Stereoselection in the Synthesis of *threo*- and *erythro*-3-Amino-2-hydroxy-4-phenylbutanoic Acid using Chiral Acetal Templates

Rosario Herranz,* Julia Castro-Pichel, Soledad Vinuesa, and Mª. Teresa García-López

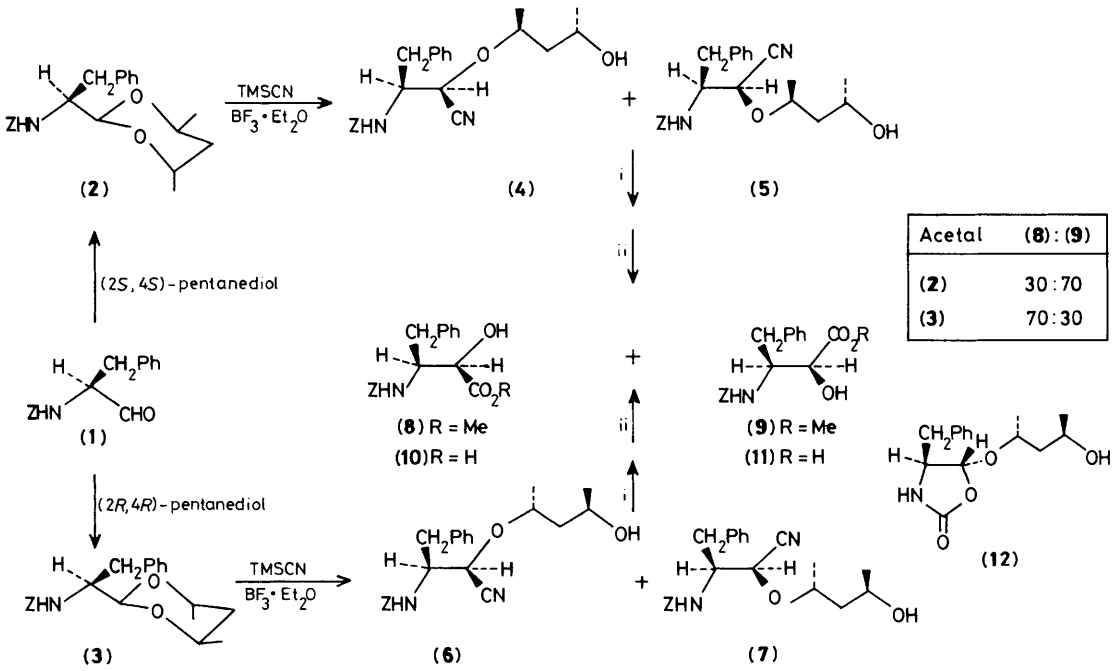
Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, 3, 28006 Madrid, Spain

Boron trifluoride–diethyl ether mediated addition of trimethylsilylcyanide (TMSCN) to the chiral acetals derived from Z-L- and Z-D-phenyl alaninal, (Z = *N*-benzyloxycarbonyl), and (+)-(2*S*,4*S*)- and (−)-(2*R*,4*R*)-2,4-pentanediol stereoselectively gave the four stereoisomers of the 3-amino-2-hydroxy-4-phenylbutanoic acid, key intermediates for bestatin and bestatin analogues.

Bestatin [(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine] is a natural potent inhibitor of aminopeptidase B and leucine aminopeptidase,[1] exhibiting antitumour and antimicrobial activities, through activation of the host defence mechanism,[2—5] and analgesic activity.[6] The clinical use of this compound has been permitted in Japan. Since its discovery in 1976 by Umezawa *et al.*,[1] various synthetic methods for the preparation of (2*S*, 3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (2*S*,3*R*)-AHPA], the key intermediate in the production of bestatin, have been reported.[7—10] However, all these methods give AHPA as a racemic mixture of the *threo*-isomers,[7,8] or as a mixture of diastereoisomers,[9,10] in low yield (<30%).

Recently, we have developed[11] a new procedure for the stereoselective preparation of the *threo*-isomers of 3-amino-2-hydroxy acids by reaction of optically pure 2-aminoaldehydes with trimethylsilyl cyanide (TMSCN) followed by hydrolysis of the cyano group to the methyl ester, through an imidate chlorohydrate intermediate. We now report the application of the effect of chiral acetal templates[12] to this procedure allowing stereocontrolled synthesis of the four stereoisomers of Z-AHPA (Z = benzyloxycarbonyl). For this purpose, acetals (**2**) (m.p. 92 °C[13]) and (**3**) (m.p. 91 °C[13]) were directly prepared in 95% yield by reaction of Z-L-phenylalaninal (**1**) with (+)-(2*S*,4*S*)- and (−)-(2*R*,4*R*)-pentane-2,4-diol in refluxing dichloromethane and in the presence of *p*-toluenesulphonic acid.

Our initial attempts to open (**2**) and (**3**) with TMSCN under the usual conditions for nucleophilic attack on chiral acetal templates,[12,13] (CH_2Cl_2, $TiCl_4$, −78 °C, 2 h), led to the recovery of the unchanged acetals. Even when the reaction was performed at 0 °C, nucleophilic attack did not take place. A higher temperature afforded, in the case of (**3**), a complex mixture from which the 2-oxazolidone derivative (**12**) could be isolated. The relative configuration 4- and 5-H in this compound was established as *trans* on the basis of the value of $J_{4,5}$ 4 Hz in the ^{1}H n.m.r. spectrum. Similar results were obtained when $SnCl_4$ was employed as a Lewis acid, while the use of $BF_3{\cdot}Et_2O$ led to the products of nucleophilic opening of the acetals. Thus, reaction of (**2**) (1 mmol) with TMSCN (5 mmol) in dry dichloromethane (20 ml) at room temperature for 2 h and in the presence of $BF_3{\cdot}Et_2O$ (3 mmol) gave a 30 : 70 mixture of (**4**) and (**5**) in 75% overall yield, which could not be separated (Scheme 1). Oxidation of (**4**) and (**5**) with pyridinium chlorochromate[14] afforded the corresponding ketones in 95% yield, which again could not be separated. Treatment of these ketones, first with dry methanolic hydrogen chloride (3 : 1 Et_2O/MeOH saturated with HCl, 4 °C, 24 h), and then with water (<5 °C) led to the methyl esters (**8**) and (**9**), in 80% yield, which were separated by flash chromatography, and were identical to those previously obtained.[11] Saponification of (**8**) and (**9**) with NaOH, in dioxane–water, afforded quantitatively the corresponding acids (**10**) and (**11**). A reversed 70 : 30 ratio of (**10**) and (**11**) was obtained when the



Acetal	(8) : (9)
(2)	30 : 70
(3)	70 : 30

Scheme 1. *Reagents and conditions:* i, pyridinium chlorochromate; ii, HCl (MeOH/Et_2O), H_2O.

acetal (**3**) was used as starting material. These ratios are similar to those obtained in the addition of allyltrimethylsilane[13] to the acetals (**2**) and (**3**).†

By following the same reaction scheme used for the Z-L-phenylalaninal, the protected *N*-terminal amino acid of bestatin, (2*S*,3*R*)-Z-AHPA, and (2*R*,3*R*)-Z-AHPA were obtained in a 30:70 ratio from the acetals of Z-D-phenylalaninal and (+)-(2*S*,4*S*)-2,4-diol, and in a 70:30 ratio from the corresponding acetal of (−)-(2*R*,4*R*)-pentane-2,4-diol.

In summary, by application of the chiral acetal methodology, it is possible to obtain stereoselectively the four stereoisomers of Z-AHPA in 50% overall yield from commercially available Z-L- or Z-D-phenylalanine. To the best of our knowledge, this is the first synthesis which gives the *erythro* isomers, (2*R*,3*R*)-AHPA and (2*S*,3*S*)-AHPA, as the main products. The first isomer, the *N*-terminal amino acid of epibestatin, can be applied to the synthesis of tiobestatin[15] and other bestatin analogues, by conversion of the 2-hydroxy group into other functional groups by S_N2 type substitution, whereas the latter can lead to a bestatin isomer with similar inhibitory properties[9] from natural L-phenylalanine.

Received, 21st January 1989; Com. 9/00355J

† All new compounds gave satisfactory microanalytical and spectral data.

References

1 H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, and T. Takeuchi, *J. Antibiot.*, 1976, **29**, 97.
2 M. Ishizuka, T. Masuda, N. Kanbayashi, S. Fukasawa, T. Takeuchi, T. Aoyagi, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 642.
3 H. Blomgren and J. Wasserman, *Cancer Lett.*, 1981, **11**, 303.
4 'Small Molecular Immunomodifiers of Microbial Origin, Fundamental and Clinical Studies of Bestatin,' ed. H. Umezawa, Japan Scientific Societies Press, Tokyo, and Pergamon Press, Oxford, 1981.
5 A. Okura, M. Ishizuka, and T. Takeuchi, *J. Antibiot.*, 1988, **41**, 261.
6 B. P. Roques, M. C. Fournié-Zaluski, E. Soroca, J. M. Leconte, B. Malfroy, C. Lloreus, and J. C. Schwartz, *Nature (London)*, 1980, **288**, 286.
7 K. Kato, T. Saino, R. Nishizawa, T. Takita, and H. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1618.
8 R. Nishizawa, T. Saino, M. Suzuki, T. Fujii, T. Shirai, T. Aoyagi, and H. Umezawa, *J. Antibiot.*, 1983, **36**, 695.
9 R. Nishizawa, T. Saino, T. Takita, H. Suda, T. Aoyagi, and H. Umezawa, *J. Med. Chem.*, 1977, **20**, 510.
10 S. Kobayashi, T. Isobe, and M. Ohno, *Tetrahedron Lett.*, 1984, **25**, 5079.
11 R. Herranz, J. Castro-Pichel, M. S. Vinuesa, and M. T. García-López, unpublished work.
12 D. J. Elliott, V. M. F. Choi, and W. S. Johnson, *J. Org. Chem.*, 1983, **48**, 2294.
13 S. Kano, T. Yokomatsu, H. Iwasawa, and S. Shibuya, *Chem. Lett.*, 1987, 1531.
14 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **31**, 2647.
15 D. H. Rich and D. T. Ocain, *J. Med. Chem.*, 1988, **31**, 2193.