New Synthetic Route for the Preparation of 4-Phenylthio-4-butanolide Derivatives by the Use of the Pummerer Rearrangement

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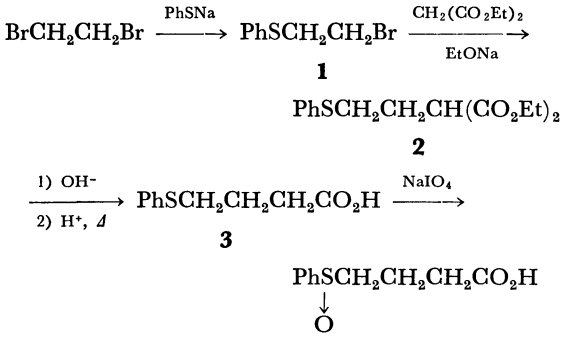
The Pummerer rearrangement reaction of 2- or 3-substituted 4-(phenylsulfinyl)butyric acids in the presence of an excess amount of acetic anhydride and a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene for 1 h afforded 2- or 3-substituted 4-phenylthio-4-butanolide (**17a—f**). Thermolysis in pyridine of 4-phenylsulfinyl 4-butanolides, which were prepared by oxidation of **17a—f**, afforded 2- or 3-substituted 2- or 3-buten-4-olides.

The Pummerer rearrangement reaction is an important reaction in the sulfoxide chemistry because of its wide applicability to the synthesis of many types of organic compounds. However, only few instances have been reported of applications of this rearrangement to a cyclization reaction. Numata and Oae reported that *o*-carboxyphenyl alkyl sulfoxide was cyclized easily by the pummerer reaction to give 3,1-benzoxathiin-4-one.[1] In our earlier studies, we showed that 2- or 3-phenylthio-4-butanolide derivatives could be used for the synthesis of 3- or 2-substituted 2-buten-4-olides.[2,3] In this paper, we wish to report a new synthetic route to 2- or 3-substituted 4-phenylthio-4-butanolides (**17a—f**) from 2- or 3-substituted 4-(phenylsulfinyl)butyric acids (**9a—f**); this route involves the Pummerer rearrangement in the cyclization step. We also investigated the dehydrosulfenylation reaction of **17a—f** to form 2- or 3-buten-4-olides.

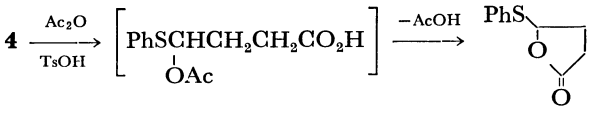
Results and Discussion

Synthesis of 4-(Phenylsulfinyl)butyric Acid (4) and Cyclization Reaction of 4 to Form 4-Phenylthio-4-butanolide (6). Preparation of 4-(phenylsulfinyl)butyric acid was carried out by the usual oxidation of 4-(phenylthio)-butyric acid, which had been synthesized by the method of Lamdan and Albarracin[4] (see Scheme 1).



Scheme 1.

It was found that when **4** was allowed to react with acetic anhydride in the presence of *p*-toluenesulfonic acid in refluxing toluene for 1 h, 4-phenylthio-4-butanolide (**6**) was obtained in 75% yield. This reaction involves an intramolecular ester exchange reaction of intermediate (**5**) which was formed by the Pummerer rearrangement of **4**.

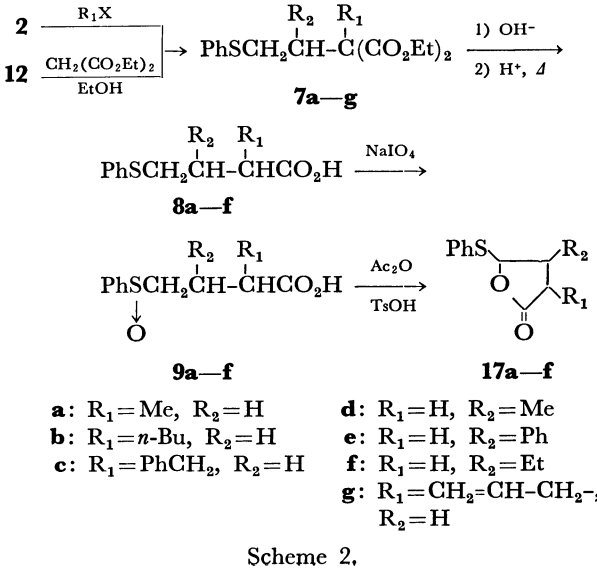


5 **6**

When the reaction was carried out in the absence of *p*-toluenesulfonic acid, starting material **4** was recovered completely. The investigation of other acid catalysts, such as phosphoric acid and chloroacetic acid, did not give good results. In this reaction, benzene and xylene were also examined as solvents, but **6** was obtained only in lower yields (see Table 1).

Preparation of 2- or 3-Substituted 4-Phenylthio-4-butanolides. The reaction sequence for the preparation of 2- or 3-substituted 4-phenylthio-4-butanolides (**17a—f**) is shown in Scheme 2.

The alkylation of **2** by alkyl halides such as methyl iodide, butyl bromide or allyl bromide were carried out in the usual way to give diethyl 2-alkyl-2-(2-phenylthioethyl)malonates (**7a—c, 7g**) in 66—89% yields (see Table 2). However, for the synthesis of **7a—c** and **7g**, when the reaction of alkyl halide with diethyl malonate was carried out as the first step and the resulting alkylated diethyl malonate was allowed to react with **1**, the yields of **7a—c** and **7g** became very low because of the formation of phenyl vinyl sulfide.



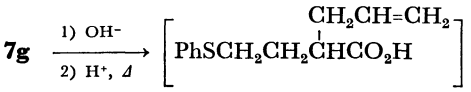
a: R_1=Me, R_2=H
b: R_1=*n*-Bu, R_2=H
c: R_1=PhCH$_2$, R_2=H
d: R_1=H, R_2=Me
e: R_1=H, R_2=Ph
f: R_1=H, R_2=Et
g: R_1=CH$_2$=CH-CH$_2$-, R_2=H

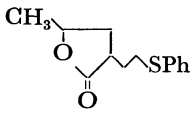
Scheme 2.

TABLE 1. THE CYCLIZATION REACTION OF **4** TO FORM **6**

Entry	Catalyst	Reaction conditions Solvent	Reflux time	Yield/%
1	—	Benzene	10 h	—
2	TsOH	Benzene	3 h	56
3	$ClCH_2CO_2H$	Benzene	14 h	10
4	H_3PO_4	Benzene	6 h	15
5	TsOH	Toluene	1 h	75
6	TsOH	Xylene	0.5 h	50
7	TsOH	$CHCl_3$	2 h	40
8	TsOH	THF	3 h	20

Further steps to form 2-substituted 4-(phenylsulfinyl)butyric acids (**9a—c**) were conducted as in the preparation of **4**. Yields and spectral data of **8a—c** are summarized in Table 3. **9a—c** could be used for the next cyclization step without further purification. In the case of the hydrolysis and decrboxylation of **7g**, it was found that the resulting carboxylic acid derivative was converted spontaneously to 4-methyl-2-(2-phenylthioethyl)-4-butanolide (**16**) in 55% yield by the intramolecular addition of a carboxyl group to the double bond.





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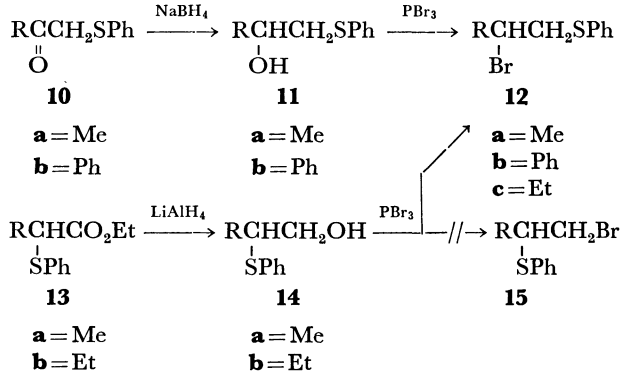
For the preparation of 3- or 4-substituted 4-(phenylsulfinyl)butyric acid, bromides **12** and **15** were required, and α-phenylthio ketones and α-phenylthio esters were employed as the starting materials. Reduction of α-(phenylthio)acetone (**10a**) or α-(phenylthio)-acetophenone (**10b**) with sodium borohydride in methanol at 0 °C gave the corresponding alcohols (**11a, b**) in high yields. These alcohols were allowed to react with phosphorus tribromide in refluxing carbon tetrachloride to give 2-bromopropyl phenyl sulfide (**12a**) and 2-bromo-2-phenylethyl phenyl sulfide (**12b**).



In a similar way, α-phenylthio esters such as ethyl 2-(phenylthio)propionate (**13a**) or ethyl 2-(phenylthio)butyrate (**13b**) were reduced with lithium aluminium hydride in THF at 0 °C to form corresponding alcohols (**14a, b**) in good yields. However, bromination of **14a** and **14b** by phosphorus tribromide gave the unexpected result of yielding **12a** and **12c** because of migration of the phenylthio group. Formation of **8d—f** to **9d—f** as performed in the usual way, as mentioned above.

The yield and spectral data of **7a—g** and **8a—f** are summarized in Table 2 and Table 3 respectively.

The reaction of **9a—f** thus obtained with acetic anhydride in the presence of *p*-toluenesulfonic acid in refluxing toluene for 1 h resulted in the formation of 4-phenylthio-4-butanolide derivatives (**17a—f**) in 27—73% yields. These results are summarized in Table 4.

*Elimination of Phenylthio Group from **17a—f** to Buten-4-olides.* It is well known that 2-phenylsulfinyl or 2-alkylsulfinyl-4-butanolide derivatives were converted smoothly to 2-buten-4-olides by thermal decomposition.[6-8] Further, in our previous paper, we described how 3-phenylsulfinyl-4-butanolides were also decom-

TABLE 2. YIELDS AND SPECTRAL DATA OF **7a—f**

Compd	Yield %	IR $\nu_{C=O}$ cm^{-1}	MS M$^+$(*m/e*)	^{1}H NMR ($CDCl_3$) δ
7a	81	1710	310	1.22 (6H, t), 1.44 (3H, s), 1.90—2.50 (2H, m) 2.94—3.10 (2H, m), 4.71 (4H, q), 7.02—7.48 (5H, m)
7b	66	1710	352	0.88 (3H, t), 1.21 (6H, t), 1.72—3.10 (10H, m), 4.71 (4H, q), 7.04—7.44 (5H, m)
7c	88	1720	384	1.17 (6H, t), 1.90—2.30 (2H, m), 2.40—3.06 (2H, m), 3.18 (2H, s), 4.08 (4H, q), 6.74—7.36 (10H, m)
7d	61	1730	310	1.15 (3H, d), 1.25 (6H, t), 2·12—3.80 (4H, m), 4.18 (4H, q), 7.10—7.54 (5H, m)
7e	39[a]	1730	372	0.94 (4H, t), 1.24 (3H, t), 2.74—4.04 (4H, m), 4.20 (4H, q), 7.00—7.38 (10H, m)
7f	65	1740	324	0.78—3.20 (14H, m), 3.67—4.43 (5H, m), 7.37—7.60 (5H, m)
7g	89	1730	336	1.20 (6H, t), 2.00—3.10 (6H, m), 4.18 (4H, q), 4.89—5.94 (3H, m), 7.10—7.54 (5H, m)

a) This yield is from alcohol **11b**.

Table 3. Yields and spectral data of **8a—f**

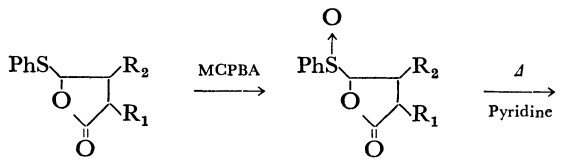
Compd	Yield %	IR $\nu_{C=O}$ cm^{-1}	MS M$^+$(*m/e*)	^{1}H NMR ($CDCl_3$) δ
8a	57	1700	210	1.20 (3H, d), 1·41—2.32 (3H, m), 2.58 (2H, q), 2.96 (2H, t), 7.14—7.54 (5H, m), 11.75 (1H, s)
8b	82	1700	252	0.90 (3H, t), 1.11—3.40 (11H, m), 7.05—7.41 (5H, m), 10.98 (1H, s)
8c	57	1720	286	1.00—1.36 (2H, m), 2.42—3.36 (4H, m), 3.84—4.30 (1H, m), 7.02—7.30 (10H, m), 10.77 (1H, s)
8d	50	1710	210	1.09, 1.07 (3H, dd), 1.64—3.40 (5H, m), 6.98—7.44 (5H, m), 10.38 (1H, s)
8e	48	1710	272	2.32—3.40 (5H, m), 6.94—7.38 (10H, m), 9.76 (1H, bs)
8f	60	1720	224	1.03 (3H, t), 1.30—2.17 (3H, m), 2.43—3.17 (4H, m), 7.03—7.53 (5H, m), 10.73 (1H, bs)

Table 4. Yields and spectral data of **17a—f**

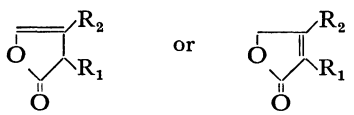
Compd	Yield %	IR $\nu_{C=O}$ cm^{-1}	MS M$^+$(*m/e*)	^{1}H NMR ($CDCl_3$) δ
17a	51	1780	208	1.27 (3H, d), 1.68—3.10 (3H, m), 5.58—5.90 (1H, m), 7.14—7.62 (5H, m)
17b	68	1780	250	0.92 (3H, t), 1.10—3.05 (9H, m), 5.55, 5.97 (1H, m), 7.27—7.85 (5H, m)
17c	63	1770	283	1.36—3.50 (5H, m), 5.50, 5.80 (1H, m), 7.00—7.58 (10H, m)
17d	52	1780	208	1.35—1.47 (3H, m), 1.97—2.87 (3H, m), 5.18—5.37 (1H, m), 7.10—7.63 (5H, m)
17e	56	1790	270	2.59—2.93 (2H, m), 3.30—4.10 (1H, m), 5.53 (1H, d), 7.03—7.53 (10H, m)
17f	22	1790	222	0.93 (3H, t), 1.16—2.68 (5H, m), 5.30—6.40 (1H, m), 7.13—7.50 (5H, m)

posed to 2-buten-4-olides by refluxing THF in the presence of triethylamine.

Oxidation of **17a—f** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at 0 °C gave 4-phenylsulfinyl-4-butanolide derivatives (**18a—f**). When the elimination reaction of **18a—f** carried out in refluxing pyridine for 3 h, the double bond of some products isomerized to 2-position from 3-position of buten-4-olide.[9] In the cases of **18d** and **18f**, the double bond



17a—f **18a—f**



19d, f **20a—c, e**

d: R_1=H, R_2=Me
f: R_1=H, R_2=Et
a: R_1=Me, R_2=H
b: R_1=*n*-Bu, R_2=H
c: R_1=$PhCH_2$, R_2=H
e: R_1=H, R_2=Ph

Table 5. Formation of 2- or 3-buten-4-olides

Compd	IR $\nu_{C=O}$ cm^{-1}	Yield %
19d	1800	73
19e	1800	57
20a	1750	27
20b	1750	70
20c	1750	64
20e	1740	48

remained at 3-position; the other cases, however, gave only products in which the double bond was isomerized to 2-position.

The structures of these compounds were determined by IR and NMR spectra. In particular, the IR spectrum of **20a—c** and **20e** showed the carbonyl absorption at 1750 cm^{-1} and **19d** and **19f** showed the carbonyl absorption at 1800 cm^{-1}.

Experimental

Preparation of 4-Phenylthio-4-butanolide (6). A mixture of 4-(phenylsulfinyl)butyric acid (**4**, 0.69 g, 3 mmol), 1.53 g (15 mmol) of acetic anhydride, and a catalytic amount of

p-toluenesulfonic acid in 20 ml of toluene was heated under reflux for 1 h. The solvent and excess acetic anhydride were removed under reduced pressure. The residue was chromatographed on silica gel using benzene, and gave 0.44 g (75%) of **6**. IR (NaCl): 1780 cm^{-1} (C=O). NMR ($CDCl_3$) δ=1.88—2.52 (4H, m), 5.44 (1H, t), 6.75—7.22 (5H, m). MS: *m/e* 194 (M^+). Found: C, 61.73; H, 5.21%. Cacld for $C_{10}H_{10}O_2S$: C, 61.85; H, 5.19%.

*Preparation of Diethyl 2-Methyl-2-(2-phenylthioethyl)malonate (**7a**).* To a solution of sodium ethoxide, prepared from sodium (0.42 g, 18 mmol) and 25 ml of ethanol, was added a solution of **2** (4.50 g, 18 mmol) in ethanol (5 ml). The mixture was refluxed for 15 min. After the reaction mixture was cooled to room temperature, methyl iodide (2.59 g, 18 mmol) was added into the reaction mixture, which was then refluxed for 4 h. The resulted precipitate was filtered and the solvent was evaporated under reduced pressure. 10% Hydrochloric acid (20 ml) was added into the residue and the mixture was extracted with ether and dried. After removal of the solvent, the residue was chromatographed on silica gel using benzene to give **7a** (3.81 g, 81%). Spectral data are summarized in Table 2.

In a similar manner, **7b**, **c**, **d** were prepared from **2** with butyl bromide, benzyl bromide, or allyl bromide. These results are also summarized in Table 2.

*Preparation of 1-Phenylthio-2-propanol (**11a**) and 1-Phenyl-2-(phenylthio)ethanol (**11b**).* Sodium borohydride (1.96 g, 52 mmol) was added slowly to a 50 ml methanol solution of α-(phenylthio)acetophenone (6.64 g, 40 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and then quenched with 10 ml of acetic acid. After removal of the solvent, 50 ml of water was added to the mixture and the mixture was extracted with ether and dried. Removal of ether and distillation of residual oil under reduced pressure gave **11a** (5.29 g, 79%). Bp 115 °C/9 mmHg.

In a similar manner, **11b** was obtained in quantitative yield. In this case, product **11b** was isolated by column chromatography on silica gel by using benzene.

*Bromination of **11a**, **b**.* A carbon tetrachloride (10 ml) solution of **11a** (10.00 g, 60 mmol) was added dropwise to phosphorus tribromide (16.13 g, 60 mmol) in 50 ml of carbon tetrachloride by refluxing gently. The reaction mixture was poured into ice-cold water, extracted with carbon tetrachloride, and dried. Removal of the solvent and distillation under reduced pressure gave 2-bromo-1-(phenylthio)-propane (**12a**) in 80% yield. Bp 115—122 °C/10 mmHg.

In the case of **11b**, the bromination reaction was conducted in a similar manner bromide **12b** was used for the next reaction without further purification because it was hydrolized easily to **11b**.

*Preparation of Diethyl (1-Substituted 2-Phenylthioethyl)malonate (**7d—f**).* To an abs ethanol solution of sodium salt of diethyl malonate, which was prepared from diethyl malonate (2.98 g, 19 mmol) and sodium (0.43 g, 19 mmol) in 50 ml of abs ethanol, was added a ethanol solution of bromide **12a** (3.58 g, 15 mmol). The reaction mixture was refluxed for 4 h. After removal of the resulting sodium bromide by filtration, the filtrate was evaporated under reduced pressure. 10% Hydrochloric acid (20 ml) was added to this residue. The mixture was extracted with ether and dried. After removal of the solvent, the excess amount of diethyl malonate was distilled away under reduced pressure. The residue was chromatographed on silica gel by using benzene–petroleum ether (1:1) and gave **7d** (2.95 g, 61%).

In a similar manner, **7e** and **7f** were obtained. The yields and spectral data are summarized in Table 2.

*Preparation of 2- or 3-Substituted 4-(Phenylthio)butyric Acid (**8a—f**).* A solution of **7a** (8.97 g, 29 mmol) and 50 ml of 20% sodium hydroxide in 50 ml of ethanol was refluxed for 6 h. After removal of ethanol, 80 ml 10% hydrochloric acid was added to this residue. The mixture was extracted with ether and then the etheral layer was evaporated under reduced pressure. To this residue was added 50 ml of 3 mol dm^{-3}-sulfuric acid. The reaction mixture was heated under reflux for 10 h and then cooled to room temperature. The reaction mixture was extracted with ether and dried. After removal of the solvent, the residue was chromatographed on silica gel using benzene–ether (10:1) to give 2-methyl-4-(phenylthio)butyric acid (**8a**, 3.03 g, 50%).

In a similar manner, **8b—f** were also obtained the yields and spectral data of **8a—d** are given in Table 3.

Elemental analyses of **8a—f** are as follows:

*2-Methyl-4-(phenylthio)butyric Acid (**8a**).* Found: C, 62.75; H, 7.09%. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71%.

*2-Butyl-4-(phenylthio)butyric Acid (**8b**).* Found: C, 66.44; H, 7.94%. Calcd for $C_{14}H_{20}O_2S$: C, 66.64; H, 7.79%.

*2-Benzyl-4-(phenylthio)butyric Acid (**8c**).* Found: C, 66.49; H, 6.28%. Calcd for $C_{17}H_{18}O_2S$: C, 66.65; H, 5.82%.

*3-Methyl-4-(phenylthio)butyric Acid (**8d**).* Found: C, 61.26; H, 6.44%. Calcd for $C_{11}H_{14}O_2S$: C, 61.21; H, 6.19%.

*3-Phenyl-4-(phenylthio)butyric Acid (**8e**).* Found: C, 69.77; H, 5.61%. Calcd for $C_{16}H_{16}O_2S$: C, 69.75; H, 5.46%.

*3-Ethyl-4-(phenylthio)butyric Acid (**8f**).* Found: C, 63.83; H, 7.10%. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19%.

*Oxidation of **8a—f**.* To a solution of sodium metaperiodate (4.00 g, 19 mmol) in water (50 ml) was added a 50 ml of ethanol solution of **8a** (3.03 g, 14 mmol) with stirring at 0 °C. The reaction mixture was stirred for 12 h at 0 °C and was then filtered. The precipitate of sodium iodate was washed with chloroform. The filtrate was extracted with chloroform and dried. After removal of the solvent, the residue was chromatographed on silica gel using benzene–ether (1:1) to give (3.10 g, 99%) of **9a**.

*Preparation of 2- or 3-Substituted 4-Phenylthio-4-butanolide (**17a—f**).* The Pummerer reaction of **9a—f** was conducted as in the preparation of **6**. These results are summarized in Table 4. Elemental analyses of **17a—f** are as follows;

*2-Methyl-4-phenylthio-4-butanolide (**17a**).* Found: C, 63.20; H, 5.67%. Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81%.

*2-Butyl-4-phenylthio-4-butanolide (**17b**).* Found: C, 67.47; H, 7.12%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25%.

*2-Benzyl-4-phenylthio-4-butanolide (**17c**).* Found: C, 71.65%; H, 5.47%. Calcd for $C_{17}H_{16}O_2S$: C, 71.82; H, 5.64%.

*3-Methyl-4-phenylthio-4-butanolide (**17d**).* Found: C, 63.51; H, 5.16%. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81%.

*3-Phenyl-4-phenylthio-4-butanolide (**17e**).* Found: C, 70.56; H, 4.95%. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22%.

*3-Ethyl-4-phenylthio-4-butanolide (**17f**).* Found: C, 64.98; H, 6.57%. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35%.

*General Procedure for Oxidation of **17a—f**.* To a solution of 4-phenylthio-4-butanolide derivative in dichloromethane (15 ml, for 1 g of the lactone) was added 1.2 equiv of *m*-chloroperbenzoic acid at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, washed with 10% aqueous sodium

hydrogencarbonate, and dried. Evaporation of the solvent under reduced pressure gave 4-phenylsulfinyl-4-butanolide derivative (**18a—f**). **18a—f** were used for subsequent thermolysis without further purification.

*General Procedure for Thermolysis of **18a—f**.* A solution of 4-(phenylsulfinyl)lactone derivative in pyridine (20 ml for 1 g of the lactone) was refluxed for 3 h. After removal of pyridine under reduced pressure, the residue was chromatographed on silica gel by using benzene–ether (3:1) as an eluent to give 2- or 3-buten-4-olide. Yields are given in Table 5.

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