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Synthesis of α-Hydroxy Ketomethylene Dipeptide Isosteres

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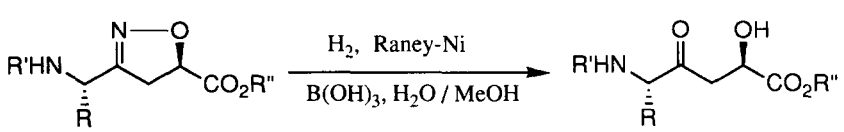
Abstract : *Novel α-hydroxy ketomethylene dipeptide isosteres were prepared efficiently from the corresponding 2-isoxazoline dipeptide isosteres.*

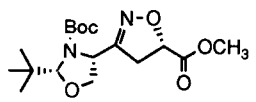
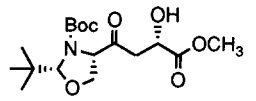
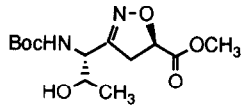
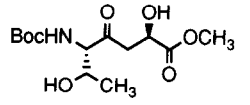
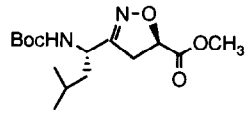
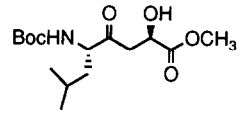
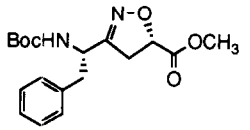
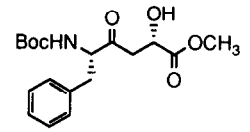
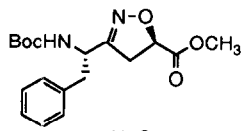
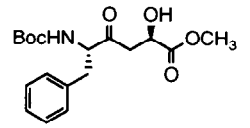
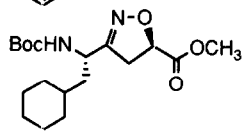
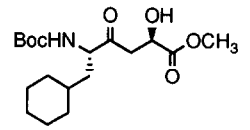
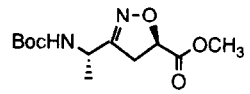
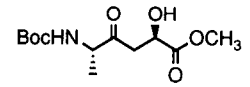
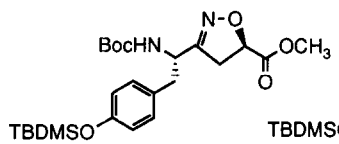
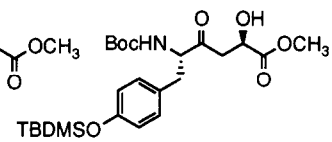
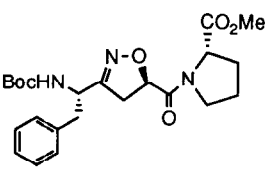
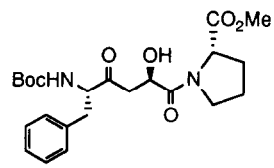
There has been a great deal of recent interest in the synthesis of peptide isosteres in which an amide bond of a peptide is replaced by an electronically and sterically similar group of elements that is not hydrolytically labile.[1] The use of isosteric replacement groups for the amide function in small peptides has recently been recognized as a potential means of improving the stability of such systems while retaining biological activity. Among more than dozen peptide isosteres,[2] the ketomethylene peptide isosteres[3] have been widely used to prepare metabolically stable peptides and various enzyme inhibitors.[4] However, this modification of the amide bond -CONH- by the isosteric ketomethylene $-COCH_2-$ group, which provides enzymatic resistance, causes a loss of the amide bond rigidity and, therefore, it increases conformational mobility. We wish to report here a facile synthesis of α-hydroxy ketomethylene dipeptide isosteres, which may find a broad spectrum of synthetic utility for enzyme inhibitors and also can be considered as conformationally restricted analogues of the ketomethylene isosteres with the intramolecular hydrogen bonding.

In the previous communication,[5] we have reported the development of the 2-isoxazoline ring as a novel dipeptide isostere. Various N-protected pseudodipeptides containing the 2-isoxazoline isosteres which were synthesized by the asymmetric dipolar cycloadditions with α-amino nitrile oxides, were subjected to the reductive cleavage conditions,[6] and novel α-hydroxy ketomethylene dipeptide isosteres were prepared in good yield (**Eq. 1**).



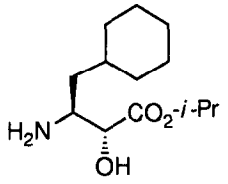
(Eq. 1)

Table 1. Synthesis of α-Hydroxy Ketomethylene Dipeptide Isosteres

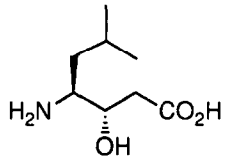
entry	starting amino acid	isoxazoline isostere	ketomethylene isostere	$[\alpha]_D$ (c , $CHCl_3$)	yield [a] (%)
1	L-Ser			-61.4 (1.43)	86
2	L-Thr			-13.8 (0.88)	70
3	L-Leu			+2.0 (1.48)	92
4	L-Phe [b]			+26.8 (1.00)	87
5	L-Phe			+18.4 (0.95)	94
6	L-Cha [c]			+10.2 (2.44)	82
7	L-Ala			+11.1 (1.10)	78
8	L-Tyr			-24.6 (1.18) [d]	80
9	L-Phe, L-Pro [e]			-34.1 (1.56)	44

[a] isolated yield [b] The absolute stereochemistry of the stereogenic center in the isoxazoline ring was confirmed by X-ray crystallography of the derivative containing camphor sultam chiral auxiliary. [c] Cyclohexylalanine [d] in MeOH [e] Tripeptide analog

The experimental results are summarized in Table 1. This reaction is stereospecific and the stereochemistry of α-carbon is retained (entry 4, 5). In no case were we able to detect any loss of stereochemical purity, as observed previously.[6] The absolute stereochemistry of the ketomethylene dipeptide isosteres was tentatively assigned based on the absolute stereochemistry of the starting isoxazoline isosteres[5] and the stereospecificity of the reductive cleavage[6] of the isoxazoline rings. Thus, we can readily prepare the ketomethylene isostere with an additional stereogenic α-carbon center possessing the hydroxyl group. The presence of an additional α-hydroxy group may be well utilized in the design of enzyme inhibitors. Recently, the isopropyl ester of nor-C-statine (**1**), a mimic of statine (**2**), has been used by Pfizer and other companies in the synthesis of renin inhibitors.[7] Stereoselective introduction of the α-hydroxy group in ketomethylene dipeptide isosteres may play a crucial role in increasing the potency of enzyme inhibitors.[8]



nor-C-Statine (**1**)



Statine (**2**)

α-Hydroxy ketomethylene dipeptide isosteres have another advantage over normal ketomethylene dipeptide isosteres in conformational control. The problem of conformational mobility faced in normal ketomethylene dipeptide isostere is partially solved in α-hydroxy ketomethylene dipeptide isostere by the intramolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen.[9]

In summary, we have prepared various α-hydroxy ketomethylene dipeptide isosteres and these isosteres will provide efficient routes to the synthesis of enzyme inhibitors, especially to the synthesis of angiotensin converting enzyme inhibitor[4c] (entry 9).

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References

1. a) Spatola, A.F., *Chemistry and Biochemistry of Amino acids, Peptides and Proteins* ; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; vol. 7, Chapter 5. b) Morgan, B. A.; Gainor, J. A., *Annual Reports in Medicinal Chemistry* ; Vinick, F. J., Ed., Academic Press: New York, 1989; Vol. 24, Chapter 26. c) Rich, D. H., *Comprehensive Medicinal Chemistry* ; Hansch, C.; Sammes, P. G.; Taylor, J. B., Eds.; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 8.

2. a) Tourwé, D., *Janssen Chim. Acta*. **1985**, *3* , 3. b) Herranz, R.; Suárez-Gea. M.L.; Vinuesa, S.; García-López, M.T.; Martínez, A., *Tetrahedron Lett.*, **1991**, *32* , 7579. c) Rivero, R.A. Greenlee, W.J.; Patchett, A. A., *Tetrahedron Lett.*, **1991**, *32*, 5263. d) Shue, Y-K.; Carrera, Jr., G.M.; Tufano, M.D.; Nadzan, A.M., *J. Org. Chem.*, **1991**, *56*, 2107. e) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y., *J. Org. Chem.*, **1991**, *56*, 4370. f) Lygo, B., *Synlett.*, **1992**, 793. g) Gómez-Monterrey, I.; Domínguez, M.J.; González-Muñiz, R.; Harto, J.R.; García-López, M.T., *Tetrahedron Lett.*, **1991**, *32*, 3563. h) Jones, D. M.; Nilsson, B. ; Szelke, M., *J. Org. Chem.*, **1993**, *58*, 2286. i) Skiles, J. W.; Sorcek, R.; Jacober, S.; Miao, C.; Mui, P. W.; McNeil, D.; Rosenthal, A. S., *BioMed. Chem. Lett.*, **1993**, *3*, 773. j) Gordon, T.; Hansen, P.; Morgan, B.; Singh, J.; Baizman, E.; Ward, S., *BioMed. Chem. Lett.*, **1993**, *3*, 915. k) Getman, D.P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H. -S.; Stallings, W. C.; Stegeman, R. A., *J. Med. Chem.*, **1993**, *36*, 288. l) Thaisrivongs, S.; Turner, S. R.; Strohbach, J. W.; TenBrink, R. E.; Tarpley, W. G.; McQuade, T. J.; Heinrikson, R. L.; Tomasselli, A.G.; Hui, J. O.; Howe, W. J., *J. Med. Chem.*, **1993**, *36*, 941.

3. a) Domínguez, M.J.; González-Munñiz, R.; García-López, M.T., *Tetrahedron*, **1992**,*48*, 2761. b) Hoffman, R.V.; Kim, H.-O., *Tetrahedron Lett.*, **1992**, *33*, 3579. c) Dondoni, A.; Perrone, D., *Tetrahedron Lett.*, **1992**, *33*, 7259. d) García-López, M.T.; González-Muñiz, R.; Harto, J.R., *Tetrahedron Lett.*, **1988**, *29*, 1577. e) Holladay, M.W.; Rich, D.H., *Tetrahedron Lett.*, **1983**, *24*, 4401. f) Jennigs-White, C.; Almquist, R.G., *Tetrahedron Lett.*, **1982**, *23*, 2533.

4. a) Ewenson, A.; Laufer, R.; Chorev, M.; Selinger, Z.; Gilon, C., *J. Med. Chem.*, **1988**, *31*, 416. b) Almquist, R.G.; Olsen, C.M.; Uyeno, E.T.; Toll, L., *J. Med. Chem.*, **1984**, *27*, 115. c) Almquist, R.G.; Chao, W.-R.; Ellis, M.E.; Johnson, H.L., *J. Med. Chem.*, **1980**, *23*, 1392.

5. Kim, B.H.; Chung, Y.J.; Keum, G.; Kim, J.; Kim, K., *Tetrahedron Lett.*, **1992**, *33*, 6811. For the preparation of amino acid derivatives containing 2-isoxazoline ring, see also Keum, G.; Chung, Y. J.; Kim, B. H., *Bull. Kor. Chem. Soc.*, **1992**, *13*, 343.

6. Curran, D.P., *J. Am. Chem. Soc.*, **1983**, *105*, 5826.

7. a) Pfizer, Inc. US Patent 4,599,198. b) Kissei Pharmaceutical Co. US Patent 4,711,958. c) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S., *Tetrahedron Lett.*, **1990**, *31*, 4175. c) Inokuchi, T.; Tanigawa, S.; Kanazaki, M.;Torii, S., *Synlett.*, **1991**, 707.

8. Ando, R.; Morinaka, Y.; Tokuyama, H.; Isaka, M.; Nakamura, E., *J. Am. Chem. Soc.*, **1993**, *115*, 1174.

9. a) Laali, K. K.; Koser, G. F.; Subramanyam, S.; Forsyth, D. A., *J. Org. Chem.*, **1993**, *58*, 1385. b) Pimentel, G. C.; McClellan, A. L., *The Hydrogen Bond* ; W.H. Freeman and Co.: San Francisco, 1960; Chapter 5.

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