Chem. Pharm. Bull. **42**(9) 1968—1970 (1994)

DETERMINATION OF THE ABSOLUTE CONFIGURATION OF BIOLOGICALLY ACTIVE (*S*)-(-)-NB 818 AND ITS STRUCTURAL CORRELATION WITH THE STEREOSELECTIVITY OF THE CHANNEL BLOCKING ACTION

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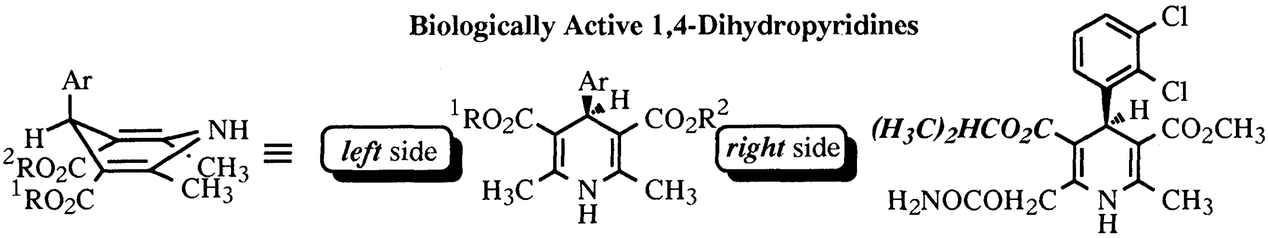
The absolute configuration of 4-(2,3-dichlorophenyl)-1,4-dihydropyridines was established by chemical correlation with (*S*)-(-)-felodipine, the absolute configuration of which had been determined by X-ray analysis.

KEYWORDS 1,4-dihydropyridine; lipase-catalyzed hydrolysis; NB 818; calcium antagonist

Enzymes are widely used for syntheses of homochiral compounds. In particular, the use of lipase-catalyzed reactions in organic solvents is a convenient method for organic synthesis because of their stereoselectivities and operational facilities.[1] 1,4-Dihydropyridines have been widely investigated as calcium channel blockers and used as antihypertensive and antianginal drugs.[2] 1,4-Dihydropyridines possessing different ester groups at their 3- and 5-position, having a stereogenic carbon at C-4 have shown stereoselectivities in the channel blocking action.[3]

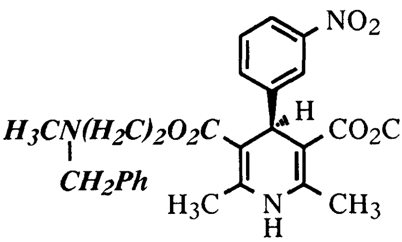
Earlier this year, Nakayama *et al.* reported[4] that (-)-NB 818 ((-)-**1**)[5] was more potent than (+)-NB 818. In a previous paper,[6] we also assigned (-)-NB 818 an *S*-absolute configuration on the assumption that the 4-substituents of the 1,4-dihydropyridines did not influence the stereoselectivity of lipase AH-catalyzed hydrolysis. These facts clearly indicate that the 3,5-diester groups have a greater effect on the biological activity than their 2,6-substituents, as shown in below. On the other hand, in (***R***)-amlodipine ((***R***)-**3**),[7] the 2,6-substituents seemed to be more important than in (***R***)-(+)-nilvadipine ((***R***)-(+)-**2**)[8] for the stereoselectivity of the channel blocking action. So we tried to confirm the absolute configuration of the (-)-NB 818 by its correlation with (*S*)-(-)-felodipine ((*S*)-(-)-**4**),[9] whose absolute configuration was determined by X-ray analysis.[10]

Biologically Active 1,4-Dihydropyridines

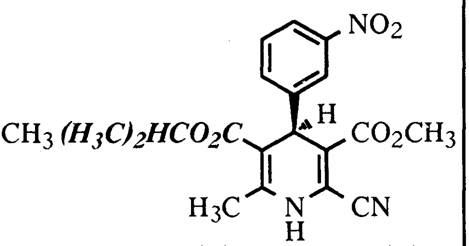


(*S*)-(-)-NB 818 (*S*)-(-)-**1**

larger ester group on the *Left* side

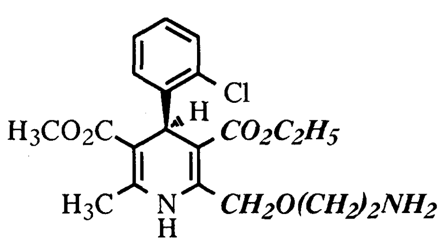


(*S*)-nicardipine



(***R***)-nilvadipine (***R***)-**2**

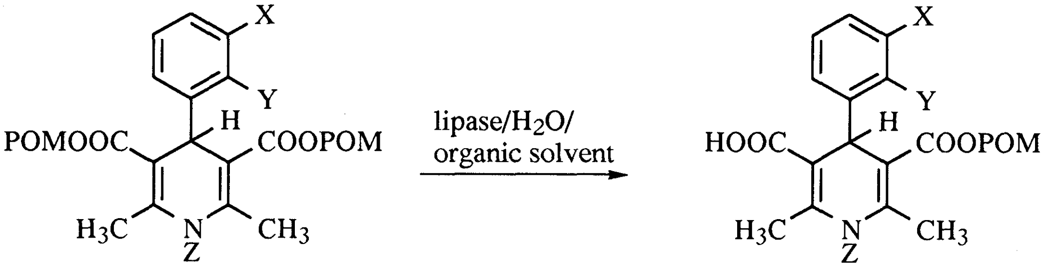
larger ester group on the ***Right*** side



(***R***)-amlodipine (***R***)-**3**

Hydrolyses of the bis(pivaloyloxymethyl) esters (**5**) catalyzed by lipase AH or PS in diisopropyl ether (IPE) or cyclohexane saturated with water are summarized in Table I. Lipase AH-catalyzed hydrolysis of the 4-(3-nitrophenyl)-1,4-dihydropyridine (**6b**) was reported to give (*S*)-**6b** in IPE and (***R***)-**6b** in cyclohexane (Table I, entries 3, 4),[11, 12] and also lipase PS-catalyzed hydrolysis of **5a** in IPE was shown to give (***R***)-**6a**. Non-inversion of the stereochemistry of **6c** was observed by using lipase PS instead of lipase AH for hydrolysis of the 4-(2,3-dichlorophenyl)-dihydropyridine (**5c**) in IPE and lipase AH-catalyzed hydrolysis in cyclohexane (Table I, entries 5,6,7). Lipase AH-catalyzed hydrolysis of **5d** gave the (+)-monoester ((+)-**6d**),[13] which was treated with diazomethane and alkaline to give the (***R***)-(+)-**7**. Esterification of (***R***)-(+)-**7** was carried out with thionyl chloride and ethanol to give (-)-**4**. The absolute configuration of (-)-**4** was assigned as *S* by comparison of a sign of its specific rotation with that of the reported (*S*)-(-)-**4**.[10] These facts clearly indicated that biologically more active (-)-NB 818,[4] which was already correlated to (***R***)-(+)-**7**[6] (Chart 1), should have *S* absolute configuration. The solvent effects on the lipase AH-catalyzed hydrolysis of **5d** are shown in Table I (entries 8,9).[12] When cyclohexane was used as a solvent, reverse stereoselectivity was observed in a manner similar to that of the 4-(3-nitrophenyl) derivative (**5b**). These results show that the reverse stereoselectivity induced by these solvents is not observed in the hydrolysis of the N-methoxymethyl-4-(2,3-dichlorophenyl) derivative (**5c**).

Table I. Enzyme and Solvent Effects on Lipase-Catalyzed Hydrolysis of 1,4-Dihydropyridines [a]



5a~d **6a~d**

Entry[f]	Substrate				Lipase	Solvent	Time (h)	Product[b]			
	No.	X	Y	Z				No.	C.Y.(%)[c]	%ee[d]	Config.[e]
1	**5a**	NO_2	H	MOM	AH	IPE	4	**6a**	95	>99	***S***
2	**5a**	NO_2	H	MOM	PS	IPE	72	**6a**	44	69	***R***
3	**5b**	NO_2	H	H	AH	IPE	35	**6b**	83	93	***S***
4	**5b**	NO_2	H	H	AH	cyclohexane	48	**6b**	88	89	***R***
5	**5c**	Cl	Cl	MOM	AH	IPE	6	**6c**	81	96	***S***
6	**5c**	Cl	Cl	MOM	PS	IPE	300	**6c**	19	81	***S***
7	**5c**	Cl	Cl	MOM	AH	cyclohexane	80	**6c**	62	93	***S***
8	**5d**	Cl	Cl	H	AH	IPE	360	**6d**	78	>99	***S***
9	**5d**	Cl	Cl	H	AH	cyclohexane	312	**6d**	88	47	***R***

a) All reactions were carried out by stirring a mixture of substrate and lipase in organic solvent saturated with water at room temperature. *b)* Satisfactory elemental analyses of all products were obtained. *c)* Isolated yields. *d)* Determined by HPLC analyses by using chiral columns. *e)* Assigned by a sign of specific rotation of the related compound. *f)* Entries 1~3, 5; see ref.11. Entries 4; see ref.12. Entries 6~9; this work.

In this work, we have determined the absolute configuration of the 4-(2,3-dichlorophenyl) derivatives including (-)-NB 818 by their stereochemical correlation with (*S*)-(-)-felodipine to confirm the importance of the 3,5-diester groups to the stereoselectivity of the channel blocking action, and also found drastic solvent effects on the stereoselectivity of lipase-AH-catalyzed hydrolysis of the N-unprotected 4-(2,3-dichlorophenyl)-1,4-dihydropyridines.

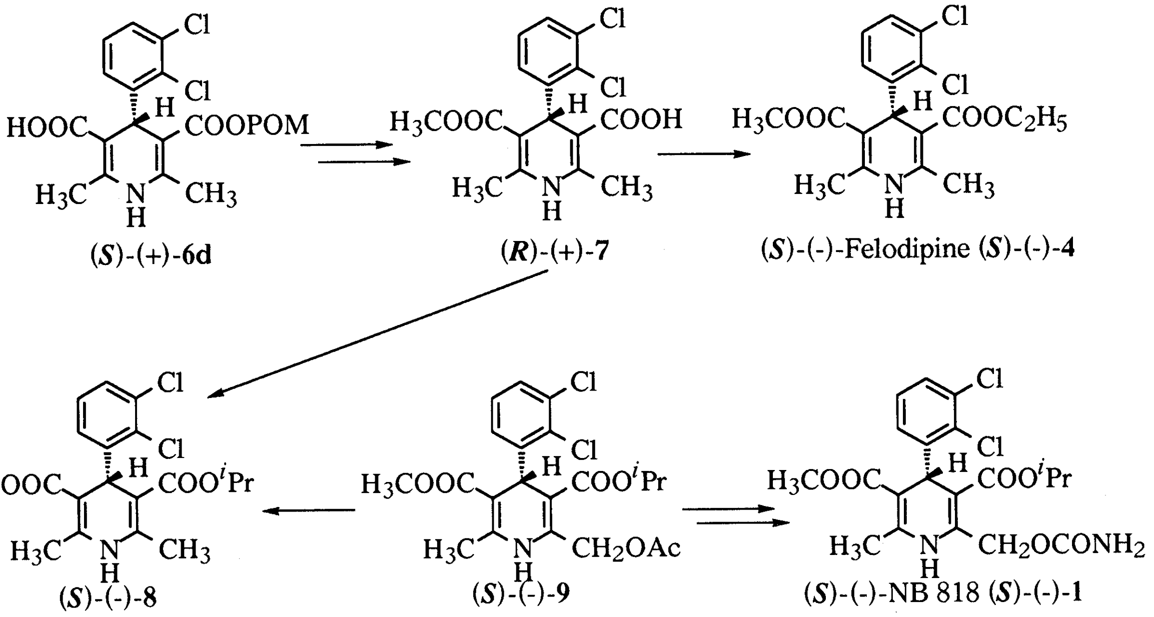


Chart 1

ACKNOWLEDGMENTS Financial support provided by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (No.05403032) and by the Sasagawa Scientific Research Grant from The Japan Science Society are gratefully acknowledged.

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13) (*S*)-(+)-**6d**: $[\alpha]_D$=+17.8° (c0.99, acetone), mp 180-181°C, ^{1}H-NMR (CD_3OD) δ: 1.06(9H, s, $(CH_3)_3$), 2.26(3H, s, CH_3), 2.29(3H, s, CH_3), 5.42(1H, s, >CH-), 5.70(2H, ABq, J=5.6Hz, OCH_2O), 7.08-7.33(3H, m, C_6H_3). IR(nujol) 3364, 1748, 1702, 1673cm^{-1}.
(*R*)-(-)-**6d**: $[\alpha]_D$=-8.3° (c1.1, acetone), mp 185-186°C.

(Received July 8, 1994; accepted August 8, 1994)