71256-72-9; **10a**, 73368-03-3; **10b**, 73368-04-4; **11a**, 73368-05-5; **11b**, 73368-06-6; **12a**, 73368-07-7; **12b**, 73395-37-6; **13**, 37133-77-0; **14**, 73368-08-8; **15**, 71256-74-1; **16**, 71256-75-2; **16**, tetrasubstituted olefinic isomer, 73368-09-9; **17**, 71256-76-3; **17**, tetrasubstituted olefinic isomer, 73368-10-2; **18**, 73368-11-3; **18**, tetrasubstituted olefinic isomer, 73368-12-4; 4-chloro-1-butene, 927-73-1; (methoxyethoxy)-methyl chloride, 3970-21-6; (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetoyl chloride, 20445-33-4.

Ketene Thioacetal Route to γ-Lactones. Effect of Carbonyl Hardness on Reaction-Site Selectivity and a Unique Preparation of 3-Methyl-5-phenyl-2(5*H*)-furanone

Alan P. Kozikowski*[1] and Yon-Yih Chen

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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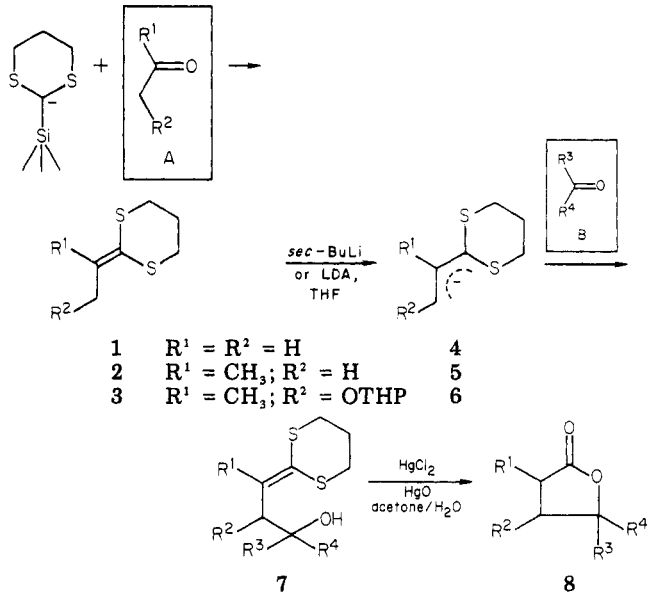
The synthesis of γ-lactones from the addition products of ketene thioacetal anions and carbonyl compounds has been achieved. A unique phenylselenenyl chloride triggered formation of dithienium ion from ketene thioacetal has been shown to directly afford a doubly protected butenolide system.

A variety of methods are now extant for the production of butanolides and their biologically important α,β-unsaturated counterparts, the butenolides. A conceptually simple method for the assembly of these products has recently been disclosed by Caine. This chemistry involves the addition of lithium β-lithiopropionate and lithium β-lithioacrylates to carbonyl compounds.[2]

We now report an alternative route to γ-lactones and a unique synthesis of 3-methyl-5-phenyl-2(5*H*)-furanone. This work is based on our observation that the carbanions prepared by direct metallation of ketene thioacetals undergo reaction predominantly at their γ-position when treated with "soft" carbonyl components (Scheme I).[3] The regiochemical course of carbonyl addition does, of course, contrast with the α-site selectivity observed in the reactions of these same anions with "hard" alkyl halides as the electrophilic addends.[4] Such a dependency of reaction-site selectivity on electrophile is well in accord with general observations previously recorded for related heteroatom-stabilized ambident nucleophiles.[5]

The results of our investigations of the reactions of ketene thioacetal anions **4**–**6** with a host of carbonyl substrates are displayed in Table I. The following points should be noted: (a) The general rule of γ-addition is violated when either cyclopentanone or cyclobutanone is employed as the electrophile (entries 5 and 6).[6] This result

Scheme I. γ-Lactone Synthesis



1 $R^1 = R^2 = H$ 4
2 $R^1 = CH_3$; $R^2 = H$ 5
3 $R^1 = CH_3$; $R^2 = OTHP$ 6

7 8

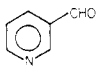
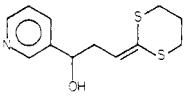
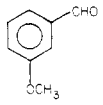
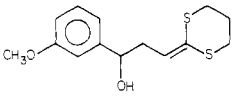
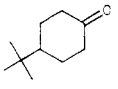
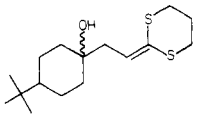
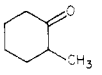
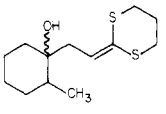
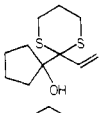
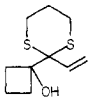
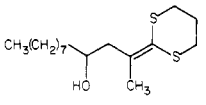
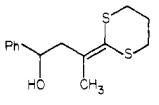
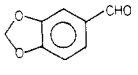
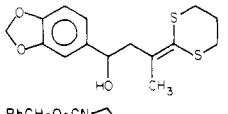
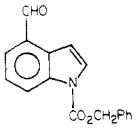
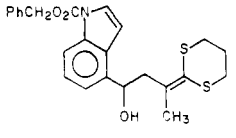
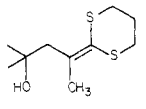
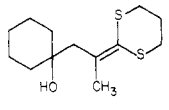
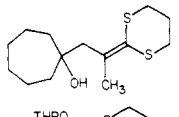
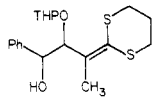
may be rationalized by the notion of hard and soft acids and bases. The four-and five-membered-ring ketones possess a carbonyl group which can be characterized as being harder (more s character in the C–O bond) and thus can be anticipated to react at the *harder α-site* of the ketene thioacetal anion. (b) Anion **6** functions in a synergistic mode, for both the oxygen and sulfur atoms direct γ to sulfur. (c) Transformation of the addition products to γ-lactones is readily brought about by hydrolysis in the presence of mercuric chloride/mercuric oxide (Table II).

Since the ketene thioacetals are most conveniently prepared by the procedure of Jones and Lappert from 2-lithio-2-(trimethylsilyl)-1,3-dithiane and a carbonyl compound,[7] ready access to diversely substituted γ-lactones is easily achieved by varying either of the two carbonyl components (A or B) employed in the reaction sequence (Scheme I).

(1) Fellow of the Alfred P. Sloan Foundation, 1978–1980.
(2) D. Caine and A. Frobese, *Tetrahedron Lett.*, 883 (1978); 5167 (1978), and references cited therein.
(3) Seebach has previously recorded the addition of two ketene thioacetals to benzophenone and the hydrolysis of one of the addition products to a γ-lactone. The generation of a mixture of α- and γ-products was suggested to take place with other aldehydes and ketones. See D. Seebach and M. Kolb, *Justus Liebigs Ann. Chem.*, 811 (1977). The generality of this approach to γ-lactones thus remained to be established.
(4) D. Seebach, M. Kolb, and B.-Th. Gröbel, *Tetrahedron Lett.*, 3171 (1974). E. J. Corey and A. P. Kozikowski, *ibid.*, 925 (1975). Allylation of ketene thioacetals can be directed toward the α-position by employing cuprous salts: F. E. Ziegler and C. C. Tam, *J. Org. Chem.*, **44**, 3428 (1979). For a study of the effect of electrophile hardness on the site of alkylation of metallated ketene thioacetals, see W. S. Murphy and S. Wattanasin, *Tetrahedron Lett.*, 1827 (1979).
(5) A. P. Kozikowski and K. Isobe, *Tetrahedron Lett.*, 833 (1979), and references cited therein.
(6) No change in the ratio of regioisomers for entry 6 was observed on allowing the reaction to proceed for longer periods of time.
(7) P. F. Jones and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 526 (1972).

0022-3263/80/1945-2236$01.00/0

Table I. Reaction of Metalated Ketene Thioacetals with Carbonyl Compounds

entry	aldehyde or ketone	ketene thioacetal anion	product[a]	isolated yield, %
1		4		50
3		4		61
2				52
4		4		73
5		4		78
6		4		69 (+ 16% γ)
7	$CH_3(CH_2)_7CHO$	5		47
8	PhCHO	5		80
9		5		62
10		5		71[b]
11		5		30
12		5		46
13		5		41
14	PhCHO	6		95

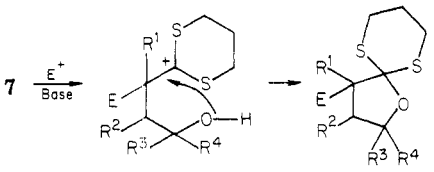
[a] In a few cases, trace amounts of the other regioisomers were detectable. [b] This reaction was performed with inverse addition.

To use this chemistry to assemble α,β-unsaturated butenolides, the primary objective of these investigations, one could reasonably consider the introduction of a double bond into the γ-lactones available from the mercury(II) hydrolysis by a selenenylation (or sulfenylation), oxidation, syn-elimination sequence. This chemistry has, of course, already been thoroughly documented by a number of workers.[8]

We recognized, however, that it should be possible to create a unique approach to the butenolides through use of the ability of the ketene thioacetal double bond to react

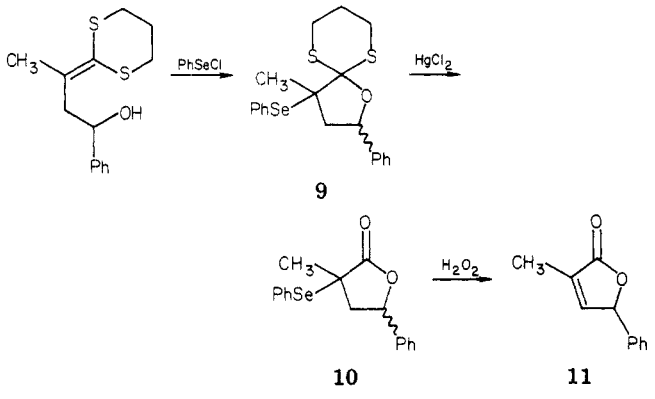
(8) B. M. Trost, T. N. Salzmann, and K. Horoi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973); P. A. Grieco and J. J. Reap, *Tetrahedron Lett.*, 1097 (1974).

with electrophilic agents. Accordingly, exposure of 7 to an electrophilic group (one that could later be eliminated,



such as Br^+ or $PhSe^+$) might generate a sulfur stabilized carbocation (dithienium ion) which could in turn be intercepted by the nucleophilic hydroxyl oxygen.[9] The overall process would thus generate a dithiaoxaspirodecane, a doubly protected butenolide ring system.

In pursuit of this strategy, we chose the commercially available phenylselenenyl chloride as the initiating electrophile. Reaction of the ketene thioacetal derived from 5 and benzaldehyde (entry 8) with this reagent at −78 °C in the presence of triethylamine directly affords the dithiaoxaspirodecane 9 on workup. Mercuric chloride hydrolysis provides the selenenylated lactone 10. Subsequent addition of hydrogen peroxide to this intermediate then produces the desired butenolide in moderate overall yield.



When this cyclization method is applied to other γ-hydroxyketene thioacetals (e.g., products listed in entries 7 and 12, Table I), none of the corresponding dithiaoxaspirodecanes are isolated. Aqueous workup provides only the corresponding γ-lactones in low yield, thus indicating that the phenylselenenyl ion probably attacks the sulfur atom instead of the double bond. While we have no good explanation to offer for this dichotomy in behavior, it does appear that the present method of butenolide generation is quite limited in scope.

The work reported herein thus establishes the ability of ketene thioacetals to behave as β-lithiopropionate equivalents toward carbonyl compounds. The preparation of a ketene thioacetal anion possessing an eliminatable group at its γ-position (e.g., PhS) might, on the other hand, provide access to a more generalized β-lithioacrylate equivalent, one that on reaction with a carbonyl compound and subsequent hydrolysis could lead directly to the butenolide system. This possibility is currently under exploration.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian T-60A spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin–Elmer 247 grating spectrophotometer. High-resolution mass spectra were recorded on a Varian MAT CH5 mass spectrometer.

The ketene thioacetals used in these experiments were prepared by the published methods. *sec*-Butyllithium was purchased from Ventron as a 1.4 M solution in hexane. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl. *N,N,N',N'*-tetramethylethylenediamine was distilled from calcium hydride and stored over molecular sieves. The generation of the ketene thioacetal anions and their addition to carbonyl compounds were conducted under an argon atmosphere.

Exemplary Procedures. Preparation of 2-(1-Methyl-3-hydroxy-3-phenylpropylidene)-1,3-dithiane. To 2-isopropylidene-1,3-dithiane (0.64 g, 4 mmol) in 10 mL of dry THF cooled to −78 °C was added dropwise 3.6 mL (5 mmol) of 1.4 M *sec*-BuLi. After the mixture was stirred for 15 min at this temperature, the dry ice/2-propanol bath was replaced by an ice bath and 10 mL of TMEDA was added. After 15 min at 0 °C, the light yellow solution was cooled to −78 °C and 0.4 mL (4 mmol) of freshly distilled benzaldehyde was introduced. The now colorless solution was stirred for an additional 30 min, then quenched with saturated ammonium chloride, and extracted with ether. The extract was dried ($MgSO_4$) and freed of solvent. Chromatography of the residue on silica gel with 25% ethyl acetate–hexane afforded 0.85 g (80%) of the γ-hydroxyketene thioacetal as a colorless oil: IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (br s, 5 H), 4.60–5.00 (m, 1 H), 2.50–3.05 (m, 6 H), 1.95–2.30 (m, 2 H), 1.90 (s, 3 H); exact mass, *m/e* 266.0803 (calcd for $C_{14}H_{18}OS_2$ 266.0799).

Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone. A mixture of the above adduct (60 mg, 0.225 mmol), mercuric chloride (158 mg, 0.582 mmol), and mercuric oxide (59 mg, 0.272 mmol) in 4 mL of wet acetone (10% water) was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue extracted with methylene chloride/hexane (1:1). The extract was dried ($MgSO_4$), filtered, and concentrated to afford 20 mg (50%) of spectroscopically pure lactone: IR ($CHCl_3$) 1763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 5.20–5.60 (m, 1 H), 1.33 (d, 3 H, J = 6 Hz); exact mass, *m/e* 176.0842 (calcd for $C_{11}H_{12}O_2$ 176.0837).

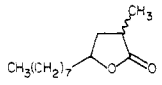
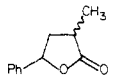
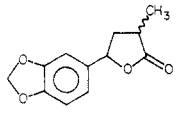
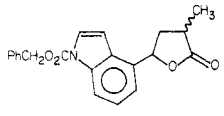
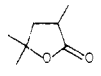
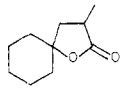
Preparation of 2-Vinyl-2-(1-hydroxycyclobutyl)-1,3-dithiane. A solution of lithium diisopropylamide was prepared by the addition of 1.79 mL (2.87 mmol) of a 1.60 M solution of *n*-butyllithium in hexane to a cold (0 °C) solution of 0.40 mL (2.87 mmol) of diisopropylamine in 4 mL of dry tetrahydrofuran. A solution of 2-ethylidene-1,3-dithiane (0.42 g, 2.87 mmol) in 2 mL of dry tetrahydrofuran and 0.433 mL (2.87 mmol) of TMEDA were added sequentially by syringe. After 20 min at 0 °C, 0.214 mL (2.87 mmol) of cyclobutanone was added to the now red reaction mixture. A saturated solution of ammonium chloride was added after an additional 30 min, and the reaction mixture was extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The crude isolated product was chromatographed on silica gel with 15% ethyl acetate–hexane to yield 98 mg (15.8%) of γ-addition product and 430 mg (69%) of α-addition product: IR (neat) 3475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40–6.20 (m, 3 H), 2.70 (m, 4 H), 1.40–2.60 (m, 9 H); exact mass, *m/e* 216.0648 (calcd for $C_{10}H_{16}OS_2$ 216.0643).

Phenylselenenyl Chloride Induced Ring Closure of 2-(1-Methyl-3-hydroxy-3-phenylpropylidene)-1,3-dithiane. To a solution of the γ-hydroxyketene thioacetal (120 mg, 0.45 mmol) and triethylamine (125 μL, 0.9 mmol) in 4 mL of THF cooled to −78 °C was added dropwise a solution of phenylselenenyl chloride (130 mg, 0.68 mmol) in 2 mL of THF. After 30 min at this temperature, the reaction mixture was warmed to room temperature and concentrated under reduced pressure. The residue was chromatographed on silica gel with 5% ethyl acetate–hexane to yield 122 mg (64%) of the dithiaoxaspirodecane. This compound was directly subjected to the following hydrolysis reaction.

Hydrolysis of 9 to Dihydro-3-(phenylseleno)-3-methyl-5-phenyl-2-furanone (10). A mixture of 9 (62 mg, 0.147 mmol), mercuric chloride (80 mg, 0.294 mmol), and mercuric oxide (38 mg, 0.176 mmol) in 5 mL of wet acetone (10% water) was stirred overnight at room temperature. The mixture was concentrated in vacuo and the residue extracted with methylene chloride/hexane (1:1). The extract was dried ($MgSO_4$), filtered, and concentrated to leave an oil. This oil was chromatographed on silica gel with 25% ethyl acetate–hexane to afford 25 mg (51%) of the desired selenenylated lactone 10: IR ($CHCl_3$) 1765 cm^{-1}; NMR ($CDCl_3$) δ 7.00–8.00 (10 H), 5.45 (d of d, 1 H), 1.95–3.00

(9) A dithienium ion generated by protonation of a ketene thioacetal has been used in a cation–olefin cyclization. See N. H. Anderson, Y. Yamamoto, and A. D. Denniston, *Tetrahedron Lett.*, 4547 (1975).

Table II. $HgCl_2$ Hydrolysis Products

ketene thioacetal[a]	γ-lactone	isolated yield, %
7		64
8		55
9		69
10		47
11		40
12		65

[a] Entry number from Table I.

(8 lines of ABX, 2 H), 1.66 (s, 3 H); exact mass, m/e 332.0314 (calcd for $C_{17}H_{16}{}^{80}SeO_2$ 332.0316).

Conversion of 10 to 3-Methyl-5-phenyl-2(5*H*)-furanone (11). To a solution of the α-phenylseleno lactone **10** (21 mg, 0.063 mmol) in 1 mL of methylene chloride at room temperature was added 12 μL of pyridine (2.4 equiv) followed by 63 μL (8.8 equiv) of 30% hydrogen peroxide. After being stirred for 1 h, the reaction mixture was dried ($MgSO_4$), filtered, and concentrated to afford 5 mg (45%) of the spectroscopically pure butenolide:[10] IR ($CHCl_3$) 1750 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (m, 5 H), 7.17 (m, 1 H), 5.88 (m, 1 H), 2.00 (m, 3 H); exact mass, m/e 174.0681 (calcd for $C_{11}H_{10}O_2$ 174.0681).

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Registry No. **1**, 51102-62-6; **2**, 36998-38-6; **3**, 73262-31-4; **7** (R^1 = R^2 = R^3 = H, R^4 = 3-pyridyl), 73262-32-5; **7** (R^1 = R^2 = R^3 = H, R^4 = *M*-anisyl), 73262-33-6; **7** (R^1 = R^2 = H, R^3 = R^4 = 4-*tert*-butyl-1,1-cyclohexylidene), 73262-34-7; **7** (R^1 = R^2 = H, R^3 = R^4 = 2-methyl-1,1-cyclohexylidene), 73262-35-8; **7** (R^1 = CH_3, R^2 = R^3 = H, R^4 = $(CH_2)_7CH_3$), 73262-36-9; **7** (R^1 = CH_3, R^2 = R^3 = H, R^4 = Ph), 73262-37-0; **7** (R^1 = CH_3, R^2 = R^3 = H, R^4 = 1,3-benzodioxol-5-yl), 73274-29-0; **7** (R^1 = CH_3, R^2 = R^3 = H, R^4 = 1-[(phenylmethyloxy)carbonyl]indol-4-yl), 73262-38-1; **7** (R^1 = R^3 = R^4 = CH_3, R^2 = H), 73262-39-2; **7** (R^1 = CH_3, R^2 = H, R^3 = R^4 = 1,1-cyclohexylidene), 73262-40-5; **7** (R^1 = CH_3, R^2 = H, R^3 = R^4 = 1,1-cycloheptylidene), 73262-41-6; **7** (R^1 = CH_3, R^2 = OTHP, R^3 = H, R^4 = Ph), 73262-42-7; **8** (R^1 = CH_3, R^2 = R^3 = H, R^4 = $(CH_2)_7CH_3$), 73262-43-8; **8** (R^1 = CH_3, R^2 = R^3 = H, R^4 = Ph), 10606-64-1; **8** (R^1 = CH_3, R^2 = R^3 = H, R^4 = 1,3-benzodioxol-5-yl), 73262-44-9; **8** (R^1 = CH_3, R^2 = R^3 = H, R^4 = 1-[(phenylmethyloxy)carbonyl]indol-4-yl), 73262-45-0; **8** (R^1 = R^3 = R^4 = CH_3, R^2 = H), 2610-96-0; **8** (R^1 = CH_3, R^2 = H, R^3 = R^4 = 1,1-cyclohexylidene), 16149-84-1; **9**, 73262-46-1; **10**, 73262-47-2; **11**, 15121-75-2; 2-vinyl-2-(1-hydroxycyclopentyl)-1,3-dithiane, 73262-48-3; 2-vinyl-2-(1-hydroxycyclobutyl)-1,3-dithiane, 73262-49-4; 2-vinyl-2-(3-oxocyclobutyl)-1,3-dithiane, 73262-50-7; 3-pyridinecarboxaldehyde, 500-22-1; 3-methoxybenzaldehyde, 591-31-1; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclohexanone, 583-60-8; cyclopentanone, 120-92-3; cyclobutanone, 1191-95-3; nonanal, 124-19-6; benzaldehyde, 100-52-7; 1,3-benzodioxole-4-carboxaldehyde, 120-57-0; benzyl 4-formylindole-1-carboxylate, 73262-51-8; acetone, 67-64-1; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; phenylselenenyl chloride, 5707-04-0.

(10) S. Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1480 (1975).