Chiral NADH Models in the Pyrido[3,2-c]azepin Series. Conformational Effect of the Carbonyl Group in the Stereocontrol of Reductions

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Asymmetric reduction of methyl benzoylformate with the chiral NADH model **2** in the pyrido[3,2-c]azepin series afforded methyl mandelate in 91% optical yield. The high enantioselectivity observed with model **2** is compared with cyclized analogues **1a** and **1b** in the naphthyridine and pyrrolo[3,4-b]pyridine series respectively. The stereochimical outcome of the reaction is discussed in relation to the out-of-plane orientation of the amide group with respect to the dihydropyridine ring in the transition state.

With common chiral NADH models the main factor involved in the stereocontrol of the reaction is caused by the presence of a sterically remote demanding group at the chiral center of the reagent which plays a fundamental role in the stereodifferentiation of the two faces of the dihydropyrine ring.[1] Additionally, the conformation of the dihydropyridine and the orientation of the carboxamide part of biomimetic models, may take part in the stereochemical outcome of the reaction as in the coenzyme itself[2]. Consequently, both of these conformational factors have recently attracted great attention in the design of new chiral NADH models.[3] With the aim to study the orientational effect of the carbonyl group, we previously described the synthesis of models **1a**[4] and **1b**[5] in naphthyridine and pyrrolo[3,4-b]pyridine series respectively in which the carboxamide rotation is prevented by cyclisation (Figure 1).

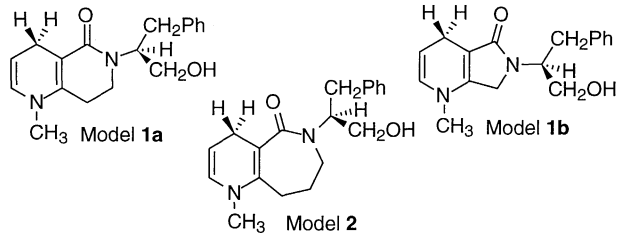
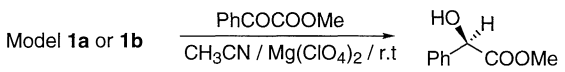


Figure 1.

Although both of these models bear the same chiral auxiliary derived from (S)-phenylalaninol and differ only in the ring size of the cyclized structure, they have shown to behave quite differently in the reduction of methyl benzoylformate (Scheme 1).



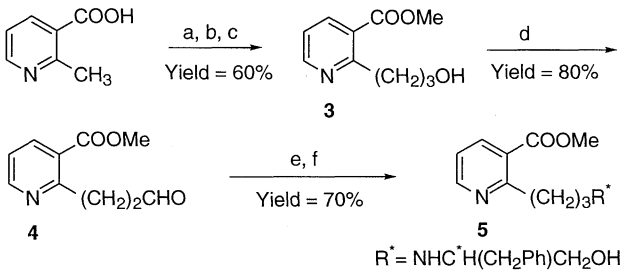
Model	ee %	Yield %
Model **1a**	88 (R)	90
Model **1b**	35 (R)	60

Scheme 1. Conditions: Model / Mg^{2+} / Substrate:1/1/1; Solvent: CH_3CN; r.t.

Reductions are usually carried out in the presence of magnesium perchlorate as co-catalyst of the reaction which is assumed to be involved in a ternary complex Model / Mg^{2+}/ Substrate. It ensures proximity and activation of the reagents as well as stereocontrol of the reaction (Scheme 1).

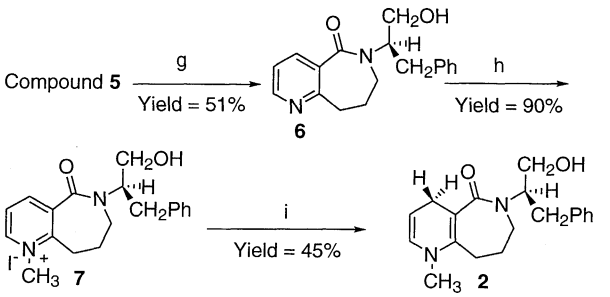
To get information on the structure of the ternary complex a detailed NMR study[6] of model **1a** in the presence of Mg^{2+} clearly indicated that the C=O amide of model **1a** is slightly out of the plane of the dihydropyridine ring (10-15°) contrary to model **1b** in which the lactam engaged in a more strained structure sets the C=O amide in the plane of the dihydropyridine ring. In this situation the out-of-plane orientation of the C=O amide may enhance the stereocontrol of the reduction by favouring the departure of the *syn* oriented hydrogen as assumed in the coenzyme itself.[2] To support this hypothesis, it was of interest to synthesize a cyclized analogue carrying the same chiral auxiliary (model **2**; Figure 1) in which the pyrido[3,2-c]azepin structure would set the carbonyl of the lactam out of the plane of the dihydropyridine ring at an angle[7] of about 50°.

Model **2** was prepared by lateral lithiation of 2-methyl nicotinic acid[8] to afford compound **3** in 60% yield by using 1-bromo-2-[(tetrahydropyran-2-yl)oxy]ethane[9] as electrophile. Swern oxidation[10] of **3** gave the corresponding aldehyde **4** in 70% yield which was subsequently treated with (S)-phenylalaninol in the presence of sodium borohydride to give compound **5** in 80% isolated yield (Scheme 2).



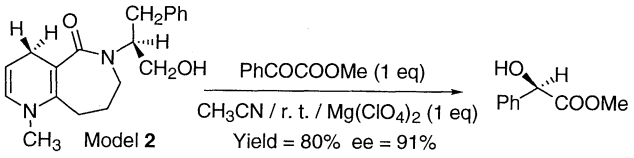
Scheme 2. a: LDA (2.2 eq) / THF / 0 °C / 30 min; b: $Br(CH_2)_2OTHP$ (2.2 eq) / -60 °C --> 20 °C / 8 h; c: MeOH / HCl / 60 °C / 24 h; d: oxalyl chloride (1.2 eq) / DMSO (2.2 eq) / NEt_3 (5 eq) / CH_2Cl_2 / -60 °C / 10 min; e: (S)-phenylalaninol (1.2 eq) / EtOH / r.t. / 30 min; f: $NaBH_4$ (1.5 eq) / 1 h / 30 min.

Cyclization of compound **5** was carried out in refluxing ethanol in the presence of potassium carbonate to give the desired pyridino[3,2-c]azepin structure **6** in 51% yield. Quaternarisation of compound **6** with methyl iodide lead to the corresponding pyridium salt **7** in 90% yield which was in turn regioselectively reduced with sodium dithionite affording 6 - (hydroxymethyl -2-phenylethyl) - 1,4,6,7,8,9 - hexahydro -1- methyl - pyrido[3,2-c] azepin - 5 - one **2**[11] in 45% yield (not optimized) (Scheme 3).



Scheme 3. g: EtOH / K_2CO_3 (2 eq) / 48 h; h: CH_3I (20 eq) / CH_3CN / 12 h; i: $Na_2S_2O_4$ (10 eq) / Na_2CO_3 (10 eq) / 1 h / N_2.

Model **2** was involved in the reduction of methyl benzoylformate under the same conditions used with models **1a** and **1b** to afford methyl mandelate with a high enantiomeric excess of 91%[12] (Scheme 4).



Scheme 4.

Table 1. Correlation between the orientation of the C=O and the stereoselectivity of reductions

Models	Orientation of the C=O	ee % (Abs. conf.)
Model **1b**	In the plane	ee = 35% (R)
Model **1a**	Out-of-plane orientation of the C=O (10-15°)[a]	ee = 88% (R)
Model **2**	Out-of-plane orientation of the C=O (50°)[a]	ee = 91% (R)

[a] See Ref. 7.

Models **1a** and **2** showed the same enantioselectivity toward methyl benzoylformate. This result compared with that obtained with model **1b** seems to confirm that the out-of-plane orientation of the carbonyl with respect to the dihydropyridine ring may be partly responsible of the high enantioselectivity observed with model **1a** and **2** (Table 1). We presumed that the chiral auxiliary in the lactam side chain would governed the orientation of the C=O amide in the ternary complex to favor the transfer of the *syn* oriented hydrogen. A detailed NMR study of model **2** in the presence of magnesium perchlorate is under progress to get information on the ternary complex.

References and Notes

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7 The dihedral angle value is estimated by molecular modeling with PC-Model on a PC-486 computer.

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11 All compounds gave spectral and analytical data consistent with the assigned structures.

12 Enantiomeric excesses were measured by high pressure liquid chromatography. Chromatographic conditions: AGP chiral column (100 x 4 mn; 5 µm) purschased from Chrom Tech. Inc. UV detection (λ=210nm); Mobile phase: phosphonate buffer / 2-propanol (99/1); Flow rate: 0.9 ml / min; Temperature: 20 °C; Injection: 20 µl (0.5 mg of sample in 20 ml of water).