Synthesis of Substituted 3(2*H*)-Furanones using Alkylative Intramolecular Cyclization of Sulfonium Salts

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Abstract

The facile alkylative intramolecular cyclization of 3-alkoxycarbonyl-2-oxopropyl diphenylsulfonium salts is described. This simple method can be readily applied to the synthesis of a novel family of 4-alkylated 3(2*H*)-furanones in moderate to high yields under mild conditions via a one-pot process.

Introduction

3(2*H*)-Furanone is a core structural unit of many natural products, such as eremantholide A,¹ geiparvarin,² pseurotin A,³ and jatrophone.⁴ In addition, 3(2*H*)-furanone derivatives exhibit antitumor,⁵ antiallergic,⁶ antiulcer,⁷ antiproliferative,⁸ selective COX-2 inhibitory,⁹ and selective MAO-B inhibitory activities.¹⁰ Consequently, a variety of synthetic methodologies for the functionalized 3(2*H*)-furanones have been developed, including acid-induced cyclization/dehydration of α' -hydroxy-1,3-diketones,¹¹ aldol reaction of 3-silyloxyfurans,¹² acid-catalyzed cyclization of α' -hydroxyenone,¹³ domino reaction of α,β -acetylenic- γ -hydroxy nitriles with arenecarboxylic acids,¹⁴ and cycloisomerization of allenic

hydroxyketones in water.¹⁵ Recently, methods based on transition-metal-catalyzed cyclizations, such as Au-catalyzed intramolecular cyclization of γ -hydroxyalkynones¹⁶ and 2-oxo-3-butynoates,¹⁷ Cu-catalyzed [4+1] annulation between α -hydroxyketones and nitriles,¹⁸ and Michael addition/Pd-catalyzed ring closure of activated alkenes and 4-chloroacetoacetates,¹⁹ have attracted considerable attention. However, the known synthetic methods have several drawbacks, such as unsatisfactory yields of the desired product, limited substrate scope, harsh conditions, and lack of a general procedure for the preparation of the starting materials. Therefore, further research is required to develop a more efficient approach to highly functionalized 3(2*H*)-furanones.

We previously reported a useful method for the synthesis of five-membered carbocycles using phosphoranes, such as allylidenetriphenylphosphorane and 2-oxopropylidenetriphenylphosphorane.²⁰ During the course of our study, we found that treatment of sulfonium salt **1** with *t*-BuOK produced 3(2*H*)-furanone **2** (Scheme 1). In addition, alkylative intramolecular cyclization of **1** leads to the formation of 4-alkylated 3(2*H*)-furanone **3**. To the best of our knowledge, the intramolecular cyclization of sulfonium salts to produce 3(2*H*)-furanones has not been reported to date. Herein, we report a detailed study of the intramolecular cyclization of sulfonium salts. Notably, this method involves the use of commercially available alkyl halides and *t*-BuOK which is easy to handle, leading to a novel family of 4-alkylated 3(2*H*)-furanones via a one-pot synthesis under mild conditions.

Scheme 1. Intramolecular cyclization of sulfonium salt **1**.

Results and Discussion

Initially, 3-ethoxycarbonyl-2-oxopropylidiphenylsulfonium tetrafluoroborate **1a** was used as a substrate for the examination of intramolecular cyclization (Table 1). When sulfonium salt **1a** was treated with *t*-BuOK in THF at room temperature, the desired 3(2*H*)-furanone **2a** was obtained in 88% yield (entry 1).

Other inorganic and organic bases were less effective (entries 2–5). Among the examined solvents, the use of THF resulted in the best yield (entries 1 and 6–8). Having defined the optimized conditions, we next examined the scope and limitations of ester part of sulfonium salts **1** (entries 9–16). Toward the substrate scope, all sulfonium salts **1b–1i** were prepared by the reaction of corresponding 4-bromoacetoacetates with diphenylsulfide in the presence of silver (I) tetrafluoroborate. Sulfonium salts **1** bearing isopropyl, cyclopentyl, and cyclohexyl esters gave the corresponding 5-alkoxy-3(2*H*)-furanones **2** in high yields (entries 9–11). Similarly, 3(2*H*)-furanones with allyloxy, propargyloxy, phenyloxy, benzyloxy, or 4-bromobenzyloxy groups in the 5 position were obtained in high yields from the corresponding sulfonium salts (entries 12–16). It is noteworthy that the efficient construction of 3(2*H*)-furanone with a variety of alkoxy groups was accomplished within 1–5 h in good yields in all cases.

Table 1. Intramolecular cyclization of sulfonium salt **1.^a**

1a: R = Et **1d:** R = Cyclohexyl **1g:** R = Ph
1b: R = *i*Pr **1e:** R = Allyl **1h:** R = Bn
1c: R = Cyclopentyl **1f:** R = Propargyl **1i:** R = 4-BrC₆H₄CH₂

Entry	1	Base	Solvent	Time (h)	Yield (%) ^b
1	1a	<i>t</i> -BuOK	THF	1	88
2	1a	K ₂ CO ₃	THF	1	23
3	1a	NaH	THF	1	57
4	1a	Et ₃ N	THF	1	82
5	1a	LiHMDS	THF	1	2
6	1a	<i>t</i> -BuOK	toluene	1	71
7	1a	<i>t</i> -BuOK	CH ₂ Cl ₂	1	68
8	1a	<i>t</i> -BuOK	Et ₂ O	1	30
9	1b	<i>t</i> -BuOK	THF	1	86
10	1c	<i>t</i> -BuOK	THF	1	92
11	1d	<i>t</i> -BuOK	THF	1	91
12	1e	<i>t</i> -BuOK	THF	5	90

13	1f	<i>t</i> -BuOK	THF	1	95
14	1g	<i>t</i> -BuOK	THF	1	91
15	1h	<i>t</i> -BuOK	THF	1	93
16	1i	<i>t</i> -BuOK	THF	3	99

^aReaction conditions: sulfonium salt **1** (0.2 mmol), base (0.2 mmol), solvent (2.0 mL). ^bIsolated yield.

We next carried out the alkylation of in situ generated enolate and subsequent ring closure to afford 4-alkylated 3(2*H*)-furanones (Table 2). When sulfonium salt **1a** was treated with 2.0 equiv of *t*-BuOK and 1.1 equiv of benzyl bromide **4a** in THF, the desired 4-benzyl-5-ethoxy-3(2*H*)-furanone **3aa** was obtained in 83% yield (entry 1). This simple one-pot process allowed to use various benzyl bromides having an electron-donating as well as an electron-withdrawing group and the corresponding alkylated products **3ab–3ag** were obtained in good yields (entries 2–7). Similar to benzyl bromide, use of methyl iodide **4h** and ethyl iodide **4i** gave the products **3ah** and **3ai** in 79% and 53% yields (entries 8 and 9). However, the reaction with isopropyl iodide resulted in a poor reaction yield, presumably because of the competing elimination reaction. More reactive halides, including allyl bromide **4j**, cinnamyl bromide **4k**, and propargyl bromide **4l** underwent alkylative intramolecular cyclization well (entries 10–12). Furthermore, ethyl bromoacetate **4m** and 2-thienylmethyl bromide **4n** were also tolerated in the reaction affording **3am** and **3an**, respectively (entries 13 and 14). Finally, the reactions were attempted using sulfonium salts **1** bearing various ester moieties and benzyl bromide and the desired products was obtained in moderate to good yields (entries 15–22). It should be emphasized that a variety of 4-alkylated 3(2*H*)-furanones were readily obtained in moderate to good yields by simple one-pot process.

Table 2. Synthesis of 4-alkylated 3(2*H*)-furanones **3.^a**

Entry	1	4	Time (h)	3	Yield (%) ^b
1	1a	BnBr (4a)	3	3aa	83
2	1a	4-MeOC ₆ H ₄ CH ₂ Br (4b)	1	3ab	64
3	1a	4-MeC ₆ H ₄ CH ₂ Br (4c)	1	3ac	81

4	1a	4-ClC ₆ H ₄ CH ₂ Br (4d)	2	3ad	76
5	1a	4-BrC ₆ H ₄ CH ₂ Br (4e)	4	3ae	72
6	1a	2-BrC ₆ H ₄ CH ₂ Br (4f)	3	3af	85
7	1a	2-FC ₆ H ₄ CH ₂ Br (4g)	3	3ag	77
8	1a	Methyl iodide (4h)	1	3ah	79
9	1a	Ethyl iodide (4i)	1	3ai	53
10	1a	Allyl bromide (4j)	3	3aj	71
11	1a	Cinnamyl bromide (4k)	3	3ak	76
12	1a	Propargyl bromide (4l)	3	3al	76
13	1a	BrCH ₂ CO ₂ Et (4m)	3	3am	73
14	1a	2-Thienylmethyl bromide (4n)	1	3an	73
15	1b	(4a)	2	3ba	70
16	1c	(4a)	1	3ca	73
17	1d	(4a)	1	3da	77
18	1e	(4a)	2	3ea	76
19	1f	(4a)	2	3fa	70
20	1g	(4a)	1	3ga	38
21	1h	(4a)	2	3ha	69
22	1i	(4a)	2	3ia	68

^aReaction conditions: sulfonium salt **1** (0.20 mmol), *t*-BuOK (0.40 mmol), alkyl-X **4** (0.22 mmol), THF (2.5 mL). ^bIsolated yield.

To obtain insight into the mechanism of the intramolecular cyclization of **1**, mechanistic studies were carried out. When ethyl 4-chloroacetoacetate **5** or ethyl 4-bromoacetoacetate **6a** were subjected to the optimal conditions, formation of trace amount of desired **2a** and dimerization product **7** were observed (Scheme 2, eq 1). Moreover, the treatment of **5** or **6a** with 2.0 equiv of *t*-BuOK in the presence of 1.1 equivalents of BnBr did not afford desired **3aa** and nucleophilic substitution product **8** was detected (Scheme 2, eq 2). These results clearly indicated that bulkiness of leaving group is important to form the desired 3(2*H*)-furanones because the substrates having smaller leaving groups (Cl: **5**, Br: **6a**) undergo the intermolecular S_N2 reaction. Furthermore, treatment of 3(2*H*)-furanone **2a** with 1.0 equiv of BnBr and 1.0 equiv of *t*-BuOK afforded 2-monobenzylated **9a** and 2,2-dibenzylated **9b** (Scheme 2, eq 3), revealing that the alkylation of furanone skeleton is not involved in the reaction. All of the results

mentioned above disclose that bulky diphenylsulfonio group would prevent undesired intermolecular side reaction and decomposition of substrate **1** by *t*-BuOK.

Scheme 2. Mechanistic studies.

Based on these experimental results, a plausible mechanism for intramolecular cyclization of **1** is described in Scheme 3. Initially, enolate **A** is generated by the treatment of **1** with *t*-BuOK. Subsequently, intramolecular nucleophilic attack of the oxygen of **A** gives 3(2*H*)-furanone **2** and diphenylsulfide (Ph₂S). With regard to the alkylative intramolecular cyclization, enolate **A** react with alkyl halides to form alkylated intermediate **B**. Subsequent deprotonation of **B** by another equivalent of *t*-BuOK and intramolecular cyclization of alkylated enolate **C** gives 4-alkylated 3(2*H*)-furanone **3** and Ph₂S.

Scheme 3. Plausible mechanism.

The 4-alkylated 3(2*H*)-furanones can be undergo further transformations to afford useful substances. For example, treatment of **3ak** with methyl 6-aminohexanoate and sodium methoxide in methanol for 2 h at room temperature afforded aza-prostaglandin analog **10** in 67% yield (Scheme 4),²¹ indicating that 4-alkyl-5-alkoxy-3(2*H*)-furanone **3** serves as an important synthetic intermediate for the synthesis of a variety of biologically important compounds.

Scheme 4. Conversion of 3ak into aza-prostaglandin analog 10.

Conclusion

In summary, we have developed a one-pot synthesis of substituted 3(2*H*)-furanones from sulfonium salts **1** via the alkylation followed by intramolecular cyclization under mild conditions. The proposed procedure shows wide substrate scope and functional group tolerance. This reaction can be extended to the short step synthesis of an aza-prostaglandin analog. The aza-prostaglandin analog was prepared in 51% overall yield over 2 steps from the sulfonium salt **1a**. This method would provide novel synthetic routes for biologically important compounds containing furanone skeleton.

Experimental Section

All reactions were performed under an argon atmosphere. The reagents and solvents were used as received from commercial suppliers without any further purification, unless otherwise indicated. Alkyl halides **4b** and **4n** were prepared according to literature procedure.²² Silica gel (40–50 mesh) was used for flash column chromatography. Components separated by thin-layer chromatography (TLC) were detected under UV light at 254 nm or by staining by using ethanoic *p*-anisaldehyde. IR spectra were recorded on an FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra recorded in CDCl_3 were referenced to TMS (0.00 ppm) and the solvent peak (77.0 ppm), respectively. ^1H NMR and ^{13}C NMR spectra recorded in CD_2Cl_2 were referenced to the residual solvent peak (5.32 ppm and 53.8 ppm), respectively.

High-resolution mass spectra (HRMS) were measured by FAB, ESI-TOF, and APCI-Orbitrap mass spectrometers.

General procedure for synthesis of 4-bromoacetoacetates (6). Dry CH₂Cl₂ (20 mL) and diketene (1.94 mL, 25.4 mmol) were added to a four-necked round bottom flask equipped with two dropping funnels and a thermometer, after the solution was cooled to −20 °C. Bromine (1.3 mL, 25.4 mmol) in dry CH₂Cl₂ (5 mL) was slowly added to the mixture at such a rate that the temperature did not rise above −10 °C, and the mixture was stirred until the color of bromine disappeared. Pyridine (2.06 mL, 25.5 mmol) and alcohol (1.0 equiv) in dry CH₂Cl₂ (5 mL) were added slowly to the mixture at such a rate that the temperature did not rise above −10 °C. The mixture was allowed to warm up to room temperature and was stirred for 1 h. The mixture was treated with water and extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 12:1) gave the 4-bromoacetoacetate **6** (keto–enol mixture).

*Ethyl 4-bromoacetoacetate (6a).*²³ Pale yellow oil (4.40 g, 84%). *R_f* = 0.40 (*n*-hexane/EtOAc = 4:1). IR (neat): 1746, 1728 cm^{−1}. ¹H NMR (500 MHz, CDCl₃): δ 4.22 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 2 H), 3.71 (s, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 194.6, 166.6, 61.8, 46.0, 33.8, 14.0. HRMS (FAB): *m/z* [M + H]⁺ calcd for C₆H₁₀⁸¹BrO₃: 210.9793, found: 210.9802; calcd for C₆H₁₀⁷⁹BrO₃: 208.9813, found: 208.9816.

Isopropyl 4-bromoacetoacetate (6b). Pale yellow oil (4.56 g, 81%). *R_f* = 0.48 (*n*-hexane/EtOAc = 4:1). IR (neat): 1741, 1724 cm^{−1}. ¹H NMR (500 MHz, CDCl₃): δ 5.07 (sept, *J* = 6.3 Hz, 1 H), 4.05 (s, 2 H), 3.67 (s, 2 H), 1.27 (d, *J* = 6.3 Hz, 6 H). ¹³C NMR (126 MHz, CDCl₃): δ 194.8, 166.1, 69.6, 46.4, 33.9, 21.7. HRMS (FAB): *m/z* [M + H]⁺ calcd for C₇H₁₂⁸¹BrO₃: 224.9949, found: 224.9935; calcd for C₇H₁₂⁷⁹BrO₃: 222.9970, found: 222.9960.

Cyclopentyl 4-bromoacetoacetate (6c). Pale yellow oil (5.20 g, 82%). *R_f* = 0.50 (*n*-hexane/EtOAc = 4:1). IR (neat): 2966, 1723 cm^{−1}. ¹H NMR (500 MHz, CDCl₃): δ 5.25–5.22 (m, 1 H), 4.04 (s, 2 H),

3.67 (s, 2 H), 1.91–1.86 (m, 2 H), 1.76–1.70 (m, 4 H), 1.64–1.58 (m, 2 H). ^{13}C NMR (150 MHz, CDCl_3): δ 194.8, 166.3, 78.8, 46.3, 33.9, 32.5, 23.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{14}^{81}\text{BrO}_3$: 251.0106, found: 251.0111; calcd for $\text{C}_9\text{H}_{14}^{79}\text{BrO}_3$: 249.0126, found: 249.0111.

Cyclohexyl 4-bromoacetoacetate (6d). Pale yellow liquid (4.09 g, 62%). R_f = 0.52 (*n*-hexane/EtOAc = 4:1). IR (neat): 2938, 2860, 1722 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.87–4.81 (m, 1 H), 4.05 (s, 2 H), 3.69 (s, 2 H), 1.89–1.85 (m, 2 H), 1.76–1.71 (m, 2 H), 1.57–1.53 (m, 1 H), 1.49–1.33 (m, 4 H), 1.31–1.24 (m, 1 H). ^{13}C NMR (150 MHz, CDCl_3): δ 194.8, 166.0, 74.4, 46.4, 33.9, 31.3, 25.2, 23.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}^{81}\text{BrO}_3$: 265.0262, found: 265.0273; calcd for $\text{C}_{10}\text{H}_{16}^{79}\text{BrO}_3$: 263.0283, found: 263.0255.

Allyl 4-bromoacetoacetate (6e). Pale yellow liquid (4.70 g, 85%). R_f = 0.44 (*n*-hexane/EtOAc = 4:1). IR (neat): 1747, 1730 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.92 (ddt, J = 17.2, 10.4, 5.8 Hz, 1 H), 5.36 (dq, J = 17.2, 1.3 Hz, 1 H), 5.29 (dq, J = 10.4, 1.3 Hz, 1 H), 4.66 (dt, J = 5.8, 1.3 Hz, 2 H), 4.05 (s, 2 H), 3.75 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 194.4, 166.3, 131.2, 119.2, 66.3, 45.9, 33.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{10}^{81}\text{BrO}_3$: 222.9793, found: 222.9802; calcd for $\text{C}_7\text{H}_{10}^{79}\text{BrO}_3$: 220.9813, found: 220.9803.

Propargyl 4-bromoacetoacetate (6f). Pale yellow liquid (4.31 g, 78%). R_f = 0.32 (*n*-hexane/EtOAc = 4:1). IR (neat): 3289, 1751, 1734 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.76 (d, J = 2.4 Hz, 2 H), 4.04 (s, 2 H), 3.78 (s, 2 H), 2.53 (t, J = 2.4 Hz, 1 H). ^{13}C NMR (126 MHz, CDCl_3): δ 194.0, 165.8, 76.7, 75.7, 53.0, 45.6, 33.7. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_8^{81}\text{BrO}_3$: 220.9636, found: 220.9632; calcd for $\text{C}_7\text{H}_8^{79}\text{BrO}_3$: 218.9657, found: 218.9660.

Phenyl 4-bromoacetoacetate (6g). Pale yellow liquid (4.61 g, 72%). R_f = 0.38 (*n*-hexane/EtOAc = 4:1). IR (neat): 1765, 1728, 733, 690 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.42–7.38 (m, 2 H), 7.28–7.25 (m, 1 H), 7.14–7.12 (m, 2 H), 4.09 (s, 2 H), 3.96 (s, 2 H). ^{13}C NMR (150 MHz, CDCl_3): δ 194.3, 165.3, 150.1, 129.5, 126.4, 121.3, 46.0, 26.9. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{10}^{81}\text{BrO}_3$: 258.9793, found: 258.9794; calcd for $\text{C}_{10}\text{H}_{10}^{79}\text{BrO}_3$: 256.9813, found: 256.9828.

Benzyl 4-bromoacetoacetate (6h).²⁴ Pale yellow liquid (5.39 g, 79%). $R_f = 0.40$ (*n*-hexane/EtOAc = 4:1). IR (neat): 1745, 1730, 749, 699 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.40–7.34 (m, 5 H), 5.19 (s, 2 H), 4.02 (s, 2 H), 3.76 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 194.4, 166.4, 134.9, 128.7, 128.6, 128.4, 67.5, 46.0, 33.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{12}^{81}\text{BrO}_3$: 272.9949, found: 272.9954; calcd for $\text{C}_{11}\text{H}_{12}^{79}\text{BrO}_3$: 270.9970, found: 270.9965.

4-Bromobenzyl 4-bromoacetoacetate (6i). White solid (7.00 g, 80%). Mp 72.0–72.8 °C. $R_f = 0.34$ (*n*-hexane/EtOAc = 4:1). IR (KBr): 1741, 1720, 708 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.51 (d, $J = 7.4$ Hz, 2 H), 7.24 (d, $J = 7.4$ Hz, 2 H), 5.14 (s, 2 H), 4.01 (s, 2 H), 3.76 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 194.3, 166.3, 134.0, 131.9, 130.1, 122.7, 66.6, 45.9, 33.7. HRMS (APCI-Orbitrap): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_9^{81}\text{Br}_2\text{O}_3$: 350.8882, found: 350.8883; calcd for $\text{C}_{11}\text{H}_9^{81}\text{Br}^{79}\text{BrO}_3$: 348.8904, found: 348.8904; calcd for $\text{C}_{11}\text{H}_9^{79}\text{Br}_2\text{O}_3$: 346.8927, found: 346.8924.

General procedure for synthesis of sulfonium salts (1). Diphenylsulfide (5.4 mL, 33 mmol) was added to a suspension of silver (I) tetrafluoroborate (1.25 g 6.42 mmol) in dry CH_2Cl_2 (5.4 mL) at 0 °C and stirred for 5 min. A solution of 4-bromoacetoacetate **6** (1.0 equiv) in dry CH_2Cl_2 (1.0 mL) was added to the mixture via cannula, and the mixture was allowed to warm up room temperature and then stirred for 48 h in the dark. The mixture was filtered through a celite-pad and concentrated under reduced pressure. The residue was applied on silica gel and eluted with CH_2Cl_2 (to remove an excess amount of diphenylsulfide) followed by $\text{CH}_2\text{Cl}_2/\text{MeOH} = 15:1$. The latter solution was concentrated under reduced pressure, and *t*-butyl methyl ether was added to the residue. The mixture was stirred until a precipitate was observed, and then the *t*-butyl methyl ether phase was decanted. After washing of the solid with *t*-butyl methyl ether was repeated several times, the solid was collected and dried under vacuum to give sulfonium salt **1**.

3-Ethoxycarbonyl-2-oxopropyl diphenylsulfonium tetrafluoroborate (1a). White solid (1.58 g, 61%). Mp 117.4–117.5 °C. $R_f = 0.40$ (dichloromethane/MeOH = 9:1). IR (KBr): 1748, 1719, 1058, 741, 689 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.96–7.94 (m, 4 H), 7.74–7.71 (m, 2 H), 7.69–7.65 (m, 4 H), 5.77 (s, 2 H), 4.17 (q, $J = 7.2$ Hz, 2 H), 3.84 (s, 2 H), 1.25 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ

193.4, 166.9, 134.7, 131.6, 130.4, 123.8, 62.1, 56.2, 47.0, 13.9. HRMS (FAB): m/z $[M]^+$ calcd for $C_{18}H_{19}O_3S$: 315.1055, found: 315.1047.

*3-Isopropoxyloxycarbonyl-2-oxopropyl*diphenylsulfonium tetrafluoroborate (**1b**). White solid (1.66 g, 62%). Mp 104.1–104.7 °C. R_f = 0.40 (dichloromethane/MeOH = 9:1). IR (KBr): 1745, 1720, 1105, 1082, 741, 690 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.96–7.74 (m, 4 H), 7.74–7.72 (m, 2 H), 7.70–7.67 (m, 4 H), 5.80 (s, 2 H), 5.02 (sept, J = 6.3 Hz, 1 H), 3.84 (s, 2 H), 1.24 (d, J = 6.3 Hz, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 166.6, 134.7, 131.6, 130.4, 123.8, 70.2, 56.3, 47.3, 21.6. HRMS (FAB): m/z $[M]^+$ calcd for $C_{19}H_{21}O_3S$: 329.1211, found: 329.1215.

*3-Cyclopentyloxycarbonyl-2-oxopropyl*diphenylsulfonium tetrafluoroborate (**1c**). White solid (1.62 g, 57%). Mp 123.2–123.6 °C. R_f = 0.40 (dichloromethane/MeOH = 9:1). IR (KBr): 2966, 1741, 1723, 1067, 740, 690 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.96–7.93 (m, 4 H), 7.75–7.71 (m, 2 H), 7.70–7.66 (m, 4 H), 5.78 (s, 2 H), 5.19–5.15 (m, 1 H), 3.83 (s, 2 H), 1.84–1.80 (m, 2 H), 1.71–1.68 (m, 4 H), 1.59–1.56 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 166.9, 134.7, 131.6, 130.4, 123.8, 79.3, 56.3, 47.3, 32.5, 23.6. HRMS (FAB): m/z $[M]^+$ calcd for $C_{21}H_{23}O_3S$: 355.1368, found: 355.1370.

*3-Cyclohexyloxycarbonyl-2-oxopropyl*diphenylsulfonium tetrafluoroborate (**1d**). White solid (1.78 g, 61%). Mp 137.7–137.9 °C. R_f = 0.40 (dichloromethane/MeOH = 9:1). IR (KBr): 2941, 2858, 1748, 1717, 1085, 1037, 750, 689 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.96–7.93 (m, 4 H), 7.74–7.71 (m, 2 H), 7.66–7.69 (m, 4 H), 5.78 (s, 2 H), 4.79–4.74 (m, 1 H), 3.84 (s, 2 H), 1.83–1.81 (m, 2 H), 1.71–1.69 (m, 2 H), 1.53–1.50 (m, 1 H), 1.45–1.38 (m, 2 H), 1.36–1.19 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 166.5, 134.7, 131.6, 130.4, 123.8, 75.0, 56.3, 47.3, 31.3, 25.1, 23.6. HRMS (FAB): m/z $[M]^+$ calcd for $C_{22}H_{25}O_3S$: 369.1524, found: 369.1508.

*3-Allyloxycarbonyl-2-oxopropyl*diphenylsulfonium tetrafluoroborate (**1e**). White solid (1.69 g, 64%). Mp 114.0–114.7 °C. R_f = 0.40 (dichloromethane/MeOH = 9:1). IR (KBr): 1750, 1720, 1060, 1032, 753, 684 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.96–7.93 (m, 4 H), 7.73–7.70 (m, 2 H), 7.68–7.65 (m, 4 H), 5.83 (ddt, J = 17.2, 10.5, 5.9 Hz, 1 H), 5.77 (s, 2 H), 5.30 (dq, J = 17.2, 1.3 Hz, 1 H), 5.25 (dq, J =

10.5, 1.3 Hz, 1 H), 4.61 (dt, $J = 5.9$, 1.3 Hz, 2 H), 3.87 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 193.3, 166.5, 134.7, 131.6, 131.1, 130.4, 123.8, 119.2, 66.5, 56.1, 46.9. HRMS (FAB): m/z $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_3\text{S}$: 327.1055, found: 327.1046.

3-Propargyloxycarbonyl-2-oxopropyl diphenylsulfonium tetrafluoroborate (If). White solid (1.37 g, 52%). Mp 87.6–87.9 °C. $R_f = 0.40$ (dichloromethane/MeOH = 9:1). IR (KBr): 3291, 1754, 1727, 1059, 741, 689 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.95–7.93 (m, 4 H), 7.73–7.70 (m, 2 H), 7.68–7.64 (m, 4 H), 5.75 (s, 2 H), 4.70 (d, $J = 2.5$ Hz, 2 H), 3.87 (s, 2 H), 2.49 (t, $J = 2.5$ Hz, 1 H). ^{13}C NMR (126 MHz, CDCl_3): δ 192.8, 165.9, 134.7, 131.6, 130.4, 123.8, 76.8, 75.7, 56.0, 53.2, 46.7. HRMS (FAB): m/z $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{17}\text{O}_3\text{S}$: 325.0898, found: 325.0895.

3-Phenyloxycarbonyl-2-oxopropyl diphenylsulfonium tetrafluoroborate (Ig). White solid (1.07 g, 37%). Mp 115.5–115.9 °C. $R_f = 0.40$ (dichloromethane/MeOH = 9:1). IR (KBr): 1764, 1719, 1057, 747, 686 cm^{-1} . ^1H NMR (500 MHz, CD_2Cl_2): δ 7.93–7.91 (m, 4 H), 7.76–7.73 (m, 2 H), 7.69–7.65 (m, 4 H), 7.40–7.36 (m, 2 H), 7.28–7.25 (m, 1 H), 7.12–7.09 (m, 2 H), 5.75 (s, 2 H), 4.10 (s, 2 H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 193.4, 166.1, 150.5, 135.2, 132.0, 130.8, 129.9, 126.8, 124.0, 121.9, 56.6, 47.4. HRMS (FAB): m/z $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3\text{S}$: 363.1055, found: 363.1053.

3-Benzylloxycarbonyl-2-oxopropyl diphenylsulfonium tetrafluoroborate (Ih). White solid (1.74 g, 58%). Mp 66.8–67.5 °C. $R_f = 0.40$ (dichloromethane/MeOH = 9:1). IR (KBr): 1749, 1720, 1056, 742, 691 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.90–7.89 (m, 4 H), 7.68–7.60 (m, 6 H), 7.35–7.29 (m, 5 H), 5.73 (s, 2 H), 5.13 (s, 2 H), 3.85 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 193.2, 166.5, 134.9, 134.6, 131.5, 130.4, 128.6, 128.5, 128.4, 123.8, 67.7, 56.1, 47.0. HRMS (FAB): m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{21}\text{O}_3\text{S}$: 377.1211, found: 377.1195.

3-(4-Bromobenzyl)oxycarbonyl-2-oxopropyl diphenylsulfonium tetrafluoroborate (Ii). White solid (1.87 g, 54%). Mp 110.6–111.0 °C. $R_f = 0.40$ (dichloromethane/MeOH = 9:1). IR (KBr): 1748, 1723, 1070, 805, 741, 690 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.91–7.89 (m, 4 H), 7.69–7.66 (m, 2 H), 7.63–7.60 (m, 4 H), 7.45 (d, $J = 8.4$ Hz, 2 H), 7.19 (d, $J = 8.4$ Hz, 2 H), 5.74 (s, 2 H), 5.07 (s, 2 H), 3.86 (s, 2

H). ^{13}C NMR (126 MHz, CDCl_3): δ 193.2, 166.4, 134.6, 133.9, 131.7, 131.5, 130.4, 130.1, 123.8, 122.5, 66.8, 56.1, 46.9. HRMS (FAB): m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{20}^{81}\text{BrO}_3\text{S}$: 457.0296, found: 457.0295; calcd for $\text{C}_{23}\text{H}_{20}^{79}\text{BrO}_3\text{S}$: 455.0317, found: 455.0315.

General procedure for synthesis of 5-alkoxy-3(2H)-furanones (2). *t*-BuOK (1.0 equiv) was added to a suspension of sulfonium salt **1** (0.2 mmol) in dry THF (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the mixture was treated with brine and extracted with EtOAc. The organic extract was dried over anhydrous Na_2SO_4 and was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:4) gave the desired 5-alkoxy-3(2H)-furanone **2**.

5-Ethoxy-3(2H)-furanone (2a).²⁵ White solid (22.0 mg, 88%). Mp 58.3–58.5 °C. R_f = 0.30 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1687, 1571 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.81 (s, 1 H), 4.57 (s, 2 H), 4.28 (q, J = 7.1 Hz, 2 H), 1.46 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.2, 185.7, 80.5, 75.1, 67.9, 14.2. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_9\text{O}_3$: 129.0552, found: 129.0551.

5-Isopropoxy-3(2H)-furanone (2b). Colorless oil (24.6 mg, 86%). R_f = 0.36 (*n*-hexane/EtOAc = 1:4). IR (neat): 1698, 1574 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.80 (s, 1 H), 4.70 (sept, J = 6.2 Hz, 1 H), 4.57 (s, 2 H), 1.43 (d, J = 6.2 Hz, 6 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.3, 185.0, 80.8, 76.7, 74.8, 21.7. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{11}\text{O}_3$: 143.0708, found: 143.0704.

5-Cyclopentyloxy-3(2H)-furanone (2c). White solid (30.8 mg, 92%). Mp 65.6–65.8 °C. R_f = 0.32 (*n*-hexane/EtOAc = 1:4). IR (KBr): 2970, 1693, 1571 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.92–4.89 (m, 1 H), 4.79 (s, 1 H), 4.56 (s, 2 H), 1.96–1.91 (m, 4 H), 1.90–1.78 (m, 2 H), 1.71–1.65 (m, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.3, 185.3, 85.7, 81.2, 74.9, 32.7, 23.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{O}_3$: 169.0865, found: 169.0867.

5-Cyclohexyloxy-3(2H)-furanone (2d). White solid (33.1 mg, 91%). Mp 89.2–89.7 °C. R_f = 0.48 (*n*-hexane/EtOAc = 1:4). IR (KBr): 2937, 2865, 1710, 1596 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.79 (s, 1 H), 4.56 (s, 2 H), 4.47–4.40 (m, 1 H), 1.99–1.96 (m, 2 H), 1.84–1.79 (m, 2 H), 1.68–1.61 (m, 2 H),

1.58–1.55 (m, 1 H), 1.43–1.32 (m, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.3, 185.0, 81.4, 80.8, 74.8, 31.3, 24.9, 23.2. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{15}\text{O}_3$: 183.1021, found: 183.1024.

5-Allyloxy-3(2H)-furanone (2e). White solid (25.1 mg, 90%). Mp 40.3–40.5 °C. R_f = 0.38 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1697, 1581 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.03–5.97 (m, 1 H), 5.48–5.40 (m, 2 H), 4.84 (s, 1 H), 4.71 (dt, J = 5.8, 1.3 Hz, 2 H), 4.59 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.3, 185.5, 129.8, 120.6, 81.1, 75.2, 72.1. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_9\text{O}_3$: 141.0552, found: 141.0544.

5-Propargyloxy-3(2H)-furanone (2f). White solid (26.2 mg, 95%). Mp 96.3–96.4 °C. R_f = 0.46 (*n*-hexane/EtOAc = 1:4). IR (KBr): 3226, 1690, 1566 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.96 (s, 1 H), 4.84 (d, J = 2.5 Hz, 2 H), 4.62 (s, 2 H), 2.69 (t, J = 2.5 Hz, 1 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.1, 185.0, 81.7, 78.2, 75.6, 75.0, 58.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_7\text{O}_3$: 139.0395, found: 139.0385.

5-Phenyloxy-3(2H)-furanone (2g). White solid (32.1 mg, 91%). Mp 82.0–82.4 °C. R_f = 0.60 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1694, 1550 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.47–7.43 (m, 2 H), 7.36–7.33 (m, 1 H), 7.22–7.19 (m, 2 H), 4.69 (s, 2 H), 4.63 (s, 1 H). ^{13}C NMR (126 MHz, CDCl_3): δ 196.9, 185.9, 152.3, 130.2, 127.3, 120.3, 82.5, 75.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{O}_3$: 177.0552, found: 177.0554.

5-Benzoyloxy-3(2H)-furanone (2h). White solid (35.6 mg, 93%). Mp 75.1–75.5 °C. R_f = 0.48 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1702, 1566 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.42–7.39 (m, 5 H), 5.23 (s, 2 H), 4.89 (s, 1 H), 4.59 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 197.2, 185.5, 133.3, 129.3, 128.9, 128.1, 81.4, 75.3, 73.2. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3$: 191.0708, found: 191.0716.

5-(4-Bromobenzoyloxy)-3(2H)-furanone (2i). White solid (53.5 mg, 99%). Mp 126.5–126.6 °C. R_f = 0.48 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1682, 1563 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.56 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.4 Hz, 2 H), 5.18 (s, 2 H), 4.88 (s, 1 H), 4.60 (s, 2 H). ^{13}C NMR (126 MHz,

CDCl₃): δ 197.1, 185.2, 132.3, 132.1, 129.6, 123.5, 81.4, 75.4, 72.2. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₁H₁₀⁸¹BrO₃: 270.9793, found: 270.9784; calcd for C₁₁H₁₀⁷⁹BrO₃: 268.9813, found: 268.9803.

General procedure for synthesis of 4-alkylated 3(2*H*)-furanones (3). *t*-BuOK (2.0 equiv) was added to a suspension of sulfonium salt **1** (0.2 mmol) in THF (2.5 mL) at 0 °C. After 20 s, the reaction mixture appeared yellow; then the alkyl halide **4** (1.1 equiv) was added, and the reaction mixture was allowed to warm to room temperature, and was monitored by TLC. After the reaction was complete, the mixture was treated with brine and extracted with EtOAc. The extract was dried over anhydrous Na₂SO₄ and was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:2) gave the desired 4-alkylated-3(2*H*)-furanone **3**.

4-Benzyl-5-ethoxy-3(2H)-furanone (3aa). Pale yellow oil (36.3 mg, 83%). R_f = 0.34 (*n*-hexane/EtOAc = 1:4). IR (neat): 1697, 1604, 728, 699 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.27–7.13 (m, 4 H), 7.18–7.15 (m, 1 H), 4.57 (s, 2 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.42 (s, 2 H), 1.39 (t, J = 7.1 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.5, 181.6, 140.2, 128.3, 128.2, 125.9, 93.7, 74.9, 65.8, 25.5, 14.7. HRMS (APCI-Orbitrap): m/z [M + H]⁺ calcd for C₁₃H₁₅O₃: 219.1021, found: 219.1016.

*5-Ethoxy-4-(4-methoxybenzyl)-3(2H)-furanone (3ab).*²⁶ Pale yellow oil (31.6 mg, 64%). R_f = 0.42 (*n*-hexane/EtOAc = 1:4). IR (neat): 1696, 1604 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.18 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 8.7 Hz, 2 H), 4.55 (s, 2 H), 4.42 (q, J = 7.1 Hz, 2 H), 3.77 (s, 3 H), 3.35 (s, 2 H), 1.40 (t, J = 7.1 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.6, 181.6, 157.9, 132.5, 129.3, 113.7, 94.2, 74.9, 65.8, 55.2, 24.7, 14.8. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₄H₁₇O₄: 249.1127, found: 249.1115.

5-Ethoxy-4-(4-methylbenzyl)-3(2H)-furanone (3ac). Pale yellow solid (37.5 mg, 81%). Mp 60.8–60.9 °C. R_f = 0.46 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1693, 1612, 823 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.16 (d, J = 7.8 Hz, 2 H), 7.06 (d, J = 7.8 Hz, 2 H), 4.55 (s, 2 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.37 (s, 2 H), 2.29 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.5, 181.5, 137.3, 135.3, 128.9, 128.2, 94.0, 74.9, 65.8, 25.1, 20.9, 14.7. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₄H₁₇O₃: 233.1178, found: 233.1169.

4-(4-Chlorobenzyl)-5-ethoxy-3(2H)-furanone (3ad). Pale yellow solid (38.4 mg, 76%). Mp 55.4–55.9 °C. $R_f = 0.30$ (*n*-hexane/EtOAc = 1:4). IR (KBr): 1686, 1593, 803 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.22–7.17 (m, 4 H), 4.57 (s, 2 H), 4.43 (q, $J = 7.1$ Hz, 2 H), 3.38 (s, 2 H), 1.40 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.4, 181.5, 138.7, 131.6, 129.7, 128.3, 93.3, 74.9, 66.0, 24.9, 14.7. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_3$ 253.0631, found: 253.0612.

4-(4-Bromobenzyl)-5-ethoxy-3(2H)-furanone (3ae). White solid (42.6 mg, 72%). Mp 53.5–53.6 °C. $R_f = 0.58$ (*n*-hexane/EtOAc = 1:4). IR (KBr): 1687, 1592, 798 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.36 (d, $J = 8.3$ Hz, 2 H), 7.13 (d, $J = 8.3$ Hz, 2 H), 4.57 (s, 2 H), 4.42 (q, $J = 7.1$ Hz, 2 H), 3.56 (s, 2 H), 1.40 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.4, 181.5, 139.2, 131.3, 130.1, 119.7, 93.3, 75.0, 66.0, 25.1, 14.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}^{81}\text{BrO}_3$: 299.0106, found: 299.0114; calcd for $\text{C}_{13}\text{H}_{14}^{79}\text{BrO}_3$: 297.0126, found: 297.0128.

4-(2-Bromobenzyl)-5-ethoxy-3(2H)-furanone (3af). Pale yellow oil (50.5 mg, 85%). $R_f = 0.58$ (*n*-hexane/EtOAc = 1:4). IR (neat): 1697, 1604, 749 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.51 (dd, $J = 7.9, 1.3$ Hz, 1 H), 7.27–7.25 (m, 1 H), 7.22–7.19 (m, 1 H), 7.08–7.02 (m, 1 H), 4.61 (s, 2 H), 4.40 (q, $J = 7.1$ Hz, 2 H), 3.55 (s, 2 H), 1.40 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.5, 181.6, 138.5, 132.4, 130.1, 127.6, 127.1, 124.2, 91.7, 74.9, 65.9, 26.1, 14.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}^{81}\text{BrO}_3$: 299.0106, found: 299.0084; calcd for $\text{C}_{13}\text{H}_{14}^{79}\text{BrO}_3$: 297.0126, found: 297.0108.

5-Ethoxy-4-(2-fluorobenzyl)-3(2H)-furanone (3ag). Pale yellow oil (36.7 mg, 77%). $R_f = 0.42$ (*n*-hexane/EtOAc = 1:4). IR (neat): 1699, 1605, 759 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.28–7.24 (m, 1 H), 7.17–7.12 (m, 1 H), 7.04–7.01 (m, 1 H), 7.00–6.96 (m, 1 H), 4.58 (s, 2 H), 4.41 (q, $J = 7.1$ Hz, 2 H), 3.46 (s, 2 H), 1.38 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.5, 181.6, 160.8 ($J = 245.6$ Hz), 130.6 ($J = 4.5$ Hz), 127.6 ($J = 8.1$ Hz), 126.6 ($J = 15.9$ Hz), 123.8 ($J = 3.6$ Hz), 115.0 ($J = 21.9$ Hz), 92.1, 74.9, 65.9, 18.5 ($J = 4.2$ Hz), 14.7. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{FO}_3$: 237.0927, found: 237.0927.

*5-Ethoxy-4-methyl-3(2H)-furanone (3ah).*²⁷ White solid (22.6 mg, 79%). Mp 55.0–55.5 °C. R_f = 0.18 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1695, 1600 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.55 (s, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 1.61 (s, 3 H), 1.44 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 196.5, 181.5, 89.3, 74.7, 65.6, 14.8, 3.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{11}\text{O}_3$: 143.0708, found: 143.0695.

5-Ethoxy-4-ethyl-3(2H)-furanone (3ai). Pale yellow oil (16.5 mg, 53%). R_f = 0.24 (*n*-hexane/EtOAc = 1:4). IR (neat): 1696, 1604 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.53 (s, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 2.12 (q, J = 7.5 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 196.2, 181.4, 95.4, 74.6, 65.6, 14.8, 12.9, 12.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{13}\text{O}_3$: 157.0865, found: 157.0853.

*4-Allyl-5-ethoxy-3(2H)-furanone (3aj).*²⁸ Pale yellow oil (23.7 mg, 71%). R_f = 0.28 (*n*-hexane/EtOAc = 1:4). IR (neat): 1698, 1603 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.83 (ddt, J = 17.0, 10.0, 6.2 Hz, 1 H), 5.04 (dq, J = 17.0, 1.5 Hz, 1 H), 4.97 (dq, J = 10.0, 1.5 Hz, 1 H), 4.57 (s, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 2.85 (dt, J = 6.2, 1.5 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.7, 181.6, 135.0, 114.8, 91.8, 74.8, 65.8, 23.7, 14.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{O}_3$: 169.0865, found: 169.0856.

*4-Cinnamyl-5-ethoxy-3(2H)-furanone (3ak).*²¹ Pale yellow oil (37.1 mg, 76%). R_f = 0.28 (*n*-hexane/EtOAc = 1:4). IR (neat): 1735, 1693, 1583, 758, 700 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.34–7.32 (m, 2 H), 7.29–7.25 (m, 2 H), 7.20–7.16 (m, 1 H), 6.41 (d, J = 15.8 Hz, 1 H), 6.21 (dt, J = 15.8, 6.7 Hz, 1 H), 4.58 (s, 2 H), 4.45 (q, J = 7.1 Hz, 2 H), 3.00 (dd, J = 6.7, 1.5 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.6, 181.6, 137.6, 130.2, 128.4, 126.93, 126.91, 126.1, 92.1, 74.9, 65.9, 23.0, 14.8. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{O}_3$: 245.1178, found: 245.1174.

5-Ethoxy-4-propargyl-3(2H)-furanone (3al). Orange oil (22.2 mg, 76%). R_f = 0.26 (*n*-hexane/EtOAc = 1:4). IR (neat): 3245, 1701, 1605 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.59 (s, 2 H), 4.49 (q, J = 7.1 Hz, 2 H), 3.03 (d, J = 2.7 Hz, 2 H), 1.94 (t, J = 2.7 Hz, 1 H), 1.46 (t, J = 7.1 Hz, 3 H). ^{13}C NMR

(126 MHz, CDCl₃): δ 194.4, 181.1, 89.4, 80.9, 75.0, 67.4, 66.3, 14.8, 9.4. HRMS (FAB): m/z [M + H]⁺ calcd for C₉H₁₁O₃: 167.0708, found: 167.0708.

5-Ethoxy-4-ethoxycarbonylmethyl-3(2H)-furanone (3am). Pale yellow oil (31.3 mg, 73%). R_f = 0.18 (*n*-hexane/EtOAc = 1:4). IR (neat): 1738, 1701, 1609 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 4.63 (s, 2 H), 4.46 (q, J = 7.1 Hz, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.12 (s, 2 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.0, 181.9, 170.6, 88.0, 75.2, 66.2, 60.9, 25.2, 14.7, 14.2. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₀H₁₅O₅: 215.0919, found: 215.0916.

5-Ethoxy-4-(2-thienylmethyl)-3(2H)-furanone (3an). Colorless oil (32.8 mg, 73%). R_f = 0.32 (*n*-hexane/EtOAc = 1:4). IR (neat): 1698, 1603, 850, 695 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.08 (dd, J = 5.1, 1.2 Hz, 1 H), 6.88 (dd, J = 5.1, 3.4 Hz, 1 H), 6.86–6.85 (m, 1 H), 4.58 (s, 2 H), 4.46 (q, J = 7.1 Hz, 2 H), 3.62 (d, J = 0.9 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.0, 181.4, 142.9, 126.7, 124.6, 123.3, 93.4, 75.0, 66.1, 19.8, 14.8. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₁H₁₃O₃S: 225.0585, found: 225.0575.

4-Benzyl-5-isopropoxy-3(2H)-furanone (3ba). Pale yellow oil (32.7 mg, 70%). R_f = 0.50 (*n*-hexane/EtOAc = 1:4). IR (neat): 1696, 1603, 731, 699 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.26–7.23 (m, 4 H), 7.18–7.14 (m, 1 H), 5.08 (sept, J = 6.2 Hz, 1 H), 4.56 (s, 2 H), 3.40 (s, 2 H), 1.37 (d, J = 6.2 Hz, 6 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.5, 181.4, 140.4, 128.4, 128.2, 125.9, 94.1, 74.8, 74.7, 25.6, 22.4. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₄H₁₇O₃: 233.1178, found: 233.1181.

4-Benzyl-5-cyclopentyloxy-3(2H)-furanone (3ca). Pale yellow oil (37.6 mg, 73%). R_f = 0.56 (*n*-hexane/EtOAc = 1:4). IR (neat): 2964, 1696, 1603, 725, 699 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.26–7.23 (m, 4 H), 7.18–7.14 (m, 1 H), 5.29–5.26 (m, 1 H), 4.56 (s, 2 H), 3.39 (s, 2 H), 1.89–1.83 (m, 4 H), 1.75–1.69 (m, 2 H), 1.66–1.59 (m, 2 H). ¹³C NMR (126 MHz, CDCl₃): δ 195.4, 181.4, 140.4, 128.4, 128.2, 125.9, 94.3, 83.6, 74.9, 33.2, 25.7, 23.4. HRMS (FAB): m/z [M + H]⁺ calcd for C₁₆H₁₉O₃: 259.1334, found: 259.1334.

4-Benzyl-5-cyclohexyloxy-3(2H)-furanone (3da). Pale yellow oil (41.2 mg, 77%). $R_f = 0.60$ (*n*-hexane/EtOAc = 1:4). IR (neat): 2938, 2860, 1696, 1604, 732, 699 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.28–7.23 (m, 4 H), 7.17–7.14 (m, 1 H), 4.87–1.82 (m, 1 H), 4.55 (s, 2 H), 3.41 (s, 2 H), 1.91–1.86 (m, 2 H), 1.75–1.69 (m, 2 H), 1.69–1.57 (m, 2 H), 1.54–1.49 (m, 1 H), 1.41–1.30 (m, 3 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.4, 181.4, 140.4, 128.4, 128.2, 125.9, 94.1, 79.1, 74.8, 31.9, 25.7, 25.0, 23.1. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{O}_3$: 273.1491, found: 273.1496.

5-Allyloxy-4-benzyl-3(2H)-furanone (3ea). Pale yellow oil (35.1 mg, 76%). $R_f = 0.52$ (*n*-hexane/EtOAc = 1:4). IR (neat): 1696, 1604, 725, 700 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.27–7.23 (m, 4 H), 7.18–7.15 (m, 1 H), 5.95 (ddt, $J = 17.1, 10.5, 5.7$ Hz, 1 H), 5.38–5.32 (m, 2 H), 4.84 (dt, $J = 5.7, 1.4$ Hz, 2 H), 4.58 (s, 2 H), 3.43 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.6, 181.3, 140.1, 130.7, 128.34, 128.30, 126.0, 119.8, 94.1, 75.0, 69.8, 25.5. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{O}_3$: 231.1021, found: 231.1011.

4-Benzyl-5-propargyloxy-3(2H)-furanone (3fa). White solid (32.1 mg, 70%). Mp 78.2–78.8 $^{\circ}\text{C}$. $R_f = 0.56$ (*n*-hexane/EtOAc = 1:4). IR (KBr): 3210, 1693, 1601, 735, 696 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.28–7.24 (m, 4 H), 7.19–7.16 (m, 1 H), 4.95 (d, $J = 2.4$ Hz, 2 H), 4.61 (s, 2 H), 3.44 (s, 2 H), 2.62 (t, $J = 2.4$ Hz, 1 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.8, 180.5, 139.8, 128.30, 128.28, 126.0, 94.1, 77.1, 76.0, 75.2, 56.7, 25.4. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{13}\text{O}_3$: 229.0865, found: 229.0862.

4-Benzyl-5-phenyloxy-3(2H)-furanone (3ga). Pale yellow oil (20.5 mg, 38%). $R_f = 0.74$ (*n*-hexane/EtOAc = 1:4). IR (neat): 1702, 1620, 724, 690 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.41–7.37 (m, 2 H), 7.31–7.25 (m, 5 H), 7.21–7.18 (m, 1 H), 7.12–7.10 (m, 2 H), 4.59 (s, 2 H), 3.53 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 196.4, 180.0, 151.3, 139.7, 129.7, 128.40, 128.36, 126.5, 126.1, 120.5, 95.9, 75.2, 25.7. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{15}\text{O}_3$: 267.1021, found: 267.1003.

4-Benzyl-5-benzyloxy-3(2H)-furanone (3ha). Pale yellow oil (38.5 mg, 69%). $R_f = 0.46$ (*n*-hexane/EtOAc = 1:4). IR (neat): 1699, 1607, 729, 698 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.39–

7.37 (m, 3 H), 7.31–7.29 (m, 2 H), 7.26–7.22 (m, 4 H), 7.19–7.15 (m, 1 H), 5.36 (s, 2 H), 4.59 (s, 2 H), 3.43 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.6, 181.3, 140.1, 134.3, 129.0, 128.8, 128.4, 128.3, 127.9, 126.0, 94.4, 75.1, 71.0, 25.6. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{O}_3$: 281.1178, found: 281.1191.

4-Benzyl-5-(4-bromobenzyl)oxy-3(2H)-furanone (3ia). Pale yellow solid (48.7 mg, 68%). Mp 92.8–93.0 °C. R_f = 0.50 (*n*-hexane/EtOAc = 1:4). IR (KBr): 1694, 1591, 806, 720, 701 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.50 (d, J = 8.5 Hz, 2 H), 7.26–7.16 (m, 5 H), 7.13 (d, J = 8.5 Hz, 2 H), 5.29 (s, 2 H), 4.58 (s, 2 H), 3.42 (s, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 195.6, 181.1, 140.0, 133.2, 132.0, 129.5, 128.4, 128.3, 126.0, 123.1, 94.5, 75.1, 70.1, 25.5. HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{16}^{81}\text{BrO}_3$: 361.0262, found: 361.0272; calcd for $\text{C}_{18}\text{H}_{16}^{79}\text{BrO}_3$: 359.0283, found: 359.0296.

Synthesis of Aza-prostaglandin analog (10).²¹ NaOMe (101.1 mg, 1.87 mmol) was added to a solution of 6-aminohexanoate hydrochloride (339.8 mg, 1.87 mmol) in dry MeOH (0.5 mL) and stirred for 30 min at room temperature. After removal of the precipitate by filtration under an argon atmosphere, to the filtrate was added **3ak** (70.3 mg, 0.288 mmol) in dry MeOH (0.5 mL) via cannula and stirred for 2 h at room temperature. After the solvent was concentrated under reduced pressure, the mixture was treated with 2 M HCl and extracted with diethyl ether. The extract was dried over anhydrous Na_2SO_4 and was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc/MeOH = 9:1) gave **10** as a pale yellow liquid (66.3 mg, 67%). R_f = 0.40 (EtOAc/MeOH = 9:1). IR (neat): 3217, 3024, 1737, 1677, 1651, 1573, 1496, 692 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.33–7.27 (m, 5 H), 7.26–7.20 (m, 1 H), 6.47 (d, J = 15.9 Hz, 1 H), 6.17 (dt, J = 15.9, 6.6 Hz, 1 H), 4.55 (s, 2 H), 3.65 (s, 3 H) 3.34 (q, J = 6.6 Hz, 2 H), 3.10 (dd, J = 6.6, 1.3 Hz, 2 H), 2.20 (t, J = 7.4 Hz, 2 H), 1.59–1.51 (m, 4 H), 1.31–1.25 (m, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ 192.3, 178.0, 173.9, 136.8, 130.6, 128.6, 127.7, 127.3, 126.0, 88.8, 74.3, 51.5, 41.0, 33.5, 29.6, 25.9, 24.1, 23.5. HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4$: 344.1856, found: 344.1862.

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Supporting Information. ^1H and ^{13}C NMR spectra data for all compounds.

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