An Efficient Stereocontrolled Strategy for the Synthesis of Hydroxyethylene Dipeptide Isosteres

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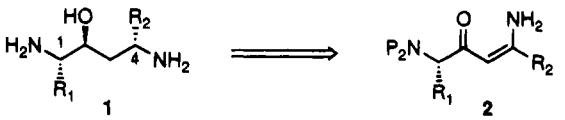
Summary: A novel and practical synthesis of hydroxyethylene dipeptide isostere **9** from L-phenylalanine via the formation and stereospecific reduction of an enaminone is described.

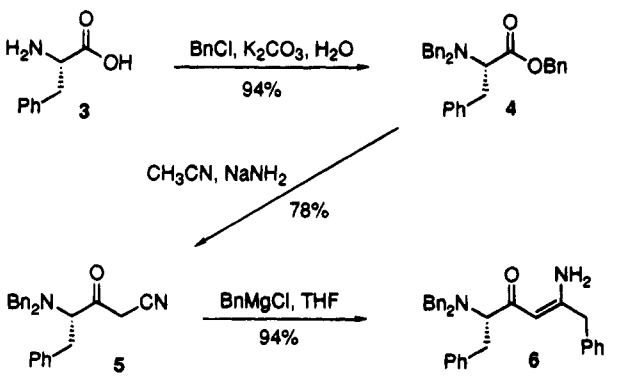
Recently, several potent inhibitors of aspartic proteases such as HIV protease and renin have been reported[1] which incorporate a nonhydrolyzable hydroxyethylene isostere as a key structural component. In light of this, considerable effort has been invested into the development of syntheses of dipeptide isosteres of general structure **1**. Synthetic approaches disclosed to date,[2] however, are not amenable to large scale production. We wish to describe herein a novel and general method to produce these isosteres that does not involve sensitive intermediates, expensive reagents, or chromatographic separations and has been readily applied to large scale (>100 kg) reactions.

Our initial target was isostere **1** in which R_1, R_2 = Bn. The key element of our synthetic strategy was to use the established stereocenter at C-1 in enaminone **2** to dictate the generation of stereocenters at C-2 and C-4. The C-1 stereocenter, in turn, would be derived from the optically pure commodity item L-phenylalanine.



In order to ensure that eventual reduction of the carbonyl would produce the desired β-alcohol, it was necessary to protect the α-amine in such a way as to bias the system against chelation-controlled addition. It is well documented[3] that ketones having a disubstituted amino group α to the carbonyl can be reduced to give threo rich products, particularly if the substitution is bulky. In light of this, the amine was protected as the dibenzyl[4] derivative. Phenylalanine (**3**) was trialkylated

Scheme 1



with BnCl/ K_2CO_3 in water at reflux to afford benzyl ester **4** (Scheme 1) in 94% yield and >99.5% ee.[5]

It has long been known[6] that cyanomethyl ketones[7] can be prepared by addition of acetonitrile nitrile anions to esters at elevated temperatures, but to our knowledge this approach has never been developed for use on an optically active amino ester.[8] We have found that this addition proceeds quite readily at low temperatures in THF, although temperature and mode of addition are all critical to minimization of racemization during this reaction. A solution of acetonitrile anion[9] in THF was added to benzyl ester **4** at less than −40 °C[10] to afford nitrile **5** in 78–85% crystallized yield and >98% ee.

The reaction of Grignard reagents with cyanomethyl ketones is relatively unknown, except in the case of benzoylacetonitrile where addition of Grignard reagents yields either 1,3-diketones[11] or dimers[12] depending upon the conditions. We have found that Grignard reagents add quite cleanly to β-keto nitriles similar to **5** at ambient temperature to afford keto enamines after mild acid quench. For example, reaction of nitrile **5** with 3 equiv[13]

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(1) (a) Huff, J. R. *J. Med. Chem.* **1991**, *34(8)*, 2305 and references cited therein. (b) Lyle, T. A.; Wiscount, C. M.; Guare, J. P.; Thompson, W. J.; Anderson, P. S.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Dixon, R. A.; Sigal, I. S.; Huff, J. R., *J. Med. Chem.* **1991**, *34*, 1228. (c) Kempf, D. J.; Norbeck, D. W.; Codavoci, L.; Wang, X. C.; Kohlenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W., Jr.; Clement, J.; Platner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687. (d) *Aspartic Proteinases and Their Inhibitors*; Kosta, V., Ed.; DeGruyter: New York, 1985; pp 421–441.

(2) (a) Kempf, D. J.; Codacovi, L. M.; Norbeck, D. W.; Plattner, J. J.; Sham, H. L.; Wittenberger, S. J.; Zhao, C. Eur. Pat. Appl. 0486948, 1991. (b) Ghosh, A. K.; McKee, S. P.; Thompson, W. J.; Darke, P. L.; Zugay, J. A. *J. Org. Chem.* **1993**, *58(5)*, 1025. (c) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*(39), 8739.

(3) For a review see: Tramontini, M. *Synthesis* **1982**, 605.

(4) (a) Muller, H. K. *Liebigs Ann. Chem.* **1956**, *598*, 70. (b) van Dijk, J.; Moed, H. D. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 22. (c) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgruen, X. *Tetrahedron: Asymmetry* **1990**, *1(6)*, 375.

(5) The enantiomeric purities of compounds **4–6** were determined by chiral HPLC analysis. See supplementary material for details.

(6) Levine, R.; Hauser, C. R. *J. Am Chem. Soc.* **1946**, *68*, 760.

(7) For a review of 3-oxoalkanenitriles, see: Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, E. H. *Synthesis* **1984**, 1.

(8) Sauve et al. have synthesized a similar compound via addition of a *tert*-butyl cyanoacetate anion to a CDI-activated amino acid followed by decarboxylation: Brillon, D.; Sauve, G. *J. Org. Chem.* **1992**, *57*, 1838.

(9) Prepared by the addition of CH_3CN (2.6 equiv) to $NaNH_2$ (2.4 equiv) in THF at −40 °C.

(10) Under these conditions, in the phenylalanine series, addition of the anion at temperatures above −40 °C causes partial racemization and above −10 °C can cause complete racemization.

(11) Mavrodin, A. *Bull. Chem. Soc. Romania* **1933**, *15*, 99.

(12) Rehberg, C. E.; Henze, H. R. *J. Am. Chem. Soc.* **1941**, *63*, 2785. The nature of the dimer is not disclosed.

(13) The first equivalent is wasted forming the enolate of the substrate. Attempts to generate the enolate with a different base followed by Grignard addition have not been as efficient.

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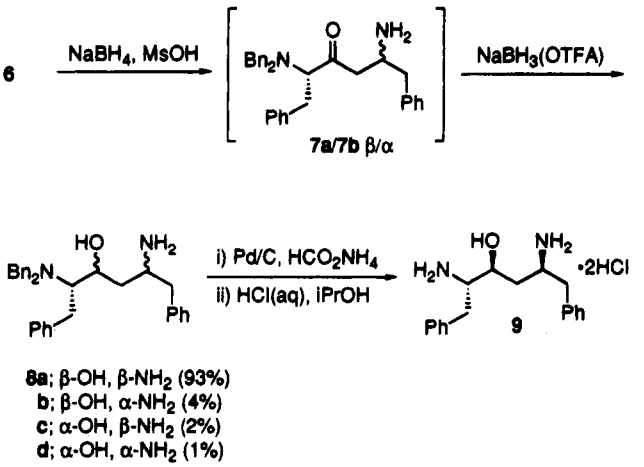
of BnMgCl in THF at 20 °C followed by aqueous citric acid quench afforded enaminone **6** in 94% crystallized yield and >99.5% ee. No racemization was ever observed[14] in this step.

The first three steps had effectively pieced together the necessary skeleton of the final product, but the critical challenge in this synthesis was to generate the C-2 and C-4 centers stereoselectivly via reduction of **6**. The enaminone[15] system is unusually resistant to reduction, although examples of the reduction of N-alkylated[16] and N-acylated[17] compounds have been published. Hydrogenation of an unprotected cyclic enaminone to an amino alcohol has been reported,[18] but very little diastereoselectivity was observed and metal hydrides were found to be ineffective. We have found that addition of enaminone **6** in THF/iPrOH to a solution of $NaBH_4$ (2.5 equiv) and MsOH (6.3 equiv) in THF at 5 °C afforded intermediate ketones[19] **7a** and **7b** in a 17−19:1 ratio (Scheme 2). It has been established that enaminones exist predominantly in the carbonyl form[20] and, therefore, are presumably fixed in a hydrogen-bonded, ciscoid conformation. It is most likely the rigidity of the system that allows for the remarkable 1,4-stereoinduction that is seen in this reduction. No further reduction of the ketones occurs under these conditions, presumably because it is bound as an unreactive boron enolate. It was found that this boron complex could be broken and reduction of the ketone could proceed by addition of a preformed solution of $NaBH_3(OTFA)$[21](4 equiv). This afforded a mixture of

Scheme 2



amino alcohols composed of 93% of the desired β,β-hydroxy amine **8a** along with 7% of the three undesired diastereomers.[22] The crude mixture was debenzylated (Pd/ C, HCO_2NH_4), and the product was purified by precipitation from iPrOH/ HCl (aq) to afford hydroxy diamine **9** in >99% purity and in 60% overall yield from enaminone **6**.

In summary, novel chemistry has been developed to provide an efficient, flexible, and economical five-step synthesis of isostere **9**. Potentially, this protocol could provide access to an unlimited number of isosteres of type **1**, the only limits being that R_1 must be incorporated into the side chain of an amino acid and that R_2 must derive from a Grignard reagent. Current investigations will expand the scope of this approach.

Acknowledgment. We wish to thank Dr. Steve Hannick for providing authentic samples of the diastereomers of **8** and Dr. Helen Yip and Dr. Dan Reno for the development of some of the analytical assays.

Supplementary Material Available: Full experimental and spectrometric data of compounds **4-9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) The ee was determined by chiral HPLC prior to crystallization because crystallization of **6** from ethanol can improve the ee from as low as 80% to >99%.

(15) For a review see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(16) (a) Nagasaka, T.; Yamamoto, H.; Hayashi, H.; Watanabe, M.; Hamaguchi, F., *Heterocycles* **1989**, *29(1)*, 155. (b) Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498. (c) Maroni, P.; Cazaux, L.; Tisnes, P.; Zambeti, M. *Bull. Soc. Chim. Fr.* **1980**, *3−4*, II-179. (d) Yamamoto, H.; Matsumura, Y.; Fujiwara, J.; Maruoka, K. *J. Am. Chem. Soc.* **1983**, *105*, 6312. (e) Yamamoto, Y.; Kashima, C. *Chem. Lett.* **1978**, 1285. (f) Ohlendorf, H. W.; Maetzel, M. U.S. Pat. 4831167. (g) Schuda, P. F.; Ebner, C. B.; Morgan, T. M. *Tetrahedron Lett.* **1986**, *27(23)*, 2567. (h) Martin, J. C.; Barton, K. R.; Gott, P. G.; Meen, R. H. *J. Am. Chem Soc.* **1966**, *88*, 943.

(17) Ban, Y.; Sato, Y.; Inoue, Y.; Yanemitsu, O. *Tetrahedron Lett.* **1965**, 2261.

(18) Greenhill, J. V.; Ramli, M.; Tomassini, T. *J. Chem. Soc., Perkins. Trans. 1* **1975**, 588.

(19) The ketones are prone to β-amino elimination and are, therefore, not routinely isolated.

(20) Greenhill, J. V. *J. Chem. Soc. B* **1969**, 299.

(21) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17-(4−5)*, 317−384.

(22) The product ratio was determined by HPLC by comparison to independently synthesized diastereomers of **8**.