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Design of new axially chiral NADH mimics. Mechanistic investigation of the enantioselective hydride transfer

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Abstract—This paper reports the design of a new axially chiral NADH model which relies on the configurational control around the C3-C=O chiral axis by means of a chiral relay installed on the cyclic structure. The conformational and configurational control of the lactam moiety was successfully achieved affording two conformational diastereoisomers (a*S*,*S*)-**1** and (a*R*,*S*)-**1** in a ratio of 95:5, respectively. Reduction of methyl benzoylformate with model **1** afforded (*R*)-methyl mandelate in up to 84% e.e. The stereoselective synthesis of 4-deuterated model **1** allowed us to establish that this enantioselective reduction arises from the migration of the *syn*-oriented hydrogen with regard to the carbonyl dipole. © 2001 Elsevier Science Ltd. All rights reserved.

It has been suggested for some time that the stereospecificity of the NADH coenzyme would originate partly from the conformation adopted by the nicotinamide moiety. In particular it has been demonstrated from X-ray and NMR analyses of dehydrogenases with bond NADH that a *trans*-conformation of the nicotinamide amide and an out-of-plane orientation of carbonyl amide with respect to the dihydropyridine ring is adopted in many cases.[1] This conformer was proposed as the active conformation of the coenzyme during a reduction reaction; the hydrogen to be transferred being *syn*-oriented (Fig. 1). An out-of-plane C=O amide orientation gives rise to a configurational element, namely, a chiral axis which may have important implications in the stereospecific hydrogen transfer. Many chiral models based on an out-of-plane orientation of the C=O amide have been reported to evaluate the role of this configurational element on the stereoselectivity of hydride transfer.[2]

With a view to mimic this configurational feature, we wish to report herein a new biomimetic chiral NADH model **1** bearing a chiral linking bridge to ensure both conformational and configurational control of the resulting lactam (Fig. 1).[3]

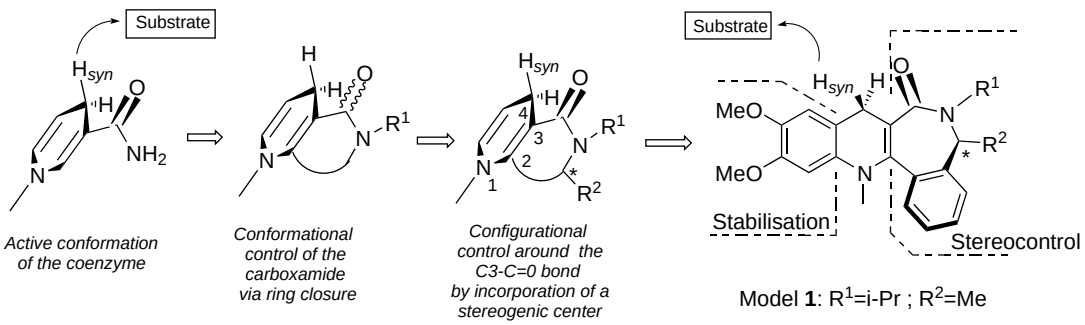

Figure 1. Biomimetic design of a new axially chiral NADH model based on conformational and configurational control of atropisomeric lactam by means of a chiral linking bridge.

Keywords: NADH; atropisomeric lactam; asymmetric reduction; mechanism.

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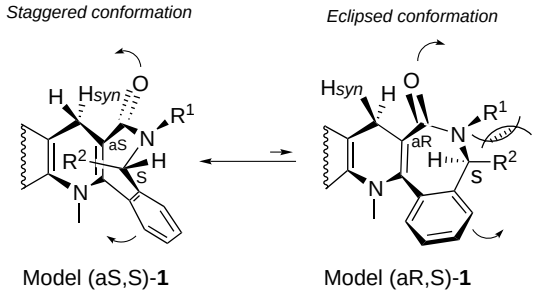
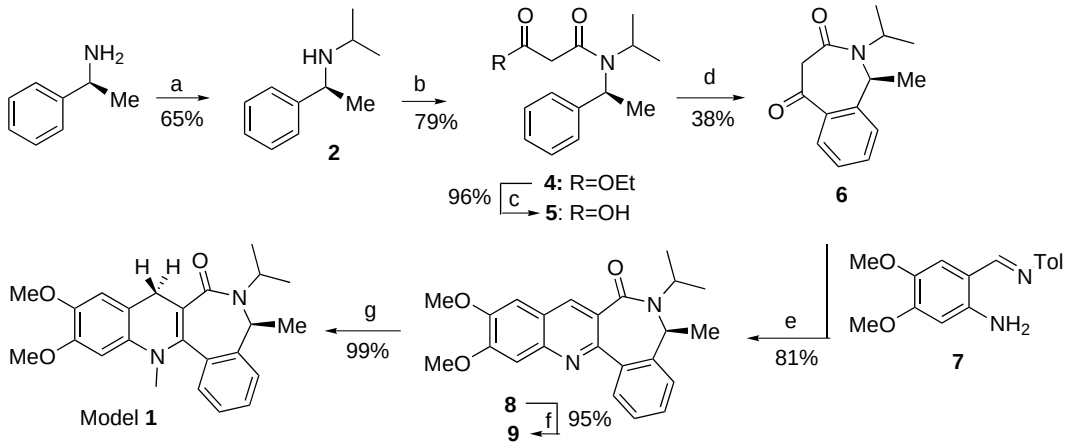


Figure 2. Conformational and configurational analysis of model **1**.

The conformational control of the carboxamide would be ensured by the cyclic structure of the seven-membered lactam to maintain a *trans*-conformation of the C=O amide. Molecular modelling of such seven-membered ring revealed that the dihydropyridine ring and the C=O lactam display a dihedral angle of about 45°. The flipping of the lactam ring induces the configurational inversion at the C3–C=O conformational chiral axis. The configurational control of this chiral axis is based on the incorporation of a second chiral element on the lactam moiety, to promote a dynamic resolution process of a pair of conformational diastereoisomers (a*R*,*S*)-**1** and (a*S*,*S*)-**1**. As shown in Fig. 2, interconversion between both diastereomeric atropisomers (a*R*,*S*)-**1** and (a*S*,*S*)-**1**, sets the substituent at the chiral centre (R^2) either in an eclipsed or staggered conformation with respect to the neighbouring *N*-R^1 substituent. According to this conformational analysis, we planned to control this conformational equilibrium in favour of the staggered conformation in consequence of steric interactions between R^1 and R^2 encountered in the eclipsed conformation. As a result of the isopropyl steric hindrance, molecular modelling[4] indicates that model **1** ($R^1 = i$-Pr and R^2 = Me) would be a good candidate to control this equilibrium in favour of (a*S*,*S*)-**1**.

Model **1** was prepared according to a Friedlander strategy between benzazepin-3,5-dione **6** and amino amine **7**[5] as shown in Scheme 1. The required benzazepin-3,5-dione **6** was obtained in 5 steps from (*S*)-α-methylbenzylamine in an overall yield of 20%. Upon treatment of (S)-α-methylbenzylamine with acetone, the intermediate imine was subsequently reduced with sodium borohydride to yield the desired amine **2** in 65% yield. Condensation of acid chloride **3** afforded β-amide ester **4** in 79% yield. After hydrolysis of the β-amide ester **4**, the resulting β-amide acid **5** was treated with oxalyl



Scheme 1. Synthesis of axially chiral model **1**. *Reagents and conditions*: (a) acetone/reflux then $NaBH_4$/MeOH/rt/2 h; (b) **3**: $EtOOCCH_2COCl/CH_2Cl_2/NEt_3$/rt/12 h; (c) KOH/EtOH/0°C/5 h; (d) $(COCl)_2/CH_2Cl_2/\varepsilon$ DMF/rt then $AlCl_3$/1 h/rt; (e) EtOH/few drops of piperidine/reflux/12 h; (f) MeOTf (1.1 equiv.)/CH_2Cl_2/rt/2 h; (g) $NaBH_4$ (1.5 equiv.)/EtOH/rt/2 h.

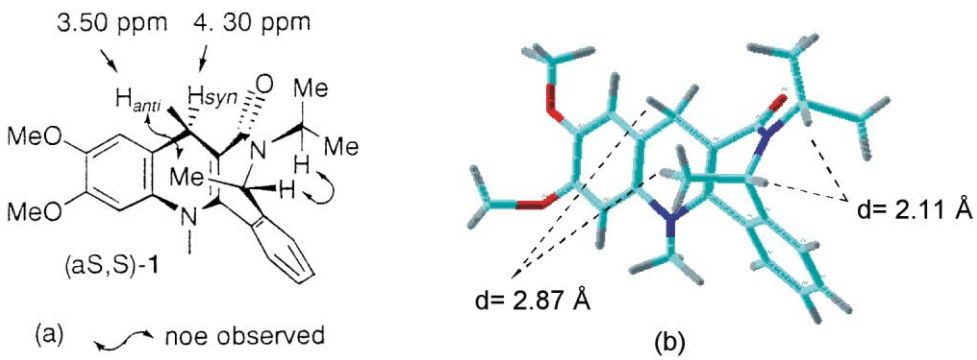
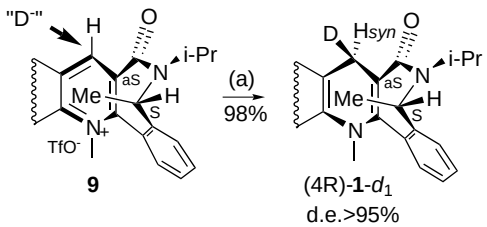


Figure 3. (a) Identification of the most stable atropisomer (a*S*,*S*)-**1** by NOESY experiment; (b) molecular modelling (MM2, PCMODEL version 7).

chloride to furnish the corresponding acid chloride. Friedel–Craft cyclisation supplied the desired benzazepin-3,5-dione **6** in 38% yield.[6] The Friedlander condensation (Borsche modification)[7] of **6** with the amino imine **7** occurred smoothly under mild conditions to provide the required benzazepino[4,5-*b*]quinolin-3-one **8** in 81% yield. After quaternisation with methyl trifluoromethanesulfonate, the resulting quinolinium salt **9** obtained in 95% yield was involved in the regioselective reduction. Under classical conditions, namely, by using sodium dithionite and sodium carbonate,[8] model **1** was obtained along with substantial amount of unidentified by-product. Contrary to all expectations,[9] it later emerged that the use of sodium borohydride resulted in regioselective reduction leading to model **1**[10] in quantitative yield (Scheme 1).

The ^{1}H NMR spectrum of model **1** revealed the presence of both diastereomeric atropisomers (a*S*,*S*)-**1** and (a*R*,*S*)-**1** in a ratio of 95:5 respectively. As it had been anticipated from molecular modelling, undesirable eclipsing interactions in (a*R*,*S*)-**1** result in the flipping of the lactam ring, the methyl at the chiral centre being oriented away from the isopropyl substituent in the resulting isomer (a*S*,*S*)-**1**. The stereochemistry of the major conformational isomer (a*S*,*S*)-**1** was assigned by a NOESY NMR experiment as indicated in Fig. 3, i.e. the NOE between the hydrogen at the stereogenic centre and the hydrogen at the *N*-isopropyl substituent.

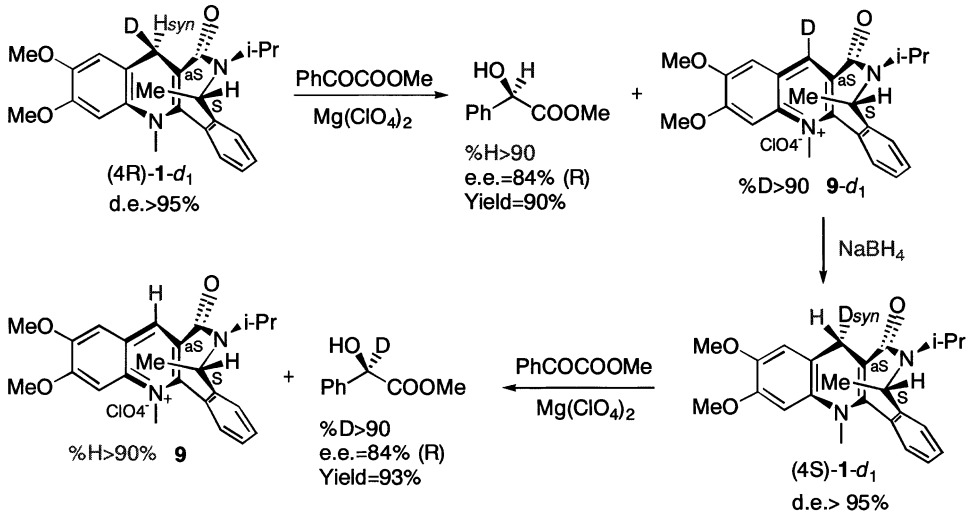


Scheme 2. Diastereoselective reduction of quinolinium salt **9** with $NaBD_4$. *Reagents and conditions*: (a) $NaBD_4$/EtOD/rt/2 h.

An additional NOE was observed between the methyl at the stereogenic centre and one of both diastereotopic hydrogen at C-4 which confirms the occurrence of (a*S*,*S*)-**1** and more interestingly, allows to assign H_{syn} and H_{anti} with respect to the C=O lactam (Fig. 3).

This former information prompted us to investigate the diastereoselective reduction of the quinolinium salt **9** with $NaBD_4$ with intent to gain afterwards an experimental evidence that the transferred hydrogen would be *syn*-oriented with respect to the C=O lactam. Interestingly, reduction of **9** with $NaBD_4$ afforded in a quantitative yield (4*R*)-**1**-d_1 in 95% d.e. The high level of diastereoselectivity and the sense of induced stereoselectivity may be attributable to the out-of-plane orientation of the C=O lactam, which would exert a steric control to favour attack of the deuteride equivalent on the opposite face of quinolinium salt **9** (Scheme 2).

With model (4*R*)-**1**-d_1 in hand, we tested the reduction of methyl benzoylformate in acetonitrile in the presence of magnesium perchlorate. As shown in Scheme 3, deuterated model (4*R*)-**1**-d_1 afforded (*R*)-methyl mandelate in up to 84% e.e. with no deuteride incorporation. The resulting quinolinium salt **9**-d_1 was recovered in good yield and high deuterium content (Scheme 3).[10] Although these results sustain the hypothesis that the *syn* orientated hydrogen in model **1** would be preferentially transferred, the observed migration of H_{syn} with model (4*R*)-**1**-d_1 may be ascribed to an isotope effect as well. To ascertain that the H_{syn} transfer observed does not originate from an isotope effect, we undertook the diastereoselective reduction of **9**-d_1 with $NaBH_4$ affording (4*S*)-**1**-d_1 in up to 95% d.e. The reduction of methyl benzoylformate with (4*S*)-**1**-d_1 provided (*R*)-d_1-methyl mandelate in up to 84% e.e. and high deuterium content. This former experiment confirms that with model (4*S*)-**1**-d_1 the effective stereodifferentiation of the diastereotopic C-4 hydrogens overrides an eventual isotope effect. To the best of our knowledge, we report herein the first experimental evidence which clearly establishes the preferential transfer of H-4 *syn* over H-4 *anti*, with regard to the carbonyl dipole.[11]



Scheme 3. Asymmetric reduction of methyl benzoylformate with (4*R*)-**1**-d_1 and (4*S*)-**1**-d_1.

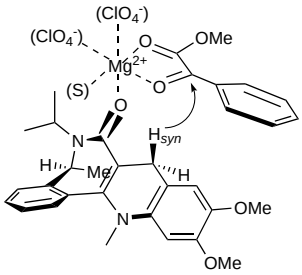


Figure 4. Proposed ternary complex model **1**/$Mg(ClO_4)_2$/substrate.

It is assumed that in the presence of magnesium perchlorate, the reduction takes place via the establishment of a ternary complex (model/Mg^{2+}/methyl benzoylformate). The transition state depicted in Fig. 4 is a working hypothesis to account for the obtained stereoinformation, namely, the preferential *syn*-oriented hydrogen transfer and the formation of (*R*)-methyl mandelate. The high degree of stereocontrol of this reduction process suggests that an out-of-plane orientation of the C=O lactam provides a configurational element enable to stereodifferenciate the two diastereotopic hydrogens at C-4 and to stereodiscriminate both enantiotopic faces of methyl benzoylformate. Consequently, this work strongly supports the hypothesis that the stereospecific transfer of one of the diastereotopic C-4 hydrogens of the coenzyme to a prochiral substrate may originate from the configurational control of this non permanent axial chirality around C3-C=O bond upon complexation with dehydrogenases.

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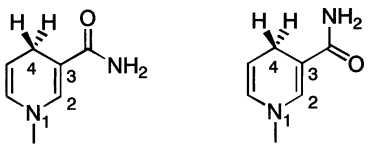

Trans-conformation *Cis*-conformation

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4. The eclipsed conformation (a*R*,*S*)-**1** was shown to be 3 kcal/mol less stable than the staggered conformation (a*S*,*S*)-**1** by MM2 calculations.
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9. Reduction of quinolinium salts with $NaBH_4$ usually produces the corresponding dihydroquinolines as a mixture of 1,2- and 1,4-regioisomers.
10. ^1H NMR data ($CDCl_3$, 200 MHz, 20°C): Model (a*S*,*S*)-**1** δ 1.02 (3H, d, $J=6.8$ Hz), 1.26 (3H, d, $J=7.2$ Hz), 1.66 (3H, d, $J=7.1$ Hz), 3.12 (3H, s), 3.50 (1H, d, $J=18.5$ Hz), 3.87 (3H, s), 3.91 (3H, s), 4.30 (1H, d, $J=18.5$ Hz), 4.54 (1H, q, $J=7.2$ Hz), 5.11 (1H, hept, $J=6.8$ Hz), 6.56 (1H, s), 6.67 (1H, s), 7.15–7.40 (4H, m). Deuterated quinolinium salt (a*S*,*S*)-**9**-d_1 δ 1.17 (3H, d, $J=6.5$ Hz), 1.27 (3H, d, $J=7.0$ Hz), 1.33 (3H, d, $J=7.0$ Hz), 4.07 (3H, s), 4.35 (3H, s), 4.64 (3H, s), 4.76 (1H, q, $J=7.5$ Hz), 5.11 (1H, hept, $J=7.0$ Hz), 7.37 (1H, s), 7.45–7.70 (4H, m), 7.86 (1H, s).
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