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A novel strategy toward [6,5]-bicyclic β-turn dipeptide

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Abstract—A novel strategy toward the syntheses of [6,5]-bicyclic β-turn dipeptides has been developed starting from δ,ε-unsaturated amino acids. This is the first example showing that this scaffold can be synthesized from a terminal alkene using a trifluoroacetyl protected amino acid. Both enantiomers of the δ,ε-unsaturated amino acid were synthesized by a modified method using Ni(II)-complexes.

The α-helix, β-sheets and β-turns are secondary structural motifs found in peptides and proteins which play a key role in imparting various functions to these biopolymers. Thus, it is important to be able to design such structures in order to fully understand how they function and exploit their properties in the design of novel ligands and therapies. By using uniquely constrained amino acids in peptide ligands, receptor selectivities, ligand potencies and the peptide stability can be dramatically improved.[1] For this purpose, our group has been actively pursuing synthetic strategies that provide peptidomimetics that mimic the β-turn. The first bicyclic β-turn mimetics were synthesized from aspartic acid derivatives and cysteine,[2,3] and used in peptides.[4] Though successful, the synthetic methods to prepare these compounds did not provide a straightforward way to introduce chiral side-chain groups on either the six or five membered rings. The introduction of chiral side chain moieties is important because the side chains on the rings generally play an important role in the biological activities of the peptides with β-turn structures.[1a,5]

Enkephalin and α-MSH are two peptides which have been extensively studied in our group (e.g. Ref. 6) We have hypothesized that in each case, β-turns in these peptides are key secondary structural features of their bioactive conformations. We have recently demonstrated an efficient method to obtain side chain functionalized [5,5]-bicyclic dipeptide in five steps by taking advantage of the Kazmaier rearrangement.[5a] However, the application of this method to the synthesis of [6,5]-bicyclic structure was not as straightforward. Thus we have been working on new strategies which are more efficient and utilize enantiomerically pure compounds as part of the synthetic strategy. This paper reports a novel synthetic method to obtain the [6,5]-bicyclic scaffold starting from chiral δ,ε-unsaturated

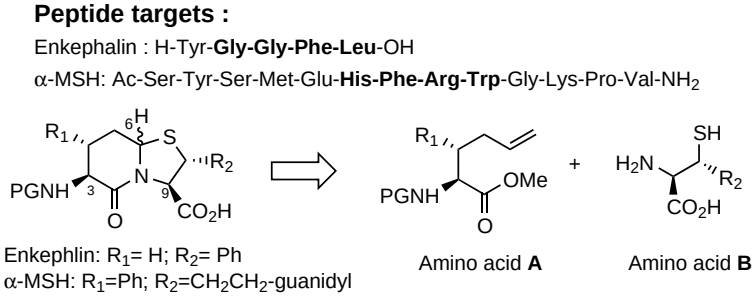

Figure 1. Peptide targets and retrosynthesis of [6,5]-bicyclic dipeptide scaffold.

Keywords: β-turn mimetic; bicyclic turned dipeptide; Ni(II)-complexes; δ,ε-unsaturated amino acids.
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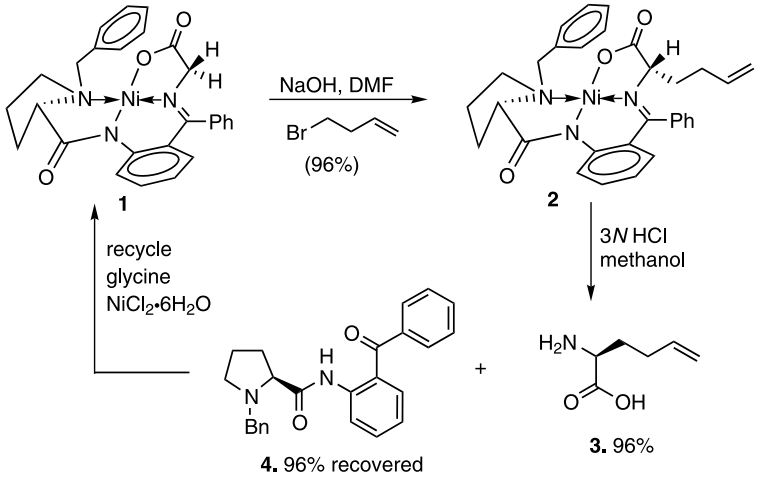
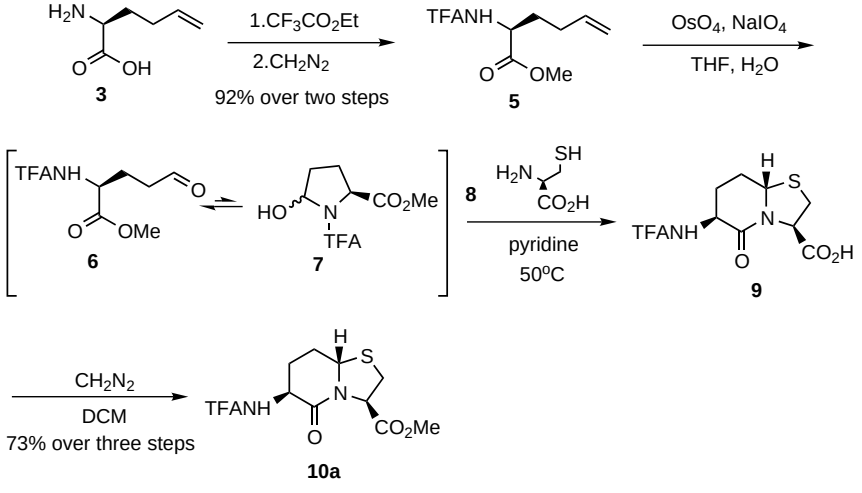
amino acids and β-thio amino acids. The retrosynthetic route to these compounds is shown in Fig. 1 which will introduce side chain functional groups at appropriate positions and with designed stereochemistry. This is now feasible because we have recently developed highly efficient methods to synthesize a wide variety of chirally pure β-substituted amino acids[7] and β-aromatic and aliphatic substituted cysteines.[8] Since the chirality centers can be controlled, the target molecules can have at least 16 different isomers and the constrained side chain groups can be controlled at their χ_1 and χ_2 angles.

Ni(II)-complex **1** has been used in amino acid synthesis since its initial development by Belokon et al.[9] The synthesis of ω-unsaturated amino acids via Ni(II)-complexes also has been reported, though in low yield.[10] We have recently modified this reaction and improved the yields to 95–98% (Scheme 1). The reaction was performed in DMF using a large excess of NaOH as base. During the reaction process, the immediate appearance of a green color indicated enolate formation, which disappeared after the addition of 4-bromo-1-butene in 3 minutes at room temperature. The alkylation also was tried in CH_3CN and methanol. However, the reaction proved to be very slow due to the poor solubility of the Ni(II)-complexes in these solvents. The product **2** (Scheme 1) generated from the *si*-face of the glycine enolate was favored and the configuration was determined as *S* by ^1H NMR.[11] We found that this reaction has very good diastereoselectivity with an isomer ratio $2S/2R = 95/5$. The product can be readily improved to >98% *de* by recrystallization from $CHCl_3$ and ether. The amino acid **3** can be generated by decomposition of Ni(II)-complex with 3N HCl and methanol in 96% yield with 96% of recovered (*S*)-BPB **4**. (2*R*)-2-Amino-5-hexenoic acid also has been synthesized on a multi gram scale with *R*-proline as starting material in the Ni(II)-complex.

With the δ,ε-unsaturated amino acids **3** synthesis completed, we first tried a strategy using N^{α}-Boc protected amino acids similar to that in the [5,5]-bicyclic dipeptide synthesis.[5a] After osmylation cleavage, however, the formation of a stable hemiaminal made reaction with cysteine difficult for thiazolidine formation. After trying other protecting groups, N^{α}-trifluoroacetyl was the final choice due to its strong electron withdrawing



Scheme 1. The alkylation and hydrolysis of Ni(II)-complex.



Scheme 2. New synthetic strategy toward [6,5]-bicyclic dipeptide.

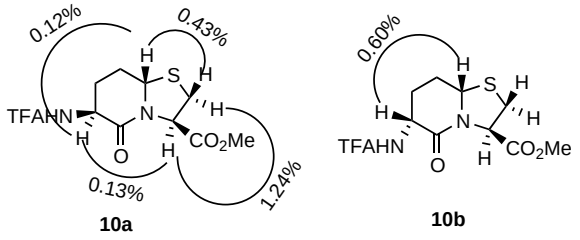


Figure 2. nOe observed for bicyclic thiazolidine lactam.

ability. Thus compound **5** can be generated from amino acid **3** in 92% yield over two steps (Scheme 2). After osmylation, the chain-ring tautomerism of **6**–**7** can be seen in the ^{1}H NMR in $CDCl_3$ in a ratio of 5:2. The diastereomers **7** also can be observed in a ratio of 3:2. The thiazolidine formation following bicyclization in pyridine can be completed in 4 days.

In order to purify and characterize the product **9**, it was esterified using diazomethane. Epimerization was found to be around 10% under the refluxing pyridine solution conditions in this one flask, three bond formation process. Fortunately, the epimerization can be diminished by using milder reaction conditions at 50°C, and the yield was improved to 73%. By starting with (2*R*)-2-amino-5-hexenoic acid, the (3*R*,6*S*,9*R*)-bicyclic product **10b** was synthesized. These two products have been purified by HPLC using a silica gel column (IBM Silica 2872053). The structures were determined by use of ^3J coupling constants and DQF-COSY.[12] Their stereochemistries have been assigned by nOe (Fig. 2) and ab initio calculations. The stereochemistry of the bridge-H is explained by its thermodynamically more stable *trans*-relationship in the formation of the thiazolidine. About 3% of the putative *cis*-product was isolated, but it was not fully characterized due to the small amount obtained and lack of good purity.

In summary, we have developed a novel and efficient strategy toward [6,5]-bicyclic dipeptides from δ,ε-unsaturated amino acid and cysteine in six steps with an overall yield of 59%. The strategy provides a bicyclic dipeptide which is ready for insertion into peptides by total synthesis.

Acknowledgements

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12. Characterization of compounds. **10a.** $[\alpha]_D^{24}$ −151° (*c* 0.67, $CHCl_3$); ^{1}H NMR, 500 MHz, $CDCl_3$, δ (ppm): 1.86–2.20 (2H, m), 2.41–2.45 (1H, m), 2.72–2.75 (1H, m), 3.19 (1H, dd, $J=5.5$, 11.5 Hz), 3.80 (3H, s), 3.41 (1H, dd, $J=8.5$, 12.0 Hz), 4.40–4.44 (1H, m), 4.95 (1H, dd, $J=4.0$, 10.5 Hz), 5.10 (1H, dd, $J=5.5$, 8.5 Hz), 7.19 (1H, bs). ^{13}C, 125 MHz, $CDCl_3$, δ (ppm): 26.7, 27.2, 31.9, 51.2, 53.0, 60.5, 62.8, 115.6 (q, $J=1144.5$ Hz), 157.5 (q, $J=150.0$ Hz),

165.6, 170.2; HRMS (FAB) MH^+ calcd for $C_{11}H_{13}F_3N_2O_4S$ 327.0626, found 327.0626. **10b.** $[\alpha]_D^{24}$ −196° (*c* 0.58, $CHCl_3$); ^1H NMR, 500 MHz, $CDCl_3$, δ (ppm): 1.72–1.80 (1H, m), 2.05–2.10 (1H, m), 2.38–2.45 (1H, m), 2.61–2.67 (1H, m), 3.28 (1H, dd, $J=4.5$, 11.5 Hz), 3.33 (1H, dd, $J=7.5$, 11.5 Hz), 3.79 (3H, s), 4.40–4.45 (1H, m), 4.99 (1H, t, $J=6.0$ Hz), 5.37 (1H, dd, $J=5.0$, 7.5 Hz), 7.49 (1H, bs). ^{13}C, 125 MHz, $CDCl_3$, δ (ppm): 23.6, 25.9, 31.7, 50.0, 53.0, 60.5, 60.6, 115.5 (q, $J=1144.0$ Hz), 157.0 (q, $J=150.0$ Hz), 167.0, 169.7; HRMS (FAB) MH^+ calcd for $C_{11}H_{13}F_3N_2O_4S$ 327.0626, found 327.0618.