Lipase-Catalyzed Enantioselective Hydrolysis of Bis(acyloxymethyl) 1,4-Dihydro-3,5-pyridinedicarboxylates Leading to Optically Active Medicines

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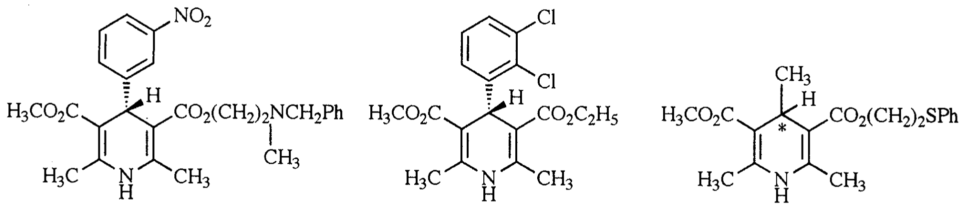
Chiral 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates and 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate have been obtained in 80—99% ee by lipase-catalyzed hydrolysis of bis(acyloxymethyl) 1,4-dihydro-3,5-pyridinedicarboxylate in an H_2O/organic solvent system. These chiral dihydropyridines were readily converted into chiral drugs, such as nicardipine, felodipine and PCA 4248.

Key words 1,4-dihydropyridine; lipase-catalyzed reaction; calcium antagonist

4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates have been well investigated from the pharmacological point of view, and their derivatives have been used as highly effective calcium antagonists and antihypertensive drugs for more than 20 years (Chart 1).[1−3] Further, recent studies showed that 4-methyl-1,4-dihydropyridines, such as PCA 4248, have platelet-activating factor (PAF)-antagonistic activity (Chart 1).[4−6] 1,4-Dihydropyridines having different ester groups on the 3 and 5 positions, possess a stereogenic carbon at the 4 position in the 1,4-dihydropyridine nucleus, and the enantiomers have been reported to show different biological activities.[7−9] For example, 2-[benzyl(methyl)amino]ethyl methyl 4-(3-nitrophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (nicardipine) has an asymmetric carbon at C-4 in the 1,4-dihydropyridine nucleus, and the (*S*)-isomer is more potent than the (*R*)-isomer.[8] Many dihydropyridines have been employed therapeutically and most of them have been developed and used as racemates, because of the lack of an efficient asymmetric synthesis, except for the optical resolution of racemates by using chiral alkaloids[8] and the separation of diastereomeric compounds.[10−14] We focused on the use of enzymes as a practical method.[15−17] The failure of our preliminary enzymatic hydrolysis of dialkyl esters suggested that lipases were not suited for the hydrolysis of sterically hindered carboxylic acid esters such as 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates. However, we have overcome the difficulties by introducing pivaloyloxymethyl esters, and have developed an efficient method for the lipase-catalyzed asymmetric synthesis of chiral 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates.[18] In this paper, we present the details of the first lipase-catalyzed asymmetric synthesis of optically active 1,4-dihydropyridine derivatives in an organic solvent.

We designed the acyloxymethyl esters[19] as suitable functional groups for the lipase-catalyzed hydrolysis.[18,20] One of the two acyloxymethyl groups in **1** has been found to be hydrolyzed enantioselectively with lipase to give optically active monoesters (**2**) through the unstable hydroxymethyl ester, as shown in Chart 2. Using bis(pivaloyloxymethyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**1a**), preliminary screening tests on various lipases revealed that lipase AH (*Pseudomonas* sp.)[21] and lipase PS (*Pseudomonas cepacia*)[21] were well suited for the hydrolysis. First, the reaction was carried out in a buffer solution (Table 1, entry 1). Although the optical purity of the monoester (**2a**) was extremely high (>99% ee), the slow reaction rate and difficult extraction procedure were impractical. Recent studies have shown that there are many advantages to the use of enzymes in an organic solvent rather than in aqueous media.[15−17] 1) The reaction procedure is convenient in an organic solvent. 2) The reactions in an organic solvent can be carried out at a higher concentration than in aqueous media. We finally found that the enzymatic hydrolysis proceeded smoothly in water-saturated diisopropyl ether (IPE) (Table 1, entry 2). The reaction was carried out by stirring a mixture of **1a** (1 mmol) and lipase AH (100 mg) in water-saturated



(*S*)-Nicardipine (*S*)-Felodipine PCA 4248

Chart 1

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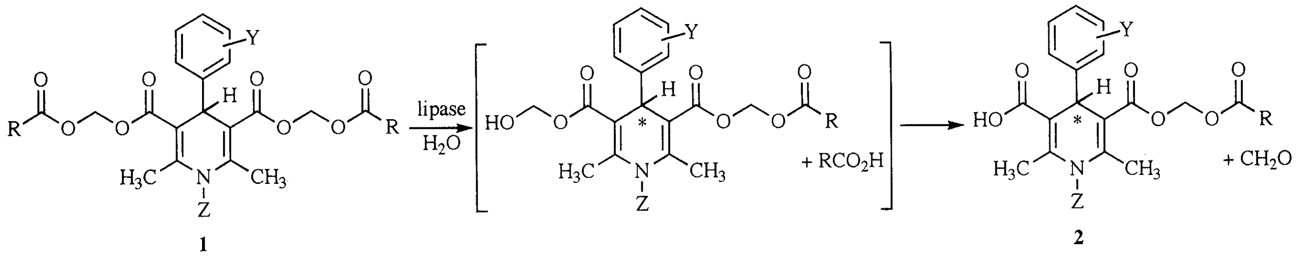

Chart 2

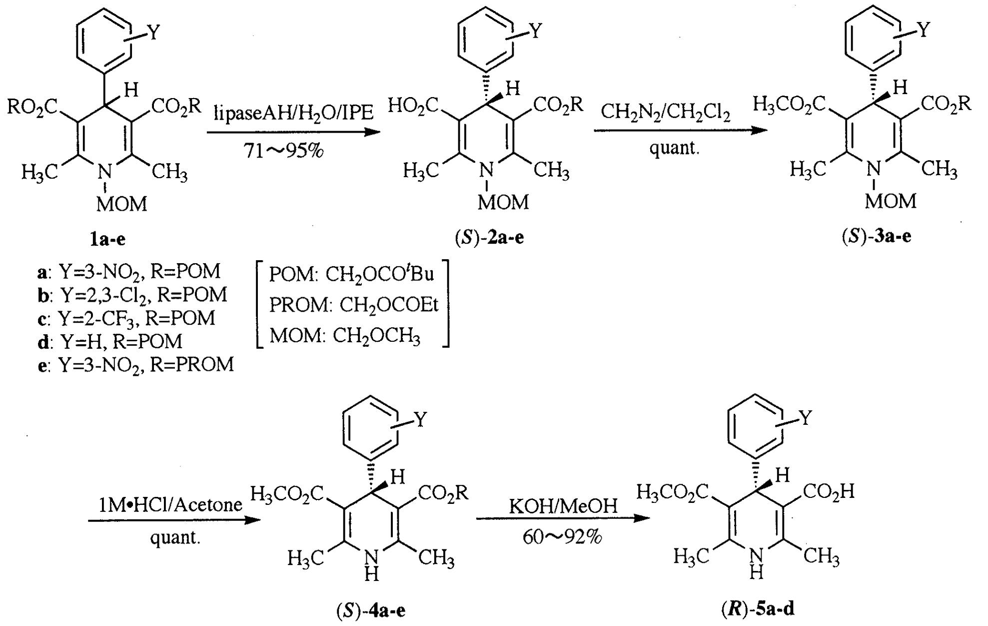

Chart 3

Table 1. Lipase-Catalyzed Enantioselective Hydrolysis of Chiral 1,4-Dihydropyridines[a)]

Entry	Substrate	Lipase	Solvent	Time (h)	Product				
					No.	C.Y. (%)[b,c)]	O.Y. (%ee)[d)]	$[\alpha]_D^{25}$ deg.[e)]	Config.
1	**1a**	AH	Buffer (pH 8)	24	**2a**	80	>99	+42.6	*S*
2	**1a**	AH	H_2O/IPE	4	**2a**	95	>99	+42.6	*S*
3	**1b**	AH	H_2O/IPE	6	**2b**	81	96	+22.0	*S*
4	**1c**	AH	H_2O/IPE	7	**2c**	83	>99	+33.8	*S*
5	**1d**	AH	H_2O/IPE	5	**2d**	76	>99	+43.5	*S*
6	**1a**	PS	H_2O/IPE	72	**2a**	44	69	−28.7	*R*
7	**1e**	AH	H_2O/IPE	8[f)]	**2e**	71	>99	+49.7	*S*
8	**1e**	PS	H_2O/IPE	10	**2e**	78	88	−42.1	*R*
9	**1f**	AH	H_2O/IPE	35	**2f**	83	93	+27.9	*S*
10	**1f**	AH	H_2O/Cyclohexane	48	**2f**	88	89	−26.7	*R*
11	**6**	AH	H_2O/IPE	8	**7**	76	91	+25.8	

a) All reactions were carried out by stirring a mixture of a substrate (1 mmol), crude lipase (AH; 100 mg, 20000 units, PS; 200 mg, 3600 units) and IPE (25 ml) saturated with water at room temperature, unless otherwise noted. *b*) Isolated yields. *c*) Satisfactory elemental analysis of all products were obtained. *d*) The optical yields were determined by HPLC analysis using a Chiralcel OD column (2-propanol/*n*-hexane) after conversion to the benzyl ester (3: R = CH_2Ph). *e*) Acetone, *c* = 1—2. *f*) At 0—5 °C.

IPE (25 ml) for 4 h at room temperature. The mixture was concentrated after removal of the enzyme, and the pure product was easily obtained by a single recrystallization or by flash silica gel column chromatography. In order to confirm the utility of this procedure, the 2,3-dichlorophenyl (**1b**),[22)] 2-trifluoromethylphenyl (**1c**)[23)] and phenyl (**1d**) derivatives were allowed to react under the same conditions, with good results (Table 1, entries 3—5). Compound (−)-**2a** has *S* configuration because (−)-**5a** derived from (+)-**2a** has the same specific rotation as that reported for (*R*)-(−)-**5a** (Chart 3).[8)] The absolute configurations of **2a**—**4a** were determined based on this result. We also confirmed the absolute configuration of **2b** obtained by the enzymatic reaction by its conversion into (*S*)-felodipine.[11)] The signs of the specific rotations of **2a**—**5a** were the same as those of **2c**—**5c** and **2d**—**5c**. Hence **2c** and **2d** should have same configuration as that of the 3-nitrophenyl derivatives. Although the hydrolysis

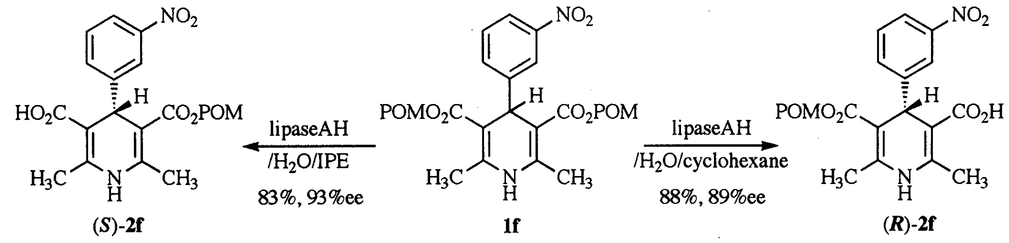

Chart 4

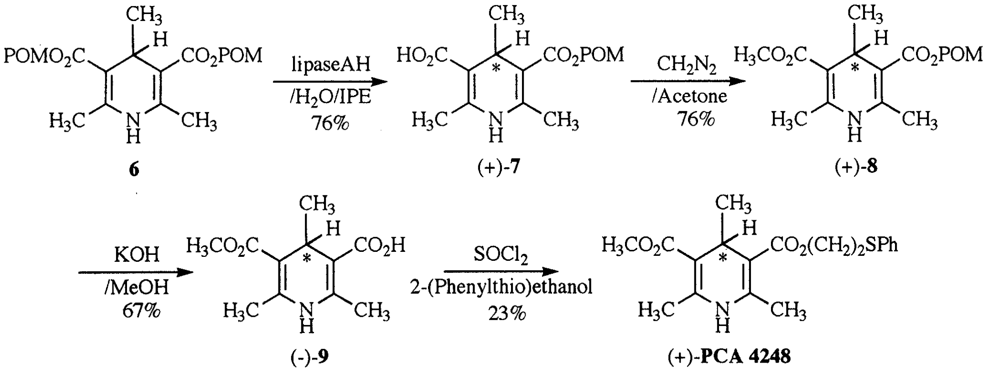

Chart 5

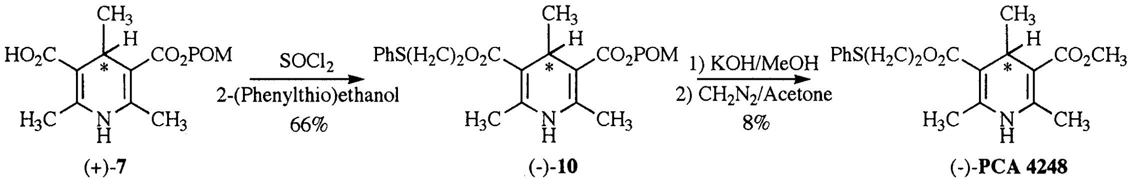

Chart 6

of **1a** with lipase PS proceeded very slowly, it is of interest that lipase PS has opposite enantioselectivity, giving (*R*)-**2a** (Table 1, entry 6). In the case of the bis(propionyloxymethyl) ester (**1e**), the hydrolysis with lipase AH was carried out at 0—5 °C because the second hydrolysis leading to the formation of dicarboxylic acid was too fast at room temperature (Table 1, entry 7). On the other hand, lipase PS seemed to be suitable for the reaction of the propionyloxymethyl ester (**1e**, Table 1, entry 8). In order to investigate the solvent effect, we examined the lipase-catalyzed hydrolysis in various organic solvents, and found that the stereoselectivity of lipase AH in IPE was opposite to that in cyclohexane (Table 1, entries 9, 10: Chart 4).[24] It has also been reported that the stereoselectivity of lipase AK (*Pseudomonas* lipase) depends on the substituents on the nitrogen of the dihydropyridine ring.[25] These results showed that both enantiomers could be obtained by using different enzymes, solvents and substrates. The (*S*)-monopivaloyloxymethyl esters (**2a**—**d**) were easily converted into the corresponding monomethyl esters (**5a**—**d**) through the intermediates **3** and **4** by successive treatment with diazomethane, hydrochloric acid and alkali (Chart 3). These monoesters (**5**) should serve as useful synthons for various non-symmetric diesters, some of which have potent biological activities.

We applied the lipase AH-catalyzed enantioselective hydrolysis of pivaloyloxymethyl esters to 4-methyl-1,4-dihydropyridine to investigate the synthesis of optically active PCA 4248 (Charts 5,6).[26] Lipase AH was well suited for the hydrolysis of bis(pivaloyloxymethyl) 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate (**6**, Table 1, entry 11), which was prepared from 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylic acid, chloromethyl pivalate and sodium hydride in *N*,*N*-dimethyl formamide (DMF). The optically active monopivaloyloxymethyl ester (**7**) obtained was converted into (+)-PCA 4248 through the intermediates **8** and **9** by treatment with diazomethane, alkali, thionyl chloride and 2-(phenylthio)ethanol. On the other hand, (−)-PCA 4248 was obtained as shown in Chart 6.

We have thus achieved the first asymmetric synthesis of chiral 1,4-dihydropyridines, and demonstrated that the enantioselective hydrolysis of the acyloxymethyl groups is applicable to the synthesis of a wide range of optically active medicines.[27] Our studies have opened up a new field of lipase-catalyzed synthesis of various useful chiral compounds.

Experimental

Melting points were measured on a micro melting point apparatus BY-1 (Yazawa) without correction. Specific rotations were measured with a JASCO DIP-140 digital polarimeter. IR spectra were taken on a JASCO IR-700 or JASCO IR-810 spectrophotometer. MS were measured with a JEOL JMS-SX 102 mass spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 270 FT-NMR, JEOL

JNM-EX 270 FT-NMR or JEOL JNM-GSX 500 FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. HPLC analyses were carried out with a JASCO Trirotar-V (ultraviolet detection) equipped with a column packed with Chiralcel OD or Chiralcel OJ (2-propanol/*n*-hexane). Column chromatography was carried out on a silica gel (Kieselgel 60, 70—230 mesh, Merck). Thin layer chromatography was also performed on silica gel (Kieselgel 60F_{254}) to monitor the reactions and to ascertain the purity of the products. The following lipases were used: lipase AH and lipase PS (Amano Pharmaceutical Co., Ltd.).

General Procedure for Syntheses of Bis(acyloxymethyl) 4-Aryl-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-3,5-pyridinedicarboxylates (1a—e) A suspension of 4-aryl-1,4-dihydro-2,6-dimethyl-1-(methoxymethyl)-3,5-pyridinedicarboxylic acid (4 mmol) and 60% sodium hydride (12 mmol) in dry DMF (20 ml) was stirred at 0 °C. Stirring was continued for 30 min, then chloromethyl pivalate (12 mmol) was added at 0 °C and the mixture was stirred for 18 h at room temperature. The reaction was quenched with acetic acid (3 ml) and the mixture was diluted with dichloromethane, washed with water, saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane) to give **1**.

Bis(pivaloyloxymethyl) 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**1a**): Pale yellow needles. Yield 43%. mp 73—74 °C. IR (Nujol) cm^{-1}: 1745, 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (18H, s, 6 × CH_3), 2.54 (6H, s, 2 × CH_3), 3.30 (3H, s, OCH_3), 4.82 (2H, s, NCH_2O), 5.18 (1H, s, >CH–), 5.79 (2H, d, J = 5.5 Hz, 2 × $OC\underline{H}_AH_BO$), 5.85 (2H, d, J = 5.5 Hz, 2 × $OCH_A\underline{H}_BO$), 7.32—8.00 (4H, m, C_6H_4). *Anal.* Calcd for $C_{29}H_{38}N_2O_{11}$: C, 58.97; H, 6.48; N, 4.74. Found: C, 59.76; H, 6.51; N, 4.57.

Bis(pivaloyloxymethyl) 4-(2,3-Dichlorophenyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**1b**): Colorless needles. Yield 90%. mp 103—104 °C. IR (Nujol) cm^{-1}: 1750, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (18H, s, 6 × CH_3), 2.46 (6H, s, 2 × CH_3), 3.37 (3H, s, OCH_3), 4.71 (2H, s, NCH_2O), 5.52 (1H, s, >CH–), 5.74 (2H, d, J = 5.6 Hz, 2 × $OC\underline{H}_AH_BO$), 5.78 (2H, d, J = 5.6 Hz, 2 × $OCH_A\underline{H}_BO$), 7.00—7.27 (3H, m, C_6H_3). *Anal.* Calcd for $C_{29}H_{37}Cl_2NO_9$: C, 56.68; H, 6.07; N, 2.28. Found: C, 56.94; H, 6.18; N, 2.03.

Bis(pivaloyloxymethyl) 4-(2-Trifluoromethylphenyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylate (**1c**): Pale yellow needles. Yield 62%. mp 96—97 °C. IR (Nujol) cm^{-1}: 1750, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (18H, s, 6 × CH_3), 2.41 (6H, s, 2 × CH_3), 3.38 (3H, s, OCH_3), 4.82 (2H, s, NCH_2O), 5.48 (1H, s, >CH–), 5.70 (2H, d, J = 5.4 Hz, 2 × $OC\underline{H}_AH_BO$), 5.76 (2H, d, J = 5.4 Hz, 2 × $OCH_A\underline{H}_BO$), 7.27—7.54 (4H, m, C_6H_4). *Anal.* Calcd for $C_{30}H_{38}F_3NO_9$: C, 58.72; H, 6.24; N, 2.28. Found: C, 59.01; H, 6.40; N, 2.58.

Bis(pivaloyloxymethyl) 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (**1d**): Colorless needles. Yield 71%. mp 89—90 °C. IR (Nujol) cm^{-1}: 1750, 1740, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (18H, s, 6 × CH_3), 2.51 (6H, s, 2 × CH_3), 3.26 (3H, s, OCH_3), 4.75 (2H, s, NCH_2O), 5.09 (1H, s, >CH–), 5.77 (2H, d, J = 5.5 Hz, 2 × $OC\underline{H}_AH_BO$), 5.85 (2H, d, J = 5.5 Hz, 2 × $OCH_A\underline{H}_BO$), 7.10—7.16 (5H, m, C_6H_5). *Anal.* Calcd for $C_{29}H_{39}NO_9$: C, 63.83; H, 7.21; N, 2.56. Found: C, 64.01; H, 7.42; N, 2.38.

Bis(propionyloxymethyl) 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**1e**): Pale yellow needles. Yield 37%. mp 86—87 °C. IR (Nujol) cm^{-1}: 1755, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, t, J = 7.3 Hz, 2 × $C\underline{H}_3CH_2$), 2.31, 2.32 (4H, each q, J = 7.3 Hz, 2 × $CH_3C\underline{H}_2$), 2.55 (6H, s, 2 × CH_3), 3.35 (3H, s, OCH_3), 4.82 (2H, s, NCH_2O), 5.14 (1H, s, >CH–), 5.78 (2H, d, J = 5.6 Hz, 2 × $OC\underline{H}_AH_BO$), 5.82 (2H, d, J = 5.6 Hz, 2 × $OCH_A\underline{H}_BO$), 7.33—8.01 (4H, m, C_6H_4). *Anal.* Calcd for $C_{25}H_{30}N_2O_{11}$: C, 56.17; H, 5.66; N, 5.24. Found: C, 56.39; H, 5.67; N, 5.13.

Bis(pivaloyloxymethyl) 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**1f**): Pale yellow needles. Yield 46%. mp 124—125 °C. IR (Nujol) cm^{-1}: 3340, 1750, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (18H, s, 6 × CH_3), 2.37 (6H, s, 2 × CH_3), 5.07 (1H, s, >CH–), 5.53 (2H, d, J = 5.8 Hz, 2 × $OC\underline{H}_AH_BO$), 5.72 (2H, d, J = 5.8 Hz, 2 × $OCH_A\underline{H}_BO$), 6.00 (1H, s, NH), 7.26—8.06 (4H, m, C_6H_4). *Anal.* Calcd for $C_{27}H_{34}N_2O_{10}$: C, 59.33; H, 6.27; N, 5.13. Found: C, 59.60; H, 6.24; N, 4.88.

General Procedure for Lipase-Catalyzed Hydrolysis of Bis(acyloxymethyl) 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (1) A mixture of **1** (2 mmol), lipase (200—400 mg) and IPE (50 ml) saturated with water was stirred at room temperature. After removal of the enzyme by filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with AcOEt/*n*-hexane. The fractions containing the product were collected and concentrated to give 4-aryl-1,4-dihydro-2,6-dimethyl-5-acyloxymethoxycarbonyl-3-pyridinecarboxylic acid (**2**). The optical yield of each product was determined by HPLC analysis after conversion to benzyl methyl 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate by successive treatment with diazomethane, alkaline and phenyldiazomethane. Yields and optical purities are listed in Table 1.

(*S*)-(+)-1,4-Dihydro-2,6-dimethyl-1-(methoxymethyl)-4-(3-nitrophenyl)-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2a**) (Entry 2): Pale yellow needles. Yield 95%. $[\alpha]_D^{25}$ +42.6° (c = 1.0, acetone). mp 84—85 °C. IR (Nujol) cm^{-1}: 1710, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (9H, s, 3 × CH_3), 2.55 (3H, s, CH_3), 2.57 (3H, s, CH_3), 3.33 (3H, s, OCH_3), 4.81 (2H, s, NCH_2O), 5.19 (1H, s, >CH–), 5.77 (1H, d, J = 5.3 Hz, $OC\underline{H}_AH_BO$), 5.83 (1H, d, J = 5.3 Hz, $OCH_A\underline{H}_BO$), 7.33—8.00 (4H, m, C_6H_4). *Anal.* Calcd for $C_{23}H_{28}N_2O_9 \cdot H_2O$: C, 55.86; H, 6.12; N, 5.67. Found: C, 55.91; H, 6.11; N, 5.46.

(*S*)-(+)-4-(2,3-Dichlorophenyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2b**) (Entry 3): Colorless needles. Yield 81%. $[\alpha]_D^{25}$ +22.0° (c = 1.0, acetone). mp 89—90 °C. IR (Nujol) cm^{-1}: 1750, 1705, 1685. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (9H, s, 3 × CH_3), 2.44 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.35 (3H, s, OCH_3), 4.78 (2H, s, NCH_2O), 5.52 (1H, s, >CH–), 5.75 (1H, d, J = 5.4 Hz, $OC\underline{H}_AH_BO$), 5.79 (1H, d, J = 5.4 Hz, $OCH_A\underline{H}_BO$), 6.99—7.27 (3H, m, C_6H_3). *Anal.* Calcd for $C_{23}H_{27}Cl_2NO_7 \cdot H_2O$: C, 53.30; H, 5.64; N, 2.70. Found: C, 53.38; H, 5.57; N, 2.63.

(*S*)-(+)-4-(2-Trifluoromethylphenyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2c**) (Entry 4): Colorless needles. Yield 83%. $[\alpha]_D^{25}$ +33.8° (c = 1.6, acetone). mp 69—70 °C. IR (Nujol) cm^{-1}: 1765, 1745, 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (9H, s, 3 × CH_3), 2.39 (3H, s, CH_3), 2.47 (3H, s, CH_3), 3.37 (3H, s, OCH_3), 4.81 (2H, s, NCH_2O), 5.52 (1H, s, >CH–), 5.70 (1H, d, J = 5.5 Hz, $OC\underline{H}_AH_BO$), 5.77 (1H, d, J = 5.5 Hz, $OCH_A\underline{H}_BO$), 7.22—7.52 (4H, m, C_6H_4). *Anal.* Calcd for $C_{24}H_{28}F_3NO_7 \cdot H_2O$: C, 55.70; H, 5.84; N, 2.71. Found: C, 55.86; H, 5.61; N, 2.63.

(*S*)-(+)-1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-phenyl-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2d**) (Entry 5): Colorless needles. Yield 76%. $[\alpha]_D^{25}$ +43.5° (c = 1.5, acetone). mp 121—122 °C. IR (Nujol) cm^{-1}: 1750, 1720, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (9H, s, 3 × CH_3), 2.51 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.24 (3H, s, OCH_3), 4.73 (2H, s, NCH_2O), 5.14 (1H, s, >CH–), 5.77 (1H, d, J = 5.5 Hz, $OC\underline{H}_AH_BO$), 5.85 (1H, d, J = 5.5 Hz, $OCH_A\underline{H}_BO$), 7.10—7.20 (5H, m, C_6H_5). *Anal.* Calcd for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.32; H, 6.96; N, 3.08.

(*S*)-(+)-1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-5-propionyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2e**) (Entry 7): Pale yellow needles. Yield 71%. $[\alpha]_D^{25}$ +49.8° (c = 0.7, acetone). mp 54—56 °C. IR (Nujol) cm^{-1}: 1750, 1710, 1695. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J = 7.3 Hz, $CH_2C\underline{H}_3$), 2.31, 2.32 (2H, each q, J = 7.3 Hz, $C\underline{H}_2CH_3$), 2.55 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.34 (3H, s, OCH_3), 4.82 (2H, s, NCH_2O), 5.19 (1H, s, >CH–), 5.78 (1H, d, J = 5.5 Hz, $OC\underline{H}_AH_BO$), 5.84 (1H, d, J = 5.5 Hz, $OCH_A\underline{H}_BO$), 7.35—8.01 (4H, m, C_6H_4). *Anal.* Calcd for $C_{21}H_{24}N_2O_9$: C, 56.24; H, 5.39; N, 6.25. Found: C, 56.38; H, 5.47; N, 6.00.

(*S*)-(+)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (**2f**) (Entry 9): Pale yellow oil. Yield 83%. $[\alpha]_D^{25}$ +27.9° (c = 0.8, acetone). IR (Nujol) cm^{-1}: 3340, 1750, 1710, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (9H, s, 3 × CH_3), 2.38 (6H, s, 2 × CH_3), 5.09 (1H, s, >CH–), 5.72 (1H, d, J = 5.3 Hz, $OC\underline{H}_AH_BO$), 5.76 (1H, d, J = 5.3 Hz, $OCH_A\underline{H}_BO$), 6.04 (1H, s, NH), 7.33—8.07 (4H, m, C_6H_4). **1f** was converted into **4a** by successive treatment with diazomethane, and satisfactory elemental analyses of **4a** were obtained as shown below. The optical purity of **2f** was determined based on the specific rotation of **4a**. **4a** (Entry 9): $[\alpha]_D^{25}$ +9.6° (c = 0.6, acetone). (93% ee).

General Procedure for Syntheses of Acyloxymethyl Methyl 4-Aryl-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-3,5-pyridinedicarboxylates (3) An excess of diazomethane–ether solution was added to an ice-cooled solution of **2** (1 mmol) in dichloromethane (5 ml), and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with acetic acid, the mixture was concentrated, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane) to give **3**.

(*S*)-(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**3a**): Pale yellow needles. Yield 94%. $[\alpha]_D^{25}$ +22.0° (*c*=1.2, acetone). mp 113—114 °C. IR (Nujol) cm^{-1}: 1750, 1710. ^{1}H-NMR (CDCl$_3$) δ: 1.13 (9H, s, 3×CH$_3$), 2.54 (6H, s, 2×CH$_3$), 3.33 (3H, s, OCH$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 4.81 (2H, s, NCH$_2$O), 5.16 (1H, s, >CH–), 5.78 (1H, d, *J*=5.3 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.83 (1H, d, *J*=5.3 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.33—8.01 (4H, m, C$_6H_4$). *Anal.* Calcd for $C_{24}H_{30}N_2O_9$: C, 58.76; H, 6.17; N, 5.71. Found: C, 59.01; H, 6.27; N, 5.78.

(*S*)-(+)-Methyl Pivaloyloxymethyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-1-(methoxymethyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**3b**): Colorless needles. Yield 83%. $[\alpha]_D^{25}$ +26.0° (*c*=0.66, acetone). mp 149—150 °C. IR (Nujol) cm^{-1}: 1760, 1720, 1695. ^{1}H-NMR (CDCl$_3$) δ: 1.12 (9H, s, 3×CH$_3$), 2.44 (3H, s, CH$_3$), 2.48 (3H, s, CH$_3$), 3.36 (3H, s, OCH$_3$), 3.66 (3H, s, CO$_2$CH$_3$), 4.80 (2H, s, NCH$_2$O), 5.53 (1H, s, >CH–), 5.74 (1H, d, *J*=5.3 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.78 (1H, d, *J*=5.3 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.00—7.27 (3H, m, C$_6H_3$). *Anal.* Calcd for $C_{24}H_{29}Cl_2NO_7$: C, 56.03; H, 5.68; N, 2.72. Found: C, 56.34; H, 5.62; N, 2.45.

(*S*)-(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylate (**3c**): Colorless needles. Yield 97%. $[\alpha]_D^{25}$ +17.1° (*c*=1.1, acetone). mp 110—112 °C. IR (Nujol) cm^{-1}: 1760, 1720, 1700. ^{1}H-NMR (CDCl$_3$) δ: 1.12 (9H, s, 3×CH$_3$), 2.39 (3H, s, CH$_3$), 2.44 (3H, s, CH$_3$), 3.38 (3H, s, OCH$_3$), 3.62 (3H, s, CO$_2$CH$_3$), 4.83 (2H, s, NCH$_2$O), 5.47 (1H, s, >CH–), 5.70 (1H, d, *J*=5.3 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.70 (1H, d, *J*=5.3 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.27—7.53 (4H, m, C$_6H_4$). *Anal.* Calcd for $C_{25}H_{30}F_3NO_7$: C, 58.47; H, 5.89; N, 2.73. Found: C, 58.21; H, 6.03; N, 2.96.

(*S*)-(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (**3d**): Colorless needles. Yield 99%. $[\alpha]_D^{25}$ +30.2° (*c*=1.0, acetone). mp 80—81 °C. IR (Nujol) cm^{-1}: 1750, 1705, 1685. ^{1}H-NMR (CDCl$_3$) δ: 1.15 (9H, s, 3×CH$_3$), 2.50 (3H, s, CH$_3$), 2.51 (3H, s, CH$_3$), 3.23 (3H, s, OCH$_3$), 3.68 (3H, s, CO$_2$CH$_3$), 4.74 (2H, s, NCH$_2$O), 5.11 (1H, s, >CH–), 5.79 (1H, d, *J*=5.6 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.86 (1H, d, *J*=5.6 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.13—7.18 (5H, m, C$_6H_5$). *Anal.* Calcd for $C_{24}H_{31}NO_7$: C, 64.70; H, 7.01; N, 3.14. Found: C, 65.01; H, 7.07; N, 2.84.

(*S*)-(+)-Methyl Propionyloxymethyl 1,4-Dihydro-1-(methoxymethyl)-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**3e**): Pale yellow oil. Yield 96%. $[\alpha]_D^{25}$ +32.5° (*c*=1.3, acetone). IR (Neat) cm^{-1}: 1750, 1710, 1695. ^{1}H-NMR (CDCl$_3$) δ: 1.10 (3H, t, *J*=7.7 Hz, $\mathrm{CH_2C\underline{H}_3}$), 2.31, 2.32 (2H, each q, *J*=7.3 Hz, $\mathrm{C\underline{H}_2CH_3}$), 2.55 (6H, s, 2×CH$_3$), 3.33 (3H, s, OCH$_3$), 3.71 (3H, s, CO$_2CH_3$), 4.81 (2H, s, NCH$_2$O), 5.16 (1H, s, >CH–), 5.79 (1H, d, *J*=5.4 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.84 (1H, d, *J*=5.4 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.33—8.02 (4H, m, C$_6H_4$). FAB-MS: *m/z*: 462 (M$^+$).

General Procedure for Syntheses of Acyloxymethyl Methyl 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (4) One of **3** (0.9 mmol) was added to a solution of 2 M hydrochloric acid (2 ml) in acetone (5 ml), and the mixture was stirred for 2 h, then neutralized with 1 M NaOH at 0 °C. After removal of acetone, the mixture was extracted with dichloromethane (twice). The organic layer was washed with brine, and dried (MgSO$_4$). After removal of the solvent, the residue was chromatographed on silica gel (AcOEt/*n*-hexane) to give **4**.

(*S*)-(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**4a**): Pale yellow needles. Yield 98%. $[\alpha]_D^{25}$ +10.3° (*c*=1.3, acetone). mp 122—123 °C. IR (Nujol) cm^{-1}: 3340, 1750, 1710. ^{1}H-NMR (CDCl$_3$) δ: 1.84 (9H, s, 3×CH$_3$), 2.37 (6H, s, 2×CH$_3$), 3.64 (3H, s, CO$_2$CH$_3$), 5.09 (1H, s, >CH–), 5.73 (1H, d, *J*=5.3 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.76 (1H, d, *J*=5.3 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 6.19 (1H, s, NH), 7.34—8.08 (4H, m, C$_6$H$_4$). *Anal.* Calcd for $C_{22}H_{26}N_2O_8$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.33; H, 6.08; N, 6.20.

(*S*)-(+)-Methyl Pivaloyloxymethyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4b**): Colorless needles. Yield 98%. $[\alpha]_D^{25}$ +18.3° (*c*=1.0, acetone). mp 154—155 °C. IR (Nujol) cm^{-1}: 3340, 1740, 1710, 1690. ^{1}H-NMR (CDCl$_3$) δ: 1.11 (9H, s, 3×CH$_3$), 2.30 (3H, s, CH$_3$), 2.32 (3H, s, CH$_3$), 3.60 (3H, s, CO$_2$CH$_3$), 5.47 (1H, s, >CH–), 5.71 (1H, d, *J*=5.5 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.74 (1H, d, *J*=5.5 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 5.94 (1H, s, NH), 7.03—7.30 (3H, m, C$_6$H$_3$). *Anal.* Calcd for $C_{22}H_{25}Cl_2NO_6$: C, 56.18; H, 5.36; N, 2.98. Found: C, 56.35; H, 5.57; N, 3.14.

(*S*)-(+)-Methyl Pivaloyloxymethyl 4-(2-Trifluoromethylphenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4c**): Pale yellow oil. Yield 94%. $[\alpha]_D^{25}$ +25.2° (*c*=0.8, acetone). IR (neat) cm^{-1}: 3340, 1750, 1720, 1705. ^{1}H-NMR (CDCl$_3$) δ: 1.11 (9H, s, 3×CH$_3$), 2.29 (3H, s, CH$_3$), 2.31 (3H, s, CH$_3$), 3.58 (3H, s, CO$_2$CH$_3$), 5.57 (1H, s, >CH–), 5.66 (1H, d, *J*=5.5 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.74 (1H, d, *J*=5.5 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 6.00 (1H, s, NH), 7.21—7.51 (4H, m, C$_6$H$_4$). FAS-MS *m/z*: 489 (M$^+$).

(*S*)-(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (**4d**): Colorless needles. Yield 98%. $[\alpha]_D^{25}$ +27.1° (*c*=0.8, acetone). mp 81—82 °C. IR (Nujol) cm^{-1}: 3390, 1750, 1710, 1700. ^{1}H-NMR (CDCl$_3$) δ: 1.19 (9H, s, 3×CH$_3$), 2.31 (6H, s, 2×CH$_3$), 3.62 (3H, s, CO$_2$CH$_3$), 4.98 (1H, s, >CH–), 5.74 (1H, d, *J*=5.4 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.78 (1H, d, *J*=5.4 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 6.14 (1H, s, NH), 7.11—7.26 (5H, m, C$_6$H$_5$). *Anal.* Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.71; H, 7.03; N, 3.25.

General Procedure for Syntheses of 4-Aryl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic Acids (5) One of **4** (0.7 mmol) was added to a methanolic solution (5 ml) of KOH (500 mg), and the mixture was stirred for 2 h at room temperature, then neutralized with 6 M hydrochloric acid at 0 °C. After removal of methanol, the mixture was extracted with AcOEt (twice) and dried (MgSO$_4$). The solvent was removed under reduced pressure to give **5**.

(*R*)-(−)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid (**5a**): Pale yellow powder. Yield 92%. $[\alpha]_D^{25}$ −19.5° (*c*=0.8, acetone). mp 187—188 °C. IR (Nujol) cm^{-1}: 3350, 1680, 1660. ^{1}H-NMR (CD$_3$OD) δ: 2.33 (6H, s, 2×CH$_3$), 3.62 (3H, s, OCH$_3$), 4.55 (1H, s, NH), 5.08 (1H, s, >CH–), 7.42—8.09 (4H, m, C$_6$H$_4$). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 58.10; H, 4.97; N, 8.27.

(*R*)-(+)-4-(2,3-Dichlorophenyl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic Acid (**5b**): Colorless powder. Yield 90%. $[\alpha]_D^{25}$ +5.2° (*c*=0.7, acetone). mp 186—187 °C. IR (Nujol) cm^{-1}: 3350, 1700, 1685. ^{1}H-NMR (acetone-*d*$_6$) δ: 2.30 (6H, s, 2×CH$_3$), 3.55 (3H, s, OCH$_3$), 5.51 (1H, s, >CH–), 7.16—7.46 (3H, m, C$_6$H$_3$), 7.98 (1H, s, NH), 10.0—10.5 (1H, br, CO$_2$H). *Anal.* Calcd for $C_{16}H_{15}Cl_2NO_4$: C, 53.95; H, 4.24; N, 3.93. Found: C, 54.10; H, 4.50; N, 3.82.

(*R*)-(−)-4-(2-Trifluoromethylphenyl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic Acid (**5c**): Colorless powder. Yield 60%. $[\alpha]_D^{25}$ −24.4° (*c*=0.6, acetone). mp 109—110 °C. IR (Nujol) cm^{-1}: 3320, 1710, 1690. ^{1}H-NMR (acetone-*d*$_6$) δ: 2.30 (3H, s, CH$_3$), 2.32 (3H, s, CH$_3$), 3.51 (3H, s, OCH$_3$), 5.59 (1H, s, >CH–), 7.27—7.67 (4H, m, C$_6$H$_4$), 7.88 (1H, s, NH), 10.0—10.3 (1H, br, CO$_2$H). *Anal.* Calcd for $C_{17}H_{16}F_3NO_4$: C, 57.47; H, 4.54; N, 3.94. Found: C, 57.59; H, 4.35; N, 4.21.

(*R*)-(−)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-phenyl-3-pyridinecarboxylic Acid (**5d**): Colorless powder. Yield 88%. $[\alpha]_D^{25}$ −10.3° (*c*=0.7, acetone). mp 158—159 °C. IR (Nujol) cm^{-1}: 3330, 1675, 1650. ^{1}H-NMR (acetone-*d*$_6$) δ: 2.33 (3H, s, CH$_3$), 2.34 (3H, s, CH$_3$), 3.92 (3H, s, OCH$_3$), 5.07 (1H, s, >CH–), 7.05—7.30 (5H, m, C$_6$H$_5$), 7.88 (1H, s, NH), 10.2—10.5 (1H, br, CO$_2$H). *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.76; H, 6.25; N, 4.58.

Bis(pivaloyloxymethyl) 1,4-Dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate (6) A DMF solution (60 ml) of 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylic acid (4.2 g, 20 mmol) was treated with 60% sodium hydride (60 mmol) at 0 °C under an argon atmosphere and stirred for 30 min. Chloromethyl pivalate (60 mmol) was added at 0 °C, and the mixture was stirred for 18 h. The reaction was quenched with acetic acid (3 ml), and the whole was diluted with dichloromethane, washed with water, saturated NaHCO$_3$ and brine, and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/3) to give **6** (3.7 g, 42%).

6: Colorless needles. mp 82—83 °C. IR (Nujol) cm^{-1}: 3332, 1749, 1713. ^{1}H-NMR (CDCl$_3$) δ: 0.95 (3H, d, *J*=6.4 Hz, CH$_3$), 1.21 (18H, s, 6×CH$_3$), 2.27 (6H, s, 2×CH$_3$), 3.81 (1H, q, *J*=6.4 Hz, >CH–), 5.80 (2H, d, *J*=5.4 Hz, 2×$\mathrm{OC\underline{H}_AH_BO}$), 5.89 (2H, d, *J*=5.4 Hz, 2×$\mathrm{OCH_A\underline{H}_BO}$), 6.17 (1H, s, NH). *Anal.* Calcd for $C_{22}H_{33}NO_8$: C, 60.12; H, 7.57; N, 3.19. Found: C, 60.12; H, 7.76; N, 3.02.

(+)-1,4-Dihydro-2,4,6-trimethyl-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (7) A mixture of **6** (1.3 g, 4 mmol), lipase AH (300 mg) and IPE (30 ml) saturated with water was stirred for 8 h at room temperature. The lipase was filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/3) to give **7** (741 mg, 76%).

7: Pale yellow powder. $[\alpha]_D^{25}$ +25.8° (*c*=1.0, acetone). mp 113—114 °C. IR (Nujol) cm^{-1}: 3350, 1755, 1690. ^{1}H-NMR (acetone-*d*$_6$) δ: 0.94 (3H, d, *J*=6.4 Hz, CH$_3$), 1.19 (9H, s, 3×CH$_3$), 2.27 (6H, s, 2×CH$_3$), 3.85 (1H, q, *J*=6.4 Hz, >CH–), 5.79 (1H, d, *J*=5.5 Hz, $\mathrm{OC\underline{H}_AH_BO}$), 5.87 (1H, d, *J*=5.5 Hz, $\mathrm{OCH_A\underline{H}_BO}$), 7.91 (1H, s, NH).

Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.86; H, 7.06; N, 4.19.

(+)-Methyl Pivaloyloxymethyl 1,4-Dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate (8) An excess of diazomethane–ether solution was added to an ice-cooling acetone solution (2 ml) of **7** (325 mg, 1 mmol) and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with acetic acid, and the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel (AcOEt/*n*-hexane) to give **8** (223 mg, 76%). The optical yield was determined by HPLC analysis with a Chiralcel OJ column (IPA/*n*-hexane = 1/15) as described in Table 1 (entry 11). The product was further purified by recrystallization to give optically pure **8** (186 mg).

8: Colorless needles. $[\alpha]_D^{25}$ +18.0° (c = 1.0, acetone). mp 113—114 °C. IR (Nujol) cm^{-1}: 3358, 1699. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J = 6.8 Hz, CH_3), 1.21 (9H, s, 3 × CH_3), 2.27 (6H, s, 2 × CH_3), 3.72 (3H, s, OCH_3), 3.83 (1H, q, J = 6.8 Hz, >CH–), 5.62 (1H, s, NH), 5.81 (1H, d, J = 5.4 Hz, $OC\underline{H}_AH_BO$), 5.89 (1H, d, J = 5.4 Hz, $OCH_A\underline{H}_BO$). *Anal.* Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.08; H, 7.68; N, 3.91.

(−)-1,4-Dihydro-5-methoxycarbonyl-2,4,6-trimethyl-3-pyridinecarboxylic Acid (9) Compound **8** (169 mg, 0.5 mmol) was added to methanolic KOH (30 mg) solution (2 ml) and the mixture was stirred for 3 h, then neutralized with 1 M hydrochloric acid at 0 °C. After removal of methanol, the residure was extracted with AcOEt/tetrahydrofuran (THF) (1/1), and the extract was washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane = 1/2) to give **9** (74 mg, 67%).

9: Colorless powder. $[\alpha]_D^{25}$ −16.7° (c = 0.6, acetone). mp 165—166 °C. IR (Nujol) cm^{-1}: 3334, 1675, 1650. ^{1}H-NMR (acetone-d_6) δ: 0.94 (3H, d, J = 6.4 Hz, CH_3), 2.26 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 3.85 (1H, q, J = 6.4 Hz, >CH–), 7.75 (1H, s, NH). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.33. Found: C, 58.42; H, 6.95; N, 6.55.

(+)-Methyl 2-(Phenylthio)ethyl 1,4-Dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate ((+)-PCA 4248) A DMF/CH_2Cl_2 (1/4) solution of **9** (56 mg, 0.26 mmol) was treated with $SOCl_2$ (45 mg) with ice-cooling for 1 h. 2-(Phenylthio)ethanol was added at 0 °C, and the mixture was stirred for 1 h, then neutralized with 1 M NaOH at 0 °C, and extracted with CH_2Cl_2. The extract was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (AcOEt/*n*-hexane = 1/2) to give (+)-PCA 4248 (21 mg, 23%).

(+)-PCA 4248: Yellow oil. $[\alpha]_D^{25}$ +15.6° (c = 0.2, acetone). IR (neat) cm^{-1}: 3344, 1720, 1690. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J = 6.4 Hz, CH_3), 2.26 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.20 (2H, t, J = 6.8 Hz, CH_2SPh), 3.72 (3H, s, OCH_3), 3.81 (1H, q, J = 6.4 Hz, >CH–), 4.26 (1H, dt, J = 11.2, 6.8 Hz, $OC\underline{H}_AH_B$), 4.33 (1H, dt, J = 11.2, 6.8 Hz, $OCH_A\underline{H}_B$), 5.62 (1H, s, NH), 7.19—7.42 (5H, m, C_6H_5). FAB-MS m/z: 360 $(M-H)^+$.

(−)-2-(Phenylthio)ethyl Pivaloyloxymethyl 1,4-Dihydro-2,4,6-trimethyl-3,5-pyridinecarboxylate (10) A DMF/CH_2Cl_2 (1/4) solution of **7** (160 mg, 0.5 mmol) was treated with $SOCl_2$ (72 mg) under ice-cooling and stirred for 1 h. 2-(Phenylthio)ethanol was added at 0 °C, and the mixture was stirred for 1 h, then neutralized with 1 M NaOH at 0 °C, and extracted with CH_2Cl_2. The extract was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (CH_2Cl_2) to give (−)-**10** (153 mg, 66%).

(−)-**10**: Yellow oil. $[\alpha]_D^{25}$ −4.9° (c = 3.1, acetone). IR (neat) cm^{-1}: 3348, 1750, 1702. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J = 6.8 Hz, CH_3), 1.21 (9H, s, 3 × CH_3), 2.24 (6H, s, 2 × CH_3), 3.09 (2H, t, J = 6.4 Hz, CH_2SPh), 3.73 (2H, t, J = 6.4 Hz, CH_2O), 3.81 (1H, q, J = 6.8 Hz, >CH–), 5.80 (1H, d, J = 5.6 Hz, $OC\underline{H}_AH_B$), 5.88 (1H, d, J = 5.6 Hz, $OCH_A\underline{H}_B$), 6.31 (1H, s, NH), 7.16—7.41 (5H, m, C_6H_5). FAB-MS m/z: 461 $(M)^+$.

(−)-Methyl 2-(Phenylthio)ethyl 1,4-Dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate ((−)-PCA 4248) Compound **10** (155 mg, 0.34 mmol) was added to 10% KOH–methanol solution (4 ml), and the mixture was stirred for 2 h, diluted with water (2 ml), neutralized with 1 M hydrochloric acid, and extracted with AcOEt. The extract was washed with brine and dried ($MgSO_4$), then CH_2Cl_2 (2 ml) was added, followed by an excess amount of diazomethane–ether solution at 0 °C. The reaction was quenched with acetic acid, the mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC (acetone/CH_2Cl_2 = 1/200) to give (−)-PCA 4248 (10 mg, 8%).

(−)-PCA 4248: Yellow oil. $[\alpha]_D^{25}$ −15.9° (c = 0.18, acetone).

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