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Enantioselective Synthesis of Functionalized Medium-Sized Oxacycles

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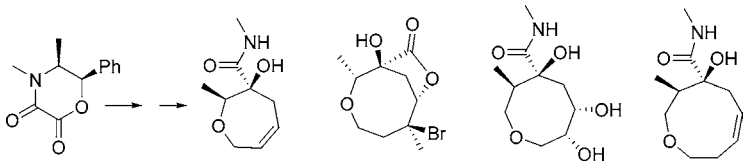
ABSTRACT



Enantioselective routes to functionalized, seven-, eight-, and nine-membered oxacycles that are amenable to further elaboration have been developed. Salient features of the methodology include highly diastereoselective and regioselective transformations of an ephedrine-derived epoxy morpholinone to functionalized precursors of the oxacycles. The ephedrine scaffold exerts remote stereocontrol in the functionalization of the appended oxacycle.

Functionalized, heteroatom-containing rings are found in several natural products, and simplified analogues as well as structural motifs resembling these natural products are interesting synthetic targets. In particular, the synthesis of medium-sized oxacycles[1] has attracted considerable attention, and general[2] as well as target-oriented[3] strategies that address the stereoselective assembly of such ring systems have been extensively investigated in recent years. We chose to examine the enantioselective construction of seven-, eight-, and nine-membered oxacycles that are readily amenable to further functionalization. Herein, we describe preliminary results toward this objective.

The focus of our approach is the incorporation of functional groups that can be utilized for further elaboration of the oxacycle. We targeted unsaturated oxacycles bearing the α-hydroxy acid functionality because the hydroxy and carboxamide groups can be exploited for transannular reactions and the alkene in the ring can be employed in various addition processes.[4] The precursors to the target oxacycles are obtained from a common starting material, an ephedrine-derived morpholine dione **1**,[5] which is readily prepared (85%) from commercially available (1*R*,2*S*)-

(1) For reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301. (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303.

(2) Recent reports: (a) Perez, M.; Canoa, P.; Gomez, G.; Teijeira, M.; Fall, Y. *Synthesis* **2005**, 411. (b) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465. (c) Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867. (d) Sibi, M. P.; Patil, K. P.; Rheault, T. R. *Eur. J. Org. Chem.* **2004**, 372. (e) Alcazar, E.; Pletcher, J. M.; McDonald, F. M. *Org. Lett.* **2004**, *6*, 3877. (f) Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 2277. (g) Martin, M.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **2001**, 117. (h) Saitoh, T.; Suzuki, T.; Onodera, N.; Sekiguchi, H.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 2709. (i) Prasad, K. R. K.; Hoppe, D. *Synlett* **2000**, 1067. (j) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (k) Mujica, M. T.; Afonso, M. M.; Galindoa, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728.

(3) Recent reports: (a) Lee, H.; Kim, H.; Yoon, T.; Kim, B.; Kim, S.; Kim, H.-D.; Kim, D. *J. Org. Chem.* **2005**, *70*, 8723. (b) Posner, G. H.; Hatcher, M. A.; Maio, W. A. *Org. Lett.* **2005**, *7*, 4301. (c) Kaliappan, K. P.; Kumar, N. *Tetrahedron* **2005**, 7461. (d) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361. (e) Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043. (f) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 15196. (g) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (h) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (i) Krueger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (j) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (k) Matthias, B.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.

(4) Recent reports on transannular etherification: (a) Nguyen, G.; Perlmutter, P.; Rose, M. L.; Vounatsos, F. *Org. Lett.* **2004**, *6*, 893. (b) Petri, F. A.; Bayer, A.; Maier, M. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5821. Recent reports on the halolactonization reaction: Mellegard, S. R.; Tuge, J. A. *J. Org. Chem.* **2004**, *69*, 8979 and refs therein.

(5) (a) Rudchenko, V. F.; Shtamburg, V. G.; Pleshkova, A. P.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1981**, *30*, 825. (b) Pansare, S. V.; Bhattacharyya, A. *Tetrahedron Lett.* **2001**, *42*, 9265. For synthetic applications of other aminoalcohol-derived morpholinones, see: (c) Cox, G. G.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *9*, 1669. (d) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11.

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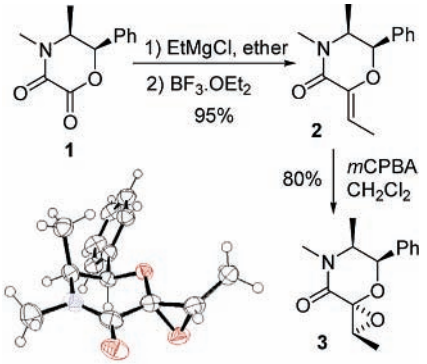
ephedrine hydrochloride and ethyloxalyl chloride. Treatment of **1** with ethylmagnesium chloride and dehydration of the resulting hemiacetal cleanly generated the alkylidene morpholinone **2**[6] (95%, Scheme 1). Epoxidation of **2** with

Scheme 1

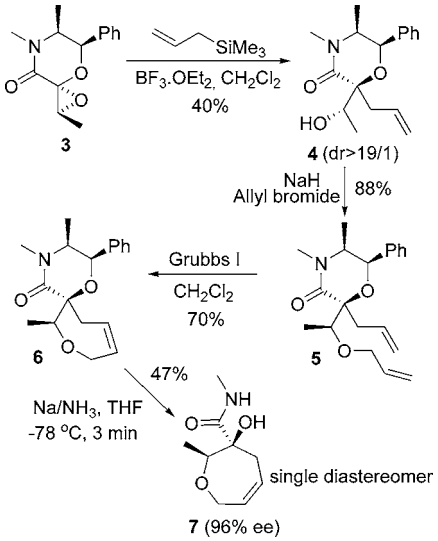


m-CPBA provided the epoxide **3** (85%) as a single diastereomer, which was stable to chromatography. The stereochemistry of **3** was established by X-ray crystallographic analysis,[7] which indicated that the epoxidation of **2** had occurred anti to the phenyl and methyl groups in the morpholinone ring.

Epoxide **3** served as the starting material for the construction of functionalized precursors to seven- and eight-membered oxacycles. We initially explored the ring opening of **3** with vinyl and butenyl magnesium bromide at low temperature (−78 °C). Surprisingly, no reaction was observed. Organocopper reagents were not beneficial, and byproducts predominated when zinc chloride or BF_3 etherate was employed as a Lewis acid in these reactions. Attempted allylation of **3** with $TiCl_4$/allyltrimethylsilane provided the chloroalcohol arising from epoxide ring opening with the chloride ion at the hemiacetal carbon. The use of boron trifluoride as the Lewis acid was beneficial, and the allylation of **3** under these conditions proceeded with excellent diastereocontrol[8] (dr > 19:1, Scheme 2) at ambient temperature to furnish the alcohol **4**. Etherification of **4** with allyl bromide and subsequent ring-closing metathesis[9] of the diene **5** with the Grubbs(I) catalyst generated the spirooxepine **6** (70%). Dissolving metal reduction of **6** generated the seven-membered oxacycle **7** as a single diastereomer.

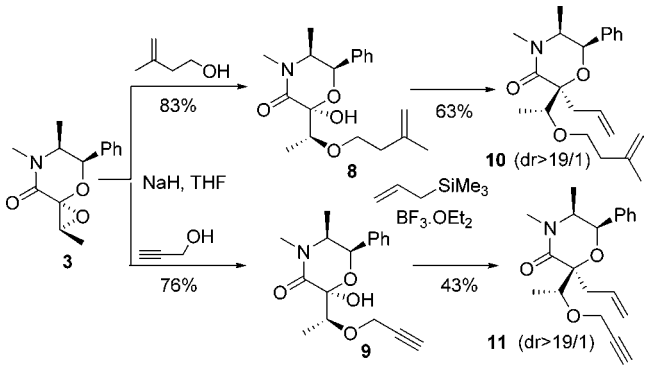
As anticipated, epoxide **3** reacted with alkoxide nucleophiles exclusively at the terminal carbon.[10] For example,

Scheme 2



treatment of **3** with the sodium salt of 3-methyl-3-buten-1-ol or propargyl alcohol cleanly generated the hemiacetals **8** and **9**, respectively. Allylation of the hemiacetals provided the diene **10** and enyne **11** as single diastereomers (Scheme 3). It is assumed that substitution proceeds with inversion at

Scheme 3



the epoxide carbon. It may be noted that these ring-opening reactions demonstrate the utility of **3** as an ambivalent electrophile and also provide a tool for inverting the stereochemistry at the nonacetal carbon of the epoxide. Thus, in principle, the alkoxide opening/allylation procedure can be used to provide the diastereomer of the product obtained by an allylation/O-alkylation reaction sequence with **3**. In addition, the use of an enantiomerically pure secondary alcohol in the epoxide opening reaction should allow for the control of two stereocenters adjacent to the ether oxygen, a structural motif that is found in the laurencin, obtusan, and lauthisan classes of marine natural products.[1]

(6) For a synthesis of **2** from ephedrine and 2-ketobutyric acid, see: Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.

(7) See the Supporting Information for details. The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, reference number CDCC619165.

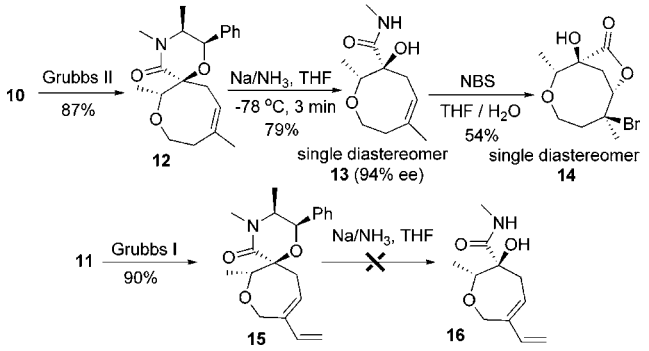
(8) The stereochemistry of allylation is assigned by analogy to other reactions of the oxocarbenium ion intermediate in the ephedrine-derived template (ref 6).

(9) For recent reviews on synthetic applications of metathesis reactions, see: (a) Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.* **2006**, *10*, 185. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(10) For regioselective ring opening of glucose-derived spiro epoxides under acidic or basic conditions, see: Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Synlett* **1995**, 167. For a recent review on the chemistry of epoxides, see: Kas'yan, L. I.; Kas'yan, A. O.; Okovityi, S. I. *Russ. J. Org. Chem.* **2006**, *42*, 307.

We next investigated the ring-closing metathesis reactions of **10** and **11**. Reaction of **10** with the Grubbs(II) catalyst was beneficial, and the spirooxocane **12** was obtained in good yield (87%, Scheme 4). Removal of the ephedrine portion

Scheme 4

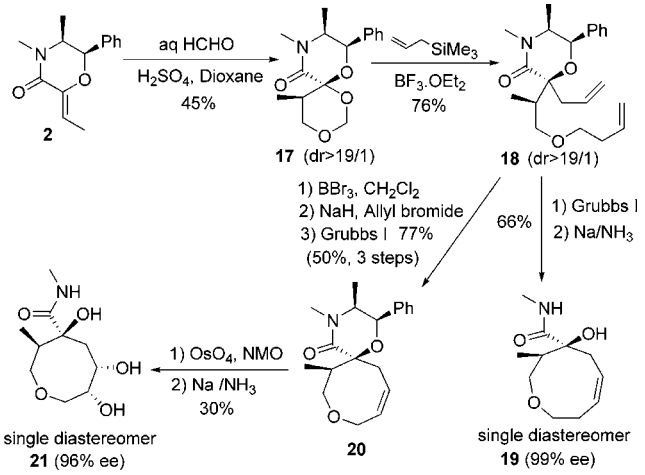


in **12** provided **13** (dr > 19:1, 94% ee). At this stage, the utility of the carboxamide for transannular functionalization was demonstrated by bromolactonization of **13** to provide the functionalized dioxabicyclo[5.2.1]decanone **14** as a single diastereomer (Scheme 4). Although enyne metathesis of **11** proceeded smoothly with the Grubbs(I) catalyst to provide the spirooxepine **15** (90%), subsequent dissolving metal reduction generated a complex mixture of products and the required product **16** could not be detected. Presumably, the diene functionality in **15** is susceptible to dissolving metal reduction. We are examining alternative procedures for removing the ephedrine portion in **15**.

In addition to the epoxide-based routes described above, we have also examined the utility of the alkylidene morpholinone **2** for the preparation of functionalized dienes. Prins reaction[11] of **2** with formaldehyde provided the spirodioxane **17** as a single diastereomer[12] (Scheme 5). Treatment of **17** with excess allyltrimethylsilane/BF_3 etherate provided diastereomerically pure bisallylation product **18** (76%). Ring closure of **18** (74%) and subsequent removal of the chiral controller provided the nine-membered oxacycle **19** (89%, 99% ee, Scheme 5). The bisallylation of **17** augurs well for the employment of functionalized allylsilanes and allylmetal reagents in the acetal opening to provide functionalized oxonines. Also, alkylidene morpholinones related to **2** with varying substitution on the double bond undergo the Prins reaction readily. For example, we have prepared analogues of **17** in which the methyl group is replaced by other alkyl or aryl groups.[13] We are currently examining the allylation reactions of these substrates.

The diene **18** was also employed in the synthesis of a functionalized eight-membered ring **20** (Scheme 5). At this

Scheme 5



stage, we decided to examine the functionalization of the double bond in **20**. Dihydroxylation of **20** (OsO_4, NMO, H_2O/THF) followed by removal of the ephedrine portion provided the diol **21** (~7:1 mixture of diastereomers). The major diastereomer was assigned the shown stereochemistry on the basis of a preferred conformation for **20** (determined by molecular modeling) in which the top face of the double bond is shielded by the phenyl ring in the morpholinone portion of the spirocycle. The chirality of the ephedrine can thus be utilized not only for stereochemical control in the morpholinone ring but also for remote stereocontrol in the appended oxacycle. The spirooxocane **20** was thus converted to the highly oxygenated oxocane **21**, which was isolated as a single diastereomer (30% (two steps), Scheme 5).

In conclusion, we have developed versatile approaches to functionalized, enantiomerically pure oxacycles. The overall strategy is quite flexible and permits the construction of seven-, eight-, or nine-membered oxacycles from readily available chiral precursors, the alkylidene morpholinone **2** and the epoxide **3**. Incorporation of unsaturation and positioning of the ring oxygen at specific locations in the ring are achieved by judicious choice of starting materials. We are currently investigating the application of these methods in the synthesis of selected naturally occurring oxacycles and their analogues.

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Supporting Information Available: Experimental methods, spectroscopic data with assignments, ^1H and ^{13}C data for all compounds, and the crystallographic information for epoxide **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For reviews on the Prins reaction, see: (a) Snyder, B. B. *Compr. Org. Synth.* **1991**, *2*, 527. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661.

(12) The stereochemistry of **17** was assigned by analogy to similar spirodioxanes prepared by us earlier: Jain, R. P. Ph.D. thesis, University of Pune, 2002 and ref 5b.

(13) Adsool, V. A., unpublished results. Also see ref 5b for disubstituted analogues of **17**.