Synthesis of *trans*-3,4-dihydroxy-3,4-dihydrophenanthro[3,2-*b*]-[1]benzothiophene, a potentially carcinogenic metabolite of sulfur heterocycle phenanthro[3,2-*b*][1]benzothiophene

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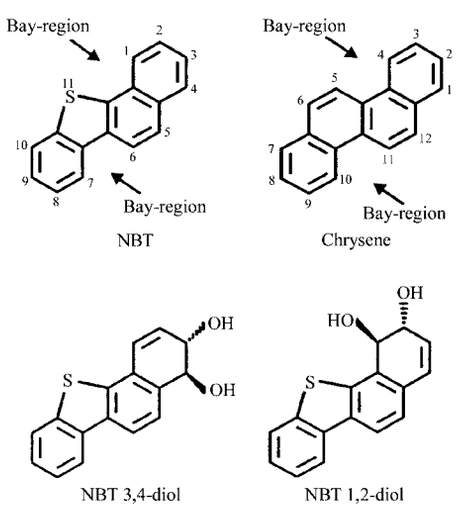
The present study describes the synthesis of *trans*-3,4-dihydroxy-3,4-dihydrophenanthro[3,2-*b*][1]benzothiophene (**3**), which is a potential proximate carcinogen of the environmentally occurring potent carcinogen phenanthro-[3,2-*b*][1]benzothiophene (**1**). Three approaches were investigated for the synthesis of **3**. In the first approach, the diarylalkene **9**, which was prepared by the Wittig reaction of ylide **7** and aldehyde **8**, was subjected to an oxidative photocyclization reaction to produce a mixture of compounds from which **5**, a synthetic precursor to **3**, was obtained only in trace amounts. The major cyclized product was **10**. The second approach entailed the Suzuki cross-coupling reaction of 2-(dihydroxyboryl)-5-methoxybenzaldehyde (**12**) with 3-bromodibenzothiophene (**11**) to produce **13** in 92% yield. The aldehyde function of **13** was elongated with trimethylsulfonium iodide in the presence of KOH to generate the ethylene oxide **14**, which, after methanesulfonic acid treatment, produced a 1 : 1 mixture of 3-methoxyphenanthro[3,2-*b*][1]benzothiophene (**6**) and 3-methoxyphenanthro[1,2-*b*][1]benzothiophene (**15**). Only the undesired compound **15** could be isolated in pure form by extracting the mixture with hot ethanol, leaving behind a 7 : 3 mixture of **6** and **15**. In the third approach, the Wittig reaction of **7** with 2-bromo-5-methoxybenzaldehyde (**16**) produced **17** predominantly as the *Z*-isomer in quantitative yield. Cyclodehydrobromination of **17** with KOH–quinoline at elevated temperature produced a mixture from which **6** and 3-methoxyphenanthro[3,4-*b*][1]benzothiophene (**18**) were easily separated by column chromatography in 23 and 51% yields, respectively. The intermediate **6** was conveniently processed to **3** following the reaction sequence: methoxy phenol→*o*-quinone→dihydrodiol. A relatively polar dihydrodiol obtained by similar processing of the mixture of **6** and **15** was identified as **3**.

Introduction

For the past two decades, numerous studies have indicated that "bay-region"[1] diol epoxides and their dihydrodiol precursors are the major carcinogenic metabolites of a number of polycyclic aromatic hydrocarbons (PAHs).[2–4] The importance of these metabolites in cancer induction has stimulated strong interest in their synthesis and their chemical and biological properties.[4] The analogous polycyclic sulfur heterocycles (thia-PAHs) are also common environmental contaminants[5] and many have been shown to possess high mutagenic/carcinogenic activity.[5–7] Although a number of thia-PAHs exhibit mutagenic and/or carcinogenic activity, not much attention has been paid to determining the nature of the intermediate(s) involved in the metabolic activation of such thia-PAHs. Thia-PAHs are metabolized[8,9] by cytochrome P-450 catalyzed oxidation reactions to sulfoxides and sulfones, as well as to dihydrodiols analogous to those produced by PAHs.[3] At the same time, a number of thia-PAHs that are capable of being metabolized to bay-region diol epoxides have been found to be considerably more carcinogenic than their carbocyclic analogues (PAHs).[6,7] These observations are consistent with the speculation that the bay-region concept of metabolic activation of PAHs[10,11] may be extended to thia-PAHs because Hückel MO calculations have predicted bay-region diol epoxides of thia-PAHs to be more electrophilic than their carbocyclic analogues.[12] Recently, synthesis and subsequent biological studies of dihydrodiols of a weak carcinogen, naphtho[1,2-*b*][1]benzothiophene (NBT, a thia-analogue of chrysene) have demonstrated that, among two major dihydrodiol metabolites of NBT,[8] *trans*-3,4-dihydroxy-3,4-dihydronaphtho[1,2-*b*][1]benzothiophene (NBT 3,4-diol), a metabolic precursor to the bay-region diol epoxide of NBT, is significantly more mutagenic than the isomeric *trans*-1,2-dihydroxy-1,2-dihydronaphtho[1,2-*b*][1]benzothiophene (NBT 1,2-diol).[13] However, in contrast to a significant difference noted between the mutagenicity of chrysene and its 1,2-diol,[14] no significant difference was noted between the mutagenicity of NBT and NBT 3,4-diol. These findings suggest that the weak carcinogenicity of NBT may be attributed to its metabolism either to the weakly carcinogenic NBT 3,4-diol or to an unknown minor metabolite(s) of high mutagenicity/carcinogenicity.



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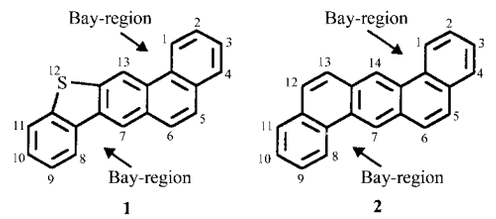
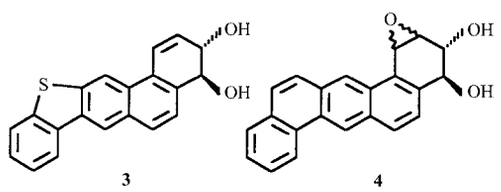
As a part of our research goal to identify the mutagenic and/or carcinogenic metabolites of thia-PAHs, and to investigate the applicability of the bay-region concept to these thia-PAHs with more certainty, we initiated our studies with an environmentally occurring[15] pentacyclic thia-PAH, phenanthro[3,2-*b*][1]benzothiophene (**1**). In contrast to NBT, **1** is a potent carcinogen,[6] and its carcinogenic activity is higher than that of its carbocyclic isostere, dibenzo[*a*,*h*]anthracene (**2**), which is considered to be metabolically activated *via* bay-region diol epoxide (**4**).[3] The present study was undertaken to synthesize *trans*-3,4-dihydroxy-3,4-dihydrophenanthro[3,2-*b*][1]benzothiophene (**3**), a precursor of the bay-region diol epoxide of **1**, in order to establish whether **3** is a mutagenic/carcinogenic metabolite of **1**. Synthesis of **3** has allowed us to confirm the structure of one of the major metabolites of **1**[16] and to evaluate its potential as a proximate mutagen/carcinogen of **1**.[17,18]



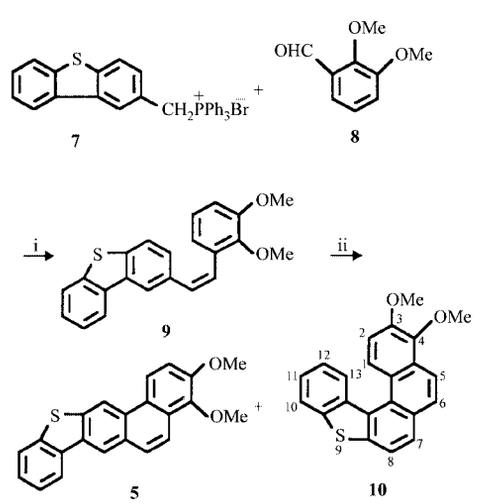
1 **2**



3 **4**

Results and discussion

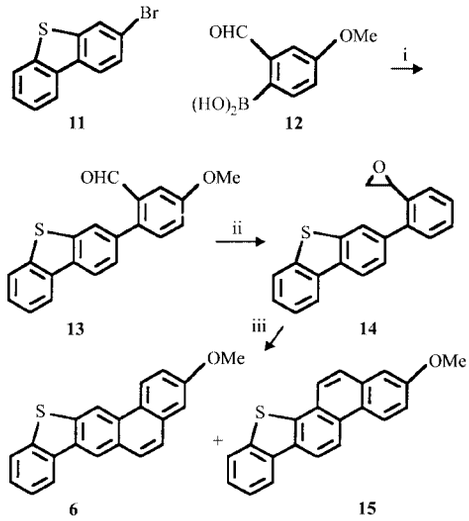
The most recent advances[13,19–21] in the synthesis of various dihydrodiol derivatives of PAHs and thia-PAHs prompted us to select 3,4-dimethoxyphenanthro[3,2-*b*][1]benzothiophene (**5**) or 3-methoxyphenanthro[3,2-*b*][1]benzothiophene (**6**) as the potential intermediates for the synthesis of **3**. Three synthetic strategies for the preparation of **5** or **6** were explored. The oxidative photocyclization route,[20] which is widely used in the synthesis of PAH derivatives analogous to **5** and which required simpler starting materials, was first investigated (Scheme 1).



7 **8** **9** **5** **10**

Scheme 1 *Reagents and conditions*: i, 50% NaOH–CH_2Cl_2; ii, *hv*.

However, this strategy was not productive since the oxidative photocyclization of 1,2-diarylethylene **9** produced a mixture of chromatographically similar compounds containing mostly **10** and trace amounts of **5** (^{1}H NMR). Because of the lack of formation of **5** in a sufficient amount *via* the oxidative photocyclization route, a second approach involving a synthetic application of the Suzuki cross-coupling reaction[22] was investigated for the synthesis of **6** (Scheme 2). Synthetic application of



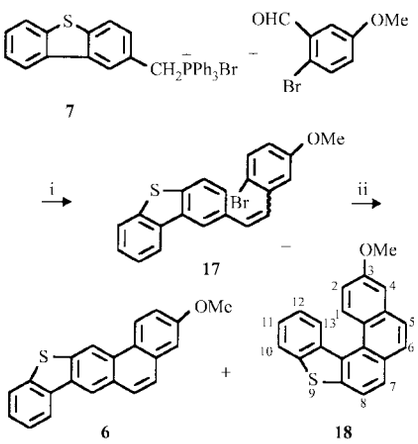
11 **12** **13** **14** **6** **15**

Scheme 2 *Reagents*: i, $Pd(PPh_3)_4$, CsF–DME; ii, $Me_3S^+I^-$, KOH–MeCN; iii, $MeSO_3H$–CH_2Cl_2.

the Suzuki cross-coupling reaction has recently been developed in our laboratory for a concise, regiospecific synthesis of methoxy-substituted PAHs,[19] which are analogous to **6**. One of the key starting materials, 2-(dihydroxyboryl)-5-methoxybenzaldehyde (**12**), has been synthesized in the literature[23] from the dimethyl acetal of 2-bromo-5-methoxybenzaldehyde (**16**) in less than 30% yield. A significant improvement in the yield (>90%) of **12** was achieved by replacing the dimethyl acetal of **16** with the ethylene acetal of **16**. The coupling reaction of 3-bromodibenzothiophene (**11**)[24] with 2-(dihydroxyboryl)-5-methoxybenzaldehyde (**12**), in the presence of anhydrous CsF and a catalytic amount of $Pd(PPh_3)_4$, produced 3-(2-formyl-4-methoxyphenyl)dibenzothiophene (**13**) in 87% yield. The aldehyde functionality of **13** was modified to ethylene epoxide by reacting it with trimethylsulfonium iodide and powdered KOH in acetonitrile at 65 °C for 12 h to produce the relatively unstable ethylene epoxide derivative **14** as an oil. This homologation procedure, which was initially developed by Borredon *et al.*,[25] was found to be superior to the method that employed a phase-transfer catalyst.[19a] The NMR spectrum of **14** which indicated the lack of an aldehydic proton at 10.01 ppm, and the appearance of three proton signals between 2.8 and 3.9 ppm as double doublets confirmed the presence of oxiranyl side chain in **14**. The acid-catalyzed cyclodehydration of **14** with $MeSO_3H$ in CH_2Cl_2 at room temperature took place smoothly. However, the reaction was not regiospecific, and produced a nearly 1 : 1 mixture of **6** and 2-methoxyphenanthro[1,2-*b*][1]benzothiophene (**15**). The presence of **6** in the mixture was indicated by NMR, which showed two singlets corresponding to two protons (H-7 and H-13) of *meso*-acenic type (*vide infra*). Separation of **6** from **15** by chromatography was not successful. However, the extraction of the mixture with hot ethanol produced a residue, which, after recrystallization from CH_2Cl_2, yielded pure **15**. The product that crystallized out from the ethanol extract contained nearly 70% of **6** and 30% of **15** (^{1}H NMR). An attempt to isolate pure **6** in a sufficient amount from the ethanol-extracted mixture by fractional recrystallization from various solvents was unsuccessful. However, the chemical transformation of the mixture containing **6** as the major product (following the procedure shown in Scheme 4) produced a mixture of two dihydrodiols from which **3** was separated by analytical HPLC. Although this procedure afforded **3** in pure form by analytical HPLC, however, due to the poor loadability of the dihydrodiol mixture, preparative HPLC was not very

successful in isolating pure **3** in the sufficient amounts for biological studies.

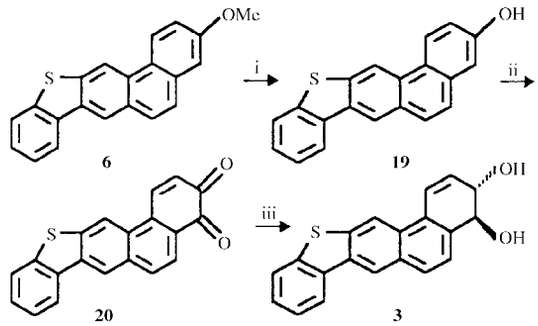
Finally, an attempt to synthesize **6** *via* cyclodehydrobromination of an *o*-bromostilbene, previously applied in constructing phenanthrene building blocks,[26,27] afforded a 1 : 2 mixture of **6** and **18** (Scheme 3), which were easily separated by column



Scheme 3 *Reagents*: i, 50% NaOH–CH_2Cl_2, ii, KOH–quinoline.

chromatography. The Wittig reaction of the phosphonium salt **7** (prepared from triphenylphosphine and 2-bromomethyldibenzothiophene[28]) with 2-bromo-5-methoxybenzaldehyde (**16**)[29] produced 1-(2-bromo-5-methoxy)-2-(2-dibenzothienyl)-ethylene (**17**) in nearly quantitative yield as a mixture of *Z*- and *E*-isomers in the ratio of $Z : E \approx 4$. The *Z* and *E*-isomers of **17** were separated by preparative TLC (2% EtOAc–hexanes), and their structures were tentatively assigned by their ^{1}H NMR on the basis of the relatively larger coupling constant exhibited by the olefinic protons of the *E*-isomer (δ 7.19, $J = 16$ Hz) *versus* the relatively less polar *Z*-isomer (δ 6.68, $J = 12$ Hz). The olefinic protons, and one phenyl proton (H-5) of the *E*-isomer were significantly deshielded compared to the corresponding protons of the *Z*-isomer. The strong preference for the formation of the *Z*-isomer in the Wittig reaction with *o*-substituted benzaldehyde is consistent with previous observations.[30,31] The treatment of **17** as a mixture with powdered KOH in refluxing quinoline (redistilled) produced a mixture of two compounds, which were easily separated by column chromatography in 23 and 51% yields, respectively. Both of these compounds showed a molecular ion (M^+) at 318 in their mass spectrum confirming that they were isomers. A comparison of the ^{1}H NMR spectra allowed us to identify these two compounds as **6** and 3-methoxyphenanthro[3,4-*b*][1]benzothiophene (**18**). The ^{1}H NMR spectrum of the relatively nonpolar product was consistent with structure **6**. This spectrum showed the presence of two downfield sharp singlets at 8.60 and 9.02 ppm of the *meso*-acenic protons H-7 and H-13 of **6**. One of these resonances was deshielded by interaction with proton H-7. The ^{1}H NMR spectrum in which the most downfield protons H-1 and H-13 were centered at 8.68 and 8.94 ppm, respectively, as doublets was consistent with the structure assigned to **18**. The presence of the two most upfield aromatic proton signals, one as a doublet with a small coupling (~2 Hz), and the other as a double doublet with a small (~2.5 Hz) and a large coupling (~9 Hz) confirmed the presence of the methoxy group at position 3 of **6** and **18**.

The chemical transformation of **6** to its *trans*-dihydrodiols **3** is illustrated in Scheme 4. Thus, demethylation of **6** to the corresponding phenol **19** was achieved in a nearly quantitative yield (96%) with boron tribromide in CH_2Cl_2. The oxidation of the phenol **19** with Fremy's salt produced highly colored *o*-quinone **20** in 95% yields. The reduction of the *o*-quinone **20** with sodium borohydride in 95% ethanol while bubbling oxygen took place stereospecifically to provide 3,4-dihydrodiol **3** in



Scheme 4 *Reagents*: i, BBr_3–CH_2Cl_2; ii, Fremy's salt; iii, $NaBH_4$, O_2–EtOH.

a moderate yield (40%). The ^{1}H NMR spectrum of **3** was consistent with its assigned structure. The large value for the coupling constant (~11.7 Hz) between the carbinol protons H-3 and H-4 of **3** indicates that the conformation of the *trans*-dihydrodiols with a *pseudo*-diaxial orientation of the carbinol protons is strongly populated. An HPLC analysis and a comparison of the UV spectra indicated that the major dihydrodiol obtained from the mixture of **6** and **15** (see above) was **3**.

Our preliminary studies[16–18] have indicated that **3** is a major metabolite of **1**, and exhibits mutagenic activity in *Salmonella typhimurium* strain TA100 that is higher than that of **1**. Details of these and other biological studies with **3** and other derivatives of **1** will be reported elsewhere.

Experimental

3-Bromodibenzothiophene (**11**),[24] 2-bromo-5-methoxybenzaldehyde (**16**),[29] and 2-bromomethyldibenzothiophene[28] were synthesized according to the published procedures. All reagents and solvents (anhydrous or otherwise) were used as received without further purification. Dry column grade silica gel was purchased from E. Merck. The ^{1}H and ^{13}C NMR spectra were recorded on 300, 400 or 500 MHz NMR spectrometers in an appropriate solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are in ppm relative to internal TMS for ^{1}H NMR spectra and relative to solvent signals for ^{13}C NMR spectra. Mass spectral data, HRMS (EI), were obtained by the mass spectral facility of the Department of Chemistry, State University of New York at Buffalo. All the melting points were uncorrected.

CAUTION: substituted phenanthro[*b*]benzothiophenes (***5***, ***6***, ***10***, ***15***, ***18***, and ***19***), *o-quinone* ***20***, *and dihydrodiol* ***3*** *are potential carcinogens and should be handled in accordance with NIH Guidelines for the Laboratory Use of Chemical Carcinogens.*

1-(2,3-Dimethoxyphenyl)-2-(dibenzo[*b*,*d*]thiophen-2-yl)ethylene (9)

2,3-Dimethoxybenzaldehyde (**8**) (1.8 g, 11 mmol) and the phosphonium salt **7** (5.4 g, 10 mmol, prepared from 2-bromomethyldibenzothiophene and triphenylphosphine) were dissolved in 125 mL of CH_2Cl_2, and the resulting solution was treated with 40 mL of 50% NaOH. The mixture was stirred under Ar at room temperature for 3 h by which time TLC indicated the absence of starting aldehyde **8**. The reaction mixture was diluted with water (100 mL), and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layer was washed with water, dried over Na_2SO_4, and concentrated to dryness to produce a solid. Recrystallization of the solid from EtOH afforded 2.91 g (85%) of **9** as colorless needles, mp 134–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 3.90 (s, 3 H), 6.80–6.85 (m, 5 H), 7.34 (dd, 1 H, $J = 1.7$ and 8.3 Hz), 7.40–7.45

(m, 2 H), 7.65 (d, 1 H, $J = 8.3$ Hz), 7.80–7.85 (m, 1 H), 7.93–7.98 (m, 1 H), 8.03 (d, 1 H, $J = 1.4$ Hz). Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.3; H, 5.2. Found: C, 76.1; H, 4.9%.

Oxidative photocyclization of 9

A solution of **9** (0.58 g, 1.67 mmol), iodine (0.42 g), and 1,2-epoxybutane (5 mL) in anhydrous benzene was irradiated by UV (Hanovia lamp) for 12 h. The solution was concentrated to 250 mL and washed with 10% $NaHSO_3$ followed by water. After drying over anhydrous Na_2SO_4, the benzene solution was evaporated under reduced pressure. The crude product was dissolved in EtOAc–hexanes, and kept at −25 °C for a week to produce ~5–6 mg of **5** as a granular solid, mp 231–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 4.05 (s, 3 H), 7.38 (d, 1 H, $J = 9.1$ Hz), 7.47–7.56 (m, 2 H), 7.88 (d, 2 H, $J = 8.4$ Hz), 8.08 (d, 1 H, $J = 9.1$ Hz), 8.26–8.32 (m, 1 H), 8.47 (d, 1 H, $J = 9.1$ Hz), 8.59 (s, 1 H), 9.01 (s, 1 H). HRMS obsd mass 344.087112, calcd for M^+, 344.087105. The mother liquor consisted of a mixture of chromatographically similar compounds including the starting alkene **9**, and a major product **10**, which could not be isolated in pure form from the mixture. ^{1}H NMR of **10** (400 MHz, $CDCl_3$) δ 4.06 (s, 6 H), 7.22 (d, 1 H, $J = 9.2$ Hz), 7.33 (t, 1 H, $J = 8.1$ Hz), 7.43 (t, 1 H, $J = 9.1$ Hz), 7.77–7.85 (m, 2 H), 7.91 (d, 1 H, $J = 8.4$ Hz), 7.95 (d, 1 H, $J = 8.4$ Hz), 8.16 (d, 1 H, $J = 9.1$ Hz), 8.69 (d, 1 H, $J = 8.1$ Hz), 8.78 (d, 1 H, $J = 9.1$ Hz).

2-(Dihydroxyboryl)-5-methoxybenzaldehyde (12)

A mixture of 2-bromo-5-methoxybenzaldehyde **16** (11.2 g, 0.052 mol), redistilled ethylene glycol (70 mL), anhydrous benzene (350 mL), and toluene-*p*-sulfonic acid (0.8 g) was heated under reflux for 20 h. After cooling to rt, the mixture was poured on to 10% aqueous K_2CO_3 (500 mL) contained in a separating funnel. The benzene layer was separated, and washed successively with 10% aqueous K_2CO_3, and brine containing K_2CO_3, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator provided 13.5 g (100%) of the ethylene acetal of **16** as colorless oil.

To a solution of this acetal (13.5 g, 0.052 mol) in dry ether (60 mL) *n*-BuLi (1.6 M, 40 mL, 0.064 mol) in hexane was added in 5 min under nitrogen at −75 °C. After 1 h of stirring of the mixture containing the solid at −75 °C, triisopropyl borate (18.5 mL, 0.08 mol) was added in one portion, and the resulting mixture was allowed to stir at ambient temperature for 2.5 h, and then decomposed by adding 60 mL of 2 M HCl. The resulting mixture was refluxed for 1.5 h with stirring. Most of the products precipitated directly, the rest was recovered by extraction of the ethereal phase with 2 M NaOH and acidification of the extract to produce a combined yield of 8.6 g (92.7%) of **12**, mp 157–161 °C (lit.[23] mp 158–160 °C).

3-(2-Formyl-4-methoxyphenyl)dibenzo[*b*,*d*]thiophene (13)

A mixture of **11** (1.5 g, 5.7 mmol), **12** (1.14 g, 6.3 mmol), anhydrous CsF (2.1 g, 13.8 mmol), and $Pd(PPh_3)_4$ (0.22 g, 0.18 mmol) in anhydrous DME (70 mL) was heated under reflux for 12–18 h under argon. The reaction was monitored by TLC (5% EtOAc–hexanes) until only a trace of or no more bromide was detected. The reaction mixture was cooled and then extracted with a 1 : 1 mixture of EtOAc and water. The ethyl acetate layer was washed with 5% NaOH followed by water to remove any unreacted boronic acid. After drying over anhydrous Na_2SO_4, the EtOAc solution was concentrated *in vacuo* to yield an oil. Column chromatography of the oily product over dry column grade silica gel using hexane as an eluant gave initially a trace amount of **5**, followed by 1.67 g (92%) of **13** as a light yellow solid, mp 148–149 °C (CH_2Cl_2–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 7.25 (dd, 1 H, $J = 2.8$ and 8.5 Hz), 7.42–7.57 (m, 5 H), 7.84 (d, 1 H, $J = 1.1$ Hz), 7.87–7.97 (m, 1 H), 8.19–8.24 (m, 2 H), 10.01 (s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.26, 159.31, 139.77, 139.72, 138.63, 136.08, 135.04, 134.98, 134.64, 132.30, 127.08, 126.87, 124.64, 124.21, 122.94, 121.78, 121.46, 121.32, 110.01, 55.68; MS (*m*/*z*) 318 (M^+, 100). Anal. Calcd for $C_{20}H_{14}O_2S$: C, 75.5; H, 4.4. Found: C, 75.3; H, 4.7%.

3-Methoxyphenanthro[3,2-*b*][1]benzothiophene (6) and 3-methoxyphenanthro[1,2-*b*][1][benzothiophene (15)

To a suspension of **13** (0.64 g, 2 mmol) and trimethylsulfonium iodide (0.44 g, 2.16 mmol) in acetonitrile (30 mL) containing a trace of water (0.1 mL) was added powdered KOH (0.2 g, 5.1 mmol), and the mixture was stirred at 60–65 °C for 20 h under argon. The mixture was poured on to ice-cold water, and extracted with EtOAc. The organic phase was washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation to afford 0.65 g (100%) of sufficiently pure ethylene epoxide **14** as a light yellow thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, 1 H, $J = 2.6$ and 5.9 Hz), 3.10 (dd, 1 H, $J = 4.0$ and 5.5 Hz), 3.85 (s, 3 H), 3.87 (dd, 1 H, $J = 2.6$ and 3.7 Hz), 6.89 (d, 1 H, $J = 2.6$ Hz), 6.92 (dd, 1 H, $J = 2.6$ and 8.4 Hz), 7.31 (d, 1 H, $J = 8.4$ Hz), 7.45–7.52 (m, 3 H), 7.84 (d, 1 H, $J = 1.1$ Hz), 7.83–7.88 (m, 1 H), 8.15–8.22 (m, 2 H).

To a stirred solution of the epoxide **14** (0.60 g, 1.8 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added dropwise 50% $MeSO_3H$ in CH_2Cl_2 (10 mL) during 10 min. The mixture was stirred at rt for 20 h. The CH_2Cl_2 solution was washed successively with water, 10% NaOH, and water, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 0.37 g (65%) of a nearly 1 : 1 mixture of **6** and **15**. The mixture of **6** and **15** (190 mg) was extracted with hot ethanol, and the residue was recrystallized from CH_2Cl_2–hexanes to produce 70 mg of **15**, mp 282–284 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3 H), 7.31 (d, 1 H, $J = 2.2$ Hz), 7.33 (dd, 1 H, $J = 11.7$ and 2.2 Hz), 7.45–7.58 (m, 2 H), 7.83 (d, 1 H, $J = 8.8$ Hz), 7.96 (d, 1 H, $J = 7.3$ Hz), 8.03 (d, 1 H, $J = 8.8$ Hz), 8.23 (d, 1 H, $J = 7.3$ Hz), 8.31 (d, 1 H, $J = 8.8$ Hz), 8.60–8.70 (m, 2 H). MS *m*/*z*: 314 (M^+). Anal. Calcd for $C_{21}H_{14}OS\cdot\frac{1}{20}CH_2Cl_2$: C, 79.4; H, 4.4. Found: C, 79.5; H, 4.6%. The product (~110 mg) isolated from the mother liquor contained 70% **6** and 30% **15**. Further recrystallization of this mixture did not improve the purity of **6**.

1-(2-Bromo-5-methoxyphenyl)-2-(dibenzo[*b*,*d*]thiophen-2-yl)-ethylene (17)

2-Bromo-5-methoxybenzaldehyde (**16**) (1.35 g, 6.3 mmol) and the phosphonium salt **7** (3.24 g, 6.0 mmol, prepared from 2-bromomethyldibenzothiophene and triphenylphosphine) were dissolved in 100 mL of CH_2Cl_2, and the resulting solution was treated with 15 mL of 50% NaOH. The mixture was stirred under Ar at room temperature for 15 h by which time TLC indicated the absence of starting aldehyde **7**. The reaction mixture was diluted with water (50 mL), and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layer was washed with water, dried over Na_2SO_4, and concentrated to dryness. The residue (4.5 g) obtained as a semisolid was stirred with 100 mL of hexane, and filtered. The filtrate was passed through a small column of dry column grade silica gel. Elution of the column with hexane afforded a mixture of the *Z*- and *E*-isomers of **17** (2.4 g, 100%) as a colorless oil, $Z : E \approx 4$. The mixture of alkenes was used in the next step. A small sample of the mixture was separated by preparative TLC using 2% EtOAc–hexane as the developing solvent. Relatively nonpolar *Z*-isomer: oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3 H), 6.68 (d, 1 H, $J = 12.0$ Hz), 6.70 (dd, 1 H, $J = 3$ and 8.6 Hz), 6.78 (d, 1 H, $J = 3$ Hz), 6.86 (d, 1 H, $J = 12.1$ Hz), 7.24–7.29 (m, 1 H), 7.39–7.56 (m, 3 H), 7.65 (d, 1 H, $J = 8.3$ Hz), 7.80–7.85 (m, 1 H), 7.93–8.00 (m, 2 H). HRMS obsd mass 393.999233, calc. for M^+, 394.002698. *E*-isomer: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 6.73 (dd, 1 H, $J = 8.8$ and 3.0 Hz), 7.19 (d, 1 H, $J = 16.1$ Hz), 7.24 (d,

1 H, J = 3 Hz), 7.46–7.57 (m, 4 H), 7.69 (dd, 1 H, J = 8.3 and 1.7 Hz), 7.82–7.88 (m, 2 H), 8.19–8.27 (m, 2 H). HRMS obsd mass 393.999233, calcd for M^+, 394.002698.

3-Methoxyphenanthro[3,2-*b*][1]benzothiophene (6) and 3-methoxyphenanthro[3,4-*b*][1]benzothiophene (18)

A solution of **17** (4.7 g, 11.88 mmol) and KOH (4.7 g, 83.8 mmol) in 40 mL of redistilled quinoline was heated at reflux for 3 h. The mixture was cooled, poured into ice, acidified carefully with concentrated sulfuric acid, and extracted with CH_2Cl_2 four times. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated, affording the products as a dark yellow–brown solid. Trituration of the solid with EtOAc produced 0.70 g (19%) of TLC pure **6**, mp 222–224 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 3 H), 7.30 (d, 1 H, J = 2.4 Hz), 7.32 (dd, 1 H, J = 2.4 and 8.8 Hz), 7.49–7.55 (m, 2 H), 7.68 (d, 1 H, J = 8.8 Hz), 7.87–7.92 (m, 2 H), 8.27–8.31 (m, 1 H), 8.60 (s, 1 H), 8.65 (d, 1 H, J = 9.1 Hz), 9.02 (s, 1 H). MS (*m*/*z*, relative intensity) 314 (M^+, 100%), 271 (70). Anal. Calcd for $C_{21}H_{14}OS$: C, 80.2; H, 4.5. Found: C, 80.1; H, 4.7%.

Chromatography of the product obtained from the mother liquor over dry column grade silica gel using hexane as eluant gave first 1.9 g (51%) of **18** [mp 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 3 H), 7.15 (dd, 1 H, J = 2.4 and 9.1 Hz), 7.33 (d, 1 H, J = 2.4 Hz), 7.35 (dd, 1 H, J = 7.9 and 7.3 Hz), 7.45 (dd, 1 H, J = 7.0 and 7.9 Hz), 7.76 (d, 1 H, J = 8.5 Hz), 7.80–7.85 (m, 2 H), 7.91 (d, 1 H, J = 8.2 Hz), 7.96 (d, 1 H, J = 8.0 Hz), 8.68 (d, 1 H, J = 8.2 Hz), 8.94 (d, 1 H, J = 9.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.87, 140.58, 140.01, 137.30, 135.18, 130.26, 130.15, 130.00, 128.78, 127.92, 127.66, 126.22, 126.20, 125.64, 123.75, 123.38, 121.02, 115.12, 107.92, 55.87. MS (*m*/*z*) 314 (M^+, 100%), 298 (12), 282 (28), 269 (49). Anal. Calcd for $C_{21}H_{14}OS{\cdot}\frac{1}{3}H_2O$: C, 79.3; H, 4.5. Found: C, 79.0; H, 4.5%] followed by 0.15 g (4.0%) of an additional amount of **6**.

3-Hydroxyphenanthro[3,2-*b*][1]benzothiophene (19)

A solution of 1 M BBr_3 (4.0 mL, 4.0 mmol) in CH_2Cl_2 was added by syringe to a stirred solution of **6** (0.6 g, 1.91 mmol) in 125 mL of anhydrous CH_2Cl_2 at 0 °C. After stirring for 12 h at rt, the mixture was hydrolyzed with ice-cold water. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford a solid. The solid was triturated with hexane and filtered to produce 0.55 g (96%) of **19** as a light brown crystalline solid, mp 294–296 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, 1 H, J = 2.4 and 8.8 Hz), 7.38 (d, 1 H, J = 2.4 Hz), 7.57–7.62 (m, 2 H), 7.72 (d, 1 H, J = 8.8 Hz), 7.96 (d, 1 H, J = 9.1 Hz), 8.01–8.05 (m, 1 H), 8.45–8.50 (m, 1 H), 8.84 (d, 1 H, J = 8.8 Hz), 8.86 (s, 1 H), 9.29 (s, 1 H), 9.97 (s, 1 H, exchangeable with D_2O). HRMS obsd mass 300.059422, calcd for M^+, 300.060887. Anal. Calcd for $C_{20}H_{12}OS{\cdot}\frac{3}{4}H_2O$: C, 76.5; H, 4.3. Found: C, 76.3; H, 4.0%.

Phenanthro[3,2-*b*][1]benzothiophene-3,4-dione (20)

To a stirred mixture of **19** (0.55 g, 1.83 mmol), $\frac{1}{6}$M KH_2PO_4 (200 mL), and Fremy's salt (1.5 g, 5.6 mmol) in 100 mL of CH_2Cl_2 and 300 mL of benzene was added 5–6 drops of Adogen 464, and stirring was continued for 12 h. The mixture was filtered to recover 0.2 g of phenol **19**. The filtrate was added to 0.25 g (0.83 mmol) of Fremy's salt, and the stirring was continued for an additional 5 h. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was triturated with CH_2Cl_2–hexane to yield 0.35 g (95% based on recovered **19**) of **20** as a bright purple crystalline solid, mp 267–269 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (d, 1 H, J = 10.4 Hz), 7.50–7.66 (m, 2 H), 7.90 (d, 1 H, J = 7.6 Hz), 8.16–8.24 (m, 2 H), 8.34 (d, 1 H, J = 7.6 Hz), 8.42 (d, 1 H, J = 10.7 Hz), 8.66 (s, 1 H), 8.75 (s, 1 H). HRMS obsd mass 314.039714, calcd for M^+, 314.040151.

(±)-*trans*-3,4-Dihydroxy-3,4-dihydrophenanthro[3,2-*b*][1]benzothiophene (3)

To a stirred suspension of **20** (0.35 g, 1.14 mmol) in 150 mL of ethanol was added $NaBH_4$ (1.2 g, 33.33 mmol) in portions. The mixture was stirred for 4 days while bubbling oxygen through the solution. A nearly colorless solution of the reaction mixture was poured on to ice, and extracted with ethyl acetate three times. The combined organic phase was washed with water, dried (Na_2SO_4), and concentrated. The resulting residue was triturated with cold ether, and filtered to afford 0.14 g (40%) of **3** as a light grey crystalline solid, mp (sealed tube) 215–218 °C (decomp.). ^{1}H NMR (300 MHz, acetone-d_6 + MeOH-d_4) δ 4.48–4.51 (m, 1 H), 4.90 (d, 1 H, J = 11.7 Hz), 6.24 (dd, 1 H, J = 2.2 and 10.1 Hz), 7.39 (dd, 1 H, J = 2.4 and 10.1 Hz), 7.50–7.62 (m, 2 H), 7.92 (d, 1 H, J = 8.6 Hz), 7.93–8.01 (m, 1 H), 8.07 (d, 1 H, J = 8.6 Hz), 8.40–8.48 (m, 1 H), 8.81 (s, 1 H), 8.86 (s, 1 H). UV λ_{max} (EtOH) 384 (ε/mol^{-1} dm^3 cm^{-1} 3830), 367 (4734), 348 (5447), 332 (7058), 302 (17175), 286 (38984). HRMS obsd mass 300.06249, calcd for $M^+ - H_2O$, 300.06089. Anal. Calcd for $C_{20}H_{14}O_2S{\cdot}\frac{1}{2}Et_2O$: C, 74.4; H, 5.4. Found: C, 74.2; H, 5.7%.

Analytical HPLC of **3** was achieved on a Zorbax C-18 column (4.6 × 250 mm) using a linear gradient (1% min^{-1}) from 70% MeOH–water to 100% MeOH for 30 min with a flow rate of 1 mL min^{-1}, and the eluants were monitored at 254 nm. These HPLC conditions showed the elution of **3** as a single peak at 18.3 min. Analytical HPLC of a mixture of the dihydrodiols obtained from a 7 : 3 mixture of **6** and **15** (*vide supra*) consisted of two peaks at 18.3 and 19.7 min, respectively. The relatively polar dihydrodiol (18.3 min) that coeluted with **3** had a UV spectrum identical to that of **3**.

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References

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