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Built-in 5-Aminooxazole as an Internal Activator of the Terminal Carboxylic Acid: An Alternative Access to Macrocyclodepsipeptides

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Abstract: A conceptually novel macrolactonization technology is described. A strategically positioned 5-aminooxazole served as an internal traceless activator of the neighboring C-terminal carboxylic acid allowing the occurrence of macrolactonization under mild acidic conditions. It is a domino process involving a sequence of: a) protonation of 5-amino oxazole leading to an electrophilic iminium salt; b) trapping the iminium species by the neighboring *C*-terminal carboxylic acid leading to a putative spirolactone; c) intramolecular nucleophilic addition of the tethered alcohol onto the spirolactone followed by fragmentation to afford the macrolactone. No coupling reagent is required and the entire sequence is triggered by trifluoroacetic acid under very mild conditions (MeCN, room temperature). By combining with a three-component synthesis of 5-aminooxazole, a two-step synthesis of structurally complex cyclodepsipeptides from readily accessible starting materials is developed.

Keywords: Cyclodepsipeptide · Isonitrile · Macrocyclization · Multicomponent reaction · Oxazole

1. Introduction

After having spent almost 20 years (as a PhD student and then as a faculty member) in Institut de Chimie des Substances Naturelles (ICSN), CNRS in France, I accepted with great pleasure and honor an offer from EPFL and integrated into the Institute of Chemical Sciences and Engineering (ISIC) on Sept 1st 2010. Total synthesis of complex natural products (*e.g.* ecteinascidin 743,[1] quinocarcin,[2] complestatin,[3] alstoscholarine,[4] Fig. 1), the development of efficient multiple-bond forming processes (metal-catalyzed domino sequence,[5] multicomponent reaction[6]) and enantioselective transformation[7] have been and will remain to be the focus of our group's research efforts.

Instead of categorizing the research subjects that we're trying to develop in ISIC, we would rather give a short account on one specific reaction, *i.e.* macrolactonization for access to diversely substituted macrocyclodepsipeptides (Scheme 1). The development of a novel macrocyclization reaction in the absence of external coupling reagents and to eventually provide a tool suitable for the construction of macrocyclodepsispeptide libraries motivated this research program.

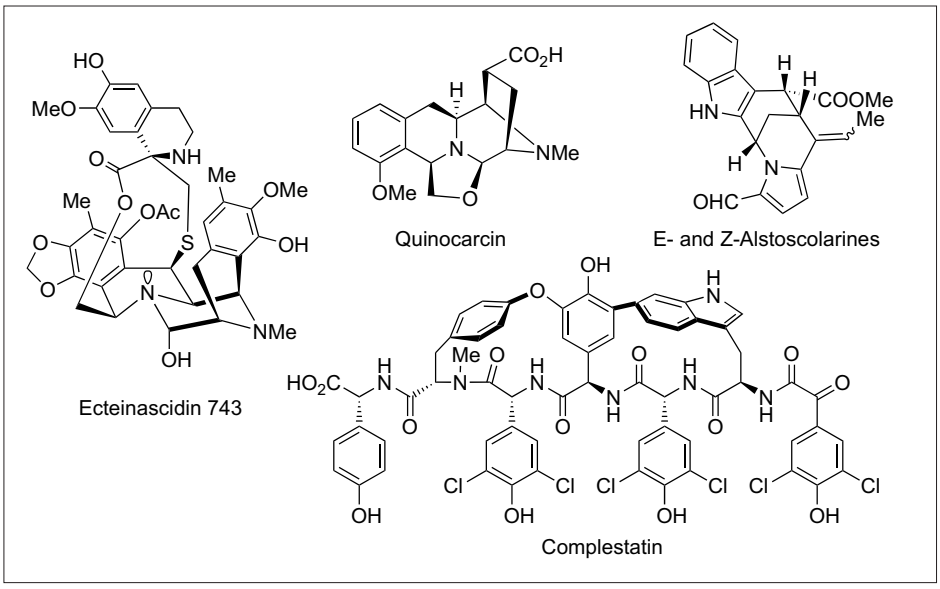
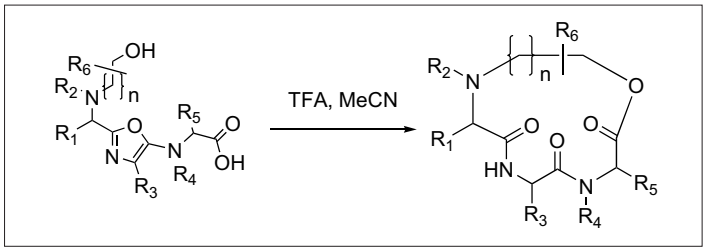


Fig. 1.



Scheme 1.

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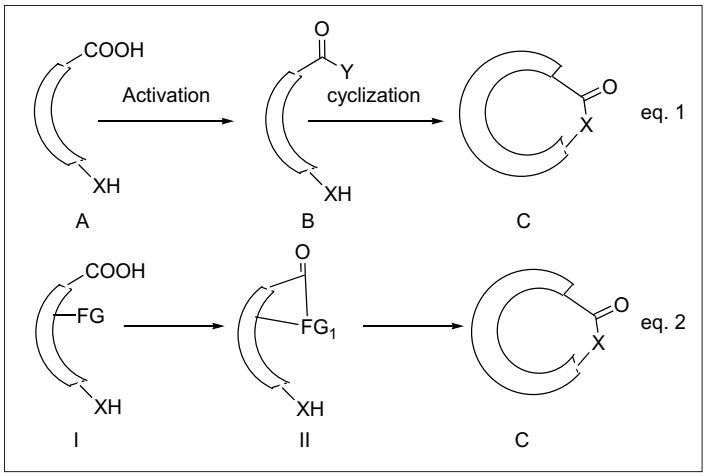
2. Background

Cyclodepsipeptides are analogues of cyclopeptides having at least one ester linkage as part of their peptidic backbone. They have been found in many natural environments and shown a wide spectrum of biological activities including anticancer, antibacterial, antiviral, antifungal, and anti-inflammatory properties. Whereas the synthesis of linear peptides (depsipeptides) generally proceeds well thanks to the development of new and efficient coupling reagents, access to cyclodepsipeptides is much more difficult. Furthermore, the cyclization outcome is highly sequence-dependent making the synthesis of cyclodepsipeptide libraries particularly challenging. This last point is particularly unfortunate since cyclodepsipeptides as well as cyclopeptides, are considered as privileged structures in medicinal chemistry.[8]

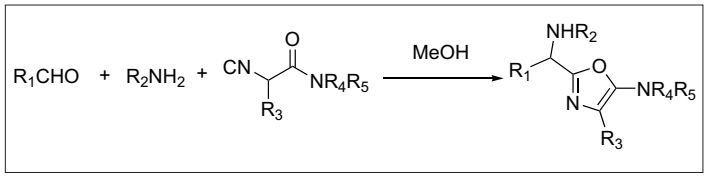
Macrolactamization and macrolactonization of a seco-acid are among the most commonly used reactions for the synthesis of cyclodepsipeptides. To perform such transformations, activation of the carboxylic acid using an external coupling reagent is generally required (eq. 1, Scheme 2). Our long-term interests in the development of novel macrocyclization reactions[9–11] brought us to investigate a new strategy for the synthesis of cyclodepsipeptide that avoids the use of an external activating agent. The underlying principle is shown in equation 2 (Scheme 2). If a functional group (FG) was incorporated into the peptide backbone and was capable of interacting with the nearby C-terminal carboxylic acid to produce a more electrophilic carbonyl group, then a cyclization would be expected if a tethered nucleophile were available. To make this approach synthetically useful, an ideal functional group (FG) must fulfill the following criteria: a) its introduction into the peptide backbone should be facile and the resulting linear peptide should have sufficient shelf stability; b) its ability to activate the carboxylic acid should be triggered under very mild conditions without using sophisticated reagents; c) the activation and the cyclization should be performed under the same conditions without requiring the isolation of any intermediate; d) after serving as an activating group, it should become an integral part of the peptide backbone (a traceless activating group).

As a prelude to this research program, we developed an efficient three-component synthesis of 5-aminooxazoles from aldehydes, amines and α-isocyanoacetamides (Scheme 3).[12] Subsequent exploitation of the chemical properties of this heterocycle, especially the diene unit of oxazole allowed us to develop a range of multicomponent reactions for the rapid access to medicinally relevant heterocycles.[13] Parallel to the exploitation of the diene activity of oxazole, we were interested in the chemistry of the protonated forms of 5-aminooxazole[14] and were wondering if its potential reactivity could be exploited for the development of a new macrocyclization methodology (Fig. 2). It turned out that 5-aminooxazole satisfied all the stringent criteria that we self-imposed allowing us to develop a conceptually new activation/cyclization strategy (*cf* eq 2, Scheme 2, FG = 5-aminooxazole).

Scheme 2.



Scheme 3.



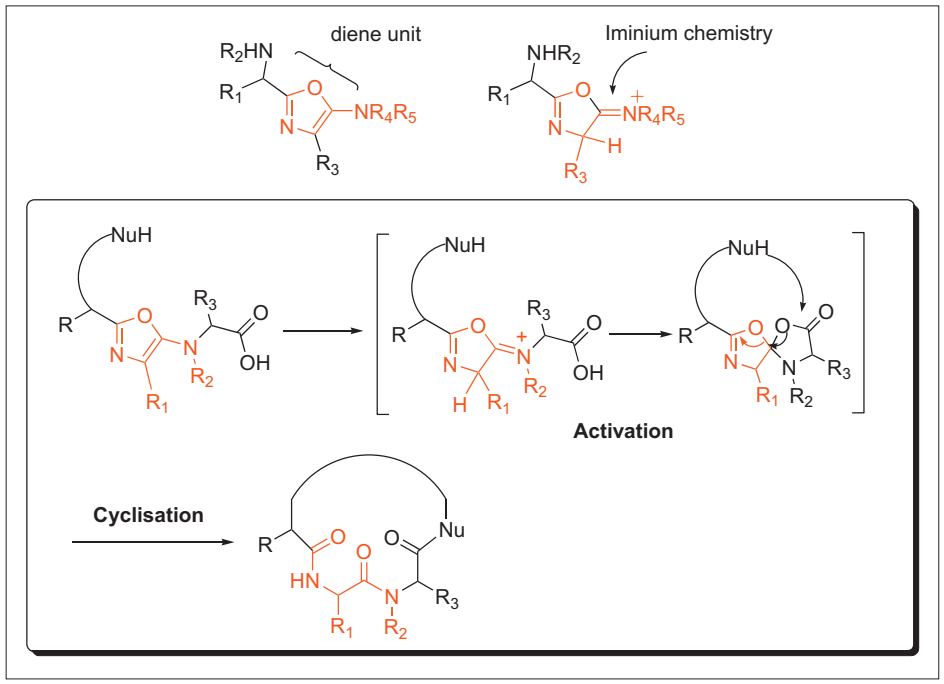
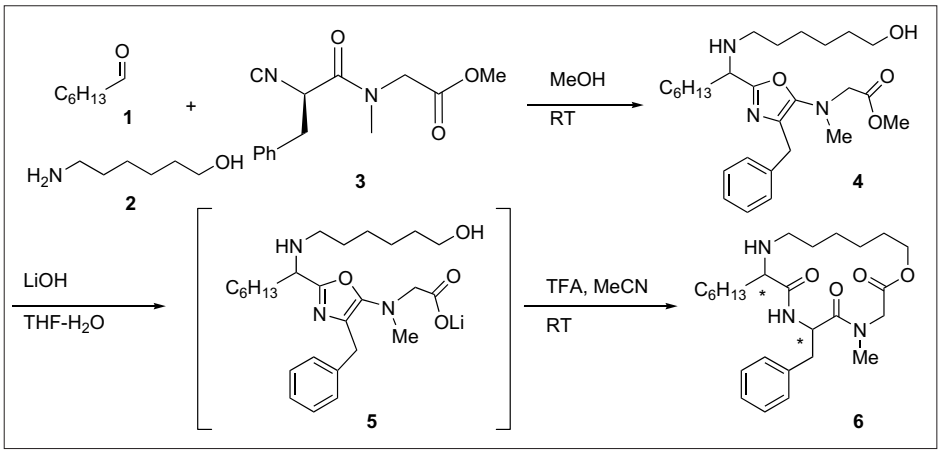


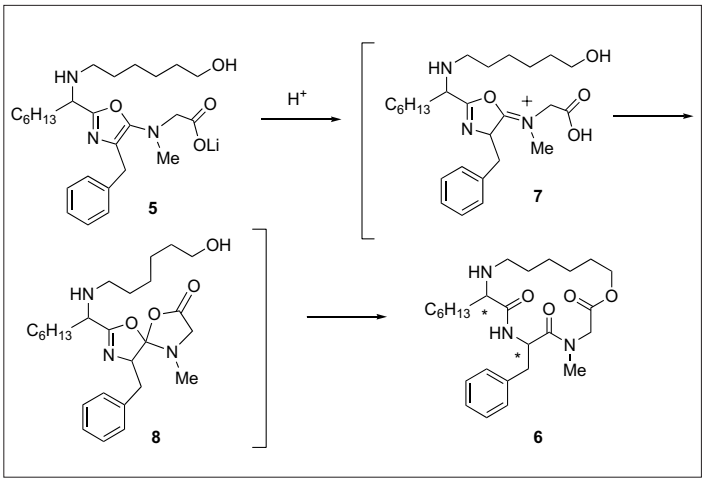
Fig. 2.

3. 5-Aminooxazole as an Internal Activator of the Terminal Carboxylic Acid: Proof of Concept and Mechanistic Implication

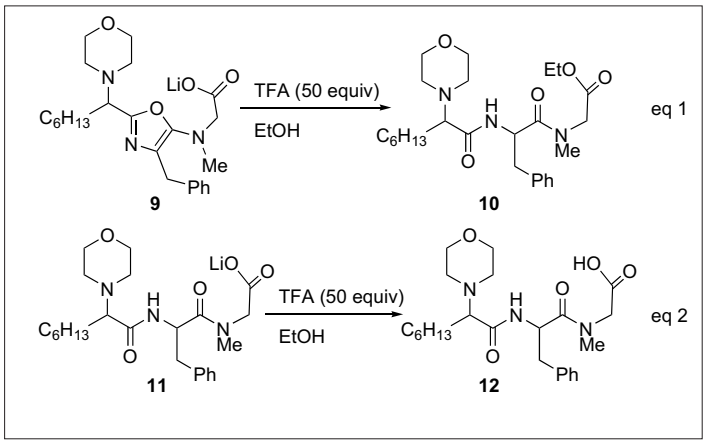
To evaluate the projected domino internal activation/cyclization process, the functionalized oxazole **4** was synthesized by a three-component reaction of heptanal (**1**), 6-aminohexan-1-ol (**2**) and isocyanide **3** at room temperature. Saponification of the methyl ester **4** (LiOH) followed by stirring of an acetonitrile solution of the lithium carboxylate **5** in the presence of TFA (50 equiv) at room temperature afforded the 16-membered cyclodepsipeptide **6** in



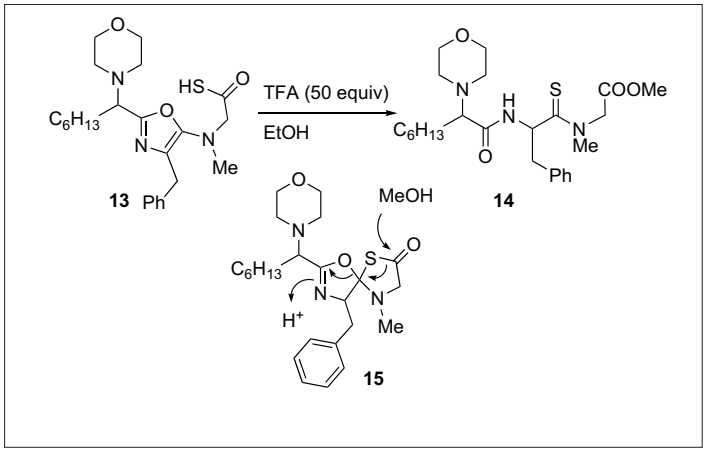
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

85% yield as a mixture of two diastereomers (*dr* = 1/1, Scheme 4).[15]

A mechanistic hypothesis accounting for the formation of cyclodepsipeptide **6** is shown in Scheme 5. Protonation of oxazole **5** under acidic conditions should produce the iminium salt **7**, which could in turn be trapped by the neighboring carboxylate ion leading to spirolactone **8**. Being highly electrophilic together with reduced conformational flexibility,[16] the carbonyl carbon of intermediate **8** could then be attacked by the tethered nucleophile leading to, after fragmentation, the desired macrocycle. It is interesting to note that the 5-aminooxazole, after having served as an activator of the terminal carboxylic acid, became an integral part of a peptide chain. It could thus be considered as a traceless activator for the present synthesis of cyclic peptides.

Two subsequent control experiments provided clear-cut, albeit indirect, evidence to the above proposed domino activation/cyclization mechanism. Firstly, stirring an ethanol solution of oxazole **9** with TFA (50 equiv) afforded cleanly the ethyl ester of tripeptide **10** (eq 1, Scheme 6). On the other hand, treatment of a lithium salt of tripeptide **11** under identical conditions produced only the corresponding acid **12** without producing even a trace amount of ethyl ester (eq 2, Scheme 6). These results clearly indicated that oxazole unit is responsible for the activation and esterification of the terminal carboxylic acid in **9**. Secondly, submitting the thioacid **13** under acidic conditions afforded the thioamide **14** resulting from the migration of sulfur atom from the terminal to the internal position (Scheme 7). Such atom migration could be nicely explained by evoking the spirolactone intermediate **15**.

Besides being conceptually novel, the overall transformation is mechanistically intriguing. The most relevant example, though conceptually different, is the so-called 'direct amide cyclization' elegantly developed by Heimgartner for the synthesis of cyclodepsipeptides containing α,α-disubstituted amino acid residues.[17]

4. 5-Aminooxazole as an Internal Activator of the Terminal Carboxylic Acid: Scope and Limitation

Using this new cyclization technology, two types of cyclodepsipeptides have been synthesized. When amino alcohol was used as a bi-functional substrate, the present methodology allowed access to **16**, structurally related to head-to-tail cyclization of cyclic peptide. On the other hand, when ω-hydroxy aldehyde was employed, a macrocycle **17**, reminiscent of the side

chain to *C*-terminal cyclization product, was obtained (Fig. 3).

By combining the three-component synthesis of 5-aminooxazoles and the present cyclization methodology, several dozens of cyclodepsipeptides of types **16** and **17** were synthesized in only two steps.[18] One example is illustrated in Scheme 8. Thus three-component condensation of dipeptide **18**, heptanal (**1**) and isocyanide **19** (MeOH, 60 °C) afforded the 5-aminooxazole **20** in 54% yield. Saponification of methyl ester followed by acidic treatment of the resulting lithium salt trigged the domino cyclization process leading to the 18-membered macrocycle **21** in 42% yield.

The same sequence has been applied to the synthesis of sugar-peptide hybrides as shown in Scheme 9.[19] A three-component reaction of a sugar amino alcohol **22**, heptanal (**1**), and a dipeptide isonitrile **19** in refluxing methanol afforded the corresponding 5-aminooxazole (structure not shown) which, after saponification, underwent a trifluoroacetic acid-promoted macrocyclization to furnish the cyclic sugar amino acid hybride **23** in 49% overall yield as a mixture of two diastereomers.[20]

Based on the same activation/cyclization principle, macrocyclodepsipetides having an α,α-disubstituted aminoacid unit(s) **24** were also readily accessible in two simple operations from very simple starting materials (Scheme 10).[21] In this case, an 5-iminooxazoline was formed as the initial three-compound adduct (**25**, isolable and characterized), which served then as an internal activator of the terminal carboxylic acid to afford the desired macrocycle **24** *via* intermediates **26** and **27**.

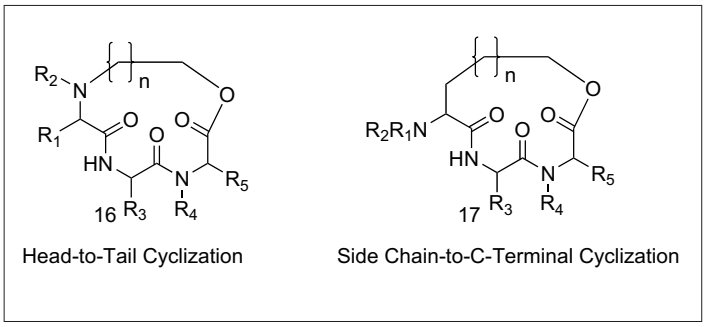
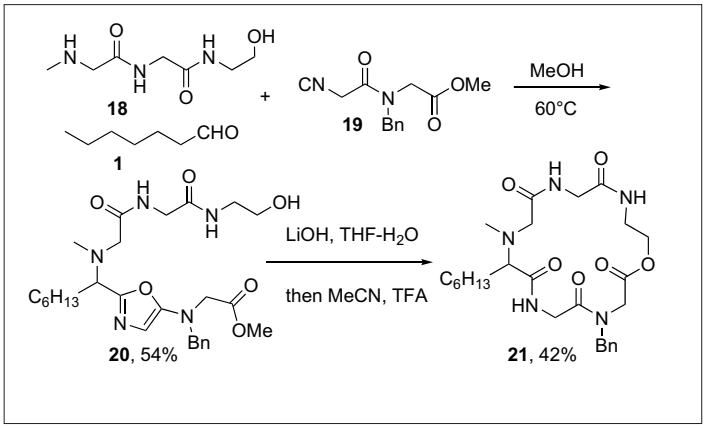
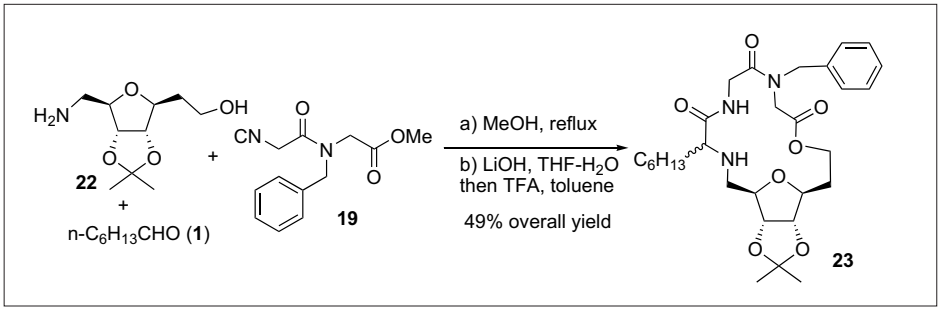


Fig. 3.



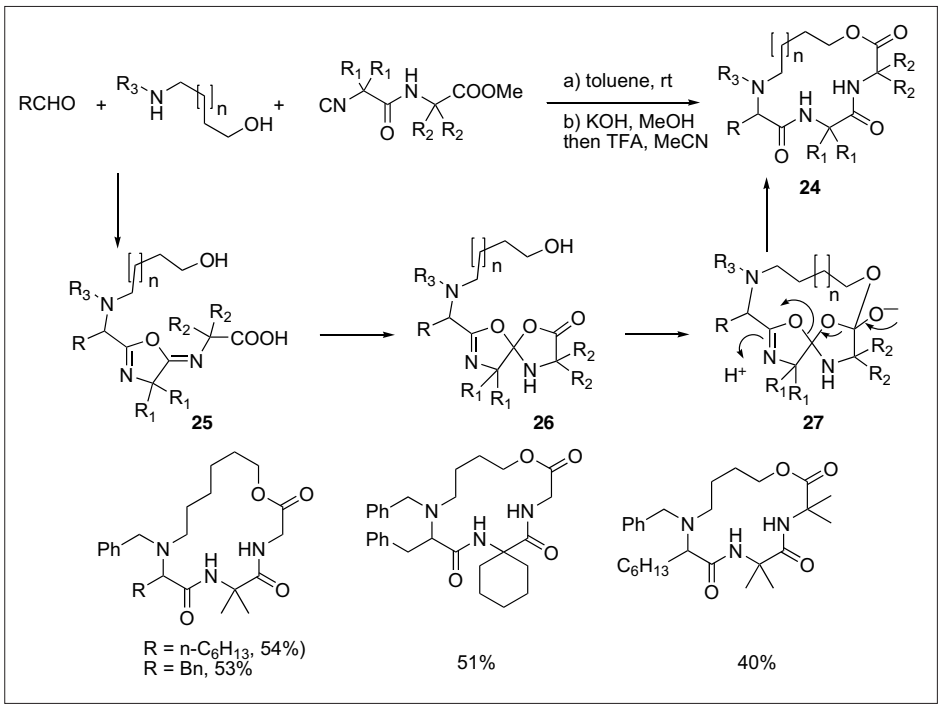
Scheme 8.



Scheme 9.

5. Conclusion

In summary, a conceptually novel macrolactonization technology is described using 5-aminooxazole as an internal activator of the terminal carboxylic acid. In this process, no coupling reagent is required and the entire sequence is triggered by just a few equivalents of trifluoroacetic acid under very mild conditions (MeCN, room temperature). The key 5-aminooxazole (or 5-iminooxazoline), after having served as an internal activator, became an integral part of the peptide backbone. It is thus a traceless internal activator. Combination of this domino process with our previously developed three-component synthesis of 5-aminooxazole allowed us to develop a two-step synthesis of structurally complex cyclodepsipeptides from readily accessible starting materials. In this operationally simple two-step sequence, a complex and difficult to access macrocycle was obtained with the concurrent formation of two C–O, one C–N and one C–C bonds.



Scheme 10.

One equivalent of base (LiOH or KOH) and trifluoroacetic acid were all what we needed to trigger this transformation with the generation of one molecule of water and methanol as the only by-products. We believed that the cyclization strategy reported herein is different from any other known approaches for this class of macrocycle and is particularly appealing in diversity oriented synthesis programs.[22]

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