# A New Route to Benzo[a]naphthacene-8,13-diones: Synthesis and Revision of the Structure Proposed for G2N

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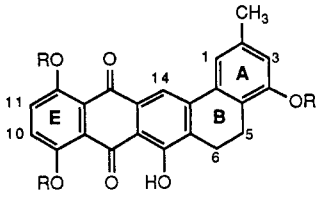
A regiospecific total synthesis of **1b**, the tris(methyl ether) derivative of the structure proposed for G2N (**1a**), was performed through condensation of the anion of the phthalidesulfone **3** with the hydrophenanthrone **4**. This preparation shows that although the ring system for these natural products is correct, the proposed substitution pattern is incorrect. The revised structures **19a** and **19b** are recommended for G2N and G2N tris(methyl ether), respectively.

The first natural products from a biological source with a benzo[*a*]naphthacene ring system were the quinoid pigments G2N (**1a**) and G2A (**2**) reported by Gerber and Lechevalier.[1,2] These substances were isolated from an actinomycetes of the genus *Frankia* G2 (ORS 020604), which fix nitrogen in a symbiotic relationship with certain higher plants.[3]

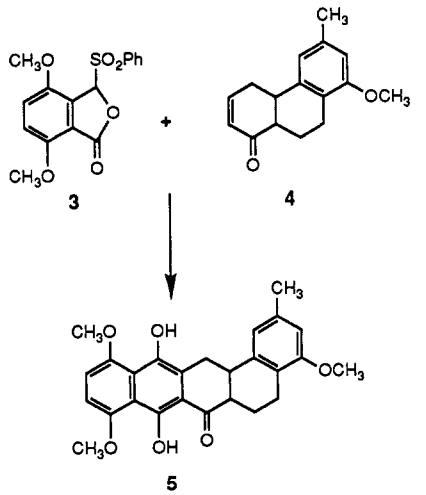


**1a** R = H G-2N
**1b** R = $CH_3$ G-2N Trimethyl ether
**2** R = H, COOH at 10 or 11 G-2A

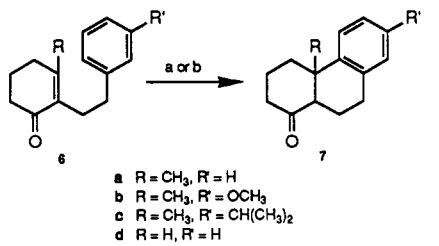
The unusual ring system of these natural products, the question of whether the proposed structures were correct, and our interest in establishing the (phenylsulfonyl)isobenzofuranone annelation as a route to angular polycyclic aromatic systems led us to undertake the synthesis of the structure **1b** proposed for the tris(methyl ether) derivative of G2N (**1a**). As discussed later in this paper, we have found that the synthetic and authentic materials are not identical and have proposed alternative structures for these compounds.

The latter stages of the synthetic plan to the proposed structure are shown in Scheme I. This approach was based on previous work in which we have demonstrated that efficient, regiospecific synthesis of polycyclic aromatic systems can be accomplished through condensation of 3-(phenylsulfonyl)isobenzofuranones with enones.[4] While the annelation methodology has been used extensively to synthesize linear polycyclic systems,[5] its use to synthesize angular polycyclic aromatic systems has been largely untested.[6] As indicated in the scheme, condensation of the sulfone **3**[7] with the hydrophenanthrenone **4** would give the

**Scheme I**



**Scheme II**[a]



**a** R = $CH_3$, R' = H
**b** R = $CH_3$, R' = $OCH_3$
**c** R = $CH_3$, R' = $CH(CH_3)_2$
**d** R = H, R' = H

[a] (a) $H_3PO_4$, $H_3PO_4$–$H_2SO_4$ or $H_2SO_4$; (b) $AlCl_3$.

hexahydrobenzonaphthacenone **5**, which in additional steps would be aromatized to G2N tris(methyl ether) (**1b**), a derivative prepared in conjunction with the original structure elucidation.

As indicated in Scheme II, intramolecular cyclization of the 2-(2-phenylethyl)-2-cyclohexen-1-ones **6a–c** with mineral acids and aluminum chloride provides a general method for the preparation of hydrophenanthrones **7a–c** with a C-1 ketone.[8–11] Our planned construction of a hydrophenanthrone intermediate to **4** would employ this approach. Although a large number of hydrophenanthrones have been prepared using this approach, none had the substitution pattern on the aromatic ring that

(1) Gerber, N. N.; Lechevalier, M. P. *Can. J. Chem.* **1984**, *62*, 2818.
(2) When we initiated our work on the synthesis of G2N tris(methyl ether), these were the only natural products with this ring system. Since then, three additional naturally occurring benz[a]naphthacenes have been reported: Yasuzawa, T.; Yoshida, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 1111. Gomi, S.; Sasaki, T.; Itoh, J.; Sezaki, M. *Ibid.* **1988**, *41*, 425. Gomi, S.; Sezaki, M.; Kondo, S.; Hara, T.; Naganawa, H.; Takeuchi, T. *Ibid.* **1988**, *41*, 1019.
(3) Gauthier, D.; Diem, H. G.; Dommergues, Y. *Appl. Environ. Microbiol.* **1981**, *41*, 306.
(4) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(5) For an example of the use of this reaction to prepare linear polycyclic aromatic systems, see: Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *22*, 4719 and references therein.
(6) Only one example of the use of this reaction to prepare an angular polycyclic aromatic system has been reported. Hauser, F. M.; Combs, D. W. *J. Org. Chem.* **1980**, *45*, 4071.
(7) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098.
(8) Stork, G.; Burgstahler, A. *J. Am. Chem. Soc.* **1951**, *73*, 3544.
(9) Saha, N. N.; Bagchi, P. N.; Dutta, P. C. *J. Am. Chem. Soc.* **1955**, *77*, 3408.
(10) Ansell, M. F.; Brown, S. S. *J. Chem. Soc.* **1958**, 3956. Ansell, M. F.; Selleck, M. E. *Ibid.* **1956**, 1238.
(11) Another potential route to the hydrophenanthrone was through cyclization of a 2-(2-phenylethyl)cyclohexane-1,3-dione. We chose not to use this approach since it had been reported that a complex mixture of products is produced. Huffmann, J. W.; Harris, P. G. *J. Org. Chem.* **1977**, *42*, 2357.

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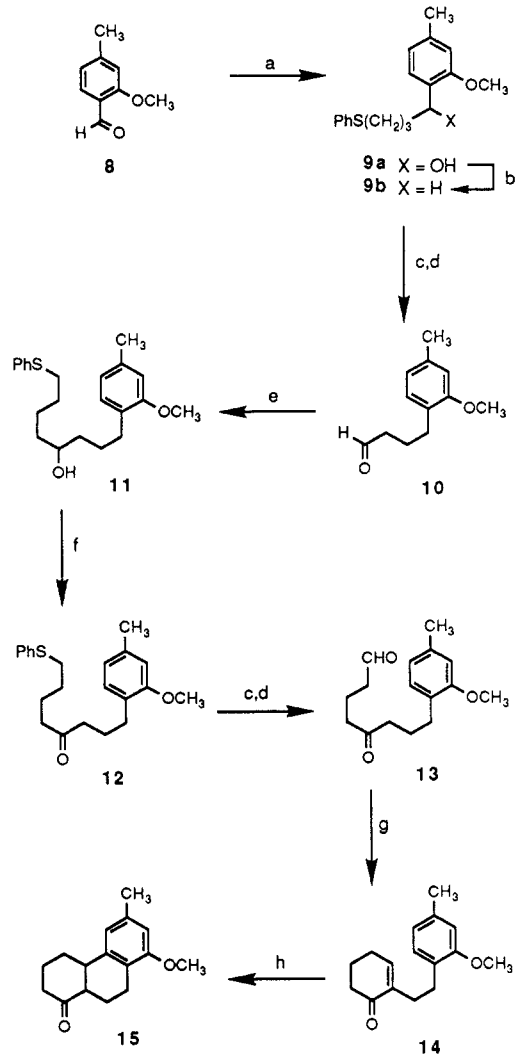
**Scheme III**[a]




[a] (a) $PhS(CH_2)_3Br$, Mg, THF; 80–85%; (b) $CF_3CO_2H$, $Et_3SiH$, $CH_2Cl_2$; 90%; (c) NCS, $CCl_4$; (d) CuO, $CuCl_2$, acetone–$H_2O$; 76%; (e) $PhS(CH_2)_4Br$, Mg, THF; 73–80%; (f) PCC–Celite, $CH_2Cl_2$; 74%; (g) $HClO_4$–THF–$H_2O$; 60–70% from **12**; (h) $TiCl_4$, $CH_2Cl_2$; 50%.

was needed and, with few exceptions,[10] most possessed an angular 10a-methyl group. Relatedly, there were conflicting reports[10,12] concerning the successful cyclization of **6d** to **7d**, which suggested that the 3-methyl group on the cyclohexenone was essential for ring closure.

A new synthetic route to 2-(2-phenylethyl)cyclohexenones was developed in conjunction with the synthesis of **14**, which was needed as an intermediate to the hydrophenanthrone **15**, and this is shown in Scheme III. Key features were our development of an improved procedure to the aldehyde **8** through regiospecific oxidation of methyl groups in dimethylanisoles[13] and the use of $\alpha,\omega$-thiophenyl alkyl halides for construction of $\alpha,\beta$-unsaturated enone systems reported by Bakuzis and co-workers.[14]

Addition of the Grignard reagent derived from 1-bromo-3-(phenylthio)propane to the aldehyde **8** furnished the hydroxy sulfide **9a** in 80–85% yield. Reductive removal of the hydroxyl group in **9a** with trifluoroacetic acid and triethylsilane[15] gave **9b** (90%). Brief treatment of **9b** with *N*-chlorosuccinimide (NCS), followed by copper oxide mediated hydrolysis of the $\alpha$-chloro sulfide intermediate, routinely furnished the homologated aldehyde **10** in 76% yield.

A second Grignard addition, this time on the aldehyde **10** with the reagent derived from 1-bromo-4-(phenylthio)butane,[14] furnished the hydroxy sulfide **11** (73–80%), which upon oxidation with PCC on Celite[16] gave the ketone **12** (74%). Treatment of **12** with NCS, followed by hydrolysis, produced the keto aldehyde **13**, which, without purification, was cyclized and dehydrated to the cyclohexenone **14** with dilute perchloric acid in aqueous THF (60–70% from **12**). The presence of a resonance in the $^1H$ NMR spectrum of **14** at 6.66 ppm for the C-3 vinyl proton and two well-defined triplets for the phenylethyl fragment supported the structure assignment.

Our concern at the outset that intramolecular cyclization of **14** to the hydrophenanthrone **15** might be difficult to accomplish, since there was no C-3 methyl group on the cyclohexenone fragment, proved to be well founded. The use of aluminum chloride in methylene chloride or carbon disulfide, or of polyphosphoric acid, conditions successfully employed to cyclize the cyclohexenones **6a–c** to the hydrophenanthrones **7a–c**, failed to effect cyclization and in each instance the starting enone **14** was recovered. Attempted use of sulfuric acid resulted in sulfonation of the aromatic ring.[17]

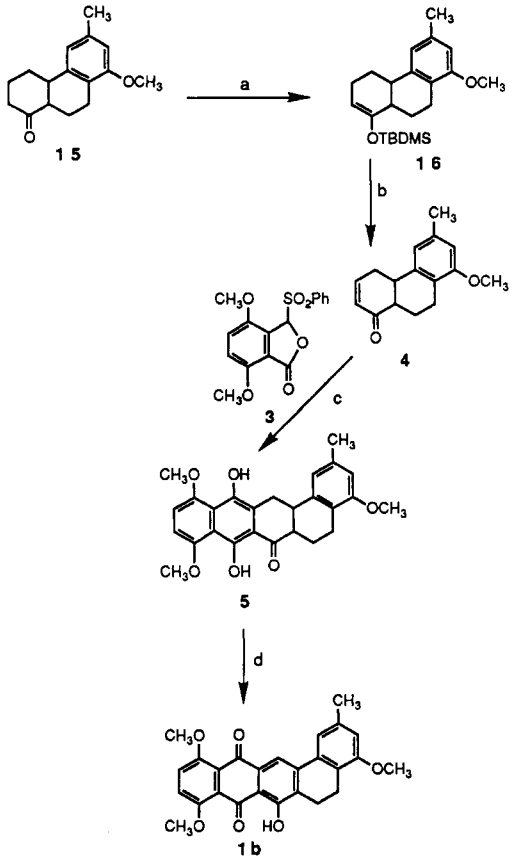
The use of Lewis acids, other than aluminum chloride, for cyclization of **14** to **15** were examined next. With $BF_3$·$OEt_2$ in methylene chloride there was no reaction, and the starting material was recovered. Although titanium tetrachloride is a weaker Lewis acid than aluminum chloride, when this reagent was employed, slow cyclization of the enone **14** to the hydrophenanthrone **15** was achieved in 50% yield. The 300-MHz $^1H$ NMR spectrum of the product indicated that it was a mixture of cis and trans isomers, and this was confirmed by GC–MS analysis. Furthermore, the ratio of cis and trans isomers depended on the reaction time. For an 8-h reaction, the ratio was 1:1.05; for an 18 h reaction 1:1.2. The individual isomers were separated through chromatography, which proved useful at a subsequent stage in the synthesis.

Introduction of 2,3-unsaturated into **15** to produce **4** proved unexpectedly difficult. The reaction sequence reported by Trost et al.,[18] in which the sulfide product from thiophenylation of the anion of **15** would be oxidized to the sulfoxide and then eliminated as phenylsulfinic acid, was investigated initially. Treatment of **15** with either LDA or potassium hydride[19] to generate the enolate anion, followed by reaction with either diphenyl disulfide or (phenylthio)phenylsulfonate, gave, in each instance, only the starting ketone.

The reaction sequence reported by Saegusa et al.,[20] wherein silyl enol ethers of cyclic ketones are oxidized to unsaturated enones with palladium acetate, was investigated next for the conversion of **15** to **4**. Repeated attempts were made to prepare the trimethyl or dimethyl-*tert*-butylsilyl enol ether through trapping of the enolate

(12) Cohen, A.; Cook, J. W. *J. Chem. Soc.* **1935**, 1570.
(13) Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723.
(14) (a) Bakuzis, P.; Bakuzis, M. L. F.; Fortes, C. C.; Santos, R. *J. Org. Chem.* **1976**, *41*, 2769. (b) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362.
(15) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.
(16) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.
(17) The major difference between the $^1H$ NMR of the starting material and the sulfonated product was the absence of one of the aromatic protons. The unsaturated enone fragment was clearly present in both the $^1H$ NMR and the IR spectra.
(18) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(19) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 1324.
(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

**Scheme IV**[a]




[a] (a) TBDMS–triflate, $Et_3N$; 95%; (b) $Pd(OAc)_2$, $CH_3CN$, $CH_2Cl_2$; 53%; (c) 3, LiOtBu, THF; 80%; (d) $O_2$, DMF, 100 °C; 80%.

anion kinetically generated with either LDA or potassium hydride.[19] In each instance the starting ketone **15** was reclaimed. The recent report by Mander and Sethi[21] that *tert*-butyldimethylsilyl triflate (TBDMS-triflate) reacts with hindered cyclic ketones to furnish predominantly the less highly substituted silyl enol ethers, led us to explore the use of this reagent, and this is shown in Scheme IV. Although we were concerned that a regioisomeric mixture of enol ethers would be produced, treatment of a cis/trans mixture of **15** with TBDMS-triflate gave what appeared to be a cis/trans mixture of exclusively the 1,2-enol ether **16**. Furthermore, the ratio of cis and trans isomers appeared to be identical with that of the starting ketone **15**, indicating that no epimerization had occurred. In order to test whether only the 1,2-enol ether was being formed, the respective cis and trans isomers of **15** were reacted with TBDMS-triflate. In both cases, the individual cis and trans 1,2-silyl enol ethers of **16** were formed exclusively without any epimerization at C-11a. Treatment of the silyl enol ether **16** derived from the major ketone isomer with palladium acetate furnished the enone **4** in 53% yield.

The anion of the sulfone **3**,[7] generated with lithium *tert*-butoxide in THF, smoothly reacted with **4** to give the hydrobenzonaphthacene **5** in 80% yield. Heating **5** in DMF under oxygen at 100 °C for several hours gave the dihydronaphthacene quinone **1b**, the structure originally proposed for the tris(methyl ether) of G2N.

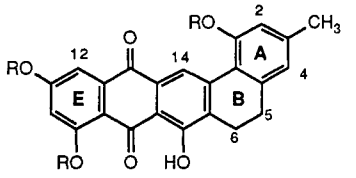
Comparison of the $^1H$ NMR of the synthetic material with that of an authentic sample of the tris(methyl ether) showed that the compounds are not identical. The chemical shifts for the protons of both compounds are given in Table I. Two striking differences are the resonances for the H-14 proton at 8.74 ppm in the methyl ether derivative of the natural product and at 8.14 ppm in the synthetic material and resonances for the H-1 and H-3 protons at 7.51 and 6.80 ppm in the natural product and at 7.37 and 6.76 ppm in the synthetic material. These data indicate that while both substances are benz[a]naphthacenes, the substitution pattern originally proposed for the natural product is incorrect.

**Table I. 300-MHz $^1H$ NMR Data for Authentic G2N Tris(methyl ether) and Synthetic 1b in $CDCl_3$**

| proton no. | authentic | synthetic |
|---|---|---|
| C-2-$CH_3$ | 2.39 (s, 3 H) | 2.42 (s, 3 H) |
| H-5 or H-6 | 2.74–2.79 (m, 2 H) | 2.83–2.88 (m, 2 H) |
| H-5 or H-6 | 2.90–2.96 (m, 2 H) | 2.93–2.98 (m, 2 H) |
| C-4-, C-9-, C-12-$OCH_3$ | 3.96, 4.00, 4.05 (s, 3 × 3 H) | 3.87, 4.01, 4.04 (s, 3 × 3 H) |
| H-3 | 6.80 (d, $J$ = 2.4 Hz, 1 H) | 6.76 (s, 1 H) |
| H-10 & H-11 | 6.74 (br s, 2 H) | 7.38 (s, 2 H)* |
| H-1 | 7.51 (d, $J$ = 2.4 Hz, 1 H) | 7.37 (s, 1 H)* |
| H-14 | 8.74 (s, 1 H) | 8.14 (s, 1 H) |
| C-7-O*H* | 13.54 (s, 1 H) | 13.13 (s, 1 H) |

* Overlapping singlets.

Since the synthetic material **1b** is not G2N tris(methyl ether), we reexamined the spectral data originally reported for these natural products. Our interpretation of the $^1H$ NMR data leads us to propose new structures **19a** and **19b** for G2N and the tris(methyl ether), respectively.[22] We




**19a** R = R' = H G-2N
**19b** R = $CH_3$, R' = H G-2N Trimethyl ether

assign the H-10 and H-12 protons on the A ring of G2N tris(methyl ether) (**19b**) to the resonances at 6.80 and 7.51 ppm, respectively. The downfield location of the H-12 proton relative to the H-10 proton is a consequence of the proximity of the H-12 proton to the quinone carbonyl at C-13. The absorptions for the C-5 and C-6 methylenes are two well defined sets of multiplets centered at 2.77 and 2.94 ppm. The H-2 and H-4 protons coincidentally absorb at 6.74 ppm; therefore, no coupling is observed. Their shielded position stems from the fact that the A ring is electron rich. Based on our synthesis of the structure originally reported for G2N tris(methyl ether) and other work, the H-14 proton at 8.7 ppm is unusually deshielded. The proximity of the H-14 proton to the C-13 carbonyl group and the steric and electronic effects due to the presence of an oxygen functionality at C-1 in our proposed structure provides an explanation for the unusual chemical shift of this proton.[23,24]

(21) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.

(22) The isomeric analogs of **19a** and **19b** with the E-ring oxygens at C-10 and C-12 is a possibility, but an unlikely one, based on biosynthetic considerations.

(23) This phenomenon is well documented for phenanthrenes with a C-5 proton and a C-4 oxygen functionality. Bhandari, S. R.; Kapadi, A. H. *Indian J. Chem.* **1985**, *24B*, 204. Miyase, T.; Ueno, A.; Takizawa, N.; Kobayashi, H.; Karasawa, H. *Chem. Pharm. Bull.* **1987**, *35*, 1109. Brown, C.; Sikkel, B. J.; Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3007. Majumder, P.; Laha, S.; Datta, N. *Phytochemistry* **1982**, *21*, 478. Letcher, R. M. *Org. Magn. Reson.* **1981**, *16*, 220.

(24) **Note Added in Proof.** Rickards has recently proposed revision of the structure of G2N to **19a** and that G2A has the carboxyl at the 2-position. Rickards, R. W. *J. Antibiot.* **1989**, *42*, 336.

In summary, this study demonstrates that while the ring system proposed for G2N and G2A is correct, the substitution pattern is incorrect and that **19a** and **19b** are likely structures for G2N and G2N tris(methyl ether). An additional finding of note is that the phthalide sulfone annelation provides a useful method for regiospecific construction of the benzo[*a*]naphthacene ring system. The final structure proof of these natural products will require additional synthetic work.

## Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 1600 FT IR spectrophotometer and are expressed in reciprocal centimeters ($cm^{-1}$). Proton nuclear magnetic resonance ($^1H$ NMR) spectra were obtained on a Varian Model XL-300 spectrometer. Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ($\delta$ 0.0) as an internal standard.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Silica gel for column chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM. Alumina column chromatography was performed with ICN Pharmaceutical GmbH & Co. neutral aluminum oxide activity 1. Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH). Methylene chloride ($CH_2Cl_2$), carbon tetrachloride ($CCl_4$), acetonitrile ($CH_3CN$), triethylamine ($Et_3N$), and *N,N*-dimethylformamide (DMF) were dried by distillation from calcium hydride.

**1-(2′-Methoxy-4′-methylphenyl)-4-(phenylthio)butanol (9a).** A solution of 2-methoxy-4-methylbenzaldehyde (**8**)[13] (16.5 g, 110 mmol) in THF (80 mL) was added to a solution of Grignard reagent prepared from magnesium (3.11 g, 128 mmol) and 1-bromo-3-(phenylthio)propane[14a] (26.7 g, 115 mmol) in dry THF (80 mL) under $N_2$ at room temperature. The mixture was stirred for 3 h at room temperature and then quenched with saturated ammonium chloride solution. The organic layer was separated, washed with water (150 mL) and brine (2 × 150 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure to furnish an orange brown oily residue. Chromatography of the residue (900 g silica gel, 2% EtOAc in $CH_2Cl_2$) furnished 27.9 g (84%) of pure alcohol **9a** as a bright yellow viscous oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.65–1.95 (m, 4 H, $SCH_2CH_2CH_2CHOH$), 2.33 (s, 3 H, $CH_3$), 2.58 (br s, 1 H, O*H*), 2.93 (t, $J$ = 7 Hz, 2 H, $SCH_2$), 3.80 (s, 3 H, $OCH_3$), 4.81 (t, $J$ = 6 Hz, 1 H, C*H*OH), 6.68 (s, 1 H, Ar*H*), 6.74 (d, $J$ = 7 Hz, 1 H, Ar*H*), 7.12–7.16 (m, 1 H, Ar*H*), 7.22–7.31 (m, 5 H, Ar*H*); IR (film) (OH) 3550 $cm^{-1}$.

**1-(2′-Methoxy-4′-methylphenyl)-4-(phenylthio)butane (9b).** To trifluoroacetic acid (66.6 g, 584 mmol) under nitrogen at room temperature was added dropwise a solution of alcohol **9a** (27 g, 89.3 mmol) in dry $CH_2Cl_2$ (50 mL). The yellow color of the alcohol solution instantaneously changed to red on contact with the acid. A solution of triethylsilane (12.7 g, 110 mmol) in dry $CH_2Cl_2$ (10 mL) was added to the reaction. The mixture was stirred overnight under nitrogen at room temperature and then evaporated at reduced pressure. The residue was diluted with ether (100 mL) and washed with saturated sodium bicarbonate solution. The organic layer was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Column chromatography of the residue (600 g silica gel; EtOAc–$CH_2Cl_2$, 1:1) furnished 23 g (90%) of pure **9b** as a nearly colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.66–1.70 (m, 4 H, $SCH_2CH_2CH_2$), 2.32 (s, 3 H, $CH_3$), 2.55–2.60 (m, 2 H, $CH_2Ph$), 2.91–2.96 (m, 2 H, $SCH_2$), 3.78 (s, 3 H, $OCH_3$), 6.65 (s, 1 H, Ar*H*), 6.68 (d, $J$ = 8 Hz, 1 H, Ar*H*), 6.96 (d, $J$ = 7 Hz, 1 H, Ar*H*), 7.15–7.33 (m, 5 H, Ar*H*).

**4-(2′-Methoxy-4′-methylphenyl)butanal (10).** A solution of **9b** (22 g, 76.8 mmol) in dry carbon tetrachloride (50 mL) was added to a solution of NCS (12.8 g, 96.0 mmol) in dry carbon tetrachloride (350 mL). The reaction mixture was stirred under nitrogen for 5 h at room temperature and then filtered, and the filtrate was evaporated under reduced pressure. Acetone (350 mL), water (8 mL), cupric oxide (26 g), and cupric chloride dihydrate (26 g) were added to the residue, and the mixture was refluxed for 15 min to hydrolyze the chloro sulfide intermediate. The reaction was cooled, diluted with ether (200 mL) and filtered. The filtrate was washed with water (100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure. Distillation of the residue furnished 11 g (76%) of the aldehyde **10**, as a yellow oil with bp 101–104 °C (0.25 mmHg): $^1H$ NMR ($CDCl_3$) $\delta$ 1.90 (quintet, $J$ = 7.2 Hz, 2 H, $CH_2CH_2Ph$), 2.32 (s, 3 H, $CH_3$), 2.40 (dt, $J$ = 7.2, 1.2 Hz, 2 H, $CH_2CHO$), 2.62 (t, $J$ = 7.3 Hz, 2 H, $CH_2Ph$), 3.79 (s, 3 H, $OCH_3$), 6.66 (s, 1 H, Ar*H*), 6.69 (d, $J$ = 8.4 Hz, 1 H, Ar*H*), 6.98 (d, $J$ = 8.1 Hz, 1 H, Ar*H*), 9.73 (t, $J$ = 2 Hz, 1 H, C*H*O); IR (neat) (C=O) 1720 $cm^{-1}$. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.29.

**1-(2′-Methoxy-4′-methylphenyl)-8-(phenylthio)-4-octanol (11).** To the Grignard reagent prepared from magnesium (1.74 g, 71.6 mmol) and 1-bromo-4-(phenylthio)butane[14a] (16.07 g, 65.5 mmol) in dry THF (80 mL) under $N_2$ at room temperature was added a solution of **10** (12 g, 62.4 mmol) in dry THF (80 mL). The mixture was stirred for 1.5 h at room temperature and then hydrolyzed with saturated $NH_4Cl$ solution. The organic layer was separated, washed with water (100 mL) and brine (100 mL), and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Column chromatography of the residue (900 g silica gel, 2% EtOAc in $CH_2Cl_2$) furnished 17.85 g (78%) of pure alcohol **11** as a white waxy material: $^1H$ NMR ($CDCl_3$) $\delta$ 1.40–1.71 (m, 11 H, $SCH_2(CH_2)_3CHOH(CH_2)_2$), 2.32 (s, 3 H, $CH_3$), 2.54–2.61 (m, 2 H, $CH_2Ph$), 2.92 (t, $J$ = 7 Hz, 2 H, $SCH_2$), 3.63 (br s, 1 H, O*H*), 3.79 (s, 3 H, $OCH_3$), 6.66 (s, 1 H, Ar*H*), 6.69 (d, $J$ = 7.8 Hz, 1 H, Ar*H*), 6.70 (d, $J$ = 7.3 Hz, 1 H, Ar*H*), 7.14–7.34 (m, 5 H, Ar*H*); IR (KBr) (OH) 3400 $cm^{-1}$.

**1-(2′-Methoxy-4′-methylphenyl)-8-(phenylthio)octan-4-one (12). Procedure A.** To a suspension of Celite (20 g) in dry $CH_2Cl_2$ (100 mL) was added pyridinium chlorochromate (5.34 g, 24.8 mmol), and the mixture was stirred for 30 min under nitrogen at room temperature. A solution of alcohol **11** (5.86 g, 16.3 mmol) in dry $CH_2Cl_2$ (50 mL) was added to the PCC–Celite suspension. The mixture was stirred for 3 h and then filtered, and the residue was washed with diethyl ether (100 mL). The combined filtrate and washings were evaporated under reduced pressure, and the residue was filtered through a short pad of silica gel ($CH_2Cl_2$). Evaporation of the solvent at reduced pressure furnished 4.28 g (74%) of pure **12** as a viscous yellow oil.

**Procedure B.** To a suspension of pyridinium chlorochromate (27 g, 125 mmol) in dry $CH_2Cl_2$ (200 mL) was added alumina (80 g), and the mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the residue was dried under vacuum for 2 h at room temperature. To a stirred suspension of the PCC/alumina reagent in dry benzene (400 mL) was added a solution of **11** (17.9 g, 49.8 mmol) in dry benzene (100 mL), and the mixture was stirred at room temperature for 6 h under nitrogen and then filtered, and the filtrate was evaporated at reduced pressure. Filtration of the residue through a short column of silica gel ($CH_2Cl_2$) gave 13.6 g (76%) of the pure ketone **12** as a yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.62–1.68 (m, 4 H, $SCH_2(CH_2)_2$), 1.83 (quintet, $J$ = 7 Hz, 2 H, $CH_2CH_2Ph$), 2.32 (s, 3 H, $CH_3$), 2.38 (t, $J$ = 7.3 Hz, 4 H, $CH_2C{=}OCH_2$) 2.56 (t, $J$ = 7.2 Hz, 2 H, $CH_2Ph$), 2.90 (t, $J$ = 7.1 Hz, 2 H, $SCH_2$), 3.79 (s, 3 H, $OCH_3$), 6.66 (s, 1 H, Ar*H*), 6.69 (d, $J$ = 7.3 Hz, 1 H, Ar*H*), 6.97 (d, $J$ = 7.2 Hz, 1 H, Ar*H*), 7.16–7.33 (m, 5 H, Ar*H*); IR (film) (C=O) 1710 $cm^{-1}$.

**2-(2-(2′-Methoxy-4′-methylphenyl)ethyl)-2-cyclohexen-1-one (14).** To a solution of NCS (6.33 g, 47.4 mmol) in dry carbon tetrachloride (250 mL) was added a solution of **12** (13 g, 36.5 mmol) in dry carbon tetrachloride (50 mL). The reaction mixture was stirred for 4 h under nitrogen at room temperature and then filtered, and the solvent was removed under reduced pressure. Cupric oxide (12.4 g), cupric chloride dihydrate (12.4 g), acetone (200 mL), and water (4 mL) were added to the crude keto chloro sulfide, and the mixture was refluxed for 15 min. The mixture was cooled, diluted with ether (200 mL), and then filtered. The filtrate was washed with water (2 × 100 mL) and brine (2 × 100 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of a small sample of the residue (10 g silica gel, 2% EtOAc in $CH_2Cl_2$) furnished pure **13**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.82–1.93 (m, 4 H, $CH_2$'s), 2.33 (s, 3 H, $CH_3$), 2.35–2.49 (m, 6 H, $CH_2$'s), 2.56 (t, $J$ = 7.4 Hz,

2 H, $CH_2Ph$), 3.79 (s, 3 H, $OCH_3$), 6.66 (s, 1 H, Ar*H*), 6.68 (d, $J$ = 7.8 Hz, 1 H, Ar*H*), 6.97 (d, $J$ = 7.3 Hz, 1 H, Ar*H*), 9.75 (t, $J$ = 1.5 Hz, 1 H, C*H*O); IR (film) 1710, 2725 $cm^{-1}$.

To a solution of the crude keto aldehyde **13** in THF (200 mL) was added perchloric acid (3 N, 100 mL) and water (200 mL), and the solution was heated at reflux overnight. The reaction was cooled, and the phases were separated. The organic layer was washed with saturated aqueous sodium bicarbonate solution (3 × 100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue (300 g silica gel, $CH_2Cl_2$) gave 5.40 g (61%) of pure **14** as a yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.95 (q, $J$ = 6.4 Hz, 2 H, $CH_2CH_2C$=O), 2.25–2.30 (m, 2 H, $CH_2C$=O), 2.32 (s, 3 H, $CH_3$), 2.39–2.46 (m, 4 H, C=CHC$H_2$), 2.67 (t, $J$ = 7 Hz, 2 H, $CH_2Ph$), 3.79 (s, 3 H, $OCH_3$), 6.59 (t, $J$ = 4.6 Hz, 1 H, C=C*H*), 6.64 (s, 1 H, Ar*H*), 6.68 (d, $J$ = 7.7 Hz, 1 H, Ar*H*), 6.96 (d, $J$ = 7.3 Hz, 1 H, Ar*H*); IR (film) (C=O) 1670 $cm^{-1}$. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72; H, 8.34.

**1-Oxo-8-methoxy-6-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (15).** To a solution of **14** (4 g, 16.4 mmol) in dry $CH_2Cl_2$ (30 mL) was added $TiCl_4$ (6.26 g, 33.0 mmol) as a 1 M solution in $CH_2Cl_2$. The mixture was stirred under $N_2$ at room temperature for 18 h, and then dilute HCl (1 N) was added cautiously. The layers were separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed (200 g silica gel, 2% EtOAc in $CH_2Cl_2$) to give 2.2 g (56%) of **15** as a mixture of cis and trans isomers. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.60; H, 8.25.

The ratio of isomers depended on the reaction time and for an 8-h reaction was 1:1.05 as determined by GC–MS. When the reaction was run for 18 h the ratio was 1:1.2. A sample was carefully chromatographed to obtain the pure isomers. The major isomer eluted first: mp 149–150 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.43–1.86 (m, 3 H, $CH_2CH$), 2.2–2.53 (m, 6 H, $CH_2CH$ and at 2.33 (s, 3 H, $CH_3$)), 2.66–2.79 (m, 1 H, C*H*), 2.74 (br t, $J$ = 13.4 Hz, 1 H, C*H*), 2.90 (dd, $J$ = 17.4, 5.7 Hz, 1 H, C*H*), 3.80 (s, 3 H, $OCH_3$), 6.55 (s, 1 H, Ar*H*), 6.79 (s, 1 H, Ar*H*). IR (KBr) (C=O) 1710 $cm^{-1}$. Minor isomer: mp 133–134 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.70–2.10 (m, 6 H, $CH_2$'s), 2.32 (s, 3 H, $CH_3$), 2.33–2.52 (m, 3 H, $CH_2CH$), 2.66 (dt, $J$ = 12.15, 3.9 Hz, 1 H, C*H*), 2.92 (ddd, $J$ = 17.46, 6.05, 2.3 Hz, 1 H, C*H*), 3.08 (q, $J$ = 5.37 Hz, 1 H, C*H*), 3.80 (s, 3 H, $OCH_3$), 6.52 (s, 1 H, Ar*H*), 6.60 (s, 1 H, Ar*H*).

**8-Methoxy-6-methyl-1-(*tert*-butyldimethylsiloxy)-3,4,4a,9,10,10a-hexahydrophenanthrenes (16).** The following procedure was used to prepare the silyl enol ethers of either the mixture or of the individual silyl enol ether isomers of **16**. To a stirred solution of tricyclic ketone **15** (300 mg, 1.23 mmol) and dry triethylamine (186 mg, 1.84 mmol) in dry $CH_2Cl_2$ (5 mL) at room temperature was added *tert*-butyldimethylsilyl triflate (0.65 g, 2.46 mmol). The mixture was stirred for an hour under nitrogen and then diluted with water (20 mL) and ether (20 mL). The organic phase was separated, washed with water (50 mL) and brine (50 mL), and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed (10 g neutral alumina, $CH_2Cl_2$) to furnish 0.42 g (95%) of the pure silyl enol ether **16**. Major isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 0.16 (s, 6 H, $Si(CH_3)_2$), 0.94 (s, 9 H, $SiC(CH_3)_3$), 1.34–1.42 (m, 2 H, $CH_2$), 2.09–2.24 (m, 3 H, $CH_2CH$), 2.34 (s, 3 H, $CH_3$), 2.43–2.65 (m, 4 H, $CH_2$'s), 2.87 (dd, $J$ = 17.7, 7.05 Hz, 1 H, C*H*), 3.80 (s, 3 H, $OCH_3$), 4.90 (m, 1 H, C=C*H*), 6.55 (s, 1 H, Ar*H*), 6.80 (s, 1 H, Ar*H*); IR (KBr) (C=C) 1665 $cm^{-1}$. Minor isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 0.14 (s, 6 H, $Si(CH_3)_2$), 0.93 (s, 9 H, $SiC(CH_3)_3$), 1.45–1.71 (m, 2 H, $CH_2$'s), 1.71–1.85 (br d, 1 H, C*H*), 1.97–2.27 (m, 2 H, $CH_2$'s), 2.30 (s, 3 H, $CH_3$), 2.43–2.65 (m, 4 H, $CH_2$'s), 2.87 (dd, $J$ = 17.7, 7.05 Hz, 1 H, C*H*), 3.80 (s, 3 H, $OCH_3$), 4.88 (m, 1 H, C=C*H*), 6.47 (s, 1 H, Ar*H*), 6.62 (s, 1 H, Ar*H*); IR (KBr) (C=C) 1667 $cm^{-1}$.

**8-Methoxy-6-methyl-1,4,4a,9,10,10a-hexahydrophenanthren-1-one (4).** To a stirred solution of $Pd(OAc)_2$ (0.59 g, 2.64 mmol) in dry acetonitrile (5 mL) was added a solution of the major silyl enol ether **16** (0.79 g, 2.20 mmol, derived from the major ketone isomer **15**) in dry $CH_2Cl_2$ (3 mL). The mixture was refluxed under nitrogen for 2 h, during which time formation of a silver mirror of $Pd^0$ was observed. The mixture was cooled and then filtered through a thin pad of cotton. The filtrate was diluted with ether (20 mL) and water (20 mL), and the layers were separated. The organic phase was washed with water (20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed (10 g silica gel, 2% EtOAc in $CH_2Cl_2$) to furnish 285 mg (53%) of the pure tricyclic enone **4** as a yellow solid with mp 165–167 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 2.26–2.61 (m, 5 H, $CH_2CH_2CH$), 2.35 (s, 3 H, $CH_3$), 2.94–3.17 (m, 3 H, $CH_2CH$), 3.82 (s, 3 H, $OCH_3$), 6.14 (dd, $J$ = 10.31, 2.93 Hz, 1 H, C=C*H*), 6.57 (s, 1 H, Ar*H*), 6.73 (s, 1 H, Ar*H*), 7.04–7.10 (m, 1 H, C=C*H*); IR (KBr) (C=O) 1680 $cm^{-1}$. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.41. Found: C, 79.40; H, 7.52.

**2-Methyl-8,13-dihydroxy-7-oxo-4,9,12-trimethoxy-5,6,6a,7,14,14a-hexahydrobenzo[*a*]naphthacene (5).** To a cold (−78 °C), magnetically stirred solution of lithium *tert*-butoxide, prepared from *tert*-butyl alcohol (92 mg, 1.24 mmol) and *n*-BuLi (0.775 mL of a 1.6 M solution, 1.24 mmol) in dry THF (5 mL) was added the dimethoxyphthalide sulfone **3**[7] (138 mg, 0.41 mmol) as a solid in one portion. The mixture was stirred for 10 min, and then a solution of the tricyclic enone **4** (110 mg, 0.45 mmol) in dry THF (5 mL) was rapidly added. The cooling bath was removed, and the mixture was allowed to stir for 1 h at room temperature. As the reaction progressed, the yellow color changed rapidly to yellow orange until finally a deep red solution was obtained. The mixture was acidified with HCl (2 N, 5 mL), and the precipitate was filtered and washed with water. The filtrate was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure. The residue was recrystallized from $CH_2Cl_2$–hexanes to give 142 mg (80%) of pure **5** as a yellow orange solid with mp 255–257 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 1.52–1.61 (m, 2 H, $CH_2$), 2.39 (s, 3 H, $CH_3$), 2.53–2.65 (m, 3 H, $OCH_3$), 2.72–2.80 (m, 1 H, C*H*), 3.0–3.2 (m, 2 H, $CH_2$), 3.84 (s, 3 H, $OCH_3$), 3.98 (s, 3 H, $CH_2CH$), 4.04 (s, 3 H, $OCH_3$), 6.59 (s, 1 H, Ar*H*), 6.74 (d, $J$ = 8.79 Hz, 1 H, Ar*H*), 6.96 (d, $J$ = 8.86 Hz, 1 H, Ar*H*), 7.01 (s, 1 H, Ar*H*), 9.70 (s, 1 H, O*H*), 14.35 (s, 1 H, O*H*).

**2-Methyl-7-hydroxy-4,9,12-trimethoxy-5,6-dihydrobenzo[*a*]naphthacene-8,13-dione (1b).** Oxygen was bubbled through a solution of **5** (64 mg, 0.15 mmol) in DMF (5 mL) heated over a steam bath for 3 h. The mixture was cooled and diluted with EtOAc (20 mL) and water (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed (5 g silica gel, 5% EtOAc in $CH_2Cl_2$) to furnish 51 mg (80.9%) of pure **2** as a red-orange solid with mp 271–273 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 2.42 (s, 3 H, $CH_3$), 2.83–2.88 (m, 2 H, $CH_2$), 2.93–2.98 (m, 2 H, $CH_2$), 3.87 (s, 3 H, $OCH_3$), 4.01 (s, 3 H, $OCH_3$), 4.04 (s, 3 H, $OCH_3$), 6.76 (s, 1 H, Ar*H*), 7.38 (s, 3 H, Ar*H*), 8.14 (s, 1 H, Ar*H*), 13.13 (s, 1 H, O*H*); IR (KBr) (OH) (weak) 3200–3600; (C=O) 1622 and 1564 $cm^{-1}$. Anal. Calcd for $C_{26}H_{22}O_6$: C, 72.54; H, 5.15. Found: C, 72.33; H, 5.37. High-resolution mass spectrum: calcd 430.142, found 430.144.

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