DIASTEREOSELECTIVE SYNTHESIS OF AN α,β-DIAMINOCARBOXYLIC ACID: AN EFFICIENT SYNTHESIS OF FR900490, AN IMMUNOMODULATING PEPTIDE ISOLATED FROM A FUNGUS

Hiroyuki SETOI, Hiroshi KAYAKIRI, and Masashi HASHIMOTO*

Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 5-2-3 Tokodai, Tsukuba, Ibaraki 300-26, Japan

A practical synthesis of FR900490 (1), a peptidyl immunomodulator of microbial origin, has been achieved through diastereoselective preparation of α,β-diaminobutyric acid 2.

KEYWORDS diastereoselective synthesis; diaminobutylic acid; immunomodulating peptide; L-threonine; L-histidine

We have recently described the structure of FR900490 (1), an immunomodulating peptide isolated from Discosia species.[1] An interesting biological activity of 1[2] has further prompted us to investigate the synthesis of this peptide so the amounts necessary for detailed biological evaluations can be apportioned. Here we report an efficient synthesis of this peptide via a diastereoselective preparation of the α,β-diaminobutyric acid fragment 2 involved in the molecule of 1.

Although some synthetic methods for β-substituted α-amino acid have been described in the literature,[3] there has been no practical method for preparing of α,β-diaminocarboxylic acids. We have now prepared the key intermediate 2 by a stereoselective reduction of imine 5 derived in situ from β-keto compound 3. The latter compound was prepared by oxidation (Me_2SO/DCC/Pyr/TFA/benzene, r.t., 4 h) of methyl N-trityl-L-threoninate.[4]

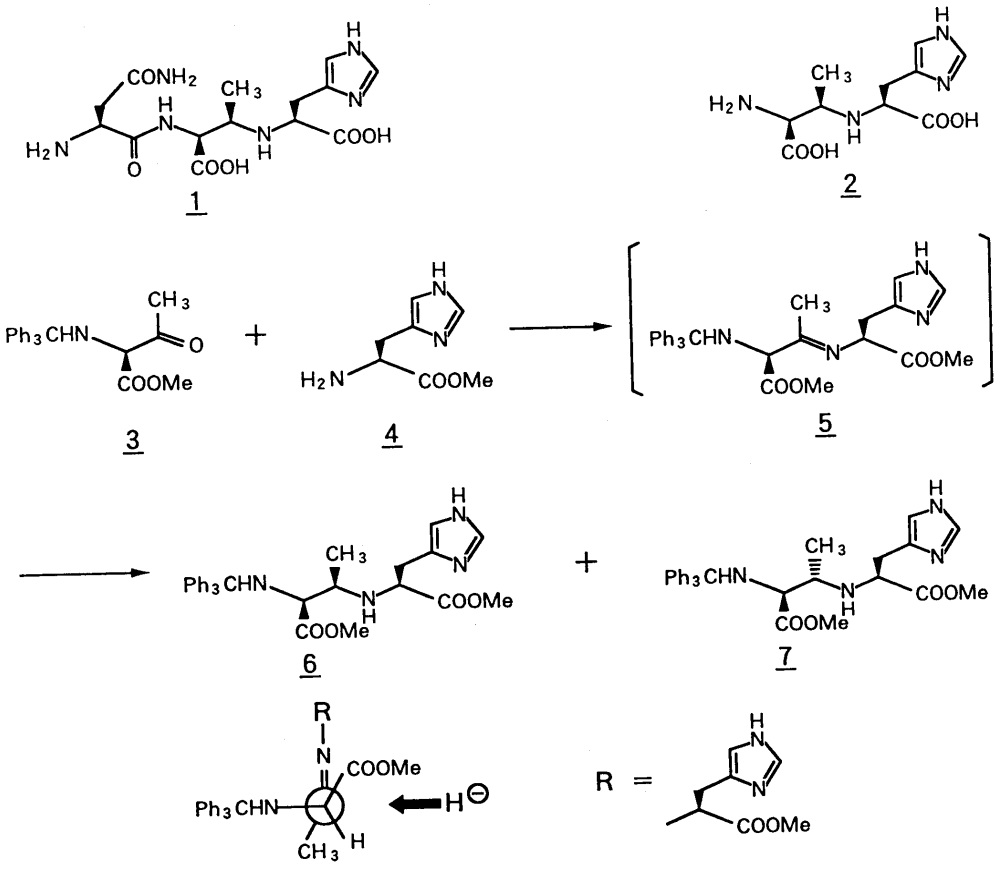

Fig. 1. Application of the Felkin-Anh Model to the Reduction of the Intermediate 5

The reductive amination of 3 with 4 using $NaBH_3CN$ as the reducing agent was carried out as follows. Ketone 2 (1 eq) and $NaBH_3CN$ (1 eq) were in turn added to a solution of methyl L-histidinate 4 (1.5 eq) in MeOH[5] with stirring at room temperature. After 7 h, the reaction mixture was worked up in the usual manner and chromatographed on silica gel, eluting with $CHCl_3$-MeOH (50:1). The desired product 6 was obtained in 55.3% yield[6] together with its diastereoisomer 7 (7.0%).[7] The structure of 6 was identified by conversion into 2 by treatment with 1 N HCl and then with 1 N NaOH (76.2% yield) and comparing 2 with the sample derived from the natural product 1.[1]

The high stereoselectivity in the above reductive amination is remarkable. It can be explained by assuming that our reaction is in comformity with the Felkin-Anh model for stereoselective reactions to acyclic chiral carbonyl compounds,[8] as depicted in Fig. 1. The amino acid 2 obtained here was converted to FR900490 by condensation with L-asparagine as described before.[1]

Thus the above diastereoselective synthesis of the divalent amino acid 2 provides a practical synthesis of FR900490 and may also be used to prepare analogous α,β-diaminocarboxylic acids.

REFERENCES AND NOTES

1) N. Shigematsu, H. Setoi, I. Uchida, T. Shibata, H. Terano, and M. Hashimoto, Tetrahedron Lett. 29, 5147 (1988).

2) T. Shibata, O. Nakayama, N. Okuhara, Y. Tsurumi, H. Terano, and M. Kohsaka, J. Antibiot. 41, 1163 (1988).

3) a) G. Guanti, L. Banfi, E. Narisano, and C. Scolastico, Tetrahedron Lett., 25, 4693 (1984) ; b) K. Nakajima, T. Tanaka, K. Morita, and K. Okawa, Bull. Chem. Soc. Jpn., 53, 283 (1980) ; c) E. Atherton and J. Meienhofer, Hoppe-Seyler's Z. Physiol. Chem., 354, 689 (1973).

4) Compound 3 was isolated by a workup in the usual manner and crystallization from n-hexane : yield, 84.9% ; mp 74-76°C, $[\alpha]_D^{27}$-71.8°(c0.9, $CHCl_3$) ; ^1H NMR($CDCl_3$) δ1.99(s, 3H), 3.50(s, 3H), 4.17(broad signal, 1H), 7.2-7.6(m, 15H). The compound was optically pure: after redution of 3 with $NaBH_4$, followed by hydrolysis with HCl, the crude mixture was subjected to HPLC using CHIRALPACK WH(Daicel), L-Thr and L-alloThr being detected (at 21.70 and 24.10 min, respectively) (eluent, 0.25 mM $CuSO_4$; flow rate, 1.0 ml/min, oven temperature, 50°C; retention time, authentic D-alloThr 12.87, D-Thr 16.04, L-Thr 21.75, L-alloThr 23.92 min).

5) We used methyl L-histidinate hydrochloride neutralized with $NaHCO_3$ in MeOH.

6) ^1H NMR ($CDCl_3$) data of 6 : δ0.99(d, J=6.5Hz, 3H), 2.82(dd, J=8.5, 15Hz, 1H), 3.04(dd, J=4, 15Hz, 1H), 3.08(m, 1H), 3.16(s, 3H), 3.42(d, J=6Hz, 1H), 3.61 (dd, J=4, 8.5Hz, 1H), 3.74(s, 3H), 6.83(s, 1H).

7) ^1H NMR ($CDCl_3$) data of 7 : δ1.03(d, J=7Hz, 3H), 2.68(dd, J=10, 15Hz, 1H), 2.95(m, 1H), 3.11(dd, J=2.5, 15Hz, 1H), 3.26(s, 1H), 3.28(m, 1H), 3.80(s, 3H), 3.96(dd, J=2.5, 10Hz, 1H), 6.92(s, 1H), 7.40(s, 1H).

8) a) M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199 ; b) M. Cherest and H. Felkin, Tetrahedron Lett., 1968, 2205 ; c) K.N.Houk and Y. Wu, "Stereochemistry of Organic and Bioorganic Transformation", Ed. by W. Bartmann and B. Sharpless, VCH Varlagesellschaft mbH, D-6940 Weinheim (Federal Republic of Germany), 1987, p.247.

(Received February 2, 1989)