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Total Synthesis of (±)-Streptonigrin: De Novo Construction of a Pentasubstituted Pyridine using Ring-Closing Metathesis

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Supporting Information

ABSTRACT: The synthesis of the potent antitumor agent (±)-streptonigrin has been achieved in 14 linear steps and 11% overall yield from ethyl glyoxalate. The synthesis features a challenging ring-closing metathesis reaction, followed by elimination and aromatization, to furnish a key pentasubstituted pyridine fragment.

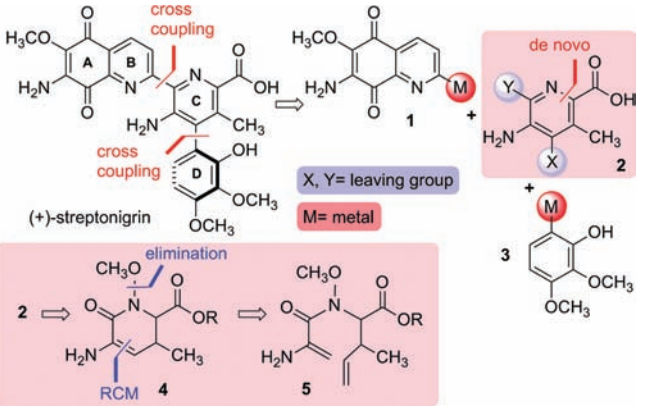
Streptonigrin is a highly functionalized aminoquinone antitumor antibiotic that has attracted considerable attention from both synthetic organic chemists and biochemists interested in its challenging molecular framework and broad-spectrum anticancer activity.[1−3] Found to be extremely effective in the treatment of cancer, streptonigrin reached phase II clinical trials; however, high levels of toxicity caused side effects which necessitated the cessation of these trials in the late 1970s.[4]

Following isolation from *Streptomyces flocculus* in 1959 by Rao and Cullen,[1] the structure of streptonigrin was established by Rao, Biemann, and Woodward in 1963 via spectroscopy and chemical degradation.[5] In 1975 Chiu and Lipscomb confirmed the structure using X-ray crystallography.[6] Subsequent investigations[7] involving truncated analogues established the cytotoxic mode of action, believed to be free radical-mediated DNA strand cleavage resulting from reductive activation by a metal ion and oxygen.[8] Elsewhere, circular dichroism studies revealed the absolute stereochemistry about the configurationally stable C−D ring axis to be (*M*).[9]

To date there has been only one total synthesis of (±)-streptonigrin in pioneering work by Weinreb in 1980.[10] Two impressive, formal, syntheses from Kende[11] in 1981 and Boger[12] in 1985 stopped five and seven steps short of the target, respectively. Weinreb's landmark synthesis of (±)-streptonigrin was 34 steps long with considerably less that 1% overall yield. The two subsequent syntheses represented a significant improvement in efficiency especially given the state of organic synthesis at the time the work was conducted. Kende's synthesis required 27 steps and Boger's just 17 if both had been taken through Weinreb's end game; however, when completed, both routes would afford streptonigrin in less than 1% overall yield.

Despite the termination of clinical trials, interest remains in generating analogues of streptonigrin so as to harness the potency of the natural product while tempering its cytotoxicity and thereby making it amenable as a potential drug.[2] In order to enable facile preparation of a range of analogues at key sites on streptonigrin, a more efficient and convergent synthesis is required. To this end, we devised a retrosynthetic strategy that would see the two biaryl units constructed by metal-catalyzed cross-coupling reactions,[13] leaving the dual activated pyridine C-ring **2** as the key fragment (Scheme 1). It was envisaged that pentasubstituted pyridine **2** could be readily accessed through methodology we had recently developed, namely the generation of heteroaromatic compounds utilizing a ring-closing metathesis (RCM) reaction as the cyclization step (see **5**→**4**).[14] Subsequent elimination and aromatization of **4** would furnish pyridine **2**. The quinone **1** would be obtained via late-stage oxidation of a functionalized quinoline component, while the D-ring precursor **3** would come from commercially available 2,3-dimethoxyphenol.

Scheme 1



Synthesis of pyridine **2** began by condensing methoxyamine with commercially available ethyl glyoxalate **6** (Scheme 2). Next, a zinc-mediated crotylation of the resulting oxime furnished **7** in 96% yield over the two steps. Acylation of **7** with *N*-phthalimide-protected α-amino acrylic acid **8** (obtained in one step from DL-serine)[15] was effected by in situ formation of the corresponding acid chloride followed by addition of **7** to afford the RCM precursor **9** in 90% yield.

The crucial RCM reaction represented a challenge, as it necessitated tolerating a 1,1-disubstituted alkene with a protected amine as one of the substituents. Through extensive optimization, we obtained the RCM product **10** in 76% yield using 5 mol % of Hoveyda−Grubbs second-generation catalyst. Key to this reaction was the slow addition of catalyst via a syringe pump, combined with the use of benzoquinone[16] to quench Ru−H species formed in situ.[17]

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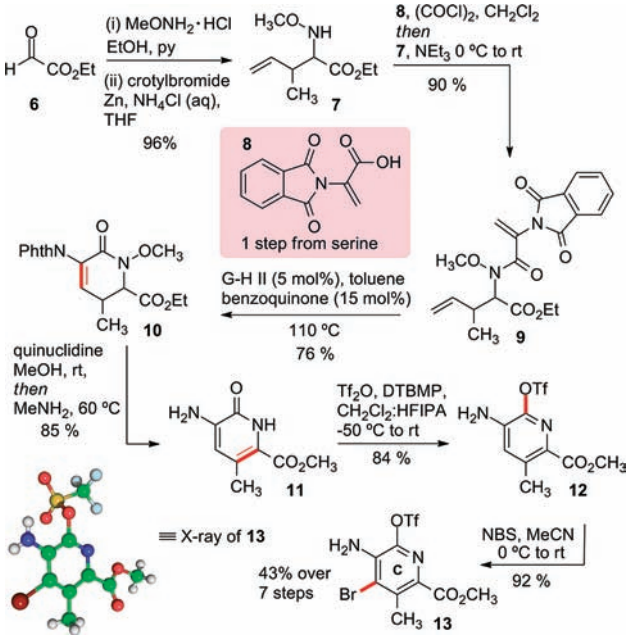
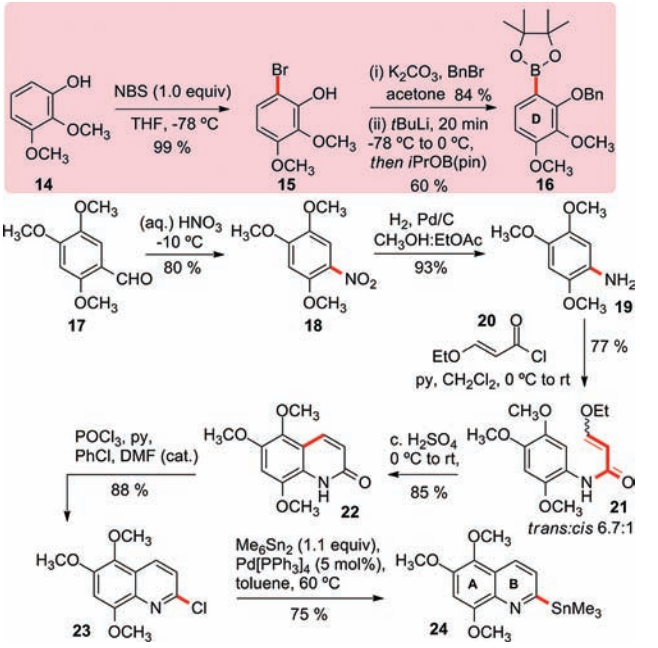
Scheme 2



Scheme 3



The next step was an elimination of the methanol leaving group, using quinuclidine as the optimum base. This reaction was performed in methanol so that a transesterification occurred, generating the corresponding methyl ester and enabling our route to converge with a late-stage intermediate from Weinreb's synthesis.[10] Moreover, methylamine was added to the reaction mixture to effect cleavage of the *N*-protecting group, resulting in an efficient one-pot, three-transformation procedure to afford aminopyridone **11** in 85% yield from dihydropyridone **10**.

With pyridine **2** in mind, we desired a bromine at the 4-position of the pyridine and a more reactive trifluoromethanesulfonyl group at the 2-position, which should preferentially react in the first of two cross-coupling reactions. As a result, pyridone **11** was converted to pyridine **12** in 84% yield using triflic anhydride, 2,6-di-*tert*-butyl-4-methyl pyridine and hexafluoroisopropanol (HFIPA). Subsequent bromination with *N*-bromosuccinimide furnished the penta-substituted pyridine **13** in 92% yield. The structure of **13** was confirmed by X-ray crystallographic analysis.

Attention then turned to the two remaining coupling partners **1** and **3**. Work by Quéguiner and Holzapfel has shown that the C−D ring axis in model systems could be constructed *via* a Suzuki cross-coupling reaction, and we followed a similar strategy to attach the D-ring fragment.[18] Consequently, borate ester **16** was synthesized in three steps from commercially available **14** (see box, Scheme 3). A regioselective bromination of **14** with *N*-bromosuccinimide[19] afforded bromophenol **15** as the sole regioisomer (confirmed by X-ray crystallographic analysis) in near quantitative yield. Protection of the phenol proceeded smoothly to generate a benzyl ether which was subsequently treated with *tert*-butyllithium and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give pinacol ester **16** in 60% yield.

It was envisaged that 2-chloro-5,6,8-trimethoxy quinoline would provide access to a range of nucleophilic coupling partners that could potentially establish the AB−C ring linkage.[20] To this end, commercially available 2,4,5-trimethoxybenzaldehyde **17** was converted to the corresponding nitro compound **18** in 80% yield with nitric acid (Scheme 3).[21] Reduction using catalytic Pd/C and hydrogen afforded aniline **19**, which was subsequently acylated with (*E*)-3-ethoxyacryloyl chloride **20**[22] to generate aryl amide **21** in 72% yield over the two steps and as an inconsequential mixture of stereoisomers. Cyclization in sulfuric acid established the AB-ring scaffold, generating **22** in 85% yield, while treatment with phosphorus oxychloride effected aromatization to chloroquinoline **23** in 88% yield.

From **23**, we attempted to construct the corresponding boron-, tin-, zinc-, and silicon-containing compounds. However, standard lithium−halogen exchange conditions followed by trapping failed to furnish any metal substituted quinolines. Following work by Padwa,[20d] we discovered that treatment of **23** with hexamethylditin and tetrakis(triphenylphosphine)-palladium gave the corresponding stannane **24**, albeit contaminated with triphenylphosphine oxide (75% conversion by ^{1}HNMR spectroscopy; stannane **24** was unstable to chromatography and used without purification).

With the three main fragments in hand, we began to construct the tetracyclic scaffold of streptonigrin. A Stille reaction with tetrakis(triphenylphosphine)palladium efficiently coupled stannylquinoline **24** with pyridine **13**, generating the AB−C framework **25** in 77% yield (Scheme 4).[23] Pleasingly, no product resulting from coupling to the 4-bromo position on the pyridine was observed.[24] Next, a Suzuki reaction involving bromopyridine **25**, aryl borate ester **16**, and tetrakis(triphenylphosphine) palladium established the C−D ring axis **26** in 74% yield.[25] Finally, a highly regioselective CAN-mediated oxidation[26] of quinoline **26** to quinone **27** resulted in the production of a late-stage intermediate in Weinreb's total synthesis and the final compound described in Kende's work. In our case this synthesis has been achieved in 10 linear steps with an overall yield of 22% from ethyl glyoxalate, which is less than half the number of steps originally required.[10]

All that remained to convert quinone **27** into streptonigrin was the introduction of the quinone amino group, removal of the

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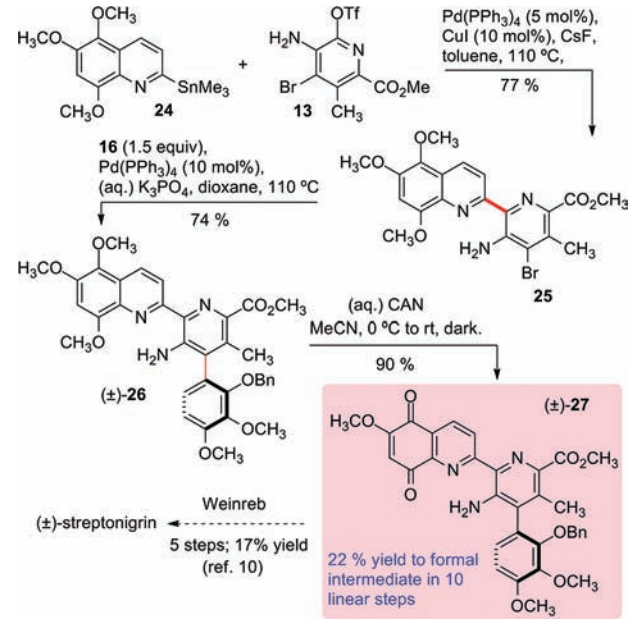
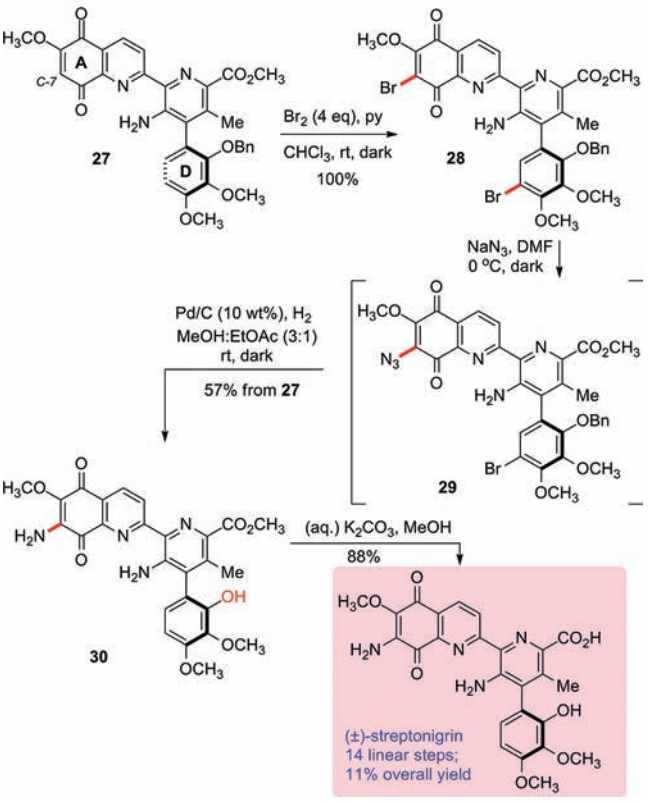
Scheme 4



Scheme 5



D-ring benzyl ether, and hydrolysis of the pyridine methyl ester. Weinreb achieved this sequence in five steps and 17% overall yield.[10,27] The end game has received virtually no attention since the original publication, and we believed that there was now the possibility to improve some of the requisite transformations.

Taking Weinreb's conditions as a starting point we sought to introduce iodine selectively at the 7-position of quinone **27** with IN_3. However, in our hands we were not able to reproduce this transformation[28] so an alternative activating group was chosen.

Having studied a range of brominating reagents we found that competing bromination on the D-ring was unavoidable; yet in the presence of excess bromine and pyridine we achieved quantitative conversion of quinone **27** to the dibrominated compound **28** (Scheme 5). This was found to be relatively unstable to chromatography and so was treated immediately with sodium azide in DMF at 0°C to furnish azidoquinone **29**. As **29** also proved to be unstable, the crude material was taken on and subjected to catalytic Pd/C under an atmosphere of hydrogen. To our satisfaction, these reaction conditions effected the 3 desired manipulations: azide reduction, benzyl ether hydrogenolysis and reduction of the unwanted aryl bromide. Pleasingly, streptonigrin methyl ester **30** was obtained in 57% overall yield from the quinone formal intermediate **27**. Finally, treatment with potassium carbonate in aqueous methanol revealed the free C-ring carboxylic acid, affording streptonigrin in 88% yield; the spectroscopic data of which matched those reported in the literature[29] and that of an authentic sample of the natural product.

To conclude, we have completed a concise and efficient total synthesis of the antitumor agent (±)-streptonigrin, in 14 linear steps from ethyl glyoxalate; this sequence has an overall yield of 11%. The synthesis showcases recent methodology in the rapid generation of a complex pyridine and revises the long-standing end game for streptonigrin, providing a shorter and more robust set of tactics. This represents the shortest and highest yielding synthesis to date. Our synthesis will allow the rapid assembly of a comprehensive range of analogues, whose potential as viable drug candidates could be readily assessed.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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