Synthesis of 3-Alkyl- and 3-Chloroalkyl-2-hydroxybenzoates Based on [3+3] Cyclizations of 4-Alkyl- and 4-Chloroalkyl-1,3-bis(trimethylsilyloxy)buta-1,3-dienes

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Abstract: The TiCl₄-mediated [3+3] cyclization of 4-alkyl- and 4-chloroalkyl-1,3-bis(trimethylsilyloxy)buta-1,3-dienes with 3-silylalk-2-en-1-ones afforded 3-alkyl- and 3-chloroalkyl-2-hydroxybenzoates, respectively; the latter containing a remote chloride functionality. The TiCl₄- and TiBr₄-mediated [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-4-chloroalkylbuta-1,3-dienes with 1,1-diacylcyclopropanes afforded salicylates containing two remote halide functionalities.

Key words: arenes, cyclizations, domino reactions, silyl enol ethers

Polyalkylated phenols and salicylates occur in a number of natural products. For example, 3-undecyl-1,2-dihydroxybenzene has been isolated from Schistochila appendiculata. Other natural products include, for example, bhalawanol, 5-chloroflexirubin, belamcandol A, amorfrutin B, and hierridin B. Chan and coworkers developed an elegant approach to salicylates based on cyclization reactions of 1,3-bis(silyl) enol ethers – electroneutral 1,3-dicarbonyl dianion equivalents – with 3-silyloxyalk-2-en-1-ones. In a recent communication, we have reported the synthesis of benzopyrans by sequential [3+3] cyclizations/Williamson reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene with 3-silyloxyalk-2-en-1-ones. We have also reported the synthesis of 3-alkyl-5-(2-chloroethyl)-2-hydroxybenzoates, and of 3-alkyl-2-hydroxybenzoates with 3-chloroalkyl-1,3-bis(trimethylsilyloxy)buta-1,3-dienes.

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(3-chloro-2-methylpropyl)-2-hydroxybenzoate (8b) was prepared by cyclization of 2a with 1,3-bis(trimethylsilyloxy)-7-chloro-6-methylhepta-1,3-diene (7b). 3-(5-Chloropentyl)-2-hydroxybenzoate (8c) and 3-(6-chlorohexyl)-2-hydroxybenzoate (8d) were prepared by cyclization of 2c with 1,3-bis(trimethylsilyloxy)-9-chloronona-1,3-diene (7c) and 1,3-bis(trimethylsilyloxy)-10-chlorodeca-1,3-diene (7d), respectively. The synthesis of 7a, d and 8a, d has been previously reported by us. Comparable yields were obtained for the synthesis of 3-alkyl- and 3-chloroalkyl-2-hydroxybenzoates.

The TiCl4-mediated cyclization of 7a with 1,1-diacetylcyclopropane (9) afforded 5-(2-chloroethyl)-3-(3-chloropropyl)-2-hydroxybenzoate (10a) which was formed by a domino [3+3] cyclization-homo-Michael reaction (Scheme 3). Likewise, the cyclization of 7a with 9, in the presence of TiBr4, afforded 5-(2-bromoethyl)-3-(3-chloropropyl)-2-hydroxybenzoate (10b).

Table 1 Compounds 3 Prepared

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<th>Yield (%)</th>
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a Yield of isolated products.

Table 2 Compounds 5–8 Prepared

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<th>n</th>
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<th>R2</th>
<th>Yield (%) 5</th>
<th>Yield (%) 6</th>
<th>Yield (%) 7</th>
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<td>4</td>
<td>H</td>
<td>H</td>
<td>88</td>
<td>95</td>
<td>96</td>
<td>55</td>
</tr>
</tbody>
</table>

a Yield of isolated products.

Scheme 2 Synthesis of 3-chloroalkyl-2-hydroxybenzoates 8a–d.

Reagents and conditions: i) LDA (2.5 equiv), THF, 0 °C, 1 h, 2. 4a–d, −78 → 20 °C; ii) Me3SiCl, Et3N, toluene, 20 °C, 24 h; iii) TiCl4, CH2Cl2, −78 → 20 °C.

Scheme 3 Synthesis of 2-hydroxybenzoates 10a,b.

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For 1H and 13C NMR, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.
β-Keto Esters 5a–d; General Procedure

A THF solution of LDA (2.5 equiv) was prepared by addition of n-BuLi (15% or 2.5 M solution in n-hexane) to a solution of disopropylamine (2.5 equiv) in THF (2.5 mL/mmol of LDA). To this solution ethyl acetocetate (1.0 equiv) was added at 0 °C. The deep yellow, clear solution was stirred at 0 °C for 1 h. To this mixture, the alkyl halide (1.2 equiv) was added at –78 °C. The temperature was allowed to rise to r.t. within 14 h and the mixture was stirred at r.t. for 2 h. After the addition of aq 10% HCl (200 mL), the mixture was extracted with Et2O (4 × 250 mL). The combined organic layers were dried (Na2SO4) filtered and the solvent removed in vacuo. The residue was purified by chromatography (silica gel, n-hexane–EtOAc) to give 5a–d.

Ethyl 7-Chloro-3-oxoheptanoate (5a)

Starting with ethyl acetocetate (9.1 mL, 71.9 mmol), disopropylamine (25.3 mL, 180 mmol), n-BuLi (72 mL, 180 mmol, 2.5 M in n-hexane) and 1-chloro-3-iodopropane (4a; 18.0 g, 86.3 mmol) in THF (350 mL), product 5a was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 10:1) as a yellowish oil (4.689 g, 95%; 7% of enol-form).

IR (neat): 2985 (m), 2971 (m), 2876 (w), 1744 (s), 1716 (s), 1647 (m), 55%; 8% of enol form).

Ca gel, THF (350 mL), product 5a was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 10:1) as a yellowish oil (4.689 g, 95%; 7% of enol-form).

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The residue was purified by chromatography (silica gel, n-hexane–EtOAc) to give 5a–d.
2 H, CH₂), 2.75 (t, J = 7.2 Hz, 2 H, CH₂), 3.56 (t, J = 6.6 Hz, 2 H, CH₂), 4.12 (dq, J = 2.1, 7.2 Hz, 2 H, OCH₂), 5.09 (s, 1 H, CH). ¹³C NMR (CDCl₃, 150 MHz): δ = 0.3 [Si(CH₃)₃], 14.6 (CH₃), 26.9, 28.8, 28.9, 32.7, 33.2, 38.3 (CH₂), 45.2 (CH₂Cl₂), 59.4 (OCH₂), 99.9 (CH=C), 165.8 (O=CO), 173.4 (O=CO).

7-Chloro-1-ethoxy-6-methyl-3-(trimethylsilyloxy)hept-2-en-1-one (6b)
Starting with 5b (9.95 g, 45.0 mmol), Et₃N (9.36 mL, 67.5 mmol) and TMSCl (8.53 mL, 67.5 mmol) in benzene (200 mL), product 6b was isolated without further purifications as a yellowish oil (12.47 g, 93%).

¹³C NMR (CDCl₃, 150 MHz): δ = 0.3 [Si(CH₃)₃], 14.6 (CH₃), 26.9, 28.8, 28.9, 32.7, 33.2, 38.3 (CH₂), 45.0 (CH₂Cl₂), 59.5 (OCH₂), 99.4 (CH=C), 167.8 (O=CO), 172.5 (O=CO).

1H NMR (CDCl₃, 300 MHz): δ = 0.18 [s, 9 H, Si(CH₃)₃], 0.27 [s, 9 H, Si(CH₃)₃], 1.28 (t, J = 7.2 Hz, 3 H, CH₃), 1.85 (m, 2 H, CH₂), 2.22 (m, 2 H, CH₂), 3.54 (t, J = 7.3 Hz, 2 H, CH₂), 3.75 (q, J = 7.1 Hz, 2 H, OCH₂), 4.83 (t, J = 7.1 Hz, 1 H, CH=CH₂), 5.13 (s, 1 H, CH=CH₂).

1,3-Bis(trimethylsilyloxy)-7-chloro-1-ethoxy-6-methylhepta-1,3-diene (7b)
Starting with 6b (11.87 g, 40.0 mmol), diisopropylamine (8.43 mL, 60.0 mmol), n-BuLi (24 mL, 60.0 mmol, 2.5 M in n-hexane) and TMSCl (7.58 mL, 60.0 mmol) in THF (200 mL), product 7b was isolated without further purification as a yellowish oil (13.50 g, 93%).

9-Chloro-1-ethoxy-3-(trimethylsilyloxy)non-2-en-1-one (6c)
Starting with 9-Chloro-1-ethoxy-3-(trimethylsilyloxy)non-2-en-1-one (6c) (12.47 g, 93%).

1H NMR (CDCl₃, 300 MHz): δ = 0.14 [s, 9 H, Si(CH₃)₃], 0.25 [s, 9 H, Si(CH₃)₃], 0.78 (d, J = 6.5 Hz, 3 H, CH₃), 1.12 (t, J = 7.2 Hz, 3 H, CH₂), 1.21 (m, 1 H, CH), 1.75 (m, 1 H, CH), 2.05 (m, 1 H, CH), 3.19 (m, 1 H, CH), 3.45 (m, 1 H, CH), 4.12 (q, J = 7.1 Hz, 2 H, OCH₂), 4.84 (t, J = 7.1 Hz, 1 H, CH=CH₂), 5.11 (s, 1 H, CH=CH₂).

1H NMR (CDCl₃, 300 MHz): δ = 0.16 [s, 9 H, Si(CH₃)₃], 0.27 [s, 9 H, Si(CH₃)₃], 1.28 (t, J = 7.2 Hz, 3 H, CH₃), 1.85 (m, 2 H, CH₂), 2.22 (m, 2 H, CH₂), 3.54 (t, J = 7.3 Hz, 2 H, CH₂), 3.75 (q, J = 7.1 Hz, 2 H, OCH₂), 4.83 (t, J = 7.1 Hz, 1 H, CH=CH₂), 5.13 (s, 1 H, CH=CH₂).

1,3-Bis(trimethylsilyloxy)-7-chloro-1-ethoxy-6-methylhepta-1,3-diene (7c)
Starting with 6c (2.64 g, 8.5 mmol), diisopropylamine (1.8 mL, 12.7 mmol), n-BuLi (5.1 mL, 12.7 mmol, 2.5 M solution in n-hexane) and TMSCl (1.61 mL, 12.7 mmol) in THF (50 mL), product 7c was isolated without further purification as a yellowish oil (2.8 g, 87%).

1-H NMR (CDCl₃, 300 MHz): δ = 0.17 [s, 9 H, Si(CH₃)₃], 0.21 [s, 9 H, Si(CH₃)₃], 1.24 (t, J = 7.2 Hz, 3 H, CH₃), 1.36 (m, 2 H, CH₂), 1.61–1.82 (m, 4 H, 2 × CH₂), 2.25 (m, 2 H, CH₂), 3.52 (m, 2 H, CH₂), 4.10 (q, J = 7.1 Hz, 2 H, OCH₂), 4.65 (t, J = 7.1 Hz, 1 H, CH=CH₂), 4.91 (s, 1 H, CH=C).

1,3-Bis(trimethylsilyloxy)-10-chloro-1-ethoxydec-1,3-diene (7d)
Starting with 6d (0.963 g, 3.0 mmol), diisopropylamine (0.63 mL, 4.5 mmol), n-BuLi (1.8 mL, 4.5 mmol, 2.5 M in n-hexane) and TMSCl (0.55 mL, 4.5 mmol) in THF (70 mL), product 7d was isolated without further purification as a brownish oil (1.123 g, 96%).

1H NMR (CDCl₃, 300 MHz): δ = 0.18 [s, 9 H, Si(CH₃)₃], 0.25 [s, 9 H, Si(CH₃)₃], 1.26–1.49 (m, 7 H, 2 × CH₂), 1.78 (quint, J = 7.5 Hz, 2 H, CH₂), 3.53 (t, J = 6.8 Hz, 2 H, CH₂), 4.91 (s, 1 H, CH=C), 5.06, 5.11 (d, 1 H, CH=CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 0.8 [3 C, Si(CH₃)₃], 1.9 [3 C, Si(CH₃)₃], 14.3 (CH₂), 25.6, 26.8, 28.7, 29.9, 32.6, 45.1 (CH₂), 59.2 (OCH₂), 98.9, 108.1 (CH=C), 144.6, 156.1 (C).

2-Hydroxybenzoates 3a–k and 8a–d: General Procedure
To a CH₂Cl₂ solution of 2a–e (1.0 equiv) and 1a–h or 7a–d (1.0 equiv), was added dropwise TiCl₄ (1.0 equiv) at –78 °C under argon. The mixture was stirred at –78 °C for 30 min and then allowed to warm to 20 °C during 18 h. A sat. aq solution of NaHCO₃ was added, the organic layer was separated and the aqueous layer was repeatedly extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, n-hexane–EtOAc, 20:1).

Methyl 2-Hydroxy-4,5,6-trimethylbenzoate (3a)
Starting with 1a (1.04 g, 4.0 mmol), 2a (0.744 g, 4.0 mmol) and TiCl₄ (0.76 g, 4.0 mmol) in CH₂Cl₂ (8 mL), product 3a was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a colorless solid (0.395 g, 51%); mp 66 °C.

IR (KBr): 3240 (w), 3002 (w), 2956 (s), 1657 (s), 1209 (s), 1263 (s), 1156 (s), 1065 (s), 805 cm⁻¹ (w).
Synthesis of 3-Alkyl- and 3-Chloroalkyl-2-hydroxybenzoates

1H NMR (CDCl3, 300 MHz): δ = 2.13 (s, 3 H, CH3), 2.27 (s, 3 H, CH3), 2.44 (s, 3 H, CH3), 3.94 (s, 3 H, CH3), 6.69 (s, 1 H, CH), 10.84 (s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 15.2, 18.8, 21.5, 51.9 (CH3), 111.6, 116.2 (CH), 133.2, 137.9, 143.4, 159.3, 159.3 (C), 169.3 (C=O).

UV-Vis (MeCN): \(\lambda_{max} (\log \varepsilon) = 217 (4.26), 257 (3.78), 323 \text{ nm} (3.34)\).


Ethyl 3-Butyl-2-hydroxy-4,5,6-trimethylbenzoate (3e)

Starting with \(1d (1.32 g, 4.0 \text{ mmol}), 2a (0.744 g, 4 \text{ mmol})\) and TiCl4 (0.38 g, 2.0 mmol) in CH2Cl2 (5 mL), product 3e was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.488 g, 46%).

IR (KBr): 2959 (s), 2932 (s), 1654 (s), 1195 (s), 1043 cm\(^{-1}\) (m).

1H NMR (CDCl3, 300 MHz): δ = 0.92 (t, \(J = 7.2 \text{ Hz}, 3 \text{ H, CH3}\)), 1.22–1.29 (m, 8 H, 4 CH2), 1.41 (t, \(J = 7.1 \text{ Hz}, 3 \text{ H, CH3}\)), 2.16 (s, 3 H, CH3), 2.25 (s, 3 H, CH3), 2.42 (s, 3 H, CH3), 2.69 (t, \(J = 7.2 \text{ Hz}, 2 \text{ H, CH2}\)), 4.43 (q, J = 7.2 Hz, 2 H, CH2), 10.69 (s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.1, 14.2, 16.1, 16.9, 19.2 (CH2), 22.8, 26.3, 31.6, 61.3 (CH3), 111.4, 127.1, 134.8, 141.6, 156.9 (C), 172.2 (C=O).

MS (EL, 70 eV): \(m/z\% = 264 (M^+, 6), 203 (24), 176 (24), 74 (31), 29 (100)\).

HRMS (EI, 70 eV): The exact molecular mass C16H24O3 \(m/z = 264.1725 \pm 2 \text{ ppm} [M^+]\).

UV-Vis (MeCN): \(\lambda_{max} (\log \varepsilon) = 217 (4.26), 256 (3.90), 315 \text{ nm} (3.56)\).


Ethyl 3-Hexyl-2-hydroxy-4,5,6-trimethylbenzoate (3f)

Starting with \(1e (1.432 g, 4.0 \text{ mmol}), 2c (1.07 g, 5.0 \text{ mmol})\) and TiCl4 (0.38 g, 2.0 mmol) in CH2Cl2 (5 mL), product 3f was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.472 g, 42%).

IR (KBr): 2958 (s), 2932 (s), 1654 (s), 1195 (s), 1043 cm\(^{-1}\) (m).

1H NMR (CDCl3, 300 MHz): δ = 0.89 (t, \(J = 7.1 \text{ Hz}, 3 \text{ H, CH3}\)), 1.24–1.29 (m, 8 H, 4 CH2), 1.41 (t, \(J = 6.9 \text{ Hz}, 3 \text{ H, CH3}\)), 2.26 (s, 3 H, CH3), 2.48 (s, 3 H, CH3), 2.60 (t, \(J = 7.1 \text{ Hz}, 2 \text{ H, CH2}\)), 4.44 (q, J = 7.1 Hz, 2 H, CH2), 10.71 (s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.1, 14.2, 19.7, 22.7, 23.9 (CH3), 26.2, 28.9, 29.7, 31.8, 61.2 (CH3), 109.5 (C), 124.6 (CH), 127.2, 137.6, 142.7, 161.0, 172.2 (C=O).

MS (EL, 70 eV): \(m/z\% = 278 (M^+, 42), 217 (57), 162 (100), 161 (72), 28 (38)\).

HRMS (EI, 70 eV): The exact molecular mass for C_{17}H_{26}O_{3} m/z = 278.1882 ± 2 ppm [M⁺].

UV-Vis (MeCN): λ_{max} (log ε) = 217 (4.39), 254 (3.98), 317 nm (3.54).

Anal. Calcd for C_{17}H_{26}O_{3} (278.39): C, 73.3; H, 9.41. Found: C, 72.23; H, 9.90.

Ethyl 3-Hexyl-2-hydroxy-4,5,6-trimethylbenzoate (3g)

Starting with 1e (1.49 g, 4.0 mmol), 2a (0.744 g, 4.0 mmol) and TiCl₄ (0.76 g, 4.0 mmol) in CH₂Cl₂ (8 mL), product 3g was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.385 g, 33%).

IR (KBr): 2957 (s), 2928 (s), 1654 (s), 1119 (s), 1045 cm⁻¹ (s).

1H NMR (CDCl₃, 300 MHz): δ = 0.89 (t, J = 6.9 Hz, 3 H, CH₃), 1.26–1.30 (m, 12 H, 6 CH₂), 1.45 (q, J = 7.1 Hz, 2 H, CH₂), 2.48 (s, 3 H, CH₃), 2.62 (t, J = 7.2 Hz, 2 H, CH₂), 4.42 (q, J = 7.1 Hz, 2 H, CH₂), 6.52 (s, 1 H, CH, 11.69 (s, 1 H, OH).

UV-Vis (MeCN): λ_{max} (log ε) = 217 (4.36), 254 (3.95), 317 nm (3.53).

Anal. Calcd for C_{17}H₂₆O₃ (278.39): C, 73.3; H, 9.41. Found: C, 72.23; H, 9.90.

Ethyl 3-Heptyl-2-hydroxy-4,5,6-dimethylbenzoate (3i)

Starting with 1e (1.49 g, 4.0 mmol), 2a (0.744 g, 4.0 mmol) and TiCl₄ (0.76 g, 4.0 mmol) in CH₂Cl₂ (8 mL), product 3i was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.601 g, 39%).

IR (KBr): 2958 (s), 2926 (s), 1654 (s), 1119 (s), 1045 cm⁻¹ (s).

1H NMR (CDCl₃, 300 MHz): δ = 0.92 (t, J = 6.9 Hz, 3 H, CH₃), 1.27–1.31 (m, 12 H, 6 CH₂), 1.45 (q, J = 7.1 Hz, 2 H, CH₂), 2.48 (s, 3 H, CH₃), 2.62 (t, J = 7.2 Hz, 2 H, CH₂), 4.42 (q, J = 7.1 Hz, 2 H, CH₂), 6.52 (s, 1 H, CH, 11.69 (s, 1 H, OH).

UV-Vis (MeCN): λ_{max} (log ε) = 217 (4.38), 257 (3.92), 321 nm (3.54).

Anal. Calcd for C_{19}H₃₀O₃ (314.8): C, 74.54; H, 9.87. Found: C, 73.53; H, 9.77.

Ethyl 2-Hydroxy-4,6-dimethyl-3-octylbenzoate (3j)

Starting with 1f (1.78 g, 5.0 mmol), 2e (0.621 g, 5.0 mmol) and TiCl₄ (0.95 g, 5.0 mmol) in CH₂Cl₂ (8 mL), product 3j was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.601 g, 39%).

IR (KBr): 2958 (s), 2926 (s), 1654 (s), 1119 (s), 1045 cm⁻¹ (s).

1H NMR (CDCl₃, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH₃), 1.26–1.31 (m, 12 H, 6 CH₂), 1.45 (q, J = 7.1 Hz, 2 H, CH₂), 2.48 (s, 3 H, CH₃), 2.62 (t, J = 7.2 Hz, 2 H, CH₂), 4.42 (q, J = 7.1 Hz, 2 H, CH₂), 6.52 (s, 1 H, CH, 11.69 (s, 1 H, OH).

UV-Vis (MeCN): λ_{max} (log ε) = 217 (4.21), 254 (3.75), 319 nm (3.23).

Anal. Calcd for C_{17}H₂₆O₃ (306.44): C, 74.47; H, 9.87. Found: C, 74.13; H, 8.73.

Ethyl 2-Hydroxy-4,6-dimethyl-3-nonylbenzoate (3k)

Starting with 1g (3.53), 2e (0.621 g, 5.0 mmol) and TiCl₄ (0.95 g, 5.0 mmol) in CH₂Cl₂ (8 mL), product 3k was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a yellowish solid (0.601 g, 39%).

IR (KBr): 2958 (s), 2926 (s), 1654 (s), 1119 (s), 1045 cm⁻¹ (s).

1H NMR (CDCl₃, 300 MHz): δ = 0.86 (t, J = 6.9 Hz, 3 H, CH₃), 1.26–1.31 (m, 12 H, 6 CH₂), 1.45 (q, J = 7.1 Hz, 2 H, CH₂), 2.48 (s, 3 H, CH₃), 2.62 (t, J = 7.2 Hz, 2 H, CH₂), 4.42 (q, J = 7.1 Hz, 2 H, CH₂), 6.52 (s, 1 H, CH, 11.69 (s, 1 H, OH).

UV-Vis (MeCN): λ_{max} (log ε) = 217 (4.36), 254 (3.95), 317 nm (3.53).
Ethyl 3-(3-Chloropropyl)-2-hydroxy-4,5,6-trimethylbenzoate (8a)
Starting with 7a (1.23 g, 3.5 mmol) and TiCl4 (0.66 g, 3.5 mmol) in CH2Cl2 (10 mL), product 8a was isolated after chromatography (silica gel, n-hexane–EtOAc, 30:1) as a colorless oil (0.516 g, 52%).

IR (neat): 3426 (m), 2964 (s), 1650 (s), 1599 (m), 1444 (m), 1401 (s), 1373 (s), 1113 (s), 1277 (s), 1200 (s), 1036 (m), 808 cm⁻¹ (m).

1H NMR (CDCl3, 300 MHz): δ = 1.43 (t, J = 7.2 Hz, 3 H, CH₃), 1.99 (quint, J = 6.6 Hz, 2 H, CH₂), 2.25 (s, 3 H, CH₃), 2.29 (s, 3 H, CH₃), 2.87 (t, J = 6.0 Hz, 2 H, CH₂), 3.61 (t, J = 6.7 Hz, 2 H, CH₂), 4.44 (q, J = 7.1 Hz, 2 H, OCH₃), 10.78 (s, 1 H, OH).


MS (EI, 70 eV): m/z = 288 (M⁺ [37Cl], 5), 284 (M⁺ [35Cl], 19), 238 (21), 203 (100), 176 (16), 162 (28), 134 (10), 105 (8), 91 (16), 29 (9).

HRMS (ESI): m/z calculated for C15H18ClO4 [M + 1]: 287.12280 [37Cl]; found: 287.12243 [35Cl].

UV-Vis (MeCN): λmax (log ε) = 216 (4.43), 256 (3.94), 321 nm (3.55).

Anal. Calcd for C15H18ClO4: C, 58.22; H, 6.44. Found: C, 58.20; H, 6.78.

Ethyl 3-(3-Chloro-2-methylpropyl)-2-hydroxy-4,5,6-trimethylbenzoate (8b)
Starting with 7b (1.09 g, 3.0 mmol), 2a (0.56 g, 3.0 mmol) and TiCl4 (0.56 g, 3.0 mmol) in CH2Cl2 (10 mL), product 8b was isolated after chromatography (silica gel, n-hexane–EtOAc, 30:1) as a colorless oil (0.398 g, 44%).

IR (neat): 2965 (m), 2931 (m), 1654 (s), 1603 (m), 1599 (m), 1444 (m), 1401 (s), 1310 (s), 1197 (m), 1092 (m), 1042 (m), 804 cm⁻¹ (m).

1H NMR (CDCl3, 300 MHz): δ = 1.06 (d, J = 6.7 Hz, 3 H, CH₃), 1.42 (t, J = 7.1 Hz, 3 H, CH₃), 2.11–2.14 (m, 1 H, CH), 2.16 (s, 3 H, CH₃), 2.16 (s, 3 H, CH₃), 2.44 (t, 3 H, CH₃), 2.69 (dq, J = 24, 7.1 Hz, 2 H, CH₂), 3.49 (m, J = 5.5 Hz, 2 H, CH₂Cl), 4.43 (q, J = 7.1 Hz, 2 H, OCH₃), 10.77 (s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.6, 16.6, 17.8, 18.3, 19.7 (CH₃), 31.4 (CH₄), 51.8, 61.9 (CH₃), 111.4, 124.2, 127.3, 135.6, 142.2, 157.4, 172.1 (C=O).

MS (EI, 70 eV): m/z = 314 (M⁺ [37Cl], 10), 312 (M⁺ [35Cl], 34), 266 (29), 251 (24), 231 (23), 189 (11), 162 (100), 161 (75), 134 (18), 91 (17), 79 (18), 41 (20), 29 (18).

UV-Vis (MeCN): λmax (log ε) = 216 (4.44), 254 (4.01), 317 nm (3.59).


Ethyl 3-(3-Chloropropyl)-2-hydroxy-4,5,6-trimethylbenzoate (8c)
Starting with 7c (1.10 g, 3.0 mmol), 2b (0.56 g, 3.0 mmol) and TiCl4 (0.56 g, 3.0 mmol) in CH2Cl2 (10 mL), product 8c was isolated after chromatography (silica gel, n-hexane–EtOAc, 30:1) as a yellowish solid (0.441 g, 50%).

IR (KBr): 3428 (br), 2938 (m), 1852 (s), 1616 (m), 1448 (m), 1394 (m), 1267 (s), 1177 (m), 1048 (w), 811 cm⁻¹ (w).

1H NMR (CDCl3, 300 MHz): δ = 1.41 (t, J = 7.1 Hz, 3 H, CH₃), 1.51–1.54 (m, 4 H, 2 × CH₂), 1.80–1.84 (m, 2 H, CH₂), 2.26 (s, 3 H, CH₃), 2.48 (s, 3 H, CH₃), 2.61–2.65 (m, 2 H, CH₂), 3.54 (t, J = 7.2 Hz, 2 H, CH₂), 4.42 (q, J = 7.1 Hz, 2 H, OCH₃), 6.53 (s, 1 H, CH), 11.72 (s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.2, 19.8, 23.9 (CH₃), 25.9, 27.1, 28.1, 32.5, 45.1, 61.3 (CH₃), 109.7 (C), 124.7 (CH), 126.7, 137.9, 142.8, 161.0, 172.3 (C=O).

MS (EI, 70 eV): m/z = 300 (M⁺ [37Cl], 3), 298 (M⁺ [35Cl], 37), 252 (28), 217 (69), 162 (100), 161 (84), 91 (9), 74 (74), 29 (50).

HRMS (ESI): m/z calculated for C15H17ClO3 [M + 1]: 300.13845 [37Cl]; found: 300.13568 [37Cl], 298.14097 [35Cl].

UV-Vis (MeCN): λmax (log ε) = 216 (4.48), 254 (4.06), 316 nm (3.65).

Anal. Calcd for C15H17ClO3: C, 64.31; H, 7.75. Found: C, 64.62; H, 8.04.
HRMS (ESI): *m/z* calcd for C_{10}H_{12}Cl_{2}O_{3} ([M + 1]^+): 333.10242 [2 × 35Cl]. Found: 333.10146 [2 × 35Cl].

UV-Vis (MeCN): $\lambda_{\text{max}}$ (log ε) = 219 (4.50), 256 (3.92), 318 nm (3.55).

Ethyl 3-(2-Bromomethyl)-5-(3-chloropropyl)-6-hydroxy-2,4-dimethylbenzoate (10b)

Starting with 7a (1.58 g, 4.5 mmol), 1,1-diacetylcyclopropane (0.38 g, 3.0 mmol) and TiBr$_4$ (2.21 g, 6.0 mmol) in CH$_2$Cl$_2$ (200 mL), product 10b was isolated after chromatography (silica gel, n-hexane–EtOAc, 20:1) as a colorless solid (0.397 g, 35%).

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