One-pot synthesis of 6-(thien-2-yl)- and 6-(fur-2-yl)salicylates based on regioselective [3 + 3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes†

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6-(Thien-2-yl) and 6-(fur-2-yl)salicylates are prepared by $TiCl_4$-mediated [3 + 3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-(thien-2-yl)- and 3-(fur-2-yl)-3-silyloxy-2-en-1-ones, respectively. The regioselectivity of the cyclization depends on the substitution pattern of the 3-silyloxy-2-en-1-one.

Introduction

Heterocyclic biaryls are of considerable pharmacological relevance and represent important lead structures in medicinal chemistry.[1] In this context, highly functionalized 2-(thien-2-yl)benzene derivatives are of special interest. For example, 6-(thien-2-yl)salicylates have been reported to show *in vitro* inhibitory activity on guinea-pig detrusor muscle contraction on electrical field stimulation.[2] 2-(Thien-2-yl)benzoates are CAAX peptidomimetics and represent potent inhibitors of farnesyltransferase (Ftase).[3] 2-(Thien-2-yl)benzoates have been prepared by the Grignard reaction of 1-bromo-2-(thien-2-yl)benzene with carbon dioxide[4] and by Stille[5] or Suzuki reactions[6] of 2-halobenzoates, or related transition metal catalyzed cross-coupling reactions. The scope of these methods is often limited by the fact that sterically encumbered substrates often fail to undergo transition metal catalyzed reactions or the yields are low. Besides, the synthesis of highly substituted and functionalized starting materials is often a difficult task.

Some years ago, Chan and Brownbridge developed[7] an elegant approach to functionalized arenes based on formal [3 + 3] cyclizations of 1,3-bis(silyl enol ethers).[8,9] Herein, we report the application of this methodology to the synthesis of arenes containing an electron-rich heterocyclic moiety. From a preparative viewpoint, the chemistry reported offers a convenient and regioselective approach to functionalized and sterically encumbered 6-(thien-2-yl)- and 6-(fur-2-yl)salicylates that are not readily available by other methods and have only scarcely been reported so far.[10] Due to the considerable importance of the trifluoromethyl group in organic and medicinal chemistry,[11] this group was included in the present studies.‡ The cyclization of 1,3-bis(silyl enol ethers) with alkyl- and CF_3-substituted substrates proceeded with different regioselectivity, which can be explained by electronic factors.

Results and discussion

The 3-(thien-2-yl)- and 3-(fur-2-yl)-1,3-diones **3a–d** were prepared by the LDA-mediated reaction of ketones **1a–c** with (thien-2-yl)- and (fur-2-yl)carboxylic acid chloride (**2a**,**b**) (Table 1). The silylation of **3a–d** afforded the silyl enol ethers **4a–d**. The $TiCl_4$-mediated [3 + 3] cyclization of **4a–d** with 1,3-bis(silyl enol ethers) **5a–e**, prepared from the corresponding 1,3-dicarbonyl compounds in two steps,[12] afforded the 6-(thien-2-yl)salicylates **6a–m** and the 6-(fur-2-yl)salicylates **6n**,**o**. 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 relatively low yields (30–47%) can be explained by hydrolysis and $TiCl_4$ mediated oxidative dimerization of dienes **5**.

The cyclocondensation of **4a** with **5a** and the regioselectivity can be explained by formation of intermediate **A**, attack of the terminal carbon atom of **5** onto the carbon located next to the methyl group to give intermediate **B**, cyclization by an S_N' mechanism with displacement of the Cl_3TiO-group (intermediate **C**), and subsequent aromatization (Scheme 1). Alternatively, the cyclization might proceed by isomerization of intermediate **A** into intermediate **D** and subsequent cyclocondensation by a mechanism similar to the one described above.

The structures of all the products were elucidated by spectroscopic methods (2D NMR). The structure of **6b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[13] The thienyl and the phenyl moiety are in plane. An intramolecular hydrogen bond is observed although the ester group is slightly twisted out of plane.

1-Propanoyl-1-(thien-2-oyl)cyclopropane (**8**) was prepared by the reaction of **3b** with 1,2-dibromoethane (Table 2). The $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-butadienes **5a–d** with

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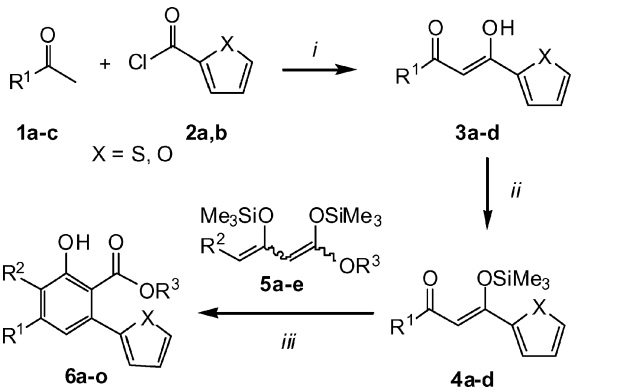
‡ While the sizes of the methyl and trifluoromethyl groups are comparable, the latter possesses a highly electron-withdrawing effect. Therefore, the replacement of a CH_3- by a CF_3-group in a molecule results in a great change in its electronic properties and reactivity. The trifluoromethyl group in drugs plays an important role in drug–receptor interactions and in their *in vivo* transport. In addition, the high chemical and biological stability of the CF_3-group allows the avoidance of unwanted metabolic transformations.

Table 1 Synthesis of **6a–o**



Reagents and conditions: *i*: LDA (1.5 equiv.), THF; *ii*: NEt_3 (1.6 equiv.), Me_3SiCl (1.8 equiv.), C_6H_6, 20 °C, 3 d; *iii*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C.

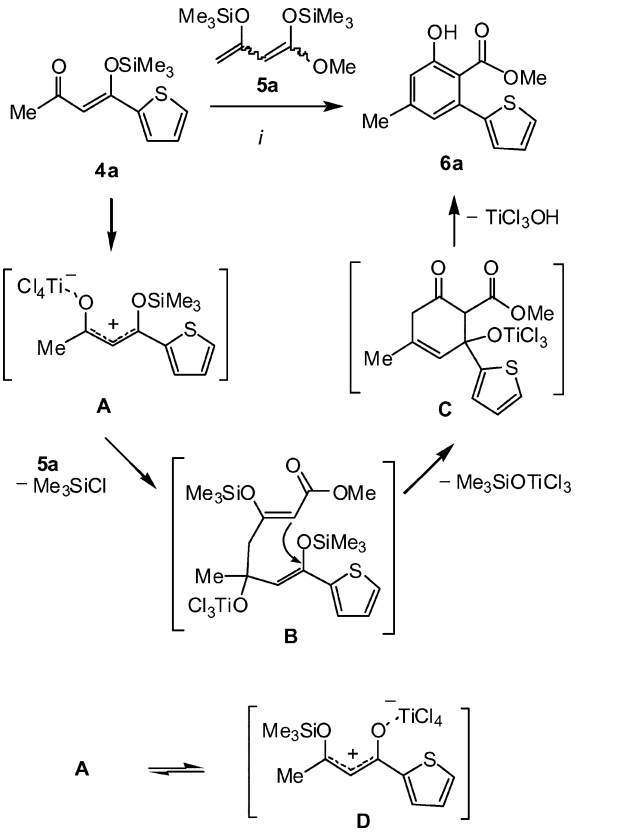
4	5	6	X	R^1	R^2	R^3	% (6)[a]
a	**a**	**a**	S	Me	H	Me	32
a	**b**	**b**	S	Me	Me	Me	33
a	**c**	**c**	S	Me	Et	Et	35
a	**d**	**d**	S	Me	*n*Hex	Me	30
a	**e**	**e**	S	Me	*n*Oct	Me	34
b	**a**	**f**	S	Et	H	Me	35
b	**b**	**g**	S	Et	Me	Me	34
b	**c**	**h**	S	Et	Et	Et	30
b	**d**	**i**	S	Et	*n*Hex	Me	30
c	**a**	**j**	S	*n*Pr	H	Me	40
c	**b**	**k**	S	*n*Pr	Me	Me	47
c	**c**	**l**	S	*n*Pr	Et	Et	42
c	**d**	**m**	S	*n*Pr	*n*Hex	Me	35
d	**a**	**n**	O	Et	H	Me	32
d	**b**	**o**	O	Et	Me	Me	30

[a] Yields of isolated products.

8 afforded the 6-(thien-2-yl)salicylates **9a–d** containing a remote chloride group (Table 2). The products are formed by a domino '[3 + 3]-cyclization–homo-Michael' reaction.[14] It is noteworthy that the regioselectivity decreased with increasing steric hindrance of the 1,3-bis(silyl enol ether).

The trifluoromethyl-substituted silyl enol ethers **4e**,**f** were prepared by silylation of the corresponding 1,3-diketones **3e**,**f**. The $TiCl_4$-mediated cyclization of **4e**,**f** with 1,3-bis(silyloxy)-1,3-butadienes **5a–e** afforded the novel 4-hetaryl-6-(trifluoromethyl)salicylates **10a–j** with very good regioselectivity (Scheme 2, Table 3). The cyclization and the regioselectivity can be explained by a mechanism similar to the one discussed above for the synthesis of **6a**.

It is noteworthy that the cyclizations of 1,3-bis(silyl enol ethers) **5** with alkyl- and CF_3-substituted silyl enol ethers **4a–d** and **4e**,**f** proceed with different regioselectivity. This might be explained by comparison of the resonance structures of the cations formed by reaction of $TiCl_4$ with silyl enol ethers **4a** and **4e** (Fig. 2). In the case of the CH_3-substituted silyl enol ethers **4a–d**, it can be expected that resonance structure $\mathbf{A_1}$ is predominant over $\mathbf{A_2}$ due to the σ-donating effect of the methyl group. The hetaryl moiety is expected to be twisted out of plane. In contrast, $\mathbf{E_2}$ is expected to be more stable than $\mathbf{E_1}$ due to the cation-destabilizing effect of the CF_3-group. The reactions presumably proceed, under kinetic reaction control, by attack of the terminal carbon atom of **5** onto the cationic intermediate that is predominantly present.



Scheme 1 Possible mechanism of the formation of **6a**. *Reagents and conditions*: *i*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C.

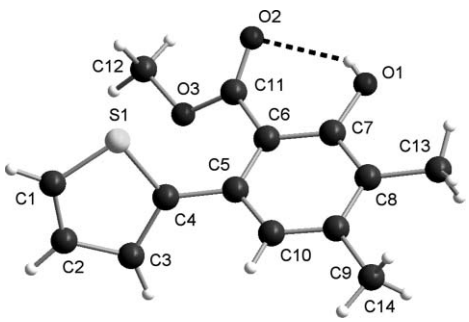


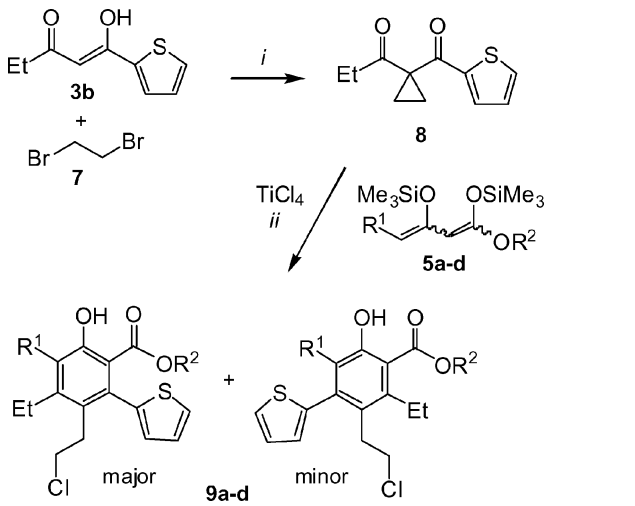
Fig. 1 Crystal structure of **6b**.

The structures of the products were elucidated by spectroscopic methods (2D NMR). The structures of **10a** and **10f** were independently confirmed by X-ray crystal structure analyses (Fig. 3 and ESI†).[13] Similarly to **6b**, the thienyl and the phenyl moiety are in plane. An intramolecular hydrogen bond is present although the ester group is slightly twisted out of plane.

Conclusions

In conclusion, a variety of sterically encumbered 6-(thien-2-yl)- and 6-(fur-2-yl)salicylates were regioselectively prepared by the Lewis acid mediated [3 + 3] cyclizations of 1,3-bis(silyl enol ethers) with novel 3-(thien-2-yl)- and 3-(fur-2-yl)-3-silyloxy-2-en-1-ones and with 1-alkanoyl-1-(thien-2-oyl)cyclopropanes. The

Table 2 Synthesis of **9a–d**

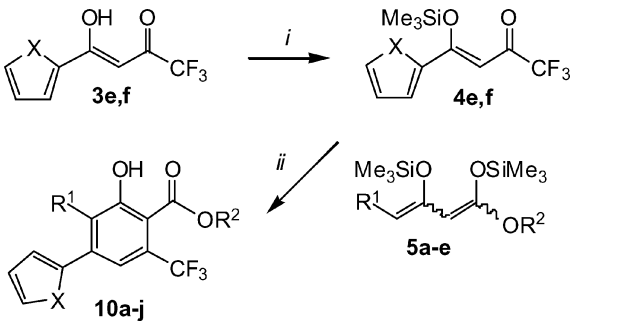


Reagents and conditions: *i*: K_2CO_3 (4.0 equiv.), DMSO; *ii*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 20 h.

5	9	R^1	R^2	% (**9**)[a]	Regioisomeric ratio
a	**a**	H	Me	42	100 : 0
b	**b**	Me	Me	40	95 : 5
c	**c**	Et	Et	34	80 : 20
d	**d**	*n*Hex	Me	32	66 : 33

[a] Yields of isolated products.

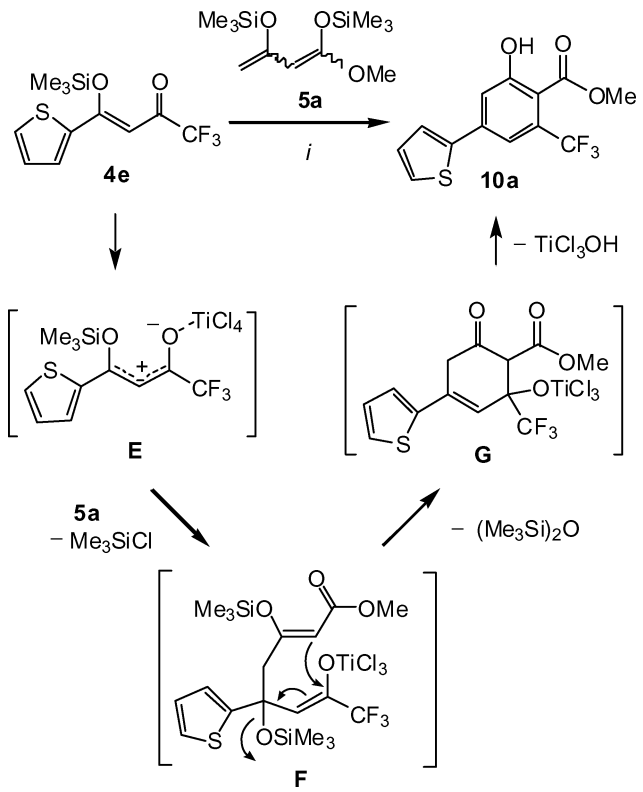
Table 3 Synthesis of **10a–j**



Reagents and conditions: *i*: NEt_3 (1.6 equiv.), Me_3SiCl (1.8 equiv.), C_6H_6, 20 °C, 3 d; *ii*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C.

4	5	10	X	R^1	R^2	% (**10**)[a]
e	**a**	**a**	S	H	Me	35
e	**b**	**b**	S	Me	Me	45
e	**c**	**c**	S	Et	Et	44
e	**d**	**d**	S	*n*Hex	Me	34
e	**e**	**e**	S	*n*Oct	Me	37
f	**a**	**f**	O	H	Me	40
f	**b**	**g**	O	Me	Me	41
f	**c**	**h**	O	Et	Et	35
f	**d**	**i**	O	*n*Hex	Me	30
f	**e**	**j**	O	*n*Oct	Me	35

[a] Yields of isolated products.



Scheme 2 Possible mechanism of the formation of **10a**. *Reagents and conditions*: *i*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C.

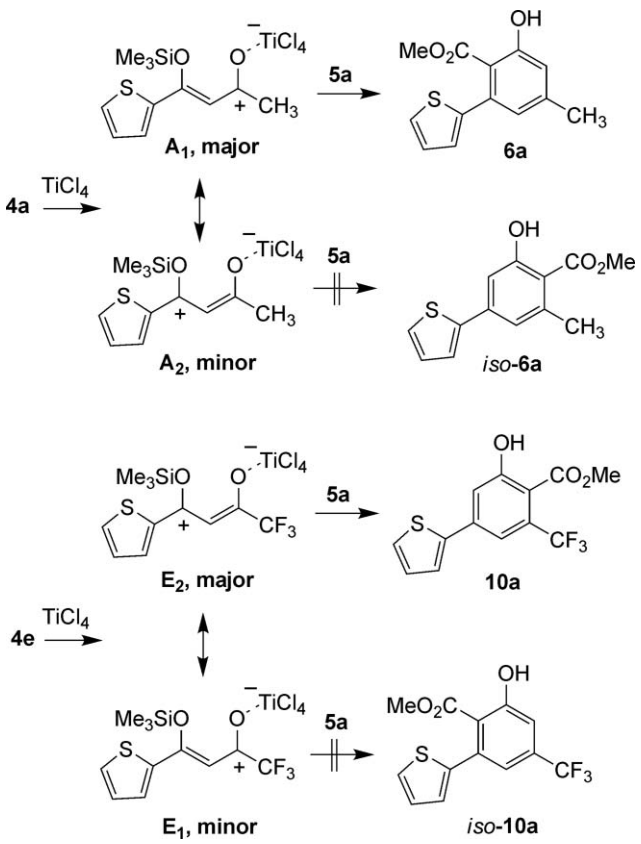


Fig. 2 Possible explanation for the different regioselectivity of formation of **6a** and **10a**.

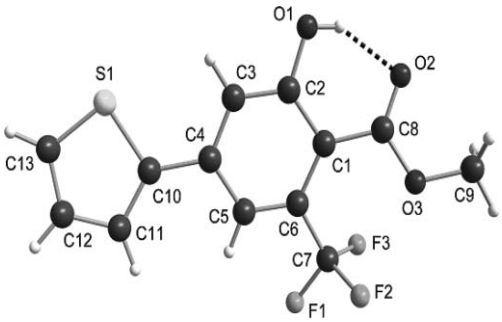


Fig. 3 Crystal structure of **10a**.

cyclizations of 1,3-bis(silyl enol ethers) with alkyl- and CF_3-substituted substrates proceeded with different regioselectivity. The products are not readily available by other methods.

Experimental section

General Comments. 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.

General procedure for the synthesis of 1,3-dicarbonyl compounds 3. To a stirred solution of LDA (75.0 mmol) in THF (1.2 mL per 1.0 mmol of LDA) was added ketone **1** (50.0 mmol) at −78 °C. After the solution was stirred for 1 h, the acid chloride **2a**,**b** (60.0 mmol) was added. The temperature of the solution was allowed to rise to 20 °C over 12 h. A saturated solution of NH_4Cl 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) and 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**. Compounds **1a–c** and **3e**,**f** are commercially available.

4-Hydroxy-4-(2-thienyl)-3-buten-2-one (3a). Starting with THF (4.8 mL), LDA (6 mmol), acetone **1a** (0.232 g, 4.0 mmol) and 2-thiophenecarbonyl chloride **2** (0.704 g, 4.8 mmol), **3a** was isolated as a yellowish oil (0.235 g, 34%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3), 5.90 (s, 1 H, CH), 6.97 (m, 1 H, CH_{Hetar}), 7.45 (dd, ^3J = 4.9 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 7.54–7.56 (m, 1 H, CH_{Hetar}), 15.59 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.70 (CH_3), 95.4 (CH), 126.7, 129.9, 132.6 (CH_{Hetar}), 140.5 (C_{Hetar}), 180.7 (COH), 186.1 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3435 (br, m), 3085 (m), 2963 (w), 1629 (s), 1519 (m), 1408 (s), 1275 (s), 1078 (m), 937 (m), 797 (m), 779 (s), 723 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 168 ([M^+], 87), 153 (45), 135 (21), 126 (18), 111 (100), 97 (7), 84 (15), 69 (53), 43 (23). HRMS (EI): calcd for $C_8H_8O_2S$ [M^+]: 168.02395; found: 168.02385.

1-Hydroxy-1-(2-thienyl)-1-penten-3-one (3b). Starting with THF (62.5 mL), LDA (75 mmol), 2-butanone **1b** (3.606 g, 50.0 mmol) and 2-thiophenecarbonyl chloride **2** (8.796 g, 60.0 mmol), **3b** was isolated as a yellowish oil (2.720 g, 30%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 6.6 Hz, 3 H, CH_2CH_3), 2.60 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 6.22 (s, 1 H, CH), 7.31–7.33 (m, 1 H, CH_{Hetar}), 7.78 (dd, ^3J = 4.9 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 7.88–7.90 (m, 1 H, CH_{Hetar}), 15.89 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5 (CH_2CH_3), 31.0 (CH_2CH_3), 95.3 (CH), 128.5, 130.4, 132.6 (CH_{Hetar}), 142.1 (C_{Hetar}), 182.1 (COH), 186.1 (CO). GC-MS (EI, 70 eV): *m*/*z* (%) = 182 ([M^+], 62), 153 (86), 126 (26), 111 (100), 97 (7), 83 (8), 69 (56), 56 (17), 53 (7), 45 (8), 39 (17), 29 (8). HRMS (EI): calcd for $C_9H_{10}O_2S$ [M^+]: 182.03960; found: 182.03933.

1-Hydroxy-1-(2-thienyl)-1-hexen-3-one (3c). Starting with THF (62.5 mL), LDA (75.0 mmol), 2-pentanone (**1c**) (4.306 g, 50.0 mmol) and 2-thiophenecarboxylic acid chloride (**2**) (8.796 g, 60.0 mmol), **3c** was isolated as a yellowish oil (2.750 g, 28%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.53–1.61 (m, 2 H, $CH_2CH_2CH_3$), 2.21 (t, ^3J = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 5.91 (s, 1 H, CH), 6.97–7.00 (m, 1 H, CH_{Hetar}), 7.46 (dd, ^3J = 4.4 Hz, ^4J = 0.9 Hz, 1 H, CH_{Hetar}), 7.56–7.57 (m, 1 H, CH_{Hetar}), 15.62 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6 ($CH_2CH_2CH_3$), 18.4 ($CH_2CH_2CH_3$), 38.2 ($CH_2CH_2CH_3$), 94.8 (CH), 126.6, 129.1, 131.9 (CH_{Hetar}), 142.6 (C_{Hetar}), 181.0 (COH), 189.1 (CO). GC-MS (EI, 70 eV): *m*/*z* (%) = 196 ([M^+], 47), 181 (3), 168 (14), 153 (100), 135 (4), 126 (34), 111 (90), 97 (7), 85 (7), 69 (53), 53 (5), 39 (18). HRMS (EI): calcd for $C_{10}H_{12}O_2S$ [M^+]: 196.05525; found: 196.05469.

General procedure for the synthesis of silyl enol ethers 4. To a stirred benzene solution (2.5 mL per 1.0 mmol of **3**) of **3** (10.0 mmol) was added triethylamine (16.0 mmol). After the solution had been stirred for 2 h, trimethylchlorosilane (18.0 mmol) was added. After the solution had been stirred 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 an argon atmosphere. The filtrate was concentrated *in vacuo* to give silyl enol ethers **4**.

4-(2-Thienyl)-4-[(trimethylsilyl)oxy]-3-buten-2-one (4a). Starting with benzene (41.0 mL), **3a** (2.757 g, 16.4 mmol), triethylamine (3.205 g, 26.2 mmol) and trimethylchlorosilane (3.205 g, 29.5 mmol), **4a** was isolated as a reddish oil (3.464 g, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 (m, 9 H, $Si(CH_3)_3$), 2.21 (s, 3 H, CH_3), 5.18 (s, 1 H, CH), 6.90–6.96 (m, 1 H, CH_{Hetar}), 7.34–7.38 (m, 1 H, CH_{Hetar}), 7.39–7.42 (m, 1 H, CH_{Hetar}).

1-(2-Thienyl)-1-[(trimethylsilyl)oxy]-1-penten-3-one (4b). Starting with benzene (30.0 mL), **3b** (1.821 g, 10.0 mmol), triethylamine (1.619 g, 16.0 mmol) and trimethylchlorosilane (1.738 g, 18.0 mmol), **4b** was isolated as a reddish oil (2.162 g, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.20 (m, 9 H, $Si(CH_3)_3$), 0.98 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 2.68 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 5.96 (s, 1 H, CH), 6.93–6.95 (m, 1 H, CH_{Hetar}), 7.36–7.38 (m, 1 H, CH_{Hetar}), 7.42–7.44 (m, 1 H, CH_{Hetar}).

1-(2-Thienyl)-1-[(trimethylsilyl)oxy]-1-hexen-3-one (4c). Starting with benzene (73.0 mL), **3c** (4.799 g, 24.5 mmol), triethylamine (3.960 g, 39.1 mmol) and trimethylchlorosilane (4.780 g, 44.0 mmol), **4c** was isolated as a yellowish oil (6.018 g, 92%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.27 (m, 9 H, $Si(CH_3)_3$), 0.90 (t, ^3J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.53 (m, 2 H, $CH_2CH_2CH_3$), 2.74 (t, ^3J = 6.1 Hz, 2 H, $CH_2CH_2CH_3$), 6.08 (s, 1 H, CH), 6.97–7.01 (m, 1 H, CH_{Hetar}), 7.43–7.45 (m, 1 H, CH_{Hetar}), 7.49–7.51 (m, 1 H,

CH_{Hetar}). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.3$ ($Si(CH_3)_3$), 12.8 ($CH_2CH_2\mathit{CH_3}$), 18.4 ($CH_2\mathit{CH_2}CH_3$), 35.3 ($\mathit{CH_2}CH_2CH_3$), 103.8 (CH), 127.5, 128.8, 132.0 (CH_{Hetar}), 147.3 (C_{Hetar}), 174.8 (C), 181.7 (CO).

1-(2-Furyl)-1-[(trimethylsilyl)oxy]-1-penten-3-one (4d). Starting with benzene (30.0 mL), **3d** (1.660 g, 10.0 mmol), triethylamine (1.619 g, 16.0 mmol) and trimethylchlorosilane (1.738 g, 18.0 mmol), **4d** was isolated as a yellowish oil (2.028 g, 84%). ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.27$ (m, 9 H, $Si(CH_3)_3$), 1.05 (t, $^3J = 7.6$ Hz, 3 H, $CH_2\mathit{CH_3}$), 2.76 (q, $^3J = 7.4$ Hz, 2 H, $\mathit{CH_2}CH_3$), 6.09 (s,1 H, CH), 6.43 (m, 1 H, CH_{Hetar}), 7.01 (m, 1 H, CH_{Hetar}), 7.44 (m, 1 H, CH_{Hetar}).

1,1,1-Trifluoro-4-(2-thienyl)-4-[(trimethylsilyl)oxy]-3-buten-2-one (4e). Starting with benzene (45.0 mL), **3e** (3.330 g, 15.0 mmol), triethylamine (2.429 g, 24.0 mmol) and trimethylchlorosilane (2.917 g, 27.0 mmol), **4e** was isolated as a reddish oil (3.175 g, 72%). ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.24$ (m, 9 H, $Si(CH_3)_3$), 6.53 (m, 1 H, CH), 7.04 (m, 1 H, CH_{Heter}), 7.56–7.62 (m, 2 H, CH_{Heter}).

1,1,1-Trifluoro-4-(2-furyl)-4-[(trimethylsilyl)oxy]-3-buten-2-one (4f). Starting with benzene (45.0 mL), **3f** (3.09 g, 15.0 mmol), triethylamine (2.429 g, 24.0 mmol) and trimethylchlorosilane (2.917 g, 27.0 mmol), **4f** was isolated as a reddish oil (3.169 g, 76%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.27$ (m, 9 H, $Si(CH_3)_3$), 6.44 (m, 1 H, CH), 6.59 (m, 1 H, CH_{Heter}), 7.12–7.19 (m, 1 H, CH_{Heter}), 7.49–7.54 (m, 1 H, CH_{Heter}).

General procedure for the synthesis of salicylates 6. To a CH_2Cl_2 solution (2 mL per 1.0 mmol of **4**) of **4** (1.0 mmol) was added **5** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C over 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer 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 **6**.

Methyl 2-hydroxy-4-methyl-6-(2-thienyl)-benzoate (6a). Starting with **4a** (0.361 g, 1.5 mmol), **5a** (0.426 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **6a** was isolated as a reddish viscous oil (0.119 g, 32%); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.24$ (s, 3 H, CH_3), 3.50 (s, 3 H, OCH_3), 6.77 (m, 1 H, CH_{Ar}), 6.74 (m, 1 H, CH_{Ar}), 6.80–6.82 (m, 1 H, CH_{Hetar}), 6.91 (dd, $^3J = 4.9$ Hz, $^4J = 1.5$ Hz, 1 H, CH_{Hetar}), 7.20 (dd, $^3J = 4.5$ Hz, $^4J = 1.8$ Hz, 1 H, CH_{Hetar}), 10.55 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.9$ (CH_3), 52.2 (OCH_3), 110.7 ($\mathit{C}COOCH_{3Ar}$), 118.2 (CH_{Ar}), 125.4 (2 CH_{Hetar}), 126.1 (CH_{Hetar}), 126.9 (CH_{Ar}), 136.8, 144.0 (C_{Ar}), 145.1 (C_{Hetar}), 161.9 (COH_{Ar}), 171.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2921$ (w), 2851 (w), 1660 (m), 1611 (m), 1569 (m), 1432 (m), 1333 (m), 1261 (m), 1222 (m), 1089 (m), 848 (w), 795 (m), 702 (m). GC-MS (EI, 70 eV): *m*/z (%) = 248 ([M^+], 53), 216 (100), 188 (52), 160 (11), 145 (3), 128 (5), 115 (16), 77 (3). HRMS (EI): calcd for $C_{13}H_{12}O_3S$ [M^+]: 248.04948; found: 248.04961.

Methyl 2-hydroxy-3,4-dimethyl-6-(2-thienyl)-benzoate (6b). Starting with **4a** (0.240 g, 1.0 mmol), **5b** (0.190 g, 1.1 mmol) and $TiCl_4$ (0.12 mL, 1.1 mmol), **6b** was isolated as a reddish solid. (0.086 g, 33%), mp = 75–81 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 3.51 (s, 3 H, OCH_3), 6.69 (m, 1 H, CH_{Ar}), 6.79 (m, 1 H, CH_{Hetar}), 6.92 (dd, $^3J = 5.1$ Hz, $^4J = 1.7$ Hz, 1 H, CH_{Hetar}), 7.19 (dd, $^3J = 5.1$ Hz, $^4J = 1.1$ Hz, 1 H, CH_{Hetar}), 10.88 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.0$, 20.7 (CH_3), 52.2 (OCH_3), 110.3 ($\mathit{C}COOCH_{3Ar}$), 125.1 (CH_{Ar}), 125.3 (C_{Ar}), 125.5, 125.9, 126.8 (CH_{Hetar}), 133.5, 143.2 (C_{Ar}), 144.5 (C_{Hetar}), 159.8 (COH_{Ar}), 172.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2948$ (w), 2854 (w), 1668 (s), 1600 (m), 1562 (w), 1433 (s), 1332 (w), 1258 (s), 1150 (s), 1089 (s), 1057 (m), 842 (s), 798 (s), 711 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 262 ([M^+], 63), 230 (100), 215 (4), 202 (58), 187 (26), 173 (17), 159 (6), 141 (3), 129 (6), 115 (12), 91 (3), 77 (3), 63 (3), 45 (4). HRMS (EI): calcd for $C_{14}H_{14}O_3S$ [M^+]: 262.06582; found: 262.06563.

Ethyl 3-ethyl-2-hydroxy-4-methyl-6-(2-thienyl)-benzoate (6c). Starting with **4a** (0.360 g, 1.5 mmol), **5c** (0.495 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **6c** was isolated as a reddish viscous oil (0.152 g, 35%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.72$ (t, $^3J = 7.2$ Hz, 3 H, $CH_2\mathit{CH_3}$), 0.97 (t, $^3J = 7.4$ Hz, 3 H, $OCH_2\mathit{CH_3}$), 2.13 (s, 3 H, CH_3), 2.56 (q, $^3J = 7.4$ Hz, 2 H, $\mathit{CH_2}CH_3$), 3.87 (q, $^3J = 7.2$ Hz, 2 H, OCH_2CH_3), 6.56 (s, 1 H, CH_{Ar}), 6.67 (m, 1 H, CH_{Hetar}), 6.79 (dd, $^3J = 5.1$ Hz, $^4J = 1.7$ Hz, 1 H, CH_{Hetar}), 7.07 (dd, $^3J = 5.1$ Hz, $^4J = 1.1$ Hz, 1 H, CH_{Hetar}), 10.89 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ ($CH_2\mathit{CH_3}$), 14.2 ($OCH_2\mathit{CH_3}$), 20.6 ($\mathit{CH_2}CH_3$), 27.7 (CH_3), 62.2 (OCH_2CH_3), 112.3 ($\mathit{C}COOCH_2CH_{3Ar}$), 126.3 ($CH_{Ar}$), 127.2, 127.3, 128.2 ($CH_{Hetar}$), 132.8, 135.2 ($C_{Ar}$), 143.7 ($C_{Hetar}$), 146.1 ($C_{Ar}$), 161.4 ($COH_{Ar}$), 173.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2928$ (m), 2872 (w), 1658 (s), 1606 (m), 1455 (m), 1389 (s), 1275 (s), 1226 (s), 1176 (m), 1104 (m), 1037 (w), 810 (w), 693 (m). GC-MS (EI, 70 eV): *m*/*z* (%) = 290 ([M^+], 78), 244 (100), 229 (60), 216 (69), 201 (34), 187 (8), 171 (16), 158 (5), 128 (10), 115 (10), 77 (5), 45 (4). HRMS (EI): calcd for $C_{16}H_{18}O_3S$ [M^+]: 290.09712; found: 290.09704.

Methyl 3-hexyl-2-hydroxy-4-methyl-6-(2-thienyl)-benzoate (6d). Starting with **4a** (0.360 g, 1.5 mmol), **5d** (0.563 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **6d** was isolated as a reddish viscous oil (0.134 g, 30%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.70$ (t(br), $^3J = 6.6$ Hz, 3 H, $CH_2(CH_2)_4\mathit{CH_3}$), 1.08 (m, 8 H, $CH_2(\mathit{CH_2})_4CH_3$), 2.13 (s, 3 H, CH_3), 2.53 (t, $^3J = 7.2$ Hz, 2 H, $\mathit{CH_2}(CH_2)_4CH_3$), 3.40 (s, 3 H, OCH_3), 6.56 (m, 1 H, CH_{Ar}), 6.68–6.70 (m, 1 H, CH_{Hetar}), 6.80 (m, 1 H, CH_{Hetar}), 7.08 (d, $^3J = 5.9$ Hz, 1 H, CH_{Hetar}), 10.71 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.2$ ($(CH_2)_5\mathit{CH_3}$), 20.9 (CH_3), 23.7, 27.5, 29.9, 30.7, 32.8 ($(\mathit{CH_2})_5CH_3$), 53.0 (OCH_3), 111.3 ($\mathit{C}COOCH_{3Ar}$), 125.9 (CH_{Ar}), 126.6, 126.7, 127.6 (CH_{Hetar}), 131.0, 134.4 (C_{Ar}), 143.4 (C_{Hetar}), 145.3 (C_{Ar}), 160.6 (COH_{Ar}), 172.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2925$ (s), 2855 (s), 1663 (s), 1607 (m), 1440 (s), 1391 (m), 1268 (s), 1226 (s), 1197 (m), 1162 (m), 1122 (w), 849 (w), 693 (m). GC-MS (EI, 70 eV): *m*/*z* (%) = 332 ([M^+], 56), 300 (24), 285 (43), 271 (3), 243 (11), 230 (100), 215 (4), 202 (20), 187 (5), 171 (11), 128 (8), 41 (4). HRMS (EI): calcd for $C_{19}H_{24}O_3S$ [M^+]: 332.14407; found: 332.14436.

Methyl 2-hydroxy-4-methyl-3-octyl-6-(2-thienyl)-benzoate (6e). Starting with **4a** (0.360 g, 1.5 mmol), **5e** (0.609 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **6e** was isolated as a reddish viscous oil (0.180 g, 34%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.70$ (t(br), $^3J = 6.2$ Hz, 3 H, $CH_2(CH_2)_6\mathit{CH_3}$), 1.09 (m, 12 H, $CH_2(\mathit{CH_2})_6CH_3$), 2.13 (s, 3 H, CH_3), 2.50 (t, $^3J = 7.4$ Hz, 2 H, $\mathit{CH_2}(CH_2)_6CH_3$), 3.53 (s, 3 H, OCH_3), 6.57 (m, 1 H, CH_{Ar}), 6.69 (m, 1 H, CH_{Hetar}),

6.80–6.82 (m, 1 H, CH_{Hetar}), 7.07–7.09 (m, 1 H, CH_{Hetar}), 10.71 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 ($(CH_2)_7CH_3$), 20.9 (CH_3), 23.8, 27.5, 28.3, 29.9, 30.5, 31.2, 33.0 (CH_2), 53.0 (OCH_3), 111.3 ($CCOOCH_{3Ar}$), 125.9 (CH_{Ar}), 126.6 (2 CH_{Hetar}), 127.6 (CH_{Hetar}), 131.0, 134.3 (C_{Ar}), 143.3 (C_{Hetar}), 145.3 (C_{Ar}), 160.7 (COH_{Ar}), 172.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2925 (s), 2855 (m), 1663 (s), 1607 (m), 1439 (m), 1360 (w), 1260 (m), 1226 (s), 1162 (m), 1025 (w), 844 (m), 693 (m). GC-MS (EI, 70 eV): m/z (%) = 360 ([M$^+$], 51), 328 (24), 313 (41), 230 (100), 202 (18), 171 (9), 128 (6), 41 (5). HRMS (EI): calcd for $C_{21}H_{28}O_3S$ [M$^+$]: 360.17537; found: 360.17496.

Methyl 4-ethyl-2-hydroxy-6-(2-thienyl)-benzoate (6f). Starting with **4b** (0.448 g, 2.0 mmol), **5a** (0.567 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6f** was isolated as a reddish viscous oil (0.184 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 2.53 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.50 (s, 3 H, OCH_3), 6.69 (s, 1 H, CH_{Ar}), 6.77 (s, 1 H, CH_{Ar}), 6.81 (m, 1 H, CH_{Hetar}), 6.91 (dd, ^3J = 5.1 Hz, ^4J = 1.7 Hz, 1 H, CH_{Hetar}), 7.21 (dd, ^3J = 4.9 Hz, ^4J = 1.3 Hz, 1 H, CH_{Hetar}), 10.55 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_2CH_3), 27.7 (CH_2CH_3), 50.8 (OCH_3), 109.0 ($CCOOCH_{3Ar}$), 115.5 (CH_{Ar}), 122.8, 123.9 (CH_{Hetar}), 124.7 (CH_{Ar}), 125.4 (CH_{Hetar}), 135.5, 142.7 (C_{Ar}), 149.7 (C_{Hetar}), 160.5 (COH_{Ar}), 170.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2967 (s), 2872 (w), 1734 (w), 1664 (s), 1610 (s), 1568 (s), 1440 (s), 1360 (s), 1265 (s), 1160 (m), 1098 (s), 1014 (m), 932 (m), 808 (m), 791 (m), 697 (s). GC-MS (EI, 70 eV): m/z (%) = 262 ([M$^+$], 43), 230 (100), 202 (26), 187 (24), 173 (7), 115 (10). HRMS (EI): calcd for $C_{14}H_{14}O_3S$ [M$^+$]: 262.0582; found: 262.06562.

Methyl 4-ethyl-2-hydroxy-3-methyl-6-(2-thienyl)-benzoate (6g). Starting with **4b** (0.448 g, 2.0 mmol), **5b** (0.598 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6g** was isolated as a reddish viscous oil. (0.180 g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 2.13 (s, 3 H, CH_3), 2.54 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.48 (s, 3 H, OCH_3), 6.67 (s, 1 H, CH_{Ar}), 6.77–6.79 (m, 1 H, CH_{Hetar}), 6.90 (dd, ^3J = 4.9 Hz, ^4J = 1.5 Hz, 1 H, CH_{Hetar}), 7.16 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 10.87 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0 (CH_2CH_3), 14.0 (CH_3), 26.8 (CH_2CH_3), 51.7 (OCH_3), 109.0 ($CCOOCH_{3Ar}$), 123.1 (CH_{Ar}), 123.5, 124.6, 126.3 (CH_{Hetar}), 133.3, 139.7 (C_{Ar}), 144.4 (C_{Hetar}), 148.4 (C_{Ar}), 159.6 (COH_{Ar}), 171.6 (CO). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 1663 (s), 1607 (m), 1561 (m), 1261 (s), 1220 (m), 1196 (m), 1160 (m), 1102 (w), 1043 (m), 1007 (m), 848 (m), 806 (m), 766 (w), 649 (s). MS (EI, 70 eV): m/z (%) = 276 ([M$^+$], 98), 244 (100), 216 (91), 201 (41), 187 (23), 173 (25), 115 (15), 97 (8), 69 (10), 55 (8), 43 (8). HRMS (CI, positive): calcd for $C_{15}H_{17}O_3S$ ([M + 1]$^+$): 277.08929; found: 277.08890.

Ethyl 3,4-diethyl-2-hydroxy-6-(2-thienyl)-benzoate (6h). Starting with **4b** (0.448 g, 2.0 mmol), **5c** (0.659 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6h** was isolated as a reddish viscous oil (0.186 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, ^3J = 7.0 Hz, 3 H, CH_2CH_3), 1.09 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.12 (t, ^3J = 7.6 Hz, 3 H, OCH_2CH_3), 2.56 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 2.64 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.96 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 6.67 (s, 1 H, CH_{Ar}), 6.76–6.78 (m, 1 H, CH_{Hetar}), 6.90 (dd, ^3J = 5.1 Hz, ^4J = 1.5 Hz, 1 H, CH_{Hetar}), 7.17 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 10.99 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_2CH_3), 14.4 (CH_2CH_3), 16.6 (OCH_2CH_3), 19.5 (CH_2CH_3), 26.4 (CH_2CH_3), 61.3 (OCH_2CH_3), 110.8 ($CCOOCH_2CH_{3Ar}$), 124.2 (CH_{Ar}), 125.9, 126.1, 127.1 (CH_{Hetar}), 134.0, 139.7 (C_{Ar}), 144.8 (C_{Hetar}), 148.1 (C_{Ar}), 160.4 (COH_{Ar}), 171.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2968 (s), 2874 (m), 1657 (s), 1606 (m), 1559 (m), 1463 (m), 1394 (s), 1322 (m), 1274 (s), 1242 (m), 1220 (s), 1175 (s), 1109 (m), 1030 (m), 870 (w), 812 (m), 694 (s). MS (EI, 70 eV): m/z (%) = 304 ([M$^+$], 47), 258 (100), 229 (31), 215 (52), 201 (6), 187 (7), 171 (13), 153 (6), 97 (11), 81(9), 69 (14), 55 (13), 41 (11). HRMS (EI): calcd for $C_{17}H_{20}O_3S$ [M$^+$]: 304.11277; found: 304.11299.

Methyl 4-ethyl-3-hexyl-2-hydroxy-6-(2-thienyl)-benzoate (6i). Starting with **4b** (0.425 g, 1.7 mmol), **5d** (0.628 g, 1.8 mmol) and $TiCl_4$ (0.20 mL, 1.8 mmol), **6i** was isolated as a reddish viscous oil (0.156 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (t(br), ^3J = 7.0 Hz, 3 H, $CH_2(CH_2)_4CH_3$), 1.03 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 1.08–1.14 (m, 8 H, $CH_2(CH_2)_4CH_3$), 2.46 (q, ^3J = 7.2 Hz, 2 H, CH_2CH_3), 2.48 (q, ^3J = 8.1 Hz, 2 H, $CH_2(CH_2)_4CH_3$), 3.41 (s, 3 H, OCH_3), 6.59 (m, 1 H, CH_{Ar}), 6.70 (m, 1 H, CH_{Hetar}), 6.82 (dd, ^3J = 6.4 Hz, ^4J = 1.7 Hz, 1 H, CH_{Hetar}), 7.07–7.09 (m, 1 H, CH_{Hetar}), 10.71 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 ($(CH_2)_5CH_3$), 20.9 (CH_2CH_3), 23.8, 27.2, 30.4, 30.7, 31.0, 33.1 (CH_2), 53.0 (OCH_3), 111.2 ($CCOOCH_{3Ar}$), 124.9 (CH_{Ar}), 125.9, 126.6, 127.6 (CH_{Hetar}), 130.4, 134.6 (C_{Ar}), 145.8 (C_{Hetar}), 149.3 (C_{Ar}), 160.8 (COH_{Ar}), 172.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2925 (s), 2854 (m), 1661 (s), 1606 (m), 1559 (m), 1439 (s), 1396 (s), 1324 (m), 1263 (s), 1220 (s), 1197 (m), 1162 (m), 1125 (w), 849 (m), 813 (w), 649 (m). GC-MS (EI, 70 eV): m/z (%) = 346 ([M$^+$], 43), 314 (8), 285 (100), 271 (5), 257 (8), 244 (55), 215 (13), 187 (4), 171 (12), 153 (4), 85 (8), 71 (11), 57 (15), 43 (13). HRMS (EI): calcd for $C_{20}H_{26}O_3S$ [M$^+$]: 346.15972; found: 346.15989.

Methyl 2-hydroxy-4-propyl-6-(2-thienyl)-benzoate (6j). Starting with **4c** (0.536 g, 2.0 mmol), **5a** (0.568 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6j** was isolated as a reddish viscous oil (0.214 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.45–1.58 (m, 2 H, $CH_2CH_2CH_3$), 2.42 (t, ^3J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 3.46 (s, 3 H, OCH_3), 6.62 (s, 1 H, CH_{Ar}), 6.70 (s, 1 H, CH_{Ar}), 6.77 (m, 1 H, CH_{Hetar}), 6.86 (m, 1 H, CH_{Hetar}), 7.15 (d, ^3J = 6.3 Hz, 1 H, CH_{Hetar}), 10.57 (s, 1 H, OH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 23.6, 37.7 (CH_2), 51.7 (OCH_3), 110.2 ($CCOOMe_{Ar}$), 117.1, 124.3 (CH_{Ar}), 124.9, 125.6, 126.4 (CH_{Hetar}), 136.7, 143.7 (C_{Ar}), 149.2 (C_{Hetar}), 161.4 (COH_{Ar}), 171.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3012 (w), 2844 (w), 1662 (s), 1499 (m), 1459 (s), 1378 (s), 1239 (s), 1106 (m), 1074 (m), 1025 (m), 806 (m). MS (EI, 70 eV): m/z (%) = 276 ([M$^+$], 60), 244 (100), 229 (5), 216 (97), 187 (24), 160 (10), 115 (20). HRMS (EI): calcd for $C_{15}H_{16}SO_3$ [M$^+$]: 276.08147; found: 276.08178.

Methyl 2-hydroxy-3-methyl-4-propyl-6-(2-thienyl)-benzoate (6k). Starting with **4c** (0.537 g, 2.0 mmol), **5b** (0.604 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6k** was isolated as a reddish viscous oil (0.274 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.46–1.49 (m, 2 H, $CH_2CH_2CH_3$), 2.14 (s, 3 H, CH_3), 2.49 (t, ^3J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 3.49 (s, 3 H, OCH_3), 6.66 (s, 1 H, CH_{Ar}), 6.78–6.79 (m, 1 H, CH_{Hetar}), 6.90 (dd, ^3J = 5.1 Hz, ^4J = 1.5 Hz, 1 H, CH_{Hetar}), 7.17 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 10.88 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7 ($CH_2CH_2CH_3$), 14.7 (CH_3), 23.1 ($CH_2CH_2CH_3$), 36.3 ($CH_2CH_2CH_3$), 52.2 (OCH_3),

110.2 ($CCOOMe_{Ar}$), 124.8 (CH_{Ar}), 125.9, 126.8, 127.5 (CH_{Hetar}), 133.5, 140.0 (C_{Ar}), 144.6 (C_{Hetar}), 147.5 (C_{Ar}), 160.1 (COH_{Ar}), 172.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2957 (s), 2871 (m), 1662 (s), 1607 (m), 1562 (m), 1438 (s), 1397 (s), 1312 (m), 1266 (s), 1198 (m), 1161 (m), 1011 (w), 849 (w), 807 (m), 747 (w), 697 (m). MS (EI, 70 eV): *m*/*z* (%) = 290 ([M^+], 72), 258 (100), 229 (18), 215 (25), 202 (55), 187 (13), 171 (13), 158 (4), 128 (9), 115 (10), 89 (3), 77 (4), 45 (3). HRMS (EI): calcd for $C_{16}H_{18}O_3S$ [M^+]: 290.09712; found: 290.09699.

Ethyl 3-ethyl-2-hydroxy-4-propyl-6-(2-thienyl)-benzoate (6l). Starting with **4c** (0.537 g, 2.0 mmol), **5c** (0.659 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6l** was isolated as a reddish viscous oil (0.245 g, 42%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, ^3J = 7.0 Hz, 3 H, $CH_2CH_2CH_3$), 0.89 (t, ^3J = 7.2 Hz, 3 H, CH_2CH_3), 1.09 (t, ^3J = 7.4 Hz, 3 H, OCH_2CH_3), 1.49–1.56 (m, 2 H, $CH_2CH_2CH_3$), 2.50 (t, ^3J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 2.64 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.96 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 6.66 (s, 1 H, CH_{Ar}), 6.76–6.77 (m, 1 H, CH_{Hetar}), 6.88 (dd, ^3J = 5.1 Hz, ^4J = 1.5 Hz, 1 H, CH_{Hetar}), 7.16 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 10.99 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 ($CH_2CH_2CH_3$), 14.3 (CH_2CH_3), 14.6 (OCH_2CH_3), 19.6 ($CH_2CH_2CH_3$), 24.5 ($CH_2CH_2CH_3$), 35.5 (CH_2CH_3), 61.3 (OCH_2CH_3), 110.8 ($CCOOCH_2CH_{3Ar}$), 124.8 (CH_{Ar}), 125.0, 125.9, 126.7 (CH_{Hetar}), 131.0, 133.7 (C_{Ar}), 142.6 (C_{Hetar}), 144.8 (C_{Ar}), 160.2 (COH_{Ar}), 171.6 (CO). GC-MS (EI, 70 eV): *m*/*z* (%) = 318 ([M^+], 62), 272 (100), 257 (64), 244 (18), 229 (45), 216 (7), 201 (7), 187 (5), 171 (14), 153 (4), 115 (7), 97 (3), 77 (3). HRMS (EI): calcd for $C_{18}H_{22}O_3S$ [M^+]: 318.12842; found: 318.12842.

Methyl 3-hexyl-2-hydroxy-4-propyl-6-(2-thienyl)-benzoate (6m). Starting with **4c** (0.537 g, 2.0 mmol), **5d** (0.812 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **6m** was isolated as a reddish viscous oil (0.273 g, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.71 (t(br), ^3J = 4.7 Hz, 3 H, $CH_2(CH_2)_4CH_3$), 0.81 (t, ^3J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.08 (m, 8 H, $CH_2(CH_2)_4CH_3$), 1.39–1.47 (m, 2 H, $CH_2CH_2CH_3$), 2.41 (t, ^3J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 2.49 (t, ^3J = 7.4 Hz, 2 H, $CH_2(CH_2)_4CH_3$), 3.41 (s, 3 H, OCH_3), 6.57 (m, 1 H, CH_{Ar}), 6.69–6.71 (m, 1 H, CH_{Hetar}), 6.81 (dd, ^3J = 4.9 Hz, ^4J = 1.5 Hz, 1 H, CH_{Hetar}), 7.10 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 10.71 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 ($(CH_2)_5CH_3$), 13.2 ($CH_2CH_2CH_3$), 21.6, 23.0, 25.0, 28.5, 28.6, 30.7, 34.2 (CH_2), 50.8 (OCH_3), 108.9 ($CCOOCH_{3Ar}$), 123.5 (CH_{Ar}), 123.6, 124.4, 125.4 (CH_{Hetar}), 128.5, 132.1 (C_{Ar}), 143.3 (C_{Hetar}), 145.7 (C_{Ar}), 158.7 (COH_{Ar}), 170.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2927 (s), 2870 (m), 1663 (s), 1605 (m), 1559 (m), 1437 (s), 1396 (s), 1268 (s), 1161 (s), 1114 (w), 1015 (w), 810 (m), 693 (s). MS (EI, 70 eV): *m*/*z* (%) = 360 ([M^+], 79), 328 (35), 311 (21), 285 (100), 271 (13), 258 (73), 243 (28), 201 (11), 171 (11), 97 (6), 83 (6), 57 (11). HRMS (CI, positive): calcd for $C_{21}H_{29}O_3S$ ([M + 1]$^+$): 361.18319; found: 361.18305.

Methyl 4-ethyl-2-(2-furyl)-6-hydroxy-benzoate (6n). Starting with **4d** (0.380 g, 1.6 mmol), **5a** (0.426 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **6n** was isolated as a yellow oil (0.125 g, 32%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 2.63 (q, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 3.71 (s, 3 H, OCH_3), 6.39 (m, 1 H, CH_{Hetar}), 6.45 (m, 1 H, CH_{Hetar}), 6.82 (s, 1 H, CH_{Ar}), 7.46 (m, 1 H, CH_{Hetar}), 10.43 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (CH_2CH_3), 29.0 (CH_2CH_3), 52.6 (OCH_3), 107.2 (CH_{Ar}), 109.4 ($CCOOCH_{3Ar}$), 111.1 (CH_{Ar}), 116.8, 122.1 (CH_{Hetar}), 132.6 (C_{Ar}), 142.1 (CH_{Hetar}), 151.1 (C_{Ar}), 154.1 (C_{Heter}), 161.2 (COH_{Ar}), 170.8 (CO). MS (EI, 70 eV): *m*/*z* (%) = 246 ([M^+], 36), 214 (100), 186 (28), 171 (19), 128 (7), 115 (12). HRMS (EI): calcd for $C_{14}H_{14}O_4$ [M^+]: 246.08866; found: 246.08807.

Methyl 4-ethyl-6-(2-furyl)-2-hydroxy-3-methyl-benzoate (6o). Starting with **4d** (0.261 g, 1.1 mmol), **5b** (0.190 g, 1.1 mmol) and $TiCl_4$ (0.12 mL, 1.1 mmol), **6o** was isolated as a yellowish viscous oil (0.085 g, 30%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.2 Hz, 3 H, CH_2CH_3), 2.16 (s, 3 H, CH_3), 2.58 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.41 (s, 3 H, OCH_3), 6.28–6.30 (m, 1 H, CH_{Hetar}), 6.36–6.39 (m, 1 H, CH_{Hetar}), 6.73 (s, 1 H, CH_{Ar}), 7.36 (m, 1 H, CH_{Hetar}), 10.72 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_2CH_3), 14.3 (CH_3), 29.8 (CH_2CH_3), 52.6 (OCH_3), 106.8, 109.1 (CH_{Hetar}), 113.3 ($CCOOCH_{3Ar}$), 122.2 (C_{Ar}), 124.9, 129.9 (C_{Ar}) 142.0 (CH_{Hetar}), 149.0 (C_{Ar}), 154.7 (C_{Hetar}), 159.6 (COH_{Ar}), 170.6 (CO). GC-MS (EI, 70 eV): *m*/*z* (%) = 260 ([M^+], 43), 228 (100), 200 (49), 185 (12), 171 (7), 157 (13), 128 (16), 115 (11). HRMS (EI): calcd for $C_{15}H_{16}O_4$ [M^+]: 260.104319; found: 260.10424.

General procedure for the synthesis of 8. To a stirred dimethylsulfoxide solution (1 mL per 1.0 mmol of **3**) of **3** (10.0 mmol) was added potassium carbonate (40.0 mmol) at room temperature. After the solution had been stirred for 30 min, 1,2-dibromoethane (20.0 mmol) was added at 20 °C. After the solution had been stirred for 12 h, an excess amount of water was added to remove dimethylsulfoxide and the mixture was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, *n*-heptane–EtOAc = 30 : 1 → 20 : 1) to give **8**.

1-[1-(2-Thienylcarbonyl)cyclopropyl]-1-ethanone (8a). Starting with dimethysulfoxide (17.8 mL), **3b** (3.250 g, 17.840 mmol), K_2CO_3 (9.863 g, 71.4 mmol) and 1,2-dibromoethane (6.704 g, 35.7 mmol), **8a** was isolated as a reddish oil (3.417 g, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.34 (t, ^3J = 3.1 Hz, 2 H, CH_2), 1.43 (t, ^3J = 3.2 Hz, 2 H, CH_2), 2.42 (q, ^3J = 7.3 Hz, 2 H, CH_2CH_3), 7.05 (dd, ^3J = 4.9 Hz, ^4J = 1.1 Hz, 1 H, CH_{Hetar}), 7.56–7.58 (m, 1 H, CH_{Hetar}), 7.60–7.62 (m, 1 H, CH_{Hetar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4 (CH_2CH_3), 16.1 (2 CH_2), 35.2 (CH_2CH_3), 41.6 (COCCO), 128.2, 133.6, 134.2 (CH_{Hetar}), 143.4 (C_{Hetar}), 188.7, 206.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2977 (w), 1700 (m), 1647 (s), 1512 (w), 1409 (s), 1315 (m), 1233 (m), 1052 (m), 972 (w), 794 (w), 721 (s), 657 (w). GC-MS (EI, 70 eV): *m*/*z* (%) = 208 ([M^+], 16), 193 (10), 179 (22), 151 (9), 111 (100), 83 (8), 57 (13), 39 (13). HRMS (EI): calcd for $C_{11}H_{12}O_2S$ [M^+]: 208.05507; found: 208.05475.

General procedure for the synthesis of salicylates 9. To a CH_2Cl_2 solution (50 mL per 1.0 mmol of **8**) of **8** (1.0 mmol) was added **5** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C over 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer 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 **9**.

Methyl 5-(2-chloroethyl)-4-ethyl-2-hydroxy-6-(2-thienyl)-benzoate (9a). Starting with **8a** (0.312 g, 1.2 mmol), **5a** (0.429 g, 1.6 mmol) and $TiCl_4$ (0.570 mL, 3.0 mmol), **9a** was isolated as reddish viscous oil (0.204 g, 42%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 2.92 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.08 (t, ^3J = 7.5 Hz, 2 H, CH_2CH_2Cl), 3.36 (t, ^3J = 8.1 Hz, 2 H, CH_2CH_2Cl), 3.92 (s, 3 H, OCH_3), 6.95 (s, 1 H, CH_{Ar}), 6.96 (s, 1 H, CH_{Hetar}), 7.03 (d, ^3J = 5.1 Hz, 1 H, CH_{Hetar}), 7.32 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1 H, CH_{Hetar}), 10.42 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 15.9 (CH_2CH_3), 26.6 (CH_2CH_3), 32.9 (CH_2CH_2Cl), 43.4 (CH_2CH_2Cl), 52.5 (OCH_3), 112.6 ($CCOOCH_{3Ar}$), 118.2 (CH_{Ar}), 126.1 (CH_{Hetar}), 126.8 (C_{Ar}), 126.9, 127.0 (CH_{Hetar}), 141.1, 141.3 (C_{Ar}), 145.8 (C_{Hetar}), 159.4 (COH_{Ar}), 170.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2923 (w), 1661 (s), 1597 (w), 1569 (m), 1434 (s), 1337 (m), 1234 (s), 1203 (s), 1142 (m), 1080 (m), 939 (w), 807 (m), 788 (m), 692 (s). MS (EI, 70 eV): *m*/*z* (%) = 326 ([M$^+$], ^{37}Cl, 8), 324 ([M$^+$], ^{35}Cl, 21), 294 (^{37}Cl, 17), 292 (^{35}Cl, 49), 275 (6), 245 (^{37}Cl, 5), 243 (^{35}Cl, 100), 215 (4), 187 (5), 171 (6), 119 (9), 97 (11), 83 (11), 69 (24), 57 (19). HRMS (EI): calcd for $C_{16}H_{17}ClO_3S$ ([M]$^+$, ^{35}Cl): 324.05796; found: 324.05780.

Methyl 5-(2-chloroethyl)-4-ethyl-2-hydroxy-3-methyl-6-(2-thienyl)-benzoate (9b). Starting with **8a** (0.312 g, 1.2 mmol), **5b** (0.452 g, 1.7 mmol) and $TiCl_4$ (0.570 mL, 3.0 mmol), **9b** was isolated as a colourless viscous oil (0.200 g, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.88 (s, 3 H, CH_3), 2.86 (q, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 2.89 (t, ^3J = 7.3 Hz, 2 H, CH_2CH_2Cl), 3.42 (t, ^3J = 6.5 Hz, 2 H, CH_2CH_2Cl), 3.92 (s, 3 H, OCH_3), 6.74–6.76 (m, 1 H, CH_{Hetar}), 7.05 (dd, ^3J = 5.2 Hz, ^4J = 1.7 Hz, 1 H, CH_{Hetar}), 7.36 (d, ^3J = 6.2 Hz, 1 H, CH_{Hetar}), 10.71 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.7 (CH_2CH_3), 15.7 (CH_3), 23.3 (CH_2CH_3), 32.8 (CH_2CH_2Cl), 42.8 (CH_2CH_2Cl), 51.5 (OCH_3), 112.0 ($CCOOCH_{3Ar}$), 124.8, 125.7, 126.1 (CH_{Hetar}), 126.7, 139.1, 139.9, 140.8 (C_{Ar}), 140.8 (C_{Hetar}), 157.1 (COH_{Ar}), 170.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 1642 (s), 1567 (w), 1434 (m), 1325 (m), 1236 (s), 1209 (s), 1122 (s), 1035 (m), 814 (s), 716 (s), 666 (m), 554 (m). MS (EI, 70 eV): *m*/*z* (%) = 340 ([M$^+$], ^{37}Cl, 17), 338 ([M$^+$], ^{35}Cl, 36), 308 (^{37}Cl, 33), 306 (^{35}Cl, 100), 289 (7), 271 (7), 257 (68), 243 (51), 229 (7), 214 (5), 177 (10), 161 (7), 135 (6), 111 (8), 97 (12), 83 (13), 69 (21), 57 (24). HRMS (EI): calcd for $C_{17}H_{19}ClO_3S$ ([M]$^+$, ^{35}Cl): 338.07361; found: 338.07354.

Ethyl 5-(2-chloroethyl)-3,4-diethyl-2-hydroxy-6-(2-thienyl)-benzoate (9c). Starting with **8a** (0.312 g, 1.2 mmol), **5c** (0.499 g, 1.6 mmol) and $TiCl_4$ (0.570 mL, 3.0 mmol), **9c** was isolated as a colourless oil (0.194 g, 34%).^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.15 (t, ^3J = 7.2 Hz, 3 H, CH_2CH_3), 1.38 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 2.32 (q, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 2.67 (t, ^3J = 7.5 Hz, 2 H, CH_2CH_2Cl), 2.88 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 3.34 (t, ^3J = 5.0 Hz, 2 H, CH_2CH_2Cl), 4.40 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 6.77 (d, ^3J = 4.6 Hz, 1 H, CH_{Hetar}), 7.04 (dd, ^3J = 5.1 Hz, ^4J = 1.7 Hz, 1 H, CH_{Hetar}), 7.33 (d, ^3J = 6.2 Hz, 1 H, CH_{Hetar}), 10.75 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.0, 13.3, (CH_2CH_3), 15.1 (OCH_2CH_3), 18.3 (CH_2CH_3), 23.3 (CH_2CH_2Cl), 32.9 (CH_2CH_3), 42.9 (CH_2CH_2Cl), 60.9 (OCH_2CH_3), 112.5 ($CCOOC_2H_{5Ar}$), 124.6 (CH_{Hetar}), 125.3 (C_{Ar}), 125.9, 126.8 (CH_{Hetar}), 130.9, 138.8, 139.1 (C_{Ar}), 140.8 (C_{Hetar}), 157.1 (COH_{Ar}), 170.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2963 (w), 1651 (s), 1589 (w), 1446 (w), 1396 (m), 1371 (s), 1277 (s), 1194 (s), 1121 (m), 1018 (m), 814 (w), 693 (s). MS (EI, 70 eV): *m*/*z* (%) = 368 ([M$^+$], ^{37}Cl, 18), 366 ([M$^+$], ^{35}Cl, 55), 341 (15), 344 (56), 322 (^{37}Cl, 38), 320 (^{35}Cl, 100), 287 (34), 271 (23), 257 (61), 243 (19), 228 (10), 213 (5), 177 (94), 161 (60), 149 (40), 129 (22). HRMS (EI): calcd for $C_{19}H_{23}ClO_3S$ ([M]$^+$, ^{35}Cl): 366.10509; found: 366.10404.

Methyl 5-(2-chloroethyl)-4-ethyl-3-hexyl-2-hydroxy-6-(2-thienyl)-benzoate (9d). Starting with **8a** (0.312 g, 1.2 mmol), **5d** (0.587 g, 1.6 mmol) and $TiCl_4$ (0.570 mL, 3.0 mmol), **9d** was isolated as a colourless oil (0.186 g, 32%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.75 (t (br), ^3J = 7.0 Hz, 3 H, $CH_2(CH_2)_4CH_3$), 1.10 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.14–1.16 (m, 8 H, $CH_2(CH_2)_4CH_3$), 1.29–1.32 (m, 2 H, $CH_2(CH_2)_4CH_3$), 2.27 (q, ^3J = 6.1 Hz, 2 H, CH_2CH_3), 2.85 (t, ^3J = 6.2 Hz, 2 H, CH_2CH_2Cl), 3.34 (t, ^3J = 5.5 Hz, 2 H, CH_2CH_2Cl), 3.91 (s, 3 H, OCH_3), 6.75–6.77 (m, 1 H, CH_{Hetar}), 7.03 (dd, ^3J = 5.2 Hz, ^4J = 1.7 Hz, 1 H, CH_{Hetar}), 7.33 (d, ^3J = 6.3 Hz, 1 H, CH_{Hetar}), 10.61 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.0 ($CH_2)_5CH_3$), 16.0, (CH_2CH_3), 22.4, 23.1, 28.3, 29.8, 29.9, 31.3, 33.9, 43.9 (8 CH_2), 52.4 (OCH_3), 112.3 ($CCOOC_2H_{5Ar}$), 122.7 (C_{Ar}), 125.3, 125.8, 126.0 (CH_{Hetar}), 130.2, 138.7, 139.4 (C_{Ar}), 140.8 (C_{Hetar}), 157.0 (COH_{Ar}), 170.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 16582 (m), 1590 (w), 1432 (m), 1316 (m), 1202 (m), 1124 (m), 1070 (w), 833 (w), 817 (w), 693 (m). GC–MS (EI, 70 eV): *m*/*z* (%) = 410 ([M$^+$], ^{37}Cl, 27), 408 ([M$^+$], ^{35}Cl, 74), 378 (^{37}Cl, 36), 376 (^{35}Cl, 100), 359 (27), 313 (42), 285 (12), 243 (48), 227 (8), 184 (7), 112 (4). HRMS (EI): calcd for $C_{22}H_{29}ClO_3S$ ([M]$^+$, ^{35}Cl): 408.15204; found: 408.15396.

General procedure for the synthesis of salicylates 10. To a CH_2Cl_2 solution (2 mL per 1 mmol of **4**) of **4** (1.0 mmol) was added **5** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C over 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer 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 **10**.

Methyl 2-hydroxy-4-(2-thienyl)-6-(trifluoromethyl)-benzoate (10a). Starting with **4e** (0.442 g, 1.5 mmol), **5a** (0.430 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **10a** was isolated as a colourless solid (0.160 g, 35%), mp = 126–128 °C.^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 7.05 (dd, ^3J = 5.1 Hz, ^4J = 1.4 Hz, 1 H, CH_{Heter}), 7.33–7.35 (m, 2 H, CH_{Heter}), 7.37–7.39 (m, 1 H, CH_{Ar}), 7.47 (m, 1 H, CH_{Ar}), 10.86 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 109.2 ($CCOOCH_{3Ar}$), 116.6 (d, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 117.8 (CH_{Ar}), 123.1 (d, $^1J_{F,C}$ = 269.7 Hz, CF_3), 125.7, 127.5, 128.5 (CH_{Heter}), 130.5 (d, $^2J_{F,C}$ = 31.6 Hz, CCF_{3Ar}), 139.7 (C_{Heter}), 141.2 (C_{Ar}), 162.4 (COH_{Ar}), 169.3 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −59.0 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2964 (w), 2857 (w), 1672 (m), 1614 (w), 1440 (m), 1422 (m), 1326 (m), 1228 (w), 1127 (m), 1030 (m), 923 (m), 869 (m), 717 (m). GC-MS (EI, 70 eV): *m*/*z* (%) = 302 ([M$^+$], 81), 270 (100), 242 (41), 223 (9), 214 (40), 194 (4), 169 (4), 145 (16), 121 (13). HRMS (EI): calcd for $C_{13}H_9O_3F_3S$: 302.02190; found: 302.02202.

Methyl 2-hydroxy-3-methyl-4-(2-thienyl)-6-(trifluoromethyl)-benzoate (10b). Starting with **4e** (0.442 g, 1.5 mmol), **5b** (0.452 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **10b** was isolated as a colourless solid (0.215 g, 45%), mp = 72–74 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 7.04 (d, $^4J_{H,F}$ = 2.2 Hz, 1 H, CH_{Ar}), 7.07 (m, 1 H, CH_{Heter}), 7.30 (m, 1 H, CH_{Heter}), 7.36 (m, 1 H, CH_{Heter}), 11.16 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.8 (CH_3), 51.8 (OCH_3), 107.7 ($CCOOCH_{3Ar}$), 119.8 (d, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 122.3 (d, $^1J_{F,C}$ = 271.5 Hz, CF_3), 125.8 (CH_{Heter}), 126.0 (d, $^2J_{F,C}$ = 31.5 Hz, CCF_{3Ar}), 126.3, 126.9 (CH_{Heter}), 128.8, 138.3 (C_{Ar}), 139.6 (C_{Heter}), 159.7 (COH_{Ar}), 169.0 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.6 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2853 (w), 1683 (m), 1606 (w), 1436 (m), 1315 (m), 1275 (s), 1112 (s), 1013 (m), 937 (m), 882 (m), 687 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 316 ([M$^+$], 66), 284 (29), 256 (100), 237 (5), 207 (11), 187 (10), 159 (8), 134 (4), 115 (6). HRMS (EI): calcd for $C_{14}H_{11}O_3F_3S$: 316.03755; found: 316.03784.

Ethyl 3-ethyl-2-hydroxy-4-(2-thienyl)-6-(trifluoromethyl)-benzoate (10c). Starting with **4e** (0.442 g, 1.5 mmol), **5c** (0.499 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **10c** was isolated as a yellow oil (0.230 g, 44%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 2.74 (q, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 4.38 (q, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 7.03 (m, 1 H, CH_{Heter}), 7.04 (d, $^4J_{H,F}$ = 1.4 Hz, 1 H, CH_{Ar}), 7.26 (m, 1 H, CH_{Heter}), 7.33–7.35 (m, 1 H, CH_{Heter}), 11.19 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2 (CH_3), 21.0 (CH_2CH_3), 62.5 (OCH_2CH_3), 109.5 ($CCOOCH_2CH_{3Ar}$), 121.2 (d, $^3J_{F,C}$ = 7.5 Hz, CH_{Ar}), 123.3 (d, $^1J_{F,C}$ = 271.5 Hz, CF_3), 126.6 (CH_{Heter}), 127.0 (d, $^2J_{F,C}$ = 31.5 Hz, CCF_{3Ar}), 127.3, 127.4 (CH_{Heter}), 136.0, 138.8 (C_{Ar}), 140.5 (C_{Heter}), 160.6 (COH_{Ar}), 169.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2930 (w), 2874 (w), 1666 (m), 1608 (w), 1463 (w), 1372 (m), 1288 (s), 1231 (m), 1137 (s), 1013 (m), 932 (m), 883 (w), 696 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 344 ([M$^+$], 45), 298 (15), 270 (100), 255 (4), 222 (4), 207 (6), 171 (5).

Methyl 3-hexyl-2-hydroxy-4-(2-thienyl)-6-(trifluoromethyl)-benzoate (10d). Starting with **4e** (0.442 g, 1.5 mmol), **5d** (0.568 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **10d** was isolated as a colourless viscous oil (0.196 g, 34%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (t(br), ^3J = 6.6 Hz, 3 H, $CH_2(CH_2)_4CH_3$), 1.18–1.51 (m, 8 H, $CH_2(CH_2)_4CH_3$), 2.69 (t, ^3J = 8.2 Hz, 2 H, $CH_2(CH_2)_4CH_3$), 3.92 (s, 3 H, OCH_3), 7.02 (m, 1 H, CH_{Ar}), 7.04–7.06 (m, 1 H, CH_{Heter}), 7.26 (m, 1 H, CH_{Heter}), 7.35 (dd, ^3J = 4.8 Hz, ^4J = 1.3 Hz, 1 H, CH_{Heter}), 11.05 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.0 (CH_3), 21.5, 26.6, 28.3, 28.4, 30.4 (CH_2), 51.8 (OCH_3), 108.2 ($CCOOCH_{3Ar}$), 120.2 (q, $^3J_{F,C}$ = 8.2 Hz, CH_{Ar}), 122.4 (d, $^1J_{F,C}$ = 250.4 Hz, CF_3), 125.7(C_{Ar}), 125.6, 126.2, 126.4 (CH_{Heter}), 134.0, 138.1 (C_{Ar}), 139.5 (C_{Heter}), 159.5 (COH_{Ar}), 169.1 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.7 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2928 (w), 2849 (w), 1672 (m), 1601 (w), 1439 (m), 1356 (m), 1298 (s), 1198 (m), 1124 (s), 1047 (w), 940 (m), 810 (m), 701 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 386 ([M$^+$], 100), 354 (25), 337 (11), 326 (94), 315 (8), 297 (14), 283 (59), 256 (54), 235 (7), 207 (28), 187 (7), 158 (14). HRMS (EI): calcd for $C_{19}H_{21}O_3F_3S$: 386.11580; found: 386.11536.

Methyl 2-hydroxy-3-octyl-4-(2-thienyl)-6-(trifluoromethyl)-benzoate (10e). Starting with **4e** (0.442 g, 1.5 mmol), **5e** (0.614 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol), **10e** was isolated as a colourless viscous oil (0.231 g, 37%), mp = 49–50 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.58 (t(br), ^3J = 6.9 Hz, 3 H, $CH_2(CH_2)_6CH_3$), 0.95–1.26 (m, 12 H, $CH_2(CH_2)_6CH_3$), 2.47 (t, ^3J = 8.1 Hz, 2 H, $CH_2(CH_2)_6CH_3$), 3.70 (s, 3 H, OCH_3), 6.80 (m, 1 H, CH_{Ar}), 6.83 (m, 1 H, CH_{Heter}), 7.04 (m, 1 H, CH_{Heter}), 7.13 (dd, ^3J = 6.3 Hz, ^4J = 1.3 Hz, 1 H, CH_{Heter}), 10.82 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 27.6, 29.1, 29.2, 29.4, 29.7, 31.8 (CH_2), 52.8 (OCH_3), 109.2 ($CCOOCH_{3Ar}$), 121.3 (q, $^3J_{F,C}$ = 6.7 Hz, CH_{Ar}), 123.3 (d, $^1J_{F,C}$ = 271.5 Hz, CF_3), 126.5 (d, $^2J_{F,C}$ = 31.5 Hz, CCF_{3Ar}), 126.6, 127.2, 127.4 (CH_{Heter}), 135.0, 139.1 (C_{Ar}), 140.5 (C_{Heter}), 160.5 (COH_{Ar}), 170.1 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.7 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2915 (w), 2848 (w), 1669 (m), 1604 (w), 1440 (m), 1338 (m), 1286 (m), 1197 (m), 1125 (s), 1048 (w), 946 (m), 852 (w), 698 (s). GC-MS (EI, 70 eV): *m*/*z* (%) = 414 ([M$^+$], 100), 382 (30), 365 (12), 297 (16), 284 (33), 283 (63), 269 (74), 256 (48), 235 (7), 207 (24), 158 (12). HRMS (EI): calcd for $C_{21}H_{25}O_3F_3S$: 414.14710; found: 414.14684.

Methyl 2-hydroxy-4-(2-furanyl)-6-(trifluoromethyl)-benzoate (10f). Starting with **4f** (0.556 g, 2.0 mmol), **5a** (0.567 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **10f** was isolated as a colourless solid (0.231 g, 40%), mp = 116–118 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 6.45 (q, $^4J_{H,F}$ = 1.7 Hz, 1 H, CH_{Ar}), 6.78 (dd, ^3J = 4.1 Hz, ^4J = 0.6 Hz, 1 H, CH_{Heter}), 7.37 (m, 1 H, CH_{Heter}), 7.47 (m, 1 H, CH_{Ar}), 7.52 (m, 1 H, CH_{Heter}), 10.84 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 108.9, 112.2 (CH_{Heter}), 114.7 (q, $^3J_{F,C}$ = 6.7 Hz, CH_{Ar}), 115.6 (CH_{Ar}), 117.7 ($CCOOCH_{3Ar}$), 123.1 (d, $^1J_{F,C}$ = 271.5 Hz, CF_3), 131.0 (d, $^2J_{F,C}$ = 32.2 Hz, CCF_{3Ar}), 135.6 (C_{Ar}), 144.0 (CH_{Heter}), 151.2 (C_{Heter}), 162.4 (COH_{Ar}), 169.4 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −59.0 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 2852 (w), 1660 (m), 1621 (w), 1440 (m), 1335 (m), 1290 (m), 1212 (m), 1126 (m), 1016 (m), 904 (m), 802 (m), 760 (m). GC-MS (EI, 70 eV): *m*/*z* (%) = 286 ([M$^+$], 81), 254 (100), 226 (69), 207 (10), 198 (23), 169 (16), 151 (21), 129 (4), 113 (8), 75 (5). HRMS (EI): calcd for $C_{13}H_9O_4F_3$: 286.04474; found: 286.04447.

Methyl 4-(2-furanyl)-2-hydroxy-3-methyl-6-(trifluoromethyl)-benzoate (10g). Starting with **4f** (0.4176 g, 1.5 mmol), **5b** (0.452 g, 1.6 mmol) and $TiCl_4$ (0.18 mL, 2.2 mmol), **10g** was isolated as a red solid (0.186 g, 41%), mp = 79–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 6.48 (dd, ^3J = 5.2 Hz, ^4J = 1.8 Hz, 1 H, CH_{Heter}), 6.65–6.67 (m, 1 H, CH_{Heter}), 7.50 (m, 1 H, CH_{Ar}), 7.60 (m, 1 H, CH_{Heter}), 11.21 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.5 (CH_3), 51.8 (OCH_3), 107.1 ($CCOOCH_{3Ar}$), 110.8, 110.9 (CH_{Heter}), 116.4 (q, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 122.4 (d, $^1J_{F,C}$ = 271.5 Hz, CF_3), 124.6 (C_{Ar}), 126.4 (d, $^2J_{F,C}$ = 32.2 Hz, CCF_{3Ar}), 133.6 (C_{Ar}), 142.1 (CH_{Heter}), 150.3 (C_{Heter}), 159.8 (COH_{Ar}), 169.1 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.8 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 2850 (w), 1798 (m), 1658 (m), 1438 (m), 1338 (m), 1282 (s), 1120 (s), 1018 (m), 936 (m), 804 (m), 754 (m). GC-MS (EI, 70 eV): *m*/*z* (%) = 300 ([M$^+$], 100), 268 (78), 248 (80), 219 (9), 192 (10), 164 (26), 133 (11), 115 (21). HRMS (EI): calcd for $C_{14}H_{11}O_4F_3$: 300.06039; found: 300.05967.

Ethyl 3-ethyl-4-(2-furanyl)-2-hydroxy-6-(trifluoromethyl)-benzoate (10h). Starting with **4f** (0.556 g, 2.0 mmol), **5c** (0.652 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **10h** was isolated as a red viscous oil (0.226 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$):

δ = 1.18 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.34 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 2.87 (q, ^3J = 7.2 Hz, 2 H, CH_2CH_3), 4.38 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 6.47 (q, $^3J_{H,F}$ = 5.1 Hz, 1 H, CH_{Ar}), 6.63 (m, 1 H, CH_{Heter}), 7.50 (m, 1 H, CH_{Heter}), 7.54 (m, 1 H, CH_{Heter}), 11.27 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.0 (CH_2CH_3), 12.5 (OCH_2CH_3), 19.6 (CH_2CH_3), 61.5 (OCH_2CH_3), 107.8 ($CCOOCH_2CH_{3Ar}$), 109.9, 110.8 (CH_{Heter}), 117.0 (q, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 122.4 (d, $^1J_{F,C}$ = 269.1 Hz, CF_3), 126.4 (d, $^2J_{F,C}$ = 32.2 Hz, CCF_{3Ar}), 132.7, 133.0 (C_{Ar}), 142.2 (CH_{Heter}), 150.3 (C_{Heter}), 159.9 (COH_{Ar}), 168.7 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.1 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2924 (w), 2853 (w), 1671 (m), 1439 (m), 1336 (m), 1282 (s), 1200 (m), 1131 (s), 1047 (m), 954 (w), 886 (w), 770 (w), 701 (s). GC-MS (EI, 70 eV): m/z (%) = 328 ([M$^+$], 61), 282 (29), 254 (100), 234 (7), 207 (7), 177 (7), 128 (7). HRMS (EI): calcd for $C_{16}H_{15}O_4F_3$: 328.09170; found: 328.09162.

Methyl 4-(2-furanyl)-3-hexyl-2-hydroxy-6-(trifluoromethyl)-benzoate (10i). Starting with **4f** (0.556 g, 2.0 mmol), **5d** (0.751 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **10i** was isolated as a viscous oil (0.222 g, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 6.8 Hz, 3 H, $CH_2(CH_2)_4CH_3$), 1.23–1.54 (m, 8 H, $CH_2(CH_2)_4CH_3$), 2.80 (t, ^3J = 7.6 Hz, 2 H, $CH_2(CH_2)_4CH_3$), 3.89 (s, 3 H, OCH_3), 6.46 (q, $^4J_{H,F}$ = 1.8 Hz, 1 H, CH_{Ar}), 6.58 (m, 1 H, CH_{Heter}), 7.48 (m, 1 H, CH_{Heter}), 7.53 (m, 1 H, CH_{Heter}), 11.14 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.0 (CH_3), 21.6, 26.2, 27.5, 28.6, 30.5 (CH_2), 51.7 (OCH_3), 107.4 ($CCOOCH_{3Ar}$), 109.9, 110.8 (CH_{Heter}), 177.0 (q, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 122.4 (d, $^1J_{F,C}$ = 269.1 Hz, CF_3), 126.3 (d, $^2J_{F,C}$ = 31.6 Hz, CCF_{3Ar}), 131.7, 133.3 (C_{Ar}), 142.1 (CH_{Heter}), 150.3 (C_{Heter}), 159.8 (COH_{Ar}), 169.1 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −59.0 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 2849 (w), 1672 (m), 1439 (m), 1336 (m), 1282 (s), 1202 (m), 1133 (s), 948 (w), 880 (w), 739 (w). GC-MS (EI, 70 eV): m/z (%) = 370 ([M$^+$], 100), 338 (24), 321 (11), 310 (42), 281 (32), 267 (68), 240 (28), 219 (31), 211 (6), 183 (14), 164 (11), 133 (15), 115 (8). HRMS (EI): calcd for $C_{19}H_{21}O_4F_3$: 370.13865; found: 370.13811.

Methyl 4-(2-furanyl)-3-octyl-2-hydroxy-6-(trifluoromethyl)-benzoate (10j). Starting with **4f** (0.556 g, 2.0 mmol), **5e** (0.812 g, 2.2 mmol) and $TiCl_4$ (0.24 mL, 2.2 mmol), **10j** was isolated as a colourless viscous oil (0.280 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, ^3J = 6.8 Hz, 3 H, $CH_2(CH_2)_6CH_3$), 1.46–1.54 (m, 12 H, $CH_2(CH_2)_6CH_3$), 2.80 (t, ^3J = 7.6 Hz, 2 H, $CH_2(CH_2)_6CH_3$), 3.89 (s, 3 H, OCH_3), 6.44 (q, $^4J_{H,F}$ = 4.1 Hz, 1 H, CH_{Ar}), 6.57 (dd, ^3J = 4.1 Hz, ^4J = 0.8 Hz, 1 H, CH_{Heter}), 7.47 (m, 1 H, CH_{Heter}), 7.52 (m, 1 H, CH_{Heter}), 11.12 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 27.2, 28.6, 29.2, 29.3, 29.9, 31.8 (CH_2), 52.7 (OCH_3), 108.4 ($CCOOCH_{3Ar}$), 110.9, 111.8 (CH_{Heter}), 118.1 (q, $^3J_{F,C}$ = 6.8 Hz, CH_{Ar}), 123.4 (d, $^1J_{F,C}$ = 269.0 Hz, CF_3), 127.4 (q, $^2J_{F,C}$ = 31.0 Hz, CCF_{3Ar}), 132.8, 134.3 (C_{Ar}), 143.1 (CH_{Heter}), 151.4 (C_{Heter}), 160.9 (COH_{Ar}), 170.1 (CO). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −58.8 (CF_3). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 2849 (w), 1672 (m), 1439 (m), 1336 (m), 1282 (s), 1202 (m), 1133 (s), 948 (w), 880 (w), 739 (w). GC-MS (EI, 70 eV): m/z (%) = 398 ([M$^+$], 100), 366 (42), 338 (8), 267 (76), 219 (37), 183 (12), 133 (11).

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