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Suzuki Cross-Coupling Reactions of γ-Alkylidenebutenolides: Application to the Synthesis of Vulpinic Acid

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α-Hydroxy-γ-alkylidenebutenolides were efficiently functionalized by Suzuki cross-coupling reactions via the corresponding enol triflates. The natural product vulpinic acid was prepared by this methodology.

γ-Alkylidenebutenolides are present in a variety of pharmacologically relevant natural products and natural product analogues.[1] We have recently reported the functionalization of the α-carbon atom of γ-alkylidenebutenolides, readily available by cyclization of 1,3-bis-silyl enol ethers[2,3] with oxalyl chloride,[4] by Stille cross-coupling reactions.[5,6] Very recently, Le Gall et al. reported a related approach, based on the Suzuki reaction, and its application to the synthesis of an analogue of norbadione A and of a pulvinic acid derivative.[7] This publication prompted us to report our own findings in this area. We report the functionalization of a variety of γ-alkylidenebutenolides by Suzuki reactions and the application of this methodology to the synthesis of vulpinic acid. The latter belongs to the pharmacologically relevant class of pulvinic acid natural products which have been isolated from a variety of terrestric sources such as mushrooms.[8,9] A number of regioselective[8d] and unselective[8a,c] syntheses of unsymmetrical pulvinic acids have been reported.[1,8] For example, pulvinic acids are available by cleavage of pulvinic lactones.[8a] However, mixtures of regioisomeric products were obtained for unsymmetrical derivatives, due to the very similar chemical environment of the two lactone moieties. Our approach allows a regioselective synthesis of pulvinic acids, since the aryl substituents of the latter are introduced independently from each other. From a practical viewpoint, the method is straightforward and the starting materials are readily available.

Results and Discussion

Triflate **3a** was prepared from butenolide **2a**[4b] in good yield. The Suzuki reaction of **3a** with phenylboronic acid afforded the γ-alkylidenebutenolide **4a** (Scheme 1). Optimal yields were obtained by application of standard reaction conditions used also by Le Gall et al. (3 mol % $Pd(PPh_3)_4$, 1.5 equiv of K_3PO_4, dioxane, reflux).[7] Surprisingly, all attempts to prepare **4a** by Stille cross-coupling reactions proved unsuccessful. The Suzuki reaction of **3a** with *p*-methoxyphenyl-, *p*-tolyl-, and *p*-chlorophenylboronic acid afforded the butenolides **4b**, **4c**, and **4d**, respectively (Table 1). Butenolide **4e** was prepared by reaction of **3a** with 2-thienylboronic acid. The high diastereomeric purity (*E*/*Z* > 98:2) of the exocyclic double bond of **2a** and **3a** was not reduced during the Suzuki reaction, due to the higher thermodynamic stability of the *E*- compared to the *Z*-configured isomer.[4b]

Triflate **3b** was prepared from ethyl-substituted butenolide **2b**. The reaction of **3b** with phenylboronic acid afforded butenolide **4f**. The application of the Stille reaction was again not successful. The reaction of 2-thienylboronic acid with triflate **3c**, prepared from methoxy-

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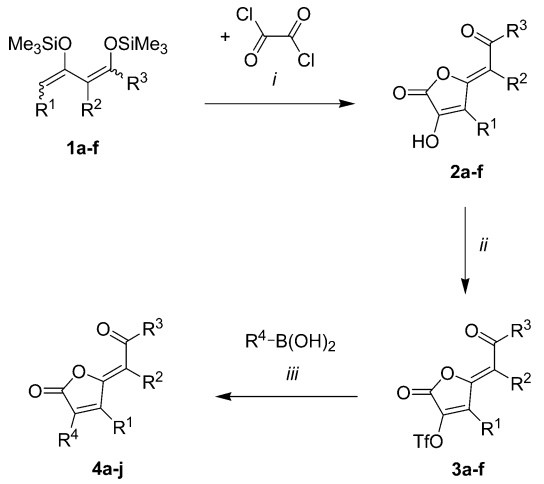
SCHEME 1. Synthesis of butenolides 4[a]



[a] Key: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78 → +20 °C; (ii) Tf_2O, pyridine, −78 → −10 °C; (iii) $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane, reflux.

TABLE 1. Synthesis of Butenolides 4a−j by Suzuki Cross-Coupling Reactions

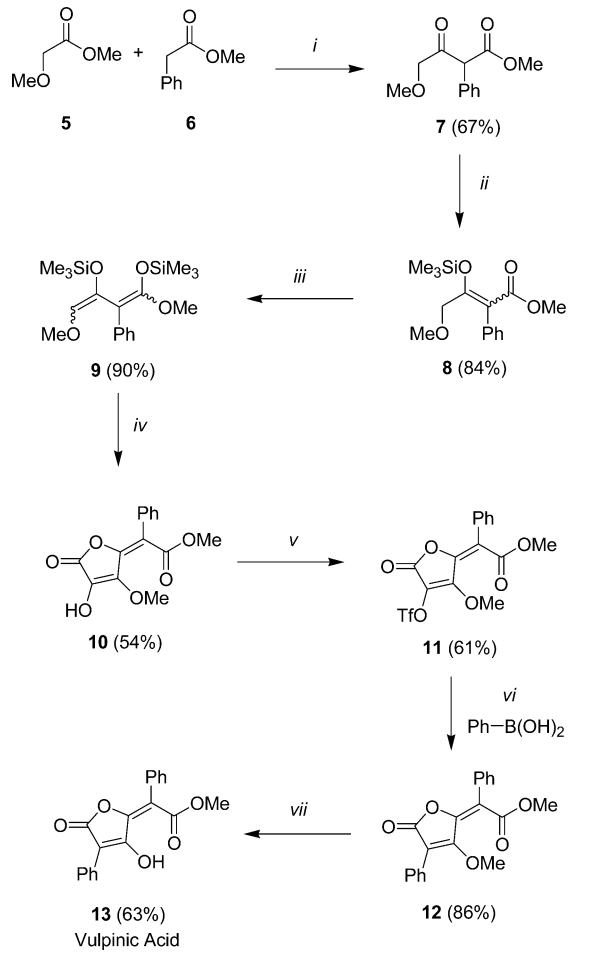
4	R^1	R^2	R^3	R^4	% (3)[a]	% (4)[a]	E/Z[b]
a	H	H	OMe	Ph	52	64	>98:2
b	H	H	OMe	*p*-(MeO)C_6H_4		73	>98:2
c	H	H	OMe	*p*-MeC_6H_4		75	>98:2
d	H	H	OMe	*p*-ClC_6H_4		58	>98:2
e	H	H	OMe	2-thienyl		53	>98:2
f	Et	H	OEt	Ph	76	61	<2:98
g	OMe	H	OMe	2-thienyl	61	54	<2:98
h	$-(CH_2)_3-$		OEt	Ph	87	65	<2:98
i	$-(CH_2)_4-$		OMe	Ph	95	87	<2:98
j	$-(CH_2)_9-$		OEt	Ph	76	70	1:1

[a] Yields of isolated products. [b] Configuration of the exocyclic double bond (by ^1H NMR).

substituted butenolide **2c**,[5] gave butenolide **4g**. The geometry of the *Z*-configured exocyclic double bond, which is thermodynamically favored due to the steric influence of the substituent R^1, was not changed during the synthesis of butenolides **4f** and **4g**. The 5,6-, 5,7-, and 5,12-bicyclic butenolides **2d−f** were prepared by cyclization of the cyclic 1,3-bis-silyl enol ethers **1d−f** with oxalyl chloride.[10] The butenolides were transformed into the corresponding triflates **3d−f**. The Suzuki cross coupling reaction of **3d−f** with phenylboronic acid afforded the bicyclic butenolides **4h−j**. The Suzuki reactions were carried out in 53−87% yields.

The synthesis of vulpinic acid was studied next (Scheme 2). The reaction of esters **5** and **6** gave the *β*-ketoester **7**. 1,3-Bis-silyl enol ether **9** was prepared from **7** in two steps via silyl enol ether **8**. The TMSOTf-catalyzed cyclization of **9** with oxalyl chloride afforded the novel *E*-configured *γ*-alkylidenebutenolide **10** which was transformed into the triflate **11**. The configuration of the exocyclic double bond of **10** is derived from the fact that vulpinic acid (**13**) is isolated in the correct stereochemical form. The Suzuki reaction of **11** with phenylboronic acid afforded **12** in good yield. The configuration of the exocyclic double bond, which was established by NOESY

SCHEME 2. Total Synthesis of Vulpinic Acid (13)[a]



[a] Key: (i) (1) LDA, THF, (2) **5** (0.5 equiv), −78 → +20 °C; (ii) Me_3SiCl, NEt_3, toluene, 20 °C; (iii) (1) LDA, THF, −78 °C, (2) Me_3SiCl, −78 → +20 °C; (iv) oxalyl chloride, Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78 → +20 °C; (v) Tf_2O, pyridine, −78 → −10 °C; (vi) $PhB(OH)_2$, $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane, reflux; (vii) BBr_3 (4 equiv), CH_2Cl_2, 0 °C.

experiments, proved again stable under the conditions of the Suzuki reaction. Treatment of butenolide **12** with BBr_3 chemoselectively afforded vulpinic acid (**13**). The spectroscopic data of **13** are identical to those reported in the literature.[8a]

In summary, we have reported the synthesis of a variety of butenolides by functionalization of the α-hydroxy group of *γ*-alkylidenebutenolides by Suzuki cross-coupling reactions. The natural product vulpinic acid was prepared. Most of the cross coupling reactions reported herein could not be realized by application of our recently published Stille approach. Our current studies are directed toward the application of the methodology reported herein to the synthesis of other butenolide 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 ^1H 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 chroma-

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tography silica gel (60−200 mesh) was used. Melting points are uncorrected. Butenolides **2a**−**f** and **3c** were prepared by published procedures.[4b,5,10]

General Procedure for the Preparation of Triflates (3). To a dichloromethane solution of butenolide **2** (1.0 equiv) were added triflic anhydride (1.2 equiv) and pyridine (2.0 equiv) at −78 °C. The solution was allowed to warm to −10 °C within 4 h. The product was isolated by rapid chromatography (silica gel, dichloromethane) of the reaction mixture.

3a. Starting with butenolide **2a** (1.90 g, 11.17 mmol), triflic anhydride (2.26 mL, 13.41 mmol), and pyridine (1.80 mL, 22.35 mmol), **3a** was isolated as a yellow solid (1.71 g, 51%): mp 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 6.10 (d, 1 H, J = 0.5 Hz, =CH), 8.20 (d, 1 H, J = 0.5 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.5 (CH_3), 106.5 (CH), 118.4 (q, J = 319.1, CF_3), 125.3 (CH), 140.6, 155.0, 159.2, 164.5 (C); IR (KBr) ν 752 (w), 848 (w), 1058 (s), 1137 (m), 1223 (s), 1241 (s), 1440 (s), 1662 (m), 1723 (m), 1819(s) cm^{-1}; MS (EI, 70 eV) *m*/*z* 302 (M^+, 7), 207 (22), 125 (22), 70 (100), 60 (17). Anal. Calcd for $C_8H_5O_7SF_3$ (302.17): C, 31.80; H, 1.66; S, 10.60. Found: C, 32.39; H, 1.72; S, 11.24.

3b. Starting with butenolide **2b** (245 mg, 1.15 mmol), triflic anhydride (0.23 mL, 1.38 mmol), and pyridine (0.18 mL, 1.38 mmol), **3b** was isolated as a yellow oil (299 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7.8 Hz, CH_3), 1.34 (t, 3 H, J = 7.2 Hz, CH_3), 2.61 (q, 2 H, J = 7.8 Hz, CH_2), 4.30 (q, 2 H, J = 7.2 Hz, OCH_2), 5.71 (s, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 14.2 (CH_3), 17.2, 61.6 (CH_2), 102.9 (CH), 118.4 (q, J = 319.3 Hz, CF_3), 135.4, 147.6, 152.2, 159.6, 162.2 (C); IR (KBr) ν 1810 (s), 1726 (m), 1663 (w), 1434 (s), 1238 (s), 1134 (m), 1034 (s), 817 (m), 608 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* 344 (M^+, 2), 299 (44), 211 (23), 183 (44), 137 (40), 97 (20), 70 (100), 29 (61). Anal. Calcd for $C_{11}H_{11}O_7SF_3$ (344.25): C, 38.37; H, 3.22; S, 9.31. Found: C, 38.68; H, 3.46; S, 9.76.

3d. Starting with butenolide **2d** (0.80 g, 3.56 mmol), triflic anhydride (0.72 mL, 4.28 mmol), and pyridine (0.58 mL, 7.13 mmol), **3d** was isolated as a yellow oil (1.11 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, 3 H, J = 7.2 Hz, CH_3), 1.95 (quint, 2 H, J = 6.3 Hz, CH_2), 2.69 (t, 2 H, J = 6.0 Hz, CH_2), 2.81 (t, 2 H, J = 6.6 Hz, CH_2), 4.32 (q, 2 H, J = 7.2 Hz, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, (CH_3), 21.2, 22.0, 24.5, 61.6 (CH_2), 116.6, 118.2 (q, J = 319.1 Hz, CF_3), 131.2, 143.3, 147.5, 160.3, 163.5 (C); IR (KBr) ν 2986 (w), 1803 (s), 1710 (s), 1657 (m), 1436 (s), 1375 (m), 1263 (s), 1137 (s), 1094 (m), 1063 (s), 815 (m), 763 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* 356 (M^+, 9), 311 (16), 195 (99), 148 (73), 121 (35), 84 (64), 49 (84), 32 (100). Anal. Calcd for $C_{12}H_{14}O_7SF_3$ (356.27): C, 40.45; H, 3.11. Found: C, 40.80; H, 3.21.

3e. Starting with butenolide **2e** (0.50 g, 2.23 mmol), triflic anhydride (0.45 mL, 2.67 mmol), and pyridine (0.36 mL, 4.46 mmol), **3e** was isolated as a pink solid (0.76 g, 95%): mp 64−65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85−1.98 (m, 4 H, CH_2), 2.75 (t, 2 H, J = 5.4 Hz, CH_2), 2.83 (t, 2 H, J = 6.3 Hz, CH_2), 3.87 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 25.3, 26.1, 28.5 (CH_2), 52.9 (CH_3), 118.3 (q, J = 319.12, CF_3), 124.8, 134.5, 145.3, 147.1, 159.5, 166.2 (C); IR (KBr) ν 2941 (w), 1788 (s), 1735 (s), 1634 (w), 1440 (s), 1266 (m), 1238 (s), 1137 (s), 1134 (m), 1093 (m), 1050 (s), 860 (m), 618 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* 356 (M^+, 10), 325 (18), 195 (100), 163 (87), 135 (27), 95 (29), 70 (27). Anal. Calcd for $C_{12}H_{11}O_7SF_3$ (356.27): C, 40.45; H, 3.11; S, 9.00. Found: C, 40.68; H, 3.13; S, 8.64.

3f. Starting with butenolide **2f** (212 mg, 0.68 mmol), triflic anhydride (0.14 mL, 0.81 mmol), and pyridine (0.11 mL, 1.36 mmol), **3f** was isolated as a yellow oil (230 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3 H, J = 7.2 Hz, CH_3), 1.43−1.69 (m, 10 H, CH_2), 2.44−2.49 (m, 2 H, CH_2), 2.63−2.69 (m, 2 H, CH_2), 4.35 (q, 2 H, J = 7.2 Hz, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 19.7, 20.2, 23.5, 23.6, 24.4, 25.6, 25.7, 25.9, 26.5, 62.1 (CH_2), 118.4 (q, J = 319.3 Hz, CF_3), 126.0, 135.3, 142.1, 146.2, 159.2, 165.9 (C); MS (EI, 70 eV) *m*/*z* 440 (M^+, 2), 395 (46), 307 (52), 279 (95), 233 (100), 205 (85), 148 (44), 95 (52), 55 (83), 29 (47). Anal. Calcd for $C_{18}H_{23}O_7SF_3$ (440.43): C, 49.08; H, 5.26. Found: C, 49.29; H, 4.95.

General Procedure for the Synthesis of Butenolides (4) by Suzuki Reactions. A dioxane solution of triflate **3** (1.0 equiv), boronic acid (1.3 equiv), K_3PO_4 (1.5 equiv), and $Pd(PPh_3)_4$ (3 mol %) was refluxed for 4 h. A saturated aqueous solution of ammonium chloride was added. The organic and the aqueous layers were separated, and the latter was extracted (3×) with ether. The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/hexane).

4a. Starting with triflate **3a** (125 mg, 0.41 mmol), phenylboronic acid (65 mg, 0.53 mmol), K_3PO_4 (140 mg, 0.65 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), **4a** was isolated as a yellow solid (60 mg, 63%): mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3 H, OCH_3), 5.92 (d, 1 H, J = 0.9 Hz, =CH), 7.26−7.47 (m, 3 H, ArH), 7.90−8.00 (m, 2 H, ArH), 8.47 (d, 1 H, J = 0.9 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.0 (CH_3), 101.2, 127.8 (2C, CH), 128.4 (C), 129.0 (2C), 130.9, 132.1 (CH), 134.8, 159.4, 165.8, 166.9 (C); IR (KBr) ν 1776 (s), 1710 (s), 1648 (s), 1447 (m), 1374 (m), 1258 (s), 1217 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* 230 (M^+, 100), 199 (60), 170 (70), 102 (92), 70 (60), 51 (8). Anal. Calcd for $C_{13}H_{10}O_4$ (230.21): C, 67.82; H, 4.37. Found: C, 67.63; H, 4.70.

4b. Starting with triflate **3a** (131 mg, 0.43 mmol), 4-methoxyphenylboronic acid (71 mg, 0.47 mmol), K_3PO_4 (137 mg, 0.64 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.012 mmol), **4b** was isolated as a yellow solid (82 mg, 73%): mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.87 (s, 1 H, =CH), 6.97 (dd, 2 H, J = 1.9, 7.0 Hz, ArH), 7.98 (dd, 2 H, J = 2.1, 6.9 Hz, ArH), 8.33 (s, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 55.4 (CH_3), 100.3, 114.5 (2C, CH), 121.8 (C), 129.4 (2C), 134.3 (CH), 159.7, 161.8, 166.0, 167.2 (C); IR (KBr) ν 833 (m), 1084 (m), 1144 (m), 1253 (s), 1510 (m), 1605 (s), 1646 (m), 1716 (m), 1781 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* 260 (M^+, 100), 229 (30), 200 (20), 132 (27), 70 (17), 28 (17). Anal. Calcd for $C_{14}H_{12}O_5$ (260.24): C, 64.61; H, 4.65. Found: C, 64.20; H, 4.90.

4c. Starting with triflate **3a** (140 mg, 0.46 mmol), 4-tolylboronic acid (81 mg, 0.59 mmol), K_3PO_4 (157 mg, 0.73 mmol), and $Pd(PPh_3)_4$ (16 mg, 0.013 mmol), **4c** was isolated as a light yellowish solid (85 mg, 75%): mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH), 5.90 (s, 1 H, =CH), 7.27 (d, 2 H, J = 7.2 Hz, ArH), 7.89 (dd, 2 H, J = 1.5 Hz, 6.3 Hz, ArH), 8.42 (s, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 52.0, (CH_3), 100.8 (CH), 125.7 (C), 127.8 (2C), 129.8 (2C), 131.5 (CH), 134.8, 141.6, 159.6, 165.9, 167.1 (C); IR (KBr) ν 3543 (w), 3436 (w), 3086 (w), 2952 (w), 1781 (s), 1650 (s), 1609 (m), 1438 (m), 1253 (s), 1223 (m), 1147 (s), 1080 (s), 1034 (m), 951 (m), 859 (m), 826 (s), 751 (w), 527 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* 244 (M^+, 100), 213 (50), 184 (60), 156 (9), 115 (48), 70 (59). Anal. Calcd for $C_{14}H_{12}O_4$ (244.24): C, 68.84; H, 4.95. Found: C, 68.92; H, 5.03.

4d. Starting with triflate **3a** (120 mg, 0.39 mmol), 4-chlorophenylboronic acid (79 mg, 0.50 mmol), K_3PO_4 (132 mg, 0.62 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.011 mmol), **4d** was isolated as a yellow solid (60 mg, 58%): mp 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 5.95 (s, 1 H, =CH), 7.46 (d, 2 H, J = 8.7 Hz, ArH), 7.95 (d, 2 H, J = 8.7 Hz, ArH), 8.48 (s, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1 (CH_3), 101.7 (CH), 126.8 (C), 129.1 (2C), 129.4, (2C), 132.3 (CH), 133.6, 137.2, 159.1, 165.7, 166.7 (C); IR (KBr) ν 3089 (w), 2952 (w), 1800 (s), 1777 (s), 1722 (s), 1650 (s), 1598 (m), 1434 (m), 1380 (m), 1254 (s), 1143 (s), 1085 (s), 959 (m), 843 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* 264 (M^+, 100), 233 (58), 204 (38), 193 (7), 148 (10), 136 (59), 70 (68), 28 (30). Anal. Calcd for $C_{13}H_9O_4Cl$ (260.66): C, 58.99; H, 3.42. Found: C, 58.64; H, 3.67.

4e. Starting with triflate **3a** (128 mg, 0.42 mmol), 2-thiopheneboronic acid (70 mg, 0.54 mmol), K_3PO_4 (143 mg, 0.67 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.012 mmol), **4e** was isolated as a yellow solid (53 mg, 53%): mp 104 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.82 (s, 3 H, OCH_3), 5.91 (s, 1 H, =CH), 7.16 (dd, 1 H, J = 5.1 Hz, 3.9 Hz, =CH), 7.56 (dd, 1 H, J = 0.91 Hz, 5.1 Hz, =CH), 7.91 (dd, 1 H, J = 0.9 Hz, 3.9 Hz =CH), 8.24 (s, 1 H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.0 (CH_3), 101.2, 128.1, 128.6 (CH), 129.7 (C), 130.5, 130.7 (CH), 131.0, 159.8, 165.8, 166.3 (C); IR (KBr) ν 3190 (w), 2952 (w), 1795 (s), 1781 (s), 1706 (s), 1643 (s), 1586 (m), 1435 (m), 1254 (s), 1139 (s), 1077 (m), 1042 (m), 840 (m), 732 (m) cm^{-1}; MS (EI, 70 eV) m/z 236 (M^+, 29), 219 (22), 205 (15), 130 (80), 107 (18), 88 (25), 70 (30), 43 (58), 28 (100). Anal. Calcd for $C_{11}H_8O_4S$ (236.24): C, 55.92; H, 3.41, S 13.57. Found: C, 55.85; H, 3.80, S 13.24.

4f. Starting with triflate **3b** (146 mg, 0.42 mmol), phenylboronic acid (67 mg, 0.55 mmol), K_3PO_4 (143 mg, 0.67 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.012 mmol), **4f** was isolated as a colorless solid (70 mg, 61%): mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7.8 Hz, CH_3), 1.36 (t, 3 H, J = 7.2 Hz, CH_3), 2.66 (q, 2 H, J = 7.8 Hz, CH_2), 4.31 (q, 2 H, J = 7.2 Hz, OCH_2), 5.59 (s, 1 H, =CH), 7.44−7.55 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.2 (CH_3), 18.3, 61.1 (CH_2), 98.2 (CH), 128.4 (C), 128.8 (2C), 128.9(2C), 129.7 (CH), 130.0, 152.4, 156.5, 163.6, 167.2 (C); IR (KBr) ν 2983 (m), 1780 (s), 1716 (s), 1655 (s), 1370 (m), 1297 (m), 1241 (m), 1188 (s), 1150 (s), 1044 (m), 967 (s), 864(w), 702 (m) cm^{-1}; MS (EI, 70 eV) m/z 272 (M^+, 46), 226 (100), 198 (62), 129 (45), 114 (60), 91 (22), 70 (49), 43 (30), 29 (44). Anal. Calcd for $C_{16}H_{16}O_4$ (273.58): C, 70.34; H, 6.36. Found: C, 70.33; H, 6.50.

4g. Starting with triflate **3c** (150 mg, 0.45 mmol), 2-thiopheneboronic acid (75 mg, 0.58 mmol), K_3PO_4 (153 mg, 0.72 mmol), and $Pd(PPh_3)_4$ (16 mg, 0.013 mmol), **4g** was isolated as a yellow solid (65 mg, 54%): mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 5.72 (s, 1 H, =CH), 7.13 (dd, 1 H, J = 5.1 Hz, 3.6 Hz, =CH), 7.51 (dd, 1 H, J = 0.91 Hz, 5.1 Hz, =CH), 7.57 (dd, 1 H, J = 0.9 Hz, 3.6 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 61.2 (CH_3), 97.0 (CH), 106.7(C), 127.4, 129.0, 130.1 (CH), 130.5, 151.5, 160.5, 163.6, 166.0 (C); IR (KBr) ν 3087 (w), 2948 (w), 1782 (s), 1718 (s), 1653 (s), 1627 (m), 1511 (w), 1436 (m), 1365 (m), 1203 (m), 1172 (m), 1124 (m), 1022 (m), 842 (m), 724 (m) cm^{-1}; MS (EI, 70 eV) m/z 266 (M^+, 100), 235 (13), 206 (25), 150 (38), 123 (39), 70 (42), 28 (67). Anal. Calcd for $C_{12}H_{10}O_5S$ (266.27): C, 54.12; H, 3.78, S 12.04. Found: C, 54.59; H, 3.96, S 12.24.

4h. Starting with triflate **3d** (250 mg, 0.70 mmol), phenylboronic acid (111 mg, 0.91 mmol), K_3PO_4 (238 mg, 1.12 mmol), and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol), **4h** was isolated as a light yellow solid (130 mg, 65%): mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3 H, J = 7.2 Hz, CH_3), 1.91 (quint, 2 H, J = 6.3 Hz, CH_2), 2.67 (t, 2 H, J = 6.0 Hz, CH_2), 2.91 (t, 2 H, J = 6.3 Hz, CH_2), 4.34 (q, 2 H, J = 7.2 Hz, OCH_2), 7.40−7.49 (m, 3 H, ArH), 7.63−7.67 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.3, 22.5, 24.6, 61.4 (CH_2) 111.6, 124.6 (C), 128. 7 (2C), 128.7 (2C), 129.2 (CH), 129.3, 148.3, 151.9, 165.0, 168.2 (C); MS (EI, 70 eV) m/z 284 (M^+, 92), 238 (83), 210 (100), 183 (19), 114 (50), 77 (9), 29 (10). Anal. Calcd for $C_{17}H_{16}O_4$ (284.31): C, 71.81; H, 5.67. Found: C, 72.02; H, 5.40.

4i. Starting with triflate **3e** (150 mg, 0.42 mmol), phenylboronic acid (68 mg, 0.54 mmol), K_3PO_4 (143 mg, 0.67 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.012 mmol), **4i** was isolated as a light yellow solid (105 mg, 87%): mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (quint, 2 H, J = 6.0 Hz, CH_2), 1.94 (quint, 2 H, J = 6.0 Hz, CH_2), 2.76 (t, 2 H, J = 6.0 Hz, CH_2), 2.89 (t, 2 H, J = 6.0 Hz, CH_2), 3.88 (s, 3 H, OCH_3), 7.40−7.50 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 26.3, 26.9, 27.0 (CH_2), 52.7 (CH_3), 118.2 (2C, C), 128.6 (2C, CH), 129.1 (C), 129.2, 129.3 (2C, CH), 151.1, 152.1, 167.4, 167.8 (C); IR (KBr) ν 2949 (m), 1763 (s), 1696 (s), 1627 (m), 1440 (m), 1306 (m), 1272 (m), 1220 (w), 1131 (m), 1060 (m), 949 (m), 789 (w), 701 (w) cm^{-1}; MS (EI, 70 eV) m/z 284 (M^+, 44), 252 (79), 224 (100), 196 (18), 168 (15), 128 (12), 114 (28), 91 (10), 59 (6). Anal. Calcd for $C_{17}H_{16}O_4$ (284.31): C, 71.81; H, 5.67. Found: C, 71.69; H, 5.76.

4j. Starting with triflate **3f** (125 mg, 0.28 mmol), phenylboronic acid (45 mg, 0.36 mmol), K_3PO_4 (95 mg, 0.44 mmol), and $Pd(PPh_3)_4$ (11 mg, 0.008 mmol), **4j** was isolated as a colorless solid (73 mg, 70%): mp 149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3 H, J = 7.2 Hz, CH_3), 1.42−1.48 (m, 10 H, CH_2), 1.57−1.65 (m, 2 H, CH_2), 1.68−1.74 (m, 2 H, CH_2), 2.48−2.59 (m, 2 H, CH_2), 2.68−2.71 (m, 2 H, CH_2), 4.36 (q, 2 H, J = 7.2 Hz, OCH_2), 7.38−7.49 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (CH_3), 19.8, 20.4, 24.2, 24.9, 25.0, 25.8, 26.0, 26.1, 28.8, 62.0 (CH_2), 128.9, (2C, CH), 129.3 (C), 129.3 (2C, CH), 129.6 (C), 129.8 (CH), 131.3, 146.6, 150.8, 167.5, 167.7 (C); IR (KBr) ν 2937 (s), 2874 (w), 1761 (s), 1722 (s), 1471 (m), 1309 (m), 1213 (m), 1160 (w), 1130 (w), 1090 (w), 1027 (w), 702 (w) cm^{-1}; MS (EI, 70 eV) m/z 368 (M^+, 27), 322 (21), 294 (34), 277 (25), 212 (22), 115 (36), 91 (18), 55 (23), 28 (100). Anal. Calcd for $C_{23}H_{28}O_4$ (368.47): C, 74.97; H, 7.66. Found: C, 74.51; H, 7.88.

Synthesis of β-Ketoester 7. The reaction was carried out analogously to a known procedure.[7] To a stirred solution of LDA (58.0 mmol) in THF (150 mL) was added methyl phenylacetate (8.10 mL, 57.6 mmol) at −78 °C. After the solution was stirred for 1 h, methyl methoxyacetate (3.00 g, 28.8 mmol) was added. The temperature of the solution was allowed to rise to 20 °C during 12 h. A saturated aqueous solution of NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **7** as a colorless oil (4.58 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.86 (s, 1 H, CH), 4.08 (s, 2 H, CH_2), 7.31−7.36 (m, 5 H, ArH); MS (EI, 70 eV) m/z 222 (M^+, 100). Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.55; H, 6.58.

Synthesis of Silyl Enol Ether 8. The reaction was carried out analogously to a known procedure.[4b] To a stirred benzene solution (10 mL) of **7** (4.50 g) was added triethylamine (4.50 mL, 32.4 mmol). After the solution was stirred for 2 h, trimethylchlorosilane (4.60 mL, 36.4 mmol) was added. After the solution was stirred for 72 h, the solvent was removed in vacuo and to the residue was added hexane (100 mL) to give a suspension. The latter was filtered under argon atmosphere. The filtrate was distilled in vacuo to give **8** as a colorless oil (5.00 g, 84%). The compound was used directly after its preparation: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.08 (s, 9 H, CH_3), 3.26 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2), 7.21−7.39 (m, 5 H, ArH).

Synthesis of Bis-Silyl Enol Ether 9. The reaction was carried out analogously to a known procedure.[4b] To a stirred THF solution (100 mL) of LDA (20.4 mmol, 1.5 equiv) was added **8** (4.00 g, 13.6 mmol) at −78 °C. After the solution was stirred for 1 h, trimethylchlorosilane (2.57 mL, 20.4 mmol) was added. The solution was allowed to warm to room temperature during 12 h with stirring. The solvent was removed in vacuo, and to the residue was added hexane (100 mL) to give a suspension. The latter was filtered under argon atmosphere. The filtrate was distilled in vacuo to give **9** as a colorless oil (4.50 g, 90%): The compound was used directly after its preparation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H, CH_3), 0.31 (s, 9 H, CH_3), 3.41 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 5.63 (s, 1 H, =CH), 7.22−7.35 (m, 5 H, ArH).

Synthesis of Butenolide 10. The reaction was carried out analogously to a known procedure.[4b] To a CH_2Cl_2 solution (120 mL) of oxalyl chloride (0.70 mL, 7.8 mmol) and of 1,3-bis-(trimethylsilyloxy)-1,3-diene **9** (2.20 g, 6.0 mmol) was added a CH_2Cl_2 solution (5 mL) of Me_3SiOTf (0.6 mL, 3.6 mmol) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After the mixture was stirred for 2 h at 20 °C, a saturated aqueous solution of NaCl was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with an aqueous solution of HCl (10%), dried (Na_2SO_4), and filtered. The solvent

of the filtrate was removed in vacuo, and the residue was purified by column chromatography (silica gel, hexane/EtOAc) to give **10** as a yellow solid (900 mg, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.84 (s, 3 H, OCH_3), 4.18 (s, 3 H, OCH_3), 7.31−7.56 (m, 5 H, ArH), 12.93 (s, 1 H, OH); MS (EI, 70 eV) *m*/*z* 276 (M^+, 100). Anal. Calcd for $C_{14}H_{12}O_6$ (276.25): C, 60.87; H, 4.38. Found: C, 60.62; H, 4.52.

Synthesis of Triflate 11. The synthesis was carried out according to the procedure given for the synthesis of triflates **3**. Starting with butenolide **10** (520 mg), triflic anhydride (0.38 mL), and pyridine (0.3 mL), **11** (469 mg, 61%) was isolated as a colorless solid: mp 118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H, OCH_3), 4.30 (s, 3 H, OCH_3), 7.42 (dd, 2 H, J = 5.2 Hz, 2.0 Hz, ArH), 7.58−7.61 (m, 3 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 61.1 (CH_3), 114.2, 118.3 (q, J = 319.9 Hz, CF_3), 120.8 (C) 128.9 (2C), 129.3 (2C, CH), 130.0 (C), 130.2 (CH), 137.1, 155.5, 160.0, 165.6 (C); IR (KBr) ν 2960 (w), 1799 (s), 1736 (s), 1662 (s), 1646 (s), 1426 (s), 1366 (m), 1332 (m), 1203 (s), 1137 (m), 1089 (s), 1048 (s), 803 (m), 625 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* 408 (M^+, 38), 275 (25), 219 (100), 191 (97), 145 (21), 89 (34), 28 (62). Anal. Calcd for $C_{15}H_{11}O_8SF_3$ (408.30): C, 44.12; H, 2.71. Found: C, 44.22; H, 2.88.

Synthesis of Butenolide 12. The synthesis was carried out according to the procedure given for the synthesis of butenolides **4**.

1. Starting with triflate **11** (140 mg, 0.34 mmol), phenylboronic acid (55 mg, 0.44 mmol), K_3PO_4 (116 mg, 0.54 mmol), and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), **12** was isolated as a light yellow solid (100 mg, 86%): mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 7.34−7.69 (m, 10 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.8, 61.3 (CH_3), 108.2, 116.3, 128.3 (C), 128.5 (2C), 128.8 (2C), 129.0, 129.1 (2C), 129.4, 129.9 (2C, CH), 131.0, 141.4, 162.6, 167.0, 167.7 (C); IR (KBr) ν 1775 (s), 1730 (s), 1622 (m), 1494 (w), 1449 (w), 1429 (w), 1368 (m), 1303 (m), 1231 (s), 1159 (m), 1042 (s), 934 (m), 698 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* 336 (M^+, 100), 249 (20), 219 (50), 191 (43), 176 (13), 145 (18), 89 (54), 77 (12). Anal. Calcd for $C_{20}H_{16}O_5$ (336.34): C, 71.42; H, 4.79. Found: C, 71.64; H, 4.83.

Synthesis of Vulpinic Acid (13). To a CH_2Cl_2 solution (20 mL) of **12** (75 mg, 0.22 mmol) was added BBr_3 (0.09 mL, 0.89 mmol) at 0 °C, and the mixture was stirred for 2 h at 0 °C. An aqueous solution of HCl (5%) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc) to give **13** as a light yellow solid (45 mg, 63%). The spectroscopic data of **13** are identical to those reported for vulpinic acid in the literature:[8a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H, OCH_3), 7.25−7.46 (m, 8 H, ArH), 8.11−8.14 (m, 2 H, ArH), 13.76 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.5 (CH_3), 105.2, 115.8 (C), 127.9 (2C), 128.1 (2C), 128.4 (2C), 128.6 (CH), 128.9 (C), 129.9 (2C, CH), 131.9, 154.9, 160.2, 165.9, 171.7 (C); IR (KBr) ν 3435 (m), 2959 (w), 2564 (w), 1771 (s), 1679 (w), 1612 (s), 1438 (s), 1306 (s), 1071 (s), 955 (m), 692 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* 322 (M^+, 29), 290 (85), 234 (15), 145 (80), 89 (100). Anal. Calcd for $C_{19}H_{14}O_5$ (322.31): C, 70.80; H, 4.37. Found: C, 70.35; H, 4.50.

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