Articles

Synthesis of Putative Intermediates in the Biosynthesis of the Kinamycin Antibiotics: Total Synthesis of Phenanthroviridin Aglycon and Related Compounds

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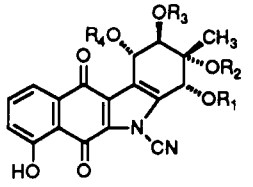
Phenanthroviridin aglycon, **14**, recently isolated from *Streptomyces viridiochromogenes* DSM 3972, and the corresponding pyridone **10** have been synthesized from the common intermediate (bromoaryl)naphthamide **42**. This was prepared by condensation of a (trimethylsilyl)ethyl (bromoaryl)cinnamate **36** and a methoxy-substituted cyanophthalide anion **15**, providing the ABD rings of the target benzo[*b*]phenanthridine skeleton. The aglycon **14** was obtained by a sequence of metal–halogen exchange and formylation, Hofmann rearrangement, cyclization, and deprotection. The pyridone was obtained by Hofmann rearrangement, metal–halogen exchange, cyclization, and deprotection. In addition, a route to cinnamate **36** via coumarin **49** was developed which would allow selective protection of the 1-hydroxyl group for synthesis of glycosidic analogues of phenanthroviridin, **13**. The methodology developed is useful for preparation of **10**, **14**, and analogues specifically labeled at C-5 for study of biosynthesis of the kinamycin antibiotics.

The kinamycin antibiotics (cf. kinamycin D, **1**) were isolated from *Streptomyces murayamaensis* and characterized by Ōmura and co-workers.[1-3] These compounds are active against Gram-positive and—to a lesser degree—Gram-negative organisms. Antitumor activity is exhibited by kinamycin C against Ehrlich ascites carcinoma and against sarcoma-180.[2] We have previously isolated four additional active metabolites: kinamycin E, **2**, kinamycin F, **3**, prekinamycin, **4**, and keto-anhydrokinamycin, **5**, from the same organism.[4] Recently, 3-*O*-isobutrylkinamycin C, **6**, and 4-deacetyl-4-*O*-isobutrylkinamycin C, **7**, which are active against Gram-positive bacteria, L1210 leukemia, IMC carcinoma, LX-1 human lung carcinoma, and SC-6 human stomach carcinoma were isolated from a *Saccharothrix* species.[5] The remarkable benzo[*b*]tetrahydrocarbazole skeleton and cyanamide moiety are unique to this group of metabolites.



	R1	R2	R3	R4
1	Ac	H	Ac	H
2	H	H	Ac	H
3	H	H	H	H
6	Ac	CO*i*-bu	H	H
7	CO*i*-bu	H	H	H

Previous investigations in our laboratory have established that the kinamycins are of polyketide origin, apparently derived from a decaketide **8**,[6,7] with the biosynthesis of the benzo[*b*]carbazole skeleton of the kinamycin antibiotics proceeding via the benzo[*a*]anthraquinone **9**[7] (Figure 1). It appears that **9** undergoes an unusual oxidation/nitrogen insertion/ring contraction process leading to the formation of the *N*-cyanobenzo[*b*]carbazole skeleton to give prekinamycin, **4**, by excision of C-5 and C-6 in which C-6 is lost and C-5 ends up in the cyanamide moiety.[6] We had predicted that the hypothetical pyridone **10**, which could be formed by oxidation[8] of **9** via a diacid intermediate **11** and/or the acid aldehyde intermediate **12**, might be an intermediate in this remarkable transformation[6] although naturally occurring compounds which have the benzo[*b*]phenanthridine skeleton were unknown at that time. However, the isolation of the first naturally occuring benzo[*b*]phenanthridine, phenanthroviridin, **13**, and its aglycon, **14**, from *S. viridiochromgenes* DSM 3972 has recently been reported.[9] Both compounds are active against lung carcinoma MBA9812 in mice. It seemed quite reasonable to also consider **14** as a potential intermediate in the formation of the benzo[*b*]carbazole skeleton, and a reasonable modification of the biosynthetic proposal which includes **14** is shown in Figure 1.

The need for compounds with strategically placed isotopic labels for biosynthetic studies and the lack of useful methods of synthesis of the potentially therapeutic benzo[*b*]phenanthridines prompted us to initiate a program to develop a divergent methodology for the preparation of compounds **9–14**. We have recently reported part of these studies leading to the total synthesis of phenanthroviridin aglycon **14**.[10] This article describes the details

(1) Ito, S.; Matsuya, T.; Otani, M.; Nakagawa, A.; Iwai, Y.; Ohtani, M.; Hata, T. *J. Antibiot.* **1970**, *23*, 315–317.
(2) Hata, S.; Ōmura, S.; Iwai, Y.; Nakagawa, A.; Otani, M. *J. Antibiot.* **1971**, *24*, 353–359.
(3) Ōmura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931–940.
(4) Seaton, P. J.; Gould, S. J. *J. Antibiot.* **1989**, *42*, 189–197.
(5) Isshiki, K.; Sawa, T.; Nakagawa, H.; Matsuda, N.; Hattori, S.; Hamada, M.; Takeuchi, T.; Oosono, M.; Ishizuka, M.; Yang, Z.; Zhu, B.; Xu, W. *J. Antibiot.* **1989**, *42*, 467–469.
(6) Seaton, P. J.; Gould, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 5912–5914.
(7) Seaton, P. J.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5282–5284.
(8) For related biological oxidations see ref 30 in ref 7.
(9) Fendrich, G.; Zimmermann, W.; Gruner, J.; Auden, J. A. L. Eur. Pat. Appl. EP 304, 400 (Cl.C07D221/18), 22 Feb 1989, CH Appl. 87/3, 196, 20 Aug 1987, 13 pages; *Chem. Abstr.* **1990**, *112*, 75295q.
(10) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1991**, *56*, 2289–2291.

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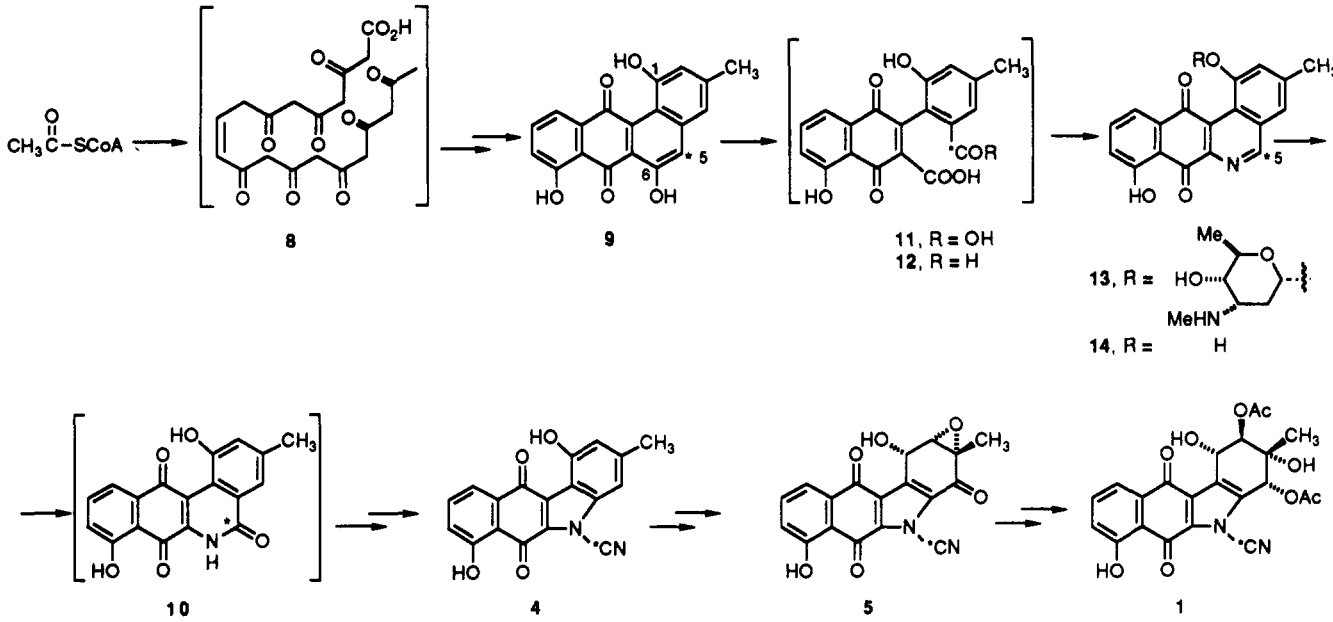
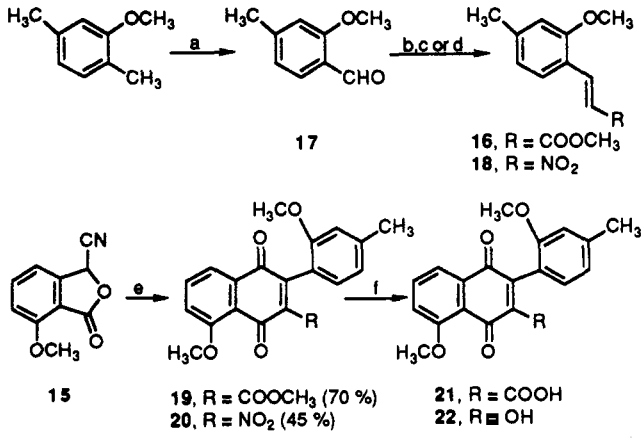


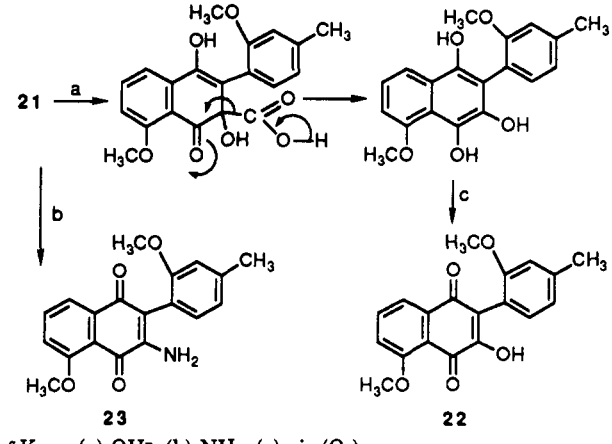
Figure 1. Biosynthesis of kinamycin D in *S. murayamaensis*.

Scheme I[a]



[a] Key: (a) $K_2S_2O_8$, Cu^{2+}; (b) malonic acid/py/piperidine; (c) CH_2N_2; (d) CH_3NO_2/bitylamine; (e) LDA then **16** or **18**; (f) KOH/H_2O/THF.

Scheme II[a]



[a] Key: (a) OH^-; (b) NH_3; (c) air (O_2).

of the divergent methodology developed for the total synthesis of **10** and **14** and analogues, along with some of the potentially biologically important aspects of the chemistry of these compounds that were discovered during these studies.

Results and Discussion

In order to obtain the angular tetracyclic ring system, we envisioned that the ABD rings could be constructed via coupling of a cyanophthalide with a substituted cinnamate or nitrostyrene.[11] This would allow specific introduction of isotopic labels at C-5 (and nitrogen at position 6 in the case of **10** and **14**) near the end of the synthesis. Readily available cyanophthalide **15**, which has the required substitution, was used for the synthesis.[12]

Initially the desired cinnamate **16** was prepared in good yield from aldehyde **17**[13] by Knoevenagel condensation[14] with malonic acid to give the corresponding cinnamic acid followed by esterification with diazomethane (Scheme I).

Later, conditions were found for successful condensation[15] with nitromethane to yield the nitrostyrene **18**. Consensation of **16** and **18** with the anion of the cyanophthalide[10,12] **15** followed by oxidative workup gave the corresponding quinones **19** and **20**[16] in 70% and 45% yields, respectively.

Treatment of **19** with potassium hydroxide in methanol yielded a mixture of two acidic products, which were soluble in $NaHCO_3$ and were reprecipitated by aqueous HCl. One of the products (43%) was the desired acid **21**. The other was shown to be the hydroxyquinone **22** (44%). The mass spectrum of **22** had a molecular ion at m/z 324 (90%), and there was no acid or ester carbonyl resonance in the ^{13}C NMR spectrum.[17] The conversion of **21** to **22** can be explained by the mechanism shown in Scheme II. The formation of **22** seemed analogous to the biogenesis proposed for **10** and **14** (Figure 2), in this case with hydroxyl as the nucleophile. Therefore, acid **21** was treated

(11) For use of cyanophthalide for synthesis of linear tetracycles see refs 5–8 in ref 10.
(12) Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7009–7011.
(13) Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723–724.
(14) Jones, G. *Org. React.* **1967**, *15*, 204–599.
(15) Schales, O.; Graete, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 4486–4490.
(16) Studies to prepare **4** using **20** are in progress.
(17) Assignment of the structure **22** was confirmed by preparation of the corresponding ethoxycarbonylated derivative. The authentic pure acid **21** could be obtained in good yield by treatment of the *tert*-butyl analogue of **19** with sulfuric acid, or by recrystallization, but the overall yields were low due to lower (~40%) yield in the phthalide cyclization reaction.

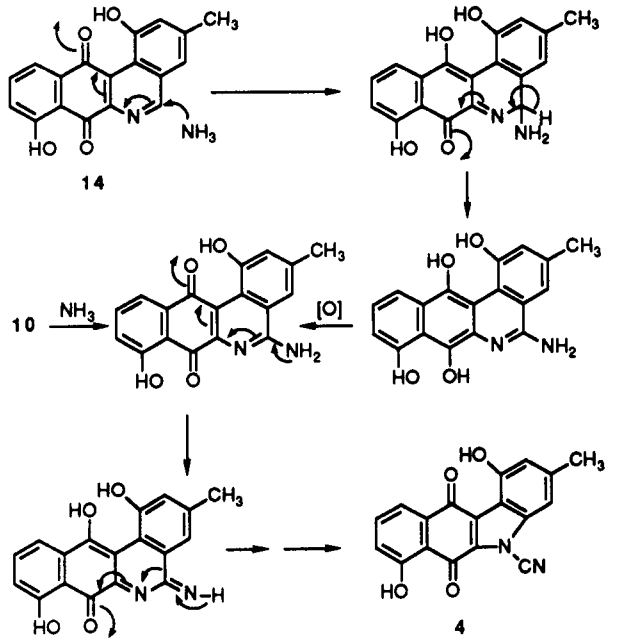
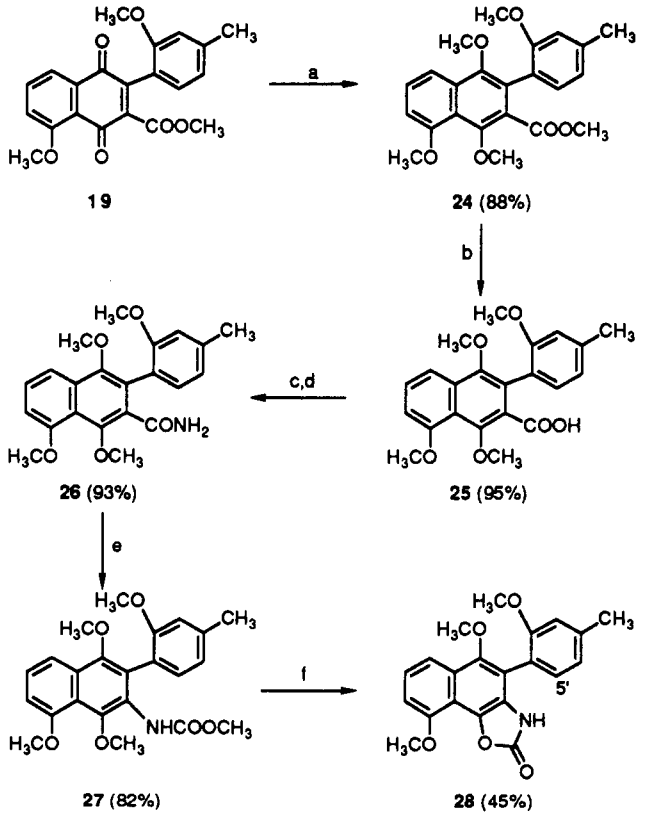


Figure 2. Possible biogenesis of 4 from 14: the naphthoquinone as a "2-proton, 4-electron sink".

Scheme III[a]

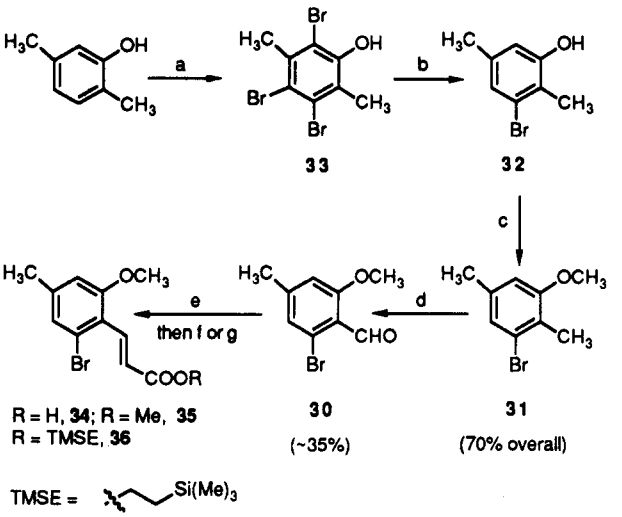


[a] Key: (a) K_2CO_3/Me_2SO_4, $Na_2S_2O_4$, acetone; (b) $K^+{}^-O$-*t*-Bu, 8 equiv, H_2O, 2 equiv, 20 h; (c) $SOCl_2$; (d) NH_3; (e) MeONa/Br_2, (−40 to 65 °C); (f) $POCl_3/SnCl_4$ or Tf_2O.

with ammonia and, as anticipated, yielded the aminoquinone **23** in 75% yield (Scheme II).

Since the quinone **19** was unstable under the conditions required for the hydrolysis, it was reduced to the corresponding hydroquinone using sodium dithionite and protected in situ by methylation with dimethyl sulfate[18] to

Scheme IV[a]



[a] Key: (a) $AlBr_3/Br_2$, CH_2Cl_2; (b) aqueous HI, reflux; (c) $(CH_3)_2SO_4$/BTBA Cl/aqueous NaOH/CH_2Cl_2; (d) $K_2S_2O_8/Cu^{2+}$/py; (e) malonic acid/py/pyridine; (f) CH_2N_2; (g) $SOCl_2$ then lithium 2-(trimethylsilyl)ethoxide.

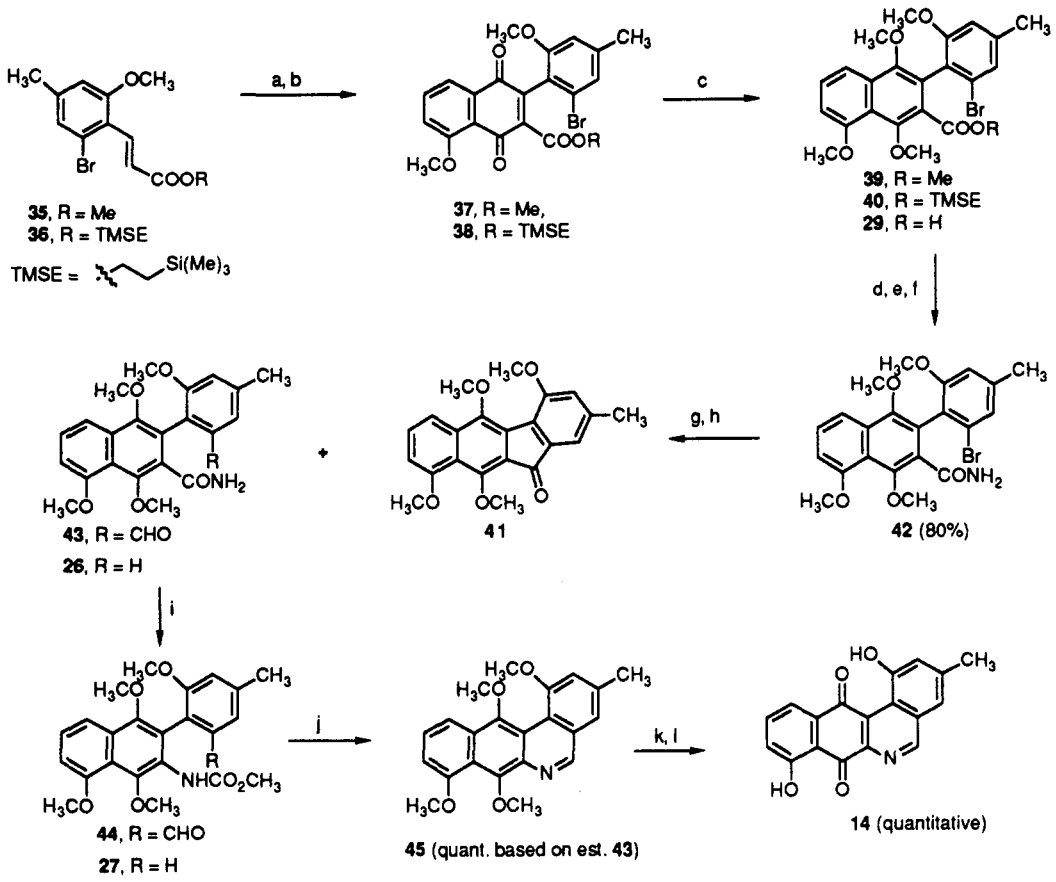
give compound **24** (Scheme III). The ester **24** proved to be extremely difficult to hydrolyze using standard reagents such as potassium hydroxide in methanol, but was successfully cleaved using 8 equiv of potassium *tert*-butoxide/2 equiv of water/ether[19] and sonication to give acid **25** in 95% yield. The acid was converted to the corresponding amide **26** via the acid chloride, and rearrangement of the amide under modified Hofmann conditions[20] gave the carbamate **27** (82%). It had been expected that the carbamate **27** would furnish the desired benzo[*b*]-phenanthridine nucleus upon intramolecular Bischler–Napieralski[21,22] or photochemical cyclization reactions.[23] Unfortunately, attempts to effect cyclization under photochemical conditions only gave decomposition, while treatment with $POCl_3$/cat. $SnCl_4$[21] or with triflic anhydride[22] gave only the oxazolidinone **28**. Presumably, the activated intermediate in the cyclization reaction prefered to cyclize on the methoxy oxygen. It was clear from these results that it was necessary to introduce functionality at the C-5′ position to achieve cyclization.

Aryl bromides can be subjected to transformations such as carbonylation[24] and metal–halogen exchange;[25] therefore 5′-bromo acid **29** (Scheme V) was next chosen for synthesis. Bromoaldehyde **30**, required for the preparation of compounds in the bromo series, was prepared from **31** via **32** and **33**, as previously described (Scheme IV),[10] and condensation with malonic acid gave the cinnamic acid **34** in 84% yield. The cinnamic acid was treated with diazomethane to furnish the methyl ester **35**. Alternatively, the 2-(trimethylsilyl)ethyl (TMSE) ester **36** was prepared via the acid chloride. The cinnamate esters **35** and **36** each reacted with the anion of the cyanophthalide to give the quinones **37** and **38** in good yields (Scheme V). Reduction

(18) Kelly, T. R.; Magee, J. A. Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798–799.

(19) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918–920.
(20) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290–292.
(21) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1922–1926.
(22) Nagubandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165–177.
(23) Yang, N. C.; Shani, A.; Lenz, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 5369.
(24) Heck, R. F. *Pallidium Reagents in Organic Synthesis*; Academic Press: New York, 1985; p 348–361.
(25) Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145–1148.
(26) McMurray, J. E.; Wong, G. B. *Synth. Commun.* **1972**, 389–394.

Scheme V[a]



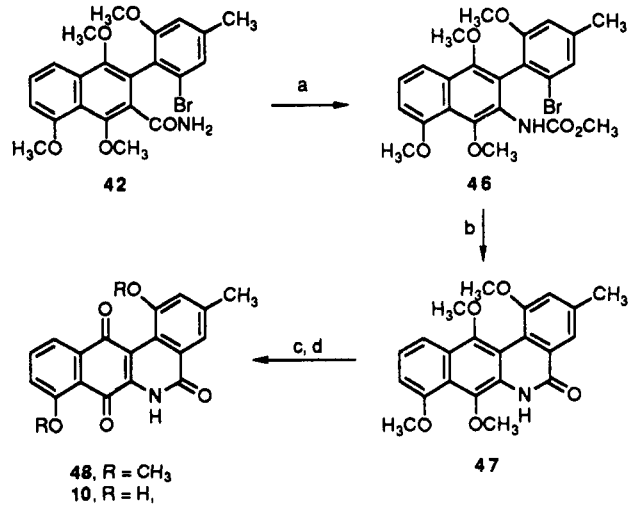
[a] Key: (a) **15**, LDA; (b) O_2; (c) $K_2CO_3/(CH_3)_2SO_4$, $Na_2S_2O_4$, acetone; (d) $Bu_4N^+F^-/THF$; (e) Tf_2O/py; (f) NH_3; (g) 2.5 equiv *t*-BuLi, −89 °C; (h) DMF; (i) $NaOMe/Br_2$ (−54 to 55 °C); (j) H_2O/reflux (NaOH); (k) BBr_3/CH_2Cl_2; (f) aqueous NaOH, O_2.

and methylation of each as in the previous case provided the permethyl ethers **39** and **40**.

The initial studies for further transformations were done with the methyl ester **39**. All attempts to carbonylate **39** at C-5′ with carbon monoxide using catalysts such as $Pd(Ph_3P)_4/Bu_3SnH/CO$,[27] $Pd(OAc)_2/Ph_3P/Bu_3N/CO$,[28] $Pd(Ph_3P)_4$/titanium butoxide,[29] or $(Co)_2CO_8/NaOH/h\nu/Bu_4NBr$[30] failed to give the desired formylated product. Conversion of the bromide to the corresponding iodide[31] using CuI/KI was also unsuccessful. Treatment of **39** with trimethylstannyl lithium[32] in the hope of obtaining the tin derivative only gave fluorenone **41** in poor yield. Surprisingly, attempts to hydrolyze **39**, again using 8 equiv of potassium *tert*-butoxide/2 equiv of water/ether[19] with sonication, gave a mixture of the bromo acid **29** (~60%) and the debrominated acid **25** (40%). Hydrolysis of the ester **39** under strongly acidic conditions such as 10 M HCl at reflux or neutral conditions such as LiI/NaCN/DMF[26] resulted in the loss of the methyl ether protecting groups, as well.

At this point it was decided to use an ester which could be cleaved under very mild and preferably neutral conditions. Thus, the TMSE ester **40** was deprotected using TBAF[33] to give a quantitative yield of the acid **29**, but

Scheme VI[a]



[a] Key: (a) $MeONa/Br_2$ (−55 to 65 °C); (b) *t*-BuLi, −98 °C; (c) CAN; (d) BBr_3.

conversion of the acid to the amide using thionyl chloride and ammonia gave very low yields of the amide **42**. It appeared that the carboxyl group is extremely hindered, and attempts to drive the reaction by heating **29** with thionyl chloride resulted in the loss of methyl ether protection. However, the carboxyl function was successfully activated using triflic anhydride in pyridine and then treated with ammonia to give an 80% yield of the amide **42**. Formylation then gave **43**, along with desbromoamide

(27) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175–7176.
(28) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684–1687.
(29) Woell, J. B.; Fergusson, S. B.; Alper, H. *J. Org. Chem.* **1985**, *50*, 2134–2136.
(30) Brunet, J.; Sidot, C.; Caubere, P. *Tetrahedron Lett.* **1981**, *22*, 1013–1016.
(31) Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* **1985**, 411–412.
(32) Corriu, R. J. P.; Guerin, C. *J. Organometal. Chem.* **1980**, *197*, C19–C21.
(33) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039–3044.

26. Fluorenone 41[34] was formed as a minor side product (3% yield), resulting from intramolecular attack of the aryl carbanion on the lithioamide. Subsequent conversion of 43 to the carbamate 44 was followed by cyclization in situ to give the protected benzo[b]phenanthridine 45 as described previously.[10] Deprotection of 45 and oxidation finally gave 14 in quantitative yield (Scheme V).

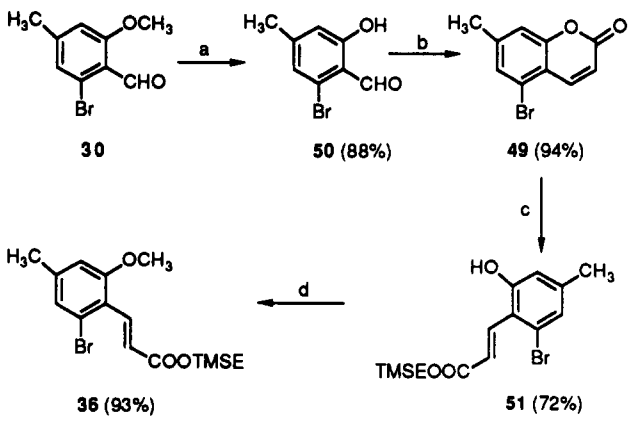
For the synthesis of benzo[b]phenanthridone 10, the bromo amide 42 was first converted to the carbamate 46 and then treated with *tert*-butyllithium at −98 °C to generate the aryllithium which cyclized with the carbamate to give phenanthridone 47 (59%), along the desbromoamide 27 (~30%) (Scheme VI). Deprotection proved to be much more difficult in this case. Attempts to remove the methoxy methyls using reagents such BBr_3,[35] NaCN in DMSO,[36] or sodium propanethiolate in DMF[37] gave only incomplete deprotection or decomposition products. However, initial oxidation with ceric ammonium nitrate (CAN)[38] furnished the quinone 48, and the last two methyl groups were then removed with BBr_3 to give the target benzo[b]phenanthridone 10 in quantitative yield.

Preparation of the (bromoaryl)naphthamide 42 has led to a facile divergent approach to the synthesis of the naturally occurring benzo[b]phenanthridine 14 and the corresponding pyridone 10, one or both of which may be intermediates in kinamycin biosynthesis. The failure of our initial approach, which required either photochemical or Bischler–Napieralski cyclization of 27 to yield the desired tetracyclic structures, may have been due to the D ring being skewed to the plane of the AB rings, since models indicate the methoxy groups would otherwise collide. However, in contrast to this, the anion of formyl carbamate 44 underwent very facile in situ cyclization and subsequent selective deacylation. Regardless, this region is clearly very hindered by the ortho disubstitution, as evidenced by the very vigorous conditions ("naked hydroxide species" and sonication) that were necessary for conversion of esters 24 and 39 to the corresponding acids and the difficulty in converting acid 29 to amide 42. The precedented methods ($SOCl_2$, oxalyl chloride, oxalyl chloride/DMF, etc.) failed to give reasonable yields, but triflic anhydride was able to provide the needed activation of the acid. "Phosphonium anhydrides" have been used to activate acids in similar fashion.[39]

The loss of bromine on treatment of 39 with *tert*-butoxide/hydroxide in ether appears to have no precedent. This may be due to metal–halogen exchange of the aryl bromide followed by protonation. In contrast, the partial debromination of 42 in preparing 43, though unfortunate, could be anticipated due to partial protonation of the aryllithium formed during the course of the reaction.

It was discovered during this work that the naphthoquinone system acts as a "2-proton, 4-electron sink" in certain transformations (Scheme II), and the resulting hydroquinone is easily oxidized to regenerate the quinone afterwards. This has led us to propose a chemically reasonable mechanism (Figure 2) for the biotransformation of either 10 or 14 to prekinamycin, 4, which may occur in the biosynthesis of the kinamycin antibiotics.

Scheme VII[a]



[a] Key: (a) BBr_3/CH_2Cl_2; (b) Ac_2O/KOAc; (c) ; (d) $K_2CO_3/(CH_3)_2SO_4$, acetone, reflux.

An alternate route to cinnamate 36 from aldehyde 30 via coumarin 49 was developed as shown in Scheme VII. Thus, 30 was deprotected[35] with BBr_3 to give 50 which, under Perkin conditions,[40] gave coumarin 49. Reaction of 49 with lithium 2-(trimethylsilyl)ethoxide produced 51, which on methylation yielded 36. This should, in principle, allow alternate protection of the C-1 phenol for glycoside synthesis.

In summary, an efficient synthetic route to the benzo[b]phenanthridine skeleton has been devised that should allow specific introduction of isotopic labels at positions 5 and 6 (Figure 2) in the putative biosynthetic intermediates 10 and 14 and that potentially can yield a variety of glycosides such as 13, as well. Further studies on the synthesis and biosynthesis of these compounds will be reported in due course.

Experimental Section

General Procedures. All commercially available reagents were used as received except where noted. The solvents used for chromatography and for reactions were distilled prior to use. Dichloromethane was distilled from calcium hydride, and THF was distilled from sodium benzophenone ketyl. The reactions requiring anhydrous conditions were performed under an argon atmosphere. Elemental analyses were done at Desert Analytics, Tuscon, AZ. A Branson 2200 sonicator was used for reactions requiring sonication.

Methyl 2-Methoxy-4-methylcinnamate, 16. A solution of malonic acid (2.77 g, 26.6 mmol), aldehyde 17 (2.00 g, 13.3 mmol), and piperidine (0.25 mL) in pyridine (8 mL) was heated at 85 °C for 2 h and 115 °C for 2 h. The solution was cooled and poured over a mixture of ice and 1 N HCl (100 mL). Recrystallization from methanol/acetone gave shining plates of cinnamic acid (2.0 g, 78%): mp 213–214 °C; IR (KBr) 2951, 1689, 1686, 1681, 1218 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 16 Hz, 1 H), 7.42 (d, J = 8 Hz, 1 H), 6.79 (br d, J = 8 Hz, 1 H), 6.73 (s, 1 H), 6.51 (d, J = 16 Hz, 1 H), 3.88 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (DMSO) δ 168.1, 157.7, 142.2, 138.8, 128.4, 121.5, 119.7, 118.1, 112.4, 55.6, 21.5; MS m/e 192.0 (100). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.86; H, 6.24.

A solution of diazomethane in ether was added to a suspension of the acid (2.0 g, 10.4 mmol) in methanol (30 mL) until a yellow color persisted. The mixture was stirred for 15 min, and the solvent was evaporated to give white crystalline solid 16 (2.1 g, quantitative): mp 44–46 °C; IR (KBr) 1719, 1715, 1627, 1610, 1274, 1190, 1174, 1166, 1160, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 16 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 6.74 (d, J = 8 Hz, 1 H), 6.71 (s, 1 H), 6.48 (d, J = 16 Hz, 1 H), 3.85 (s, 3 H), 3.78

(34) We have recently isolated the 4,5,10-triacetoxy-9-methoxy analogue of 41 from fermentations of *S. murayamaensis*: Cone, M. C.; Gore, M. P.; Melville, C.; Gould, S. J. Unpublished results.
(35) McOmie, J. F. W.; West, D. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol V, pp 412–414.
(36) McCarthy, J. R.; Moore, J. L.; Cregge, R. J. *Tetrahedron Lett.* 1978, 5183–5186.
(37) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* 1970, 4459–4462.
(38) Jacob, P., III; Callery, P.; Shulgin, A.; Castagnoli, N., Jr. *J. Org. Chem.* 1976, *41*, 2134–2136.
(39) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* 1989, *54*, 1144–1149.
(40) Johnson, J. R. *Org. React.* 1942, *1*, 210–265.

(s, 3 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.0, 158.1, 142.1, 140.1, 128.6, 121.3, 120.4, 116.9, 111.8, 55.1, 51.3, 21.7; MS *m/e* 206.0 (100%). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.84; H, 6.92.

2-Methoxy-3-methyl-β-nitrostyrene, 18. A solution of the aldehyde **17** (1.50 g, 10 mmol), nitromethane (0.61 g, 10 mmol), and butylamine (0.05 mL) in ethanol was heated at reflux for 7 h. The volatile components were evaporated in vacuo to give a red oil. Compound **18** was recrystallized from this oil in refluxing ether/hexane to give fluffy yellow crystals (1.20 g, 62%) of **18**: mp 182–183 °C dec; IR (KBr) 1623, 1608, 1505, 1493, 1341, 1329, 1267, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 13 Hz, 1 H), 7.80 (d, *J* = 13 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H), 6.79 (d, *J* = 8 Hz, 1 H), 6.76 (s, 1 H), 3.90 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.3, 144.8, 137.0, 135.4, 132.2, 121.8, 116.1, 112.0, 55.3, 21.9; MS *m/e* 193.0 (55), 146.0 (100); HRMS calcd for $C_{10}H_{11}NO_3$ 193.0738, found 193.0739.

Methyl 3-(2-Methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone-2-carboxylate, 19. A solution of the cyanophthalide **15** (0.378 g, 2.00 mmol) in dry THF (5.0 mL) was added to a solution of LDA (prepared from diisopropylamine (0.34 mL, 2.4 mmol) and butyllithium (1.60 mL, 1.41 M in hexanes, 2.25 mmol)) in dry THF (20 mL) at −78 °C. The solution was stirred for 1 h, and a yellow precipitate appeared. A solution of the cinnamate **16** (0.412 g, 2.00 mmol) in dry THF was added, and the mixture was warmed to room temperature over ~3 h and stirred for 16 h. A solution of *p*-toluenesulfonic acid (0.380 g, 2.00 mmol) in dry THF (5 mL) was added, and the solution was poured into water and brought to pH 2.0 using 1 N HCl. Extraction with EtOAc (4 × 20 mL), separation, drying and concentration of the EtOAc layers gave an orange solid. The orange solid was dissolved in 0.5 M KOH (10 mL) and THF (10 mL), and air was bubbled through the solution for 2 h. The precipitated solid was extracted with EtOAc (3 × 30 mL); drying, concentration, and purification by recrystallization (EtOAc/hexane) and/or by flash chromatography (2.5 × 35 cm, 50% EtOAc/hexane) gave yellow crystalline solid **19** (0.516 g, 70%): mp 183–185 °C; IR (KBr) 1738, 1673, 1651, 1289, 1279, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, *J* = 8, 1 Hz, 1 H), 7.70 (br t, *J* = 8 Hz, 1 H), 7.32 (dd, *J* = 8, 1 Hz, 1 H), 7.07 (br d, *J* = 8 Hz, 1 H), 6.79 (d, *J* = 8 Hz, 1 H), 6.76 (s, 1 H), 4.01 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.3, 181.1, 164.8, 159.8, 156.9, 142.5, 141.7, 141.5, 135.2, 134.2, 129.5, 121.2, 119.7, 119.3, 118.1, 117.8, 112.1, 56.5, 55.7, 52.3, 21.8; MS *m/e* 366.1 (89), 149.0 (100); HRMS calcd for $C_{21}H_{18}O_6$ 366.1103, found 366.1103.

2-Nitro-3-(2-methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone, 20. The procedure used for preparation of **19** was performed using **15** (0.163 g, 0.86 mmol), LDA (0.958 mmol), and nitrostyrene **18** (0.166 g, 0.86 mmol) except the mixture was stirred for 48 h at room temperature and then quenched with acid. The oxidation procedure (solution in KOH and treatment with oxygen) was not necessary since the hydroquinone easily oxidized on exposure to air. Flash chromatography (2.5 × 30 cm, 50% EtOAc/hexane) gave an orange solid. Recrystallization from EtOAc/hexane gave orange needles (0.147 g, 47%) of **20**: mp 234–235 °C; IR (KBr) 1673, 1581, 1545, 1471, 1288, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83–7.74 (m, 2 H), 7.39 (dd, *J* = 8, 1 Hz, 1 H), 7.06 (d, *J* = 8 Hz, 1 H), 6.82 (d, *J* = 8 Hz, 1 H), 6.78 (s, 1 H), 4.04 (s, 3 H), 3.74 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 182.6, 182.2, 174.0, 160.4, 156.9, 143.0, 136.1, 135.2, 133.8, 129.3, 121.6, 120.1, 118.5, 117.9, 114.1, 112.2, 56.6, 55.7, 21.9; MS *m/e* 353.1 (89), 307.2 (100). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.27; N, 3.96. Found: C, 64.29; H, 4.03; N, 3.92.

3-(2-Methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone-2-carboxylic Acid, 21, and 2-Hydroxy-3-(2-methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone, 22. A solution of **19** (0.177 g, 0.48 mmol) and KOH (0.190 g, 85%, 2.8 mmol) in 50% aqueous THF (10 mL) was heated at reflux for 16 h. The mixture was cooled and acidified to pH 2.0 using 1 N HCl, and the precipitate formed was extracted with EtOAc (3 × 20 mL). The EtOAc layers were back-extracted with saturated aqueous $NaHCO_3$ (3 × 20 mL), and this was acidified to pH 2.0 using concd HCl. After extraction with EtOAc (3 × 20 mL) and drying, TLC of the mixture in 50% EtOAc/hexane indicated two components were present (R_f's 0 and ~0.35). The mixture was purified using flash chromatography (2 × 30 cm, 50% EtOAc/hexane) to give orange solid **22** (0.069 g, 44%). Although the acid was lost on the column in this experiment standard samples of the acid were prepared by hydrolysis of the *tert*-butyl ester analogue of **19**. The acid was also purified by recrystallization (EtOAc/hexane) in a similar experiment before chromatography.

For compound **21**: mp 213–215 °C dec; IR (KBr) 2950, 1709, 1650, 1586, 1472, 1287, 1250, 1034 cm^{-1}; ^{1}H NMR (DMSO) δ 7.84 (t, *J* = 8 Hz, 1 H), 7.61 (d, *J* = 7 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H), 7.05 (d, *J* = 7 Hz, 1 H), 6.90 (s, 1 H), 6.79 (d, *J* = 8 Hz, 1 H), 3.94 (s, 3 H), 3.64 (s, 3 H), 3.35 (br s, 1 H), 2.33 (s, 3 H); ^{13}C NMR (DMSO) δ 183.1, 180.6, 165.1, 159.4, 156.8, 142.4, 140.9, 140.2, 136.0, 133.4, 129.6, 120.7, 119.2, 118.9, 118.3,[41] 112.1, 56.5, 55.6, 21.3; MS *m/e* 321.1 (100), 352.1 (11); HRMS calcd for $C_{20}H_{16}O_6$ 352.0946, found 352.0946.

For compound **22**: mp >265 °C; IR (KBr) 3303, 1660, 1585, 1382, 1283, 1001 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, *J* = 8, 1 Hz, 1 H), 7.80 (br s, 1 H), 7.72 (t, *J* = 8 Hz, 1 H), 7.27 (d, *J* = 8 Hz, 1 H), 7.12 (d, *J* = 8 Hz, 1 H), 6.86 (d, *J* = 8 Hz, 1 H), 6.82 (s, 1 H), 4.05 (s, 3 H), 3.76 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.0, 180.1, 160.1, 157.0, 153.2, 140.4, 136.4, 135.4, 131.0, 121.2, 120.0, 118.7, 117.0, 116.6, 116.5, 112.2, 56.5, 55.7, 21.8; MS *m/e* 324.1 (90); HRMS calcd for $C_{19}H_{16}O_5$ 324.0997, found 324.0997.

2-Amino-3-(2-methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone, 23. Aqueous ammonia (1 mL, 30%, xs) was added to a suspension of the acid **21** (0.012 g, 0.03 mmol) in methanol (2 mL), and the solution was stirred for 24 h, and after addition of EtOAc (3 mL), the organic solvents and excess ammonia were evaporated. The residual aqueous suspension was extracted with EtOAc (3 × 5 mL) and $CHCl_3$ (5 mL). Drying and concentration gave an orange solid. Flash chromatography (50% EtOAc/hexane, 1 × 30 cm) gave an orange solid (0.010 g) which contained **23** (70% based on ^{1}H NMR) and an unidentified component. Recrystallization from CH_2Cl_2/hexane gave **23** (0.006 g, ~54% yield): mp 205–207 °C dec; IR (KBr) 3465, 3352, 1610, 1577, 1551, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, *J* = 8 Hz, 1 H), 7.65 (t, *J* = 8 Hz, 1 H), 7.19 (d, *J* = 8 Hz, 1 H), 7.09 (d, *J* = 8 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 1 H), 6.82 (s, 1 H), 5.4–4.8 (br s, 2 H), 4.02 (s, 3 H), 3.77 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 181.1, 180.3, 159.7, 157.0, 146.6, 140.0, 136.0, 135.6, 131.6, 121.9, 119.6, 118.6, 118.2, 115.9, 113.0, 112.7, 56.5, 55.8, 21.7; MS *m/e* 323.1 (99); HRMS calcd for $C_{19}H_{17}NO_4$ 323.1157, found 323.1157.

Methyl 1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)-naphthalene-2-carboxylate, 24. A suspension of the quinone **19** (0.100 g, 0.27 mmol), dimethyl sulfate (1.0 mL, 10.50 mmol), anhydrous K_2CO_3 (1.50 g, 10.85 mmol), and sodium dithionite (0.200 g, 1.14 mmol) in acetone (10 mL) under argon was heated at reflux for 17 h. Water (0.5 mL) was added dropwise, and the mixture was heated at reflux an additional 3 h and then cooled to room temperature. Acetone was evaporated from the mixture, and water (10 mL) and 10% aqueous NaOH (1 mL) were added. After being stirred for 2 h, the mixture was extracted with ether (3 × 50 mL). Drying and concentration gave a yellowish oil. Purification by flash chromatography (0.8 × 30 cm, 40% EtOAc/hexane) gave white flaky crystals of **24** (0.095 g, 88%): mp 146–148 °C; IR (KBr) 1734, 1719, 1458, 1370, 1343, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 1 H), 7.46 (t, *J* = 8 Hz, 1 H), 7.13 (d, *J* = 8 Hz, 1 H), 6.92 (d, *J* = 8 Hz, 1 H), 6.81 (d, *J* = 8 Hz, 1 H), 6.78 (s, 1 H), 4.01 (s, 3 H), 3.90 (s, 3 H), 3.73 (s, 3 H), 3.57 (s, 3 H), 3.55 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.8, 156.9, 156.6, 150.1, 149.5, 139.3, 131.9, 131.0, 127.6, 127.2, 125.9, 121.6, 120.9, 120.0, 115.3, 112.0, 106.7, 63.9, 61.3, 56.2, 55.7, 51.7, 21.7; MS *m/e* 396.2 (100); HRMS calcd for $C_{23}H_{24}O_6$ 396.1572, found 396.1573.

1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)-2-naphthoic Acid, 25. The hydrolysis mixture was prepared by addition of water (0.12 mL, 6.7 mmol) to a suspension of potassium *tert*-butoxide (2.60 g, 26 mmol) in ether (50 mL) at 0 °C. The suspension (25 mL) was added to a solution of **24** (0.320 g, 0.82 mmol) in ether (2 mL), and the mixture was sonicated for 0.5 h and stirred for 24 h. Water was added until two clear layers were formed, and the ether layer was separated. The aqueous layer was acidified to pH 2.0 using 10 N HCl, and the precipitated acid was extracted with EtOAc (3 × 20 mL). The EtOAc layers were

(41) This represents two coincidental resonances (cf. spectrum of **19** where these are resolved).

dried and concentrated to give pure white crystalline acid **25**[42] (0.293 g, 95%): mp 188–189 °C; IR (KBr) 2940, 1699, 1572, 1369, 1341, 1263, 1057 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (dd, J = 8, 1 Hz, 1 H), 7.48 (t, J = 8 Hz, 1 H), 7.19 (d, J = 8 Hz, 1 H), 6.93 (dd, J = 8, 1 Hz, 1 H), 6.83 (d, J = 8 Hz, 1 H), 6.76 (s, 1 H), 4.01 (s, 3 H), 3.91 (s, 3 H), 3.67 (s, 3 H), 3.50 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 156.7, 156.6, 150.3, 149.9, 139.4, 132.4, 131.3, 127.7, 126.2, 126.0, 121.4, 121.3, 119.8, 115.4, 111.9, 106.9, 64.0, 61.2, 56.2, 55.4, 21.8; MS m/e 382.2 (100); HRMS calcd for $C_{22}H_{22}O_6$ 382.1416, found 382.1416.

1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)-naphthalene-2-carboxamide, 26. Thionyl chloride (0.5 mL, xs) was added to a solution of the acid **25** (0.100 g, 0.26 mmol) in dry CH_2Cl_2 (1 mL), and the solution was stirred for 20 h. The volatile components were evaporated in vacuo, and the residual oil was dissolved in dry CH_2Cl_2 (4 mL). Ammonia was bubbled through the solution for 15 min, and after stirring for an additional 15 min, the solvent was evaporated. EtOAc (10 mL) was added to the residue, and the mixture was washed with water (2 × 10 mL). Drying and concentration gave a light pink solid. Flash chromatography (2 × 30 cm, EtOAc) gave white solid **26** (0.092 g, 93% yield): mp 179–180 °C; IR (KBr) 3458, 3158, 1683, 1667, 1611, 1570, 1461, 1374, 1262, 1071, 1053, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (dd, J = 1, 8 Hz, 1 H), 7.44 (t, J = 8 Hz, 1 H), 7.18 (d, J = 7 Hz, 1 H), 6.91 (d, J = 7 Hz, 1 H), 6.83 (d, J = 8 Hz, 1 H), 6.77 (s, 1 H), 5.89 (br s, 1 H), 5.76 (br s, 1 H), 4.01 (s, 3 H), 3.90 (s, 3 H), 3.69 (s, 3 H), 3.53 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1; 156.5; 156.4; 150.0; 148.9; 139.2; 131.6; 131.2; 129.8; 127.0; 126.1; 121.6; 121.2; 120.1; 115.2; 111.6; 106.4; 64.0; 61.2; 56.0; 55.3; 21.7; HRMS calcd for $C_{22}H_{23}NO_5$ 381.1576, found 381.1576. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.07; N, 3.67. Found: C, 68.85; H, 6.00; N, 3.49.

Methyl (1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)naphthalen-2-yl)carbamate, 27. Bromine (0.017 mL) was added to a solution of sodium methoxide (prepared by reacting sodium (0.100 g, 4.37 mmol) in dry methanol (4 mL) at −40 °C (dry ice/acetonitrile bath)), and the solution was stirred for 5 min. A solution of the amide **26** (0.092 g, 0.24 mmol) in methanol (3 mL) was added, and the mixture was warmed to room temperature over ~0.5 h and heated at reflux for 0.5 h. Acetic acid (0.270 g, 4.5 mmol) was added after cooling, and the volatile components were removed in vacuo. Water (10 mL) was added to the residue, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were dried and concentrated to give a light pink oil. Flash chromatography (2 × 40 cm, 90% EtOAc/hexane) gave white solid (0.081 g, 82%) **27**: mp 207–208 °C dec; IR (KBr) 3279, 2932, 1718, 1664, 1573, 1457, 1366, 1351, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 8 Hz, 1 H), 7.39 (t, J = 8 Hz, 1 H), 7.18 (d, J = 8 Hz, 1 H), 6.88 (d, J = 8 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H), 6.81 (s, 1 H), 6.18 (br s, 1 H), 3.98 (s, 3 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.52 (s, 3 H), 3.45 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.4, 156.3, 155.6, 149.9, 148.4, 139.2, 131.8, 130.5, 127.5, 126.7, 126.2, 121.3, 120.4, 120.3, 115.0, 111.6, 106.5, 61.9, 60.9, 56.1, 55.4, 52.2, 21.6; HRMS calcd for $C_{23}H_{25}NO_6$ 411.1681, found 411.1682. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.41. Found: C, 67.13; H, 5.96; N, 3.37.

Oxazolidinone 28. Anhydrous $SnCl_4$ (~0.05 mL, xs) was added to a solution of the carbamate **27** (0.050 g, 0.12 mmol) in $POCl_3$ (1 mL), and the mixture was heated at reflux for 4 h. The mixture was cooled and poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The EtOAc layers were dried and concentrated. Flash chromatography (2 × 40 cm, 15% $CHCl_3$/EtOAc) of the residue gave 0.016 g (36%) of **28**: mp >265 °C; IR (KBr) 1762, 1379, 1288, 1254, 1104, 1058, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 9 Hz, 1 H), 7.69 (br s, 1 H), 7.37–7.32 (m, 2 H), 6.92 and 6.90 (m, 3 H), 4.05 (s, 3 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 155.5, 154.2, 150.4, 140.7, 133.1, 132.1, 126.3, 125.7, 124.7, 122.0, 117.7, 115.2, 114.2, 112.9, 112.2, 105.9, 61.6, 55.9, 55.8, 21.8; MS m/e 365.2 (100); HRMS calcd for $C_{21}H_{19}NO_5$ 365.1263, found 365.1263.

3,4,6-Tribromo-2,5-dimethylphenol, 33. A modification of the procedure of Sargent[43] was used to transform 2,5-dimethylphenol to the perbromo derivative. Aluminum (4.00 g, 0.15 mol) was cautiously added in small portions to bromine (100 mL, 1.87 mol) cooled to 0 °C, and the mixture was stirred until the sparks ceased (~2 h). A solution of 2,5-dimethylphenol (40.0 g, 0.33 mol) in dry CH_2Cl_2 (200 mL) was added over 1.5 h, and the mixture was stirred for additional 2 h. (Caution! a copius amount of HBr is evolved in this reaction which can be trapped by a water trap connected to an aqueous sodium carbonate scrubber.) The solvent and excess bromine were removed at reduced pressure using a water aspirator (with the traps still in place). The residue was stirred with 10% aqueous HCl for 16 h, and the mixture was filtered to retrieve the precipitated yellow solid. Recrystallization from hot ethanol gave fine white needles of **33** (99.4 g, 84% yield): mp 175–177 °C; IR (KBr) 3495, 1366, 1289, 1214, 1145, 1033, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (s, 1 H), 2.63 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.6, 136.0, 128.0, 125.1, 118.2, 112.5, 26.3, 18.9; MS m/e 357.7 (100), 359.7 (77). Anal. Calcd for $C_8H_7Br_3O$: C, 26.77; H, 1.96; Br, 66.79. Found: C, 27.04; H, 1.86; Br, 66.48.

3-Bromo-2,5-dimethylphenol, 32. The procedure of Newman[44] was used to debrominate **33**. A suspension of the perbromophenol **33** (97.7 g, 0.255 mol) in aqueous HI (46%, 120 mL) was heated at reflux under argon for 16 h and cooled. $CHCl_3$ (100 mL) was added, and the mixture was decolorized using aqueous saturated sodium thiosulfate and was then extracted with $CHCl_3$ (3 × 100 mL). The organic layers were combined, dried, and concentrated to give a yellow powder. Recrystallization from hexane, using charcoal for decolorization, gave yellowish crystals of **32** (45.6 g, 88%): mp 90–92 °C; IR (KBr) 3342, 3335, 3319, 3311, 1400, 1279, 1122, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (s, 1 H), 6.53 (s, 1 H), 4.69 (br s, 1 H), 2.28 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.8, 137.6, 125.6, 125.5, 121.2, 114.9, 20.6, 15.1; MS m/e 200.0 (53), 202.0 (47); HRMS calcd for $C_8H_9{}^{79}BrO$ 199.9837, found 199.9850.

3-Bromo-2,5-dimethylanisole, 31. Dimethyl sulfate (6.62 mL, 70 mmol) was added to a mixture of the bromophenol **32** (6.89 g, 34.32 mmol), benzyltributylammonium chloride (1.24 g, 4.0 mmol) in CH_2Cl_2 (50 mL), and 1.4 M aqueous NaOH (100 mL), and the mixture was stirred vigorously for 4 h. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with water (3 × 100 mL), dried, and concentrated to give a yellowish oil. Flash chromatography (4 × 15 cm, 10% EtOAc/hexane) gave 7.10 g (96% yield) of **31**: bp 78–80 °C (0.1 Torr); IR (KBr) 2953, 1604, 1565, 1481, 1460, 1403, 1267, 1146, 1049, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (s, 1 H), 6.57 (s, 1 H), 3.78 (s, 3 H), 2.27 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.0, 137.2, 125.4, 124.8, 123.6, 110.1, 55.7, 21.1, 15.3; MS m/e 214.0 (39), 216.0 (38). Anal. Calcd for $C_9H_{11}BrO$: C, 50.25; H, 5.15; Br, 37.14. Found: C, 49.95; H, 5.16; Br, 36.91.

2-Bromo-6-methoxy-4-methylbenzaldehyde, 30. A solution of **31** (5.0 g, 23.25 mmol), potassium persulfate (18.85 g, 69.74 mmol), copper sulfate pentahydrate (5.80 g, 23.25 mmol) and pyridine (15 mL, 0.18 mol) in 50% aqueous CH_3CN (160 mL) was heated at reflux for 15 min under argon and cooled. Acetonitrile was evaporated using a rotary evaporator, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layers were combined, dried, and concentrated to give a crude yellow solid. This was distilled under high vacuum to give **30** (1.90 g, 35%). Alternatively, extraction in ether and purification by flash chromatography (25% EtOAc/hexane) afforded aldehyde **30**: bp 120–125 °C (0.1 Torr); IR (KBr) 2996, 1688, 1595, 1552, 1451, 1289, 1191, 1044, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.33 (s, 1 H), 7.03 (s, 1 H), 6.73 (s, 1 H), 3.88 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.7, 161.8, 146.5, 127.0, 124.7, 120.3, 111.7, 55.9, 21.6; MS m/e 227.9 (92), 229.9 (100). Anal. Calcd for $C_9H_9BrO_2$: C, 47.18; H, 3.96; Br, 34.88. Found: C, 47.29; H, 3.90; Br, 35.13.

2-Bromo-6-methoxy-4-methylcinnamic Acid, 34. A solution of the aldehyde **30** (1.70 g, 7.42 mmol) and malonic acid (1.60 g, 14.84 mmol) in pyridine (3 mL) and piperidine (0.125 mL) was heated at 85 °C for 2 h and then at 115 °C for 2 h. The mixture was cooled to 90 °C and poured into 10% aqueous HCl (50 mL).

(42) The carboxylic acid proton resonance is very broad (δ 8.0–8.5) and is not always observed.

(43) Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 505–508.

(44) Britlain, J. M.; de la Mare, P. B. D.; Newman, P. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 32–41.

The precipitate formed was filtered and was recrystallized from acetone to give shiny plates of **34** (1.70 g, 84%): mp 232–233 °C; IR (KBr) 2975, 1691, 1616, 1599, 1544, 1457, 1421, 1325, 1280, 1214, 1097; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 16 Hz, 1 H), 7.11 (s, 1 H), 6.85 (d, J = 16 Hz, 1 H), 6.70 (s, 1 H), 3.90 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 160.0, 142.3, 142.1, 127.5, 126.4, 121.6, 119.9, 111.3, 55.7, 21.5; MS m/e 269.9 (4), 271.9 (6), 191.0 (100). Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.08; Br, 29.47. Found: C, 48.85; H, 4.05; Br, 29.34.

Methyl 2-Bromo-6-methoxy-4-methylcinnamate, 35. A solution of diazomethane in ether was added to a suspension of the acid (1.10 g, 4.05 mmol) in methanol (50 mL) until a slight yellow color persisted. The solution was concentrated, and the solid obtained was purified by flash chromatography (1.5 × 40 cm, 25% EtOAc/hexane) to furnish 1.14 g (quantitative yield) of white crystalline solid **35**: mp 103–104 °C; IR (KBr) 1717, 1318, 1280, 1205, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 16 Hz, 1 H), 7.00 (s, 1 H), 6.78 (d, J = 16 Hz, 1 H), 6.62 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.9, 159.4, 141.7, 139.7, 126.8, 125.9, 122.1, 119.7, 111.0, 55.4, 51.3, 21.1; MS m/e 286.0 (10), 284.0 (8), 205.1 (100); HRMS calcd for $C_{12}H_{13}{}^{79}BrO_3$ 284.0048, found 284.0048.

2-(Trimethylsilyl)ethyl 3-(2-Bromo-6-methoxy-4-methyl)cinnamate, 36. Procedure a. From Acid 34. Thionyl chloride (1.00 mL, 13.7 mmol) was added to the acid **34** (1.875 g, 0.69 mmol), and the solution was stirred for 1 h. The volatile components were evaporated in vacuo and the residual yellow oil was treated with the alkoxide as follows. Butyllithium (6.0 mL, 1.41 M in hexane, 8.4 mmol) was added to a solution of 2-(trimethylsilyl)ethanol (1.40 mL, 9.76 mmol) in THF at −78 °C, and the solution was stirred at room temperature for 15 min. The yellow oil obtained from the acid chloride preparation above was added in THF (10 mL) at −78 °C, and the solution was heated at reflux for 2 h. Evaporation of the solvent, addition of water (50 mL) and EtOAc (25 mL), and extraction of the water layer with additional EtOAc (3 × 20 mL) followed by drying of the EtOAc extracts and concentration gave a yellow solid. The residue was purified by flash chromatography (3 × 20 cm, 20% EtOAc/hexane) to give white solid **36** (2.407 g, 93%): mp 83–84 °C; IR (KBr) 2958, 1711, 1621, 1600, 1311, 1276, 1192, 1159, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 16 Hz, 1 H), 6.97 (s, 1 H), 6.71 (d, J = 16 Hz, 1 H), 6.57 (s, 1 H), 4.25–4.20 (m, 2 H), 3.77 (s, 3 H), 2.22 (s, 3 H), 1.03–0.97 (m, 2 H), 0.001 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.8, 159.5, 141.6, 139.5, 126.9, 126.1, 123.1, 120.1, 111.1, 62.4, 55.5, 21.3, 17.3, −1.5; MS m/e 370.0 (2), 371.9 (2), 263.1 (69). Anal. Calcd for $C_{16}H_{23}BrO_3Si$: C, 51.75; H, 6.24; Br, 21.51. Found: C, 51.47; H, 6.16; Br, 21.64.

Procedure b. From 51. A mixture of **51** (0.497 g, 1.34 mmol), dimethyl sulfate (0.250 mL, 2.64 mmol), and potassium carbonate (0.500 g, 3.62 mmol) in acetone (10 mL) was heated at reflux until TLC showed the disappearance of the starting material (2 h). The solvent was evaporated, and the residue was partitioned between EtOAc (25 mL) and water (25 mL). The water layers were further extracted with EtOAc (3 × 15 mL), and the EtOAc layers were combined, dried, and concentrated to give a white solid. Flash chromatography (2 × 20 cm, 15% EtOAc/hexane) gave white crystalline solid **36** (0.464 g, 93% yield).

Methyl 3-(2-Bromo-4-methyl-6-methoxyphenyl)-8-methoxy-1,4-naphthoquinone-2-carboxylate, 37. A solution of cyanophthalide **15** (0.378 g, 2.00 mmol) in dry THF was added to a solution of LDA (prepared from diisopropylamine (0.31 mL, 2.21 mmol) and butyllithium (1.60 mL, 1.41 M in hexane, 2.25 mmol)) in dry THF (10 mL) at −78 °C. The solution was stirred for 1 h, and a solution of the cinnamate **35** (0.540 g, 1.89 mmol) in dry THF (5 mL) was added. This solution was warmed to room temperature and stirred for 48 h. Oxygen was bubbled through the mixture for 3 h. The solvent was evaporated, EtOAc (50 mL) was added to the residue, and the mixture was filtered over a Celite pad. The filtrate was dried and concentrated to give an orange solid. Flash chromatography (4 × 30 cm, 4% EtOAc/CH_2Cl_2, 600 mL, then 10% EtOAc/hexane, 600 mL) gave 0.518 (61%) of yellow crystalline **37**: mp 202–203 °C; IR (KBr) 1733, 1665, 1659, 1586, 1280, 1273, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 8, 1 Hz, 1 H), 7.71 (t, J = 8 Hz, 1 H), 7.35 (dd, J = 1, 8 Hz, 1 H), 7.05 (s, 1 H), 6.70 (s, 1 H), 4.02 (s, 3 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 182.9, 180.9, 164.2, 159.9, 157.6, 142.4, 141.9, 141.5, 135.3, 133.9, 125.0, 122.8, 119.8, 119.5, 119.4, 118.1, 110.8, 56.5, 56.1, 52.4, 21.6; MS m/e 446.0 (9), 444.0 (7), 333.0 (100); HRMS calcd for $C_{21}H_{17}{}^{79}BrO_6$ 444.0209, found 444.0209.

2-(Trimethylsilyl)ethyl 3-(2-Bromo-6-methoxy-4-methylphenyl)-8-methoxy-1,4-naphthoquinone-2-carboxylate, 38. The procedure used for preparation of **37** was repeated using **15** (1.134 g, 6.00 mmol) and **36** (2.188 g, 5.89 mmol). The product was purified by flash chromatography (5 × 18 cm, 50% EtOAc/hexane) to give the starting cinnamate (0.480 g, 25% recovery) and 1.850 g (69% yield) of the yellow crystalline quinone **38**: mp 156–157 °C; IR (KBr) 1725, 1664, 1658, 1586, 1279, 1246, 1045, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 1, 8 Hz, 1 H), 7.71 (t, J = 8 Hz, 1 H), 7.36 (dd, J = 1, 8 Hz, 1 H), 7.06 (s, 1 H), 6.70 (s, 1 H), 4.18–4.12 (m, 2 H), 4.02 (s, 3 H), 3.73 (s, 3 H), 2.36 (s, 3 H), 0.86–0.78 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 183.0, 180.8, 163.6, 159.8, 157.6, 142.5, 141.7, 140.9, 135.2, 133.8, 124.8, 122.9, 119.6, 119.5, 119.4, 118.1, 110.6, 63.8, 56.4, 56.0, 21.5, 17.1, −1.7; MS m/e 529.9 (4), 531.9 (5), 423.0 (100). Anal. Calcd for $C_{25}H_{27}BrO_6Si$: C, 56.49; H, 5.12; Br, 15.03. Found: C, 56.25; H, 5.07; Br, 14.78.

Methyl 1,4,8-Trimethoxy-3-(2-bromo-4-methyl-6-methoxyphenyl)naphthalene-2-carboxylate, 39. The procedure used for reductive methylation of **19** was used. Quinone **37** (0.237 g, 0.61 mmol) was transformed and gave (purification by flash chromatography (2.5 × 30 cm, 45% EtOAc/hexane)) 0.238 g (81%) of white crystalline **39**: mp 144–145 °C; IR (KBr) 1733, 1368, 1340, 1057, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8 Hz, 1 H), 7.47 (t, J = 8 Hz, 1 H), 7.11 (s, 1 H), 6.94 (d, J = 8.0 Hz, 1 H), 6.72 (s, 1 H), 4.01 (s, 3 H), 3.91 (s, 3 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.56 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.2, 158.1, 156.7, 150.1, 149.8, 140.3, 131.9, 127.3, 126.8, 125.2, 125.1, 125.0, 123.3, 120.5, 115.4, 110.8, 106.9, 64.0, 61.3, 56.2, 56.0, 51.7, 21.4; MS m/e 476.0 (96), 474.0 (100); HRMS calcd for $C_{23}H_{23}{}^{79}BrO_6$ 474.0678, found 474.0678.

2-(Trimethylsilyl)ethyl 1,4,8-Trimethoxy-3-(2-bromo-6-methoxy-4-methylphenyl)naphthalene-2-carboxylate, 40. A mixture of the quinone **38** (0.254 g, 0.48 mmol), dimethyl sulfate (1.60 mL, 16.90 mmol), anhydrous potassium carbonate (2.40 g, 17.4 mmol), and sodium dithionite (0.167 g, 0.96 mmol) in acetone (15 mL) was heated at reflux for 20 h; water (0.5 mL) was then added, and the mixture was heated for an additional 4 h. Acetone from the mixture was removed in vacuo, and the residue was partitioned between water (40 mL) and EtOAc (15 mL). The water layer was extracted with EtOAc (2 × 15 mL), and the combined EtOAc layers were dried and concentrated. The residue was purified by flash chromatography (2 × 20 cm, 20% EtOAc/hexane) to give **40** as a white foam (0.208 g, 77%): IR (KBr) 2951, 1730, 1459, 1403, 1368, 1280, 1212, 1179, 1043, 860, 834 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8 Hz, 1 H), 7.47 (t, J = 8 Hz, 1 H), 7.12 (s, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.73 (s, 1 H), 4.07–4.01 (m, 2 H), 4.04 (s, 3 H), 3.94 (s, 3 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 2.38 (s, 3 H), 0.76–0.67 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 158.2, 156.7, 149.9, 149.7, 140.1, 131.8, 127.2, 127.1, 125.3, 125.2, 125.0, 123.5, 120.6, 115.4, 110.7, 106.8, 64.0, 62.8, 61.2, 56.2, 56.0, 21.3, 17.0, −1.7; MS m/e 560.0 (38), 562.0 (44). Anal. Calcd for $C_{27}H_{33}BrO_6Si$: C, 57.75; H, 5.92; Br, 14.22. Found: C, 58.08; H, 5.84; Br, 13.92.

1,4,8-Trimethoxy-3-(2-bromo-4-methyl-6-methoxyphenyl)naphthalene-2-carboxylic Acid, 29. Tetrabutylammonium fluoride (0.74 mL, 1.0 M in THF, 0.74 mmol) was added to a solution of the ester **40** (0.207 g, 0.37 mmol) in dry THF (2.0 mL), and the mixture was stirred for 8 h. Sulfuric acid (2.0 mL, 2 M, 4.00 mmol) was added, and the mixture was evaporated to near dryness. Water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The EtOAc layers were extracted with saturated aqueous $NaHCO_3$ (3 × 10 mL), and the combined aqueous layers were acidified to pH 2 with 10% aqueous HCl. The mixture was extracted with EtOAc (3 × 15 mL), dried, and concentrated to give the carboxylic acid **29** as a white solid (0.161 g, 94% yield): mp 204–205 °C; IR (KBr) 2936, 1687, 1682, 1572, 1460, 1369, 1339, 1267, 1058, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.90–8.20 (br s, 1 H), 7.78 (d, J = 8 Hz, 1 H), 7.49 (t, J = 8 Hz, 1 H), 7.11 (s, 1 H), 6.94 (d, J = 8 Hz, 1 H), 6.71 (s, 1 H), 4.00 (s, 3 H), 3.92 (s, 3 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 157.9, 156.7, 150.5, 150.1, 140.3, 132.3, 127.8, 125.5, 125.2, 125.1, 124.8, 123.2, 120.2, 115.4,

110.9, 107.1, 64.1, 61.2, 56.1, 55.9, 21.4; MS *m/e* 460.1 (100), 462.1 (93). Anal. Calcd for $C_{22}H_{21}BrO_6$: C, 57.28; H, 4.58; Br, 17.32. Found: C, 57.39; H, 4.43; Br, 16.95.

1,4,8-Trimethoxy-3-(2-bromo-4-methyl-6-methoxyphenyl)naphthalene-2-carboxamide, 42. Triflic anhydride (0.190 mL, 1.13 mmol) was added to a solution of the acid **29** (0.241 g, 0.52 mmol) and pyridine (1.00 mL, 12.4 mmol) in dry CH_2Cl_2 (5 mL) cooled to 0 °C, and the mixture was stirred for 0.5 h. Ammonia gas was then bubbled through the mixture for 0.5 h, and the volatile components were removed in vacuo. The residue was dissolved in EtOAc (4 mL), and ammonia was bubbled through the solution for an additional 0.5 h. The solvent was evaporated, and the residue was chromatographed through a flash silica gel column (2 × 20 cm, EtOAc) to give 0.205 g (85%) of white solid **42**: mp 205–206 °C; IR (KBr) 3856, 3421, 1677, 1668, 1607, 1573, 1457, 1372, 1338, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 8 Hz, 1 H), 7.46 (t, J = 8 Hz, 1 H), 7.10 (s, 1 H), 6.94 (d, J = 8 Hz, 1 H), 6.73 (s, 1 H), 5.93 (br s, 1 H), 5.74 (br s, 1 H), 4.02 (s, 3 H), 3.93 (s, 3 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.3, 158.0, 156.6, 149.8, 149.4, 140.4, 131.6, 129.0, 127.1, 125.4, 125.1, 125.0, 123.4, 120.5, 115.4, 111.0, 106.6, 64.1, 61.2, 56.0, 55.9, 21.4; MS *m/e* 459.0 (29), 461.0 (29), 380.2 (100). Anal. Calcd for $C_{22}H_{22}BrNO_5$: C, 57.40; H, 4.81; Br, 17.35; N, 3.04. Found: C, 57.21; H, 4.61; Br, 17.46; N, 2.93.

1,4,8-Trimethoxy-3-(2-methoxy-6-formyl-4-methylphenyl)naphthalene-2-carboxamide, 43, 1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)naphthalene-2-carboxamide, 26, and 4,5,9,10-Tetramethoxy-2-methyl-11*H*-benzo[*b*]fluoren-11-one, 41. *tert*-Butyllithium (0.33 mL, 1.7 M in pentane, 0.56 mmol) was added to a solution of the bromoamide **42** (0.085 g, 0.18 mmol) in THF (1 mL) cooled to −98 °C (MeOH/liquid N_2), and the mixture was stirred at −98 °C for 1 h. Dry DMF (0.080 mL, 0.10 mmol) in dry THF (2 mL) was added, and the solution was stirred at −78 °C for 0.5 h and then at 0 °C for 0.5 h. *p*-Toluenesulfonic acid (0.095 g, 0.50 mmol) was added, and the solvent was evaporated. The residue was purified by flash chromatography (1.5 cm × 15 cm, EtOAc) to give a 1:1 mixture of **43** and **26** which was directly used for Hofmann rearrangement (vide infra). A small amount (0.002 g, ~3%) of florenone **41**, which eluted much faster than the amines from the column, was isolated from this reaction. Amide **43** was separated from **26** using MPLC (1.5 × 30 cm, ANALTECH silica gel 60 10 ± 4 μm, 5 mL/min, ~90 psi). For amide **43**: mp 191–193 °C dec; IR (KBr) 1693, 1657, 1605, 1371, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.74 (dd, J = 1, 8 Hz, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.48 (br s, 1 H), 7.01 (br s, 1 H); 6.98 (d, J = 8 Hz, 1 H), 6.04 (br s, 1 H), 5.52 (br s, 1 H), 4.06 (s, 3 H), 3.92 (s, 3 H), 3.75 (s, 3 H), 3.46 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.3, 168.4, 157.0, 156.7, 150.6, 149.6, 139.6, 135.2, 131.6, 129.0, 127.7, 125.4, 122.0, 120.5, 120.0, 116.9, 115.3, 107.0, 64.0, 60.9, 56.2, 55.9, 21.7; HRMS calcd for $C_{23}H_{23}NO_6$ 409.1525, found 409.1524.

For fluorenone **41**: mp 104–112 °C dec; IR (KBr) 2933, 1733, 1694, 1609, 1576, 1571, 1450, 1365, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (dd, J = 8, 1 Hz, 1 H), 7.48 (t, J = 8 Hz, 1 H), 7.24 (s, 1 H), 6.93 (s, 1 H), 6.89 (d, J = 8 Hz, 1 H), 4.03 (s, 6 H), 3.99 (s, 3 H), 3.89 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.5, 159.4, 155.3, 155.1, 146.4, 141.3, 138.8, 137.3, 129.9, 127.8, 126.8, 123.0, 121.7, 118.9, 117.2, 116.1, 108.2, 63.2, 62.5, 56.4, 56.2, 21.5; MS *m/e* 364.2 (2%); HRMS calcd for $C_{22}H_{20}O_5$ 364.1310, found 364.1311.

1,7,8,12-Tetramethoxy-3-methylbenzo[*b*]phenanthridine, 45, and Methyl (1,4,8-Trimethoxy-3-(2-methoxy-4-methylphenyl)naphthalen-2-yl)carbamate, carbamate, 27. Sodium (0.110 g, 4.78 mmol) was dissolved in methanol (1 mL), and the solution was cooled to −52 °C (2-propanol/dry ice). Bromine (0.008 mL, 0.15 mmol) was added, and after the solution was for 15 min a solution of the mixture of amides **43** and **26** (0.060 g, ~0.15 mmol) was added. The mixture was warmed to room temperature over 1 h and then heated to 55 °C for 45 min. Water (0.5 mL) was added, and the mixture was heated at reflux for 1 h. The solvent was evaporated in vacuo, and the residue was diluted with water (5 mL) and acidified to pH 2.0 with 10% aqueous HCl. This was extracted with EtOAc (3 × 10 mL). The acidic layer was then brought to pH 10 using aqueous saturated sodium bicarbonate and then extracted with EtOAc (3 × 10 mL). These organic extracts were dried and concentrated to give pure **45** (0.026 g, quantitative yield). Carbamate **27** (0.023 g, 79%) was recovered from the EtOAc extracts of the acidic layer. For **45**: mp 102–106 °C dec; IR (KBr) 2950, 1730, 1675, 1592, 1476, 1376, 1301, 1270, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 8.09 (dd, J = 1, 8 Hz, 1 H), 7.48 (t, J = 8 Hz, 1 H), 7.39 (s, 1 H), 7.15 (d, J = 1 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 4.14 (s, 3 H), 4.07 (s, 3 H), 4.02 (s, 3 H), 3.55 (s, 3 H), 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.1, 156.9, 152.7, 150.1, 147.6, 139.3, 135.3, 129.8, 128.6, 126.2, 120.3, 120.0, 118.6, 115.4, 115.1, 111.9, 106.0, 63.7, 60.4, 56.5, 56.3, 21.6; HRMS calcd for $C_{22}H_{21}NO_4$ 363.1470, found 363.1470.

Phenanthroviridin Aglycon, 14. Boron tribromide (0.20 mL, 1.0 M in CH_2Cl_2, 0.20 mmol) was added to a solution of **45** (0.014 g, 0.04 mmol) in CH_2Cl_2 (1.5 mL) cooled to −78 °C, and the solution was allowed to warm to room temperature over 2 h. After stirring for 1 additional h the resulting mixture was poured on 5% ice-cold aqueous HCl (15 mL) and was stirred for 15 min. The mixture was then brought to pH 10 by addition of solid sodium carbonate, and sodium hydroxide (0.100 g, xs) was added. Oxygen was bubbled through the mixture for 0.5 h, and the mixture was acidified to pH 3.0 using 10% aqueous HCl. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and then dried. Evaporation of the solvent gave brown crystals (0.011 g, quantitative yield) of **14**: mp 227–229 °C; IR (KBr) 2964, 1639, 1585, 1496, 1455, 1351, 1314, 1274, 1088, 1026, 794 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 9.41 (s, 1 H), 7.93 (d, J = 7 Hz, 1 H), 7.79 (t, J = 7 Hz, 1 H), 7.53 (s, 1 H), 7.43 (d, J = 7 Hz, 1 H), 7.35 (s, 1 H), 2.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.5, 185.1, 161.0, 159.0, 153.8, 144.3, 143.5, 136.4, 132.7, 131.7, 127.6, 124.7, 122.8, 120.7, 120.6, 119.5, 113.5, 20.2; MS *m/e* 305.1 (69).

Methyl (1,4,8-Trimethoxy-3-(5-bromo-2-methoxy-4-methylphenyl)naphthalen-2-yl)carbamate, 46. Sodium (0.022 g, 0.96 mmol) was dissolved in methanol (2.0 mL) under argon, and bromine (0.013 mL, 0.24 mmol) was added at −50 °C (dry ice/2-propanol bath). The solution was stirred for 15 min, the amide **42** (0.108 g, 0.23 mmol) was added, and the mixture was allowed to warm to room temperature and then heated at reflux for 0.5 h. The solution was cooled to room temperature and acidified with 10% aqueous HCl (2 mL). Methanol from the mixture was evaporated, and the mixture was extracted with EtOAc (3 × 5 mL). The EtOAc layers were dried and concentrated to give a yellowish solid. Flash chromatography (2 × 20 cm, 70% EtOAc/hexane) gave a white solid (0.094 g, 81%) which was recrystallized from EtOAc/hexane to yield an analytical sample of **46**: mp 185–186 °C; IR (KBr) 1714, 1454, 1370, 1350, 1064, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (dd, J = 1, 8 Hz, 1 H); 7.41 (t, J = 8 Hz, 1 H), 7.13 (s, 1 H), 6.91 (dd, J = 1, 8 Hz, 1 H), 6.75 (s, 1 H); 6.02 (br s, 1 H), 4.00 (s, 3 H), 3.83 (s, 3 H), 3.72 (s, 3 H), 3.53 (s, 6 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.0, 156.4, 155.5, 150.0, 148.6, 140.3, 130.3, 126.7, 126.3, 126.2, 125.3, 125.0, 122.2, 120.8, 115.3, 110.9, 106.6, 62.1, 61.2, 56.1, 56.0, 52.3, 21.4; MS *m/e* 491.0 (100), 489.0 (99); HRMS calcd for $C_{23}H_{24}{}^{79}BrNO_6$ 489.0787, found 489.0787.

1,7,8,12-Tetramethoxy-3-methyl-6*H*-benzo[*b*]phenanthridin-5-one, 47. A solution of *tert*-butyllithium (0.13 mL, 1.7 M in pentane, 0.22 mmol) was added to a solution of the carbamate **46** (0.035 g, 0.07 mmol) in dry THF (2 mL) at −98 °C (solid MeOH, liquid N_2), and the mixture was stirred at −98 °C for 45 min. The MeOH bath was replaced by dry ice/acetone bath, and the solution was allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). After washing the organic layers with saturated NaCl, drying, and concentration gave a yellow solid. Purification by flash chromatography (1 × 25 cm, 30% EtOAc/CH_2Cl_2) gave 0.016 g (59% yield) of orange solid **47**: mp 202–203 °C; IR (KBr) 2931, 1659, 1607, 1554, 1507, 1456, 1375, 1347, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (br s, 1 H), 7.99 (br d, J = 8 Hz, 1 H), 7.94 (br s, 1 H), 7.34 (dd, J = 8, 7 Hz, 1 H), 7.15 (d, J = 1 Hz, 1 H), 6.92 (d, J = 7 Hz, 1 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 3.92 (s, 3 H), 3.56 (s, 3 H), 2.54 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.8, 157.0, 155.0, 151.3, 139.9, 134.7, 128.4, 127.3, 126.8, 124.2, 120.2, 119.9, 119.4, 116.6, 115.9, 108.3, 106.7, 62.5, 60.6, 56.3, 56.2, 21.6; MS *m/e* 379.2 (100%); HRMS calcd for $C_{22}H_{21}NO_5$ 379.1420, found 379.1419.

1,8-Dimethoxy-3-methyl-6*H*-benzo[*b*]phenanthrido-7,12-quin-5-one, 48. A solution of ceric ammonium nitrate (0.058 g,

0.11 mmol) in water (2 mL) was added dropwise to a solution of the pyridone **47** (0.020 g, 0.05 mmol) in CH_3CN (2 mL) over 5 min, and the mixture was stirred for 1 h. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ (5 mL) and water (5 mL). The aqueous layer was extracted with additional $CHCl_3$ (2 × 5 mL), and the combined organic layers were dried and evaporated to give a yellow-orange solid. Flash chromatography (1 × 20 cm, 100% EtOAc) gave 0.017 g (92%) of yellow crystalline **48**: mp >270 °C dec; IR (KBr) 3336, 1681, 1653, 1583, 1479, 1338, 1285, 1246, 1123, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.43 (br s, 1 H), 7.89 (d, J = 1 Hz, 1 H), 7.72 (m, 2 H), 7.27–7.24 (m, 1 H), 7.13 (d, J = 1 Hz, 1 H), 4.05 (s, 3 H), 3.97 (s, 3 H), 2.53 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 181.2, 176.2, 161.0, 160.0, 157.6, 142.4, 137.9, 136.4, 135.4, 129.9, 120.0, 119.9, 119.5, 118.0, 117.6, 117.5, 116.4, 56.6, 56.4, 22.0; MS m/e 349.1 (100); HRMS calcd for $C_{20}H_{15}NO_5$ 349.0950, found 349.0949.

3-Methyl-6*H*-benzo[*b*]phenanthrido-7,12-quin-5-one, 10. A solution of BBr_3 (0.1 mL, 1.0 M in CH_2Cl_2, 0.1 mmol) was added to a solution of **51** (0.004 g, 0.01 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the mixture was warmed to room temperature and stirred for 1 h. Ethylene dichloride (1 mL) was added, and the mixture was sonicated for 3 h and then stirred for 23 h. Methanol (3 × 3 mL) was added, and the solution was concentrated (3 ×) to ca. 2 mL by boiling. The solvent was then completely evaporated, and the residue was dissolved in 1 M aqueous NaOH. Acidification to pH 2.0 using concd HCl, extraction with $CHCl_3$ (3 × 5 mL), drying of the organic layers, and concentration gave purple crystalline **10**[45] (0.003 g, ~81% yield): mp >265 °C; IR (KBr) 3475, 3276, 1684, 1638, 1463 cm^{-1}; ^1H NMR (D_2O, NaOD) δ 7.40 (t, J = 8 Hz, 1 H), 7.17 (s, 1 H), 7.06 (d, J = 8 Hz, 1 H), 6.89 (d, J = 8 Hz, 1 H), 6.72 (s, 1 H), 2.38 (s, 3 H); ^{13}C NMR (CF_3COOD, $CDCl_3$) δ 186.3, 180.6, 163.2, 161.9, 154.8, 145.3, 138.8, 132.7, 127.9, 126.4, 125.9, 123.1, 122.2, 119.2, 118.2, 21.3; FAB HRMS calcd for $C_{18}H_{12}NO_5$ 322.0720, found 322.0720 (MH^+).

2-Bromo-6-hydroxy-4-methylbenzaldehyde, 50. Boron tribromide (1.0 mL, 1.0 M in CH_2Cl_2, 1.00 mmol) was added to a solution of the aldehyde **30** (0.229 g, 1.00 mmol) in CH_2Cl_2 (3 mL) cooled to −78 °C. The mixture was stirred for 15 min at −78 °C and 1 h at room temperature. The mixture was then poured cautiously onto ice–water (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) and was stirred for 15 min. Extraction with EtOAc (3 × 10 mL), drying of the organic layers, and concentration gave a pink oil. Flash chromatography (1.5 × 17.5 cm, 25% CH_2Cl_2/hexane) gave rhombic colorless plates of **50** (0.190 g, 88%): mp 53–54 °C; IR (KBr) 2800, 1650, 1561, 1514, 1388, 1303, 1211, 1183, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.00 (s, 1 H), 10.24 (s, 1 H), 6.99 (d, J = 1 Hz, 1 H), 6.74 (br s, 1 H), 2.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.9, 163.7, 149.6, 127.1, 125.5, 117.8, 115.6, 21.8; MS m/e 213.9 (71), 215.9 (30). Anal. Calcd for $C_8H_7BrO_2$: C, 44.68, H, 3.28; Br, 37.15. Found: C, 44.65; H, 3.13; Br, 37.13.

5-Bromo-7-methylcoumarin, 49. A solution of salicylaldehyde **50** (0.130 g, 0.60 mmol) and freshly fused potassium acetate (0.035 g, 0.35 mmol) in acetic anhydride (0.5 mL, xs) was heated at reflux (bath temperature 150–160 °C) for 5 h. The mixture was cooled to ~100 °C and poured into water (10 mL) and then extracted with EtOAc (3 × 10 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and dried. Evaporation gave a yellowish solid which was purified by flash chromatography (1.5 × 15 cm, CH_2Cl_2) to give white needles (0.136 g, 94%) of **49**: mp 140–141 °C; IR (KBr) 1750, 1739, 1726, 1610, 1201, 1139, 1108, 855, 843 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, J = 9 Hz, 1 H), 7.30 (br s, 1 H), 7.04 (d, J = 1 Hz, 1 H), 6.39 (d, J = 9 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.0, 154.4, 143.7, 141.9, 129.2, 121.7, 116.5, 116.3, 116.2, 21.3; MS m/e 237.9 (72), 239.9 (81). Anal. Calcd for $C_{10}H_7BrO_2$: C, 50.24; H, 2.95; Br, 33.42. Found: C, 49.89; H, 2.98; Br, 33.45.

2-(Trimethylsilyl)ethyl 2-Bromo-4-methyl-6-hydroxycinnamate, 51. A solution of butyllithium (1.50 mL, 1.41 M in hexanes, 2.11 mmol) was added to a solution of 2-(trimethylsilyl)ethanol (0.35 mL, 2.44 mmol) in dry THF (4 mL) at −78 °C, and the solution was warmed to room temperature and stirred for 15 min. A solution of coumarin **49** (0.478 g, 2.00 mmol) in dry THF (4 mL) was added at −78 °C, and the mixture was heated at reflux for 2 h. The reaction was quenched using acetic acid (0.2 mL, xs), and the solvent was evaporated. Extraction with ether (3 × 10 mL), drying, and evaporation of the ether layers gave a yellow solid. Flash chromatography (2 × 20 cm, 18% EtOAc/hexane) gave 0.699 (72% yield) of white crystalline **51**: mp 145–147 °C; IR (KBr) 3234, 3226, 3212, 1685, 1675, 1603, 1565, 1380, 1317, 1285, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.81 (br s, 1 H), 7.93 (d, J = 16 Hz, 1 H), 7.07 (d, J = 16 Hz, 1 H), 6.90 (s, 1 H), 6.61 (s, 1 H), 4.28 (br t, 2 H), 2.15 (s, 3 H), 1.02 (br t, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 157.6, 142.2, 141.2, 127.0, 125.7, 121.9, 118.3, 116.5, 63.5, 21.0, 17.3, −1.4; CIMS (CH_4) m/e 359 (18), 357 (18), 315 (98), 313 (100). Anal. Calcd for $C_{15}H_{21}BrO_3Si$: C, 50.42, H, 5.92; Br, 22.36. Found: C, 50.43; H, 5.90; Br, 22.32.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of selected compounds (38 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(45) Phenanthridone **10** is only sparingly soluble in most of the solvents including DMSO. We believe that two of the carbon resonances in the aromatic region are not visible due to overlap with the solvent (CF_3COOD) signals.