Asymmetric Synthesis of (*R*)-Nilvadipine and (*S*)-NB 818 *via* Regioselective Bromination of Chiral 1,4-Dihydropyridines as a Key Step and Enzymatic Resolution of Racemic 2-Hydroxymethyl-1,4-dihydropyridine Derivatives

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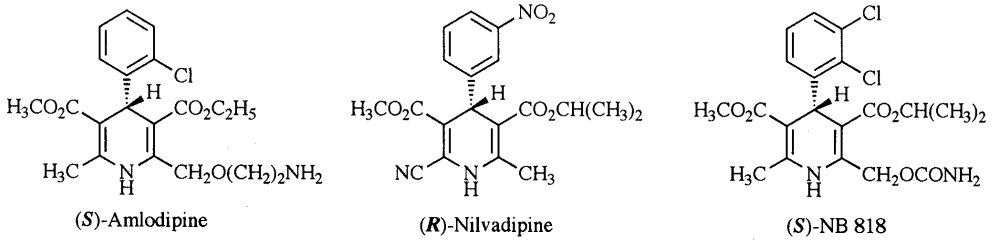
Optically active 2-hydroxymethyl-1,4-dihydropyridines were obtained by lipase-catalyzed hydrolysis or transesterification of racemic materials. Chiral NB 818 and nilvadipine have been synthesized from chiral 2-hydroxymethyl-1,4-dihydropyridine. On the other hand, chiral 1,4-dihydropyridines obtained from prochiral substrates have been converted into (*S*)-NB 818 and (*R*)-nilvadipine *via* regioselective bromination of methyl groups under mild conditions.

Key words 1,4-dihydropyridine; enzymatic synthesis; calcium antagonist

Calcium antagonists are of potential value as antihypertensive drugs. Many 4-aryl-1,4-dihydropyridines have been investigated from the pharmacological point of view and some of them have been employed therapeutically.[1,2] Recent studies have shown that 1,4-dihydropyridines with a basic side chain at the 2 position, such as amlodipine,[3] nilvadipine[4] or NB 818[5,6] (Chart 1), exhibit prolonged biological activity.[7,8] In these cases, the enantiomers have been reported to have different pharmacological properties. Optically active 2-substituted-1,4-dihydropyridines have been prepared by diastereoselective separation of the antipodes or by chiral column chromatographic resolution of racemates. Our laboratory has already reported the lipase-catalyzed enantioselective synthesis of chiral 1,4-dihydropyridines *via* the hydrolysis of acyloxymethyl esters.[9] As a continuation of that work, we report here the results of enzyme-catalyzed stereoselective hydrolysis of racemic 2-acetoxymethyl-1,4-dihydropyridines and catalytic asymmetric synthesis of optically active NB 818 and nilvadipine. First, we focused on optical resolution from racemic materials. 2-Hydroxymethyl-1,4-dihydropyridines seemed suitable as substrates for the lipase-catalyzed synthesis. The synthesis of 2-acetoxymethyl-1,4-dihydropyridine (**3a**) by Hantzsch condensation[10,11] is illustrated in Chart 2. The preliminary screening tests revealed that lipase AH[12] (*Pseudomonas* sp.), lipase PS[12] (*Pseudomonas cepacia*) and cholesterol esterase[12] (CHE) were effective for the hydrolysis of 2-acetoxymethyl-1,4-dihydropyridines and the transesterification of 2-hydroxymethyl-1,4-dihydropyridines in vinyl acetate. The enzyme-catalyzed resolution of 2-acetoxymethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine (**3a**) was carried out by stirring a mixture of **3a** and CHE in diisopropyl ether (IPE) saturated with water containing 10% of acetone to give (*S*)-**3a** and (*R*)-**4a** in high optical yield. 2-Acetoxymethyl-4-(2-chlorophenyl)-1,4-dihydropyridine (**3b**), which could be led to amlodipine, was also resolved by lipase AH-catalyzed enantioselective hydrolysis in the same manner (Table 1, run 5). The optically active (*S*)-**3a** and (*R*)-**4a** thus obtained were converted into (*S*)-NB 818 and (*R*)-NB 818 by successive treatment with chlorosulfonyl isocyanate, respectively (Chart 2).[13] The absolute configuration of **3a** was determined to be *S* by conversion to (*S*)-**5**, which was obtained from (*R*)-**6**[14] (Chart 3). Optically active nilvadipine was synthesized from (±)-**7** by lipase PS-catalyzed reaction (Chart 4).[15] First, we tried the enzymatic hydrolysis of the acetate (**7**) in IPE saturated with water (Table 2). The reaction with lipase PS proceeded to give (*S*)-**7** in 74% ee and (*R*)-**8** in 81% ee. The transesterification of (±)-**8** with vinyl acetate[16,17] was examined in various organic solvents to improve the optical yield (Table 3). The reaction proceeded more smoothly than the hydrolysis to give (*R*)-**7** and (*S*)-**8** in higher optical yields. The absolute configurations of **7** and **8** were assigned by conversion to (*R*)-nilvadipine, which was obtained successive Swern oxidation of (*R*)-**8**, followed by treatment of the aldehyde (**9**) with hydroxylamine hydrochloride and acetic anhydride (Chart 4).[4]

In continuing our studies on the enantioselective synthesis of 1,4-dihydropyridines, we found that a methyl group in the dihydropyridine ring was brominated regioselectively under mild conditions. We then developed a new synthetic method for (*R*)-nilvadipine and (*S*)-NB 818 from prochiral substrates *via* regioselective bromination



(*S*)-Amlodipine (*R*)-Nilvadipine (*S*)-NB 818

Chart 1

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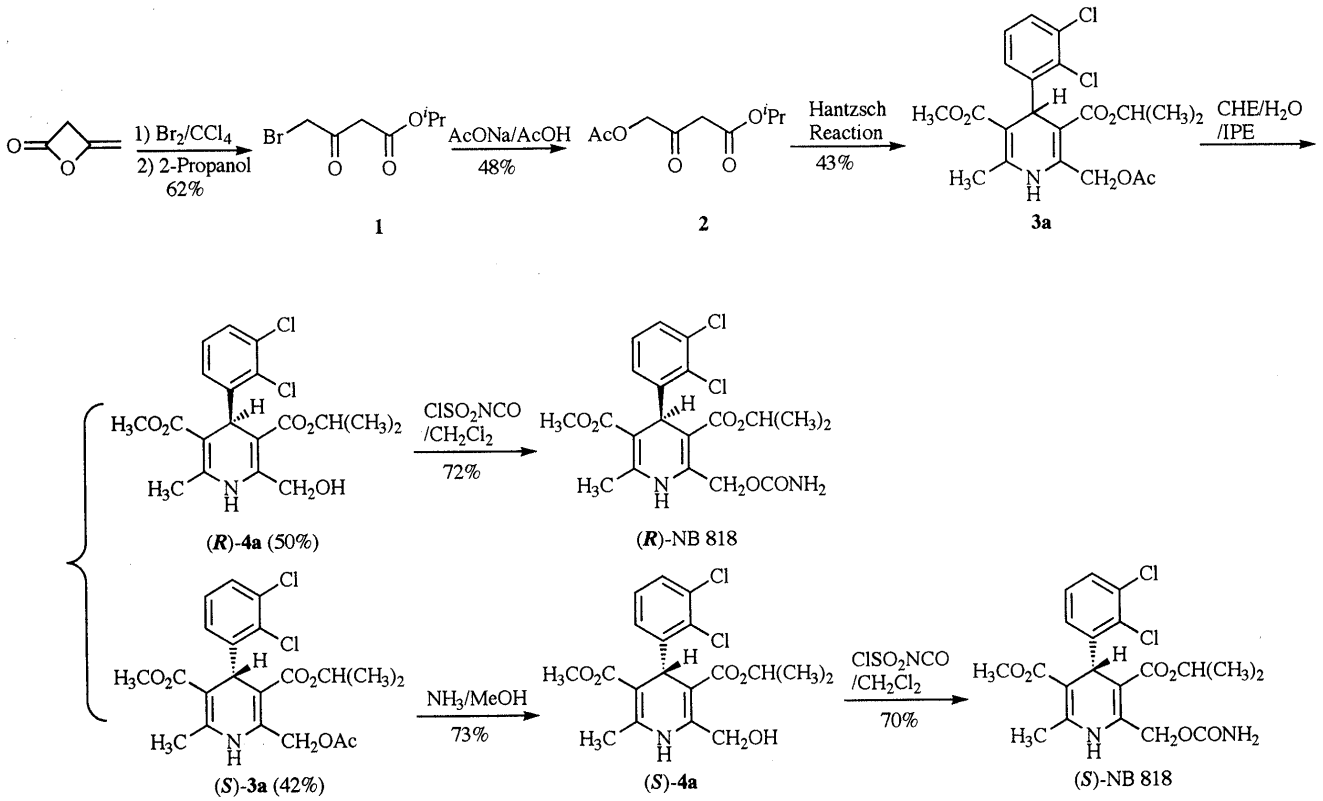
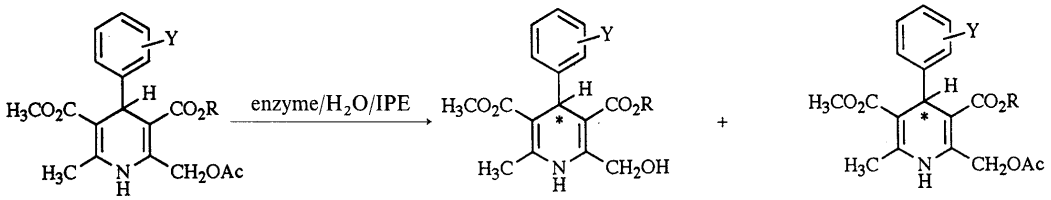


Chart 2

Table 1. Enzyme-Catalyzed Optical Resolution of 2-Hydroxymethyl-1,4-dihydropyridine Derivatives[a]



Entry	(±)-3 X	(±)-3 R	Enzyme (mg/mmol)	Time (d)	4 C.Y. (%)[b,c]	4 O.Y. (%ee)[d]	4 $[\alpha]_D^{20}$ deg[e]	3 C.Y. (%)[b,c]	3 O.Y. (%ee)[d]	3 $[\alpha]_D^{20}$ deg.[e]
1	2,3-Cl_2	iso-Pr	CHE (100 mg)	3	42	92	+34.4	50	98	−37.6
2	2,3-Cl_2	iso-Pr	Lipase AH (400 mg)	11	11	11	−2.0	75	3	+1.2
3	2,3-Cl_2	iso-Pr	Lipase PS (400 mg)	11	9	63	−14.7	78	6	+2.2
4	2-Cl	Et	CHE (200 mg)	4	50	75	+11.2	50	75	−23.8
5	2-Cl	Et	Lipase AH (200 mg)	4	50	91	+14.3	50	98	−29.1
6	2-Cl	Et	Lipase PS (400 mg)	9	36	55	+8.1	54	41	−12.9

a) All reactions were carried out by stirring a mixture of substrate (**3**), enzyme and IPE saturated with water containing 10% acetone at room temperature. *b*) Isolated yields. *c*) Satisfactory elemental analyses of all products were obtained. *d*) Optical yields of **3** were determined by HPLC analyses using a Chiralcel OD column (Entries 1—3) or a Chiralpak AS column (entries 4—6) (2-propanol/*n*-hexane), and those of **4** were determined after conversion to **3**. *e*) Acetone, $c=0.5$—1.

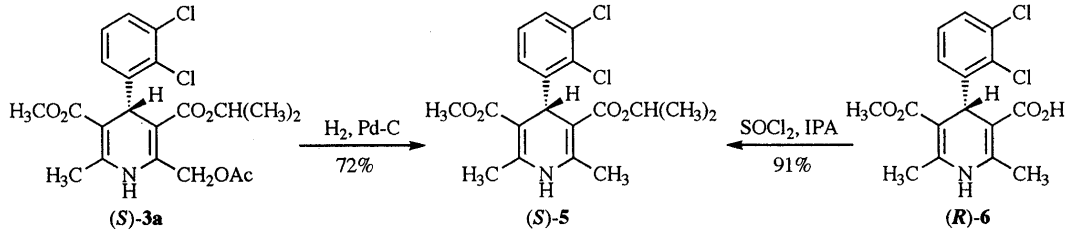


Chart 3

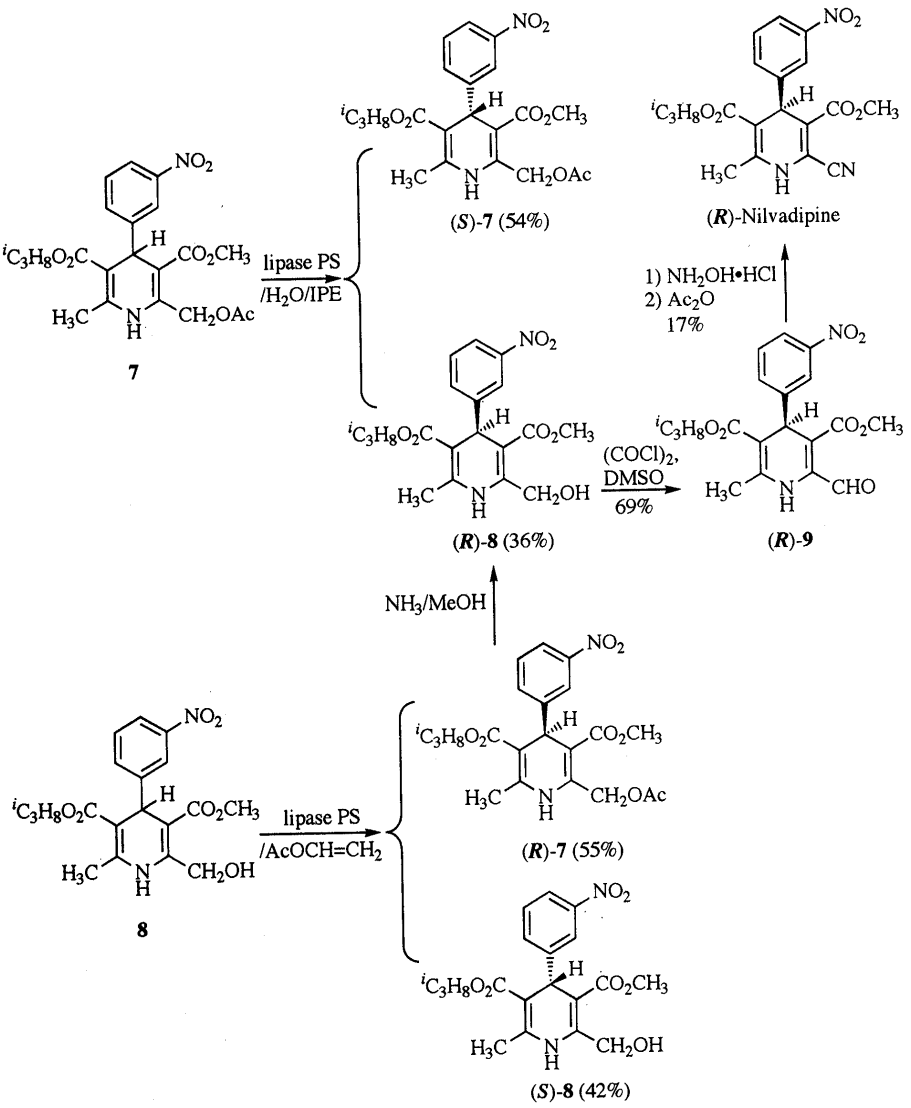
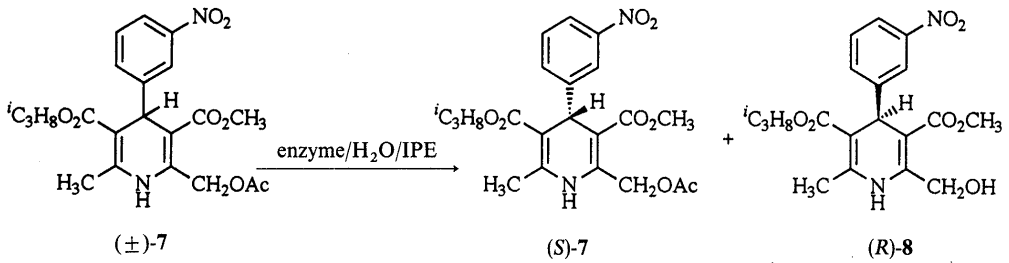


Chart 4

Table 2. Enzyme-Catalyzed Optical Resolution of 2-Acetoxymethyl-1,4-dihydropyridine Derivatives[a]

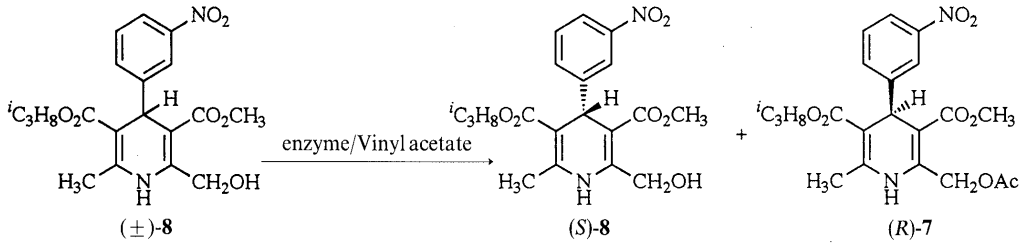


Entry	Enzyme	Solvent	Time (h)	7		8	
				C.Y. (%)[b,c]	O.Y. (%ee)[d]	C.Y. (%)[b,c]	O.Y. (%ee)[d]
1	Lipase PS	IPE	96	42	74[e]	36	81[f]
2	CHE	IPE	24	32	39	50	25

a) All reactions were carried out by stirring a mixture of substrate (**7**, 1 mmol), enzyme (200 mg) and IPE (10 ml) saturated with water containing 10% acetone at room temperature. *b*) Isolated yields. *c*) Satisfactory elemental analyses of all products were obtained. *d*) Optical yields of **7** were determined by HPLC analyses using a Chiralpak AS column (2-propanol/*n*-hexane), and those of **8** were determined after conversion to **7**. *e*) $[\alpha]_D$ −9.8° (c=1.8, acetone). *f*) $[\alpha]_D$ −2.2° (c=1.4, acetone).

of chiral 1,4-dihydropyridines (**12**, **20**) (Charts 5, 7).[18-21] (*R*)-Nilvadipine was synthesized from bis(pivaloyloxymethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinecarboxylate (**10**), which was hydrolyzed enantioselectively by lipase AH-catalyzed reaction according to our previous report.[9] The diester (**12**) obtained by

Table 3. Enzyme-Catalyzed Optical Resolution of 2-Hydroxymethyl-1,4-dihydropyridine Derivatives[a]



Entry	Enzyme	Solvent	Time (h)	8		7	
				C.Y. (%)[b,c]	O.Y. (%ee)[d]	C.Y. (%)[b,c]	O.Y. (%ee)[d]
1	Lipase AH	Acetone	33	49	68	46	90[e]
2	CHE	Acetone	19	49	29	41	35
3	Lipase PS	Acetone	41	46	78	40	89
4	Lipase PS	DMF	136	52	40	26	46
5	Lipase PS	THF	71	46	78	44	89
6	Lipase PS	Acetone[f]	136	40	76	39	89
7	Lipase PS	Acetone[f]	64	40	68	38	82
8	Lipase PS	Acetone[g]	44	42	97[h]	55	72

a) All reactions were carried out by stirring a mixture of substrate (**8**, 1 mmol), enzyme (200 mg), vinyl acetate (25 ml) and solvent (10 ml) at room temperature. *b*) Isolated yields. *c*) Satisfactory elemental analyses of all products were obtained. *d*) Optical yields of **7** were determined by HPLC analyses using a Chiralpak AS column (2-propanol/*n*-hexane), and those of **8** were determined after conversion to **7**. *e*) $[\alpha]_D$ +12.6° (c=1.8, acetone). *f*) At 0 °C. *g*) At 40 °C. *h*) $[\alpha]_D$ +3.0° (c=1.6, acetone).

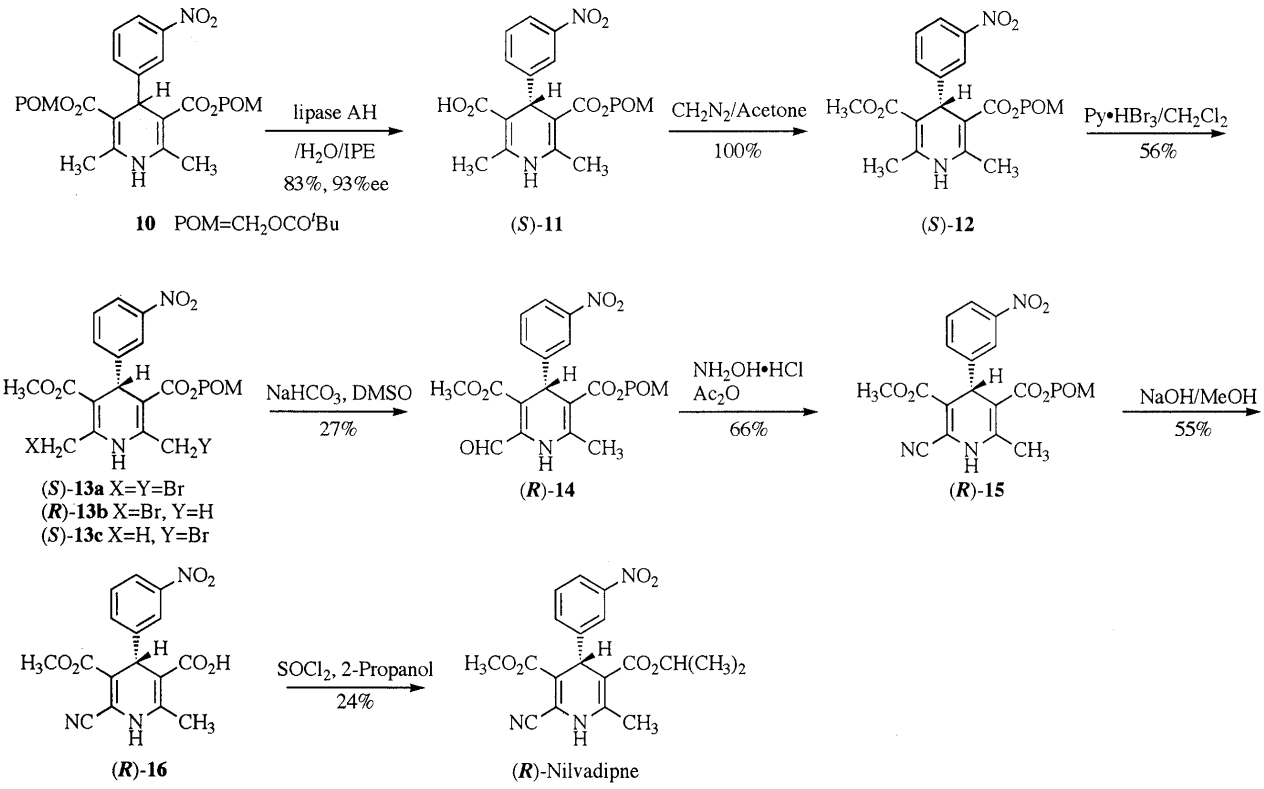
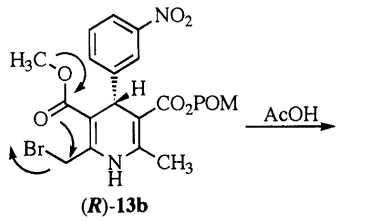


Chart 5

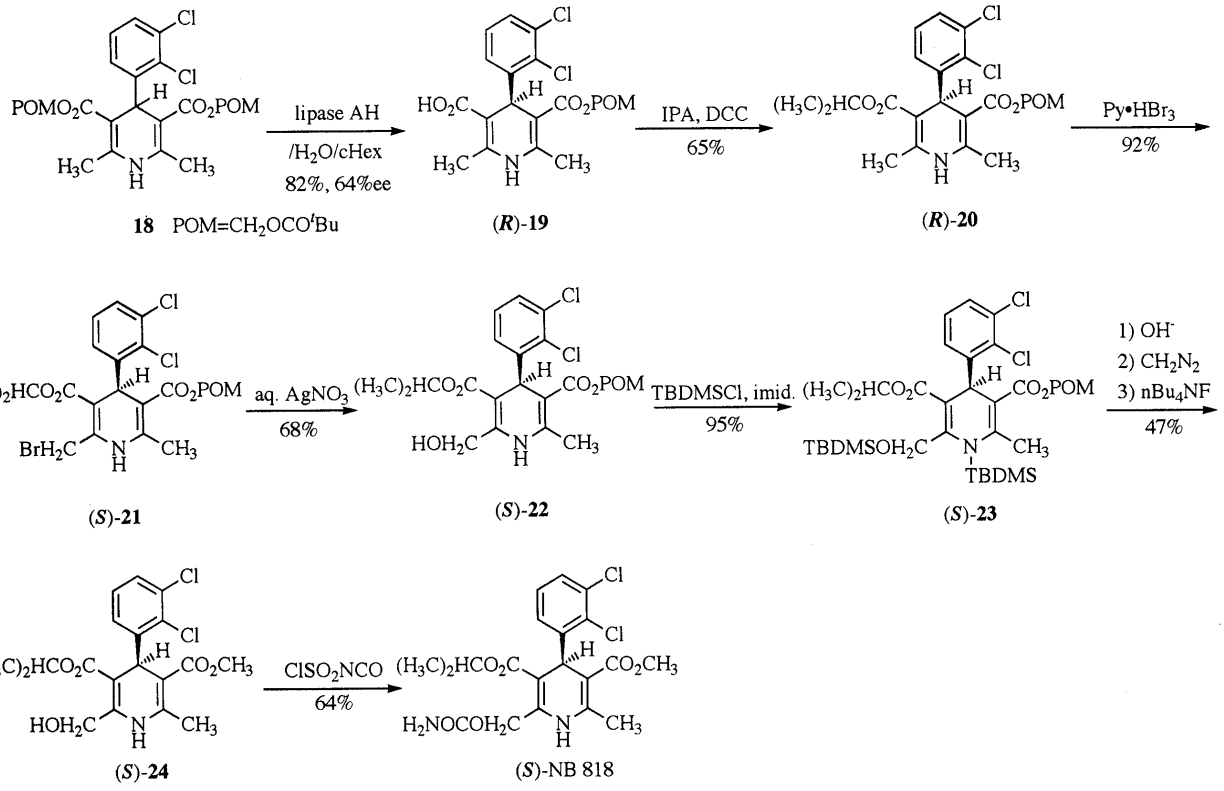
treatment of the chiral monoester (**11**) with diazomethane was brominated with 4-dimethylaminopyridinium bromoperbromide in the presence of pyridine at −20 °C.[20,21] The reaction was monitored by HPLC analysis, and the mixture was worked up after the substrate was consumed. The bromination proceeded regioselectively, and the contaminants (**13a**, **13c**) were easily removed by medium-pressure chromatography. The structure of **13b** was confirmed by ^{1}H-NMR analysis after conversion to the corresponding lactone (**17**) by treatment of **13b** in acetic acid (Chart 6). The reaction conditions and results were examined (Table 4). The brominating reagent tended to react from the less-hindered site and excess reagent led to formation of the dibromide (**13a**). The bromide (**13b**) was oxidized with dimethyl sulfoxide (DMSO) in the presence of sodium bicarbonate to give the unstable aldehyde (**14**), which was purified by flash column chromatography. Treatment of **14** with hydroxylamine hydrochloride and

acetic anhydride gave the cyano compound (**15**), which was converted to (*R*)-nilvadipine by esterification with thionyl chloride and 2-propanol after removal of the POM group (Chart 5). The synthetic route to (*S*)-NB 818 is shown in Chart 7.[19] Lipase AH-catalyzed enantioselective hydrolysis of **18** gave the (*R*)-monoester (**19**) in 64% ee. Esterification of **19** was carried out with dicyclohexylcarbodiimide (DCC) and 2-propanol to give the diester (**20**), whose enantiomeric purity was 79% ee after recrystallization from IPE/*n*-hexane. One of the two methyl groups on the 2 and 6 positions of the diester (**20**) was brominated regioselectively from the less sterically hindered side with pyridinium bromoperbromide. The bromide (**21**) was reacted with $AgNO_3$ in 50% aqueous acetone to give the alcohol (**22**), followed by protection with *tert*-butyldimethylchlorosilane (TBDMSCl) to give **23**. The alcohol (**24**) was obtained after removal of the POM group, methylation with diazomethane and deprotection of silyl groups with tetrabutylammonium fluoride. The alcohol (**24**) was reacted with chlorosulfonyl isocyanate to give (*S*)-NB 818, whose optical purity was



(*R*)-**13b** (*R*)-**17**

Chart 6



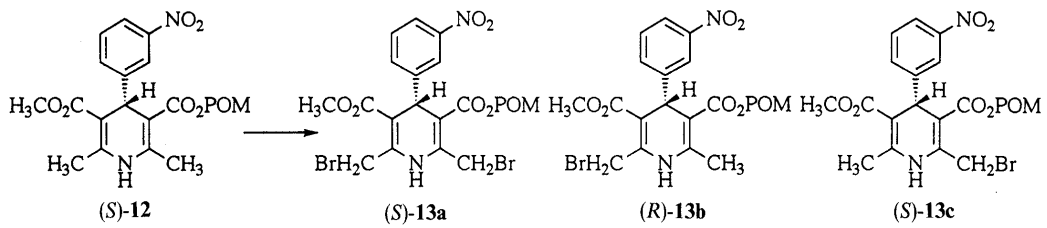
18 POM=CH_2OCO^tBu (*R*)-**19** (*R*)-**20**

(*S*)-**21** (*S*)-**22** (*S*)-**23**

(*S*)-**24** (*S*)-NB 818

Chart 7

Table 4. Bromination with Bromoperbromide Salt[a-c]



(*S*)-**12** (*S*)-**13a** (*R*)-**13b** (*S*)-**13c**

Reagent	Time (h)	(*S*)-**13a**	(*R*)-**13b**	(*S*)-**13c**	Yield of (*R*)-**13b** (%)[d]
1.5 eq DMAP·HBr·Br_2	3	1.1	7.3	1	56
2.2 eq DMAP·HBr·Br_2	3	34	1	0	Trace
1.5 eq Pyridine·HBr·Br_2	3	0.7	6.5	1	65
1.7 eq Collidine·HBr·Br_2	5	1.7	8.9	1	56

a) All reactons were carried out by stirring a mixture of (*S*)-**12**, 1.2 eq of pyridine and bromoperbromide salt in dichloromethane under an argon atmosphere. *b*) Satisfactory elemental analyses of all products were obtained. *c*) The ratio of **13a—c** was measured by HPLC analysis using a YMC Pack SIL column (2-propanol/*n*-hexane = 1/20). *d*) Isolated yield.

95% ee after recrystallization from IPE/*n*-hexane. This lipase-catalyzed reaction and regioselective bromination should provide a new method for preparation of various chiral 2-hydroxymethyl-1,4-dihydropyridines.

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, lipase PS and CHE (Amano Pharmaceutical Co., Ltd.).

Isopropyl 4-Bromoacetoacetate (1) A solution of bromine (20 ml) in carbon tetrachloride (50 ml) was added dropwise to a solution of diketene (21 g) in carbon tetrachloride (50 ml) over the period of 1 h at 0 °C. The mixture was stirred for 1 h at room temperature, then 2-propanol (20 ml) was added, and the whole was further stirred for 1 h at room temperature. The solvent was removed *in vacuo*, and the residue was distilled under reduced pressure to give a pale brown liquid (62%, bp 75—85 °C (25 mmHg)).

Isopropyl 4-Acetoxyacetoacetate (2) Compound **1** was added to a solution of sodium acetate (120 mmol) in acetic acid (100 ml), and the mixture was stirred for 18 h at 90 °C. The mixture was diluted with CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled under reduced pressure to give a colorless oil (48%, bp 115 °C (5 mmHg)).

Isopropyl 2-Acetoxymethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-5-methoxycarbonyl-6-methyl-3-pyridinecarboxylate (3a) Methyl 3-aminocrotonate, 2,3-dichlorobenzaldehyde and **2** were dissolved in 2-propanol, and the solution was refluxed for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give **3a** (43%).

3a: Pale yellow needles. mp 66—69 °C. IR (Nujol) cm^{-1}: 3362, 1747, 1724, 1689. ^{1}H-NMR ($CDCl_3$) δ: 1.03, 1.26 (6H, each d, J=6.3 Hz, $OCH(CH_3)_2$), 2.19 (3H, s, CH_3), 2.32 (3H, s, CH_3CO), 3.62 (3H, s, OCH_3), 4.98 (1H, m, >CHO–), 5.32 (2H, ABq, J=15.1 Hz, CH_2O), 5.47 (1H, s, >CH–), 6.59 (1H, s, NH), 7.05—7.30 (3H, m, C_6H_3). *Anal.* Calcd for $C_{21}H_{23}Cl_2NO_6$: C, 55.27; H, 5.08; N, 3.07. Found: C, 55.27; H, 5.30; N, 2.80.

Ethyl 2-acetoxymethyl-4-(2-chlorophenyl)-1,4-dihydro-5-methoxycarbonyl-6-methyl-3-pyridinecarboxylate (**3b**) and isopropyl 2-acetoxymethyl-1,4-dihydro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (**7**) were obtained similarly.

3b: Pale yellow powder. Yield 33%. mp 122—124 °C. IR (Nujol) cm^{-1}: 3324, 1717, 1699, 1686. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 2.19 (3H, s, CH_3), 2.33 (3H, s, CH_3CO), 3.62 (3H, s, CH_3O), 4.08, 4.10 (2H, dq, J=7.0, 10.7 Hz, 2×$C\underline{H}_A\underline{H}_BCH_3$), 5.27, 5.39 (2H, d, J=15.0 Hz, $C\underline{H}_A\underline{H}_BOAc$), 5.43 (1H, s, >CH–), 6.58 (1H, s, NH), 7.00—7.37 (4H, m, C_6H_4). *Anal.* Calcd for $C_{20}H_{22}ClNO_6$: C, 58.90; H, 5.44; N, 3.43. Found: C, 59.07; H, 5.31; N, 3.16.

7: Yellow powder. Yield 20%. mp 95—97 °C. IR (Nujol) cm^{-1}: 3346, 1696, 1523. ^{1}H-NMR ($CDCl_3$) δ: 1.11, 1.27 (6H, each d, J=6.4 Hz, $CH(CH_3)_2$), 2.21 (3H, s, CH_3), 2.38 (3H, s, CH_3CO), 3.67 (3H, s, OCH_3), 4.92—5.01 (1H, m, >CHO–), 5.10 (1H, s, >CH–), 5.34 (2H, ABq, J=14.9 Hz, $OC\underline{H}_A\underline{H}_B$), 6.71 (1H, s, NH), 7.36—8.12 (4H, m, C_6H_4). *Anal.* Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48. Found: C, 58.26; H, 5.55; N, 6.24.

Isopropyl 1,4-Dihydro-2-hydroxymethyl-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (8) Methanolic ammonia solution (4.5 ml) was added to a solution of **7** (3.0 g) in MeOH (80 ml) at 0 °C, and the mixture was stirred for 30 min. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/2) to give **8** (2.3 g, 85%).

8: Pale yellow powder. mp 161—166 °C. IR (Nujol) cm^{-1}: 3454, 3336, 1693, 1673. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=6.4 Hz, $C\underline{H}_3CH<$), 1.26 (3H, d, J=5.9 Hz, $C\underline{H}_3CH<$), 2.39 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 4.82 (2H, s, CH_2O), 4.91—5.00 (1H, m, >CHO–), 5.08 (1H, s, >CH–), 7.24 (1H, s, NH), 7.35—8.12 (4H, m, C_6H_4). *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.45; H, 5.68; N, 7.18. Found: C, 58.60; H, 5.64; N, 6.91.

Enzyme-Catalyzed Synthesis of (*S*)-3a and (*R*)-4a CHE was added to a solution of **3a** in IPE containing 10% of acetone, and the mixture was stirred for 3 d. After filtration to remove the enzyme, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel to give (*S*)-**3a** and (*R*)-**4a**.

(*S*)-**3a**: Yellow needles. Yield 50% (98% ee). $[\alpha]_D^{25}$ −37.6° (c=0.5, acetone). mp 112—113 °C.

(*R*)-**4a**: Yellow oil. Yield 42% (92% ee). $[\alpha]_D^{25}$ +34.4° (c=0.5, acetone). IR (Nujol) cm^{-1}: 3500, 3380, 1700, 1686. ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.25 (6H, each d, J=6.3 Hz, $CH(CH_3)_2$), 2.31 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 4.74 (2H, s, OCH_2), 4.93 (1H, m, >CHO–), 5.45 (1H, s, >CH–), 7.03—7.32 (3H, m, C_6H_3), 7.35 (1H, s, NH). FAB-MS m/z: 414 $(M)^+$.

(*S*)-Isopropyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2-hydroxymethyl-3-methoxycarbonyl-6-methyl-5-pyridinecarboxylate (4a) A solution of (*S*)-**3a** (2.59 g) in MeOH (25 ml) was treated with 7% methanolic ammonia (25 ml), and the mixture was stirred for 30 min at 0 °C. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give a yellow oil.

(*S*)-Isopropyl 1,4-Dihydro-2-carbamoyloxymethyl-4-(2,3-dichlorophenyl)-5-methoxycarbonyl-6-methyl-3-pyridinecarboxylate (NB 818) Chlorosulfonyl isocyanate (165 ml) was added to a solution of **4a** in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred for 3 h. Water (5 ml) was added and the whole was stirred for 2 h. The solvent was removed under pressure and the residure was extracted with AcOEt/tetrahydrofuran (THF) (4/1) twice. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under pressure, and the residue was purified by PTLC (MeOH/CH_2Cl_2=1/20) to give pale yellow needles (171 mg, 70%).

(*S*)-NB 818: Pale yellow needles. mp 130—131 °C. $[\alpha]_D^{25}$ −38.4° (c=0.6, acetone). IR (Nujol) cm^{-1}: 3378, 3320, 1721, 1704, 1664. ^{1}H-NMR (acetone-d_6) δ: 1.01, 1.24 (6H, each d, J=6.4 Hz, $CH(C\underline{H}_3)_2$), 2.32 (3H, s, CH_3), 3.58 (3H, s, OCH_3), 4.89—4.98 (1H, m, >CHO–), 5.23 (2H, ABq, J=14.9 Hz, OCH_2), 5.48 (1H, s, >CH–), 6.03 (1H, s, NH), 7.10—7.73 (3H, m, C_6H_3). *Anal.* Calcd for $C_{20}H_{22}Cl_2N_2O_6$: C, 52.53 H, 4.85, N, 6.13. Found: C, 52.66; H, 4.72; N, 5.98. (*R*)-NB 818 was obtained similarly. $[\alpha]_D^{25}$ +39.9° (c=1.0, acetone).

(*S*)-Isopropyl Methyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (5) (Method 1) Thionyl chloride (6 mg) was added to a solution of (*S*)-**6** in dimethylformamide (DMF)/CH_2Cl_2 (1/4) at 0 °C, and the mixture was stirred for 1 h. 2-Propanol (3 mg) was added, and the whole was stirred for 2 h at room temperature. The mixture was neutralized with 1 M NaOH, and extracted with AcOEt. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by PTLC (AcOEt/*n*-hexane=2/3) to give a pale yellow oil (13 mg, 91%).

(*S*)-**5**: $[\alpha]_D^{25}$ −9.5° (c=0.26, acetone). ^{1}H-NMR ($CHCl_3$) δ: 1.03, 1.25 (6H, each d, J=6.4 Hz, $CH(C\underline{H}_3)_2$), 2.32, 2.28 (6H, each s, 2×CH_3), 3.61 (3H, s, OCH_3), 4.93—4.99 (1H, m, >CHO–), 5.44 (1H, s, >CH–), 6.04 (1H, s, NH), 7.04—7.31 (3H, m, C_6H_3).

(Method 2) A solution of (*S*)-**3a** (130 mg) in MeOH (2 ml) was stirred with Pd–C under a hydrogen atmosphere for 2 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was purified by PTLC (AcOEt/*n*-hexane=2/3) to give a pale yellow oil (82 mg, 72%).

(*S*)-**5**: $[\alpha]_D^{25}$ −10.0° (c=0.5, acetone). The ^{1}H-NMR spectral data of the product were consistent with those of the product obtained by method 1.

Enzyme-Catalyzed Synthesis of (*R*)-7 and (*S*)-8 Lipase PS (100 mg) was added to a soution of **8** (195 mg) in acetone/vinyl acetate (1/2, 12 ml) and the mixture was stirred for 44 h at 40 °C. The enzyme was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2) to give a yellow oil (**7**, 119 mg, 55% and **8**, 82 mg, 42%), respectively. The optical purities of **7** and **8** were determined by HPLC analyses using a Chiralpak AS column (2-propanol/*n*-hexane=1/4) after conversion to **7**.

(*S*)-**7**: $[\alpha]_D^{25}$ +9.3° (c=2.38, acetone). All spectral data were consistent with those given above.

(*R*)-**8**: $[\alpha]_D^{25}$ +3.0° (c=1.64, acetone). All spectral data were consistent with those given above.

(*R*)-Isopropyl 2-Formyl-1,4-dihydro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (9) Oxalyl chloride (240 mg) in CH_2Cl_2 (2.8 ml) was added to a solution of DMSO (368 mg) in CH_2Cl_2 (31 ml) at −78 °C under an argon atmosphere, and the whole was stirred for 10 min. To this solution was added **8** (368 mg) in CH_2Cl_2 (17 ml), and the mixture was stirred for 1 h at −10 °C. Triethylamine (667 mg) in CH_2Cl_2 (3 ml) was added and stirring was continued for 30 min at room temperature. The reaction mixture was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, AcOEt/*n*-hexane=1/4) to give **9** (252 mg, 69%). This unstable aldehyde was subjected to the next reaction without further purification.

(*R*)-Isopropyl 2-Cyano-1,4-dihydro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (Nilvadipine) Sodium acetate (80 mg) and hydroxylamine hydrochloride (54 mg) and **9** (252 mg) were dissolved in acetic acid (6.5 ml), and the solution was stirred for 30 min at room temperature. Acetic anhydride (80 mg) was added, and the mixture was stirred for 30 min at room temperature. The temperature was raised to 100 °C, and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure, and water was added. The aqueous solution was neutralized with saturated $NaHCO_3$, and extracted with AcOEt twice. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by PTLC ($MeOH/CH_2Cl_2$=1/50) to give nilvadipine (42 mg, 17%).

(*R*)-Nilvadipine: Yellow oil. $[\alpha]_D^{25}$ +164.3° (c=0.84, MeOH). IR (Nujol) cm^{-1}: 3320, 2234, 1710. ^{1}H-NMR ($CHCl_3$) δ: 1.09 (3H, d, J=5.9 Hz, >CHC<u>H</u>$_3$), 1.26 (3H, d, J=6.3 Hz, >CHC<u>H</u>$_3$), 2.42 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.91—5.01 (1H, m, >CHO–), 5.18 (1H, s, >CH–), 6.55 (1H, s, NH), 7.42—8.12 (4H, m, C_6H_4).

(*R*)-Methyl Pivaloyloxymethyl 2-Bromomethyl-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (13b) Pyridine (190 mg), pyridinium bromoperbromide (798 mg) and (*S*)-**12** (893 mg) were dissolved in CH_2Cl_2 (20 ml), and the solution was stirred for 2 h at −20 °C. The solvent was removed under reduced pressure, and the residue was diluted with ether. The solution was washed with water and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was chomomatographed on silica gel (AcOEt/*n*-hexane=1/5) to give **13b** (526 mg, 56%). The product was subjected to the next reaction without further purification.

(*R*)-**13b**: Yellow oil. ^{1}H-NMR ($CHCl_3$) δ: 1.12 (9H, s, 3×CH_3), 2.42 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 4.71 (2H, s, CH_2Br), 5.14 (1H, s, >CH–), 5.79 (2H, ABq, J=5.5 Hz, OCH_AH_BO), 7.17 (1H, s, NH), 7.38—8.13 (4H, m, C_6H_4).

(*R*)-Methyl Pivaloyloxymethyl 2-Formyl-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (14) $NaHCO_3$ (588 mg) and **13b** (526 mg) were dissolved in DMSO (16 ml), and the mixture was stirred for 2 h at 50 °C. It was then poured into ice-water, and extracted with AcOEt twice. The organic layer 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=1/4) to give unstable **14** (122 mg, 27%) as a yellow oil. The product was subjected to the next reaction without purification.

(*R*)-Methyl Pivaloyloxymethyl 2-Cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (15) Hydroxylamine hydrochloride (21 mg), sodium acetate (33 mg) and **14** were dissolved in AcOH (3 ml), and the solution was stirred for 1 h at room temperature. Acetic anhydride (102 mg) was added, and the mixture was stirred for 3 h at 100 °C. The solvent was removed under reduced pressure, then the residue was neutralized with saturated $NaHCO_3$, and extracted with AcOEt. 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=1/4) to give **15** (80 mg, 66%).

(*R*)-**15**: Yellow oil. $[\alpha]_D^{25}$ +179.0° (c=0.74, acetone). IR (neat) cm^{-1}: 3308, 2236, 1760, 1719. ^{1}H-NMR ($CHCl_3$) δ: 1.09 (9H, s, 3×CH_3), 2.44 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 5.19 (1H, s, >CH–), 5.74 (2H, ABq, J=5.5 Hz, OCH_AH_BO), 6.55 (1H, s, NH), 7.42—8.10 (4H, m, C_6H_4). FAB-MS m/z: 458 $(M+1)^+$.

(*R*)-2-Cyano-1,4-dihydro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (16) A solution of (*R*)-**15** (73 mg) in MeOH (2 ml) containing 1 M NaOH (1 ml) was stirred 1 h at room temperature. The mixture was neutralized with 1 M hydrochloric acid, and extracted with AcOEt twice. The organic layer was washed with brine, and dried ($MgSO_4$). The solvent was removed, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/2) to give **16** (30 mg, 55%).

(*R*)-**16**: Yellow powder. $[\alpha]_D^{25}$ +204.6° (c=0.6, MeOH). IR (Nujol) cm^{-1}: 3310, 2234, 1685. ^{1}H-NMR (acetone-d_6) δ: 2.47 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 5.24 (1H, s, >CH–), 7.56—8.16 (4H, m, C_6H_4), 9.14 (1H, s, NH).

(*R*)-Isopropyl 2-Cyano-1,4-dihydro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (Nilvadipine) (*R*)-**16** was dissolved in thionyl chloride (2 ml), and the mixture was stirred for 2 h at room temperature. 2-Propanol was added with ice-cooling, and the solution was further stirred for 18 h. The solvent was removed under reduced pressure, and the mixture was diluted with water, neutralized with 1 M NaOH, and extracted with AcOEt twice. The organic layer was washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/4) to give nilvadipine (14 mg, 24%).

(*R*)-Nilvadipine: Yellow oil. $[\alpha]_D^{25}$ +198.8° (c=0.28, MeOH). All spectral data were consistent with those given above.

(*R*)-4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-5-pivaloyloxymethoxycarbonyl-3-pyridinecarboxylic Acid (19) Lipase AH (900 mg) was added to a solution of **18** (2.57 g) in cyclohexane (600 ml), and the mixture was stirred for 95 h at room temperature. The enzyme was removed by filtration, the filtrate was evaporated, and the residue obtained was chromatographed on silica gel (AcOEt/*n*-hexane=1/1) to give **19** (1.69 g, 82%).

(*R*)-**19**: Colorless powder. $[\alpha]_D^{25}$ −10.0° (c=1.0, acetone). mp 185—186 °C. IR (Nujol) cm^{-1}: 3364, 1748, 1702, 1673. ^{1}H-NMR (CD_3OD) δ: 1.06 (9H, s, CH_3), 2.26, 2.29 (6H, each s, 2×CH_3), 5.42 (1H, s, >CH–), 5.65, 5.73 (2H, each d, J=5.5 Hz, OCH_AH_BO), 7.11—7.32 (3H, m, C_6H_3). *Anal.* Calcd for $C_{21}H_{23}Cl_2NO_6$: C, 55.28; H, 5.08; N, 3.07. Found: C, 55.42; H, 5.12; N, 3.02.

(*R*)-Isopropyl Pivaloyloxymethyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (20) DCC (1.05 g), 4-dimethylaminopyridine (90 mg), and 2-propanol (20 ml) were added to a solution of **19** in THF (50 ml). The mixture was stirred for 18 h, then a small mount of AcOEt was added and DCurea was removed by filtration. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (AcOEt/*n*-hexane=1/2). The colorless powder obtained was recrystallized from IPE/*n*-hexane to give **20** (966 mg, 65%, 79% ee). The optical purity of **20** was determined by HPLC analysis with a Chiralpak AS column (2-propanol/*n*-hexane).

(*R*)-**20**: Colorless powder. $[\alpha]_D^{25}$ −22.5° (c=1.0, acetone). IR (Nujol) cm^{-1}: 3320, 1622, 1572. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6.2 Hz, $CH_3CH<$), 1.11 (9H, s, 3×CH_3), 1.24 (3H, d, J=6.2 Hz, $CH_3CH<$), 2.30 (6H, s, 2×CH_3), 4.93—4.98 (1H, m, >CHO–), 5.43 (1H, s, >CH–), 5.73 (2H, s, OCH_2O), 6.06 (1H, s, NH), 7.06—7.31 (3H, m, C_6H_3). *Anal.* Calcd for $C_{24}H_{29}Cl_2NO_6$: C, 57.84; H, 5.86; N, 2.81. Found: C, 58.03; H, 5.97; N, 2.79.

(*S*)-Isopropyl Pivaloyloxymethyl 2-Bromomethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate (21) Pyridinium bromoperbromide (463 mg) was added to a solution of **20** (723 mg) in CH_2Cl_2 (10 ml) at −20 °C under an argon atmosphere, and stirred for 1 h. The mixture 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=1/4) to give **21** (770 mg, 92%).

(*S*)-**21**: Yellow oil. $[\alpha]_D^{25}$ −37.2° (c=1.0, acetone). IR (Nujol) cm^{-1}: 3580, 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, J=6.2 Hz, C<u>H</u>$_3$CH<), 1.23 (9H, s, 3×CH_3), 1.28 (3H, d, J=6.0 Hz, $CH_3CH<$), 2.33 (3H, s, CH_3), 4.63 (2H, s, CH_2Br), 5.00—5.04 (1H, m, >CHO–), 5.48 (1H, s, >CH–), 5.77 (2H, s, OCH_2O), 7.09—7.34 (3H, m, C_6H_3). FAB-MS m/z: 576 $(M+1)^+$, 577 $(M+2)^+$.

(*S*)-Isopropyl Pivaloyloxymethyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2-hydroxymethyl-6-methyl-3,5-pyridinedicarboxylate (22) Silver nitrate (721 mg) was added to a solution of **21** (721 mg) in 50% aqueous acetone (10 ml) and the mixture was stirred for 18 h at room temperature, then extracted with AcOEt twice. The organic layer was washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/1) to give **22** (420 mg, 68%).

(*S*)-**22**: Yellow oil. $[\alpha]_D^{25}$ −42.7° (c=1.1, acetone). IR (neat) cm^{-1}: 3374, 1689, 1598. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=6.2 Hz,

$C\underline{H}_3CH<$), 1.11 (9H, s, $3\times CH_3$), 1.25 (3H, d, $J=6.4$ Hz, $C\underline{H}_3CH<$), 2.33 (3H, s, CH_3), 4.74 (2H, s, CH_2O), 4.90—4.94 (1H, m, >CHO–), 5.45 (1H, s, >CH–), 5.74 (2H, s, OCH_2O), 7.06—7.30 (3H, m, C_6H_3). *Anal.* Calcd for $C_{24}H_{29}Cl_2NO_9$: C, 56.04; H, 5.68; N, 2.72. Found: C, 56.10; H, 5.74; N, 2.67. FAB-MS *m/z*: 514 $(M+1)^+$.

(*S*)-Isopropyl Pivaloyloxymethyl 1-(*tert*-Butyldimethylsilyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate (23) Imidazole (68 mg) and TBDMSCl (339 mg) were added to a DMF solution (10 ml) of **22** (259 mg), and the solution was stirred for 5 h at room temperature under an argon atmosphere. After aqueous quenching, the mixture was extracted with AcOEt three times, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane = 1/5) to give **23** (297 mg, 95%).

(*S*)-**23**: Yellow oil. $[\alpha]_D^{25}$ −18.3° ($c=1.1$, acetone). IR (neat) cm^{-1}: 3390, 2952, 1752, 1717, 1692, 1598, 1473. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, $2\times CH_3$), 0.88 (9H, s, $3\times CH_3$), 0.96 (3H, d, $J=6.5$ Hz, $C\underline{H}_3CH<$), 1.09 (9H, s, $3\times CH_3$), 1.22 (3H, d, $J=6.2$ Hz, $C\underline{H}_3CH<$), 2.30 (6H, s, $2\times CH_3$), 4.76, 4.89 (2H, each d, $J=17.2$ Hz, OCH_AH_B), 4.86—4.92 (1H, m, >CHO–), 5.44 (1H, s, >CH–), 5.71 (2H, s, OCH_2O), 7.04—7.30 (3H, m, C_6H_3).

(*S*)-Isopropyl Methyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2-hydroxymethyl-6-methyl-3,5-pyridinedicarboxylate (24) An acetone solution (25 ml) of **23** (302 mg) was treated with 5% NaOH–NaOH (0.5 ml) under ice-cooling, and the mixture was stirred for 1.5 h. After aqueous quenching, the mixture was extracted with AcOEt/THF (4/1) three times, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, the residue was dissolved in acetone (10 ml), and excess diazomethane–ether solution was added to this solution at 0 °C. The mixture was stirred for 30 min, acetic acid was added, and the solvent was removed under reduced pressure. The residue was dissolved in THF (10 ml), 1.0 M tetrabutylammonium fluoride (0.74 ml) was added under an argon atmosphere, and the mixture was stirred 15 min at 0 °C. After aqueous quenching, the solution was extracted with AcOEt/THF (4/1) three times, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/*n*-hexane = 1/2) to give **24** (94 mg, 47%).

(*S*)-**24**: Yellow oil. $[\alpha]_D^{25}$ −16.8° ($c=1.4$, acetone). IR (neat) cm^{-1}: 3378, 1702, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, $J=6.2$ Hz, $C\underline{H}_3CH<$), 1.26 (3H, d, $J=6.2$ Hz, $C\underline{H}_3CH<$), 2.32 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 4.75 (2H, s, CH_2O), 4.89—4.98 (1H, m, >CHO–), 5.45 (1H, s, >CH–), 7.06—7.32 (3H, m, C_6H_3). FAB-MS *m/z*: 414 $(M+1)^+$.

(*S*)-Isopropyl 2-Carbamoyloxymethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-5-methoxycarbonyl-6-methyl-3-pyridinecarboxylate (NB 818) Chlorosulfonyl isocyanate (65 mg) was added to a dichloromethane solution (10 ml) of **24** at −20 °C under an argon atmosphere, and the mixture was stirred for 2 h. The temperature was raised to room temperature, and water was added. The whole was stirred for 3 h, then the organic layer was separated. The aqueous layer was extracted with AcOEt/THF (4/1) four times, and the extracts was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by medium-pressure chromatography ($MeOH/CH_2Cl_2=1/20$) to give (*S*)-NB 818 (67 mg, 64%). The pale yellow crystals were recrystallized from IPE/*n*-hexane.

(*S*)-NB 818: Pale yellow crystals. mp 128—129 °C. $[\alpha]_D^{25}$ −16.8° ($c=1.4$, acetone) (95% ee). All spectral data were consistent with those given above.

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