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Asymmetric Reduction of Ethyl Benzoylformate with Chiral NADH Model Systems: Mechanistic and Stereochemical Consideration of the Reactions Based on the Complexation Properties of the Model Compounds

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Asymmetric reductions of ethyl benzoylformate were conducted by use of NADH model compounds with C_1 or C_2 symmetry in the presence of magnesium perchlorate. It was found that NADH model compounds which form 2 : 1 chelation complexes with the magnesium ion showed the dependence of optical yield on the reaction conversion. The stereochemical behaviors of the model compounds were classified into three reaction types on the basis of the component ratio in the chelation complex between the reductants and the magnesium ion.

INTRODUCTION

Modeling of enzyme and coenzyme function by use of their simple analogs has been extensively studied in the field of bioorganic chemistry (*1*) as well as asymmetric synthesis (*2*).

It is well known that in the redox reaction catalyzed by NAD(H)-dependent dehydrogenases, only one of the diastereotopic hydrogens, at the 4-position of the dihydronicotinamide, is transferred to substrate (*3*). This stereochemical choice is ascribed to the blockage of the other face of the dihydropyridine by the amino acid residue(s) at the active site (*4*).

Recently, such specific blockage of dihydronicotinamide was found to occur in nonenzymatic NADH model reactions as well. This is exemplified by the two experimental findings. One is the asymmetric reduction with chiral bis-type NADH analogs whose C_2 symmetry constrains the equivalent dihydropyridine nuclei to block the specific face of each other in an intramolecular manner (*5*). The other example is an unusual phenomenon in that, in asymmetric reduction of ethyl benzoylformate with chiral NADH model compounds, the optical yield increased as the reaction proceeded. This finding has been explained in terms of the intermolecular specific blockage of diastereotopic faces of dihydropyridine nucleus by the oxidized form of the coenzyme models formed in the reaction mixture (*6*, *7*). However, we recently found that there existed chiral NADH model compounds which did not show any dependence of product stereochemistry on the reaction

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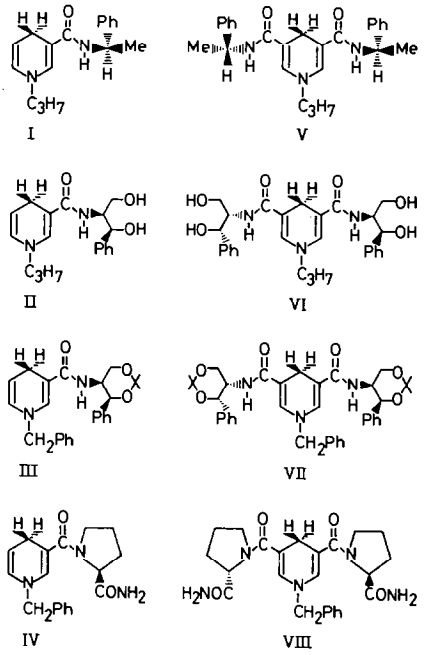


SCHEME 1

conversion as presented in this report.[1] This fact unambiguously indicates that such time-dependent phenomena are not always a general feature in the reactions of chiral NADH model compounds. From this view, we now report about what situation is necessary for the appearance of stereochemical anomalies of this kind.

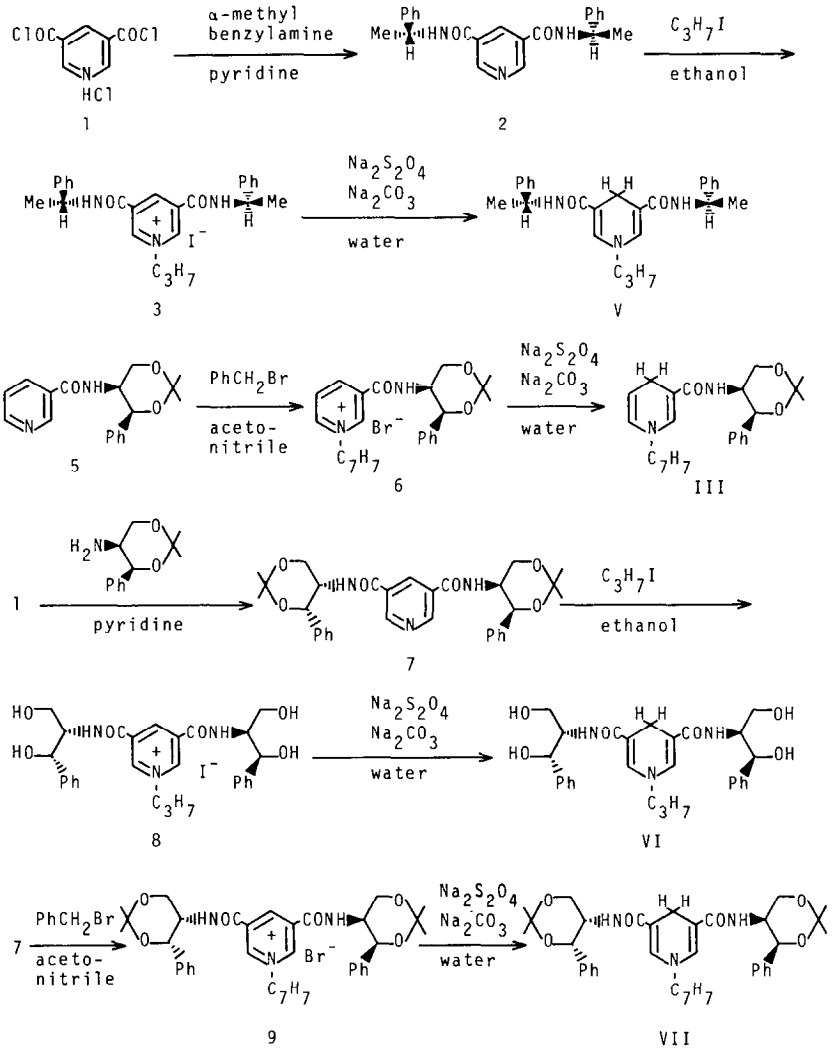
RESULTS AND DISCUSSION

Synthesis of Chiral NADH Model Compounds

The chiral 1,4-dihydropyridine reductants **I–VIII** (Scheme 1) were chosen as model compounds to test the importance of the effect of functional groups chelative with metal ion and/or symmetry factors (C_1 and C_2 symmetry) (*8*) on the stereochemical course of the hydrogen transfer. Among the reductants, the preparations and asymmetric reductions with **I** (*6*), **II** (*7*), **IV** (*9*) and **VIII** (*9*) were already reported, and the others were prepared in the present study according to Scheme 2.

3,5-Dinicotinoyl chloride hydrochloride(**1**) was prepared by a modification reported by Dittmer and Blindner (*10*). The reductant **V**, with C_2 symmetry, bearing α-methylbenzylamine as the chiral source, was synthesized in the following way.

[1] About the bis-type model compounds, two examples have been reported where such dependence was not deserved [see Refs. (*5*, *8*)].



SCHEME 2

3,5-Dinicotinoyl chloride hydrochloride (**1**) was condensed with α-methylbenzylamine, and the amide **2** obtained was quaternized with *n*-propyl iodide to the oxidized form **3**, followed by sodium dithionite reduction. The dihydropyridine **V** was isolated pure by silica gel column chromatography eluted with chloroform–methanol in the dark. When the compound was dissolved in a small amount of dichloromethane, and an excess of petroleum ether was added to the solution, model compound **V** was obtained as a light yellow precipitate, which was dried over phosphorus pentoxide *in vacuo* after filtration.

The C_1- and C_2-NADH model compounds **III, VI,** and **VII,** having aminodiol or its dioxane as a chiral center, were synthesized as follows. Nicotinic acid deriva-

tive **5** was prepared by condensation of nicotinoyl chloride hydrochloride with (4*S*, 5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**4**) in dry pyridine. The oxidized form **6**, obtained by quaternization, was reduced to C_1-model compound **III** with sodium dithionite. C_2-Model compounds **VI** and **VII** were obtained from the dichloride **1** via diamide **7** in the same manner as **V**. Because of the low solubility of **VI** in chloroform, the extraction from the aqueous phase was effected by a mixture of chloroform and methanol (2 : 1). In the preparation of **9**, the use of dry acetonitrile was needed as a solvent, otherwise hydrolysis of the isopropylidene group occurred during the process. The sodium dithionite reduction of the bromide **9** was carried out as usual, and pure **VII** was obtained by liquid chromatography.

Complexation of the NADH Model Compounds with Magnesium Perchlorate as Studied by Means of UV Spectroscopy[2] *(12)*

The model compounds **I–VIII** showed the characteristic absorption maximum at 349–386 nm attributed to a π–π^* transition in dihydropyridine nucleus (*11*). Upon addition of magnesium perchlorate to a solution of the reductants, red shift of the band was observed. According to the mole ratio method, when the uv absorbance of the reductants in the presence of varying amounts of magnesium perchlorate was plotted against the mole ratio of the two components at appropriate wavelengths, an inflection point will appear if it forms a chelation complex with the metal. This point represents the component ratio of the complex between the model and magnesium ion. This method was applied for the model compounds listed in Scheme 1 and the results were shown in Fig. 1.

In the case of NAH-**I**,[3] a spectral change was observed, but there was no clear-cut inflection. However, interaction between the reductant and magnesium was detected by ir spectroscopy. Upon addition of magnesium perchlorate to **I**, the stretching vibration of the secondary amide carbonyl group shifted by about 6 cm^{-1} to lower frequency. NAH-**V** showed no spectral change, which indicates the absence of complex formation between the reductant and magnesium ion. The same was the case with NAH-**III** and **VII**. For NAH-**II** and **IV**, an unambiguous inflection point appeared at the mole ratio of 0.5, indicating that these model compounds form a 2 : 1 complex between the NAH and magnesium ion.

However, when the two chiral moieties were introduced into one reductant molecule, **VI** was found to show an inflection point at the mole ratio of 1.0 ($NAH : Mg^{2+} = 1 : 1$). On the other hand, **VIII** showed two inflection points at the mole ratios of 0.5 and 2.0. This finding suggests the capability of the reductant to form two kinds of complexes, involving different stoichiometries of the partners.

It was concluded from these results that the characteristic of the NADH model compounds was largely ascribed to the polar functions capable of chelating with the magnesium ion. As discussed in the following section, this feature is closely related to the dynamic aspect of stereochemistry in the asymmetric reduction by use of these model compounds.

[2] There have been a number of complexation studies of NADH model compounds, e.g. (*8*) and references cited within.

[3] Abbreviation used: NAH, NADH model compound.

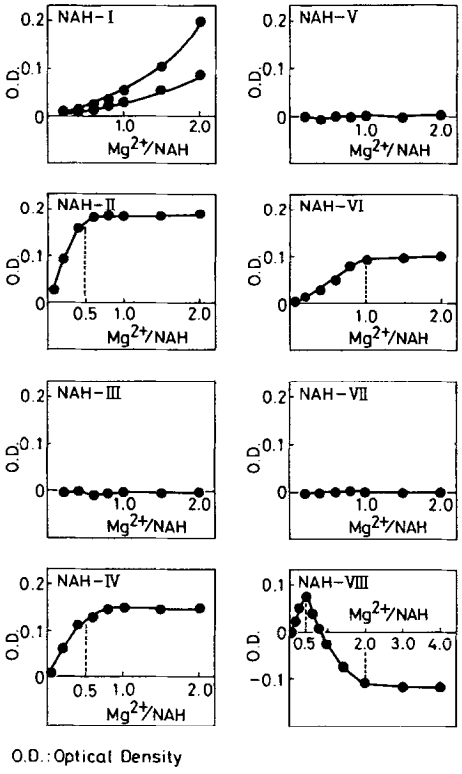
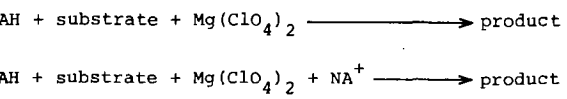


FIG. 1. Determination of the mole ratio in the complexes of NAHs with magnesium perchlorate by uv spectroscopy.

Asymmetric Reduction with NADH Model Compounds and the Dependence of Optical Yields on the Reaction Conversion

As described in the introduction, an increase of the optical yield with the reaction conversion have been reported by Ohno (*6*) and Inouye (*7, 12*) in the asymmetric reduction of ethyl benzoylformate with model compounds **I** and **II**. To explain this phenomenon, the authors assumed that the asymmetric reduction was composed of two processes as shown in Schemes 3A and B, and that the two pathways afford different enantioselectivity. Since the relative contribution of these processes changes as the reaction proceeds, the final optical yield of the product, ethyl mandelate, should be varied. It has been claimed (*7*) that functional groups capable of chelating with the magnesium ion were important for the operation of this mechanism. However, the assessment of the functionality and the model structure to determine how a given model compound behaves in this respect has not been persued yet in detail.

Thus, in the present study, ethyl benzoylformate was reduced by use of model compounds **III, V, VI, VII,** and **VIII** for varying reaction times, and the optical yields of the mandelate were plotted against the time. The results are summarized in Fig. 2 in addition to those cited from references for **I** (*6*), **II**(*7*) and **IV** (*9b*). One



SCHEME 3

of the noteworthy findings is that NAH-**III**, -**V**, -**VI**, and -**VII** showed no dependence of enantiomeric excess on the reaction conversion, in contrast to the cases with **I**, **II**, and **IV**. When these results were compared with complexation properties of the model compound described in Fig. 1, it was clear that **II** and **IV**, capable of complexing with the magnesium ion at the ratio of NAH : Mg^{2+} = 2 : 1, showed the dependence of the optical yield on the reaction time, whereas such dependence was not observed with **VI**, which formed complex at the ratio of 1 : 1, and with **III**, **V**, **VII**, which showed no complex formation. Although NAH-**I** was found to show no inflection point, the dependence is known to occur (*6*). In the case of **VIII**, when the ratio was VIII : Mg^{2+} = 2 : 1, the dependence appeared, however, at the ratio of VIII : Mg^{2+} = 1 : 2, no change of the optical yield was observed at all. As summarized in Table 1, asymmetric reactions mentioned above could be

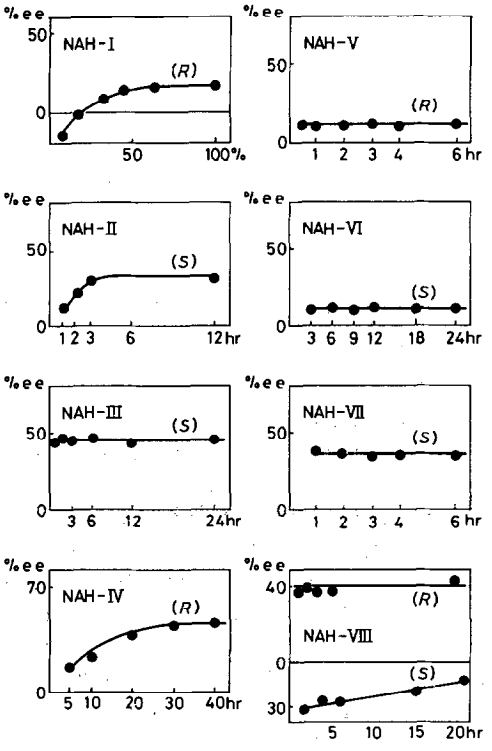


FIG. 2. Dependence of e.e. on the reaction conversion or reaction time in the asymmetric reductions of ethyl benzoylformate with NAHs **I**–**VIII**. Relative amounts of magnesium perchlorate to the models are as follows: $Mg(ClO_4)_2$/NAH = 0.5 (**I**, **II**, **IV**), 1.0 (**III**, **V**, **VI**), and 2.0 (**VII**). $Mg(ClO_4)_2$/**VIII** = 0.5 (lower) and 2.0 (upper).

TABLE 1

SUMMARY OF EXPERIMENTAL RESULTS IN THE ASYMMETRIC REDUCTIONS WITH NADH MODEL COMPOUNDS **I–VIII**

NADH model reductants	Dependence of e.e. on the reaction conversion	Symmetry of NAH	NAH/Mg^{2+} ratio	Type of reaction
I	Dependent	C_1	Equivocal	A
V	Independent	C_2	No complex	C
II	Dependent	C_1	2 : 1	A
VI	Independent	C_2	1 : 1	B_1
III	Independent	C_1	No complex	C
VII	Independent	C_2	No complex	C
IV	Independent	C_1	No complex	C
VIII	Dependent	C_2	2 : 1	A
	Independent		1 : 2	B_2

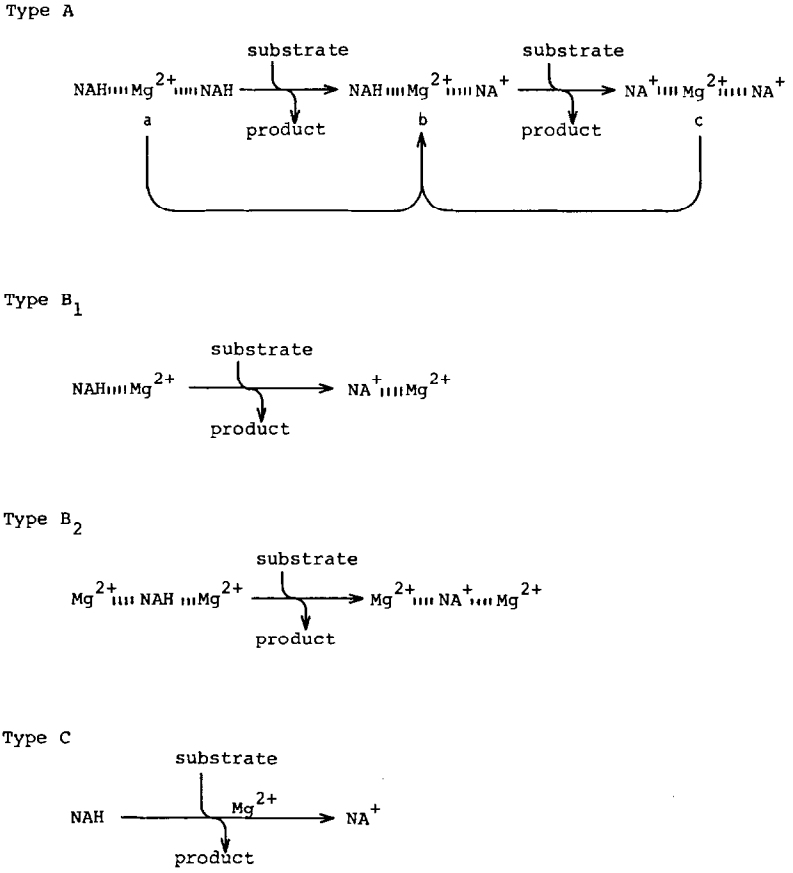
classified in three types, A, B (B_1 and B_2), and C, based on the observed component ratio of the complex with magnesium ion. Although the mechanism of the stereochemical determining step in the asymmetric reductions is not yet clear, the following explanation presented in Scheme 4 will afford a key to better understanding of the complexity in the NADH model reactions.

Type A: This type is essentially the same as that given in Schemes 3A and B. The NAHs are capable of complexing with magnesium at the ratio of NAH : Mg $(ClO_4)_2$ = 2 : 1. Scheme 4 shows that, in the early stage of reduction, the fully reduced complex **a** may operate solely as a reductant and produce half-oxidized reductant **b**, which has still reducing power of the substrate but with different enantioselectivity. However, as the reaction proceeds, the reduction, with half-oxidized form **b** predominating and giving the same product in different enantiomeric excess and inactive **c**, which may reproduce the reaction species **b** through the probable exchange reaction (*9b, 12*) with the complex **a**. It then follows that the overall optical yield of the product varies gradually as the reaction proceeds.

Type B: The NAHs can form complexes with magnesium at mole ratios of NAH : Mg = 1 : 1 (Type B_1) or 1 : 2 (Type B_2). In these model compounds, the oxidized form produced during the reaction can no longer take part in the reduction. Also, if the oxidized form interacts with the reductant complex, it could not produce half-oxidized reductant such as **b** in Type A. Accordingly, the [reductant–Mg^{2+}] or [Mg^{2+}–reductant–Mg^{2+}] complex operate solely through the reaction course, and the optical yield remains constant.

Type c: The NAHs which can not form complexes with metal ion are categorized herein. The absence of complex formation in these systems excludes the oxidized form from the reduction process, and the optical yield should be constant.

Thus, the time-dependent nature of the product stereochemistry will occur only when the reaction species produced from the original reductant still has reduction activity with different enantioselectivity.



SCHEME 4. Classification of the reaction types based on the observed component ratio of the complexes with magnesium ions.

Here, the experimental results should be considered in relation to the symmetry of the model compounds (C_1 or C_2). About C_1-model compounds, they have diastereotopic faces of the dihydronicotinamides. Accordingly, specific blockage of one of the faces may cause a change of enantioselectivity, as described in the Introduction. On the other hand, since model compounds with C_2 symmetry have homotopic faces, blockage of either of the faces by their oxidized forms may afford the same new reductants with equal enantioselectivity. However, if the new reductant (blocked) and the original have different enantioselectivity, the conversion dependence of the optical yield should be observed even with the C_2-type model compounds as well. This may be the case with **VIII** at Mg^{2+}/**VIII** = 0.5, where enantioselectivity was found to be conversion dependent.

In the present study, it was found that the dependence of optical yield on the reaction conversion arising from the feedback effect of the oxidized form did not always occur for any NADH model compounds, and their stereochemical behavior has been reasonably related to the complexation ability of NADH model compounds and/or the constitution ratio of the complex as an index. This relation

may be applied in the prediction of the stereochemical behavior of NADH model compounds in the asymmetric reduction therewith.

EXPERIMENTAL PROCEDURES

Instrument

IR spectra were recorded in a KBr discus with a Hitachi 215 spectrometer, and PMR spectra with a Varian EM-360 spectrometer in chloroform-d_1 unless otherwise specified, with tetramethyl silane as an internal standard. UV spectra were recorded with Hitachi 340 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. VPC analyses were performed on Simadzu GC-4CM with 15% polyethylene glycol succinate on chromosorb W at 150°C. Preparative VPC was performed by Varian Aerograph Model 920 with an aluminum column (3 m) packed with 15% Apiezone L at 190°C.

Material

Ethyl benzylformate from a commercial source was purified by column chromatography (Kieselgel 60, 70–230 mesh) eluted with benzene followed by distillation. Anhydrous magnesium perchlorate was kept in a vacuum desicator over phosphorus pentoxide. Acetonitrile and ethanol were distilled over phosphorus pentoxide and calcium hydride, respectively.

General Procedure for Asymmetric Reduction

A solution of ethyl benzoylformate, model compound, and magnesium perchlorate in dry acetonitrile (10 ml/1.0 mmol) was stirred for 24–48 h at room temperature under nitrogen in the dark, after which water (1 ml) was added to the reaction mixture and the product was extracted with dichloromethane. The organic layer was concentrated and the residue was chromatographed on TLC (Kiesel gel G, Type 60), with benzene giving pure ethyl mandelate. Optical yield was determined based on the reported maximum rotation, $[\alpha]_D^{25}$ +104.4° (ethanol) (*13*).

3,5-Dinicotinoyl chloride hydrochloride (**1**). This compound was prepared by the method of Dittmer and Blindner (*10*) with a slight modification. Dry 3,5-dinicotinic acid (50 g, 0.30 mol) was added portionwise to thionyl chloride (120 ml, 1.66 mol) with stirring at room temperature. After the addition, 8 drops of *N,N*-dimethylformamide were added as catalyst, and the solution was refluxed for 1.5 h. After standing overnight, the reaction mixture was refluxed for 1 h. Then, excess thionyl chloride was distilled off under reduced pressure, followed by addition of benzene (80 ml) and evaporation of the solvent. This procedure was repeated three times. Crystalline 3,5-dinicotinoyl chloride hydrochloride thus formed was used for acylation of chiral amino compounds.

3,5-Di[(R)-α-methylbenzylaminocarbonyl]pyridine (**2**). Into a suspension of the chloride (**1**) (9.7 g, 40.3 mmol), (*R*)-α-methylbenzylamine (9.7 g, 80.3 mmol, $[\alpha]_D^{25}$ +39.7°, neat) in pyridine (30 ml) was added dropwise at room temperature. After the addition, the reaction mixture was kept at 85°C for 1 h, and was allowed to

cool to room temperature. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate. The product was extracted with dichloromethane, and the organic layer was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residual brown oil was chromatographed on a silica gel column with chloroform and methanol to yield an yellow oil, which was crystallized from ethyl acetate–*n*-hexane. Yield, 11.7 g (90%); mp, 182–183°C (decomp.); $[\alpha]_D^{25}$ −5.6° (*c* 1.00, ethanol); PMR δ (ppm, $CDCl_3$): 1.50 (6H, d, $-CH_3$), 5.20 (2H, dd, $-CH_2Me$), 7.30 (10H, m, aromatic protons), 7.80 (1H, s, pyr-C_4-H), 9.05 (2H, br, pyr-$C_{2,6}$-2H).

N_1-Propyl-3,5-di[(R)-α-methylbenzylaminocarbonyl]-1,4-dihydropyridine (**V**). The above pyridine derivative (**2**) (11.4 g, 30.6 mmol) and *n*-propyl iodide (21 g, 123.5 mmol) in dry ethanol (100 ml) were heated under reflux for 6 h, and low-boiling materials were evaporated *in vacuo*. The residual oil was dissolved in a minimum volume of ethanol, and was poured into an excess of ether with vigorous stirring; the precipitated yellow solid was collected by filtration. This solid was a mixture of the iodide, the dihydropyridine, and degradation product as shown by TLC (silica gel, chloroform–methanol). Sodium dithionite (15.7 g, 90 mmol) and a solution of the yellow solid in methanol (200 ml) were added successively into an aqueous solution of sodium carbonate (1.6 g, 15.1 mmol in 200 ml of water) after saturating with carbon dioxide. The mixture was kept in the dark at room temperature overnight. After removal of methanol at 30°C under reduced pressure, the mixture was extracted three times with dichloromethane, and the solution was dried over anhydrous sodium sulfate. The solvent and low-boiling materials were evaporated *in vacuo*. The residual oil was chromatographed on silica gel with chloroform and methanol to afford yellow fluorescent oil, whose purity was assured by TLC (silica gel, chloroform). The oil was dissolved in a minimum volume of a mixture of chloroform and methanol, and poured into an excess of petroleum ether to give **V** as powder. Yield, 85 mg (68%). $[\alpha]_D^{25}$ −253.6° (*c* 1.42, ethanol); UV λ_{max} (ethanol): 386 nm (ε_{max} 6853). PMR δ (ppm, $CDCl_3$): 0.84 (3H, t, $-CH_3$), 1.50 (8H, m, $-CH_2Me$, $-CPhCH_3$), 3.25 (2H, s, pyr-C_4-2H), 5.10–5.20 (2H, br, —CHPhMe), 6.72 (2H, s, pyr-$C_{2,6}$-2H), 7.28 (10H, m, s, aromatic protons).

N_1-Benzyl-3-[(4'S,5'S)-2',2'-dimethyl-4'-phenyl-1',3'-dioxane-5'-yl-aminocarbonyl]pyridinium bromide (**6**). A mixture of the amide **5** (15.5 g, 50 mmol) and benzyl bromide (42.8 g, 0.25 mmol) in dry acetonitrile (100 ml) was stirred at room temperature overnight. The precipitate was filtered, and was washed with dry acetonitrile to give **6**. Yield, 22.3 g (93.0%); $[\alpha]_D^{25}$ +62.83° (*c* 1.095, DMSO). PMR δ (ppm, $CDCl_3$): 1.65, 1.80 (6H, s, $-CH_3$), 2.63 (1H, br, —NCH—), 4.33 (2H, m, $-CH_2O$-), 5.33 (1H, d, —CHPh), 5.96 (2H, s, $-CH_2$-Ph), 7.16-7.70 (10H, m, aromatic protons), 8.30–9.20 (4H, m, pyridine).

N_1-Benzyl-3-[(4'S,5'S)-2',2'-dimethyl-4'-phenyl-1',3'-dioxane-5'-yl-aminocarbonyl]-1,4-dihydropyridine (**III**). The quaternized salt **6** (11.0 g, 22.0 mmol) was dissolved in water (100 ml) and chilled to 0°C. To the solution were added methanol (10 ml), sodium carbonate (11.0 g, 0.104 mol), and sodium dithionite (100 g, 0.57 mol) with stirring under nitrogen atmosphere. After 3 h, the mixture was extracted with chloroform, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated, giving **III** as amorphous pow-

der. Yield, 7.8 g (84.8%); $[\alpha]_D^{25}$ +190.0° (*c* 1.02, ethanol); UV λ_{max} (ethanol): 350 nm(ε_{max} 4780). IR ν(cm^{-1}, KBr): 3460 ν(N—H), 1690 ν(C=O), 690–850 δ (aromatic C—H). PMR δ (ppm, $CDCl_3$): 1.53 (6H, s, —CH_3), 3.00 (2H, m, pyr-C_4-2H), 4.16 (2H, s, —CHPh), 4.16 (2H, m, —CH_2O—), 4.66 (1H, m, pyr-C_5-H), 5.20 (1H, m, —CHPh), 5.70 (3H, m, pyr-C_6-H, —NCH_2Ph), 6.90 (1H, s, aromatic protons).

3,5-Di[(4'S,5'S)-2',2'-dimethyl-4'-phenyl-1',3'-dioxane-5'-yl-aminocarbonyl] pyridine (**7**). To a solution of the chloride (**1**) (13.0 g, 54.0 mmol) in pyridine (100 ml) was added the dioxane derivative **4** (23.1 g, 0.11 mmol) in pyridine (50 ml), maintaining the reaction temperature at 0°C. The reaction mixture was then heated at 50°C for 2 h, cooled, and concentrated at reduced pressure. The residue was poured into saturated sodium hydrogen carbonate (300 ml), and the organic material was extracted with chloroform. The organic layer was washed with water and brine, and was dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a syrup, which was chromatographed on silica gel column with chloroform–methanol (10 : 1) to give pure **7.** Yield, 17.0 g (57.6%), $[\alpha]_D^{25}$ +106.1° (c 0.54, DMSO). IR ν (cm^{-1}, KBr): 3400 ν (N—H), 1670 ν (C=O), 1520 (C=C), 680–880 δ (aromatic C—H). PMR δ (ppm, $CDCl_3$): 1.46, 1.50 (6H, s, —CH_3), 2.63 (2H, br, —NCH—), 4.00 (4H, dd, J = 12 Hz, —CH_2O—), 4.93 (2H, br, —CHPh), 7.36 (10H, s, aromatic protons), 8.16 (1H, br, pyr-C_4-H), 8.63 (2H, dd, J = 2 Hz, pyr-$C_{2,6}$-2H).

N_1-n-Propyl-3,5-di[(1'S,2'S)-1',3'-dihydroxy-1'-phenyl-propane-2'-yl-aminocarbonyl]pyridinium iodide (**8**). The amide **7** (5.45 g, 10.0 mmol) and *n*-propyl iodide (5.0 g, 29.0 mmol) were dissolved in ethanol and heated at reflux for 7 h. The mixture was concentrated under reduced pressure to give **8** as amorphous powder. Yield, 5.0 g (80.5%); $[\alpha]_D^{25}$ +84.8° (*c* 1.28, ethanol). IR ν (cm^{-1}, KBr): 3350 ν (O—H), 1660 ν (C=O), 660–800 δ (aromatic C—H). PMR δ (ppm, DMSO-d_6): 1.00 (3H, m, —CH_3), 2.00 (2H, m, —CH_2Me), 3.36 (4H, s, —OH), 3.53 (6H, m, —CH_2O—, NCH—), 4.30 (2H, m, —NCH_2), 5.00 (2H, m, —CHPh), 7.33 (10H, m, aromatic protons), 8.33 (2H, m, NH), 9.33 (1H, s, pyr-C_4-H), 9.50 (2H, s, pyr-$C_{2,6}$-2H).

N_1-n-Propyl-3,5-di[(1'S,2'S)-1',3'-dihydroxy-1'-phenyl-propane-2'-yl-aminocarnonyl]-1,4-dihydropyridine (**VI**). The iodide 8 (5.3 g, 8.4 mmol) was dissolved in minimum volume of methanol and water. The mixture was extracted with chloroform in order to remove insoluble material. The aqueous phase was added dropwise to an aqueous sodium carbonate solution (pH 8.0) containing sodium dithionite (10.0 g, 5.74 mmol) with stirring at room temperature. After 3 h, the reaction mixture was extracted with a mixture of chloroform and methanol (1 : 1). The organic phase was concentrated to give yellow fluorescent powder. Yield, 2.2 g, (51.6%); $[\alpha]_D^{25}$ +248.2° (*c* 1.08, ethanol). UV λ_{max} (ethanol): 385 nm (ε_{max} 7573). IR ν (cm^{-1}, KBr): 3300 ν (O—H), 1695 ν (C=O), 1470 ν (C=C), 700–780 (aromatic C—H). PMR δ (ppm, CD_3OD): 0.7–2.0 (5H m, —CH_2CH_3), 3.0–3.4 (4H, m, pyr-C_4-2H, NCH_2—), 3.66 (4H, m, —CH_2O), 4.26 (2H, dd, J = 5Hz, NCH—), 5.66 (2H, d, J = 5Hz, —CHPh), 6.87 (2H, s, pyr-$C_{2,6}$-2H), 7.36 (10H, m, aromatic protons).

N_1-Benzyl-3,5-di[(4'S,5'S)-2',2'-dimethyl-4'-phenyl-1',3'-dioxane-5'-yl-aminocarbonyl]pyridinium bromide (**9**). Into an acetonitrile (100 ml) solution of the

amide **7** (5.45 g, 10 mmol), benzyl bromide (8.55 g, 50 mmol) was added and heated under reflux with stirring. During 1 h, colorless crystalline material precipitated, and the mixture was kept at room temperature for 10 h. The bromide **9** precipitated was filtered, washed with ether, and dried over phosphorous pentoxide. Yield, 2.0 g (28%); $[\alpha]_D^{25}$ +113.7° (*c* 1.04, DMSO). IR ν (cm^{-1}, KBr): 1675 ν (C=O), 1530 ν (C=C), 680–760 δ (aromatic C—H). PMR δ (ppm, $CDCl_3$): 1.40, 1.53 (6H, s, $—CH_3$), 2.20 (2H, br, —NCH—), 4.10 (4H, m, $—CH_2O—$), 5.13 (2H, br, —CHPh), 5.80 (2H, s, $—NCH_2Ph$), 6.80–7.30 (10H, m, aromatic protons), 7.33 (5H, s, aromatic protons), 8.20–8.50 (3H, m, pyr-C_4-H), 9.33 (2H, s, pyr-$C_{2,6}$-2H).

N_1-Benzyl-3,5-di[(4'S,5'S)-2',2'-dimethyl-4'-phenyl-1',3'-dioxane-5'-yl-aminocarbonyl]-1,4-dihydropyridine (**VII**). Sodium carbonate (371 mg, 3.5 mmol) was dissolved in water (5 ml), and the solution was adjusted to pH 8.0 by bubbling with carbon dioxide. To the solution were added the bromide **9** (500 mg, 0.7 mmol) in methanol (10 ml) and sodium dithionite (3.7 g, 21.2 mmol), and the mixture was kept in the dark overnight. Yellow precipitate was filtered, washed with water, and dried over phosphorous pentoxide to give **VII**. Yield, 230 mg (69.7%); $[\alpha]_D^{25}$ +328.3° (*c* 0.98, ethanol). UV λ_{max} (ethanol): 380 nm (ε_{max} 8016). IR ν (cm^{-1}, KBr), 3450 ν (N—H), 1690 ν (C=O), 1580 ν (C=C), 700–850 δ (aromatic C—H). PMR δ (ppm, $CDCl_3$): 1.60 (6H, s, $—CH_3$), 1.93 (2H, br, —NCH—), 2.90 (2H, s, pyr-C_4-2H), 4.16 (4H, m, $—CH_2—$), 4.20 (2H, s, $—NCH_2Ph$), 5.26 (2H, d, J = 2Hz, —CHPh), 5.83 (2H, m, NH), 6.86 (2H, s, pyr-$C_{2,6}$-2H), 7.33 (15H, s, aromatic protons).

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