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An Efficient Synthesis of Bicyclic ß-Turn Dipeptides via a Photochemical Key Step

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Abstract

A novel synthetic route to bicyclic ß-turn dipeptides (BTD) is described. It starts with L-ß-benzoylalanine **1**, which is *N*-protected and coupled with proline esters yielding the dipeptides **3**. Upon irradiation **3a-c** undergo a cyclization to the indolizinones **4** in a highly stereoselective manner. **4a** and **4c** were converted into the *N*-protected BTD derivatives suited for peptide synthesis. The absolute configuration of products **4** and **5** were unambiguously elucidated from NOE results.

Keywords: Amino acids and derivatives; Bicyclic heterocyclic compounds; Photochemistry; Peptide analogues/mimetics.

Among the different secondary structures of peptides the ß-turn plays a central role due to its common occurrence in the active site of peptides. Many structures were developed which simulate the central two amino acids of a ß-turn motif. Bicyclic ß-turn dipeptides (BTD) containing the indolizinone skeleton or the appropriate 7-thia analogue (X=S) proved particularly successful. Since the first synthesis of a BTD by Nagai and Sato in 1984 [1] and the impressive application on a gramicidin S analogue [2] several synthetic routes to BTD type mimetics were developed [3]. Most of them involved many synthetic steps and poor overall-yields.

We now wish to report on an efficient synthesis of bicyclic ß-turn dipeptides with indolizine skeleton. Recently, we described a straightforward synthesis of L-ß-benzoylalanine **1**, which could be accomplished in gram-amounts for the first time [4]. Starting with **1** we introduced some different *N*-protecting groups according to standard procedures yielding the acids **2a-d** in good yields. Reaction of **2** with L-proline methyl- or benzylester using the novel peptide coupling reagent TPfTU [5] afforded the dipeptides **3a-d**. Based on our recent investigations of the photochemical behaviour of γ-ketoamides [4,6] which gave δ-lactams upon irradiation in a stereoselective manner we subjected **3a-d** to the same conditions. Our aim, the photocyclization to indolizinones was achieved in the case of **3a-c** whereas **3d** did not undergo any photochemical reaction. The behaviour of **3d** was not surprising because the Fmoc group contains a biphenyl substructure. Biphenyl with a triplet energy of 66 kcal/mol may act as an efficient triplet quencher for alkyl aryl ketones which have a triplet energy of 74 kcal/mol [7]. Obviously, the Fmoc group suppresses the intramolecular H-transfer by quenching the triplet excited benzoyl group.

The photocyclization to indolizinones **4** proceeds with high stereoselectivity. The moderate yields are caused by undefined decomposition products and loss of material during purification. In order to provide BTD derivatives suited for peptide synthesis we prepared the acids **5a** and **5b**. Saponification of **4a** with LiOH afforded the Cbz-amino acid **5a** with nearly quantitative yield. Since the Fmoc group is presently the most used *N*-protecting group in solid phase peptide synthesis we developed a synthetic route to the Fmoc-BTD **5b** starting with **4c**. After removal of the Boc group the Fmoc group was introduced with FmocOSu. Finally the benzyl ester was cleaved by hydrogenation giving **5b** [8] (Scheme 1).

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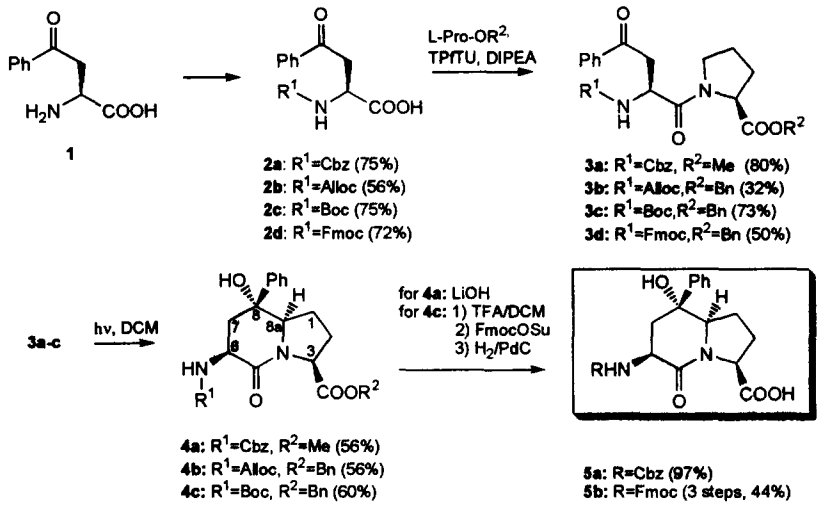

Scheme 1

An unambiguous clarification of the absolute configuration of the four chirality centres in **4a-c** succeeded by NOE experiments. Since a racemization on the centres C(3), C(6) that caused by the reactants can be ruled out the structure determination demands the evaluation of the relative configuration at C(6), C(8) and C(8a). A strong transannular NOE effect between H(6) and H(8a) is in agreement with our previous findings [4] and proves the asymmetric induction of C(6) on the bridgehead atom C(8a). The configuration at C(8) was established by a strong NOE effect between the C(8) phenyl group and H(7A), which is *trans* orientated to H(6). Thus, our route provided indolizinones with (3*S*, 6*S*, 8*R*, 8a*R*) configuration. Noteworthy, the irradiation of a dipeptide consisting of N-Cbz-D-ß-benzoylalanine and L-proline methylester yielded a indolizine derivative, which had the same relative configuration at C(6), C(8) and C(8a), *i.e.* (3*S*, 6*R*, 8*S*, 8a*S*) configuration. Obviously, there is no influence of the chirality centre in the proline ring on the relative configuration at C(6), C(8) and C(8a) of the indolizine skeleton during the cyclization.

In conclusion, we have described a novel facile entry to BTD derivatives under neutral conditions of the ring closure. A study to establish the mechanism by means of MO calculations and synthetic applications of our new BTD derivatives are under investigation. The results will be the subject of a future report.

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[5] TPfTU = *O*-Pentafluorphenyl-1,1:3,3-tetramethyluronium tetrafluoroborate. An analogous synthesis of the hexafluorophosphate was described by: Habermann, J.; Kunz, H. *J. prakt. Chem.* **1998**, *340*, 233.

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[8] analytical data of **5b**: $[\alpha]_D^{20}$ + 46.0 ° (c = 0.37, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) 1.08-1.25 (m, 1H, H(1A)), 1.50-1.65 (m, 1H, H(1B), 1.98-2.05 (m, 2H, H(2)), 2.89-2.68 (m, 2H, H(7)), 3.88-3.94 (m, 1H, H(8a)), 4.42-4.46 (m, 1H, H(3)), 4.78-4.86 (m, 1H, H(6)), 5.04 (s, 2H, Cbz(CH_2)), 6.24 (d. 1H, NH, *J* = 5.7 Hz), 7.19-7.50 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz) 27.7 (CH_2, C(1),C(2)), 44.6 (CH_2, C(7)), 49.6 (CH, C(6)), 58.4 (CH, C(3)), 67.1 (CH_2, Cbz), 68.2 (CH, C(8a)), 74.6 (C_q, C(8)), 125.7, 127.5, 127.9, 128.1, 128.2, 128.3, 128.5, 136.1, 143.5 (C(Ph)), 156.4 (CO), 171.4 (CO), 173.0 (CO). Numbering matches that of **4**, which is depicted in scheme 1.