Synthetic Studies on the Kinamycin Family of Antibiotics: Synthesis of 2-(Diazobenzyl)-*p*-naphthoquinone, 1,7-Dideoxy-3-demethylprekinamycin, and 1-Deoxy-3-demethylprekinamycin

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2-(Diazobenzyl)-*p*-naphthoquinone was synthesized from 2-benzyl-1,4-dimethoxynaphthalene by cerric ammonium nitrate oxidation to 2-benzyl-*p*-naphthoquinone followed by diazo transfer with tosyl azide. 1,7-Dideoxy-3-demethylprekinamycin was prepared from 1,4-dimethoxynaphthalene by bromination, lithiation, and condensation with acetanthranil to give 2-(2′-*N*-acetaminobenzoyl)-1,4-dimethoxynaphthalene, which, following deacylation, was subjected to Pschorr cyclization to give 1,3,7-trihydro-*O*,*O*-dimethylkinafluorenone. This was then demethylated, subjected to hydrazinolysis, and then oxidized with Fetizon's reagent to complete the synthesis. 1-Deoxy-3-demethylprekinamycin was synthesized from 3-bromo-1,5-dimethoxy-4-naphthol by an identical route.

Introduction

Pursuant to our goals of studying the DNA cleaving and/or alkylating properties of the kinamycin family of antibiotics and within the context of our previous work on the design of novel DNA cleaving reagents,[1,2] we wish to report the synthesis of a number of prekinamycin analogues. These were chosen with an eye toward the simplification of our synthetic strategy while preserving essential functionality in the target molecule.

The kinamycin antibiotics were first isolated from *Streptomyces murayamaensis*[3,4] and originally characterized by Omura and co-workers as being benzo[*b*]carbazole cyanamides **1** (Figure 1). They have been shown to possess activity against Gram-positive, and to a lesser extent, Gram-negative bacteria, as well as against Ehrlich ascites carcinoma and sarcoma-180.[4] Their structures were later revised by Gould[5] using spectroscopic methods to be 5-diazobenzo[*b*]fluorenes **2**. Additionally, the cyanocarbazole prekinamycin structure **3** was regioselectively synthesized by Dmitrienko[6] and used to demonstrate by IR and NMR spectroscopy that authentic kinamycins do not possess the cyanamide functionality. The 5-diazobenzo[*b*]fluorene structure remains to date

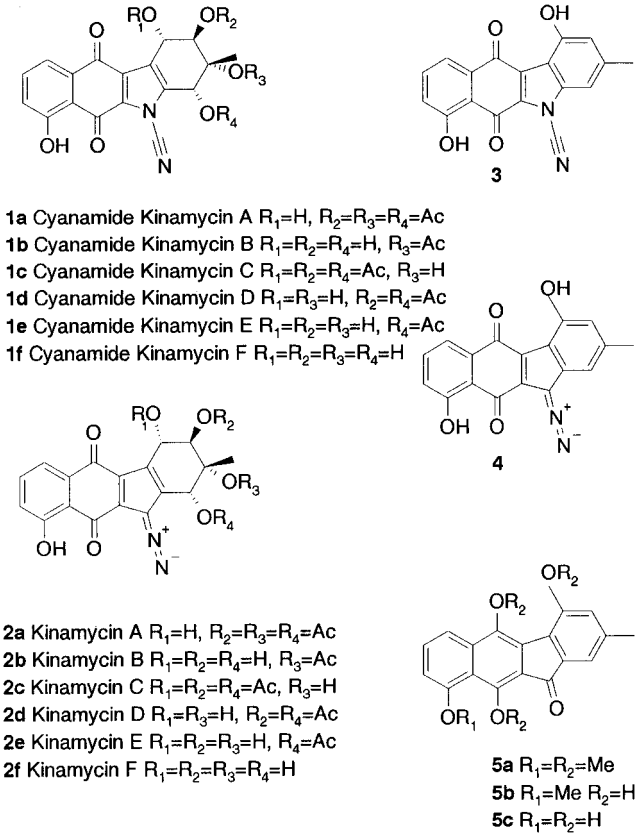

Figure 1.

the best fit to experimental data, although Hauser[7] recently completed the synthesis of prekinamycin **4** and found it to not be identical to the fraction previously characterized by Gould[8] as prekinamycin. Subsequently, Gould[9] has identified a *S. murayamaensis* metabolite identical to the compound synthesized by Hauser and named it prekinamycin, while leaving the structure of the original choice an open question.

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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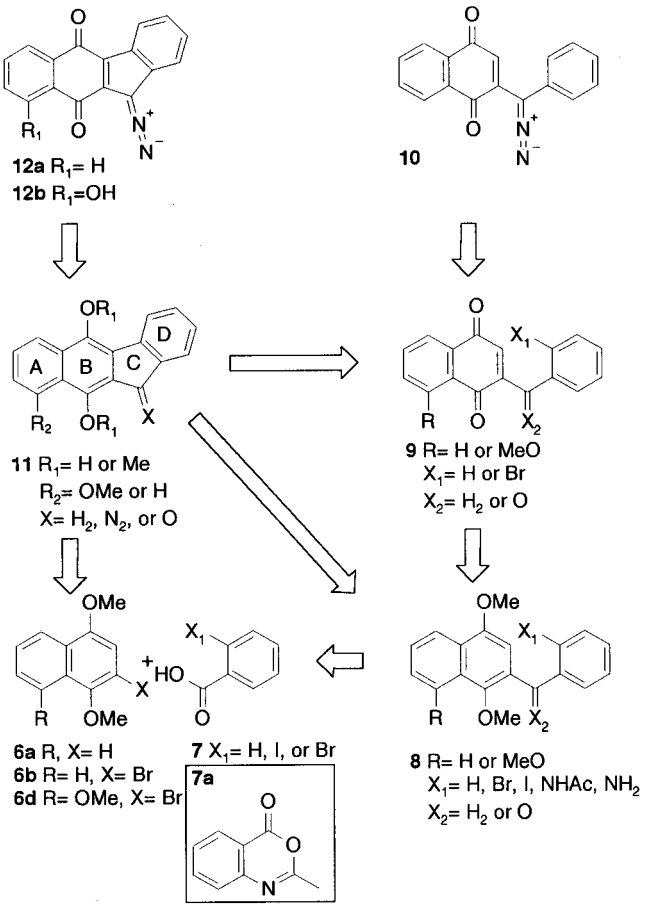
Scheme 1

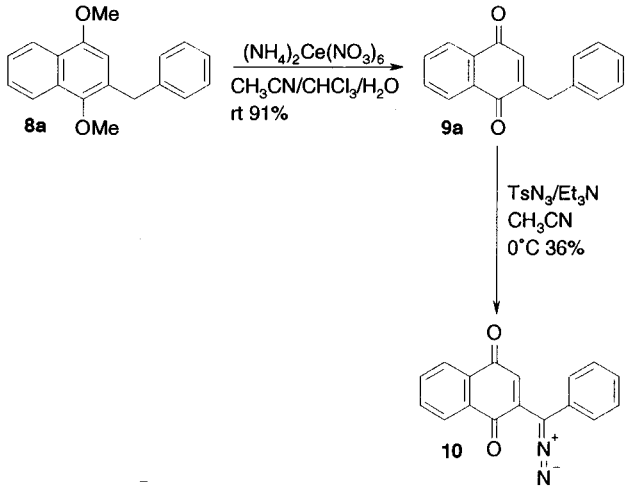


The goal of our current research is the development of easily accessible prekinamycin analogs that will be useful for future mechanistic and biological studies. The unusual diazo functionality and benzo[*b*]fluorene structure[5] offer intriguing possibilities in this regard.

Results and Discussion

Retrosynthetic Analysis (Scheme 1). In our strategy for the synthesis of kinamycin analogs, we sought to utilize a unified approach, so as to develop several compounds from a single synthesis. As we were interested in both the open (2-diazobenzyl-*p*-naphthoquinone (**10**)) and closed (prekinamycins **12**) forms, we chose to make our primary disconnection at the phenyl−phenyl bond of the C-ring[10] (Scheme 1). Additionally, due to the likely reactivity of the diazo functionality, it seemed prudent to introduce it at the last step of the synthesis, either by hydrazinolysis/oxidation of ketone forms of **11** (Scheme 1) or by diazotransfer[11] from the methylene quinones **9a** (Scheme 2) and **15** (Scheme 4). Formation of the phenyl−phenyl bond could, in principal, be accomplished by photolysis of the aryl iodide **8**, by a Pd-catalyzed Heck reaction of **8** or **9**, by a reductive free-radical addition, or by a Pschorr coupling of **8** (Scheme 1).[12] We thus identified compounds **8** or **9** and **11** as key intermediates offering potential access to a wide array of open and closed kinamycin analogs. Furthermore, it

Scheme 2



seemed that compounds **8** should be readily accessible through Friedel−Crafts acylation of naphthalenes **6** with electrophiles **7** (Scheme 1), all of which are commercially available or readily accessible.[13−15] The analogous compound **5a** (Figure 1) had been synthesized previously by Gould,[16] but only as a side product en route to a different synthetic goal. Kinafluorenone **5b** had been identified as a *S. murayamaensis* metabolite,[17] and kinobscurinone **5c** had been shown to be a biosynthetic precursor of kinamycin.[18] 1,7-Dideoxy-3-demethyl-*O*,*O*- dimethylkinafluorenone (**11a**) (Scheme 3) has since been synthesized by Mal and Hazra[19] as well.

Synthesis of 2-(Diazobenzyl)-*p*-naphthoquinone (Scheme 2). Our initial investigations were into the facile synthesis of **10** (Scheme 2), an open-chain analogue of prekinamycin **4**. In this manner, we could both rapidly establish the viability of our synthetic strategy and obtain a compound that retains only the diazo and quinone functionalities of kinamycin. This could in principal be accomplished from the known and easily accessible 2-benzyl-1,4- dimethoxynaphthalene[20] (**8a**) by cerric ammonium nitrate oxidative demethylation[21] to give 2-benzyl-*p*-naphthoquinone (**9a**) followed by a diazotransfer reaction with tosyl azide[11] in the presence of triethylamine (Scheme 2). This sequence indeed proceeded as desired, with the initial oxidative demethylation giving a single product in 91% yield and the subsequent diazotransfer also giving a single significant product **10**,

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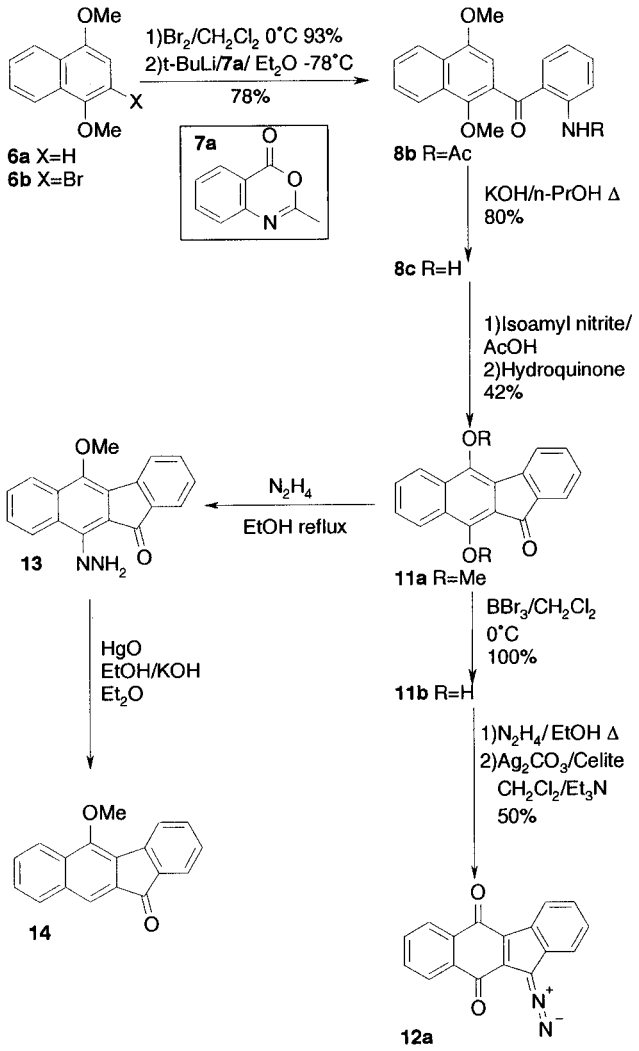
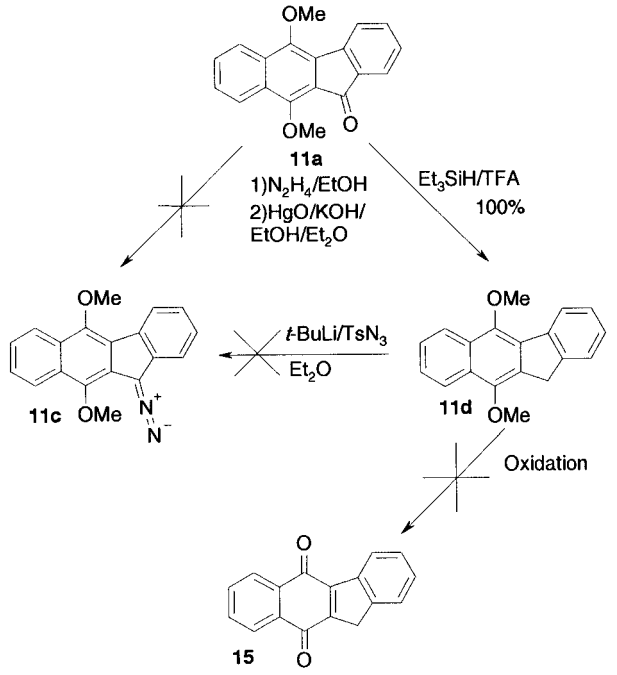
Scheme 3



albeit in only 36% yield. The poor mass recovery during purification may well be due to decomposition on the column.

Synthesis of 1,7-Dideoxy-3-demethylprekinamycin (Scheme 3). Encouraged by our success, we set out on the synthesis of our primary target **11a** (Scheme 3). Our initial strategy for the construction of the kinamycin ring system sought to exploit the easy accessability of compounds of the form **8** (Scheme 1) through Friedel–Crafts acylation of dimethoxynaphthalene (**6a**)[13] followed by reduction with triethylsilane.[20] All attempts, however, to close the C-ring, utilizing various nonamino derivatives of **8**, failed, while the 2′-amino series proved inaccessible through Friedel–Crafts methodology. We therefore turned to an anionic coupling of 2-bromo-1,4-dimethoxynaphthalene (**6b**) with acetanthranil[14] (**7a**) to form ketone **8b**[22] followed by use of the Pschorr reaction to close the C-ring (Scheme 3). The synthesis of **11a** thus proceeded as follows: Regioselective bromination of 1,4-dimethoxynaphthalene (**6a**) with bromine in methylene chloride yielded 2-bromo-1,4-dimethoxynaphthalene (**6b**) in 93% yield. The bromide **6b** was then lithiated in Et_2O at −78 °C and quenched in a reverse addition to acetanthranil[14] (**7a**) to give 2-(2′-acetaminobenzoyl)-1,4-dimethoxynaphthalene (**8b**) in 78% yield. This was then subjected to basic hydrolysis with KOH in *n*-PrOH/H_2O to give the deacylated product **8c** in 80% yield. Ring closure was accomplished by a hydroquinone-catalyzed Pschorr reaction[12] with isoamyl nitrite in AcOH to give 1,7-dideoxy-3-demethyl-*O*,*O*-dimethylkinafluorenone (**11a**) in 42% yield.

Scheme 4



With the dimethylkinafluorenone **11a** in hand, we attempted the synthesis of our second target molecule, 5-diazo-1,7-dideoxy-3-demethyl-*O*,*O*-dimethylkinafluorene (**11c**) (Scheme 4). Hydrazinolysis in EtOH followed by oxidation with HgO in Et_2O, however, gave instead the kinafluorenone **14** (Scheme 3). This, we postulate, resulted from an unusual nucleophilic attack of hydrazine at the 6-position instead of the expected 5-position, followed by elimination of methanol to give the aryl hydrazide **13**, which upon oxidation gave **14**. Our results in this regard are in concurrence with those of Gould.[9]

We then considered the use of our proven diazotransfer methodology for introduction of the diazo functionality. Triethylsilane reduction of the ketone **11a** proceed smoothly (Scheme 4), but all attempts to selectively oxidize the hydroquinone to quinone, either by oxidative demethylation[21] or by demethylation followed by oxidation (HgO, O_2, NO^+), while retaining the methylene group, failed. We were also unable to effect diazotransfer on 1,7-dideoxy-3- demethylkinafluorene (**11d**) to give **11c**, utilizing *t*-BuLi and TsN_3 in Et_2O.

At this point, we determined that the best course of action was to return to our original strategy, despite the discouraging results of the hydrazinolysis of ketone **11a** (Schemes 3 and 4). To this end, we demethylated **11a** with BBr_3 in CH_2Cl_2 in quantitative yield (Scheme 3) to give 1,7-dideoxy-3-demethylkinafluorenone (**11b**). The related compound, kinobscurinone, had been synthesized by Gould[18] as the quinone and found to be an NMR silent species related to the stealthins.[23] Compound **11b** gave no detectable ^{13}C NMR signal in nonacidic solvents (acetone-d_6, DMSO-d_6, methanol-d_4), while the ^1H spectrum in these solvents showed extensive band broadening

(22) Directed lithiation of 1,4-dimethoxynaphthalene (**6a**) followed by quenching with acetanthranil (**7a**) produced a complex mixture and low yield.

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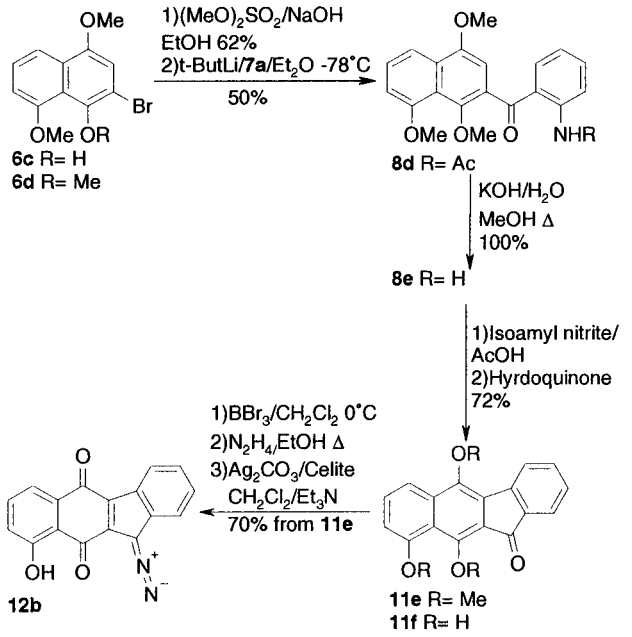
Scheme 5



of the aromatic region. This behavior appears to be characteristic of 5-hetero-substituted benzo[*b*]fluorene hydroquinones, as reported by Seto,[23] with whom our results are in concurrence. We were, however, able to obtain both ^{13}C and ^{1}H spectra of **11b** in DMSO-d_6 containing 20% TFA-d_1−DMSO-d_6.[24] Hydrazinolysis of the crude product followed by HgO (EtOH/KOH) oxidation produced a complex product mixture. Hydrazinolysis followed by oxidation with Fetizon's reagent,[25] however, produced the desired product, 1,7-dideoxy-3-demethylprekinamycin (**12a**) in 50% overall yield from **11a**.

Synthesis of 1-Deoxy-3-demethylprekinamycin (12b) Scheme 5). Our final goal was the synthesis of a prekinamycin analog retaining the A-ring hydroxyl (Scheme 5). The synthetic sequence followed that of 1,7-dideoxy-3-demethylprekinamycin (**12a**), beginning with *O*-methylation of the known 3-bromo-1,5-dimethoxy-4-naphthol (**6c**)[15] to give **6d** (62%). This was followed by lithiation and condensation by reverse addition to acetanthranil[14] **7a**, giving amide **8d** in 50% yield. The amide was then subjected to basic hydrolysis with KOH in methanol to give aniline **8e** quantitatively and then diazotized in situ with isoamyl nitrite in AcOH and cyclized reductively with hydroquinone[12] to give 1-deoxy-3-demethyl-*O*,*O*-dimethylkinafluorenone (**11e**) in 72% yield. This material was then demethylated with BBr_3 and the crude product subjected to hydrazinolysis and then oxidized with Fetizon's reagent[25] to give 1-deoxy-3-demethylprekinamycin (**12b**) in 70% overall yield from **11e**.

Conclusion

This work offers rapid routes to a series of both open- and closed-chain prekinamycin analogues that will be utilized in the future and current work on the mode of action of the kinamycin antibiotics. This is postulated to be either bioreductive alkylation of DNA nucleotides[26] leading to cross-linking, or possibly radical or carbene cleavage of the sugar backbone, demonstrated by us for 9-diazofluorene and β-naphthylphenyldiazomethane under oxidative conditions.[2] The role of the quinone moiety in the bioreductive alkylation[26] of both prekinamycin (**4**) and kinamycin (**2**) is of particular interest.

Experimental Section

General Procedure. NMR peak frequencies were recorded on a 300 MHz ^{1}H/75 MHz ^{13}C spectrometer and reported in ppm from TMS. IR spectra were recorded using KBr pellets or in CCl_4 at a resolution of 4 cm^{-1} with peak frequencies reported in cm^{-1}. Elemental analyses were performed at Desert Analytics of Tucson, AZ, or at Galbraith Laboratories of Knoxville, TN.

Compounds **8a**,[20] **6a**,[15] were prepared by known procedures.

Materials. Flash chromatography was carried out utilizing silica gel-60, 230−400 mesh (EM-9385). Dry solvents were distilled from CaH_2 and N_2, except for Et_2O, which was distilled from Na/benzophenone.

2-Benzyl-1,4-naphthoquinone (9a). 2-Benzyl-1,4-dimethoxynaphthalene (**8a**)[20] (1.31 g, 4.71 mmol) was dissolved in 10 mL of acetonitrile and 2 mL of chloroform. Cerric ammonium nitrate (3 equiv, 7.75 g, 14.1 mmol) in 10 mL of H_2O was added dropwise with stirring and the mixture stirred for 15 min at room temperature. The reaction mixture was extracted into ethyl acetate, washed with saturated $NaHCO_3$ (aq) and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give **9a** (1.06 g, 4.27 mmol, 91%) as a yellow powder that was used without further purification: mp 97−99 °C; IR (KBr) 3033, 2960, 1678 (vs); ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, m), 8.02 (1H, m), 7.70 (2H, m), 7.33 (2H, m), 7.26 (3H, m), 6.60 (1H, s), 3.89 (2H, s); ^{13}C NMR ($CDCl_3$) δ 185.09, 184.95, 150.88, 136.76, 135.65, 133.75, 133.69, 132.17, 132.08, 129.46, 128.88, 127.10, 126.66, 126.11, 35.74. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 81.88; H, 5.01.

2-(Diazobenzyl)-*p*-naphthoquinone (10). 2-Benzyl-1,4-naphthoquinone (**9a**) (0.10 g, 0.403 mmol) and *p*-toluenesulfonyl azide (0.08 g, 0.403 mmol) were dissolved in 4.0 mL of dry CH_3CN under N_2 at 0 °C. This was cannulated at 0 °C into Et_3N (3.0 equiv, 0.17 mL) in 1.0 mL of CH_3CN and stirred overnight, warming to room temperature. The product mixture was extracted into EtOAc, washed with 1 g of NaOH in 40 mL of H_2O and then brine, and dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography with 98% hexanes/2% EtOAc and crystallized from MeOH, yielding **10** (0.04 g, 0.146 mmol, 36%) as golden needles: IR (KBr) 3033, 2095 (vs), 1684 (s); ^{1}H NMR ($CDCl_3$) δ 8.28 (1H, d, J = 6.9 Hz), 8.24 (1H, d, J = 7.2 Hz), 7.92 (1H, s), 7.76 (2H, t, J = 7.2 Hz), 7.41 (2H, m), 7.34 (3H, m); ^{13}C NMR ($CDCl_3$) δ 180.94, 178.58, 134.47, 134.29, 134.00, 133.84, 133.61, 131.20, 129.29, 129.15, 128.33, 128.12, 126.27, 120.14. 77.27 (buried in $CDCl_3$ peak, but visible). Note: elemental analysis of compound **10** was not performed due to its apparent instability.

2-Bromo-1,4-dimethoxynaphthalene (6b). To 1,4-dimethoxynaphthalene (**6a**)[13] (2.00 g, 7.49 mmol) in 20 mL of dry CH_2Cl_2 under N_2 at 0 °C was added dropwise with stirring Br_2 (1.1 equiv, 1.87 g, 8.23 mmol) in 1 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min at 0 °C and then extracted into CH_2Cl_2 and washed with saturated $NaHCO_3$ (aqueous), saturated $Na_2S_2O_5$ (aqueous), and brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under vacuum, yielding a light brown oil. The crude product was purified by flash chromatography with 95% hexanes/5% ethyl acetate to yield **6b** (2.63 g, 6.97 mmol, 93%) as a colorless oil that crystallized from MeOH to give a white

(24) The lack of any ^{13}C NMR signals within the region characteristic of a quinone allows unambiguous assignment to **11b** of the hydroquinone oxidation state. Further, an exchangeable peak was visible at ~3.35 ppm in the acetone-d_6 ^{1}H NMR spectrum, and the IR spectrum has a broad peak at 3364 cm^{-1}. Elemental analysis and mass spectroscopy also favor the hydroquinone. See the Experimental Section and Supporing Information.

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(26) Moore, H. W. *Science* **1977**, *197*, 527−532.

powder. Note: A very small amount of inseparable material thought to be the 5-bromo isomer was also present in the product (detected by TLC and NMR), but purity appeared to be sufficient for synthetic purposes: mp 54−58 °C; IR (CCl_4) 2938, 2844, 1589; ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, d, J = 7.2 Hz), 8.08 (1H, d, J = 6.6 Hz), 7.60−7.49 (2H, m), 6.90 (1H, s), 3.972 and 3.969 (6H, 2s); ^{13}C NMR ($CDCl_3$) δ 152.25, 146.67, 128.94, 127.35, 125.82, 122.80, 122.62, 121.86, 111.94, 107.82, 61.46, 55.92.

2-(2′-*N*-Acetaminobenzoyl)-1,4-dimethoxynaphthalene (8b). 2-Bromo-1,4-dimethoxynaphthalene (**6b**) (4.00g, 11.4 mmol) was dissolved in 30 mL of dry Et_2O under N_2 and then brought to −78 °C. *t*-Bu Li (1.7 M in pentane, 1.2 equiv, 10.57 mL) was then added dropwise with stirring, and after 5 min the mixture was cannulated rapidly into acetanthranil[14] (**7a**) (1.2 eq, 2.90 g, 13.7 mmol) in 50 mL of dry Et_2O, N_2, −78 °C. The reaction mixture was stirred overnight, warming to room temperature. The product mixture was extracted into ethyl acetate, washed with saturated NH_4Cl (aqueous) and dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The product was purified by flash chromatography with 90% hexanes/10% ethyl acetate to give **8b** (4.07 g, 8.89 mmol, 78% yield) as a light yellow powder: mp 168−169 °C; IR (KBr) 3255, 2938, 1705 (s); ^{1}H NMR ($CDCl_3$) δ 11.59 (1H, br, s), 8.77 (1H, d, J = 9.3 Hz), 8.31 (1H, m), 8.15 (1H, m), 7.63−7.56 (4H, m), 7.01 (4H, t, J = 7.2 Hz), 6.67 (1H, s), 3.97 (3H, s), 3.80 (3H, s), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.75, 169.54, 151.72, 147.97, 141.34, 135.36, 134.89, 128.46, 127.76, 127.62, 127.36, 127.20, 122.77, 122.57, 122.48, 122.30, 120.61, 102.42, 63.68, 55.86, 25.57. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.85; H, 5.61; N, 3.97.

2-(2′-Aminobenzoyl)-1,4-dimethoxynaphthalene (8c). Compound **8b** (5.37g, 17.5 mmol) was dissolved in 80 mL of *n*-propanol at reflux. KOH, 3.45 g in 30 mL of H_2O, was added dropwise with stirring and the reaction mixture refluxed for 3 h under N_2. The product mixture was poured into H_2O, extracted into ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was then removed under vacuum and the crude product crystallized from MeOH to give **8c** (3.79 g, 14.0 mmol, 80%) as light yellow crystals: mp 145−147 °C; IR (KBr) 3455, 3339, 1610 (vs); ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, d, J = 7.2 Hz), 8.17 (1H, d, J = 7.2 Hz), 7.59 (2H, m), 7.40 (1H, d, J = 8.7 Hz), 7.29 (1H, t, J = 8.1 Hz), 6.75 (1H, d, J = 8.4 Hz), 6.70 (1H, s), 6.55 (1H, t, J = 7.5 Hz), 6.47 (2H, s, br), 3.98 (3H, s), 3.84 (3H, s); ^{13}C NMR ($CDCl_3$): δ 199.08, 151.63, 150.80, 146.83, 135.20, 134.93, 128.67, 128.51, 127.20, 127.06, 126.57, 122.61, 122.43, 118.50, 116.94, 116.05, 102.76, 63.37, 55.82. Anal. Calcd for $C_{19}H_{16}NO_2$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.06; H, 5.42; N, 4.53.

1,7-Dideoxy-3-demethyl-*O*,*O*-dimethylkinafluorenone (11a). Compound **8c** (1.06 g, 3.45 mmol) was dissolved by warming in 150 mL of acetic acid with stirring, under N_2, and then cooled to ∼15 °C. Isoamyl nitrite (2 equiv, 6.90 mmol, 0.93 mL) was then added *at once* with rapid stirring. The deep red reaction mixture was stirred for 0.5 h covered with aluminum foil at ∼15 °C, under N_2, and then hydroquinone (1.2 equiv, 0.46 g) in 10 mL of acetone was added dropwise. N_2 gas evolved, and the reaction mixture became clear. The reaction was stirred overnight and the solvent removed under vacuum. The solids were then extracted into ethyl acetate, washed with saturated $NaHCO_3$ (aqueous) and then with brine, and dried over anhydrous Na_2SO_4, and the solvent was again removed under vacuum. The product was purified by flash chromatography with 99% hexanes/1% ethyl acetate and then crystallized from MeOH. The unresolved fraction from chromatography was combined with filtrate from the crystallization, rechromatographed with same solvent, and then recrystallized from MeOH to yield **11a** (0.42 g, 1.45 mmol, 42%) as brilliant yellow spars: mp 173−174 °C; IR (KBr) 2949, 2854, 1705 (vs); ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, d, J = 8.4 Hz), 8.04 (1H, d, J = 8.1 Hz), 8.00 (1H, d, J = 7.5 Hz), 7.74 (1H, d, J = 7.5 Hz), 7.64−7.47 (3H, m), 7.33 (1H, t, J = 7.5 Hz), 4.30 (3H, s), 4.00 (3H, s); ^{13}C NMR ($CDCl_3$) δ 190.30, 153.90, 146.99, 142.61, 136.14, 134.80, 133.64, 131.06, 129.62, 128.64, 127.70, 127.01, 125.65, 124.42, 124.04, 122.60, 119.60, 63.20, 61.33. Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.45; H, 4.97.

1,7-Dideoxy-3-demethylkinafluorenone (11b). Compound **11a** (0.50 g, 1.72 mmol) was dissolved in 40 mL of dry CH_2Cl_2 under N_2 and brought to −78 °C. BBr_3 (1 M in CH_2Cl_2, 3.0 equiv, 5.16 mmol, 5.2 mL) was added dropwise with stirring and the reaction mixture stirred overnight, warming to room temperature. The reaction mixture was then poured into H_2O, washed with saturated $NaHCO_3$ (aqueous) and then saturated $Na_2S_2O_5$ (aqueous), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, yielding **11b** (0.46g, 1.72 mmol, 100%) as a brown-red solid, which was judged pure enough by TLC to be used in subsequent steps without further purification. A small portion of material was recrystallized from chloroform and used for spectroscopic purposes, as NMR spectra of this compound proved to be difficult to obtain: mp 257−258 °C; IR (KBr) 3364 (br, vs), 1667 (vs), 1619 (vs); ^{1}H NMR (acetone-d_6) δ 8.24 (br, d, J = 7.8 Hz), 7.69 (br, t, J = 7.2 Hz), ∼3.35 (vbr); ^{1}H NMR (DMSO-d_6/20% TFA-d_1): δ 8.29 (1H, d, J = 9.1 Hz), 8.23 (1H, d, J = 8.4 Hz), 8.14 (1H, d, J = 7.3 Hz), 7.66 (2H, m), 7.61 (1H, t, J = 7.7 Hz), 7.54 (1H, t, J = 6.9 Hz), 7.32 (1H, t, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6/20% TFA-d_1) δ 193.66, 149.59, 144.19, 142.23, 135.63, 135.11, 133.22, 129.86, 127.99, 127.16, 125.35, 124.91, 123.89, 123.76, 118.82, 113.14; MS (rel int) m/z 263 $(M + H)^+$; CID of 263 m/z 263 ($[M + H]^+$, 100), 262 (M^+, 71), 189 (80). Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.86; H, 3.84. Found: C, 76.48; H, 3.89. See ref 24.

1,7-Dideoxy-3-demethylprekinamycin (12a). Compound **11b** (0.10 g, 0.381 mmol) was dissolved in 16 mL of 100% EtOH and anhydrous hydrazine (0.878 mL, 70 equiv) added at once. The reaction mixture was refluxed for 0.5 h and then cooled to room temperature, and the solvent was removed under vacuum. The solids were dissolved again in anhydrous EtOH, which was again removed under vacuum to remove traces of hydrazine. The 0.108 g of crude hydrazone was then suspended in 10 mL of dry CH_2Cl_2 under N_2 with 1.03 mL of Et_3N, and Fetizon's reagent (2.83 g, ∼4.97 mmol Ag_2CO_3, ∼13 equiv) added at once with stirring. The reaction mixture was stirred for 5 min, then the solids were removed by gravity filtration and washed with CH_2Cl_2. The solvent was removed under vacuum and the crude product purified by flash chromatography with 65% hexanes/35% CH_2Cl_2, yielding **12b** (0.063 g, 0.191 mmol, 50%) as a bright red solid: mp 168 °C dec; IR (KBr) 2966, 2097 (vs), 1656 (s); ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, m), 8.16 (1H, d, J = 7.5 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.68 (2H, m), 7.45 (1H, m), 7.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ 180.69, 180.05, 134.41, 134.26, 133.93, 133.89, 133.21, 132.88, 130.38, 127.28, 126.84, 126.76, 126.68, 126.09, 125.92, 118.44, 77.25 (buried in $CDCl_3$ peak, but visible); MS (rel int) m/z 273, $(M + H)^+$; CID of 273 m/z 272 (M^+, 57), 40 (100). Anal. Calcd for $C_{17}H_8N_2O_2$: C, 75.00; H, 2.96; N, 10.29. Found: C, 74.44; H, 3.07; N, 9.76.

3-Bromo-1,4,5-trimethoxynaphthalene (6d). 3-Bromo-1,5-dimethoxy-4-naphthol (**6c**)[15] (800 mg, 2.827 mmol) was dissolved in 150 mL of 14% aqueous sodium hydroxide solution and 1 mL of EtOH added. Dimethyl sulfate (2.64 mL) was added in five portions over a 24 h period. The reaction solution was extracted into two volumes (250 mL) of CH_2Cl_2. The organic phases were combined and washed with two 250 mL volumes of 14% aqueous sodium hydroxide solution and then twice with 250 mL of water and twice with 250 mL of brine. The organic phase was dried over anhydrous sodium sulfate and the solvent removed under vacuum. The crude product was dissolved in hexane (120 mL) and filtered to remove solids and the solvent removed under vacuum to give 0.52 g (1.75 mmol, 62%) of 1,4,8-trimethoxy-2-bromonaphthalene (**6d**), which was judged pure enough by TLC and NMR to be used in subsequent steps without further purification: mp 85−87 °C; IR (CCl_4) 2910, 2810, 1570; ^{1}H NMR ($CDCl_3$) δ 7.83 (1H, d, J = 8.6 Hz), 7.38 (1H, t, J = 8.1 Hz), 6.95 (1H, s), 6.93 (1H, d, J = 7.8 Hz), 3.98 (3H, s), 3.92 (3H, s), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 155.42, 151.76, 146.70, 128.13, 126.10, 121.20, 115.01, 114.19, 108.95, 107.93, 61.68, 56.37, 55.92; MS (rel int)

m/*z* 299 ([M + H]$^+$, 30, ^{81}Br), 297 ([M + H]$^+$, 26, ^{79}Br); CID of 297 *m*/*z* 297 ([M + H]$^+$, 57), 282 (100), 267 (99). Anal. Calcd for $C_{13}H_{13}Br$: C, 52.50; H, 4.38; Br, 26.90. Found: C, 52.48; H, 4.58; Br, 26.39.

3-(2′-*N*-Acetaminobenzoyl)-1,4,5-trimethoxynaphthalene (8d). Compound **6d** (970 mg, 3.27 mmol) was dissolved in dry ethyl ether (20 mL) and stirred under N_2 at −78 °C for 30 min. *t*-BuLi (1.7 M in pentane, 1.55 equiv, 5.05 mmol, 2.97 mL) was slowly added, and after 15 min, the mixture was cannulated in a reverse addition to acetanthranil[14] (**7a**) (1.056 g, 2 equiv, 6.534 mmol), which was dissolved in 30 mL of diethyl ether at −78 °C. The reaction was followed by TLC. After 12 h of warming to room temperature, 20 mL of water was added to the reaction solution, which was extracted into methylene chloride, washed twice with water, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the crude product purified by flash chromatography (80% hexane/20% EtOAc) to yield 620 mg (50.1%) of 3-(2′-*N*-acetaminobenzoyl)-1,4,5-trimethoxynaphthalene: mp 141−143 °C; IR (CCl_4) 3480 (br), 2920, 1570; ^{1}H NMR ($CDCl_3$) δ 8.76 (1H, d, J = 9.0 Hz), 7.92 (1H, d, J = 8.5 Hz), 7.52 (3H, m), 6.98 (2H, m), 6.63 (1H, s), 3.99 (3H, s), 3.94 (3H, s), 3.73 (3H, s), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 201.35, 169.54, 156.53, 151.57, 147.39, 141.36, 135.27, 135.10, 129.96, 129.72, 127.19, 122.47, 122.35, 120.37, 114.92, 107.57, 102.77, 64.02, 56.17, 55.90, 25.61; MS (rel int) *m*/*z* 380 (M + H$^+$); CID of 380 *m*/*z* 380 ([M + H]$^+$, 36), 162 (98), 120 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.60; H, 5.54; N, 3.69. Found: C, 69.07; H, 5.57; N, 3.48.

3-(2′-Aminobenzoyl)-1,4,5-trimethoxynaphthalene (8e). Compound **8d** (440 mg, 1.16 mmol) was dissolved in methanol (39.4 mL), and 900 mg of KOH in 19.7 mL of H_2O was added to the reaction mixture, which was refluxed for 12 h and followed by TLC. The reaction mixture was extracted twice into methylene chloride (10 mL). The organic phases were combined, washed twice with 10 mL of saturated aqueous ammonium chloride, and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give 400 mg of **8e** (100%), which was judged pure enough by TLC and NMR to be utilized in subsequent steps without further purification: mp 137.5−138 °C; IR (CCl_4) 3460 (br), 2920, 1530; ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, d, J = 8.3 Hz), 7.46 (1H, t, J = 8.4 Hz), 7.34 (1H, d, J = 8.2 Hz), 7.25 (1H, t, J = 7.2 Hz), 6.97 (1H, d, J = 7.8 Hz), 6.70 (1H, d, J = 8.3 Hz), 6.67 (1H, s), 6.50 (1H, t , J = 7.6 Hz), 6.45 (2H, br, s), 3.99 (3H, s), 3.94 (3H, s), 3.76 (3H, s); ^{13}C NMR ($CDCl_3$) δ 199.45, 156.46, 151.48, 150.92, 146.56, 135.37, 134.74, 131.16, 129.24, 126.52, 120.55, 118.58, 116.66, 115.93, 114.86, 107.34, 103.19, 63.86, 56.17, 55.84; MS (rel int) *m*/*z* 338 (M + H)$^+$; CID of 338 *m*/*z* 338 ([M + H]$^+$, 12), 245 (34), 120 (100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.60; N, 4.15. Found: C, 69.11; H, 5.35; N, 3.97.

1-Deoxy-3-demethyl-*O*,*O*-dimethylkinafluorenone (11e). Compound **8e** (400 mg, 1.187 mmol) was dissolved in HOAc. Isoamyl nitrite (2 equiv, 2.374 mmol, 0.321 mL) was added and the mixture stirred for 0.5 h. Hydroquinone (130.7 mg, 1.187 mmol) dissolved in 2 mL of acetone was added to the red reaction mixture. The reaction mixture was stirred overnight and then extracted twice into 15 mL of methylene chloride. The organic phases were combined and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum to give the crude product. After flash chromatography (95% hexanes/5% EtOAc), **11e**, 274 mg, was obtained in 72% yield: mp 219−220 °C; IR (CCl_4) 1530, 1240, 1060; ^{1}H NMR ($CDCl_3$) δ 7.97 (1H, d, J = 7.8 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.69 (1H, d, J = 8.3 Hz), 7.54 (2H, m), 7.34 (1H, t, J = 7.1 Hz), 6.92 (1H, d, J = 7.8 Hz), 4.08 (3H, s), 4.00 (3H, s), 3.99 (3H, s); ^{13}C NMR ($CDCl_3$) δ 189.20, 158.76, 154.30, 145.96, 140.81, 135.36, 133.46, 128.94, 127.63, 127.17, 123.24, 122.89, 121.14, 114.14, 107.26, 61.62, 60.06, 55.35; MS (rel int) *m*/*z* 321 (M + H)$^+$; CID of 321 *m*/*z* 321 ([M + H]$^+$, 73), 306 (51), 291 (100). Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.00; H, 5.03. Found: C, 72.15; H, 4.91.

1-Deoxy-3-demethylprekinamycin (12b). Compound **11e** (41 mg, 0.128 mmol) was dissolved in 4 mL of dry CH_2Cl_2 under N_2 at −78 °C. BBr_3 (1 M in CH_2Cl_2, 3 equiv, 0.4612 mmol, 0.4612 mL) was added dropwise at −78 °C. The reaction mixture was stirred overnight, warming to room temperature. The product mixture was poured into water and extracted with CH_2Cl_2 and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product **11f** (28.2 mg, 0.101 mmol) carried over to the next step.

Compound **11f** (28.2 mg, 0.101 mmol) was dissolved in 4.26 mL of EtOH with anhydrous hydrazine (73.5 equiv, 7.45 mmol, 0.2337 mL). The reaction mixture was refluxed for 0.5 h under N_2. The reaction was cooled to room temperature and the solvent removed under vacuum to give the crude hydrazone (29.2 mg, 0.0999 mmol), which was carried over into the next step.

The crude hydrazone (29.2 mg, 0.0999 mmol) was dissolved in 2.66 mL of CH_2Cl_2 with 0.274 mL of Et_3N. Fetizon's reagent (0.753 g, ∼1.31 mmol Ag_2CO_3, ∼13 equiv) was added at once and the resulting mixture stirred for 5 min at room temperature. The suspension was then gravity filtered to remove solids, which were washed with several volumes of CH_2Cl_2. The solvent was removed under vacuum and the crude product purified by flash chromatography (65% hexanes/35% CH_2Cl_2) to give **12b** (26 mg, 70% over three steps from **11e**); mp 178 °C dec; IR (KBr) 3132 (br), 2962, 2095 (vs); ^{1}H NMR ($CDCl_3$) δ 12.13 (1H, s), 8.53 (1H, m), 7.76 (1H, d, J =7.2 Hz), 7.63 (1H, d, J = 8.7 Hz), 7.57 (1H, d, J = 6.0 Hz), 7.45 (2H, m), 7.21 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 185.87, 179.56, 162.06, 136.50, 134.63, 134.25, 133.54, 130.49, 127.66, 127.00, 126.11, 123.83, 119.58, 118.56, 115.94, 115.56, 77.23 (buried in $CDCl_3$ peak, but visible); MS (rel int) *m*/*z* 289 (M + H)$^+$; CID of 289 *m*/*z* 289 ([M + H]$^+$, 68), 261 (80), 91 (95).

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Supporting Information Available: ^{1}H NMR spectra for compounds **10**, **6b**, **11b**, and **12b** and a ^{13}C NMR spectrum for **11b** (6 pages). This material is contained in 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.

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