Stereospecific 4-Hydrogen Transfer in the Asymmetric Reduction Using (S_S)-3-(p-Tolylsulfinyl)-1,4-dihydropyridines, NADH Model Compounds

Satoshi Obika, Toshihiko Nishiyama, Satoshi Tatematsu, Kazuyuki Miyashita, and Takeshi Imanishi*
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565

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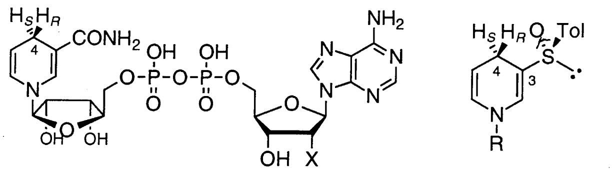
In asymmetric reduction of ketones with (S_S)-1-benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine as a NADH model compound, a stereospecific transfer of the 4-hydrogen was experimentally proved by the use of the 2-methyl congener and the 4-deuterated derivatives.

In the enzymatic reduction requiring a coenzyme NAD(P)H, it is well known that one of the prochiral hydrogens (H_S or H_R) at C-4 of the coenzyme is strictly differentiated and stereospecifically transferred to a carbonyl carbon of substrates.[1] Although a large number of asymmetric reductions with various chiral NADH model compounds have been demonstrated,[2] such a stereospecific transfer of the 4-hydrogen in these model systems has not been directly verified so far. In the previous papers,[3] we have reported synthesis of a simple and novel chiral NADH model compound, (S_S)-1-benzyl-3-(p-tolylsulfinyl)-1,4-dihydropyridine (**1**), which was found to reduce methyl benzoylformate to methyl (R)-mandelate in a high optical yield (Figure 1). Now, we wish to present here the first experimental evidence clearly demonstrating the stereospecific 4-hydrogen transfer process in *in vitro* asymmetric reduction with NADH model compound **1**.



NADH: X = OH
NADPH: X = OPO_2H_2

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Figure 1. Structures of NAD(P)H and our model compound **1**.

The previously reported asymmetric ketone reduction[3a] with compound **1** is easily assumed to be largely attributable to conformation of the sulfinyl function in **1**. Although the detailed ^{1}H-NMR spectral consideration and X-ray analysis of compound **1** indicate that the compound mainly exists in conformer **A**,[3b] the PM3 calculation[4] shows that the alternative conformer **B** is also preferred (Figure 2). To confirm the real preferred conformation of **1**, we synthesized its 2-methyl congener **2** as a conformationally restricted compound at the state **A**,[5] as shown in Scheme 1. The 4-protons NMR signals of compound **2** were found to be fairly coincident with those of compound **1**.[6]

On the other hand, reduction of methyl benzoylformate with **2** under the same conditions as that with **1** gave also methyl (R)-mandelate in an excellent optical yield (Table 1). From these observations, there is no doubt that **1** has the same conformation

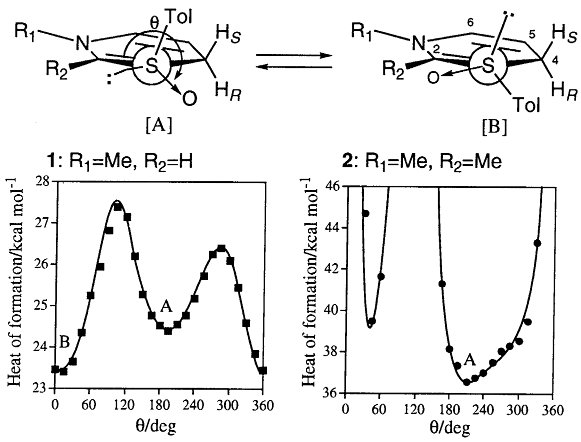
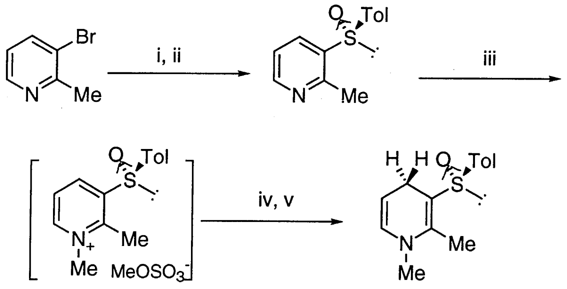


Figure 2. Conformational analysis of the sulfinyl group of **1** and **2**.



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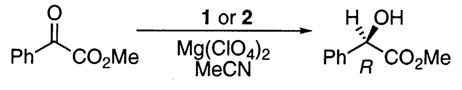
Scheme 1. *Reagents and conditions*: i, n-BuLi, Et_2O, -78°C, 30 min, then $MgBr_2$, 0°C, 30 min, ii, (1R, 2S, 5R)-(-)-mentyl (S)-p-toluenesulfinate, 0°C, 12 h, 69%, iii, dimethyl sulfate, 60°C, 12 h, iv, NaI, H_2O, r.t., 30 min, v, $Na_2S_2O_4$, 1M aq. $NaHCO_3$, r.t., 3 h, 86%.

Table 1. Asymmetric reduction of methyl benzoylformate with model compound **1** (R=Bn) or **2**^{a}

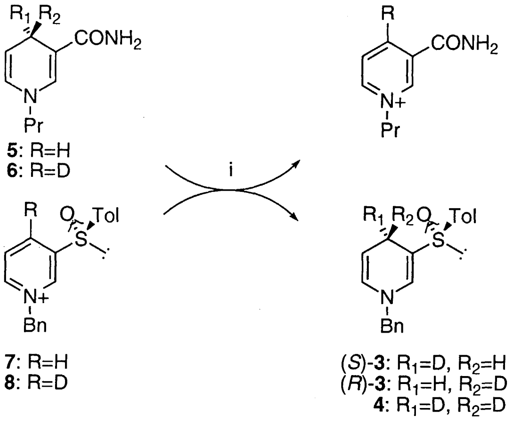


NADH Models	Yield/%	ee/%
1	77	94
2	72	99

^{a} Under an Ar atmosphere, a solution of **1** or **2** (0.3 mmol) in MeCN (2 cm^3) was added to a solution of methyl benzoylformate (0.3 mmol) and $Mg(ClO_4)_2$ (0.3 mmol) in MeCN (6 cm^3). The whole mixture was stirred at 303 K under dark for 14 d.

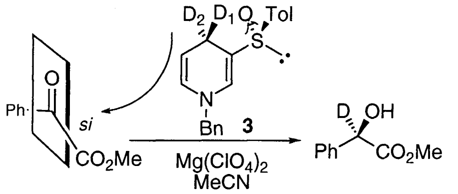
A of the *p*-tolylsulfinyl group as the 2-methyl derivative **2**, both in the ground and transition states.

Next, in order to examine the stereospecificity of the 4-hydrogen transfer in compound **1**, the 4-deuterated NADH model compounds, (*R*)-**3** (24% de), (*S*)-**3** (32% de) and **4**, were prepared by combinational redox reactions between 1-propyl-1,4-dihydronicotinamide **5** or its 4-D_2 derivative **6** and a pyridinium salt **7**[3b] or the 4-D congener **8**,[7] as illustrated in Scheme 2.[8] Thus obtained 1,4-dihydropyridines were used for asymmetric reduction of methyl benzoylformate. The results are summarized in Table 2, which shows that the deuteration ratio of α-hydrogen in methyl (*R*)-mandelate is completely coincident with that of the pro-*S* hydrogen in the dihydropyridines.



Scheme 2. *Reagents and conditions*: i, MeOH, r.t., 3 h, quant.

Table 2. Reduction of methyl benzoylformate with 4-deuterated model compounds **3**[a]



NADH Models	Ratio of deuteration/%[b]		
	D_1	D_2	(*R*)-Mandelate
(*R*)-**3**	62	38	39
(*S*)-**3**	34	66	66

[a] See footnote in Table 1. [b] Determined by ^{1}H-NMR.

Furthermore, a kinetic isotope effect of the asymmetric reaction with compound **1** and **4** was measured, monitoring by the UV absorption at 330 nm characteristic of 1,4-dihydropyridine moiety. As a result, the primary kinetic isotope effect between two compounds was not observed.[9] These results not only show that the pro-*S* hydrogen is only transferred to the prochiral ketone from the *si* face, but also suggest the possibility that the model reaction proceeds *via* a three-step mechanism (electron, proton, and then electron transfers)[10] and the rate determining step should be situated at the first electron transfer step.

In conclusion, the evidence of stereospecific transfer process of the hydrogen at C-4 which is *syn* to the S-O bond of the sulfinyl group. This strongly suggests that, in the reduction with **1** and **2**, the S-O bond works in place of the amide carbonyl group of NAD(P)H.[11]

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References and Notes

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