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A simple and efficient synthesis of an Asp-Gly dipeptide mimetic ☆

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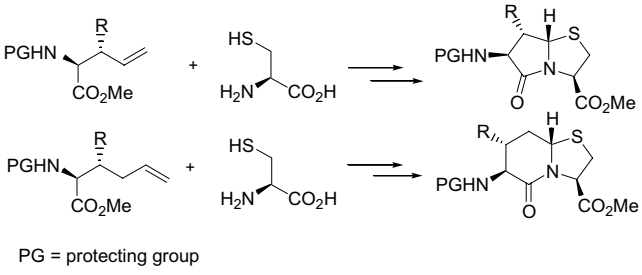
Abstract—Alkylation of N^{α}-Boc protected aspartic acid with allyl bromide in the presence of lithium bis(trimethylsilyl)amide (LHMDS) and hexamethylphosphoramide (HMPA) afforded chiral β-allyl substituted aspartic acid in good yields. After deprotection of the N^{α}-Boc group and reprotection as a trifluoroacetamide, the terminal alkene was oxidized to an aldehyde. The aldehyde was then coupled with L-cysteine through a cascade three-bond formation process to afford aspartic acid–glycine bicyclic dipeptide mimetics.

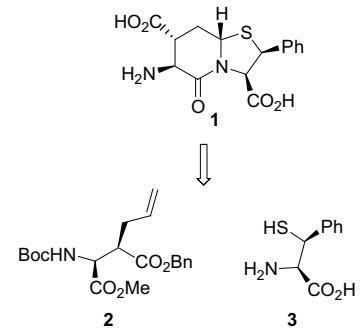
The properties of biologically active peptides have inspired the targeting of peptides as lead structures for the development of many novel drugs.[1] However, the problems of metabolic stability, bioavailability, and non-selectivity toward different receptor and receptor subtypes have hampered their utilization as therapeutics. This has necessitated the development of strategies for the synthesis of biologically stable peptides and converting the native peptides into constrained analogues[2] to improve their pharmacokinetic properties. A field that is gaining momentum is the synthesis of constrained or rigidified dipeptide units as exemplified by bicyclic dipeptide mimetics.[3,4] To fully elucidate the conformation(s) required for biological activity, these bicyclic dipeptide mimetics should incorporate the critical pharmacophores (side chain groups) that are necessary for biological activities.

In our group, asymmetric synthetic methodologies toward the scaffolds for [5,5]- and [6,6,5]-bicyclic dipeptides have been developed.[5] The [5,5]-bicyclic dipeptides are synthesized from γ,δ-unsaturated amino acids while the syntheses of the [6,5]-analogues employs δ,ε-unsaturated amino acids (Scheme 1).

In our efforts toward the synthesis of constrained analogues of cholecystokinin (CCK) peptides, a bicyclic dipeptide mimetic for aspartic acid–phenylalanine **1** (Scheme 2), was designed. Considerable interest is devoted to the pharmacology of CCK-B receptors, since



Scheme 1. Synthetic strategy for [5,5]- and [6,5]-bicyclic dipeptide mimetics.



Scheme 2. Retrosynthetic analysis for Asp-Phe bicyclic dipeptide mimetic.

Keywords: Bicyclic dipeptide; β-substituted aspartic acid; Trifluoroacetamide; Cholecystokinin.

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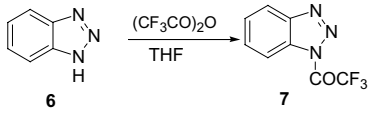
administration of selective agonists produces behavioral changes such as anxiety, perturbation of memory, and hyperalgesia, and dysfunctions of CCK-B related neural pathways could be involved in neuropsychiatric disorders.[6] Retrosynthetically, the synthesis would employ β-allyl substituted aspartic acids **2**, and β-phenyl substituted cysteines **3** (Scheme 2). Whereas chiral β-phenylcysteines have been synthesized in our laboratory,[7] asymmetric synthesis of β-allyl aspartic acids needs further development.

In this paper, progress toward the synthesis of β-carboxylate containing [6,5]-bicyclic dipeptide mimetic is discussed. Alkylation of aspartic acid has been reported by a number of groups.[8] The enolate is formed without loss of stereochemical integrity of the α-center and can be reacted with different electrophiles to give β-substituted aspartic acid. In a typical procedure, a protected aspartic acid was treated with lithium bis(trimethylsilyl)amide (LHMDS) at −78 °C, warmed to −30 °C for 45 min before cooling back to −78 °C and adding the electrophile. However, when this protocol was applied to N^{α}-Boc aspartic acid, the reaction would not go to completion necessitating the development of a modified procedure. Thus, the protected amino acid was dissolved in THF and cooled to −42 °C. LHMDS followed by hexamethylphosphoramide (HMPA) (26%) were then added and the mixture stirred at −42 °C for 30 min before adding the electrophile. When the electrophile was allyl bromide, products **5a** and **5b** in a total yield of 58% and a ratio of 3:1 were obtained after purification by flash column chromatography (Scheme 3). The major isomer was found to be the (2*S*,3*R*) isomer on NMR analysis of the final bicyclic dipeptide, in agreement with results reported in literature.[8]

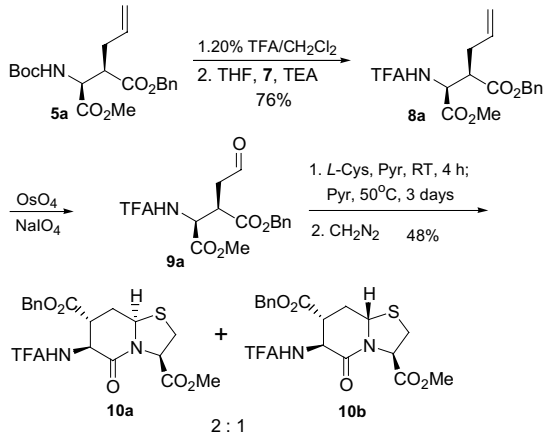
It has been established that oxidation of carbamate protected β-allyl amino acids leads to a five-membered cyclic hemiaminal instead of the free aldehyde, a dead end for our strategy. However, this problem can be avoided by protecting the amino group as a trifluoroacetamide[5b] or by bisprotection. Introduction of a second Boc group was unsuccessful due to steric hindrance of β-substitution. A number of methods for protection of an amino group as a trifluoroacetamide were attempted. Deprotection of the N^{α}-Boc group followed by coupling with ethyl trifluoroacetate[9] gave the product in non-reproducible and variable yields (25–45%), while use of trifluoroacetic anhydride[10] led to the formation of a mixture of products. A recently reported method[11] that uses trifluoroacetyl benzotriazole **7**, was found to be more efficient and clean. This reagent is easily synthesized in large scale from benzotriazole and trifluoroacetic acid in THF (Scheme 4).



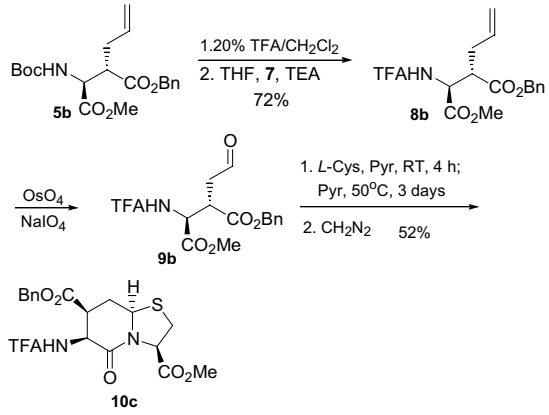
Scheme 4. Synthesis of trifluoroacetyl benzotriazole.

When **5a** was treated with 20% TFA in DCM followed by reaction with trifluoroacetyl benzotriazole **7**, the N^{α}-trifluoroacetyl amino acid **8a** was obtained in good yield (Scheme 5). Compound **8a** was then subjected to oxidation with osmium tetraoxide and $NaIO_4$ to afford aldehyde **9a**. Without further purification, the aldehyde was coupled with L-cysteine in a one pot reaction to form two bicyclic dipeptide mimetics via the formation of an *N*,*S*-thiazolidine and bicyclization, which was then followed by methylation.

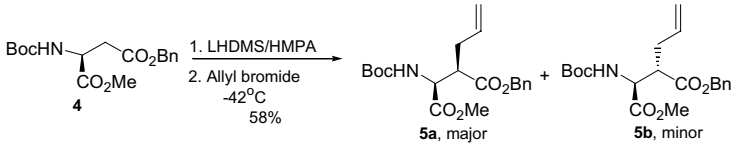
Subjecting the minor isomer **5b** to the same set of reaction conditions afforded only one bicyclic dipeptide **10c** (Scheme 6).



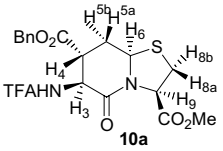
Scheme 5. Synthesis of Asp-Gly bicyclic dipeptide mimetics.



Scheme 6. Synthesis of Asp-Gly bicyclic dipeptide mimetics.

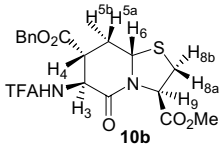


Scheme 3. Alkylation of aspartic acid.



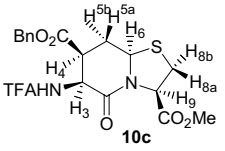
10a

proton		%nOe
*H_3	H_4	0.60
	H_6	1.50
*H_{8a}	H_9	0.96
*H_{8b}	H_6	0.60
	H_9	1.81



10b

proton		%nOe
*H_3	H_4	0.55
	H_6	0.20
	H_{5b}	1.40
*H_6	H_3	0.17
	H_{5a}	1.75
	H_{5b}	0.60



10c

proton		%nOe
*H_3	H_4	2.32
	H_6	2.52
*H_{8a}	H_6	0.23
	H_9	1.18
*H_{8b}	H_9	2.12
	H_6	0.83

* the irradiated proton in nOe experiments

Figure 1. NOE observed for Asp-Gly bicyclic dipeptide mimetics.

The proton NMR spectra were assigned by DQF-COSY, and the stereochemistry of the three bicyclic compounds assigned by 1D transient NOE experiments (Fig. 1). Highly resolved NOE data was obtained for compounds **10c** and **10a**, but there were some overlaps for compound **10b**. The coupling constants could not be used to assign the stereochemistries due to overlap of the desired hydrogens. Fortunately in all the isomers, H_3 was well resolved and was irradiated to determine the stereochemistry at C_4 and C_6. In **10a** and **10b**, a weak NOE indicative of a *trans* relationship was observed for H_3 and H_4. In **10c**, a *cis* relationship between H_3 and H_4 is proved by the strong NOE value. A *cis* relationship for the bridge-head H_6 with H_3 in **10a** and **10c** is confirmed by the strong NOE's (1.50% and 2.52%, respectively). In comparison, **10b** shows a NOE value of 0.20% that would be as a result of a *trans* relationship. The stereochemical outcome at C_6 is 'unusual' in that the favored product has the bridge head-H 'down' (*R* configuration) instead of 'up' (*S* configuration) as has been the result in our earlier work. These abnormal results may be caused by dipole–dipole intermolecular affinity in the starting material. In other words, a methyl ester and benzyl ester interaction in thiazolidine formation step favors the generation of *cis*-instead of the sterically favored *trans*-conformation.

In summary, the synthesis of an Asp-Gly bicyclic dipeptide mimetic has been accomplished by using alkylated aspartic acid derivatives. This protocol will be applied toward the synthesis of an Asp-Phe bicyclic dipeptide mimetic, which will then be incorporated into CCK peptides.

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

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