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Enzymatic Synthesis of Optically Active 2-Carbamoyl-oxymethyl-1,4-dihydropyridines, (*R*)-(+)- and (*S*)-(-)-NB 818

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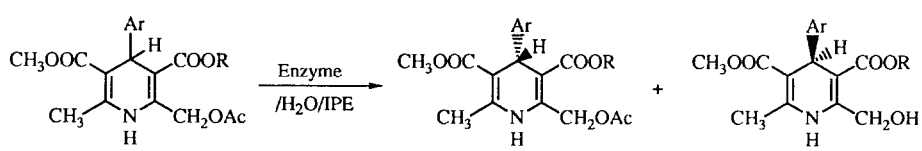
Abstract: Racemic dihydropyridines were resolved by enzyme-catalyzed hydrolysis in an organic solvent saturated with water. The chiral derivatives obtained were converted to (*S*)- and (*R*)-NB 818.

4-Aryl-1,4-dihydropyridinedicarboxylic diesters are known as calcium antagonists, and this series of derivatives have been widely investigated and introduced on the market as an antihypertensive drug[1]. When the two ester groups are different, C_4 of the dihydropyridine ring becomes chiral, and the two enantiomers were reported to show much different biological activities[2]. In previous papers, we reported asymmetric synthesis of their derivatives from prochiral substrates (bisacyloxymethyl 4-aryl- and 4-alkyl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates) using lipase catalysts[3,4].

Recently, 1,4-dihydropyridines substituted with basic side chains at their 2-position were reported to show longer bioactivity and greater tissue selectivity[5]. These 2-substituted-1,4-dihydropyridines also possesses an asymmetric carbon at the 4-position, and stereoselectivity of antagonism is observed. Herein, we report the synthesis of optically active 2-substituted-1,4-dihydropyridines using enzyme-catalyzed kinetic resolution of racemic materials.



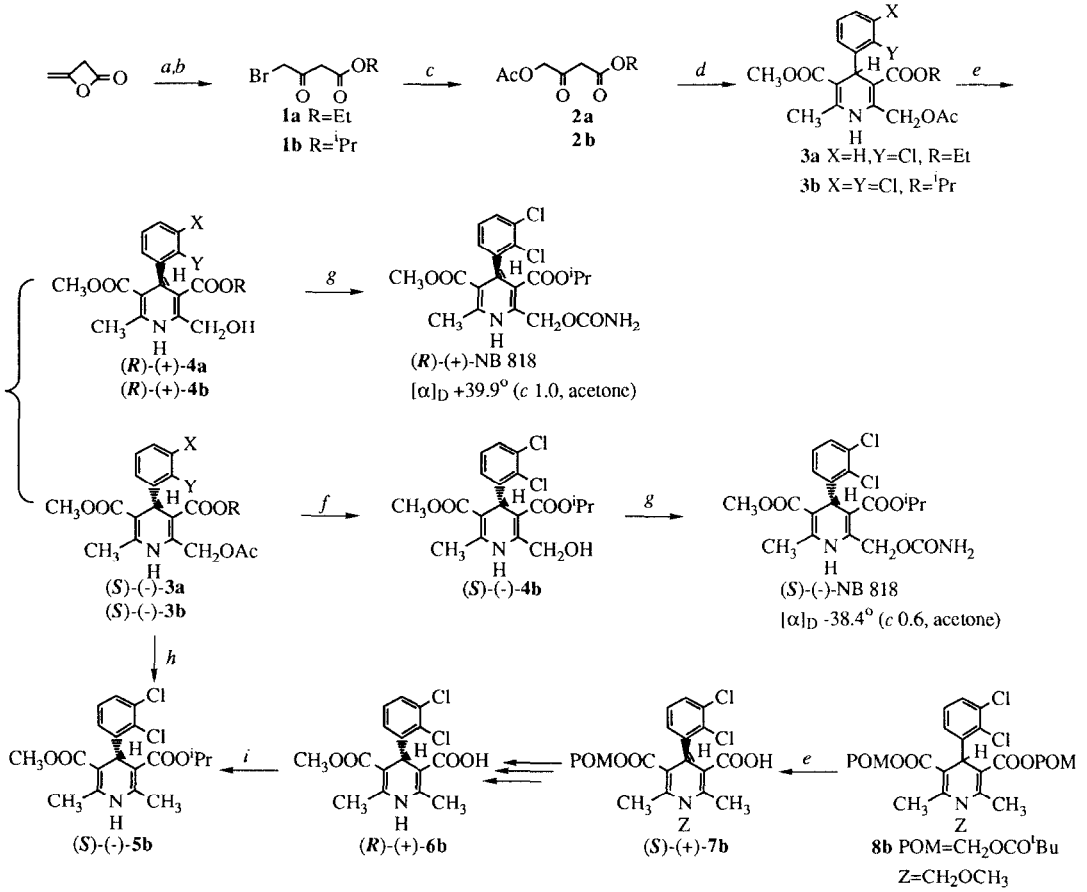
3 Ar=2-Cl-C_6H_4 or 2,3-Cl_2-C_6H_3
R=C_2H_5 or $CH(CH_3)_2$

Scheme 1

The synthesis of 2-acetoxymethyl-1,4-dihydropyridines (**3**)[6] by a Hantzsch condensation are shown in Scheme 2. The preliminary investigations revealed that lipase AH-SE (*Pseudomonas sp.*), PS-SE (*Pseudomonas cepacia*), and CHE-SE (cholesterol esterase)[7] were effective for hydrolysis of **3**. All reactions were carried out by stirring a mixture of the substrate and a crude enzyme in diisopropyl ether (IPE) saturated with water containing 10% acetone. Table 1 shows the results of their asymmetric hydrolysis. The hydrolysis of **3a** with lipase AH-SE gave (+)-**4a** and (-)-**3a**[8], and **3b** with CHE-SE gave (+)-**4b** and (-)-**3b**[9] in high optical yields,

respectively. The absolute configuration of **3b** was determined by comparison of a specific rotation of (-)-**5b** led from (-)-**3b** with that of (-)-**5b** from (*R*)-(+)-**6b** which we previously reported[3].

Enzymatic Synthesis of Optically Active 2-Carbamoyloxymethyl-1,4-dihydropyridines, (*R*)-(+)- and (*S*)-(-)-NB 818



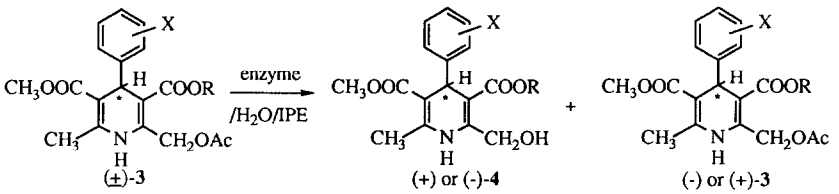
Reagents; *a* Br_2/CCl_4 *b* ROH *c* AcONa/AcOH *d* **2**, Substituted-benzaldehyde, Alkyl acetoacetate/IPA *e* enzyme/H_2O/IPE *f* NH_3/MeOH *g* $ClSO_2NCO/CH_2Cl_2$ *h* H_2,Pd-C/MeOH *i* $SOCl_2$,IPA/CH_2Cl_2,DMF

Scheme 2

The synthesis of enantiomers of (*R*)-(+)- and (*S*)-(-)-NB 818 was accomplished as shown in Scheme 2. (*S*)-(-)-**3b** was hydrolyzed with ammonia-methanol to give (*S*)-(-)-**4b**. (Desired **4b** was not obtained, when NaOH or aquous ammonia were used.) (*R*)-(+)- and (*S*)-(-)-**4b** were converted to (*R*)-(+)- and (*S*)-(-)-NB 818 by treatment with chlorosurfonyl isocyanate. Single recrystallization of chiral NB 818 from AcOEt/hexane gave the optically pure products[10].

It should be noted that the same side acyl group of **8b** and **3b** were found to be hydrolyzed stereoselectively with the enzyme. The lipase-catalyzed optical resolution of 2-acetoxymethyl-1,4-dihydropyridines provides a new method for preparation of chiral 1,4-dihydropyridines such as NB 818 and amlodipine[4] as chiral medicines.

Table 1. Lipase-catalyzed Kinetic Resolution of 2-Hydroxymethyl-1,4-dihydropyridine Derivatives [a]



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

a All reactions were carried out by stirring a mixture of substate, lipase, and IPE saturated with water (containing10% acetone) at 25°C. *b* Isolated yields. *c* Satisfactory elemental analyses of all products were obtained. *d* Optical yields of **3** were determined by HPLC analyses using a column packed with Chiralcel AS (entry 1~3) or Chiralcel OD (entry 4~6) (2-propanol/hexane), and **4** were determined after conversion to **3**. *e* Acetone, *c*0.5~1.

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6. **3a**: mp 122-124°C, ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0Hz, $CH_2C\underline{H_3}$), 2.19 (3H, s, CH_3), 2.33 (3H, s, CH_3CO), 3.62 (3H, s, OCH_3), 4.08, 4.10 (2H, dt, J=7.0, 10.7Hz, $C\underline{H_A}\underline{H_B}CH_3$), 5.27, 5.39 (2H, d, J=15.0Hz, $C\underline{H_A}\underline{H_B}OAc$), 5.43 (1H, S, >CH-), 6.58 (1H, s, NH), 7.00-7.25, 7.28-7.37 (4H, m, C_6H_4).

4b: mp 74-75°C, ^{1}H-NMR ($CDCl_3$) δ: 1.03, 1.26 (6H, d, J=6.3Hz, $OCH(C\underline{H}_3)_2$), 2.19 (3H, s, CH_3), 2.32 (3H, s, CH_3CO), 3.62 (3H, s, OCH_3), 4.98 (1H, m, OCH), 5.32 (2H, ABq, J=15.1Hz, CH_2O), 5.47 (1H, s, >CH-), 6.59 (1H, s, NH), 7.05-7.30 (3H, m, C_6H_3).

7. Lipase AH-SE, lipase PS-SE, and CHE-SE were kindly supplied by Amano Pharmaceutical Co., Ltd.
8. (-)-**3a**: mp 113-114°C, $[\alpha]_D$ -29.1 (*c* 1.0, acetone). (+)-**4a**: yellow oil, $[\alpha]_D$ +14.3 (*c* 0.6, acetone), ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.3Hz, $CH_2C\underline{H}_3$), 2.31 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 4.05, (2H, q, J=7.3Hz, $C\underline{H}_2CH_3$), 4.73 (2H, ABq, J=6.4Hz, $C\underline{H}_2OH$), 5.41 (1H, S, >CH-), 7.00-7.39 (4H, m, C_6H_4 and 1H, s, NH).
9. (-)-**3b**: mp 112-113°C, $[\alpha]_D$ -37.6 (*c* 0.5, acetone). (+)-**4b**: yellow oil, $[\alpha]_D$ +34.4 (*c* 0.5, acetone), ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.25 (6H, d, J=6.3Hz, $CH(C\underline{H}_3)_2$), 2.31 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 4.74 (2H, s, CH_2O), 4.93 (1H, m, OCH), 5.45 (1H, s, >CH-), 7.03-7.32 (3H, m, C_6H_3), 7.35 (1H, s, NH).
10. (***R***)-(+)-**NB 818**: $[\alpha]_D$ =+39.9 (*c* 1.0, acetone), mp 130-131°C, ^{1}H-NMR (d_6-acetone) δ: 1.01 (3H, d, J=6.4Hz, $>CH(C\underline{H}_3)_2$), 1.24 (3H, d, J=6.4Hz, $>CH(C\underline{H}_3)_2$), 2.32 (3H, s, CH_3), 3.58 (3H, s, OCH_3), 4.89-4.98 (1H, m, >CHO-), 5.23 (2H, ABq, J=14.9Hz, CH_2O), 5.48 (1H, s, >CH-), 6.03 (1H, s, NH), 7.10 (3H, m, C_6H_3), IR (nujol) 3378, 3320, 1721, 1704, 1664 cm^{-1}.
(***S***)-(+)-**NB 818**: $[\alpha]_D$ =-38.4 (*c* 0.6, acetone)