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A Versatile Synthesis of Four-, Five-, and Six-membered Cyclic Ketones Using Methyl Methylthiomethyl Sulfoxide

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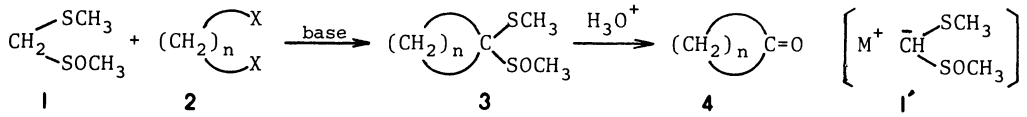
Cyclization of 1,*n*-dihalo[or bis(tosyloxy)]alkanes with methyl methylthiomethyl sulfoxide in the presence of a base (*n*-BuLi or KH) gave three-, four-, five-, and six-membered 1-methylsulfinyl-1-methylthiocycloalkanes. These cyclization products were easily converted to the corresponding ketones by acid hydrolysis except 1-methylsulfinyl-1-methylthiocyclopropane which afforded a complicated mixture. The combination of the cyclization with the acid hydrolysis thus provides a new method for synthesizing four-, five-, and six-membered cycloalkanones. Several representative preparations, such as those of substituted cyclobutanones, 3-cyclopentenone, and tetrahydro-4-pyrone, are described.

Cyclic ketones, especially five- and six-membered cycloalkanones, are widely spreaded skeletons in naturally occurring organic compounds, and development of a new methodology for constructing these skeletons is one of the most important problems in organic synthesis. Further, exploitation of various methods for ring expansion of cyclobutanones to cyclopentanones[1] is looking forward to an efficient way to make four-membered cyclic ketones. In this paper, we report a novel synthetic method of cyclobutanones, cyclopentanones, and cyclohexanones using methyl methylthiomethyl sulfoxide (**1**).[2] A previous paper[3] revealed that **1** undergoes monoalkylation on treatment with an alkyl halide (RX) in the presence of NaH and the acid hydrolysis of the resultant alkylated product gives an aldehyde (RCHO).[4] The present method for synthesis of cycloalkanones (**4**) comprizes the reaction of 1,*n*-dihalo[or bis(tosyloxy)]alkanes (**2**) with **1** to give 1-methylsulfinyl-1-methylthiocycloalkanes (**3**) and the subsequent acid-hydrolysis of **3** leading to **4**, as shown in Scheme 1.[11] The characteristic features of this cycloalkanone synthesis are as follows: i) one-step cyclization of **1** with **2** is achieved; ii) ring-strained cyclobutanone is conveniently made in a high yield, and (iii) cycloalkanones having many kinds of substituents can be easily synthesized.

Results and Discussion

For the reaction of 1,*n*-dihalo[or bis(tosyloxy)]-alkanes (**2**) with methyl methylthiomethyl sulfoxide (**1**), two types of procedures were employed: (a) with 2.2—2.8 equiv of KH in tetrahydrofuran (THF) (−10 °C—room temperature; "Method A") and (b) with 2.0—2.5 equiv of the lithio derivative (**1′**; M=Li) of **1** in THF (−70 °C—room temperature; "Method B"). The results are summarized in Table 1, showing that both Method A and Method B gave the dithioacetal *S*-oxides (**3**; *n*=3, 4, 5) of cyclobutanone, cyclopentanone, and cyclohexanone in fair to good yields starting from either the corresponding 1,*n*-dibromoalkanes (**2**; X=Br) or 1,*n*-bis(tosyloxy)alkanes (**2**; X=TolSO$_3$). However, 1-methylsulfinyl-1-methylthiocyclopropane (**3**; *n*=2) could be produced in 78% yield only by applying Method B to 1,2-bis(tosyloxy)ethane (**2**; *n*=2, X=TolSO$_3$). For the reaction of **1** with **2**, NaH could be employed as a base in place of KH, but heating the reaction mixture at 50 °C was required and the yields of **3** were relatively low [*n*=5 42%; *n*=4 46%]. The reaction of **1** with 1,3-dibromopropane (**2**; *n*=3, X=Br) in the presence of NaH in THF (50 °C/6 h) was



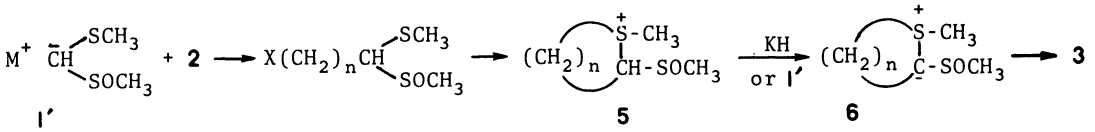
1 2 3 4 1′

Scheme 1

TABLE 1. REACTION CONDITIONS AND YIELDS IN THE CONVERSION OF **1** TO **3**

2	X=Br		X=TolSO$_3$	
	Method A[a]	Method B[b]	Method B[b]	
n=2	−15 °C/4 h→rt/48 h	4%	−15 °C/1 h→rt/48 h	33%	−15 °C/4 h→rt/19 h	78%
n=3	0 °C/1 h→rt/17 h	78%	0 °C/0.5 h→rt/ 2 h	70%	rt/18 h	91%
n=4	0 °C/1 h→rt/19 h	80%	−60 °C/1 h→rt/16 h	80%	rt/18 h	84%[c]
n=5	0 °C/1 h→rt/19 h	82%	−60 °C/2 h→rt/16 h	74%	rt/17 h	80%
n=6	0 °C—rt/20 h	None[d]	−15 °C/3 h→rt/18 h	None[e]	−15 °C/3 h→rt/19 h	None[f]

a) With 2.2—2.8 equiv of KH in THF. b) With 2.0—2.5 equiv of the lithio derivative (**1′**, M=Li) in THF. c) When Method A was employed, the yield of **3** (*n*=4) was 31%. d) 1,8-Bis(methylsulfinyl)-1,8-bis(methylthio) octane (**19**) and 1-methylsulfinyl-1-methylthio-7-bromoheptane (**20**) were obtained in 24 and 11% yields, respectively. e) The yields of **19** and **20** were 20 and 22%, respectively. f) The yield of **19** was 23%.



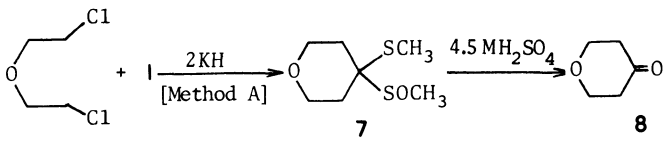
Scheme 2

accompanied with dehydrobromination to give 4-methylsulfinyl-4-methylthio-1-butene in 38% yield (82% yield based on the unrecovered **1**).

It should be noted that 1,6-dibromo [or bis(tosyloxy)]-hexane (**2**; n=6, X=Br or $TolSO_3$) did not produce the corresponding **3** (n=6) by ether Method A or Method B, in a contrast to the base-assisted cyclization of diethyl malonate with 1,n-dihaloalkanes, where a seven-membered cycloalkane derivative is favorably produced.[12] Furthermore, in the present cyclization reaction, **2** afforded the cyclic compounds (**3**) in high yields by the reaction with 2 equiv of the lithio derivative (**1'**; M=Li), indicating the involvement of a more acidic intermediate than **1**. The ring-strained **3** (n=3) is produced at a comparable rate to that of **3** (n=4 or 5). These facts seem to be in accord with the hypothesis that the cyclization may pass through an intermediary sulfonium salt (**5**), followed by the Stevens-type rearrangement to form **3**.

When **3** (n=4 or 5) was treated with a small amount of 4.5 M† sulfuric acid in diethyl ether or ethanol, an acid hydrolysis took place smoothly at room temperature to give cyclopentanone (92%) or cyclohexanone (88%), respectively. These yields were obtained by their derivation into the corresponding 2,4-dinitrophenylhydrazones. When the acid-catalyzed hydrolysis of **3** (n=5) was performed in the presence of trietyl orthoformate in ethanol, the corresponding diethyl acetal of **4** (n=5) was obtained in 83% yield. In the case of 1-methylsulfinyl-1-methylthiocyclobutane (**3**; n=3), an elevated temperature (45 °C) was required for completing the conversion to cyclobutanone. 1-Methylsulfinyl-1-methylthiocyclopropane (**3**; n=2) resisted the acid hydrolysis. Prolonged heating **3** (n=2) with sulfuric acid in ethanol resulted in complicated decomposition. Thus, the present method was shown to be suitable to the synthesis of four-, five-, and six-membered cycloalkanones. Versatility of this method is demonstrated by making certain cycloalkanone derivatives described in the following sections.

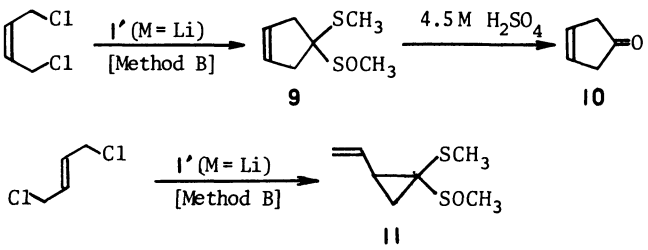
Synthesis of Tetrahydro-4-pyrone (8). The reaction of **1** with bis(2-chloroethyl) ether in the presence of KH (2.4 equiv) in THF at 0 °C—room temperature [Method A] afforded the dithioacetal *S*-oxide (**7**) which was subjected to the acid hydrolysis with 4.5 M sulfuric acid in diethyl ether (room temperature/2 h) to give **8** in an overall yield of 66%.



Scheme 3

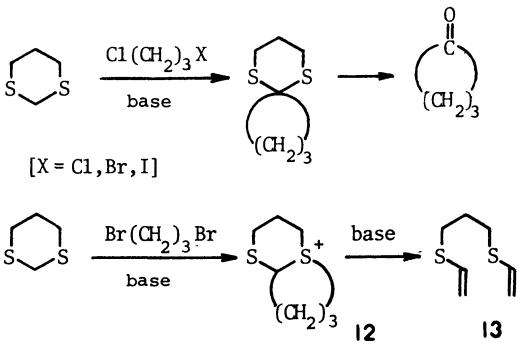
†1 M=1 mol dm^{-3}.

Synthesis of 3-Cyclopentenone (10). When *cis*-1,4-dichloro-2-butene was allowed to react with 2.5 equiv of **1'** (M=Li) in THF at −78 °C—room temperature, 4-methylsulfinyl-4-methylthio-1-cyclopentene (**9**) was obtained in 78% yield. On the other hand, *trans*-1,4-dichloro-2-butene gave 1-methylsulfinyl-1-methylthio-2-vinylcyclopropane (**11**) in 76% yield under the similar reaction conditions.[13] On treatment of **9** with 4.5 M sulfuric acid in acetone-water (9:1) at room temperature, the expected 3-cyclopentenone was formed in 60% yield along with 2-cyclopentenone (6%) (by a GLC analysis). The ratio of 3-cyclopentenone/2-cyclopentenone decreased with the increase of the reaction time and reached to 2.5 after 24 h.



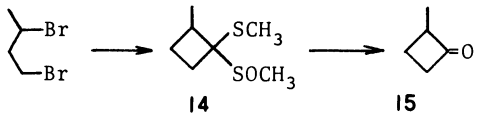
Scheme 4

Synthesis of 2- or 3-Substituted Cyclobutanones. Seebach and Corey reported an elegant synthesis of cyclobutanone by the reaction of 1,3-dithiane with 1,3-dihalopropane.[14] To practice this synthesis, a somewhat complicated procedure is necessitated to avoid the formation of the undesirable disubstituted product: After 2-(3-chloro-1-propyl)-1,3-dithiane is once produced by the reaction of the lithiated 1,3-dithiane with 1-bromo-3-chloropropane, 1-chloro-3-iodopropane, or 1,3-dichloropropane (an excessive amount), this product is again treated with n-BuLi. The use of 1,3-dibromopropane appeared to be impractical because of the formation of a cyclic sulfonium salt (**12**), which gave 1,3-bis(vinylthio)propane (**13**) on treatment with a base.[14]



Scheme 5

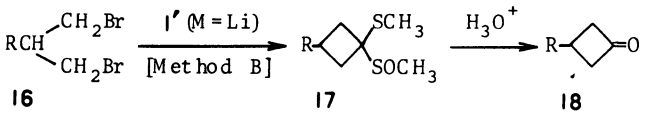
In contrast, 1,3-dibromo[or bis(tosyloxy)]propane can be preferably employed for conversion of **1** to 1-methylsulfinyl-1-methylthiocyclobutane (**3**; $n=3$), a synthetic precursor of cyclobutanone as above mentioned. Furthermore, the reaction of 1,3-dibromobutane with 2.4 equiv of **1'** (M=Li) at room temperature for 46.5 h in THF furnished 1-methylsulfinyl-1-methylthio-2-methylcyclobutane (**14**) (80% yield), which consisted mainly of two diastereomer in the ratio of 1:2.[15] The acid hydrolysis of cyclization product (**14**) afforded 2-methylcyclobutanone (**15**) which was isolated as its 2,4-dinitrophenylhydrazone (77% yield).



14 **15**

Scheme 6

By the present method, 3-substituted cyclobutanones (**18**) are simply and conveniently synthesized. Treatment of 2-benzyl-1,3-dibromopropane (**16a**) with 2.3 equiv of **1'** (M=Li) in THF [Method B] resulted in the formation of 3-benzyl-1-methylsulfinyl-1-methylthiocyclobutane (**17a**) (77% yield) as a 2:1 mixture of two diastereomers.[15] The acid hydrolysis of **17a** was effected with 4.5 M sulfuric acid in refluxing diethyl ether to yield 3-benzylcyclobutanone (**18a**) in 78% yield.



16 **17** **18**

[a: R = $PhCH_2$ b: R = $PhCH_2O$]

Scheme 7

When 2-benzyloxy-1,3-dibromopropane (**16b**) was allowed to react with **1** according to Method B, a cyclization product (**17b**) was formed in 77% yield as a mixture of two diastereomers (1.1:1). The product (**17b**) gave 3-benzyloxycyclobutannone (**18b**) (60% yield) on treatment with perchloric acid in diethyl ether at room temperature for 24 h.

In conclusion, methyl methylthiomethyl sulfoxide (**1**) is a novel reagent for the synthesis of four-, five-, and six-membered cycloalkanones. By the use of **1**, many kinds of their derivatives can be simply and conveniently prepared.

Experimental

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and were uncorrected. ^1H NMR spectra were obtained on Varian HA-100 and Varian EM-390 spectrometers. IR spectra were measured with a Hitachi EPI-G3 infrared spectrometer.

Reaction of 1,3-Dibromopropane with 1. A Typical Procedure: *(a) Method A*; To a suspension containing KH (1.01 g: 25.3 mmol) in THF (15 ml), was added to **1** (1.04 g: 8.39 mmol) under an argon atmosphere and the resulting mixture was stirred for 1 h under ice-cooling. After dropwise addition of 1,3-dibromopropane (2.07 g: 10.3 mmol) over 10 min, the mixture was further stirred for 1 h under ice-cooling and then at room temperatre for 17 h. CH_2Cl_2 (100 ml) was added and the deposited insoluble matter was filtered off. The filtrate was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel using CH_2Cl_2 and Et_2O as eluents to give **3** ($n=3$) as a pale yellow oil (1.08 g: 78%) along with **1** (199 mg). **3** ($n=3$): IR (neat) 1052 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.5$—3.1 (6H, m), 2.13 (3H, s), and 2.47 (3H, s).

This compound was transformed into the corresponding disulfone: To a solution of **3** ($n=3$) (261 mg: 1.59 mmol) in MeOH (5 ml), were added Na_2WO_4-$2H_2O$ (10 mg) and 30% aq solution (1 ml) of H_2O_2 and the resulting mixture was stirred at room temperature for 2 d. Addition of water (10 ml) deposited the disulfone as colorless crystals: mp 141.5—142 °C (from CH_2Cl_2-CCl_4); IR (KBr) 1295, 1140, 1110, 945, 771, and 505 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=2.0$—2.6 (2H, m), 2.7—3.1 (4H, m), and 3.15 (6H, s). Calcd for $C_6H_{12}O_4S_2$: C, 33.94; H, 5.70; S, 30.21%. Found: C, 33.99; H, 5.66; S, 30.27%.

(b) Method B; To a solution containing **1** (657 mg: 5.30 mmol) in THF (10 ml), was added a 1.44 mol/l hexane solution (4.0 ml) of *n*-BuLi (5.8 mmol) at −10 °C, and the mixture was stirred for 2 h. After addition of 1,3-dibromopropane (530 mg: 2.63 mmol) together with THF (3 ml), the resulting mixture was stirred under ice-cooling for 0.5 h and then at room temperature for 2 h. CH_2Cl_2 (100 ml) was added and the mixture was washed with water (30 ml). The aqueous layer was extracted with four 50-ml portions of CH_2Cl_2. The organic layer and the extracts were combined and dried (Na_2SO_4). The solvents were evaporated, and the residue was column-chromatographed on silica gel [elution with CH_2Cl_2 and CH_2Cl_2-Et_2O (4:1)] to give **3** ($n=3$) as a pale yellow oil (300 mg: 70% yield based on 1,3-dibromopropane). Employment of 1,3-bis(tosyloxy)propane in place of 1,3-dibromopropane gave **3** ($n=3$) in 91% yield as shown in Table 1.

Similarly, the following compounds were prepared. **3** ($n=2$): an oil; IR (neat) 1055 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=0.89$—1.60 (4H, m), 2.23 (3H, s), and 2.56 (3H, s). The disulfone of **3**($n=2$): mp 140—140.5 °C (from methanol); IR (KBr) 1332, 1318, 1300, and 1125 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.83$ (4H, s) and 3.27 (6H, s). Calcd for $C_5H_{10}O_4S_2$: C, 30.29; H, 5.08; S, 32.35%. Found: C, 30.13; H, 5.04; S, 32.34%.

3 ($n=4$): an oil; IR (neat) 1045 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.6$—2.3 (8H, m), 2.18 (3H, s), and 2.64 (3H, s). The disulfone of **3** ($n=4$): mp 173—173.5 °C (from CH_2Cl_2-CCl_4-hexane); IR (KBr) 1315, 1305, 1288, and 1132 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.7$—2.2 (4H, m), 2.2—2.7 (4H, m), and 3.17 (6H, s). Calcd for $C_7H_{14}O_4S_2$: C, 37.15; H, 6.24; S, 28.34%. Found: C, 37.29; H, 6.22; S, 28.31%. **3** ($n=5$): mp 57.5—58.5 °C (from benzene-hexane); IR (KBr) 1045 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.5$—2.1 (10H, m), 2.08 (3H, s), and 2.60 (3H, s). Calcd for $C_8H_{16}OS_2$: C, 49.95; H, 8.39; S, 33.34%. Found: C, 50.18; H, 8.22; S, 33.26%.

Reaction of 1,6-Dibromohexane with 1. A Typical Procedure: To a solution containing **1** (1.32 g: 10.6 mmol) in THF (10 ml), was added to 1.30 mol/l hexane solution (8.2 ml) of *n*-BuLi (10.7 mmol) and the reaction mixture was stirred at −15 °C for 2 h. After addition of 1,6-dibromohexane (1.01 g: 4.14 mmol), the resulting mixture was further stirred at −15 °C for 3 h and then at room temperature for 18 h. CH_2Cl_2 (15 ml) was added and the deposited solid was filtered off. The filtrate was concentrated, and the residue was subjected to column chromatography on Florisil using CH_2Cl_2 and AcOEt as eluents to give 1,8-bis(methylsulfinyl)-1,8-bis(methylthio)octane (**19**) as a pale brown oil (273 mg: 20% yield) and 1-methylsulfinyl-1-methylthio-7-bromoheptane (**20**) as a pale brown oil (256

mg: 22% yield). The compound **19** was identified by its derivation to 1,1,8,8-tetrakis(methylsulfonyl)octane: mp 163.5—165.5 °C; IR (KBr) 1310, 1150, and 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.39 (4H, broad s), 1.59 (4H, broad s) 2.07 (4H, broad s), 3.19 (12H, s), and 5.08 (t, 2H, J=5.8 Hz). Calcd for $C_{12}H_{26}O_8S_4$: C, 33.78; H, 6.14; S, 30.07%. Found: C, 33.69; H, 6.11; S, 30.31%. The compound **20** was also converted to its disulfone derivative: mp 56—58 °C; IR (KBr) 1335, 1315, 1310, 1140, 1125, 1120, and 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.3—1.6 (4H, m), 1.6—2.0 (4H, m), 2.0—2.3 (2H, m), 3.15 (6H, s), and 3.93 (1H, t, J=5.5 Hz). Calcd for $C_9H_{19}O_4S_2Br$: C, 32.24; H, 5.71; S. 19.13%. Found: C, 32.64; H, 5.73; S, 19.13%.

Acid-catalyzed Hydrolysis of **3** (n=3). To a solution of **3** (n=3) (432 mg: 2.63 mmol) in EtOH (3 ml), was added 8 drops of 4.5 M sulfuric acid, and the resulting solution was stirred at room temperature for 18 h and then at 45 °C for 5 h. This solution was shown not to contain **3** (n=3) by a TLC analysis. A 2,4-dinitrophenylhydrazine solution (25 ml) [3.0 g/sulfuric acid (30 ml)+H_2O (20 ml)+EtOH (70 ml)] was added and the mixture was allowed to stand overnight at room temperature. Addition of water (20 ml) deposited cyclobutanone 2,4-dinitrophenylhydrazone (518 mg: 79%) as orange crystals: mp 146.5—148 °C (from EtOH and CCl_4-hexane) (lit,[16] mp 146 °C); IR (KBr) 3280, 3080, 1615, 1587, 1510, 1338, 1310, and 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.9—2.5 (2H, m), 2.8—3.4 (4H, m), 7.87 (1H, d, J=10 Hz), 8.27 (1H, dd, J=2.5 and 10 Hz), 9.12 (1H, d, J=2.5 Hz), and 10.73 (1H, broad, NH). Calcd for $C_{10}H_{10}N_4O_4$: C,48.00; H, 4.02; N, 22.39%. Found: C, 47.97; H, 4.02; N, 22.17%.

Acid Hydrolysis of **3** (n=4). To a solution of **3** (n=4) (211 mg: 1.19 mmol) in EtOH (5 ml), was added 5 drops of 4.5 M sulfuric acid and the resulting solution was stirred at room temperature for 15 h. By the above-mentioned procedure, the resulting ketone was converted to the corresponding 2,4-dinitrophenylhydrazone (290 mg: 92%) which was identified as cyclopentanone 2,4-dinitrophenylhydrazone by comparison of its IR spectrum with that of the authentic sample.

Acid Hydrolysis of **3** (n=5). *a)*: To a solution of **3** (n=5) (293 mg: 1.53 mmol) in EtOH (3 ml), was added 3 drops of 4.5 M sulfuric acid and the resulting solution was stirred at room temperature for 4 h. The above-mentioned work-up gave yellow crystals (375 mg: 88%) which were identified as cyclohexanone 2,4-dinitrophenylhydrazone by comparison of their IR spectrum with that of the authentic sample.

b): To a mixture containing **3** (n=5) (10.79 g: 56.2 mmol) in Et_2O (50 ml), was added 4.5 M sulfuric acid (0.5 ml), and the resulting mixture was stirred at room temperature. Then $NaHCO_3$ (800 mg) and Na_2SO_4 were added. After the insoluble solid was filtered off, the filtrate was evaporated under atmospheric pressure. The residue was subjected to fractional distillation to afford three fractions: (i) bp 56—75 °C/80 Torr (1 Torr=133.322 pa) which was shown by an NMR analysis to consist of dimethyl disulfide (765 mg) and cyclohexanone (655 mg); (ii) bp 75—84 °C/80 Torr which consisted of dimethyl disulfide (258 mg) and cyclohexanone (1.64 g); and (iii) 50—56 °C/20—14 Torr which consisted of dimethyl disulfide (50 mg) and cyclohexanone (2.03 g). The last fraction showed the same IR spectrum to that of cyclohexanone. The yield of cyclohexanone was calculated to be 79%.

c): A mixture containing **3** (n=5) (9.18 g: 47.8 mmol), EtOH (14 ml), triethyl orthoformate (12 ml), and sulfuric acid (0.2 ml) was stirred at room temperature for 14 h. K_2CO_3 (1.5 g) was added and the mixture was further stirred for 30 min. After addition of 0.5 M aq solution (50 ml) of K_2CO_3 and extraction with three 70-ml portions of Et_2O, the extracts were combined and dried (K_2CO_3). The solvents were evaporated, and the residue was subjected to fractional distillation to give cyclohexanone diethyl acetal (6.84 g: 83% yield) as a colorless liquid having bp 100—105 °C/57 Torr (lit,[17] bp 78—85 °C/18 Torr): IR (near) 2890—2830 and 1090—1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (6H, t, J=7 Hz), 1.2—1.8 (10H, broad), and 3.45 (4H, q, J=7 Hz). Calcd for $C_{10}H_{20}O_2$: C, 69,72; H, 11.70%. Found: C, 69.62; H, 11.43%.

Synthesis of Tetrahydro-4-pyrone (8). To a suspension containing KH (3.81 g: 95.3 mmol) in THF (30 ml), was dropwise added to **1** (4.98 g: 40.2 mmol) under ice-cooling over 30 min. After the resulting mixture was stirred for 45 min at the same temperature, bis(2-chloroethyl) ether (5.82 g: 40.7 mmol) was dropwise added over 30 min and the reaction mixture was further stirred under ice-cooling for 1 h and then at room temperature for 4 h. CH_2Cl_2 (100 ml) was added and the deposited solid was filtered off. The filtrate was evaporated and the residue was subjected to column chromatography on silica gel using Et_2O as an eluent to give 4-methylsulfinyl-4-methylthiotetrahydro-4-pyrane (**7**) contaminated with a small amount of **1** as a pale yellow oil (6.17 g).

This oil was dissolved in Et_2O (100 ml) and 4.5 M sulfuric acid (1 ml) was added. After the reaction mixture was stirred at room temperature for 2 h, $NaHCO_3$ (1.5 g) was added to neutralize the acid and then anhydrous Na_2SO_4 was added. After the mixture was allowed to stand overnight, the insoluble solid was filtered off and the filtrate was concentrated *in vacuo*. Distillation of the residue gave two fractions, a colorless liquid (384 mg) having bp 86—88 °C/59 Torr and a colorless oil (2.40 g) having bp 88—91 °C/59 Torr. The former was shown by an NMR analysis to consist of dimethyl dislfide (92 mg) and 8 (292 mg) and latter was pure **8**: IR (neat) 1720, 1217, 1088, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.50 (4H, t, J=6 Hz) and 3.98 (4H, t, J=6 Hz). Its 2,4-dinitrophenylhydrazone: mp 191.5—192.5 °C (from water-EtOH) (lit,[18] mp 186.5—187 °C). Calcd for $C_{11}H_{12}N_4O_5$: C, 47.14; H, 4.32; N, 19.99%. Found: C, 47.24; H, 4.36; N, 19.74%.

Reaction of cis-1,4-Dichloro-2-butene with **1**. To a solution of lithio derivative **1'** (M=Li) in THF (150 ml) which was prepared from 1 (24.9 g: 0.200 mol) and n-BuLi (0.200 mol), was added *cis*-1,4-dichloro-2-butene (10.0 g: 0.08 mol). The mixture was further stirred at −70 °C for 3.5 h and then at room temperature for 16.5 h, and then CH_2Cl_2 (400 ml) was added. The mixture was washed with water (100 ml) and the aqueous layer was extracted with five 100 ml-portions of CH_2Cl_2. The organic layers were combined and dried ($MgSO_4$). The solvents were evaporated, and the residue was subjected to column chromatography on Florisil using AcOEt as an eluent to give 4-methylsulfinyl-4-methylthio-1-cyclopentene (**9**) as a pale yellow oil (11.1 g: 78% yield): IR (neat) 1617 and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.24 (3H, s), 2.60 (3H, s), 2.35—3.4 (4H, m), and 5.68 (2H, s). The *S,S,S',S'*-tetraoxide derivative: mp 168—169 °C (from CCl_4); IR (KBr) 1630, 1320—1305, 1295, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.20 (6H, s), 3.23 (4H, s), and 5.69 (2H, s). Calcd for $C_7H_{12}O_4S_2$: C, 37.48; H, 5.39; S, 28.59%. Found: C, 37.48; H, 5.38; S, 28.58%.

Acid Hydrolysis of **9** *Leading to 3-Cyclopentenone (10).* The authentic sample of **10** was synthesized by pyrolysis of tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-ol according to a literature.[19] To a solution of **9** (105 mg: 0.597 mmol) in 10 ml of acetone-water (8:1) was added 2 drops of 4.5 M sulfuric acid, and the mixture was stirred at room temperature for 5 h. By a GLC analysis (20% XF1150 column, 1 m, 130 °C; nitrogen, 1 kg/cm^2; internal standard, cyclopentanone), the yields of 3-cyclopentenone and 2-cyclopentenone were shown to be 60% and 6%, espectively.

Reaction of trans-*1,4-Dichloro-2-butene with 1.* To a solution of **1'** (M=Li) in THF (30 ml) which was prepared from **1** (2.91 g: 23.5 mmol) and *n*-BuLi (23.0 mmol), was added to *trans*-1,4-dichloro-2-butene (1.32 g: 10.6 mmol) at −70 °C, and then the reaction mixture was stirred at room temperature for 2.5 h. Water (30 ml) was added and the mixture was extracted with four 50 ml-portions of CH_2Cl_2. The extracts were combined and dried (Na_2SO_4). The solvents were evaporated, and the residue was subjected to column chromatography on silica gel using CH_2Cl_2-Et_2O (4:1) as an eluent to afford 1-methylsulfinyl-1-methylthio-2-vinylcyclopropane (**11**) as a pale yellow oil (1.41 g: 76% yield):[13] IR (neat) 1632 and 1060 cm^{-1}. The corresponding *S,S,S',S'*-tetraoxide: mp 102—102.5 °C (from CCl_4 and MeOH-water); IR (KBr) 1640, 1625, 1335, 1325, 1305, 1290, of CH_2Cl_2. The extracts were combined and dried (Na_2SO_4). The solvents were evaporated, and the residue was subjected to column chromatography on silica gel using CH_2Cl_2-Et_2O (4:1) as an eluent to afford 1-methylsulfinyl-1-methylthio-2-vinylcyclopropane (**11**) as a pale yellow oil (1.41 g: 76% yield):[13] IR (neat) 1632 and 1060 cm^{-1}. The corresponding *S,S,S',S'*-tetraoxide: mp 102—102.5 °C (from CCl_4 and MeOH-water); IR (KBr) 1640, 1625, 1335, 1325, 1305, 1290, 1160, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.80 (1H, dd, J=6.5 and 10 Hz), 2.18 (1H, dd, J=6.5 and 8 Hz), 2.96—3.22 (1H, m), 3.14 (3H, s), 3.20 (3H, s), 5.22—6.02 (3H, m). Calcd for $C_7H_{12}O_4S_2$: C, 37.48; H, 5.39; S, 28.59%. Found: C, 37.22; H, 5.23; S, 28.37%.

Synthesis of 2-Methylcyclobutanone (14) Using 1. To a solution of **1'** (M=Li) in THF (15 ml) which was prepared from **1** (1.57 g: 12.6 mmol) and *n*-BuLi (12.6 mmol), was added to 1,3-dibromobutane (1.13 g: 5.2 mmol) at −70 °C, and the reaction mixture was stirred at room temperature for 46.5 h. Water (20 ml) was added and the mixture was extracted with one 100 ml-portion and four 20 ml-portions of CH_2Cl_2. The extracts were combined, washed with brine (20 ml), and dried ($MgSO_4$). The solvents were evaporated, and the residue was subjected to colum chromatography on Florisil using CH_2Cl_2 as an eluent to afford 1-methylsulfinyl-1-methylthio-2-methylcyclobutane as a pale yellow oil (746 mg: 80% yield), which consisted mainly of two diastereomers in the ratio of 1:2; IR (neat) 1050 cm^{-1}; ^1H NMR of the major isomer ($CDCl_3$): δ=1.18 (3H, d, J=7 Hz), 1.6—4.0 (5H, m), 2.33 (3H, s), and 2.67 (3H, s); ^1H NMR of the minor isomer ($CDCl_3$): δ=1.39 (3H, d, J=7 Hz), 1.6—4.0 (5H, m), 2.18 (3H, s), and 2.47 (3H, s).

This *S*-oxide (212 mg) was dissolved in EtOH (3 ml) and 8 drops of 4.5 M sulfuric acid were added. The resulting mixture was stirred at room temperature for 15 h and then at 43—47 °C for 24 h. The thus-formed 2-methylcyclobutanone was trapped as its 2,4-dinitrophenylhydrazone (241 mg: 77%): orange crystals; mp 119.5—122 °C (from CCl_4-Et_2O); IR (KBr) 3260, 3075 2935, 2895, 1667, 1615, 1588, 1515, 1500, 1420, 1335, 1310, and 1268 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (3H, d, J=7 Hz), 1.72 (1H, m), 2.33 (1H, m), 2.97 (2H, m), 3.40 (1H, m), 7.81 (1H, d, J=10 Hz), 8.22 (1H, dd, J=2.6 and 10 Hz), 9.04 (1H, d, J=2.6 Hz), and 10.67 (1H, broad, NH). Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20%. Found: C, 50.07; H, 4.49; N, 20.99%.

Synthesis of 3-Benzylcyclobutanone (18a). The starting material 2-benzyl-1,3-dibromopropane (**16a**) was synthesized by reduction of diethyl benzylmalonate with $LiAlH_4$ in Et_2O leading to 2-benzyl-1,3-propanediol and the subsequent treatment of this diol with CBr_4 and PPh_3 in CH_3CN.[20] To a solution of **1'** (M=Li) in THF (15 ml) which was prepared from **1** (1.01 g: 8.15 mmol) and *n*-BuLi (8.64 mmol), was added **16a** (1.03 g: 3.53 mmol) at −10 °C and the mixture was further stirred at −10 °C for 100 min and then at room temperature for 3 h. CH_2Cl_2 (100 ml) was added and washed with water (30 ml). The aqueous layer was extracted with two 50 ml-portions of CH_2Cl_2. The organic layers were combined, washed with brine (20 ml), and dried (Na_2SO_4). The solvenrs were evaporated, and the residue was subjected to column chromatography on silica gel using CH_2Cl_2-AcOEt (9:1) as an eluent to give 1-methylsulfinyl-1-methylthio-3-benzylcyclobutane (**17a**) as a pale yellow oil (686 mg: 77% yield): IR (neat) 1055 and 1035 (sh) cm^{-1}. ^1H-NMR ($CDCl_3$) showed that this oil consisted of two diastereomers (2:1). The methyl signals of the major isomer appeared at δ=2.12 and 2.49, while the minor isomer exhibited the methyl signals at δ=2.08 and 2.42.

The *S*-oxide (2.70 g: 10.6 mmol) was dissolved in Et_2O (140 ml), and 4.5 M sulfuric acid (2.8 ml) was added. The resulting mixture was stirred at room temperature for 2 d and then heated under a reflux for 2 d. After addition of $NaHCO_3$ and $MgSO_4$, the mixture was further stirred for a while and the insoluble solid was filterd off. The filtrate was concentrated, and the residue was subjected to column chromatography on silica gel using CH_2Cl_2 and hexane as eluents to give 3-benzylcyclobutanone (**18a**) as a colorless oil (1.13 g: 66% yield) IR (neat) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.43—3.49 (7H, m) and 7.21 (5H, s). Its 2,4-dinitrophenylhydrazone derivative: mp 138—139.5 °C (from CCl_4-hexane). Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46%. Found: C, 60.02; H, 4.70; N, 16.46%.

The *S*-oxide (398 mg) was dissolved in Et_2O (20 ml). Then 4.5 M sulfuric acid (0.4 ml) was added and the resulting mixture was stirred at room temperature for 1 d and then heated under a reflux for 7 h. After addition of $NaHCO_3$ and $MgSO_4$, the mixture was stirred for a while and the insoluble solid was filterd off. The filtrate was subjected to the reaction with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of **18a** (417 mg: 78% yield).

Synthesis of 3-Benzyloxycyclobutanone (18b) Using 1. To a solution of **1'** (M=Li) in THF (40 ml) which was preparted from **1** (4.81 g: 38.7 mmol) and *n*-BuLi (38.5 mmol), was dropwise added to 2-benzyloxy-1,3-dibromopropane[21] (4.95 g: 16.1 mmol) at −70 °C over 15 min, and the reaction mixture was stirred at −70 °C for 2 h and then at room temperature for 15.5 h. After addition of CH_2Cl_2 (200 ml), the mixture was washed with water (30 ml). The washings were extracted with four 50 ml-portions of CH_2Cl_2. The organic layers were combined, washed with brine (30 ml), and dried ($MgSO_4$). The solvents were evaporated, and the residue was subjected to column chromatography on Florisil using AcOEt to afford 1-methylsulfinyl-1-methylthio-3-benzyloxycyclobutane (**17b**) as a pale yellow oil (3.35 g: 77% yield), which was shown by its ^1H NMR spectrum to consist of two diastereomers (1.1: 1). In the ^1H NMR spectrum, the sulfinylmethyl protons appeared at δ 2.38 (s) and 2.48 (s) in the relative intensity of 1.1:1.

After this *S*-oxide (593 mg) was dissolved in Et_2O (10 ml), 35% perchloric acid (0.45 ml) was added. The resulting mixture was stirred at room temperature for 25 h. After addition of $NaHCO_3$ and $MgSO_4$, the mixture was stirred for a while and the insoluble solid was filterred off. The filtrate was concetrated and the residue was subjected to column chromatography on silica gel using $CHCl_3$ as an eluent to give **18b** (233 mg: 60% yield) as a colorless oil; IR (neat) 1795 (sh) and 1787 cm^{-1}; ^1H NMR ($CDCl_3$) 3.10 (4H, d, J=6 Hz), 4.28 (1H, quintet, J=6 Hz), 4.45 (2H, s), and 7.28 (5H, s). Its semicarbazone: mp 164—166.5 °C (from acetone-water); IR (KBr) 3445, 3260, 3145, 2895, 2850, 1667, 1593, 1485, and 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.00 (4H, m), 4.16 (1H, m), 4.42 (2H, S), 5.50 (2H, broad s), 7.29 (5H, s), and 8.70 (1H, broad s). Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01%. Found: C, 61.80; H, 6.45; N, 17.89%.

References

1) K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Chem. Lett.*, **1982**, 93 and the references cited therein; R. C. Gadwood, *J. Org. Chem.*, **48**, 2098 (1983) and the references cited therein.

2) This was preliminarily reported: K. Ogura, M. Yamashita, M. Suzuki, G. Tsuchihashi, *Tetrahedron Lett.*, **1974**, 3653; K. Ogura, M. Yamashita, S. Furukawa, M. Suzuki, and G. Tsuchihashi, *ibid.*, **1975**, 2767.

3) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1971**, 3151; G. R. Newkome, J. M. Robinson, and J. D. Sauer, *J. Chem. Soc., Chem. Commun.*, **1974**, 410.

4) Methyl methylthiomethyl sulfoxide (**1**) is also utilized as a synthetic reagent for making α-hydroxy aldehydes,[5] α-amino acids,[6] α-keto acides,[7] arylacetic esters,[8] α-bromo-α-arylacetic acids,[9] and α-arylpropionic acids.[10]

5) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 2681; K. Ogura, S. Furukawa, and G. Tsuchihashi, *Chem. Lett.*, **1974**, 659.

6) K. Ogura and G. Tsuchihashi, *J. Am. Chem. Soc.*, **96**. 1960 (1974); K. Ogura, I. Yoshimura, and G. Tsuchihashi, *Chem. Lett.*, **1975**, 803.

7) K. Ogura, N. Katoh, I. Yoshimura, and G. Tsuchihashi, *Tetrahedron Lett.*, **1978**, 375.

8) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 1383; K. Ogura, Y. Itoh, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **52**, 2013 (1979); K. Ogura, Y. Itoh, and G. Tsuchihashi, *Synthesis*, **1980**, 736.

9) K. Ogura, S. Furukawa, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **48**, 2219 (1975).

10) K. Ogura, S. Mitamura, K. Kishi, and G. Tsuchihashi, *Synthesis*, **1979**, 880.

11) Acylic ketones can be synthesized by dialkylation of **1**, followed by an acid hydrolysis: G. Schill and P. R Jones, *Synthesis*, **1974**, 117.

12) H. O. House, "Modern Synthetic Reactions," Benjamin, California (1972), pp. 541—543.

13) Although four diastereomers are possible for **11**, one diastereomer showing two methyl signals at δ 2.35 and 2.72 along with the olefinic protons at δ 4.9—6.3 in the ^{1}H NMR spectrum was predominantly produced.

14) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 and 1077 (1965); D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968); D. Seebach and A. K. Beck *Org. Syn.*, **51**, 76 (1971).

15) At the present time, the stereochemical structures for these isomers are not determined.

16) N. J. Demjanow and M. Dojarenko, *Chem. Ber.*, **55**, 2737 (1922).

17) J. Boeseken and F. Tellegen, *Recl. Trav. Chim Pays-Bas*, **57**, 133 (1938).

18) M. I. Farberov, E. P. Tepenitsyna, and N. K. Shemyakina, *Dokl. Akad. Nauk SSSR*, **99**, 793 (1954); *C. A.*, **49**, 8315b (1955).

19) H. M. Hess and H. C. Brown, *J. Org. Chem.*, **32**, 4138 (1967).

20) E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **92**, 2139 (1970).

21) M. Avram, C. D. Nenitzescu, and M. Mexim, *Chem. Ber.*, **90**, 1424 (1957).