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Synthesis of bicyclic dipeptide mimetics for the cholecystokinin and opioid receptors ☆

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Abstract—The cholecystokinin C-terminal octapeptide analogue H-Asp-Tyr-D-Phe-Gly-Trp-(N-Me)-Nle-Asp-Phe-NH_2 (SNF 9007) is a potent and selective ligand for both the CCK-B and δ-opioid receptors. To constrain the peptide into the biologically active conformation(s), bicyclic dipeptide mimetics for Nle-Gly and homoPhe-Gly were designed and synthesized from β-substituted aspartic acids. Alkylation of L-aspartic acid using lithium bis(trimethylsilyl)amide (LHMDS) in the presence of hexamethylphosphoramide (HMPA) gave β-substituted aspartic acids, with the major product being the (2*S*,3*R*) isomer. Additional isomers of Nle-Gly bicyclic dipeptide mimetic were obtained via the Kazmaier–Claisen rearrangement reaction. The stereochemistries of the bicyclic dipeptide mimetics were assigned by X-ray and NMR.

Conformationally constrained amino acids and dipeptide units can serve in mimicry of specific secondary structures for the elucidation of the bioactive conformations that are required for biological recognition.[1] To understand the stereochemical requirements of side chain groups necessary for peptide-receptor interactions, bicyclic dipeptide mimetics have been designed and synthesized to conformationally constrain dipeptide units in peptides.[2,3] Recently, our group has been involved in the synthesis of peptide ligands that interact with both cholecystokinin and opioid receptors.[4] Cholecystokinin (CCK) is a 33-residue peptide hormone that has been shown to govern various gastrointestinal (GI) functions and acts as a neuromodulator and/or neurotransmitter, respectively.[5] It also has long been considered as an 'anti-opioid' peptide because it diminishes opioid induced analgesia.[6] The two subtypes of receptors for CCK are CCK-A, found predominantly in the peripheral tissues, and CCK-B, that is localized in the central nervous system (CNS). Among the ligands we have synthesized is the octapeptide H-Asp-Tyr-D-Phe-Gly-Trp-(N-Me)-Nle-Asp-Phe-NH_2 (SNF 9007), which was found to be extremely selective for the CCK-B receptor and also was potent for the δ-opioid receptor.[7] In our efforts toward the synthesis of constrained peptides for the CCK and opioid receptors, the [3.3.0] bicyclic compounds **1** and **2** were designed (Fig. 1). Compound **1** was designed as a bicyclic dipeptide mimetic for Nle-Gly while **2** was designed to replace the Phe-Gly dipeptide unit in SNF 9007. To do a comprehensive study of the interaction of ligands with the two receptors, different isomers of the target compounds are required.

Retrosynthetically, the two compounds can be obtained by coupling of β-substituted homoserines (Fig. 2) using a protocol that we have developed in our labs.[8] β-Substituted homoserines can be obtained by the reduction of β-substituted aspartic acids, the products of β-alkylation of aspartic acid.

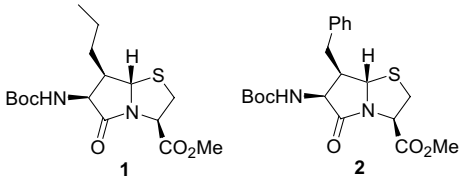

Figure 1. Target bicyclic dipeptide mimetics.

Keywords: Constrained peptides; Bicyclic dipeptide; β-Substituted aspartic acid; Kazmaier–Claisen rearrangement; Cholecystokinin.

☆ Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2004.03.146

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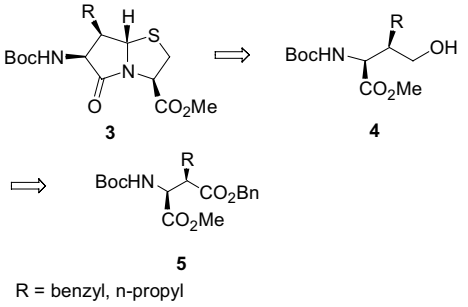
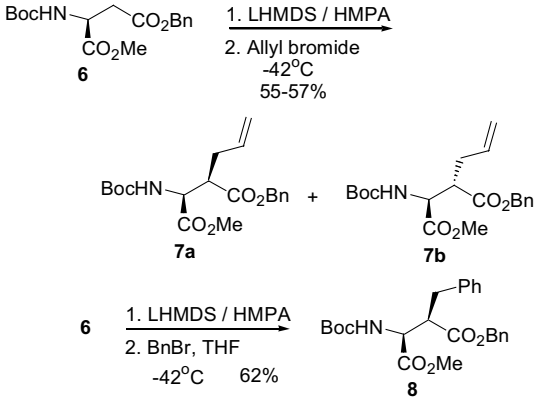


Figure 2. Retrosynthetic route to the synthesis of **1** and **2**.

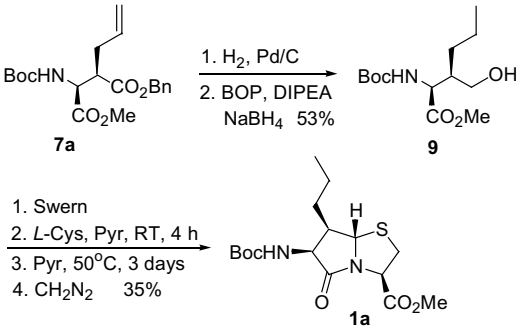
Alkylation of aspartic acid with different electrophiles has been reported in the literature.[9] In our efforts to alkylate N^{α}-Boc aspartic acid, a modified methodology was developed after the alkylation failed to go to completion using the reported method. Addition of hexamethylphosphoramide (HMPA) was found to facilitate the reaction and gave reproducible results in large scale syntheses. Alkylation with allyl bromide in the presence of lithium bis(trimethylsilyl)amide (LHMDS) and HMPA resulted in the formation of two β-allyl substituted aspartic acids in a total yield of 57% and a ratio of 3:1 in favor of the (2*S*,3*R*)-**7a** isomer (Scheme 1). When the electrophile was benzyl bromide only the (2*S*,3*R*) product **8** was obtained in a yield of 62%.

Hydrogenation of compound **7a** reduced the alkene and deprotected the benzyl ester to afford a carboxylic acid, which was then subjected to reduction (Scheme 2). Reduction of the carboxylic acid using borane and sodium perborate[10] failed to give the desired product. Utilization of a recently reported method that uses BOP, DIPEA, and $NaBH_4$[11] gave the desired alcohol in a yield of 53%, contaminated with <5% of the five-membered ring lactone resulting from cyclization. The lactone formation also was found to happen during column purification.

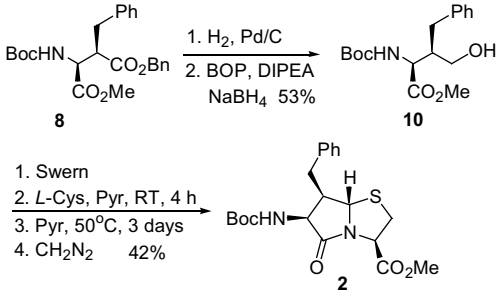
Swern oxidation of the alcohol afforded the aldehyde, which without purification was coupled with L-Cys to form an intermediate thiazolidine. Bicyclization was



Scheme 1. Alkylation of aspartic acid with allyl bromide and benzyl bromide.



Scheme 2. Synthesis of Nle-Gly bicyclic dipeptide mimetic.



Scheme 3. Synthesis of homoPhe-Gly bicyclic dipeptide mimetic.

then achieved by heating the reaction mixture at 50 °C for 3 days, followed by methylation to afford a bicyclic dipeptide mimetic for Nle-Gly **1a** in 35% yield from the alcohol **9**.

When **8** was subjected to hydrogenation and reduction, the alcohol **10**, contaminated by the lactone, was obtained in 53% yield (Scheme 3). The alcohol was then subjected to the same set of reaction conditions as described above to give **2** in 42% yield. The stereochemistry of compound **2** was confirmed from its crystal structure (Fig. 3).

When the minor product **7b** was subjected to hydrogenation followed by BOP/DIPEA/$NaBH_4$ reduction, only the cyclized product **11** was obtained in 58% yield (Scheme 4). Obviously, a *trans*-relationship of the

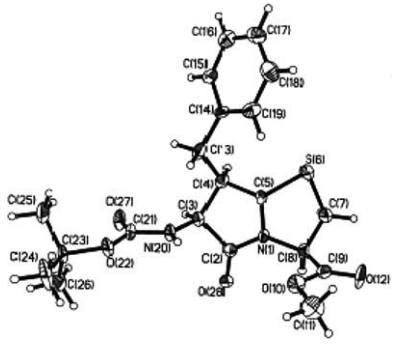
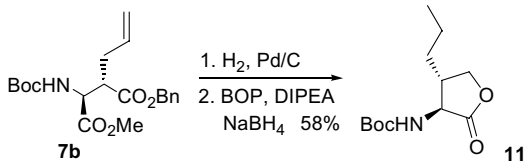


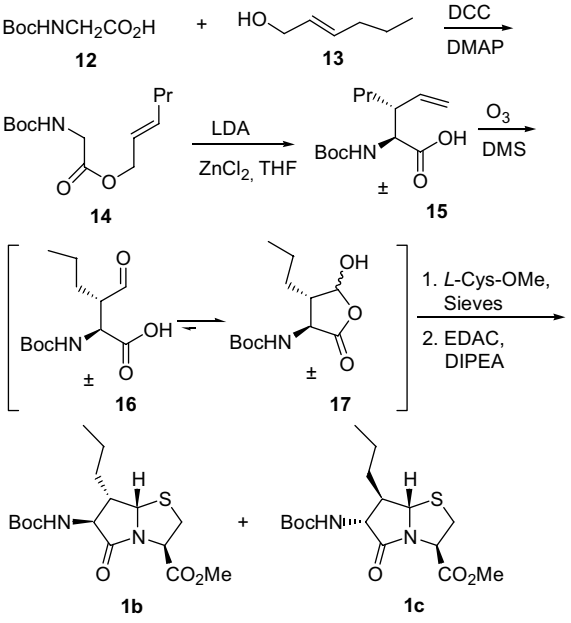
Figure 3. X-Ray crystal structure of homoPhe-Gly bicyclic dipeptide mimetic.



Scheme 4. Hydrogenation and reduction of (2*S*,3*S*)-β-allyl-substituted aspartic acid.

β-substituent makes this lactone thermodynamically more stable compared to the *cis*-analogue.

To fully investigate the stereochemical and topographical requirements of the receptors, other isomers of Nle-Gly bicyclic dipeptide mimetic were synthesized via the Kazmaier–Claisen rearrangement reaction[12] (Scheme 5). Coupling of Boc-Gly with commercially available *trans*-2-hexen-1-ol gave **14**. Compound **14** was then subjected to a Kazmaier–Claisen rearrangement to give the racemic β-vinyl substituted Nle **15**. The crude product was then subjected to ozonolysis and the resultant crude aldehyde coupled with L-Cys–OMe in a two-step strategy involving thiazolidine formation and bicyclization. Two bicyclic dipeptide mimetics **1b**, and **1c**



Scheme 5. Synthesis of Nle-Gly BTD via the Kazmaier–Claisen rearrangement reaction.

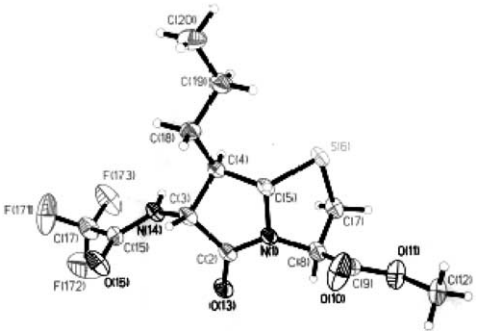


Figure 5. X-Ray crystal structure of a Nle-Gly bicyclic **18c** dipeptide mimetic.

were isolated in a total yield of 50% from **14**. These products can easily be separated on a silica gel column.

The three Nle-Gly bicyclic dipeptide mimetics were characterized by DQF-COSY and 1D-transient NOE NMR studies. The NOE's from the N^{α}-Boc products were not sufficient to assign the chiral centers since not all the NOE relationships were observable particularly for the left-hand ring. As a result, the *N*-trifluoroacetamide analogues (**18a**–**c**) were synthesized and their 1D-transient NOE data used to assign the chiral centers. Compounds **18a** and **18c** showed a small value for NOE between H^4 and H^5 (1.12% and 0.83%, respectively) compared to a value of 5.43% observed for **18b** (Fig. 4). This is an indication of a *trans* relationship for H^4 and H^5 in compounds **18a** and **18c** and a *cis* relationship in **18b**. A similar *trans* relationship is observed in **18b** and **18c** for H^3 and H^4 while a strong NOE (4.45%) indicative of a *cis* relationship is observed for **18a**. Additionally, the structure of compound **18c** was confirmed by an X-ray crystal structure analysis (Fig. 5).

In conclusion, we have synthesized bicyclic dipeptide mimetics for Nle-Gly from aspartic acid and by use of the Kazmaier–Claisen rearrangement reaction. Their stereochemistries have been well characterized by X-ray and NMR. These BTD's will be inserted in the chimeric peptides for opioid and CCK receptors to study their structure–activity relationships.

Supporting information available

Supplementary data. Experimental procedures and spectroscopic characterization ($[\alpha]_D$, ^1H NMR, ^{13}C NMR, HRMS) of all new compounds.

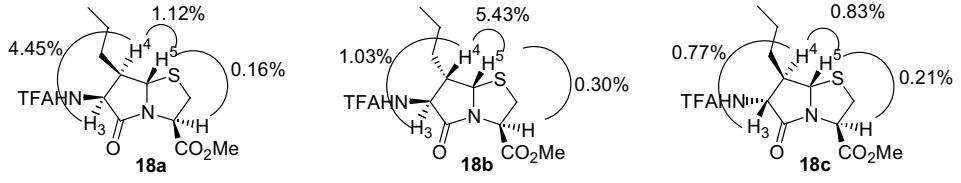


Figure 4. NOE data for the Nle-Gly bicyclic dipeptide mimetics.

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