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Synthesis of a novel benzyl-octahydropyrazino[1,2-*a*]pyrimidin-6-one derivative as a convenient internal bicyclic peptidomimetic

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Abstract

A substituted hydropyrazino[1,2-*a*]pyrimidin-6-one derivative was synthesized stereoselectively via the intramolecular *N*-acyliminium ion cyclization between an amide nitrogen and an N^{α}-acetal derived from Cbz-protected aminopropyl-phenylalaninamide in very good yields. The formation of a single diastereomer is due to the low energy chairlike conformation of its bicyclic structure. This methodology provides a convenient tool to build internal bicyclic peptidomimetics.
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It has been well recognized that β-turns are important structural features in biologically active peptides and proteins in terms of their function.[1] A large amount of research has been pursued to investigate peptide–protein or protein–protein interactions that also could be induced by small molecules bearing similar local structural features.[2] Recently, our group has developed the external β-turn mimetics **1** (Fig. 1) containing the thiazolo[3,2-*a*]-pyridine-5-one moiety via both solution and solid phase synthesis.[3] It has been known that for interactions with a target protein, side chains of internal β-turn mimetics are more accessible than those of external mimetics, which are more sterically hindered by the support.[4] Therefore, we have designed and synthesized a novel internal bicyclic scaffold for peptidomimetic **2** (Fig. 1). For structure characterization and configuration assignment, a density functional theory (DFT) calculation, solution NMR spectroscopy, and X-ray crystallography were performed.

Compound **8** was designed as a model compound to investigate the synthesis of 1,3,6,8-substituted tetrahydro-

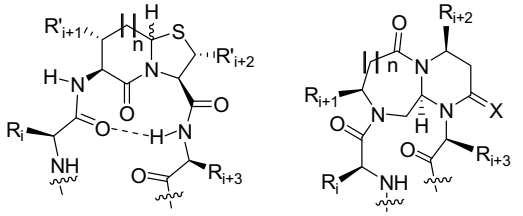

Fig. 1. Bicyclic external (**1**) and internal (**2**) β-turn mimetics.

2*H*-pyrazino[1,2-*a*]pyrimidine-4,7-diones (**2**) derivatives (Scheme 1). The straightforward approach to this bicyclic scaffold was to introduce an acetal moiety at the α-amino group of the phenylalanine, which can be attacked first by the amide to yield acyliminium ion **7** and then by the carbamate nitrogen atoms in a one-pot fashion to construct the bicyclic structure. The reaction was expected to give a corresponding diastereomeric mixture, as the nucleophilic attack may take place from both the *si*-face and *re*-face of the planar iminium ion double bond.[4,5] Surprisingly, a single diastereomer was generated and isolated from the reaction, and its purity was confirmed by HPLC. Here,

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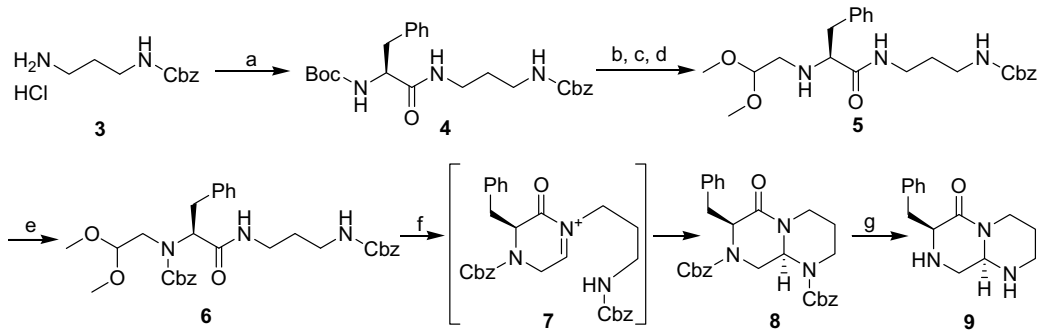


Scheme 1. Synthesis of 7-benzyl-octahydropyrazino[1,2-a]pyrimidin-6-one (**9**). Reagents and conditions: (a) Boc-L-Phe-OH, BOP, HOBt, NMM, DMF, 92%; (b) TFA, CH_2Cl_2; (c) 2,2-dimethoxyacetaldehyde, THF; (d) $NaBH(OAc)_3$, AcOH, THF, 90% (3 steps overall); (e) Cbz-Cl, DIEA, CH_2Cl_2, 96%; (f) formic acid, 89%; (g) H_2, Pd/C, MeOH, 95%.

we provide details for the synthesis, the rationalization of diastereoselectivity, and its absolute stereochemistry.

(3-Aminopropyl)-carbamic acid benzyl ester **3** was conjugated with N^{α}-Boc-L-Phe-OH using BOP, HOBt, and NMM to afford amide **4** in 92% isolated yield (Scheme 1).[6] After deprotection of the N^{α}-Boc group by TFA, reductive amination was performed by sequential additions of 2,2-dimethoxyacetaldehyde and sodium triacetoxyborohydride in the presence of a catalytic amount of acetic acid in THF.[7] This one-pot 3-step reaction generated the secondary amine **5** with an acetal moiety in 90% yield after purification. The Cbz group was chosen to protect the secondary amine, though other protection groups could be used for the orthogonal protection. After protection, the corresponding acetal **6** was subjected to acid-catalyzed cyclization in the presence of formic acid to give bicyclic product **8** in 89% yield. Interestingly, this bicyclic product **8** only showed a single diastereomer both in crude NMR and HPLC analyses. In order to confirm the stereochemistry and the optical purity of the diastereomer, various NMR analyses were performed, but the result was not conclusive due to the existence of rotamers. Thus, the two Cbz groups of **8** were removed by hydrogenation. The NMR spectrum as well as HPLC analysis of product **9** clearly indicated that compound **9** was a single diastereomer.[8] The product was crystallized in a mixed solvent CH_2Cl_2, EtOAc, and MeOH. The X-ray crystal structure of **9** confirmed that the bridged head hydrogen has a *cis*-configuration to the hydrogen at position 7, and that the pyrimidine and piperazine rings have a chairlike conformation with the benzyl group in an axial position (Fig. 2).[9] In the structural conformation of **9**, the anomeric effect could be one possible factor for its chairlike structure, since the lone pair of the nitrogen stabilizes the axial benzyl group in the chairlike conformation more than the equatorial one in the boatlike conformation.[10]

To confirm their configurations, density functional theory (DFT) calculations were performed using the GAUSSIAN 03 program.[11] Structure optimization followed by a frequency calculation was performed on **9** at the B3LYP/6-31G(d) level (no imaginary frequencies were found). Zeropoint energies (ZPEs) of the DFT results were scaled by 0.9806.[12] Compound **9** was studied to compare the obtained calculated conformation with its X-ray crystal structure. It turns out that the calculated structure of **9** was shown to be well overlapped with the X-ray crystal structure. For simplicity with low calculational costs, the model compounds of two diastereomers, in which a Cbz group at position 1 in **9** was replaced by an acetyl group, were calculated by the same method.

As anticipated, diastereomer **10**, whose pyrimidine ring has a chairlike conformation, is more stable than diastereomer **11**, which has a twist boatlike conformation, implying that the bis-acylated benzyl-octahydropyrazino[1,2-*a*]pyrimidin-6-one derivative also prefers a chairlike conformation rather than a boatlike one (Fig. 3). The energy difference between the two diastereromers is 1.5 kcal/mol, which leads to a 9/1 product ratio. On the basis of the

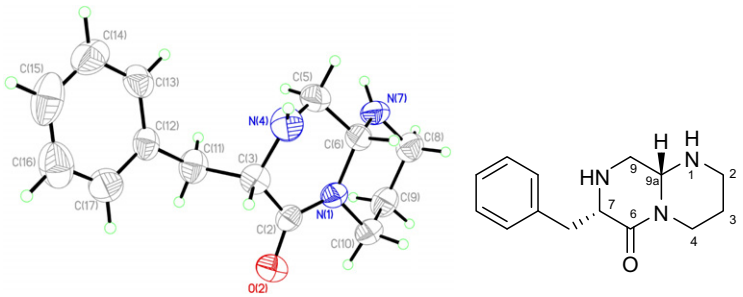


Fig. 2. X-ray crystal structure of (7*S*,9a*R*)-7-benzyl-octahydropyrazino[1,2-*a*]pyrimidin-6-one, **9**.

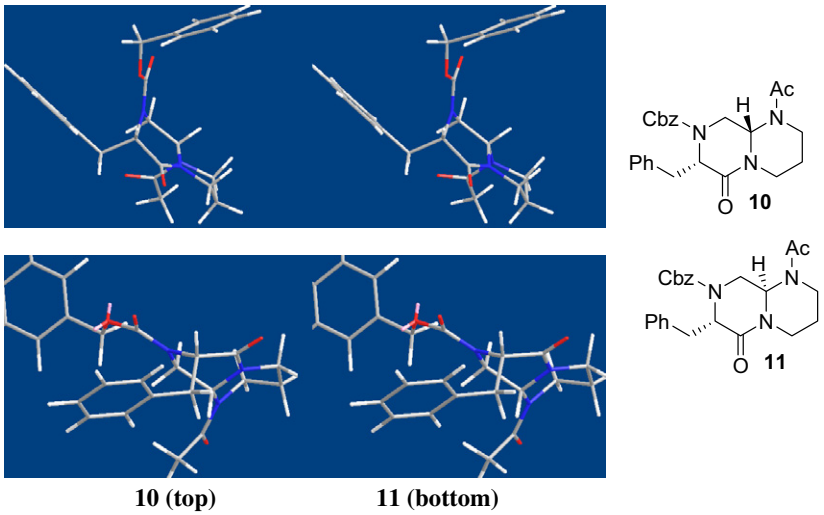
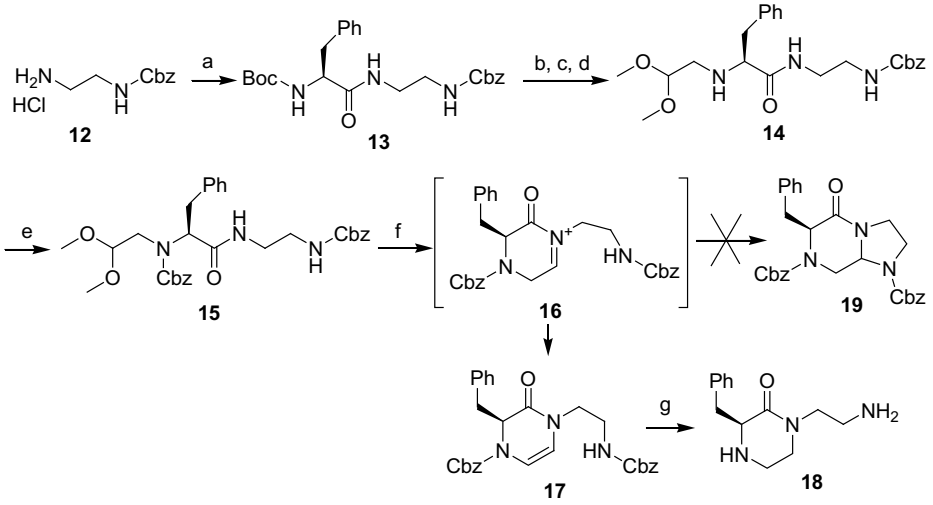


Fig. 3. The lowest energy conformational structures of two diastereomers (**10** and **11**, stereoviews) from DFT calculation using GAUSSIAN 03.

results from the DFT calculation and X-ray crystal structure, the thermodynamically preferred diastereomer was confirmed.

An interesting result was found when the synthesis of 6,5-membered ring **19** (Scheme 2) was attempted. 6,5-Bicyclic compound **19** could not be generated by the same strategy (Scheme 2). Acetal **15** did not go on to cyclization even with reaction times of up to 5 days and heating for 4 h, but instead underwent β-elimination to generate enamide product **17** in 10% yield, which was the only isolated product along with the starting material.[13] We speculate that the elimination reaction is the major side reaction for this type of tandem bicyclization. Thermodynamically driven 6,6-membered bicyclic formation could be a stable pathway to yield the desired product while the kinetically driven 6,5-membered bicyclic needs higher energy compared to the eliminated enamide product **17**. Therefore, compound **17** was the only isolated product under the harsh reaction condition. Other ring-size bicyclic constructions are currently under investigation.

In summary, we have developed a simple and efficient methodology to synthesize a substituted octahydropyrazino[1,2-*a*]pyrimidin-6-one as a scaffold for the formation of internal bicyclic peptidomimetics. Installing an acetal moiety on α-amino group following by tandem acid-catalyzed *N*-acyliminium ion bicyclization was the key for this transformation. The formation of the bicyclic scaffold is considered to follow a thermodynamically driven pathway to yield only a single diastereomer. We expect that this methodology will bring a simple and efficient tool to develop new types of peptide-based ligands.



Scheme 2. Synthesis of 1-(2-aminoethyl)-3-benzylpiperazin-2-one, **18**. Reagents and conditions: (a) Boc-L-Phe-OH, BOP, HOBt, NMM, DMF, 95%; (b) TFA, DCM; (c) 2,2-dimethoxyacetaldehyde, THF; (d) $NaBH(OAc)_3$, AcOH, THF, 90% (3 steps overall); (e) Cbz-Cl, DIEA, DCM, 81%; (f) formic acid, 10%; (g) H_2, Pd/C, MeOH, 60%.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.137.

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