One-Pot Synthesis of 6-(Pyridyl)salicylates by Formal [3+3] Cyclizations of 1,3-Bis(silyl enol ethers) with 3-Pyridyl-3-silyloxy-2-en-1-ones

Mirza A. Yawer,[a] Abdolmajid Riahi,[a,b] Muhammad Adeel,[a] Ibrar Hussain,[a] Christine Fischer,[b] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany

[b] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert Einstein Str. 29a, 18059 Rostock, Germany

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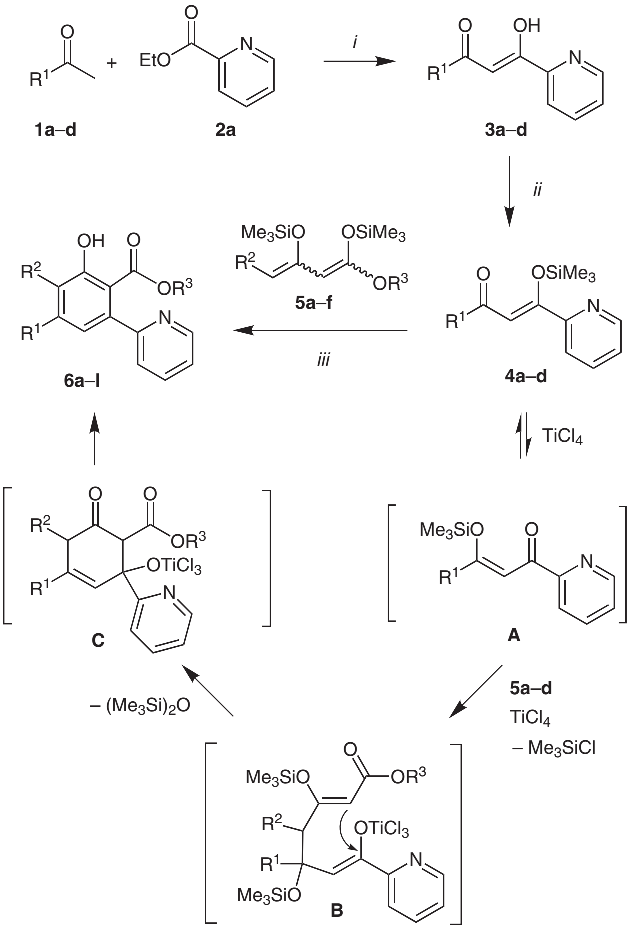
Abstract: 6-(Pyridyl)salicylates were regioselectively prepared by formal [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-(pyridyl)-3-silyloxy-2-en-1-ones. These reactions represent what are, to the best of our knowledge, the first [3+3] cyclizations of 1,3-bis(silyl enol ethers) with heterocyclic substrates.

Key words: cyclizations, heterocycles, regioselectivity, pyridines, silyl enol ethers

Pyridines are of considerable pharmacological relevance and occur in a variety of natural products.[1,2] (Pyrid-2-yl)arenes are present in natural 4-azafluorenones (e.g., kinabaline, darienine, and onychine), which exhibit a strong antimicrobial activity.[3] In addition, they are present in natural products containing the 1,6-diazabenzo[*de*]anthracen-7-one moiety, such as sampangin or eupomatidine.[4] The latter were shown to induce apoptosis and are active against human leukemia HL-60 cells.[4] Hetaryl-substituted arenes are available, for example, by palladium(0)-catalyzed cross-coupling reactions.[5] Despite their great synthetic utility, the scope of all these methods is limited by the availability of the starting materials. In fact, the synthesis of more complex aryl halides or triflates by regioselective functionalization of arenes is often rather difficult. In addition, transition metal catalyzed reactions of sterically encumbered substrates often proceed in low yield or not at all. Some years ago, Chan and co-workers presented[6] an elegant approach to salicylates by cyclization of 1,3-bis(silyl enol ethers)[7] with 3-(silyloxy)alk-2-en-1-ones. Recently, we described the application of this method to the synthesis of a variety of functionalized arenes.[8] Herein, we report a new synthesis of functionalized 3-(pyrid-2-yl)phenols based on formal [3+3] cyclizations of 1,3-bis(silyl enol ethers). These reactions represent what are, to the best of our knowledge, the first [3+3] cyclizations of heterocyclic substrates. From a preparative viewpoint, they offer a convenient and regioselective approach to functionalized and sterically encumbered 6-(pyridyl)salicylates, which are not readily available by other methods.



Scheme 1 Synthesis of **6a–l**. *Reagents and conditions*: (*i*) LDA (1.5 equiv), THF; (*ii*) Et_3N (1.6 equiv), Me_3SiCl (3.6 equiv), C_6H_6, 20 °C, 3 d; (*iii*) $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 → 20 °C.

The 1-(pyrid-2-yl)-1,3-diones **3a–d** were prepared by LDA-mediated reaction of ketones **1a–d** with ethyl (pyrid-2-yl)carboxylate (**2a**). The silylation of **3a–d** afforded the silyl enol ethers **4a–d**. The $TiCl_4$-mediated formal [3+3] cyclization of **4a–d** with 1,3-bis(silyl enol ethers) **5a–f** – prepared from the corresponding 1,3-dicarbonyl compounds in two steps[9] – afforded the 6-(pyrid-2-yl)salicylates **6a–l** (Scheme 1, Table 1). All products were formed with very good regioselectivity. During the optimization of this reaction, the (high) concentration and the temperature played an important role.

The cyclization of **4** with **5** can be explained by $TiCl_4$-mediated isomerization of **4** by shift of the silyl group (intermediate **A**), $TiCl_4$-mediated attack of the terminal carbon atom of **5** onto the carbon located next to substituent R^1 to give intermediate **B** (conjugate addition), cyclization

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Table 1 Compounds **6a**–**l** Prepared

4	5	6	R^1	R^2	R^3	Yield of **6** (%)^a
a	**a**	**a**	Me	H	Me	31
a	**d**	**b**	Me	n-C_6H_{13}	Me	30
a	**e**	**c**	Me	n-C_8H_{17}	Me	30
a	**f**	**d**	Me	Cl	Et	33
b	**a**	**e**	Et	H	Me	40
b	**b**	**f**	Et	Me	Me	44
b	**c**	**g**	Et	Et	Et	38
b	**d**	**h**	Et	n-C_6H_{13}	Me	30
b	**e**	**i**	Et	n-C_8H_{17}	Me	30
c	**a**	**j**	n-Pr	H	Me	33
c	**b**	**k**	n-Pr	Et	Et	31
d	**a**	**l**	i-Pr	H	Me	26

[a] Yields of isolated products.

Table 2 Compounds **9a**–**c** Prepared

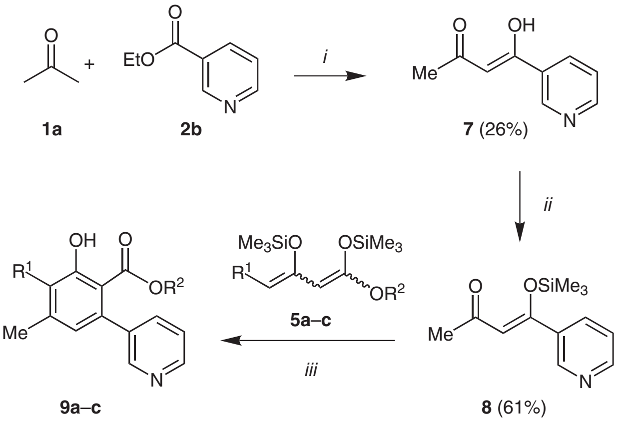
5	9	R^1	R^2	Yield of **9** (%)^a
a	**a**	H	Me	44
b	**b**	Me	Me	38
c	**c**	Et	Et	32

[a] Yields of isolated products.

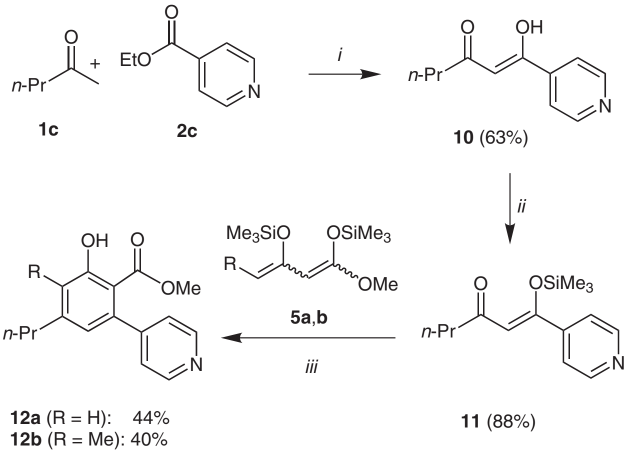
(intermediate **C**), and subsequent aromatization. This mechanism has been previously proposed[6] by Chan et al. for the cyclization of **5a** with 1-phenyl-1-(trimethylsilyloxy)but-1-en-3-one. However, a $TiCl_4$-mediated attack of **5a** onto the carbonyl group of **4a** and subsequent cyclization by an S_N' mechanism with displacement of the Cl_3TiO group cannot be excluded. It is noteworthy, that the lone pairs of the nitrogen atom of the pyridine moiety did not hinder the [3+3] cyclization to proceed.

The NaH-mediated reaction of acetone (**1a**) with ethyl nicotinate (**2b**) afforded 1-(pyrid-3-yl)-1,3-dione **7**. The silylation of **7** afforded the silyl enol ether **8**. The $TiCl_4$-mediated formal [3+3] cyclization of **8** with 1,3-bis(silyl enol ethers) **5a**–**c** afforded the 6-(pyrid-3-yl)salicylates **9a**–**c** (Scheme 2, Table 2).

The 1-(pyrid-4-yl)-1,3-dione **10** was prepared by LDA-mediated reaction of pentan-2-one (**1c**) with ethyl (pyrid-4-yl)carboxylate (**2c**). The silylation of **10** gave the silyl enol ether **11**. The $TiCl_4$-mediated cyclization of **11** with 1,3-bis(silyl enol ethers) **5a**,**b** afforded the 6-(pyrid-4-yl)salicylates **12a**,**b** (Scheme 3).



Scheme 2 Synthesis of **9a**–**c**. *Reagents and conditions*: (*i*) NaH (4.0 equiv), ethyl nicotinate (1.0 equiv), acetone (2.0 equiv), Et_2O, reflux, 2 h; (*ii*) Et_3N (1.6 equiv), Me_3SiCl (3.6 equiv), C_6H_6, 20 °C, 3 d; (*iii*) $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 → 20 °C.



Scheme 3 Synthesis of **12a**,**b** *Reagents and conditions*: (*i*) LDA (1.5 equiv), THF; (*ii*) Et_3N (1.6 equiv), Me_3SiCl (3.6 equiv), C_6H_6, 20 °C, 3 d; (*iii*) $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 → 20 °C.

In conclusion, a variety of 6-(pyridyl)salicylates were regioselectively prepared by formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3-pyridyl-3-silyloxy-2-en-1-ones. These reactions represent what are, to the best of our knowledge, the first [3+3] cyclizations of 1,3-bis(silyl enol ethers) with heterocyclic substrates.

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected. Compounds **1a**–**d** and **2a**–**c** are commercially available.

1,3-Dicarbonyl Compounds 3a–d and 10; General Procedure

To a stirred solution of LDA (75.0 mmol) in THF (1.2 mL/1.0 mmol of LDA) was added ketone **1** (50.0 mmol) at –78 °C. After stirring the solution for 1 h, compound **2** or **8** (60.0 mmol) was added. The temperature of the solution was allowed to rise to 20 °C over 12 h. Aq sat. NH_4Cl (100 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane–EtOAc, 30:1 → 20:1) to give **3**.

1-Hydroxy-1-(2-pyridyl)but-1-en-3-one (3a)

Starting from LDA (1.5 equiv) in THF (62 mL), acetone (3.7 mL, 50.0 mmol), and **2a** (8.0 mL, 60.0 mmol), **3a** was isolated as a yellowish solid (8.53 g, 64%); mp 48–50 °C.

IR (KBr): 3452 (s), 3117 (w), 3068 (w), 2916 (w), 1611 (s), 1581 (s), 1465 (m), 1431 (s), 1355 (m), 1288 (s), 1247 (m), 1185 (m), 1159 (w), 1080 (m), 1043 (w), 991 (s), 848 (m), 788 (s), 747 (m), 621 (m), 551 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 6.70 (s, 1 H, CH), 7.24–7.28 (m, 1 H, ArH), 7.65–7.71 (m, 1 H, ArH), 7.91 (d, ^3J = 7.8 Hz, 1 H, ArH), 8.51 (m, 1 H, ArH), 15.58 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 97.5 (CH), 122.3, 126.5, 127.7, 137.2 (CH_{Ar}), 150.9 (C_{Ar}), 181.2 (COH), 195.1 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 163 (M^+, 34), 148 (84), 134 (6), 121 (35), 106 (63), 85 (15), 78(100), 43(32).

HRMS (EI): *m*/*z* calcd for $C_9H_9NO_2$: 163.06278; found: 163.063007.

1-Hydroxy-1-(2-pyridyl)pent-1-en-3-one (3b)

Starting from LDA (1.5 equiv) in THF (62 mL), butan-2-one (4.4 mL, 50.0 mmol), and **2a** (8.0 mL, 60.0 mmol), **3b** was isolated as a yellow oil (4.76 g, 54%).

IR (neat): 2976 (w), 2879 (w), 1600 (s), 1577 (s), 1563 (s), 1460 (m), 1311 (m), 1240 (m), 1048 (m), 781 (s), 742 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.4 Hz, 3 H, $CH_2C\mathit{H}_3$), 2.41 (q, ^3J = 7.3 Hz, 2 H, $C\mathit{H}_2CH_3$), 6.73 (s, 1 H, CH), 7.27–7.31 (m, 1 H, ArH), 7.68–7.74 (m, 1 H, ArH), 7.94–7.98 (m, 1 H, ArH), 8.54–8.56 (m, 1 H, ArH), 15.61 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8 ($CH_2\mathit{C}H_3$), 33.0 ($\mathit{C}H_2CH_3$), 96.4 (CH), 122.3, 126.4, 137.2, 149.5 (CH_{Ar}), 152.4 (C_{Ar}), 180.6 (COH), 199.6 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 177 ([M^+], 13), 162 (4), 148 (100), 106 (69), 78 (74), 51 (14).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}NO_2$: 177.07843; found: 177.07890.

1-Hydroxy-1-(2-pyridyl)hex-1-en-3-one (3c)

Starting from LDA (1.5 equiv) in THF (62 mL), pentan-2-one (5.3 mL, 50.0 mmol), and **2a** (8.0 mL, 60.0 mmol), **3c** was isolated as a yellow oil (5.32 g, 56%).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2C\mathit{H}_3$), 1.59–1.67 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 2.35 (t, ^3J = 7.6 Hz, 2 H, $C\mathit{H}_2CH_2CH_3$), 6.73 (s, 1 H, CH), 7.29–7.31 (m, 1 H, ArH), 7.71–7.72 (m, 1 H, ArH), 7.97 (d, ^3J = 8.0 Hz, 1 H, ArH), 8.54 (m, 1 H, ArH), 15.68 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 ($CH_2CH_2\mathit{C}H_3$), 19.3 ($CH_2\mathit{C}H_2CH_3$), 41.6 ($\mathit{C}H_2CH_2CH_3$), 97.0 (CH), 122.3, 126.4, 137.3, 149.5 (CH_{Ar}), 152.7 (C_{Ar}), 181.4 (COH), 198.3 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 191 ([M^+], 10), 163 (14), 148 (100), 121 (21), 106 (77), 93 (14), 78.(83), 51 (15), 43 (14).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}NO_2$: 191.09408; found: 191.09468.

1-Hydroxy-4-methyl-1-(pyrid-2-yl)pent-1-en-3-one (3d)

Starting from LDA (1.5 equiv) in THF (62 mL), 3-methylbutan-2-one (5.3 mL, 50.0 mmol), and **2a** (8.0 mL, 60.0 mmol), **3d** was isolated as a yellowish oil (5.653 g, 54%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 [m, 6 H, $CH(C\mathit{H}_3)_2$], 2.50–2.56 [m, 1 H, $C\mathit{H}(CH_3)_2$], 6.73 (br s, 1 H, CH), 7.23–7.25 (m, 1 H, ArH), 7.64–7.67 (m, 1 H, ArH), 7.92 (m, 1 H, ArH), 8.51 (m, 1 H, ArH), 15.70 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 [$CH(\mathit{C}H_3)_2$], 38.0 [$\mathit{C}H(CH_3)_2$], 95.0 (CH), 122.1, 125.9, 137.1, 149.1 (CH_{Ar}), 152.5 (C_{Ar}), 181.5 (COH), 202.5 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 191 ([M^+], 11), 148 (100), 121 (22), 106 (37), 93 (4), 78 (80), 43 (40).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}NO_2$: 191.09408; found: 191.09466.

1-Hydroxy-1-(pyrid-4-yl)hex-1-en-3-one (10)

Starting from LDA (1.5 equiv) in THF (62 mL), pentan-2-one (5.3 mL, 50.0 mmol), and **2c** (5.3 mL, 35.0 mmol), **10** was isolated as a yellow solid (4.208 g, 63%).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2C\mathit{H}_3$), 1.55–1.64 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 2.33 (t, ^3J = 7.5 Hz, 2 H, $C\mathit{H}_2CH_2CH_3$), 6.13 (s, 1 H, CH), 7.57 (d, ^3J = 6.3 Hz, 2 H, ArH), 8.61 (d, ^3J = 5.3 Hz, 2 H, ArH), 15.06 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3 ($CH_2CH_2\mathit{C}H_3$), 18.4 ($CH_2\mathit{C}H_2CH_3$), 41.3 ($\mathit{C}H_2CH_2CH_3$), 96.8 (CH), 120.1 (2 CH_{Ar}), 141.5 (C_{Ar}), 150.7 (2 CH_{Ar}), 178.2 (COH), 199.6 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 191 ([M^+], 18), 163 (19), 148 (100), 121 (9), 106 (27), 93 (4), 78 (20), 51 (15), 43 (10).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}NO_2$: 191.09408; found: 191.09411.

4-Hydroxy-4-(pyrid-3-yl)but-3-en-2-one (7)

To a stirred suspension of NaH (0.38 g, 15.9 mmol) in anhyd Et_2O (6 mL) at 0 °C, were added ethyl nicotinate (**2b**; 0.60 mL, 4.0 mmol) and acetone (**1a**; 0.59 mL, 8.0 mmol) at r.t. This mixture was refluxed for 2 h, subsequently cooled to r.t., and aq 3 M HCl (100 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane–EtOAc, 30:1 → 20:1) to give **7** as slightly red to yellow solid (0.34 g, 26%).

IR (neat): 2952 (w), 2919 (w), 1926 (w), 1584 (s), 1411 (m), 1371 (s), 1204 (m), 1077 (s), 824 (m), 872 (s), 695 (s), 543 cm^{-1} (w).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 6.13 (s, 1 H, CH), 7.32–7.37 (m, 1 H, ArH), 8.08–8.12 (m, 1 H, ArH), 8.67 (s, 1 H, ArH), 9.01 (s, 1 H, ArH), 15.92 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.0 (CH_3), 97.2 (CH), 123.7, 128.5, 148.4, 152.7 (CH_{Ar}), 134.5 (C_{Ar}), 181.2 (COH), 194.6 (C=O).

GC-MS (EI, 70 eV): *m*/*z* (%) = 163 ([M^+], 67), 162 (100), 148 (97), 106 (66), 104 (9), 85 (25), 79 (26), 78 (53), 69 (18), 65 (10), 51 (29), 50 (13), 43 (33), 39 (11).

HRMS (EI): *m*/*z* calcd for $C_9H_9NO_2$: 163.06278; found: 163.062897.

Silyl Enol Ethers 4, 8, and 11; General Procedure

To a stirred solution of **3** (10.0 mmol) in benzene (2.5 mL/1.0 mmol of **3**) was added Et_3N (16.0 mmol). After stirring the solution for 2 h, Me_3SiCl (36.0 mmol) was added. After stirring the solution for 72 h, the solvent was removed in vacuo, and hexane (25 mL) was added to the residue to give a suspension. The latter was filtered under argon. The filtrate was concentrated in vacuo to give silyl enol ethers **4a**–**d**, **8**, and **11**. Due to the unstable nature of the silyl enol ethers, they were characterized only by NMR spectroscopy.

4-(2-Pyridyl)-4-[(trimethylsilyl)oxy]but-3-en-2-one (4a)

Starting from benzene (38.0 mL), **3a** (2.50 g, 15.3 mmol), Et_3N (6.9 mL, 49.0 mmol), and Me_3SiCl (6.96 mL, 55.1 mmol), **4a** was isolated as a reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.29$ [s, 9 H, $OSi(CH_3)_3$], 2.38 (s, 3 H, CH_3), 7.10 (s, 1 H, CH), 7.52–7.33 (m, 1 H, ArH), 7.70–7.75 (m, 1 H, ArH), 7.99 (d, $^3J = 8.8$ Hz, 1 H, ArH), 8.56 (m, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.74$ [$OSi(CH_3)_3$], 22.4 (CH_3), 103.1 (CH), 121.5, 125.7, 136.4, 148.3 (CH_{Ar}), 155.3 (C_{Ar}), 172.3 (C), 189.3 (C=O).

1-(2-Pyridyl)-1-[(trimethylsilyl)oxy]pent-1-en-3-one (4b)

Starting from benzene (38.0 mL), **3b** (4.73 g, 15.3 mmol), Et_3N (6.1 mL, 43.0 mmol), and Me_3SiCl (10.51 mL, 83.2 mmol), **4b** was isolated as a reddish oil (5.10 g, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.25$ [m, 9 H, $OSi(CH_3)_3$], 1.05–1.08 (m, 3 H, CH_2CH_3), 2.80–2.88 (m, 2 H, CH_2CH_3), 7.07 (s, 1 H, CH), 7.29–7.31 (m, 1 H, ArH), 7.68–7.72 (m, 1 H, ArH), 8.02–8.06 (m, 1 H, ArH), 8.54–8.56 (m, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.12$ [$OSi(CH_3)_3$], 11.1 (CH_2CH_3), 27.7 (CH_2CH_3), 102.0 (CH), 121.7, 125.9, 136.6, 148.5 (CH_{Ar}), 155.6 (C_{Ar}), 177.3 (C), 188.9 (C=O).

1-(2-Pyridyl)-1-[(trimethylsilyl)oxy]hex-1-en-3-one (4c)

Starting from benzene (69.5 mL), **3c** (5.31 g, 27.8 mmol), Et_3N (6.23 mL, 44.5 mmol), and Me_3SiCl (12.6 mL, 100.1 mmol), **4c** was isolated as a reddish oil (6.20 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.24$–0.29 [m, 9 H, $OSi(CH_3)_3$], 0.87–0.95 (m, 3 H, $CH_2CH_2CH_3$), 1.56–1.66 (m, 2 H, $CH_2CH_2CH_3$), 2.34–2.39 (m, 2 H, $CH_2CH_2CH_3$), 7.26 (s, 1 H, CH), 7.32 (m, 1 H, ArH), 7.26–7.36 (m, 1 H, ArH), 7.98–8.05 (m, 1 H, ArH), 8.54–8.58 (m, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.09$ [$OSi(CH_3)_3$], 13.6 ($CH_2CH_2CH_3$), 20.2 ($CH_2CH_2CH_3$), 30.0 ($CH_2CH_2CH_3$), 102.0 (CH), 120.5, 125.8, 136.6, 148.4 (CH_{Ar}), 155.5 (C_{Ar}), 176.2 (C), 188.7 (C=O).

1-(2-Pyridyl)-1-[(trimethylsilyl)oxy]hex-1-en-3-one (4d)

Starting from benzene (38.0 mL), **3d** (5.65 g, 29.5 mmol), Et_3N (6.58 mL, 47.0 mmol), and Me_3SiCl (13.4 mL, 106.2 mmol), **4d** was isolated as a reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.25$ [$OSi(CH_3)_3$], 1.07–1.10 [m, 6 H, $CH(CH_3)_2$], 2.54–2.66 [m, 1 H, $CH(CH_3)_2$], 6.90 (s, 1 H, CH), 7.25–7.30 (m, 1 H, ArH), 7.70–7.72 (m, 1 H, ArH), 7.97–7.98 (m, 1 H, ArH), 8.52 (m, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.3$ [$OSi(CH_3)_3$], 10.9 [$CH(CH_3)_2$], 32.2 [$CH(CH_3)_2$], 103.2 (CH), 127.5, 129.2, 129.8, 133.4 (CH_{Ar}), 147.2 (C_{Ar}), 176.5 (C), 185.9 (C=O).

4-(3-Pyridyl)-4-[(trimethylsilyl)oxy]but-3-en-2-one (8)

Starting from benzene (36.0 mL), **7** (2.01 g, 12.4 mmol), Et_3N (2.75 mL, 19.7 mmol), and Me_3SiCl (2.80 mL, 22.2 mmol), **8** was isolated as a reddish oil (1.77 g, 61%).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.17$ [s, 9 H, $OSi(CH_3)_3$], 2.20 (s, 3 H, CH_3), 6.02 (s, 1 H, CH), 7.13–7.19 (m, 1 H, ArH), 7.90–7.95 (m, 1 H, ArH), 8.50 (d, $^3J = 7.5$ Hz, 1 H, ArH), 8.83 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 1.0$ [$OSi(CH_3)_3$], 21.2 (CH_3), 96.2 (CH), 122.5, 134.2, 148.0, 151.8 (CH_{Ar}), 134.4 (C_{Ar}), 172.2 (COH), 187.6 (C=O).

4-Methyl-1-(2-pyridyl)-1-[(trimethylsilyl)oxy]pent-1-en-3-one (11)

Starting from benzene (65.0 mL), **10** (5.00 g, 26.1 mmol), Et_3N (5.8 mL, 41.8 mmol), and Me_3SiCl (11.9 mL, 94.1 mmol), **11** was isolated as a reddish oil (6.05 g, 88%).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.04$ [m, 9 H, $OSi(CH_3)_3$], 0.70–0.73 (m, 3 H, $CH_2CH_2CH_3$), 1.37–1.44 (m, 2 H, $CH_2CH_2CH_3$), 2.19 (t, $^3J = 7.4$ Hz, 2 H, $CH_2CH_2CH_3$), 5.90 (s, 1 H, CH), 7.36–7.42 (m, 2 H, ArH), 8.46–8.50 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.1$ [$OSi(CH_3)_3$], 13.0 ($CH_2CH_2CH_3$), 19.5 ($CH_2CH_2CH_3$), 35.5 ($CH_2CH_2CH_3$), 102.6 (CH), 120.1 (2 CH_{Ar}), 127.4 (C_{Ar}), 149.5 (2 CH_{Ar}), 176.8 (COH), 187.4 (C=O).

Salicylates 6a–l, 9a–c, and 12a,b; General Procedure

To a CH_2Cl_2 solution of **4** (10.0 mmol, 2 mL/1.0 mmol of **4**) were added **5** (11.0 mmol), and subsequently $TiCl_4$ (11.0 mmol) at –78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added 10% aq HCl (20 mL) and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane–EtOAc) to give **6a–l**, **9a–c**, and **12a**,**b**.

Methyl 2-Hydroxy-4-methyl-6-(pyrid-2-yl)benzoate (6a)

Starting from **4a** (0.47 g, 2.0 mmol), **5a** (0.573 g, 2.2 mmol), and $TiCl_4$ (0.24 mL, 2.2 mmol), **6a** was isolated as a highly viscous reddish oil (0.148 g, 31%).

IR (neat): 3473 (m), 2918 (m), 2849 (m), 1731 (w), 1660 (m), 1605 (m), 1582 (s), 1494 (m), 1455 (m), 1409 (m), 1351 (s), 1294 (s), 1261 (m), 1158 (s), 1090 (m), 1015 (m), 980 (m), 850 (m), 823 (s), 755 (s), 602 cm^{-1} (s).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3 H, CH_3), 3.48 (s, 3 H, OCH_3), 6.67 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 7.29 (m, 1 H, ArH), 7.68 (m, 2 H, ArH), 8.58 (br s, 1 H, ArH), 10.61 (s, 1 H, OH).

^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 20.6$ (CH_3), 50.8 (OCH_3), 108.1 (C_{Ar}), 117.2 (2 C, CH_{Ar}), 122.3 (2 C, CH_{Ar}), 135.4 (2 C, CH_{Ar}), 140.5, 144.2, 159.3, 160.6 (C_{Ar}), 169.6 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 243 ([M$^+$], 41), 211 (69), 182 (100), 154 (23), 127 (9), 91 (8), 77 (11).

HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO_3$: 243.08899; found: 243.089361.

Methyl 3-Hexyl-2-hydroxy-4-methyl-6-(pyrid-2-yl)benzoate (6b)

Starting from **4a** (0.47 g, 2.0 mmol), **5d** (0.756 g, 2.2 mmol), and $TiCl_4$ (0.241mL, 2.2 mmol), **6b** was isolated as a highly viscous reddish oil (0.185 g, 30%).

IR (neat): 2952 (m), 2923 (s), 2854 (m), 1662 (s), 1608 (w), 1587 (m), 1561 (w), 1436 (s), 1391 (m), 1354 (m), 1269 (s), 1224 (s), 1148 (s), 1116 (m), 1049 (w), 991 (w), 863 (w), 810 (w), 784 (s), 745 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (t, $^3J = 7.2$ Hz, 3 H, CH_3), 1.27–1.60 (m, 8 H, CH_2), 2.27 (s, 3 H, CH_3), 2.63 (t, $^3J = 7.8$ Hz, 2 H, CH_2), 3.39 (s, 3 H, OCH_3), 6.65 (s, 1 H, ArH), 7.13–7.25 (m, 2 H, ArH), 7.63 (m, 1 H, ArH), 8.53 (br s, 1 H, ArH), 10.80 (s, 1 H, OH).

^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 19.8 (CH_3), 22.6, 26.3, 28.6, 29.6, 31.7 (CH_2), 51.6 (OCH_3), 109.0 (C_{Ar}), 121.4 (CH_{Ar}), 123.6 (2 CH_{Ar}), 130.0 (C_{Ar}), 135.7 (2 CH_{Ar}), 142.6 (C_{Ar}), 148.4 (CH_{Ar}), 159.3, 160.6 (C_{Ar}), 171.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 327 ([M$^+$], 11), 294 (4), 280 (6), 257 (90), 238 (46), 225 (100), 196 (15), 167 (22).

HRMS (EI): *m/z* calcd for $\mathrm{C_{20}H_{25}NO_3}$: 327.18290; found: 327.182616.

Methyl 2-Hydroxy-4-methyl-3-octyl-6-(pyrid-2-yl)benzoate (6c)

Starting from **4a** (0.47 g, 2.0 mmol), **5e** (0.818 g, 2.2 mmol), and $\mathrm{TiCl_4}$ (0.24 mL, 2.2 mmol), **6c** was isolated as a highly viscous reddish oil (0.195 g, 30%).

IR (neat): 2952 (m), 2921 (s), 2852 (m), 1663 (s), 1608 (w), 1587 (m), 1561 (w), 1436 (s), 1391 (m), 1354 (m), 1272 (s), 1224 (s), 1195 (m), 1148 (s), 1118 (m), 1049 (w), 992 (w), 863 (w), 785 (m), 745 (s), 634 cm^{-1} (m).

^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.81 (t, ^3J = 7.4 Hz, 3 H, $\mathrm{CH_3}$), 1.21–1.45 (m, 12 H, $\mathrm{CH_2}$), 2.27 (s, 3 H, $\mathrm{CH_3}$), 2.63 (t, ^3J = 7.9 Hz, 2 H, $\mathrm{CH_2}$), 3.43 (s, 3 H, $\mathrm{OCH_3}$), 6.65 (s, 1 H, ArH), 7.31 (m, 2 H, ArH), 7.77 (m, 1 H, ArH), 8.59 (br s , 1 H, ArH), 10.94 (s, 1 H, OH).

^{13}C NMR (62 MHz, $\mathrm{CDCl_3}$): δ = 14.0 ($\mathrm{CH_3}$), 19.8 ($\mathrm{CH_3}$), 22.6, 26.3, 28.6, 29.2, 29.5, 30.0, 31.9 ($\mathrm{CH_2}$), 51.9 ($\mathrm{OCH_3}$), 108.8 ($\mathrm{C_{Ar}}$), 123.9 (2 C, $\mathrm{CH_{Ar}}$), 130.9 ($\mathrm{C_{Ar}}$), 137.0 ($\mathrm{C_{Ar}}$), 137.5 (2 C, $\mathrm{CH_{Ar}}$), 142.8 ($\mathrm{C_{Ar}}$), 146.6 ($\mathrm{CH_{Ar}}$), 159.3, 159.8 ($\mathrm{C_{Ar}}$), 170.9 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 355 ([M$^+$], 9), 324 (8), 257 (100), 238 (30), 225 (90), 196 (10), 139 (25), 97 (19).

HRMS (EI): *m/z* calcd for $\mathrm{C_{22}H_{29}NO_3}$: 355.21420; found: 355.214056.

Ethyl 3-Chloro-2-hydroxy-4-methyl-6-(pyrid-2-yl)benzoate (6d)

Starting from **4a** (0.353 g, 1.5 mmol), **5f** (0.508 g, 1.65 mmol), and $\mathrm{TiCl_4}$ (0.18 mL, 1.65 mmol), **6d** was isolated as a highly viscous reddish oil (0.141 g, 33%).

IR (neat): 3058 (w), 2981 (m), 2924 (m), 1723 (m), 1655 (s), 1607 (m), 1584 (m), 1471 (m), 1447 (m), 1430 (m), 1380 (s), 1299 (s), 1269 (s), 1218 (s), 1166 (s), 1012 (s), 880 (m), 800 (s), 756 (s), 614 cm^{-1} (m).

^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): δ = 0.70 (s, ^3J = 7.1 Hz, 3 H, $\mathrm{CH_3}$), 2.37 (s, 3 H, $\mathrm{CH_3}$), 3.89 (q, ^3J = 7.1 Hz, 2 H, $\mathrm{OCH_2}$), 6.74 (s, 1 H, ArH), 7.18–7.24 (m, 2 H, ArH), 7.64 (m, 1 H, ArH), 8.52 (m, 1 H, ArH), 11.41 (s, 1 H, OH).

^{13}C NMR (62 MHz, $\mathrm{CDCl_3}$): δ = 12.1 ($\mathrm{CH_3}$), 19.7 ($\mathrm{CH_3}$), 60.38 ($\mathrm{OCH_2}$), 109.6 ($\mathrm{C_{Ar}}$), 120.9 ($\mathrm{C_{Ar}}$), 121.5 ($\mathrm{CH_{Ar}}$), 122.0 ($\mathrm{CH_{Ar}}$), 122.4 ($\mathrm{CH_{Ar}}$), 134.8 ($\mathrm{CH_{Ar}}$), 139.9 ($\mathrm{C_{Ar}}$), 141.6 ($\mathrm{C_{Ar}}$), 147.6 ($\mathrm{CH_{Ar}}$), 156.3, 158.9 ($\mathrm{C_{Ar}}$), 169.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 293 ([M$^+$], ^{37}Cl, 10), 291 ([M$^+$], ^{35}Cl, 28), 245 (100), 216 (54), 210 (21), 182 (23), 154 (26), 127 (14).

HRMS (EI): *m/z* calcd for $\mathrm{C_{15}H_{14}ClNO_3}$ (M$^+$, ^{35}Cl): 291.06567; found: 291.065867.

Methyl 4-Ethyl-2-hydroxy-6-(pyrid-2-yl)benzoate (6e)

Starting from **4b** (0.425 g, 1.67 mmol), **5a** (0.627 g, 1.82 mmol), and $\mathrm{TiCl_4}$ (0.20 mL, 1.67 mmol), **6e** was isolated as a highly viscous reddish oil (0.154 g, 40%).

IR (neat): 2970 (w), 2930 (w), 1603 (s), 1578 (s), 1422 (s), 1239 (s), 1214 (s), 1158 (s), 1088 (m), 1056 (m), 818 cm^{-1} (m).

^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.17 (t, ^3J = 7.6 Hz, 3 H, $\mathrm{CH_2}\mathit{CH_3}$), 2.60 (q, ^3J = 7.6 Hz, 2 H, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 3.39 (s, 3 H, $\mathrm{OCH_3}$), 6.68 (d, ^4J = 1.7 Hz, 1 H, ArH), 6.83 (d, ^4J = 1.4 Hz, 1 H, ArH), 7.00 (ddd, ^3J = 6.4 Hz, ^3J = 6.0 Hz, ^4J = 1.5 Hz, 1 H, ArH), 7.24 (d, ^3J = 7.8 Hz, 1 H, ArH), 7.61–7.67 (m, 1 H, ArH), 8.53–8.54 (m, 1 H, ArH), 10.58 (s, 1 H, OH).

^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 13.6 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 27.8 ($\mathit{C}\mathrm{H_2CH_3}$), 50.7 ($\mathrm{OCH_3}$), 108.4 ($\mathrm{C_{Ar}}$), 115.6 ($\mathrm{CH_{Ar}}$), 120.6 ($\mathrm{CH_{Ar}}$), 121.9 ($\mathrm{CH_{Ar}}$), 122.0, 134.7 ($\mathrm{CH_{Ar}}$), 142.4 ($\mathrm{C_{Ar}}$), 147.4 ($\mathrm{CH_{Ar}}$), 151.1 ($\mathrm{C_{Ar}}$), 159.4 ($\mathrm{C_{Ar}}$), 160.5 (COH), 169.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 257 ([M$^+$], 32), 225 (61), 211 (8), 197 (11), 182 (100), 154 (10), 127 (8), 84 (9).

HRMS (EI): *m/z* calcd for $\mathrm{C_{15}H_{15}NO_3}$: 257.10464; found: 257.10461.

Methyl 4-Ethyl-2-hydroxy-3-methyl-6-(pyrid-2-yl)benzoate (6f)

Starting from **4b** (0.374 g, 1.5 mmol), **5b** (0.448 g, 1.65 mmol), and $\mathrm{TiCl_4}$ (0.18 mL, 1.65 mmol), **6f** was isolated as a highly viscous reddish oil (0.180, 44%).

IR (neat): 2953 (w), 2870 (w), 1657 (m), 1364 (m), 1378 (m), 1378 (s), 1260 (m), 1195 (s), 1105 (s), 1009 cm^{-1} (m).

^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.12 (t, ^3J = 7.7 Hz, 3 H, $\mathrm{CH_2}\mathit{CH_3}$), 2.18 (s, 3 H, $\mathrm{CH_3}$), 2.60 (d, ^3J = 7.3 Hz, 2 H, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 3.39 (s, 3 H, $\mathrm{OCH_3}$), 6.67 (s, 1 H, ArH), 7.12–7.24 (m, 2 H, ArH), 7.59–7.65 (m, 1 H, ArH), 8.52 (m, 1 H, ArH), 10.80 (s, 1 H, OH).

^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 11.4 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 14.5 ($\mathrm{CH_3}$), 27.4 ($\mathit{C}\mathrm{H_2CH_3}$), 52.1 ($\mathrm{OCH_3}$), 109.2 ($\mathrm{C_{Ar}}$), 121.8, 122.2, 123.4 ($\mathrm{CH_{Ar}}$), 124.7 ($\mathrm{C_{Ar}}$), 136.1 ($\mathrm{CH_{Ar}}$), 140.7 ($\mathrm{C_{Ar}}$), 148.8 ($\mathrm{CH_{Ar}}$), 149.1, 160.0 ($\mathrm{C_{Ar}}$), 161.1 (COH), 171.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 271 ([M$^+$], 35), 239 (100), 224 (23), 211 (20), 196 (20), 182 (10), 167 (17), 154 (7), 84 (7), 78 (5).

HRMS (EI): *m/z* calcd for $\mathrm{C_{16}H_{17}NO_3}$: 271.12029; found: 271.11995.

Ethyl 3,4-Diethyl-2-hydroxy-6-(pyrid-2-yl)benzoate (6g)

Starting from **4b** (0.498 g, 2.0 mmol), **5c** (0.659 g, 2.2 mmol), and $\mathrm{TiCl_4}$ (0.24 mL, 2.2 mmol), **6g** was isolated as a highly viscous reddish oil (0.230 g, 38%).

IR (KBr): 2965 (w), 2873 (w), 1655 (s), 1587 (m), 1392 (m), 1371 (s), 1273 (s), 1183 (s), 1031 (s), 1031 cm^{-1} (m).

^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.83 (t, ^3J = 7.3 Hz, 3 H, $\mathrm{OCH_2}\mathit{CH_3}$), 1.24–1.33 (m, 6 H, $\mathrm{CH_2}\mathit{CH_3}$), 2.73–2.87 (m, 4 H, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 4.05 (q, ^3J = 7.2 Hz, 2 H, $\mathrm{CO_2CH_2}$), 6.81 (s, 1 H, ArH), 7.29–7.33 (m, 1 H, ArH), 7.40 (d, ^3J = 7.8 Hz, 1 H, ArH), 7.74–7.80 (m, 1 H, ArH), 8.66–8.68 (m, 1 H, ArH), 11.20 (s, 1 H, OH).

^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 13.5 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 14.2, 15.5 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 19.4, 26.5 ($\mathit{C}\mathrm{H_2CH_3}$), 61.1 ($\mathrm{CO_2}\mathit{C}\mathrm{H_2}$), 109.5 ($\mathrm{C_{Ar}}$), 121.8, 122.3, 123.4 ($\mathrm{CH_{Ar}}$), 130.8 ($\mathrm{C_{Ar}}$), 136.0 ($\mathrm{CH_{Ar}}$), 140.9 ($\mathrm{C_{Ar}}$), 148.4 ($\mathrm{CH_{Ar}}$), 148.8, 160.2 ($\mathrm{C_{Ar}}$), 161.5 (COH), 171.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 299 ([M$^+$], 44), 253 (100), 238 (70), 224 (25), 210 (13), 167 (14), 117 (8), 78 (5).

HRMS (EI): *m/z* calcd for $\mathrm{C_{18}H_{21}NO_3}$: 299.15160; found: 299.15122.

Methyl 4-Ethyl-3-hexyl-2-hydroxy-6-(pyrid-2-yl)benzoate (6h)

Starting from **4b** (0.498 g, 2.0 mmol), **5d** (0.751 g, 2.2 mmol), and $\mathrm{TiCl_4}$ (0.24 mL, 2.2 mmol), **6h** was isolated as a highly viscous reddish oil (0.150 g, 30%).

IR (neat): 2952 (w), 2852 (w), 1663 (m), 1436 (m), 1397 (m), 1318 (m), 1271 (m), 1195 (s), 1119 (s), 745 cm^{-1} (m).

^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.86 [br t, ^3J = 6.8 Hz, 3 H, $\mathrm{(CH_2)_5}\mathit{CH_3}$], 1.12 (br t, ^3J = 5.5 Hz, 3 H, $\mathrm{CH_2}\mathit{CH_3}$), 1.22–1.28 (m, 8 H, $\mathrm{CH_2}$), 2.64 [t, ^3J = 7.6 Hz, 2 H, $\mathrm{C}\mathit{H_2}\mathrm{(C_5H_{11})}$], 2.68 (q, ^3J = 7.2 Hz, 2 H, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$), 3.44 (s, 3 H, $\mathrm{OCH_3}$), 6.72 (s, 1 H, ArH), 7.17–7.21 (m, 1 H, ArH), 7.28–7.31 (m, 1 H, ArH), 7.65–7.70 (m, 1 H, ArH), 8.56–8.58 (m, 1 H, ArH), 10.86 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 ($C_5H_{11}\mathit{C}H_3$), 15.4 ($CH_2\mathit{C}H_3$), 23.0, 26.3, 26.6, 29.9, 30.1 [$(\mathit{C}H_2)_5CH_3$], 33.1 ($\mathit{C}H_2CH_3$), 52.0 (OCH_3), 109.4 (C_{Ar}), 121.8, 122.4, 123.3 (CH_{Ar}), 129.7 (C_{Ar}), 136.1 (CH_{Ar}), 140.7 (C_{Ar}), 148.7 (CH_{Ar}), 149.6, 160.0 (C_{Ar}), 161.1 (COH), 171.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 341 ([M$^+$], 18), 308 (5), 271 (77), 239 (100), 167 (13), 117 (3), 78 (4), 57 (5), 43 (7).

HRMS (EI): *m/z* calcd for $C_{21}H_{27}NO_3$: 341.19855; found: 341.19815.

Methyl 4-Ethyl-2-hydroxy-3-octyl-6-(pyrid-2-yl)benzoate (6i)
Starting from **4b** (0.498 g, 2.0 mmol), **5e** (0.812 g, 2.2 mmol), and $TiCl_4$ (0.24 mL, 2.2 mmol), **6i** was isolated as a dark highly viscous reddish oil (0.220 g, 30%).

IR (neat): 2953 (m), 2854 (w), 1663 (m), 1436 (m), 1397 (m), 1318 (m), 1270 (m), 1195 (s), 1149 (m), 1010 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.84 (m, 6 H, CH_3), 1.12–1.27 (m, 12 H, CH_2), 2.59–2.65 (m, 4 H, CH_2), 3.39 (s, 3 H, OCH_3), 6.67 (s, 1 H, ArH), 7.13–7.17 (m, 1 H, ArH), 7.23–7.26 (m, 1 H, ArH), 7.61–7.66 (m, 1 H, ArH), 8.51–8.54 (m, 1 H, ArH), 10.82 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 ($C_7H_{13}\mathit{C}H_3$), 15.5 ($CH_2\mathit{C}H_3$), 22.9, 23.1, 26.3, 26.6, 29.9, 30.0, 30.1, 32.1 (CH_2), 52.0 (OCH_3), 109.3 (C_{Ar}), 121.9, 122.4, 123.4 (CH_{Ar}), 129.8 (2 C_{Ar}), 136.2 (CH_{Ar}), 140.7 (C_{Ar}), 148.7 (CH_{Ar}), 160.0 (C_{Ar}), 161.1 (COH), 171.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 369 ([M$^+$], 11), 341 (30), 310 (5), 271 (94), 252 (60), 239 (100), 177 (13), 127 (4), 78 (4).

HRMS (EI): *m/z* calcd for $C_{23}H_{31}NO_3$: 369.22985; found: 369.22968.

Methyl 2-Hydroxy-4-propyl-6-(pyrid-2-yl)benzoate (6j)
Starting from **4c** (0.527 g, 2.0 mmol), **5a** (0.565 g, 2.2 mmol), and $TiCl_4$ (0.24 mL, 2.2 mmol), **6j** was isolated as a highly viscous reddish oil (0.200 g, 33%).

IR (KBr): 3012 (w), 2844 (w), 1662 (s), 1499 (m), 1459 (s), 1378 (s), 1239 (s), 1106 (m), 1074 (m), 1025 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 7.2 Hz, 3 H, $CH_2CH_2C\mathit{H}_3$), 1.55–1.63 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 2.51 (t, ^3J = 7.2 Hz, 2 H, $C\mathit{H}_2CH_2CH_3$), 3.40 (s, 3 H, OCH_3), 6.67 (s, 1 H, ArH), 6.80 (s, 1 H, ArH), 7.14–7.17 (m, 1 H, ArH), 7.24 (d, ^3J = 7.9 Hz, 1 H, ArH), 7.61–7.66 (m, 1 H, ArH), 8.53–8.54 (m, 1 H, ArH), 10.55 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 ($CH_2CH_2\mathit{C}H_3$), 24.1 ($CH_2\mathit{C}H_2CH_3$), 38.3 ($\mathit{C}H_2CH_2CH_3$), 52.1 ($O\mathit{C}H_3$), 109.8 (C_{Ar}), 117.7, 122.1, 123.0, 123.3, 136.1 (CH_{Ar}), 143.6 (C_{Ar}), 148.9 (CH_{Ar}), 150.1, 160.8 (C_{Ar}), 161.1 (COH), 171.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 277 ([M$^+$], 39), 239 (69), 211 (73), 182 (100), 167 (6), 154 (17), 127 (12), 78 (5).

HRMS (EI): *m/z* calcd for $C_{16}H_{17}NO_3$: 271.12029; found: 271.12028.

Ethyl 3-Ethyl-2-hydroxy-4-propyl-6-(pyrid-2-yl)benzoate (6k)
Starting from **4c** (0.527 g, 2.0 mmol), **5b** (0.659 g, 2.2 mmol), and $TiCl_4$ (0.239 mL, 2.2 mmol), **6k** was isolated as a highly viscous reddish oil (0.200 g, 31%).

IR (neat): 2958 (w), 2871 (w), 1658 (m), 1464 (m), 1393 (m), 1371 (m), 1273 (m), 1183 (s), 1110 (s), 1027 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67 (t, ^3J = 7.0 Hz, 3 H, $CH_2CH_2C\mathit{H}_3$), 0.91 (t, ^3J = 7.4 Hz, 3 H, $CH_2C\mathit{H}_3$), 1.10 (t, ^3J = 8.5 Hz, 2 H, $CH_2C\mathit{H}_3$), 1.51–1.59 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 2.53 (t, ^3J = 7.8 Hz, 2 H, $C\mathit{H}_2CH_2CH_3$), 2.67 (q, ^3J = 7.4 Hz, 2 H, $C\mathit{H}_2CH_3$), 3.89 (q, ^3J = 7.2 Hz, 2 H, $OC\mathit{H}_2CH_3$), 6.63 (s, 1 H, ArH), 6.63 (s, 1 H, ArH), 7.17–7.26 (m, 2 H, ArH), 7.60–7.65 (m, 1 H, ArH), 8.52 (m, 1 H, ArH), 11.04 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 ($CH_2CH_2\mathit{C}H_3$), 12.8 ($CH_2\mathit{C}H_3$), 13.2 ($OCH_2\mathit{C}H_3$), 18.1 ($CH_2\mathit{C}H_2CH_3$), 23.1 ($\mathit{C}H_2CH_2CH_3$), 34.2 ($\mathit{C}H_2CH_3$), 59.7 ($O\mathit{C}H_2CH_3$), 108.0 (C_{Ar}), 121.7 (CH_{Ar}), 129.7 (2 CH_{Ar}), 134.7 (C_{Ar}), 145.6 (2 CH_{Ar}), 158.9 (2 C_{Ar}), 160.1 (2 C_{Ar}), 170.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 313 ([M$^+$], 33), 267 (19), 252 (100), 238 (29), 210 (6), 195 (3), 167 (8), 154 (3), 78 (5).

HRMS (EI): *m/z* calcd for $C_{19}H_{23}NO_3$: 313.16725; found: 313.16693.

Methyl 2-Hydroxy-4-isopropyl-6-(pyrid-2-yl)benzoate (6l)
Starting from **4d** (0.527 g, 2.0 mmol), **5a** (0.565 g, 2.2 mmol), and $TiCl_4$ (0.24 mL, 2.2 mmol), **6l** was isolated as a highly viscous reddish oil (0.142 g, 26%).

IR (neat): 3109 (w), 2868 (w), 1666 (m), 1601 (m), 1423 (m), 1353 (m), 1300 (s), 1270 (s), 1160 (s), 1058 (m), 809 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 [d, ^3J = 7.1 Hz, 6 H, $CH(C\mathit{H}_3)_2$], 2.75–2.89 [m, 1 H, $\mathit{C}H(CH_3)_2$], 3.41 (s, 3 H, CO_2CH_3), 6.71 (d, ^4J = 1.3 Hz, 1 H, ArH), 6.86 (d, ^4J = 1.3 Hz, 1 H, ArH), 7.17–7.18 (m, 1 H, ArH), 7.26 (d, ^3J = 7.6 Hz, 1 H, ArH), 7.64 (ddd, ^3J = 7.8 Hz, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, ArH), 8.54 (m, 1 H, ArH), 10.57 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7 [$CH(\mathit{C}H_3)_2$], 34.6 [$C\mathit{H}(CH_3)_2$], 52.1 ($CO_2\mathit{C}H_3$), 109.9 (C_{Ar}), 115.6, 121.1, 122.1, 123.4, 136.2 (CH_{Ar}), 143.7 (C_{Ar}), 148.9 (CH_{Ar}), 156.2, 160.9 (C_{Ar}), 162.0 (COH), 177.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 271 ([M$^+$], 33), 239 (69), 224 (16), 196 (100), 167 (23), 141 (5), 78 (4).

HRMS (EI): *m/z* calcd for $C_{16}H_{17}NO_3$: 271.12029; found: 271.12038.

Methyl 2-Hydroxy-4-methyl-6-(pyrid-3-yl)benzoate (9a)
Starting from **8** (0.353 g, 1.5 mmol), **5b** (0.425 g, 1.65 mmol), and $TiCl_4$ (0.18 mL, 1.65 mmol), **9a** was isolated as a yellow gummy solid (0.160 g, 44%).

IR (neat): 2955 (w), 1658 (w), 1577 (w), 1434 (w), 1352 (w), 1334 (w), 1316 (w), 1261 (w), 1215 (w), 1189 (w), 1092 (w), 994 (w), 842 (w), 705 (w), 613 cm^{-1} (w).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.34 (s, 3 H, OCH_3), 6.50 (s, 1 H, ArH), 6.80 (s, 1 H, ArH), 7.20–7.51 (m, 3 H, ArH), 8.64 (br s, 1 H, ArH), 10.79 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (CH_3), 50.8 (OCH_3), 108.1 (C_{Ar}), 117.0 (3 CH_{Ar}), 123.2 (2 CH_{Ar}), 134.5 (CH_{Ar}), 139.8 (C_{Ar}), 144.4 (2 C_{Ar}), 161.3 (COH), 169.9 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 243 ([M$^+$], 38), 211 (100), 183 (46), 154 (26), 127 (9), 77 (6).

HRMS (EI): *m/z* calcd for $C_{14}H_{13}O_3N$: 243.08899; found: 243.08950.

Methyl 2-Hydroxy-3,4-dimethyl-6-(pyrid-3-yl)benzoate (9b)
Starting from **8** (0.470 g, 2.0 mmol), **5b** (0.598 g, 2.2 mmol), and $TiCl_4$ (0.24 mL, 2.2 mmol), **9b** was isolated as a yellow oil (0.158 g, 38%).

IR (neat): 2952 (w), 2923 (w), 1605 (w), 1656 (s), 1432 (m), 1383 (m), 1271 (s), 1191 (s), 1142 (m), 1094 (m), 919 (w), 832 (m), 768 (w), 615 cm^{-1} (m).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 3.36 (s, 3 H, OCH_3), 6.45 (s, 1 H, ArH), 7.15–7.30 (m, 1 H, ArH), 7.40 (d, ^3J = 8.6 Hz, 1 H, ArH), 8.10–8.30 (m, 2 H, ArH), 11.22 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.6 (CH$_3$), 20.5 (CH$_3$), 51.8 (OCH$_3$), 108.7 (C$_{Ar}$), 124.3 (1 C, 1 CH$_{Ar}$), 125.1 (CH$_{Ar}$), 135.4 (2 C$_{Ar,}$), 137.6 (CH$_{Ar}$), 143.5 (C$_{Ar}$), 147.7 (CH$_{Ar}$), 149.0 (CH$_{Ar}$), 160.4 (COH), 171.1 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 257 ([M$^+$], 44), 225 (100), 197 (17), 182 (45), 168 (28), 154 (16), 115 (8).

HRMS (EI): *m/z* calcd for C$_{15}$H$_{15}$O$_3$N: 257.10464; found: 257.10536.

Ethyl 3-Ethyl-2-hydroxy-4-methyl-6-(pyrid-3-yl)benzoate (9c)

Starting from **8** (0.470 g, 2.0 mmol), **5c** (0.659 g, 2.2 mmol), and TiCl$_4$ (0.239 mL, 2.2 mmol), **9c** was isolated as an orange oil (0.180 g, 32%).

IR (neat): 2917 (w), 1642 (s), 1613 (m), 1378 (s), 1283 (s), 1247 (m), 1227 (s), 1178 (s), 1103 (m), 1010 (m), 809 (s), 722 (s), 618 (m), 526 cm^{-1} (w).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.65 (t, ^3J = 7.5 Hz, 3 H, CH$_2$C*H*$_3$), 1.04 (t, ^3J = 7.5 Hz, 3 H, OCH$_2$C*H*$_3$), 2.22 (s, 3 H, CH$_3$), 2.62 (q, ^3J = 7.5 Hz, 2 H, C*H*$_2$CH$_3$), 3.87 (q, ^3J = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 6.43 (s, 1 H, ArH), 7.15–7.20 (m, 1 H, ArH), 7.41 (d, ^3J = 7.9 Hz, 1 H, ArH), 7.74–9.24 (m, 2 H, ArH), 11.29 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1 (OCH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$), 19.6 (*C*H$_2$CH$_3$), 19.7 (CH$_3$), 61.1 (O*C*H$_2$CH$_3$), 109.1 (C$_{Ar}$), 124.5 (3 CH$_{Ar,}$), 131.0 (2 C$_{Ar,}$), 135.4 (2 CH$_{Ar}$), 137.8, 142.6 (C$_{Ar}$), 160.4 (COH), 171.1 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 285 ([M$^+$], 60), 239 (100), 224 (40), 211 (78), 196 (63), 182 (13), 115 (8), 77 (5).

HRMS (EI): *m/z* calcd for C$_{17}$H$_{19}$O$_3$N: 285.13594; found: 243.135775.

Methyl 2-Hydroxy-4-propyl-6-(pyrid-4-yl)benzoate (12a)

Starting from **11** (0.392 g, 1.5 mmol), **5a** (0.429 g, 1.65 mmol), and TiCl$_4$ (0.18 mL, 1.65 mmol), **12a** was isolated as a highly viscous reddish oil (0.180 g, 44%).

IR (neat): 2962 (w), 2873 (w), 1601 (m), 1577 (s), 1403 (m), 1283 (m), 1086 (m), 11042 (m), 993 (m), 742 cm^{-1} (m).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.87 (t, ^3J = 7.2 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$), 1.54–1.63 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 2.50 (t, ^3J = 7.2 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 3.42 (s, 3 H, OCH$_3$), 6.48 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 7.09–7.12 (m, 2 H, ArH), 8.54–8.69 (m, 2 H, ArH), 10.87 (br s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.7 (CH$_2$CH$_2$*C*H$_3$), 23.6 (CH$_2$*C*H$_2$CH$_3$), 37.9 (*C*H$_2$CH$_2$CH$_3$), 51.6 (OCH$_3$), 108.7 (C$_{Ar}$), 117.4 (2 CH$_{Ar}$), 122.7 (CH$_{Ar}$), 141.6 (C$_{Ar}$), 148.9 (CH$_{Ar}$), 150.2 (C$_{Ar}$), 150.7 (2 CH$_{Ar}$), 151.3 (C$_{Ar}$), 162.2 (COH), 170.5 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 271 ([M$^+$], 48), 239 (100), 211 (99), 182 (30), 167 (5), 154 (4), 127 (16), 78 (4).

HRMS (EI): *m/z* calcd for C$_{16}$H$_{17}$NO$_3$: 271.12029; found: 271.11994.

Methyl 2-Hydroxy-3-methyl-4-propyl-6-(pyrid-4-yl)benzoate (12b)

Starting from **11** (0.395 g, 1.5 mmol), **5b** (0.429 g, 1.65 mmol), and TiCl$_4$ (0.180 mL, 1.65 mmol), **12b** was isolated as a highly viscous reddish oil (0.170 g, 40%).

IR (neat): 2956 (w), 2871 (w), 1699 (m), 1429 (m), 1398 (m), 1300 (m), 1267 (m), 1200 (s), 1114 (s), 753 cm^{-1} (m).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.90 (t, ^3J = 6.5 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$), 1.48–1.57 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 2.21 (s, 3 H, CH$_3$), 2.52 (t, ^3J = 6.0 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 3.43 (s, 3 H, OCH$_3$), 6.40 (s, 1 H, ArH), 7.11 (m, 1 H, ArH), 7.60–7.62 (m, 1 H, ArH), 8.69 (m, 2 H, ArH), 10.87 (br s, 1 H, OH).

^{13}C NMR (62 MHz, CDCl$_3$): δ = 10.2 (CH$_2$CH$_2$*C*H$_3$), 13.0 (CH$_3$), 22.2 (CH$_2$*C*H$_2$CH$_3$), 35.0 (*C*H$_2$CH$_2$CH$_3$), 50.6 (OCH$_3$), 106.7 (C$_{Ar}$), 121.3 (3 CH$_{Ar}$), 124.0, 137.7 (C$_{Ar}$), 146.7 (2 C$_{Ar}$), 149.6 (2 CH$_{Ar}$), 159.3 (COH), 170.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%) = 285 ([M$^+$], 45), 238 (100), 225 (35), 210 (11), 196 (16), 182 (8), 167 (17), 154 (6), 139 (5), 84 (4), 78 (4).

HRMS (EI): *m/z* calcd for C$_{17}$H$_{19}$NO$_3$: 285.13594; found: 285.13545.

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