Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3651-3654, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00692-8

An Approach to Enantiomerically Pure Inverse γ-Turn Mimetics for Use in Solid-phase Synthesis

Kay Brickmann,[1] Peter Somfai*, and Jan Kihlberg*[1]

Organic Chemistry 2, Center for Chemistry and Chemical Engineering, The Lund Institute of Technology, Lund University, P.O. Box 124, S-221 00 Lund, Sweden

Abstract: An inverse γ-turn mimetic, having a morpholin-3-one ring as the key structural unit, was prepared in enantiomerically pure form in seven steps and 37% overall yield starting from 2(*R*)-[1'(*S*)-azido-2'-phenylethyl]oxirane (**3**). The mimetic has side-chains corresponding to a Phe-Ala-Ala tripeptide but the synthetic route was designed to allow incorporation also of other side chains. Molecular mechanics calculations revealed that the torsional angles of the second residue of the mimetic were effectively locked into an inverse γ-turn like conformation. © 1997 Elsevier Science Ltd.

Proteins and peptides display a multitude of important biomedicinal activities in fields as diverse as endocrinology, microbiology and immunology. However, direct use of peptides as drugs is often severely hampered by poor pharmacokinetic properties, such as low uptake on oral administration, rapid enzymatic degradation and facile excretion.[2] In addition, conformational flexibility may reduce the biological activity and receptor selectivity of peptides, whereas unfavourable solubility often imposes restrictions on their use under physiological conditions. To circumvent these problems large efforts have been devoted to the design and preparation of peptidomimetics, *i.e.* compounds which have structures different from those of peptides but still interact with a specific receptor.[3-9]

Turns are important secondary structural elements in proteins and mediate reversal of the overall direction of the polypeptide chain. In β- and γ-turns this reversal occurs over four and three amino acid residues, respectively, so that the C=O of the first residue is located close in space to the NH of the last residue enabling formation of a hydrogen bond between these residues. Turns are usually situated at the surface of proteins allowing the outwardly projecting side chains to mediate important biological functions such as receptor binding, antibody recognition and posttranslational modification.[10] Structural studies have also revealed the presence of both β- and γ-turns in several small peptide hormones of pharmacological importance such as somatostatin,[10] oxytocin,[11-14] vasopressin[15-17] and LHRH.[18,19] The β-turn is the most common form of turn found in peptides and proteins and substantial interest has therefore been directed towards synthesis of β-turn mimetics (cf. 4,6,8,20 for leading references). The related γ- and inverse γ-turns,

which are defined by the torsional angles of the second residue in the turn,[10,21] have attracted less attention and only a few approaches to γ-turn mimetics have been described.[22-24] As the first part of a project directed towards development of general syntheses of turn mimetics we now report the design and synthesis of the inverse γ-turn mimetic **1**. In **1** the amide bond between residues 1 and 2 in the turn has been replaced by a methylene ether isostere simultaneously with ensuring the close spatial location of residues 1 and 3 through a covalent methylene bridge (Figure 1). Molecular mechanics calculations revealed that this backbone to backbone linkage, which gives a six-membered morpholin-3-one ring, effectively restricts the torsional angles of the second residue to values close to those of an inverse γ-turn.

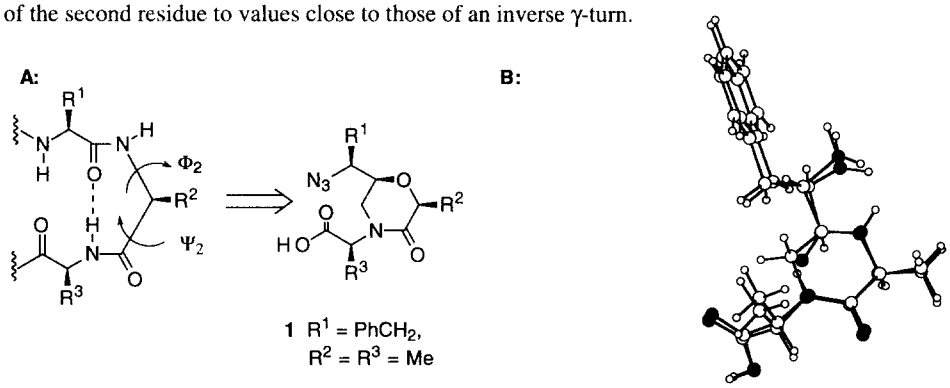
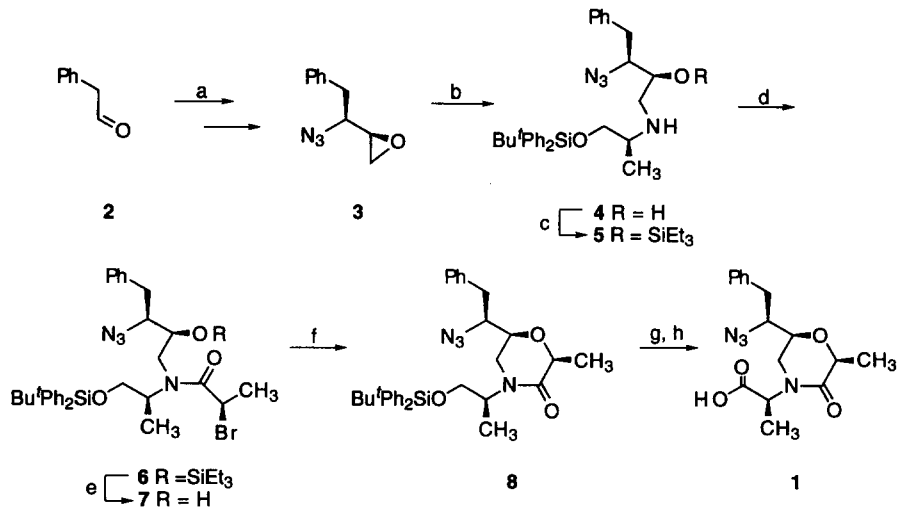


Figure 1. A: A schematic inverse γ-turn and the mimetic **1**. **B:** A superimposition of a Phe-Ala-Ala tripeptide oriented as an inverse γ-turn (Φ = -57°, Ψ = 32°) and the mimetic **1**. Compound **1** was energy minimized by molecular mechanics calculations using the MM3 92 program and then superimposed on the tripeptide using the MacMimic 3 program.[25]

Enantiomerically pure 2(*R*)-[1'(*S*)-azido-2'-phenylethyl]oxirane (**3**), prepared from commercially available phenylacetaldehyde (**2**, 46% over 7 steps) according to the literature,[26,27] was used as starting material in the synthesis of the mimetic **1** (Scheme 1). The azido group in **3** serves as a precursor of the α-amino group of the first residue in the turn. Regioselective, nucleophilic opening at the primary position[28] of the epoxide **3** was achieved with (*S*)-(+)-2-amino-1-propanol, protected as the *tert*-butyldiphenylsilyl ether, in refluxing EtOH to give the aminoalcohol **4** (71%). Opening of the epoxide could also be performed with unprotected (*S*)-(+)-2-amino-1-propanol but in a somewhat lower yield (60%). In order to allow acylation of the amino group in **4** protection of the secondary hydroxyl group was found to be essential. This was achieved by silylation with triethylsilyl chloride (→ **5**) and acylation with (*R*)-(+)-2-bromopropionic acid was then effected using diisopropylcarbodiimide to give **6** (81% over two steps). 1-Hydroxybenzotriazole (HOBt) is commonly used to suppress razemization in synthesis of peptides,[29] but the presence of HOBt during the preparation of **6** resulted in considerable deprotection of the secondary hydroxyl group of **5** thereby lowering the yield of **6**. Selective, acid catalysed deprotection[30] of the secondary hydroxyl group in **6** gave the alcohol **7** which, on conversion into the corresponding alkoxide, underwent intramolecular ring closure[31] to give the oxa lactam **8** as a single diastereomer (86%). Elimination was found to be a competing side-reaction in the formation of **8** under various conditions, but could be completely avoided when alkoxide formation was performed with neat KH in a mixture of THF and DMF at 0 °C. Finally, deprotection of the primary hydroxyl function in **8** with TBAF (quantitative) and subsequent oxidation to the carboxylic acid stage with the $RuCl_3$-$NaIO_4$ biphasic system of Sharpless[32] gave the desired inverse γ-turn mimetic **1**.[33]



Scheme 1. a) 7 steps.[26,27] b) (*S*)-2-amino-1-*tert*-butyldiphenylsilyloxypropane (1.0 eq), EtOH, reflux, 72 h; 71%. c) Et_3SiCl (2.2 eq), imidazole (2.3 eq), CH_2Cl_2, 0 °C → room temp., 26 h; 90%. d) (*R*)-(+)-2-bromopropionic acid (4.0 eq), diisopropylcarbodiimide (4.0 eq), CH_2Cl_2, 0 °C, 3 h; 90%. e) 1 M aq. HCl:THF 3:2, room temp. → 40 °C, 24 h; 86%. f) KH (1.3 eq), THF:DMF 3:1, 0 °C, 1 h; 86%. g) TBAF (1.1 eq), THF, room temp., 2 h; 100%. h) $NaIO_4$ (3 eq), $[RuCl_3(H_2O)_1]$ cat., H_2O:CCl_4:CH_3CN 3:2:2, room temp., 2 h; 86%.

The synthetic approach described in the present paper yielded the enantiomerically pure, inverse γ-turn mimetic **1** in seven steps starting from **3** with an overall yield of 37%. In contrast, previous γ-turn mimetics have been obtained without stereocontrol at the second residue of the turn, and even though the diastereomers were separated their configuration was not assigned.[22,23] Variation of the building blocks phenylacetaldehyde (**2**), (*S*)-(+)-2-amino-1-propanol, and (*R*)-(+)-2-bromopropionic acid employed in the synthesis of **1** should allow introduction also of other side chains into the mimetic. The carboxyl group of the mimetic may be linked to a peptide by standard methodology and, after reduction of the azido group, further elongation at the *N*-terminus of the mimetic should be possible, thus allowing use in solid-phase synthesis. Such further development, as well as incorporation of the resulting inverse γ-turn mimetics in biomedicinally active peptides, is now under progress in our laboratories.

Acknowledgements. This work was funded by grants from the Swedish Natural Science Research Council, the Swedish National Board for Industrial and Technical Development and the Swedish Medical Research Council.

REFERENCES AND NOTES

1. Present address: Organic Chemistry, Umeå University, S-901 87 Umeå, Sweden.
2. Plattner, J. J.; Norbeck, D. W. Obstacles to drug development from peptide leads. In *Drug discovery technologies;* Clark, C. R.; Moos, W. R., Eds.; Ellis Harwood Ltd.-Halstead Press: Chichester, England, 1989; pp. 92-126.
3. Spatola, A. P. Peptide backbone modifications: A structure activity analysis of peptides containing amide bond surrogates, conformational constraints, and related backbone replacements. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins;* Weinstein, B., Ed.; Marcel Dekker, Inc.: New York & Basel, 1983; Vol. 7; pp. 267-357.

4. Hölzemann, G. *Kontakte (Darmstadt)* **1991**, 3-12, 55-63.
5. Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; 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. E. *J. Med. Chem* . **1993**, *36*, 3039-3049.
6. Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244-1267.
7. Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547-3558.
8. Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1-19.
9. Rees, D. C. *Curr. Med. Chem.* **1994**, *1*, 145-158.
10. Rose, G. D.; Gierasch, L. M.; Smith, J. A. Turns in peptides and proteins. In *Advances in Protein Chemistry;* Anfinsen, C. B.; Edsall, J. T.; Richards, F. M., Eds.; Academic Press: Orlando, Florida, 1985; Vol. 37; pp. 1-109.
11. Wood, S. P.; Tickle, I. J.; Treharne, A. M.; Pitts, J. E.; Mascarenhas, Y.; Li, J. Y.; Husain, J.; Cooper, S.; Blundell, T. L.; Hruby, V. J.; Buku, A.; Fischman, A. J.; Wyssbrod, H. R. *Science* **1986**, *232*, 633-636.
12. Husain, J.; Blundell, T. L.; Cooper, S.; Pitts, J. E.; Tickle, I. J.; Wood, S. P.; Hruby, V. J.; Buku, A.; Fischman, A. J.; Wyssbrod, H. R.; Mascarenhas, Y. *Phil. Trans. R. Soc. Lond. B* **1990**, *327*, 625-654.
13. Lippens, G.; Hallenga, K.; Van Belle, D.; Wodak, S. J.; Nirmala, N. R.; Hill, P.; Russell, K. C.; Smith, D. D.; Hruby, V. J. *Biochemistry* **1993**, *32*, 9423-9434.
14. Rose, J. P.; Wu, C.-K.; Hsiao, C.-D.; Breslow, E.; Wang, B.-C. *Nature Struct. Biol.* **1996**, *3*, 163-169.
15. Langs, D. A.; Smith, G. D.; Stezowski, J. J.; Hughes, R. E. *Science* **1986**, *232*, 1240-1242.
16. Kihlberg, J.; Åhman, J.; Walse, B.; Drakenberg, T.; Nilsson, A.; Söderberg-Ahlm, C.; Bengtsson, B.; Olsson, H. *J. Med. Chem.* **1995**, *38*, 161-169.
17. Wang, J.; Breslow, E.; Sykes, B. D. *J. Biol. Chem.* **1996**, *271*, 31354-31359.
18. Nikiforovich, G. V.; Marshall, G. R. *Int. J. Peptide Protein Res.* **1993**, *42*, 181-193.
19. Guarnieri, F.; Weinstein, H. *J. Am. Chem. Soc.* **1996**, *118*, 5580-5589.
20. Slomczynska, U.; Chalmers, D. K.; Cornille, F.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Org. Chem.* **1996**, *61*, 1198-1204.
21. The torsional angles for the second residue differentiates between a γ-turn (Φ = 70 to 85°, Ψ = -60 to -70°) and an inverse γ-turn (Φ = -70 to -85°, Ψ = 60 to 70°), cf. reference 10. An open turn has been used for a situation in which no hydrogen bond exists and the Φ,Ψ-angles are then within 30° of the cited ones.
22. Newlander, K. A.; Callahan, J. F.; Moore, M. L.; Tomaszek Jr., T. A.; Huffman, W. F. *J. Med. Chem.* **1993**, *36*, 2321-2331.
23. Callahan, J. F.; Newlander, K. A.; Burgess, J. L.; Eggleston, D. S.; Nichols, A.; Wong, A.; Huffman, W. F. *Tetrahedron* **1993**, *49*, 3479-3488.
24. Curran, T. P.; Chandler, N. M.; Kennedy, R. J.; Keaney, M. T. *Tetrahedron Lett.* **1996**, *37*, 1933-1936.
25. InStar Software AB, IDEON Research Park, S-223 70 Lund, Sweden.
26. Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. J. *J. Chem. Soc., Chem. Commun.* **1992**, 273-274.
27. Bennett, F.; Girijavallabhan, V. M.; Patel, N. *J. Chem. Soc., Chem. Commun.* **1993**, 737-738.
28. Barrish, J. C.; Gordon, E.; Alam, M.; Lin, P.-F.; Bisacchi, G. S.; Chen, P.; Cheng, P. T. W.; Fritz, A. W.; Greytok, J. A.; Hermsmeier, M. A.; Humphreys, W. G.; Lis, K. A.; Marella, M. A.; Merchant, Z.; Mitt, T.; Morrison, R. A.; Obermeier, M. T.; Pluscec, J.; Skoog, M.; Slusarchyk, W. A.; Spergel, S. H.; Stevenson, J. M.; Sun, C.-q.; Sundeen, J. E.; Taunk, P.; Tino, J. A.; Warrack, B. M.; Colonno, R. J.; Zahler, R. *J. Med. Chem.* **1994**, *37*, 1758-1768.
29. König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788-798.
30. Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031-1069.
31. TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418-422.
32. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
33. Data for (*2S,6S*)-6-[1'(S)-Azido-2'-phenylethyl]-2-methyl-4-[1"(S)-methylcarboxymethyl]morpholin-3-one (**1**): $[\alpha]^{20}_D$ -42° (*c* 0.43, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ = 7.26 ppm): δ 7.65 (br.s, COOH), 7.21-7.36 (m, Ph), 5.13 (q, J 7.4 Hz, H-1"), 4.25 (q, J 6.8 Hz, H-2), 3.80 (ddd, J 10.7, 3.2 and 3.2 Hz, H-6), 3.63 (dd, J 10.9 and 10.9 Hz, H-5_{ax}), 3.45 (ddd, J 7.9, 7.0 and 3.4 Hz, H-1'), 3.12 (dd, J 11.3 and 2.7 Hz, H-5_{eq}), 3.06 (AB-signal, J 13.7 and 6.9 Hz, H-2'A), 3.02 (AB-signal, J 13.7 and 8.0 Hz, H-2'B), 1.52 (d, J 6.8 Hz, 2-CH_3), 1.46 (d, J 7.5 Hz, 1"-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ = 77.0 ppm): δ 175.0, 170.5, 136.5, 129.2, 128.9, 127.2, 74.6, 73.3, 62.9, 51.6, 45.4, 36.2, 18.2, 13.7. COSY (400 MHz) and NOESY (500 MHz) spectroscopy was used to assign the proton resonances in the ^1H NMR spectrum of **1** and to confirm the configuration of the six-membered ring.

(*Received in UK* 2 *April* 1997; *accepted* 10 *April* 1997)