JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Tandem Nucleophilic Addition/Oxy-2-azonia-Cope Rearrangement for the Formation of Homoallylic Amides and Lactams: Total Synthesis and Structural Verification of Motuporamine G

Lijun Zhou,[†,§] Zhiming Li,[†] Yue Zou,[§] Quanrui Wang,*[,†] Italo A. Sanhueza,[‡] Franziska Schoenebeck,*[,‡] and Andreas Goeke*[,§]

[†]Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[‡]Laboratory for Organic Chemistry, ETH Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland
[§]Givaudan Fragrances (Shanghai) Ltd, 298 Li Shi Zhen Road, Shanghai 201203, China

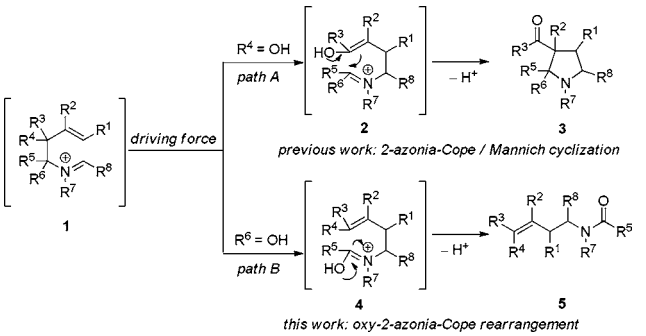
Supporting Information

ABSTRACT: In the presence of a Lewis acid, β,γ-unsaturated ketones and oximes or imines undergo nucleophilic addition to produce zwitterion intermediates, and subsequent oxy-2-azonia-Cope rearrangements give homoallylic amides. In the case of 2-vinylcycloalkanones, the process results in ring enlargement, providing a novel route to 9- to 16-membered lactams. The preparative significance of this protocol was evidenced by a short synthesis of macrocyclic alkaloid motuporamine G. The stereochemistry-defining step of this oxy-azonia-Cope rearrangement was further studied computationally. Despite a high-energy preequilibrium in the formation of zwitterionic intermediates, the [3,3]-sigmatropic step is the rate- and product-determining step. Chairlike transition states are generally preferred over boatlike ones.

Amides are ubiquitous motifs in natural products, pharmaceuticals, and materials.[1] The widespread occurrence of amides often makes us overlook the fact that amide formation under neutral conditions and without generation of waste is a contemporary challenge in organic synthesis. In 2005, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (comprising members from leading global pharmaceutical corporations) voted "amide formation avoiding poor atom economy reagents" as the top-priority research area in organic chemistry.[2] Diversified or improved methods for the synthesis of amide functionality are in great demand.[3]

2-Azonia-Cope rearrangements constitute highly efficient means for constructing C−C bonds under mild conditions.[4] The inherent problem of the method is the reversibility of the process. There have been four major approches to drive 2-azonia-Cope rearrangements to completion: (1) aryl conjugation of the iminium ion;[4,5] (2) trapping of the iminium ion in a subsequent nucleophile-induced ene−iminium cyclization;[6] (3) selective cleavage of the iminium ion of one sigmatropic isomer;[7−9] and (4) a tandem Mannich cyclization process. This fourth method is the particularly well established 2-azonia-Cope/Mannich cyclization process, which was first introduced by Overman and co-workers (Scheme 1, path A). The reaction has been used as the key step in a number of alkaloid total syntheses.[10] Herein we describe a new method to overcome the problem of reversibility: an oxy-2-azonia-Cope rearrangement of the cross-addition products **4** into homoallylic amides **5** (Scheme 1, path B).

Scheme 1. The 2-Azonia-Cope Rearrangement and its Novel Extension to an Oxy-2-azonia-Cope Rearrangement



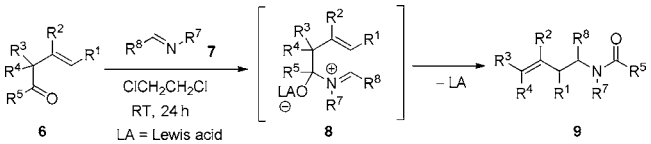
We recently discovered a novel cross-dimerization of β,γ-unsaturated carbonyl compounds with another aldehyde to produce homoallylic esters in an atom-economical way.[11] The proposed well-organized intermediates occurring in this oxy-oxonia-Cope rearrangement enable high degrees of diastereoselectivity and transfer of chirality. It has been successfully applied to a new synthesis of macrocyclic musks.[11b] In continuation of our studies of atom-economical rearrangement chemistry, we decided to examine the oxy-2-azonia-Cope rearrangement in the context of the synthesis of odorants[12] and natural products. Macrolactams and related azacycles are attractive targets that are often encountered in biologically active natural products,[13,14] especially in drug candidates such as bioisosteres of macrolides.[15] However, direct cyclization approaches to the synthesis of macrolactams are often limited by entropic factors, applications that require high-dilution techniques, and the lack of functional diversity.[16]

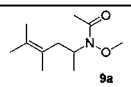
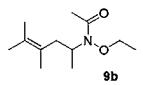
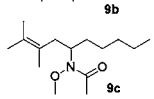
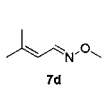
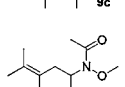
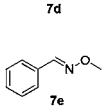
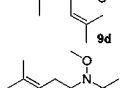
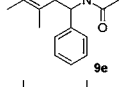
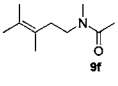
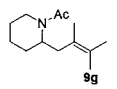
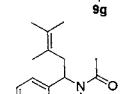
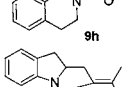
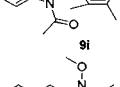
Our design of the oxy-2-azonia-Cope concept is based on the assumption that intermediate **8** can be formed via nucleophilic addition of an imine derivative to the carbonyl group of **6**, activated by a rather oxophilic Lewis acid (Table 1). Initial experiments revealed that an oxy-azonia-Cope rearrangement

Received: October 15, 2012
Published: November 27, 2012

dx.doi.org/10.1021/ja310002m | J. Am. Chem. Soc. 2012, 134, 20009−20012

Table 1. Scope of the Oxy-2-azonia-Cope Rearrangement[a]



entry	substrate 6	substrate 7	Lewis acid (1.0 eq.)	Product 9	Yield (%)[b]
1	 6a	 7a	$SnCl_4$	 9a	97
2	6a	 7b	$SnCl_4$	 9b	89
3	6a	 n=4 7c	$SnCl_4$	 9c	94
4	6a	 7d	$SnCl_4$	 9d	67
5	6a	 7e	$SnCl_4$	 9e	39
6	6a	 7f	$EtAlCl_2$	 9f	92[c]
7	6a	 7g	$EtAlCl_2$	 9g	29[c]
8	6a	 7h	$EtAlCl_2$	 9h	83[c]
9	6a	 7i	$EtAlCl_2$	 9i	58[c]
10	6b	7a	$SnCl_4$	 9j	84
11	 6c	7a	$SnCl_4$	 9k	93

[a]Experimental conditions: a 1,2-dichloroethane solution (50 mL) of **6** (10 mmol), imine **7** (12 mmol) and the Lewis acid (10 mmol) was stirred under an argon atmosphere for 24 h at room temperature. [b]Isolated yields after chromatography or Kugelrohr distillation. [c]When 1.0 equiv of $SnCl_4$ was used, the conversion was less than 20% as detected by GC analysis.

can indeed be performed by conversion of β,γ-unsaturated ketone **6a** with oxime ether **7a** and a Lewis acid such as $SnCl_4$ (entry 1). The expected homoallylic amide **9a** was obtained in excellent yield in the presence of 1.0 equiv of $SnCl_4$ at room temperature for 24 h. The reaction also worked with a catalytic amount of Lewis acid (20 mol % $SnCl_4$), but a much longer reaction time (>6 days) was required to reach quantitative conversion.[17] We therefore decided to use stoichometric amounts of the Lewis acid in the following investigations.

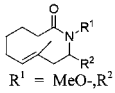
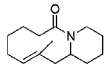
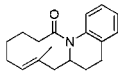
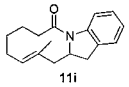
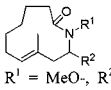
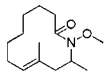
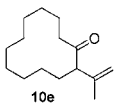
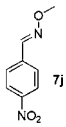
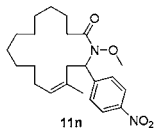
Encouraged by the efficiency of this concept, we employed β,γ-unsaturated ketones **6a**–**c** to define the scope of this novel rearrangement with regard to the tolerated diversity of imine substrates (Table 1). Oxime ethers and imine derivatives **7** smoothly underwent the desired transformation to give homoallylic amides **9b**–**k** in moderate to excellent yields. The reactions with oxime ethers were run in the presence of 1.0 equiv of $SnCl_4$ at room temperature (entries 1–5, 10, and 11). Lower yields were obtained with oxime ethers of decreased nucleophilicity, such as those derived from α,β-unsaturated and aromatic aldehydes (entries 4 and 5). Comparatively electron-rich imines **7f**–**i** were beneficially converted using 1.0 equiv of the more oxophilic Lewis acid $EtAlCl_2$ (entries 6–9). Notably, precursor **7f**, the trimeric form of *N*-methylenemethanamine, was cleaved in situ to generate the desired rearrangement product **9f** in excellent yield (entry 6). Reactions with cyclic imines such as **7g** and **7h** resulted in acetyl-protected piperidines **9g** and **9h** (entries 7 and 8). Interestingly, 1*H*-indole reacted with **6a** via its tautomeric form 3*H*-indole[18] to give indoline acetamide **9i** (entry 9). Rearrangement reactions of β,γ-unsaturated ketones carrying α protons (i.e., **6b** and **6c**) were also investigated. These two substrates were converted into the corresponding amides **9j** and **9k** in excellent yields (entries 10 and 11). Importantly, the double bond in product **9j** is exclusively *E*-configured (entry 10). Overall, with regard to substrate diversity, the scope of the oxy-2-azonia-Cope rearrangement was found to be surprisingly broad.

In an attempt to design a new synthetic access to macrolactams, we next investigated the oxy-2-azonia-Cope reaction of 2-vinylcycloalkanones **10** derived simply by linking R^3 and R^5 in substrate **6** by a carbon chain of a given length. After nucleophilic addition of imine **7**, the resulting zwitterionic intermediates of type **8** were expected to undergo spontaneous rearrangements to afford the corresponding ring-expanded lactams **11** (Table 2).[17,19] Depending on the size of the ring in **10**, the products are medium-sized or macrocyclic homoallylic lactams. In comparison with the classical formation of macrocyclic lactams, which requires activated carboxylic acid derivatives at high dilution,[20] the described lactam formation is rather an $[n + 4]$ ring enlargement, offering a new approach for the rapid assembly of complex macrolactams. As illustrated in Table 2, cyclic 5–8- and 12-membered substrates **10a**–**e** and various oxime ethers and imines **7a**–**j** were smoothly converted to the desired homoallylic macrolactams. Nine-membered lactam **11a** was exclusively obtained with the *Z* configuration (entry 1). The 10-, 11-, and 12-membered lactam products were formed with prevailing *E* configuration (entries 2–13), while the double bond in the 16-membered ring (entry 14) was constructed less stereoselectively. Notably, cyclic imines such as **7g**, **7h**, and indole **7i** were also applicable and resulted in bicyclic and tricyclic lactam products with greater structural complexity (entries 7–9). The structures and double-bond configurations of these lactams were unequivocally determined by NMR analysis and confirmed in several cases by X-ray analysis.[17]

To demonstrate the preparative benefit, the new protocol was further utilized to synthesize motuporamine G (**16**; Scheme 2), a natural alkaloid isolated from the marine sponge *Xestospongia exigua* by Andersen and co-workers.[21] The reaction of compound **12** and imine **13** with $EtAlCl_2$ gave 13-membered lactam **14** in excellent yield.[22] Three additional simple standard transformations (hydrogenation of **14**, conversion to **15**, and reduction of both amide groups) completed this short total synthesis of *rac*-**16**. In the crude extract of the sponge, motuporamines A, B, and C and the mixture of motuporamines G, H, and I were found to be primarily responsible for anti-invasion activity against cancer cells.[21b] However, as motuporamines G, H, and I were all obtained in very small quantities, the exact locations of the methyl branch in their macrocyclic rings had only been tentatively assigned. By comparison of the NMR data for **16** with the corresponding data

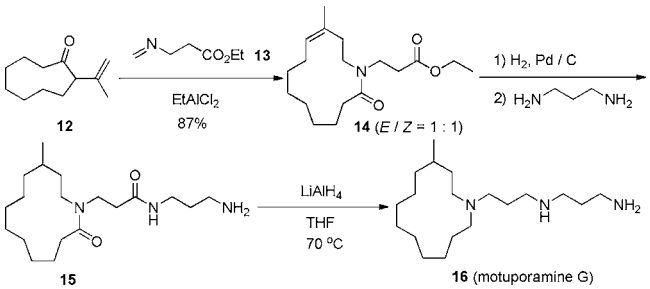
dx.doi.org/10.1021/ja310002m | *J. Am. Chem. Soc.* 2012, 134, 20009–20012

Table 2. Oxy-2-azonia-Cope [*n* + 4] Ring Enlargement To Give Macrocyclic Lactams[a]

entry	substrate **10**	substrate **7**	Lewis acid (1.0 eq.)	Product **11**	Yield (%)[b] [E/Z]
1	 **10a**	**7a**	$SnCl_4$	 **11a**	35 [<1:99]
2	 **10b**	**7a**	$SnCl_4$	 **11b**: R^1 = MeO-,R^2 = Me	84 [>99:1]
3	**10b**	**7b**	$SnCl_4$	**11c**: R^1 = EtO-, R^2 = Me	80 [>99:1]
4	**10b**	**7c**	$SnCl_4$	**11d**: R^1 = MeO-, R^2 = n-pentyl	59 [98:2]
5	**10b**	**7e**	$SnCl_4$	**11e**: R^1 = MeO-, R^2 = Ph	70 [>99:1]
6	**10b**	**7f**	$EtAlCl_2$	**11f**: R^1 = Me, R^2 = H	96[c] [>99:1]
7	**10b**	**7g**	$EtAlCl_2$	 **11g**	69[c] [>99:1]
8	**10b**	**7h**	$EtAlCl_2$	 **11h**	92[c] [>99:1]
9	**10b**	**7i**	$EtAlCl_2$	 **11i**	77[c] [>99:1]
10	 **10c**	**7a**	$SnCl_4$	 **11j**: R^1 = MeO-, R^2 = Me	90 [>99:1]
11	**10c**	**7b**	$SnCl_4$	**11k**: R^1 = EtO-, R^2 = Me	73 [>99:1]
12	**10c**	**7f**	$SnCl_4$	**11l**: R^1 = Me, R^2 = H	59 [>99:1]
13	 **10d**	**7a**	$SnCl_4$	 **11m**	89 [95:5]
14	 **10e**	 **7j**	$EtAlCl_2$	 **11n**	35[c] [25:75]

[a]Experimental conditions: a 1,2-dichloroethane solution (50 mL) of **10** (10 mmol), imine **7** (12 mmol), and the Lewis acid (10 mmol) was stirred under an argon atmosphere for 24 h at room temperature. [b]Isolated yields after chromatography or Kugelrohr distillation. [c]When 1.0 equiv of $SnCl_4$ was used, the conversion was less than 20% as detected by GC analysis.

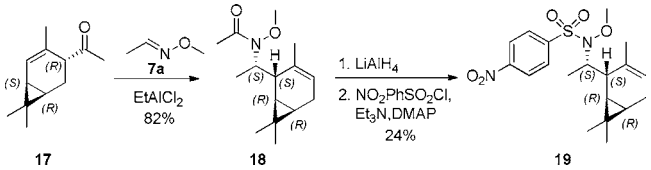
Scheme 2. Application of the Oxy-2-azonia-Cope Rearrangement to the Total Synthesis of Motuporamine G



reported for authentic samples of motuporamines G, H, and I,[21b] we confirmed that the constitution of **16** is identical with that of motuporamine G.

To gain deeper insight into the stereochemistry-defining step of the oxy-2-azonia-Cope rearrangement, the reaction of acetylcarene **17** with oxime ether **7a** in the presence of $EtAlCl_2$ (Scheme 3) was

Scheme 3. Chirality Transfer Study of the Oxy-2-azonia-Cope Rearrangement of Acetylcarene 17 and Oxime 7a



investigated experimentally and also computationally using density functional theory.[23,24] The transformation of **17** to **18** was calculated to proceed via the mechanism illustrated in Figure 1.

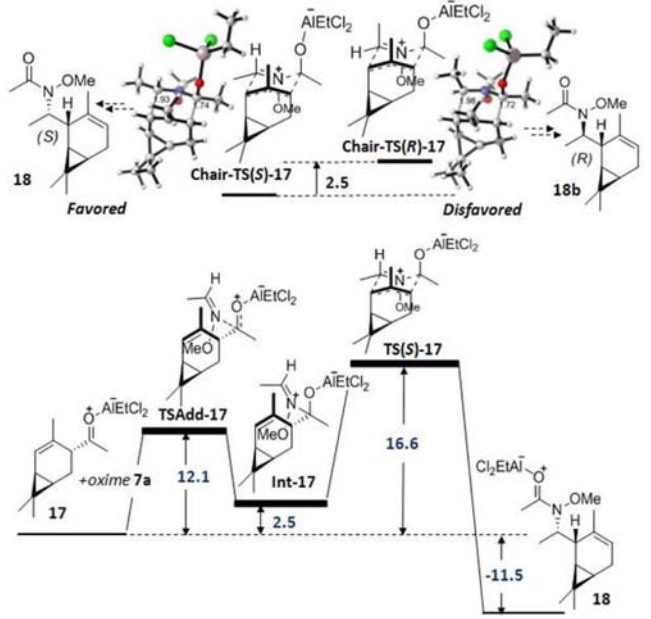


Figure 1. (top) Selectivity ($\Delta\Delta G^{\ddagger}$) in favor of **18** and (bottom) free energy reaction profile leading to product **18** with $EtAlCl_2$ as the Lewis acid, calculated at the CPCM(DCE) M06-2X/6-31+G(d,p)//B3LYP/6-31G(d) with SDD (for Al) level. The standard state was converted to 1 M.

The relative configuration of compound **18** was determined by x-ray analysis of derivative **19**. After initial addition of the oxime ether to Lewis acid-activated **17**, the zwitterionic intermediate **Int-17** is formed. A concerted, asynchronous Cope rearrangement subsequently takes place as the rate-determining step to give **18**. The reaction was calculated to be relatively facile and exergonic ($\Delta G^{\ddagger}$ = 16.6 kcal/mol and ΔG_{rxn} = −11.5 kcal/mol at the M06-2X level of theory; see Figure 1). As such, it mirrors the reactivity of our recently investigated oxonia-Cope transformation,[11a,25] and the Cope rearrangement constitutes the selectivity-determining step.

The chairlike transition state **TS(*S*)-17** was calculated to be significantly favored in the oxy-2-azonia Cope rearrangement, consistent with the experimental finding of *S* stereochemistry in the product.[17] The TS that is next highest in energy, **TS(*R*)-17** ($\Delta\Delta G^{\ddagger}$ = 2.5 kcal/mol), would lead to **18b**, the product of opposite stereochemistry with respect to the forming C−N bond (Figure 1 top). This selectivity trend was found to be largely method- and Lewis acid-independent (see the SI for further details).[24,25]

dx.doi.org/10.1021/ja310002m | *J. Am. Chem. Soc.* 2012, 134, 20009−20012

In summary, we have found a novel, atom-economical way to prepare homoallylic tertiary amides and macrolactams via a tandem nucleophilic addition/oxy-2-azonia-Cope rearrangement mediated by a Lewis acid. The transformation proceeds at room temperature. Most of the transformations proceed with high *E*/*Z* selectivity. The synthetic potential of the present protocol was illustrated by the total synthesis and structure verification of motuporamine G. In addition, a chirality transfer study and computational analysis disclosed a highly ordered TS for this transformation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, computational data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*qrwang@fudan.edu.cn; schoenebeck@org.chem.ethz.ch; andreas.goeke@givaudan.com

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. G. Brunner for NMR experiments, Dr. Z. Chen (Fudan University) for X-ray measurements, G. Tang (Fudan University) for high-resolution mass spectrometry data, and the National Natural Science Foundation of China (21102019) for support. Calculations were performed on the ETH High-Performance Cluster Brutus.

■ REFERENCES

(1) (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (c) Gaudin, J.-M.; Lander, T.; Nikolaenko, O. *Chem. Biodiversity* **2008**, *5*, 617. (d) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.

(2) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

(3) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(4) For the first description, see: Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518.

(5) (a) Geisel, M.; Grob, C. A.; Wohl, R. A. *Helv. Chim. Acta* **1969**, *52*, 2206. (b) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.

(6) Gelas-Mialh, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73.

(7) (a) Agami, C.; Couty, F.; Poursoulis, M. *Synlett* **1992**, 847. (b) Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961.

(8) Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913.

(9) Ito, T.; Overman, L. E.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 3272.

(10) (a) Overman, L. E.; Kahimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310. (b) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (d) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662. (e) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (f) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (g) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064. (h) Carballo, R. M.; Purino, M.; Ramirez, M. A.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2010**, *12*, 5334.

(11) (a) Zou, Y.; Ding, C.; Zhou, L.; Li, Z.; Wang, Q.; Schoenebeck, F.; Goeke, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5647. (b) Zou, Y.; Mouhib, H.; Stahl, W.; Goeke, A.; Wang, Q.; Kraft, P. *Chem.—Eur. J.* **2012**, *18*, 7010.

(12) Selected reviews of fragrance chemistry: (a) Ohloff, G.; Pickenhagen, W.; Kraft, P. *Scent and Chemistry: The Molecular World of Odors*; Wiley-VCH: Weinheim, Germany, 2011. (b) Kraft, P.; Denis, C.; Bajgrowicz, J.; Fráter, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980.

(13) Selected reviews: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149. (c) Mutlak, H.; Hassan, A. *Chem. Commun.* **2010**, *46*, 9100. (d) Madsen, C. M.; Clausen, M. H. *Eur. J. Org. Chem.* **2011**, 3107.

(14) Selected examples: (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6403. (b) Futamura, Y.; Sawa, R.; Umezawa, Y.; Lgarashi, M.; Nakamura, H.; Hasegawa, K.; Yamasaki, M.; Tashiro, E.; Takahashi, Y.; Akamatsu, Y.; Imoto, M. *J. Am. Chem. Soc.* **2008**, *130*, 1822. (c) Willians, D. E.; Craig, K. S.; Patrick, B.; McHardy, L. M.; Soest, R. V.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2002**, *67*, 245. (d) Yang, S.-X.; Gao, J.-M.; Zhang, A.-L.; Laatsch, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3905.

(15) Selected examples of lactam analogues as lactone bioisosteres to enhance the stability and bioavailability of the natural product: (a) Borzilleri, R. M.; Zheng, X.; Schmidt, R. J.; Johnson, J. A.; Kim, S.-H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890. (b) Paek, S.-M.; Seo, S.-Y.; Min, K.-H.; Shin, D. M.; Chung, Y. K.; Suh, Y.-G. *Heterocycles* **2007**, *71*, 1059. (c) Anquetin, G.; Horgan, G.; Rawe, S.; Murray, D.; Madden, A.; MacMathuna, P.; Doran, P.; Murphy, P. V. *Eur. J. Org. Chem.* **2008**, 1953.

(16) Suh, Y.-G.; Lee, Y.-S.; Kim, S.-H.; Jung, J.-K.; Yun, H.; Jang, J.; Kim, N.-J.; Jung, J.-W. *Org. Biomol. Chem.* **2012**, *10*, 561.

(17) For screening of Lewis acids, compound characterization, X-ray crystal structure analysis, additional experimental and computational details, and a compilation of all possible TS conformers and their relative energies, see the Supporting Information (SI).

(18) (a) Gut, I. G.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1153. (b) Ghavtadze, N.; Fröhlich, R.; Würthwein, E. *Eur. J. Org. Chem.* **2010**, 1787.

(19) An example of tandem ring expansion via a 3-aza-Cope rearrangement: Weston, M. H.; NaKajima, K.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4630.

(20) Selected examples: (a) Nicolaou, K. C.; Ramanjulu, J. M.; Natarajan, S.; Bräse, S.; Li, H.; Boddy, C. N. C.; Rübsam, F. *Chem. Commun.* **1997**, 1899. (b) Wen, S.; Packham, G.; Ganesan, A. *J. Org. Chem.* **2008**, *73*, 9353. (c) Dai, C.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3453.

(21) (a) Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838. (b) Williams, D. E.; Craig, K. S.; Patrick, B.; McHardy, L. M.; van Soest, R.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2002**, *67*, 245.

(22) (a) Preparation of cyclononanone: Furstner, A.; Radkowski, K.; Peters, H.; Seidel, G.; Wirtz, G.; Mynott, R.; Lehmann, C. W. *Chem.—Eur. J.* **2007**, *13*, 1929. (b) For the preparation of ketone **12**, see the SI.

(23) Calculations were performed using Gaussian 09 (see the SI for the complete reference and computational details).

(24) Calculations were also performed with the Lewis acids BF_3 and $SnCl_4$ (see the SI for further details).

(25) Calculations on the 2-oxonia-Cope rearrangement also suggested a chairlike TS to be favored. The predicted selectivity in the 2-oxonia Cope reaction was $\Delta\Delta G^{\ddagger} = 3.5-4.8$ kcal/mol, depending on the level of theory (see ref 11a).