

Total Synthesis of Streptonigrone

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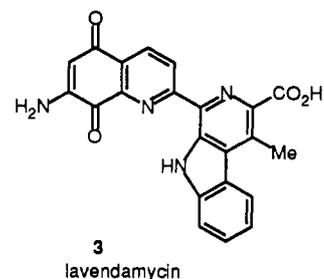
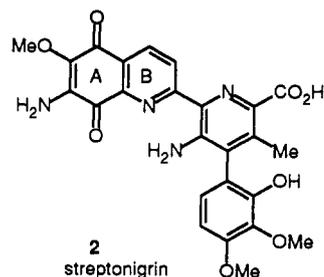
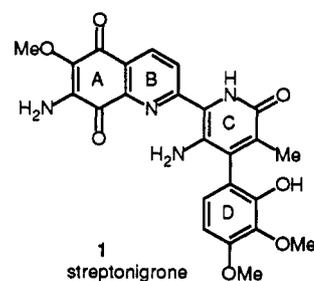
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Abstract: The first total synthesis of streptonigrone (**1**) is detailed and is based on the implementation of a room-temperature, inverse electron demand Diels–Alder reaction of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for introduction of the fully substituted pyridone (C ring) central to the agent structure. Azadiene **11** generation was effectively accomplished through conversion of the corresponding oxime to the *O*-sulfinate followed by in situ, room-temperature homolytic rearrangement to the *N*-sulfonylimine. Following the room-temperature [4 + 2] cycloaddition of **11** with 1,1-dimethoxypropene, which completed the assemblage of the carbon skeleton of **1**, a unique reaction sequence leading to aromatization of the central C ring was implemented taking special advantage of a base-catalyzed elimination of the methanesulfonamide via a sulfene. Subsequent introduction of the C ring C5 amine through modified Curtius rearrangement of the carboxylic acid **18** preceded a gratifying selective Fremy's salt oxidation of **20** to the key 7-bromoquinoline-5,8-quinone **21** conducted under biphasic, phase-transfer reaction conditions. The late-stage introduction of the 7-amino-6-methoxyquinoline-5,8-quinone AB ring system completed the synthesis of **1** and required the development and implementation of an improved metal-catalyzed (Ti(*O*-*i*-Pr)₄) methoxide C6 nucleophilic substitution reaction.

Streptonigrone (**1**), a highly substituted and densely functionalized quinoline-5,8-quinone isolated from an unidentified *Streptomyces* species (IA-CAS isolate no. 114)^{1a} or *Streptomyces albus* var. *bruneomycini*^{1b} as a minor component of the culture broths and identified through extensive spectroscopic characterization,^{1a} represents the newest number of a historically important class of potent antitumor antibiotics including streptonigrin (**2**),^{2,3} lavendamycin (**3**),⁴ and related congeners.⁵ Recent investigations have detailed additional potent antiviral and reverse transcriptase inhibitory activity for streptonigrin⁶ and have demonstrated that simple quinoline-5,8-quinones related to its AB ring system also display this potent biological activity.⁷ In a

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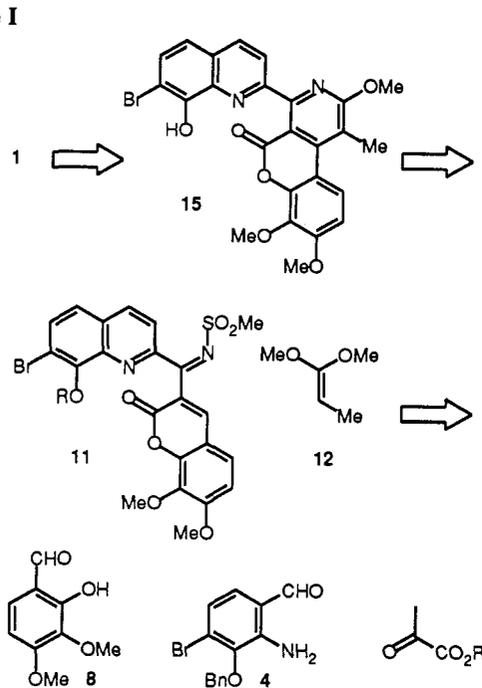
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continued effort to achieve the total synthesis of natural^{8,9} and synthetic^{10,11} members of this important class of antitumor antibiotics and in conjunction with efforts to delineate the structural and functional features contributing to their biological properties, herein we detail a convergent total synthesis of streptonigrone.¹²

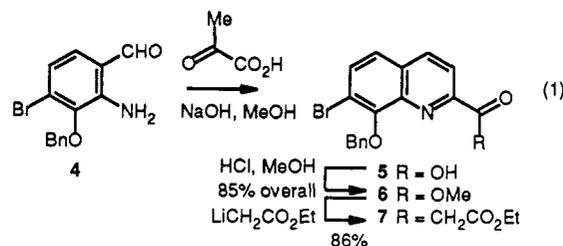
Central to our synthetic strategy was the implementation of a room-temperature, inverse electron demand Diels–Alder reaction¹² of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for the intro-

Scheme I



duction of the central pyridone C ring¹³ with completion of the assemblage of the full carbon skeleton of **1** (Scheme I). The deliberate complementary incorporation of a C3 electron-withdrawing substituent into the electron-deficient azadiene **11** could be expected to further accelerate its rate of participation in the LUMO_{diene}-controlled Diels–Alder reaction and reinforce the inherent cycloaddition regioselectivity.¹⁴ The use of the C3 carboxylate incorporated into the azadiene as a lactone was anticipated to serve two additional strategic functions. First, it was anticipated to serve as a convenient means of selectively protecting the D ring phenol, and ultimately, it was expected to serve as a suitable functionality for the introduction of the pyridone C5 amine through implementation of a modified Curtius rearrangement. Finally, the use of **4**¹⁵ and its incorporation into the 7-bromo-8-hydroxyquinoline **15** was anticipated to provide an appropriately functionalized precursor for the late-stage introduction of the fully functionalized AB quinone of **1** following a novel protocol introduced in our past studies.¹⁶

Friedlander condensation¹⁷ of pyruvic acid with 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**4**; NaOH, CH₃OH, 58 °C, 6 h) followed by Fischer esterification (HCl, CH₃OH, 24 °C, 5 h) of the crude carboxylic acid **5** provided **6** in excellent conversions (85%) (eq 1). Initial attempts to conduct the Friedlander condensation of **4** with methyl pyruvate to provide **6** directly



under a variety of reaction conditions led to mixtures of **5** and **6** due to in situ ester hydrolysis by adventitious water liberated in the initial condensation. Subsequent low-temperature addition of the lithium enolate of ethyl acetate to **6** provided the β -keto ester **7** and proved to proceed in highest conversions (71–86%) if nearly stoichiometric (1.25–1.5 equiv) rather than the typical 2-fold excess enolate was employed. Presumably this is the consequence of a slow breakdown of the initial ester–enolate tetrahedral addition product due to metal alkoxide complexation with the adjacent quinolinyl nitrogen, resulting in slow liberation of the acidic β -keto ester. Condensation of **7** with 3,4-dimethoxy-2-hydroxybenzaldehyde (**8**)¹⁸ provided **9** smoothly in high yield (75–81%) in refluxing EtOH containing a catalytic amount of piperidine (Scheme II). Typically, the large-scale conversion of **6** to **9** could be conducted without the deliberate chromatographic purification of **7** and generally provided **9** in 60–65% overall yield for the two steps.

Two approaches to the generation of **11** required for use in the LUMO_{diene}-controlled Diels–Alder reaction were examined (Scheme III). The first, which proved to be very reliable, required conversion of **9** to the oxime (**10** (NH₂OH–HCl, EtOH, reflux, 5 h) followed by oxime *O*-methanesulfinate formation (CH₃SOCl, Et₃N, CH₂Cl₂, 0 °C, 15 min) and room-temperature, in situ homolytic rearrangement.^{14,19,20} This sequence dependably provided the desired *N*-(methylsulfonyl)-1-aza-1,3-butadiene **11** in good overall yield (51–63%), and only the major anti versus minor syn oxime isomer was found to productively participate in the homolytic *O*-sulfinate \rightarrow *N*-sulfonyl rearrangement reaction. In addition, the *N*-sulfonylimine **11** proved to be sensitive to hydrolysis by adventitious water. Consequently, the conversions of *anti*-**10** to **11** were found to be optimal if crude **11** was not subjected to a standard aqueous workup procedure but subjected directly to a short SiO₂ plug purification followed by CHCl₃–hexane trituration to remove the final trace impurities, and material prepared using this protocol could be dependably employed in the subsequent [4 + 2] cycloaddition cascade. Alternatively, a direct TiCl₄-promoted (1.3 equiv) condensation of **9** with methanesulfonamide (1.2 equiv, 3 equiv of Et₃N, CH₂Cl₂, 0–25 °C, 6 h) could be employed to provide **11** in high yield (60–84%). However, the material prepared using this procedure proved somewhat capricious to subsequent purification (SiO₂) and to its participation in a productive [4 + 2] cycloaddition reaction. Presumably this may be attributed to the hydrolytic lability of the *N*-sulfonylimine as well as the subsequent sensitivity of the dienophile **12** and the [4 + 2] cycloadduct **13** to contaminants derived from the TiCl₄-promoted condensation reaction. The preparative material employed in our synthetic efforts was derived from the former two-step generation of **11** via the intermediate oxime **10** prior to investigation of the direct conversion of **9** to **11**. In our optimization of this former reaction sequence, the anti isomer of oxime **10** which was determined to productively participate in the homolytic *O*-sulfinate \rightarrow *N*-sulfonyl rear-

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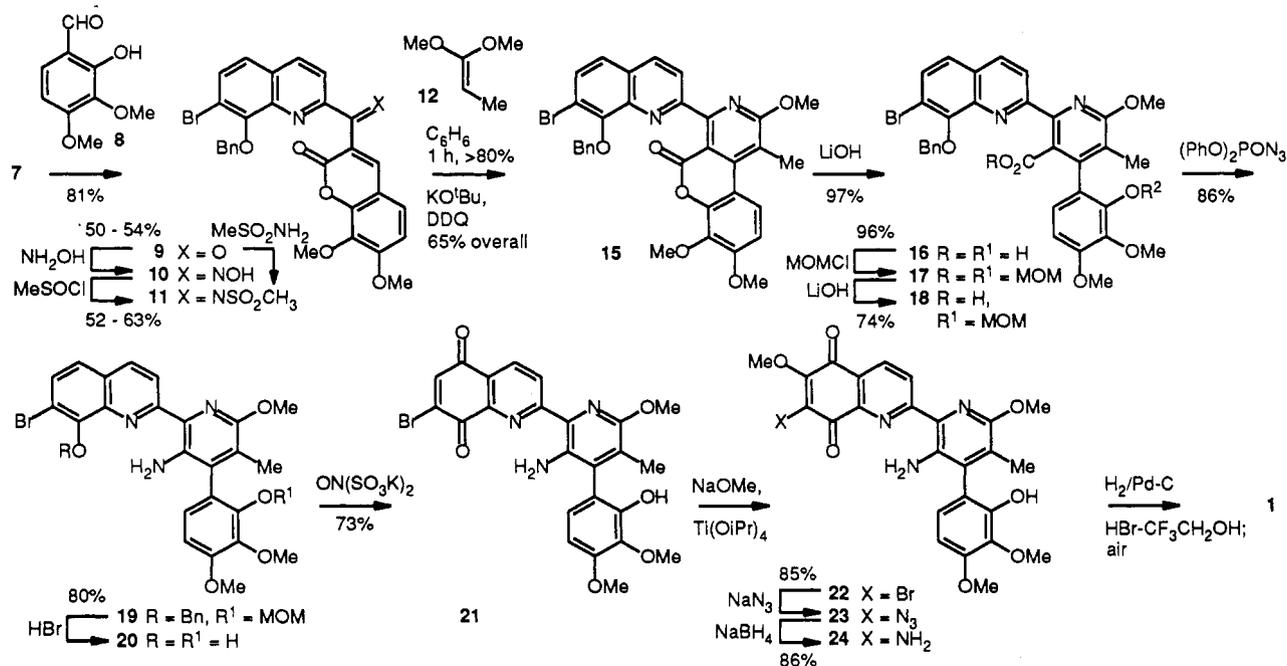
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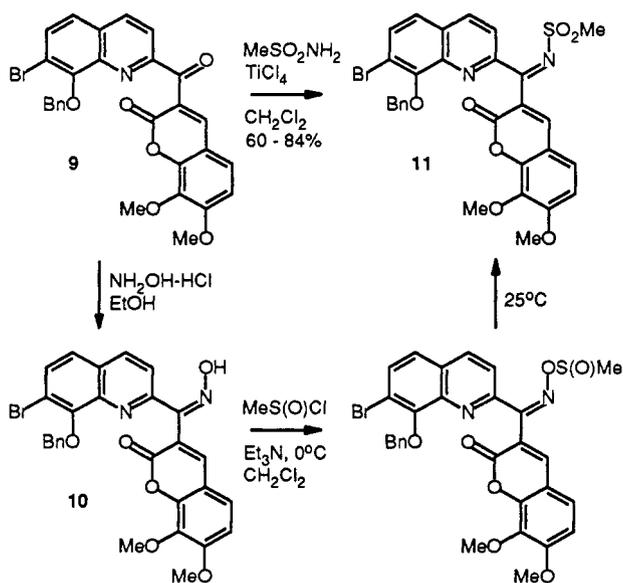
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Scheme II



Scheme III



rangement conveniently crystallized directly from the reaction mixture and was isolated free of contaminant syn oxime by simple filtration.

Treatment of 11 with 1,1-dimethoxypropene **12**²² at room temperature (1 h, C₆H₆) led to the formation of the sensitive [4 + 2] cycloadduct **13**²³ (Scheme IV). Efforts to purify and characterize **13** led to hydrolysis,²⁴ and consequently it was most expediently taken on without attempted purification. Following an aromatization protocol disclosed in prior studies,¹³ treatment

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(23) No reaction was observed when 11 was treated with ethoxyacetylene (20 equiv, 25–90 °C, 16–24 h).

(24) Flash chromatography of the crude Diels–Alder product resulted in hydrolysis of the orthoester to provide the corresponding methyl ester: ¹H NMR (CDCl₃, 200 MHz) δ 11.01 (br s, 1H, NH), 8.32 (d, 1H, J = 8.8 Hz), 7.82 (m, 1H), 7.76–7.45 (m, 4H), 7.43–7.24 (m, 3H), 6.57 (s, 2H), 5.30 (m, 2H), 4.01 (s, 3H, OCH₃), 3.9–3.75 (m, 1H), 3.82 (s, 3H, OCH₃), 3.43 and 3.41 (two s, 3H, OCH₃), 3.21 and 3.19 (two s, 3H, SO₂Me), 2.52 (m, 1H), 0.98 and 0.97 (two d, 3H, J = 5 Hz); CIMS (2-methylpropane) *m/e* 713/711 (M⁺ + H), 633/631 (base).

of **13** with *t*-BuOK (THF, –30 °C, 1 h) followed by DDQ (CH₂Cl₂, 25 °C, 1 h) provided **15**. Analogous to prior observations,¹³ this unusual aromatization sequence presumably proceeds with intermediate generation of an imidate of **14** derived from deprotonation of the methansulfonamide, loss of sulfene facilitated by vinylogous amide activation of the departing amine, and finally loss of methoxide. Subsequent aromatization of **14** upon DDQ treatment provided **15**. Although the isolation and characterization of **13**–**14** were attempted in initial studies, the conversion of **13** to **15** proved most convenient without their deliberate intermediate purification and typically provided **15** in 52–65% overall yield for the three steps. In our optimization of this sequence, it was determined that the source, and consequently the purity, of the dienophile **12** had a significant effect on the observed conversions. Ketene acetal **12** prepared by Fe(CO)₅-catalyzed isomerization of acrolein dimethyl acetal (0.05–0.01 equiv, *hv*, neat, Pyrex, 25 °C, 3 h)²² proved substantially superior to the material prepared by strong base-catalyzed isomerization (KNH₂, NH₃–Et₂O, –30 °C, 2 h).²⁵

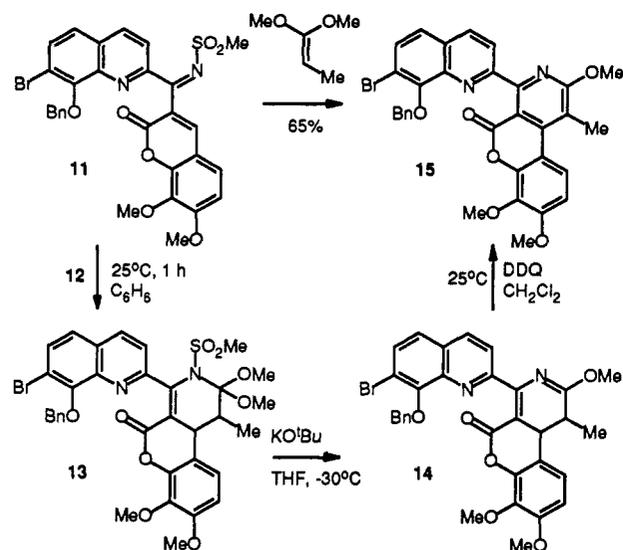
Hydrolysis of the lactone **15** (4 N LiOH, DMSO, 60 °C, 6 h) followed by protection of the free phenol as its methoxymethyl ether under conditions that led to carboxylic acid esterification (NaH, DMF, ClCH₂OCH₃, 25 °C, 1–1.5 h, 96%) afforded **17**. Subsequent ester hydrolysis (4 N LiOH, DMSO, 130–135 °C, 6 h, 71–76%) provided **18** in excellent overall yield, and this two-step conversion of **16** to **18** proved superior to efforts to selectively protect the phenol in the presence of the free carboxylic acid. Modified Curtius rearrangement on the free carboxylic acid employing the Shioiri–Yamada reagent ((PhO)₂P(O)N₃, benzene–H₂O)^{26,27} provided **19** and permitted the introduction of the pyridone C5 amine. Surprisingly, the intermediate isocyanate derived from Curtius rearrangement of the acyl azide proved unusually stable, and the conversion of **18** to **19** required the deliberate addition of hydroxide (4 N LiOH, THF–H₂O) to the reaction mixture to complete the isocyanate hydrolysis. Attempts to trap the isocyanate in situ with H₂O or *tert*-butyl alcohol to provide **19** or the corresponding *tert*-butylcarbamate

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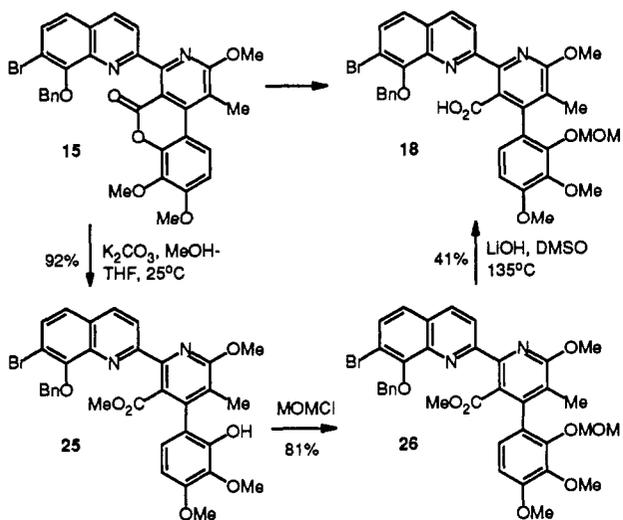
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(27) Attempted Curtius rearrangement on **16** directly ((PhO)₂P(O)N₃, Et₃N, *t*-BuOH, reflux, 3.5 h) provided predominantly **15** (50%).

Scheme IV



Scheme V



proved unsuccessful and led to isolation of the isocyanate and/or its corresponding acyl azide derivative.²⁸

Several additional observations made in regard to the conduct of the conversion of 15 to 19 proved important. Similar to the results of prior studies with related substrates,^{8,9,13} the C5 ester of 17 proved unusually resistant to hydrolysis as a consequence of the steric hindrance provided by the two flanking ortho aryl substituents. While this sterically hindered ester hydrolysis was not satisfactorily addressed in prior studies and although standard hydrolysis conditions failed to effect the conversion of 17 to 18, the use of the more vigorous conditions detailed herein (130–135 °C, DMSO, 71–80%) coupled with the use of the methoxymethyl ester provided a satisfactory solution to this refractory problem. In addition, the use of LiOH–H₂O₂²⁹ (THF–H₂O 6:1, 25 °C, 12–24 h, 63–74%) provided an alternative hydrolysis procedure that employed milder reaction conditions but was found to generally provide 18 in lower conversions. Mild methanolysis of the lactone 15 to provide the methyl ester 25³⁰ (Na₂CO₃, CH₃-

OH–THF 6.5:1, 25 °C, 4 h, 92%), phenol protection as the methoxymethyl ether 26³⁰ (MOMCl, *i*-Pr₂NEt, CHCl₃, reflux, 6 h, 81%), and subsequent methyl ester hydrolysis of 26 (4 N LiOH, DMSO, 130–135 °C, 26 h, 42%) provided an alternative sequence for the conversion of 15 to 18 (Scheme V). However, 26 proved more resistant to hydrolysis than 17 (76 vs 42%) and, unlike 17, failed to provide 18 upon treatment with LiOH–H₂O₂ (THF–H₂O, 60 °C),²⁹ LiOH (THF–H₂O, 100 °C), or KOH (EtOH–H₂O or *n*-PrOH–H₂O, reflux, 24h).

The remaining task of introducing the fully functionalized streptonigrone AB quinone was designed to follow selective deprotection of the benzyl ether 19 with the anticipated, but unfounded, potential that a D ring free phenol would undergo competitive quinone oxidation. After considerable effort to selectively deprotect the benzyl ether of 19^{30b} in the presence of the methoxymethyl ether, the deliberate conversion of 19 to 20 with deprotection of both the benzyl and MOM ethers was found to proceed in high yield (saturated HBr–CH₂Cl₂, 0 °C, 2–6 h, 70–80%). Although not essential to our synthetic efforts, a gratifying and predictably selective oxidation of the 8-hydroxyquinoline of 20 to provide 21 was accomplished cleanly with potassium nitrosodisulfonate (8–12 equiv of Fremy's salt)³¹ under the conditions of Kende's two-phase reaction system⁹ (1:1 CH₂Cl₂–0.05 M KH₂PO₄, 1.1 equiv of Bu₄NHSO₄, 25 °C, 3–6 h, 64–73%). The selective oxidation of the A versus D ring phenol of 20 may be attributed in part to the ease of carbon versus oxygen phenoxyl radical trap by the reagent with loss of quinolyl versus aryl delocalization energy. It is also notable that the C ring C5 amine did not competitively interfere with this oxidation reaction and, thus, could be carried through the synthesis without deliberate protection. Alternative procedures for the use of Fremy's salt (4–6 equiv) including the conventional homogeneous reaction conditions of acetone–0.05 M NaH₂PO₄ (1:1) and CH₃OH–0.05 M NaH₂PO₄ (1:1 or 6:1) proved much less effective, resulting in no or slow reaction, and the omission of the phase-transfer agent (Bu₄NHSO₄) from the Kende two-phase reaction conditions led to recovered starting material.

In the conduct of the optimization of the conversion of 19 to 20, we determined that treatment with HBr(g) for shorter reaction periods under the mild reaction conditions (0 °C) led to clean cleavage of the methoxymethyl ether and only partial cleavage of the benzyl ether, while substantially longer treatment (0 °C) or treatment under more vigorous reaction conditions (refluxing CH₂Cl₂) led to diminished yields resulting from presumed cleavage of the C ring C2 methyl ether. The finely tailored conditions devised for the conversion of 19 to 20 proved technically uneventful to conduct, but as detailed later, the observations made in their development provided an effective solution to the selective cleavage of the C ring C2 methyl ether and the final step of the total synthesis.

This set the stage for the final- and late-stage introduction of the fully functionalized 7-amino-6-methoxyquinoline-5,8-quinone AB ring system of 1. In conjunction with efforts to achieve the

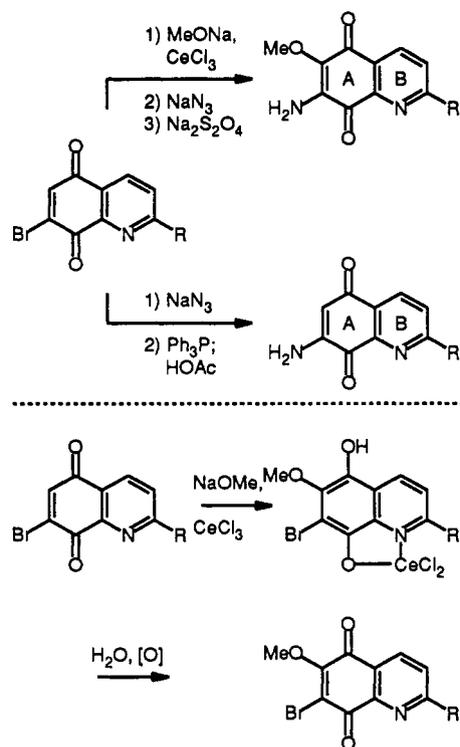
(28) For the acyl azide derivative of the isocyanate of 19: ¹H NMR (CDCl₃, 200 MHz) δ 9.13 (s, 1H, NH), 8.31 (d, 1H, *J* = 8.7 Hz), 8.29 (d, 1H, *J* = 8.7 Hz), 7.71 (d, 1H, *J* = 8.8 Hz), 7.69 (m, 2H), 7.51 (d, 1H, *J* = 8.7 Hz), 7.49–7.28 (m, 3H), 6.93 (d, 1H, *J* = 8.6 Hz), 5.41 (s, 2H, OCH₂Ph), 4.94 (d, 1H, *J* = 6.1 Hz, OCHHOMe), 4.84 (d, 1H, *J* = 6.1 Hz, OCHHOMe), 4.07 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.94 (s, 3H), 2.08 (s, 3H); IR (KBr) ν_{max} 3856, 2942, 2140, 1712, 1654, 1490, 1360, 1160 cm⁻¹.

(29) Corey, E. J.; Hopkins, P. B.; Yoo, S.; Kim, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* 1979, 101, 7131.

(30) (a) For 25: ¹H NMR (CDCl₃, 300 MHz) δ 8.48 (d, 1H, *J* = 8.6 Hz), 8.23 (d, 1H, *J* = 8.6 Hz), 7.62 (d, 1H, *J* = 8.9 Hz), 7.54 (m, 2H), 7.43 (d, 1H, *J* = 8.9 Hz), 7.41–7.28 (m, 3H), 6.79 (d, 1H, *J* = 8.7 Hz), 6.53 (d, 1H, *J* = 8.7 Hz), 5.92 (s, 1H, OH), 5.56 (d, 1H, *J* = 11.2 Hz), 5.53 (d, 1H, *J* = 11.2 Hz), 4.15 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 3.43 (s, 3H), 2.07 (s, 3H). For 26: ¹H NMR (CDCl₃, 300 MHz) δ 8.43 (d, 1H, *J* = 8.6 Hz), 8.24 (d, 1H, *J* = 8.6 Hz), 7.63 (d, 1H, *J* = 8.8 Hz), 7.52 (m, 2H), 7.45 (d, 1H, *J* = 8.8 Hz), 7.41–7.27 (m, 3H), 6.81 (d, 1H, *J* = 8.6 Hz), 6.54 (d, 1H, *J* = 8.6 Hz), 5.58 (d, 1H, *J* = 11 Hz), 5.21 (d, 1H, *J* = 11 Hz), 5.18 (d, 1H, *J* = 5 Hz), 4.85 (d, 1H, *J* = 5 Hz), 4.15 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.37 (s, 3H), 3.20 (s, 3H), 2.08 (s, 3H). (b) Catalytic hydrogenolysis (H₂, 10% Pd–C, CH₃OH, 25 °C, 30 min, 75% or 10% Pd–C, 25% aqueous HCO₂–NH₄, THF, 25 °C, 2 h, 75%) was accompanied by debromination to provide 3-amino-4-(3,4-dimethoxy-2-hydroxyphenyl)-2-(8-hydroxyquinolin-2-yl)-6-methoxy-5-methylpyridine: ¹H NMR (acetone-*d*₆, 250 MHz) δ 8.78 (d, 1H, *J* = 8.8 Hz), 8.51 (br s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz), 7.85 (m, 2H), 7.13 (m, 1H), 7.02 (d, 1H, *J* = 8.5 Hz), 6.89 (d, 1H, *J* = 8.5 Hz), 6.41 (br s, 2H), 4.94 (d, 1H, *J* = 5.8 Hz, OCHHOMe), 4.90 (d, 1H, *J* = 5.8 Hz, OCHHOMe), 4.03 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.03 (s, 3H), 1.95 (s, 3H).

(31) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* 1971, 71, 229.

Scheme VI



total synthesis of 2–3^{8,9} and structurally simplified analogs,^{9,11,15,16} we previously disclosed a divergent introduction of the lavendamyacin 7-aminoquinoline-5,8-quinone and streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone AB ring systems from a common 7-bromoquinoline-5,8-quinone intermediate (Scheme VI). Key to the introduction of the 7-amino-6-methoxyquinoline-5,8-quinone system was the metal-catalyzed (CeCl_3) C6 nucleophilic addition of methoxide to a 7-bromoquinoline-5,8-quinone. In this reaction, the coordination of Ce(III) with the substrate reverses the normal C7 regioselectivity of methoxide nucleophilic addition and stabilizes the hydroquinone addition product, preventing reversal of the C6 nucleophilic substitution reaction. In the course of our efforts, we encountered difficulty implementing the CeCl_3 -catalyzed C6 methoxide addition reaction with **21**. Consequently, we conducted a more extensive study of the metal-catalyzed³² nucleophilic C6 substitution reaction of 7-bromoquinoline-5,8-quinones with methoxide which extends the observations made with CeCl_3 to additional more effective metal catalysts.

Representative results of this study with the simple bromoquinones **27a,b** are provided in Table I. From a survey of a range of Lewis acids, $\text{Ti}(\text{O-}i\text{-Pr})_4$ and ZnBr_2 were found to cleanly catalyze the C6 nucleophilic substitution reaction of NaOMe with **27a** to provide **28a** in high yield without evidence of competitive C7 substitution (Scheme VII). Of the Lewis acids examined, those which possess the capabilities for ligand complexation through a higher coordination sphere, *i.e.* Ti(IV), were found to provide clean and high-yielding conversions of **27** to **28**, although simple Lewis acids including LiCl were capable of reversing the regioselectivity of the NaOMe addition. Of the successful metal catalysts examined, $\text{Ti}(\text{O-}i\text{-Pr})_4$ has proven the most effective for use with highly functionalized and Lewis acid sensitive substrates.

Unlike the reaction with **27**, treatment of **21** with NaOMe in

(32) Pratt, Y. T. *J. Org. Chem.* **1962**, *27*, 3905.

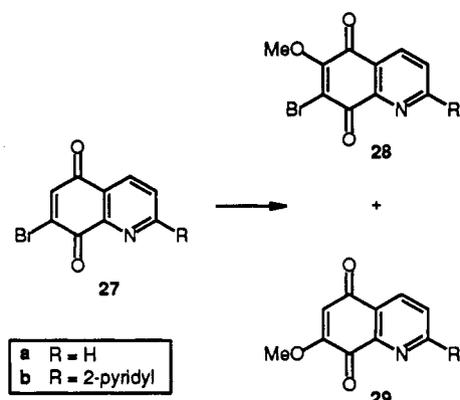
(33) $\text{Ti}(\text{O-}i\text{-Pr})_4$ was distilled prior to use, and a 0.5 M solution in THF was prepared. LiCl and ZnBr_2 were dried in vacuo, and 0.5 M THF solutions were prepared. $\text{Mg}(\text{OMe})_2$ was prepared as a 0.5 M solution in MeOH from Mg metal and anhydrous methanol. A 0.5 M solution of $\text{Ti}(\text{OMe})_4$ was prepared in situ with the addition of NaOMe to TiCl_4 in THF at 0 °C.

Table I

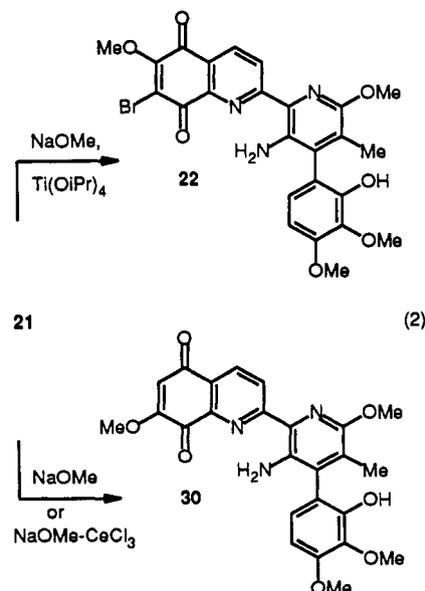
substrate	equiv of NaOMe	equiv, Lewis acid ^a	temp, °C (time, h)	product	% yield
27a	2.0	none	0 (0.5), 25 (1)	28a	22
				29a	58
27a	2.5	1.5, CeCl_3	0 (0.5), 25 (1)	28a	58
27a	2.5	1.5, $\text{Ti}(\text{O-}i\text{-Pr})_4$	0 (0.5), 25 (1)	28a	57
27a	2.0	1.5, ZnBr_2	0 (0.5), 25 (1)	28a	57
27a	0	2.0, $\text{Mg}(\text{OMe})_2$	0 (0.5), 25 (1)	28a	29
27a	2.0	2.0, $\text{Ti}(\text{OMe})_4$	0 (0.5), 25 (1)	28a	22
27a	2.0	2.0, LiCl	0 (0.5), 25 (1)	28a	29
				29a	5
27b	2.0	1.5, CeCl_3	0 (0.5), 25 (1)	28b	52
27b	2.0	2.0, $\text{Ti}(\text{O-}i\text{-Pr})_4$	0 (0.5)	28b	53
21	6.0	2.0, CeCl_3	0 (1)	22	0
				30	60–65
21	4.0	4.0, CeCl_3	0 (0.5), 25 (1)	22	0
				30	54
21	2.0	3.0, LiCl	0 (3)	22	29
				30	0
21	2.0	1.2, $\text{Ti}(\text{O-}i\text{-Pr})_4$	0 (1)	22	54
				30	19

^a See ref 33.

Scheme VII

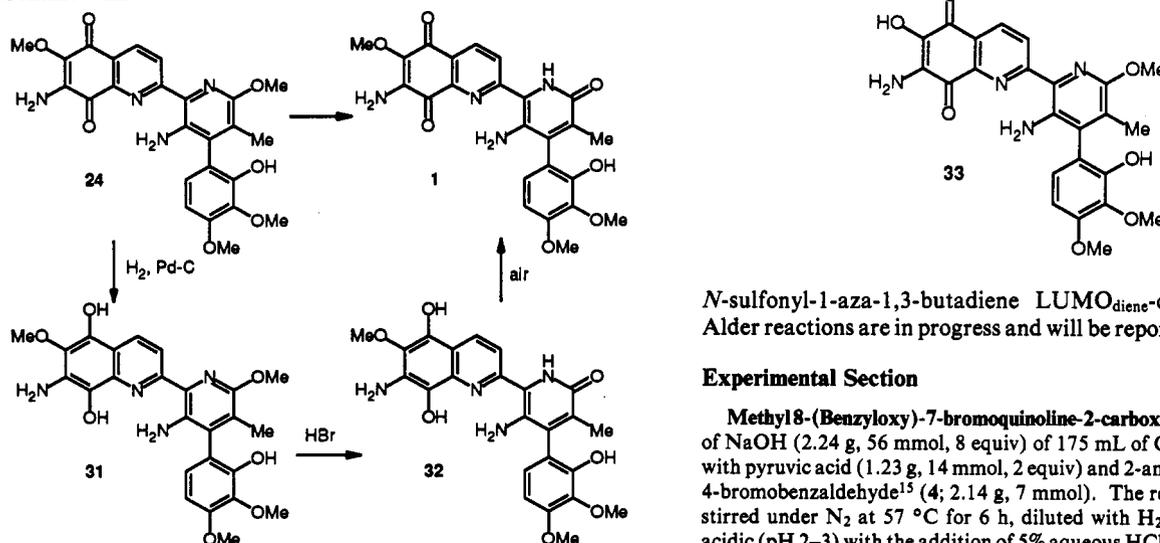


the presence of CeCl_3 led to the generation of **30**³⁴ derived from C7 methoxide addition–elimination (eq 2). Presumably, the more



densely functionalized substrate **21** failed to effectively complex the CeCl_3 in a manner that leads to productive C6 methoxide

Scheme VIII



addition. In contrast, both $\text{Ti}(\text{O}-i\text{-Pr})_4$ and LiCl catalyzed the C6 addition of methoxide to **21** with the former reagent providing good conversions to **22** upon workup and air oxidation (Table I).

Treatment of **22** with NaN_3 (1.1 equiv, $\text{THF}-\text{H}_2\text{O}$, 25 °C, 20 h) provided the sensitive deep green azide **23** (85%), and subsequent reduction (NaBH_4 , $\text{THF}-\text{MeOH}$, 25 °C, 1 h, 86%) afforded **24** possessing the fully functionalized AB quinone of **1**. In practice, these two steps were conducted without the intermediate purification of the sensitive azido quinone **23** and the overall yields for the conversion of **22** to **24** improved. Interestingly, the reduction of **23** using more conventional protocols including $\text{Na}_2\text{S}_2\text{O}_4$ ($\text{THF}-\text{H}_2\text{O}$, slow reduction)¹⁶ or Ph_3P , $\text{CH}_2\text{-Cl}_2$ -HOAc in $\text{H}_2\text{O}-\text{THF}$ (51%)^{15,16} proved less effective than the simple use of NaBH_4 ,³⁵ although this was not investigated in detail.

Final conversion of **24** to streptonigrone (**1**) required deprotection of the C ring C2 methyl ether which had admirably served its purpose throughout the synthesis. This was effectively accomplished by treatment of **24** with $\text{HBr}(\text{g})-\text{CF}_3\text{CH}_2\text{OH}$ (reflux, 1.5 h) under an atmosphere of H_2 (5% Pd-C, H_2) which served to prereduce the quinone **24** to the corresponding hydroquinone **31** (Scheme VIII). Acid-catalyzed methyl ether cleavage of **31**, which predictably proceeds through preferential pyridine N-protonation with selective activation of the C ring C2 methyl ether toward cleavage, followed by workup and air oxidation of **32** provided a sample of streptonigrone (**1**) identical in all compared respects with authentic material (^1H NMR, IR, MS, TLC R_f , UV, mp).¹ Efforts to deprotect **24** without reducing the quinone through direct treatment of **24** with $\text{HCl}(\text{g})-\text{CH}_2\text{Cl}_2$ (25 °C, 2 h) or $\text{HBr}(\text{g})-\text{CH}_2\text{Cl}_2$ (reflux, 1.5 h, 76%) led to preferential A ring methyl ether cleavage to provide **33**.³⁶ Alternative reagents for pyridone methyl ether cleavage³⁷ did not prove as successful as the mild treatment with $\text{HBr}(\text{g})$, although this was not investigated in detail.

Extension of these studies to the preparation of key, nonnatural quinoline-5,8-quinones as well as additional studies of the

(34) For **30**: ^1H NMR (CDCl_3 , 400 MHz) δ 8.79 (d, 1H, $J = 8.7$ Hz), 8.38 (d, 1H, $J = 8.7$ Hz), 6.83 (d, 1H, $J = 8.5$ Hz), 6.65 (br s, 2H, NH₂), 6.64 (d, 1H, $J = 8.5$ Hz), 6.23 (s, 1H, C6-H), 5.91 (br s, 1H, OH), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 1.99 (s, 3H); FABMS (NBA) m/e 478 ($M^+ + \text{H}$, base).

(35) Rao, H. V.; Beach, J. W. *J. Med. Chem.* 1991, 34, 1871.

(36) For **33**: ^1H NMR (CDCl_3 , 400 MHz) δ 8.72 (d, 1H, $J = 8.4$ Hz), 8.25 (d, 1H, $J = 8.4$ Hz), 6.80 (d, 1H, $J = 8.7$ Hz), 6.62 (d, 1H, $J = 8.7$ Hz), 6.42 (br s, 1H), 5.81 (br s, 1H), 4.68 (br s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 1.98 (s, 3H).

(37) This included an examination of the following: $\text{TMSCl}-\text{NaBr}$, $\text{CH}_2\text{-CN}$, 16 h; $\text{MeSO}_3\text{H}-\text{NaBr}$, $i\text{-PrOH}$, reflux, 14 h; $\text{TsOH}-\text{NaBr}$, $\text{CF}_3\text{CH}_2\text{OH}$, 80 °C, 6 h, 10 equiv of SnCl_2 ; $\text{HBr}(\text{g})-\text{CH}_2\text{Cl}_2$, 100 °C, 1 h; 48% $\text{HBr}-\text{HOAc}$; concentrated HCl , 100 °C, 1-3 h, 10 equiv of SnCl_2 .

N-sulfonyl-1-aza-1,3-butadiene LUMO_{diene}-controlled Diels-Alder reactions are in progress and will be reported in due course.

Experimental Section

Methyl(8-(Benzyloxy)-7-bromoquinoline-2-carboxylate (6). A solution of NaOH (2.24 g, 56 mmol, 8 equiv) of 175 mL of CH_3OH was treated with pyruvic acid (1.23 g, 14 mmol, 2 equiv) and 2-amino-3-(benzyloxy)-4-bromobenzaldehyde¹⁵ (**4**; 2.14 g, 7 mmol). The reaction mixture was stirred under N_2 at 57 °C for 6 h, diluted with H_2O (420 mL), made acidic (pH 2-3) with the addition of 5% aqueous HCl , and extracted with EtOAc (420 mL). The organic extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). The solvent was evaporated, and the residue was dissolved in 40 mL of CH_3OH and treated with saturated $\text{HCl}-\text{CH}_3\text{OH}$ (20 mL). The solution was allowed to stir at 24 °C for 5 h. The reaction mixture was diluted with H_2O (70 mL) and the precipitate **6** collected by filtration. Flash chromatography (3 × 20 cm SiO_2 , 20% EtOAc -hexane eluant) afforded pure **6** (2.21 g, 2.61 g theoretical, 85%; typically 80-86%, 5-10 mmol) as a white solid: mp 95-96 °C (CHCl_3 -hexane); ^1H NMR (CDCl_3 , 200 MHz) δ 8.28 (d, 1H, $J = 8.6$ Hz), 8.19 (d, 1H, $J = 8.6$ Hz), 7.78-7.72 (m, 2H), 7.76 (d, 1H, $J = 8.8$ Hz), 7.48 (d, 1H, $J = 8.8$ Hz), 7.43-7.32 (m, 3H), 5.60 (s, 2H, OCH_2Ph), 4.07 (s, 3H, CO_2CH_3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.8, 153.0, 147.2, 142.5, 137.5, 137.2, 132.8, 129.9, 129.1, 128.2, 128.0, 123.4, 121.3, 117.6, 76.8, 52.9; IR (KBr) ν_{max} 1750, 1714, 1442, 1326, 1262, 1136, 1116, 1088, 726 cm^{-1} ; EIMS m/e (relative intensity) 373/371 (M^+ , 4), 91 (base); CIMS (2-methylpropane) m/e 374/372 ($M^+ + \text{H}$, base); EIHRMS m/e 371.0163 ($\text{C}_{18}\text{H}_{14}\text{BrNO}_3$ requires 371.0157). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{BrNO}_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 58.07; H, 3.68; N, 3.70.

Ethyl 3-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-3-oxopropionate (7). Ethyl acetate (0.73 mL, 7.5 mmol, 1.5 equiv) was added dropwise to a solution of lithium diisopropylamine (7.5 mmol, 1.5 equiv) in THF -hexane (10 mL) freshly prepared from diisopropylamine (1.05 mL, 7.5 mmol, 1.5 equiv) and $n\text{-BuLi}$ (3 mL of 2.5 M, 7.5 mmol, 1.5 equiv) at -78 °C. After 15 min at -78 °C, a solution of **6** (1.86 g, 5.0 mmol) in 8 mL of THF was added slowly. The reaction mixture was stirred at -78 °C for 40 min before being allowed to warm to 24 °C. The reaction mixture was poured onto 150 mL of H_2O and extracted with EtOAc (120 mL). The organic extract was washed with saturated aqueous NaCl (40 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (4 × 15 cm SiO_2 , 10% EtOAc -hexane eluant) afforded **7** (1.53 g, 2.14 g theoretical, 71%; typically 71-86%, 5-10 mmol) as a white, crystalline solid: mp 84-85 °C (EtOAc -hexane); ^1H NMR (CDCl_3 , 200 MHz) δ 8.30 (d, 1H, $J = 8.6$ Hz), 8.18 (d, 1H, $J = 8.6$ Hz), 7.79 (d, 1H, $J = 8.8$ Hz), 7.66-7.61 (m, 2H), 7.51 (d, 1H, $J = 8.8$ Hz), 7.41-7.34 (m, 3H), 5.52 (s, 2H, OCH_2Ph), 4.33 (s, 2H, COCH_2), 4.41 (q, 2H, $J = 7.2$ Hz), 1.17 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 194.5, 168.1, 151.3, 147.2, 142.0, 137.8, 133.3, 131.8, 130.5, 128.6, 128.4, 128.3, 123.7, 118.6, 76.8, 61.3, 44.4, 14.0; IR (KBr) ν_{max} 1726, 1700, 1444, 1364, 1338, 1312, 1304, 1286, 1142, 1082, 856, 758, 694 cm^{-1} ; EIMS m/e (relative intensity) 429/427 (M^+ , 5), 91 (base); CIMS (2-methylpropane) m/e 430/428 ($M^+ + \text{H}$, base); EIHRMS m/e 427.0429 ($\text{C}_{21}\text{H}_{18}\text{BrNO}_4$ requires 427.0419). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{BrNO}_4$: C, 59.74; H, 4.56; N, 3.17. Found: C, 59.60; H, 4.26; N, 3.34.

8-(Benzyloxy)-7-bromoquinolin-2-yl 7,8-Dimethoxy-2-oxo-2H-1-benzopyran-3-yl Ketone (9). A solution of 3,4-dimethoxy-2-hydroxybenzaldehyde¹⁸ (**8**; 1.02 g, 5.61 mmol, 1.3 equiv) in 30 mL of absolute EtOH was treated with **7** (1.85 g, 4.32 mmol) and 5 drops of piperidine. The reaction mixture was warmed at reflux for 1 h. After the mixture was cooled (0 °C), the crystalline product was collected by filtration (EtOH wash). Recrystallization from CHCl_3 -hexane afforded **9** (1.91 g, 2.36 g, theoretical, 81%; typically 75-81%, 0.1-7 mmol) as a yellow, crystalline solid: mp 177-178 °C (CHCl_3 -hexane); ^1H NMR (CDCl_3 , 200 MHz)

δ 8.33 (d, 1H, $J = 8.5$ Hz), 8.31 (s, 1H), 8.13 (d, 1H, $J = 8.5$ Hz), 7.77 (d, 1H, $J = 8.9$ Hz), 7.52 (d, 1H, $J = 8.9$ Hz), 7.40 (m, 2H), 7.29 (d, 1H, $J = 8.7$ Hz), 7.08–6.96 (m, 3H), 6.90 (d, 1H, $J = 8.7$ Hz), 5.32 (s, 2H, OCH₂Ph), 3.99 (s, 3H), 3.75 (s, 3H); ¹H NMR (DMSO-*d*₆, 250 MHz) δ 8.73 (d, 1H, $J = 8.3$ Hz), 8.66 (s, 1H), 8.16 (d, 1H, $J = 8.3$ Hz), 7.96 (d, 1H, $J = 8.2$ Hz), 7.86 (d, 1H, $J = 8.2$ Hz), 7.67 (d, 1H, $J = 8.2$ Hz), 7.24 (m, 3H), 7.13 (m, 1H), 6.97 (m, 2H), 5.21 (s, 2H, OCH₂-Ph), 3.99 (s, 3H), 3.61 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz), δ 192.0, 158.3, 157.2, 152.9, 152.8, 148.8, 141.9, 137.8, 137.1, 136.0, 132.9, 130.3, 128.1, 128.0, 127.7, 124.9, 123.9, 123.8, 119.6, 117.8, 113.2, 109.0, 77.2, 61.3, 56.6; IR (KBr) ν_{\max} 1730, 1672, 1608, 1588, 1566, 1500, 1436, 1366, 1326, 1284, 1254, 1162, 1110, 1076, 976, 856 cm⁻¹; EIMS *m/e* (relative intensity) 547/545 (M⁺, 2), 91 (base). Anal. Calcd for C₂₈H₂₀BrNO₆: C, 61.55; H, 3.69; N, 2.56. Found: C, 61.22; H, 3.58; N, 2.50.

1-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-1-hydroxyimino-1-(7',8'-dimethoxy-2'-oxo-2'H-1'-benzopyran-3'-yl)methane (10). Hydroxylamine hydrochloride (760 mg, 10.9 mmol, 3 equiv) was added to a stirred solution of **9** (2.0 g, 3.66 mmol) in 100 mL of EtOH at 24 °C. The reaction mixture was warmed at reflux for 5 h and diluted with H₂O (80 mL), and the pH was adjusted to 7.5–8.0 with the addition of saturated aqueous NaHCO₃. The precipitated oxime was collected by filtration (CHCl₃ wash), and recrystallization from CHCl₃ afforded *anti*-**10** (1.13 g, 2.05 g theoretical, 53%; typically 50–54%, 0.1–4 mmol) as a white, crystalline solid: mp 223–224 °C (CHCl₃); ¹H NMR (DMSO-*d*₆, 200 MHz) δ 12.38 (s, 1H, NOH), 8.53 (d, 1H, $J = 9$ Hz), 8.42 (s, 1H), 8.26 (d, 1H, $J = 9$ Hz), 7.84 (d, 1H, $J = 8.8$ Hz), 7.76 (d, 1H, $J = 8.8$ Hz), 7.68 (d, 1H, $J = 9.1$ Hz), 7.24 (d, 1H, $J = 9.1$ Hz), 7.14–6.92 (m, 5H), 5.06 (s, 2H, OCH₂Ph), 3.96 (s, 3H), 3.52 (s, 3H); ¹³C NMR (DMSO-*d*₆, 75 MHz), δ 159.2, 155.7, 151.6, 151.3, 150.8, 147.4, 143.2, 141.7, 136.6, 136.4, 135.0, 131.1, 128.4, 128.1, 128.0, 127.8, 124.6, 124.5, 124.2, 122.1, 116.2, 113.7, 109.7, 75.6, 60.3, 56.5; IR (KBr) ν_{\max} 3424, 1714, 1702, 1510, 1560, 1542, 1506, 1458, 1432, 1374, 1292, 1260, 1188, 1116, 1080, 910, 852, 696 cm⁻¹; EIMS *m/e* (relative intensity) 562/560 (M⁺, 0.2), 91 (base); CIMS (2-methylpropane) *m/e* (relative intensity) 563/561 (M⁺ + H, 7), 182 (base); EIHRMS *m/e* 560.0583 (C₂₈H₂₁BrN₂O₆ requires 560.0583). Anal. Calcd for C₂₈H₂₁BrN₂O₆: C, 59.91; H, 3.77; N, 4.99. Found: C, 59.65; H, 3.74; N, 5.03.

The CHCl₃ washings were concentrated in vacuo, and the residue was triturated with CH₂Cl₂ (1 mL) to afford the syn oxime isomer (18%, typically 10–18%) as a white, crystalline solid: mp 180–181 °C; ¹H NMR (DMSO-*d*₆, 200 MHz) δ 12.45 (s, 1H, NOH), 8.49 (d, 1H, $J = 8.6$ Hz), 8.21 (s, 1H), 8.19 (d, 1H, $J = 8.6$ Hz), 7.81 (d, 1H, $J = 8.8$ Hz), 7.73 (d, 1H, $J = 8.8$ Hz), 7.55 (d, 1H, $J = 8.9$ Hz), 7.21 (d, 1H, $J = 8.9$ Hz), 7.23–6.97 (m, 6H), 5.12 (s, 2H, OCH₂Ph), 3.98 (s, 3H), 3.64 (s, 3H); IR (KBr) ν_{\max} 3366, 1708, 1604, 1504, 1458, 1438, 1430, 1288, 1108, 1084, 988, 850 cm⁻¹; EIMS *m/e* (relative intensity) 562/560 (M⁺, 1), 91 (base); CIMS (2-methylpropane) *m/e* (relative intensity) 563/561 (M⁺ + H, 30), 182 (base); EIHRMS *m/e* 560.0588 (M⁺, C₂₈H₂₁-BrN₂O₆ requires 560.0583).

1-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-1-((methylsulfonyl)imino)-1-(7',8'-dimethoxy-2'-oxo-2'H-1'-benzopyran-3'-yl)methane (11). Method A: A solution of **10** (600 mg, 1.07 mmol) in 40 mL of CH₂Cl₂ cooled to 2 °C under N₂ was treated with Et₃N (0.49 mL, 3.5 mmol, 3.2 equiv) and methanesulfonyl chloride (0.216 mL, 3.2 mmol, 3 equiv). The resulting reaction mixture was stirred at 2 °C for 15 min and at 24 °C for 1 h under N₂. The solvent was evaporated, and the residue was purified by flash chromatography (2 × 5 cm SiO₂, 30% EtOAc–hexane eluant) to afford **11** (394 mg, 665 mg theoretical, 59%; typically 53–63%, 0.1–1.1 mmol) as a yellow, crystalline solid: mp 231–232 °C (CHCl₃–hexane); ¹H NMR (CDCl₃, 200 MHz) δ 8.34 (d, 1H, $J = 8.8$ Hz), 8.29 (d, 1H, $J = 8.8$ Hz), 8.05 (s, 1H), 7.77 (d, 1H, $J = 8.7$ Hz), 7.51 (d, 1H, $J = 8.7$ Hz), 7.38 (d, 1H, $J = 8.8$ Hz), 7.18–7.01 (m, 5H), 5.22 (s, 2H, OCH₂Ph), 3.99 (s, 3H), 3.75 (s, 3H), 3.34 (s, 3H, SO₂CH₃); IR (KBr) ν_{\max} 1726, 1602, 1570, 1504, 1458, 1436, 1318, 1286, 1144, 1106, 1080, 982, 806 cm⁻¹; CIMS (2-methylpropane) *m/e* (relative intensity) 625/623 (M⁺ + H, 35), 81 (base); CIHRMS *m/e* 623.0487 (M⁺ + H, C₂₉H₂₃BrN₂O₇S requires 623.0487). Anal. Calcd for C₂₉H₂₃BrN₂O₇S: C, 55.87; H, 3.72; N, 4.50. Found: C, 55.50; H, 3.67; N, 4.35.

Method B: A solution of **9** (310 mg, 0.57 mmol) and methanesulfonamide (65 mg, 0.69 mmol, 1.2 equiv) in 20 mL of CH₂Cl₂ was treated with TiCl₄ (0.7 mL, 0.63 mmol, 1.15 equiv) and Et₃N (0.25 mL, 1.8 mmol, 3.1 equiv) at 0 °C. The resulting reaction mixture was stirred 30 min at 0 °C before being allowed to warm to 25 °C. After 6 h, the reaction mixture was diluted with 20 mL of CHCl₃ and filtered through Celite, after which the solvent was removed in vacuo. Flash chroma-

tography (2 × 10 cm SiO₂, 20% EtOAc–CH₂Cl₂ eluant) afforded **11** (260 mg, 355 mg theoretical, 75%).

4-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-1-methyl-2,7,8-trimethoxy-5H-1-benzopyrano[3,4-*c*]pyridin-5-one (15). A solution of **11** (312 mg, 0.5 mmol) and 1,1-dimethoxy-1-propene²² (590 μ L, 5.0 mmol, 10 equiv) in 3 mL of C₆H₆ was stirred at 24 °C for 3 h under N₂. The reaction mixture was concentrated in vacuo. The residue was dissolved in 5 mL of THF and was treated with *t*-BuOK (281 mg, 2.5 mmol, 5 equiv). The reaction mixture was stirred at –30 °C for 1 h before it was poured onto 40 mL of H₂O and extracted with EtOAc (50 mL). The organic extract was washed with saturated aqueous NaCl (30 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was taken up in CH₂Cl₂ (4 mL) and treated with DDQ (115 mg, 0.5 mmol, 1 equiv), and the reaction mixture was stirred at 24 °C for 1 h. The precipitate (hydroquinone) was removed by filtration, and the filtrate was concentrated in vacuo. Flash chromatography (2 × 5 cm SiO₂, CH₂Cl₂ eluant) afforded **15** (199 mg, 307 mg theoretical, 65%; typically 52–65%, 0.1–1.5 mmol) as a white, crystalline solid: mp 227–228 °C (CHCl₃–hexane); ¹H NMR (CDCl₃, 200 MHz) δ 8.27 (d, 1H, $J = 8.5$ Hz), 7.98 (d, 1H, $J = 9.2$ Hz), 7.80 (d, 1H, $J = 8.5$ Hz), 7.76 (d, 1H, $J = 8.8$ Hz), 7.60–7.56 (m, 2H), 7.50 (d, 1H, $J = 8.8$ Hz), 7.16–7.12 (m, 3H), 6.91 (d, 1H, $J = 9.2$ Hz), 5.43 (s, 2H, OCH₂Ph), 4.07 (s, 3H), 3.97 (s, 3H), 3.79 (s, 3H), 2.69 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 164.5, 159.4, 159.0, 158.2, 154.7, 152.6, 146.9, 143.5, 142.7, 137.7, 136.7, 136.5, 130.8, 128.7, 128.5, 128.0, 127.6, 123.8, 123.5, 121.6, 117.0, 113.8, 112.8, 109.9, 107.3, 76.8, 61.4, 56.3, 54.7, 15.3; IR (KBr) ν_{\max} 1734, 1606, 1562, 1544, 1514, 1362, 1302, 1272, 1222, 1120, 1082, 1004 cm⁻¹; EIMS *m/e* (relative intensity) 614/612 (M⁺, 2), 91 (base); CIMS (2-methylpropane) *m/e* 615/613 (M⁺ + H, base); CIHRMS *m/e* 613.0918 (M⁺ + H, C₃₂H₂₅BrN₂O₆ requires 613.0918). Anal. Calcd for C₃₂H₂₅BrN₂O₆: C, 62.65; H, 4.11; N, 4.57. Found: C, 62.44; H, 3.86; N, 4.65.

2-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine-3-carboxylic Acid (16). A solution of **15** (150 mg, 0.24 mmol) and 4 N aqueous LiOH (1.96 mmol, 0.49 mL, 8 equiv) in 1.5 mL of DMSO was warmed at 60 °C for 7 h. The reaction mixture was allowed to cool to 25 °C, poured into 40 mL of saturated aqueous NH₄Cl, and extracted with EtOAc (3 × 15 mL). The organic extract was washed with saturated aqueous NaCl (10 mL) and dried (Na₂SO₄). Removal of the solvent in vacuo afforded **16** (149 mg, 154 mg theoretical, 97%; typically 89–97%) as a white solid: mp 124–125 °C (CHCl₃–hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.45 (d, 1H, $J = 8.6$ Hz), 8.26 (d, 1H, $J = 8.6$ Hz), 7.67 (d, 1H, $J = 8.7$ Hz), 7.65–7.58 (m, 2H), 7.49 (d, 1H, $J = 8.7$ Hz), 7.34–7.29 (m, 3H), 6.80 (d, 1H, $J = 8.6$ Hz), 6.52 (d, 1H, $J = 8.6$ Hz), 5.43 (d, 1H, $J = 10.9$ Hz, OCH₂HPh), 5.30 (d, 1H, $J = 10.9$ Hz, OCH₂HPh), 4.12 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.7, 161.5, 156.3, 152.4, 152.0, 146.9, 146.8, 146.7, 141.8, 137.1, 137.0, 135.8, 131.2, 128.7, 128.5, 128.2, 127.9, 124.6, 124.1, 123.5, 121.9, 121.6, 117.9, 117.4, 103.9, 76.6, 61.0, 55.7, 53.8, 12.9; IR (KBr) ν_{\max} 3282 (br), 2942, 1725, 1605, 1521, 1508, 1461, 1437, 1386, 1293, 1273, 1213, 1115, 1097, 1004 cm⁻¹; FABHRMS (NBA) *m/e* 631.1080 (M⁺ + H, C₃₂H₂₇BrN₂O₇ requires 631.1059).

Methoxymethyl 2-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-4-(3',4'-dimethoxy-2'-(methoxymethoxy)phenyl)-6-methoxy-5-methylpyridine-3-carboxylate (17). A solution of **16** (154 mg, 0.24 mmol) in 2 mL of dry DMF was cooled to 0 °C and treated with NaH (60% in oil, 37 mg, 0.90 mmol, 4.0 equiv) under N₂. The reaction mixture was stirred at 0 °C for 15 min before being treated with CH₃OCH₂Cl (75 μ L, 0.9 mmol, 4.0 equiv). After 15 min at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirred for 1 h before being poured into 10 mL of H₂O. The white precipitate which formed was collected by filtration and dried in vacuo to afford pure **17** (168 mg, 175 mg theoretical, 96%; typically 92–96%)³⁸ as a white solid: mp 136–137 °C (CHCl₃–hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.46 (d, 1H, $J = 8.6$ Hz), 8.24 (d, 1H, $J = 8.7$ Hz), 7.63 (d, 1H, $J = 8.7$ Hz), 7.55 (m, 2H), 7.43 (d, 1H, $J = 8.8$ Hz), 7.29 (m, 3H), 6.88 (d, 1H, $J = 8.6$ Hz), 6.73 (d, 1H, $J = 8.6$ Hz), 5.55 (d, 1H, $J = 11$ Hz, OCH₂HPh), 5.18 (m, 3H), 4.98 (d, 1H, $J = 6.1$ Hz), 4.88 (d, 1H, $J = 5.1$ Hz), 4.15 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.20 (s,

(38) In instances when the reaction was not allowed to proceed to completion, the corresponding methoxymethyl ester phenol was detected as the major byproduct: ¹H NMR (CDCl₃, 200 MHz) δ 8.51 (d, 1H, $J = 8.6$ Hz), 8.22 (d, 1H, $J = 8.7$ Hz), 7.60 (d, 1H, $J = 8.7$ Hz), 7.52–7.49 (m, 2H), 7.41 (d, 1H, $J = 8.7$ Hz), 7.28–7.24 (m, 3H), 6.86 (d, 1H, $J = 8.6$ Hz), 6.54 (d, 1H, $J = 8.6$ Hz), 5.93 (s, 1H, OH), 5.49 (d, 1H, $J = 11.2$ Hz), 5.32 (d, 1H, $J = 11.2$ Hz), 5.20 (d, 1H, $J = 6.2$ Hz), 5.04 (d, 1H, $J = 6.2$ Hz), 4.15 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 2.79 (s, 3H), 2.05 (s, 3H).

3H), 2.76 (s, 3H), 2.07 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.2, 168.0, 161.5, 155.6, 153.9, 152.8, 148.1, 148.0, 147.1, 142.5, 142.4, 137.5, 136.8, 131.1, 129.2, 128.6, 128.0, 127.9, 124.0, 123.9, 123.6, 121.8, 121.0, 117.5, 107.5, 98.9, 92.5, 76.8, 61.0, 57.2, 56.7, 55.9, 53.9, 12.9; IR (KBr) ν_{\max} 2925, 1732, 1603, 1492, 1429, 1399, 1293, 1259, 1217, 1160, 1139, 1095, 1016 cm⁻¹; FABHRMS (NBA-CsI) *m/e* 851.0599 (M⁺ + Cs, C₃₆H₃₅BrN₂O₉ requires 851.0580). Anal. Calcd for C₃₆H₃₅BrN₂O₉: C, 60.09; H, 4.90; N, 3.89. Found: C, 60.09; H, 4.91; N, 3.95.

2-(8'-(Benzyloxy)-7'-bromoquinolin-2'-yl)-4-(3',4'-dimethoxy-2'-(methoxymethoxy)phenyl)-6-methoxy-5-methylpyridine-3-carboxylic Acid (18). A solution of **17** (72 mg, 0.10 mmol) in 1.0 mL of 4 N aqueous LiOH and 1.0 mL of DMSO was warmed at 130 °C for 6 h. The mixture was allowed to cool to 25 °C, poured into 25 mL of saturated aqueous NH₄Cl, and extracted with EtOAc (60 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (2 × 10 cm SiO₂, 20% EtOAc-CHCl₃ eluant) afforded **18** (54 mg, 67.5 mg theoretical, 80%; typically 71–80%) as a white solid: mp 185–186 °C (CHCl₃-hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.28 (m, 2H), 7.67 (d, 1H, *J* = 8 Hz), 7.56 (m, 2H), 7.48 (d, 1H, *J* = 8.7 Hz), 7.29 (m, 3H), 6.88 (d, 1H, *J* = 8.6 Hz), 6.82 (d, 1H, *J* = 8.7 Hz), 5.62 (d, 1H, *J* = 11.1 Hz, OCHHPh), 5.29 (d, 1H, *J* = 11 Hz, OCHHPh), 5.09 (d, 1H, *J* = 7.2 Hz, OCHHOME), 4.86 (d, 1H, *J* = 7.2 Hz, OCHHOME), 4.11 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 2.90 (s, 3H), 2.04 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.7, 161.2, 156.4, 154.2, 152.7, 148.9, 148.3, 146.1, 142.8, 141.9, 137.8, 137.0, 131.2, 128.8, 128.4, 127.9, 127.5, 125.6, 124.5, 123.9, 123.6, 121.5, 121.1, 118.2, 109.2, 99.4, 76.6, 61.1, 56.5, 56.0, 53.9, 12.7; IR (KBr) ν_{\max} 3416, 2944, 1736, 1606, 1586, 1508, 1492, 1460, 1294, 1098 cm⁻¹; FABHRMS (NBA-CsI) *m/e* 807.0318 (M⁺ + Cs, C₃₄H₃₁BrN₂O₈ requires 807.0318).

3-Amino-2-(8'-(benzyloxy)-7'-bromoquinolin-2'-yl)-4-(3',4'-dimethoxy-2'-(methoxymethoxy)phenyl)-6-methoxy-5-methylpyridine (19). A solution of **18** (50 mg, 0.074 mmol) in 7 mL of benzene was treated with Et₃N (0.105 mL, 0.74 mmol, 10 equiv) and diphenyl phosphorazidate (DPPA, 0.100 mL, 0.74 mmol, 10 equiv) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 15 min and warmed at reflux for 7 h. The solvent was removed, and the residue was dissolved in 1 mL of THF. The solution was treated with 4 N aqueous LiOH (0.400 mL, 1.6 mmol, 21 equiv), and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H₂O (12 mL) and extracted with EtOAc (40 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (2 × 8 cm SiO₂, 10% EtOAc-hexane eluant) afforded **19** (40 mg, 47.8 mg theoretical, 84%; typically 79–86%) as a yellow solid: mp 124–125 °C (Et₂O-hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.78 (d, 1H, *J* = 8.9 Hz), 8.17 (d, 1H, *J* = 8.9 Hz), 7.62 (d, 1H, *J* = 8.8 Hz), 7.59 (m, 2H), 7.47 (d, 1H, *J* = 8.7 Hz), 7.29 (m, 3H), 6.86 (s, 2H), 6.47 (br s, 2H, NH₂), 5.29 (s, 2H, OCH₂Ph), 4.95 (d, 1H, *J* = 5.9 Hz, OCHHOME), 4.90 (d, 1H, *J* = 5.9 Hz, OCHHOME), 4.06 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.06 (s, 3H), 1.90 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 159.6, 153.8, 153.0, 151.5, 148.6, 143.0, 141.7, 139.3, 137.6, 137.0, 135.6, 129.6, 128.3, 128.2, 128.0, 127.1, 125.6, 125.0, 124.1, 123.6, 122.7, 120.7, 117.2, 108.6, 98.8, 75.1, 61.0, 56.5, 56.1, 53.1, 13.7; IR (KBr) ν_{\max} 3460, 2940, 1592, 1544, 1466, 1430, 1394, 1294, 1244, 1072, 967 cm⁻¹; EIMS *m/e* 647/645 (M⁺, base); FABHRMS (NBA-CsI) *m/e* 778.0553 (M⁺ + Cs, C₃₃H₃₂BrN₃O₆ requires 778.0529).

3-Amino-2-(7'-bromo-8'-hydroxyquinolin-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine (20). A solution of **19** (28 mg, 0.043 mmol) in 0.5 mL of CH₂Cl₂ was treated with 2.5 mL of saturated HBr(g)-CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 2 h (generally 2–6 h) before being quenched with the addition of saturated aqueous NaHCO₃ (10 mL). After all the solids had dissolved, the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (1 × 4 cm SiO₂, 20% EtOAc-hexane eluant) afforded **20** (17.6 mg, 22.0 mg theoretical, 80%; typically 70–80%)³⁹ as a yellow powder: mp 168–169 °C (Et₂O-hexane); ¹H NMR (acetone-*d*₆, 400 MHz) δ 8.80 (d, 1H, *J* = 8.8 Hz), 8.36 (d, 1H,

J = 8.8 Hz), 7.63 (d, 1H, *J* = 8.7 Hz), 7.41 (d, 1H, *J* = 8.7 Hz), 6.83 (d, 1H, *J* = 8.6 Hz), 6.75 (d, 1H, *J* = 8.6 Hz), 4.02 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H), 1.96 (s, 3H); ¹H NMR (CDCl₃, 400 MHz) δ 8.71 (d, 1H, *J* = 8.8 Hz), 8.37 (d, 1H, *J* = 8.8 Hz), 7.56 (d, 1H, *J* = 8.7 Hz), 7.23 (d, 1H, *J* = 8.7 Hz), 6.85 (d, 1H, *J* = 8.6 Hz), 6.64 (d, 1H, *J* = 8.6 Hz), 5.70 (very br s, 4H), 4.04 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 2.00 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.9, 154.0, 153.2, 148.7, 146.8, 137.7, 136.7, 136.5, 136.0, 135.9, 130.0, 128.54, 128.48, 126.0, 125.0, 123.7, 122.1, 119.0, 114.8, 104.8, 61.2, 55.9, 53.2, 13.6; IR (KBr) ν_{\max} 3844, 3681, 2920, 1691, 1664, 1612, 1551, 1492, 1372, 1189, 1095 cm⁻¹; FABHRMS (NBA) *m/e* 512.0821 (M⁺ + H, C₂₄H₂₂BrN₃O₅ requires 512.0821).

3-Amino-2-(7'-bromoquinoline-5',8'-quinon-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine (21). A solution of **20** (15 mg, 0.029 mmol) in CH₂Cl₂ (1.5 mL) was added to a solution of potassium nitrosulfonate (Fremy's salt, 78 mg, 0.29 mmol, 10 equiv) and Bu₄NHSO₄ (10 mg, 0.029 mmol, 1 equiv) in 1 mL of H₂O at 25 °C. The two-phase reaction mixture was stirred vigorously for 4 h before it was diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (2 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (1 × 5 cm SiO₂, 10% EtOAc-CHCl₃ eluant) afforded **21** (10.6 mg, 15.3 mg theoretical, 69%; typically 64–73%) as a dark green solid: mp 249–250 °C (Et₂O-hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.88 (d, 1H, *J* = 8.6 Hz), 8.34 (d, 1H, *J* = 8.6 Hz), 7.52 (s, 1H), 6.82 (d, 1H, *J* = 8.6 Hz), 6.65 (d, 1H, *J* = 8.6 Hz), 6.65 (overlapping br s, 2H), 5.89 (br s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 1.97 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 181.9, 176.1, 163.7, 153.2, 152.6, 146.9, 144.7, 140.7, 139.8, 139.7, 139.3, 136.3, 136.2, 133.7, 126.1, 125.2, 125.0, 118.4, 114.2, 104.8, 61.2, 55.9, 53.1, 13.8; IR (KBr) ν_{\max} 3461, 2922, 2854, 1693, 1656, 1580, 1451, 1382, 1267, 1094 cm⁻¹; FABHRMS (NBA-NaI) *m/e* 527.0686 (M⁺ + 2H, C₂₄H₂₂BrN₃O₆ (hydroquinone) requires 527.0692).

3-Amino-2-(7'-bromo-6'-methoxyquinoline-5',8'-quinon-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine (22). A solution of **21** (5.0 mg, 0.001 mmol) in dry THF (0.3 mL) was cooled to 0 °C and treated with a THF solution of Ti(O-*i*-Pr)₄ (82 μL of 0.2 M). After 45 min at 0 °C, NaOMe (0.002 mmol, 2 equiv, 47 μL of 0.5 M in MeOH) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with 1 mL of 0.25 M aqueous EDTA and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (1 × 5 cm SiO₂, 10% EtOAc-CHCl₃ eluant) afforded **22** (2.3 mg) as a dark green solid: mp 285–287 °C (Et₂O-hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.82 (d, 1H, *J* = 8.8 Hz), 8.33 (d, 1H, *J* = 8.8 Hz), 6.81 (d, 1H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 8.7 Hz), 6.62 (br s, 2H, NH₂), 5.86 (br s, 1H, OH), 4.35 (s, 3H, C6-OCH₃), 4.01 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 1.98 (s, 3H); IR (KBr) ν_{\max} 3464, 2960, 2854, 1695, 1660, 1580, 1503, 1451, 1386, 1292 cm⁻¹; FABHRMS (NBA) *m/e* 556.0719 (M⁺ + H, C₂₅H₂₂-BrN₃O₇ requires 556.0719).

3-Amino-2-(7'-azido-6'-methoxyquinoline-5',8'-quinon-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine (23). A stirred solution of **22** (3.7 mg, 0.0066 mmol) in 0.40 mL of THF was treated with a solution of NaN₃ (0.47 mg, 0.0073 mmol, 1.1 equiv) in 20 μL of H₂O at 25 °C under N₂, and the mixture was stirred at 25 °C for 21 h with protection from light. The solution was poured into 5 mL of H₂O and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. In practice, crude **23** was used immediately in the subsequent reaction without further purification, and this provided higher overall yields for the two-step conversion of **22** to **24**. For the reaction above, chromatography (1 × 2 cm SiO₂, 40% EtOAc-hexane eluant) afforded **23** (3.0 mg, 3.45 mg theoretical, 85%) as a green solid: mp >300 °C (dec, Et₂O-hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.81 (d, 1H, *J* = 8.8 Hz), 8.31 (d, 1H, *J* = 8.8 Hz), 6.80 (d, 1H, *J* = 8.4 Hz), 6.63 (d, 1H, *J* = 8.4 Hz, and overlapping br s, 2H), 5.86 (br s, 1H, OH), 4.24 (s, 3H), 4.00 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 1.98 (s, 3H); IR (KBr) ν_{\max} 3455, 2950, 2111 (N₃), 1656, 1572, 1449, 1291, 1241, 1097 cm⁻¹; FABHRMS (NBA) *m/e* 518.1561 (C₂₅H₂₂N₆O₇ requires 518.1550).

3-Amino-2-(7'-amino-6'-methoxyquinoline-5',8'-quinon-2'-yl)-4-(3',4'-dimethoxy-2'-hydroxyphenyl)-6-methoxy-5-methylpyridine (24). A stirred solution of **23** (2.3 mg, 0.0038 mmol) in 0.4 mL of THF and 0.1 mL of MeOH was treated with powdered NaBH₄ (1.5 mg, 0.0039 mmol, 10 equiv) at 25 °C under N₂, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with the addition of H₂O (1 mL),

(39) Treatment of **19** with HBr(g)-CH₂Cl₂ for shorter reaction periods (0 °C, 20 min, 64%) led to clean deprotection of the methoxymethyl ether: ¹H NMR (CDCl₃, 200 MHz) δ 8.81 (d, 1H, *J* = 8.8 Hz), 8.15 (d, 1H, *J* = 8.7 Hz), 7.61 (d, 1H, *J* = 8.6 Hz), 7.54 (m, 2H), 7.46 (d, 1H, *J* = 8.6 Hz), 7.39–7.24 (m, 3H), 6.81 (d, 1H, *J* = 8.6 Hz), 6.61 (d, 1H, *J* = 8.6 Hz), 5.26 (s, 3H, OCH₂Ph), 4.06 (s, 3H), 3.96 (s, 3H), 3.87 (s, 3H), 2.01 (s, 3H). This phenol could be cleanly generated by CF₃CO₂H treatment of **19** (CH₂Cl₂ or C₆H₆, 25 °C, 30 min, 97–100%) and subsequently converted to **20** upon treatment with HBr(g)-CH₂Cl₂.

extracted with EtOAc (2 × 10 mL), dried (Na₂SO₄), and concentrated in vacuo. Chromatography (0.5 × 2 cm SiO₂, 50% EtOAc–hexane eluant), afforded **24** (1.8 mg, 2.2 mg theoretical, 86%) as a dark solid: mp 295–297 °C (dec, Et₂O–hexane); ¹H NMR (CDCl₃, 400 MHz) δ 8.80 (d, 1H, *J* = 8.4 Hz), 8.34 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1H, *J* = 8.1 Hz), 6.64 (d, 1H, *J* = 8.1 Hz), 5.04 (br s, 2H, NH₂), 4.07 (s, 3H), 4.02 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 1.99 (s, 3H); IR (KBr) ν_{max} 3460, 3347, 2939, 1678, 1610, 1585, 1449, 1381, 1346, 1291, 1230, 1097, 1072, 1013 cm⁻¹; FABHRMS (NBA–CsI) *m/e* 625.0695 (M⁺ + Cs + 2H, C₂₅H₂₆N₄O₇ (hydroquinone) requires 625.0699).

In practice, the conversion of **22** was conducted without the purification of **23** and afforded **24** (65–72%, 0.002–0.005 mmol).

Streptonigrone (1). A stirred solution of **24** (1.5 mg, 0.003 mmol) in 200 μL of CF₃CH₂OH was treated with 10% Pd–C (3 mg, 0.003 mmol, 1 equiv). While under a H₂ atmosphere, 200 μL of CF₃CH₂OH saturated with HBr(g) was added. The sealed reaction vessel was warmed in an 80 °C oil bath for 1 h. After being cooled to 25 °C, the reaction mixture was poured into H₂O, neutralized with the addition of saturated aqueous NaHCO₃, and extracted with CH₂Cl₂ (3 × 2 mL). The residual Pd was removed by filtration, the combined organic layers were dried (Na₂SO₄), and the solvent was removed in vacuo. Chromatography (0.2 × 2 cm SiO₂, 8:1:1 CHCl₃–MeOH–acetone eluant) afforded streptonigrone (**1**; *R_f* = 0.56, SiO₂, 8:1:1 CHCl₃–MeOH–acetone), identical in all respects with the properties of a sample of authentic material: mp >300 °C (CH₂Cl₂–hexane), lit mp 268–69 °C^{1a} and >300 °C^{1b}; ¹H NMR (CDCl₃, 400 MHz) δ 8.34 (d, 1H, *J* = 8.6 Hz), 8.30 (d, 1H, *J* = 8.6 Hz), 6.81 (d, 1H, *J* = 8.5 Hz), 6.63 (d, 1H, *J* = 8.5 Hz), 6.20 (very br s, 1H), 5.04 (br s, 1H), 4.06 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 2.00 (s, 3H); IR (KBr) ν_{max} 3453, 3344, 2923, 2850, 1684, 1645, 1610, 1582, 1507, 1460, 1350,

1292, 1236, 1098, 1075, 999, 918, 794, 754, cm⁻¹; UV (CH₃OH) λ_{max} 425 nm (ε 12 500); UV (CH₃OH–HCl) λ_{max} 342 nm (ε 15 000); FABHRMS (NBA) *m/e* 479.1582 (M⁺ + H, C₂₄H₂₂N₄O₇ requires 479.1567).⁴⁰

General Procedure for the Preparation of 7-Bromo-6-methoxyquinoline-5,8-quinones 28 (Table I). A stirred solution of the anhydrous Lewis acid in THF was treated with substrate (**27a,b**, 0.01 mmol) at 0 °C under N₂, and the mixture was stirred for 30 min. NaOCH₃ (0.5 M) in CH₃OH was added, and the mixture was stirred for 0.5 h at 0 °C and 1 h at 25 °C. The solution was diluted with H₂O (5 mL) or 0.25 M aqueous EDTA (5 mL, for Ti(OR)₄) and extracted with EtOAc (3 × 10 mL). The organic phases were combined and washed with saturated aqueous NaCl (1 × 10 mL), dried (Na₂SO₄), and concentrated in vacuo. Chromatography (SiO₂, 20–40% EtOAc–hexane gradient elution) afforded the 7-bromo-6-methoxyquinoline-5,8-quinones **28a,b** as solids, identical in all respects with authentic materials.¹⁶

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(40) Synthetic **1** and naturally derived **1**, unlike streptonigrin (**2**), are racemic: R. W. Rickards, personal communication.