Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2879-2882, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

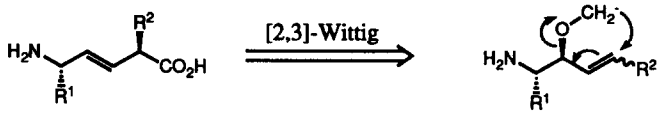
THE STEREOSELECTIVE SYNTHESIS OF (*E*)-ALKENE DIPEPTIDE ISOSTERES[1]

Yaw Fui Yong and Mark A. Lipton*
Department of Chemistry, Purdue University, West Lafayette, IN 47907-1393

(*Received in USA* 30 *September* 1993; *accepted* 25 *October* 1993)

Abstract: A diastereo- and enantio- selective synthesis of the (*E*)-alkene dipeptide isostere of L-Ala-L-Ala from L-alanine has been developed which proceeds via stereocontrolled addition of a (*Z*)-vinyllithium reagent followed by a [2,3]-Wittig rearrangement. The synthesis proceeds in seven steps overall from L-alanine methyl ester. It is believed that this approach will provide a fairly general and convenient route to isosteres of a number of different dipeptides.

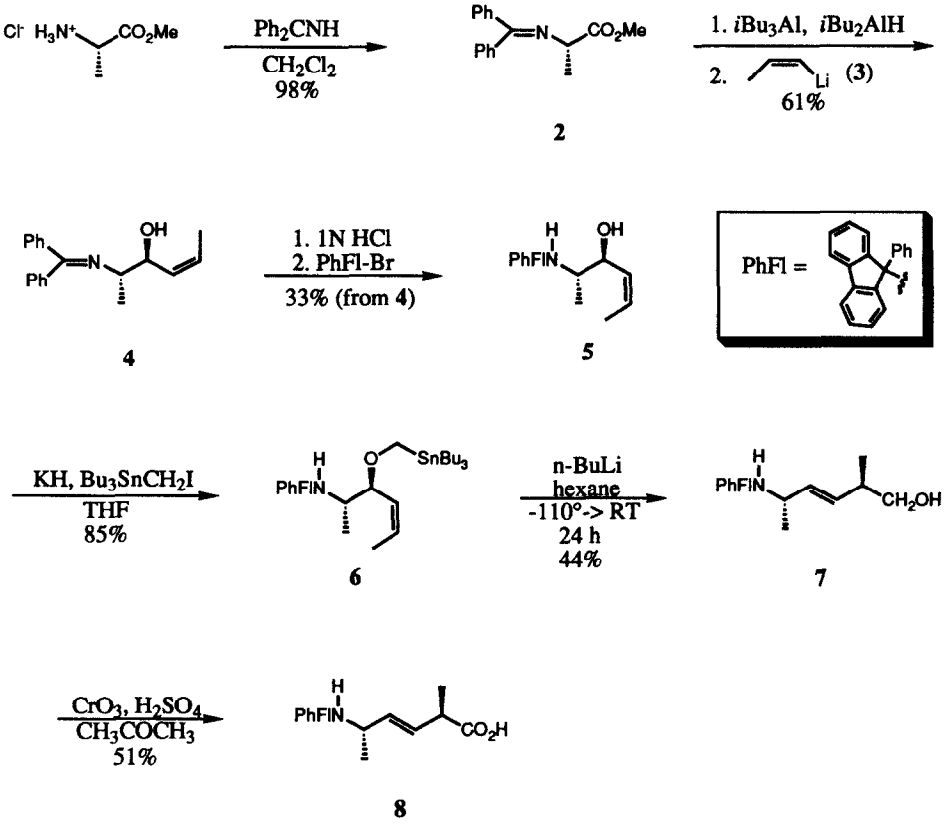
An appealing strategy toward the creation of therapeutic molecules with peptide-like activity is to modify the structure of a biologically active peptide to alleviate the principal problem associated with the use of peptides: the instability of amide bonds toward hydrolysis *in vivo*.[2] One of the oldest solutions to this problem is the replacement of a peptidic amide bond with an (*E*)-alkene, a close structural analogue of a *trans* secondary amide which is hydrolytically inert. Such (*E*)-alkene dipeptide isosteres (**1**) - first introduced by Sammes[3] and Cox[4] over a decade ago - have become increasingly popular in recent years, as evidenced by the numerous approaches toward the synthesis of these isosteres which have appeared.[3-6] The most attractive of these approaches has been the [2,3]-Wittig rearrangement reported by Liskamp[6] in which the regiochemistry of the alkene and the oxygenation of the incipient C-terminus are installed in one operation. The one drawback to this approach was the lack of stereocontrol which limited its application to "Gly-Xxx" and "Xxx-Gly" dipeptides. Herein we report a solution to the problem in the form of a concise synthesis of the (*E*)-alkene isostere of L-Ala-L-Ala (**1**, R^1=R^2=CH_3) from L-alanine methyl ester in which the [2,3]-Wittig reaction is used to establish the new stereogenic center of the dipeptide analogue in stereocontrolled fashion.[7]



1 *threo*

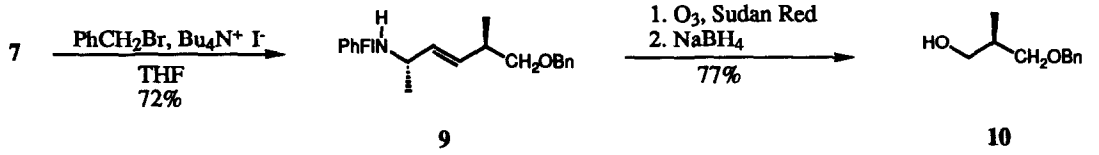
In order to produce the new stereogenic center with the proper configuration, it was necessary to obtain a *threo* β–amino alcohol for the [2,3]-Wittig rearrangement. The best method for obtaining them from amino acids in high diastereomeric excess is that of Polt,[8] which begins with the protection of the alanine nitrogen (Scheme 1) as a benzophenone Schiff base(**2**)[9] to allow chelation-controlled reduction and addition of the intended nucleophile, (*Z*)-1-lithiopropene (**3**). The desired *threo* β–amino alcohol **4** was obtained in 61% yield as a 7:1 mixture with its *erythro* isomer.[10] The sensitivity of the Schiff base necessitated reprotection with the 9-phenylfluorenyl group[11] to afford **5** free of diastereomeric impurities after chromatography. The [2,3]-Wittig rearrangement was accomplished using Still's modification[12] by forming the tributylstannylmethyl ether **6** in 85% yield followed by transmetallation and subsequent rearrangement in hexane to afford the homoallylic alcohol **7** in 44% yield as a single diastereomer. Like Liskamp and Bol, we found THF to be an inferior solvent

for this reaction; however, we did not observe any [1,2] rearrangement product in THF but simply a sharp decrease in the yield of the [2,3] product. The synthesis of the dipeptide isostere was completed by oxidation to the carboxylic acid **8** in 51% yield using Jones's reagent .[13]



Scheme 1. Synthesis of the dipeptide isostere **8** from L-alanine methyl ester

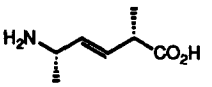
The choice of a (*Z*)-alkene as a precursor to the [2,3]-Wittig rearrangement was based on the findings of Midland,[14] in which a system closely related to **5** was shown to undergo [2,3]-Wittig rearrangement to afford a product with stereochemistry analogous to that of **7** free of diastereomeric impurities. In contrast, when an (*E*)-olefin was used in Midland's system a mixture of two products was obtained, neither of which corresponded to the stereochemistry of **7**. This latter finding was closely in accord with the results of Liskamp. The precedent of Midland also suggests that the new stereogenic center obtained via [2,3]-Wittig rearrangement should possess an (*R*) configuration as shown in Scheme 1. Proof of the stereochemistry was obtained (Scheme 2) by conversion of the intermediate **7** to the known benzylated diol **10**.[15,5t] Thus, **7** was converted to the corresponding ether **9** in 72% yield and subjected to ozonolysis and reduction with borohydride to afford the desired alcohol **10**. The optical rotation of **10** matched that of the expected (*R*) isomer ($[\alpha]_D$ +17.2°, c 0.5).[5t]



9 **10**

Scheme 2. Determination of the stereochemistry of **7** via correlation

We believe that this methodology should prove broadly applicable to the synthesis of isosteres of L-, L-dipeptides. Current efforts are underway to improve the overall yield of the synthesis and to extend this methodology to the stereocomplementary synthesis of isosteres of dipeptides containing D-amino acids (e.g., **11**).



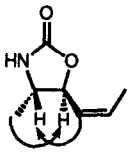
11

References and Notes

1. This work was presented at the Keystone Symposium on "Prospects and Progress in Drug Design Based on Peptides and Proteins", March 8-14, 1993 in Taos, NM. An abstract of this work has appeared in print: Lipton, M.; Koscho, M. *J. Cell Biochem.* **1993**, Supp. 17C, 217.
2. Spatola, A.F. *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B., Ed. Marcel Dekker: New York, 1983; Vol. 7, pp. 267-357.
3. Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. *J. Chem. Soc. Chem. Comm.* **1980**, 234-235; *Ibid., J. Chem.. Soc. Perkin I*, **1982**, 307-314.
4. Cox, M.T.; Heaton, D.W.; Horbury, J. *J. Chem. Soc. Chem. Comm.* **1980**, 799-800; Cox, M.T.; Gormley, J.J; Hayward, C.F.; Petter, N.N. *Ibid.* **1980**, 800-802.
5. (a) Johnson, R.L. *J. Med. Chem.* **1984**, *27*, 1351-1354; Miles, N.J.; (b) Sammes, P.G.; Kennewell, P.D.; Westwood, R. *J. Chem. Soc. Perkin Trans. I* **1985**, 2299-2305; (c) Hanson, G.J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399-5401; (d) Allan, R.D.; Dickenson, H.W.; Johnston, G.A.R.; Kazlauskas, R.; Tran, H.W. *Aust. J. Chem.* **1985**, *38*, 1651-1656; (e) Spaltenstein, A.; Carpino, P.A.; Miyake, F.; Hopkins, P.B. *Tetrahedron Lett.* **1986**, *27*, 2095-2098; (f) *Ibid., J. Org. Chem.* **1987**, *52*, 3759-3766; (g) Shue, Y.-K.; Carrera Jr.,G.M.; Nadzan, A.M. *Tetrahedron Lett.* **1987**, *28*, 3225-3228; (h) Shue, Y.-K.; Tufano, M.D.; Nadzan, A.M., *ibid.*, **1988**, *29*, 4041-4044; (i) Precigoux, G.; Benholouche, M.; Geoffre, S.; Hospital, M. *Peptides 1988*, Jung, G., Bayer, E., Eds.Walter de Gruyter: Berlin & New York, 1989; pp. 525; (j) Tourwé, D.; de Cock, E.; van Marsenille, M.; van der Auwera, L.; van Binst, G.; Viville, R.; Degelaen, J.; Scarso, A. *Peptides 1988*, Jung, G., Bayer, E., Eds.Walter de Gruyter: Berlin & New York, 1989; pp. 562; (k) Lehman de Gaeta, L.S.; Czarnicki, M. *J. Org. Chem.* **1989**, *54*, 4004-4005; (l) Whitesell, J.K.; Lawrence, R.M. *Chirality* **1989**, *1*, 89-91; (m) Elseviers, M.; Jaspers, H.; Delaet, N.; De Vadder, S.; Depermans, H.; Tourwé, D.; van Binst, G. *Peptides: Chemistry, Structure, and Biology*, Rivier, J.E.; Marshall, G.R., Eds.ESCOM: Leiden, 1990; pp. 198; (n) Kaltenbronn, J.S.; Hudspeth, J.P.; Lunney, E.A.; Michniewicz, B.M.; Nicolaides, E.D.; Repine, J.T.; Roark, W.H.; Stier,

M.A.; Tinney, F.J.; Woo, P.K.W.; Essenbrug, A.D. *J. Med. Chem.* **1990**, *33*, 838-845; (o) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 801-803; (p) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297-7300; (q) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301-7304; (r) Thompson, W.J.; Tucker, T.J.; Schwering, J.E.; Barnes, J.L. *Tetrahedron Lett.* **1990**, *31*, 6819-6822; (s) Shue, Y.-K.; Carrera Jr., G.M.; Tufano, M.D.; Nadzan, A.M. *J. Org. Chem.* **1991**, *56*, 2107-2111; (t) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370-4382.

6. Bol, K.M.; Liskamp, R.M.J. *Tetrahedron Lett.* **1991**, *32*, 5401-5404; *Ibid., Tetrahedron* **1992**, *48*, 6425-6438.
7. During the preparation of this manuscript, the abstract of a related approach appeared: Bohnstedt, A.C.; Vara Prasad, J.V.N; Rich, D.H. *Abstracts of Papers*, 206th National Meeting of the American Chemical Society, Chicago, IL, August 21-26, 1993; American Chemical Society, Washington, DC, 1993; ORGN 304.
8. Polt, R.; Peterson, M. *Tetrahedron Lett.* **1990**, *31*, 4985-4986; Polt, R.;Peterson, M.A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469-5480.
9. O'Donnell, M.J.; Polt, R.L. *J. Org. Chem.* **1982**, *47*, 2663-2666.
10. All intermediates were characterized by ^{1}H-NMR, ^{13}C-NMR and CIMS. The identity of the major diastereomer of **4** was determined by deprotection and treatment with carbonyl diimidazole to give the cyclic oxazolidinone **12**. The NOE enhancements shown unambiguously identified **12** as the *trans*-substituted isomer. This finding was in accord with the results obtained by Polt.[9]



12

11. Lubell, W.D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236-239.
12. Still, W.C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927-1928; Still, W.C.; McDonald, III, J.H.; Collum, D.B.; Mitra, A. *Tetrahedron Lett.* **1979**, *20*, 593-594.
13. spectral data for **8**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ7.12–7.71 (13H, m), 5.21 (1H, dd, J=15.4, 7.6), 4.89 (1H, dd, J=15.4, 7.3), 3.3-3.6 (br. s, 2H), 2.70-2.91 (2H, m), 0.95 (3H, d, J=6.5), 0.94 (3H, d, J=7.7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ190.0, 150.0, 149.5, 145.4, 141.4, 140.6, 137.1, 128.8, 128.7, 128.6, 128.3, 128.1, 127.6, 127.5, 126.5, 126.4, 125.5, 120.5, 120.3, 73.7, 52.2, 42.9, 23.9, 17.3
14. Midland, M.M.; Kwon, Y.C. *Tetrahedron Lett.* **1985**, *26*, 5013-5016.
15. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888; Marshall, J.A.; Trometer, J.D.; Cleary, D.J. *Tetrahedron* **1989**, *45*, 391-402 and references therein; Marshall, J.A.; Blough, B.E. *J. Org. Chem.* **1990**, *55*, 1540-1547.