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CARBAMOYLMETHYL GROUP AS AN ACTIVATED GROUP IN PROTEASE- AND BASE-CATALYZED TRANSESTERIFICATION OF 1,4-DIHYDROPYRIDINES : A NOVEL ASYMMETRIC SYNTHESIS OF VALNIDIPINE

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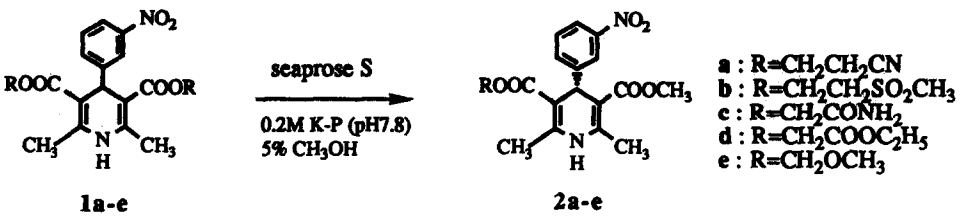
Abstract: The first protease-catalyzed enantioselective transesterification of 1,4-dihydropyridine-3,5-dicarboxylates in an aqueous solution was developed with high optical purity. Carbamoylmethyl ester group was enantioselectively transesterificated with (*S*)-N-benzyl-3-pyrroridinol by the protease and successive base-catalyzed transesterification proceeded smoothly to give the chiral drug, valnidipine, in a good yield.

4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates are well-known as calcium antagonists and many derivatives have been widely used as antihypertensive drugs and cerebral vasodilators.[1] Different substituents in these compounds lead to the chiral derivatives possessing an asymmetric carbon at the 4-position and enantiomers have been reported to show different biological activities,[2] although almost 1,4-dihydropyridines were purchased as racemates. It was reported that dialkyl 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates were inert to chemical[3] and enzymatic hydrolysis[4a,b] due to their steric hindrance and inactivity. Recently, Sih *et al* and our group independently reported the lipase-catalyzed enantioselective hydrolysis of 1,4-dihydropyridines possessing acyloxymethyl groups at 3,5-positions.[4] Modification of alkyl esters to acyloxymethyl ester make it possible to hydrolyze ester groups which couldn't be directly hydrolyzed by lipases. We have found that protease could catalyze enantioselective hydrolysis of esters of prochiral 1,4-dihydropyridines directly.[5] The half esters of 1,4-dihydropyridines obtained by above two methods were important intermediates for the synthesis of optically active derivatives.

We describe in this report protease-catalyzed enantioselective transesterification of 1,4-dihydropyridines in an aqueous solution. Our finding enables the direct synthesis of 1,4-dihydropyridine drugs. The enzymatic reaction was carried out by stirring a mixture of **1a-e** and seaprose S (*Aspergillus melleus*)[6] in 0.2M phosphate buffer (pH 7.8) containing 5% methanol. The protease-catalyzed transesterification instead of hydrolysis proceeded smoothly to give the corresponding methyl esters (**2a-e**). Results were summarized in Table 1. The absolute configurations of the methyl esters (**2a-e**) were assigned to be (*R*)-form by the optical rotation and the optical purities were found to be more than 99%.[5] The protease-catalyzed transesterification proceeded even in an aqueous solution (5% methanol) at the same side of the 1,4-dihydropyridine ring as the case of hydrolysis.

Bis(carbamoylmethyl) 1,4-dihydropyridine-3,5-dicarboxylate (**1c**) was the most reactive substrate for this reaction.



1a-e **2a-e**

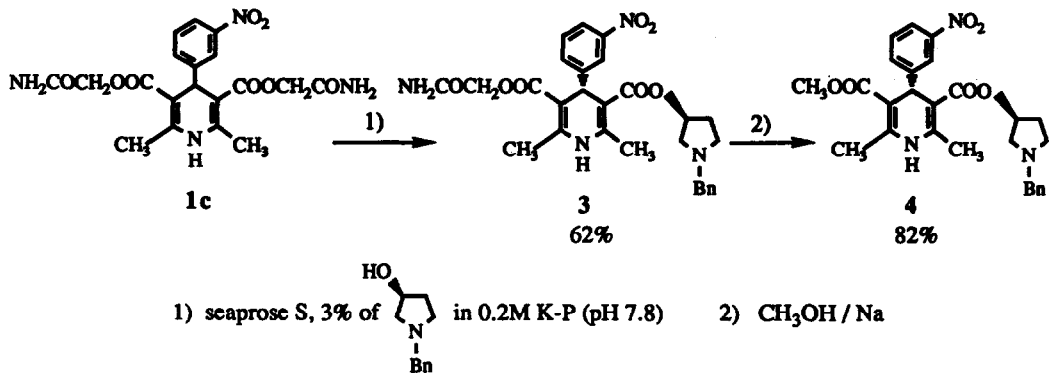
Scheme 1

Table 1 Seaprose S-Catalyzed Enantioselective Transesterifications[a]

			Product			
Entry	Substrate	Time(hr)	No.	Yield(%)[b]	ee(%)[c]	$[\alpha]_D^{20}$(°)[d]
1	**1a**	120	**2a**	35	99%	-32.6°
2	**1b**	120	**2b**	48	99%	-64.0°
3	**1c**	20	**2c**	83	99%	-16.0°
4	**1d**	48	**2d**	52	99%	-34.8°
5	**1e**	120	**2e**	26	99%	-15.5°

a) All reactions were carried out by stirring a mixture of the substrate (200mg) and 1.0 g of seaprose S in 20 ml of 0.2M phosphate buffer (pH 7.8) containing 1ml of methanol at 30°C. b) The chemical yields were measured by HPLC on an ODS column (CH_3CN / H_2O) c) The optical yields were determined by HPLC on a Chiralcel OJ or AS (Daicel, Japan) column (EtOH / hexane).[5] d) c = 0.4 - 1.0, acetone.

Valnidipine,[7] the chiral antihypertensive drug, was synthesized by protease- and base-catalyzed transesterification of **1c**. The enzymatic transesterification with (*S*)-N-benzyl-3-pyrroridinol[8] afforded the (*S*)-diester (**3**) and **3** was smoothly transesterificated without racemization in the presence of sodium methoxide[9,10] to give the desired derivative (**4**) in 51% yield based on **1c** with the appropriate stereochemistry for clinical use. The optical yield of **4** was more than 99%ee.[11]



Scheme 2

In summary, carbamoylmethyl ester group of 1,4-dihydropyridines was easily undertaken transesterification with various alcohols by the protease and base. Although further optimization of the reaction conditions is necessary, the combination of two transesterifications provides a practical method for the syntheses of optically active 1,4-dihydropyridine derivatives.

REFERENCES AND NOTES

1. Recent review, see for example : Goldmann, S.; Stoltefuss, J. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1559.
2. a) Shibanuma, T.; Iwanani, M.; Okuda, K.; Takenaka, T.; Murakami, M. *Chem. Pharm. Bull.* **1980**, 28, 2809. b) Tamazawa, K.; Arima, H.; Kojima, T.; Isomura, Y.; Okada, M.; Fujita, S.; Furuya, T.; Takenaka, T.; Inagaki, O.; Terai, M. *J. Med. Chem.* **1986**, 29, 2504. c) Kajino, M.; Wada, Y.; Nagai, Y.; Nagaoka, A.; Meguro, K. *Chem. Pharm. Bull.* **1989**, 37, 2225. d) Ashimori, A.; Uchida, T.; Ohtaki, Y.; Tanaka, M.; Ohe, K.; Fukaya, C.; Watanabe, M.; Kagitani, M.; Yokoyama, K. *ibid.* **1991**, 39, 108.
3. Leov, B.; Goodman, M. M. *J. Heterocycl. Chem.* **1975**, 363.
4. a) Holdgrün, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, 32, 3465. b) Ebiike, H.; Terao, Y.; Achiwa, K. *ibid.* **1991**, 32, 5805. c) Ebiike, H.; Maruyama, K.; Achiwa, K. *Chem. Pharm. Bull.* **1992**, 40, 1083. d) Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, 33, 7157.
5. Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Achiwa, K. *Tetrahedron Lett.* in press.
6. Seaprose S is a serine protease produced by Amano Pharmaceutical Co., Ltd.
7. Valnidipine was a first chiral antihypertensive drug commercialized in 1992 and is the hydrochloride of 4.[2b] See the following patents.; a) Arima, H.; Tamazawa, K. *Japan Patent (Kokai)* **1987**, 174071. b) Tamazawa, K.; Kojima, T.; Arima, H.; Murakami, Y.; Isomura, Y.; Takanobu, K. *ibid.* **1985**, 258179. c) Item. *ibid.* **1985**, 231673. d) Kojima, T.; Takenaka, T. *Japan Patent (Kokoku)* **1982**, 30111.

8. (*S*)-N-benzyl-3-pyrroridinol is commercially available from Aldrich in 99% purity and was used without further purification. $[\alpha]_D^{20}$ -3.7° (c= 5.0, methanol). (ref.[2b] $[\alpha]_D^{20}$ -3.77° (c= 5, methanol)).
9. Wehinger, E.; Meyer, H.; Bossert, F.; Vater, W.; Towart, R.; Stoepel, K.; Kazda, S. DE **1981**, 2935451.: 2-Phenylmethoxyethyl ester group of 1,4-dihydropyridines was regioselectively transesterificated with sodium methoxide to give the methyl ester in 30% yield.
10. To a suspension of **1a-d** (10mmol) in methanol (200ml) was added dropwise sodium (0.67g) in methanol (20ml) and the mixture was stirred at room temperature. After **1a-d** was disappeared, the mixture was poured into ice-cooled 1N-hydrochloride or water to give the precipitates. Only **1c** afforded the dimethyl ester under these conditions.
11. The data for **3** and **4** were as follows;
    3 : $[\alpha]_D^{20}$ +5.8° (c=0.8, acetone), ^{1}N-NMR($CDCl_3$) ppm : 1.32-2.78 (6H, m, 3xCH_2), 2.31 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.61 (2H, s, CH_2N), 4.51 (2H, ABq, *J*=3.6Hz, OCH_2CO), 5.09 (1H, s, CH), 5.10-5.30 (1H, m, CH), 5.60 (2H, s, NH_2), 6.42 (1H, s, NH), 7.18-8.17 (9H, m, aromatic).
    4 : $[\alpha]_D^{20}$ +64.3° (c=0.9, methanol), ^{1}N-NMR($CDCl_3$) ppm : 1.30-2.92 (6H, m, 3xCH_2), 2.33 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.64 (5H, s, CH_2+CH_3O), 5.06 (1H, s, CH), 5.02-5.28 (1H, m, CH), 5.93 (1H, s, NH), 7.12-8.17 (9H, m, aromatic). (ref.[2b] $[\alpha]_D^{20}$ +64.8° (c=1.0, methanol)).

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