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New NADH models bearing a phosphonate or a chiral oxazaphospholidine oxide at the dihydropyridine ring

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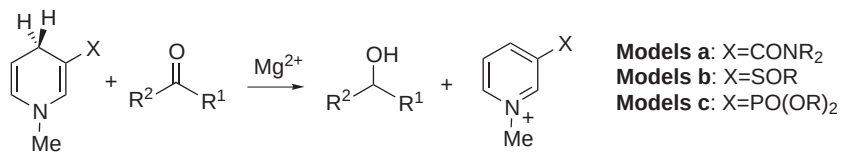
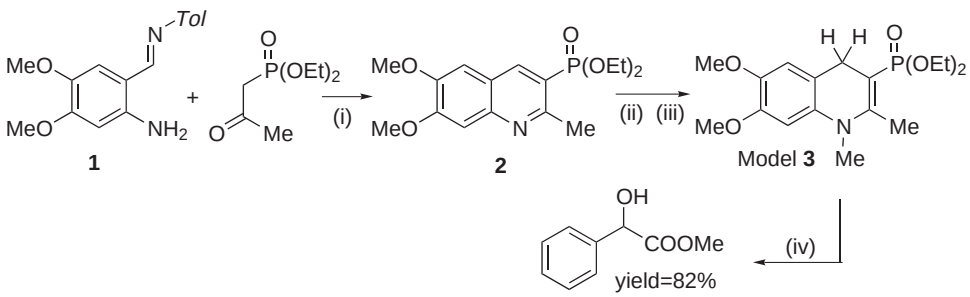
Abstract—Novel NADH models bearing a phosphonate at the 3-position of a stable 1,4-dihydroquinoline structure were successfully involved in the reduction of methyl benzoylformate. Asymmetric reduction of the former ketone with a NADH model bearing a chiral oxazaphospholidine oxide is reported affording methyl benzoylformate in 45% e.e.

The crucial role of NAD(P)H as coenzyme in biological reductions has stimulated a great deal of interest in the field of biomimetic organic chemistry.[1] Numerous non chiral and chiral NADH models were studied with a view to developing new chemoselective and enantioselective reducing agents. Most of these biomimetic models carry an amide group at the 3-position of the 1,4-dihydropyridine (model **a** in Scheme 1). Reduction of a substrate is generally achieved in the presence of divalent metal ions (most often Mg^{2+}) which play a fundamental role in the hydrogen mechanism transfer.[2] In the past, NADH models bearing a sulfinyl group instead of a carbonylated derivative at the 3-position were described (model **b** in Scheme 1).[3] In models **a** or **b**, the main role of the C=O or S=O bond is to stabilize the labile dihydropyridine structure through their electron withdrawing character.



Scheme 1.



Scheme 2. Reagents and conditions: (i) Piperidine/EtOH/reflux/2.5 h (50%); (ii) MeOTf/CH_2Cl_2/rt/1 h (100%); (iii) $Na_2S_2O_4$/Na_2CO_3/EtOH (97%); (iv) methyl benzoylformate/$Mg(ClO_4)_2$/CH_3CN/rt/24 h (82%).

Keywords: biomimetic reduction; coenzyme models; non chiral or chiral phosphonic acid derivatives.

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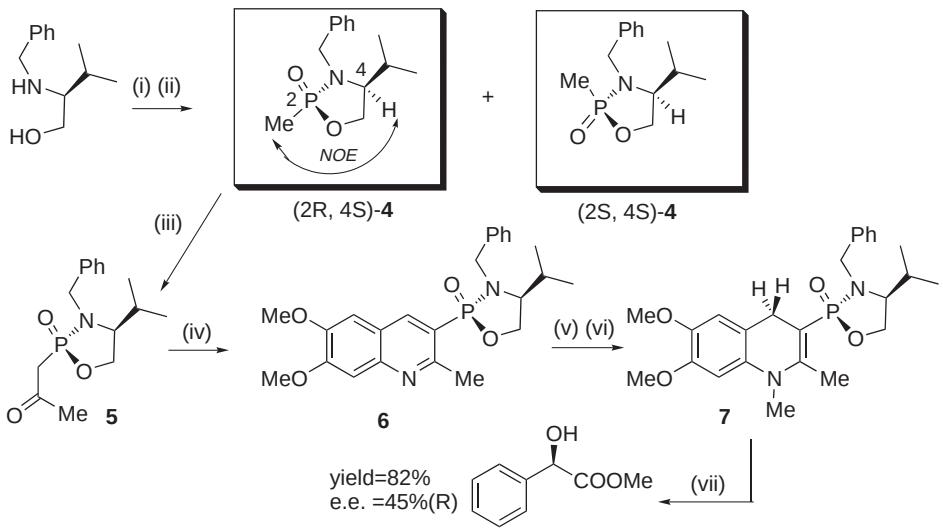
The phosphonate group is able to exhibit electronic properties similar to C=O or S=O groups and possesses a good affinity with magnesium ions which play a fundamental role in reductions mediated with NADH models. We wish to report herein the synthesis of a novel generation of NADH models bearing this type of substituent at the 3-position of a dihydropyridine ring (model **c** in Scheme 1).[4]

With a view to protecting the 5,6 double bond against pernicious side reactions and with respect to previous works in our group,[5] we intended to synthesize an annelated model in the quinoline series. For that purpose, commercially available diethyl(2-oxopropyl)-phosphonate was condensed with imine **1** derived from 2-amino-4,5-dimethoxybenzaldehyde according to the Borsche modification of the Friedlander reaction[6] affording quinoline **2**.[7] Quaternization followed by regioselective 1,4-reduction gave the desired model **3**[8] in 48% overall yield (Scheme 2). The resulting reagent **3** was successfully involved in the reduction of methyl benzoylformate in the presence of Mg^{2+} ions providing the corresponding methyl mandelate in 82% yield (Scheme 2).

Given that a phosphonate group linked to a 1,4-dihydropyridine structure is able to mediate a biomimetic reduction, it was of interest to investigate the potential of a chiral analog to promote an asymmetric reduction. We turned our interest in the synthesis of chiral oxazaphospholidine oxide derivatives such as **7**, readily available from a chiral aminoalcohol (Scheme 3). According to a literature procedure,[8] condensation of *N*-benzyl-(*S*)-valinol with methyl phosphonic dichloride supplied the oxazaphospholidine oxide **4** as a diastereoisomeric mixture (ratio 55:45).[9] The absolute configuration at the phosphorus atom of both diastereoisomers (2*S*,4*S*)-**4** and (2*R*,4*S*)-**4** were established by comparing their elution order during a chromatographic separation to those observed for similar compounds of known configurations.[8] Supporting evidence for this assignment may be found from the NOESY spectrum of the more polar diastereoisomer. It shows an NOE between the C4(H) and the methyl connected to the phosphorus atom (Scheme 3). Such a correlation is only consistent with the isomer (2*R*,4*S*)-**4**. The next steps of this synthesis were accomplished with the diastereoisomer (2*R*,4*S*)-**4**, the only one which has been isolated properly in an enantiomerically pure form. Under the basic conditions used for the formation of **2**, Borsche condensation with oxazaphospholidine oxide (2*R*,4*S*)-**4** and imine **1** led exclusively to the formation of tarry material. To circumvent this problem, Borsche condensation had to be performed under acidic conditions, affording compound **6** in good yield. Finally, compound **7**[9] was obtained according to a classic route by quaternization followed by regioselective reduction. With model **7** in hands, reduction of methyl benzoylformate gave the corresponding (*R*)-methyl mandelate in 45% e.e.[10]

In summary this work describes the first biomimetic reduction with an NADH model bearing a phosphonic acid derivative. Although reagent **7** is not as effective as models **a** or **b** in terms of enantioselectivity,[11] the use of an oxazaphospholidine oxide as chiral inductor corresponds to the first asymmetric reduction with a NADH model based on a chiral phosphorus. In models **a** or **b**, the C=O or S=O groups seem to play a crucial role in the stereospecific transfer of the hydride equivalent mediated by a ternary complex substrate/Mg^{2+}/model. Studies showed that the transferred hydrogen is *syn* to the C=O or S=O groups, which would adopt an out of plane orientation with respect to the dihydropyridine ring.[12] The stereoselection of the reduction leading to (*R*)-methyl mandelate is probably correlated with the



Scheme 3. Reagents and conditions: (i) $MeP(O)Cl_2/NEt_3/CH_2Cl_2$; (ii) flash chromatography on silica gel *i*-PrOH/heptane: 1/9 as eluent to separate both diastereoisomers (2*S*,4*S*)-**4** (less polar) and (2*R*,4*S*)-**4** (more polar); (iii) LDA/AcOEt/THF/−78°C (67%); (iv) toluene/*p*-TSA (74%); (v) TfOMe/CH_2Cl_2/2 h (95%); (vi) $Na_2S_2O_4/Na_2CO_3$/EtOH (91%); (vii) methyl benzoylformate/$Mg(ClO_4)_2/CH_3CN$/rt/24 h (82%).

necessary out of plane orientation of the P=O bond owing to the steric hindrance between the oxazaphospholidine structure and the methyl at the 2-position. The mechanism of the enantioselective hydrogen transfer with model **7** and with other similar models is under progress.

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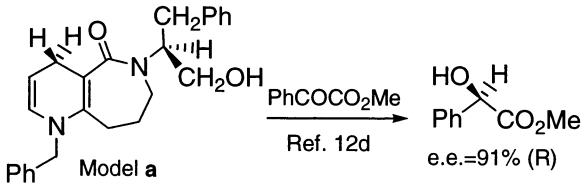

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7. Spectral data ^{1}H NMR ($CDCl_3$) compound **2**: 8.60 (d, $J=16$ Hz, 1H); 7.35 (s, 1H); 7.09 (s, 1H); 4.16 (m, 4H); 4.05 (s, 3H); 4.01 (s, 3H); 2.87 (s, 3H), 1.36 (t, $J=7$ Hz, 6H). Compound **3**: 6.57 (s, 1H); 6.42 (s, 1H); 4.0 (m, 4H); 3.86 (s, 3H); 3.81 (s, 3H); 3.34 (d, $J=7$ Hz, 2H); 3.26 (s, 3H); 2.38 (s, 3H); 1.26 (t, $J=7$ Hz, 6H).
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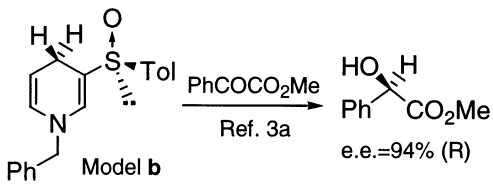
9. Spectral data ^{1}H NMR ($CDCl_3$) compound (2*R*,4*S*)-**4** (more polar): 7.38–7.19 (m, 5H); 4.32–3.95 (m, 4H); 3.21 (m, 1H); 2.00 (m, 1H); 1.41 (d, $J=16$ Hz, 3H); 0.93 (d, $J=7$ Hz, 3H); 0.75 (d, $J=7$ Hz, 3H). Compound (2*S*,4*S*)-**4** (less polar): 7.52–7.42 (m, 2H); 7.37–7.27 (m, 3H); 4.13–3.81 (m, 4H); 3.03 (m, 1H); 1.80 (m, 1H); 1.40 (d, $J=16$ Hz, 3H); 0.78 (d, $J=7$ Hz, 3H); 0.82 (d, $J=7$ Hz, 3H). Compound **5**: 7.30–7.10 (m, 5H); 4.23–3.85 (m, 4H); 3.30–2.82 (m, 3H); 2.17 (s, 3H); 1.85 (m, 1H); 0.80 (d, $J=7$ Hz, 3H); 0.64 (d, $J=7$ Hz, 3H). Compound **6**: 8.50 (d, $J=16$ Hz, 1H); 7.25–6.90 (m, 7H); 4.42–4.05 (m, 4H); 3.96 (s, 3H); 3.90 (s, 3H); 3.55 (m, 1H); 2.62 (s, 3H); 2.20 (m, 1H); 1.00 (d, $J=7$ Hz, 3H); 0.75 (d, $J=7$ Hz, 3H). Compound **7**: 7.30 (m, 5H); 6.45 (s, 1H); 6.35 (s, 1H); 4.30–3.85 (m, 4H); 3.80 (s, 3H); 3.75 (s, 3H); 3.45 (m, 1H); 3.20 (m, 1H); 3.15 (s, 3H); 3.05 (m, 1H); 2.35 (s, 3H); 2.02 (m, 1H); 0.95 (d, $J=7$ Hz, 3H); 0.75 (d, $J=7$ Hz, 3H).
10. Enantiomeric excesses were measured by HPLC. AGP chiral column (100×4 mm; 5 μm) purchased from Chrom Tech. Inc. UV detection ($\lambda=210$ nm); Eluent: Phosphate 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).
11. Reduction of methyl benzoylformate with models **a** or **b** afforded methyl mandelate in good to excellent enantiomeric excesses. See the following examples.



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