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Asymmetric Synthesis of a Novel Phenylogous Amino Acid Mimicking an Extended Dipeptide

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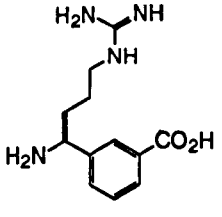
Abstract: Synthesis of an orthogonally protected form of phenylogous amino acid **1** which mimics an extended conformation of the dipeptide Arg–Gly was achieved. Key steps involve a diastereoselective addition of allylic organometallic reagents to chiral imine **2** and a palladium mediated carboalkoxylation of aryl bromide **5**.

Interleukin-2 (IL-2) is a 15.5 kDa cytokine responsible for the proliferation of activated T cells. It binds to a heterotrimeric receptor complex consisting of α, ß, and γ chains with picomolar affinity.[1] Antibodies against the IL-2Rα chain have proven clinically effective as immunosuppressive agents[1] and thus we have sought small molecules capable of blocking the IL-2–IL-2Rα interaction as potential orally active successors to the antibody drugs. The design of such agents is based on a combination of structural information obtained by X-ray crystallographic studies of IL-2[2,3] and site-directed mutagenesis[4] which identified a linear region comprising Lys^{35}, Arg^{38}, Phe^{42} and Lys^{43} as being critical for the binding of IL-2 to IL-2Rα. Molecular modeling experiments suggested that the pentapeptide Lys–Arg–Gly–Phe–Lys in an extended conformation could span the region from Lys^{35} to Lys^{43} and achieve good overlap of its side chains with the corresponding key residues of IL-2.

While such peptides are only weak IL-2 antagonists, incorporation of elements which promote the bioactive conformation would be expected to improve potency. In keeping with recent interest in the design of rigid spacers capable of promoting particular conformational preferences in flexible linear peptides[5], we perceived that the phenylogous arginine **1** incorporates the geometry of the extended dipeptide Arg–Gly as illustrated in figure 1. Below we report the synthesis of **10**, a protected form of **1**, which permits its convenient insertion into polypeptides.



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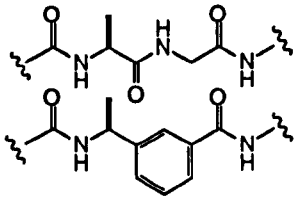
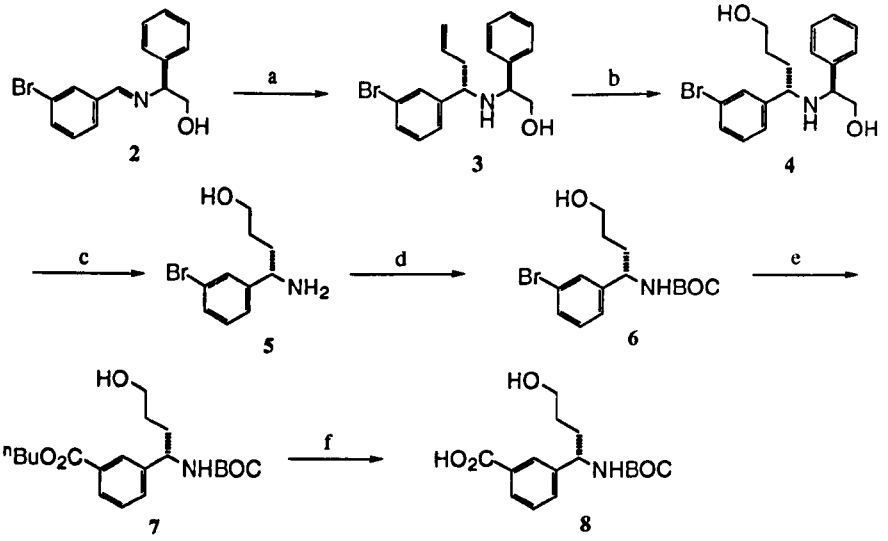


Figure 1. Comparison of an extended conformation of Ala–Gly with the corresponding dipeptide mimic

The synthesis of **10** relies on the diastereoselective addition of an allylic organometallic reagent[6] to a chiral imine[7] derived from 3-bromobenzaldehyde as shown in Scheme 1. The allyl group in this adduct serves as a masked amino acid side chain and the bromine serves as a functional handle that can be converted to the carboxyl group through a palladium mediated carboalkoxylation reaction.[8] We have selected phenylglycinol as the chiral auxiliary because it is readily available and gives good asymmetric induction.[7c,e] Addition of allylcerium dichloride to the the chiral imine **2** derived from S-(+)-phenylglycinol gave homoallylic amine **3** in 85–90% yield with excellent diastereoselectivity as reported.[7e] Hydroboration of **3** with borane-DMS in THF at -10 °C followed by oxidative workup gave primary alcohol **4** in 74 % yield together with 7% of the regioisomeric secondary alcohol. Oxidative cleavage of the chiral auxiliary with $Pb(OAc)_4$ gave the aminoalcohol **5**[9a] in 53% yield whose S absolute stereochemistry was confirmed by X-ray crystallography based on the anomalous scattering of the bromine atom and refinement of both enantiomers.[9b] Protection of the amino group with Boc_2O provided Boc-aminoalcohol **6** which is suitable for the carboalkoxylation reaction. Treatment of **6** with a catalytic amount of $Pd(Ph_3P)_2Cl_2$ in a mixture of n-butanol, DMF and Et_3N (4/3/3 by volume) at 80 °C under 40 psi of carbon monoxide gave the desired product **7** in 84% isolated yield.[10] Hydrolysis of **7** gave carboxylic acid **8** in 90% yield (Scheme 1).

Scheme 1

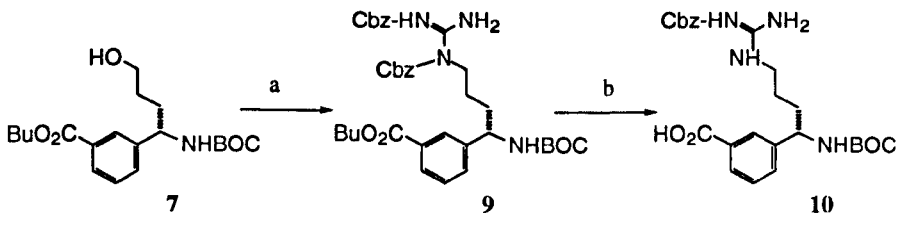


(a) Allylmegnisium bromide, $CeCl_3$, THF, -50°C, 85-90%; (b) BH_3-DMS, H_2O_2/NaOH, 74% (c) $Pb(OAc)_4$, then H_2O/HCl, 53%; (d) $(BOC)_2O$, Et_3N, THF, 95%; (e) n-BuOH, CO, Pd (0). DMF/Et_3N, 84%; (f) NaOH, EtOH/H_2O, 90%.

Compound **7** represents a versatile intermediate for the preparation of dipeptide mimics. In order to demonstrate the utility of **7** and to prepare the Arg-Gly mimic **10** required for the synthesis of IL-2 antagonists, we proceeded as shown in Scheme 2. Reaction of **7** with N,N-bis-Cbz-guanidine[11] under

Mitsunobu conditions gave differentially protected Arg-Gly mimic **9** in 90% yield.[12] The 8:1 ratio of enantiomers was determined by ^{19}F NMR analysis of the Mosher amide[13] derivative of **9**. Hydrolysis of **9** with lithium hydroxide in MeOH/THF/H_2O gave a 77% yield of benzoic acid **10** as a white solid with mp 113-115 °C (decomposition). Compound **10** constitutes a suitable protected form of Arg-Gly mimic **1** that can be used directly in peptide synthesis. The general methodology described above should be useful for preparation of other extended Xxx-Gly dipeptide mimics either derived directly from compound **7** or from **2** utilizing the broad array of organometallic reagents available for the stereoselective introduction of the Xxx side chain.

Scheme 2



7 **9** **10**

(a) DEAD, Ph_3P, N,N-BisCBZ-guanidine, 90%; (b) LiOH, MeOH/THF/H_2O, 79%;

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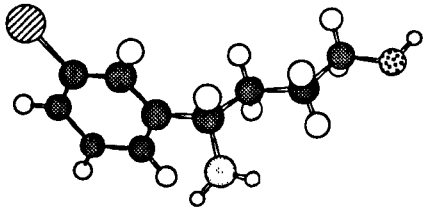
References and Notes

1. Waldmann, T. A. *Immunology Today* **1993**, *14*, 264–270.
2. Bazan, J. F. *Science* **1992**, *257*, 410–412.
3. McKay, D. B. *Science* **1992**, *257*, 412-413.
4. Sauvé, K.; Nachman, M.; Spence, C.; Bailon, P.; Campbell, E.; Tsien, W.-H.; Kondas J. A.; Hakimi, J.; Ju, G. *Proc. Nat Acad. Sci.* **1991**, *88*, 4636–4640.
5. (a) Giannis, A; Kolter, T. *Angew. Chem. Int. Engl.* **1993**, *32*, 1244–1267. (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; B. Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. *J. Med. Chem.* **1993**, *36*, 3039–3049. (c) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568–6571. (d) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901–1904. (e) McKinney, J. A.; Eppley, D. E.; Keenan, R. M. *Tetrahedron Lett.* **1994**, *35*, 5985–5988. (f) Roberts, J. C.; Pallai, P. V.; Rebek, J. *Tetrahedron Lett.* **1995**, *36*, 691–694. (g) Smith, A. M.; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. C.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672–10674.
6. For a recent review on the application of allylic organometallic compounds in stereoselective synthesis, see Yamamoto, Y; Asao, N. *Chem. Rev*. **1993**, *93*, 2207–2235.

7. For the use of chiral auxiliaries in the formation of chiral imines, see: (a) Yamamoto, Y.; Nishii, S.; Maruyama, Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778–7786. (b) Eleveld, E.; Hogeveen, H.; Schedde, E. *J. Org. Chem.* **1986**, *51*, 3635-3642. (c) Takahashi, H.; Chida, Y.; Yoshii, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071–2077. (d) Denmark, S.; Weber, T.; Piotrowski, D. *J. Am. Chem. Soc.* **1987**, *109*, 2224–2225. (e) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.*, **1991**, *56*, 1340-1344. (f) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883–5889. (g) Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong , T.-T. *J. Org. Chem.* **1994**, *59*, 914-921. (h) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi , A. *J. Org. Chem.* **1994**, *59*, 7766-7773.

8. a. Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318-3326. b. Davies, S.; D. Pyatt *Heterocycles* **1989**, *28*, 163

9. a. Compound **5** has the following properties: mp 76-78 °C; $[\alpha]_D$ = -20.91, (c = 0.82%, $CHCl_3$); ^{1}HNMR ($CDCl_3$, δ, ppm) 1.67 (m, 2H, CH_2-CH_2-CH_2), 1.70 (m, 1H), 1.86 (m, 1H), 2.41 (br, 3H, NH2 + OH), 3.67 (m, 2H, CH_2-CH_2-OH), 3.88 (m, 1H, NH_2-CH-), 7.20 (m, 2H), 7.37(m, 1H), 7.45 (s, 1H); IR (cm^{-1}) 3336, 3270, 1618; MS (FAB, M+1) 244; Analysis (%) calc. C 49.20, H5.78, N 5.74, Br 32.73, Found C 49.52, H 5.93, N 5.71, Br 32.30. X-ray structure of **5** is shown below:



3D drawing of **5**.

b. The final weighted R values of **5** for S configuration and its antipode were obtained and evaluated by Hamilton's test: Hamilton, W. C. *Acta Cryst.* **1965**,*18*, 502.

10. This procedure worked well in several cases. For example, 7-bromo-α-tetralone was converted to the 7-butoxycarbonyl-α-tetralone in 95% yield.

11. Dodd, D. S.; Kozikowski, A. *Tetrahedron Letters*, **1994**, *50*, 977-980

12. Compounds **8** and **9** gave following properties: **8**, mp 145-147 °C; $[\alpha]_D$ = -51.15 (MeOH, c = 0.31%); ^{1}HNMR (DMSO-d6, δ, ppm) 1.35 (S, 9H), 1.40 (m, 2H), 1.63 (m, 2H), 4.41 (s, 1H), 4.47 (m, 1H, NH-CH-), 7.41 (t, J = 7.7 Hz, 1H), 7.49 (s, 1H, NH), 7.50 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.89 (s, 1H), 12.96 (br, 1H, COOH); MS (M+H) 310; HRMS (M+H) calc. 310.1654, obsd. 310.1654; X-Ray structure. **9**, mp = 73.4-75 °C; [α]D = -13.2 ($CHCl_3$, c = 1.0%); ^{1}HNMR ($CDCl_3$, δ, ppm) 0.98 (t, J = 7.4 Hz, 3H) 1.40 (s, 9H), 1.46 (m, 2H), 1.66 (m, 2H), 1.75 (m, 2H), 3.99 (m, 2H), 4.31 (t, J = 6.7 Hz, 2H), 4.66 (s, 1H), 5.10 (s, 1H), 5.15, (q, 2H), 5.20 (s, 2H), 7.35 (m, 12H), 7.39 (s, 1H), 4.40 (d, J = 6.6 Hz, 1H), 7.89 (s, 1H), 7.91 (s, 1H); IR (cm^{-1}) 3377, 3346, 1718, 1678, 1523, 699; MS (FAB, M+H) 675; Analysis (%), calc. C 65.86, H 6.87, N 8.30, found C 65.65, H 6.82, N 8.25.

13. Dale, J.; Mosher H. *J. Am. Chem. Soc.* **1973**, *95*, 512; Sulivan, G.; Dale, J.; Mosher, H. *J. Org. Chem.* **1973**, *38*, 2143. Compound **9** was selectively deprotected with TFA/Et3SiH in methylene chloride to give a benzylamine which was converted to the Mosher amide by reaction with MTPA chloride. ^{19}F NMR spectra of the crude amide indicated an 8:1 ratio of diastereomers.

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