ORGANIC LETTERS

2004
Vol. 6, No. 23
4351−4353

Use of N–N Bond Stereodynamics in Ring-Closing Metathesis to Form Medium-Sized Rings and Macrocycles

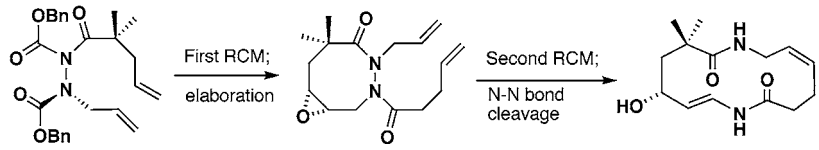
Yi Jin Kim and Daesung Lee*

Department of Chemistry, University of Wisconsin-Madison, Madison, Wisconsin 53706

dlee@chem.wisc.edu

Received September 14, 2004

ABSTRACT



A unique strategy based on double ring-closing metathesis for the formation of a 14-membered macrocyclic enamide has been developed. This strategy hinges upon the well-known stereodynamic and conformational behavior of *N*-substituted diacylhydrazines, which promotes an effective ring-closing metathesis of hydrazine-derived dienes and enynes to form 8- to 14-membered rings.

Macrocyclic structures are found in numerous biologically active natural and synthetic compounds. From the standpoint of generating molecular diversity and complexity in diversity-oriented synthesis,[1] macrocyclic frameworks have played a significant role for the synthesis of libraries of natural-product-like compounds.[2] Among many strategies to construct this structural motif, ring-closing metathesis (RCM) has emerged as a powerful tool.[3] Despite the general utility and effectiveness of the RCM reaction, care must be taken when employing it in synthetic designs because many factors will affect the efficiency of the ring-closure event.[4] Effort has been made to facilitate the RCM reaction using a template effect,[5] as well as conformational and stereoelectronic constraint.[6]

In our effort to develop an efficient synthesis of macrocyclic amides to study their nanotube-forming propensity[7] and biological performance as cyclic peptide mimics,[8] we became interested in a double-RCM strategy utilizing the well-known stereodynamic behavior of the N−N functionality.[9] High-level ab initio calculations and X-ray crystallographic data show that *N*-substituted diacylhydrazines (**1**) maintain CO−N−N−CO dihedral angles near 90° in their lowest energy conformations and the rotation about the N−N bond is hindered (E_a = ∼19 kcal/mol) (Figure 1).[10] This

(1) Schreiber, S, L. *Science* **2000**, *287*, 1964.

(2) (a) Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2003**, *5*, 2149. (b) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 10648. (c) Mayes, B. A.; Cowley, A. R.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 163.

(3) For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 1900. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (e) Giessert, A. J.; Diver, S. T. *Chem. Rev*. **2004**, *104*, 1317. (f) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (g) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176−204. (h) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199.

(4) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(5) (a) Marsella, M.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1101. (b) Chuchuryukin, A. V.; Dijkstra, H. P.; Suijkerbuijk, B. M. J. M.; Klein Gebbink, R. J. M.; van Klink, G. P. M.; Mills, A. M.; Spek, A. L.; van Koten, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 228.

(6) (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc*. **2003**, *125*, 9582. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc*. **1999**, *121*, 5653.

(7) (a) Sanchez-Quesada, J.; Isler, M. P.; Ghadiri, M. R. *J. Am. Chem. Soc*. **2002**, *124*, 10004. (b) Horne, W. S.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc*. **2003**, *125*, 9372 and references therein.

(8) (a) Barrett, A. G. M.; Hennessy, A. J.; Vezouet, R. L.; Procopiou, P. A.; Seale, P. W.; Stefaniak, S.; Upton, R. J.; White, A. J. P.; Williams, D. J. *J. Org. Chem*. **2004**, *69*, 1028 and references therein. (b) Ripka, A. S.; Bohacek, R. S.; Rich, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 357. (c) Reichwein, J. F.; Wels, B.; Kruijzer, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3684.

(9) The use of a N−N bond in RCM reactions was reported recently; see: Tae, J.; Hahn, D.-W. *Tetrahedron Lett.* **2004**, *45*, 3757.

(10) Reynolds, C.; Hormann, R. E. *J. Am. Chem. Soc.* **1996**, *118*, 9395 and references therein.

10.1021/ol048136f CCC: $27.50 © 2004 American Chemical Society
Published on Web 10/09/2004

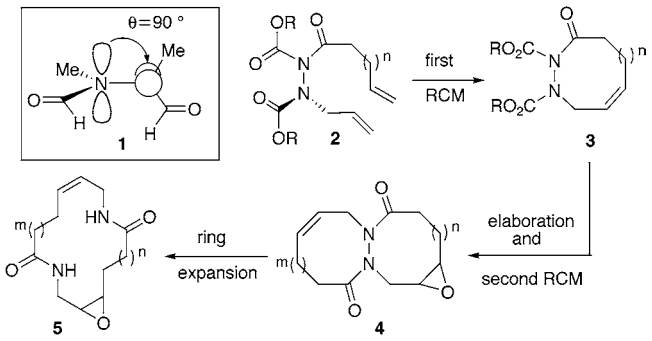


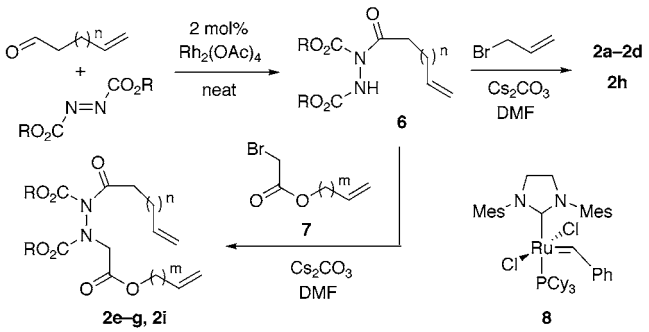
Figure 1. Double RCM strategy for the synthesis of macrocyclic dilactams.

property will fix *N*,*N*′-vicinal substituents in proximity to one another in a *gauche*-like arrangement that, in a molecule such as **2**, would facilitate the RCM reaction. Furthermore, sequential RCM reactions with a properly substituted N−N moiety to generate hydrazine derivatives **3** and **4** followed by ring expansion via the N−N bond cleavage would provide unique and efficient access to macrocyclic bis-lactam **5**.

The strategy using N−N functionality in the RCM reaction is particularly appealing for several reasons. First, it will generate new information regarding the conformational properties of the N−N bond constrained in macrocycles.[11] Second, it will provide new tools to synthesize various medicinally and agriculturally important hydrazine derivatives.[12] Third, the resultant RCM products containing an N−N bond can serve as conformationally constrained peptidomimetics.[13] Finally, this strategy will allow a unique route for the synthesis of macrocyclic peptide-like molecules.[14] We report herein the development of a hydrazine-based RCM platform to generate medium-sized rings and macrocycles of type **3** and an illustration of their conversion to macrocyclic bis-lactam **5**.

To prepare the required trisubstituted hydrazine derivatives **6**, a rhodium-catalyzed redox process between dialkylazodicarboxylates and alkenyl aldehydes was employed.[15] Subsequent allylation or alkylation of **6** with α-bromoacetate derivatives **7** provided RCM substrates **2a**−**i** in a two-step process that avoids protecting groups (Scheme 1). In this

Scheme 1. Synthesis of RCM Substrates



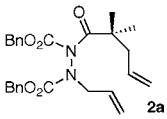
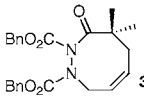
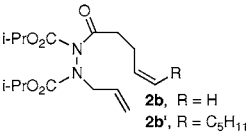
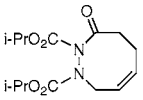
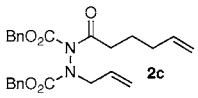
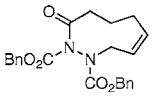
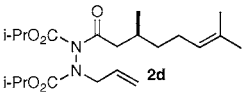
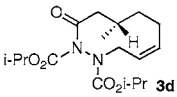
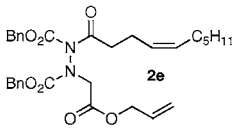
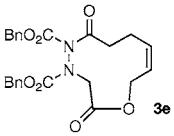
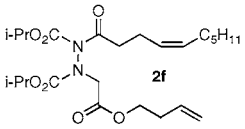
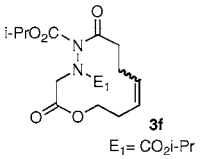
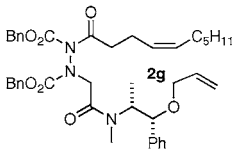
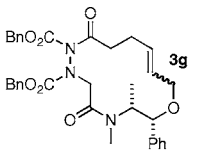
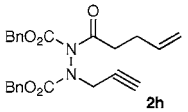
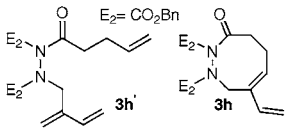
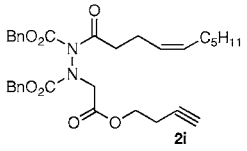
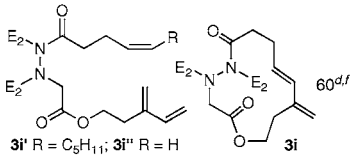
synthetic maneuver, structural diversity and complexity were introduced by altering the substituents and/or the length of the tether between the two unsaturated components. However, a conceptually different and more important diversity element, scaffold diversity,[16] was implemented by the cleavage of the N−N bond to convert a bicyclic framework **4** to a macrocycle **5** (Figure 1).

We explored the RCM reaction of **2** under typical conditions (0.002 M in CH_2Cl_2, 5−10 mol % of **8**,[17] reflux), which provided ring-closed products **3a**−**g** smoothly in 42−94% yields (Table 1). As a testimonial for the effectiveness of the N−N bond tether for RCM, eight-membered ring-closure product **3a** was obtained in 93% yield from **2a** (entry 1). A closely related substrate **2b**, which lacks the geminal dimethyl groups, afforded slightly lower efficiency (88%) (entry 2). This is probably the manifestation of the well-known gemdialkyl effect.[18] Comparison between **2b** and **2b′** having terminal alkene versus internal alkene shows the former to be more reactive, thereby providing higher yield (88% vs 65%) of **3b**. The RCM reactions of **2c,d** to form 9- and 10-membered rings were uneventful, although the isolated yields of these products were moderate (entries 3 and 4). The RCM of slightly different substrates **2e,f** having an additional carbonyl group in the tether gave good yields of 11- and 12-membered rings, respectively (entries 5 and 6). Surprisingly, the highest yielding RCM reaction was observed with **2g**, which forms 14-membered ring product **3g**, the largest ring in the series, in 94% yield (entry 7). A notable trend in the RCM reactions of substrates **2c**−**g** is the gradual increase of the ring-closure efficiency going from 9- to 14-membered rings. This may be due to the increased deformation of the optimal dihedral angle of the CO−N−N−CO moiety for the smaller rings. The *Z*/*E* ratio observed for the cyclic alkenes shows that most ring closures result in *Z*-alkene formation. A slight decrease in the *Z*/*E* ratio was observed for the larger sized rings (**3f,g**). The scope of the RCM reaction of hydrazine-based substrate was further examined with enynes **2h,i**, which provided 1,3-dienes **3h,i** in moderate yields (entries 8 and 9). The endocyclic alkene in **3i** was of exclusively *E*-stereochemistry, and all cyclic compounds were formed as a mixture of rotamers.

Having realized an excellent RCM reaction of **2a** to eight-membered ring hydrazine derivative **3a**, its straightforward elaboration to **10** followed by the second RCM reaction to

(11) Nelsen, S. F. In *Acyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH Publishers: New York, 1992; Chapter 3, pp 89−121.
(12) Billas, I. M.; Iwema, T.; Garnier, J.-M.; Mitschler, A.; Rochel, N.; Moras, D. *Nature* **2003**, *426*, 91.
(13) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539 and references therein.
(14) (a) Meng, Q.; Hesse, M. *Synlett* **1990**, 148. (b) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461.
(15) Lee, D.; Otte, R. D. *J. Org. Chem.* **2004**, *69*, 3569.
(16) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613.
(17) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *125*, 2546.
(18) (a) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

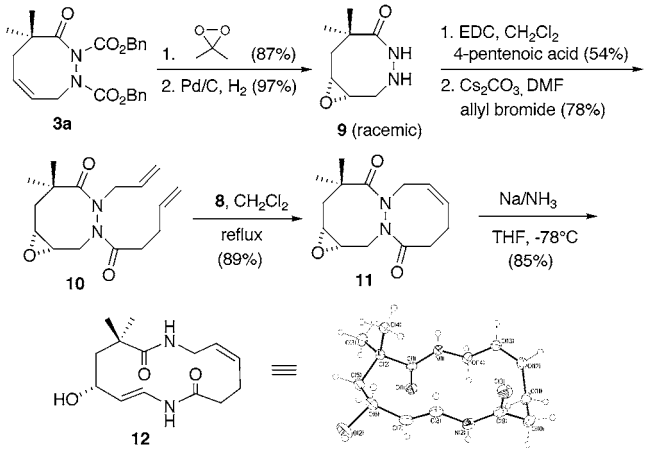
Table 1. Formation of Cyclic Hydrazine Derivatives via RCM[a]

entry	RCM substrate (**2**)	product (**3**)	yield (%)[b]
1	 **2a**	 **3a**	93
2	 **2b**, R = H **2b'**, R = C_5H_{11}	 **3b**	88 (65)[c]
3	 **2c**	 **3c**	42
4	 **2d**	 **3d**	46
5	 **2e**	 **3e**	65
6	 **2f**	 **3f** E_1= CO_2i-Pr	72 2:1 *Z:E*
7	 **2g**	 **3g**	94 3:2 *Z:E*
8	 **2h**	 **3h'** **3h**	47[d,e]
9	 **2i**	 **3i'** R = C_5H_{11}; **3i''** R = H **3i**	60[d,f]

[a] Reactions are carried out in CH_2Cl_2 (0.002 M) with 5−10 mol % of **8** for 2−5 h. [b] Isolated yield. [c] Yield for **2b'**. [d] Reaction under ethylene. [e] 1:1 for **3h**:**3h'**. [f] 2:1:1 for **3i**:**3i'**:**3i''**.

generate bicycle **11**, en route to macrocyclic bis-lactam **12**, was demonstrated (Scheme 2). The eight-membered cyclic hydrazine **3a** was first subjected to epoxidation conditions (Oxone, acetone, $NaHCO_3$) followed by deprotection of the *N*-carbobenzyloxy groups (Pd/C, H_2), which provided **9** in 84% (yield for two steps). Acylation of the amine functionality with 4-pentenoic acid followed by allylation of the amide nitrogen moiety provided the second RCM substrate **10** in moderate yield (42% for two steps). Treatment of **10** with Grubbs catalyst **8**[17] afforded the bicyclic hydrazine derivative **11** (89%) as a single atropisomer. The N−N bond cleavage[14] and the epoxide-opening generated macrocyclic enamide **12** (85%), the structure of which was confirmed by X-ray crystallography.[19]

Scheme 2. Synthesis of Macrocycle



In conclusion, we have developed a hydrazine-based RCM platform that utilizes the conformational constraint of *N*-substituted diacylhydrazines. We have also demonstrated a new strategy for rapid access to a macrocyclic amide from a bicyclic hydrazine derivative by ring expansion induced by N−N bond cleavage. Further investigation of more elaborated macrocyclic-peptide-like molecules with different ring sizes and their nanotube-forming behavior is in progress.

Acknowledgment. D.L. gratefully acknowledges NSF, Wisconsin Alumni Research Foundation, and the Camille and Henry Dreyfus Foundation for financial support. We thank Dr. Ilia Guzei for crystal structure determination. Support for NMR and MS instrumentation from NSF and NIH is greatly acknowledged.

Supporting Information Available: Spectral data for cyclic hydrazine derivatives, experimental procedures, and X-ray structure for **12** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048136F

(19) Single crystals were obtained from EtOAc−MeOH by slow evaporation. For crystal structure determination, see Supporting Information.