

Synthesis of  $\gamma$ -Lactones by the Intramolecular Radical Cyclization of 2-Bromo-3,3-bis(methylthio)propionates. A Useful Ketene Radical Synthon

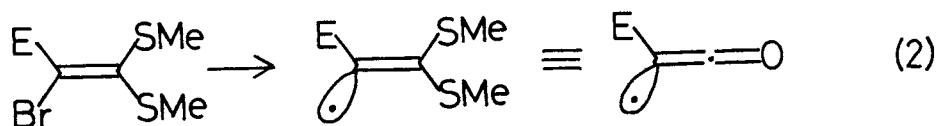
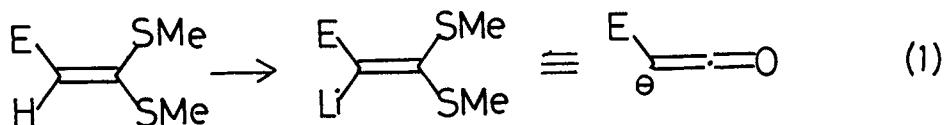
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The first example of intramolecular radical cyclization of ketene radical synthon is presented. Intramolecular radical cyclization of 2-bromo-ketene-S,S-acetals proceeded highly regioselectively to give the corresponding 5-exo-trig cyclized  $\gamma$ -lactones.

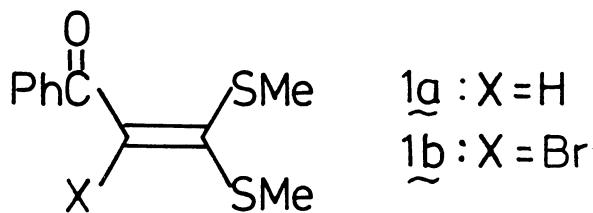
Synthetic applications of ketene-S,S-acetals substituted with electron withdrawing groups at C(2)-position have been well studied to construct a variety of heterocyclic systems.<sup>1)</sup> The advantage of this method is that acetal can be easily prepared by the known procedure<sup>2)</sup> and the C(2) carbon atom is highly activated by the effect, generally known as push-pull or donor-acceptor effect. Thus an anion or a radical can be generated at this position by the effective stabilization. In previous studies, we demonstrated the preparation of ketene enolate anions from ketene-S,S-acetals and its synthetic utility (Eq. 1).<sup>3)</sup> In this paper, our interest has been focused on the generation of the radical version of ketene radical synthon (Eq. 2).



E = electron-withdrawing group

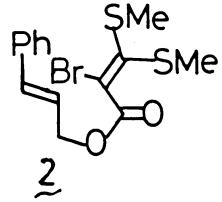
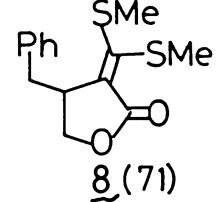
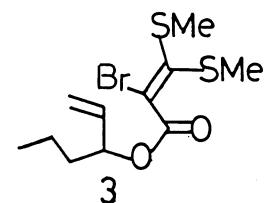
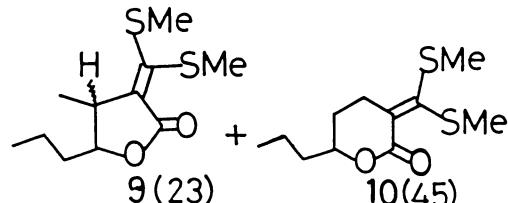
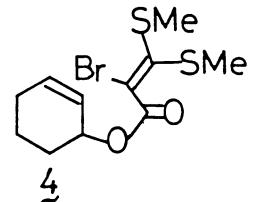
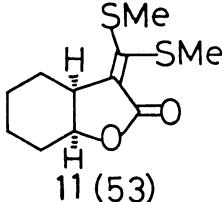
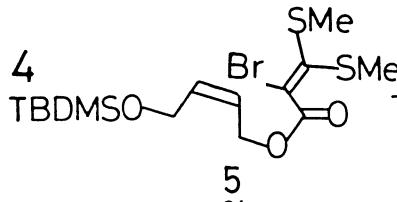
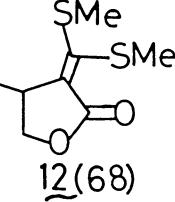
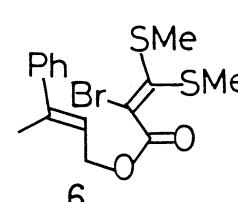
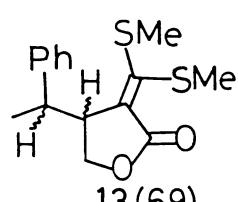
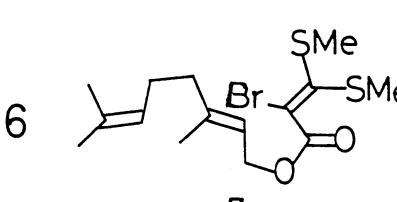
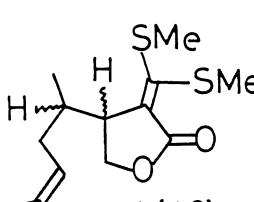
This is a unique concept since radicals have never been accounted to be utilized as ketene radical synthon.<sup>4)</sup> Exposure of ketene-S,S-acetals to a radical reaction would result in a nasty reaction, because carbon-sulfur bonds are believed to be fragile under those conditions.<sup>5)</sup> We looked for a possibility to create a hitherto unknown type of ketene radical synthon and we reported here the successful preparation of ketene radical synthon and its intramolecular radical cyclization reaction assisted by tri-n-butyltin hydride.<sup>6)</sup>

At first, we found that ketene-S,S-acetal unit as a protecting group was stable under the standard radical reaction condition.<sup>7)</sup> The ketene radical precursor was prepared via an introduction of bromine at C(2) position by the reaction of ketene-S,S-acetals with N-bromosuccinimide (NBS) in  $\text{CCl}_4$  at room temperature.<sup>8)</sup> 2-Benzoyl-2-bromo-ketene-S,S-acetal (1b) obtained was reduced efficiently to 2-benzoyl-ketene-S,S-acetal (1a) by treating with tri-n-butyltin hydride and azobisisobutyronitrile (AIBN) at 80 °C in dry toluene.



Since the S,S-dimethyl acetal group was inactive under the above mentioned radical reaction conditions, we attempted an intramolecular radical cyclization using this synthon. The results are shown in Table 1.<sup>9)</sup> The radical cyclization proceeded highly regioselectively to give 5-exo-trig cyclized  $\gamma$ -lactones with ketene-S,S-acetals at  $\alpha$ -position (in entries 1, 3, 4, 5, and 6). In the case of entry 2, 5-exo-trig cyclized compound 9 and thermodynamically stable product 10 were obtained in the ratio of 1:1 respectively.<sup>10)</sup> In entries 5 and 6, the stereoselectivity of the radical cyclization was almost 1:1.<sup>11)</sup> However, in cyclic system, the radical cyclization of the ketene radical synthon showed high regio and stereoselectivity (entry 3). The obtained cyclized ketene-S,S-acetals 8—14 could be converted to the corresponding  $\gamma$ -lactones with carboalkoxy group at  $\alpha$ -position.

Table 1. Intramolecular Radical Cyclizations of Ketene Radical Synthon

Entry	Ketene-S,S-acetals	Products (Yield/%) <sup>a)</sup>	syn:anti <sup>b)</sup>
1			
2			
3			(>99:1)
4			
5			(1:1)
6			(1:1)

a) Isolated yield. b) Determined by 270 MHz <sup>1</sup>H-NMR analysis.

## References

- 1) For recent reviews, see M. Yokoyama, and Y. Tominaga, *Yuki Gosei Kagaku Kyokaishi*, 47, 413 (1989); H. Junjappa, H. Ila, and C.W. Asokan, *Tetrahedron*, 46, 5423 (1990) and references therein.
- 2) R. K. Dieter, *J. Org. Chem.*, 46, 5031 (1981).
- 3) M. Yamamoto, T. Takemori, S. Iwasa, S. Kohmoto, and K. Yamada, *J. Org. Chem.*, 54, 1457 (1989).
- 4) For acyl radical synthon; A. Nishida, M. Nishida, and O. Yonemitsu, *Tetrahedron Lett.*, 31, 7035 (1990).
- 5) J. M. McIntosh and C. K. Scharn, *Can. J. Chem.*, 55, 3755 (1977); G. G. Gutierrez, R. A. Stringham, T. Nitasaka, and K. G. Glasscock, *J. Org. Chem.*, 45, 3393 (1980); G. G. Gutierrez, and L. R. Summerhays, *ibid.*, 49, 5206 (1984).
- 6) For reviews see B. Giese, "Radicals in Organic Synthesis, Formation of Carbon-Carbon Bonds," Pergamon Press, Oxford (1986), and references therein.
- 7) Dithioacetal 1a was found to be inert under heating at 80°C in toluene with tri-n-butylltin hydride and AIBN.
- 8) G. Singh, H. Ila, and H. Junjappa, *Synthesis*, 1985, 165.
- 9) General Procedure: Intramolecular Radical Cyclization of 2b; A mixture of 2b (0.1100 g, 0.30 mmol), tri-n-butylltin hydride (0.1050 g, 0.36 mmol), and catalytic amount of azobisisobutyronitrile (AIBN) (0.0050 g, 0.1 equiv.) in dry and degassed benzene (150 mL) (0.002 M) was heated at 80°C under an argon for 2 h. The mixture was purified by flash column chromatography on silica gel using benzene as an eluent to give cyclized product,  $\gamma$ -lactone 8 in 71%. 8; IR (neat) 1740, 1560, 1210, 1090  $\text{cm}^{-1}$   $^1\text{H-NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  2.49 (s, 3H), 2.52 (s, 3H), 2.65 (dd, 1H,  $J$  = 13.9 and 10.8 Hz), 3.12 (dd, 1H,  $J$  = 13.9 and 4.2 Hz), 3.66 (dd, 1H,  $J$  = 10.8, 4.2, 4.2, and 4.2 Hz), 4.20 (d, 2H,  $J$  = 4.2 Hz), 7.18-7.36 (m, 5H).  $^{13}\text{C-NMR}$  (67.8 MHz,  $\text{CDCl}_3$ )  $\delta$  (INEPT) 17.79 ( $\text{CH}_3$ ), 18.37 ( $\text{CH}_3$ ), 39.03 ( $\text{CH}_2$ ), 45.15 (CH), 68.34 ( $\text{CH}_2$ ), 126.80 (CH), 128.40 (C), 128.69 (CH), 129.15 (CH), 138.31 (C), 153.13 (C), 167.21 (C). HRMS  $\text{M}^+$ , found m/z 280.0590 calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}_2$   $\text{M}^+$  280.0549.
- 10) The determination of the ratio and separation of the diastereomers were carried out with a Hitachi L-6000 HPLC system using a 250X10 mm column packed with Merck Lichrosorb Si 60.
- 11) Reference 6, p. 147 in Chap. 4.

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