CHIRAL NADH MODELS DERIVED FROM OPTICALLY ACTIVE AMINO ALCOHOLS

Georges Dupas, Vincent Levacher, Jean Bourguignon*, and Guy Quéguiner

Laboratoire de Chimie Organique Fine et Hétérocyclique de l'IRCOF,
URA 1429 CNRS, Institut National des Sciences Appliquées de Rouen,
BP08, 76131 Mont-Saint-Aignan Cédex, France

Abstract-After a short description of the main characteristics of biomimetic NADH models, the choice of optically active amino alcohols as chiral auxiliaries is justified. The literature results in this field are then reviewed. The results obtained with 1,4-dihydropyridines, annelated models in the thiophene and pyrrole series are particularly discussed. The main factors responsible of a good enantioselectivity are emphasized and applied to the design of a highly enantioselective NADH model in the 1,6-naphtyridinone series.

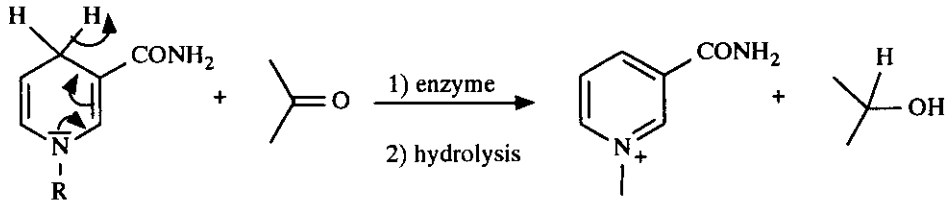
SUMMARY:

INTRODUCTION

The enantioselective reduction of a prochiral unsaturated derivative is a challenge for organic chemists. One of the main reasons for interest in this area is that a large variety of compounds obtained by this way are precursors of very important molecules, particularly in the field of pharmaceuticals.[1]

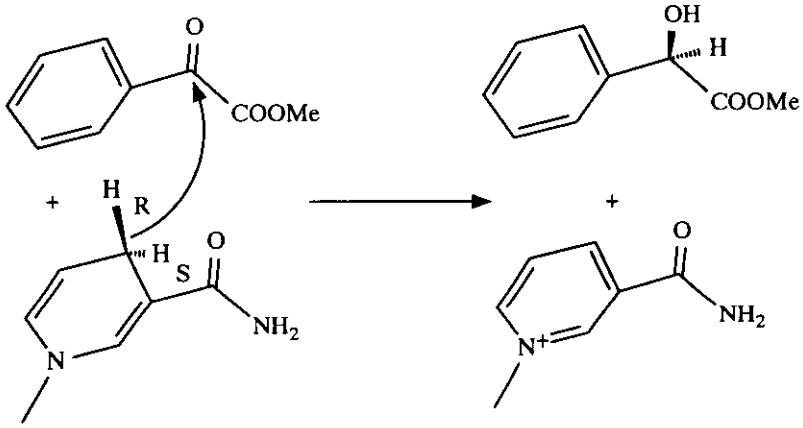
In nature many such transformations are carried out easily with a high degree of selectivity by using enzymes. This behaviour has mostly interested chemists who developed biomimetic systems with a view to obtaining reagents with similar properties which could be used in synthesis.[2]

In biological systems, enzymes involved in redox processes generally require coenzymes such as nicotinamide adenine dinucleotide (NADH/ NAD^+) which are the effective reagents at the active site of the enzyme (designated as the apoenzyme). The active part of the coenzyme NADH is the 1,4-dihydronicotinamide moiety[3] and the reduction of a carbonyl substrate can be represented by the following scheme.



Scheme I

With a given enzyme, only one of the two prochiral hydrogens on C_4 of the 1,4-dihydronicotinamide ring of NADH is transferred to a prochiral substrate.[4] For example, some enzymes catalyze pro-(R) hydrogen removal from NADH and others catalyze pro-(S) hydrogen removal. This stereospecificity was attributed to the shielding of one side of the nicotinamide plane by the protein structure. This simple assumption could explain that during the reduction of a prochiral ketone (i.e. methyl benzoylformate), pathway A leading to (R)-methyl mandelate would be favoured at the active site of the enzyme.



Scheme II (pathway A)

In this case the *si*-face of the substrate approaches the pro(R) hydrogen of the reagent. In this transition state, many points would be fixed by the enzyme: 1) The polar ester function of the substrate lies over the polar amide function of the enzyme. 2) The carbonyl dipoles of these two carbonyls are pointed in the same direction. 3) The carbonyl of the amide part of the enzyme would be syn oriented with respect to the C_4 atom. Finally, many different pathways leading to either the (R)- or the (S)-methyl mandelate can occur. In an

enzymic reaction only one situation is encountered : Pathway A, in the above example, is described with a defined enzyme which plays a fundamental role in the correct arrangement of the substrate and the coenzyme.

I) BIOMIMETIC NADH MODELS

Biomimetic NADH models are 1,4-dihydronicotinamides bearing a simple substituent at the ring nitrogen atom.[5] These reagents allow the reduction of an activated carbonyl derivative by a mechanism very similar to that described with the coenzyme itself. However, there is an important difference that is the absence of the enzyme. It was earlier shown that with model compounds, it was essential to conduct the reaction in the presence of magnesium ions. Ohno[6] showed that most of the reductions performed with NADH models occur through the formation of a ternary complex of the type : substrate - metal ion - dihydronicotinamide.

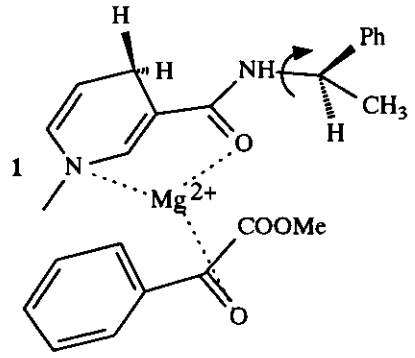
The metal ion has several roles. Firstly as a Lewis acid which polarizes the carbonyl group of the substrate in order to facilitate the reduction. And secondly, the metal ion binds to the 1,4-dihydropyridine structure and to the substrate to facilitate the hydrogen transfer and furthermore to orientate the reactants : the ketone carbonyl of the substrate and the amide C=O of the reagent are facing each other. Moreover, the phenyl group of the benzoylformate lays over the 1,4-dihydronicotinamide structure. So in the ternary complex the number of arrangements between the partners is lowered.[6]

1) Asymmetric reductions with chiral NADH models.

Starting from this approach, in order to envisage an asymmetric reduction of a prochiral substrate, it would be necessary to specifically block one face of the dihydropyridine structure. This can be achieved by the stereocontrolled incorporation of a sterically demanding chiral auxiliary.

In 1975, Ohno[7] reported the first stereoselective reduction of ethyl benzoylformate with model (**1**) possessing a chiral carboxamide at C-3 (e.e. = 20 %). Since this encouraging result, a lot of chiral models bearing various chiral auxiliaries at the 1, 3 or 4 position of the 1,4-dihydropyridine structure have been synthesized and studied.[8] It appears that some chiral models at the C-4 position are efficient, but, after reduction, the chirality is lost in the obtained pyridinium salt : The reagent is involved in a self-immolative reaction. So, with a view to developing new reagents which can be recycled, it seems that the best position for introduction of a chiral auxiliary is at the C=O of the 3 position as in the above mentioned Ohno's model. With this last reagent, the stereodifferentiation of the two faces of the 1,4-dihydropyridine ring is achieved by the α-methylbenzylamine

group (scheme below).



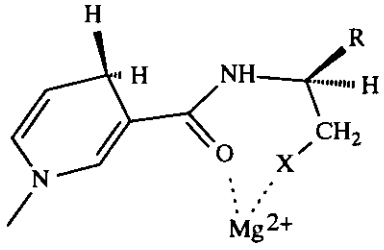
In the ternary complex, Ohno assumed a trans orientation of the C=O amide through a supplementary complexation of Mg^{2+} with the nitrogen atom at the 1-position.

Scheme III

The proposed structure for the ternary complex above is the most probable because Mg^{2+} ions are complexed at the lower face of the dihydropyridine which is the less hindered. However, it must be noticed that, due to the free rotating ability around the NH-chiral carbon bond, other conformations can be easily involved leading to other ternary complexes. The specific blocking of one face of the 1,4-dihydropyridine is not very good and the obtention of a preferred enantiomer is not very much favoured. This can explain the modest e.e. observed. However, this result was encouraging since the chiral centre was quite far from the active site of the reagent (five bonds: see Scheme III).

2) Choice of amino alcohols as chiral auxiliaries

In order to increase the efficiency of the reagent, it is necessary to make more rigid the sterically demanding chiral auxiliary. As already postulated, reductions with NADH models occur *via* a ternary complex involving complexations with magnesium ions. So, if a supplementary complexing group is added to the chiral auxiliary, it can be envisaged that this auxiliary will be more rigid and also that the efficiency of the so-obtained reagent will be improved.



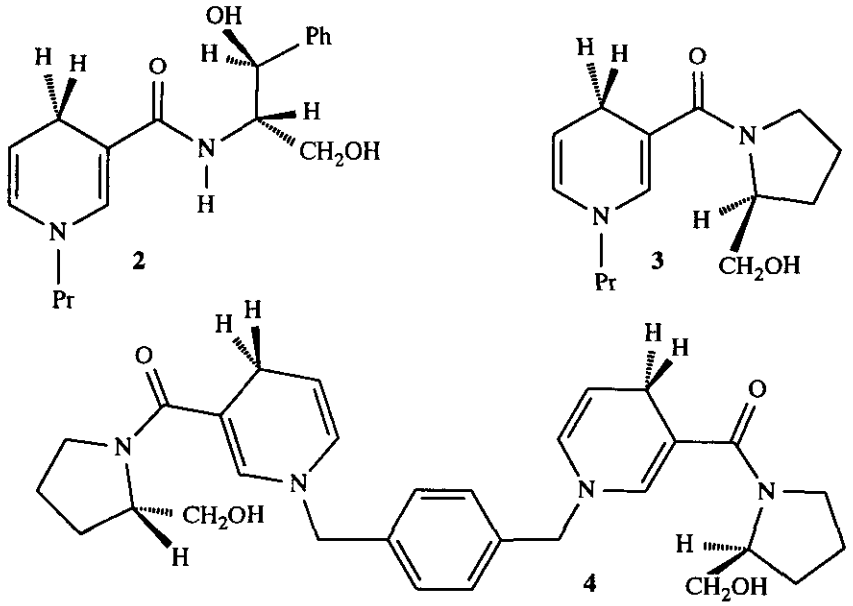
Scheme IV

With this objective in view we chose to insert a 2-amino alcohol derivative at the C-3 carbonyl position. This choice was guided by the following considerations : 1) Optically pure 2-amino alcohols are easily obtained by

reduction of the corresponding amino acids.[9] 2) The oxygen atom can be complexed by magnesium as well as the carbonyl group. By this method it can be expected that the geometry of the chiral auxiliary would be more rigid leading to a better stereodifferentiation of the two faces of the 1,4-dihydropyridine ring in the ternary complex.

II) LITERATURE SURVEY OF CHIRAL NADH MODELS BEARING A CHIRAL AUXILIARY DERIVED FROM AMINO ALCOHOLS.

This survey shows that there were only a few reports concerning such models.



Scheme V

Inouye *et al.*[10] reported the results obtained with *N*-[2-hydroxy-1-(α-hydroxybenzyl)]-1-propyl-1,4-dihydronicotinamide (**2**) during the reduction of ethyl benzoylformate. The e.e. was affected remarkably by the amount of magnesium ions and changed through out the reaction. It was suggested by the authors that the optical yield was influenced by the formed chiral pyridinium salt during the reaction. It was also suggested that polar functions able to chelate magnesium ions (two free hydroxyl groups in the case of (**2**) are responsible for the observed dependence of e.e. on the experimental conditions. Moreover, it was safely

concluded that hydroxyl groups play an important role in the discrimination of the two diastereotopic hydrogens at C-4.

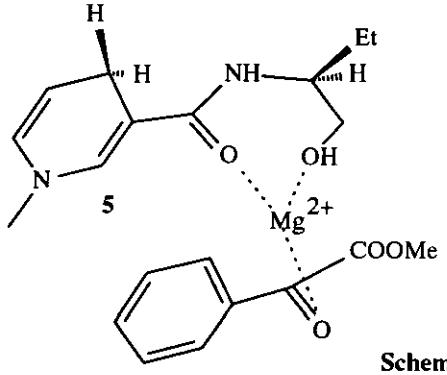
Another model, (3) issued from prolinol was briefly studied.[11] It allowed the obtention of a 54.5 % e.e. (chemical yield 54.9 %).

Another type of bis NADH model with a C-2 axis was synthesized by Inouye *et al.* [12] The obtained e.e. was low (3%). This result is surprising when compared to the high e.e. (98.1 %) obtained with a similar reagent where the prolinol groups were replaced by prolinamide groups.

When we started our study, there were, to our knowledge, no other substantial results obtained with NADH models bearing a chiral 2-amino alcohol at the 3-carbonyl function and no further information concerning the role played by the alcohol group of the chiral auxiliary in asymmetric reductions. We wish now to report our main results in this field.

III) NEW CHIRAL MODELS BEARING AMINOALCOHOLS IN THE 1,4-DIHYDROPYRIDINE SERIES.

The chiral 2-amino alcohol studied first was (S)-2-aminobutan-1-ol which is readily available in an optically pure form as it is used in the synthesis of the antibacterial drug ethambutol. Model (**5**) was synthesized by conventional methods [13] and used for the reduction of methyl benzoylformate. The e.e. was 49 % which is much better than with model (**1**).



Conditions :

Model/Mg^{2+}/PhCOCOOMe : 1/1/1

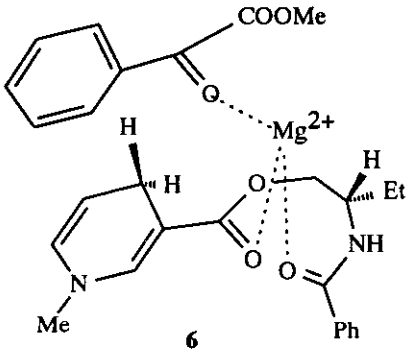
60 °C; solvent MeCN

Scheme VI

This large improvment can be supported by the previouly reported asumption that the rigidity of the chiral

auxiliary is considerably reinforced by the supplementary chelation due to the oxygen atom of the hydroxy group (see Scheme VI).

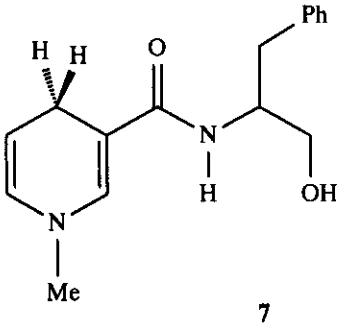
An original result was obtained with model (**6**) where the amino function was converted into a benzamide group and the linkage to the dihydropyridine structure was an ester group instead of an amide group as in **5**.



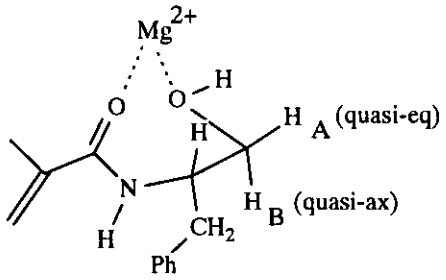
6

Scheme VII

The opposite enantiomer of methyl mandelate was obtained with a 52 % e.e. So with the same chiral auxiliary, i.e. (S)-2-aminobutanol, it is possible to obtain preferentially one enantiomer or the other depending on the function of the amino alcohol which has been linked to the 1,4-dihydropyridine part. This is due to the different position of the ethyl group with respect to the plane of the 1,4-dihydropyridine ring. When (S)-2-aminobutanol is replaced by (S)-phenylalaninol (model **7**, Scheme VIII), the e.e. was better (58 %) probably because the benzyl group is bulkier than the ethyl group.



7



Scheme VIII

The nmr spectra of compound (**7**) was studied in absence or in presence of magnesium ions. The results clearly show the importance of the alcohol function to make more rigid the chiral auxiliary :

-Without Mg^{2+} the methylene group of CH_2OH appears as two doublets of doublets with a large coupling constant (J_{gem}= 10 Hz) for the *gem* hydrogens and smaller coupling constants (3.4 and 5.8 Hz) corresponding to the coupling between the two magnetically different *gem* hydrogens and the proton at the chiral carbon.

-With magnesium, the results obtained can be explained by the quasi-cyclic structure proposed above (scheme VIII). The proton H_A (δ = 3.80 ppm in CD_3CN) looks like two triplets. This proton has a quasi-equatorial position and is coupled with H_B (J_{AB} = 10.7 Hz), the hydrogen of the chiral carbon (J = 3 Hz) and the alcohol hydrogen (J = 3 Hz). It is logical to assume that the hydrogen at the chiral carbon adopts preferentially a quasi-axial position. The proton H_B (δ = 3.56 ppm) looks like a triplet of doublets. It has preferentially a quasi-axial position and is coupled with H_A(J_{AB} = 10.7 Hz), with the quasi-axial hydrogen of the chiral carbon (J = 10.3 Hz) and the alcohol hydrogen (J = 3 Hz).

It can be assumed that with Mg^{2+} ions, the chiral auxiliary adopts a quasi-cyclohexane conformation and as a consequence the sterically demanding benzyl group hinders preferentially one face of the structure.

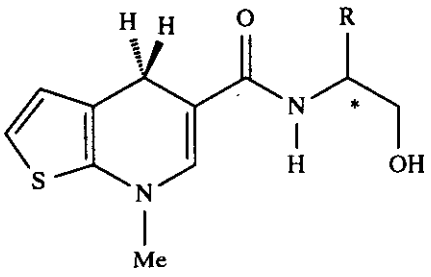
The results obtained with the models described above were encouraging but, at this point, it is necessary to discuss the chemical yields and the convenience of such reductions. With simple pyridine NADH models the reduction of a substrate competes with important side-reactions caused by the presence of traces of water which reacts with the 5,6 double bond of the 1,4-dihydropyridine structure.[14] The presence of a hydrophylic substituent on the model enhances the pernicious role of water and it is necessary to work in extremely-dry conditions in order to obtain good chemical yields (60 % with model **5**, 89 % with model (**6**) and 60 % with model (**7**).

So, very early in our laboratory work, we synthesized annelated NADH models where a thiophene ring protects the 5,6-double bond. These models are a lot more useful for synthetic purposes, since the experimental conditions are milder and the yields are higher.[15] In order to optimize the use of these models, further experiments were performed, concerning as follows: 1) Variations of the nature of the amino alcohols: 2) The influence of physical parameters: 3) The replacement of the OH function by a OMe function: 4) The role of magnesium ions amount: 5) The possibility of supplementary interactions. These experiments were studied with models in the 5,7-dihydrothieno[2,3-*b*]pyridine series.

IV) CHIRAL ANNELATED MODELS IN THE THIOPHENE SERIES

1) Variations on the amino alcohol

In a first approach, models bearing various chiral auxiliaries were studied.[16] The results are summarized in figure 1.



8a-d

	Yield (%)	e.e. (%)
8a R=Et	100	42
8b R=Ph	100	34
8c R=iPr	100	46
8d R=$PhCH_2$	100	53

Conditions: Model **8a-d**/Mg^{2+}/PhCOCOOMe : 1/1/1
Temperature : 65 °C; solvent MeCN

Figure 1

There is no appreciable change in the e.e. when the same chiral auxiliary is used with a simple model or with an annelated model (compare models (**5**) and (**8a**)). But the most interesting feature concerns the quantitative yield obtained with models (**8a-d**) despite the use of technical grade solvents. The best e.e. is obtained with model (**8d**) issued from phenylalaninol (compare with model (**7**)).

2) Factors which can influence the e.e.

The following experiments were performed with this model (see tables 1 and 2).

Temperature (°C)	Reaction time	Yield (%)	e.e.(%)
65	24 h	100	53
20	72 h	100	58
0	96 h	68	60

Table 1
Influence of temperature

Mg^{2+}/Model	Yield (%)	e.e.(%)
0.5	100	43
1.0	100	58
2.0	100	60

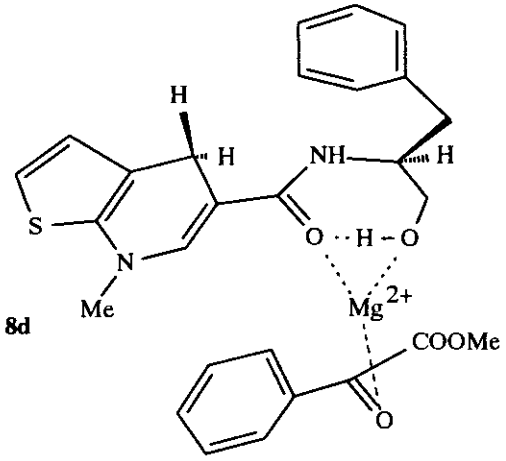
Table 2
Influence of $Mg(ClO_4)_2$ concentration

By lowering the temperature, a small enhancement of the e.e. is observed but at 0°C the reactivity of the reagent is too low and only a 68 % chemical yield was obtained. Concerning the role of the concentration of

Mg^{2+}, there is no significant change with 1 or 2 equivalents of Mg^{2+}. This is contrary to a 0.5 equivalent of Mg^{2+} where a substantial lowering of the e.e. was observed. It can be assumed that, in these conditions, the geometry of the ternary complex is not well defined. Moreover, a part of the reduction could occur without the establishment of this ternary complex, Mg^{2+} only being involved in the activation of the substrate.

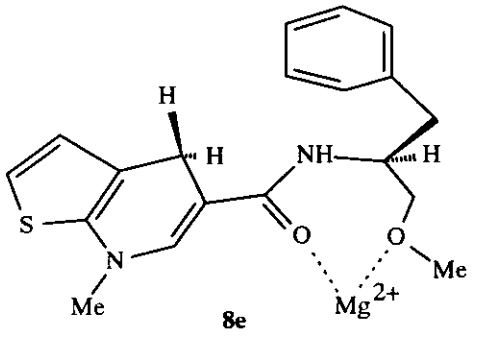
This result can be compared to the result obtained during the reduction of $PhCOCF_3$ with model (1) in the presence or in the absence of Mg^{2+} (e.e. 16 % or 0 %).[17]

The rigidity of the ternary complex may be due, in part, to the occurence of a hydrogen bond between the hydrogen of the alcohol and the carbonyl function of the amide in a seven bond structure (see scheme IX).



8d

e.e. = 58 %



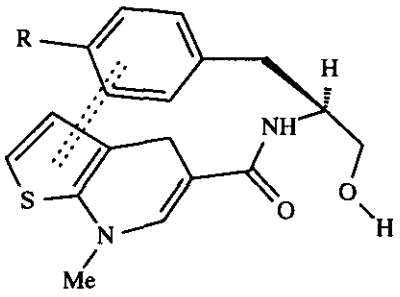
8e

e.e. = 41 %

Scheme IX

In order to examine this, we studied the *O*-methylated derivative (**8e**). The decreased e.e. (58 % → 41 %) indicates that the most important factor in the geometry of the ternary complex is probably the supplementary complexation of the magnesium ions with the oxygen atom. With model (**8d**) the occurence of a hydrogen bond reinforces the rigidity of the complex to a minor extent.

Another important factor can be found in the geometry of the complex. As can be seen from the study of molecular models, a charge transfer complex can be established between the π electron excessive system (thiophene ring) and the π electron system of the phenyl ring of phenylalaninol. This interaction was reinforced by replacing the phenyl group by a *p*-nitrophenyl group (model (**8f**)) and then a 75 % e.e. was obtained.[16]



R = H : **8d**, e.e. = 58 %

R = NO_2 : **8f**, e.e. = 75 %

Scheme X

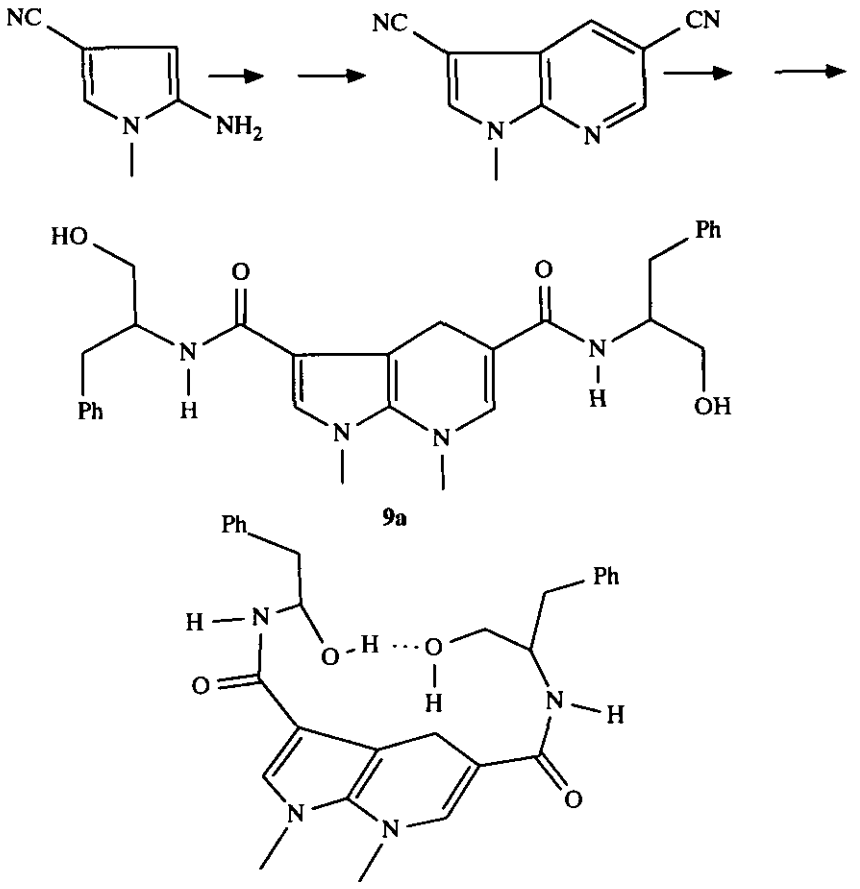
V) CHIRAL MODELS WITH AN ANNELATED PYRROLE RING

The above results are interesting since they were obtained with easily handled reagents. However, the reactivity of thiophene models is lower compared to that of simple pyridine reagents. For example the reduction of methyl benzoylformate requires 24 hours with model (**7**) at room temperature and requires 72 hours with model (**8d**) in the same conditions. Two factors can explain these results : 1) The annelation of the dihydropyridine structure with a highly aromatic thiophene ring stabilizes the reagent and hence makes it less reactive. The gain in energy when the reagent is transformed into an aromatic pyridinium ring during the reduction is relatively less favourable in the thienodihydropyridine series compared to the simple dihydropyridine series. 2) The electron donating effect of the thiophene ring is medium and does not exert a large influence on the departure of the hydride equivalent from C_4.

So, it appears that the synthesis of models in the pyrrolodihydropyridine series would be of interest since pyrrole has a less aromatic character than thiophene and also has a much higher electron donating effect.

1) Pyrrolo[2,3-*b*]pyridine series

a) Syntheses: The key compound for the synthesis of the annellated models described above is 2-aminothiophene. But its isoster in the pyrrole series is too instable to be used. So we started from the readily available 2-amino-4-cyanopyrrole leading to model (**9a**).[18]



Scheme XI

b) Results. Owing to its synthesis, model (**9a**) has two chiral auxiliaries, one at the pyrrole ring and one at the dihydropyridine ring. The study of molecular models clearly shows that an interaction can be established between the two auxiliaries i.e. by forming an hydrogen bond between the two hydroxyl functions (see scheme XI). This interaction can be influenced by Mg^{2+} ions. As a consequence, the geometry of model can be modified depending on the existence or the absence of this hydrogen bond and the stereodifferentiation of the two faces of dihydropyridine structure could be modified.

The reduction of methyl benzoylformate was, therefore, conducted in the presence of various amounts of Mg^{2+}. The same experiments were performed with model (**9b**) where the two CH_2OH groups were replaced by CH_2OMe groups thus prohibiting the occurence of hydrogen bonds. The results are summarized on the

following curves.

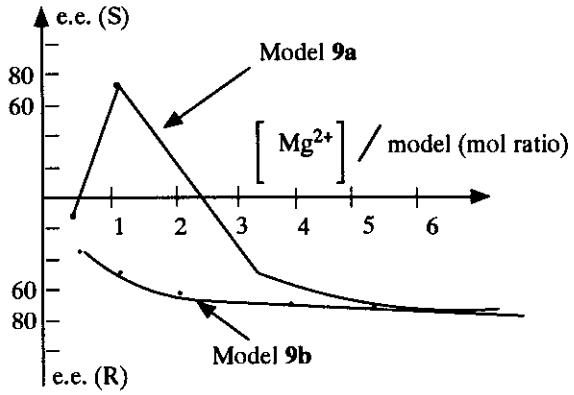


Figure 2

With **9a** in the absence of Mg^{2+} the e.e. was zero. This result affords a supplementary probe of the fundamental role played by Mg^{2+} in the hydrogen transfer. More importantly, as can be seen with **9a** the major enantiomer of methyl mandelate can be either the (S) or the (R) depending solely on the magnesium ions concentration. The dependance of e.e. on the concentration of magnesium ions was already reported with models possessing a C2 symmetry axis but the e.es were lower and the study was performed in a smaller interval of concentration. With **9a** the (S)-methyl mandelate was obtained with a 65 % e.e. with 1 equivalent of Mg^{2+}. The (R)-methyl mandelate was obtained with a 78 % e.e. with 6 or more equivalents of Mg^{2+}.

This model examplifies a possibility not open to a single enzyme, namely the obtention of either enantiomer of the product by variation of experimental conditions.

With **9b** there is no appreciable variation of the e.e. Whatever the concentration of Mg^{2+}, the result is similar to that obtained with **9a** in presence of large amounts of Mg^{2+}.

c) Spectroscopic studies. With a view to obtaining information about the interactions between Mg^{2+} and model **9a** we tried to perform a ^{13}C nmr study of the fully aromatic precursor of **9a** in presence of Mg^{2+} (under the dihydropyridine form, i.e. **9a**, the compound was partly destroyed in the presence of Mg^{2+} ions [19] during the recording of the spectra). Unfortunately, we were as yet unable to record spectra : in all cases there were no signals. This behaviour is probably a consequence of the high degree of association of magnesium ions with (**9a**).

Another study was then performed by ir spectroscopy by examining the shifts of the absorption in the region of C=O (1650-1700 cm^{-1}) and of secondary amides (1510-1550 cm^{-1}) in the presence of increased amounts of Mg^{2+}.

From the results we can postulate the existence of two complexes depending of the Mg^{2+}concentration. A shift of the C=O and N-H absorptions by adding increasing amounts of Mg^{2+} was observed (Figure 3).

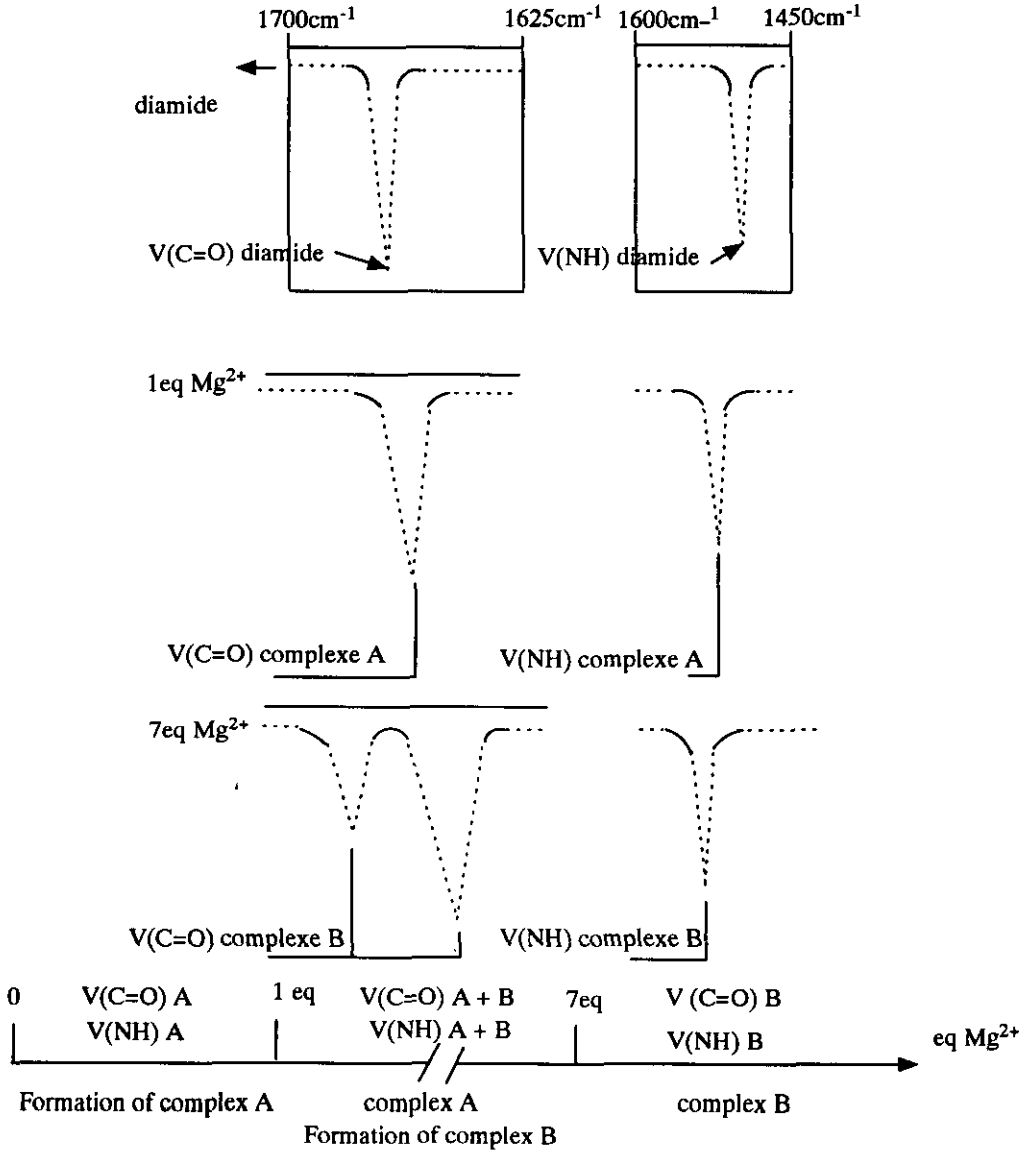
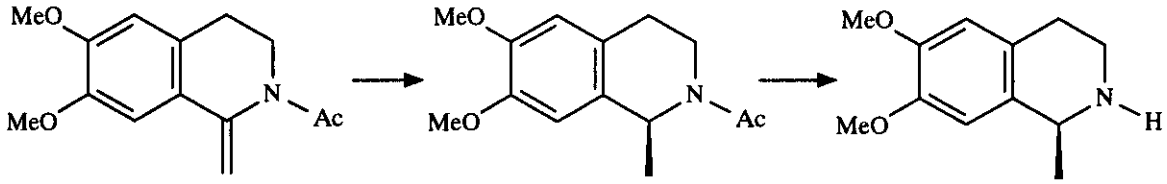


Figure 3

d) Discussion. In the case of complex B, the two C=O are different since two signals appear in the 1650-1700 cm^{-1} region. These two complexes are probably in equilibrium with each other. With 1 Mg^{2+}equiv., all the Mg^{2+} ions would be involved in the complexation between the carbonyl of the amide part at the 3 position on the 1,4-dihydropyridine and the complexation of the carbonyl part of the substrate (see Scheme XI). By this method the hydrogen bond between the two hydroxy groups can exist and, as can be seen by study of molecular models, the two sterically demanding groups hinder the lower face of the reagent and favour the departure of the pro-(S) hydrogen at the 4 position preferentially leading to the (S)- methyl mandelate. This hypothesis implies that the behaviour of Mg^{2+} is different with models having a single chiral auxiliary. In the latter case, the hydroxy oxygen would be involved in the complexation with Mg^{2+} whereas in the former, the hydroxy groups would be involved in the establishment of the hydrogen bond insuring the rigidity of the chiral auxiliary. With more Mg^{2+} ions, each amide part of **9a** would be complexed by Mg^{2+} and the oxygen atoms of the hydroxy groups involved in this complexation. So, the two chiral auxiliaries become independant from each other, a behaviour which is encountered in **9b** where there is, of course, no hydrogen bond..

So, in these two cases, the upper face of the NADH model is hindered as with other simple models (**5**, **7**, **8**) preferentially leading to the (R)-methyl mandelate.

e) Synthesis of (S)-Salsolidine. With **9a**, the e.es are as high as about 80 %. This good result led us to perform the asymmetric synthesis of a target molecule, i.e. (S)-salsolidine by following Scheme.



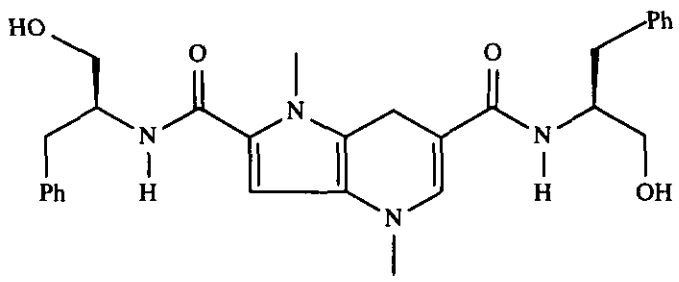
Reduction conditions : Mg^{2+} / model **9a** / substrate : 1 / 1 / 1
60 °C in MeCN

Scheme XII

(S)-Salsolidine was obtained with a 87 % e.e. that is a very good result in this field.

2) Pyrrolo[3,2-*b*]pyridine series.

An isoster of **9a**, model (**9c**)was synthesized [20] in the pyrrolo[3,2-*b*]pyridine series.



9c

Scheme XIII

The reduction of methyl benzoylformate with this reagent afford preferentially the (R)-methyl mandelate with a 50-55 % e.e. whatever the Mg^{2+} concentration. The study of molecular models shows that the methyl group of the pyrrole ring can suppress the interaction between the two chiral auxiliaries observed with **9a**. As a consequence, the behaviour of this reagent is very similar to that of **9b** where the enantioselectivity is essentially controlled by the chirality on the 1,4-dihydropyridine moiety.

VI) IMPROVING THE E.E.

1) Position of the problem.

It must be stated that many points concerning the mechanism of the enantioselectivity of the hydrogen transfer with most of the models described in the literature remain unclear. Some chiral NADH models allow the obtention of very high e.e. For example a model described by Ohno [21] gave a 98 % e.e (see scheme XV below). In the ternary complex of the reaction it was assumed that the carbonyl lies over the dihydropyridine ring with the oxygen of the carbonyl directed towards the ring nitrogen (cis with respect to C2). On the other hand, the results obtained with some other very efficient NADH models were explained by directing the carbonyl group away from the ring nitrogen.[22]

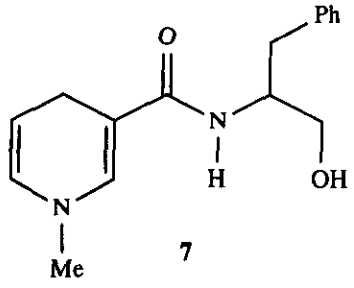
Most of the NADH models have a freely rotating amide part, so these hypothesis are plausible. The conformation of the carbonyl part have been also widely discussed for the coenzyme itself. Some recent papers[23] have established from theoretical simulation, that at the active site of the enzyme system the 1,4-dihydronicotinamide part of the coenzyme probably has the following features : 1) The ring has a quasi-boat conformation; the pseudo axial H at the C_4 position is preferentially transfered to a substrate. There would be a kinetic advantage to this transfer. 2) The amide C=O would be trans with respect to C_2. Moreover,

this C=O would be out of plane in a quasi-syn position with respect to the pseudo-axial C_4H, which is transferred. It has been suggested that the position of the carbonyl amide plays a very important role for both the catalysis and stereochemistry of hydride transfer.

In order to develop biomimetic models with a high efficiency, it appears that it would be of interest to mimick the main factors involved with the coenzyme. Among them, one of the most important seems the conformation of the amide C=O .

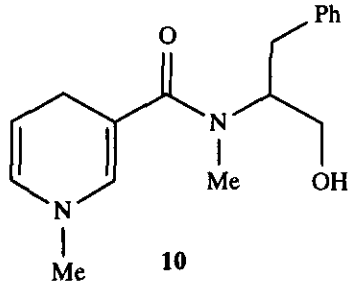
2) Conformation of the amide C=O.

We studied the 3 following models.



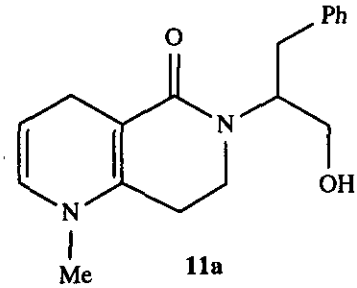
7

The free rotation about the C_3-C=O amide bond is not hindered.



10

The presence of a methyl group on the amide nitrogen could be sufficient to cause a steric hindrance forcing the carbonyl group to be out of the plane.



11a

The cyclized structure of the amide part forces the carbonyl to be in a trans conformation with respect to C_2

Scheme XIV

a) Results.

The results obtained in the reduction of methyl benzoylformate are summarized in Table 3.

Model	$t_{1/2}$*	e.e. (%)
7	6 h	58
10	5 min	3
11a	5 min	90

Reaction conditions:
Model/Mg^{2+}/Substrate: 1/1/1
R.T.; Solvent CH_3CN

* $t_{1/2}$: time for a 50 % conversion in methyl mandelate.

Table 3

b) Discussion. With model (**10**), the out of plane position of the amide carbonyl leads to its non-conjugation with the 1,4-dihydropyridine ring. In this situation there are two factors which can explain the observed high reactivity : 1) The non-conjugation does not disfavour the departure of the hydride equivalent from C_4. 2) The amide C=O would be syn with the transferred hydrogen in a trans position with respect to C_2 that corresponds to a kinetic advantage.[23] In this case, molecular models show that the remote steric blocking group i.e. the $PhCH_2$ group is located in the mean plane of the 1,4-dihydropyridine ring and does not preferentially hinder one face or the other. The stereodifferentiation of the two faces of the dihydropyridine is very low and could explain the small observed e.e.

With model (**7**), different ternary complexes can exist. Those of the A type where there is conjugation of the C=O amide with the 1,4-dihydropyridine ring : The reactivity of the reagent is lowered but stereodifferentiation of the two faces is easily achieved. Those of the B type which are identical to the situation with model (**10**) and the reduction of the substrate would give the above results. Even if conformations of type A are less probable than conformations of type B, their high reactivity can lead to a lowering of the e.e.

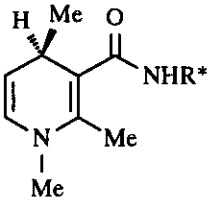
The most interesting result is, of course obtained with model (**11a**) : high reactivity and high enantioselectivity.

The high e.e. can be easily explained by the fact that the more rigid structure allows a precise location of the benzyl group in a definite region of the dihydropyridine ring thus allowing a good stereodifferentiation of the two faces of the reagent. The observed high reactivity could be a consequence of the loss of the rotational entropy in the more rigid structure which facilitates the establishment of the ternary complex (compared with **7**

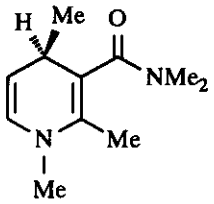
where the free rotation about the C_3-C=O bond could perturb the formation of the ternary complex).

The excellent performances obtained with this reagent were confirmed at 0°C : reduction of the substrate in 15 minutes with a 94 % e.e.

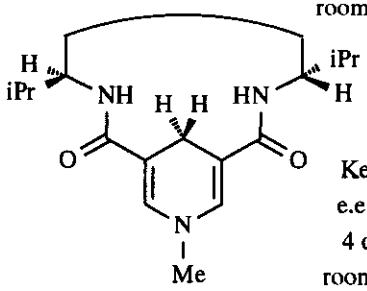
This model is, therefore, one of the most high performing NADH models in asymmetric synthesis as can be seen from the comparison with other efficient models [24] (scheme XV).



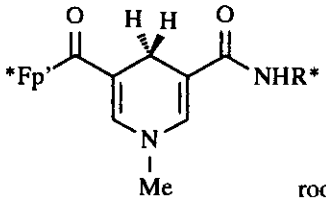
Ohno [21]
e.e. = 98 % (R)
2 days
room temperature



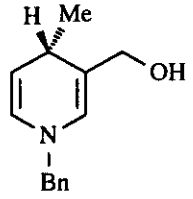
Vekemans [22a]
e.e. = 92 % (R)
1 hour (-25 °C)



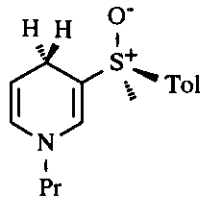
Kellog [22b]
e.e. = 90 % (S)
4 days
room temperature



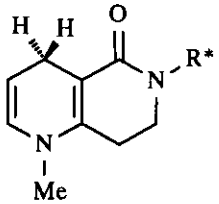
Davies [25]
e.e. = 98 % (R)
90 min
room temperature



Meyers [26]
e.e. = 83 % (S)
5 days
room temperature



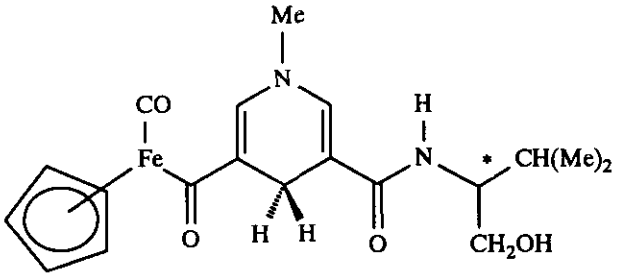
Iwata [27]
e.e. = 96 % (R)
7 days
room temperature



Combret [24]
e.e. = 94 % (R)
15 min (0 °C)

Scheme XV

In some recent papers, Davies [25] has reported the excellent results obtained with model (**12**) where the sterically demanding chiral auxiliary is the [(η^5-C_5H_5) Fe (CO) Ph_2O-(l) menthyl)] group incorporated at the C-3 position.



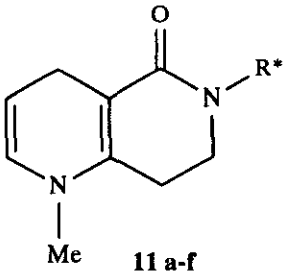
12

Scheme XVI

The amino alcohol at the C_5 position allows the control of the position of the substrate through chelation of magnesium ions with the carbonyl of the C_5 carboxamido group. The high e.e. observed (97 %) was attributed to a tightly bound transition state resulting from the additionnal chelation provided by the alcohol function.

3) Variations of amino alcohol in model 11.

Various amino alcohols were used instead of (S)-phenylalaninol.[28] The reduction of methyl benzoylformate at room temperature gave the results reported in Table 4 (the major enantiomer was always the (R) one).



11 a-f

Nature of R*		e.e. (%)
— CH(S)(CH$_2$OH)— CH$_2$—Ph	**11a**	88
— CH(S)(CH$_2$OH)— CH$_2$—β-Naphtyl	**11b**	91
— CH(S)(CH$_2$OH)— CH$_2$—CH$_2$Ph	**11c**	85
— CH(S)(CH$_2$OH)— CH$_2$—PhCF$_3$-*p*	**11d**	79
— CH(S)(CH$_2$OH)— CH$_2$—PhOMe-*p*	**11e**	85
(S) (R) - CH(Me)— CH(OH)- Ph	**11f**	88

As can be seen, the best result is obtained with the β-naphthyl derivative (**11b**). The enhancement in the

efficiency due to the larger size of the naphthyl group, compared to the phenyl group in (**11a**) is rather modest. The introduction of a supplementary methylene group in the chain between the phenyl group and the chiral carbon does not modify significantly the e.e. (model (**11c**) compared with model (**11a**)). Despite the greater mobility of the hindering group, the stereodifferentiation of the two faces of the dihydropyridine is always well assured. The results obtained with models (**11d**) and (**11e**) are surprising. It could be assumed that the electron withdrawing CF_3 group would favour the formation of a charge transfer complex as was previously proposed for the *p*-nitrophenyl group in the thienopyridine series. On the other hand, the electron donating MeO group would disfavour this charge transfer complex. As can be seen, the results do not confirm this hypothesis. We believe that, in the thienopyridine series, the charge transfer complex was the result of a strong interaction between the paranitrophenyl substituent and the π-excessive thiophene ring.

The last substituent is derived from norephedrine. A study of molecular models suggests that the methyle and phenyle groups could exert an additional influence on the stereodifferentiation of the two faces of the dihydropyridine. It appears that the behaviour of norephedrine is similar to that of phenylalaninol. However, norephedrine is a cheap, readily available reagent and, on this point alone, it can be claimed that model (**11f**) is *a readily available, highly enantioselctive chiral NADH model.*

CONCLUSION

The challenging goal of reductions performed with NADH biomimetic models is to use highly reactive and stereoselective reagents in a synthetic purpose. To achieve this objective at least two major problems have to be solved :

- stabilization of the reagent against side reaction by annelation with a π excessive ring.

- make reductions catalytic, by recycling the pyridinium salt back to the dihydropyridine derivative. This could be achieved by grafting the reagent on an insoluble support which facilitates the use and recycling of NADH models. Some preliminary results show that chiral models grafted on insoluble supports (Merrifield resin or silica) were as efficient as free models in asymmetric reductions.[29] These researches are presently under progress in our laboratory.

REFERENCES

1. See for example: "Chirality in Industry", ed. by A. N. Collins, G. N. Sheldrake, and J. Crosby, John Wiley and Sons, 1992.
2. a) R. Breslow, A. W. Czarnik, M. Lauer, R. Leppkes, J. Winkler, and S. Zimmerman, *J. Am. Chem. Soc.*, 1986, **108**, 1969.

   b) I. Tabushi, Y. Kuroda, M. Yamada, H. Higashimura, and R. Breslow, *J. Am. Chem. Soc.*, 1985, **107**, 5545.
3. J. Jeffery, "Dehydrogenases Requiring Nicotinamide Coenzymes", ed. by J. Jeffery, Birkhauser Verlag Basel, 1980, pp.85-125.
4. H. Dugas, "Biorganic Chemistry, A Chemical Approach to Enzyme Action", 2nd edition, ed. by C. R. Cantor, Springer Verlag New York, 1988, pp. 187-189.
5. a) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

   b) D.M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223.
6. a) A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Japan*, 1977, **50**, 1535.

   b) A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Japan*, 1977, **50**, 2385.
7. Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, 1975, **97**, 4766.
8. a) Y. Inouye, J. Oda, and N. Baba, "Reductions with Chiral Dihydropyridine Reagents" in Asymmetric Synthesis, Vol. 2, ed. by J. D. Morrison, Academic Press New York, London, 1983, pp. 92-124.

   b) A. Ohno and S. Ushida, "Mechanistic Models of Asymmetric Reductions" in Lecture Notes in Bio-Organic Chemistry, ed. by E. Baulieu, L. Jaenicke, V. Massey, R. J. P. Williams, E. L. Winnacker, and B. Zerner, Springer Verlag Berlin, 1986, pp. 1-105.

   c) V. A. Burgess, S. G. Davies and R. T. Skerlj, *Tetrahedron Asymmetry*, 1991, **2**, 299.
9. a) P. L. Rinaldi and M. Wilk, *J. Org. Chem.*, 1983, **48**, 2141.

   b) C. Stetin, B. De Jeso, and J. C. Pommier, *J. Org. Chem.*, 1985, **50**, 3863.

10. a) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *Tetrahedron Lett.*, 1979, 1683.

b) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *J. Chem. Soc., Perkin Trans. I*, 1980, 7.

11. See 8a p. 102.

12. M. Seki, N. Baba, J. Oda, and Y. Inouye, *J. Am. Chem. Soc.*, 1981, **103**, 4613.

13. P. Binay, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron Lett.*, 1988, **29**, 931.

14. a) W. Tagaki, H. Sakai, Y. Yano, K. Ozeki, and Y. Shimizu, *Tetrahedron Lett.*, 1976, 2541.

b) P. Van Eikeren, D. L. Grier, and J. Eliason, *J. Am. Chem. Soc.*, 1979, **101**, 7406.

c) B. Eling, G. Challa, and U. K. Pandit, *J. Polym. Sc.; Polym. Chem. Ed.*, 1984, **22**, 1945.

15. J. Cazin, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron*, 1988, **44**, 1079.

16. J. Cazin, J. Duflos, G. Dupas, J. Bourguignon, and G. Quéguiner, *J. Chem. Soc., Perkin Trans. I*, 1989, 867.

17. Y. Ohnishi, T. Numakunai, and A. Ohno, *Tetrahedron Lett.*, 1975, 3813.

18. V. Levacher, R. Benoit, J. Duflos, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron*, 1991, **47**, 429.

19. N. A. Beijer, J. A. J. M. Vekemans, and H. M. Buck, *Rec. Trav. Chim. Pays Bas*, 1990, **109**, 434.

20. M. O. Monnet, P. Prévost, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron*, 1993, **49**, 5831.

21. a) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 1978, 328.

b) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, 1979, **101**, 7036.

22. a) P. M. T. De Kok, L. A. M. Bastiaansen, P. M. Van Lier, J. A. J. M. Vekemans, and H. M. Buck, *J. Org. Chem.*, 1989, **54**, 1313.

b) A. G. Talma, P. Jouin, J. G. De Vries, C. B. Trootswijk, G. H. W. Buning, J. K. Waninge, J. Vissher, and R. M. Kellogg, *J. Am. Chem. Soc.*, 1985, **107**, 3981.

23. a) O. Almarsson and T. C. Bruice, *J. Am. Chem. Soc.*, 1993, **115**, 2125.

b) Y. D. Wu and K. N. Houk, *J. Org. Chem.*, 1993, **58**, 2043.

24. Y. Combret, J. Duflos, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron*, 1993, **49**, 5237.

25. a) See 8c.

b) V. A. Burgess, S. G. Davies, and R. T. Skerlj, *J. Chem. Soc., Chem. Commun.*, 1990, 1759.

26. a) A. I. Meyers and T. Oppenlaender, *J. Am. Chem. Soc.*, 1986, **108**, 1989.

b) A. I. Meyers and J. D. Brown, *J. Am. Chem. Soc.*, 1987, **109**, 3155.

27. T. Imanishi, Y. Hamano, H. Yoshikawa, and C. Iwata, *J. Chem. Soc., Chem. Commun.*, 1988, 473.

28. Y. Combret, J. Duflos, G. Dupas, J. Bourguignon, and G. Quéguiner, *Tetrahedron Asymmetry*, 1993, **4**, 1635.

29. a) D. Losset, G. Dupas, J. Bourguignon, and G. Quéguiner, *Polymer Bulletin*, 1989, **21**, 649.

b) J. Bourguignon, P. Tintillier, T. Tréfouel, D. Losset, G. Dupas, and G. Quéguiner, *Bull. Soc. Chim. Fr.*, 1989, 264.

Received, 28th January, 1994