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (6.0 mL, 6.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, and quenched with water (1 mL) in an ice bath. The mixture was poured into a stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 366 mg (62%) of (*R*)-**49** as a solid: $[\alpha]_D$ −54.8 (*c* 1.01, $CHCl_3$; lit.[48] $[\alpha]_D$ −70.3 (*c* 1.0, $CHCl_3$)).

(*R*)-3,3′-Bis(2′,4′,6′-trimethylbiphenyl-4-yl)[1,1′]binaphthalenyl-2,2′-diol [(*R*)-57]. To a solution of (*R*)-**56** (804 mg, 2.0 mmol) in degassed dioxane/water (16 mL, 3/1) were added **52** (1.65 g, 6.0 mmol), $Ba(OH)_2 \cdot 8H_2O$ (1.74 g, 5.5 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol). The reaction mixture was heated at reflux for 24 h and cooled to room temperature. Dioxane was removed, and the resulting residue was redis-



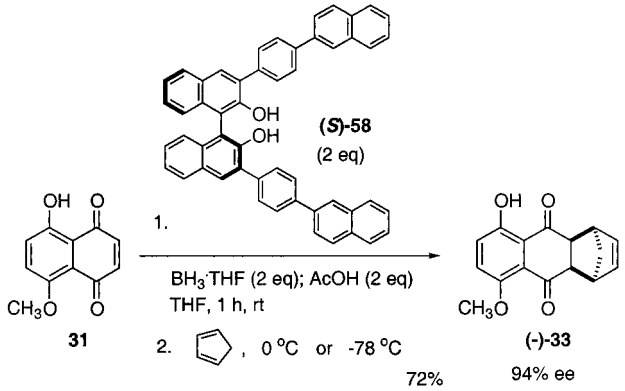
solved in methylene chloride, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give crude coupling products. To a solution of these crude products in CH_2Cl_2 (50 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (6.0 mL, 6.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, and quenched with water (1 mL) in an ice bath. The mixture was poured into the stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 1.22 g (90%) of (*R*)-**57** as a solid: mp >185 °C dec (hexanes/EtOAc); $[\alpha]_D$ −25.5 (*c* 1.03, $CHCl_3$); IR (neat) 3519, 1619 cm^{-1}; ^1H NMR δ 8.17 (s, 2 H), 7.99 (d, 2 H, J = 7.9 Hz), 7.85 (d, 4 H, J = 8.0 Hz), 7.45 (t, 2 H, J = 7.3 Hz), 7.37 (t, 2 H, J = 7.4 Hz), 7.31 (d, 6 H, J = 7.6 Hz), 7.01 (s, 4 H), 5.49 (s, 2 H, OH), 2.38 (s, 6 H), 2.12 (s, 12 H); ^{13}C NMR δ 150.3, 140.7, 138.7, 136.8, 136.1, 135.6, 133.0, 131.5, 130.5, 129.6, 128.5, 128.2, 127.4, 124.4, 112.5, 21.1, 21.0; MS (EI) *m*/*z* (rel intens) 674 (M^+, 100), 337 (12), 309 (15); HRMS (EI) calcd for $C_{50}H_{42}O_2$ 674.3185, found 674.3173.

(*S*)-3,3′-Bis(4-naphthalen-2-yl-phenyl)[1,1′]binaphthalenyl-2,2′-diol ((*S*)-58). To a solution of (*S*)-**56** (2.14 g, 5.32 mmol)) in degassed dioxane/water (40 mL, 3:1) were added **55** (4.52 g, 15.96 mmol), $Ba(OH)_2 \cdot 8H_2O$ (5.04 g, 15.96 mmol), and $Pd(PPh_3)_4$ (242 mg, 0.21 mmol). The reaction mixture was



heated at reflux for 24 h and cooled to room temperature. Dioxane was removed, and the resulting residue was redissolved in methylene chloride, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated in vacuo to give crude coupling products. To a solution of these crude products in CH_2Cl_2 (100 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (12.0 mL, 12.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, and quenched with water (3 mL) in an ice bath. The mixture was poured into a stirred mixture of methylene chloride and water. The organic layer was washed with brine, dried (Na_2CO_3), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 3:1) gave 3.5 g of crude product. Additional chromatography on neutral alumina (benzene and then ethyl acetate) gave 2.40 g (65%) of (*S*)-**58** as a solid: mp 205−207 °C (benzene/EtOAc); $[\alpha]_D$ +149.2 (*c* 1.0, $CHCl_3$); IR (neat) 3511, 1621, 1597 cm^{-1}; ^1H NMR δ 8.14 (s, 4 H), 7.99−7.82 (m, 18 H), 7.56−7.48 (m, 4 H), 7.44 (td, 2 H, J = 7.4, 0.9 Hz), 7.37 (td, 2 H, J = 7.5, 0.9 Hz), 7.29 (d, 2 H, J = 8.0 Hz), 5.46 (s, 2 H, OH); ^{13}C NMR δ 150.4, 140.5, 138.1, 136.6, 133.7, 133.0, 132.7, 131.5, 130.3, 130.2, 129.6, 128.6, 128.4, 128.3, 127.7, 127.5, 126.4, 126.1, 125.9, 125.6, 124.5, 124.4, 112.4; MS (EI) *m*/*z* (rel intens) 690 (M^+, 100), 674 (52), 317 (35); HRMS (EI) calcd for $C_{52}H_{34}O_2$ 690.2559, found 690.2541.

(5*R*,8*S*,8a*R*,10a*S*)-4-Hydroxy-1-methoxy-9,10-dioxo-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene ((−)-33). To a solution of **(*S*)-58** (691 mg, 1.0 mmol) and $BH_3 \cdot THF$ (1.0 mL of a 1 M solution in THF, 1.0 mmol) in THF (10 mL) was added AcOH (57.2 μL, 1.0 mmol) at room temperature. After



10 min, volatiles were removed under high vacuum. The residue was dissolved in THF (15 mL), a red solution of **31** (102 mg, 0.5 mmol) in THF (7 mL) was added, and the resulting deep violet solution was stirred at room temperature for 1 h and then cooled to −78 °C. To the mixture was added at −78 °C cyclopentadiene (0.1 mL) that had been freshly distilled under anhydrous conditions. The reaction mixture was stirred for 2 h at −78 °C, quenched with H_2O (0.5 mL), and diluted with EtOAc. The solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 97 mg [72%, 94% ee determined by chiral HPLC (Chiralcel OD, hexanes/EtOAc, 4:1] of **(−)-33** as a yellow oil: $[\alpha]_D$ −4.9 (*c* 1.0, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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