Studies on Novel and Chiral 1,4-Dihydropyridines. I. Synthesis and Conformational Analysis of Novel NADH Model Compounds, *N*-Substituted (*S*)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridines[1)]

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Novel NADH model compounds, (S_S)-1-alkyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridines (2) and (R_S)-1-benzyl-3-[1-oxo-2-(*p*-tolylsulfinyl)ethyl]-1,4-dihydropyridine (3), were synthesized. ^{1}H-NMR study and X-ray analysis of 2 revealed its preferred conformation.

Key words NADH model; 1,4-dihydropyridine; chiral *p*-tolylsulfinyl group; conformational analysis; ^{1}H-NMR; X-ray analysis

Since Ohno and coworkers reported the first example of asymmetric reduction of a ketone with a model compound of reduced pyridine adenine dinucleotide (**1**, NADH or NADPH),[2)] numerous examples of such asymmetric reductions have been reported.[3)] Chiral NADH model compounds having chiral groups on the ring nitrogen or the C(3)-amido nitrogen atom are known to show rather low asymmetric induction ability in the reduction of ketones, probably due to the long distance between the chiral and reactive centers in the model compounds.[4)] On the other hand, highly enantioselective reductions have been achieved by the use of NADH model compounds with a chiral C(4) center,[5)] or with two chiral functional groups at the C(3) and C(5) positions,[6)] or with a C_2 symmetrical structure.[7)] We are interested in developing research on chiral NADH model compounds with simple structure, but with high asymmetric induction ability for ketone reductions.

The great majority of the known NADH model compounds have a carbonyl group (*e.g.*, an amide or an ester) at the C(3) position in the 1,4-dihydropyridine nucleus, and this functional group plays an important role in determining the stability and reactivity of the labile dihydropyridine moiety. Now we have designed a novel, chiral NADH model compound **2**, which possesses an asymmetric sulfinyl group at the C(3) position in place of an amide. A sulfinyl group has a moderate electron-withdrawing character similar to that of an amido group, and has potential as a chiral auxiliary for many kinds of asymmetric reactions.[8)] Therefore, the C(4) prochiral protons in the dihydropyridine **2** are expected to be diastereotopically distinguished by the neighboring chiral *p*-tolylsulfinyl group and the hydrogen transfer from the model compound **2** to a carbonyl compound should occur in a highly stereoselective manner. We also wished to prepare the 1,4-dihydropyridine **3**, in which the chiral *p*-tolylsulfinyl group is attached indirectly at the C(3) position, as an alternative NADH model compound. In this paper, we describe the synthesis and conformational analysis of the novel and simple chiral NADH model compounds **2** and **3**.

Synthesis of the NADH Model Compounds 2 and 3

3-Bromopyridine was lithiated with *n*-butyllithium (*n*-BuLi) according to the literature[9)] and then treated with (−)-menthyl (*S*)-*p*-tolylsulfinate[10)] (**4**) to afford the desired 3-(*p*-tolylsulfinyl)pyridine (**5**) in 73% yield (method A). The enantiomeric excess (ee) value of this compound was found to be 62% by means of a lanthanide-induced shift (LIS) experiment. In the ^{1}H-NMR spectrum of the product **5**, the C(4) hydrogen resonates at 7.96 ppm and this signal splits in two peaks in a ratio of 81 : 19 at 10.87 and 11.17 ppm upon addition of 20 mol% of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) (Eu(tfc)$_3$),[11)] while the integral ratio of the two peaks is 50:50 in the case of racemic **5** prepared from 3-pyridyllithium and methyl (±)-*p*-tolylsulfinate.[12)] In each run of method A, the same reaction gave a different ee value for the product **5**. To our knowledge, this is the first example of racemization of the chiral sulfinyl group under these conditions.[13)] This problem was overcome as

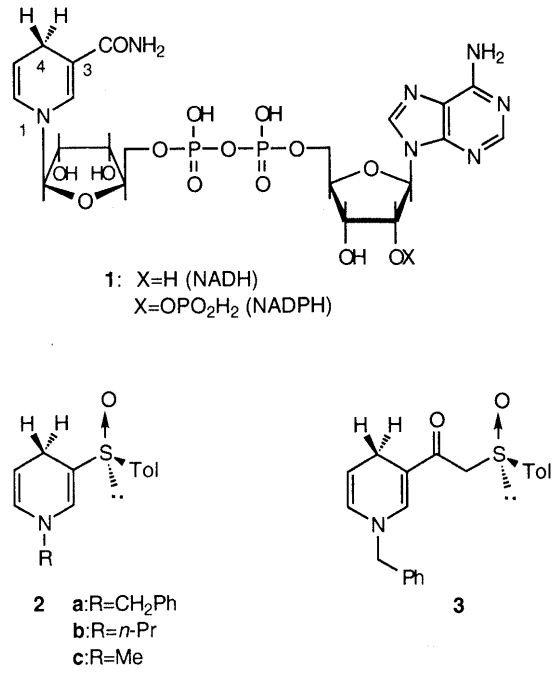

Fig. 1. The Structures of NADH (NADPH) and Our Model Compounds

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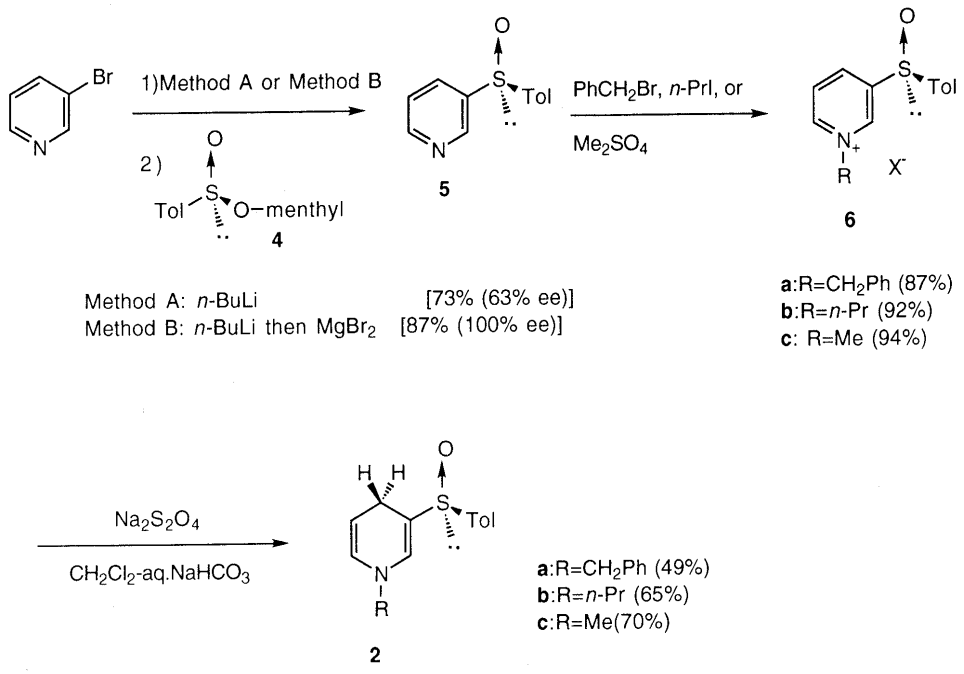

Chart 1

follows. According to the known method,[14] 3-pyridyllithium was converted into the organomagnesium derivative, which was then allowed to react with the optically active sulfinate **4** to afford **5** in 87% yield (method B) and in almost 100% ee. Quaternization of the pyridine **5** in the usual manner with benzyl bromide, *n*-propyl iodide, and dimethyl sulfate gave the pyridinium salts **6a**—**c** in 87, 92, and 94% yields, respectively. The partial reduction of **6a** was achieved by treatment with sodium dithionite in dichloromethane–water to afford the desired 1,4-dihydropyridine **2a** in 49% yield. Similarly the salt **6b** was also reduced to **2b** in 65% yield. In the case of the *N*-methyl pyridinium salt **6c**, the reduction was found to take place under the same conditions only after the counter anion had been exchanged to iodide, providing **2c** in 70% overall yield. The structures of these dihydropyridine derivatives **2a**—**c** were confirmed by spectroscopic evidence. In the UV spectra of these compounds **2a**—**c**, the maximum absorption was observed at *ca.* 330 nm, which is characteristic of 1,4-dihydropyridine structure.[15] In the ^{1}H-NMR spectra, the C(4) protons resonated at near 2.4 and 3.0 ppm and the olefinic protons (C(2)-H, C(5)-H, and C(6)-H) at near 6.6, 4.5, and 5.6 ppm, respectively (Table 1).

Table 1. ^{1}H-NMR Data (δ ppm in $CDCl_3$) for the Dihydropyridines **2a**—**c**

	2a	**2b**	**2c**
C(2)-H	6.87 (d, J=1.5 Hz)	6.63 (d, J=1.5 Hz)	6.62 (d, J=1.5 Hz)
C(4)-H	2.55, 3.16 (dm, J=18 Hz)	2.40, 3.05 (dm, J=18 Hz)	2.38, 3.07 (dm, J=18 Hz)
C(5)-H	4.67 (dd, J=9, 4 Hz)	4.50 (dd, J=9, 4 Hz)	4.54 (dd, J=9, 4 Hz)
C(6)-H	5.79 (dq, J=9, 1.5 Hz)	5.60 (dq, J=9, 1.5 Hz)	5.58 (dq, J=9, 1.5 Hz)
Tol	2.44 (3H, s) 7.41, 7.56 (4H, AA′BB′ type J=8.5 Hz)	2.34 (3H, s) 7.19, 7.41 (4H, AA′BB′ type J=8.5 Hz)	2.38 (3H, s) 7.23, 7.43 (4H, AA′BB′ type J=8.5 Hz)
R	4.37 (2H, s) 7.40 (5H, br s)	0.92 (3H, t, J=7.5 Hz) 1.58 (2H, sextet, J=7.5 Hz) 3.03 (2H, t, J=7.5 Hz)	2.92 (3H, s)

The other model compound **3** was synthesized by the use of methyl nicotinate and (*R*)-methyl *p*-tolyl sulfoxide (**7**)[10] as starting materials. The carbanion generated from **7** by treatment with lithium diethylamide was allowed to react with methyl nicotinate, affording the ketosulfoxide **8** in 72% yield, and this was treated with benzyl bromide to give the quaternary salt **9** in 92% yield. Sodium dithionite reduction of **9** afforded only the desulfinated product under the usual conditions, while reduction of **9** with sodium cyanoborohydride[16] afforded the desired 1,4-dihydropyridine derivative **3** in 41% yield. The dihydropyridine structure of **3** was confirmed by spectroscopic evidence. The maximum absorption in the UV spectrum appeared at 328 nm and three olefinic protons in the ^{1}H-NMR spectrum were found to resonate at 5.01 (C(5)-H), 5.80 (C(6)-H), and 7.21 ppm (C(2)-H).

Conformational Analysis of 2 and 3 It is noteworthy that, in the ^{1}H-NMR spectra of **2**, a large difference of the chemical shifts between the two prochiral C(4) protons was observed ($\Delta\delta$ = *ca.* 0.6 ppm). As shown in Fig. 2, this is one of the largest chemical shift differences between the two prochiral C(4) protons of the chiral 1,4-dihydropyridines so far reported.[17] This significant feature suggests that the conformational flexibility of **2** is greatly restricted and thereby the prochiral C(4) protons are highly diastereotopically distinguished by the neighboring *p*-tolylsulfinyl group.

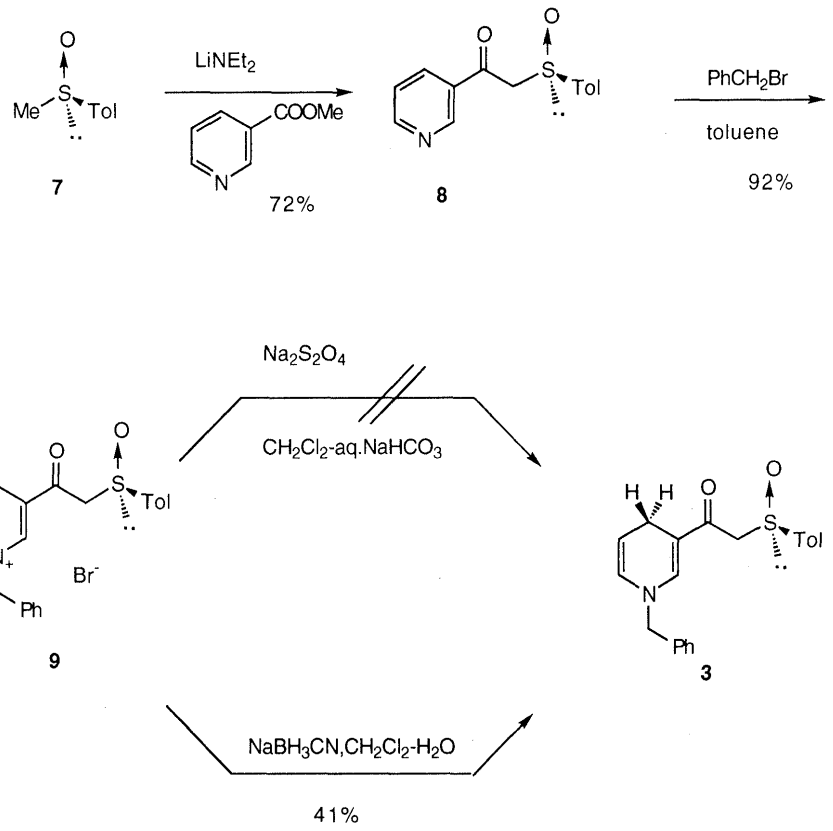

Chart 2

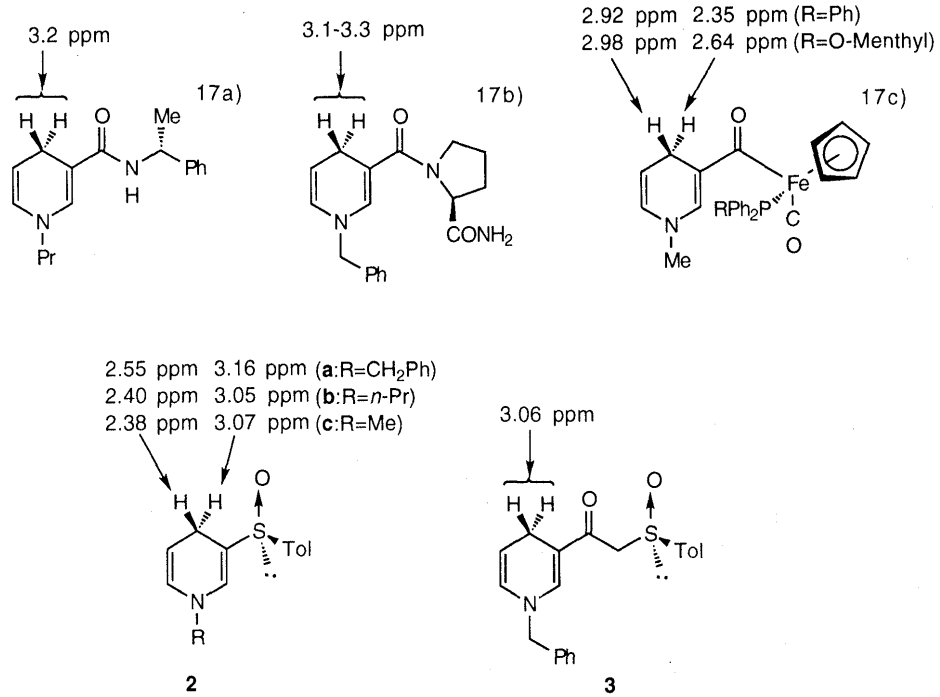

Fig. 2. Chemical Shifts of C(4) Protons in Various NADH Model Compounds

Taking account of the allylic 1,3-strain[18] between the bulky sulfinyl group at the 3-position and the C(2)-H coupled with the dipolar repulsion between the ring nitrogen and the sulfinyl oxygen, the conformation [A] seems to be the most stable conformation for **2**. This assumption is strongly supported by the ^{1}H-NMR assignments for the C(4) protons as shown in Fig. 3. The C(4)-H_a was observed to resonate at lower field than the C(4)-H_b, due to the anisotropic effect of the neighboring sulfinyl oxygen atom. Furthermore, the preferred conformation of **2** was confirmed to be [A] by comparison of the LIS results for **2c** and the pyridine derivative **5**. In the LIS experiment on **5**, the chemical shift of the C(2) proton was found to be more markedly shifted by gradual addition of Eu(tfc)$_3$ than that of the C(4) protons. This phenomenon could be interpreted in terms of an equi-

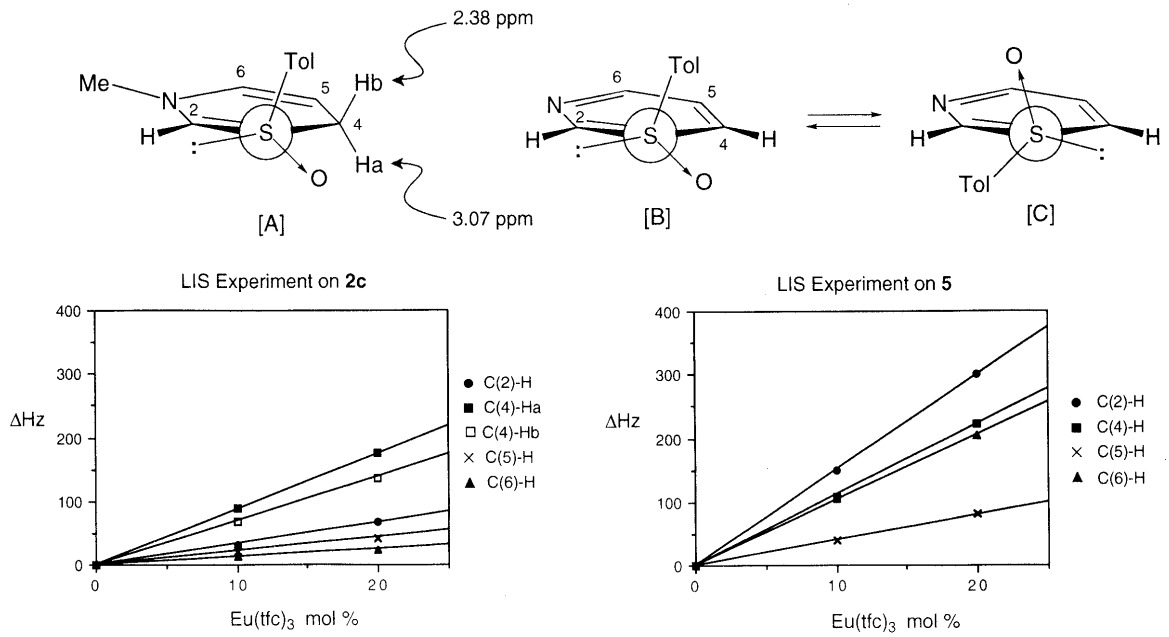

Fig. 3. Conformations and LIS Results of **2c** and **5**

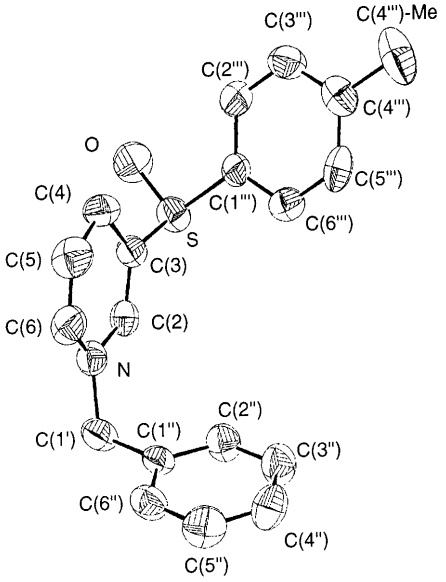

Fig. 4. ORTEP Diagram of **2a** with Vibration Ellipsoids Drawn at the 50% Probability Level

librium between the two major conformations, [B] and [C], while compound **2c** exists exclusively in conformer [A] and the chemical shifts of the C(4) protons, especially C(4)-H_a, moved more markedly than that of the C(2) proton upon addition of the shift reagent. These results indicate that the C(4) protons, which play an important role in asymmetric reduction, are strongly influenced by the chiral *p*-tolylsulfinyl group, suggesting the effectiveness of **2** for asymmetric reduction.

In contrast, in the case of the model compound **3**, the C(4) protons resonated at 3.06 ppm, appearing as a narrow multiplet ($W_{1/2}=8$ Hz), in the ^{1}H-NMR spectrum. This finding indicates that, in the model compound **3**, the prochiral C(4) protons can be little distinguished diastereotopically by the chiral *p*-tolylsulfinyl group attached on the C(3) side chain.

The structure of **2a** in the solid state was also determined by X-ray crystallography analysis. A perspective view of **2a** is given in Fig. 4.

Table 2. Positional Parameters and Equivalent Isotropic Thermal Parameters of Non-H Atoms of **2a** with Estimated S.D.'s in Parentheses

Atom	*x*	*y*	*z*	B_{eq} [a]
S	0.8127 (2)	0.40088 (6)	0.3140 (1)	3.92 (6)
O	0.7358 (4)	0.3365 (2)	0.2788 (4)	5.5 (2)
N	0.6741 (4)	0.5386 (2)	0.0090 (4)	3.6 (2)
C(2)	0.7102 (5)	0.4991 (3)	0.1320 (6)	3.2 (2)
C(3)	0.7810 (5)	0.4427 (2)	0.1440 (5)	3.2 (2)
C(4)	0.8235 (8)	0.4149 (3)	0.0174 (6)	4.4 (3)
C(5)	0.7941 (8)	0.4637 (3)	−0.1042 (6)	5.0 (3)
C(6)	0.7275 (7)	0.5192 (3)	−0.1058 (6)	4.6 (3)
C(1')	0.6324 (6)	0.6060 (3)	0.0178 (7)	4.1 (3)
C(1'')	0.7771 (5)	0.6493 (2)	0.0718 (5)	3.1 (2)
C(2'')	0.8931 (6)	0.6443 (3)	0.2177 (6)	4.1 (3)
C(3'')	1.0269 (7)	0.6828 (3)	0.2689 (7)	4.7 (3)
C(4'')	1.0463 (7)	0.7282 (3)	0.1715 (7)	5.1 (3)
C(5'')	0.9320 (8)	0.7345 (3)	0.0266 (7)	5.1 (3)
C(6'')	0.7989 (7)	0.6953 (3)	−0.0225 (7)	4.0 (3)
C(1''')	1.0260 (6)	0.3876 (2)	0.3748 (5)	3.3 (2)
C(2''')	1.0843 (7)	0.3261 (3)	0.3754 (6)	4.3 (3)
C(3''')	1.2476 (7)	0.3152 (3)	0.4311 (6)	4.6 (3)
C(4''')	1.3566 (6)	0.3643 (3)	0.4869 (6)	4.3 (3)
C(5''')	1.2951 (7)	0.4258 (3)	0.4840 (6)	4.4 (3)
C(6''')	1.1326 (7)	0.4372 (3)	0.4289 (6)	3.8 (3)
C(4''')-Me	1.5354 (9)	0.3523 (6)	0.549 (1)	7.3 (5)

a) $B_{eq}=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*a_ia_j$.

This X-ray crystallographic analysis shows that the lone pair of the sulfur atom in **2a** is in the *syn* arrangement with respect to the C(2)–C(3) bond of the dihydropyridine ring, as expected from the ^{1}H-NMR studies. In addition, the torsion angle of the C(2)–C(3)–S–O bonds is found to be 53.3°, indicating that the sulfinyl dipole is oriented *syn* with respect to the pro-*S* hydrogen at C(4). The pro-*R* hydrogen is shielded by the *p*-tolyl group of the sulfinyl moiety and thereby, the large difference of the chemical shifts between the two prochiral protons of C(4) is clearly explained.

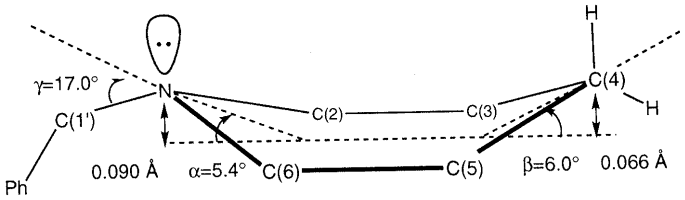

Fig. 5. The Dihydropyridine Ring Conformation of Compound **2a** (X-Ray Analysis)

For many years, it has been discussed whether the 1,4-dihydropyridine ring is planar or not.[19] According to the X-ray analysis, the dihydropyridine ring of **2a** exists in the flattened boat conformation with the nitrogen 0.066 Å ($\alpha=5.2°$) and the carbon C(4) 0.090 Å ($\beta=6.0°$) above the plane of the four sp^2 ring carbons as shown in Fig. 5. Pyramidalization of the ring nitrogen is observed ($\gamma=17.0°$) and the carbon C(1′) is located at an equatorial position. Furthermore, the phenyl ring occupies the *anti* position to the lone pair of the nitrogen atom to minimize the electrostatic repulsion. As a result of this conformation, the approach of the substrate to one face of the dihydropyridine ring seems to be restricted by the *p*-tolyl group and the benzyl group.

The asymmetric reduction of carbonyl compounds with these NADH model compounds **2** and **3** will be reported elsewhere.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer, and ^{1}H-NMR spectra on a Hitachi R-22 (90 MHz) or a JEOL JNM-FX90Q (90 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 (High MS) with a JEOL JMS-D300 instrument. UV spectra were recorded on a Hitachi 124 or a Shimadzu UV-2100 spectrometer, and $[\alpha]_D$ on a JASCO DIP-360 instrument. For column chromatography, Merck Kieselgel 60 (0.063—0.200 μm) was used.

3-(*p*-Tolylsulfinyl)pyridine (5) Method A: A solution of 3-bromopyridine (1.0 g, 6.3 mmol) in dry ether (15 ml) was added dropwise to a stirred solution of *n*-BuLi (1.5 M in hexane, 4.6 ml, 6.9 mmol) in dry ether (30 ml) at −78 °C. Stirring was continued for 30 min at −78 °C, then a solution of **4** (2.2 g, 7.6 mmol) in dry tetrahydrofuran (THF, 30 ml) was added dropwise to the stirred reaction mixture at the same temperature. 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 (S_S)-**5** (1.0 g) as a light yellow solid in 73% yield (62% ee), which was recrystallized from benzene–iso-Pr_2O to give colorless needles, mp 56—59 °C, $[\alpha]_D^{22}$ +47.4° (c = 0.54, $CHCl_3$). IR ($CHCl_3$): 3000, 1600, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $-C_6H_4-C\underline{H}_3$), 7.26, 7.52 (4H, AA′BB′ type, J=8 Hz, $-C_6\underline{H}_4-CH_3$), 7.37 (1H, m, C(5)-H), 7.96 (1H, dt, J=8, 1.5 Hz, C(6)-H), 8.62 (1H, dd, J=6, 1.5 Hz, C(6)-H), 8.74 (1H, d, J=2 Hz, C(2)-H). MS m/z: 217 (M^+, 25.1%), 201 (M^+-O, 20.3%), 200 (M^+-OH, 64.6%). *Anal.* Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 4.98; N, 6.37; S, 14.51. Found: C, 66.33; H, 5.10; N, 6.45; S, 14.75.

Method B: A solution of 3-pyridylmagnesium bromide in dry THF–ether [2 : 1 (v/v)] solution (0.125 M, 33.0 ml, 4.1 mmol) prepared according to the literature[14] was slowly added to a stirred solution of **4** (1.0 g, 3.4 mmol) in dry THF (30 ml) at −78 °C and stirring was continued for 1 h at the same temperature. Saturated NH_4Cl solution was added to the reaction mixture and the whole was extracted with ether. Usual work-up and purification by SiO_2 column chromatography [AcOEt–hexane (7 : 1)] afforded (S_S)-**5** (390 mg) as a light yellow solid in 87% yield (100% ee). It was recrystallized from benzene–iso-Pr_2O to give colorless needles, mp 60—62 °C, $[\alpha]_D^{26}$ +79.8° (c=0.57, $CHCl_3$).

Preparation of (±)-**5**: Methyl (±)-*p*-tolylsulfinate (2.04 g, 16 mmol) prepared according to the literature[12] was treated with 3-lithiopyridine prepared from 3-bromopyridine (3 g, 19 mmol) and *n*-BuLi (1.6 M in hexane, 13 ml, 21 mmol) according to method A to give (±)-**5** (2.47 g) as a light yellow solid in 70% yield, which was recrystallized from benzene–iso-Pr_2O to give colorless needles, mp 62—63 °C.

(S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)pyridinium Bromide (6a) A solution of **5** (503 mg, 2.32 mmol) and benzyl bromide (0.55 ml, 4.64 mmol) in dry toluene (4 ml) was heated overnight at 80 °C. After cooling to room temperature, the precipitate was collected, washed with ether, and dried under reduced pressure to afford **6a** (783 mg) as a hygroscopic white powder in 87% yield. This product was used for the subsequent reaction without further purification, mp 160—163 °C, $[\alpha]_D^{21}$ +110.8° (c=0.13, MeOH). IR (KBr): 2950, 1625, 1600, 1500, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, $-C_6H_4-C\underline{H}_3$), 6.13 (2H, s, $-C\underline{H}_2C_6H_5$), 7.30—7.78 (5H, m, $-CH_2C_6\underline{H}_5$), 7.37, 7.82 (4H, AA′BB′ type, J=8 Hz, $-C_6\underline{H}_4-CH_3$), 8.32 (1H, dd, J=6, 8 Hz, C(5)-H), 9.00 (1H, br d, J=8 Hz, C(6)-H), 9.64 (1H, br d, J=6 Hz, C(4)-H), 10.07 (1H, s, C(2)-H).

(S_S)-1-Propyl-3-(*p*-tolylsulfinyl)pyridinium Iodide (6b) A solution of **5** (100 mg, 0.46 mmol) in propyl iodide (2 ml) was heated at 80 °C in a sealed tube overnight. After cooling to room temperature, the precipitate was collected, and worked up as described above to afford **6b** (156 mg) as a hygroscopic white powder in 87% yield, mp 214—216 °C, $[\alpha]_D^{24}$ +96.9° (c=0.195, MeOH). IR (KBr): 2950, 1600, 1495, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz, $N-CH_2CH_2C\underline{H}_3$), 1.97 (2H, sextet, J=7 Hz, $N-CH_2C\underline{H}_2CH_3$), 2.36 (3H, s, $-C_6H_4-C\underline{H}_3$), 4.64 (2H, d, J=7 Hz, $N-C\underline{H}_2CH_2CH_3$), 7.38, 7.74 (4H, AA′BB′ type, J=8 Hz, $-C_6\underline{H}_4-CH_3$), 8.24 (1H, dd, J=6, 8 Hz, C(5)-H), 8.74 (1H, br d, J=8 Hz, C(6)-H), 9.31 (1H, br d, J=6 Hz, C(4)-H), 9.60 (1H, s, C(2)-H).

Methyl (S_S)-1-Methyl-3-(*p*-tolylsulfinyl)pyridinium Sulfate (6c) A suspension of **5** (202 mg, 0.93 mmol) in dimethyl sulfate (0.097 ml, 1.02 mmol) was heated at 60 °C for 6 h and worked up as described above to afford **6c** (301 mg) as a hygroscopic white powder in 94% yield, mp 128—130 °C, $[\alpha]_D^{22}$ +98.5° (c=0.16, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, $-C_6H_4-C\underline{H}_3$), 4.52 (3H, s, $N-CH_3$), 7.28, 7.68 (4H, AA′BB′ type, J=8 Hz, $-C_6\underline{H}_4-CH_3$), 8.13 (1H, dd, J=6, 8 Hz, C(5)-H), 8.55 (1H, br d, J=8 Hz, C(6)-H), 9.22 (1H, br d, J=6 Hz, C(4)-H), 9.36 (1H, s, C(2)-H).

(S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (2a) Under an Ar atmosphere, a solution of $Na_2S_2O_4$ (142 mg, 0.78 mmol) in water (2 ml) was added dropwise to a stirred solution of **6a** (200 mg, 0.52 mmol) in CH_2Cl_2 (10 ml) and 1 N $NaHCO_3$ solution (10 ml) at room temperature. Stirring was continued for 3 h in the dark, 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 **2a** (80.3 mg) as a light yellow solid in 49% yield. It was recrystallized from benzene–hexane to give colorless plates, mp 109—112 °C, $[\alpha]_D^{24}$ +160.8° (c=0.25, $CHCl_3$). IR ($CHCl_3$): 3000, 1600, 1500, 1410, 1065 cm^{-1}. MS m/z: 309 (M^+, 1.3%), 293 (M^+-O, 22.7%), 292 (M^+-OH, 83.7%). *Anal.* Calcd for $C_{19}H_{14}NOS$: C, 73.98; H, 6.12; N, 4.53; S, 10.36. Found: C, 73.75; H, 6.19; N, 4.53; S, 10.36. The ^{1}H-NMR data for **2a** are summarized in Table 1.

(S_S)-1-Propyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (2b) The pyridinium salt **6b** (300 mg, 0.78 mmol) in CH_2Cl_2 (15 ml) and 1 N $NaHCO_3$ solution (15 ml) was treated with an aqueous solution (3 ml) of $Na_2S_2O_4$ (208.8 mg, 1.2 mmol) according to the procedure described above to afford **2b** (135.7 mg) as a light yellow solid in 65% yield, mp 62—64 °C, $[\alpha]_D^{24}$ +305.3° (c=0.095, $CHCl_3$). IR ($CHCl_3$): 2975, 1600, 1500, 1410, 1065 cm^{-1}. MS m/z: 261 (M^+, 3.7%), 245 (M^+-O, 24.7%), 244 (M^+-OH, 100%). High-MS: 261.1187 (M^+, Calcd for $C_{15}H_{19}NOS$: 261.1199). The ^{1}H-NMR data for **2b** are summarized in Table 1.

(S_S)-1-Methyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (2c) Under an Ar atmosphere, NaI (155.5 mg) was added to a stirred solution of **6c** (301 mg, 0.88 mmol) in CH_2Cl_2 (15 ml) and stirring was continued for 30 min at room temperature in the dark. An aqueous solution (3 ml) of $Na_2S_2O_4$ (241 mg, 1.39 mmol) and 1 N $NaHCO_3$ solution (10 ml) were added to the reaction mixture and the whole was stirred for 3 h at room temperature then worked up as described above to afford **2c** (143.5 mg) as a light yellow solid in 70% yield, mp 92—94 °C, $[\alpha]_D^{22}$ +371.0° (c=0.10, $CHCl_3$). IR ($CHCl_3$): 2995, 1605, 1500, 1050 cm^{-1}. MS m/z: 233 (M^+, 2.5%), 217 (M^+-O, 22%), 216 (M^+-OH, 100%). High-MS: 233.0861 (M^+, Calcd for $C_{13}H_{15}NOS$: 233.0872). The ^{1}H-NMR data for **2c** are summarized in Table 1.

(R_S)-3-[1-Oxo-2-(*p*-tolylsulfinyl)ethyl]pyridine (8) Under a N_2 atmosphere, *n*-BuLi (1.5 M in hexane, 10.7 ml, 16.0 mmol) was added to a stirred solution of diethylamine (3.5 ml, 16.0 mmol) in dry THF (30 ml)

at −40 °C and stirring was continued at −20 °C for 30 min. A solution of **7** (1.94 g, 14.0 mmol) in dry THF (50 ml) was added to the above mixture at −40 °C and the whole was stirred at −20 °C for 30 min. It was cooled to −78 °C, then a dry THF (30 ml) solution of methyl nicotinate (1.1 g, 7.0 mmol) was added dropwise and stirring was continued for 2 h. After neutralization with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were worked up as usual and the residue was purified by SiO_2 column chromatography (AcOEt) to afford **8** (1.3 g) as a light yellow solid in 72% yield. This product was recrystallized from benzene–hexane to give colorless prisms, mp 102.5—104.0 °C, $[\alpha]_D^{25}$ +239.0° (c=0.53, $CHCl_3$). IR ($CHCl_3$): 3050, 1680, 1590, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s, $-C_6H_4-CH_3$), 4.94, 5.11 (2H, AB type, J=14 Hz, $-COCH_2S(O)Tol$), 7.40, 7.63 (4H, AA′BB′ type, J=7 Hz, $-C_6H_4-CH_3$), 7.58 (1H, m, C(5)-H), 8.39 (1H, dt, J=8, 1.5 Hz, C(4)-H), 8.89 (1H, m, C(6)-H), 9.22 (1H, br s, C(2)-H). MS m/z: 260 (M^++1, 1.7%), 259 (M^+, 9.7%), 243 (M^+−O, 14.5%), 242 (M^+−OH, 47.3%). *Anal.* Calcd for $C_{14}H_{13}NO_2S$: C, 65.04; H, 4.95; N, 5.37; S, 12.18. Found: C, 64.84; H, 5.05; N, 5.40; S, 12.36.

(R_S)-1-Benzyl-3-[1-oxo-2-(*p*-tolylsulfinyl)ethyl]pyridinium Bromide (9) Compound **8** (129.7 mg, 0.5 mmol) and benzyl bromide (171.3 mg, 0.75 mmol) were treated in toluene (2 ml) according to the procedure described for the preparation of **6a** to afford **9** (197.8 mg) as a hygroscopic white powder in 92% yield, mp 139—142 °C, $[\alpha]_D^{21}$ +126.1° (c=0.12, MeOH). IR ($CHCl_3$): 2950, 1695, 1630, 1030 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.36 (3H, s, $-C_6H_4-CH_3$), 4.94, 5.11 (2H, AB type, J=14 Hz, $-COCH_2S(O)Tol$), 6.16 (2H, s, benzyl protons), 7.41, 7.70 (4H, AA′BB′ type, J=8 Hz, $-C_6H_4-CH_3$), 7.43—7.50 (5H, m, $N-CH_2-C_6H_5$), 8.41 (1H, dd, J=6, 8 Hz, C(5)-H), 9.13 (1H, d, J=8 Hz, C(6)-H), 9.62 (1H, d, J=6 Hz, C(4)-H), 10.10 (1H, s, C(2)-H).

(R_S)-1-Benzyl-3-[1-oxo-2-(*p*-tolylsulfinyl)ethyl]-1,4-dihydropyridine (3) Sodium cyanoborohydride (10 mg, 0.2 mmol) was added to a stirred solution of **9** (100.0 mg, 0.24 mmol) in CH_2Cl_2 (5 ml) under ice cooling. After having been stirred for 30 min at room temperature, the reaction mixture was diluted with CH_2Cl_2, worked up as usual, and purified by SiO_2 column chromatography [AcOEt–hexane (2:1)] to afford **3** (33.5 mg) as a light yellow solid in 41% yield. This product was recrystallized from benzene–hexane to give colorless needles, mp 124—126 °C, $[\alpha]_D^{25}$ +247.9° (c=1.06, $CHCl_3$). IR ($CHCl_3$): 3000, 1680, 1500, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, $-C_6H_4-CH_3$), 3.06 (2H, m, C(4)-H), 3.82, 4.18 (2H, AB type, J=13 Hz, $-COCH_2S(O)Tol$), 4.42 (2H, s, $-CH_2-C_6H_5$), 5.01 (1H, dt, J=8, 4 Hz, C(5)-H), 5.80 (1H, dq, J=8, 1.5 Hz, C(6)-H), 7.21 (1H, d, J=1.5 Hz, C(2)-H), 7.30—7.75 (9H, m, aromatic protons). MS m/z: 351 (M^+, 1.0%), 335 (M^+−O, 1.3%), 334 (M^+−OH, 2.2%). High-MS: 351.1298 (M^+, Calcd for $C_{21}H_{21}NO_2S$: 351.1293).

X-Ray Crystallography Analysis A colorless rod-like crystal of **2a** (racemate) having approximate dimensions of 0.3×0.3×0.3 mm was mounted on a Rigaku AFC-5S four-circle automated diffractometer with graphite-monochromated Mo$K\alpha$ radiation. Crystal data: $C_{19}H_{19}NOS$, M_r=309.43, monoclinic, space group $P2_1/a$, a=8.987(3) Å, b=20.915(3) Å, c=9.437(2) Å, β=112.61(2)°, V=1637.6(6) Å^3, Z=4, D_c=1.255 g/cm^3 and μ(MoK_α)=1.89 cm^{-1}. The data were collected using the ω-2θ scan technique to a maximum 2θ value of 50°. Three reference reflections monitored periodically showed no significant intensity fluctuations during the course of data collection. Finally, 2949 independent reflections were collected. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. The structure was solved by the direct method. The resulting E map revealed all the non-H atoms. All H atoms were located in a difference Fourier synthesis. The refinement of atomic parameters was carried out by full-matrix least-squares refinement, using anisotropic temperature factors for all non-H atoms and isotropic ones for H atoms. The final refinement was based on 1306 observed reflections ($I>3\sigma(I)$) and 275 variable parameters and converged to R=0.047, R_w=0.049. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.26 and −0.22 e^-/Å^3, respectively. Neutral atomic scattering factors were taken from Cromer and Waber.[20] All calculations were performed using the TEXSAN[21] crystallographic software package of Molecular Structure Corporation. The final positional parameters and equivalent isotropic thermal parameters of non-H atoms are given in Table 2.

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