Efficient Synthesis of γ-Alkylidenetetronic Esters by Sequential Lewis Acid Catalyzed [3 + 2] Cyclizations and Palladium-Catalyzed Cross-Coupling Reactions

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A new approach for the synthesis of γ-alkylidenetetronic acids and esters is reported which involves Me_3SiOTf-catalyzed, regio- and stereoselective cyclization of 4-alkoxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride. The α-hydroxy group of the butenolides is efficiently functionalized by palladium-catalyzed cross-coupling reactions via the corresponding enol triflates.

Many natural products, such as pulvinic or pinastric acid, belong to the pharmacologically relevant substance class of γ-alkylidenetetronic acid derivatives.[1,2] These heterocycles have been used as building blocks in natural product syntheses, for example, in an approach[3] to the spirocyclic fragment of the antibiotic chlorotricolide.[4] The preparation of γ-alkylidenetetronic acid derivatives from ascorbic acid requires several steps and has the disadvantage that no additional substituents can be introduced at the exocyclic double bond and at the butenolide moiety.[5a] In addition, regioselective protection of the two hydroxy groups of ascorbic acid derivatives is problematic and requires additional steps.[5b,c] We have recently reported[6] the first Lewis acid catalyzed cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes, electroneutral 1,3-dicarbonyl dianion equivalents,[7] with oxalyl chloride to give γ-alkylidenebutenolides. Herein, we wish to report full details of a significant extension of this methodology to the synthesis of γ-alkylidenetetronic acid derivatives.[8] In addition, we report, to our knowledge, the first palladium-catalyzed cross-coupling reactions of α-hydroxy-γ-alkylidenetetronic esters.

Scheme 1. Synthesis of the γ-Alkylidenetetronic Esters 4a−d

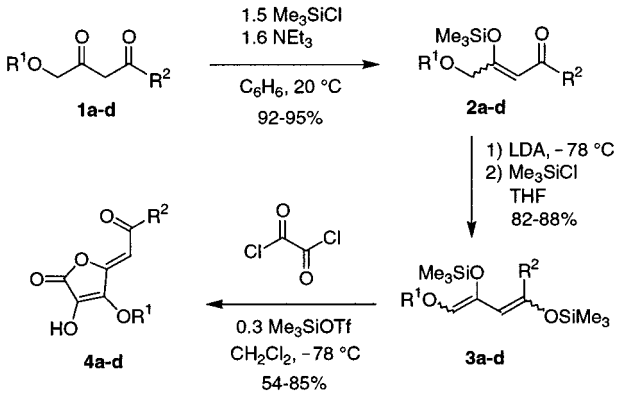

Table 1. Synthesis of γ-Alkylidenetetronic Esters 4a−d

entry	R^1	R^2	**2**[a] (%)	**3**[a] (%)	**4**[a] (%)	δ[b] (ppm)
a	Me	OMe	92	88	85	5.44
b	Me	Me	93	72	72	5.52
c	Allyl	OEt	93	82	54	5.42
d	Bn	OEt	95	86	70	5.43

[a] Isolated yields (*Z*/*E* > 98:2 for **4a**−**d**). [b] Chemical shift (^{1}H NMR) of the proton of the exocyclic double bond of **4a**−**d**.

Results and Discussion

Commercially available methyl 4-methoxyacetoacetate **1a** and the known 1,3-diketone **1b**[9] were converted into the silyl enol ethers **2a**,**b** and subsequently treated with LDA and Me_3SiCl at −78 °C to give the 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3a**,**b** (Scheme 1).[10] The Me_3SiOTf-catalyzed cyclization of **3a**,**b** with oxalyl chloride resulted in regioselective formation of the *Z*-configured γ-alkylidenetetronic esters **4a**,**b** in good yields (Table 1). The application of our recently published

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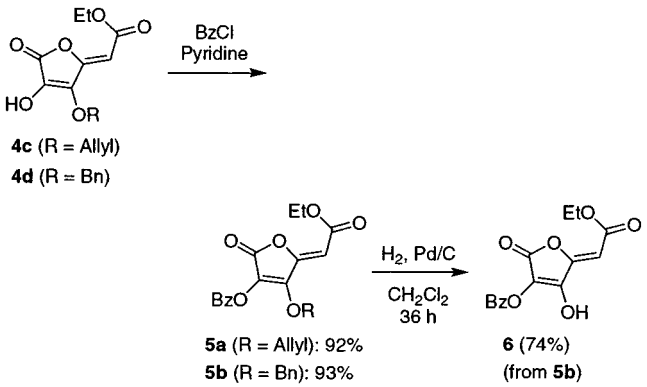
Table 2. Optimization of the Synthesis of the γ-Alkylidenetetronic Ester 8a

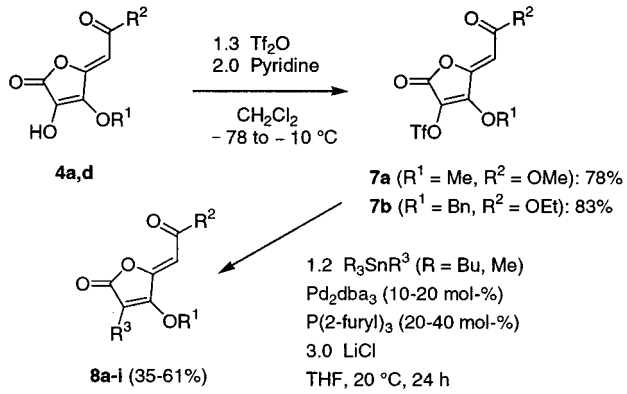
entry	catalyst (mol %)	additive (equiv)	*T* (°C)	solvent	*t* (h)	yield (**8a**)[a]
1	$Pd(OAc)_2$ (10)[b]	LiCl (3.0)	60−80	DMF	48	0
2	$Pd(PPh_3)_4$ (10)	LiCl (3.0)	20	THF	48	6
3	$Pd(PPh_3)_4$ (10)	CsF (3.0), LiCl (0.1)	20	THF	48	7
4	Pd_2dba_3·$CHCl_3$ (10)[c]		20	THF	48	0
5	Pd_2dba_3·$CHCl_3$ (10)[c]	LiCl (3.0)	20	THF	48	41
6	Pd_2dba_3·$CHCl_3$ (10)[c]	LiCl (3.0)	20	THF	24	42
7	Pd_2dba_3·$CHCl_3$ (10)[c]	LiCl (3.0)	55	THF	24	40

[a] Isolated yield. [b] PPh_3 (60 mol %) was added. [c] P(2-furyl)$_3$ (20−40 mol %) was added.

Scheme 2. Synthesis of γ-Alkylidenetetronic Acid 6



Scheme 3. Synthesis and Cross-Coupling Reactions of Enol Triflates 7a,b



dianion methodology[6a] for the synthesis of γ-alkylidenebutenolides to the preparation of **4a**−**d** proved unsuccessul, since the dianions of **1a**−**d** could not be generated.[11] The structure and the *Z*-configuration of **4a** were independently confirmed by X-ray crystallography (Figure 1, Supporting Information).

The free γ-alkylidenetetronic acid **6** was prepared from tetronic ester **4d** as depicted in Scheme 2.[8] The benzyl protecting group could be chemoselectively removed from **5b**, whereas deprotection of **5a** resulted in decomposition under a variety of conditions.

We next focused on the functionalization of the α-carbon of the γ-alkylidenetetronic esters by palladium-catalyzed cross-coupling reactions. The butenolides **4a** and **4d** were transformed by trifluoromethanesulfonic anhydride/pyridine into the corresponding triflates **7a** and **7b**, respectively. Our first attempts to induce a palladium-catalyzed cross-coupling reaction of triflate **7a** with tributylphenylstannane using $Pd(OAc)_2$ as the catalyst were unsuccessful.[13,14] The use of $Pd(PPh_3)_4$ resulted in formation of the desired coupling product **8a**, however, in only low yield. The initial problems can be explained by the low reactivity of hindered, electron-rich enol triflates toward palladium-catalyzed cross-coupling reactions.[15,16]

Table 3. Palladium-Catalyzed Cross-Coupling Reactions of Triflates 7a,b

7	8	R^1	R^2	R^3	R	yield[a] (%)
a	**a**	Me	OMe	Ph	Bu	34
a	**a**	Me	OMe	Ph	Me	42
a	**b**	Me	OMe	2-furyl	Bu	46
a	**c**	Me	OMe	−C≡CPh	Me	35
a	**d**	Me	OMe	Me	Me	37
a	**e**	Me	OMe	$-CH=CH_2$	Bu	37
b	**f**	Bn	OEt	Ph	Me	46
b	**g**	Bn	OEt	*p*-$MeOC_6H_4$	Me	57
b	**h**	Bn	OEt	2-furyl	Bu	61
b	**i**	Bn	OEt	−C≡CPh	Me	30

[a] Isolated yields.

We have eventually found that optimal yields were obtained when Pd_2dba_3·$CHCl_3$ (10−20 mol %) in the presence of LiCl (3.0 equiv) and P(2-furyl)$_3$ (20−40 mol %) was used (Scheme 3, Table 2).[17] Related conditions have been previously employed by Brückner et al. in butenolide syntheses.[2b] It was difficult to isolate the product in pure form, since Bu_3SnCl could not be completely removed. However, the problem could be solved by the use of Me_3SnPh (rather than Bu_3SnPh), which resulted in formation of water-soluble Me_3SnCl.

Palladium-catalyzed cross-coupling of triflate **7a** with trimethylphenylstannane, tributyl(2-furyl)stannane, trimethyl(phenylalkynyl)stannane, tetramethylstannane, and tributylvinylstannane afforded the γ-alkylidenetetronic esters **8a**−**e** in acceptable yields (Table 3). Stille couplings of the benzyloxy-substituted triflate **7b** were next studied: reaction of **7b** with trimethylphenylstannane, trimethyl(*p*-tolyl)stannane, tributyl(2-furyl)stannane, and trimethyl(phenylalkynyl)stannane gave the γ-alkylidenetetronic esters **8f**−**i** in acceptable yields.

In summary, we have developed a conceptually new approach to γ-alkylidenetetronic esters by a [3 + 2]

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cyclization−Stille coupling strategy. A free γ-alkylidenetetronic acid was prepared from the corresponding benzoate ester by chemoselective debenzylation. The γ-alkylidenetetronic acid derivatives reported herein are of pharmacological relevance and represent analogues of pulvinic acid and related natural products.

Experimental Section

General Comments. All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For the ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectral data (MS) were obtained using the electron ionization (70 eV) or the chemical ionization technique (CI, H_2O). For preparative scale chromatography silica gel (60−200 mesh) was used. Melting points are uncorrected. Elemental analyses were performed at the microanalytical laboratory of the University of Göttingen.

General Procedure for the Preparation of γ-Alkylidenetetronic Esters 4a−d. To a CH_2Cl_2 solution (30 mL) of oxalyl chloride (1.5 mmol, 0.13 mL) were added the 1,3-bis-(trimethylsilyloxy)-1,3-diene (1.5 mmol) and a CH_2Cl_2 solution (7 mL) of Me_3SiOTf (0.45 mmol) at −78 °C. The solution was warmed within 6 h to 20 °C and stirred for 14 h at 20 °C. A saturated aqueous solution of brine was added and the aqueous layer was extracted with ether (4 × 200 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:10 → 1:3).

4-Methoxy-5-[*Z*-(methoxycarbonylmethylidene]-3-hydroxy-2-furanone (4a).[6b] Starting with 1,4-dimethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a** (436 mg, 1.50 mmol), tetronic ester **4a** was isolated as a colorless solid (255 mg, 85%): mp 87 °C; ^{1}H NMR (MeOH-d_4, 250 MHz) δ 3.75 (s, 3 H, OCH_3), 4.18 (t, 3 H, CO_2CH_3), 5.44 (s, 1 H, CH). ^{13}C NMR (MeOH-d_4, 62.5 MHz) δ_C 52.14 (OCH_3), 59.86 (CO_2CH_3), 94.29 (CH), 126.31, 142.53, 154.34 (C), 165.57, 165.70 (CO). IR (KBr) $\tilde{\nu}$ 3208, 3082, 2877, 1795, 1682, 1466, 1442, 1372, 1348, 1302, 1195, 1119, 1089, 1024 cm^{-1}; MS (EI, 70 eV) *m*/*z* 200 (M^+, 61), 169 (50), 140 (30), 113 (64), 85 (42), 69 (100). The exact molecular mass *m*/*z* = 200.0320 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_8H_8O_6$: C, 48.01; H, 4.03. Found: C, 47.71;, H, 4.28.

X-ray Structure Analysis.[18−21] For the data collection, a Stoe-Siemens-Huber four-circle diffractometer equipped with a Siemens SMART CCD area detector using graphite-monochromated Mo Kα radiation was used. The structures were solved by direct methods (SHELXS) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. A riding model starting from calculated positions was employed for the hydrogen atoms bond to carbon, while the hydrogen bond to O(3) was refined freely.

Crystal data of 4a: empirical formula, $C_{16}H_{16}O_{12}$; formula weight, 400.29; T = 133(2) K; wavelength, 0.71073 Å; crystal system, monoclinic; space group, $P2(1)/c$; unit cell dimensions, a = 13.013(2) Å, b = 16.890(2) Å, c = 7.6550(10) Å, β = 90.55(2)°; V = 1682.4(4) Å^3; Z = 4; density (calcd), 1.580 Mg/m^3; absorption coefficient, 0.139 mm^{-1}; F(000): 832; crystal size, 0.40 × 0.30 × 0.20 mm^3; θ range for data collection, 2.88−25.02°; index ranges, 15 ≤ h ≤ 15, 0 ≤ k ≤ 20, 0 ≤ l ≤ 9; reflections collected, 21221; independent reflections, 2956 [R(int) = 0.0724]; completeness to θ = 25.02°, 99.9%; absorption correction, semiempirical from equivalents; maximum and minimum transmission, 0.9728 and 0.9466; refinement method, full-matrix least-squares on F^2; data/restraints/parameters, 2956/1/265; GOF, 1.166; final R indices [$I > 2\sigma(I)$], R1 = 0.0628, wR2 = 0.1445; R indices (all data), R1 = 0.0790, wR2 = 0.1515; extinction coefficient, 0.0075(14); largest difference peak and hole, 0.346 and −0.313 e·Å^{-3}.

4-Methoxy-5-[*Z*-(acetylmethylidene]-3-hydroxy-2-furanone (4b). Starting with diene **3b** (405 mg, 1.48 mmol), **4b** was isolated as a colorless solid (196 mg, 72%): mp 82 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.35 (s, 3 H, $COCH_3$), 4.20 (s, 3 H, OCH_3), 5.52 (s, 1 H, CH); ^{13}C NMR (acetone-d_6, 75 MHz) δ_C 31.04 ($COCH_3$), 59.82 (OCH_3), 104.25 (CH), 125.03, 142.84, 151.48 (OCC), 164.48 (OCO), 194.97 (CO); IR (KBr) $\tilde{\nu}$ 3565, 3164, 1783, 1693, 1623, 1464, 1424, 1364, 1271, 1195, 1117, 1086, 1033, 1011 cm^{-1}; MS (EI, 70 eV) *m*/*z* 184 (M^+, 71), 169 (100), 141 (35), 128 (72), 113 (90), 85 (48). The exact molecular mass *m*/*z* = 184.0371 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.38; H, 4.32.

4-Allyloxy-5-[*Z*-(ethoxycarbonylmethylidene]-3-hydroxy-2-furanone (4c). Starting with diene **3c** (1.63 mmol, 0.54 g), **4c** was isolated as a colorless oil (212 mg, 54%): ^{1}H NMR (acetone-d_6, 250 MHz) δ 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 4.17 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.94−5.04 (m, 2 H, OCH_2CHCH_2), 5.21−5.51 (m, 3 H, =CH−, $OCH_2CH=CH_2$), 6.01−6.19 (m, 1 H, $OCH_2CH=CH_2$); ^{13}C NMR (acetone-d_6, 50 MHz) δ_C 14.48 (OCH_2CH_3), 60.83 (OCH_2CH_3), 72.59 ($OCH_2CH=CH_2$), 95.03 (CHC=O), 119.02 ($OCH_2CH=CH_2$), 125.39 (C), 133.53 ($OCH_2CH=CH_2$), 141.24, 153.10 (C), 163.30, 164.94 (C=O); MS (CI, NH_3) *m*/*z* 240 (100, M^+).

4-Benzyloxy-5-[*Z*-(ethoxycarbonylmethylidene)]-3-hydroxy-2-furanone (4d). Starting with 4-benzyloxy-1,3-bis-(trimethylsilyloxy)-1,3-diene **3d** (1.5 mmol), **4d** was isolated as a colorless solid (302 mg, 70%): mp 67−69 °C; ^{1}H NMR (acetone-d_6, 250 MHz) δ 1.23 (t, J = 6 Hz, 3 H, CH_3), 2.85 (br, 1 H, OH), 4.15 (q, J = 6 Hz, 2 H, OCH_2CH_3), 5.43 (s, 1 H, CCHCO), 5.55 (s, 2 H, CH_2Ph), 7.30−7.55 (m, 5 H, Ph); ^{13}C NMR (acetone-d_6, 50 MHz) δ_C 14.42 (CH_3), 60.81 (OCH_2CH_3), 73.61 (OCH_2Ph), 95.06 (CCHCO), 125.63 (C), 128.77, 129.15, 129.30 (CH, Ph), 136.91, 141.32, 153.10 (C), 163.30, 164.88 (CO); MS (EI, 70 eV) *m*/*z* 290 (M^+, 100). Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 62.32; H, 4.63.

3-Benzoyloxy-4-benzyloxy-5-[*Z*-(ethoxycarbonylmethylidene)]-2-furanone (5b). To a pyridine solution (30 mL) of **4d** (100 mg, 0.34 mmol) was added benzoyl chloride (0.14 mL, 1.14 mmol) at 0 °C. After the solution was stirred for 24 h at 0 °C, the mixture was poured into a saturated aqueous solution of $NaHCO_3$. The organic layer was extracted with water (3 × 40 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo to give **5b** as a colorless solid (126 mg, 93%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (t, J = 7 Hz, 3 H, OCH_2CH_3), 4.27 (q, J = 7 Hz, 2 H, OCH_2CH_3), 5.38 (s, 2 H, OCH_2Ph), 5.77 (s, 1 H, CHC=O), 7.26−7.39 (m, 5 H, Ph), 7.51−7.63 (m, 2 H, Ph), 7.67−7.78 (m, 1 H, Ph), 8.05−8.15 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C 14.12 (OCH_2CH_3), 61.08 (OCH_2CH_3), 73.95 (OCH_2Ph), 98.21 (CHC=O), 126.99, 127.58, 128.53, 128.79, 128.81, 129.16 (CH, Ph), 130.57, 133.96, 134.66 (C-3, Ph), 149.77, 152.07 (C-4, C-5), 161.76, 162.78, 163.02 (C=O); MS (EI, 70 eV) *m*/*z* 394 (M^+, 20). Anal. Calcd for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 66.65; H, 4.74.

3-Benzoyloxy-5-[*Z*-(ethoxycarbonylmethyliden)]-4-hydroxy-2-furanone (6). See ref 8.

4-Methoxy-5-[*Z*-(methoxycarbonylmethylidene)]-3-(trifluoromethanesulfonyloxy)-2-furanone (7a). To a CH_2Cl_2 solution (10 mL) of **4a** (213 mg, 1.06 mmol) were added pyridine (168 mg, 2.12 mmol) and trifluoromethane sulfonic anhydride (330 mg, 1.17 mmol) at −78 °C. The solution was warmed within 4 h to −10 °C. The mixture was purified by chromatography (silica gel, CH_2Cl_2) to give **7a** as a slight yellow oil (276 mg, 78%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3 H, OCH_3), 4.31 (s, 3 H, OCH_3), 5.82 (s, 1 H, $CHCO_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C 52.33, 60.67, 100.15, 114.08, 117.45 (q, CF_3), 148.08, 155.05, 159.71, 162.54 (C); MS (70 eV, EI) *m*/*z* 331 (M^+, 19). The exact molecular mass *m*/*z* = 331.9814 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV).

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4-Benzyloxy-5-[*Z*-(ethoxycarbonylmethylidene)]-3-(trifluormethansulfonyloxy)-2-furanone (7b). Compound **7b** was prepared according to the procedure given for the preparation of **7a**. Starting with **4d** (100 mg, 0.34 mmol), **7b** was isolated as a slight yellow oil (121 mg, 83%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.31 (t, J = 7 Hz, 3 H, CH_3), 4.26 (q, J = 7 Hz, 2 H, OCH_2CH_3), 5.51 (s, 2 H, OCH_2Ph), 5.83 (s, 1 H, $CHCO_2Et$), 7.40−7.47 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C 14.03 (OCH_2CH_3), 61.40 (OCH_2CH_3), 75.27 (OCH_2Ph), 100.63 ($CHCO_2$-Et), 114.35 (C-3), 124.71 (q, CF_3), 128.30, 129.01, 129.78 (CH, Ph), 132.85 (C, Ph), 148.15, 154.17 (C), 159.75, 162.05 (CO); MS (EI, 70 eV) m/z 422 (M^+, 8), 377 (20), 289 (6), 91 (100). The exact molecular mass m/z = 422.0283 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV).

4-Methoxy-5-[*Z*-(methoxycarbonylmethylidene)]-3-phenyl-2-furanone (8a). To a thoroughly degassed THF solution (7 mL) of triflate **7a** (0.30 mmol, 101 mg) were added Pd_2dba_3·$CHCl_3$ (5 mol %, 16 mg), P(2-furyl)$_3$ (20 mol %, 14 mg), and LiCl (39 mg, 300 mol %). After the mixture was stirred for 5 min, trimethylphenylstannane (0.37 mmol, 0.086 mL) was added. After the resulting mixture was stirred for 24 h at 20 °C, water (100 mL) was added. The aqueous layer was extracted with ether (4 × 100 mL), and the organic layer was dried ($MgSO_4$), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography to give **8a** as a yellow solid (33 mg, 42%): ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.82 (2 × s, 2 × 3 H, 2 × OCH_3), 5.73 (s, 1 H, $CHCO_2CH_3$), 7.43 (s, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_C 52.08 (OCH_3), 61.04 (OCH_3), 96.21 (CH), 107.89 (C), 127.85 (C), 128.40 129.18, 130.23 (CH, Ph) 151.95, 162.18, 163.91 (C, CO, OCOC), 167.46 (CO); MS (70 eV, EI) m/z 260 (M^+, 100), 177 (15), 57 (27). The exact molecular mass m/z = 260.0685 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV).

4-Methoxy-5-[*Z*-(methoxycarbonylmethylidene)]-3-(2-furyl)-2-furanone (8b). To a degassed THF solution (5 mL) of triflate **7a** (0.59 mmol, 196 mg) were added Pd_2dba_3·$CHCl_3$ (5 mol %, 31 mg), P(2-furyl)$_3$ (20 mol %, 27 mg), and LiCl (1.80 mmol, 75 mg). After the mixture was stirred for 5 min, tributyl-(2-furyl)stannane (0.71 mmol, 0.24 mL) was added. After the resulting mixture was stirred for 24 h at 20 °C, a saturated aqueous KF solution (100 mL) was added. The aqueous layer was extracted with ether (4 × 150 mL), the organic layer was dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (using a 1 cm KF layer on the top of the column) and by subsequent washing with petroleum ether to give **8b** as a yellow solid (68 mg, 46%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3 H, OCH_3), 4.20 (s, 3 H, OCH_3), 5.75 (s, 1 H, $CHCO_2CH_3$), 6.55 (dd, J = 3.6 Hz, J = 1.8 Hz, 1 H, 4′-H), 7.03 (dd, J = 3.4 Hz, J = 0.8 Hz, 1 H, 3′-H), 7.56 (dd, J = 1.8 Hz, 0.8 Hz, 1 H, 5′-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 52.01, 61.95 (OCH_3), 96.54, 99.60, 111.98, 113.53, 142.26, 143.93, 152.14, 159.60, 163.72, 165.74; MS (70 eV, EI) m/z 250 (M^+, 100), 219 (11), 135 (15), 107 (23). Anal. Calcd for $C_{12}H_{10}O_6$ (250.2): C, 57.61; H, 4.03. Found: C, 57.26; H, 3.94.

4-Methoxy-5-[*Z*-2-(methoxycarbonylmethylidene)]-3-(phenylethynyl)-2-furanone (8c). To a degassed THF solution (5 mL) of triflate **7a** (0.83 mmol, 277 mg) were added Pd_2dba_3·$CHCl_3$ (5 mol %, 43 mg), P(2-furyl)$_3$ (20 mol %, 39 mg), and LiCl (300 mol %, 106 mg). After the mixture was stirred for 5 min, trimethyl(phenylethynyl)stannane (1.00 mmol, 265 mg) was added. After the resulting mixture was stirred for 24 h at 20 °C, a saturated aqueous KF-solution (200 mL) was added. The aqueous layer was extracted with ether (4 × 150 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:3) to give **8c** as a yellow solid (83 mg, 35%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.81 (s, 3 H, OCH_3), 4.49 (s, 3 H, OCH_3), 5.70 (s, 1 H, $CHCO_2CH_3$), 7.28−7.57 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 52.15, 60.26 (OCH_3), 91.07 (C), 96.94 (CH), 98.70, 121.73 (C), 128.49, 129.43 (2 × CH, Ph), 131.47 (C), 131.51 (CH, Ph), 151.33, 163.47, 164.95, 165.18 (C); MS (70 eV, EI) m/z 284 (M^+, 100), 234 (16), 113 (21). The exact molecular mass m/z = 284.0685 ± 2 mD (M^+) for $C_{16}H_{12}O_5$ was confirmed by HRMS (EI, 70 eV).

4-Methoxy-5-[*Z*-2-(methoxycarbonylmethylidene)]-3-methyl-2-furanone (8d): To a degassed THF solution (5 mL) of triflate **7a** (0.46 mmol, 154 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 48 mg), P(2-furyl)$_3$ (40 mol %, 43 mg), and LiCl (1.38 mmol, 59 mg). After the mixture was stirred for 5 min, tetramethylstannane (0.60 mmol, 0.08 mL) was added. After the resulting mixture was stirred for 24 h at 20 °C, a saturated aqueous KF solution (200 mL) was added. The aqueous layer was extracted with ether (4 × 150 mL), the organic layer was dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:4) to give **8d** as a yellow solid (34 mg, 37%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.17 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 4.32 (s, 3 H, OCH_3), 5.82 (s, 1 H, $CHCO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 8.04 (CH_3), 52.35 (OCH_3), 59.36 (OCH_3), 96.28 (CH), 102.80, 152.72, 160.22 (C), 164.20, 169.85 (CO); MS (70 eV, EI) m/z 198 (M^+, 41), 167 (100), 97 (32), 83 (44). The exact molecular mass m/z = 198.0528 ± 2 mD (M^+) for $C_9H_{10}O_5$ was confirmed by HRMS (EI, 70 eV).

4-Methoxy-5-[*Z*-2-(methoxycarbonylmethylidene)]-3-vinyl-2-furanone (8e): To a degassed THF solution (7 mL) of triflate **7a** (0.45 mmol, 150 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 47 mg), P(2-furyl)$_3$ (20 mol %, 21 mg), and LiCl (1.35 mmol, 57 mg). After the mixture was stirred for 5 min, tributylvinylstannane (0.54 mmol, 0.16 mL, d = 1.086 g/mL) was added. After the resulting mixture was stirred for 24 h at 20 °C, a saturated aqueous KF solution (200 mL) was added. The aqueous layer was extracted with ether (4 × 150 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (2 ×, silica gel, ether/petroleum ether = 1:4) to give **8e** as a yellow solid (36 mg, 37%). Tributylchlorostannane could not be completely removed from the product: ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.78 (s, 3 H, OCH_3), 4.21 (s, 3 H, OCH_3), 5.54 [d, J = 11 Hz, 1 H, HC=CH-H(cis)], 5.63 (1 H, $CHCO_2CH_3$), 6.26 [d, J = 18 Hz, 1 H, HC=CH-H(trans)], 6.72 [dd, J = 18, 11 Hz, 1 H, HC=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_C 51.97, 60.67 (OCH_3), 96.03 (=$CHCO_2$Me), 104.42 (C), 121.93, 122.77 (HC=CH_2, CH=CH_2), 151.55, 160.30, 163.82, 166.26 (C). Tributylchlorstannane could not be completely removed.

4-Benzyloxy-5-[*Z*-2-(ethoxycarbonylmethylidene)]-3-phenyl-2-furanone (8f). To a degassed THF solution of triflate **7b** (0.24 mmol, 100 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 25 mg), P(2-furyl)$_3$ (40 mol %, 22 mg), and LiCl (0.72 mmol, 30 mg). After the mixture was stirred for 5 min, trimethylphenylstannane (0.26 mmol, 70 mg) was added. After the resulting mixture was stirred for 24 h at 20 °C, a saturated aqueous KF solution (200 mL) was added. The aqueous layer was extracted with ether (4 × 150 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:4) to give **8f** as a yellow solid (38 mg, 46%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.03 (s, 2 H, OCH_2Ph), 5.75 (s, 1 H, $CHCO_2Et$), 7.08−7.11 (m, 2 H, Ph), 7.31−7.34 (m, 3 H, Ph), 7.43−7.45 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C 14.21 (OCH_2CH_3), 61.04 (OCH_2CH_3), 74.72 (OCH_2Ph), 96.75 (CHC=O), 109.08 (C-3), 127.79, 128.51, 128.70, 129.03, 129.33, 130.11 (CH, Ph), 128.05, 134.26 (C, Ph), 152.21 (C-4), 161.22 (C-5), 163.45, 167.39 (C=O); MS (70 eV, EI) m/z 350 (M^+, 20), 332 (28), 304 (8), 276 (4), 145 (6), 91 (100). The exact molecular mass m/z = 350.1154 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.20; H, 5.02.

4-Benzyloxy-5-[*Z*-2-(ethoxycarbonylmethylidene)]-3-(4-methoxyphenyl)-2-furanone (8g). To a THF solution of triflate **7b** (0.24 mmol, 100 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 25 mg), P(2-furyl)$_3$ (40 mol %, 22 mg), and LiCl (0.72 mmol, 30 mg). After the mixture was stirred for 5 min, trimethyl(4-methoxyphenyl)stannane (0.26 mmol, 70 mg) was added. After the resluting mixture was stirred for 24 h at 20

°C, a saturated aqueous KF solution (200 mL) was added. The aqueous layer was extracted with ether (4 × 100 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:4) to give **8g** as a yellow solid (52 mg, 57%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 4.27 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.05 (s, 2 H, OCH_2Ph), 5.70 (s, 1 H, CHC=O), 6.90-6.99 (m, 2 H, Ph), 7.12−7.23 (m, 2 H, Ph), 7.27−7.36 (m, 3 H, Ph), 7.38−7.49 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C 14.20 (OCH_2CH_3), 55.34 (OMe), 60.98 (OCH_2CH_3), 74.48 (OCH_2Ph), 96.38 (CHC=O), 109.59 (C-3), 127.71, 127.86, 128.41, 128.46, 128.99, 131.28 (CH, Ph), 131.61, 134.41 (C, Ph), 152.41 (C-4), 160.35 (C-5), 163.49, 167.58 (C=O); MS (70 eV, EI) m/z 380 (M^+, 18). The exact molecular mass m/z = 380.1260 ± 2 mD (M^+) for $C_{22}H_{20}O_6$ was confirmed by HRMS (EI, 70 eV).

4-Benzyloxy-5-[*Z*-2-(ethoxycarbonylmethylidene)]-3-(2-furyl)-2-furanone (8h). To a THF solution of triflate **7b** (0.24 mmol, 100 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 25 mg), P(2-furyl)$_3$ (40 mol %, 22 mg), and LiCl (0.72 mmol, 30 mg). After the mixture was stirred for 5 min, tributyl(2-furyl)stannane (0.26 mmol, 0.08 mL, d = 1.139) was added. After the resulting mixture was stirred for 24 h at 20 °C, water (100 mL) was added. The aqueous layer was extracted with ether (4 × 100 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:3), and subsequent washing of the product with petroleum ether to give **8h** as a yellow solid (50 mg, 61%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.31 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.45 (s, 2 H, OCH_2Ph), 5.72 (s, 1 H, CHC=O), 6.58 (dd, J = 3.5 Hz, J = 1.8 Hz, 1 H, 4′-H), 7.06 (dd, J = 3.5 Hz, J = 0.7 Hz, 1 H, 5′-H), 7.27-7.39 (m, 5 H, Ph), 7.61 (dd, J = 1.8 Hz, J = 0.7 Hz, 1 H, 3′-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C 14.15 (OCH_2CH_3), 60.96 (OCH_2CH_3), 76.31 (OCH_2Ph), 97.13 (CHC=O), 100.75 (C-3), 112.19, 113.70 (C-3′, C-4′, furane), 128.18, 128.74, 129.07 (CH, Ph), 134.61 (C-5′, furane), 142.68, 144.08 (C-4, C, Ph), 152.46, 158.32 (C-5, C-2′, furane), 163.25, 165.69 (C=O); MS (70 eV, EI) m/z 340 (M^+, 4), 322 (4), 294 (8), 215 (6), 204 (5), 91 (100). The exact molecular mass m/z = 340.0947 ± 2 mD (M^+) for $C_{19}H_{16}O_6$ was confirmed by HRMS (EI, 70 eV).

4-Benzyloxy-5-[*Z*-2-(ethoxycarbonylmethylidene)]-3-(phenylethynyl)-2-furanone (8i). To a THF solution of triflate **7b** (0.24 mmol, 100 mg) were added Pd_2dba_3·$CHCl_3$ (10 mol %, 25 mg), P(2-furyl)$_3$ (40 mol %, 22 mg), and LiCl (0.72 mmol, 30 mg). After the mixture was stirred for 5 min, trimethyl(phenylethynyl)stannane (0.26 mmol, 70 mg) was added. After the resulting mixture was stirred for 24 h at 20 °C, water (100 mL) was added. The aqueous layer was extracted with ether (4 × 100 mL), the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography to give **8i** as a yellow solid (27 mg, 30%): ^{1}H NMR (acetone-d_6, 250 MHz) δ 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 4.20 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.65 (s, 1 H, $CHCO_2Et$), 6.00 (s, 2 H, OCH_2Ph), 7.24−7.59 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C 14.43 (CH_3), 61.31 (OCH_2CH_3), 75.41 (OCH_2Ph), 79.91, 91.02 (C, alkyne), 97.51 (CHC=O), 100.01 (C-3), 129.01, 129.47, 129.58, 129.77, 130.37, 132.26 (CH, Ph), 135.85 (C, Ph), 152.51, 152.56 (C-4, C, Ph), 163.46 (C-5), 166.25, 167.89 (C=O); MS (70 eV, EI) m/z 374 (M^+, 4), 328 (8), 301 (18), 165 (12), 113 (6), 91 (100). The exact molecular mass m/z = 374.1154 ± 2 mD (M^+) for $C_{23}H_{18}O_5$ was confirmed by HRMS (EI, 70 eV).

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Supporting Information Available: Details of the structure determination for **4a** including atomic coordinates, H-atom coordinates, bond distances and bond angles, and an ORTEP plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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