A Novel Coenzyme NAD(P)$^+$–NAD(P)H Model with Axial Chirality. Its Preparation and Stereoselectivity

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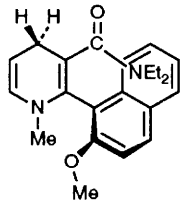
An axially chiral NAD(P)H model **1** bearing a 2′-methoxy-1′-naphthyl group at the C-2 position is prepared; the reduction of methyl benzoylformate with the optically active model, (+)- or (−)-**1**, in the presence of magnesium ion gives (*R*)- or (*S*)-isomer of methyl mandelate, respectively, in over 95% enantiomeric excess.

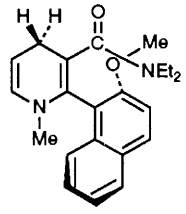
In the reduction of carbonyl compounds with NAD(P)H models, magnesium ion plays an important role not only in accelerating the reaction but in fixing the conformation of the reactive ternary complex.[1] It has also been proved that an electron-withdrawing group on a carbonyl substrate opposes the carbamoyl substituent on the nicotinamide ring, and that the carbonyl-oxygen of the substrate points toward the ring nitrogen of the nicotinamide in the ternary complex.[2] Therefore, a highly stereoselective reduction of carbonyl compounds can be expected when the two faces of the nicotinamide ring are discriminated efficiently—the third element in determining the stereochemistry.[3]

In this communication, we report the preparation and reaction of both enantiomers of 1-methyl-2-(2′-methoxy-1′-naphthyl)-*N*,*N*-diethyl-1,4-dihydronicotinamide **1**, an axially chiral coenzyme NAD(P)H model with the aim of differentiating enantiotopic faces of the dihydropyridine ring with the aid of the rotationally restricted 2-methoxy-1-naphthyl group.

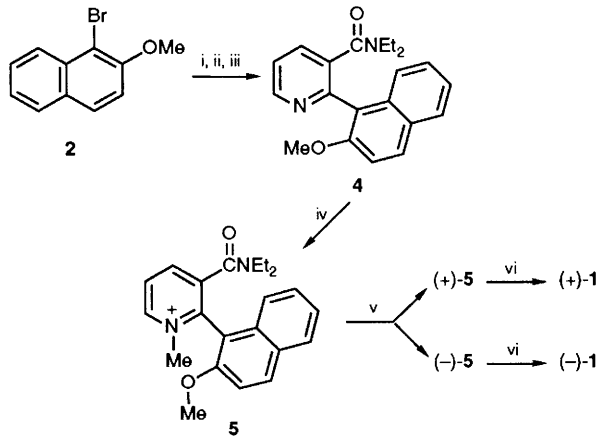
Preparation of **1** was achieved as shown in Scheme 1. Cross coupling of the Grignard reagent derived from **2** and 2-chloro-*N*,*N*-diethylnicotinamide **3** in the presence of



(*R*)-**1**



(*S*)-**1**



Scheme 1 *Reagents and conditions*: i, Mg, tetrahydrofuran (THF), N_2, 60 °C; ii, $NiCl_2(dppp)_2$, room temp.; iii, 2-chloro-*N*,*N*-diethylnicotinamide, THF, room temp., 24 h, 32%; iv, excess MeI, MeOH, reflux, 12 h; v, optical resolution on HPLC (DAICEL CHIRALCEL OD, hexane–propan-2-ol = 9 : 1, 0.4 ml min^{-1}); vi, $Na_2S_2O_4$, CH_2Cl_2/H_2O, Na_2CO_3, 86%

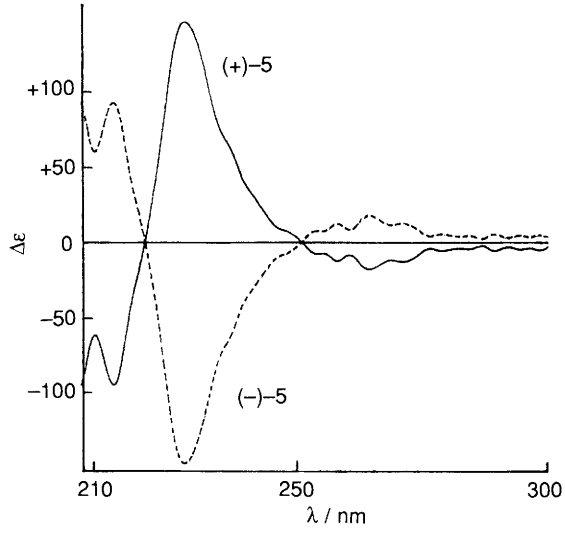
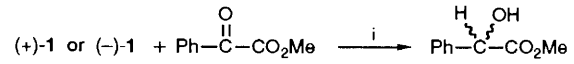


Fig. 1 CD spectra (in MeOH) measured on a JASCO 7-720 spectrometer: (+)-**5** (——) and (-)-**5** (- - - - - -)

$NiCl_2(dppp)_2$ (dppp = 1,3-diphenylphosphinopropane) gave **4** in 32% yield.[4] Quaternization of **4** with MeI in refluxing methanol gave **5** quantitatively. The optical resolution of **5** was performed on HPLC equipped with an optically active column (Daicel Chiralcel OD, hexane–propan-2-ol = 9:1; 0.4 ml min^{-1}). The first fraction with a retention time of 35.42 min had $[\alpha]_D^{22}$ +31.02 (*c* = 0.83, MeOH), and the second fraction with a retention time of 42.34 min had $[\alpha]_D^{22}$ −28.89 (*c* = 0.65, MeOH). The circular dichroism (CD) spectra thus obtained (+)- and (−)-**5** show that they are a pair of the enantiomers (Fig. 1). Reduction of (+)- and (−)-**5** with $Na_2S_2O_4$ afforded (+)-**1** $[\alpha]_D^{20}$ + 35.63 (*c* = 0.12, MeOH) and (−)-**1** $[\alpha]_D^{20}$ −33.17 (*c* = 0.14, MeOH), respectively.

Reduction of methyl benzoylformate **6** with (+)- or (−)-**1** offers interesting results as shown in Table 1. Whereas no reduction proceeds without magnesium ion, reduction with (+)- and (−)-**1** in MeCN at room temperature gives (*R*)- and (*S*)-methyl mandelate, respectively, in over 95% enantiomeric excess (e.e.), in the presence of an equivalent amount of magnesium perchlorate. The e.e. was determined on the basis of HPLC analyses (Daicel Chiralcel OK, hexane–propan-2-ol = 9 : 1), see Scheme 2.



Scheme 2 *Reagents and conditions*: i, MeCN, room temp., N_2

Table 1 Reduction of methyl benzoylformate by models, (+)- and (−)-**1**

Model	Catalyst	Time/h	Yield (%)	E.e. (%)[a]	Configuration
(+)-**1**	$Mg(ClO_4)_2$	72	23	>95	*R*
(+)-**1**	None	72	0	—	
(−)-**1**	$Mg(ClO_4)_2$	72	28	>95	*S*
(−)-**1**	None	72	0	—	

[a] Determined on HPLC (Daicel Chiralcel OK, hexane–propan-2-ol = 9 : 1.

The results indicate that the axial chirality in **1** exerts a large effect on the stereochemistry of the (net) hydride transfer, *i.e.* the discrimination of the diastereotopic faces of the 1,4-dihydronicotinamide ring. Both ethereal and carbamoyl oxygens in **1** chelate the magnesium ion, and it is the magnesium ion-containing face that is attacked by the carbonyl substrate.[1] Thus, not only steric inhibition by the 2-methoxynaphthyl group but also the orientation of the carbonyl dipole operate to accelerate the (net) hydride transfer from one particular side of the ring more than the other.[5,6]

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References

1 Y. Ohnishi, M. Kagami and A. Ohno, *J. Am. Chem. Soc.*, 1975, **97**, 4766.
2 A. Ohno, T. Goto, J. Nakai and S. Oka, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3478; A. Ohno, J. Nakai, K. Nakamura, T. Goto and S. Oka, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3482.
3 For reviews, see A. Ohno and S. Ushida, *Mechanistic Models of Asymmetric Reductions*, vol. 1, *Lecture Notes in Bioorganic Chemistry*, Springer Verlag, Heidelberg, 1986; Y. Inouye, J. Oda and N. Baba, *Asymmetric Synthesis*, vol. 2, ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2, pp. 92–124.
4 K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 4347.
5 H. Eklund, J. P. Samama and T. A. Jones, *Biochemistry*, 1984, **23**, 5982; A. Ohno, M. Kashiwagi, Y. Ishihara, S. Ushida and S. Oka, *Tetrahedron*, 1986, **42**, 961; P. M. T. de Kok, M. C. A. Donkersloot, P. M. van Lier, G. H. W. M. Meulendijks, L. A. M. Bastiaansen, H. J. G. van Hooff, J. A. Kanters and H. M. Buck, *Tetrahedron*, 1986, **42**, 941.
6 A. Ohno, M. Goto, Y. Mikata, T. Kashiwagi and T. Maruyama, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 87.