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Synthesis of β-Halobutenolides and Their Pd(0)-Catalyzed Cross-Coupling Reactions with Terminal Alkynes and Organozinc Reagents. A General Route to β-Substituted Butenolides and Formal Synthesis of *cis*-Whisky Lactone

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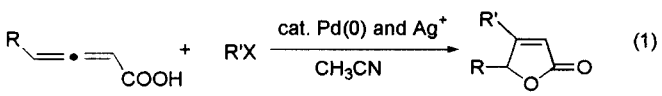
Abstract: An improved procedure for the efficient synthesis of β-halobutenolides was developed. The Pd(0)-catalyzed coupling reactions of β-halobutenolides with terminal alkynes or organozinc reagents, *i.e.*, 1-alkenyl, aryl, and alkyl zinc reagents, to afford β-substituted butenolides were carefully studied. Using the coupling protocol of γ-(*n*-butyl)-β-iodobutenolide with methylzinc halide, we performed an efficient formal synthesis of whisky lactone.

Introduction

Recently much attention has been paid to the synthesis of butenolides with different substitution patterns due to their potential biological activities. Butenolide-containing compounds are considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, anti-inflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors, and phospholipase A_2 inhibitors, etc.[1] Recently, we developed a Pd(0)/Ag^+-cocatalyzed one-step methodology for the efficient synthesis of butenolides starting from 1,2-allenic carboxylic acids and organic halides (eq. 1).[2]



(1)

However, there are some intrinsic limitations for this reaction since it is difficult to introduce a β–alkyl group due to the potential stability problem of alkyl palladium species. In addition, under the standard conditions for the above cyclization reaction, 1-alkynyl halides did not afford the expected products. On

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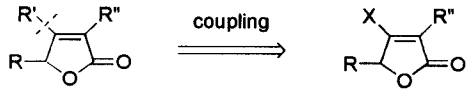
the other hand, transition metal-catalyzed coupling reactions of terminal alkynes or organometallic reagents with organohalides have been proven to be one of the most successful pathways for the formation of C-C single bonds. Thus, from the view point of retrosynthesis, β-halobutenolides might be an important class of building blocks for the connection of different types of R' with butenolides at the β-position (**Scheme 1**). In a preliminary communication,[3] we established a high-yielding procedure for the synthesis of β–halobutenolides and the corresponding Pd(0)-catalyzed coupling reaction with 1-alkynes. In this paper, we wish to disclose the experimental details of our study on this improved synthesis of β-halobutenolides from 1,2-allenic acids and the corresponding Pd(0)-catalyzed coupling reaction of β-halobutenolides with terminal alkynes as well as organozinc reagents.

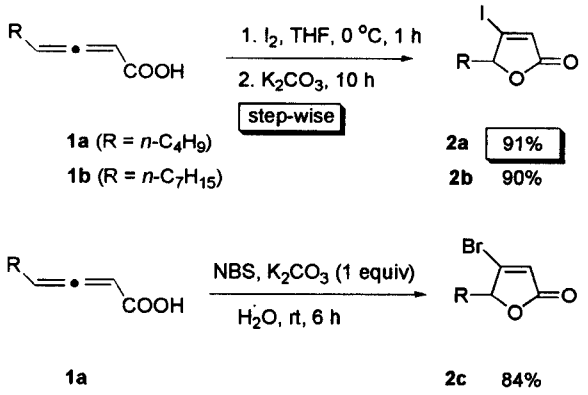
Scheme 1



Results and Discussion

X^+ (X = Br, I)-mediated lactonization reactions of 1,2-allenic carboxylic acids[4,5] and esters[5] to afford β-halobutenolides have been studied. Starting from 2,3-octadienoic acid (**1a**) or 2,3-undecadienoic acid (**1b**) and using the procedure reported by Gill and Idvis,[5] the reaction afforded β-iodobutenolide **2a** in only 42% yield. In order to improve the yield of this iodolactonization reaction, several conditions were screened, the results being summarized in **Scheme 2**. *A step-wise procedure of adding I_2 in THF at 0 °C first followed by the addition of K_2CO_3 afforded 2a in 91% yield.* We prepared γ-(*n*-heptyl)-β-iodobutenolide **2b** in 90% yield under these modified conditions (**Scheme 2**).

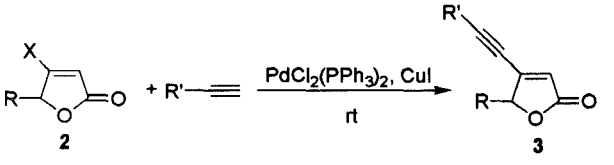
Scheme 2



β-Bromobutenolides **2c** and **2d** were prepared by the reaction of 2,3-octadienoic acid or 2,3-undecadienoic acid with NBS and K_2CO_3 in an environmentally benign solvent H_2O at rt for 6 h in 84% and 81% yields, respectively (**Scheme 2**).

Pd(0)/CuI-Cocatalyzed Sonogashira Coupling Reactions of β-Halobutenolides with Terminal Alkynes. Sonogashira coupling reaction[6] has been developed as one of the most powerful tools for the synthesis of disubstituted alkynes. We tested the coupling reaction of γ-(*n*-butyl)-β–iodobutenolide **2a** with phenylacetylene using Et_3N as the base and THF or CH_3CN as the solvent. Under the catalysis of $PdCl_2(PPh_3)_2$ and CuI, the coupling reaction did occur, but the yield was poor (~42%). Here, probably the instability of β-iodobutenolide **2a** towards Et_3N might be the reason for a low-yielding reaction. Under Sonogashira's original conditions, *i.e.*, using Et_3N as both the solvent and the base, the yield was 67%. If the coupling reaction was carried out in DMF, the yield was similar (66%). However, after further screening we found that when K_2CO_3 was used in place of Et_3N as the base, the coupling product **3a** was formed cleanly in CH_3CN and isolated in 99% yield (entry 1, **Table 1**).

Table 1. Sonogoshira Coupling Reactions of β–Halobutenolides with Terminal Alkynes[a]



2 **3**

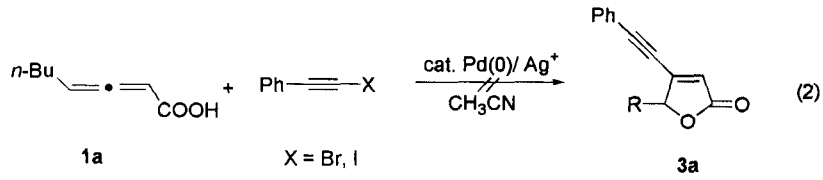
Entry	**2**	R'	Time (h)	product **3**	yield (%)
1	**2a**	Ph	3	**3a**	99
2[b]	**2a**	*n*-butyl	2	**3b**	<5[c]
3	**2a**	*n*-butyl	4.3	**3b**	93
4	**2a**	$HOCH_2$	2	**3c**	95
5	**2a**	TMS	3	**3d**	65
6	**2b**	Ph	3	**3e**	95
7	**2b**	*n*-butyl	2.25	**3f**	86
8	**2b**	$HOCH_2$	4.3	**3g**	79
9	**2b**	TMS	3	**3h**	70
10	**2c**	Ph	3	**3a**	78

[a] **2**:alkyne:K_2CO_3:CuI:$PdCl_2(PPh_3)_2$ = 1:1.02:1:0.01:0.01; [b] Et_3N and THF were used as the base and solvent, respectively; [c] Determined by ^1H NMR using CH_2Br_2 as the internal standard.

Some typical examples are summarized in Table 1. Under these new reaction conditions, (1) the coupling

reaction went smoothly with phenylacetylene, 1-hexyne, and trimethylsilylacetylene. Using trimethylsilylacetylene as the terminal alkyne in the reaction leaves another terminal of the C-C triple bond for further elaboration (entries 5 and 9, **Table 1**); (2) when propargyl alcohol was employed as a terminal alkyne, no protection of the hydroxy group was necessary (entries 4 and 8, **Table 1**); (3) the corresponding bromoanalogue **2c** also coupled with phenylacetylene smoothly to afford **3a** in 78% yield (entry 10, **Table 1**).

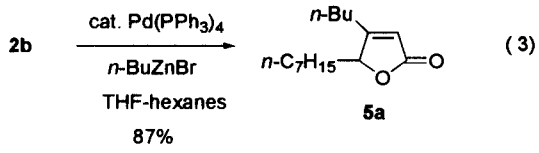
Under the reaction conditions described in ref. 2, the Pd(0)/Ag^+-cocatalyzed cyclization reaction of 1-alkynyl halide with 1,2-allenic carboxylic acids did not yield the corresponding butenolides in decent yields (eq. 2). Thus, the current Sonogashira coupling protocol supplements the methodology described in ref. 2.



Pd(0)-Catalyzed Coupling Reactions of β-Halobutenolides with Aryl or 1-Alkenylzinc Reagents. Under the catalysis of $Pd(PPh_3)_4$, β-halobutenolides can cross-couple with aryl or alkenyl zinc reagents.[7,8] Some typical examples are listed in **Table 2**. The following points should be noted: (1) aromatic zinc reagents were prepared efficiently *via* the transmetalation reaction of $ZnBr_2$ with aromatic lithiums, which were prepared by the halogen-lithium exchange reactions of the corresponding aromatic halides with *n*-BuLi.[9] The subsequent coupling reaction went smoothly with THF as the solvent (entries 1, 2, and 3, **Table 2**); (2) vinylzinc bromide was prepared by the transmetalation reaction of vinylmagnesium bromide with $ZnBr_2$, while (*E*)-1-hexenylzinc bromide was prepared from (*E*)-1-hexenyl iodide by its treatment with *n*-BuLi followed the addition of $ZnBr_2$. The reaction was heterogeneous and did not occur in pure THF (entry 5, **Table 2**). *However, with the addition of DMF as the cosolvent, the coupling reaction was homogeneous and afforded the β-vinyl butenolides* ***4*** *in moderate to good yields* (entries 4, 6, and 7, **Table 2**); (3) γ-(*n*-butyl)-β–bromobutenolide **2c** also coupled with vinylzinc bromide to afford **4e** (entry 8, **Table 2**).

Pd(0)-Catalyzed Coupling Reactions of β-Halobutenolides with Alkylzinc Reagents. Formal Synthesis of *cis*-Whisky Lactone. Due to the predicted problem in the oxidative addition reaction of alkyl halides with low-valent metal complexes and the instability of alkyl palladium species because of the intrinsic β-H elimination reaction, the new methodology recently developed by us[2] would not be suitable for the synthesis of β-alkyl substituted butenolides. Using the cross-coupling protocol, when a solution of β-iodobutenolide and the Pd catalyst in THF was added to *n*-butylzinc bromide, no cross-coupling product was formed. *However, to our surprise, when the solution of n-butylzinc bromide was added to the solution of the Pd catalyst and β-iodobutenolide* ***2b****, the reaction afforded the corresponding product* ***5a*** *in 87% yield* (eq. 3). *n*-BuZnBr used in

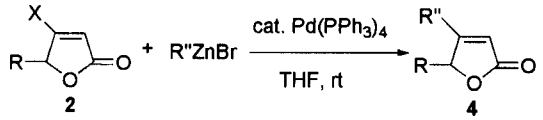
eq. 3 was prepared *in situ* by the treatment of the commercially available *n*-BuLi in hexanes with a solution of $ZnBr_2$ in THF.



(3)

The coupling reaction of γ-butyl-β-iodobutenolide **2a** with methylzinc bromide afforded γ-butyl-β-methylbutenolide **5b** in 92% yield. Here the addition of HMPA is crucial since the reaction was heterogeneous and sluggish. **5b** could be converted to *cis*-whisky lactone according to the known procedure[9] (Scheme 3). Thus, by using this coupling protocol, we performed an efficient formal synthesis of *cis*-whisky lactone.

Table 2. $Pd(PPh_3)_4$ -Catalyzed Coupling Reactions of β-Halobutenolides with Aryl/1-Alkenyl Zinc Reagents[a]



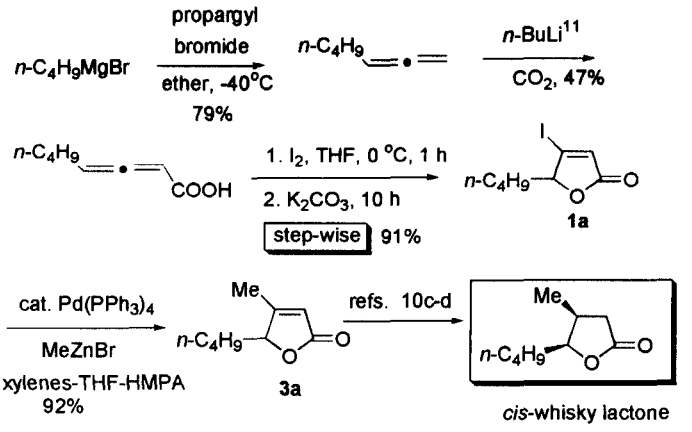
entry	2	R''	additive	time (h)	product 4	yield (%)
1	**2b**	phenyl	—	2	**4a**	93
2	**2b**	*p*-methylphenyl	—	8	**4b**	83
3	**2a**	naphthyl	—	40 min	**4c**	70
4	**2b**	1(*E*)-hexenyl	DMF	50 min	**4d**	77
5	**2a**	vinyl	—	16	**4e**	<5[b]
6	**2a**	vinyl	DMF	10 min	**4e**	92
7	**2b**	vinyl	DMF	10	**4f**	82
8	**2c**	vinyl	DMF	10	**4e**	78

[a]ArZnBr or (*E*)-1-hexenylzinc bromide:**2**:$Pd(PPh_3)_4$ = 2.9:1:0.05; vinylzinc bromide:**2**:$Pd(PPh_3)_4$ = 3.3:1:0.05.

In conclusion, we have developed an improved procedure for the synthesis of β-halobutenolides, in which the C-X bonds can readily couple with terminal alkynes and organozincs under the catalysis of Pd(0) to provide a variety of butenolides with different functional groups at the β-position in good to excellent yields. The methodology described here supplements the method in ref. 2, especially for the synthesis of butenolides

with β-sp^3-C and *sp*-C-centered substituents.

Scheme 3



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Experimental Section

Starting Materials. 2,3-Octadienoic acid and 2,3-undecadienoic acid were prepared according to a published procedure[11] *via* the reaction of CO_2 with the corresponding 1,2-allenic lithiums, which, in turn, were prepared from the treatment of the corresponding 1,2-allenes with *n*-BuLi. Methylzinc halide (bromide or iodide) was prepared *via* the reaction of zinc bromide with methylmagnesium iodide, which was prepared according to the published procedure[12] from the reaction of methyliodide with magnesium turning in xylenes. Trimethylsilylacetylene was prepared *via* the reaction of TMSCl with ethynylmagnesium bromide.[13] Phenylacetylene, 1-hexyne, propargyl alcohol, phenyl iodide, *p*-methylphenyl iodide, 1-iodonaphthalene, *n*-BuLi solution (1.6 M in hexanes), and methyl iodide were commercially available and used without further purification. (*E*)-1-Iodo-1-hexene was prepared from the hydroalumination reaction of 1-hexyne with DIBAL-H and the subsequent iodination reaction.[14] ^{1}H NMR spectra were recorded using $CDCl_3$ as the solvent and TMS as the internal standard.

Iodolactonization of 1,2-Allenic Acids. Preparation of 4-Iodo-5-(*n*-butyl)-2(5H)-furanone (2a). A solution of 2,3-octadienoic acid (154 mg, 1.0 mmol) and iodine (508 mg, 2.2 mmol) in 5 mL of dry THF was kept at 0 °C for 1 h. Then K_2CO_3 (76 mg, 0.55 mmol) was added quickly at 0 °C and stirred for 10 h at this temperature. The reaction mixture was quenched with an aqueous sodium thiosulfate solution, extracted with diethyl ether (3 x 15 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 241 mg

(91%) of **2a**: white solid; mp: 62-63 °C (*n*-hexane); IR (KBr) 1754, 1618, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (1H, d, *J* 1.7 Hz, =CH), 4.89 (1H, ddd, *J* 7.5, 3.4, 1.7 Hz, CHOCO), 1.98-2.04 (1H, m, CH_aH_bCHO), 1.48-1.60 (1H, m, CH_aH_bCHO), 1.20-1.40 (4H, m, CH_2CH_2Me), 0.82 (3H, t, *J* 6.9 Hz Me); m/z (EI, He) 267 (5, MH^+), 210 (100), 209 (85), 55 (51) , 41 (61%); HRMS (EI): M^+, found: 265.9797. $C_8H_{11}IO_2$ requires 265.9802.

4-Iodo-5-(*n*-heptyl)-2(5H)-furanone (2b) was prepared similarly: starting from **1b** (182 mg, 1.0 mmol), I_2 (512 mg, 2.0 mmol), and K_2CO_3 (71 mg, 0.5 mmol) to afford 277 mg (90%) of **2b**: white solid; mp: 78-79 °C (*n*-hexane); [Found: C, 43.01; H, 5.56; $C_{11}H_{17}IO_2$ requires C, 42.87; H, 5.56%]; IR (KBr) 1750, 1622, 1170 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.50 (1H, d, *J* 1.6 Hz, =CH), 4.92-4.98 (1H, m, CHOCO), 1.95-2.05 (1H, m, CH_aH_bCHO), 1.55-1.65 (1H, m, CH_aH_bCHO), 1.20-1.40 (10H, m, $(CH_2)_5Me$), 0.85 (3H, t, *J* 6.9 Hz, Me); m/z (EI, He) 309 (35, MH^+), 308 (11, M^+), 223 (70), 210 (100), 209 (81), 57 (61%).

Bromolactonization of 1,2-Allenic Carboxylic Acids. Preparation of 4-Bromo-5-(*n*-butyl)-2(5H)-furanone (2c). A mixture of 2,3-octadienoic acid (140 mg, 1.0 mmol), potassium carbonate (138 mg, 1 mmol), and NBS (354 mg, 2 mmol) in water (5 mL) was stirred for 6 h at 25 °C. Then the reaction mixture was extracted with diethyl ether (3 x 10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 184 mg (84%) of **2c**: yellow oil; IR (KBr) 1751, 1633, 1171 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.32 (1H, d, *J* 1.2 Hz, =CH), 4.98-5.08 (1H, m, CHOCO), 2.02-2.08 (m, 1H, CH_aH_bCHO), 1.52-1.65 (m, 1H, CH_aH_bCHO),1.35-1.48 (m, 4H, CH_2CH_2Me), 0.92 (3H, t, *J* 6.9 Hz, Me); m/z (EI He) 164 (79, $M^+(^{81}Br)$-Bu), 162 (78, $M^+(^{79}Br)$-Bu), 139 (100%); HRMS (EI): (M^+ - Br), found: 139.0777. $C_8H_{11}O_2$ reqires 139.0760; (M^+ - Bu), found: 161.9307 (^{79}Br); 163.9287 (^{81}Br). $C_4H_2BrO_2$ requires 161.9316 (^{79}Br); 163.9296 (^{81}Br).

4-Bromo-5-(*n*-heptyl)-2(5H)-furanone (2d) was prepared similarly: starting from **1b** (182 mg, 1.0 mmol) K_2CO_3 (138 mg, 1.0 mmol), and NBS (354 mg, 2.0 mmol) to afford 214 mg (81%) of **2d**: white solid; mp: 40-41.5 °C (*n*-hexane) ; [Found: C, 50.55; H, 6.71; $C_{11}H_{17}BrO_2$ requires C, 50.59; H, 6.56%]; IR (KBr) 1752, 1628, 1168 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.38 (1H, s, =CH), 4.95-5.05 (1H, m, CHOCO), 1.95-2.05 (1H, m, CH_aH_bCHO), 1.54-1.64 (1H, m, CH_aH_bCHO), 1.14-1.44 (10H, m, $(CH_2)_5Me$), 0.86 (3H, t, *J* 6.9 Hz, Me); m/z (EI, He) 263 (11, $MH^+(^{81}Br)$), 261 (11, $MH^+(^{79}Br)$), 57 (100), 41 (95), 55 (49%).

Coupling Reactions of β-Halobutenolides with Terminal Alkynes. Typical Procedure. Preparation of Compound (3a). To a mixture of **2a** (66.5 mg, 0.25 mmol), phenylacetylene (27 mg, 0.26 mmol), and K_2CO_3 (36 mg, 0.26 mmol) in CH_3CN (1 mL) was added $PdCl_2(PPh_3)_2$ (1.8 mg, 0.0025 mmol) and copper(I) iodide (0.5 mg, 0.0025 mmol) under Ar and the reaction was stirred at 20 °C for 4 h. The mixture was filtered through a short column of silica gel and evaporated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) to afford 59.6 mg (99%) of **3a**: pale yellow oil; [found: C, 79.64; H, 6.72. $C_{16}H_{16}O_2$ reqires C, 79.97; H, 6.71%]; IR (neat) 2200, 1707, 1616, 1601 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 7.53-7.36 (5H, m, Ph), 6.20 (1H, d, *J* 1.6 Hz, =C<u>H</u>), 5.02 (1H, ddd, *J* 7.7, 3.7, 1.6 Hz, C<u>H</u>OCO), 2.07-2.00 (1H, m, CH_aH_bCHO), 1.73-1.62 (1H, m, CH_aH_bCHO), 1.53-1.34 (4H, m, CH_2CH_2Me), 0.97 (3H, t, *J* 7.1 Hz, <u>Me</u>); m/z (EI, He) 241 (100, MH^+), 240 (49, M^+), 127 (50) , 126 (74%).

The following compounds (**3b-3h**) were prepared similarly using the conditions listed in Table 1.

4-(1′-Hexynyl)-5-(*n*-butyl)-2(5H)-furanone (3b): starting from **2a** (66.5 mg, 0.25 mmol) and 1-hexyne (21.3 mg, 0.26 mmol) to afford 51.2 mg (93%) of **3b**: yellow oil; [Found: C, 75.91; H, 9.59. $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.]. IR (neat) 2226, 1758, 1610 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.02 (1H, d, *J* 1.5 Hz, =C<u>H</u>), 4.87 (1H, ddd, *J* 7.6, 3.7, 1. 5 Hz, C<u>H</u>OCO), 2.46 (2H, t, *J* 6.9 Hz, C-$C\underline{H}_2$), 1.90-2.02 (1H, m, $C\underline{H}_aH_bCHO$), 1.60-1.52 (3H, m, CH_aH_bCHO, and C-$CH_2C\underline{H}_2$), 1.39-1.50 (6H, m, $(C\underline{H}_2)_2Me$ and $C\underline{H}_2Me$), 0.96-0.88 (6H, m, 2<u>Me</u>); m/z (EI, He) 221 (100, MH^+), 163 (18), 135 (15), 91 (15%).

4-(3′-Hydroxypropargyl)-5-(*n*-butyl)-2(5H)-furanone (3c): starting from **2a** (66.5 mg, 0.25 mmol) and propargyl alcohol (14.6 mg, 0.26 mmol) to afford 47.9 mg (95%) of **3c** (eluent: petroleum ether/ethyl acetate = 3/1): yellow oil; IR (neat) 3424 (br), 2228, 1748, 1608 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.13 (1H, d, *J* 1.2 Hz, =C<u>H</u>), 4.92 (1H, ddd, *J* 7.78, 3.48, 1.20 Hz, C<u>H</u>OCO), 4.51 (2H, d, *J* 4. 6 Hz, $C\underline{H}_2OH$), 2.73 (1H, t, *J* 4.6 Hz, O<u>H</u>), 2.01-1.93 (1H, m, $C\underline{H}_aH_bCHO$), 1.62-1.52 (1H, m, CH_aH_bCHO), 1.44-1.29 (4H, m, $(C\underline{H}_2)_2Me$), 0.89 (3H, t, *J* 7.0 Hz, Me); m/z (EI, He) 195 (100, MH^+), 137 (28), 53 (41), 52 (32%); HRMS (EI): M^+, found: 194.0934. $C_{11}H_{14}O_3$ requires 194.0943.

4-(Trimethylsilylethynyl)-5-(*n*-butyl)-2(5H)-furanone (3d): starting from **2a** (26.6 mg, 0.10 mmol) and trimethylsilylacetylene (12 mg, 0.12 mmol) to afford 16.4 mg (65%) of **3d**: yellow oil; [Found: C, 65.72; H, 8.47. $C_{13}H_{20}SiO_2$ requires C, 66.05; H, 8.53%]; IR (neat) 1760, 1604 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.11 (1H, d, *J* 1.9 Hz, =C<u>H</u>), 4.90 (1H, ddd, *J* 7.5, 3.9, 1.9 Hz, C<u>H</u>OCO), 1.99-1.9 (1H, m, $C\underline{H}_aH_bCHO$), 1.65-1.55 (1H, m, CH_aH_bCHO), 1.47-1.31(4H, m, $(C\underline{H}_2)_2Me$), 0.90 (3H, t, *J* 7.1 Hz, $CH_2\underline{Me}$), 0.26 (9H, s, $Si\underline{Me}_3$); m/z (EI, He) 336 (4, M^+), 221(100), 180 (49), 151 (38%).

4-(Phenylacetylenyl)-5-(*n*-heptyl)-2(5H)-furanone (3e): starting from **2b** (111.3 mg, 0.36 mmol) and phenylacetylene (40.8 mg, 0.40 mmol) to afford 94.1 mg (95%) of **3e** (eluent: petroleum ether/ethyl acetate = 20/1): white solid; mp: 43.5-44.5 °C (*n*-hexane); [Found: C, 80.83; H, 7.86. $C_{19}H_{22}O_2$ requires C, 80.86; H, 7.86%]; IR (KBr) 2206, 1758, 1612, 1592 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 7.53-7.25 (5H, m, Ph), 6.19 (1H, d, *J* 1.7 Hz, =C<u>H</u>), 5.02 (1H, ddd, *J* 7.6, 3. 8, 1.7 Hz, C<u>H</u>OCO), 2.05-2.01 (1H,m, $C\underline{H}_aH_bCHO$), 1.72-1.61 282(1H, m, CH_aH_bCHO), 1.51-1.45 (2H, m, $CH_aH_bC\underline{H}_2$), 1.37-1.26 (8H, m, $(C\underline{H}_2)_4Me$), 0.86 (3H, t, *J* 7.2 Hz, <u>Me</u>); m/z (EI, He) 282 (21, M^+), 155 (41), 127 (100), 126 (97%).

4-(1′-Hexynyl)-5-(*n*-heptyl)-2(5H)-furanone (3f): starting from **2b** (77 mg, 0.25 mmol) and 1-hexyne (21.3 mg, 0.26 mmol) to afford 56.3 mg (86%) of **3f** (eluent: petroleum ether/ethyl acetate = 20/1): yellow oil; [Found: C, 78.01; H, 9.76. $C_{17}H_{26}O_2$ requires C, 77.87; H, 9.99%]; IR (neat) 2224, 1760, 1652 cm^{-1}; ^1H NMR

(300M MHz , $CDCl_3$) δ 6.04 (1H, d, *J* 1.3 Hz, =C<u>H</u>), 4.91-4.86 (1H, ddd, *J* 7.5, 3.6, 1.3 Hz, C<u>H</u>OCO), 2.47 (2H, t, *J* 6.9 Hz, C-C<u>H</u>$_2$), 2.01-1.90 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.66-1.27 (15H, m, CH$_a$<u>H</u>$_b$CHO, (C<u>H</u>$_2$)$_2$Me and (C<u>H</u>$_2$)$_5$Me), 0.97-0.86 (6H, m, 2<u>Me</u>); m/z (EI, He) 262 (5, M^+), 91 (90), 57 (100), 43 (70%).

4-(3'-Hydroxy-1-propynyl)-5-(*n*-heptyl)-2(5H)-furanone (3g): starting from **2b** (77 mg, 0.25 mmol) and propargyl alcohol (14.6 mg, 0.26 mmol) to afford 46.6 mg (79%) of **3g** (eluent: petroleum ether/ethyl acetate = 3/1): white solid; mp: 75—76 °C (ethyl acetate); IR (KBr) 3426, 2156, 1760, 1604 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.14 (1H, d, *J* 1.6 Hz, =C<u>H</u>), 4.92 (1H, ddd, *J* 8.3, 5.0, 1.6 Hz, C<u>H</u>OCO), 4.52 (2H, d, *J* 3.0 Hz, C<u>H</u>$_2$OH), 2.1 (1H, bs, O<u>H</u>), 2.0-1.92 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.65-1.52 (1H, m, CH$_a$<u>H</u>$_b$CHO), 1.45-1.26 (10H, m, (C<u>H</u>$_2$)$_5$Me), 0.87 (3H, t, *J* 6.4 Hz, <u>Me</u>); m/z (EI, He) 237 (10, MH^+), 138 (80), 57(100), 43 (76%); HRMS (EI): M^+, found: 236.1413. $C_{14}H_{20}O_3$ requires 236.1412.

4-(Trimethylsilylethynyl)-5-(*n*-heptyl)-2(5H)-furanone (3h): starting from **2b** (77 mg, 0.25 mmol) and trimethylsilylacetylene (25.5 mg, 0.26 mmol) to afford 48.7 mg (70%) of **3h** (eluent: petroleum ether/ethyl acetate = 30/1): yellow oil; IR (neat) 2340, 1760, 1604 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.07 (1H, d, *J* 1.9 Hz, =C<u>H</u>), 4.85 (1H, ddd, *J* 7.6, 3.9, 1.9 Hz, C<u>H</u>OCO), 1.93-1.84 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.62-1.49 (1H, m, CH$_a$<u>H</u>$_b$CHO), 1.41-1.30 (2H, m, CH$_a$H$_b$C<u>H</u>$_2$), 1.24-1.21 (8H, m, (C<u>H</u>$_2$)$_4$Me), 0.82 (3H, t, *J* 7.0 Hz, CH$_2$<u>Me</u>), 0.19 (9H, s, <u>Me</u>$_3$Si); m/z (EI, He) 278 (M^+), 193 (49), 73 (100), 57 (89%); HRMS (EI): M^+, found: 278.1701. $C_{16}H_{26}O_2Si$ requires 278.1702.

Coupling Reaction of 3-Halobutenolides with Arylzinc Halides. Typical Procedure . Preparation of 4-Phenyl-5-(*n*-butyl)-2(5H)-furanone (4a). To a solution of phenyl iodide (149 mg, 0.73 mmol) in THF (1 mL) was added a solution of *n*-BuLi (0.46 mL, 1.6 M in hexanes, 0.73 mmol) at -78 °C. After 1 h at -40 °C, a solution of $ZnBr_2$ (250 mg, 1.1 mmol) in 1.5 mL of THF was added by syringe. After the addition, the reaction mixture was stirred for another 10 min, warmed up to 25 °C naturally, and kept at 25 °C for 30 min. $Pd(PPh_3)_4$ (15 mg, 0.0125 mmol) and 4-iodo-5-(*n*-butyl)-2(5H)-furanone (**2a**) (66.5 mg, 0.25 mmol) were added subsequently under Ar. The reaction finished after 4 h as monitored by TLC. The reaction mixture was quenched with dilute aqueous HCl (0.5 M), extracted with ethyl ether (3 x 15 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 60 mg (93%) of **4a**. The spectra data were the same as reported in ref. 2.

The following compounds were prepared similarly.

4-(4'-Methylphenyl)-5-(*n*-heptyl)-2(5H)-furanone (4b): starting from **2b** (46.2 mg, 0.15 mmol) and 4-iodotoluene (93.7 mg, 0.43mmol) to afford 33.9 mg (83%) of **4b** (eluent: petroleum ether/ethyl acetate = 20/1): yellow oil; IR (neat) 1760, 1648 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 7.48 (2H, d, *J* 7.7 Hz, =C<u>H</u> of C_6H_4Me), 7.30 (2H, d, *J* 7.7 Hz, =C<u>H</u> of C_6H_4Me), 6.21 (1H, d, *J* 1.1 Hz, =C<u>H</u>), 5.50 (1H, ddd, *J* 8.1, 3.3, 1.4 Hz, C<u>H</u>OCO), 2.42 (3H, s, C_6H_4<u>Me</u>), 1.88-2.00 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.50-1.60 (1H, m, CH$_a$<u>H</u>$_b$CHO), 1.10-1.50 (10H, m, (C<u>H</u>$_2$)$_5$Me), 0.86 (3H, t, *J* 7.0 Hz, <u>Me</u>); m/z (EI, He) 272 (9, M^+), 174 (100), 145 (99), 117 (92%);

HRMS (EI): M^+, found: 272.1764. $C_{18}H_{24}O_2$ requires 272.1776.

4-(1′-Naphthyl)-5-(*n*-butyl)-2(5H)-furanone (4c): starting from **(2a)** (40 mg, 0.15 mmol) and 1-iodonaphthylene (112 mg, 0.44 mmol) to afford 28 mg (70%) of **4c** (eluent: petroleum ether/ethyl acetate = 20/1). The spectral data were the same as reported in ref. 2.

Coupling Reactions of 2b with 1(*E*)-Hexenylzinc Bromide. Preparation of 4-(1′(*E*)-hexenyl)-5-(*n*-heptyl)-2(5H)-furanone (4d). To a solution of (*E*)-1-iodo-1-hexene (90 mg, 0.438 mmol) in THF (2 mL) was added a solution of *n*-BuLi (0.27 mL, 1.6 M in hexanes, 0.438 mmol) at -78 °C. After 1 h at -40 °C, a solution of $ZnBr_2$ (148 mg, 0.658 mmol) in 2 mL of THF was added with syringe. After the addition, the reaction mixture was stirred for 10 min, warmed up to 25 °C naturally, and kept at 25 °C for 30 min. 1 mL of dry DMF was added and the reaction mixture became homogeneous. $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) and 4-iodo-5-(*n*-heptyl)-2(5H)-furanone (**2b**) (46 mg, 0.15 mmol) were added quickly under Ar and the reaction mixture was stirred for 0.5 h (monitored by TLC). Then the reaction mixture was quenched with dilute aqueous HCl (0.5 M), extracted with ethyl ether (3 x 15 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 60 mg (77%) of **4d**: yellow oil; IR (neat) 1747, 1646, 1466, 1162, 977 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.13 (1H, d, *J* 16.0 Hz, =C-C<u>H</u>=CH), 6.10 (1H, dt, *J* 16.0 5.6 Hz, $CH_2C\underline{H}$=), 5.73 (1H, s, =C<u>H</u>), 5.00-5.05 (1H, m, C<u>H</u>OCO), 2.15 (2H, q, *J* 7.3 Hz, $C\underline{H}_2CH$), 1.82-1.97 (1H, m, $C\underline{H}_aH_bCHO$), 1.10-1.51 (15H, m, $CH_a\underline{H}_bCHO$, $(C\underline{H}_2)_5Me$, and$(C\underline{H}_2)_2Me$), 0.81 (3H, t, *J* 7.1 Hz, <u>Me</u>), 0.78 (3H, t, *J* 7.0 Hz, <u>Me</u>); m/z (EI, He) 265 (100, MH^+), 179(69), 166 (70), 109 (68%); HRMS (EI): M^+, found: 264.2093. $C_{17}H_{28}O_2$ requires 264.2089.

The Coupling Reactions of β-Halobutenolides with Vinylzinc bromide. Preparation of 4-Vinyl-5-(*n*-butyl)-2(5H)-furanone (4e). A solution of $ZnBr_2$ (150 mg, 0.66 mmol) in 2 mL of THF was added into a solution of vinylmagnesium bromide (0.5 mL, 1 M in THF, 0.5 mmol) with syringe at rt under Ar. 1 mL of dry DMF was added after 30 min at rt and the reaction mixture became homogeneous. After the addition, the reaction mixture was stirred for 2 h at 25 °C. $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) and 4-iodo-5-(*n*-butyl)-2(5H)-furanone (**2a**) (40 mg, 0.15 mmol) were added subsequently under Ar. The reaction was complete after 10 h as monitored by TLC and quenched with dilute aqueous HCl (0.5 M). After extraction with ethyl ether (3 x 15 mL), drying over $MgSO_4$, and evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 22.9 mg (92%) of **4e**: yellow oil; IR (neat) 1740, 1627, 1466, 1182, 1047 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 6.48 (1H, dd, *J* 17.9, 11.1 Hz, $CH_c\underline{H}_d$=C<u>H</u>), 5.89 (1H, s, =C<u>H</u>), 5.58 (1H, d, *J* 17.9 Hz, $C\underline{H}_cH_d$=CH), 5.49 (1H, d, *J* 11.0 Hz, $CH_c\underline{H}_d$=CH), 5.05-5.12 (1H, m, C<u>H</u>OCO), 1.89-1.98 (1H, m, $C\underline{H}_aH_bCHO$), 1.48-1.52 (1H, m, $CH_a\underline{H}_bCHO$), 1.15-1.35 (4H, m, $(C\underline{H}_2)_2Me$), 0.81 (3H, t, *J* 7.0 Hz, <u>Me</u>); m/z (EI, He) 167 (100, MH^+), 110 (50), 109 (56), 53 (34%); HRMS (EI): M^+, found: 166.0984. $C_{10}H_{14}O_2$ requires 166.0994.

4-Vinyl-5-(*n*-heptyl)-2(5H)-furanone (4f) was prepared similarly: starting from **2b** (46 mg, 0.15 mmol) and vinylmagnesium bromide (0.5 mL, 1 M in THF, 0.5 mmol) to afford 25.6 mg (82%) of **4f** (eluent: petroleum ether/ethyl acetate = 20/1): yelllow oil; IR (neat) 1747, 1670, 1458, 1160, 1037 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) 6.78 (1H, dd, *J* 18.0, 11.0 Hz, CH_cH_d=C<u>H</u>), 5.98 (1H, s, =C<u>H</u>), 5.68 (1H, d, *J* 18.0 Hz, C<u>H</u>$_c$H$_d$=CH), 5.62 (1H, d, *J* 11.0 Hz, CH_c<u>H</u>$_d$=CH), 5.12-5.16 (1H, m, C<u>H</u>OCO), 1.90-2.05 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.76-1.86 (1H, m, CH_aH_bCHO), 1.12-1.40 (10H, m, (C<u>H</u>$_2$)$_5$Me), 0.92 (3H, t, *J* 6.9 Hz, <u>Me</u>); m/z (EI, He) 209 (100, MH^+), 208 (19, M^+), 110 (49), 109 (45), 57 (33%); HRMS (EI): M^+, found: 208.1469. $C_{13}H_{20}O_2$ requires 208.1463.

Coupling Reaction of β-Iodobutenolides with Alkylzinc Halides. Preparation of 4-(*n*-Butyl)-5-(*n*-heptyl)-2(5H)-furanone (5a). A solution of $ZnBr_2$ (150 mg, 0.66 mmol) in 2 mL of THF was added into a solution of *n*-BuLi (0.3 mL, 1.6 M in hexanes, 0.48 mmol) by syringe at -78 °C under Ar. After the addition, the reaction mixture was stirred and warmed up to 25 °C naturally. A solution of $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) and 4-iodo-5-(*n*-heptyl)-2(5H)-furanone (**2b**) (46 mg, 0.15 mmol) in 2 mL of THF was stirred and cooled to -78 °C, then the above prepared solution of *n*-butylzinc bromide was transferred quickly into this mixture *via* a cannula under Ar. The reaction mixture was warmed up to rt slowly and quenched after 10 h with dilute aqueous HCl (0.5 M) (monitored by TLC). Then the mixture was extracted with ethyl ether (3 x 15 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 31 mg (82%) of **5a**: yellow oil; IR (neat) 1748, 1634, 1466, 1173 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 5.70 (1H, d, *J* 1.2 Hz, =C<u>H</u>), 4.75-4.83 (1H, m, C<u>H</u>OCO), 2.10-2.30 (2H, m, =CC<u>H</u>$_2$), 1.70-1.82 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.10-1.55 (15H, m, CH_aH_bCHO, (C<u>H</u>$_2$)$_5$Me and (C<u>H</u>$_2$)$_2$Me), 0.88 (3H, t, *J* = 7.4 Hz, <u>Me</u>), 0.80 (3H, t, *J* 6.4 Hz, <u>Me</u>); m/z (EI, He) 239 (100, MH^+), 111 (34), 55 (12%); HRMS (EI): M^+, found: 238.1931. $C_{15}H_{26}O_2$ requires 238.1933.

Preparation of 4-Methyl-5-(*n*-butyl)-2(5H)-furanone (5b). $ZnBr_2$ (148 mg, 0.658 mmol) in 2 mL of THF was added into 1 mL of methylmagnesium iodide solution prepared from magnesium (240 mg, 10 mmol), methyl iodide (142 mg, 10 mmol), and THF (144 mg, 20 mmol) in 10 mL of xylenes according to the reported procedure[12] with syringe at rt under Ar. After the addition, the reaction mixture was stirred for 1 h and transferred *via* a cannula to a solution of $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) and 4-iodo-5-(*n*-butyl)-2(5H)-furanone (**2a**) (40 mg, 0.15 mmol) in 2 mL of THF at -78 °C under Ar. After 1 h at rt, no reaction was observed, and the reaction was heterogeneous. After the addition of dry HMPA (0.5 mL), the reaction became homogeneous and was complete within 10 h at rt as monitored by TLC. The reaction mixture was quenched with dilute aqueous HCl (0.5 M), extracted with ethyl ether (3 x15 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to afford 21 mg (92%) of **5b**: yellow oil. IR (neat) 1756, 1640, 1439, 1182 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$) δ 5.82 (1H, d, *J* 1.3 Hz, =C<u>H</u>), 4.80-4.90 (1H, m, C<u>H</u>OCO), 2.06 (3H, s, =C<u>Me</u>), 1.82-1.93 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.15-1.50 (5H, m, CH_aH_bCHO, and (C<u>H</u>$_2$)$_2$Me), 0.90 (3H, t, *J* 7.0 Hz, (CH$_2$)$_2$<u>Me</u>); m/z (EI He) 155 (100, MH^+), 97 (35),

69 (36), 41 (35%). The spectral data of this compound was the same as reported in ref. 10d.

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