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PREPARATION OF MEDIUM- AND LARGE-SIZED CARBOCYCLES BY MEANS OF SmI_2-PROMOTED INTRAMOLECULAR REFORMATSKY REACTION

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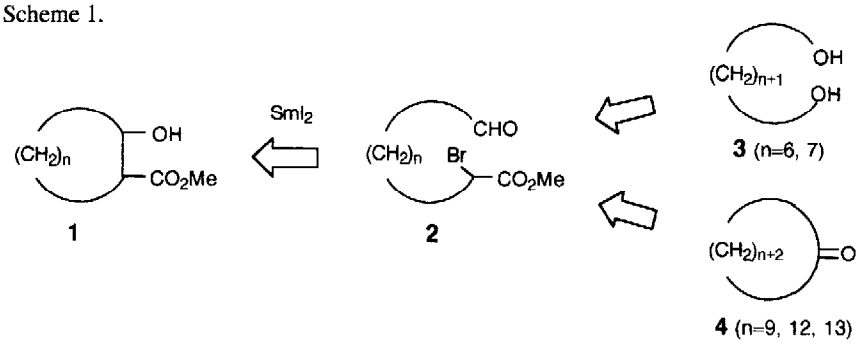
Summary: Medium- as well as large-sized carbocyclic compounds whose ring skeletons are composed entirely of sp^3 carbons have been prepared in high yields under mild conditions by utilizing SmI_2-promoted intramolecular Reformatsky reaction.

The development of new methods for the synthesis of medium-sized carbocyclic rings is of intense current interest[1,2] because of the difficulty in its construction and the interesting biological properties exhibited by a number of natural products containing medium-sized rings such as the taxane family. For the construction of such compounds, direct cyclization of open chain precursors is most straightforward and seems most generally applicable to the synthesis of a wide range of carbocyclic compounds. Recently several useful methods have been developed along this line,[1] however, most of them have still some limitations that *cis*-double bonds, sp^2 carbons, or geminally disubstituted carbonds, which can be expected to lighten the steric strain and unfavorable entropy factor, are often required for effective cyclization.

We report herein an efficient and general method, which is based upon SmI_2-promoted intramolecular Reformatsky reaction,[3] for the formation of medium- as well as large-sized carbocyles whose ring skeletons are composed entirely of sp^3 carbons.[4] The strategy for the synthesis of carbocycles (**1**) is shown in Scheme 1.

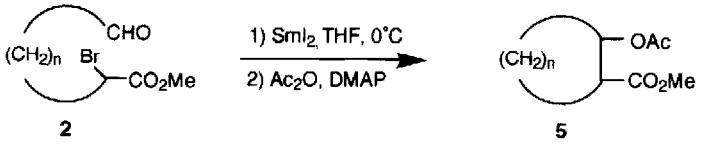
Scheme 1.



The open chain precursors **2** (n=6, 7, 9, 12, and 13) were prepared form 1,ω-diols **3** (n=6 and 7) in 7 steps or from cycloalkanones **4** (n=9, 12, and 13) in 4 steps, respectively.[5]

The cyclization reaction was carried out as follows: To a cold (0~5°C) solution of SmI_2 in THF (0.1 mol dm^{-3}, 30 ml) was added dropwise a solution of freshly prepared α-bromo-ω-oxo esters (**2**, 0.5 mmol) in THF

(10~100 ml) over 2~3 h under nitrogen. After stirring for additional 5 min, excess SmI_2 was quenched by exposing the mixture to air and the crude products were directly acetylated with excess Ac_2O and DMAP. Usual workup followed by chromatographic purification on silica gel gave the corresponding methyl 2-acetoxy-cycloalkane-1-carboxylates (**5**) as mixtures of diastereomers (ca. 1:1).[6] (Eq. 1) The results are summarized in Table 1.



2 **5** (1)

Table 1. SmI_2-Promoted Cyclization of α-Bromo-ω-oxo Esters [a)]

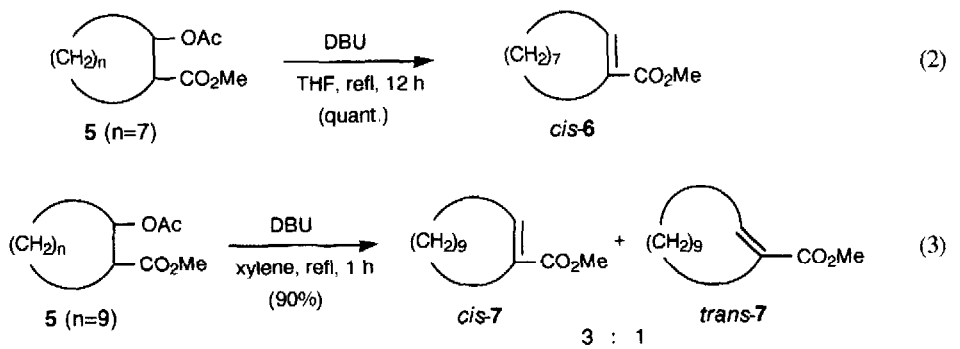
Entry	α-Bromo-ω-oxo ester (**2**) (n)	Concentration (mmol/l)	Carbocycle (**5**)[b)]	
			Ring size (n+2)	Yield (%)[c)]
1	6	5	8	68
2		50		69
3	7	5	9	70
4		50		63
5	9	2	11	74
6		10		75
7	12	2	14	82
8	13	2	15	82

a) For the reaction conditions, see the text. b) Satisfactory ^1H NMR (400 MHz) and mass (FAB and CI) spectra were obtained. c) Isolated yield.

As shown in Table 1, not only large rings but also medium-sized carbocycles were obtained in high yields even under non-high-dilution conditions (entries 2 and 4).

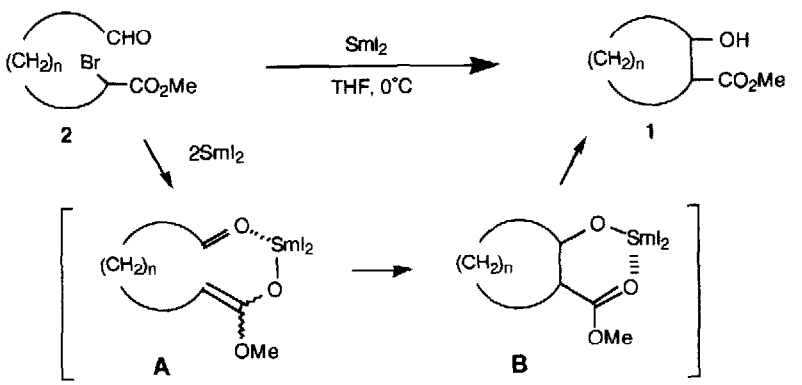
In spite of a mixture of diastereomers, heating of **5** (n=7) with DBU produced the corresponding α,β-unsaturated ester (**6**) with *cis*-cycloalkene structure[7] in quantitative yield. (Eq. 2) Similarly, the reaction of **5** (n=9) in refluxing xylene afforded the corresponding unsaturated esters as a mixture of *cis* and *trans* isomers[8] in 90% overall yield. (Eq. 3)

The cyclization reaction seems to proceed through samarium enolate intermediate[3b] as the result of successive two electron reduction of α-bromo esters. The precise mechanism how both the ends of the chain are put together against the so-called medium-ring effect is not clear, but the distinct property of samarium such as



large ionic radius, flexible coordination, and high oxophilicity[9] should play an important role for the cyclization: The samarium-linked large-sized chelate (**A**), from which the carbon-carbon bond formation would take place like a ring contraction, and the six-membered chelate (**B**) after cyclization might be involved in the process (Scheme 2).

Scheme 2.



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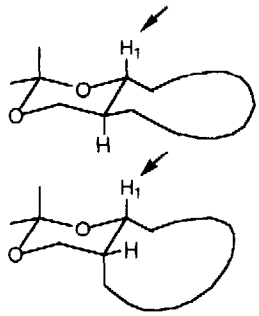
References and Notes

1. a) T. Takahashi, H. Nemoto, and J. Tsuji, *Tetrahedron Lett.*, **24**, 2005 (1983). b) N. A. Porter, D. R. Magnin, and B. T. Wright, *J. Am. Chem. Soc.*, **108**, 2787 (1986). c) P. A. Wender and M. L. Snapper, *Tetrahedron Lett.*, **28**, 2221 (1987). d) M. Rowley and Y. Kishi, *ibid.*, **29**, 4909 (1988); M. Rowley, M. Tsukamoto, and Y. Kishi, *J. Am. Chem. Soc.*, **111**, 2735 (1989). e) J. E. Merritt, M. Sasson, S. A. Kates, and B. B. Snider, *Tetrahedron Lett.*, **29**, 5209 (1988). f) J. E. McMurry and J. G. Rico, *ibid.*, **30**, 1169 (1989); J. E. McMurry, *Acc. Chem. Res.*, **16**, 405 (1983). g) Y. Horiguchi, T. Furukawa, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 8277 (1989).

2. a) M. R. Karim and P. Sampson, *Tetrahedron Lett.*, **29**, 6897 (1988). b) K. C. Nicolaou, Y. Ogawa, G. Zuccarello, and H. Kataoka, *J. Am. Chem. Soc.*, **110**, 7247 (1988). c) C. W. Ellwood and G. Pattenden, *Tetrahedron Lett.*, **32**, 1591 (1991).
3. a) For the synthesis of medium- and large-sized lactones, see T. Tabuchi, K. Kawamura, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, 27, 3889 (1986). b) For the stereoselective synthesis of 6-membered lactones, see G. A. Molander and J. B. Etter, *J. Am. Chem. Soc.*, **109**, 6556 (1987). c) For intermolecular reactions, see P. Girard, J. L. Namy, and H. B. Kagan, *ibid.*, **102** (1980).
4. A part of this work was presented at the 7th Symposium of the Rare Earth Society of Japan, May, Kyoto (1990).
5. 1,ω-Diols **3** (n=6 and 7) were half protected as the THP ethers. Swern oxidation followed by Horner-Emmons reaction gave the corresponding conjugated esters, which were then hydrogenated (H_2, Pd-C) to afford the saturated esters. α-Bromination of the esters were performed via ketene trimethylsilyl acetals (LDA, TMSCl; NBS). Deprotection of THP groups followed by PCC oxidation gave the precursors **2**. On the other hand, cycloalkanones **4** (n=9, 12 , and 13) were subjected to Baeyer-Villiger oxidation to give the lactones, the α-bromination of which was accomplished in a similar way described above. Methanolysis (MeOH, K_2CO_3) followed by PCC oxidation gave the precursors **2**.
6. The diastereomeric ratios were determined by ^1H NMR (400 MHz) analysis by comparing the relative intensities of the acetyl methyl protons. The isomeric ratios were further confirmed by reducing the cyclization products **5** (n=6 and 9) with $LiAlH_4$ followed by acetonide formation: Selected ^1H NMR data of which are shown below.



Carbocycle (ring size)	8	11
H_1: δ (ppm) / J (Hz)	3.96 (dd) / (11.2, 3.7)	4.00 (ddd) / (11.2, 2.4, 1.5)
	3.89 (dt) / (10.2, 3.7)	3.90 (dt) / (10.7, 2.9)

7. *cis*-**6**: ^1H NMR ($CDCl_3$) δ=6.85 (t, 1H, J=5.26 Hz).
8. *cis*-**7**: ^1H NMR ($CDCl_3$) δ=6.69 (dd, 1H, J=7.59 and 7.92 Hz). *trans*-**7**: ^1H NMR ($CDCl_3$) δ=6.09 (t, 1H, J=8.75 Hz).
9. H. B. Kagan, "*4f-Elements in Organic Synthesis*" in *Fundamental and Technological Aspects of Organo-f-Element Chemistry*, Ed by T. J. Marks and I. L. Fragala, p. 49, D. Reidel, New York (1985).

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