Pergamon

Tetrahedron Letters, Vol. 37, No. 10, pp. 1563-1566, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00091-3

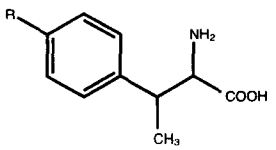
Asymmetric Synthesis of Optically Pure β-Isopropylphenylalanine: A New β-Branched Unusual Amino Acid

Subo Liao and Victor J. Hruby *

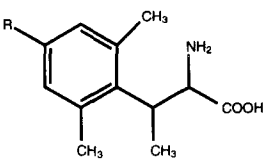
Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

Abstracts: All four optically pure isomers of a highly conformationally constrained unusual amino acid, β-isopropylphenylalanine, have been asymmetrically synthesized.

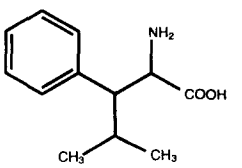
There is overwhelming evidence that the stereostructural properties of side chain groups of amino acid residues in bioactive peptides are often highly important in receptor-peptide recognition and in biological activity.[1] Topographical considerations are a major approach for the rational peptide design of peptide ligands to explore the side chain stereochemical requirements for binding to their receptors and for signal transduction.[2] This approach can be realized by incorporation of side chain constrained unusual amino acids into backbone-constrained polypeptide and non-peptide templates. Therefore, design and synthesis of unusual amino acids with specific conformationally constrained side chain groups are extremely important in the design of highly selective and potent peptide hormone and neurotransmitter analogues. β–Branched unusual amino acids are such a type of unusual amino acids, in which substitution of the diastereotopic β–hydrogens of many α–amino acids provides an approach to topographic control of peptide structure.[3] Incorporating β–branched unusual amino acids, such as β-methylphenylalanine, β-methyltyrosine (**I**) and β-methyl-2′,6′-dimethyltyrosine (**II**) into peptide hormones has produced highly selective and potent peptide analogues, and provided new insights



(**I**) R = H, OH



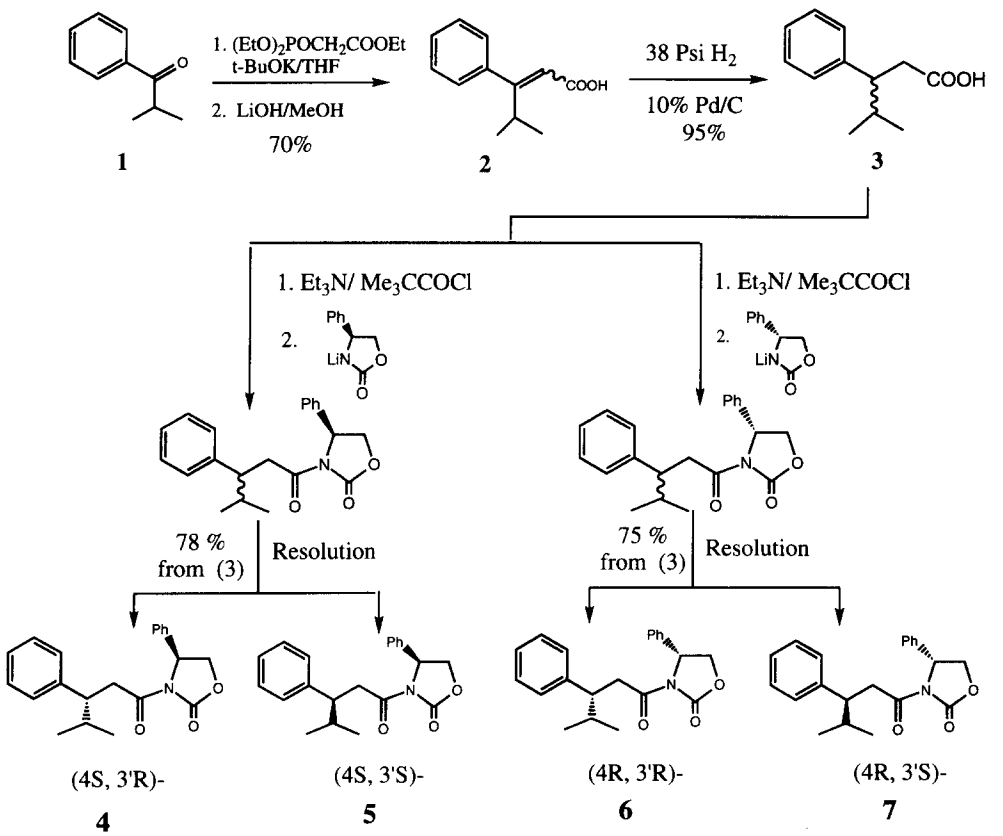
(**II**) R = H, OH



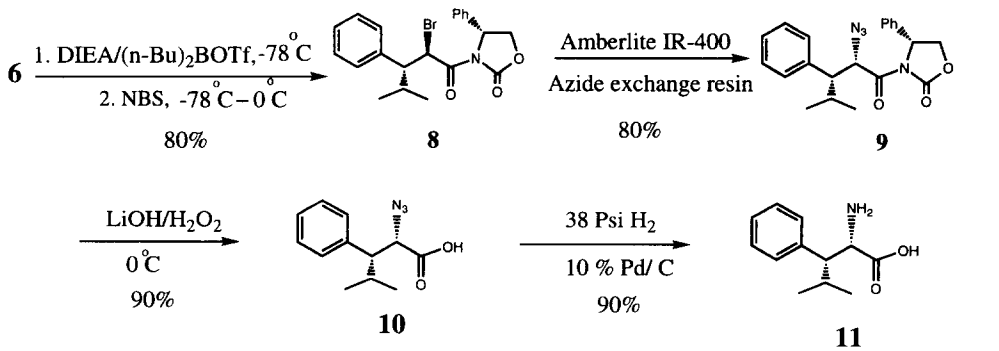
(**III**)

into the stereochemical requirements in peptide-receptor interactions.[4] In this communication, we wish to report the asymmetric synthesis of the first analogue in a new generation of β-branched unusual amino acids: β-isopropylphenylalanine (**III**). This generation of unusual amino acids is characterized by having a very bulky β-substituted isopropyl group, which simultaneously constrains both χ_1 and χ_2 torsional rotations to a small

Scheme 1



Scheme 2



(2S,3R)-β-Isopropylphenylalanine

range of torsional angles with much higher energy barriers than the corresponding β-methyl amino acid analogues.[5] Thus, topographic design of peptide ligands using these unusual amino acids will provide new and additional detailed information about the stereochemical requirements of the peptide ligand-receptor interactions.

After experiencing failures with several other asymmetric synthetic routes, we found that the approach illustrated in Schemes 1 and 2 led to the successful syntheses of all four diastereoisomers of β-isopropylphenylalanine. The synthesis started from commercially available isobutyrophenone **1**, which was transformed into a (Z,E)-mixture of the α,β-unsaturated acid **2** via a Wittig reaction in refluxing, followed by hydrolysis under basic conditions.[6] Hydrogenation of the mixture of the (Z) and (E)-α,β–unsaturated acid **2** gave racemic β-phenylisohexanoic acid **3**, which was coupled with the optically pure (4R)- or (4S)-4-phenyloxazolidinone, respectively, to yield the (4R)- or (4S)-4-phenyl-3-[3′-phenylisohexanyl)-2-oxazolidinones via the formation of the mixed anhydride with pivaloyl chloride (Scheme 1).[7] The resulting diastereoisomeric mixtures were resolved into four individual optical pure isomers through silica gel flash chromatography using EtOAc/Hexane mixtures as developing solvents.

The conversion of all four individual diastereoisomers of 4-phenyl-3-(3′-phenylisohexanyl)-2-oxazolidinone into the corresponding optically pure aminoacids is illustrated using (4R, 3′R)-4-phenyl-3-[3′-phenylisohexanyl)-2-oxazolidinone in Scheme 2. The bromination procedure was similar to that described by Evans and coworkers.[8] Azide **9** was prepared by displacement of the bromo group in **8** with azide exchange resin via an S_N2 mechanism.[3f] Then the chiral auxiliary was removed by hydrolysis under basic conditions to produce **10** (Scheme 2), and recovered for further use. Hydrogenolysis of the α-azide intermediate at 38 psi H_2 in the presence of 10% palladium/carbon catalyst and subsequent purification through ion-exchange column chromatography, gave the corresponding optically pure α-amino acids.[9]

The absolute configuration of intermediate (4R,2′R,3′R)-4-phenyl-3-[2′-bromo-3′-phenylisohexanyl)-2-oxazolidinones was determined by x-ray diffraction crystal structure determination.[10] Further conformational studies of these unusual amino acids are currently underway, as is incorporation of these unusual amino acids into peptide hormones and neurotransmitters.

Acknowledgment: The authors wish to acknowledge the financial support of grants from NIDA DA06284 and U.S. Public Health Service DK21085.

References and Notes

1. Hruby, V.J. *Life Sci.* **1983**, 31, 189-199.
2. (a) Hruby, V. J. *Biopolymers* **1993**, 1073-1082; (b) Toniolo, C. *Int. J. Peptide. Protein Res.* **1990**, 35, 287-300; (c) Hruby, V. J.; Al-Obeidi, F. and Kazmierski, W. *Biochem. J.* **1990**, 268, 249-262.
3. (a) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L. and Hruby, V. J. *Tetrahedron* **1992**, 48, 4733-4748; (b) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, 58, 766-770; (c) Nicolas, E.; Russell, K. C.; Knollenberg, J. and Hruby, V. J. *J. Org. Chem.* **1993**, 58, 7565-7571; (d) Jiao, D.; Russell, K.C. and Hruby, V. J. *Tetrahedron* **1993**, 49, 3511-3520; (e) Li, G.; Patel, D. and Hruby, V. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3057-3059; (f) Qian, X.; Russell, K. C.; Boteju, L. W. and Hruby, V. J. *Tetrahedron* **1995**, 51, 1033-1054; (g) Shapiro, G.; Buechler, D.; Marzi, M.; Schmidt, K. and Gomez-Lor, B. *J. Org. Chem.* **1995**, 60, 4978 -4979; (h) Burk, M.; Gross, M. F. and Martinez, J. P. *J. Am. Chem. Soc.* **1995**, 117, 9375-9376.

4. (a) Qian, X.; Kövér K. E.; Shenderovich, M. D.; Lou, B-S.; Misicka, A.; Zalewska, T.; Horvàth, R.; Davis, P.; Bilsky, E. J.; Porreca, F.; Yamamura, H. I. and Hruby, V. J. *J. Med. Chem.* **1994**, 37, 1746-1757; (b) Nikiforovich, G. V.; Prakash, O. M.; Gehrig, C. A. and Hruby, V. J. *Int. J. Peptide Protein Res.* **1993**, 41, 347-361; (c) Huang, Z.; He, Y-B.; Raynor, K.; Tallent, M.; Reisine, T. and Goodman, M. *J. Am. Chem. Soc.* **1992**, 9390-9401; (d) Toth, G.; Russell, K. C.; Landis, G.; Kramer, T. H.; Fang, L.; Knapp, R.; Davis, P.; Burks, T. F.; Yamamura, H. I. and Hruby, V .J. *J. Med.Chem.* **1992**, 35, 2383-2391, and references therein.
5. Liao, S.; Shenderovich, M. and Hruby, V.J. unpublished results.
6. The **2Z/2E** = 6:4 based on NMR spectra. The ^{1}H NMR($CDCl_3$) of some intermediate compounds follows: δ ppm **2Z:** 11.94(s, broad, 1H, -COOH), 7.34-7.19(m, 5H, aromatic protons), 5.75(s, 1H, -CH=), 4.16[m, 1H, -CH(CH3)$_2$], 1.09[d, J=7.0Hz, 6H, -CH(CH_3)$_2$]; **2E:** 10.88(s, broad, 1H, -COOH), 7.32-7.05(m, 5H, aromatic protons), 5.80(s, 1H, -CH=), 2.63[m, 1H, -CH(CH_3)$_2$], 1.05[(d, J=6.8 Hz, 6H, -CH(CH_3)$_2$]; **4**: 7.35-7.12(m, 10H, aromatic protons), 5.17(dd, J=8.6, 3.4Hz, 1H, oxazolidi-none PhCH-), 4.43(t, J=8.6Hz, 1H, oxazolidinone, -CH_2-*/proR*), 4.16(dd, J=8.6, 3.4Hz, 1H, oxazoli-dinone, -CH_2-*/proS*), 3.58(dd, J=16.5, 10.6Hz, 1H, -C_αH-*/proS*), 3.16(dd, J=16.5, 4.3Hz, 1H, -C_αH-*/proR*), 2.93(m, 1H, -C_βH-), 1.83[(m, 1H, -CH(CH_3)$_2$], 0.93(d, J=6.7Hz, 3H, -CH_3), 0.72(d, J=6.7Hz, 3H, -CH_3); **5**: 7.25-6.77(m, 10H, aromatic protons), 5.29(dd, J=8.7, 4.1Hz, 1H, oxazolidinone Ph-CH-), 4.56(t, 1H, J=8.7Hz, oxazolidinone, -CH_2-*/proR*), 4.07(dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -CH_2-*/proS*), 3.74(dd, J=15.7, 10Hz, 1H, -C_αH-*/ProS*), 3.13(dd, J=15.7, 5.2Hz, 1H, -C_αH-*/ProR*), 2.95(m, 1H, -C_βH-), 2.88[m, 1H, -CH(CH_3)$_2$], 0.96(d, J=6.7Hz, 3H, -CH_3), 0.74(d, J=6.7Hz, 3H, -CH_3).
7. Evans, D.A. and Weber, A. E. *J. Am. Chem. Soc.* **1986**, 108, 6757-6761.
8. (a) Evans, D. A.; Ellman, J. A. and Dorow, R. L. *Tetrahedron Lett.* **1987**, 28, 1123-1126; (b) Evans, D. A.; Britton, T.; Ellman, J. and Dorow, R. *J. Am. Chem. Soc.* **1990**, 112, 4011-4030.
9. a) Chiralplate® reverse phase silica gel impregnated with a chiral selector and Copper (II) ions (Machery-Nagel Co., FGR). The seperation of optical isomers is based on ligand exchange. Eluent: CH_3CN: CH_3OH :H_2O (4:1:1). The optical isomers of β-isopropylphenylalanine revealed single spots with Rf values of 0.55(2R,3S), 0.49(2R,3R), 0.74(2S,3R), 0.76(2S,2S); b) The ^{1}H NMR(D_2O) of all four optical isomers are: δ ppm (2S,3R): 7.25-7.08(m, 5H, -C_6H_5), 4.05(d, J=4.6Hz, 1H, -C_αH–), 2.52(dd, J=10.0, 4.6Hz, 1H, -C_βH–), 2.28(m, 1H, –CH(CH_3)$_2$], 1.02(d, J=6.4 Hz 3H, -CH_3), 0.54(d, J=6.4 Hz, 3H,-CH_3); (2S,3S): 7.26-7.05(m, 5H, -C_6H_5), 3.96(d, J=5.5 Hz,1H, -C_αH-), 2.81(dd, J=9.1, 5.5Hz, 1H,-C_βH-), 2.01[(m, 1H, -CH(CH_3)$_2$], 0.84(d, J=6.6 Hz, 3H, -CH_3), 0.63(d, J=6.6 Hz, 3H, -CH_3); (2R,3S): 7.25-7.08(m, 5H, -C_6H_5), 4.05(d, J=4.6Hz, 1H, -C_αH), 2.51(dd, J=10.0, 4.6Hz, 1H, -C_βH–), 2.24[m, 1H, –CH(CH_3)$_2$], 1.01(d, J=6.4Hz, 3H, -CH_3), 0.54(d, J=6.4Hz, 3H, -CH_3); (2R,3R): 7.27-7.09(m, 5H, -C_6H_5), 4.05(d, J=5.5Hz, 1H, -C_aH-), 2.85(dd, J=9.1, 5.5Hz, 1H,-C_βH-), 2.05[m, 1H, -CH(CH_3)$_2$], 0.88(d, J=6.6 Hz, 3H, -CH_3), 0.66(d, J=6.6 Hz, 3H, -CH_3); c) Due to the relative small coupling constant values between the α proton and β proton in the products, qauntitative description of the biased conformation needs more studies. For related NMR method to describe the conformational properties of β–branched aminoacids, please see Kövër, E. K.; Jiao, D.; Fang, S. and Hruby, V.J. *Magnetic Resonance In Chemistry* **1993**, 31, 1072-1076.
10. Liao, S.; Bruck, M. and Hruby, V.J. in preparation for publication.

(*Received in USA* 30 *November* 1995; *revised* 19 *December* 1995; *accepted* 3 *January* 1996)