Tetrahedron Letters, Vol. 33, No. 47, pp. 7259-7262, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Homologation of L-Phenylalanine to Ketomethylene and Hydroxyethylene Dipeptide Isosteres via 2-Thiazolyl Amino Ketone Intermediate

Alessandro Dondoni* and Daniela Perrone

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy.

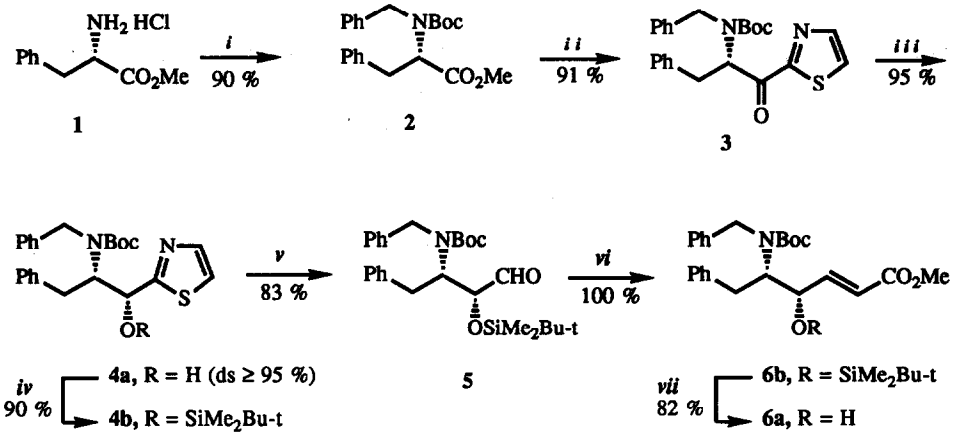
Key Words: thiazole, L-phenylalanine, homologation, dipeptide isosters

Abstract: *: A highly efficient route is presented for the synthesis of N-protected isosteric dipeptides Pheψ[$COCH_2$]Gly and Pheψ[$CH(OH)CH_2$]Phe from L-phenylalanine through 2-thiazolyl α-amino ketone and δ-amino-γ-hydroxy-(E)-α,β-enoate derivatives as key intermediates.*

Renin and HIV-1 protease inhibitor isosteric dipeptides[1] have stimulated in recent years a considerable effort in the development of stereoselective approaches to the synthesis of various classes of these compounds.[2] Most of these approaches employ natural sugars and amino acids as chiral starting materials. Synthetic elaborations of α-amino acids are usually carried out through the corresponding amino aldehydes which however suffer some chemical and configurational instability.[3] The major problem is the stereocontrol of the addition reactions to the carbonyl since the configuration of the newly formed stereocenter is often crucial to the inhibitory activity of the pseudopeptide under construction. For example, hydroxyethylene isosteres with a *4S*-stereocenter are far more potent than the *4R*-epimers.[4] We have recently described the highly stereoselective one-carbon chain extension of L-threonine to either *syn* and *anti* α-hydroxy-β-amino aldehydes involving differentially *N*-protected 2-thiazolyl amino ketone intermediates.[5] In this strategy the thiazole ring serves as an effective synthetic equivalent to the formyl group.[6] We wish to report here a high yielding and stereoselective route, based on this strategy, to ketomethylene and hydroxyethylene dipeptide isosteres starting from L-phenylalanine.

The commercially available L-phenylalanine methyl ester hydrochloride **1** was readily converted by standard methods[7] into the *N*-benzyl-*N*-Boc methyl ester **2** (90 %) (Scheme 1).[8] Treatment of the ester **2** in diethyl ether at low temperature with 2-lithiothiazole produced the 2-thiazolyl amino ketone **3** in ca. 91 % yield.[9] The enantiomeric purity of a freshly prepared sample[10] of **3** proved to be ≥ 95 % by ^{1}H NMR of the alcohol **4a** as the Mosher ester.[11] The *syn* amino alcohol **4a** (95 %)[12] was obtained by stereoselective reduction (ds ≥ 95 % by ^{1}H NMR) of **3** in methanol with sodium borohydride. The stereochemistry of **4a** arising from the expected non-chelation controlled reduction of the carbonyl[13] was demonstrated by NMR analysis of the oxazolidinone derived from it.[14] After conversion of **4a** to the t-butyldimethylsilyl ether **4b** (90 %), the application of the improved one-pot thiazolyl-to-formyl deblocking protocol[6,15] afforded the aldehyde **5** in 83 % isolated yield.[16] The olefination of crude **5** with the stabilized (methoxycarbonylmethylene)triphenylphosphorane produced the protected δ-amino-γ-hydroxy-α,β-(*E*)-enoate **6b** in essentially quantitative yield[17] (58 % from **1**).

Scheme 1

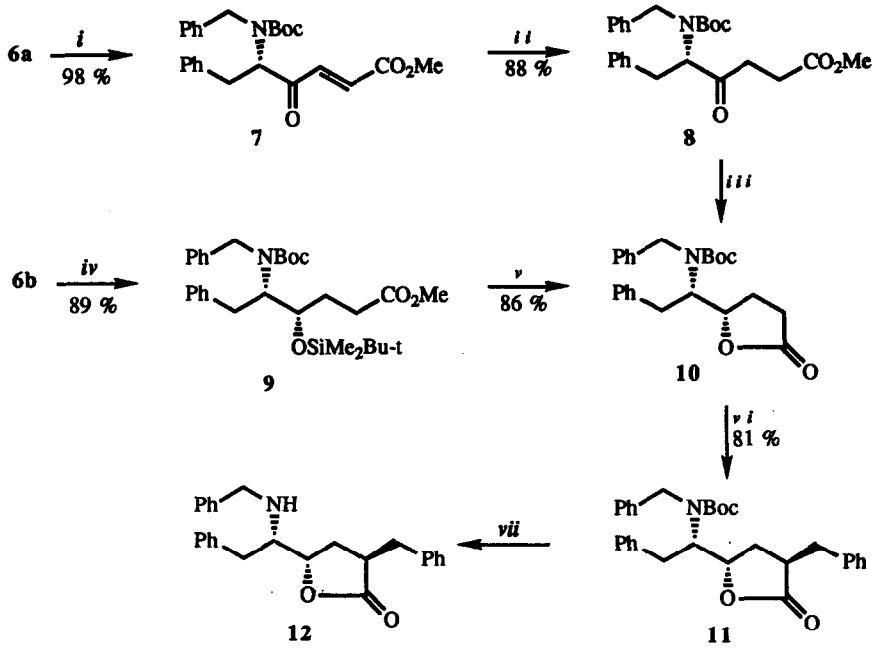


Reagents and conditions: *i*, Et_3N-PhCHO, CH_2Cl_2, rt, 18 h then $NaBH_4$, MeOH, 0 °C, 30 min. then Boc_2O, dioxane, rt, 18 h; *ii*, 2-lithiothiazole, Et_2O, -78 °C then -45°C, 6 h; *iii*, $NaBH_4$, MeOH, -80°C, 30 min.; *v*, $CF_3SO_3SiMe_2Bu$-t, DMF, r.t., 40 min.; *v*, ref.6 and 15; *vi*, Ph_3P=CH-CO_2Me, C_6H_6, r.t., 36 h.

The chiral unsaturated ester **6** proved to be a convenient precursor to dipeptide isosteres incorporating the phenylalanine unit. Efforts were first addressed to the conversion of **6a** to a ketomethylene pseudopeptide with sacrifice of the stereocenter bearing the hydroxymethyl group (Scheme 2).[8] To this end, Moffatt oxidation of **6a** afforded the (*E*)-enone **7** (88 %) whose ethylenic double bond was readily reduced with hydrogen over $Pd/BaSO_4$ in methanol to give the *N*-protected δ-amino-γ-ketoester **8** in almost quantitative yield.[18] This compound corresponds to the Pheψ[$COCH_2$]Gly dipeptide isostere which has been incorporated in various peptides to produce angiotensin converting enzyme inhibitors.[19] The stereoselective reduction of the ketoester **8** with $NaBH_4$ at -50°C restored the chiral hydroxymethyl group to give the lactone **10** along with a 10 % (^{1}H NMR) of the C-4 epimer in 89 % overall yield. The minor isomer was conveniently removed from the mixture by crystallization from ethyl ether-hexane.[20]

A more straightforward entry to the lactone **10** was achieved by reduction of the ethylenic double bond of the (*E*)-enoate **6b** to the saturated ester **9** (89 %) with nickel boride and desilylation of the latter (86 %). The compound **10** obtained in this way was identical (mp, optical rotation, spectra) with the sample obtained from the ketoester **8**. Aiming at obtaining a hydroxyethylene Phe-Phe isostere, the stereoselective introduction of a benzyl group at C-2 of **10** was carried out by generation of its dianion with hexamethyldisilazide (2.2 equiv.) in tetrahydrofuran and treatment with benzyl iodide (1.1 equiv.) as recently reported[2p] for the alkylation of a lactone structurally identical to **10**. The benzylated *trans* lactone **11** was obtained with good diastereoselectivity (ds 92 %) and isolated yield (81 %) after chromatographic separation (silica, toluene-diethyl ether 95:5) of the minor *cis* isomer.[21] The overall yield of **11** from the commercial amino ester **1** is 35.9 %. The use of 1 equiv. of base resulted in incomplete consumption of **10** and isolation of **11** in ca. 40 % yield. The stereochemistry of the C-2 benzylated lactone **11** was assigned following its conversion to **12** by removal of the *N*-Boc protecting group. ^{1}H NMR NOE experiments with **12** showed a mutual enhancement of signals between one of the two methylene protons of the C-2 benzyl group and the H-4 proton of the lactone ring. Lactones **11** and **12**

Scheme 2



Reagents and conditions: *i*, Ac_2O-DMSO, r.t., 18 h.; *ii*, 1 atm H_2, Pd-$BaSO_4$, MeOH, r.t., 4 h.; *iii*, $NaBH_4$, MeOH, -50°C, 2 h; *iv*, $NiCl_2$ $6H_2O$-$NaBH_4$, MeOH, 0°C, 1 h then r.t., 18 h; *v*, Bu_4NF H_2O, THF, r.t., 4 h; *vi*, LHMDS (2.2 equiv.), THF,-78°C, 30 min. then $PhCH_2I$ (1.1 equiv.), -78°C, 30 min.; *vii*, 40 % TFA in CH_2Cl_4, r.t., 10 min..

correspond to *N*-protected derivatives of the Pheψ[CH(OH)CH_2]Phe dipeptide isostere. The *N*-debenzylated analog of **11** prepared from D-mannose (ca.19 % overall yield) has been used[2p] as a precursor to potent and selective hydroxyethylene dipeptide isostere inhibitors of HIV-1 protease.

It is now of interest to explore the scope of this strategy centred on 2-thiazolyl amino ketone intermediates for the synthesis of other interesting hydroxyethylene dipeptide isosteres[4] designed on the transition-state mimetic concept.[22]

Acknowledgment. We thank Mr. Paolo Formaglio for technical assistance in NMR spectroscopy and MURST (Ministero Università Ricerca Scientifica Tecnologica, Rome) for financial support.

References and Notes

1. a) Spatola, A. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B. (Ed.), Marcel Dekker, New York, **1983**, Vol. 27, p. 267. b) Rich, D. H. *Proteinase Inhibitors*, Barret, A. J.; Salveson, G. (Eds.), Elsevier, New York, **1986**, p. 179. c) Tourwé, D. *Janssen Chimica Acta* **1985**, *3*, 3.

2. Selected recent papers : a) Kano, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1991**, *32*, 233. b) Moree, W. J. ; van der Marel, G. A. *Ibid.* p. 409. c) DeCamp , A. E.; Kawaguchi, A. T.; Volante, R. P.;

Shinkai, I. *Ibid.* p. 1867. d) Chakraborty, T. K.; Gangakhedkar, K. K. *Ibid.* p. 1897. e) Plata, D. J.; Leanna, M. R.; Morton, H. E. *Ibid.* p. 3623. f) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Ibid.* p. 4503. g) Rivero, R. A.; Greenlee, W. J.; Patchett, A. A. *Ibid.* p. 5263. h) Bol, K. M.; Liskamp, R. M. J. *Ibid.* p. 5401. i) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *Ibid.* p. 5729. j) Vara Prasad, J. V. N.; Rich, D. H. *Ibid.* p. 5857. k) Rosenberg, S. H.; Boyd, S. A.; Mantei, R. A. *Ibid.* p. 6507. l) Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Ibid.* p. 6819. m) Hanko, R.; Rabe, K.; Dally, R. Hoppe, D. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1690. n) Cushman, M.; Oh, Y.; Copeland, T. D.; Oroszlan, S.; Snyder, S. W. *J. Org. Chem.* **1991**, *56*, 4161. o) Ibuka, T.; Habashita, H.; Otaka, A. Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Ibid.* p. 4370. p) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *Ibid.* p. 6500. q) Garret, G. S.; Emge, T.J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K; McIver, J. M. *Ibid.* p. 4823. r) Alewood, P. F.; Brinkworth, R. I.; Dancer, R. J.; Garnham, B.; Jones, A.; Kent, S. B. H. *Tetrahedron Lett.* **1992**, *33*, 977. s) Baker, W. R., Condon, S. L. *Ibid.* p. 1581.

3. Jurczack, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

4. Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828.

5. Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313..

6. Dondoni, A. *Pure and Appl. Chem.* **1990**, *62*, 643. Dondoni, A. *Carbohydrate Synthesis via Thiazoles* In *Modern Synthetic Methods*, Scheffold, R. (Ed.), Verlag Helvetica Chimica Acta, Basel Switzerland, **1992**, p. 377.

7. Golebiowski, A.; Raczko, J.; Jurczak, J. *Bull. Pol. Ac. Chem.* **1988**, *36*, 209.

8. All isolated compounds had satisfactory analytical data and NMR spectra consistent with their structures. For compounds existing as amide rotamers at room temperature, the NMR spectra were recorded at higher temperatures.

9. **3** : syrup, $[\alpha]^{25}_D$ = -94.5 (c 1.20, $CHCl_3$).

10. The optical rotation of **3** remained unchanged after ten days in a refrigerator.

11. Dale, J. A.; Dull, D. L., Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

12. **4a** : syrup, $[\alpha]^{25}_D$ = +18.1 (c 1.11, $CHCl_3$).

13. Dondoni, A.; Fantin, G.; Fogagnolo, M; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702.

14. See : Dondoni, A., Fantin, G., Fogagnolo, M., Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. Kano, S., Yokomatsu, T., Shibuya, S. *J. Org. Chem.* **1989**, *54*, 514.

15. Dondoni, A; Marra, A.; Perrone, D. *J. Org. Chem.*, submitted.

16. The aldehyde **5** , mp 92-93 °C, was unstable to chromatographic purification.

17. **6b** : syrup, $[\alpha]^{25}_D$ = -34.9 (c 1.90, $CHCl_3$).

18. **8** : syrup, $[\alpha]^{25}_D$ = -110.3 (c 1.03, $CHCl_3$)

19. Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.

20. **10** : mp 81-83 °C (diethyl ether-hexane), $[\alpha]^{25}_D$ = -16.3 (c 1.03, $CHCl_3$)

21. **11** : mp 123-125 °C (diethyl ether-hexane), $[\alpha]^{25}_D$ = -23.3 (c 1.30, $CHCl_3$).

22. Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375. Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10.

(Received in UK 1 September 1992)