New Method for Synthesis of Various Types of Substituted 2(5*H*)-Furanones

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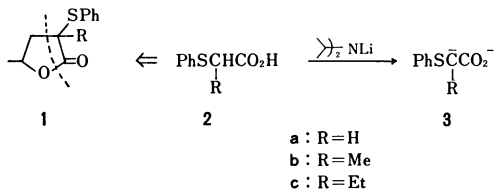
A combination of the reaction of dianions of (phenylthio) acetic acid and its homologs with epoxides, the conjugate addition reaction of 3-phenylthio-2-(5*H*)-furanones with carbanion species, and the α-alkylation reaction of α-phenylthio-γ-butyrolactones is shown to provide a general method for the synthesis of a variety of substituted α-phenylthio-γ-butyrolactones. Oxidation of these α-phenylthiolactones to the corresponding sulfoxides, followed by pyrolysis furnishes all the types of substituted (3-, 4-, and 5-mono-; 3,4-, 3,5- 4,5-, and 5,5-di-; 3,4,5-tri-) 2(5*H*)-furanones in good overall yields.

Recently a number of methods for the synthesis of 2(5*H*)-furanones (γ-crotonolactones, 2-buten-4-olides, $\Delta^{\alpha,\beta}$-butenolides) have been reported,[1] in view of their abundance in nature[2] and usefulness as synthetic intermediates.[1d,3] Concerning the synthesis of natural products by the application of photocycloaddition reactions of 2(5*H*)-furanones to olefins,[3f] we became interested in the development of a convenient method for the synthesis of a variety of 2(5*H*)-furanones.[4]

Results

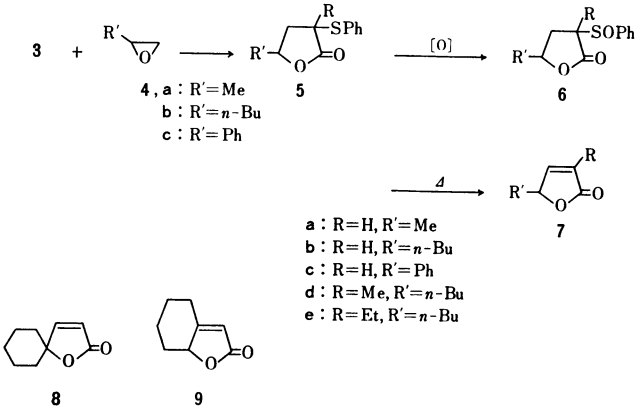
The method includes α-phenylthio-γ-butyrolactones **1** as the key intermediate. (Phenylthio)acetic acid (**2a**) might be suitable as the starting material for the construction of the C-2, 3 unit in 2(5*H*)-furanones (indicated by a dotted line in **1**). The phenylthio group was chosen since it appears (1) to facilitate the generation of the adjacent carbanion species which would have sufficient nucleophilicity to react with epoxides or alkyl



halides before or after the construction of γ-lactone ring, and (2) to be oxidized easily to the sulfinyl group which would be further transformed into other useful intermediary functional groups (vinyl sulfide or sulfoxide) through the Pummerer rearrangement and serve as a facile eliminating group to produce a double bond in the final products.

The dianion **3a** was easily prepared by treating **2a** with lithium diisopropylamide, and reacted smoothly with methyl iodide and ethyl bromide to give α-(phenylthio)propionic acid (**2b**) and -butyric acid (**2c**) in quantitative yields, respectively.[5] The homologous acids **2b** and **2c** also produced the corresponding dianions **3b** and **3c** in the same manner.

The reactions of the dianions **3** with epoxides **4** and subsequent transformation into 5-mono- and 3,5-disubstituted 2(5*H*)-furanones are shown in Scheme 1. The reactions of **3** with propylene oxide (**4a**), 1-hexene oxide (**4b**), or styrene oxide (**4c**) proceeded smoothly to give the corresponding phenylthiobutyrolactones **5** in excel-



Scheme 1.

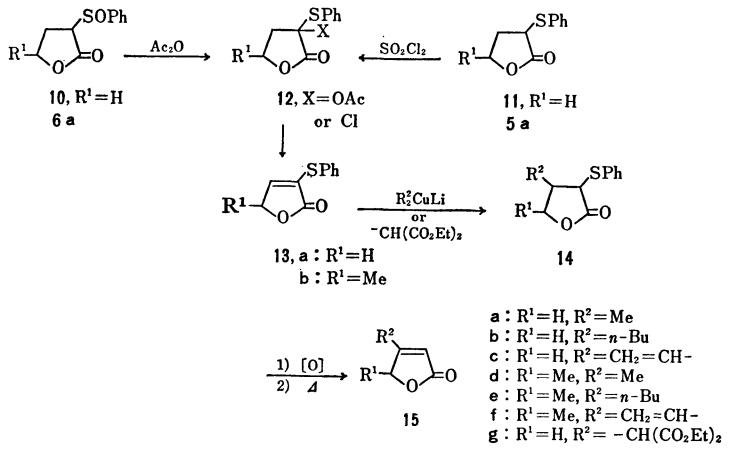
lent yields. Each lactone **5** was obtained as a mixture of stereoisomers. On treatment of **5** with *m*-chloroperbenzoic acid, hydrogen peroxide, or sodium periodate, the corresponding sulfoxides **6** were obtained quantitatively and were pyrolyzed (at *ca.* 110 °C for **6a—c** and *ca.* 70 °C for **6d**, **e**) to give 5-mono- and 3,5-disubstituted 2(5*H*)-furanones **7** in high yields. It should be noted that, in the cases of **6d** and **6e**, a double bond was exclusively introduced into an endocyclic position, neither α-methylene- nor α-ethylidene- γ-butyrolactone being detected.[1g]

In a similar way, the use of methylenecyclohexane oxide (1,1-disubstituted epoxide) or cyclohexene oxide (symmetrical 1,2-disubstituted epoxide) gave 5,5-pentamethylene-2(5*H*)-furanone (**8**) (5,5-disubstituted) and 4,5-tetramethylene-2(5*H*)-furanone (**9**) (4,5-disubstituted), respectively.

An attempt to use the anion of the ester of **2a**, PhS-$\overline{\text{C}}\text{HCO}_2\text{Et}$, for the reaction with **4a** gave an unsatisfactory result, **5a** being obtained in a low (30%) yield. Thus, the present α-phenylthio carboxylic acid dianion procedure would be very useful for the synthesis of 5-mono, 3,5-di, 5,5-di, and 4,5-di (the same substituents)-substituted 2(5*H*)-furanone derivatives, because of ready availability of the starting materials, simple operation of the reactions, and high yield of the products.

Among the number of methods for the synthesis of 2(5*H*)-furanones,[1] the procedure for 4-substituted derivatives has so far been very limited. Thus the development of a convenient synthetic method for them would be of considerable interest.

In order to introduce a substituent to the C-4 position

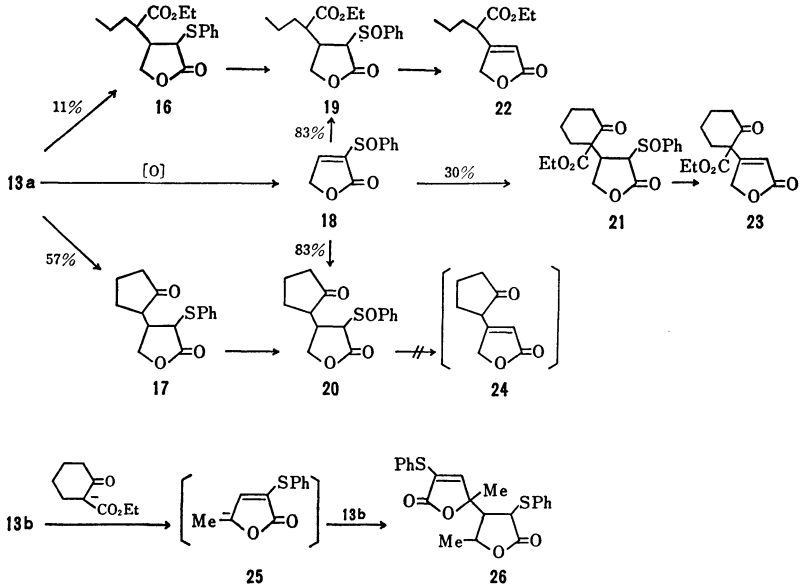


Scheme 2.

of 2(5*H*)-furanone system, we adopted the 1,4-conjugate addition reaction of 3-phenylthio- (**13**) or 3-phenylsulfinyl-2(5*H*)-furanones (**18**). The preparation of **13** was satisfactorily accomplished in two ways through the intermediates **12**: one by the Pummerer rearrangement[6] of α-phenylsulfinyl-γ-butyrolactones (**10** and **6a**) and the subsequent elimination of acetic acid by heating in acetic anhydride (60—70 °C and then 150 °C) (86 and 93% overall) and the other by the chlorination of α-phenylthio-γ-butyrolactones (**11** and **5a**) with sulfuryl chloride, followed by dehydrochlorination (93 and 88% overall) (Scheme 2). Phenylthiofuranones **13** thus obtained underwent conjugate addition with lithium dialkylcuprates (dialkyl=dimethyl, dibutyl, or divinyl) to give the adducts **14a—f** in good yields. These could be converted into the expected 4-mono- and 4,5-disubstituted 2(5*H*)-furanones **15a—f** in good yields. Combined use of the Grignard reagent and cuprous iodide for the conjugate addition gave an unsatisfactory result (low yields of **14** due to formation of a considerable amount of by-products).

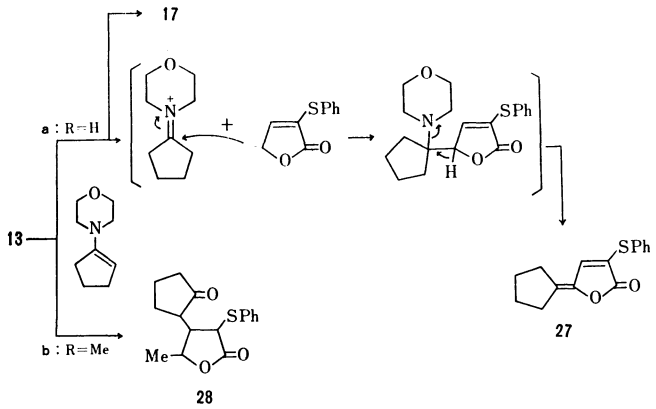
In contrast to the successful addition of dialkylcuprate to **13**, the reaction of **13a** with other enolates (diethyl malonate, ethyl valerate, or cyclopentanone) did not necessarily give good results, the low yields of the adducts: 60% for **14g**, 11% for **16**, and 57% for **17**, presumably because of an unfavorable equilibrium (Scheme 3). Hence, the more effective stabilization of the α-anion in the adducts would favor the equilibration to the adduct side, facilitating the conjugate addition reaction of enolates. In fact, 3-phenylsulfinyl-2(5*H*)-furanone (**18**) underwent smoothly the conjugate addition with the enolates of ethyl valerate and cyclopentanone to give the desired adducts **19** and **20**, respectively, in good yields.[7] Unlike **13a**, **18** also reacted with ethyl 2-oxocyclohexanecarboxylate to afford a 30% yield of the adduct **21**. Pyrolysis of **19** and **21** furnished the 4-substituted 2(5*H*)-furanones **22** and **23**, respectively, in good yields, but the 2(5*H*)-furanone **24** derived from **20** was extremely unstable, polymerizing during the course of isolation. The reaction of **13a** with ethyl 2-oxocyclohexanecarboxylate produced only the polymers of **13a** itself, which would arise from self-addition of the 5-anion of **13a** (such as **25**). Actually, the dimer **26** was isolated in the reaction of **13b** in 38% yield.

The preferential abstraction of the 5-hydrogen atom



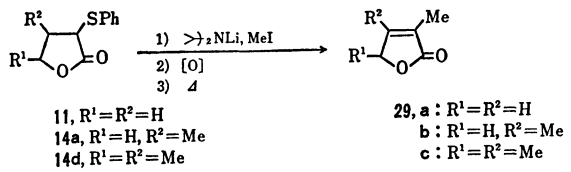
Scheme 3.

was also observed in the reaction of **13a** with an enamine. The reaction of **13a** with 1-morpholino-1-cyclopentene gave, in addition to a 22% yield of **17**, 5-cyclopentylidene-3-phenylthio-2(5*H*)-furanone (**27**) (30%), which would be formed through the reaction of the 5-anion of **13a** with the protonated enamine and the subsequent elimination of morpholine as depicted in Scheme 4. The 5-methyl derivative **13b** gave only the conjugate addition product **28** in low yield.



Scheme 4.

Finally, the application of α-alkylation to the α-phenylthio-γ-butyrolactones,[1g] through the subsequent oxidation and dehydrosulfenylation, led to the remaining 3-mono-, 3,4-di-, and 3,4,5-trisubstituted 2(5*H*)-furanone derivatives. Typical examples are shown in Scheme 5.



Scheme 5.

The procedures we gave provide useful methods for the synthesis of all types of substituted 2(5*H*)-furanones starting from readily available substances through simple and high-yield operations.

Experimental

All the melting points were taken on a Yamato melting point apparatus and are uncorrected. Distillation of the liquid products was usually carried out evaporatively using a modified sublimation apparatus and the oil bath temperatures were recorded. IR spectra were taken on a Hitachi EPI-S2 or G2 spectrometer. NMR spectra were obtained on a JEOL C-60HL (60 MHz) instrument using TMS as an internal standard. Reported values are given in the δ scale. Both spectra were recorded in CCl_4 solution unless otherwise stated. Elementary analyses were carried out in the microanalytical laboratory of this Institute. Progress of all the reactions was followed by TLC, silica gel (Merck GF_{254} Typ 60). The developing solvent system was petroleum ether–ether mixture, visualization being effected with a fluorescent lamp or concd H_2SO_4 spray.

Generation of the Dianion (3) of (Phenylthio)acetic Acid and its Homologs (2). To a solution of freshly prepared lithium diisopropylamide (0.02 mol) in THF–ether was added dropwise a solution of (phenylthio)acetic acid (**2a**)[8] (1.68 g, 0.01 mol) in THF (7 ml) at 0 °C under nitrogen. The mixture was stirred at 0—4 °C for 1 h. An aliquout (3 ml) was taken with a syringe and quenched with D_2O. Incorporation of one deuterium atom at the α-position in the recovered **2a** (acidification and extraction) was confirmed from the NMR spectrum: δ 3.58 (1H, s).

In the same manner, solutions of the dianions (**3b**) and (**3c**) of the propionic (**2b**) and butyric acid derivatives (**2c**) could be prepared.

Alkylation of the Dianion (3a). A solution of excess methyl iodide (17.6 g) in THF (5 ml) was added dropwise at −60——70 °C to a solution of the dianion (**3a**) (0.01 mol) under nitrogen, and the mixture was stirred overnight and warmed gradually to room temperature. A saturated solution of NH_4Cl and then 30% H_2SO_4 (to Congo Red) were added, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with saturated brine and freed from the solvent. A small amount of ether was added to the residue and the insoluble material was removed by filtration. Evaporation of the solvent, and distillation (100—140 °C/<1 Torr) of the pale yellow oil remaining afforded 1.70 g (93%) of α-(phenylthio)propionic acid (**2b**). NMR 1.50 (3H, d, J=7 Hz, $-CHC\underline{H}_3$), 3.60 (1H, q, J=7 Hz, $-C\underline{H}CH_3$), 7.10—7.60 (5H, m, Ph), and 12.0 (1H, s, COOH).

In the same manner, the alkylation of **3a** with ethyl bromide gave α-(phenylthio)butyric acid (**2c**) in 99% yield. Bp 100—140 °C/<1 Torr; NMR 1.55 (3H, t, J=7.5 Hz, $-CH_2C\underline{H}_3$), 1.60—2.15 (2H, m, $-C\underline{H}C\underline{H}_2CH_3$), 3.47 (1H, t, J=7.2 Hz, $-C\underline{H}CH_2-$), 7.10—7.60 (5H, m, Ph), and 11.4 (1H, s, COOH).

Compound **2b** was also prepared by the reaction of ethyl α-bromopropionate with sodium thiophenolate as in the preparation of **2a**. To a stirred slurry of sodium thiophenolate (1.4 g) in THF (20 ml) was added a solution of ethyl α-bromopropionate (1.18 g) in THF (10 ml) at 0 °C, and the mixture was stirred at room temperature for 6 h. After the removal of inorganic salt and solvent, distillation of the residual oil gave 2.0 g (95%) of ethyl α-(phenylthio)propionate. A mixture of this ester (1.8 g) and aqueous potassium hydroxide (720 mg in 10 ml) was heated under reflux for 3 h. At this stage the mixture became homogeneous. The cooled mixture was acidified with 30% H_2SO_4 turing to Congo Red and extracted with ether. The combined extracts were washed with saturated brine and dried. After evaporation of the solvent, distillation of the residue afforded 1.56 g (99%) of **2b**.

General Procedure for Reaction of the Dianions (3) with Epoxides. To a solution of dianion **3** was added a solution of the freshly purified epoxide (a slightly excess molar amount except propylene oxide) in dry THF at *ca.* −60 °C under nitrogen, and the reaction mixture was stirred at this temperature for 1 h and then gradually warmed to room temperature within a period of *ca.* 15 h. For 1 g of an epoxide, *ca.* 3 ml of THF was used. Aqueous NH_4Cl was added to the mixture and the solvent was then removed under reduced pressure. The residue was poured into a mixture of ether and dil H_2SO_4 (sufficient amount for neutralization), and the water layer was thoroughly extracted with ether. The combined ether layers were washed with water and saturated brine, and dried. After removal of the solvent, the residual oil was heated in benzene (*ca.* 10 ml for 1 g) containing a trace of concd H_2SO_4 under reflux for 3 h using a water-separator. The cooled reaction mixture was diluted with ether and successively washed with dil NaOH, water, and saturated brine. Removal of the solvent gave a mixture of *cis* and *trans* γ-substituted α-phenylthio-γ-butyrolactones (**5**) in 70—94% yield, which

were usually separable by chromatography on silica gel using petroleum ether–ether as an eluting agent. In the cases of **5d** and **5e**, the extraction was carried out with $CHCl_3$, and the concentration of the extracts at 80 °C under ordinary pressure resulted in complete lactonization.

General Procedure for Oxidation of α-Phenylthio-γ-butyrolactones. To a solution of the α-phenylthiolactone derivative in CH_2Cl_2 (*ca.* 20 ml for 1 g of the lactone) was added a solution of *m*-chloroperbenzoic acid (MCPBA, 85%, 1.0—1.2 equiv) in CH_2Cl_2 (*ca.* 30 ml for 1 g of the peracid) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5—1 h, diluted with CH_2Cl_2, successively washed with dil $NaHCO_3$ solution and saturated brine, and dried. Evaporation of the solvent under reduced pressure left the α-phenylsulfinyl-γ-butyrolactone derivative in nearly quantitative yield.

The α-phenylthiolactone derivative was treated at room temperature with either $NaIO_4$ (*ca.* 1.2 equiv) in 40—50% methanol (*ca.* 20 ml for 1 g of the lactone) for 12 h or 30% hydrogen peroxide (*ca.* 2 ml) in 50% methanol for 4 days, and the usual work-up (extraction with CH_2Cl_2) gave also the α-phenylsulfinyllactone derivative (**6**) in excellent yield. In all cases, the sample thus obtained was sufficiently pure for the subsequent pyrolysis.

General Procedure for Pyrolysis of α-Phenylsulfinyl-γ-butyrolactones. A solution of the α-phenylsulfinyllactone derivative in toluene (10—20 ml for 1 g of the lactone) or in pyridine (*ca.* 5 ml) was heated under reflux for 0.5—1 h. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel using petroleum ether–ether as an eluting agent to give the 2(5*H*)-furanone derivative, which was purified by evaporative distillation.

*α-Phenylthio-γ-butyrolactone (**11**).* A solution of α-bromo-γ-butyrolactone[9] (15.1 g) in THF (30 ml) was added dropwise to a suspension of sodium thiophenolate (12.1 g) in THF (70 ml) at room temperature, and the reaction mixture was stirred for 2 days. After the removal of insoluble material and solvent, distillation (165—175 °C/1 Torr) of the residual oil afforded 17.1 g (96%) of **11**. Found: C, 61.56; H, 5.20%. Calcd for $C_{10}H_{10}O_2S$: C, 61.85; H, 5.15%.

*α-Phenylsulfinyl-γ-butyrolactone (**10**)*, yield 86% ($NaIO_4$): mp 100—104 °C from $CHCl_3$–CCl_4. Found: C, 57.11; H, 4.82%. Calcd for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.80%.[10]

*3-Phenylthio-2(5H)-furanone (**13a**).* (a) A solution of **10** (4.4 g) in acetic anhydride (25 ml) was heated at 60—70 °C overnight and then refluxed for 2 h. After the removal of acetic anhydride and acetic acid under reduced pressure, the residue was recrystallized from ethanol to give 3.3 g (86%) of **13a**; mp 57.5—59 °C; IR ($CHCl_3$) 1760 and 1600 cm^{-1}; NMR ($CDCl_3$) 4.84 (2H, d, J=2.2 Hz), 6.75 (1H, t, J=2.2 Hz), and 7.40—7.80 (5H, m). Found: C, 62.57; H, 4.05%. Calcd for $C_{10}H_8O_2S$: C, 62.50; H, 4.20%. When the reaction was stopped at the stage of 70 °C heating, a small amount of α-acetoxy-α-phenylthio-γ-butyrolactone (**12**, R^1=H, X=OAc) was isolated.

(b) A solution of sulfuryl chloride (9.8 g) in CCl_4 (30 ml) was added dropwise (1 h) to a solution of **11** (11.9 g) in CCl_4 (70 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 2 h, poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined extracts were successively washed with $NaHCO_3$ solution, water, and saturated brine, and dried. Evaporation of the solvent under reduced pressure left 13.2 g of α-chloro-α-phenylthio-γ-butyrolactone (**12**, R^1=H, X=Cl). The crude product, dissolved in THF (60 ml), was added to a mixture of LiBr (17 g) and Li_2CO_3 (13 g) in THF (60 ml) at room temperature. The reaction mixture was refluxed for 30 min under nitrogen. After the removal of inorganic salts and solvent, the residue was dissolved in CH_2Cl_2, and the solution was washed with $NaHCO_3$ solution and saturated brine, and dried. Evaporation of the solvent gave 9.94 g (93%) of **13a**.

*5-Methyl-3-phenylthio-2(5H)-furanone (**13b**).* This compound was prepared from either of **6a** or **5a** as in the preceding experiment. (a) from **6a**. Yield 93%; (b) from **5a**. Yield 88%. Bp 160—170 °C/1 Torr; IR 1770 and 1600 cm^{-1}; NMR 1.35 (3H, d, J=6.8 Hz), 4.98 (1H, dq, J=1.5 and 6.8 Hz), 6.60 (1H, d, J=1.5 Hz), and 7.20—7.80 (5H, m). Found: C, 63.71; H, 5.15%. Calcd for $C_{11}H_{10}O_2S$: C, 64.07; H, 4.89%.

*General Procedure for the Reaction of **13** with Lithium Dialkylcuprates.* To a freshly prepared solution of lithium dimethyl, dibutyl, or divinylcuprate[11] (2 equiv) in ether or ether–hexane was added dropwise a solution of **13** in ether (60 ml for *ca.* 1.5 g) under nitrogen. The reaction temperature and time for each cuprate are as follows: 0 °C for 2—3 h for dimethylcuprate; −78 °C for 3—4 h for dibutylcuprate; −60—−50 °C for 1.5—2 h for divinylcuprate. The reaction mixture was poured into a cold NH_4Cl solution and thoroughly extracted with ether. The combined extracts were washed with water and saturated brine, and dried. After removal of the solvent, the residual oil was chromatographed on silica gel using petroleum ether–ether as an eluting agent. Yields of **14** were 75—100%.

*β-[Bis(ethoxycarbonyl)methyl]-α-phenylthio-γ-butyrolactone (**14g**).* A mixture of diethyl malonate (350 mg) and lithium hydride (25 mg) in THF (15 ml) was stirred at room temperature for 30 min under nitrogen. To this solution was added a solution of **13a** (384 mg) in THF (10 ml) at room temperature, and the reaction mixture was stirred for 2 h and then refluxed for 30 min. The cooled mixture was poured into a cold NH_4Cl solution and the solvent was removed under reduced pressure. The organic residue was extracted with ether. The extract was washed with saturated brine and evaporated. The oil remaining was chromatographed on silica gel (10 g) using petroleum ether–ether to give 423 mg (60%) of **14g**.

*β-(1-Ethoxycarbonylbutyl)-α-phenylthio-γ-butyrolactone (**16**).* To a solution of lithium diisopropylamide (1 equiv) in THF (10 ml) was added a solution of ethyl valerate (390 mg) in THF (10 ml) at −78 °C under nitrogen, and the mixture was stirred at −78 °C for 1 h. A solution of **13a** (576 mg) in THF (10 ml) was added to this solution, and the reaction mixture was stirred at −78 °C for 20 h and then warmed to room temperature within a period of 8 h. A cold NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed with water and saturated brine, and dried. After removal of the solvent, chromatography of the residual oil on silica gel (100 g) using 1:1 petroleum ether–ether as an eluent gave 110 mg (11%) of **16** accompanied by the recovery of 140 mg of **13a**.

*β-(2-Oxocyclopentyl)-α-phenylthio-γ-butyrolactone (**17**).* A solution of cyclopentanone (280 mg) in THF (10 ml) was added to a solution of lithium diisopropylamide (1 equiv), and the mixture was stirred for 1 h. To this solution was added a solution of **13a** (576 mg) in THF (15 ml), and the reaction mixture was stirred for 4 h. All the operations were carried out at −78 °C under nitrogen. A cold NH_4Cl solution was added to the mixture, and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2. The combined extracts were washed with saturated brine. After removal of the solvent, the residual oil was chromatographed on silica gel (100 g) using 2:1 petroleum ether–ether as an eluent to give 500 mg (57%) of **17**.

*γ-Methyl-β-(2-oxocyclopentyl)-α-phenylthio-γ-butyrolactone (**28**).* The reaction of **13b** with cyclopentanone or its morpholine enamine was carried out in the same manner as **13a**. Yields:

64% (cyclopentanone) and 31% (enamine).

3-Phenylsulfinyl-2(5H)-furanone (18). Oxidation of **13a** was carried out using MCPBA (−20——10 °C for 1 h) and work-up was carried out as described earlier. Yield. 80%. Mp 86—88 °C from ether. IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) 5.00 (2H, br. s), 7.50—8.00 (5H, m), and 8.10 (1H, br. s). Found: C, 57.62; H, 4.01%. Calcd for $C_{10}H_8O_3S$: C, 57.69; H, 3.87%.

β-(1-Ethoxycarbonylbutyl)-α-phenylsulfinyl-γ-butyrolactone (19). The reaction of **18** with ethyl valerate was carried out in the same manner as for **13a** except for quenching at −78 °C Yield 83%. The compound was also obtained by MCPBA oxidation of **16**.

β-(2-Oxocyclopentyl)-α-phenylsulfinyl-γ-butyrolactone (20). The reaction of **18** with cyclopentanone was carried out in the same manner as for **13a**. Yield 82%.

β-(1-Ethoxycarbonyl-2-oxocyclohexyl)-α-phenylsulfinyl-γ-butyrolactone (21). To a solution of lithium diisopropylamide (1 equiv) in THF (15 ml) was added a solution of ethyl 2-oxocyclohexanecarboxylate (425 mg) in THF (15 ml), and the mixture was stirred for 1 h. A solution of **18** (520 mg) in THF (15 ml) was added to the above enolate solution, and the reaction mixture was stirred for 3 h. All the operations were carried out at −78 °C under nitrogen. A cold NH_4Cl solution was added, and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and the combined extracts were washed with saturated brine. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (80 g) using 1:5 petroleum ether–ether as an eluent to give 280 mg (30%) of **21**.

Reaction of 13b with Ethyl 2-Oxocyclohexanecarboxylate. To a solution of the enolate of ethyl 2-oxocyclohexanecarboxylate (374 mg) in THF, prepared according to the manner described earlier, was added a solution of **13b** (412 mg) in THF (10 ml) at −50 °C under nitrogen, and the reaction mixture was gradually warmed to −20 °C within a period of 3 h under stirring. Aqueous NH_4Cl was added, and the solvent was removed under reduced pressure. The organic residue was extracted with ether, and the extracts were washed with saturated brine and dried. After removal of the solvent, the residue was chromatographed on silica gel (60 g) using 1:1 petroleum ether–ether as an eluent to give 155 mg (38%) of 2,2′-dimethyl-4,4′-bis(phenylthio)-2,2′,3′,4′,5,5′-hexahydro-2,3′-bifuran-5,5′-dione (**26**), bp 200 °C/1 Torr; IR ($CHCl_3$) 1760 cm^{-1}; NMR ($CDCl_3$) 1.20 (3H, d, J=6.8 Hz), 1.43 (3H, s), 2.30 (1H, dd, J=6.8 and 8.2 Hz), 3.35 (1H, d, J=8.2 Hz), 4.48 (1H, quint, J=6.8 Hz), 6.05 (1H, s) and 7.20—7.80 (10H, m). Found: C, 63.88; H, 5.01%. Calcd for $C_{22}H_{20}O_4S_2$: C, 64.07; H, 4.89%.

5-Cyclopentylidene-3-phenylthio-2(5H)-furanone (27). To a solution of 1-morpholino-1-cyclopentene (306 mg)[12] in MeCN (5 ml) was added a solution of **13a** (384 mg) in MeCN (5 ml) at room temperature under nitrogen, and the reaction mixture was stirred at room temperature for 5 h. Dilute HCl (2 M, 10 ml) was added, and the resulting solution was stirred for 1 h, then poured into water, and extracted with ether. The combined extracts were washed with water several times and then saturated brine. After removal of the solvent, the residue was chromatographed on preparative TLC of silica gel with 1:1 petroleum ether–ether to give 120 mg (22%) of **17** and 165 mg (30%) of **27**, mp 138—139 °C from ethanol; IR ($CDCl_3$) 1750 cm^{-1}; NMR ($CDCl_3$) 1.40—2.00 (4H, m), 2.20—2.80 (4H, m), 6.85 (1H, s), and 7.50 (5H, m). Found: C, 69.55; H, 5.48%. Calcd for $C_{15}H_{14}O_2S$: C, 69.75; H, 5.46%.

Methylation of α-Phenylthio-γ-butyrolactones. A solution of the α-phenylthiobutyrolactone derivative (**11**, **14a**, **14d**) in THF (10 ml for 1 g) was added to a solution of lithium diisopropylamide (1.3 equiv) in THF at −60 °C under nitrogen. After being stirred for 1 h, methyl iodide (large excess) was added, and the mixture was stirred at −60 °C overnight. The usual work-up (quenching, extraction, distillation) gave the α-methylated product in quantitative yield.

α-Phenylthio-γ-butyrolactones. All the α-phenylthio-γ-butyrolactones (**5**, **14**, **16**, **17**, the γ,γ-pentamethylene-, β,γ-tetramethylene-, α-methyl, α,β-dimethyl-, and α,β,γ-trimethyl-derivatives) gave satisfactory analytical and spectral results.

Yield (from the corresponding α-phenylthio-γ-butyrolactones), Bps (Torr), ν_{CO}, Proton Chemical Shifts, and Analytical Data of 2-(5H)-Furanones.

5-Methyl- (7a) (β-Angelica Lactone). 74%. Identified with the authentic sample.[13]

5-Butyl- (7b). 82%. 130—140 °C/2. 1770 cm^{-1}. δ 0.70—2.00 (9H, m), 4.80—5.20 (1H, m), 6.00 (1H, dd, J= 1.5 and 6 Hz), and 7.55 (1H, dd, J=1.5 and 6 Hz). Found: C, 67.94; H, 8.28%. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

5-Phenyl- (7c). 57%, in addition to 23% of 2(3*H*)-isomer, after chromatographic separation. 90—120 °C/l. 1790, 1760, and 1700 cm^{-1}. δ 5.90 (1H, t, J=2.3 Hz), 6.10 (1H, dd, J=2.3 and 6 Hz), 7.30 (5H, s), and 7.45 (1H, dd, J=2.3 and 6 Hz). Found: C, 75.15; H, 5.01%. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03%.

5-Butyl-3-methyl- (7d). 63%. 90—110 °C/l. 1760 cm^{-1}. δ 0.70—1.80 (9H, m), 1.87 (3H, t, J=2.3 Hz), 4.65—5.00 (1H, m), and 7.15 (1H, m). Found: C, 70.27; H, 9.01%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

5-Butyl-3-ethyl- (7e). 78% (in this case the pyrolysis was carried out in boiling CCl_4 containing 2-mercaptobenzothiazole).[14] 70—90 °C/l. 1760 cm^{-1}. δ 0.70—2.00 (9H, m), 1.13 (3H, t, J=7.5 Hz), 2.25 (2H, tq, J=1.6 and 7.5 Hz), 4.65—5.00 (1H, m), and 7.05 (1H, dt, J=1.6 and 1.6 Hz). Found: C, 71.49; H, 9.49%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

5,5-Pentamethylene- (8). 83%. 130—140 °C/4. 1770 cm^{-1}. δ 1.70 (10H, br. s), 5.92 (1H, d, J=6 Hz), and 7.52 (1H, d, J=6 Hz). Found: C, 71.24; H, 7.68%. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95%.

4,5-Tetramethylene- (9). 82%. 70—90 °C/1. 1780 and 1760 cm^{-1}. δ 0.90—3.10 (8H, m), 4.40—4.90 (1H, m), and 5.60 (1H, m). Found: C, 69.68; H, 7.08%. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30%.

4-Methyl- (15a). 87%. Identified with the authentic sample.[15]

4-Butyl- (15b). 80%. 140 °C/1. 1780 and 1750 cm^{-1}. δ 0.95 (7H, m), 2.45 (2H, br. t, J=7.2 Hz), 4.75 (2H, br. s), and 5.75 (1H, br. s). Found: C, 68.51; H, 8.79%. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

4-Vinyl- (15c).[16] 51%. 1780 and 1760 ($CHCl_3$) cm^{-1}. δ ($CDCl_3$) 5.06 (2H, br. d, J=1.5 Hz), 5.70 (1H, d, J=10.5 Hz), 5.70 (1H, d, J=18 Hz), 6.05 (1H, br. t, J= 1.5 Hz), and 6.82 (1H, dd, J=10.5 and 18 Hz). This compound is unstable, and decomposed partially on distillation. The sample, which was chromatographically and spectroscopically homogeneous, did not give satisfactory analytical results.

4,5-Dimethyl- (15d). 87%. 85 °C/1. 1780 and 1760 cm^{-1}. δ 1.40 (3H, d, J=7.1 Hz), 2.08 (3H, br. s), 4.95 (1H, br. q. J=7.1 Hz), and 5.75 (1H, br. s). Found: C, 64.59; H, 6.80%. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19%.

4-Butyl-5-methyl- (15e). 82%. 140 °C/1. 1770 cm^{-1}. δ 0.95—1.19 (7H, m), 1.36 (3H, d, J=6.8 Hz), 2.10—2.60 (2H, m) 4.90 (1H, br. q, J=6.8 Hz), and 5.67 (1H, br. s). Found: C, 69.87; H, 8.98%. Calcd for $C_9H_{14}O_2$: C, 70.10;

H, 9.15%.

*5-Methyl-4-vinyl- (**15f**).* 89%. 1780 and 1760 cm^{-1}. δ 1.55 (3H, d, J=7.5 Hz), 5.30 (1H, q, J=7.5 Hz), 5.72 (1H, d, J=18 Hz), 5.75 (1H, d, J=10.5 Hz), 6.07 (1H, s), and 6.73 (1H, dd, J=10.5 and 18 Hz). The thermal property of **15f** is similar to that of **15c**.

*4-[Bis(ethoxycarbonyl)methyl]- (**15g**).* 68%. 140—160 °C/1. 1780, 1750, and 1740 cm^{-1}. δ 1.30 (6H, t, J=7 Hz), 4.30 (4H, q, J=7 Hz), 4.70 (1H, br. s), 5.02 (2H, d, J=2.3 Hz), and 6.20 (1H, br. s). Found: C, 54.68; H, 5.72%. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83%.

*4-(1-Ethoxycarbonylbutyl)- (**22**).* 90%. 140—150 °C/1. 1780, 1750, and 1735 cm^{-1}. δ 0.70—2.10 (7H, m), 1.30 (3H, t, J=7.2 Hz), 3.50 (1H, br. t, J=7.5 Hz), 4.15 (2H, q, J=7.2 Hz), 4.80 (2H, br. d, J=1.9 Hz), and 5.87 (1H, br. s). Found: C, 62.22; H, 7.75%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

*4-(1-Ethoxycarbonyl-2-oxocyclohexyl)- (**23**).* 83%. 160 °C/1. 1780, 1750, and 1720 ($CHCl_3$) cm^{-1}. δ ($CDCl_3$) 1.30 (3H, t, J=7.5 Hz), 1.10—3.00 (8H, m), 4.32 (2H, q, J=7.5 Hz), 4.80 (1H, dd, J=18 and 2.1 Hz), 5.10 (1H, dd, J=18 and 2.1 Hz), and 6.00 (1H, m). Found: C, 61.48; H, 6.45%. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39%.

*3-Methyl- (**29a**).* 65%. Identified with the authentic sample.[1g,17]

*3,4-Dimethyl- (**29b**).* 75%, in addition to 8% of the *exo*-methylene isomer. 70 °C/1. 1760 cm^{-1}. δ 1.75 (3H, br. s), 2.02 (3H, br. s), and 4.60 (2H, br. s). Found: C, 64.18; H, 7.51%. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19%.

*3,4,5-Trimethyl- (**29c**).* 93%. 60—80 °C/1. 1760 cm^{-1}. δ 1.38 (3H, d, J=6.8 Hz), 1.77 (3H, br. s), 2.00 (3H, br. s), and 4.78 (1H, br. q, J=6.8 Hz). Found: C, 66.73; H, 8.03%. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99%.

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