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A Novel Strategy for the Synthesis of Medium-Sized Lactams

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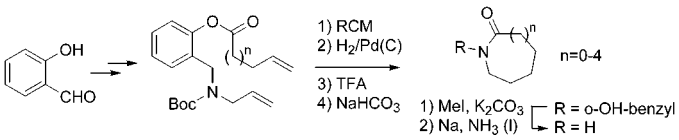
ABSTRACT

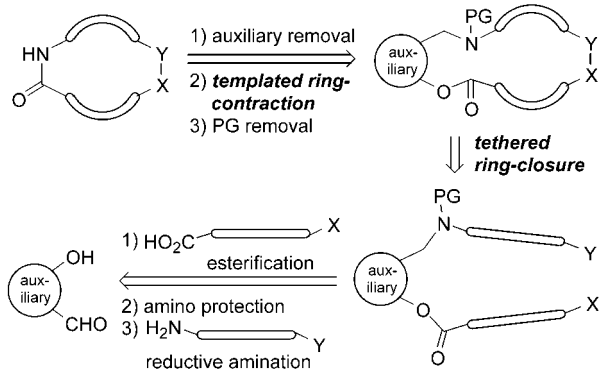


A novel method for the synthesis of medium-sized lactams based on an auxiliary-mediated combined tethered/templated strategy is presented. Cyclization by a tethered ring-closing metathesis reaction was followed by a templated transannular aminolysis reaction to give seven- to ten-membered lactams in good yields.

Medium-sized lactams (seven- to ten-membered) find wide application in important fields such as natural product chemistry and pharmaceutical research. Despite their relevance, the closure of seven- to ten-membered lactams especially remains a synthetic challenge.[1] Direct closure by lactamization proceeds in high yields only if appropriate substituents on the chain induce a conformation to the linear precursor molecule that brings the terminal groups in close proximity.[2] In the case of ω-amino acids lacking a structural bias to facilitate ring-closure, the main product is often the dimeric lactam. Besides conducting the reaction at high dilution, difficult lactams were closed by the use of templating metals,[2a−c] within micelles[2e] and within polymers.[2f] However, all of the methods described have drawbacks and often only moderate cyclization yields were obtained.

In this letter our first results are presented on the development of novel and generally applicable methods for the closure of medium-sized lactams. Our approach is based on the use of an auxiliary that facilitates *two* subsequent key reactions by playing a dual tethering and templating role (Scheme 1). The final templated transannular ring-contracting lactamization step is preceded by a macrocyclization reaction in which the auxiliary serves as a tether to bring together the mutually reactive X and Y groups.

Scheme 1. Retrosynthetic Outline of the Combined Tethered/Templated Approach toward Lactams



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(1) For review articles, see: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.

(2) For some earlier work on difficult lactamizations, see: (a) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. (b) Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 3049. (c) Yamamoto, Y.; Furuta, T. *Chem. Lett.* **1989**, 797. (d) Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671. (e) Rico, I.; Halvorsen, K.; Dubrule, C.; Lattes, A. *J. Org. Chem.* **1994**, *59*, 415. (f) Huang, W.; Kalivretenos, A. G. *Tetrahedron Lett.* **1995**, *36*, 9113. See also references cited in these articles.

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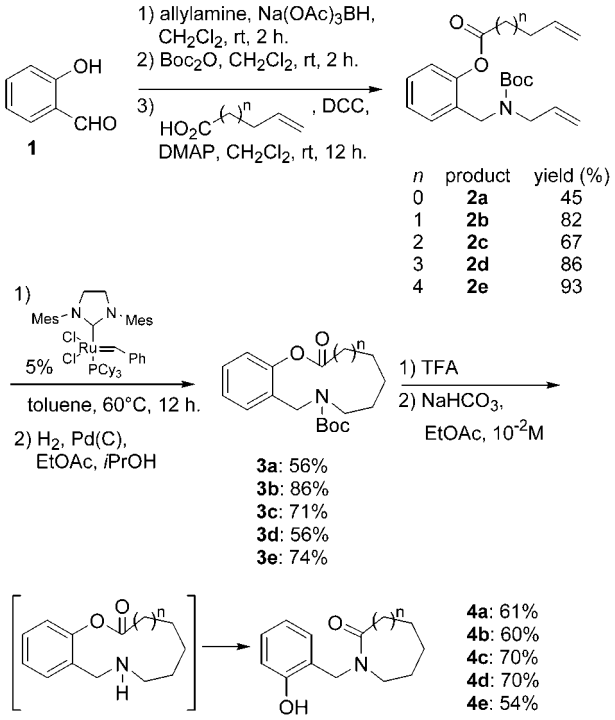
For this first proof of principle, salicylaldehyde was chosen as the auxiliary. Pioneering work of Meutermans and coworkers showed the power of similar auxiliaries in an approach toward difficult small cyclopeptides.[3]

The high reactivity of an aryl ester to aminolysis is combined with a correct spatial positioning of the secondary amine and carbonyl functional groups for the transannular ring-contraction reaction. As a model reaction, the versatile ring-closing metathesis (RCM) process was chosen for the tethered macrocyclization step.[4]

The synthesis of the starting materials commenced with a reductive amination reaction of salicylaldehyde (**1**) with allylamine using $Na(OAc)_3BH$ as the reducing agent (Scheme 2). After Boc-protection of the resulting secondary amine,

Scheme 2. Synthesis of Cyclization Precursors and Tethered RCM and Templated Lactamization Reactions



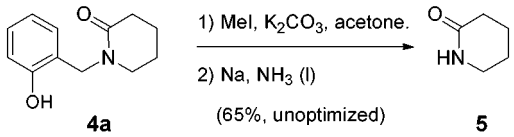
the phenolic alcohol was esterified with several ω-alkenyl acids employing DCC/DMAP activation, giving the precursors **2a**−**e** for the tethered RCM reactions in high overall yields.

All tethered RCM reactions were conducted with the second-generation Ru-imidazolidine type catalysts and gave, after hydrogenation of the double bonds, the macrocyclic lactones **3a**−**e** in good overall yields from **2a**−**e**.[5]

After removal of the Boc protective group by TFA treatment, the stage was set for the final transannular O → N acyl transfer reaction. Prior to liberation of the amine by the addition of base, the solution was diluted to a concentration of 0.01 M with EtOAc. In contrast to tertiary amine bases the use of $NaHCO_3$ gave a clean conversion to the medium-sized lactams **4a**−**e** in isolated yields ranging from 54% to 70%.[6]

Removal of the remaining 1-(2-hydroxy-benzyl) group was easily accomplished by mild reduction with sodium in liquid ammonia after methylation of the phenolic-OH group, as was demonstrated for **4a** to give caprolactam **5** in an overall yield of 65% (Scheme 3).[7]

Scheme 3. Removal of Remaining 1-(2-Hydroxy-benzyl) Group



In conclusion, a powerful method was developed for difficult lactamizations. Studies are ongoing to expand this strategy toward the synthesis of small homo- and heterodetic cyclopeptides, which are synthetically inaccessible by current methods.[8]

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Supporting Information Available: Representative experimental procedures and spectroscopic data of the compounds **2a**−**e**, **3a**−**e**, **4a**−**e**, and **5** are available free of charge via the Internet at http://pubs.acs.org.

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(3) Meutermans, W. D. F.; Golding, S. W.; Bourne, G. T.; Miranda, L. P.; Dooley, M. J.; Alewood, P. F.; Smythe, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 9790. In their approach, the auxiliary solely facilitated the final transannular lactamization step.

(4) For review articles, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(5) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc*. **1999**, *121*, 8251. (e) Wheaterhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828. (f) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chemistry* **2001**, *7*, 3236.

(6) Especially in the case of the six-membered lactam, conducting the final lactamization reaction at a higher concentration also gave the dimeric 12-membered bislactam. At 0.01 M the content of dimer was <5%.

(7) Treatment with trifluoromethane sulfonic acid (see: Johnson, T.; Quibell, M. *Tetrahedron Lett.* **1994**, *35*, 463) gave unsatisfactory results. Treatment with other strong acids (i.e., concentrated H_2SO_4, concentrated HBr) or oxidative methods (cerium ammonium nitrate or DDQ) gave complex mixtures. Finally, catalytic reduction (H_2, Pd(C) or H_2, $Pd(OH)_2$) resulted in full recovery of the starting material.

(8) For an excellent review on modern approaches towards cyclic peptides, see: Lambert, J. N.; Mitchell, J. P.; Roberts, K. D. *J. Chem. Soc. Perkin Trans. 1* **2001**, 471.