Pergamon

Tetrahedron Letters 42 (2001) 3713–3716

TETRAHEDRON LETTERS

# Rational design of novel axially chiral NADH models based on configurational control of atropisomeric lactams

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Received 27 March 2001; revised 30 March 2001; accepted 3 April 2001

**Abstract**—The preparation of a new class of axially chiral NADH models based on configurational control of atropisomeric lactams is described. The configurational control of this chiral axis is achieved via the presence of a second chirality element installed on the lactam moiety of the reagent **2**. Reduction of methyl benzoylformate led to methyl mandelate in 89% yield and 92% e.e. This result suggests that the chiral axis about C3–C=O bond is the main configurational element responsible for the high enantioselectivity observed with this biomimetic model. 

The out-of-plane orientation of the nicotinamide amide adopted in the coenzyme seems to be an important conformational feature in the stereochemical outcome of the hydride transfer. It has been suggested that the amide carbonyl dipole would be *syn* oriented with respect to the transferring hydrogen (Fig. 1).[1] Consequently it was of interest to mimic this conformational effect by considering the out-of-plane orientation of the C=O as a novel chiral element in the design of axially chiral NADH models.

A number of research groups[2] have been interested in the use of atropisomeric amides as a chiral relay for the preparation of enantiopure NADH models chiral at C-4 (Fig. 2). Indeed, it allows the stereoselective reduction of quinolinium **A** to provide enantiopure model **B**. This former model was shown to be highly enantioselective during the reduction of methyl benzoylformate. In the course of this reduction process, axial chirality of quinolinium **A** is restored with a high level of stereocontrol. Although, it has been suggested an out-of-plane orientation of the carbonyl, the presence of a chiral centre at C-4 prevents us from appreciating the role played by this conformational effect and its degree of participation in the stereochemical outcome of the reduction (Fig. 2). From a practical point of view, the enantiopure preparation of such models seriously limits their potential as asymmetric reducing agents.

We previously reported the high performance of models **1** during the reduction of methyl benzoylformate.[3] Our interpretation for the high stereoselectivity observed is founded on the following considerations. The cyclic structure sets the C=O lactam out-of-plane with respect to the dihydropyridine ring with a dihedral angle of about 50°. If one assumes that the stereoselective departure of the *syn* oriented hydrogen is favoured, an out-of-plane orientation of the carbonyl lactam raises questions about the stereocontrol of this masked chiral axis. Given the good performance of model **1**, it may be assumed that the stereocontrol of this new chiral axis would be ensured via the presence of the chiral auxiliary at the nitrogen lactam which would give rise to a dynamic resolution process of both conformational atropodiastereoisomers (a*R*,*S*)-**1** and (a*S*,*S*)-**1** (Fig. 3). To argue for this hypothesis and to design new axially

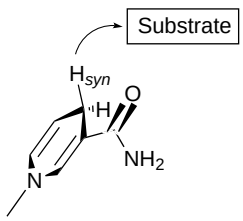


**Figure 1.** Out-of-plane orientation of nicotinamide amide moiety in the active conformation of the coenzyme NADH.

*Keywords*: NADH; atropisomeric lactam; conformational atropisomers; asymmetric reduction.

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0040-4039/01/$ - see front matter 
PII: S0040-4039(01)00555-X

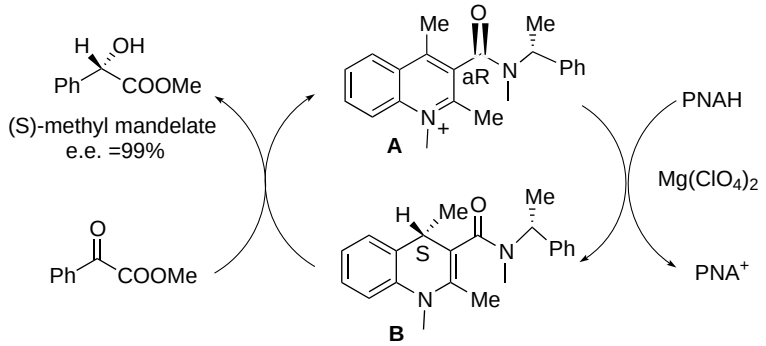



**Figure 2.** Use of atropisomeric lactams as chiral relay in the design of chiral NADH models. Intramolecular transfer of an axial chiral element to a central chiral element and vice versa.

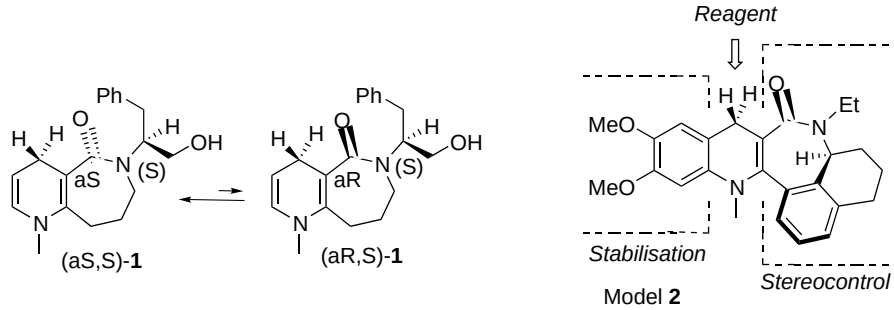


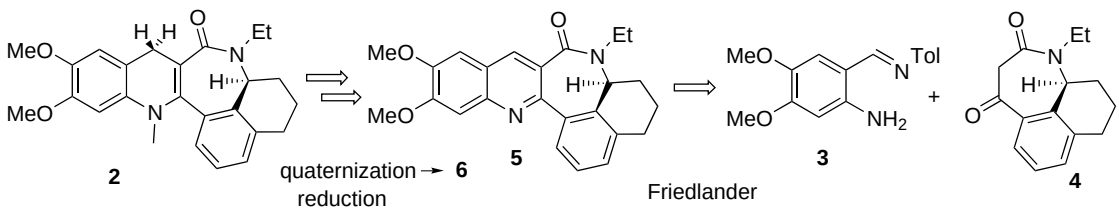

**Figure 3.** (a) Configurational analysis of model **1** and (b) design of a new axially chiral NADH model **2**.

chiral NADH models based on configurational control of atropisomeric lactams, we planned to prevent this interconversion between the two atropodiastereoisomers by means of a chiral auxiliary carried out on the lactam moiety as depicted in Fig. 3. We report herein the stereoselective synthesis of such a model and its potential as an enantioselective reducing agent in the reduction of methyl benzoylformate. The high stability of annelated models,[3b,c] incited us to undertake the stereoselective synthesis of model **2** in benzazepino[4,5-*b*]quinoline series (Fig. 3).

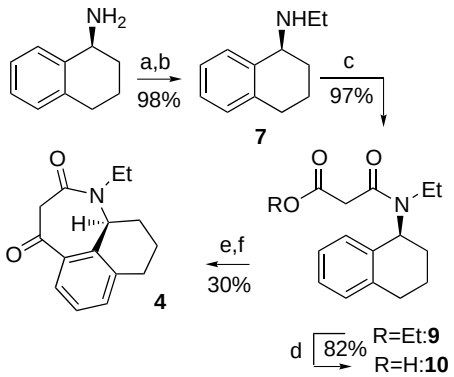
The synthesis of model **2** is based on a Friedlander type condensation[4] of the amino imine **3** and the tetrahydronapht[1,8-*bc*]azepine-2,4-dione **4** to afford the quinoline derivative **5** followed by the classical steps of quaternization and regioselective reduction of the corresponding quinolinium salt **6** (Scheme 1).

The preparation of the desired tetrahydro-napht[1,8-*bc*]azepine-2,4-dione **4** was achieved in five steps starting from the commercially available (*S*)-1,2,3,4-tetrahydronapht-1-yl-amine. The *N*-ethyl derivative **6** was obtained by acetylation followed by reduction in 98% overall yield. Treatment of **7** with the acid chloride **8**[5] derived from ethyl malonate afforded the requisite amide ester **9** in 97% yield which was subsequently hydrolysed to furnish the expected amide acid **10** in 82% yield. The crux of this reaction scheme is the cyclisation step of **10** via an intramolecular Friedel–Crafts acylation. Investigation of the literature indicated that similar SEAr cyclisation have been achieved to effect seven-membered rings closure in high yields with an acid chloride in the presence of $AlCl_3$ in $CH_2Cl_2$.[6] Compound **10** was thus converted into the corresponding acid chloride prior to cyclisation. The desired β-keto lactam **4** was obtained under the former conditions, albeit in a modest yield of 30% (Scheme 2).

The known amino imine **3**[7] was then involved in the Friedlander reaction under Borsche conditions with the β-keto lactam **4** to afford the benzazepino[5,4-*b*]quinoline **5** in 76% yield. Treatment of the former with methyl trifluoromethanesulfonate gave rise to the benzazepino[5,4-*b*]quinolinium salt **6** in 95% yield. The regioselective reduction was then investigated under




**Scheme 1.** Retrosynthetic analysis of model **2**.



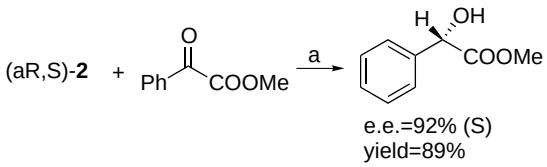

**Scheme 2.** *Reagents and conditions*: (a) $CH_3COCl/NEt_3/CH_2Cl_2/0°C/2$ h; (b) $BH_3/I_2$/reflux/12 h; (c) $EtOOCCH_2COCl$ **8**/$NEt_3/CH_2Cl_2$/rt/12 h; (d) KOH/EtOH/rt/5 h; (e) $(COCl)_2/CH_2Cl_2$/DMF cat/rt/; (f) $AlCl_3$ (2.2 equiv.)/rt/1 h.

classical reduction conditions, i.e. with sodium dithionite.[8] Under these conditions, a mixture of unidentified products was obtained. After screening various reducing agents, we found out that sodium borohydride lead in good yield (97%) to the desired model **2** without formation of by-products (Scheme 3).

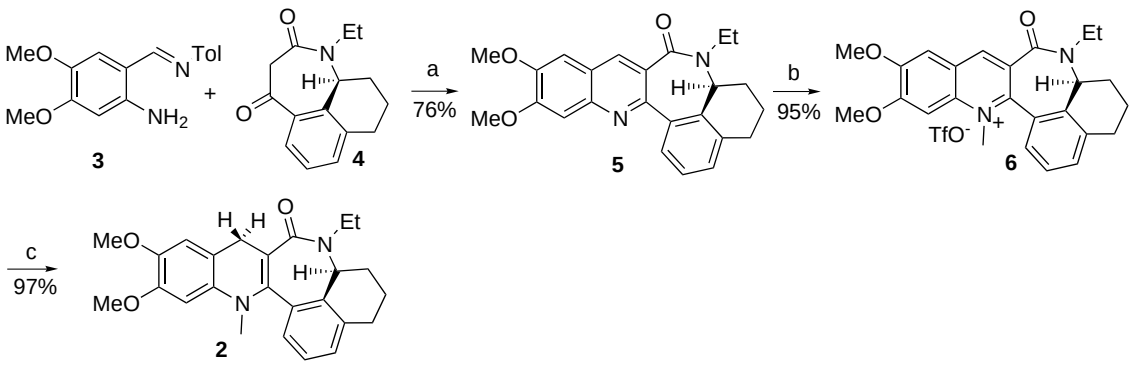
As it could be anticipated from a conformational analysis, $^1H$ NMR spectra of model **2**[9] reveals the presence of a single conformational diastereoisomer. Indeed, owing to conformational restraints, the methylene at the chiral centre of the cyclic chiral auxiliary is constrained to adopt an eclipsed conformation with the neighbouring *N*-ethyl substituent. As a consequence of this conformational control, the absolute configuration of the chiral axis about the C3–C=O bond is maintained and subordinated to the absolute configuration of this cyclic chiral auxiliary. Thus, starting from (*S*)-tetrahydro-napht[1,8-*bc*]azepine-2,4-dione **4** as chiral auxiliary, the resulting masked chiral axis of model **2** possesses an (a*R*) absolute configuration. The conformational analysis also indicated that the $C_{(4)}–C_{(3)}–C=0$ dihedral angle is about 46° (Fig. 4).

With model (a*R*,*S*)-**2** in hand, we investigated the reduction of methyl benzoylformate in the presence of magnesium perchlorate in acetonitrile (Scheme 4).[11] Under those conditions, model **2** is shown to be highly enantioselective, affording methyl mandelate in up to 92% e.e. (*S*).

As shown in Fig. 4, the conformation adopted by the model sets the chiral auxiliary in the middle plane of the dihydroquinoline leaving both diastereotopic hydrogen atoms at C-4 accessible to the substrate. It is reasonable to assume that the stereocontrol of the reduction arises from the axial chirality based on




**Scheme 4.** Asymmetric reduction of methyl benzoyformate. *Reagents and conditions*: (a) $Mg(ClO_4)_2/CH_3CN$/rt/24 h.




**Scheme 3.** *Reagents and conditions*: (a) piperidine/EtOH/reflux/12 h; (b) $TfOMe/CH_2Cl_2$/rt/2 h; (c) $NaBH_4$/EtOH/rt/2 h.


**Figure 4.** (a) Conformational and configurational analysis of model **2**; (b) molecular modelling (MM2, PCMODEL) of model **2**.[10]

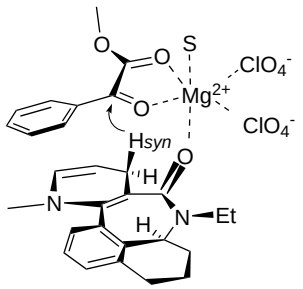



**Figure 5.** Proposed ternary complex involved in the reduction of methyl benzoyformate to account for the formation of (*S*)-methyl mandelate.

C–3–C=O bond. As previously proposed in the literature,[2a] the sense of the stereoselectivity observed may be tentatively explained by the establishment of a ternary complex model/$Mg^{2+}$/substrate via the complexation of the C=O lactam with magnesium ion to promote the stereoselective transfer of the *syn* oriented hydrogen (Fig. 5).

In contrast to previous models reported in literature, absence of chirality at C-4 does not throw discredit on the role played by this conformational effect in the stereochemical outcome of the reduction. This configurational control process of atropisomeric lactams by means of a second chirality element on the lactam moiety opens up interesting perspectives to design new axially chiral NADH models and to gain further insight into the role of the out-of plane orientation of the carbonyl amide in the coenzyme itself.

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9. Spectral data $^1$H NMR ($CDCl_3$, 200 MHz). Compound **2**: $\delta$ 0.84 (3H, t, $J=7.0$ Hz), 1.92–2.42 (4H, m), 2.78–2.95 (2H, m), 3.03 (3H, s), 3.32 (1H, six, $J=7.0$ Hz), 3.58 (1H, d, $J=18.0$ Hz), 3.82 (1H, six, $J=7.0$ Hz), 3.86 (3H, s), 3.90 (3H, s), 4.35 (1H, d, $J=18.0$ Hz), 4.67 (1H, dd, $J=7.0$ Hz, $J=3.8$ Hz), 6.55 (1H, s), 6.68 (1H, s), 7.12–7.22 (3H, m). Compound **6**: $\delta$ 1.04 (3H, t, $J=7.0$ Hz), 2.08 (2H, m), 2.35 (2H, m), 2.86–3.03 (2H, m), 3.57 (1H, quint, $J=7.0$ Hz,) 3.84 (1H, quint, $J=7.0$ Hz), 4.07 (3H, s), 4.21 (3H, s), 4.41 (3H, s), 4.93 (1H, m), 7.36 (1H, s), 7.37–7.44 (4H, m), 7.61 (1H, s), 9.10 (1H, s). Compound **5**: $\delta$ 1.07 (3H, t, $J=7.0$ Hz), 1.90–2.15 (3H, m), 2.36 (1H, m), 2.70–2.82 (1H, m), 2.92–3.05 (1H, dt, $J=17.0$, 3.5 Hz), 3.55 (1H, six, $J=7.0$ Hz), 4.00 (1H, six, $J=7.0$ Hz), 4.02 (3H, s), 4.04 (3H, s), 4.86 (1H, m), 7.13 (1H, s), 7.20 (1H, d, $J=7.5$ Hz), 7.38 (1H, t, $J=7.5$ Hz), 7.96 (1H, d, $J=7.5$ Hz), 8.62 (1H, s).
10. Molecular mechanics (MM2) and MOPAC (PM3) program led to the same conformation.
11. **Procedure for the reduction of methyl benzoylformate:** In a flask, flushed with argon, were introduced model (a*R*,*S*)-**2** (405 mg, 1 mmol), acetonitrile (3 mL), methyl benzoylformate (142 μL, 1 mmol) and magnesium perchlorate (220 mg, 1 mmol). The resulting solution was stirred at room temperature for 24 h in the dark. After addition of water (10 mL), the organic solvent was evaporated under reduced pressure and the resulting aqueous phase was extracted with $CH_2Cl_2$ (3×10 mL). After drying ($MgSO_4$) and evaporation of the solvent, the residue was chromatographed on silica gel (eluent $Et_2O$/cyclohexane:2/1). Yield: 89%. Enantiomeric excesses were determined by HPLC analysis using a Chiracel OD column (250×4.6 mm, 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of methyl mandelate in 10 mL of hexane). Eluent: hexane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 22°C. UV detection: $\lambda=$ 235 nm. Retention time: 9.2 min [(*S*)-enantiomer] and 14.8 min [(*R*)-enantiomer]. Enantiomeric excess: 92% (*S*).