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Atropoisomeric quinolinium salt promoting the access to both enantiomeric forms of methyl mandelate: a versatile NADH mimic†

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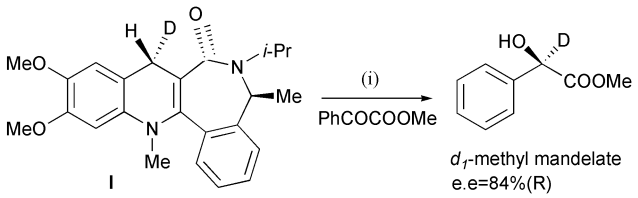
Received (in Cambridge, UK) 30th July 2002, Accepted 28th August 2002
First published as an Advance Article on the web 10th September 2002

Asymmetric reduction of methyl benzoylformate by a new NADH mimic is reported; depending on the hydride source used to reduce the NAD$^+$ precursor, NADH mimics so obtained lead to an inversion of enantioselectivity, affording either (*R*)-methyl mandelate in 88% ee or (*S*)-methyl mandelate in 78% ee.

The development of versatile chiral systems that are able to selectively form either enantiomer of a given product is a very exiting challenge as sometimes only one enantiomer of the required chiral auxiliary is readily available. In the enzymatic reductions requiring NAD(P)H, it is known that depending on the substrate associated with its oxidoreductase enzyme, the pro-(*R*) or pro-(*S*) hydrogen is differentiated and stereospecifically transferred to the substrate.[1] It has been suggested that this specificity originated from the *trans* out-of-plane orientation adopted by the amide function which exhibits the transfer of the H^{syn} with respect to the carbonyl.[2] 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 stereochemistry of the hydride transfer.[3] We have previously reported this selective *syn*-hydrogen transfer using labelled models **I** (Scheme 1).[4]



Scheme 1 Experimental proof of the *syn*-hydrogen transfer to methyl benzoylformate using labelled models **I**. *Reagents and conditions*: (i) $Mg(ClO_4)_2/CH_3CN$/rt.

In such series of models as **I**, a slow equilibrium between the two conformational diastereoisomers (*aS*,*S*)-**I** and (*aR*,*S*)-**I** occurs by flipping of the C-3–C=O chiral axis. This equilibrium is biased towards (*aS*,*S*)-**I** as consequence of steric repulsions in (*aR*,*S*)-**I** between the bulky isopropyl chain and the methyl group (Fig. 1).

From the labelled study, we and others[5] have shown that only the *syn*-hydrogen with respect to the carbonyl group is transferred to the substrate. In this series of NADH models, a slow equilibrium between the two conformational diastereoisomers occurs. To enhance the reactivity of the pro-(*S*)-H (H in model **I**, Scheme1), the reactivity of the pro-(*R*)-H (D in model **I**, Scheme 1), should be blocked to allow only the transfer of the pro-(*S*)-H after conformational interconversion of the seven-membered ring. This could be achieved by introduction of a methyl group at C-4 and diastereoselective reduction using an appropriate hydride source. In this communication, we wish to report the *cis* and *trans* introduction of the hydrogen at C-4 with respect to the carbonyl group, and the results obtained in the reduction of the methyl benzoylformate (MBF) using these two mimics generated from one enantiopure quinolinium salt. (Fig. 2).

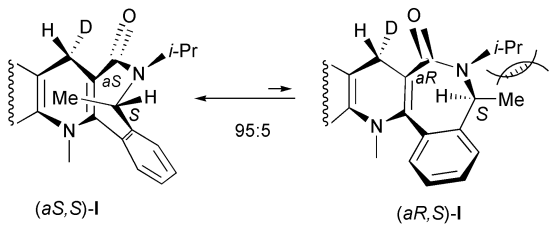


Fig. 1 Equilibrium between the two conformational diastereoisomers (a*S*,*S*)-**I** and (a*R*,*S*)-**I**.

The synthesis of the quinolinium salt **3** was carried out from quinoline **1**[4] by addition of methyllithium to yield the intermediate 1,4-dihydropyridine. Subsequent NCS oxidation[6] of the 1,4-dihydropyridine followed by quaternisation of the resulting quinoline **2** afforded the desired quinolinium salt (*aS*,*1S*)- **3** in 81% overall yield from **1** (Scheme 2).

Reduction of the quinolinium salt **3** with BH_3·THF complex afforded NADH model **4** in 95% yield as a single stereoisomer (d.e. > 95%) assigned as (*aS*,*1S*,*4R*)-**4** by a NOESY experiment. The high level of diastereoselection may be explained by chelation-control between the lactam and the boron empty-p-orbital which activates the *cis* adduct formation (Scheme 3). The resulting reactive model (*aS*,*1S*,*4R*)-**4** bearing the hydride equivalent *syn* with respect to the carbonyl function leads to (*R*)-methyl mandelate in 52% yield and an enantiomeric excess of 88% (Scheme 3, path A).

As previously reported with model **I**,[4b] *trans* introduction of the hydrogen at C-4 was accomplished by $NaBH_4$ reduction of quinolinium salt **3** resulting in a mixture of conformational diastereoisomers (*aS*,*1S*,*4S*)-**4** and (*aR*,*1S*,*4S*)-**4**. This partial epimerisation of C-3–C=O chiral axis, not observed with model

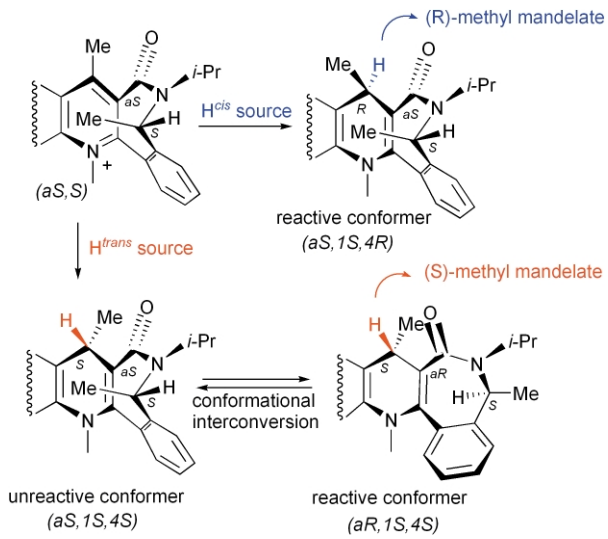
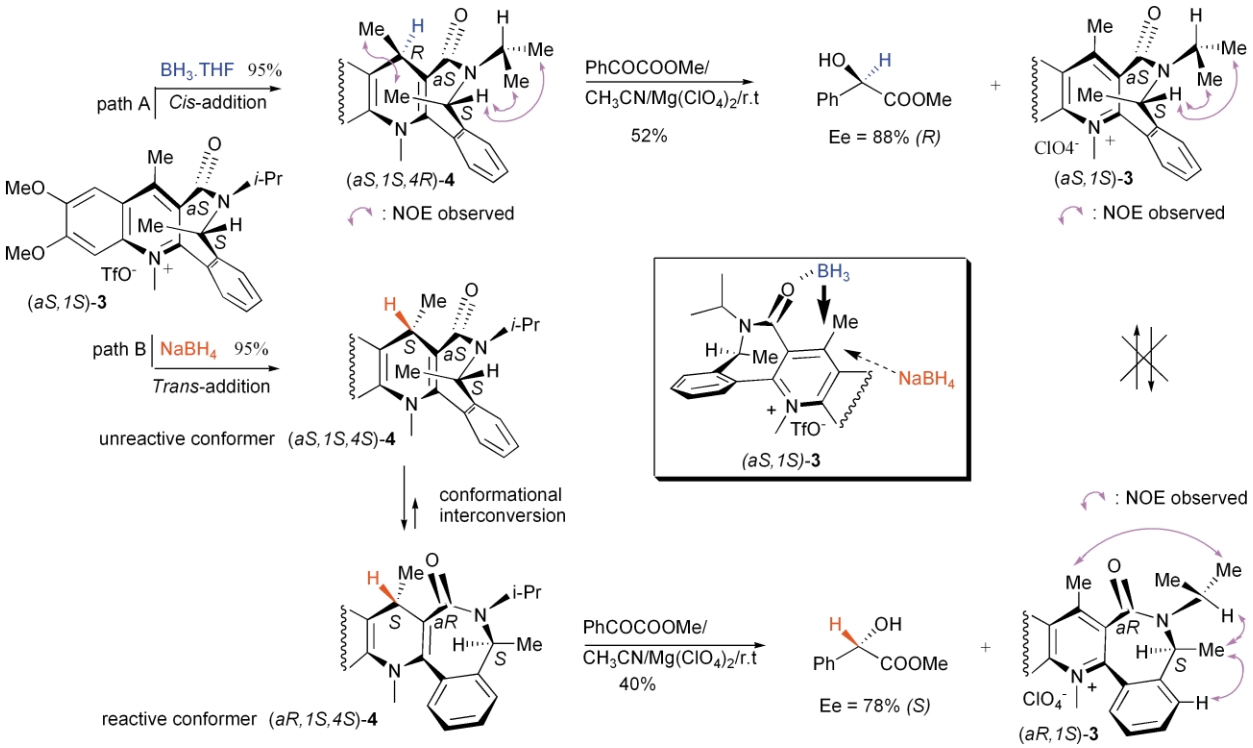


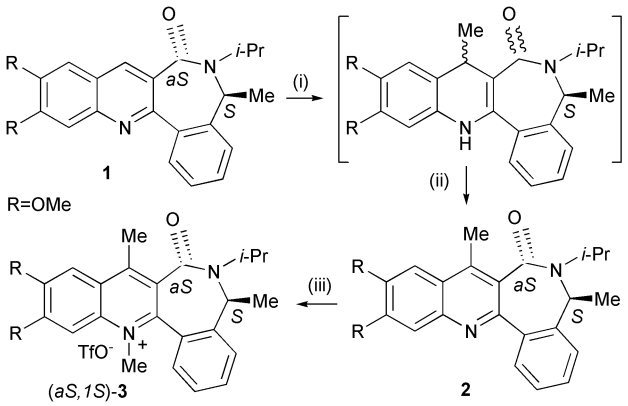
Fig. 2 Design of a new NAD$^+$ mimic promoting the access to both enantiomeric forms of methyl mandelate.

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b2/b207434f/

DOI: 10.1039/b207434f



Scheme 3 Reversal of stereochemistry in the reduction of quinolinium salt **3**. Access to (*S*) or (*R*)-methyl mandelate from the same NAD^+ mimic **3**.



Scheme 2 *Reagents and conditions*: (i) MeLi/THF/−40 °C/2 h; (ii) NCS/MeOH/rt/1 h; (iii) $TfOMe/CH_2Cl_2$/2 h.

I, is likely due to steric repulsion between the carbonyl and the methyl group at C-4 in the initially formed conformational diastereoisomer (*aS,1S,4S*)-**4**. Nevertheless, as the absolute configuration at C-4 is controlled by a *trans* introduction of the hydride,[4a] the crude mixture was assessed in the reduction of MBF, leading to (*S*)-methyl mandelate in 40% yield with an enantiomeric excess of 78% (Scheme 3, path B). In the mechanism depicted in Scheme 3, $NaBH_4$-mediated reduction of NAD^+ mimic **3** results initially in the formation of the unreactive conformer (*aS,1S,4S*)-**4** which undergoes a conformational interconversion prior to reducing MBF into (*S*)-methyl mandelate. This scenario is supported by a conformational study of the recovered quinolinium salt **3** by means of NOESY experiments. In contrast to NADH mimics **4**, their oxidized forms (*aS,1S*)-**3** and (*aR,1S*)-**3** do not interconvert and are configurationally stable for many days in CH_3CN at room temperature. Consequently, one can consider that the reactive conformation of mimic **4** is imprinted on the recovered quinolium salt **3**. As expected, reduction of MBF with (*aS,1S,4R*)-**4** affords the quinolinium perchlorate salt (*aS,1S*)-**3** (path A), whereas the two conformational diastereoisomers (*aS,1S,4S*)-**4** and (*aR,1S,4S*)-**4** lead to the exclusive formation of the conformational diastereoisomer (*aR,1S*)-**3** (path B). This clearly indicated that in (*aR,1S,4S*)-**4**, placing the hydride equivalent *syn* with respect to the carbonyl lactam is the only reactive conformation of the model.

To summarize, the control of the axial chirality in the seven-membered fused ring in NAD^+ mimic **3** allowed the stereoselective introduction of a latent (*R*)-director or (*S*)-director hydride equivalent at the C-4 position. The absolute stereochemistry of the product could therefore be controlled by choice of the appropriate primary hydrogen source. Finally, these results open the way for further investigations of this class of NADH models as molecular switches. Indeed, if one could control the equilibrium between both conformational diastereoisomers (*aS,1S,4S*)-**4** and (*aR,1S,4S*)-**4**, in a predictable manner, it would offer the opportunity to switch-on/off, on demand, the reducing properties of these biconformational chiral NADH mimics.

Notes and references

1 (*a*) F. H. Westheimer, H. F. Fisher, E. E. Conn and B. Vennesland, *J. Am. Chem. Soc.*, 1951, **73**, 2403; (*b*) H. F. Fischer, E. E. Conn, B. Vennesland and E. E. Weisteimer, *J. Biol. Chem.*, 1953, **202**, 687.

2 (*a*) H. Ecklund, J. P. Samama and T. A. Jones, *Biochemistry*, 1984, **23**, 5982; (*b*) T. Skarzynski, P. C. E. Moody and A. J. Wonacott, *J. Mol. Biol.*, 1987, **193**, 171; (*c*) Ö. Almarsson and T. C. Bruice, *J. Am. Chem. Soc.*, 1993, **115**, 2125; (*d*) Y.-D. Wu and K. N. Houk, *J. Org. Chem.*, 1993, **58**, 2043.

3 (*a*) P. M. T. De Kok, L. A. M. Bastianansien, P. M. van Lier, J. A. J. M. Vekemans and H. M. Buck, *J. Org. Chem.*, 1989, **54**, 1313; (*b*) Y. Mikita, K. Hayashi, K. Mizukami, S. Matsumoto, S. Yano, N. Yamazaki and A. Ohno, *Tetrahedron Lett.*, 2000, **41**, 1035; (*c*) M. Fujii, T. Kamata, M. Okamura and A. Ohno, *J. Chem. Soc., Chem. Commun.*, 1992, 905; (*d*) A. Ohno, A. Tsutsumi, Y. Kawai, N. Yamazaki, Y. Mikata and M. Okamura, *J. Am. Chem. Soc.*, 1994, **116**, 8133; (*e*) A. Ohno, A. Tsutsumi, N. Yamazaki and M. Okamura, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1679.

4 (*a*) J.-L. Vasse, G. Dupas, J. Duflos, G. Quéguiner, J. Bourguignon and V. Levacher, *Tetrahedron Lett.*, 2001, **42**, 4613; (*b*) J.-L. Vasse, G. Dupas, J. Duflos, G. Quéguiner, J. Bourguignon and V. Levacher, *Tetrahedron Lett.*, 2001, **42**, 3713.

5 S. Obika, T. Nishiyama; S. Tatematsu, K. Miyashita and T. Imanishi, *Tetrahedron*, 1997, **53**, 3073.

6 (*a*) A. I. Meyers and T. Oppenlaender, *J Am. Chem. Soc.*, 1986, **108**, 1989; (*b*) A. I. Meyers and T. Oppenlaender, *J. Chem. Soc., Chem. Commun.*, 1986, 920.