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Homochiral NADH models in the pyrrolo[2,3-*b*]pyridine series bearing one or two chiral auxiliaries. Asymmetric reduction of methyl benzoylformate and *N*-acetyl-enamines. Influence of the magnesium salt concentration on the asymmetric induction of reductions

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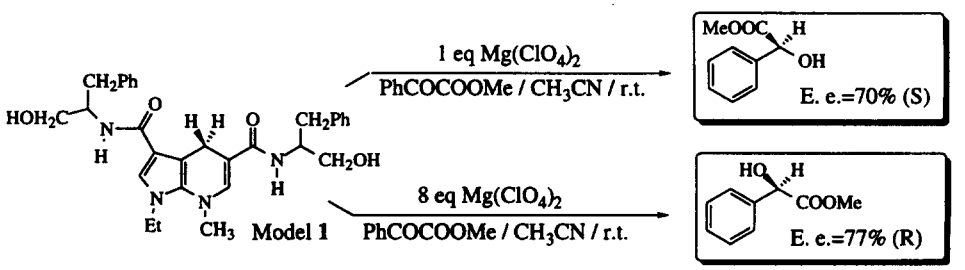
Abstract: The synthesis of NADH models in the pyrrolo[2,3-*b*]pyridine series bearing one or two chiral auxiliaries either at the pyridine or at the pyrrole ring is described. These models were involved in the reduction of methyl benzoylformate. The reactivity of these reagents and the stereochemical outcome of reductions are discussed in relation to the nature of the chiral auxiliary at the pyrrole ring and the magnesium ions concentration. Reagent **3** showed an exceptional reactivity in the reduction of methyl benzoylformate affording methyl mandelate within a few minutes in a good enantiomeric excess (e.e.=84%). Lastly, model **1** was involved in the asymmetric reduction of *N*-acetyl-enamines **15** and **16**, precursors of Salsolidine and Carnegine respectively. In the course of this study, *N*-acetyl-enamine **15** could be reduced in up to 87% e.e. © 1997 Published by Elsevier Science Ltd

In the past, we described the synthesis of the chiral NADH model **1** in the pyrrolo[2,3-*b*]pyridine series[1] bearing two chiral auxiliaries derived from (S)-phenylalaninol at the dihydropyridine and at the pyrrole rings (Scheme 1). An original behaviour of model **1** was observed during the reduction of methyl benzoylformate. Interestingly, methyl mandelate was obtained in good enantiomeric excesses with either (S) or (R) configuration simply by changing the magnesium ions concentration (Scheme 1).



Scheme 1.

Its original behaviour is exemplified by the results obtained with reagent **2** in the asymmetric reduction of methyl benzoylformate.[2] Indeed, under the same conditions (1 eq Mg^{2+}/r.t./CH_3CN) model **2** which bears only one chiral auxiliary derived from the same aminoalcohol, provided methyl mandelate with a configuration which is opposite to that obtained with model **1**.

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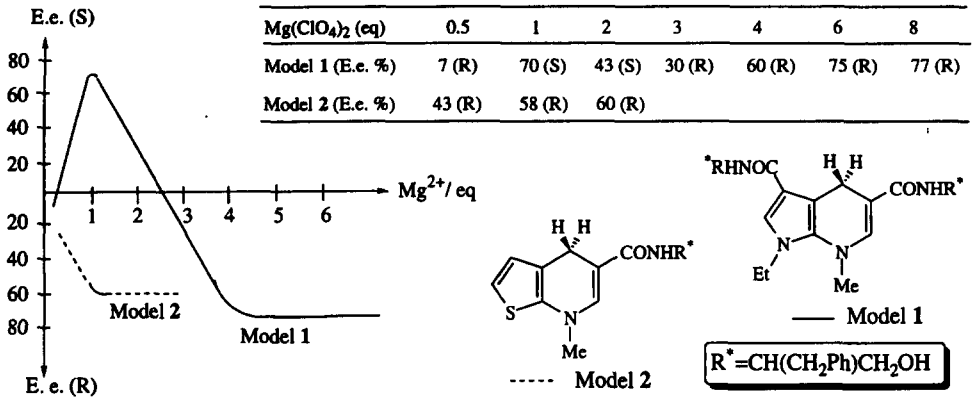


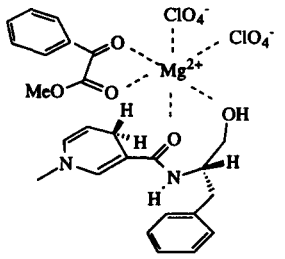
$Mg(ClO_4)_2$ (eq)	0.5	1	2	3	4	6	8
Model 1 (E.e. %)	7 (R)	70 (S)	43 (S)	30 (R)	60 (R)	75 (R)	77 (R)
Model 2 (E.e. %)	43 (R)	58 (R)	60 (R)				

Figure 1. Stereochemical course of the reduction of methyl benzoylformate with reagents **1** and **2** in the presence of increasing amounts of $Mg(ClO_4)_2$.

In addition, although the enantioselectivity was slightly improved upon addition of increasing amounts of magnesium perchlorate, model **2** did not undergo inversion of stereoselectivity as observed with reagent **1**. The stereochemical course of both reagents **1** and **2** is outlined in Figure 1.

It is commonly assumed that the enantioselective hydrogen transfer from a chiral NADH model to a prochiral substrate in the presence of magnesium perchlorate is governed by the occurence of a ternary complex model/Mg^{2+}/substrate.[3] The structure of this ternary complex is still abundantly studied to understand the main structural features responsible for the stereocontrol of the reaction. In this respect, we could clear up the role of an aminoalcohol as chiral auxiliary in the stereodifferentiation of the two faces of the dihydropyridine ring. Indeed, a detailed NMR study of a model bearing a chiral auxiliary derived from phenylalaninol in the presence of magnesium perchlorate clearly indicated the formation of a quasi cyclic structure of the chiral auxiliary *via* complexation of the magnesium ion with both carbonyl amide and alcohol function.[4]

This supplementary internal chelation site would promote the rigidification of the chiral auxiliary to improve the stereodifferentiation of the two diastereotopic faces of the dihydropyridine in the ternary complex. According to this spectroscopic NMR study, the following ternary complex can be proposed to explain the preferential formation of (R)-methyl mandelate (e.e.=58%) during the reduction of methyl benzoylformate (Scheme 2).



Scheme 2. Proposed ternary complex.

These results seem to imply that the original behaviour of model **1** depicted in Figure 1 may be imputed to the presence of the substituent at the pyrrole ring likely modifying the structure of the ternary complex proposed in Scheme 2.

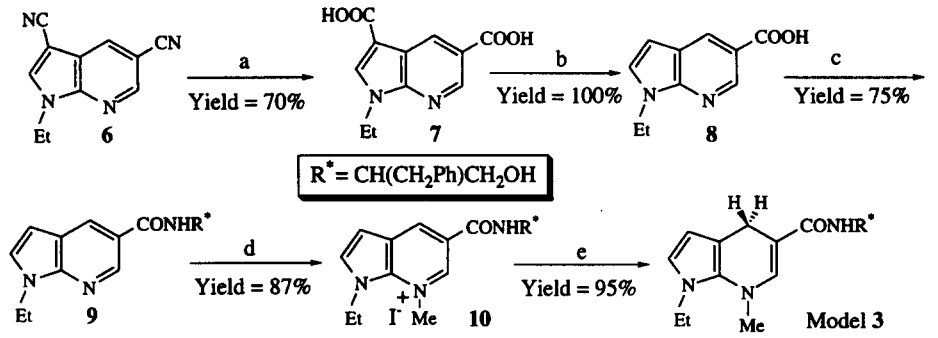
Towards the elucidation on the origin of this inversion of enantioselectivity with model **1**, we report herein the detailed results concerning the synthesis of analog models in the pyrrolo[2,3-*b*]pyridine series and their behaviour in the asymmetric reduction of methyl benzoylformate. With

a view to explore the scope of NADH models in asymmetric synthesis, model **1** will be involved in the asymmetric reduction of *N*-acetyl-enamine derivatives in the tetrahydroisoquinoline series, precursors of Salsolidine and Carnegine. Some aspects of this work has been briefly communicated in a preliminary form.[5]

Results and discussion

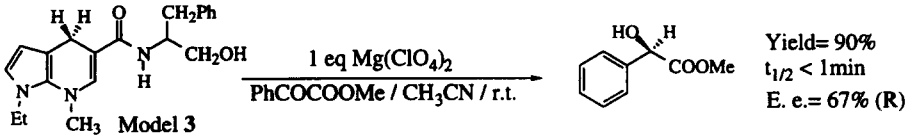
Synthesis of model 3 and asymmetric reduction of methyl benzoylformate

Firstly, to ascertain that the chiral amide at the pyrrole ring of model **1** takes part in the stereocontrol of the reduction, reagent **3** was synthesized following the route depicted in Scheme 3. The readily available dicarbonitrile **6**[6] was hydrolyzed in the presence of sodium hydroxide to yield the diacid **7** in 70% yield. Compound **7** was decarboxylated to give monoacid **8** (100%). Exclusively, decarboxylation occured at the pyrrole ring.[7] Treatment of **8** with *N*-methyl-2-chloropyridinium and (S)-phenylalaninol in the presence of triethylamine afforded amide **9** (75%). The desired model **3** was obtained by quaternization of compound **9** (87%) followed by regioselective reduction of compound **10** (95%).



Scheme 3. a: EtOH/25% NaOH aq; b: 6M HCl aq/reflux /48 h; c: *N*-methyl-2-chloropyridinium (1.1 eq)/NEt_3 (2.2 eq)/(S)-phenylalaninol (1.1 eq)/CH_2Cl_2/reflux/5 days; d: CH_3I/CH_3CN/reflux/4 days; e: $Na_2S_2O_4$ (8 eq)/Na_2CO_3 (5 eq)/N_2/r.t./30 min.

The dihydropyridine reagent **3** is unstable and was engaged immediately without further purification in the reduction of methyl benzoylformate in the presence of increasing amounts of magnesium perchlorate, in acetonitrile under nitrogen. Reagent **3** showed an exceptional reactivity affording methyl mandelate (e.e.=67%) quantitatively at room temperature in less than one minute whereas model **1** required 2 hours under the same conditions (r.t./1 eq Mg^{2+}). In this respect, reagent **3** is probably the most reactive NADH model described in the literature towards the reduction of methyl benzoylformate (Scheme 4).



Scheme 4. Asymmetric reduction of methyl benzoylformate with model **3**.

It is thought that the high reactivity observed would be due to the strong electron donating effect of the annelated pyrrole ring favouring the transfer of the hydride equivalent. The lower reactivity of reagent **1** may be imputed to the presence of the carboxamide function at C-3 reducing the electron donating effect of the pyrrole ring and increasing the steric hindrance at the active site of the reagent.

Model **3** remains efficient at lower temperatures yielding methyl mandelate in a somewhat higher enantioselectivity ($-35°C/t_{1/2}$=8 min/e.e.=84%). The course of the stereoselectivity follows roughly

Table 1. Asymmetric reduction of methyl benzoylformate with model 3

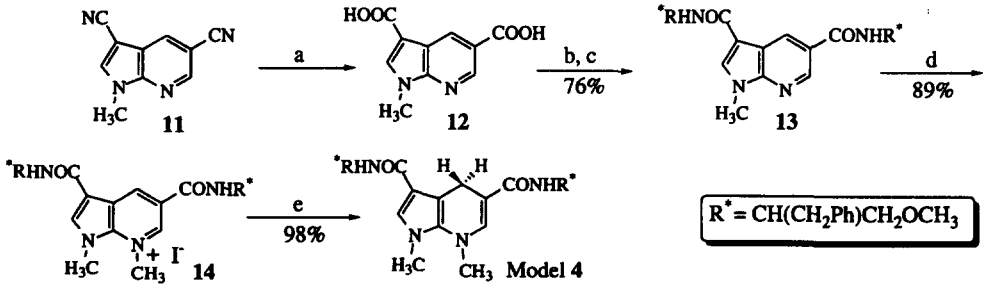
$Mg(ClO_4)_2$ (eq)	0.5	1	2	4	1	1
Temp.(°C)	20	20	20	20	0	-35
E. e. % (Abs.Conf.)	36 (R)	67 (R)	69 (R)	73 (R)	79 (R)	84 (R)

that observed with model **2** giving rise to (R)-methyl mandelate in modest to good enantiomeric excesses (e.e.=36–84%) whatever the amount of magnesium perchlorate (Table 1). This result suggests that the mechanism of asymmetric induction proceeds in a similar manner to that of **2**. The sense of the induction may be explained by a similar ternary complex to that previously depicted in Scheme 2. Lastly, the behaviour of model **3** in the asymmetric reduction of methyl benzoylformate confirms that the presence of the second chiral auxiliary at the pyrrole ring in model **1** is involved in the preferential formation of (S)-methyl mandelate in the presence of 1 eq of magnesium perchlorate and in the preferential formation of (R)-methyl mandelate when an excess of magnesium perchlorate is used.

To account for the formation of the (S)-enantiomer when 1 eq of magnesium ion was used, one may envision an intramolecular interaction between the two chiral auxiliaries in model **1**. Indeed, examination of CPK models reveals that an intramolecular hydrogen bond could occur between the two alcohol functions of the chiral auxiliaries. Consequently, this intramolecular hydrogen bonding could disturb complexation of the magnesium ion with both amide and alcohol functions of the chiral auxiliary as observed in model **2**, modifying the sense of the asymmetric induction. To ascertain this hypothesis, it was of interest to study the behaviour of model **4** in which that potential intramolecular hydrogen bond has been suppressed (Scheme 4).

Synthesis of model 4 and asymmetric reduction of methyl benzoylformate

Model **4** was prepared in a similar manner as model **1**[1] starting from dicarbonitrile **11**[6] and following the general route described in Scheme 6. Diacid **12** was transformed to its corresponding diacid chloride which was subsequently condensed with (S)-2-amino-1-methoxy-3-phenylpropane[8] to provide the chiral diamide **13** in 76% yield. Quaternization of **13** afforded compound **14** in 89% yield. Regioselective reduction of **14** occured quantitatively to yield the desired model **4** (Scheme 5).



Scheme 5. a: EtOH/25% NaOH aq; b: $SOCl_2$/80°C/12h; c: (S)-2-amino-1-methoxy-3-phenylpropane (2 eq)/CH_2Cl_2/NEt_3 (2 eq)/0°C; d: CH_3I (20 eq)/CH_3CN/reflux/10 days; e: $Na_2S_2O_4$ (5 eq)/Na_2CO_3 (8 eq)/r.t./8 h.

With reagent **4** in hand, reduction of methyl benzoylformate was carried out in acetonitrile at room temperature in the presence of different amounts of magnesium perchlorate. It is interesting to note that with most common NADH models possessing a single chiral auxiliary, including model **3**, optimum enantioselectivity are usually observed when 1 eq of magnesium ion is employed. In the case of model **4**, a large amount of magnesium salt is required to attain optimum levels of asymmetric induction. This result may be ascribed to the fact that an additional complexation site for magnesium ion at

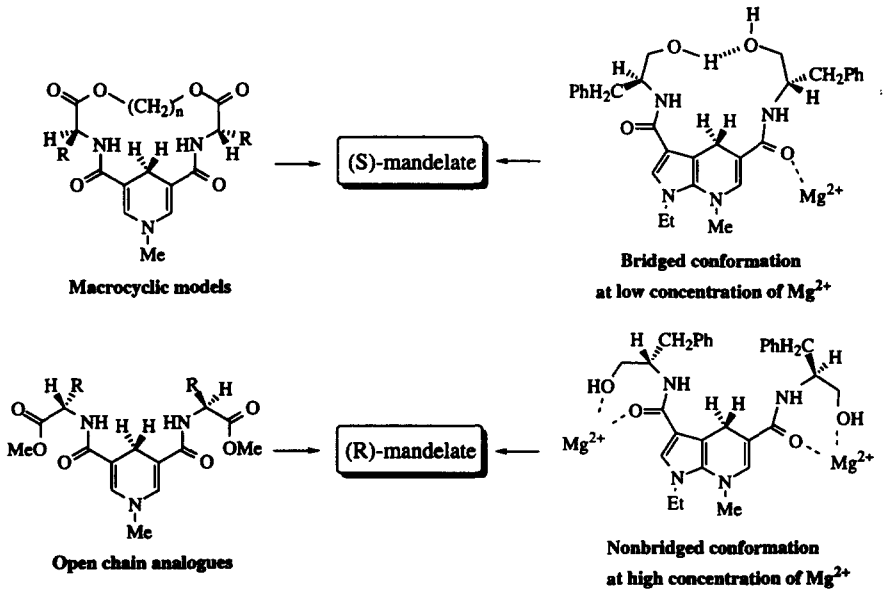
Table 2. Asymmetric reduction of methyl benzoylformate with model **4**

$Mg(ClO_4)_2$ (eq)	0.5	1	2	4	8
E. e. % (Abs.Conf.)	38 (R)	48 (R)	63 (R)	71 (R)	80 (R)

the pyrrole ring requires the use of a large excess of magnesium ions to ensure a good rigidification of both chiral auxiliaries. Although the enantioselectivity is strongly dependent on the concentration of magnesium ions (e.e.=38–80%), the stereochemical course of the reduction does not undergo an inversion of enantioselectivity. Thus, in all cases (R)-methyl mandelate was obtained (Table 2).

As previously evoked, model **4** bears out that the reversal in the absolute stereochemistry of the product obtained from the reduction on increasing amounts of magnesium ions is due to the presence of alcohol functions of both chiral auxiliaries. The result obtained with model **1** in the reduction of methyl benzoylformate can be related to that obtained with chiral NADH models wherein 1,4-dihydropyridines were incorporated in a macrocyclic ring.[9]

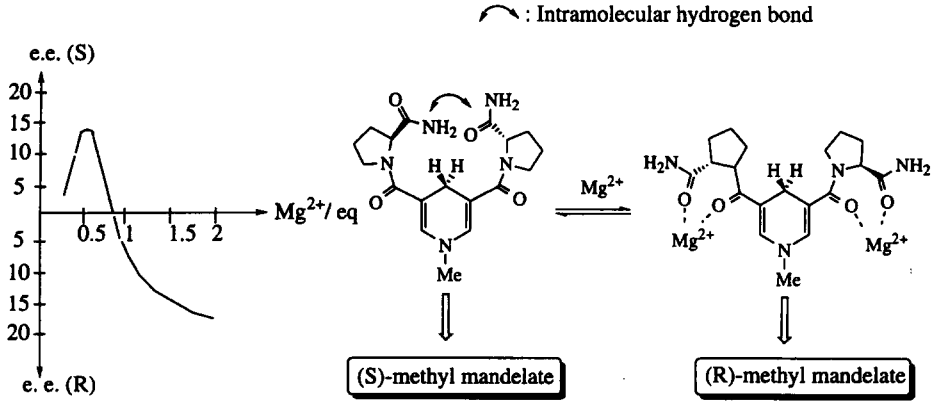
Whereas reduction of ethyl benzoylformate with these reagents afforded (S)-ethyl mandelate (e.e.=20–90%) whatever the bridge length of the macrocycle, analogues with open chains gave rise to (R)-ethyl mandelate (e.e.=5–18%). It can be presumed that at low concentration of magnesium ions, model **1** would mimic this macrocyclic structure through the intervention of an intramolecular hydrogen bond to yield (S)-methyl mandelate. An excess of magnesium perchlorate would promote complexation of the magnesium salt with both chiral auxiliaries *via* hydroxy and carbonyl moities as observed with model **2**. This nonbridged conformation would afford (R)-methyl mandelate as open chain models reported by these authors (Scheme 6).



Scheme 6.

To substantiate this hypothesis, it is worthy of note that such an inversion of enantioselectivity has been observed at a lower extent in the reduction of methyl benzoylformate with a C_2-symmetric chiral NADH model bearing two chiral auxiliaries derived from prolinamide at C-3 and C-5.[10] The authors shown by an U. V. study the formation of two different complexes (model/Mg^{2+}) in the presence of various amounts of magnesium perchlorate.[11] No information was given about the structure of these

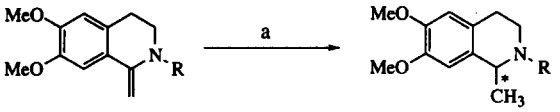
complexes. Common to that model and model **1** is the presence of two chiral auxiliaries bearing an additional functional group capable to form an intramolecular hydrogen bond or to complex magnesium ions depending on the concentration of the metal salt. Based on the above hypothesis, we assumed that the origin of these two complexes are related to the presence of the two primary amide functions to form an intramolecular hydrogen bond at low concentration of magnesium ions which might interfere with the chelation of the magnesium ion at higher concentration of magnesium perchlorate. Both of these two complexes affording (S) and (R)-methyl mandelate respectively (Scheme 7).



Scheme 7.

Asymmetric reduction of N-*acetyl-enamines* ***15*** *and* ***16*** *with model* ***1***

Lastly, for purpose of synthetic applications and with a view to compare the behaviour of model **1** in the asymmetric reduction of other substrates, we investigated the asymmetric reduction of *N*-acetyl enamine derivatives **15** and **16** precursors of Salsolidine and Carnegine. We have previously reported[12] the reduction of enamine derivatives with nonchiral NADH models and shown that compounds **15** and **16** could be reduced in good yields. Model **1** was involved in the asymmetric reduction of enamine derivatives **15** and **16** in the presence of increasing amounts of magnesium perchlorate to yield the desired compounds **17** and **18** in 95% yield (Scheme 8).



15: R=$COCH_3$
16: R=$COOCH_3$

17: R=$COCH_3$ Yield=95%
18: R=$COOCH_3$ Yield=95%

Scheme 8. a: Model **1**/$Mg(ClO_4)_2$ 1 eq/r.t./CH_3CN.

As shown in Table 3, the use of 1eq of magnesium perchlorate lead to modest asymmetric induction in the reduction of **15** (e.e.=32%), whereas a large excess of magnesium perchlorate is needed to achieve high asymmetric induction (e.e.=87%). However, in contrast to methyl benzoylformate, the reduction of *N*-acetyl-enamines **15** and **16** do not undergo inversion of enantioselectivity. Surprisingly, in spite of their similar structures, whereas *N*-acetyl-enamine **15** was reduced with 87% e.e., *N*-acetyl-enamine **16** gave rise to low enantioselectivity (0%<e.e.<26%) whatever the amount of magnesium perchlorate used.

These facts indicate that with model **1**, both sense and level of asymmetric induction are not only dependent on the conformation of the model adopted in the ternary complex but are highly influenced by the nature of the substrate as well.

Table 3. Asymmetric reduction of enamine derivatives **15** and **16** with model **1**

$Mg(ClO_4)_2$ (eq)	0.25	0.5	0.75	1	2	4	8
compound **15** E. e. % (Abs.Conf.)[a]	13 (R)	20 (R)	25 (R)	32 (R)	51 (R)	80 (R)	87 (R)
compound **16** E. e. %[b]	-	-	0	+7	+13	+18	+26

[a] After hydrolysis of the N-acetyl group, the absolute configuration was deduced by comparison of the specific rotation of the so-obtained Salsolidine with literature values. [b] The absolute configuration has not been determined. The sense of induction is indicated arbitrarily by the sign (+).

In conclusion, the synthesis of models **3** and **4** and their use in asymmetric reduction of methyl benzoylformate allows us to throw light on the reversal asymmetric induction observed with model **1** upon addition of increasing amounts of magnesium perchlorate. Thus, it is assumed that the original behaviour of model **1** is most likely to be due to the ability of model **1** to adopt two different conformations in the ternary complex through the intervention of alcohol functions, yielding (S) or (R)-methyl mandelate respectively. Although this interesting behaviour seems to be restricted to some substrates as indicated by the reduction of *N*-acetyl-enamines **15** and **16**, model **1** proved to be efficient in the reduction of **15**, affording **17**, precursor of Salsolidine in 87% of enantiomeric excess.

Experimental

The following compounds were prepared by literature methods: model **1**,[1] compounds **6** and **11**,[6] (S)-2-amino-1-methoxy-3-phenylpropane,[8] *N*-acetyl-enamines **15** and **16**.[12] The infra-red spectra were recorded on a Beckman IR 4250 spectrometer. ^1H and ^{13}C NMR spectra ($SiMe_4$ as an internal standard) were recorded on a 200 MHz Brucker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuterio dimethyl sulfoxide. Elemental analyses were obtained from a Carlo Erba 1106 apparatus.

*1-Ethylpyrrolo[2,3-*b*]pyridine-3,5-dicarboxylic acid 7*

To a suspension of compound **6** (10 g, 51 mmol) in 20 ml of ethanol was added an aqueous solution of NaOH (6 M, 25 ml). The resulting suspension was stirred for 12 hours at 80°C. After ice-cooling, the solution was neutralized with 1M aqueous HCl. The resulting precipitate was filtered off and dried under vacuum for at least 12 hours affording 11 g (92%) of a white solid. Recrystallization from EtOH–H_2O gave white needles of mp>260°C. IR (KBr): 1715 cm^{-1}. ^1H NMR (DMSO-d6) δ 8.90 (s, 1H); 8.85 (s, 1H); 8.40 (s, 1H); 6.80 (br s, 2H); 4.35 (q, 2H, *J*=7.0 Hz); 1.40 (t, 3H, *J*=7.0 Hz). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.20; H, 4.05; N, 11.77.

*1-Ethylpyrrolo[2,3-*b*]pyridine-5-carboxylic acid 8*

Diacid **7** (11.70 g, 50 mmol) in 6 M aqueous HCl (600 ml) was stirred at reflux for 2 days. After concentration, the residue was taken in methanol, and filtered off leading to crude 1-ethylpyrrolo[2,3-*b*]pyridine-5-carboxylic acid **7** (9.50 g, 100%). The crude acid **8** was used without further purification in the next step. IR (KBr): 1720 cm^{-1}. ^1H NMR (DMSO-d6) δ 8.80 (d, 1H, *J*=1.9 Hz); 8.52 (d, 1H, *J*=1.9 Hz); 8.17 (br s, 1H); 7.70 (d, 1H, *J*=3.4 Hz); 6.62 (d, 1H, *J*=3.4 Hz); 4.32 (q, 2H, *J*=7.2 Hz); 1.33 (t, 3H, *J*=7.2 Hz).

*(S)-5-N(1-Hydroxymethyl-2-phenylethyl)carboxamido-1-ethylpyrrolo[2,3-*b*] pyridine 9*

The crude acid **8** (3.8 g, 20 mmol), (S)-phenylalaninol (3.32 g, 22 mmol), *N*-methyl-2-chloropyridinium iodide (5.60 g, 22 mmol) and triethylamine (6 ml, 44 mmol) were warmed at reflux in dichloromethane (200 ml) for 5 days. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on neutral alumina (eluent: ethyl acetate

with gradual addition 0–5% of methanol) to afford **8** as a white solid (4.84 g, 75%). IR (KBr): 1624 cm^{-1}. ^1H NMR (DMSO-d6) δ 8.67 (d, 1H, *J*=1.9 Hz); 8.37 (d, 1H, *J*=1.9 Hz); 8.22 (d, 1H, *J*=8.4 Hz); 7.65 (d, 1H, *J*=3.5 Hz); 7.23 (m, 5H); 6.56 (d, 1H, *J*=3.5 Hz); 4.86 (t, 1H, *J*=5.7 Hz); 4.27 (m, 3H); 3.45 (m, 2H); 2.92 (m, 2H); 1.36 (t, 3H, *J*=7.2 Hz). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.59; H, 6.50; N, 13.00. Found: C, 70.44; H, 6.35; N, 12.95.

*(S)-5-*N*(1-Hydroxymethyl-2-phenylethyl)carboxamido-1-ethyl-7-methylpyrrolo[2,3-*b*] pyridinium iodide* ***10***

A solution of amide **9** (323 mg, 1 mmol) in 10 ml of acetonitrile and 1 ml of methyl iodide, was heated to reflux for 10 days. Each day, 1 ml of methyl iodide was added and the reaction monitored by ^1H NMR. The volatile compounds were evaporated under vacuum and the resulting crude product purified by chromatography on neutral alumina. The starting material **9** was first eluted with ethyl acetate/methanol (80/20) and the pyridinium salt **10** was then eluted with methanol yielding 405 mg (87%) of a yellow solid. mp=190°C. IR (KBr): 1655 cm^{-1}. ^1H NMR (DMSO-d6) δ 9.03 (s, 1H); 8.99 (s, 1H); 8.68 (d, 1H, *J*=8.4 Hz); 7.96 (d, 1H, *J*=3.8 Hz); 7.18 (m, 5H); 7.09 (d, 1H, *J*=3.8 Hz); 4.98 (m, 1H); 4.65 (m, 5H); 4.22 (m, 1H); 3.51 (m, 2H); 2.90 (m, 2H); 1.47 (t, 3H, *J*=7.0 Hz). Anal. Calcd for $C_{20}H_{24}IN_3O_2$: C, 51.61; H, 5.20; N, 9.03. Found: C, 51.80; H, 5.10; N, 8.90.

*(S)-5-*N*(1-Hydroxymethyl-2-phenylethyl)carboxamido-1-ethyl-7-methyl-4,7-dihydropyrrolo [2,3-*b*] pyridine* ***3***

To a solution of pyridinium salt **10** (465 mg, 1 mmol) in 10 ml of ethanol was added 20 ml of water under nitrogen at room temperature. A solution of sodium carbonate (530 mg, 5 mmol) and sodium dithionite (1.39 g, 8 mmol) in 10 ml of water was added. The resulting solution was stirred in the dark under nitrogen at the same temperature for 30 min. After evaporation of ethanol under vacuum (t<30°C), the aqueous layer was extracted with dichloromethane (3×20 ml). The resulting organic phase was dried ($MgSO_4$) and evaporated under vacuum (t<30°C) to give 322 mg (95%) of a yellow solid. ^1H NMR (DMSO-d6) δ 7.22 (m, 5H); 6.62 (s, 1H); 6.61 (d, 1H, *J*=9.0 Hz); 6.34 (d, 1H, *J*=3.0 Hz); 5.67 (d, 1H, *J*=3.0 Hz); 4.76 (m, 1H); 3.93 (m, 3H); 3.33 (m, 7H); 2.75 (m, 2H); 1.22 (t, 3H, *J*=7.2 Hz).

*1-Methylpyrrolo[2,3-*b*]pyridine-3,5-dicarboxylic acid* ***12***

Compound **12** was synthesized by the same procedure to that described for the preparation of **7** from dicarbonitrile **11**. Yield=85%. Recrystallization from EtOH–H_2O gave white needles of mp>260°C. IR (KBr): 1715 cm^{-1}. ^1H NMR (DMSO-d6) δ 8.90 (s, 1H); 8.80 (s, 1H); 8.35 (s, 1H); 5.00 (br s, 2H); 3.90 (s, 3H). Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.63; N, 12.73. Found: C, 54.25; H, 3.44; N, 12.67.

*(S,S)-3,5-Di[*N*-(1-methoxymethyl-2-phenylethyl)carboxamido]-1-methylpyrrolo[2,3-*b*]pyridine* ***13***

A solution of diacid **12** (1.89 g, 8.6 mmol) in 35 ml of thionyl chloride was warmed at reflux for 12 hours. After evaporation of thionyl chloride, the residue was taken in benzene (30 ml) and evaporated to dryness. The resulting residue was dissolved in dichloromethane (40 ml) and added dropwise to a precooled (−10°C) solution of (S)-2-amino-1-methoxy-3-phenyl propane (2.38 g, 14.4 mmol) and triethylamine (2 ml, 14.4 mmol) in dichloromethane (40 ml). The solution was allowed to reach room temperature over a period of 1 hour and stirred for 12 hours after which water (40 ml) was added. After phase separation, the aqueous layer was extracted with ethyl acetate (3×30 ml). The combined organic phases were dried ($MgSO_4$) and organic solvents evaporated under vacuum. The crude product was purified by flash chromatography on neutral alumina (eluent: ethyl acetate/methanol: 98/2). Yield: 76%. IR (KBr): 1629 cm^{-1}. ^1H NMR (DMSO-d6): 8.83 (d, 1H, *J*=2.1 Hz); 8.68 (d, 1H, *J*=2.1 Hz); 8.51 (d, 1H, *J*=8.4 Hz); 8.27 (s, 1H); 7.99 (d, 1H, *J*=8.4 Hz); 7.20 (m, 10H); 4.33 (m, 2H); 3.85 (s, 3H); 3.41 (m, 4H); 3.28 (s, 6H); 2.86 (m, 4H). Anal. Calcd for $C_{30}H_{34}N_4O_4$: C, 70.04; H, 6.62; N, 10.89. Found: C, 69.90; H, 6.58; N, 11.06.

*(S,S)-3,5-Di[*N*-(1-methoxymethyl-2-phenylethyl)carboxamido]-1,7-dimethylpyrrolo[2,3-*b*]pyridinium iodide **14***

Compound **14** was prepared in the same manner as **10**, from **11** (514 mg, 1 mmol) in acetonitrile (7 ml). Yield=89%. IR (KBr): 1648 cm^{-1}. 1H NMR (DMSO-d6): 9.42 (d, 1H, *J*=2.0 Hz); 9.09 (d, 1H, *J*=8.0 Hz); 9.07 (d, 1H, *J*=2.0 Hz); 8.46 (d, 1H, *J*=8.0 Hz); 8.45 (s, 1H); 7.24 (m, 10H); 4.71 (s, 3H); 4.40 (m, 2H); 4.28 (s, 3H); 3.43 (m, 4H); 3.28 (s, 6H); 2.67 (m, 4H). Anal. Calcd for $C_{31}H_{37}IN_4O_4$: C, 56.71; H, 5.64; N, 8.54. Found: C, 56.51; H, 5.70; N, 8.44.

*(S,S)-3,5-Di[*N*-(-1-methoxymethyl-2-phenylethyl)carboxamido]-1,7-dimethyl-4,7-dihydropyrrolo[2,3-*b*] pyridine **4***

To a solution of pyridinium salt **14** (656 mg, 1 mmol) in 10 ml of ethanol was added 20 ml of water under nitrogen at room temperature (all solvents used in this procedure have been degassed with nitrogen). A solution of sodium carbonate (106 mg, 1 mmol) and sodium dithionite (174 mg, 1 mmol) in 10 ml of water was added. The whole was stirred in the dark and under nitrogen for 1 hour. After addition of an aqueous solution (3 ml) of sodium dithionite (174 mg, 1 mmol) and sodium carbonate (106 mg, 1 mmol), the reaction mixture was stirred for a further 1 hour. This operation was repeated 3 times. Then, an aqueous solution (10 ml) of sodium dithionite (700 mg, 4 mmol) was added over a period of 3 hours. The reaction mixture was stirred for a further 12 hours in the dark under nitrogen. After addition of 40 ml of water, the reaction mixture was extracted with dichloromethane (3×25 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum (t<30°C) to yield 520 mg (98%) of an orange solid. IR (KBr): 1660 cm^{-1}. ^1H NMR ($CDCl_3$): 7.27 (m, 10H); 7.04 (s, 1H); 6.61 (s, 1H); 6.00 (d, 1H, *J*=7.3 Hz); 5.80 (d, 1H, *J*=7.3 Hz); 4.43 (m, 2H); 3.74 (s, 2H); 3.64 (s, 3H); 3.32 (m, 13H); 2.92 (m, 4H).

Typical procedure for reductions

To a solution of reagent **4** (531 mg, 1 mmol), methyl benzoylformate (150 mg, 0.90 mmol) and magnesium perchlorate (1.78 g, 8 mmol) in 5 ml of degassed acetonitrile were stirred at room temperature in the dark, under nitrogen for 24 hours. A few drops of water were then added and the solvent evaporated. The resulting crude product was purified by chromatography.

Methyl mandelate

The crude product was purified on silica gel (eluent: cyclohexane/diethyl ether: 1/1). Yield=95%. Enantiomeric excesses were determined after derivatization with Mosher acid chloride and analysis by gas phase chromatography: Column DB1 (30 m, 250×0.25 mm); injector and detector: temperature 250°C; oven temperature: 170°C; vector gas: helium (pressure 0.9 bar).

*1-Methyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **17***

The crude product was purified on silica gel (eluent: ethyl acetate). Yield=95%. ^1H NMR ($CDCl_3$): 6.60 (s, 1H); 6.56 (s, 1H); 5.58 (q, 0.6H, *J*=6.7 Hz); 4.87 (q, 0.4H, *J*=6.7 Hz); 3.84 (s, 3H); 3.83 (s, 3H); 3.65 (m, 2H); 2.83 (m, 2H); 2.17 (s, 1.2H); 2.15 (s, 1.8H);.1.52 (d, 1.2H, *J*=6.7 Hz); 1.43 (d, 1.8H, *J*=6.7 Hz). Enantiomeric excesses were measured by high pressure liquid chromatography. Chromatographic conditions: Enantiopac LKB chiral column (100×4 mn; 10 μm). UV detection (λ=254nm); Mobile phase: phosphonate buffer/2-propanol (99/1); Flow rate: 0.2 ml/min; Temperature: 20°C; Injection: 20 μl (0.7 mg of sample in 10 ml of eluent).

*Methyl 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate **18***

The crude product was purified on silica gel (eluent: ethyl acetate). Yield=95%. ^1H NMR ($CDCl_3$): 6.50 (s, 2H); 5.05 (m, 1H); 3.75 (s, 6H); 3.65 (s, 3H); 3.20 (m, 2H); 2.60 (m, 2H); 1.35 (d, 3H, *J*=7.1 Hz). Enantiomeric excesses were measured by high pressure liquid chromatography. Chromatographic conditions: AGP chiral column (100×4 mn; 5 μm) purschased from Chrom Tech.

Inc. UV detection (λ=210nm); Mobile phase: phosphonate buffer/2-propanol (98.5/1.5); Flow rate: 0.9 ml/mn; Temperature: 20°C; Injection: 20 µl (0.3 mg of sample in 10 ml of eluent).

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