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Synthesis of Chiral NADH Model Compounds in the Pyrrolo[3,2-b]pyridine series : Models with a Chiral Group on the Pyrrole Nitrogen or on the Carboxamide Side Chain

Marie-Odile Monnet, Pierre Prévost, Georges Dupas, Jean Bourguignon* and Guy Quéguiner.

URA 1429 CNRS / Institut National des Sciences Appliquées
BP 08. 76131 Mont Saint Aignan Cedex (France)

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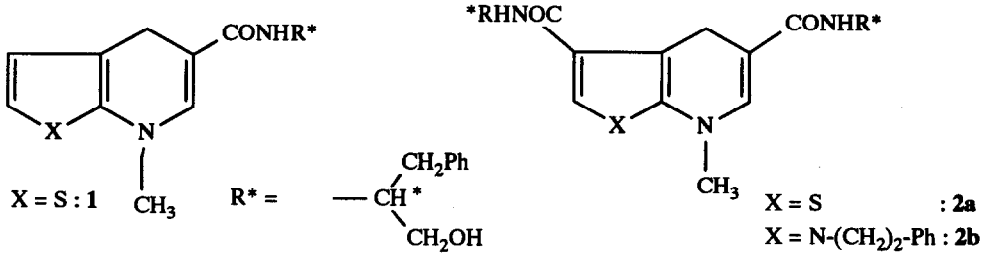
Abstract: *The synthesis of chiral NADH model compounds in the pyrrolo[3,2-b]pyridine series is described, using various strategies. The first route involved alkylation of the pyrrole nitrogen of a nitropyrrole carboxylate followed by a ring closure reaction in a [3+3] process. The same [3+3] process was used in the second route in order to synthesize the pyrrolo[3,2-b]pyridine structure. Various alkylation methods were tested with the view of introducing a chiral moiety on the pyrrole nitrogen. The best results were obtained with the Mitsunobu reaction. The efficiency of the two chiral models obtained was investigated in the reduction of methyl benzoylformate.*

NADH models bearing a chiral auxiliary have been widely studied in asymmetric reductions of prochiral compounds. The major contributions to these kinds of reductions via chiral 1,4-dihydropyridines have been by Ohno (1), Inouye (2), Kellogg (3) and Meyers (4). Some models gave excellent results in the reduction of highly electrophilic substrates e.g. benzoylformic esters. The chiral auxiliary can be introduced in several positions on the 1,4-dihydropyridine structure : most of the models contain this chiral moiety in the carbamoyl side chain. In our laboratory, we first used this strategy with optically active 2-aminoalcohols (5). However, with simple pyridine models, two competing processes are involved : the reduction itself and side reactions affecting the 5,6 double bond of the dihydropyridine structure. In order to solve this problem we synthesized annelated NADH models where a thiophene ring (6) and later a pyrrole ring protect the 5,6 double bond. The models thus obtained allowed very fast reductions under mild conditions, even in technical grade acetonitrile (only hyper dry acetonitrile can be used with non-protected models). We recently reported the synthesis of chiral NADH models in the thieno (7) and pyrrolo[2,3-b] series (8).

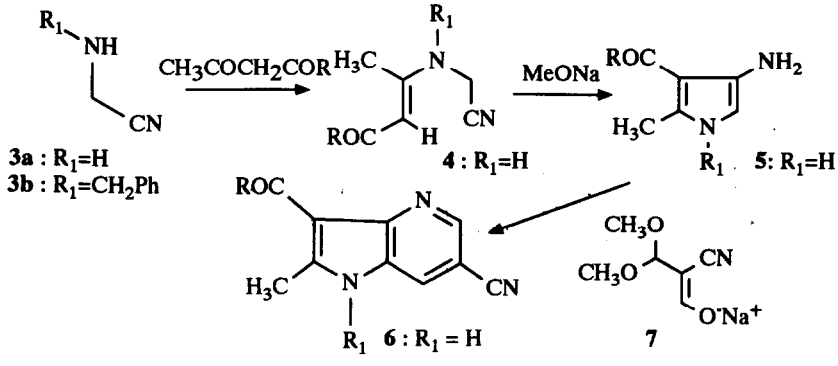


Scheme 1

The structures of these compounds are given in scheme 1. It should be emphasized that the presence of an annelated ring allows other possibilities for introducing a chiral auxiliary. To our knowledge, there are no reports dealing with asymmetric centres not directly linked to the dihydropyridine structure. We now wish to report our attempts concerning the synthesis of annelated chiral NADH models in the pyrrolo[3,2-b]pyridine series: the pyrrole nitrogen allows the insertion of a chiral auxiliary in the vicinity of the reactive site of the molecule. In order to obtain good precursors to this type of model, two different strategies are possible : alkylation of the pyrrole nitrogen of a pyrrolo[3,2-b]pyridine with a chiral alkyl halide or synthesis of a 3-aminopyrrole bearing a chiral group in the 1-position followed by ring closure in a 3+3 process. These two routes will now be discussed.

Alkylation Reactions Before Construction of the Pyridine Ring

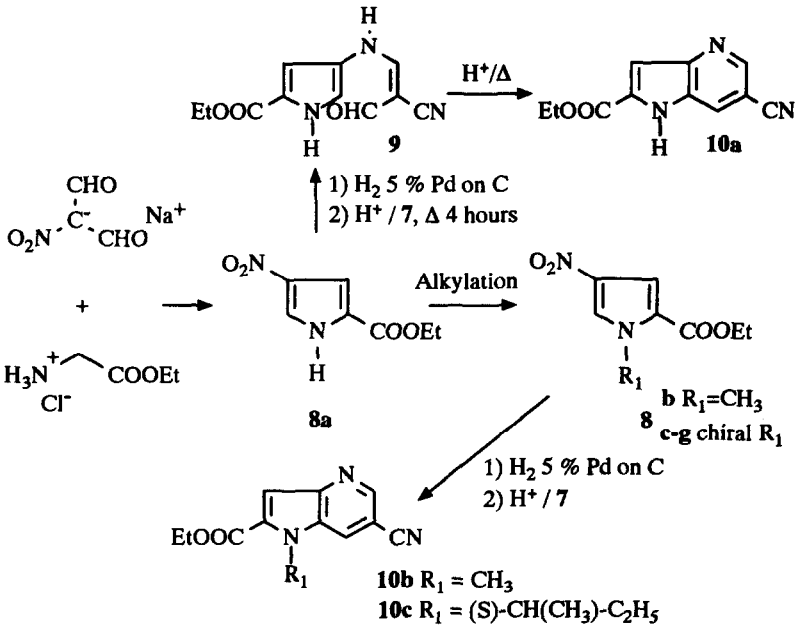
In order to obtain the pyrrolo[3,2-b]pyridine structure, we used the method described in a previous paper (8) (scheme 2, R_1 = H) : α-aminoacetonitrile **3a** was converted into an enamine **4** by reaction with a 1,3-dicarbonyl compound. This enamine afforded an unstable 3-aminopyrrole **5** which was subsequently worked up with the sodium salt of 3,3-dimethoxy-2-formyl-propanenitrile **7** leading to **6** as described before (8, 9):



Scheme 2

We first tried to expand the scope of this synthesis to cover N-alkylated aminoacetonitriles. The advantage of this strategy would have been to insert the chiral moiety at the beginning of the synthesis. However, it was very difficult to get N-benzylaminoacetonitrile (10) (R_1 = CH_2Ph, compound **3b**) to react with acetylacetone. Whatever the conditions, the reaction was always partial and the purification of the final

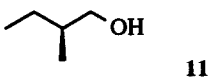
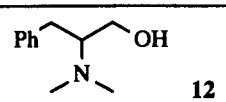
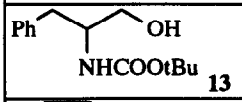
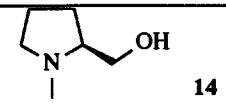
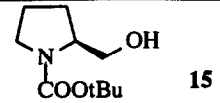
product was very tedious. Hence, we tried another possibility: N-alkylation of the pyrrole ring with a chiral reagent. However, in the case of compound **5**, this reaction was impossible because the 3-aminopyrrole was unstable and could not be isolated. A 3-aminopyrrole can alternatively be obtained by catalytic reduction of a 3-nitropyrrole which is a stable compound and can be N-alkylated by various methods. The presence of a supplementary electron-withdrawing substituent is required in order to stabilize the 3-aminopyrrole after reduction of the nitro group. For these reasons, we selected ethyl 4-nitropyrrole-2-carboxylate **8a**, readily prepared from glycine ethyl ester hydrochloride and sodium nitromalonic aldehyde as described by Lee et al (11) (scheme 3). The required sodium nitromalonic aldehyde was obtained according to a published procedure (12) but was neither isolated nor dried because it has been described as a potentially explosive compound.

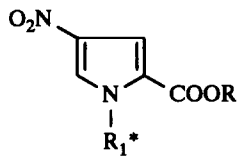


Scheme 3

The validity of the proposed synthetic scheme was verified as follows : the alkylation reaction of **8a** with methyl iodide was carried out with sodium methoxide as a base but in medium yield (60 %) due to the formation of much tarry material. Hydrogenation of the nitro compound proceeded smoothly at room temperature, using 5 % palladium on carbon as catalyst (it should be emphazised that compound **8b** must be absolutely pure to prevent poisoning of the catalyst). After filtration of the catalyst, the resulting solution was allowed to react with the synthon **7** and afforded the pyrrolo[3,2-b]pyridine **10b** in very good yield (80 % based on **8b**). When the nitropyrrole was not alkylated, the corresponding aminopyrrole was less stable and tarry material was also obtained during the reaction with **7**. As a consequence, the yield was lower (48 %) and the product was very difficult to purify. In this case compound **9** was isolated after a few hours heating in acidic medium and it was necessary to increase the reaction time with a view to ensuring the ring closure leading to **10a**.

Having at hand a versatile route to obtain the target compound, we focused our attention towards the alkylation of pyrrole **8a** with other reagents and especially with chiral compounds of the type R_1^*X. In these compounds, X must be a good leaving group like a halogen or tosyl and the chiral group R_1^* must contain one or more groups able to coordinate magnesium ions. It is well established that enantioselective reductions with chiral NADH models must be performed in the presence of magnesium ions. These ions are involved in a ternary complex substrate/ Mg^{2+}/ model. In this complex, magnesium ions are coordinated with polar groups in the model. In our laboratory, we have developed chiral NADH models bearing amino alcohol derivatives and we have shown that the alcohol function plays an important role in the enantioselectivity of the hydrogen transfer. Thus, we tried to alkylate the pyrrole **8a** with the p-toluene sulfonate of a N-protected (S)-phenylalaninol **13** using powdered potassium hydroxide and TDA-1 (14). A complex mixture of products was thus obtained and the yield in purified alkylated product **8e** was always poor. The N-H bond of nitropyrrole is sufficiently acidic to undergo the Mitsunobu reaction which usually involves the dehydration reaction between an alcohol and an acidic compound (15). This reaction is often used in the synthesis of esters or in alkylations of phenols, amines or heterocyclic compounds (16).

Alkylation reagent R_1^*OH	R	Yield (%)	Compound nb
 **11**	Et	70	**8c**
 **12**	Et	40	**8d**
 **13**	Et	60	**8e**
 **14**	tBu	52	**8f**
 **15**	Et	42	**8g**



Compounds **8c-g**

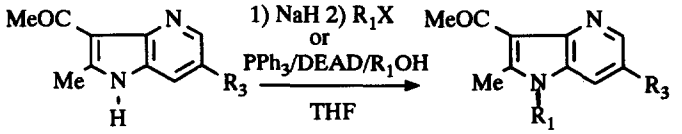
Table 1 : Mitsunobu reaction of chiral alcohols with nitropyrroles

In this case, the reaction was interesting because various chiral primary or secondary alcohols can be used, many of which are commercially available or can be synthesized in a few steps. N,N-dimethyl phenylalaninol **12** was prepared by N,N-dimethylation of phenylalaninol under Eschweiller-Clarke conditions (17). Prolinol derivatives **14** and **15** were obtained according to published procedures (18) (19). The application of the Mitsunobu reaction gave products **8c-g** in yields varying from 45 to 70 % depending of the alcohol used and, as usual, the main problem was the removal of triphenylphosphine oxide from the crude reaction mixture. Purification of compounds **8c-g** was achieved by flash chromatography on alumina. All structures were confirmed by ^1H NMR spectrometry. In order to facilitate the distinction between ($N-CH_2$) protons and CH_2 protons of the ethyl group we found it convenient to use a tert-butyl nitropyrrole carboxylate (20) in the case of compound **8f**. The 400 MHz ^1H NMR spectrum of **8f** was recorded in $CDCl_3$

and showed a characteristic signal centered at 4.12 ppm corresponding to a methylene group adjacent to a chiral carbon bearing a single proton (two coupling constants of 5.5 and 13.5 Hz were observed). The nitropyrroles **8c-g** were reduced with hydrogen according to scheme 3. In the case of compound **8c** (R = chiral sec-butyl), the reduction reaction proceeded quickly. The amino derivative was subsequently cyclized with synthon **7** and afforded the pyrrolo[3,2-c]pyridine **10c** in excellent overall yield. Unfortunately, the same reduction reaction did not give any results in the case of compounds **8d-g**. The absorption of hydrogen stopped after a few minutes and simply increasing of the amount of catalyst was unsuccessful. However, as can be seen, the application of the Mitsunobu reaction allowed the obtention of a series of nitropyrroles having a chiral centre on the pyrrole nitrogen.

Alkylation reactions after construction of the pyridine ring

Another possibility consists in alkylation of the pyrrole nitrogen of a previously constructed pyrrolo[3,2-b]pyridine. As mentioned above, the reaction scheme 3 afforded poor yields in non-alkylated pyrrolopyridine **10a**. Thus, we tried to alkylate compound **6** and its corresponding carboxamide derivative **17**, obtained after controlled hydrolysis.



6 R_3 = CN
17 R_3 = $CONH_2$

Scheme 4

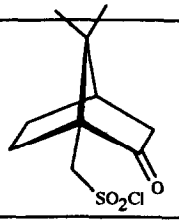
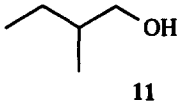
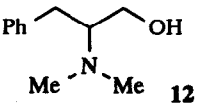
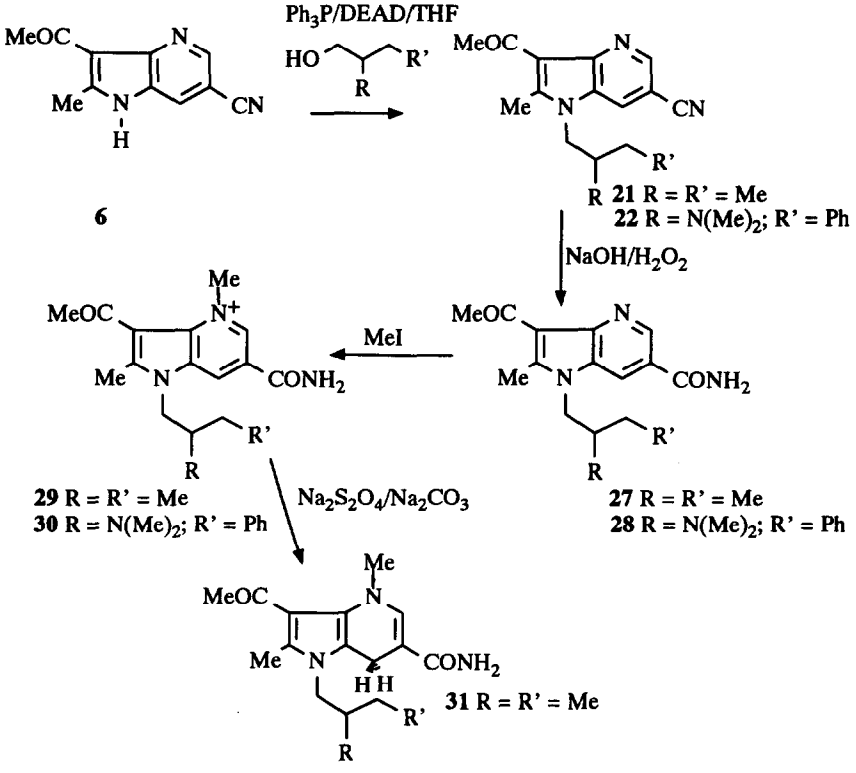
entry	R_3	R_1X	conditions	result (yield %)
1	$CONH_2$	EtI	NaH/THF 50°C/24h	**18** (63 %)
2	$CONH_2$	TsCl	NaH/THF r. t. / 20h	**19** (47 %)
3	$CONH_2$		NaH/THF r. t. / 48h	**20** (40 %) + **17**
4	CN	 **11**	PPh_3/DEAD THF reflux 48h	**21** (46 %)
5	CN	 **12**	PPh_3/DEAD THF reflux 48h	**22** (60 %)

Table 2 : Reactions of **17** with halides or sulfonylating reagents and Mitsunobu reactions of **6** with chiral alcohols

Carboxamide **17** (scheme 4) was allowed to react with sodium hydride in THF and the anionic species was then trapped with various alkylating reagents R_1-X. The results are listed in table 2. The yield was acceptable (63 %) only in the case of R_1= Et (entry 1). In the other cases, the initial product **17** was recovered, sometimes with some tarry material. The yields of alkylated product were always very poor.

The situation was the same when sulfonylating reagents were used (table 3). With tosyl chloride , compound **19** was obtained in 47 % yield (entry 1) and with (+)-10-camphor sulfonyl chloride, the reaction was partial and pyrroloyridine **20** was obtained , only in 40 % yield, with great difficulties at the purification stage, due to the presence of the unchanged compound **17**. At this stage of our study, we can conclude that several factors hinder the alkylation of the pyrrole nitrogen of compound **17** : 1) the methyl group in 2-position causes significant steric hindrance and, as a consequence, substitution of the pyrrole nitrogen with a secondary carbon atom is impossible. 2) compound **17** is only poorly soluble in organic solvents. 3) the 2-methyl and the 3-acetyl groups can both modify the reactivity of the pyrrole nitrogen and can be responsible for side reactions, especially in basic medium, leading to degradation products. The 2-methyl substituent can also be involved in side reactions in basic medium favoured by the presence of the 3-acetyl group leading to C-alkylation instead of N-alkylation.

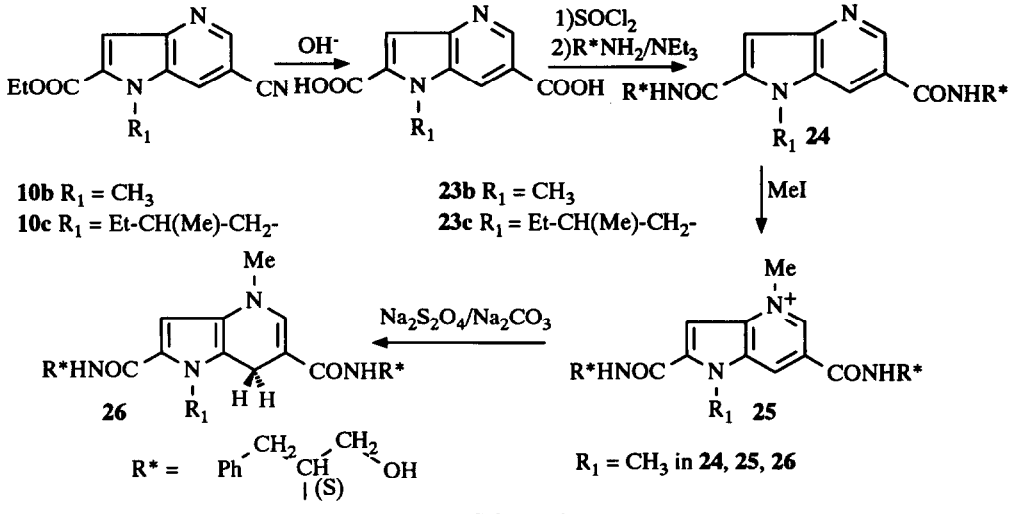
For these reasons, we decided to use the Mitsunobu reaction again but with a more soluble pyrrolopyridine derivative, compound **6**. The two chiral alcohols **11** and **12** were used leading to N-alkylated pyrrolopyridines **21** and **22** in 46 and 60 % yield respectively (scheme 5).



Scheme 5

Application to the synthesis of chiral NADH models :

Despite the difficulties encountered, four new pyrrolo[3,2-b]pyridine derivatives were obtained (compounds **10b, 10c, 21, 22**), three of them possessing a chiral center on the pyrrole nitrogen.



Scheme 6

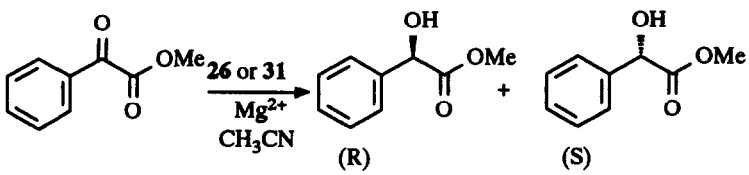
The nitrile and ester groups of **10a** were hydrolyzed and the diacid so obtained was converted in the chiral dicarboxamide **24** by condensation with two equivalents of (S)-phenylalaninol (scheme 6). After quaternization with methyl iodide followed by regioselective reduction with sodium dithionite of the intermediate pyridinium salt **25**, the chiral 1,4-dihydropyridine **26** was obtained.

The nitriles **21** and **22** (scheme 5) were converted in carboxamides **27, 28** by mild alkaline hydrolysis using the hydrogen peroxide/sodium hydroxide system (scheme 5). Quaternization of these derivatives was achieved in DMF with methyl iodide with a quantitative yield in the case of **28.**

Unfortunately, it was impossible to convert the pyridinium salt **30** into 1,4-dihydropyridine by reduction with sodium dithionite. Given that type of reaction is known to be very sensitive to the steric hindrance in the vicinity of the 4-position of the pyridine ring, we think that the bulkiness of the chiral moiety is responsible of this negative result. With the less bulky sec-amyl group the reduction was possible and dihydropyridine **31** was obtained in 80 % yield.

Reduction of a prochiral compound with chiral NADH models 26 and 31.

The dihydropyridines **26** and **31** were employed in the reduction of methyl benzoylformate, the standard substrate for this type of reaction. The results are collated in table 4.



Compound	Conditions Mg^{2+}/(model)	e. e. (c) (%)	Yield (%)	major enantiomer
26	1 (a)	54	55	R
26	3 (a)	45	50	R
26	5,5 (a)	51	53	R
31	1 (b)	6	73	S
31	1 (a)	6	64	S

(a) temperature 60°C ; time 24 h

(b) r.t. during 72h then 60°C/24h

(c) determined by HPLC separation

Table 4 : reductions of methyl benzoylformate with NADH models **26** and **31**

First of all, it can be seen that the enantiomeric excess obtained with **31** is low (6 %), the major enantiomer having (S) configuration. This low enantioselectivity may be attributed to the lack of complexing groups in the chiral moiety (a good complexation with Mg^{2+} ions is necessary to obtain good e.e. as explained before).

With compound **26**, possessing two chiral moieties the e.e. is better. In a previous paper (8), we reported that model **2b** (scheme 1), its isoster in the pyrrolo[2,3-b]pyridine series, allowed the obtention either of the (R) or the (S) enantiomer depending on the magnesium ion concentration, with a good e.e. It could be presumed that this behaviour was a consequence of an interaction which could be established between the two chiral auxiliaries. This interaction could be of different types depending on the amount of magnesium ions, leading to different stereodifferentiations of the two faces of the dihydropyridine. For these reasons, we performed the reductions with **26** in the presence of various amounts of magnesium ions and we observed that the e.e. were not notably influenced by the amount of magnesium ions. Moreover, the average chemical yield was not improved. The lower enantiomeric excess observed (about 55 %) might be attributed to the absence of interaction between the two chiral moieties. The geometries of the two dihydropyridines **2b** and **26** are quite different. The methyl group of the pyrrole nitrogen of **26** can suppress these interaction and the enantioselectivity observed is similar to that observed with a single chiral centre (5).

Finally, we can conclude that the concept of a chiral centre on the pyrrole nitrogen of a pyrrolo[3,2-b]pyridine was very attractive but its application involves many synthetic difficulties.

Moreover, when the chiral centre was successfully introduced, it diminished both the yields at the final stage of the synthesis and the reductive possibilities of the model.

EXPERIMENTAL

The infra red spectra were recorded on a Beckman IR 4250 spectrometer. The ^1H NMR spectra were recorded on a 60 MHz Varian EM 360 L spectrometer, on a 200 MHz or on 400 MHz Brucker AM 400 spectrometer. Unless otherwise stated, the NMR spectra were recorded in deuteriochloroform. Microanalyses were obtained from a Carlo Erba 1106 apparatus. Enantiomeric excesses were determined by HPLC, after separation of the enantiomers by using a Waters apparatus and a L.K.B. Enantiopac as a chiral column (21) or after derivatization of the chiral alcohols by Mosher's method and analysis by GPC (22). Solvents used in the reductions with NADH model compounds were degassed after bubbling with dry argon for, at least, a quarter of an hour before use. Acetonitrile was distilled on calcium hydride prior to use. Tetrahydrofuran was distilled from sodium-benzophenone ketyl.

Ethyl 1-methyl-4-nitropyrrole-2-carboxylate: 8b

A mixture of sodium ethoxide (prepared with 0.27g of sodium and 10 ml of ethanol) in ethyl alcohol (10 ml), 1.8 g (9.78 mmol) of nitropyrrole ester **8a** and 2.2 ml (35.3 mmol) of methyl iodide was stirred 48 h at room temperature. The reaction was monitored by TLC [dichloromethane , R_f = 0.35 for the target compound]. The solvent was removed, the remaining solid dissolved in water (10 ml) and extracted twice with dichloromethane. The organic extracts were dried over magnesium sulphate and evaporated to dryness to yield 2.9 g (70 %) of crude **8b**. This compound was recrystallized from ethanol (60 mg/ml) before catalytic reduction. m.p. = 115 °C. ^1H NMR: 1.2 (t, 3H, J = 7 Hz, CH_3 ester), 3.7 (s, 3H, N-CH_3), 4.25 (q, 2H, J = 7 Hz, CH_2 ester), 7.2 (d, 1H, J = 2 Hz, H_3), 8.3 (d, 1H, J = 2 Hz, H_5). IR: 1710 (C=O), 1500 (NO_2). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.3; H, 4.9; N, 13.9.

3-acetyl-1-ethyl-2-methylpyrrolo[3,2-b]pyridine-6-carboxamide : 18

To a stirred suspension of sodium hydride (80 % dispersion in mineral oil, 0.09 g, 3 mmol) in anhydrous THF (10 ml) were added compound **17** (0.245 g, 1 mmol) and ethyliodide (1 ml, 12.5 mmol). The mixture was gradually heated to 50°C and maintained at this temperature during 24h. The solvent was then removed under reduced pressure, water (10 ml) was added and the product extracted with ethylacetate (30 ml). The organic layer was washed with water and dried. After removal of the solvent, carboxamide **18** was obtained in 63 % yield. ^1H NMR (DMSO-d_6) : δ 1.3 (t, J= 7Hz, 3H, CH_3), 2.8 (s, 6H, $COCH_3$ and 2-CH_3), 4.3 (9, J = 7Hz, 2H, N-CH_2), 7.5 (m, 1H, $CONH_2$) ; 8.1 (m, 1H, $CONH_2$), 8.4 (d, J = 2 Hz, 1H, H_7), 9.0 (d, J = 2 Hz, 1H, H_5). IR (cm^{-1}) : 1650 (C=O).

General procedure for the sulfonylation of 17.

A mixture of carboxamide **17** (0.49 g, 2 mmol) and sodium hydride [2.6 mmol; 80 % dispersion in mineral oil] in anhydrous THF (20 ml) was heated at 55°C for two hours. After ice cooling, a solution of sulfonylating agent RSO_2Cl (4 mmol) in anhydrous THF (5 ml) was added dropwise. The mixture was subsequenty worked up as mentioned in table 2. After removal of the solvent, the residue was dissolved in dichloromethane and washed with water. The organic layer was dried and concentrated under reduced pressure.

3-acetyl-2-methyl-1-p-toluenesulfonylpyrrolo[3,2-b]pyridine-6-carboxamide 19 :

The crude product was purified by flash chromatography on neutral alumina using a dichloromethane / ethanol (97 / 3) mixture. The yield was 47 %. ^1H NMR (DMSO-d6) : δ 2.3 (s, 3H, CH_3 tosyle) ; 2.8 and 2.75 (2s, 6H, $COCH_3$ and 2-CH_3) ; 7.4 (d, J = 8 Hz, 2H) ; 8.3 and 7.65 (m, 2H, NH_2) ; 7.9 (d, J = 8 Hz, 2H) ; 8.8 (d, J = 2 Hz, 1H, H_7) ; 9.0 (d, J = 2 Hz, 1H, H_5). IR: 1670 (C=O), 1650 (C=O), 1190 and 1170 (SO_2).

3-acetyl-1-camphorsulfonyl-2-methylpyrrolo[3,2-b]pyridine-6-carboxamide : 20

The reaction was conducted as above with (+)-10-camphorsulfonyl chloride. A mixture of **20** and initial compound **17** was obtained (40/60 %). Carboxamide **20** was not isolated. In the ^1H NMR spectra of the crude product, the signals corresponding to pyridine protons H_5 and H_7 were notably deshielded. ^1H NMR (DMSO-d_6) :

Compound **17** : 8.2 (d, J = 2 Hz, 1H, H_7) ; 8.9 (d, J = 2 Hz, 1H, H_5)

Compound **20** : 8.7 (d, J = 2 Hz, 1H, H_7) ; 9.05 (d, J = 2 Hz, 1H, H_5)

General procedure for the Mitsunobu reaction of chiral alcohols with 4-nitropyrroles-2-carboxylates.

In a 250 ml three-necked flask, flushed with dry argon, were dissolved 10 mmol of 4-nitropyrrole-2-carboxylate, 2.62 g (10 mmol) of triphenylphosphine, 10 mmol of the appropriate chiral alcohol in 15 ml of anhydrous THF. A solution of 1.74 g (10 mmol) of diethyl azodicarboxylate in 5 ml of anhydrous THF was then added dropwise with a syringe. During this addition, the temperature was maintained at 18-20 °C by cooling with a waterbath. The reaction mixture was stirred 1 h at room temperature and gently heated to reflux for 24 h. The solvent was removed and ether (50 ml) was added. The triphenyl phophine oxyde was slowly filtered and the ethereal solution evaporated to dryness. The residual viscous oil was purified by flash chromatography (alumina, ether).

Ethyl 1-(2-methylbutyl)-4-nitropyrrole-2-carboxylate: 8c

Starting with 1.84 g (10 mmol) of ethyl 4-nitropyrrole-2-carboxylate, we obtained 1.78 g (70 %) of ester **8c** as a very viscous oil. ^{1}H NMR: 2.0 (m, 12H, CH, CH_3, C_2H_5 and CH_3 ester); 4-5 (m, 4H, N-CH_2 and CH_2 ester) ; 7.45 (d, J = 2 Hz, 1H, H_3); 7.65 (d, J = 2 Hz, 1H, H_5). IR: 1720 (C=O), 1500 (NO_2). Anal.Calcd for $C_{12}H_{18}N_2O_4$: C, 56.58; H, 7.13; N, 11.02. Found: C, 56.9; H, 6.95; N, 9.9.

Ethyl 1-[2-(N,N)-dimethylamino-3-phenylpropyl]-4-nitropyrrole-2-carboxylate: 8d

Starting with 1.84 g (10 mmol) of ethyl 4-nitropyrrole-2-carboxylate, we obtained 1.38 g (40 %) of ester **8d** as a viscous oil. ^{1}H NMR: 1.3 (t, J = 7 Hz, 3H, CH_3 ester); 2.3 (s, 6H, $N(CH_3)_2$); 2.5-4.5 (m, 7H, N-CH_2, chiral CH, CH_2-Ph, CH_2 ester); 7.0-8.0 (m, 7H, phenyle ring, H_3, H_5). Anal. Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.3 ; H, 6.6; N, 12.0.

Ethyl 1-[3-phenyl-2-tert-butoxycarbonylaminopropyl]-4-nitropyrrole-2-carboxylate: 8e

Starting with 1.84 g (10 mmol) of ethyl 4-nitropyrrole-2-carboxylate, we obtained 2.5 g (60 %) of ester **8e** as an oil. ^{1}H NMR: 1.25 (m, 12H, tBu, CH_3 ester); 2.9 (m, 2H, CH_2-Ph); 4.0-5.0 (m, 5H, N-CH_2, CH_2 ester, chiral CH); 7.15 (s, 5H, phenyle ring); 7.25 (d, J = 2 Hz, 1H, H_3); 7.4 (d, J = 2 Hz, 1H, H_5). IR: 1520 (NO_2); 1715 (C=O); 3360 (NH). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 61.0; H, 6.2; N, 9.6.

tert-butyl 1-[-2-[N-methylpyrrolidine]-ylmethyl]-4-nitropyrrole-2-carboxylate: 8f

Starting with 2.12 g (10 mmol) of tert-butyl 4-nitropyrrole-2-carboxylate (20) and 1.15 g (10 mmol) of N-methyl (S) prolinol (19), we obtained 1.6 g (52 %) of a viscous yellow oil wich crystallized slowly. ^{1}H NMR: (400 MHz): 1.4-1.8 (m, 4H, 3 and 4 CH_2 in pyrrolidine ring); 1.53 (s, 9H, tert-butyle); 2.22 (s, 3H, N-CH_3); 2.25 and 2.61 (m, 2H, 5-CH_2 in pyrrolidine ring); 3.03 (m, 1H, chiral CH); 4.12 (dd, J = 5.5 and 13.3 Hz, 1H, one H on N-CH_2); 4.53 (dd, J=5.5 and 13.3 Hz, 1H, the other H on N-CH_2); 7.3 (d, J = 2 Hz, 1H, H_3); 7.68 (d, J = 2 Hz, 1H, H_5). Anal. Calcd for $C_{15}H_{23}N_3O_4$: C, 58.24; H, 7.49; N,13.58. Found: C, 58.0; H, 7.2; N, 13.2.

Ethyl 1-[-2-[N-tert-butoxycarbonylpyrrolidine]-ylmethyl]-4-nitropyrrole-2-carboxylate: 8g

Starting with 1.84 g (10 mmol) of ethyl 4-nitropyrrole-2-carboxylate, we obtained 1.52 g (42 %) of a yellow oil with crystallized slowly. m.p. = 97°C. ^{1}H NMR: 1.15-2.0 (m, 13H, 3 and 4 CH_2 in pyrrolidine ring , tert-butyl); 3.2-3.6 (m, 2H, 5-CH_2 in pyrrolidine ring); 4.8 (m, 5H, CH_2 ester, N-CH_2, chiral CH); 7.4 (d, J = 2 Hz, 1H , H_3); 7.6 (d, J = 2 Hz; 1H, H_5). Anal. Calcd for $C_{17}H_{25}N_3O_6$: C, 55.58; H, 6.86; N, 11.44. Found: C, 55.5; H, 6.6; N, 10.9

General procedure for the ring closure reaction of 2-nitropyrroles in pyrrolo[3.2-b]pyridines.

A solution of the appropriate 4-nitropyrrole-2-carboxylate (20 mmol) and 5 % palladium on charcoal (0.65g) in methanol (75 ml) was hydrogenated at atmospheric pressure and room temperature until TLC analysis indicated complete reduction of the nitrocompound. The catalyst was removed by filtration and the filtrate immediatly tranferred to a dropping funnel placed under an argon atmosphere. This solution was gradually added to a stirred mixture of the sodium salt of 3,3-dimethoxy-2-formyl-propionitrile **7** (2.25g , 13.6 mmol) in methanol (25 ml) and concentrated aqueous hydrochloric acid (1 ml).

After this addition, the mixture was acidified with approximately 0.5 ml of concentrated hydrochloric acid to pH 1. The reaction mixture was then heated to reflux for two hours and acidified again with the same amount of concentrated hydrochloric acid to pH 1. The mixture was heated to reflux overnight. After cooling at room temperature, the solvent was eliminated and gradually replaced with water. The further work up depended upon the target compound.

2-ethoxycarbonylpyrrolo[3,2-b]pyridine-6-carbonitrile : 10a

Starting from 3.68 g (20 mmol) of ethyl 4-nitropyrrole-2-carboxylate **8a** (recrystallized from methanol), 2 g (48 %) of nitrile ester **10a** were obtained and could be purified by flash chromatography with neutral alumina (ethyl acetate as eluant). ^{1}H NMR (DMSO-d_6) : 1.35 (t, J = 7 Hz, 3H, CH_3 ester) ; 4.4 (q, J = 7 Hz, 2H, CH_2 ester), 7.33 (s, 1H, H_3) ; 8.33 (s, 1H, H_7) ; 8.80 (s, 1H, H_5). IR : 2230 (CN) ; 1720 (C=0). Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39 ; H, 4.22 ; N, 19.52. Found : C, 61.5 ; H, 4.15 ; N, 19.2.

2-ethoxycarbonyl-1-methyl-pyrrolo[3,2-b]pyridine-6-carbonitrile: 10b

Starting with 4.0 g (20.2 mmol) of ethyl 1-methyl-4-nitropyrrole-2-carboxylate **8b**, 4.5 g of crude nitrile ester **10b** were obtained and could be used without further purification. This compound was recrystallized from ethanol (1 g / 35 ml). m.p. = 188 °C. ^{1}H NMR : 1.3 (t, J = 7 Hz, 3H, CH_3 ester); 4.0 (s, 3H, N-CH_3); 4.3 (t, J = 7 Hz, 2H, CH_2 ester); 7.35 (s, 1H, H_3); 8.75 (s, 2H, H_5 and H_7). IR : 1720 (C=O); 2220 (CN). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.8; H, 4.7; N, 18.4.

2-ethoxycarbonyl-1-(2-methylbutyl)-pyrrolo[3,2-b]pyridine-6-carbonitrile: 10c

Starting with 5.1 g (20 mmol) of ethyl 1-(2-methylbutyl)-4-nitropyrrole-2-carboxylate **8c**, 1.71 g (30 %) of pure nitrile ester **10c** were obtained after recrystallization of the crude product in ethanol/water (70/30). m.p. = 157 °C. ^{1}H NMR (DMSO-d6): 0.5-2 (m, 12H, CH_3 ester, chiral CH, CH_3-CH_2 and CH_3); 4.0-4.5 (m, 4H, N-CH_2 and CH_2 ester); 7.4 (s, 1H, H_3); 8.8 (m, 2H, H_5 and H_7). IR : 1720 (C=O); 2220 (CN). Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.15; H, 6.8; N, 14.55.

1-methyl-pyrrolo[3,2-b]pyridine-2,6-dicarboxylic acid: 23b

A mixture of nitrile ester **10b** (2.0 g, 9.3 mmol) in ethanol (25 ml) and 25 % aqueous sodium hydroxide (38 ml) was heated to reflux for 24 h. After cooling, the alcohol was removed under reduced pressure and the remaining aqueous solution was acidified cautiously to pH 1 with concentrated hydrochloric acid. The solid material was filtered and thoroughly washed with cold water. The yield was 1.54 g (75 %). m.p. > 250 °C. ^{1}H NMR (CF_3COOD): 4.0 (s, 3H, CH_3); 7.4 (s, 1H, H_3); 8.9 (s, 2H, H_5 and H_7). IR: 1700 (C=O). Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55, H, 3.66, N, 12.7. Found: C, 54.0; H, 3.5; N, 12.3.

1-(2-methylbutyl)-pyrrolo[3,2-b]pyridine-2,6-dicarboxylic acid: 23c

Similarly, a mixture of nitrile ester **10c** (0.76 g, 2.7 mmol), ethanol (7 ml) and 25 % aqueous sodium hydroxide (11 ml) was refluxed for 48 h. After cooling, the alcohol was removed under reduced pressure and the remaining aqueous solution was acidified cautiously to pH 1 with concentrated hydrochloric acid. The solid material was collected and treated, under magnetic stirring with powdered sodium hydroxide (0.22 g) and water (10 ml). After one hour stirring, the solution was filtered and the filtrate acidified with concentrated hydrochloric acid to pH 1. The solid was collected and dried. The yield was 0.6 g (80 %). m.p. > 250 °C. ^{1}H NMR (CF_3COOD): 0.5-2.0 (m, 9H, chiral CH, CH_3-CH_2 and CH_3); 4.3 (m, 2H, N-CH_2); 7.4 (s, 1H, H_3); 8.9 (s, 2H, H_5 and H_7). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.5; H, 5.5; N, 9.8.

3-acetyl-1-[(S)-2-methylbutyl]-2-methylpyrrolo[3,2-b]pyridine -6-carbonitrile : 21.

To a mixture of pyrrolopyridine **6** (4 g, 0.02 mole), triphenylphosphine (5.35 g, 0.02 mol) and (S)-2-methylbutane-1-ol (1.76 g, 0.02 mol) in anhydrous THF (40 ml) was added dropwise a solution of diethyl azodicarboxylate (DEAD, 3.15 ml, 0.02 mol) in THF (8 ml), the temperature being maintained around 20°C. The mixture was heated under reflux for 40h. The solvent was eliminated and the residue submitted to a flash chromatography on silica with hexane/ethylacetate (2/1). The product (R_f= 0.65) was isolated as a yellow solid in 46 % yield. m.p. = 152°C. α_D^{23} = - 4.8 (c = 1.5 ; chloroform). ^{1}H NMR : 0.8-1.1 (m, 1H, 2CH_3) ; 1.3 (m, 2H, CH_2) ; 2.0 (m, 1H, CH) ; 2.9 and 2.85 (2s, 6H, $COCH_3$ and 2-CH_3) ; 4.1 (d, J = 7 Hz, 2H, N-CH_2) ; 7.9 (d, J = 2 Hz, 1H, H_7) ; 8.8 (d, J = 2 Hz, 1H, H_5). IR : 2230 (CN) ; 1670 (C=O). Anal. calcd for $C_{16}H_{19}N_3O$: C, 71.35 ; H, 7.11 ; N, 15.60. Found C, 70.8 ; H, 6.9 ; N, 15.4.

3-acetyl-[(S)-2,(N,N)dimethyl-3-phenylpropyl]-2-methylpyrrolo[3,2-b]py ridine-6-carbonitrile: 22.

The procedure was the same as above. (S)-2-methylbutane-1-ol was replaced by (S)-2-(N,N) dimethylamino-3-phenylpropanol (compound **12**).

The product was purified by flash chromatography on alumina (dichloromethane as eluent). The yield was 60 %. It was impossible to obtain an analytical sample of this product. ^{1}H NMR : 2.4 (s, 6H, 2-N-CH_3) ; 2.7 (s, 3H, CH_3 in 2 position) ; 2.9 (s, 3H, acetyl group) ; 3.2 (m, 2H, CH_2-Ph) ; 4.0 (m, 3H, N-CH_2 and CH) ; 6.6 (d, J = 2 Hz, 1H, H_7) ; 7.15-7.65 (m, 5H, Ph) ; 8.6 (d, 1H, H_5).

2,6-di(1-hydroxymethyl-2-phenylethyl)aminocarbonyl-1-methyl-pyrrolo[3,2-b]pyridine: 24

A mixture of the above dicarboxylic acid **23b** (2.64 g, 12 mmol) and freshly distilled (on linseed oil) thionyl chloride (25 ml) was heated to reflux for 24 h. After cooling, the excess of thionyl chloride was removed by distillation under reduced pressure and the residue treated twice with benzene and the resulting solution distilled again. The crude acid chloride was dissolved in anhydrous dichloromethane (30 ml) and added dropwise, with a syringe, to a stirred solution of 2-amino-3-phenylpropanol (3.84 g, 0.025 mol) and anhydrous triethylamine (3.53 ml, 0.025 mmol) in dichoromethane (20 ml). During this addition the temperature was maintained at -10 °C by cooling with a ice-salt mixture. The mixture was allowed to warm to room temperature and then stirred for 12 h. The dichloromethane was removed and water (20 ml) was added. The solid was collected by filtration and recrystallized in ethanol/water (3/2) to afford 2.97 g (51 %) of chiral diamide. ^{1}H NMR (400 MHz, DMSO-d6): 2.82 (m, 2H, CH_2Ph); 3.00 (m, 2H, CH_2Ph); 3.53 (m, 4H, CH_2OH), 3.93 (s, 3H, N-CH_3); 4.23 (m, 2H, chiral CH); 4.94 (m, 2H, OH); 7.28 (m, 10H, phenyle groups); 8.38 (s, 1H, H_2); 8.38 (d, J = 2 Hz, 1H, H_7); 8.49 (d, J = 2 Hz, 1H, H_5); 8.83 (s, 1H, NH). IR: 1645 cm^{-1} (C=O). Anal. Calcd for $C_{28}H_{30}N_4O_4$: C, 69.12; H, 6.21; N, 11.51. Found: C, 68.9 ; H, 6.0; N, 11.1.

General procedure for the conversion of nitrile group in carboxamide group using the hydrogen peroxide - sodium hydroxide system.

A solution of nitrile (11 mmol) in ethanol (100 ml) was treated with 30 % hydrogen peroxide (5.6 ml, 55 mmol) and 3N aqueous sodium hydroxide (1.8 ml, 54 mmol). During this operation, the temperature was maintained below 40°C. The resulting mixture was stirred at 30-35°C for 30 h. The suspension was made neutral with a few drops of 1N sulfuric acid and concentrated under reduced pressure. The final compound was collected by filtration and washed with a small amount of cold water.

3-acetyl-2-methyl-1-[(S)-2-methylbutyl]pyrrolo[3,2-b]pyridine-6-carboxamide : 27.

Starting from compound **21**, the yield was 95 %. Decomposition of the product was observed at about 100°C. As a consequence, the melting point is not reported. ^{1}H NMR (DMSO-d_6) : 2.8 and 2.9 (2s, 6H, CH_3 in 2-position and CH_3 acetyl) ; 4.0 (m, 2H, N-CH_2) ; 8.3 (d, 1H, H_7) ; 9.0 (d, 1H, H_5). IR : 1640 (C=O) ; 1665 (C=O). Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.87 ; H, 7.37 ; N, 14.62. Found C, 64.4 ; H, 7.2 ; N, 13.4.

3-acetyl-2-methyl-1-[(S)-2-(N,N)dimethyl-3-phenylpropyl]pyrrolo[3,2-b]pyridine-6-carboxamide : 28.

Starting from compound **22**, the yield was 90 %.

F > 250°C. ^{1}H NMR (DMSO-d_6) : 2.2 (s, 6H, 2XN-CH_3) ; 2.5 and 2.7 (2s, 6H, CH_3 in 2 position and CH_3 acetyl) ; 4.1 (m, 2H, N-CH_2) ; 7.2 (s, 5H, Ph) ; 7.4-8.0 (m, 2H, NH_2 amide) ; 8.1 (d, J = 2 Hz, 1H, H_7) ; 8.9 (d, J = 2 Hz, 1H, H_5). IR : 1640 and 1660 (C=O). Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.89 ; H, 6.92 ; N, 14.80. Found : C, 70.2 ; H, 6.5 ; N, 14.6.

3-acetyl-1-[(S)-2-methylbutyl]-6-aminocarbonyl-2,4-dimethylpyrrolo[3,2-b]pyridinium iodide : 29

A mixture of carboxamide **27** (4 mmoles) in DMF (7 ml) and methyl iodide (2 ml, 32.1 mmoles) was heated at 70°C in an oil bath for 3 days. After dilution with diethyl ether, the pyridinium salt was filtered and dried. ^{1}H NMR (DMSO-d_6) : 0.65-1.45 (m, 9H, aliphatic protons) ; 2.7-2.8 (2s, 6H, $COCH_3$ and 2-CH_3) ; 3.9 (s, 3H, N-CH_3) ; 4.3 (m, 5H, N-CH_2 and N-CH_3) ; 8.25 (m, 2H, NH_2) ; 9.2 (m, 2H, H_5 and H_7).

3-acetyl-6-carboxamido-2,4-dimethyl-1-[(S)-2-(N,N)dimethyl-3-phenylpropyl]pyrrolo[3,2-b]pyridi nium iodide : 30.

Similarly with the quaternization of **27** described above, the pyridinium salt **30** was obtained in 100 % yield. ^{1}H NMR (DMSO-d_6) : 2.2 (s, 6H, 2XN-CH_3) ; 2.5 and 2.7 (2s, 6H, CH_3 in 2-position and CH_3 acetyl)

; 4.1 (m, 2H, N-CH_2) ; 7.2 (s, 5H, Ph) ; 7.4-8.0 (m, 2H, NH_2 amide) ; 9.1 (s, 2H, H_5 and H_7). IR : 1640 and 1660 (C=0). Anal. Calcd for $C_{23}H_{29}IN_4O_2$: C, 53.08 ; H, 5.61 ; N, 10.76. Found : C, 52.5 ; H, 5.2 ; N, 10.2.

2,6-di(1-hydroxymethyl-2-phenylethyl)aminocarbonyl-1,4-dimethyl-pyrrolo[3,2-b]pyridinium iodide: 25

A mixture of dicarboxamide (2 g, 4.1 mmol) in DMF (7 ml) and methyl iodide (2 ml, 32.1 mmol) was heated at 70 °C, in an oil bath for 4 days. The reaction was monitored by TLC (Al_2O_3 plates and elution with ethyl acetate and methanol 95/5). After cooling, a large amount of anhydrous ether was added and the pyridinium salt filtered quickly. The yield was 1.55 g (60 %) of a very hygroscopic crystallized solid with no defined melting point. ^1H NMR (DMSO-d6): 2.7-3.8 (m, 10 H, CH_2ph and CH_2OH); 4.0 (s, 3H, pyrrole N-CH_3); 4.4 (s, 3H, pyridine N-CH_3); 4.9 (m, 2H, chiral CH); 7.3 (s, 10H, phenyle groups); 7.5 (s, 1H, H_3); 8.7 (m, 2H, NH); 9.3 (m, 2H, H_5 and H_7). IR: 3350 (N-H); 1660 (C=O). Anal. calcd for $C_{29}H_{33}IN_4O_4$: C, 55.41; H, 5.29; N, 8.91. Found: C, 54.5; H, 4.8; N, 8.5.

General procedure for the reduction of chiral pyridinium salts with sodium dithionite :

The pyridinium salt was dissolved with heating in the minimum of a methanol/water mixture (2/1). One equivalent of sodium carbonate and one equivalent of sodium dithionite were then added to the solution, under stirring and an argon atmosphere. After stirring for 45 mn, the same amounts of sodium carbonate and dithionite were added. This procedure was repeated five times. After the additions, the solution was stirred overnight. The dihydropyridine was extracted three times with dichloromethane. The extracts dried with magnesium sulfate afforded, after evaporation of the solvent, a crude dihydropyridine which can be used for reduction without further purification.

2,6-di[N-((S)-(1-hydroxymethyl-2-phenyl)ethyl)]aminocarbonyl-1-methyl-4,7-dihydropyrrolo[3,2-b]pyridine : 26

Starting from **25**, the yield in crude dihydropyridine **26** was 60 % Yellow oil. ^1H NMR (DMSO-d6) : 2.6-3.7 (m, 16H) ; 6.5 (m, 1H, H_5) ; 7.2 (m, 11H, H_3 et 2 Ph).

3-acetyl-1-[(S)-2-methybutyl]-2,4-dimethyl-4,7-dihydropyrrolo[3,2-b]pyridine-6-carboxamide: 31

Starting from **29**, the yield in crude dihydropyridine **31** was 80 %. Yellow oil. ^1H NMR : 0.7-1.4 (m, 9H, aliphatic protons) ; 2.45 and 2.3 (2s, 6H, $COCH_3$ and 2-CH_3) ; 2.9 (d, J = 7 Hz, 2H, N-CH_2) ; 3.15 (s, 3H, N-CH_3) ; 3.65 (s, 2H, $2H_7$) ; 7.0 (s, 1H, H_5).

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