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Extremely Convenient Cyclization of Medium Rings Using SmI_2

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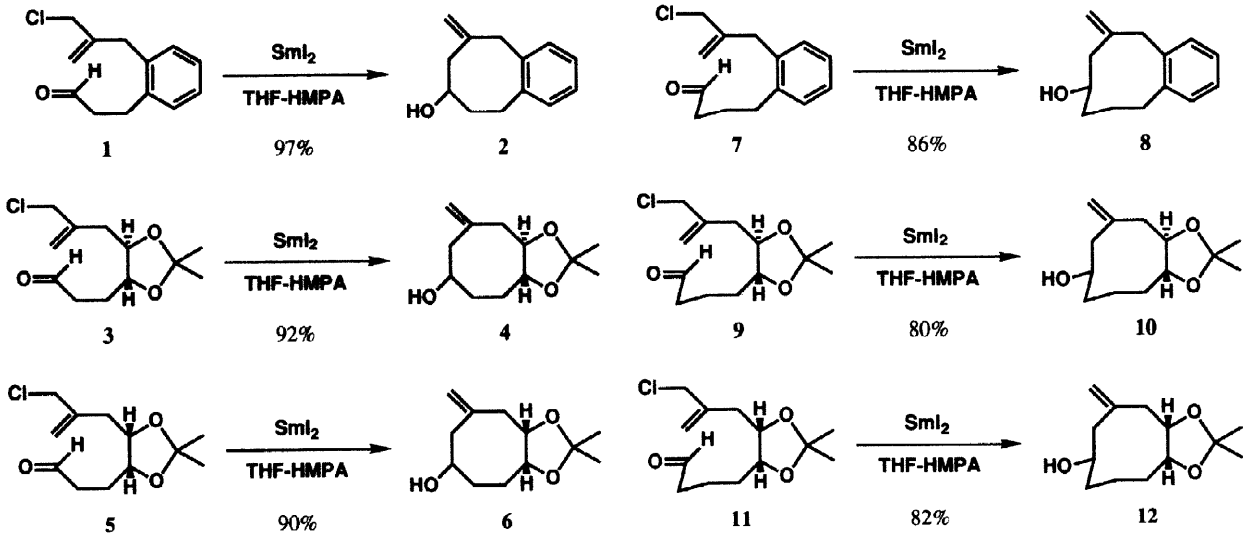
Abstract: *Under non-high-dilution conditions, the medium-sized (8- and 9-membered) carbocycles were obtained in excellent yields utilizing the intramolecular reductive couplings promoted by SmI_2.*

Naturally occurring compounds having a medium-ring framework have historically attracted much attention because of their potential biological activity and the synthetic challenge posed by the required formation of the ring itself. While various annulation methods for the construction of the medium rings have been reported,[1] the development of a general and efficient method for preparing medium-sized carbocycles by simple cyclization of acyclic precursors *via* the carbon-carbon bond formation reaction has not proven as easy. Herein, we describe that 8- and 9-membered carbocycles are assembled with high efficiency *via* the intramolecular coupling reactions induced by SmI_2.[2-4] It is particularly noteworthy that ready formation of the medium rings can be accomplished *without resorting to high-dilution.*

For example, when an aldehyde **1** was treated with SmI_2 in the presence of HMPA at room temperature, the 8-membered ring closing reaction instantaneously proceeded to form the 8-6 fused ring **2** in quantitative yield. Even the more conformationally flexible aldehydes **3** and **5** are good substrates for the SmI_2-mediated cyclizations and afforded the 8-5 *trans*-fused ring **4** and 8-5 *cis*-fused ring **6**, respectively.[5,6] The almost *quantitative yields* of the cyclooctanols **2**, **4**, and **6** are remarkable in view of the difficulties normally encountered during the cyclization of 8-membered rings. Nine-membered rings are also readily accessed by the SmI_2-induced couplings. Treatment of the one-carbon homologated aldehydes **7**, **9**, and **11** with SmI_2



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under the same conditions led to the 9-6 fused ring **8**, 9-5 *trans*-fused ring **10**, and 9-5 *cis*-fused ring **12**, respectively, in good yields.

The reaction is operationally quite simple. Particularly impressive is the fact that these 8- and 9-membered carbocycles were obtained in excellent yields *under non-high-dilution conditions*. The optimum reaction conditions for the coupling cyclizations involved the addition of a 0.1 M solution of SmI_2-HMPA in THF (2.5 equiv) to a 2.0 M solution of the starting material in THF at room temperature. In all cases, *reactions were completed within seconds after SmI_2-HMPA was added.* The addition of HMPA (8.0 equiv to SmI_2) was essential for the reductive cyclization.[7]

In summary, we have developed a general, efficient, and experimentally simple method for generating medium (8- and 9-membered) ring carbocycles utilizing the intramolecular reductive couplings promoted by SmI_2. *The process does not require high-dilution conditions and, amazingly, quantitative yields of these frequently inaccessible medium-sized ring carbocycles are obtained.* Apparently, the SmI_2-induced annulation reaction is among the most convenient entries into medium-sized rings.

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References and Notes

(1) For review, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(2) Samarium(II) iodide (SmI_2) has become an exceedingly useful reagent for promoting reductive coupling reactions. For reviews, see: (a) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A.; Harris, R. H. *Chem. Rev.* **1996**, *96*, 307.

(3) Recently, we described the new types of stereoselective reductive couplings mediated by SmI_2. See: (a) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391. (b) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (c) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111. (d) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532. (e) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (f) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (g) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 987. (h) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (i) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (j) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479.

(4) The SmI_2-mediated Reformatsky reactions, ketone-olefin reductive couplings, and pinacol couplings have been adapted to permit construction of medium ring molecules. See: (a) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889. (b) Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (d) Shiina, I.; Uoto, K.; Mori, N.; Kosugi, T.; Mukaiyama, T. *Chem. Lett.* **1995**, 181. (e) Swindell, C. S.; Fan, W. *Tetrahedron Lett.* **1996**, *37*, 2321.

(5) Recently, we used identical reaction conditions to construct the 8-6 fused ring system of vinigrol, an unusual tricyclic diterpene.[6] However, in this special case, the favorable orientation of the two ends towards cyclization through a rigid conformation greatly facilitates 8-membered ring formation. Subsequent to this early study, we found that the introduction of a much smaller conformational constraint sufficiently enhances the ability of acyclic precursors to undergo the SmI_2-promoted cyclization of medium rings as described in the text. In contrast, 7-chloromethyl-7-octenal gave a mixture of unidentified products without any formation of the 8-membered ring product.

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(7) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (c) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487.