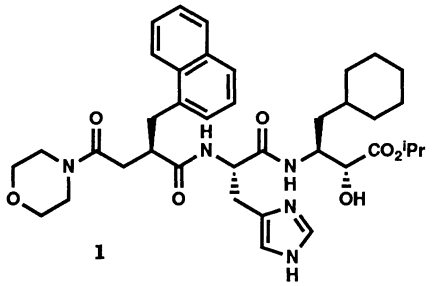
CHEMISTRY LETTERS, pp. 723-724, 1990.

An Expeditious Synthesis of the (2*R*,3*S*)- and (2*S*,3*R*)-3-Amino-2-hydroxycarboxylic Acids, the Key Components of a Renin Inhibitor and Bestatin, from (*S*)- and (*R*)-Phenylalanine

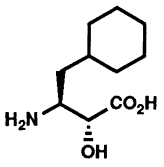
Fuyuhiko MATSUDA, Teruyo MATSUMOTO, Masako OHSAKI, Yoshio ITO, and Shiro TERASHIMA*
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

The title synthesis could be achieved by featuring highly diastereoselective formation of a cyanohydrin acetate from an aldehyde under the phase-transfer conditions.

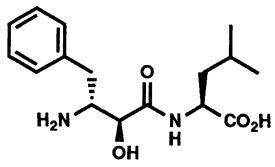
Some of the medicinally important compounds involve optically active 3-amino-2-hydroxycarboxylic acids as their key components. Thus, one of the promising renin inhibitor (**1**)[1] bears (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid (**2**) as its C-terminal moiety, and bestatin (**3**), the famous immunological response modifier,[2] consists of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid (**4**) and (*S*)-leucine. We wish to report here an expeditious synthesis of these antipodal compounds (**2** and **4**) from (*S*)- and (*R*)-phenylalanine [(*S*)- and (*R*)-Phe], in which formation of the cyanohydrin acetates from the aldehydes (**5** and **9**) under the phase-transfer conditions is employed as a key diastereoselective reaction.



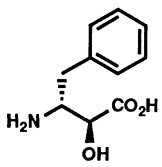
1



2



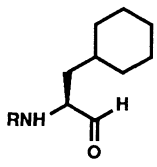
3



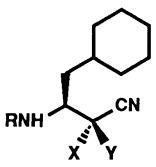
4

The aldehyde (**5**) was prepared from (*S*)-Phe in 5 steps in 72% overall yield according to the reported method.[1b] Treatment of **5** with sodium cyanide and acetic anhydride under the phase transfer conditions[3,4] ($BnBu_3NCl$, CH_2Cl_2-H_2O, 0 °C) was found to give a mixture of the *threo*-cyanohydrin acetate (**6**) and the *erythro*-isomer (**7**) (85:15)[5] in 98% yield. On the other hand, when **5** was first allowed to react with sodium cyanide under the same conditions in the absence of acetic anhydride and the formed cyanohydrins were subsequently acetylated (Ac_2O, DMAP, Py), a mixture of **6** and **7** (58:42)[5] was obtained in 95% overall yield. These results obviously suggest that, under the phase-transfer conditions where acetic anhydride is present, the *threo*-cyanohydrin *in situ* produced as a kinetically more favored isomer can be

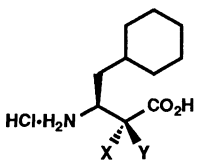
immediately trapped with acetic anhydride prior to equilibrium with the *erythro*-isomer, resulting in the stereoselective formation of **6**. Without separation, the mixture (**6**:**7**=85:15) was subjected to acidic hydrolysis (20% HCl, 80-100 °C), giving rise to a mixture of the HCl salts of the *threo*-amino acid (**2**) and the *erythro*-isomer (**8**) in the same ratio as for **6** and **7** in 100% yield. When the acidic reaction mixture was concentrated to a small volume and kept standing at 0 °C, a pure sample of **2•HCl**, mp 190 °C (dec.), $[\alpha]_D^{20}$ -12.4° (c 0.482, 4% HCl), and $[\alpha]_D^{20}$ -12.2° (c 2.05, H_2O),[6] could be obtained in 52% yield.



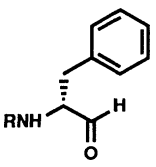
5
R=^{i}PrOCO



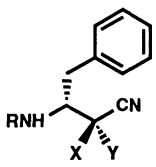
X=OAc, Y=H **6**
X=H, Y=OAc **7**



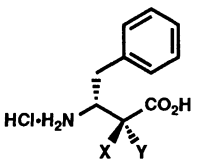
X=OH, Y=H **2•HCl**
X=H, Y=OH **8•HCl**



9
R=^{i}PrOCO



X=OAc, Y=H **10**
X=H, Y=OAc **11**



X=OH, Y=H **4•HCl**
X=H, Y=OH **12•HCl**

In completely the same manner, a mixture of **10** and **11** (81:19)[5] could be prepared from **9** in 100% yield. Synthesis of **9** was achieved starting from (*R*)-Phe in 4 steps in 71% overall yield following the similar procedure as for **5**[1b] without hydrogenation of the benzene ring. Subsequent acidic hydrolysis of the mixture of **10** and **11** similarly gave a mixture of **4•HCl** and **12•HCl** in 100% yield or a pure sample of **4•HCl**, mp 191 °C (dec.) and $[\alpha]_D^{20}$ +25.8° (c 0.737, 4% HCl),[7] in 50% yield after direct crystallization from concentrated reaction mixture.

The explored overall process may be applicable to industrial scale preparation of **2** and **4** because of its operational simplicity and uses of cheap reagents.

References

1) a) K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, **1989**, 1678; b) T. Kamijo, H. Harada, A. Tsubaki, T. Yamaguchi, A. Iyobe, K. Iizuka, and Y. Kiso, *Japan Kokai Tokkyo Koho*, JP 1-172365 (1989).

2) a) K. Shibuya, E. Hayashi, F. Abe, K. Takahashi, H. Horinishi, M. Ishizuka, T. Takeuchi, and H. Umezawa, *J. Antibiotics*, **40**, 363 (1987); b) H. Suda, T. Takita, T. Aoyagi, and H. Umezawa, *ibid.*, **29**, 600 (1976) and references cited.

3) J.M. McIntosh, *Can. J. Chem.*, **55**, 4200 (1977).

4) Other phase-transfer catalysts ($BnEt_3NCl$, Bu_4NBr, $MeOc_3NCl$, Oc_4NBr, (-)-*N*-benzylquininium chloride, and (+)-*N*-benzylquinidinium chloride) gave the same result.

5) Ratio of the two diastereomers was rigorously determined by measuring the ^{1}H-NMR spectrum of the *N,O*-diacetyl methyl esters prepared from a mixture of the amino acids by sequential esterification ($SOCl_2$, MeOH) and acetylation (Ac_2O, DMAP, Py).

6) An authentic sample of **2•HCl** prepared according to the reported method[1b] showed mp 191 °C (dec.) and $[\alpha]_D^{20}$ -12.2° (c 0.490, 4% HCl). The melting point and optical rotation of **2•HCl** previously reported are mp 172-175 °C and $[\alpha]_D^{23}$ -11.16° (c 2.35, H_2O).[1b]

7) The reported optical rotation of **4•HCl** is $[\alpha]_D^{22}$ +27.7° (c 1.00, 4% HCl).[2b]

(Received January 31, 1990)