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Article

Brønsted Acid-Promoted Cyclodimerization of α,β-Unsaturated γ-Ketoesters: Construction of Fused Pyrano-ketal-lactones and γ-Ylidene-butenolides

Ramavath Vinodkumar, Ashwini K. Nakate, Himanshu Sharma, Kumar Vanka, Gamidi Rama Krishna, and Ravindar Kontham*

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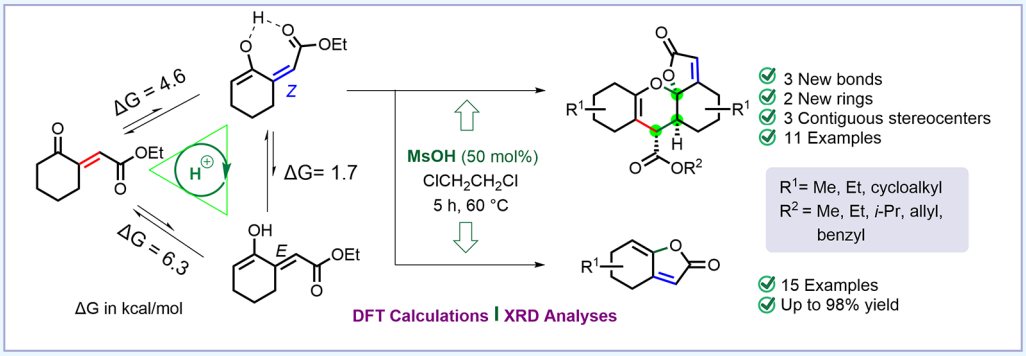

ABSTRACT: Unprecedented MsOH-promoted diastereoselective cascade dimerization and intramolecular lactonization of readily accessible α,β-unsaturated γ-ketoesters are presented. The results obtained in this work, control experiments, and density functional theory (DFT) calculations suggested that the initial enolization and *E* to *Z* isomerization/equilibration of olefin (C═C) of substrate α,β-unsaturated γ-ketoesters give a *Z*-isomer preferentially over an *E*-isomer. Subsequently, the *Z*-isomer undergoes intermolecular annulation with α,β-unsaturated γ-ketoesters via domino Michael addition/ketalization/lactonization steps to furnish fused tetracyclic pyrano-ketal-lactone. However, the *Z*-isomer prefers intramolecular trans-esterification in a competing pathway and gives bicyclic γ-ylidene-butenolide. The key features of this work include simple Brønsted acid catalysis, the formation of three bonds, two rings, and three contiguous stereogenic centers in a single step, DFT calculations, and the assignment of relative stereochemistry through X-ray diffraction (XRD) and two-dimensional (2D) nuclear magnetic resonance (NMR) analyses.

INTRODUCTION

The biological activity, stereochemical and structural complexity of natural and unnatural molecules is a longstanding motivation for organic chemists to develop novel synthetic methodologies. In recent times, the expansion of the chemical space in drug discovery has encountered the inclusion of diverse three-dimensional small molecules possessing sp^3-rich scaffolds.[1] Major problems associated with the sp^3-rich molecules-based drug discovery include the lack of efficient synthetic methods, stereochemical selectivity, and supply. In the last four decades, an upsurge in the development of cascade/domino reactions enabling the construction of intricate molecular scaffolds from simple building blocks with brevity has been witnessed to address these concerns.[2] Notably, dimerization reactions represent synthetically powerful strategies for rapidly constructing molecular complexity in organic synthesis.[3]

So far, various dimerization reactions have been disclosed for the facile stereoselective construction of natural and unnatural molecules, which include [1 + 1] radical dimerization of resveratrol,[4] oxidation of isatins,[5] alkynols,[6] the [4 + 4]-cycloaddition reaction to give eight-membered rings, and others.[7] Moreover, diverse domino dimerization reactions involving the initial addition of *p*-quinol alcohol onto an electrophilic enone followed by 5-*exo*-trig ring-closure to give fused oxa-heterocycles are well-documented, and Carreño's quadruple domino reaction to afford a pentacyclic trimer is one of the notable examples.[8]

Recently disclosed Duarte and Lawrence's dimerization (domino [1,4]/[1,4]/[1,4]/[1,4] addition) of *p*-quinols to construct tetracyclic caged oxa-heterocycles (via the con-

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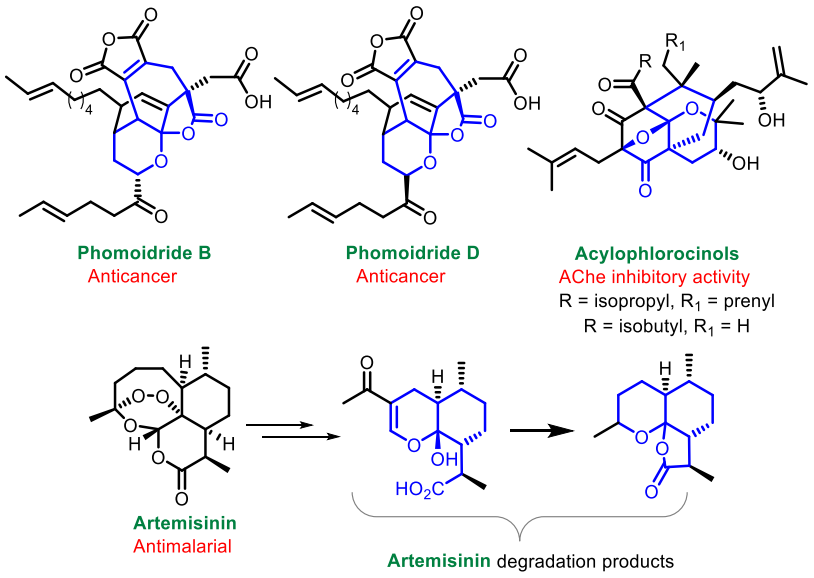
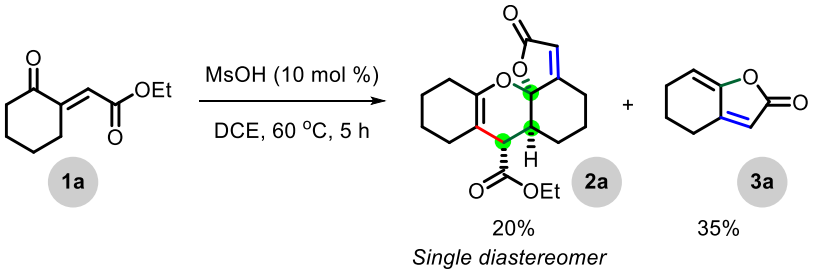


Figure 1. Natural products containing fused pyrano-ketal-lactones and pyrano-ketals.

Scheme 1. Initial Synthesis of the Fused Pyrano-ketal-lactone (2a) and γ-Ylidene-butenolide (3a)



ORTEP Diagram of **2a**
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struction of four new bonds, four rings, and eight stereogenic centers) is considered as a most complex example of the dimerization reaction ever disclosed.[9] However, dimerization cascades of unsaturated ketoesters involving Brønsted acid catalysis and carbon-based nucleophiles remain elusive.

Fused pyrano-ketal scaffolds found in numerous bioactive natural products (for instance, alboartins, xyloketals A−D and H, hyperaspidinol, myxostiolides, spicatolide-C, guaianolide, and others)[10] and fused pyrano-ketal-lactones are key structural units in diverse bioactive natural products phomoidride B and D,[11] acylophlorocinols,[12] and artemisinin degradation products (Figure 1).[13] Inspired by the exciting structural and biochemical features of furo-pyran-containing molecules, our research group recently reported novel synthetic methodologies for the facile construction of furo-pyranones (fused pyrano-ketal-lactones),[14a] chromanol-lactones,[14b] and other oxygen-heterocycles via intermolecular cascade annulation reactions.[14] Herein, we disclose our fortuitous findings of MsOH (methanesulfonic acid)-mediated enolization and *E* to *Z* isomerization/equilibration of *α,β*-unsaturated *γ*-ketoesters **1**,[15] wherein the *Z*-isomer undergoes domino Michael addition/ketalization/lactonization with **1** to furnish complex pyrano-ketal-lactones **2**, and also delivers the bicyclic *γ*-ylidene-butenolide **3** through competing intramolecular lactonization (*vide infra*) (Scheme 1).

RESULTS AND DISCUSSION

The initial scouting reaction was performed using a known *α,β*-unsaturated *γ*-ketoester (**1a**)[14b] as a model substrate. The first experiment using 10 mol % MsOH as a promoter in dichloroethane (DCE) solvent at room temperature (rt) for 24 h did not lead to any conversion (Table 1, entry 1). To our delight, when the reaction temperature was increased to 60 °C, cyclodimerization product **2a** was obtained as a single diastereomer and also *γ*-ylidene-butanolide **3a** in 20 and 35% yield, respectively, in a long reaction time of 24 h (Table 1, entry 2). Nuclear magnetic resonance (NMR), mass spectrometry (MS), and single-crystal X-ray diffraction analyses unambiguously established the structure and relative stereochemistry of **2a**. Product **3a** was confirmed by

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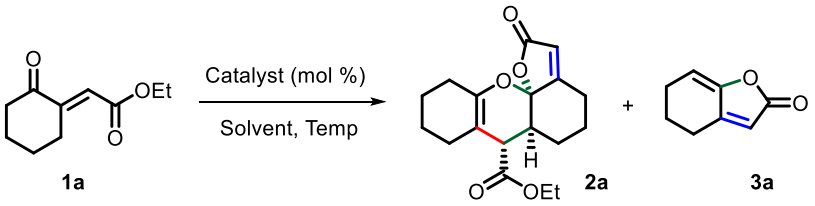
Table 1. Reaction Optimization Studies[a]



entry	catalyst (mol %)	solvent, temp	2a[b]	3a[b]
1[c,d]	MsOH (10 mol %)	DCE, rt	-	-
2[d]	MsOH (10 mol %)	DCE, 60 °C	20	35
3[c,d]	*p*-TSA (10 mol %)	DCE, rt	-	-
4[d]	*p*-TSA (10 mol %)	DCE, 60 °C	8	25
5[c,d]	PPTS (10 mol %)	DCE, rt	-	-
6[c,d]	PPTS (10 mol %)	DCE, 60 °C	-	-
7[d]	TFA (10 mol %)	DCE, 60 °C	10	32
8[d]	TfOH (10 mol %)	DCE, 60 °C	10	25
9[c,d]	AcOH (10 mol %)	DCE, 60 °C	-	-
10[c,d]	CSA (50 mol %)	DCE, rt	-	-
11[c,d]	CSA (50 mol %)	DCE, 60 °C	-	-
12[c,d]	L-proline (10 mol %)	DCE, 60 °C	-	-
13[c,d]	(*R*)-BINOL-phosphoric acid (10 mol %)	DCE, 60 °C	-	-
14[e]	MsOH (50 mol %)	DCE, 60 °C	24	70
15[e]	MsOH (100 mol %)	DCE, 60 °C	20	68
16[c,d]	MsOH (10 mol %)	CH_3CN, rt	-	-
17[c,d]	MsOH (10 mol %)	CH_3CN, 60 °C	-	-
18[c,d]	MsOH (100 mol %)	CH_3CN, rt	-	-
19[c,d]	MsOH (100 mol %)	CH_3CN, 60 °C	-	-
20[c,d]	no catalyst	DCE, 60 °C	-	-

[a]Reaction conditions unless otherwise specified: **1a** (0.5 mmol) was used in 2 mL of solvent. [b]Isolated % yields. [c]No conversion was observed. [d]The reaction time is 24 h. [e]The reaction time is 5 h. DCE = dichloroethane.

comparison of its NMR data with the reported data.[16] The imparted exclusive diastereoselectivity of the dimerized product **2a** could be attributed to the extra stability of the *axial* ketal-lactone group by anomeric and associated effects (Scheme 1; entries 1 and 2 of Table 1).[17]

Encouraged by these initial results and to improve the outcome of the reaction, we further verified the effect of other Brønsted acid catalysts and reaction parameters (Table 1). The reaction using *para*-toluenesulfonic acid (*p*-TSA), pyridinium *p*-toluenesulfonate (PPTS), trifluoromethanesulfonic acid (TfOH), and trifluoroacetic acid (TFA) at room temperature did not lead to any conversion. However, products **2a** and **3a** were formed at 60 °C in good yields with moderate selectivity and close to MsOH in 24 h (entries 1−8). No conversion was observed using AcOH and CSA at rt and in DCE at 60 °C even in a prolonged reaction time of 24 h (entries 9−11). It was also found that increased catalyst loading, reaction temperature, and reaction time had a detrimental effect on the outcome using these Brønsted acid catalysts (entries 3−11). Next, we verified the influence of chiral Brønsted acid catalysts L-proline and (*R*)-BINOL-derived phosphoric acid and found that they are incompatible with this cascade reaction (entries 12 and 13). As an ultimate option, MsOH was chosen as a reliable promoter due to its clean reaction profile and the effects of its loading (using 30, 40, 50, and 100 mol %) and solvents (DCE, ACN) at 60 and 100 °C (entries 14 and 15) were further verified. To our delight, the reaction using 50 mol % MsOH in DCE at 60 °C for 5 h was found to be optimal for this transformation by giving **2a** and **3a** in 24 and 70% isolated yields, respectively (Table 1, entry 14).[16]

Having optimal reaction conditions in hand, we set out to synthesize diverse α,β-unsaturated γ-ketoesters **1** using our earlier optimized reaction conditions (aldol reaction of cyclohexanones with ethyl glyoxylate, mesylation, and elimination sequence)[14b16] and then embarked onto the substrate scope studies.

Substrates possessing 2-methyl cyclohexanone, 3-methyl cyclohexanone, 4-methyl cyclohexanone, and 4-ethyl cyclohexanone participated well in this transformation and delivered anticipated products **2b**−**2e** (**2b** with a 2:1 diastereomeric ratio and **2c**−**2e** with 1:1 dr) and **3b**−**3e** in good yields (entries 2−4, Scheme 2). Switching of enone-ethyl esters to methyl, isopropyl, allyl, and benzyl esters delivered corresponding products **2f**, **2g**, **2h**, and **2i** and butenolide **3a** with equal ease and outcome (entry 5). Cycloheptane-tethered enone also participated well and produced the corresponding dimer **2m** and butenolide **3m** (entry 6). However, cyclooctane-tethered enone-ester gave the dimer **2n** exclusively (with a 2:1 diastereomeric ratio), and no trace amount of butenolide **3n** was noticed (entry 7). X-ray diffraction analyses rigorously assigned products **2a**, **2f**, and **2i**; the analogy confirmed the remaining products (Scheme 2 and Figure 2).

In contrast to these results, 3,3-dimethyl- and 3,3,5-trimethyl-cyclohexanone-derived substrates (**1j** and **1k**) failed to produce dimers and instead furnished corresponding butenolides **3j** and **3k** exclusively in good yields (Scheme 3, entries A and B).[18,19] In contrast, cyclopentane-derived enone-ester underwent inward double-bond isomerization and gave **4a** instead of lactonization or dimerization products (Scheme 3, entry C).[14b]

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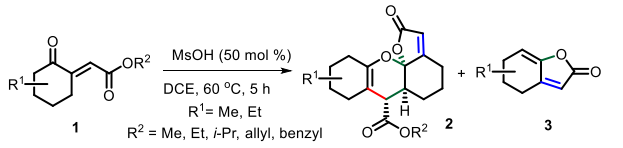
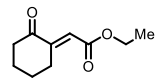
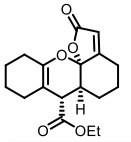
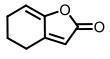
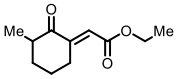
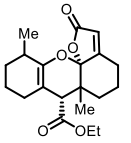
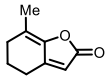
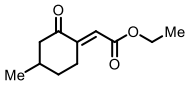
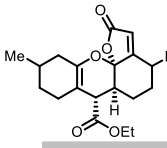
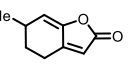
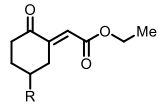
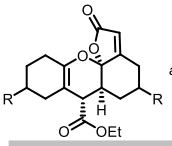
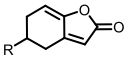
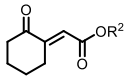
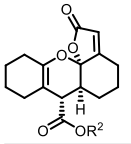
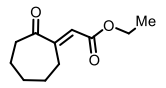
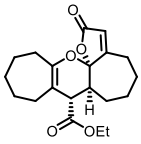
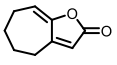
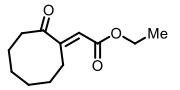
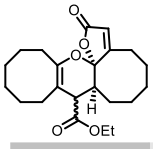
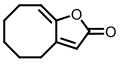
Scheme 2. Synthesis of Fused Pyrano-ketal-lactones 2 and γ-Ylidene-butenolides 3[a,b]



Entry	Substrate (1)	Product (2 and 3)	
1	 1a	 and 	2a, 24% *1 g scale*, 22% / 3a, 70% *1 g scale*, 70%
2	 1b	 and 	2b, 26% (dr 2:1) / 3b, 41%
3	 1c	 and 	2c, 20% (dr 1:1) / 3c, 46%
4	 1d (R = Me) 1e (R = Et)	 and 	2d (R = Me), 19% (dr 1:1) / 3d (R = Me), 46% 2e (R = Et), 24% (dr 1:1) / 3e (R = Et), 57%
5	 1f (R = Me) 1g (R = *i*-Pr) 1h (R = allyl) 1i (R = Bn)	 and 3a	2f (R = Me), 25% / 3a, 52% 2g (R = *i*-Pr), 28% / 3a, 65% 2h (R = allyl), 27% / 3a, 48% 2i (R = Bn), 21% / 3a, 78%
6	 1m	 and 	2m, 26% / 3m, 59%
7	 1n	 and 	2n, 32% (dr 2:1) / 3n, 0%

[a]See the Supporting Information (SI) for the synthesis of starting materials **1**. [b]Isolated yield.

Next, we were curious to verify the reactivity of α,β-unsaturated γ-ketoesters **1** possessing an acyclic ketone moiety, for which the $E \rightarrow Z$ isomerization profile can be quite different, leading to differential selectivity over the formation of products **2** and **3**. Accordingly, a series of substrates **1** containing methyl, isopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, and ethyl-tethered ketones were synthesized and subjected to the annulation reaction using optimized conditions, which delivered corresponding γ-ylidene-butenolides[18,19] **3o**−**3u** in moderate to good yields (61−98%) exclusively (entries 1−7, Scheme 4). This outcome could be attributed to the preferential $E \rightarrow Z$ isomerization of enone **1** and subsequent enolization-induced lactonization (in previous reports, similar products were obtained through the ring-closure of corresponding keto-acids).[18] Ketoester **1v** possessing trisubstituted olefin gave the ketal-lactone **3v** (entry 8) instead of the expected γ-ylidene-butenolide. The structure and stereochemistry of butenolides **3u** and **3t** were established by comparison of NMR data with the reported data[19] and nuclear over-Hauser effect spectroscopy (NOESY) correlations.[16] Further, the utility of this protocol was exemplified by performing gram-scale experiments and preparing products **2a**/**3a** (Scheme 2) and **3p** (Scheme 4) with good yields.

To gain insight into the mechanistic sequence of this protocol, we performed a reaction of **3a** with MsOH (using optimized conditions) to verify the probable ring opening and dimerization, where we did not observe any change and the conversion of **3a** into starting material **1a** or dimer **2a** (entry A, Scheme 5). Next, we tested the reaction between butenolide **3b** and ketoester **1a** under optimal reaction conditions to verify the probable inverse electron-demand Diels−Alder reaction, which delivered butenolide **3a**, homodimer **2a**, and unreacted butenolides **3b**, providing evidence for the absence of the suspected [4 + 2]-cycloaddition pathway (entry B, Scheme 5).

In order to provide a comprehensive analysis of the formation of products γ-ylidene-butenolide (**3a**) and pyrano-ketal-lactones (**2a**), we employed density functional theory (DFT) to perform full quantum chemical calculations. In the presence of MsOH, the α,β-unsaturated γ-ketoester (**1a**) undergoes a tautomerization process, resulting in the formation of *E* and *Z* isomers, denoted as **T1** and **T2**, respectively. Despite this process being endergonic, there exists a thermodynamic preference favoring the *Z*-isomer (**T2**) over the *E*-isomer (**T1**) by 1.7 kcal/mol. This preference can be attributed to the presence of a hydrogen bond in the **T2** isomer, providing increased stability compared to **T1**, as illustrated in Figure 3A. In the subsequent step, the *Z*-isomer (**T2**) undergoes lactonization with the assistance of MsOH acid, forming major product **3a** through an eight-membered cyclic transition state (**TS**). The lactonization is an exergonic step, with a free-energy change (ΔG_{sol}) of 1.4 kcal/mol and a corresponding free-energy barrier ($\Delta G_{sol}^{\#}$) of 21.4 kcal/mol, as illustrated in Figure 3B.

Furthermore, to gain a deeper comprehensive understanding of the formation of the minor product [pyrano-ketal-lactones (**2a**)], we have investigated a mechanism where the α,β-unsaturated γ-ketoester (**1a**) reacts with the more thermodynamically favorable tautomer, the *Z*-isomer (**T2**). The nucleophilic carbon of the *Z*-isomer (**T2**) initiates a Michael addition reaction by attacking the electrophilic carbon of the α,β-unsaturated γ-ketoester (**1a**). This reaction leads to the formation of an intermediate **T3**, which contains a newly formed C−C bond. This exergonic addition reaction releases 8.4 kcal/mol of energy and occurs via a six-membered transition state **TS1**, with an activation energy of 26.9 kcal/mol. The next step involves the enolization process in which

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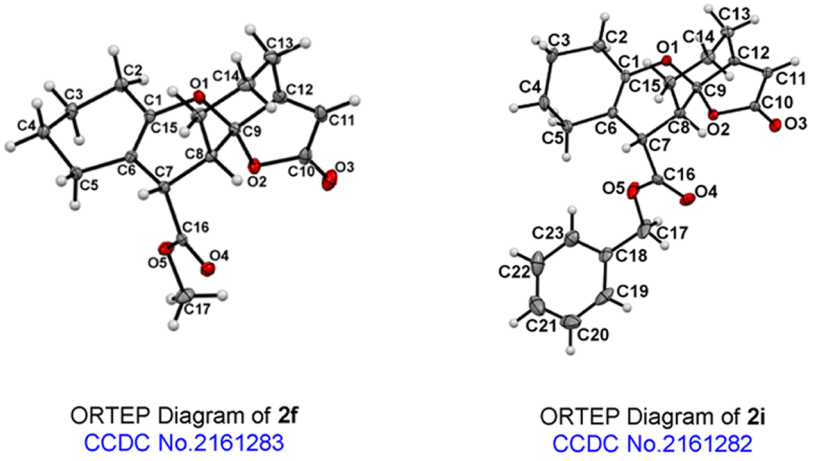
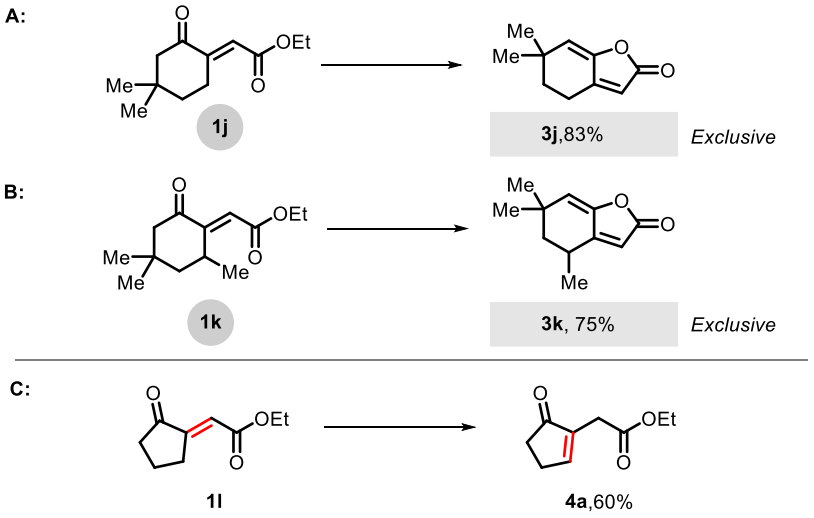


Figure 2. ORTEP diagrams of fused pyrano-ketal-lactones **2f** and **2i**.

Scheme 3. Reaction Profiles of Other α,β-Unsaturated γ-Ketoesters[a,b]



[a]See the Supporting Information (SI) for the synthesis of starting materials **1**. [b]Reaction conditions: MsOH (50 mol %), DCE, 60 °C, Isolated yield.

intermediate **T3** generates intermediate **T4** with the assistance of MsOH acid. This enolization process is highly endergonic, with a ΔG_{sol} of 6.3 kcal/mol, and occurs through an eight-membered transition state **TS2**, which presents an energy barrier of 18.7 kcal/mol. Subsequently, intermediate **T4** initiates a hemiketalization reaction, progressing through the eight-membered transition state **TS3** ($\Delta G_{sol}^{\#}$ = 10.7 kcal/mol), which releases a modest 0.1 kcal/mol of free energy and results in the formation of intermediate **T5**. It is important to note that this step is reversible, allowing for the conversion of **T5** back to **T4** with an equivalent energy barrier of 10.8 kcal/mol (Figure 4).

In the final stage of the reaction mechanism, intermediate **T5** undergoes lactonization to yield the desired product **2a**. This lactonization process is exergonic, releasing 4.3 kcal/mol of free energy. However, it is marked by a notable free-energy barrier (**TS4**) of 19.3 kcal/mol, which stands 8.5 kcal/mol higher than the reverse energy barrier for **T5** to revert to **T4**.

Upon a thorough analysis of the energy profiles for the formation of **3a** and **2a**, a noticeable difference emerges. The overall free-energy barrier for the formation of **2a** is measured at 26.9 kcal/mol, involving four sequential steps. Conversely, the formation of **3a** from **1a** presents a significantly lower free-energy barrier of 26.0 kcal/mol, requiring only a single-step process. In light of these findings and in accordance with the Eyring equation, it is reasonable to anticipate the coexistence of both products, with **3a** being the major product and **2a** the minor one, under the specified reaction conditions.

Based on results obtained in this work, control experiments, DFT calculations, and previous reports,[14,15] a plausible mechanistic sequence is presented in Scheme 6. The reaction is initiated by the Brønsted acid (MsOH)-mediated equilibration of substrate **1** into its *E* (**T1**) and *Z* (**T2**, favored and stabilized by intramolecular hydrogen bonding) reaction intermediates, which would diversify the outcome. The *Z*-isomer **T2** would lead to the formation of γ-ylidene-butenolide **3** through lactonization (Scheme 6, Path A). In contrast, the *E*-isomer **1** would undergo dimerization reaction via MsOH-promoted Michael addition (conjugate addition) of **T2** on to **1** to give **T3**. Subsequent enolization of **T3** to form **T4** (via **TS2**) followed by the intramolecular hemiketalization (to give **T5**) and lactonization cascade delivers fused pyrano-ketal-lactone **2** (Scheme 6, Path B).

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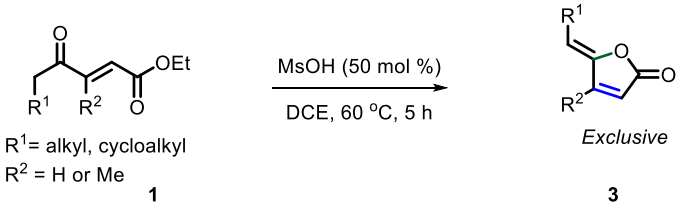
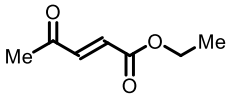
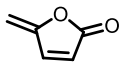
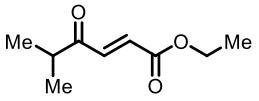
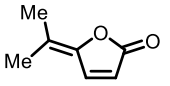
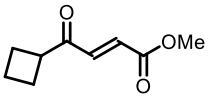
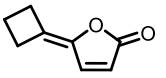
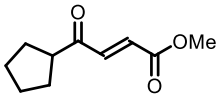
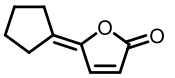
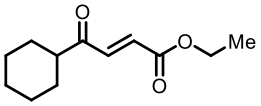
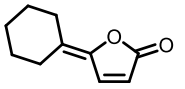
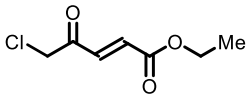
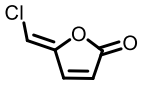
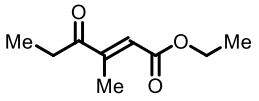
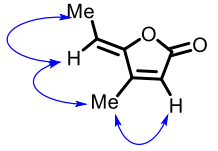
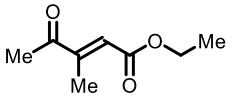
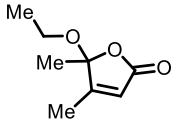
Scheme 4. Synthesis of γ-Ylidene-butenolides 3[a,b]



R[1]= alkyl, cycloalkyl
R[2] = H or Me

1 **3**

Entry	Substrate (**1**)	Product (**3**)
1	 **1o**	 **3o**, 67%
2	 **1p**	 **3p**, 98% ***1 g scale***, 90%
3	 **1q**	 **3q**, 94%
4	 **1r**	 **3r**, 95%
5	 **1s**	 **3s**, 61%
6	 **1t**	 **3t**, 75% *Single isomer*
7	 **1u** NOESY Correlations	 **3u**, 89% *Single isomer*
8	 **1v**	 **3v**, 65%

[a]See the Supporting Information (SI) for the synthesis of starting materials **1**. [b]Isolated yield.

CONCLUSIONS

In conclusion, we have identified the first MsOH-promoted divergent access to complex fused pyrano-ketal-lactones by forming three new bonds, two rings, and three contiguous stereocenters, and γ-ylidene-butenolides related to bioactive natural products from readily accessible α,β-unsaturated γ-ketoesters. Cycloalkanone-derived substrates furnished both products (pyrano-ketal-lactones and γ-ylidene-butenolides), whereas substrates containing acyclic ketones delivered exclusively known γ-ylidene-butenolides. Products were

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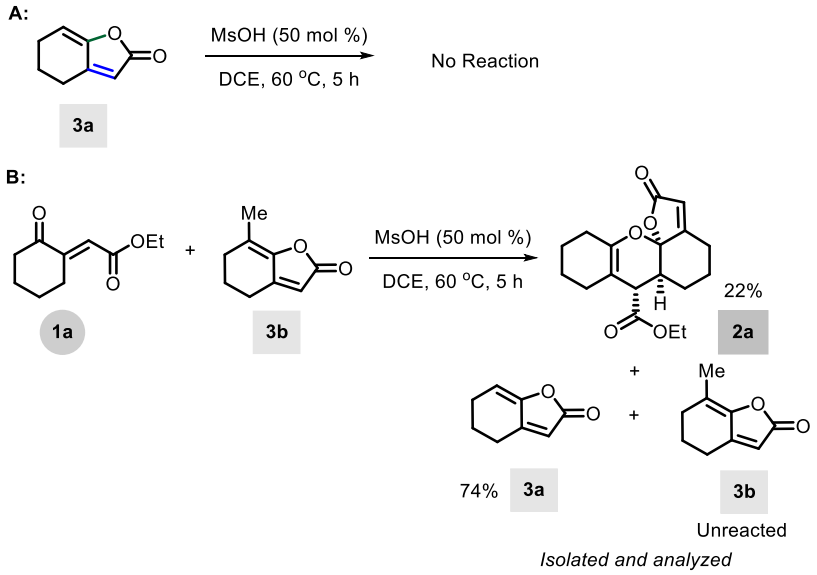
Scheme 5. Supporting Experiments for the Mechanism



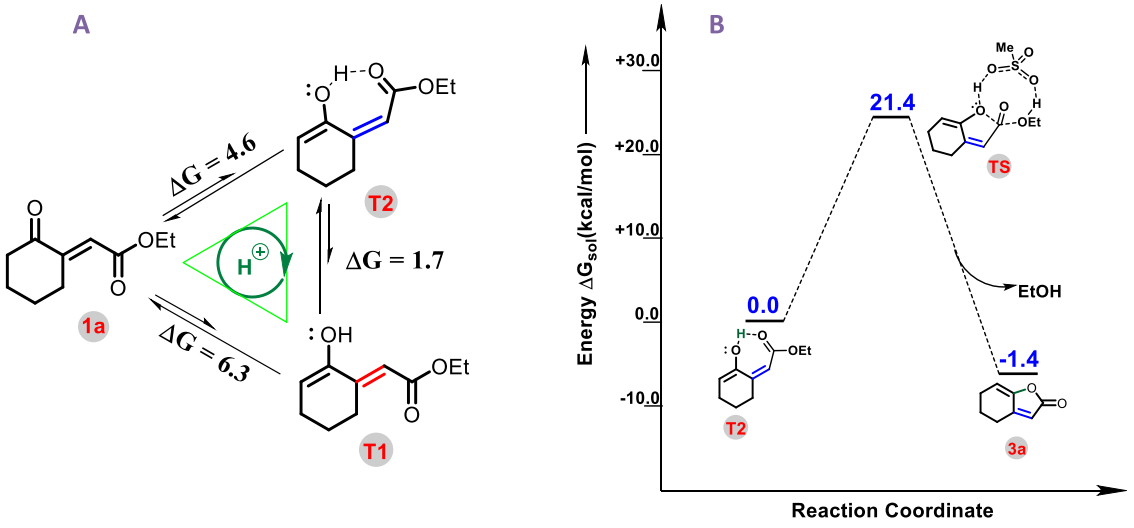


Figure 3. (A) Tautomerization of the α,β-unsaturated γ-ketoester (**1a**) and (B) free-energy profile for the formation of product γ-ylidene-butenolide (**3a**) have been shown here. The DFT calculations have been done at the PBE-D3/def2-TZVP level of theory using DCE as the solvent (ε = 10.36). All of the values are in kcal/mol.

unambiguously confirmed by NMR and single-crystal X-ray analyses and analogy. DFT calculations supported the experimental outcome and provided insights into the most probable mechanistic sequences. This protocol provided novel chemical entities with structural and stereochemical complexity in good yields, employing a simple Brønsted acid as a promoter. This protocol provided novel chemical entities with structural and stereochemical complexity, employing a simple Brønsted acid as a promoter. This work may provide solutions for designing unique cascade dimerization reactions and pave the way for building a complex three-dimensional chemical space.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under an argon atmosphere immediately before use. Anhydrous dichloromethane, dichloroethane, methanol, and fluorobenzene were purchased from commercial sources and used without further treatment. Reaction temperatures are reported as the bath temperature surrounding the reaction vessel, and 30 °C corresponded to the laboratory's room temperature (rt) when the experiments were carried out. Analytical thin-layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with short-wave UV light, anisaldehyde, or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (100−200 mesh) by standard techniques eluting with solvents as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 in solvents, as shown. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references, and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.27 ppm, δC = 77.00 ppm). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet;

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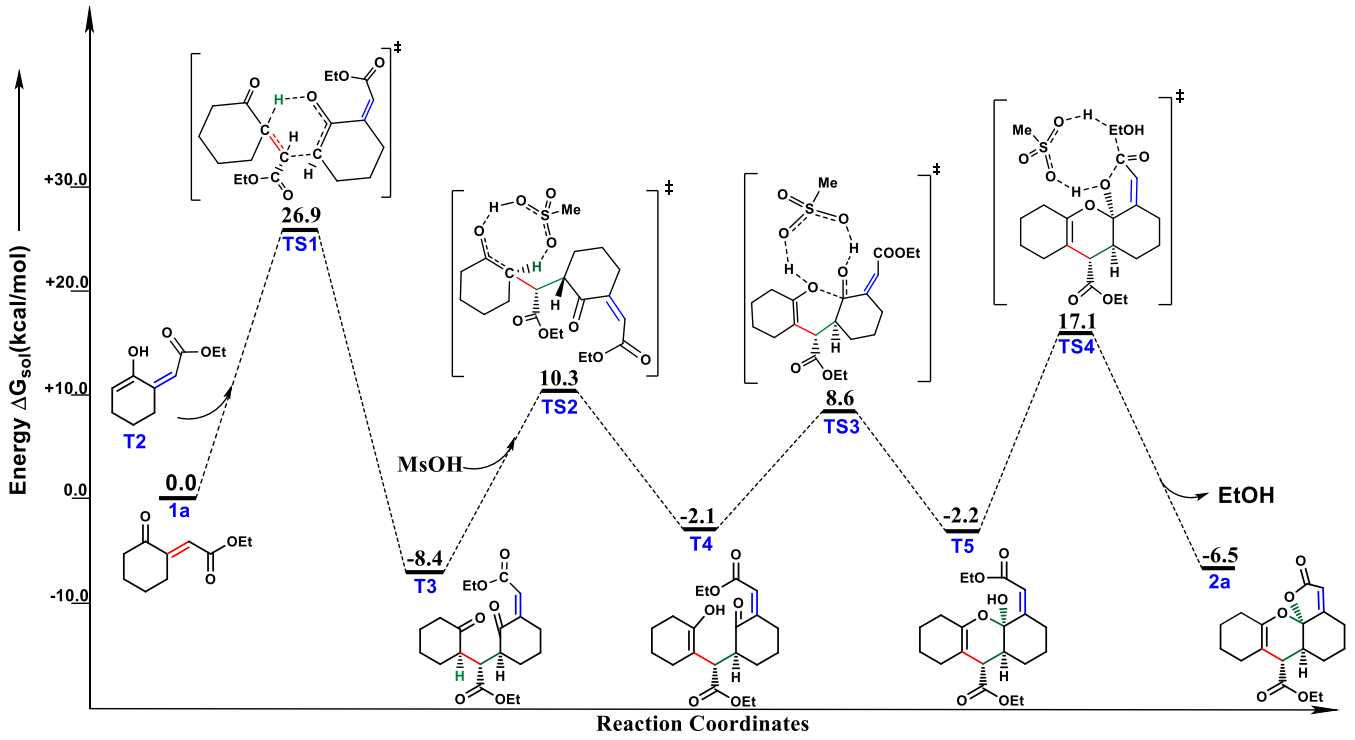
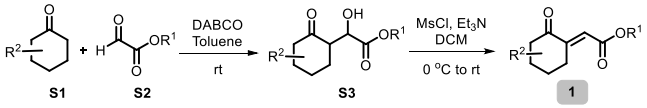


Figure 4. Free-energy profiles with volume correction, for the formation of product **2a** has been shown here. The DFT calculations have been done at the PBE-D3/def2-TZVP level of theory using dichloroethane (DCE) as a solvent (ε = 10.36). All of the values are in kcal/mol.

dd, doublet of doublet; td, triplet doublet; and br, broad. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. High-resolution mass spectrometry (HRMS) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump, FT-IR instrument (Bruker α Model), at normal temperature with a KBr pellet (IR grade). Experimental procedures for all new and known compounds without published experimental procedures are described below.

Synthesis of α,β-Unsaturated γ-Ketoesters (1) (Method A).[16]



*Ethyl (E)-2-(4-Methyl-2-oxocyclohexylidene)acetate (**1c**).* 3-Methyl cyclohexanone (**A**, 10.9 g, 97 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture, DABCO (1.31 g, 11 mmol) was added slowly over 10 min at rt, followed by ethyl glyoxalate (1 g, 9 mmol) dropwise. Then, the reaction mixture was stirred overnight at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(4-methyl-2-oxocyclohexyl)acetate (**S3c**) (0.92 g, 44%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Compound **S3c** (0.92 g, 4.29 mmol) was taken in a flame-dried two-neck 100 mL round-bottom flask, dissolved in anhydrous dichloromethane (DCM, 40 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then, Et_3N (0.72 mL, 5.11 mmol) was added slowly, followed by $MeSO_2Cl$ (0.39 mL, 5.1 mmol) dropwise at 0 °C. The reaction mixture was allowed to stir at rt overnight. Then, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-2-(4-methyl-2-oxocyclohexylidene)acetate (**1c**) (0.54 g, 40%), overall yield (17.6%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (br. s., 1H), 4.34−4.05 (m, 2H), 3.60 (d, J = 17.55 Hz, 1H), 2.77−2.48 (m, 2H), 2.12−1.98 (m, 2H), 1.62 (br. s., 2H), 1.32−1.26 (m, 4H), 1.05 (dd, J = 6.10, 3.05 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 201.3, 166.1, 150.7, 122.1, 60.6, 49.1, 31.5, 30.4, 27.5, 21.7, 14.2; HRMS (ESI) m/z calcd for $C_{11}H_{16}O_3Na$ $[M + Na]^+$, 219.0992; found, 219.0986.

*Ethyl (E)-2-(5-Methyl-2-oxocyclohexylidene)acetate (**1d**).* 4-Methyl cyclohexanone (10.99 g, 97 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture, DABCO (1.31 g, 11.6 mmol) was added slowly over 10 min at rt, followed by ethyl glyoxylate (1 g, 9.8 mmol) dropwise. Then, the reaction mixture was stirred overnight at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(5-methyl-2-oxocyclohexyl)acetate (**S3d**) (1.33 g, 64%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Next, **S3d** (1.33 g, 6.2 mmol) was forwarded to the

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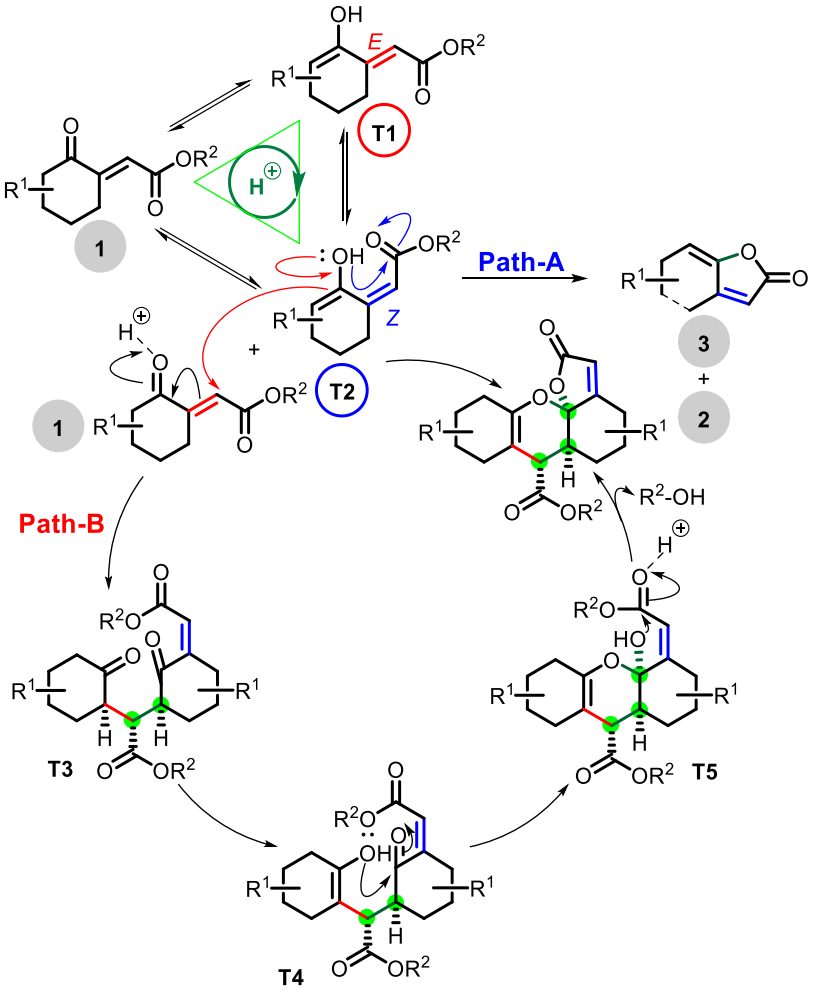
Scheme 6. Plausible Reaction Mechanism



next step without purification. Anhydrous DCM (40 mL) was added **S3d** under an argon atmosphere and the mixture was cooled to 0 °C. Then, Et_3N (1.04 mL, 7.4 mmol) was added slowly, followed by $MeSO_2Cl$ (0.57 mL, 7.4 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at 0 °C to rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution, and extraction with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to obtain ethyl (*E*)-2-(5-methyl-2-oxocyclohexylidene)acetate (**1d**) (1.33 g, 40%), overall yield (25.6%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 6.46−6.43 (m, 1H), 4.19 (q, J = 7.12 Hz, 2H), 3.67−3.48 (m, 1H), 2.68−2.60 (m, 1H), 2.49−2.35 (m, 1H), 2.28 (ddd, J = 16.98, 11.25, 3.05 Hz, 1H), 2.03−1.86 (m, 2H), 1.62−1.50 (m, 1H), 1.33−1.23 (m, 3H), 1.07 (d, J = 6.87 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.2, 166.1, 150.6, 122.2, 60.5, 39.7, 36.7, 31.3, 29.9, 21.5, 14.1; HRMS (ESI) m/z calcd for $C_{11}H_{16}O_3Na$ $[M + Na]^+$, 219.0992; found, 219.0986.

*Ethyl (E)-2-(5-Ethyl-2-oxocyclohexylidene)acetate (**1e**).* 4-Ethyl cyclohexanone (12.36 g, 97 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture, DABCO (1.31 g, 11.6 mmol) was added slowly over 10 min at rt, followed by ethyl glyoxylate (1 g, 9.8 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-(5-ethyl-2-oxocyclohexyl)-2-hydroxyacetate (**S3e**) (1.2 g, 54%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). This product **S3e** was forwarded to the next step, **S3e** (1.2 g, 5.2 mmol) was added to a flame-dried two-neck 100 mL round-bottom flask and dissolved in anhydrous DCM (40 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then, Et_3N (1.39 mL, 6.2 mmol) was added slowly, followed by $MeSO_2Cl$ (0.48 mL, 6.28 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at 0 °C to rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to obtain ethyl (*E*)-2-(5-ethyl-2-oxocyclohexylidene)acetate (**1e**) (0.66 g 55%), overall yield (29.7%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 6.41 (dd, J = 1.53, 3.05 Hz, 1H), 4.16 (q, J = 6.87,

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13.73 Hz, 2H), 3.65−3.40 (m, 1H), 2.68−2.49 (m, 1H), 2.43−2.18 (m, 2H), 1.99 (m, 1H), 1.62 (m, 1H), 1.52−1.33 (m, 3H), 1.25 (t, J = 7.63 Hz, 3H), 0.92 (t, J = 7.63 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.6, 166.3, 150.9, 122.4, 77.6, 60.7, 39.8, 36.6, 34.7, 28.9, 28.8, 14.01, 13.95, 11.7; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3$ Na $[M + Na]^+$, 233.1148; found, 233.1141.

*Methyl (E)-2-(2-Oxocyclohexylidene)acetate (**1f**).* Cyclohexanone (13.38 g, 136 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture was added DABCO (1.8 g, 16.04 mmol) at rt, followed by methyl glyoxylate (1.2 g, 11.7 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford methyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3f**) (1.4 g, 56%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). This product **S3f** (1.4 g, 7.5 mmol) was forwarded to the next step, dissolved in anhydrous DCM (40 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then, Et_3N (1.26 mL, 8.9 mmol) was added, followed by $MeSO_2Cl$ (0.69 mL, 9 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at rt. After completion of the reaction (1 h), it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford methyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1f**) (0.58 g, 38%), overall yield (21.28%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 6.44−6.17 (m, 1H), 3.67−3.58 (m, 3H), 2.98 (ddd, J = 7.63, 5.34, 2.29 Hz, 2H), 2.48−2.37 (m, 2H), 1.90−1.74 (m, 3H), 1.72−1.60 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 200.8, 166.1, 151.4, 121.3, 51.3, 40.7, 28.5, 23.1; HRMS (ESI) m/z calcd for $C_9H_{13}O_3$ $[M + H]^+$, 169.0859; found, 169.0855.

*Isopropyl (E)-2-(2-Oxocyclohexylidene)acetate (**1g**).* Cyclohexanone (16.9 g, 172.2 mmol) was taken in a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture, DABCO (2.31 g, 20.5 mmol) was added at rt, followed by isopropyl glyoxylate (2 g, 17.2 mmol) dropwise. Then, the reaction mixture was stirred overnight at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford isopropyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3g**) (3 g, 83%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Isopropyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3g**) (3 g, 14.0 mmol) was forwarded to the next step, taken in a flame-dried two-neck 100 mL round-bottom flask, dissolved in anhydrous DCM (40 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then, Et_3N (2.2 mL, 15.8 mmol) was added slowly, followed by $MeSO_2Cl$ (1.2 mL, 16.7 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at 0 °C to rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford isopropyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1g**) (0.56 g, 47%), overall yield (39.01%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 2.29 Hz, 1H), 5.07−4.83 (m, 1H), 3.03 (td, J = 6.29, 1.91 Hz, 3H) 2.51−2.44 (m, 2H), 1.91−1.83 (m, 2H),1.79−1.70 (m, 3H), 1.23−1.22 (m, 4H), 1.2 (d, J = 2.29 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.5, 165.8, 151.1, 122.8, 77.6, 68.1, 41.1, 28.9, 23.6, 22.0; HRMS (ESI) m/z calcd for $C_{11}H_{16}O_3Na$ $[M + Na]^+$, 219.0892; found, 219.0987.

*Allyl (E)-2-(2-Oxocyclohexylidene)acetate (**1h**).* Cyclohexanone (7.8 g, 79 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture, DABCO (1.07 g, 9.5 mmol) was added at rt, followed by allyl 2-oxoacetate (1 g, 8.7 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to allyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3h**) (0.61 g, 64%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Allyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3h**) was forwarded to the next step, taken in a flame-dried two-neck 100 mL round-bottom flask (0.61 g, 2.87 mmol), and dissolved in anhydrous DCM (40 mL) under an argon atmosphere and the mixture was cooled to 0 °C. Then, Et_3N (0.48 mL, 3.4 mmol) was added, followed by $MeSO_2Cl$ (0.26 mL, 3.4 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at 0 °C to rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford allyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1h**) (1.6 g, 59%), overall yield (37.76%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (t, J = 2.29 Hz, 1H), 6.02−5.74 (m, 1H), 5.47−5.26 (m, 1H), 5.22 (d, J = 11.44 Hz, 1H), 4.71−4.41 (m, 2H), 3.21−2.94 (m, 2H), 2.56−2.39 (m, 2H), 1.94−1.81 (m, 2H), 1.80−1.67 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.0, 165.6, 151.8, 131.8, 121.6, 118.3, 65.1, 40.9, 28.8, 23.3; HRMS (ESI) m/z calcd for $C_{11}H_{15}O_3$ $[M + H]^+$, 195.2300; found, 195.2301.

*Benzyl (E)-2-(2-Oxocyclohexylidene)acetate (**1i**).* Cyclohexanone (**4j**) (6.18 g, 62 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture was added DABCO (0.84 g, 7.4 mmol) at rt, followed by benzyl 2-oxoacetate (1 g, 6 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic

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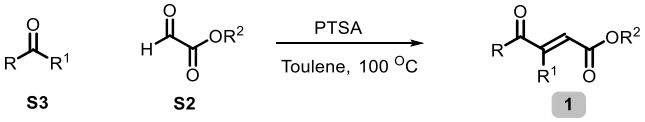
layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to access benzyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (**S3i**) (3.17 g, 64%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). The **S3i** (0.31 g, 1.46 mmol) was forwarded to the next step, dissolved in anhydrous DCM (40 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then, Et_3N (2.03 mL, 13.8 mmol) was added, followed by $MeSO_2Cl$ (1.12 mL, 14.4 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to give benzyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1i**) (0.15 g, 53%), overall yield (33.92%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (br. s., 5H), 6.54 (br. s., 1H) 5.20, (s, 2H), 3.21−3.04 (m, 2H), 2.53 (t, J = 6.28 Hz, 2H), 2.00−1.72 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.1, 165.8, 152.0, 135.6, 128.5.

*Ethyl (E)-2-(4,4-Dimethyl-2-oxocyclohexylidene)acetate (**1j**).* 3,3-Dimethyl cyclohexanone (12.3 g, 97.6 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture was added DABCO (1.31 g, 11.6 mmol) at rt, followed by ethyl glyoxylate (1 g, 9.8 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-(4,4-dimethyl-2-oxocyclohexyl)-2-hydroxyacetate (**S3j**) (1.07 g, 48%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Ethyl 2-(4,4-dimethyl-2-oxocyclohexyl)-2-hydroxyacetate (**S3j**) (1.07 g, 4.6 mmol) was forwarded to the next step, taken in a flame-dried two-neck 100 mL round-bottom flask, dissolved in anhydrous DCM (40 mL) under an argon atmosphere and the mixture was cooled to 0 °C. Then, Et_3N (0.78 mL, 5.5 mmol) was added slowly, followed by $MeSO_2Cl$ (0.43 mL, 5.5 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-2-(4,4-dimethyl-2-oxocyclohexylidene)acetate (**1j**) (0.98 g, 53%), overall yield (25.44%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (t, J = 2.31 Hz, 1H), 4.19 (q, J = 7.13 Hz, 2H), 3.11 (td, J = 6.88, 2.38 Hz, 2H), 2.31 (s, 2H), 1.65 (t, J = 6.88 Hz, 2H) 1.28 (t, J = 7.13 Hz, 3H), 1.01 (s, 6H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.4, 166.1, 150.1, 122.1, 60.5, 54.2, 36.0, 32.6, 28.2, 24.7, 14.1; HRMS (ESI) m/z calcd for $C_{12}H_{19}O_3$ $[M + H]^+$, 211.1329; found, 211.1321.

*Ethyl (E)-2-(2,4,4-Trimethyl-6-oxocyclohexylidene)acetate (**1k**).* 3,3,5-Trimethyl cyclohexanone (13.7 g, 97.7 mmol) was taken in a single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL) at room temperature. To this mixture was added DABCO (1.31 g, 11.6 mmol) at rt, followed by ethyl glyoxylate (1 g, 9.8 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at rt. After completion of the reaction, neutralization with aqueous 2 N HCl, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl 2-hydroxy-2-(2,4,4-trimethyl-6-oxocyclohexyl)acetate (**S3k**) (0.9 g, 48%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane). Ethyl 2-hydroxy-2-(2,4,4-trimethyl-6-oxocyclohexyl)acetate (**S3k**) was forwarded to the next step. Product **S3k** (0.9 g, 3.7 mmol) was dissolved in anhydrous DCM (40 mL) under an argon atmosphere and the mixture was cooled to 0 °C. Then, Et_3N (0.62 mL, 4.4 mmol) was added, followed by $MeSO_2Cl$ (0.34 mL, 4.4 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight at rt. After completion of the reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to obtain ethyl (*E*)-2-(2,4,4-trimethyl-6-oxocyclohexylidene)acetate (**1k**) (0.9 g, 91%), overall yield (43.68%), as a yellow oil. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (d, J = 2.00 Hz, 1H), 4.37−4.08 (m, 2H), 3.90−3.76 (m, 1H), 2.33−2.24 (m, 2H), 2.12 (s, 1H), 1.86 (dd, J = 13.88, 7.75 Hz, 1H), 1.34−1.28 (m, 4H), 1.19 (d, J = 7.00 Hz, 3H), 1.05 (s, 3H), 0.99 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 202.5, 165.9, 155.5, 122.9, 60.6, 52.9, 44.2, 31.3, 31.1, 29.3 27.4, 22.9, 14.2; HRMS (ESI) m/z calcd for $C_{13}H_{21}O_3$ $[M + H]^+$, 225.1329; found, 225.1321.

Synthesis of Open-Chain α,β-Unsaturated γ-Ketoesters (Method B).[16]



*Ethyl (E)-4-Oxopent-2-enoate (**1o**).* Acetone (1 g, 17.2 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL). To this mixture, *para*-toluenesulfonic acid (PTSA) (2.9 g, 17.2 mmol) was added at rt, followed by glyoxalate in toluene (1.75 g, 17.2 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at 100 °C. After completion of the reaction, neutralization with aqueous $NaHCO_3$, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-4-oxopent-2-enoate (**1o**) (0.64 g, 58%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 16.13 Hz, 1H), 6.64 (d, J = 16.13 Hz, 1H), 4.27 (q, J = 7.13, 14.26 Hz, 2H), 2.35 (s, 3H), 1.32 (t, J = 7.13 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 165.4, 139.9, 131.6, 61.4, 28.1, 14.1; HRMS (ESI) m/z calcd for $C_7H_{11}O_3$ $[M + H]^+$, 142.1540; found, 142.1542.

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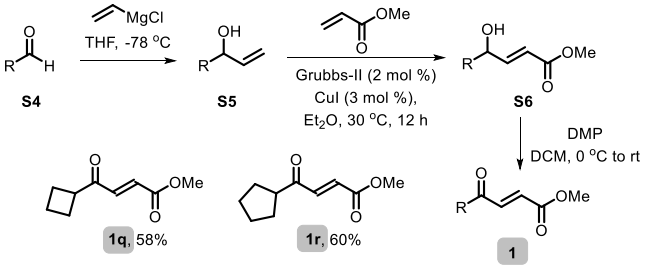
*Ethyl (E)-5-Chloro-4-oxopent-2-enoate (**1t**).* Chloroacetone (1 g, 10.8 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL). To this mixture, PTSA (1.8 g, 10.8 mmol) was added slowly at rt, followed by glyoxalate (1.1 g, 10.8 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at 100 °C. After completion of the reaction, neutralization with aqueous $NaHCO_3$, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-5-chloro-4-oxopent-2-enoate (**1t**) (0.3 g, 60%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.46 (m, 2H), 7.10 (d, J = 16.01 Hz, 1H), 4.61−4.51 (m, 5H), 1.61 (t, J = 7.13 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 190.7, 164.8, 135.2, 133.3, 61.6, 47.3, 14.1; HRMS (ESI) m/z calcd for $C_7H_{10}ClO_3$ $[M + H]^+$, 176.5960; found, 176.5965.

*Ethyl (E)-3-Methyl-4-oxohex-2-enoate (**1u**).* 3-Pentanone (1 g, 11 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL). To this mixture, PTSA (1.89 g, 11 mmol) was added at rt, followed by glyoxalate (1.12 g, 11 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at 100 °C. After completion of the reaction, neutralization with aqueous $NaHCO_3$, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-3-methyl-4-oxohex-2-enoate (**1u**) (0.15 g, 52%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 4.21 (q, J = 7.13, 14.26 Hz, 2H), 2.71 (q, J = 7.25, 14.51 Hz, 2H), 2.20 (s, 3H), 1.29 (t, J = 7.25 Hz, 3H), 1.09 (t, J = 7.25 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 202.7, 166.3, 150.4, 125.1, 60.7, 31.4, 14.2, 13.4, 8.1; HRMS (ESI) m/z calcd for $C_9H_{14}O_3$ $[M + Na]^+$, 193.0835; found, 193.0830.

*Ethyl (E)-3-Methyl-4-oxopent-2-enoate (**1v**).* Methyl ethyl ketone (1 g, 13.8 mmol) was added to a flame-dried single-neck round-bottom flask (250 mL) followed by anhydrous toluene (10 mL). To this mixture, *p*-TSA (2.3 g, 13.8 mmol) was added at rt, followed by glyoxalate (1.41 g, 13.8 mmol) dropwise. Then, the reaction mixture was stirred for 24 h at 100 °C. After completion of the reaction, neutralization with aqueous $NaHCO_3$, and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford ethyl (*E*)-3-methyl-4-oxopent-2-enoate (**1v**) (0.2 g, 41%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 1H), 3.51−3.39 (m, 1H), 3.20 (dd, J = 7.13, 14.26 Hz, 1H), 1.98 (s, 4H), 1.57 (s, 4H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 199.6, 161.0, 150.2, 126.3, 60.6, 26.0, 14.0, 12.8.

Synthesis of Open-Chain α,β-Unsaturated γ-Ketoesters (Method C). Ketoesters **1q** and **1r** were synthesized in three linear steps (as described below) following the known literature procedures.[20]



General Procedure for the Synthesis of Fused Pyrano-ketal-lactones (2) and Bicyclic γ-Ylidene-butenolides (3) from α,β-Unsaturated γ-Ketoesters (1). Ethyl (*E*)-2-(2-oxocyclohexylidene)acetate **1** (1.01 mmol) was taken into a single-neck 10 mL round-bottom flask equipped with positive argon flow and dissolved in 2 mL of anhydrous DCE. Then, MsOH (0.101 mmol) was added under an argon atmosphere at room temperature (rt), then the reaction mixture was moved to 60 °C. The resulting reaction mixture was stirred at 60 °C for 4−5 h. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica gel column chromatography (100−200 mesh) to afford the corresponding complex pyrano-ketal-lactones **2** and bicyclic γ-ylidene-butenolide.

Synthesis of Fused Pyrano-ketal-lactones and Bicyclic γ-Ylidene-butenolides from α,β-Unsaturated γ-Ketoesters.[16] *Ethyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2a**) and 5,6-Dihydrobenzofuran-2(4H)-one (**3a**).* Following the General Procedure, ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1a**) (0.1 g, 0.5 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.026 g, 0.27 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was heated in an oil bath with temperature 60 °C. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford ethyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2a**) (0.042 g, 24%) as a white crystal (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.052 g, 70%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)).

*Gram-Scale Synthesis of **2a** and **3a**.* Following the General Procedure, ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1a**) (1 g, 5.4 mmol) treated with MsOH (0.263 g, 2.7 mmol) in anhydrous $ClCH_2CH_2Cl$ (10 mL) to obtain **2a** with a yield of 22% (0.384 g) and **3a** with a yield of 70% (0.523 g).

2a. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.75 (d, J = 1.53 Hz, 1H), 4.30−4.09 (m, 2H), 2.79−2.71 (m, 1H), 2.57 (s, 1H), 2.49−2.29 (m, 3H), 2.18−1.98 (m, 3H), 1.84−1.64 (m, 6H), 1.56−1.46 (m, 2H), 1.28 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 171.9, 169.7, 167.3, 144.5, 114.7, 102.5, 101.9, 61.2, 45.2, 42.2, 28.6, 28.5, 26.6, 26.2, 25.6, 22.8, 22.6, 14.1; IR (KBr, cm^{-1}): υ 3685, 3022, 1768, 1596, 1575, 1217, 1020, 921,

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767, 670; HRMS (ESI) m/z calcd for $C_{18}H_{22}O_5Na$ $[M + Na]^+$, 341.1359; found, 341.1350.

3a. ^1H NMR (400 MHz, $CDCl_3$): δ 5.87 (t, J = 4.63 Hz, 1H), 5.75 (s, 1H), 2.71 (t, J = 6.63, Hz, 2H), 2.39 (q, J = 5.50, 10.76 Hz, 2H), 1.86 (quin, J = 6.00, 12.13 Hz, 2H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$): δ 170.1, 155.7, 150.3, 111.0, 24.2, 23.7, 22.6; IR (KBr, cm^{-1}): υ 3685, 3022, 1720, 1595, 1520, 1216, 927, 768, 671; HRMS (ESI) m/z calcd for $C_8H_8O_2$ $[M + H]^+$, 137.0597; found, 137.0592.

*Ethyl 6a,11-Dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2b**) and 7-Methyl-5,6-dihydrobenzofuran-2(4H)-one (**3b**).* Following the General Procedure, to ethyl (E)-2-(3-methyl-2-oxocyclohexylidene)acetate (**1b**) (0.1 g, 1 mmol) in 2 mL of anhydrous DCE, MsOH (0.048 g, 0.49 mmol) was added under an argon atmosphere at room temperature (rt) and then the reaction mixture moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford ethyl 6a,11-dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]-xanthene-7-carboxylate (**2b**) as a colorless liquid (0.039 g, 26%) in d.r. ratio 2:1 (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 7-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3b**) (0.032 g, 41%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)).

2b. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (t, J = 2.29 Hz, 1H), 5.31 (minor) (s, 0.23H), 4.31−4.21 (minor) (m, 1H), 4.11−4.05 (m, 2H), 2.83−2.76 (m, 2H), 2.73−2.65 (m, 2H), 2.58−2.40 (m, 3H), 2.30−2.17 (m, 3H), 1.97−1.76 (m, 7H), 1.74−1.61 (m, 4H), 1.35−1.28 (m, 3H), 1.27−1.24 (m, 4H), 1.24−1.21 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.1, (minor) 172.0, 171.9, 169.9, (minor) 169.7, 169.7, (minor) 167.0, 165.6, (minor) 144.3, 144.2, (minor) 144.1, (minor) 116.9, 116.8, (minor) 114.6, 102.6, (minor) 102.5, (minor) 102.4, 102.2, 101.1, (minor) 101.0, (minor) 100.9, 61.2, 45.7, (minor) 45.6, 44.4, (minor) 44.3, 41.4, (minor) 41.1, 37.3, 37.1, (minor) 37.1, 36.8, (minor) 36.7, 34.4, (minor) 34.2, 34.2, 33.4, 32.3, 30.9, 30.5, 29.7, 28.8, (minor) 28.7, 28.7, (minor) 26.6, (minor) 26.3, 21.5, (minor) 21.4, 20.8, 18.2, 14.1; IR (KBr, cm^{-1}): υ 3685, 3022, 2940, 2403, 1732, 1673, 1519, 1217, 1030, 921, 769, 671; HRMS (ESI) m/z calcd for $C_{20}H_{26}O_5Na$ $[M + Na]^+$, 369.4231; found, 369.4226.

3b. ^1H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H), 2.72−2.64 (m, 2H), 2.33−2.30 (m, 2H), 1.97 (s, 3H), 1.90−1.84 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 175.8, 170.5, 155.5, 123.0, 109.3, 30.0, 24.1, 22.6, 16.9; IR (KBr, cm^{-1}): υ 3685, 3022, 2928, 2402, 1760, 1600, 1520, 1216, 923, 772, 672; HRMS (ESI) m/z calcd for $C_9H_{11}O_2$ $[M + H]^+$, 151.0754; found, 151.0751.

*Ethyl 4,10-Dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2c**) and 6-Methyl-5,6-dihydrobenzofuran-2(4H)-one (**3c**).* Following the General Procedure, ethyl (E)-2-(4-methyl-2-oxocyclohexylidene)acetate (**1c**) (0.2 g, 1.01 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.048 g, 0.49 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford ethyl 4,10-dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2c**) (0.072 g, 20%) as a colorless liquid in d.r. ratio 1:1 (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 6-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3c**) (0.066 g, 46%) as a yellow liquid (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)).

2c. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, J = 1.53 Hz, 1H), 4.31−4.21 (m, 1H), 4.19−4.11 (m, 1H), 2.89 (s, 1H), 2.76−2.71 (m, 1H),2.60 (s, 1H), 2.51−2.10 (m, 1H), 2.20−2.10 (m, 2H), 2.05−1.96 (m, 2H), 1.85−1.58 (m, 6H), 1.27 (d, J = 6.87 Hz, 6H), 1.01−0.98(m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.5, 172.4, 169.7, 167.3, 144.3, 144.2, 114.2, 102.6, 102.5, 101.3, 61.2, 48.3, 48.0, 41.9, 40.7, 34.8, 34.7, 34.7, 31.2, 31.1, 30.8, 30.7, 29.7, 29.3, 28.7, 28.5, 28.2, 25.8, 21.4, 21.2, 18.4, 14.1; IR (KBr, cm^{-1}): υ 3021, 2926, 2403, 1765, 1449, 1377, 1217, 927, 767, 762, 669; HRMS (ESI) m/z calcd for $C_{20}H_{26}O_5Na$ $[M + Na]^+$, 369.1785; found, 369.1780.

3c. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (s, 1H), 5.73 (br. s., 1H), 2.87−2.80 (m, 1H), 2.62−2.58 (m, 1H), 1.98 (dd, J = 8.85, 13.38 Hz, 1H), 1.51−1.44 (m, 1H), 1.28 (d, J = 10.38 Hz, 1H), 1.15 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.2, 155.5, 150.0, 116.6, 110.9, 31.0, 29.8, 29.7, 23.1, 201.0; IR (KBr, cm^{-1}): υ 3383, 3023, 2932, 1720, 1648, 1520, 1216, 767, 671; HRMS (ESI) m/z calcd for $C_9H_{11}O_2$ $[M + H]^+$, 151.0754; found, 151.0751.

*Ethyl 5,9-Dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2d**) and 5-Methyl-5,6-dihydrobenzofuran-2(4H)-one (**3d**).* Following the General Procedure, ethyl (E)-2-(5-methyl-2-oxocyclohexylidene)acetate (**1d**) (0.2 g, 1.01 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.048 g, 0.101 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford ethyl 5,9-dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2d**) (0.068 g, 19%) as a colorless liquid in d.r. ratio 1:1 (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 5-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3d**) (0.071 g, 46%) as a yellow liquid (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)).

2d. ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, J = 1.53 Hz, 1H), 5.74 (d, J = 1.53 Hz, 0.31H), 4.26−4.14 (m, 3H), 2.66−2.60 (m, 2H), 2.49−2.45 (m, 2H), 2.41−2.34 (m, 2H), 2.22−2.03 (m, 4), 1.88−1.69 (m, 6H), 1.53−1.45 (m, 2H), 1.32−1.24 (m, 8H), 1.02−1.00 (m, 3H), 0.99−0.98 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.1, 172.0, 169.7,

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169.7, 165.6, 144.3, 144.2, 116.9, 116.8, 102.6, 102.5, 101.0, 100.9, 61.2, 45.6, 44.3, 37.3, 37.1, 37.1, 36.8, 36.7, 34.4, 34.2, 34.2, 33.4, 32.3, 30.9, 30.5, 28.8, 28.7, 28.7, 26.6, 26.3, 21.5, 21.4, 20.8, 18.2, 14.1; IR (KBr, cm^{-1}): υ 3687, 3022, 2402, 1727, 1520, 1424, 1215, 92, 764, 671; HRMS (ESI) m/z calcd for $C_{20}H_{26}O_5Na$ $[M + Na]^+$, 369.1621; found, 369.1616.

3d. ^1H NMR (400 MHz, $CDCl_3$): δ 5.82−5.76 (m, 1H), 5.72 (s, 1H), 2.83−2.78 (m, 1H), 2.47−2.34 (m, 1H), 2.27 (dd, J = 16.78, 9.92 Hz, 2H), 2.10−1.98 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.2, 155.8, 150.0, 110.8, 110.0, 32.0, 31.8, 30.1 20.7; IR (KBr, cm^{-1}): υ 3687, 3022, 2402, 1769, 1595, 1520, 1215, 927, 772, 672; HRMS (ESI) m/z calcd for $C_9H_{10}O_2$ $[M + H]^+$, 151.0754; found, 151.0751.

*5-Ethyl 5,9-Diethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2e**) and 5-Ethyl-5,6-dihydrobenzofuran-2(4H)-one (**3e**)*. Following the General Procedure, ethyl (*E*)-2-(5-ethyl-2-oxocyclohexylidene)acetate (**1e**) (0.2 g, 0.95 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.045 g, 0.46 mmol) was added under an argon atmosphere at room temperature (rt) and then the reaction mixture moved v. The resulting reaction mixture was stirred at 60 °C for 6 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure, and purification by column chromatography (SiO_2, 5% EtOAc/hexanes) afforded 5-ethyl 5,9-dimethyl-2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2e**) (0.085 g, 24%) as a colorless liquid in d.r. ratio 1:1 (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 5-ethyl-5,6-dihydrobenzofuran-2(4*H*)-one (**3e**) (0.091 g, 57%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)).

2e. ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, J = 1.53 Hz, 1H), 5.74 (d, J = 1.53 Hz, 0.33H), 4.26−4.14 (m, 3H), 2.66−2.60 (m, 2H), 2.51−2.44 (m, 3H), 2.42−2.34 (m, 2H), 2.25−2.2.00 (m, 6H), 1.86−1.67 (m, 8H), 1.54−1.45 (m, 3H), 1.32−1.20 (m, 10H), 1.02−0.96 (m, 10H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.1, 172.0, 169.7, 169.7, 165.6, 144.3, 144.2, 116.9, 116.8, 102.6, 102.5, 101.0, 100.1, 61.2, 45.6, 44.3, 37.3, 37.1, 36.8, 36.7, 34.4, 34.2, 34.2, 33.4, 32.4, 31.0, 30.5, 29.7, 28.8, 28.7, 28.7, 26.6, 26.3, 21.5, 21.4, 20.8, 18.2, 14.1; IR (KBr, cm^{-1}): υ 3686, 3022, 2402, 1746, 1520, 1425, 1216, 927, 768, 671; HRMS (ESI) m/z calcd for $C_{22}H_{31}O_5$ $[M + H]^+$, 375.2155; found, 375.2161.

3e. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85−5.80 (m, 1H), 5.74 (s, 1H), 2.87 (dd, J = 3.81, 16.78 Hz, 1H), 2.47 (m, 1H), 2.27 (ddd, J = 3.05, 5.34, 16.78 Hz, 1H), 1.90−1.78 (m, 1H), 1.89−1.78 (m, 1H), 1.45−1.39 (m, 2H), 0.95 (t, J = 7.63 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.3, 155.9, 150.3, 111.1, 110.1, 36.9, 30.0, 298, 28.2, 11.3; IR (KBr, cm^{-1}): υ 3687, 3022, 2929, 2402, 1755, 1519, 1427, 1216, 927, 768, 671; HRMS (ESI) m/z calcd for $C_{10}H_{13}O_2$ $[M + H]^+$, 165.0910; found, 165.0910.

*Methyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2f**) and 5,6-Dihydrobenzofuran-2(4H)-one (**3a**)*. Following the General Procedure, methyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1f**) (0.2 g, 1.19 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.057 g, 0.59 mmol) was added under an argon atmosphere at room temperature (rt) and then the reaction mixture moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford methyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2f**) (0.089 g, 25%) as a colorless liquid. TLC: R_f = 0.50 (SiO_2, 15% EtOAc/hexanes). **2f** was confirmed by ^1H, ^{13}C, DEPT, HRMS, and X-ray analysis and 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.085 g, 52%) was obtained as a colorless liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

2f. ^1H NMR (400 MHz, $CDCl_3$): δ 5.77 (d, J = 2.29 Hz, 1H), 3.74 (s, 3H), 2.80−2.71 (m, 1H), 2.60 (s, 1H), 2.49−2.35 (m, 3H), 2.15−2.11 (m, 1H), 2.08−2.01 (m, 2H), 1.85−1.78(m, 2H), 1.70−1.62 (m, 5H), 1.55−1.47 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 171.7, 169.7, 167.3, 144.6, 114.6, 102.4, 101.7, 52.4, 45.1, 42.3, 28.6, 28.5, 26.7, 26.2, 25.6, 22.8, 22.6; IR (KBr, cm^{-1}): υ 3685, 3022, 2403, 1731, 1519, 1439, 1216, 1028, 768, 671; HRMS (ESI) m/z calcd for $C_{17}H_{20}O_5Na$ $[M + Na]^+$, 327.1203; found, 327.1198.

*Isopropyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2g**) and 5,6-Dihydrobenzofuran-2(4H)-one (**3a**)*. Following the General Procedure, isopropyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1g**) (0.2 g, 1.02 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.049 g, 0.50 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford isopropyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2g**) (0.095 g, 28%) as a colorless liquid (TLC: R_f = 0.50 (SiO_2, 15% EtOAc/hexanes)) and 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.091 g, 65%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)).

2g. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, J = 2.29 Hz, 1H), 5.11−5.03 (m, 1H), 2.81−2.69 (m, 1H), 2.54 (s, 1H), 2.45−2.38 (m, 2H), 2.15−2.09 (m, 1H), 2.06−1.99 (m, 2H), 1.83−1.72 (m, 3H), 1.69−1.63 (m, 4H), 1.59−1.46 (m, 2H), 1.29−1.24 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 171.4, 169.7, 167.3, 144.4, 114.7, 102.5, 102.1, 68.7, 45.3, 42.3, 28.6, 28.5, 26.7, 26.2, 25.6, 22.8, 22.6, 21,64, 21.59; IR (KBr, cm^{-1}): υ 3685, 3022, 2403, 2403, 1770, 1611, 1519, 1217, 965, 768, 670; HRMS (ESI) m/z calcd for $C_{19}H_{24}O_5Na$ $[M + Na]^+$, 355.1506; found, 355.1501.

*Allyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]-xanthene-7-carboxylate (**2h**) and 5,6-Dihydrobenzofuran-2(4H)-one (**3a**)*. Following the General Procedure, allyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1h**) (0.150 g, 0.77 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.037 g, 0.38 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at

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60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford allyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2h**) (0.069 g, 27%) as a colorless liquid (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)) and 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.051 g, 48%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)).

2h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99−5.82 (m, 1H), 5.47−5.19 (m, 2H), 4.78−4.54 (m, 2H), 3.04 (s, 1H), 2.52−2.27 (m, 2H), 2.13 (br. s., 3H), 1.86−1.59 (m, 8H), 1.31−1.22 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.6, 169.7, 167.2, 144.7, 132.2,118.3, 114.7, 102.4, 101.7, 65.9, 45.2, 42.2, 28.6, 28.5, 26.7, 26.2, 25.6, 22.8, 22.7, 14.1; IR (KBr, cm^{-1}): υ 3687, 3022, 2402, 1764, 1596, 1520, 1220, 1055, 926, 768, 671; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}O_5Na$ [M + Na]$^+$, 353.1359; found, 353.1343.

*Benzyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]xanthene-7-carboxylate (**2i**) and 5,6-Dihydrobenzofuran-2(4H)-one (**3a**).* Following the General Procedure, benzyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1i**) (0.5 g, 2.04 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.098 g, 0.101 mmol) was added under an argon atmosphere at room temperature (rt) and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford benzyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2i**) (0.2 g, 21%) as a colorless liquid. TLC: R_f = 0.50 (SiO_2, 15% EtOAc/hexanes). **2i** was confirmed by ^{1}H, ^{13}C, DEPT, HRMS, and X-ray analysis, and 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.230 g, 78%) was obtained as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

2i. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.35 (m, 5H), 5.77 (d, *J* = 2.00 Hz, 1H), 5.27 (d, *J* = 12.26 Hz, 1H), 5.11 (d, *J* = 12.38 Hz, 1H), 2.78−2.72 (m, 1H), 2.64 (s, 1H), 2.51−2.33 (m, 4H), 2.13−1.99 (m, 4H), 1.85−1.78 (m, 2H), 1.70−1.63 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.7, 169.6, 167.2, 144.7, 135.9,128.5, 128.2, 128.1 114.7, 102.4, 101.7, 67.0, 45.2, 42.1, 28.6, 28.5, 26.7, 26.2, 25.5, 22.8, 22.6; IR (KBr, cm^{-1}): υ 3687, 3022, 2402, 1764, 1594, 1519, 1216, 928, 765, 669.

*Ethyl 2-Oxo-2,4,5,6,7,7a,8,9,10,11,12,13-dodecahydrocyclohepta[b]furo[2′,3′:2,3]cyclohepta[1,2-e]-pyran-8-carboxylate (**2m**) and 4,5,6,7-Tetrahydro-2H-cyclohepta[b]furan-2-one (**3m**).* Following the General Procedure, ethyl (*E*)-2-(4-methyl-2-oxocycloheptylidene)-acetate (**1m**) (0.2 g, 1.01 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.048 g, 0.49 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 1% EtOAc/hexanes) to give ethyl 2-oxo-2,4,5,6,7,7a,8,9,10,11,12,13-dodecahydrocyclohepta[*b*]furo-[2′,3′:2,3]cyclohepta[1,2-*e*]pyran-8-carboxylate (**2m**) (0.093 g, 26%) as a colorless liquid (TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes)) and 4,5,6,7-tetrahydro-2*H*-cyclohepta[*b*]furan-2-one (**3m**) (0.091 g, 59%) as a yellow liquid (TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes)).

2m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (s, 1H), 3.59−3.50 (m, 1H), 3.36−3.27 (m, 1H), 2.79−2.67 (m, 1H), 2.58−2.45 (m, 1H), 2.39−2.26 (m, 1H), 1.87−1.61 (m, 12H), 1.50−1.38 (m, 2H), 1.28−1.20 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.9, 169.7, 167.3, 144.5, 114.7, 102.5, 101.9, 61.2, 45.2, 42.2, 31.9, 29.7, 28.6, 28.5, 26.7, 26.2, 25.6, 22.8, 22.7, 14.1; IR (KBr, cm^{-1}): υ 3686, 3022, 2927, 2402, 1747, 1632, 1520, 1215, 1022, 925, 770, 671; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{26}O_5Na$ [M + Na]$^+$, 369.1672; found, 369.1661.

3m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98−5.95 (m, 1H), 5.88−5.87 (m, 1H), 2.78−2.75 (m, 2H), 2.44 (d, *J* = 5.75, 11.26 Hz, 2H), 1.82−1.75 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.6, 158.6, 150.2, 117.8, 116.8, 29.5, 28.0, 27.5, 24.6; IR (KBr, cm-1): υ 3687, 3023, 2402, 1770, 1597, 1520, 1216, 928, 765, 671; HRMS (ESI) *m*/*z* calcd for $C_9H_{11}O_2$ [M + H]$^+$, 151.0754; found, 151.0750.

*Ethyl 2-Oxo-4,5,6,7,7a,8,9,10,11,12,13,14-dodecahydro-2H-cycloocta[b]furo[2′,3′:2,3]cycloocta[1,2-e]pyran-9-carboxylate (**2n**).* Following the General Procedure, ethyl (*E*)-2-(4-methyl-2-oxocycloheptylidene)acetate (**1n**)(0.2 g, 1.01 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.048 g, 0.49 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 1% EtOAc/hexanes) to afford ethyl 2-oxo-4,5,6,7,7a,8,9,10,11,12,13,14-dodecahydro-2*H*-cycloocta[*b*]furo[2′,3′:2,3]cycloocta[1,2-*e*]pyran-9-carboxylate (**2n**) (0.108 g, 32%) as a colorless liquid in d.r. ratio 2:1. TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

2n. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (s, 1H), 3.51−3.45 (m, 1H), 3.25−3.20 (m, 1H), 2.88−2.85 (m, 1H), 2.66−2.49 (m, 3H), 2.41−2.35 (m, 1H), 2.25−2.09 (m, 3H), 1.85−1.79 (m, 2H), 1.78−1.73 (m, 2H), 1.69−1.61 (m, 6H), 1.57−1.51 (m, 3H), 1.48−1.38 (m, 3H), 1.31−1.25 (m, 2H), 1.19 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.2, 170.0, 169.8, 157.7, 153.6, 121.0, 117.5, 112.0, 111.4, 58.7, 34.4, 28.0, 27.4, 26.9, 26.8, 25.8, 25.0, 24.8, 23.3, 21.6, 20.7, 15.1; IR (KBr, cm^{-1}): υ 3686, 3022, 2927, 2402, 1747, 1632, 1520, 1215, 1022, 925, 770, 671; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{29}O_5$ [M + H]$^+$, 375.2166; found, 375.2159.

Synthesis of γ-Ylidene-butenolides from α,β-Unsaturated γ-Ketoesters.[16] *6,6-Dimethyl-5,6-dihydrobenzofuran-2(4H)-one (**3j**).* Following the General Procedure, ethyl

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(*E*)-2-(4,4-dimethyl-2-oxocyclohexylidene)acetate (**1j**) (0.2 g, 0.95 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.045 g, 0.46 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford 6,6-dimethyl-5,6-dihydrobenzofuran-2(4*H*)-one (**3j**) (0.131 g, 83%) as a yellow liquid. TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79−5.72 (m, 1H), 5.65 (d, J = 1.53 Hz, 1H), 2.80−2.70 (m, 2H), 1.69 (t, J = 6.48 Hz, 2H), 1.16 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.3, 155.0, 148.9, 120.4, 111.0, 36.5, 32.9, 28.6, 21.2; IR (KBr, cm^{-1}): υ 3687, 3022, 2929, 2402, 1727, 1598, 1520, 1216, 912, 769, 671; HRMS (ESI) m/z calcd for $C_{10}H_{13}O_2$ [M + H]$^+$, 165.0910; found, 165.0904.

*4,6,6-Trimethyl-5,6-dihydrobenzofuran-2(4H)-one (**3k**).* Following the General Procedure, ethyl (*E*)-2-(2,4,4-trimethyl-6-oxocyclohexylidene)acetate (**1k**) (0.2 g, 0.89 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.042 g, 0.43 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford 4,6,6-trimethyl-5,6-dihydrobenzofuran-2(4*H*)-one (**3k**) (0.12 g, 75%) as a yellow liquid. TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (t, J = 2.20 Hz, 1H), 5.69−5.61 (m, 1H), 2.89 (m, 1H), 1.71−1.63 (m, 1H), 1.44 (t, J = 13.13 Hz, 1H), 1.29 (d, J = 6.63 Hz, 3H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.2, 160.5, 148.8, 120.1, 110.1, 45.9, 33.3, 31.1, 27.4, 26.6, 18.2; IR (KBr, cm^{-1}): υ 3686, 3022, 2926, 2402, 1729, 1599, 1521, 1216, 925, 768, 671; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_2Na$ [M + Na]$^+$, 201.0886; found, 201.0879.

*Ethyl 2-(5-Oxocyclopent-1-en-1-yl)acetate (**4a**).* Following the General Procedure, ethyl (*E*)-2-(2-oxocycloheptylidene)-acetate (**1l**) (0.25 g, 1.48 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.057 g, 0.59 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 1% EtOAc/hexanes) to afford ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**4a**) (0.15 g, 60%) as a yellow liquid. TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (s, 1H), 4.16−3.96 (m, 2H), 3.00−2.86 (m, 2H), 2.30−2.17 (m, 2H), 1.91−1.78 (m, 2H), 1.19−1.09 (m, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 206.7, 165.8, 150.5, 119.0, 60.7, 37.4, 28.9, 19.1, 13.7; IR (KBr, cm^{-1}): υ 3636, 2986, 2014, 1749, 1451, 1373, 1226, 1047, 930, 847, 670; HRMS (ESI) m/z calcd for $C_9H_{13}O_3$ [M + H]$^+$, 169.0859; found, 169.0855.

*5-Methylenefuran-2(5H)-one (**3o**).* Following the General Procedure, ethyl (*E*)-4-oxopent-2-enoate (**1o**) (0.1 g, 0.7 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.033 g, 0.35 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) affording 5-methylenefuran-2(5*H*)-one (**3o**) (0.045 g, 67%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

3o. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 5.72 Hz, 1H), 6.29−6.25 (m, 1H), 5.25 (t, J = 2.10 Hz, 1H), 4.93 (d, J = 2.67 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.8, 154.9, 143.4, 128.3, 121.7, 98.1; IR (KBr, cm^{-1}): υ 3682, 3022, 2933, 1746, 1546, 1514, 1216, 908, 767, 668; HRMS (ESI) m/z calcd for $C_5H_5O_2$ [M + H]$^+$, 97.0850; found, 97.0851.

*5-(Propan-2-ylidene)furan-2(5H)-one (**3p**).* Following the General Procedure, ethyl (*E*)-5-methyl-4-oxohex-2-enoate (**1p**) (0.1 g, 0.58 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.028 g, 0.29 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) affording 5-(propan-2-ylidene)furan-2(5*H*)-one (**3p**) (0.058 g, 98%) as a white crystal. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

*Gram-Scale Synthesis of **3p**.* Following the General Procedure, ethyl (*E*)-5-methyl-4-oxohex-2-enoate (**1a**)(1 g, 5.87 mmol) was treated with MsOH (0.282 g, 2.93 mmol) in anhydrous $ClCH_2CH_2Cl$ (10 mL) to obtain **3p** in 90% yield (0.656 g).

3p. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 5.50 Hz, 1H), 6.10 (d, J = 5.50 Hz, 1H), 2.02 (s, 3H), 1.97−1.94 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 170.6, 146.1, 139.7, 123.6, 117.9, 18.70, 18.66; IR (KBr, cm^{-1}): υ 3682, 3022, 2933, 1746, 1546, 1514, 1216, 908, 767, 668; HRMS (ESI) m/z calcd for $C_7H_9O_2$ [M + H]$^+$, 125.0597; found, 125.0594.

*5-Cyclobutylidenefuran-2(5H)-one (**3q**).* Following the General Procedure, ethyl (*E*)-4-cyclohexyl-4-oxobut-2-enoate (**1q**) (0.1 g, 0.4 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.022 g, 0.2 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc/

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hexanes) afforded 5-cyclobutylidenefuran-2(5*H*)-one (**3q**) (0.085 g, 94%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 5.38 Hz, 1H), 6.07 (d, J = 5.38 Hz, 1H), 3.02−2.93 (m, 4H), 2.25−2.17 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.5, 143.1, 139.8, 132.3, 117.2, 29.1, 27.7, 17.7; IR (KBr, cm^{-1}): υ 3682, 3022, 2933, 1746, 1546, 1514, 1216, 908, 767, 668; HRMS (ESI) m/z calcd for $C_8H_9O_2$ [M + H]$^+$, 137.1499; found, 137. 1496.

*5-Cyclopentylidenefuran-2(5H)-one (**3r**).* Following the General Procedure, ethyl (*E*)-4-cyclohexyl-4-oxobut-2-enoate (**1r**) (0.1 g, 0.4 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.022 g, 0.2 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford 5-cyclopentylidenefuran-2(5*H*)-one (**3r**) (0.078 g, 95%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 5.38 Hz, 1H), 6.07 (d, J = 5.38 Hz, 1H), 2.64 (m, Hz, 2H), 2.58−2.52 (m, 2H), 1.83−1.78 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.6, 143.3, 140.8, 134.8, 117.2, 30.4, 29.6, 26.6, 25.9; IR (KBr, cm^{-1}): υ 3682, 3022, 2933, 1746, 1546, 1514, 1216, 908, 767, 668; HRMS (ESI) m/z calcd for $C_9H_{11}O_2$ [M + H]$^+$, 150.1775; found, 150.1762.

*5-Cyclohexylidenefuran-2(5H)-one (**3s**).* Following the General Procedure, ethyl (*E*)-4-cyclohexyl-4-oxobut-2-enoate (**1s**) (0.1 g, 0.4 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.022 g, 0.2 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to obtain 5-cyclohexylidenefuran-2(5*H*)-one (**3s**) (0.048 g, 61%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

3s. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 5.50 Hz, 1H), 6.11 (d, J = 5.50 Hz, 1H), 2.02 (s, 3H), 2.52 (m, 2H), 2.39−2.31 (m, 2H), 1.66−1.64 (m, 2H), 1.25 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.7, 143.5, 139.4, 131.7, 117.9, 28.8, 28.1, 27.1, 26.1; IR (KBr, cm^{-1}): υ 3682, 3022, 2933, 1746, 1546, 1514, 1216, 908, 767, 668; HRMS (ESI) m/z calcd for $C_{10}H_{12}O_2Na$ [M + Na]$^+$, 187.0730; found, 187.0722.

*(Z)-5-(Chloromethylene)furan-2(5H)-one (**3t**).* Following the General Procedure, ethyl (*E*)-5-chloro-4-oxopent-2-enoate (**1t**) (0.1 g, 0.5 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.027 g, 0.28 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford (*Z*)-5-(chloromethylene) furan-2(5*H*)-one (**3t**) (0.055 g, 75%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

3t. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 5.50 Hz, 1H), 6.29, (dd, J = 5.50, 0.75 Hz, 1H), 5.99 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.9, 141.6, 120.3, 104.1; IR (KBr, cm^{-1}): υ 3687, 3022, 2923, 2402, 1595, 1520, 1215, 920, 766, 671; HRMS (ESI) m/z calcd for $C_5H_4ClO_2$ [M + H]$^+$, 131.5270; found, 131.5267.

*(Z)-5-Ethylidene-4-methylfuran-2(5H)-one (**3u**).* Following the General Procedure, ethyl (*E*)-3-methyl-4-oxohex-2-enoate (**1u**) (0.1 g, 0.58 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.028 g, 0.29 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure, and purification by column chromatography (SiO_2, 5% EtOAc/hexanes) afforded (*Z*)-5-ethylidene-4-methylfuran-2(5*H*)-one (**3u**) (0.064 g, 89%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

3u. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (s, 1H), 5.35 (q, J = 7.32, 14.65 Hz, 1H), 2.13 (d, J = 0.92 Hz, m, 3H), 1.92 (d, J = 7.32 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.5, 154.5, 151.4, 115.8, 107.9, 11.64, 11.60; IR (KBr, cm^{-1}): υ 3686, 3022, 2924, 2402, 1758, 1605, 1521, 1427, 1215, 1022, 926, 769, 672; HRMS (ESI) m/z calcd for $C_7H_9O_2$ [M + H]$^+$, 125.0597; found, 125.0595.

*5-Ethoxy-4,5-dimethylfuran-2(5H)-one (**3v**).* Following the General Procedure, ethyl (*E*)-3-methyl-4-oxopent-2-enoate (**1v**) (0.1 g, 0.64 mmol) was dissolved in 2 mL of anhydrous DCE. MsOH (0.030 g, 0.32 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was moved to a 60 °C oil bath. The resulting reaction mixture was stirred at 60 °C for 3 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL), and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford 5-ethoxy-4,5-dimethylfuran-2(5*H*)-one (**3v**) (0.065 g, 65%) as a yellow liquid. TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

3v. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (q, J = 1.58 Hz, 1H), 3.49 (dd, J = 9.01, 7.13 Hz, 1H), 3.23 (dd, J = 8.88, 7.00 Hz, 1H), 2.01 (d, J = 1.63 Hz, 3H), 1.60 (s, 3H), 1.20 (t, J = 7.07 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.9, 166.5, 118.8, 109.1, 77.3, 76.7, 58.9, 29.7, 22.8, 15.1, 12.5; IR (KBr, cm-1): υ 3687, 3022, 2924, 2402, 1595, 1521, 1426, 1215, 1023, 924, 770, 671; HRMS (ESI) m/z calcd for $C_8H_{13}O_3$ [M + H]$^+$, 156.1811; found, 156.1810.

*Ethyl 2-Oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-d]-xanthene-7-carboxylate (**2a**), 5,6-Dihydrobenzofuran-*

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*2(4H)-one (**3a**), and 7-Methyl-5,6-dihydrobenzofuran-2(4H)-one (**3b**).* Following the General Procedure, ethyl (*E*)-2-(2-oxocyclohexylidene)acetate (**1a**) (0.1 g, 0.54 mmol) and 7-methyl-5,6-dihydrobenzofuran-2(4*H*)-one (**3b**) (0.082 g, 0.54 mmol) were dissolved in 2 mL of anhydrous DCE. MsOH (0.026 g, 0.27 mmol) was added under an argon atmosphere at room temperature (rt), and then the reaction mixture was heated (oil bath temperature 60 °C). The resulting reaction mixture was stirred at 60 °C for 6 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2 × 5 mL) and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% EtOAc/hexanes) to afford ethyl 2-oxo-2,4,5,6,6a,7,8,9,10,11-decahydrofuro[3,2-*d*]xanthene-7-carboxylate (**2a**) (0.039 g, 22%) as a white crystal (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)), 5,6-dihydrobenzofuran-2(4*H*)-one (**3a**) (0.055 g, 74%) as a yellow liquid (TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes)), and 7-methyl-5,6-dihydrobenzofuran-2(4*H*)-one (**3b**) (0.080 g, 97%) as a yellow liquid (TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes)).

2a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, J = 1.53 Hz, 1H), 4.32−4.09 (m, 2H), 2.83−2.67 (m, 1H), 2.57 (s, 1H), 2.49−2.29 (m, 3H), 2.18−1.98 (m, 4H), 1.84−1.64 (m, 6H), 1.56−1.46 (m, 2H), 1.30−1.26 (m, 3H).

3a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (t, J = 4.63 Hz, 1H), 5.75 (s, 1H), 2.71 (t, J = 6.63 Hz, 2H), 2.39 (q, J = 5.50, 10.76 Hz, 2H), 1.89−1.83 (m, 2H).

3b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H), 2.70−2.65 (m, 2H), 2.32 (t, J = 5.34 Hz, 2H), 1.97 (s, 3H), 1.87 (quin, J = 6.10, 12.21 Hz, 2H).

Computational Details. Our protocol began with an initial conformational sampling using Grimme's semiempirical Conformer−Rotamer Ensemble Sampling Tool (CREST)[21] at xTB-GFN2[22−24] level of theory. This step aimed to identify potential conformers of various *E*/*Z* reactants, intermediates, and transition states involved in the chemical reaction. To enhance the accuracy of our conformational search, we performed geometry optimizations on all structures obtained from CREST at the Perdew−Burke−Ernzerhof (PBE) density functional method[25] and def2-TZVP basis set,[26] facilitated by the Turbomole 7.5.0 suite of programs.[27] Long-range interactions were taken into account through the application of Grimme's dispersion correction (D3).[28] To ensure precise and efficient treatment of the electronic Coulomb term in the DFT calculations, we employed the resolution of identity (RI)[29] and multipole-accelerated resolution of identity (Marij)[30] approximations. Furthermore, solvent corrections were incorporated by conducting optimization calculations using the COSMO model.[31] In our DFT calculation, dichloroethane (DCE; ε = 10.36) was used as the explicit solvent. To validate whether the stationary points were local minima or transition-state structures, harmonic frequency calculations were conducted at a temperature of 298.15 K. The reported values correspond to ΔG values, incorporating zero-point energy corrections as well as internal energy and entropic contributions through frequency calculations on the optimized minima. The absence of imaginary frequencies confirmed the minima, while the presence of a single imaginary frequency verified the transition states. Additionally, intrinsic reaction coordinate (IRC)[32] calculations were performed on all transition states to further validate their authenticity and confirm the correct determination of reactant and product structures. The translational entropy term in the calculated structures was corrected through a free volume correction introduced by Mammen et al.[33]

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c08873.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray crystallography data, and computational details (PDF)

Accession Codes

CCDC 2161281, 2161283, and 2161282 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Ravindar Kontham − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-5837-2777; Email: k.ravindar@ncl.res.in, konthamravindar@gmail.com

Authors

Ramavath Vinodkumar − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Ashwini K. Nakate − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Himanshu Sharma − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Kumar Vanka − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0001-7301-7573

Gamidi Rama Krishna − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Center for Materials Characterization, CSIR-National Chemical Laboratory, Pune 411008, India;* orcid.org/0000-0001-5313-7746

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c08873

Notes

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