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The total synthesis of streptonigrin and related antitumor antibiotic natural products

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Dedicated to Professor Helmut Werner on the occasion of his 70th birthday

Contents

1. Introduction

The remarkable capability of *Streptomyces* and *Actinomyces* species to produce a wide variety of structurally diverse natural products with biological activity[1] has received considerable attention from the chemical community, especially from biochemists and synthetic organic chemists who are concerned with human and animal health problems. The chemistry of streptonigrin (**1**, Fig. 1) dates back to 1959. Rao and Cullen[2] disclosed the isolation of an initially un-named dark-brown metabolite of *Streptomyces flocculus* that exhibited striking activity against several animal tumors.[3–7] Subsequently, the same crystalline compound was isolated from *S. rufochromogenes* and *S. echinatus*, here named rufochromomycin,[8] and from *Actinomyces albus var. bruneomycini*, now called bruneomycin.[9,10] The active agent common to all these *Streptomyces* and *Actinomyces* species came to be called streptonigrin (**1**).[10] Since then, intense efforts have been undertaken towards the isolation of bioactive compounds with variations on the same molecular framework.[11–14] In the course of this work, two closely related further antibiotics, streptonigrone (**2**)[15,16] and lavendamycin (**3**), were also isolated.[17]

The use of streptonigrin (**1**) as an anticancer drug, its synthesis and biosynthesis, and its cytotoxic mechanism of action have been studied in depth.[18–21] The stereochemistry of streptonigrin (**1**) has also been investigated.[22,23] Due to the presence of a rotationally hindered biaryl linkage between rings C and D, natural streptonigrin is axially chiral and optically active. Its configuration has initially

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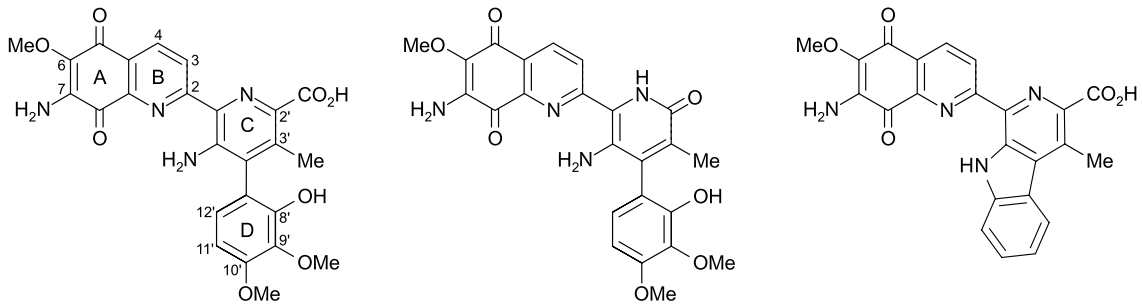


Figure 1.

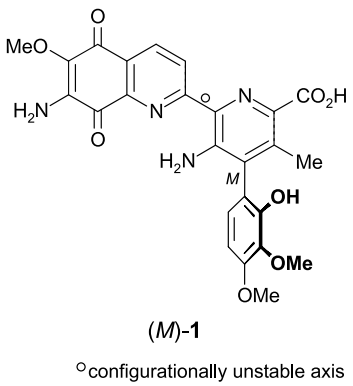


Figure 2.

been reported as *P*,[22] but more recent work has deduced the absolute stereostructure of streptonigrin to be (*M*)-**1** (Fig. 2).[23]

In addition to their biological activity, streptonigrin (**1**) and related analogs are also of interest because of their unique structural and biosynthetic features. The synthetic chemistry of these natural products has been extensively studied and discussed in two reviews[24,25] and two chapters in antibiotic books,[26,27] but no surveys have been published during the past 13 years. Despite the removal of streptonigrin from clinical trials,[28] newer aspects of its chemistry continue to emerge. Our aim in this review is to provide a comprehensive summary covering the years 1960 through November 2003, with special emphasis on methods for the synthesis of streptonigrin (**1**), streptonigrone (**2**), and lavendamycin (**3**).

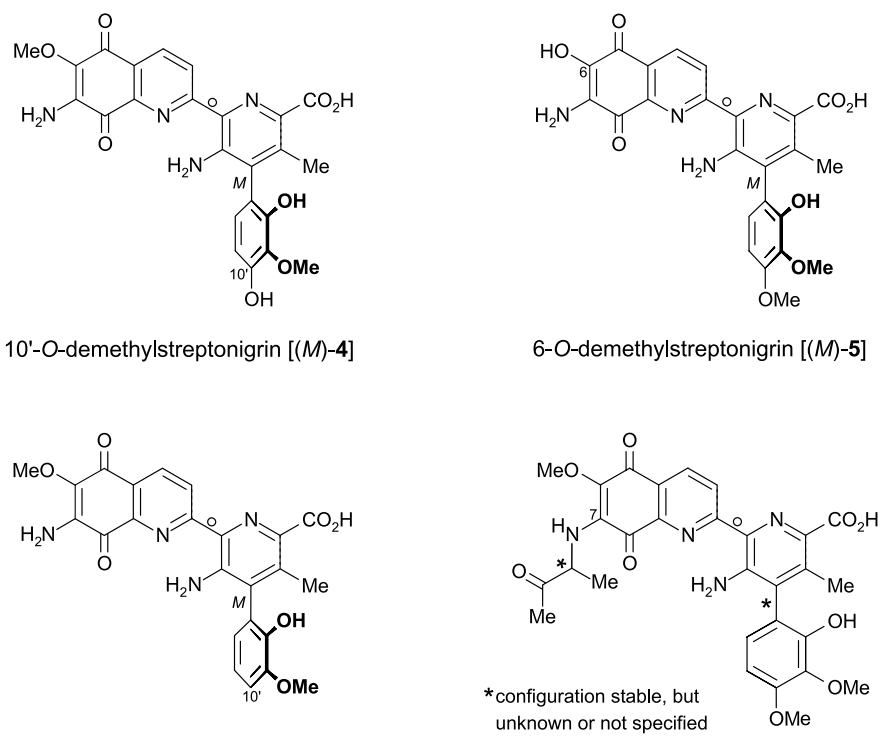


Figure 3.

Biosynthetic features, modes of action, and structure–activity relationships will be dealt with briefly, but will not be exhaustively reviewed.

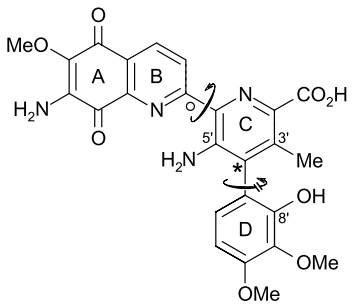
2. Isolation and structural elucidation of streptonigrin and related compounds

Rao and Cullen[2] isolated streptonigrin (**1**) from *S. flocculus* utilizing countercurrent distribution chromatography (ethyl acetate–aqueous 3% phosphate buffer, pH 7.5). The progress of the distribution was monitored by UV measurement at 370 nm, with subsequent crystallization of the isolated material, but, unfortunately, no yields were given. Although countercurrent distribution has more recently been replaced by fast centrifugal partitioning chromatography (FCPC),[29] no report has appeared on the use of FCPC to screen other *Streptomyces* species for streptonigrin (**1**) or for closely related streptonigrins that might be more potent, but less toxic. Extraction of **1** from the culture filtrate (3 l) from a fermentation of a *Streptomyces* species (IA-CAS isolate No. 144), followed by chromatography on a Sephadex column, gave reasonable quantities (110 mg) of streptonigrin, making this simple procedure much more straightforward for isolation.[15,23] Degradative and spectral studies established the unique phenylpyridylquinolinequinone structure **1** for streptonigrin in 1963,[30] without consideration of the phenomenon of axial chirality (see below). In 1975, Chiu and Lipscomb[31] confirmed this constitution by X-ray diffraction analysis. When Lown and Begleiter[32] reported ^{13}C NMR data in pyridine-d_5 in 1974, progress in analytical instrumentation had significantly improved since the original isolation of streptonigrin in the late 1950s. Their assignments were, however, revised by Gould in an independent study in DMSO-d_6 in 1982.[25] Due to the presence of two amino groups (in rings A and C) and two pyridine portions (rings B and C), there are four nitrogen atoms in streptonigrin (**1**), the resonances of which were, however, not attributed unambiguously.[25] Using modern HMBC, HMQC, NOESY, and NOE techniques, Harding and co-workers succeeded in assigning all carbon, hydrogen, and nitrogen resonances to substantiate the structure of streptonigrin as **1**.[33,34] This group also conducted variable temperature studies to assign the four nitrogen resonances, and similar experiments proved to be most useful in analyzing metal complexes of streptonigrin.[35] Their efforts paved the way for the attribution of the signals in streptonigrone (**2**) and lavendamycin (**3**).

Streptomyces species are most prolific producers of drug molecules, and it is therefore no coincidence that numerous streptonigrin-related antibiotics have since been isolated from different subspecies. As an example, four further fascinating structures, **4**-**7**, are shown in Figure 3.

3. Absolute configuration of streptonigrin

Streptonigrin (**1**) has numerous rotatable bonds, of which only two are stereochemically significant (see Fig. 4). These are the two biaryl axes, one of which connects ring B with ring C and the other joins the CD rings. For the axis between



1

Figure 4.

the B and C rings, relatively free rotation may be expected, since there is only one substituent next to the axis, viz. the amino group at C-5′. The CD-ring linkage, by contrast, is flanked by three *ortho* substituents, namely the same that amino function at C-5′, together with a methyl group at C-3′ (both on pyridine ring C), and a phenolic hydroxyl (at C-8′, on ring D). This results in restricted rotation and accounts for the observed optical activity of streptonigrin (**1**),[24,32] which therefore arises from atropisomerism about the pyridyl–phenyl C–D linkage. Curiously, however, there have been no reports to date in the literature on the concrete optical rotation of streptonigrin (**1**), that is, no α_D in any solvent or at any wavelength has ever been given.[36]

In the course of their X-ray study of streptonigrin (**1**, as its solvate with ethyl acetate), Chiu and Lipscomb[31] discovered that the rings A, B, and C are oriented essentially coplanar with each other, while the phenolic ring D is nearly perpendicular to that plane. The co-planarity of the pyridyl ring C with the AB–quinolinequinone system is a consequence of hydrogen bonding between the amino group of ring C and the quinoline nitrogen in ring B. Harding and Long[37] probed the conformation of streptonigrin (**1**) in solution by using variable temperature NMR spectroscopy and confirmed this finding.

An important aspect of the structural work in natural product chemistry is the assignment of the absolute stereostructure of chiral compounds.[38] During the past three decades, several such methods have been applied in order to attribute the absolute axial configuration of streptonigrin (**1**). An X-ray structure analysis of **1** was carried out,[31] but without the benefit of a heavy atom such as bromine, iodine, or silicon in the molecule, so that the absolute configuration could not be determined by this procedure. Atropisomerism in streptonigrin (**1**) and closely related compounds are the only known examples within the numerous axially chiral biarylic natural products[39] in which a pyridine ring is involved. Although naturally occurring biaryls and the phenomenon of atropisomerism have been extensively treated in the literature,[39] newly isolated, apparently likewise axially chiral, biaryl natural products, including closely related streptonigrins, have more recently been published without taking into consideration the phenomenon of hindered rotation,[14] with the exception of Dholakia and Gillard,[22] who, as early as 1981, investigated the stereochemistry of streptonigrin (**1**). From their circular

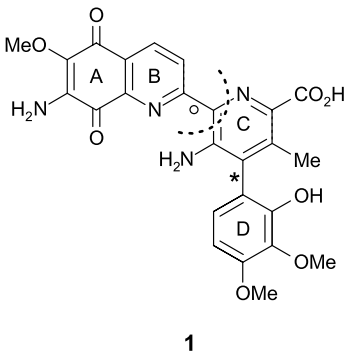
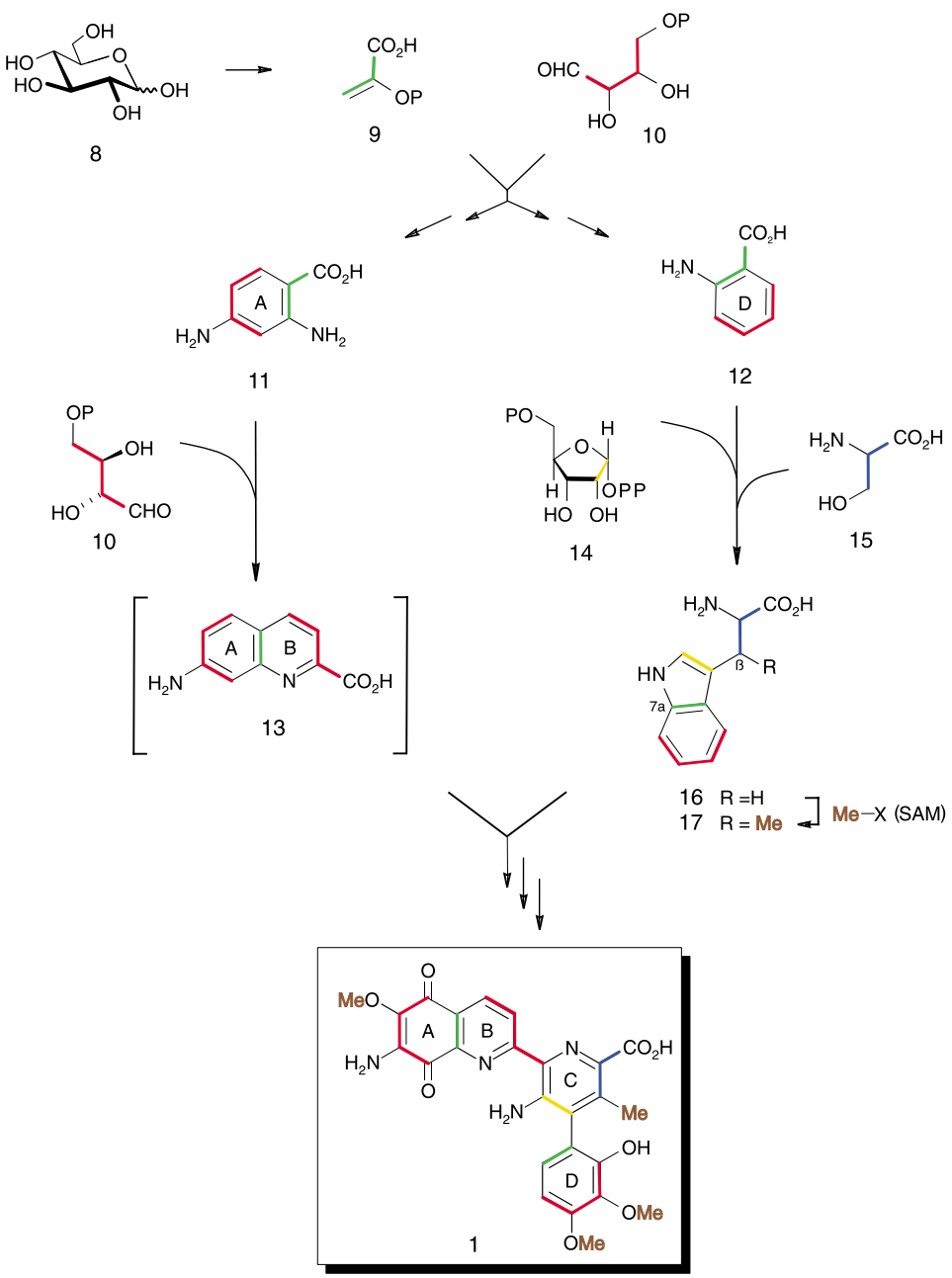
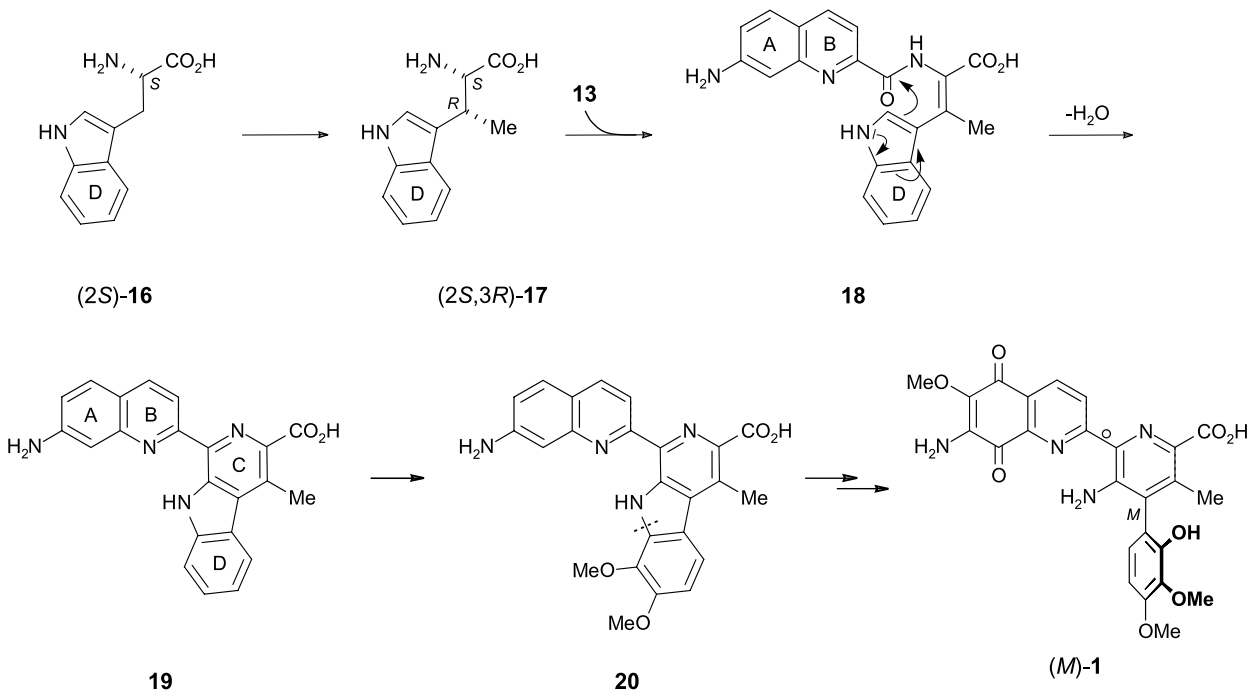


Figure 5.

dichroism (CD) measurements in ethanol, they reached the conclusion that **1** has a *P*-configuration. This assignment was based on the shorter wavelength Cotton effect in the CD spectrum of **1**. On the basis of the CD spectra of a number of derivatives and that of streptonigrin (**1**), Tennent and Rickards, by contrast, have more recently established an *M*-configuration[23]—a conclusion opposite to that of Dholakia and Gillard,[22] although both groups used the same solvent in the CD measurements. The CD spectra are indeed different, particularly in the long-wavelength region, which might possibly be due to different experimental details (presence of metal cations?). An additional complication might be varying enantiomeric ratios of the natural products, as also found in other studies.[39] In addition,



Scheme 1.



Scheme 2.

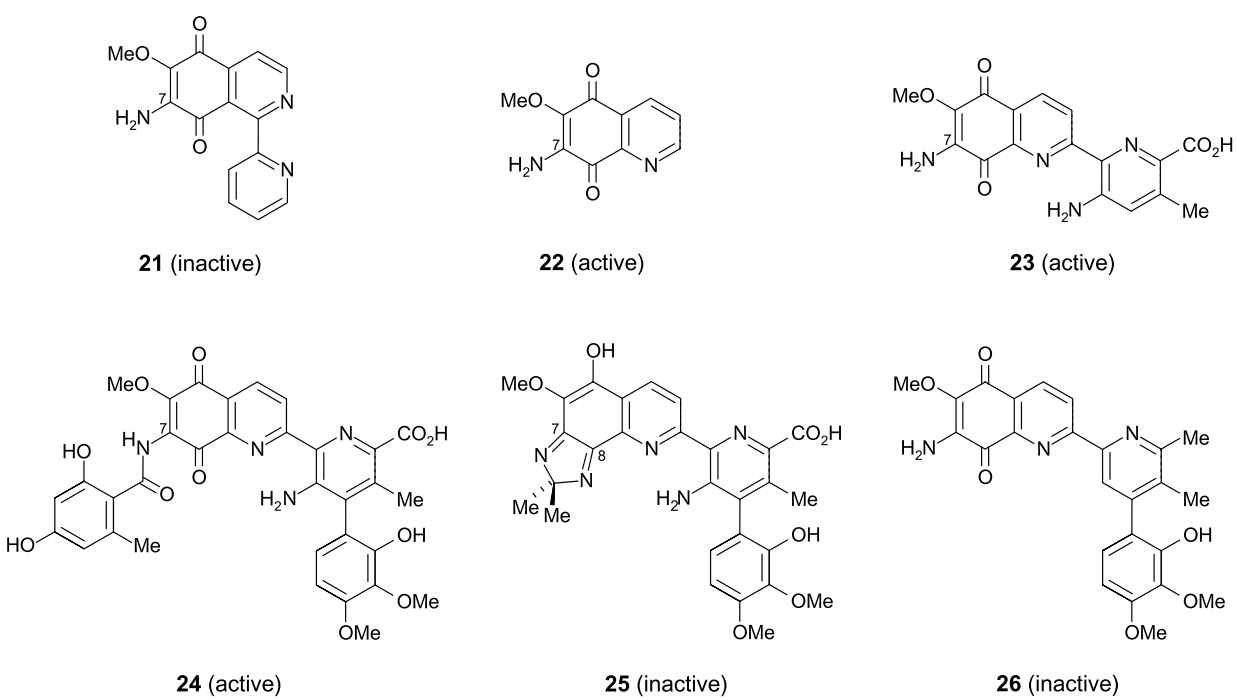
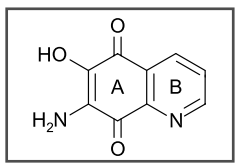
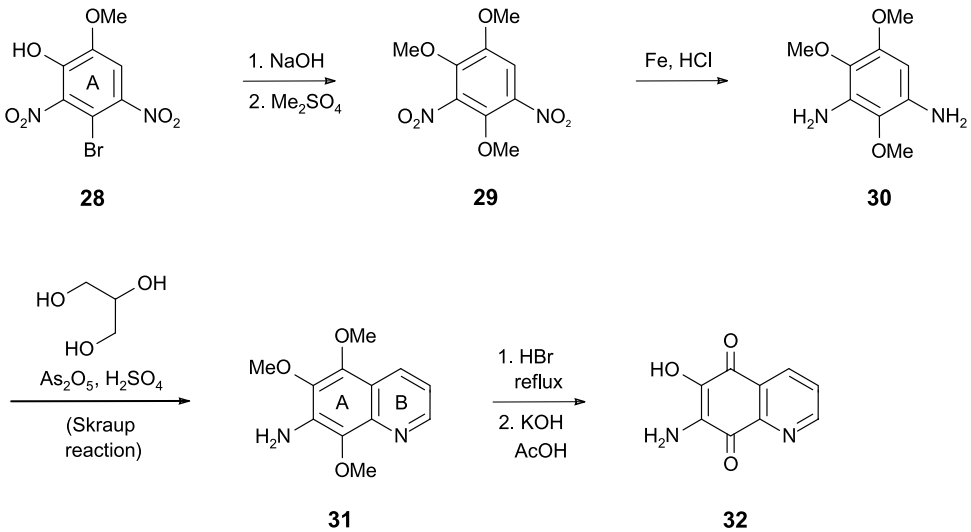


Figure 6.

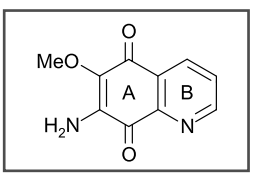


Kametani's first AB-ring model system

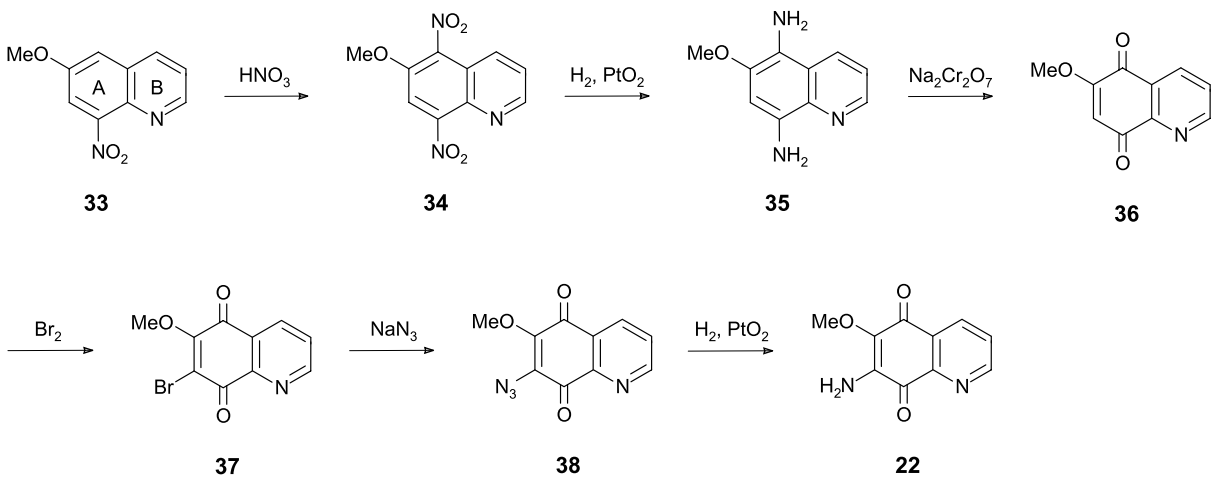


Scheme 3.

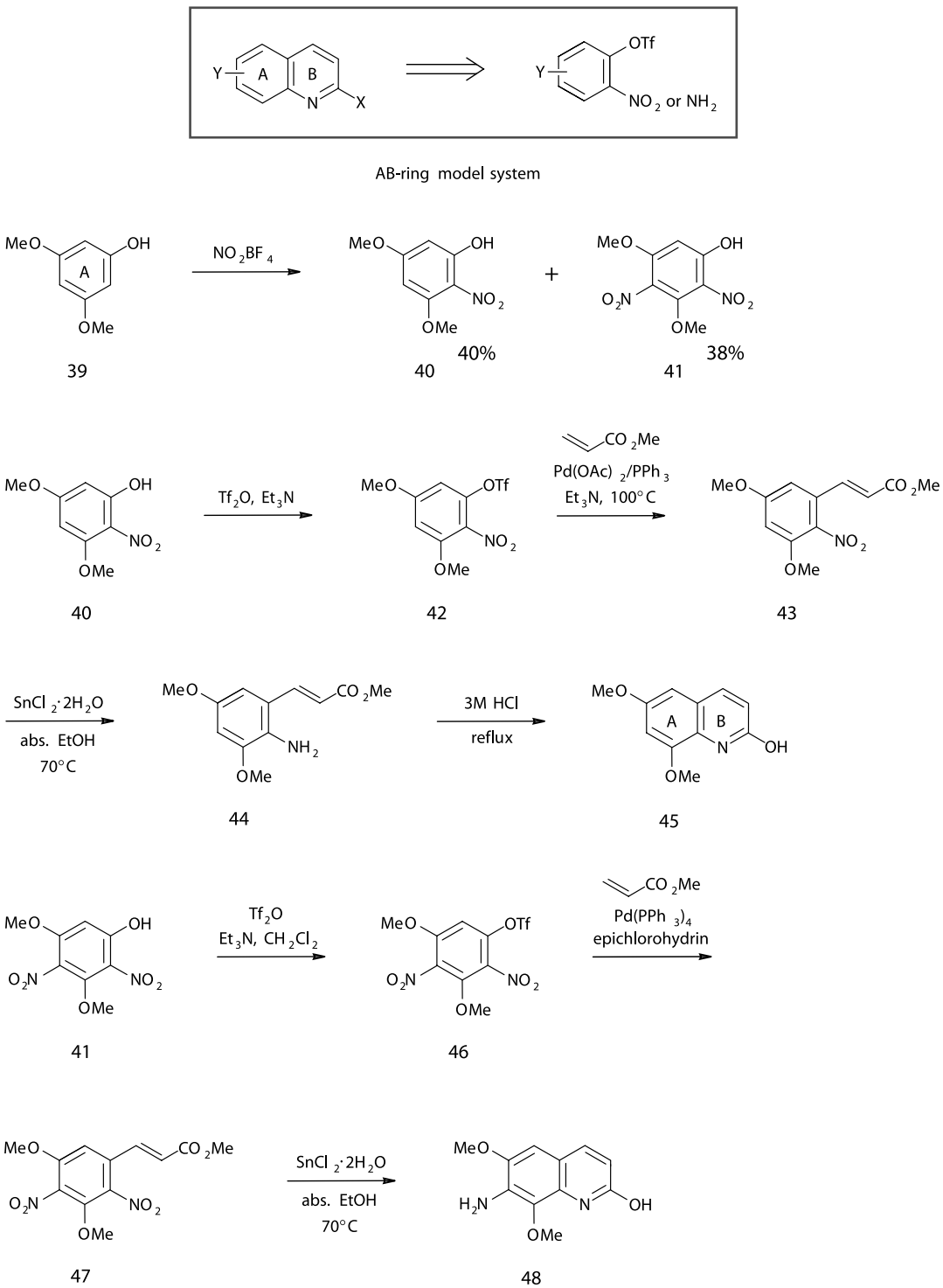
natural 10′-*O*-demethylstreptonigrin (**4**, Fig. 3) has been assigned as being *M*-configured by comparison of its chiroptical properties with those of streptonigrin (**1**).[23] On biogenetic grounds, it might be assumed that 6-*O*-demethylstreptonigrin (**5**) and 10′-demethoxystreptonigrin (**6**) also probably have an *M*-configured absolute stereostructure,[23] but this remains to be proven. No stereochemical assignment has been carried out for of 7-*N*-(1-methyl-2-oxopropyl)streptonigrin (**7**),[14] either for the axis or for the additional stereogenic center in the side



AB-ring model system



Scheme 4.



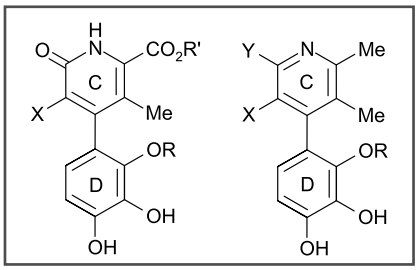
Scheme 5.

chain. The recent appearance of new methods for the determination of absolute configurations by quantum chemical CD calculations[40] might help to firmly establish the absolute configuration of streptonigrin (**1**), but this remains to be pursued.

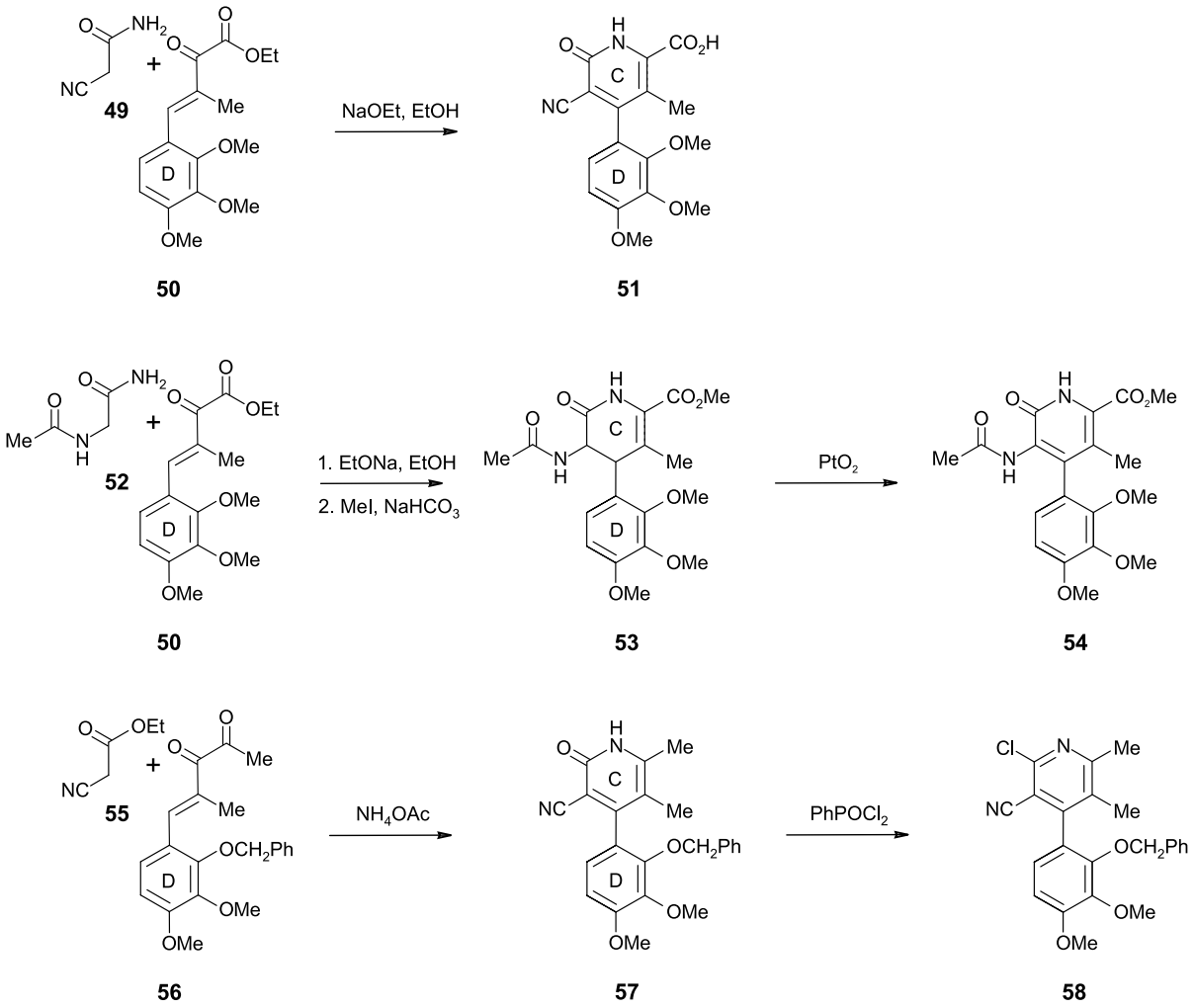
4. Biosynthetic origin

The biosynthesis of streptonigrin (**1**) is now well established, thanks to the detailed studies by Gould and co-workers that have appeared in a series of elegant publications.[25,41–47] Accordingly, streptonigrin (**1**) arises through a convergent pathway involving the assembly of two major units (shown by dotted lines in Fig. 5), possibly linked together in a key Pictet–Spengler condensation step via an intermediate β-carboline (see below).

Gould's group discovered that the quinoline and pyridine subunits of streptonigrin are formed by previously unknown

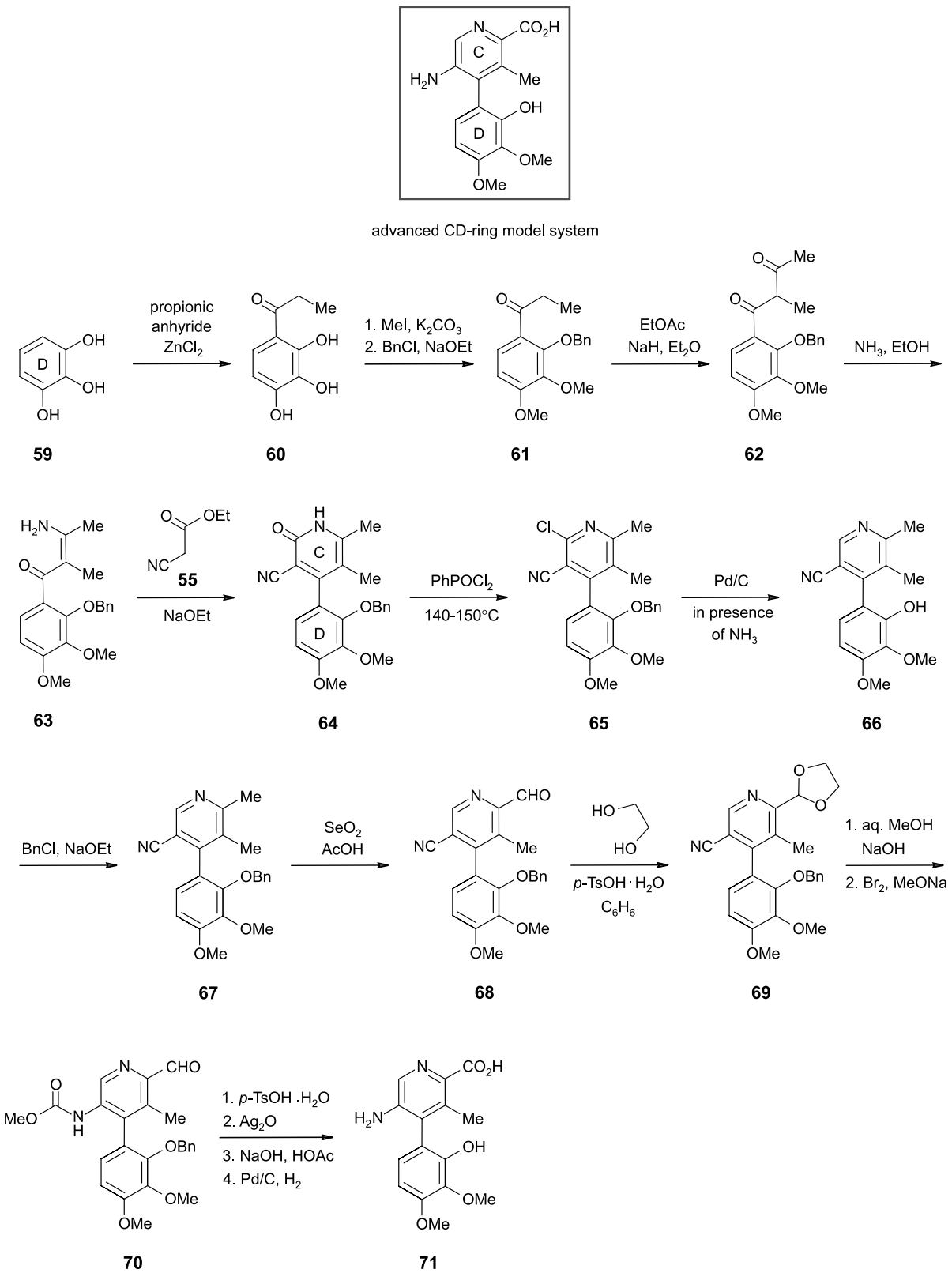


first simple CD-ring models



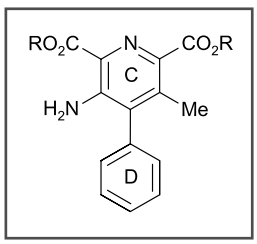
Scheme 6.

pathways (see Scheme 1).[41,43,46] Feeding the labeled precursors, [β-^{14}C, 7a-^{14}C]-tryptophan, [^{14}COOH]-anthranilic acid, [U-^{14}C]-shikimic acid, [2-^{14}C]-pyruvic acid, [β-^{14}C]-tyrosine, [β-^{14}C]-phenylalanine, [2-^{14}C]-acetate, [1,2-$^{13}C_2$]-acetate, [4-^{14}C]-aspartate, [1-^{14}C]-fumarate, [3,4-^{14}C]-glutamate, and [1,4-^{14}C]-succinate, failed to give significant incorporation rates into the quinoline portion of **1**,[43] clearly indicating that none of the known pathways for the formation of this part of **1** is involved. Incorporation experiments with [U-$^{13}C_6$]-**8**, that is, with uniformly ^{13}C-labeled D-glucose, into *S. flocculus* established that all carbon atoms can be traced back to this precursor molecule. The labeling pattern of the non-tryptophan portion of **1** is mostly explained by involving a modified shikimate pathway, which, via phosphoenolpyruvate (**9**) and D-erythrose-4-phosphate (**10**), leads to the amino-substituted anthranilic acid **11**. This condenses with a third molecule of D-erythrose-4-phosphate (**10**) as an equivalent four-carbon source. The carboxy group of the aminoanthranilate **11** is presumably lost in the cyclization and aromatization with the formation of the quinoline AB **13** portion of **1**.[43] The introduction of the three oxygen substituents of the A-ring occurs at a later stage.[46]

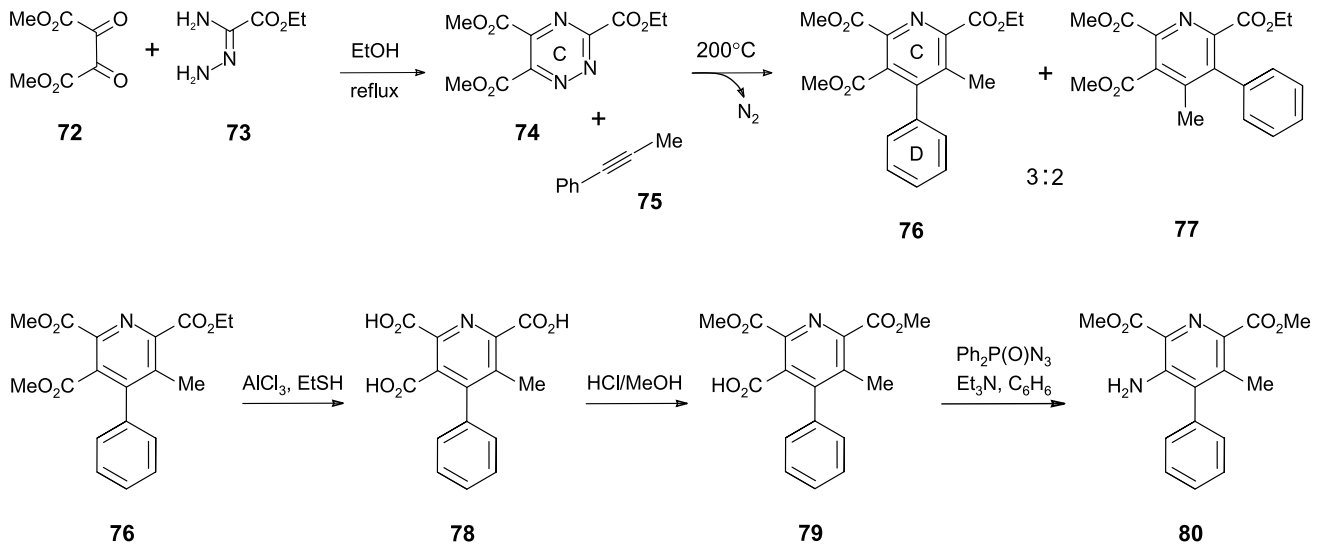


Scheme 7.

L-Tryptophan (**16**) and β-methyl-L-tryptophan (**17**), as formed from the assumed starting materials **12**, **14**, and **15**, are precursors for the C- and D-rings, as proven by feeding these compounds in a ^{13}C-labeled form to *S. flocculus* (see Scheme 2).[41–43] The highly substituted pyridine C-ring, with five substituents, is derived from the β-carboline **19**, this being formed from the quinolinecarboxylic acid AB-ring precursor **13** and β-methyl-L-tryptophan



CD-ring model system

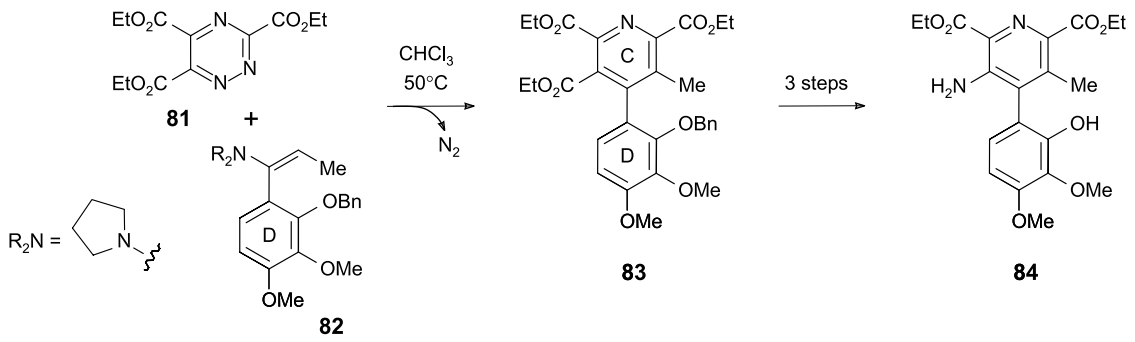


Scheme 8.

(**17**), possibly via **18** or by a Pictet–Spengler reaction with the aldehyde related to **13**. From the feeding experiment, Gould and co-workers also isolated lavendamycin (**3**),[17] which has a β-carboline unit, as in **19**. Possibly, atropo-enantioselective cleavage of the C8′–N bond of the pentacyclic intermediate **20** leads to the axially chiral 4-phenylpyridine CD-ring system of steptonigrin (**1**). This type of cleavage of an indole or a β-carboline is unprecedented to date in synthetic chemistry. An as yet unresolved issue in the biosynthesis of **1** is the role of lavendamycin (**3**) as a real intermediate or as a shunt metabolite.

5. Structure–activity relationships and mode of action

Most of the research into the mode of action and structure–activity of **1** and its analogs was reported after cessation of the clinical trials in 1977. Although streptonigrin (**1**) was extremely effective in the treatment of cancer, the main reason for the discontinuation was its high toxicity, which caused severe side effects, therefore decreasing its potential clinical use.[48–51] Since then, three review articles have appeared on this subject, the first by Gould and Weinreb[25] in 1982, the second by Hajdu in 1985,[18] and the third by Harding and Long in 1997.[37] Studies on the structure–activity relationships of **1** involved ascertaining the key functional groups and/or ring systems essential for its biological activity. Several teams have synthesized streptonigrin analogs[52–55] (see Fig. 6) by changing the functional groups and the rings, one example being the simplified pyridyl isoquinoline–quinone analog **21**, which was found to be inactive. The potency of the analogs **22** and **23** indicates the importance of the quinoline–quinone system equipped with a 7-amino group (even if acylated, as in **24**; see below!), and this was further confirmed by replacement of this amino function by OH or OMe, which provided inactive compounds.[56] The analog **25**, in which an amino group and part of the quinone moiety are blocked by an isopropylidene unit, that is, as a 2*H*-imidazole, proved to be inactive. Rosazza[57] prepared the amide **24** of streptonigrin (**1**) and orsellinic acid, by using a strain of *Streptomyces griseus*. This compound showed significant in vivo activity, but further studies of its toxicity have not yet been reported. Kende[55] described the synthesis of the analog **26**, which was inactive, underscoring the importance of the COOH and NH_2 groups in the C-ring. The substituted D-ring in streptonigrin (**1**) is obviously important in adding a structural element orthogonal to the flat (see above) ABC ring system and therefore also conferring chirality to the molecule. The role of the D-ring unit (e.g., with respect to the element of axial chirality) in the biological activity of **1** is, however, not yet fully understood. On the basis of the finding that **22** and **23** are bioactive, although lacking ring D, Harding and Long proposed that this phenyl ring is not essential for bioactivity.[37] Further support for this assumption was provided by Inouye and co-workers,[58] who derivatized semisynthetic racemic streptonigrin (**1**) at the

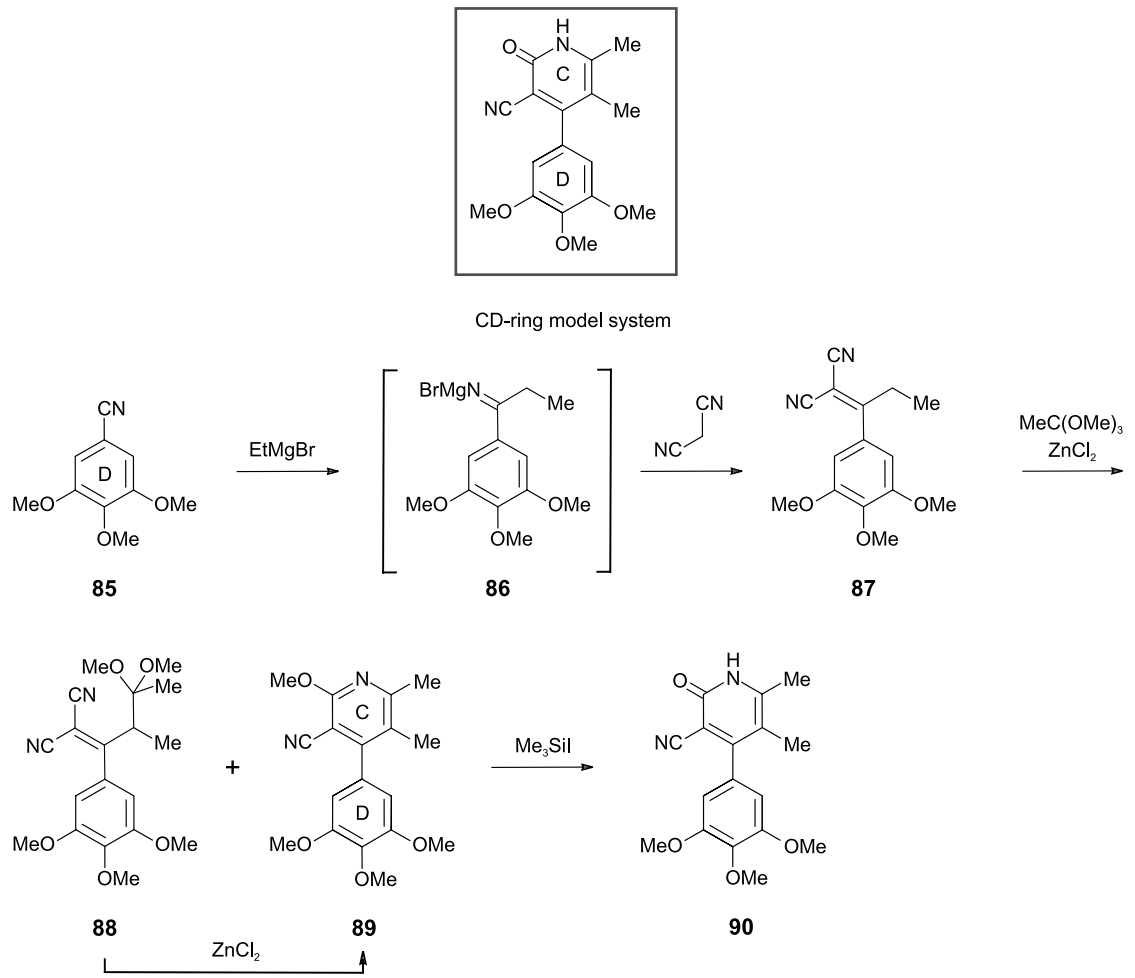


Scheme 9.

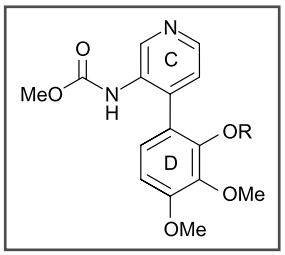
carboxy group in ring C with a chiral, non-racemic amino acid. The resulting two atropo-diastereomeric derivatives were resolved and were tested separately, yet they showed identical biological activities. Rao[56] examined various published studies of the biological properties and biochemical effects of **1**. The extensive data acquired suggested the partial structure **27** (Fig. 6) as a minimal requirement for the biological activity of streptonigrin (**1**). Of particular significance is the finding that this subunit **27** contains the fundamental metal-coordinating groups in **1**.

6. Synthetic efforts towards the AB-rings (quinolinequinone) of streptonigrin

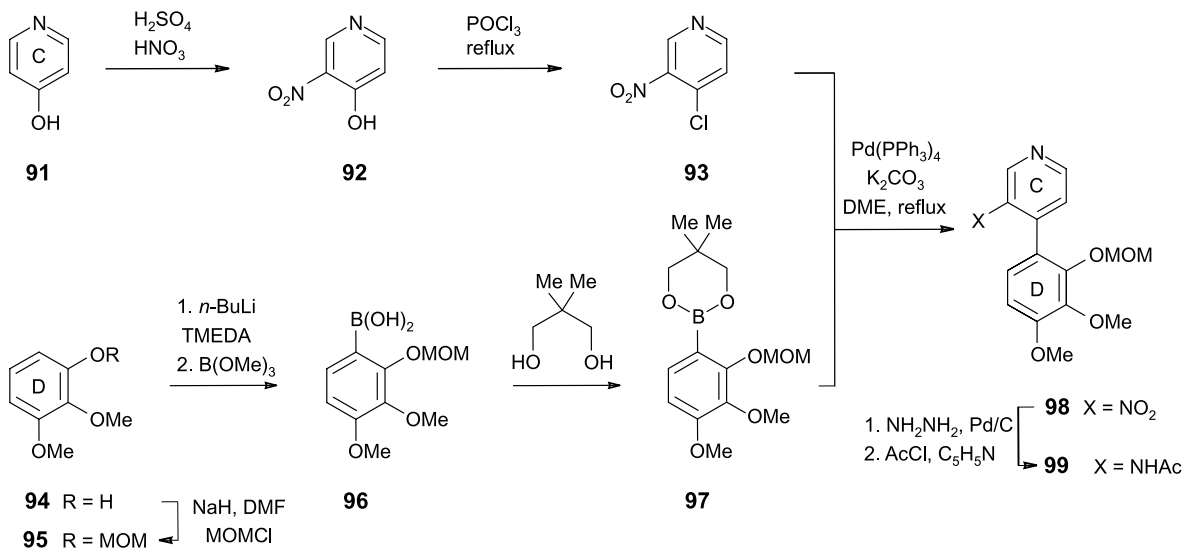
When Woodward and co-workers[30] disclosed the constitution of streptonigrin (**1**), an antitumor antibiotic metabolite of *S. flocculus* of unprecedented structure in 1963, its total synthesis presented a huge challenge to the synthetic chemist. Preliminary approaches dealt with developing methods for constructing a quinolinequinone, viz. the AB-ring system of streptonigrin (**1**) having the



Scheme 10.



CD-ring model system by Suzuki reaction



Scheme 11.

proper substitution in ring A. A route to 7-amino-6-hydoxyquinolinequinone (**32**) had already been developed earlier by Kametani,[59,60] using a classical Skraup synthesis for the formation of the intermediate quinoline **31**, as prepared from the bromodinitrophenol **28**, via the trimethoxy derivative **29** and the *m*-phenylenediamine **30** (see Scheme 3).

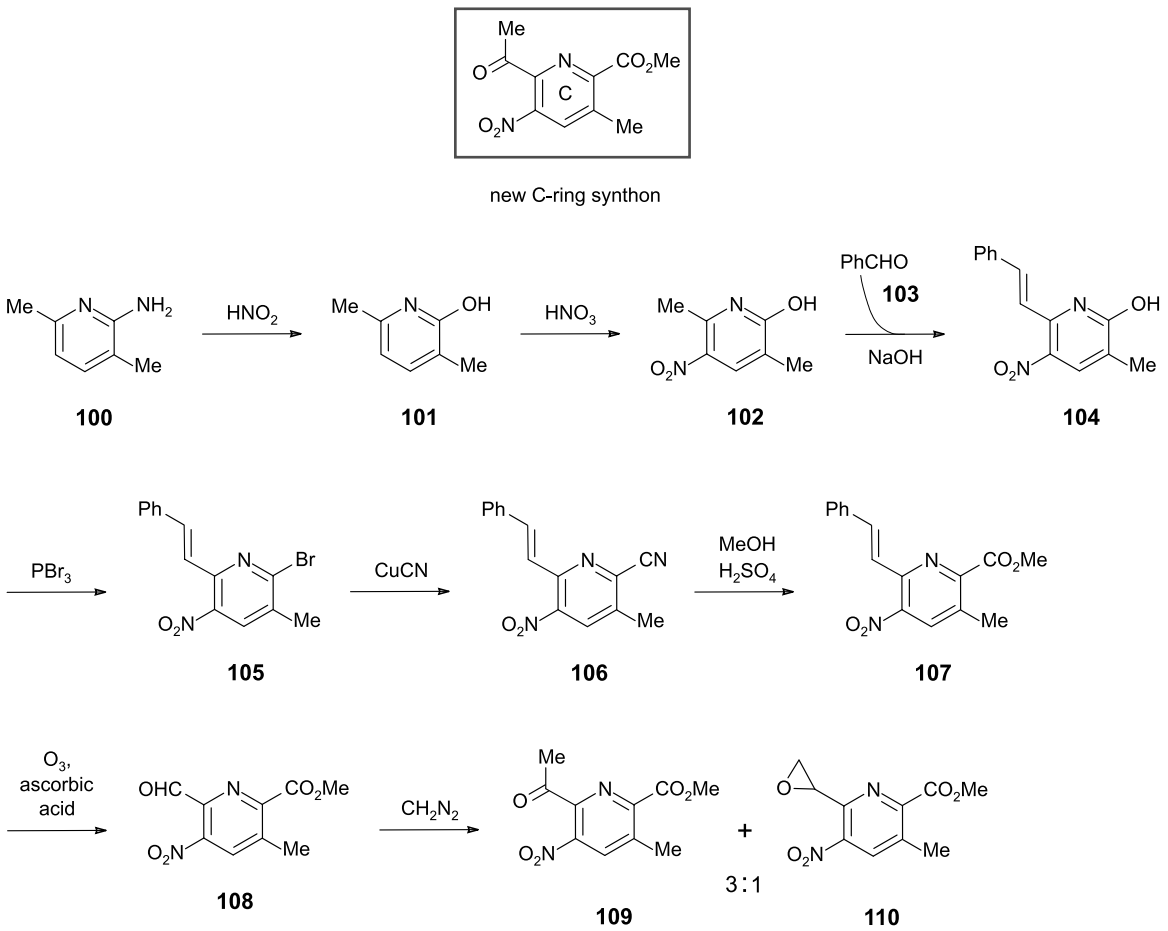
A potentially attractive route to the properly substituted AB system of streptonigrin was reported by Liao, Nyberg, and Cheng[54] (see Scheme 4). The quinoline **33**, previously prepared from 2-nitro-*p*-anisidine via a Skraup reaction,[61] was further nitrated to give **34**. This dinitro compound was subsequently reduced to the diamine **35** and then oxidized to the methoxyquinone **36**, which was cleanly brominated to deliver the bromoquinone **37**. The bromine substituent was then replaced to give the azidoquinone **38**, which, on reduction, gave the amino-quinolinequinone. The strategy shown in Scheme 4 for the conversion of **36** to **22** was later utilized by others and therefore became an important constituent of both subsequent total syntheses of streptonigrin.

In the course of their work on the synthesis of streptonigrin (**1**), Holzapfel and Dwyer[62] used the Heck reaction to assemble the AB quinolinequinone moiety (see Scheme 5). The 2-hydroxy-7-amino-6,8-dimethoxyquinoline as a potential precursor to the quinolinequinone structure might be generated by a simple Fremy's salt oxidation of **48**, which, however, had not been reported previously. Nitration of 3,5-dimethoxyphenol (**39**) with nitronium tetrafluoroborate provided a separable 1:1 mixture of the mono- and dinitro products **40** and **42**. Upon triflation, the mononitro compound **40** gave **42**, and a subsequent Heck reaction of **42** with methyl acrylate produced the cinnamic ester **43**. Reduction of **43** with tin(II) chloride dehydrate to **44**, followed by acid-catalyzed cyclization, afforded the 2-hydroxyquinoline **45** (overall yield of 25% from **39**). A similar sequence on the dinitro compound **41**, via the *O*-triflate **46** and the cinnamic acid derivative **47**, led to the aminoquinolinequinone **48**, a potential precursor to 2-hydroxy-7-amino-6-methoxyquinolinequinone. Although some difficulties were encountered in the Heck reaction, these were overcome by the use of epichlorohydrin and excess palladium catalyst. This route therefore provided a convenient synthetic equivalent of the AB-ring system.

Prior to this work, Quéguiner and his group[63] had also reported a potential streptonigrin AB-ring precursor via a similar approach.

7. Formation of the CD-rings in streptonigrin

The challenge to synthesize the CD-rings of streptonigrin (**1**) was taken up by several groups. In a series of publications beginning as early as 1966, Kametani and

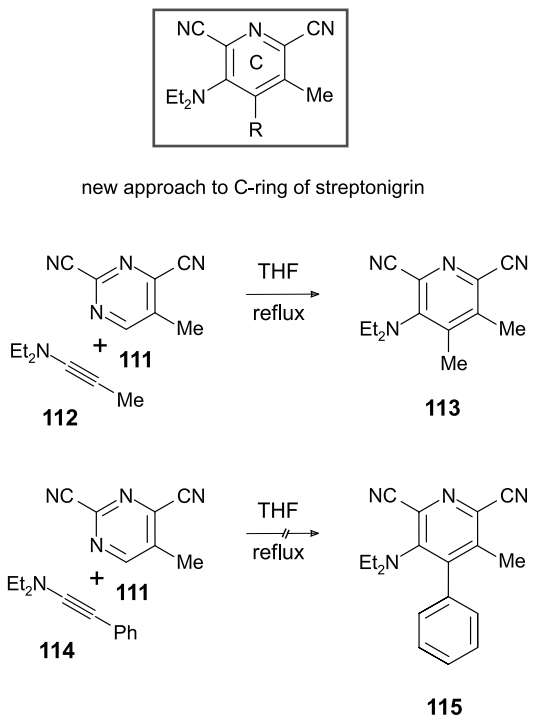


Scheme 12.

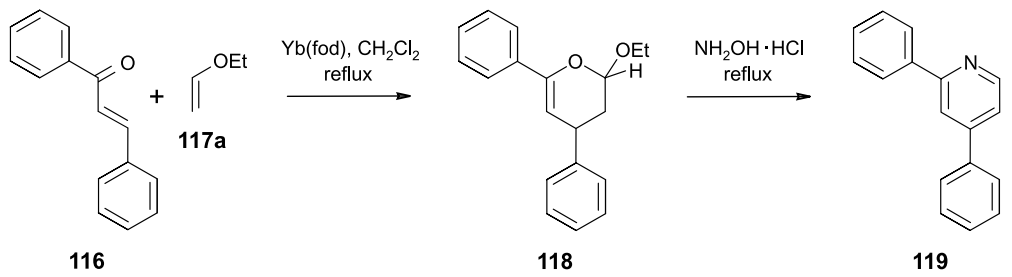
co-workers[64–71] reported several approaches. A few of the successful routes that resulted in the 2-pyridones **51** (from **49** and **50**), **54** (from **52** and **50** via **53**), and **57** (from **55** and **56**) are outlined in Scheme 6. The compound **57** was converted to the respective 2-chloropyridine **58**.

Cheng and his group[72,73] (see Scheme 7) described the synthesis of the CD-ring model system **71** from the commercially available pyrogallol (**59**). This was converted to **71** in a series of steps via the mono- and bicyclic intermediates **60**-**70**, with an overall yield of 15–18%. This synthesis of the CD-ring model system in 1976 paved the way for several further total syntheses of other CD-ring models, each reflecting to some extent the state of the art at the respective time.

It had been well known from the work of Sauer[74,75] and of Boger[76] that the reaction of ynamines and enamines with electron-deficient 1,2,4-triazines, with the subsequent extrusion of dinitrogen, gives substituted pyridines. Such a reaction of an arylpropyne had, however, not been known, nor was the regiochemical outcome anticipated. Using this concept, Martin[77] investigated the synthesis of the CD-rings of streptonigrin (**1**). Condensation of the dioxosuccinate **72** with the amidrazone **73** produced the appropriate triazine **74** (see Scheme 8), the reaction of which with 1-phenylpropyne (**75**) gave a mixture of the pyridines **76** and **77**, which were separated and structurally assigned by NMR. The desired



Scheme 13.



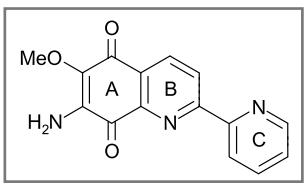
Scheme 14.

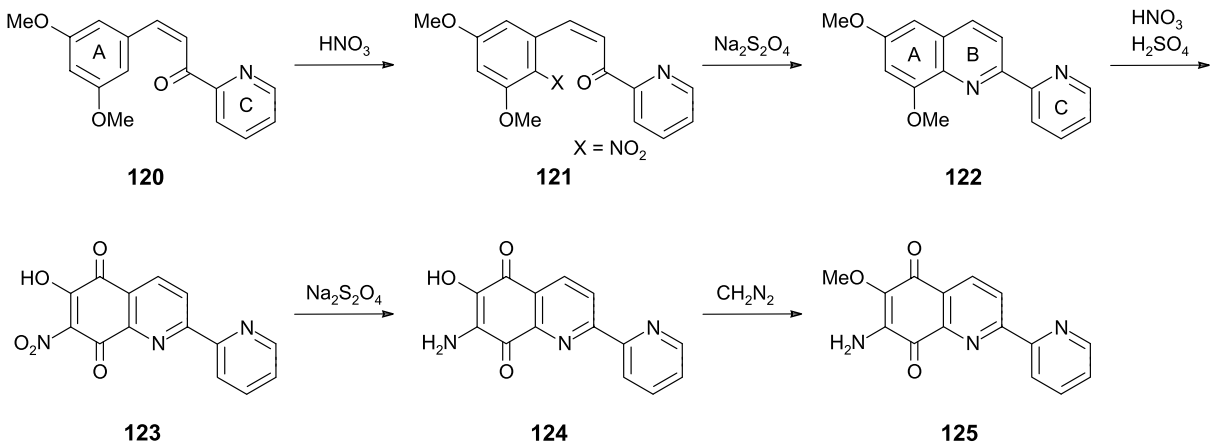
isomer **76** was converted to the highly substituted pyridine **80** via the triacid **78** and the acid **79**. The need for harsh reaction conditions, as well as the formation of a mixture of regioisomeric pyridines, however, precluded further progress.

In a related approach, Boger and Panek[78] employed 1,2,4-triazines and pyrrolidine-derived enamines for the construction of pyridylbiaryl CD-ring model systems of streptonigrin. Their starting enamine **82** was readily prepared, while the triazine **81** was a known compound.[79] Importantly, they found that this cycloaddition to give **83** is highly regioselective (see Scheme 9). The simplicity of these reactions, ultimately leading to **84**, is a hallmark of Boger's work.

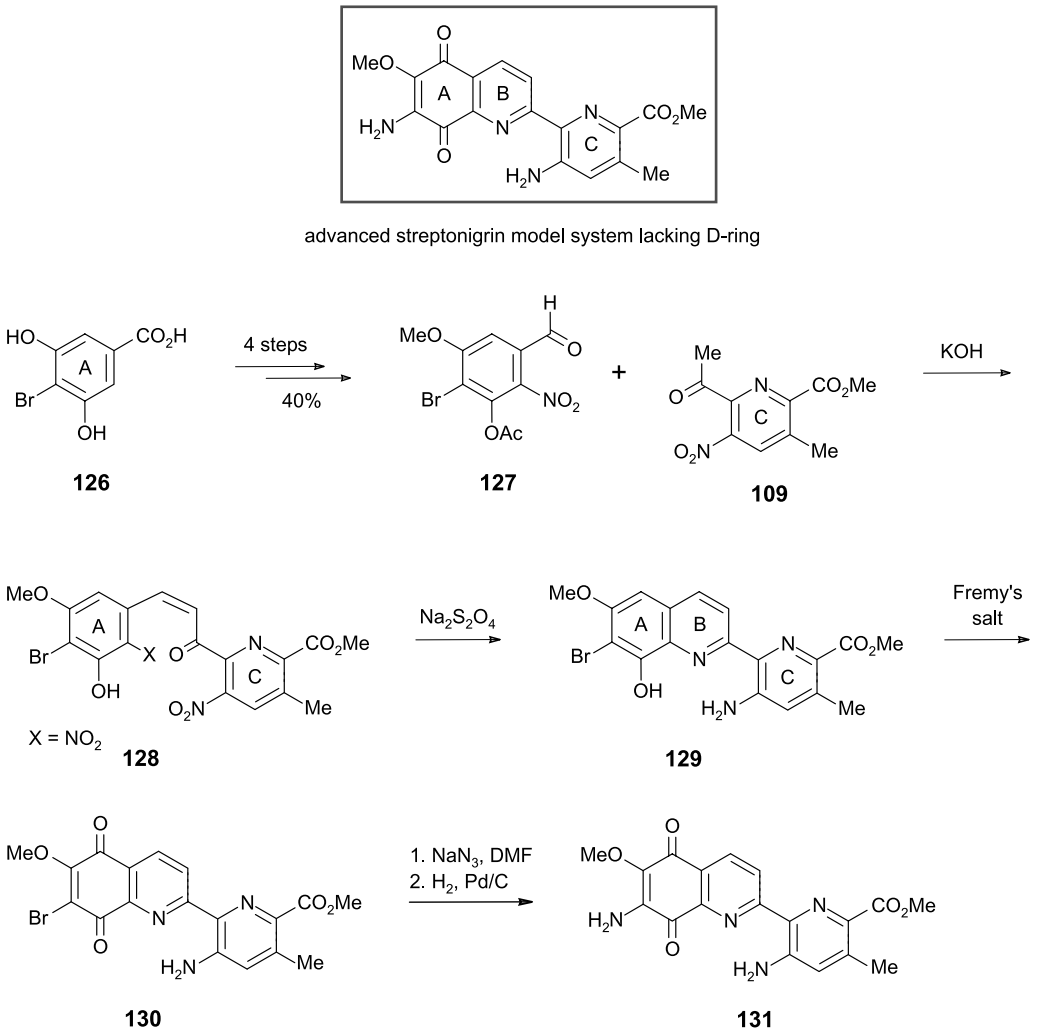
Kilama, Remers and their colleagues[80] successfully prepared the closely related analog **90** (see Scheme 10). This structure was chosen because the starting material, 3,4,5-trimethoxybenzonitrile (**85**), was commercially available and inexpensive. The reaction of **85** with ethylmagnesium bromide in THF, followed by treatment of the intermediate Grignard product **86** with an excess of malonodinitrile, provided **87** in 91% yield. Condensation of **87** with trimethyl orthoacetate in the presence of zinc chloride gave **88** (40% yield) and **89** (45% yield). A significant improvement of the procedure resulted from the fact that **88** can be converted to **89** in 51% yield by further treatment with zinc chloride in trimethyl orthoformate, which raised the final yield of **89** to 66%. Cleavage of the methyl ether with iodotrimethylsilane[81] gave **90** in 85% yield. This method has considerable potential and merits further exploration.

Holzapfel[82] used his cross-coupling strategy for the formation of a model system of the streptonigrin CD rings from the commercially available 4-hydroxypyridine (**91**) and 2,3-dimethoxyphenol (**94**) (see Scheme 11). The first coupling partner, 4-chloro-3-nitropyridine (**93**), was prepared in two steps from 4-hydroxypyridine (**91**) via the compound **92**. Treatment of the D-ring starting material, **94**, with sodium hydride and methoxymethyl chloride in DMF gave the derivative **95**, the MOM group of which was used as an *ortho*-directing group[83,84] to introduce the borate ester.





Scheme 15.



Scheme 16.

Due to incomplete metallation, which complicated the isolation of the boronic acid **96**, this intermediate was then converted to the cyclic 2,2-dimethylpropylidene ester **97**. Suzuki coupling of **93** with **97** gave the desired product **98** in 71% yield. Selective reduction of the nitro group to the amine was achieved using hydrazine and Pd/C and the amine was characterized as its acetamide derivative **99**.

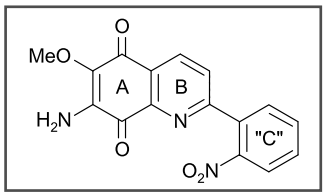
As an alternative to the Suzuki coupling reaction for the formation of the carbon–carbon bond between rings C and D, silicon-derived reagents have more recently been used.[85]

8. New pyridine syntheses for the construction of ring C

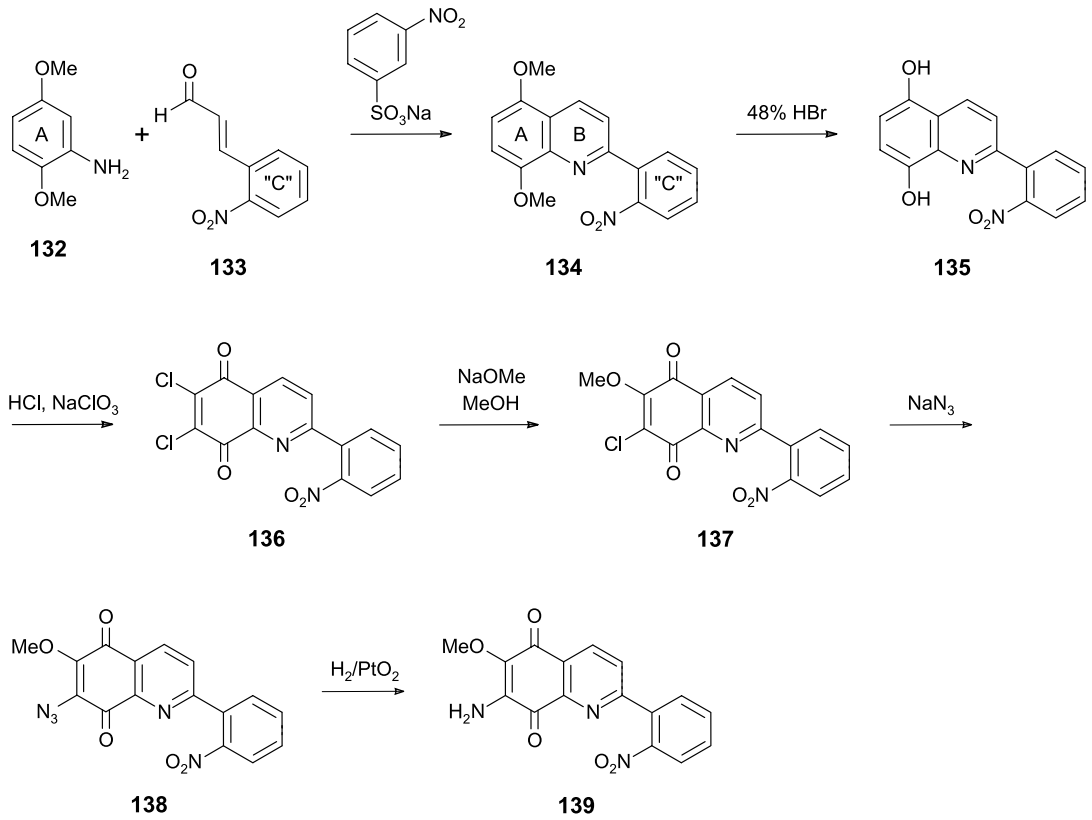
For the construction of the highly substituted pyridine C-ring of streptonigrin (**1**), several research groups have focussed on designing new pyridine ring syntheses. Rao and co-workers[86] have, for example, described the synthesis of the pyridine **109** (see Scheme 12), which still lacks the D-ring. Starting from the aminopyridine **100**, this monocycle was prepared in a straightforward sequence, requiring only eight steps: the conversion into the 2-pyridinol **101**, the nitration to obtain **102**, Knoevenagel reaction with benzaldehyde (**103**) to give **104**, its conversion to the ester **107**, via the bromide **105** and the cyanide **106**, and ozonolysis of **107** to give the aldehyde **108**. Only the last step, which gave a mixture of the desired building block **109** and the epoxide **110**, needs further improvement.

A noteworthy strategy for the synthesis of streptonigrin-related pyridines was described by Martin (Scheme 13).[87] The key step of this approach was a Diels–Alder cycloaddition of pyrimidines, such as **111**, with ynamines, such as **112**, with in situ cyclo-reversion, to afford the respective pentasubstituted pyridine, in this example, the derivative **113**. Unfortunately, no reaction was observed for the phenylynamine **114** with the same pyrimidine **111**, and the desired 4-phenylpyridine **115** was not obtained. Possibly, high-pressure cycloaddition conditions[88–90] might be a solution to force the reaction, but this has not yet been attempted.

Ciufolini and Byrne[91] have developed a modified Knoevenagel–Stobbe condensation for the preparation of substituted pyridines. They found that the required 1,5-dicarbonyl compounds could be obtained in a dihydropyran-protected form, such as **118** (see Scheme 14), by a



AB-ring model system, with C replaced by a nitro-substituted phenyl ring



Scheme 17.

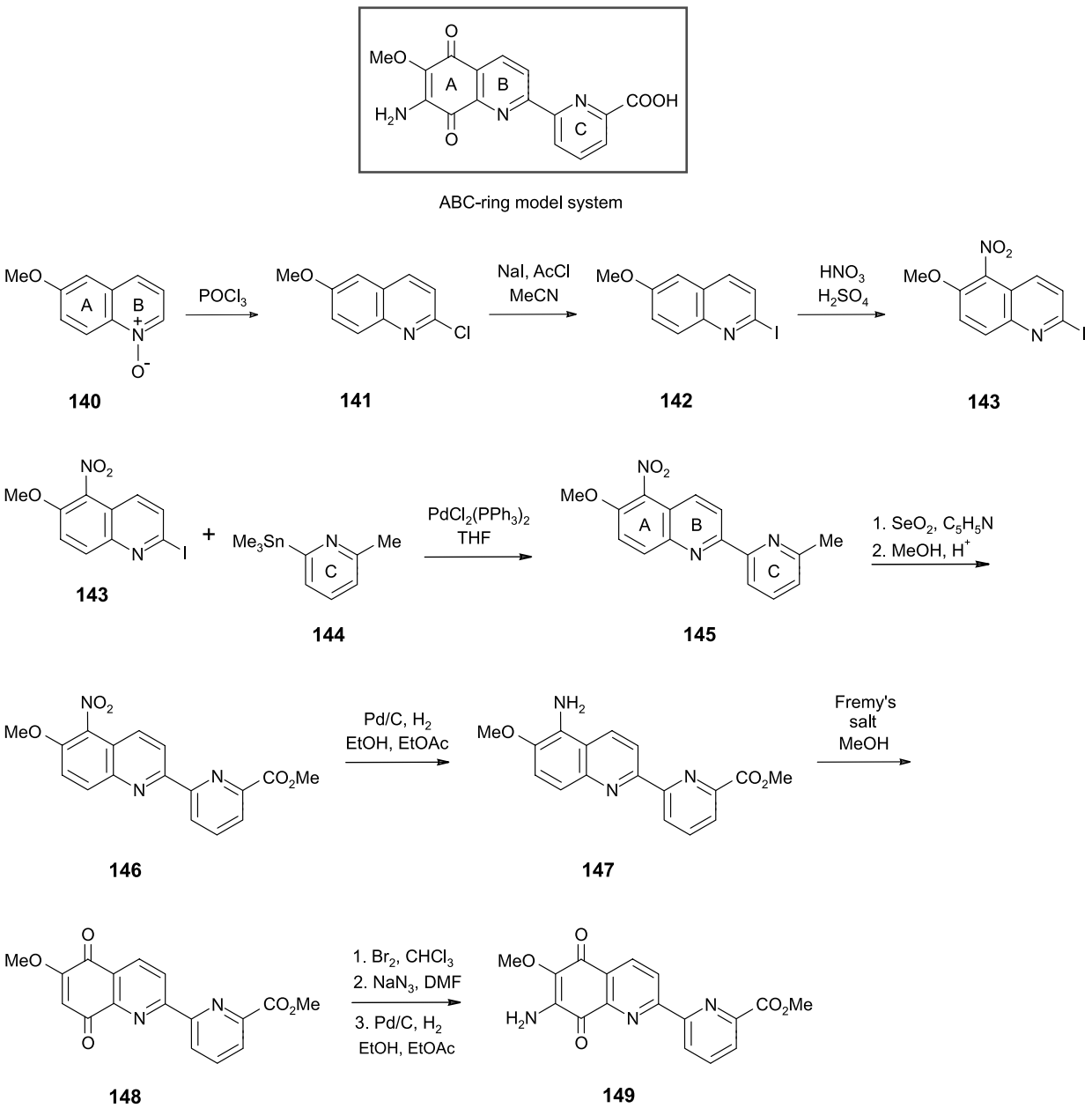
cycloaddition of enones (here **116**) with vinyl ethers (here **117a**) according to the methodology of Danishefsky and Bednarski.[92] On treatment with hydroxylamine hydrochloride,[93] the dihydropyrans provided the corresponding pyridines, for example, **119**. The cycloaddition step has, however, some limitations, the enones failing to react with cyclic vinyl ethers and at least one aryl group in conjugation with the enone carbonyl also being required for the cycloaddition with the vinyl ether.

9. ABC-rings (quinolinequinone) fused to a pyridine ring

Four different routes were developed for the assembly of the ABC-rings of streptonigrin. Rao reported a five-step synthesis of the tricyclic system **125** (Scheme 15).[94] Upon nitration, the chalcone **120** gave the mononitro derivative **121**, which, on reduction with sodium hydrosulfite (sodium dithionite), produced the pyridylquinoline **122**. Nitration of **122** with a 1:1 mixture of sulfuric acid and nitric acid gave 6-hydroxy-7-nitro-2-(2-pyridinyl)-5,8-quinolinedione (**123**), which was then reduced with sodium hydrosulfite to generate **124**. Finally, O-methylation with diazomethane gave the 6-methoxy derivative **125**.

Kuo and Rao[95] synthesized the advanced streptonigrin ABC-ring analog **131**, which still lacks the D-ring (Scheme 16), utilizing an intermediate **109** previously prepared (see Scheme 12) in their own laboratories. Their route to **131** started with the commercially available bromoacid **126**, which was readily converted to the nitroaldehyde **127**. Condensation of **127** with the acetylpyridine **109** gave the dinitrochalcone **128**, and its subsequent reduction with sodium hydrosulfite resulted in the quinoline **129**. Fremy's salt oxidation afforded the quinolinequinone **130**. The A-ring of streptonigrin was elaborated through the established methodology and gave the desired tricyclic compound **131**.

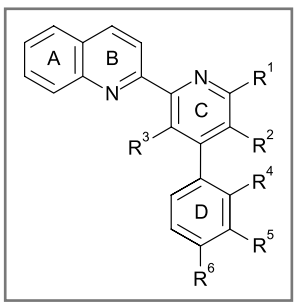
For their structure–activity relationship investigations, Lown and Sim[96] prepared several streptonigrin analogs. Their approach encompassed the formation of **134** by a



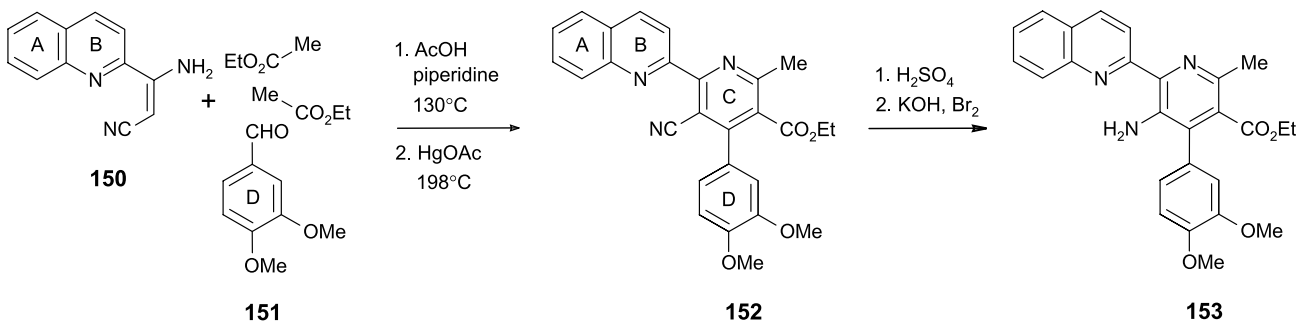
Scheme 18.

modified Skraup reaction of the commercially available dimethoxyaniline **132** and the α,β-unsaturated aldehyde **133** (see Scheme 17). The quinoline **134** was O-demethylated to **135** and further converted to the dichloroquinolinequinone **136**. Stepwise displacement of the chlorine substituents, the first by methoxide to give **137**, and the second by azide, delivered the methoxyazidoquinone **138**, which was catalytically reduced with PtO_2 and H_2 to furnish the aminoquinone **139**.

Harding and co-workers[97] described the synthesis of a tricyclic analog that contained the redox active quinone group with a 7-amino-6-methoxy-substitution pattern, as well as the pyridine-2-carboxylic acid present in streptonigrin (see Scheme 18). The key step was a Stille coupling of the properly substituted 2-iodoquinoline **143** with 2-trimethylstannyl-6-methylpyridine (**144**). Their starting material for **143** was the known[98] 2-chloro-6-methoxyquinoline (**141**), as obtained by reaction of the *N*-oxide **140** with phosphoryl chloride. On treatment with sodium iodide and acetyl chloride, **141** yielded the 2-iodo analog **142**. Nitration of **142** gave 2-iodo-6-methoxy-5-nitroquinoline (**143**, 81% yield), which was coupled to 2-(trimethylstannyl)-6-methylpyridine (**144**) with Pd catalysis to afford the required ABC-ring system **145**. Oxidation of the C-ring methyl group with selenium dioxide, followed by esterification, provided the ester **146**. Reduction to the amine **147**, followed by Fremy's salt oxidation, gave **148**. Following the method developed by Liao (cf. Scheme 4, compounds **36→22**),[60] this quinolinequinone was converted to the final 7-amino derivative **149**.

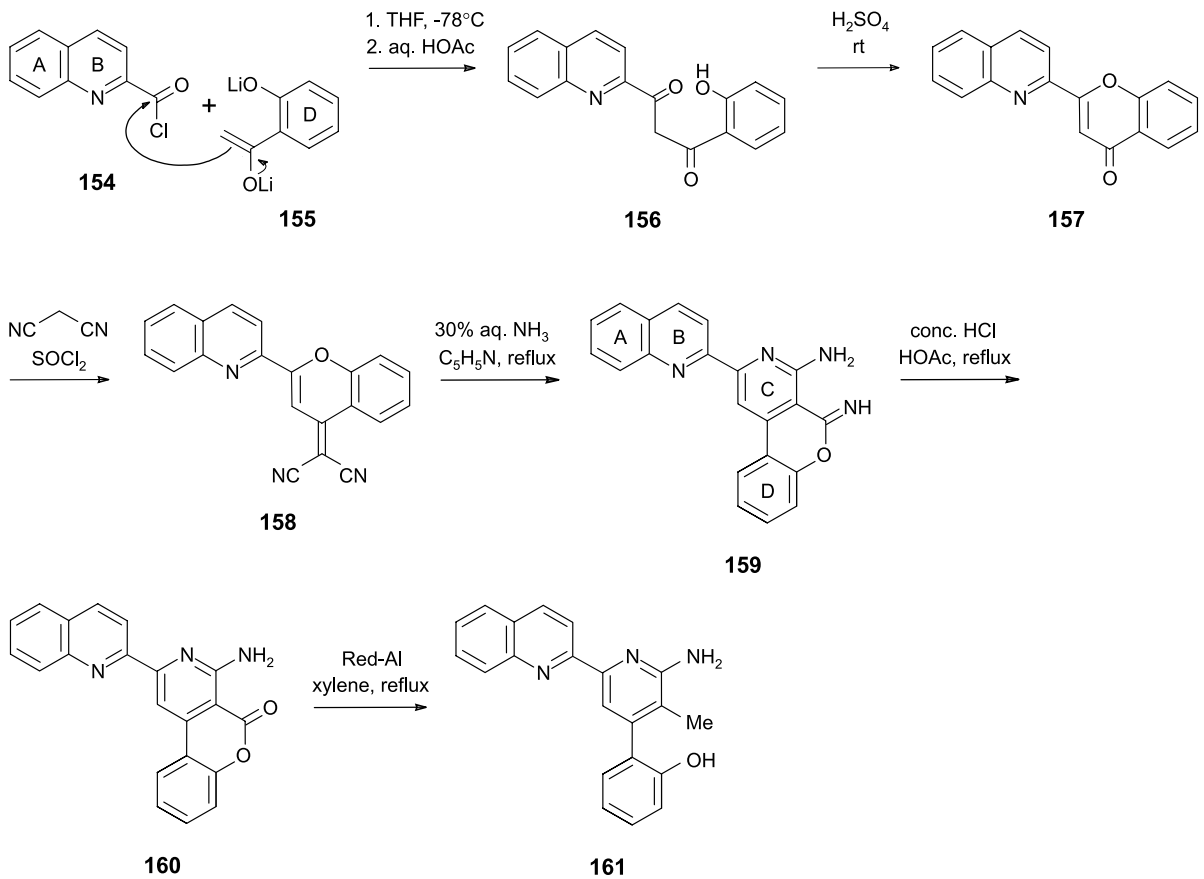


first, largely simplified ABCD-ring model system



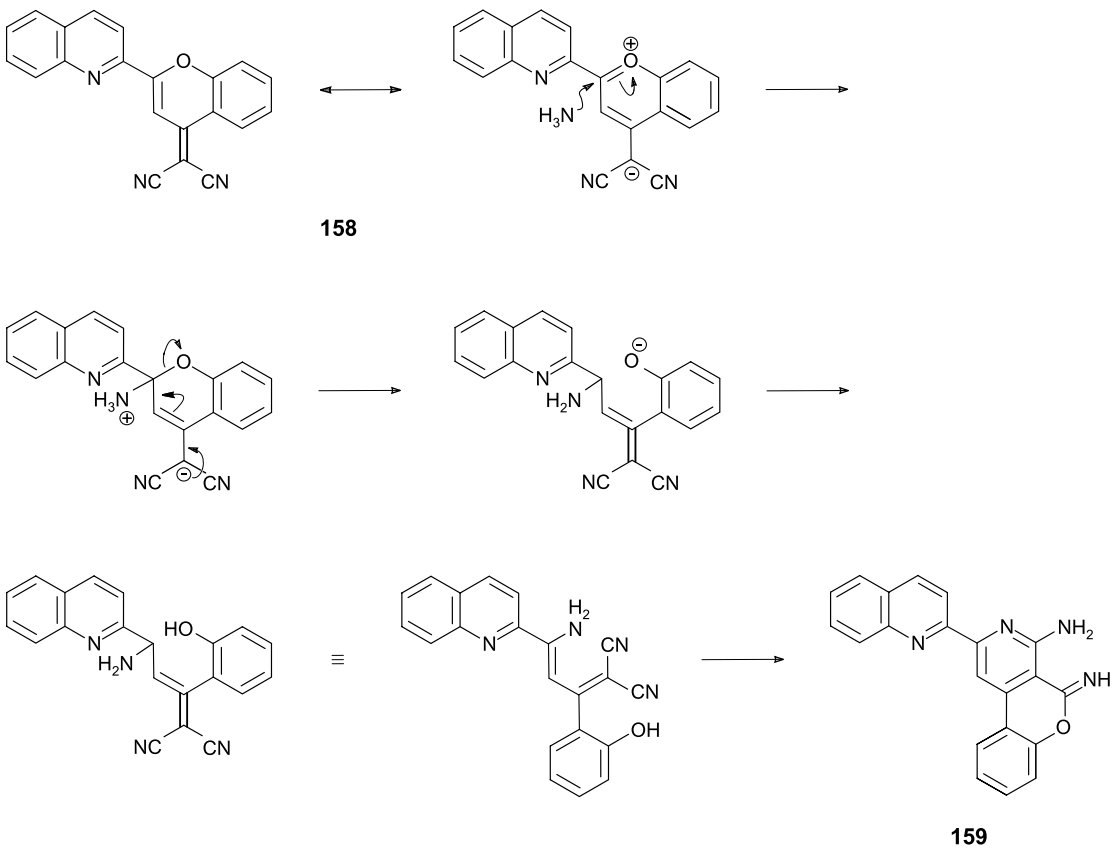
150 **151** **152** **153**

Scheme 19.



154 **155** **156** **157** **158** **159** **160** **161**

Scheme 20.



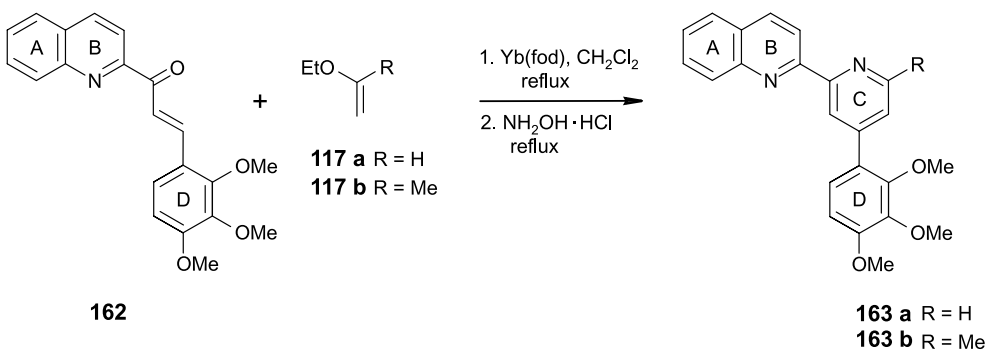
Scheme 21.

10. ABCD-ring model systems

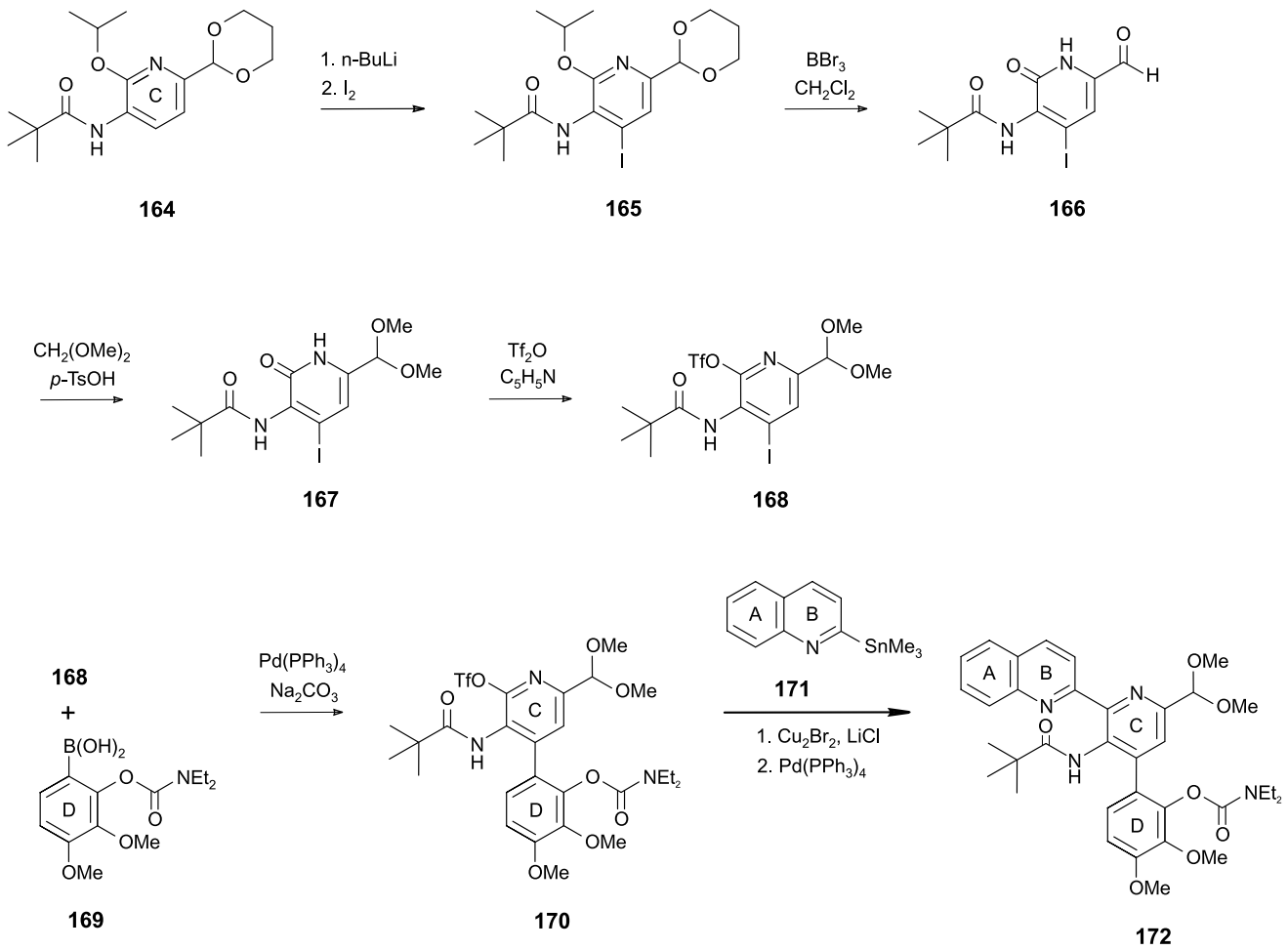
Four syntheses have appeared for model systems of the ABCD-rings, each of which has its own merits. The first tetracyclic model related to streptonigrin (**1**) was published by Kametani, Ogasawara, and Kozuka[65] in 1966 (see Scheme 19). The enamino-nitrile **150**, on heating with ethyl acetate and the aldehyde **151** (the latter supposedly giving the respective benzalacetone), resulted in a dihydropyridine, which was oxidized to the tetracyclic pyridine **152**. The nitrile unit in **152** was converted to the amide, which, on Hoffmann rearrangement with potassium hydroxide and bromine, gave the desired amine **153**.

A novel and completely different approach to the tetracyclic ring system of streptonigrin was reported by Cushman and Mathew (Scheme 20).[99] The dilithium dianion **155** derived from *o*-hydroxyacetophenone was treated with quinaldic acid chloride (**154**) to give the β-diketone **156**, which, on cyclodehydration, afforded the chromone **157** and then, on further treatment with malonodinitrile in thionyl chloride, the dinitrile **158**. By a reaction of the dinitrile **158** with ammonium hydroxide in hot pyridine, the pyridine imino-lactone **159** was obtained. Acid hydrolysis yielded **160**, the oxolactone function of which was reduced down to the methyl group present in the model compound **161** by using sodium bis(2-methoxyethoxy)aluminum hydride (‘Red-Al’)—a novel and intriguing approach to the synthesis of either biologically active analogs of streptonigrin or to the natural product itself!

The conversion of the dicyanomethylene dinitrile **158**



Scheme 22.



Scheme 23.

to the substituted pyridine iminolactone **159** is of mechanistic interest and a likely sequence of steps as suggested by the work of Reynolds[100] is outlined in Scheme 21.

Earlier in this report (Scheme 14), we outlined a new synthesis of substituted pyridines developed by Ciufolini and Byrne,[91] who subsequently used their method to prepare an ABCD-ring model system (see Scheme 22). The enone **162** prepared from 2-acetylquinoline and 2,3,4-trimethoxybenzaldehyde was subjected to cyclocondensation with ethyl vinyl ether (**117a**). The derived primary cycloadduct was converted to **163a** by the use of hydroxylamine hydrochloride. In related work, the same authors synthesized the additionally *C*-methylated analog **163b**, demonstrating an easy entry into the streptonigrin skeleton.[89]

Quéguiner and co-workers[63] have pursued several model systems in the streptonigrin area. Their work on the ABCD-ring system,[101–104] which has considerable potential in total synthesis, is outlined in Scheme 23. These researchers focused on two key reactions, namely *ortho* metallation[84] and Pd-catalyzed cross-coupling under Suzuki conditions. The 1,3-dioxan-2-yl-, *O*-isopropyl-, and 3-*N*-pivaloyl-protected aminopyridine derivative **164** was converted to the iodotriflate **168** in five steps, via the iodide **165**, the 6-formyl-2-pyranone **166** and the acetal **167**. Cross-coupling of **168** with the phenylboronic acid **169** afforded the 2-*O*-triflate-activated 4-phenylpyridine **170** with high selectivity. Coupling of **170** with 2-(trimethylstannyl)quinoline (**171**, prepared from 2-chloroquinoline and chlorotrimethylstannane in the presence of sodium in 1,2-dimethoxyethane as a solvent) gave the tetracycle **172**. If elaborated with a properly substituted A-ring, this would be a candidate for a short and efficient route to streptonigrin (**1**).

11. Total synthesis: general comments

Natural products provide outstanding opportunities for synthetic organic chemists to display creativity in the construction of complex molecules. For streptonigrin and its congeners, several new methods and reagents have evolved and these have helped to advance the organic synthetic methodology. In 1960, the total synthesis of streptonigrin (**1**) was considered to be a monumental—if not impossible—task, owing to its high degree of functionality coupled with an intricate arrangement of aromatic rings. Only after 20 years of careful and extensive preliminary studies did Weinreb complete the first total synthesis of

streptonigrin.[105–107] The extraordinary approaches by Kende's[55,108,109] and Boger's[76,110,111] laboratories soon followed. In the next three sections, we will highlight the synthetic strategies adopted by the respective groups rather than concentrating on the reactions and reagents. Weinreb's pathway is the longest of the three, but he deserves accolades for reaching the target first and at a time when the artistry of synthesis was not as mature as it is now.

12. Weinreb's approach

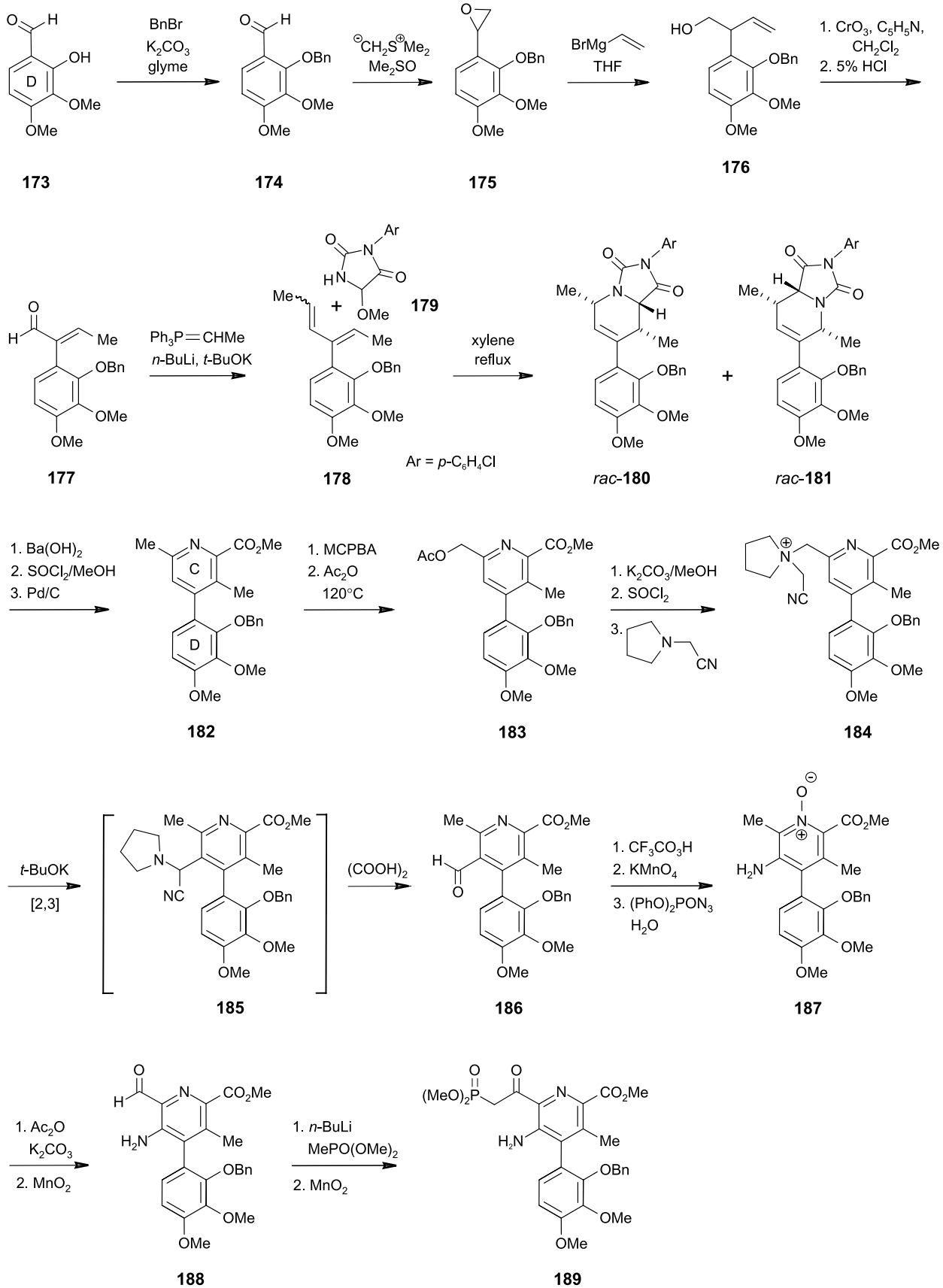
Weinreb adopted a modified Friedländer reaction to form the quinoline portion, that is, the AB-rings (see Scheme 24a).[106] The central strategy involved an imino Diels–Alder reaction for the construction of the CD-rings. The easily available aldehyde **173**[112] was converted in three straightforward steps to the 2-arylated α,β-unsaturated aldehyde **177**, by O-benzylation to **174**, conversion of the formyl function into the oxirane **175**, and its subsequent ring cleavage using vinyl magnesium bromide to give **176**, and eventual oxidation of the primary alcohol to an aldehyde function. Treatment with ethylidene triphenylphosphorane at low temperature, followed by *n*-butyllithium and then potassium *t*-butoxide in *t*-butanol,[113] afforded **178**. The reaction between this diene **178** and the methoxyhydantoin **179** generated the dienophile by elimination of methanol and led to a 3:1 mixture of the regioisomeric adducts **180** and **181**. Without separation, this mixture was transformed to the key tetrasubstituted pyridine **182** in three steps. The next task was the introduction of the amino group as the fifth substituent on the pyridine ring of **182**. This required excellent planning and its execution in 10 steps was a major achievement. It included three key reactions, namely the rearrangement of the *N*-oxide of **182** under Polonovski reaction conditions[114] to the acetoxy compound **183**, another [2,3]-sigmatropic (Sommelet–Hauser-type) rearrangement of **184** to functionalize the 3-position of the pyridine, and the Yamada modification[115] of the Curtius rearrangement, to provide the amine **187**. The final stages involved the renewed functionalization of the 2-methyl group of the pyridine by another Polonovski-type rearrangement and the stepwise formation of the chalcone derivative **191**, via a Wordsworth–Emmons–Horner reaction of **189** with **190** (see Scheme 24b),[116] followed by reduction with sodium hydrosulfite, which proceeded smoothly to give **192**. Cleavage of the *O*-sulfonyl group with sodium methoxide yielded the tetracyclic phenol quinoline-5-ol derivative, which was oxidized to the quinone **193** using Fremy's salt. Final elaboration of **193** to the aminoquinone **194** and further to streptonigrin (**1**) used known procedures developed by Weinreb[25,117] and others.[55]

13. Kende's approach

The basic strategy developed by Kende and co-workers[55,108,109] was to concentrate on the regiocontrolled synthesis of the CD-ring portion and then utilize a Friedländer synthesis for the attachment of the AB-ring system (see Scheme 25a or Scheme 25b). The known ketoenamine intermediate **63**, as prepared earlier by Liao, Wittek, and Cheng (see also Scheme 7),[73] was condensed with methyl acetoacetate to form the 3-acetyl-4-arylpyridone **195**. The acetyl group was reduced to the alcohol **196** (possibly a diastereomeric mixture, due to the presence of both central and axial chirality, but not specified) and further converted to the 2-chloro-3-vinylpyridine **197** by using phenylphosphoryl dichloride. On treatment with cuprous cyanide, this compound gave the respective nitrile, which was *C*-methyl-ated to yield the 2-acetylpyridine **198**. The A-ring precursor was prepared in three steps from the known[118] aldehyde **199**, which, upon imination with *p*-toluidine and O-benzyl-ation of the phenolic function with *p*-methoxybenzyl bromide, afforded the nitroimine **200**. This, when reduced with disodium sulfide in methanol, gave the iminoaniline **201**. Reaction of this second building block **201** with the ketone **198** led to the intact phenylpyridylquinoline **202**. Selective cleavage of its A-ring protecting group to give **203** allowed the introduction of the nitro group, followed by O-methylation with dimethyl sulfate, to give the nitro tetracyclic methyl ether **204**, the vinyl unit of which was then oxidatively degraded to deliver a carboxylic group on the pyridine ring.[119,120] Selenium dioxide[72] was found to oxidize the 2-methyl group of the pyridine to give the respective aldehyde, which, on sodium chlorite oxidation, gave the diacid, the selective methylation of which yielded the monoester **205**. Application of the Yamada modification[115] of the Curtius rearrangement produced the aminopyridine **206**. The A-ring nitro group was reduced to the amine with sodium hydrosulfite, followed by Fremy's salt oxidation to the quinolinequinone **193**, which had also been prepared by the Weinreb group (cf. Scheme 24b).[105–107] In this pathway by Kende, the A-ring amino function of **1** was introduced in four steps from **193**, by taking advantage of Weinreb's method developed previously.[25,117] The decision to use the vinyl group at C-5′ in the C-ring to serve as a precursor to the amino group[115,119,120] was a keen insight, and became an elegant feature in Kende's approach, simultaneously resulting in a shorter synthesis.

14. Boger's approach

Boger[76,110,111] reported a convergent seven-step synthesis of the tetracycle **215** (see Scheme 26), with the benefit of a considerable amount of preliminary work first conducted on model systems. Two consecutive Diels–Alder reactions with inverse electron demand and subsequent in situ cycloreversion formed the basis of their approach. The key starting material was the thioimidate **210**, which was prepared from the commercially available 6-methoxyquinoline (**207**). Treatment of **207** with *p*-toluenesulfonyl chloride and then with potassium cyanide gave the 2-cyanoquinoline **208**. Nitration yielded **209**, which, on further reaction with hydrogen sulfide in diethylamine, generated the thioamide, which was converted to the desired *S*-methylthioimidate **210** with methyl iodide. A Diels–Alder reaction of **210** with the 1,2,4,5-tetrazine-3,6-dicarboxylate (**211**)[121] with N_2 extrusion provided the 1,2,4-triazine **212** in 82% yield. Subsequent treatment of **212** with the morpholino enamine **213** of 2-(benzyloxy)-3,4-dimethoxypropiophenone afforded a 1:1 mixture of the Diels–Alder adducts **214** and **215**. Four further steps transformed **215** into **206**,[110] which had previously been converted (Scheme 25a or


BnBr
K2CO3
glyme
CH2SMe2
Me2SO
BrMg
THF
1. CrO3, C5H5N,
CH2Cl2
2. 5% HCl
Ph3P=CHMe
n-BuLi, t-BuOK
xylene
reflux
Ar = p-C6H4Cl
1. Ba(OH)2
2. SOCl2/MeOH
3. Pd/C
1. MCPBA
2. Ac2O
120°C
1. K2CO3/MeOH
2. SOCl2
3.
t-BuOK
[2,3]
(COOH)2
1. CF3CO3H
2. KMnO4
3. (PhO)2PON3
H2O
1. Ac2O
K2CO3
2. MnO2
1. n-BuLi
MePO(OMe)2
2. MnO2
173
174
175
176
177
178
179
rac-180
rac-181
182
183
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187
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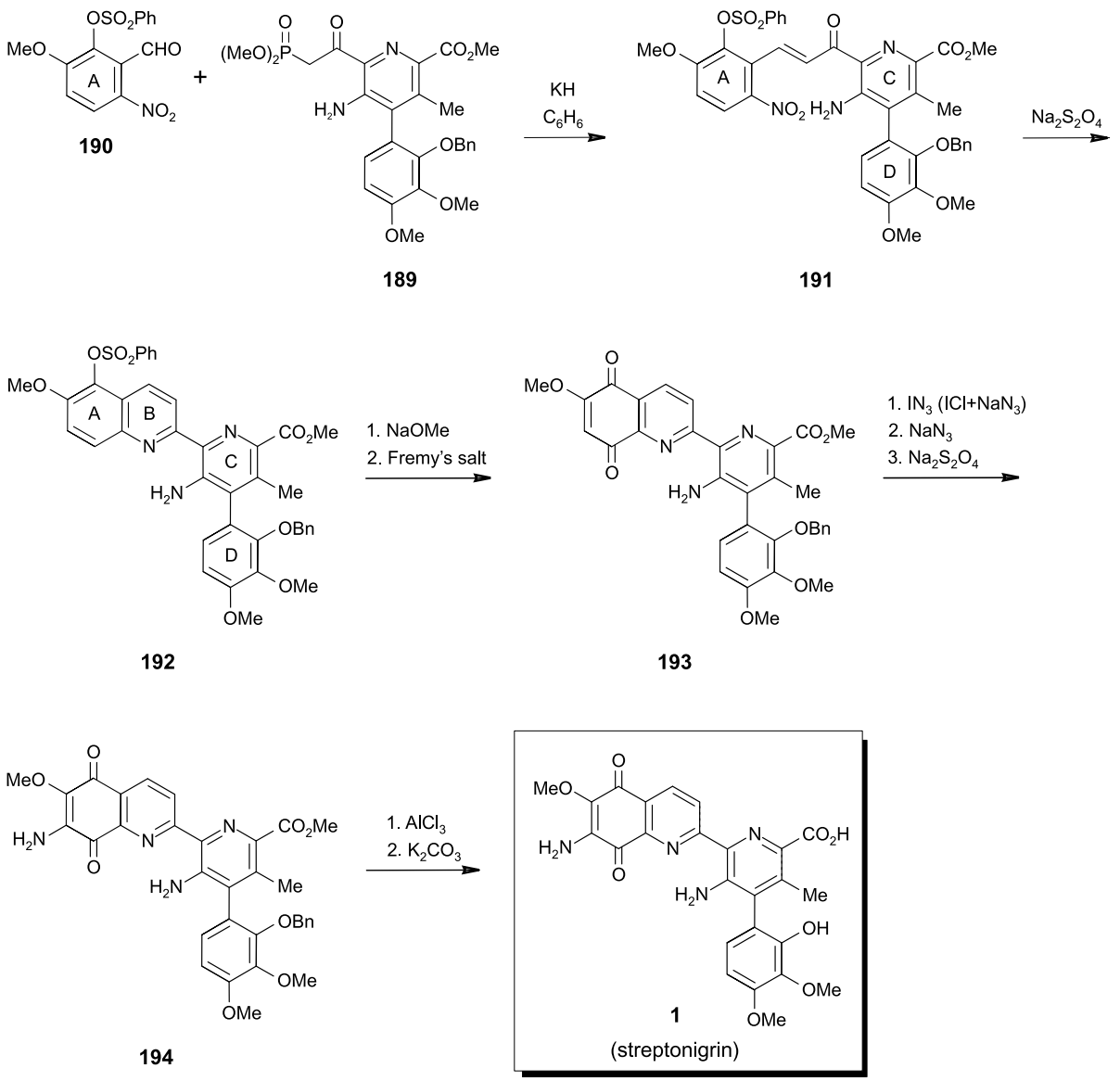
189

Scheme 24a.

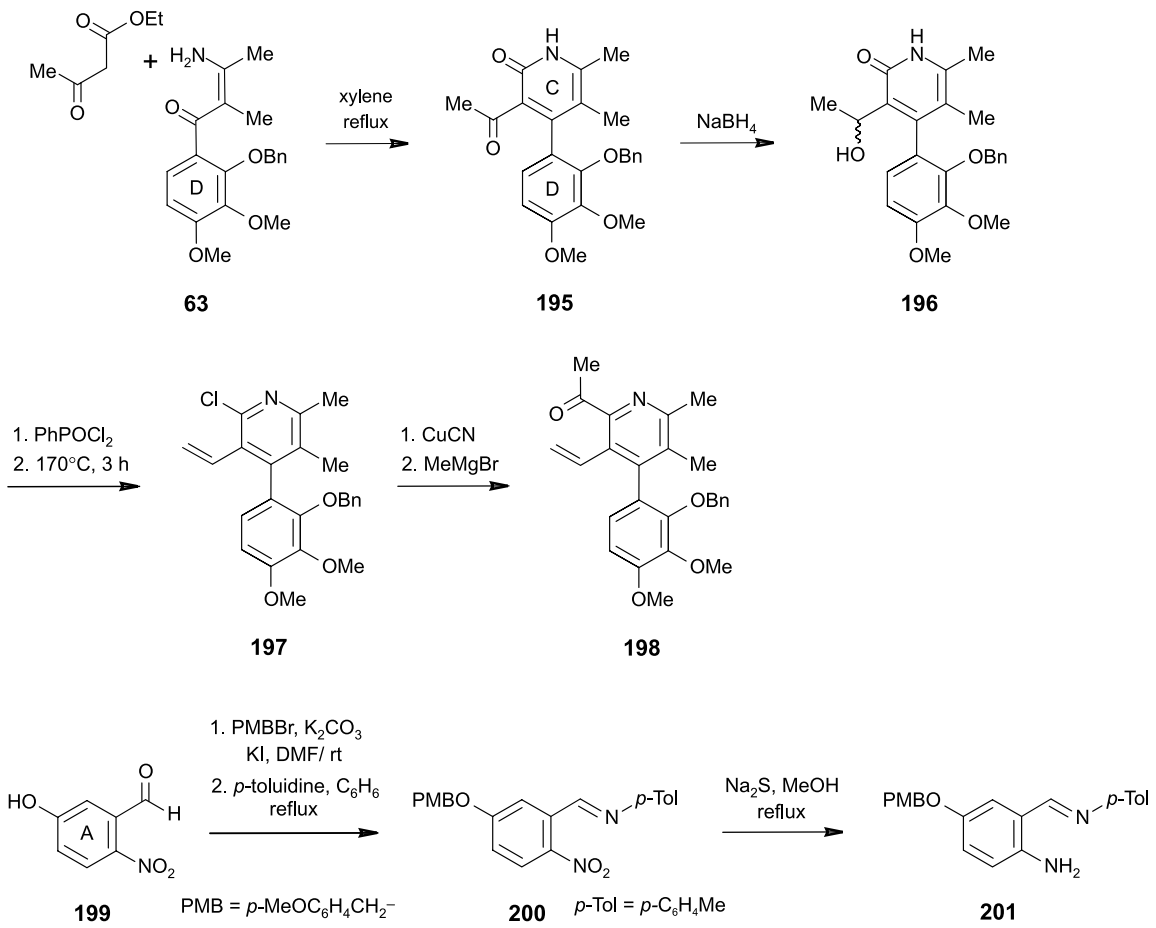


Scheme 24b.

Scheme 25b) to streptonigrin (**1**).[102] Boger's approach therefore corresponds formally to another total synthesis of streptonigrin.

15. Structure and synthesis of streptonigrone

Streptonigrone (**2**) was isolated, along with streptonigrin (**1**), from an unidentified *Streptomyces* species (IA-CAS isolate No. 114) by Rickards and his colleagues,[15] and, additionally, a Russian team isolated **2** from *Streptomyces albus* var. *bruneomycini* as a minor component from both of the species.[16] Streptonigrone (**2**) has a mp of 268–269 °C and the molecular formula $C_{24}H_{22}N_4O_7$, which differs from that of streptonigrin **1** ($C_{25}H_{22}N_4O_8$) by the lack of one C and one O atom. The assigned structure is based mainly on the ^1H and ^{13}C NMR spectra, the characteristics of which are very similar to those of streptonigrin (**1**). In contrast to **1**, however, the lack of any circular dichroism effect[23] demonstrates that streptonigrone (**2**) is a racemate, either due to a non-enantioselective formation or because it is possibly configurationally unstable. Again in contrast to streptonigrin (**1**), **2** showed no antimicrobial activity in disc assays at 50 μg/ml against strains of *Streptomyces aureofaciens*. The only synthesis of streptonigrone (**2**) so far reported was developed by Boger and his group[122] and is outlined in Scheme 27. Their strategy was to use an inverse electron demand Diels–Alder reaction[121,123] of the *N*-sulfonyl-1-aza-1,3-butadiene **221** with the ketene acetal **222** to generate ring C. A Friedländer condensation of pyruvic acid (**217**) with 2-amino-3-benzyloxy-4-bromobenzaldehyde (**216**) and esterification gave the quinoline **218**, which, on treatment with the lithium enolate of ethyl acetate, provided the β-keto ester **219**. A piperidine-catalyzed condensation of **219** with 3,4-dimethoxy-2-hydroxybenzaldehyde[112] (**173**) afforded the benzopyranyl ketone **220**. This ketone was converted to the desired azadiene **221** in two steps by the action of hydroxylamine hydrochloride and methanesulfinyl chloride. A hetero-Diels–Alder reaction of **221** with 1,1-dimethoxypropene (**222**) led to the respective



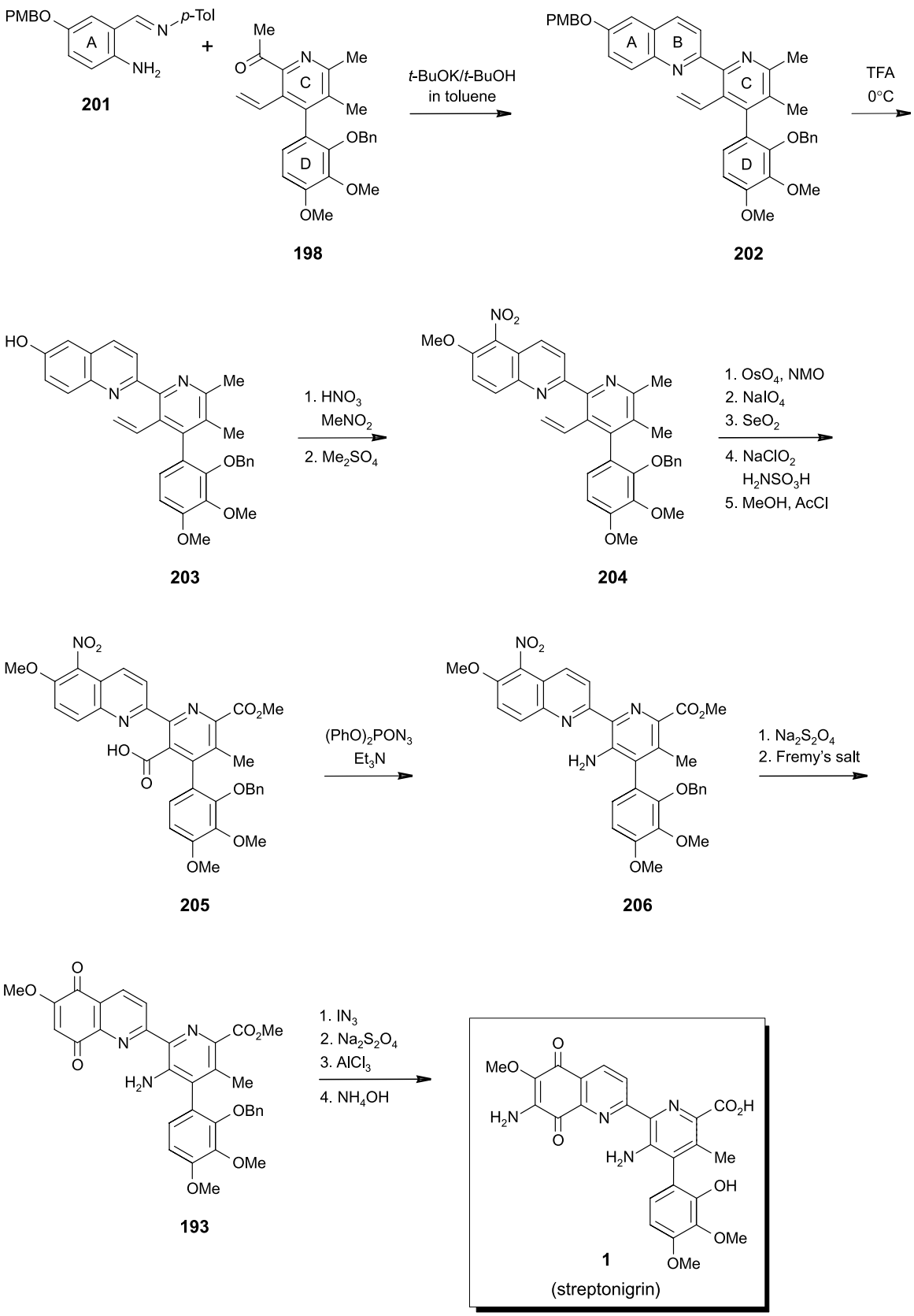
Scheme 25a.

[4+2]-cycloadduct which, on treatment with potassium *t*-butoxide followed by dichlorodicyanoquinone, provided the pyridine lactone **223**. Methanolysis opened the lactone ring and the resulting phenol function was protected as a methoxymethyl (MOM) ether, hydrolysis of the methyl ester with lithium hydroxide giving the nicotinic acid derivative **224**. This intermediate was converted to the benzyl ether of **225** and then further to streptonigrone (**2**) by standard reactions, most of which have already been previously discussed (see Scheme 25a) in connection with the synthesis of streptonigrin (**1**). Two aspects of the Boger synthesis of streptonigrone (**2**) are worthy of note, namely his prediction of a high regioselectivity in the Diels–Alder reaction (**221**+**222**→**223**), which proved to be correct, and the development and application of an improved Lewis acid-catalyzed nucleophilic substitution reaction at C-6 with sodium methoxide (**226**→**227**).

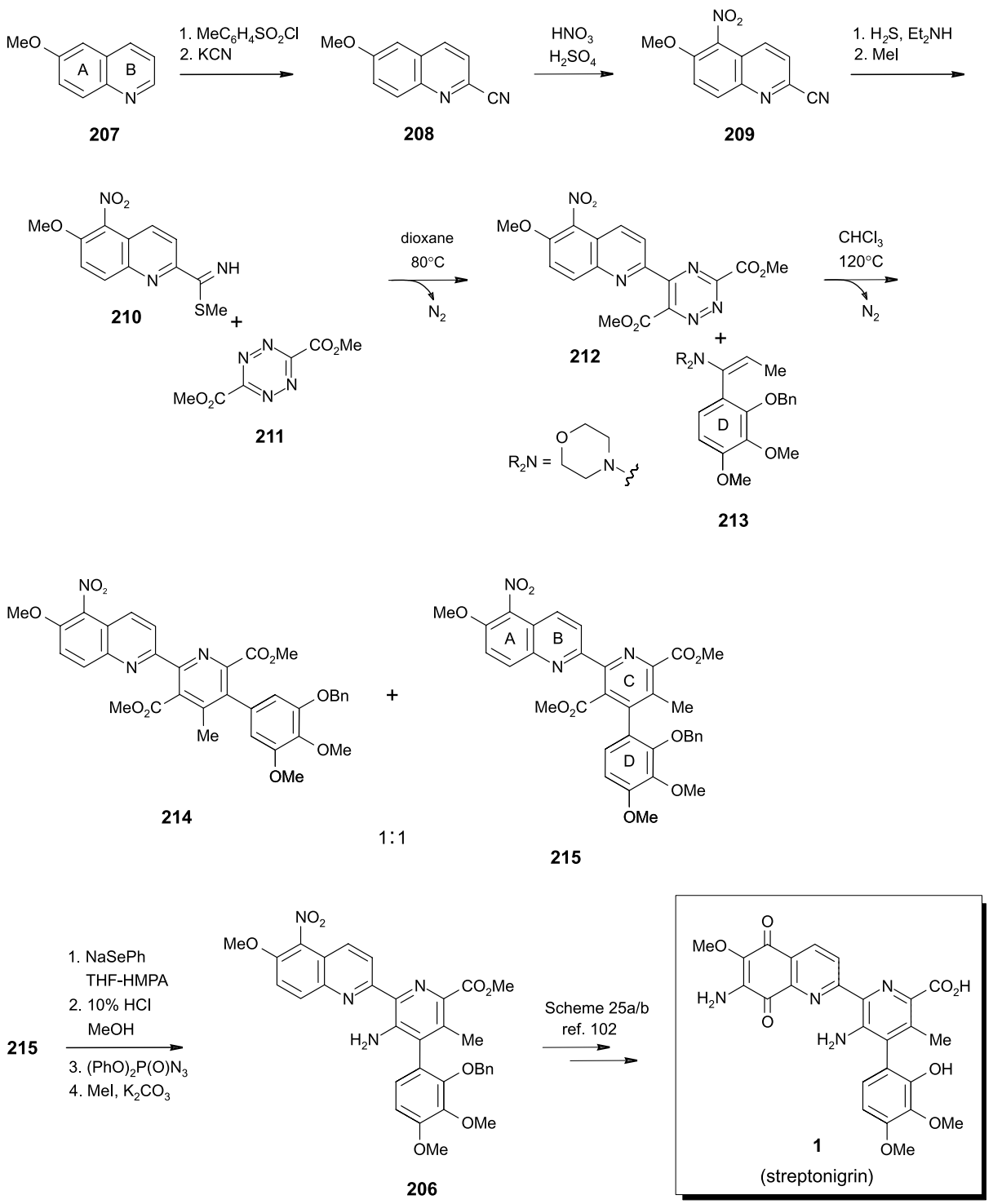
16. Structure and total syntheses of lavendamycin and an analog

While investigating the fermentation broth of *Streptomyces lavendulae* strain C22030, Doyle and his group[17] isolated an antibiotic that was named lavendamycin, a red solid, mp >300 °C, with the molecular formula $C_{22}H_{14}N_4O_4$. Lavendamycin was found to possess a limited solubility in organic solvents, which precluded efforts to grow crystals suitable for an X-ray structure analysis. Only minute quantities of the natural product were available and chemical degradation was therefore not feasible. The NMR, IR, UV, and high resolution mass spectral studies, together with biogenetic consideration, were used to assign structure **3** to lavendamycin. It has antibiotic activity comparable to that of streptonigrin (**1**) and, most importantly, antitumor activity against P-388 and L-1210 cell lines. The biological activity, coupled with novel structural features such as a tricyclic β-carboline subunit attached to a 7-amino-quinolinequinone, were challenging enough for organic chemists to undertake its synthesis. Since the structural assignment of lavendamycin (**3**) by Doyle, Gould, and their collaborators in 1981,[17] four research groups have synthesized its methyl ester between 1984 and 1986.

The first total synthesis was achieved by Kende and Ebetino[124] and their route is outlined in Scheme 28. The key intermediate **231** was prepared in three steps from 2-amino-3-methoxybenzaldehyde (**228**) and pyruvic acid (**217**). A Friedländer condensation[106] gave the 8-methoxyquinaldic acid (**229**), which was nitrated to deliver the 5-nitro derivative **230**. Bromination in the presence of silver trifluoroacetate gave the desired key intermediate **231** in 45% overall yield for the three steps. Reaction of this acid with the methyl ester **232** of β-methyltryptophan


PMBO
p-Tol
A
NH2
201
Me
O
N
Me
C
Me
OBn
D
OMe
OMe
198
t-BuOK/t-BuOH
in toluene
PMBO
A
B
N
Me
C
Me
OBn
D
OMe
OMe
202
TFA
0°C
HO
N
Me
Me
OBn
OMe
OMe
203
1. HNO3
MeNO2
2. Me2SO4
NO2
MeO
204
1. OsO4, NMO
2. NaIO4
3. SeO2
4. NaClO2
H2NSO3H
5. MeOH, AcCl
CO2Me
HO
O
205
(PhO)2PON3
Et3N
H2N
206
1. Na2S2O4
2. Fremy's salt
O
1. IN3
2. Na2S2O4
3. AlCl3
4. NH4OH
CO2H
OH
1
(streptonigrin)

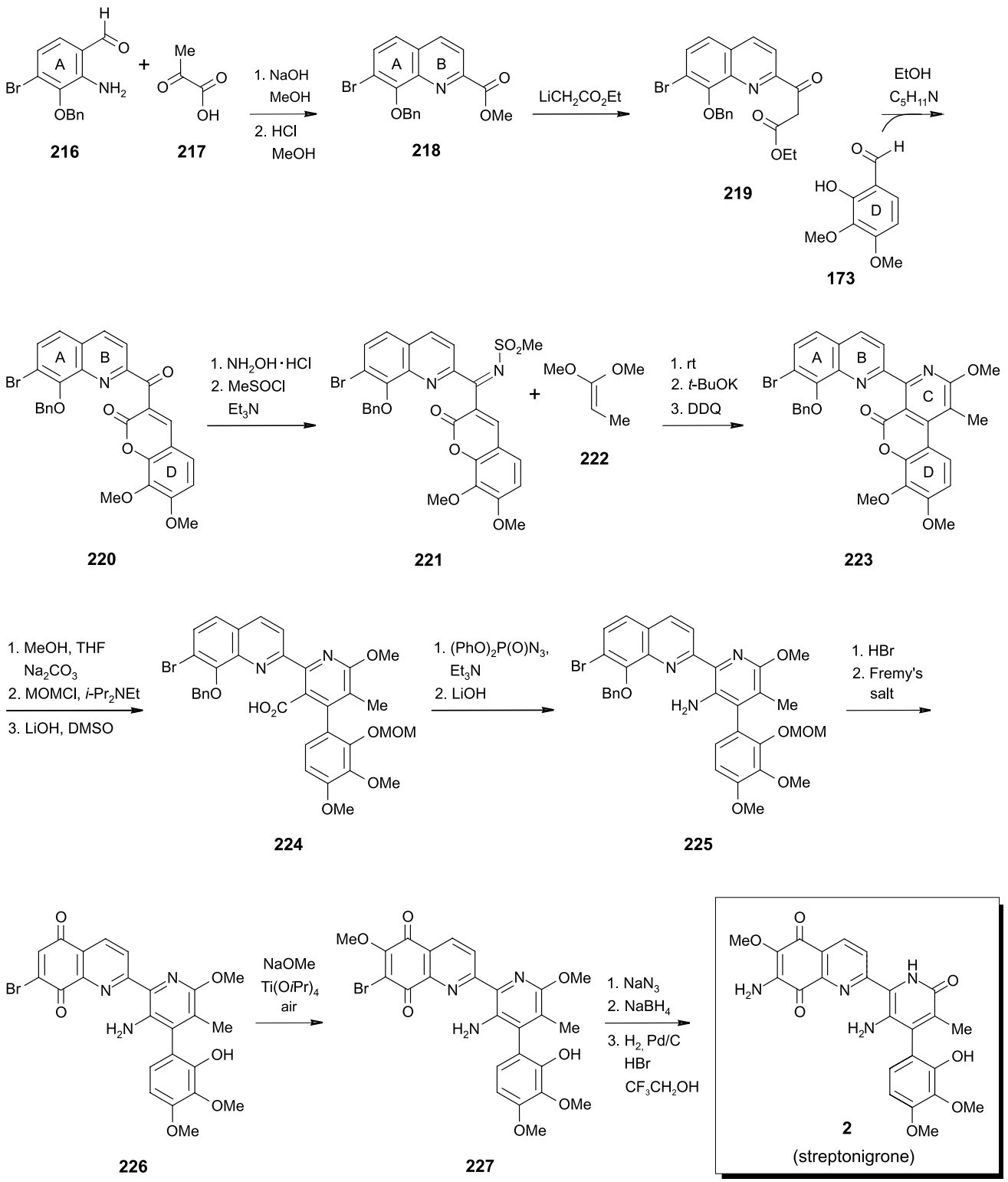
Scheme 25b.



Scheme 26.

(stereoisomeric mixture)[125] in the presence of a carbodiimide gave the amide **233**, which was condensed to the pentacyclic β-carboline ester **234** with polyphosphate esters (PPE)[126] by using a Bischler–Napieralski-type cyclocondensation with a concomitant dehydrogenation reaction. In a straightforward sequence of four steps, this pentacyclic product was converted to the amine **235** and the quinolinequinone **236** and eventually to lavendamycin methyl ester (**237**), which was identical with the methyl ester prepared directly from lavendamycin (**3**).

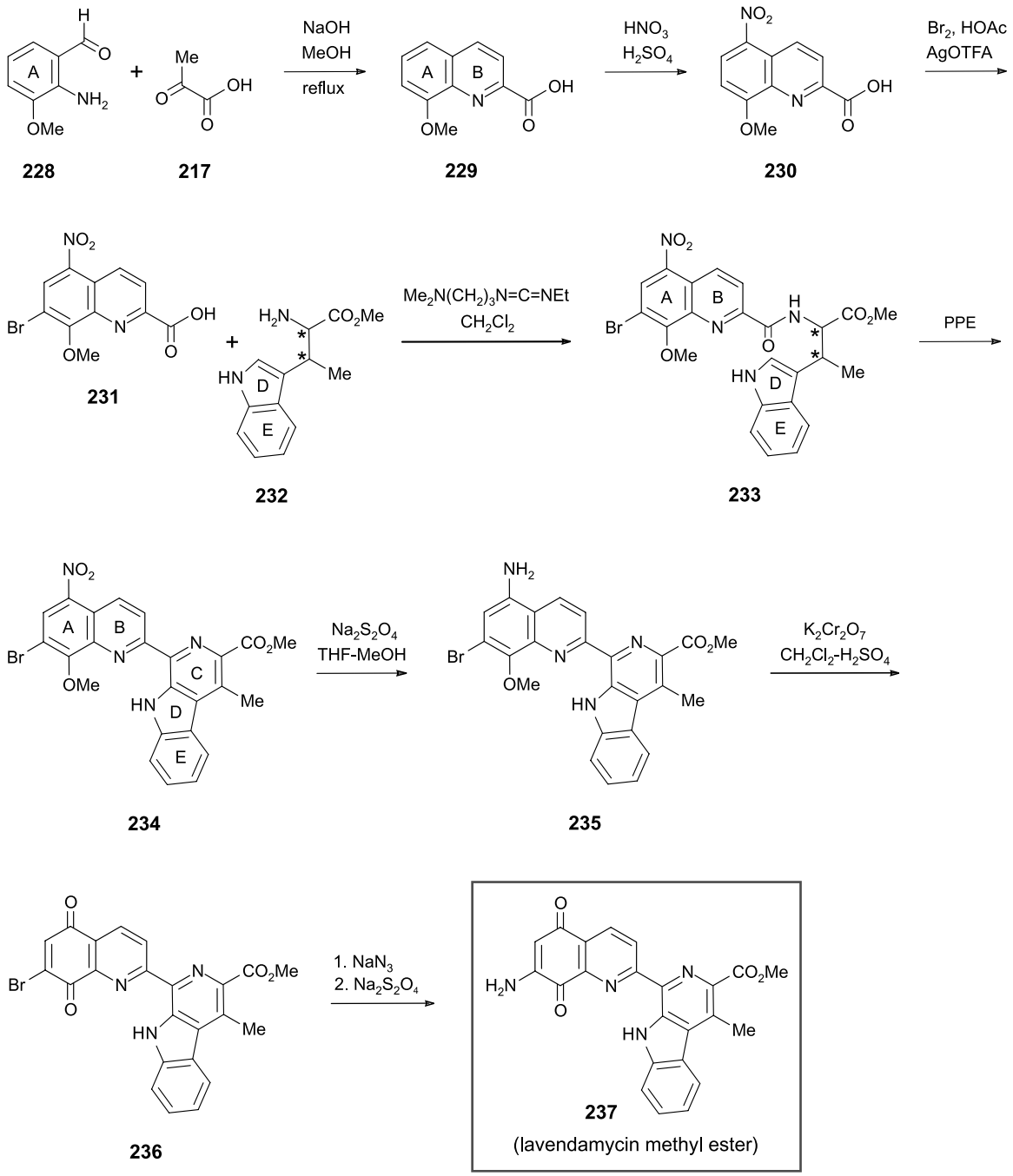
Hibino's[127,128] and Rao's[129,130] groups have independently reported regiospecific formal total syntheses of lavendamycin methyl ester (**237**) in eight and 16 steps, respectively, the first starting from the 2-formylquinoline **238** and β-methyltryptophane ethyl ester (**239**), via the pentacyclic compounds **240**, **241**, **242**, **243**, and **236**, and the second from quinoline-8-ol (**244**), via **245**-**253**. The latter compound, after amidation with the tryptophan derivative **232** to give **254**, was submitted to a Bischler–Napieralski cyclization to give **255**, which was converted to **237** via the



Scheme 27.

bromoquinone **236**. Although both approaches were similar to that of Kende, different starting materials and reagents were used. This does not detract from the value of the ideas presented in these two syntheses, which are outlined in Schemes 29 and 30. It is of interest to note the probably biomimetic-type Pictet–Spengler-based approach by Hibino (see Scheme 29).

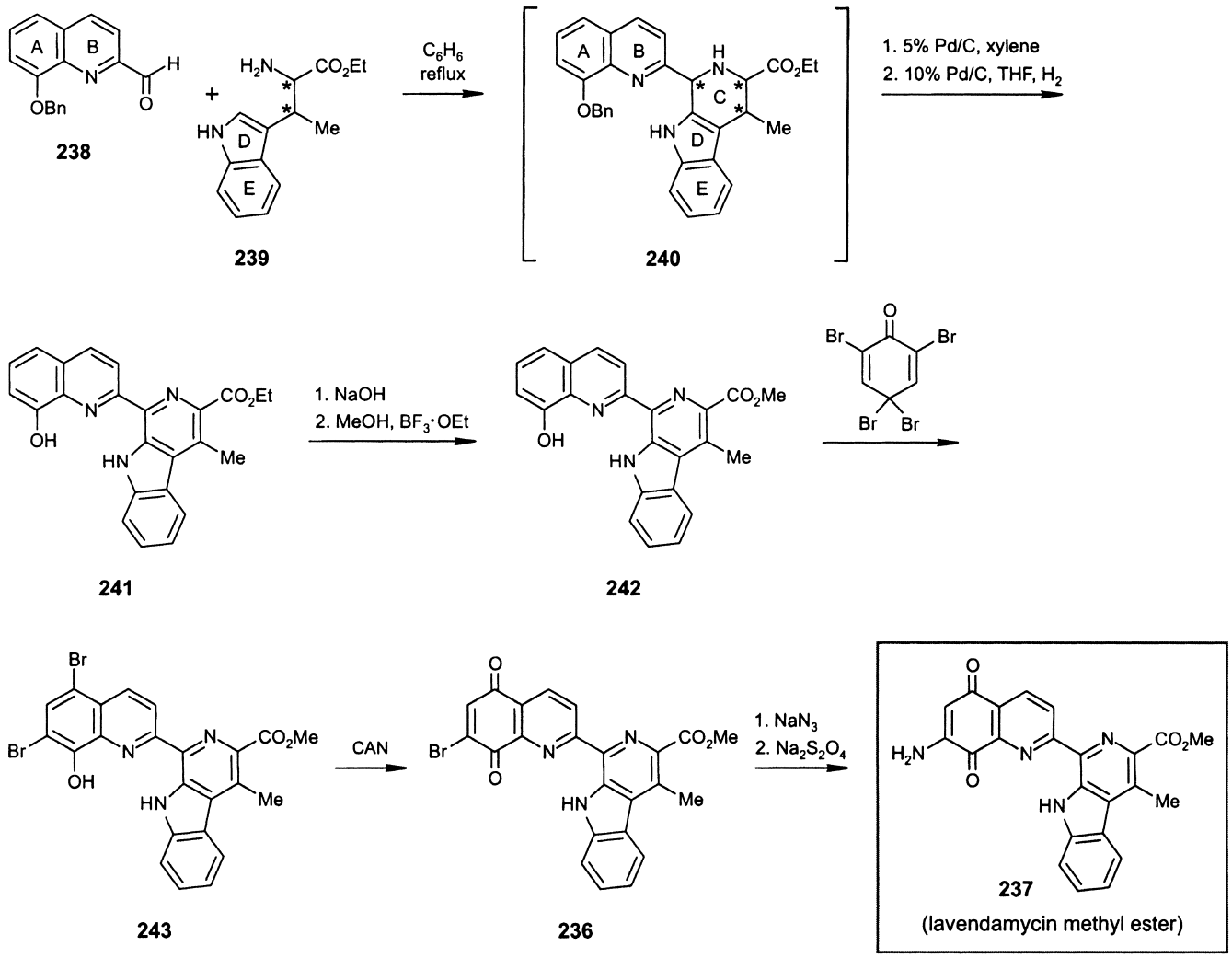
Boger and co-workers[131] succeeded in applying their inverse electron demand [4+2]-cycloaddition of an electron-deficient 1,2,4-triazine with an α-aryl enamine to form the CE-rings as the basis of a synthesis of lavendamycin methyl ester (**237**). Another notable feature was the formation of a D-ring of a β-carboline unit by the oxidative insertion of an aryl halide in the presence of palladium(0). In



Scheme 28.

addition, a Friedländer condensation between a suitable aryl aldehyde and a properly-substituted β-carboline unit was used to form the ABCDE-rings of lavendamycin methyl ester. These three key reactions contributed to the success of Boger's synthesis, which is outlined in Scheme 31. The oxazinone **261** was prepared in a six-step sequence from 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine (**81**), by a regioselective inverse-electron demand [4+2]-cycloaddition with the pyrrolidine enamine **257** of 2-bromopropiophenone, as prepared from the aldehyde **256**, with concomitant N_2 extrusion. Standard steps completed the conversion of the cycloadduct **258** to **261**, via the monoacid **259** and the acetamido compound **260**. Another four steps were required to convert **261** to the free 2-acetyl-3-aminopyridine **262** and then to **263**. This 2-acetyl-β-carboline, which was condensed with 2-amino-3-benzyloxy-4-bromobenzaldehyde (**264**) to give 1-(8-benzyloxy-7-bromo-2-quinolinyl)-3-(methoxycarbonyl)-4-methyl-β-carboline (**265**). From **265**, the synthesis of the pentacyclic carboline molecule of lavendamycin methyl ester (**237**) was accomplished employing standard reaction conditions.

In 1996, Behforouz[132] reported a short and practical approach for the total synthesis of lavendamycin methyl ester (**237**), attaining a high overall yield of as much as 32%! The novel bis-acetamide **268** was prepared from the



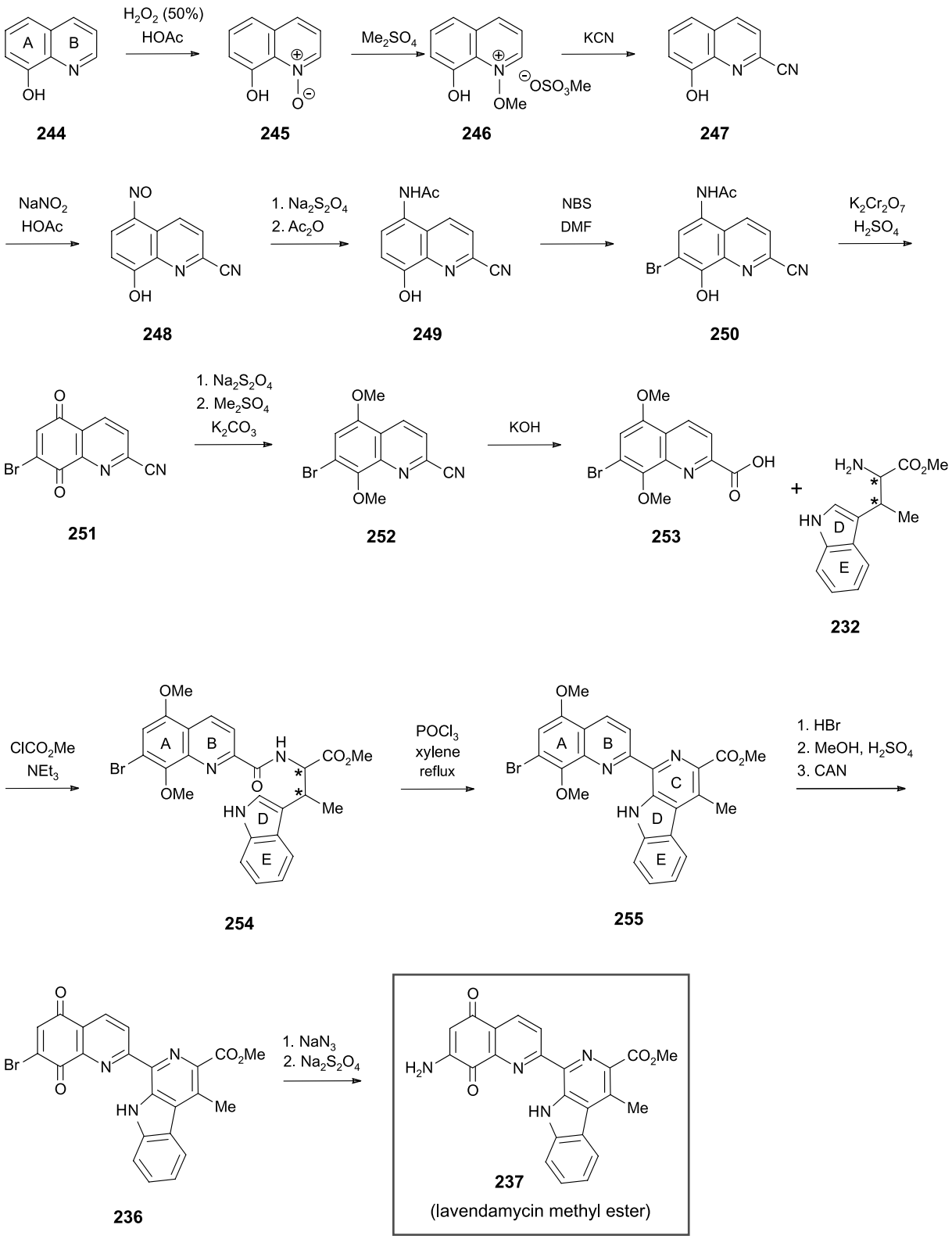
Scheme 29.

commercially available 8-hydroxy-2-methylquinoline (**266**) in three steps via the dinitro compound **267** (see Scheme 32). It was then converted into the pentacyclic product **237** by the selective oxidative cleavage of the 5-acetamide function to give the quinone **269**, followed by the oxidation to the aldehyde **270**, which underwent a Pictet–Spengler reaction with the methyl ester **232** of β-methyltryptophan to give directly the dehydrogenated β-carboline **271**, the treatment of which with aqueous sulfuric acid gave **237**[133] (see also Schemes 28–30).

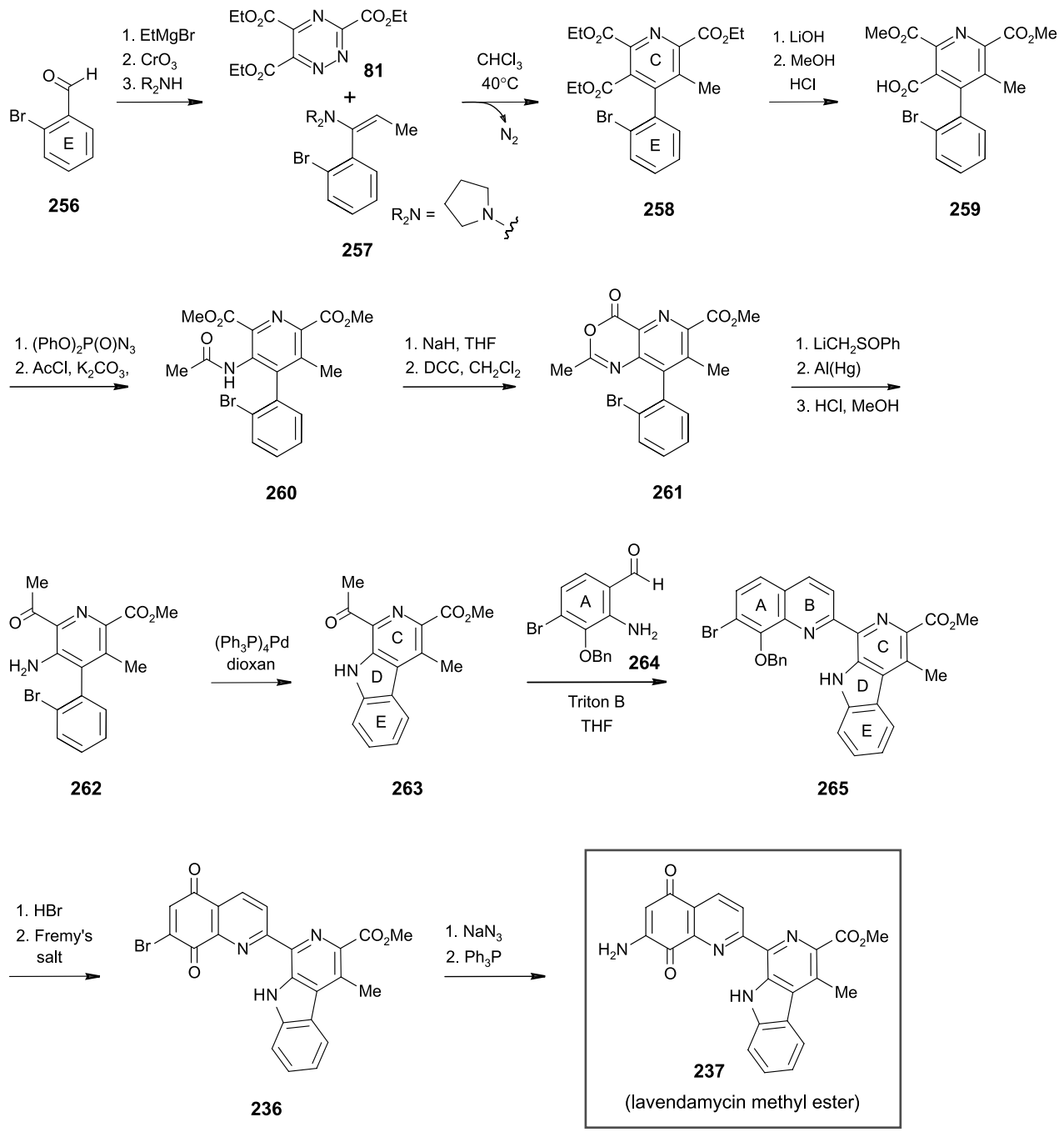
In order to study the structure–activity relationships of lavendamycin (**3**) and its analogs, Godard, Quéguiner and co-workers[104] in 1993 reported a convergent synthesis of a model system. A retrosynthetic analysis suggested that lavendamycin analogs could be obtained in four steps including a cross-coupling involving heterocycles, an indole cyclization by nucleophilic substitution of fluoride, and a final oxidation of the 5,8-dioxyquinoline unit (see Scheme 33). The reaction of the arylstannane **272** with the 2-chloropyridine **273** in the presence of $Pd(PPh_3)_4$ as the catalyst[134] gave the tetracyclic product **274**, the treatment of which with pyridinium chloride afforded **275**. Finally, oxidation with Fremy's salt gave the lavendamycin analog **276** (24% overall yield for these four steps). No biological activity has yet been reported, however, for this analog.

17. Conclusions and outlook

The story of streptonigrin is extremely captivating. It began in 1960 in an industrial environment and ended up in an academic institution world renowned for its structure elucidation, which was reported in 1963 by Rao, Biemann, and Woodward. The structure of streptonigrin is unique and challenging. The last four decades have witnessed considerable progress in the area of its total synthesis, its likewise unprecedented biosynthesis, its structure–activity relationships, its mode of action, and its absolute configuration. The aim of this review has been to describe on the strategies for the synthesis of streptonigrin, streptonigrone, and lavendamycin in a more detailed manner than other reports. The schemes included show a high degree of creativity at the time when applied to the synthesis of these antibiotics. The fascination with streptonigrin and related compounds exhibited especially by organic and medicinal chemists will continue for years to come, with a strong


H2O2 (50%)
HOAc
Me2SO4
KCN
244
245
246
247
NaNO2
HOAc
1. Na2S2O4
2. Ac2O
NBS
DMF
K2Cr2O7
H2SO4
248
249
250
1. Na2S2O4
2. Me2SO4
K2CO3
KOH
251
252
253
232
ClCO2Me
NEt3
POCl3
xylene
reflux
1. HBr
2. MeOH, H2SO4
3. CAN
254
255
1. NaN3
2. Na2S2O4
236
237
(lavendamycin methyl ester)

Scheme 30.



Scheme 31.

emphasis on improved methods and on shorter, more practicable syntheses that will also take into consideration the chirality of the molecule due to the rotationally-hindered biaryl axis.

There are several areas for future investigation, one being to target the metal complexes of streptonigrin (**1**) and related compounds as potential therapeutical agents. These metal complexes of **1** have never been assayed in clinical trials, but might develop into second-generation anticancer compounds based on the streptonigrin skeleton. It would be interesting to evaluate if any of the metabolites of streptonigrin (**1**)[135] are more active and/or less toxic than the parent compound **1**. One of the main goals, however, will be that synthetic organic chemistry will in the near future have to provide analogs of streptonigrin (**1**), streptonigrone (**2**), and lavendamycin (**3**) with hopefully higher antitumor activity and lower toxicity. We hope that this review will stimulate interest in the streptonigrin family of antibiotics in the future.

Acknowledgements

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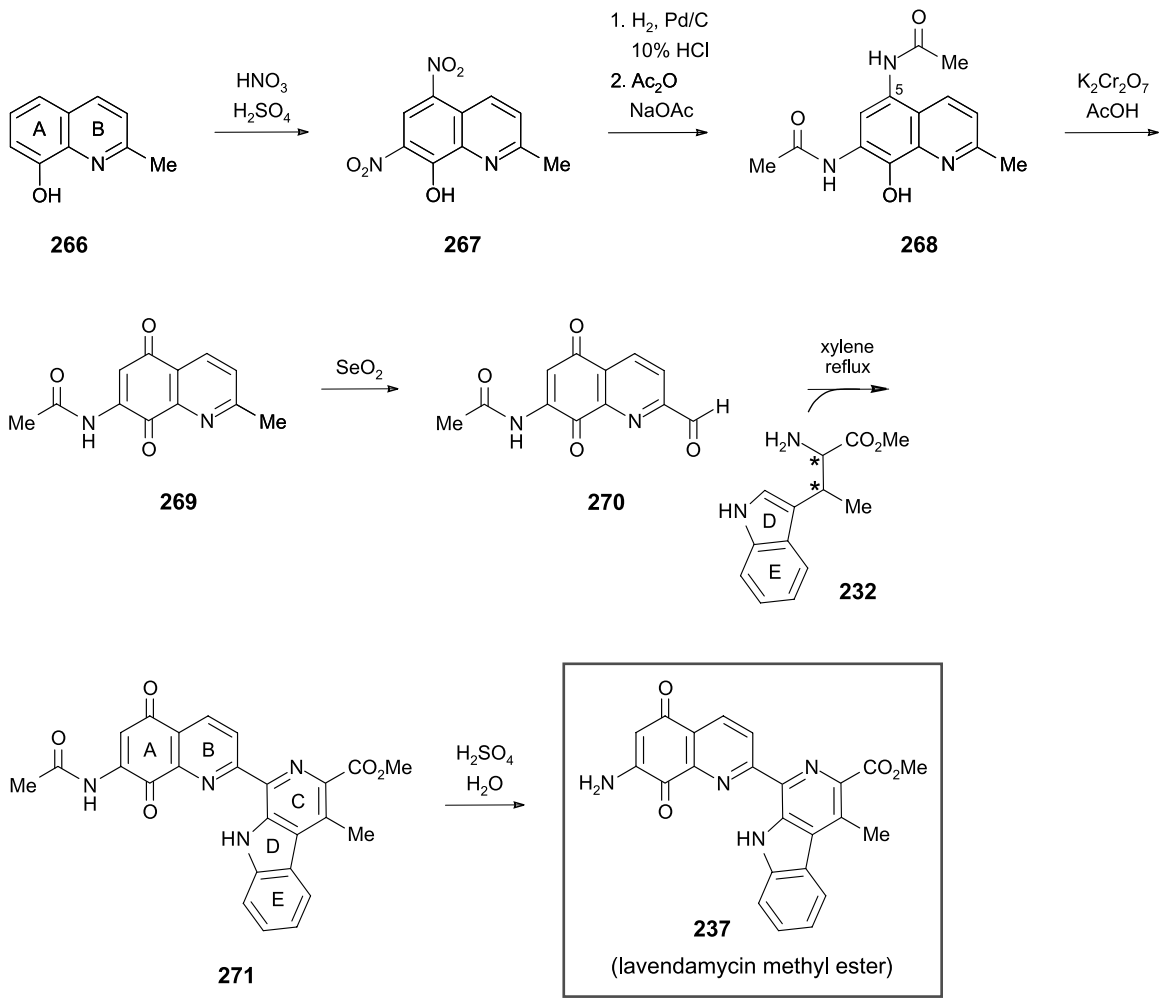
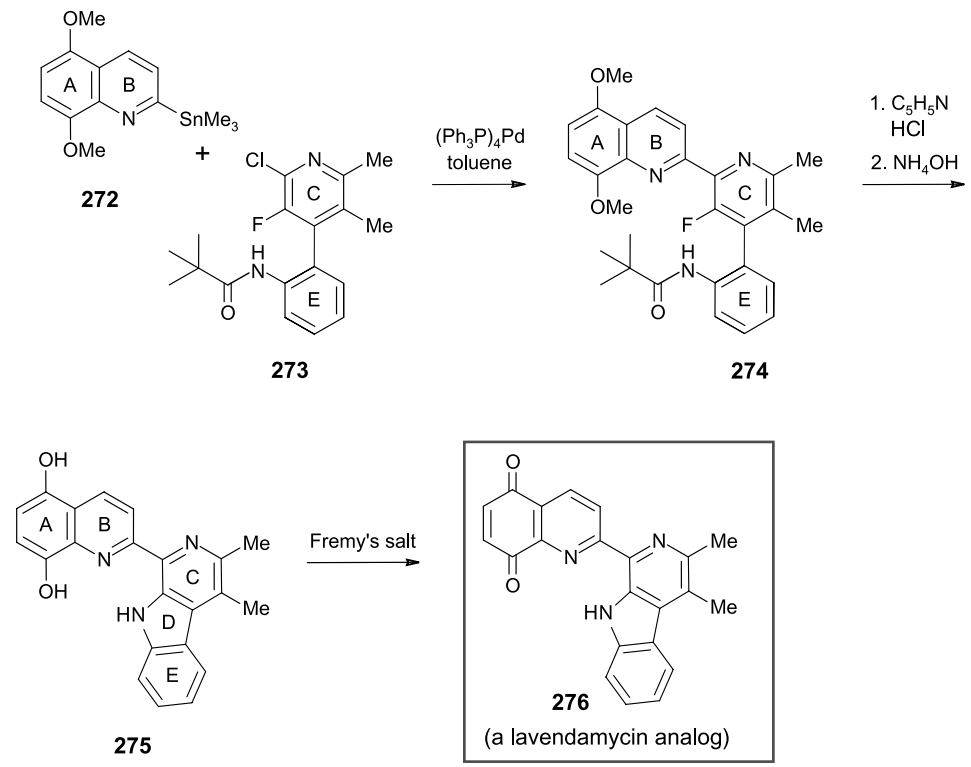


Scheme 32.



Scheme 33.

for providing difficult-to-access literature and for fruitful discussions, P. Leckert and M. Reichert for assistance in preparing the manuscript and the members of the Würzburg group for stimulating comments and helpful suggestions. V.V.K. thanks Professor Kenneth J. Shea, University of California, Irvine (UCI), for his interest and encouragement.

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