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Total Synthesis of Streptonigrone

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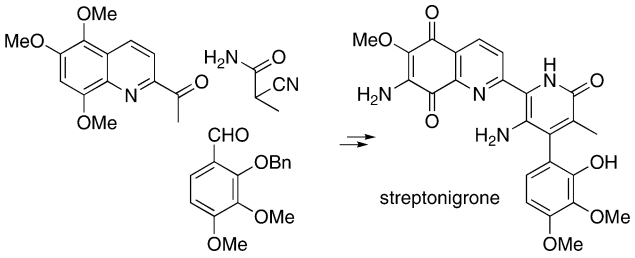
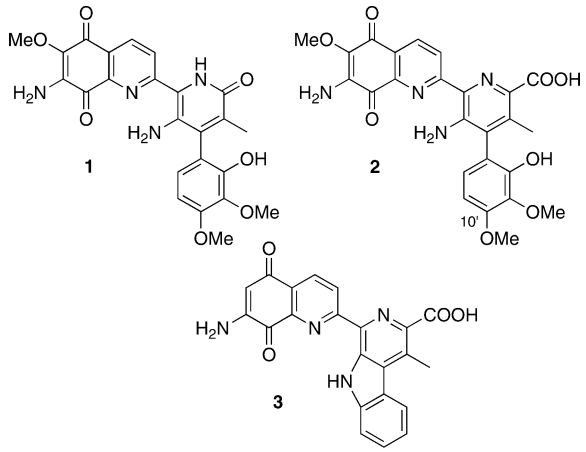


A total synthesis of streptonigrone, **1**, is described, which incorporates a one-step synthesis of substituted pyridones devised in our laboratory. Other aspects of the synthesis that differentiate the present approach from previous ones are the use of a Conrad−Limpach reaction, rather than the customary Friedländer methodology, to assemble the quinoline segment of **1**, and the implementation of an anionic sequence for the functionalization of a key pyridone intermediate.

Introduction

Streptonigrone, **1**,[1] is a member of a family of natural products ("streptonigrinoids", Scheme 1) that includes streptonigrin, **2**, lavendamycin, **3** (the putative biosynthetic precursor of all streptonigrinoids), and related substances.[2] Streptonigrinoids were discovered during a search for new antitumor antibiotics on accounts of their cytotoxic properties.[2] They are now known to be endowed with diverse and noteworthy bioactivities. For instance, both **1** and **2** inhibit the NO-dependent activation of soluble guanylyl cyclase,[3] while, the 10′ demethoxy analogue of **2** displays intriguing *ras* farnesylation inhibitory action.[4] Streptonigrin induces mammalian topoisomerase II-dependent DNA cleavage,[5] it interferes with oxidative phosphorylation, it is a potent inhibitor of reverse transcriptase,[6] and, upon bioreductive activation, it promotes formation of oxygen radicals.[2] It is not surprising that such a panoply of biological properties continues to inspire significant medicinal chemistry research.[7]

SCHEME 1



(1) Isolation: (a) Herlt, A. J.; Rickards, R. W.; Wu, J. P. *J. Antibiot.* **1985**, *38*, 516. (b) Kozlova, N. V.; L'vova, N. A.; Lapchinskaya, O. A.; Dokuchaeva, E. B.; Rubasheva, L. M.; Rozynov, B. V.; Preobrazhenskaya, M. N. *Antibiot. Khim.* **1990**, *35*, 13. Preparation by oxidative decarboxylation of streptonigrin: (c) Preobrazhenskaya, M. N.; Holpne-Kozlova, N. V.; Lazhko, E. I. *J. Antibiot.* **1991**, *45*, 227. Imino derivative and bioactivity thereof: (d) Tolstikov, V. V.; Preobrazhenskaya, M. N.; Balzarini, J.; De Clercq, E. *J. Antibiot.* **1992**, *45*, 1002.

(2) Reviews: (a) Gould, S. J.; Weinreb, S. M. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 77. (b) Bringmann, G.; Reichert, Y.; Kane, V. V. *Tetrahedron* **2004**, *60*, 3539. Structural work: (c) Tennant, S.; Rickards, R. W. *Tetrahedron* **1997**, *53*, 15101.

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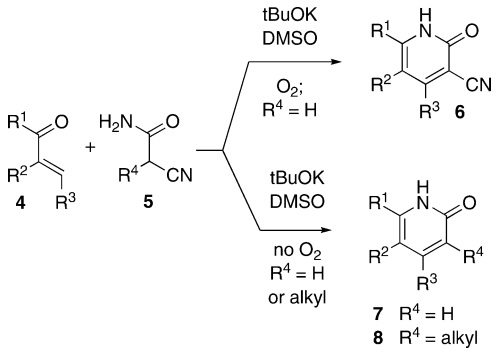
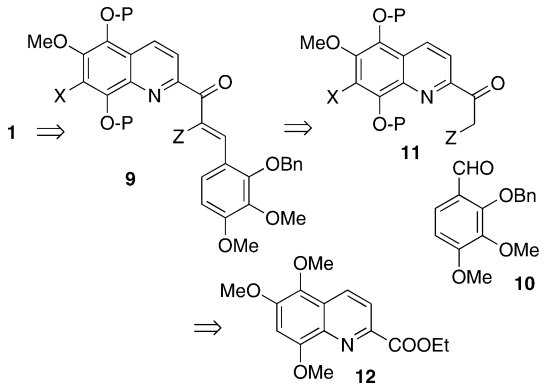
SCHEME 2



Streptonigrinoids are attractive molecules at the chemical level as well, in that their densely functionalized structure constitutes a significant synthetic challenge. This is clearly borne out of the pioneering efforts by Weinreb,[8] Kende,[9] and Boger,[10] as well as the work of numerous other researchers.[11]

Our continuing interest in streptonigrinoids[12] engendered a desire to evaluate an avenue to **1** on the basis of chemistry developed in our laboratory for the rapid construction of functionalized pyridones (Scheme 2). Briefly, we have shown that the condensation of an enone, **4**, with an α-cyanoamide, **5**, selectively produces either a 3-cyanopyridone, **6**,[13] or a 3-unsubstituted pyridone, **7**, or a 3-alkylpyridone, **8**,[14] depending on the nature of R^4 and on precise experimental conditions (Scheme 2). Our syntheses of camptothecin[15] and of nothapodytine B[14] feature these transformations as key steps. Herein, we describe the extension of the methodology to the total synthesis of streptonigrone: a feat that had previously been accomplished only by Boger and collaborators.[16]

SCHEME 3



Retrosynthetic Considerations and Model Studies

Application of the above pyridone-forming process to the construction of an intermediate suitable for elaboration into **1** required enone **9**, which is available by condensation of quinoline ketone **11** with the known **10**[17] (Scheme 3). Substituents P stand for appropriate protecting groups, while X and Z represent suitable nitrogenous functionalities, or precursors thereof. A practical building block for **11**, regardless of the nature of X and Z, was **12**, which may be readily accessed through a Conrad−Limpach quinoline synthesis. Thus, the conjugate adduct **14** of aniline **13**[18] with dimethylacetylene dicarboxylate yielded quinolone **15** upon thermolysis in diphenyl ether.[19] The desired **12** was obtained in good overall yield upon chlorination of **15** and hydrogenolysis of the Cl atom (Scheme 4). The presence of a base such as Et_3N in the latter reaction was essential to avoid overreduction: conduct of the reaction in the absence of Et_3N provided **17** in excellent yield (Scheme 5).[20]

Preliminary studies served to define the appropriate choice of groups X and Z in **9**.[21] In that connection, attempted C-7 nitration[22] of, e.g., **16**, in the interest of introducing a requisite nitrogenous functionality at an early stage, resulted only in oxidation to quinone **18** (Scheme 5). Thus, we chose to employ

(7) For a recent contribution see: Fryatt, T.; Pettersson, H. I.; Gardipee, W. T.; Green, S. J.; Slawin, A. M. Z.; Beall, H. D.; Moody, C. J. *Bioorg. Med. Chem.* **2004**, *12*, 1667, and references cited therein.

(8) Streptonigrin: (a) Weinreb, S. M. *Strategies Tactics Org. Synth.* **1984**, *1*, 325. (b) 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. (c) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962.

(9) Streptonigrin: (a) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. (b) Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles* **1981**, *21*, 91. Lavendamycin: (c) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923.

(10) Reviews: (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L. *Strategies Tactics Org. Synth.* **1988**, *2*, 1. Streptonigrin: (c) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (d) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. Lavendamycin: (e) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. (f) Medicinal, chemistry studies: Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918.

(11) See ref 2, as well as: (a) Kametani, T.; Kozuka, A.; Terui, T. *Yakugaku Zasshi* **1973**, *93*, 406. (b) Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261. (c) Rama Rao, A. V.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065. (d) Rama Rao, A. V. *Recent Prog. Chem. Synth. Antibiot.* **1990**, 497. (e) Godard, A.; Rocca, P.; Fourquez, J.-M.; Rovera, J.-C.; Marsais, F.; Queguiner, G. *Tetrahedron Lett.* **1993**, *34*, 7919. (f) Molina, P.; Murcia, F.; Fresneda, P. M. *Tetrahedron Lett.* **1994**, *35*, 1453. (g) Godard, A.; Marsais, F.; Ple, N.; Trecourt, F.; Turck, A.; Queguiner, G. *Heterocycles* **1995**, *40*, 1055. (h) Behforouz, M.; Haddad, J.; Cai, W.; Arnold, M. B.; Mohammadi, F.; Sousa, A. C.; Horn, M. A. *J. Org. Chem.* **1996**, *61*, 6552. (i) Robinson, J. M.; Ahmed, M.; Alaniz, N. J.; Boyles, T. P.; Brasher, C. D.; Floyd, K. A.; Holland, P. L.; Maruffo, L. D.; McMahan, T. L.; Middleton, S.; O'Hara, K. D.; Pack, M. J.; Reynolds, B. D.; Rodriquez, R. R.; Sawyer, D. E.; Sharp, E.; Simpson, S. L.; Vanlandingham, C. L.; Velasquez, R. S.; Welch, B. M.; Wright, C. D. *J. Hetercycl. Chem.* **1998**, *35*, 65. (j) Holzapfel, C. W.; Marais, W. *J. Chem. Res., Synop.* **2002**, 22. (k) McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779.

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(14) Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2002**, *66*, 4304.

(15) (a) Ciufolini, M. A.; Roschangar, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1692. (b) Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049. (c) Ciufolini, M. A.; Roschangar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 25.

(16) (a) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733. (b) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880. See also (c) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149.

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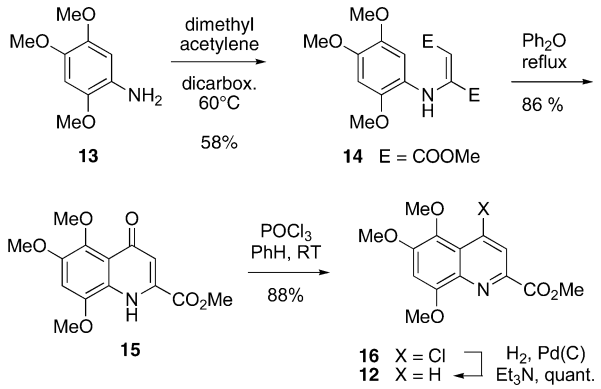
(19) (a) Heindel, N. D.; Bechara, I. S.; Kennewell, P. D.; Molnar, J.; Ohnmacht, C. J.; Lemke, S. M.; Lemke, T. F. *J. Med. Chem.* **1968**, *11*, 1218. (b) Kaslow, C. E.; Nix, S. J. *J. Org. Chem.* **1951**, *16*, 895.

(20) In the presence of Et_3N, a minor degree of overreduction of **12** to **17** occurs only after an extended (>12 h) contact time.

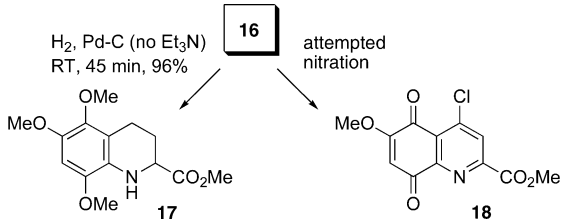
(21) Experimental procedures and characterization data for compounds not directly related to **1** are provided as Supporting Information.

(22) Reagents tried: (i) 90% HNO_3, Ac_2O; (ii) 90% HNO_3, $Hg(OAc)_2$, Ac_2O, AcOH; (iii) 70% HNO_3, AcOH; (iv) 70% HNO_3, CH_2Cl_2.

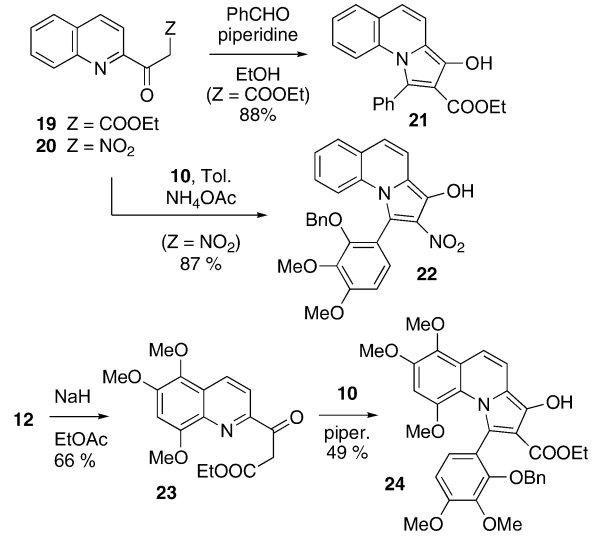
SCHEME 4



SCHEME 5



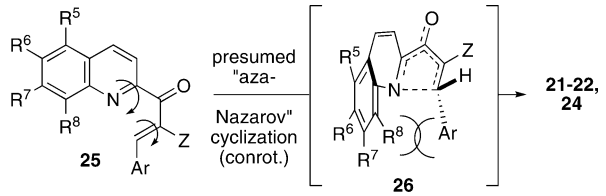
SCHEME 6



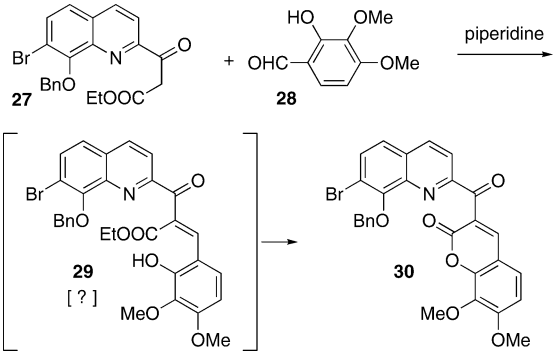
C-7 unsubstituted educts (cf. **9** and **11**: X = H) in the initial phases of the synthesis. On the other hand, the nature of Z was dictated by the results of experiments involving intermediates **19**−**20**[21] and **23**, wherein a carboxy or nitro functionality serves as a precursor of an ultimate NH_2 group. Knoevenagel condensation of the foregoing compounds with PhCHO or with **10** afforded none of the anticipated benzylidene derivatives, providing instead air-sensitive benzindolizines **21**, **22**, and **24** (Scheme 6). The latter, on account of its highly electron-rich character, was significantly more air-sensitive than **21** and **22**.[23]

In accord with observations recorded during our work on camptothecin,[15,24] we presume that these indolizines arise via "aza-Nazarov" cyclization (Scheme 7) of the *Z*-isomer of an initially formed enone **25** (not detected). It should be noted that all such indolizines were entirely resistant to conversion to pyridones under the conditions of Scheme 2, signaling that they do not equilibrate with the corresponding enones **25**. Indeed,

SCHEME 7



SCHEME 8



we estimate (MNDO)[25] that the $\Delta\Delta H_f$ incurred during the conversion of, e.g., **25** (R^5−R^8 = H, Ar = Ph) to **21** is approximately equal to −6.5 kcal/mol.

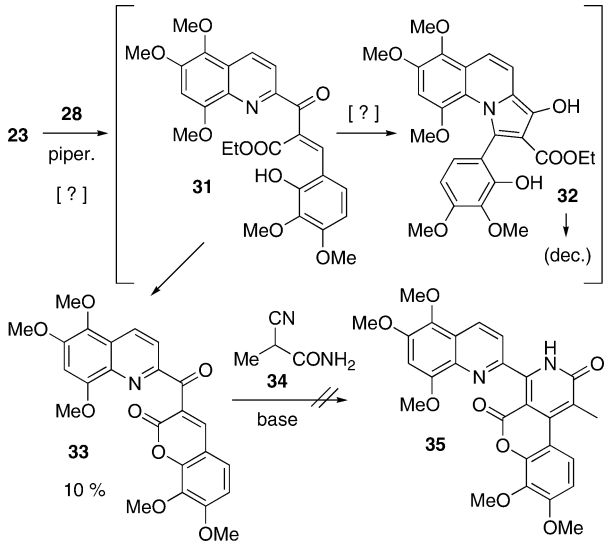
The results of Scheme 6, especially the behavior of **23**, stand in contrast to the smooth formation of coumarin **30** upon condensation of **27** with **28** (Scheme 8).[16] Compound **30** is recognized as a key intermediate in Boger's brilliant synthesis of **1**. Again, we assume that the interaction of **27** and **28** yields a transient enone **29**, which apparently displays no proclivity toward indolizine formation, preferring instead to lactonize to **30**. While a number of effects may be invoked to account for such a preference, the following experiments suggest a steric origin for the reluctance of the presumed **29** to form an indolizine. Thus, Knoevenagel condensation of **23** with **28** (Scheme 9) produced some coumarin **33** as a minor component (10%) of a mixture of largely intractable products. Such polymeric materials are likely to arise through air oxidation of a presumed indolizine **32** (not isolated nor detected), which we imagine to be excessively electron-rich to survive in the presence of O_2. Assuming that the rates of lactonization (=coumarin formation) of probable reaction intermediates **29** and **31** are comparable, then the rate of aza-Nazarov cyclization of **29** must be significantly slower than that of **31**. Recognizing that a nonbonding interaction develops between the quinoline R^8 substituent (Scheme 7) and the aryl group at the β position of the enone segment at (or near) the transition state for a Nazarov-like reaction, we conclude that an OMe group engenders insufficient steric bias against indolizine formation, while a bulkier OBn group effectively suppresses such an event.

(23) The structural assignment of all such indolizines rests on the following spectral properties. Proton NMR spectra ($CDCl_3$) displayed a singlet at ca. 8.5 ppm (1H) that disappeared upon addition of D_2O. Carbon-13 NMR spectra exhibited no resonances consistent with the presence of a ketone. Furthermore, HSQC spectra showed no ^1J H−C correlations involving the exchangeable ^1H signal at 8.5 ppm, while HMBC spectra revealed only three correlations between the above ^1H resonance and ^{13}C lines at ca. 104, 118, and 142 ppm. Hardcopy spectra are provided as Supporting Information.

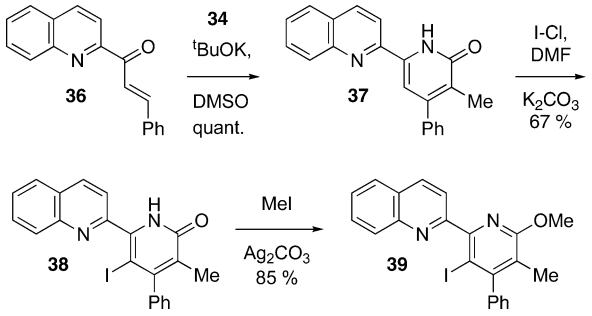
(24) Substituent Z was H in chalcones **25** related to camptothecin. Such enones cyclized to indolizines only upon exposure to Lewis acidic agents, in contrast to the more electrophilic, "doubly activated" enones (Z = COOEt, etc.), which cyclize spontaneously.

(25) Calculations carried out with the Hyperchem package.

SCHEME 9



SCHEME 10



It soon transpired that **33** is not a substrate for the pyridone-forming reaction of Scheme 2. The diminished electrophilic character of the coumarin, an aromatic system, relative to an ordinary enone, hampered the occurrence of an obligatory 1,4-addition of the weakly nucleophilic enolate of **34**, suppressing the sequence of events leading to **35**. Therefore, we saw no advantage in pursuing an improved avenue to **33** or to its congeners.

Fortunately, enones of the type **25** in which Z = H behaved normally and reacted efficiently under the conditions of Scheme 2 to deliver the desired pyridones. To illustrate (Scheme 10), condensation of 2-acetylquinoline[21] with PhCHO yielded a stable enone **36**, which advanced to **37** in virtually quantitative yield upon reaction with **34** and *t*-BuOK. Incidentally, pyridone **37** was a useful system to test methods for the functionalization of the unsubstituted position. In that respect, derivatization under acidic (HCHO/(aqueous HCl);[26] azodicarboxylate esters/acid,[27] no reaction) or basic (NaH and HCHO, no reaction; NaH and azodicarboxylate esters/$ZnCl_2$,[26] intractable mixture) conditions proved fruitless, as did halogenation with I_2 or with NIS. However, the more reactive I−Cl promoted clean conversion to iodopyridone **38**, which then underwent uneventful *O*-methylation to **39**. In principle, this iodopyridine could undergo nucleophilic displacement of iodine by an S_NAr mechanism, given the favorable position of the halogen vis-à-vis the activating quinoline ring. However, attempts to induce reaction

(26) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org Chem.* **1993**, *58*, 611.

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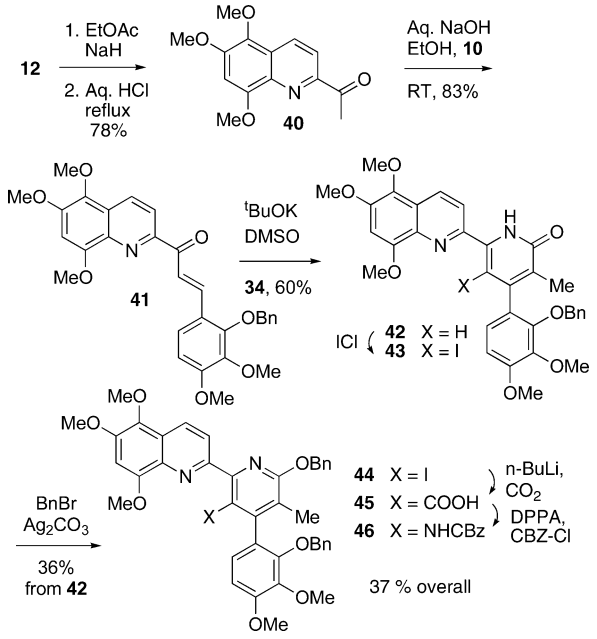
SCHEME 11



with nitrogen nucleophiles[28] were unproductive, as were Buchwald-type substitutions promoted by diverse Cu(I) or Pd(0) complexes (no reaction in all cases). Some aminopyridone was obtained upon reaction of **39** with NH_4OH in the presence of $CuSO_4$,[29] but the reaction was not synthetically useful.

A final series of experiments aimed to determine whether one could generate an enone of the type of **25**, where Z was a nitrogenous functionality. We reasoned that since indolizine formation appeared to be a problem when Z was an electron-withdrawing group, perhaps having Z as an electron-releasing nitrogenous substituent would discourage aza-Nazarov cyclization, and render the enone amenable to direct conversion to a 5-aminopyridone. Regrettably, the preparation of such enones proved not to be straightforward.[30] Therefore, we concentrated on intermediates **9** wherein X = Z = H.

Synthesis of Streptonigrone

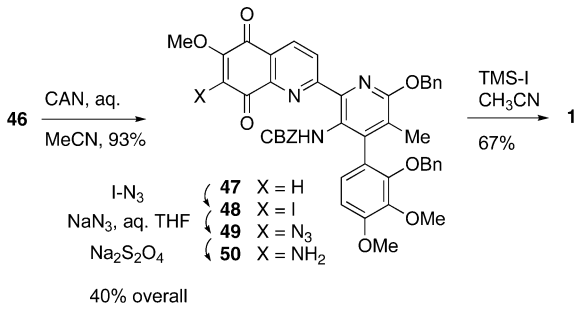
Enone **41** emerged upon the union of **40** with **10**, and it reacted with 2-cyanopropionamide, **34**, to afford **42**, mp 93−95 °C, in 60% chromatographed yield (Scheme 11). Consistent with the observations adumbrated in Scheme 10, **42** underwent highly selective iodination with I−Cl to furnish **43**, a sensitive material that was best advanced to benzyloxypyridine **44** (BnBr,

(28) Such as: anhydrous NH_3; aqueous NH_4OH; $NaNH_2$, NaN_3, $BnNH_2$; 4-MeO-$C_6H_4CH_2NH_2$.

(29) (a) Tamura, Y.; Fujita, M.; Chen, L. C.; Kiyokawa, H.; Ueno, K.; Kita, Y. *Heterocycles* **1981**, *15*, 871. (b) Schoenen, B.; Zymalkowski, F. *Archiv. Pharm.* **1981**, *314*, 464.

(30) Condensation of **12** and related substances with protected glycine esters, as well as reduction of nitroketones such as **20** (H_2, Pd−C, MeOH, or EtOAc, RT, 1 h; H_2, Pd−C, HCl, MeOH−H_2O, RT, 5 h; H_2, Ra.Ni, MeOH, RT, 1−4 h; Zn, AcOH, RT, 30 min; $SnCl_2$, HCl, H_2O, EtOH, 60 °C, 1 h; $SnCl_2$, EtOAc, 60 °C, 1 h) afforded largely intractable mixtures of products. Only reduction with $SnCl_2$ followed by treatment with ethyl chloroformate afforded some of the desired material. Customary methods for the conversion of **40** and related compounds to the corresponding bromoketones (Br_2, $CHCl_3$, RT, 4 h; Br_2, AcOH, RT, 15 min; Br_2, AcOH, dioxane, RT, 1−18 h; pyridinium tribromide, AcOH, RT, 1.5 h; $CuBr_2$, $CHCl_3$, RT, 18 h; NBS, NH_4OAc, CCl_4, 80 °C, 4−24 h.) were inefficient, and the reaction of the bromoketones with NaN_3 or with MsNHNa proceeded poorly.

SCHEME 12



Ag_2CO_3) without purification. Interestingly, no desired **44** was obtained upon reaction of **43** with $BnCl/Ag_2CO_3$. A methoxy analogue of **44** was readily accessible by *O*-methylation of **43** with MeI/Ag_2CO_3, whereas treatment with the Meerwein reagent gave a mixture of overmethylated products. Installation of the requisite amino functionality proceeded by a two-step sequence involving halogen−metal exchange (*n*-BuLi) and carboxylation (dry CO_2 gas), followed by a time-honored Yamada−Curtius reaction[31] that culminated with hydrolysis of the intermediate isocyanate and protection of the free amino group either as a CBZ or as a BOC derivative. The resultant **46** was obtained in 36% overall chromatographed yield from **44**. In situ capture of the Yamada−Curtius isocyanate with benzyl alcohol or with *tert*-butanol was less efficient, providing variable quantities of the free amine in addition to the desired carbamate.

The terminal phase of the synthesis commenced with oxidation of the electron-rich quinoline to the corresponding quinone. The success of this step was a function of both the protecting group applied to the pyridone amino group and of the oxidant employed. Silver oxide, DDQ, and nitric acid were ineffective (no desired quinone formed), while ceric ammonium nitrate (CAN) in aqueous acetonitrile gave good results. Highest yields (93%) were obtained upon oxidation of an *N*-CBZ substrate, while BOC-protected intermediates reacted poorly, seemingly due to partial release of the *N*- blocking group during the reaction (probably a consequence of the acidity of aqueous solutions of CAN), and consequent overoxidation of the liberated aminopyridine. Compound **46** was thus oxidized to quinone **47** (Scheme 12), which, in accord with the work of Weinreb, was treated with iodine azide to provide iodoquinone **48**. This delicate intermediate was best advanced to the next step without purification. Reaction with NaN_3 therefore furnished azidoquinone **49**, also a very sensitive material, which was immediately reduced to aminoquinone **50** with sodium dithionite.[8] Conduct of the same transformation by the use of $NaBH_4$ or by hydrogenolysis,[16] either with *N*-unprotected or with *N*-CBZ or *N*-BOC intermediates, produced inferior results in the present case.

The final step of the synthesis entailed global deblocking of **50**. Like many other aspects of streptonigrinoid chemistry, this operation turned out to be rather delicate.[2,8−10,16] First of all, problems were encountered during the deprotection of a compound analogous to **50** but incorporating a methoxy group on the pyridone in lieu of a benzyloxy substituent. Diverse sequences afforded mixtures of partially deprotected products. More forcing conditions promoted an undesired demethylation of the quinone OMe group. Deprotection in the benzyloxy series created a new set of problems: substrate **50** was now intolerant of Boger conditions[16] (preliminary reduction of the quinone with H_2, Pd(C), CF_3CH_2OH, followed by HBr(g), 80 °C: loss of material). A modification of that procedure wherein quinone reduction was effected with $Na_2S_2O_4$, instead of catalytic hydrogenation, again provided a mixture of partially deblocked products. Longer reaction times resulted in undesired demethylation elsewhere in the molecule, as well as decomposition of the product. Loss of material was especially problematic upon attempted deprotection using Lewis acids such as $AlCl_3$ and BBr_3.[8,9] Ultimately, TMS−I[32] emerged as the best deprotecting agent—with a twist. Reaction of **50** with TMS−I induces formation of benzyl iodide, a reactive alkylating agent that tends to convert the liberated streptonigrone to *N*-benzyl derivatives during the customary extractive workup. To prevent such an undesirable occurrence, it was essential not to concentrate the organic extracts but rather to apply them directly to a silica gel column. Initial elution with CH_2Cl_2 quickly removed unwanted benzyl iodide. The desired product was then eluted with 5% MeOH in CH_2Cl_2. Fully synthetic streptonigrone was thus obtained in 67% yield from **50**. The ^1H spectral data measured for synthetic **1** were in perfect accord with those recorded in the literature for natural material.[33]

The scope of the pyridone-forming reaction outlined in Scheme 2 has thus been extended to the domain of streptonigrinoids. Further applications of that chemistry are under study and will be described in due course.

Experimental Section[34]

2-[(2,4,5-Trimethoxyphenyl)amino]-2-butenedioic Acid, Dimethyl Ester, 14. A solution of **13** (5.20 g, 28.4 mmol) and dimethyl acetylenedicarboxylate (3.83 mL, 31.2 mmol) in MeOH (150 mL) was refluxed for 15 h. The mixture was then concentrated in vacuo, and the residue was flash chromatographed (EtOAc:hexanes, 1:3) to give **14** (5.35 g, 58%) as an orange paste. ^1H: δ 9.52 (s, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 5.34 (s, 1H), 3.88 (s, 3H), 3.79 (s, 6H), 3.74 (s, 3H), 3.71 (s, 3H). ^{13}C: δ 171.1, 165.6, 149.8, 147.3, 146.4, 144.0, 122.8, 108.0, 99.6, 91.7, 57.5, 57.4, 53.5, 52.0. IR: 3293, 1740. ESI-MS: 326.1 $[M + H]^+$, 348.1 $[M + Na]^+$, 673.1 $[2M + Na]^+$. HRMS: Calcd for $C_{15}H_{19}NO_7$ $[M + Na]^+ = 348.1059$, found 348.1055.

5,6,8-Trimethoxy-(1*H*)-quinolin-4-one-2-carboxylic Acid, Methyl Ester, 15. A solution of **14** (5.35 g, 16.5 mmol) in phenyl ether (150 mL) was refluxed for 2 h; then it was cooled to RT and poured into petroleum ether (300 mL) to give a yellow precipitate. The solid was collected by filtration and washed with more petroleum ether (4 × 30 mL) to give **15** (4.15 g, 86%) as a dark yellow solid; mp 170.5−171.5 °C. ^1H (MeOH-d_4): δ 7.22 (s, 1H), 6.74 (s, 1H), 4.11 (s, 3H), 4.03 (s, 3H), 3.97 (s, 3H), 3.80 (s, 3H). ^{13}C (MeOH-d_4): δ 179.2, 161.8, 148.9, 144.9, 139.0, 135.1, 125.3, 120.4, 109.7, 101.4, 60.4, 56.0, 55.4. IR: 3410, 1737. ESI-MS: 294.2 $[M + H]^+$. HRMS: Calcd for $C_{14}H_{15}NO_6$ $[M + H]^+ = 294.0978$, found 294.0977.

4-Chloro-5,6,8-trimethoxyquinoline-2-carboxylic Acid, Methyl Ester 16. A suspension of **15** (4.15 g, 14.1 mmol) in benzene (120 mL; *CAUTION*! cancer suspect agent) and $POCl_3$ (60 mL; *CAUTION*! corrosive, toxic) was stirred at RT for 24 h; then it was then poured over ice (200 mL), neutralized by addition of solid $NaHCO_3$ (*CAUTION*! vigorous foaming) and extracted with EtOAc

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

(32) (a) Jung, M. E.; Lyster, M. A. *J. Org Chem.* **1977**, *42*, 3761. (b) Peters, R.; Althaus, M.; Diolez, C.; Rolland, A.; Manginot, E.; Veyrat, M. *J. Org. Chem.* **2006**, *71*, 7583.

(33) A tabulation of ^1H and ^{13}C NMR chemical shifts for synthetic and natural **1** is provided as Supporting Information.

(34) Experimental protocols are provided as Supporting Information.

(5 × 100 mL). The combined extracts were then washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to afford analytically pure **16** (3.87 g, 88%) as an orange crystalline solid; mp 193.5−195 °C. ^{1}H**:** δ 8.20 (s, 1H), 6.93 (s, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.87 (s, 3H). ^{13}C: δ 166.0, 154.8, 154.2, 144.7, 141.3, 137.0, 136.7, 125.6, 124.6, 99.7, 62.9, 57.9, 57.4, 54.1. **IR**: 1704. ESI-MS: 334.1 [M(^{35}Cl) + Na]$^+$, 336.1 [M(^{37}Cl) + Na]$^+$. HRMS: Calcd for $C_{14}H_{14}{}^{35}ClNO_5$ [M + Na]$^+$ = 334.0458, found 334.0459. EA**:** Calcd C 53.9%, H 4.53%, N 4.49%; found C 54.28%, H 4.86%, N 4.57%.

5,6,8-Trimethoxyquinoline-2-carboxylic Acid, Methyl Ester, 12. A mixture of **16** (636 mg, 2.04 mmol), 10% Pd−C (120 mg, 0.113 mmol), Et_3N (1.0 mL, 7.2 mmol) in EtOAc (50 mL) was stirred under a H_2 atmosphere at RT for 45 min; then it was filtered over Celite and concentrated to afford pure **12** (567 mg, quant.) as an orange crystalline solid; mp 164−165.5 °C. ^{1}H**:** δ 8.47 (d, 1H, J = 8.76), 8.15 (d, 1H, J = 8.76), 6.84 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.89 (s, 3H). ^{13}C: δ 167.0, 154.4, 151.6, 145.5, 135.8, 135.5, 132.0, 126.8, 122.7, 99.2, 62.4, 57.9, 57.2, 53.9. **IR**: 1708. ESI-MS: 278.1 [M + H]$^+$, 300.1 [M + Na]$^+$. HRMS: Calcd for $C_{14}H_{15}NO_5$ [M + H]$^+$ = 278.1028, found 278.1034. EA**:** Calcd C 60.64%, H 5.45%, N 5.05%; found C 60.80%, H 5.66%, N 5.09%.

1-[(5,6,8-Trimethoxy)-2-quinolinyl]-ethanone, 40. A suspension of **12** (7.00 g, 25.3 mmol) and NaH (60% in oil, 2.5 g, 62.5 mmol) in EtOAc (100 mL) and toluene (350 mL) was stirred at 110 °C for 15 h (*CAUTION*! vigorous evolution of highly flammable H_2 gas). The reaction was then cooled to RT and diluted with sat. aq. NH_4Cl (100 mL; *CAUTION*!). The aqueous phase was acidified to pH 4 with 1 M HCl and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was then dissolved in 1,4-dioxane (150 mL; *CAUTION*! cancer suspect agent). Aqueous 1 N HCl (100 mL) was added, and the mixture was heated at 70 °C for 15 h. The solution was concentrated, the wet residue was neutralized (sat. aq. $NaHCO_3$), and the mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc:hexanes:DCM, 1:3:1) of the residue afforded **40** (5.17 g, 78% over 2 steps): yellow solid; mp 144−145 °C. ^{1}H: δ 8.48 (d, 1H, J = 8.82), 8.13 (d, 1H, J = 8.78), 6.91 (s, 1H), 4.13 (s, 3H), 4.06 (s, 3H), 3.93 (s, 3H), 2.87 (s, 3H). ^{13}C: δ 200.6, 153.8, 150.8, 150.7, 135.7, 134.6, 130.9, 126.3, 119.0, 99.3, 61.7, 57.2, 57.0, 25.6. IR: 1690. ESI-MS: 284.1 [M + Na]$^+$, 545 [2M + Na]$^+$. HRMS: Calcd for $C_{14}H_{15}NO_4$ [M + Na]$^+$ = 284.0899, found 284.0903. EA: Calcd C 64.36%, H 5.79%, N 5.36%; found C 64.52%, H 5.86%, N 5.54%.

(*E*)-3-[(3,4-Dimethoxy-2-phenylmetoxy)phenyl]-1-[(5,6,8-trimethoxy) -2-quinolyl]-2-propen-1-one, 41. To a solution of **40** (156 mg, 0.597 mmol) in EtOH (25 mL) was added dropwise a solution of NaOH (1 g, 25 mmol) in water (5 mL). The mixture was then stirred for 5 min at RT. A solution of the 2-benzyloxy-3,4-dimethoxybenzaldehyde (120 mg, 0.657 mmol) in EtOH (2 mL) was then added. After 15 h of stirring at RT, the reaction was diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (EtOAc:hexanes, 1:2) afforded **41** (256 mg, 83%) as a yellow foam. ^{1}H: δ 8.53 (d, 1H, J = 8.78), 8.32 (m, 2H, overlapping resonances), 8.28 (d, 1H, J = 8.68), 7.64 (d, 1H, J = 8.82), 7.52 (m, 2H, overlapping resonances), 7.26−7.35 (m, 3H), 6.91 (s, 1H), 6.78 (d, 1H, J = 8.85), 5.14 (s, 2H), 4.11 (s, 3H), 4.08 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H). ^{13}C: δ 189.6, 155.9, 153.8, 152.9, 151.7, 150.7, 142.8, 139.7, 137.3, 135.7, 134.5, 131.0, 128.9, 128.6, 128.3, 126.1, 123.6, 123.4, 120.5, 120.3, 108.0, 99.0, 76.4, 61.8, 61.3, 57.2, 56.8, 56.3. IR: 1661. ESI-MS: 516.1 [M + H]$^+$. HRMS: Calcd for $C_{30}H_{29}NO_7$ [M + Na]$^+$ = 538.1842, found 538.1857.

3-Methyl-4-[(3,4-dimethoxy-2-phenylmethoxy)phenyl]-6-[(5,6,8-trimethoxy)-2-quolinyl]-(1*H*)-2-pyridinone, 42. A solution of enone **41** (1.54, 2.98 mmol) and 2-cyanopropanamide (**34**, 300 mg, 3.00 mmol) in DMSO (75 mL) was degassed for 20 min (bubbled through with argon) prior to the addition of potassium *tert*-butoxide (670 mg, 6.00 mmol). The reaction was then stirred at RT for 5 min and at 100 °C for 5 h. After cooling to RT, 1 M HCl (100 mL) was then added dropwise (*CAUTION*! evolution of highly toxic HCN gas), and the resulting mixture was extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography of the residue (100% EtOAc then MeOH:DCM, 1:9) afforded **42** (1.02 g, 60%) as a yellow solid; mp 92.5−95 °C. ^{1}H: δ 10.80 (s, br, 1H), 8.38 (d, 1H, J = 8.92), 7.70 (d, 1H, J = 8.99), 7.05−7.15 (m, 5H), 6.90 (s, 1H), 6.89 (d, 1H, J = 8.40), 6.78 (d, 1H, J = 8.58), 6.69 (s, 1H), 4.93 (s, 2H), 4.11 (s, 3H), 4.05 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 2.02 (s, 3H). ^{13}C: δ 163.5, 154.1, 153.2, 149.8, 149.7, 147.5, 145.1, 143.1, 137.6, 137.1, 135.6, 134.6, 131.2, 130.1, 128.6, 128.4, 128.2, 127.1, 124.5, 124.3, 117.6, 108.1, 107.8, 99.4, 75.8, 61.7, 61.4, 57.3, 56.4, 56.3, 14.6. IR: 1642, 1610. ESI-MS: 569.1 [M + H]$^+$. HRMS: Calcd for $C_{33}H_{33}N_2O_7$ [M + H]$^+$ = 569.2288, found 569.2285. EA: Calcd C 69.70%, H 5.67%, N 4.93%; found C 69.34%, H 5.85%, N 5.18%.

2-[5,6,8-Trimethoxy-2-quinolinyl]-4-[3,4-dimethoxy-2-(phenylmethoxy)phenyl]-6-methoxy-5-methyl-3-iodopyridine, 44. A mixture of **42** (1.48 g, 2.61 mmol) and potassium carbonate (2.15 g, 15.6 mmol) in DMF (110 mL) was stirred at RT for 5 min. Iodine monochloride (2.11 g, 13.1 mmol) was then added, and the resulting mixture was stirred in the dark at RT for 16 h. The reaction was then diluted with sat. aq. NH_4Cl (150 mL) and extracted with EtOAc (4 × 75 mL). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (75 mL) and brine (75 mL), dried (Na_2SO_4), and concentrated to give the sensitive iodopyridone. The crude iodopyridone (1.27 g, 1.83 mmol) was immediately dissolved in benzene (55 mL) and treated with Ag_2CO_3 (0.505 g, 1.83 mmol) and benzyl bromide (0.450 mL, 3.66 mmol). The resulting mixture was stirred in the dark for 3 days; then it was filtered through a bed of Celite and concentrated. Purification by flash chromatography (EtOAc : hexanes, 1:3) afforded **44** (520 mg, 36% over 2 steps) as a pale-yellow foam. ^{1}H: δ 8.46 (d, 1H, J = 8.68), 7.62 (d, 1H, J = 8.63), 7.26−7.46 (m, 5H), 7.03−7.22 (m, 5H), 6.90 (s, 1H), 6.77−6.79 (m, 2H, AB system), 5.43 (m, 2H, AB system), 5.06 (m, 2H, AB system), 4.07 (s, 3H), 4.04 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 2.04 (s, 3H). ^{13}C: δ 161.4, 157.3, 154.7, 154.1, 153.9, 153.5, 150.0, 149.0, 142.9, 138.3, 138.0, 135.9, 134.8, 130.5, 130.2, 128.6, 128.3, 128.0, 127.8, 127.7, 127.5, 124.5, 124.1, 123.0, 121.9, 107.7, 99.4, 91.6, 77.4, 75.0, 68.1, 61.7, 61.3, 57.5, 56.9, 56.2, 14.6. IR: 2937, 1601, 1496, 1099. ESI-MS: 785.1 [M + H]$^+$. HRMS: Calcd for $C_{40}H_{37}N_2O_7I$ [M + H]$^+$ = 785.1724, found 785.1727. EA: Calcd C 61.23%, H 4.75%, N 3.57%; found C 61.47%, H 4.96%, N 3.65%.

2-[5,6,8-Trimethoxy-2-quinolinyl]-4-[3,4-dimethoxy-2-(phenylmethoxy)phenyl]-6-methoxy-5-methyl-3-(*N*-phenylmethoxycarbonyl)pyridinamine, 46. A solution of **44** (222 mg, 0.283 mmol) in THF (2 mL) was added dropwise to a cold (−78 °C) solution of *n*-butyllithium (0.354 mL of 1.6 M solution in hexanes, 0.566 mmol) in THF (30 mL). Bone dry CO_2 gas was immediately bubbled through the solution for 10 min at −78 °C and at RT for 20 min. The reaction was then quenched with water (2 × 30 mL) and extracted with EtOAc (30 mL). The aqueous phase was further acidified to pH 2 by addition of 1 M HCl and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The crude residue was filtered through a bed of silica gel (washed with EtOAc: hexanes, 1:1; eluted with MeOH:DCM, 5:95) to afford a yellow paste (134 mg). A solution of this material plus diphenyl phosphoryl azide (0.26 g, 0.21 mL, 0.96 mmol) and Et_3N (0.70 mL, 5.0 mmol) in benzene (40 mL) was refluxed for 15 h; then it was cooled to

RT and concentrated in vacuo. The residue was taken up in THF (10 mL) and 1 M LiOH (10 mL). The resulting mixture was stirred at RT for 1 h; then it was diluted with brine (20 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude aminopyridine was then immediately taken up in THF (25 mL) and cooled to 0 °C before the addition of $NaHCO_3$ (160 mg, 1.90 mmol) and benzyl chloroformate (0.10 mL, 0.70 mmol). The reaction was then allowed to warm up to RT and stirred at RT for 18 h before quenching with water (50 mL). The product was then extracted with EtOAc (4 × 25 mL), washed with brine (25 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (EtOAc:hexanes, 1:4) gave **46** (85 mg, 37% over 3 steps) as a yellow paste. ^{1}H: δ 10.07 (s, br, 1H), 8.44−8.49 (m, 2H, AB system), 6.98−7.57 (m, 16H), 6.81 (s, 1H), 6.73 (d, 1H, J = 8.63), 5.54−5.61 (m, 2H, AB system), 5.02−5.12 (m, 2H, AB system), 4.80−4.88 (m, 2H, AB system), 4.05 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.01 (s, 3H). ^{13}C: δ 158.5, 154.8, 153.5, 153.0, 150.2, 149.2, 146.8, 142.5, 138.5, 138.4, 137.4, 135.8, 134.0, 130.4, 128.6, 128.3, 128.1, 127.9, 127.77, 127.72, 127.6, 127.5, 127.4, 126.3, 124.2, 123.6, 122.2, 121.8, 107.0, 98.9, 74.8, 67.8, 66.3, 61.8, 61.2, 57.5, 56.3, 56.1, 14.0. IR: 2941, 1733. ESI-MS: 808.3 $[M + H]^+$, 830.3 $[M + Na]^+$. HRMS: Calcd for $C_{48}H_{45}N_3O_9$ $[M + H]^+$ = 808.3234, found 808.3244.

2-[3-(*N*-Phenylmethoxycarbonyl)amino-4-(2-phenylmethoxy-3,4-dimethoxy)phenyl-5-methyl-6-phenylmethoxy]2-pyridinyl-6-methoxyquinolin-5,8-dione, 47. To a cold (0 °C) solution of **46** (85 mg, 0.105 mmol) in CH_3CN (20 mL) was added dropwise a solution of ceric ammonium nitrate (175 mg, 0.316 mmol) in water (8 mL). The resulting solution was stirred at 0 °C for 45 min before diluted with water (50 mL) and extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed (EtOAc:hexanes, 1:1) to give **47** (75 mg, 93%) as an orange paste. ^{1}H: δ 8.74 (s, br, 1H), 8.47 (m, 2H, AB system), 7.04−7.50 (m, 15H), 6.91 (d, 1H, J = 8.65), 6.70 (d, 1H, J = 8.64), 6.31 (s, 1H), 5.47−5.54 (m, 2H, AB system), 4.92−5.05 (m, 2H, AB system), 4.79−4.88 (m, 2H, AB system), 3.96 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 1.95 (s, 3H). ^{13}C: δ 182.6, 179.8, 162.8, 160.3, 159.1, 154.6, 153.9, 149.9, 147.9, 146.1, 142.6, 138.04, 137.99, 137.1, 135.2, 128.7, 128.3, 128.2, 127.93, 127.91, 127.72, 127.66, 127.1, 126.4, 125.9, 124.0, 123.2, 110.7, 107.2, 74.9, 68.1, 66.4, 64.5, 61.2, 56.9, 56.1, 14.1. IR: 2937, 1734, 1578. ESI-MS: 778.3 $[M + H]^+$, 800.3 $[M + Na]^+$. HRMS: Calcd for $C_{46}H_{39}N_3O_9$ $[M + H]^+$ = 778.2765, found 778.2779.

2-[3-(*N*-Phenylmethoxycarbonyl)amino-4-(2-phenylmethoxy-3,4-dimethoxy)phenyl-5-methyl-6-phenylmethoxy]2-pyridinyl-7-amino-6-methoxyquinolin-5,8-dione, 50. To a suspension of NaN_3 (1.0 g, 15.4 mmol) in CH_3CN (36 mL) in a MeOH/ice bath (−10 °C) was added ICl (0.80 g, 4.93 mmol). The suspension was stirred at −10 °C for 15 min and filtered to give a yellow IN_3 solution. To a cold (−10 °C) solution of **47** (75 mg, 0.097 mmol) in CH_3CN (50 mL) was added the above IN_3 solution (16 mL), and the resulting solution was stirred at RT for 4 h. The mixture was then diluted with DCM (50 mL) and washed with water (15 mL) and 50% aq. $Na_2S_2O_3$ (15 mL), dried (Na_2SO_4), and concentrated in vacuo to give the sensitive **48**. This material was dissolved in THF (10 mL). A solution of NaN_3 (7 mg, 0.108 mmol) in water (2 mL) was added, and the resulting mixture was stirred in the dark at RT for 15 h. The reaction was then quenched with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give the sensitive **49**. A mixture of crude **49** and sodium dithionite (220 mg, 1.07 mmol; 85% tech. grade) in MeOH (40 mL) and water (20 mL) was refluxed in the dark for 4 h. The mixture was then cooled to RT, quenched with water (20 mL), and extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification of the crude residue by preparative TLC (EtOAc:hexanes, 2:1) afforded **50** (30 mg, 40% over 3 steps) as a dark purple wax. ^{1}H: δ 8.41 (m, 2H), 7.00−7.50 (m, 15H), 6.92 (d, 1H, J = 8.19), 6.70 (d, 1H, J = 8.60), 5.48−5.55 (m, 2H, AB system), 5.14 (s, br, 2H), 4.91−5.06 (m, 2H, AB system), 4.80−4.89 (m, 2H, AB system), 4.10 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H), 1.96 (s, 3H). ^{13}C: δ 179.7, 177.5, 160.9, 159.2, 154.7, 153.9, 149.9, 148.0, 144.8, 142.6, 139.6, 138.1, 138.0, 137.4, 137.1, 134.4, 128.7, 128.3, 128.2, 127.92, 127.88, 127.77 (overlapping resonances), 127.68, 127.5, 125.9, 123.3, 107.3, 74.9, 68.0, 66.4, 61.2, 60.7, 56.2, 14.0. IR: 3355, 2938, 1732, 1614. ESI-MS: 793.4 $[M + H]^+$, 815.3 $[M + Na]^+$. HRMS: Calcd for $C_{46}H_{40}N_4O_9$ $[M + K]^+$ = 831.2432, found 831.2444.

Totally Synthetic Streptonigrone, 1. A solution of **50** (15 mg, 0.019 mmol) and TMS−I (0.50 mL, 3.51 mmol) in CH_3CN (2 mL) was stirred at RT for 1.5 h and then heated at 55 °C for 2 h. The mixture was then cooled to RT and quenched with MeOH (5 mL). The resulting solution was stirred at RT for 10 min prior to the addition of water (10 mL) and extraction with DCM (5 × 10 mL). The combined organic extracts were washed with 50% aq. $Na_2S_2O_3$ (10 mL) and water (10 mL), dried (Na_2SO_4), and immediately filtered through a bed of silica gel (washed with DCM, followed by elution with 5% MeOH in DCM). The elutant was concentrated, and purification by preparative TLC (CH_3Cl : acetone : MeOH, 8:1:1) afforded streptonigrone (6 mg, 67%) as a dark solid. ^{1}H: δ 8.31−8.37 (m, 2H, AB system), 6.83 (d, 1H, J = 8.56), 6.65 (d, 1H, J = 8.59), 6.31 (broad s, 1H), 5.04 (broad s, 2H), 4.07 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 2.03 (s, 3H). ^{13}C: δ 180.0, 177.4, 158.4, 156.8, 153.0, 147.0, 145.0, 140.4, 139.1, 137.5, 136.5, 135.9, 134.3, 131.3, 125.2, 124.8, 123.0, 117.9, 114.4, 105.0, 61.4, 60.8, 56.2, 14.7. IR: 3355, 2923, 2852, 1734, 1637, 1609, 1458, 1245, 1098, 797. ESI-MS: 501.0 $[M + Na]^+$. HRMS: Calcd for $C_{24}H_{22}N_4O_7$ $[M + Na]^+$ = 501.1386, found 501.1392.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra of the compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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