TOTAL SYNTHESIS OF STREPTONIGRONE

by

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Abstract

This thesis describes the total synthesis of streptonigrone. The centerpiece of our route to the target molecule is a facile one-pot construction of 3-alkylpyridones developed in our laboratory. The quinoline segment of the target molecule, prepared through a Conrad-Limpach synthesis, was condensed with 2-benzyloxy-3,4-dimethoxybenzaldehyde to afford a chalcone intermediate suitable for our pyridone-forming reaction. The assembly of the central 3-methylpyridone ring of the natural product was then accomplished through the merger of the chalcone with 2-cyanopropanamide. Functionalization of the pyridone was then completed through an anionic sequence.

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List of Abbreviations

Ac	acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
Bu	butyl
<i>ca.</i>	<i>circa</i> (Latin)
cat	catalytic
calcd	calculated
CBZ	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
<i>cf.</i>	<i>confer</i> (Latin)
CHF	congestive heart failure
conc.	concentrated
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
Et	ethyl
ESI	electrospray ionization
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione
h	hour(s)
HIV	Human Immunodeficiency Virus (AIDS virus)
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	hexamethyl phosphoramide

HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrum
Hz	Hertz (s^{-1})
<i>i</i>	<i>iso</i>
IR	infrared
LG	leaving group
LUMO	lowest unoccupied molecular orbital
m	multiplet
Me	methyl
min	minute(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
<i>n</i>	normal (as an alkyl group)
<i>n</i> -BuLi	<i>n</i> -butyllithium
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
PDC	pyridinium dichromate
Ph	phenyl
Pht	1,2-phenylenedicarbonyl
PPE	polyphosphoric ester
ppm	parts per million
Pr	propyl
q	quartet
Qu	quinoline
RT	room temperature

s	singlet
SAR	structure-activity relationship
sat.	saturated
<i>t</i>	tertiary (as an alkyl group)
TBDMS	<i>tert</i> -butyldimethylsilyl
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl

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1. INTRODUCTION

Streptonigrone (**1**), a quinoline-5,8-quinone alkaloid, was first isolated in 1985 from the culture broth of an unidentified *Streptomyces* species (IA-CAS isolate No. 114).¹ Along with its congeners, streptonigrin (**2**)² and lavendamyacin (**3**),³ streptonigrone belongs to a class of antitumor antibiotics known as the “streptonigrinoids.” Due to their diverse biological activities and complex, densely-functionalized structures, streptonigrinoids have generated considerable interest in both the biomedical and the chemical fields.⁴

Figure 1. Streptonigrinoids

1.1 Biological activity

Streptonigrinoids exhibit a number of interesting biological properties. For instance, streptonigrin (**2**) is a potent cytotoxic agent which is active not only toward common murine cell lines such as L1210 leukemia and mammary carcinoma, but also against a wide spectrum of human cancers, such as epidermoid and bronchogenic carcinoma.⁵ Streptonigrin also displays antimicrobial activity against fungal and bacterial organisms, including gram-positive, gram-negative, and acid-fast bacteria.^{6,7}

Although the precise mechanism of action of **2** remains unclear, its cytotoxic properties may be attributed at least in part to its potent inhibitory action against DNA topoisomerase II, an essential enzyme required for DNA replication,⁸ and a privileged target for chemotherapeutic intervention.⁹ DNA topoisomerase II is a nuclear enzyme responsible for the relaxation of torsional strain in supercoiled DNA during replication. The enzyme alters the conformation of DNA through a concerted breaking and rejoining of both DNA strands (**Scheme 1**). Evidences have suggested that topoisomerase II inhibitors prevent the rejoining of the DNA strands, leading to DNA cleavage and ultimately apoptosis.¹⁰

Scheme 1. Proposed mechanism of topoisomerase II action

Furthermore, *in vitro* studies have shown that streptonigrin promotes the formation of oxygen radicals through an initial single electron reduction of the quinone system by NADPH, followed by the transfer of the single electron to molecular oxygen to generate superoxide radicals.¹¹ As a consequence of its ability to undergo bioreduction, streptonigrin interferes with oxidative phosphorylation, causing a substantial depletion of cellular ATP.¹² In addition, both **1** and **2** are inhibitors of NO-dependent activation of

human platelet guanylyl cyclase, an important enzyme involved in intracellular signaling pathways.¹³ Lastly, streptonigrin is a strong inhibitor of reverse transcriptase, an enzyme found only in retroviruses such as HIV, and an essential component of the replication machinery of such viral species.¹⁴

Clinical trials of streptonigrin in humans have revealed severe side effects that limit application in cancer treatment.¹⁵ Nevertheless, significant medicinal chemistry research focusing on **1** continues to this date.¹⁶ Results from those studies indicated that the quinoline-quinone fragment (A and B rings), which is identical in both streptonigrin and streptonigrone, is an essential pharmacophore of streptonigrinoids.¹⁶ This renders streptonigrone an interesting target for both synthetic and pharmacological investigations.

1.2 Previous syntheses

Since the determination of the structure of streptonigrin, the namesake of the family, by Woodward and collaborators in 1963,² streptonigrinoids have generated intense efforts in the synthetic arena.⁴ Interest in these molecules is motivated not only by their noteworthy biological properties, but also by their intricate and highly functionalized structures. Initial synthetic studies were mainly focused on the synthesis of the quinoline-5,8-quinone (AB rings) segment as a standalone model system. In 1965, Kametani and coworkers reported a synthesis of the fully functionalized quinoline quinone **8** via a classical Skraup quinoline synthesis, as outlined in **Scheme 2**.¹⁷ Methoxylation and reduction of bromodinitrophenol **4** afforded aniline **5**, which was advanced to quinoline **7** upon treatment with glycerol under acidic conditions.

Deprotection of the methyl ethers by HBr furnished the complete AB ring system of streptonigrone.

a. aq. NaOH (71%); b. Me_2SO_4 , K_2CO_3 , PhNO_2 , 130°C (68%);
 c. Fe, aq. HCl, EtOH (76%); d. As_2O_5 , H_2SO_4 , 160°C (9%);
 e. aq. HBr, 100°C (87%)

Scheme 2. Kametani's synthesis of the AB ring segment

In 1967, Liao and collaborators also completed a synthesis of the AB ring fragment using Skraup technology.^{18,19} This entailed the merger of nitroaniline **9** and acrolein to access the quinoline core of streptonigrin (**Scheme 3**). However, due to the

a. acrolein, H_2SO_4 , As_2O_5 , H_2O (42%); b. HNO_3 (no details given); c. H_2 , PtO_2 (no details given); d. $\text{Na}_2\text{Cr}_2\text{O}_7$, H_2SO_4 , CHCl_3 (60%); e. Br_2 (no details given);
 f. NaN_3 , aq. EtOH, RT (100%); g. H_2 , PtO_2 , MeOH, RT (no yield given)

Scheme 3. Liao's synthesis of the AB ring segment

lack of a handle for further elaboration, the resultant quinolines from those early works were synthetic dead ends for the total synthesis of streptonigrinoids.

It was not until 1980 that the first total synthesis of streptonigrin was achieved by Weinreb and coworkers.²⁰ Since then, the synthesis of streptonigrin also has been accomplished in the research groups of Kende and Boger.^{21,22} Nevertheless, the work of Weinreb undeniably laid the groundwork for the later syntheses of streptonigrinoids.

1.2.1 The Weinreb synthesis of streptonigrin

Weinreb's approach relied on an imino Diels-Alder reaction to construct the CD rings of **2** (Scheme 4). Treatment of diene **13** with methoxyhydantoin **12** in refluxing xylenes furnished **14**, which was advanced to pyridine **15** in three steps. Installation of the C-ring amino group was then achieved through an elegant 10-step sequence involving a Polonovski oxidation,²³ a Sommelet-Hauser-type²⁴ [2,3]-sigmatropic rearrangement, and a Yamada-Curtius²⁵ reaction to reach **16**. Conversion of **16** to phosphonate **17** then set the stage for the assembly of the quinoline. A modified Friedländer²⁶ quinoline synthesis involving an initial Horner-Wadsworth-Emmons²⁷ coupling of **17** and **19**, followed by reductive cyclization and subsequent oxidation of the quinoline then afforded the complete carbon framework of **2**. The final functionalization of the quinone was achieved in three steps: iodination by IN_3 , displacement of iodide with NaN_3 and reduction of the azide by sodium dithionite. The Weinreb total synthesis of **2** was completed upon deprotection of the D ring benzyl ether by excess AlCl_3 and hydrolysis of the C ring ester.

Scheme 4. The Weinreb synthesis of streptonigrin

1.2.2 The Kende synthesis of streptonigrin

In parallel to Weinreb's approach, Kende's strategy towards streptonigrin focused on an early construction of the CD ring fragment, followed by a late stage assembly of the quinoline AB ring system through a modified Friedländer synthesis (**Scheme 5**).²¹ The construction of the CD ring system proceeded through a regioselective condensation of the known β -keto enamine **21**²⁸ with methyl acetoacetate (**20**) to provide the acylpyridone **22**. In contrast to Weinreb's Diels-Alder approach, this route led to a pyridone intermediate possessing a methyl ketone functionality, which served as a convenient precursor of the amino group. Elaboration of **22** to pyridine **23** then provided

a substrate suitable for a modified Friedländer quinoline synthesis. Condensation of pyridine **23** and imine **24** furnished the complete carbon framework of **2**. Advancement to streptonigrin was then accomplished through a route similar to that of Weinreb.

a. xylenes, reflux (97%); b. NaBH₄, THF, *i*-PrOH, RT (100%); c. PhPOCl₂, 170 °C (67%); d. CuCN, DMF, reflux (85%); e. MeMgBr, PhH, RT (83%); f. *t*-BuOK, PhMe, *t*-BuOH, reflux (90%); g. TFA, 0 °C (85%); h. HNO₃, CH₃NO₂, RT; i. Me₂SO₄, K₂CO₃, acetone, reflux (55% g-h); j. OsO₄, NMO, aq. acetone, *t*-BuOH, RT; k. NaIO₄, aq. dioxane, 80 °C (75% j-k); l. SeO₂, AcOH, reflux (74%); m. NaClO₂, H₂NSO₃H, NaOAc, aq. dioxane, RT (92%); n. AcCl, MeOH, RT (95%); o. DPPA, Et₃N, PhH, reflux then H₂O, reflux (43%); p. Na₂S₂O₄, THF, aq. MeOH, reflux (80%); q. Fremy's salt, aq. acetone, RT (92%)

Scheme 5. The Kende synthesis of streptonigrin

1.2.3 The Boger formal synthesis of streptonigrin

Boger's synthetic approach to **2** was based on the implementation of two consecutive inverse electron demand Diels-Alder reactions to construct the biaryl CD ring system.²² This innovative sequence began with the [4 + 2] merger of quinoline **29** and tetrazine **34** to give **30** (Scheme 6). Subsequent treatment of this intermediate with enamine **35** then provided a mixture of Diels-Alder adducts **31** and **32** in a 1 : 4 ratio, favoring the desired isomer. Advancement of **32** to the tetracyclic amine **27**, an intermediate in Kende's synthesis,²¹ completed the formal synthesis of **2**.

a. **34**, dioxane, 80 °C (82%); b. **35**, DCM, 6.2 kbar, RT (58% of **31** & **32**, 1:4);
c. NaSePh, THF-HMPA, 70 °C; d. aq. HCl, MeOH, RT; e. DPPA, Et₃N, PhH, reflux
(40% c-e); f. MeI, K₂CO₃, THF, 65 °C (94%)

Scheme 6. The Boger formal synthesis of streptonigrin

1.2.4 The Kende synthesis of lavendamycin methyl ester

The total synthesis of lavendamycin, the putative biosynthetic precursor of **1** and **2**,²⁹ was first completed by Kende and coworkers in 1984.³⁰ The highlight of their elegant biomimetic approach was the rapid assembly of the pentacyclic framework of **3** via a polyphosphate ester-catalyzed Bischler-Napieralski cyclodehydration of **38**, which was readily accessed through the coupling of quinoline **36** with β -methyltryptophan (Scheme 7). Elaboration of the resultant **39** to lavendamycin methyl ester (**40**) was then carried out in four steps using conventional transformations. Due to the poor solubility of the natural product in organic solvents, both synthetic and natural **3** were characterized as the methyl esters.

a. $\text{Me}_2\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NEt}$, DCM, RT (90%); b. PPE, 90 °C (31%);
c. $\text{Na}_2\text{S}_2\text{O}_4$, aq. THF-MeOH, reflux (70%); d. $\text{K}_2\text{Cr}_2\text{O}_7$, H_2SO_4 , H_2O , DCM, RT (50%);
e. NaN_3 , aq. THF, RT; f. $\text{Na}_2\text{S}_2\text{O}_4$, aq. THF-MeOH, reflux (30% e-f)

Scheme 7. The Kende synthesis of lavendamycin

1.2.5 The Boger synthesis of streptonigrone

To this day, the only published total synthesis of streptonigrone was accomplished by Boger and coworkers in 1993.³¹ Boger's strategy (Scheme 8) again relied on a

Friedländer reaction to assemble the quinoline AB ring system. However, the pyridone ring emerged through an inverse electron demand Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-butadiene **42** with ketene acetal **43**.

Scheme 8. Boger's retrosynthetic analysis of streptonigrone

Thus, 2-amino-3-benzyloxy-4-bromobenzaldehyde³² (**46**) was condensed with pyruvic acid to give the quinaldic acid **49**, which was then converted to the methyl ester (**Scheme 9**). This substance underwent cross-Claisen condensation with ethyl acetate, and the emerging **50** participated in a Knoevenagel condensation with the known 2-hydroxybenzaldehyde **44**.³³ The resultant was coumarin **51**, which was elaborated to *N*-sulfonyl-1-aza-butadiene **42** through a 3-step sequence. This set the stage for the inverse-demand Diels-Alder reaction with ketene acetal **43** to give the 2-methoxypyridine **41**. A 3-step deprotection-reprotection sequence then afforded carboxylic acid **52**, which was advanced to the corresponding amine **53** via a Yamada-Curtius²⁵ reaction (**Scheme 10**).

a. Br₂, AcOH, RT; b. HNO₃, AcOH, RT; c. HCl, MeOH, RT; d. NaH, BnBr, DMF (85% a-d); e. LiBH₄, THF, RT (93%); f. PDC, DCM, RT (83%); g. Na₂S₂O₄, aq. THF, reflux (93%); h. pyruvic acid, NaOH, MeOH, RT; i. HCl, MeOH, RT (85% h-i); j. LiCH₂CO₂Et, THF, -78°C (86%); k. **44**, cat. piperidine, EtOH, 80°C (81%); l. NH₂OH.HCl, EtOH, RT (53%); m. MeSOCl, Et₃N, DCM, RT (59%); n. 1,1-dimethoxy-1-propene, PhH, RT; o. *t*-BuOK, THF, -30°C; p. DDQ, DCM, RT (52% n-p).

Scheme 9. Boger's inverse demand Diels-Alder approach

Experiment revealed that *in situ* trapping of the Curtius isocyanate intermediate was ineffective. This was due to partial hydrolysis of the isocyanate to the corresponding amine, leading to a mixture of aminopyridone and carbamate derivative thereof. Our own experience confirmed this undesirable property of the isocyanate in question (*vide infra*). Accordingly, the isocyanate was hydrolyzed with aqueous LiOH to the corresponding amine, which was left unprotected during the remainder of the synthesis. The endgame involved Fremy's salt (potassium nitrosodisulfonate) oxidation of the quinoline, Lewis acid-catalyzed methoxylation to install the quinone methoxy substituent, and amination of the quinone through an azido intermediate. The final deprotection of the emerging **54** was then achieved by treatment with HBr under reducing condition to give streptonigrone in 23 linear steps from commercially available materials.

a. aq. LiOH, DMSO, 60 °C (89%); b. MOMCl, NaH, DMF, RT (92%); c. aq. LiOH, DMSO, 130 °C (80%);
 d. DPPA, Et₃N, PhH, reflux then aq. LiOH, THF, RT (84%); e. HBr, DCM, RT (80%);
 f. Fremy's salt, DCM, Bu₄NHSO₄, H₂O, RT (69%); g. Ti(O*i*-Pr)₄, NaOMe, THF, 0 °C;
 h. NaN₃, THF-H₂O, RT (85%); i. NaBH₄, MeOH, THF, RT (86%); j. HBr, Pd-C, H₂, CF₃CH₂OH, 80 °C
 (no yield given)

Scheme 10. Boger's synthesis of streptonigrone

1.3 Background on pyridone synthesis

The foregoing discussion suggests that the assembly of a fully substituted C-ring constitutes the key strategic aspect of any attack on streptonigrinoids. It is also apparent that in the context of streptonigrone, the construction of that pyridone unit is a challenging endeavor that tests the limits of pyridone-forming reactions. Indeed, very few methods for pyridone synthesis have proven capable of addressing that problem. In the next few paragraphs, we shall review some common techniques for the synthesis of pyridones, concluding with a method developed by Ciufolini and coworkers that constitutes the central feature of our own synthesis of **1**.

1.3.1 Common methods for pyridone synthesis

The synthesis of 2-pyridones has generated vast interest from both synthetic and medicinal chemists due to the prominent presence of pyridones in biologically active molecules.^{34,35} Examples of such molecules include natural products such as (+)-camptothecin (**55**, antitumor agent),³⁶ pyridone L-697,661 (**56**, HIV reverse transcriptase inhibitor),³⁷ and leporine A (**57**, insecticide),³⁸ as well as drugs like milrinone (**58**, cardiotonic drug for CHF)³⁹ and ABT-719 (**59**, antimicrobial agent).⁴⁰

Figure 2. Pyridone-containing natural products and pharmaceuticals

Strategies for the synthesis of 2-pyridones can be generalized into three main categories: (i) modification of preexisting heterocycles, most notably from pyridines, (ii) cyclization of an acyclic system, or (iii) fusion of two or more acyclic fragments.⁴¹

Manipulation of pyridines has long been recognized as a convenient avenue to 2-pyridones.^{34,41} For instance, conversion of 2-unsubstituted pyridines to pyridones can be accomplished by a Polonovski-type oxidation via a pyridine *N*-oxide intermediate

(Scheme 11). Similarly, 2-pyridones can be accessed through hydrolysis of 2-halopyridines, which in turn, can be obtained from a pyridine *N*-oxide. This approach was exemplified in Kametani's synthesis of camptothecin analogues where pyridone **65** served as a central synthetic intermediate (Scheme 12).⁴²

Scheme 11. Polonovski rearrangement

a. POCl₃, HCl, CH₃Cl, 80 °C (69%); b. aq. HCl, 180 °C (no yield given)

Scheme 12. Synthesis of pyridone via 2-chloropyridine

Construction of 2-pyridones via cyclization of linear system can be found in many natural product syntheses. For example, in David Williams' work on tenellin⁴³ and illicicolin H,⁴⁴ a Dieckmann condensation of **67**, followed by oxidation of the resulting dihydropyridone **68** smoothly afforded the protected 2-pyridone core **69** (Scheme 13). Another example of pyridone-forming cyclization can be found in the total synthesis of nothapodytine B (**74**) by Greene and coworkers.⁴⁵ In contrast to Williams' approach, Greene's relied on tandem intramolecular Michael reactions to establish the framework of the central pyridone as part of the tetracyclic system of **74** (Scheme 14). Decarboxylative oxidation of the resulting dihydropyridone (**73**) was then accomplished

a. LiOH, THF-H₂O, RT (99%); b. CDI, THF; c. NaH, THF, RT (91% b-c); d. chloranil, PhEt, reflux (85%)

Scheme 13. Williams' synthesis of ilicicolin

by a basic hydrolysis, followed by treatment with palladium on carbon in refluxing *p*-cymene to furnish **74**. Despite the elegant synthetic planning displayed in both of those examples, it could be argued that accessing pyridones via cyclization of linear systems requires considerable linear operations and lacks the flexibility required for SAR studies.

a. TBDMSOTf, Et₃N, DCM, RT (84%); b. O₃, DCM, -78 °C then DMS (60%)
c. aq. NaOH, MeOH, DCM, RT.; d. Pd-C, *p*-cymene, reflux (60% c-d)

Scheme 14. Greene's synthesis of nothaptydine B

In contrast to the preceding approaches that involved C-C bond formation, cyclization of linear systems of 1,5-dicarbonyl compounds involving C-N bond construction is also common in the synthesis of simple pyridones (**Scheme 15**).^{34,41} For instance, reaction of glutaconic acid (**75**) with ammonia or derivatives efficiently provided 6-hydroxyl-2-pyridones (**76**).⁴⁶ Likewise, condensation between 2-acetylglutarate derivatives (**77**) and ammonium acetate provided 3,4-dihydropyridone **78**,⁴⁷ which could be oxidized to the corresponding pyridone **79** (**Scheme 16**).³⁴ The use of this approach, however, has been mostly limited to the synthesis of simple pyridones, since the construction of the requisite 1,5-dicarbonyl compounds often involves a Michael-type reaction, which, incidentally, corresponds to the initial step of the [3 + 3] annulation approach to pyridones (*vide infra*).⁴¹ Thus, unless the required 1,5-dicarbonyl substrate is readily accessible, the [3 + 3] strategy is often preferred.

Scheme 15. Synthesis of pyridones from glutaconic acid

Scheme 16. Synthesis of pyridones from 1,5-dicarbonyl

The [3 + 3] merger of a 1,3-dinucleophile and a 1,3-dielectrophile arguably can be considered as the most popular avenue to 2-pyridones.³⁴ For example, it is long-

recognized that reactions of 1,3-diketones with cyanoacetamide or malonitrile, in the presence of catalytic base, efficiently afford 3-cyanopyridones. An especially significant application of this process may be found in a 1939 Merck & Co. synthesis of vitamin B₆, **83**, a key step in which was a piperidine-catalyzed condensation of **80** with **81** to provide pyridone **82** as a key intermediate (Scheme 17).⁴⁸

Scheme 17. Synthesis of vitamin B₆

Alternatively, 2-pyridones can also be accessed through the merger of an enecarbonyl compound and cyanoacetamide or malonitrile (Scheme 18).⁴¹ Mechanistically, such [3 + 3] annulations generally involve an initial Michael addition of the activated methylene compound (**85**) to give an acyclic adduct (**86**), which undergoes dehydration to furnish the corresponding 3,4-dihydropyridone **87**. Oxidative aromatization of the dihydropyridone then affords the 3-cyanopyridone **88**. Unsurprisingly, numerous permutations of this general method involving different oxidants have been developed. For instance, DDQ,⁴⁹ nitric acid⁵⁰ and FeCl₃⁵¹ have all been demonstrated to be effective.

Scheme 18. [3 + 3] annulation

Alternatively, incorporation of a leaving group, such as benzotriazole⁵² or pyridine,⁵³ on the nucleophile, allows the final aromatization to occur via an eliminative pathway; that is, in the absence of an oxidant (**Scheme 19**). Similarly, the presence of a potential leaving group in the β -position of the enecarbonyl also facilitates aromatization (**Scheme 20**).^{54,55}

Scheme 19. Aromatization via expulsion of leaving group on nucleophile

Scheme 20. Aromatization via expulsion of leaving group on electrophile

An example of a pyridone-forming [3 + 3] annulation applied in natural product total synthesis can be found in Danishefsky's work on camptothecin (**Scheme 21**).⁵⁵ To access the central pyridone of camptothecin, enamine **97** was treated with chloroglutaconate **98** in the presence of Et₃N to give pyridone **99**.

Scheme 21. Danishefsky's approach toward camptothecin

1.3.2 A convenient pyridone synthesis developed in our laboratory

Building on the classical [3 + 3] annulation protocols, experiments in our laboratory revealed that the merger of an active methylene compound, such as cyanoacetamide, with an enone to yield a pyridone may be accomplished as a one-pot operation.^{56,57} Depending on precise reaction conditions, the process affords either 3-cyanopyridones, 3-unsubstituted pyridones or 3-alkylpyridones (**Scheme 22**).

Scheme 22. A convenient pyridone synthesis developed in our laboratory

This “tunable” reaction is believed to proceed (**Scheme 23**) via an initial *t*-BuOK-catalyzed Michael addition of the anion of cyanoacetamide to an enone to give an adduct such as **105** as an isolable compound. However, when operating at elevated temperatures (90-100 °C), the Michael adduct undergoes a base-catalyzed dehydration *in situ* to generate anions **106** ($\text{R}^4 = \text{H}$) or **110** ($\text{R}^4 = \text{alkyl}$). When an α -unsubstituted cyanoacetamide ($\text{R}^4 = \text{H}$) is used, the strongly basic environment promotes formation of dianion **107**. In presence of oxygen, this intermediate is oxidized to a 3-cyanopyridone **103**. It was proposed that the oxidation proceeds via a single electron transfer to molecular oxygen and subsequent formal loss of a hydrogen atom. On the other hand, in the absence of oxygen, 3-unsubstituted pyridone **102** emerges as the major product. Mechanistically, it was envisioned that the strongly basic reaction conditions⁵⁸ facilitate an equilibration between the initially formed dianion **107** with the isomeric **108**. Expulsion of cyanide ion then furnishes the anion of unsubstituted pyridone **102**, which is ultimately protonated following an acidic aqueous workup. The absence of oxygen is especially critical for the establishment of this equilibrium, since the oxidation of **107** by O_2 appears to be quite fast. Likewise, in cases where R^4 is alkyl, the corresponding anion **110** undergoes a “decyanidative aromatization” to yield 3-alkylpyridones **104**. It should be noted that this reaction embodies one of a very limited number of techniques for the

Scheme 23. The pyridone synthesis developed in our laboratory

direct assembly of 3-alkylpyridones, which are often difficult to access.^{52, 57, 59}

Significantly, variants of the Thiesing-Muller reaction⁵³ involving pyridinium ylides **112**

or sulfonyl substituted amides **113** (**Scheme 24**) failed to reach 3-alkyl pyridones.⁶⁰

Scheme 24. Attempted formations of 3-alkylpyridones

An application of this technology was initially sought in connection with our group's synthesis of (+)-camptothecin (**55**).^{60,61} To this end, it was envisioned that construction the pyridone ring of **55** could be achieved through the condensation of enone **114** and α -cyanoacetamide under aerobic conditions. However, an unexpected radical fragmentation of reactive intermediate **115** (Scheme 25) prevented the implementation of this strategy. Ultimately, this obstacle was circumvented through the oxidation of Michael adduct **117** with SeO_2 (Scheme 26). The resultant pyridone **118** was then advanced to (+)-camptothecin in a straightforward fashion.

Scheme 25. Radical fragmentation

Scheme 26. The Ciufolini total synthesis of camptothecin

A more successful application of the direct synthesis of 3-alkylpyridones is apparent in our group's synthesis of nothapodytine B (**74**).⁵⁷ Akin to the work on camptothecin, it was envisioned that the central pyridone could be assembled through the condensation of enone **120** and 2-cyanopropionamide (**Scheme 27**). However, due to the incompatibility of the 1,2-diacylethylene functionality of **120** with an excess of *t*-BuOK, the pyridone-forming reaction was performed with a modification to the above procedure. Treatment of **120** with 2-cyanopropionamide and DBU in pyridine furnished the Michael adduct **122** (**Scheme 28**). Subsequent *in situ* dehydration and decyanidation were then

Scheme 27. Retrosynthesis of nothapodytine B

triggered by the addition of acetic anhydride and heating to afford the *O*-acetyl derivatives of the pyridone (**123** and **124**). Treatment of the mixture with HBr in CF₃CH₂OH smoothly affected the deprotection and *N*-alkylation of the pyridone to furnish totally synthetic nothapodytine B.

a. 2-cyanopropionamide, pyridine, DBU, 80 °C; b. Ac_2O , 80 °C
(50% of **123** and **124** a-b); c. HBr, $\text{CF}_3\text{CH}_2\text{OH}$, RT (91%)

Scheme 28. The Ciufolini total synthesis of nothapodytine B

2. TOTAL SYNTHESIS OF STREPTONIGRONE

2.1 Retrosynthetic analysis

Encouraged by the successful implementation of our 3-alkylpyridone synthesis in the effort leading to nothapodytine B,⁵⁷ we envisioned that a similar strategy could be employed to assemble the central pyridone ring of the considerably more challenging natural product, streptonigrone. To that end, enone **126** would be required as a substrate for the pyridone-forming reaction. Substituent X and Z represent precursors of an amino group. Their precise identity would have to be determined through model studies. Regardless, compound **126** is available through the condensation of quinoline ketone **128** with aldehyde **127**⁶² (Scheme 29). Accordingly, the synthesis of quinoline ester **129** embodies the first sub-goal of our venture.

Scheme 29. Retrosynthetic analysis

2.2 Quinoline Synthesis

Despite the existence of numerous methods for the preparation of quinolines,⁶³ all the previous syntheses of streptonigrinoids have employed a Friedländer²⁶ quinoline construction.^{20-22,31-32} This is no accident: the substitution pattern of the quinoline quinone segment of streptonigrinoids creates requirements and limitations that only a limited number of quinoline-forming techniques are capable of satisfying. The Friedländer reaction is one of these. Even so, the Friedländer reaction can become problematic with substituted aminoaldehydes. In fact, in the work of Weinreb and Kende, “strictly defined” reaction conditions were required for the Friedländer-type cyclization to succeed.^{20,21} Furthermore, 2-aminobenzaldehydes carrying substituents at position 6 (cf. **R**⁶ in **130**, **Scheme 30**) react poorly.^{26,32} The substituent in question ultimately becomes the C-5 oxygen functionality of the final quinone of **132**. The inability to carry this functionality through the synthesis from the beginning translates into a requirement for a number of late steps to adjust the substitution pattern and oxidation state of the quinoline.

Scheme 30. Friedländer quinoline synthesis

On the other hand, no syntheses of streptonigrinoids have yet evolved from a quinoline precursor that incorporates the ultimate **NH₂** group in **132** either in a latent or in an expressed form. Indeed, the **NH₂** group in question has always been introduced during

the final stages of the syntheses.^{20-22,31} It would seem that it is difficult to devise a suitable protection scheme for intermediates incorporating the amino functionality in question. Also, these intermediates may be too reactive and difficult to advance through the synthesis. The number of operations that would then be necessary to introduce and protect an NH₂ group (or equivalent) at an early stage becomes too numerous relative to the sequence necessary to introduce that functionality later on.

Scheme 31. Hypothetical Friedländer reaction

In light of the foregoing, and in an effort to reach a quinoline carrying the largest possible number of appropriate substituents at an early stage, we avoided the Friedländer construction delineated in **Scheme 31**, opting instead to employ a Conrad-Limpach reaction⁶⁴ to gain access to **129** (**Scheme 32**). Thus, the commercially available 1,2,4-trimethoxybenzene (**136**) was nitrated regioselectively and then reduced under standard conditions to give aniline **137**. Enamino-ester **138** was readily obtained following treatment with dimethyl acetylenedicarboxylate. Thermolysis in diphenyl ether then afforded quinolone **139**. The thermal cyclization has been proposed to proceed through a 6π electrocyclic mechanism as depicted in **Scheme 33**.⁶⁵

a. HNO_3 , AcOH , RT (63%); b. H_2 , Pd-C, MeOH, RT (quant.); c. dimethyl acetylenedicarboxylate, MeOH, 60 °C (58%); d. Ph_2O , reflux (86%); e. POCl_3 , PhH, RT (88%); f. H_2 , Pd-C, Et_3N , EtOAc, RT (quant.)

Scheme 32. Conrad-Limpach synthesis

Scheme 33. Cyclization mechanism

Treatment of **139** with phosphorous oxychloride, followed by catalytic hydrogenolysis, efficiently afforded the key quinoline ester **129**. It is noteworthy that the reduction of chloroquinoline **140** by catalytic hydrogenation was somewhat problematic. Initial experiments involving the customary exposure of **140** to a hydrogen atmosphere in the presence of palladium on activated carbon, either in methanol, ethanol, or ethyl acetate, resulted in overreduction of the pyridine moiety, in spite of close monitoring of the reaction (**Scheme 34**). It soon transpired that the addition of a base, such as triethylamine, suppressed that undesirable side reaction. We thus presume that

overreduction was due to activation of the pyridine segment toward hydrogenation through protonation of the quinoline by the hydrochloric acid liberated during the reaction. The external base reacts preferentially with HCl, avoiding quinoline protonation and thereby preventing overreduction.

Scheme 34. Manipulation of chloroquinoline **140**

Because **140** was destined to undergo hydrogenolysis to the desired **129**, it seemed that introduction of a nitro group at position 7 (quinoline numbering) prior to reduction might ultimately provide a 7-aminoquinoline possessing all the ring-A substituents required for streptonigrone. Nitration of **140** was therefore attempted under various conditions. Unfortunately, all such attempts met with failure. In most cases, only oxidation of the quinoline to the corresponding quinone (**145**) was observed.

2.3 Synthesis of Aldehyde 127

The preparation of the known aldehyde **127**⁶² commenced with a regioselective demethylation of 2,3,4-trimethoxybenzaldehyde (**146**) by AlCl_3 in refluxing benzene to give the 2-hydroxylaldehyde **44**.^{33,66} Reprotection of the phenol with benzyl bromide and K_2CO_3 in DMF efficiently afforded the desired **127** in excellent yields. The regiochemical course of the demethylation reaction has been rationalized on the basis of chelation of the aluminum(III) atom between the carbonyl oxygen and the *ortho*-methoxy oxygen (cf. **149**, Scheme 35).³³

a. AlCl_3 , PhH, reflux (98%); b. BnBr , K_2CO_3 , DMF, RT (98%)

Scheme 35. Synthesis of aldehyde **127**

2.4 Model studies

Again in the interest of minimizing late-stage operations, we wished to convert ester **129** into a suitably functionalized ketone **128**, wherein group Z represents a precursor of an amino group. Subsequent condensation of ketone **128** with aldehyde **127** was anticipated to furnish enone **150**, which would then participate in our pyridone-forming reaction, leading to a fully functionalized pyridone **151** (Scheme 36). At this

juncture, model studies were required to define the nature of Z. Initial experiments focused on intermediates where Z = COOR, CN, or NO₂.

Scheme 36. Model studies

Quinoline ketones **153-155**⁶⁷ were synthesized according to **Scheme 37** and subsequently condensed with benzaldehyde or its derivatives. All such attempted Knoevenagel reactions resulted in the formation of indolizines **156-158**, instead of the expected benzylidene derivatives **161** (**Scheme 38**). Similarly, the substituted quinoline ketone **159** provided indolizine **160** when treated with aldehyde **127** under identical conditions. Not unexpectedly, all such indolizines proved to be air-sensitive, turning from

a. MeOH, HCl, MeOH, RT (82%) b. EtOAc, *t*-BuOK, RT (98%); c. CH₃CN, *t*-BuOK, RT (54%);
d. CDI, THF then CH₃NO₂, *t*-BuOK, RT (61%)

Scheme 37. Preparation of model quinolines

bright yellow to dark brown over a period of time upon exposure to the atmosphere. It is worthy to note that the more electron-rich indolizine **160** was much more prone to degradation than its less substituted, electron-poor analogs. Thus, significant darkening occurred after several hours at room temperature, while **156** was stable for days at room temperature.

Scheme 38. Formation of indolizines

The formation of the indolizines can be rationalized as being the result of an *in situ* aza-Nazarov cyclization of the Z-isomer of the initially formed enone **163** (**Scheme 39**). Upon protonation of the enone carbonyl, the system is poised to undergo a 4 π -electron conrotatory electrocyclozation. Subsequent deprotonation of presumed intermediate **165** leads to the product.

Scheme 39. Aza-Nazarov cyclization

The structural assignment of the indolizines was based on the results of several spectroscopic experiments. No carbonyl resonance was observed in the ^{13}C NMR spectrum of the products. Their ^1H NMR spectra exhibited a resonance at *ca.* 8.5 ppm, accounting for one proton, which was found to be exchangeable with D_2O . Heteronuclear NMR correlation spectra ($^1\text{H}/^{13}\text{C}$ HMQC experiments) revealed that the exchangeable proton displayed no correlations to C atoms, indicating that the proton was not directly bonded to any carbon atom. These properties suggested that the proton in question belonged to a hydroxyl functionality (**Figure 3**). Those observations ruled out benzyldiene structures **161**, which possess no exchangeable protons, and in which all protons are directly attached to a carbon atom. Furthermore, the exchangeable proton displayed three $^1\text{H}/^{13}\text{C}$ correlations in the $^1\text{H}/^{13}\text{C}$ HMBC spectrum, as expected for the indolizine structure. It is also noteworthy that treatment of the indolizines with 2-cyanopropionamide under our pyridone-forming conditions did not provide any of the

corresponding pyridone, signaling that the indolizines do not equilibrate with the corresponding enones under the reaction conditions.

Figure 3. HMBC correlations

A similar aza-Nazarov cyclization was previously observed in our laboratory during work on camptothecin.⁶⁰ However, in that case the reaction occurred only in benzyloxy systems **167**, and it required the catalytic action of Lewis acids such as lanthanide diketonates. Cyclization was attributed to activation of the carbonyl function through chelation of the lanthanide ion as shown in **Scheme 40**. Its occurrence in our current system remained surprising not only because of the mildness of the Knoevenagel conditions, but also because of a close precedent described by Boger in connection with

Scheme 40. Previously observed aza-Nazarov cyclization

his synthesis of streptonigrone.³¹ In their work, ketone **50** and aldehyde **44** condensed uneventfully to give coumarin **51** (**Scheme 41**). Seemingly, neither **51** nor its presumed forerunner **171** exhibited any propensity to cyclize to indolizines **172-173**.

Scheme 41. Boger's approach to streptonigrone

A possible explanation for the reluctance of **51** and **171** to cyclise may be found in the severe nonbonded interaction that develops as a result of steric compression between the benzyloxy substituent and the aryl residue in indolizines **172-173** (dashed semicircles in **Scheme 41**). This being the case, we reasoned that methoxy-substituted quinoline **159** may condense successfully with **44** to furnish **175**. This coumarin, being a potential Michael acceptor, may well be capable of engaging 2-cyanopropionamide in our pyridone-forming reaction. In our hands, however, the condensation between quinoline ketone **159** and aldehyde **44** produced only a meager 10% yield of coumarin **175** as a component of a largely intractable mixture (**Scheme 42**). We hypothesized that, akin to the above reactions, the predominant product of this condensation was the sensitive,

electron-rich indolizine **174**, which decomposed readily in the presence of oxygen. A simple comparison between the results from our experiments and those of Boger evidently suggested that the propensity of the aza-Nazarov cyclization to occur is greatly dependent on sterics: whereas a benzyloxy group (*cf.* **50**) is sufficiently encumbered to block indolizine formation, the steric demand of a methoxy group (*cf.* **159**) is inadequate to suppress cyclization. In addition, coumarin **175** was not a substrate for our pyridone-forming reaction. This may be due possibly to the reduced Michael-type reactivity of the aromatic coumarin system.

Scheme 42. Coumarin synthesis

Continuing efforts to obtain a substrate of the type **161** led us to explore a Conrad-Limpach synthesis of the benzyl-protected quinoline **183**, hoping that the increased steric bulk at the C-8 position (quinoline numbering) might suppress indolizine formation. Benzylation of the commercially available 2-methylhydroquinone (**177**)

followed by a standard nitration provided nitrobenzene **178** (Scheme 43). To avoid cleavage of the benzyl ethers, the subsequent reduction of the nitrobenzene was achieved with zinc and aqueous HCl, instead of catalytic hydrogenation. Aniline **179** reacted normally with dimethyl acetylenedicarboxylate to afford **180**. Unfortunately, the key thermolytic cyclization step in the Conrad-Limpach quinoline synthesis now furnished only an intractable mixture containing none of the desired **182**. This failure was possibly due to an unfavourable steric interaction engendered by the future C-5 (quinoline numbering) OBn substituent (*cf.* **181**).

Scheme 43. Attempted synthesis of the benzyl protected quinoline

Although experiment suggested that the propensity of intermediates **163** to undergo aza-Nazarov cyclization was quite sensitive to sterics, we also felt that the presence of an electron withdrawing group, such as an ester or nitrile, at the α position of enones **163** was biasing the system towards cyclization. In fact, such electron-withdrawing substituents may be anticipated to lower the energy of the LUMO of the

enone segment, bringing it closer to the energy of the HOMO of the neighbouring imino linkage (the lone pair on the N atom). This facilitates cyclization. Conversely, the

Scheme 44. Attempted synthesis of aminoketones

presence of an electron-releasing functionality, such as a protected amine, might raise the LUMO energy and disfavor indolizine formation. The preparation of such enones required aminoketones **185-186**, the synthesis of which, unfortunately, proved to be everything but straightforward. For instance, the Claisen-type condensation of protected glycine **184** with activated quinaldic acid **152** (**Scheme 44**) was unsuccessful (complex

* No reaction with: (a) Br_2 , CHCl_3 , RT; (b) NBS, NH_4OAc , CCl_4 , 80 °C; (c) CuBr_2 , CHCl_3 , reflux
 Overbromination with no desired product with: (a) Br_2 , AcOH, RT; (b) Br_2 , AcOH, dioxane, RT; (c) Pyridium tribromide, AcOH, RT.

Scheme 45. Attempted bromination of the quinoline methyl ketone

mixtures, no desired product). Reduction of nitroketone **155** to the corresponding aminoketone was also problematic and poor yielding. Introduction of the amino group via an intermediate bromide was also fruitless, due to complications experienced during the direct bromination of methyl ketone **187** (Scheme 45). Limited success was observed in attempts to access the bromoketone **190** via a diazoketone intermediate **189** (Scheme 46). However, the subsequent displacement by a nitrogen nucleophile, such as azide ion or methanesulfonamide, was unsuccessful (again, complex mixtures). Due to the failure encountered on this front and the encouraging results from the acetylquinoline experiments (*vide infra*), this route was abandoned in favour of the construction of a pyridone lacking a substituent at position 5.

Scheme 46. Synthesis of aminoketone via diazo intermediate

Initial model work focused on enone **193**. Thus, 2-acetylquinoline⁶⁸ (**192**) was uneventfully condensed with benzaldehyde in the presence of aqueous NaOH solution to give enone **193**,⁶⁹ which efficiently combined with 2-cyanopropionamide ($t\text{-BuOK}$, DMSO , $95\text{ }^\circ\text{C}$) to furnish pyridone **194** in essentially quantitative yield (Scheme 47). The

Scheme 47. Pyridone synthesis model studies

latter compound served as a convenient model for the installation of the 5-amino functionality through a novel reaction sequence. Indeed, reaction of **194** with iodine monochloride and K_2CO_3 in DMF resulted in smooth iodination to give iodopyridone **195** (Scheme 48). We note that **194** was recovered unchanged after exposure to the less reactive I_2 or even *N*-iodosuccinimide (NIS). Iodopyridone **195** was thermally sensitive, but *O*-methylation (Ag_2CO_3 , MeI) yielded the stable methoxypyridine **196**. It is noteworthy that the use of Meerwein's salt (trimethyloxonium tetrafluoroborate) as the methylating agent resulted in overmethylation.

Scheme 48. Preparation of iodopyridine

In principle, the iodo substituent in **196** is amenable to displacement with appropriate nitrogen nucleophiles. Whereas such a substitution reaction normally requires transition metal catalysts (Cu, Pd, etc.), the carbon atom bearing the iodine in **196** is in

direct conjugation with the electron-withdrawing quinoline ring. The halogen is thus poised for substitution via an S_NAr mechanism (**Scheme 49**). However, attempts to induce direct displacement with nitrogen nucleophiles, such as ammonia, ammonium hydroxide, benzylamine, *p*-methoxybenzylamine and sodium amide,⁷⁰ were all unproductive. Traces of 5-aminopyridone (**198** where Nu = NH₂) were obtained when iodopyridine **196** was treated with ammonium hydroxide in the presence of cupric sulphate at 135 °C in a sealed tube for 24 h,⁷¹ but the reaction was not synthetically useful.

Scheme 49. S_NAr mechanism

Alternatively, installation of the amino group through Pd(0) or Cu(I) promoted Buchwald-type couplings was investigated.⁷² However, experiments with a number of different ligands and nucleophiles, under various reaction conditions, failed to produce the desired aminopyridine. For example, treatment of **196** with Pd(OAc)₂ and BnNH₂, a typical amine nucleophile for Buchwald couplings, in the presence of *t*-BuONa or Cs₂CO₃ as the base and **199**, **200** or **201** as the ligands, provided an intractable mixture of products. Similarly, coupling using a catalyst system generated from ethylene glycol and copper(I) iodide⁷³ failed to give the desired product. Due to unfavourable steric interactions, coupling reactions involving simple *ortho*-substituted aryl halides are known to proceed in considerably poorer yields than their *ortho*-unsubstituted counterparts.^{72,74}

Thus, the difficulties encountered with our system may be attributed to severe steric hindrance around the iodo substituent, which is flanked by two bulky aryl systems. Bulky ligands such as **199-201** may well exacerbate this problem. However, coupling reactions performed with the Fukuyama ligand-free system (CuI, CsOAc, DMSO, 90 °C)⁷⁴ also failed to provide the desired product.

Figure 4. Ligands for Buchwald couplings

The failure of **196** to participate in nucleophilic substitution reactions led us to investigate the possibility of employing the iodopyridine moiety to engender nucleophilicity at C-5. To that end, an initial metal-halogen exchange would generate a reactive organometallic species, which could be trapped with a suitable electrophile amenable to elaboration into the ultimate amine. This objective was achieved through a two-step sequence. Reaction of **196** with *n*-butyllithium and trapping of the intermediate aryllithium species with dry carbon dioxide yielded carboxylic acid **203** (Scheme 50). This substance is a plausible substrate for a Curtius-type rearrangement²⁵ leading to the requisite aminopyridone. Such a reaction was not attempted on substrate **203**, but it proved to be quite successful with an actual synthetic intermediate (*vide infra*).

Scheme 50. Carboxylation of pyridine

The foregoing discussion focuses largely on the successful avenue to a functionalized pyridone. It should be stressed that a number of alternative pathways were investigated, which regrettably turned out to be synthetic dead ends. For instance, drawing on Danishefsky's work on camptothecin,⁵⁵ the 5-unsubstituted pyridone **194** was treated with formaldehyde under acidic conditions in hope of introducing a hydroxymethyl group as a precursor of a carboxylic acid and ultimately, an amino group (**Scheme 51**). However, no reaction was observed, possibly due to the hindered nature of the C-5 position in **194**. Direct introduction of a nitrogenous functionality through reaction of **194** with azodicarboxylate esters, according to a protocol developed by LeBlanc and collaborators at Merck Frosst Canada,⁷⁵ also met with failure.

Scheme 51. Derivatization of pyridone

Attempts to functionalize C-5 in **194** under basic conditions fared no better. It was envisioned that upon *N*-deprotonation a partial negative charge would arise at the desired 5-position of the pyridone, permitting reaction with appropriate electrophiles. The functionality thus introduced might then be elaborated to an ultimate amino group (**Scheme 52**). However, deprotonation with NaH or K₂CO₃ and subsequent trapping with

Scheme 52. Derivatization of pyridone under basic condition

formaldehyde, azodicarboxylate esters or methyl cyanoformate proved fruitless. These disappointing results induced us to focus a final attack based on the chemistry of **Scheme 50**.

2.5 Synthesis of streptonigrone

Armed with the technology to access the elusive aminopyridone, attention was focused on the total synthesis of streptonigrone. Thus, acetylquinoline **187** was obtained through a Claisen condensation of quinoline ester **129** with ethyl acetate, followed by an acid catalyzed hydrolytic decarboxylation (**Scheme 53**). In accord with our model studies,

a. EtOAc, NaH, PhMe, reflux; b. aq. HCl, dioxane, 70 °C (78% a-b); c. **127**, aq. NaOH, EtOH, RT (83%);
d. 2-cyanopropionamide, *t*-BuOK, DMSO, 100 °C (60%)

Scheme 53. Synthesis of tetracyclic core

aldol condensation of ketone **187** with aldehyde **127** furnished chalcone **207**. The stage was then set for the pyridone synthesis outlined earlier. Treatment of **207** with 2-cyanopropionamide and potassium *tert*-butoxide in DMSO afforded pyridone **208** in 60% yield after chromatography. Iodination using ICl, in the presence of potassium carbonate in DMF yielded iodopyridone **209**, a sensitive compound, which was immediately protected as the benzyloxypyridine **210** by treatment with silver carbonate and benzyl bromide (Scheme 54).

a. ICl, K₂CO₃, DMF, RT; b. BnBr, Ag₂CO₃, PhH, RT (36% overall)

Scheme 54. Preparation of iodopyridine

The two-step sequence of metal-halogen exchange followed by CO₂ trapping performed admirably in the real system, leading to carboxylic acid **211** (Scheme 55). The acid was advanced to the corresponding amine via a Yamada-Curtius rearrangement.²⁵ In accord with the observations reported by Boger,³¹ *in situ* capture of the isocyanate intermediate by either *tert*-butyl alcohol or benzyl alcohol was less effective (possibly due to severe steric hindrance), providing variable quantities of the free amine in addition to the desired carbamate. Thus, formation of the carbamate was best achieved by LiOH-mediated hydrolysis of the isocyanate to the corresponding amine, followed by *N*-protection with benzyl chloroformate or di-*tert*-butyl dicarbonate.

Scheme 55. Preparation of aminopyridine

The next step of the synthesis entailed oxidation of **212-213** to quinolinoquinones **214-215**. In the Weinreb,²⁰ Kende,²¹ and Boger^{22,31} syntheses of streptonigrinoids, a free OH or NH₂ group is present on the quinoline at this stage. Such electron-rich substituents greatly facilitate quinone formation, which in all previous cases was carried out with Fremy's salt. By contrast, our intermediate exhibits only methyl ethers on ring A. We

therefore anticipated that a stronger oxidant would be required to effect the desired transformation in the present case. Indeed, treatment of **212** with mild oxidants, such as DDQ, left the compound untouched (**Scheme 56**). Attempted oxidation with the stronger Ag_2O / 70% aqueous HNO_3 combination resulted in decomposition of the material. Oxidation of **212** and **213** with CAN (ammonium cerium(IV) nitrate) in aqueous acetonitrile did afford the desired quinoline quinones **214** and **215**. However, the success of this oxidation was highly dependent on the protecting group present on the pyridinyl amine. Highest yields (93%) were obtained upon oxidation of an *N*-CBZ substrate, while BOC-protected intermediates reacted poorly. We attribute this to partial release of the *N*-blocking group during contact with the acidic CAN solution, resulting in the overoxidation of the liberated aminopyridine to a multitude of byproducts.

Scheme 56. Oxidation of quinoline

The successful oxidation of **213** to quinone **215** set the stage for the introduction of C-7 (quinoline numbering) amino group. In accord to the work of Weinreb,²⁰ quinone **215** was treated with IN_3 , prepared *in situ* from NaN_3 and ICl . This provided iodoquinone

216 (Scheme 57), a delicate intermediate which was immediately advanced to the light-sensitive azidoquinone **217** by reaction with sodium azide in aqueous THF with protection from light. Reduction of **217** with sodium dithionite in refluxing aqueous methanol afforded the protected streptonigrone **218**. By contrast, azide reduction with NaBH_4 ³¹ or by catalytic hydrogenation resulted in intractable mixtures.

Scheme 57. Functionalization of quinoline quinone

The final step in the total synthesis involved a global deprotection of **218**. Consistent with the observations of other researchers who have confronted streptonigrinoids in the past, this operation turned out to be nontrivial. To illustrate, Weinreb had to resort to the use of 458 equivalents of AlCl_3 to effect the debenzylation of **219** to **220 (Scheme 58)**.²⁰

Scheme 58. Weinreb's debenzylation of streptonigrin precursor

The Boger synthesis of streptonigrone required extensive experimentation at this stage, ultimately leading the Scripps chemists to reduce the quinone unit *in situ* (H_2 , Pd-C) prior to deprotection with HBr gas in $\text{CF}_3\text{CH}_2\text{OH}$ (Scheme 59).³¹

Scheme 59. Boger's deprotection of **54**

We rapidly determined that **218** was intolerant of large excesses of AlCl_3 , undergoing ether cleavage at various sites with this reagent, as well as partial conversion to high molecular weight byproducts. The same was true of BBr_3 or aqueous acids (conc. HCl , HBr). The carefully tailored Boger deblocking sequence failed to convert **218** to streptonigrone, resulting instead in loss of material. A modification of that procedure wherein the initial quinone reduction was effected with $\text{Na}_2\text{S}_2\text{O}_4$, instead of catalytic hydrogenation, provided a mixture of partially deblocked products. Attempts to achieve

complete deprotection by extending the reaction time, raising the reaction temperature, or increasing the amount of the reagents used, only led to complex, intractable mixtures.

Ultimately, TMS-I⁷⁶ emerged as the best deprotecting agent. Initial attempts to deblock **218** relied on close monitoring of the progress of the reaction by electrospray mass spectrometry. This technique indicated that TMS-I cleanly converted **218** to **1** in about 1.5 h at room temperature followed by an additional 2 h at 55 °C. However, only a benzylated derivative of streptonigrone was obtained upon the customary aqueous workup of the reaction mixture. The precise structure of this benzylated derivative of **1** remains undetermined. Considerable troubleshooting revealed that benzyl iodide, a byproduct of the deprotection step, was responsible for the undesired benzylation of the initially produced free streptonigrone. Furthermore, it transpired that such an undesirable event occurred during the concentration phase of the workup, and not during the actual deprotection reaction. Evidently, benzyl iodide was being extracted from the aqueous-organic workup mixture together with free **1**. Concentration of the extracts then promoted benzylation.

The reason why benzylation did not occur during deprotection, despite the elevated reaction temperature (55 °C) and high reactivity of benzyl iodide, remains unclear. We surmise that temporary “protection” of the nucleophilic sites of **218**, especially the amino groups, by the excess TMS-I present in the medium, or protonation of these by HI produced by reaction of TMS-I with adventitious moisture, might have delayed / suppressed the alkylation event (**Scheme 60**).

A simple cure for the above ills was readily devised. Thus, the raw extracts from the biphasic workup were not concentrated, but rather applied directly to a silica gel

column. Initial elution with CH_2Cl_2 quickly removed unwanted benzyl iodide and other nonpolar contaminants. The desired product was then eluted with 5% MeOH in CH_2Cl_2 .

Scheme 60. Global deprotection with TMS-I

Fully synthetic **1** was thus obtained in 67% yield from **218**. The spectral data measured for synthetic **1** were in perfect accord with those recorded in the literature¹ for natural material, as apparent from **Table 1**.

A final comment is in order before closing. The present synthesis of **1** deviates from Boger's,³¹ *inter alia*, for the use of an *O*-benzyl protecting group on the pyridine unit in lieu of a methoxy group. The reason is that problems emerged at a late stage of the synthesis with a methoxypyridine analog of **218**. Such a compound was synthesized from **208** by a sequence analogous to the one outlined in **Scheme 54** (**Scheme 61**), and it was further elaborated to streptonigrone precursor **226**, which is structurally very similar

Table 1: Reported vs. measured ^1H chemical shifts for natural and synthetic **1**.

Reported ^1H Shifts (ppm, natural 1)	Measured ^1H Shifts (ppm, synthetic 1)
8.36 (ABq, 2H)	8.37 (ABq, 2H)
6.84 (d, 1H, $J = 9.0$)	6.83 (d, 1H, $J = 8.6$)
6.66 (d, 1H, $J = 9.0$)	6.65 (d, 1H, $J = 8.6$)
6.34 (broad s, 1H)	6.31 (broad s, 1H)
5.05 (broad s, 2H)	5.04 (broad s, 2H)
4.06 (s, 3H)	4.07 (s, 3H)
3.99 (s, 3H)	3.99 (s, 3H)
3.95 (s, 3H)	3.95 (s, 3H)
2.03 (s, 3H)	2.03 (s, 3H)

to the Boger intermediate **54**. Contrary to its close relative, deblocking of **226** under a variety of conditions was unsatisfactory. Deprotection under Boger conditions (preliminary reduction of the quinone with H_2 , Pd-C, $\text{CF}_3\text{CH}_2\text{OH}$, followed by $\text{HBr}_{(\text{g})}$, 80°C) afforded a mixture of partially deprotected products. Similar results were obtained when deblocking was carried out with aqueous or gaseous HCl or HBr, or with Lewis acids such as BBr_3 and AlCl_3 . Modified reaction conditions involving changes in the ratios of reagents, solvent, reaction times, and temperatures failed to give the desired product. More forcing conditions (excess of deprotecting agent and elevated reaction temperatures) only resulted in demethylation of the OMe groups or decomposition of material. Thus, it appears that seemingly trivial differences between **54** and **226** (protection of the ring D phenol as a benzyl ether and of the pyridone amino group as a BOC derivative) actually have a profound influence on the feasibility of the final deblocking sequence. Fortunately, benzyl protected intermediate **218** allowed us to circumvent these unpleasant obstacles.

a. ICl, K₂CO₃, DMF, RT; b. MeI, Ag₂CO₃, CH₃Cl, RT (66% a-b); c. *n*-BuLi, THF, -78 °C then CO₂ (66%); d. DPPA, Et₃N, *t*-BuOH, reflux; e. BOC₂O, THF, 55 °C (59% d-e); f. CAN, CH₃CN, H₂O, 0 °C (55%); g. IN₃, CH₃CN, RT; h. NaN₃, aq. THF, RT; i. Na₂S₂O₄, aq. MeOH, reflux (18% g-i)

Scheme 61. Preparation of methoxypyridine **226**

In conclusion, the total synthesis of streptonigrone was completed in 20 linear steps (0.36% overall yield) by the use of technology developed in our laboratory for the synthesis of 3-alkylpyridones from an enone precursor. Further studies aiming to improve the overall efficiency of the synthesis, as well as investigations on the indolizine-forming reaction, are currently underway in our laboratory.

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Experimental Protocols

Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded on Bruker models AV-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C), AV-400dir (400 MHz for ^1H and 100.6 MHz for ^{13}C), AV-400inv (400 MHz for ^1H and 100.6 MHz for ^{13}C) or AV-600 (600 MHz for ^1H and 150 MHz for ^{13}C) spectrometers using deuteriochloroform (CDCl_3) as the solvent. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, J , are in hertz (Hz). Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "dd" (doublet of doublets), "td" (triplet of doublets), "m" (multiplet), "br" (broad). Infrared (IR) spectra (cm^{-1}) were recorded on a Perkin-Elmer model 1710 Fourier transform spectrophotometer from films deposited on NaCl plates. Low-resolution mass spectra (m/z) were obtained in the electrospray (ESI) mode on a Waters Micromass ZQ mass spectrometer. High-resolution mass spectra (m/z) were recorded in the electrospray (ESI) mode on a Micromass LCT mass spectrometer by the UBC Mass Spectrometry laboratory. Elemental analyses were performed on a Carlo Erba EA model 1108 elemental analyzer by the UBC Microanalysis Laboratory. Melting points (uncorrected) were measured on a Mel-Temp apparatus.

All reagents and solvents were commercial products and used without further purification except THF (freshly distilled from Na/benzophenone under argon) and CH_2Cl_2 (freshly distilled from CaH_2 under argon). Commercial $n\text{-BuLi}$ was titrated against N -benzylbenzamide in THF at $-78\text{ }^\circ\text{C}$ until persistence of a light blue color. Flash chromatography was performed on Silicycle 230 – 400 mesh silica gel. Analytic and preparative TLC was carried out with Merck silica gel 60 plates with fluorescent indicator. Spots were visualized with UV light. All reactions were performed under dry

Ar in flame- or oven-dried flasks equipped with TeflonTM stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.

Preparation of 2,4,5-trimethoxynitrobenzene

A solution of 70% HNO₃ (5 mL) in AcOH (20 mL) was added dropwise to a solution of 1,2,4-trimethoxybenzene (16.3 g, 96.9 mmol) in AcOH (120 mL). The mixture was stirred at RT for 10 min, resulting in a yellow slurry that was diluted with water (100 mL). The yellow solid was filtered, washed with ice-water (3 x 100 mL), and taken up in DCM (200 mL). The resulting solution was washed with sat. aq. NaHCO₃ (2 x 50 mL), dried (Na₂SO₄) and concentrated. The residue was recrystallized (MeOH) to afford the title compound (13.0 g, 63%) as a yellow crystalline solid, m.p. 124.0-126.0 °C (lit. 123-124 °C: Downer, N. K.; Jackson, A. J. *Org. Biomol. Chem.* **2004**, 2, 3039).

¹H NMR (CDCl₃, 400 MHz): 7.56 (s, 1H), 6.55 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 155.8, 151.4, 143.4, 131.9, 110.0, 98.6, 58.2, 57.52, 57.45

IR: 2950, 1583, 1519, 1330, 1261

MS: 236.2 [M + Na]⁺

HRMS: calcd for C₉H₁₁NO₅: 236.0535 [M + Na]⁺
found: 236.0532 [M + Na]⁺

Scheme A1. ^1H NMR spectrum of 2,4,5-trimethoxynitrobenzene

Scheme A2. ^{13}C NMR spectrum of 2,4,5-trimethoxynitrobenzene

Scheme A3. IR Spectrum of 2,4,5-trimethoxynitrobenzene

Preparation of 2,4,5-trimethoxyaniline (**137**)

A suspension of the above nitro compound (5.13 g, 24.0 mmol) and 10% Pd-C (300 mg, 280 mmol) in MeOH (225 mL) was stirred under a H₂ atmosphere at RT for 24 h. The suspension was then filtered over Celite[®] and concentrated. The residue was dissolved in DCM (150 mL), washed with sat. aq. NaHCO₃ (2 x 50 mL), dried (Na₂SO₄) and concentrated to furnish **137** (4.4 g, quant.) as a purple crystalline solid, m.p. 90.0-91.0 °C (lit. 89.5-90.5 °C: Downer, N. K.; Jackson, A. J. *Org. Biomol. Chem.* **2004**, 2, 3039).

¹H NMR (MeOH-d₄, 300 MHz): 6.62 (s, 1H), 6.53 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H)

¹³C NMR (MeOH-d₄, 100 MHz): 145.5, 143.40, 143.37, 131.5, 104.5, 102.1, 58.3, 57.5, 57.1

IR: 3393, 2940, 1527, 1469, 1234, 1205

MS: 206.3 [M + Na]⁺

HRMS: calcd for C₉H₁₃NO₃: 206.0793 [M + Na]⁺
found: 206.0791 [M + Na]⁺

Scheme A4. ^1H NMR spectrum of 2,4,5-trimethoxyaniline

Scheme A5. ^{13}C NMR spectrum of 2,4,5-trimethoxyaniline

Scheme A6. IR spectrum of 2,4,5-trimethoxyaniline

Preparation of 2-[(2,4,5-Trimethoxyphenyl)amino]-2-butenedioic acid, dimethyl ester

(138)

A solution of **137** (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 **138** (5.35 g, 58%) as an orange paste.

^1H NMR (CDCl₃, 400 MHz): 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 NMR (CDCl₃, 100 MHz): 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, 2954, 1740, 1670, 1617, 1525, 1271, 1217

MS: 326.1 [M + H]⁺

HRMS: calcd for C₁₅H₁₉NO₇: 348.1059 [M + Na]⁺
found: 348.1055 [M + Na]⁺

Scheme A7. ¹H NMR spectrum of **138**

Scheme A8. ¹³C NMR spectrum of **138**

Scheme A9. IR Spectrum of 138

Preparation of 5,6,8-trimethoxy-(1*H*)-quinolin-4-one-2-carboxylic acid, methyl ester

(139)

A solution of **138** (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 x 30 mL) to give **139** (4.15 g, 86%) as a dark yellow solid, m.p. 170.5-171.5 °C.

¹H NMR (MeOH-d₄, 400 MHz): 7.22 (s, 1H), 6.74 (s, 1H), 4.11 (s, 3H), 4.03 (s, 3H), 3.97 (s, 3H), 3.80 (s, 3H)

¹³C NMR (MeOH-d₄, 150 MHz): 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, 1592, 1527, 1267, 1070

MS: 294.2 [M + H]⁺

HRMS: calcd for C₁₄H₁₅NO₆: 294.0978 [M + H]⁺
found: 294.0977 [M + H]⁺

Scheme A10. ^1H NMR spectrum of **139**

Scheme A11. ^{13}C NMR spectrum of **139**

Scheme A12. IR spectrum of **139**

Preparation of 4-chloro-5,6,8-trimethoxyquinoline-2-carboxylic acid, methyl ester (**140**)

A suspension of **139** (4.15 g, 14.1 mmol) in benzene (120 mL; **CAUTION**: cancer suspect agent) and POCl₃ (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 NaHCO₃ (**CAUTION**: vigorous foaming) and extracted with EtOAc (5 x 100 mL). The combined extracts were then washed with sat. aq. NaHCO₃ (2 x 50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated to afford analytically pure **140** (3.87 g, 88%) as an orange crystalline solid, m.p. 193.5-195.0 °C.

¹H NMR (CDCl₃, 400 MHz): 8.20 (s, 1H), 6.93 (s, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.87 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 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: 2945, 1704, 1606, 1470, 1369, 1250, 1016

MS: 334.1 [M(³⁵Cl) + Na]⁺, 336.1 [M(³⁷Cl) + Na]⁺

HRMS: calcd for C₁₄H₁₄³⁵ClNO₅: 334.0458 [M + Na]⁺
found: 334.0459 [M + Na]⁺

EA: calcd: C 53.94%, H 4.53%, N 4.49%
found: C 54.28%, H 4.86%, N 4.57%

Scheme A13. ¹H NMR spectrum of **140**

Scheme A14. ¹³C NMR spectrum of **140**

Scheme A15. IR Spectrum of 140

Preparation of 5,6,8-trimethoxyquinoline-2-carboxylic acid, methyl ester (**129**)

A mixture of **140** (636 mg, 2.04 mmol), 10% Pd-C (120 mg, 0.113 mmol), Et₃N (1.0 mL, 7.2 mmol) in EtOAc (50 mL) was stirred under a H₂ atmosphere at RT for 45 min, then it was filtered over Celite[®] and concentrated to afford pure **129** (567 mg, quant.) as an orange crystalline solid, m.p. 164.0-165.5 °C.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz):: 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, 1612, 1256, 1108

MS: 278.1 [M + H]⁺, 300.1 [M + Na]⁺

HRMS: calcd for C₁₄H₁₅NO₅: 278.1028 [M + H]⁺
found: 278.1034 [M + H]⁺

EA: calcd: C 60.64%, H 5.45%, N 5.05%
found: C 60.80%, H 5.66%, N 5.09 %

Scheme A16. ^1H NMR spectrum of **129**

Scheme A17. ^{13}C NMR spectrum of **129**

Scheme A18. IR spectrum of 129

Preparation of ethyl 3-oxo-3-(5,6,8-trimethoxyquinolin-2-yl)propanoate (**159**)

A suspension of **129** (1.05 g, 3.79 mmol) and NaH (60% dispersion, 0.50 g, 13 mmol) in EtOAc (20 mL) and toluene (50 mL) was stirred at 110 °C for 15 h (**CAUTION**: vigorous evolution of highly flammable H₂ gas). The reaction was then cooled to RT and diluted with sat. aq. NH₄Cl (100 mL; **CAUTION**). The aqueous phase was acidified to pH 4 with 1M HCl and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (Et₂O : hexanes, 1:2) of the residue afforded **159** (0.830 g, 66%) as a yellow solid, m.p. 101.0-102.0 °C.

¹ H NMR (CDCl ₃ , 400 MHz):	(major keto-tautomer) 8.49 (d, 1H, <i>J</i> = 8.78), 8.13 (d, 1H, <i>J</i> = 8.78), 6.91 (s, 1H), 4.38 (s, 2H), 4.22 (q, 2H, <i>J</i> = 7.14), 4.11 (s, 3H), 4.07 (s, 3H), 3.93 (s, 3H), 1.26 (t, 3H, <i>J</i> = 7.13)
¹³ C NMR (CDCl ₃ , 100 MHz):	195.8, 169.6, 154.7, 152.0, 149.9, 136.3, 135.1, 131.7, 127.2, 119.8, 100.1, 62.5, 62.0, 57.9, 57.7, 45.6, 15.1
IR:	2984, 1743, 1716, 1688, 1607, 1469, 1360, 1255, 1104
MS:	334.1 [M + H] ⁺ , 356.1 [M + Na] ⁺
HRMS:	calcd for C ₁₇ H ₁₉ NO ₆ : 356.1110 [M + Na] ⁺ found: 356.1100 [M + Na] ⁺
EA:	calcd: C 61.25%, H 5.75%, N 4.20% found: C 61.19%, H 5.75%, N 4.18%

Scheme A19. ^1H NMR spectrum of **159**

Scheme A20. ^{13}C NMR spectrum of **159**

Scheme A21. IR spectrum of **159**

Preparation of 1-(5,6,8-trimethoxyquinolin-2-yl)ethanone (**187**)

A suspension of **129** (7.00 g, 25.3 mmol) and NaH (60% in oil, 2.5 g, 63 mmol) in EtOAc (100 mL) and toluene (350 mL) was stirred at 110 °C for 15 h (**CAUTION**: vigorous evolution of highly flammable H₂ gas). The reaction was then cooled to RT and diluted with sat. aq. NH₄Cl (100 mL; **CAUTION**). The aqueous phase was acidified to pH 4 with 1M HCl and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was then dissolved in 1,4-dioxane (150 mL; **CAUTION**: cancer suspect agent). Aqueous 1M 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. NaHCO₃), and the mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with sat. aq. NaHCO₃ (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated. Flash chromatography (EtOAc:hexanes:DCM, 1:3:1) of the residue afforded **187** (5.17 g, 78% over 2 steps), yellow solid, m.p. 144.0-145.0 °C.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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, 1608, 1357, 1254

MS: 284.1 [M + Na]⁺, 545 [2M + Na]⁺

HRMS: calcd for C₁₄H₁₅NO₄: 284.0899 [M + Na]⁺

	found:	284.0903 [M + Na] ⁺
EA:	calcd:	C 64.36%, H 5.79%, N 5.36%
	found:	C 64.52%, H 5.86%, N 5.54 %

)

Scheme A22. ¹H NMR spectrum of **187**

Scheme A23. ¹³C spectrum NMR of **187**

Scheme A24. IR spectrum of **187**

Preparation of 2-hydroxy-3,4-dimethoxybenzaldehyde (**44**)

A mixture of commercial 2,3,4-trimethoxybenzaldehyde (10.0 g, 51.2 mmol) and anhydrous AlCl_3 (6.90 g, 51.7 mmol) in PhH (130 mL; **CAUTION**: cancer suspect agent) was stirred at RT for 5 min, then it was heated at 75 °C for 5 h. The mixture was then cooled to RT and quenched with water (50 mL) and conc. aq. HCl (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (Na_2SO_4) and concentrated to give **44** (9.14 g, 98.0 %), off-white solid, m.p. 69.5-70.0 °C (lit. 70-72 °C: Reichstein, T.; Oppenauer, R.; Grussner, A.; Rhyner, L.; Glatthaar, C. *Helv. Chim. Acta*. **1935**, 18, 816).

^1H NMR (CDCl₃, 300 MHz): 11.20 (s, 1H), 9.75 (s, 1H), 7.29 (d, 2H, $J = 8.72$), 6.61 (d, 2H, $J = 8.72$), 3.95 (s, 3H), 3.91 (s, 3H)

^{13}C NMR (CDCl₃, 100 MHz): 195.1, 159.5, 155.9, 136.3, 130.4, 116.7, 104.2, 60.9, 56.4

IR: 2939, 1642, 1505, 1451, 1292, 1265, 1109

MS: 183.3 $[\text{M} + \text{H}]^+$, 205.2 $[\text{M} + \text{Na}]^+$

HRMS: calcd for $\text{C}_9\text{H}_{10}\text{O}_4$: 205.0477 $[\text{M} + \text{Na}]^+$
found: 205.0484 $[\text{M} + \text{Na}]^+$

Scheme A25. ¹H NMR spectrum of **44**

Scheme A26. ¹³C NMR spectrum of **44**

Scheme A27. IR spectrum of **44**

Preparation of 2-(benzyloxy)-3,4-dimethoxybenzaldehyde (**127**)

A mixture of **44** (9.14 g, 50.5 mmol), K_2CO_3 (20.0 g, 151 mmol) and BnBr (6.08 mL, 51.2 mmol) in DMF (150 mL) was stirred at RT for 18 h. The mixture was then quenched with water (200 mL) and extracted with Et_2O (5 x 100 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried (Na_2SO_4) and concentrated to give **127** (13.4 g, 98%) as a yellow oil.

1H NMR (CDCl₃, 300 MHz): 10.09 (s, 1H), 7.55 (d, 1H, $J = 8.79$), 7.25-7.39 (m, 5H), 6.72 (d, 1H, $J = 8.77$), 5.19 (s, 2H), 3.88 (s, 6H)

^{13}C NMR (CDCl₃, 100 MHz): 188.8, 159.4, 155.6, 142.0, 136.6, 128.73, 128.72, 128.6, 124.1, 124.0, 107.9, 76.8, 61.1, 56.3

IR: 2942, 2841, 1679, 1590, 1495, 1455, 1290, 1262, 1094

MS: 295.1 $[M + Na]^+$

HRMS: calcd for $C_{16}H_{16}O_4$: 295.0946 $[M + Na]^+$
found: 295.0952 $[M + Na]^+$

Scheme A28. ^1H NMR spectrum of **127**

Scheme A29. ^{13}C NMR spectrum **127**

Scheme A30. IR spectrum of **127**

Preparation of (E)-3-(2-(benzyloxy)-3,4-dimethoxyphenyl)-1-(5,6,8-trimethoxyquinolin-2-yl)prop-2-en-1-one (**207**)

To a solution of **187** (156 mg, 0.597 mmol) in EtOH (25 mL) was added dropwise a solution of NaOH (1.0 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 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (MgSO₄) and concentrated. Flash chromatography of the residue (EtOAc : hexanes, 1:2) afforded **207** (256 mg, 83%) as a yellow foam.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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: 2935, 1661, 1608, 1584, 1495, 1252, 1095, 1062

MS: 516.1 [M + H]⁺

HRMS: calcd for C₃₀H₂₉NO₇: 538.1842 [M + Na]⁺
found: 538.1857 [M + Na]⁺

Scheme A31. ^1H NMR spectrum of **207**

Scheme A32. ^{13}C NMR spectrum of **207**

Scheme A33. IR spectrum of 207

Preparation of 2-cyanopropionamide (**121**)

Anhydrous NH_3 gas (**CAUTION**: toxic and corrosive) was bubbled through a solution of 2-cyanopropanoic acid ethyl ester (4.00 g, 31.5 mmol) in ethanol (30 mL) for 20 min. The solution was then stirred at RT for 15 h and concentrated to give **121** (3.00 g, 98%) as an off-white solid, m.p. 99.5-101.0 °C.

^1H NMR (MeOH- d_4 , 400 MHz): 6.13 (s, br, 1H), 5.62 (s, br, 1H), 3.96 (q, 1H, $J = 7.30$), 1.52 (d, 3H, $J = 7.30$)

^{13}C NMR (MeOH- d_4 , 100 MHz): 170.6, 119.7, 32.8, 16.1

IR: 3360, 3192, 1668

HRMS: calcd for $\text{C}_4\text{H}_6\text{N}_2\text{O}$: 99.0558 $[\text{M} + \text{H}]^+$
found: 99.0560 $[\text{M} + \text{H}]^+$

EA: calcd: C 48.97%, H 6.16%, N 28.56%
found: C 49.26%, H 6.22%, N 28.68%

Scheme A34. ^1H NMR spectrum of **121**

Scheme A35. ^{13}C NMR spectrum of **121**

Scheme A36. IR spectrum of **121**

Preparation of 4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-methyl-6-(5,6,8-trimethoxyquinolin-2-yl)pyridin-2(1H)-one (208)

A solution of enone **207** (1.54, 2.98 mmol) and 2-cyanopropanamide (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, 1M HCl (100 mL) was then added dropwise (**CAUTION**: evolution of highly toxic HCN gas) and the resulting mixture was extracted with EtOAc (5 x 50 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography of the residue (100% EtOAc then MeOH:DCM, 1:9) afforded **208** (1.02 g, 60%) as a yellow solid, m.p. 92.5-95°C.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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: 2938, 1642, 1610, 1497, 1456, 1354, 1293, 1100

MS:	569.1 [M + H] ⁺	
HRMS:	calcd for C ₃₃ H ₃₂ N ₂ O ₇ :	569.2288 [M + H] ⁺
	found:	569.2285 [M + H] ⁺
EA:	calcd:	C 69.70%, H 5.67%, N 4.93%
	found:	C 69.34%, H 5.85%, N 5.18%

Scheme A37. ¹H NMR spectrum of **208**

Scheme A38. ¹³C NMR spectrum of **208**

Scheme A39. IR spectrum of **208**

Preparation of 2-(6-(benzyloxy)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-iodo-5-methylpyridin-2-yl)-5,6,8-trimethoxyquinoline (**210**)

A mixture of **208** (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 x 75 mL). The combined organic extracts were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (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 d, then it was filtered through a bed of Celite[®] and concentrated. Purification by flash chromatography (EtOAc : hexanes, 1:3) afforded **210** (520 mg, 36% over 2 steps) as a pale-yellow foam.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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, 1342, 1099

MS: 785.1 [M + H]⁺

HRMS: calcd for C₄₀H₃₇N₂O₇I: 785.1724 [M + H]⁺
found: 785.1727 [M + H]⁺

EA: calcd: C 61.23%, H 4.75%, N 3.57%
found: C 61.47%, H 4.96%, N 3.65%

Scheme A40. ^1H NMR spectrum of **210**

Scheme A41. ^{13}C NMR spectrum of **210**

Scheme A42. IR spectrum of **210**

Preparation of benzyl 6-(benzyloxy)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-5-methyl-2-(5,6,8-trimethoxyquinolin-2-yl)pyridin-3-ylcarbamate (**213**)

A solution of **210** (222 mg, 0.283 mmol) in THF (2 mL) was added dropwise to a cold (-78 °C) solution of *n*-butyllithium (0.35 mL of 1.6 M solution in hexanes, 0.57 mmol) in THF (30 mL). Bone dry CO₂ 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 x 30 mL) and extracted with EtOAc (30 mL). The aqueous phase was further acidified to pH 2 by addition of 1M HCl and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na₂SO₄) 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 Et₃N (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 1M 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 x 10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. The crude aminopyridine was then immediately taken up in THF (25 mL) and cooled to 0 °C before the addition of NaHCO₃.

(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 x 25 mL), washed with brine (25 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (EtOAc:hexanes, 1:4) gave **213** (85 mg, 37% over 3 steps) as a yellow paste.

^1H NMR (CDCl₃, 400 MHz): 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 NMR (CDCl₃, 100 MHz): 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, 1601, 1481, 1354, 1226, 1102

MS: 808.3 $[\text{M} + \text{H}]^+$, 830.3 $[\text{M} + \text{Na}]^+$

HRMS: calcd for $\text{C}_{48}\text{H}_{45}\text{N}_3\text{O}_9$: 808.3234 $[\text{M} + \text{H}]^+$
found: 808.3244 $[\text{M} + \text{H}]^+$

Scheme A43. ^1H NMR spectrum of **213**

Scheme A44. ^{13}C NMR spectrum of **213**

Scheme A45. IR spectrum of 213

Preparation of benzyl 6-(benzyloxy)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-2-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-5-methylpyridin-3-ylcarbamate (**215**)

To a cold (0 °C) solution of **213** (85 mg, 0.11 mmol) in CH₃CN (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 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na₂SO₄) and concentrated. The residue was chromatographed (EtOAc:hexanes, 1:1) to give the **215** (75 mg, 93%) as an orange paste.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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, 1497, 1244, 1101

MS: 778.3 [M + H]⁺, 800.3 [M + Na]⁺

HRMS: calcd for C₄₆H₃₉N₃O₉: 778.2765 [M + H]⁺
found: 778.2779 [M + H]⁺

Scheme A46. ^1H NMR spectrum of **215**

Scheme A47. ^{13}C NMR spectrum of **215**

Scheme A48. IR spectrum of **215**

Preparation of benzyl 2-(7-amino-6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-6-(benzyloxy)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-5-methylpyridin-3-ylcarbamate
(218)

To a suspension of NaN_3 (1.0 g, 15 mmol) in CH_3CN (36 mL) in MeOH/ice bath ($-10\text{ }^\circ\text{C}$) was added ICl (0.80 g, 4.93 mmol). The suspension was stirred at $-10\text{ }^\circ\text{C}$ for 15 min and filtered to give a yellow IN_3 solution. To a cold ($-10\text{ }^\circ\text{C}$) solution of **215** (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. $\text{Na}_2\text{S}_2\text{O}_3$ (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the sensitive **216**. This material was dissolved in THF (10 mL). A solution of NaN_3 (7.0 mg, 0.11 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 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to give the sensitive **217**. A mixture of crude **217** 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 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried

(Na₂SO₄) and concentrated. Purification of the crude residue by preparative TLC (EtOAc : hexanes, 2:1) afforded **218** (30 mg, 40% over 3 steps) as a dark purple wax.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 100 MHz): 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, 1497, 1455, 1351, 1231, 1100

MS: 793.4 [M + H]⁺, 815.3 [M + Na]⁺

HRMS: calcd for C₄₆H₄₀N₄O₉: 831.2432 [M + K]⁺
found: 831.2444 [M + K]⁺

Scheme A49. ^1H NMR spectrum of **218**

Scheme A50. ^{13}C NMR spectrum of **218**

Scheme A51. IR spectrum of **218**

Preparation of totally synthetic streptonigrone (1)

A solution of **218** (15 mg, 0.019 mmol) and TMS-I (0.50 mL, 3.5 mmol) in CH₃CN (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 x 10 mL). The combined organic extracts were washed with 50% aq. Na₂S₂O₃ (10 mL) and water (10 mL), dried (Na₂SO₄) 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 (CH₃Cl : acetone : MeOH, 8:1:1) afforded streptonigrone (6 mg, 67%) as a dark solid.

¹H NMR (CDCl₃, 400 MHz): 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)

¹³C NMR (CDCl₃, 150 MHz): 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

MS: 501.0 [M + Na]⁺

HRMS: calcd for C₂₄H₂₂N₄O₇: 501.1386 [M + Na]⁺
found: 501.1392 [M + Na]⁺

Scheme A52. ^1H NMR spectrum of synthetic streptonigrone

Scheme A53. ^{13}C NMR spectrum of synthetic streptonigrone

Scheme A54. IR spectrum of synthetic streptonigrone

Preparation of methyl 5,6,8-trimethoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate (**144**)

A mixture of **140** (60 mg, 0.19 mmol), 10% Pd-C (20 mg, 0.019 mmol) in EtOH (7 mL) was stirred under an H₂ atmosphere at RT for 45 min, then it was filtered over Celite[®] and concentrated to afford pure **144** (50 mg, 96%) as a yellow paste.

¹H NMR (CDCl₃, 400 MHz): 6.40 (s, 1H), 4.49 (br. s, 1H), 4.0 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 2.74-2.84 (m, 2H), 2.24-2.31 (m, 1H), 1.98-2.07 (m, 1H)

MS: 282.1 [M + H]⁺

Scheme A55. ^1H NMR spectrum of **144**

Preparation of methyl quinaldate

To a suspension of quinaldic acid (6.58 g, 38.0 mmol) in MeOH (70 mL) was added a 1.25 M HCl in methanol solution (70 mL). The resulting solution was refluxed for 15 h. The mixture was then cooled to RT and concentrated *in vacuo*. The residue was partitioned between sat. aq. NaHCO₃ (100 mL) and EtOAc (3 x 75 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (25 mL) and water (25 mL), dried (Na₂SO₄), and concentrated *in vacuo* to give the desired ester (5.85 g, 82%), white solid, m.p. 82.0-83.0 °C (lit. 81-83 °C: Weitgenant, J. A.; Mortison, J. D.; Helquist, P. *Org. Lett.* **2005**, 7, 3609).

¹H NMR (CDCl₃, 400 MHz): 8.30 (d, 2H, *J* = 8.48), 8.19 (d, 1H, *J* = 8.50), 7.87 (d, 1H, *J* = 8.27), 7.78 (t, 1H, *J* = 7.17), 7.64 (t, 1H, *J* = 7.40), 4.08 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 167.0, 148.9, 148.6, 138.3, 131.7, 131.3, 130.4, 129.6, 128.6, 122.0, 54.2

IR: 1714, 1450, 1320, 1144

MS: 210.2 [M + Na]⁺

HRMS: calcd for C₁₁H₉NO₂: 210.0531 [M + Na]⁺
found: 210.0536 [M + Na]⁺

EA: calcd: C 70.58%, H 4.85%, N 7.48%
found: C 70.50%, H 4.75%, N 7.52%

Scheme A56. ^1H NMR spectrum of methyl quinaldate

Scheme A57. ^{13}C NMR spectrum of methyl quinaldate

Scheme A58. IR spectrum of methyl quinaldate

Preparation of ethyl 3-oxo-3-(quinolin-2-yl)propanoate (**153**)

Solid *t*-BuOK (3.00 g, 26.7 mmol) was slowly added to a solution of methyl quinaldate (3.73 g, 19.9 mmol) in EtOAc (75 mL) at RT. The mixture was stirred for 15 min at RT, then it was quenched with water (120 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated. Purification of the crude residue by flash chromatography (EtOAc : hexanes, 1:4) afforded **153** (5.91 g, 98%) as an off-white paste.

¹H NMR (CDCl₃, 400 MHz): 8.24 (d, 1H, *J* = 8.50), 8.13 (m, 2H, overlapping resonance signals), 7.84 (d, 1H, *J* = 8.17), 7.75 (td, 1H, *J* = 6.92, *J* = 1.35), 7.62 (td, 1H, *J* = 8.06, *J* = 1.05), 4.34 (s, 2H), 4.20 (q, 2H, *J* = 7.13), 1.22 (t, 3H, *J* = 7.13)

¹³C NMR (CDCl₃, 100 MHz): 195.9, 169.4, 152.9, 148.0, 138.1, 131.5, 131.1, 130.7, 129.9, 128.7, 119.0, 62.1, 45.7, 15.1

IR: 2983, 1742, 1702, 1332, 1198

MS: 266.1 [M + Na]⁺, 509.1 [2M + Na]⁺

HRMS: calcd for C₁₄H₁₃NO₃: 266.0793 [M + Na]⁺
found: 266.0798 [M + Na]⁺

EA: calcd: C 69.12%, H 5.39%, N 5.76%
found: C 68.86%, H 5.45%, N 6.02%

Scheme A59. ¹H NMR spectrum of **153**

Scheme A60. ¹³C NMR spectrum of **153**

Scheme A61. IR spectrum of **153**

Preparation of 2-nitro-1-(quinolin-2-yl)ethanone (**155**)

1,1'-Carbonyldiimidazole (7.08 g, 43.7 mmol) was added in portions to a solution of quinaldic acid (6.05 g, 34.9 mmol) in THF (70 mL) and stirred at RT for 30 min before the addition of CH_3NO_2 (11.3 mL, 210 mmol) and *t*-BuOK (15.7 g, 140 mmol). The mixture was stirred for 2 h at RT, then it was concentrated and partitioned between EtOAc (100 mL) and 0.1M HCl (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc : hexanes, 1:3) of the residue afforded **155** (4.53 g, 61%) as a yellow solid.

^1H NMR (CDCl₃, 300 MHz): 8.37 (d, 1H, $J = 8.59$), 8.17 (d, 1H, $J = 8.50$), 8.16 (d, 1H, $J = 8.81$), 7.93 (d, 1H, $J = 8.06$), 7.81-7.87 (m, 1H), 7.69-7.75 (m, 1H), 6.62 (s, 2H)

Scheme A62. ^1H NMR spectrum of **155**

Preparation of ethyl 3-hydroxy-1-phenylpyrrolo[1,2-a]quinoline-2-carboxylate (**156**)

Piperidine (1.5 mL, 15.1 mmol) was added dropwise at RT to a solution of **153** (5.91 g, 24.3 mmol) and PhCHO (3.0 mL, 29 mmol) in EtOH (12 mL). The mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was diluted with EtOAc (100 mL) and water (50 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (2 x 25 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (EtOAc : hexane, 1:19) to afford **156** (7.05 g, 87.5%) as a yellow solid, m.p. 114.0-116.0 °C.

¹H NMR (CDCl₃, 400 MHz): 8.30 (s, 1H), 7.41-7.52 (m, 6H), 7.36 (d, 1H, *J* = 9.31), 7.17 (td, 1H, *J* = 7.07 Hz, *J* = 1.02), 7.03 (d, 1H, *J* = 8.52), 6.93 (m, 1H), 6.73 (d, 1H, *J* = 9.30), 4.11 (q, 2H, *J* = 7.21), 0.97 (t, 3H, *J* = 7.18)

¹³C NMR (CDCl₃, 100 MHz): 168.4, 140.9, 135.2, 134.9, 131.9, 129.8, 129.5, 128.22, 128.17, 127.5, 125.5, 118.9, 117.8, 117.2, 117.0, 105.7, 61.1, 14.7

IR: 3338, 2982, 1674, 1498, 1452, 1377, 1243

MS: 354.1 [M + Na]⁺

HRMS: calcd for C₂₁H₁₇NO₃: 354.1106 [M + Na]⁺
found: 354.1107 [M + Na]⁺

EA: calcd: C 76.12%, H 5.17%, N 4.23%
found: C 75.92%, H 5.26%, N 4.60%

Scheme A63. ^1H NMR spectrum of **156**

Scheme A64. ^{13}C NMR spectrum of **156**

Scheme A65. $^1\text{H}/^{13}\text{C}$ HMQC spectrum of **156**

Scheme A66. IR spectrum of **156**

Preparation of 1-(2-(benzyloxy)-3,4-dimethoxyphenyl)-2-nitropyrrolo[1,2-a]quinolin-3-ol
(158)

A mixture of **155** (185 mg, 0.856 mmol), aldehyde **127** (256 mg, 0.942 mmol), NH_4OAc (75 mg, 0.94 mmol) in toluene (10 mL) was refluxed for 3.5 h. The reaction was then quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc : hexanes, 1:5) of the residue afforded **158** (349 mg, 87%) as a dark red paste.

^1H NMR (CDCl₃, 300 MHz): 8.11 (s, 1H), 7.47 (d, 1H, $J = 7.68$), 7.33 (d, 1H, $J = 9.46$), 7.21 (d, 1H, $J = 7.85$), 6.94-7.13 (m, 6H), 6.74-6.88 (m, 4H), 4.88 (s, 2H), 4.01 (s, 3H), 3.92 (s, 3H)

Scheme A67. ^1H NMR spectrum of **158**

Preparation of ethyl 1-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-hydroxy-6,7,9-trimethoxypyrrolo[1,2-a]quinoline-2-carboxylate (**160**)

Piperidine (0.010 mL, 0.101 mmol) was added dropwise to a solution of **159** (119 mg, 0.357 mmol) and 2-benzyloxy-3,4-dimethoxybenzaldehyde (100 mg, 0.358 mmol) in ethanol (15 mL). The mixture was refluxed for 35 min, then it was diluted with water (30 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with more EtOAc (3 x 15 mL). The combined extracts were washed with brine (25 mL), dried (Na₂SO₄) and concentrated. Flash chromatography (EtOAc : hexane, 1:4) of the residue afforded the sensitive **160** (103 mg, 49.3%) as a yellow paste.

¹H NMR (CDCl₃, 400 MHz): 8.49 (s, 1H), 7.34 (d, 1H, *J* = 9.45), 7.08-7.17 (m, 4H), 6.98 (d, 1H, *J* = 9.45), 6.70-6.77 (m, 3H), 6.26 (s, 1H), 4.52 (m, 2H, AB system), 4.03-4.23 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.795 (s, 3H), 3.790 (s, 3H), 3.09 (s, 3H), 1.12 (t, 3H, *J* = 7.12)

¹³C NMR (CDCl₃, 100 MHz): 168.3, 154.0, 151.1, 150.5, 147.4, 143.0, 142.7, 138.3, 130.2, 128.9, 128.6, 128.3, 127.3, 126.0, 124.2, 118.8, 118.6, 118.4, 110.3, 107.3, 104.6, 96.3, 96.2, 75.4, 62.4, 61.9, 61.0, 57.3, 57.2, 55.2, 15.0

IR: 3254, 2936, 1666, 1597, 1477, 1381, 1260, 1093, 1075

MS: 610.1 [M + Na]⁺

HRMS: calcd for C₃₃H₃₃NO₉: 610.2053 [M + Na]⁺
found: 610.2046 [M + Na]⁺

Scheme A68. ^1H NMR spectrum of **160**

Scheme A69. ^{13}C NMR spectrum of **160**

Scheme A70. $^1\text{H}/^{13}\text{C}$ HMBC spectrum of 160

Scheme A71. $^1\text{H}/^{13}\text{C}$ HMQC spectrum of 160

Scheme A72. IR spectrum of **160**

Preparation of 7,8-dimethoxy-3-(5,6,8-trimethoxyquinoline-2-carbonyl)-2H-chromen-2-one (175)

Piperidine (2 drops) was added to a solution of **159** (128 mg, 0.384 mmol) and 2-hydroxy-3,4-dimethoxybenzaldehyde (105 mg, 0.384 mmol) in EtOH (5 mL), and the mixture was refluxed for 1 h. After cooling to RT, the mixture was diluted with water (10 mL) and extracted with EtOAc (4 x 10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. Flash chromatography (EtOAc : hexanes, 1:1) of the residue gave **175** (17 mg, 10%) as a yellow solid.

¹H NMR (CDCl₃, 400 MHz): 8.54 (d, 1H, *J* = 8.76), 8.45 (s, 1H), 8.13 (d, 1H, *J* = 8.77), 7.35 (d, 1H, *J* = 8.71), 6.94 (d, 1H, *J* = 8.73), 6.88 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 191.1, 158.1, 157.1, 153.7, 150.8, 150.3, 149.0, 147.6, 136.1, 135.5, 134.2, 130.9, 126.0, 124.9, 123.2, 120.1, 113.5, 108.9, 99.5, 61.55, 61.50, 57.0 (2 overlapping resonances), 56.5

IR: 2944, 2842, 1747, 1610, 1505, 1465, 1362, 1253, 1109, 1064

MS: 452.1 [M + H]⁺, 474.1 [M + Na]⁺, 903.3 [2M + H]⁺, 925.3 [2M + Na]⁺

HRMS: calcd for C₂₄H₂₁NO₈: 474.1165 [M + Na]⁺
found: 474.1181 [M + Na]⁺

Scheme A73. ^1H NMR spectrum of **175**

Scheme A74. ^{13}C NMR spectrum of **175**

Scheme A75. $^1\text{H}/^{13}\text{C}$ HMQC spectrum of 175

Scheme A76. IR spectrum of **175**

Preparation of 2-acetylquinoline (192)

A solution of **153** (1.75 g, 7.19 mmol) in 1,4-dioxane (20 mL) containing aq. 1M HCl (20 mL) was stirred at 100 °C for 15 h, then it was concentrated *in vacuo*. The residual aqueous phase was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with sat. aq. NaHCO₃ solution (25 mL) and brine (25 mL), dried (Na₂SO₄) and evaporated. The residue was filtered through a bed of silica gel (hexanes : CH₂Cl₂, 1:4) and concentrated to give 2-acetylquinoline (0.74 g, 60%), white solid, m.p. 48.0-50.5 °C (lit. 53 °C: Capuano, L. *Chem. Ber.* **1959**, 92, 2670).

¹H NMR (CDCl₃, 300 MHz): 8.24 (d, 1H, *J* = 8.54), 8.19 (d, 1H, *J* = 8.52), 8.11 (d, 1H, *J* = 8.51), 7.85 (d, 1H, *J* = 8.10), 7.77 (td, 1H, *J* = 6.93, *J* = 1.30), 7.63 (td, 1H, *J* = 7.93, *J* = 0.92), 2.86 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 201.6, 154.2, 148.2, 137.8, 131.6, 130.9, 130.6, 129.5, 128.6, 118.9, 26.5

IR: 1697, 1359

HRMS: calcd for C₁₁H₉NO: 194.0582 [M + Na]⁺
found: 194.0576 [M + Na]⁺

EA: calcd: C 77.17%, H 5.30%, N 8.18%
found: C 77.09%, H 5.36%, N 8.35%

Scheme A77. ^1H NMR spectrum of **192**

Scheme A78. ^{13}C NMR spectrum of **192**

Scheme A79. IR spectrum of **192**

Preparation of (*E*)-3-phenyl-1-(quinolin-2-yl)prop-2-en-1-one (**193**)

Water was added dropwise to a solution of 2-acetylquinoline (0.74 g, 4.3 mmol) in EtOH (40 mL) until the solution became slightly cloudy. Aqueous 10% NaOH solution (10 mL) was then added dropwise and the mixture was stirred at RT for 5 min before the dropwise addition of PhCHO (0.30 mL, 4.3 mmol). An orange precipitate started to form. After stirring at RT for 2 h, the solid was filtered and washed with ice-cold water (10 mL) to give **193** (0.93 g, 83%), orange powder, m.p. 128.5-131.0 °C.

¹H NMR (CDCl₃, 400 MHz): 8.55 (d, 1H, *J* = 16.1), 8.18-8.40 (m, 3H), 8.00 (d, 1H, *J* = 16.1), 7.57-7.93 (m, 5H), 7.33-7.54 (m, 3H)

¹³C NMR (CDCl₃, 100 MHz): 190.6, 154.9, 148.2, 145.6, 138.0, 136.3, 131.6, 131.5, 131.0, 130.5, 129.9 (overlapping resonance signals), 129.6, 128.7, 122.1, 120.1

IR: 1669, 1605, 1576, 1449, 1336

MS: 260.2 [M + H]⁺, 282.1 [M + Na]⁺

HRMS: calcd for C₁₈H₁₃NO: 282.0895 [M + Na]⁺
found: 282.0887 [M + Na]⁺

EA: calcd: C 83.37%, H 5.05%, N 5.40%
found: C 83.35%, H 5.14%, N 5.53%

Scheme A80. ¹H NMR spectrum of **193**

Scheme A81. ¹³C NMR spectrum of **193**

Scheme A82. IR spectrum of **193**

Preparation of 3-methyl-4-phenyl-6-(quinolin-2-yl)pyridin-2(1H)-one (**194**)

To a degassed solution of **193** (100 mg, 0.386 mmol) and 2-cyanopropionamide (42 mg, 0.43 mmol) in DMSO (2 mL) was added potassium *tert*-butoxide (90 mg, 0.78 mmol). The mixture was stirred at 95°C for 3.5 h. After cooling to RT, the reaction was then quenched with 1M HCl (15 mL) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (2 x 20 mL), dried (Na₂SO₄) and concentrated. Flash chromatography (EtOAc : hexanes, 1:3) of the residue afforded **194** (120 mg, quant.) as a yellow solid, m.p. 210.0-211.0 °C.

¹H NMR (CDCl₃, 400 MHz): 10.91 (s, br, 1H), 8.22 (d, 1H, *J* = 8.68), 8.13 (d, 1H, *J* = 8.45), 7.82-7.85 (m, 2H), 7.76-7.80 (m, 1H), 7.57-7.61 (m, 1H), 7.39-7.52 (m, 5H), 6.92 (s, 1H), 2.19 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz): 164.4, 151.3, 148.6, 148.2, 140.6, 138.7, 138.4, 131.5, 130.5, 130.0, 129.6, 129.24, 129.20, 129.0, 128.5, 117.4, 108.3, 15.2

IR: 3328, 3059, 1640, 1620, 1510

MS: 313.2 [M + H]⁺

HRMS: calcd for C₂₁H₁₆N₂O: 313.1341 [M + H]⁺
found: 313.1336 [M + H]⁺

Scheme A83. ^1H NMR spectrum of **194**

Scheme A84. ^{13}C NMR spectrum of **194**

Scheme A85. IR spectrum of 194

Preparation of 5-iodo-3-methyl-4-phenyl-6-(quinolin-2-yl)pyridin-2(1H)-one (**195**)

A mixture of **194** (20 mg, 0.064 mmol) and potassium carbonate (60 mg, 0.45 mmol) in DMF (1.5 mL) was stirred at RT for 5 min. Iodine monochloride (20 mg, 0.12 mmol) was then added and the resulting mixture was stirred in the dark at RT for 15 h. The reaction was then diluted with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and brine (2 x 10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc : hexanes, 1:3) of the residue afforded **195** (20 mg, 67%) as an off-white foamy solid.

^1H NMR (CDCl₃, 400 MHz): 8.34 (d, 1H, J = 8.63), 8.29 (d, 1H, J = 8.66), 8.17 (d, 1H, J = 8.53), 7.90 (d, 1H, J = 8.11), 7.82 (t, 1H, J = 8.29), 7.66 (t, 1H, J = 8.06), 7.42-7.53 (m, 3H), 7.14-7.18 (m, 2H), 2.03 (s, 3H)

MS: 439.0 $[\text{M} + \text{H}]^+$

Scheme A86. ^1H NMR spectrum of **195**

Preparation of 2-(3-iodo-6-methoxy-5-methyl-4-phenylpyridin-2-yl)quinoline (**196**)

A suspension of **195** (8.0 mg, 0.018 mmol), Ag_2CO_3 (6.5 mg, 0.024 mmol) and MeI (0.010 mL, 0.16 mmol; **CAUTION**: cancer suspect agent) was stirred in the dark for 4 d. The resulting mixture was filtered through a bed of Celite[®] and concentrated to give **196** (7.0 mg, 85%) as a yellow paste.

¹H NMR (CDCl₃, 400 MHz): 8.27 (d, 1H, $J = 8.5$), 8.20 (d, 1H, $J = 8.5$), 7.88 (d, 1H, $J = 7.9$), 7.74-7.77 (m, 2H), 7.58 (t, 1H, $J = 7.3$), 7.39-7.51 (m, 3H), 7.14-7.18 (m, 2H), 4.00 (s, 3H), 2.03 (s, 3H)

MS: 453.1 $[\text{M} + \text{H}]^+$

Scheme A87. ^1H NMR spectrum of **196**