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AN EFFICIENT ENANTIOSELECTIVE PREPARATION OF 2-SUBSTITUTED-3-HYDROXYPROPIONIC ACIDS VIA CHEMO-ENZYMATIC REACTION

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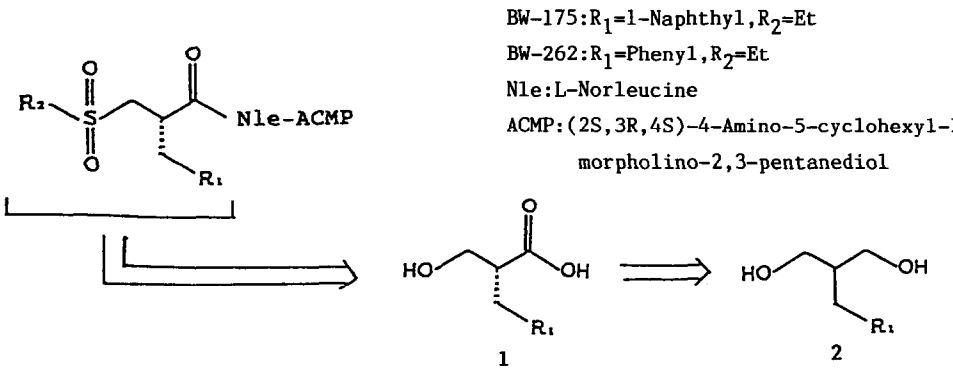
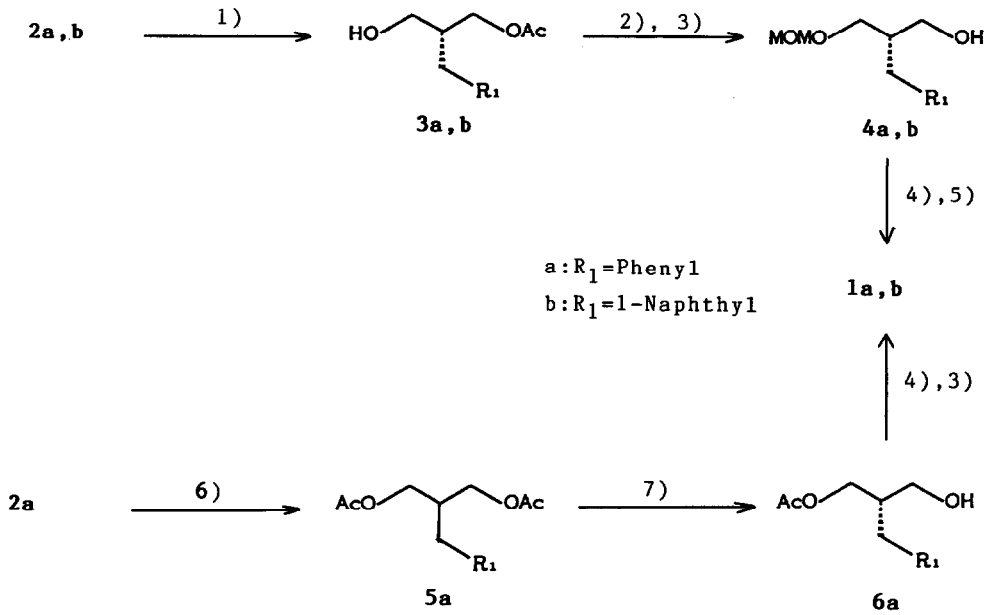
Summary: The key intermediates, 2-substituted-3-hydroxypropionic acids **1**, of the potent renin inhibitors were synthesized enantioselectively starting from 2-substituted-1,3-propanediols via chemo-enzymatic reaction.

Recently we reported[1] a novel renin inhibitor, BW-175, which is a non-peptidic and orally active low molecular inhibitor having (2S)-3-ethylsulfonyl-2-(1-naphthylmethyl)propionic acid.[2] Its benzyl analogue at position-2, BW-262, is also a potent renin inhibitor. Our strategy for the synthesis of enantiomerically pure 2-substituted-3-alkyl(or aryl)sulfonylpropionic acids is based on retro synthetic analysis shown in Fig. 1. 2-Substituted-3-hydroxypropionic acids **1** were chosen as the versatile key intermediates. The optically active 3-hydroxypropionic acid derivatives are fundamental chiral building blocks. However only a few approaches to their preparation have been reported.[3] In this paper we report the enantioselective synthesis of 2-substituted-3-hydroxypropionic acids **1** from 2-substituted-1,3-propanediols **2** via lipase-catalyzed reaction.[4]



BW-175:R_1=1-Naphthyl,R_2=Et
BW-262:R_1=Phenyl,R_2=Et
Nle:L-Norleucine
ACMP:(2S,3R,4S)-4-Amino-5-cyclohexyl-1-morpholino-2,3-pentanediol

Figure 1



1) Lipase P, vinyl acetate 2) MOM-Cl, $Et(^{i}Pr)_2N$, CH_2Cl_2 3) K_2CO_3, MeOH-H_2O
4) Jones reagent 5) HCl-H_2O-THF 6) Ac_2O, DMAP, Et_3N, CH_2Cl_2
7) Lipase P, 0.1 M KPB (pH7.0) -30% Acetone

Scheme 1

Table 1

	Yield (%)	$[\alpha]_D^{20}CHCl_3$ (conc.)	e.e. (%)
3a	quant.	+28.6 (1.07)	>94[a]
3b	93	+35.7 (1.03)	86[a]
4a	99	-18.1 (1.04)	>94[b]
4b	91	-20.7 (0.98)	86[b]
1a	68	+13.9 (0.97)	>98[c,d]
1b	50	+33.1 (0.98)	96[c,d]
6a	41	-28.1 (1.01)	>94[a]

a) determined by HPLC analysis using a column packed with CHIRALCEL OC (iPrOH/hexane =1/9). b) CHIRALCEL OC (iPrOH/hexane=1/19). c) Senshu Pak. Silica-1151-N (ethyl acetate/hexane=1/1) after coupling with L-norleucine tert-butyl ester. d) after recrystallization.

The synthetic route is outlined in Scheme 1.

After a preliminary screening test to find the desirable enzyme, we selected commercially available Lipase P from Pseudomonas fluorecens.[5] The esterification of 2-substituted-1,3-propanediols **2**[6] catalyzed by Lipase P using vinyl acetate[7] as the solvent at room temperature proceeded enantioselectively to afford (2R)-2-substituted-1,3-propanediol-1-acetates **3**[8] in high yield. Treatment of **3** with chloromethylmethyl ether, followed by hydrolysis with potassium carbonate, provided **4** in excellent yield. After Jones oxidation of **4**, deprotection with hydrochloric acid gave crude 2-substituted-3-hydroxypropionic acids **1**. A single recrystallization yielded **1** in high enantiomeric purity.[9]

The optically pure **1a** was also obtained from the diacetate **5a** via enantioselective hydrolysis using Lipase P. The diol **2a** was allowed to react with acetic anhydride in the presence of 4-dimethylaminopyridine-triethylamine to give the diacetate **5a** quantitatively. The incubation of **5a** with Lipase P in 0.1 M phosphate buffer(containing 30% acetone, pH7.0) at 30°C gave (2S)-2-benzyl-1,3-propanediol-1-acetate **6a** in 41% yield.[10] The Jones oxidation of **6a** followed by hydrolysis with potassium carbonate yielded **1a** in 64% yield.

Thus, we have established the efficient enantioselective synthesis of 2-substituted-3-hydroxypropionic acids from 2-substituted-1,3-propanediols.

References and Notes

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   Synthesis: Y. Koike, M. Nakano, S. Atsuumi, H. Funabashi, J. Hashimoto, H. Morishima, in preparation.
2. Another renin inhibitor having (2S)-2-benzyl-3-tert-butylsulfonylpropionic acid has been reported. But the optically pure propionic acid was obtained by optical resolution. P. Bühlmayer, A, Caselli, W. Fuhrer, R. Göschke, V. Rasetti, H. Rüeger, J. L. Stanton, L. Criscione, J. Med. Chem., **31**, 1839 (1988). J. Nussberger, A. Delabays, M. D. Gasparo, F. Cumin, B. Waeber, H. R. Brunner, J. Ménard, Hypertension, **13**, 948 (1989).
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5. Supplied by Amano Pharmaceutical Co.
6. Compound **2a** was derived from commercially available diethyl benzylmalonate quantitatively. Compound **2b** was synthesized starting from 1-naphthaldehyde and diethyl malonate via diethyl 1-naphthalmalonate in 90% yield.
7. M. D.-Castaing, B. D. Jeso, S. Drouillard, B.Maillard, Tetrahedron Lett., **28**, 953 (1987). Y.-F. Wang, J. J. Lalonde, M. Momongan, D. E. Bergbreiter, C.-H. Wong, J. Am. Chem. Soc.,**110**, 7200 (1988).
8. The absolute configuration was determined by comparison of the measured optical rotations to that of the authentic compound synthesized by the method of D. A. Evans. M. Nakano, S. Atsuumi, Y. Koike, S. Tanaka, H. Funabashi, J. Hashimoto, H. Morishima, in preparation.
9. **1a**:mp 67.5-68.5°C (colorless needles from diethyl ether-hexane).
   1b:mp 116.5-118.0°C (pale brown powder from benzene).
10. The synthesis of both **6a** and its enantiomer using porcine pancreas lipase was reported. G. M. R. Tombo, H.-P. Schar, X. Fernandez I Busquest, O. Ghisalba, Tetrahedron Lett., **27**, 5707 (1986).

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