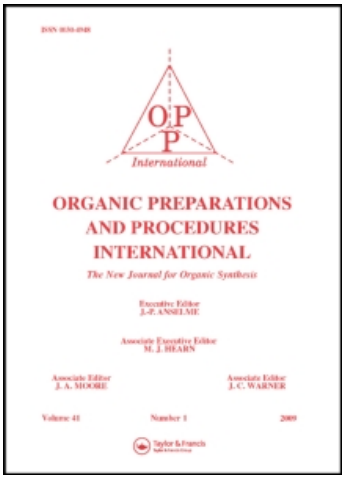

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SYNTHESIS OF β-CARBOLINES. A REVIEW

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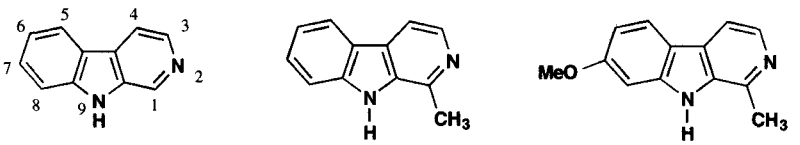
INTRODUCTION

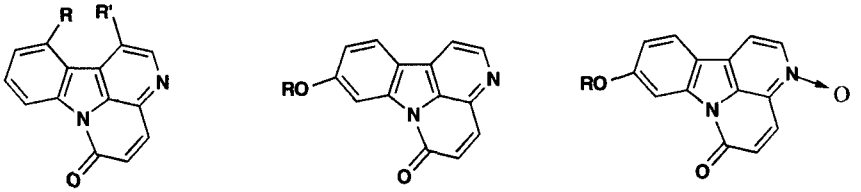
β-Carbolines are widely distributed in nature, the basic ring system **1** (*Fig.* 1) being found in several families of natural products.[1] For example, some of the simplest β-carboline natural products are harman **2** and the closely related harmine **3** which have been isolated from a number of sources.[2]



1 **2** **3**

Fig. 1

The canthin-6-ones represent a series of tetracyclic β-carboline alkaloids, which likewise have been isolated from various plant sources.[3] A few representative members of this class of compounds are shown in *Fig.* 2. Many canthin-6-ones possess significant biological activity (see below).



4 R = R' = H
5 R = R' = OMe
6 R = H, R' = OMe
7 R = H, R' = OH
8 R = OH, R' = H

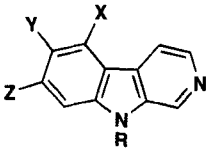
9 R = H
10 R = CH_3

11 R = H
12 R = CH_3

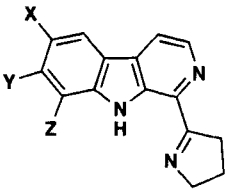
Fig. 2

More recently discovered β-carboline natural products are the eudistomins and the closely related eudistomidins, a large assortment of which have been isolated from the Caribbean tunicate

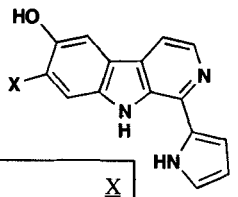
Eudistoma olivaceum[4-6] and the Okinawan tunicate *Eudistoma glaucus*,[7-9] as well as other sources[10] (*Fig.* 3). Even more recently reported are the oxopropalines, which have been isolated from *Streptomyces* species[11], and are illustrated in *Fig.* 4. There exist several naturally occurring β-carbolines



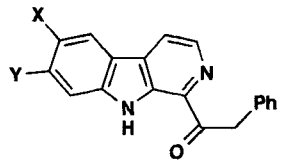
		R	X	Y	Z
Eudistomin	D	H	Br	OH	H
	J	H	H	OH	Br
	N	H	H	Br	H
	O	H	H	H	Br
Eudistomidin	D	Me	Br	OH	H



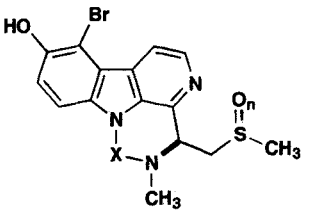
		X	Y	Z
Eudistomin	G	H	Br	H
	H	Br	H	H
	I	H	H	H
	P	OH	Br	H
	Q	OH	H	H
Eudistomidin	A	Br	H	OH



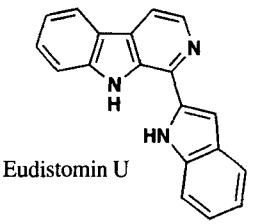
		X
Eudistomin	A	Br
	M	H



		X	Y
Eudistomin	R	H	Br
	S	Br	H
	T	H	H



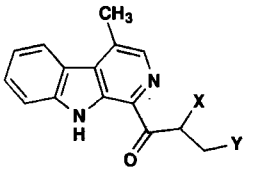
		X	n
Eudistomidin	C	H, H	0
	E	CH_2	1
	F	CH_2	0



Eudistomin U

Fig. 3

which possess furyl groups at C-1 of the β-carboline ring system, a few examples being shown in *Fig.* 5. These compounds have been isolated from a number of sources, including ginseng[12] and other medicinal herbs,[13] as well as soy sauce.[14,15] Several β-carbolinium salts have been isolated from marine sponges of the *Fascaplysinopsis* genus,[16-18] as well as the neutral compound **19** (*Fig.* 6). Counterions for the cationic β-carbolines could be as simple as chloride, as was observed in fascaplysin **17**



		X	Y
Oxopropaline	A	O(Sugar)	OH
	B	OH	O (Sugar)
	D	OH	OH
	E	H	O (Sugar)
	G	H	OH

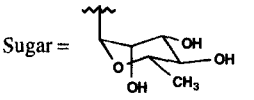
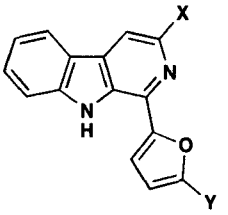
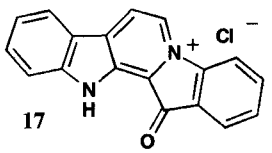


Fig. 4

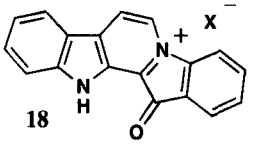


13 X = Y = H
14 X = H, Y = CH_2OH
15 X = CO_2H, Y = H
16 X = CO_2H, Y = CH_2OH

Fig. 5



17



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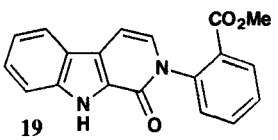

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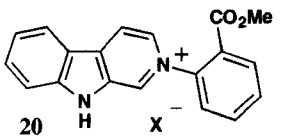

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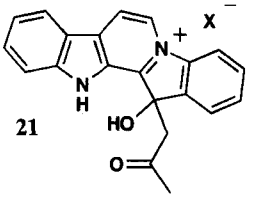

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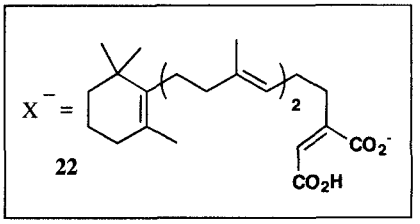
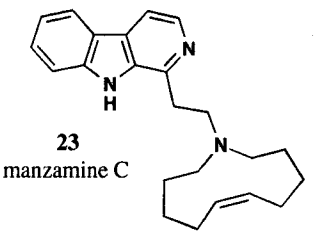


22

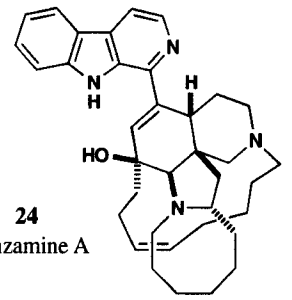
Fig. 6

or as complex as the dehydroluffariellolide diacid monoanion **22** found in fascaplysin A **18**. This same anion constituted the anionic portion of reticulatine B **20** and homofascaplysin A **21**.

Two other classes of marine natural products are the manzamines,[19] and the closely related keramamines.[20,21] These compounds typically possess a complex substituent at C-1, with the remainder of the β-carboline ring being either unsubstituted or having only a hydroxyl group at C-8. The simplest manzamine is manzamine C **23**, while manzamine A **24** is typical of the more complex manzamines (*Fig.* 7). A suggestion regarding the biosynthesis of these compounds has recently been made by Baldwin.[22]



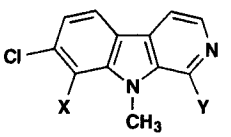
23
manzamine C



24
manzamine A

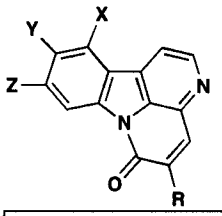
Fig. 7

New β-carboline natural products and new sources of those previously identified are constantly being reported. *Fig.* 8 illustrates a few such compounds which have been reported within the last year.



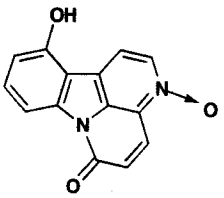
		X	Y
Bauerine	A	H	H
	B	Cl	H
	C	Cl	OH

(Reference 23)



R	X	Y	Z
H	H	OH	OMe
H	OH	OMe	H
OMe	H	H	OMe
H	H	OMe	OMe

(Reference 24)



(Reference 25)

Fig. 8

There exists much interest in the synthesis and reactivity of β-carbolines, owing to the wide range of biological activity possessed by members of this class of compounds. For example, eudistomidin C (*Fig.* 3) has shown anti-leukemic activity,[8] as has 1-methoxycanthin-6-one **5** (*Fig.* 2).[26] Other canthin-6-ones, such as 9-hydroxycanthin-6-one **9** and its methyl ether **10**, as well as their corresponding N-oxides **11** and **12**, also show activity against several human cancer cell types.[27] Additionally, lavendamycin **25** (*Fig.* 9) has shown both antitumor and antibiotic properties.[28]

Even some relatively simple β-carbolines possess significant biological activity. For example, 7-methoxy-β-carboline-1-propionic acid **26** (*Fig.* 9) possesses antimalarial activity,[27] and 8-hydroxy-1-vinyl-β-carboline **27** has demonstrated antileukemic activity.[29] Not all of the pharmacological effects of β-carbolines are beneficial, however. Studies have found several of the furyl-substituted compounds shown in *Fig.* 5 to be mutagenic toward *Salmonella typhimurium* TA 100.[30,31]

Interest in β-carbolines was further spurred by the finding that many β-carbolines have a high affinity for benzodiazepine receptors in the brain.[32] Many β-carbolines bind as effectively to

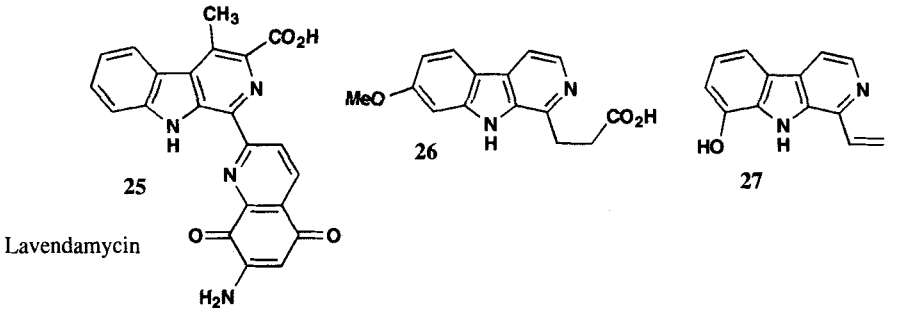


Fig. 9

these receptors as some clinically active benzodiazepines, and thus can block the activity of such compounds.[33] The pharmacological properties of β-carbolines span everything from full agonists such as ZK-93423 **28**[34] to inverse agonists such as β-carboline-3-carboxylic acid ethyl ester **29**[35] (*Fig.* 10). As might be expected, a wide variety of synthetic β-carbolines has been prepared, and structure/activity relationships for these compounds studied.[36]

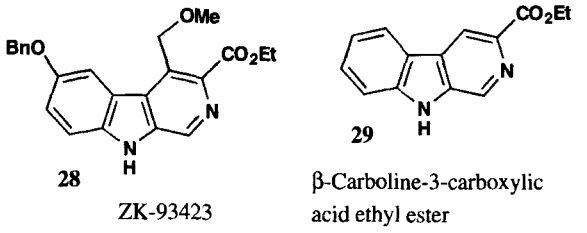


Fig. 10

The diverse nature of β-carboline chemistry requires the scope of this review to be somewhat limited. Studies relating to the biosynthesis of β-carbolines, as well as the biological activity of these compounds, will for the most part not be discussed. Instead, the review will, as the title suggests, focus mainly on the synthesis of these compounds. Additionally, only the chemistry of fully aromatic β-carbolines will be taken up. While tetrahydro-β-carbolines are interesting and biologically significant compounds in their own right (indeed, the tetrahydro-β-carboline ring system can be found in myriad families of indole alkaloids), they will not be discussed, except with regard to their intermediacy in the formation of fully aromatic β-carbolines. Owing to the breadth of the literature involving β-carbolines, it is impractical for this review to be comprehensive in its coverage. Instead, an attempt has been made to present representative examples of a variety of methods employed in the preparation and functionalization of β-carbolines as well as their limitations. Comments regarding methods which have not been included but perhaps ought to have been are welcomed.

Finally, although the last comprehensive review of β-carboline chemistry was published in 1964,[37] followed by a more limited review in 1985,[38] results reported in the past 10 years (up to the end of 1994) will be emphasized. A review concerning the structures and synthesis of marine indole

natural products, which included a discussion of the isolation and synthesis of naturally occurring β-carbolines, has been published recently.[39]

I. SYNTHESIS OF β-CARBOLINES

A. Cyclization Methods

1. Annulation of the Pyridine Ring

a. Pictet-Spengler

By far the most commonly employed method for the preparation of β-carbolines is the Pictet-Spengler reaction.[40] The reaction, which produces tetrahydro-β-carbolines from tryptamine derivatives and aldehydes, is generally thought to proceed through spiroindolenium species **32** shown in *Fig.* 11.[41] The stereochemistry of this reaction has been investigated[41b,42] and can be controlled by

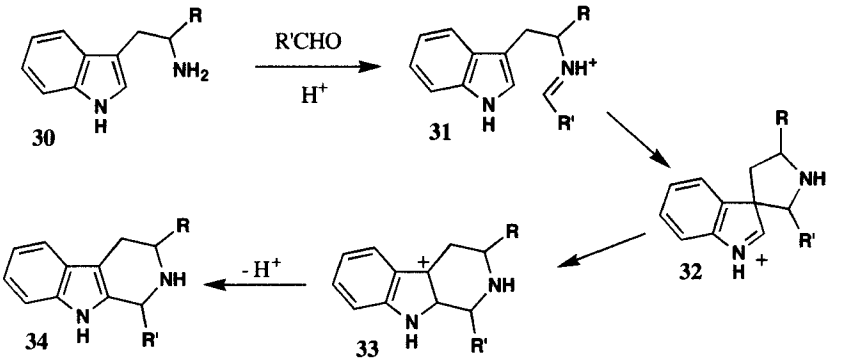


Fig. 11

appropriate choice of reaction conditions and substrates. For example, the *trans* isomer can be formed stereospecifically by using N_b-benzyl tryptophan derivatives,[43] and the *cis* isomer predominates when the reaction is run at low temperature.[44] Methods for converting a *cis* tetrahydro-β-carboline into the corresponding *trans* isomer have also been reported,[45] as have asymmetric versions of the Pictet-Spengler reaction.[46]

Though other reaction conditions have been explored (and will be discussed subsequently), the reaction is typically catalyzed by Brønsted acids. For example, in Rinehart's synthesis of eudistomins H, I and Q,[6] the initial starting materials were prepared by condensation of tryptamine derivatives **35** with glyoxylic acid[47,48] at low pH, which produced the corresponding tetrahydro-β-carbolines **36** (*Fig.* 12). These tetrahydro-β-carbolines were then esterified and converted to the corresponding amide by treatment with methanolic HCl, followed by ammonium hydroxide to yield **38**.

As the Pictet-Spengler reaction initially yields tetrahydro-β-carbolines, a method of oxidizing these substrates to the fully aromatic β-carbolines is required. One of the most commonly employed reagents for this purpose is palladium on carbon, which indeed is what Rinehart used to effect this particular dehydrogenation. Typically, the tetrahydro-β-carboline substrate is heated at

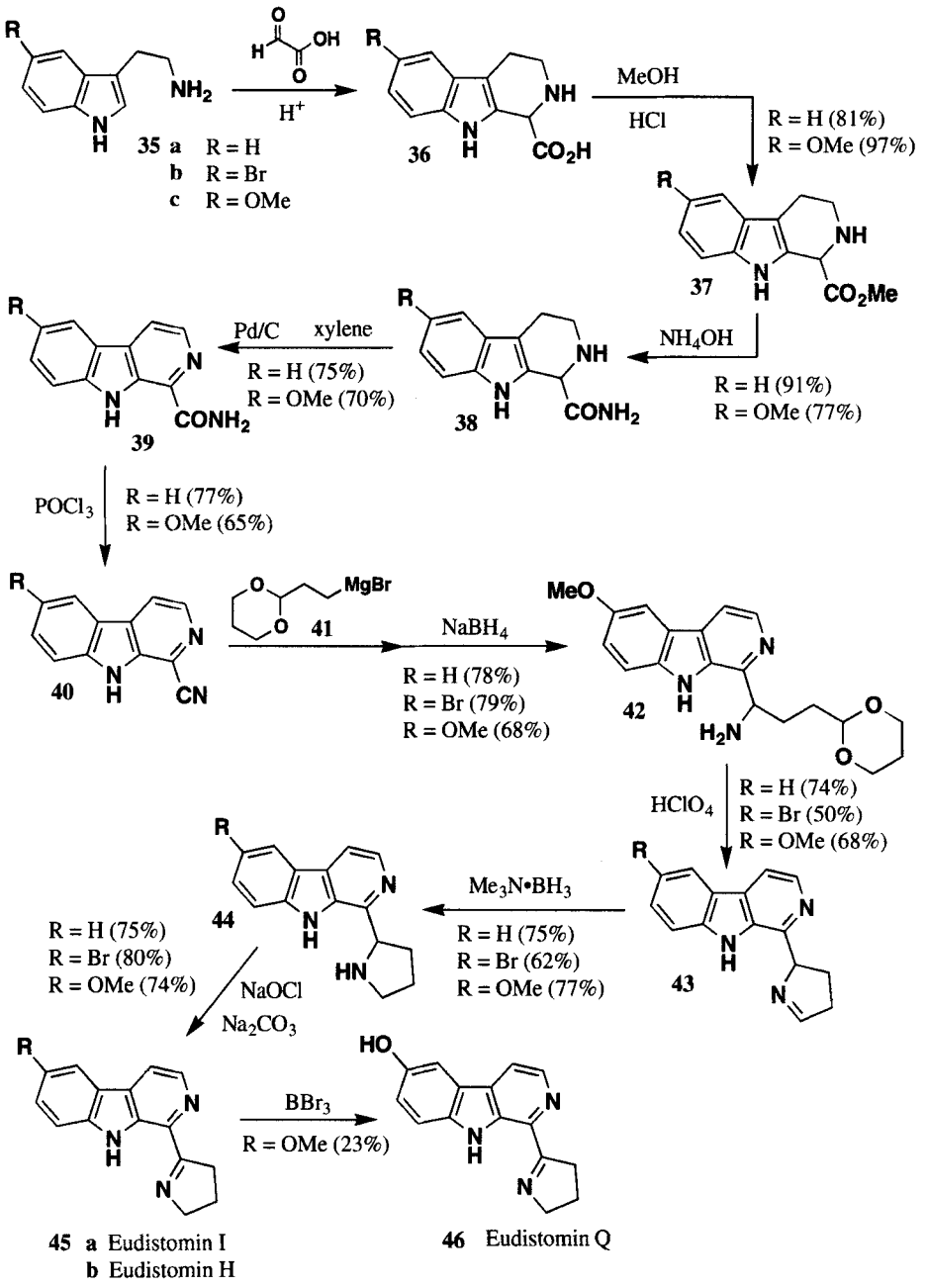


Fig. 12

reflux in a high boiling solvent for several hours in the presence of palladium on carbon, though platinum on carbon in the presence of air has also been used.[49]

Conversion of β-carboline amide **39** to nitrile **40** was accomplished using $POCl_3$ (nitrile **40b**, however, was prepared in 94% yield by bromination of **40a**). Reaction of **40** with Grignard

reagent **41** followed by reduction of the resulting imine provided **42**, which could be deprotected and cyclized under acidic conditions to yield **43**. Unfortunately, **43** could not be isomerized to the desired eudistomins, so the reduction/oxidation sequence depicted in *Fig.* 12 was followed.

Rinehart's synthesis of eudistomin M proceeded along similar lines, starting from β-carboline nitrile **40c** (*Fig.* 13). In this case, the imine derived from reaction of **40c** with Grignard reagent **41** was hydrolyzed to produce ketone **47**. Deprotection/cyclization to produce the pyrrole substituent and subsequent demethylation of the aryl ether proceeded as indicated.

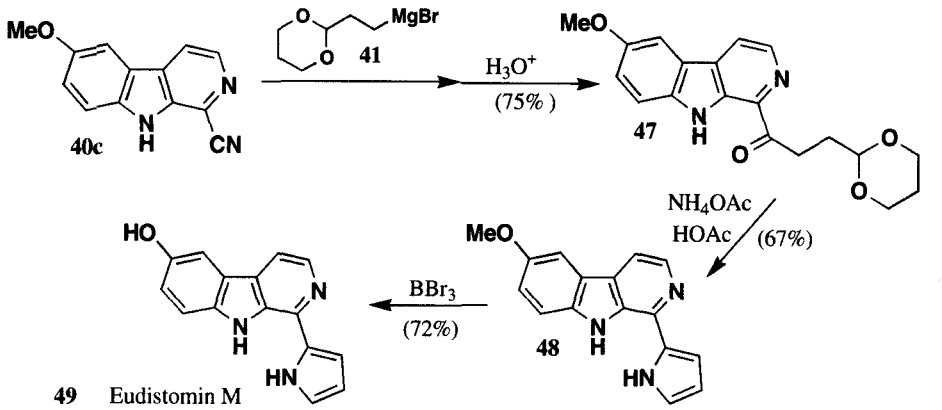


Fig. 13

An acid-catalyzed Pictet-Spengler reaction was also utilized in Still's formal synthesis of eudistomins H and I (*Fig.* 14).[50] Tryptamine **35a** was condensed with prolinal **51** to give tetrahydro-β-carboline **52** as a mixture of diastereomers. As in Rinehart's synthesis, palladium on carbon was used to aromatize **52** and produce β-carboline **53**. Deprotection of **53** to give **54** completed Still's synthesis, as **54** had previously been used to prepare both eudistomin I **45a**, and eudistomin H **45b**.[6,51] This synthesis was described as biomimetic, for indeed, biosynthetic studies have shown that eudistomins H[52] and I[53] are derived from tryptophan and proline.

A "biomimetic" Pictet-Spengler reaction was also used to prepare flazin **16** and perlolyrine **14** (*Fig.* 15).[49] 5-(Acetoxymethyl)furfural **55** was condensed with either tryptamine **35a** or L-tryptophan methyl ester **56** to give tetrahydro-β-carbolines **57** and **58**, respectively, as a mixture of isomers. Condensation of **55** with L-tryptophan itself was not successful. The tetrahydro-β-carbolines **57** and **58** were dehydrogenated using platinum on carbon in the presence of air to produce the corresponding β-carbolines **59** and **60**, which were then hydrolyzed to produce the desired natural products.

Another oxidant for converting tetrahydro-β-carbolines to the fully aromatic system is elemental sulfur, which is commonly employed when use of palladium or platinum is not feasible. For example, in Still's synthesis of eudistomins S and T,[54] (*Fig.* 16) aromatic esters **61** were produced by heating **37** with sulfur in xylenes at reflux, as use of palladium was not possible with substrate **37b**, owing to the presence of the bromine atom. Use of a modified Grignard reaction provided a short synthesis of eudistomin S **62b** and eudistomin T **62a**.

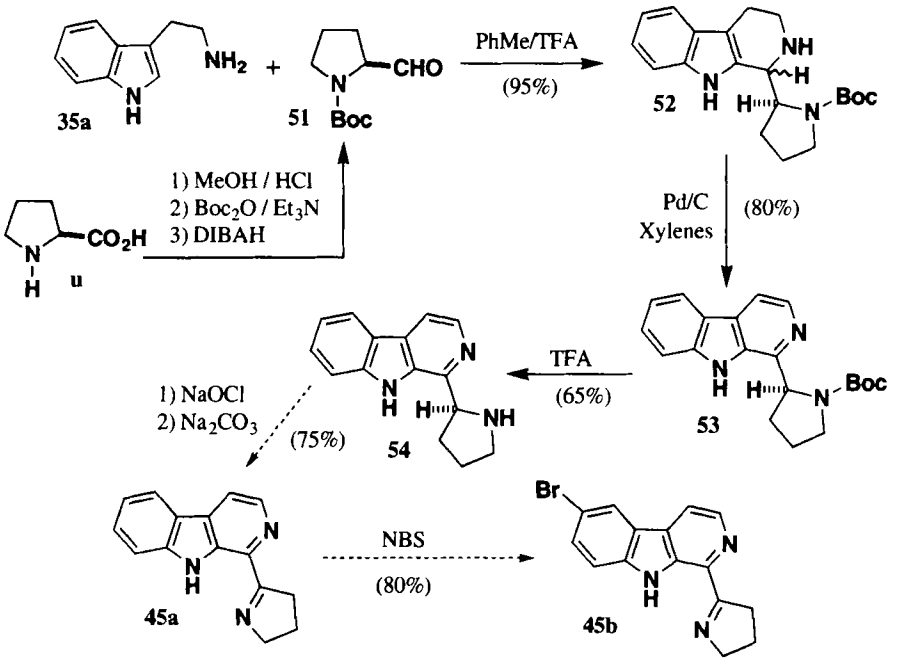


Fig. 14

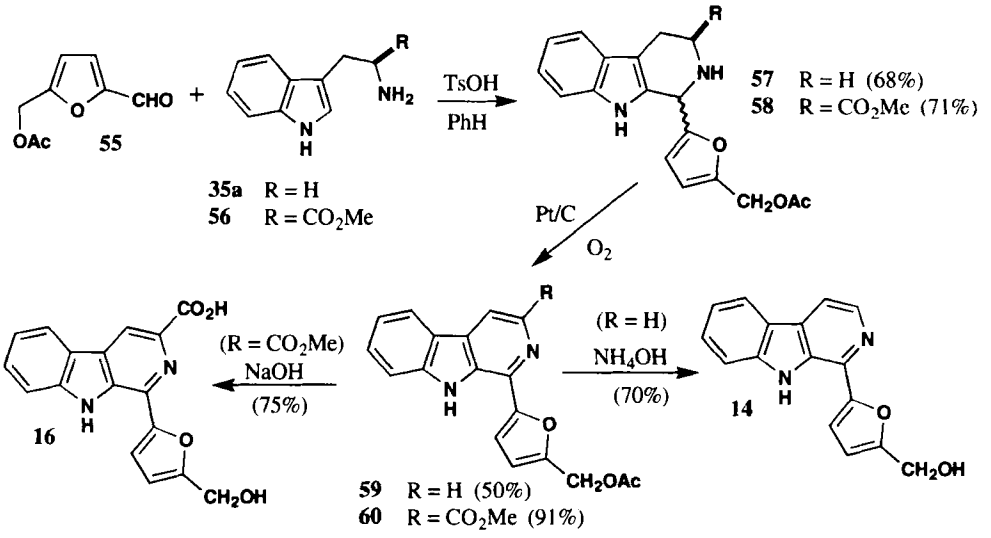


Fig. 15

Oxidation of tetrahydro-β-carbolines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has also found much utility, especially in the synthesis of 4-alkoxy-β-carbolines. For example, Cook reported that oxidation of tetrahydro-β-carboline **64** with DDQ produced **65** (*Fig.* 17) in 71%

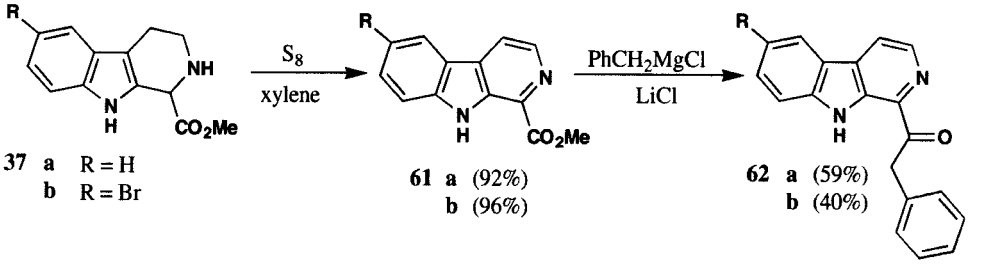


Fig. 16

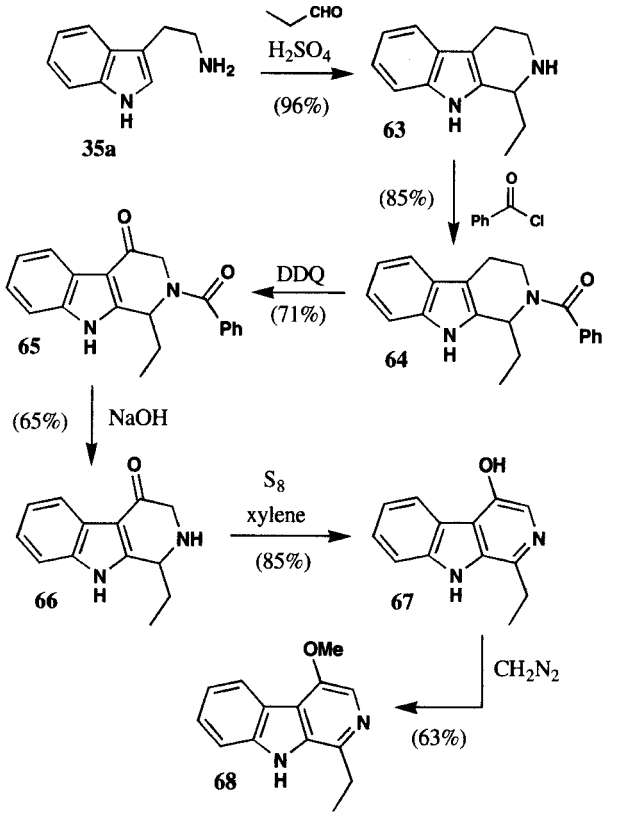


Fig. 17

yield.[55] Hydrolysis of the benzamide and oxidation with elemental sulfur then produced hydroxy-β-carboline **67**, which, upon treatment with diazomethane, completed the synthesis of crenatine **68**.

Intermediates similar to **65** have also been used to prepare a number of other substituted β-carbolines. For example, heating **69** (*Fig.* 18) with allyl alcohol in the presence of *p*-toluenesulfonic acid produced β-carboline **70**.[56] This compound, upon heating at 200° for thirty minutes, underwent a Claisen rearrangement to produce **71** in 84% yield.

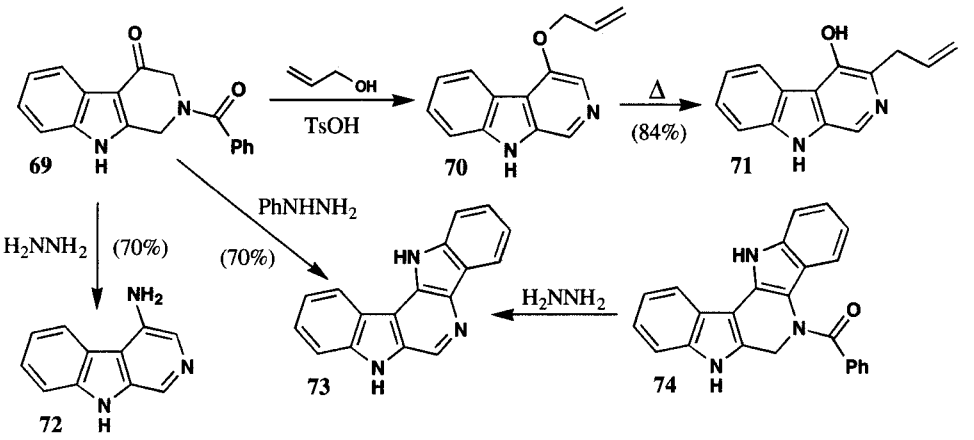


Fig. 18

Alternatively, heating **69** with hydrazine produced 4-amino-β-carboline **72**, a reaction which is postulated to occur via initial hydrazone formation, followed by isomerization and loss of ammonia.[56] Heating **69** with excess phenylhydrazine produced 7,12-dihydropyrido[3,2-b:5,4-b']diindole **73** in 70% yield via a Fischer indole synthesis.[57] Under different reaction conditions, intermediate **74** could be isolated and converted to **73** upon treatment with hydrazine.[58] Substituted analogs of **72** and **73** have also been prepared.[56,58]

DDQ oxidation of a tetrahydro-β-carboline also proved useful in Cook's synthesis[59] of the antileukemic alkaloid 1-methoxy canthine-6-one **6** (*Fig.* 19). The tetrahydro-β-carboline **75b** was

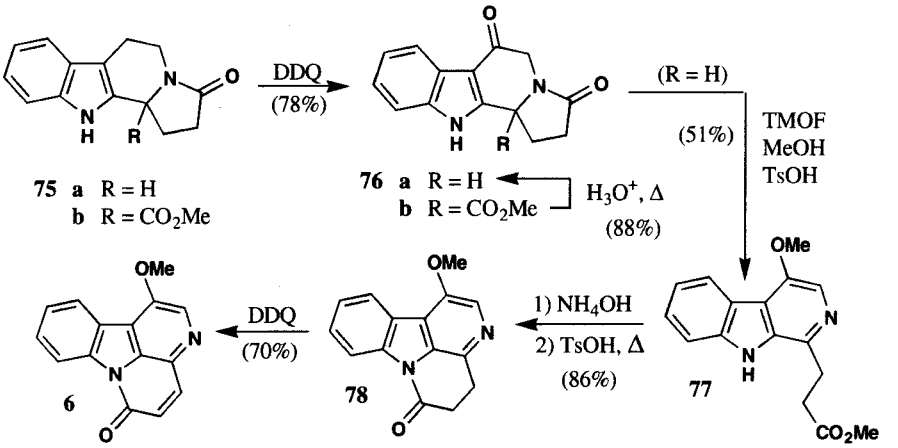
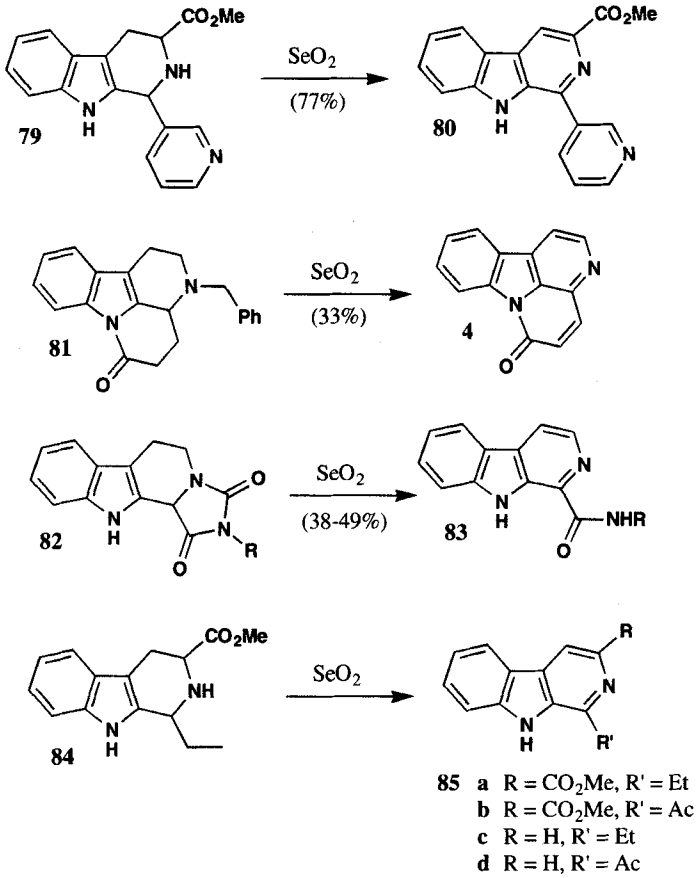


Fig. 19

prepared in 92% yield by a Pictet-Spengler reaction using tryptamine and dimethyl α-ketoglutarate. Oxidation of **75b** with DDQ then produced **76b** which was hydrolyzed and decarboxylated to give **76a**. Reaction of **75a** with DDQ failed to give any of the desired **76a**. Treatment of **76a** with trimethyl

orthoformate (TMOF) in the presence of *p*-toluenesulfonic acid then produced β-carboline **77**, which was hydrolyzed to the corresponding carboxylic acid using 6% NH_4OH. Cyclization was effected by heating with a catalytic amount of *p*-toluenesulfonic acid in a mixture of dimethylformamide and benzene to yield **78**, which was oxidized to the target molecule **6** using DDQ.

Though dehydrogenations using palladium, platinum or sulfur and oxidations using DDQ are perhaps the most commonly employed methods of converting tetrahydro-β-carbolines into the fully aromatic analogues, other oxidants are also occasionally used. For example, when neither palladium on carbon nor sulfur would effect the oxidation of **79** (*Fig.* 20) to the aromatic **80** in appreciable



85 **a** R = CO_2Me, R' = Et
b R = CO_2Me, R' = Ac
c R = H, R' = Et
d R = H, R' = Ac

Fig. 20

yield, selenium dioxide was found to achieve this transformation in 77% yield.[60] N_b-benzyl tetrahydro-β-carbolines can also be oxidized with this reagent, as illustrated by the conversion of **81** to natural product canthin-6-one **4**.[60]

Similarly, tetracyclic compounds **82**,[61] prepared by reaction of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid **36a** (*Fig.* 12) with isocyanates, yielded β-carboline amides **83** upon treatment with SeO_2 in dioxane.[62] The same transformation was also effected using DDQ, though yields for the

DDQ oxidations were not reported.

One limitation of selenium dioxide oxidations, however, is that side chains are often susceptible to oxidation as well. For example, though treatment of **84** with SeO_2 produced some of β-carboline **85a**, it was contaminated with **85b-d**, with **85b** being the major product of this reaction.[60]

Other selenium-based oxidants have also been used to oxidize tetrahydro-β-carbolines. For example, in Rinehart's synthesis of eudistomin O,[6] 7-bromo-1,2,3,4-tetrahydro-β-carboline **86** (*Fig.* 21) was treated with diphenylselenium bis(trifluoroacetate) (generated *in situ* by adding trifluoroacetic

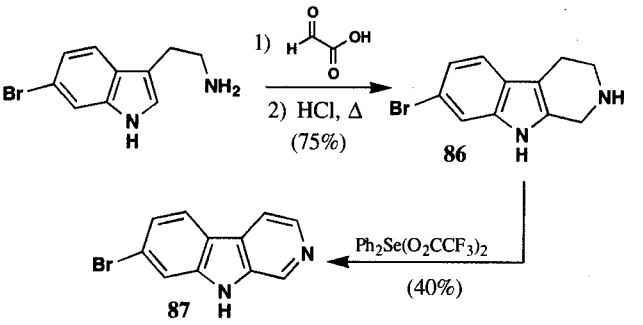


Fig. 21

anhydride to diphenyl selenoxide) to give eudistomin O **87** in 40% yield. Preparation of **86** was accomplished via a Pictet-Spengler reaction between 6-bromotryptamine and glyoxylic acid, and decarboxylation of the resulting product.

Though powerful oxidants such as chromium (VI) based reagents are rarely used to oxidize tetrahydro-β-carbolines, Lewin has reported the oxidation of vincamine **88** with Jones reagent (CrO_3/H_2SO_4/acetone) to give **89** (*Fig.* 22).[63] Heating **89** with mercuric acetate at reflux in trifluoroacetic acid for four hours produced the fully aromatic analog **90** (thallium trifluoroacetate effected the same transformation in the same yield).[64]

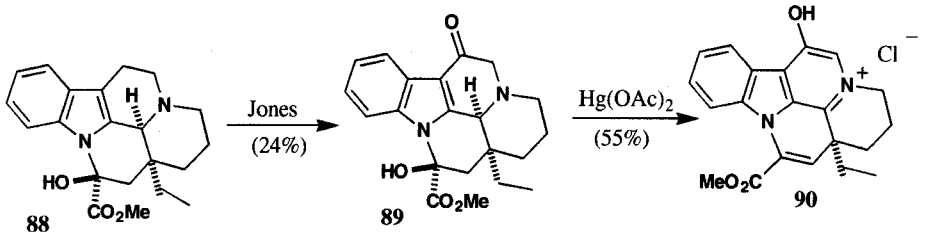


Fig. 22

Thus far we have focused our attention on Pictet-Spengler reactions which utilized either tryptamine or tryptophan as their initial starting materials. Introduction of substituents at C-4 of the β-carboline ring, however, requires preparation of β-substituted tryptamine (or tryptophan) derivatives. One method of preparing such substituted tryptophans is illustrated by the synthesis of β-methyltryp-

tophan methyl ester **93** (*Fig.* 23), which was required for a formal total synthesis of lavendamycin.[65]

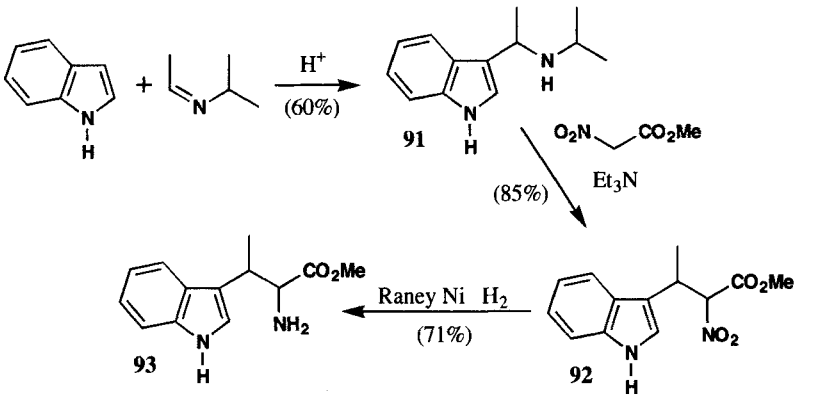


Fig. 23

Though **93** could be prepared in reasonable yield as shown, one of the key reagents, methyl nitroacetate, is quite expensive ($35.75 for one gram),[66] which limits the utility of this approach. Behforouz has published an improved procedure for producing **93** (by essentially the same route as shown) which produces this compound in even greater yield.[67] Despite the expense of nitroacetate esters, a number of 4-substituted β-carbolines have been prepared by this and similar routes.[68]

Optically pure β-substituted tryptophans have been prepared via copper-catalyzed addition of Grignard reagents to 3-indoleacrylic acid derivative **96** (*Fig.* 24).[69] Preparation of just one pair of diastereomers is shown, though the other two diastereomers were prepared in an analogous manner using the enantiomer of chiral auxiliary **95**.

Several other routes to β-substituted tryptamines or tryptophans are known, and an extensive discussion of these methods is beyond the scope of this review. Such methods have been reviewed,[70] and some of the more commonly employed approaches are shown in *Fig.* 25.

Similarly, introduction of substituents at C-3 of the β-carboline ring, other than those derived from a carboxyl group, requires the synthesis of an α-substituted tryptamine derivative. Frequently used methods of preparing such compounds are also shown in *Fig.* 25.

Introduction of substituents on the benzene ring of tryptamine likewise allows the preparation of β-carbolines substituted at carbons 5-8. One method of preparing such compounds is that reported by Abramovitch and Shapiro,[71] which initially produces tryptamine-2-carboxylic acids **104**, which can then be decarboxylated to give the desired substituted tryptamines **105** (*Fig.* 26). As this decarboxylation step can sometimes be problematic, Cook's finding[72] that the tryptamine-2-carboxylic acids themselves can be condensed with aldehydes under Pictet-Spengler conditions to produce tetrahydro-β-carbolines **106** has increased the utility of this method. A few of the other known methods for preparing such substituted tryptamines are also shown in *Fig.* 26.[70] Naturally, use of substituted indoles **107** in any of the methods illustrated in *Fig.* 25 could also lead to substituted tryptamines **105**.

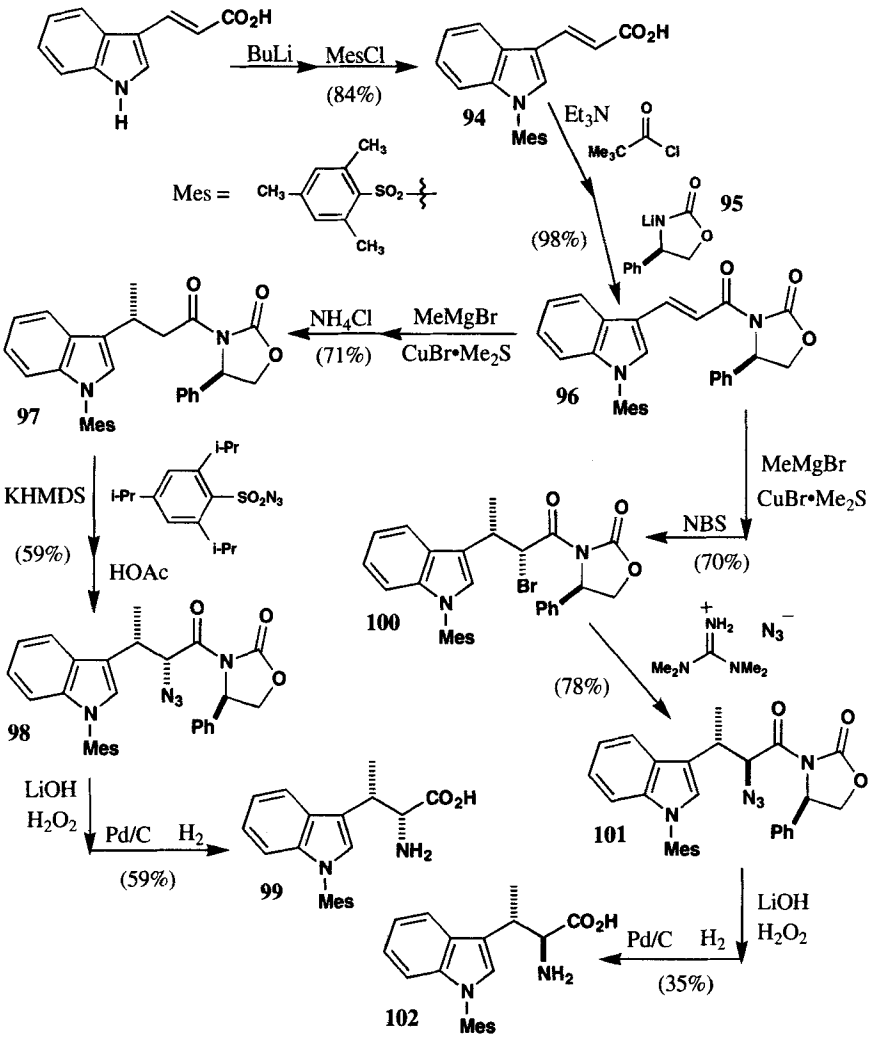


Fig. 24

While Pictet-Spengler reactions are most commonly catalyzed by Brønsted acids, Lewis acids are also known to effect the cyclization of imines derived from tryptamine to produce β-carbolines. For example, imine **108** produced tetrahydro-β-carboline **109** in good yield when treated with either trimethylsilyl chloride (TMSCl), trimethylsilyl iodide (TMSI)/pyridine, or bromodimethylborane (*Fig.* 27).[41a] Use of boron trifluoride etherate, TMSCl in the presence of pyridine, or TMSI in the absence of pyridine gave inferior yields of **109**.

Similarly, imine **110a** produced **111a** upon treatment with *p*-toluenesulfonyl chloride and pyridine,[73] while **112** could be prepared using methyl chloroformate.[74,75] Interestingly, **110b** failed to produce **111b** under these conditions, and neither **110a** nor **110b** would produce **111** under acidic conditions.[73,76]

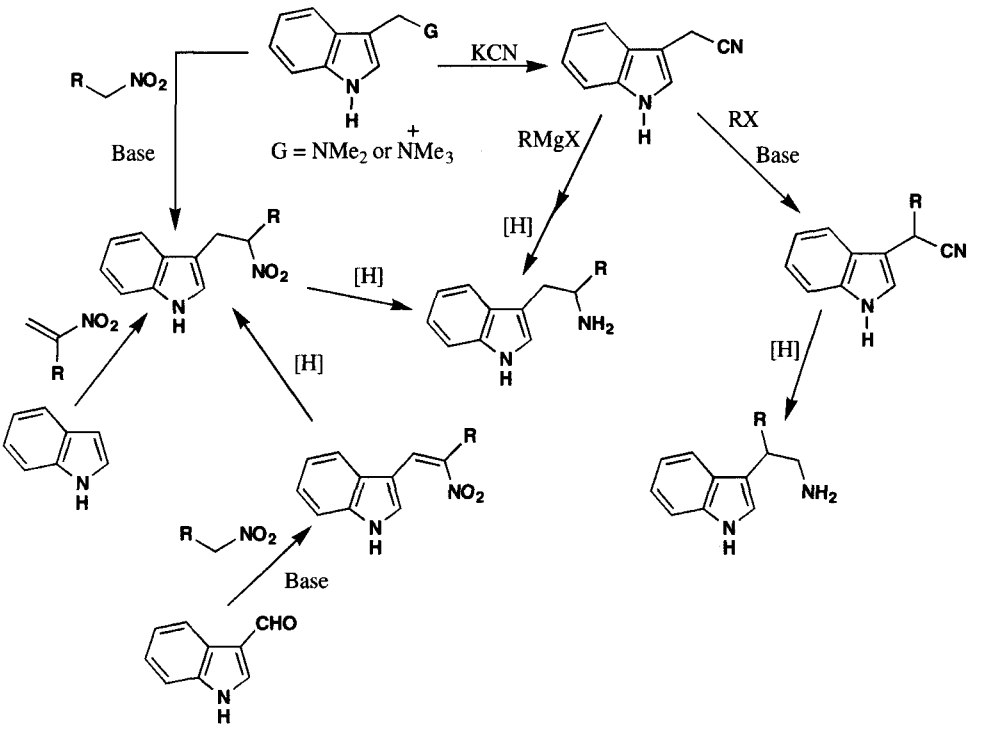


Fig. 25

The discovery that certain tryptamine derivatives will undergo Pictet-Spengler reactions under neutral conditions in aprotic solvents has further extended the utility of this reaction. For example, the key step in Cook's synthesis of pyridindolol **117** is the reaction of tryptophan methyl ester **113** with glyceraldehyde acetonide **114** (*Fig.* 28).[77] Under aqueous acidic conditions, reaction of **113** with **114** produced intractable tars, yet heating the two substrates at reflux in benzene produced a 90% yield of tetrahydro-β-carboline **115**. Dehydrogenation with palladium on carbon in cumene afforded the fully aromatic β-carboline **116** in 70% yield. Reduction of the ester with borohydride (either lithium or sodium) followed by removal of the acetonide produced the target pyridindolol **117**. It might be noted that Pandit later prepared tetrahydro-β-carboline **115** in 72% yield by reacting tryptophan methyl ester with imidazolidine derivative **118** under acidic conditions.[78]

Unfortunately, not all substrates are amenable to cyclization under neutral conditions. It appears that only tryptophan derivatives and N_b-benzyl tryptamines work well.[77] Nevertheless, such conditions have been used successfully in a number of syntheses. For example, heating tryptophan ethyl ester **119** with 2-quinolinecarbaldehyde **120** at reflux in benzene, followed by further heating in xylene with palladium on carbon produced β-carboline **121** in 63% yield (*Fig.* 29).[79]

Saponification of **121** followed by decarboxylation produced natural product nitramarine **122** "quantitatively."

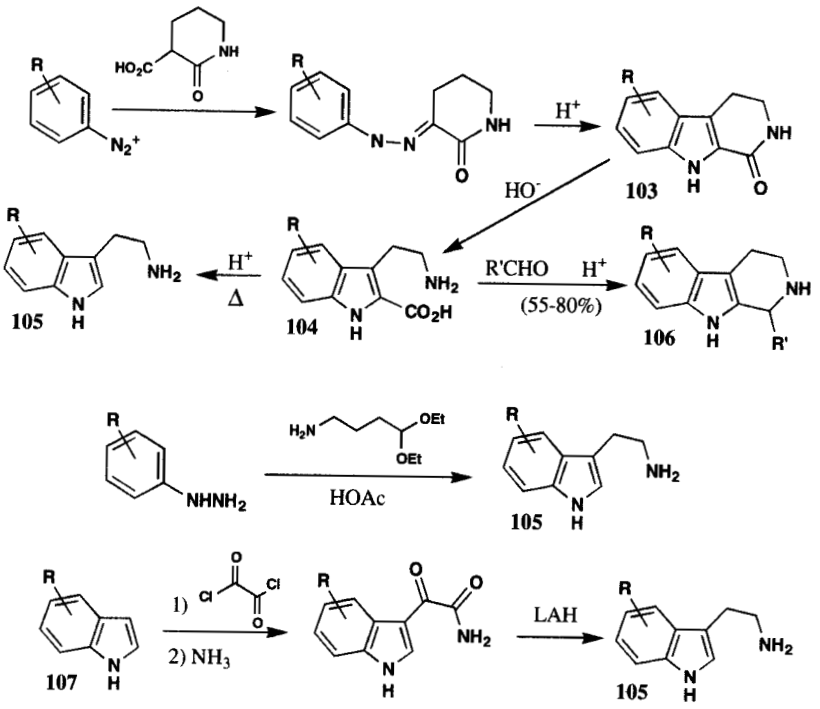


Fig. 26

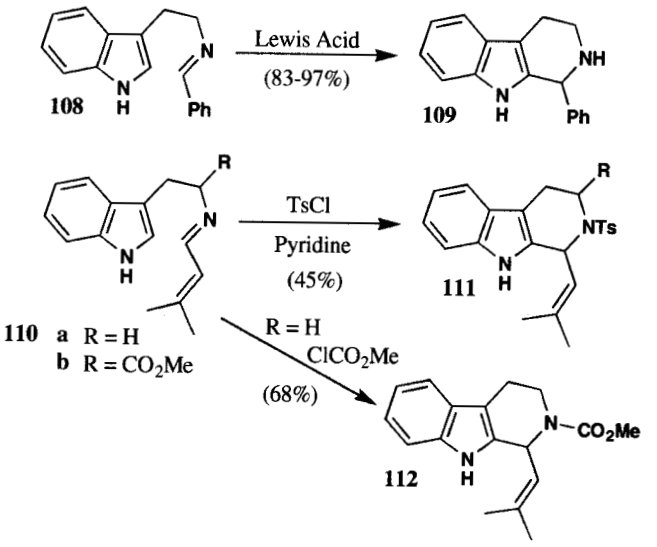


Fig. 27

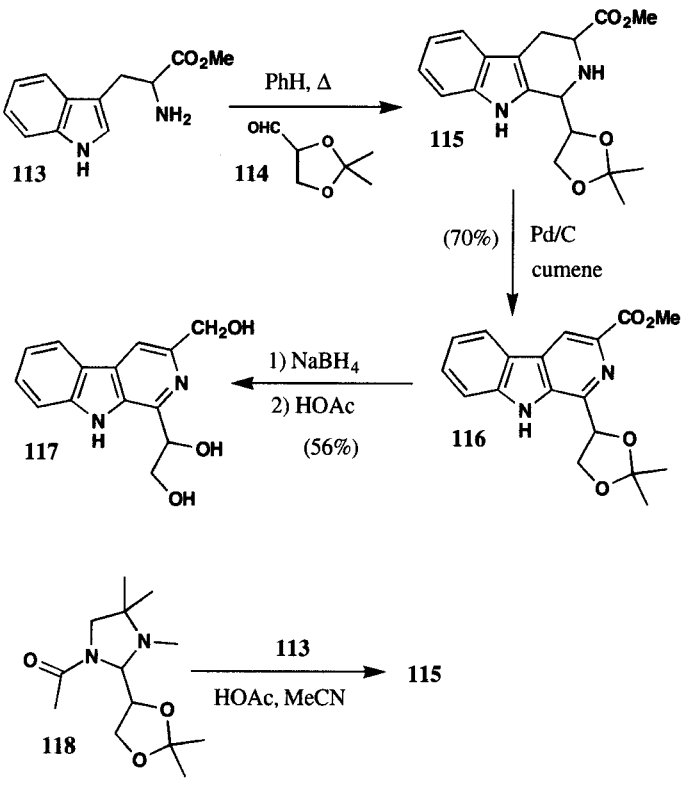


Fig. 28

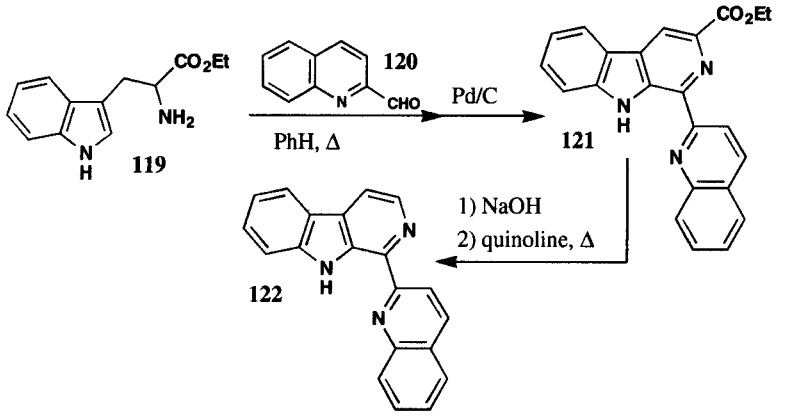


Fig. 29

A Pictet-Spengler reaction under neutral conditions was also a key step in Cook's synthesis of roeharmine **126** (*Fig.* 30).[80] Tryptamine derivative **123** (prepared in six steps and 30% overall yield) was condensed with acetaldehyde to give tetrahydro-β-carboline **124** as a 1.8:1 mixture of diastereomers. Removal of the protecting group and oxidation with activated manganese dioxide

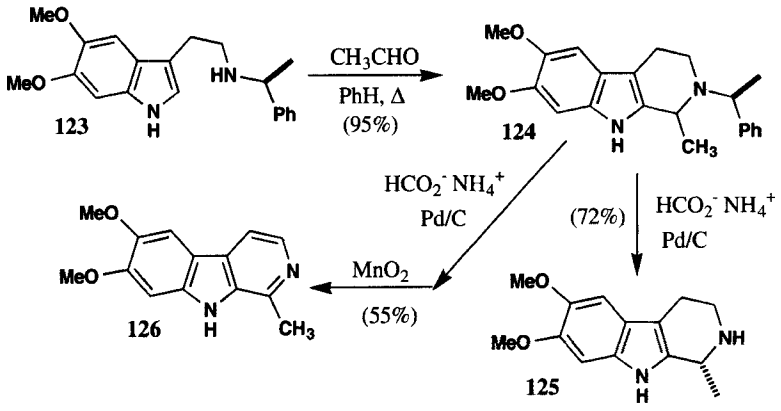


Fig. 30

furnished the target molecule **126** in 55% yield. While not essential for the synthesis of roeharmine **126**, use of the neutral cyclization conditions was significant in the synthesis of (-) 1,2,3,4-tetrahydro-roeharmine **125**, which was prepared by catalytic debenzylation of the major diastereomer of **124** (separated from the minor diastereomer by flash chromatography). It was found that **125** racemizes under acidic conditions,[81] and thus its preparation under acidic conditions would most likely lead to the racemic product.

Such Pictet-Spengler reactions under neutral conditions have also been successful with substituted tryptophan derivatives. For example, substituted tryptophans **130** (prepared as shown in *Fig.* 31) have been reacted with glyoxylic acid to yield β-carbolines **131** after decarboxylation and aromatization.[82] Preparation of this series of β-carbolines **131** was prompted by the finding that **131** (R = BnO, R' = CH_2OCH_3) was a full agonist for the benzodiazepine receptor.[83]

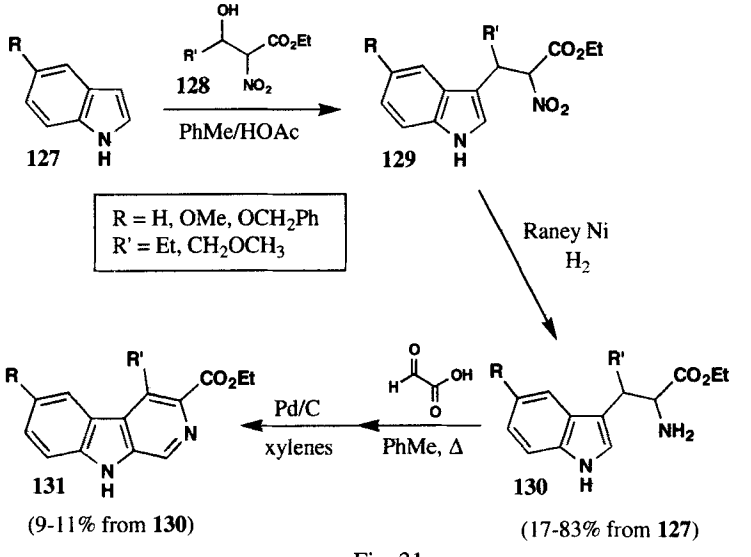


Fig. 31

Another useful example of this reaction is the cyclization of β-methyltryptophan ester **132a** with aldehyde **133** to give **134** (*Fig.* 32), which was a key step in Behforouz's synthesis of lavendamycin methyl ester **135**.[84] Interestingly, the fully aromatic β-carboline was formed directly, without the need of an additional oxidation step. (Similar behavior has been observed for the condensation of

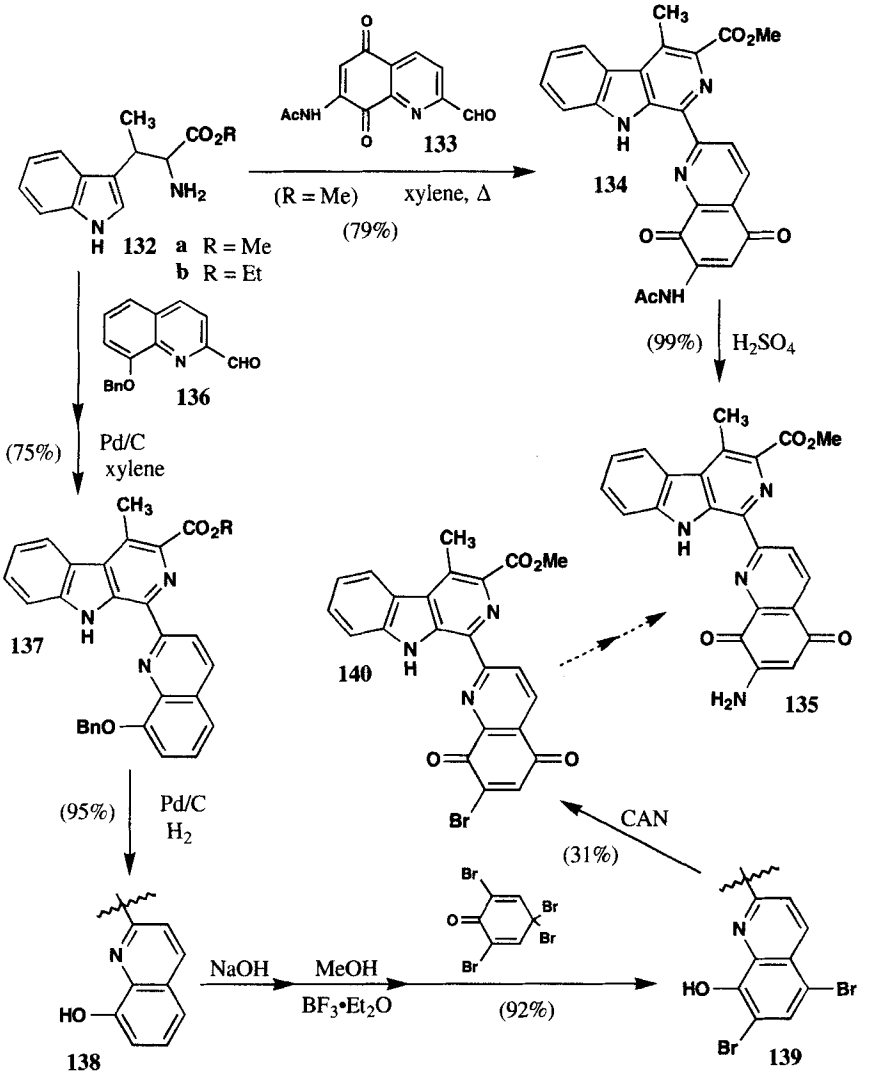


Fig. 32

132a with pyruvaldehyde, although most other aldehydes yielded tetrahydro-β-carbolines upon reaction with **132a**).[67] Selective hydrolysis of the acetamide function in **134** then completed an exceptionally short synthesis of lavendamycin methyl ester **135**.

A similar cyclization was used in Hibino's formal total synthesis of lavendamycin methyl ester.[85] Ester **132b** was condensed with aldehyde **136** to give a tetrahydro-β-carboline, which was then

heated with palladium on carbon in xylenes to give **137**. Deprotection of the benzyl group in **137** by catalytic hydrogenation produced **138** in 95% yield. In order to make direct comparisons with previously reported intermediates, the ethyl ester in **138** was converted to the corresponding methyl ester before being reacted with 2,4,4,6-tetrabromo-2,5-cyclohexadienone to give brominated derivative **139**. Oxidation of **139** with ceric ammonium nitrate produced quinolinequinone **140**. This completed Hibino's formal total synthesis of lavendamycin methyl ester, as Kende had previously converted **140** into lavendamycin methyl ester.[86]

Pictet-Spengler reactions conducted under neutral conditions have been especially useful in condensations between tryptamine derivatives and carbohydrates. For example, a series of peracetylated aldoses **141** were reacted with tryptophan methyl ester to give the corresponding tetrahydro-β-carbolines. These were then aromatized without isolation using DDQ to give **142** in 50-60% yield (*Fig.* 33).[87] β-Carbolines with polyhydroxylated sidechains at C-1 were then obtained in approximately 60% yield by reduction of the methyl ester at C-3 with $LiBH_4$ followed by hydrolysis of the acetates.

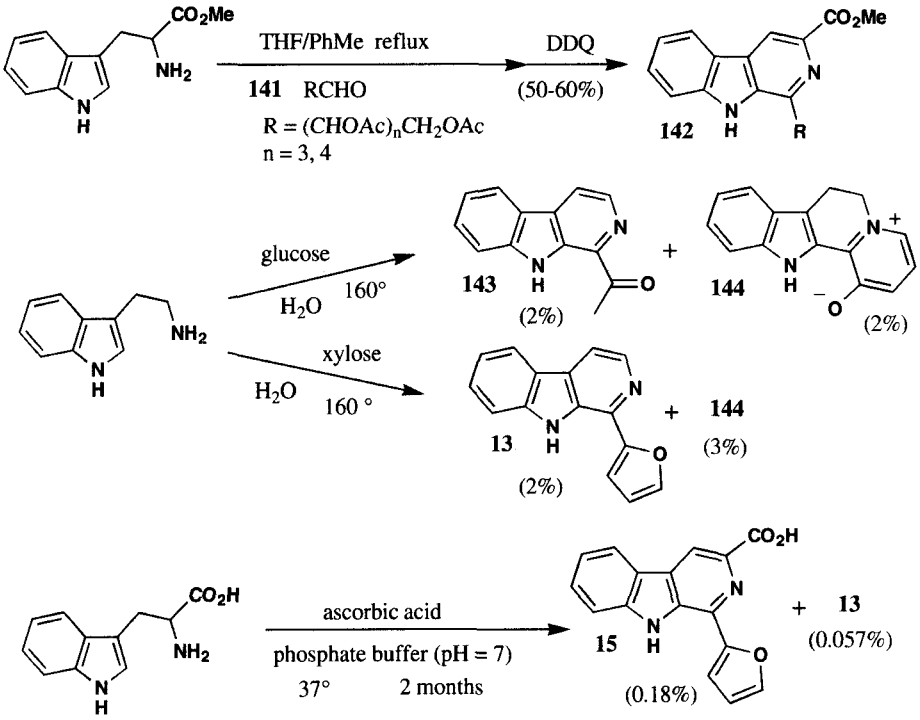


Fig. 33

Reactions involving unprotected carbohydrates tend to give much lower yields. For example, heating tryptamine with glucose under neutral conditions produced a 2% yield of β-carboline **143** (*Fig.* 33), along with a 2% yield of betaine **144**.[88] Under similar conditions, xylose produced the same betaine **144** in 3% yield, accompanied by β-carboline **13** in 2% yield.

Furyl β-carboline **13** was also produced (albeit in extremely low yield) by the reaction of L-

ascorbic acid with L-tryptophan under biomimetic conditions.[89] A small amount of β-carboline **15** was also produced under these conditions (*Fig.* 33).

Though the Pictet-Spengler reaction is tremendously useful in the preparation of β-carbolines, it does not always proceed in high yield. For example, Plieninger and Kiefer required tetrahydro β-carboline **146** in their synthesis of some yohimbine derivatives (*Fig.* 34).[90] Condensation of tryptamine with 3,5-dimethoxyphenylacetaldehyde **145** gave only a 10% yield of **146**, even after optimization of conditions.

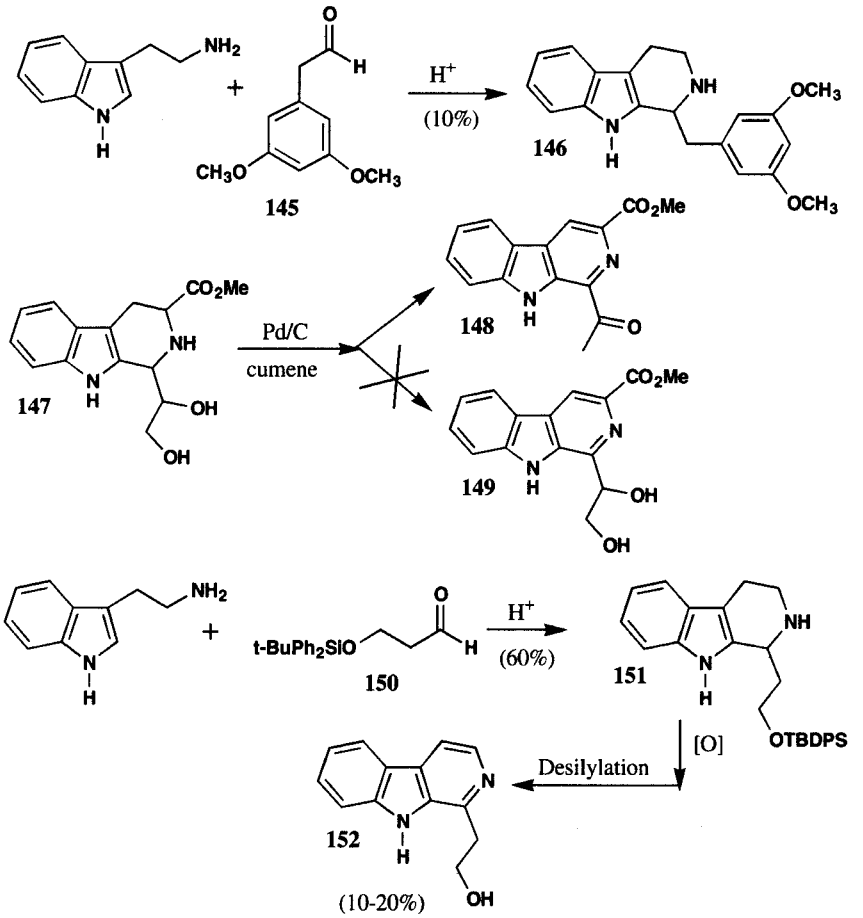


Fig. 34

Often the oxidation of tetrahydro-β-carbolines to the fully aromatic systems proves problematic. For example, in Cook's synthesis of pyridindolol, dehydrogenation of tetrahydro-β-carboline **147** using palladium on carbon in cumene gave **148** instead of the desired β-carboline **149** (*Fig.* 34).[77] As seen earlier (*Fig.* 28), protection of the diol unit was required for the success of this reaction.

Even relatively simple tetrahydro-β-carbolines can prove difficult to oxidize, however. For example, Hino and coworkers required β-carboline **152** (*Fig.* 34) as part of their synthesis of the anti-

tumor agent manzamine C.[91] While condensation of tryptamine with aldehyde **150** gave a 60% yield of tetrahydro β-carboline **151**, oxidation of **151** with typical oxidants produced only traces of the desired **152**. Optimal conditions were eventually found, using 10% Pd/C and *p*-cymene, but these still only gave a 10-20% yield of **152**.[91] Ultimately, another route to manzamine C had to be developed.

Another example of a natural product synthesis in which the oxidation step proved difficult is Still's synthesis of eudistomin T and related compounds (*Fig.* 35).[92] A Pictet-Spengler reaction between tryptamine **35a** and (L)-*N*-*tert*-butoxycarbonylphenylalaninal **154** produced tetrahydro-β-carboline **155** in quantitative yield. Attempts to dehydrogenate **155** to give **156** by heating at reflux in xylenes with Pd/C returned only starting material, while use of elemental sulfur in the same solvent simply decomposed **155**. Eventually it was found that heating **155** to 200° with Pd/C in the absence of solvent produced the desired compound **156** in 70% yield. Although irrelevant to the synthesis of

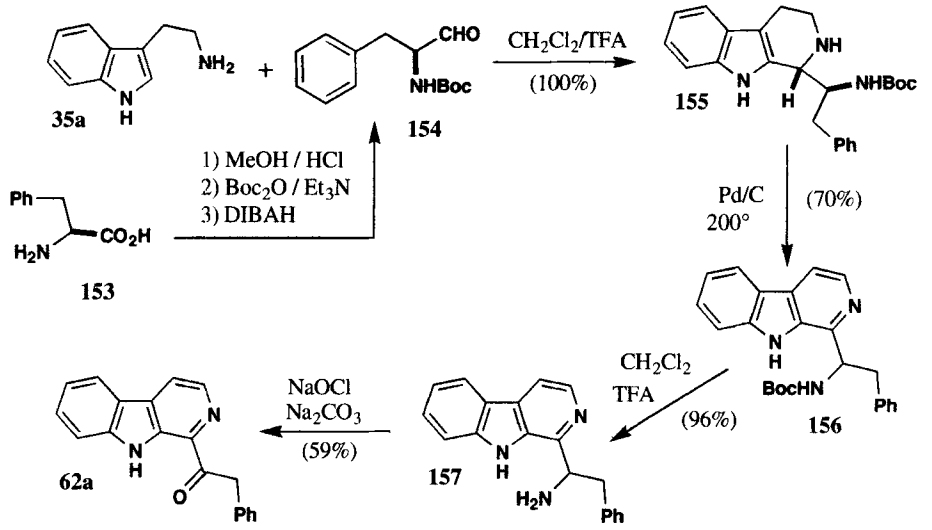


Fig. 35

eudistomin T, the product obtained under these conditions was found to be racemic. Optical activity could be retained if **155** were heated to 200° with elemental sulfur (again without solvent), though the yield was only 35%.[92] Once the appropriate oxidation conditions were found, simple deprotection of the t-Boc group and oxidation of the resulting amine to the corresponding ketone using NaOCl provided eudistomin T in good yield.

Attempts to circumvent the oxidation of a tetrahydro β-carboline by starting with a more highly oxidized tryptamine derivative will not necessarily solve these oxidation problems. For example, cyclization of dehydrotryptophan methyl ester **158** (*Fig.* 36) with aldehydes, catalyzed by either camphorsulfonic acid or boron trifluoride etherate, did not produce dihydro-β-carbolines **160**.[93] Although small amounts of the corresponding β-carbolines were detected, the major products obtained were 5,6-dihydroazepino[5,4,3-cd]indoles **159**.

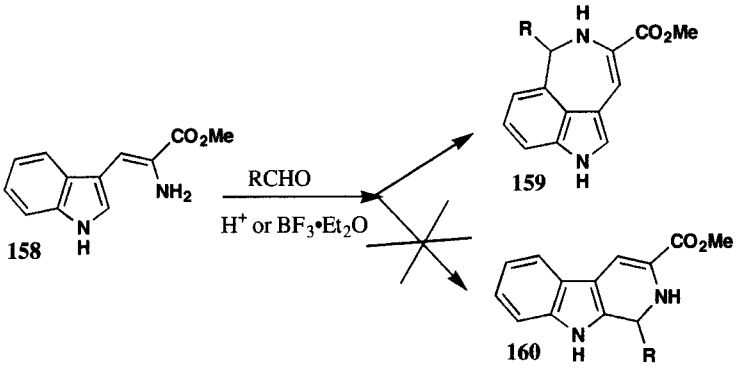


Fig. 36

b. Bischler-Napieralski

Another commonly employed method for preparing β-carbolines is the Bischler-Napieralski reaction (*Fig.* 37).[37,94] Like the Pictet-Spengler reaction, tryptophan or tryptamine derivatives are the usual starting materials for this reaction. Acylation of the exocyclic amine followed by treatment with any of several dehydrating agents (phosphorus pentoxide and phosphorus oxychloride are common choices) results in cyclization to give dihydro-β-carbolines **162**. These compounds are then treated with an oxidant to provide β-carbolines **163**. Relative to the Pictet-Spengler reaction, the Bischler-Napieralski reaction offers the advantage of providing dihydro-β-carbolines, which generally are more easily oxidized to the fully aromatic β-carbolines than are tetrahydro-β-carbolines. It suffers, however, from the disadvantage that it usually requires more vigorous reaction conditions than are commonly necessary for the Pictet-Spengler reaction.

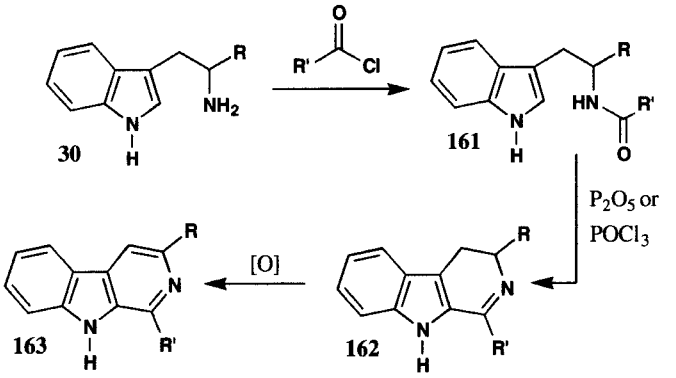


Fig. 37

Despite its more severe reaction conditions, the Bischler-Napieralski reaction has found considerable use in the preparation of β-carbolines. For example, Hino used a Bischler-Napieralski cyclization of **164**[95] to give **165** (*Fig.* 38) as a key step in his synthesis of manzamine C **23**.[91,96] As mentioned previously, Hino's attempts to make **23** via a Pictet-Spengler reaction were disappointing.

Dehydrogenation of **165** produced β-carboline **166**, which could be converted to amide **168** either by prolonged heating with amine **167**, or by reaction of **167** with **169** in the presence of diphenylphosphoryl azide. (Amine **167** was prepared from known acetylene **170** in 6 steps). Reduction of **168** with lithium aluminum hydride (LAH) completed Hino's synthesis of manzamine C **23**.

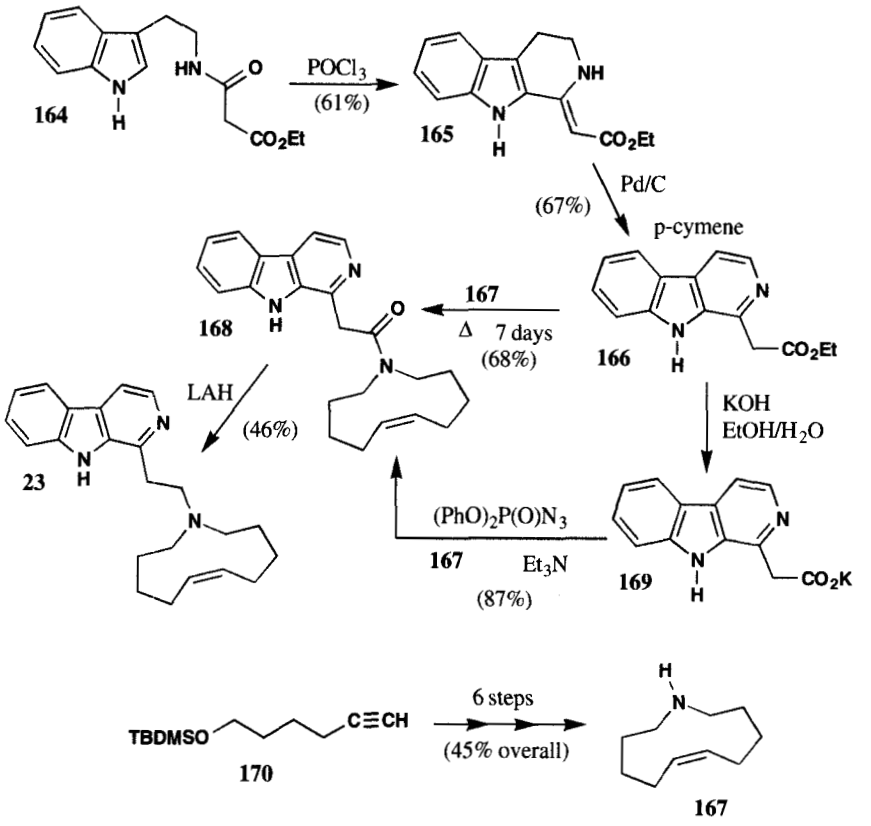


Fig. 38

Hino also utilized the Bischler-Napieralski reaction in his synthesis of eudistomins H, I, and P (*Fig.* 39).[51] Amide **172** was isolated in 94% crude yield after reaction of tryptamine **35a** with the anhydride of **171**, which was prepared by treatment of **171** with 1,3-dicyclohexylcarbodiimide (DCC). Cyclization using polyphosphoric ester in dichloromethane produced dihydro-β-carboline **173** directly, the authors speculating that deprotection and oxidation had occurred on work-up. Oxidation with DDQ furnished eudistomin I **45a**, which was brominated using NBS to afford eudistomin H **45b** in 80% yield.

A similar approach was used for the preparation of eudistomin P **176** starting from 6-bromo-5-methoxytryptamine **174**.[97] In this instance, oxidation of dihydro-β-carboline **175** with NBS produced a higher yield of the fully aromatic β-carboline than did DDQ. Heating the resultant β-carboline with an excess of boron tribromide then completed the synthesis of eudistomin P **176**.

The same cyclization strategy was adopted by Murakami in the first total synthesis of eudis-

tomidin A **179**, though the yield of the cyclization/aromatization sequence was rather low (*Fig.* 39).[98] Manganese dioxide was used as the oxidant rather than DDQ, and the synthesis was completed by deprotection of tosylate **178** using KOH.

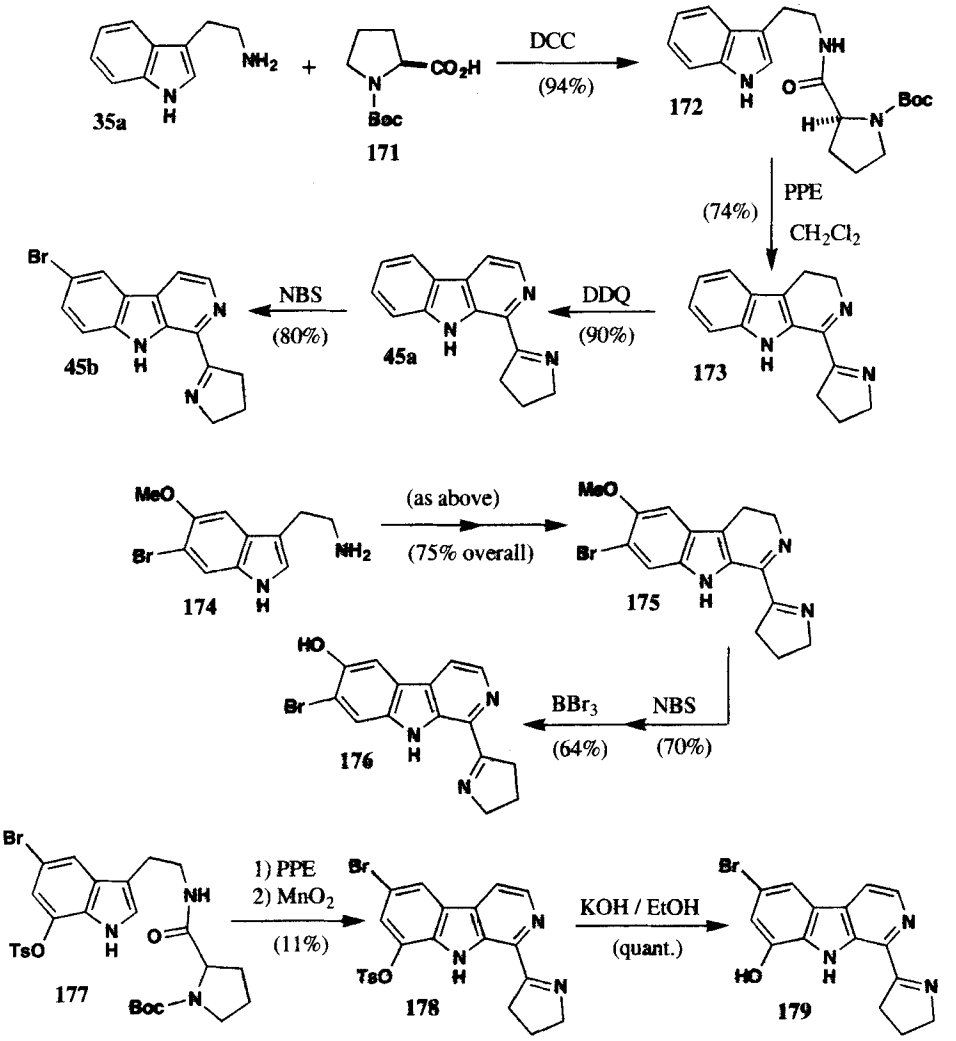


Fig. 39

A Bischler-Napieralski reaction also provided the β-carboline portion of lavendamycin methyl ester **135** in Kende's synthesis of this important compound (*Fig.* 40).[86] Quinoline carboxylic acid **180**[99] was condensed with β-methyltryptophan methyl ester **93** in the presence of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide to give amide **181** in 90% yield. Heating **181** at 90° for 16 hrs with polyphosphate ester induced cyclization to give β-carboline **182** in 31% yield. Reduction of the nitro group to a primary amine was accomplished using sodium dithionite, and the resulting **183** was then oxidized with potassium dichromate in a two phase system of CH_2Cl_2 and dilute sulfuric acid to give

bromoquinone **140**. Conversion of **140** to **135** involved displacement of the bromine by sodium azide to give **184**, and reduction of the azido group using sodium dithionite, providing lavendamycin methyl ester **135** in 30% yield.

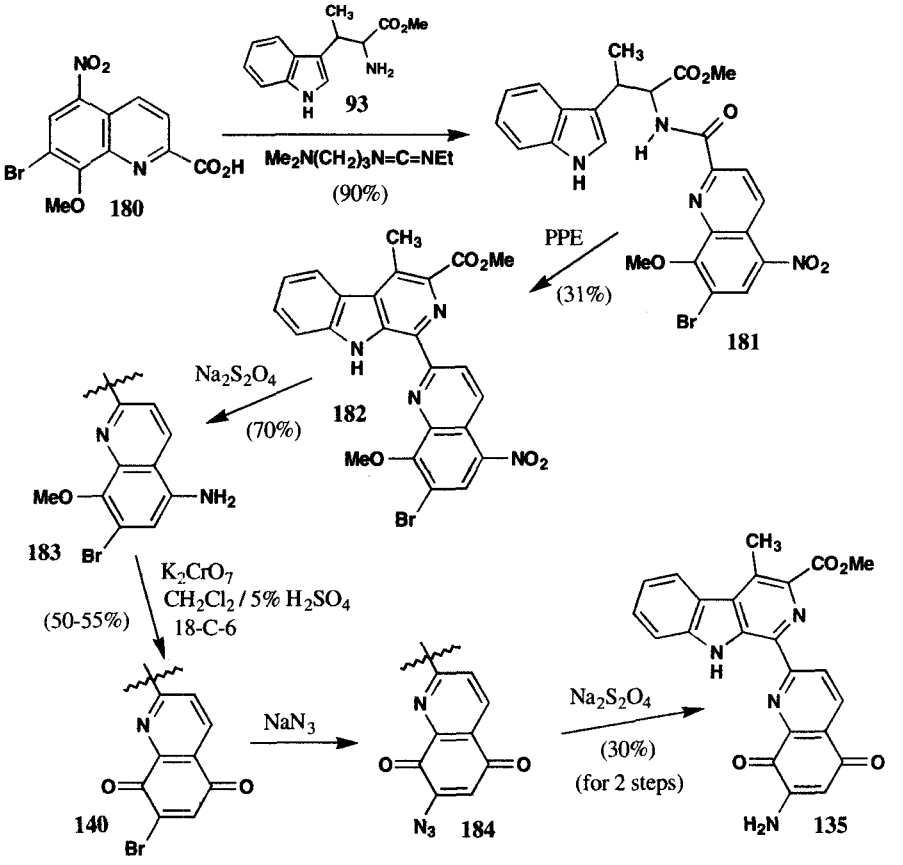


Fig. 40

Rao's synthesis of this same molecule also utilized a Bischler-Napieralski reaction (*Fig.* 41).[65] Condensation of quinoline **185**[100] with β-methyltryptophan methyl ester **93** produced amide **186**, which was cyclized using $POCl_3$ to give β-carboline **187**. Though attempts to oxidize **187** directly to quinone **140** (*Fig.* 40) were unsuccessful, this intermediate was able to be prepared by the three step process shown, concluding Rao's formal total synthesis of lavendamycin methyl ester.

Bischler-Napieralski cyclizations have proven to be especially useful in the preparation of tetracyclic β-carboline derivatives, a recent example being Fujii's synthesis of 3,4,5,6-tetrahydro-17-hydroxycoryanium **192** (*Fig.* 42).[101] The ester functionality in amide **188**, prepared previously by the same authors as part of another total synthesis, was first converted to the corresponding acetate by borohydride reduction followed by acetylation to give **189**. Treatment of **189** with phosphorus oxychloride initiated the Bischler-Napieralski reaction. Without isolation, the product of this reaction

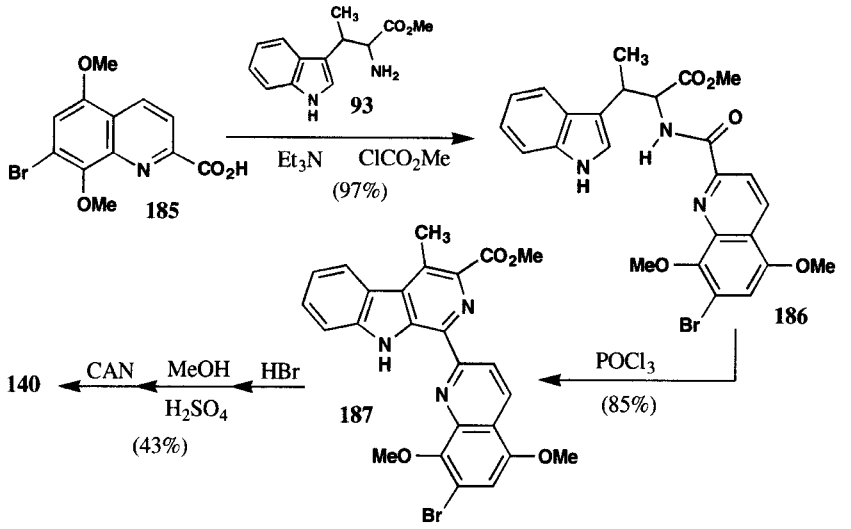


Fig. 41

was treated with aqueous potassium carbonate followed by hydrochloric acid and sodium perchlorate to yield perchlorate salt **190**. Dehydrogenation with palladium black produced the β-carbolinium salt **191** in 91% yield, while deprotonation of **191** yielded the zwitterionic natural product **192**. The yield of this last step was not reported, and curiously, the sign of the specific rotation of **192** was the opposite of that reported for the natural product.

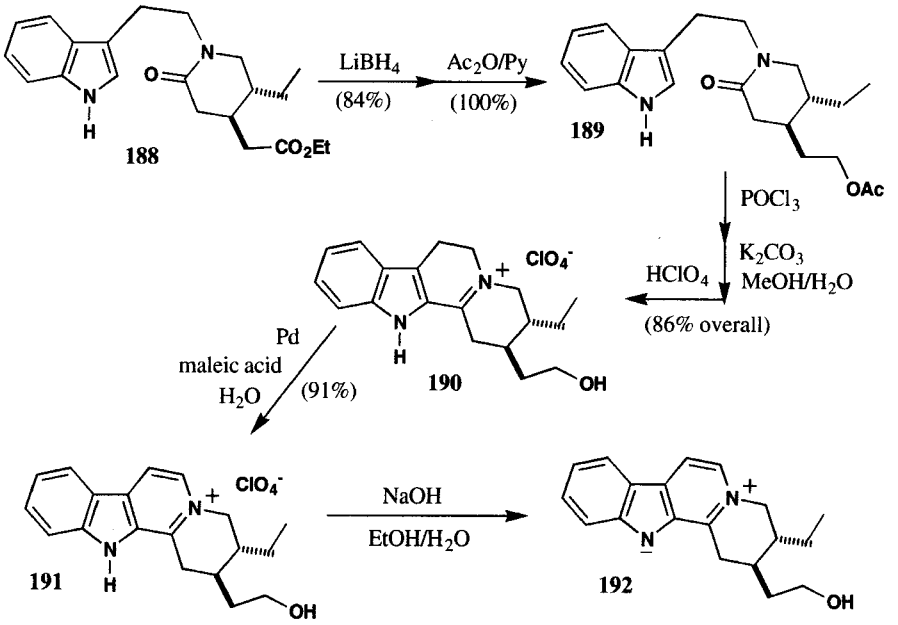


Fig. 42

Though a useful method of constructing the β-carboline nucleus, like the Pictet-Spengler, the Bischler-Napieralski reaction is not always successful. For example, Murakami had hoped to use this reaction to prepare 1-ethyl-4-hydroxy-β-carboline **67** (*Fig.* 43), as methylation of the phenol would produce the natural product crenatine. Direct reaction of indole **194** was not attempted, as this reaction had been reported to produce oxazole **193**,[102] so routes to **67** using protected versions of **194** were investigated. The authors were unable to prepare ketal **195**, although thioketal **196** could be prepared in 60% yield.[103] The reason for the inability to isolate **195** was not stated, though deacylation of 3-acylindoles upon attempted ketalization has subsequently been reported.[104]

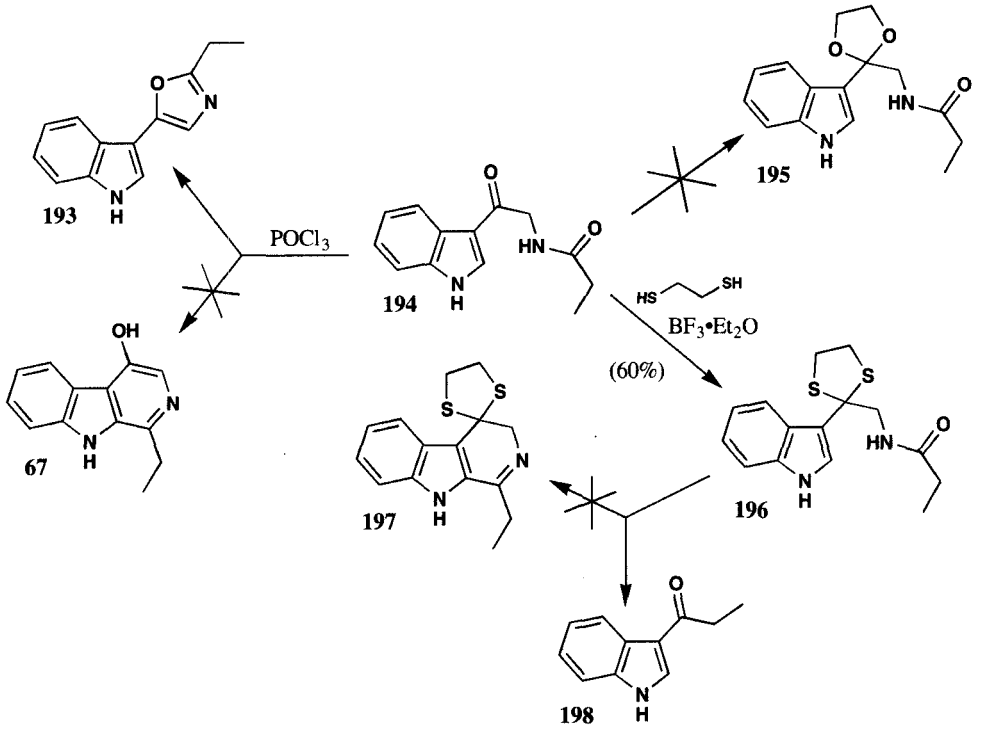


Fig. 43

Though thioketal **196** could be prepared, it failed to undergo a Bischler-Napieralski reaction to produce the desired product **197**, acylindole **198** being isolated in 81% yield instead. A mechanism for this rearrangement has been proposed by Cook.[59]

c. Other Methods

Though the Pictet-Spengler and Bischler-Napieralski reactions are perhaps those most commonly employed for preparing β-carbolines, other methods which proceed via cyclization to form the pyridine ring have also been used. For example, Gribble has reported an entirely different route to flavopereirine **201a** and sempervirine **201b**, zwitterionic β-carbolines similar to **192** (*Fig.* 44).[105,106] Treatment of pyridoindoles **199** with *n*-BuLi followed by anhydrous bromoacetaldehyde and an acetic

acid work-up produced salts **200**. Removal of the phenylsulfonyl protecting group and dehydration were accomplished by heating at reflux with sodium hydroxide in aqueous methanol, producing zwitterionic products **201**.

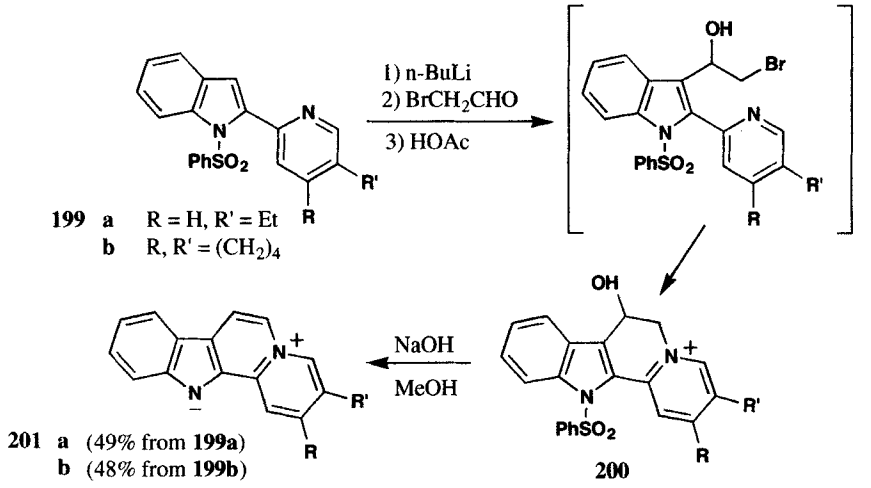


Fig. 44

The requisite pyridoindoles **199** were prepared by completely different methods. Condensation of the dianion of *N*-trimethylsilyl-o-toluidine **202** (*Fig.* 45) with ethyl 5-ethylpicolinate **203** produced pyridylindole **204** in 67% yield. Standard protection of the indole nitrogen then provided **199a**, also in 67% yield.[105]

Reaction of 2-acetyl-1-phenylsulfonylindole **205**[107] with selenium dioxide afforded ketoaldehyde **206**, which was condensed with methylthiosemicarbazide hydriodide to give 1,2,4-triazine derivative **207** (*Fig.* 45). Oxidation of sulfide **207** to the corresponding sulfone followed by reaction with enamine **208** thus produced **209**. Selective removal of the methylsulfonyl group was unsuccessful, and thus **199b** was eventually obtained by removal of both sulfonyl groups, followed by reprotection of the indole nitrogen.[106]

Intramolecular cyclization of a nitrogen nucleophile onto a tryptophyl bromide derivative was also the method of ring closure chosen by Love in his synthesis of the β-carboline ring system (*Fig.* 46).[108] Starting from known[109] vinyl indole **211**, treatment with LDA followed by *N*-tosylaldimines **212** produced sulfonamides **213** in 59-77% yield. Alkoxybromination followed by base-induced ring closure gave tetrahydro-β-carbolines **215**. Acid-catalyzed elimination of methanol produced dihydro-β-carbolines **216**, which could be aromatized and deprotected using either butyl lithium, KOH in DMSO, or 50% NaOH in toluene in the presence of a phase transfer catalyst. Later studies showed that **214** could be converted directly into **217** in yields ranging from 71-79% by heating with 50% NaOH in toluene under phase transfer catalysis.[110] This alternate route to **217** was not only shorter, but avoided the use of acid during all steps of the synthesis.

β-Carbolines possessing alkyl groups at C-3 have also been prepared by this route, starting

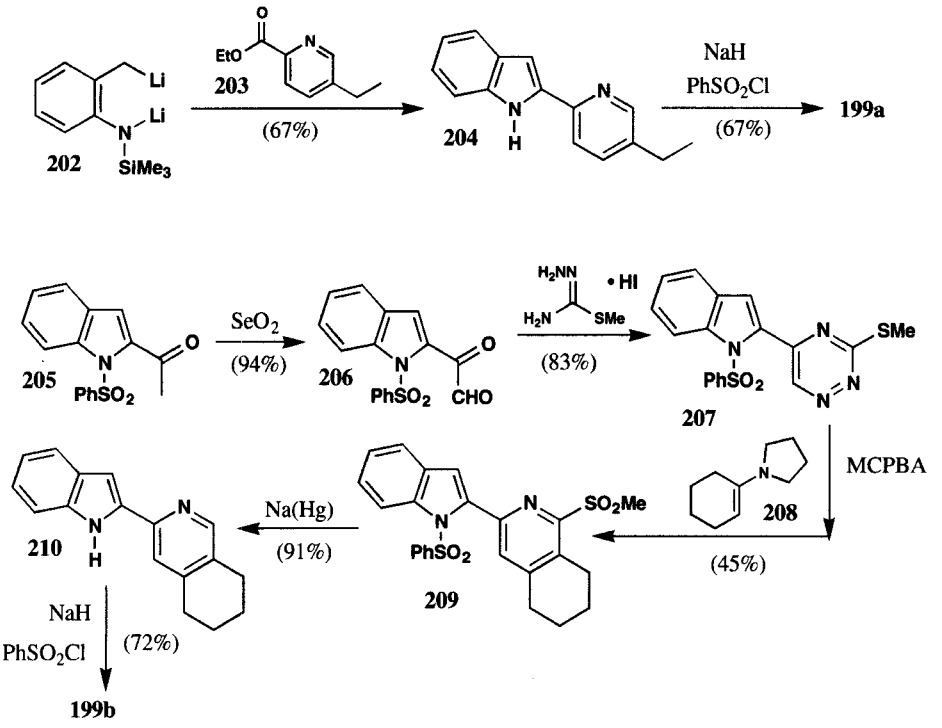


Fig. 45

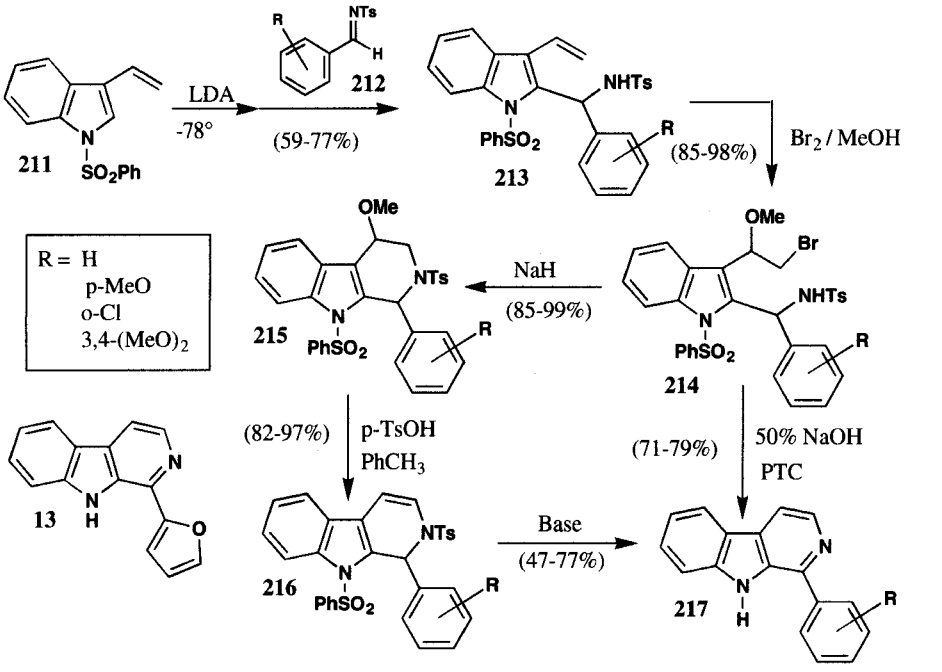


Fig. 46

from the appropriately substituted vinyl indole derivatives.[111] Additionally, naturally occurring furyl-β-carboline **13** has been synthesized in 3 steps (60% yield overall) from **211** using this method, though use of N-bromosuccinimide instead of bromine in the alkoxybromination step was necessary.[110]

Another β-carboline synthesis in which α-lithiation of an indole derivative played a key role is Hibino's synthesis of nitramarine **122** (*Fig.* 47).[79] Treatment of vinyl indole **211** with LDA followed by 2-quinolinecarboxaldehyde produced indolylketone **219a** in 23% yield, though the mechanism of the apparent oxidation was not elucidated. Heating **219a** for two days at reflux in toluene with ten equivalents of hydroxylamine hydrochloride produced nitramarine **122** in 37% yield, presumably through electrocyclic ring closure and dehydration of the intermediate oxime, although this oxime was not isolated. An analogous series of reactions also produced β-carboline ester **121**.

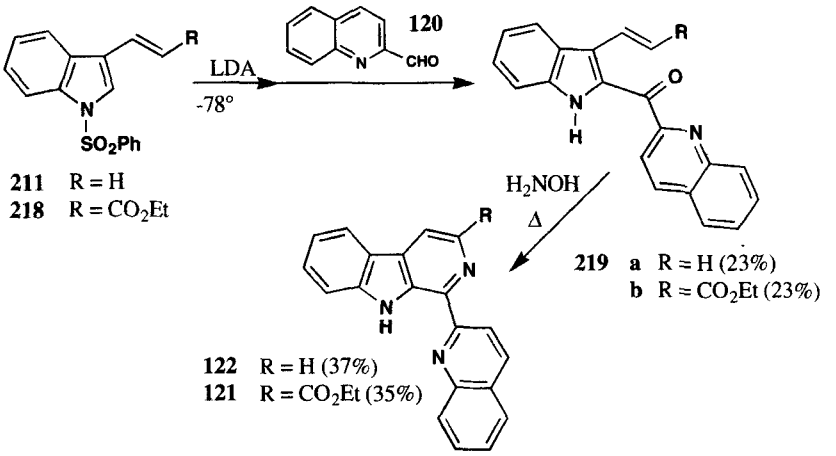


Fig. 47

4-Alkoxy-β-carbolines have been prepared by intramolecular acylation, as illustrated by Murakami's synthesis of crenatine **68** (*Fig.* 48).[103,112] Ethyl 1-benzylindole-2-carboxylate **220** underwent a Claisen condensation with ethyl propionate, which, after hydrolysis and decarboxylation, gave acyl indole **221**. Attempts to introduce the aminoacetate moiety in **223** by reductive amination of **221** with ethyl glycinate met with failure, thus **223** was prepared using the oximation/reduction/acylation/alkylation sequence shown in *Fig.* 48.

Intramolecular cyclization of **223** was effected with polyphosphoric acid (PPA) to give **224** in 80% yield. Hydrolysis of the formamide group followed by dehydrogenation with palladium on carbon (in decalin at 140°) and alkylation with dimethyl sulfate produced β-carboline **225** in 24% yield. Removal of the benzyl group was then effected by aluminum trichloride in anisole, thus completing the synthesis of crenatine **68**.

Murakami also applied this method to the synthesis of 4-alkoxy-β-carbolines which were unsubstituted at C-1 (*Fig.* 49).[113] Unlike ketone **221**, however, aldehyde **226** underwent reductive amination with ethyl glycinate to give **227** (after formylation with ethyl formate). Once again, PPA

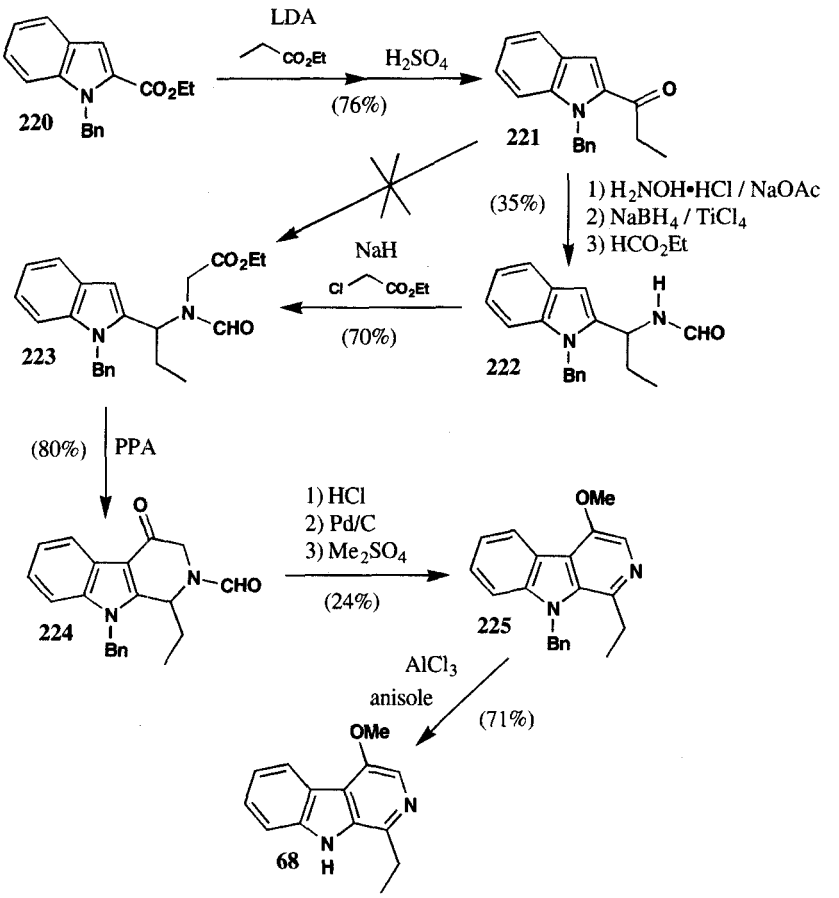


Fig. 48

was used to effect cyclization, though hydrolysis of the formamide, oxidation, and methylation were carried out simultaneously using a mixture of dimethyl sulfate, *p*-toluenesulfonic acid, and chloranil, which produced 9-benzyl-4-methoxy-β-carboline **229**. A cyano group was introduced at C-1 by reacting N-oxide **230** with diethyl phosphorocyanidate, and this nitrile was converted to the corresponding acetyl compound by reaction with methyllithium. Removal of the benzyl protecting group with $AlCl_3$ then furnished 1-acetyl-4-methoxy-β-carboline **232** (a natural product).

An example of β-carboline synthesis which proceeds via intramolecular alkylation at C-3 of the indole ring has also recently been reported by Dodd (*Fig.* 50).[114] Condensation of indole-2-carboxaldehyde **233** with amino ester derivatives **234** produced imines **235** in excellent yield. Attempts to cyclize **235** directly to **237** were unsuccessful, therefore the imine functionality was reduced to give **236**, which was then cyclized by heating with $TiCl_4$ in benzene. As indicated in *Fig.* 50, this method allows the introduction of substituents at C-4 of the β-carboline ring through use of the appropriate amino ester derivative.

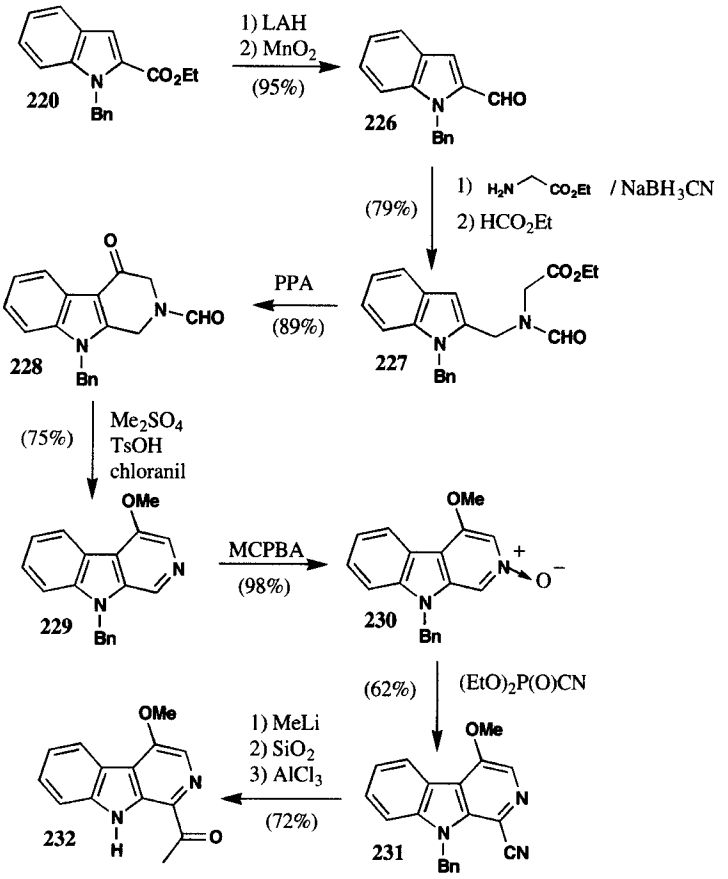


Fig. 49

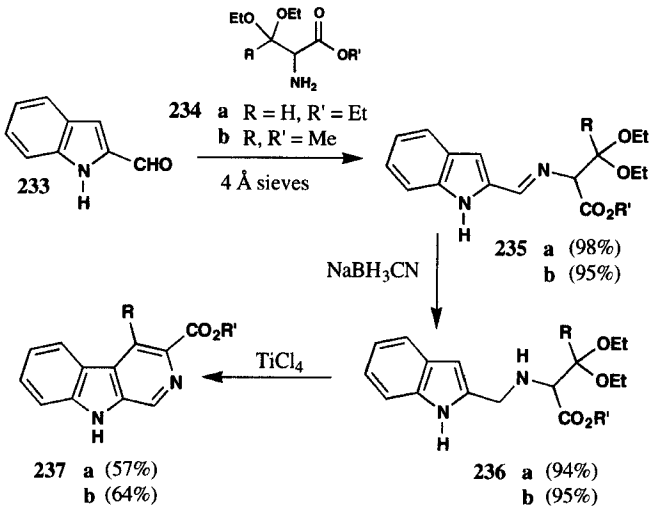


Fig. 50

A novel cyclization route to β-carbolines involving the use of vinyl azide **239**, prepared by condensation of indole aldehyde **238** with ethyl azidoacetate, has been reported by Moody (*Fig.* 51).[115] Heating **239** in xylene gave β-carboline **240** in good yield, which could be hydrolyzed to

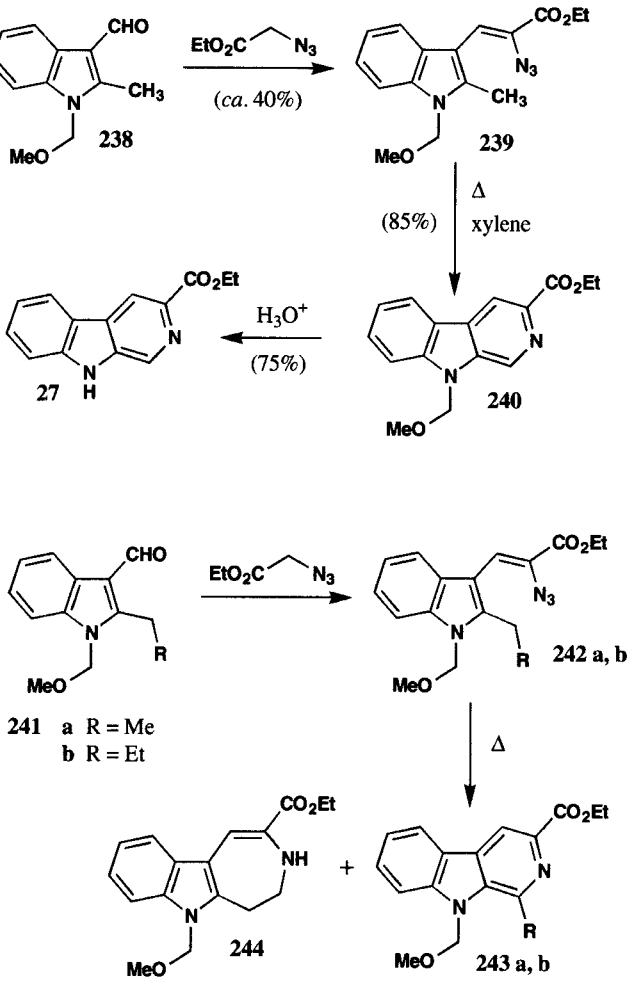


Fig. 51

produce β-carboline 3-carboxylic acid ethyl ester **27**. The presumed intermediate dihydro-β-carboline was detected by NMR shortly after the completion of the thermolysis, but oxidized to **240** before it could be isolated. Attempts to extend this methodology to the synthesis of 1-substituted β-carbolines proved disappointing, however. Preparation of vinyl azides **242** proceeded in lower (though unspecified) yields than obtained for **239**. Additionally, heating **242a** in xylene produced not only the desired β-carboline **243a**, but also an approximately equal amount of azepino[4,5-b]indole **244**. Heating **242a** in *o*-dichloro-benzene did, however, produce a 45% yield of **243a** uncontaminated by **244**. Attempts to cyclize **242b** produced only trace amounts of **243b**.

Other "alternate" routes to β-carbolines often share many similarities with the "classic" Pictet-Spengler and Bischler-Napieralski reactions. For example, Molina has used his "tandem aza-Wittig/electrocyclic ring closure" process to prepare a variety of 1-substituted β-carbolines (*Fig.* 52).[116] Iminophosphorane **245** can be prepared in 60% yield from 1-methylindole-3-carboxaldehyde by treatment with ethyl azidoacetate and sodium ethoxide followed by triphenylphosphine.[117] Heating a toluene solution of **245** in a sealed tube with a variety of aldehydes produced the β-carbolines shown, generally in good yield. This reaction presumably occurs through an imine intermediate analogous to those employed in Pictet-Spengler reactions, although these imines were not isolated.

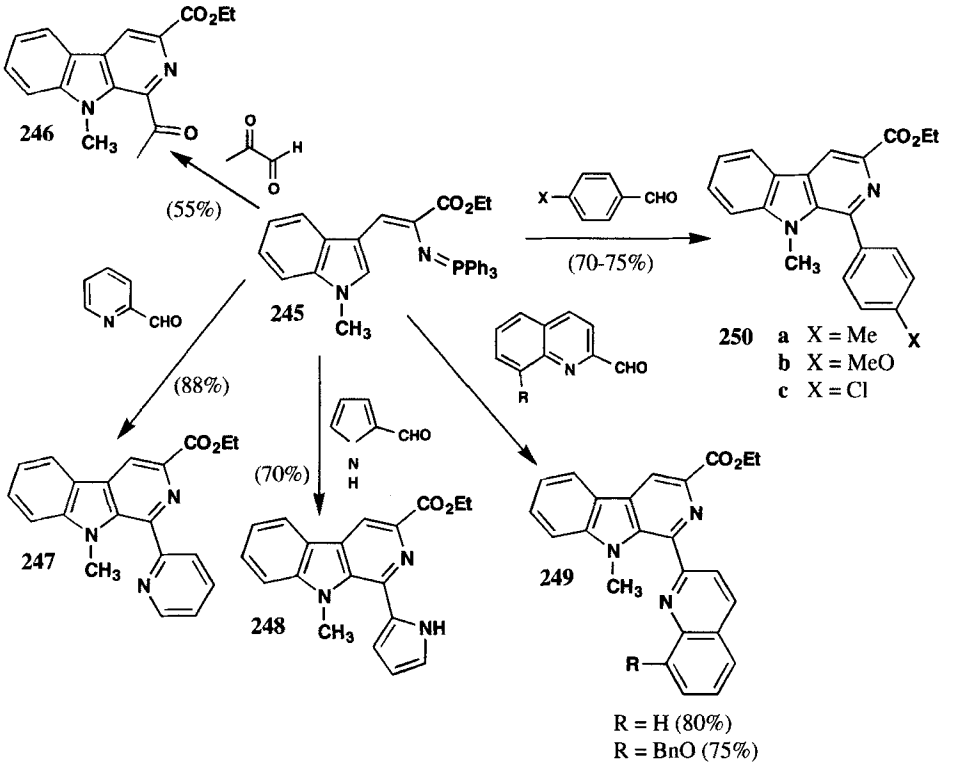


Fig. 52

This reaction sequence was a key feature in Molina's formal total synthesis of lavendamycin ethyl ester (*Fig.* 53).[118] Treatment of azide **251**, prepared by either of two routes, with tributyl phosphine gave iminophosphorane **252** (triphenyl phosphine failed to produce the corresponding iminophosphorane). Heating **252** with aldehyde **255** at 165° for 20 hours in the presence of 10% palladium on carbon gave a 45% yield of **253**, which completed Molina's formal total synthesis, as Boger had previously converted the corresponding methyl ester into lavendamycin methyl ester.[119] Quinoline **255** was prepared in two steps from 2-amino-3-benzyloxy-4-bromobenzaldehyde **254** as shown.

Molina has used a similar strategy to prepare other β-carboline natural products, such as nitramarine **122** and fascaplysin **17** (*Fig.* 54).[120] The synthesis of nitramarine **122** was initiated by

heating iminophosphorane **256** with 2-quinolinecarboxaldehyde **120** in toluene, to produce β-carboline ester **121** after acidic removal of the MOM protecting group. Saponification ("near quantitative") followed by decarboxylation at 260° then gave nitramarine **122**.

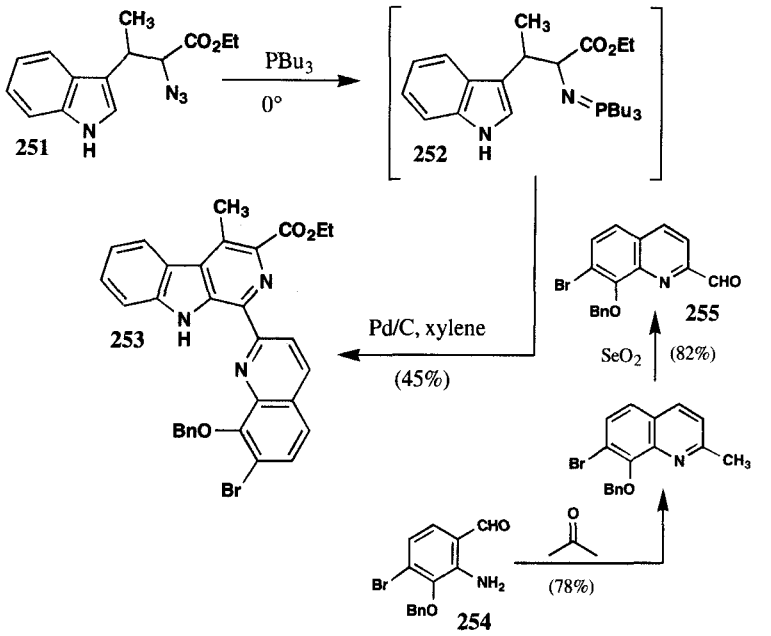


Fig. 53

The synthesis of fascaplysin **17** also utilized **256**. β-Carbolines **259a-c** were produced by heating **256** with arylglyoxals **258a-c** in a sealed tube at 160°. Though heating **259a** and **259b** at reflux in formic acid failed to produce fascaplysin **17**, yielding **260** instead, **259c** could be converted to **17** as shown (*Fig.* 54).

Iminophosphoranes similar to **256** can also be used to prepare β-carbolines substituted with heteroatoms at C-1. For example, heating **245** (*Fig.* 55) with aromatic isothiocyanates at reflux in toluene for 12 hours produced β-carbolines **263** in good yield, presumably via the corresponding carbodiimides **262**.[117b] Heating **245** with carbon disulfide under similar conditions only produced isothiocyanate **264**, but heating **264** at 170° (in the absence of solvent) then produced β-carbolinethione **265** in 90% yield. Similarly, amide **266** could be converted into the corresponding substituted β-carbolines **267** and **268**.[121]

β-Carbolines possessing heteroatoms at C-1 have also been made by another variation on the Pictet-Spengler reaction (*Fig.* 56). When **269**, prepared from tryptophan ethyl ester and *N*-methylisatoic anhydride, was heated with triethyl orthoformate, tetrahydro-β-carboline **270** was formed in 70% yield. Dehydrogenation with palladium on carbon then induced a rearrangement to produce **271** (a hybrid between a β-carboline and a 1,4-benzodiazepine) in 42% yield.[122]

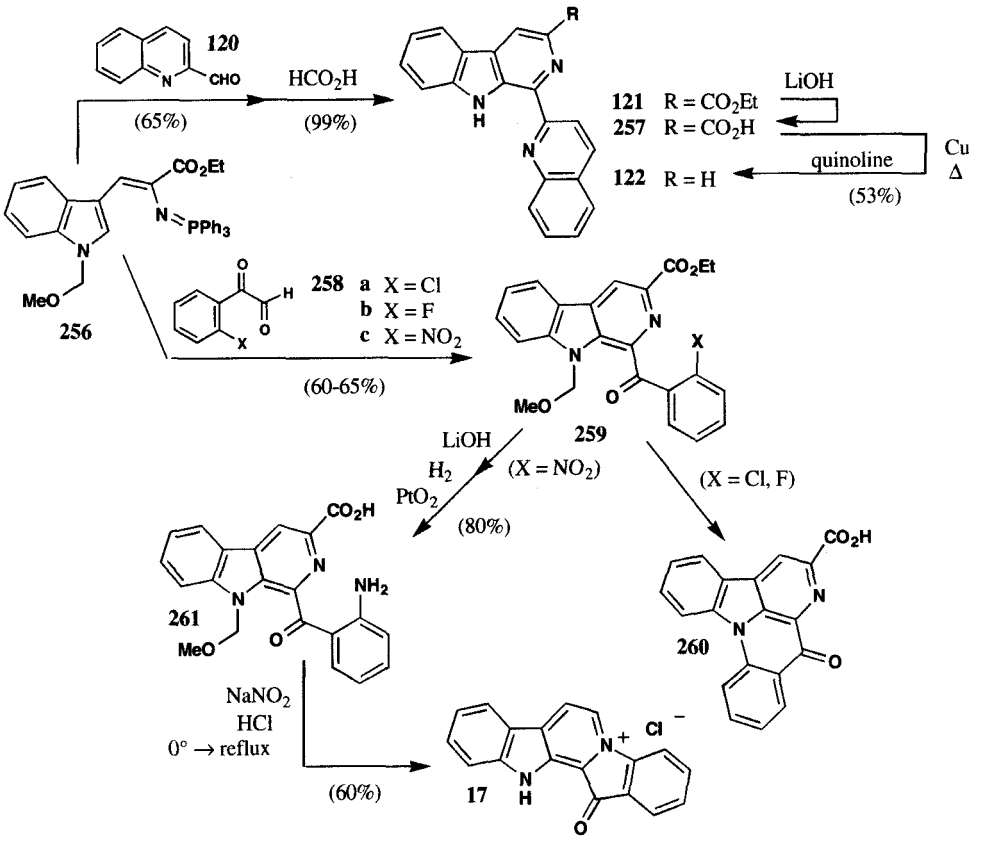


Fig. 54

Trimethyl orthoformate has also been used to prepare dihydro-β-carboline **273** from hydroxylamine **272** (*Fig.* 57).[123,124] Oxidation with DDQ then produced β-carboline *N*-oxide **274** quantitatively. Alternatively, if **273** was allowed to sit for three weeks, ester **27** was isolated, also in quantitative yield.

N-hydroxytryptamine derivatives such as **272** are usually prepared by either of two routes (*Fig.* 58).[125] Reaction of indole with nitrosoalkenes (generated *in situ* from the corresponding α-halooximes) produces oximes **275**, which can be reduced to hydroxylamines **276**. This method is generally only useful for the preparation of compounds in which R is an electron withdrawing group.

Alternatively, gramine can be methylated and reacted with aliphatic nitro compounds (in one step) to give nitroindoles **277**, which likewise can be reduced to **276**. This approach is applicable to a variety of nitro compounds, though when R = H, a large excess of nitromethane must be used in order to lessen the formation of the corresponding bisindole.

Interestingly, β-carbolines possessing sulfur at C-1 can also be made via indole oximes such as **275**. For example, reaction of indole-2-carboxaldehyde **233** with nitrosoalkene **278** (*Fig.* 59) produced **279** in 69% yield.[124] Treatment of **279** dissolved in thioacetic acid with trifluoroacetic acid at 4° for 18 hours yielded β-carbolinethione **280** in 81% yield.[126]

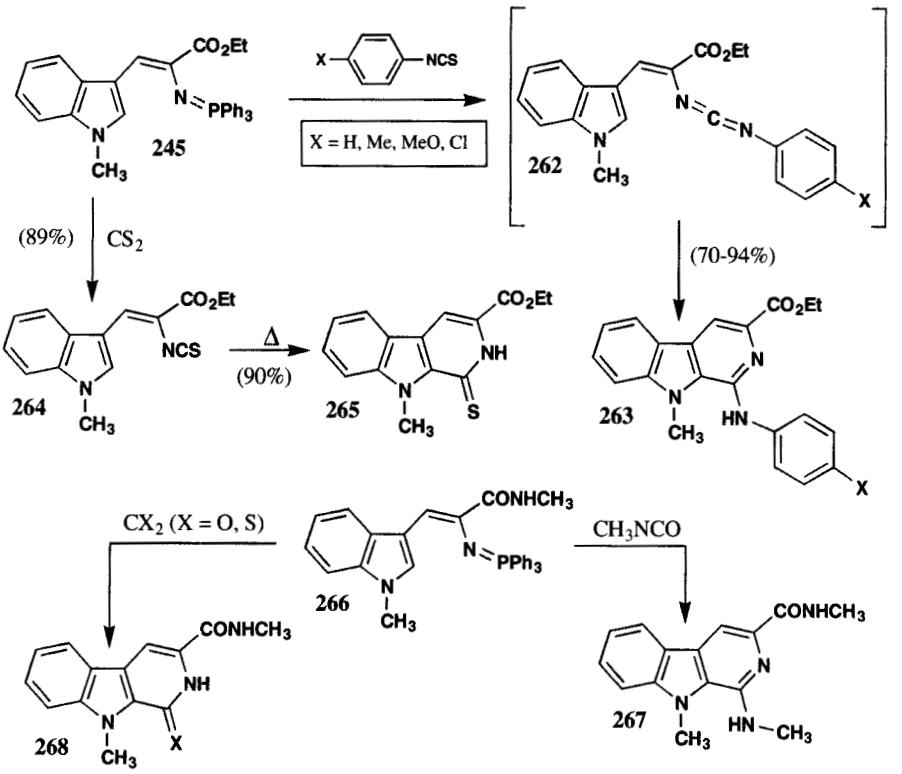


Fig. 55

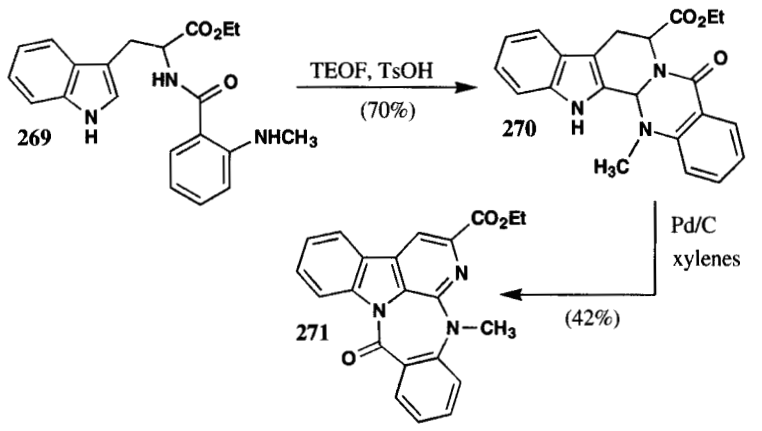


Fig. 56

Indole oxime **281** has also been used in a somewhat unusual β-carboline synthesis (*Fig.* 60).[127] Alkylation of **281** with protected 4-chlorobutanal **282** produced **283**, which, upon treatment with HCl in THF, gave β-carboline **284** in 96% yield (attempts to reduce **283** to the corresponding hydroxylamine derivative with trimethylamineborane in the presence of HCl also gave a small amount of **284**). Formation of **284** is apparently occurring by means of an intramolecular Pictet-Spengler reaction.

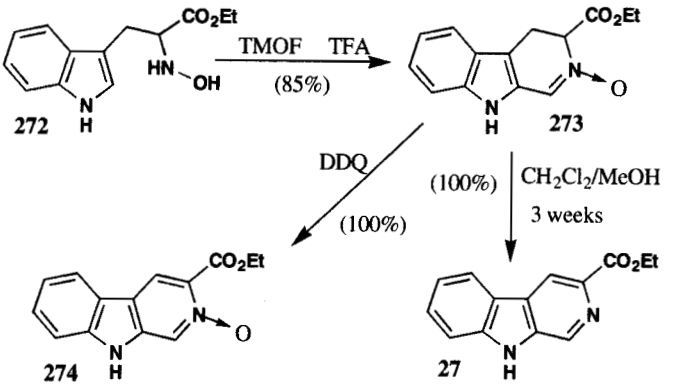


Fig. 57

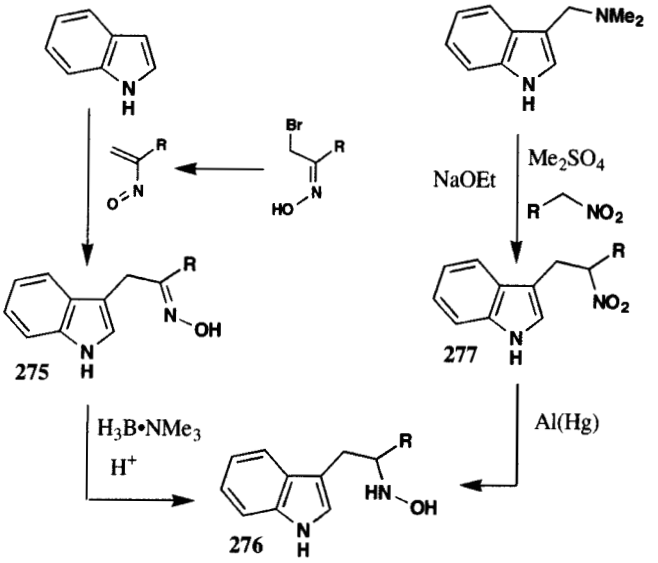


Fig. 58

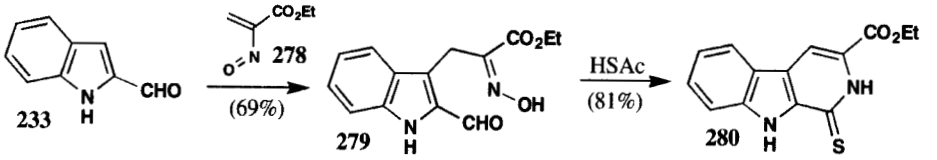


Fig. 59

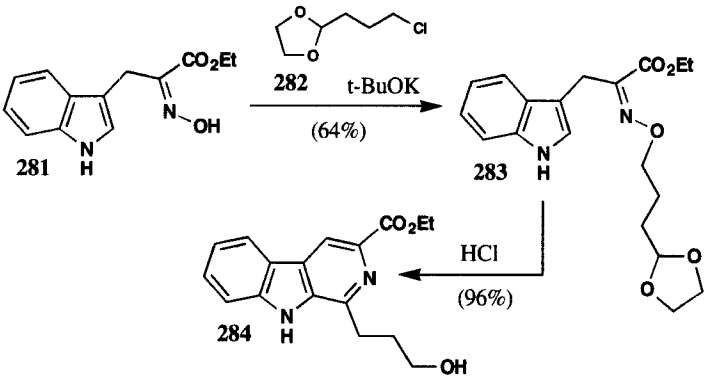


Fig. 60

Gribble has recently reported another interesting route to the natural product fascaplysin **17** (*Fig.* 61).[128] Treatment of bisindole **285** (available in 82% overall yield in four steps from indole),

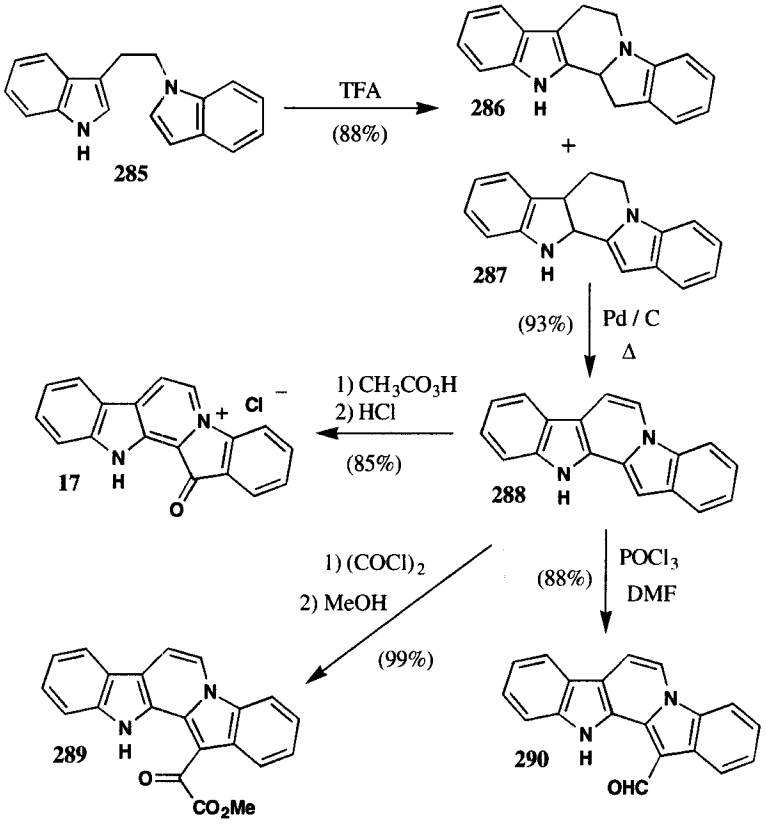


Fig. 61

with trifluoroacetic acid (TFA) at room temperature for thirty minutes produced a 10:1 mixture of **286**:**287**. Dehydrogenation of this mixture with palladium on carbon by heating at 180-190° in

2-ethoxyethyl ether provided **288** in 93% yield. Oxidation of **288** with peracetic acid followed by concentrated hydrochloric acid completed this exceptionally short synthesis of fascaplysin **17**. The natural products homofascaplysin B **289** and homofascaplysin C **290** were likewise prepared by electrophilic attack on pentacyclic intermediate **288**, as shown in *Fig.* 61.

One final method of producing β-carbolines via cyclization to form a pyridine ring is one which closely resembles the Bischler-Napieralski cyclization. Patterned after the work of Livinghouse,[129] Cardellina has used isonitrile **291** (*Fig.* 62) to prepare eudistomins I **45a** and T **62a**.[130] Acylation of **291** with phenacyl chloride produced an α-ketoimidoyl chloride, which was not isolated, but was instead treated with silver tetrafluoroborate to give dihydro-β-carboline **292** in 92% yield. Though several traditional dehydrogenation reagents failed to give good yields of the corresponding β-carboline, it was found that heating at 200° for 4 minutes with elemental sulfur both oxidized and deprotected **292**, giving eudistomin T **62a** in 73% yield.

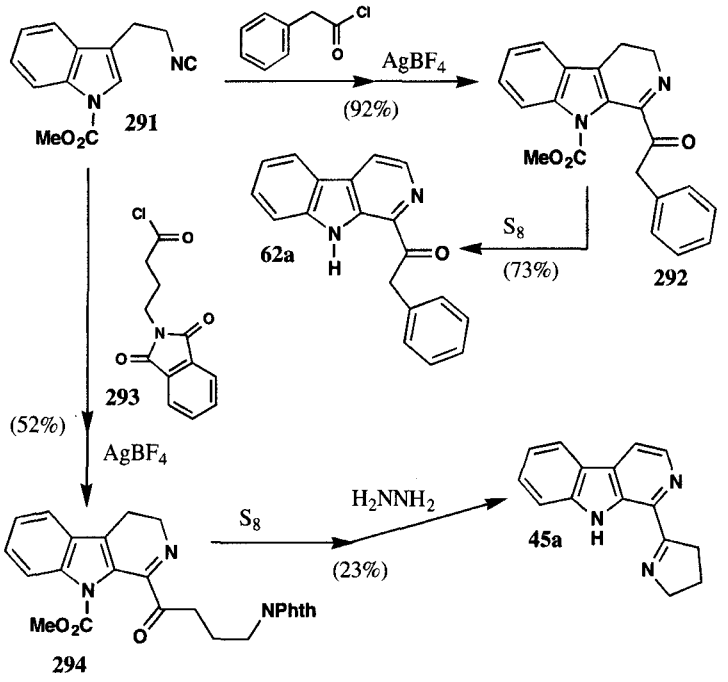


Fig. 62

Eudistomin I **45a** was prepared in a similar manner by reacting **291** with 4-phthalimidobutyryl chloride **293** followed by silver tetrafluoroborate, to give **294** in 52% yield. Oxidation with sulfur at 200° followed by deprotection and cyclization promoted by methanolic hydrazine produced eudistomin I **45a** in 23% yield.

2. Annulation of the Indole Ring

Although starting with a preformed indole ring is by far the most common strategy adopted for the synthesis of β-carbolines, a number of synthetic approaches have been reported in which

cyclization to form an indole ring is the key step in putting together the β-carboline ring system. For example, in Boger's synthesis of lavendamycin methyl ester **135**,[119,131] pyridine derivative **295** (*Fig.* 63) was treated with 1.5 equivalents of Pd(0) at 100° for 36 hours to give β-carboline **296** in 89% yield. Condensation of **296** with aminoaldehyde **254** produced **297**, which was then debenzylated with HBr to give **298**. Oxidation of **298** with Fremy's salt gave the corresponding quinone **140**, the bromine of which was cleanly displaced using sodium azide, though these last two reactions were somewhat sensitive to reaction conditions. Finally, lavendamycin methyl ester **135** was produced by reduction of the azide using triphenylphosphine. The cyclization precursor, pyridine derivative **295**, was prepared in 10 steps in 6.5% overall yield starting with an inverse electron demand Diels-Alder reaction between enamine **299** and triazine **300**.[119,131]

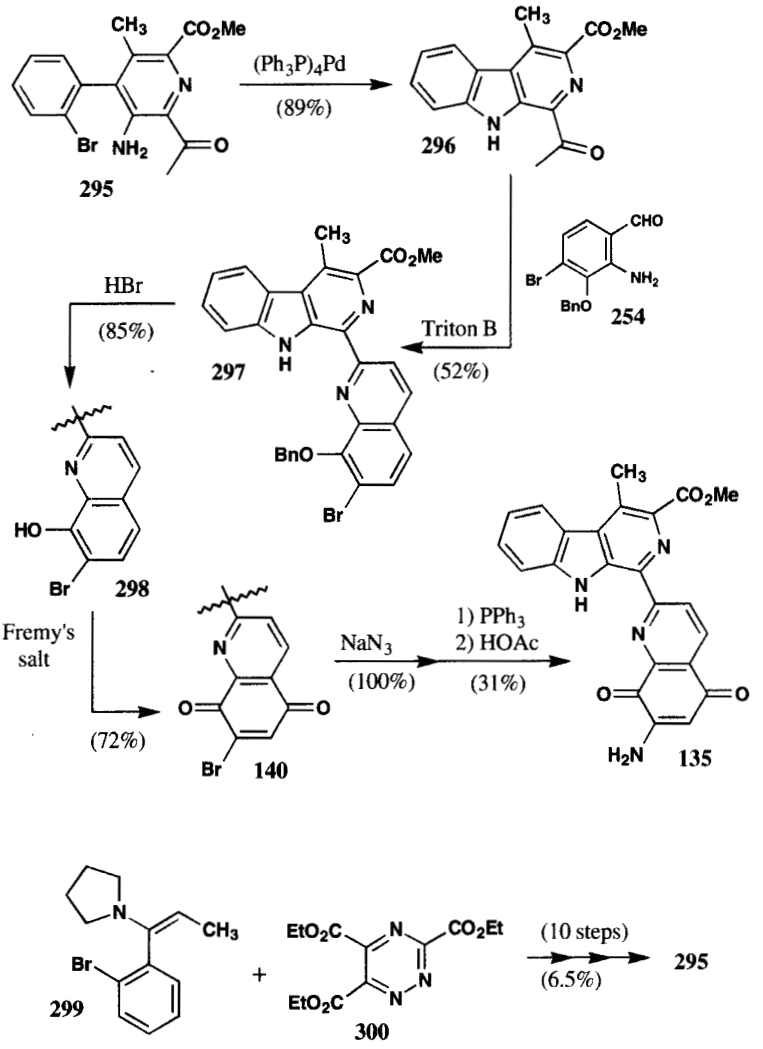


Fig. 63

Cyclization via nucleophilic attack on a pyridyl halide has also been reported recently by Quéguiner.[132] The requisite aryl pyridine **304** was prepared in high yield via Suzuki coupling (*Fig.* 64), and cyclization was effected by heating **304** at reflux (210°) in anhydrous pyridinium chloride (it was found that **304** could not be cyclized under either neutral or basic conditions).

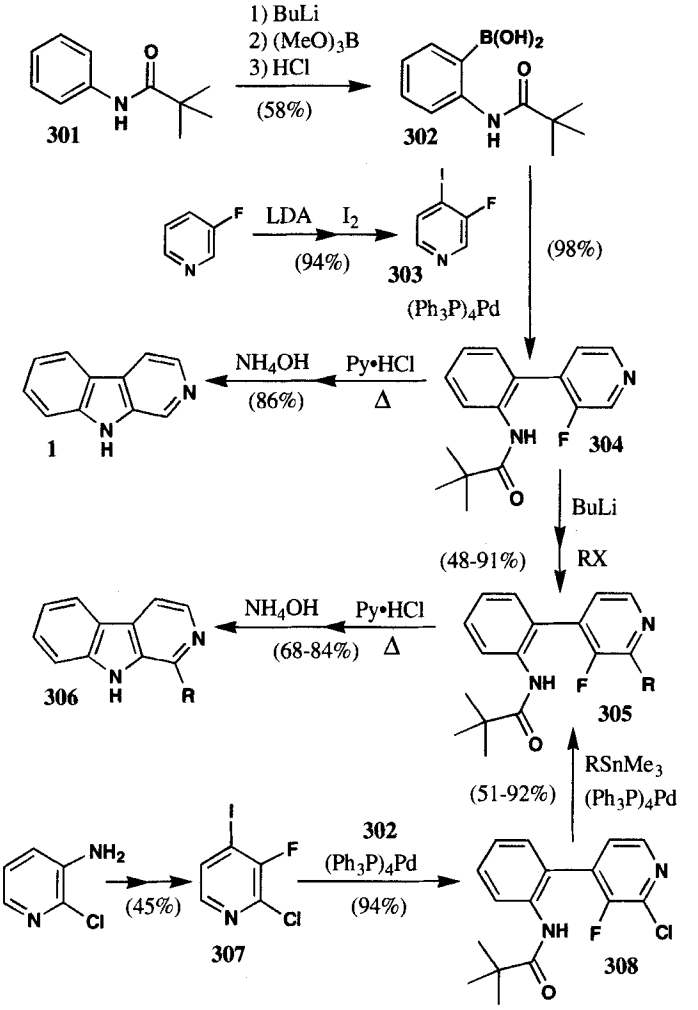


Fig. 64

β-Carbolines substituted at C-1 have also been prepared by this method.[133] For example, lithiation of **304** with BuLi followed by treatment with any of a variety of electrophiles produced 2-substituted pyridines **305**, which could be cyclized to the corresponding β-carbolines **306** under the same conditions used to prepare **1**. Alternatively, pyridines **305** (R = aryl) were prepared by coupling chloropyridine **308** with aryl stannanes.[134] Chloropyridine **308** was itself prepared by coupling **302** with 2-chloro-3-fluoro-4-iodopyridine **307** (prepared in two steps in 45% overall yield from 2-chloro-3-aminopyridine).

Quéguiner has used this methodology to prepare several β-carboline natural products. For example, both 6-hydroxyharman **313**[135] and fascaplysin **17**[136] (*Fig.* 65) have been synthesized by this method. Compound **318**, an analogue of lavendamycin, has also been prepared using this synthetic strategy (*Fig.* 66).[137] The requisite aryl stannane **315** was prepared in 85% yield from the corresponding bromoquinoline, while aryl pyridine derivative **314** was prepared in 83% yield from **302** and the corresponding 4-iodopyridine derivative, itself prepared in 5 steps and 32% yield from nitroacetamide.[138]

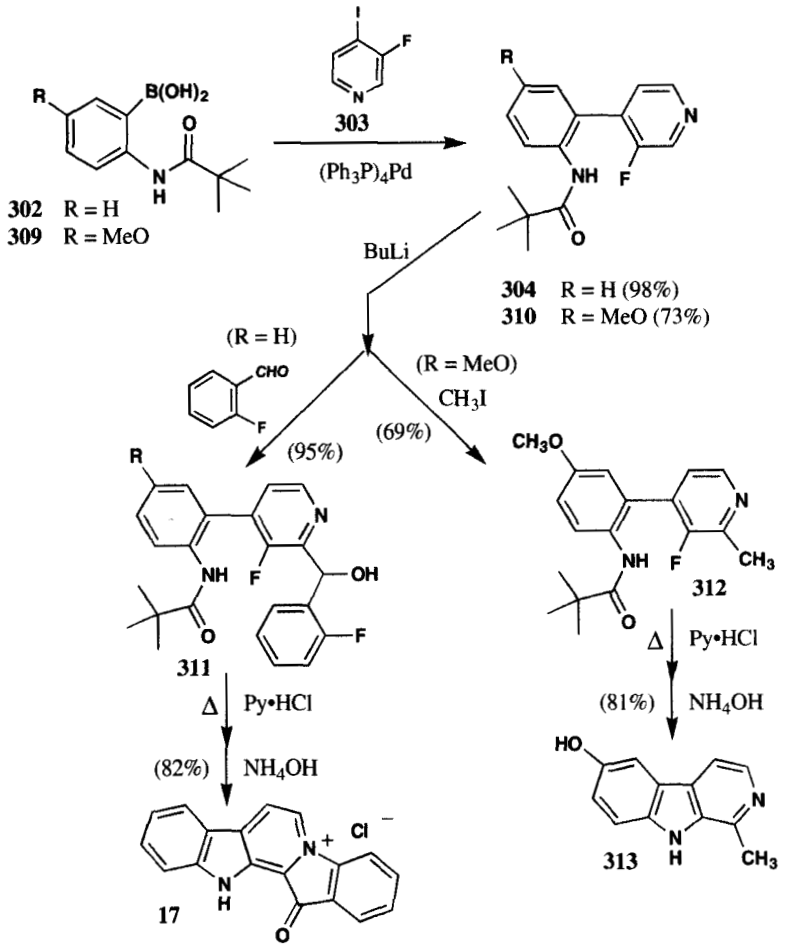


Fig. 65

Ciufolini has recently reported another route to lavendamycin analogues in which formation of the β-carboline also proceeds by cyclization to form the indole ring (*Fig.* 67).[139] Condensation of quinoline **319** with 2-azidobenzaldehyde produced chalcone **320**, which was cyclized with 2-ethoxy-2-butene (along with 2-ethoxy-1-butene) in the presence of $Yb(fod)_3$ to give dihydropyran **321** in "nearly quantitative" yield. Conversion of the dihydropyran into a pyridine ring was accomplished with hydroxylamine hydrochloride, and the methyl group at C-2 of this pyridine ring could be selectively oxidized to the corresponding aldehyde using freshly sublimed selenium dioxide. Thermolysis

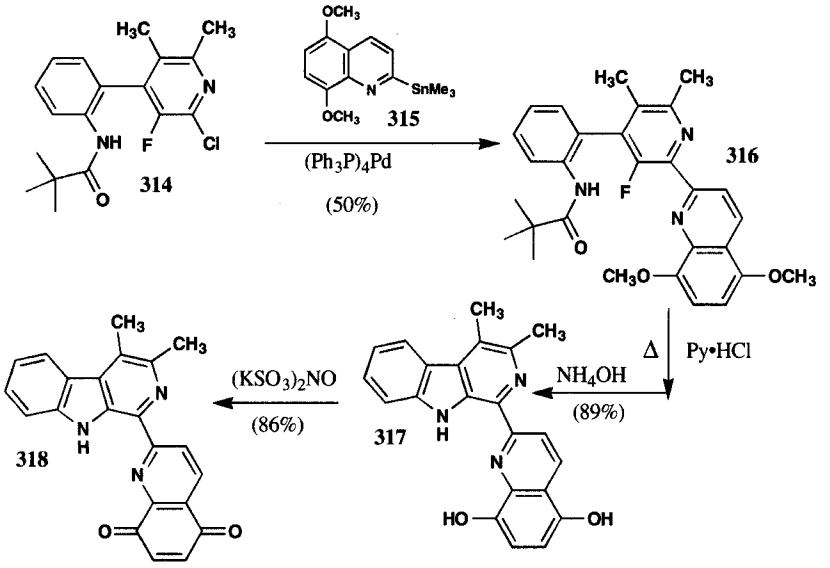


Fig. 66

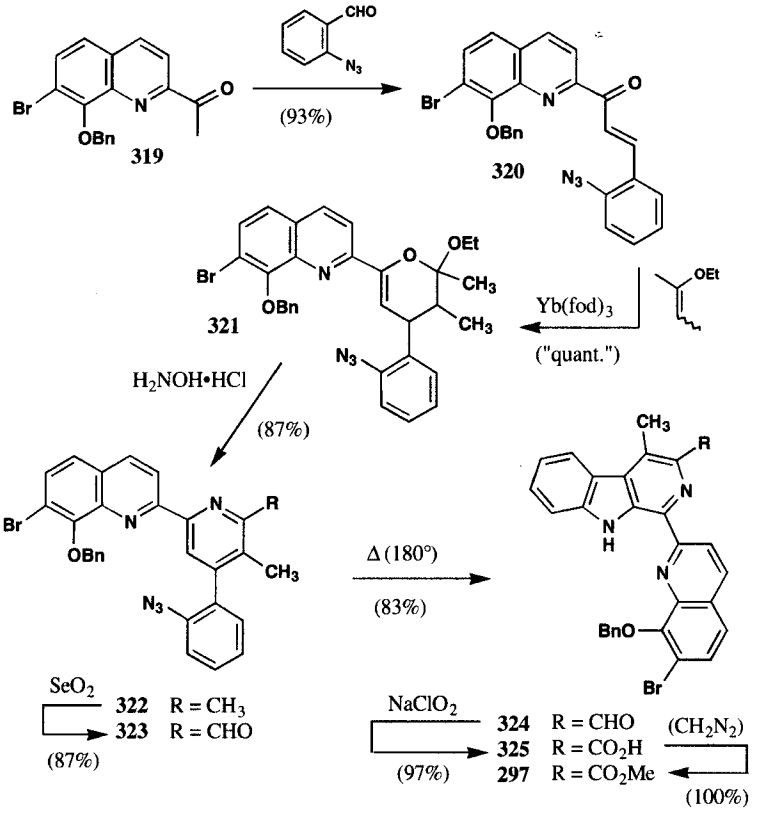
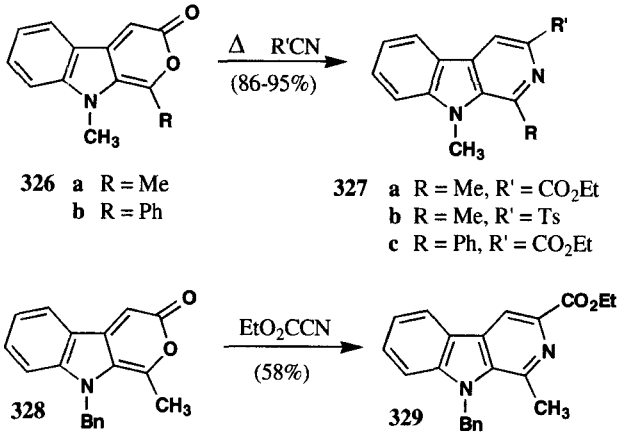


Fig. 67

of the azido functionality by heating **323** at reflux in o-dichlorobenzene furnished β-carboline **324** in 83% yield. Oxidation of the aldehyde and subsequent esterification produced ester **297**, thus completing Ciufolini's formal total synthesis, as **297** was an intermediate in Boger's synthesis of lavendamycin methyl ester.

B. Cycloaddition Methods

Thus far we have considered synthetic routes to β-carbolines which proceed via cyclizations. A few methods in which the β-carboline nucleus is prepared utilizing cycloaddition methodology have also been reported. For example, Hoornaert has reacted pyrano[3,4-b]indoles **326** (*Fig.* 68) with electron-deficient nitriles such as ethyl cyanoformate and *p*-toluenesulfonyl cyanide to give β-carbolines **327** in high yield via a Diels-Alder/retro Diels-Alder sequence.[140] The requisite pyrano[3,4-b]indoles can be prepared from indole-3-acetic acid by reaction with an anhydride in the presence of boron trifluoride etherate.[141] The *N*-benzyl analog **328** could also be used, although the yield was somewhat lower, while reaction of N-unsubstituted pyrano[3,4-b]indoles with ethyl cyanoformate reportedly results in acylation.



326 **a** R = Me
b R = Ph

327 **a** R = Me, R' = CO_2Et
b R = Me, R' = Ts
c R = Ph, R' = CO_2Et

328

329

Fig. 68

Cycloadditions in which the indole moiety serves as the dienophile have also been investigated. While intermolecular reactions between indole and 1,2,4-triazines frequently give low or nonexistent yields of β-carbolines (γ-carbolines often being the major product),[142] Snyder has demonstrated that intramolecular cycloadditions can be used to produce tetracyclic β-carbolines **333** in very good yield (*Fig.* 69).[143] Indole and substituted indoles were converted to 4-(1-indolyl)butyric acids **330** in excellent yield by treatment with potassium hydride followed by γ-butyrolactone. (Only the synthesis utilizing indole is shown). Esterification followed by treatment with hydrazine then yielded the corresponding hydrazide **331**, which in turn produced 1,2,4-triazines **332** when reacted with 1,2-dicarbonyl compounds.[144] Heating **332** at reflux in triisopropylbenzene produced β-carbolines **333** in good yield, once again via a Diels-Alder/retro Diels-Alder sequence, though followed by an air oxidation to produce the fully aromatic **333**.

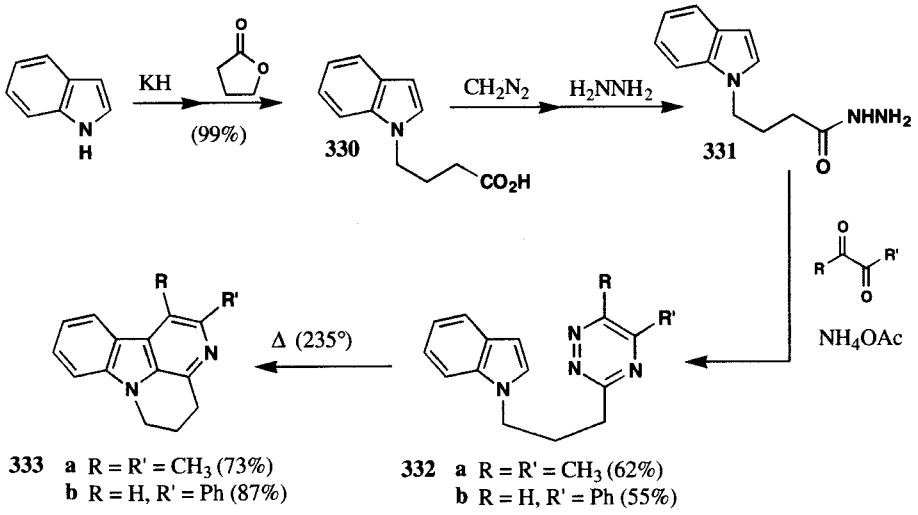


Fig. 69

Other triazines **332** were also prepared using slightly different methodology, and produced the corresponding β-carbolines in comparable yields. Use of shorter and longer "tethers," leading to five-membered and seven-membered rings, respectively was also investigated. Yield of the five-membered ring product was only 4%, while the seven-membered ring analogs were produced in yields ranging from 38-51%.

Snyder has further extended the utility of this synthetic method by oxidizing these tetracyclic β-carbolines with benzyltriethylammonium permanganate (BTAP) to give canthin-6-one and substituted analogs **334** (*Fig.* 70).[145] Yields for these oxidations were generally good, though somewhat sensitive to reaction conditions.

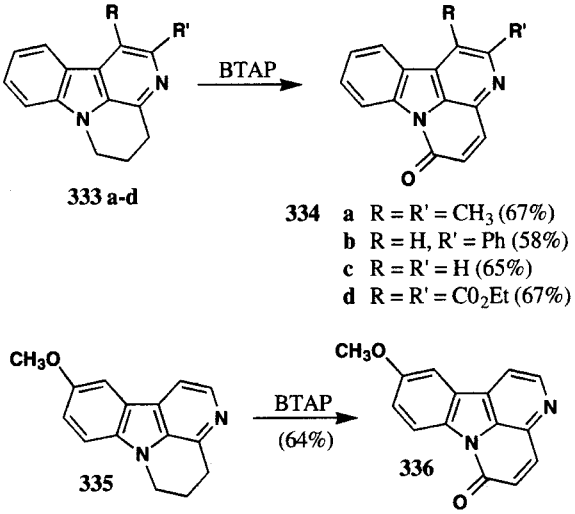


Fig. 70

II. FUNCTIONALIZATION OF β-CARBOLINES

Thus far we have examined a variety of methods by which the β-carboline nucleus may be prepared. We shall now consider very briefly a few significant reactions of β-carbolines. Though clearly thousands of reactions have been performed on β-carbolines, we shall restrict our attention to a few examples in which simple β-carbolines are easily elaborated into either more complex derivatives or natural products.

A. Introduction of New Functionality at Unsubstituted Positions

Simple halogenation has been used to prepare halogen-containing β-carboline natural products. For example, β-carboline **1**, upon treatment with bromine in THF produces eudistomin N **337** (*Fig.* 71).[27] Similarly, bromination of 6-methoxy-β-carboline **338**, followed by demethylation produces eudistomin D **340**.

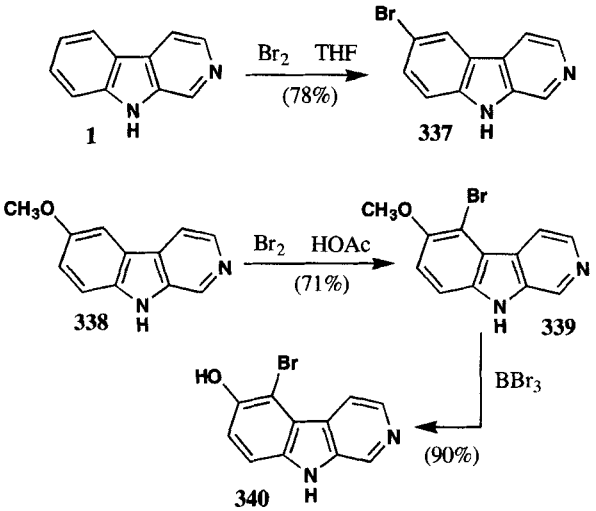


Fig. 71

More recently, lithiation has been shown to be an effective means by which substituents may be introduced into the β-carboline ring system. For example, Dodd lithiated β-carboline amide **342** using methyllithium (other lithiating agents were found to be less satisfactory) and introduced a variety of electrophiles at C-4 (*Fig.* 72).[146] Yields for these reactions were generally quite good.

B. Transformation of Existing Functional Groups

Selective introduction of substituents into the β-carboline ring system has also been achieved by reactions involving simple substituents already present. For example, harman **2**, when heated with benzaldehyde, produces the corresponding alkene **348** in 84% yield (*Fig.* 73).[147] Protection of **348** followed by ozonolysis allows introduction of an aldehyde group at C-1.[148] Kelly has used aldehyde **349** in his synthesis of the reported[149] structure of maxonine **350**, and has used alkene **348** in his synthesis of the actual structure of maxonine **351**.

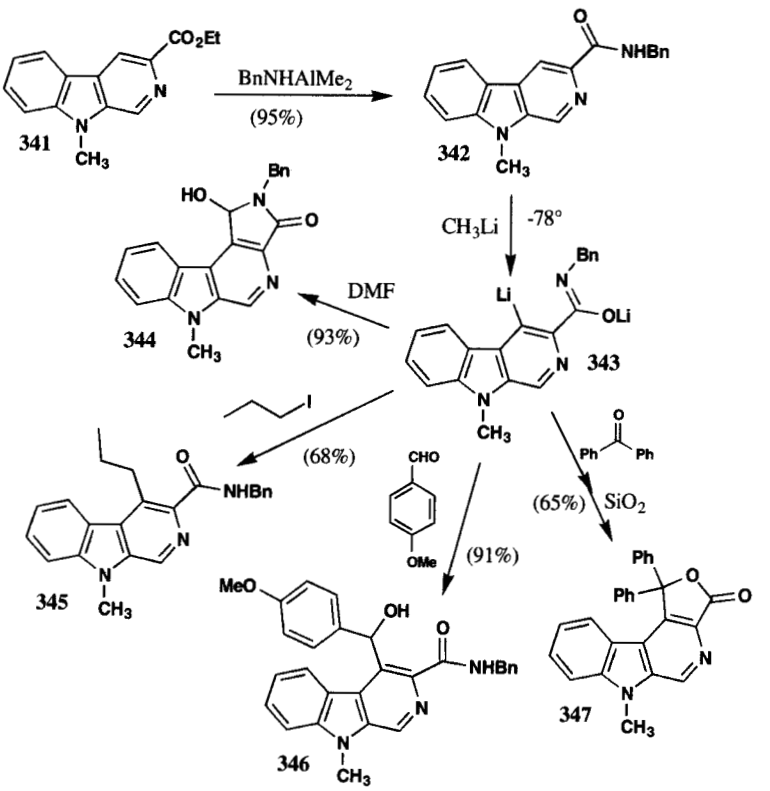


Fig. 72

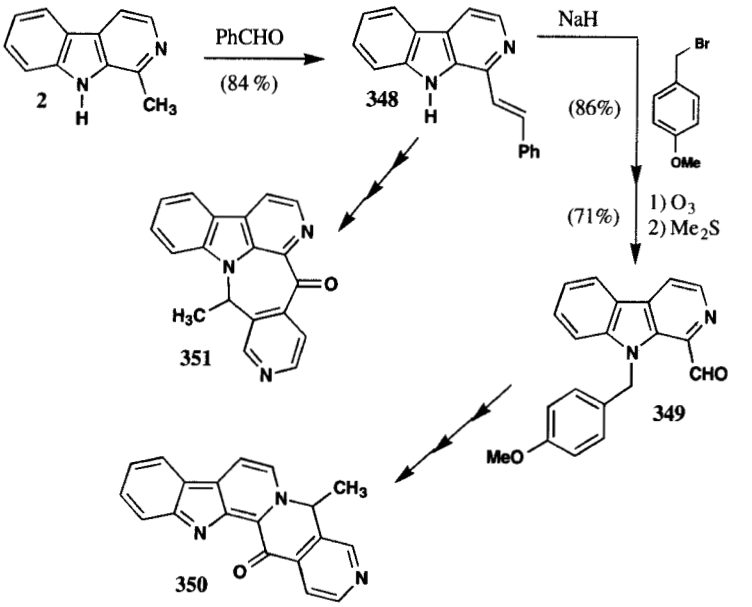


Fig. 73

Aldehyde **353** has been prepared by selenium dioxide oxidation of β-carboline ester **352** (*Fig.* 74).[150] Heating **353** at reflux with pyridine in either acetic or propionic anhydride then provided canthin-6-one derivatives **354** in good yield.

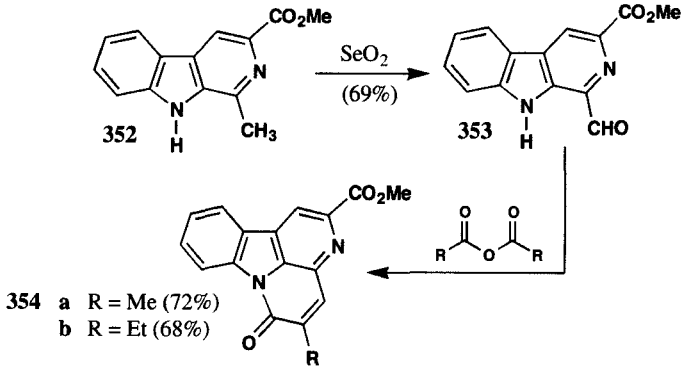


Fig. 74

Bracher has made extensive use of palladium-catalyzed coupling reactions to produce substituted β-carbolines from the corresponding halogenated derivatives. 1-Chloro-β-carboline **357**, prepared in three steps and 49% yield from tryptamine has been coupled with phenylboronic acid to produce 1-phenyl β-carboline **358** in excellent yield (*Fig.* 75).[151] This methodology was also used to prepare natural products komaroin **359** and perlolyrine **14**, although the yields in these syntheses were significantly lower.

Simple 1-alkyl β-carbolines have also been prepared by reaction of **357** with alkyl boranes or organoaluminum reagents. For example, harmane **2** was prepared by treatment with trimethylaluminum followed by aqueous work-up.[152] Similarly, 1-ethyl-β-carboline **360** (also a natural product) was prepared using triethylboron.

Bracher has also coupled **357** with organotin reagents to synthesize a number of other β-carboline natural products (*Fig.* 76). For example, reaction with tributylvinylstannane produced 1-vinyl-β-carboline **361** ("pavettine").[151] Similarly, palladium-catalyzed coupling of **357** with tributyl(1-ethoxyvinyl)stannane, followed by hydrolysis, produced 1-acetyl-β-carboline **363** in 83% yield, which was then easily transformed into nitramarine **122**, annomontine **366**, and 1-(1-hydroxyethyl)-β-carboline **364**.[153] The bromine analog of **357**, 1-bromo-β-carboline **367**, can be used to prepare lithiated-β-carboline **368**, which in turn can be reacted with any of a number of electrophiles (*Fig.* 77).[154] Such a synthetic sequence was used to prepare the natural product pauridianthine **372** in 30% yield from **367**.

Finally, Bracher has reported an alternate route to nitramarine **122** which utilizes lithiated-β-carboline **368** (*Fig.* 78).[154] Transmetallation of **368** with zinc chloride produces an organozinc species which can undergo palladium-catalyzed coupling with 2-chloroquinoline to provide nitramarine **122** in 53% yield.

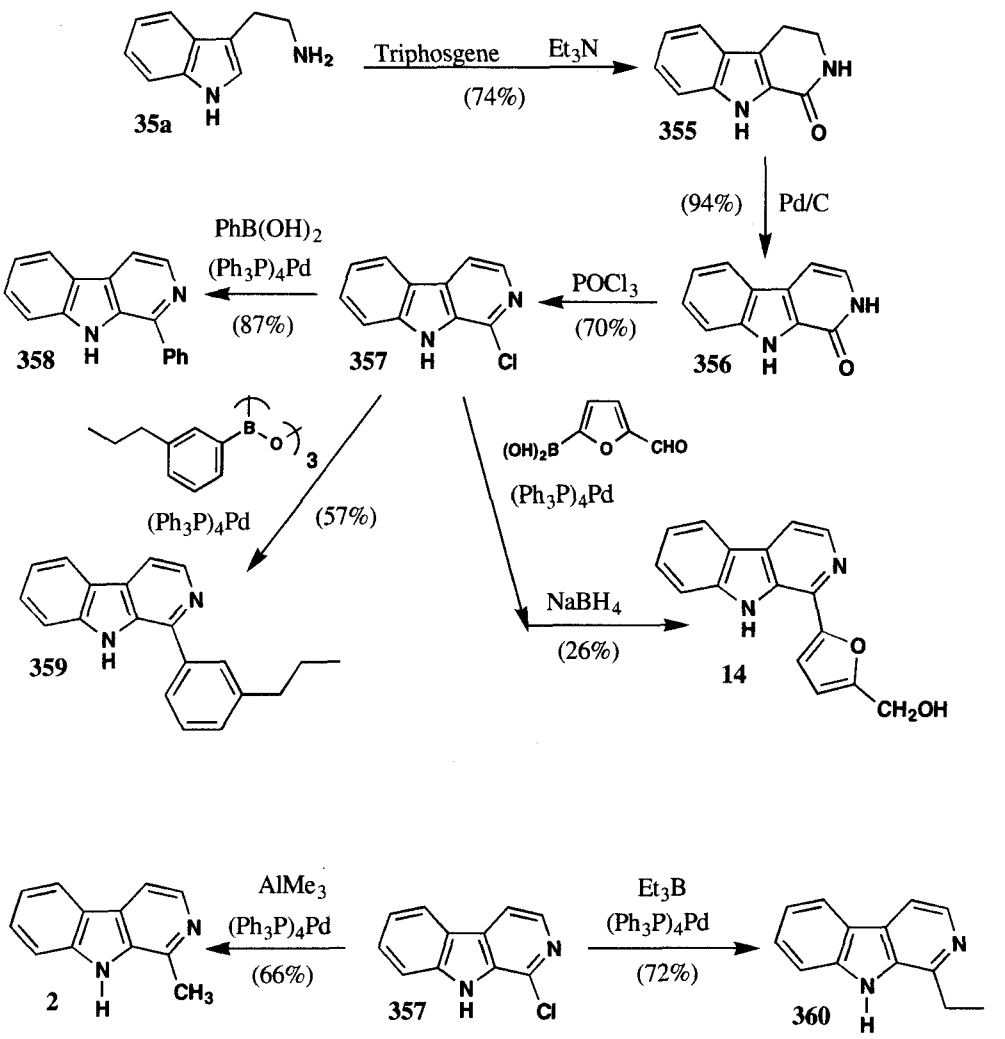


Fig. 75

III. CONCLUSION

Though the coverage of recent advances in the synthesis of β-carbolines has been far from exhaustive, one can appreciate the broad level of interest in this important ring system. New β-carboline natural products continue to be discovered, and the biological activity of a wide range of natural and synthetic β-carbolines is likewise being explored. Though traditional synthetic methods such as the Pictet-Spengler and Bischler-Napieralski reactions still find considerable use in the preparation of β-carbolines, newer methods, especially those involving organometallic species, are finding increased utility.

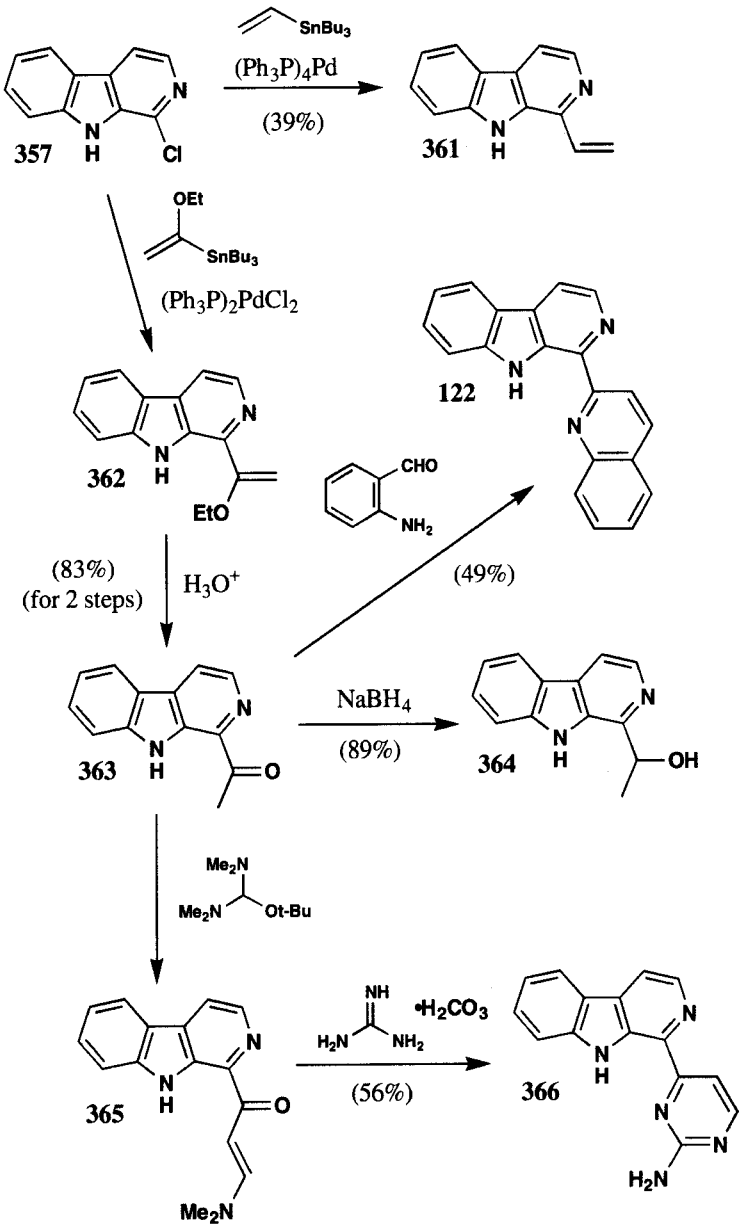


Fig. 76

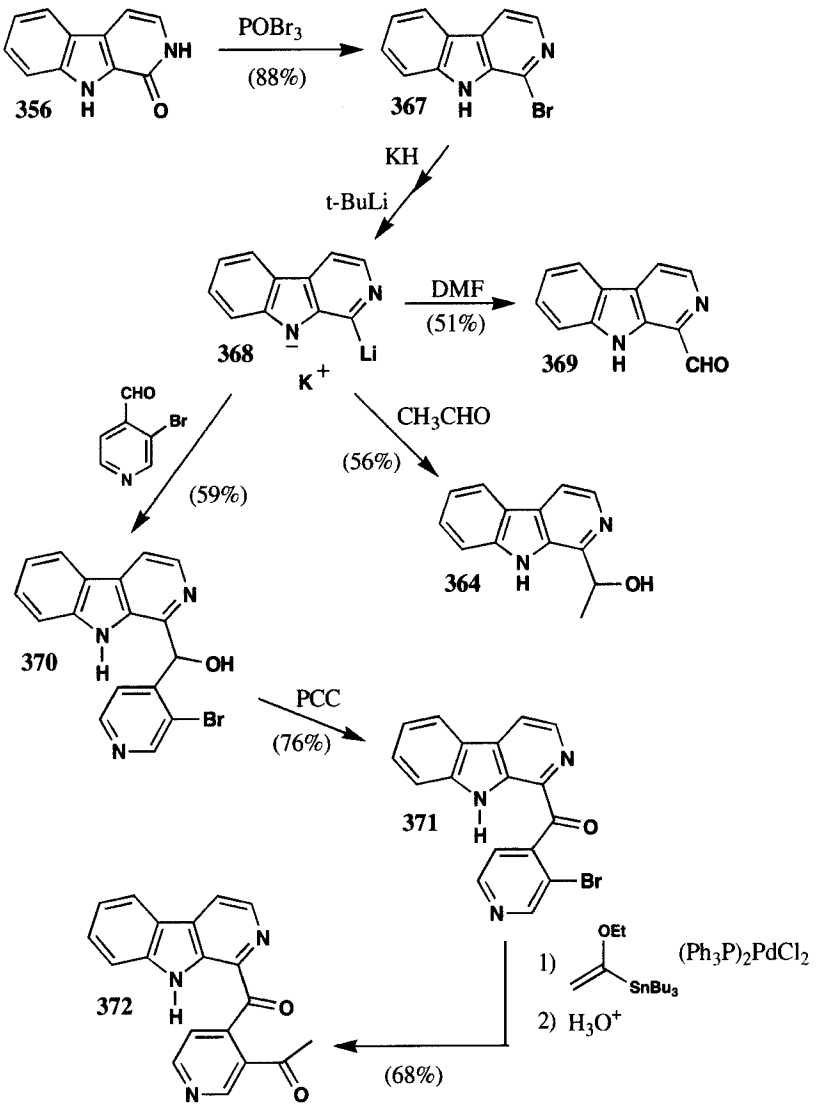


Fig. 77

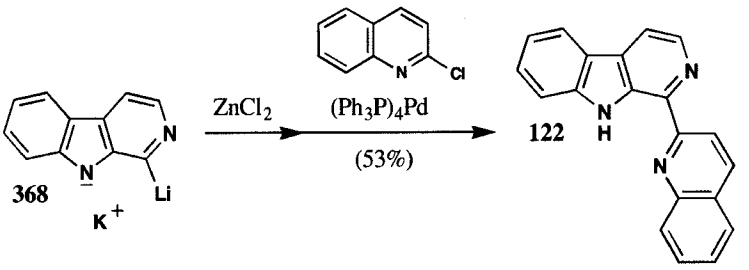


Fig. 78

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