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$TiCl_4$-Et_3N-mediated one-step synthesis of γ-alkylidenebutenolides from ketones: Application to natural product synthesis

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Abstract

$TiCl_4$-Et_3N-mediated condensation of ketones with methyl pyruvate afforded γ-alkylidene butenolides via a tandem cross-aldol addition/dehydroxylation/intramolecular lactonization process in one-pot. The application of the methodology to the straightforward synthesis of elem-1,3,7,8-tetraen-8,12-olide, chloranthalactone A, and dehydromenthofurolactone, is demonstrated.

1 | INTRODUCTION

Natural products are an exceptional source of small-molecule drug leads and a continuous source of inspiration for the design of compound libraries for drug discovery.[1] Among them, γ-alkylidene butenolides are an important class of compounds that are responsible for a diverse range of biological activities.[1b, c] Further, this skeletal motif can be found frequently in countless natural products, such as 1β-hydroxy-6α-isobutyryloxy-9-noreremophil-7(11), 8(10)-dien-8(12)-olide,[2] piptocarphin A,[3] menverin A,[4] elem-1,3,7,8-tetraen-8,12-olide,[5] chloranthalactone A,[6] and dehydromenthofurolactone[7] (Figure 1). In addition, γ-alkylidene butenolides are also important synthons in organic synthesis.[8]

Owing to their structural diversity and potential medicinal value, various strategies have been published on the synthesis of γ-alkylidene butenolide structures.[9–11] Despite their effectiveness, in the synthesis of γ-alkylidene butenolides, these methods require the challenging synthesis of the heterocyclic starting materials and also suffer from poor substrate scope. Thus, the development of more concise and effective methods using simple starting materials is highly desirable.

The use of ketones for the construction of fused γ-alkylidene butenolides directly, or via structural modification, or their use in late-stage construction of the natural products are important strategies.[5a, 6b, 12] Interestingly, Kontham's group and us were inspired to work on the synthesis of γ-alkylidenebutenolides at the same time by Tanabe's protocol for the synthesis of trialkylsubstituted 2-(5H)-furanones (butenolides) using ketones and α,α-dimethoxy ketones (Scheme 1, a) and the combination of $TiCl_4$-n-Bu_3N.[13] Recently, Kontham et al. reported a method for the construction of γ-alkylidenebutenolides through direct $TiCl_4$-$^nBu_3N$ mediated cascade annulation

of ketones with α-ketoesters (Scheme 1, b).[14] Our work involves the development of a similar methodology that differs in the use of a different ketoester and the base (Scheme 1, c). While our reaction is similar to Kontham's report, we discovered some interesting aspects of this reaction in our study, and importantly, the study reveals the precise mechanism of the reaction. Our reaction, described in Scheme 1c, involves a concise tandem reaction of ketones with methyl pyruvate, that affords highly substituted fused γ-alkylidenebutenolides from a tandem cross-aldol addition/dehydroxylation/intramolecular lactonization (Scheme 1, c).

2 | RESULTS AND DISCUSSION

We chose cyclohexanone (**1a**) and methyl pyruvate (**2a**) as the model reaction system and screened different reaction conditions (Table 1). We began the evaluation by screening different bases. Gratifyingly, all the bases screened, including $^{n}Bu_3N$, Et_3N, and DBU afforded the desired product **3a** (Table 1, entries 1-3), and among them, Et_3N was more efficient than the others. Next, we screened various combinations of $TiCl_4$ and Et_3N (Table 1, entries 4-6), and found that the reaction affords a good yield with the use of the $TiCl_4/Et_3N$ (1.5:3.0) combination (Table 1, entry 6). Particularly, with the use of methyl pyruvate (**2a**), the yield of **3a** dramatically improved when Et_3N was used in the reaction (Table 1, entry 6), relative to $^{n}Bu_3N$ (Table 1, entry 7). Whereas the ethyl pyruvate combined with $^{n}Bu_3N$ reported by Palange and co-workers is optimal combination,[14] which also confirmed by us (Table 1, entry 7). This dramatic difference in the reactivity may be attributed to the difference in the electron-withdrawing ability between –OMe and –OEt.

Encouraged by this finding, we explored the scope of ketone compounds in combination with methyl pyruvate **2a**, and the results are presented in Table 2. The cyclic 3,3-dimethylcyclohexanone (**1b**) participated in the annulation with **2a** smoothly, to afford the desired product in good yield (Tables 2, **3b**). Further, halogen-substituted cyclohexanones were also compatible with the reaction conditions (Table 2, **3c** and **3d**). Cycloheptanone (**1e**) and cyclooctanone (**1f**) furnished the corresponding butenolides in a moderate yield (Table 2, **3e**, **3f**). The scope was not limited to cyclic ketones alone, and the acyclic 5-nonanone (**1g**) afforded the butenolide product **3g** in 48% yield. It is noteworthy that beta-tetralone (1 h)

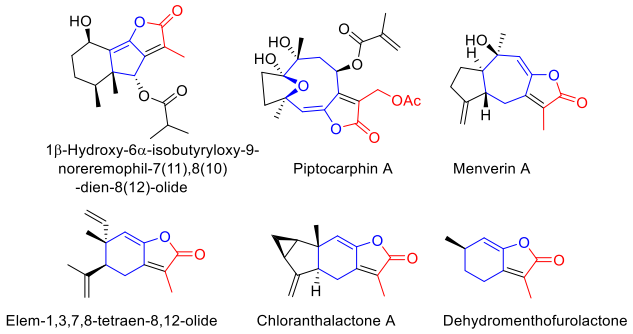
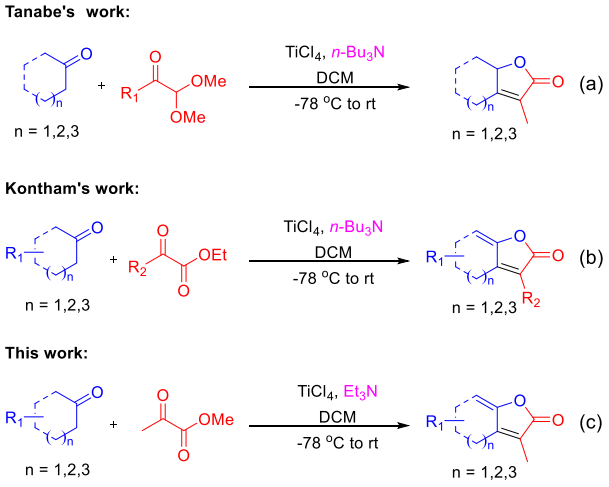


FIGURE 1 Representative natural products containing the γ-alkylidenebutenolide scaffold



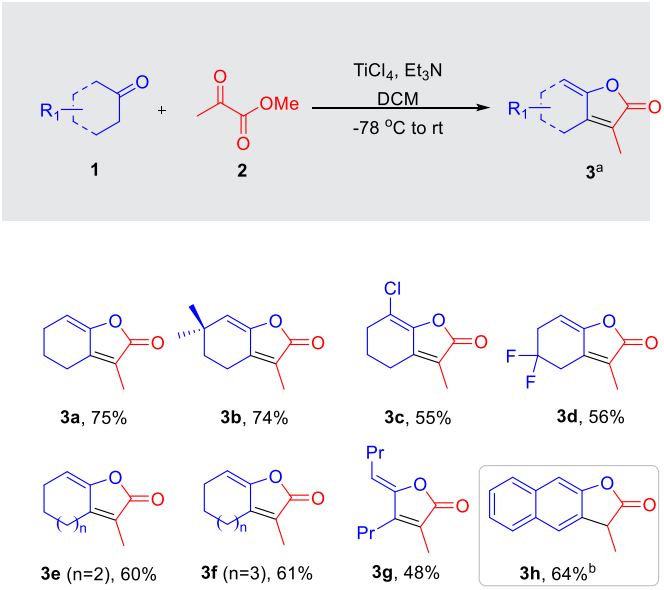
SCHEME 1 Synthesis of γ-alkylidenebutenolides

TABLE 1 Optimization of reaction conditions[a]

Entry	$TiCl_4$(eq)	base	*t*(h)	yield(%)[b]
1	1.5	$^{n}Bu_3N$	9	27
2	1.5	Et_3N	9	50.8
3	1.5	DBU	20	28
4	3.0	Et_3N[c]	9	56
5	1.5	Et_3N[c]	9	54.6
6	1.5	Et_3N[d]	9	74
7[e]	1.5	$^{n}Bu_3N$	9	71

[a]Reaction conditions: $TiCl_4$ (1.5 mmol) and base (2.0 mmol) were successively added to a stirred solution of **1a** (1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 1 h. To the reaction mixture, **2a** (2.0 mmol) was added. Then, the mixture was allowed to warm to room temperature, and was stirred for 9 h.
[b]Isolated yield.
[c]Et_3N (4.0 mmol) was used.
[d]Et_3N (3.0 mmol) was used.
[e]Ethyl pyruvate instead of **2a**.

TABLE 2 Scope of γ-alkylidenebutenolide synthesis

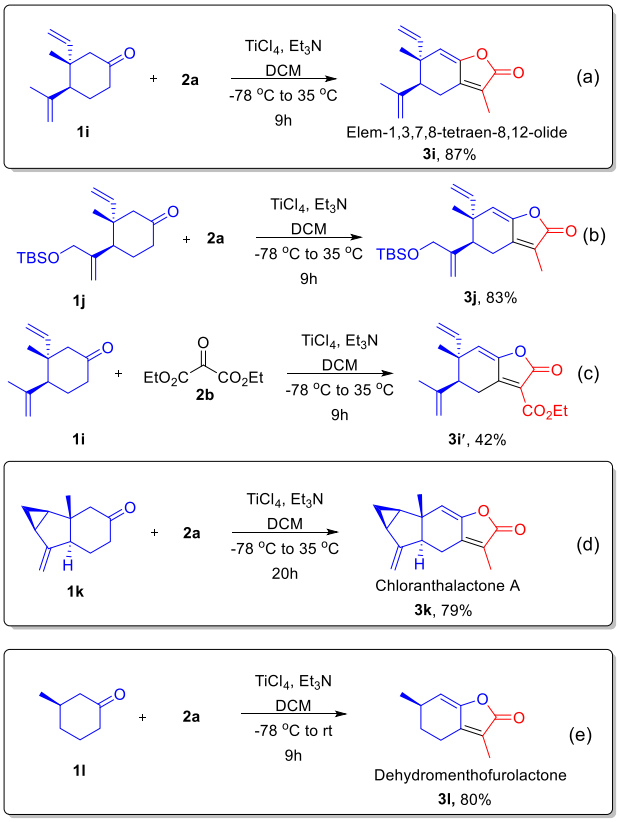


underwent further rearrangement after annulation with **2a**, and the thermodynamically stable product 3 h was the only isolated product (Table 2, 3 h).

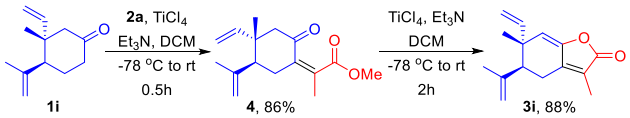
Reaction conditions: $TiCl_4$ (1.5 mmol) and Et_3N (3.0 mmol) were successively added to a stirred solution of **1** (1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 1 h. To the reaction mixture, **2** (2.0 mmol) was added. Then, the mixture was allowed to warm to room temperature, and was stirred for 9 h. (a) Isolated yields. (b) After **2** was added, the mixture was heated to 35°C, and was stirred for 9 h.

To extend the applications of this protocol, we performed a direct and straightforward synthesis of the natural products, elem-1,3,7,8-tetraen-8,12-olide (**3i**), chloranthalactone A (**3 k**), and dehydromenthofurolactone (**3 L**), as shown in Scheme 2 (1 mmol scale). Delightfully, with slightly modified standard conditions, the reactions of ketones **1i**, **1k**, and **1L** with methyl pyruvate **2a** furnished the butenolides **3i**, **3k**, and **3L**, respectively, in excellent yields (Scheme 2, a, d, and e), which represents a significant improvement in the synthesis efficiency for these transformations, which typically require three steps.[5b, 6b, 15] Furthermore, the ketone with an acid-sensitive group (**1j**) was well tolerated and afforded the desired products **3j** in 83% yield, displaying the mildness of the developed reaction conditions (Scheme 2, b). In addition, diethyl ketomalonate (**2b**) also participated well in this transformation and delivered **3i′** in a moderate yield of 42% (Scheme 2, c).

A closer examination of the reaction revealed another interesting aspect of this reaction pathway. Upon warming the reaction mixture to room temperature from −78°C



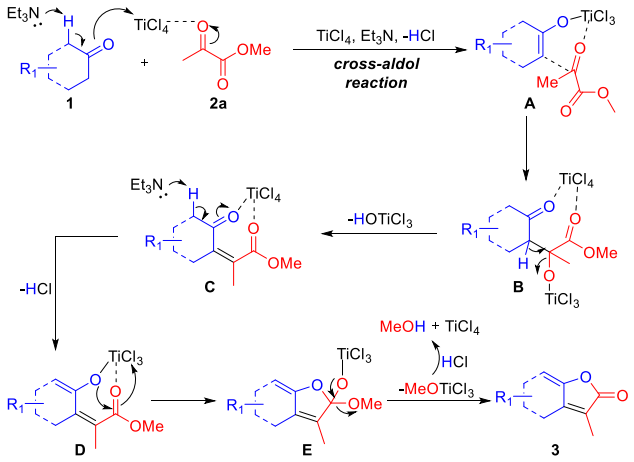
SCHEME 2 Total synthesis of elem-1,3,7,8-tetraen-8,12-olide (**3j**), chloranthalactone A (**3 k**), and dehydromenthofurolactone (**3 L**)



SCHEME 3 Probing the mechanism of the cascade

over 30 min, we detected the formation of an intermediate by TLC, which transformed into the final butenolide products with time. We conducted further analysis to gain insight into this process for understanding the mechanism of the reaction, and conducted a control experiment (Scheme 3). After experimentation, finally, the aldol/dehydroxylation intermediate **4** was isolated in 85% yield by premature termination of the reaction process, and the structure of intermediate **4** was determined by ^1H NMR, ^{13}C NMR spectroscopy, and HRMS analysis. Importantly, when the intermediate **4** was subjected to the standard condition again, **3i** was obtained in 88% yield.

Overall, based on our results and literature reports,[13,14] a modified Palange's reaction pathway is proposed (Scheme 4).[14] The $TiCl_4$-Et_3N combination directs the cross-aldol addition through the transition state **A** and gives



SCHEME 4 Proposed reaction mechanism

the adduct **B**, which undergoes the elimination of $Ti(OH)Cl_3$ to afford the tetra-substituted alkene **C**. Subsequent second enolization of **C** with concomitant enol-lactonization delivers the intermediate **E**, which transforms into the butenolide **3** through the expulsion of $MeOTiCl_3$.

3 | CONCLUSIONS

A tandem reaction of ketones and methyl pyruvate catalyzed by $TiCl_4$-Et_3N, is demonstrated to furnish γ-ylidene butenolides in moderate to good yields. This process was also applied to the straightforward synthesis of elem-1,3,7,8-tetraen-8,12-olide (**3i**), chloranthalactone A (**3k**), and dehydromenthofurolactone (**3L**). Finally, a mechanism has been proposed to explain the reaction sequence.

4 | EXPERIMENTAL SECTION

4.1 | General information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dichloromethane (DCM) was distilled from calcium hydride under argon; All the chemicals were purchased commercially and used without further purification, unless otherwise stated. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm), I_2 and by developing the plates with *p*-anisaldehyde or $KMnO_4$. ^1H and ^{13}C NMR were recorded on Bruker DRX-400 MHz and Bruker DRX-600 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^1H NMR = 7.26, ^{13}C NMR = 77.16; d_6-Acetone: ^1H NMR = 2.05, ^{13}C NMR = 29.8, 206.3). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a FTMS-7 spectrometers and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M + Na]^+$, $[M + H]^+$. Infrared (IR) spectra were recorded on a NEXUS 670 FT-IR Fourier transform infrared spectrophotometer and are reported in wavenumbers (cm^{-1}). Compounds **1i** and **1k** can be prepared known reference. [5b, 12c]

4.2 | Procedure for the preparation of compound 1j

Starting from a known compound (3*S*,4*R*)-4-(3-hydroxyprop-1-en-2-yl)-3-methyl-3-vinylcyclohexan-1-one (**I**), [12c, d] to a solution of compound **I** (2.60 g, 10.80 mmol) in acetone (80 mL) was added *p*-TsOH (0.93 g, 5.40 mmol) at 0°C. Then the reaction was allowed to warm to rt and stirred for 16 h, before it was quenched with saturated aqueous $NaHCO_3$ (100 mL) at 0°C. The mixture was concentrated under reduced pressure, and aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 petroleum ether-EtOAc) to provide **II** (1.82 g, 87%) as a white solid.

To a solution of **II** (1.82 g, 9.40 mmol) and imidazole (1.28 g, 18.8 mmol) in DCM (70 mL) was added TBSCl (2.10 g, 14.1 mmol) at rt. After stirring for 4 h at rt, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20:1 petroleum ether-EtOAc) to furnish **1j** (2.37 g, 82%) as a colorless oil.

(3S,4R)-4-(3-([tert-butyldimethylsilyl]oxy)prop-1-en-2-yl)-3-methyl-3-vinylcyclohexan-1-one (**1j**)

Colorless oil. IR (thin film): 2955, 2857, 1716, 1472, 1253, 1108, 1005, 905, 837, 777 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.26 (d, *J* = 1.2 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 17.4 Hz, 1H), 4.85 (s, 1H), 4.10 (d, *J* = 14.4 Hz, 1H), 4.01 (d, *J* = 14.4 Hz, 1H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.44-2.40 (m, 1H), 2.39-2.33 (m, 1H), 2.29 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.12 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.08-1.99 (m, 1H), 1.95-1.91 (m, 1H), 0.99 (s, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 210.8, 148.9, 146.5, 111.8, 111.0, 67.5, 53.5, 46.5, 44.0, 41.4, 28.7, 26.1, 18.5, 17.6, −5.1, −5.2. HRMS (ESI): m/z calcd for $C_{18}H_{33}O_2Si^+$ $[M + H]^+$ 309.2244 found 309.2235.

4.3 | General procedure for synthesis of γ-alkylidenebutenolides 3

$TiCl_4$ (1.0 M in DCM, 1.5 mL, 1.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) were successively added to a stirred solution of **1** (1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 1 h. To the reaction mixture, **2** (2.0 mmol) was added. Then the mixture was allowed to warm to room temperature, and was stirred for 9 h before the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Pure products **3** were obtained by column chromatography on silica gel (petroleum ether-EtOAc).

3-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3a**).

10:1 petroleum ether-EtOAc, White solid. Mp: 35-38°C. Yield 75%. IR (thin film): 2931, 1766, 1443, 1285, 1119, 986, 922, 735 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.74 (t, J = 4.2 Hz, 1H), 2.62-2.57 (m, 2H), 2.36 (dd, J = 10.8, 5.4 Hz, 2H), 1.87 (s, 3H), 1.86-1.83 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 149.6, 148.4, 119.9, 108.4, 23.8, 22.9, 22.6, 8.5. HRMS (EI): m/z calcd for $C_9H_{11}O_2^+$ $[M + H]^+$ 151.0754 found 151.0752.

3,6,6-trimethyl-5,6-dihydrobenzofuran-2(4H)-one (**3b**).

10:1 petroleum ether-EtOAc, White solid. Mp: 41-43°C. Yield 74%. IR (thin film): 2961, 2871, 1769, 1455, 1294, 1280, 1259, 1115, 1023, 996, 940, 759 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.53 (s, 1H), 2.68-2.58 (m, 2H), 1.88 (s, 3H), 1.67 (t, J = 6.6 Hz, 2H), 1.14 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.3, 147.7, 120.0, 118.1, 36.7, 33.0, 28.9, 20.0, 8.6. HRMS (EI): m/z calcd for $C_{11}H_{15}O_2^+$ $[M + H]^+$ 179.1067 found 179.1065.

7-chloro-3-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3c**).

10:1 petroleum ether-EtOAc, White solid. Yield 55%. Mp: 107-109°C. IR (thin film): 2920, 1765, 1673, 1645, 1434, 1282, 1026, 994, 912, 753 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 2.62 (t, J = 6.6 Hz, 2H), 2.59 (t, J = 6.6 Hz, 2H), 2.00-1.95 (m, 2H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 148.4, 145.4, 119.7, 114.6, 32.2, 23.4, 22.2, 8.8. HRMS (EI): m/z calcd for $C_9H_{10}ClO_2^+$ $[M + H]^+$ 185.0364 found 185.0358.

5,5-difluoro-3-methyl-5,6-dihydrobenzofuran-2(4H)-one (**3d**).

10:1 petroleum ether-EtOAc, Yellow oil. Yield 56%. IR (thin film): 2924, 1771, 1661, 1367, 1269, 1214, 1144, 1065, 1034, 913, 867, 830, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.64-5.53 (m, 1H), 3.12 (td, J = 14.0, 1.2 Hz, 2H), 2.89 (td, J = 13.2, 4.4 Hz, 2H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.5, 143.2, 124.4, 123.7, 121.3, 118.9, 101.7, 101.6, 33.7, 33.5, 33.2, 32.9, 32.6, 32.3, 8.8. HRMS (EI): m/z calcd for $C_9H_9F_2O_2^+$ $[M + H]^+$ 187.0565 found 187.0558.

3-methyl-4,5,6,7-tetrahydro-2H-cyclohepta[*b*]furan-2-one (**3e**).

10:1 petroleum ether-EtOAc, Colourless oil. Yield 60%. IR (thin film): 3021, 2927, 2849, 1765, 1449, 1216, 925, 757, 668 cm^{-1}. ^1H NMR (400 MHz, d_6-Acetone) δ 5.85 (t, J = 5.2 Hz, 1H), 2.72-2.70 (m, 2H), 2.44 (dd, J = 10.8, 5.2 Hz, 2H), 1.84-1.78 (m, 7H). ^{13}C NMR (100 MHz, d_6-Acetone) δ 170.50, 151.5, 150.2, 125.8, 115.2, 28.7, 28.5, 28.3, 25.7, 8.6. HRMS (EI): m/z calcd for $C_{10}H_{13}O_2^+$ $[M + H]^+$ 165.0910 found 165.0909.

3-methyl-5,6,7,8-tetrahydrocycloocta[b]furan-2(4H)-one (**3f**).

10:1 petroleum ether-EtOAc, Colourless oil. Yield 61%. IR (thin film): 2934, 2862, 1766, 1447, 1277, 1119, 1048, 991, 924, 756, 667 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.71 (t, J = 9.0 Hz, 1H), 2.79 (t, J = 7.2 Hz, 2H), 2.51 (dd, J = 15.6, 6.6 Hz, 2H), 1.89 (s, 3H), 1.75-1.69 (m, 2H), 1.66-1.62 (m, 2H), 1.53-1.49 (m, 2H). ^{13}C NMR (100 MHz, d_6-Acetone) δ 171.1, 154.2, 150.5, 126.0, 109.5, 26.4, 26.0, 25.4, 23.6, 22.5, 8.1. HRMS (EI): m/z calcd for $C_{11}H_{15}O_2^+$ $[M + H]^+$ 179.1067 found 179.1066.

5-butylidene-3-methyl-4-propylfuran-2(5H)-one (**3 g**).

10:1 petroleum ether-EtOAc, Colourless oil. Yield 48%. IR (thin film): 2964, 2934, 2875, 1767, 1459, 1384, 1280, 1102, 993, 904, 733 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.20 (t, J = 7.8 Hz, 1H), 2.39 (t, J = 7.8 Hz, 2H), 2.34 (q, J = 7.8 Hz, 2H), 1.89 (s, 3H), 1.59-1.53 (m, 2H), 1.51-1.45 (m, 2H), 0.94 (dt, J = 13.2, 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 151.2, 149.6, 124.0, 111.1, 28.1, 26.7, 22.7, 22.6, 14.1, 13.9, 8.8. HRMS (EI): m/z calcd for $C_{12}H_{19}O_2^+$ $[M + H]^+$ 195.1380 found 195.1382.

Dehydromenthofurolactone (**3 L**).

10:1 petroleum ether-EtOAc, Colourless oil. Yield 80%. Known compound.[3] ^1H NMR (600 MHz, $CDCl_3$) δ 5.61 (d, J = 3.0 Hz, 1H), 2.73 (dt, J = 17.4, 4.8 Hz, 1H), 2.64-2.54 (m, 1H), 2.52-2.43 (m, 1H), 2.00-1.95 (m, 1H), 1.87 (s, 3H), 1.49-1.42 (m, 1H), 1.14 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 149.3, 148.2, 119.9, 114.2, 31.1, 29.9, 21.7, 21.3, 8.5. HRMS (EI): m/z calcd for $C_{10}H_{13}O_2^+$ $[M + H]^+$ 165.0910 found 165.0905.

4.4 | Modified general procedure for synthesis of γ-alkylidenebutenolides 3

$TiCl_4$ (1.0 M in DCM, 1.5 mL, 1.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) were successively added to a

stirred solution of **1** (1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 1 h. To the reaction mixture, **2** (2.0 mmol) was added. Then the mixture was allowed to warm to rt, and was stirred for 0.5 h before the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Pure products **3** were obtained by column chromatography on silica gel (petroleum ether-EtOAc).

3-methylnaphtho[2,3-b]furan-2(3H)-one (3h).

10:1 petroleum ether-EtOAc, White solid. Mp:114-117°C. Yield 64%. IR (thin film): 1805, 1446, 1248, 1175, 1129, 1096, 1028, 877, 752, 485 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (t, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 0.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.47-7.42 (m, 2H), 3.88 (qd, *J* = 7.8, 1.2 Hz, 1H), 1.67 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.6, 151.7, 133.83, 131.0, 129.6, 128.0, 127.9, 126.9, 125.3, 123.5, 106.6, 38.1, 16.4. HRMS (EI): m/z calcd for $C_{13}H_{11}O_2^+$ $[M + H]^+$ 199.0754 found 199.0755.

elem- 1,3,7,8-tetraen-8,12-olide (**3i**).

15:1 petroleum ether-EtOAc, White solid. Mp: 70-71°C. Yield 87%. IR (thin film): 3082, 2967, 2925, 1771, 1670, 1651, 1378, 1318, 1293, 1221, 1062, 918, 870, 758, 580, 553 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.47 (s, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.92-4.92 (m, 1H), 4.78 (s, 1H), 2.74 (ddd, *J* = 16.8, 4.8, 1.2 Hz, 1H), 2.63 (ddd, *J* = 17.3, 8.4, 1.2 Hz, 1H), 2.47 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.89 (s, 3H), 1.70 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 149.0, 148.0, 146.0, 145.3, 120.5, 114.9, 114.5, 113.6, 50.9, 42.0, 25.6, 23.9, 22.2, 8.6. HRMS (ESI): m/z calcd for $C_{15}H_{18}NaO_2$ $[M + Na]^+$ 253.1199 found 253.1195.

ethyl(5S,6S)-6-methyl-2-oxo-5-(prop-1-en-2-yl)-6-vinyl-2,4,5,6-tetrahydrobenzofuran-3-carboxylate (**3i′**).

10:1 petroleum ether-EtOAc, White solid. Mp: 75-76°C. Yield 42%. IR (thin film): 3082, 2979, 1791, 1732, 1714, 1680, 1620, 1448, 1408, 1370, 1219, 1032, 983, 919, 801 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.85 (dd, *J* = 17.4, 10.2 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 4.97 (s, 1H), 4.82 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.27 (dd, *J* = 19.2, 5.4 Hz, 1H), 3.09 (dd, *J* = 19.2, 9.0 Hz, 1H), 2.55 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.71 (s, 3H), 1.37 (t, *J* = 6.6 Hz, 3H), 1.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 161.6, 161.5, 147.8, 144.9, 144.4, 122.9, 115.7, 114.3, 113.8, 61.5, 50.7, 42.1, 27.6, 24.0, 21.6, 14.4. HRMS (ESI): m/z calcd for $C_{17}H_{21}O_4^+$ $[M + H]^+$ 289.1434 found 289.1432.

(5R,6S)-5-(3-([tert-butyldimethylsilyl]oxy)prop-1-en-2-yl)-3,6-dimethyl-6-vinyl-5,6-dihydrobenzofuran-2(4H)-one (**3j**)

20:1 petroleum ether-EtOAc, Colorless oil. Yield 83%. IR (thin film): 2929, 2858, 1777, 1653, 1463, 1253, 1114, 1020, 907, 837, 776, 757 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.50 (s, 1H), 5.31 (d, *J* = 7.8 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 17.4 Hz, 1H), 4.96 (s, 1H), 4.04 (d, *J* = 15.0 Hz, 1H), 3.97 (d, *J* = 15.0 Hz, 1H), 2.74-2.61 (m, 2H), 2.36 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.88 (s, 3H), 1.17 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 148.9, 148.2, 147.9, 145.7, 121.0, 115.0, 114.0, 112.1, 66.9, 46.0, 42.2, 26.2, 26.0, 21.4, 18.5, 8.6, −5.2, −5.2. HRMS (ESI): m/z calcd for $C_{21}H_{33}O_3Si^+$ $[M + H]^+$ 361.2193 found 361.2194.

Natural product chloranthalacone A (**3 k**).

10:1 petroleum ether-EtOAc, known compound.[6b] Yield 79%. ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.06 (s, 1H), 4.79 (s, 1H), 3.04-2.90 (m, 1H), 2.71 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.27 (ddd, *J* = 16.8, 13.6, 1.6 Hz, 1H), 2.00-1.95 (m, 1H), 1.914 (d, *J* = 1.6 Hz, 3H), 1.67 (ddd, *J* = 11.2, 7.6, 4.0 Hz, 1H), 0.98-0.87 (m, 2H), 0.79 (s, 3H).

4.5 | Procedure for probing the mechanism of the cascade

$TiCl_4$ (1.0 M in DCM, 1.5 mL, 1.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) were successively added to a stirred solution of **1i** (178.3 mg, 1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 0.5 h. To the reaction mixture, **2a** (2.0 mmol) was added. Then the mixture was allowed to warm to 35°C, and was stirred for 9 h but **3k** for 20 h before the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15:1 petroleum ether-EtOAc) to provide **4** (226.4 mg, 86%) as a colorless oil.

$TiCl_4$ (1.0 M in DCM, 1.5 mL, 1.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) were successively added to a stirred solution of **4** (262 mg, 1.0 mmol) in dry DCM (1.0 mL) at −78°C under an argon atmosphere, followed by stirring for 1 h. Then the mixture was allowed to warm to rt, and was stirred for 2 h before the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10:1 petroleum ether-EtOAc) to provide **3i** (201.8 mg, 88%) as a white solid.

Methyl(Z)-2-((4S,5S)-4-methyl-2-oxo-5-(prop-1-en-2-yl)-4-vinylcyclohexylidene)propanoate (**4**).

15:1 petroleum ether-EtOAc, Colorless oil. Yield 86%. IR (thin film): 2951, 1732, 1692, 1639, 1434, 1377, 1288, 1192, 1165, 1105, 913, 771 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ

5.79 (dd, J = 17.4, 10.8 Hz, 1H), 5.00 (d, J = 10.8 Hz, 1H), 4.98-4.96 (m, 1H), 4.95 (d, J = 17.4 Hz, 1H), 4.78 (s, 1H), 3.76 (s, 3H), 2.64 (dd, J = 16.2, 4.8 Hz, 1H), 2.60-2.54 (m, 2H), 2.45 (dd, J = 10.8, 5.4 Hz, 1H), 2.37 (d, J = 15.6 Hz, 1H), 1.93 (s, 3H), 1.80 (s, 3H), 1.05 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3, 171.5, 146.0, 145.6, 136.4, 135.7, 113.7, 112.0, 52.3, 52.1, 50.1, 41.9, 30.9, 24.9, 19.6, 16.4. HRMS (ESI): m/z calcd for $C_{16}H_{23}O_3^+$ $[M + H]^+$ 263.1642 found 263.1637.

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