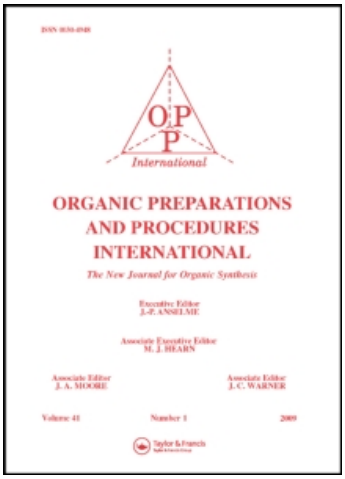

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TETRAHYDROPYRANYLOXY-DIRECTED *ortho* LITHIATION OF AROMATIC SYSTEMS. SYNTHESIS OF *o*-HYDROXYCINNAMATE ESTERS FROM PHENOLS

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OPPI BRIEFS

TETRAHYDROPYRANYLOXY-DIRECTED *ortho* LITHIATION OF AROMATIC SYSTEMS. SYNTHESIS OF *o*-HYDROXYCINNAMATE ESTERS FROM PHENOLS

Submitted by (8/17/96)

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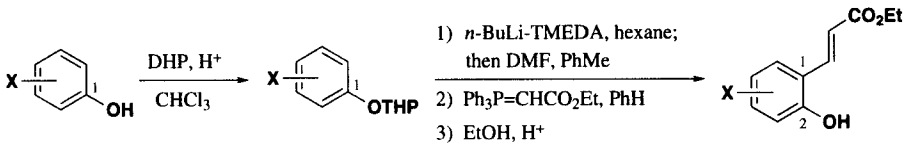
Several recent synthetic projects in our laboratory required access to *o*-hydroxycinnamate esters. While these compounds can be easily prepared from the salicylaldehyde derivatives, surprisingly few substituted salicylaldehydes are commercially available. A review of the literature shows that salicylaldehydes are generally accessible only by low yield processes (Reimer-Tiemann reaction,[1] Duff reaction[2]) or reactions requiring the use of hazardous reagents (Gattermann reaction,[3] lithiation and formylation of methoxymethyl (MOM)-protected phenols[4]). An efficient and safe synthesis of these highly functionalized aromatics is a worthwhile goal since cinnamic acid derivatives are known to exhibit a variety of biological activities.[5,6]

Though heteroatom-facilitated lithiations of aromatic systems have been well-studied,[7] relatively little has appeared on *ortho* metalation of 2-tetrahydropyranyl (THP)-protected phenols.[8] Additionally, studies of competitive metalations in systems bearing two *para*-oriented activating groups are sparse. We now report a simple preparation of *o*-hydroxycinnamate esters involving lithiation, formylation, and olefination of phenol THP ethers and present our results on competitive metalations.

The synthesis, described for 2-methylphenol (**1**), was applied similarly to phenols **2-6**. Conversion to the THP ether was accomplished by treating a solution of **1** in $CHCl_3$ with 2 equivalents of dihydropyran and catalytic *p*-TsOH. Reaction of the ether with 1.1 equivalents of *n*-BuLi-TMEDA in hexanes at 0° for 2.5 hrs followed by cannula transfer of the lithiated species to a solution of 3.5 equivalents of DMF in toluene afforded aldehyde **7**. The aldehyde was carried on directly to the THP-protected *o*-hydroxycinnamate ester by reaction with excess ethyl (triphenylphosphoranylidene)acetate in refluxing benzene. Finally, ethanolysis of the THP ether gave **13** in an overall yield of 50% from **1**.



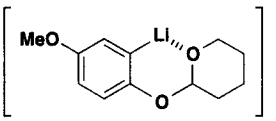
1 X = 2-Me
2 X = 3-Me
3 X = 4-Me
4 X = 2,5-diMe
5 X = 4-Cl
6 X = 4-OMe

7 X = 2-Me
8 X = 3-Me
9 X = 4-Me
10 X = 2,5-diMe
11 X = 4-Cl
12 X = 4-OMe

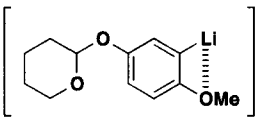
13 X = 3-Me
14a X = 4-Me
14b X = 6-Me
15 X = 5-Me
16 X = 3,6-diMe
17 X = 5-Cl
18a X = 5-OMe
18b X = 5-OH (2-OMe)

Several of the lithiation results merit further comment. In the reaction of 3-methylphenol THP ether **8**, lithiation was possible at C6 or C2. Under the conditions used, reaction occurred at both positions in a C6:C2 ratio of 12.5:1 (GC and isolated).[9] Thus, when the meta ring substituent does not chelate the metal, steric factors strongly favor lithiation at the less hindered site. The finding that **10** also gave an *o*-hydroxycinnamate ester in good yield further demonstrated that steric hindrance does not preclude reaction when only there is only one possible reaction site.

Metalation of **11** and **12** was also of interest since each possessed two substituents capable of stabilizing an adjacent lithiated center. The 4-chlorophenol THP ether **11** gave only the product derived from lithiation *ortho* to the OTHP group.[10] Reaction of 4-methoxyphenol THP ether **12**, however, did undergo competitive metalation, presumably *via* six-centered intermediate **19** *ortho* to OTHP and four-centered intermediate **20** *ortho* to OMe. The product ratio obtained proved to be



19



20

dependent on the temperature at which the lithiation was performed. At 0° (*n*-BuLi-TMEDA hexane, 2.5 hrs; then addition to DMF in PhMe and slow warming to rt, 90% conv.), the 2-hydroxy-5-methoxy product **18a**, from metalation and formylation *ortho* to OTHP, was favored by 9.5:1 (GC and isolated) over the 2-methoxy-5-hydroxy product **18b**. At -23° (8 hrs, 75% conv.) the ratio of **18a**:**18b** improved to 18:1 (GC), and at -42° (12 hrs, 62% conv.) to 40:1 (GC).

The formation of two product regioisomers from **12** stands in contrast to results reported for the MOM-protected 4-methoxyphenol where only one product, derived from lithiation *ortho* to the OMOM group, was observed.[4b] Though molecular models indicate that lithium chelation can occur with the aryloxy group either axial or equatorial on the THP ring, the anomeric effect favors the axial orientation[11] which would allow six-centered chelation to only the ring oxygen. The greater selectivity at low temperature reflects better stabilization of the lithiated center as would be expected with reduced conformational mobility in the THP ring.

In summary, the OTHP group has been used to promote *ortho* lithiation of aromatic systems in a synthesis of *o*-hydroxycinnamate esters. Competitive lithiations are guided by steric factors, but hindered centers can be metalated in good yields when no other site is available. In lithiations of rings bearing two activating groups, OTHP is more effective at promoting lithiations than Cl or OMe but is not as selective as the OMOM group. Finally, although yields and selectivities are lower than those observed with the OMOM director, the current method circumvents the use of highly toxic MOMCl.

EXPERIMENTAL SECTION

DMF was distilled from BaO (28 mm Hg) and TMEDA was distilled (760 mm Hg) from KOH; each was stored over 4 Å molecular sieves. All reactions were run under dry N_2 in oven-dried glassware. Reaction temperatures were controlled using the following cold baths: dry ice-CH_3CN (-42°), dry ice-CCl_4 (-23°), ice-H_2O (0°). Reactions were monitored using one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) or (2) capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-300°. The 10% NaOH, 1 M HCl, and NaCl used in workup procedures refer to aqueous solutions. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech) or (2) flash chromatography[12] on silica gel (Grace, grade 62, 60-200 mesh, quartz column) containing UV-active phosphor (Sylvania no. 2282); band elution, where appropriate, was monitored using a hand-held UV lamp. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively, and are referenced to internal Me_4Si. High resolution mass spectra (EI/DP) were obtained at 70 eV. Elemental analyses were ± 0.3%.

Representative Procedure for the Preparation of Tetrahydropyranyl Ethers: Tetrahydro-2-(2-methylphenoxy)-2*H*-pyran (7).- To a solution of 21.6 g (0.200 mol) of 2-methylphenol (**1**) and 33.6 g (0.400 mol) of dihydropyran in 100 mL of $CHCl_3$ was added 5 mg of *p*-TsOH. The solution became warm and stirring was continued for 2.5 hrs as the reaction returned to rt. The $CHCl_3$ was removed under vacuum and the crude product was diluted with ether, washed with 10% NaOH (3x) and NaCl (1x), dried (Na_2SO_4), and concentrated under vacuum. The resulting oil was vacuum distilled from NaOH pellets (*ca.* 1 g) to give 33.8 g (0.176 mol, 88%) of **7** as a colorless oil, bp. 73-74° (0.5 mm Hg), lit.[13] bp. 110° (6 mm Hg).

IR (thin film): 3062, 3033, 1606, 1597, 1385, 755 cm^{-1}; ^1H NMR: δ 7.12 (t, 2 H, *J* = 7.3 Hz), 7.06 (d, 1 H, *J* = 8.0 Hz), 6.88 (t, 1 H, *J* = 7.3 Hz), 5.41 (t, 1 H, *J* = 2.9 Hz), 3.89 (td, 1 H, *J* = 10.4, 2.9 Hz), 3.59 (dt, 1 H, *J* = 10.4, 4.1 Hz), 2.26 (s, 3 H), 2.10 (m, 1 H), 1.88 (m, 2 H), 1.74-1.52 (complex, 3 H); ^{13}C NMR: δ 155.0, 130.6, 127.2, 126.7, 121.1, 114.0, 96.0, 61.9, 30.5, 25.3, 18.9, 16.2; HRMS: *m/e* Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1152.

Tetrahydro-2-(3-methylphenoxy)-2*H*-pyran (8): 34.3 g (0.179 mol, 90%); bp. 74-75° (0.5 mm Hg); IR (thin film): 3040, 1612, 1590, 1502, 1370, 777, 696 cm^{-1}; ^1H NMR: δ 7.14 (t, 1 H, *J* = 7.6 Hz), 6.87 (s, 1 H), 6.86 (d, 1 H, *J* = 7.6 Hz), 6.78 (d, 1 H, *J* = 7.6 Hz), 5.39 (t, 1 H, *J* = 2.9 Hz), 3.91 (td, 1 H, *J* = 10.4, 2.9 Hz), 3.59 (dt, 1 H, *J* = 10.4, 4.1 Hz), 2.31 (s, 3 H), 2.00 (m, 1 H), 1.84 (m, 2 H), 1.71-1.53 (complex, 3 H); ^{13}C NMR: δ 157.0, 139.3, 129.0, 122.3, 117.1, 113.3, 96.1, 61.9, 30.3, 25.2,

21.4, 18.7; HRMS: *m/e* Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1145.

Tetrahydro-2-(4-methylphenoxy)-2*H*-pyran (9): 34.5 g (0.180 mol, 90%); bp. 76-78° (0.5 mm Hg), lit.[14] bp. 70° (0.3 mm Hg); IR (thin film): 3062, 3033, 1619, 1516, 1392, 821 cm^{-1}; ^1H NMR: δ 7.05 (d, 2 H, *J* = 8.7 Hz), 6.94 (d, 2 H, *J* = 8.7 Hz), 5.35 (t, 1 H, *J* = 3.1 Hz), 3.90 (td, 1 H, *J* = 11.1, 3.1 Hz), 3.57 (dt, 1 H, *J* = 11.1, 4.1 Hz), 2.27 (s, 3 H), 1.99 (m, 1 H), 1.83 (m, 2 H), 1.72-1.54 (complex, 3 H); ^{13}C NMR: δ 154.8, 130.7, 130.0, 116.3, 96.4, 61.8, 30.3, 25.2, 20.4, 18.8; HRMS: *m/e* Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1149.

Tetrahydro-2-(2,5-dimethylphenoxy)-2*H*-pyran (10): 34.6 g (0.168 mol, 84%); bp. 80-82° (0.5 mm Hg); IR (thin film): 3055, 3026, 1619, 1590, 1385 cm^{-1}; ^1H NMR: δ 6.99 (d, 1 H, *J* = 7.6 Hz), 6.89 (s, 1 H), 6.69 (d, 1 H, *J* = 7.6 Hz), 5.40 (t, 1 H, *J* = 3.1 Hz), 3.88 (td, 1 H, *J* = 11.0, 3.1 Hz), 3.59 (dt, 1 H, *J* = 11.0, 4.0 Hz), 2.29 (s, 3 H), 2.21 (s, 3 H), 2.01 (m, 1 H), 1.86 (m, 2 H), 1.73-1.54 (complex, 3 H); ^{13}C NMR: δ 154.8, 136.4, 130.2, 123.9, 121.8, 114.8, 95.9, 61.8, 30.5, 25.3, 21.3, 18.8, 15.8; HRMS: *m/e* Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1306.

Tetrahydro-2-(4-chlorophenoxy)-2*H*-pyran (11): 36.0 g (0.170 mol, 85%); bp. 88-89° (0.5 mm Hg); mp. 47-48°, lit.[15] mp. 48-49°; IR (thin film): 3089, 3062, 3033, 1597, 1496, 821 cm^{-1}; ^1H NMR: δ 7.21 (d, 2 H, *J* = 9.1 Hz), 6.97 (d, 2 H, *J* = 9.1 Hz), 5.35 (t, 1 H, *J* = 3.2 Hz), 3.85 (tm, 1 H, *J* = 11.3 Hz), 3.57 (dt, 1 H, *J* = 11.3, 4.1 Hz), 1.97 (m, 1 H), 1.83 (m, 2 H), 1.73-1.54 (complex, 3 H); ^{13}C NMR: δ 155.6, 129.1, 126.3, 117.7, 96.4, 61.9, 30.2, 25.0, 18.6; HRMS: *m/e* Calcd for $C_{11}H_{13}{}^{35}ClO_2$: 212.0604. Found: 212.0603.

Tetrahydro-2-(4-methoxyphenoxy)-2*H*-pyran (12): 34.5 g (0.166 mol, 83%); bp. 97-99° (0.5 mm Hg), lit.[15] bp. 120° (1.5 mm Hg); IR (thin film): 3055, 2835, 1597, 1506, 1392, 827 cm^{-1}; ^1H NMR: δ 6.98 (d, 2 H, *J* = 9.2 Hz), 6.81 (d, 2 H, *J* = 9.2 Hz), 5.28 (t, 1 H, *J* = 3.3 Hz), 3.92 (tm, 1 H, *J* = 11.3 Hz), 3.73 (s, 3 H), 3.57 (dt, 1 H, *J* = 11.3, 4.0 Hz), 1.98 (m, 1 H), 1.83 (m, 2 H), 1.71-1.52 (complex, 3 H); ^{13}C NMR: δ 154.4, 151.0, 117.6, 114.3, 97.1, 61.9, 55.4, 30.4, 21.1, 18.8; HRMS: *m/e* Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1099.

Representative Procedure for the Synthesis of *o*-Hydroxycinnamate Esters: Ethyl (*E*)-3-(2-Hydroxy-3-methylphenyl)propenoate (13).- To 16.3 mL of 1.35 M *n*-BuLi in hexanes (22.0 mmol) at 0° was added 2.55 g (3.31 mL, 22.0 mmol) of TMEDA dropwise with stirring. The solution was stirred for 30 min at 0° and a solution of 3.84 g (20 mmol) of tetrahydro-2-(2-methylphenoxy)-2*H*-pyran (**7**) in 3.0 mL of hexanes was added dropwise during 30 min. The reaction was stirred at 0° for 2.5 hrs during which time a white precipitate formed. The slurry was transferred by cannula under N_2 pressure to a 0° solution of 5.12 g (5.42 mL, 70.0 mmol) of DMF in 15 mL of toluene. The reaction was warmed to rt and stirred for 6 hrs, then transferred to a separatory funnel containing 100 mL of ice-cold 1 M HCl, and extracted with ether (2x). The combined ether extracts were washed with NaCl, dried (Na_2SO_4), and concentrated under vacuum.

To the resulting yellow oil was added 100 mL of benzene and 10.0 g (28.7 mmol) of ethyl (triphenylphosphoranylidene)acetate. The solution was heated under reflux for 6 hrs, then cooled, and concentrated to afford a yellow semi-solid mass. The residue was loaded onto a 10-cm x 10-cm plug

of silica gel in a sintered glass frit and 1 L of 15% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate gave the THP-protected *o*-hydroxycinnamate ester as a light yellow oil.

The ester was dissolved in 100 mL of absolute EtOH, 0.5 g of *p*-TsOH was added, and the solution was stirred at rt for 12 hrs. The EtOH was removed under vacuum, ether (*ca.* 25 mL) and silica gel (*ca.* 5 g) were added, and the mixture was concentrated to dryness. The silica gel-product mixture was loaded onto a 10-cm x 5-cm plug of silica gel and 1 L of 20% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate gave the *o*-hydroxycinnamate ester as an off-white solid. The product was triturated with hexanes and filtered to give 2.35 g (0.114 mol, 57%) of **13** as a white powder, mp. 113-114°.

IR (thin film): 3319, 1685, 1634, 1590, 1377 cm^{-1}; ^1H NMR: δ 8.25 (d, 1 H, *J* = 16.1 Hz), 7.36 (d, 1 H, *J* = 7.5 Hz), 7.14 (d, 1 H, *J* = 7.5 Hz), 6.83 (t, 1 H, *J* = 7.5 Hz), 6.70 (s, 1 H), 6.53 (d, 1 H, *J* = 16.1 Hz), 4.27 (q, 2 H, *J* = 7.1 Hz), 2.32 (s, 3 H), 1.34 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 168.4, 153.8, 141.0, 132.8, 126.0, 124.3, 121.6, 120.2, 117.6, 60.6, 16.0, 14.3; HRMS: *m/e* Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0944.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.99; H, 6.77

A combination of flash chromatography (eluted with 5% ether in hexanes) and PTLC (10% ether in hexanes) was used to separate **14a** from **14b** and **17a** from **17b** prepared in reactions run at 25°. The products were recrystallized from ether-hexanes.

Ethyl (*E*)-3-(2-Hydroxy-4-methylphenyl)propenoate (14a): 2.14 g (10.4 mmol, 52%); mp. 95-96°; IR (thin film): 3216, 1685, 1624, 1612, 1370 cm^{-1}; ^1H NMR: δ 8.04 (d, 1 H, *J* = 16.2), 7.34 (d, 1 H, *J* = 7.7 Hz), 7.32 (bs, 1 H), 6.70 (d, 1 H, *J* = 7.7 Hz), 6.69 (s, 1 H), 6.63 (d, 1 H, *J* = 16.2 Hz), 4.29 (q, 2 H, *J* = 7.0 Hz), 2.28 (s, 3 H), 1.35 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR: δ 168.8, 155.5, 142.3, 140.8, 129.1, 121.6, 119.0, 117.2, 117.0, 60.6, 21.4, 14.3; HRMS: *m/e* Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0939.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.87; H, 6.79

Ethyl (*E*)-3-(2-Hydroxy-6-methylphenyl)propenoate (14b): 172 mg (0.83 mmol, 4.2%); mp. 149-151°; IR (thin film): 3319, 1677, 1618, 1597, 1370 cm^{-1}; ^1H NMR: δ 7.93 (d, 1 H, *J* = 16.1 Hz), 7.18 (s, 1 H), 7.08 (t, 1 H, *J* = 7.8 Hz), 6.86 (d, 1 H, *J* = 16.1 Hz), 6.75 (d, 2 H, *J* = 8.2 Hz), 4.30 (q, 2 H, *J* = 7.1 Hz), 2.40 (s, 3 H), 1.35 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 169.0, 156.1, 139.8, 139.4, 130.2, 122.6, 121.7, 120.4, 114.1, 60.8, 20.7, 14.3; HRMS: *m/e* Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0941.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.71; H, 6.76

Ethyl (*E*)-3-(2-Hydroxy-5-methylphenyl)propenoate (15): 2.31 g (11.2 mmol, 56%); mp. 87-88°; IR (thin film): 3355, 1692, 1634, 1612, 1516, 1370 cm^{-1}; ^1H NMR: δ 8.03 (d, 1 H, *J* = 16.1 Hz), 7.25 (s, 1 H), 7.04 (bs, 1 H), 7.02 (d, 1 H, *J* = 8.2 Hz), 6.78 (d, 1 H, *J* = 8.2 Hz), 6.63 (d, 1 H, *J* = 16.1 Hz), 4.28 (q, 2 H, *J* = 7.1 Hz), 2.26 (s, 3 H), 1.34 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 168.7, 153.5, 141.0, 132.1, 129.6, 129.3, 121.2, 117.8, 116.3, 60.7, 20.4, 14.3; HRMS: *m/e* Calcd for $C_{12}H_{14}O_3$: 206.0943.

Found: 206.0943.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.77; H, 6.79

Ethyl (*E*)-3-(2-Hydroxy-3,6-dimethylphenyl)propenoate (16): 2.52 g (11.5 mmol, 57%); mp. 77-78°; IR (thin film): 3224, 1678, 1604, 1575, 1377 cm^{-1}; ^1H NMR: δ 7.92 (d, 1 H, *J* = 16.2 Hz), 6.97 (d, 1 H, *J* = 7.6 Hz), 6.67 (d, 1 H, *J* = 7.6 Hz), 6.64 (d, 1 H, 16.2 Hz), 6.22 (s, 1 H), 4.26 (q, 2 H, *J* = 7.1 Hz), 2.34 (s, 3 H), 2.25 (s, 3 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 168.0, 153.5, 139.9, 136.7, 131.4, 122.1, 122.0, 121.6, 120.5, 60.5, 20.5, 15.8, 14.2; HRMS: *m/e* Calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1095.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.83; H, 7.26

Ethyl (*E*)-3-(5-Chloro-2-hydroxyphenyl)propenoate (17): 2.73 g (12.1 mmol, 60%); mp. 107-108°; IR (thin film): 3333, 1692, 1634, 1604, 1502, 1371 cm^{-1}; ^1H NMR: δ 7.99 (d, 1 H, *J* = 16.2 Hz), 7.69 (s, 1 H), 7.42 (d, 1 H, *J* = 2.5 Hz), 7.17 (dd, 1 H, *J* = 8.6, 2.5 Hz), 6.84 (d, 1 H, *J* = 8.6 Hz), 6.64 (d, 1 H, *J* = 16.2 Hz), 4.30 (q, 2 H, *J* = 7.1 Hz), 1.36 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 168.7, 154.3, 139.7, 131.0, 128.3, 125.3, 123.0, 119.0, 117.7, 61.1, 14.2; HRMS: *m/e* Calcd for $C_{11}H_{11}{}^{35}ClO_3$: 226.0397. Found: 226.0396.

Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.41; H, 4.87. Found: C, 58.27; H, 4.84

Ethyl (*E*)-3-(2-Hydroxy-5-methoxyphenyl)propenoate (18a): 2.22 g (10.0 mmol, 50%); mp. 105-106°, lit.[4b] mp. 105-106°; IR (thin film): 3341, 2836, 1678, 1626, 1611, 1597, 1509, 1370 cm^{-1}; ^1H NMR: δ 8.05 (d, 1 H, *J* = 16.2 Hz), 7.20 (s, 1 H, exchanges with D_2O), 6.96 (s, 1 H), 6.81 (s, 2 H), 6.59 (d, 1 H, *J* = 16.2 Hz), 4.28 (q, 2 H, *J* = 7.1 Hz), 3.76 (s, 3 H), 1.34 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 168.6, 153.1, 150.0, 140.8, 121.9, 118.1, 118.0, 117.4, 112.4, 60.8, 55.8, 14.2; HRMS: *m/e* Calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0891.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.80; H, 6.28

Ethyl (*E*)-3-(5-Hydroxy-2-methoxyphenyl)propenoate (18b): 231 mg (1.04 mmol, 5.2%); mp. 87-88°; IR (thin film): 3377, 2843, 1692, 1634, 1590, 1502, 1370 cm^{-1}; ^1H NMR: δ 7.94 (d, 1 H, *J* = 16.2 Hz), 7.03 (d, 1 H, *J* = 2.8 Hz), 6.87 (dd, 1 H, *J* = 8.9, 2.8 Hz), 6.79 (d, 1 H, *J* = 8.9 Hz), 6.48 (d, 1 H, *J* = 16.2 Hz), 4.27 (q, 2 H, *J* = 7.1 Hz), 3.77 (s, 3 H), 1.34 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 167.9, 152.7, 149.6, 140.1, 123.9, 118.8, 118.4, 115.1, 112.6, 60.7, 56.0, 14.3; HRMS: *m/e* Calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0887.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.91; H, 6.29

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