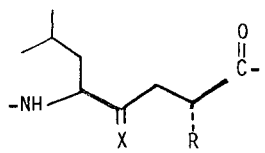
Tetrahedron Letters,Vol.24,No.41,pp 4401-4404,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF HYDROXYETHYLENE AND KETOMETHYLENE DIPEPTIDE ISOSTERES

Mark W. Holladay and Daniel H. Rich*
School of Pharmacy
University of Wisconsin
425 North Charter Street
Madison, Wisconsin 53706

Summary: A general stereo-directed synthesis of "ketomethylene" and "hydroxyethylene" dipeptide isosteres is reported. Peptides containing the amino acids, (2R,5S)-5-amino-4-oxo-2,8-dimethyloctanoic acid (the "ketomethylene" analog of L-Leu-L-Ala), and (2R,5S)-5-amino-4-hydroxy-2,8-dimethyloctanoic acid (the "hydroxyethylene" analog of L-Leu-L-Ala) were synthesized as analogs of pepstatin with statine replaced by the Leu-Ala isosteres.

Dipeptide isosteres, i.e. dipeptides in which the amide -CONH- linkage has been replaced by some approximately isosteric functional group, eg. the ketomethylene,[1,2] hydroxyethylene,[2] thioamide,[3] C-C double bond[4] or thiomethylene group,[5] have been used to prepare either metabolically stable peptides or mechanism based enzyme inhibitors. In order to study further[6] the interactions of pseudosubstrate ketones with aspartyl proteases, such as pepsin, an efficient synthesis of the hydroxyethylene (1) and ketomethylene (2) dipeptide isosteres was desired which would: (1) allow the stereochemistry at C-2 to be selectively established with known configuration; (2) minimize the potential for epimerization at C-5; and (3) be practical for the synthesis of 4-^{13}C analogs from 1-^{13}C-L-leucine. We wish to describe a straightforward route to peptides containing the amino acids, (2R,5S)-5-amino-4-hydroxy-2,8-dimethyloctanoic acid (1) and (2R,5S)-5-amino-4-oxo-2,8-dimethyloctanoic acid (2) (R=CH_3) which satisfies the above requirements.

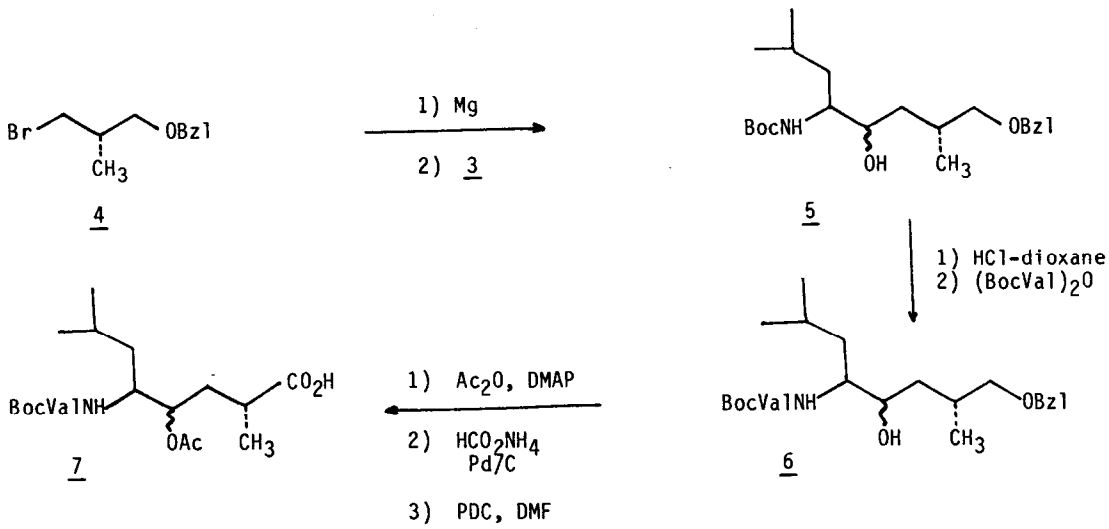


1 (X = H, OH)
2 (X = O)

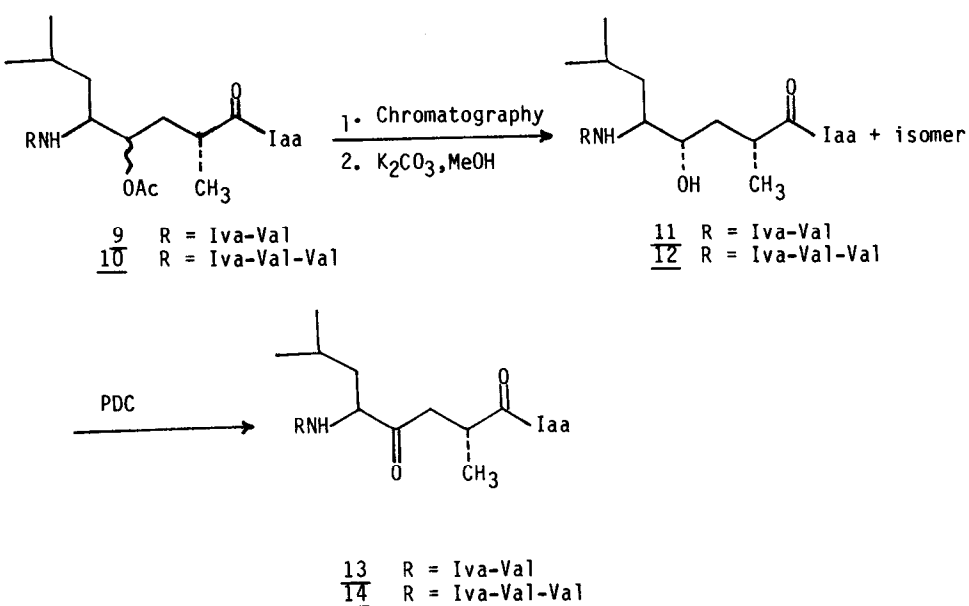
Our approach, outlined in Scheme I, uses as starting materials Boc-L-leucinal (3)[7,8] and the chiral bromoether 4, obtained[9] from the corresponding hydroxyether, which was prepared by the method of Evans.[10] Conversion of 2.5 equiv. of 4 ($[\alpha]_D^{24}$ + 13° (c 1.0, EtOH); lit.[9] $[\alpha]_D^{24}$ + 12.48° (c 0.89, EtOH)) to the Grignard reagent followed by dropwise addition of 1 equiv. of aldehyde 3 (THF, 22°C) afforded a ca. 4:1 mixture of the C-4 epimers of hydroxy ether 5,[11,13] in

67% combined yield after silica gel chromatography (9:1 toluene:EtOAc). Although the diastereomers were readily separable at this point, subsequent transformations were carried out on the mixture, which could be separated at later stages where required.

Scheme I



Scheme II

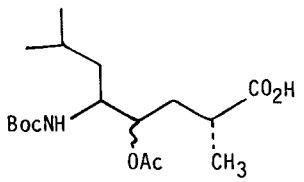


9 R = Iva-Val
10 R = Iva-Val-Val

11 R = Iva-Val
12 R = Iva-Val-Val

13 R = Iva-Val
14 R = Iva-Val-Val

As indicated below, the protection strategy is facilitated and potential side reactions are minimized when the N-terminus of 5 is extended by at least one amino acid residue prior to elaboration of the C-terminus. Thus, cleavage of Boc (4N HCl-dioxane) followed by N-acylation with $(BocVal)_2O$ and flash chromatography gave 6[13] in 89% yield. Acetylation (Ac_2O, DMAP) of the hydroxyl group, followed by benzyl ether cleavage (HCO_2NH_4, Pd-C, 1:1 iPrOH-HOAc),[14] and oxidation of the resultant primary alcohol (PDC, DMF)[15] afforded acid 7[13] (m.p. 68-70°C) in an 80% overall yield from 6. Acid 8 was prepared in 61% overall yield from 5 in a similar manner except that $KMnO_4$-n-Bu_4I in C_6H_6-H_2O-HOAc was used in place of PDC-DMF for the final oxidation.[17]



8

Acids 7 and 8 were incorporated into peptides using DCC-HOBt for coupling the carboxyl group, and the symmetrical anhydride method for extension of the N-terminus. In the case of 8, O-deacetylation (K_2CO_3, MeOH) had to precede N-deprotection and coupling to prevent O to N transacetylation.[18]

After incorporation into the required peptides, e.g. 9 and 10 (Scheme II), diastereomers were separated[19] by flash chromatography (1% MeOH/$CHCl_3$) and then deacetylated (K_2CO_3, MeOH; 70-90%) to give the hydroxyethylene analogs 11[13,20] and 12.[13,21] The corresponding ketones 13[13,22] and 14[13,23] were obtained by PDC oxidation[15] of 11 and 12 respectively. The rate of oxidation depended both on solvent[24] and the peptide chain. Thus, reaction of 11 with 6 equiv. of PDC in DMF for 75 h gave a 53% yield of 13, whereas oxidation of 12 with a large excess of PDC in DMF was far from complete after 80 h, even after addition of pyridinium trifluoroacetate[15] and warming to 40-50°C. In contrast, both 11 and 12 were completely consumed in less than 24 h using 3 equiv. of PDC in HOAc to afford 13 and 14 in 69 and 60% isolated yields, respectively.

Full synthetic details and biological data for compounds 11-14 will be reported separately.

Acknowledgement: This work was supported by grants from The National Institutes of Health (AM 20100) and from Merck Sharp and Dohme.

REFERENCES

1. Jennings-White, C.; Almquist, R.G. Tetrahedron Lett., 1982, 23, 2533.
2. Szelke, M.; Jones, D.M.; Hallett, A. Eur. Pat. Appl EP 45665 (1982) CA: 97:39405 (1982).
3. a. Clausen, K.; Thorsen, M.; and Lawesson, S.-O. Tetrahedron 1981, 37, 3635.
   b. Bartlett, P.A.; Spear, K.L.; and Jacobsen, N.E. Biochemistry 1982, 21, 1608.
4. Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. J. Chem. Soc. Perkin I 1982, 307.
5. Spatola, A.F.; Agarwal, N.S.; Bettag, A.L.; Yankeelov, J.A.; Bowers, C.Y.; Vale, W.W. Biochem. Biophys. Res. Comm. 1980, 97, 1014.

6. a. Rich, D.H.; Sun, E.T.O., Ulm E. J. Med. Chem., 1980, 23, 27.
   b. Rich, D.H.; and Sun, E.T.O. Biochem. Pharmacol., 1980, 29, 2205.
   c. Rich, D.H.; Bernatowicz, M.S.; Schmidt, P.G. J. Am. Chem. Soc., 1982, 104, 3535.
7. Hamada, Y. and Shioiri, T. Chem. Pharm. Bull., 1982, 30, 1921.
8. Abbreviations follow IUPAC-IUP tentative rules as described in J. Biol. Chem. 1972, 247, 977. Other abbreviations used are DMAP, 4-dimethylaminopyridine; PDC, pyridinium dichromate; DCC, N,N'-dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; Iaa, isoamylamide; Iva, isovaleryl.
9. Branca, Q. and Fischli, A. Helv. Chim. Acta, 1977, 60, 925.
10. Evans, D.A.; Ennis, M.D. and Mathre, D.J. J. Am. Chem. Soc., 1982, 104, 1737.
11. Stereochemistry at C-4 for the epimers of 5 was assigned based on $J_{4,5}$ in the ^{1}H-NMR spectra of the corresponding oxazolidinones;[12] major (4S): oil; $[\alpha]_D^{24}$ - 22.3° (c 2.8, $CHCl_3$); R_f (4:1 PhMe-EtOAc) 0.31; minor (4R): m.p. 77-81°; $[\alpha]_D^{24}$ - 26.0° (c 2.8, $CHCl_3$); R_f (4:1 PhMe-EtOAc) 0.25.
12. Futagawa, S; Inui, T.; Shiba, T. Bull. Chem. Soc. Japan, 1973, 46, 3308.
13. Characterized by ^{1}H-NMR, mass spectroscopy, and elemental analysis.
14. Anwer, M.K.; Spatola, A.F. Synthesis, 1980, 929.
15. Corey, E.J. and Schmidt, G. Tetrahedron Lett., 1979, 399. PDC was prepared according to the reference and stored under N_2.
16. Herriott, A.W. and Picker, D. Tetrahedron Lett., 1974, 1511.
17. PDC in DMF gave poor results for this conversion in each of several trials.
18. Phillips, P.A. and Baltzly, R.J. J. Am. Chem. Soc., 1947, 69, 200.
19. For both 9 and 10, the isomer possessing S-stereochemistry at C-4 of the dipeptide isostere was the faster eluting component.
20. (4S)-11: m.p. 238-239°C; $[\alpha]_D^{24}$ - 51° (c 0.1, MeOH);
    (4R)-11: m.p. 234-237°C; $[\alpha]_D^{24}$ - 67° (c 0.06, MeOH).
21. (4S)-12: m.p. 262°C; $[\alpha]_D^{24}$ - 66° (c 0.05, MeOH);
    (4R)-12: m.p. 262°C; $[\alpha]_D^{24}$ - 86° (c 0.1, MeOH).
22. 13: m.p. 192-193°C; $[\alpha]_D^{24}$ - 56° (c 0.03, MeOH); ^{13}C-NMR ($CDCl_3$) δ 208.2.
23. 14: m.p. 239-240°C; $[\alpha]_D^{24}$ - 72° (c 0.13, MeOH); ^{13}C-NMR ($CDCl_3$-MeOH-d_4) δ 208.7.
24. Compare pyridinium fluorochromate oxidations in CH_2Cl_2 vs. HOAc: Bhattacharjee, M.N.; Chaudhuri, M.K.; Dasgupta, H.S.; Roy, N. and Khathing, D.T. Synthesis, 1982, 588.

(Received in USA 7 July 1983)