Reduction by a Model of NAD(P)H. 25. A Chiral Model Which Induces High Asymmetry

Atsuyoshi Ohno,* Masahiko Ikeguchi, Takahide Kimura, and Shinzaburo Oka

Contribution from the Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan. *Received May 8, 1979*

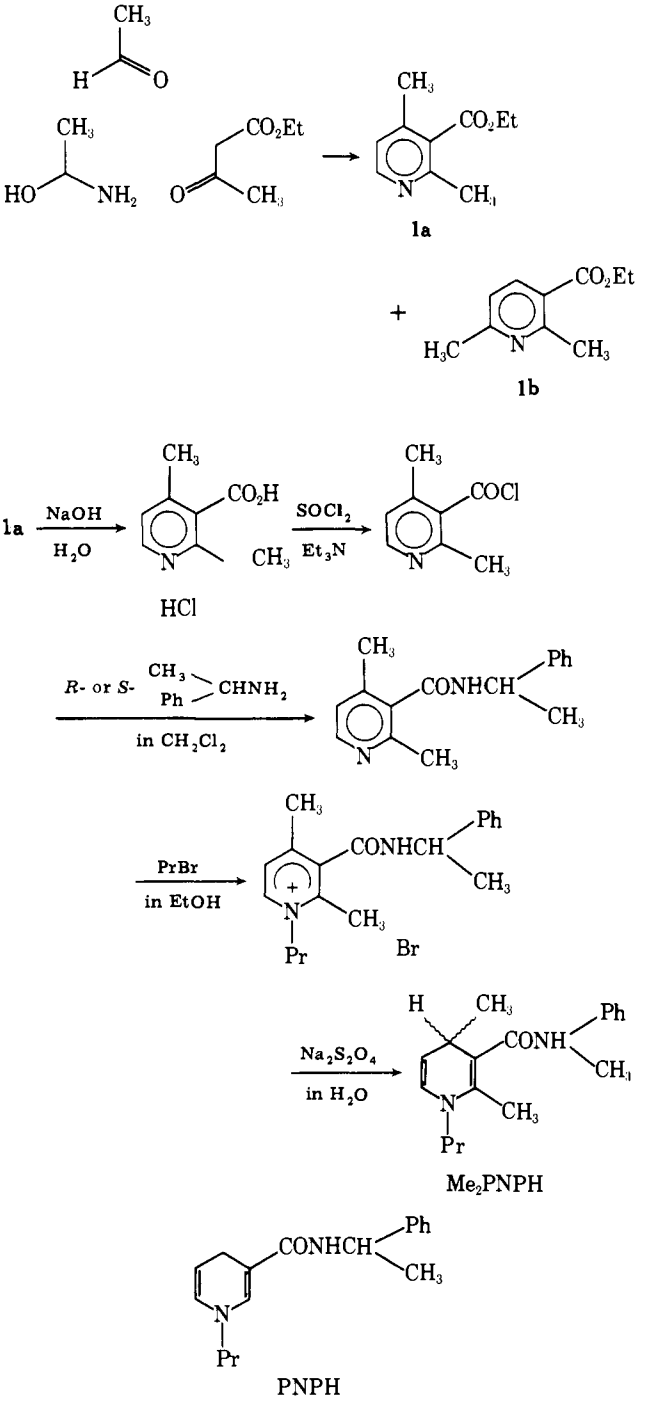
Abstract: Optically active *N*-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, a chiral model of NAD(P)H, has been synthesized and its absolute configuration has been determined. It has been found that the model compound exerts high enantiospecificity in the reduction of certain carbonyl compounds in the presence of magnesium perchlorate. The results seem to show that the enantiospecificity is controlled by both the electronic and steric effects of substituents in the carbonyl compounds. The polar substituent of the substrate undergoing reduction faces the carbamoyl group of the model compound in the transition state for the reaction.

Because of their enhanced reactivity and high stereospecificity, biochemical transformations are of interest to many organic chemists. This is certainly the case for reductions of carbonyl and other unsaturated compounds with NAD(P)H-dependent dehydrogenases, for which, recently, we developed a new model.[1] We have found that, in the reduction of certain substrates by a model of NAD(P)H, magnesium ion plays the role of a catalyst. When a chiral group is substituted on the amide nitrogen of a model compound, asymmetric reduction takes place in the presence of magnesium ion in 5–40% optical yields, depending on the substrate and reaction conditions.[1,2] Nishiyama and his co-workers reported 78% optical yield in a similar mimetic reduction with doubly chiral reagents.[3] The role of magnesium ion in the mimetic reaction can be compared with a dehydrogenase in an enzymic reaction in the sense of both rate-enhancement and enantiospecificity. However, since the chiral model compounds so far synthesized have the chiral center at a position far apart from the reaction center, the enantiospecificities demonstrated by them have been quite unsatisfactory compared with those from enzymic reactions. We considered that enantiospecificity in the mimetic reduction would be improved if the model compound has reaction and chiral centers at the same position. We therefore synthesized a model compound with a chiral center at the C_4 position and have found that this model compound does indeed induce excellent asymmetry in the reductions of certain substrates. However, for others the specificity is not as satisfactory. These results are discussed in relation to the electronic and steric requirements of the molecules in the transition state of the reaction.

Results

Preparation of *N*-α-Methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH). The reaction of ethyl acetoacetate, acetaldehyde, and acetaldehyde ammonia gave a 6:4 mixture of ethyl 2,4- and 2,6-dimethylpyridine-3-carboxylates (**1a** and **1b**).[4] Since only **1b** was susceptible to hydrolysis under acidic conditions, the ester **1a** could easily be isolated from the mixture. Thus obtained **1a** was hydrolyzed under alkaline conditions to afford 2,4-dimethylpyridine-3-carboxylic acid hydrogen chloride. The acid was converted into the corresponding acid chloride, then into a 1:1 diastereomeric mixture of Me_2PNPH after a series of reactions similar to those described for the preparation of *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide (PNPH).[2e] The mixture was fractionally recrystallized from ethanol containing an appropriate amount of water. The *RR* (or *SS*) isomer[5] appeared first; then the *SR* (or *RS*) isomer crystallized after the amount of water in the solvent was increased.

Figure 1 shows the CD spectra of *RR*- and *SR*-Me_2PNPH. Subtraction and addition of the CD spectrum of *SR*-



0002-7863/79/1501-7036$01.00/0

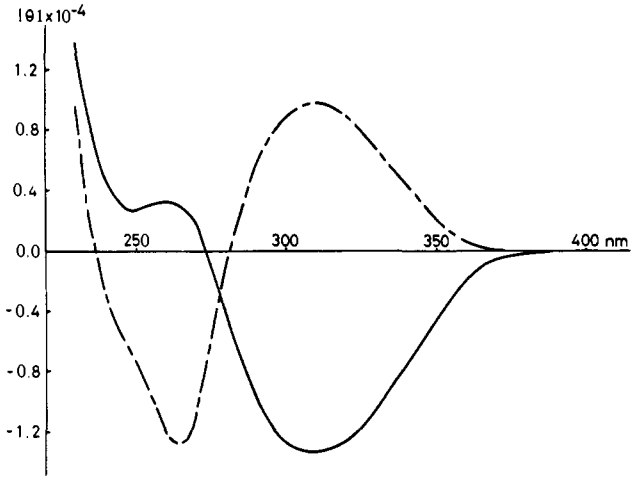


Figure 1. The CD spectra of (4*R*,9*R*)-(−)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, *RR*-Me_2PNPH (—), and (4*S*,9*R*)-(+)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, *SR*-Me_2PNPH (- - -).

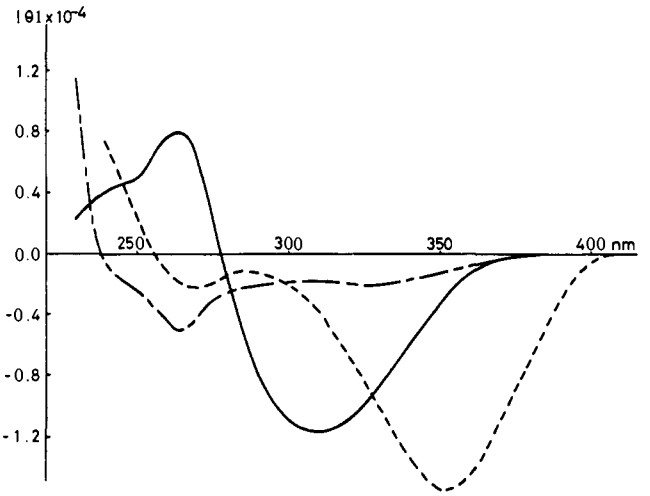
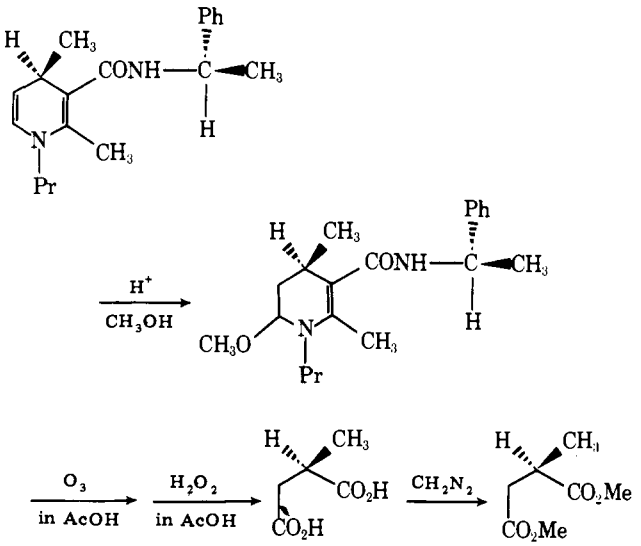


Figure 2. The difference CD spectra for (4*R*,9*R*)-(−)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, *RR*-Me_2PNPH, and (4*S*,9*R*)-(+)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, *SR*-Me_2PNPH. The solid and broken lines represent the spectra for (*RR*-Me_2PNPH − *SR*-Me_2PNPH)/2 and (*RR*-Me_2PNPH + *SR*-Me_2PNPH)/2, respectively. The dotted line is the CD spectrum of (9*R*)-(−)-*N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide, *R*-PNPH.

Me_2PNPH from and to that of *RR*-Me_2PNPH give difference spectra that are characteristic to the configurations at the C_4 and benzylic positions, respectively. The difference spectra are shown in Figure 2 together with the CD spectrum of *R*-PNPH. From these spectra it is apparent that the conformation at the benzylic side chain in Me_2PNPH is distorted to a considerable extent from that of PNPH.

Absolute Configuration of *N*-α-Methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide. The absolute configuration of Me_2PNPH was determined by using the isomer prepared by the reaction with (*R*)-(+)-α-methylbenzylamine and obtained from the first fraction of recrystallization. Following the procedure reported by Cornforth and co-workers,[6] Me_2PNPH was subjected to the addition of methanol, ozonolysis, oxidation by hydrogen peroxide in acetic acid, and methylation with diazomethane. The signs of optical rotation and the Cotton effect observed in the CD spectrum of the product, dimethyl methylsuccinate, were the same as that of



an authentic sample derived from partially resolved (*R*)-methylsuccinic acid.[7] This confirms that the isomer of Me_2PNPH subjected to the analysis has the *R* configuration at the C_4 position.

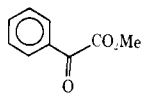
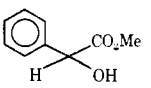
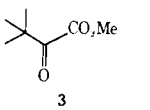
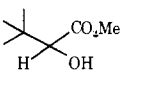
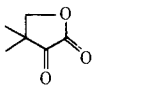
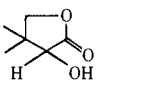
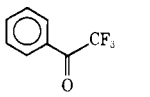
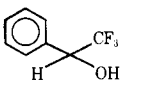
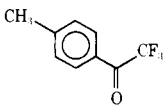
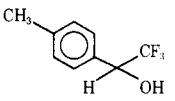
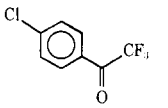
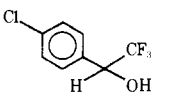
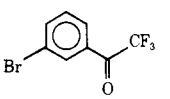
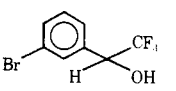
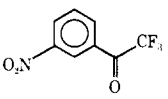
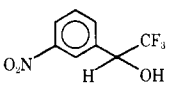
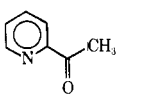
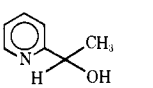
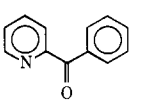
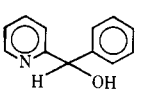
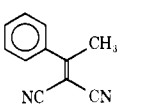
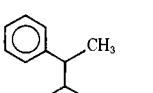
Asymmetric Reductions. Reductions were carried out in acetonitrile at room temperature mostly in the presence of magnesium perchlorate. Product analyses confirmed that there was no side reaction except for the reduction of 1,1-dicyano-2-phenylprop-1-ene (**12**), where a small amount of cyclid dimer of the olefin was formed.[2b] The reaction conditions and results are summarized in Table I. Table I also lists the configurations and optical yields (or excess percentages) of the predominant enantiomers of products together, for comparison, with those of products from the reduction with *R*-PNPH.

Discussion

Several interesting characteristics of the reductions with Me_2PNPH can be seen by inspecting the results reported in Table I. First of all, when the reduction is carried out in the presence of magnesium ion, the configurations of the predominant enantiomer of the product is determined by the configuration at the C_4 position of Me_2PNPH. It is independent of the configuration at the benzylic carbon. This is in marked contrast to the reductions with PNPH, where the configuration at the benzylic carbon has played an exclusive role in determining the stereochemistry of the products. On the other hand, in the absence of magnesium ion, the configuration at the benzylic carbon in Me_2PNPH again exerts an influence, as can be seen in the reduction of **2** and **5**. This fact implies that the conformation of Me_2PNPH in the presence of magnesium ion differs from that in the absence of magnesium ion.[2d,16] The difference of 11% in optical yield between the reduction of **5** with *RR*- and *SR*-Me_2PNPH in the absence of magnesium ion is almost comparable to the optical yield observed with PNPH in the presence of magnesium ion. This may suggest that the stereochemical behavior of the carbamoyl side chain in Me_2PNPH in the absence of magnesium ion resembles that shown in PNPH in the presence of magnesium ion. Thus, there is no doubt that magnesium ion not only functions as an electrophilic catalyst coordinating the substrate but also acts to freeze the conformation of the model compound. In other words, our observations support the hypothesis that the magnesium ion positions itself between the substrate and model compound in the transition state of the reduction as proposed previously.[16]

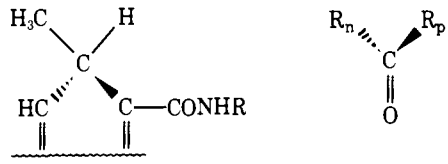
The second significant aspect of our results can be seen in the stereochemical course of the reduction, with the stereochemistry of the product being determined by the electronic effects of substituents in the substrate. By making the reasonable assumption that the carbonyl oxygen (or dicy-

Table I. Reduction of Unsaturated Compounds by a Chiral NAD(P)H-Model Compound

substrate	config of Me_2PNPH	reactn time, day	conv,[a] %	product[b] structure	$[\alpha]_D^{25}$	c	(solvent)	reduction by Me_2PNPH config	reduction by Me_2PNPH opt yield, %[d]	reduction by PNPH config	reduction by PNPH opt yield, %	ref[c]
 2	*RR*	2	100		−130.7	1.03	(EtOH)	*R*	97.6	*R*	16	8
	SR	2	100		+129.2	1.03	(EtOH)	*S*	96.5			
	SS	2	100		+126.8	2.84	(EtOH)	*S*	94.7			
	RR[e]	5	100		−70.3	2.84	(EtOH)	*R*	52.5			
 3	*RR*	5	95		−21.8	1.24	(EtOH)	*R* >99		*R*	7	9
 4	*RR*	5	100		−25.6	1.19	(H_2O)	*R*	50.6	*R*	8	10
 5	*RR*	5	60		−10.4	0.810	(PhH)	*R*	70.3 (92)	*S*	16	11
	SR	5	56		+10.4	0.490	(PhH)	*S*	70.5			
	RR[e]	7	59		−9.32	1.10	(PhH)	*R*	63.1			
	SR[e]	7	79		+6.11	0.950	(PhH)	*S*	41.4			
 6	*RR*	5	74		−31.2	0.814	(EtOH)	*R*	(95)			
 7	*SS*	3.5	75		+31.2	1.26	(EtOH)	*S* (>95)				
 8	*RR*	3	77		−25.1	2.49	(EtOH)	*R*	89.2 (90)			12
 9	*SS*	2	85		+26.9	2.54	(EtOH)	*S* (>99)				
 10	*RR*	2.5	100		+35.6	1.03	(EtOH)	*R*	62.0	*R*	25	13
	RR[f]	3	37		+26.7	1.95	(EtOH)	*R*	47.2	*R*	36	
 11	*SS*	2.5	97		+66.0	0.570	($CHCl_3$)	*g*	76.6	*g*	59	14
 12	*RR*	4	52		+2.78	0.540	(EtOH)	*R*	17.0	*R*	8	15

[a] The amount of consumed substrate. [b] The yields of products were quantitative based on the consumed substrate except for the reduction of **12**, where the dimer of olefin was isolated in about 10% yield. [c] References for absolute configurations and maximum $[\alpha]_D$ values. [d] Numbers in parentheses are percentages for enantiomer excess measured on an ^{19}F NMR spectrometer. [e] Reaction without magnesium perchlorate. [f] Reaction with a half-equivalency of magnesium perchlorate. [g] Absolute configuration is unknown.

anomethylidene group in the case of **12**) of the substrate points toward the dihydropyridine ring nitrogen of Me_2PNPH in the transition state,[17] the stereochemistry of the product can be predicted, without exception, polar groups facing each other, as shown in **13**. In particular, the configuration of 1-(2-pyridinyl)ethanol, the reduction product from **10**, is such that it appears to be formed through a transition state in which the polar pyridinyl moiety faces the carbamoyl group of Me_2PNPH with the remaining nonpolar methyl group of **10** facing the open C_5 side of Me_2PNPH, in spite of the bulk of the pyridinyl group being larger than that of the methyl group. In contrast, if one postulated that the pyridinyl group were less



13

R_p = polar substituent
R_n = nonpolar substituent

bulky than the methyl group, this interpretation would be in contradiction with the result from the reduction of **5** or its derivatives, where the trifluoromethyl group faces the C_3 side. On the other hand, in the reduction of **12,** the methyl group faces the carbamoyl group of Me_2PNPH in the transition state. We cannot tell whether the result is due to steric effects or to polar participation of the methyl group. Clearly, the relative bulk of the substituents is also important in defining the configuration of the product since the optical yield of pyridinylbenzyl alcohol, the reduction product from **11,** is higher than that of pyridinylethanol.[18] In this case, the steric and electronic effects operate with opposite orienting effects on the molecules in the transition state for the reduction of **10.** The large enantiospecificity observed in the reduction of α-ketoesters and trifluoromethyl aryl ketones may be due to the cooperation of favorable electronic and steric effects.

The third noteworthy point of the reduction process is that **2** and **5** are reduced by Me_2PNPH to products of the same configuration, whereas the reduction of these substrates by PNPH gives products of opposite configuration. Furthermore, the optical yield from the reduction of **10** by Me_2PNPH with an equivalent amount of magnesium perchlorate is higher than that with a half-equivalency of magnesium perchlorate. The situation is inverted for the reduction by PNPH. These observations suggest that the factors affecting the molecular arrangement in the transition states of the reduction involving Me_2PNPH and PNPH are not comparable, despite the similarity of molecular structures.

Experimental Section

Instruments. UV, IR, NMR, and mass spectra were recorded on Union Giken SM-401, Hitachi EPI-S2, JEOL JNM-FX 100, and Hitachi RMU-6E spectrometers, respectively. The optical activity was measured on a Perkin-Elmer 241 polarimeter. The CD spectra were obtained with a JASCO J-20 spectropolarimeter. A Yanaco G-1800F and Varian Aerograph Model 920 were used for VPC, and a Yanaco Model L-2000 was used for high-pressure liquid chromatography. Melting and boiling points were not corrected.

Materials. α-Keto-β,β-dimethyl-γ-butyrolactone, **4**, α,α,α-trifluoroacetophenone, **5**, 2-acetylpyridine, **10**, and 2-benzoylpyridine, **11**, were obtained from commercial sources. Acetonitrile was distilled three times over phosphorus pentoxide and stored over 4A molecular sieves under an atmosphere of argon. Anhydrous magnesium perchlorate was dried at 100 °C and stored in a vacuum desiccator over phosphorus pentoxide. Optically active α-methylbenzylamine was purchased from Norse Laboratories.

Methyl benzoylformate (bp 110–111 °C/6 mm), **2**,[2e] methyl trimethylpyruvate (bp 59–60 °C/18 mm), **3**,[2e] *p*-methyl-α,α,α-trifluoroacetophenone (bp 82–83 °C/18 mm), **6**,[19] *p*-chloro-α,α,α-trifluoroacetophenone (bp 82 °C/20 mm), **7**,[20] *m*-bromo-α,α,α-trifluoroacetophenone (bp 78 °C/15 mm), **8**,[19] *m*-nitro-α,α,α-trifluoroacetophenone (mp 54–55 °C), **9**,[19] and α-methylbenzylidenemalononitrile (mp 95–96 °C), **12**,[21] were prepared according to literature procedures. The purity of these materials was confirmed by NMR, IR, VPC, and elemental analyses together with the comparison of their melting or boiling points with those reported.

2,4-Dimethyl-3-carboethoxypyridine.[4] In a three-necked flask provided with a reflux condenser and magnetic stirrer, 130 g of ethyl acetoacetate and 55 g of acetaldehyde were mixed and cooled below 0 °C. Therein 61 g of crystalline acetaldehyde ammonia was added in small portions. After the addition was complete, the red solution was carefully warmed to 80 °C and kept at 80–90 °C in an oil bath for 71 h with vigorous stirring. The warm solution was then submitted to distillation under reduced pressure. After the removal of water at 80 °C with an aspirator, the black-red residue was distilled by using a vacuum pump to give 20 g of a mixture of 2,4-dimethyl-3-carboethoxypyridine, **1a**, and 2,6-dimethyl-3-carboethoxypyridine, **1b**, as a yellow oil: bp 57–71 °C/0.5 mm.

Thirty-four grams of a mixture of **1a** and **1b** was dissolved in 90 mL of concentrated hydrochloric acid and refluxed at 100 °C in an oil bath for 1 h. After the ethanol produced was distilled out, the residual red oil was treated three times with active charcoal. After the complete evaporation of water under reduced pressure, the residue was extracted several times with acetone to isolate the hydrochloride of **1a.** 2,6-Dimethyl-3-carboxypyridine remained unextracted. After the evaporation of acetone from the acetone solution, the remaining pale yellow emulsion was neutralized with aqueous sodium bicarbonate and the oil which separated was extracted three times with ether. Evaporation of the ether gave 16 g of a yellow oil, which was distilled under reduced pressure to give **1a** as a colorless oil: bp 70 °C/0.5 mm. The yield was quantitative: NMR in $CDCl_3$ (Me_4Si) δ 1.40 (t, 3 H), 2.32 (s, 3 H), 2.56 (s, 3 H), 4.46 (q, 2 H), 6.96 (d, 1 H), and 8.40 (d, 1 H); IR (neat) 1727 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10; H, 7.52; N, 7.64.

2,4-Dimethyl-3-carboxypyridine.[4] Forty milliliters of water, 40 mL of ethanol, and 4.2 g of sodium hydroxide were placed in a flask equipped with a reflux condenser. To the solution 16 g of **1a** dissolved in ethanol was added, and the mixture was refluxed for 4 h with stirring. After the evaporation of ethanol under reduced pressure, 100 mL of water was added to the residue, and the impurities insoluble in water were extracted with ether. Then the water layer was cooled with ice and was neutralized with 60 mL of 6 N hydrochloric acid. The water was evaporated under reduced pressure. The pale yellow residue was extracted three times with hot ethanol. The extracted portions were combined and the solvent was evaporated under reduced pressure giving 15.5 g (92.5% yield) of white crystalline 2,4-dimethyl-3-carboxypyridine hydrochloride, which was hygroscopic: NMR in D_2O (Me_4Si) δ 2.69 (s, 3 H), 2.83 (s, 3 H), 7.83 (d, 1 H), and 8.52 (d, 1 H); IR (KBr) 2800 (ν_{OH}) and 1715 cm^{-1} ($\nu_{C=O}$).

***R*-*N*-α-Methylbenzyl-2,4-dimethylnicotinamide.**[2e,22] In a three-necked flask equipped with a $CaCl_2$ tube and a reflux condenser, 4.74 g of 2,4-dimethyl-3-carboxypyridine hydrochloride and 25 mL of thionyl chloride were placed and heated to 80–90 °C for 1 h with stirring. After the excess thionyl chloride was evaporated under reduced pressure at 80 °C in an oil bath, a pink residue was obtained. A solution of 8.5 mL of triethylamine dissolved in 10 mL of dichloromethane was poured onto the residue through a syringe with stirring and cooling with ice. The solution turned brown and a white precipitate appeared gradually.

To this solution, 3.12 g of (*R*)-(+)-α-methylbenzylamine dissolved in 16 mL of dichloromethane was added via injection by using a syringe during 20 min and the mixture was kept at room temperature for 1.5 h with stirring. Evaporation of the solvent at 30 °C under reduced pressure gave a brown residue. Twenty-two milliliters of concentrated hydrochloric acid in 135 mL of water was then added to the residue and the solution was treated three times with active charcoal. The pale yellow solution was neutralized with solid sodium carbonate to pH 7 employing Merck universal indicator paper and the organic material was extracted with dichloromethane. The combined dichloromethane layers were washed with aqueous sodium bicarbonate followed by two portions of water. The solution was then dried over sodium sulfate. Evaporation of the solvent gave a white solid, which was recrystallized from benzene to give 4.98 g (77.4% yield) of (*R*)-*N*-α-methylbenzyl-2,4-dimethylnicotinamide: mp 176.5–177 °C; NMR in $CDCl_3$ (Me_4Si) δ 1.62 (d, 3 H), 2.09 (s, 3 H), 2.29 (s, 3 H), 5.23 (dq, 1 H), 6.72 (d, 1 H), 7.03 (broad s, 1 H), 7.26 (s, 5 H), and 8.06 (d, 1 H); IR (KBr) 3300 (ν_{NH}) and 1630 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.87; H, 7.31; N, 11.03.

(*R*)-*N*-α-Methylbenzyl-1-propyl-2,4-dimethyl-3-carbamoylpyridinium Bromide.[2e] In a flask equipped with a $CaCl_2$-protected reflux condenser, 2.70 g of (*R*)-*N*-α-methylbenzyl-2,4-dimethylnicotinamide and 30 mL of propyl bromide were mixed and heated at 80–90 °C for 58 h with stirring. The mixture was cooled to room temperature and the precipitate which formed was filtered off. The precipitate was washed with ether twice giving 2.95 g (74% yield) of (*R*)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-3-carbamoylpyridinium

bromide: mp 199–200 °C; NMR in $CDCl_3$ (Me_4Si) δ 1.00 (t, 3 H), 1.60 (d, 3 H), 1.32–2.20 (m, 2 H), 2.43 (s, 3 H), 2.66 (s, 3 H), 4.52 (t, 2 H), 4.92–5.49 (m, 2 H), 7.06–7.77 (m, 5 H), 9.09 (d, 1 H), and 9.74 (d, 1 H); IR (KBr) 3150 (ν_{NH}) and 1657 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_{19}H_{25}N_2OBr$: C, 60.48; H, 6.68; N, 7.42. Found: C, 60.54; H, 6.81; N, 7.38.

N-α-Methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide.[2e] The reduction was carried out at room temperature in the dark under an atmosphere of argon. Three hundred and three milligrams of (*R*)-*N*-α-methylbenzyl-1-propyl-2,4-dimethyl-3-carbamoylpyridinium bromide dissolved in 50 mL of 1 N aqueous sodium bicarbonate was mixed with 60 mL of dichloromethane and stirred vigorously with a magnetic stirrer in an argon-flushed flask. Subsequently, 565 mg of sodium dithionite dissolved in 5 mL of water was injected dropwise by using a syringe. The reaction was run for 5 h and the dichloromethane layer was then separated from the water layer. The water layer was extracted twice with dichloromethane, and the combined dichloromethane layers were washed with water and dried over sodium sulfate. After the dichloromethane was removed under reduced pressure at room temperature, 170 mg of two diasteroisomers of *N*-α-methyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, Me_2PNPH, was obtained as a mixture of yellow solids.

The solids were dissolved in the smallest possible volume of ethanol at 30–40 °C. To the ethanol solution of Me_2PNPH, water was added dropwise until crystals began to appear. The flask was flushed with argon and was placed in the dark at room temperature for overnight. The yellow precipitate which appeared was collected and washed twice with water; then the precipitate was dried over calcium chloride under reduced pressure for 6 h. After repeating the recrystallization process several times, white needles were obtained. To obtain the other isomer, the filtrate was cooled in a refrigerator and the precipitate which formed was collected and washed twice with water. After repetition of the recrystallization procedure, white needles of the other diastereoisomer were obtained. Each diastereoisomer has the following properties. *RR*-Me_2PNPH: mp 119.5 °C (dec); $[\alpha]_D^{25}$ −115.9° (*c* 0.99, CH_3CN); UV (EtOH) 322 nm (ϵ 3.18 × 10^3); CD(CH_3CN) 310 nm ($[\theta]$ = −1.33 × 10^4); NMR in $CDCl_3$ (Me_4Si) δ 0.88 (t, 3 H), 1.03 (d, 3 H), 1.49 (d, 3 H), 1.20–1.70 (m, 2 H), 2.02 (s, 3 H), 3.11 (tq, 2 H), 3.24 (dq, 1 H), 4.77 (dd, 1 H), 5.22 (q, 1 H), 5.66 (broad s, 1 H), 5.74 (d, 1 H), and 7.28 (s, 5 H); IR (KBr) 3320 (ν_{NH}) and 1670 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.17; H, 8.79; N, 9.08.

SR-Me_2PNPH: mp 99 °C (dec); $[\alpha]_D^{25}$ +84.5° (*c* 0.115, CH_3CN); UV (EtOH) 322 nm (ϵ 3.28 × 10^3); CD(CH_3CN) 310 nm ($[\theta]$ = +9.70 × 10^3) and 262 nm ($[\theta]$ = −1.29 × 10^4); NMR in $CDCl_3$ (Me_4Si) δ 0.88 (t, 3 H), 1.01 (d, 3 H), 1.49 (d, 3 H), 1.20–1.70 m, 2 H), 2.02 (s, 3 H), 3.11 (tq, 2 H), 3.26 (dq, 1 H), 4.77 (dd, 1 H), 5.22 (q, 1 H), 5.66 (broad s, 1 H), 5.74 (d, 1 H), and 7.28 (s, 5 H); IR (KBr) 3350 (ν_{NH}) and 1675 cm^{-1} ($\nu_{C=O}$).

Anal. Found: C, 76.73; H, 8.92; N, 9.45.

SS-Me_2PNPH: mp 119 °C (dec); $[\alpha]_D^{25}$ +114° (*c* 0.915, CH_3CN); UV (EtOH) 322 nm (ϵ 3.39 × 10^3); CD(CH_3CN) 310 nm ($[\theta]$ = +1.21 × 10^4); NMR in $CDCl_3$ (Me_4Si) δ 0.88 (t, 3 H), 1.03 (d, 3 H), 1.49 (d, 3 H), 1.20–1.70 (m, 2 H), 2.02 (s, 3 H), 3.11 (tq, 2 H), 3.24 (dq, 1 H), 4.77 (dd, 1 H), 5.22 (q, 1 H), 5.66 (broad s, 1 H), 5.74 (d, 1 H), and 7.28 (s, 5 H); IR (KBr) 3350 (ν_{NH}) and 1670 cm^{-1} ($\nu_{C=O}$).

Anal. Found: C, 76.27; H, 8.85; N, 9.12.

RS-Me_2PNPH: mp 101 °C (dec); $[\alpha]_D^{25}$ −81.3° (*c* 0.890, CH_3CN); UV (EtOH) 322 nm (ϵ 3.69 × 10^3); CD(CH_3CN) 310 nm ($[\theta]$ = −5.13 × 10^3) and 262 nm ($[\theta]$ = +4.40 × 10^3); NMR in $CDCl_3$ (Me_4Si) δ 0.88 (t, 3 H), 1.01 (d, 3 H), 1.49 (d, 3 H), 1.20–1.70 (m, 2 H), 2.02 (s, 3 H), 3.11 (tq, 2 H), 3.26 (dq, 1 H), 4.77 (dd, 1 H), 5.22 (q, 1 H), 5.66 (broad s, 1 H), 5.74 (d, 1 H), and 7.28 (s, 5 H); IR (KBr) 3360 (ν_{NH}) and 1670 cm^{-1} ($\nu_{C=O}$).

Anal. Found: C, 76.29; H, 8.80; N, 9.06.

Determination of Absolute Configuration of Me_2PNPH.[6] In a two-necked trap tube was placed 792 mg of Me_2PNPH (obtained by the reaction with (*R*)-(+)-α-methylbenzylamine and isolated from the first fraction of the recrystallization) dissolved in 45 mL of methanol. Twenty-eight milliliters of glacial acetic acid was then poured into the methanol solution to give a yellow solution. The addition of methanol to Me_2PNPH was confirmed by the disappearance of the absorption maximum at 322 nm, a characteristic band of Me_2PNPH. Ozone was passed through the solution for 3 h at room temperature. Immediately after the ozonization, the solution was placed in a three-necked flask equipped with a $CaCl_2$-protected reflux condenser. Fifty-two milliliters of 30% aqueous hydrogen peroxide and 1.38 mL of concentrated sulfuric acid were added to the solution, and the mixture was heated to 45–50 °C in an oil bath for 44 h. After being cooled to room temperature, the mixture was neutralized to pH 7 (Merck universal indicator paper) with solid sodium carbonate. The impurities were removed by extracting the solution with ether. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and the organic materials were extracted three times with ether. The combined ether layer was dried over sodium sulfate and treated with an ethereal solution of diazomethane. Evaporation of the solvent gave an oil which was purified by three times preparative VPC (5% PEG, 1 M, 140 °C) to give 5.2 mg (1.2% yield) of dimethyl 2-methylsuccinate. The purity of the material was confirmed by VPC (5% PEG, 1 M, 140 °C and 5% Silicon DC 200, 1 M, 60 °C); $[\alpha]_D^{25}$ −3.27° (*c* 0.260, absolute EtOH); CD 208 nm ($[\theta]$ = +1.43 × 10^3, 3.3 mg/2 mL of absolute EtOH).

General Procedure for the Reduction. One millimole each of Me_2PNPH and magnesium perchlorate were dissolved in 10 mL of anhydrous acetonitrile in a sealed flask. One millimole of the substrate in 10 mL of anhydrous acetonitrile was added by injection by using a syringe, and the mixture was allowed to react at room temperature (about 25 °C) for an appropriate reaction time (2–7 days) in the dark in an argon atmosphere. The reaction was stopped by the addition of water, and the product was extracted three times with dichloromethane. The combined dichloromethane solution was dried over sodium sulfate. After evaporation of the solvent at below 30 °C under reduced pressure, the residue was chromatographed on a column of silica gel. The product was further purified by preparative VPC or high-pressure liquid chromatography when necessary. The purity of the product was confirmed by VPC and by elemental analyses. Columns used for VPC were mainly 10% DEGS or 5% Silicon DC 200. Appropriate mixtures of benzene–ether or benzene–ethyl acetate were employed as the eluents for column chromatography.

References and Notes

(1) Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, **97**, 4766 (1975).
(2) (a) Y. Ohnishi, T. Numakunai, and A. Ohno, *Tetrahedron Lett.*, 3813 (1975); (b) Y. Ohnishi, M. Kagami, T. Numakunai, and A. Ohno, *Chem. Lett.*, 915 (1976); (c) Y. Ohnishi, T. Numakunai, T. Kimura, and A. Ohno, *Tetrahedron Lett.*, 2699 (1976); (d) A. Ohno, H. Yamamoto, T. Kimura, S. Oka, and Y. Ohnishi, *ibid.*, 4585 (1976); (e) A. Ohno, T. Kimura, S. G. Kim, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bioorg. Chem.*, **6**, 21 (1977); (f) A. Ohno, T. Kimura, S. Oka, and Y. Ohnishi, *Tetrahedron Lett.*, 757 (1978).
(3) K. Nishiyama, N. Baba, J. Oda, and Y. Inouye, *J. Chem. Soc., Chem. Commun.*, 101 (1976).
(4) Cf. R. Michael, *Ber.*, **18**, 2020 (1885).
(5) Hereafter, we will denote *XY*-Me_2PNPH for an isomer of Me_2PNPH which has configurations *X* at the ring C_4 and *Y* at the benzylic carbon.
(6) J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popják, G. Ryback, and G. J. Schroepfer, Jr., *Proc. R. Soc. London, Ser. B*, **163**, 436 (1965).
(7) It should be noted that the sign of $[\alpha]_D$ for this ester changes depending on the concentration of solution used for the measurement. Therefore, great care is necessary when $[\alpha]_D$'s are compared for two samples: E. Berner and R. Leonardsen, *Justus Liebigs Ann. Chem.*, **538**, 1 (1939).
(8) G. W. Clough, *J. Chem. Soc.*, 2808 (1925).
(9) J.-P. Guetté and N. Spassky, *Bull. Soc. Chim. Fr.*, 4217 (1972).
(10) E. T. Sliller, S. A. Harris, J. Feinkelstein, J. C. Keresztesy, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 1785 (1940).
(11) (a) H. M. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968); (b) D. M. Feigl and H. S. Mosher, *ibid.*, **33**, 4242 (1968). The optical yield observed polarimetrically does not coincide with the enantiomer excess measured by NMR. Probably the reported maximum $[\alpha]_D$ value was not accurate. However, it is also possible that there is no linear relationship between enantiomer excess and $[\alpha]_D$.
(12) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89**, 5485 (1967).
(13) M. Imuta and H. Ziffer, *J. Org. Chem.*, **43**, 3530 (1978).
(14) A. G. Davies, J. Kenyon, and K. Thaker, *J. Chem. Soc.*, 3394 (1956).
(15) (a) D. Cabaret and Z. Welvart, *J. Chem. Soc., Chem. Commun.*, 1064 (1970); (b) D. Cabaret and Z. Welvart, *J. Organomet. Chem.*, **80**, 199 (1974).
(16) A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **50**, 1535 (1977).
(17) The same assumption has been applied for NAD(P)H-dependent enzymic reactions: R. Bentley, in "Molecular Asymmetry in Biology", Vol. II, Academic Press, New York, 1970, pp 36–39.
(18) Although we do not know the absolute configuration of 2-pyridylbenzyl alcohol, we may assume that (+)-2-pyridylbenzyl alcohol as the *R* configuration on the basis of configuration of 1-(2-pyridyl)ethanol.
(19) R. Stewart and R. van der Linden, *Can. J. Chem.*, **38**, 399 (1960).
(20) F. E. Herkes and D. J. Burton, *J. Org. Chem.*, **32**, 1311 (1967).
(21) D. T. Mowry, *J. Am. Chem. Soc.*, **65**, 991 (1943).
(22) F. J. Villani and M. B. King, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, 1963, p 88.