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LETTERS

One-Carbon Ring Enlargement of Lactones

Tsuyoshi Satoh* and Toshiyuki Kurihara

Department of Chemistry, Faculty of Sciences, Science University of Tokyo; Kagurazaka, Shinjuku-ku Tokyo 162-8601, Japan

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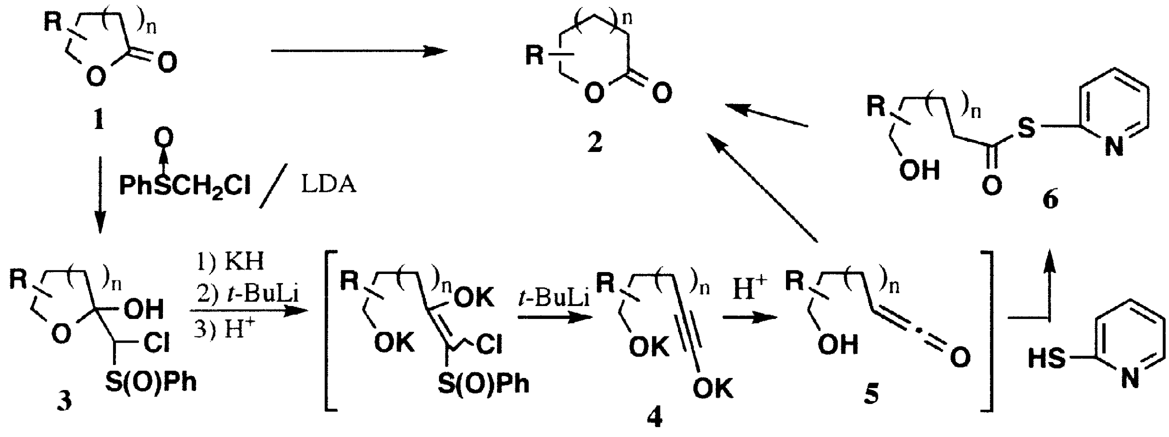
Abstract: Two-step or three-step one-carbon ring enlargement of lactones is realized from lactones and chloromethyl phenyl sulfoxide via a rearrangement of alkylidene carbenoid followed by intramolecular cyclization of the ω-hydroxyalkyl ketene intermediate or via a 2-pyridinethiol ester. © 1998 Elsevier Science Ltd. All rights reserved.

Ring enlargement is a quite interesting and important method for obtaining the desired cyclic compounds from lower cyclic compounds.[1] There are many one-carbon ring enlargement reactions for carbocyclic compounds and cyclic ketones; however, the one-carbon ring enlargement of lactones is rare.[2]

Recently, we reported a new method for synthesis of carboxylic acids and their derivatives from methyl esters with one-carbon homologation.[3] In this letter, in continuation of our studies on the homologation of carbonyl compounds,[4] we describe a novel two-step or three-step procedure for one-carbon enlargement of lactones **1** via carbenoid rearrangement (to give alkynolate **4**) and ω-hydroxy ketenes **5** or via 2-pyridinethiol esters **6**[5] (Scheme 1).



Scheme 1

The described procedure uses γ-phenyl γ-butyrolactone **7** as a typical lactone (Scheme 2). Reaction of the lithium carbanion of chloromethyl phenyl sulfoxide with **7** at -78 °C afforded a diastereomeric mixture of the adduct **8** in 94% yield.[3] The structure of the adduct was found not to be the α-sulfinyl ketone but a hemiacetal. The adduct **8** was treated with three equivalents of KH in THF at 0 °C for 30 min, then the reaction mixture was cooled to -78 °C. To the solution of the potassium enolate, four equivalents of t-BuLi were added and the reaction mixture was stirred at -78 °C for 20 min. Finally, in order to generate the ω-hydroxyalkyl ketene, the

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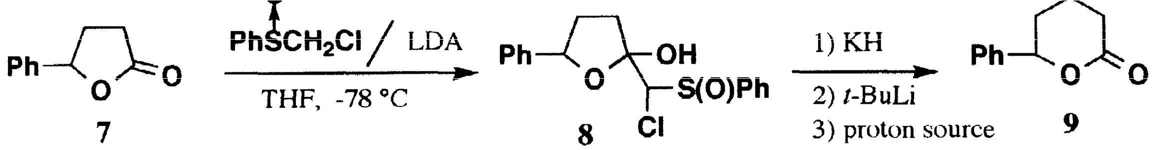
reaction was quenched by adding a proton source. We expected that if the above-mentioned treatment gave the ω-hydroxyalkyl ketene, it would be cyclized to give δ-phenyl δ-valerolactone **9**.[6]

Scheme 2



Proton source	Conditions	Concentration mol / L	**9** (Yield/%)
Et_3N HCl (8 eq.)	-78 °C 1 h, then 0 °C 1 h	0.1	45
Et_3N HCl (Finely ground; 8 eq.)	-78 °C 1 h, then 0 °C 2 h	0.1	59
H_2SO_4 (3 eq.)	-78 °C 1 h, then 0 °C 1 h	0.05	69

First, the above-mentioned reaction was treated with 8 equivalents of dry triethylamine hydrochloride.[7] Fortunately, this treatment gave the desired one-carbon homologated lactone **9** in 45% yield. The yield was improved to 59% by using finely ground, dry triethylamine hydrochloride. After some investigation, the best yield (69%) was obtained with 95% sulfuric acid[8] (Scheme 2).

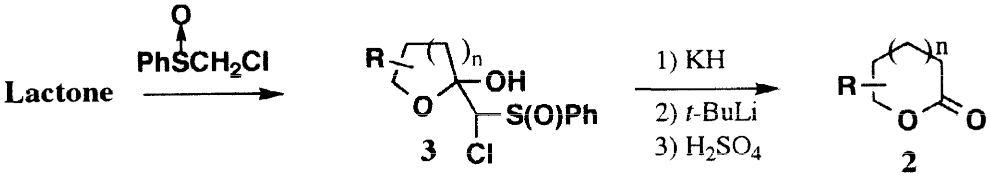
The preliminary results for the one-carbon ring enlargement of 5-, 6-, and 9-membered lactones are summarized in Table 1. Entries 1-5 show that the reaction of the lithium carbanion of chloromethyl phenyl sulfoxide with γ- and δ-lactones gave a diastereomeric mixture of hemiacetals in almost quantitative yields. In the case of the 9-membered lactone, the adduct was found to be β-ketosulfoxide (entry 6).

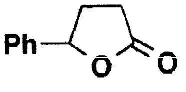
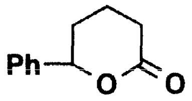
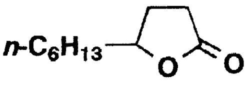
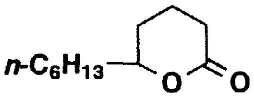
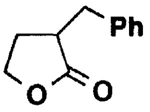
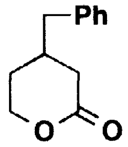
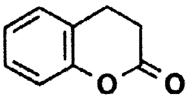
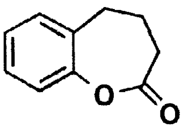
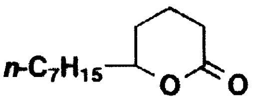
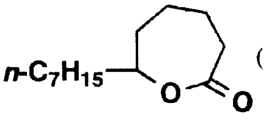
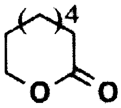
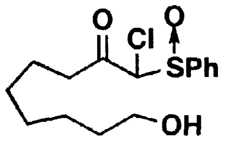
Formation of a potassium enolate of the adducts and the treatment of the generated enolate with *t*-BuLi followed by sulfuric acid was carried out in a similar way to that described above. Entries 1-3 indicate that the reaction proceeded smoothly to give the desired one-carbon homologated δ-lactones in good yields. In contrast to this, conversion of the 6-membered lactones to 7-membered lactones (entries 4 and 5) was found to be problematical. Especially the reaction shown in entry 5 gave only a complex mixture when the reaction was carried out at the concentration of 0.05 mol/L. Even in a much more diluted solution, the yield of the desired lactone was low. The by-products of this reaction were thought to be dimer, trimer, and polymers, although they have not be isolated yet.

Entry 6 shows that the reaction of β-ketosulfoxide to 10-membered lactone (medium-sized cyclic compound) also is very difficult.

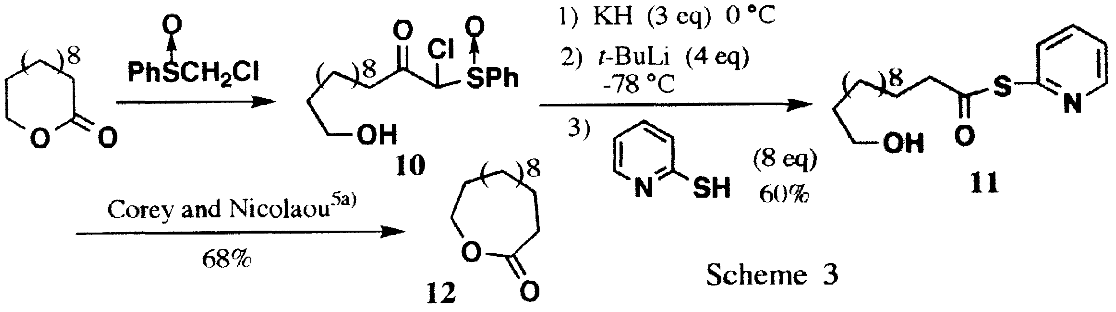
Synthesis of macro lactones is an interesting subject. We tried to synthesize macrolides by using our above-mentioned method (Scheme 3). 13-Membered lactone was reacted with chloromethyl phenyl sulfoxide to give the desired β-ketosulfoxide **10** in 94% yield. This sulfoxide was treated with KH-*t*-BuLi, followed by sulfuric acid. However, the treatment again gave only a complex mixture. We then changed to use of the so-called Mukaiyama-Corey method.[5, 9)]

Table 1. One-Carbon Ring Enlargement of 5-, 6-, and 9-Membered Lactones



Entry	Lactone	3 (Yield / %)[a]	Conc. (mol/L)[b]	2 (Yield / %)[c]
1		(94)	0.05	 (69)
2		(94)	0.05	 (59)
3		(88)	0.05	 (65)
4		(91)	0.05	 (36)
5		(91)	0.005[d]	 (19)
6		 (94)	0.05 0.005	complex mixture complex mixture

a) The isolated yields of the reaction of lithium carbanion of chloromethyl phenyl sulfoxide with the lactones. b) The concentration of the treatment of the reaction mixture with sulfuric acid. c) Isolated purified yield after silica gel column chromatography. d) When the protonation was conducted at 0.05 mol/L a rather complex mixture was obtained.



Scheme 3

We have already reported one-carbon homologation of methylesters to thiol esters.[3)] β-Ketosulfoxide **10** was treated with KH-*t*-BuLi as above and the reaction was finally treated with 2-mercaptopyridine. Fortunately, this reaction gave the desired 2-pyridinethiol ester **11** in 60% yield. Corey and Nicolaou have already converted **11** to 14-membered lactone **12** in 68% yield.[5a)]

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References and Notes

1. Some reviews and a monograph: Conia, J. M.; Robson, M. J. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 473. Hiyama, T.; Nozaki, H. *J. Syn. Org. Chem. Jpn.* **1977**, *35*, 979. Krow, G. R.; *Tetrahedron* **1987**, *43*, 3. Roxburg, C. J. *Tetrahedron* **1993**, *49*, 10749. Tochtermann, W.; Kraft, P. *Synlett* **1996**, 1029. Hesse, M. *"Ring Enlargement in Organic Chemistry"* VHC, Weinheim, 1991.

2. Hirao, T.; Fujihara, Y.; Kurokawa, K.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1986**, *51*, 2830. Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661. Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4807.

3. Satoh, T.; Unno, H.; Mizu, Y.; Hayashi, Y. *Tetrahedron* **1997**, *53*, 7843.

4. Satoh, T.; Onda, K.; Yamakawa, K. *J. Org. Chem.* **1991**, *56*, 4129. Satoh, T.; Ogura, A.; Ikeda, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1582. Satoh, T.; Itoh, N.; Onda, K.; Kitoh, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2800. Satoh, T.; Itoh, N.; Gengyo, K.; Takada, S.; Asakawa, N.; Yamani, Y.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 11839. Satoh, T.; Hayashi, Y.; Mizu, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1412. Satoh, T.; Mizu, Y.; Kawashima, T.; Yamakawa, K. *Tetrahedron* **1995**, *51*, 703.

5. a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. b) Corey, E. J.; Ulrich, P.; Fitzpatrick, M. *J. Am. Chem. Soc.* **1976**, *98*, 222. c) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, 3405.

6. Boeckman, Jr. R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. Petasis, N. A.; Patane, M. A. *J. Chem. Soc., Chem. Commun.* **1990**, 836. Sato, M.; Sakaki, J-I.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. *Tetrahedron* **1991**, *47*, 5689. Sakaki, J-I.; Sugita, Y.; Sato, M.; Kandko, C. *Tetrahedron* **1991**, *47*, 6197.

7. Commercial triethylamine hydrochloride was dried over P_2O_5 under vacuum.

8. In a 30-ml flame-dried flask was added KH (36 mg; 0.9 mmol) and 3 ml of dry THF. This suspension was cooled in an ice bath and to this was added a solution of **8** (101 mg; 0.3 mmol) in 1 ml of dry THF. The reaction mixture was stirred at 0 °C for 30 min. Within this time the evolution of H_2 ceased. The reaction mixture was cooled to -78 °C. *t*-BuLi (1.6M in pentane; 0.73 ml; 1.2 mmol) was added dropwise to the reaction mixture and the solution was stirred at -78 °C for 20 min. A solution of 95% sulfuric acid (0.051 ml; 0.9 mmol) in 2 ml of THF was added dropwise to the reaction mixture and the solution was stirred at -78 °C for 1 h and at 0 °C for 1 h. The reaction was quenched by adding sat. aq NH_4Cl and the whole was extracted with benzene-ether. The organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography (Hexane:AcOEt=5:1) to give **9** (36.6 mg; 69%) as a colorless oil.

9. Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901. Mukaiyama, T.; Matsueda, R.; Maruyama, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1271. Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.