and $CH_2ClSSO_2CH_3$ (δ 5.20 and 3.50, 68%).

Reaction of Methanesulfinyl Chloride with Excess Pyridine. The general procedure described above was used with methanesulfinyl chloride (0.98 g, 10 mmol) and pyridine (2.37 g, 30 mmol). After workup, ^1H NMR analysis ($CDCl_3$) of the organic products gave resonances at δ 3.32 and 2.71 ($CH_3SSO_2CH_3$) and δ 5.21 and 3.51 ($CH_2ClSSO_2CH_3$).

***S*-Alkyl and *S*-1-Chloroalkyl Alkanesulfonothioates 4 and 5. General Procedures.** In a flame-dried nitrogen-flushed 10-mL round-bottomed flask fitted with a septum was placed 10 mmol of alkanesulfinyl chloride via a glass syringe fitted with a Teflon needle under predried deoxygenated dinitrogen flow. Dry amide (30 mmol) was added via syringe. The reaction mixture was magnetically stirred at 22 to 24 °C under a dinitrogen atmosphere until TLC analysis showed the absence of alkanesulfinyl chloride. The reaction mixture was transferred to a 60-mL separatory funnel which contained 10 mL of deionized water. The solution was extracted (3×) with 10 mL of diethyl ether. The combined organic solution was dried (Na_2SO_4). After solvent removal, the product mixture was purified via flash column chromatography and then analyzed for 4 and 5 via ^1H NMR and ^{13}C NMR. Product yields were based on relative integral values from ^1H NMR. In some cases the product mixture (4 and 5) was separated via flash column chromatography.

The general procedure described above was used (50-mL round-bottom flask containing 25 mL of dry solvent) in order to study solvent effects (Table I).

Reaction of Alkanesulfinyl Chlorides and Benzenesulfinyl Chloride; General Procedure. In a flame-dried dinitrogen-flushed 25-mL round-bottom flask fitted with a septum were placed 0.74 g (7.5 mmol) of methanesulfinyl chloride and 0.40 g (2.5 mmol) of benzenesulfinyl chloride under an inert atmosphere. While stirring under dinitrogen flow, 2.19 g (30 mmol) of DMF was added via syringe. The reaction mixture was stirred under a dinitrogen atmosphere until the reaction was complete (48–96 h, TLC analysis). The product mixture was purified via flash column chromatography, eluting with 1 L of ethyl ethanoate–hexanes–trichloromethane (1:4:1 v/v). After solvent removal, the first fraction (R_f 0.50) gave evidence for *S*-1-chloromethyl benzenesulfonothioate (6) and *S*-phenyl benzenesulfonothioate (8). The second fraction (R_f 0.33) gave evidence for *S*-chloromethyl methanesulfonothioate (5) and *S*-phenyl methanesulfonothioate (7). In some experiments, HPLC (vide supra) was used to separate the product mixture.

The general procedure described above was also used to study the effects of radical inhibitors during the reaction of alkanesulfinyl chlorides, benzenesulfinyl chloride, and DMF (Table III).

Prepareation of *S*-1-Chloropropyl Methanesulfonothioate (9). Fresh white globe onions (1 kg) were peeled, quartered, and frozen in dry ice in a cold room (0 °C). The frozen onions were crushed to a powder, and the powder was placed in 1 L of trichlorofluoromethane in a blender. The mixture was blended for 10 min, and the $CFCl_3$ layer was separated and then dried over $MgSO_4$. The $CFCl_3$ solution was placed in a round-bottomed flask at −78 °C and the $CFCl_3$ was distilled into a flask at −100 °C (0.2 mm). Distillation of the residue (−20 °C; 0.05 mm) into a flask at −100 °C gave propanethial *S*-oxide: ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H), 2.79 (q, 2 H), 8.18 (t, 1 H).[32]

To propanethial *S*-oxide in a 25-mL round-bottomed flask at −40 °C was added dropwise 0.98 g (0.01 mmol) of methanesulfinyl chloride in 10 mL of $CFCl_3$. The product mixture was warmed to 22–24 °C, and the excess methanesulfinyl chloride was removed by chromatography on silica gel using 1:9 ethyl ethanoate/hexanes as eluant. *S*-1-Chloropropyl methanesulfonothioate (9)[3,32,33] was the only product isolated: ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H), 2.15 (q, 2 H), 5.60 (t, 1 H), 3.50 (s, 1 H).

Acknowledgment is made to the National Science Foundation (CHE-86-19651) for support of this research and for assistance in the purchase of the NMR spectrometers and to the University of California, Irvine Research Committee for the purchase of the RI detector. Thanks are extended to Professor Sir Derek H. R. Barton, Institut de Chimie des Substances Naturelles, for his gracious hospitality during the preparation of this manuscript.

Synthesis of α-Pyrones from Vinylogous Thiol Esters and α-Oxo Ketene Dithioacetals†

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Vinylogous thiol esters and α-oxo ketene dithioacetals can be converted into α-pyrones by a strategy involving 1,2-nucleophilic addition of ester, ketone, or hydrazone enolate anions, followed by acid-promoted rearrangement to a δ-keto ester, thiol ester, or acid and subsequent enol lactonization. These multistep procedures can be carried out without isolation and purification of intermediates and afford α-pyrones in good overall yields. The synthetic routes are complementary in terms of substitution patterns and limitations.

Introduction

We have, over the past few years, developed several synthetic routes to α-pyrones [2*H*-pyran-2-ones] from β-(alkylthio)-α,β-unsaturated ketones (vinylogous thiol esters)[1] and α-oxo ketene dithioacetals.[2] These procedures emerged from extensive studies on the chemistry of α-oxo ketene dithioacetals[3] which have proven to be versatile three-carbon synthons that provide ample opportunities for the regio-, stereo-, and chemoselective construction of new carbon–carbon bonds. The basic strategy (Scheme I) in these approaches involves the 1,2-nucleophilic addition of an ester, ketone, or hydrazone enolate anion to the carbonyl carbon of a vinylogous thiol ester or α-oxo ketene dithioacetal, followed by an acid-promoted 1,3-carbonyl transposition and enol lactonization to afford the α-pyrone. The execution of these approaches was dependent upon the successful development of the chemoselective reactions of α-oxo ketene dithioacetals with organocuprates[4] and of the utilization of α-oxo ketene di-

† Dedicated to Professor Walter J. Gensler, 1917–1987.

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(3) For a review, see: Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029.

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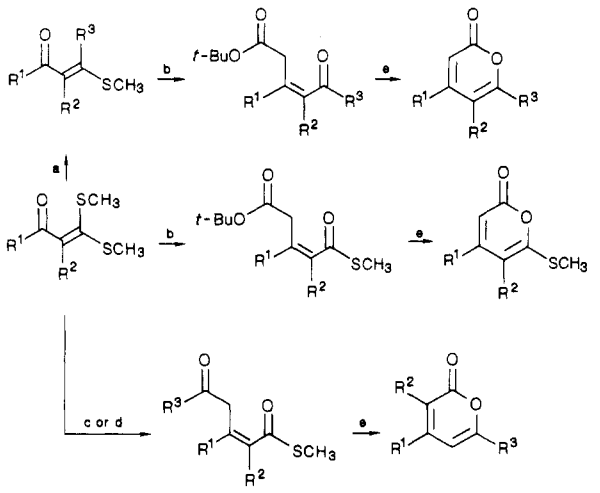
Scheme I[a]



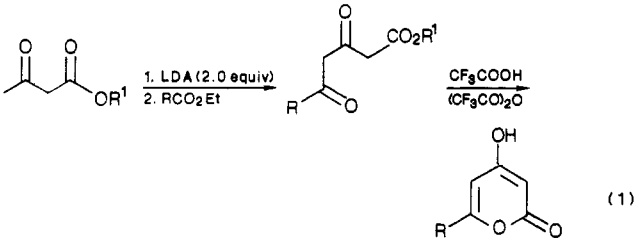
[a] (a) $(R^3CuSPh)Li$; (b) $LiCH_2CO_2$-*t*-Bu; (c) R^3COCH_2Li; (d) $R^3C(=NNMe_2)CH_2Li$; (e) ester hydrolysis and enol lactonization.

thioacetals in a 1,3-carbonyl transposition[5] process. These approaches to α-pyrones are complementary in terms of synthetic objectives and opportunities. The synthetic route from α-oxo ketene dithioacetals via vinylogous thiol esters allows for the introduction of alkyl substituents at all four olefinic carbon atoms of the pyrone ring but will be limited for 3-alkylpyrones because of the need to use α-substituted acetate enolates. The direct utilization of α-oxo ketene dithioacetals provides an efficient entry into 6-(alkylthio)-α-pyrones and a shorter route to alkyl-substituted pyrones employing ketone enolates. Use of ketone enolates is limited by their reluctance to participate in aldol additions with other ketones[6,7] and this problem can be partially solved by utilization of hydrazone enolates.[8] The 3-substituent is derived from the α-oxo ketene dithioacetals when ketone enolates are employed and provides a different regiochemistry in annulation strategies than the vinylogous thiol ester route.

An initial report demonstrated that both cyclic and acyclic vinylogous thiol esters could be cleanly converted into α-pyrones[1] and a latter report[2] focused on the preparation of 6-(alkylthio)-α-pyrones and the use of ketone enolates. In this full account of our work, the effect of substitution patterns in the reactants, the sensitivity of the ester enolate and aldol addition products to acid-promoted hydrolysis and rearrangement, the use of hydrazone enolates, and limitations of the routes are examined in detail. The use of an aldehyde-derived ketene dithioacetal has also been utilized in the synthesis of an α-pyrone with no alkyl substituent in the 4-position. Although the synthetic routes to α-pyrones are multistep and involve transformations that are occasionally fickle and sensitive to reaction conditions, these detailed studies have shown that high overall yields of α-pyrones can be obtained without isolation and purification of intermediate products.

Background

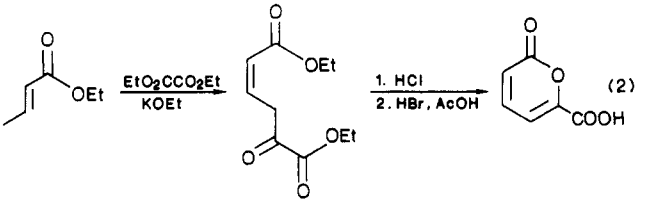
The synthesis of α-pyrones[9] has generally focused on the preparation of δ-keto acids that can be cyclized to α-pyrones under acidic reaction conditions. Many of these procedures lead to carbalkoxy-substituted α-pyrones that can afford alkyl-substituted derivatives in indirect procedures involving decarboxylation. Decarboxylation occurs readily at the 3- and 5-positions of the pyrone ring[9a] under strongly acidic conditions and can also be effected at the 6-position with copper powder.[10] The 4-hydroxypyrones represent an important pyrone substitution pattern that can be exploited in the synthesis of alkyl-substituted analogues. Treatment of the 4-hydroxypyrone with $POCl_3$ affords the 4-chloro analogue, which can be reductively cleaved with zinc in acetic acid.[11] The most facile route to 4-hydroxy-α-pyrones involves acylation of β-keto ester dienolate dianions (eq 1).[12]



(1)

Three principal strategies have been developed for pyrone synthesis. These include γ-acylation of an ester dienolate or equivalent, reaction of a ketone enolate with a 2-carbalkoxy vinyl cation equivalent (e.g., α,β-acetylenic esters, β-diacid dichlorides), and reaction of an ester enolate anion with a 2-acyl vinyl cation equivalent (e.g., an α,β-acetylenic ketone, β-chloro α,β-enone) which is the most widely applied strategy.

The first strategy is represented by the facile dienolate dianion approach[12] to 4-hydroxy pyrones (eq 1) and has been applied to simple dienolates[10,11] with oxalic esters (eq 2). γ-Acylation of an ester dienolate with an acid chloride



(2)

could provide the 3,4,5,6-tetraalkyl substitution pattern. Although this direct approach appears not to have been employed, dihydropyrones have been prepared by alkylation of ester dienolates with aldehydes.[13] Friedel–Crafts acylation of glutaconic anhydrides[14] (via the 6-hydroxypyrone tautomer) and β,γ-unsaturated esters[15] represents

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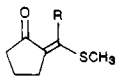
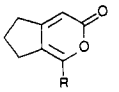
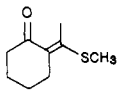
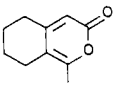
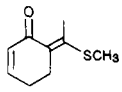
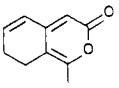
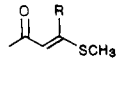
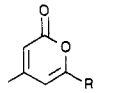
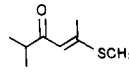
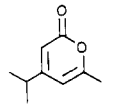
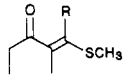
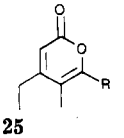
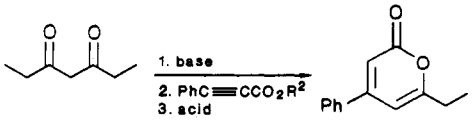
Table I. Synthesis of α-Pyrones from Vinylogous Thiol Esters via *tert*-Butyl δ-Keto-β,γ-unsaturated Esters 14

entry	substrate	R	yield[a] from 14,[b] %	overall yield,[a] %	product
					
1	1	H	80	71[c]	16
2	2	Me	93	82[d]	17
3	3	*sec*-Bu		70[c,e]	18
					
4	4		94	70[d]	19
					
5	5		99	66[d]	20
					
6	6	Me		72[c,f]	21
7	7	*n*-Bu	95	88[d]	22
8				52[c,f]	
9	8	*sec*-Bu	91	62[d]	23
					
10	9		92	84[d]	24
11				76[c,f]	
					
12	10	H		49[c]	25
13	11	Me	91	67[d]	26
14				81[c,f]	

[a] Yields are based upon isolated products purified by medium pressure liquid chromatography (MPLC). [b] Purified δ-keto ester was employed [CF_3COOH, $(CF_3CO)_2O$]. [c] Overall yield of α-pyrone from the vinylogous thiol ester without purification of intermediates. [d] Overall yield is the product of the individual yields of δ-keto ester (eq 6) and α-pyrone (Table I) formation. [e] The *tert*-butyl ester was hydrolyzed upon treatment of the allylic alcohol with HBF_4 and this is the yield of α-pyrone from the δ-keto acid. [f] α-Pyrone was formed directly from the ester enolate addition product upon treatment with HBF_4 for longer (16 h) periods of time.

an indirect approach and has been exploited in syntheses of 4,6-dialkyl-substituted pyrones.

The second and third strategies are formally the same except for the roles of the ketone and ester components, which are interchanged. Reaction of symmetrical β-diketone enolates with acetylenic esters leads to either 4,6-dialkyl- (eq 3)[16] or 4,5,6-trialkylpyrones.



(3)

In the third strategy the ester component functions as the nucleophile and the ketone moiety acts as the electrophile.[17] This strategy has frequently involved the

(15) (a) Pittet, A. O.; Schuster, E. J. U.S. Pat. 3 996 170. (b) Vinals, J. F.; Quin, A. D.; Pittet, A. O. U.S. Pat. 3 890 981 and 3 861 403. (c) Klaiber, E. M.; Pittet, A. O. U.S. Pat. 3 946 054.

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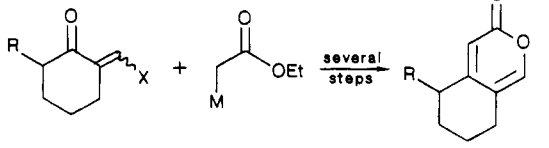
Table II. Aldol Reactions of Ketone Metal Enolates with α-Oxo Ketene Dithioacetals

substrate	enolate[b]	% yield[a] aldol product counterion (M^+) Li	Zn	Ce
32a	A	91	62	56
	B	44	32	
	C	24	30	
32b	A	93		
	B		20	
	C	9	25	
32c	A	36	19	40
	B		3	
	C	3	17	
32d	A	12	14	20
	B		5	
	C		15	

[a] Yields are based upon isolated products purified by MPLC. [b] A = $Me_2CHCOCH_2M$. B = $CH_3CH_2COCHMCH_3$. C = enolate of cyclohexanone.

Michael reactions of malonates or β-keto esters with α,β-acetylenic ketones[18] or β-chloro[19] (or β-alkoxy)[11] α,β-enones. These procedures give rise to 3-carbalkoxy-α-pyrones, which are readily decarboxylated with strong acid. Use of acetylenic ketones affords 4,6-dialkyl-substituted α-pyrones, although use of substituted malonates would afford 3,4,6-trialkyl-α-pyrones. Although the β-chloro α,β-enones could in principle provide greater substitution patterns, this is limited by their general preparation from β-diketones which is largely restricted to symmetrical diketones. Nevertheless, the simple enones[19] provide a facile route to 6-alkylpyrones or 3,6-dialkylpyrones from substituted β-diketones.

The use of α,β-enones containing a good leaving group at the β-carbon atom does not require conjugate addition–elimination since a 1,2-nucleophilic addition in conjunction with a 1,3-carbonyl transposition can be employed. This variation of the third strategy provides for different regioisomers or substitution patterns and allows for the use of simple ester enolates in place of the malonates. This strategy has been employed with vinylogous acids,[20a] esters,[20b] and thio esters[20c] (eq 4). Only the vinylogous thiol esters afforded good yields of pyrones and the method was limited by the inability to easily introduce substituents into the 6-position of the pyrone ring.



(4)

R	X	M	% yield
H	OH	Zn	25
H	$OCOCH_3$	Zn	23
Me	^{n}BuS	Li	66

(17) The complementarity of the two strategies is illustrated by the dimerization of ethyl acetoacetate which is reported to give different pyrones under different reaction conditions. See: (a) Gross, F. R.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1923**, 327. Hantzsch, A. *Liebigs Ann. Chem.* **1883**, *222*, 1. (b) Arndt, F. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 231. Geuther, A. *Z. Chem.* **1886**, 8.

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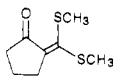
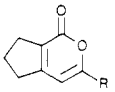
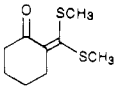
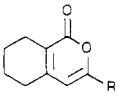
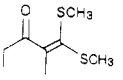
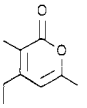
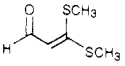
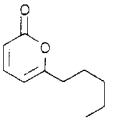
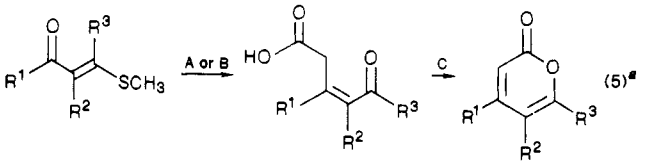
Table III. Synthesis of α-Pyrones from α-Oxo Ketene Dithioacetals and Ketone or Hydrazone Enolate Anions

entry	substrate	enolate[b]	% yield[a] from (cpd)	overall yield,[a,c] %	product
					
1	**32a**	A	96 (**37a**)[d]	42[e]	**39**, R = *i*-Pr
2		45	90 (**48a**)[d]	75–78	**40**, R = Me
					
3	**32b**	A	52 (**38b**)[f]	32[f]	**41**, R = *i*-Pr
4				48[f]	
5		45	98 (**48c**)[d]	73	**42**, R = Me
					
6	**32c**	45	92 (**50**)[d]	80	**43**
					
7	**51b**	B		37[g]	**44**

[a] Yields are based upon isolated products purified by MPLC. [b] A = $Me_2CHCOCH_2Li$. B = $C_5H_{11}C(NLiNMe_2)CH_2$. [c] Overall yield of pyrone from α-oxo ketene dithioacetal without purification of intermediates unless otherwise noted. [d] Cyclization to pyrone was achieved with HgOAc, CF_3COOH, and $(CF_3CO)_2O$. [e] Overall yield based upon purified intermediates. [f] Cyclization to pyrone was achieved with 0.7–1.5 M HBF_4 in THF. [g] Cyclization to pyrone was effected with $HgCl_2$ in CH_3CN/H_2O heated to reflux followed by treatment with CF_3COOH.



12

substr	R^1	R^2	R^3	reactn condn	δ-keto acid	% yield[b]	pyrone	% yield[b]
2	$-(CH_2)_3-$		Me	A	**12a**	55		
				B		63–72	**17**	95
4	$-(CH_2)_4-$		Me	B	**12b**	77	**19**	70
9	*i*-Pr	H	Me	B	**12c**[c]	24	**24**	93
11	Et	Me	Me	A	**12d**[c]	43	**26**	90
				B		25		

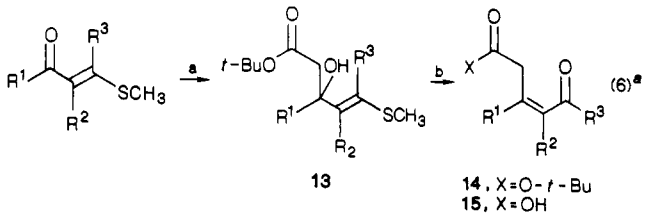
[a] A = $LiCH_2CO_2Li$, THF/HMPA, rt. B = $LiCH_2CO_2SiMe_3$, THF, −78 °C. C = $(CF_3CO)_2O$. [b] Yields are based upon isolated products purified by column chromatography or MPLC. [c] A mixture of *E* and *Z* isomers.

Alkyl-substituted pyrones have also been prepared by the reaction of enamines with 2 equiv of ketene[21] and in low yields by flash vacuum pyrolysis of an epoxy ketone.[22] α-Pyrones have also been prepared by the conjugate addition of methyl 2-lithio-2-(phenylthio)acetate to α,β-enones[23] and butadienolides have been prepared by the addition of 1-(phenylthio)-1-(trimethylsilyl)-2-propene to α-alkoxy C20 steroidal ketones.[24] More recently, α-pyrones have been prepared by transformations involving transition-metal reagents[25] although these procedures do not provide for the synthesis of annulated α-pyrones.

α-Pyrones from Vinylogous Thiol Esters. Vinylogous thiol esters **2–9** and **11** (Table I) were prepared (62–96% yields) by reaction of lithium alkylphenylthiocuprates with the appropriate α-oxo ketene dithioacetals according to an established procedure.[4] Substrate **1** was prepared (32%) according to the procedure of Ireland and Marshall[26] while **10** was prepared in 68% yield by reduction[27] of the corresponding α-oxo ketene dithioacetal (i.e. **32c**).

The synthetic strategy outlined in Scheme I required the addition of an acetate unit to the ketone functionality of the vinylogous thiol esters. In a preliminary study, the efficiency of carboxylic acid dianions and of various ester enolate anions in 1,2-nucleophilic addition reactions to the ketone carbonyls was examined. The dianion of acetic acid[28] was prepared according to a literature procedure[29]

(21) Berchtold, G. A.; Harvey, G. R.; Wilson, G. E. *J. Org. Chem.* **1965**, *30*, 2642.
(22) Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557.
(23) Bornak, W. K., Jr. *Diss. Abstr. Int. B* **1981**, *42*, 208; *Chem. Abstr.* **1981**, *95*, 168918r.
(24) Bauer, P. E.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 34 and references cited therein.
(25) (a) Semmelhack, M. F.; Tamura, R. *J. Am. Chem. Soc.* **1983**, *105*, 4099. (b) Semmelhack, M. F.; Tamura, R.; Schnatter, W.; Springer, J. *Ibid.* **1984**, *106*, 5363. (c) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2634.
(26) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 6336.
(27) Myrboh, B.; Singh, L. W.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 307.
(28) For a review on carboxylic acid dianions, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.



substr	R^1	R^2	R^3	allylic alcohol	δ-keto ester	% yield[b] (E:Z)[c]
1	$-(CH_2)_3-$		H	**13a**	**14a**	32
2	$-(CH_2)_3-$		Me	**13b**	**14b**	88
3	$-(CH_2)_3-$		*sec*-Bu	**13c**	**15**[d]	64–73[d]
4	$-(CH_2)_4-$		Me	**13d**	**14d**	74
5	$-(CH{=}CHCH_2CH_2)-$		Me	**13e**	**14e**[e]	58–67
7	Me	H	*n*-Bu	**13f**	**14f**	93 (3:2)
8	Me	H	*sec*-Bu	**13g**	**14g**	68 (7:3)
9	*i*-Pr	H	Me	**13h**	**14h**	91 (1:1)
10	Et	Me	H	**13i**	**14i**	95 (1:1)
11	Et	Me	Me	**13j**	**14j**	74 (1:1)

[a] (a) $LiCH_2CO_2$-*t*-Bu, THF, −78 to −60 °C, 1.75 h; (b) 1.5 M HBF_4, room temperature, 0.5–2 h. [b] Yields are based upon isolated products purified by MPLC. [c] Isomer ratios were determined by NMR. [d] The workup conditions afforded the δ-keto acid **15** instead of the ester **14c**. [e] The ester, acid (10%) and pyrone **20** (10%) were obtained as a complex mixture.

and afforded modest yields of δ-keto acids with both cyclic and acyclic vinylogous thiol esters (eq 5). The dianion was allowed to react with **2** for 2 days at room temperature and generally gave lower yields for both shorter and longer periods of time and at higher reaction temperatures (40 °C, 14 h). In an effort to improve the yields of the nucleophilic addition reaction, acetic acid dianion equivalents were examined. The tetrahydropyranyl ester enolate[30] was examined without success. The enolate anion of trimethylsilyl acetate[31] afforded higher yields of δ-keto acids with the cyclic substrates and lower yields with the acyclic substrates (eq 5). Reaction of the trimethylsilyl acetate enolate with **2** afforded slightly higher yields in THF (eq 5) than in toluene (61%) at −78 °C. Solutions of the trimethylsilyl enolate anion turned milky white above −20 °C and under these conditions afforded very little addition product. The thermal stability of this enolate appears to be similar to that of the methyl and ethyl ester enolates of acetic acid.[32]

Although the trimethylsilyl ester enolates provided facile access to the δ-keto acids, the modest yields warrented examination of additional ester enolate anions. Although *tert*-butyl esters are more difficult to hydrolyze, the *tert*-butyl ester enolates are thermally stable at room temperature under an inert atmosphere.[33] Reaction of vinylogous thiol esters **1–2**, **4–5**, and **7–11** with *tert*-butyl lithioacetate afforded, after rearrangement with HBF_4, δ-keto *tert*-butyl esters **14a,b** and **14d-j** in good to excellent (except for **14a**) isolated yields (eq 6). Quenching the reactions with 2 N HCl afforded the β-hydroxy esters **13**, which underwent rearrangement very slowly under these conditions. Treatment of allylic alcohol **13c** with 2 N HCl for 12 h gave recovered alcohol and after 30 h gave the rearranged δ-keto acid **15** (14%) and recovered alcohol **13c** (68%). The low yield of **14a** appears to be an artifact of purification since crude material gave a good overall yield of the α-pyrone **16** (Table I, entry 1). In general, the highest yields of δ-keto esters were obtained when the reaction mixtures were quenched with 1.5 M HBF_4 at −60 °C, allowed to warm to room temperature, and stirred until rearrangement was complete as determined by TLC. This rearrangement is very sensitive to the concentration of HBF_4 and hence to the volume of solvents employed. Generally, 1.5 M HBF_4 was employed and this was often diluted further by subsequent addition of THF and H_2O to the reaction mixture. It has been noted[20c] that the temperature at which these reactions are quenched can significantly affect the yield of addition product since the reaction is reversible under the workup conditions. Similar yields of **14b** were obtained on 1-mmol (83%) and 20-mmol (93%) scales with 1.6 equiv of *tert*-butyl lithioacetate.

Rearrangement of the acyclic allylic alcohols **13f–j** afforded mixtures of *E*- and *Z*-unsaturated δ-keto esters, the ratios of which could be readily determined from the NMR spectra. The *E* isomers **14f**-E–**14g**-E and **14i**-E–**14j**-E display absorptions (δ 3.02, 3.04, 3.23, and 2.97, respectively) for the γ-methylene protons anti to the ketone carbonyl, which are upfield relative to those for the *Z* isomers (δ 3.60, 3.59, 3.53, and 3.65). In 14h E the γ-methylene protons are syn to the ketone carbonyl and adsorb downfield relative to the *Z* isomer (δ 3.44 vs 2.96).

The HBF_4-promoted rearrangement and hydrolysis of the intermediate γ-hydroxy vinyl sulfides was sensitive to various substitution patterns. The allylic alcohol **13c** underwent rearrangement and ester hydrolysis (HBF_4, 14 h) to the δ-keto acid **15** while the allylic alcohol from **6** underwent rearrangement, ester hydrolysis, and enol lactonization (HBF_4, 16 h) to directly afford α-pyrone **21** in 72% yield (Table I, entry 6). The allylic alcohol **13e** afforded (HBF_4, 1 h) keto ester **14e** (58%), keto acid (10%), and pyrone **20** (10%) with relatively short reaction times. The allylic alcohol **13f** gave results that illustrate the sensitivity of these hydrolysis conditions. Treatment of the alcohol with HBF_4 for 2 h afforded **14f** (93%) while treatment for longer times gave **14f** (5 h, 18%; 14 h, 0%) and pyrone **22** (5 h, 77%; 14 h, 52%). The decreased yield of pyrone **22** over time indicates the necessity of monitoring these HBF_4 rearrangements closely. The products obtained are time-dependent in that short reaction times generally afford δ-keto esters **14** cleanly while mixtures of δ-keto esters, δ-keto acids, and pyrones are obtained with longer reaction times. Best results are obtained when the

(29) (a) Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1970**, *35*, 262. (b) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. *Ibid.* **1972**, *37*, 451. (c) Lawson, J. A.; Colwell, W. T.; DeGraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Synthesis* **1975**, 729.

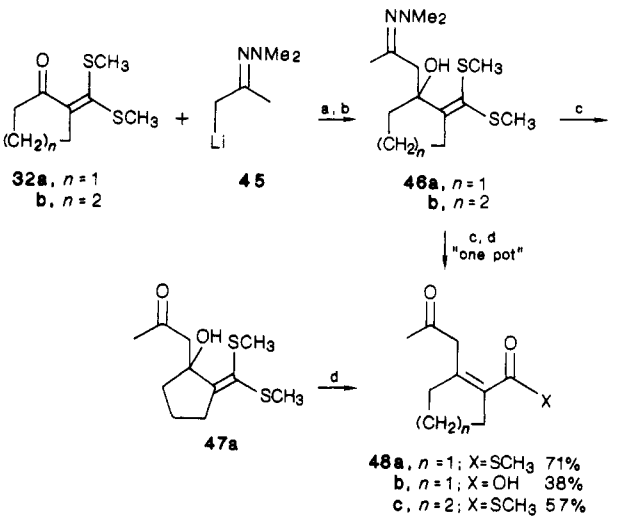
(30) (a) Bernady, K. F.; Floyd, M. B.; Poletto, J. F: Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438. (b) Corey, E. J.; Weigel, L. O.; Chamberlain, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

(31) (a) Banerji, A.; Kalena, G. P. *Synth. Commun.* **1982**, *12*, 225. (b) Rathke, M. W.; Cowan, P. J. *Ibid.* **1983**, *13*, 183.

(32) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

(33) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050.

Scheme II[a]



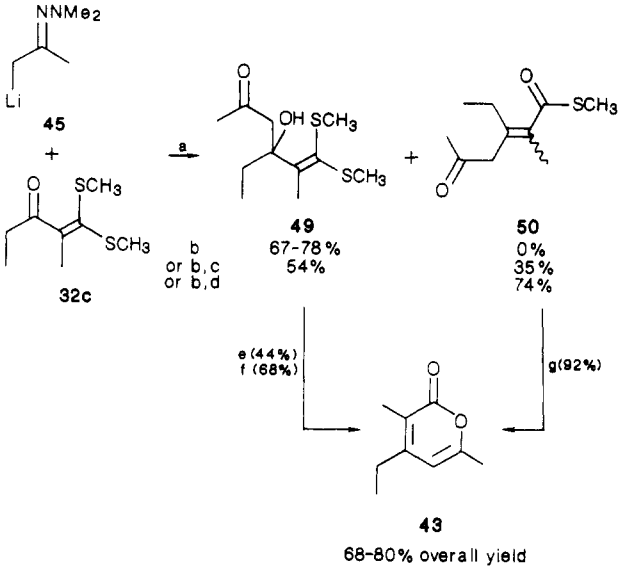
[a] (a) Yield of **47**, solvent: (71%, THF), (80%, Et_2O), (81%, $PhCH_3$), (61%, pentane); (b) $NH_4Cl/NH_4OH/H_2O$, pH 8.5; (c) THF, $CH_3COOH/CH_3CO_2Na/H_2O$ pH 4.5, $Cu(OAc)_2 \cdot H_2O$, 14 h; (d) THF, H_2O, HBF_4, HgO (1.0 equiv for **48a,c**, 0.5–1 h; 4.6 equiv for **48b**, 36 h).

reaction is stopped after complete disappearance of the allylic alcohol, although the above complications arise when the rearrangement is slow for a particular substrate.

The pure δ-keto acids **12a–d** (eq 5) and the pure δ-keto esters **14a,b,d–h,j** (eq 6) were converted directly into α-pyrones in excellent yields with CF_3COOH in $(CF_3CO)_2O$ (Table I). α-Pyrones **17**, **24**, and **26** were obtained in nearly identical yields from either the keto acids **12** or from the keto esters **14**. The yield of pyrone **17** increased monotonically from 70% with 3 equiv of CF_3COOH to 94% with 10 equiv of the acid. Enol lactonization of keto acid **12a** could not be effected with acetic anhydride at room temperature, although pyrone **17** could be obtained in 67% yield upon heating the solution to reflux for 1 h. The overall yields from vinylogous thiol esters are good to excellent for substrates and procedures which afforded readily isolated keto ester intermediates (Table I, entries 2, 4–5, 7, 9–10, and 13), although the crude keto esters need not be purified and can be directly converted into the pyrones. When the intermediate allylic alcohols (**13**) were rearranged with concurrent ester hydrolysis or ester hydrolysis and enol lactionization, the overall yields were generally lower (Table I, entries 1, 3, 6, 8, 11, and 12), although this was not always the case (entry 14). It is noteworthy that the δ-keto esters **14f–h** and **14j**, which exist as mixtures of *E* and *Z* double-bond isomers, gave excellent yields of α-pyrones (Table I, entries 7, 9, 10, and 13). These results indicate that the necessary isomerizations of the *E* isomers (*Z* for **14h**) occur readily under the enol lactonization conditions without deleterious side reactions. The lowest overall yield of pyrone corresponded to **25** (entry 12), which does not contain a C6-alkyl substituent, although the annulated pyrone **16** with the same substitution pattern was formed in good overall yield.

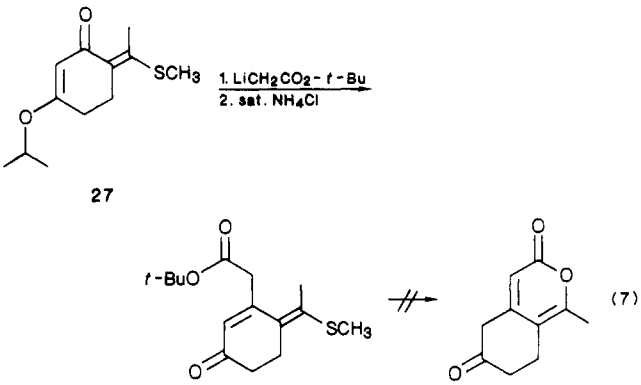
The intermediacy of δ-keto-β,γ-unsaturated acids could pose problems because of the ease with which these compounds undergo decarboxylation.[34] Although this problem was not observed with keto esters 14a-i, the annulated pyrone **29** could not be prepared because of facile decarboxylation.[35] Treatment of **27** with *tert*-butyl lithioacetate

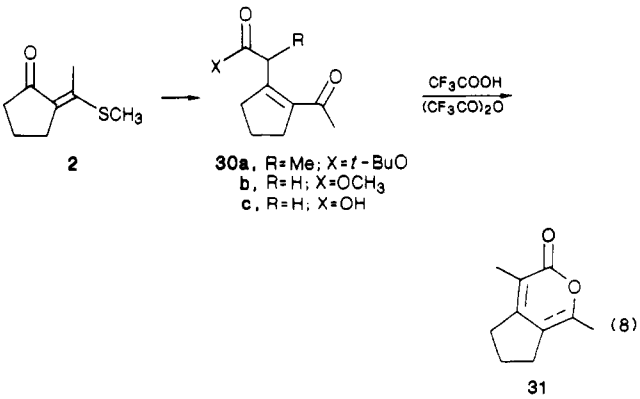
Scheme III[a]



[a] (a) i. Et_2O, ii. $NH_4Cl/NH_4OH/H_2O$ pH 8.5; (b) THF, $CH_3COOH/CH_3CO_2Na/H_2O$, pH 4.5, $Cu(OAc)_2 \cdot H_2O$, 14 h; (c) HBF_4, H_2O, THF, 0.5 h; (d) i. CF_3COOH, 0.5 h, ii. H_2O, room temperature, 12 h; (e) HBF_4, 4.0 equiv of HgO, THF, H_2O, 36 h; (f) $HgCl_2$, H_2O, CH_3CN, heat, 16 h; (g) $Hg(OAc)_2$, CF_3COOH, $(CF_3CO)_2O$, 16 h.

followed by quenching with HBF_4 afforded dienone **28** in 38% yield (eq 7) which could not be converted to either the diketone or pyrone **29** because of facile decarboxylation under the reaction conditions.

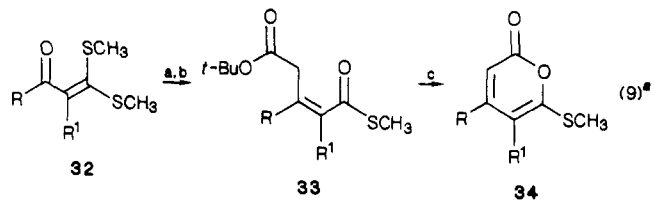




The enolate anion of *tert*-butyl propionate added cleanly to **2** to afford keto ester **30a**, which could be converted into the tetrasubstituted pyrone **31** (eq 8). Yields of **30a**

(34) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; pp 569–572.

(35) The original results described for the preparation of **29** (see ref 1) could not be reproduced. All attempts yielded primarily products arising from decarboxylation of **28** or compounds arising from **28**.



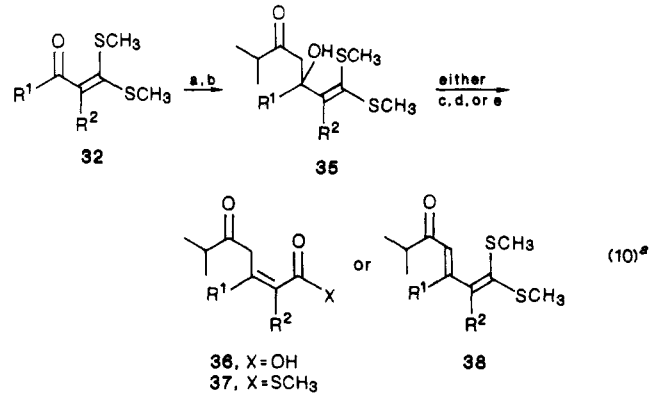
substr	R	R^1	hydrolysis time (h)	thiol ester	% yield[b]		pyrone	% yield[b]
32a	$-(CH_2)_3-$		7	**33a**	87		**34a**	93
32b	$-(CH_2)_4-$		6	**33b**	76		**34b**	85
32c	Et	Me	24	**33c**	21	+	**34c**	74[c]
								92[d]

[a] (a) $LiCH_2CO_2$-*t*-Bu, THF, −78 °C. (b) 1.5 M HBF_4, THF, H_2O. (c) CF_3COOH, $(CF_3CO)_2O$. [b] Yields are based upon isolated products purified by MPLC. [c] Yield of pyrone obtained upon quenching the ester enolate addition reaction with HBF_4 and stirring for 1 day. [d] This conversion affords a 93% overall yield for pyrone **34c** (74% + 19%).

ranged from 51% to 57% with 1.6 equiv of the enolate to 87% with 2 equiv of the reagent. The efficiency of nucleophilic 1,2 additions with enolates from α-substituted esters was not extensively examined, although the propensity of cyclopentanones to undergo enolization suggests that generally good yields should be obtainable from a variety of substrates. The enolate anion of methyl acetate underwent clean 1,2-nucleophilic addition to **2** to afford **30b** (87%) after quenching with 2 M HCl and stirring for 1 h. The methyl ester was converted into acid **30c** in nearly quantitative yield with KOH in a methanol/water solvent mixture. Although the use of methyl ester enolate anions was not extensively examined, the procedure provides an alternative to *tert*-butyl esters and might be useful for acid-sensitive substrates.

α-Pyrones from α-Oxo Ketene Dithioacetals. Direct application of the vinylogous thiol ester strategy to α-oxo ketene dithioacetals provides a short and efficient synthesis of 6-(alkylthio)-α-pyrones. The corresponding 6-alkoxy analogues[36] have been employed in elegant routes to the anthracyclines and the ease of preparation of the sulfur derivatives should encourage synthetic applications. Initial studies with **32a** and *tert*-butyl lithioacetate employing the one-pot nucleophilic addition and HBF_4-promoted rearrangement were unsuccessful as indicated by 11 spots on analytical TLC. Reaction of **32a–c** with *tert*-butyl lithioacetate follow by quenching with 2 M HCl at −60 °C afforded the α-hydroxy ketene dithioacetals in nearly quantitative yield. Treatment of the crude allylic alcohols from **32a,b** with 1.5 M HBF_4 in a 1:1 THF/H_2O mixture afforded the mixed diesters **33a,b** in good overall yields (eq 9). Treatment of the allylic alcohol from **32b** with HBF_4 for 60 h or with HBF_4 and HgO for 4 h afforded a mixture of alcohol, pyrone **34b**, and the corresponding δ-carboxy thiol ester. The yield of **34b** under these reaction conditions never exceeded 40%. The allylic alcohol from **32c** underwent rearrangement and hydrolysis (1.5 M HBF_4, THF/H_2O, 24 h) very slowly to afford a mixture of pyrone **34c** (74%) and mixed diester **33c** (21%). Shorter reaction times gave complex mixtures that included unreacted alcohol. The mixed diesters could be converted into pyrones **34a–c** with CF_3COOH (5.0 equiv, 20 h) in $(CF_3CO)_2O$ uneventfully.

The reaction of ketone enolates with α-oxo ketene dithioacetals provides a shorter route to alkyl-substituted α-pyrones. The major problem with this approach involves the intermolecular aldol reaction between two different ketones. With the procedure of House,[6c] the kinetic enolate anion of methyl isopropyl ketone was generated in diethyl ether, **32a** was added to the cold (−40 °C) solution, and the solution was stirred for 5 min before the reaction was quenched with 1 M HCl to afford the allylic alcohol **35a** in excellent yield (eq 10). Treatment of aldol **35a** with



substr	R^1	R^2	allylic alcohol	% yield[b,c]	product[d] (cond)	% yield[b]
32a	$-(CH_2)_3-$		**35a**	91	**36a** (c)	63
					37a (d)	46
32b	$-(CH_2)_4-$		**35b**		**38b** (e)	93
32c	Et	Me	**35c**	36		
32d	Me	H	**35d**	12[e]		

[a] (a) $Me_2CHCOCH_2Li$, Et_2O, −40 °C. (b) 1 M HCl, 5 min. (c) i, HBF_4; ii, HBF_4, HgO, THF, 18 h. (d) i, HBF_4; ii, HBF_4, THF, 2 h. [b] Yields are based upon isolated products purified by MPLC. [c] Allylic alcohols were obtained by quenching the aldol addition reactions according to condition b. [d] Products were obtained by quenching the aldol addition reactions and treating the crude aldols according to conditions c or d or by purification (condition e) of the aldol obtained upon quenching with 1 M HCl (condition b). [e] Yield based upon ^1H NMR ratios.

1.5 M HBF_4 for 18 h gave δ-keto acid **36a**. The δ-keto thiol ester **37a** could also be obtained with milder reaction conditions (1.5 M HBF_4, 2 h, 46%). Reaction of **32b** with the kinetic enolate of methyl isopropyl ketone afforded dienone **38b** (eq 10) in excellent yield after treatment with 1 M HCl for 5 min. Quenching the same reaction with HBF_4 (18 h) gave pyrone **41** (Table III) in 32% yield. This yield was not significantly effected by changing the reaction time or by adding HgO. Treatment of isolated **38b** with 1.5 M HBF_4 (THF/H_2O, 20 h) afforded pyrone **41** in 52% yield. The acyclic ketones **32c–d** afforded very low yields of aldol addition products upon treatment with the kinetic enolate of methyl isopropyl ketone (eq 10, Table II). A similar pattern was observed for the enolate anions of 3-pentanone and cyclohexanone, which gave very modest yields for the cyclic ketones and very poor yields for the acyclic substrates (Table II). The yields of aldol addition

(36) (a) Jung, M. E.; Brown, R. W.; Hagenah, J. A.; Strouse, C. E. *Tetrahedron Lett.* **1984**, *25*, 3659. (b) Jung, M. E.; Node, M.; Pfluger, R. W.; Lyster, M. A.; Lowe, J. A., III. *J. Org. Chem.* **1982**, *47*, 1150.

products from the corresponding Zn[6c] and Ce[7a] enolates were uniformly lower than those obtained from the Li enolates (Table II) except for the secondary carbanions which gave similar or slightly better results.

Keto acid **36a** could be cyclized to the pyrone with $(CF_3CO)_2O$ in 62% yield. The corresponding δ-keto thiol ester **37a** did not undergo cyclization when treated with $(CF_3CO)_2O$ but did afford the pyrone in 96% and 86% yields (Table III), respectively, when treated with $Hg(OAc)_2$ or $Hg(CF_3CO_2)_2$ in $CF_3COOH/(CF_3CO)_2$ mixture. In these reactions the mercuric salts either facilitate hydrolysis of the thiol esters or enable the thiol ester to participate directly in the enol lactonization process.

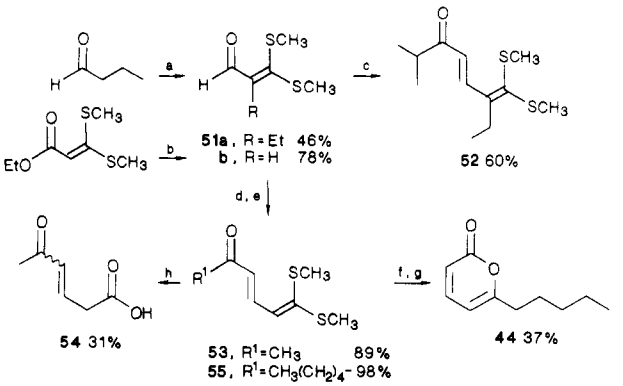
In an effort to circumvent the low yields obtained with the acyclic α-oxo ketene dithioacetals, the use of hydrazone enolate anions was examined. Addition of **32a** to hydrazone enolate **45** in THF gave allylic alcohol **46a** (Scheme II), which was not isolated. Hydrolysis of the hydrazone with $Cu(OAc)_2$ for 48 h afforded a mixture of **47a** (27%) and pyrone **40** (40%) while shorter times (14 h) gave ketone **47a** (71%) cleanly. Nucleophilic addition of the hydrazone enolate **45** to **32a** afforded higher yields in Et_2O and toluene than in THF, although these were still lower than the yield obtained with the kinetic enolate of methyl isopropyl ketone (eq 10). Consistent with this observation, addition of more than 1 equiv of HMPA to THF solutions afforded the lowest observed yields (56–58%) for formation of **47a**. The hydrazones **46** and allylic alcohol **47** could be hydrolyzed and rearranged in "one pot" by the sequential addition of $Cu(OAc)_2$ and HBF_4 with HgO to produce δ-keto thiol esters **48** in fair to good yields.

The acyclic substrates **32c,d** posed several problems that were not encountered with the cyclic ketones **32a,b**. Reaction of hydrazone enolate **45** with **32c** gave an adduct that was very sensitive to the hydrolysis conditions. Treatment of the adduct with $Cu(OAc)_2$ gave good yields of ketone **49** while use of HBF_4 gave a mixture of **49** and δ-keto thiol ester **50** (Scheme III). Interestingly, **49** could not be converted to **50** with HBF_4, suggesting that the rearrangement occurs before hydrazone hydrolysis. The most effective procedure involved use of CF_3COOH for 30 min followed by the addition of water and stirring overnight. Enolate **45** did not undergo addition to **32c** in THF reflecting probable enolization of this substrate, although use of less polar solvents was not examined. The hydrazone enolate derived from 3-pentanone afforded very low isolated yields of adduct with **32a** (10%) or **32b** (11%).

The hydrazones **46a,b** could be converted directly to pyrones **40** (48–78%) and **42** (32%) in poor to good yields, which were quite variable from run to run. The pure δ-keto thiol esters **48a,c** and **50** afforded excellent yields (90–98%, Table III) of pyrones **40** and **42–43**. *The most efficient procedure for the preparation of pyrones **40** (75–78%), **42** (73%), and **43** (66–80%) involved a three-pot process for the generation and reaction of the crude intermediate δ-keto thiol esters. These high overall yields were obtained without isolation and purification of intermediates and by combining several steps into a few procedures.*

Aldehyde-derived ketene dithioacetals were briefly examined in potential synthetic routes to 4-unsubstituted α-pyrones. Ketene dithioacetals cannot be prepared directly from aldehyde enolate anions in good yields.[3] Ketene dithioacetal **51a** was prepared directly from butanal in low yield (46%) while aldehyde **51b** was prepared from the ester via reduction and subsequent MnO_2 oxidation[37] (Scheme IV). The kinetic enolate of 3-methyl-2-butanone underwent an aldol condensation reaction with **51a** to afford dienone **52**. Similarly, hydrazone enolates afforded, after hydrazone hydrolysis, dienones **53** and **55** (Scheme IV), which could be hydrolyzed to δ-keto acids in poor yields. 6-Pentyl-2*H*-pyran-2-one (**44**) found in peaches could be prepared in 37% overall (Table II) yield by using a hydrazone enolate and **51b**. The low overall yield reflects the difficulty of hydrolyzing the dienone **55** to the required δ-keto acid.

Scheme IV[a]



[a] (a) KH, CS_2, MeI, THF; (b) i. DIBAL, $PhCH_3$, −60 to 0 °C (>95%), ii. MnO_2, petroleum ether, 1 h (82%); (c) i. $Me_2CHCOCH_2Li$, Et_2O, −40 °C, ii. 2 M HCl; (d) i. $R^1C(=NNMe_2)CH_2Li$, Et_2O, −78 °C, ii. $NH_4Cl/NH_4OH/H_2O$ pH 8.5. (e) THF, $CH_3COOH/CH_3CO_2Na/H_2O$ pH 4.5, $Cu(OAc)_2 \cdot H_2O$, 14 h; (f) $HgCl_2$, CH_3CN, H_2O, reflux, 12 h; (g) $(CF_3CO)_2O$, 12 h; (h) 1.5 M HBF_4, HgO, THF, H_2O, 15 h.

Conclusion

The readily prepared vinylogous thiol esters and α-oxo ketene dithioacetals provide versatile routes to α-pyrones. The key transformation involves an alkylative 1,3-carbonyl transposition to afford an unsaturated δ-keto ester, thiol ester, or carboxylic acid, which can be cyclized to the α-pyrone. Appropriate combination of the electrophilic vinylogous thiol esters or α-oxo ketene dithioacetals with the nucleophilic ester, ketone, or hydrazone enolates provides for facile entry into a variety of substitution patterns. These routes are complementary since the limitations of one route can generally be avoided by utilization of a different one.

The vinylogous thiol ester route (Scheme I) conveniently provides for the 4,5,6-trialkyl substitution pattern and can lead to the 3,4,5,6-tetraalkyl substitution pattern although the use of substituted acetate enolates could prove problematic with acyclic substrates and more highly substituted cyclic ketones. Use of α-oxo ketene dithioacetals derived from cyclic ketones leads to 4,5-annulated pyrones. This route also leads to the 3,4,5-trialkyl and the 4,5- and 4,6-dialkyl substitution patterns. The overall yield of pyrone is low for nonannulated 4,5-substituted pyrones (i.e., the 4,5-substituents derive from an acyclic ketone instead of a cyclic one) and synthesis of 4,6-dialkyl pyrones is limited by the difficulty of preparing α-oxo ketene dithioacetals from methyl *n*-alkyl ketones.[3] The overall procedure requires three pots and does not require isolation of intermediates. From a preparative perspective, the synthesis of the prerequiste vinylogous thiol ester from the α-oxo ketene dithioacetal via organocopper chemistry appears to be the limiting step, although this reaction has been done on a 20-mmol scale.

Ketene dithioacetals prepared from aldehydes provide routes to the 3,5,6-trialkyl, 3,6-dialkyl, and 6-monoalkyl substitution patterns. The aldehyde-derived ketene di-

(37) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616 and references cited therein.

thioacetals cannot be prepared in good yields directly from aldehydes, although they are available from the esters via reduction and reoxidation. The major limitation of this route is that the aldehydes afford aldol condensation products with ketone or hydrazone enolates and the resulting dienones are difficult to hydrolyze leading to low yields of pyrones.

The α-oxo ketene dithioacetal route with ester enolates can lead to the 3,4,5-trialkyl-, 3,4- and 4,5-dialkyl-, and 4-monoalkyl-6-(alkythio)-α-pyrones. Limitations involving use of substituted acetate enolates and synthesis of α-oxo ketene dithioacetals from methyl ketones will be applicable. The use of ketone and hydrazone enolates provide routes to 3,4,5-trialkyl (including 3,4-annulated pyrones) and 4,5-dialkyl substitution patterns. These procedures do not provide for 5-substitution since secondary carbanions do not undergo nucleophilic addition to α-oxo ketene dithioacetals in useful yields. Ketone enolates gave useful yields of aldol adducts only with α-oxo ketene dithioacetals derived from cyclic ketones and hydrazone enolates must be employed with substrates derived from acyclic ketones. The overall procedures require two to three pots depending upon procedure.

In summary, α-oxo ketene dithioacetals and vinylogous thiol esters can be converted into α-pyrones in good overall yields. Although the procedures are multistep, they can be carried out in a few pots without isolation and purification of intermediates. The synthetic routes are complementary and provide for a wide range of substitution patterns.

Experimental Section

Proton NMR spectra were recorded as $CDCl_3$ solutions on a JEOL-FX90Q instrument. Chemical shifts are reported as δ values in parts per million downfield relative to tetramethylsilane as internal standard. The carbon NMR (^{13}C NMR) chemical shifts are in parts per million downfield from tetramethylsilane and are referenced with respect to internal $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer Model 1310 spectrophotometer as $CHCl_3$ solutions unless otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were determined by Atlanta Microlab Inc., Atlanta, GA. High-resolution mass spectra were run on a Dupont CEC-110 mass spectrometer at the Massachusetts Institute of Technology Mass Spectroscopy Laboratory.

Mercuric acetate, mercuric oxide, cupric acetate monohydrate, 1,1-dimethylhydrazine, trifluoroacetic acid, trifluoroacetic anhydride, 3-methyl-2-butanone, and *tert*-butyl acetate were purchased from Aldrich and used without further purification. Activated manganese dioxide was purchased from Alfa and used without further purification. Trimethylsilyl acetate and tetrahydropyranyl acetate were prepared according to established procedures.[30,31] Hexamethylphosphoramide (HMPA) was distilled over CaH_2 under reduced pressure and stored over molecular sieves. Toluene was distilled and stored under $LiAlH_4$. The pH 8.5 buffer contained ammonium chloride (1 mol)/ammonium hydroxide (0.2 mol) in water while the pH 4.5 buffer contained acetic acid (1 mmol)/sodium acetate (0.56 mmol) in water. All compounds were purified by medium-pressure liquid chromatography (MPLC) unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone prior to use.

General Procedure A: Trimethylsilyl Ester Enolate Addition Reactions. *n*-Butyllithium (0.70 mL, 2.28 M, 1.60 mmol) was added to a 0 °C solution of diisopropylamine (0.23 mL, 1.60 mmol) in 5 mL of THF. The solution was stirred for 15 min at 0 °C and cooled to −78 °C. Trimethylsilyl acetate (211 mg, 1.60 mmol) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C.[30] A solution of the vinylogous thiol ester (1.00 mmol/1 mL of THF) was added to the enolate solution, then stirred for 40 min, quenched with 5 mL of 2.0 M HCl, and warmed to room temperature. The reaction mixture was poured into 20 mL of ether/20 mL of saturated NH_4Cl(aq), extracted with 2 × 20 mL of ether, and dried over Na_2SO_4. Concentration in vacuo afforded the crude δ-keto acid.

2-Acetylcyclopentene-1-acetic Acid (12a). The dianion of acetic acid was produced according to the method of Pfeffer[29] by using 2 mmol (2 equiv) of lithium diisopropylamide and 1 mmol of acetic acid in 10 mL of THF at room temperature. Vinylogous thiol ester **2** was added to the 0 °C dianion solution. After stirring for 2 days at room temperature, the reaction was quenched with 2 mL of 2.0 M HCl and stirred for an additional 20 min. The reaction mixture was poured into 20 mL of ethyl acetate and 20 mL of saturated NH_4Cl(aq) and separated and the aqueous layer was extracted with 2 × 20 mL of ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by gravity column chromatography (R_f 0.05, petroleum ether/10% ethyl acetate, v/v) afforded **12a** in 54% yield: IR 3400–2500 (v br, m), 3020 (s), 2985 (m), 1760 (s), 1750 (s), 1715 (s), 1680 (m), 1650 (s), 1600 (s), 1420 (s), 1370 (m), 1225 (br, m) cm^{-1}; ^1H NMR δ 1.95 (p, J = 7.0 Hz, 2 H), 2.20–2.90 (m, 4 H), 2.29 (s, 3 H), 3.54 (br s, 2 H), 9.70 (v br s, 1 H); ^{13}C NMR δ 202.3, 173.6, 151.2, 140.1, 39.0, 37.1, 34.0, 29.1, 21.5.

In a separate experiment, general procedure A was employed with the exception that the vinylogous thiol ester **2** (467 mg, 3.01 mmol) was treated with 3.85 mmol (1.28 equiv) of the trimethylsilyl acetate enolate in 15 mL of THF. The reaction mixture was stirred at −55 °C for 90 min, quenched with 5 mL of 2 M HCl, warmed to room temperature, and worked up as described in general procedure A. Purification by MPLC afforded **12a** in 72% yield.

2-Acetylcyclohexene-1-acetic Acid (12b). General Procedure A was followed and afforded **12b** after purification by MPLC (R_f 0.16, petroleum ether/20% ethyl acetate, v/v) in 77% yield: IR 3500–2600 (v br m), 3000 (m), 2965 (m), 1715 (s), 1650 (m), 1595 (m), 1425 (s), 1220 (s) cm^{-1}; ^1H NMR δ 1.30–1.90 (m, 4 H), 2.00–2.60 (m, 4 H), 2.25 (s, 3 H), 3.45 (s, 2 H), 9.10 (br s, 1 H).

3-(1-Methylethyl)-5-oxo-3-hexenoic Acid (12c). General Procedure A was employed, with the exception that the reaction was stirred for 90 min at −60 °C and quenched with 4 mL of 2 M HCl. Purification by gravity column chromatography afforded **12c** (R_f 0.15, petroleum ether/20% ethyl acetate, v/v) as a mixture of *E* and *Z* isomers in 24% yield: mixture of (*E*)- and (*Z*)-**12c** IR 3500–2500 (br s), 3020 (s), 2980 (s), 2940 (s), 1740–1680 (br s), 1615 (s), 1560 (m), 1470 (m), 1430 (m), 1410 (m), 1390 (m) cm^{-1}. *E* isomer: NMR δ 1.02 (d, J = 7.0 Hz, 6 H), 2.21 (s, 3 H), 3.10 (s, 2 H), 3.55–4.10 (m, 1 H), 6.10 (br s, 1 H), 6.66 (v br s, 1 H).

3-Ethyl-4-methyl-5-oxo-3-hexenoic Acid (12d). The dianion of acetic acid (1 mmol) was generated according to Pfeffer's procedure[29] described above, with the exception that **11** (240 mg, 1.35 mmol) was treated with 1.5 mmol (1.12 equiv) of the acetic acid dianion. The reaction was stirred for 3 days at room temperature and then worked up by using the above procedure. Purification by gravity column chromatography afforded **12d** (R_f 0.08, petroleum ether/15% ethyl acetate, v/v) as a mixture of *E* and *Z* isomers in 43% yield: ^1H NMR δ 1.05 (t, J = 7.1 Hz, 3 H), 1.87 (s, 3 H), 2.10–2.45 (m, 2 H), 2.30 (s, 3 H), 3.16 (s, 2 H), 8.90 (br s, 1 H).

In a separate experiment, general procedure A was followed by using the enolate of trimethylsilyl acetate, with the exception that 245 mg (1.50 mmol) of the vinylogous thiol ester **11** was treated with 1.88 mmol (1.25 equiv) of the enolate. The reaction was stirred for 2 h at −55 °C, quenched with 5 mL of 2 M HCl, and worked up as described in procedure A. Purification by gravity column chromatography gave **12d** in 25% yield.

General Procedure B. *tert*-Butyl Ester Enolate Addition Reactions. *n*-Butyllithium (1.20 mL, 2.00 M, 2.40 mmol) was added to a 0 °C solution of diisopropylamine (0.32 mL, 2.41 mmol) and 5 mL of THF under N_2. The solution was stirred for 15 min at 0 °C and then cooled to −78 °C. *tert*-Butyl acetate (0.32 mL, 2.40 mmol) was added to the LDA solution and stirred at −78 °C for 30 min. A solution of vinylogous thiol ester (1.50 mmol/2 mL of THF) was added to the enolate solution, then stirred (*tert*-butyl lithioacetate, 45 min at −78 °C, *tert*-butyl lithiopropanoate, 1 h, −78 to −60 °C), quenched with 4 mL of 1.5 M HBF_4, and warmed to room temperature. The hydrolysis was followed by TLC (30–120 min) and upon completion the reaction mixture was poured into ether/brine and separated, and the aqueous layer

was extracted with 2 × 25 mL of ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford the crude δ-keto ester.

1,1-Dimethylethyl 2-Formylcyclopentene-1-acetate (14a). General Procedure B was employed, with the exception that the reaction mixture was stirred at −60 °C for 40 min, quenched with 3 mL of 1.5 M HBF_4, and warmed to room temperature. Mercuric oxide (216 mg, 1.00 mmol, 1.00 equiv), 4 mL of water, and 4 mL of 1.5 M HBF_4 were added to the reaction mixture which was stirred for 1 h at room temperature and worked up as in procedure B. TLC of the crude reaction mixture showed only one spot, i.e., **14a**. Purification by MPLC (R_f 0.60, petroleum ether/15% ethyl acetate, v/v) afforded **14a** in only 32% yield: IR 3000 (m), 2970 (s), 2920 (m), 2720 (w), 1720 (vs), 1665 (vs), 1620 (m), 1450 (w), 1415 (w), 1380 (m), 1370 (s), 1330 (m) cm^{-1}; ^1H NMR δ 1.45 (s, 9 H), 1.89 (p, J = 7.1 Hz, 2 H), 2.40–2.75 (m, 4 H), 3.52 (s, 2 H), 9.98 (s, 1 H); ^{13}C NMR δ 198.3, 172.5, 154.7, 136.2, 79.6, 40.2, 34.2, 34.0, 30.2, 27.8 (3 C), 25.6, 15.2.

In a separate experiment using the same reaction conditions for enolate addition and subsequent hydrolysis, **14a** was afforded in 100% crude yield and this material was cyclized to give 2*H*-pyran-2-one **16**.

1,1-Dimethylethyl 2-Acetylcyclopentene-1-acetate (14b). General procedure B was employed, with the exception that 468 mg (3.00 mmol) of the vinylogous thiol ester **2** was treated with 4.80 mmol (1.60 equiv) of *tert*-butyl lithioacetate in 35 mL of THF. The reaction was stirred for 45 min at −78 °C and quenched with 8 mL of 1.5 M HBF_4. After warming to room temperature, 15 mL of water and 10 mL of 1.5 M HBF_4 were added and stirring was continued for an additional 2 h. The reaction was worked up as described in procedure B. Purification by MPLC (R_f 0.35, petroleum ether/10% ethyl acetate, v/v) yielded **14b** in 88% yield: IR 2990 (m), 2950 (m), 1730 (s), 1680 (s), 1625 (m), 1590 (m), 1375 (m), 1175 (s), 815 (vs) cm^{-1}; ^1H NMR δ 1.44 (s, 9 H), 1.70–2.10 (m, 2 H), 2.16 (s, 3 H), 2.30–2.90 (m, 4 H), 3.45 (br s, 2 H); ^{13}C NMR δ 198.0, 172.4, 154.5, 136.0, 80.3, 40.3, 34.1, 30.3, 27.8 (3 C), 21.6, 15.2.

In a separate experiment, solid *tert*-butyl lithioacetate[33] (191 mg, 156 mmol, 1.08 equiv) was weighed out in a round-bottom flask. The flask was purged with N_2, flamed-out, and cooled to 0 °C. Enough toluene (5 mL) was added to dissolve the solid lithium *tert*-butyl acetate and a solution of the vinylogous thiol ester **2** (225 mg, 1.44 mmol) in 2 mL of toluene was added. The reaction mixture was stirred for 1 h, quenched with 5 mL of 2 M HCl, and warmed to room temperature. THF (10 mL) was added to the reaction mixture and stirring was continued for 1 h. Workup according to general procedure B and purification by MPLC gave **14b** in 55% yield and starting material in 30% yield.

1,1-Dimethylethyl 2-Acetylcyclohexene-1-acetate (14d). General procedure B was employed with the exception that the vinylogous thiol ester **4** (265 mg, 1.55 mmol) was treated with 2.40 mmol (1.55 equiv) of *tert*-butyl lithioacetate in 7 mL of THF. The reaction was stirred for 40 min at −65 °C and quenched with 5 mL of 1.5 M HBF_4. After warming to room temperature, 5 mL of water and 3 mL of 1.5 M HBF_4 were added and stirring was continued for an additional hour. The workup was performed as in procedure B. Purification by MPLC (R_f 0.45, petroleum ether/10% ethyl acetate, v/v) afforded **14d** in 74% yield: IR 3010 (m), 2990 (m), 2940 (s), 2860 (w), 1720 (vs), 1680 (s), 1605 (m), 1440 (m), 1415 (m), 1390 (m), 1365 (s), 1330 (m), 1120 (s) cm^{-1}; ^1H NMR δ 1.40–2.00 (m, 4 H), 1.48 (s, 9 H), 2.05–2.50 (m, 4 H), 2.22 (s, 3 H), 3.19 (s, 2 H).

1,1-Dimethylethyl 1-Acetyl-1,3-cyclohexadiene-2-acetate (14e). General procedure B was employed, with the exception that 80 mg (0.47 mmol) of vinylogous thiol ester **5** was treated with 0.81 mmol of *tert*-butyl lithioacetate in 6 mL of THF. The reaction was stirred for 30 min at −70 °C and quenched with 2 mL of 1.5 M HBF_4. The reaction mixture was warmed to room temperature, 2 mL of 1.5 M HBF_4 and 4 mL of water were added, and the solution was stirred for 3 h at room temperature. The workup was done as described above and purification by MPLC (R_f 0.68, petroleum ether/20% ethyl acetate, v/v) gave **14e** in 67% yield: IR 3020 (w), 2990 (m), 2960 (s), 2905 (m), 2860 (w), 1725 (vs), 1690 (s), 1630 (w), 1550 (w), 1380 (m), 1360 (s), 1340 (s), 1330 (s), 1150 (vs) cm^{-1}; ^1H NMR δ 1.44 (s, 9 H), 2.05–2.60 (m, 4 H), 2.25 (s, 3 H), 3.40 (s, 2 H), 5.80–6.20 (m, 2 H); ^{13}C NMR δ 200.9, 170.0, 135.5, 132.0, 131.7, 129.8, 80.5, 39.7, 28.6, 27.9 (3 C), 24.2, 22.8.

1,1-Dimethylethyl 3-Methyl-5-oxo-3-nonenoate (14f). General procedure B was employed, with the exception that 66 mg (0.38 mmol) of vinylogous thiol ester **7** was treated with 0.62 mmol (1.63 equiv) of *tert*-butyl lithioacetate in 5 mL of THF. The reaction mixture was stirred for 50 min at −70 °C, quenched with 2 mL of 1.5 M HBF_4, warmed to room temperature, stirred for 2 h, and worked up as in procedure B. Purification by MPLC (R_f 0.82, petroleum ether/20% ethyl acetate, v/v) gave 3:2 mixture of (*E*/*Z*)-**14f** in 93% yield: IR 3020 (w), 3010 (m), 2980 (s), 2960 (s), 2930 (s), 2860 (m), 1725 (vs), 1685 (s), 1620 (s), 1390 (m), 1370 (s), 1330 (m), 1145 (s), cm^{-1}; ^1H NMR δ 0.90 (t, J = 6.6 Hz, 3 H), 1.20–1.25 (m, 4 H), 1.45 (s, 9 H), 1.93 [(s, 3 H), *Z* isomer], 2.17 [(s, 3 H), *E* isomer], 2.43 (t, J = 6.6 Hz, 2 H), 3.02 [(s, 2 H), *E* isomer], 3.60 [(br s, 2 H), *Z* isomer], 6.14 [(s, 1 H), *E* isomer], 6.20 [(s, 1 H), *Z* isomer]; mass spectrum, m/e 240.1732 (calcd for $C_{14}H_{24}O_3$, 240.1725).

1,1-Dimethylethyl 3,6-Dimethyl-5-oxo-3-octenoate (14g). General procedure B was followed, with the exception that 347 mg (2.02 mmol) of vinylogous thiol ester **8** was treated with 3.40 mmol (1.68 equiv) of *tert*-butyl lithioacetate in 25 mL of THF. The reaction mixture was stirred for 45 min at −60 °C, quenched with 5 mL of 1.5 M HBF_4, and warmed to room temperature. The reaction mixture was diluted with 10 mL of water and 10 mL of 1.5 M HBF_4, stirred for 3 h, and worked up as in procedure B. Purification by MPLC (R_f 0.82, petroleum ether/20% ethyl acetate, v/v) afforded a 7:3 mixture of *E* and *Z* isomers in 68% yield. Mixture of (*E*)- and (*Z*)-**14g**: IR 3020 (w), 3000 (w), 2940 (m), 2870 (w), 1725 (vs), 1680 (s), 1605 (s), 1460 (m), 1380 (w), 1360 (s), 1250 (m), 1225 (w), 1140 (vs) cm^{-1}; ^1H NMR δ 0.96 (t, J = 7.5 Hz, 3 H), 1.07 (d, J = 6.84 Hz, 3 H), 1.20–1.55 (m, 2 H), 1.44 [(s, 9 H), *Z* isomer], 1.46 [(s, 9 H), *E* isomer], 1.96 [(d, J = 1.2 Hz, 3 H), *Z* isomer], 2.18 [(d, J = 1.2 Hz, 3 H), *E* isomer], 2.20–2.60 (m, 1 H), 3.04 [(d, J = 0.97 Hz, 2 H), *E* isomer], 3.59 [(br s, 2 H), *Z* isomer], 6.20 (br s, 1 H).

1,1-Dimethylethyl 3-(1-Methylethyl)-5-oxo-3-hexenoate (14h). General procedure B was followed with the exception that 3.70 g (23.5 mmol) of vinylogous thiol ester **9** was treated with 40 mmol (1.70 equiv) of *tert*-butyl lithioacetate in 250 mL of THF. The reaction was stirred for 55 min at −78 °C, quenched with 25 mL of 1.5 M HBF_4, and warmed to room temperature. Water (100 mL) and 1.5 M HBF_4 (100 mL) were added and the reaction mixture was stirred for 1 h. The workup conditions detailed in procedure B were used. Purification by MPLC (R_f 0.20, petroleum ether/5% ethyl acetate, v/v) afforded the *Z* isomer, (*Z*)-**14h** in 46% yield: IR 3020 (m), 3000 (m), 2975 (s), 2920 (m), 2860 (w), 1720 (vs), 1680 (s), 1605 (vs), 1460 (m), 1450 (m), 1390 (m), 1365 (s), 1330 (m), 1310 (m), 1140 (vs) cm^{-1}; ^1H NMR δ 0.98 (d, J = 6.8 Hz, 6 H), 1.43 (s, 9 H), 2.16 (s, 3 H), 2.96 (s, 2 H), 3.80 (sept, J = 6.8 Hz, 1 H), 6.07 (br s, 1 H).

Purification also afforded the *E* isomer (*E*)-**14h** (R_f 0.15, petroleum ether/5% ethyl acetate, v/v) in 45% yield: IR 3020 (m), 2980 (s), 2930 (m), 2880 (w), 1730 (s), 1685 (s), 1620 (s), 1460 (m), 1420 (m), 1395 (m), 1370 (s), 1330 (m), 1115 (m) cm^{-1}; ^1H NMR δ 1.02 (d, J = 6.8 Hz, 6 H), 1.38 (s, 9 H), 2.13 (s, 3 H), 2.15–2.40 (m, 1 H), 3.44 (s, 2 H), 6.15 (s, 1 H).

1,1-Dimethylethyl 3-Ethyl-4-formyl-3-pentenoate (14i). General procedure B was followed, with the exception that 250 mg (1.74 mmol) of vinylogous thiol ester **10** was treated with 2.67 mmol (1.53 equiv) of *tert*-butyl lithioacetate in 10 mL of THF. The reaction mixture was stirred for 45 min at −60 °C, quenched with 3 mL of 1.5 M HBF_4, and warmed to room temperature. The reaction mixture was diluted with 5 mL of water and 5 mL of 1.5 M HBF_4, stirred for 45 min, and worked up as in procedure B. Crude NMR spectra showed an equal mixture of *E* and *Z* isomers. Compound **14i** was formed in approximately (351 mg crude, NMR pure) 95% yield. Mixture of (*E*)- and (*Z*)-**14i**: IR 3000 (s), 2980 (m), 2940 (w), 1725 (s), 1690 (s), 1520 (m), 1425 (m), 1375 (m), 1170 (s), 930 (m) cm^{-1}; ^1H NMR δ 1.15 (t, J = 7.6 Hz, 3 H), 1.44 [(s, 9 H), *Z* isomer], 1.45 [(s, 9 H), *E* isomer] 1.77 (br s, 3 H), 2.68 (q, J = 7.6 Hz, 2 H), 3.23 [(br s, 2 H), *E* isomer], 3.53 [(br s, 2 H), *Z* isomer], 10.01 [(s, 1 H), *Z* isomer], 10.15 [(s, 1 H), *E* isomer].

The crude material was not purified and it was used to synthesize 2*H*-pyran-2-one **25**.

1,1-Dimethylethyl 3-Ethyl-4-methyl-5-oxo-3-hexenoate (14j). General procedure B was employed with the exception that 317 mg (2.00 mmol) of the vinylogous thiol ester **11** was treated with 3.20 mmol (1.60 equiv) of *tert*-butyl lithioacetate in 25 mL of THF. The reaction was stirred for 75 min at −55 °C, quenched with 6 mL of 1.5 M HBF_4, and warmed to room temperature, whereupon 15 mL of water and 15 mL of 1.5 M HBF_4 were added. The reaction mixture was stirred for 15 min at room temperature and then worked up as described in procedure B. Purification by MPLC afforded a 1:1 mixture of *E* and *Z* isomers in 74% yield. Mixture of (*E*)- and (*Z*)-**14j**: ^1H NMR δ 1.02 (t, *J* = 7.4 Hz, 3 H), 1.48 (s, 9 H), 1.85 (s, 3 H), 1.90–2.30 (m, 2 H), 2.21 (s, 3 H), 2.97 [(br s, 2 H), *E* isomer], 3.65 [(br s, 2 H), *Z* isomer].

2-(2-Methyl-1-oxobutyl)cyclopentene-1-acetic Acid (15). General procedure B was followed with the exception that 196 mg (0.99 mmol) of vinylogous thiol ester **3** was treated with 2.00 mmol (2.02 equiv) of *tert*-butyl lithioacetate in 8 mL of THF. The reaction was stirred for 75 min at −65 °C, quenched with 5 mL of 1.5 M HBF_4, and warmed to room temperature, whereupon 5 mL of water and 5 mL of 1.5 M HBF_4 were added. The reaction mixture was stirred for 18 h and worked up according to procedure B. Purification by gravity column chromatography (R_f 0.19, petroleum ether/20% ethyl acetate, v/v) afforded **15** in 64% yield: IR 3600–2700 (br m), 2985 (m), 2960 (m), 1715 (s), 1655 (w), 1580 (w), 1425 (m), 1210 (m), 1090 (m), 905 (vs) cm^{-1}; ^1H NMR δ 0.70–1.20 (m, 3 H), 1.19 (d, *J* = 7.1 Hz, 3 H), 1.50–2.00 (m, 4 H), 2.15–2.80 (m, 5 H), 3.06 (s, 2 H), 8.90 (br s, 1 H).

Methyl 2-Acetylcyclopentene-1-acetate (30b). *n*-Butyllithium (0.80 mL, 2.00 M, 1.60 mmol) was added dropwise to a 0 °C solution of hexamethyldisilazane (0.33 mL, 1.60 mmol) in 8 mL of THF. The clear reaction mixture was stirred for 15 min and cooled to −78 °C. Methyl acetate was added to the LHMDS solution and stirred for 30 min. A solution of vinylogous thiol ester **2** (156 mg, 1 mmol) in 2 mL of THF was transferred into the −78 °C enolate solution via double-tipped needle. The reaction mixture was stirred for 45 min at −78 °C, quenched with 5 mL of 2 M HCl, warmed to room temperature, stirred for 1 h, and worked up as in procedure B. Purification by MPLC (R_f 0.28, petroleum ether/10% ethyl acetate, v/v) afforded the methyl ester in 86% yield: IR 2995 (vs), 2965 (w), 1725 (w), 1675 (m), 1605 (w), 1515 (m), 1425 (s), 1410 (m), 1350 (m), 1290 (m), 1140 (m), 1020 (w), 925 (m) cm^{-1}; ^1H NMR δ 1.89 (p, *J* = 7.1 Hz, 2 H), 2.20 (s, 3 H), 2.40–2.90 (m, 4 H), 3.63 (s, 2 H), 3.67 (s, 3 H); ^{13}C NMR δ 197.9, 170.5, 148.1, 137.4, 51.5, 38.2, 35.0, 34.0, 29.8, 21.3.

General Procedure C: Enol Lactonization of δ-Keto Acids to 2*H*-Pyran-2-ones. The δ-keto acid (0.50 mmol) was weighed in a round-bottom flask which was purged with N_2 and cooled to 0 °C. Trifluoroacetic anhydride (2 mL) was added to the δ-keto acid and stirred for 6 h at room temperature under N_2. The reaction mixture was poured into a beaker containing 20 mL of ether, then water (20 mL) was added slowly and separated, and the aqueous layer was extracted with 2 × 20 mL of ether. The combined organic layers were washed with water and brine and dried over $MgSO_4$. Concentration in vacuo afforded the crude 2*H*-pyran-2-one.

General Procedure D: Cyclization of δ-Keto Esters to 2*H*-Pyran-2-ones. The δ-keto ester (0.50 mmol) was weighed out in a round-bottom flask, which was poured with N_2 and cooled to 0 °C. Trifluoroacetic anhydride (2 mL) was added followed by the addition of trifluoroacetic acid (5 mmol, 10 equiv). The reaction mixture was warmed to room temperature, stirred for 8 h, and then slowly poured into a beaker containing 20 mL of ether/20 mL of water. The layers were separated and the aqueous phase was extracted with 2 × 20 mL of ether. The organic layers were combined, washed with water and brine, and dried over $MgSO_4$. Concentration in vacuo afforded the crude 2*H*-pyran-2-one.

6,7-Dihydrocyclopenta[*c*]pyran-3(5*H*)-one (16). General procedure D was employed, with the exception that 52 mg (0.25 mmol) of crude δ-aldehyde ester **14a** was dissolved in trifluoroacetic anhydride (TFAA) at 0 °C. Trifluoroacetic acid (0.10 mL, 1.3 mmol, 5.2 equiv) was added to the 0 °C solution and the reaction mixture was stirred for 14 h at room temperature. Workup and purification gave **16** (R_f 0.10, petroleum ether/12% ethyl acetate, v/v) in an overall yield of 71% from the vinylogous thiol ester: IR 3020 (m), 2980 (m), 2920 (w), 1715 (vs), 1660 (s), 1565 (s), 1430 (w), 1390 (m), 1360 (w), 1320 (w), 1075 (s) cm^{-1}; ^1H NMR δ 2.03 (p, *J* = 7.0 Hz, 2 H), 2.70 (app q, *J* = 7.0 Hz, 4 H), 6.17 (br s, 1 H), 7.33 (d, *J* = 1.4 Hz, 1 H); ^{13}C NMR δ 165.1, 162.8, 144.1, 123.6, 109.1, 32.4, 26.7, 25.8.

In a separate experiment general procedure D was followed, with the exception that 30 mg (0.14 mmol) of pure δ-aldehyde ester **14a** was dissolved in 1 mL of TFAA at 0 °C. Trifluoroacetic acid (0.05 mL, 0.65 mmol, 4.6 equiv) was added to the 0 °C solution. The reaction mixture was warmed to room temperature and stirred for 24 h. Workup and purification afforded **16** in 80% yield.

6,7-Dihydro-1-methylcyclopenta[*c*]pyran-3(5*H*)-one (17). The δ-keto acid **12a** (98 mg, 0.58 mmol) was dissolved in 3.5 mL of trifluoroacetic anhydride as described in general procedure C. The reaction was stirred for 2.5 h. Purification by MPLC (R_f 0.12, petroleum ether/12% ethyl acetate, v/v) yielded **17** in 95% yield: UV max (C_2H_5OH) 303 (ε 6000); IR 3000 (m), 2960 (m), 1715 (vs), 1655 (s), 1580 (s), 1420 (m), 1385 (m), 930 (m), 850 (s) cm^{-1}; ^1H NMR δ 1.93 (p, *J* = 7.1 Hz, 2 H), 2.12 (d, *J* = 0.49 Hz, 3 H), 2.30–2.75 (m, 4 H), 5.92 (q, *J* = 0.48 Hz, 1 H); ^{13}C NMR δ 165.6, 163.8, 154.4, 119.6, 105.8, 32.5, 27.2, 25.0, 17.6.

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.98; H, 6.74.

In a separate experiment, the δ-keto ester **14b** (108 mg, 0.48 mmol) was dissolved in 3 mL of trifluoroacetic anhydride (TFAA) at 0 °C as described in general procedure D. Trifluoroacetic acid (0.37 mL, 4.8 mmol, 10 equiv) was added to the 0 °C solution. The reaction mixture was then stirred for 6 h and worked up as described in procedure D. Purification afforded the 2*H*-pyran-2-one **17** in 93% yield.

6,7-Dihydro-1-(1-methylpropyl)cyclopenta[*c*]pyran-3-(5*H*)-one (18). The crude mixture of δ-keto acid **15** and 2-(*H*)-pyran-2-one **18** (6:1) was purified by MPLC (R_f 0.31, petroleum ether/20% ethyl acetate, v/v) and afforded **18** in 70% overall yield from vinylogous thiol ester **3**: UV max (CH_3OH) 305 (ε 7800); IR 3020 (m), 2975 (m), 2940 (w), 1725 (vs), 1655 (m), 1585 (s), 1390 (m), 1205 (m), 1070 (w), 855 (w) cm^{-1}; ^1H NMR δ 0.82 (t, *J* = 7.3 Hz, 3 H), 1.18 (d, *J* = 6.9 Hz, 3 H), 1.57 (p, *J* = 7.3 Hz, 2 H), 1.97 (p, *J* = 6.9 Hz, 2 H), 2.30–2.80 (m, 5 H), 5.96 (br s, 1 H); ^{13}C NMR δ 165.6, 164.0, 161.1, 119.0, 106.0, 38.4, 32.6, 27.4, 27.2, 25.2, 17.8, 12.0.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.94; H, 8.41.

1-Methyl-5,6,7,8-tetrahydro-3*H*-2-benzopyran-3-one (19). General procedure C was employed which afforded **19** (R_f 0.14, petroleum ether/12% ethyl acetate, v/v) in 70% yield: UV max (C_2H_5OH) 310 (ε 6400); IR 2950 (s), 1725 (vs), 1625 (s), 1535 (s), 1400 (m), 1225 (br m), 850 (s) cm^{-1}; ^1H NMR δ 1.40–1.85 (m, 4 H), 2.08 (d, *J* = 0.73 Hz, 3 H), 2.15–2.85 (m, 4 H), 5.80 (q, *J* = 0.48 Hz, 1 H); ^{13}C NMR δ 162.6, 158.0, 157.6, 112.0, 109.5, 29.7, 23.3, 22.4, 21.5, 16.8.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.05; H, 7.40.

In a separate experiment, the δ-keto ester **14d** was converted into 2*H*-pyran-2-one **19** by using 20 equiv of TFA, according to procedure D. Purification by MPLC afforded **19** in 94% yield.

7,8-Dihydro-1-methyl-3*H*-2-benzopyran-3-one (20). General procedure D was employed with the exception that 38 mg (0.16 mmol) of δ-keto ester **14e** was dissolved in 2.5 mL of TFAA at 0 °C. Trifluoroacetic acid (0.04 mL, 0.56 mmol, 3 equiv) was added to the 0 °C solution. The reaction mixture was warmed to room temperature and stirred for 14 h. Workup and purification afforded **20** (R_f 0.29, petroleum ether/20% ethyl acetate, v/v) in 99% yield: ^1H NMR δ 2.10–2.70 (m, 4 H), 2.22 (s, 3 H), 5.85 (s, 1 H), 6.20–6.60 (m, 2 H); ^{13}C NMR δ 170.6, 163.8, 149.1, 139.4, 125.6, 107.3, 99.3, 23.8, 20.6, 16.6.

4,6-Dimethyl-2*H*-pyran-2-one (21).[38] General procedure B was employed with the exception that the reaction was quenched with 6 mL of 1.5 M HBF_4, stirred 16 h at room temperature, and worked up as in procedure B. Purification afforded 2*H*-pyran-2-one **21** (R_f 0.23, petroleum ether/20% ethyl acetate, v/v) in 72% yield: UV max 296 (ε 7100); IR 3010 (m), 2960 (w), 2920 (w), 1720 (vs), 1645 (s), 1565 (vs), 1450 (m), 1440 (m), 1400 (m), 1375 (m),

(38) Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1673.

1160 (m), 1140 (m) cm^{-1}; ^1H NMR δ 1.95 (s, 3 H), 2.04 (s, 3 H), 5.73 (s, 2 H); ^{13}C NMR δ 162.7, 160.8, 156.1, 109.8, 106.0, 20.9, 19.3.

6-Butyl-4-methyl-2*H*-pyran-2-one (22).[39] General procedure D was employed with the exception that 54 mg (0.23 mmol) of δ-keto ester **14f** was dissolved in 2 mL of TFAA at 0 °C. Trifluoroacetic acid (0.75 mL, 1.10 mmol, 5 equiv) was added to the 0 °C solution, and the reaction mixture was stirred for 16 h. Workup and purification by MPLC (R_f 0.43, petroleum ether/20% ethyl acetate, v/v) gave the 2*H*-pyran-2-one **22** in 95% yield: IR 3010 (m), 2960 (s), 2930 (m), 2870 (m), 1715 (vs), 1645 (s), 1565 (s), 1470 (w), 1445 (w), 1410 (m), 1380 (w), 1265 (w), 1150 (m) cm^{-1}; ^1H NMR δ 0.93 (t, J = 6.35 Hz, 3 H), 1.17–1.86 (m, 4 H), 2.13 (d, J = 0.98 Hz, 3 H), 2.47 (t, J = 7.20 Hz, 2 H), 5.88 (br s, 1 H), 5.93 (br s, 1 H); ^{13}C NMR δ 164.8, 163.0, 156.0, 110.3, 105.5, 33.1, 28.7, 21.9, 21.1, 13.5.

In a separate experiment general procedure B was followed, with the exception that the reaction mixture was stirred at −60 °C, quenched with 5 mL of 1.5 M HBF_4, and stirred for 16 h at room temperature. Workup and purification afforded **22** in 52% yield.

4-Methyl-6-(1-methylpropyl)-2*H*-pyran-2-one (23). General procedure D was followed, with the exception that 230 mg (0.96 mmol) of δ-keto ester **14g** was dissolved in 6 mL of TFAA at 0 °C. Trifluoroacetic acid (0.40 mL, 5.19 mmol, 5.41 equiv) was added to the 0 °C solution and the reaction mixture was stirred for 15 h. Workup and purification by MPLC (R_f 0.45, petroleum ether/20% ethyl acetate, v/v) afforded **23** in 91% yield: IR 3010 (m), 2970 (m), 2930 (w), 2870 (w), 1710 (vs), 1640 (m), 1550 (s), 1450 (w), 1410 (w), 1380 (w), 1080 (w) cm^{-1}; ^1H NMR δ 1.05 (t, J = 7.3 Hz, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.51 (p, J = 7.2 Hz, 2 H), 2.05 (s, 3 H), 2.39 (sept, J = 7.0 Hz, 1 H), 5.78 (s, 1 H), 5.85 (s, 1 H); ^{13}C NMR δ 168.2, 163.0, 156.0, 110.3, 104.6, 39.5, 27.1, 21.1, 17.6, 11.3; mass spectrum, m/e 166.0998 (calcd for $C_{10}H_{14}O_2$, 166.0994).

4-(1-Methylethyl)-6-methyl-2*H*-pyran-2-one (24). General procedure D was employed with the exception that 500 mg (2.21 mmol) of crude δ-keto ester **14h** was dissolved in 3 mL of TFAA at 0 °C. Trifluoroacetic acid (0.90 mL, 5 equiv) was added to the 0 °C solution and the reaction mixture was stirred for 12 h. The reaction was worked up as in procedure D and purification by MPLC (R_f 0.32, petroleum ether/20% ethyl acetate, v/v) yielded **24** in 92% yield: UV max (CH_3OH) 296 (ϵ 6300); IR 3010 (m), 2970 (m), 1715 (s), 1635 (m), 1555 (m), 1460 (w), 1020 (w), 940 (w) cm^{-1}; ^1H NMR δ 1.18 (d, J = 6.8 Hz, 6 H), 2.25 (d, J = 0.73 Hz, 3 H), 2.66 (sept, J = 6.8 Hz, 1 H), 5.93 (br s, 1 H), 6.01 (br s, 1 H); ^{13}C NMR δ 165.2, 162.6, 160.7, 106.5, 103.4, 32.7, 20.5 (2 C), 19.0.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.98; H, 7.98.

In a separate experiment, general procedure C was employed, with the exception that the reaction mixture was stirred overnight. Workup and purification afforded a 93% yield of 2*H*-pyran-2-one **24**.

In another experiment, general procedure B was followed, with the exception that 390 mg (2.46 mmol) of vinylogous thiol ester **9** was treated with 4.00 mmol (1.62 equiv) of *tert*-butyl lithioacetate in 20 mL of THF. The reaction mixture was stirred for 40 min at −70 °C, quenched with 5 mL of 1.5 M HBF_4, warmed to room temperature, stirred for 18 h, and worked up as in procedure B. Purification of the crude mixture of acid and 2*H*-pyran-2-one gave 2*H*-pyran-2-one **24** in 76% yield.

4-Ethyl-5-methyl-2*H*-pyran-2-one (25). General procedure D was employed with the exception that 380 mg (1.7 mmol) of crude δ-aldehyde ester **14i** was dissolved in TFAA at 0 °C. Trifluoroacetic acid (0.65 mL, 8.5 mmol, 5 equiv) was added to the 0 °C solution. The reaction mixture was warmed to room temperature and then stirred for 16 h. Workup and purification by MPLC (R_f 0.27, petroleum ether/20% ethyl acetate, v/v) afforded **25** in 49% overall yield from the vinylogous thiol ester: IR 3020 (s), 2980 (m), 2840 (w), 1728 (vs), 1640 (m), 1550 (m), 1425 (m), 1270 (s), 1020 (s) cm^{-1}; ^1H NMR δ 1.21 (t, J = 7.6 Hz, 3 H), 1.95 (d, J = 0.95 Hz, 3 H), 2.46 (q, J = 7.6 Hz, 2 H), 6.13 (br s, 1 H), 7.15–7.30 (m, 1 H); ^{13}C NMR δ 162.6, 161.2, 146.5, 115.2, 111.2, 25.3, 12.3, 11.1; mass spectrum, m/e 138.0678 (calcd for $C_8H_{10}O_2$, 138.0681).

5,6-Dimethyl-4-ethyl-2*H*-pyran-2-one (26). General procedure D was followed, with the exception that 82 mg (0.36 mmol) of δ-keto ester **14j** was dissolved in 3.0 mL of TFAA at 0 °C. Trifluoroacetic acid (0.28 mL, 3.6 mmol, 10 equiv) was added to the 0 °C solution and the reaction mixture was stirred for 16 h. Workup and purification by MPLC gave the 2*H*-pyran-2-one **26** (R_f 0.25, petroleum ether/20% ethyl acetate, v/v) in 91% yield: UV max 302 (ϵ 6300); IR 3030 (m), 3010 (m), 2980 (m), 2940 (w), 1710 (vs), 1625 (s), 1545 (s), 1460 (w), 1420 (w), 1410 (w), 1275 (w), 1130 (m), 920 (m) cm^{-1}; ^1H NMR δ 1.12 (t, J = 7.32 Hz, 3 H), 1.87 (br s, 3 H), 2.17 (br s, 3 H), 2.37 (q, J = 7.32 Hz, 2 H), 5.94 (br s, 1 H); ^{13}C NMR δ 163.1, 162.3, 156.7, 111.0, 109.3, 26.1, 17.6, 12.0, 11.8.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.96; H, 7.99.

In a separate experiment general procedure B was followed, with the exception that after the δ-keto acid **12d** was dissolved in TFAA, the reaction mixture was stirred overnight. Workup and purification by MPLC afforded the 2*H*-pyran-2-one **26** in 90% yield.

In another experiment general procedure B was followed with the exception that 240 mg (1.51 mmol) of vinylogous thiol ester **11** was treated with 2.41 mmol (1.60 equiv) of *tert*-butyl lithioacetate in 10 mL of THF. The reaction mixture was stirred for 1 h at −78 °C, quenched with 10 mL of 1.5 M HBF_4, and stirred overnight at room temperature. Workup and purification afforded **26** in 81% yield.

1,1-Dimethylethyl [6-(1-(Methylthio)ethylidene)-3-oxo-1-cyclohexenyl]acetate (28). General procedure B was followed, with the exception that 5 equiv of *tert*-butyl lithioacetate was employed. The reaction was quenched with 5 mL of 2 M HCl, warmed to room temperature, and stirred 30 min. Usual workup and purification by MPLC (R_f 0.41, petroleum ether/20% ethyl acetate, v/v) afforded **28** in 38% yield: ^1H NMR δ 1.37 (s, 9 H), 2.13 (s, 3 H), 2.28 (s, 3 H), 2.30–2.55 (m, 2 H), 2.91 (t, J = 6.7 Hz, 2 H), 3.37 (s, 2 H), 5.80 (s, 1 H).

1,1-Dimethylethyl 2-(2-Acetyl-1-cyclopentenyl)propionate (30a). General procedure B was employed, with the exception that 155 mg (0.994 mmol) of vinylogous thiol ester **2** was treated with 2.49 mmol (2.50 equiv) of the enolate of *tert*-butyl propionate in 6 mL of THF. The reaction mixture was stirred for 45 min at −55 °C, quenched with 4 mL of 1.5 M HBF_4, warmed to room temperature, stirred for 1 h, and worked up as in procedure B. Purification by MPLC (R_f 0.49, petroleum ether/10% ethyl acetate, v/v) afforded **30a** in 84% yield: IR 3015 (m), 3000 (s), 2980 (m), 1730 (vs), 1680 (s), 1610 (m), 1460 (m), 1400 (w), 1375 (s), 1260 (s), 1165 (s), 1090 (w), 1070 (w) cm^{-1}; ^1H NMR δ 1.23 (d, J = 7.1 Hz, 3 H), 1.46 (s, 9 H), 1.60–2.10 (m, 2 H), 2.24 (s, 3 H), 2.35–2.80 (m, 4 H), 4.36 (q, J = 7.1 Hz, 1 H); ^{13}C NMR δ 198.1, 172.5, 154.6, 136.1, 80.2, 40.3, 34.2, 34.1, 30.1, 27.8 (3 C), 21.7, 15.3; mass spectrum, m/e 238.1579 (calcd for $C_{14}H_{22}O_3$, 238.1569).

1,6-Dimethyl-6,7-dihydrocyclopenta[*d*]pyran-3(5*H*)-one (31). General procedure D was employed, with the exception that 56 mg (0.23 mmol) of δ-keto ester **30** was dissolved in 1 mL of TFAA at 0 °C. Trifluoroacetic acid (0.19 mL, 2.4 mmol, 10.5 equiv) was added to the 0 °C solution and the reaction mixture was stirred for 12 h. Workup and purification by MPLC (R_f 0.36, petroleum ether/20% ethyl acetate, v/v) afforded **31** in 71% yield: UV max 303 (ϵ 7000); IR 3015 (m), 2960 (m), 2920 (w), 1700 (vs), 1665 (s), 1600 (s), 1450 (w), 1430 (w), 1395 (w), 1330 (w), 1165 (w), 1040 (w), 925 (w) cm^{-1}; ^1H NMR δ 1.75–2.20 (m, 2 H), 1.99 (s, 3 H), 2.16 (s, 3 H), 2.45–2.90 (m, 4 H); ^{13}C NMR 164.9, 159.8, 150.9, 119.5, 114.5, 31.4, 27.8, 24.9, 17.4, 12.8.

General Procedure E: Hydrolysis of Aldol or Ester Enolate Addition Products to δ-Keto Thiol Esters. The crude aldol (1 mmol) was dissolved in 10 mL of THF and 5 mL of water. Tetrafluoroboric acid (5 mL, 1.5 M) was added followed by the addition of mercuric oxide (216 mg, 1 mmol) to the reaction mixture and stirred for 1 h. The reaction mixture was poured into ether/water and extracted with 2 × 20 mL of ether. The organic phases were combined, washed with brine, and dried over $MgSO_4$. Concentration in vacuo afforded the crude thiol ester.

(39) Pittet, A. O.; Klaiber, E. M. *J. Agric. Food Chem.* **1975**, *23*, 1189.

1,1-Dimethylethyl [2-[(Methylthio)carbonyl]-1-cyclopentenyl]acetate (33a). General procedure B was employed with **32a**, with the exception that the reaction was quenched with 2 mL of 2 M HCl. Workup and concentration in vacuo afforded the crude allylic alcohol adduct in approximately quantitative yield: ^{1}H NMR δ 1.45 (s, 9 H), 1.55–1.90 (m, 2 H), 2.12–2.35 (m, 2 H), 2.27 (s, 3 H), 2.29 (s, 3 H), 2.40–2.70 (m, 2 H), 2.86 (center of AB quartet, J_{AB} = 14.2 Hz, $\Delta\nu_{AB}$ = 29.5 Hz, δ_A = 2.69, δ_B = 3.03, 2 H), 3.91 (s, 1 H).

The allylic alcohol was subjected to general procedure E, with the exception that mercuric oxide was not used. The reaction was stirred for 7 h, worked up, and purified by MPLC (R_f 0.78, petroleum ether/10% ethyl acetate v/v) to afford **33a** in 87% yield: IR 3000 (w), 2980 (m), 2930 (m), 1725 (vs), 1650 (s), 1620 (s), 1460 (w), 1430 (w), 1410 (w), 1395 (m), 1370 (s), 1330 (m), 1170 (s) cm^{-1}; ^{1}H NMR δ 1.44 (s, 9 H), 1.91 (p, J = 7.1 Hz, 2 H), 2.31 (s, 3 H), 2.40–2.88 (m, 4 H), 3.60 (br s, 2 H); ^{13}C NMR δ 189.4, 169.0, 148.1, 135.7, 80.6, 38.4, 36.8, 32.8, 27.8 (3 C), 21.7, 11.1; mass spectrum, m/e 209.1176 [calcd for $C_{12}H_{17}O_3$, 209.1177 (M − SCH_3)$^+$].

1,1-Dimethylethyl [2-[(Methylthio)carbonyl]-1-cyclohexenyl]acetate (33b). General procedure B was employed, with the exception that the reaction with **32b** was quenched with 3 mL of 2 M HCl. Workup and concentration in vacuo afforded the crude allylic alcohol: ^{1}H NMR δ 1.46 (s, 9 H), 1.50–2.25 (m, 7 H), 2.29 (s, 3 H), 2.37 (s, 3 H), 2.71 (center of AB quartet, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 30.6 Hz, δ_A = 2.53, δ_B = 2.89, 2 H), 3.35–3.65 (m, 1 H), 6.01 (s, 1 H).

General procedure E was employed, with the exception that mercuric oxide was not used. The reaction was stirred for 6 h, whereupon workup and purification by MPLC (R_f 0.85, petroleum ether/15% ethyl acetate, v/v) afforded **33b** in 76% yield: IR 3010 (w), 2990 (m), 2940 (s), 2880 (m), 1730 (vs), 1660 (s), 1625 (m), 1455 (w), 1425 (w), 1400 (w), 1375 (s), 1340 (m), 1160 (s) cm^{-1}; ^{1}H NMR δ 1.47 (s, 9 H), 1.55–1.85 (m, 4 H), 2.00–2.50 (m, 4 H), 2.32 (s, 3 H), 3.28 (br s, 2 H); ^{13}C NMR δ 194.2, 169.5, 138.2, 133.4, 80.0, 41.3, 31.8, 27.6 (3 C), 26.2, 21.8, 21.6, 11.1; mass spectrum, m/e 214.0668 [calcd for $C_{10}H_{14}O_3S$, (M − C_4H_8)$^{\cdot+}$].

1,1-Dimethylethyl 3-Ethyl-4-[(methylthio)carbonyl]-3-pentenoate (33c) and 4-Ethyl-5-methyl-6-(methylthio)-2*H*-pyran-2-one (34c). General procedure B was employed, with the exception that the reaction was quenched with 2 mL of 1.5 M HBF_4, warmed to room temperature, and worked up as in procedure B. The NMR spectrum of the crude material showed that the addition product was formed almost quantitatively: ^{1}H NMR δ 0.89 (t, J = 7.0 Hz, 3 H), 1.45 (s, 9 H), 1.65–2.15 (m, 2 H), 2.19 (s, 3 H), 2.28 (s, 3 H), 2.34 (s, 3 H), 3.07 (center of AB quartet, J_{AB} = 14.9 Hz, $\Delta\nu_{AB}$ = 98.5 Hz, δ_A = 2.50, δ_B = 3.64, 2 H), 4.60–4.80 (br s, 1 H).

The crude alcohol was dissolved in 10 mL of THF/10 mL of 0.7 M HBF_4, stirred for 18 h, and worked up as described in procedure B. Purification by MPLC (R_f 0.84, petroleum ether/15% ethyl acetate, v/v) afforded 2(*H*)-pyran-2-one **34c** in 74% yield and **33c** (*E*:*Z* ratio, 69:31) in 21% yield. Mixture of (*E*)- and (*Z*)-**33c**: IR 2980 (s), 2940 (s), 2880 (m), 1725 (vs), 1665 (s), 1620 (w), 1460 (m), 1390 (w), 1370 (s), 1280 (m), 1260 (m), 1170 (vs) cm^{-1}; ^{1}H NMR δ 1.04 (t, J = 7.1 Hz, 3 H), 1.43 [(s, 9 H), *Z* isomer], 1.45 [(s, 9 H), *E* isomer], 1.92 [(s, 3 H), *E* isomer], 2.00 [(s, 3 H), *Z* isomer], 2.05–2.50 (m, 2 H), 2.31 [(s, 3 H), *Z* isomer], 2.34 [(s, 3 H), *E* isomer], 3.04 [(s, 2 H), *E* isomer], 3.27 [(s, 2 H), *Z* isomer].

General procedure D was employed on **33c**, with the exception that the reaction was stirred for 16 h. Workup and purification by MPLC (R_f 0.31, petroleum ether/20% ethyl acetate, v/v) afforded **34c** in 88% yield: IR 3000 (m), 2970 (m), 2920 (m), 1705 (vs), 1600 (m), 1490 (s), 1430 (m), 1410 (m), 1380 (m), 1310 (m), 1260 (m), 1100 (m), 1040 (m) cm^{-1}; ^{1}H NMR δ 1.18 (t, J = 7.3 Hz, 3 H), 1.98 (s, 3 H), 2.43 (q, J = 7.3 Hz, 2 H), 2.54 (s, 3 H), 5.89 (br s, 1 H); ^{13}C NMR δ 162.8, 161.8, 156.7, 111.2, 106.1, 26.2, 13.3, 12.0, 11.9.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.66; H, 6.56. Found: C, 58.51; H, 6.56.

6,7-Dihydro-1-(methylthio)cyclopenta[*c*]pyran-3(5*H*)-one (34a). General procedure D was employed, with the exception that 94 mg (0.37 mmol) of thiol ester **33a** was dissolved in 3 mL of TFAA and then TFA (0.15 mL, 1.9 mmol, 5 equiv) was added. The reaction was stirred for 21 h, whereupon workup and purification by MPLC (R_f 0.20, petroleum ether/10% ethyl acetate, v/v) afforded **34a** in 93% yield: IR 2980 (m), 2940 (w), 2900 (w), 1705 (vs), 1615 (m), 1510 (vs), 1425 (w), 1410 (w), 1400 (w), 1380 (m), 1270 (w) cm^{-1}; ^{1}H NMR δ 2.02 (p, J = 6.85 Hz, 2 H), 2.40–2.90 (m, 4 H), 2.56 (s, 3 H), 5.89 (t, J = 1.45 Hz, 1 H); ^{13}C NMR δ 165.4, 163.5, 153.2, 120.3, 102.9, 32.8, 27.6, 24.9, 13.0; mass spectrum, m/e 182.0400 (calcd for $C_9H_{10}O_2S$, 182.0402).

1-(Methylthio)-5,6,7,8-tetrahydro-3*H*-2-benzopyran-3-one (34b). General procedure D was employed with **33b** and afforded **34b** in 85% yield after purification by MPLC (R_f 0.32, petroleum ether/20% ethyl acetate, v/v): IR 3000 (m), 2940 (s), 2870 (w), 1700 (vs), 1595 (w), 1480 (vs), 1430 (w), 1400 (w), 1350 (w), 1330 (w), 1320 (w), 1170 (m) cm^{-1}; ^{1}H NMR δ 1.55–1.95 (m, 4 H), 2.20–2.40 (m, 2 H), 2.45–2.70 (m, 2 H), 2.56 (s, 3 H), 5.75 (br s, 1 H); ^{13}C NMR δ 162.6, 157.7, 157.6, 111.9, 105.6, 29.6, 23.0, 22.1, 21.4, 12.7; mass spectrum, m/e 196.0554 (calcd for $C_{10}H_{12}O_2S$, 196.0558).

General Procedure F: Ketone Enolate Addition Reactions. *n*-Butyllithium (0.70 mL, 2.30 M, 1.61 mmol) was added to a 0 °C solution of diisopropylamine (0.225 mL, 1.61 mmol)/5 mL of ether under N_2. The reaction mixture was stirred for 15 min and cooled to −40 °C. The ketone (1.60 mmol) was added to the −40 °C solution and then stirred for 30 min. A solution of [α-oxo ketene dithioacetal (1.00 mmol)/2 mL of ether] was added to the enolate solution. The reaction mixture was stirred for 20 min at −35 to −30 °C and quenched with 2 mL of 2 M HCl. The reaction mixture was poured into ether/brine, extracted with 2 × 20 mL of ether, washed with water, brine, and dried over $MgSO_4$. Concentration in vacuo afforded the crude aldol product.

2-(Bis(methylthio)methylene)-1-(3-methyl-2-oxobutyl)-1-cyclopentanol (35a). General procedure F was employed and workup and purification by MPLC afforded **35a** in 91% yield: ^{1}H NMR δ 1.11 (d, J = 7.1 Hz, 6 H), 1.45–2.08 (m, 4 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 2.35–2.95 (m, 3 H), 3.17 (center of AB quartet, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 59 Hz, δ_A = 2.83, δ_B = 3.52, 2 H), 4.24 (s, 1 H).

1,1-Bis(methylthio)-3,6-dimethyl-3-hydroxy-1-hepten-5-one (35d). General procedure F was employed, with the exception that α-oxo ketene dithioacetal **32d** (162 mg, 1.00 mmol) was treated with 1.60 mmol of the kinetic enolate of methyl isopropyl ketone. Usual workup afforded a mixture which was 87% **32d** and 12% **35d** by its NMR spectrum. **35d**: ^{1}H NMR δ 1.09 (d, J = 6.9 Hz, 6 H), 1.47 (s, 3 H), 2.26 (s, 3 H), 2.34 (s, 3 H), 2.35–2.70 (m, 1 H), 3.09 (center of AB quartet, J_{AB} = 16 Hz, $\Delta\nu_{AB}$ = 40 Hz, δ_A = 2.85, δ_B = 3.32, 2 H), 4.77 (br s, 1 H), 6.12 (s, 1 H).

1,1-Bis(methylthio)-2,6-dimethyl-3-ethyl-3-hydroxy-1-hepten-5-one (35c). General procedure F was followed, with the exception that α-oxo ketene dithioacetal **32c** (95 mg, 0.50 mmol) was treated with 0.75 mmol of the kinetic enolate of methyl isopropyl ketone. Usual workup and purification by MPLC afforded **32c** in 49% yield and **35c** in 36% yield: IR 3600–3300 (br m), 2950 (s), 2910 (s), 2870 (s), 1690 (s), 1470 (m), 1390 (m), 1370 (m), 1310 (m) cm^{-1}; ^{1}H NMR δ 0.85 (t, J = 7.2 Hz, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.45–2.20 (m, 2 H), 2.20 (s, 3 H), 2.22 (s, 3 H), 2.29 (s, 3 H), 2.30–2.70 (m, 1 H), 3.31 (center of AB quartet, J_{AB} = 17.1 Hz, $\Delta\nu_{AB}$ = 97.3 Hz, δ_A = 2.74, δ_B = 3.87, 2 H), 4.74 (br s, 1 H); ^{13}C NMR δ 216.4, 152.5, 125.3, 78.6, 49.4, 41.7, 33.2, 22.1, 18.1, 17.9, 17.7, 17.3, 7.6.

2-(3-Methyl-2-oxobutyl)-1-cyclopentene-1-carboxylic Acid (36a). General procedure F was followed, with the exception that the aldol reaction with **32a** was quenched with 1.5 mL of 1.5 M HBF_4, warmed to room temperature, and concentrated in vacuo. The concentrate was dissolved in 10 mL of THF/10 mL of 0.7 M HBF_4, whereupon mercuric oxide (378 mg, 1.75 mmol, 1.75 equiv) was added. The reaction mixture was stirred for 18 h at room temperature, worked up, and purified by gravity column chromatography (R_f 0.25, petroleum ether/15% ethyl acetate, v/v) which afforded **36a** in 63% yield: IR 3400–2400 (br s), 2970 (s), 2940 (s), 2870 (m), 1710 (s), 1680 (vs), 1640 (s), 1580 (s), 1460 (m), 1420 (m), 1400 (m), 1380 (w), 1340 (w), 1290 (m), 1270 (s) cm^{-1}; ^{1}H NMR δ 1.11 (d, J = 6.8 Hz, 6 H), 1.87 (p, J = 7.2 Hz, 2 H), 2.30–3.00 (m, 5 H), 3.83 (br s, 2 H), 8.80–9.60 (br s, 1 H); ^{13}C NMR δ 210.6, 171.0, 155.2, 129.8, 42.1, 40.9, 39.6, 33.1, 21.3, 18.1 (2 C).

In a separate experiment, general procedure E was employed on aldol **35a**, with the exception that the reaction was only stirred

for 4 h. Workup and purification by gravity column chromatography afforded **36a** in 48% yield.

***S*-Methyl 2-(3-Methyl-2-oxobutyl)-1-cyclopentene-1-thiocarboxylate (37a).** General procedure F was employed, with the exception that the reaction was quenched with 2 mL of 1.5 M HBF_4, warmed to room temperature, and concentrated in vacuo. The concentrate was dissolved in 10 mL of THF/10 mL of 0.7 M HBF_4 and stirred for 2 h. Workup and purification by MPLC (R_f 0.77, petroleum ether/15% ethyl acetate, v/v) afforded **37a** in 46% yield: IR 2980 (s), 2940 (s), 2880 (s), 1710 (vs), 1645 (vs), 1620 (s), 1470 (m), 1430 (w), 1405 (w), 1385 (w), 1270 (m), 1170 (m) cm^{-1}; ^1H NMR δ 1.12 (d, J = 6.8 Hz, 6 H), 1.60–2.25 (m, 2 H), 2.31 (s, 3 H), 2.35–2.95 (m, 5 H), 3.83 (br s, 2 H); ^{13}C NMR δ 210.6, 192.7, 149.5, 135.8, 42.2, 41.0, 39.1, 32.9, 21.9, 18.1 (2C), 11.3; mass spectrum, m/e 226.1029 (calcd for $C_{12}H_{18}O_2S$, 226.1028).

2-(Bis(methylthio)methylene)-1-(3-methyl-2-oxobutylidene)cyclohexane (38b). General procedure F was employed, with the exception that the initial aldol product was dehydrated when filtered through a silica gel plug. Compound **38b** was afforded in 93% crude yield (>95% pure by NMR): ^1H NMR δ 1.09 (d, J = 7.1 Hz, 6 H), 1.30–2.10 (m, 6 H), 2.28 (s, 3 H), 2.35 (s, 3 H), 2.40–2.80 (m, 3 H), 6.10 (s, 1 H).

General Procedure G: Cyclization of δ-Keto Thiol Esters to 2*H*-Pyran-2-ones. Mercuric acetate (85 mg, 0.20 mmol) and the δ-keto thiol ester were weighed in a round-bottom flask, purged with N_2, and cooled to 0 °C. Trifluoroacetic anhydride (3 mL) was added followed by the addition of trifluoroacetic acid (0.70 mL, 9 mmol). The reaction mixture was stirred for 14 h at room temperature, slowly poured into 20 mL of ether/20 mL of water, and filtered. The filtrate was separated and the aqueous layer was extracted with 2 × 20 mL of ether. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to afford the crude 2*H*-pyran-2-one.

6,7-Dihydro-3-(1-methylethyl)cyclopenta[*c*]pyran-1-(5*H*)-one (39). General procedure C was employed with acid **36a**, with the exception that the reaction was stirred 10 h in 4 mL of TFAA. Usual workup and purification by MPLC (R_f 0.20, petroleum ether/10% ethyl acetate, v/v) afforded **39** in 62% yield: IR 3020 (m), 2980 (m), 2950 (m), 2890 (w), 1710 (vs), 1635 (m), 1575 (s), 1470 (w), 1390 (w), 1370 (w), 1090 (w) cm^{-1}; ^1H NMR δ 1.23 (d, J = 6.8 Hz, 6 H), 2.06 (p, J = 7.1 Hz, 2 H), 2.55–2.95 (m, 5 H), 6.02 (s, 1 H); ^{13}C NMR δ 169.5, 162.1, 160.0, 124.0, 99.8, 34.3, 32.5, 29.2, 22.7, 20.2 (2 C).

In a separate experiment, general procedure G was followed, with the exception that the thiol ester **37a** (30 mg, 0.13 mmol) and mercuric acetate (54 mg, 0.16 mmol) were dissolved in 3 mL of TFAA/0.7 mL of trifluoroacetic acid. The reaction was stirred for 20 h and worked up as in procedure G. Purification by MPLC afforded **39** in 96% yield.

3-(1-Methylethyl)-5,6,7,8-tetrahydro-1*H*-2-benzopyran-1-one (41). General procedure E was employed, with the exception that 53 mg (0.20 mmol) of crude **38b** was dissolved in 3 mL of THF/3 mL of 0.7 M HBF_4 and stirred for 20 h. Usual workup and purification by MPLC (R_f 0.15, petroleum ether/15% ethyl acetate, v/v) afforded **41** in 52% yield: IR 3010 (m), 2980 (s), 2945 (s), 2880 (m), 1770 (vs), 1645 (s), 1580 (s), 1460 (m), 1450 (m), 1390 (m), 1365 (m), 1170 (m), 1070 (s) cm^{-1}; ^1H NMR δ 1.22 (d, J = 6.8 Hz, 6 H), 1.60–1.95 (m, 4 H), 2.25–2.60 (m, 4 H), 2.69 (sept, J = 6.8 Hz, 1 H), 5.72 (s, 1 H); ^{13}C NMR δ 165.8, 164.0, 151.3, 119.6, 103.2, 32.2, 29.2, 23.0, 22.0, 21.5, 20.2 (2 C); mass spectrum, m/e 192.1151 (calcd for $C_{12}H_{16}O_2$, 192.1150).

In a separate experiment, general procedure F was employed, with the exception that the reaction was quenched with 1.5 mL of 1.5 M HBF_4, warmed to room temperature, and concentrated in vacuo. The concentrate was dissolved in 10 mL of THF/10 mL of 0.7 M HBF_4 whereupon HgO (378 mg, 1.75 mmol, 1.75 equiv) was added. The reaction mixture was stirred for 18 h at room temperature, worked up, and purified by MPLC to afford **41** in 32% yield.

General Procedure H: Metalated Hydrazone Addition Reactions in Ether. *n*-Butyllithium (0.34 mL, 2.40 M, 0.82 mmol) was added to a 0 °C solution of diisopropylamine [(0.115 mL, 0.82 mmol)/4 mL of ether]. The solution was stirred for 15 min and then cooled to −78 °C. The hydrazone (0.81 mmol) was added to the LDA solution, warmed to −10 °C over a 45-min period, and then cooled to −78 °C. A solution of α-oxo ketene dithioacetal [(0.50 mmol)/1 mL of ether] was added to the metalated hydrazone solution, warmed to 0 °C over a 1-h period, and quenched with aqueous pH 8.5 buffer. The mixture was extracted with 3 × 25 mL of CH_2Cl_2; the combined organic layers were washed with brine and dried over $MgSO_4$. Concentration in vacuo afforded the β-hydroxy hydrazone.

The β-hydroxy hydrazone was hydrolyzed by dissolving the crude reaction mixture in 10 mL of THF/10 mL of aqueous pH 4.5 buffer. Copper acetate monohydrate (220 mg, 1.10 mmol) was added, and the reaction mixture was stirred for 14 h and then worked up. The mixture was poured into water/CH_2Cl_2, and the aqueous phase was extracted with 2 × 25 mL of CH_2Cl_2. The combined organic phases were washed with brine and dried over $MgSO_4$. Concentration in vacuo afforded the aldol product.

2-[Bis(methylthio)methylene]-1-(2-dimethylhydrazinopropyl)-1-cyclopentanol (46a). General procedure H was employed, with the exception that the addition adduct **46a** was not hydrolyzed. The adduct was formed in crude quantitative yield: ^1H NMR δ 1.40–2.00 (m, 4 H), 1.88 (s, 3 H), 1.95–2.60 (m, 2 H), 2.10 (s, 6 H), 2.30 (s, 6 H), 2.72 (center of AB quartet, J_{AB} = 14.5 Hz, $\Delta\nu_{AB}$ = 116 Hz, δ_A = 2.07, δ_B = 3.37, 2 H), 5.60–5.80 (br s, 1 H).

2-[Bis(methylthio)methylene]-1-(2-dimethylhydrazinopropyl)-1-cyclohexanol (46b). General procedure H was employed to yield the crude addition adduct **46b** in quantitative yield: ^1H NMR δ 1.40–1.90 (m, 6 H), 2.02 (s, 3 H), 2.26 (s, 3 H), 2.31 (s, 3 H), 2.35–2.70 (m, 1 H), 2.45 (s, 6 H), 2.91 (center of AB quartet, J_{AB} = 14 Hz, $\Delta\nu_{AB}$ = 60 Hz, δ_A = 2.56, δ_B = 3.26, 2 H), 3.35–3.75 (m, 1 H), 7.20–7.60 (br s, 1 H).

2-[Bis(methylthio)methylene]-1-(2-oxopropyl)-1-cyclopentanol (47a). General procedure H was employed and afforded **47a** (R_f 0.32, petroleum ether/15% ethyl acetate, v/v) in 80% yield from α-oxo ketene dithioacetal **32a**: ^1H NMR δ 1.45–2.20 (m, 4 H), 2.27 (s, 3 H), 2.31 (s, 3 H), 2.35 (s, 3 H), 2.40–3.00 (m, 2 H), 3.04 (center of AB quartet, J_{AB} = 15 Hz, $\Delta\nu_{AB}$ = 54 Hz, δ_A = 2.74, δ_B = 3.34, 2 H), 4.90–5.30 (br s, 1 H).

***S*-Methyl 2-(2-Oxopropyl)-1-cyclopentene-1-thiocarboxylate (48a).** General procedure E was followed with **47a** and afforded **48a** (R_f 0.28, petroleum ether/8% ethyl acetate, v/v) in 32% yield: IR 2980 (m), 2940 (m), 2900 (m), 2860 (w), 1720 (s), 1620 (s), 1600 (s), 1410 (m), 1345 (m), 1300 (m), 1170 (m) cm^{-1}; ^1H NMR δ 1.93 (p, J = 7.4 Hz, 2 H), 2.21 (s, 3 H), 2.33 (s, 3 H), 2.35–2.90 (m, 4 H), 3.76 (s, 2 H); ^{13}C NMR δ 204.7, 190.1, 148.8, 136.0, 45.2, 39.1, 32.8, 30.0, 21.9, 11.1.

In a separate experiment, general procedure H was employed, with the exception that after 14 h, HBF_4 (4 mL, 1.5 M) and HgO (110 mg, 0.51 mmol) were added. The reaction was stirred for 40 min and then worked up as in procedure H. Purification by MPLC afforded **48a** in 71% overall yield from α-oxo ketene dithioacetal **32a**.

2-(2-Oxopropyl)-1-cyclopentene-1-carboxylic Acid (48b). General procedure G was employed, with the exception that 4.6 equiv of HgO was used and the reaction was stirred for 36 h. Usual workup and filtration through a silica gel plug afforded **48b** in 38% crude yield: ^1H NMR δ 1.65–2.95 (m, 6 H), 2.18 (s, 3 H), 3.78 (s, 2 H), 6.85–7.20 (br s, 1 H).

***S*-Methyl 2-(2-Oxopropyl)-1-cyclohexene-1-thiocarboxylate (48c).** General procedure H was followed, with the exception that 101 mg (0.50 mmol) of α-oxo ketene dithioacetal **32b** was treated with 0.80 mmol of metalated hydrazone **45**. The reaction mixture was warmed to 0 °C over 1 h and the usual workup afforded the crude addition adduct **46b**. The adduct was hydrolyzed as in procedure H, with the exception that after 14 h, HBF_4 (4 mL, 1.5 M) and HgO (110 mg, 0.51 mmol) were added. The reaction was stirred for 30 min; usual workup and purification by MPLC (R_f 0.32, petroleum ether/8% ethyl acetate, v/v) afforded **48c** in 57% yield: IR 3000 (w), 2940 (s), 2870 (m), 1720 (s), 1660 (s), 1610 (m), 1450 (w), 1420 (m), 1360 (m), 1315 (m), 1280 (w) cm^{-1}; ^1H NMR δ 1.55–1.85 (m, 4 H), 2.10–2.60 (m, 4 H), 2.19 (s, 3 H), 2.29 (s, 3 H), 3.44 (br s, 2 H); ^{13}C NMR δ 205.3, 194.5, 140.18 133.3, 50.0, 33.0, 29.5, 26.3, 22.0, 21.6, 11.4.

5-[Bis(methylthio)methylene]-4-ethyl-4-hydroxy-2-hexanone (49). General procedure H was employed with **32c** and afforded the aldol product **49** in 78% yield: IR 3600–3200 (br m), 2960 (s), 2920 (s), 2860 (m), 1700 (s), 1470 (m), 1430 (m), 1420 (m), 1370 (s), 1350 (s), 1300 (m) cm^{-1}; ^1H NMR δ 0.84 (t, J = 7.3

Hz, 3 H), 1.40–2.10 (m, 2 H), 2.16 (s, 6 H), 2.24 (s, 3 H), 2.29 (s, 3 H), 3.23 (center AB quartet, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 90 Hz, δ_A = 2.73, δ_B = 3.73, 2 H), 4.90–5.15 (br s, 1 H); ^{13}C NMR δ 209.9, 151.3, 125.8, 78.7, 52.1, 33.4, 31.4, 21.8, 18.1, 17.1, 7.4.

***S*-Methyl 3-Ethyl-2-methyl-5-oxo-2-hexenethioate (50).** General procedure H was followed, with the exception that 95 mg (0.50 mmol) of α-oxo ketene dithioacetal **32c** was treated with 0.80 mmol of metalated hydrazone **45**. The reaction mixture was warmed to 0 °C over 1 h and usual workup afforded the crude addition adduct. The adduct was hydrolyzed as in procedure H, with the exception that after 14 h, HBF_4 (4 mL, 1.5 M) and HgO (110 mg, 0.51 mmol) were added. The reaction mixture was stirred for 30 min and then worked up. Purification by MPLC (R_f 0.28, petroleum ether/8% ethyl acetate, v/v) afforded **50** (*E*:*Z* ratio, 10:90) in 35% yield. Mixture of (*E*)- and (*Z*)-**50**: IR 2980 (vs), 2940 (s), 2900 (m), 2870 (w), 1700 (s), 1635 (s), 1590 (m), 1510 (m), 1405 (s), 1345 (m), 1300 (m) cm^{-1}; mixture of (*E*)- and (*Z*)-**50** NMR δ 1.00 (t, *J* = 7.3 Hz, 3 H), 1.31 (q, *J* = 7.3 Hz, 2 H), 1.89 [(br s, 3 H), *E* isomer], 2.05 [(br s, 3 H), *Z* isomer], 2.20 (s, 3 H), 2.30 (s, 3 H), 3.20 [(br s, 2 H), *E* isomer], 3.47 [(s, 2 H), *Z* isomer]; ^{13}C NMR (*Z* isomer) δ 205.6, 195.4, 142.7, 131.4, 48.5, 29.5, 28.2, 15.1, 11.8, 11.1.

In a separate experiment, alcohol **49** (24.8 mg, 0.10 mmol) was dissolved in trifluoroacetic acid (0.45 mL, 5.8 mmol, 58 equiv) in a 5-mL flask under N_2. The reaction mixture was stirred for 45 min, whereupon water (1.0 mL) was added. The reaction was stirred for 14 h and worked up as in general procedure C to afford 20 mg (95%, >99% pure by NMR) of **50**.

6,7-Dihydro-3-methylcyclopenta[*c*]pyran-1(5*H*)-one (40). General procedure G was employed, with the exception that 20 mg (0.10 mmol) of thiol ester **48a** was treated with mercuric acetate (35 mg, 0.11 mmol) in 2 mL of TFAA/1 mL of TFA. The reaction was stirred for 12 h at room temperature; usual workup and purification by MPLC (R_f 0.38, petroleum ether/20% ethyl acetate, v/v) afforded **40** in 90% yield: IR 3000 (w), 2980 (m), 2940 (m), 2880 (m), 1715 (vs), 1620 (m), 1560 (s), 1430 (w), 1415 (w), 1360 (w) cm^{-1}; ^{1}H NMR δ 2.05 (p, *J* = 7.4 Hz, 2 H), 2.23 (s, 3 H), 2.76 (t, *J* = 7.4 Hz, 4 H), 6.01 (s, 1 H); ^{13}C NMR δ 162.0, 161.1, 159.9, 123.9, 102.8, 34.3, 29.3, 22.7, 19.8; mass spectrum, *m*/*e* 150.0688 (calcd for $C_9H_{10}O_2$, 150.0681).

In a separate experiment, general procedure H was employed, with the exception that after 14 h, HBF_4 (4 mL, 1.5 M) and HgO (108 mg, 0.50 mmol, 1 equiv) were added. The reaction was stirred for 30 min and usual workup afforded crude thiol ester **48a**. The thiol ester was treated with mercuric acetate as in general procedure G which afforded **40** in 78% overall yield from α-oxo ketene dithioacetal **32a**.

3-Methyl-5,6,7,8-tetrahydro-1*H*-2-benzopyran-1-one (42). General procedure G was employed, with the exception that 38 mg (0.18 mmol) of thiol ester **48c** was treated with mercuric acetate (319 mg, 0.20 mmol, 1.1 equiv) in 2 mL of TFAA/1 mL of TFA. The reaction was stirred for 12 h and worked up as in procedure G. Purification by MPLC (R_f 0.40, petroleum ether/20% ethyl acetate, v/v) afforded **42** in 98% yield: IR 3030 (m), 2995 (s), 2940 (m), 1700 (vs), 1655 (m), 1580 (s), 1420 (m), 1390 (w), 1370 (w), 1270 (s), 1180 (m) cm^{-1}; ^{1}H NMR δ 1.55–1.95 (m, 4 H), 2.19 (s, 3 H), 2.20–2.60 (m, 4 H), 5.77 (br s, 1 H); ^{13}C NMR δ 163.9, 157.2, 151.3, 119.1, 106.1, 28.9, 22.8, 21.8, 21.4, 19.3; mass spectrum, *m*/*e* 164.0821 (M^+) (calcd for $C_{10}H_{12}O_2$, 164.0837).

In a separate experiment, general procedure H was employed, with the exception that after 14 h, HBF_4 (4 mL, 1.5 M) and HgO (110 mg, 0.51 mmol, 1 equiv) were added. The reaction was stirred 35 min and worked up as usual to afford the crude thiol ester **48c**. General procedure G was followed using the crude thiol ester; usual workup and purification by MPLC afforded **42** in 73% overall yield from α-oxo ketene dithioacetal **32b**.

3,6-Dimethyl-4-ethyl-2*H*-pyran-2-one (43). General procedure G was employed, with the exception that 24 mg (0.12 mmol) of thiol ester **50** was treated with mercuric acetate (41.5 mg, 0.13 mmol) in 2 mL of TFAA/1 mL of TFA. The reaction mixture was stirred for 16 h and worked up as in procedure G. Purification by MPLC (R_f 0.45, petroleum ether/20% ethyl acetate, v/v) afforded **43** in 92% yield: IR 3020 (m), 3000 (s), 2920 (m), 2820 (w), 1705 (s), 1650 (s), 1570 (s), 1410 (m), 1380 (w), 1350 (m), 1260 (s) cm^{-1}; ^{1}H NMR δ 1.13 (t, *J* = 7.6 Hz, 3 H), 2.01 (s, 3 H), 2.19 (s, 3 H), 2.41 (q, *J* = 7.6 Hz, 2 H), 5.84 (s, 1 H); ^{13}C NMR δ 164.6, 157.8, 155.2, 116.0, 105.6, 26.0, 19.4, 12.5, 11.5; mass spectrum, *m*/*e* 152.0843 (calcd for $C_9H_{12}O_2$, 152.0837).

In a separate experiment, general procedure H was followed, with the exception that the aldol product **49** was not isolated. The crude aldol was refluxed in a solution of acetonitrile (3 mL)/water (0.75 mL)/mercuric chloride (111 mg, 0.41 mmol, 2 equiv) for 16 h. The crude mixture contained the δ-keto acid and 2*H*-pyran-2-one **43**. This mixture was dissolved in TFAA and stirred for 14 h to afford **43** after purification in 80% overall yield from α-oxo ketene dithioacetal **32d**.

2-[Bis(methylthio)methylene]butanal (51a).[40] Potassium hydride (273 mg, 6.82 mmol, 2.2 equiv) was weighed out under N_2 (KH/oil suspension was added to a round-bottom flask and was washed with 3 × 20 mL pentane which yielded solid KH). Tetrahydrofuran (12 mL) was added to the flask and the resulting suspension was cooled to 0 °C. A solution of 0.27 mL (3.1 mmol) of butanal/1 mL of THF was added to the 0 °C suspension and stirred for 15 min at room temperature. The reaction mixture bubbled vigorously during the first minute of stirring. A solution of 0.38 mL (6.3 mmol) CS_2/2 mL of THF was added to the enolate solution which slowly turned orange over a 45-min period. Methyl iodide (0.63 mL, 10 mmol) was added to the orange solution and the reaction was stirred for 6 h. The reaction was worked up by slowly pouring the reaction mixture into ether/saturated $NaHCO_3$(aq). The organic layer was separated and the aqueous phase was extracted with 2 × 25 mL of ether and the combined organic phases were dried over $MgSO_4$. Concentration in vacuo and purification by MPLC (R_f 0.54, petroleum ether/10% ethyl acetate, v/v) afforded **51a** in 46% yield: IR 3000 (m), 2980 (s), 2940 (s), 2880 (m), 2860 (m), 2740 (m), 1660 (vs), 1525 (s), 1455 (m), 1430 (m), 1380 (m), 1280 (s), 1260 (m) cm^{-1}; ^{1}H NMR δ 0.97 (t, *J* = 7.5 Hz, 3 H), 2.38 (s, 3 H), 2.50 (s, 3 H), 2.54 (q, *J* = 7.5 Hz, 2 H), 10.26 (s, 1 H); ^{13}C NMR δ 188.7, 158.6, 146.4, 22.8, 18.7, 16.3, 12.8.

3,3-Bis(methylthio)propenal (51b). Ethyl 3,3-bis(methylthio)propenoate was synthesized according to an established procedure[41] in 64% yield (R_f 0.70, petroleum ether/20% ethyl acetate, v/v): IR 3000 (m), 2920 (m), 1680 (s), 1520 (s), 1425 (m), 1360 (w), 1320 (m), 1295 (m), 1170 (s) cm^{-1}; NMR δ 1.28 (t, *J* = 7.1 Hz, 3 H), 2.42 (s, 3 H), 2.49 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 5.57 (s, 1 H); ^{13}C NMR δ 164.9, 161.2, 104.8, 59.4, 16.8, 14.5, 14.3; mass spectrum, *m*/*e* 192.0279 (calcd for $C_7H_{12}O_2S_2$, 192.0279).

Diisobutylaluminum hydride (2.20 mL, 1.0 M, 2.2 mmol) was added to a −60 °C solution of 95 mg (0.54 mmol) of ethyl 3,3-bis(methylthio)propenoate in 10 mL of toluene. The reaction was warmed to 0 °C over 75 min, quenched with 10 mL of 2 M NaOH, and warmed to room temperature. The reaction mixture was poured into 50 mL of ether/20 mL of 2 M NaOH. The aqueous phase was extracted with 3 × 25 mL of ether and the combined organic phases were washed with brine and dried over K_2CO_3. Concentration in vacuo afforded 3,3-bis(methylthio)-2-propen-1-ol (R_f 0.30, petroleum ether/20% ethyl acetate, v/v) in quantitative yield: IR 3600 (m), 3550 (br m), 3000 (s), 2920 (s), 2860 (s), 1580 (m), 1430 (m), 1410 (m), 1365 (m), 1260 (m) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 2.29 (s, 6 H), 3.87 (s, 1 H), 4.32 (d, *J* = 6.1 Hz, 2 H), 5.92 (t, *J* = 6.1 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 135.4, 133.3, 61.0, 17.7, 17.0.

Manganese dioxide (570 mg, 6.57 mmol, 18 equiv) was added to a solution of 54 mg (0.36 mmol) of alcohol in 25 mL of petroleum ether. The reaction mixture was stirred for 1 h and worked up by filtering off the excess MnO_2. Concentration in vacuo and purification by MPLC (R_f 0.37, petroleum ether/20% ethyl acetate, v/v) afforded ketene dithioacetal **51b** in 82% yield: IR 3010 (m), 2940 (w), 2830 (w), 2740 (vw), 1650 (vs), 1525 (s), 1480 (s), 1435 (m), 1380 (m), 1330 (w), 1260 (m), 1160 (s) cm^{-1}; ^{1}H NMR δ 2.44 (s, 3 H), 2.55 (s, 3 H), 5.99 (d, *J* = 6.6 Hz, 1 H), 9.92 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR δ 186.1, 166.5, 120.8, 16.7, 16.4; mass spectrum, *m*/*e* 148.0013 (calcd for $C_5H_8OS_2$, 148.0017).

(*E*)-2-Methyl-6-[bis(methylthio)methylene]-4-octen-3-one (52). General procedure F was employed, with the exception that 44 mg (0.25 mmol) of ketene dithioacetal **51a** was treated with 0.38 mmol (1.5 equiv) of the kinetic enolate of methyl isopropyl ketone. The reaction was warmed to 0 °C over 50 min, quenched

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with HBF_4 (1 mL, 1.5 M), and warmed to room temperature. Water (3 mL) and HBF_4 (2.5 mL, 1.5 M) were added to the reaction mixture which was stirred for 12 h. Usual workup and purification afforded **52** (R_f 0.40, petroleum ether/5% ethyl acetate, v/v) in 60% yield: ^1H NMR δ 1.03 (t, J = 7.7 Hz, 3 H), 1.15 (d, J = 6.9 Hz, 6 H), 2.32 (s, 3 H), 2.42 (s, 3 H), 2.67 (q, J = 7.7 Hz, 2 H), 2.96 (sept, J = 6.9 Hz, 1 H), 6.26 (d, J = 16 Hz, 1 H), 8.18 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 204.7, 144.7, 144.0, 139.8, 124.5, 38.4, 24.9, 18.7 (2 C), 18.3, 17.2, 13.2.

(*E*)-1,1-Bis(methylthio)-1,3-hexadien-5-one (53). *n*-Butyllithium (0.33 mL, 2.42 M, 0.80 mmol) was added to a −78 °C solution of hydrazone [$CH_3C(=NNMe)CH_3$ (0.80 mmol)/5 mL of THF] under N_2. The reaction mixture was stirred for 20 min at −78 °C. A solution of ketene dithioacetal **51b** (40 mg, 0.27 mmol, 2 mL THF) was added to the metalated hydrazone **45** solution, stirred 90 min (−78 to −20 °C), and quenched with 2 mL of 2 M HCl. The reaction mixture was poured into aqueous pH 8.5 buffer/CH_2Cl_2 and extracted with 2 × 20 mL of CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. Concentration in vacuo afforded the crude addition adduct.

The adduct was hydrolyzed as in procedure H. The crude material was a mixture of alcohol and **53**; however, purification by MPLC afforded only **53** in 89% yield: IR 3010 (m), 2920 (w), 1660 (s), 1580 (s), 1560 (m), 1520 (w), 1410 (w), 1350 (w), 1180 (s) cm^{-1}; ^1H NMR δ 2.30 (s, 3 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 6.09 (d, J = 15.6 Hz, 1 H), 6.25 (d, J = 10.7 Hz, 1 H), 7.74 (dd, J = 15.6 Hz, J = 10.7 Hz, 1 H).

(*Z*)-5-Oxo-3-hexenoic Acid (54). General procedure E was followed, with the exception that 23 mg (0.12 mmol) of **53** was treated with 0.28 mmol (2.3 equiv) of mercuric oxide and stirred 15 h at room temperature. Usual workup and purification by gravity column chromatography afforded **54** in 32% yield: ^1H NMR δ 2.37 (s, 3 H), 3.65 (s, 2 H), 7.18 (d, J = 9 Hz, 1 H), 7.74 (d, J = 9 Hz, 1 H), 8.60 (br s, 1 H).

(*E*)-1,1-Bis(methylthio)-1,3-decadien-5-one (55). General procedure H was employed, with the exception that 146 mg (0.99 mmol) of ketene dithioacetal **51b** was reacted with 1.60 mmol of metalated hydrazone [$C_5H_{11}C(=NNMe_2)CH_2Li$], warmed to 0 °C over 75 min and then quenched with 5 mL of pH 8.5 buffer. Usual workup and concentration in vacuo afforded the crude adduct.

The adduct was hydrolyzed as in general procedure H, with the exception that 3 equiv of copper acetate monohydrate was employed. The reaction mixture was stirred for 14 h, whereupon HBF_4 (4 mL, 1.5 M) and HgO (110 mg, 0.51 mmol) were added. The reaction mixture was stirred for 3.5 h and worked up as in procedure E. Concentration in vacuo followed by purification by MPLC afforded **55** (R_f 0.19, petroleum ether/5% ethyl acetate, v/v) in 98% yield: ^1H NMR δ 0.90 (t, J = 5.7 Hz, 3 H), 1.10–1.80 (m, 6 H), 2.41 (s, 3 H), 2.43 (s, 3 H), 2.58 (t, J = 7.2 Hz, 2 H), 6.11 (d, J = 15 Hz, 1 H), 6.27 (d, J = 11 Hz, 1 H), 7.77 (dd, J = 15 Hz, J = 11 Hz, 1 H); ^{13}C NMR δ 201.2, 148.7, 137.5, 127.5, 124.5, 40.2, 31.4, 24.2, 22.4, 17.5, 16.5, 13.8.

6-Pentyl-2*H*-pyran-2-one (44).[42] Dienone **55** (29 mg, 0.12 mmol) was dissolved in a solution of 4 mL of acetonitrile/1 mL of water/mercuric chloride (65 mg, 0.24 mmol, 2.0 equiv). The reaction mixture was heated to reflux for 12 h and then worked up by filtering off the mercuric salts. The filtrate was poured into ether/saturated aqueous NH_4Cl, separated, extracted with 2 × 25 mL ethyl acetate, washed with brine, and dried over $MgSO_4$. The NMR spectrum showed that the crude material was approximately a 1:1 mixture of carboxylic acid and **44**.

The crude material was dissolved in 2 mL of TFAA as in general procedure C and stirred 12 h. Purification by MPLC afforded **44** (R_f 0.47, petroleum ether/20% ethyl acetate, v/v) in 37% overall yield: IR 3030 (m), 2980 (s), 2940 (s), 2870 (m), 1725 (vs), 1635 (s), 1565 (s), 1430 (m), 1380 (m) cm^{-1}; ^1H NMR δ 0.89 (t, J = 6.1 Hz, 3 H), 1.00–2.30 (m, 6 H), 2.49 (t, J = 7.4 Hz, 2 H), 5.97 (dd, J = 6.6 Hz, J = 1.0 Hz, 1 H), 6.15 (dd, J = 9.2 Hz, J = 1.0 Hz, 1 H), 7.26 (dd, J = 9.2 Hz, J = 6.6 Hz, 1 H); ^{13}C NMR δ 166.8, 163.0, 143.7, 113.8, 102.6, 33.8, 31.1, 26.5, 22.3, 13.8.

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