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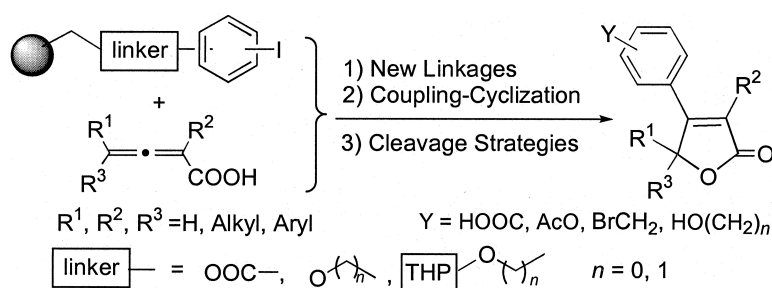
Palladium(0)-Catalyzed Coupling–Cyclization Reaction of Polymer-Supported Aryl Iodides with 1,2-Allenyl Carboxylic Acids. Solid-Phase Parallel Synthesis of Butenolides

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Palladium(0)-Catalyzed Coupling−Cyclization Reaction of Polymer-Supported Aryl Iodides with 1,2-Allenyl Carboxylic Acids. Solid-Phase Parallel Synthesis of Butenolides

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In this contribution, we constructed a library of butenolides with 77 members by parallel synthesis strategy on Merrifield resin. Sixteen 2,3-allenoic acids and 12 polymer-bound aryl iodides were combined to react with each other, and then the polymer-supported products were cleaved to release butenolide derivatives. The reactions with alkyl-substituted 2,3-allenoic acids in acetonitrile afforded the corresponding products in high yields and high purities, whereas those with aryl-substituted acids in acetonitrile failed. After some reaction conditions were screened, the solid-phase reactions with aryl-substituted 2,3-allenoic acids were realized in toluene, and the products are of good purities albeit in slightly low yields. In the benzyl ether linkage, a new cleavage model was found. By adding 6 equiv of acetyl bromide, we can get single (5-oxo-2,5-dihydrofuran-3-yl)benzyl bromide other than the corresponding benzyl acetate. To further increase the diversities, a dihydropyran (DHP) linker was introduced into our combinatorial synthesis of butenolides. By reversing the addition sequence of 2,3-allenoic acids and organic base, we realized the solid-phase cyclization reaction of polymer-bound aryl iodides with the THP linkage in moderate yields and good purities. Now the library of butenolides includes (5-oxo-2,5-dihydrofuran-3-yl)benzoic acids, -aryl acetates, -benzyl bromides, -benzyl alcohols, and -phenols, which are difficult to synthesize with conventional solution methods.
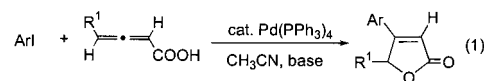
Introduction

Butenolides have attracted significant interest because they often occur in natural products[1] and exhibit a broad range of biological activities.[2] These compounds were considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antipsoriasis agents, cyclooxygenase inhibits, and phospholipase A2 inhibitors.[2] So the syntheses of butenolide-containing natural and unnatural products have become the highlight of the field. Recent typical synthetic strategies include linear coupling of chromium hexacarbonyl via Fisher-type carbene complexes,[3] Lewis acid catalyzed cyclization of bis(trimethylsilyloxy)-1,3-dienes with oxalyl chloride,[4] ruthenium-catalyzed insertion of CO into allenic alcohol,[5] enyne metathesis,[6] and our own work of the transition-metal-catalyzed or -mediated cyclic transformations of 2,3-allenoic acids or their derivatives.[7] Undoubtedly, the above-mentioned methods in the solution are very successful in preparing some structure-defined butenolides but unsatisfactory in acquiring diversity.

Combinatorial synthesis as a high-throughput method enables the rapid production of hundreds times more compounds than the conventional serial organic synthesis.[8] Combinatorial libraries can be prepared by parallel synthesis, which offers the advantage that each compound is substantially "pure" in its local area, provided that the synthesis has proceeded with high efficiency at each stage.[9] Because of the easy parallel workup procedures (filtration), accelerated

reactions with higher yields by employing excess reagents and amenability to automation, the solid-phase organic synthesis (SPOS) technique has been proven to be one of the most powerful tools for the preparation of compound libraries.[10] To screen systematic biological activities of butenolide derivatives and even to find lead structures, we paid our attention to the construction of libraries of butenolides by parallel combinatorial synthesis on a solid-phase support.

In 1998 our group reported an efficient synthesis of butenolides via Pd(0)/Ag⁺ cocatalyzed coupling−cyclization reaction of 2,3-allenoic acids with aryl iodides (eq 1).[7h] To

$$\text{ArI} + \begin{array}{c} R^1 \\ H \end{array}\!\!>\!\!=\!\!=\!\!<\begin{array}{c} H \\ COOH \end{array} \xrightarrow[\text{CH}_3\text{CN, base}]{\text{cat. Pd(PPh}_3)_4} \quad (1)$$

construct the library of butenolides, the first challenge we confronted is how to realize the reaction in the solid phase. Obviously aryl iodides can be easily tethered to a solid-phase resin and also easily cleaved by well-established methods.[11] With this assumption in mind, we have indeed realized the SPOS of butenolides in fairly satisfactory results (Scheme 1).[12]

Now the second challenge is how to diversify. Three solutions should be effective: (1) synthesizing more differently substituted 2,3-allenoic acids for diversity of substrates, which is the exact advantage of 2,3-allenoic acids;[13] (2) developing new linkages and cleavage strategies for diversity

Table 1. Pd(PPh$_3$)$_4$-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with a Carboxyl Linkage with 4-Alkyl-Substituted 1,2-Allenic Carboxylic Acids[a]

entry	resin **1**	acid **2** R^1, R^2, R^3	resin **3**	product[b] **4**	yield[c] (%)	purity[d] (%)
1	**1a**	*n*-hep, H, H (**2a**)	**3aa**	**4aa**[e]	100 (100)[e]	90
2	**1b**	**2a**	**3ba**	**4ba**	75 (69)[e]	82
3	**1c**	**2a**	**3ca**	**4ca**[e]	99	93
4	**1a**	*n*-Bu, H, H (**2b**)	**3ab**	**4ab**	100	85
5	**1b**	**2b**	**3bb**	**4bb**	83	91
6	**1c**	**2b**	**3cb**	**4cb**[f]	93	95
7	**1a**	*c*-hex, H, H (**2c**)	**3ac**	**4ac**[f]	100	96
8	**1b**	**2c**	**3bc**	**4bc**	100	86
9	**1c**	**2c**	**3cc**	**4cc**[f]	100	94
10	**1a**	*t*-Bu, H, H (**2d**)	**3ad**	**4ad**	87	95
11	**1b**	**2d**	**3bd**	**4bd**	85	86
12	**1c**	**2d**	**3cd**	**4cd**	92	96
13	**1b**	*n*-hex, Me, H (**2e**)	**3be**	**4be**	74	94
14	**1c**	**2e**	**3ce**	**4ce**[e]	84	85
15	**1a**	*n*-Pr, Me, H (**2f**)	**3af**	**4af**	84	73
16	**1b**	**2f**	**3bf**	**4bf**	100	91
17	**1b**	*n*-Pr, allyl, H (**2g**)	**3bg**	**4bg**	76	80
18	**1b**	Me, benzyl, H (**2h**)	**3bh**	**4bh**	71	81
19	**1b**	H, benzyl, H (**2i**)	**3bi**	**4bi**	70	73
20	**1c**	Me, Me, Me (**2j**)	**3cj**	**4cj**	41	75

[a] Conditions A: See text. Key to the labeling of compounds **3** and **4**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used. [b] All new compounds were characterized by ^{1}H NMR, MS (EI), HRMS (EI), and FT-IR spectra of the crude products. [c] Overall yield based on the maximum theoretical loading of aryl iodides on resin (1.636 mequiv/g resin). [d] Determined by HPLC (DIKMA C18 column 4.6 mm × 150 mm, gradient elution with CH$_3$CN/TFA and H$_2$O/TFA, ultraviolet absorption detector at 254 nm). [e] Isolated yield. [f] Our previous results, only for the comparison with other results here.

Scheme 1
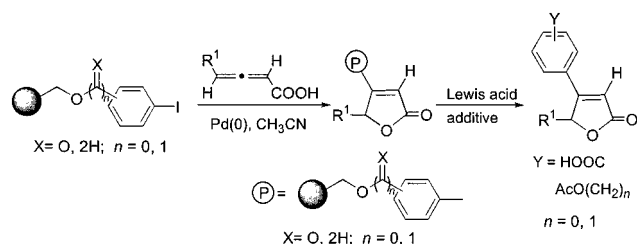
of solid-phase reagents; (3) developing more different combinations between substrates and reagents.

Results and Discussions

Library of Butenolides from the Palladium-Catalyzed Coupling−Cyclization Reaction of Polymer-Bound Aryl Iodides with Carboxylic Ester Linkage and Alkyl-Substituted 2,3-Allenoic Acids. With our successful model of carboxyl linkage in hand,[12] we tested more 2,3-allenoic acids and their combinations with differently substituted aryl iodides on solid-phase resin under conditions A (4 equiv of 2,3-allenoic acids, 15 mol % Pd(PPh$_3$)$_4$, *i*-Pr$_2$NEt as the base, in CH$_3$CN at 70 °C for 3 days under an argon atmosphere) (Scheme 2 and Table 1).

The treatments of 4-monoalkyl-substituted 2,3-allenoic acids afforded the corresponding products in high yields and high purities (entries 1−12, Table 1), while those reactions with 2-monoalkyl-substituted 2,3-allenoic acids only gave the products in moderate yields and good purities (entry 19, Table 1). 2,4-Bisalkyl-substituted 2,3-allenoic acids underwent the same reaction sequence to give the products in good to high yields and purities (entries 13−18, Table 1). The reaction with trisubstituted acid **2j** gave the corresponding product in low yield and good purity (entry 20, Table 1). So

Scheme 2[a]
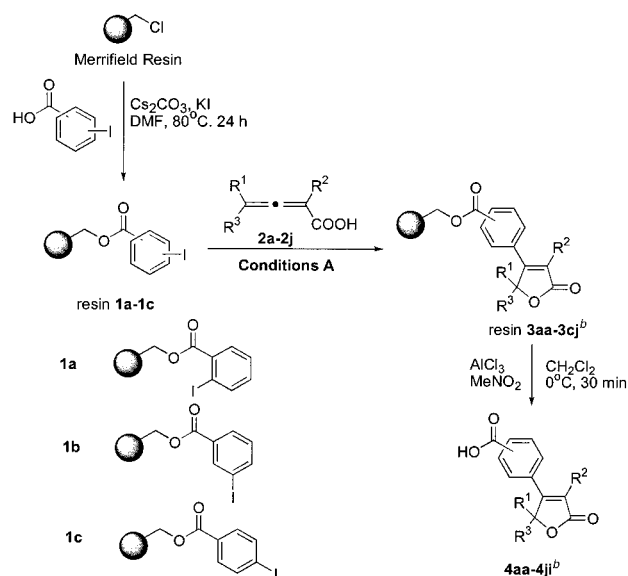
[a] Conditions A: 4 equiv of 2,3-allenoic acids, 15 mol % Pd(PPh$_3$)$_4$, and *i*-Pr$_2$NEt as the base in CH$_3$CN at 70 °C for 3 days under an argon atmosphere. [b] Key to the labeling of compounds **3** and **4**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used.

both the steric and electronic effects of 2,3-allenoic acids play important roles in the reactions. As observed previously, the steric effect of aryl iodides is not very obvious because the reactions of ortho-substituted resin **1a** and para-substituted resin **1c** gave similar results (compare entry 1 with entry 3, entry 4 with entry 6, entry 7 with entry 9, entry 10 with entry 12, Table 1). However, meta-substituted resin **1b** exhibits different reaction activity with resin **1a** and **1c**, since the reaction with resin **1b** gave the products in decreasing yields and purities (compare entry 2 with entries

Table 2. $Pd(PPh_3)_4$-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with a Carboxyl Linkage with 4-Aryl-Substituted 1,2-Allenic Carboxylic Acids[a]

		acid 2				
entry	resin 1	Ar, R^2, R^3	resin 5	product[b] 6	yield[c] (%)	purity[d] (%)
1	1c	Ph, Me, H (2k)	5ck	6ck	33	93
2	1c	Ph, *n*-Pr, H (2l)	5cl	6cl	42	74
3	1c	Ph, benzyl, H (2m)	5cm	6cm	42	81
4	1c	α-nap, Me, H (2n)	5cn	6cn	42 (42)[e]	95
5[f]	1a	α-nap, *n*-Pr, H (2o)	5ao	6ao	96	89
6[f]	1b	2o	5bo	6bo	77	82
7	1c	2o	5co	6co	52	90
8	1c	Ph, Me, Et (2p)	5cp	6cp	70	93

[a] Conditions B: See text. Key to the labeling of compounds **5** and **6**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used. [b] All new compounds were characterized by ^{1}H NMR, MS (EI), HRMS (EI), and FT-IR spectra of the crude products. [c] Overall yield based on the maximum theoretical loading of aryl iodides on resin (1.636 mequiv/g resin). [d] Determined by HPLC (Kromasil C18 column 4.6 mm × 150 mm, gradient elution with $CH_3CN/H_2O/TFA$ (0.1%), ultraviolet absorption detector at 254 nm). [e] Isolated yield. [f] Conditions C (at 70 °C) was applied. The other parameters are the same as those of Conditions B.

Scheme 3
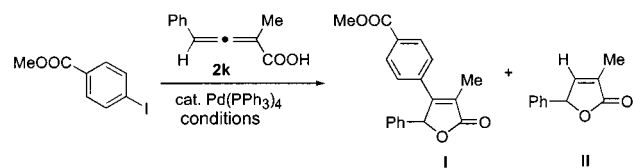
conditions		yield (%)
	I	II
K_2CO_3/cat. Ag_2CO_3 as the base in *CH_3CN*	no	99
i-Pr_2NEt as the base in *CH_3CN*	no	99
K_2CO_3 as the base and TBAB as the PTC in *PhMe*	65	trace
i-Pr_2NEt as the base in *PhMe*	35	trace

1 and 3, entry 11 with entries 10 and 12, Table 1), which shows that the electronic effect of aryl iodides cannot be ignored.

Library of Butenolides from the Palladium-Catalyzed Coupling−Cyclization Reaction of Polymer-Bound Aryl Iodides with Carboxylic Ester Linkage and 4-Aryl-Substituted 2,3-Allenoic Acids. When we switched from 4-alkyl-substituted 2,3-allenoic acid to 4-aryl-substituted 2,3-allenoic acids, the formation of coupling−cyclization product **I** (Scheme 3) was not observed, and instead, we obtained quantitatively the cycloisomerization product **II** (Scheme 3), which requires us to seek a set of appropriate conditions for the coupling−cyclization of 4-aryl-substituted 2,3-allenoic acid. We first studied the model reaction of acid **2k** with *p*-methoxycarbonylphenyl iodide in solution (Scheme 3).

Regardless of using K_2CO_3/cat. Ag_2CO_3 or *i*-Pr_2NEt as the base, in CH_3CN, we only obtained cycloisomerization product **II** in quantitative yield. After screening over some conditions, we found the tendency of cycloisomerization can be inhibited by using PhMe as the solvent. When K_2CO_3 was used as the base in the presence of tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst (PTC), the coupling−cyclization product **I** was obtained in 65% yield while the reaction with *i*-Pr_2NEt as the base gave **I** in 35% yield. When the two conditions were each applied to SPOS, as predicted, the reaction with organic base *i*-Pr_2NEt gave better results (33% yield and 91% purity) than the same reaction with inorganic base K_2CO_3 (50% yield and 28% purity). We selected conditions B (4 equiv of acids, 15 mol % $Pd(PPh_3)_4$, and 8 equiv of *i*-Pr_2NEt in toluene at 90 °C
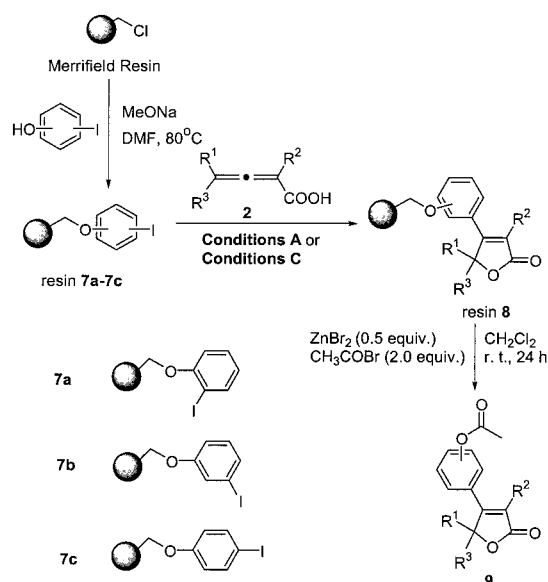
Scheme 4[a]
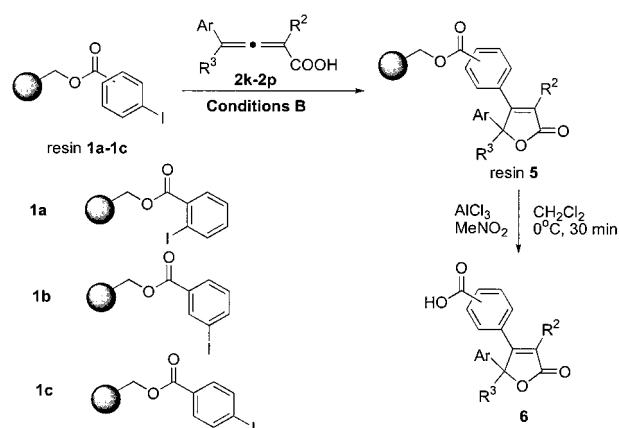
[a] Conditions B: 4 equiv of acids, 15 mol % $Pd(PPh_3)_4$, 8 equiv of *i*-Pr_2NEt in toluene at 90 °C for 3 days under an argon atmosphere.

for 3 days under an argon atmosphere) to study the solid-phase coupling−cyclization of aryl-substituted 2,3-allenoic acid (Scheme 4).

Although the purities of the products are high, the reactions usually afforded the products in lower yields than the reactions with alkyl-substituted acids except for entry 5 of Table 2 (compare Table 2 with Table 1), which was also verified by their FT-IR spectra. Although both resins **5** and **3** each have the characteristic double carbonyl absorptions at 1760 and 1720 cm^{-1}, the two peaks for the carbonyl group of resin **3** are stronger than those of the former.

Library of Butenolides from the Palladium-Catalyzed Coupling−Cyclization Reaction of Polymer-Bound Aryl Iodides with Phenolic Ether Linkage and 2,3-Allenoic Acids. The coupling−cyclization reaction of polymer-bound aryl iodides **7** with a phenolic ether linkage is another successful SPOS model that we have established.[12] With the optimized conditions in hand, we extended it to more 2,3-allenoic acids (Scheme 5 and Table 3).

Alkyl-substituted 2,3-allenoic acids **2a−2e** and aryl-substituted acids **2k−2p** were treated respectively under conditions A and under the more moderate conditions C (4 equiv of acids, 15 mol % $Pd(PPh_3)_4$, 8 equiv of *i*-Pr_2NEt in toluene at 70 °C for 3 days under an argon atmosphere). Three points should be noted: (1) The reactions with meta-substituted aryl iodides **7b** afforded the products in higher

Scheme 5[a]

[a] Conditions A: 4 equiv of 2,3-allenoic acids, 15 mol % Pd(PPh₃)₄, 8 equiv of *i*-Pr₂NEt in CH₃CN at 70 °C for 3 days under an argon atmosphere. Conditions C: 4 equiv of acids, 15 mol % Pd(PPh₃)₄, 8 equiv of *i*-Pr₂NEt in toluene at 70 °C for 3 days under an argon atmosphere.

Table 3. Pd(PPh₃)₄-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with a Phenol Ether Linkage with 1,2-Allenic Carboxylic Acids[a]

entry	resin 7	acid[b] 2	resin 8	product[c] 9	yield[d] (%)	purity[e] (%)
1	**7a**	**2a**	**8aa**	**9aa**	55	92
2	**7b**	**2a**	**8ba**	**9ba**	100	98
3	**7c**	**2a**	**8ca**	**9ca**[f]	89	94
4	**7a**	**2b**	**8ab**	**9ab**	57	91
5	**7b**	**2b**	**8bb**	**9bb**	100	91
6	**7c**	**2b**	**8cb**	**9cb**[f]	87	83
7	**7a**	**2c**	**8ac**	**9ac**	72	95
8	**7b**	**2c**	**8bc**	**9bc**	100	93
9	**7c**	**2c**	**8cc**	**9cc**[f]	84	87
10	**7a**	**2d**	**8ad**	**9ad**	82	90
11	**7b**	**2d**	**8bd**	**9bd**	100	98
12	**7c**	**2d**	**8cd**	**9cd**	75	82
13	**7b**	**2e**	**8be**	**9be**	89	94
14	**7c**	**2e**	**8ce**	**9ce**[f]	82	76
15	**7c**	**2k**	**8ck**	**9ck**	80	59
16	**7c**	**2l**	**8cl**	**9cl**	74	73
17	**7c**	**2m**	**8cc**	**9cc**	63	82
18	**7c**	**2n**	**8cn**	**9cn**	75	92
19	**7a**	**2o**	**8ao**	**9ao**	63	90
20	**7b**	**2o**	**8bo**	**9bo**	65	92
21	**7c**	**2o**	**8co**	**9co**	84	89
22	**7b**	**2p**	**8bp**	**9bp**	93	82
23	**7c**	**2p**	**8cp**	**9cp**	71	82

[a] Entries 1−14 with conditions A, entries 15−23 with conditions **C** (see text). Key to the labeling of compounds **8** and **9**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used. [b] See Tables 1 and 2. [c] All new compounds were characterized by ¹H NMR, MS (EI), HRMS (EI), and FT-IR spectra of the crude products. [d] Overall yield based on the maximum theoretical loading of aryl iodides on resin (1.714 mequiv/g resin). [e] Determined by HPLC (Diamonsil C18 column 4.6 mm × 150 mm, gradient elution with CH₃CN/H₂O, ultraviolet absorption detector at 254 nm). [f] Our previous results, only for the comparison with other results here.

yields and purities than those with ortho- or para-substituted aryl iodides **7a** or **7c**, especially for the series of the alkyl-

Scheme 6[a]
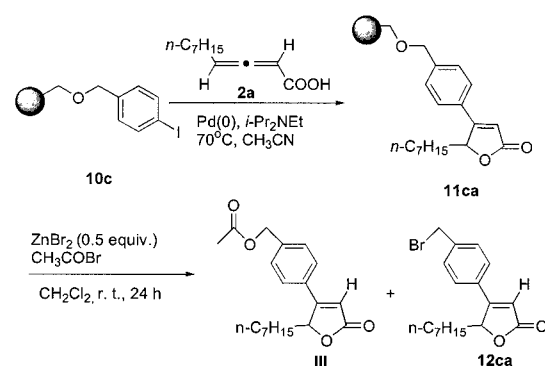
| entry	CH₃COBr (equiv.)	yield (%) (purity (%))	
a	2.0	75 (82) (68%(isolated))	trace
b	4.0	a mixture of **III** and **12ca**	
c	6.0	trace	70 (86)

[a] Key to the labeling of compounds **11** and **12**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used.

substituted acids (compare entry 2 with entries 1 and 3, entry 5 with entries 4 and 6, entry 10 with entries 9 and 11, Table 3). Therein the electronic effect plays an important role again. Because of the strong electron-donating ability of the alkoxyl substituents, meta-substituted aryl iodide resin **7b** is more active in the oxidative addition reaction with the palladium-(0) catalyst than resins **7a** and **7b**. (2) Compared with aryl-substituted acids **2k**−**2o**, usually the higher yields and purities are observed with alkyl-substituted acids **2a**−**2e** (compare entries 1−14 with entries 15−21, Table 3). (3) The reactions with trisubstituted acid **2p** also gave good results (entries 22 and 23, Table 3).

Library of Butenolides from the Palladium-Catalyzed Coupling−Cyclization Reaction of Polymer-Bound Aryl Iodides with Benzylic Ether Linkage and 2,3-Allenoic Acids. Previously, we only reported the reaction of polymer-bound aryl iodide with benzyl ether linkage **10c** with acid **2a**. The final product was verified to be benzyl acetate **III** in 75% yield and 82% purity (entry a, Scheme 6).[12]

When increasing the amount of acetyl bromide to 4.0 equiv, we observed a mixture of product **III** and an unknown compound (entry b, Scheme 6). When 6 equiv of CH₃COBr was applied, an unknown compound was predominantly obtained. After purification via column chromatography on silica gel, we got the pure compound. Its MS spectrum exhibits the characteristic molecular ion peak of a mono-bromine-containing compound, and in its ¹H NMR spectrum there is no methyl signal of an acetyl group. Integrating other data, we concluded it was a benzylic bromide derivative (**12ca**). If acid **2a** was treated under conditions C, followed by cleavage with 6.0 equiv of acetyl bromide, the benzyl bromide derivative (**12ca**) can be obtained in 70% yield and 86% purity (entry c, Scheme 6), which means that a new model of SPOS butenolides was established. When the same conditions were applied to other 2,3-allenoic acids, the corresponding benzyl bromide derivatives were obtained in good yields and high purities (Scheme 7 and Table 4).

Unexpectedly, compared with para-substituted analogue **10c**, better results were achieved with ortho-substituted aryl

Scheme 7[a]
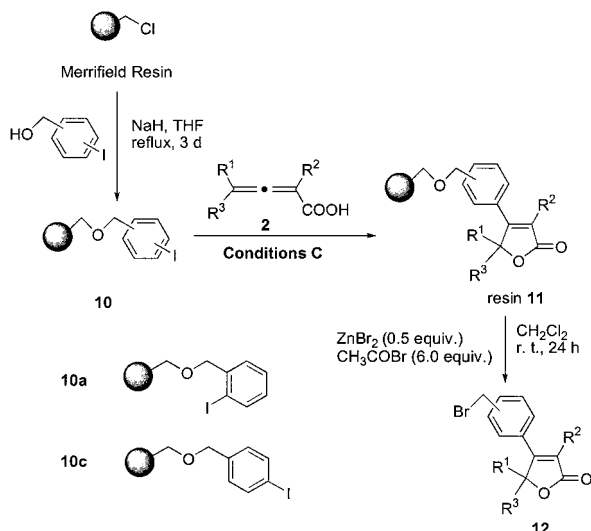
[a] Conditions C: 4 equiv of acids, 15 mol % Pd(PPh$_3$)$_4$, 8 equiv of *i*-Pr$_2$NEt in toluene at 70 °C for 3 days under an argon atmosphere.

Table 4. Pd(PPh$_3$)$_4$-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with a Benzyl Ether Linkage with 1, 2-Allenic Carboxylic Acids[a]

entry	resin 10	acid[b] 2	resin 11	product[c] 12	yield[d] (%)	purity[e] (%)
1	10c	2a	11ca	12ca	70	86
2	10a	2b	11ab	12ab	96	84
3	10c	2b	11cb	12cb	77	74
4	10a	2c	11ac	12ac	100	89
5	10c	2c	11cc	12cc	75	93
6	10a	2d	11ad	12ad	100	82
7	10c	2d	11cd	12cd	81	77
8	10c	2e	11ce	12ce	59	85
9	10c	2o	11co	12co	99	81
10	10c	2p	11cp	12cp	87	90

[a] Entries 1−6 with conditions A, entries 7 and 8 with conditions C (see text). Key to the labeling of compounds **11** and **12**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used. [b] See Table 1 or Table 2. [c] All new compounds were characterized by ^{1}H NMR, MS (EI), HRMS (EI), and FT-IR spectra of the crude products. [d] Overall yield based on the maximum theoretical loading of aryl iodides on resin (1.674 mequiv/g resin). [e] Determined by HPLC (Kromasil C18 column 4.6 mm × 150 mm, gradient elution with CH$_3$CN/H$_2$O, ultraviolet absorption detector at 254 nm).

iodide resin **10a** (compare entry 2 with entry 3, entry 6 with entry 7, Table 4). With a naked benzyl bromide group, these compounds are easily converted to other butenolide-containing compounds.

Library of Butenolides from the Palladium-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with THP Linkage and 2,3-Allenoic Acids. To further increase the diversities of butenolides, our attention was directed toward the development of other linkage strategies. In 1994, Ellman et al. reported a straightforward and general method for coupling alcohols to solid supports employing dihydropyran (DHP)-functionalized resin.[14] Phenols have also been attached with this linker.[15] The attachment functionality is stable to both strongly basic and nucleophilic reagents. Efforts were made to introduce the linker into our SPOS of butenolides. The initial experiment was unsuccessful because of the addition of 2,3-allenoic acid prior to the organic base

Scheme 8[a]
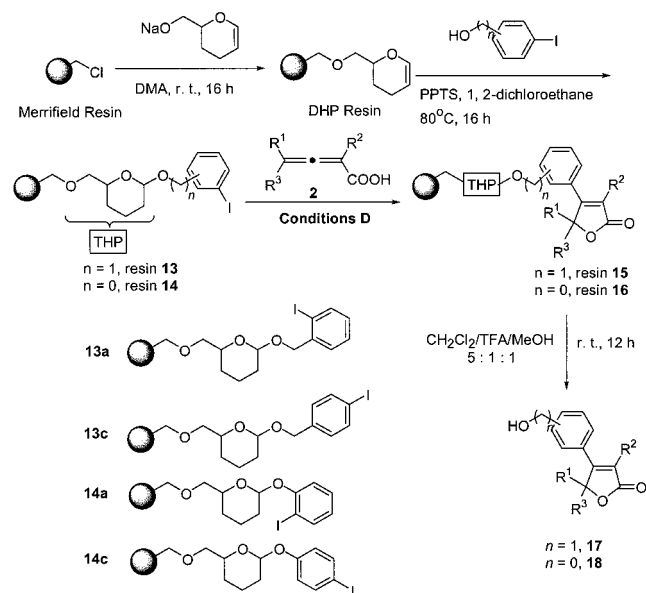
[a] Conditions D: 8 equiv of *i*-Pr$_2$NEt prior to 4 equiv of 2,3-allenoic acid and 15 mol % Pd(PPh$_3$)$_4$ in toluene at 70 °C for 3 days under an argon atmosphere.

N,N-diisopropyl-*N*-ethylamine, since the acidity of 2,3-allenoic acid is strong enough to cleave the linker from the Merrifield resin. When reversing the addition sequence, we realized the solid-phase cyclization of polymer-bound aryl iodides with THP linkage under conditions D (8 equiv of *i*-Pr$_2$NEt prior to 4 equiv of 2,3-allenoic acid and 15 mol % Pd(PPh$_3$)$_4$ in toluene at 70 °C for 3 days under an argon atmosphere). The results are good regardless of aryl iodide resin **13** with a benzyl alcoholic acetal linkage or resin **14** with a phenolic acetal linkage, which was verified by the strong carbonyl absorption at 1750 cm^{-1} in the FT-IR spectra of resins **15** and **16** (Scheme 8). The alternative cleavage methods include PPTS in 1:1 *n*-butanol/1,2-dichloroethane[14] or 95% TFA in water.[16] We chose a moderate cleavage method with a 5:1:1 mixture of CH$_2$Cl$_2$/TFA/MeOH at room temperature for 12 h. The yields and purities of final products are illustrated in Table 5.

Several points should be noted: (1) The reactions with aryl iodide resin **13** afforded the products in higher yields than those with resin **14** (compare entries 1−10 with entries 11−15, Table 5). This is ascribed to the stronger electron-donating ability of alkoxyl groups in resin **14**, which is unfavorable in the oxidative addition of aryl iodide with the palladium(0) catalyst. (2) The steric effect has a little influence on the reaction. Lower yields were obtained with ortho-substituted aryl iodides **13a** and **14a** (compare entry 7 with entry 8, entry 11 with entry 12, Table 5). (3) The reactions with trisubstituted 2,3-allenoic acid **2p** also gave the products in low yields, despite in high purities (entries 10 and 15, Table 5).

Conclusion

The combinations between 16 2,3-allenoic acid and 12 aryl iodides anchored to Merrifield resin gave a 77-membered library of butenolides with good quality (purities range from moderate to excellent). The establishment of 4 SPOS models

Table 5. Pd(PPh₃)₄-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with DHP Linker with 1,2-Allenic Carboxylic Acids[a]

entry	resin 13 or 14	acid[b] 2	resin 15 or 16	product[c] 9	yield[d] (%)	purity[e] (%)
1	13c	2a	15ca	17ca	64	83
2	13c	2b	15cb	17cb	65	88
3	13c	2c	15cc	17cc	75	82
4	13c	2d	15cd	17cd	67	77
5	13c	2k	15ck	17ck	68	66
6	13c	2l	15cl	17cl	52	51
7	13a	2n	15an	17an	36	54
8	13c	2n	15cn	17cn	73	75
9	13c	2o	15co	17co	63	81
10	13c	2p	15cp	17cp	34	92
11	14a	2a	16aa	18aa	22	89
12	14c	2a	16ca	18ca	42	72
13	14c	2l	16cl	18cl	43	68
14	14c	2o	16co	18co	45	78
15	14c	2p	16cp	18cp	23	83

[a] Conditions D: See text. Key to the labeling of compounds **16** and **17**: the first letter refers to the aryl iodide used, and the second letter refers to the acid used. [b] See Table 1 or Table 2. [c] All new compounds were characterized by ¹H NMR, MS (EI), HRMS (EI), and FT-IR spectra of the crude products. [d] Overall yield based on the maximum theoretical loading of aryl iodides on resin (1.434 mequiv/g resin). [e] Determined by HPLC (Kromasil C18 column 4.6 mm × 150 mm, gradient elution with CH_3CN/H_2O, ultraviolet absorption detector at 214 nm).

further realizes the diversity of the library. Now the library includes (5-oxo-2,5-dihydrofuran-3-yl)benzoic acids, -acetyl aryl esters, -benzyl bromides, -benzyl alcohols, and -phenols together with different alkyl or aryl substituents at the 3 or 5 position of the butenolide structure. In addition, because of the use of the SPOS technique, we acquired many butenolide derivatives in good yields and purities only by a simple filtration, employing the easy isolation advantage of SPOS. These compounds also contain some naked functional group like carboxylic acid, benzyl bromide, phenol, and benzyl alcohol with the great potential to be further derived. Noteworthy, these SPOS models that we have established in the synthesis of butenolides may be extended to other transition-metal-catalyzed coupling reactions.

Experimental Section

Starting Materials. Merrifield's peptide resin (2% cross-linked, 2−2.5 mequiv of Cl/g, 200−400 mesh) from Acros Organic was used in all of the experiments. All aryl iodides were commercially available except 4-iodobenzyl alcohol, which was obtained by the conversion of 4-bromobenzyl alcohol with *n*-BuLi/I₂.[17] 2,3-Allenoic acids **2a**−**2d** were obtained 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.[13b] The other 2,3-allenoic acids **2e**−**2p** were prepared according to a known method[18] by the treatment of the acid chlorides with ethyl 2-(triphenylphosphoranylidene)propionates and subsequent hydrolysis of the 2,3-allenoates with 2 N NaOH.[7d,e] All solvents are of analytic grade and were dried via refluxing over P₂O₅ or CaH and redistillation. ¹H NMR spectra were recorded with a Brucker AM 300 spectrometer

using CDCl₃ as the solvent and the internal standard unless otherwise stated. MS and HRMS spectra were obtained with electron impact ionization (EI). The yields were determined based on the maximum loading of the Merrifield resin, and the purities were determined by HPLC.

Typical Procedure for Anchoring Iodobenzoic Acid to Merrifield Resin. To a round-bottom flask charged with Merrifield resin (2.724 g, 6.80 mmol, according to its maximum loading of 2.5 mequiv/g) and DMF (80 mL) was added 2-iodobenzoic acid (2.534 g, 10.20 mmol), Cs₂CO₃ (6.648 g, 20.40 mmol), and KI (0.560 g, 3.40 mmol). The mixture was heated to 80 °C for 24 h. After cooling to room temperature, the resin was filtered and washed with DMF (3×), 1:1 DMF/H₂O (3×), H₂O (3×), DMF (2×), and MeOH (3×). Drying under vacuum overnight afforded the loaded resin **1a** (4.095 g, maximum loading of 1.636 mequiv/g).

Typical Procedure for Pd(PPh₃)₄-Catalyzed Coupling− Cyclization of Polymer-Bound Aryl Iodides with Carboxyl Linkage and 4-Alkyl-2,3-allenoic Acids (Conditions A). To a degassed suspension of resin **1a** (92 mg, 0.15 mmol) in dry CH₃CN (4 mL) was added 5,5-dimethyl-2,3-hexadi-enoic acid **2d** (84 mg, 0.60 mmol), *i*-Pr₂NEt (0.21 mL, 1.20 mmol), and Pd(PPh₃)₄ (26 mg, 22.5 μmol) subsequently. The mixture was stirred at 70 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered on a glass filter. The resin was washed successively with DMF (5 mL × 3), 1:1 DMF/H₂O (5 mL × 3), H₂O (5 mL × 3), DMF (5 mL × 2), and MeOH (10 mL × 3), then dried under high vacuum overnight to afford resin **3ad** (92 mg).

Typical Procedure for AlCl₃-Assisted Cleavage of Resins 3ac−3cj. Resin **3ad** (92 mg, 0.15 mmol) was swelled in CH₂Cl₂ (3 mL) for 30 min at room temperature. After it was cooled to 0 °C, a solution of AlCl₃ in MeNO₂ (3 mL, 0.50 mol/L, 1.50 mmol) was added and the mixture was stirred for 30 min at the same temperature. The resin was filtered and washed with EtOAc. The filtrate was transferred to a separatory funnel and was washed with 0.5 N HCl twice, and the combined aqueous layer was extracted with EtOAc. The combined extracts were dried and evaporated to give the cleavage product **4ad** (34 mg, 87% overall yield from Merrifield resin and 95% purity).

5-(*n*-Heptyl)-4-(2′-hydroxycarbonylphenyl)-2(5*H*)-fura-none (4aa): yield 100%; purity 90%; solid; ¹H NMR (CDCl₃) δ 8.11 (d, *J* = 7.5 Hz, 1H), 7.49−7.63 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 5.44 (t, *J* = 4.2 Hz, 1H), 1.05−1.61 (m, 12H), 0.76 (t, *J* = 6.9 Hz, 3H); MS (*m/e*) 302 (M⁺, 6), 146 (100); FT-IR (KBr) 2929, 2858, 1732 cm⁻¹; HRMS calcd for C₁₈H₂₂O₄ 302.1512, found 302.1513.

Typical Procedure for Pd(PPh₃)₄-Catalyzed Coupling Cyclization of Polymer-Bound Aryl Iodides with Carboxylic Linkage and 4-Aryl-2,3-allenoic Acids (Conditions B). To a degassed suspension of the resin **1c** (122 mg, 0.20 mmol) in dry toluene (4 mL) was added 2-methyl-4-phenyl-2,3-hexadienoic acid **2p** (162 mg, 0.80 mmol) and *i*-Pr₂NEt (0.28 mL, 1.60 mmol) and Pd(PPh₃)₄ (36 mg, 30 μmol) subsequently. The mixture was stirred at 90 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered on a glass filter. The resin was

washed successively with DMF (5 mL × 3) and 1:1 DMF/ H_2O (5 mL × 3), H_2O (5 mL × 3), DMF (5 mL × 2), and MeOH (10 mL × 3) and was then dried under high vacuum overnight to afford resin **5cp** (173 mg).

Typical Procedure for AlCl$_3$-Assisted Cleavage of Resins 5ck−5cp. The resin **5cp** (173 mg, 0.2 mmol) was swelled in CH_2Cl_2 (4 mL) for 30 min at room temperature. After cooling to 0 °C, a solution of AlCl$_3$ in MeNO$_2$ (4 mL, 0.50 mol/L, 2.0 mmol) was added and the mixture was stirred for additional 30 min at the same temperature. The resin was filtered and washed with EtOAc. The filtrate was transferred to a separatory funnel and was washed with 0.5 N HCl twice, and the combined aqueous layer was extracted with EtOAc. The combined extracts were dried and evaporated to give the cleaved product **6cp** (34 mg, 70% overall yield from Merrifield resin and 93% purity).

5-Ethyl-4-(4′-hydroxycarbonylphenyl)-3-methyl-5-phenyl-2(5H)-furanone (6cp): yield 70%; purity 93%; solid; ^{1}H NMR δ 8.11 (d, $J = 7.6$ Hz, 2H), 7.18−7.62 (m, 5H), 6.91 (d, $J = 7.6$ Hz, 2H), 2.55−2.48 (m, 1H), 1.98−2.19 (m, 1H), 1.88 (s, 3H), 0.86 (t, $J = 7.3$ Hz, 3H); MS (m/e) 322 (M^+, 4), 293 (100); FT-IR (KBr) 2975, 1749, 1689 cm^{-1}; HRMS calcd for $C_{20}H_{18}O_4$ 322.1200, found 322.1246.

Typical Procedure for Anchoring Iodophenol to Merrifield Resin. To a round-bottom flask charged with Merrifield resin (4.000 g, 10.00 mmol, according to its maximum loading of 2.5 mequiv/g) and DMF (120 mL) was added 3-iodophenol (4.404 g, 20.00 mmol) and CH_3ONa (2.160 g, 40.00 mmol). The mixture was heated to 80 °C for 24 h. After cooling to room temperature, the mixture was filtered and washed with DMF (3×), DMF/H_2O (3×), H_2O (3×), DMF (2×), and MeOH (3×). Drying under vacuum overnight afforded the loaded resin **7b** (5.343 g, maximum loading of 1.714 mequiv/g).

Typical Procedure for Pd(PPh$_3$)$_4$-Catalyzed Coupling− Cyclization of Polymer-Bound Aryl Iodides with Phenol Ether Linkage and 2,3-Allenoic Acids. 1. Conditions A for Acids 2a−2e. To a degassed suspension of resin **7b** (92 mg, 0.15 mmol) in dry CH_3CN (4 mL) was added 5,5-dimethyl-2,3-hexadienoic acid **2d** (84 mg, 0.60 mmol) and i-Pr$_2$NEt (0.21 mL, 1.20 mmol) and Pd(PPh$_3$)$_4$ (26 mg, 22.5 μmol) subsequently. The mixture was stirred at 70 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered on a glass filter. The resin was washed successively with DMF (5 mL × 3), 1:1 DMF/H_2O (5 mL × 3), H_2O (5 mL × 3), DMF (5 mL × 2), and MeOH (10 mL × 3) and then dried under high vacuum overnight to afford resin **8bd** (92 mg).

2. Conditions C for Acids 2k−2p. To a degassed suspension of resin **7b** (92 mg, 0.15 mmol) in dry toluene (4 mL) was added 2-methyl-4-phenyl-2,3-hexadienoic acid **2p** (122 mg, 0.60 mmol), i-Pr$_2$NEt (0.21 mL, 1.20 mmol), and Pd(PPh$_3$)$_4$ (26 mg, 22.5 μmol) subsequently. The mixture was stirred at 70 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered on a glass filter. The resin was washed successively with DMF (5 mL × 3), 1:1 DMF/H_2O (5 mL × 3), H_2O (5 mL × 3), DMF (5 mL × 2), and MeOH (10 mL × 3) and then dried under high vacuum overnight to afford resin **8bp** (100 mg).

Typical Procedure for ZnBr$_2$-Assisted Cleavage of Resins 8aa−8cp. To resin **8bp** (100 mg, 0.15 mmol) was added ZnBr$_2$ (17 mg, 75.6 μmol) and a solution of acetyl bromide in CH_2Cl_2 (2 mL, 0.15 mmol/mL, 0.30 mmol) under an argon atmosphere. The mixture was stirred for 24 h at room temperature, then the resin was collected by filtration. The filtrate was washed successively with 5% NaHCO$_3$, 5% HCl, and saturated NaCl solution. The organic layer was dried, filtered, and concentrated to afford the product **9bp** (93% overall yield and 82% purity).

4-(3′-Acetoxyphenyl)-5-ethyl-3-methyl-5-phenyl-2(5H)-furanone (9bp): yield 93%; purity 82%; oil; ^{1}H NMR δ 7.11−7.50 (m, 7H), 6.62−6.69 (m, 2H), 2.32−2.47 (m, 1H), 2.29 (s, 3H), 1.99−2.18 (m, 1H), 1.92 (s, 3H), 0.95 (t, $J = 7.0$ Hz, 3H); MS (m/e) 336 (M^+, 4), 84 (100); FT-IR (neat) 1755, 1710 cm^{-1}; HRMS calcd for $C_{21}H_{20}O_4$ 336.1356, found 336.1325.

Typical Procedure for Anchoring Iodobenzyl Alcohol to Merrifield Resin. To a round-bottom flask charged with Merrifield resin (1.007 g, 2.50 mmol, according to its maximum loading of 2.5 mequiv/g) and THF (30 mL) was added 4-iodobenzyl alcohol (1.200 g, 5.00 mmol) and NaH (0.180 g, 7.50 mmol). The mixture was refluxed for 3 days. After cooling to room temperature, the mixture was filtered and washed with DMF (3×), 1:1 DMF/H_2O (3×), H_2O (3×), DMF (2×), and MeOH (3×). Drying under vacuum overnight afforded the loaded resin **10c** (1.385 g, 1.674 mequiv/ g).

Typical Procedure for Pd(PPh$_3$)$_4$-Catalyzed Coupling− Cyclization of Polymer-Bound Aryl Iodides with Benzyl Ether Linkage and 2,3-Allenoic Acids (Conditions A for Acids 2a−2e and Conditions C for Acids 2o and 2p). The operation procedure is the same as the procedure for polymer-bound aryl iodides with phenol ether linkage and 2,3-allenoic acids.

Resin **11ca** was treated subsequently with CH_2Cl_2 (2 mL), ZnBr$_2$ (12 mg), and CH$_3$COBr (15 μL, added via a syringe). After the usual workup, 29 mg of crude product **III** was obtained and further purified by PTLC (eluent: ether/n-hexane = 1:4) to afford 22 mg (68%) of pure **III**.

4-(4′-Acetoxymethylphenyl)-5-(n-heptyl)-2(5H)-furanone (III): yield 75%; purity 82%; solid; ^{1}H NMR δ 7.45 (s, 4H), 6.27 (d, $J = 1.5$ Hz, 1H), 5.47−5.51 (m, 1H), 5.14 (s, 2H), 2.13 (s, 3H), 1.92−2.03 (m, 1H), 1.21−1.54 (m, 11H), 0.84 (t, $J = 7.2$ Hz, 3H); MS (m/e) 331 ($M^+ + 1$, 7), 115 (100); FT-IR (KBr): 2920, 1741, 1616 cm^{-1}; HRMS calcd for $C_{20}H_{26}O_4$ 330.1824, found 330.1850.

Typical Procedure for ZnBr$_2$-Assisted Cleavage of Resins 11ca−11cp with 6.0 Equiv of Acetyl Bromide. To resin **11cp** (100 mg, 0.15 mmol) was added ZnBr$_2$ (17 mg, 75.6 μmol) and a solution of acetyl bromide in CH_2Cl_2 (3 mL, 0.30 mmol/mL, 0.90 mmol) under an argon atmosphere. The mixture was stirred for 24 h at room temperature, and then the resin was collected by filtration. The filtrate was washed successively with 5% NaHCO$_3$, 5% HCl, and saturated NaCl solution. The organic layer was dried, filtered, and concentrated to afford the product **12cp** (87% overall yield and 90% purity).

4-(4′-Bromomethylphenyl)-5-ethyl-3-methyl-5-phenyl-

2(5*H*)-furanone (12cp): yield 87%; purity 90%; solid; ^{1}H NMR δ 7.12−7.27 (m, 7H), 6.71−6.74 (m, 2H), 4.38 (s, 2H), 2.26−2.34 (m, 1H), 2.00−2.07 (m, 1H), 1.82 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H); MS (*m/e*) 372 (M$^+$ (^{81}Br), 6), 370 (M$^+$ (^{79}Br), 6), 105 (100); FT-IR (KBr): 1755 cm^{-1}; HRMS calcd for $C_{20}H_{19}BrO_2$ 370.0563 (^{79}Br), found 370.0543 (^{79}Br).

Procedure for Preparing the DHP Resin. To a round-bottom flask charged with (2-hydroxymethyl)-3,4-dihydro-2*H*-pyran (1.710 g, 15.0 mmol) and DMA (75 mL) was added NaH (0.480 g, 20.0 mmol). After the mixture was stirred for 30 min at room temperature, Merrifield resin (2.000 g, 5.00 mmol, according to its maximum loading of 2.5 mequiv/g) was added and the mixture was stirred to react for 16 h at room temperature. Then it was filtered and washed with CH$_2$Cl$_2$ (1×), 1:1 DMF/H$_2$O (4×), DMF (3×), and CH$_2$-Cl$_2$ (3×). Drying under vacuum overnight afforded the DHP resin (2.236 g, maximum loading of 2.094 mequiv/g).

Typical Procedure for Anchoring Iodobenzyl Alcohol or Iodophenol to DHP Resin. To a round-bottom flask charged with DHP resin (1.000 g, 2.094 mmol) and 1,2-dichloroethane (21 mL) was added 4-iodophenol (2.304 g, 10.47 mmol) and PPTS (1.047 g, 4.29 mmol). The mixture was heated to 80 °C for 16 h. After cooling to room temperature, the mixture was filtered and washed with CH$_2$-Cl$_2$ (1×), 1:1 DMF/H$_2$O (4×), DMF (3×), and CH$_2$Cl$_2$ (3×). Drying under vacuum overnight afforded the loaded resin **14c** (1.117 g, maximum loading of 1.434 mequiv/g).

Typical Procedure for Pd(PPh$_3$)$_4$-Catalyzed Coupling−Cyclization of Polymer-Bound Aryl Iodides with a THP Linker and 2,3-Allenoic Acids (Conditions D). To a degassed suspension of resin **14c** (140 mg, 0.20 mmol) in dry toluene (2 mL) was added *i*-Pr$_2$NEt (0.28 mL, 1.60 mmol), 2,3-undecadienoic acid **2a** (146 mg, 0.80 mmol), Pd(PPh$_3$)$_4$ (36 mg, 30 μmol), and toluene (2 mL) subsequently. The mixture was stirred at 70 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered on a glass filter. The resin was washed successively with DMF (5 mL × 3), 1:1 DMF/H$_2$O (5 mL × 3), H$_2$O (5 mL × 3), DMF (5 mL × 2), and MeOH (10 mL × 3), then dried under high vacuum overnight to afford resin **16ca** (241 mg).

Typical Procedure for Cleavage of Resins 15ca−15cp and 16aa−16cp. Resin **16ca** (241 mg) was treated with a solution of 5:1:1 CH$_2$Cl$_2$/TFA/MeOH (4 mL). The mixture was stirred for 12 h at room temperature and then filtered. The filtrate was washed twice with a saturated NaHCO$_3$ solution, and the aqueous phase was extracted twice with CH$_2$Cl$_2$ solution. The organic layer was combined and dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated to afford the product **18ca** (23 mg, 42% overall yield from Merrifield resin and 72% purity).

5-(*n*-Heptyl)-4-(4′-hydroxyphenyl)-2(5*H*)-furanone (18ca): yield 42%; purity 72%; solid; ^{1}H NMR δ 7.27 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.05 (d, J = 1.3 Hz, 1H), 5.33−5.37 (m, 1H), 1.89−1.91 (m, 2H), 1.14−1.50 (m, 11H), 0.76 (t, J = 6.8 Hz, 3H); MS (*m/e*) 274 (M$^+$, 34), 119 (100); FT-IR (KBr) 3234, 1709 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_3$ 274.1563, found 274.1535.

Supporting Information Available. Analytical data for all the products not listed in the text and ^{1}H NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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