CONNECTION BETWEEN METALATION OF AZINES AND DIAZINES AND CROSS-COUPLING STRATEGIES FOR THE SYNTHESIS OF NATURAL AND BIOLOGICALLY ACTIVE MOLECULES

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Abstract - When connected to transition metal catalyzed reaction, metalation becomes a very efficient tool for the synthesis of complex molecules. The methodology is applied to the preparation of some natural and biologically active molecules. The synthesis of streptonigrin models, orelline, azacarbazoles, ellipticine, bacimethrin analogues, trimethoprim and leshmanacides is presented here.

CONTENTS

1. Introduction.

In view of the broad scope of the directed metalation reaction, its connection to the transition metal-catalyzed cross coupling reaction becomes an efficient tool for asymetrical biaryl constructions and thus for synthesis of natural products containing such framework.

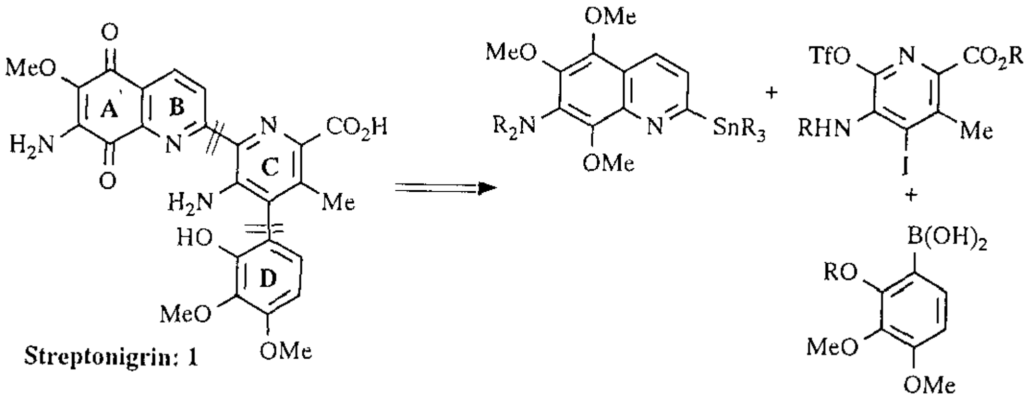
Metalation of π-deficient heterocycles is studied and developped by our laboratory.[1] This methodology allows the functionalisation of azines and diazines in good yields with a high regioselectivity.

On the other hand, the transition metal catalyzed cross-coupling reaction of organometallic reagents with organic halides is an important synthetic methodology for carbon-carbon formation.[2]

It was thus interesting to connect these two methodologies to synthesize complex polyaromatics of biological interests.[3] We wish to present here our syntheses of natural or biologically active molecules based on such strategies.

2. A convergent synthesis of streptonigrin models.

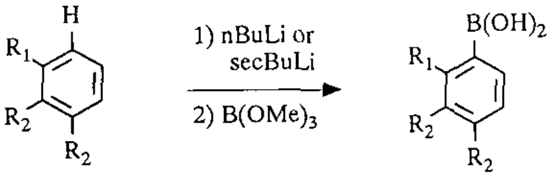
Steptonigrin (**1**) is an antitumor antibiotic produced by *Streptomyces flocculus*.[4] This alkaloid has been shown to possess antitumor and antiviral activity. Its structure incorporates a highly substituted 2-(2-pyridyl)-5,8-quinone.[5] The biological properties and potential applications of this alkaloid (**1**) has led to many studies on its synthesis as well as for analogues.[6] This research has resulted in three elegant total syntheses[7] which involve multistep routes with mild or poor over-all yields. Thus we have investigated a new approach to streptonigrin using metalation and palladium catalyzed cross-coupling reactions as key steps of the synthesis[8] (Scheme 1).



Scheme 1

2-1 Synthesis of phenyl precursors of D ring.

Phenyl boronic acids (**2**) were most often prepared by directed metalation followed by boronation with $B(OMe)_3$ (Scheme 2).



2

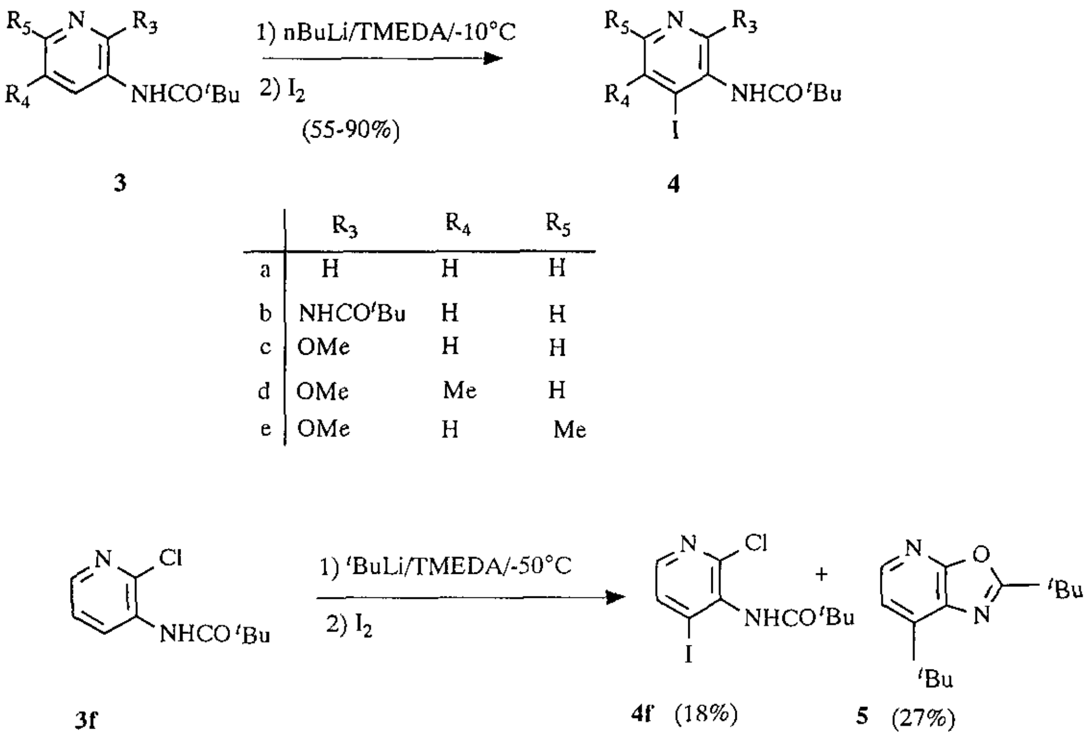
	R_1	R_2
a	H	H
b	OMe	H
c	CON^iPr_2	H
d	$OCONEt_2$	H
e	$OCONEt_2$	OMe

Scheme 2

2-2 Synthesis of polysubstituted pyridines precusors of C ring.

The retrosynthetic pathway indicates that biaryl cross-coupling step requires pyridines suitably substituted at C-2 and C-4.

We previously published the functionalization of aminopyridines by metalation of 3-pivaloylaminopyridine (**3a**),[9] which was applied to prepare 4-iodo-3-pivaloylaminopyridines (**4**) as well (Scheme 3). n-Butyllithium was used for the metalation at -10°C. However, the metalation of 2-chloro-3-pivaloylaminopyridine (**3f**) with *tert*-butyllithium at low temperature (-50°C), resulted in **4f** in low yield (18%) and substential formation of 2,7-ditertiobutyloxazolo[5,4-*b*]pyridine (**5**) (27%).



3

4

	R_3	R_4	R_5
a	H	H	H
b	NHCO'Bu	H	H
c	OMe	H	H
d	OMe	Me	H
e	OMe	H	Me

3f

4f (18%)

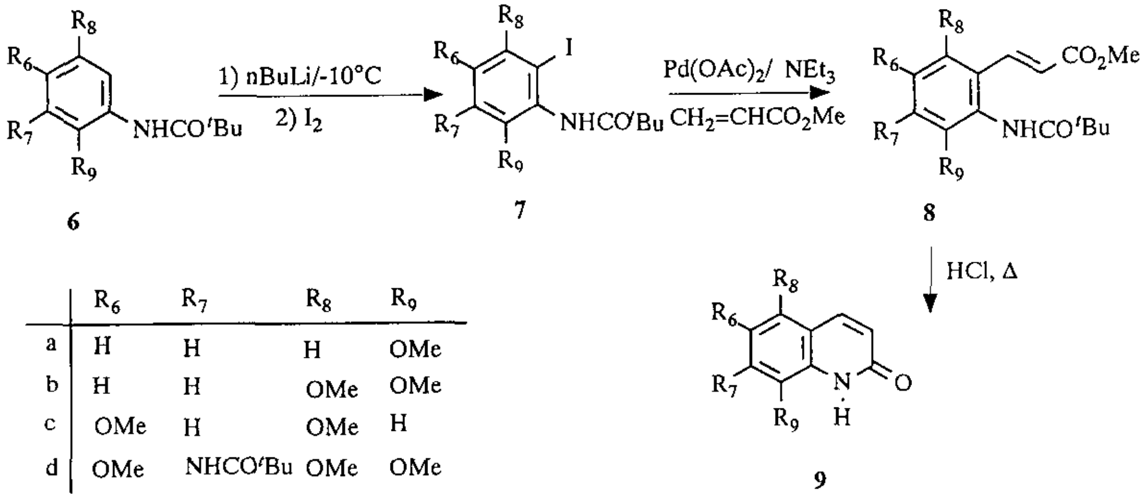
5 (27%)

Scheme 3

2-3 Synthesis of quinoline precursors of AB ring systems.

Quinolines bearing suitable groups at C-5 and/or C-8 for elaboration of the final quinone and a function at C-2 allowing the cross-coupling with the precusor of pyridine C were needed.

As shown on Scheme 4, quinolones (**8**) were derived from **6** through a series of sequences : the regioselective orthodirected metalation and iodination of **6**, followed by treatment with methyl acrylate under Heck reaction condition (**7** → **8**) and cyclisation under acidic condition (**8** → **9**) in fairly good yields. However, the reaction of methyl acrylate with hindered 1,5-dipivaloylamino-2-iodo-3,4,6-trimethoxybenzene (**7**) (R_6=R_8=R_9=OMe ; R_7=NHCO'Bu) required drastic condition, in a sealed tube at 140°C (76%).

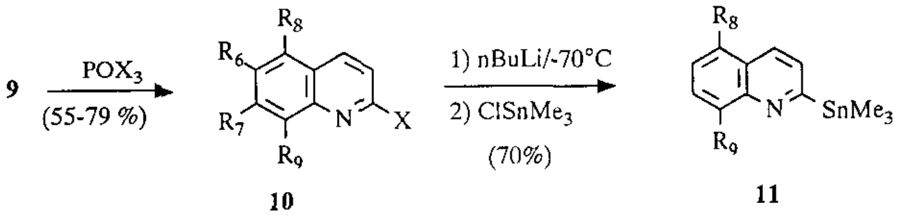


	R_6	R_7	R_8	R_9
a	H	H	H	OMe
b	H	H	OMe	OMe
c	OMe	H	OMe	H
d	OMe	NHCO^{t}Bu	OMe	OMe

(overall yield : 41%-63%)

Scheme 4

Sequentially, quinolones (**9**) were transformed to 2-halo- (**10**) and 2-trimethylstannyl quinolines (**11**) (Scheme 5).

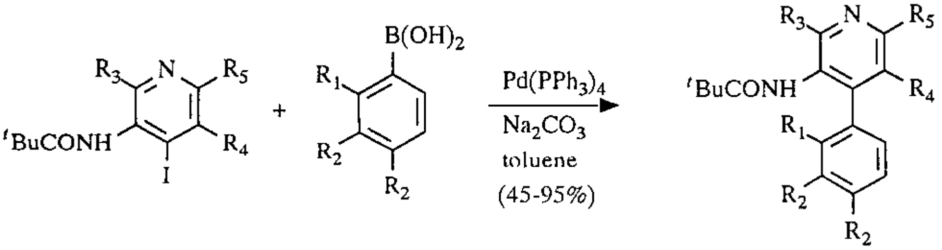


	X	R_6	R_7	R_8	R_9
a	Br	H	H	H	OMe
b	Br	H	H	OMe	OMe
c	Br	OMe	H	OMe	H
d	Cl	OMe	NH_2	OMe	OMe

Scheme 5

2-4 Synthesis of CD ring sytems.

4-Iodopyridines (**4**) were subjected to the cross-coupling reaction with phenyl boronic acids (**2**). Under Suzuki's procedure,[11] allowing the formation of expected 4-phenyl-3-pivaloylaminopyridines (**12**) in good yields (45-95%)(Scheme 6).

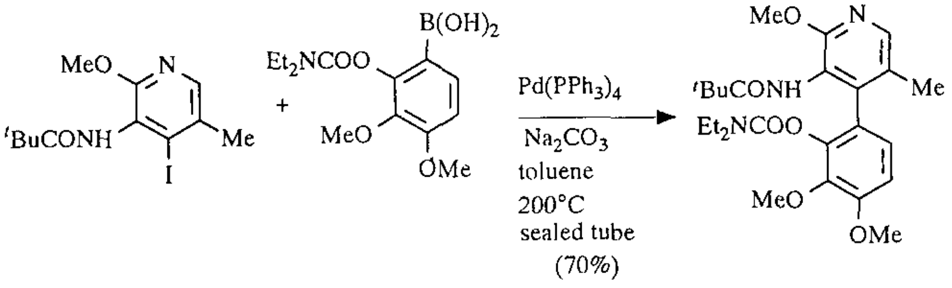


4 **2** **12**

	R_1	R_2	R_3	R_4	R_5
a	H	H	H	H	H
b	OMe	H	H	H	H
c	$\mathrm{CON^{i}Pr_2}$	H	H	H	H
d	$\mathrm{OCONEt_2}$	H	H	H	H
e	$\mathrm{OCONEt_2}$	OMe	H	H	H
f	H	H	$\mathrm{NHCO^{t}Bu}$	H	H
g	$\mathrm{OCONEt_2}$	OMe	$\mathrm{NHCO^{t}Bu}$	H	H
h	H	H	OMe	H	H
i	H	OMe	OMe	H	H
j	$\mathrm{CON^{i}Pr_2}$	H	OMe	H	H
k	$\mathrm{OCONEt_2}$	OMe	OMe	H	H
l	H	H	Cl	H	H
m	H	H	OMe	Me	H
n	$\mathrm{OCONEt_2}$	OMe	OMe	H	Me

Scheme 6

However, sterically hindered 4-iodo-5-methyl-2-methoxy-3-pivaloylaminopyridine (**4m**) and 2,3-dimethoxy-diethylaminocarbamoyloxybenzene (**2e**) resulted in only trace amount of the expected compound (**12o**), which could be improved by working under pressure in a sealed tube (Scheme 7).

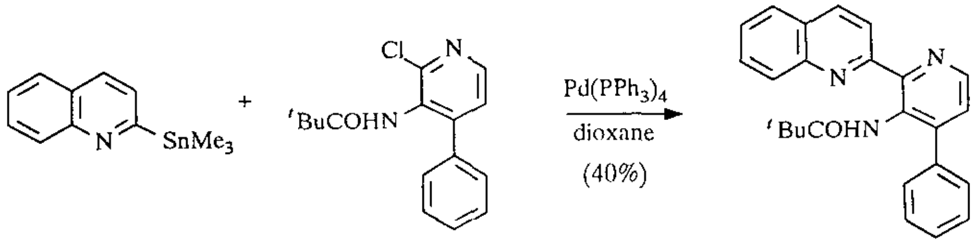


4m **2e** **12o**

Scheme 7

2-5 Synthesis of ABCD ring systems.

The reaction of 2-Chloro-4-phenyl-3-pivaloylaminopyridine (**12b**) with 2-(quinolyl)trimethylstannnane (**11a**) in the presence of $Pd(PPh_3)_4$ gave tetracyclic ring compound (**13**) in 40% yield (Scheme 8).



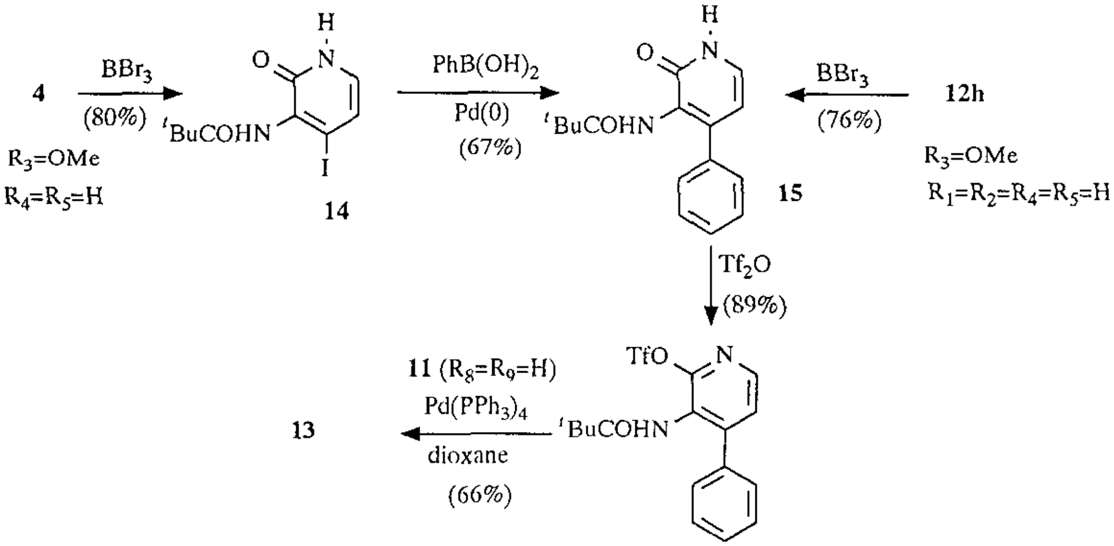
11a **12b** **13**

Scheme 8

Thus, our strategy could be shown to be effective on the transformation (**3** → **12**). However, the low overall yield (5%) obtained from the starting 2-chloro-3-pivaloylaminopyridine (**3f**) was needed to improve and another C-2 substituted pyridine ring was investigated.

Methoxy group of **12h** was transformed to triflate function in two steps. Methoxy group was first cleaved by BBr_3 to yield the 4-phenyl-2-pyridone (**15**). Pyridone (**15**) could be also obtained by the following sequences: treatment of 4-iodo-2-methoxy-3-pivaloylaminopyridine (**4c**) with BBr_3 afforded 4-iodo-2-pyridone (**14**) (80%) which was coupled with phenylboronic acid (67%). Treatment of **15** with triflic anhydride afforded 2-(4-phenyl-3-pivaloylaminopyridyl) triflate (**16**).

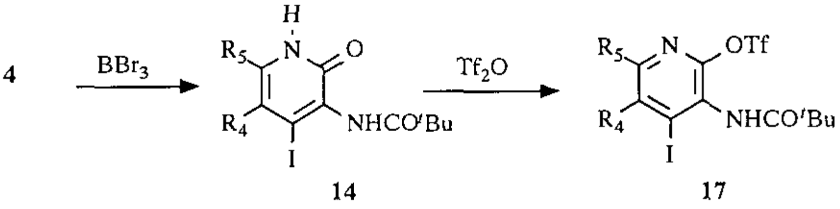
Compound (**16**) was treated with quinolylstannane (**11a**) under Stille's condition[12] to give the expected tetracyclic compound (**13**) (Scheme 9).



Scheme 9

Extension of the previous strategy to the synthesis of streptonigrin required the selective cleavage of the C-2 methoxy group on the pyridine ring in the presence of a polymethoxylated benzene ring. Selective cleavage was undertaken on some models. Unfortunately this could not be achieved either by BBr_3 or NaSEt or LiI. Reactivities between methoxy groups at C-2 on the pyridine ring and on the benzene ring are too close.

It was thus necessary to find another strategy to avoid this problem. The new methodoly was based on a more convergent route, which required preparation of polysubstituted pyridine bearing substituents sequentially usuable for the selective cross-coupling at C-2 and C-4. Thus, drawbacks of selective methoxy group cleavage on bicyclic polysubstituted CD ring system would not be required. The previously described 2-chloro-4-iodo-3-pivaloylaminopyridine (**4f**) was a suitable example. However, unsuccessful yield of **4f** led us to choose 2-(4-iodo-3-pivaloylamino)pyridyl triflates (**17**) derived from the corresponding pyridones (**14**) in good yield as shown on Scheme 10.

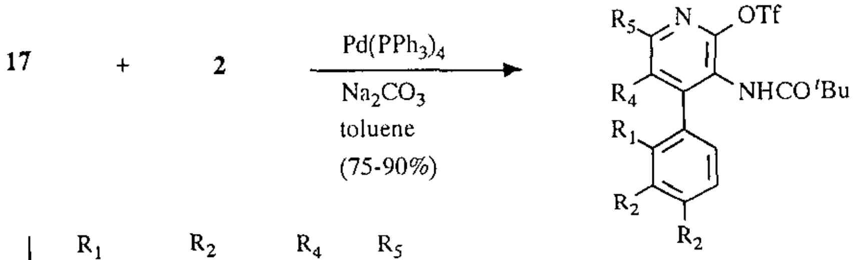


Overall yield : 66-73%

	R_4	R_5
a	H	H
b	H	Me
c	Me	H

Scheme 10

As previously described for other 4-iodopyridines, the reaction of pyridines (**17**) and phenyl boronic acids (**2**) under Suzuki's conditions afforded 2-(4-phenyl-3-pivaloylaminopyridyl) triflates (**18**) in fairly good yields (Scheme 11).

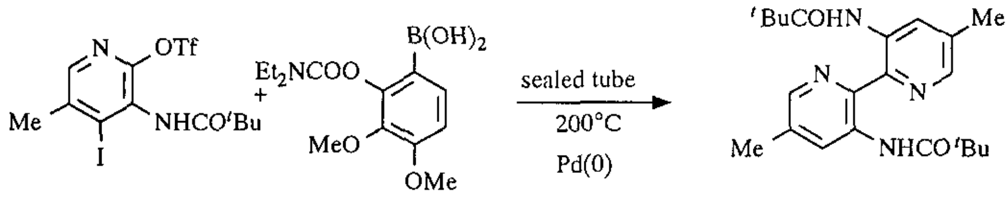


18

	R_1	R_2	R_4	R_5
a	H	H	H	H
b	OMe	H	H	H
c	$CON^{i}Pr_2$	H	H	H
d	$OCONEt_2$	OMe	H	H
e	$OCONEt_2$	OMe	H	Me

Scheme 11

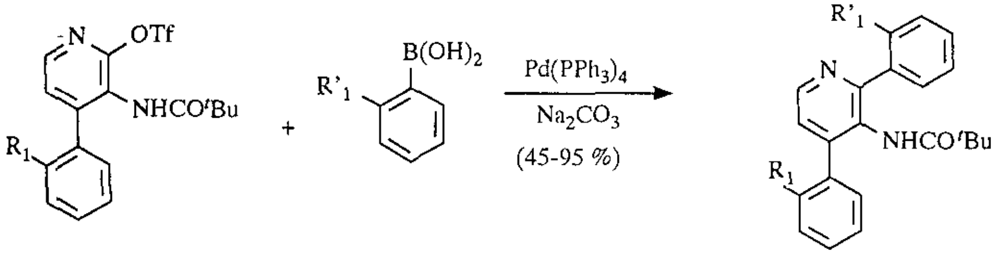
The reaction of sterically hindered 2-(4-iodo-5-methyl-3-pivaloyaminopyridyl) triflate (**17f**) and phenylboronic acid (**2e**) didn't afford the expected phenylpyridine. When reaction was carried out under pressure at 200°C, in a sealed tube, homocoupling compound (**19**) was isolated (Scheme 12).



17f **2e** **19**

Scheme 12

On the coupling reaction of **17a** with phenylboronic acid (**2a**), the formation of 2,4-diphenyl-3-pivaloylaminopyridine (**20a**) (12%) could be seen, which means that aryl triflates could react with arylboronic acids. We examined this possibility to prepare disymetric 2,4-diphenyl-3-pivaloylaminopyridines (**20**) starting from compounds (**18**) ($R_2=R_4=R_5=H$) (Scheme 13).

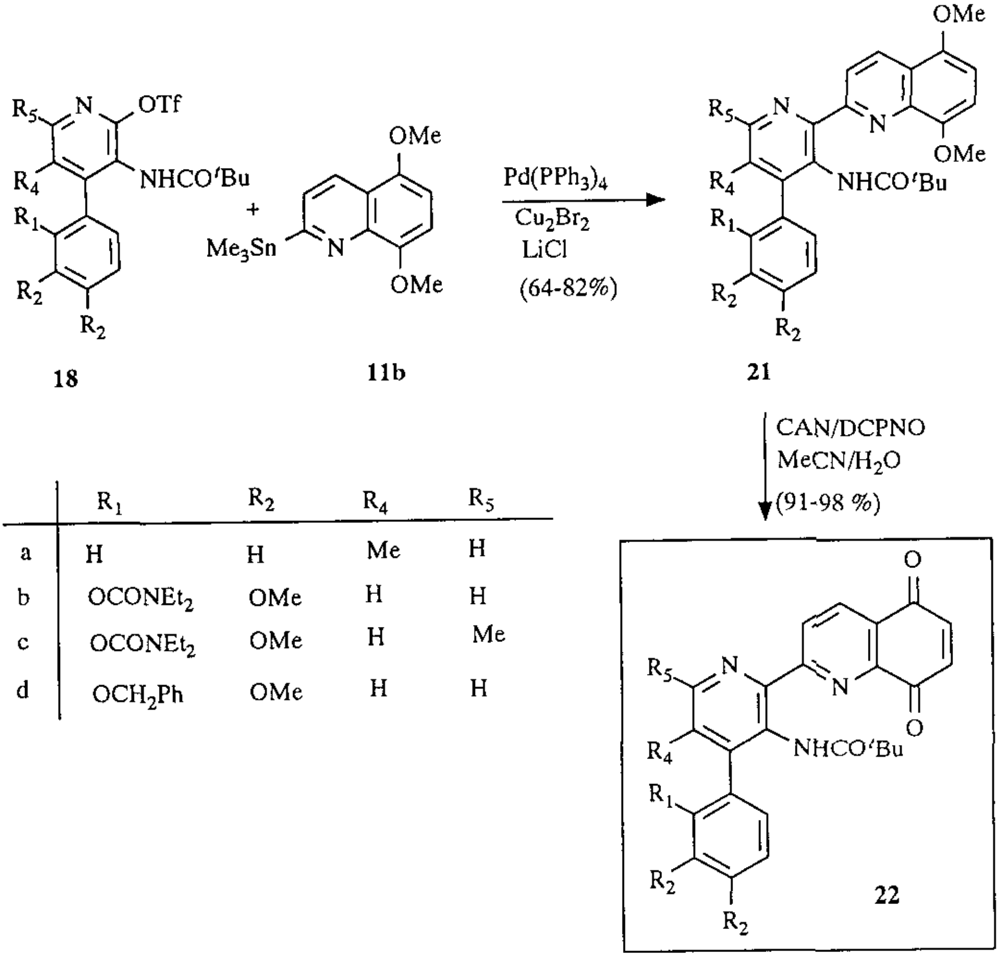


18a **20**

	R_1	R'_1
a	H	H
b	H	CON^{i}Pr$_2$
c	H	OMe
d	CON^{i}Pr$_2$	H
e	OMe	H

Scheme 13

In order to synthesize tetracyclic compounds (**21**) precursors of streptonigrin models, compounds (**18**) were reacted with quinolines (**11b**) under the conditions previously described for the cross-coupling between aryl triflates and arylstannanes. Direct oxidative demethylation of compounds (**21**) was carried out with cerium ammonium nitrate (CAN) in the presence of 2,6-pyridinedicarboxylic acid *N*-oxide (DCPNO) to give 2-substituted quinoline-5,6-diones (**22**) in high yields (Scheme 14).



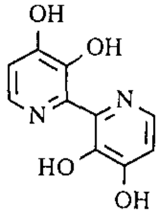
	R_1	R_2	R_4	R_5
a	H	H	Me	H
b	$OCONEt_2$	OMe	H	H
c	$OCONEt_2$	OMe	H	Me
d	OCH_2Ph	OMe	H	H

Scheme 14

Studies on the synthesis of streptonigrin alkaloid and their analogues are now in progress.

3. Synthesis of a bipyridyl alkaloid: Orelline.

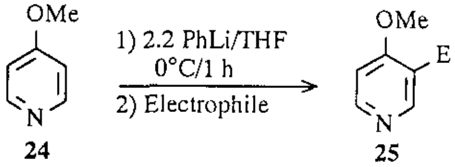
We here report a new five steps synthesis of orelline[13] (23), which is one of three substances isolated from poisonous mushroom *Cortinarius Orellanus*.[14-17] The methodology involved a series of conversions: metalation of methoxypyridines followed by halogenation to afford 2-halo-3,4-dimethoxypyridine, and the homocoupling reaction to build the 2,2'-bipyridyl structure of the alkaloid.



23 : Orelline

Scheme 15

In the first step, metalation of 4-methoxypyridine (**24**) occurred at C3 as previously reported by Comins *et al.*;[18] these authors used 1.3 eq. of mesityllithium in THF at -23°C during 3 h. We used a more common metalation reagent: phenyllithium, since Mallet[19] has proved that this reagent is as efficient as mesityllithium especially for the metalation of alkoxypyridines. The 3-lithio-4-methoxypyridine was then quenched by various electrophiles to give **25** (Scheme 16).

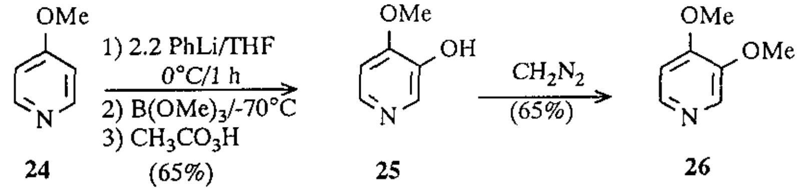


E = D, I, Br, OH, CH(OH)Ar (65-98 %)

Scheme 16

Introduction of a methoxy group at C3 required two steps: hydroxylation followed by *O*-methylation.

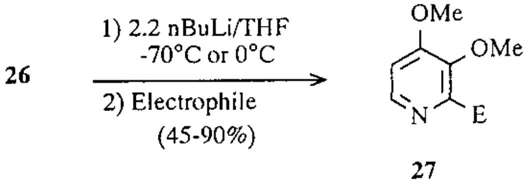
Several oxidation procedures were attempted to prepare 3-hydroxy-4-methoxypyridine (**25**) (E=OH) from 3-lithio-4-methoxypyridine. The oxidation with MoO_5 / pyridine / HMPA complex,[20] and oxygen[21] gave low yield of **25**, whereas action of trimethylborate at low temperature on the lithiopyridine followed by oxydation with peracetic acid[22] gave 3-hydroxy-4-methoxypyridine (**25**) in 65 % yield. Although, the *O*-methylation of **25** was not easy to realize using several current methylation conditions, resulting in only poor yields of **26**. The reaction was successfully achieved with diazomethane in presence of a catalytic amount of fluoroboric acid to give 3,4-dimethoxypyridine (**26**) (Scheme 17).



Scheme 17

3,4-Dimethoxypyridine (**26**) was thus prepared from 4-methoxypyridine in 2 steps with an overall yield of 42%. Note that **26** has been already prepared in lower overall yield of 22% from 3-aminopyridine (**29**)[23] in five steps.

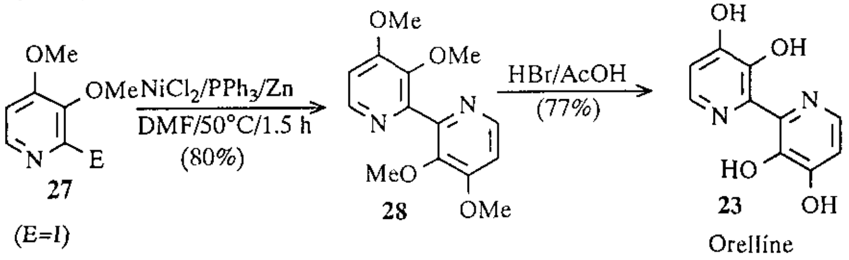
Several metalation conditions were tested on 3,4-dimethoxypyridine (**26**). LDA was too weak to deprotonate from **26**, and mesityllithium is also known to be inefficient in this purpose.[24] Butyllithium successfully attained the regioselective metalation at C2 (either at -70°C or 0°C) without side reactions and significant yield variation (Scheme 18).



E = D, Br, I, $SiMe_3$, Me, CHO, CH(OH)R

Scheme 18

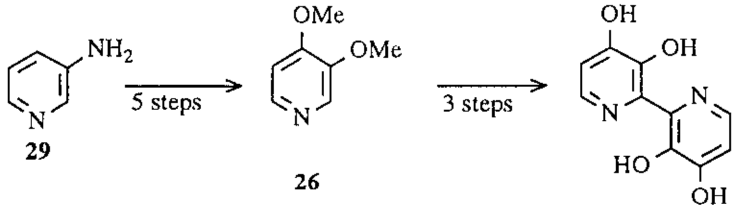
The nickel-phosphine complex-mediated homocoupling of 3,4-dimethoxy-2-halopyridines (**27**) (E=Cl,Br,I) afforded 3,3',4,4'-tetramethoxy-2,2'-bipyridyl (**28**) in excellent yields according to the general procedure described by Tiecco *et al.*[25] The cleavage of the methoxy groups was performed under acidic conditions to give **23** in 77% yield (Scheme 19).



Scheme 19

In previous reports, orelline (**23**) has been prepared from 3-aminopyridine (**29**) in 8 steps in 1.4% yield by Dehmlow and Schulz,[15] from 3-hydroxypyridine in 8 steps in 4.4% yield by Tiecco *et al.*[16] and in 5 steps in 4.8% yield by Hasseberg and Gerlach.[17]

Our strategy involved the metalation reaction on substituted pyridines in twice and the homocoupling reaction, so that this new 5 steps total synthesis considerably improved the overall yield (21%). Note that we also prepared orelline (**23**) from 3-aminopyridine (**29**) in 8 steps sequences in overall yield of 11% (Scheme 20).



23: Orelline

Scheme 20

4. Synthesis of biologically active molecules in the diazine series.

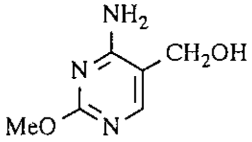
4-1 Pyrimidines.

The pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides and herbicides.

Reported preparations of such pyrimidines have been based on classical condensation reactions forming the pyrimidine ring. The ortho directed lithiation reaction is an efficient method due to its high regioselectivity to afford biologically active pyrimidine derivatives.

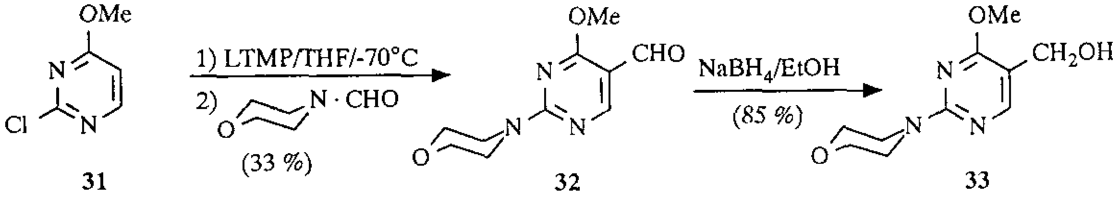
a) Synthesis of an analogue of Bacimethrin.

Bacimethrin (**30**), known as a thiamine antagonist is produced by *Bacillus mégatherium.*[26]



30

The synthesis of an analogue of bacimethrin has been performed by metalation of 2-chloro-4-methoxypyrimidine (**31**).[27] Reaction of **31** with 2.3 equivalents of LTMP at -70°C in THF followed by addition of 4-formylmorpholine led to a formyl derivative (**32**) in poor yield (33 %) accompanied by substitution of chlorine atom by morpholine. A further reduction of **32** with sodium borohydride gave primary alcohol (**33**) bacimethrin analogue in good yield (85 %) (Scheme 21).

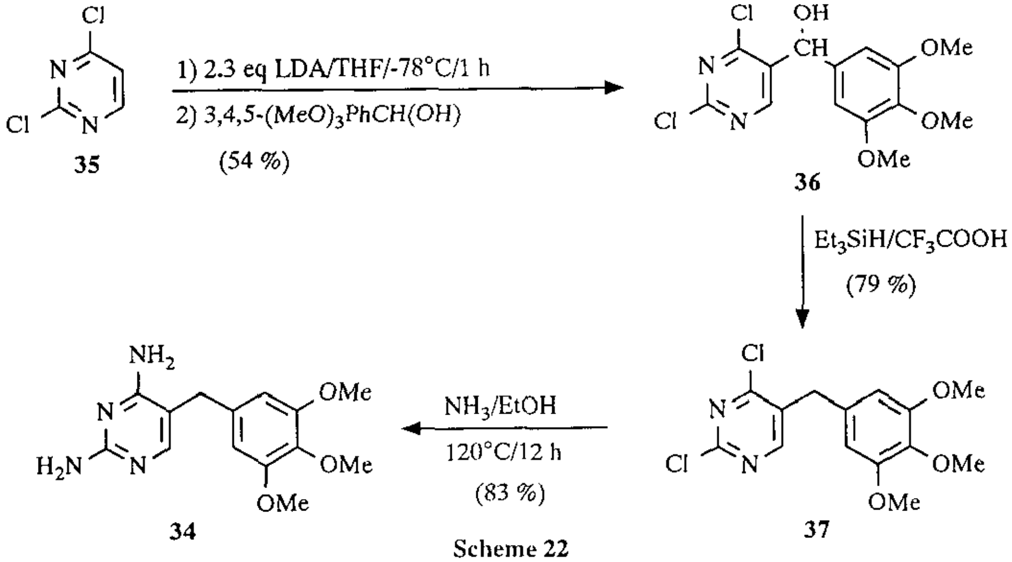


Scheme 21

b) Synthesis of Trimethoprim.

Trimethoprim (**34**), a benzyldiaminopyrimidine derivative, is one of the most powerful antibacterial agents. It is used to treat a wide range of bacterial diseases in humans. Used in combinaison with sulfamethoxyazole, this gives one of the best selling antibacterial agents : Bactrim^R.

The high ortho regioselectivity to chlorine atom on the metalation of 4-chloropyrimidines with LDA allowed a new short synthesis of *trimethoprim*[28] (**34**) *starting from* 2,4-dichloropyrimidine (**35**) (Scheme 22).



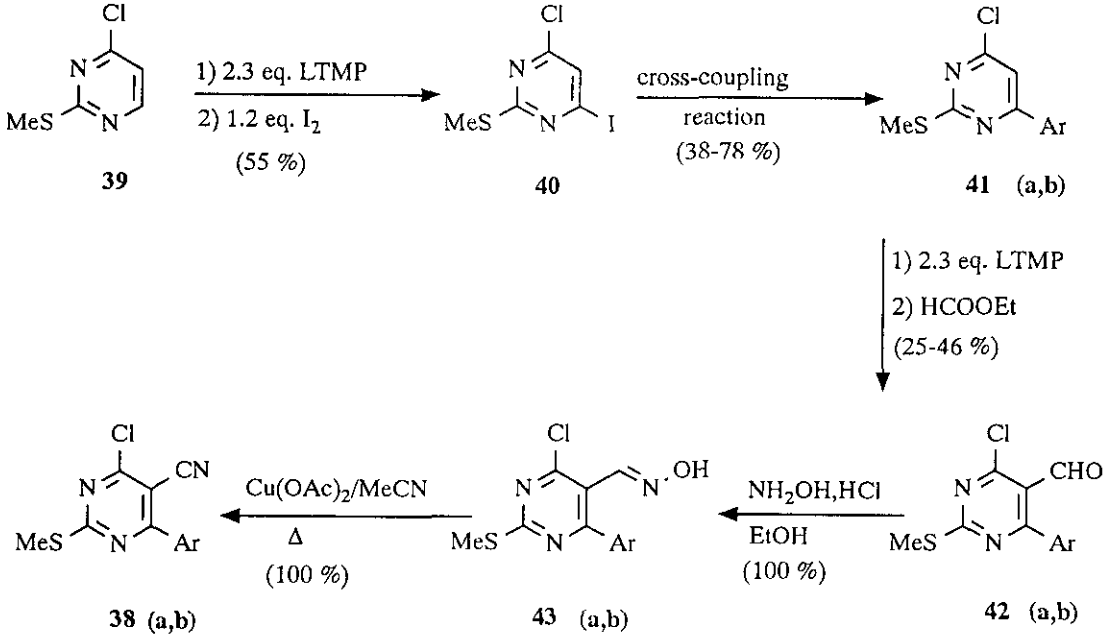
Scheme 22

Our synthesis is based on the lithiation of **35** with LDA followed by reaction of 3,4,5-trimethoxybenzaldehyde leading to the secondary alcohol (**36**). Hydrogenolysis of **36** by triethylsilane in trifluoroacetic acid afforded the methylenic hydrocarbon (**37**) in moderate yield (79 %). A further nucleophilic substitution of chlorines by amino groups with ammonia under high pressure led to trimethoprim (**34**) in good yield (83 %).

c) Synthesis of leshmaniacides.

Some thiopyrimidine are known to present antileshmanial and immunoadjuvant activities,[29-30] among them 4-chloro-6-aryl-2-trimethylpyrimidine-5-carbonitriles (**38**), (particulary compound (**38b**) with a *m*-methoxyphenyl substituent), show a high order antileshmanial activity against *L. donovani in vivo*.

The synthetic route to these compounds has been performed using the metalation of pyrimidines in the key step and the cross-coupling reaction (Scheme 23).



a Ar = Ph
b Ar = 3-(MeO)Ph

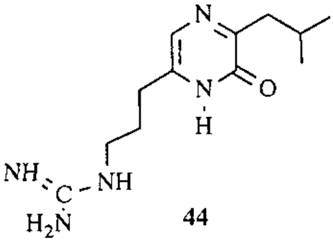
Scheme 23

The regioselective lithiation at C-6 position of 2-thiomethyl-4-chloropyrimidine (**39**) was used to synthesize these biologically active pyrimidines. The cross-coupling reaction of 6-iododerivative (**40**) with phenylboronic acid and *m*-anisylzinc iodide gave **41a**, and **41b**, respectively. Subsequent lithiation of compounds (**41**) followed by reaction with ethyl formate led the aldehydes (**42**). Then the reaction of **42** with hydroxylamine gave the oximes (**43**) and further dehydration of **43** in acetonitrile with copper acetate led quantitatively to the biologically active pyrimidine (**38**).

4-2 Pyridazines and pyrazines.

In the pyrazine and pyridazine series some biologically active molecules have also been synthetized *via* metalation and cross-coupling sequences.

a) Arglecin



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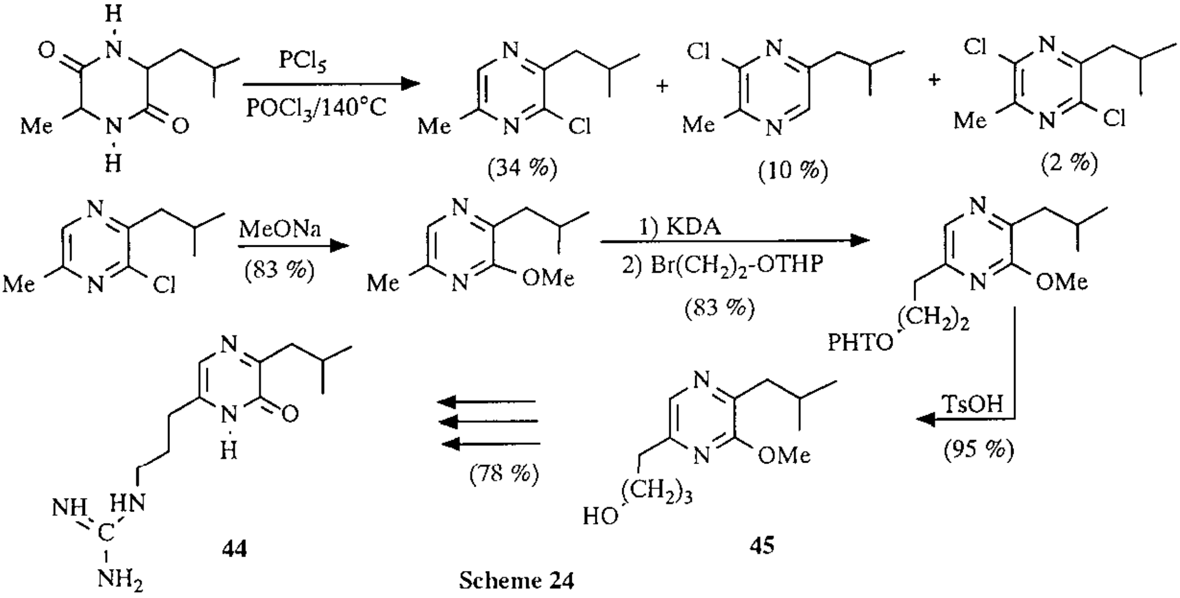
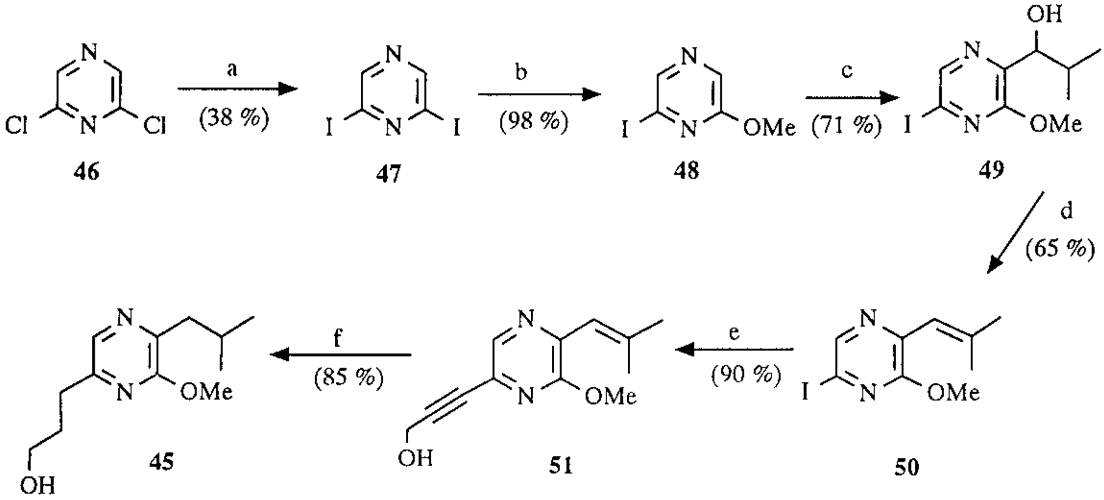
Arglecin (**44**), (natural antiarythmic drug), has been extracted from the culture filtrates of *Streptomyces toxytricini* and was first synthesized by Ohta in 1988 (Scheme 24).[31]



Scheme 24

The first step of this synthesis was a chlorination which afforded three isomers difficult to separate (hplc), so a synthesis starting from a suitably substituted pyrazine was devised to avoid this difficulty and to prepare Ohta's key intermediate (**45**).[32a]

After having tested some ways to prepare compound (**45**) an efficient route was developped (Scheme 25).

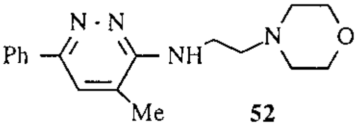


(a) *p*-TsOH, NaI, 15 crown-5, sulfolane, 150°C (2h); (b) MeONa, MeOH, room temperature (15 h); (c) LDA, THF, -70°C, ^{i}PrCHO; (d) *p*-TsOH, toluene, 110°C (6 h); (e) 1-propynol $Pd(PPh_3)_3Cl_2$, CuI, NEt_3, reflux (2 h); (f) H_2, 5% Pd/C, EtOH, room temperature.

Scheme 25

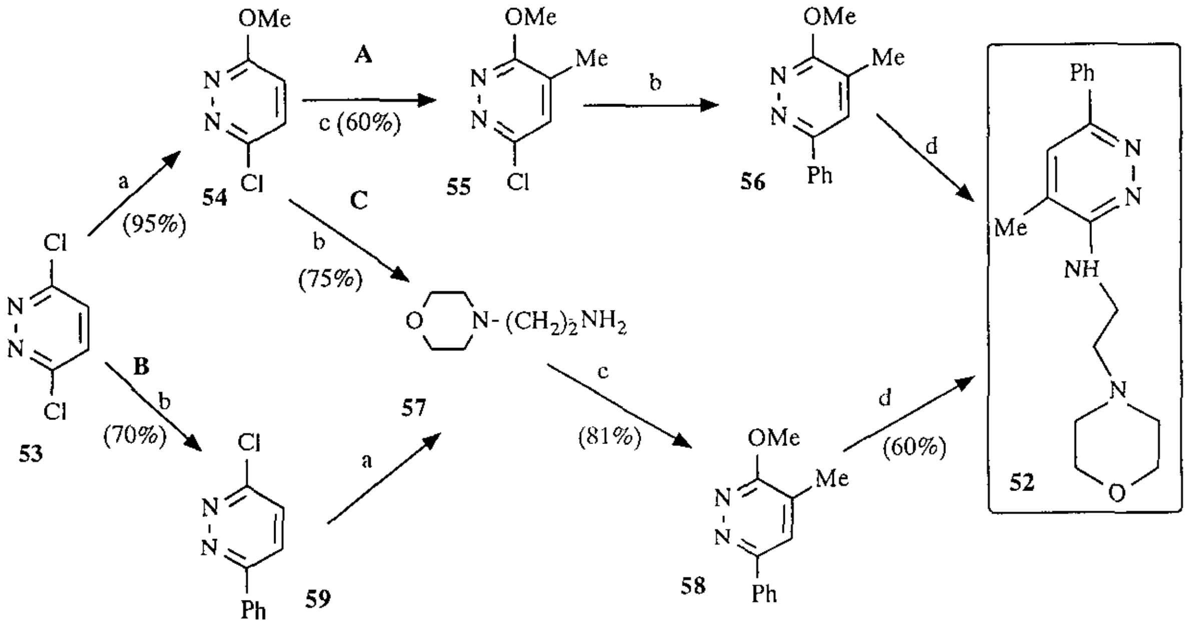
The metalation reaction of **48** was regioselective in ortho to methoxy group (**48** → **49**) and alcohol (**49**) was dehydrated to give **50**. The final hydrogenation of **51** was easily performed under atmospheric pressure of hydrogen.

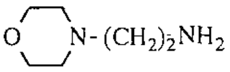
b) Minaprine



52

Minaprine (**52**) is an antidepressant which is sold in many countries. Its first synthesis was developped by Wermuth *et al.*[33] who prepared numerous derivatives with different substituents to study their biological activities. The synthesis was based on the ring closure of a suitably substituted pyridazine in the last step. Our synthesis started from 3,6-dichloropyridazine (a cheap commercial product) which was functionnalized by the metalation and the cross-coupling. Methyl group was introduced by metalation, phenyl group by the cross-coupling reaction and amino chain by nucleophilic substitution but the order of these operations may be varied leading to three main pathways A,B,C (Scheme 26).



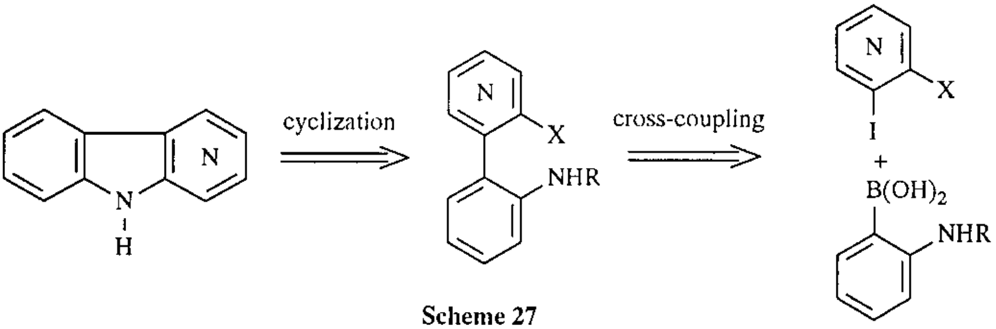
(a) MeONa, MeOH, reflux; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux; (c) LTMP, -70°C, THF, MeI; (d) HI then $POCl_3$ then 

Scheme 26

Path C was the best choice of these conversions, because path A had lower regioselectivity on the metalation, and path B had the problem of chemioselectivity on the cross-coupling.

5. A new convergent pathway to azacarbazoles

Many natural alkaloids belong to the carboline series,[34] mainly β-carboline (harman derivatives,[35] Eudistomins,[36] Lavendamycine,[37] Picrasma Javanica alkaloids[38]). Some of these β-carbolines bear various substituents at the alpha-position and show interesting biological properties. Until now most syntheses have used indole or its derivatives as starting materials[34] and are based on condensation reactions[35] between tryptophan or tryptamine and aldehydes. α-Substituted compounds are often prepared from available β-carboline reagents such as norharman or harman[36] through specific reactions. From a retrosynthetic analysis (Scheme 27), all four azacarbazoles can be prepared by cyclization of a phenylpyridine to form the pyrrole ring under acid conditions. The requisite phenylpyridines can be prepared through the palladium catalyzed cross-coupling reaction[2] of *o*-aminophenylboronic acid with *o*-haloiodopyridine. The introduction of suitable substituents (iodine and boronic acid) on benzene and pyridine rings could be achieved by the metalation strategy.



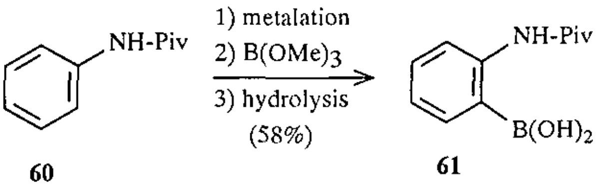
Scheme 27

5-1 Synthesis of the parent carbolines.

a) Synthesis of 2-aminophenylboronic acid.[39]

The metalation of pivaloylaminobenzene[40] (**60**) with n-butyllithium in THF and the reaction of trimethyl borate[41] gave phenylboronic acid (**61**) after hydrolysis and acidification (Scheme 28).

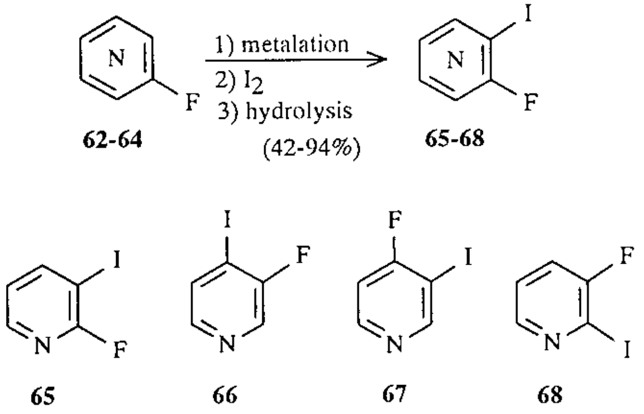
Both the metalation and boronation steps are almost quantitative, but protodeboronation cannot be avoided upon acid treatment leading to lowering of yields.



Scheme 28

b) Synthesis of iodopyridines.

The metalation[42] of 2-, 3- and 4-fluoropyridines (**62-64**), by LDA in THF at low temperature and reaction of the resulting lithio derivatives with iodine afforded in good yields the corresponding *o*-iodopyridines (**65-68**) (Scheme 29).

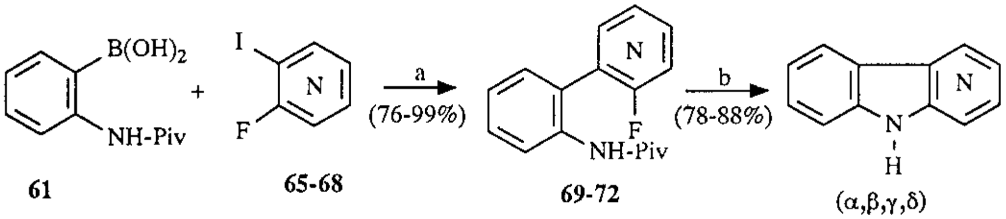


Scheme 29

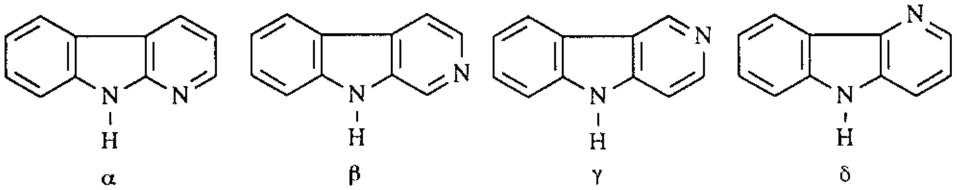
3-Fluoro-2-iodopyridine (**68**) was synthesized from 3-fluoropyridine (**63**) using modified metalation conditions[43] (n-butyllithium/DABCO in ether).

c) Cross-coupling and cyclization.

The cross-coupling reaction between 2-pivaloylaminobenzeneboronic acid (**61**) and ortho-fluoroiodopyridines (**65-68**) with Suzuki's procedure[11] gave the corresponding heterobiaryls (**69-72**). Cyclization of the resulting 4-phenylpyridines (**69-72**) was best achieved in boiling pyridinium chloride (nucleophilic displacement of the fluoro atom is favoured by combining activation of the pyridine ring as pyridinium with the cleavage of the pivaloyl group in strong acid medium). Thus the four parent carbolines (α, β, γ and δ) are obtained in good to high yields after basic workup (Scheme 30).



(a) $Pd(PPh_3)_4$, 2M K_2CO_3, toluene, EtOH, reflux, 48 h; (b) pyridinium chloride, 215°C, 15 min



Scheme 30

The link between the metalation and the cross-coupling provided a new convergent and regioselective way to the carboline skeleton in few steps from aniline and fluoropyridines. The important natural β-carboline (norharman) could be thus prepared in three steps in 79% overall yield.

5-2 Synthesis of natural 2-substituted β-carbolines.

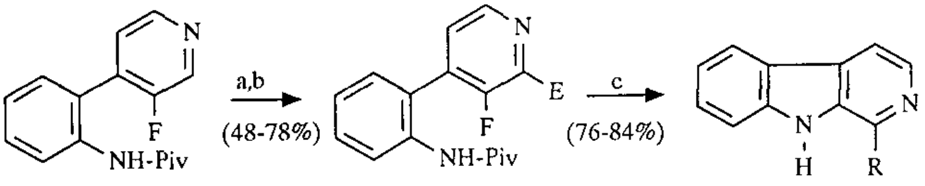
The previously described methodology was fitted to the synthesis of natural α-substituted β-carbolines such as harman, 2-ethyl-β-carboline, pavettine, 6-hydroxyharman and fascaplysin.

a) Synthesis of harman, 2-ethyl-β-carboline and pavettine.[44]

The 2-substituent on the pyridine ring of these alcaloids could be easily introduced using the metalation stategy.

So, the previously described 3-fluoro-4-phenylpyridine (**71**) still possesses a free site ortho to the fluoro atom which could be deprotonated and functionalized.

The 3-fluoro-4-phenylpyridine (**71**) was lithiated quantitatively and regioselectively at the C-2 position with n-butyllithium at -75°C. The reaction of the resulting lithio species with electrophiles allowed the introduction of methyl, ethyl and 1-hydroxyethyl (Scheme 31). The intermediary 2-substituted pyridines are cyclized to the expected 2-methyl-, 2-ethyl- and 2-vinyl-β-carboline derivatives.



71

E = Me , Et or CH(OH)Me

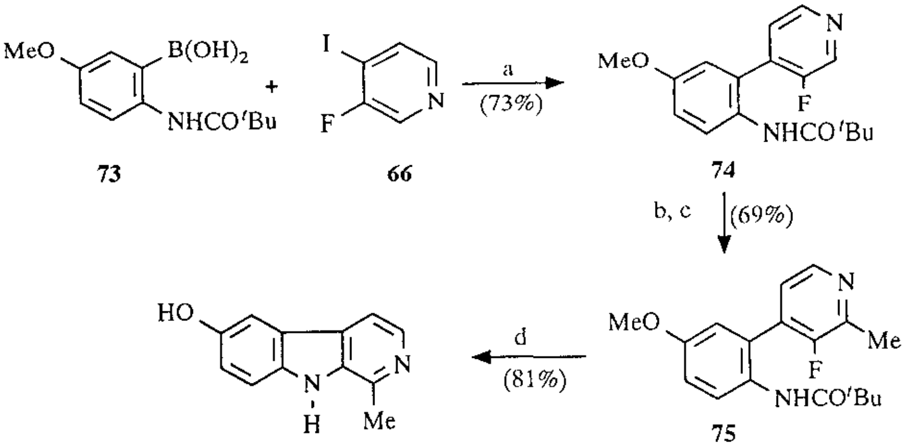
R = Me (Harman)
R = Et
R = vinyl (Pavettine)

(a) n-BuLi, THF, -75°C; (b) E^+, -75°C;
(c) pyridinium chloride, 215°C.

Scheme 31

b) Synthesis of 6-hydroxyharman.[45]

5-Methoxy-2-pivaloylaminophenylboronic acid (**73**) was prepared by the metalation-boronation of the corresponding 4-methoxyaniline. The palladium-catalyzed cross-coupling reaction between boronic acid (**73**) and 3-fluoro-4-iodopyridine (**66**) afforded biaryl (**74**) which was selectively metalated by n-butyllithium in THF. The reaction of the resulting lithio derivative with methyl iodide gave 2-methylpyridine (**75**) which was then cyclized in boiling pyridinium chloride (Scheme 32). Under these conditions, cleavage of methoxy group was observed leading to 6-hydroxyharman, an alcaloid isolated in 1978 by Blomster[47] from roots of *Grewis mollis*.



73 **66** **74** **75**

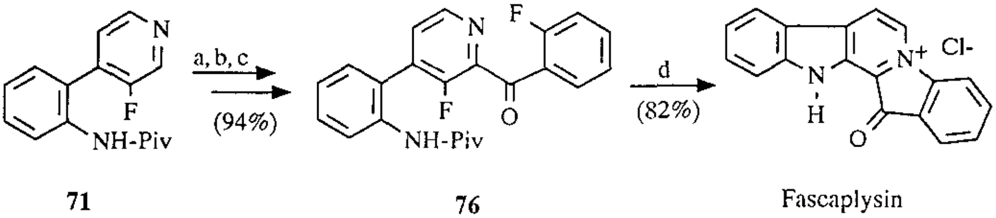
(a) $Pd(PPh_3)_4$, 2M K_2CO_3, PhMe, EtOH, reflux, 48 h; (b) nBuLi, THF, -78°C; (c) MeI, -75°C; (d) pyridinium chloride, 215°C, 15 min.

Scheme 32

6-Methoxyharman (isoharmine), isolated in 1970 by Willaman and Li[46] from Virola species and in 1990 by Ayoub and Rashan[48] from seeds of *Peganum harmala*, could be obtained by methylation of 6-hydroxyharman with diazomethane.[47]

c) Synthesis of fascaplysin.[49]

The previously described phenylpyridine (**71**) was metalated[44] with n-butyllithium before the treatment with 2-fluorobenzaldehyde. The intermediary secondary alcohol was quantitatively oxydized by MnO_2 in refluxing toluene to give the ketone (**76**). The one-pot double cyclization of **76** in pyridinium chloride at 170 °C gave fascaplysin (an antimicrobial and cytotoxic red pigment isolated in 1988 by Ireland and Clardy from the Fijian sponge *Fascaplysinopsis Bergquist* sp.[50] and prepared in 1990 by Gribble[51] in 7 steps in 65% yield from indole) (Scheme 33).

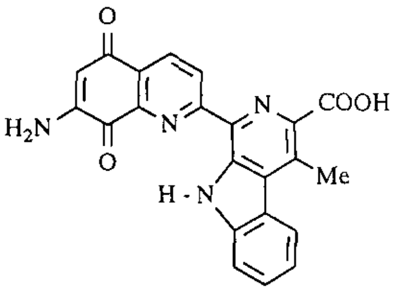


(a) n-BuLi, THF, -75°C; (b) 2-F-PhCHO, -75°C; (c) MnO_2, toluene, reflux;
(d) pyridinium chloride, 170°C, 10 min.

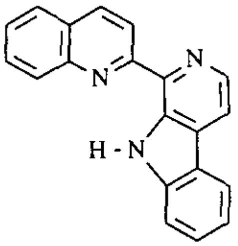
Scheme 33

5-3 Synthesis of Lavendamycin derivatives.

Lavendamycin[52] was isolated in 1981 by Doyle from the fermentation broths of *Streptomyces lavendulae*. Its structure incorporates a substituted 2-(2-pyridyl)quinoline-5,8-dione similar to that of the antitumor antibiotic *Streptonigrin*.[3] Nitramarine isolated in 1990 by Yunusov[53] also possesses the 2-(2-pyridyl)quinoline skeleton but without any substituent.



Lavendamycin



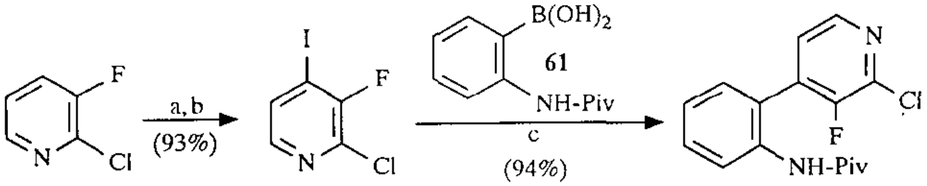
Nitramarine

The 2-(2-quinolyl)-β-carboline skeleton of both Nitramarine and Lavendamycin could be obtained from benzene and pyridine building blocks as previously described and the 2-quinolyl moiety could be introduced using the cross-coupling strategy.

a) Synthesis of nitramarine.[44]

Directed metalation of 2-chloro-3-fluoropyridine (**77**)[23] by LDA in THF at -75°C followed by the reaction of iodine gave the expected 4-iodopyridine (**78**) in high yield.

The cross-coupling reaction between **78** and 2-pivaloylaminobenzeneboronic acid (**61**) regioselectively and almost quantitatively gave 4-phenylpyridine (**79**) (Scheme 34).

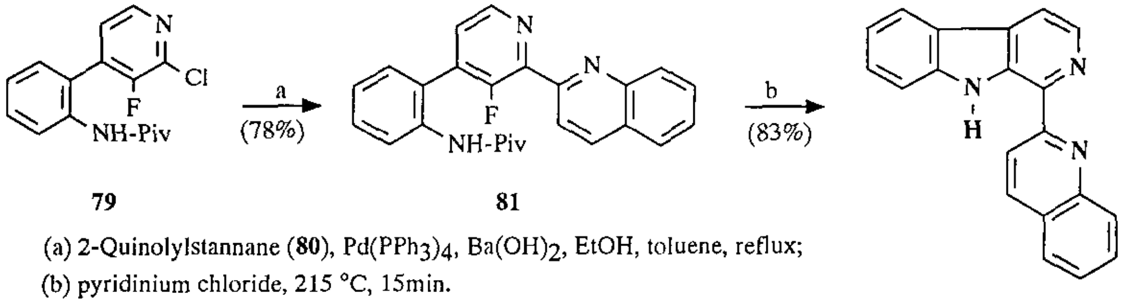


77 **78** **79**

(a) LDA, THF, -75°C; (b) I_2, -75°C; (c) $Pd(PPh_3)_4$, 2M K_2CO_3, toluene, EtOH, reflux.

Scheme 34

The palladium catalyzed cross-coupling reaction between 2-chloropyridine (**79**) and 2-quinolylstannane (**80**) led to the intermediary triaryl compound (**81**) which was readily cyclized into nitramarine (Scheme 35).



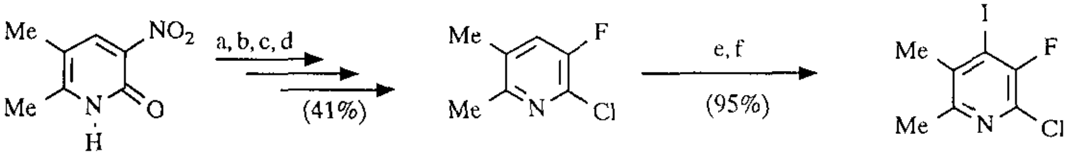
79 **81** Nitramarine

(a) 2-Quinolylstannane (**80**), Pd(PPh_3)$_4$, Ba(OH)$_2$, EtOH, toluene, reflux;
(b) pyridinium chloride, 215 °C, 15min.

Scheme 35

b) Synthesis of model of lavendamycin.[54]

2-(3,4-Dimethylpyrido[3,4-*b*]indol-1-yl)quinoline-5,8-dione was prepared from 2-chloro-5,6-dimethyl-3-fluoropyridine according to the same strategy as for nitramarine. The starting chlorofluoropyridine (**83**) was previously obtained in 3 steps from 5,6-dimethyl-3-nitro-2-pyridone (**82**).[55] The metalation of the fluoropyridine (**83**) with LDA followed by the reaction of iodine affords the corresponding iodo compound (**84**) (Scheme 36).

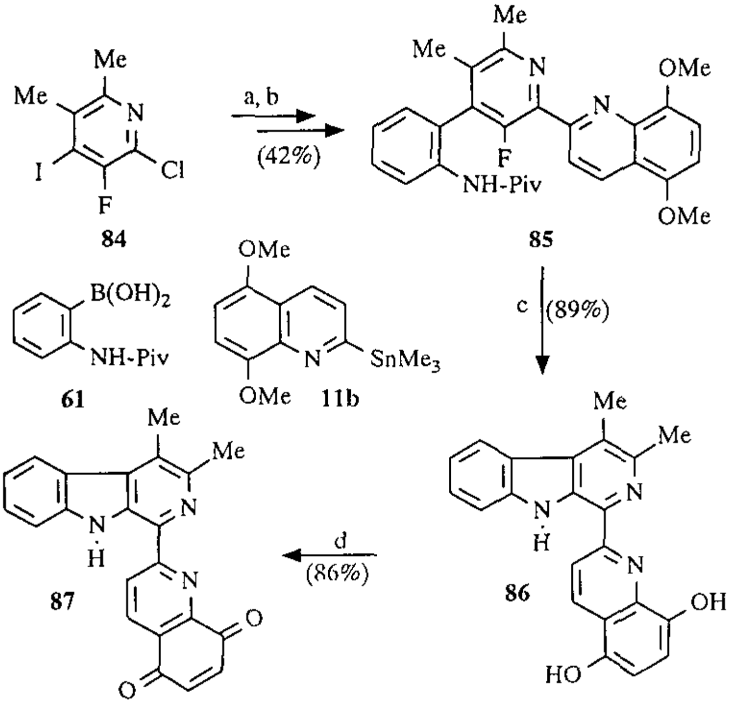


82 **83** **84**

(a) $POCl_3$, PhCl, reflux; (b) Fe, HCl, EtOH, H_2O, 70°C; (c) EtONO, Et_2O, HBF_4; (d) hexane, 60°C; (e) LDA, THF, -78°C; (f) I_2, -75°C.

Scheme 36

Iodopyridine (**84**) was subjected to the palladium-catalyzed cross-coupling reaction twice ; firstly with aminophenylboronic acid (**61**) and secondly with 5,8-dimethoxy-2-trimethylstannylquinoline (**11b**). The resulting triaryl (**85**) was then cyclized to the β-carboline (**86**) with simultaneous hydrolysis of the two methoxy groups. Ultimately, the oxidation of the 5,8-dihydroxyquinoline (**86**) with the Fremy's salt[56] afforded the quinoline-5,8-dione (**87**) in very good yield (Scheme 37).



(a) $Pd(PPh_3)_4$, EtOH, $Ba(OH)_2$, toluene, reflux; (b) $Pd(PPh_3)_4$, toluene, reflux; (c) pyridinium chloride, 215°C; (d) $(KSO_3)_2NO$, KH_2PH_4

Scheme 37

6. Halogen dance and application to synthesis of alkaloids.

Compared to the metalation of chloro and fluoro aromatics,[1] few has been done with the other halogens. However, the metalation of bromo- and iodoaromatics was a promising challenge due to the high reactivity of these halogens in such useful reactions as halogen-lithium exchange, S_{RN1}, Heck reaction, cross-coupling or carbonylation. Some interesting results have been obtained in the field of the lithiation of aryl bromides. Thus metalation of bromobenzene derivatives has been carried out and the "halogen-dance" phenomenon has been discovered.[57] Similarly, the inductive effect of bromine provides an excellent regioselectivity in the metalation of hetaryl bromides[1] like bromothiophen or bromoisothiazole derivatives.

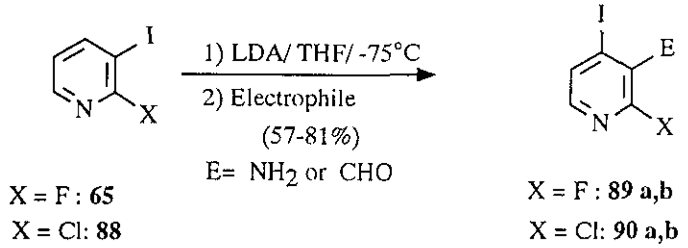
In the last 20 years, 2-bromopyridine and 3-bromopyridine were regio- and chemoselectively ortho-lithiated either by LDA or n-butyllithium at low temperature.[58] Metalation of the pyridine ring and bromo migration were observed. A mechanism was proposed to explain the bromo migration and this reaction was operated for synthetic purpose.[59] Until recently, no iodo-directed metalation of aromatics has been described whatever the series excepted the α-lithiation of iodothiophens[60] or iodoisothiazoles.[61]

However, the directed metalation of bromo- and iodopyridines has been developped as a key step in the syntheses of complex polyaromatics of biological interest.

6-1 Metalation of iodopyridines.[62]

a) Metalation of 2-halo-3-iodopyridines (chloro and fluoro).

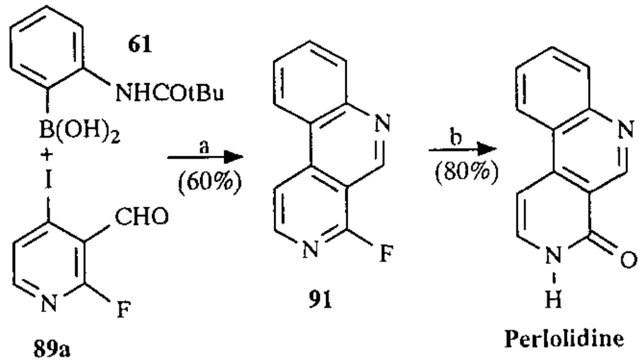
2-Fluoro- and 2-chloro-3-iodopyridines (**65**) and (**88**) were readily prepared from the corresponding 2-halopyridines by metalation-iodination sequences.[39] Treatment of these iodopyridines with LDA at -75°C followed by quenching with electrophiles led to the 3-substituted 2-halo-4-iodopyridines (**89a,b** and **90a,b**) in good to high yields (Scheme 38).



Scheme 38

b) Synthesis of perlolidine.

The reaction between 2-fluoro-4-iodo-3-pyridinecarboxaldehyde (**89a**) and 2-pivaloylaminophenylboronic acid[39] (**61**) under Suzuki's conditions[11] resulted in heteroring cross-coupling and subsequent cyclization to diazaphenanthrene (**91**). Hot acid treatment of the fluoro compound (**91**) induces hydrolysis to perlolidine[63] (an alkaloid of the New Zealand perennial rye grass *"Lolium perenne L."* which is effective on plant growth) (Scheme 39).



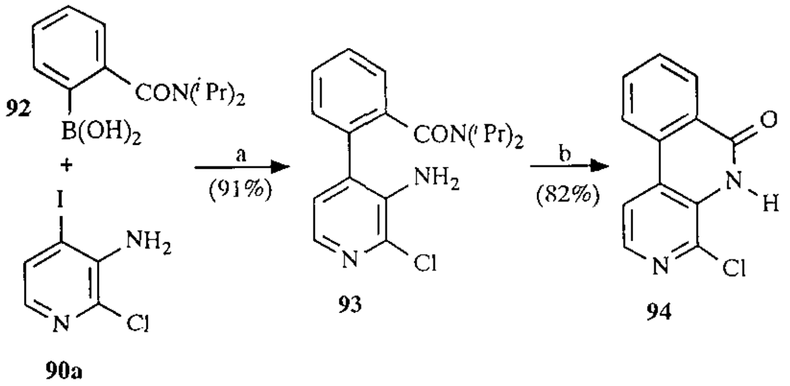
(a) Pd(PPh$_3$)$_4$, 2M K$_2$CO$_3$, EtOH, toluene, reflux; (b) 4.8M HCl, reflux.

Scheme 39

c) Synthesis of 2,10-diazaphenanthrenes.

Little has been done in the field of 2,10-diazaphenanthrenes[64] which is an isomeric structure of the 2,9-diaza skeleton found in numerous alkaloïds of the "Marine Sponge" family.

Heteroring cross-coupling between the 3-amino-4-iodopyridine (**90a**) and 2-diisopropylaminocarbonyl-phenylboronic acid[1b] (**92**) using Pd(0) catalyst gave the 4-phenyl-3-aminopyridines (**93**) which was readily cyclized to the corresponding halonaphthyridinones (**94**) by treatment with LDA.[65] (Scheme 40).



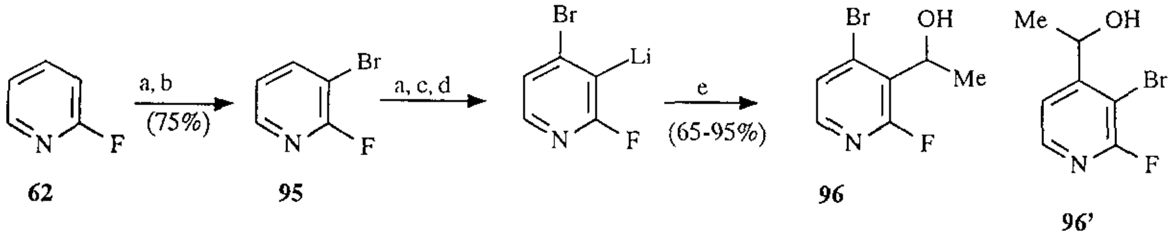
(a) Pd(PPh$_3$)$_4$, 2M K$_2$CO$_3$, EtOH, toluene, reflux; (b) 3 equiv. LDA, THF, -75°C to room temperature.

Scheme 40

6-2 Metalation of bromopyridines.

a) Metalation of 2-halo-3-bromopyridines (chloro and fluoro).

Directed lithiation of 2-fluoropyridine (**62**) with LDA at -78°C,[42b] followed by treatment with bromine gave 3-bromo-2-fluoropyridine (**95**). This crude compound was lithiated and isomerized with LDA at -78°C to give 4-bromo-2-fluoro-3-lithiopyridine, as proved by reaction with acetaldehyde. This last reagent has to be added as fast as possible to the lithiation mixture in order to avoid competitive formation of 4-pyridyl isomer (**96'**) (slow addition of acetaldehyde caused the isomerozation to **96'** in a 5-15% yield) (Scheme 41).

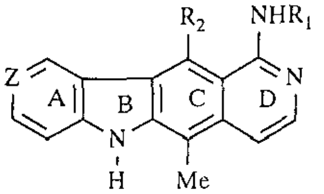


(a) LDA, THF, -75°C; (b) Br_2, -75°C; (c) trace Br_2, -75°C; (d) -75°C to -50°C; (e) MeCHO, -75°C.

Scheme 41

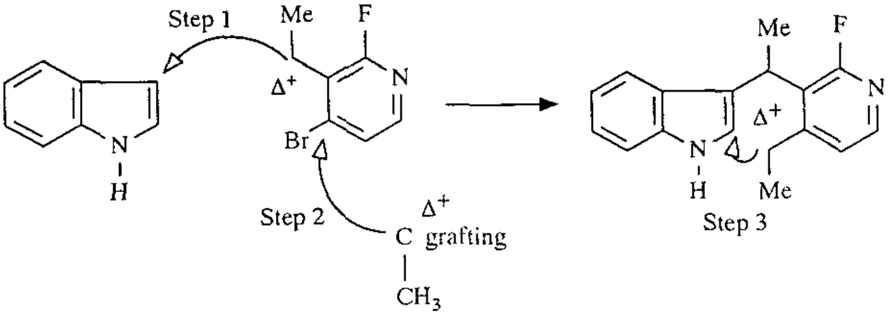
b) Synthesis of 1-fluoroellipticine.[66]

In the field of antitumor compounds, some ellipticine derivatives, such as 9-aza and 9-methoxy derivatives of 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole bearing a dialkylaminopropylamino moiety at the C-1 position show a high anticancer activity against myeloblastic leukemias as well as solid tumors[67] with lower cardiovascular effects compared with the parent ellipticines.



Z = C-H, C-OMe, N ; R_2 = H, Me ; $R_1 = (CH_2)_nNEt_2$

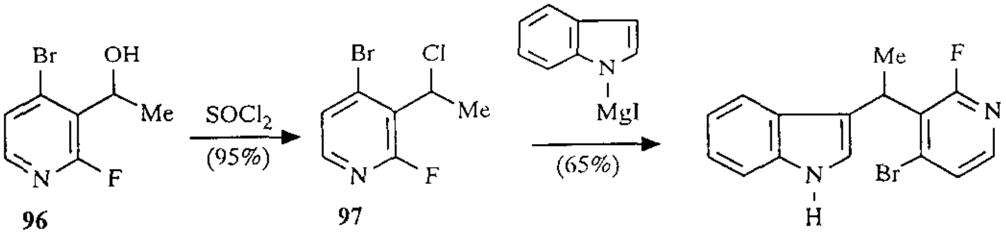
The main reported syntheses of such 1,9-difunctionalized ellipticines involve multi-step strategies.[68] Another route to 1-substituted ellipticines relies on the condensation of a conveniently substituted pyridine building block with indole. Such pyridine requires an electrophilic center at the α position of the two-carbon chain and a precursor of the required two-carbon chain at the C-4 position (Scheme 42).



Scheme 42

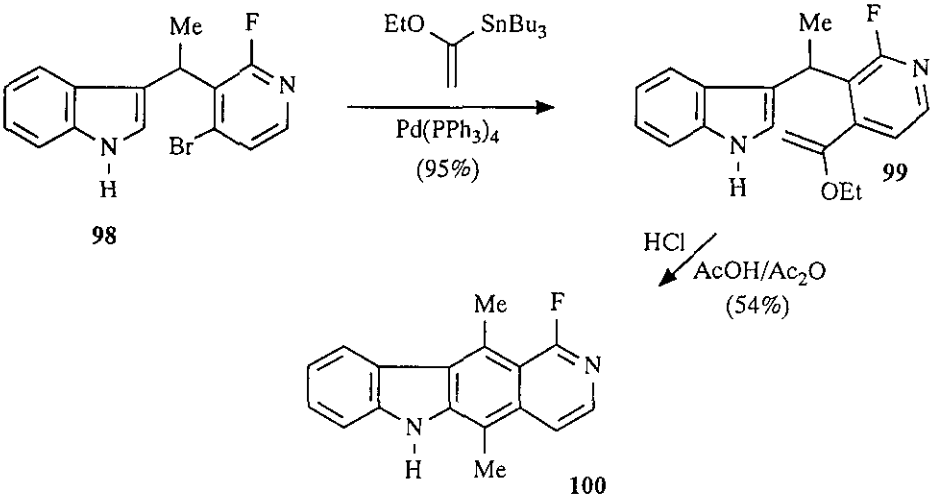
One of the possible ways was to use a 4-bromopyridine and to achieve the second step *via* a cross-coupling pathway.

The chloro derivative (**97**) available from 1-(3-pyridyl)ethanol (**96**) was treated with 1-indolylmagnesium iodide in refluxing benzene according to De Graw's procedure[69] to give the expected condensed product (**98**) (Scheme 43).



Scheme 43

The last part of the synthesis consisted in introducing at the pyridine C-4 bromo site a suitable two-carbon moiety bearing a proelectrophilic α-carbon for the final cyclization step. The functionalization of the pyridine C-4 bromo site was realized by means of (1-ethoxyvinyl)tributylstannane, which was achieved in refluxing toluene with a palladium(0) catalyst to give the expected 4-vinylpyridine (**99**) (Scheme 44).



Scheme 44

Acidic treatment of compound (**99**) allowed the final "C-ring" closure to give 1-fluoroellipticine (**100**).

ACKNOWLEDGMENTS

The works whose results are reported herein were carried out within framework of theses. This paper could not have been without the collaboration of O. Mongin, M. Mallet, J.C. Rovera, J.M. Fourquez, P. Rocca, F. Nivoliers, L. Mojovic, C. Cochennec, C. Harmoy, D. Dognon, K. Couture.

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Received, 13th May, 1994