Pergamon

Tetrahedron Letters 40 (1999) 477–478

TETRAHEDRON LETTERS

Synthesis and Structure of a Hydrophilic β-Turn Mimetic

Armin Geyer,* Dirk Bockelmann, Kerstin Weissenbach, and Helmut Fischer

Fakultät für Chemie, Universität Konstanz, D-78457 Konstanz, Germany

Received 14 September 1998; revised 9 November 1998; accepted 10 November 1998

Abstract: D-Glucurono-3,6-lactone (**1a**) and L-cysteine form the thiazolidine lactam **2a** in a stereoselective and quantitative reaction. Condensation of 5-azido-5-deoxy-D-glucurono-3,6-lactone (**1b**) with L-cysteine methyl ester followed by the reduction of the azido group yields the rigid β-turn mimetic **2d** in a minimum of reaction steps.

The structure-activity relationships of many biological processes are studied with conformationally restricted peptides [1]. Dipeptide mimetics are either rigid substitutes for secondary structural elements or they bear pharmacophoric groups themselves [2]. Bicyclic thiazolidine lactams belong to the former as they stabilize turn structures in peptides. Several analogues of BTD (β-turn dipeptide) [3] have been described in the literature [4]. Basing on the synthesis of penicilline V [5], cysteine and the side chain formyl group of a second amino acid form a thiazolidine which is then acylated in an intramolecular reaction. These turn mimetics require multistep syntheses; without additional functional groups to mimic amino acid side chains, they are only proline analogues. We describe the stereoselective two-step synthesis of a new thiazolidine lactam dipeptide. With three hydroxyl substituents it is soluble in water and can be further functionalized.

D-Glucurono-3,6-lactone condensates with L-cysteine in the solvent mixture water/pyridine (4:1) quantitatively to the thiazolidine lactam **2a**. Intermediate steps of the reaction were investigated by NMR spectroscopy. Both epimeric thiohemiacetals form rapidly, they are in equilibrium with the two epimeric thiazolidines [6]. The intramolecular aminolysis of the γ-lactone starts with the addition of pyridine at room temperature, this second ring closure is fast

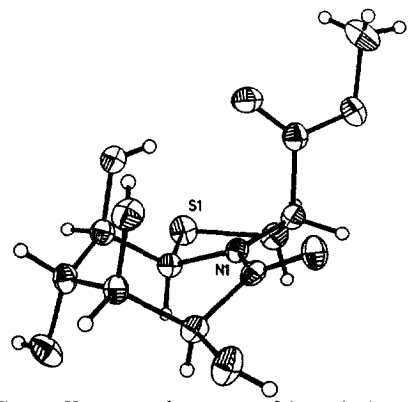
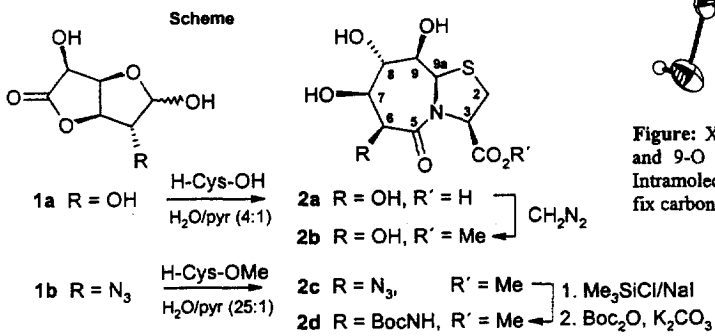


Figure: X-ray crystal structure of **1a**. 7-O, 8-O, and 9-O show axial orientation at the 7-ring. Intramolecular hydrogen bonds from 7-O via 9-O fix carbonyl group of the methyl ester.

Scheme



0040-4039/99/$ - see front matter
PII: S0040-4039(98)02445-9

at 90°C. 6-H and 9a-H appear as singlets and show an intense cross signal in the ROESY spectrum, proving the *R*-configuration at 9a-C. The methyl ester was formed with diazomethane and crystals of **2b** were obtained (Fig.) [7]. Tosylation or triflate activation of **2b** are selective at 6-O but substitution reactions with nitrogen nucleophiles were not successful at this position. Nitrogen was therefore incorporated as an azido group before the formation of the thiazolidine lactam. The easily available 5-azido-5-deoxy-D-glucurono-3,6-lactone (**1b**) [8] condensates with one equivalent of the hydrochloride of L-cysteine methyl ester in the solvent mixture water/pyridine (25:1) to the bicyclic compound **2c**. Again, only *R*-configuration at 9a-C is observed. Also the α,β-unsaturated compound forms but it can be easily separated due to its low solubility. The reduction of the azido group with trimethylsilyliodide [9], followed by the introduction of the Boc-protecting group, yields the reverse turn mimetic **2d** in a 30 % overall yield after column chromatography [10]. This building block mimics sequences like Ser-Pro or Thr-Cys. Counting the bonds from the amino terminus along the seven-membered ring to the C-terminus, **2d** is also the polyhydroxy analogue of a tripeptide sequence and therefore a so-called sugar amino acid [11].

Bicyclic thiazolidine lactams induce reverse turns in peptides [3,12]. BTD fixes the torsions $\psi_{(i+1)}$ and $\phi_{(i+2)}$ of a reverse turn to the values of –157° and –66° [6]. 169° (O6-C6-C5-N4) and –88° (C5-N4-C3-CO) were found for **2b** (Fig.) and ^3J coupling constants and intramolecular NOE buildup rates indicate a similar conformation for **2d** in water. BTD was incorporated in numerous peptides and even in proteins [13]. **2d** is easier accessible than BTD, it is more hydrophilic and offers functional groups for further derivatisation. The protection of secondary alcohols is not required during peptide synthesis [11].

References and Notes:

[1] H. Kessler, B. Diefenbach, D. Finsinger, A. Geyer, M. Gurrath, S. L. Goodman, G. Hölzemann, R. Haubner, A. Jonczyk, G. Müller, E. Graf v. Roedern, J. Wermuth, *Letters in Peptide Science* **1995**, *2*, 155-160.

[2] C. Toniolo, *Int. J. Peptide Protein Res. J.* **1990**, *35*, 287-300; R. Hirschmann, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1287-1301; J. Gante, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699-1720.

[3] U. Nagai, K. Sato, *Tetrahedron Lett.* **1985**, *26*, 647-650; U. Nagai, K. Sato, R. Nakamura, R. Kato, *Tetrahedron* **1993**, *49*, 3577-3592.

[4] N. L. Subasinghe, R. J. Bontms, E. McIntee, R. K. Mishra, R. L. Johnson, *J. Med. Chem.* **1993**, *36*, 2356-2361; M. A. Siddiqui, P. Preville, M. Tarazi, S. E. Warder, P. Eby, E. Gorseth, K. Puumala, J. DiMaio, *Tetrahedron Lett.* **1997**, *38*, 8807-8810; *J. Med. Chem.* **1997**, *40*, 3594-3600; Y. Takeuchi, G. R. Marshall, *J. Am. Chem. Soc.* **1998**, *120*, 5363-5372.

[5] J. C. Sheehan, K.-R. Henery-Logan, *J. Am. Chem. Soc.* **1959**, *81*, 3089-3094.

[6] CAS 96: 143262e; Jpn. Kokai Tokkyo Koho JP 81,166,189 (Cl. C07D417/06)

[7] X-ray structural analysis of **1b** (K. Weissenbach, H. Fischer): $C_{10}H_{15}NO_7S$, crystals from water; monocline, space group $P2_1$, a = 6.928(3) Å, b = 8.165(3) Å; c = 10.908(4) Å, β= 102.01(4)°; cell volume = 7603.5(4) Å^3; all hydrogen atoms were found. The structure was deposited at the CCDC, No 102538.

[8] T. M. Krülle, B. Davis, H. Ardron, D. D. Long, N. A. Hindle, C. Smith, D. Brown, A. L. Lane, D. J. Watkin, D. G. Marquess, G. W. J. Fleet, *Chem. Commun.* **1996**, 1271-1272.

[9] A. Kamal, N. V. Rao, E. Laxman, *Tetrahedron Lett.* **1997**, *38*, 6945-6948.

[10] **2**: colourless solid, mp. 114°C, $[\alpha]_D^{20}$ = -35° (c=0.1, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-$_{d6}$): δ = 1.37 (s, 9H, tBu), 3.29 (m, 2H, 2-H), 3.55 (dd, $^3J_{9,9\text{-OH}}$ = 11.6, $^3J_{9,8}$ = 3.7, 1H, 9-H), 3.62 (s, 3H, OMe), 3.77 (t, $^3J_{7,7\text{-OH}}$ = 4.5, $^3J_{7,6}$ = 4.7, 1H, 7-H), 3.82 (m, $^3J_{8,8\text{-OH}}$ = 4.0, $^3J_{8,7}$ = 4.7, 1H, 8-H), 4.13 (d, $^3J_{9\text{-OH},9}$ = 11.6, 1H, 9-OH), 4.69 (m, 1H, 3-H), 4.77 (d, $^3J_{6,\text{NH}}$ = 9.0, 1H, 6-H), 5.32 (d, $^3J_{7\text{-OH},7}$ = 4.5, 1H, 7-OH), 5.45 (s, 1H, 9a-H), 5.66 (d, $^3J_{8\text{-OH},8}$ = 4.0, 1H, 8-OH), 6.54 (d, $^3J_{\text{NH},6}$ = 9.0, 1H, NH); EI-MS: m/z = 392 (M^+) calc.: 392.43; C,H,N analysis: found C 45.15, H 6.08, N 7.27 %.

[11] E. Graf v. Roedern, E. Lohof, G. Hessler, M. Hoffmann, H. Kessler, *J. Am. Chem. Soc.* **1996**, *118*, 10156-10167; L. Szabo, B. L. Smith, K. D. McReynolds, A. L. Parrill, E. R. Morris, J. Gervay, *J. Org. Chem.* **1998**, *63*, 1074-1078.

[12] R. Haubner, W. Schmitt, G. Hölzemann, S. L. Goodman, A. Jonczyk, H. Kessler, *J. Am. Chem. Soc.* **1996**, *118*, 7881-7891.

[13] J. H. Viles, S. U. Patel, J. B. O. Mitchell, C. M. Moody, D. E. Justice, J. Uppenbrink, P. M. Doyle C. J. Harris, P. J. Sadler, J. M. Thornton, *J. Mol. Biol.* **1998**, *279*, 973-986.