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Synthesis of a Val-Pro Diaminodiol Dipeptide Isostere by Epoxyamine Cyclization

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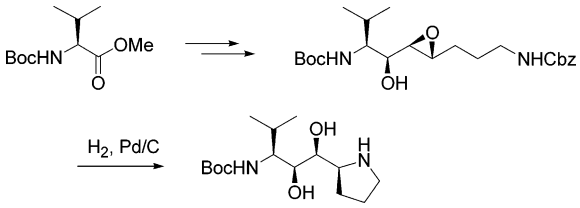
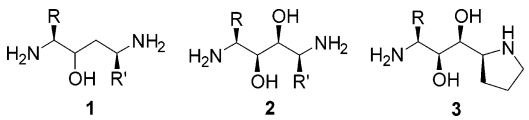
ABSTRACT



The stereoselective synthesis of a novel proline-containing dipeptide isostere is described. Starting from L-valine, three new contiguous stereocenters are generated by asymmetric induction and epoxide chemistry, while the pyrrolidine ring of proline is introduced in the final step via intramolecular ring opening of the amino acid derived epoxyamine. Proline-containing peptidomimetics are potentially attractive as selective inhibitors of proline-specific enzymes, such as PPIases and retroviral proteases, and as analogues of bioactive peptides.

Replacement of a dipeptide by a dipeptide isostere is a useful tool in medicinal chemistry. This approach is used to improve the stability of peptides toward proteolysis, which is often a severe limitation to their in vivo applications, and in the design of peptidomimetic inhibitors for enzymes that act on the peptide bond.[1]

Proline is unique among natural amino acids for the presence of a secondary amino group that imparts peculiar structural and functional characteristics to proline-containing peptides and proteins. Proline is present in several bioactive peptides including antimicrobial peptides[2] and inhibitors of angiotensin-converting enzyme (ACE)[3a] and thrombin,[3b] which control blood pressure and coagulation, respectively. Among enzymes specific for proline-containing peptides are the peptidyl-prolyl *cis*/*trans* isomerases (PPIases), which assist the process of protein folding by catalyzing the isomerization of Xaa-Pro peptide bonds and are receptors for immunosuppressive drugs,[4] and a number of retroviral proteases involved in the development and propagation of viral infections.[5] The important biological role of these species has stimulated intense research efforts into the synthesis of proline analogues and peptidomimetics based on Xaa-Pro isosteres.[6] In the case of the human immunodeficiency virus protease (HIV-PR), in particular, several efficient inhibitors based on Phe-Pro isosteres have been developed; two of them (Saquinavir and Nelfinavir) have rapidly reached the market and are currently used in the therapy of AIDS.[7]



Peptidomimetics based on hydroxyethylene (**1**) and dihydroxyethylene dipeptide isosteres (**2**) are effective HIV-

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(1) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.
(2) Gennaro, R.; Zanetti, M.; Benincasa, M.; Podda, E.; Miani, M. *Curr. Pharm. Des.* **2002**, *8*, 763.
(3) (a) Ulm, E. H.; Greenlee, W. J. In *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J. Eds.; Oxford University Press: 1989; pp 146−177. (b) Markwardt, F.; Stürtzebecher, J. In *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J. Eds.; Oxford University Press: 1989; pp 619−649.

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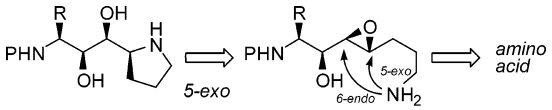
PR inhibitors,[8,9] and several synthetic approaches have been developed for these structures.[9,10] These, however, have been generally limited to the synthesis of isosteres with benzylic or alkyl side chains R, R′. Recently, we have developed a general strategy for the synthesis of isosteres **1** and **2** starting from amino acids.[11] We now report on the extension of this approach to the synthesis of proline-containing dihydroxyethylene isosteres **3**.

The synthesis is based on the analysis shown in Scheme 1. It was anticipated that formation of a five-membered ring

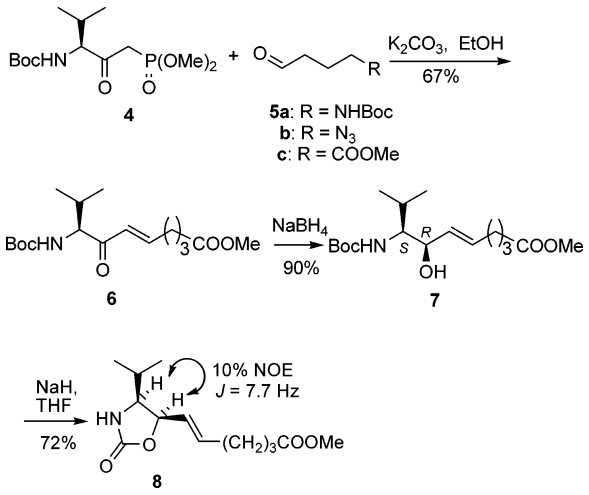
Scheme 1



P = protecting group

by *exo* ring opening of the oxirane would be preferred over the competing 6-*endo* cyclization, leading thus to the required pyrrolidine.[12] The general approach is illustrated by the synthesis of the Val-Pro dipeptide isostere **13**. The synthesis starts from the known phosphonate **4**,[13] readily obtained from N-Boc valine methyl ester. Our initial attempts to directly introduce an ω-amino alkene chain via Horner−Emmons olefination[14] of **4** with Boc-protected amino aldehyde **5a** (Scheme 2) were frustrated by the propensity of the latter to

Scheme 2



cyclize giving *N*-Boc-2-hydroxypyrrolidine, which did not react with **4** under a variety of Horner−Emmons conditions. Aldehyde **5b**[15] also failed to give the expected product **6b**, as elimination of azide took place under the basic conditions required for the olefination. We thus resorted to introducing the amino group at a later stage via the Curtius reaction of the corresponding acid; to this end phosphonate **4** was subjected to the Horner−Emmons olefination with aldehyde **5c**,[16] which proceeded smoothly giving the *E*-enone **6** as a single isomer characterized by a 15.6 Hz coupling constant between the vinyl protons.

Stereoselective reduction of the carbonyl group of **6** with $NaBH_4$ in methanol (Scheme 2) follows the Cram-chelate rule,[17] resulting in a 8:1 mixture of *S*,*R* (**7**) and *S*,*S* diastereoisomers.[10a,18] The major isomer **7** could be easily isolated in pure form by column chromatography and was converted into the corresponding oxazolidinone **8** in order to confirm the stereochemical assignment (Scheme 2). The value of 7.7 Hz for the coupling constant between the vicinal ring protons of **8** and 10% NOE measured for the same protons are both consistent with a *cis* disposition of the substituents and therefore with the *S*,*R* configuration of **7**.[19]

The second amino group was introduced at this stage of the synthesis (Scheme 3); to this end the alcohol **7** was

(4) (a) Dugave, C.; Demange, L. *Chem. Rev.* **2003**, 103, 2475. (b) Fischer, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1415.

(5) (a) Pearl, L.; Taylor, W. *Nature* **1987**, *328*, 482. (b) DeClercq, E. *Nature Rev. Drug Discovery* **2002**, *1*, 13.

(6) Recent examples: (a) Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003**, *59*, 7047. (b) Wang, X. D. J.; Hart, S. A.; Xu, B. L.; Mason, M. D.; Goodell, J. R.; Etzkorn, F. A. *J. Org. Chem.* **2003**, *68*, 2343. (c) Otaka, A.; Katagiri, F.; Kinoshita, T.; Odagaki, Y.; Oishi, S.; Tamamura, H.; Hamanaka, N.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6152. (d) Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240. (e) Saha, B.; Nandy P. J.; Shukla, S.; Siddiqui, I.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 7858. (f) Courcambeck, J.; Bihel, F.; De Michelis, C.; Quéléver, G.; Kraus, J. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1421. (g) Edmonds, M. K.; Abell, A. D. *J. Org. Chem.* **2001**, *66*, 3747. (h) Kraus, J. L.; Bouygues, M.; Courcambeck, J.; Chermann, J. C. *Bioorg. Med Chem. Lett.* **2000**, *10*, 2023. (i) Nöteberg, D.; Brånalt, J.; Kvarnström, I.; Linschoten, M.; Musil, D.; Nyström, J.-E.; Zuccarello, G.; Samuelsson, B. *J. Med. Chem.* **2000**, *43*, 1705.

(7) (a) *HIV Medicine 2003*; Hoffmann, C., Kamps, B. S., Eds.; Flying Publisher: Paris, 2003 (www.HIVMedicine.com). (b) Richman, D. D. *Nature* **2001**, *410*, 995. (c) Tomasselli, A. G.; Heinrikson, R. L. *Biochim. Biophys. Acta* **2000**, *1477*, 189. (d) Moyle, G.; Gazzard, D. *Drugs* **1996**, *51*, 701.

(8) (a) Brik, A.; Wong, C.-H. *Org. Biomol. Chem.* **2003**, *1*, 5. (b) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305. (c) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.

(9) (a) Tossi, A.; Bonin, I.; Antcheva, N.; Norbedo, S.; Benedetti, F.; Miertus, S.; Nair, A. C.; Maliar, T.; Dal Bello, F.; Palù, G.; Romeo, D. *Eur. J. Biochem.* **2000**, *267*, 1715. (b) Tossi, A.; Benedetti, F.; Norbedo, S.; Skrbec, D.; Berti, F.; Romeo, D. *Bioorg. Med. Chem.* **2003**, *11*, 4719.

(10) (a) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (b) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L. M.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692.

(11) (a) Benedetti, F.; Miertus, S.; Norbedo, S.; Tossi, A.; Zlatoidzky, P. *J. Org. Chem.* **1997**, *62*, 9348. (b) Benedetti, F. Berti, F.; Norbedo S. *J. Org. Chem.* **2002**, *67*, 8635.

(12) Recent examples: (a) Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582. (b) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223. (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546.

(13) Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J.-S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996**, *61*, 2901.

(14) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1987**, 659.

(15) Carrington, S.; Renault, J.; Tomasi, S.; Corbel, J.-C.; Uriac, P.; Blagbrough, I. S. *Chem. Commun.* **1999**, 1341.

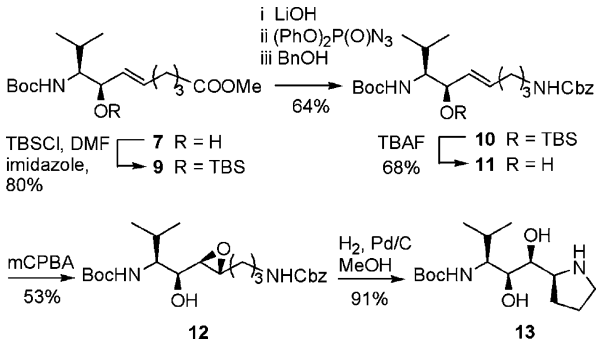
(16) Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. *Synthesis* **1982**, 881.

(17) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(18) (a) Albeck, A.; Persky, R. *Tetrahedron* **1994**, *21*, 6333. (b) Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron* **1990**, *46*, 2807. (c) Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895. (d) Tramontini, M. *Synthesis* **1982**, 605.

(19) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.

Scheme 3



temporarily protected as *tert*-butyl dimethylsilyl ether **9**. Conversion of the ester group of **9** into amine was performed in two steps: **9** was hydrolyzed to the free acid, and the latter was reacted with diphenylphosphoryl azide and benzyl alcohol, under Curtius rearrangement conditions, giving the orthogonally protected diamine **10** in 64% yield for the two steps. The free hydroxy group was now restored in order to control the stereoselectivity of the next step. Accordingly, peracid epoxidation of the allylic alcohol **11** gave the *syn*-2,3-epoxyalcohol **12** as a single diastereoisomer.[10,20]

Finally, removal of the Cbz protecting group by catalytic hydrogenation gave the corresponding free amine, which spontaneously cyclized onto the epoxide by a 5-*exo* process, as predicted, affording the mono-Boc-protected Val-Pro isostere **13** as a single diastereoisomer, in 10% overall yield from the phosphonate **4**. The X-ray crystal structure of **13** is shown in Figure 1 and confirms the stereochemical assignments.[21]

The conformation adopted by the isostere **13** in the solid state (Figure 1) mimics that of a *trans* peptide bond, with the pyrrolidyl and α-aminoisobutyl residues antiperiplanar with respect to the central C10−C11 bond. A water molecule is bridged between the carbonyl of the Boc group and one of the hydroxy groups with hydrogen bonds to O2 (O2−O1W, 2.871(4)) and O4 (O4−O1W, 2.781(4)). A genetic algorithm driven conformational search carried out with the Cornell version of the AMBER force field[22] locates two minima for the isolated molecule **13**, separated by less than

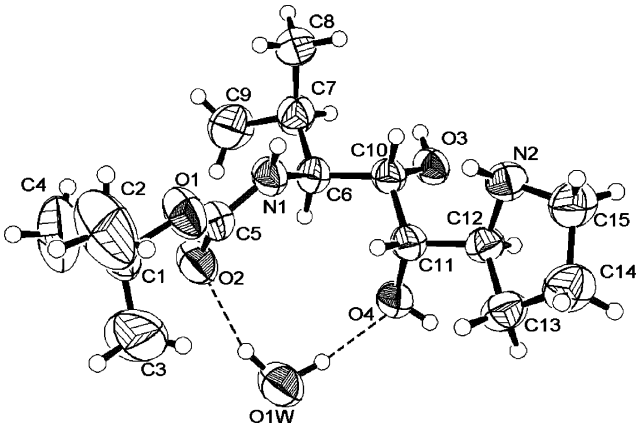


Figure 1. Solid-state structure of Val-Pro isostere **13** with crystallographic numbering scheme. A crystallization water molecule hydrogen-bonded to O2 and O4 is also shown.

1 kcal/mol, corresponding to *gauche* (as in Figure 1) and *anti* conformations of the diol's hydroxy groups (O3 and O4). When the same analysis is carried out including a water molecule, a single minimum is found, corresponding to the *gauche* conformation observed in the solid state. The water molecule present in the crystal appears thus essential for stabilizing this conformer.

In summary, we have developed a synthetic approach to a novel type of proline-based dihydroxyethylene isostere exemplified by the synthesis of the Val-Pro surrogate **13**. For their (pseudo) symmetric structure, with two amino terminals, diaminodiols such as **13** are isosteric replacements for both the Xaa-Pro and Pro-Xaa dipeptides and introduce a point of inversion in the direction of the chain, when inserted between two peptide residues, thus expanding the repertoire of structural motifs available for the design of new peptidomimetics.

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Supporting Information Available: Detailed descriptions of experimental procedure and analytical and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Rossiter, B. A.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733. (c) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 2017.

(21) CCDC 227391 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033.

(22) (a) Judson, R. S.; Rabitz H. *Phys. Rev. Lett.* **1992**, *68*, 1500. (b) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M., Jr; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. D.; Kollmann, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.