Intramolecular Radical Cyclization of Ketene Dithioacetals

Makoto YAMAMOTO,* Atsuko FURUSAWA, Seiji IWASA,
Shigeo KOHMOTO, and Kazutoshi YAMADA
Department of Materials Science, Faculty of Engineering, Chiba University,
1-33 Yayoi-cho, Inage-ku, Chiba 263
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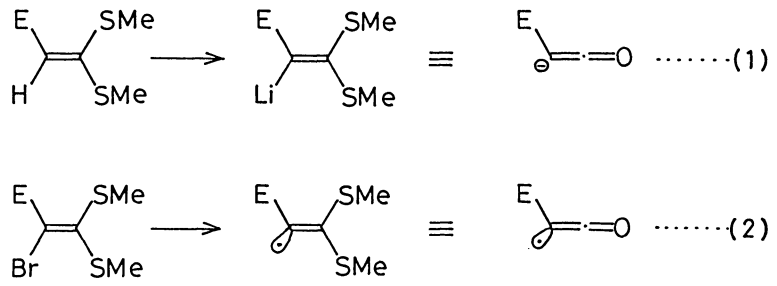
A novel intramolecular ketene radical cyclization was described. Treatment of α-bromo-β-alkoxycarbonyl- and α-bromo-β-oxoketene dithioacetals with tributyltin hydride and AIBN gave lactones and cyclic ketones bearing bis(methylthio)methylene substituent at α-position in moderate yields. Tandem radical cyclization of ketene radical synthons were also carried out.

It is well-known that the dithioacetal unit is widely used for a carbonyl protecting group. Many kinds of protecting groups are reported in the literature.[1] However, recent organic chemistry requires not only the protection but also additional functionalities for these protecting groups. Method of dipole inversion (=Umpolung), which was offered by Seebach,[2] is considered to be based on this concept. According to the similar consideration we have designed a new ketene anion synthon, which was formed from a 2-(phenylsulfonyl)dithioacetal with butyllithium[3] (Eq. 1).

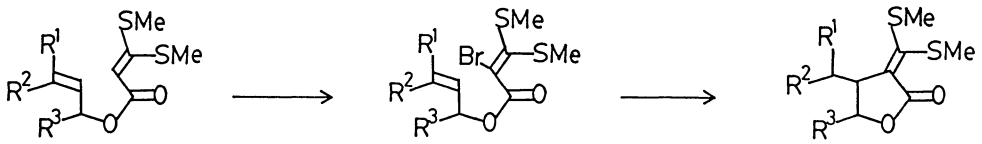
By analogy with the ketene anion synthon approach, we have attempted to the formation of a ketene radical synthon[4] (Eq. 2).

Although carbon-sulfur bonds are believed to be fragile under radical reaction condition,[5] it was proved that the ketene dithioacetal was stable under those conditions,[6] and we reported here the successful preparation of ketene radical synthon and its intramolecular radical cyclization reaction assisted by tributyltin hydride.[7] In this paper we will describe the scope and the limitation of the ketene radical synthon in detail.

The ketene radical precursors (**5**—**8**) were prepared via an introduction of bromine atom at C_2-position by the reaction of corresponding ketene dithioacetals (**1**)—(**4**) with *N*-bromosuccinimide (NBS) in carbon tetrachloride at room temperature.[8] Then we attempted an intramolecular radical cyclization. A mixture of azobisisobutyronitrile (AIBN) in dry and degassed benzene was heated at 80 °C under argon for 2 h. The reaction mixture was purified by flash column chromatography on silica gel using benzene as an eluent to give cyclized

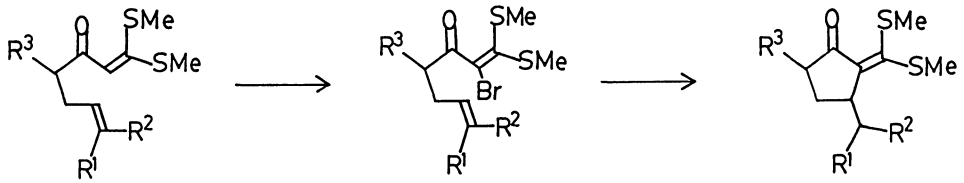


Scheme 1.

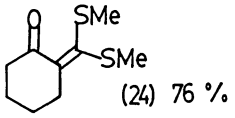


(1): R^1=Ph, R^2=R^3=H	(5)	69 %	(9) 71 %
(2): R^1=H, R^2,R^3=-$(CH_2)_3$-	(6)	95	(10) 53
(3): R^1=R^3=H, R^2=CH_2OTBDMS	(7)	52	(11) 68
(4): R^1=Ph, R^2=Me, R^3=H	(8)	71	(12) 69

Scheme 2.



(13): $R^1=R^2=Me, R^3=H$ (18) 86 % (23) 42 %
(14): $R^1=R^2=R^3=H$ (19) 70
(15): $R^1=R^3=H, R^2=Ph$ (20) Quant. (25) 54
(16): $R^1=H, R^2=Ph, R^3=CH_2CH=CH-Ph$ (21) 73 (26) 16
(17): $R^1=R^3=H, R^2=Me$ (22) 76 (27) 35



Scheme 3.

product, γ-lactone (**9**) in 71% yield, accompanied by a small amount of a simple reduction product **1**. The results of the cyclization bearing the other substituents are shown in Scheme 2.

This radical cyclization proceeded highly regioselectively to give 5-Exo-Trig cyclized[9] γ-lactone with ketene dithioacetals at α-position. In the case of compound **8**, the stereoselectivity of the cyclization was almost 1 : 1. However, in cyclic system, the radical cyclization of the ketene radical synthon showed high regio- and stereoselectivity (**6**—**10**).

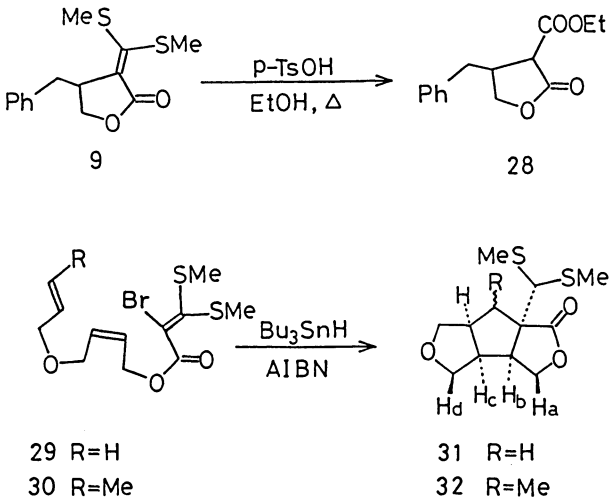
We have applied this radical cyclization to corresponding β-oxoketene dithioacetals (**18**)—(**22**). The radical cyclizations were conducted by the same procedure as the case of **1**, and the corresponding cyclic ketones were obtained in moderate yields (Scheme 3).

In the case of the compound (**19**) only 6-Endo-Trig cyclized product **24**[9] was detected. However, none of the expected 6-Endo-Trig product was obtained in the cyclization of **20**, but only **25** was obtained in 54% yield. The difficulty of 6-Endo-Trig mode of cyclization is probably because the steric factor between a phenyl and two methylthio groups.

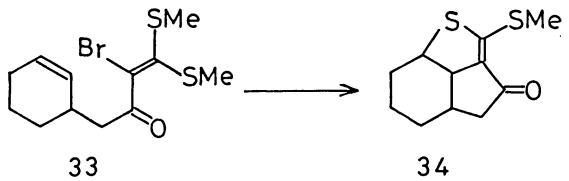
The relative low yield of the radical cyclization products is considered that the cyclic β-oxoketene dithioacetals are unstable and difficult to purify by silica-gel column chromatography.

We also checked that obtained cyclic ketene dithioacetals are the synthetic equivalents of corresponding ketones. Removal of the protecting group in **9** was easily proceeded, i.e., **9** was treated with *p*-toluenesulfonic acid in refluxing ethanol[3] to give ethyl ester **28** in 90% yield.

Finally we also applied this method to the tandem radical cyclization. Bromo trienes **29** and **30** were



Scheme 4.



Scheme 5.

cyclized by the procedure described above to give tricyclic lactones **31** and **32** in 26 and 19% yields, respectively. The stereochemistry of **31** was assigned by detailed ^1H NMR, ^{13}C NMR and NOESY spectroscopic studies. NOE cross peak between H_a and H_d, and also both protons of ring junction (H_b and H_c) in the NOESY spectrum of **31** provides the basis for the stereochemical

assignment shown below. Compound **32** was also assigned as syn configuration.

Thus, we have demonstrated that bromoketene dithioacetals gave a novel ketene radical which was a new synthetic equivalent of ketene. Although ketenes are relatively fragile in acidic and basic reaction conditions, this ketene radical is stable under aforementioned cyclization conditions. This method is applicable for some fields of organic synthesis.

Experimental

^{1}H NMR spectra were observed with Hitachi R-24B, R-600, JEOL JNM-GX270, JNM-FX270, GSX-400, and GSX-500 spectrometers. ^{13}C NMR spectra were observed on JEOL JNM-GX270 and JNM-FX270 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard in CCl_4 or $CDCl_3$. Infrared spectra were obtained on a Hitachi 215 and JASCO A-202 infrared spectrometers. Mass spectra were taken with RMU-7M mass spectrometer at 70 eV. Column chromatography was performed on Merck Art 7734, Wakogel C-200, Fujigel BW-200 and BW-820MH. All solvents were freshly distilled and stored under nitrogen. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and stored over molecular sieves 5A. Toluene, benzene, and hexane were dried over sodium wire. Unless otherwise noted, other solvents were used after simple distillation. High-pressure liquid chromatography was performed on a Merck Lichrosorb Si 60 column.

Cinnamyl 3,3-Bis(methylthio)-2-propenoate (1). General Procedure A: A solution containing 20 ml of dry THF and 2.20 ml (13 mmol) of freshly distilled hexamethyldisilazane was cooled under nitrogen to 0—5 °C, and 7.9 ml (1.58 M solution in hexane, 1.1 equiv) (1 M=1 mol dm^{-3}) of butyllithium was added. After 15 min the solution was cooled to −78 °C and 2.2 ml of dry HMPA was added. Approximately 30 min later, 2.01 g (11.4 mmol) of cinnamyl acetate in 5 ml of dry THF was added dropwise over a period of 30 min. The solution was stirred at −78 °C for an additional 30 min and 945 mg (1.1 equiv) of dry carbon disulfide was added in one portion. The reaction mixture was immediately turn to red and was allowed to warm to 0 °C over 2 h. The solution was again cooled to −78 °C and a solution of lithium hexamethyldisilazanide (LHMDS: prepared from 2.2 ml of hexamethyldisilazane and 7.9 ml of BuLi) in 20 ml of dry THF was added via syringe. The solution was stirred at −78 °C for 30 min upon completion of the addition and 3.5 ml of methyl iodide was added in one portion. The reaction mixture was warmed to room temperature and the stirring was continued additional 2 h. The reaction mixture was poured into saturated ammonium chloride solution and extracted with ether. The organic layer was washed with saturated ammonium chloride, water, brine and dried over anhydrous magnesium sulfate. After concentration the residue was purified by flash column chromatography to give 1.59 g (50%) of solid, mp 66—67 °C, of ketene dithioacetal (**1**). IR(neat) 1685, 1520, 1180 and 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.32(s, 3H), 2.45(s, 3H), 4.75(d, 2H, J=6.0 Hz), 5.60(s, 1H), 6.20—6.80(m, 2H), and 7.25(br s, 5H); ^{13}C NMR(100. 4 MHz, $CDCl_3$) (INEPT) δ=14.76(CH_3), 16.97(CH_3), 64.41(CH_2), 104.5(CH), 123.8(CH), 126.6(CH×2), 127.9(CH), 128.6(CH×2), 134.0(CH), 136.4(C), 162.4 (C), and 164.8(C); High Res. MS (m/z) Found: M$^+$, 280.0604. Calcd for $C_{14}H_{16}O_2S_2$: M, 280.0603

2-Cyclohexenyl 3,3-Bis(methylthio)-2-propenoate (2). IR(neat) 2975, 1690, 1540, and 1190 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.60—2.10(m, 6H), 2.40(s, 3H), 2.50(s, 3H), 5.30(br s, 1H), 5.58(s, 1H), 5.75(dddd, 1H, J=9.3, 6.0, 1.5, and 1.5 Hz), 5.95(dddd, 1H, J=9.3, 3.9, 3.9, and 1.2 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=14.78(CH_3), 16.96(CH_3) 18.93(CH_2), 24.92(CH_2), 28.52(CH_2), 67.26(CH) , 105.31(CH), 126.16(CH), 132.51(CH), 161.36(C), and 164.78(C); High Res. MS (m/z) Found: M$^+$, 244.0587. Calcd for $C_{11}H_{16}O_2S_2$: M, 244.0590.

4-(*t*-Butyldimethylsiloxy)-2-butenyl 3,3-Bis(methylthio)-2-propenoate (3). IR(neat) 2925, 2850, 1695, 1525, 1170, 1090 and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.10(s, 6H), 0.90(s, 9H), 2.40(s, 3H), 2.50(s, 3H), 4.30(dd, 2H, J=4.2 and 1.2 Hz), 4.70(dd, 2H, J=4.6 and 0.8 Hz), 5.57(s, 1H), 5.60(dtt, 1H J=8.5, 4.6 and 1.2 Hz), and 5.72(dtt, 1H, J=8.5, 4.2 and 0.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=−5.18(CH_3), 14.21(CH_3), 16.96(CH_3), 18.33(C), 25.93(CH_3), 59.51(CH_2), 59.68(CH_2), 104.52(CH), 124.55(CH), 133.99(CH), and 162.20(C); High Res. MS (m/z) Found: M$^+$ −CH_3, 333.0999. Calcd for $C_{14}H_{25}O_3S_2Si$: M−CH_3, 333.1012.

3-Phenyl-2-butenyl 3,3-Bis(methylthio)-2-propenoate (4). IR(neat) 1680, 1520 and 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.12(s, 3H), 2.40(s, 3H), 2.49(s, 3H), 4.83(d, 2H, J=7.7 Hz), 5.60(s, 1H), 5.94 (t, 1H, J=7.7 Hz), and 7.20—7.45(m, 5H); ^{13}C NMR (100.4 MHz, $CDCl_3$)(INEPT) δ=14.73(CH_3), 16.20(CH_3), 16.96(CH_3), 60.95(CH_2), 104.65(CH), 121.89(CH), 125.86(CH×2), 127.40(CH), 128.22(CH×2), 139.94(C), 142.67(C), 162.01(C), and 165.01(C); High Res. MS (m/z) Found: M$^+$, 294.0744. Calcd for $C_{15}H_{18}O_2S_2$: M, 294.0746.

Bromination of Ketene Dithioacetals. General Procedure B: A mixture of 1.59 g (5.7 mmol) of ketene dithioacetal (**1**) and 1.11 g of NBS in 50 ml of dry CCl_4 was stirred for 2 h.[8] The solvent was removed and the residue was purified by flash column chromatography to give 1.21 g (60%) of 2-bromoketene dithioacetal (**5**). IR(neat) 3025, 1730, 1215, 1030, and 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.32(s, 3H), 2.42(s, 3H), 4.80(d, 2H, J=6.0 Hz), 6.25(dd, 1H, J=16.0 and 6.0 Hz), 6.70(d, 1H, J=16.0 Hz), and 7.25(br s, 5H). Bromoketene dithioacetals were unstable and could not get any elemental analysis data. According to the general procedure B, compounds **6**—**8** were also synthesized.

2-Cyclohexenyl 3,3-Bis(methylthio)-2-bromo-2-propenoate (6). IR(neat) 3025, 1720, 1650, 1230, 1020, and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.45—2.20(m, 6H), 2.30(s, 3H), 2.40(s, 3H), 5.20—5.55(m, 1H), and 5.60—6.10(m, 2H); High Res. MS (m/z) Found: M$^+$, 323.9662. Calcd for $C_{11}H_{15}O_2S_2Br$: M, 323.9676.

4-(*t*-Butyldimethylsiloxy)-2-butenyl 3,3-Bis(methylthio)-2-bromo-2-propenoate (7). IR(neat) 1730, 1230, 1090, and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.20(s, 6H), 0.85(s, 9H), 2.35(s, 3H), 2.48(s, 3H), 4.20(m, 2H), 4.72(br d, 2H, J=6.0 Hz), 5.65(m, 2H); High Res. MS (m/z) Found: M$^+$−C_4H_{10}, 367.9599. Calcd for $C_{11}H_{17}O_3S_2SiBr$: M−C_4H_{10}, 367.9571.

3-Phenyl-2-butenyl 3,3-Bis(methylthio)-2-bromo-2-propenoate (8). IR(neat) 1725 and 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.15(s, 3H), 2.35(s, 3H), 2.45(s, 3H), 4.98(d, 2H, J=6.0 Hz), 5.40—5.70(m, 1H), 5.80—6.20(m, 1H), and 7.25(br s, 5H).

Radical Cyclization of Bromoketene Dithioacetal. General Prodcedure C: A mixture of **5** (110 mg, 0.3 mmol), tributyltin hydride (105 mg, 0.36 mmol) and catalytic amount of AIBN (5 mg, 0.1 equiv) in dry and degassed benzene (150 ml) (2 mmol solution) was heated at 80 °C under an argon for 2 h.

The reaction mixture was quenched by 5% ammonium chloride aqueous solution, then extracted with ether (30 ml), washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel using benzene as an eluent to give cyclized product, lactone (**9**) in 71% yield. IR(neat) 1740, 1560, 1210, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ=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), 3.60(dddd, 1H, J=10.8, 4.2, 4.2 and 4.2 Hz), 4.20(d, 2H, J=4.2 Hz) and 7.18—7.36 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=17.79(CH_3), 18.37(CH_3), 39.03(CH_3), 45.15(CH), 68.34(CH_2), 126.80(CH), 128.40(C), 128.69(CH), 129.15(CH), 138.31(C), 153.13(C), and 167.21(C); High Res. MS (m/z) Found: M^+, 280.0590. Calcd for $C_{14}H_{16}O_2S_2$: M, 280.0549. After purification of the same flash column chromatography a simple reduction product **1** was also isolated (17—20%). According to the general procedure C, cyclized products **10**—**12** were synthesized.

3-[Bis(methylyhio)methylene]hexahydro-2(3*H*)-benzofuranone (10). IR(neat) 1740, 1570, 1210, and 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10—1.75 (m, 6H), 1.20(d, 1H, J=15.4 Hz), 2.00(m, 1H), 2.44(s, 3H), 2.47(s, 3H), 3.20(ddd, 1H, J=11.6, 5.0, and 5.0 Hz), 4.40(ddd, 1H, J=5.0, 4.2, and 3.1 Hz); High Res. MS (m/z) Found: M^+, 244.0571. Calcd for $C_{11}H_{16}O_2S_2$: M, 244.0590.

4-[2-(*t*-Butyldimethylsiloxy)ethyl]-3-(bis(methylthio) methylene) Dihydro-2(3*H*)-furanone (11). IR(neat) 1750, 1570, 1205, 1100, and 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.07(s, 6H), 0.90(s, 9H), 1.74(ddt, 1H, J=13.9, 10.0, and 5.4 Hz), 1.92(dtd, 1H, J=13.9, 6.2, and 3.1 Hz), 2.47(s, 3H), 2.48(s, 3H), 3.46(dtd, 1H, J=10.0, 3.9, and 3.1 Hz), 3.72(dd, 2H J=6.2 and 5.4 Hz), and 4.25(d, 2H, J=3.9 Hz); High Res. MS (m/z) Found: M^+-CH_3, 333.1012. Calcd for $C_{14}H_{25}O_3S_2Si$: $M-CH_3$, 333.1012.

3-[Bis(methylthio)methylene]-3-(-1-phenylethyl)dihydro-2(3*H*)-furanone (12). IR(neat) 1740, 1560, 1210, and 1080 cm^{-1}; ^1H NMR (CDC_3) δ=1.35(d, 3H, J=7.7 Hz), 2.45(s, 3H), 2.51(s, 3H), 3.12 (dd, 1H, J=8.3 and 5.1 Hz), 3.60(ddd, 1H, J=7.7, 5.8, and 1.9 Hz), 4.05(dd, 1H, J=8.3 and 1.9 Hz), and 4.10(dd, 1H, J=8.3 and 5.8 Hz); High Res. MS (m/z) Found: M^+, 294.0758. Calcd for $C_{15}H_{18}O_2S_2$: M, 294.0747. Although two diastereomers could not be isolated by HPLC, almost 1 : 1 mixture of these isomers were detected from the intensity of two broad peaks, after repeating HPLC.

Synthesis of 1-Alkene-1,3-dione Dithioacetals (13—17). General Procedure D: 4,4-Bis(methylthio)-3-buten-2-one was prepared by the known method.[8] To a THF solution (14 ml) of lithium diisopropylamide (LDA)(8.5 mmol) was added 4,4-bis(methylthio)-3-buten-2-one (1.3 g, 7.8 mmol) in 10 ml of THF at −78 °C. After stirring for 15 min, 1-bromo-3-methyl-2-butene (1.1 ml, 9.4 mmol) was added and the reaction mixture was warmed gradually to room temperature within 1.5 h. The reaction mixture was quenched with ammonium chloride solution. The organic layer was separated, and the aqueous phase was extracted with ether (3×50 ml). The combined organic layer was dried, concentrated, and the residue was purified by flash column chromatography to give 815 mg (46%) of **13**, which was identified by the spectral data with those of the authentic sample.[10]

1,1-Bis(methylthio)-1,6-heptadien-3-one (14). IR(neat) 2920, 1640, 1480, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.33—2.44(m, 2H), 2.44 (s, 3H), 2.47(s, 3H), 2.54(m, 2H), 4.97(ddd, 1H, J=10.4, 2.7, and 0.8 Hz), 5.50(ddd, 1H, J=16.9, 3.5, and 0.8 Hz), 5.85(ddd, 1H, J=16.9, 10.4, and 5.8 Hz), and 6.02(s, 1H); ^{13}C NMR (56.0 MHz, $CDCl_3$)(INEPT) δ=14.82(CH_3), 17.13(CH_3), 28.75(CH_2), 42.17(CH_2), 112.52(CH), 114.93(CH_2), 137.69(CH), 163.29(C), and 194.44(C); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 203.0545. Calcd for $C_9H_{15}OS_2$: (MH), 203.0564.

1,1-Bis(methylthio)-7-phenyl-1,6-heptadien-3-one (15). IR(neat) 2916, 1644, 1500, 1432, 1122, and 966 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.42(s, 3H), 2.46(s, 3H), 2.50—2.66(m, 4H), 6.03(s, 1H), 6.24(dd, 1H, J=15.4 and 6.2 Hz), 6.42(d, 1H, J=15.4 Hz) and 7.12—7.38(m, 5H); ^{13}C NMR (22.4 MHz, $CDCl_3$)(INEPT) δ=14.65(CH_3), 16.94(CH_3), 27.95(CH_2), 42.42(CH_2), 112.33(CH), 125.84(CH×2), 126.80(CH), 128.29(CH), 129.45(CH×2), 130.26(CH), 137.42(C), 163.28(C), and 194.10 (C); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 279.0871. Calcd for $C_{15}H_{19}OS_2$ (MH), 279.0877.

1,1-Bis(methylthio)-4-cinnamyl-7-phenyl-1,6-heptadien-3-one (16). IR(neat) 2922, 1642, 1490, 1432, 1126, and 966 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.34(s, 3H), 2.40(m, 2H), 2.45(s, 3H), 2.58(ddd, 2H, J=13.9, 6.9, and 6.9 Hz), 2.72(tt, 1H, J=6.9 Hz), 6.03(s, 1H), 6.18(dt, 2H, J=15.4 and 6.9 Hz), 6.40(d, 2H, J=15.4 Hz) and 7.30(m, 10H); ^{13}C NMR (103.7 MHz, $CDCl_3$)(INEPT) δ=14.90(CH_3), 17.12(CH_3), 35.39(CH_2×2), 52.19(CH), 112.82(CH×2), 126.06(CH×4), 127.05(CH×2), 127.99(CH×2), 128.47(CH×4), 131.85(CH), 137.51(C×2), 164.25(C) and 196.81(C); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 395.1483. Calcd for $C_{24}H_{27}OS_2$: (MH), 395.1503.

1,1-Bis(methylthio)-1,6-octadien-3-one (17). IR(neat) 2920, 1648, 1494, 1432, and 1124 cm^{-1}: ^1H NMR ($CDCl_3$) δ=1.63(m, 3H), 2.26—2.36(m, 2H), 2.48—2.53(m, 2H), 2.44(s, 3H), 2.47(s, 3H), 5.45(m, 2H), and 6.00(s, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$)(INEPT) δ=14.81(CH_3), 17.12(CH_3), 17.91(CH_3), 27.76(CH_2), 43.01(CH_2), 112.63(CH), 125.52(CH), 130.15(CH), 162.97(C), and 194.85(C); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 217.0720. Calcd for $C_{10}H_{17}OS_2$: (MH), 217.0721.

According to the general procedure B, α-bromoketene dithioacetals **18**—**22** were synthesized.

1,1-Bis(methylthio)-2-bromo-7-methyl-1,6-octadien-3-one (18). IR(neat) 1700, 1430, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.12—1.90(m, 6H), 2.10—2.50(m, 2H), 2.50—2.80(m, 2H), 2.25(s, 3H), 2.39(s, 3H), and 4.76—5.25(m, 1H).

1,1-Bis(methylthio)-2-bromo-1,6-heptadien-3-one (19). IR(neat) 1700, 1430, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) 2.30—2.68(m, 2H), 2.35(s, 3H), 2.49(s, 3H), 2.68—3.12(m, 2H), 4.90—5.35(m, 2H), and 5.50—6.20(m, 1H).

1,1-Bis(methylthio)-2-bromo-7-phenyl-1,6-heptadien-3-one (20). IR(neat) 1704, 1496, 1432, and 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.35(s, 3H), 2.49(s, 3H), 2.50—3.20(m, 4H), 6.40(m, 2H), and 7.20—7.55 (m, 5H).

1,1-Bis(methylthio)-2-bromo-4-cinnamyl-7-phenyl-1,6-heptadien-3-one (21). IR(neat) 1692, 1496, 1432, and 1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.34(s, 3H), 2.40(s, 3H), 2.20—2.80(m, 4H), 3.30—3.70(m, 1H), 6.10—6.50(m, 4H), and 7.10—7.50(m, 10H).

1,1-Bis(methylthio)-2-bromo-1,6-octadien-3-one (22). IR(neat) 1704, 1434, and 1126 cm^{-1}; ^1H NMR ($CDCl_3$) 1.60—1.85(m, 3H), 2.35—2.60(m, 2H), 2.40(s, 3H), 2.50(s, 3H), 2.70—3.30(m, 2H), and 5.40—5.70(m, 2H).

According to the general procedure C, cyclic ketones (**23**—**27**) were synthesized. In each of this cyclization considerable amount (5—37%) of reduction product (**13**—**17**) was yielded.

2-[Bis(methylthio)methylene]-3-isopropylcyclopentanone (23). IR(neat) 1690, 1472, and 1218 cm^{-1}; ^1H NMR ($CDCl_3$)

δ=0.82(d, 3H, *J*=6.9 Hz), 0.99(d, 3H, *J*=6.9 Hz), 1.90(m, 2H), 2.07(qqd, 1H, *J*=6.9, 6.9, and 5.4 Hz), 2.38(m, 2H), 2.41(s, 3H), 2.48(s, 3H), and 3.19(m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=18.24(CH_3), 18.41(CH_3), 20.36(CH_2), 21.27(CH_3×2), 31.98(CH), 38.93(CH_2), 50.11(CH), 141.35(C), 150.03(C), and 203.26(C); High Res. MS (*m/z*) Found: M^+, 230.0785. Calcd for $C_{11}H_{18}OS_2$: M, 230.0799.

2-[Bis(methylthio)methylene]cyclohexanone (24). IR(neat) 1678, 1422, and 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.72—1.92(m, 4H), 2.35(s, 3H), 2.36(s, 3H), 2.46(t, 2H, *J*=6.5 Hz) and 2.87(t, 2H, *J*=6.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$)(INEPT) δ=18.15(CH_3), 18.27(CH_3), 24.32(CH_2), 24.61(CH_2), 33.51(CH_2), 41.54(CH_2), 139.61(C), 146.19(C), and 200.34(C); High Res. MS (*m/z*) Found: M^+, 202.0505. Calcd for $C_9H_{14}OS_2$: M, 202.0486.

3-Benzyl-2-[bis(methylthio)methylene]cyclopentanone (25). IR(KBr) 1680, 1426, and 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.73—1.89(m, 2H), 2.30—2.40(m, 2H), 2.46(s, 3H), 2.49(s, 3H), 2.67(dd, 1H, *J*=13.5 and 10.4 Hz), 3.00(dd, 1H, *J*=13.5 and 4.2 Hz), 3.48—3.60(m, 2H), and 7.10—7.38(m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=18.16 (CH_3), 18.27(CH_3), 23.27(CH_3), 37.88(CH_2), 39.65(CH_2), 46.45(CH), 126.30(CH), 128.40(CH), 129.21(CH), 140.05(C), 140.63(C), 150.52(C), and 202.59(C); High Res. MS (*m/z*) Found: M^+, 278.0836. Calcd for $C_{15}H_{18}OS_2$: M, 278.0800.

3-Benzyl-2-[bis(methylthio)methylene]-5-cinnamylcyclopentanone (26). IR(KBr) 1694 and 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.95—2.05(m, 1H), 2.10(m, 1H), 2.20—2.35(m, 1H), 2.40(s, 3H), 2.50(s, 3H), 2.55(m, 1H), 2.60(m, 1H), 2.70(br s, 1H), 3.18(br s, 1H), 3.35(br s, 1H), 6.75(br, 2H), and 7.10—7.40(m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=17.94(CH_3), 18.59(CH_3) 28.16(CH_2), 34.60(CH_2), 39.55(CH_2,) 48.81(CH), 48.97(CH), 50.64(CH), 125.78(CH), 126.16(CH), 128.03(CH), 128.13(CH), 128.87(CH), 130.32(CH), 140.04(C), 140.08(C), 143.03(C), 147.61(C), and 204.92(C); High Res. MS (*m/z*) Found: M^+, 394.1410. Calcd for $C_{24}H_{26}OS_2$: M, 394.1425.

2-[Bis(methylthio)methylene]-3-ethylcyclopentanone (27). IR(neat) 1690, 1460, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.99(t, 3H *J*=7.3 Hz), 1.30—1.50(m, 1H), 1.50—1.70(m, 1H), 1.78—2.10(m, 2H), 2.26—2.49(m, 2H), 2.45(s, 6H), and 3.06—3.19(m, 1H); ^{13}C NMR (22.4 MHz, $CDCl_3$)(INEPT) δ=12.11(CH_3), 18.11(CH_3) 18.26(CH_3), 23.57(CH_2), 27.00(CH_2), 38.13(CH_2), 46.24(CH), 141.65(C), 149.68 (C), and 202.96(C); High Res. MS (*m/z*) Found: M^+, 216.0646. Calcd for $C_{10}H_{16}OS_2$: M, 216.0643.

Attempt of the Cyclization of 3-Bromo-4,4-bis(methylthio)-1-(2-cyclohexenyl)-3-buten-2-one (33). According to the general procedure D, 4,4-bis(methylthio)-1-(2-cyclohexenyl)-3-buten-2-one was prepared. IR(neat) 3012, 2920, 1644, 1492, 1118, and 786 cm^{-1} ^{1}H NMR ($CDCl_3$) δ=1.25(m, 1H), 1.55(m, 1H), 1.64—1.71(m, 1H), 1.82(m, 1H), 1.92—2.01(m, 2H), 2.37(dd, 1H, *J*=14.6 and 6.9 Hz), 2.44(s, 3H), 2.46(s, 3H), 2.46(m, 1H), 2.62—2.74(m, 1H), 5.55(ddd, 1H, *J*=10.1, 4.2, and 1.9 Hz), 5.68(ddd, 1H, *J*=10.1, 5.4, and 3.1 Hz), and 6.30(s, 1H); ^{13}C NMR (22.4 MHz, $CDCl_3$)(INEPT) δ=14.71(CH_3), 17.03(CH_3), 21.00(CH_2) 25.00(CH_2) 28.94(CH_2), 32.22(CH), 49.43(CH_2), 112.92(CH), 127.45(CH), 130.97(CH), 163.04(C), and 194.49(C); High Res. MS (FAB) (*m/z*) Found: $(MH)^+$ 243. 0878. Calcd for $C_2H_{19}SO_2$: MH, 243.0878.

Bromination of 4,4-bis(methylthio)-1-(2-cyclohexenyl)-3-buten-2-one was carried out by the general procedure B, and compound **33** was obtained in 71% yield. IR(neat) 1702, 1116, and 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20—2.28(m, 6H), 2.40(s, 3H), 2.50(s, 3H), 2.50—3.00(m, 3H) , and 5.60—5.80(m, 2H).

Radical cyclization was attempted according to the general procedure C, from 750 mg (2.35 mmol) of **33** and 818 mg (2.82 mmol) of tributyltin hydride with a catalytic amount of AIBN (30 mg). The reaction mixture was treated as the case of **9**, and the tricyclic compound **34** (40 mg, 17%) was isolated. None of the desired bicyclic ketone was detected. IR(neat) of **34** 1745, 1520, and 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) of **34** δ=1.01—1.20(m, 1H), 1.49—1.59(m, 1H), 1.59—1.72(m, 1H), 1.72—1.89(m, 1H), 1.89—2.10(m, 1H), 2.20—2.38(m, 1H), 2.38(d, 1H, *J*=17.3 Hz), 2.53(s, 3H), 2.82(dd, 1H, *J*=17.3 and 6.9 Hz), 3.56(ddd, 1H, *J*=11.6, 7.7, and 6.9 Hz), and 3.90(dd, 1H, *J*=6.9 and 6.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) of **34** (INEPT) δ=17.74(CH_3), 23.37(CH_2), 29.11(CH_2), 32.32(CH_2), 33.38(CH), 50.24(CH), 52.78(CH_2), 56.00(CH), 128.59(C), 152.54(C), and 194.85(C); High Res. MS of **34** (*m/z*) Found: M^+ 226.0479. Calcd for $C_{11}H_{14}OS_2$: M, 226.0486.

Conversion of 9 into Corresponding Ester 28. The mixture of 560 mg (2.0 mmol) of **9**, 1.20 g (6 mmol) of *p*-toluenesulfonic acid in 40 ml of ethanol was heated to reflux for 24 h. Ethanol was evaporated and the residue was chromatographed on silica-gel column with benzene–ethyl acetate (5 : 1) as eluent to give 446 mg (90%) of ethyl ester **28**. IR(neat) 1780, 1740, 1140, and 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20(t, 3H), 2.82(d, 2H), 3.30(m, 1H), 4.00(m, 1H), 4.11(m, 3H), 4.43(m, 1H), and 7.10—7.38(m, 5H). In this NMR spectrum a small amount of enol form of **28** was recognized. High Res. MS (*m/z*) Found: M^+, 248.1049. Calcd for $C_{14}H_{16}O_4$: M, 248.1048.

Synthesis of Bromoketene Dithioacetal (29). The mixture of *cis*-2-butene-1,4-diol monoallyl ether (2.56 g, 20 mmol), 4.08 g (40 mmol) of acetic anhydride and 3.16 g (40 mmol) of dry pyridine was stirred at room temperature for 3 h. The reaction mixture was quenched with diluted hydrochloric acid solution and then extracted with ether (50 ml). The organic phase was washed with brine (20 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the resulting residue was purified by flash column chromatography on silica gel with benzene to give 2.99 g (88%) of acetate. IR(neat) 1745, 1650, 1235, 1090, and 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.90(s, 3H), 3.90(t, 4H, *J*=6.0 Hz), 4.55(d, 2H, *J*=6.0 Hz), 4.90—5.38(m, 2H), and 5.46—6.10(m, 3H). According to the general procedure A, from 2.50 g (14.7 mmol) of this acetate, corresponding ketene dithioacetal was synthesized (yield 68%). IR(neat) 1690, 1645, 1530, and 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.40(s, 3H), 2.50(s, 3H), 3.98(dt, 2H, *J*=5.39 and 1.16 Hz), 4.11(d, 2H, *J*=5.01 Hz), 4.69(d, 2H, *J*=5.39 Hz) 5.18(ddd, 1H, *J*=10.0, 3.08, and 1.16 Hz), 5.28(m, 1H), 5.58(s, 1H), 5.76(m, 2H), and 5.91(ddt, 1H, *J*=17.3, 10.4, and 5.4 Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$)(INEPT) δ=14.73(CH_3), 16.97(CH_3), 59.55(CH_2), 65.62(CH_2), 71.31 (CH_2), 104.36(CH), 117.30(CH_2), 127.07(CH) 130.68(CH), 134.61(CH), 162.37(C), and 164.77(C); High Res. MS (*m/z*) Found: M^+-CH_3, 259.0444. Calcd for $C_{11}H_{15}O_3S_2$: $M-CH_3$, 259.0427. Bromoketene dithioacetal (**29**) was synthesized from corresponding ketene dithioacetal which was obtained above, by the general procedure B, in 51% yield. IR(neat) 1715, 1640, 1210, and 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.34(s, 3H), 2.45(s, 3H), 3.86—4.23(m, 4H), 4.65—4.90(m, 2H), 5.00—5.45(m, 2H), and 5.60—6.20(m, 3H).

Synthesis of Bromoketene Dithioacetal (30). According to the general procedure A, 4-crotonyloxy-*cis*-2-butenyl 3,3-

bis(methylthio)-2-propenoate was synthesized. IR(neat) 2920, 2852, 1690, 1530, and 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.71(dd, 3H, J=6.2 and 1.2 Hz), 2.40(s, 3H), 2.50(s, 3H), 3.91(dt, 2H, J=6.2 and 1.2 Hz), 4.08(d, 2H, J=5.0 Hz), 4.69(d, 2H, J=5.0 Hz), 5.51—5.65(m, 1H), 5.57(s, 1H), and 5.65—5.83(m, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$)(INEPT) 14.74(CH_3), 16.97(CH_3), 17.78(CH_3), 59.58(CH_2), 65.37(CH_2), 71.08(CH_2), 104.44(CH), 126.88(CH), 127.40(CH), 129.90(CH), 130.89(CH), 162.31(C), and 164.80(C); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 289.0930. Calcd for $C_{13}H_{21}O_3S_2$: MH, 289.0932. This ketene dithioacetal was brominated by the general procedure B to give 4-crotonyloxy-*cis*-2-butenyl 2-bromo-3,3-bis(methylthio)-2-propenoate (**30**) in 62% yield. IR(neat) 1730 and 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.71(d, 3H, J=6.2 Hz), 2.30(s, 3H), 2.40(s, 3H), 3.85(dt, 2H, J=6.2 and 1.2 Hz), 4.02(d, 2H, J=5.0 Hz), 4.72(d, 2H, J=5.0 Hz), and 5.42—5.98(m, 4H).

Tandem Radical Cyclization of 29. According to the general procedure C, tricyclic lactone (**31**) was prepared from 168 mg (0.48 mmol) of **29** and 170 mg (0.58 mmol) of tributyltin hydride in the presence of a catalytic amount of AIBN (8 mg) in refluxing benzene (50 ml) under argon atmosphere for 1 h. The solvent was removed and the resulting residue was purified by HPLC (hexane–ethyl acetate =1 : 1) to give 35 mg(26%) of pure **31**, solid, mp 99—101 °C. IR(KBr) 1754 and 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2.00(dd, 1H, J=14.2 and 6.9 Hz), 2.25(s, 3H), 2.30(s, 3H), 2.53(dd, 1H, J=14.2 and 8.1 Hz), 3.03(dddd, 1H, J=9.2, 8.8, 7.0, and 3.6 Hz), 3.11(m, Hz), 3.23(td, 1H, J=8.8 and 5.2 Hz), 3.63(dd, 1H, J=9.6 and 3.6 Hz), 3.69(dd, 1H, J=9.6 and 7.0 Hz), 3.74(t, 1H, J=9.6 Hz), and 3.75(dd, 1H, J=9.6 and 5.6 Hz). NOE differences between H_a and H_d, and also H_b and H_c were observed in the NOESY spectra. ^{13}C NMR (67.8 MHz, $CDCl_3$)(INEPT) δ=15.51(CH_3), 17.84(CH_3), 41.48(CH_3), 45.38(CH), 47.10(CH), 48.95(CH), 61.71 (CH), 64.88(C), 68.15(CH_2), 69.17(CH_2), 73.56(CH_2), and 180.0(C); High Res. MS (m/z) Found: M^+, 274.0691. Calcd for $C_{12}H_{18}O_3S_2$: M, 274.0698.

Tandem Radical Cyclization of 30. According to the general procedure C, tricyclic lactone (**32**) was obtained from 176 mg (0.48 mmol) of **30** and 154 mg (0.53 mmol) of tributyltin hydride in the presence of 7 mg of AIBN in refluxing benzene (50 ml) to give 22 mg(19%) of **32**. IR(neat) 1750 and 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.27(d, 3H, J=7.3 Hz), 2.02(dt, 1H, J=8.3 and 7.3 Hz), 2.28(s, 3H), 2.31(s, 3H), 2.96—3.08(m, 2H), 3.38(ddd, 1H, J=8.3 Hz), 3.46(dd, 1H, J=9.4 and 6.2 Hz), 3.47(dd, 1H, J=9.4 and 6.2 Hz), 3.69(dd, 1H, J=16.6 and 8.3 Hz), 3.70(dd, 1H, J=18.7 and 8.3 Hz), 3.86(s, 1H) and 4.34(dd, 2H, J=8.3 Hz); High Res. MS (FAB) (m/z) Found: $(MH)^+$, 289.0927. Calcd for $C_{13}H_{21}O_3S_2$: (MH), 289.0922.

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