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Chiral NADH models with restricted or blocked rotation at the amide function: attempts to interpret the mechanism of the enantioselective hydrogen transfer to methyl benzoylformate

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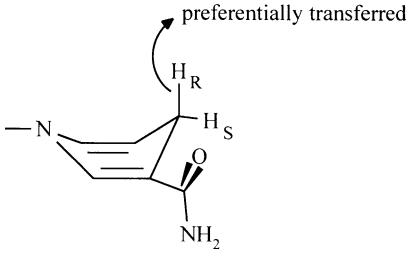
Abstract—Various NADH models with the following characteristics were studied and compared with previously reported models: (1) use of (*S*)-phenylalaninol as chiral auxiliary; (2) orientation in or out of the plane of the amide carbonyl. Despite the occurrence of apparently similar characteristics, they gave very different results in the asymmetric reduction of methyl benzoylformate. A detailed NMR study was performed in order to explain the behaviour of these models.

1. Introduction

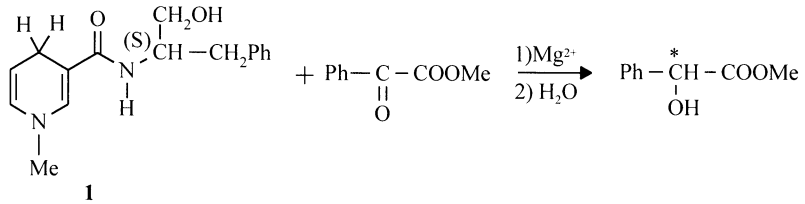
Enzyme catalysed reductions requiring NAD(P)H as a coenzyme are generally highly enantiospecific.[1] It is assumed that during the reduction of a prochiral substrate the 1,4-dihydronicotinamide presents the following features in the transition state:[2] (1) The dihydropyridine ring would adopt a flat boat conformation. (2) The amide group would be twisted out of the mean plane of the ring. (3) The carbonyl group of the amide is on the same side as the hydrogen that is transferred (*syn*-orientation). As a consequence, one of the prochiral hydrogen atom at C-4 (H_S or H_R) is stereospecifically transferred to one enantiotopic face of a prochiral ketone (Scheme 1).



Scheme 1. Enantioselective hydride transfer with the coenzyme.

A large variety of chiral NADH mimics have been described allowing, in several cases, the obtention of high e.e. in the reduction of methyl benzoylformate.[3] Previous work within our group has focussed on chiral NADH models bearing the (*S*)-phenylalaninol moiety as a chiral auxiliary attached to the amide. The first representative example of this series was reagent **1**[4] where the amide is free to rotate about the C_3–C=O bond. Reduction of methyl benzoylformate in the presence of Mg^{2+} ions (Scheme 2) gave the corresponding alcohol in 60% yield and 57% e.e. (Table 1, entry 1).

It was assumed that reductions occurred through the formation of a ternary complex: Model/Mg^{2+}/Substrate governing



Scheme 2.

Keywords: NADH models; blocked rotation; NMR study.
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Table 1. Reductions performed under standard conditions. Molar ratio: model/Mg^{2+}/substrate: 1/1/1 in CH_3CN as solvent at rt for 24 h

Entry	Reagent	Chemical yield (%)	e.e.% (major enantiomer)	
1	**1**	60	57	(*R*)
2	**2**	95	88	(*R*)
3	**3**	60	3	(*S*)
4	**4**	58	34[8]	(*R*)
5	**5**	36	80	(*R*)
6	**6**	91	90[9]	(*R*)

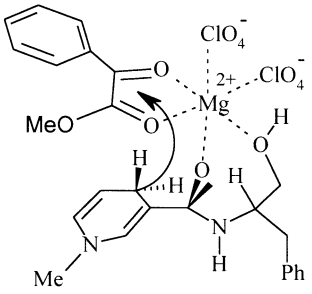
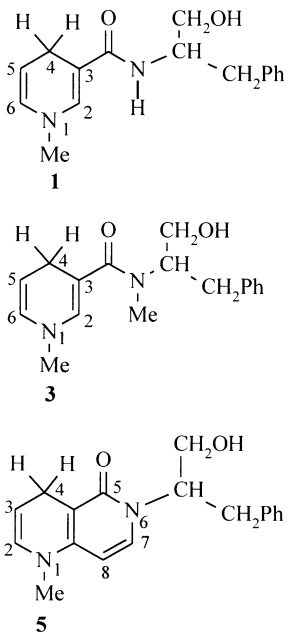


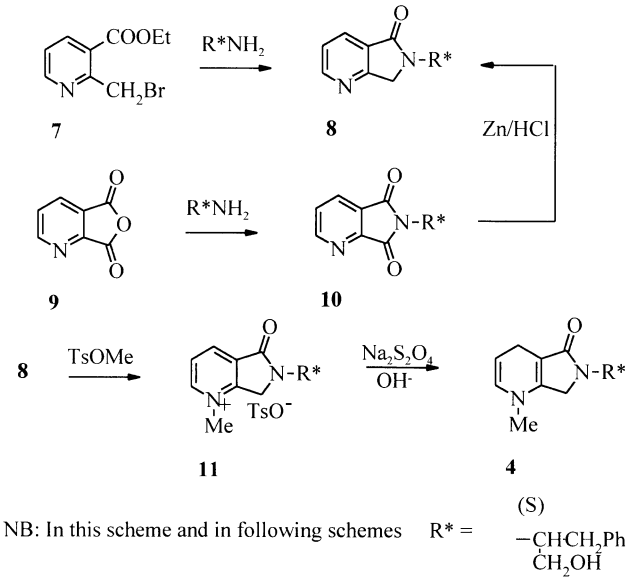
Figure 1.

the enantioselectivity of the hydrogen transfer.[5] The structure of this complex was probed by a NMR study.[6] This study showed that the dihydropyridine ring was planar and the chiral auxiliary adopted a quasi-cyclic conformation due to complexation of Mg^{2+} with both the carbonyl of the amide and the oxygen of the alcohol. These observations allowed us to propose a structure for the ternary complex (Fig. 1) in which the quasi-cyclic structure of the chiral auxiliary plays an important role in the stereodifferentiation of the two faces of the dihydropyridine ring.

In this paper, we present the results obtained from a further five NADH mimics (**2**–**6**) which throw further light on the mechanism of the hydrogen transfer process (Scheme 3).



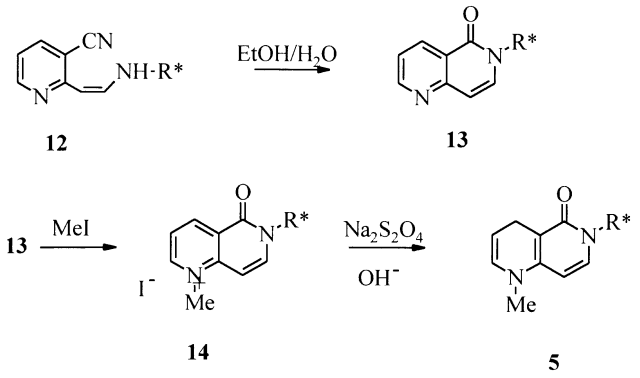
Scheme 3. Structures **2**–**6**.



Scheme 4.

For NADH models **2** and **3**, molecular modelling clearly shows that the amide carbonyl is twisted out of the plane of the dihydropyridine moiety.[7] However, the behaviour of these two reagents is very different in the reduction of methylbenzoylformate, (model **2**, giving an e.e. of 88%, while model **3** gives an e.e. of only 3%). With a view to explaining this surprising difference, we decided to examine (Table 1, entries 2 and 3):

Models **4**[8] and **5**: where the dihedral angle of the amide carbonyl with the ring is necessarily 0°.
Model **6**:[9] where molecular modelling indicates a dihedral angle of 45°. Preliminary results concerning models **4** and **6** have been published by our group.[8,9]

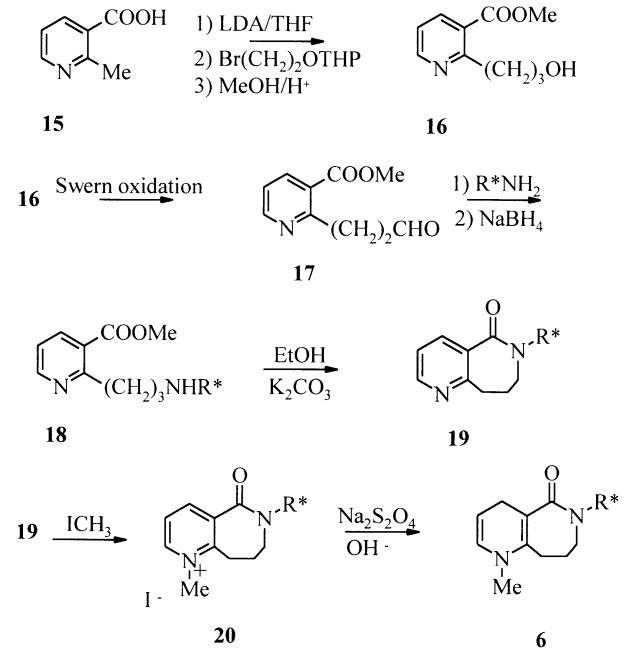


Scheme 5.

2. Results and discussion

2.1. Synthesis of NADH mimics 4, 5 and 6

1. *Model* **4**. Our synthesis of NADH model **4** began with the lateral bromination of ethyl 2-methylnicotinate to give **7**.[10] Treatment of this material with the chiral auxiliary (i.e. (*S*)-phenylalaninol) then gave lactam **8**. Quaternisation of the pyridine with methyl *p*-toluenesulfonate (methyl iodide being ineffective in this regard) and reduction of the resulting salt with sodium dithionite provided **4**. An alternative approach to the intermediate **8** from anhydride **9**[11] was also developed and proved equally effective (Scheme 4).
2. *Model* **5** (Scheme 5). Model **5** was prepared from the known enamine **12**[7] according to the route used for model **2**
3. *Model* **6** (Scheme 6). The synthesis of NADH model mimic **6** was more protracted and began with the lateral lithiation and subsequent alkylation of 2-methylnicotinic acid[12] with the tetrahydropyranyl derivative of 2-bromoethanol.[13] Sequential deprotection to **16**, Swern oxidation to **17** and reductive animation to **18** were followed by ring-closure into the advanced precursor **19**. Quaternisation of the pyridine moiety with methyl iodide and subsequent reduction of the resulting pyridinium salt **20** with sodium dithionite completed the synthesis (Scheme 6).



Scheme 6.

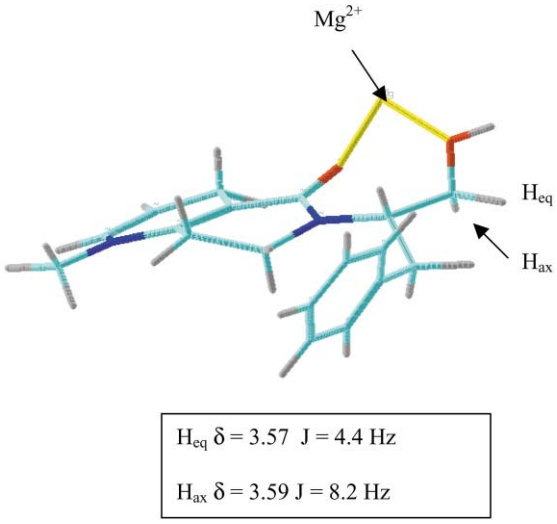


Figure 2.

2.2. Proposals concerning the mechanism of the enantioselective transfer to methyl benzoylformate

The reduction of methyl benzoylformate with the NADH models **1**–**6** gave the results reported in Table 1.

Best results were obtained with analogues **2** and **6** which gave good chemical yields (>90%) and high e.e.s (88 and 90%, respectively). A series of NMR experiments designed to probe the mechanistic details of the reaction was then conducted. Following on from our earlier work with NADH mimics **1** and **2** we planned to see how the NMR characteristics of our new models changed when Mg^{2+} ions were added. Unfortunately, **3** proved to be unstable in the presence of Mg^{2+} so our study was limited to models **4** to **6.** The detailed spectra are presented in the experimental part and the main features are as follows: (i) In the absence or in the presence of Mg^{2+} ions the dihydropyridine ring adopts a planar structure in each of the six compounds: as evidenced by the doublet of triplets observed for protons H_5 or H_6 in models **1** and **3** or H_2 and H_3 in models **2**, **4**, **5** and **6** (indicating that the coupling constants of these protons with the two protons at the 4 position are identical). (ii) The chiral auxiliary in models **1**, **3**, **5** and **6** adopts a quasi-cyclic structure in the presence of Mg^{2+} ions as suggested by the occurrence of characteristic coupling patterns (a doublet of triplets and a triplet of doublets for the two protons at the CH_2 of the hydroxymethyl group). In the case of model **2**, a high field NMR study allowed us, to elucidate the ^1H NMR spectra of the protons at the CH_2OH group in the presence of Mg^{2+} ions. They correspond to a degenerated ABX system

Figure 3.

in which the two protons have close chemical shifts. The coupling constants with the proton at the chiral carbon were obtained after calculations leading to two solutions. After simulation, the appropriate solution was obtained and confirmed the occurrence of a quasi-cyclic structure for the chiral auxiliary in the presence of Mg^{2+} (Fig. 2).[14]

The spectra also indicate that the hydrogen at the stereogenic centre adopts an axial position in the quasi-cyclic structure. Notably, NMR data obtained for model **4** in the presence of Mg^{2+} ions do not support the existence of a quasi-cyclic structure for the chiral auxiliary. (iii) In the case of model **3** in the presence of Mg^{2+} ions, a NOESY experiment shows a correlation between the H_2 proton and the protons at the *N*-methyl group suggesting a *syn*-orientation of the amide carbonyl with respect to the H_4 protons.

Despite the high similar characteristics displayed by **2** and **3** (i.e. out of plane orientation of the carbonyl amide, *syn*-orientation with respect to the H_4 protons, occurrence of a quasi-cyclic structure for the chiral auxiliary in the presence of Mg^{2+}), their behaviour in the reduction of methyl benzoylformate is quite different. An examination of the ^1H NMR spectra of the two H_7 protons and the two H_8 protons of model **2** in the presence of Mg^{2+} reveals a high degree of complexity (octuplets) which can be explained only by considering that these protons exist in staggered conformations caused by the deformation of the lactam ring due to the out of plane orientation of the amide carbonyl. So two conformations can be proposed (Fig. 3).

Due to the presence of a stereogenic centre in the chiral auxiliary these conformations are effectively diastereoisomers. A NOESY experiment shows that the two *ortho* protons of the phenyl ring of the chiral auxiliary are in the vicinity of the H_7 equatorial and H_8 axial protons of the lactam. Two additional observations of note are: (i) The proton in axial positon at the stereogenic carbon is correlated with the two *ortho*-protons of the phenyl ring. (ii) The two benzylic protons are correlated with the two H_7 protons of the lactam (Fig. 4). Molecular models and molecular mechanics calculations showed that only conformation A of the lactam ring is compatible with all the so described observations (Fig. 4).

In conformation B, where the amide carbonyl is under the plane of the ring, it would be impossible to observe simultaneous NOESY correlations between the axial proton at the stereogenic carbon and the *ortho*-protons of the phenyl ring if this ring is also in close proximity to the H_7 equatorial and H_8 axial protons. Our proposal is that a thermodynamic equilibrium favouring A occurs between the two conformations A and B. As a consequence, this species is mainly responsible for the reduction of the substrate. In this situation the amide carbonyl would point above the plane of the dihydropyridine, the Mg^{2+} ions would then form a complex above the plane of the ring. Complexation of the substrate now holds this in an orientation suitable for *syn*-transfer of the hydride (Fig. 5).

In this ternary complex the carbonyl group serves to relay the chiral information from the stereogenic carbon to the metal centre A similar proposal can be made for model **6**. Some examples of chirality transfer are described in the literature in the case of NADH models.[15]

In the case of model **3**, it was not possible to perform a detailed NMR study due to its unstability in the presence of Mg^{2+} ions. However it can be assumed that, in this case, the tertiary amide is free to rotate and can exist in the form of two enantiomeric conformers (Scheme 7).[16] If these are

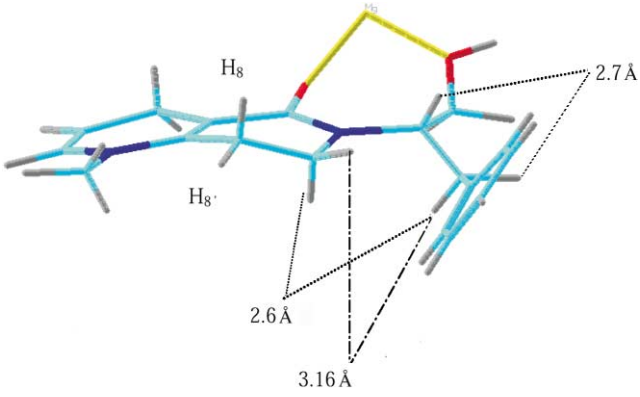


Figure 4.

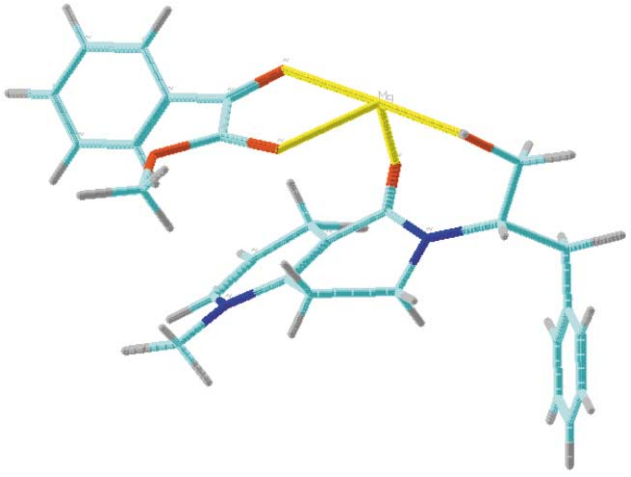
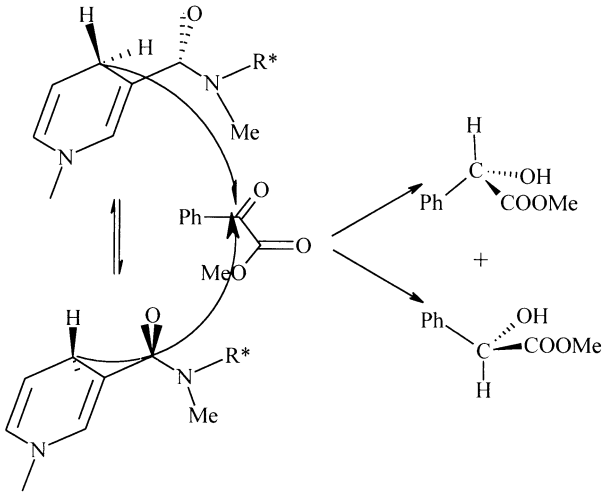


Figure 5.



Scheme 7.

present in nearly equivalent population the reduction of methylbenzoylformate would no longer be biased in favour of hydrogen transfer from one face or the other of the dihydronicotinamide.

In model **5** the amide carbonyl is necessarily planar with respect to the dihydropyridine ring and the chiral auxiliary adopts a quasi-cyclic structure in the presence of Mg^{2+} ions. A NOESY experiment in the presence of Mg^{2+} ions shows a clear correlations between the H_7 proton and the two protons at the benzylic group of the chiral auxiliary and with the proton at the stereogenic carbon. This suggests that the magnesium atom is influenced by the chiral auxiliary and located on the upper face of the dihydropyridine ring. Hydrogen transfer to methyl benzoylformate is therefore directed by the magnesium in a manner similar to that proposed for model **1**[4] with the chiral auxiliary inducing a stereodifferentiation of the two faces of the substrate (see Fig. 1).

The poor e.e. obtained with model **4** may be attributed to the planarity of the amide with respect to the ring. In this case no quasi-cyclic structure was observed with added Mg^{2+} so the chiral auxiliary cannot influence the transition state to any great extent. Stereodifferentiation of the two faces of the reagent is therefore poor in this case.

3. Conclusion

A careful examination of the NMR spectra of six selected NADH models allowed us to propose explanations to the very different behaviour of these reagents during the reduction of methyl benzoylformate promoted by magnesium ions.

4. Experimental

4.1. General

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The ^1H and ^{13}C NMR spectra were recorded either on a 200, 400 or 500 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform, in acetonitrile-d_3 or in hexadeuteriodimethylsulfoxide (DMSO-d_6). Chemicals were purchased from Aldrich or Janssen and, unless otherwise stated, were used without further purification. Flash chromatographies were performed with silica gel 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F_{254}).

4.1.1. Ethyl 2-(bromomethyl)nicotinate (7). A mixture of ethyl 2-methylnicotinate (1.00 g, 6 mmol), *N*-bromosuccinimide (1.43 g, 8 mmol) and acetic acid (0.383 L) was stirred for 16 h under the irradiation of a 250 W tungsten lamp. The reaction mixture was filtered and the precipitate was washed twice with CCl_4 (30 mL). The filtrate was evaporated under reduced pressure to afford crude ethyl 2-(bromomethyl)nicotinate (**7**) as a yellow oil which was used immediately in the next step without further purification.

4.1.2. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (8). Crude ethyl 2-(bromomethyl)nicotinate (**7**) (1.39 g, 5 mmol) and (*S*)-phenylalaninol (0.77 g, 5 mmol) were dissolved in DMF (2 mL). K_2CO_3 (0.90 g, 6.7 mmol) was added and the reaction mixture was stirred for 12 h at rt. The reaction mixture was quenched with water (20 mL), neutralised with acetic acid and extracted with CH_2Cl_2. The organic layers were dried, filtered and evaporated under vacuum to afford an orange oil. The crude product was purified by chromatography on neutral alumina (AcOEt/MeOH, 95/5) to give **8** (0.49 g, 30% yield from ethyl 2-methylnicotinate) as a yellow oil. IR (film) 1674 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.54 (dd, 1H, J=1.5 and 5.0 Hz); 7.98 (dd, 1H, J=1.5 and 7.7 Hz); 7.32–7.13 (m, 6H); 4.66–4.50 (m, 1H, CH_3); 4.43 (d, 1H, J=18.0 Hz, H_7); 4.30 (d, 1H, J=18.0 Hz); 4.02–3.83 (m, 3H); 3.06 (d_{app}, 2H, J=8.0 Hz). Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.61; H, 6.01; N, 10.45. Found: C, 71.50; H, 6.12; N, 10.57.

4.1.3. 2,3-Pyridinedicarboxylic anhydride (9). 2,3-Pyridinedicarboxylic acid (10 g, 60 mmol) was dissolved in freshly distilled acetic anhydride (30 mL) and the solution was heated at reflux for 3 h. The excess of acetic anhydride was then distilled off to afford a brown solid which was purified by sublimation to give **9** (6.6 g, 74% yield) as a white solid (mp 135°C).

4.1.4. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-dione (10). Anhydride **9** (3.0 g, 2 mmol) and (*S*)-phenylalaninol (3.04 g, 2 mmol) were dissolved in a toluene/ethanol mixture (80/20). The solution was heated to reflux for 12 h and the solvents were evaporated under reduced pressure. Purification by chromatography on silica gel (CH_2Cl_2/EtOH, 95/5) afforded pure **10** (3.12 g, 55% yield) as a white solid (mp 60°C). IR (KBr) 1755 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.95 (dd, 1H, J=1.5 and 5.0 Hz); 8.10 (dd, 1H, J=1.5 and 7.7 Hz); 7.60 (dd, 1H, J=5.0 and 7.7 Hz); 7.35–7.13 (m, 5H, Ph); 4.82–4.65 (m, 1H, chiral CH); 4.28–4.08 (m, 1H); 4.08–3.90 (m, 1H); 3.4–3.15 (m, 2H). Anal. calcd for $C_{16}H_{14}N_2O_3$: C, 68.06; H, 5.00; 9.93. Found: C, 67.95; H, 4.87; N, 9.74.

4.1.5. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (8). Imide **10** (1 g, 3.5 mmol), zinc powder (1.8 g) and 12N HCl (4.7 mL) were heated at 100°C for 5 h. After cooling, zinc powder (1.3 g) was added and the mixture was stirred for 12 h at room temperature. Zinc in excess was filtered, the filtrate was basified with aqueous ammonia and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum to afford an oil. The crude product was purified by chromatography on silica gel (CH_2Cl_2/EtOH, 95/5) to give **8** (0.57 g, 60% yield) as a yellow oil.

4.1.6. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-6,7-dihydro-1-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridinium tosylate (11). Compound **8** (1.07 g, 4 mmol) was dissolved in acetonitrile (5 mL) and methyl tosylate (0.75 g, 4 mmol) was added. The reaction mixture was heated to reflux of acetonitrile for 12 h. After evaporation of the two-thirds of the solvent under vacuum, ether was added dropwise until precipitation of a salt which was filtered and washed with ether to afford **11** (1.54 g, 85% yield) as a pale yellow solid (mp 60°C). IR (KBr) 1697 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): 9.14 (d, 1H, J=5.0 Hz); 8.74 (d, 1H, J=7.7 Hz); 8.16 (t_{app}, 1H); 7.45 (d, 2H, J=8 Hz); 7.30–7.13 (m, 5H); 7.09 (d, 2H, J=8.0 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); 2.57 (s, 3H). Anal. calcd for $C_{24}H_{26}N_2O_5S$: C, 63,41; H, 5.77; N, 6.17. Found: C, 63.45; H, 5.85; N, 6.02.

4.1.7. 1-Methyl-6-[(*S*)-2-benzyl-1-hydroxyethyl]-1,4,6,7-tetrahydro-5*H*-pyrrolo[3,4-b]pyridin-5-one (4). The pyridinium salt **11** (0.455 g, 1 mmol) was placed under argon and dissolved in degassed water (5 mL) at 40°C. After cooling to rt, Na_2CO_3 (0.53 g, 5 mmol) and a solution of sodium dithionite (0.7 g, 4 mmol) in degassed water (3 mL) were added. The reaction mixture was vigorously stirred for 0.5 h and filtrated. The precipitate was washed with degassed water and dried under vacuum to afford model **4** (0.242 g, 85% yield) as a pale green solid. ^1H NMR (500 MHz, CD_3 CN): 7.35–7.20 (m, 5H); 5.81 (dt, 1H, J=1.7 and 8.1 Hz); 4.66 (dt, 1H, J=3.3 and 8.0 Hz); 4.27–4.08 (m, 1H); 3.95–3.80 (m, 2H); 3.69–3.63 (m, 3H); 3.01–2.86 (m, 4H); 2.84 (s, 3H).

Spectrum in the presence of 1 equiv. $Mg(ClO_4)_2$ (500 MHz, CD_3CN): 7.35–7.20 (m, 5H); 5.84 (dt, 1H, J=1.6 and 8.1 Hz); 4.72 (dt, 1H, J=3.3 and 8.0 Hz); 4.54–4.42 (m, 1H); 4.10–3.90 (m, 2H); 3.75–3.67 (m, 2H); 3.07–2.85 (m, 4H); 2.89 (s, 3H).

4.1.8. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-5,6-dihydro-1,6-naphthyridin-5-one (13). Compound **12**[7] (2.79 g, 10 mmol) was heated to reflux in a mixture of ethanol/water: 95/5 (20 mL) for 48 h. After evaporation of the solvents the obtained solid was purified by chromatography on silica gel (CH_2Cl_2/EtOH: 95/5) leading to 1.45 g of a yellow solid. Yield 52%. IR (KBr): 1645 cm^{-1}. ^1H NMR (200 MHz $CDCl_3$): 8.70 (q, 1H); 8.39 (q, 1H); 7.28 (d, 1H, J=8.0 Hz); 7.20–7.05 (m, 6H); 6.58 (d, 1H, J=8.0 Hz); 5.20 (m, 1H); 3.93 (d, 2H); 3.13 (d, 2H).

4.1.9. 6-[(*S*)-2-Benzyl-1-hydroxyethyl]-1-methyl-5,6-dihydro-5-oxo-1,6-naphthyridinium iodide (14). The above compound **13** (1.12 g, 4 mmol) was heated to reflux for 12 h in a mixture of methyl iodide (5 mL, large excess) and acetonitrile (5 mL). After concentration at 2/3 of the initial volume ether was added. The obtained precipitate was filtered. Yellow solid: 1.43 g. Yield 85%. IR (KBr): 1648 cm^{-1}. ^1H NMR (200 MHz): 9.03 (q, 1H); 8.71 (q, 1H); 7.79 (d, 1H, J=8.0 Hz); 7.52 (q, 1H); 7.28–7.10 (m, 5H); 6.63 (d, 1H, J=8.0 Hz); 4.17 (s, 3H); 3.65 (d, 2H); 3.14 (d, 2H).

4.1.10. 1-Methyl-6-[(*S*)-2-benzyl-1-hydroxyethyl]-1,4,5,6-tetrahydro-1,6-naphthyridin-5-one (5). The above pyridinium salt **14** (0.422 g, 1 mmol) was dissolved in degassed water (5 mL) at 40°C. At rt, under argon, Na_2CO_3 (0.53 g, 5 mmol) was added, followed by the dropwise addition of a solution of sodium dithionite (0.70 g, 4 mmol) in degassed water (3 mL). After stirring for 30 min, the precipitate was filtered, washed with degassed water and dried. A yellow light solid was obtained: 2.66 g Yield 90%. IR (KBr) 1645 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): 7.30–7.18 (m, 5H); 7.16 (d, 1H, J=7.75 Hz); 5.84 (dt, 1H, J=1.70 and 8.10 Hz); 5.77 (d, 1H, J=7.75 Hz); 4.95–4.86 (m, 1H); 4.67 (dt, 1H, J=3.55 and 8.00 Hz); 3.90–3.72 (m, 3H); 3.20–3.10 (m, 4H); 2.95 (s, 3H). Spectrum in the presence of 1 equiv. of $Mg(ClO_4)_2$ (500 MHz, CD_3CN): 7.34 (d, 1H, J=7.75 Hz); 7.30–7.15 (m, 5H); 6.11 (d, 1H, J=7.75 Hz); 5.88 (dt, 1H, J=1.60 and 8.00 Hz); 5.20–5.07 (m, 1H); 4.76 (dt, 1H, J=3.55 and 8.00 Hz); 4.00–3.90 (m, 2H); 3.25–3.05 (m, 4H); 3.00 (s, 3H).

4.1.11. 3-[(3-Methoxycarbonylpyridin)3-yl]propanol (16). A suspension of 2-methylnicotinic acid (1.51 g, 11 mmol) in dry THF (100 mL) under argon was cooled at −78°C. A LDA solution (24 mmol) was added dropwise and the purple reaction mixture was held at −78°C for 0.5 h and then at 0°C for 1 h. After recooling to −78°C, 1-bromo-2-[(tetrahydropyran-2-yl)oxy]ethane **14** (3.45 g, 16.5 mmol) was added dropwise to this solution at −55°C and the reaction mixture was allowed to rise slowly rt for 16 h. The solvent was evaporated under reduced pressure. The residue was dissolved in a solution of HCl in methanol (5% w/w, 100 mL) and the resulting mixture was heated to reflux for 24 h. After removal of the solvent, the residue was taken up with water, neutralised with $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to give a brown liquid. A flash chromatography on silica gel (CH_2Cl_2/MeOH, 98/2) afforded **16** (2.14 g, 60% yield) as a yellow liquid. IR (film) 1727 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.59 (dd, 1H, J=4.8 and 1.7 Hz); 8.14 (dd, 1H, J=7.9 and 1.7 Hz); 7.19 (dd, 1H, J=4.8 and 7.9 Hz); 3.88 (s, 3H); 3.78 (br, 1H); 3.61 (t_{app}, 2H); 3.25 (t_{app}, 2H, J=7.1 Hz): 1. 98 (q_{app}, 2H). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.18. Found: C, 61.45; H,7.92; N, 7.07.

4.1.12. 3-[(3-Methoxycarbonylpyridin)-2-yl]propanal (17). A 150 mL three-necked round-bottom flask under argon was equipped with a thermometer and two pressure-equalising dropping funnel containing freshly distilled dimethylsulfoxide (1.33 mL, 18.5 mmol) diluted in CH_2Cl_2 (5 mL) and alcohol **16** (1.5 g, 7.7 mmol) diluted in CH_2Cl_2 (5 mL), respectively. A solution of oxalyl

chloride (0.805 mL, 9 mmol) diluted in CH_2Cl_2 (5 mL) was introduced and cooled to −55°C. The solution of DMSO was added dropwise to this solution at −55°C and the reaction mixture was stirred for 2 min. The alcohol solution was added dropwise within 5 min and stirring was continued for an additional 15 min. Freshly distilled triethylamine (5.35 mL, 38.5 mmol) was added, the reaction mixture was stirred for 5 min and then allowed to warm to rt before quenching with water (20 mL). After extraction with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure to give crude **17** as a dark green oil (78% yield) which was used immediately in the next step without any further purification. ^{1}H NMR (200 MHz, $CDCl_3$): 9.88 (s, 1H); 8.61 (dd, 1H, *J*=7.9 and 1.7 Hz); 8.19 (dd, 1H, *J*=7.9 and 1.7 Hz; 7.23 (dd, 1H, *J*=4.8 and 7.9 Hz); 3.91 (s, 3H); 3.54 (t_{app}, 2H, *J*=5.8 Hz); 2.88 (t_{app}, 2H, *J*=7.1 Hz); 2.03 (q_{app}, 2H).

4.1.13. *N*-(1-Hydroxymethyl-2-phenylethyl)-3-[(3-methoxycarbonylpyridin)-2-yl]propylamine (18). To a solution of aldehyde **17** (1.5 g, 7.8 mmol) in dry EtOH (50 mL) was added (*S*)-phenylalaninol (1.17 g, 7.8 mmol) and the reaction mixture was stirred for 1 h at room temperature. After cooling to 0°C, $NaBH_4$ (294 mg, 7.8 mmol) was added and the reaction mixture was stirred to room temperature for 1 h. The solution was quenched with water, neutralised with 1N HCl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude yellow oil obtained was purified by flash chromatography on silica gel (CH_2Cl_2/EtOH, 95/5) to afford **18** (1.94 g, 76% yield) as a yellow oil. IR (film): 1720 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 8.55 (dd, 1H, *J*=4.8 and 1.7 Hz); 8.16 (dd, 1H, *J*=7.9 and 1.7 Hz); 7.27–7.18 (m, 6H); 3.88 (s, 3H); 3.74–3.61 (m, 2H); 3.32–2.99 (m, 7H); 2.28 (qn_{app}, 2H). Anal. calcd for $C_{19}H_{24}N_2O_3$: C, 61.54; H, 6,67. N, 7.18. Found: C, 60.45; H, 7.06; N, 7.07.

4.1.14. 6-(1-Hydroxymethyl-2-phenylethyl-)-6,7,8,9-tetrahydropyrido[3,2-*c*]azepin-5-one (19). To a solution of amine **18** (2 g, 6 mmol) in dry EtOH (100 mL) was added K_2CO_3 (1.26 g, 9 mmol) and the suspension was stirred at reflux for three days. After cooling, the mixture was quenched with water, neutralised with 1N HCl and extracted with CH_2Cl_2. The combined organic layers were dried filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOH, 95/5) to give **19** (0.810 g, 45% yield) as a beige solid (mp 143°C). IR (KBr): 3510 and 1618 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 8.54 (dd, 1H, *J*=4.8 and 1.7 Hz); 7.92 (dd, 1H, *J*=7.9 and 1.7 Hz) 7.40–7.23 (m, 6H); 4.71 (m, 1H); 4.02 (br s, 1H); 3.81 (br d, 2H); 3.16–2.97 (m, 4H); 2.84–2.62 (m, 2H); 1.93 (qn, 2H). Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 72.89; H, 6.65; N, 9.40.

4.1.15. 6-(1-Hydroxymethyl-2-phenylethyl-)-6,7,8,9-5-oxo-tetrahydropyrido[3,2-*c*]azepinium iodide (20). To a solution of amide **19** (0.740 g, 2.5 mmol) in acetonitrile (20 mL) was added methyl iodide (3.1 mL, 50 mmol) and the reaction mixture was heated to reflux for two days. After concentration at 2/3 of the initial volume, diethyl ether (20 mL) was added dropwise in order to precipitate the pyridinium salt. Filtration, washing with Et_2O and drying afforded the desired pure pyridinium salt **20** (0.800 g, 80% yield) as a pale yellow solid. IR. (KBr): 1648 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): 8.99 (d, 1H, *J*=5.9 Hz); 8.33 (d, 1H, *J*=7.9 Hz); 7.99 (t_{app}, 1H, *J*=6.3 Hz) 7.38–7.19 (m, 5H); 4.98 (t, 1H, *J*=5.7 Hz); 4.27 (s, 3H); 3.60 (m, 2H); 2.07 (m, 2H). (Note: the other protons are hidden behind the DMSO and H_2O peaks). Anal. calcd for $C_{19}H_{23}N_2O_2I$: C, 52.05; H, 5.25; N, 6.39. Found: C, 51.83; H, 5.12; N, 6.16.

4.1.16. 6-(1-Hydroxymethyl-2-phenylethyl)-1,4,6,7,8,9-hexahydro-1-methyl-pyrido[3,2-*c*]azepin-5-one (6). A 10 mL round-bottomed flask containing the pyridinium salt **20** (0.104 g, 0.25 mmol) was placed under argon and in the dark. Aqueous degassed 0.5 M Na_2CO_3 solution (1.5 mL) followed by degassed CH_2Cl_2 (3 mL) and then $Na_2S_2O_4$ (0.435 g, 2.5 mmol) dissolved in 0.5 M Na_2CO_3/H_2O degassed solution (1.5 mL) were added through a syringe. The reaction mixture was stirred for 1 h at room temperature. The organic and layer was separated, dried and concentrated under reduced pressure to give model **6** (0.066 g, 85% yield) as a pale brown solid. The whole work-up was made as quick as possible in the dark because this compound was very light-sensitive and unstable. ^{1}H NMR (500 MHz, CD_3CN): 6.96–6.89 (m, 5H); 5.41 (dt, 1H, *J*=1.3 and 7.9 Hz); 4.31–4.25 (m, 1H); 4.19 (dt, 1H, *J*=3.6 and 7.9 Hz); 3.39–3.25 (m, 3H); 2.86 (t, 2H, *J*=6.7); 2.67–2.55 (m, 4H); 2.53 (s, 3H); 1.77–1.61 (m, 2H); 1.39 (qn, 2H, *J*=6.85 Hz).

Spectrum in the presence of equivalent of $Mg(ClO_4)_2$ (500 MHz, CD_3CN): 7.00–6.85 (m, 5H); 5.49 (dt, 1H, *J*=7.9 Hz); 4.70 (m, 1H); 4.36 (dt, 1H, *J*=7.6 and 3.8 Hz); 3.45 (td, 1H); 3.35 (dt, 1H); 3.10 (m, 2H); 2.85 (m, 2H); 2.65 (m, 2H); 2.60 (s, 3H); 1.38 (m, 2H).

4.2. General procedure for the asymmetric reduction of methyl benzoylformate by NADH mimics

A 10 mL round-bottomed flask containing 1.1 mmol of the appropriate NADH model was placed under argon and in the dark. Freshly distilled and degassed acetonitrile (2 mL), methyl benzoylformate (0.140 mL, 1 mmol) and anhydrous magnesium perchlorate (0.240 g, 1.1 mmol) were added successively in this order and the reaction mixture was stirred for 24 h at rt. The mixture was then quenched with water (2 mL) and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et_2O, 50/50) to afford methyl mandelate as a white solid (mp 33°C).

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