Synthesis of *trans*-Dihydrodiol Derivatives of Phenanthro[3,4-*b*]-thiophene and Phenanthro[4,3-*b*]thiophene†

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The present study describes the synthesis of phenanthro[3,4-*b*]thiophene (**3**), phenanthro[4,3-*b*]thiophene (**4**) and its potential dihydrodiol metabolites, *trans*-6,7-dihydroxy-6,7-dihydrophenanthro[3,4-*b*]thiophene (**5**) and *trans*-8,9-dihydroxy-8,9-dihydrophenanthro[3,4-*b*]thiophene (**6**), *trans*-6,7-dihydroxy-6,7-dihydrophenanthro[4,3-*b*]thiophene (**7**) and *trans*-8,9-dihydroxy-8,9-dihydrophenanthro[4,3-*b*]thiophene (**8**) from Suzuki coupled intermediates. The UV spectra of these dihydrodiols are presented. These spectra are useful tools for identifying these dihydrodiols among unknown metabolites of **1** and **2** produced *in vitro* or *in vivo*.

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Introduction.

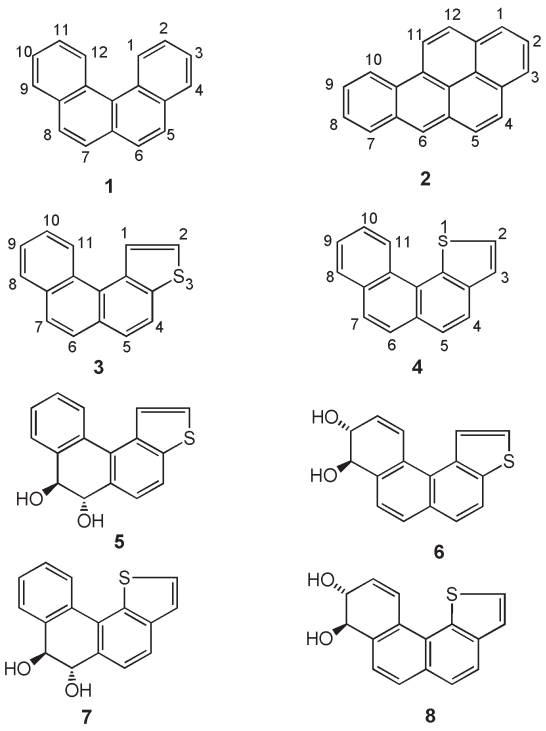
Polynuclear aromatic hydrocarbons (PAHs) are well identified in cigarette smoke condensate and tobacco products [1,2]. In contrast, the presence of polynuclear aromatic sulfur heterocycles (thia-PAHs) in tobacco smoke or products is not well documented. However, there is now increasing evidence that thia-PAHs concomitantly occurs with PAHs in these matrices [3-9]. In addition, some of the thia-PAHs are relatively more persistent [10-12] and carcinogenic [13,14] than the well studied PAHs, and consequently may pose greater risk to human health compared to PAHs. Although a number of thia-PAHs are known carcinogens and mutagens [3,15,16], not much is known about the mechanism of their mutagenic/carcinogenic action.

Metabolically formed bay-region and fjord-region diol epoxides [17] are known ultimate carcinogens of polycyclic aromatic hydrocarbons [18,19]. However, it is yet to be established whether analogous diol epoxides are the ultimate carcinogens of carcinogenic thia-PAHs. Synthesis of dihydrodiol and other derivatives of benzo[*b*]naphtho[2,1-*d*]thiophene [20] and benzo[*b*]phenanthro[2,3-*d*]thiophene [21] has made it possible to obtain data on the metabolic activation of thia-PAHs with central thiophene ring. These data show that the dihydrodiols with a bay-region double bond are the metabolites of these thia-PAHs [22,23], and exhibit mutagenic activity similar to or higher than that of the parent thia-PAHs [20,24]. In addition to dihydrodiols, sulfoxide and sulfones are also the major metabolites of these thia-PAHs [22,23]. Interestingly, our recent study [24] has shown for the first time that benzo[*b*]phenanthro[2,3-*d*]thiophene sulfoxide is more mutagenic than the dihydrodiol derivative of benzo[*b*]phenanthro[2,3-*b*]thiophene, suggesting the potential role of thia-PAH sulfoxides in the metabolic activation of carcinogenic thia-PAHs with central thiophene ring.

In addition to thia-PAHs with central thiophene ring, thia-PAHs with peripheral thiophene ring (thiophene-annulated PAHs) are also highly mutagenic [3,16]. In fact, some of the tri- and tetracyclic thia-PAHs of this class exhibit much higher mutagenic activity [3,16] compared to their carbon analogs [25,26]. Structure-activity relationship studies of thia-PAHs with peripheral thiophene ring have indicated that both the presence and the position of sulfur heteroatom in a PAH have a marked influence on the mutagenic/carcinogenic activity of these hydrocarbons [3,16]. For example, phenanthro[3,4-*b*]thiophene (**3**), a sulfur analog of weakly mutagenic benzo[*c*]phenanthrene (**1**) [25], is as potent a mutagen as benzo[*a*]pyrene (**2**) [16]. In contrast, phenanthro[4,3-*b*]thiophene (**4**), an isoster of **3**, is relatively non-mutagenic. The high mutagenic activity of **3** in contrast to weak mutagenicity of the two closely related isosteric molecules **1** and **4** is interesting from a structure-activity standpoint. In order to examine factors involved in determining the mutagenicity/carcinogenicity of thia-PAHs, and to determine whether fjord-region diol epoxide pathway can explain underlying differences in the biological activities of **3** and **4**, we required various dihydrodiol derivatives of **3** and **4** in sufficient amounts for assessing their role in the metabolic activation of these thia-PAHs. In the present study, we report the synthesis of **3**, **4** and of their 6,7-dihydrodiols (**5** and **7**) and 8,9-dihydrodiols (**6** and **8**).

Results and Discussion.

The synthesis of dihydrodiols **5** - **8** is not reported in the literature. However, several procedures for the syntheses of the parent thia-PAHs **3** and **4** have been described [3,27]. Among these, the Wadsworth-Emmons reaction between 2-naphthaldehyde and 3-thenylphosphonate (or 2-thenylphosphonate) with a subsequent photocyclization of resulting olefins appears to be the most convenient one. The analogous procedure has also been applied for the synthesis of various dihydrodiol derivatives of PAHs [28-30], and can be used for the synthesis of **5** - **8**. However, the overall low yield (~ 12%) of **3**, and the involvement of photocyclization as a scale-limiting step prompted us to investigate Suzuki cross coupling reaction [31] for their synthesis. We have applied this versatile reaction



previously for developing synthesis of thia-PAHs with a central thiophene ring, and their dihydrodiol derivatives [21,32,33]. However, its application in synthesis of thiophene-annulated PAHs and their dihydrodiol derivatives has not been investigated.

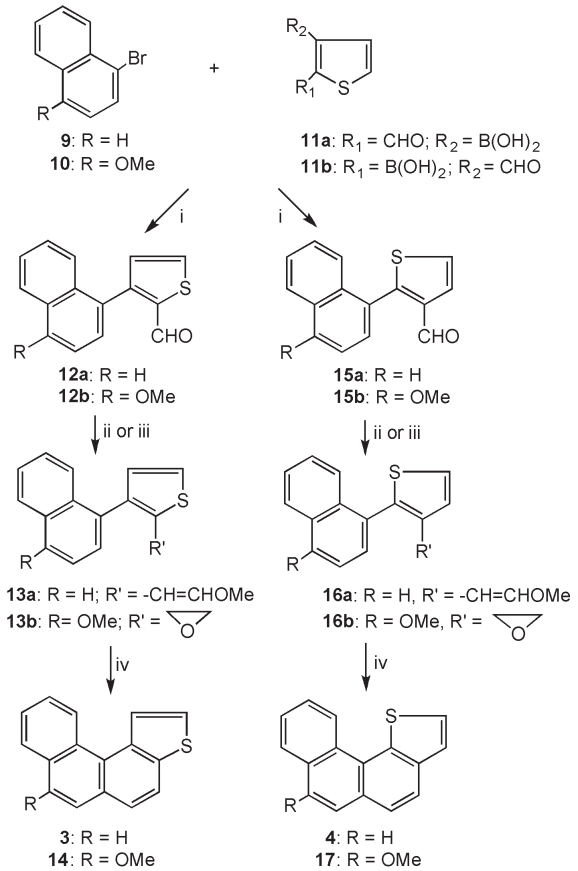
Synthesis of **3** and **4**.

Synthesis of the parent thia-PAHs **3** and **4** began with the Suzuki cross coupling reaction of 1-bromonaphthalene (**9**) with 2-formylthiophene 3-boronic acid (**11a**) and 3-formylthiophene 2-boronic acid (**11b**) to produce the coupling product **12a** and **15a** in 96% and 58% yield, respectively (Scheme 1). Of the two approaches described earlier [34], ethylene epoxide approach was initially investigated for the transformation of **12a** and **15a** to the corresponding thia-PAHs **3** and **4**. However, this approach was not very productive due to an overall low yield (~ 7%) of these thia-PAHs. Therefore, we investigated the second approach (Scheme 1) in which **12a** and **15a** were treated with the Wittig reagent obtained from (methoxymethyl)triphenylphosphonium chloride. In previous studies [29,34], Wittig reagent from (methoxymethyl)-triphenylphosphonium chloride has been generated by phenyl lithium, which is not available any more from commercial sources. Therefore, potassium *t*-butoxide which has recently been developed by Upadhaya *et al.* [35] to generate ylide was substituted for phenyl lithium to generate Wittig reagent from (methoxymethyl)triphenylphosphonium chloride *in situ* that reacted with **12a** and **15a** to produce **13a** and **16a** as a mixture of *cis* and *trans* isomers (^{1}H NMR). Acid-catalyzed cyclization of the *cis*/*trans* mixture of **13a** and **16a** with $MeSO_3H$ afforded **3** and **4** in 40-63% overall yield. In a parallel study, **4** was also synthesized by the Suzuki reaction of 2-formylphenylboronic acid (**33a**) with 7-bromobenzo[*b*]-thiophene (**34**) (Scheme 5). However, the overall yield of **4** was higher when synthesized *via* Scheme 1.

Synthesis of Dihydrodiols **5** and **7**.

The procedure successfully used in the past in the synthesis of K-region dihydrodiols of PAHs involves sodium borohydride mediated reduction of the corresponding dione [36]. However, the synthesis of these dione requires initial oxidation of carcinogenic PAHs with highly toxic osmium tetroxide [19]. There is a precedent in the literature [37] for the synthesis of K-region dione in high yields by the oxidation of the corresponding K-region phenols with Fremy's salt. Consequently, 7-methoxy derivatives of **3** and **4** (*i.e.* **14** and **17**) were selected as starting intermediates for the synthesis of **5** and **7**. The success of the approach involving Suzuki cross coupling reaction in the synthesis of **3** and **4** prompted us to develop similar approach for the synthesis of their 7-methoxy derivatives **14** and **17** (Scheme 1). However, this approach was later abandoned due to the formation of **14** or **17** in impractical

Scheme 1 [a]

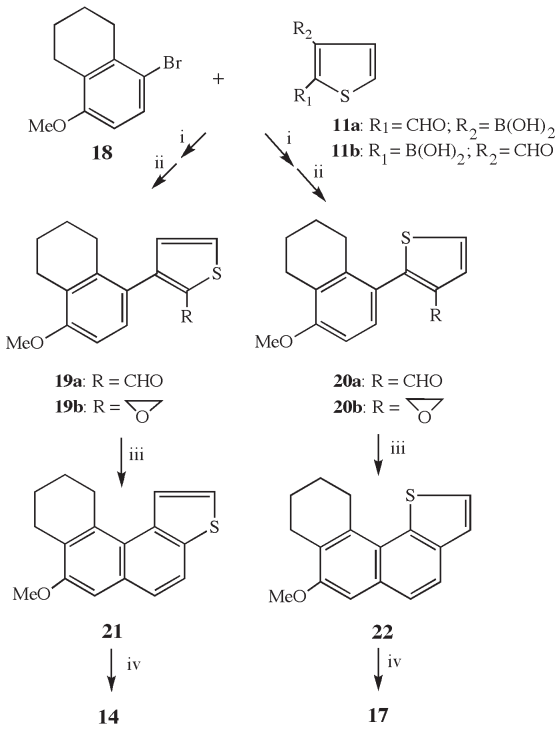


[a] Reagents: i, $Pd(PPh_3)_4$-CsF/DME; ii, $Me_3S^+I^-$-KOH/MeCN; iii MeOCH = PPh_3/THF; iv, $MeSO_3H/CH_2Cl_2$

amounts (2-5%) during acid-catalyzed cyclization of ethylene epoxide **13b** or **16b**. Lack of activation at position 2 of the naphthalene moiety of **13b** or **16b** due to the presence of the methoxy substituent at *meta* position, presumably, does not facilitate intramolecular cyclization reaction at position 2 in these molecules. In view of this difficulty, an alternate approach involving the synthesis of the 5,6,7,8-tetrahydro analogs **21** and **22** was considered (Scheme 2) with the belief that the presence of electron donating tetrahydro-ring will enhance the acid-catalyzed intramolecular cyclization at position 2 of **19b** and **20b**. Synthesis of **21** and **22** required 1-bromo-4-methoxy-5,6,7,8-tetrahydronaphthalene (**18**) which was synthesized by bromination of 1-methoxy 5,6,7,8-tertahydronaphthalene [38] in acetic acid following a procedure analogous to that reported for 4-methoxyindan [39]. Coupling of **18** with boronic acid **11a** or **11b** occurred in low yield (< 10%) in the presence of $Pd(Ph_3P)_4$, presumably, because electron rich aryl halides are usually difficult to be activated in cross coupling reactions [40]. Recently, Littke *et al*. [41] have used catalytic condition involving $Pd_2(dba)_3$, $(t\text{-}Bu)_3P$ and KF for preparing coupling products in high yields from a number of aryl halides including those which are highly electron-rich. We also noted that the coupling of **18** with **11a** and **11b** under these conditions produced the corresponding **19a** and **20a** in reasonably good yield (57-75%). The aldehydes **19a** and **20a** were converted to the corresponding tetrahydro analogs **21** and **22** *via* ethylene epoxides **19b** and **20b** in 20-21% yield. Aromatization of the tetrahydro-ring of **21** and **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene afforded **14** and **17**, respectively, in 87-91% yield.

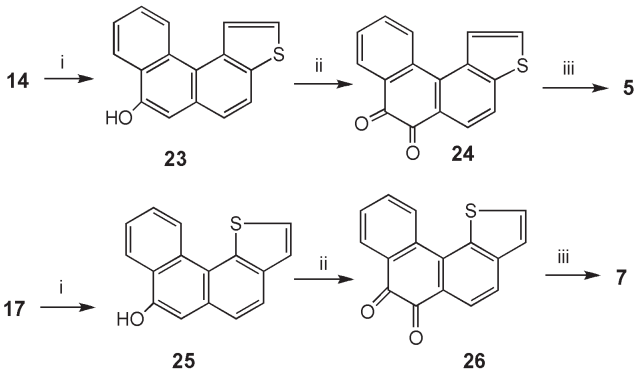
The conversion of the methoxy derivatives **14** and **17** to the corresponding K-region dihydrodiols **5** and **7** (Scheme 3) was accomplished by their demethylation with BBr_3 to phenols **23** and **25** (80-90% yields), which were then oxidized by Fremy's salt to produce the diones **24** and **26** in 75% and 35%, respectively. Finally, the reduction of the diones **24** and **26** to the corresponding dihydrodiols **5** and **7** with *trans*-stereospecificity was achieved in 27% and 60% yield, respectively, by $NaBH_4$ in the presence of O_2. The presence of oxygen is essential for the successful reduction of *o*-quinone to dihydrodiol because it reoxidizes the catechol, a major product of such a reaction, back to *o*-quinone. Consequently, the end product of this reduction-oxidation process in the presence of oxygen is pure dihydrodiol.

Scheme 2 [a]



[a] Reagents: i, $Pd_2(dba)_3$-KF-(t-Bu_3)P/THF; ii, $Me_3S^+I^-$-KOH/MeCN; iii, $BF_3.Et_2O/Et_2O$; iv, DDQ/benzene

Scheme 3 [a]

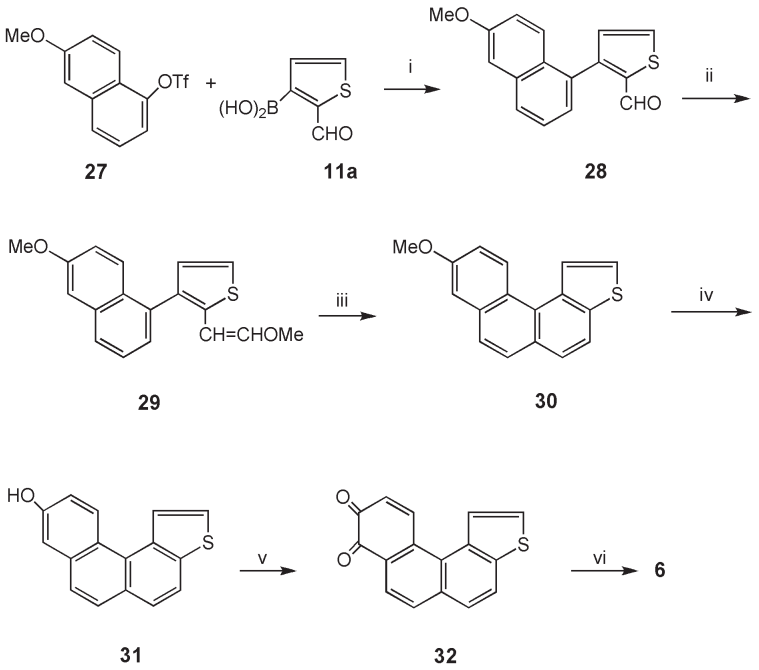


[a] Reagents: i, BBr_3/CH_2Cl_2; ii, Fremy's salt/CH_2Cl_2-Phosphate buffer; iii, $NaBH_4$-O_2/EtOH

Synthesis of Dihydrodiols **6** and **8**.

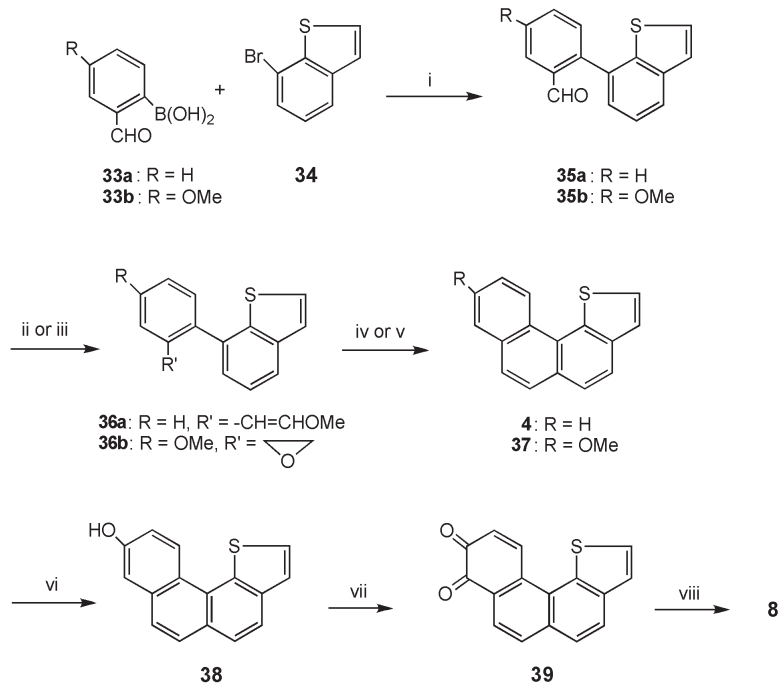
The synthetic route to **6** (Scheme 4) involves in the key step Suzuki coupling of 2-formylthiophene 3-boronic acid (**11a**) with 6-methoxy-1-naphthyl triflate (**27**). The triflate **27** was synthesized from 6-methoxy-1-tetralone *via* 6-methoxy-1-naphthol. Dehydrogenation of 6-methoxy-1-tetralone with Pd/C was not satisfactory, especially, when the reaction was carried out in large scale [42]. However, the use of *p*-cymene as a co-solvent produced the desired 6-methoxy-1-naphthol in fairly good yield (70%). Subsequent treatment of 6-methoxy-1-naphthol with triflic anhydride in the presence of Et_3N gave **27** in 50% yield. Coupling of **27** with **11a** proceeded smoothly in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 and KBr to furnish **28** in 70% yield. The yield of **28** was nearly 50% when the coupling reaction was

Scheme 4 [a]



[a] Reagents: i, $Pd(PPh_3)_4$-KBr-Na_2CO_3/DME; ii, MeOCH = PPh_3/THF; iii, $MeSO_3H/CH_2Cl_2$; iv, BBr_3/CH_2Cl_2; v, Fremy's salt/CH_2Cl_2-Phosphate buffer; vi, $NaBH_4$-O_2/EtOH

Scheme 5[a]



[a] Reagents: i, $Pd(PPh_3)_4$-CsF/DME; ii, $Me_3S^+I^-$-KOH/MeCN; iii, MeOCH = PPh_3/THF; iv, $MeSO_3H/CH_2Cl_2$; v, $BF_3.Et_2O/Et_2O$; vi, BBr_3/CH_2Cl_2; vii, Fremy's salt/CH_2Cl_2-Phosphate buffer; viii, $NaBH_4$-O_2/EtOH

carried out in the presence of CsF as described for **12a** (Scheme 1). Wittig reaction of **28** with methoxymethylene-triphenylphosphine gave methoxyethylene derivative **29** as a 3:1 mixture of *cis* and *trans* isomers. Acid-catalyzed cyclization of **29** with $MeSO_3H$ in CH_2Cl_2 produced **30** in overall 56% yield based on aldehyde **28**. The presence of two characteristic doublet peaks at 8.57 and 9.02 ppm as expected for the fjord-region H-1 and H-11 protons in the ^1H NMR of **30** was consistent with its structure. Demethylation of **30** with BBr_3 provided the free phenol **31** as a sole product. Oxidation of **31** with Fremy's salt gave the dione **32** in 66% yield. Reduction of dione **32** with $NaBH_4$ in the presence of O_2 provided the dihydrodiol **6** in 31-48% yield with *trans*-stereospecificity as judged by its ^1H NMR.

Synthesis of the dihydrodiol **8** was accomplished by $Pd[PPh_3)_4$–catalyzed coupling of 2-formyl-4-methoxy-phenylboronic acid (**33b**) [21] with 7-bromobenzo[*b*]thiophene (**34**) [43] (Scheme 5). Thus, the Suzuki coupling of **33b** with **34** furnished the expected coupling product **35b** in 85% yield. The aldehyde **35b** was subsequently converted to **37** *via* the ethylene epoxide **36b** in an overall yield of 45-55%. Conversion of **37** to dihydrodiol **8** with *trans*-stereoselectivity was carried out as described above for the synthesis of **6** from **30**. In this case, the synthesis of phenol **38**, dione **39**, and dihydrodiol **8** was accomplished in equal or greater than 80% yields.

The ^1H NMR spectra of isomeric dihydrodiols **5** – **8** are consistent with their structure. A relatively small coupling constants between carbinol protons of **5** in DMSO-d_6 ($J_{6,7}$ = 4.14 Hz) compared to in $CDCl_3$ ($J_{6,7}$ = 11.0 Hz) indicates that the carbinol protons of **5** in DMSO-d_6 exist in *quasi*-diequitorial conformation. Evidently, *quasi*-diequitorial hydroxyl groups in **5** are extensively hydrogen bonded intramolecularly to each other when $CDCl_3$ is the solvent, whereas in DMSO the presence of stronger intermolecular hydrogen bonds to solvent results in the *quasi*-diaxial conformation of vicinal hydroxyl group of **5**. As expected, the fjord-region proton (H-11) of **3**, **4** and their methoxy derivatives absorbs at very low field (9.05 – 9.24 ppm), and its chemical shift is not very much affected (< 0.2 ppm) by the presence of sulfur heteroatom in the same fjord-region. The UV spectra of dihydrodiols **5** - **8** are shown in Figure 1 and Figure 2. These spectra are useful tools for identifying these dihydrodiols among unknown metabolites of **1** and **2** produced *in vitro* or *in vivo*.

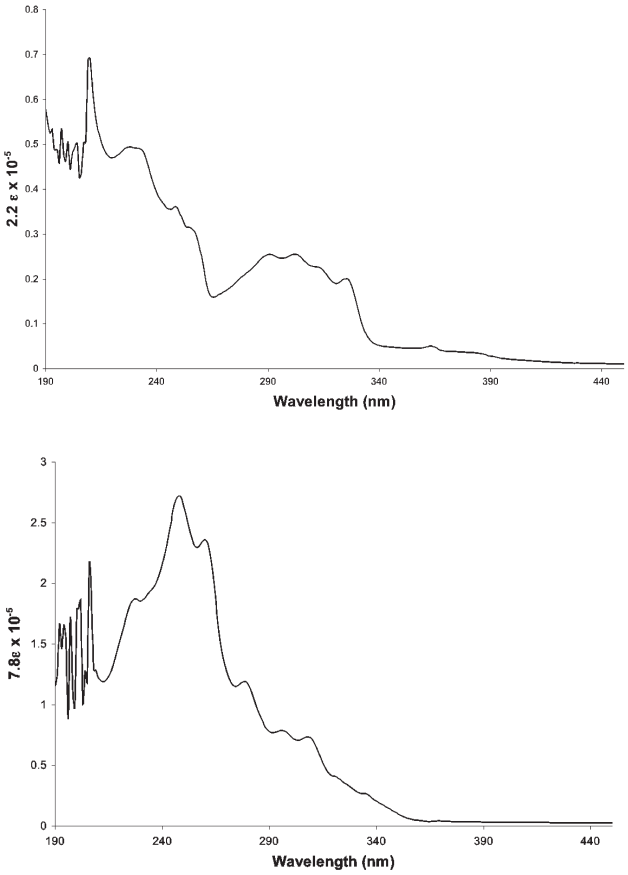


Figure 1. UV spectra of dihydrodiols **5** (top) and **6** (bottom) in 10% THF-EtOH.

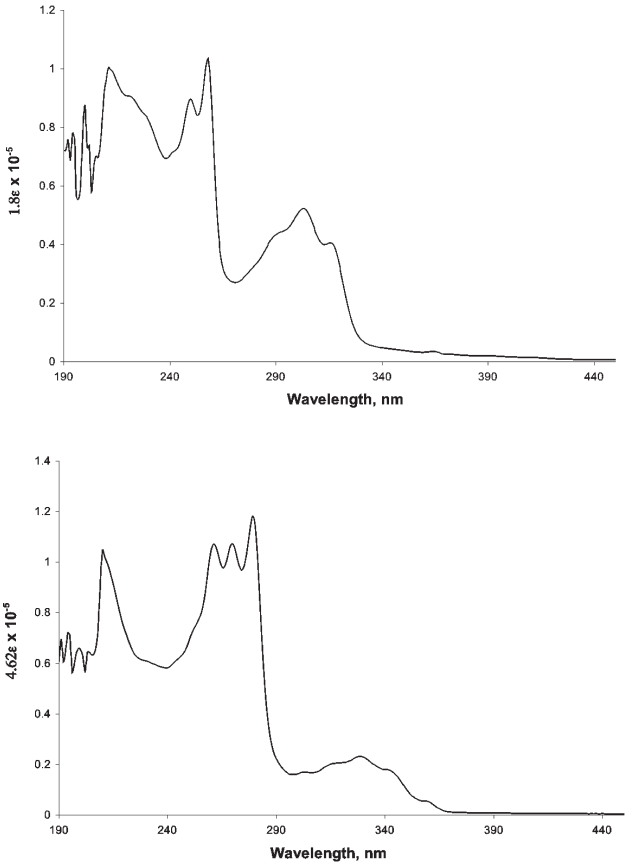


Figure 2. UV spectra of dihydrodiols **7** (top) and **8** (bottom) in 10% THF-EtOH.

EXPERIMENTAL

1-Methoxy-5,6,7,8-tetrahydronaphthalene [38], and 7-Bromobenzo[b]thiophene (**34**) [43] were prepared as described in the literature. 2-Formyl-4-methoxyphenylboronic acid (**33b**) was synthesized by a published procedure [21]. 2-Formylphenylboronic acid (**33a**), 2-formylthiophene 3-boronic acid (**11a**) and 3-formylthiophene 2-boronic acid (**11b**), $Pd(PPh_3)_4$, tris(dibenzylideneacetone)dipalladium(0), other reagents and solvents (anhydrous or otherwise) were obtained commercially and used as received. Dry column grade silica gel (63-200 μm) was purchased from E-Merck. ^{1}H- and ^{13}C-NMR spectra were recorded on a 300 MHz NMR spectrometer in an appropriate solvent with tetramethylsilane (TMS) as an 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. High resolution mass spectral data were obtained at the mass spectral facility of the Department of Chemistry, State University of New York at Buffalo. All the melting points were uncorrected.

*Caution! Phenanthro[3,4-b]thiophene (**3**), phenanthro[4,3-b]-thiophene (**4**), and their derivatives are potential mutagens/ carcinogens and should be handled in accordance with NIH guidelines for the Laboratory Use of Chemical Carcinogens.*

3-(1-Naphthyl)thiophene-2-carboxaldehyde (**12a**).

A reaction mixture containing 1-bromonaphthalene (**9**) (2.0 g, 10 mmol), 2-formylthiophene 3-boronic acid (**11a**) (1.72 g, 11 mmol), CsF (3.5 g, 23 mmol), and $Pd(PPh_3)_4$ (200 mg, 0.17 mmol) in DME (35 mL) was heated at reflux for 4 h. The mixture was cooled, concentrated under reduced pressure, and then extracted with EtOAc (2 x 50 mL). The combined EtOAc solution was washed with 5% NaOH and water, and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column. Elution of the column with hexane followed by 30% CH_2Cl_2-hexane provided (2.22 g, 96%) of **12a** as a light yellow oil; ^{1}H NMR($CDCl_3$) δ 7.28 (d, 1 H, *J* = 4.9 Hz), 7.44-7.59 (m, 4 H), 7.71-7.79 (m, 1 H), 7.81-7.87 (m, 1 H), 7.91-7.99 (m, 2 H) , 9.59 (d, 1 H, *J* =1.3 Hz). ^{13}C NMR ($CDCl_3$) δ 184.0, 149.9, 140.3, 133.7, 133.6, 132.3, 131.9, 131.5, 129.3, 128.6, 128.5, 126.9, 126.4, 125.6, 125.1.

Anal. Calcd. for $C_{15}H_{10}OS$ (M^+): 238.0447. Found (EI): [M^+], 238.0445.

Phenanthro[3,4-*b*]thiophene (**3**).

To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (0.15 g, 0.46 mmol) in dry THF (15 mL) was added potassium *tert*-butoxide (0.05 g, 0.45 mmol) under argon, and the mixture was stirred for 30 min. A solution of the aldehyde **12a** (0.1 g, 0.42 mmol) in dry THF (5 mL) was added dropwise, and the reaction mixture was stirred at rt for 1 h. After treating with ice-cold water, the reaction mixture was extracted with EtOAc, and the EtOAc layer was washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oily product containing **13a** as a 1:2 mixture of *cis* and *trans* isomers. Partial ^{1}H NMR ($CDCl_3$): for *cis* isomer, two doublet at δ 5.30 and 5.98 (*J* = 6 Hz); for *trans* isomer, two doublets at δ 5.65 and 6.97 (*J* = 12 Hz). MS (EI): m/z 267 (M^+ + 1).

To a stirred solution of the isomeric mixture of alkene **13a** (0.2 g, 0.75 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added $MeSO_3H$ (0.5 mL) in 5 min. The reaction mixture was then stirred for an additional 2 h at 0 °C, and diluted with water. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. Concentration of the solution *in vacuo* produce a semisolid which was further purified by column chromatography over dry column grade silica gel using hexane as eluant to produce 0.12 g (68%) of **3** as a colorless crystalline solid, mp 82-83 °C (Reported [27] mp 82.5-83.5 °C). ^{1} H NMR ($CDCl_3$) δ 7.72 (dt, 1 H, *J* = 1.1 and 8.0 Hz), 7.75-7.85 (m, 2 H), 7.87- 7.99 (m, 3 H), 8.08 (d,1 H, *J* = 7.8 Hz), 8.16 (d, 1 H, *J* = 8.4 Hz), 8.72 (d, 1 H, *J* = 5.6 Hz), 9.23 (d, 1 H, *J* = 8.4 Hz).

2-(1-Naphthyl)thiophene-3-carboxaldehyde (**15a**).

A mixture of 3-formylthiophene-2-boronic acid (**11b**) (1.72 g, 11 mmol), 1-bromonaphthalene (**9**) (2.0 g, 10 mmol), anhydrous CsF (3.5 g, 23 mmol), and $Pd(PPh_3)_4$ (0.2 g, 0.17mmol) in anhydrous DME (60 mL) was refluxed for 18 h under argon. The reaction mixture was worked up and purified by column chromatography as described for **12a** to afford 1.06 g (46%) of **15a** as a colorless solid, mp 74-75 °C. ^{1}H NMR ($CDCl_3$): δ 7.42 (dd, 1 H, *J* = 0.8 and 5.4Hz), 7.48-7.60 (m, 4 H), 7.65 (d, 1 H, *J* = 5.4 Hz), 7.77-7.82 (m, 1 H), 7.90-8.01 (m, 2 H), 9.49 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 185.7, 153.5, 139.4, 133.6, 133.1, 130.1, 129.7, 128.5, 128.4, 127.3, 126.5, 126.0, 125.6, 125.3, 124.9.

Anal. Calcd. for $C_{15}H_{10}OS$: C, 75.63; H, 4.20. Found: C, 75.75; H, 4.39. *Anal.* Calcd. for $C_{15}H_{10}OS$ [M^+]: 238.0447. Found (EI): [M^+], 238.0443.

7-(2-Formylphenyl)benzo[*b*]thiophene (**35a**).

A mixture of 2-formylphenylboronic acid (**33a**) (0.74 g, 5 mmol), 7-bromobenzo[b]thiophene (**34**) (1.06 g, 5 mmol), anhydrous CsF (1.57 g, 10.3 mmol), and $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol) in anhydrous DME (30 mL) was heated under reflux for 20 h under argon. The reaction was monitored by TLC (5% EtOAc-hexane) until no more bromide was detected. The reaction mixture was then cooled, mixed with water, and then extracted with EtOAc (2 X 100 mL). The EtOAc layer was separated, washed with cold 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 produce 0.58 g (49%) of **35a** as an oil. ^{1}H NMR ($CDCl_3$): δ 7.27 (dd, 1 H, *J* = ~ 7 and 0.7 Hz), 7.41-7.53 (m, 3 H), 7.60 (m, 2 H), 7.68-7.75 (m, 1 H), 7.90 (dd, 1 H, *J* = 8 and 1 Hz), 8.09-8.13 (m, 1 H), 9.77 (d, 1 H, *J* = 0.6 Hz); ^{13}C NMR ($CDCl_3$): δ 192.4, 144.2, 140.9, 140.0, 134.0, 133.8, 132.6, 130.5, 128.7, 127.7, 127.4, 126.1, 124.5, 124.4, 123.6.

Anal. Calcd. for $C_{15}H_{10}OS$ (M^+): 210.0503. Found (EI): [M^+], 210.0496.

Phenanthro[4,3-*b*]thiophene (**4**).

Method A: Potassium *t*-butoxide (40 mg, 0.36 mmol) was added in a single portion to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (0.12 g, 0.36 mmol) in anhydrous THF (10 mL) at rt under argon. After stirring the reaction mixture for 0.5 h, a solution of the aldehyde **15a** (1.0 g, 4.1 mmol) in anhydrous THF (40 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was diluted with ice-cold water, and extracted with EtOAc. The EtOAc layer was separated, washed with ice-cold water and dried (Na_2SO_4). Removal of the solvent gave 1.08 g (100%) of an oil containing a 1:1 mixture of *cis* and *trans* isomer of **16a**. Partial ^{1}H NMR: for *cis* isomer, two doublets at 4.89 and 5.88 ppm (*J* = 6 Hz); for *trans* isomer, two doublets at 5.43 and 6.96 (*J* = 12 Hz).

$MeSO_3H$ (7.0 mL) was added over 5 min to a stirred solution of the isomeric mixture of **16a** (1.0 g) in 50 mL of anhydrous CH_2Cl_2 at 0 °C under argon. The mixture was then stirred for additional 2 h at 0 °C, diluted with ice-water, and the CH_2Cl_2 layer was separated. The CH_2Cl_2 layer was washed with cold water and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was chromatographed over dry column grade silica gel using hexane as an eluant to produce 0.62 g (70%) of **4** as colorless crystalline solid, mp 93-94 °C (reported [27] mp 94-95 °C). ^1H NMR ($CDCl_3$): δ 7.63 (d, 1 H, *J* = 5.5 Hz), 7.66-7.74 (m, 2 H), 7.82-7.96 (m, 4 H), 8.04 (dd, 1 H, *J* = 1.3 and 7.8 Hz), 8.08 (d, 1 H, *J* = 8.4 Hz), 9.24 (d, 1 H, *J* = 8.5 Hz).

Method B: Potassium *t*-butoxide (0.7 g, 0.69 mmol) was added to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (0.23 g, 0.69 mmol) in dry THF (15 mL) under Ar, and the mixture was stirred for 30 min. A solution of the aldehyde **35a** (0.15 g, 0.63 mmol) in dry THF (10 mL) was added dropwise, and the reaction mixture was stirred at rt for 1 h. The usual work-up of the reaction mixture and purification of the resulting product as described for **16a** (*vide supra*) gave 0.15 g (58%) of **36a** as a 2:3 mixture of *cis* and *trans* isomers. Partial ^1H NMR ($CDCl_3$): for *cis* isomer, two doublets at δ 4.95 and 5.94 (*J* = 6 Hz); for *trans* isomer, two doublets at δ 5.54 and 6.96 (*J* = 12 Hz).

$MeSO_3H$ (0.25 mL) was added over 5 min to a stirred solution of the isomeric mixture of **36a** (0.1 g, 0.37 mmol) in anhydrous CH_2Cl_2 at 0 °C. After stirring for 2 h at 0 °C, the product was isolated and purified as described above in an alternate synthesis of **4** produced 0.06 g (67%) of **4** as a colorless crystalline solid, mp 93-94 °C

1-Bromo-4-methoxy-5,6,7,8-tetrahydronaphthalene (**18**).

A solution of bromine (3.6 mL, 62 mmol) in acetic acid (3.6 mL) was added dropwise to a well stirred cold solution of 1-methoxy-5,6,7,8-tetrahydronaphthalene (10.0 g, 62 mmol) in acetic acid (20 mL). After complete addition of bromine in 10 min, the mixture was vigorously shaken with cold water (100 mL). The oil initially separated turned into crystalline solid, which was filtered, washed with cold water, and dried to produce 15.5 g (~ 100%) of bromo compound **18** as a colorless crystalline solid, mp 62-63 °C. ^1H NMR ($CDCl_3$) δ 1.72-1.83 (m, 4 H), 2.62-2.76 (m, 4 H), 3.81 (s, 3 H), 6.58 (d, 1 H, *J* = 8.7 Hz), 7.35 (d, 1 H, *J* = 8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 156.1, 136.8, 128.9, 128.3, 116.0, 108.0, 55.0 (O*C*H_3), 30.2, 23.3, 22.4, 21.7.

3-(4-Methoxy-5,6,7,8-tetrahydro-1-naphthyl)thiophene-2-carboxaldehyde (**19a**).

In an oven-dried flask flushed with argon was added **18** (2.21 g, 10 mmol), boronic acid **11a** (1.40 g, 10 mmol), KF (1.92 g, 40 mmol), $Pd_2(dba)_3$ (48 mg, 0.052 mmol) and THF (15 mL), successively. While stirring the mixture under argon, a solution of P(*t*-Bu)$_3$ (0.5 mL, 0.2 *M*) in CH_2Cl_2, and the resulting reaction mixture with green suspension was stirred for additional 20 h at rt. The mixture was diluted with EtOAc, and filtered through celite, and the filtrate was washed with 5% NaOH, and water. After drying (Na_2SO_4), the EtOAc solution was concentrated *in vacuo* to afford a pale yellow oil which was chromatographed over dry column grade silica gel. The elution of the column with 5% EtOAc-hexane produced 1.94 g (75%) of **19a** as a colorless crystalline solid. A small sample of the solid was recrystallized from hexane to produce colorless crystals, solid, mp 93-94 °C. ^1H NMR ($CDCl_3$) δ 1.70-1.81 (m, 4 H), 2.48-2.80 (m, 4 H), 3.89 (s, 3 H), 6.76 (d, 1 H, *J* = 8.3 Hz), 7.06 (d, 1 H, *J* = 8.3 Hz), 7.10 (d, 1 H, *J* = 5 Hz), 7.73 (dd, 1 H, *J* = 4.9 and 1.2 Hz), 9.6 (d, 1 H, *J* = 1.3 Hz). ^{13}C NMR ($CDCl_3$) δ 184.5 (CHO), 137.0, 133.4, 131.4, 128.5, 106.5, 55.4, 28.7, 23.5, 22.7, 22.3.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 70.58; H, 5.88. Found: C, 70.18; H, 6.04.

7-Methoxy-8,9,10,11-tetrahydrophenanthro[3,4-*b*]thiophene (**21**).

A mixture containing aldehyde **19a** (0.75 g, 2.9 mmol), trimethylsulfonium iodide (0.62 g, 3.0 mmol), and powdered KOH (0.27 g, 6.9 mmol) in acetonitrile (30 mL) was stirred at 60-65 °C for 15 h. The mixture was then diluted with water, and the product was extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to produce 0.85 g (100%) of sufficiently pure **19b** as an oil, ^1H NMR ($CDCl_3$) δ 1.63-1.88 (m, 4 H), 2.42-2.62 (m, 2 H), 2.68-2.78 (m, 2 H), 3.03 (dd, 1 H, *J* = 2.7 and 5.4 Hz), 3.13 (dd, 1 H, *J* = 4.1 and 5.5 Hz), 3.85-3.93 (m, 4 H), 6.75 (d, 1 H, *J* = 6.2 Hz), 6.91 (d, 1 H, *J* = 4.1 Hz), 7.08 (d, 1 H, *J* = 6.2 Hz), 7.26 (d, 1 H, *J* = 4.1 Hz)].

To a stirred solution of **19b** (0.8 g, 2.8 mmol) in anhydrous Et_2O (40 mL) at 0 °C was added dropwise a solution of $BF_3.Et_2O$ (3.42 mL) in 20 mL of Et_2O in 5 min under argon. The mixture was allowed to warm to rt, and stirred for additional 10 h. Isolation of the crude product as described gave an oil which was chromatographed over a short column of dry column grade silica gel. The elution of the column with petroleum ether (60-80 °C) to afford 0.16 g (21%) of **21** as colorless plates, solid, mp 141-143 °C; ^1H NMR ($CDCl_3$) δ 1.87-1.97 (m, 4 H), 2.85-2.90 (m, 2 H), 3.44-3.48 (m, 2 H), 3.96 (s, 3 H), 7.12 (s, 1 H), 7.54 (d, 1 H, *J* = 5.7 Hz), 7.64 (d, 1 H, *J* = 8.6 Hz), 7.84 (d, 1 H, *J* = 8.6 Hz), 8.24 (d, 1 H, *J* = 5.6 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.3, 137.7, 134.6, 131.4, 127.7, 125.4, 123.6, 120.2, 104.4, 55.2, 32.0, 24.7, 23.6, 22.0.

Anal. Calcd. for $C_{17}H_{16}OS.1/20\ H_2O$: C, 75.86; H, 5.99; Found: C, 75.45; H, 6.00.

7-Methoxyphenanthro[3,4-*b*]thiophene (**14**).

A mixture of 7-methoxy-8,9,10,11-tetrahydrophenanthro[3,4-*b*]thiophene **21** (0.1 g, 0.37 mmol), DDQ (200 mg, 0.88 mmol) in anhydrous benzene (25 mL) was refluxed for 4 h. After cooling the mixture to rt, it was stirred with 10% Na_2SO_3. Nearly colorless organic solution was washed with water, 5% NaOH, and water, successively. After drying over anhydrous Na_2SO_4, the solution was concentrated, and the residue was triturated with ice-cold EtOH and filtered to afford 86 mg (87%) of **14** as colorless crystals, solid, mp 96-98 °C (yield, 82%): ^1H NMR ($CDCl_3$) δ 4.15 (s, 3 H), 7.15 (s, 1 H), 7.65-7.79 (m, 4 H), 8.04 (d, 1 H, *J* = 8.5 Hz), 8.50 (dd, 1 H, *J* = 8.1 Hz and 1.6 Hz), 8.58 (d, 1 H, *J* = 5.6 Hz), 9.13 (d, 1 H, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 153.0, 138.2, 135.0, 131.6, 131.2, 126.9, 126.3, 126.2, 125.9, 125.2, 125.0, 122.5, 122.4, 121.7, 103.1, 55.6.

Anal.Calcd. for $C_{16}H_{12}OS.1/9CH_2Cl_2$: C, 74.72; H, 4.44. Found: C, 74.37; H, 4.87. *Anal.* Calcd. for $C_{17}H_{12}OS$ [M^+]: 264.0603. Found (EI): [M^+], 264.0606.

7-Hydroxyphenanthro[3,4-*b*]thiophene (**23**).

A solution of 1 *M* BBr_3 (0.9 mL, 0.9 mmol) in anhydrous CH_2Cl_2 was added to a stirred solution of **14** (0.084 g, 0.32 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0-5 °C under argon over a period

of 2-3 min. The mixture was stirred at the ambient temperature for 12 h, and then treated with ice-cold water. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to afford a solid. Trituration of the solid with hexane produced 0.066 g (90%) of **23** as greenish yellow solid, mp 148-150 °C. ^{1}H NMR ($CDCl_3$) δ 7.13 (d, 1 H, *J* = 3.6), 7.17 (d, 1 H, *J* = 3 Hz),7.26-7.31 (m, 1 H), 7.32-7.38(m, 2 H), 7.43-7.48 (m, 1 H) , 7.65-7.70 (m, 1 H), 7.80 (d, 1 H, *J* = 3.4 Hz), 7.89 (d, 1 H, *J* = 2.6 Hz), 9.12(d, 1 H, *J* = 4.0 Hz).

Anal. Calcd. for $C_{16}H_{10}OS$ [M+]: 250.0452. Found (EI): [M+], 250.0458.

Phenanthro[3,4-*b*]thiophene-6,7-dione (**24**).

To a solution of **23** (0.06 g, 0.24 mmol) in 16% CH_2Cl_2-benzene (10 mL) was added 0.17 *M* KH_2PO_4 (5 mL), 1 drop of adogen-64 and Fremy's salt (0.194 g, 0.72 mmol), successively. The mixture was stirred vigorously for 3 h. The dark organic layer was separated, washed with water and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was triturated with EtOH, and the resulting brick red solid was filtered to afford 0.048 g (75%) of pure dione **24**, mp 210-212 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (dt, 1 H, J = 0.8 and 6.8 Hz), 7.69 (d, 1 H, *J* = 5.8 Hz), 7.74 (dt, 1 H, *J* = 1.5 and 8.0 Hz), 7.92 (d, 1H, *J* = 8.4 Hz), 8.03 (d, 1 H, *J* = 5.7 Hz), 8.10 (d, 1 H, *J* = 8.4 Hz), 8.15 (dd, 1 H, *J* = 1.4 and 7.7 Hz), 8.20 (d, 1 H, *J* = 8.0 Hz).

Anal. Calcd. for $C_{16}H_8O_2S$ (M^+): 264.0245. Found (EI): [M^+], 264.0233.

trans-6,7-Dihydroxy-6,7-dihydrophenanthro[3,4-*b*]thiophene (**5**).

A solution containing **24** (0.04 g, 0.15 mmol) and $NaBH_4$ (0.46 g, 12.8 mmol) in ethanol (20 mL) was stirred while a stream of O_2 was gradually passed through the solution. After 12 h of stirring, the resulting nearly colorless solution was concentrated *in vacuo* to 5-6 mL, diluted with water (15 mL), and then extracted with EtOAc (2 X 25 mL). The combined EtOAc layer was washed with brine, and dried (Na_2SO_4). The concentration of the solvent under reduced pressure, and the trituration of the residual solid with peroxide-free diethyl ether gave 10 mg (27%) of **5** as a pale yellow solid, mp 124-127 °C. ^{1}H NMR (DMSO-d_6 + MeOH-d_4) δ 5.67 (d, 1 H, $J_{6,7}$ = 4.14 Hz), 5.72 (d, 1 H, $J_{6,7}$ = 4.14 Hz), 7.35-7.45 (m, 2 H), 7.62-7.69 (m, 2 H), 7.86-8.02 (m, 4 H). ^{1}H NMR ($CDCl_3$ + MeOH-d_4) δ 4.72 (d, 1 H, $J_{6,7}$ = 11.0 Hz), 5.72 (d, 1 H, $J_{6,7}$ = 11.0 Hz), 7.39-7.51 (m, 2 H), 7.60 (d, 1 H, *J* = 7.0), 7.67-7.77 (m, 2 H), 7.88-8.02 (m, 3 H).

Anal. Calcd for $C_{16}H_{12}O_2S$ [M^+]: 268.0553. Found (EI): [M^+], 268.0556.

2-(4-Methoxy-5,6,7,8-tetrahydro-1-naphthyl)thiophene-3-carboxaldehyde (**20a**).

In an oven-dried flask flushed with argon was added **18** (2.25 g, 10 mmol), boronic acid **11b** (1.38 g, 10 mmol), KF (1.92 g, 40 mmol), $Pd_2(dba)_3$ (48 mg, 0.052 mmol) and THF (15 mL), successively. While stirring the mixture under argon, a solution of P(t-Bu)$_3$ (0.5 mL, 0.2 *M*) in CH_2Cl_2, and the resulting reaction mixture with green suspension was stirred for additional 20 h at rt. The mixture was processed according to the procedure described for **19a** to produce 1.51 g (57%) of **20a** as a colorless crystalline solid. A small sample of the solid was recrystallized from hexane to produce colorless crystals, mp 110-111 °C. ^{1}H NMR ($CDCl_3$): δ 1.70-1.81 (m, 4 H), 2.52-2.57 (m, 2 H), 2.70-2.76 (m, 2 H), 3.89 (s, 3 H), 6.76 (d, 1 H, *J* = 8.4 Hz), 7.16 (d, 1 H, *J* = 8.3 Hz), 7.29 (dd, 1 H, *J* = 5.8 and 0.9 Hz), 7.53 (d, 1 H, *J* = 5.4 Hz), 9.55 (d, 1 H, *J* = 0.4 Hz); ^{13}C NMR ($CDCl_3$): δ 186.0 (CHO), 158.4, 156.2, 138.5, 138.0, 129.5, 126.9, 125.2, 122.3, 106.5, 55.4, 28.7, 23.5, 22.7, 22.2.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 70.58; H, 5.88%; Found: C, 70.44; H, 5.88.

7-Methoxy-8,9,10,11-tetrahydrophenanthro[4,3-*b*]thiophene (**22**).

A mixture containing the aldehyde **20a** (1.24 g, 4.8 mmol), trimethylsulfonium iodide (1.03 g, 5.0 mmol), and powdered KOH (0.44 g, 7.8 mmol) in acetonitrile (40 mL) was stirred at 60-65 °C for 13 h. The usual workup of the reaction mixture as described above for the epoxide **19b** gave 1.28 g (100%) of sufficiently pure **20b** as an oil [^{1}H NMR ($CDCl_3$): δ 1.65-1.90 (m, 4 H), 2.50-2.66 (m, 2 H), 2.68-2.77 (m, 2 H), 2.96 (dd, 1 H, *J* = 2.6 Hz and 5.2 Hz), 3.08 (dd, 1 H, *J* = 4 Hz and 5 Hz), 3.60 (dd, 1 H, *J* = 2.6 Hz and 3.6 Hz), 6.75 (d, 1 H, *J* = 8.2 Hz), 6.83 (d, 1 H, *J* = 5.5 Hz), 7.17 (d, 1 H, *J* = 8.2 Hz), 7.27 (d, 1 H, *J* = 5.5 Hz)].

A solution of BF_3.Et_2O (5.3 mL) in 20 mL of Et_2O was added dropwise under argon over 5 min to a stirred solution of the **20b** (1.24 g, 4.33 mmol) in anhydrous Et_2O (50 mL) at 0 °C. The mixture was stirred at the ambient temperature for an additional 10 h. Isolation of the crude product as described for **21** gave an oil which was chromatographed over a short column of dry column grade silica gel. Elution of the column with petroleum ether (60-80 °C) afforded 233 mg (20%) of **22** as colorless plates, mp 110-112 °C. ^{1}H NMR ($CDCl_3$): δ 1.86-1.92 (m, 2 H), 1.98-2.05 (m, 2 H), 2.84-2.89 (m, 2 H), 3.42-3.47 (m, 2 H), 3.96 (s, 3 H), 7.15 (s, 1 H), 7.49 (d, 1 H, *J* = 5.5 Hz), 7.52 (d, 1 H, *J* = 5.5 Hz), 7.66 (d, 1 H, *J* = 8.5 Hz), 7.80 (d, 1 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 155.3, 136.7, 135.2, 133.8, 131.4, 127.6, 125.5, 124.9, 124.4, 124.2, 121.7, 104.3, 55.3, 30.1, 24.5, 23.4, 21.8.

Anal. Calcd. for $C_{17}H_{16}OS$: C, 76.11; H, 5.97%; Found: C, 76.28; H, 5.95.

7-Methoxyphenanthro[4,3-*b*]thiophene (**17**).

7-Methoxy-8,9,10,11-tetrahydrophenanthro[4,3-*b*]thiophene **22** (140 mg, 0.53 mmol) was dehydrogenated with DDQ (280 mg, 1.23 mmol) in anhydrous benzene (30 mL) as described for **14** to afford 126 mg (91%) of **17** as colorless crystals, mp 130-132 °C. ^{1}H NMR ($CDCl_3$): δ 4.16 (s, 3 H), 7.20 (s, 1 H), 7.55-7.65 (m, 2 H), 7.68-7.79 (m, 1 H, 7.80-7.95 (m, 2 H), 8.03 (d, 1 H, *J* = 8.3 Hz), 8.55 (d, 1 H, *J* = 8.3 Hz), 9.22 (d, 1 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 155.1, 141.3, 132.7, 129.8, 127.4, 127.0, 126.7, 125.7, 125.6, 125.2, 125.1, 123.0, 122.3, 103.4, 55.6.

Anal. Calcd. for $C_{17}H_{12}OS.1/20CH_2Cl_2$: C, 76.11; H, 4.50%; Found: C, 76.16; H, 4.88. *Anal.* Calcd. for $C_{17}H_{12}OS$ [M^+]: 264.0603. Found (EI): [M^+], 264.0651.

7-Hydroxyphenanthro[4,3-*b*]thiophene (**25**).

Demethylation of **17** (0.1 g, 0.38 mmol) in anhydrous CH_2Cl_2 (20 mL) with 1 *M* solution of BBr_3 (1.1 mL, 1.1 mmol) in CH_2Cl_2 was carried out under argon as described in the preparation of **23**. The isolated product was purified by trituration with hexane to give 0.082 g (80%) of **25** as light yellow crystals, mp 187-190 °C. ^{1}H NMR ($CDCl_3$): δ 2.70 (bs, 1 H, exchangeable with D_2O), 7.25 (s, 1 H), 7.52 (pseudo s, 2 H), 7.64-7.71 (m, 2 H), 7.92 (d, 1 H, *J* = 8.4 Hz), 8.51 (d, 1 H, *J* = 8.0 Hz), 9.14 (d, 1 H, *J* = 8.3 Hz).

Anal. Calcd. for $C_{16}H_{10}OS$ [M^+]: 250.0452. Found (EI): [M^+], 250.0451.

Phenanthro[4,3-*b*]thiophene-6,7-dione (**26**).

Oxidation of **25** (0.08 g, 0.32 mmol) with Fremy's salt (0.42 g, 1.56 mmol) according to the procedure employed for the preparation of **24** yielded, after trituration with 50% CH_2Cl_2-benzene, 0.029 g (35%) of **26** as a brick-red solid, mp 200-202 °C. ^{1}H NMR ($CDCl_3$): δ 7.54 (d, 1 H, *J* = 5.6 Hz), 7.58 (d, 1 H, *J* = 7.5 Hz), 7.83-7.88 (m, 2 H), 7.95 (d, 1 H, *J* = 8.4 Hz), 8.28 (d, 1 H, *J* = 8.3 Hz), 8.29 (dd, 1 H, *J* = 1.5 and 7.0 Hz), 8.64 (d, 1 H, *J* = 8.1 Hz).

Calcd. for $C_{16}H_8O_2S$ (M^+): 264.0245. Found (EI): [M^+], 264.0249.

trans-6,7-Dihydroxy-6,7-dihydrophenanthro[4,3-*b*]thiophene (**7**).

Reduction of **26** (0.06 g, 0.23 mmol) with $NaBH_4$ (0.8 g, 28 mmol) in ethanol (70 mL) while bubbling oxygen was carried out as described above for **5** gave a product which was purified by trituration with 10% EtOAc-hexane to yield 0.036 g (60%) of **7** as a light yellow crystalline solid, mp 197-200 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 4.60 (d, 1 H, *J* = 10.4 Hz), 4.72 (d, 1 H, *J* = 10.8 Hz), 7.43 (dt, 1 H, *J* = 1.3 and 7.4 Hz), 7.48-7.55 (m, 2 H), 7.70 (d, 1 H, *J* = 5.6 Hz), 7.80-7.87 (m, 2 H), 7.92 (d, 1 H, *J* = 8.2 Hz), 8.31 (dd, 1 H, *J* = 1.3 and 7.7 Hz).

Calcd. for $C_{16}H_{12}O_2S$ [M^+]: 268.0558. Found (EI): [M^+], 268.0566.

6-Methoxy-1-naphthyltriflate (**27**).

A well-stirred mixture of 6-methoxy-1-teralone (10.0 g, 57 mmol) and 10% Pd-C (3.0 g) in 75 mL of *p*-cymene was refluxed for 48 h. The mixture was cooled, diluted with CH_2Cl_2 (150 mL), and then extracted with 100 mL of 10% NaOH. The aqueous layer was seprated, and acidified with ice-cold 5 *M* HCl to pH 2. The precipitated product was extracted with CH_2Cl_2. CH_2Cl_2 solution was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 7.0 g (70%) of 6-methoxy-1-naphthol as light brown solid, mp 82-84 °C (lit42 mp 85 °C). ^{1}H NMR ($CDCl_3$): δ 2.98 (s, 3 H), 5.22 (s, 1 H, exchangeable with D_2O), 6.66 (dd, 1 H, *J* = 9 Hz, 2 Hz), 7.00-7.40 (m, 4 H), 8.08 (d, 1 H *J* = 9.0 Hz).

To a stirred solution of 6-methoxy-1-naphthol (8.0 g, 46 mmol) in anhydrous CH_2Cl_2 was added triethylamine (15 mL). After stirring the resulting solution for 5 min at 0 °C, trifilic anhydride (14 mL) was added dropwise. The recation mixture was stirred for 5 h at ambient temperature, decomposed with ice-water, and then extracted with CH_2Cl_2. The resuolting CH_2Cl_2 solution was washed with cold water, dried, and concentrated *in vacuo* to yield an oily product. The chromatography of the oily product on dry column grade silica gel using 5% EtOAc-hexane as eluant produced 7.0 g (50%) of **27** as light yellow oil which was used as such in the next step. ^{1}H NMR ($CDCl_3$): δ 7.18 (d, 1 H, *J* = 3 Hz), 7.25-7.31 (m, 2 H), 7.38-7.48 (m, 2 H), 7.74 (d, 1 H, *J* = 9.0 Hz), 7.96 (d, 1 H, *J* = 9 Hz).

3-(6-Methoxy-1-naphthyl)thiophene-2-carboxaldehyde (**28**).

A reaction mixture containing triflate **27** (2.0 g, 6.5 mmol), 2-formylthiophene-3-boronic acid (**11a**) (1.0 g, 7 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), KBr (0.8 g, 6.72 mmol), and 2 *M* Na_2CO_3 (8 mL) in THF (75 mL) was heated under reflux in argon atmosphere for 10 h. The reaction mixture was cooled and diluted with EtOAc (100 mL), and then the organic layer was washed with 5% NaOH (50 mL) and water (50 mL), successively. After drying over Na_2SO_4, the organic solution was concentrated under reduced pressure to produce a yellow crystalline solid, which was triturated with 10% THF-hexane, and filtered to afford 1.2 g (70%) of **28** as a light yellow crystalline solid, mp 142-145 °C. ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.16 (dd, 1 H, *J* = 2.7 and 9.2 Hz), 7.20-7.35 (m, 2 H), 7.34 (d, 1 H, *J* = 7.1 Hz), 7.50-7.56 (m, 1 H), 7.66 (d, 1 H, *J* = 9.1 Hz),7.83-7.88 (m, 2 H), 9.61 (d, 1 H, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 184.1, 157.9, 150.1, 140.2, 135.1, 133.6, 131.8, 131.4, 128.1, 127.7, 127.1, 126.5, 125.7, 119.6, 106.4, 55.4.

Anal. Calcd. for $C_{16}H_{12}O_2S.1/10CH_2Cl_2$: C, 69.57; H, 4.39. Found: C, 69.77; H, 4.31. *Anal.* Calcd. for $C_{16}H_{12}O_2S$ (M^+): 268.0558. Found (EI): [M^+], 268.0554.

9-Methoxyphenanthro[3,4-*b*]thiophene (**30**).

Potassium *tert*-butoxide (0.33 g, 3 mmol) was added in one portion to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (1.0 g, 3 mmol) in anhydrous THF (50 mL) at rt under argon. After stirring the reaction mixture for 1 h, a solution of aldehyde **28** (0.72 g, 2.68 mmol) in anhydrous THF (25 mL) was added, and the mixture was stirred at rt for 2 h. The mixture was treated with ice-cold water, and extracted with EtOAc. The EtOAc layer was separated, washed with ice-cold water and dried (Na_2SO_4). Removal of the solvent gave 0.8 g (100 %) of an oil containing a ~ 1 : 3 mixture of *cis* and *trans* isomer of **29**. Partial ^{1}H NMR: for *cis* isomer, two doublets at δ 5.34 and 6.01 (*J* = 9 Hz); for *trans* isomer, one doublet at δ 5.68 (*J* = 15 Hz).

To a stirred solution of the isomeric mixture of **29** (0.80 g) in 25 mL of anhydrous CH_2Cl_2 at 0 °C under argon was added $MeSO_3H$ (5 mL) in 5 min. The mixture was then stirred for additional 2 h at 0 °C, diluted with ice-water, and then CH_2Cl_2 layer was separated. The CH_2Cl_2 layer was wahed with ice-cold water and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was chromatographed over dry column grade silica gel using hexane as eluant to afford 0.4 g (56%) of **30** as light yellow crystalline solid, mp 90-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 3 H), 7.32-7.37 (m, 2 H), 7.68-7.88 (m, 4 H), 8.01 (d, 1 H, *J* = 9.0 Hz), 8.57 (d, 1 H, *J* = 6.0), 9.05 (d, 1 H, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 157.7, 140.3, 134.7, 134.5, 129.3, 128.1, 127.9, 126.9, 126.0, 125.9, 125.8, 125.5, 125.1, 120.6117.0, 108.6, 55.4.

Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.27; H, 4.54. Found: C, 76.70; H, 4.83. *Anal.* Calcd. for $C_{17}H_{12}OS$ (M^+): 264.0603. Found (EI): [M^+], 264.0608.

9-Hydroxyphenanthro[3,4-*b*]thiophene (**31**).

To an ice-cooled solution of **30** (0.4 g, 1.5 mmol) in CH_2Cl_2 (25 mL) was added dropwise a 1 *M* solution of BBr_3 in CH_2Cl_2 (4 mL, 4 mmol). The resulting dark solution was stirred at rt for 10 h, and then poured on to 50 mL ice-cold solution of 5% NaOH. After stirring, the aqueous phase was separated, washed once with hexane, acidified with 5 *M* HCl, and then extracted with EtOAc (2 X 50 mL). The combined EtOAc solution was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to furnish 0.3 g (90%) of **31** as a greenish yellow solid, mp 139-140 °C. ^{1} H NMR ($CDCl_3$) δ 5.35 (bs, 1 H, exchangeable with D_2O), 7.30 (dd, 1 H, *J* = 9.1 Hz and 2.7 Hz), 7.34 (d, 1 H, *J* = 2.7 Hz), 7.68 (d, 1 H, *J* = 8.7 Hz), 7.72 (d, 1 H, *J* = 5.6 Hz), 7.80 (d, 1 H, *J* = 8.6 Hz), 7.83 (d, 1 H, *J* = 8.8 Hz), 8.02 (d, 1 H, *J* = 8.5 Hz), 8.56 (d, 1 H, *J* = 5.6 Hz), 9.04 (d, 1 H, *J* = 9.1 Hz). ^{13}C NMR ($CDCl_3$) δ 154.3, 141.0, 135.4, 135.1, 129.9, 128.9, 128.9, 127.5, 126.8, 126.4, 126.2, 126.1, 125.8, 121.3, 117.2, 112.4.

Anal. Calcd for $C_{16}H_{10}OS$ (M^+): 250.0452. Found (EI): [M^+], 250.0456.

Phenanthro[3,4-*b*]thiophene-8,9-dione (**32**).

To a solution of phenol **31** (0.15 g, 0.6 mmol) in 30% benzene-CH_2Cl_2 was added 0.17 *M* KH_2PO_4 (16 mL), 1 drop of adogen-64, and Fremy's salt (0.45 g, 1.67 mmol). The resulting dark red color biphasic solution was stirred at rt for 24 h. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to produce a dark red color sticky residue. Trituration of the residue with ethanol afforded 0.1 g (66%) of pure **32** as a dark brown solid, mp 165 °C. ^{1}H NMR ($CDCl_3$) δ 6.62 (d, 1 H, *J* = 12.0 Hz), 7.55 (d, 1 H, *J* = 6 Hz), 7.71 (d, 1 H, *J* = 6 Hz), 7.75 (d, 1 H, *J* = 9 Hz), 7.99 (d, 1 H, *J* = 9 Hz), 8.04 (d, 1 H, *J* = 9 Hz), 8.21 (d, 1 H, *J* = 9 Hz), 9.02 (d, 1 H, *J* = 9 Hz).

Anal. Calcd. for $C_{16}H_8O_2S$ (M^+): 264.0240. Found (EI): [M^+], 264.0246.

trans-8,9-Dihydroxy-8,9-dihydrophenanthro[3,4-*b*]thiophene (**6**).

A suspension of **32** (35 mg, 0.13 mmol) in ethanol (75 mL) was stirred with $NaBH_4$ (0.45, 1.25 mmol) for 24 h while a stream of O_2 was bubbled through the solution. Nearly colorless solution of the reaction mixture was concentrated to half of its original volume, diluted with water, and then extracted with EtOAc (2 X 50 mL). The combined EtOAc solution was washed with water, dried (Na_2SO_4), and concentrated to dryness. Trituration of the residue with 10% EtOAc-hexane resulted in 11-17 mg (31-48%) of **6**, mp 195-196 °C. ^{1}H NMR (Acetone-d_6+MeOH-d_4) δ 4.54 (dt,1 H, *J* = 2.4 and 11.8 Hz), 4.79 (d, 1 H, *J* = 11.8 Hz), 6.33 (dd, 1 H, *J* = 2.1 and 10.3 Hz), 7.47 (dd, 1 H, *J* = 2.7 and 10.2 Hz), 7.76-7.85 (m, 2 H), 7.88-8.04 (m, 3 H), 8.25 (d, 1 H, *J* = 5.5 Hz).

Anal. Calcd. for $C_{16}H_{12}O_2S$ (M^+): 268.0558. Found (EI): [M^+], 268.0556.

7-(2-Formyl-4-methoxyphenyl)benzo[*b*]thiophene (**35b**).

A mixture of 7-bromobenzo[*b*]thiophene (**34**) (1.36 g, 6.4 mmol), 2-formyl-4-methoxyphenylboronic acid (**33b**) (1.14 g, 6.3 mmol), anhydrous CsF (3.4 g, 18.9 mmol), and $Pd(PPh_3)_4$ (0.31 g, 0.27 mmol) in anhydrous DME (60 mL) was refluxed for 18 h under argon. The reaction mixture was worked up and purified by column chromatography as described for **35a** to afford 1.4 g (85%) of **35b** as a light yellow crystalline solid, mp 70-72 °C. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3 H), 7.22-7.28 (m, 2 H), 7.41-7.54 (m, 4 H), 7.59 (d, 1 H, *J* = 2.8 Hz), 7.87 (dd, 1 H, *J* = 8 Hz and 0.9 Hz), 9.73 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 192.0 (CHO), 160.1, 141.7, 140.3, 137.6, 135.1, 132.6, 132.1, 127.7, 126.8, 124.9, 124.8, 123.8, 122.1, 110.5, 56.0.

Anal. Calcd. for $C_{16}H_{12}O_2S.1/20\ CH_2Cl_2$: C, 70.74; H, 4.44. Found: C, 70.52; H, 4.74. *Anal.* Calcd. for $C_{16}H_{12}O_2S$ [M^+]: 268.0558. Found (EI): [M^+], 268.0557.

9-Methoxyphenanthro[4,3-*b*]thiophene (**37**).

A mixture of **35** (1.0 g, 3.72 mmol), trimethylsulfonium iodide (1.0 g, 4.90 mmol) and powdered KOH (0.5 g, 8.9 mmol) in acetonitrile (50 mL) was stirred for 16 h at 65 °C. The mixture was then diluted with water, and the product was extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), and then concentrated *in vacuo* to produce 1.0 g (100%) of sufficiently pure epoxide **36b** as a light yellow oil [^{1}H NMR ($CDCl_3$): δ 2.74 (dd, 1 H, *J* = 2.6 and 5.7 Hz), 2.93 (dd, 1 H, *J* = 4.3 and 5.5 Hz), 3.62 (dd, 1 H, *J* = 2.6 and 4.1 Hz), 3.87 (s, 3 H), 6.89 (d, 1 H, *J* = 2.7 Hz), 6.94 (dd, 1 H, *J* = 2.7 and 8.4 Hz), 7.25 (d, 1 H, *J* = 7.5 Hz), 7.36 (d, 1 H, *J* = 8.3 Hz), 7.39-7.47 (m, 3 H), 7.83 (dd, 1 H, *J* = 1.0 and 8.0 Hz)].

Method A: A solution of 15% $MeSO_3H$ in CH_2Cl_2 (12 mL) was added dropwise to a stirred solution of **36b** (1.0 g, 3.7 mmol) in 15 mL of CH_2Cl_2 at 0 °C. After stirring for additional 18 h at rt, the reaction mixture was diluted with ice-water, and the CH_2Cl_2 layer was separated, washed with water, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure produced crude **37** as a semisolid which was chromatographed over dry column grade silica gel using hexane to produce 0.52 g (54%) of **37** as light yellow crystals, mp 85-86 °C (Lit [44] mp 88.5-90 °C). ^{1}H NMR ($CDCl_3$): δ 4.11 (s, 3 H), 7.39 (d, 1 H, *J* = 3 Hz), 7.47 (dd, 1 H, *J* = 10 Hz and 3 Hz), 7.61 (d, 1 H, *J* = 5 Hz), 7.68 (d, 1 H, *J* = 5 Hz), 7.77 (d, 1 H, *J* = 8.4 Hz), 7.89 (d, 1 H, *J* = 7 Hz), 7.92 (d, 1 H, *J* = 7 Hz), 8.00 (d, 1 H, *J* = 8.4 Hz), 9.16 (d, 1 H, 10 Hz); ^{13}C NMR ($CDCl_3$): δ 157.7, 139.4, 134.5, 134.2, 129.5, 128.4, 127.5, 126.5, 126.3, 126.2, 125.9, 124.7, 124.0, 122.0, 117.2, 109.1, 55.4.

Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.27; H, 4.54%; found. C, 76.89; H, 4.74. *Anal.* Calcd. for $C_{17}H_{12}OS$ (M^+): 264.0609. Found (EI): [M^+], 264.05954.

Method B: In an alternate procedure, a solution of $BF_3.Et_2O$ (0.75 mL, 6.1 mmol) in 10 mL of dry Et_2O was added dropwise to a solution of **36b** (0.21 g, 0.76 mmol) in 10 mL of anhydrous Et_2O while stirring at 0 °C under argon atmosphere. After complete addition, the mixture was stirred at rt for 16 h, decomposed with ice, and extracted with EtOAc (1 x 100 mL). The organic phase was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was chromatographed as described above (Method A) to afford 0.13 g (65%) of **37** as a light yellow crystalline solid, mp 85-86 °C

9-Hydroxyphenanthro[4,3-*b*]thiophene (**38**).

To a stirred solution of **37** (0.2 g, 0.75 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0-5 °C under argon was added a 1 *M* solution of BBr_3 (2 mL, 2 mmol) over a period of 2-3 min. 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 then rotary evaporated to afford a solid. The solid was triturated with hexane and filtered to give 0.19 g (95%) of **38** as a greenish yellow crystalline solid, mp 125-127 °C. ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 1 H, exchangeable with D_2O), 7.38-7.44 (m, 2 H), 7.61 (d, 1 H, *J* = 5.0 Hz), 7.68 (d, 1 H, *J* = 5.0 Hz), 7.73 (d, 1 H, *J* = 8.3 Hz), 7.86-7.92 (m, 2 H), 8.02 (d, 1 H, *J* = 8.3 Hz), 9.15 (d, 1 H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$): δ 155.1, 139.4, 134.8, 134.2, 129.3, 128.2, 127.6, 126.7, 126.3, 126.0, 125.8, 124.6, 123.5, 121.7, 117.4, 112.3.

Anal. Calcd. for $C_{16}H_{10}OS.1/10\ CH_2Cl_2$: C, 74.39; H, 3.92%; found, C, 74.56; H, 4.25%.

Phenanthro[4,3-*b*]thiophene-8,9-dione (**39**).

A solution of **38** (0.1 g, 0.38 mmol) in 35 mL of CH_2Cl_2/benzene (16:84) containing 3 drops of adogen-64 and 0.17 *M* KH_2PO_4 (11 mL) was stirred at rt while Fremy's salt (0.4 g, 1.49 mmol) was added in one portion with vigorous stirring. After stirring the solution for 3 h, the reaction mixture was worked-up as described for **32** to produce 0.089 g (90%) of pure dione **39** as a brick red solid, mp 183-185 °C. ^{1}H NMR ($CDCl_3$): δ 6.61 (d, 1 H, *J* = 10.6), 7.57 (d, 1 H, *J* = 5.5 Hz), 7.71-7.77 (m, 2 H), 7.97-8.05 (m, 2 H), 8.19 (d, 1 H, *J* = 8.3 Hz), 8.99 (d, 1 H, *J* = 10.7 Hz).

Anal. Calcd. for $C_{16}H_8O_2S$ [M+]: 264.0245. Found (EI): [M+], 264.0236.

(±)-*trans*-8,9-Dihydroxy-8,9-dihydrophenanthro[4,3-*b*]thiophene (**8**).

To a well-stirred suspension of dione **39** (0.130 g, 0.49 mmol) in ethanol (100 mL) was added $NaBH_4$ (1.2 g, 42 mmol). The mixture was stirred at rt while a stream of oxygen was bubbled through the solution. After 18 h of stirring, the resulting light yellow solution was concentrated at rt *in vacuo* to 30 mL, diluted with water, and extracted with EtOAc (2 x 75 mL). The EtOAc solution was dried (Na_2SO_4) and rotary evaporated to yield a solid, which was triturated with cold ether and purified by preparative tlc (silica gel, 50% EtOAc-hexane) to afford 0.09 – 0.1 g (70 - 80%) of **8** as a colorless solid, mp 191-193 °C. ^{1}H NMR (Acetone-d_6 + MeOH-d_4): δ 4.50 (dt, 1 H, *J* = 12, and 2.3 Hz), 4.86 (d, 1 H, *J* = 12 Hz), 6.37 (dd, 1 H, *J* = 2.0 and 10.3 Hz), 7.62 (d, 1 H, *J* = 5.4 Hz), 7.70 (dd, 1 H, *J* = 2.3 and 10.3 Hz), 7.79-7.87 (m, 2 H), 7.89-8.01 (m, 3 H).

Anal. Calcd. for $C_{16}H_{12}O_2S$ (M+): 268.0558. Found (EI): [M+], 268.05682.

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