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Total Synthesis of the Antitumor Antibiotic (±)-Streptonigrin: First- and Second-Generation Routes for de Novo Pyridine Formation Using Ring-Closing Metathesis

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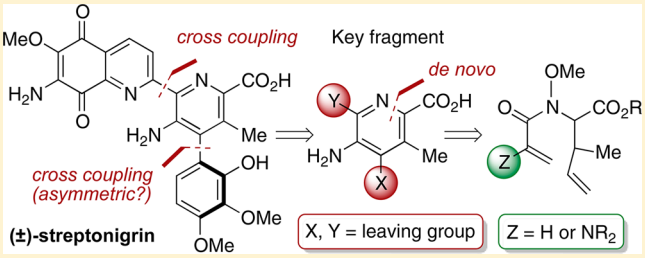
Supporting Information

ABSTRACT: The total synthesis of (±)-streptonigrin, a potent tetracyclic aminoquinoline-5,8-dione antitumor antibiotic that reached phase II clinical trials in the 1970s, is described. Two routes to construct a key pentasubstituted pyridine fragment are depicted, both relying on ring-closing metathesis but differing in the substitution and complexity of the precursor to cyclization. Both routes are short and high yielding, with the second-generation approach ultimately furnishing (±)-streptonigrin in 14 linear steps and 11% overall yield from inexpensive ethyl glyoxalate. This synthesis will allow for the design and creation of druglike late-stage natural product analogues to address pharmacological limitations. Furthermore, assessment of a number of chiral ligands in a challenging asymmetric Suzuki–Miyaura cross-coupling reaction has enabled enantioenriched (up to 42% ee) synthetic streptonigrin intermediates to be prepared for the first time.



INTRODUCTION

Ever since its isolation from *Streptomyces flocculus* in 1959 by Rao and Cullen, the chemistry of streptonigrin (**1**) (Figure 1)

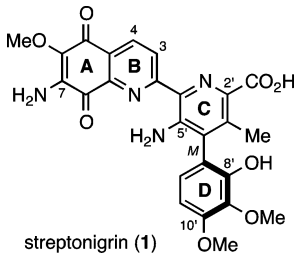


Figure 1. Streptonigrin.

has received considerable interest from both the synthetic organic and biochemical communities.[1,2] Rao, Biemann, and Woodward established the structure of the metabolite four years later through a series of elegant spectroscopic and chemical degradation studies, and the connectivity was then confirmed in 1975 by Chiu and Lipscomb via X-ray crystallographic analysis.[3,4]

The broad-spectrum anticancer activity displayed by streptonigrin has made it extremely attractive for medical application, reaching phase II clinical trials in the late 1970s.[5] However, allied to this activity was an unavoidably high degree of toxicity that caused the cessation of these trials. Subsequent structure–activity investigations involving **1** and a series of truncated analogs, as well as recent genome scanning studies, have led to a proposed biosynthesis and established the cytotoxic mode of action.[6−14] Mechanistically, it is believed that streptonigrin binds irreversibly to DNA in the presence of certain metal cations (e.g., Zn, Cu, Fe, Mn, Cd, Au) and is then activated via a one- or two-electron reductase, with NAD(P)H as a cofactor, to form a semiquinone or hydroquinone intermediate. Both of these species can react with in situ oxygen, through a Fenton-type reaction catalyzed by the metal, to regenerate streptonigrin and produce hydroxyl radicals that are ultimately responsible for DNA strand cleavage. The key structural elements responsible for this activity include the two pyridyl nitrogens in rings B and C, the C-ring carboxylic acid, and the 7-aminoquinoline-5,8-dione AB-ring system. Interestingly, streptonigrin has also been shown to be a potent and selective protein arginine deiminase (PAD 4) inhibitor.[15] Another important structural feature of streptonigrin is the configurationally stable C–D ring axis, which accounts for the observed optical activity of the natural product; circular dichroism studies determined the absolute stereochemistry as *M*.[16]

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Prior to our recent communication,[17] Weinreb and coworkers had reported the only total synthesis of streptonigrin in 1980.[18,19] Two subsequent formal syntheses from the groups of Kende[20] in 1981 and Boger[21] in 1985 stopped five and seven steps short of the target, respectively. Strategically, Weinreb constructed the pyridine C-ring via an imino Diels–Alder reaction, Kende utilized a regioselective condensation of a β-ketoenamine with methyl acetoacetate, and Boger employed an inverse-electron-demand Diels–Alder reaction of a heterocyclic azadiene.

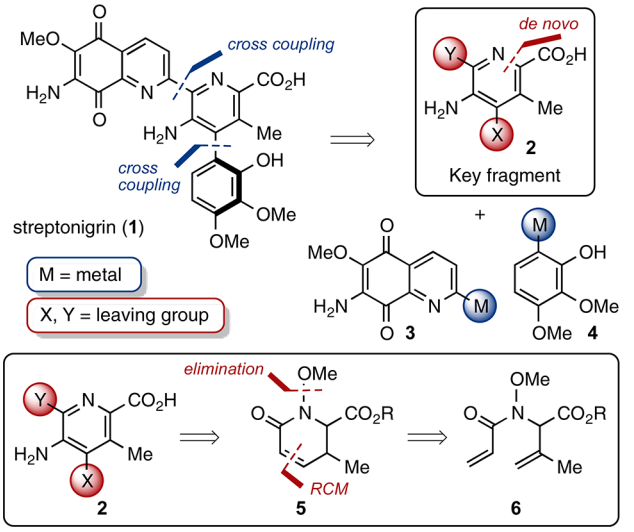
Despite the termination of clinical trials, interest has remained in generating analogues of streptonigrin as potential drug candidates.[2] However, these compounds have tended to be abridged versions of **1**, as the synthetic routes available to late-stage analogues can be lengthy.[18−21] Elsewhere, attempts to derivatize the metabolite itself have been limited to basic transformations,[16,22] as direct isolation from the fermentation of *Streptomyces* species yields only 13 mg per 1 L of culture filtrates.[23] The ability to generate late-stage streptonigrin analogues would enable a range of previously untried structural elements to be evaluated at key sites on **1**, therein revealing the potential to address the fundamental pharmacological limitations of streptonigrin. In order to facilitate this, it became evident that a more efficient and convergent pathway to **1** was required. To this end, we recently communicated a total synthesis of (±)-streptonigrin that should enable the preparation of such a set of compounds.[17] Herein, we report our full investigations into the synthesis of **1**, including a first-generation route to the core pentasubstituted pyridine fragment that is higher yielding overall, but two steps longer than the second generation approach. There is also a full discussion of Weinreb's end game, which proved capricious in our hands, and how we came to a revised route, plus recent studies evaluating chiral ligands for a demanding asymmetric Suzuki–Miyaura cross-coupling reaction.

Synthesis Plan. With a view toward future analogue preparation, our principal design objective was to assemble the core tetracyclic framework of streptonigrin at a late stage of the synthesis to allow for the greatest amount of derivatization on each ring prior to convergence. Inspired by reports on the coupling of biaryl fragments of streptonigrin,[24−28] we devised a retrosynthetic strategy that would see both the challenging 2,2′-bipyridyl AB-C linkage and the chiral C–D ring axis constructed via metal-catalyzed cross-coupling reactions, leaving the dual-activated pyridine C-ring **2** as the key fragment (Scheme 1). Here, we would also study the innate reactivity differences between the C-4 and C-6 leaving groups on the pyridine. It was envisaged that pentasubstituted pyridine **2** could be readily accessed through methodology recently developed in the group,[29−31] namely the generation of heteroaromatic compounds utilizing a ring closing metathesis (RCM) reaction as the cyclization step (Scheme 1 bottom). Subsequent elimination of the *N*-methoxy leaving group, functionalization, and aromatization would furnish pyridine **2**. The relatively sensitive quinoline-5,8-dione moiety **3** would be generated via a late-stage oxidation of a functionalized methoxy quinoline component, while the D-ring precursor **4** would come from commercial 2,3-dimethoxyphenol.

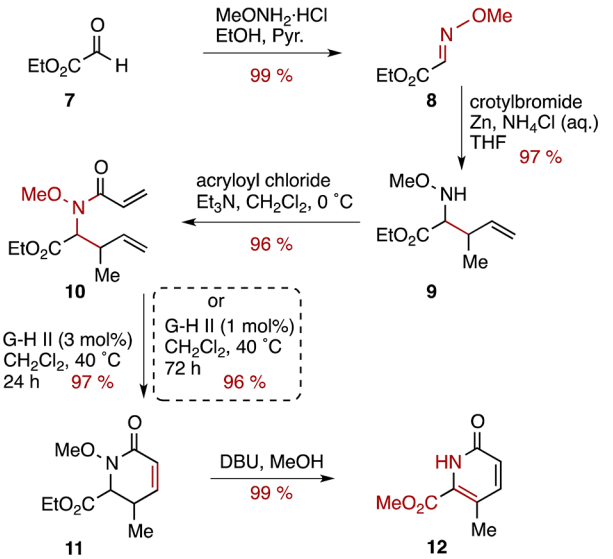
RESULTS AND DISCUSSION

Synthesis of Pentasubstituted Pyridine: First-Generation Route. According to the proposed RCM methodology, a suitable diene of type **6** was easily prepared in 92% yield over

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Disubstituted Pyridone 12



three steps from ethyl glyoxalate **7** (Scheme 2). Initial condensation of methoxyamine hydrochloride with ethyl glyoxalate, followed by a regioselective zinc-mediated crotylation of the resulting oxime ether **8**, furnished methoxyamine **9** in 96% yield over the two steps and as an inconsequential 3:2 mixture of diastereoisomers. Next, acylation with acryloyl chloride proceeded smoothly to generate the RCM precursor **10**. Pleasingly, the key RCM step was effected extremely efficiently using Hoveyda–Grubbs second-generation catalyst (3.0 mol % catalyst loading), which afforded dihydropyridone **11** in 97% yield. This reaction has been carried out on a 3.5 g (14.5 mmol) scale, and the catalyst loading can also be lowered to 1.0 mol % without a drop in yield, although reducing the amount of catalyst resulted in an increase in reaction time (from 24 to 72 h).

Next, elimination of the methoxy leaving group on nitrogen was effected using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base. Having observed a mixture of ethyl and methyl ester dihydropyridones when ethanol was used as the solvent, complete transesterification to a single methyl ester product **12** was achieved when the reaction was performed in methanol

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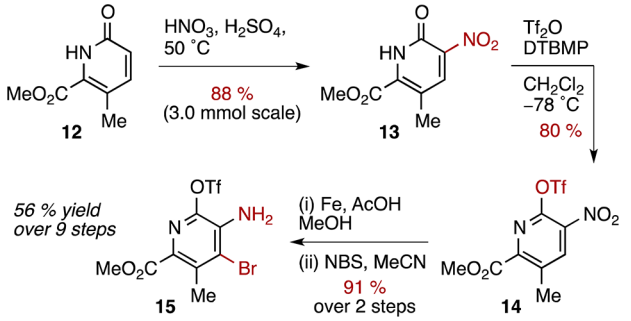
(note: this ester interconversion enabled our route to converge to a late-stage formal intermediate from Weinreb's synthesis).[18]

With the core pyridone **12** in hand, we had to attach the appropriate functionality that adorns pyridine **2**. Central to our synthetic strategy is the ability to control the regioselectivity of the first of the late-stage cross-coupling reactions with dual-activated pyridine **2**, as there will be two sites capable of undergoing oxidative addition (C-4 and C-6). While pyridine is known to exert an innate preference for addition of Pd(0) into C−X bonds *ortho* to the pyridyl nitrogen,[32] aryl bromotriflates have been shown to undergo oxidative addition into either activated bond through the appropriate selection of reaction conditions.[33] It was therefore reasoned that installation of a bromine atom at the C-4 position of **2** and a trifluoromethanesulfonyl group at C-6 should offer both reagent and substrate control as potential sources of regioselectivity.

Owing to the inherent preference of pyridone **12** to undergo electrophilic substitution at C-5, it followed that nitration was the next step, and we were pleased to find that heating **12** in a 2:1 mixture of nitric and sulfuric acids in a sealed tube afforded the highly polar nitropyridone **13** in an excellent 88% yield (Scheme 3). This process proved capricious upon scale-up

Scheme 3. Synthesis of Pentasubstituted Pyridine 15

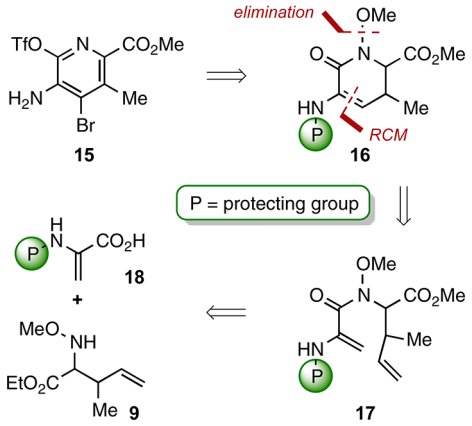


(>3.0 mmol) due to competing ester hydrolysis. Despite attempts to reliably reproduce the nitration on larger scales, the extent to which hydrolysis occurred proved to be highly batch-specific. While a good amount of nitropyridone was generated via this route and some of the acid byproduct could be restored to the methyl ester upon a separate addition of methanol, we would ultimately seek an alternative strategy for the synthesis of pyridine **2** to facilitate our objective of producing gram-quantities of late-stage streptonigrin compounds (vide infra).

Nevertheless, with nitropyridone **13** in hand, we treated this compound with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to furnish 6-triflylpyridine **14** in 80% yield. Reduction of the nitro group in the presence of iron powder and acetic acid afforded the free amine, and subsequent bromination with *N*-bromosuccinimide (NBS) gave the desired pyridine **15** in nine steps and 56% overall yield from ethyl glyoxalate. X-ray crystallographic analysis of **15** confirmed the correct substitution pattern around the pyridine core (see the Supporting Information).[34]

Synthesis of Pentasubstituted Pyridine 15: Second-Generation Route. During the course of our investigations into the synthesis of pyridine **15**, it became evident that the nitration of pyridone **12** was unreliable upon scale-up. As such we devised a shorter and more convergent RCM route to **15** that would not require this late-stage functionalization (Scheme 4). Introduction of the amine prior to RCM was a much more

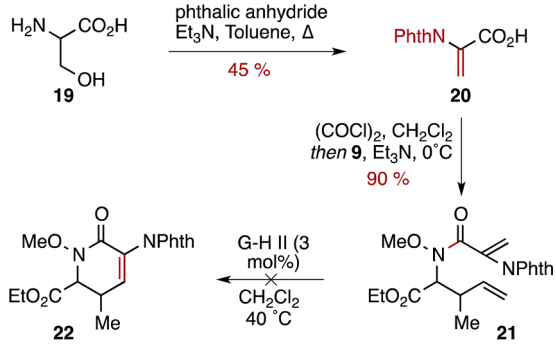
Scheme 4. Second-Generation Route to Key Pentasubstituted Pyridine 15



challenging proposition for the methodology, as it not only necessitated tolerating a bulky 1,1-disubstituted alkene **17**, but also an enamine moiety which had not previously been employed.

The choice of a suitable protecting group for α-amino acrylic acid **18** was crucial to the success of this new approach, as it had to be compatible with RCM as well as being easy to prepare and then remove following cyclization. Initial attempts to couple commercially available 2-acetamidoacrylic acid with methoxyamine **9** proved unsuccessful: the preparation of activated acids from peptide coupling reagents (HOBt, CDI, and DCC), a pentafluorophenyl ester, mixed anhydrides, and acid chloride all led to decomposition. Although no products could be isolated, it was postulated that the nucleophilic nature of the acetamide carbonyl oxygen was causing competing reactivity. With this in mind, we investigated the suitability of a phthalimide group, as the imide carbonyl was anticipated to be less nucleophilic than the amide and the requisite protected acid **20** can be readily prepared in one step from DL-serine and phthalic anhydride (Scheme 5).[35] Gratifyingly, when *N*-

Scheme 5. Attempted Synthesis of Amino-Substituted Dihydropyridone 22



protected α-amino acrylic acid **20** was treated with oxalyl chloride it displayed no signs of decomposition and could be coupled in situ with methoxyamine **9** to furnish the RCM precursor **21** in 90% yield.

The challenging nature of the 1,1-disubstituted alkene substrate **21** was confirmed when application of the previous RCM reaction conditions (see Schemes 2 and 5) led to complete recovery of starting material. Increasing the catalyst loading to 10 mol % gave the same result (Table 1, entry 1).

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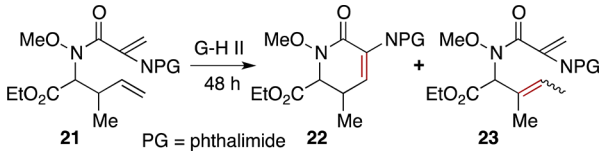
Table 1. Initial Studies into Ring-Closing Metathesis of 1,1-Disubstituted Diene 21



entry	catalyst loading (mol %)	solvent	temp (°C)	additive (20 mol %)	% 22[a]	% 23[a]
1	10	CH_2Cl_2	40	none	0	
2	10	CH_2Cl_2	70[b]	none	47	38
3	10	CH_2Cl_2	70[b]	BQ	48	
4	10 + 5[c]	CH_2Cl_2	70[b]	BQ	55	
5	10 + 5[c]	CH_2Cl_2	70[b]	TCBQ	39	
6	10 + 5[c]	toluene	110	BQ	58	
7	10	CH_2Cl_2	95[d]	BQ	47[e]	
8	10	toluene	160[b]	BQ	62[e]	
9	5 + 5[f]	toluene	160[b]	BQ	64[e]	
10	10	toluene	160[b]	BQ	70[g]	

[a]Isolated yield following chromatography. [b]Reaction performed in a sealed tube. [c]Second catalyst addition after 24 h. [d]Reaction performed in a microwave. [e]Reaction time 10 min. [f]Second catalyst addition after 5 min. [g]Reaction time 1 h. BQ = benzoquinone; TCBQ = tetrachlorobenzoquinone.

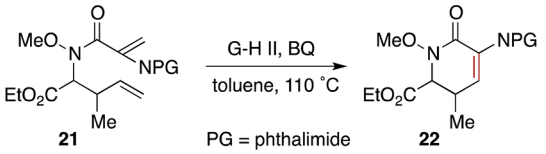
However, we were encouraged to find that upon raising the temperature to 70 °C (reaction carried out in a sealed tube) the desired dihydropyridone **22** could be isolated in 47% yield (entry 2).

With reaction at elevated temperatures, the recovered starting material **21** had actually undergone isomerization to the internal alkene **23**, present as an inseparable 2:1 mixture of *E*/*Z* isomers. Isomerizations of this kind are well documented, and commonly proposed mechanisms invoke the participation of ruthenium hydride species formed by decomposition of the metathesis catalyst.[36] Grubbs has reported that this process can be inhibited by the addition of species that quench any [Ru−H] formed in situ before isomerization can occur.[37] As a result, we performed the same reaction in the presence of benzoquinone (BQ) and tetrachlorobenzoquinone (TCBQ), with both additives preventing the formation of **23** (entries 3 and 5). Despite this improvement, significant amounts of starting material (unisomerized) were still recovered, prompting the addition of a second portion of metathesis catalyst part way through the reaction (entry 4). Switching the solvent to toluene enabled the reaction to be run at higher temperatures and again resulted in a small improvement in the yield (entry 6).

With the aim of increasing the reaction rate so that it might out-compete the rate of catalyst decomposition, the RCM was carried out in a microwave reactor under a variety of conditions (entries 7−10). We were pleased to discover that a catalyst loading of 10 mol % at 160 °C for 1 h produced dihydropyridone **22** in 70% yield. Unfortunately, upon attempted scale-up, these conditions were found to be reliable only on relatively small quantities of starting material (<0.25 g, 0.65 mmol). With the microwave presenting both chemical and logistical constraints with respect to scale-up, we decided to revert to thermal conditions in our pursuit of a reliably high-yielding process.

During the synthesis of the 10-membered macrolactone (−)-diplodialide C, Stoltz demonstrated that slow addition of a metathesis catalyst was crucial to the success of a challenging RCM.[38] In our case, gradual introduction of the catalyst appeared to offer a solution to the problems relating to decomposition. Thus, we attempted the RCM with slow addition of catalyst via syringe pump (Table 2).

Table 2. Ring-Closing Metathesis of 1,1-Disubstituted Diene 21 with Slow Catalyst Addition



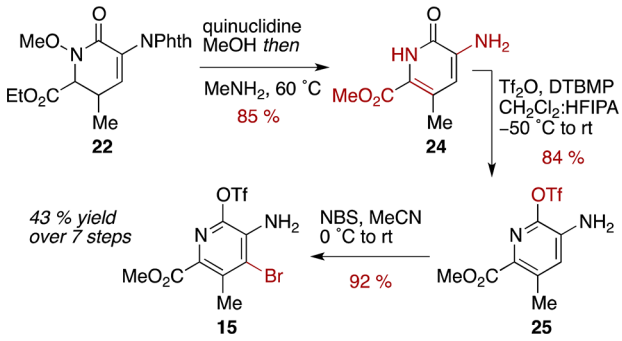
entry	catalyst loading (mol %)	catalyst addition time (h)	% 22[a]
1	10	5	63
2	10	10	78
3	10	20	61
4	5	10	76

[a]Isolated yield following chromatography, BQ = benzoquinone.

Pleasingly, this regimen worked extremely well, and we were able to efficiently generate RCM product **22** in 76% yield using just 5.0 mol % of Hoveyda−Grubbs second-generation catalyst added as a solution in toluene over 10 h to a mixture of precursor **21** and BQ in refluxing toluene (entry 4). Moreover, this reaction has been performed reliably on a 1.5 g (3.9 mmol) scale, which has facilitated the production of gram-quantities of late-stage synthetic material.

With an efficient and scaleable RCM protocol in place, attention turned to the manipulations required to convert *N*-phthalimide-protected dihydropyridone **22** to pentasubstituted pyridine **15**. To our surprise, treatment of **22** with DBU in methanol only led to decomposition, instead of the corresponding pyridone. As a result, we tested a range of bases with pK_a values similar to DBU and found that quinuclidine reliably effected elimination of the *N*-methoxy leaving group (Scheme 6). Because of partial phthalimide

Scheme 6. One-Pot, Trifunctional Procedure en Route to Pentasubstituted Pyridine 15



opening under these conditions, we identified an opportunity to extend the tandem elimination−transterification sequence (see Scheme 2). To this end, methylamine was added to the reaction mixture, once elimination was complete, to finish cleavage of the phthalimide group, affording aminopyridone **24** in an excellent 85% yield from dihydropyridone **22**. Thus, an efficient trifunctional one-pot procedure has been developed

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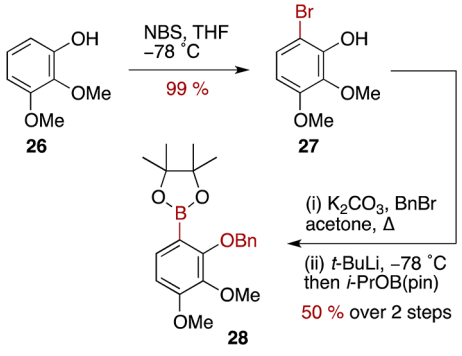
that accomplishes elimination, transesterification, and deprotection.

In order to converge with pyridine **15** from the first route, it was necessary to introduce a trifluoromethanesulfonyl group selectively on the pyridone oxygen, as opposed to the arylamine. Due to its high polarity, **24** proved to be only sparingly soluble in all but the most polar solvents, and when treated with triflic anhydride in DMF, the sole product isolated was that from sulfonylation at the aryl amine; evidenced in the ^{1}H NMR spectrum by the appearance of a downfield 1H singlet corresponding to the electron deficient sulfonamide N–H. Pleasingly, when the triflation was conducted in a 25:1 mixture (by volume) of dichloromethane and hexafluoroisopropyl alcohol (HFIPA), a highly polar but only weakly nucleophilic solvent, **24** was converted to pyridine **25** in 84% yield (Scheme 6). Neither *N*-sulfonylation nor a deleterious reaction between the alcohol and triflic anhydride were observed. The spectroscopic data of **25** were an exact match to the data obtained via the first-generation route.

Having intercepted the previous route, we could see that the second-generation approach afforded key pyridine fragment **15** in 43% yield and seven steps from ethyl glyoxalate (counting the one-pot transformation of **22** into **24** as one step). This compares to 56% yield over nine steps from the first synthesis. Crucially though, the second-generation route proved to be more scaleable and has been used routinely to prepare multigram-quantities of material for the latter stages of the synthesis. Both of the approaches described have showcased the utility of the RCM methodology to efficiently prepare highly substituted pyridines in few synthetic transformations from commercial chemicals.

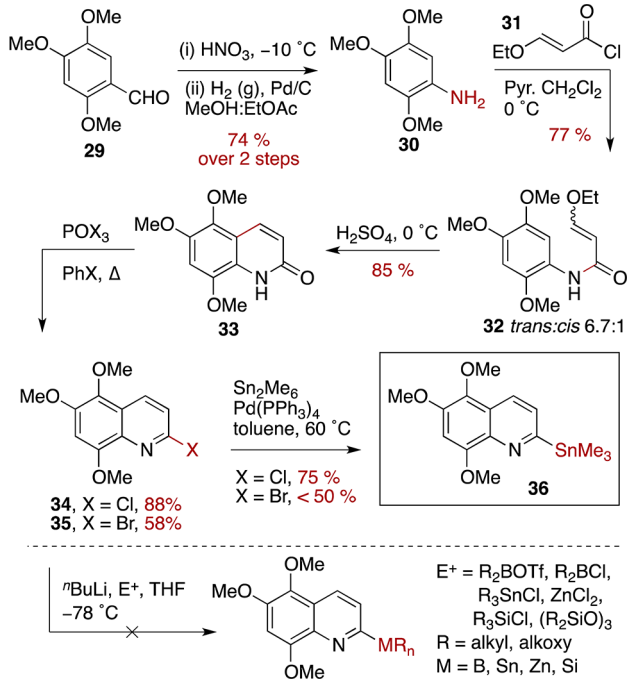
Synthesis of the D-Ring Fragment. Both Quéguiner[39] and Holzapfel[25] have shown that the C–D ring linkage in model streptonigrin systems can be constructed using a Suzuki–Miyaura cross-coupling reaction. Following a similar strategy here necessitated the preparation of a boronate ester derivative of the D-ring fragment **4**. Consequently, commercially available 2,3-dimethoxyphenol (**26**) was brominated[40] with NBS in THF at −78 °C to give bromophenol **27** as a single regioisomer (confirmed by X-ray crystallography; see the Supporting Information)[41] in near-quantitative yield (Scheme 7). Next, phenol **27** was *O*-benzyl protected; as Weinreb's synthesis had employed the same protecting group this would enable our route to converge to a late-stage intermediate from that synthesis. Finally, treatment of the benzylated compound with *t*-BuLi and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane furnished boronic acid pinacol ester **28**.

Scheme 7. Synthesis of D-Ring Boronate Ester 28



Synthesis of the AB-Ring Fragment. Establishing unsymmetrical 2,2′-bipyridyl motifs, as present around the AB–C ring linkage of **1**, via metal-catalyzed cross-coupling reactions can be challenging.[42,43] Most notably the preparation of an organometallic partner is potentially problematic due to the increased reactivity at the site *ortho* to the pyridyl nitrogen. However, this strategy has been successful in model streptonigrin systems, although functionality was often reduced on one or both of the components.[26,27] In order to provide as much tactical variation as possible, it was envisaged that 5,6,8-trimethoxyquinolines **34** and **35** (see Scheme 8), with appropriate leaving groups in the C-2 position, would provide access to a range of possible metal-substituted coupling partners.

Scheme 8. Synthesis of 2-Stannylquinoline 36



Synthesis of the quinolines began with the conversion of commercially available 2,4,5-trimethoxybenzaldehyde (**29**) to the corresponding nitro compound in 80% yield upon treatment with a cold aqueous solution of nitric acid (Scheme 8).[44] Reduction of this nitro group with Pd/C and hydrogen smoothly afforded aniline **30**, which was subsequently acylated with (*E*)-3-ethoxyacryloyl chloride[45] **31** to generate aryl amide **32** in 72% yield over the two steps and as an inconsequential 6.7:1 ratio of *trans*/*cis* stereoisomers. Cyclization to **33** proceeded efficiently in sulfuric acid to establish the AB-ring scaffold in 85% yield, while subsequent treatment with phosphorus oxychloride effected aromatization to chloroquinoline **34** in 88% yield. The corresponding 2-bromoquinoline **35** was synthesized using phosphorus oxybromide in 58% yield.

With quinolines **34** and **35** in hand, we attempted to construct the corresponding boron-, tin-, zinc-, and silicon-containing compounds (Scheme 8 bottom). However, standard lithium/halogen exchange conditions, followed by trapping of the resultant anion, failed to furnish any 2-metalated quinolines, instead yielding mixtures of protodehalogenated quinoline and dimerized 5,5′,6,6′,8,8′-hexamethoxy-2,2′-biquinoline.

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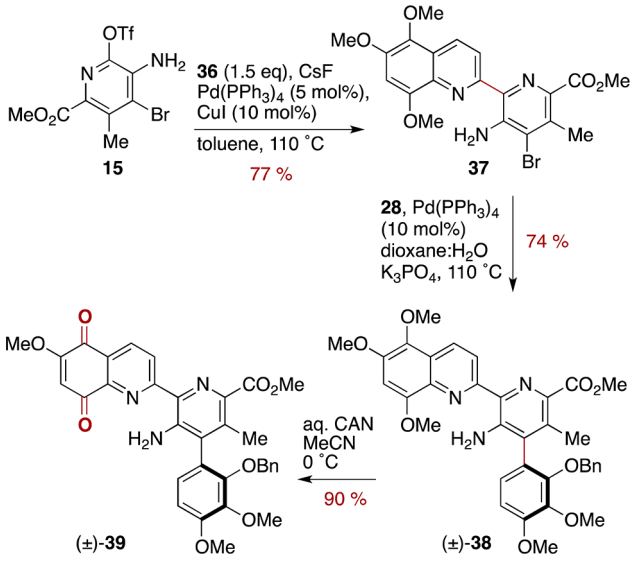
At this stage, we were encouraged by Padwa's report into the synthesis of analogues of lavendamycin,[46] whereby 2-stannylquinolines were generated using hexamethylditin and Pd(0), a different mode of reactivity to the electrophilic trapping described above. Gratifyingly, when chloroquinoline **34** was treated with hexamethylditin and catalytic $Pd(PPh_3)_4$, the corresponding stannane **36** was obtained in 75% yield, albeit contaminated with triphenylphosphine oxide (4:1 stannane/$POPh_3$ by ^1H NMR spectroscopy). Stannane **36** was unstable to chromatography so was used without purification. Applying these conditions to the more reactive bromoquinoline **35** led to added complexity in the crude reaction mixture, with less than 50% conversion to stannane **36** by analysis of the ^1H NMR spectrum.

Unification of the Ring Fragments. We now had access to the three principal fragments **15**, **28**, and **36** required to construct the tetracyclic framework of streptonigrin (see Scheme 1). The next task was to test the hypothesis that the C-6 position of pyridine **15** would be more reactive than C-4 toward oxidative addition of Pd(0). With this prediction in mind, we began by investigating the Stille reaction between **15** and **36** that would potentially establish the AB−C ring linkage of **1** (Scheme 9). We were pleased to verify that coupling

Scheme 9. Synthesis of Tetracyclic Quinone 39



occurred exclusively at C-6 and that no products relating to either competing reaction at C-4 nor protodebromination were observed. Following optimization of reaction conditions it was found that the addition of CuI and CsF to $Pd(PPh_3)_4$ (5.0 mol %) in toluene at reflux with 1.5 equiv of stannane **36** afforded the greatest yield of the tricyclic ABC fragment **37** (77% yield compared to 62% in the absence of additives, and just 52% when equimolar amounts of **15** and **36** were used).[47]

Next, a Suzuki−Miyaura coupling of bromopyridine **37** and aryl borate ester **28** was studied. Initial investigations using $Pd(OAc)_2$ (25 mol %) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) (30 mol %) in the presence of an aqueous solution of Na_2CO_3 led to the formation of tetracyclic fragment **38** in an encouraging 71% yield. However, subsequent attempts to reduce the catalyst loading had a significant detrimental effect on the yield (10 mol % $Pd(OAc)_2$ led to 53% of **38**). Further investigations revealed that $Pd(PPh_3)_4$ was the most efficient catalyst; loadings of 10 mol % afforded **38** in 74% yield with aqueous K_3PO_4 as the optimal base.

With the tetracyclic framework of **1** established, a highly regioselective ceric ammonium nitrate (CAN)-mediated oxidation[48] of quinoline **38** to quinoline-5,8-dione **39** resulted in the interception of a late-stage intermediate in Weinreb's total synthesis. The preparation of an aged aqueous CAN solution proved to be key to this transformation, as solutions made immediately prior to the reaction led to significant decomposition and only produced **39** in 20−35% yields. It was postulated that by allowing the CAN solution to stand for a period of time it had tempered the acidity and/or oxidizing potential of the one electron oxidant and reduced the propensity for decomposition. Consequently, it was discovered that a solution prepared 24 h in advance would reliably produce the desired *p*-quinone in 90% yield, without any decomposition or trace of the regioisomeric *o*-quinone.

Having intercepted Weinreb's late-stage intermediate, we were able to verify that our spectroscopic data matched those previously reported. A summary of our streptonigrin formal synthesis illustrates the convergent modular strategy: quinoline-5,8-dione **39** has been prepared in ten linear steps in an overall yield of 22% from inexpensive ethyl glyoxalate.[18−21]

Asymmetric Suzuki−Miyaura Cross-Coupling Reactions. Cross-coupling reactions to form hindered biaryl units are challenging by their nature.[49] In terms of catalytic asymmetric variants, following pioneering studies from Buchwald[50] and Cammidge,[51] there have been a number of further reports, although the level of generality has typically been modest.[52,53] In line with our design criteria, we embarked on a program to investigate the feasibility of rendering asymmetric the Suzuki−Miyaura reaction between pyridyl bromide **37** and aryl boronate ester **28** that constructs the chiral C-D ring axis of streptonigrin. This would potentially enable the synthesis of enantiomerically enriched streptonigrin, as well as late-stage analogues, for the first time.

Preliminary investigations revealed that an enantiomeric excess (ee) of 22% can be obtained by using (*R*)-BINAP, instead of S-Phos, in the presence of $Pd(OAc)_2$ at 60 °C (Table 3, entry 1).[17] These initial studies also revealed that chiral monodentate phosphine ligands, such as (*R*)-(+)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ((*R*)-MOP),[54] do not impart any degree of stereocontrol, while the bidentate amino phosphine ligand, (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino)ferrocene,[51] showed very little catalytic activity. Given these results, we were encouraged to pursue this transformation further and focused our attention on bidentate phosphines.

To this end, lowering the reaction temperature to 40 °C with (*R*)-BINAP led to the desired increase in enantioselectivity but with a decrease in yield (entry 2). Employing a number of commercially available chiral bidentate bisphosphine ligands revealed that those based around a BINAP scaffold (entries 1−5) tended to afford higher levels of atroposelectivity compared to standard SEGPHOS ligands (entries 6−8); (*R*)-DM-BINAP generated the tetracyclic compound **38** in 36% ee (entry 5).

Lassaletta and co-workers have recently shown that phosphino hydrazone precatalysts such as **40** are effective at catalyzing Suzuki−Miyaura cross-coupling reactions of hindered biaryls with a good degree of stereocontrol.[53] When **40** was employed in our system, we were pleased to observe an increase in enantioselectivity (note: the product was the opposite enantiomer to that obtained with (*R*)-BINAP), albeit

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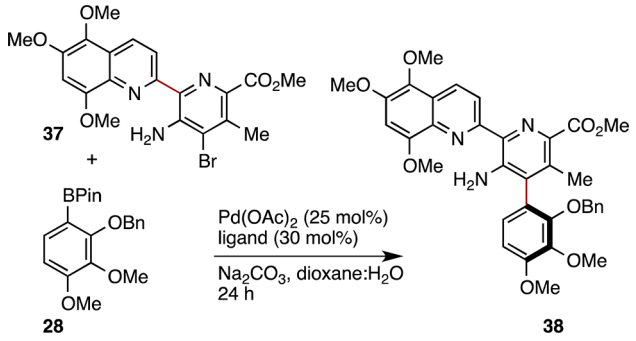
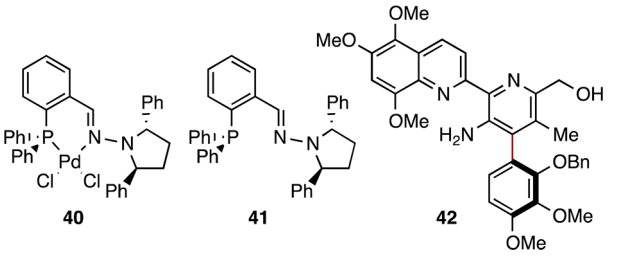
Table 3. Investigating Chiral Bidentate Phosphine Ligands



entry	ligand	temp (°C)	yield (%)[a]	ee (%)[b]
1	(*R*)-BINAP	60	65	(−) 22
2	(*R*)-BINAP	40	37	(−) 27 [20][c]
3	(*R*)-tol-BINAP	40	20	(−) 35
4	(*R*)-H_8−BINAP	40	43	(−) 27
5	(*R*)-DM-BINAP	40	25	(−) 36
6	(*R*)-SEGPHOS	40	41	(−) 13
7	(*R*)-DM-SEGPHOS	40	38	(−) 15
8	(*R*)-DTBM-SEGPHOS	40	15	(−) 22
9[d]	precatatyst **40**	40	17	(+) 40 [35][c]
10[e]	phosphino hydrazone **41**	40	65	(+) 42
11[e]	phosphino hydrazone **41**	60	85	(+) 29 [22][c]
12[e]	phosphino hydrazone **41**	110	54	(+) 8

[a]Isolated yield following chromatography. [b]Determined by chiral HPLC analysis (the absolute stereochemistry of the major enantomer is unknown). [c]Figure in square brackets determined by analysis of the ^{1}H NMR spectrum of the Mosher's ester derivative of the corresponding primary alcohol **42**. [d]Palladium−phosphino hydrazone precatalyst **40** (25 mol %) used. [e]Phosphino hydrazone ligand **41** (25 mol %) and $Pd_2(dba)_3$ (12.5 mol %) used.



with a lower yield (entry 9). Gratifyingly, catalytic activity improved markedly when the free phosphino hydrazone ligand **41** was used in conjunction with $Pd_2(dba)_3$, affording cross-coupled product **38** in 65% yield and 42% ee (entry 10). Attempts to further improve conversion by increasing the temperature resulted in lower levels of stereocontrol (entries 11 and 12). The use of alternative bases such as CsF[55] and Ag_2O[56] resulted in no reaction, while the employment of CuI as an additive[57] to improve catalytic activity also returned starting material.

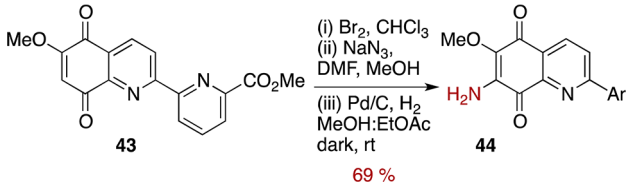
During the course of these studies, we became aware of a potential small inaccuracy in the data obtained from chiral HPLC analysis. This was attributed to a few causes, including the limited solubility of the product, broad peaks in the UV traces, as well as the presence of a small impurity with the same retention time as one of the enantiomers that could not be removed despite many attempts at purification. As a result, a representative sample of the products obtained in Table 3 were each reduced to primary alcohol **42** and then acylated with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to afford the corresponding Mosher's esters. Subsequent analysis of the ^{1}H and ^{19}F NMR spectra of these samples (see figures in square brackets in Table 3)[58] largely corroborated the previous data, although it did suggest that a slight overestimation of the atroposelectivity (approximately 5−7%) had resulted from chiral HPLC analysis.

At this stage, having studied a number of variables in an attempt to improve both the activity and selectivity of this demanding transformation, we decided to move on to investigating the end game for synthesizing the natural product. The preparation of a late-stage tetracyclic streptonigrin intermediate **38** has been achieved in 65% yield and with a moderate level of enantiocontrol (42% ee from chiral HPLC analysis), using a phosphino hydrazone ligand **41**. This is the first report of an enantioenriched intermediate or analog of **1** to be obtained via synthesis and work to augment the degree of atroposelectivity is ongoing in our laboratories.

End Game. Returning to the synthesis of (±)-streptonigrin, conversion of intermediate quinoline-5,8-dione **39** into the natural product required the introduction of the C-7 amino group, removal of the D-ring benzyl ether, and hydrolysis of the pyridine methyl ester. Weinreb had already achieved these transformations in 17% yield over five steps in his synthesis,[19,59] but the end game itself has received virtually no attention since the original publication; hence, we decided to look more closely at the sequence.

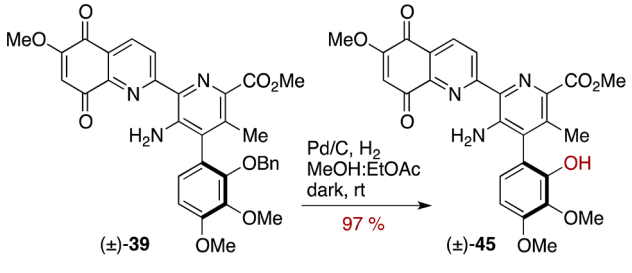
During their synthesis of ABC-ring analogues of streptonigrin, Harding demonstrated that an azide could be installed on quinoline-5,8-dione **43** and then efficiently reduced to primary amine **44** using Pd/C and hydrogen (Scheme 10).[27] Similarly, we found that exposing quinoline-5,8-dione intermediate **39** to the reducing conditions led smoothly to the deprotected phenol **45** (Scheme 11).

Scheme 10. Harding's Azide Reduction in Streptonigrin Analog Synthesis Using Pd/C and Hydrogen



Given these observations, we believed that there was the opportunity to telescope the azide reduction and hydrogenolysis steps from Weinreb's end game (**47** → **48**, Scheme 12) and so we began investigating a modified approach that would shorten the sequence from five to four steps.

Scheme 11. Model Streptonigrin Benzyl Ether Hydrogenolysis Using Pd/C and Hydrogen



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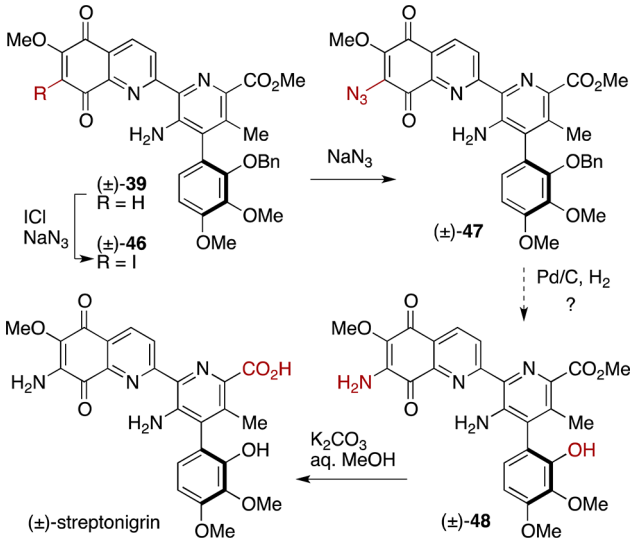
Scheme 12. Proposed Shortened Sequence for the End Game



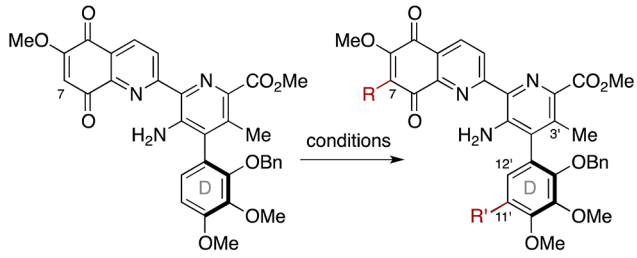
Taking the established tactics as a starting point, we sought to introduce iodine at the 7-position of **39** using IN_3 generated in situ from ICl and sodium azide. However, in our hands, we were unable to reliably reproduce this transformation, and despite exhaustively studying the preparation and handling of IN_3 we consistently obtained a complex mixture of products; only small amounts (<10%) of the desired iodo compound **46** were detected in the ^{1}H NMR spectra of crude material. We confirmed in situ generation of iodine azide[60] by successfully performing an iodoazidation of cinnamaldehyde dimethyl acetal;[61] while Ciufolini has used these tactics effectively at the end of his synthesis of streptinigrone,[48] it should be noted that the C-5′ amino pyridine is protected as a Cbz group and the authors do draw attention to the instability of their intermediates.

Having been unable to accomplish the initial iodination step of the end game, we briefly investigated alternative reagents for the direct installation of nitrogen on either quinoline-5,8-dione **39** or quinoline **38**. Disappointingly, electrophilic amination[62] of **39** using chloramine[63] returned starting material, whereas methods to nitrate quinoline **38** led predominantly to the quinoline-5,8-dione **39**, as a product of oxidation, without introducing the desired nitro group.[64]

As a result of these findings, we ceased investigations into direct amination and returned our attention to the functionalization of **39** via initial halogenation and subsequent nucleophilic azide displacement. In order to develop an understanding of the inherent reactivity of the quinoline-5,8-dione toward halogenation, **39** was exposed to a series of halogenating reagents (Table 4).

Treatment of **39** with various iodinating and chlorinating reagents resulted in no reaction and complete recovery of starting material (Table 4, entries 1 to 5). On the other hand, **39** proved to be reactive toward a range of brominating agents. Interestingly, it was found that initial bromination occurred preferentially on the D-ring to afford **49**, and when **39** was treated with 1.1 equiv of brominating reagent a mixture of **49**, dibrominated **50**, and starting material was observed (entries 6–8). Increasing the amount of bromine led to complete consumption of starting material, producing 80% of the dibrominated derivative **50** (entry 9), with a small amount of

Table 4. Halogenation of Quinoline-5,8-dione 39



entry	conditions[a]	conversion[b] (%)
1	ICl, MeCN, 0 °C	no reaction
2	NIS, $CHCl_3$, rt	no reaction
3	I_2, $CHCl_3$, 0 °C to rt	no reaction
4	I_2, $AgNO_3$, $CHCl_3$, 0 °C to rt	no reaction
5	NCS, $CHCl_3$, 0 °C to rt	no reaction
6	NBS, $CHCl_3$, rt	**39**:**49**:**50**(1:1:1)
7	TBCO, $CHCl_3$, rt	**39**:**49**:**50**(1:1:1)
8	Br_2, $CHCl_3$, rt	**39**:**49**:**50** (2:1:2)
9[c]	Br_2, $CHCl_3$, rt	**50**, 80%
10[c]	Br_2, pyr, $CHCl_3$, rt	**50**, 99%

[a]1.1 equiv of halogenating reagent used. [b]Conversions measured by ^{1}H NMR spectroscopy. [c]4.0 equiv of bromine used. NIS = *N*-iodosuccinimide, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, TBCO = 2,4,4,6-tetrabromo-2,5-cyclohexadienone.

decomposition visible in the ^{1}H NMR spectrum of the crude material. It was postulated that this decomposition resulted from the generation of HBr during the reaction, so an excess of pyridine was added to buffer the reaction mixture. Pleasingly, this led to the complete conversion of **39** to the dibrominated compound **50** (entry 10). Based on a steric rationale, the site of D-ring bromination was presumed to be C-11′, and this was confirmed by an observed NOE correlation between the C-3′ methyl group and the remaining proton on the D-ring, indicating that the proton is at C-12′.[17] This innate preference for D-ring bromination is advantageous, as it represents an attractive handle for possible manipulation in future streptonigrin analog syntheses, yet it should be readily removed under the proposed hydrogenation conditions later in the end game; overall, **50** appeared to be a viable alternative to the iodo compound **46** from Weinreb's route.

Dibrominated compound **50** was found to be unstable to chromatography, so it was immediately treated with sodium azide in DMF at 0 °C to furnish azido derivative **51** (Scheme 13). This compound also proved to be unstable, so **51** was subjected directly to the hydrogenation conditions used previously (see Schemes 11 and 12). To our satisfaction, catalytic Pd/C and hydrogen in a mixture of methanol and ethyl acetate did indeed effect the three planned transformations: azide reduction, benzyl ether hydrogenolysis, and reduction of the D-ring aryl bromide. Pleasingly, this trifunctional hydrogenative procedure proved to be robust and reliable. Including bromination and the nucleophilic displacement with azide, streptonigrin methyl ester **48** was generated in 57% overall yield from the formal quinoline-5,8-dione intermediate **39**.

Finally, according to Weinreb's synthesis,[19] treatment of **48** with potassium carbonate in aqueous methanol revealed the free C-ring carboxylic acid, affording (±)-streptonigrin **1** in

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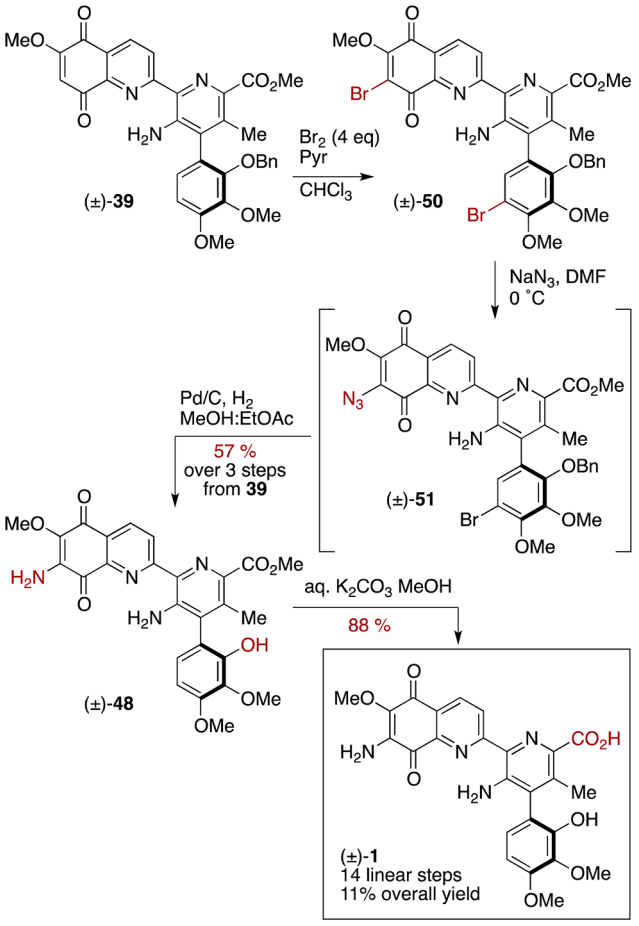
Scheme 13. Revised Streptonigrin End Game



88% yield, the spectroscopic data of which matched those reported in the literature and that of an authentic sample of the natural product.[65] Attempts to reduce the relatively long reaction time for hydrolysis (48 h) by increasing the concentration led to lower yields of the acid.

Overall, the synthetic sequence for converting late-stage formal intermediate **39** into the natural product has been revised and now stands at 50% yield over four steps. Key to the success of this approach was the development of a trifunctional hydrogenative protocol, which has enabled the revised route to be both reliable and robust and will facilitate the future synthesis of a library of late-stage streptonigrin analogs for biological evaluation.

CONCLUSION

We have completed a concise and efficient total synthesis of the antitumor agent (±)-streptonigrin (**1**) in 14 linear steps from inexpensive ethyl glyoxalate with an overall yield of 11% (counting the one-pot transformation of **22** into **24** as one step). The synthesis showcases recent methodology in the rapid generation of a complex substituted pyridine, which has been accessed via two different pathways, and also revises the long-standing end game for streptonigrin, providing a more streamlined and robust set of tactics. The first-generation route to pyridine **15** afforded streptonigrin in a slightly longer sequence (16 linear steps) but an increased 14% overall yield. However, this approach is limited to small-scale synthesis and hence the second-generation route offers a more practical alternative to prepare the natural product and late-stage analogues whose biological activity could be quickly evaluated. Finally, investigations into the use of chiral ligands to effect a challenging asymmetric Suzuki–Miyaura cross-coupling reaction, and so enable the synthesis of enantioenriched streptonigrin, revealed moderate levels of enantioselectivity in the presence of bidentate phosphino hydrazone and bisphosphine ligands.

EXPERIMENTAL SECTION

General experimental considerations are provided in the Supporting Information. Experimental procedures and spectroscopic analysis for new compounds are listed below; for the experimental procedures and characterization data of the remaining compounds, see ref 17.

Ethyl 2-(*N*-Methoxyacrylamido)-3-methylpent-4-enoate (10). Acryloyl chloride (2.9 mL, 35 mmol) was added dropwise to a stirred solution of methoxylamine **9** (4.40 g, 23.5 mmol) and triethylamine (6.9 mL, 50 mmol) in dichloromethane (47 mL) at 0 °C. The mixture was allowed to warm to rt and was stirred for 16 h. The mixture was diluted with dichloromethane (50 mL) and quenched with water (50 mL). The aqueous phase was re-extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (gradient 8:1 to 4:1 PE/EtOAc, R_f 0.31 in 8:1) to afford **10** as a light yellow oil (5.44 g, 96%) as a 2:1 mixture of diastereoisomers which were not separated. The ^{1}H and ^{13}C NMR data provided are for the major diastereomer. ^{1}H (400 MHz, $CDCl_3$) δ: 6.71 (1H, dd, J = 10.4, 17.6 Hz, COC=CH_2), 6.46 (1H, dd, J = 1.6, 17.0 Hz, COCH=CH_2), 5.83–5.67 (2H, m, COCH=CH_2 and CH(CH_3)CH=CH_2), 5.13 (1H, d, J = 17.3 Hz, CH(CH_3)CH=CH_2), 5.03 (1H, d, J = 10.1 Hz, CH(CH_3)CH=CH_2), 4.82 (1H, d, J = 9.8 Hz, C$H$$CO_2$Et), 4.20–4.12 (2H, m, $CO_2CH_2CH_3$), 3.81 (3H, s, OCH_3), 3.04–2.98 (1H, m, C$H$$CH_3$), 1.24 (3H, t, J = 6.9 Hz, $CO_2CH_2CH_3$), 1.03 (3H, d, J = 6.7 Hz, CHCH_3). ^{13}C (101 MHz, $CDCl_3$) δ: 169.9, 168.1, 139.5, 130.7, 126.1, 116.4, 64.9, 64.7, 61.4, 37.8, 17.5, 14.4. IR (thin film) ν_{max}: 3082 (w), 2981 (m), 2940 (w), 1744 (s), 1669 (s), 1621 (m), 1409 (s), 1270 (m), 1194 (m), 1029 (m), 787 (m) cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{19}NO_4Na$ 264.1206, found 264.1205.

Ethyl 1-Methoxy-3-methyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate (11). To a solution of Hoveyda–Grubbs second-generation catalyst (170 mg, 0.271 mmol) in dichloromethane (280 mL) was added a solution of **10** (2.18 g, 9.04 mmol) in dichloromethane (20 mL). The solution was heated at reflux for 24 h. The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was purified by column chromatography (1:1 PE/EtOAc, R_f 0.29) to afford **11** as a light brown oil (1.87 g, 97%) as a 2:1 mixture of diastereoisomers which were not separated. The ^{1}H and ^{13}C NMR data provided are for the major diastereomer. ^{1}H (400 MHz, $CDCl_3$) δ: 6.16 (1H, dd, J = 10.0, 1.4 Hz, COCH=CH), 5.84 (1H, dd, J = 9.9, 2.8 Hz, COCH=CH), 4.33 (1H, d, J = 7.3 Hz, C$H$$CO_2$Et), 4.16 (2H, q, J = 7.19 Hz, OCH_2CH_3), 3.77 (3H, s, OCH_3), 3.29–3.21 (1H, m, C$H$$CH_3$), 1.26 (3H, t, J = 7.3 Hz, $CO_2CH_2CH_3$), 1.20 (3H, d, J = 7.5 Hz, CHCH_3). ^{13}C (101 MHz, $CDCl_3$) δ: 168.9, 166.3, 143.2, 123.9, 66.7, 63.2, 61.9, 34.5, 16.2, 14.5. IR (thin film) ν_{max}: 2979 (s), 2940 (s), 2904 (s), 2818 (w), 1669 (s), 1625 (s), 1460 (s), 1385 (s), 1199 (s), 1022 (s), 818 (s), 706 (s) cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{10}H_{15}NO_4Na$ 236.0893, found 236.0895.

Methyl 3-Methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (12). DBU (1.67 mL, 11.2 mmol) was added to a solution of **11** (1.69 g, 7.93 mmol) in methanol (23 mL), and the resulting mixture was stirred for 15 h at rt. The reaction mixture was concentrated in vacuo to yield the crude product which was purified by column chromatography (gradient EtOAc to 9:1 EtOAc/MeOH, R_f 0.12 in EtOAc) to afford **12** as a white solid (1.31 g, 99%). ^{1}H (400 MHz, $CDCl_3$) δ: 9.84 (1H, br s, NH), 7.29 (1H, d, J = 9.5 Hz, COCH=CH), 6.71 (1H, d, J = 9.2 Hz, COCH=CH), 3.95 (3H, s, OCH_3), 2.40 (3H, s, CCH_3). ^{13}C (101 MHz, $CDCl_3$) δ: 162.2, 161.7, 145.8,

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129.7, 126.9, 121.8, 53.4, 18.6. Mp: 120−121 °C (recrystallized from CH_2Cl_2) (lit.[31] mp 120−123 °C). These data were in accordance with the literature values.[31]

Methyl 3-Methyl-5-nitro-6-oxo-1,6-dihydropyridine-2-carboxylate (13). Concentrated sulfuric acid (1.2 mL) was added dropwise to a screw-top tube containing a solution of pyridone **12** (0.500 g, 2.99 mmol) in concd nitric acid (2.0 mL) at 0 °C, and the reaction vessel was then sealed. After 5 min, the reaction mixture was allowed to warm to rt and then heated at 50 °C. After 7 h, the reaction mixture was allowed to cool to rt and then poured into ice−water. The aqueous layer was extracted six times with ethyl acetate (until the yellow color had faded), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was then purified by column chromatography (19:1 EtOAc/MeOH, R_f 0.50) to afford **13** as a yellow solid (0.558 g, 88%). ^{1}H (400 MHz, DMSO-d_6) δ: 12.82 (1H, br s, N−H), 8.41 (1H, s, C^4-*H*), 3.88 (3H, s, OCH_3), 2.31 (3H, s, CH_3). ^{13}C (126 MHz, DMSO-d_6) δ: 162.1, 153.3, 141.0, 139.1, 118.8, 53.0, 16.6 (note: one peak not observed in ^{13}C NMR spectrum). IR (thin film) ν_{max}: 3054 (br), 2956 (w), 2851 (m), 1670 (s), 1271 (s), 1208 (s) cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_8H_8N_2O_5Na$ 235.0331, found 235.0326.

Methyl 3-Methyl-5-nitro-6-(((trifluoromethyl)sulfonyl)oxy)-picolinate (14). Trifluoromethanesulfonic anhydride (0.71 mL, 4.25 mmol) was added dropwise to a solution of nitropyridone **13** (0.500 g, 2.36 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.723 g, 3.54 mmol) in dichloromethane (25 mL) at −78 °C. The solution was allowed to warm to 0 °C and was stirred at 0 °C for 4 h. The reaction mixture was washed with satd aq $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was then purified by column chromatography (4:1 PE/EtOAc, R_f 0.60) to afford **14** as a pale yellow oil (0.649 g, 80%). ^{1}H (400 MHz, $CDCl_3$) δ: 8.47 (1H, s, Ar*H*), 4.01 (3H, s, OCH_3), 2.72 (3H, s, CH_3). ^{13}C (101 MHz, $CDCl_3$) δ: 163.4, 149.0, 143.8, 139.9, 137.8, 136.8, 118.4 (q, J = 319 Hz, CF_3), 53.3, 19.0. IR (thin film) ν_{max}: 3001 (w), 2941 (w), 1736 (s), 1582 (s), 1540 (s), 1427 (s), 1321 (s), 1212 (s), 1126 (s), 1037 (s), 881 (s), 829 (s) cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_9H_7F_3N_2O_7Na$ 366.9818, found 366.9809.

Methyl 5-Amino-3-methyl-6-(((trifluoromethyl)sulfonyl)-oxy)picolinate (25). Iron powder (325 mesh, 0.975 g, 17.4 mmol) was added to a solution of nitropyridine **14** (0.400 g, 1.16 mmol) in methanol (7.0 mL) and acetic acid (7.0 mL). The reaction mixture was heated at reflux for 2 h and then allowed to cool to rt and neutralized through the addition of solid Na_2CO_3. Water (10 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (4:1 PE/EtOAc, R_f 0.48) to afford **25** as a colorless crystalline solid (0.361 g, 99%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.01 (1H, s, Ar-H), 4.31 (2H, br s, NH_2), 3.89 (3H, s, OCH_3), 2.58 (3H, s, CH_3); ^{13}C (126 MHz, $CDCl_3$) δ: 164.9, 139.8, 139.6, 136.2, 132.4, 127.1, 118.5 (q, J = 319 Hz, CF_3), 52.2, 19.9. Mp: 108−110 °C (recrystallized from CH_2Cl_2). These data were in accordance with the literature values.[17]

Methyl 5-Amino-4-bromo-3-methyl-6-(trifluoromethylsulfonyloxy)picolinate (15). *N*-Bromosuccinimide (0.260 g, 1.46 mmol) was added to a solution of **25** (0.418 g, 1.33 mmol) in acetonitrile (13 mL) at 0 °C, and the reaction mixture was allowed to warm to rt and was stirred for 4 h. Solvent was removed in vacuo, and the residue was redissolved in dichloromethane (30 mL) and was washed with 1 M HCl (30 mL), satd aq $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (7:1 PE/EtOAc, R_f 0.22) to afford **15** as a colorless crystalline solid (0.480 g, 92%). ^{1}H (500 MHz, $CDCl_3$) δ: 4.81 (2H, br s, NH_2), 3.92 (3H, s, OCH_3), 2.71 (3H, s, CH_3). ^{13}C (126 MHz, $CDCl_3$) δ: 164.8, 138.8, 138.1, 135.0, 132.8, 123.0, 118.5 (q, J = 319 Hz, CF_3), 52.6, 19.5. Mp: 117−118 °C (recrystallized from CH_2Cl_2). These data were in accordance with the literature values.[17]

Ring-Closing Metathesis Procedures Using Diene 21. *Procedure A: Thermal without Benzoquinone Additive.* Hoveyda−Grubbs second-generation catalyst (0.016 g, 0.026 mmol) was added to a reaction tube charged with diene **21** (0.100 g, 0.259 mmol) in dichloromethane (2.6 mL). The solution was degassed by bubbling argon through for 5 min; the tube was then sealed and the reaction heated to 70 °C for 48 h. The reaction mixture was cooled to rt and concentrated in vacuo to yield a mixture that was purified by flash column chromatography to afford the desired product **22** (0.044 g, 47%, 3:2 PE/EtOAc R_f 0.20) and the isomerized starting material **23** (0.038 g, 38%, 1:1 PE:EtOAc, R_f 0.36), both as olive-colored oils. Each was obtained as an inseparable 2:1 mixture of diastereoisomers.

Procedure B: Microwave. Hoveyda−Grubbs second-generation catalyst (0.041 g, 0.065 mmol) was added to a reaction tube charged with diene **21** (0.250 g, 0.648 mmol) and benzoquinone (0.014 g, 0.130 mmol) in toluene (6.5 mL). The solution was degassed by bubbling argon through for 5 min; the tube was then sealed and the reaction subjected to microwave irradiation at 160 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to yield the crude product which was purified by flash chromatography (3:2 PE/EtOAc, R_f 0.20) to afford **22** as an olive-colored oil (0.162 g, 70%) and as an inseparable 2:1 mixture of diastereoisomers.

Procedure C: Optimized. A solution of Hoveyda-Grubbs' second generation catalyst (0.126 g, 0.201 mmol) in toluene (10 mL) was added dropwise over 10 h *via* a syringe pump to a refluxing solution of **21** (1.55 g, 4.01 mmol) and benzoquinone (0.065 g, 0.602 mmol) in toluene (40 mL). Once addition was complete, the mixture was heated at reflux for a further 6 h. The reaction mixture was allowed to cool to rt; dimethyl sulfoxide (1.07 mL, 15.0 mmol) was added, and the resulting solution was stirred at rt for 1 h. The crude mixture was preadsorbed onto silica gel (3.0 g) and the solvent removed in vacuo. The product was then purified by column chromatography (3:2 PE/EtOAc, R_f 0.20) to afford **22** as a colorless oil (1.09 g, 76%) and as an inseparable 2:1 mixture of diastereoisomers.

Ethyl 5-(1,3-Dioxoisoindolin-2-yl)-1-methoxy-3-methyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate (22). The ^{1}H and ^{13}C NMR spectroscopic data provided for **22** are for the major diastereoisomer. ^{1}H (500 MHz, $CDCl_3$) δ: 7.90−7.87 (2H, m, 2 × Ar-H), 7.76−7.74 (2H, m, 2 × Ar-H), 6.39 (1H, d, J = 2.6 Hz, C^4−H), 4.46 (1H, dd, J = 7.3 Hz, C*H*CO$_2$Et), 4.36−4.26 (2H, m, CO$_2$CH_2CH$_3$), 3.83 (3H, s, OCH_3), 3.52 (1H, dqn, J = 7.3, 2.5 Hz, C*H*CH$_3$), 1.33−1.31 (6H, m, CO$_2$CH$_2$CH_3 and CHCH_3). ^{13}C (126 MHz, $CDCl_3$) δ: 167.9, 166.9, 162.0, 143.0, 134.3, 131.9, 124.3, 123.7, 66.3, 62.5, 62.0, 32.5, 15.7, 14.1. These data were in accordance with the literature values.[17]

Ethyl 2-(2-(1,3-Dioxoisoindolin-2-yl)-*N*-methoxyacrylamido)-3-methylpent-3-enoate (23). The ^{1}H and ^{13}C NMR spectroscopic data provided for **23** are for the major diastereoisomer. ^{1}H (500 MHz, $CDCl_3$) δ: 7.88 (2H, dd, J = 3.2, 5.4 Hz, 2 × Ar*H*), 7.75 (2H, dd, J = 3.2, 5.4 Hz, 2 × Ar*H*), 6.23 (1H, s, NC=CH_2), 5.97 (1H, d, J = 1.0 Hz, NC=CH_2), 5.59 (1H, qt, J = 1.3, 6.6 Hz, CH$_3$C*H*=C), 5.30 (1H, s, NC*H*CO$_2$Et), 4.21 (2H, q, J = 7.3 Hz, OCH_2CH$_3$), 3.76 (3H, s, OCH_3), 1.74 (3H, s, C(CH_3)=C), 1.67 (3H, d, J = 7.6 Hz, CH_3CH=C), 1.27 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C (126 MHz, $CDCl_3$) δ: 168.9, 166.2, 164.2, 134.5, 131.7, 130.1, 128.2, 127.5, 123.8, 121.3, 67.6, 64.8, 61.6, 15.2, 14.1, 13.7. IR (thin film) ν_{max} 2962 (w), 2941 (w), 1789 (w), 1726 (s), 1660 (m), 1630 (m), 1369 (m), 1210 (m), 1101 (m), 1027 (m), 919 (m), 731 (m), 716 (m) cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{20}H_{22}N_2O_6Na$ 409.1370, found 409.1369.

2-Bromo-5,6,8-trimethoxyquinoline (35). Phosphorus oxybromide (0.129 mL, 1.27 mmol) was added to a solution of **33** (0.050 g, 0.212 mmol), pyridine (0.103 mL, 1.27 mmol), and DMF (0.005 mL) in bromobenzene (1.0 mL) at rt, and the resulting mixture was heated at reflux for 1.5 h. The reaction mixture was allowed to cool to rt and quenched upon slow addition of satd aq $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (2:1 PE/EtOAc, R_f 0.40) to afford **35** as a colorless crystalline solid (0.037 g, 58%). ^{1}H (400 MHz,

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$CDCl_3$) δ: 8.21 (1H, d, J = 8.8 Hz, 2 × Ar*H*), 7.50 (1H, d, J = 8.8 Hz, 2 × Ar*H*), 6.86 (1H, s, Ar*H*), 4.05 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 3.91 (3H, s, OCH_3). ^{13}C (100 MHz, $CDCl_3$) δ: 151.7, 149.0, 138.8, 135.5, 135.3, 132.5, 126.8, 123.4, 99.2, 61.5, 57.0, 56.2. IR (thin film) ν_{max} 3002 (w), 2931 (w), 2847 (w), 1610 (m), 1567 (s), 1384 (s), 1238 (s), 1098 (s), 913 (s), 826 (s), 777 (s) cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{13}BrNO_3$ 298.0073 and 300.0053, found 298.0070 and 300.0047. Mp: 149−150 °C (recrystallized from CH_2Cl_2).

General Procedure for the Asymmetric Suzuki−Miyaura Reaction. A solution of the palladium source (0.008 mmol) and ligand (0.010 mmol) in dioxane (0.1 mL) was stirred at rt for 30 min. A solution of aryl boronate ester **28** (0.049 mmol) and pyridine **37** (0.032 mmol) in dioxane (0.22 mL) was subsequently added. The reaction mixture was degassed and refilled with argon five times, and then a solution of sodium carbonate (1.0 M, 0.10 mL) was added. The mixture was degassed and refilled with argon five times again and then heated at the designated temperature for 24 h. The mixture was allowed to cool to rt, diluted with EtOAc (1.0 mL), and washed with brine (1.0 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (2:1 PE:EtOAc, R_f 0.32) to afford **38** as a yellow solid. A sample obtained using phosphino hydrazone ligand **41** that afforded product with 30% ee (by chiral HPLC analysis) gave $[\alpha]_D^{25}$ + 51.5 (c = 0.29, $CHCl_3$).

Methyl 5-Amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-methyl-6-(5,6,8-trimethoxyquinolin-2-yl)picolinate (38). ^{1}H (200 MHz, $CDCl_3$) δ: 8.88 (1H, d, J = 9.1 Hz, Ar-H), 8.49 (1H, d, J = 9.1 Hz, Ar-H), 7.12−7.10 (3H, m, Ar-H), 7.05−7.01 (2H, m, Ar-H), 6.88 (2H, s, Ar-H), 6.83 (1H, s, Ar-H), 4.93 (1H, d, J = 11.0 Hz, OCH_2Ph), 4.86 (1H, d, J = 11.0 Hz, OCH_2Ph), 4.04 (3H, s, OCH_3), 4.01 (6H, s, 2 × OCH_3), 3.97 (6H, s, 2 × OCH_3), 3.95 (3H, s, OCH_3), 2.29 (3H, s, CH_3). ^{13}C (62.5 MHz, $CDCl_3$) δ: 167.2, 155.7, 154.1, 152.1, 150.7, 148.7, 145.2, 143.4, 137.1, 136.6, 135.8, 134.4, 133.1, 133.0, 132.7, 130.0, 128.1 (2 × C), 128.0 (2 × C), 127.7, 125.1, 123.0, 122.1, 120.9, 108.4, 98.3, 75.2, 61.6, 61.1, 57.2, 56.1 (2 × C), 52.1, 17.5. Mp 209−210 °C (recrystallized from CH_2Cl_2). These data were in accordance with the literature values.[17]

(*S*)-(5-Amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-methyl-6-(5,6,8-trimethoxyquinolin-2-yl)pyridin-2-yl)methyl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (52). A solution of $LiAlH_4$ (1.0 M, 0.062 mL) was added to a solution of racemic **38** (0.013 g, 0.021 mmol) in THF (0.20 mL) at −30 °C. The mixture was warmed to rt and stirred for 4 h. A saturated aqueous solution of Na_2SO_4 was added until excess $LiAlH_4$ was quenched, and solid Na_2SO_4 had precipitated. The solution was then filtered and concentrated in vacuo. The crude product **42** was used without further purification. DMAP (0.011 g, 0.086 mmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.013 mL, 0.069 mmol) were added to a solution of **42** (0.0079 g, 0.013 mmol) in dichloromethane (0.13 mL). The reaction was stirred at rt for 16 h or until TLC indicated consumption of the starting material. The reaction was filtered through a small silica plug and then purified by column chromatography (gradient PE to 2:1 PE/EtOAc, R_f 0.30 in 2:1) to afford **52** as a red solid (0.0087 mg, 48%). ^{1}H (400 MHz, $CDCl_3$) δ: 8.80 (1H, d, J = 9.2 Hz, Ar-H), 8.42 (1H, d, J = 9.2 Hz, Ar-H), 7.58−7.54 (2H, m, Ph), 7.33−7.29 (3H, m, Ph), 7.08−6.93 (5H, m, Mosher Ph), 6.87 (2H, s, Ar-H), 6.83 (1H, s, Ar-H), 5.65−5.57 (1H, m, $CH_2OC(O)$), 5.48−5.41 (1H, m, $CH_2OC(O)$), 4.93−4.86 (1H, m, CH_2Ph), 4.80−4.77 (1H, m, CH_2Ph), 4.04 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.96 (6H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.52 (3H, s, Mosher OCH_3), 1.92 (3H, s, CH_3). ^{13}C (126 MHz, toluene-d_8) δ: 166.6 (2 × C), 156.9, 154.5 (2 × C), 152.5, 151.5, 151.4, 148.9, 144.3 (q, CF_3), 139.5, 139.4, 134.2, 133.7, 133.6, 133.5, 133.3 (2 × C), 133.2, 129.9, 123.5, 123.1 (2 × C), 121.2, 108.8, 99.8, 69.2, 68.9, 60.9, 60.7, 57.2, 55.6, 55.4, 14.4. δ_F (472 MHz, toluene-d_8): 71.73, 71.76. IR (thin film) ν_{max}: 3460 (w), 3321 (w), 2930 (m), 2850 (m), 1746 (m), 1625 (m), 1600 (m), 1581 (m), 1490 (m), 1465 (m), 1422 (w), 1358 (m), 1228.21 (br m), 1169 (w), 1098 (s), 1069 (w), 1001 (w), 921 (w), 719 (w) cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{44}H_{42}F_3N_3O_9Na$ 836.2771, found 836.2736. Mp: 190−195 °C (recrystallized from CH_2Cl_2).

(±)-Methyl 5-Amino-4-(2-hydroxy-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (45). Palladium (10 wt.% on carbon, 0.007 g) was added to a solution of quinoline-5,8-dione **39** (0.020 g, 0.034 mmol) in methanol/EtOAc (3:1 by volume, 13.5 mL total). The reaction mixture was degassed in vacuo, placed under an atmosphere of H_2 (g), and stirred in the dark at rt for 12 h. The mixture was filtered through a pad of Celite eluting with EtOAc (10 mL), and the combined organic layers were concentrated in vacuo. The crude product was purified by column chromatography (1:1 PE/EtOAc, R_f 0.28) to afford debenzylated **45** as a dark red/brown solid (0.017 g, 97%). ^{1}H (200 MHz, $CDCl_3$) δ: 9.04 (1H, d, J = 8.4 Hz, Ar-H), 8.50 (1H, d, J = 8.4 Hz, Ar-H), 6.82 (1H, d, J = 8.7 Hz, Ar-H), 6.67 (1H, d, J = 8.6 Hz, Ar-H), 6.29 (1H, s, Ar-H), 5.89 (1H, br s, OH), 3.99 (6H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 2.34 (3H, s, CH_3). ^{13}C (126 MHz, $CDCl_3$) δ: 182.8, 179.4, 167.0, 163.1, 160.5, 152.7, 147.0, 146.2, 145.6, 138.0, 136.3, 135.7, 134.4, 132.9, 130.7, 125.7, 125.4, 125.1, 113.7, 109.9, 105.1, 61.2, 56.6, 56.0, 55.2, 17.4. IR (thin film) ν_{max}: 3467 (br), 3249 (br), 2953 (w), 1707 (s), 1687 (s), 1656 (m), 1610 (s), 1586 (s), 1460 (m), 1296 (s), 1243 (s), 1088 (s) cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Ccalcd for $C_{26}H_{23}N_3O_8Na$ 528.1377, found 528.1355. Mp: 113−114 °C (recrystallized from CH_2Cl_2).

(±)-Methyl 5-Amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (39). Example of an attempted nitration of quinoline **38**: Silver(II) oxide (0.016 g, 0.128 mmol) and nitric acid (35% aq, 0.04 mL) were added to a solution of quinoline (0.020 g, 0.032 mmol) in acetonitrile/water (4:1 by volume, 0.20 mL in total). The reaction mixture was allowed to stir at rt for 16 h, water was then added, and the mixture was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with satd aq $NaHCO_3$ and , brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (1:1 PE/EtOAc, R_f 0.52) to afford *p*-quinoline-5,8-dione **39** as a dark red crystalline solid (0.013 g, 68%). ^{1}H (200 MHz, $CDCl_3$) δ: 9.02 (1H, d, J = 8.5 Hz, Ar-H), 8.49 (1H, d, J = 8.5 Hz, Ar-H), 7.13−7.07 (3H, m, Ar-H), 7.02−6.98 (2H, m, Ar-H), 6.87 (1H, d, J = 8.7 Hz, Ar-H), 6.82 (1H, d, J = 8.7 Hz, Ar-H), 6.28 (1H, s, Ar-H), 4.96 (1H, d, J = 11.2 Hz, OCH_2Ph), 4.89 (1H, d, J = 11.2 Hz, OCH_2Ph), 3.99 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.94 (6H, s, OCH_3), 2.24 (3H, s, CH_3). ^{13}C (62.5 MHz, $CDCl_3$) δ: 182.7, 179.3, 166.9, 163.0, 160.4, 154.3, 150.5, 146.2, 145.5, 143.4, 137.8, 137.1, 135.5, 134.3, 133.9, 130.4, 128.1 (2 × C), 127.9 (2 × C), 127.8, 125.4, 125.3, 124.8, 121.3, 109.8, 108.6, 75.1, 61.1, 56.6, 56.1, 52.2, 17.6. Mp: 242−246 °C (recrystallized from CH_2Cl_2) (lit.[19] mp 242−243 °C). These data were in accordance with the literature values.[17]

(±)-Methyl 5-Amino-4-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)-6-(7-bromo-6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (50) and (±)-Methyl 5-Amino-4-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (49). Example bromination with 1.1 equiv of brominating reagent: Bromine (19 μL, 0.037 mmol) was added to a solution of quinoline-5,8-dione **39** (0.020 g, 0.034 mmol) in chloroform (1.1 mL) in the dark at rt The resulting reaction mixture was stirred for 8 h. Water (5.0 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a mixture of starting material **39**, monobrominated quinone **49**, and dibromo-quinone **50** in a 2:1:2 ratio (by analysis of the ^{1}H NMR spectrum of the crude material, quantitative recovery). The brominated compounds were unstable to silica, but small quantities of purified dibromo **50** (2:1 PE/EtOAc, R_f 0.70) and monobromo **49** (2:1 PE/EtOAc, R_f 0.50) could be obtained following silica gel chromatography, the data for which follows:

Dibromo **50**. ^{1}H (500 MHz, $CDCl_3$) δ: 9.05 (1H, d, J = 8.5 Hz, Ar-H), 8.46 (1H, d, J = 8.5 Hz, Ar-H), 7.14−7.11 (3H, m, Ar-H), 7.10 (1H, s, Ar-H), 7.01−6.99 (2H, m, Ar-H), 4.95 (1H, d, J = 11.3 Hz, OCH_2Ph), 4.88 (1H, d, J = 11.3 Hz, OCH_2Ph), 4.37 (3H, s, OCH_3),

4.04 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 2.25 (3H, s, CH_3). ^{13}C (125 MHz, $CDCl_3$) δ: 178.5, 176.7, 166.7, 162.8, 158.6, 151.9, 150.2, 148.8, 145.7, 144.5, 137.7, 136.6, 135.6, 134.4, 132.5, 130.4, 128.2, 128.1, 127.9 (2 × C), 125.9, 125.6, 125.2, 121.8, 112.9, 75.2, 62.1, 61.3, 61.2, 52.2, 17.6. Mp: 115−116 °C (recrystallized from CH_2Cl_2). These data were in accordance with the literature values.[17]

Monobromo **49**. ^1H (500 MHz, $CDCl_3$) δ: 9.04 (1H, d, J = 8.6 Hz, Ar-H), 8.52 (1H, d, J = 8.5 Hz, Ar-H), 7.14−7.10 (4H, m, Ar-H), 7.02−7.00 (2H, m, Ar-H), 6.31 (1H, s, Ar-H), 4.94 (1H, d, J = 11.2 Hz, OCH_2Ph), 4.88 (1H, d, J = 11.2 Hz, OCH_2Ph), 4.03 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 2.26 (3H, s, CH_3). ^{13}C (126 MHz, $CDCl_3$) δ: 182.7, 179.3, 166.7, 162.8, 160.5, 151.9, 150.2, 148.8, 145.7, 145.5, 137.6, 136.6, 135.6, 134.4, 132.4, 130.8, 128.3, 128.1, 128.0, 127.9, 125.7, 125.5 (2 × C), 112.9, 110.0, 75.3, 61.4, 61.2, 56.7, 52.2, 17.6. IR (thin film) ν_{max}: 3431 (br), 3235 (br), 2946 (w), 1711 (s), 1685 (s), 1661 (m), 1609 (m), 1586 (s), 1453 (m), 1242 (s), 1212 (s) cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{33}H_{28}BrN_3O_8Na$ 696.0963 and 798.0934, found 696.0963 and 698.0966; mp 252−254 °C (recrystallized from CH_2Cl_2).

(±)-Streptonigrin (1). Potassium carbonate (0.167 g, 1.21 mmol) was added to a solution of streptonigrin methyl ester **48** (0.007 g, 0.013 mmol) in methanol/water (2:1 by volume, 10.8 mL total), and the resulting solution was stirred at rt for 48 h. The methanol was removed *in vacuo* and the resulting mixture neutralized with 3 M HCl. The mixture was extracted with dichloromethane (3 × 5.0 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography using pH 6.8 buffered silica gel[66] (49:1 CH_2Cl_2/CH_3OH, R_f 0.20) to afford streptonigrin (**1**) as a dark brown/black crystalline solid (0.006 g, 88%). ^1H (500 MHz, DMSO-d_6) δ: 12.32 (1H, br s, CO_2H), 9.01 (1H, d, J = 8.4 Hz, Ar-H), 8.92 (1H, s, Ar−OH), 8.36 (1H, d, J = 8.5 Hz, Ar-H), 6.92 (2H, br s, Ar-NH_2), 6.73 (1H, d, J = 8.5 Hz, Ar-H), 6.70 (1H, d, J = 8.6 Hz, Ar-H), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.18 (3H, s, CH_3). ^{13}C (126 MHz, DMSO-d_6) δ: 180.3, 175.9, 167.0, 159.8, 153.1, 148.1, 145.7, 144.1, 141.6, 136.9, 136.2, 135.7, 134.5, 134.0, 133.4, 129.5, 126.7, 125.9, 124.6, 114.9, 104.4, 60.3, 59.7, 55.7, 17.0. Mp: 289−290 °C (recrystallized from CH_2Cl_2). These data were in accordance with the literature values.[17,65]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of all new compounds in addition to HPLC traces and Mosher's ester analysis of enantioenriched **38** and details of the attempted amination of quinoline-5,8-dione **39** and nitration of quinoline **38**. Details of the X-ray crystal structures of compounds **15** and **27** and the relevant crystallographic data are also included. This material is available free of charge via the Internet: http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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