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NEW TACTICS IN HETEROCYCLIC SYNTHESIS

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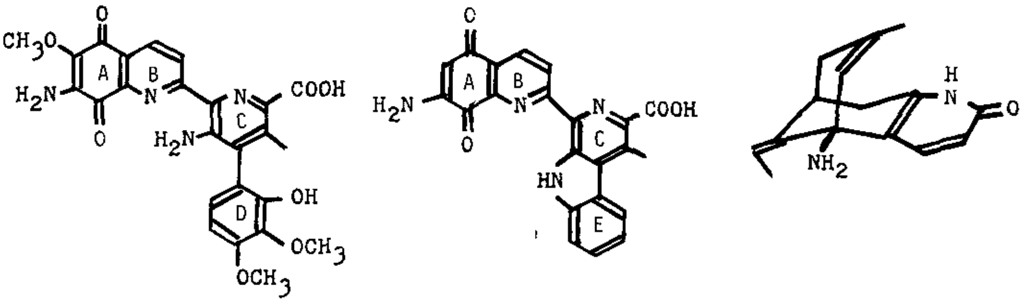
Abstract — Recent approaches from our laboratories directed toward the total syntheses of the antitumor quinones streptonigrin and lavendamycin and the alkaloid selagine are described.

Contents

1. Total Synthesis of Streptonigrin
2. Lavendamycin
3. The Bicycloalkene Core of Selagine

Although the total synthesis of natural products containing the pyridine ring has occupied heterocyclic chemists since the 19th century, the efficient and regiospecific construction of functionalized polycyclic pyridine antibiotics and alkaloids remains to this day a significant challenge to the synthetic chemist. In the last several years our program at Rochester has in part examined new solutions to this problem, as exemplified by our 1981 synthesis of the spirocyclic alkaloid sesbanine[1] and by ongoing efforts toward three interesting synthetic targets. These targets are the tetracyclic antitumor quinone streptonigrin (1),[2] the pentacyclic antibiotic quinone lavendamycin (2),[3] and the bridged tricyclic alkaloid selagine (3).[4]



1 2 3

Fig. 1

1. Total Synthesis of Streptonigrin

The isolation of the antitumor compound streptonigrin (1) from a culture of Streptomyces flocculus in 1959[5] was followed four years later with the elucidation of its structure by Rao, Biemann and Woodward using a combination of spectroscopic and degradative methods.[6] This structure, subsequently confirmed by X-ray crystallography,[7] has been the subject of much biochemical interest because of the substantial activity of streptonigrin against a variety of human cancers[2] and the possibility that DNA degradation by streptonigrin may involve the enzymatic reduction of the quinone to the semiquinone radical which, either directly or through generation of superoxide or hydroxyl radicals, reacts with DNA.[8]

The streptonigrin structure (1) has likewise attracted strong synthetic interest for the past two decades. Important model studies by the groups of T. Kametani, K. V. Rao and T. K. Liao with C. C. Cheng provided valuable information on the construction of the molecular subunits.[9] The first construction of the complete quinone carbon framework was secured in 1978,[10] and the first total synthesis of streptonigrin itself was achieved in 1980 by the Weinreb group.[11] This extremely imaginative synthetic scheme, shown here in highly abbreviated form, was based on the imino-Diels Alder reaction of diene 4 to give an approximately 3:1 regioisomeric mixture of adducts from which the major tetrahydropyridine 5 could be obtained in about 30% yield (42% after one recycle of unreacted diene). However, extensive manipulations of the C-ring were required to ultimately generate the key tetracyclic quinone 6, which Weinreb converted to streptonigrin over a four-step sequence in approximately 30% yield.

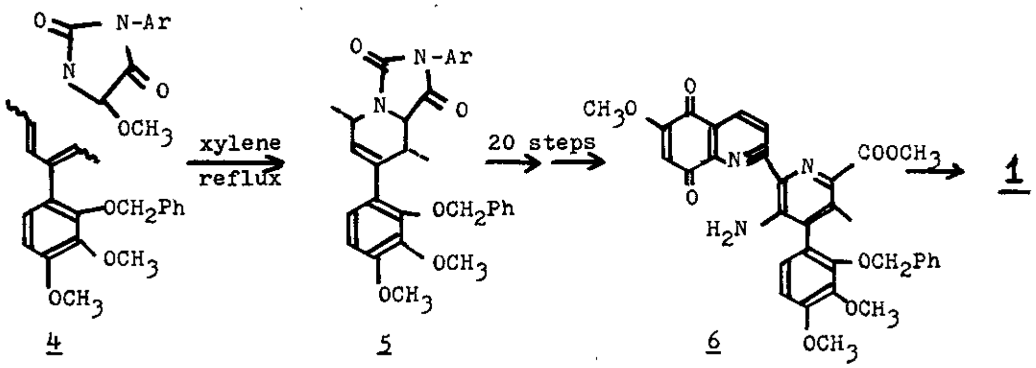


Fig. 2

A few months after publication of the Weinreb synthesis our group completed an independent synthesis of the pentacyclic quinone 6 (and hence a formal synthesis of streptonigrin).[16] The Rochester synthesis involved a different overall strategy, as illustrated in Fig. 3. Construction of the ring C was to involve a Hantsch-type condensation of an enaminoketone (7) with a 1,3-dicarbonyl acceptor, and the quinoline B-ring was to be constructed by a Friedländer condensation.

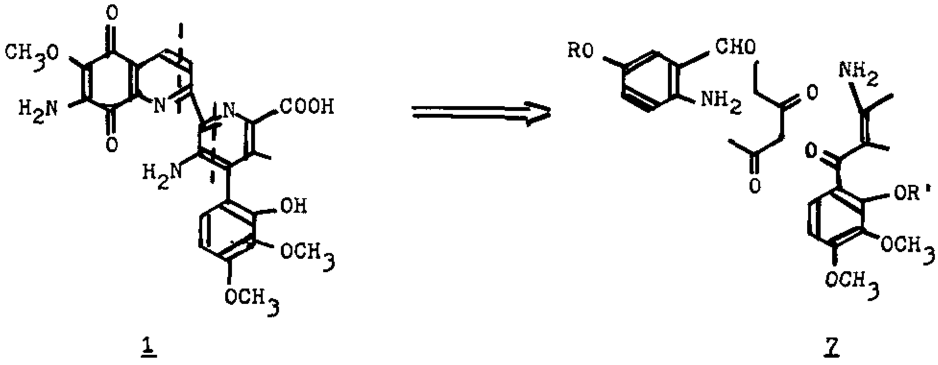
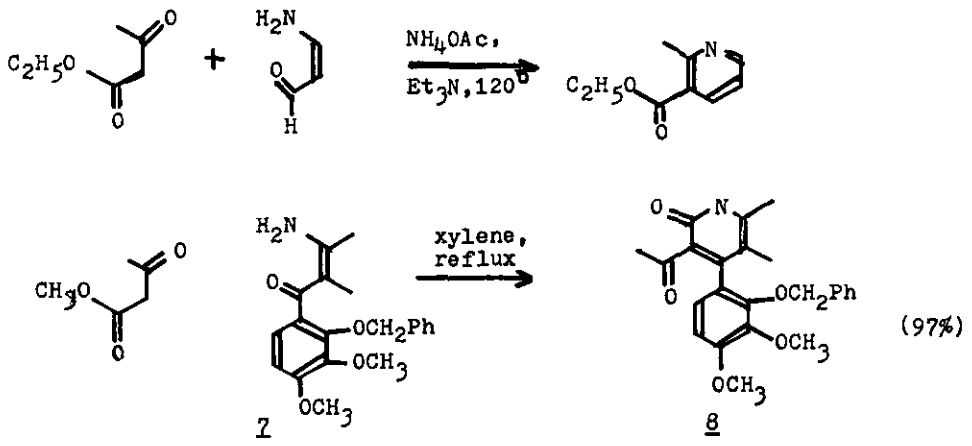


Fig. 3

The availability of enaminoketone 7 and its reactivity toward simple acceptors had already been established by the Kametani and Liao-Cheng groups.[12] However, the choice of the optimum 1,3-dicarbonyl acceptor was not immediately obvious. In 1970, Breitmaier described the condensation of simple β-enamino aldehydes with β-ketoesters under weakly basic conditions to yield pyridine esters.[13] We found, somewhat unexpectedly, that condensation of enaminoketone 7 with ethyl acetoacetate under similar conditions or, more simply, in refluxing xylene containing molecular sieves led to the inverse regiochemistry and gave the 3-acetyl-2-pyridone 8 in very high yield (Fig. 4.).

Fig. 4



Studies with related reactant pairs confirmed this regiochemistry, providing a facile route to various 3-acyl-2-pyridones in generally good yields (Fig. 5).

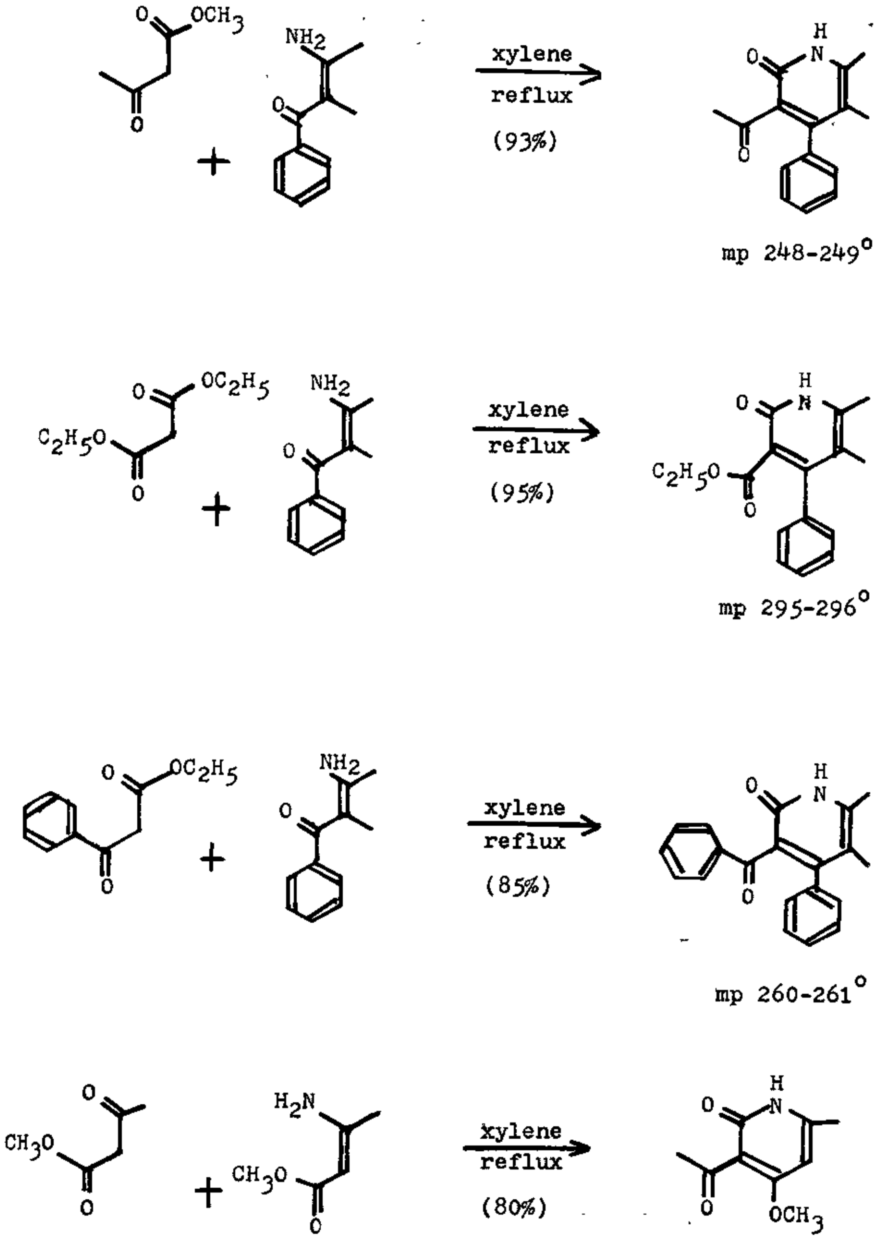


Fig. 5

Exploitation of this regiochemical observation required elaboration of a two-carbon chain at the C-2 carbon of pyridone 8 and suitable differentiation of that new chain from the one at C-3. The ketone was reduced with sodium borohydride and the product treated with $PhPOCl_2$ to give the vinyl-chloropyridine 9, which was converted with cuprous cyanide in dimethylformamide to the vinyl-cyanopyridine 10 in 55% overall yield. Reaction of the nitrile with methylmagnesium bromide gave 83% of the methyl ketone 11.

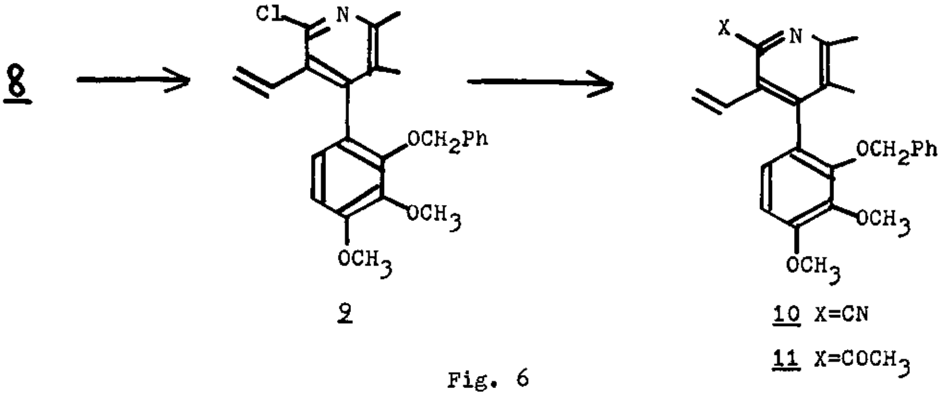
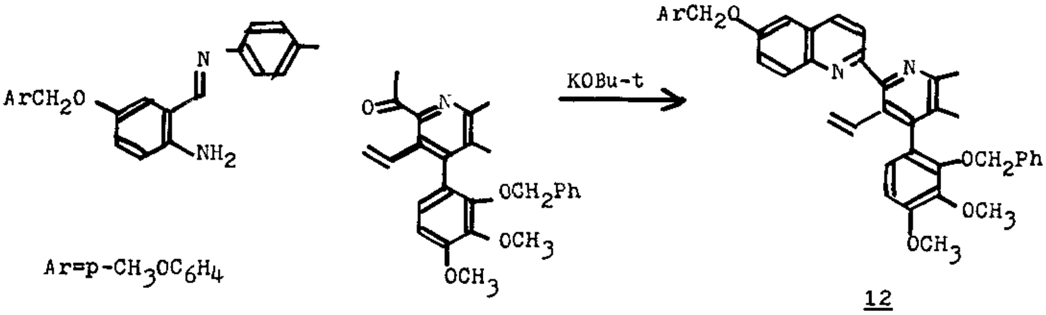
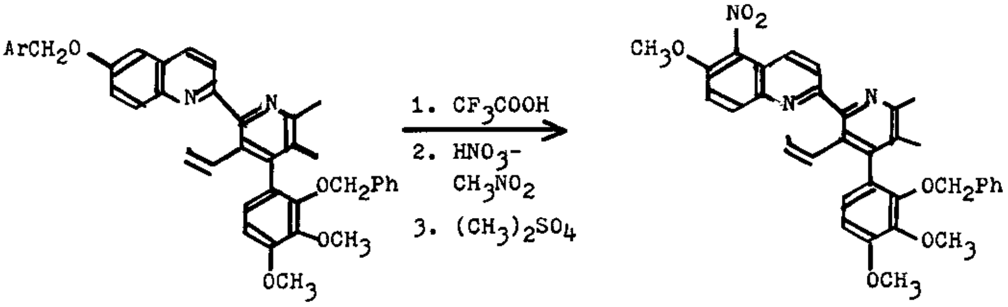


Fig. 6

A prolonged study of conditions to convert the methyl ketone 11 to a quinoline led us to the preferred variant of the Friedländer condensation. This proved to be the use of freshly prepared excess potassium t-butoxide in toluene-t-butanol at reflux for 10 hours. These conditions (Fig. 7) were especially satisfactory using the Borsche modification, in which the aminoaldehyde component was stabilized as the preformed p-toluidine imine.[14] In the event, the synthesis was carried forward using the p-toluidine imine of 2-amino-4-(p-methoxybenzyloxy)benzaldehyde to give an excellent yield of the corresponding quinoline. This quinoline (12) was selectively deprotected at the quinoline oxygen (CF_3COOH, 0°, 1 hr) and the resulting phenol nitrated at C-5 then O-methylated to give the nitromethoxyquinoline in Fig. 8.

Fig. 7





$Ar=p\text{-}CH_3OC_6H_4$ 12

Fig. 8

The oxidative scission of the vinyl group was followed by SeO_2 oxidation of the C-6 methyl on ring C to give the crystalline diacid 13 (Fig. 9).

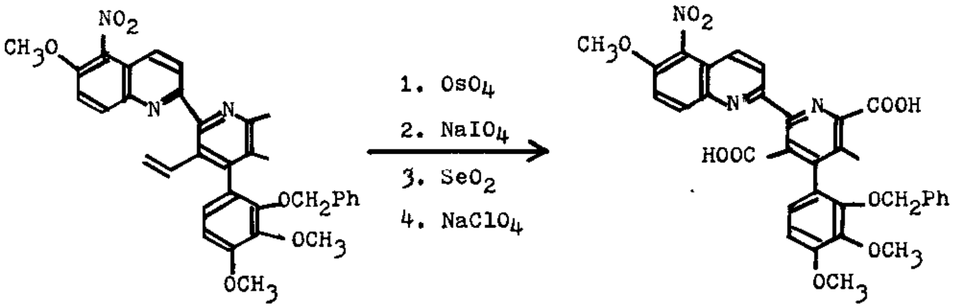


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Fig. 9

Selective Fischer esterification at C-6 then Curtius rearrangement of the other carboxyl using the Yamada modification[15] gave the aminoester 14 (Fig. 10).

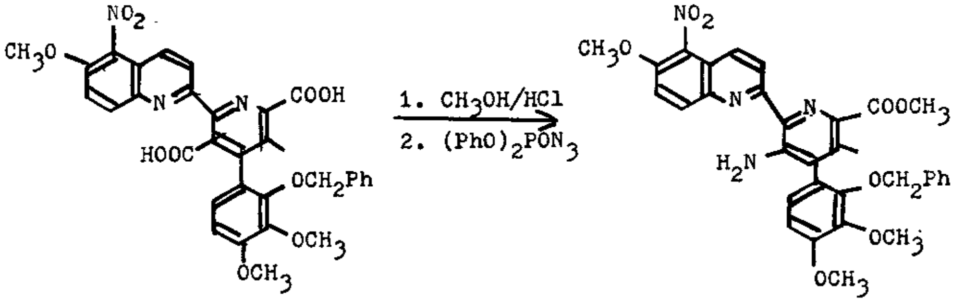

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Fig. 10

14

To complete the formal synthesis, the nitro group of 14 was reduced with sodium dithionite and the resulting methoxyamine ring D was oxidized with Fremy's salt (as previously modeled in our laboratories)[10] to produce the Weinreb methoxyquinone 6.

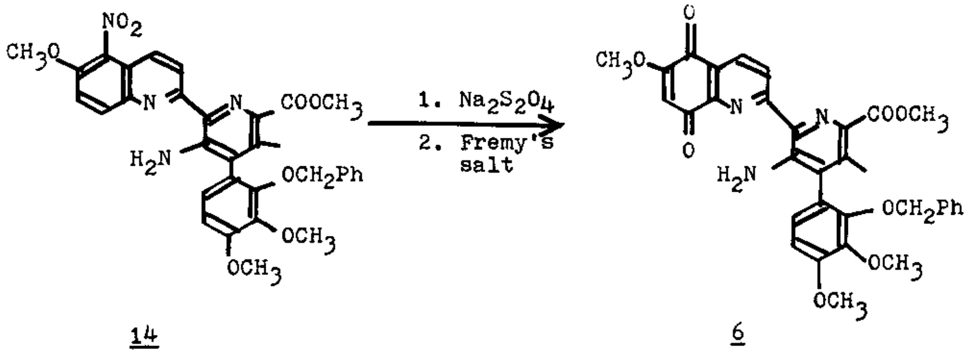


Fig. 11

The Rochester synthesis[16] proceeds from the enamine 7 to methoxyquinone 6 in 18 steps and approximately 1.3% yield, whereas the earlier Weinreb route had required about 25 steps to reach this intermediate in much lower yield. Within the last year, however, Boger and Panek have devised a novel formal synthesis of streptonigrin by means of a series of cycloadditions and cycloreversions (Fig. 12).[17] This short and convergent sequence corresponds to a 12 step synthesis of methoxyquinone 6, but the overall yield is only about 0.7%.

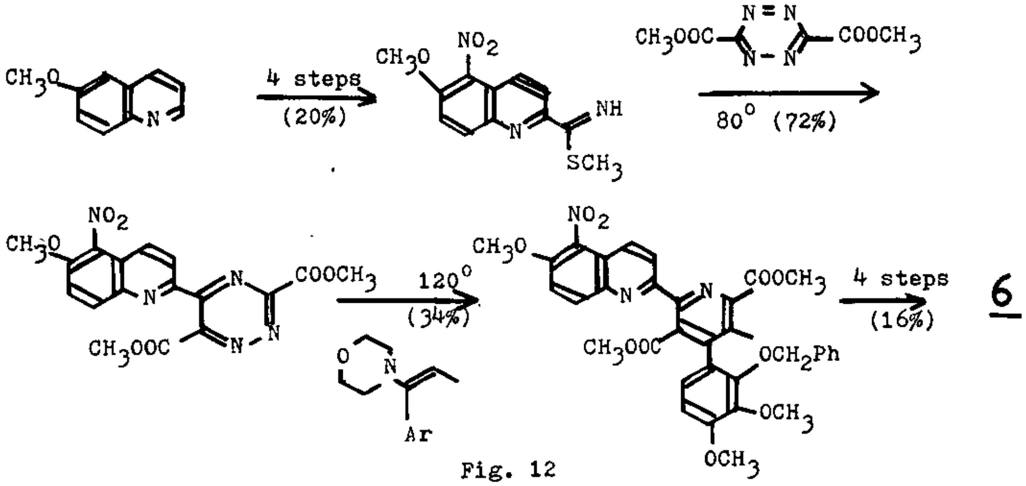


Fig. 12

2. Lavendamycin

The biosynthesis of streptonigrin has also attracted much attention, particularly through the work of S. Gould.[18] Gould has shown that rings C and D probably arise from β-methyltryptophan by way of a β-carboline intermediate, which could undergo oxidative scission of the bond from indole N to the D-ring to give the streptonigrin system.

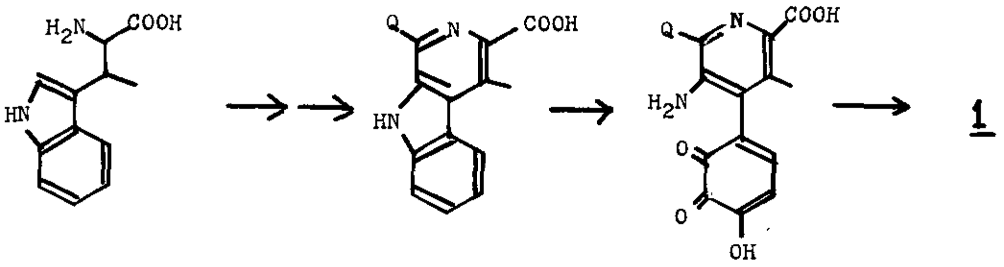


Fig. 13

This postulate received circumstantial support from the very recent isolation and structure determination of an aminoquinone antibiotic from Streptomyces lavendulae named lavendamycin.[19] Lavendamycin was assigned the β-carboline structure depicted in Fig. 14 and may represent a biosynthetic link between β-methyltryptophan and streptonigrin.

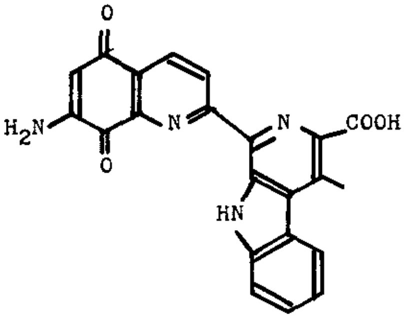


Fig. 14

The synthesis of lavendamycin was initiated in our laboratories less than a year ago. We recognized at once that the 7-amino substituent pattern of the quinonoid A-ring provided a greater challenge than in the case of streptonigrin. Thus it was known from the work of Baxter and Phillips[20] that addition of hydrazoic acid and other nucleophiles to unsubstituted quinoline-5,8-quinone derivatives normally occurs at position 6 rather than at position 7. In order to facilitate introduction of NH_2- at C-7, that position would have to be activated by placement of a halogen substituent (turning it into a vinylogous acyl halide). Our retrosynthetic scheme therefore was established as in Fig. 15.

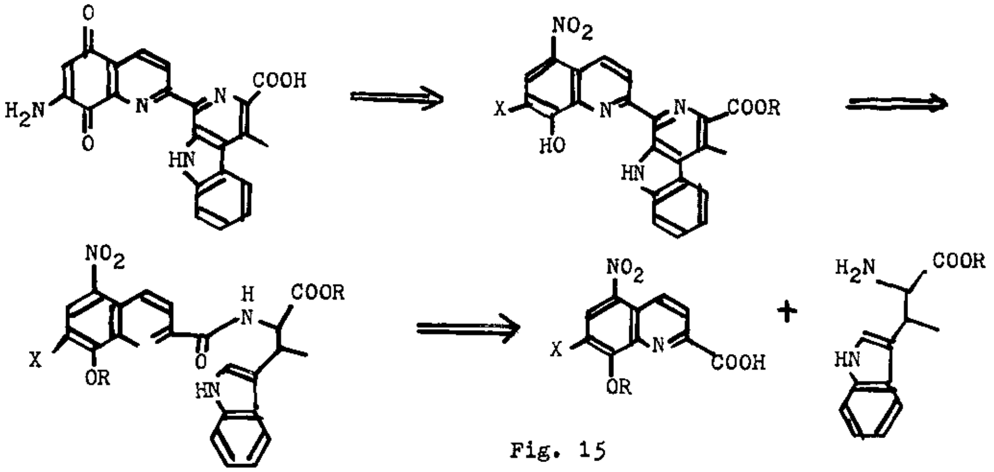


Fig. 15

Synthesis of a suitable 7-halogenated quinoline unit started from 8-methoxyquinaldic acid, which underwent selective nitration at C-5 to the 5-nitro-8-methoxyquinaldic acid, mp 183-184°C. It was not possible to cleanly brominate the latter compound. Therefore, the methyl ether was dealkylated using nucleophilic demethylation (sodium methoxide in dimethylformamide at 90°C) and the resulting phenol was brominated (bromine in acetic acid) to give the required 7-bromo-8-hydroxy-5-nitroquinaldic acid in acceptable yield.

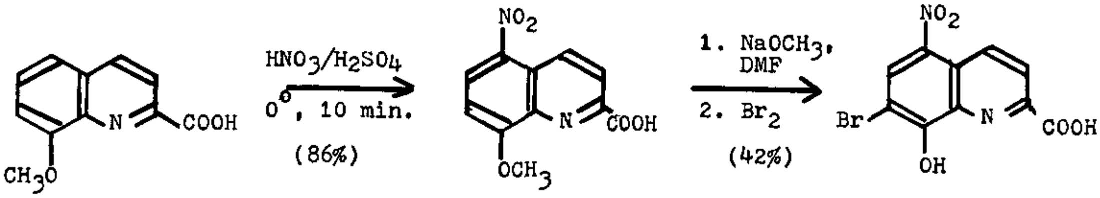
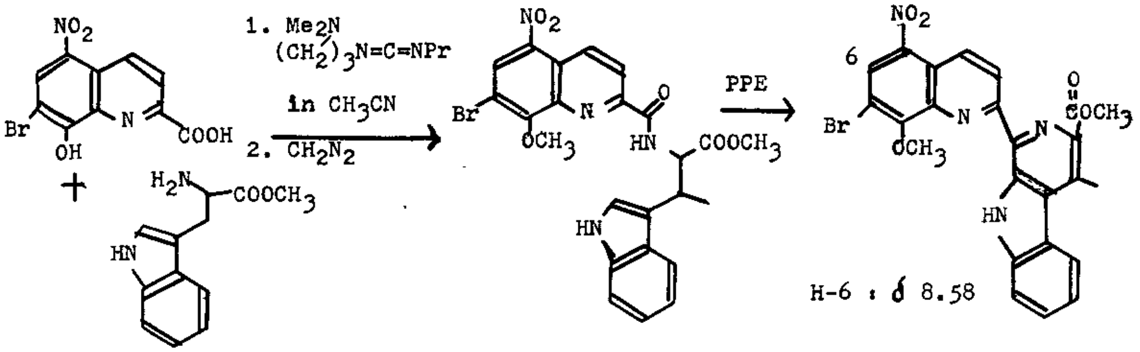


Fig. 16

Condensation of the above quinaldic acid with β-methyltryptophan[21] using the basic carbodiimide shown in Fig. 17, followed by direct methylation of the crude product with diazomethane, gave 75% of the methoxyquinoline amide <u>15</u> (mixture of diastereomers). We now had the pleasure of using a fine method developed by Kanaoka, Sato and Ban[22] in which polyphosphoric ester is employed to achieve a mild Bischler-Napieralski type closure of sensitive tryptophan amides to form the dihydro-β-carboline ring system. In our hands these conditions converted our amide directly to the fully aromatic β-carboline ester 16, mp 230-233°C, in approximately 30% yield.



15

16

Fig. 17

Now came the extremely delicate task of converting the quinoline portion of this substituted β-carboline ester into a bromoquinone system. Dithionite reduction proceeded smoothly to give the 5-amino-7-bromo-8-methoxyquinoline unit. However, numerous attempts to oxidize this to the bromoquinone using conventional conditions (acidic dichromate, ceric ammonium nitrate, argentic oxide, chromic acid, etc.) led to destruction of the molecule. Success was ultimately achieved by using potassium dichromate as oxidant in a two-phase system consisting of methylene chloride and dilute aqueous sulfuric acid in the presence of an equivalent of 18-crown-6. By this technique the sensitive bromoquinone 17 could be prepared, isolated and characterized by mass spectrometry and 400 MHz proton NMR, as noted in Fig. 18.

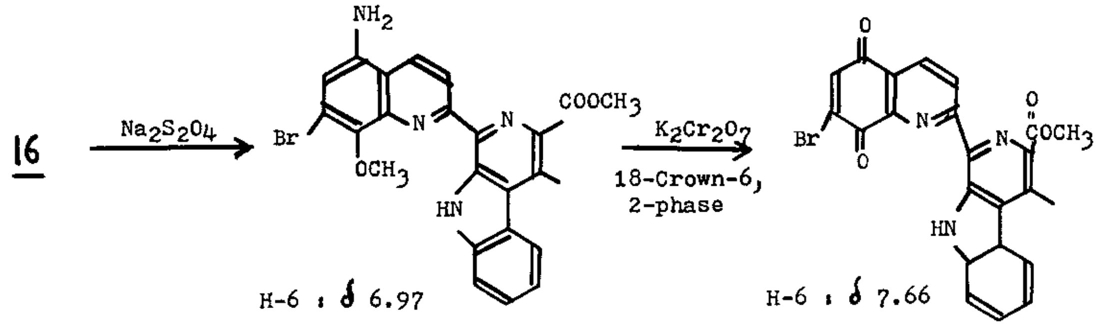


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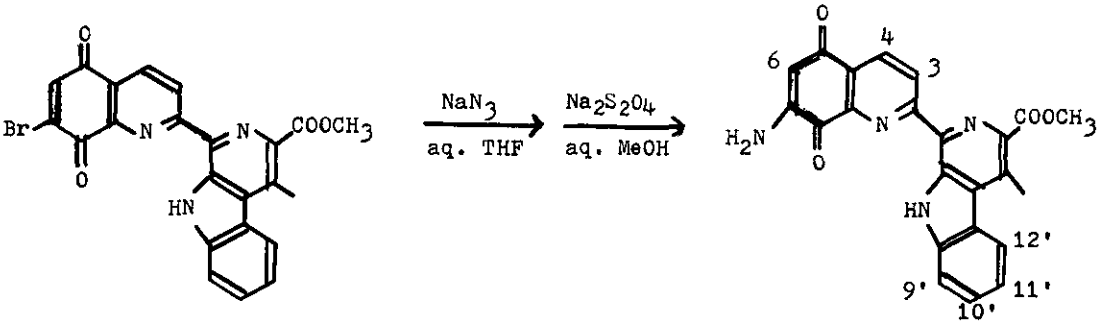
Fig. 18

The highly reactive orange bromoquinone 17 was then reacted with sodium azide in aqueous THF at room temperature for 3 h, followed by reduction of the azido group with excess sodium dithionite in aqueous THF-methanol at reflux. From this reaction was obtained by silica gel chromatography a bright orange substance having all of the spectroscopic and chromatographic properties of authentic lavendamycin methyl ester.[23] The ^1H-NMR spectra at 400 MHz of methyl esters from synthetic and natural sources are compared in the accompanying table. The two samples cochromatographed perfectly in four different systems.



H-6 : δ 7.66

H-6 : δ 6.14

lavendamycin methyl ester

Fig. 19

Although additional synthetic ester must be prepared to confirm its identity using ^{13}C-NMR spectrometry, the data so far obtained strongly suggest that the synthetic and naturally-derived esters are structurally identical.

400 MHz NMR ($CDCl_3$)

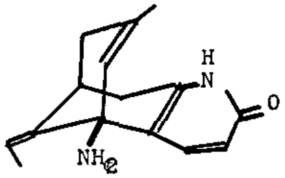
lavendamycin methyl ester

Ref: $CHCl_3$=7.259

proton	"synthetic" (ppm)		"natural" (ppm)	
H-6	6.14	s	6.14	s
H-4	9.12	d	9.12	d
H-3	8.57	d	8.57	d
H-9'	7.82	d	7.82	d
H-10'	7.67	dd	7.67	dd
H-11'	7.41	dd	7.41	dd
H-12'	8.39	d	8.39	d
$-OCH_3$	4.09	s	4.09	s
$-CH_3$	3.23	s	3.23	s
$-NH_2$	5.33	br s	5.33	br s
-NH	12.02	br s	12.02	br s

3. The Bicycloalkene Core of Selagine.

Unlike the two previous syntheses, the synthesis of selagine, a pyridone alkaloid, has as its central challenge the construction of the bicyclononadiene framework to which the pyridone is fused. Previous endeavors toward this end from our laboratories[24] and from those of Professor D. Gravel[25] have not succeeded in solving this problem for the fully elaborated series, leaving the synthesis of selagine an open challenge.



Selagine (3)

Our retrosynthetic analysis of selagine supposes that the immediate precursor could be a pyridone ketal ester (19) which in turn could arise by addition of a C-3 "acrylate" chain to the appropriate enolizable carbon of a bicyclic ketal ketone (18).

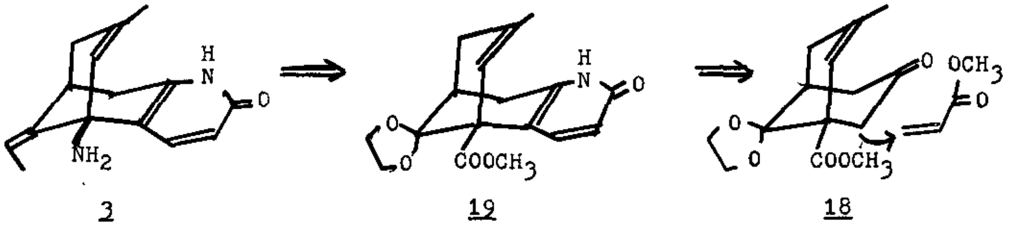
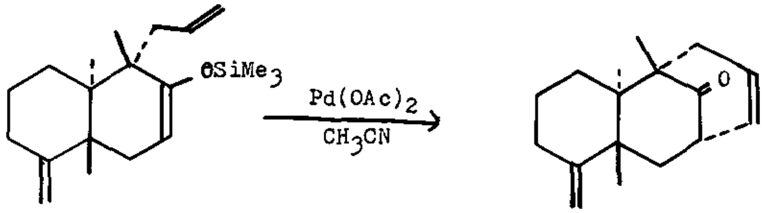


Fig. 20

In order to efficiently prepare a bicyclic ketone such as 18, we propose to use a novel cycloalkenylation sequence recently developed in our laboratories. Thus we have found, for example, that the allylic enolsilane 20 cyclizes smoothly under the influence of palladium (II) acetate in acetonitrile to yield the tricyclic ketone 21, and that this reaction is fairly general.[26]



20 21

Fig. 21

Based on earlier observations by Y. Ito, T. Saegusa and their associates, as well as our more recent mechanistic studies, we can distinguish between two types of reactions in such systems.[27] For trimethylsilyl enol ethers, or for the lithium enolates themselves, simple dehydrosilylation may take place, possibly through an oxa-π-allyl Pd species as proposed by the Kyoto group (path A, Fig. 22), to yield enones. However, for t-butyldimethylsilyl enol ethers, methyl enol ethers, and sometimes even for trimethylsilyl enol ethers, a cycloalkenylation pathway (path B, Fig. 22) supervenes. In such cycloalkenylations, the key step is attack by the nucleophilic enol double bond on the Pd-complexed side chain alkene.

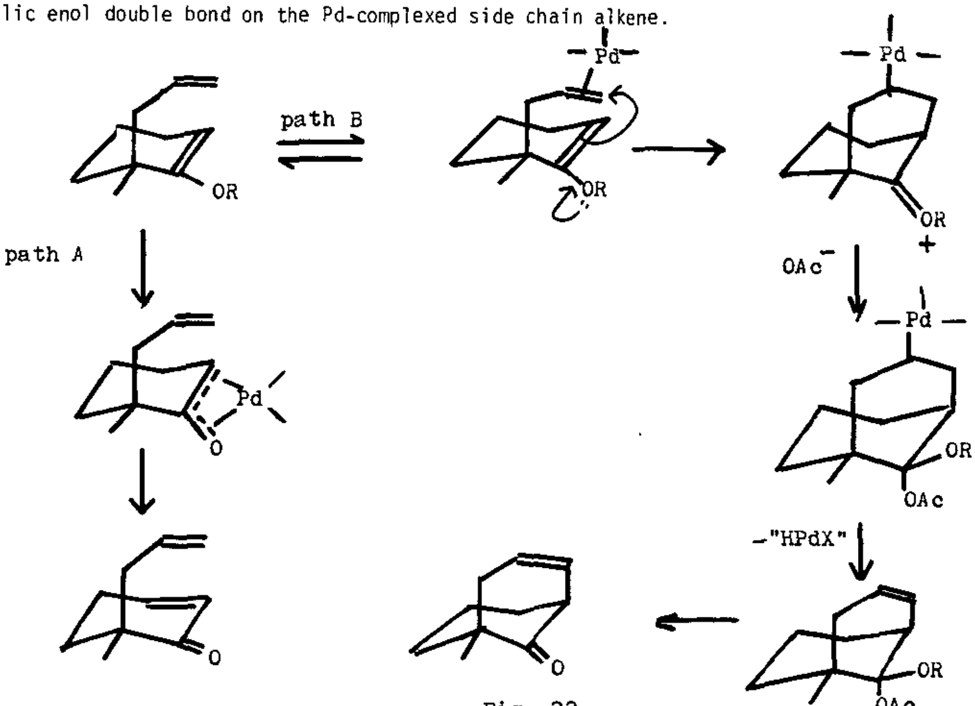
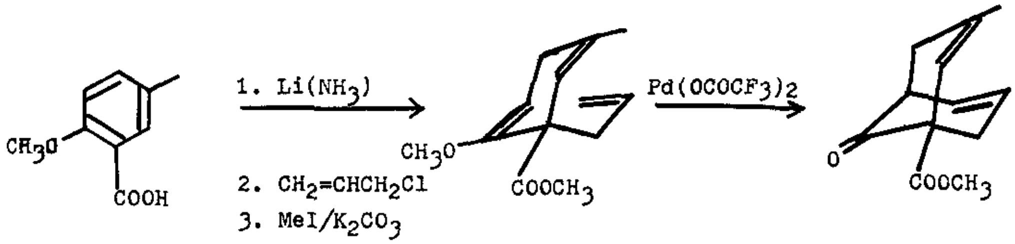


Fig. 22

We have now used this concept to efficiently construct our requisite bicyclononene system. Thus, the Birch reduction of 2-methoxy-5-methylbenzoic acid, followed by alkylation of the *dianion*, yields after methylation the cyclohexadiene ester 22. Reaction of this ester with palladium(II) trifluoroacetate in acetonitrile gives ca 60% of a major product identified as the bicyclic ketone 23. Reaction with ethylene glycol gives the crystalline ketal 24, which on hydroboration-oxidation produces the required bicyclononene ketone 18.

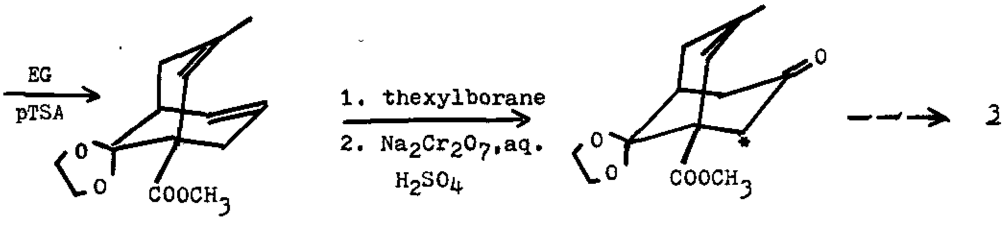


22

23

Fig. 23

Preliminary studies by R. Battista in our laboratories indicate that attachment of a $CH_2CH_2COOCH_3$ unit at the starred carbon of 18 will be feasible, providing a major advance in the quest for a total synthesis of selagine.



24

18

Fig. 24

The chemistry described in this review contains some novel and generally useful tactical features. In our streptonigrin synthesis, a vinyl group was the masked precursor of an amino group in a highly functionalized system. For lavendamycin, a haloquinone was used to direct nucleophilic attack at the halogenated carbon. Finally, the formation of a functionalized bicyclononadiene system could be achieved by a simple intramolecular palladium(II)-mediated cycloalkenylation of a Birch-alkylation product.

ACKNOWLEDGMENTS

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