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Studies on Novel and Chiral 1,4-Dihydropyridines. IV.[1] Mechanistic Aspects of the Asymmetric Reduction with Chiral NADH Model Compounds, (S_S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridines[2]

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Abstract: In the reduction of ketones with NADH mimics, (S_S)-1-substituted 3-(*p*-tolylsulfinyl)-1,4-dihydropyridines **1**, the stereospecific transfer of one of the C-4 hydrogens, which is *syn* to the S-O bond, was experimentally revealed to be involved by employing the 2-methyl derivative **2** and the 4-deuterated derivatives **3a** and **3b**. The transition state model of this reaction was also proposed by consideration of the results obtained. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

In the enzymatic reduction requiring NAD(P)H as a coenzyme, it is known that, depending on the enzyme, one of the prochiral hydrogens at C-4 (H_S or H_R) of NAD(P)H as well as the enantioface of the ketone is strictly differentiated and is stereospecifically transferred.[3] It was reported that the amide group of NAD(P)H does not occupy the same plane with the C_2-C_3 double bond in the transition state and plays an important role in this stereospecific hydrogen transfer.[4] Calculation studies on a NAD(P)H model also revealed that the hydrogen transfer to a positively charged species is assisted by the amide dipole and that one of the hydrogens at C-4, which is in the *syn* arrangement to the carbonyl bond, is stereospecifically transferred.[5]

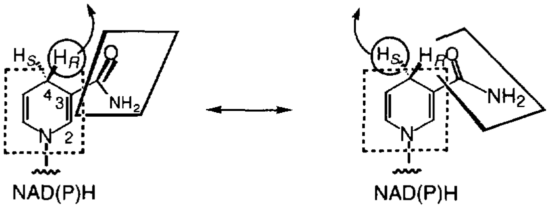
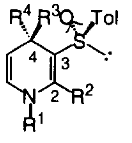


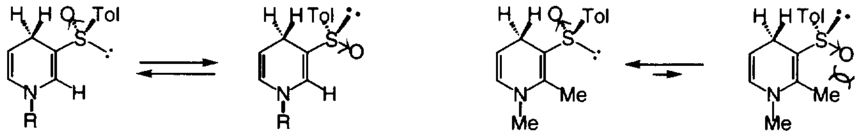
Fig. 1.

On the other hand, a number of NADH model compounds with various chiral auxiliaries have been reported[6] since Ohno and co-workers disclosed the first example of asymmetric reduction by such compound.[7] Similarly to the enzymatic reactions, the stereospecific transfer of the hydrogen at C-4 is naturally believed to be involved in the asymmetric reductions with the model compounds as well, but this has not been clearly demonstrated so far.

In previous papers, we have reported novel and highly efficient NADH chiral model compounds, 1-substituted 3-(*p*-tolylsulfinyl)-1,4-dihydropyridines **1**, which enantioselectively reduce ketones in the presence of magnesium or zinc salt to the corresponding alcohols.[1,8] The sulfinyl group could be taken as a three-dimensional analog of an amide group and, as a consequence, would be a useful functional group to study the stereospecific hydrogen-transfer at C-4 in the model system. Since, in the reaction of **1**, the conformation of the sulfinyl group apparently is deeply involved in this phenomenon, it is quite important to obtain relevant information on this point. The conformation of the sulfinyl group of **1** in the crystalline form was revealed to be conformation **1A** by X-ray crystallographic analysis, and their ^{1}H NMR spectra also suggested that compound **1** existed mainly in conformation **1A**. This predominance of conformation **1A** is explainable in terms of the allylic 1,3-strain[9] and the dipole repulsion. However, in spite of this information, the other conformation **1B**, having an oxygen in the same plane of the double bond, in the transition state could not be excluded completely for the following reasons. 1) In general, typical vinyl sulfoxides are known to have the same conformation with **1B**[9] and, furthermore, a number of stereoselectivities in relation to the sulfinyl group have been explained by taking this conformation into account.[10] 2) As described later, the conformation **1A** was shown to be *ca.* 1 kcal/mol less stable than the conformation **1B** by PM3 calculations. In order to clarify this aspect, we examined the reduction with 2-methyl derivative **2**, in which the conformation of the sulfinyl group should be restricted as shown in **2A** to avoid the steric repulsion between the C-2 methyl and sulfinyl oxygen in conformation **2B**. Next, to investigate the stereospecificity of the hydrogen-transfer at C-4, we synthesized the 4-deuterated derivatives **3a-c** and examined the reductions with these compounds. In this paper, we describe these studies in detail, demonstrating the first experimental evidence of the stereospecific hydrogen-transfer in the model system and also wish to discuss the mechanistic aspects of the reduction of ketones with our NADH model compound **1**.



1 : R^1= alkyl, R^2, R^3, R^4= H
2 : R^1, R^2= Me, R^3, R^4= H
3a : R^1= Bn, R^2, R^3= H, R^4= D
3b : R^1= Bn, R^2= H, R^3= D, R^4= H
3c : R^1= Bn, R^2= H, R^3, R^4= D



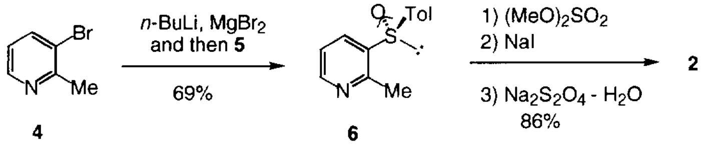
1A **1B** **2A** **2B**

Fig. 2.

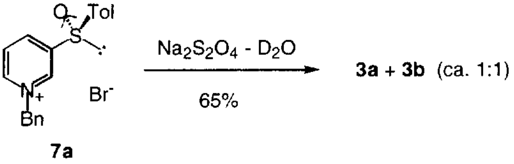
RESULTS AND DISCUSSION

*Syntheses of 2-methyl derivative **2** and 4-deuterio derivatives **3a-c***

Synthesis of **2** was easily accomplished starting from 3-bromo-2-methylpyridine (**4**)[11] as shown in Scheme 1. The organomagnesium derivative of compound **4** was coupled with (1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate (**5**)[12] to afford **6** in 69% yield. Quaternization of the pyridine **6** followed by reduction with sodium dithionite ($Na_2S_2O_4$) gave the desired 2-methyl derivative **2** in 86% yield.

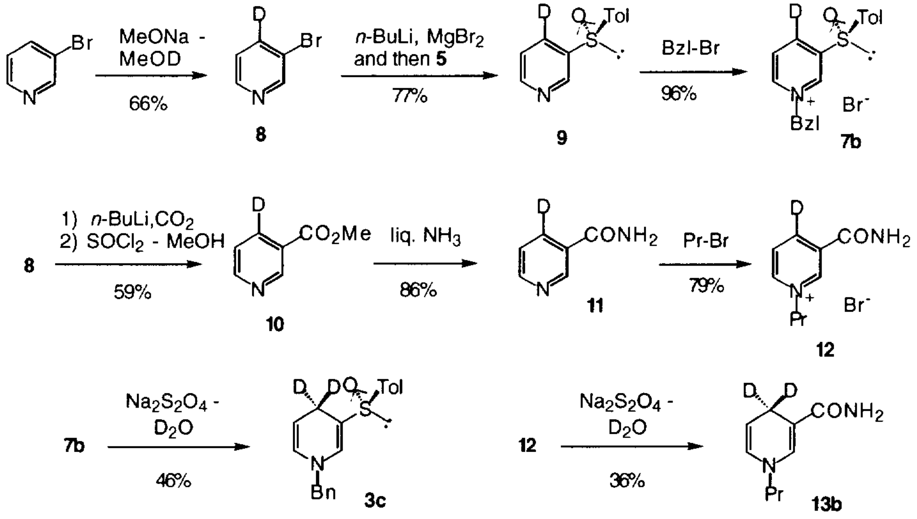


Scheme 1



Scheme 2

On the other hand, diastereoselective synthesis of 4-deuterated derivatives **3a** and **3b** was somewhat troublesome. The stereoselective synthesis of similar compounds by chemical methods had been reported only by a few groups[13]. In our case, reduction of pyridinium salt **7a** under the typical conditions ($Na_2S_2O_4$ in D_2O) only afforded a 1:1 mixture of the 4-deuterated derivatives **3a** and **3b** (Scheme 2).

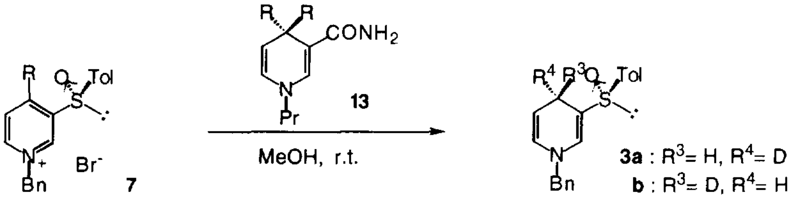


Scheme 3

Next, we attempted to prepare **3a** and **3b** by hydrogen transfer reaction between the sulfinylpyridinium salts **7** and the dihydronicotinamides **13**. 3-Bromopyridine was regiospecifically deuterated with MeONa in MeOD by a modification of the known method[14] to give 4-deuterated derivative **8** in 66% yield and the ratio of deuteration was almost 100% (^{1}H NMR analysis). Deuteriopyridine **8** was converted into the pyridinium salt **7b** *via* sulfinylpyridine **9** according to the same procedure described above.[8b] Reduction of **7b** with $Na_2S_2O_4$ in D_2O afforded the 4,4-dideuterio derivative **3c** in moderate yield. On the other hand, **8** was also transferred to 4,4-dideuterio-1,4-dihydronicotinamide **13b** as follows. Carboxylation of **8** *via* lithiation and subsequent esterification afforded methyl 4-deuterionicotinate (**10**) in 59% yield, which was reacted with ammonia to give 4-deuterionicotinamide (**11**) in 86% yield. According to the literature,[15] treatment of **11** with *n*-propyl bromide gave the pyridinium salt **12** in 79% yield, which was reduced with $Na_2S_2O_4$ in D_2O to afford the desired 4,4-dideuterio-1,4-dihydronicotinamide (**13b**) in 36% yield (Scheme 3).

The hydrogen transfer reaction of the pyridinium salt **7a** with **13b** in MeOH afforded **3a** as the major product, while that of the 4-deuteriopyridinium salt **7b** with 1,4-dihydronicotinamide **13a** afforded **3b** as the major product as shown in Table 1. These results indicate that the hydrogen or deuterium transfer occurred mainly from the *si*-face of the pyridinium salt **7** to avoid the steric hindrance of the *p*-tolyl group.[16]

Table 1. Hydrogen exchange reaction of pyridinium salts **7** with dihydronicotinamides **13**.

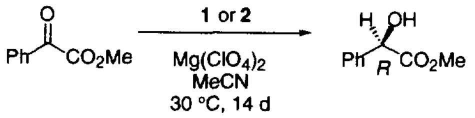


Pyridinium Salt **7**	Dihydronicotine **13**	Yield (**3a** : **3b**)
7a : R = H	**13b** : R = D	quant. (66 : 34)
7b : R = D	**13a** : R = H	quant. (38 : 62)

Reductions with 2-methyl derivative 2 and 4-deuterio derivatives 3a-c; Mechanistic considerations

Reduction of methyl benzoylformate with **2** was achieved under the same conditions reported for **1** [in acetonitrile (MeCN), **2**/Mg^{2+}/methyl benzoylformate = 1/1/1, at 30 °C, in the dark][1] and gave methyl (*R*)-mandelate in good chemical yield with excellent enantioselectivity as shown in Table 2. These results were basically the same as those obtained with **1** and strongly indicate that the reaction path, including the transition state, of **2** would be identical to that of **1**.

Table 2. Reduction of methyl benzoylformate with model compound **1** or **2**.



NADH Model	Yield %	ee %
1 (R^1= Bn)	77	94
2	72	99

The conformations of the sulfinyl group at C-3 of **1** and **2** were investigated by PM3 calculations and the results are shown in Fig. 3. In the case of **1**, the existence of two stable conformations, **1A** and **1B**, was suggested and the conformation **1B** was estimated to be *ca.* 1 kcal/mol more stable than the other **1A**. However, as reported previously, the ^{1}H NMR spectrum of **1** showed that the hydrogens at C-4 are highly differentiated from each other by the neighboring sulfinyl group and this is well explained by taking the conformation **1A** into account.[8b] On the other hand, the result of PM3 calculations of **2** indicated that the only conformation **2A** is the most stable as expected and the conformation corresponding to **1B** must be excluded. In ^{1}H NMR spectra of **1** and **2**, the hydrogens at C-4 are observed quite similarly, which demonstrates that, as expected, these hydrogens of **1** are affected by the sulfinyl group identically with those of **2**.

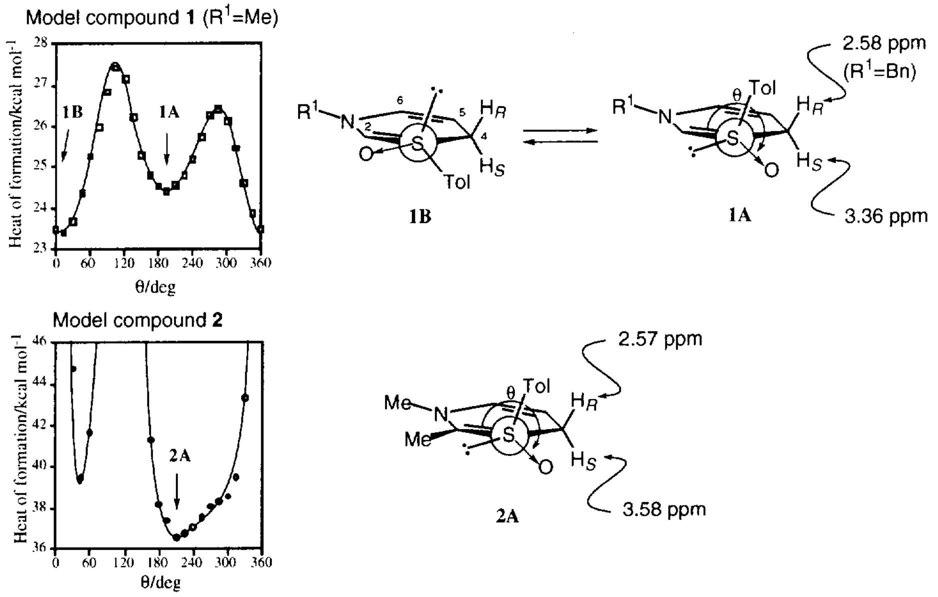
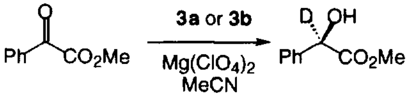


Fig. 3. Conformational analysis of the sulfinyl group of **1** and **2** by PM3 calculations

From these results, it appears that the reaction of **1** proceeds *via* the same conformation to that of **2**, namely, *via* **1A**. Encouraged by this finding, we examined the stereospecificity of the hydrogen-transfer by employing the 4-deuterio derivatives **3a** and **3b**. The results of the reduction of methyl benzoylformate with 4-deuterio compounds **3a** and **3b** are summarized in Table 3, which shows that the deuteration ratio of methyl (*R*)-mandelate completely reflects that of the pro-*S* hydrogen (R^4). This means that the hydrogen which is in the *syn* arrangement to the S-O bond is stereospecifically transferred to benzoylformate from its *si*-face. To the best of our knowledge, this is the first experimental evidence in the model system, which clearly indicates that one of the hydrogens at C-4 is clearly recognized and specifically transferred to a prochiral ketone.

Table 3. Reduction of methyl benzoylformate with 4-deuterated model compound **3a** or **3b**.



NADH Model	Ratio of deuteration %[a]		
	R^3	R^4	(*R*)-Mandelate
3a	34	66	66
3b	62	38	39

[a] Determined by ^{1}H-NMR.

Kinetic studies using the 4,4-dideuterated model compound **3c** were also carried out by tracing the UV absorption at 330 nm, which is characteristic for the 1,4-dihydropyridine moiety.[17] No difference in the reaction rate between the model compound **1** (R = Bn) and the 4,4-dideuterated model compound **3c** was observed (k_H: 1.3×10^{-2} M^{-1} s^{-1}, k_D: 1.2×10^{-2} M^{-1} s^{-1}). This finding differs from many cases of other NADH model compounds having an amide group at C-3.[18] Although two mechanisms, a one-step mechanism (hydride transfer)[19] and a three-step mechanism (electron, proton, and electron transfer),[20] were proposed for the NADH reduction, the latter is becoming to be considered mainly. From the results described above, the reaction with our model compounds **1** could proceed *via* a three-step mechanism and the rate-determining step would appear to be the step of the first electron transfer.

In previous papers,[1,21] we revealed that the formation of the ternary complex is essential for the reaction with our model compound **1** and also mentioned that the sulfinyl oxygen would be responsible for coordination with Mg^{2+}. Although some possible structures of the ternary complex for asymmetric reductions with NADH mimics have been proposed,[22] the one proposed by Kakinuma *et al.*,[23] wherein the amido carbonyl group is responsible for coordination with Mg^{2+}, appears to be the most reasonable for our model compound. Taking all the results obtained into account, the ternary complex proposed in Fig. 4 most reasonably explains all the apparent phenomena. It is noteworthy and quite interesting that, in our model compound, the S-O bond of the sulfinyl group could play an important role as does the amido carbonyl group in the enzymatic system. Apparently, the stereochemical relation of the ternary complex can explain the preferential transfer of the pro-*S* hydrogen (H_S) which is in the *syn* arrangement to the S-O bond. In addition, the S-O bond, like an amido carbonyl group, could also assist the stereospecific release of the hydrogen (H_S).[24] As illustrated in Fig. 5, this would suggest the possibility that the S-O bond could lower the energy level of the H_S transfer effectively due to its favorably restricted conformation compared with that of an amide group and might make the first electron-transfer the rate-determining step as a result.

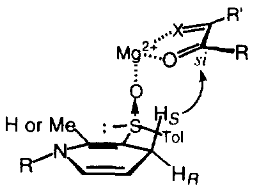


Fig. 4. Possible structure of the ternary complex

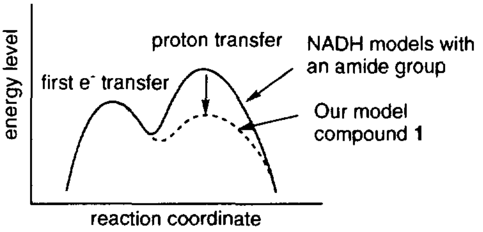


Fig. 5. Relation between the energy level and the reaction coordinate

In conclusion, we clearly proved that, in asymmetric reduction with our NADH mimic **1**, one of the C-4 hydrogens which is in the *syn* arrangement to the S-O bond is stereospecifically transferred to ketones by employing the 2-methyl derivative **2** and 4-deuterio derivatives **3a** and **3b**. This is the first experimental evidence in a model system, and although the detailed pathway remains to be elucidated, it is deduced from the fact that there was no kinetic isotope effect that the reduction with **1** apparently proceeds *via* a three-step mechanism.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-200 spectrometer, and ^{1}H NMR spectra were taken on a Varian VXR-200 (200 MHz), JEOL EX-270 (270 MHz) or JEOL GX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Low resolution mass spectra (MS) were obtained with a Shimadzu GCMS-QP1000 or a JEOL JMS-D300 instrument, and high resolution mass spectra (HRMS) with a JEOL JMS-D300 instrument. Optical rotations were recorded on a JASCO DIP-370 instrument. Dihydropyridine **1** was prepared according to the procedure previously reported[8h] and 1-propyl-1,4-dihydropyridine-3-carboxamide (**13a**) was prepared according to the literature.[15] Anhydrous acetonitrile was obtained by twice distillation over CaH_2 under a nitrogen atmosphere after reflux with CaH_2. Magnesium perchlorate and methyl benzoylformate were purchased from Wako Pure Chemical Industries, Ltd. and Tokyo Kasei Kogyo Co., Ltd., respectively, and used without further purification. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used.

(S_S)-2-Methyl-3-(*p*-tolylsulfinyl)pyridine (6). A solution of 3-bromo-2-methylpyridine[11] (1.00 g, 5.81 mmol) in dry ether (15 ml) was added dropwise to a stirred solution of *n*-BuLi (1.5 M in hexane, 4.3 ml, 6.4 mmol) in dry ether (30 ml) at -78 °C. Stirring was continued for 30 min at -78 °C, then a solution of magnesium bromide (1.18 g, 6.4 mmol) in dry tetrahydrofuran (THF, 26 ml) was added dropwise to the stirred reaction mixture at the same temperature. After stirring was continued for 30 min, **5** (1.75 g, 5.81 mmol) in dry benzene (6 ml) was added to the stirred reaction mixture. The reaction mixture was stirred for 1 h, partitioned with saturated NH_4Cl solution, and extracted with $CHCl_3$. Usual work-up and purification by SiO_2 column chromatography [AcOEt-hexane (7:1)] afforded **6** (0.92 g, 69%) as a light yellow solid, which was recrystallized from benzene-*i*-Pr_2O to give colorless needles, mp 61.5-62.5°C. $[\alpha]_D^{22}$ -45.7 ° (*c* 0.93, $CHCl_3$). IR ($CHCl_3$): 2970, 1570, 1430, 1080, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.51 (3H, s), 7.27, 7.50 (4H, AA'BB' type, *J* = 8 Hz), 7.39 (1H, dd, *J* = 8, 5 Hz), 8.31 (1H, dd, *J* = 8, 2 Hz), 8.57 (1H, dd, *J* = 5, 2 Hz). MS *m/z*: 231 (M$^+$, 25.1%), 215 (5.9%), 214 (21.9%), 123 (6.4%). *Anal.* Calcd for $C_{13}H_{13}NOS$: C, 67.45; H, 5.72; N, 6.13; S, 13.62%. Found: C, 67.50; H, 5.66; N, 6.06; S, 13.86%.

(S_S)-1,2-Dimethyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (2). A suspension of **6** (191 mg, 0.83 mmol) in dimethyl sulfate (0.10 ml, 1.06 mmol) was heated at 60 °C for 10 h. After cooling to room temperature, the precipitate was collected, washed with ether, and dried under reduced pressure. Under an Ar atmosphere, the residue was dissolved in CH_2Cl_2 (8 ml) and NaI (156 mg, 1.05 mmol) was added and stirred for 30 min at room temperature in the dark. An aqueous solution (3 ml) of $Na_2S_2O_4$ (160 mg, 0.93 mmol) and 1 M $NaHCO_3$ solution (8 ml) were added to the reaction mixture and the whole was stirred for 3 h at room temperature, then the CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were worked up as usual to afford **2** (176 mg, 86%) as a light yellow solid, mp 48-49°C. $[\alpha]_D^{24}$ +274.5° (*c* 0.97, $CHCl_3$). IR ($CHCl_3$): 2975, 1680, 1590, 1380, 1320 1000 cm^{-1}. ^{1}H NMR (C_6D_6) δ: 1.72 (3H, s), 2.02 (3H, s), 2.06 (3H, s), 2.57 (1H, dm, *J* = 18 Hz), 3.58 (1H, dm, *J* = 18 Hz), 4.36 (1H, dt, *J* = 8, 4 Hz), 5.09 (1H, dt, *J* = 8, 2 Hz), 6.99, 7.65 (4H, AA'BB', *J* = 8 Hz). MS *m/z*: 247 (M$^+$, 3.6%), 246 (M$^+$-H, 19.6%), 231 (M$^+$-O, 68.5%), 230 (M$^+$-OH, 54.1%). HRMS: 247.1039 (M$^+$, calcd for $C_{14}H_{17}NOS$: 247.1031).

[4-$^2H_1$]-3-Bromopyridine (8). Under a N_2 atmosphere, 3-bromopyridine (1.64 g, 10.5 mmol) was added dropwise to

3 M MeONa-MeOD solution (10 ml), which was prepared by addition of Na (690 mg, 30 mmol) into MeOD (10 ml). The mixture was refluxed for 24 h and after cooling, the water was added and extracted with ether. The organic layer was washed with brine and dried and concentrated. The whole procedure was repeated twice and the residue was distilled (bp 58 °C/ 8 mmHg) to afford **8** (1.08 g, 66%) as a colorless oil. The deuteration ratio of the 4-hydrogen was determined to be almost 100% by ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$) δ: 7.19 (1H, dd, *J* = 5, 1 Hz), 8.52 (1H, d, *J* = 5 Hz), 8.58 (1H, d, *J* = 1 Hz). HRMS: 157.9588, 159.9571 (M^+, calcd for C_5H_3NBrD: 157.9588, 159.9576).

(S_S)-[4-^{2}H$_1$]-1-Benzyl-3-(*p*-tolylsulfinyl)pyridinium Bromide (7b). Pyridinium salt **7b** was prepared from **8** *via* **9** according to the procedure reported previously.[8b] Physical properties of **9** and **7b** are as follows. **(S_S)-[4-^{2}H$_1$]-3-(*p*-tolylsulfinyl)pyridine (9).** Colorless needles, mp 60-61 °C. ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, s), 7.23, 7.54 (4H, AA'BB', *J* = 8 Hz), 7.39 (1H, dd, *J* = 5, 1 Hz), 8.65 (1H, d, *J* = 5 Hz), 8.74 (1H, d, *J* = 1 Hz). HRMS: 218.0628 (M^+, calcd for $C_{12}H_{10}NOSD$: 218.0625). **7b.** A white solid, mp 162-164 °C. ^{1}H NMR (DMSO-d_6) δ: 2.36 (3H, s), 5.92 (2H, s), 7.4-7.8 (9H, m), 8.23 (1H, d, *J* = 6 Hz), 9.24 (1H, d, *J* = 6 Hz), 9.60 (1H, s).

(S_S)-[4,4-^{2}H$_2$]-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (1c). Under an Ar atmosphere, a solution of $Na_2S_2O_4$ (167 mg, 0.96 mmol) in D_2O (2 ml) was added to a stirred solution of the mixture of **7b** (250 mg, 0.64 mmol) and $NaHCO_3$ (840 mg, 10 mmol) in CH_2Cl_2 (10 ml) and D_2O (8 ml) at room temperature. Stirring was continued for 3 h in the dark, then the CH_2Cl_2 layer was separated, and the D_2O layer was extracted with CH_2Cl_2. The combined organic layers were worked up as usual to afford **3c** (78 mg, 46%) as a light yellow solid, mp 107-110 °C. ^{1}H NMR (C_6D_6) δ: 2.00 (3H, s), 3.54 (2H, s), 4.27 (1H, d, *J* = 8 Hz), 5.19 (1H, d, *J* = 8 Hz), 6.43 (1H, s), 6.90-7.70 (9H, m).

Methyl [4-^{2}H$_1$]-Pyridine-3-carboxylate (10). Under a N_2 atmosphere, a solution of *n*-BuLi (1.6 M in *n*-hexane, 0.69 ml, 1.0 mmol) was added dropwise to a stirred solution of **8** (159 mg, 1.0 mmol) in dry ether (2.5 ml) at -78 °C. After stirring was continued for 20 min at -78 °C and for 10 min at 0 °C, CO_2 gas was bubbled into the reaction mixture for 2 h at 0 °C. The solution was concentrated under vacuum, and the residue was dissolved into absolute MeOH (1 ml). To the mixture a solution of thionyl chloride (0.9 ml, 12.3 mmol) in absolute MeOH (3 ml) was added dropwise at 0 °C, and the whole mixture was stirred for 15 h at 25 °C. After addition of aq. $NaHCO_3$ and CH_2Cl_2, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were worked up as usual to afford **10** (81 mg, 59%) as a white solid, mp 35-37 °C. ^{1}H NMR ($CDCl_3$) δ: 4.00 (3H, s), 7.40 (1H, d, *J* = 5 Hz), 8.79 (1H, d, *J* = 5 Hz), 9.23 (1H, d, *J* = 5 Hz).

[4-^{2}H$_1$]-Pyridine-3-carboxamide (11). Excess amount of liq. NH_3 was added to a stirred solution of **10** (273 mg, 1.98 mmol) in absolute MeOH (5 ml) at -78 °C. After stirring was continued for 36 h, the reaction mixture was evaporated under vacuum. The residue was recrystallized from acetone to give **11** (210 mg, 86%) as a colorless rods, mp 130-133 °C (lit.[25] 132-133 °C). ^{1}H NMR ($CDCl_3$) δ: 7.54 (1H, d, *J* = 4 Hz), 8.69 (1H, d, *J* = 4 Hz), 9.02 (1H, s).

[4,4-^{2}H$_2$]-1-Propyl-1,4-dihydropyridine-3-carboxamide (13b). Dideuterio derivatives **13b** were prepared from **11** *via* **12** according to the literature.[17] Physical properties of **12** and **13b** are as follows. **[4-^{2}H$_1$]-1-Propyl-3-carbamoylpyridinium Bromide (12).** A white solid, mp 169-174 °C. ^{1}H NMR (DMSO-d_6) δ: 0.92 (3H, t, *J* = 7 Hz), 2.01 (2H, sx, *J* = 7 Hz), 4.68 (2H, t, *J* = 7 Hz), 8.34 (1H, d, *J* = 6 Hz), 9.28 (1H, d, *J* = 6 Hz), 9.58 (1H, s). **13b.** A light yellow solid, mp 88-90 °C (lit.[26] 92-93 °C). ^{1}H NMR ($CDCl_3$) δ: 0.97 (3H, t, *J* = 7 Hz), 1.59 (2H, sx, *J* = 7 Hz), 3.13 (2H, t, *J* = 7 Hz), 4.77 (1H, d, *J* = 8 Hz), 5.34 (2H, br s), 5.75 (1H, dd, *J* = 2, 8 Hz), 7.10 (1H, d, *J* = 2 Hz).

Typical Procedure for Hydrogen Exchange Reaction. Under a N_2 atmosphere, a solution of **7a** (30 mg, 0.18 mmol) in absolute MeOH (2 ml) was added to a stirred solution of **13b** (60 mg, 0.15 mmol) at room temperature. Stirring was continued for 3 h in the dark, then the solution was diluted with CH_2Cl_2 and water. The CH_2Cl_2 layer was separated, and the D_2O layer was extracted with CH_2Cl_2. The combined organic layers were worked up as usual to afford 4-deuterated derivative **3a** as the main product (**3a** : **3b** = 66 : 34). Reaction of **7b** with **13a** according to the same procedure gave **3b** as the main product (**3a** : **3b** = 38 : 62). The ratio of **3a** and **3b** was determined by ^{1}H NMR spectra.

Typical Procedure for Reduction of Methyl Benzoylformate with Model Compound. Under an Ar atmosphere, a solution of model compound **1** (R^1=Bn, 93 mg, 0.3 mmol) in anhydrous MeCN (3 ml) was added to a stirred solution of methyl benzoylformate (49 mg, 0.3 mmol) and $Mg(ClO_4)_2$ (67 mg, 0.3 mmol) in anhydrous MeCN (6 ml) at room temperature. The whole mixture was stirred at 30 °C in the dark for 14 days. After dilution with H_2O (2 ml) and CH_2Cl_2 (20 ml), the organic layer was separated, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (AcOEt) to afford methyl mandelate.

Computation. The MOPAC (version 6.03) molecular orbital package[27] utilizing the MNDO-PM3 Hamiltonian[28] was used for the semi-empirical MO calculations. All initial structures used for the MO calculations were taken from the X-ray structure of **1**.[8b] Numerical calculations were performed with a SX-2N computer system at the Computation Center, Osaka University.

Kinetic Measurements. Kinetic measurements were carried out by using a SHIMADZU UV-2100PC spectrometer under pseudo-first-order conditions in the presence of 30-fold excess of Mg^{2+} ion and methyl benzoylformate in anhydrous MeCN at 303 K under an Ar atmosphere. The kinetics were followed by observing the decrease in the intensity at 330 nm. The initial concentrations are as follows; [**1**] = [**3c**] = 0.2 mM, [Mg^{2+}] = [methyl benzoylformate] = 6.0 mM. The k_H/k_D value calculated was nearly 1.1 (k_H: 1.3×10^{-2} M^{-1} s^{-1}, k_D: 1.2×10^{-2} M^{-1} s^{-1}).

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