Tetrahedron Vol. 47, No. 45, pp. 9369-9382, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
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Stereoselectivity of Hydrogen Transfer with Chiral NADH Models as a Function of Configuration and Conformation

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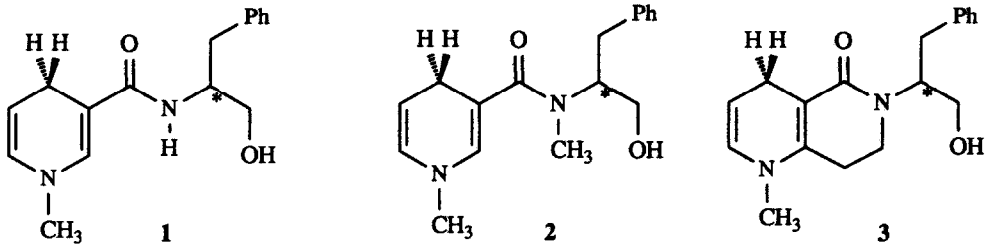
(*Received in Belgium* 11 *September* 1991)

Key words: NADH models, reduction, asymmetric reduction, NMR spectroscopy, cross coupling reaction.

Abstract: *NADH model compounds bearing chiral amide groups have been synthesized. One of these models, 3, possessed the 1,6-naphtyridinone structure and the key step of its synthesis was a cross coupling reaction which was optimized on the basis of consideration of the mechanism. In this bicyclic model 3, the amide carbonyl dipole is forced in a transoid orientation. In model 1, the free rotation around the C-3-C=O amide bond is not hindered contrary to the behavior of model 2, where the presence of a methyl group on the nitrogen of the amide moiety is sufficient to force the carbonyl group to be out of the plane. The NMR spectra of these compounds and their precursors were studied from which it could be assumed that model 2 and its derivatives could have two conformers due to the restricted rotation of the amide moiety. Model 3 reduced methyl benzoylformate with a good enantioselectivity (e.e.= 85 %).*

For more than a decade efforts have been expended to create model compounds mimicking the activity of the NAD^+/NADH redox couple. Many publications have been devoted to the behavior of such model compounds (1). Some of them, bearing a chiral auxiliary, have been used in the asymmetric reduction of prochiral substrates. In some cases, high e.e. have been obtained (2). Many points concerning the mechanism of the enantioselectivity of the hydrogen transfer (3) remain unclear. Most of the asymmetric reductions performed with NADH models are efficient only in the presence of magnesium ions. The hydrogen transfer occurs through a ternary complex between the model, Mg^{2+} and the substrate (2a). In our laboratory, we have synthesized and studied NADH models derived from rarely used (4) optically active amino alcohols (5). It was shown that the oxygen of the alcohol aided in attaining rigidity of the chiral auxiliary. In the ternary complex, it is generally assumed that the dipole of the amide carbonyl of the model compound and the dipole carbonyl of the substrate point in the same direction. Moreover, the polar parts of the model and the substrate face each other. However, in the ternary complex, other possibilities may be envisaged e.g.: i) the two carbonyl dipoles can be in opposite directions; it must be noted that in most of the common chiral models it is assumed that the carbonyl dipole of the amide segment is directed towards the nitrogen atom of the pyridine ring. ii) the carboxamide group can be out of the plane; models having methyl groups in the 2 and 4 positions, forcing the carbonyl to be out of the plane, have been studied (6). It was shown that the amide carbonyl dipole

and the departing C-4 hydrogen were syn oriented during the hydride transfer. So, it appears that it would be of interest to develop models without methyl groups at the 2 and 4 positions which could provide information concerning these crucial points in the enantioselectivity of the hydrogen transfer with chiral NADH model compounds. For this purpose, the three following derivatives were synthesized and studied :

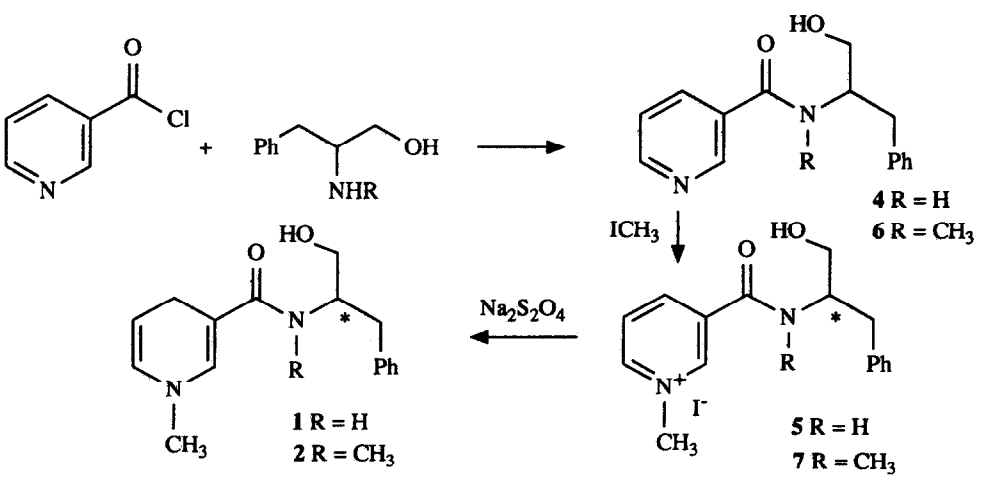


Scheme 1

In model **1**, the free rotation around the C-3-C=O amide bond shall not be hindered contrary to the behavior of model **2**, where the presence of a methyl group on the nitrogen of the amide moiety could be sufficient to cause a steric hindrance which forces the carbonyl group to be out of the plane. It must be mentioned that in previously described models having related structures, the out of the plane position of the carbonyl group was a consequence of the disubstitution on the nitrogen atom and/or of the presence of methyl groups at the 2 and 4 positions of the pyridine ring (3a) (6). In these models, the active site is chiral (C_4 atom) and, in some cases, the reagent was involved in a self immolative reaction. Model **2** would be the first example of a chiral NADH model where the carbonyl group would be out of plane without the presence of substituents at the 2 or 4 position of the pyridine ring. In model **3**, which was briefly described previously (5c) together with model **1**, the amide carbonyl dipole is forced in a transoid orientation in a cyclized structure. The aim of this paper is the description of the synthesis of these compounds, their spectroscopic study and the comparison of their behavior in the reduction of methyl benzoyl formate.

I) Syntheses:

1)Model 1 :



Scheme 2

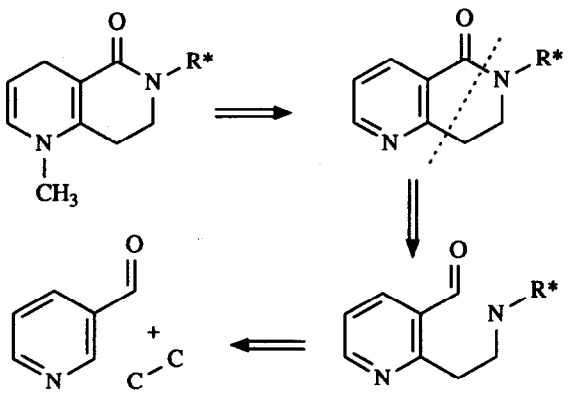
Model **1** was obtained by following the classical way (2e) shown in scheme 2 (R = H). The only critical point during this synthesis was the condensation leading to **4**, which must be performed at 0 °C in order to avoid reaction of the alcohol function of L-phenylalaninol.

2) Model 2: The scheme was very similar (scheme 2, R= CH_3), L-phenylalaninol was replaced by N-methyl-L-phenylalaninol.

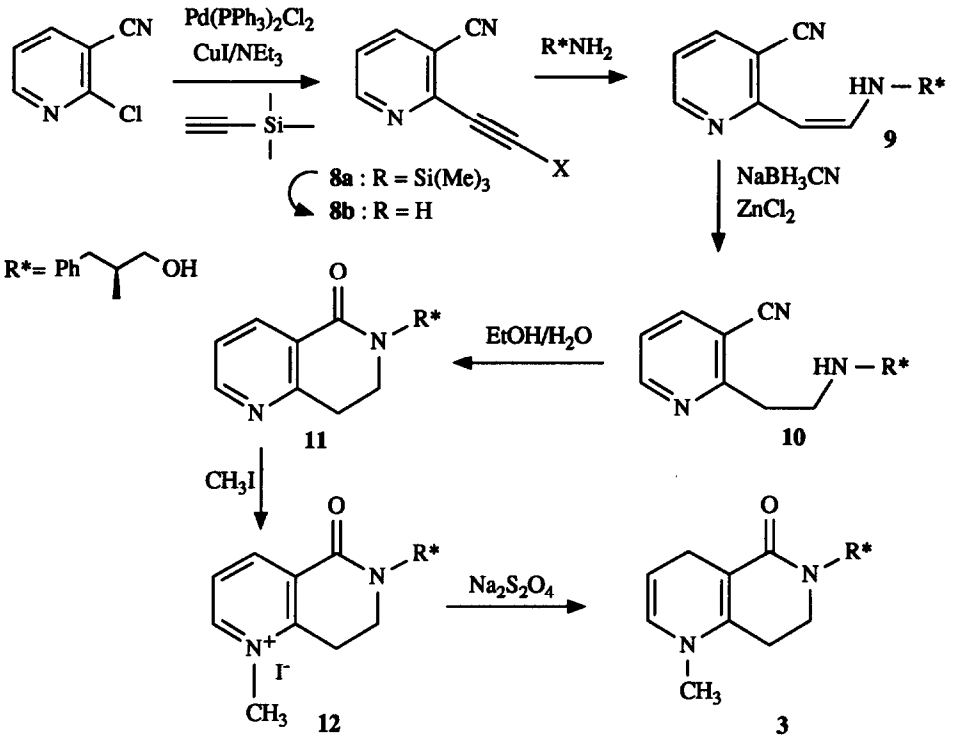
In this case, an important problem was the obtention of optically pure N-methyl-L-phenylalaninol. This compound was obtained after reduction of the N-formyl derivative of (S)-methyl phenylalaninate (7). It has been mentioned (7) that this procedure seems to lead to less racemization than others. We decided, however, to perform an experiment to establish the optical purity of the N-methylamino alcohol. Several methods were tested on the racemic mixture obtained from racemic phenylalanine: i) use of Mosher's derivatization (8) and attempt to separate diastereoisomers by g.p.c., this method failed; ii) attempt to separate the enantiomers of the racemic mixture by HPLC on a chiral column, this method also failed; iii) finally by using chiral 2,2'-dihydroxy-1,1'-binaphthyl (9) as a complexing agent, the two methyl groups of the racemic mixture could be distinguished by ^1H NMR spectroscopy on a 200 MHz spectrometer. δ: 2.055 ppm and δ: 2.060 ppm. By these means, it was possible to establish that the compound issued from (*S*)-phenylalanine was enantiomerically pure (in the limits of the NMR detection method).

During the obtention of **2**, it must be noted that the reduction yields of the pyridinium salt **7** were always average (about 55 % on several experiments). This point will be discussed later.

3) Model 3: This compound possesses the hexahydro-1,6-naphtyridinone structure. There are only a few reports concerning the synthesis of such compounds (10). The key-step is the formation of a carbon-carbon bond at the 2-position of a nicotinic derivative. Our retrosynthetic approach is summarized in scheme 3 and its elaboration is depicted in scheme 4:



Scheme 3



Scheme 4

Starting from 2-chloronicotinonitrile (11) the cross-coupling reaction with the cuprous trimethylsilylacetylide was performed in the presence of Pd° (generated from $PdCl_2$ + PPh_3). By working in the conditions described in the literature (12), i.e. by mixing the reagents and refluxing, the reaction showed much inconstancy from one experiment to another. So it was decided to reinvestigate the overall process: during the reaction two catalytic cycles are assumed to occur: that of cuprous salt and that of Pd° (13). Our method consisted in the sequential generation of these two cycles : first the cuprous cycle was started by reaction of CuI and a part of trimethylsilylacetylene leading to cuprous acetylide, which reacts with bis-triphenyl phosphine palladium chloride, which liberates in situ Pd°. The palladium cycle can then start: insertion of Pd° in the carbon halogen bond of 2-chloronicotinonitrile. At this point, the remaining trimethyl silylacetylene can be added and the chlorine atom of the above insertion product is replaced by the acetylide group and in the final step compound **8a** is obtained after liberation of Pd°, which is recycled. Highly reproducible yields of 80 % for **8a** could be obtained by following this procedure. Desilylation of **8a** leading to **8b** was easily performed in basic medium. At this point, in initial experiments, the obtention of **10** was performed by reductive amination of **8b**. Numerous secondary products leading to tarry material were formed during this one-pot process and the yields in **10** were low. (S)-phenylalaninol was first added to **8b** leading to the enamine **9**, which was not purified, but could be identified by the presence in the ^1H NMR spectra of two doublets at 6.70 and 5.30 ppm (14). The reduction of compound **9** was achieved by the $NaBH_3CN$-$ZnCl_2$ couple (15). The crude product **10** was nicely cyclized by simple refluxing in ethanol/water mixture.

Presumably the cyano group is transformed to a reactive iminoether derivative, which is easily attacked further by the amine function, leading to the cyclized product **11**.

At this point, it appeared essential to establish the optical purity of **11**, the method used for its synthesis being notably different from that used for the obtention of compounds **4** and **6**. The enamine **9** can also exist as its imine tautomer which may be susceptible to partial racemization on the chiral carbon. So the overall process leading to **11** was reproduced with racemic phenylalaninol. Resolution of the racemate on a chiral HPLC column did prove that **11** was indeed enantiomerically pure. Subsequently this compound was transformed into model **3** under standard conditions.

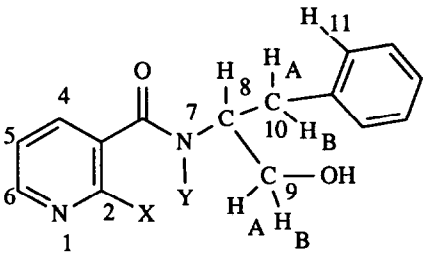
II - N.M.R. Spectroscopic study:

The ^1H NMR spectra were recorded with Brucker 200 AC and 400 AM spectrometers and were fully assigned using 1D and 2D chemical shift correlation spectroscopy. The structural features of compounds were deduced from proton coupling constants and chemical shift data.

First of all it must be mentioned that in the model **2** series, the ^1H NMR spectra of the pyridine derivative **6** and the pyridinium derivative **7** show the existence of two isomers (which will be called **6 minor** or **major** and **7 minor** or **major**). In principle, two types of conformational isomerism can occur, i.e. syn-anti rotamerism about the amide bond and axial chirality around the C_3-C_{amide} axis (caused by the out of plane rotation of the amide group).

In this chapter, we will only discuss some points concerning the behavior of the compounds described in the following tables. A complete analysis of the different compounds and a study of the behavior of models **1**, **2** and **3** in the presence of magnesium ions will be published later.

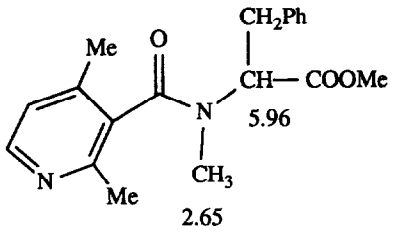
*a) Pyridine series. Compounds **4, 6, 11** (spectra recorded in $CDCl_3$):*



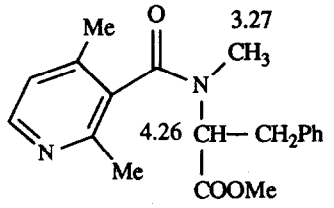
	1	X	4	5	6	Y	8	9A	9B	10A	10B	H_{11}	Ph
4 X=Y=H		8.83	7.96	7.35	8.53	7.53	4.37	3.68	3.72	2.95		7.2	
6 minor 35 % X=H; Y = Me		8.28	7.45	7.25	8.55	2.72	4.82	3.82		2.94		6.88	7.2
6 major 65 %		8.09	6.94	7.07	8.43	3.03	3.87	3.55	3.72	2.57	2.64	6.88	
11 X-Y = CH_2-CH_2		2.9	8.20	7.20	8.50	3.45	4.8	3.85		3.0		7.17	7.20

Table 1

The occurence of only one isomer in the case of **4** and **11** leads us to consider that, in these compounds, the amide carbonyl is coplanar with the ring. In compound **11**, the N-CH_8 bond is necessarily syn with respect to the C=O amide. The chemical shift of this hydrogen is 4.80 ppm, which can be related to the chemical shift (δ = 4.82 ppm) of the same hydrogen in **6 minor**. So, it can be assumed that, in this isomer the N-CH_8 bond is also syn with respect to the C=O amide. On the other hand in **6 major** the H_8 proton shows a chemical shift δ = 3.87 ppm and the N-CH_3 protons are at 3.03 ppm (instead of δ = 2.72 ppm in **6 minor**). These chemical shifts can be compared with the chemical shifts of similar protons in compounds of known conformations (16).



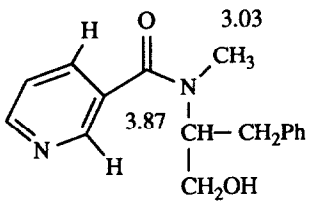
major : syn



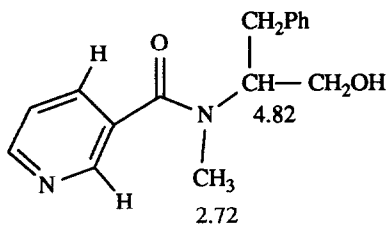
minor : anti

Scheme 5

Moreover, the H_2 and H_4 protons in **6 minor** and **major** are shielded with respect to the corresponding protons in **4** or **11**. This is probably a consequence of the anisotropy caused by the carbonyl group and the phenyl group which forces the corresponding protons to be in the shielding regions of these groups. Therefore it can be assumed that the isomers of **6** have the following structures (scheme 6):



6 major : anti



6 minor : syn

Scheme 6

It can be noticed that the proportions of anti and syn isomers of compounds described in schemes 5 and 6 are reversed. Several factors may be involved to explain this isomer distribution (steric or electronic factors, conjugation, intramolecular interactions, etc (17)). In the case of **6 major**, a hydrogen interaction between the hydroxymethyl group and the pyridine nitrogen may be invoked. In this stucture the carbonyl of the amide group is forced to be out of the plane of the pyridine ring.

The conformation of compound **4** is not easy to define : the chemical shift of H_8 is δ = 4.37 ppm. This is the average between δH_8 in **6 minor** or **6 major**.

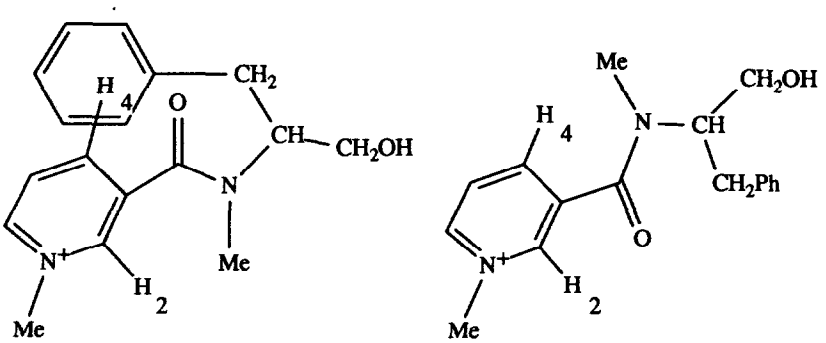
b) Pyridinium series. Compounds 5, 7, 12 (spectra recorded in DMSO):

	1-CH_3	X	4	5	6	Y	8	9A	9B	10A	10B	H_{11}	Ph
5 X=Y=H	4.36	9.29	8.82	8.22	9.07	8.82	4.17	3.49		2.80	2.95	7.18	7.22
7 minor 22 % X=H; Y=Me	4.35	8.23	7.38	8.15	9.01	2.82	4.89	3.60	3.65	2.90		7.03	7.29
7 major 78 %	4.27	8.22	7.76	8.07	8.97	2.95	5.1	3.48	3.64	2.65	2.76	7.03	7.29
12 X-Y = CH_2-CH_2	4.26	3.24 3.40	8.79	8.02	9.06	3.69	4.88	3.57	3.69	2.86	2.93	7.15	7.20

Table 2

In compound **12** the N-CH_8 bond is obviously syn with respect to the amide C=O. Its chemical shift is 4.88 ppm. The behavior of compound **7** is quite different from that of its precursor **6** in the pyridine series. Several hypothesis can be formulated:

i)in compounds **7 minor** or **major** the H_8 protons feature a very similar chemical shift (4.89 and 5.1 ppm) to that of the corresponding proton in **11**. These protons are deshielded with respect to corresponding protons in **5** (δ = 4.17 ppm). It can therefore be assumed that in compounds **7 minor** or **major** and **12** the N-CH_8 bond is syn and in compound **5**, this bond is rather anti with respect to the amide C=O. In the two isomers of **7** the H_2 protons are strongly shielded compared to the corresponding protons in **5** ($\Delta\delta$ - 1 ppm). This is probably a consequence of the anisotropy exerted by the carbonyl group as was already observed in the pyridine series. Moreover, in the minor isomer, the H_4 proton is more shielded than the corresponding proton in **7 major**. We can suppose that in the former, the phenyl group is in the vicinity of the H_4 proton which is then submitted to the shielding effect of the phenyl ring (scheme 7):

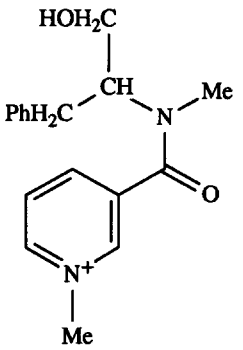


7 minor **7 major**

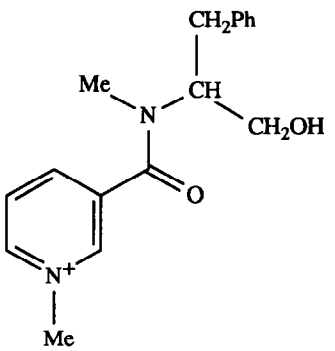
Scheme 7

This behavior can explain that during the reduction of the pyridinium salt with sodium dithionite some of the starting material was not reduced : in **7 minor** the access to the 4 position of the pyridinium ring is probably hindered by the proximity of the phenyl ring. Although the solvent of the reduction is different from that used in the NMR study, this steric hindrance can account for the observed experimental result. Morover, there are various reports in the literature in which some hindered pyridinium salts could not be reduced (18). It must be noticed that in this hypothesis the two isomers have a syn structure. The hydrogen interaction between the hydroxymethyl group and the charged nitrogen atom of the pyridinium ring cannot of course occur. Hence, the bulkier substituent is normally syn to the carbonyl oxygen (17).

ii)another explanation can be proposed: the chemical shift of CO-N-CH_x protons is not always a reliable criterion for the assignment of a syn or anti structure (19). Hence it may be assumed once again that a syn-anti isomerism is present instead of an axial chirality. So, **7 minor** and **7 major** would be the two isomers issued from the precursors **5 minor** and **5 major**. On the basis of fair yield during the reduction of **7** with sodium dithionite it can be assumed that **7 minor** has the structure depicted in scheme 8:



Isomer **7 minor** : anti

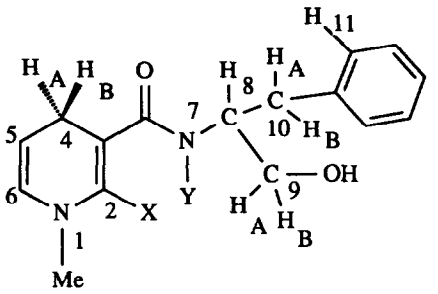


Isomer **7 major** : syn

Scheme 8

In **7 minor** the vicinity of the bulkier substituent in the anti conformer with the C_4 position disfavours the approach of the reagent during the reduction with sodium dithionite.

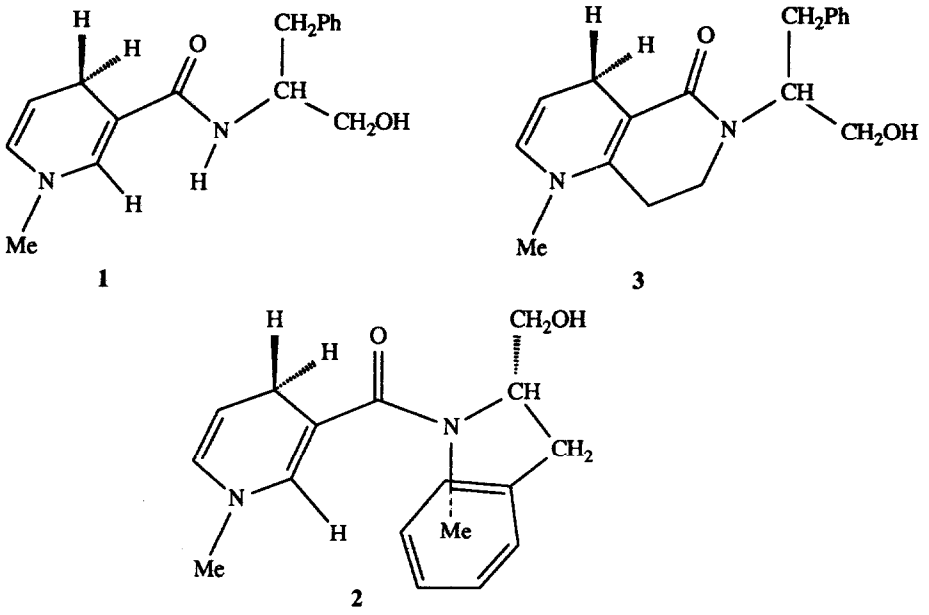
c) Dihydropyridine series. Compounds 1, 2 and 3 (Spectra recorded in $CDCl_3$):



	1-CH_3	X	4	5	6	Y	8	9A	9B	10A	10B	H_{11}	Ph
1 X=Y=H	2.80	6.85	2.94	4.60	5.60	5.69	4.18	3.55		2.88		7.20	
2 X=H;Y=Me	2.70	5.70	2.74 2.90	4.47	5.55	2.80 2.70	4.40	3.71		2.81		7.25	7.16
3 X-Y = CH_2-CH_2	2.77	2.10	3.05	4.66	5.57	3.02	4.21	3.68	3.72	2.88	2.98	7.18	

Table 3

First of all, compound **2** is almost pure. Less than 5 % of a minor isomer could be detected in the ^1H NMR spectra. (This isomer is probably a 1,6-dihydropyridine derivative as suggested by the high chemical shift (3.95 ppm) of the methylene protons.) The major point is that the chemical shift of the H_8 proton is very similar in the three compounds. This behavior can mean that the N-CH_8 bond is, in the three cases, syn with respect to the C=O amide (as in **3**). In fact, due to the energetically favoured cross conjugation of the dihydropyridine moiety with the amide carbonyl a syn-anti isomerism may not be observed because this phenomenon would diminish the barrier to rotation around the amide bond. Moreover, it can be observed that, all the given protons have very similar chemical shifts in **1**, **2** or **3** except the H_2 proton in **2** which is shielded strongly ($\Delta\delta$ about 1 ppm). This may be a consequence of the anisotropy exerted by the carbonyl group or by the phenyl group on this hydrogen (scheme 9, compound **2**).



Scheme 9

Finally, the most important point is that, in compound **2**, the two faces of the dihydropyridine ring are nearly equally hindered by the C-3 substituent. This behavior is quite different in compounds **1** and **3** where the coplanarity between the carbonyl and the ring allows the preferential hindrance of one face of the ring (see later)

III - Reduction of methyl benzoylformate:

Reductions of methyl benzoylformate were performed in standard conditions (2e), leading to (R) or (S) methyl mandelate.

The following results were obtained:

Model	1	2	3	3
Time (h)	48	48	72	48
Temperature (°C)	60	60	20	60
Chem. yield (%)	60	60	70	82
e.e. (%)	57	3	88	85
Major Config.	R	S	R	R

Table 4

The obtention of (R)-mandelate with models **1** and **3** suggests that, in the ternary complex, the carbonyl dipoles of the substrate and the models are pointing towards the same direction . That means that the

orientation of the carbonyl amide opposite to the ring nitrogen is not inconvenient, contrary to the generally accepted idea (2a). Moreover, the e.e. is very high (> 85 %) with **3** and this result is very interesting compared with the nearly null e.e. obtained with compound **2**. It can be suggested that this result is a consequence of the out of plane position of the amide carbonyl as it can be deduced from the NMR study. In this case, the careful observation of molecular models shows that the hindered group, that is the phenyl substituent on the chiral atom, can be located in a position related very closely to the middle plane of the dihydropyridine structure (see scheme 9). In these conditions, the stereodifferentiation of the two faces of the dihydropyridine does not occur and the departure of either the pro (R) or the pro (S) hydrogen from C_4 is favoured leading to a quasi racemic methyl mandelate. To our knowledge, this result is the first example of the dramatic influence of a small modification of the chiral auxiliary generating a large modification in the enantioselectivity of the hydrogen transfer.

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 a 400 MHz Brucker AM 400 spectrometer. Microanalyses were obtained from a Carlo Erba 1106 apparatus. Optical rotations were determined on a Perkin Elmer 241 micropolarimeter. 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 (5d) or after derivatization of the chiral alcohols by Mosher's method (8) and analysis by GPC. Solvents 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.

3-N-(S)-(1-benzylhydroxyethyl)aminocarbonylpyridine **4**

In a flask, (S)-phenylalaninol (1.66 g, 11 mmol) was introduced in dichloromethane (15 ml). Then triethylamine (0.91 g, 9 mmol) and nicotinoyl chloride (1.41 g, 10 mmol) were introduced at 0°C. After 3 hours at 0°C, the solvent was eliminated and the crude amide purified by column chromatography (silica eluent CH_2Cl_2/EtOH : 90/10). Yield 33 %; m.p. = 127°C ; $[\alpha]^{20}_D$ = -62.78° (c= 1.5, $CHCl_3$).

Analysis $C_{15}H_{16}N_2O_2$: Calcd: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.4; H, 6.3; N, 11.0. I.R. ν (C=O): 1640 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 8.83 (d, 1H); 8.53 (d, 1H); 7.96 (d, 1H); 7.35 (d, 1H); 7.20 (m, 6H); 4.37 (m, 1H); 3.72 (dd, 1H); 3.68 (dd, 1H); 2.95 (d, 2H).

1-Methyl-3-N-(S)-(1-benzylhydroxyethyl)aminocarbonylpyridinium iodide **5**

Amide **4** (1 g, 0.0039 mol) in acetonitrile (5 ml) was heated under reflux with a large excess of methyl iodide, for 12 hours. After elimination of 2/3 of the solvent the mixture was cooled and the pyridinium salt **5** was filtered and washed with diethyl ether. Yield 98 %. m.p. = 140°C.

Analysis $C_{16}H_{19}IN_2O_2$: Calcd: C, 48.26; H, 4.76; N, 7.08. Found: C, 48.3; H, 4.8; N, 7.1. I.R. ν (C=O): 1600 cm^{-1}. ^1H N.M.R. (DMSO d_6): 9.29 (s, 1H); 9.07 (d, 1H); 8.82 (d, 2H); 8.22 (t, 1H); 7.22 (m, 4H); 7.18 (m, 1H); 4.36 (s, 3H); 4.17 (m, 1H); 3.49 (d, 2H); 2.90 (dd, 1H); 2.80 (dd, 1H).

1-Methyl-3-N-(S)-(1-benzylhydroxyethyl)aminocarbonyl-1,4-dihydropyridine **1**

General procedure: the pyridinium salt (1 mmol) was dissolved in degassed water (2 ml). To the solution, 5 equivalents of sodium carbonate decahydrate in degassed water (1 ml) were added at 40-50°C under argon in the dark. A solution of 8 equivalents of sodium dithionite in degassed water (4 ml) was then added dropwise with stirring. After 10 minutes, the solution was extracted with chloroform (3 x 20 ml), the organic phase was washed with water and dried. The crude dihydropyridine **1** was not purified and was stored in the dark. Yield 80 %. I.R.: ν (C=O): 1590 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 7.20 (m, 5H); 6.85 (s, 1H); 5.69 (d, 1H); 5.60 (d, 1H); 4.76 (m, 1H); 4.60 (t, 1H); 4.18 (m, 1H); 3.55 (m, 2H); 2.88 (m, 4H); 2.80 (s, 3H).

3-(N,N)'-[(S)-(1-benzylhydroxyethyl)methyl]aminocarbonylpyridine **6**

N-methylphenylalaninol was obtained by following the method described previously (7). Its optical purity was determined by NMR (see theoretical part).

Compound **6** was obtained in the same way as compound **4**. Yield 47 %. m.p. = 100°C. $[\alpha]^{20}_D$ = -46.96 (c = 1.5, $CHCl_3$).

Analysis $C_{16}H_{18}N_2O_2$: Calcd: C, 71.09; H, 8.71; N, 10.36. Found: C, 71.0; H, 8.6; N, 10.3. I.R. ν (C=O): 1630 cm^{-1}. ^1H N.M.R. ($CDCl_3$) Minor conformer: 8.55 (d, 1H); 8.28 (s, 1H); 7.45 (d, 1H); 7.25 (m, 5H); 6.88 (d, 1H); 4.82 (m, 1H); 3.82 (m, 2H); 2.94 (d, 2H); 2.72 (s, 3H). Major conformer: 8.43 (d, 1H); 8.09 (s, 1H); 7.25 (m, 4H); 7.07 (m 1H); 6.94 (d, 1H); 6.88 (d, 1H); 3.87 (m, 1H); 3.72 (d, 1H); 3,55 (d, 1H); 3,03 (s,3H); 2.64 (d, 1H); 2.57 (d, 1H).

1-Methyl-3-(N,N')-[(S)-(1-benzylhydroxyethyl)methyl]aminocarbonylpyridinium iodide **7**

Obtained by the same procedure as used for compound **5**. Yield 98 %. m.p. = 162°C.

Analysis $C_{17}H_{21}IN_2O_2$: Calcd: C, 49.53; H, 5.13; N, 6.79. Found: C, 49.2; H, 5.1; N, 6.7. I.R. ν (C=O): 1640 cm^{-1}. ^1H N.M.R. (DMSO d_6). Minor conformer: 9.01 (d, 1H); 8.23 (s, 1H); 8.15 (t, 1H); 7.76 (d, 1H); 7.29 (m, 4H); 7.03 (dd, 1H); 4.89 (m, 1H); 4.35 (s, 3H); 3.65 (dd, 1H); 3.60 (dd, 1H); 2.90 (m, 2H); 2.82 (s, 3H). Major conformer: 8.97 (d, 1H); 8.22 (s, 1H); 8.07 (t, 1H); 7.76 (d, 1H); 7.29 (m, 4H); 7.03 (dd, 1H); 5.10 (m, 1H); 4.27 (s, 3H); 3.64 (dd, 1H); 3.48 (dd, 1H); 2.95 (s, 3H); 2.76 (dd, 1H); 2.65 (dd, 1H).

1-Methyl-3-(N,N')-[(S)-(1-benzylhydroxyethyl)methyl]aminocarbonyl-1,4-dihydropyridine **2**

The pyridinium salt **7** (1 mmol) was dissolved in degassed water (3 ml) at about 35 °C. To the resulting solution was added a freshly prepared solution of sodium carbonate decahydrate (4.5 eq) and sodium dithionite (7 eq) in degassed water (4.5 ml). After a few seconds, a yellow solid appeared. The mixture was stirred at room temperature for 30 mn. The solid was collected and dried under vacuum, in the dark. Yield 56 % (reproducible). No improvement of this yield was observed by increasing the temperature, the reaction time and the dithionite amount. ^1H NMR ($CDCl_3$) Minor isomer: 7.25 (m, 2H); 7.16 (m, 3H); 6.61 (s, 1H); 5.61 (dd, 1H); 4.82 (m, 1H); 4.72 (m, 1H); 3.95 (m, 1H); 3.70 (m, 2H);2.81 (m, 2H). Major isomer: 7.25 (m, 2H); 7.16 (m, 2H); 5.70 (s, 1H); 5.55 (dd, 1H); 4.47 (m, 1H); 4.40 (m, 1H); 3.71 (m, 2H); 2.90 (m, 1H); 2.81 (m, 2H); 2.80 (s, 3H); 2.74 (m, 1H); 2.70 (s, 3H).

2-Trimethylsilylethynylnicotinonitrile **8a**

In a flask flushed with argon were introduced, dry cuprous iodide (0.38 g, 0.002 mol) in triethylamine (10 ml) at 60-90°C. After cooling at room temperature, trimethylsilylacetylene (0.4 ml) was added under stirring. After 10 minutes, bis(triphenylphosphine) palladium II chloride (0.7 g, 0.001 mol) was added and the mixture stirred further for 10 minutes. 2-chloronicotinonitrile (2.75 g, 0.02 mol) (11) in triethylamine (6 ml) was then added and the mixture stirred again 10 minutes. At this point, trimethylsilylacetylene (4 ml, 0.028 mol) was introduced and the mixture warmed at 100°C for 20 hours. After elimination of the volatile products, the residue was taken up with ether, filtered and concentrated to dryness. The dark solid was purified by sublimation (50°C/1 mm Hg). Yield 77 %. m.p. = 55°C.

Analysis $C_{11}H_{12}N_2Si$: Calcd: C, 65.95; H, 6.04; N, 13.98. Found: C, 65.9; H, 5.8; N, 13.8. I.R. ν (C≡N): 2210 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 8.8 (dd, 1H); 8.0 (dd, 1H); 7.35 (dd, 1H); 0.35 (s, 9H).

2-Ethynylnicotinonitrile **8b**

The above compound **8a** (0.75 g, 0.0037 mol) in tetrahydrofuran (20 ml) and 0.1 N sodium hydroxide (15 ml) was stirred at room temperature for 2 hours. After evaporation of the solvents, the aqueous phase was extracted with ether (3 x 20 ml). After drying and concentration, the brown solid was purified by sublimation (50°C/1 mm Hg). Yield 70 %. m.p. = 125°C.

Analysis $C_8H_4N_2$: Calcd: C, 74.99; H, 3.15; N, 21.86. Found: C, 74.6; H, 3.0; N, 21.2. I.R. ν (C≡N): 2240 cm^{-1}; ν (C≡C): 2110 cm^{-1}. ^1H NMR ($CDCl_3$): 8.85 (d, J = 4 Hz, 1H); 8.05 (d, J= 8 Hz, 1H); 7.45 (dd, J = 8 Hz and J = 4 Hz, 1H); 3.60 (s,1H).

2-[2-(N-(S)-(1-benzylhydroxyethyl)amino]ethenylnicotinonitrile **9**

The above compound **8b** (1.28 g, 0.010 mol) and (S)-phenylalaninol (1.66 g, 0.011 mol) were heated under reflux for 24 hours in tetrahydrofuran (50 ml). After cooling, the solvent was eliminated and the crude orange oil was not purified further. I.R. ν (C≡N): 2220 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 9.10 (m, 1H); 8.40 (dd, 1H); 7.65 (dd, 1H); 7.20 (s, 5H); 6.75 (q, 1H); 6.45 (d, 1H); 5.30 (d, 1H); 3.60 (m, 4H); 2.95 (m, 2H).

2-[2-(N-(S)-1-benzylhydroxyethyl)amino]ethyl-nicotinonitrile **10**

In a flask protected against moisture, were introduced compound **9** (1.674 g , 0.006 mol), anhydrous zinc chloride (1.206 g, 0.006 mol) and sodium cyanoborohydride (0.756 g, 0.012 mol) in methanol(30 ml). The mixture was stirred at room temperature for 1 hour, then zinc chloride (0.603 g, 0.003 mol) and sodium cyanoborohydride (0.378 g, 0.006 mol) were introduced and stirring was maintained for 1 hour. After adding 1N NaOH (30 ml), the mixture was extracted with dichloromethane (2 x 20 ml). After drying and elimination of volatile products, the crude orange oil was not purified. I.R. ν (C≡N): 2200 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 8.60 (d, 1H); 7.95 (d, 1H); 7.25 (s, 6H); 4.75 (m, 1H); 8.80 (m, 1H); 3.6 (m, 2H); 3.0 (m, 6H).

6-[(S)-1-benzylhydroxyethyl]-5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridine **11**

The above crude product **10** (6,2 g) was heated under reflux in 70 ml of a 95/5 mixture ethanol-water for 48 hours. After evaporation of the solvent, the product was purified by column chromatography (silica, eluent CH_2Cl_2/EtOH : 90/10). Overall yield 56 % (with respect to compound **8b**) m.p.= 125°C. $[\alpha]^{20}_D$ = -66.96° (c= 1.5; $CHCl_3$).

Analysis $C_{17}H_{18}N_2O_2$: Calcd: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.24; H, 6.37 N, 9.99. I.R. ν (C=O): 1630 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 8.50 (dd, 1H); 8.20 (dd, 1H); 7.20 (m, 5H); 7.17 (m, 1H); 4.78 (m, 1H); 3.85 (m, 2H); 3.80 (m, 1H); 3.46 (m, 2H); 3.00 (d, 2H); 2.89 (m, 2H).

Optical purity of **11**

Compound (R,S)-**11** was synthesized from racemic phenylalaninol. The two enantiomers were separated by HPLC using a chiral LKB enantiopac column in the following conditions: sample 0.2 mg in 25 ml of solvent (phosphate buffer pH 7 and methanol 90/10); injection: 20 µl; pressure 1200-1500 psi; temperature 23°C; flow rate 0.2 ml/min. Detector Varian Polychrom 9060: λ: 275 nm. Retention times: 11 mn for the (R) and 17 mn for the (S).

1-Methyl-6-[(S)-1-benzylhydroxyethyl]-5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridinium iodide **12**

Compound **11** was heated under reflux in a large excess of methyl iodide as described for compound **5**. Yield 98 %. m.p. = 192°C.

Analysis $C_{18}H_{21}IN_2O_2$: Calcd: C, 50.96; H, 4.99; N, 6.60. Found: C, 51.04; H, 4.88; N, 6.65. I.R. ν (C=O): 1660 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 9.06 (d, 1H); 8.79 (d, 1H); 8.02 (t, 1H); 7.20 (m, 4H); 7.15 (m, 1H); 4.88 (m, 1H); 4.06 (s, 3H); 3.69 (m, 3H); 3.57 (dd, 1H); 3.40 (m, 1H); 3.24 (m, 1H); 2.93 (dd, 1H); 2.86 (dd, 1H).

1-Methyl-6-[(S)-1-benzylhydroxyethyl]-1,4,5,6,7,8-hexahydro-5 -oxo-1,6-naphthyridine **3**

Obtained by reduction of **12**, by a procedure similar to that described for the obtention of **1**. Yield 80 %. I.R. ν (C=O): 1680 cm^{-1}. ^1H N.M.R. ($CDCl_3$): 7.18 (m, 5H); 5.57 (d, 1H); 4.66 (m, 1H); 4.21 (m, 1H); 3.72 (dd, 1H); 3.68 (dd, 1H); 3.14 (m, 1H); 3.05 (m, 2H); 3.02 (m, 1H); 2.98 (dd, 1H); 2.88 (dd, 1H) 2.77 (q, 3H); 2.10 (t, 2H).

Reduction of methyl benzoylformate and determination of e.e.

In a flask flushed with dry argon, the appropriate NADH model (1mmol), methyl benzoylformate (0.9 mmol) and magnesium perchlorate (1 mmol) were dissolved in acetonitrile (5 ml). The reaction mixture was stirred in the dark, under argon (temperatures and reaction times are mentioned in table 4). Water (0.5 ml) was then added and the product extracted with dichloromethane. After drying, methyl mandelate was isolated by preparative TLC (silica plates, eluent: ether/hexane 1/2) and the e.e. determined by HPLC as mentioned above but with the following modifications: sample 1.5 mg in 50 ml of solvent (phosphate buffer pH 7 and propanol 98/2; λ = 210 nm; temperature 15 °C; retention times: 15 mn for the (S) and 18 mn for the (R). The same results were obtained by GPC analysis of the diastereoisomers after derivatization by Mosher's method (8). Sample 1 µl. Capillary column DB1 (l = 50 m). Oven temperature: 170 °C. FID detector and injector temperatures: 250 °C. Vector gas: He, pressure 1 bar. Retention times: 36 mn for the (R,S) and 38.8 mn for the (S,S). The accuracy was 5 % with a very good reproducibility.

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