LIPASE-CATALYZED ENANTIOSYNTHESIS OF (*R*)- AND (*S*)-2-[BENZYL(PHENYL)AMINO]ETHYL 5-(5,5-DIMETHYL-2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YL)-1,4-DIHYDRO-2,6-DIMETHYL-4-(3-NITROPHENYL)-3-PYRIDINECARBOXYLATE (NZ 105)

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Homochiral 4-Aryl-1,4-dihydropyridine-5-phosphate (NZ 105) was synthesized from the racemic materials. The enantioselective hydrolysis by lipase catalyst was smoothly proceeded and optically active carboxylic acid was converted into optically active medicine.

KEY WORDS 1,4-Dihydropyridine; calcium channel blocker; NZ 105; lipase-catalyzed enantioselective synthesis

4-Aryl-1,4-dihydropyridines are novel and potent calcium antagonists; their derivatives have been widely investigated from the pharmacological points of view, and some of them have already been employed therapeutically as antihypertensive drugs.1) These agents are known to exhibit their vasodilative activities owing to their affinity with voltage-dependent calcium channels. Different substituents in their compounds lead to chiral derivatives possessing an asymmetric carbon at the 4-position, and the enantiomers have been reported to show different biological activities,2) although most 1,4-dihydropyridines have been investigated as racemates.

In recent studies on 1,4-dihydropyridine-3,5-dicarboxylic acid diesters, replacement of one of the carboxylic ester moieties by phosphonate, such as 1,4-dihydropyridine-5-phosphonates, have been reported to maintain the calcium-antagonistic activities.3) In this paper, we will describe the enzymatic synthesis of optically active novel calcium antagonist, 2-[benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)3-pyridinecarboxylate (NZ 105), which possesses considerably high channel blocking action and the stereoselectivity of lipase AH-catalyzed hydrolysis of 1,4-dihydropyridines. In our previous studies on the synthesis of optically active 1,4-dihydropyridines using lipase-catalysts, acyloxymethyl esters were found to be hydrolyzed enantioselectively with lipase AH to give the optically active 1,4-dihydropyridines.4) We selected the propionyloxymethyl (PROM) ester, which was more easily hydrolyzed than pivaloyloxymethyl (POM) ester, as a substrate for lipase-catalyzed enantioselective hydrolysis in an organic solvent. The preliminary screening tests on various enzymes revealed that lipase AH (*Pseudomonas sp.*) 5) was suited well for the hydrolysis.6)

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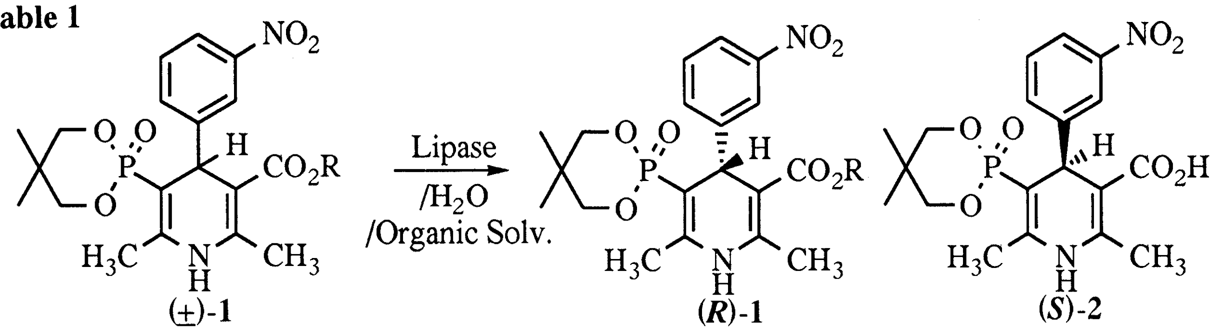
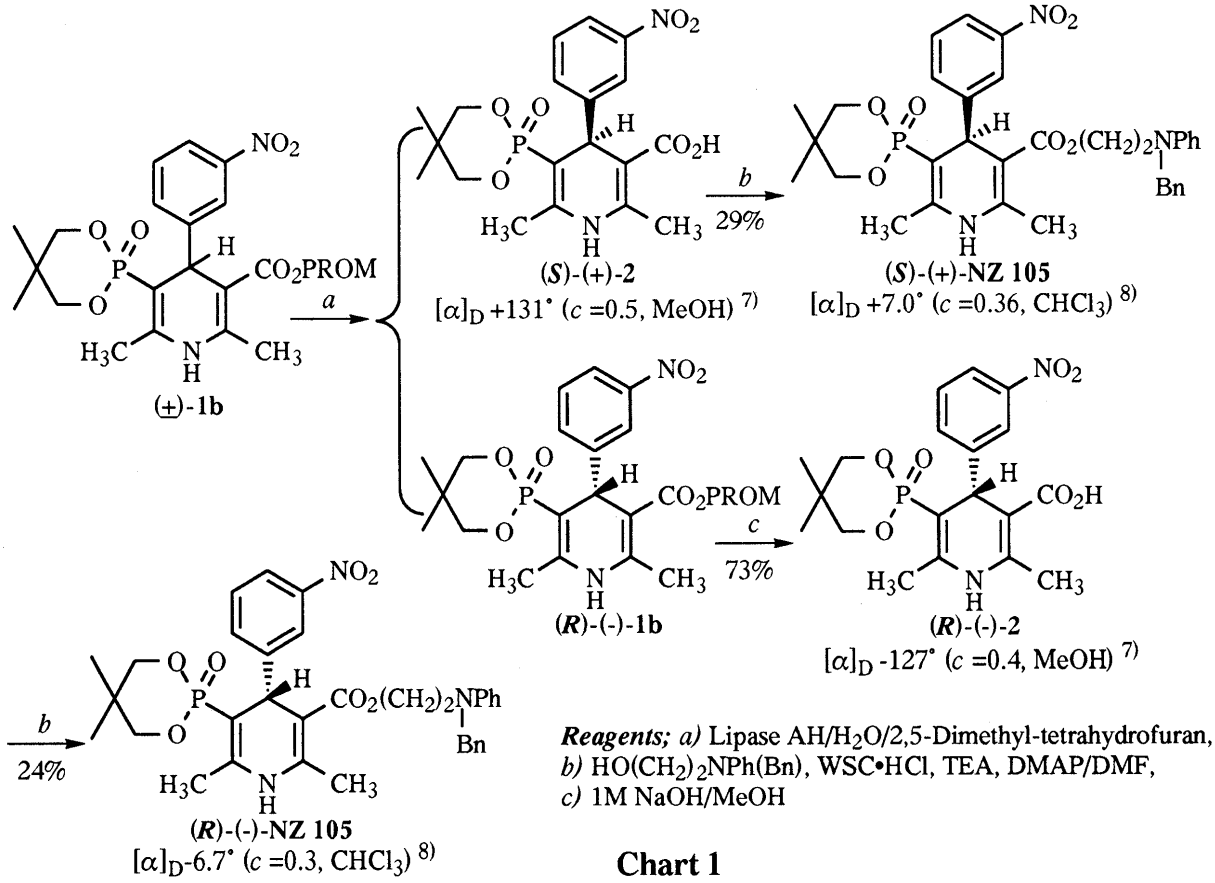
The enzymatic reactions were carried out as follows: A mixture of substrate and lipase AH in 2,5-dimethyl-tetrahydrofuran (2,5-dime-THF) saturated with water was stirred for 6 hours at room temperature. The reaction was followed by HPLC analysis, and the mixture was worked up when the conversion reached 50%. The PROM ester and carboxylic acid were conveniently purified by flush column chromatography, and their optical purities were determined by HPLC analysis using a

Table 1



Entry	Substrate R	Lipase	Solvent	Time	Ester C.Y.(%)[b]	Ester O.Y.(%ee)[c]	Carboxylic acid C.Y.(%)[b]	Carboxylic acid O.Y.(%ee)[c]
1	POM	AH	IPE	7 days	>99	0	0	0
2	PROM	AH	IPE	6 hours	50	60	40	70
3	PROM	AH	2,5-dime-THF	6 hours	50	69	40	82

a)All reactions were carried out by stirring a mixture of substrate, lipase powder and organic solvent (IPE; diisopropylether and 2,5-dime-THF; 2,5-dimethyl-tetrahydrofuran) saturated with water/acetone (= 7/3).
b)Conversions were determined by HPLC analysis using a column packed with 5C18-HG (70%MeOH). t_R:3.7min.(CO_2H) 6.5min.(PROM ester). *c*)Optical yields were determined by HPLC analysis using Chiralcel OD-H (n-hexane/2-propanol=10/1).



Reagents; a) Lipase AH/H_2O/2,5-Dimethyl-tetrahydrofuran,
b) $HO(CH_2)_2NPh(Bn)$, WSC•HCl, TEA, DMAP/DMF,
c) 1M NaOH/MeOH

Chart 1

chiral column (Table 1).

The synthesis of optically active NZ 105 is shown in Chart 1. The (***R***)-PROM ester ((***R***)-**1b**)[7] was easily converted into (***R***)-carboxylic acid ((***R***)-**2**) . The (***R***)- and (***S***)-carboxylic acid ((***R***)-**2** and (***S***)-**2**) were recrystallized with MeOH/ H_2O, and their optical purities became 100%ee. The (***R***)- and (***S***)-NZ 105[8] was obtained by esterification of optically pure (***R***)- and (***S***)-carboxylic acid ((***R***)-**2** and (***S***)-**2**),[7] respectively. The absolute configurations of this series of dihydropyridines were determined by conversion to NZ 105, which showed the same optical rotation as that of (***S***)- and (***R***)-NZ 105.[3]

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REFERENCES AND NOTES

1) Bossert F., Yater W., *Naturwissenschaften*, **58**, 578, (1971).

2) For recent review, see: Goldmann F., Stolesfuss J., *Angew. Chem. Int. Ed. Eng.*, **30**, 1559, (1991).

3) *a*) Sakoda R., Kamikawaji Y., Seto K., *Chem. Pharm. Bull.*, **40**, 2362, (1992); *b*) *idem*, *ibid.*, **40**, 2370, (1992); *c*) Sakoda R., Matsumoto H., Seto K., *ibid.*, **40**, 2377, (1992).

4) Ebiike H., Terao Y., Achiwa K., *Tetrahedron Lett.*, **32**, 5805, (1991).

5) Lipase AH was kindly supplied by Amano Pharmaceutical Co., Ltd.

6) A preliminary screening test indicated that hydrolysis with lipase AH and 2,5-dimethyl-tetrahydrofuran saturated with water was best. 2,5-Dimethyl-tetrahydrofuran has higher solubility of the substrate than diisopropylether.

7) (***R***)-and (***S***)-**2** were recrystallized with MeOH/H_2O and their optical purity became 100%ee.

(***S***)-**2**: mp 231-232°C (MeOH/H_2O). $[\alpha]_D$ +131° (*c* =0.6, MeOH). IR (nujol) 3278, 3194, 3074, 1669, 1642, 1610 (cm^{-1}). ^{1}H-NMR (CD_3OD) δ: 0.91 (3H, s, CH_3), 1.02 (3H, s, CH_3), 3.60-3.78 (2H, m, OCH_2), 4.05-4.13 (2H, m, OCH_2), 4.82 (1H, d, J=10.8Hz, >CH-), 7.53-8.04 (4H, m, C_6H_4), 9.11 (1H, d, J=5.1Hz, NH).

(***R***)-**1b**: mp 145-146°C (AcOEt/n-Hexane). $[\alpha]_D$ -40.4° (*c* =1.6, acetone). IR (nujol) 3283, 3200, 3086, 1761, 1711, 1646, 1622 (cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.10 (3H, t, J=7.4Hz, $C\underline{H}_2CH_3$), 2.30 (3H, s, CH_3), 2.33 (3H, d, J=2.4Hz, CH_3), 3.67, 3.71 (2H, each ddd, J=16.5, 11.1, 2.0Hz, OCH_2), 4.17, 4.21 (2H, dd, J=11.1, 6.7Hz, OCH_2), 4.88 (1H, d, J=10.7Hz, >CH-), 5.41 (1H, ABq, J=6.4Hz, >CH-), 5.41 (1H, ABq, J=6.4Hz, OCH_AH_BO), 7.34-8.14 (4H, m, C_6H_4), 7.40 (1H, d, J=7.4Hz, NH).

(***R***)-**2**: mp 231-232°C (MeOH/H_2O). $[\alpha]_D$ -127° (*c* =0.4, MeOH).

8) (***S***)-NZ 105: mp 190-192°C (EtOH). $[\alpha]_D$ +7.0° (*c* =0.36, $CHCl_3$).[lit. mp 190-192°C. $[\alpha]_D$ +7.0° (*c* =0.50, $CHCl_3$).; See reference 3)-*a*)] IR (neat) 3280, 3202, 3084, 1735, 1700, 1639 (cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.38 (3H, d, J=2.4Hz, CH_3), 3.56 (1H, ddd, J=17.8, 11.1, 2.4Hz, $POC\underline{H}_AH_B$), 3.63-3.68 (1H, m, $POCH_A\underline{H}_B$), 3.67 (2H, t, J=6.7Hz, NCH_2), 4.19, 4.24 (2H, each dd, J=11.1, 5.4Hz, $POCH_2$), 4.31 (2H, dt, J=6.7, 3.4Hz, OCH_2), 4.92 (1H, d, J=10.8Hz, >CH-), 6.32 (1H, d, J=5.4Hz, NH), 6.99-8.10 (14H, m, C_6H_4 & $2xC_6H_5$). Positive FAB-MS: m/z 632 $(M+1)^+$.

(***R***)-NZ 105: mp 190-192°C (EtOH). $[\alpha]_D$ -6.7° (*c* =0.3, $CHCl_3$).[lit. mp 190-192°C. $[\alpha]_D$ -7.0° (*c* =0.50, $CHCl_3$).; See reference 3)-*a*]

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