J|A|C|S
COMMUNICATIONS

# Asymmetric Modular Synthesis of Highly Functionalized Medium-Sized Carbocycles and Lactones via Ring-Closing Metathesis of Sulfoximine-Substituted Trienes

Michal Lejkowski, Hans-Joachim Gais,* Prabal Banerjee, and Cornelia Vermeeren
*Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Landoltweg 1, 52056 Aachen, Germany*

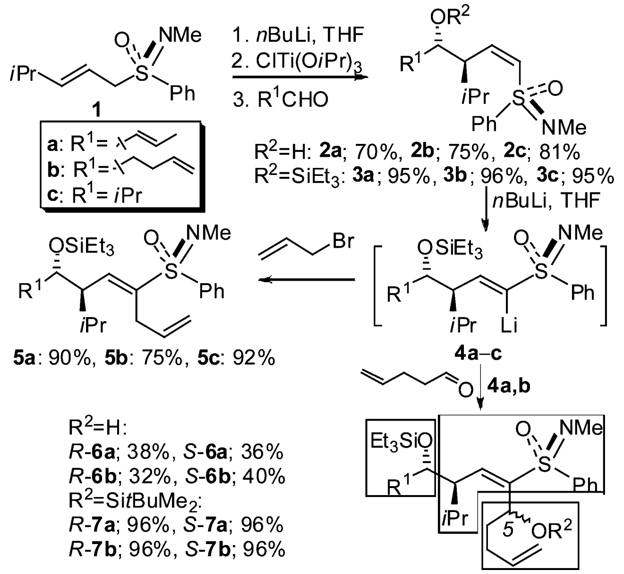
Received July 19, 2006; E-mail: gais@rwth-aachen.de

The asymmetric synthesis of highly substituted medium-sized rings is a topic of considerable interest.[1−3] Medium-sized carbocycles and lactones for example are found as structural motifs in a number of biologically relevant natural products.[2−4] In this Communication we describe a new asymmetric synthesis of highly substituted medium-sized carbocycles and lactones. Its key elements are the modular synthesis of sulfoximine-substituted trienes starting from enantiopure allylic sulfoximines and their ring-closing metathesis (RCM).[2,3]

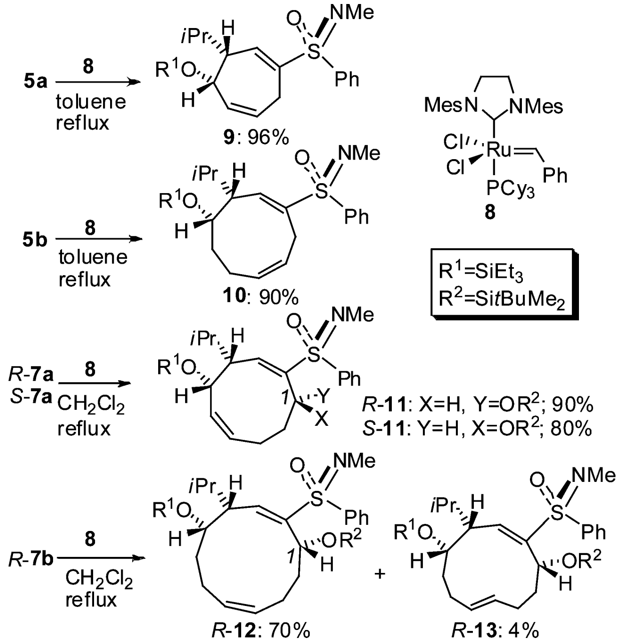
The successive treatment of the allylic sulfoximine **1**[5] with *n*BuLi, 2.1 equiv of $\text{ClTi(O}i\text{Pr)}_3$, 2-butenal, 4-pentenal, and 2-methylpropanal at −78 °C afforded the corresponding sulfoximine-substituted homoallylic alcohols **2a**, **2b**, and **2c**,[5a] each with ≥96% de in 70−81% yield (Scheme 1). Their silylation ($\text{ClSiEt}_3$, DMF, and imidazol) furnished sulfoximines **3a**, **3b**, and **3c**[5a] in 95−96% yield. The lithiation of the *Z*-alkenyl sulfoximines[5b,6] **3a**−**c** with *n*BuLi at −78 °C occurred selectively at the α-position and gave the corresponding *Z*-alkenyllithium derivatives which suffered at −30 °C a complete isomerization to the *E*-configured alkenyllithium derivatives[5b,6] **4a**−**c**. Their treatment with allyl bromide furnished the *E*-configured sulfoximine-substituted trienes **5a**−**c** each as a single isomer in 75−92 overall yield based on **3a**−**c**. The analogous reaction of **4a** and **4b** with 4-pentanal proceeded efficiently but was nearly unselective in regard to C-5 and gave the *E*-configured allylic alcohols *R*-**6a**, *S*-**6a**, *R*-**6b**, and *S*-**6b**, respectively. Their separation and silylation ($\text{ClSi}t\text{BuMe}_2$, DMF, and imidazol) afforded the silyl ethers *R*-**7a**, *S*-**7a**, *R*-**7b**, and *S*-**7b**, respectively, in high overall yield based on **3a**−**c**. With the enantio- and diastereopure sulfoximine-substituted trienes in hand, their RCM was studied. Treatment of the 1,4,8-triene **5a** (0.005 M) with 5 mol % of the ruthenium complex **8**[2] in toluene at reflux for 12 h gave the 7-membered carbocycle **9** in 96% yield (Scheme 2). A similar RCM reaction of the 1,4,10-triene **5b** with **8** furnished the *Z*-configured nine-membered carbocycle **10** in 90% yield. Despite their congested structure, the epimeric 1,6,10-trienes *R*-**7a** and *S*-**7a** also underwent a facile RCM reaction. Thus treatment of *R*-**7a** and *S*-**7a** (0.005 M) with 5 mol % of **8** in $\text{CH}_2\text{Cl}_2$ at reflux for 12 h gave the *Z*-configured nine-membered carbocycles *R*-**11** and *S*-**11**, respectively, in 90% and 80% yield. The configurations of *R*-**11** and *S*-**11** at C-1 were determined by NOE experiments. The treatment of the 1,6,12-triene *R*-**7b** with **8** under the above conditions afforded the *Z*-configured 11-membered carbocycle **12** in 70% yield and its *E*-configured isomer **13** in 5% yield.[7] The configurations of *R*-**12** at C-1 was determined by NOE experiments.

The advantages offered by the modular synthesis of the sulfoximine-substituted trienes are demonstrated by the stereoselective synthesis of triene **14** (Scheme 3) containing a tertiary C-atom. Reaction of the alkenyllithium derivative **4a** with propanal gave a mixture of the epimeric allylic alcohols *R*-**13** and *S*-**14** in 80% yield. Oxidation of the alcohols with Dess−Martin periodinane (DMP) afforded enone **15** in 96% yield. The allylation of enone **15** with allylmagnesium bromide gave the tertiary alcohol **16** with 96% de in 90% yield. Thus, contrary to what was observed in the hydroxyalkylation of **4a** and **4b** the sulfoximine group of enone **15** provided a high degree of asymmetric induction in the addition to the carbonyl group. The treatment of the 1,5,9-triene **16** with 5

*Scheme 1*

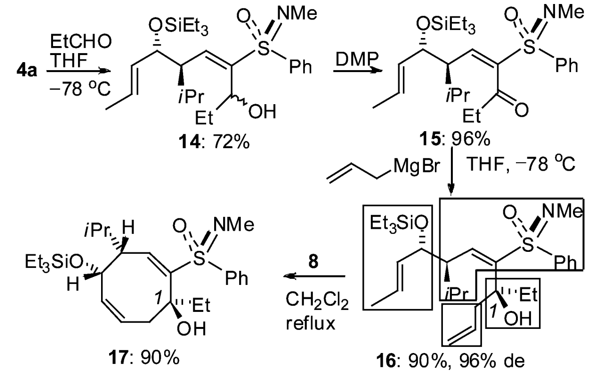


*Scheme 2*

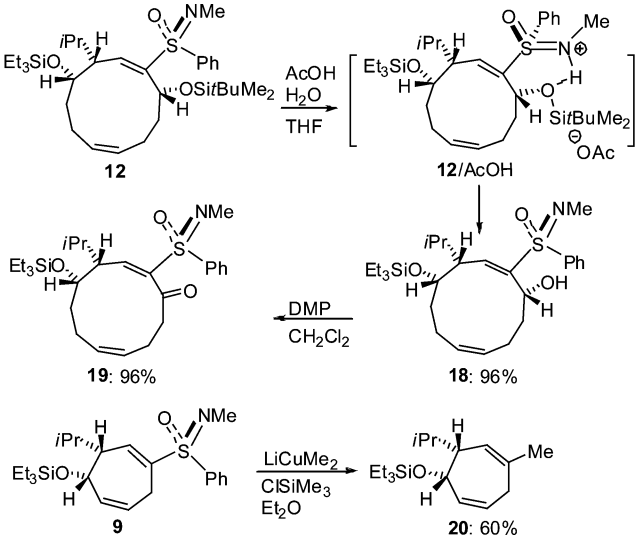


10.1021/ja0651658 CCC: $33.50 © 2006 American Chemical Society

Scheme 3



Scheme 4

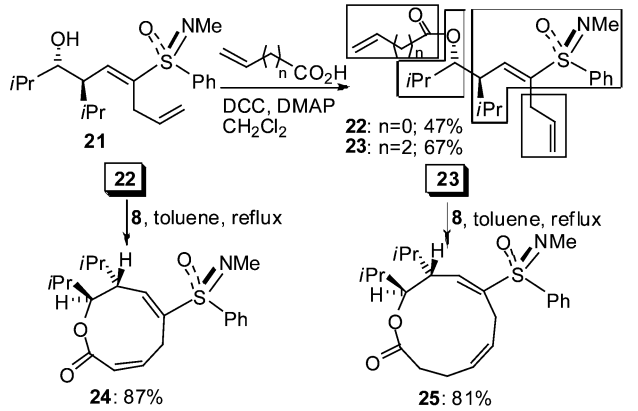


mol % of **8** in $CH_2Cl_2$ at reflux for 16 h furnished the eight-membered carbocycle **17** in 90% yield. The *S*-configuration of **16** and **17** at C1 was tentatively assigned on the basis of model considerations of the addition of the Grignard reagent to **15**.

To demonstrate the synthetic potential of the sulfoximine-substituted carbocycles, the 11-membered derivative **12** was treated with AcOH/$H_2O$ in THF, which gave the allylic alcohol **18** in 96% yield (Scheme 4). We ascribe the highly selective cleavage of the *t*BuMe$_2$Si group in the presence of the Et$_3$Si group to a neighboring effect exerted by the protonated sulfoximine group. Protonation of sulfoximine **12** should give salt **12**/AcOH in which the *t*BuMe$_2$Si group could be selectively activated toward a nucleophilic attack by an intramolecular hydrogen bond. Oxidation of alcohol **18** with DMP afforded enone **19** in 90%. An example for the facile substitution of the sulfoximine group is provided by the cross-coupling reaction of the alkenyl sulfoximine **9** with $LiCuMe_2$ (3 equiv) in the presence of $ClSiMe_3$, which gave the methylated carbocycle **20** in 60% yield (95% based on recovered **9**).

Because of the strong interest in the synthesis of medium-sized lactones by RCM,[1,2,3a] their synthesis starting from the sulfoximine-substituted diene **3c** was probed. The esterification of alcohol **21**, obtained by desilylation of **5c** (HF/pyridine, THF, 95%), with acrylic acid and pent-4-enoic acid by using DCC/DMAP afforded ester **22** in 47% yield (80% yield based on recovered **21**) and ester **23** in 67% yield (97% yield based on recovered **21**), respectively (Scheme 5). The treatment of the 1,4,10-triene **22** (0.005 M) with 8 mol % of **8** in toluene at reflux for 16 h gave the *Z*-configured 9-membered lactone **24** in 87% yield. The similar RCM reaction of the 1,4,12-triene **23** with **8** furnished the *Z*-configured 11-membered lactone **25** in 81% yield.

Scheme 5



In summary, we have developed a highly flexible asymmetric synthesis of functionalized medium-sized carbocycles and lactones through RCM of sulfoximine-substituted trienes. Because of the alkenyl sulfoximine moiety[8] of the carbocycles and lactones, further transformations can be envisioned including a Michael addition[8] followed by a Cl-substitution of the sulfoximine group,[6b] a Ni-catalyzed cross-coupling reaction with organometal reagents[9] and a migratory Cl-substitution of the sulfoximine group.[10]

**Acknowledgment.** Financial support of this work by the Deutsche Forschungsgemeinschaft (SFB 380) is gratefully acknowledged. We thank Prof. S. Blechert for his collaboration in a study of the RCM of sulfoximine-substituted dienes.

**Supporting Information Available:** Experimental procedures and characterization data for **2a**, **5a**, **9**, **17**, **21**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (b) Molander, G. A.; Brown, G. A.; Storch de Gracia, I. *J. Org. Chem.* **2002**, *67*, 3459−3463. (c) Hodgson, D. M.; Maxwell, C. R.; Miles, T. J.; Paruch, E.; Stent, M. A. H.; Matthews, I. R.; Wilson, F. X.; Witherington, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4313−4316. (d) Torres, E.; Chen, Y.; Kim, I. C.; Fuchs, P. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 3124−3131. (e) Baluenga, J.; Alonso, J.; Fañanás, F. J. *Chem.*−*Eur. J.* **2005**, *11*, 4995−5006. (f) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895−3899. (g) Deng, L.; Giessert, A. J.; Gerlitz, O. O.; Dai, X.; Diver, S. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2005**, *127*, 1342−1343.

(2) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(3) (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goodard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. (b) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264−10266.

(4) (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (b) Rigby, J. H. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 1993; Vol. 12, pp 233−274. (c) Nicolaou, K. C.; Vourloumis, D.; Baran, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 44−122.

(5) (a) Gais, H.-J.; Hainz, R.; Müller, H.; Bruns, P. R.; Giesen, N.; Raabe, G.; Runsink, J.; Nienstedt, S.; Decker, J.; Schleusner, M.; Hachtel, J.; Loo, R.; Woo, C.-W.; Das, P. *Eur. J. Org. Chem.* **2000**, 3973−4009. (b) Reddy, L. R.; Gais, H.-J.; Woo, C.-W.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 10427−10434.

(6) (a) Gais, H.-J.; Müller, H.; Decker, J.; Hainz, R. *Tetrahedron Lett.* **1995**, *36*, 7433−7436. (b) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500−1526.

(7) Interestingly, the treatment of the 1,6,12-triene *S*-**7b** with **8** gave the corresponding asymmetric and $C_2$-symmetric 22-membered carbocycles (32% and 38%) through a combination of CM and RCM reactions.

(8) Reggelin, M; Zur, C. *Synthesis* **2000**, 1−64.

(9) (a) Erdelmeier, I.; Gais, H.-J. *J. Am. Chem. Soc.* **1989**, *111*, 1125−1126. (b) Gais, H.-J.; Bülow, G. *Tetrahedron Lett.* **1992**, *33*, 461−464. (c) Gais, H.-J.; Bülow, G. *Tetrahedron Lett.* **1992**, *33*, 465−468.

(10) Tiwari, S. K.; Gais, H.-J.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, *128*, 7360−7373.

JA0651658