A SIMPLE DIASTEREOSELECTIVE SYNTHESIS OF CYCLOHEXYLNORSTATINE AND ALLOCYCLOHEXYLNORSTATINE

Hiromu HARADA,[a,b] Atsushi TSUBAKI,[a] Tetsuhide KAMIJO,[a] Kinji IIZUKA,[a] and Yoshiaki KISO*,[b]

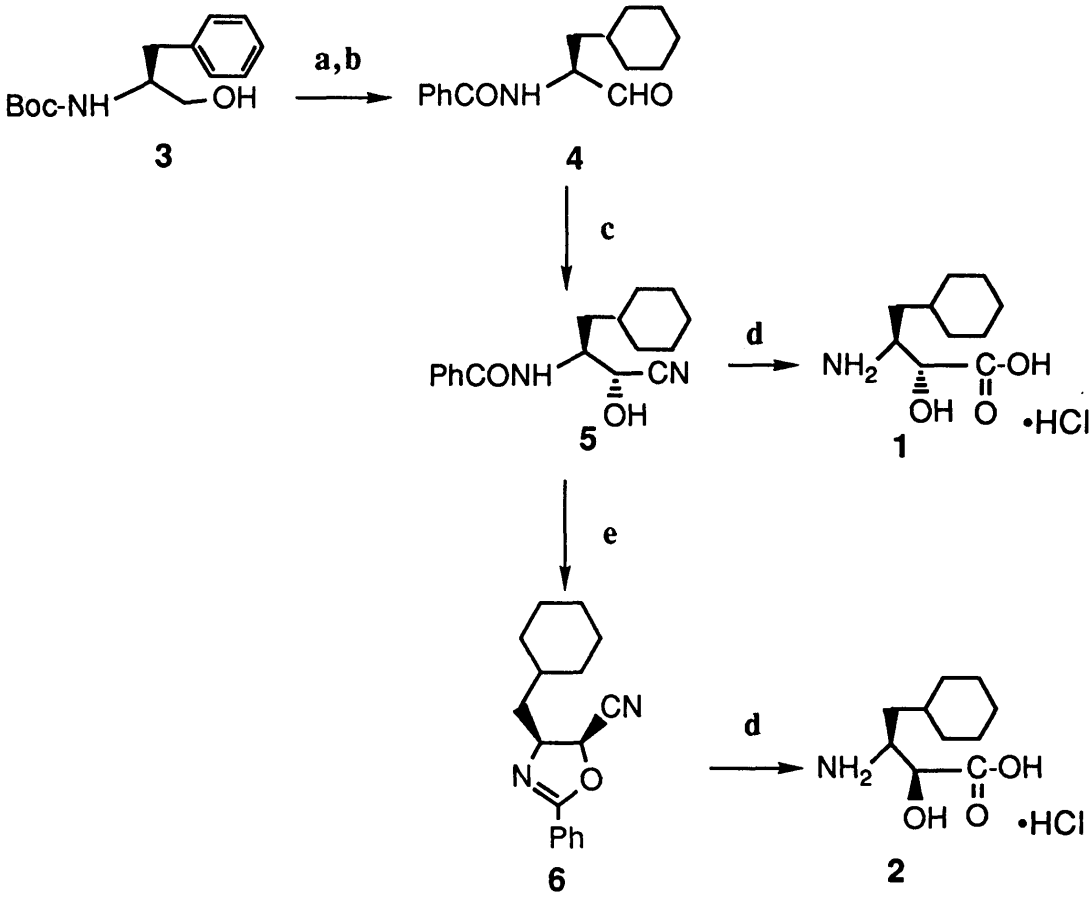
Central Research Laboratories, Kissei Pharmaceutical Co., Ltd.,[a] Yoshino, Matsumoto, Nagano 399, Japan and Department of Medicinal Chemistry, Kyoto Pharmaceutial University,[b] Yamashina-ku, Kyoto 607, Japan

Cyclohexylnorstatine [(2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid] (**1**) and allocyclohexylnorstatine [(2*S*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid] (**2**), designed as key amino acids in renin inhibitors, were synthesized diastereoselectively and simply from Boc-L-phenylalaninol.

KEYWORDS cyclohexylnorstatine; allocyclohexylnorstatine; α-hydroxy-β-amino acid; transition-state analogue; renin inhibitor

A large number of inhibitors of renin, an aspartic protease, have been investigated as therapeutic agents for hypertension.[1] Displacement of P1 leucine with statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid],[2] a non-protein amino acid, in the angiotensinogen sequence has led to potent renin inhibitors.[3] The importance of the configuration of the hydroxyl group of statine as inhibitors was demonstrated by the fact that the 3*S* isomer was about 500 times more potent than the 3*R* isomer.[4] Recently, we demonstrated that norstatine [(2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid] was a more useful component of the renin inhibitors than statine.[5] In this paper we report the simple diastereoselective synthesis of novel amino acids, (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid (**1**) named cyclohexylnorstatine and (2*S*, 3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid (**2**) named allocyclohexylnorstatine. These were designed as key amino acids in potent renin inhibitors on the basis of the interaction between renin and angiotensinogen transition-state analogues.[6]

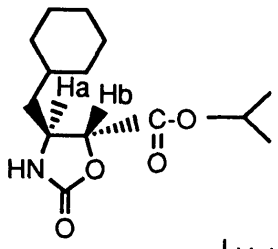
Boc-L-phenyalaninol (**3**) was converted to *N*-benzoylcyclohexylalaninal (**4**) by hydrogenation (quant.), deprotection (98.5%), and reprotection (quant.) of the amino group followed by oxidation of alcohol.[7] The aldehyde (**4**) was hydrocyanated with NaCN and HCl in $CHCl_3/H_2O$ to obtain 3-benzoylamino-4-cyclohexyl-2-hydroxybutyronitrile (**5**) (2*R*:2*S* ~ 4:1).[8] Cyanohydrin (**5**) was hydrolyzed with 23%HCl at 80°C for 11 h to provide the cyclohexylnorstatine as a 4:1 (2*R*:2*S*) diastereomeric mixture,[9] and pure cyclohexylnorstatine (**1**) was exclusively crystallized out of the reaction mixture in the form of HCl salt; mp 172-175°C, $[\alpha]^{23}_D$ -11.2° (*c* 2.0, H_2O) (60% overall yield at b, c, and d steps). The diastereomeric ratio of cyclohexylnorstatine was influenced by an amino protecting group, *e.g.*, formyl group (2*R*:2*S*=1:1) and phthaloyl group (2*R*:2*S*=3:7) and by a solvent used in hydrocyana-



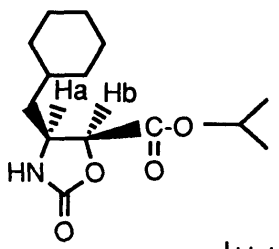
Reagents: **a**, H_2 (4atm) / Rh-Al_2O_3, then HCl; **b**, PhCOCl / Et_3N, then Py•SO_3 (3eq) / DMSO, 20 to 25°C; **c**, NaCN (5eq)-HCl(5eq)/$CHCl_3$-H_2O, 0°C; **d**, HCl; **e**, $SOCl_2$ / benzene, 0°C.

tion (c), *e.g.*, MeOH (2*R*:2*S*=1:1), DMF/H_2O (2*R*:2*S*=1:1), benzene/H_2O (2*R*:2*S*=13:5), and EtOAc/H_2O (2*R*:2*S*=7:3). In addition, the hydrocyanation of (**4**) without HCl gave a mixture (1:1) of (**5**). Treatment of (**1**) with isopropanol-HCl gave the cyclohexylnorstatine isopropyl ester HCl salt; mp 118-119°C, $[\alpha]^{23}_D$-7.4°(*c* 2.4, H_2O)(95% yield), which was the P1-P1' moiety in the renin inhibitors.

Allocyclohexylnorstatine (**2**) (3:1 diastereomeric mixture) was prepared from diastereomeric cyanohydrin (**5**) (2*R*:2*S* ~ 4:1) by inversion of the configuration at C2 with $SOCl_2$ (1eq.) in benzene (e)[10] followed by hydrolysis of the resulting oxazoline ring (**6**), then it was converted to optically pure allocyclohexylnorstatine isopropyl ester HCl salt; mp 127-133°C, $[\alpha]^{22}_D$-15.4° (*c* 1.00, H_2O).



7 J_{HaHb} = 4.94Hz
NOE_{HaHb} =2.7%



8 J_{HaHb} = 8.79Hz
NOE_{HaHb} =23.4%

Definitive stereochemistry was assigned by the cyclized 2-oxazolidinone (**7**) and (**8**) (obtained from the isopropyl ester of (**1**) and (**2**) with *N,N'*-carbonyldiimidazole in CH_2Cl_2, respectively, quant.). The NOEs[11] and the coupling constants[12] of the ring protons of (**7**) and (**8**) are consistent with *trans* and *cis* stereochemistry showing that the configurations at the C2-carbon are *R* for (**1**) and *S* for (**2**).

We have demonstrated a simple diastereoselective method for synthesizing novel cyclohexylnorstatine (**1**) and allocyclohexylnorstatine (**2**) which is easily applicable to industrial production. The exchange of the protective group (benzoyl group from Boc group) is not essential in the synthesis of cyclohexylnorstatine (**1**). The activities of the renin inhibitors containing (**1**) or (**2**) will be reported elsewhere.

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8) The diastereomeric ratio was calculated from the NMR spectra.
9) The diastereomeric ratio was calculated from the NMR spectra. The relevant portions of the 270 MHz ^1H NMR spectra of (**1**) and (**2**) in D_2O with DSS as the internal standard are: (**1**) 0.8-1.9 (m, 13H), 3.75 (m, Ha), 4.47 (d; J=3.3Hz, Hb); (**2**) 0.8-1.9 (m, 13H), 385 (m, Ha), 4.60 (d; J=3.3Hz, Hb).
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