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A Divergent Synthesis of Functionalized Unsaturated δ-Lactones from α-Alkenoyl-α-carboxyl Ketene Dithioacetals

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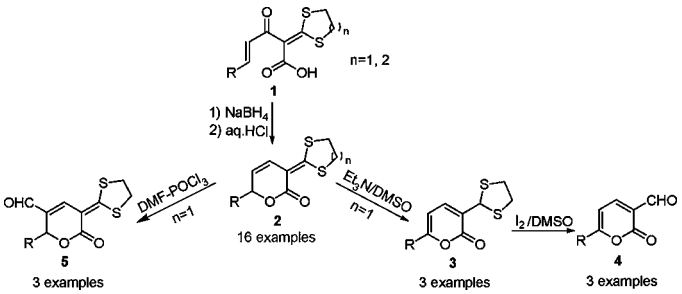

A divergent synthesis of functionalized unsaturated δ-lactones **2**, **3**, **4**, and **5** has been developed starting from the readily available α-alkenoyl-α-carboxyl ketene dithioacetals **1** in high to excellent yields under mild reaction conditions. Thus, 6-substituted 3-(1,3-dithiolan/dithian-2-ylidene)-3*H*-pyran-2(6*H*)-ones **2**, obtained from a consecutive reduction with $NaBH_4$ and acidic workup of **1** via a novel vinylogous Pummerer cyclization, can be further transformed into α-pyranones **3**, **4**, and **5** upon a sequential isomerization catalyzed by triethylamine (to give **3**), followed by dethioacetalization (to give **4**) or a formylation with Vilsmeier reagent (to give **5**).

Introduction

Unsaturated δ-lactones are found in a variety of biologically important natural products[1] and widely used as intermediates in organic synthesis.[2] To date, a number of inventive approaches for accessing the unsaturated δ-lactone structural motif have been reported.[3−15] Of these synthetic methods, the divergent strategy seems to be more efficient due to the diversity of products.[4e,15] Therefore, it is desirable to develop a divergent methodology toward unsaturated δ-lactones with the advantages of readily available starting materials, cheap reagents, mild reaction conditions, high yields, and considerable flexibility.

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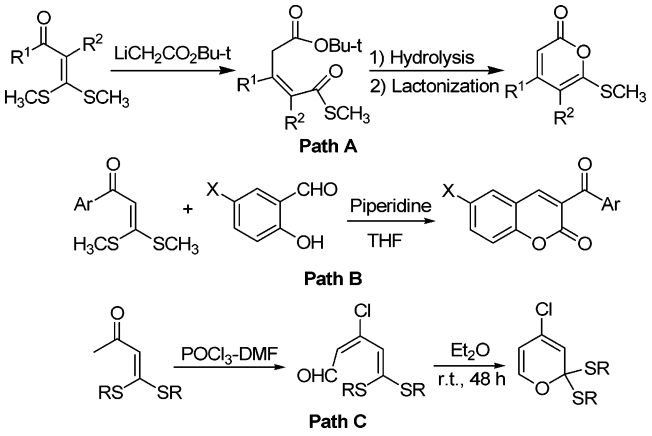
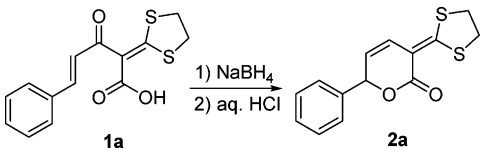
SCHEME 1



On the other hand, functionalized ketene dithioacetals are versatile synthons[16] and have found wide applications in the synthesis of various carbo-[17] and heterocyclic compounds.[18] In 1988, Dieter and Fishpaugh reported that α-oxo ketene dithioacetals could be converted into α-pyrones in good yields by a strategy involving 1,2-nucleophilic addition of ester, ketone, or hydrazone enolate anion, followed by acid-promoted rearrangement to a δ-keto ester, thiol ester, or acid and subsequent enol lactonization (Scheme 1, path A).[19a] Recently, Rao and Sivakumar also reported a facile and efficient synthesis of a combinatorial library of 3-aroylcoumarins by the condensation of α-aroylketene dithioacetals and 2-hydroxybenzaldehydes (or 2-hydroxy-1-naphthaldehyde) in the presence of a catalytic amount of piperidine (Scheme 1, path B).[19b] A little earlier, 4-chloro-2,2-bis(methylthio/benzylthio)-2*H*-pyrans (precursors of the corresponding α-pyrones) were successfully prepared by us from 4,4-bis(methylthio/benzylthio)but-3-en-2-one via the Vilsmeier−Haack reaction (Scheme 1, path C).[19c]

TABLE 1. Optimization of Conditions for the Reaction of 1a with $NaBH_4$[a]



entry	substrate	solvent	time (h)	product	yield[b] (%)
1	**1a**	MeOH	24	*c*	*c*
2	**1a**	MeOH−CH_2Cl_2 (v/v, 1:10)	3.0	**2a**	90
3	**1a**	MeOH−DMF (v/v, 1:10)	3.5	**2a**	60
4	**1a**	MeOH−THF (v/v, 1:10)	6.0	**2a**	82

[a] $NaBH_4$ (2.5 equiv), rt, then quenched by aq HCl at 0 °C. [b] Isolated yields after silica column chromatography. [c] No reaction.

In our research on the functionalized ketene dithioacetal chemistry,[20] we found that the easily available and structurally flexible α-alkenoyl ketene dithioacetals showed fascinating structural features as novel synthetic intermediates.[21] As a part of these research efforts, some tetronic acid derivatives were prepared by performing the acid-mediated intramolecular oxapyridylethylation of the corresponding α-alkenoyl-α-carboxyl ketene dithioacetals **1**.[21d] Although this cyclization is strongly dependent on the substituent at the 5-position of **1** (a 2- or 4-pyridinyl is required), the simplicity of the procedure prompted us to further explore the synthetic utility of the readily available α-alkenoyl-α-carboxyl ketene dithioacetals **1**. In this paper, a divergent synthesis of functionalized unsaturated δ-lactones **2**, **3**, **4**, and **5** starting from a wide range of ketene dithioacetals **1** is described.

Results and Discussion

α-Alkenoyl-α-carboxyl ketene dithioacetals **1** were prepared by aldol condensation of the corresponding α-acetyl-α-ethoxycarbonyl ketene dithioacetals with various aldehydes (including aliphatic, aromatic, and α,β-unsaturated aldehydes) in high yields as described in our previous reports.[21d,22] As an initial attempt, the reaction of (*E*)-2-(1,3-dithiolan-2-ylidene)-3-oxo-5- phenylpent-4-enoic acid **1a** with $NaBH_4$ was carried out at room temperature in methanol to reduce the carbonyl group at the 3-position. However, no satisfying results were obtained due to the poor solubility of **1a** in methanol (Table 1, entry 1). To improve the solubility of **1a**, mixed solvent systems, such as

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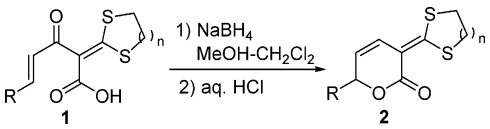
TABLE 2. Tandem Reduction and Acid-Catalyzed Lactonization of 1[a]



1 2

entry	substrate	n	R	product	time (h)	yield[b] (%)
1	**1a**	1	C_6H_5	**2a**	3.0	90
2	**1b**	1	4-FC_6H_4	**2b**	3.5	87
3	**1c**	1	2-ClC_6H_4	**2c**	4.5	80
4	**1d**	1	4-ClC_6H_4	**2d**	4.0	85
5	**1e**	1	3-$NO_2C_6H_4$	**2e**	4.0	82
6	**1f**	1	4-MeC_6H_4	**2f**	2.5	89
7	**1g**	1	4-$MeOC_6H_4$	**2g**	2.0	92
8	**1h**	1	3,4-$O_2CH_2C_6H_3$	**2h**	3.0	90
9	**1i**	1	4-$(Me)_2N$ C_6H_4	**2i**	2.0	91
10	**1j**	1	2-furyl	**2j**	4.5	84
11	**1k**	1	2-thienyl	**2k**	4.0	82
12	**1*l***	1	4-$NO_2C_6H_4$	**2*l***	5.0[c]	35[d]
13	**1m**	1	t-Bu	**2m**	3.5	78
14	**1n**	1	cyclohexyl	**2n**	12.0	37[e]
15	**1o**	1	$C_6H_5CH{=}CH$	**2o**	3.0	86
16	**1p**	2	C_6H_5	**2p**	3.0	89

[a] $NaBH_4$ (2.5 equiv), MeOH−CH_2Cl_2 (v/v, 1:10), rt, then quenched by aq HCl at 0 °C. [b] Isolated yields after silica column chromatography. [c] At reflux temperature. [d] With recovery of **1*l*** in 52%. [e] With recovery of **1n** in 51%.

TABLE 3. Experimental Results of Isomerization of 2 and Dethioacetalization of 3

entry	substrate	R	product	time (h)	yield[c] (%)
1[a]	**2a**	C_6H_5	**3a**	1	85
2[a]	**2d**	4-ClC_6H_4	**3d**	1	84
3[a]	**2f**	4-MeC_6H_4	**3f**	1.5	82
4[b]	**3a**	C_6H_5	**4a**	2.5	93
5[b]	**3d**	4-ClC_6H_4	**4d**	2	92
6[b]	**3f**	4-MeC_6H_4	**4f**	3	91

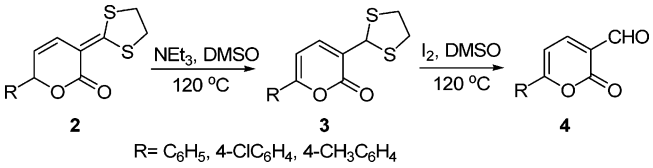
[a] NEt_3 (1.2 equiv), DMSO, 120 °C. [b] I_2 (1.0 equiv), DMSO, 120 °C. [c] Isolated yields.

MeOH−CH_2Cl_2, MeOH−DMF, and MeOH−THF, were then examined and the experimental results are listed in Table 1. Interestingly, all the reactions performed in the mixed solvent systems proceeded smoothly to directly yield unsaturated *δ*-lactone, 3-(1,3-dithiolan-2-ylidene)-6-phenyl-3*H*-pyran-2(6*H*)-one **2a** (assigned based on its ^1H NMR, ^{13}C NMR, MS spectra, and single-crystal X-ray diffraction analysis[23]) as the only product after acidic workup. By comparison, MeOH−CH_2Cl_2 (v/v, 1:10) was the best choice for this reaction (Table 1, entry 2).

The above reaction sequence indicates that the transformation of ketene dithioacetal **1a** to *δ*-lactone **2a** may serve as an efficient route to functionalized unsaturated *δ*-lactones. To expand the scope of this reaction, ketene dithioacetals **1b**−**p** with various substituents at the 5-position, for example, alkyl, aryl, heteroaryl, and α,*β*-unsaturated groups (Table 2), were selected and the lactonization reactions were performed under the optimized conditions.

It is clear that, from the results shown in Table 2, the cyclization of **1** allows a wide range of substituents at their 5-position. All of the substrates bearing an electron-donating or electron-withdrawing aryl group can efficiently afford the corresponding ring-closing products **2b**−**k** at room temperature

SCHEME 2



2 3 4

R= C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$

SCHEME 3

2 5

	R	Yield
5a:	C_6H_5	81%
5d:	4-ClC_6H_4	79%
5f:	4-$CH_3C_6H_4$	76%

in excellent yields (Table 2, entries 2−11). In the case of the strongly electron-withdrawing 4-nitrophenyl group at the 5-position, the reaction had to be performed at reflux temperature to give the desired lactone **2*l*** in fair yield (Table 2, entry 12) with the recovery of the starting material **1*l*** in 52% yield. In our research, substrates bearing both aliphatic and styryl groups at the 5-position of **1** were also tried under the identical conditions. As expected, the corresponding *δ*-lactones **2m** and **2o** were afforded in high yields (Table 2, entries 13 and 15, respectively), but **2n** was obtained only in moderate yield with recovery of **1n** in 51% yield (Table 2, entry 14) even after 12 h of reaction. Similarly, *δ*-lactone **2p** was also successfully prepared in 89% yield from **1p** bearing a 1,3-dithian-2-ylidene group at the 2-position (Table 2, entry 16).

With the consideration that *δ*-lactones **2** possess the general structural features of the synthetically versatile α-oxo ketene dithioacetals[16−22] and can be easily prepared by a one-pot procedure as described above, the transformation from *δ*-lactones **2** into diverse unsaturated *δ*-lactones was then probed. The reaction of **2a** in DMSO at 120 °C in the presence of triethylamine for 1 h gave α-pyranone **3a** in 85% yield through an olefin isomerization process (Scheme 2). Then an aldehyde **4a**, the dethioacetalization product of **3a**, was successfully produced in 93% yield by treating **3a** in DMSO at 120 °C with iodine as catalyst.[24] Similarly, functionalized α-pyranones **3d**, **3f**, **4d**, and **4f** (Table 3) were prepared in high to excellent yields starting from **2d** (with an electron-withdrawing aryl at the 6-position) and **2f** (with an electron-donating aryl at the 6-position), respectively.

In our previous research[25a,b] and also Asokan's work,[25c] the nucleophilicity of the α-carbon atom of α-EWG ketene dithioacetals (EWG = electron-withdrawing group) has been well developed and a series of heteroatom and carbon electrophiles are successfully introduced into their α-position. Accordingly, *δ*-lactones **2** can be regarded as the α-EWG ketene dithioacetal analogues with a vinylketene dithioacetal structure. To examine the nucleophilicity of the C-5 of *δ*-lactones **2**, the reaction of **2** with Vilsmeier reagent was attempted. This was successful and a formyl group was selectively introduced at the 5-position of

(23) Crystal data for **2a**: $C_{14}H_{12}O_2S_2$, colorless, M = 276.36, orthorhombic, space group $P2(1)2(1)2(1)$, a = 8.379(5) Å, b = 17.493(5) Å, c = 17.621(5) Å, V = 2582.8(19) Å^3, α = 90.000(5)°, β = 90.000(5)°, γ = 90.000(5)°, Z = 8, T = 293 K, F_{000} = 1152, R_1 = 0.0624, wR_2 = 0.1030.

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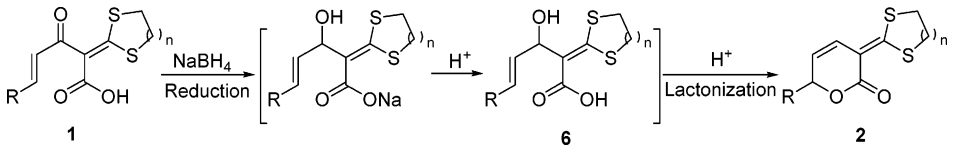
SCHEME 4



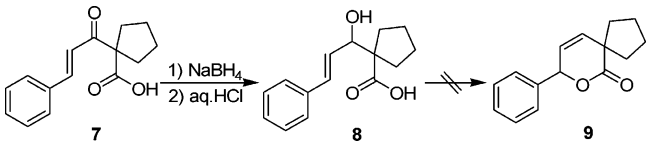
the lactone ring of **2** to give the polyfunctionalized unsaturated δ-lactones **5** in high yields (three examples are included, Scheme 3).

As presented above, we have developed a practical method to rapidly synthesize diverse unsaturated δ-lactones **2**, **3**, **4**, and **5**. These lactones possess powerful and useful functionality and are expected to be useful building blocks in the library synthesis and screening of potential bio-/pharmacological compounds. As the precursors of unsaturated δ-lactones **3**, **4**, and **5**, unsaturated δ-lactones **2** are believed to be formed via hydroxy acids **6** in a one-pot, two-step procedure (Scheme 4). However, in all cases, δ-lactones **2** were directly achieved and hydroxy acids **6** could not be isolated after acidic workup. These results imply that acids **6** are very sensitive to acid treatment, which drives the formation of lactones **2**.

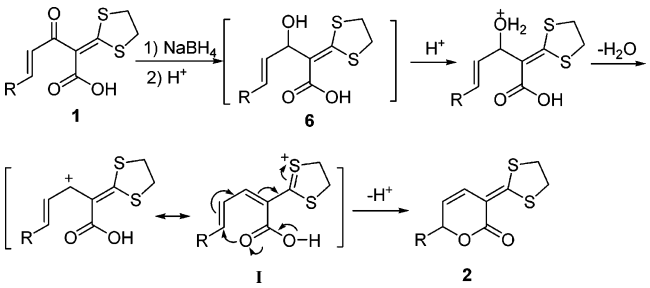
Hydroxy acids **6** can be considered as a kind of special 3-hydroxy pent-4-enoic acids with a 1,3-dithiolan/dithian-2-ylidene unit at the 2-position. It has been proved that simple 3-hydroxy pent-4-enoic acids are generally stable under acidic conditions. Their lactonizations can be accomplished with assistance of an electrophile, such as halogen[26] and selenenyl halides,[27] to afford the corresponding halolactonization and selenolactonization products. In 1993, Mestres and Aurell reported that the lactonization of 3-hydroxy-3,5-dimethylhex-4-enoic acid had to be carried out under cold concentrated sulfuric acid to afford 4,6-dimethyl-4,5-unsaturated δ-lactone via a carbocation intermediate, but this 3-hydroxy acid was proved to be inert under concentrated hydrochloric acid.[28] Compared with simple 3-hydroxy pent-4-enoic acids, functionalized 3-hydroxy pent-4-enoic acids **6** are apt to lactonize just upon the aqueous acidic conditions without requiring an electrophile as mentioned. Apparently, the ketene dithioacetal functionality of **6** plays a crucial role in this lactonization reaction.

To discover the important role of the ketene dithioacetal functionality in the reaction, a simple 3-hydroxy pent-4-enoic acid, 1-cinnamoylcyclopentanecarboxylic acid **7**, was prepared through the alkylation of ethyl acetoacetate with 1,4-dibromobutane[29] followed by the aldol condensation with benzaldehyde. Thus, hydroxy acid **8** was obtained in 80% isolated yield by treating **7** with $NaBH_4$ in MeOH−CH_2Cl_2 (v/v, 1:10) at room temperature for 1 h followed by acidic workup (Scheme 5), while lactone **9** was not observed. Moreover, acid **8** was proved to be stable and no significant changes were found when it was heated in aqueous hydrochloric acid for 5 h at reflux temperature.

SCHEME 5



SCHEME 6. Proposed Mechanism for Thionium Ion-Induced Lactonization



On the basis of all of the results mentioned above, obviously, the ketene dithioacetal functionality is crucial for the lactonization reaction. Thus, a possible mechanism, which involves a novel vinylogous Pummerer cyclization,[30] is proposed as outlined in Scheme 6. Initiated by protonation of the hydroxyl of intermediate **6** and subsequent dehydration, unsaturated thionium ion **I** is generated to result in a highly delocalized system. Subsequently, δ-lactones **2** are easily formed via the internal trapping of thionium ion **I** by the nucleophilic carboxyl group at the 5-position.

Conclusion

In summary, we have described a rapid and divergent synthesis of functionalized unsaturated δ-lactones from readily available α-alkenoyl-α-carboxyl ketene dithioacetals **1** under mild reaction conditions in high yields. As a key step for the formation of unsaturated δ-lactones **2**, a novel thionium ion-induced lactonization is proposed. Various unsaturated δ-lactones **3**, **4**, and **5**, which bear powerful and useful functionality, are obtained via simple modifications of **2**. This methodology provides an efficient and practical route to the functionalized unsaturated δ-lactones which are expected to be useful building blocks in library synthesis for the screening of potential bio-/pharmacological compounds. Further research is in progress.

Experimental Section

Starting Materials. Compounds **1** are prepared by the aldol condensation of the corresponding α-acetyl-α-ethoxycarbonyl ketene dithioacetals with various aldehydes according to our previous reports.[21d,22]

General Procedure for the Synthesis of 2 (with 2a as an example). To a well-stirred suspension of **1a** (292 mg, 1.0 mmol)

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(29) Muthusamy, S.; Gnanaprakasam, B. *Tetrahedron Lett.* **2005**, *46*, 635.

(30) (a) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. (b) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401. (c) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003.

in MeOH−CH_2Cl_2 (v/v, 1:10, 11 mL) was added $NaBH_4$ (90 mg, 2.5 mmol). The reaction mixture was stirred for 4 h at room temperature and then poured into ice−water (80 mL). The suspension was acidified by concentrated hydrochloric acid to pH 3 and extracted by CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent, petroleum ether:diethyl ether = 3:1, v/v) to give **2a** (248 mg, 90%) as a white solid.

3-(1,3-Dithiolan-2-ylidene)-6-phenyl-3*H*-pyran-2(6*H*)-one (2a): mp 126−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42−3.50 (m, 4H), 5.73 (dd, *J* = 4.0, 10.0 Hz, 1H), 6.02 (d, *J* = 1.5 Hz, 1H), 6.62 (dd, *J* = 1.5, 10.0 Hz, 1H), 7.31−7.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.5, 138.1, 127.8, 127.7 (2C), 125.9 (2C), 123.7, 119.6, 107.6, 80.7, 38.4, 35.8. IR (KBr, cm^{-1}) 3020, 2942, 2362, 1684, 1505, 1280, 1141, 1048, 894. MS calcd *m*/*z* 276.0, found 277.0 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{12}O_2S_2$: C, 60.84; H, 4.38. Found: C, 60.70; H, 4.31.

Representative Procedure for the Preparation of 3 (with 3a as an example). To a solution of **2a** (276 mg, 1.0 mmol) in DMSO (10 mL) was added Et_3N (0.17 mL, 1.2 mmol) at room temperature. After being stirred at 120 °C for 1 h, the reaction mixture was quenched with ice−water (80 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate = 10:1, v/v) to give **3a** (235 mg, 85% yield) as a yellow solid.

3-(1,3-Dithiolan-2-yl)-6-phenyl-2*H*-pyran-2-one (3a): mp 134−136 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29−3.35 (m, 4H), 5.68 (s, 1H), 6.69 (d, *J* = 7.0 Hz, 1H), 7.44−7.46 (m, 3H), 7.78 (d, *J* = 7.0 Hz, 1H), 7.81−7.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 158.4, 137.7, 130.1, 129.8, 128.0 (2C), 126.4, 124.5 (2C), 100.1, 48.9, 37.9 (2C). IR (KBr, cm^{-1}) 3073, 2360, 2342, 1701, 1558, 1491, 1110, 761. MS calcd *m*/*z* 276.0, found 277.1 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{12}O_2S_2$: C, 60.80; H, 4.38. Found: C, 60.68; H, 4.32.

General Procedure for the Preparation of 4 (with 4a as an example). To a well-stirred suspension of **3a** (138 mg, 0.5 mmol) in DMSO (5 mL) was added I_2 (127 mg, 0.5 mmol) at room temperature. After being stirred at 120 °C for 2 h, the reaction mixture was quenched with ice−water (40 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate = 9:1, v/v) to give **4a** (93 mg, 93% yield) as a yellow solid.

2-Oxo-6-phenyl-2*H*-pyran-3-carbaldehyde (4a): mp 122−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, *J* = 7.0 Hz, 1H), 7.53−7.58 (m, 3H), 7.92 (d, *J* = 7.5 Hz, 2H), 8.18 (d, *J* = 7.0 Hz, 1H), 10.17 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.6, 166.2, 160.0, 145.6, 131.9, 129.4, 128.4 (2C), 125.8 (2C), 118.0, 100.8. IR (KBr, cm^{-1}) 3041, 2871, 2361, 1717, 1543, 1345, 1186, 827. MS calcd *m*/*z* 200.1, found 201.0 $[(M + 1)]^+$. Anal. Calcd for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 71.89; H, 3.96.

Typical Procedure for the Synthesis of 5 (with 5a as an example). To a solution of **2a** (276 mg, 1.0 mmol) in DMF (10 mL) was added $POCl_3$ (0.46 mL, 5 mmol) at room temperature. After being stirred at 60 °C for 6 h, the reaction mixture was quenched with ice−water (80 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate = 3:1, v/v) to give **5a** (246 mg, 81% yield) as a yellow solid.

5-(1,3-Dithiolan-2-ylidene)-6-oxo-2-phenyl-5,6-dihydro-2*H*-pyran-3-carbaldehyde (5a): mp 136−138 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52−3.68 (m, 4H), 6.35 (s, 1H), 7.31 (br s, 5H), 7.50 (s, 1H), 9.54 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 174.5, 162.6, 140.4, 138.4, 130.1, 128.9, 128.8 (2C), 126.7 (2C), 108.6, 78.7, 40.1, 37.2. IR (KBr, cm^{-1}) 3066, 2361, 2343, 1661, 1613, 1478, 1178, 793. MS calcd *m*/*z* 304.0, found 304.9 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{12}O_3S_2$: C, 59.19; H, 3.97. Found: C, 59.05; H, 3.90.

Synthesis of 7. Ethyl 1-acetylcyclopentanecarboxylate was first synthesized according to the literature.[29] Then, to a solution of ethyl 1-acetylcyclopentanecarboxylate (184 mg, 1.0 mmol) in EtOH (10 mL) was added benzaldehyde (0.10 mL, 1.1 mmol) and NaOEt−EtOH (4.0 mL, M = 1 mol/L, 4.0 mmol). The reaction was allowed to proceed at room temperature and complete in 1 h. The reaction mixture was quenched with water, acidified by concentrated hydrochloric acid to pH 3, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate = 1:1, v/v) to give **7** (182 mg, 75%) as a white solid.

1-Cinnamoylcyclopentanecarboxylic acid (7): mp 87−89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67−1.75 (m, 4H), 2.22−2.30 (m, 4H), 6.86 (d, *J* = 15.5 Hz, 1H), 7.37−7.41 (m, 3H), 7.55 (d, *J* = 6.0 Hz, 2H), 7.74 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 179.7, 144.3, 134.3, 130.7, 128.9 (2C), 128.6 (2C), 121.8, 65.6, 33.4 (2C), 25.9 (2C). IR (KBr, cm^{-1}) 3062, 2956, 2360, 2345, 1715, 1608, 1450, 1205. MS calcd *m*/*z* 244.1, found 245.0 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.70; H, 6.52.

Synthesis of 8. To a well-stirred suspension of **7** (244 mg, 1.0 mmol) in MeOH−CH_2Cl_2 (v/v, 1:10, 11 mL) was added $NaBH_4$ (90 mg, 2.5 mmol). The reaction mixture was stirred for 1 h at room temperature and then poured into ice−water (80 mL). The suspension was acidified by concentrated hydrochloric acid to pH 6, then extracted by CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent, petroleum ether: ethyl acetate = 1:1, v/v) to give **8** (197 mg, 80%) as a colorless oil.

(*E*)-1-(1-Hydroxy-3-phenylallyl)cyclopentanecarboxylic acid (8): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (br s, 1H), 1.65−1.77 (m, 5H), 1.98−2.21 (m, 3H), 4.34 (d, *J* = 7.0 Hz, 1H), 6.24 (dd, *J* = 7.0, 16.0 Hz, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 135.2, 132.4, 127.6 (2C), 127.0, 126.4, 125.6 (2C), 76.5, 56.8, 34.0, 31.3, 25.0, 24.7. IR (KBr, cm^{-1}) 3076, 2924, 2853, 1715, 1653, 1333, 1200. MS calcd *m*/*z* 246.1, found 247.0 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.32.

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Supporting Information Available: Experimental details, spectral and analytical data for compounds **1**, **2**, **3**, **4**, **5**, **7**, and **8**, copies of ^{1}H NMR and ^{13}C NMR spectra of **1n**, **2**, **3**, **4**, **5**, **7**, and **8**, and crystallographic data for **2a** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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