

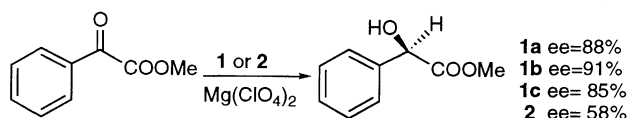
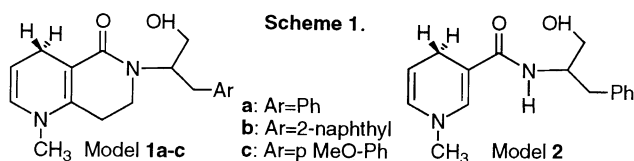
NADH Models in the Pyrrolo[3,4-b]pyridine Series. Role of the Cyclized Structure in the Stereocontrol of Reductions

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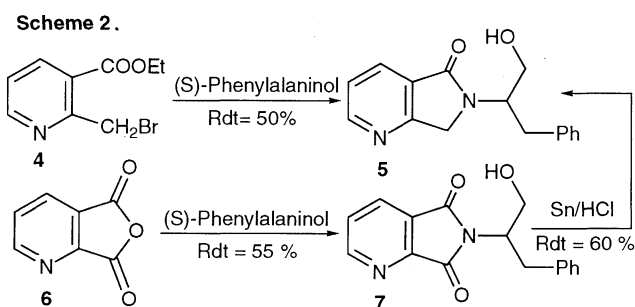
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The synthesis of a chiral NADH model in pyrrolo[3,4-b]pyridine series is described and the asymmetric reduction of methyl benzoylformate is studied. Its asymmetric behavior compared with a cyclized analogue in naphthyridine series suggests that the orientation of the carbonyl group of the lactam plays an important role in the stereochemical control of the reduction.

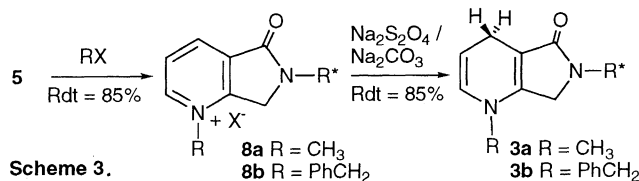
Enantioselective reductions with NADH models have in recent years attracted great interest.¹ The reduction is usually carried out with magnesium ions as cofactor: It is generally assumed that a ternary complex (model/Mg²⁺/substrat) is involved, which ensures proximity and activation of reagents as well as stereocontrol of the reaction. This ternary complex has been abundantly studied in recent years to define the structural factors which may influence the stereocontrol of the reaction.² Among them, the orientation of the carbonyl group is very much discussed³ and seems to be an important factor in the stereocontrol of the reduction. In previous papers⁴ we described the synthesis of chiral NADH models **1a-c** where the free rotating ability of the carbonyl part of the amide was suppressed. The so obtained models in naphthyridine series, have been involved in the reduction of methyl benzoylformate, and have proven to be highly efficient since the enantioselectivity observed (ee>90%) was considerably higher to that obtained with its analogue **2** (ee = 58%) in which the carbonyl part of the amide has free rotating ability (Scheme 1). As it can be noted the rigidification caused a dramatic change in the stereochemical control of the reaction. A major difference between models **1a-c** and **2** seems to be the fact that in the presence of magnesium ions the carbonyl part of the lactam in models **1a-c** is slightly out of the plane of the dihydropyridine ring, contrary to the model **2** where the carbonyl would be in the plane of the ring.⁵ This point seems to be crucial to explain the very high obtained e.e. with models **1a-c**: it has been shown that the syn orientation of the hydrogen at 4-position in the coenzyme itself, is very favourable for a high stereoselective control.⁶ In the case of model **2**, it seems that the stereodifferentiation of the two faces of the dihydropyridine structure is essentially ensured by the occurrence of a quasi cyclic structure adopted by the chiral amino alcohol in the presence of magnesium ions.⁵ It should be noted that the nature of the chiral aminoalcohol of models **1a-c** does not cause dramatic changes in the stereochemical control of the reaction and therefore suggests that the rigidification of the carbonyl is the main factor to take into account to explain this difference of enantioselective behavior.



In order to obtain information on the orientational effect of the carbonyl it was of interest to study the enantioselective behavior of a cyclized analogue, in the pyrrolopyridine series, differing only in the ring size. Indeed, the carbonyl group in model **3** (Scheme 3) is forced to stay in the plane of the dihydropyridine ring, in contrast to models **1a-c**, in which the carbonyl group of the lactam, involved in a larger cyclized structure, could be orientated out of the plane through conformational changes. For this purpose, model **3** was prepared via two different ways. In the first one, ethyl 2-(bromomethyl)nicotinate **4**,⁷ was condensed with (S)-phenylalaninol (DMF/K₂CO₃/20°C/24h) to give compound **5**⁸ in 50% isolated yield. An alternative method was used for the preparation of compound **5**, by reaction of the anhydride of 2,3-pyridinedicarboxylic acid **6** with (S)-phenylalaninol (toluene/ethanol/reflux/24h) to yield compound **7**,¹⁰ (55% yield) which was reduced regioselectively¹¹ to give compound **5** (60% yield) (Scheme 2). In order to establish that the overall procedure was not racemizing, compound **5** was prepared following the same procedure described above, using racemic phenylalaninol. The enantioseparation of the racemic compound **5** was performed by chiral HPLC. It could be thus concluded from chiral HPLC analysis, that compound **5** obtained from (S)-phenylalaninol by the second method was optically pure.



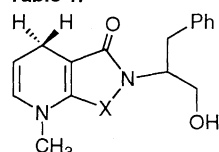
Attempts to react compound **5** with methyl iodide in acetonitrile or in DMF to prepare pyridinium salt **8a** were unsuccessful, giving unidentified byproducts. Nevertheless, reaction with methyl p-toluene sulfonate or benzyl bromide, respectively, afforded the desired pyridinium salts **8a** and **8b**¹² (85% yield), which were subsequently regioselectively reduced with sodium dithionite leading to 1,4,5,6,7-pentahydro-5-oxo-pyrrolo[3,4-b]pyridines **3a** and **3b**¹³ (85% yield) (Scheme 3). It could be assumed that model **3a** and **3b** were obtained optically pure, these two last steps being non racemizing.



With the models **3a** and **3b** so obtained, reduction of methyl benzoylformate was performed under the same conditions used with models **1a-c** and model **2**. The results summarized in table 1 show an important lowering of the enantioselectivity of the reduction with reagents **3a** and **3b** in comparison with models **1a-c**. Thus, we assume that the main structural difference in the ternary complex, of these two cyclized analogues **1a** and **3a-b**, responsible of this behavior, is the orientation of the carbonyl group with respect to the plane of the dihydropyridine ring. According to a detailed NMR study⁵ of model **1a** in presence of magnesium ions, the conformation adopted by the cyclized structure would set the carbonyl group out of the plane of the dihydropyridine ring. Thus, in addition to the stereodifferentiation of the two faces of the dihydropyridine, the chiral auxiliary would promote the stereoselective orientation of the carbonyl group, favouring the enantioselective transfer of the syn orientated hydrogen, as in the coenzyme itself. This behavior is probably responsible of the high e.e. observed with models **1a-c**. On the other hand, the medium e.e. obtained with **2** is probably due to the occurrence of a quasi cyclic structure of the aminoalcohol in presence of magnesium ions which improve the stereodifferentiation of the two faces of the reagent.⁵ It can be thus assumed that this rigidification of the aminoalcohol does not occur with reagents **3a-b**. A detailed NMR study will be further performed and published. In conclusion, this result seems to confirm the importance of the role played by the orientation of the carbonyl group, in the stereocontrol of the reduction and should be considered as an important conformational factor in the design of new efficient enantioselective NADH models.

X	R	Model	ee
-(CH ₂) ₂ -	CH ₃	3a	35%
-(CH ₂) ₂ -	CH ₂ Ph	3b	25%
-(CH ₂) ₂ -	CH ₃	1a	88%
-	-	2	58%

Table 1.



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- Compound **5**: ¹H NMR (200 MHz, CDCl₃) δ 8.54 (dd, 1H, J = 5, 1.5 Hz), 7.98 (dd, 1H, J = 7.7, 1.5 Hz), 7.20 (m, 6H), 4.60 (m, 1H), 4.43 (d, 1H, J = 18 Hz), 4.30 (d, 1H, J = 18 Hz), 3.93 (m, 3H), 3.06 (app d, 2H, J = 8 Hz). IR (KBr) 1674 cm⁻¹. Anal. Calcd for C₁₆H₁₆N₂O₂: C, 71.61; H, 6.01; N, 10.45. Found: C, 71.50; H, 6.12; N, 10.57.
- Compound **7**: ¹H NMR (200 MHz, CDCl₃) δ 8.95 (dd, 1H, J = 5, 1.5 Hz), 8.10 (dd, 1H, J = 7.7, 1.5 Hz), 7.60 (dd, 1H, J = 7.7, 5 Hz), 7.35-7.13 (m, 5H), 4.82-4.65 (m, 1H), 4.28-4.08 (m, 1H), 4.08-3.90 (m, 1H), 3.40-3.15 (m, 2H). IR (KBr) 1775 cm⁻¹. Anal. Calcd for C₁₆H₁₄N₂O₃: C, 68.06; H, 5.00; N, 9.93. Found: C, 67.95; H, 4.87; N, 9.74.
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- Compound **8a**: ¹H NMR (200 MHz, DMSO) δ 9.14 (d, 1H, J = 5 Hz), 8.74 (d, 1H, J = 7.7 Hz), 8.16 (app t, 1H, J = 5 Hz), 7.45 (d, 2H, J = 8 Hz), 7.30-7.13 (m, 5H), 7.09 (d, 2H, J = 8 Hz), 5.03 (s, 2H), 4.68-4.48 (m, 1H), 4.34 (s, 3H), 3.75-3.60 (m, 3H), 3.10-2.80 (m, 2H), 2.27 (s, 3H). IR (KBr) 1697 cm⁻¹. Anal. Calcd for C₂₄H₂₆N₂O₅S: C, 63.41; H, 5.77; N, 6.17. Found: C, 63.45; H, 5.85; N, 6.02. Compound **8b**: ¹H NMR (200 MHz, CDCl₃) δ 9.32 (d, 1H, J = 5 Hz), 8.55 (d, 1H, J = 7.7 Hz), 8.02 (app t, 1H, J = 5 Hz), 7.30-7.13 (m, 5H), 6.22 (d, 1H, J = 14 Hz), 6.05 (d, 1H, J = 14 Hz), 5.69 (d, 1H, J = 20 Hz), 4.68 (d, 1H, J = 20 Hz), 4.65 (m, 1H), 3.80-3.60 (m, 2H), 3.05-2.80 (m, 2H). IR (KBr) 1700 cm⁻¹. Anal. Calcd for C₂₃H₂₃N₂O₂Br: C, 63.00; H, 5.29; N, 6.39. Found: C, 63.19; H, 5.36; N, 6.49.
- Compound **3a**: ¹H NMR (200 MHz, CDCl₃) δ 7.35-7.11 (m, 5H), 5.67 (dt, 1H, J = 8, 1.7 Hz), 4.69 (dt, 1H, J = 8, 3.2 Hz), 4.15-4.05 (m, 1H), 4.05-3.68 (m, 3H), 3.75 (d, 1H, J = 17 Hz), 3.51 (d, 1H, J = 17 Hz), 3.20-2.90 (m, 4H), 2.74 (s, 3H). Compound **3b**: ¹H NMR (200 MHz, CDCl₃) δ 7.40-7.10 (m, 10H), 5.76 (dt, 1H, J = 8, 1.7 Hz), 4.76 (dt, 1H, J = 8, 3.3 Hz), 4.17 (s, 2H), 3.88-3.70 (m, 3H), 3.65 (d, 1H, J = 17 Hz), 3.38 (d, 1H, J = 17 Hz), 3.18 (s, 2H), 3.07 (dd, 1H, J = 13.8, 8.0 Hz), 2.92 (dd, 1H, J = 13.8, 6.0 Hz).