Communication

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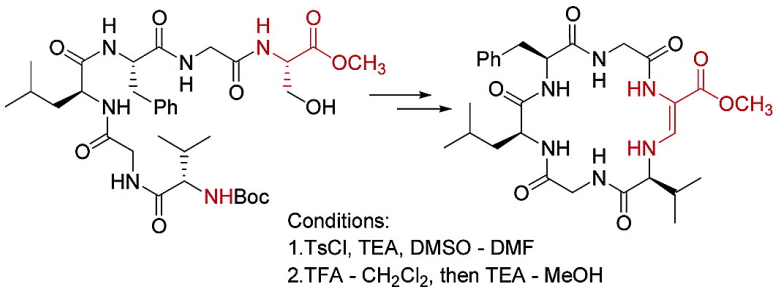

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Synthesis of Cyclic Endiamino Peptides

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Cyclic endiamino peptides, represented by callynormine A (Figure 1),[1] are a new class of heterodetic peptides embodying the α-amino-β-aminoacrylamide functionality (instead of the ester group of depsipeptides). It is suggested that the endiamino group is derived from the condensation of the formyl group of FGly[2,3] and the amino group of another amino acid (Ile in the case of compound **1**).[1] α-Formylglycine (FGly) was recently reported for both eukaryotic and prokaryotic sulfatases—located within the catalytic site of the enzyme.[2,3] It was shown that the formylglycine is generated by oxidation of cysteine or serine and, furthermore, that the FGly hydrate is covalently sulfated[2] or covalently phosphorylated[3] during catalysis. To the best of our knowledge, there are no reports of natural compounds embodying the endiamino group. Indeed, synthetic linear compounds with this group are known.[4,5] The endiamino group is of special interest for the synthesis of biomimetic cyclic peptides, as it is expected to introduce additional rigidity into their structure. Hereafter we report the first synthesis of several cyclic endiamino peptides, including 2-(1*H*)-pyrazinone, which, formally, is the smallest member of this new group. We also demonstrate the preparation of endiamino-containing building blocks for biomimetic peptides. FGly is very unstable. However, its enol-tosylate derivative, prepared from serine, is stable and acts with amino groups as an aldehyde to produce the α-amido-β-aminoacrylamide functionality.[4]

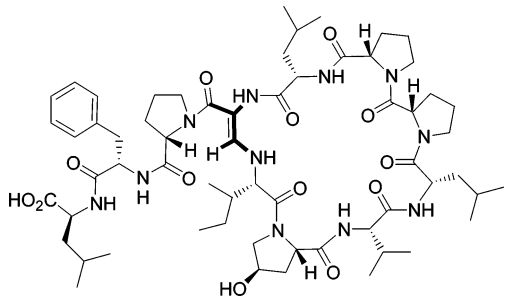


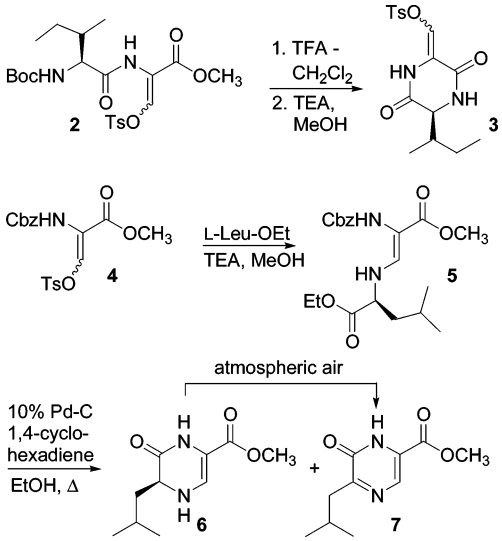
Figure 1. Callynormine A (**1**).

Cyclic peptides and depsipeptides have been characterized in many organisms and show a wide spectrum of biological activities. Hence, the cyclic peptides are promising lead compounds for potential drugs. The special quality of these cyclic peptides stems, inter alia, from the reduction in conformational freedom brought about by the cyclization, which is expected to result in higher receptor binding affinities. Replacing an amide bond, or the ester group of depsipeptides, with the endiamino functionality is anticipated to introduce additional rigidity in the cyclic endiamino peptides.

The macrocyclization step, which is known to be the yield-determining step for cyclic peptides, can, in the case of the cyclic endiamino peptides, be achieved by the formation of either an amide or the endiamino functionality.[1] Examples of both routes follow. It could also be expected that the tendency to cyclize will change with the size of the ring, as is known for cyclic peptides.[6]

Like dipeptides, which have a high tendency to cyclize to diketopiperazines, enol-tosylates of FGly amino acid methyl esters (e.g. compound **2**, Scheme 1) may also give the corresponding diketo-

Scheme 1



piperazine, rather than the cyclic six-membered endiamino peptide, carrying the enol-tosylate functionality, an anchor for the connection of additional amino acids. In this event, deprotection of the Boc group from the enol-tosylate derivative of *N*-Boc-Ile-FGly methyl ester (**2**) indeed afforded the diketo-piperazine (**3**), rather than the endiamino cyclic peptide (Scheme 1). Compound **3** can potentially react further with amines to give interesting synthons.

In fact, a six-membered endiamino peptide (e.g. **6**) could be obtained by first preparing the endiamino functionality followed by internal amidation, from the reaction of the deprotected amino group of FGly with the ester group of the second amino acid. An example is the synthesis of compound **6** from **4** via **5** (Scheme 1). As expected, compound **6** readily oxidizes to the 2-(1*H*)-pyrazinone **7**.[7] Elimination of the chiral center of the leucine of **6** brought about the expected collapse of the two doublets of the leucine methyls (δ_H 0.92 and 0.95 ppm) into a single doublet (δ_H 0.96 ppm) in **7**. The latter synthesis is a new route to the preparation of substituted 2-(1*H*)-pyrazinones,[8] known as secondary metabolites, produced by *Aspergillus* and *Streptomyces* and was recently carried out in a different way.[9]

All-L cyclotripeptides with all α-amino acids are almost impossible to construct, as the corresponding cyclodimers, the cyclohexapeptides, are the main products.[6] This was also the case with the enol-tosylate of tripeptide **8**, which gave the cyclic dimeric endiamino hexapeptide **9** together with the corresponding trimeric nonapeptide **10**[10] (Scheme 2). Similarly, tetrapeptide **11** afforded the symmetric dimeric cyclic endiamino octapeptide **12**[11] (Scheme 2). From hexapeptide **13**, it was already possible to obtain the

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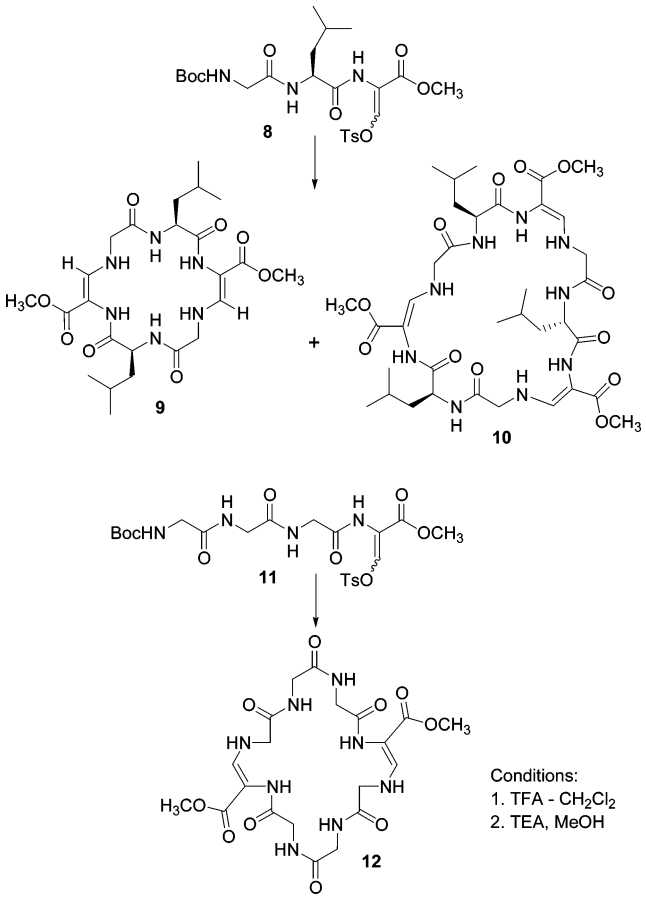
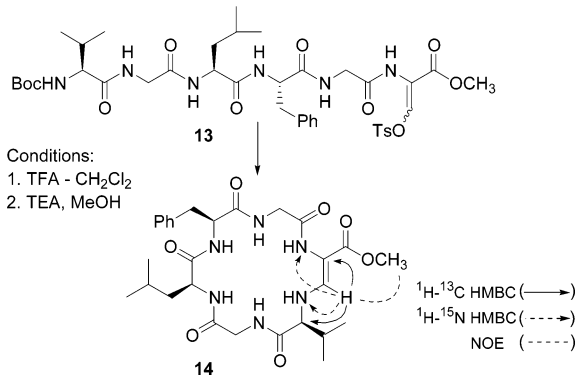
Scheme 2



desired monomeric cyclic endiamino peptide **14**[12] (Scheme 3). Characteristic of the endiamino group in **1** and all synthesized cyclic compounds are their NMR resonances: e.g. δ_H 7.29 ppm (d, J = 13.5 Hz) and δ_C 145.2 ppm (d) for the ═*CH*NH− group in **14**.

Scheme 3



Furthermore, a *Z* stereochemistry was established for the endiamino group in all synthesized cyclic compounds, according to the low-field resonance of the endiamino proton (δ_H 7.2−7.3 ppm) and an NOE between the latter proton and the neighboring ester OCH_3 group. Suitable for compound **14**, and for the other cyclic endiamino peptide, were the observed $^1H^{13}C$- and $^1H^{15}N$-HMBC correlations, as shown for **14** in Scheme 3.[12]

For the reaction of the enol-tosylate of the FGly group in the various peptides with amines in MeOH, we suggest an addition−elimination mechanism rather than the mechanism reported earlier;[4] experimental results will be reported in detail elsewhere.

In summary, the above results describe the first synthesis of cyclic endiamino peptides and endiamino building blocks, where the preparations of compounds **9**, **10**, **12**, and **14** demonstrate the possibility of incorporation of the endiamino functionality in cyclic peptides, with the endiamino group replacing the lactone of depsipeptides, further reducing the conformational freedom. In addition, the applied methodology enabled the synthesis of interesting endiamino building blocks and pyrazin-6-ones.

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Supporting Information Available: Experimental procedures and spectral characterization data for all compounds and ^1H 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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(7) All new structures were confirmed by HRMS and 1D and 2D NMR experiments.
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(10) According to the NMR data both **9** and **10** are symmetric, exhibiting a single tripeptide moiety. Both give the suitable HRESMS data for the suggested structure (*m*/*z* 561.2890 $(M + Na)^+$ and 830.4018 $(M + Na)^+$ for **9** and **10**, respectively). The characteristic vinyl endiamine proton (originating from the FGly acid) resonances at δ 7.33 (d, J = 14 Hz) and 7.26 (d, J = 14 Hz) for **9** and **10**, respectively.
(11) Compound **12** exhibited the proper HRESMS (*m*/*z* 563.2086 $(M + Na)^+$) and ^1H NMR data, confirming a symmetric dimeric structure.
(12) The structure of **14** was established from the ^1H,^{13}C NMR and HRESMS (*m*/*z* 573.3002 $(MH)^+$) data as well from the δ_N values and their NH correlations derived from NH-HMBC and NH-HSQC-TOCSY experiments.

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