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β-Turn Mimetic: Synthesis of Cyclic Thioenamino Peptides

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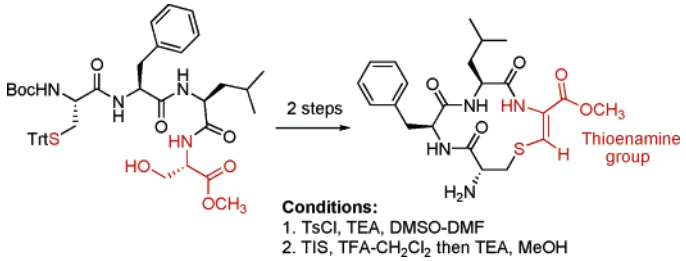
ABSTRACT



Following the discovery of callynormine A, a marine metabolite of a new class, the cyclic endiamino peptides, and the synthesis of compounds of this group, we have now prepared an analogue group of compounds, i.e., cyclic thioenamine peptides. The latter peptides contain the α-amino-β-thioacrylamide functionality, a potential new type of β-turn mimic. The superiority of the SH group over the NH_2 group in the reaction with enol-tosylates was demonstrated.

Callynormine A (Figure 1), isolated from the marine sponge *Callyspongia abnormis*, represents a new class of cyclic peptides, designated cyclic endiamino peptides.[1,2] A synthesis of the latter cyclic peptides based on the attack of an amino acid amino group on the masked formyl group of FGly (in the enol-tosylate form)[3] was developed.[2] The planar endiamino functionality is expected to reduce the conformational freedom of the cyclic peptides, i.e., to introduce a β-turn

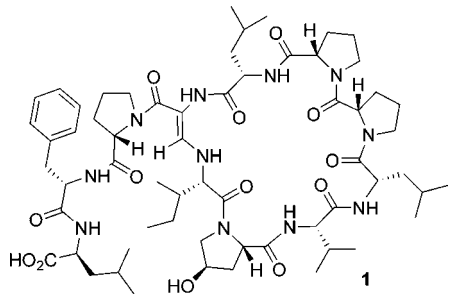


Figure 1. Callynormine A (**1**).

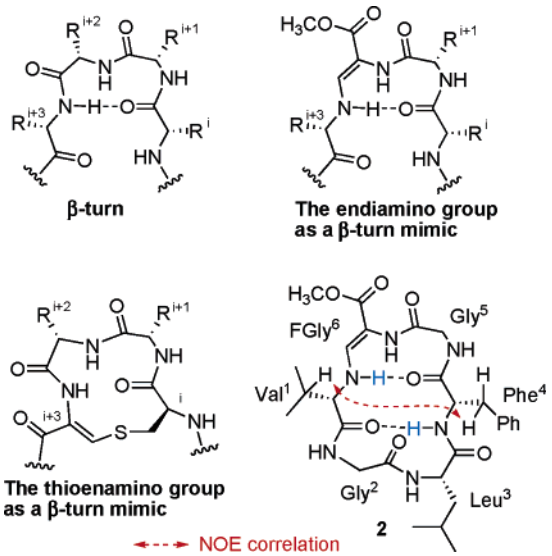


Figure 2. Endiamino and thioenamino groups as β-turn mimics, e.g., for the former hexapeptide **2**.[2]

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Table 1. Temperature Coefficients of the NH's of **2** in ppb/K[8]

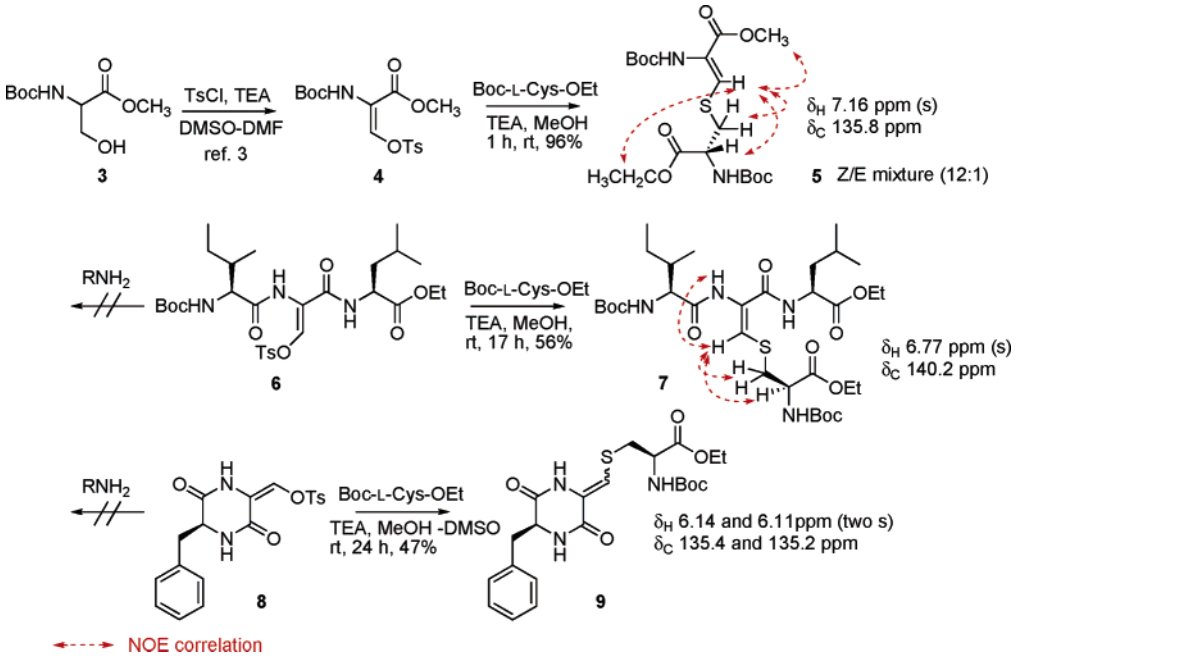
Val[1]	Gly[(2+5)]	Leu[3]	Phe[4]	FGly[5]
−3.8	−8.1	−9.3	−0.9	−7.0

(Figure 2). The β-turn is one of the important secondary structure elements in proteins.[4,5] There is a great deal of interest in the synthesis of small molecules that mimic a β-turn structure, for example, mimicking or interfering with protein−protein interactions[6] or binding with biological targets.[7] The α-amino-β-aminoacrylamide functionality, the endiamino group, represents a new class of β-turn mimic, as seen in the cyclic endiamino hexapeptide **2**[2] (Figure 2). The β-turn in **2**, as depicted in Figure 2, was confirmed by the temperature coefficients[8] of the N*H* groups of compound **2**; i.e., small coefficients were measured for the Val and Phe N*H* protons (Table 1) and further supported by a NOESY cross-peak between Val Hβ and Phe Hβ.

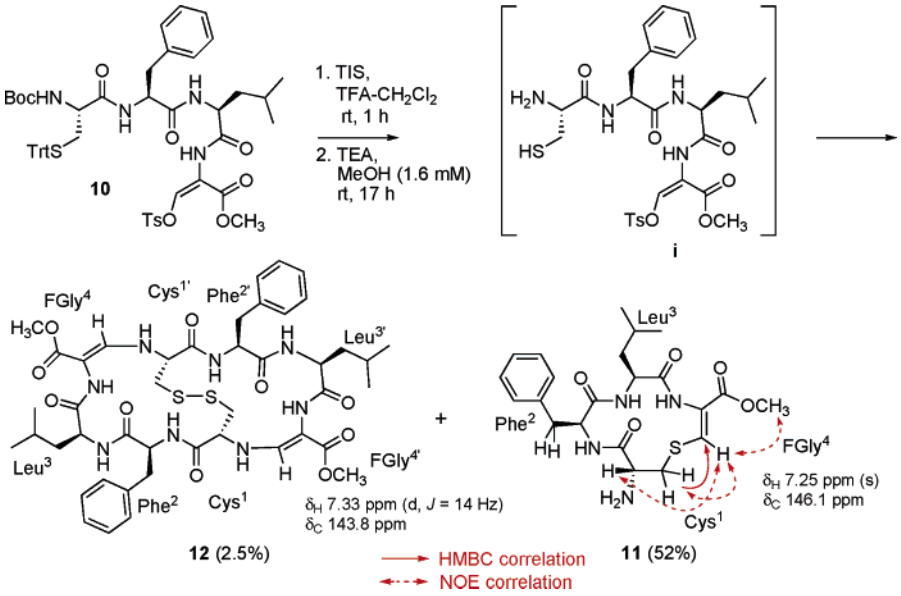
Triggered by the above synthesis of cyclic endiamino peptides, we synthesized another class of cyclic peptides possessing the α-amino-β-thioacrylamide functionality, designated cyclic thioenamino peptides, expected to reverse the direction of the peptide chain, i.e., become a β-turn (Figure 2). The latter new class of cyclic peptides was prepared by cyclization of an appropriate peptide via the nucleophilic attack of a Cys−*S*H group on the enol-tosylate of FGly, a reaction first tested by the reaction of Boc−Gly(OTs)−OMe (**4**, prepared from protected serine **3**) with Boc−L-Cys−OEt (Scheme 1). Indeed, this reaction yielded the expected dipeptide linked by the thioenamine group[9] (compound **5**).[10] Not only did the thiol substitute the OTs group but also this substitution even exceeded the reaction with primary amino groups. Namely, when tripeptide **6** was reacted with the abovementioned thiol (Boc−L-Cys−OEt), it afforded the expected adduct **7**[11] whereas the reaction of **6** with primary amines under similar conditions failed to give the endiamino group. Whereas enol-tosylates of the esters of FGly indeed react with amines, amidation of the FGly carboxylic group reduces the reactivity of the double bond of the enol-tosylate, e.g., in diketopiperazine **8** which no longer reacts with amines even under more severe conditions. On the contrary, compound **8** reacts with the thiol group of Boc−L-Cys−OEt to give compound **9**[12] as a 7 to 3 mixture of the geometric isomers, Compound **8**'s reactivity toward thiols affords interesting synthons for attractive DKP derivatives in the drug discovery search.[13]

The reactions of compounds **4** and **6** (Scheme 1) demonstrate the possibility to connect amine and thiol substituents to the Ser residue of peptides, via the FGly(OTs) derivative of the Ser. After verifying the reaction of the enol-tosylate of FGly with the thiol group vide supra, L-Cys-L-Phe-L-Leu-FGly(OTs)−OMe (**i**) was prepared by deprotection of compound **10** (Scheme 2). Overnight stirring of **i**, which was not further purified, in methanol at room temperature yielded the desired cyclic thioenamino peptide **11**[14] in 50% yield, accompanied by minute amounts of the dimeric cyclic endiamino peptide **12**[15] (2.5%, Scheme 2). This reaction confirmed again the superiority of the SH group over the NH_2 group in the reaction with the enol-tosylate group. According to the HRESMS spectrum of **12**, it became clear that the two trans-annular thiol groups oxidized to form, by the known air-oxidation of thiol groups,[16] a disulfide bridge. Whether the oxidation to the disulfide bridge takes place before or after obtaining the endiamino groups is unknown.

Scheme 1. Synthesis of Thioenamino Peptides



Scheme 2. Synthesis of Cyclic Thioenamino Peptide **11** and Cyclic Endiamino Peptide **12**



The structure elucidation of additional products, obtained in minute amounts, is ongoing.

The thioenamino group as in **11** (Scheme 2), supported by the low-temperature coefficients of the NH groups (ca. 1 ppb/K) vide supra, is another β-turn mimic. The β-turn is one of the three major motifs of peptide and protein secondary structure. The β-turn plays a key role in many biological molecular events. Hence, the construction of new β-turn mimetics, namely, the endiamino and thioenamino functionalities, is an important contribution to the field.

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Supporting Information Available: Experimental procedures and spectral characterization of all compounds. ^{1}H NMR and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The structure of compound **5** (obtained as a colorless oil) was established from the ^{1}H, ^{13}C NMR, and HRESMS (*m*/*z* 449.1966 (MH+)) data. The characteristic vinyl thioenamine proton resonances were at δ 7.16 (s) ppm, and its carbon resonances were at 135.8 ppm.

(11) The structure of compound **7** (obtained as a colorless oil) was established from the ^{1}H, ^{13}C NMR, and HRESMS (*m*/*z* 711.3547 (M + Na$^+$)) data. The characteristic vinyl thioenamine proton resonances were at δ 6.77 (s) ppm, and its carbon resonances were at 140.2 (d) ppm.

(12) Compound **9** (obtained as an amorphous solid) was isolated as an *E*/*Z* mixture (7:3) of the geometric isomers. Its structure was established from the ^{1}H, ^{13}C NMR, and HRESMS (*m*/*z* 486.1674 (M + Na+)) data. The characteristic vinyl thioenamine proton resonances were at δ 6.14 and 6.11 (two s) ppm, and their carbon resonances were at 135.4 and 135.2 (two d) ppm.

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(14) The structure of compound **11** (obtained as an amorphous solid) was established from the 1D and 2D NMR and HRESMS (*m*/*z* 458.1873 (M + Na+)) data. The characteristic vinyl thioenamine proton resonances were at δ 7.25 (s) ppm, and its carbon resonances were at 146.1 (d) ppm. HMBC correlation from Cys−Hβ to the vinyl carbon and NOESY correlations between the vinyl proton and Cys−Hα, Cis−Hβ, and the OCH3 group ensured the structure.

(15) The structure of compound **12** (obtained as a colorless oil) was established from the ^{1}H NMR and HRESMS (*m*/*z* 945.3602 (M + Na$^+$)) data. The characteristic vinyl thioenamine proton resonances were at δ 7.33 (d, J = 13 Hz) ppm.

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