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Design and Synthesis of Novel Conformationally Restricted Peptide Secondary Structure Mimetics

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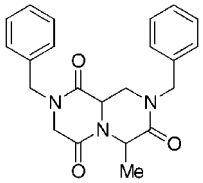
ABSTRACT

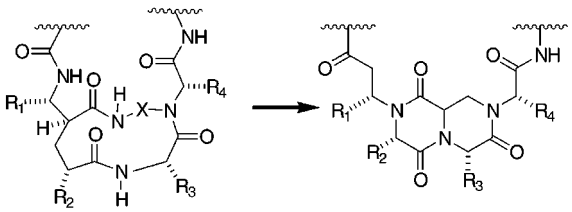


A facile synthesis of the novel conformationally restricted reverse turn mimetic is described. The key features are the preparation of the α-keto amide and tandem bicyclic ring formation.

As part of our continuing research program in the area of peptide secondary structure mimetics,[1] we are investigating the synthesis of new types of β-turn mimetics.[2]

We envisioned that the general structure **1** would be a good candidate, based upon molecular modeling (Scheme 1).

Scheme 1



3rd Generation **1**

To test the feasibility of the synthesis of **1** from readily available starting material, we chose **1a** as a model compound for the synthesis (Scheme 2). Acylation of the *N*-benzylglycine ethyl ester **2** with *N*-Boc-Ala-OH using EDCI and HOBt provided the sterically hindered secondary amide **3** in quantitative yield. Hydrolysis of the ethyl ester and subsequent coupling of the carboxylic acid with cyanomethylenetriphenylphosphorane using EDCI and DMAP, as previously described,[3] furnished **4** in 71% (from **3**) after purification by flash chromatography. Treatment of **4** with ozone, followed by coupling with secondary amino ester **2**, afforded the α-keto amide **5** in 40% yield.[3]

With α-keto amide **5** in hand, we attempted tandem cyclization by deprotection of the Boc protecting group with TFA and subsequent reductive amination ($ZnCl_2$/$NaBH_3CN$,

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(1) (a) Kahn, M.; Eguchi, M.; Kim, H.-O. WO98/49168. (b) Peptide Secondary Structure Mimetics. *Tetrahedron* (Symposia-in-print; no. 50, Kahn, M., Ed.) **1993**, *49*, 3444. (c) Kahn, M. *Synlett* **1993**, 821. (d) Kim, H.-O.; Kahn, M. *Tetrahedron Lett*. **1997**, *38*, 6483. (e) Kim, H.-O.; Lum, C.; Lee, M. S. *Tetrahedron Lett*. **1997**, *38*, 4935. (f). Ogbu, C. O.; Qabar, M.N.; Boatman, P. D.; Urban, J.; Meara, J. P.; Ferguson, M. D.; Tulinsky, J.; Lum, C.; Babu, S.; Blaskovich, M. A.; Nakanishi, H.; Ruan, F.; Cao, B.; Minarik, R.; Little, T.; Nelson, S.; Nguyen, M.; Gall, A.; Kahn, M. *Bioorganic Med. Chem. Lett.* **1998**, *8*, 2321. (g) Eguchi, M.; Lee, M. S.; Nakanishi, H.; Kahn, M. *J. Am. Chem. Soc.*, in press.

(2) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

(3) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364.

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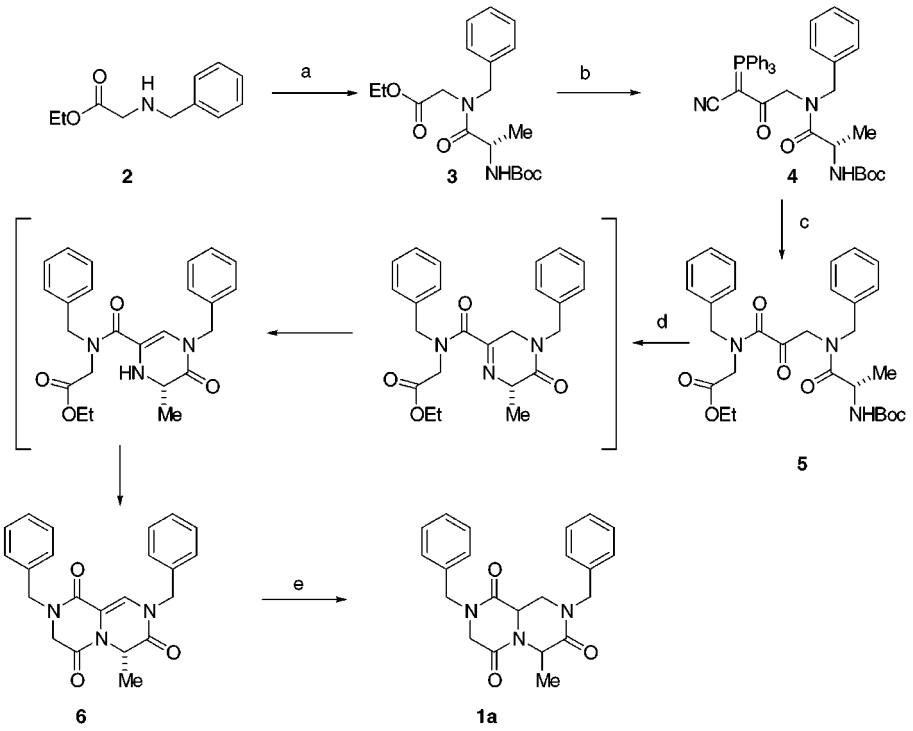
Scheme 2[a]



[a] Reagents and conditions: (a) Boc-Ala-OH, EDCI, HOBt, 100%; (b) (i) LiOH, H_2O/THF, 100%; (ii) $Ph_3P{=}CHCN$, EDCI, DMAP, CH_2Cl_2, 71%; (c) (i) O_3, CH_2Cl_2, −78 °C; (ii) *N*-benzyl-Gly-OEt, 41%; (d) TFA, then workup with saturated $NaHCO_3$, 77%; (e) H_2, PtO_2, MeOH, 56%.

MeOH) in order to form the desired compound **1a**. However, the enamino bicyclic triaza compound **6** was isolated in 77%.[4] Presumably, isomerization is faster than reduction of the imine by $ZnCl_2$/$NaBH_4CN$. When compound **6** was treated under H_2 (20 atm) in the presence of PtO_2, the desired compound **1a** was afforded in 56% yield[5] along with the unreacted **6**. The diastereomeric ratio of **1a** was determined by HPLC to be 2:1.[5] However, the absolute stereochemsitry was not determined.

In summary, we have demonstrated a facile synthesis of novel peptide secondary structure mimetics from simple α-amino acids.

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(4) Spectral data of **6**: TLC R_f 0.58 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3H, J = 6.5 Hz, CHCH_3), 3.93 (ABq, 2H, J = 18 Hz, CH_2 in Gly), 4.46 and 4.75 (ABq, 1H each, J = 14.5 Hz, CH_2Ph), 4.76 (ABq, 2H, J = 14 Hz, CH_2Ph), 5.22 (q, 1H, J = 7 Hz, C*H*CH$_3$), 6.83 (s, 1H, ═CH), 7.33 (m, 10H, phenyls); ^{13}C NMR ($CDCl_3$) δ 16.6, 49.6, 49.7, 49.8, 51.0, 111.9, 119.2, 128.1, 128.2, 128.3, 128.5, 128.9, 129.0, 134.8, 134.4, 158.0, 160.7, 165.3; MS ES$^+$ *m*/*z* 376.3 (M + H$^+$).

(5) Spectral data of **1a**: TLC R_f 0.49 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 1.5H, J = 7 Hz, CHCH_3), 1.52 (d, 1.5H, J = 7 Hz, CHCH_3), 3.2−4.8 (set of m, 10H), 7.33 (m, 10H, phenyls); MS ES$^+$ *m*/*z* 378 (M + H$^+$); HPLC (C-18 reverse phase column, 0 to 90% of acetonitrile/H_2O gradient, 40 min) analysis 250 nm t_R 24.1 and 24.7; 2:1 ratio.