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Total Synthesis of Streptonigrone

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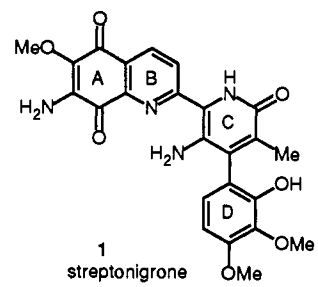
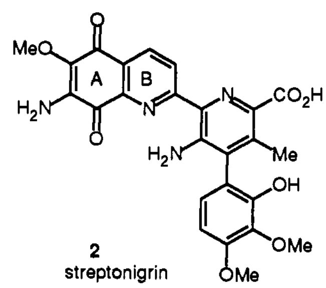
Abstract: The first total synthesis of streptonigrone (**1**) is detailed and is based on the implementation of a room-temperature, inverse electron demand Diels–Alder reaction of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for introduction of the fully substituted pyridone (C ring) central to the agent 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 ($Ti(O\text{-}i\text{-}Pr)_4$) methoxide C6 nucleophilic substitution reaction.

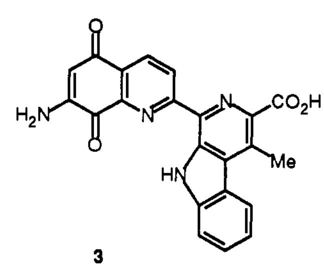
Streptonigrone (**1**), a highly substituted and densely functionalized quinoline-5,8-quinone isolated from an unidentified *Streptomyces* species (IA-CAS isolate no. 114)[1a] or *Streptomyces albus* var. *bruneomycini*[1b] as a minor component of the culture broths and identified through extensive spectroscopic 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 streptonigrin[6] and have demonstrated that simple quinoline-5,8-quinones related to its AB ring system also display this potent biological activity.[7] In a 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]



1
streptonigrone



2
streptonigrin



3
lavendamycin

Central to our synthetic strategy was the implementation of a room-temperature, inverse electron demand Diels–Alder reaction[12] of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for the intro-

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(1) (a) Herlt, A. J.; Rickards, R. W.; Wu, J. P. *J. Antibiot.* **1985**, *38*, 516. (b) Kozlova, N. V.; Lvova, N. A.; Lapchinskaya, O. A.; Dokuchaeva, E. B.; Rubasheva, L. M.; Rozynov, B. V.; Preobrzhenskaya, M. N. *Antibiot. Khim.* **1990**, *35*, 13. (c) Preobrazhenskaya, M. N.; Holpne-Kozlova, N. V.; Lazhko, E. I. *J. Antibiot.* **1992**, *45*, 227.

(2) Rao, K. V.; Biemann, K.; Woodward, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2532. Chiu, Y.-Y.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1975**, *97*, 2525.

(3) Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 77.

(4) Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.; Moews, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595. Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259.

(5) Liu, W. C.; Barbacid, M.; Bulgar, M.; Clark, J. M.; Crosswell, A. R.; Dean, L.; Doyle, T. W.; Fernandes, P. B.; Huang, S.; Manne, V.; Pirnik, D. M.; Wells, J. S.; Meyers, E. *J. Antibiot.* **1992**, *45*, 454.

(6) Take, Y.; Inouye, Y.; Nakamura, S.; Allaudeen, H. S.; Kubo, A. *J. Antibiot.* **1989**, *42*, 107. Okada, H.; Mukai, H.; Inouye, Y.; Nakamura, S. *J. Antibiot.* **1986**, *39*, 306.

(7) Inouye, Y.; Take, Y.; Oogose, K.; Kubo, A.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 105. Take, Y.; Oogose, K.; Kubo, T.; Inouye, Y.; Nakamura, S.; Kitahara, Y.; Kubo, A. *J. Antibiot.* **1987**, *40*, 679. Inouye, Y.; Oogose, K.; Take, Y.; Kubo, T.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 702. Oogose, K.; Hafuri, Y.; Takemori, E.; Nakata, E.; Inouye, Y.; Nakamura, S.; Kubo, A. *J. Antibiot.* **1987**, *40*, 1778. Inouye, Y.; Take, Y.; Nakamura, S.; Nakashima, H.; Yamamoto, N.; Kawaguchi, H. *J. Antibiot.* **1987**, *40*, 100. Hafuri, Y.; Takemori, E.; Oogose, K.; Inouye, Y.; Nakamura, S.; Kitahara, Y.; Nakahara, S.; Kubo, A. *J. Antibiot.* **1988**, *41*, 1471.

(8) Streptonigrin: Weinreb, S. M. *Strategies Tactics Org. Synth.* **1984**, *1*, 325. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1982**, *104*, 536. Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962. Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles* **1981**, *21*, 91. Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621.

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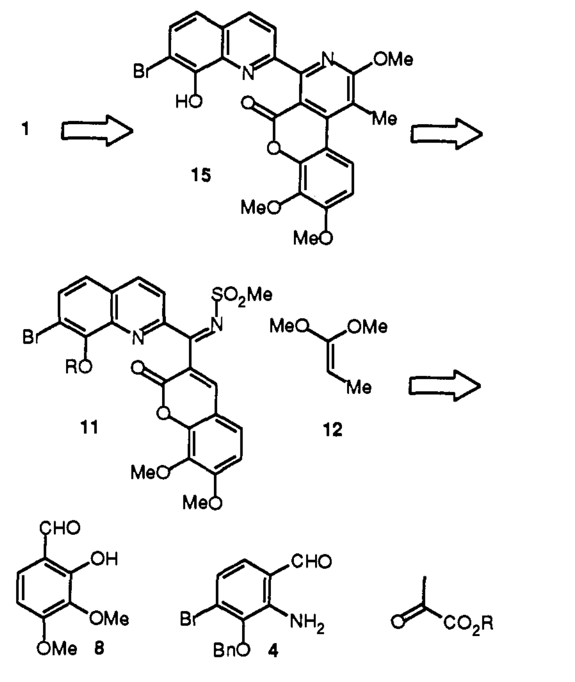
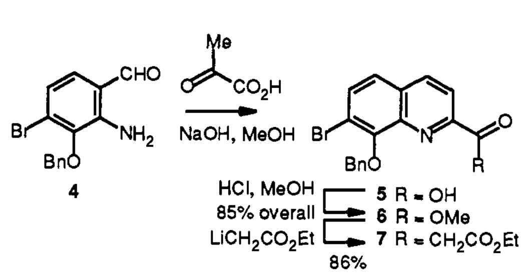
Scheme I




(1)

duction of the central pyridone C ring[13] 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 condensation[17] of pyruvic acid with 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**4**; NaOH, CH_3OH, 58 °C, 6 h) followed by Fischer esterification (HCl, CH_3OH, 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** (NH_2OH–HCl, EtOH, reflux, 5 h) followed by oxime *O*-methanesulfinate formation (CH_3SOCl, Et_3N, CH_2Cl_2, 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 → *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 SiO_2 plug purification followed by $CHCl_3$–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 $TiCl_4$-promoted (1.3 equiv) condensation of **9** with methanesulfonamide (1.2 equiv, 3 equiv of Et_3N, CH_2Cl_2, 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 (SiO_2) 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 contaminates derived form the $TiCl_4$-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 → *N*-sulfonyl rear-

(9) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261. Rao, A. V. R.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065.

(10) Review: Boger, D. L. *Strategies Tactics Org. Synth.* **1988**, *2*, 1.

(11) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918.

(12) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L. *Bull. Soc. Chim. Belg.* **1990**, *99*, 599. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987. (c) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

(13) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880.

(14) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068. Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, *55*, 5439. Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999. Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. For related studies, see: Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646. Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481.

(15) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(16) Boger, D. L.; Yasuda, M. *Heterocycles* **1986**, *24*, 1067.

(17) Cheng, C. C.; Yan, S. J. *Org. React.* **1982**, *28*, 37.

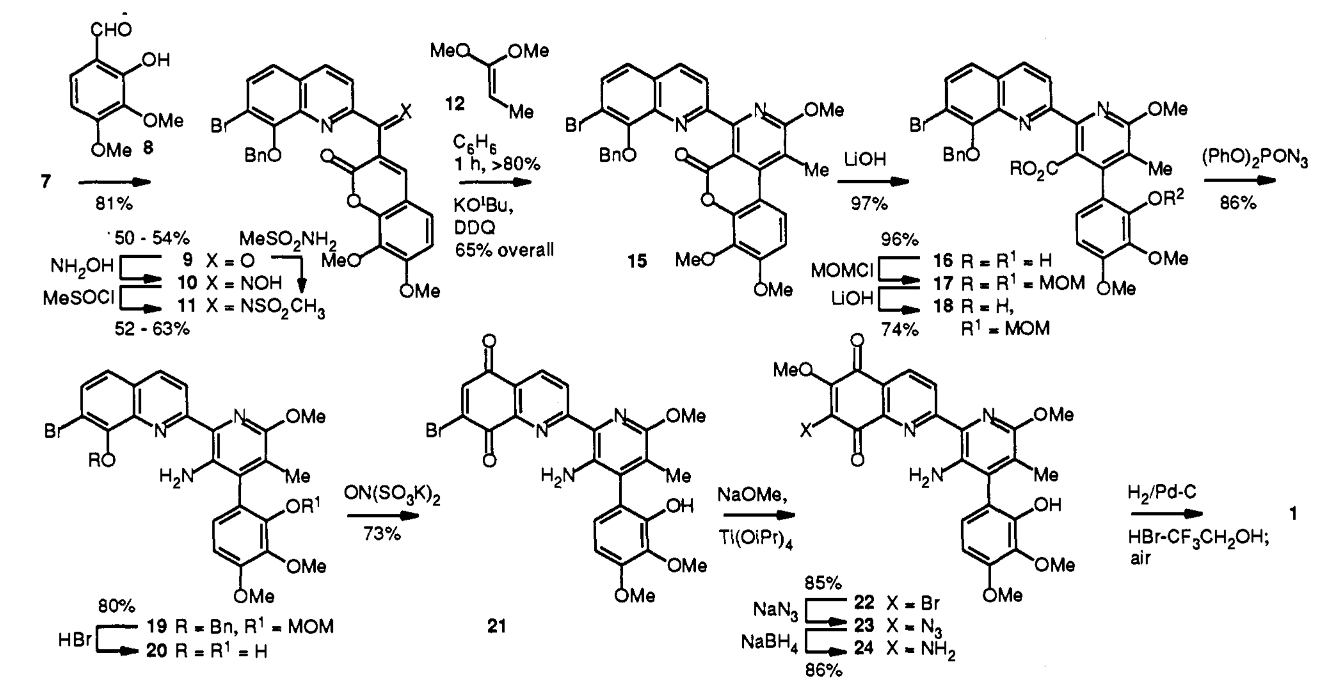
(18) Reichstein, T.; Oppenauer, R.; Grussner, A.; Hirt, R.; Rhyner, L.; Glatthaar, C. *Helv. Chim. Acta* **1935**, *18*, 816.

(19) Brown, C.; Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 822. Brown, C.; Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1977**, 540. Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1976**, 831.

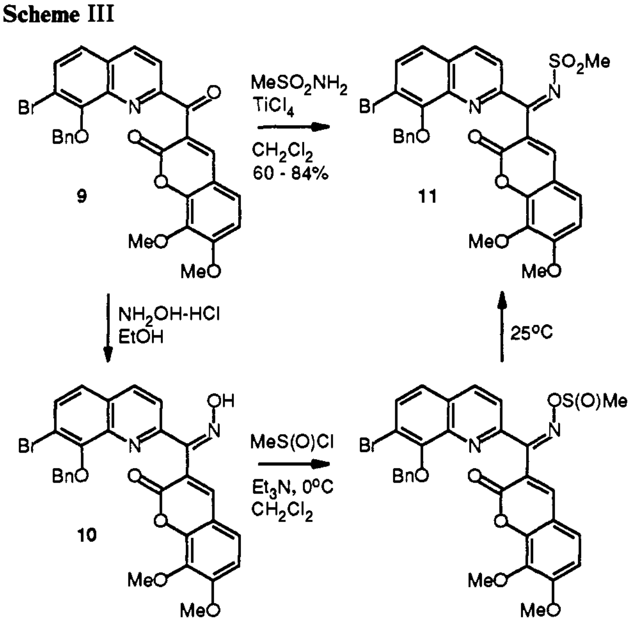
(20) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777.

(21) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.

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, C_6H_6) 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 of **13** with *t*-BuOK (THF, −30 °C, 1 h) followed by DDQ (CH_2Cl_2, 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, h*ν*, neat, Pyrex, 25 °C, 3 h)[22] proved substantially superior to the material prepared by strong base-catalyzed isomerization (KNH_2, NH_3–Et_2O, −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, $ClCH_2OCH_3$, 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 ($(PhO)_2P(O)N_3$, benzene–H_2O)[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–H_2O) to the reaction mixture to complete the isocyanate hydrolysis. Attempts to trap the isocyanate in situ with H_2O or *tert*-butyl alcohol to provide **19** or the corresponding *tert*-butylcarbamate

(22) Mueller, F. J.; Eichen, K. German Patent 2331675; *Chem. Abstr.* **1974**, *81*, 63153v.

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

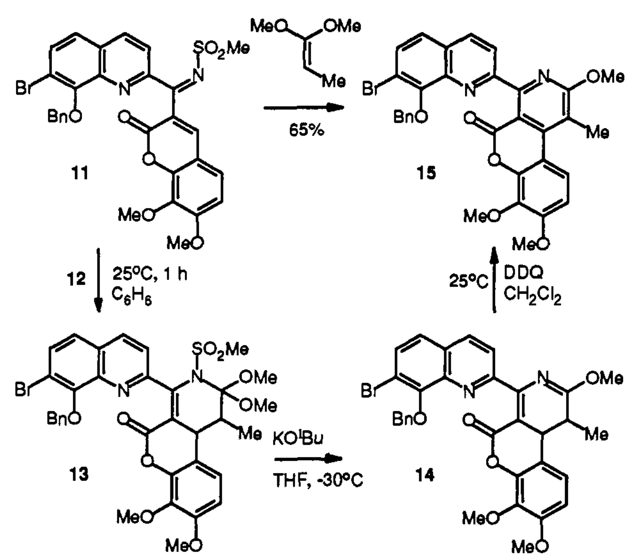
(24) Flash chromatography of the crude Diels–Alder product resulted in hydrolysis of the orthoester to provide the corresponding methyl ester: ^1H NMR ($CDCl_3$, 200 MHz) *δ* 11.01 (br s, 1H, NH), 8.32 (d, 1H, *J* = 8.8 Hz), 7.82 (m, 1H), 7.76–7.45 (m, 4H), 7.43–7.24 (m, 3H), 6.57 (s, 2H), 5.30 (m, 2H), 4.01 (s, 3H, OCH_3), 3.9–3.75 (m, 1H), 3.82 (s, 3H, OCH_3), 3.43 and 3.41 (two s, 3H, OCH_3), 3.21 and 3.19 (two s, 3H, SO_2Me), 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).

(25) Scheeren, H. W.; Aben, R. W. M.; Ooms, P. H. J.; Nivard, R. J. F. *J. Org. Chem.* **1977**, *42*, 3128.

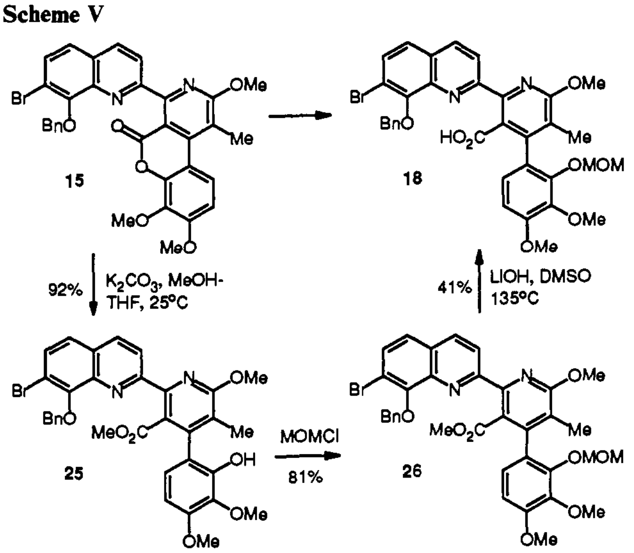
(26) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(27) Attempted Curtius rearrangement on **16** directly ($(PhO)_2P(O)N_3$, Et_3N, *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 hinderance provded 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 $LiOH-H_2O_2$[29] ($THF-H_2O$ 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 **25**[30] (Na_2CO_3, $CH_3OH-THF$ 6.5:1, 25 °C, 4 h, 92%), phenol protection as the methoxymethyl ether **26**[30] (MOMCl, *i*-Pr_2NEt, $CHCl_3$, 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 $LiOH-H_2O_2$ ($THF-H_2O$, 60 °C),[29] LiOH ($THF-H_2O$, 100 °C), or KOH ($EtOH-H_2O$ or *n*-$PrOH-H_2O$, 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 $HBr-CH_2Cl_2$, 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 system[9] (1:1 CH_2Cl_2–0.05 M KH_2PO_4, 1.1 equiv of Bu_4NHSO_4, 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 NaH_2PO_4 (1:1) and CH_3OH–0.05 M NaH_2PO_4 (1:1 or 6:1) proved much less effective, resulting in no or slow reaction, and the omission of the phase-transfer agent (Bu_4NHSO_4) 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 CH_2Cl_2) 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

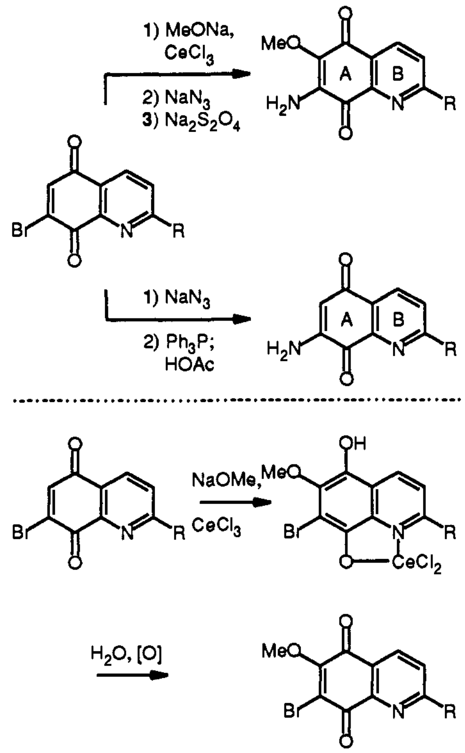
(28) For the acyl azide derivative of the isocyanate of **19**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.13 (s, 1H, NH), 8.31 (d, 1H, *J* = 8.7 Hz), 8.29 (d, 1H, *J* = 8.7 Hz), 7.71 (d, 1H, *J* = 8.8 Hz), 7.69 (m, 2H), 7.51 (d, 1H, *J* = 8.7 Hz), 7.49–7.28 (m, 3H), 6.93 (d, 1H, *J* = 8.6 Hz), 5.41 (s, 2H, OCH_2Ph), 4.94 (d, 1H, *J* = 6.1 Hz, OC*H*HOMe), 4.84 (d, 1H, *J* = 6.1 Hz, OCH*H*OMe), 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**: ^{1}H NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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 (H_2, 10% Pd–C, CH_3OH, 25 °C, 30 min, 75% or 10% Pd–C, 25% aqueous HCO_2NH_4, 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: ^{1}H 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, OC*H*HOMe), 4.90 (d, 1H, *J* = 5.8 Hz, OCH*H*OMe), 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 lavendamycin 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-catalyzed[32] 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, Ti(O-*i*-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, Ti(O-*i*-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.

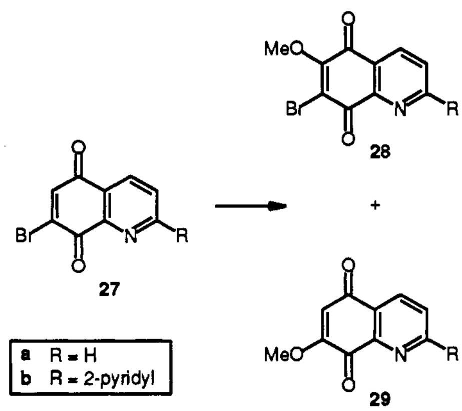
(33) Ti(O-*i*-Pr)$_4$ was distilled prior to use, and a 0.5 M solution in THF was prepared. LiCl and $ZnBr_2$ were dried in vacuo, and 0.5 M THF solutions were prepared. Mg(OMe)$_2$ was prepared as a 0.5 M solution in MeOH from Mg metal and anhydrous methanol. A 0.5 M solution of Ti(OMe)$_4$ was prepared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

Table I

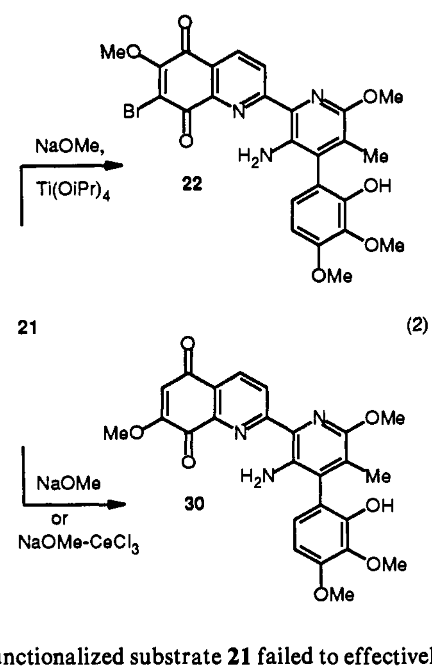
substrate	equiv of NaOMe	equiv, Lewis acid[a]	temp, °C (time, h)	product	% yield
27a	2.0	none	0 (0.5), 25 (1)	**28a**	22
				29a	58
27a	2.5	1.5, $CeCl_3$	0 (0.5), 25 (1)	**28a**	58
27a	2.5	1.5, Ti(O-*i*-Pr)$_4$	0 (0.5), 25 (1)	**28a**	57
27a	2.0	1.5, $ZnBr_2$	0 (0.5), 25 (1)	**28a**	57
27a	0	2.0, Mg(OMe)$_2$	0 (0.5), 25 (1)	**28a**	29
27a	2.0	2.0, Ti(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, Ti(O-*i*-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, Ti(O-*i*-Pr)$_4$	0 (1)	**22**	54
				30	19

[a] See ref 33.

Scheme VII

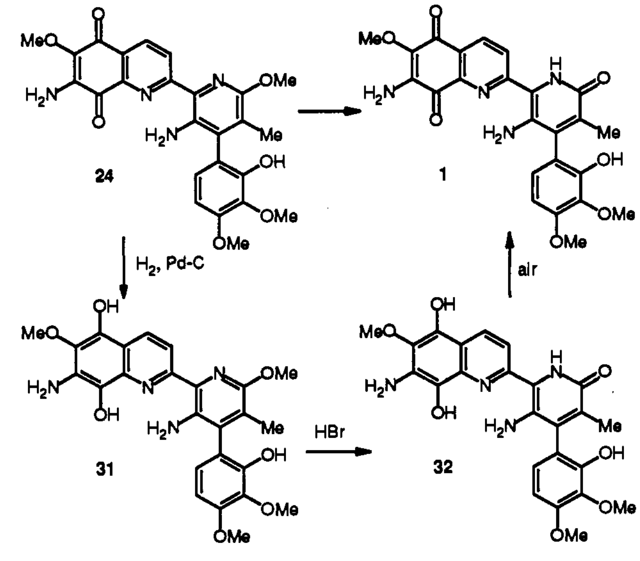


the presence of $CeCl_3$ led to the generation of **30**[34] derived from C7 methoxide addition–elimination (eq 2). Presumably, the more



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

Scheme VIII

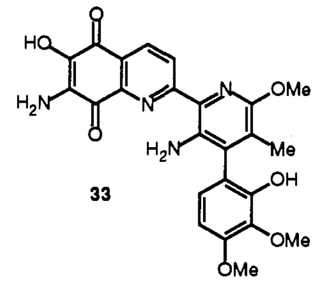


addition. In contrast, both Ti(O-*i*-Pr)$_4$ and LiCl catalyzed the C6 addition of methoxide to **21** with the former reagent providing good conversions to **22** upon workup and air oxidation (Table I).

Treatment of **22** with NaN_3 (1.1 equiv, THF–H_2O, 25 °C, 20 h) provided the sensitive deep green azide **23** (85%), and subsequent reduction ($NaBH_4$, THF–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 $Na_2S_2O_4$ (THF–H_2O, slow reduction)[16] or Ph_3P, CH_2Cl_2–HOAc in H_2O–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 HBr(g)–CF_3CH_2OH (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 (^{1}H NMR, IR, MS, TLC R_f, UV, mp).[1] Efforts to deprotect **24** without reducing the quinone through direct treatment of **24** with HCl(g)–CH_2Cl_2 (25 °C, 2 h) or HBr(g)–CH_2Cl_2 (reflux, 1.5 h, 76%) led to preferential A ring methyl ether cleavage to provide **33**.[36] Alternative reagents for pyridone methyl ether cleavage[37] did not prove as successful as the mild treatment with HBr(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



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-bromobenzaldehyde[15] (**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 HCl–CH_3OH (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); ^{1}H 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^+ + H, base); EIHRMS m/e 371.0163 ($C_{18}H_{14}BrNO_3$ requires 371.0157). Anal. Calcd for $C_{18}H_{14}BrNO_3$: 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*-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); ^{1}H 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^+ + H, base); EIHRMS m/e 427.0429 ($C_{21}H_{18}BrNO_4$ requires 427.0419). Anal. Calcd for $C_{21}H_{18}BrNO_4$: 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-2*H*-1-benzopyran-3-yl Ketone (9). A solution of 3,4-dimethoxy-2-hydroxybenzaldehyde[18] (**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); ^{1}H NMR ($CDCl_3$, 200 MHz)

(34) For **30**: ^{1}H 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, NH_2), 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^+ + H, base).

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

(36) For **33**: ^{1}H 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: TMSCl–NaBr, CH_3CN, 16 h; $MeSO_3H$–NaBr, *i*-PrOH, reflux, 14 h; TsOH–NaBr, CF_3CH_2OH, 80 °C, 6 h, 10 equiv of $SnCl_2$; HBr(g)–CH_2Cl_2, 100 °C, 1 h; 48% HBr–HOAc; concentrated HCl, 100 °C, 1–3 h, 10 equiv of $SnCl_2$.

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, OCH_2Ph), 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, OCH_2-Ph), 3.99 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 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 $C_{28}H_{20}BrNO_6$: 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 H_2O (80 mL), and the pH was adjusted to 7.5–8.0 with the addition of saturated aqueous $NaHCO_3$. The precipitated oxime was collected by filtration ($CHCl_3$ wash), and recrystallization from $CHCl_3$ 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 ($CHCl_3$); ^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, OCH_2Ph), 3.96 (s, 3H), 3.52 (s, 3H); ^{13}C 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 ($C_{28}H_{21}BrN_2O_6$ requires 560.0583). Anal. Calcd for $C_{28}H_{21}BrN_2O_6$: C, 59.91; H, 3.77; N, 4.99. Found: C, 59.65; H, 3.74; N, 5.03.

The $CHCl_3$ washings were concentrated in vacuo, and the residue was triturated with CH_2Cl_2 (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, OCH_2Ph), 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^+, $C_{28}H_{21}BrN_2O_6$ 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 CH_2Cl_2 cooled to 2 °C under N_2 was treated with Et_3N (0.49 mL, 3.5 mmol, 3.2 equiv) and methanesulfinyl 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 N_2. The solvent was evaporated, and the residue was purified by flash chromatography (2 × 5 cm SiO_2, 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 ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 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, OCH_2Ph), 3.99 (s, 3H), 3.75 (s, 3H), 3.34 (s, 3H, SO_2CH_3); 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, $C_{29}H_{23}BrN_2O_7S$ requires 623.0487). Anal. Calcd for $C_{29}H_{23}BrN_2O_7S$: 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 CH_2Cl_2 was treated with $TiCl_4$ (0.7 mL, 0.63 mmol, 1.15 equiv) and Et_3N (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 $CHCl_3$ and filtered through Celite, after which the solvent was removed in vacuo. Flash chromatography (2 × 10 cm SiO_2, 20% EtOAc–CH_2Cl_2 eluant) afforded **11** (260 mg, 355 mg theoretical, 75%).

4-(8′-(Benzyloxy)-7′-bromoquinolin-2′-yl)-1-methyl-2,7,8-trimethoxy-5*H*-1-benzopyrano[3,4-*c*]pyridin-5-one (15). A solution of **11** (312 mg, 0.5 mmol) and 1,1-dimethoxy-1-propene[22] (590 μL, 5.0 mmol, 10 equiv) in 3 mL of C_6H_6 was stirred at 24 °C for 3 h under N_2. 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 H_2O and extracted with EtOAc (50 mL). The organic extract was washed with saturated aqueous NaCl (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (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 SiO_2, CH_2Cl_2 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 ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 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, OCH_2Ph), 4.07 (s, 3H), 3.97 (s, 3H), 3.79 (s, 3H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 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, $C_{32}H_{25}BrN_2O_6$ requires 613.0974). Anal. Calcd for $C_{32}H_{25}BrN_2O_6$: 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 NH_4Cl, and extracted with EtOAc (3 × 15 mL). The organic extract was washed with saturated aqueous NaCl (10 mL) and dried (Na_2SO_4). 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 ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 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, OC*H*HPh), 5.30 (d, 1H, J = 10.9 Hz, OCH*H*Ph), 4.12 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 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, $C_{32}H_{27}BrN_2O_7$ 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 N_2. The reaction mixture was stirred at 0 °C for 15 min before being treated with CH_3OCH_2Cl (75 μL, 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 H_2O. 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 ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 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, OC*H*HPh), 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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, $C_{36}H_{35}BrN_2O_9$ requires 851.0580). Anal. Calcd for $C_{36}H_{35}BrN_2O_9$: 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 NH_4Cl, and extracted with EtOAc (60 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (2 × 10 cm SiO_2, 20% EtOAc–$CHCl_3$ eluant) afford **18** (54 mg, 67.5 mg theoretical, 80%; typically 71–80%) as a white solid: mp 185–186 °C ($CHCl_3$–hexane); ^{1}H NMR ($CDCl_3$, 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, OC*H*HPh), 5.29 (d, 1H, *J* = 11 Hz, OCH*H*Ph), 5.09 (d, 1H, *J* = 7.2 Hz, OC*H*HOMe), 4.86 (d, 1H, *J* = 7.2 Hz, OCH*H*OMe), 4.11 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 2.90 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 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, $C_{34}H_{31}BrN_2O_8$ 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 Et_3N (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 H_2O (12 mL) and extracted with EtOAc (40 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (2 × 8 cm SiO_2, 10% EtOAc–hexane eluant) afforded **19** (40 mg, 47.8 mg theoretical, 84%; typically 79–86%) as a yellow solid: mp 124–125 °C (Et_2O–hexane); ^{1}H NMR ($CDCl_3$, 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, NH_2), 5.29 (s, 2H, OCH_2Ph), 4.95 (d, 1H, *J* = 5.9 Hz, OC*H*HOMe), 4.90 (d, 1H, *J* = 5.9 Hz, OCH*H*OMe), 4.06 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.06 (s, 3H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 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, $C_{33}H_{32}BrN_3O_6$ 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 CH_2Cl_2 was treated with 2.5 mL of saturated HBr(g)–CH_2Cl_2 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 $NaHCO_3$ (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 (Na_2SO_4), and concentrated in vacuo. Flash chromatography (1 × 4 cm SiO_2, 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 (Et_2O–hexane); ^{1}H 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); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, $C_{24}H_{22}BrN_3O_5$ 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 CH_2Cl_2 (1.5 mL) was added to a solution of potassium nitrodisulfonate (Fremy's salt, 78 mg, 0.29 mmol, 10 equiv) and Bu_4NHSO_4 (10 mg, 0.029 mmol, 1 equiv) in 1 mL of H_2O at 25 °C. The two-phase reaction mixture was stirred vigorously for 4 h before it was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (1 × 5 cm SiO_2, 10% EtOAc–$CHCl_3$ eluant) afforded **21** (10.6 mg, 15.3 mg theoretical, 69%; typically 64–73%) as a dark green solid: mp 249–250 °C (Et_2O–hexane); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, $C_{24}H_{22}BrN_3O_6$ (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 (Na_2SO_4), and concentrated in vacuo. Flash chromatography (1 × 5 cm SiO_2, 10% EtOAc–$CHCl_3$ eluant) afforded **22** (2.3 mg) as a dark green solid: mp 285–287 °C (Et_2O–hexane); ^{1}H NMR ($CDCl_3$, 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, NH_2), 5.86 (br s, 1H, OH), 4.35 (s, 3H, C6–OCH_3), 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, $C_{25}H_{22}BrN_3O_7$ 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 NaN_3 (0.47 mg, 0.0073 mmol, 1.1 equiv) in 20 μL of H_2O at 25 °C under N_2, and the mixture was stirred at 25 °C for 21 h with protection from light. The solution was poured into 5 mL of H_2O and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) 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 SiO_2, 40% EtOAc–hexane eluant) afforded **23** (3.0 mg, 3.45 mg theoretical, 85%) as a green solid: mp >300 °C (dec, Et_2O–hexane); ^{1}H NMR ($CDCl_3$, 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 (N_3), 1656, 1572, 1449, 1291, 1241, 1097 cm^{-1}; FABHRMS (NBA) *m/e* 518.1561 ($C_{25}H_{22}N_6O_7$ 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 $NaBH_4$ (1.5 mg, 0.0039 mmol, 10 equiv) at 25 °C under N_2, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with the addition of H_2O (1 mL),

(39) Treatment of **19** with HBr(g)–CH_2Cl_2 for shorter reaction periods (0 °C, 20 min, 64%) led to clean deprotection of the methoxymethyl ether: ^{1}H NMR ($CDCl_3$, 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, OCH_2Ph), 4.06 (s, 3H), 3.96 (s, 3H), 3.87 (s, 3H), 2.01 (s, 3H). This phenol could be cleanly generated by CF_3CO_2H treatment of **19** (CH_2Cl_2 or C_6H_6, 25 °C, 30 min, 97–100%) and subsequently converted to **20** upon treatment with HBr(g)–CH_2Cl_2.

extracted with EtOAc (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (0.5 × 2 cm SiO_2, 50% EtOAc–hexane eluant) afforded **24** (1.8 mg, 2.2 mg theoretical, 86%) as a dark solid: mp 295–297 °C (dec, Et_2O–hexane); ^1H NMR ($CDCl_3$, 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, NH_2), 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, $C_{25}H_{26}N_4O_7$ (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 CF_3CH_2OH was treated with 10% Pd–C (3 mg, 0.003 mmol, 1 equiv). While under a H_2 atmosphere, 200 μL of CF_3CH_2OH 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 H_2O, neutralized with the addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 2 mL). The residual Pd was removed by filtration, the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography (0.2 × 2 cm SiO_2, 8:1:1 $CHCl_3$–MeOH–acetone eluant) afforded streptonigrone (**1**; R_f = 0.56, SiO_2, 8:1:1 $CHCl_3$–MeOH–acetone), identical in all respects with the properties of a sample of authentic material: mp >300 °C (CH_2Cl_2–hexane), lit mp 268–69 °C[1a] and >300 °C[1b]; ^1H NMR ($CDCl_3$, 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 (CH_3OH) λ_{max} 425 nm (ε 12 500); UV (CH_3OH–HCl) λ_{max} 342 nm (ε 15 000); FABHRMS (NBA) m/e 479.1582 (M^+ + H, $C_{24}H_{22}N_4O_7$ 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 N_2, and the mixture was stirred for 30 min. $NaOCH_3$ (0.5 M) in CH_3OH 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 H_2O (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 (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 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.