Activation of a Terminal Carboxylic Acid by an Internal Oxazole: A Novel Synthesis of Macrocyclodepsipeptide

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An increasing large number of bioactive cyclopeptides and cyclodepsipeptides have been found in nature.[1] Their reduced conformational flexibility, bioavailability, and metabolic stability make them important leads for drug discovery.[2] Neither as completely rigid as small ring heterocycles nor as flexible as acyclic counterparts, macrocycles provide a unique coverage of three-dimensional space that is useful for elucidating the bioactive conformation and for protein surface mimetics in the increasingly important area of protein−protein interactions.[3] Not surprisingly, they have been for years one of the privileged structures in medicinal chemistry.[4] With the advances in the fields of functional genomics[5] and chemical genetics,[6] efficient combinatorial synthesis of natural product-like and drug-like compounds such as cyclodepsipeptides will be welcomed.[7] We report herein a conceptually novel synthesis of macrocyclodepsipeptide **1** as outlined in Scheme 1. A three-component synthesis of the functionalized oxazole followed by an internal activation of the terminal carboxylate and a controlled macrocyclization are the keys to the present process. Fleury's mechanistic study on acidic hydrolysis of the 5-amino oxazole constitutes the basis of the projected activation−cyclization sequence.[8]

Applying our recently developed three-component reaction,[9] a range of highly functionalized 5-amino oxazoles (**5a**−**5j**, Figure 1) were synthesized in good to excellent yield by simply heating a methanol solution of an aldehyde (**2**), an amino alcohol (**3**), and a dipeptide isocyanide (**4**).[10] Saponification of methyl ester (LiOH, THF−H_2O) gave the corresponding lithium salt without affecting the oxazole core.[11] Using **8a** as a testing compound, cyclization conditions were surveyed under various conditions. Some representative results are summarized in Table 1.

As it is seen, the trifluoroacetic acid turned out to be the acid of choice among those investigated (entries 1, vs 5 and 6).

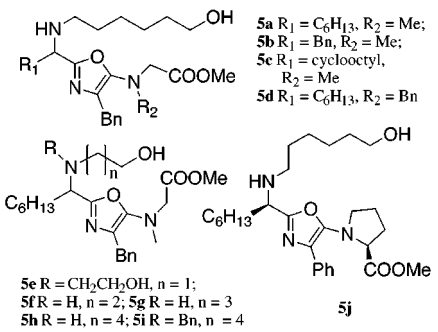


Figure 1. Three-component synthesis of 5-amino oxazole.

Scheme 1

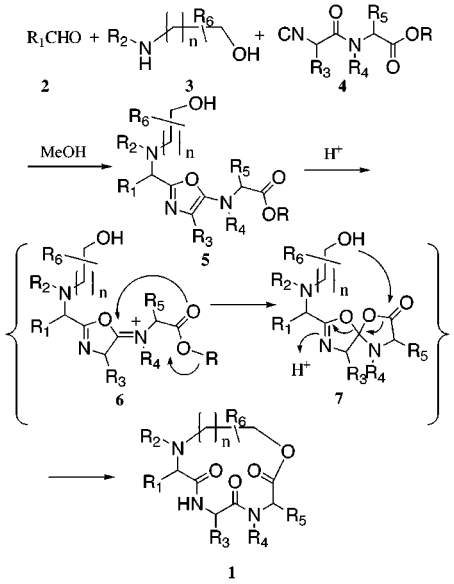
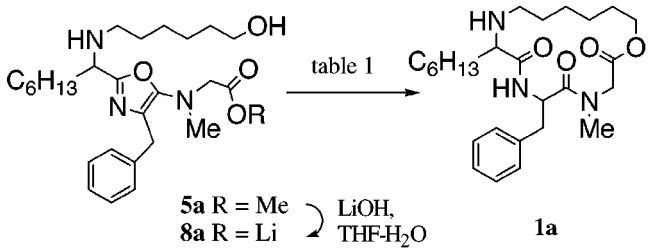


Table 1. Survey of Macrolactonization Conditions



entries	solvent[a]	acid	yield (%)	dr[b]
1	toluene	TFA	85	1/1
2	MeCN	TFA	81	1/2
3	DMF	TFA	63	1/1.9
4	THF	TFA	59	1/2.1
5	toluene	TsOH	9	1/1.7
6	toluene	$HClO_4$	7	1/2.3

[a] Concentration of substrate **5a**: 0.001 M, abbreviation: MeCN = acetonitrile, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TsOH = *p*-toluenesulfonic acid. [b] dr = diastereomeric ratio.

Curiously, the cyclization worked in both nonpolar and aprotic dipolar solvents, with toluene and acetonitrile being the best reaction mediums. A moderate asymmetric induction was observed during the protonation step of oxazole, leading to two diastereomers in a one-to-two ratio.[12] Figure 2 lists the cyclodepsipeptides synthesized.[13] Keeping in mind its potential application

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(1) (a) Fusetani, N.; Matsunaga, S. *Chem. Rev.* **1993**, *93*, 1793−1806. (b) Tang, Y. Q.; Yuan, J.; Osapay, K.; Tran, D.; Miller, C. J.; Quellete, A. J.; Selsted, M. E. *Science* **1999**, *286*, 498−502.
(2) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654−686.
(3) (a) Kessler, H. C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−513. (b) Toniolo, *Int. J. Pept. Protein Res.* **1990**, *35*, 287−300
(4) (a) Shu, Y. Z. *J. Nat. Prod.* **1998**, *61*, 1053−1071. (b) Newman, D. J.; Gragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215−234.
(5) Palfreyman, M. G. *Expert Opin. Invest. Drugs* **1998**, 1201−1207.
(6) (a) Mitchison, T. J. *Chem. Biol.* **1994**, *1*, 3−6. (b) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152.
(7) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Arya, P.; Chou, D. T. H.; Baek, M. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339−346.
(8) (a) Clerin, D.; Fleury, J. P. *Bull. Soc. Chim. Fr.* **1973**, 3127−3142. (b) Clerin, D.; Fleury, J. P. *Tetrahedron* **1974**, *30*, 469−474.
(9) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877−880.
(10) Three aldehydes, eight amino alcohols, and three isocyanides were used in this preliminary study (cf. Supporting Information).
(11) Model studies indicated that methyl ester terminal could not be activated by oxazole under the acidic conditions.

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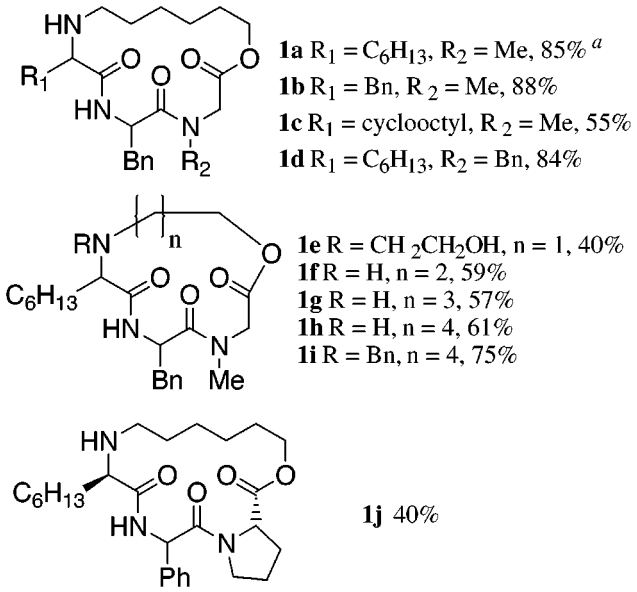


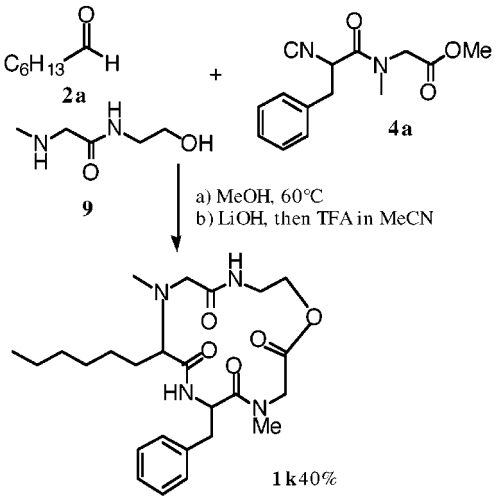
Figure 2. Total yield of two diastereomers.

in combinatorial synthesis, the reaction conditions have not been individually optimized. The molecular mass of the cyclodepsipeptide was determined by ES-MS at high dilution that enabled us to differentiate between the cyclic monomer and the cyclic dimer. As it is evident, all substituents at the peripheral of the macrocycle (from R_1 to R_5, see general structure of **1** in Scheme 1) can be varied at will, as well as the ring size (carbon chain number *n*). Indeed, 12-, 13-, 14-, 15-, and 16-membered macrocycles were synthesized with good to excellent yield.

To further demonstrate the generality of this methodology, a two-step synthesis of cyclodepsipeptide **1k** was performed using a sarcosine derivative as an amino alcohol input (Scheme 2). Thus, heating a solution of compounds **2a**, **9**, and **4a** gave the corresponding 5-amino oxazole, which after saponification and acidic treatment gave the cyclodepsipeptide **1k** in 40% overall yield.

An efficient activation and a favorable conformation of the linear precursor are two key factors that dictate the outcome of a given cyclization. While the carboxylic acid in intermediate **7**

Scheme 2



(Scheme 1) was certainly activated enough for nucleophilic attack, the present cyclization is also driven by the reduced entropy loss. Indeed, comparing the structure **7** and that of the classic cyclization precursor, one realized that there are at least six free bond rotations less in the former, thus decreasing the conformational mobility and consequently facilitating the end-to-end macrocyclization.

In conclusion, a new concept for the construction of macrocyclodepsipeptides from simple and readily available starting materials has been developed. The sequence consists of (a) a multicomponent reaction[14] and (b) a domino process[15] involving an activation of the terminal carboxylic acid function by a built-in oxazole followed by a macrocyclization under *acidic conditions*. The synthesis is atom-economic[16] since only a molecule of water and "MeO" is lost in the entire sequence. The overall process is also ecologically benign since LiOH and TFA are the only reagents used, while water and low-molecular weight alcohol (MeOH) are the only side products formed. Besides the significant methodological advance in the field of cyclopeptide synthesis, the strategy is especially suitable for combinatorial synthesis. Work is in progress to refine the stereoselectivity as well as to define the scope and limitation of this new cyclization technology.

Acknowledgment. Postdoctoral fellowships from Phône-Poulenc Industrialisation to Drs. G. Zhao and X. W. Sun are gratefully acknowledged. This paper is dedicated with deep respect to Professor S. Yamamura.

Supporting Information Available: Experimental procedures and physical data for compounds **1a**−**1i** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015854D

(12) Complete stereocontrol leading to *lk* relative stereochemistry has been reported by Lipshutz: (a) Lipshutz, B. H.; Hungate, R. W.; McCarthy, K. E. *Tetrahedron Lett.* **1983**, *24*, 5155−5158. (b) Lipshutz, B. H.; Huff, B. E.; McCarthy, K. E.; Miller, T. A.; Mukarram, S. M. J.; Siahaan, T. J.; Vaccaro, W. D.; Webb, H.; Falick, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 7032−7041.

(13) General procedure: A solution of 5-amino oxazole (**5**) and LiOH. H_2O (1.05 equiv) in THF/H_2O (3/1) was stirred at room temperature for 3 h and evaporated to dryness in vacuo. The residue obtained was dissolved in MeCN ($C = 10^{-3}$ M) and TFA (50 equiv) was added under a stream of Argon. The reaction mixture was stirred at room temperature and followed by TLC. When the reaction was completed, the volatile was evaporated under reduced pressure. A few drops of dichloromethane was added, and the resulting solution was basified to pH = 8−10 by adding a few drops of triethylamine. The light-yellow solution was immediately subjected to purification by preparative TLC.

(14) For recent reviews: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A. Brown, S. D. Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210 and references therein.

(15) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322.

(16) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.