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Synthesis of 6-formylsalicylates based on regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones

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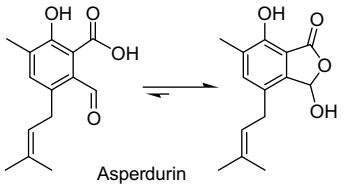
ABSTRACT

6-Formylsalicylates are prepared by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones and subsequent transformation of the dichloromethyl into a formyl group.

1. Introduction

Polyfunctionalized benzene derivatives occur in many natural products and synthetic compounds, which are of pharmacological relevance.[1] In addition, they are versatile synthetic building blocks. A number of natural products combine hydroxyl, formyl and carboxylic acid groups in one molecule. Examples include rubramin and hexyl rhizoglyphinate.[2] 2-Formylbenzoic acid is known to exclusively exist in its lactol tautomeric form (i.e., 3-hydroxy-L-(3*H*)-isobenzofuranone).[3] This type of pseudo acid is also present in a number of pharmacologically important natural products, such as salazinic acid, dihydrogladiolic acid, xylaral, asperdurin, and rubralide C (Scheme 1).[2a,4]



Scheme 1.

Benzene derivatives containing hydroxyl, formyl and ester groups at specific positions are not readily available by electrophilic substitution reactions, due to problems associated with the regioselectivity. In addition, several side-reactions are possible for functionalized substrates, due to the harsh reaction conditions. 6-Formylsalicylates have been previously prepared by cleavage of 6,7-dioxa-bicyclo[3.2.2]nona-3,8-dienes,[5a] electrophilic substitutions,[5b–e] oxidative cleavage of 6-alkenylsalicylates,[5f] alkylation of 1-(3*H*)-isobenzofuranones,[5g,h] and oxidation of 6-methylsalicylates.[5i] These strategies have several drawbacks with regard to the preparative scope. The synthesis of polyfunctionalized benzene derivatives by palladium(0)-catalyzed coupling reactions[6] suffers from the fact that the synthesis of the required starting materials, highly functionalized or sterically encumbered aryl halides or triflates, can be a difficult and tedious task.

An alternative approach to functionalized arenes is based on the application of a building block strategy. Chan and Brownbridge developed[7] a new approach to salicylates based on the formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes, electroneutral 1,3-dicarbonyl dianion equivalents,[8] with 3-silyloxy-2-en-1-ones. In recent years, this strategy has been applied to the synthesis of various functionalized arenes.[9] Recently, we have reported the synthesis of 6-formylsalicylates by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones.[10] Herein, we report the application of this method to the synthesis of formyl-substituted arenes. It is worth to be noted that dichloromethyl-substituted arenes are also interesting in their own right. They show antiasthmatic activity,[11] irreversible inhibition of yeast α-glucosidase,[12] and antibiotic activity.[13]

2. Results and discussion

The reaction of ethylvinyl ether and ethyl(prop-1-enyl)ether with dichloroacetyl chloride afforded, following a known procedure,[14] the 1,1-dichloro-4-ethoxy-3-buten-2-ones **1a**,**b** as mixtures of *E*/*Z*-isomers. The $TiCl_4$-mediated formal [3+3] cyclization of **1a** with 1,3-bis(silyloxy)-1,3-butadiene **2a**, prepared from methyl acetoacetate in two steps,[7] afforded the 6-(dichloromethyl)salicylate **3a** (Scheme 2). The best yield was obtained when the reaction was carried out in

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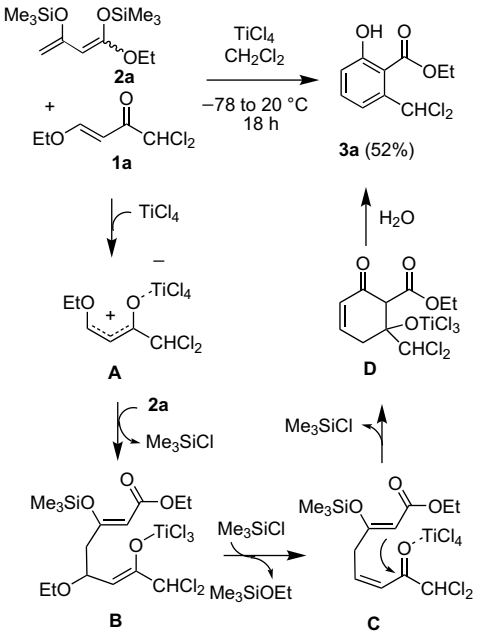
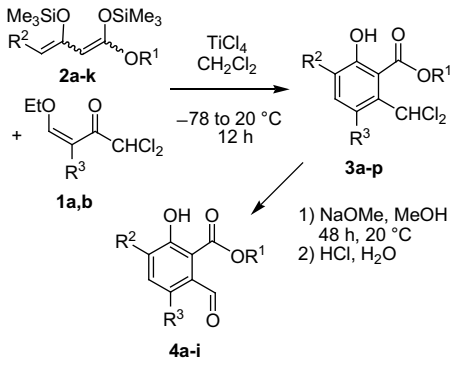


Scheme 2. Possible mechanism of the formation of **3a**.

a highly concentrated solution (2 mL/1.0 mmol of **1a**) and when ammonium chloride (10%) was employed for the aqueous work-up. The formation of **3a** can be explained by reaction of **1a** with $TiCl_4$ to give intermediate **A**. The attack of the terminal carbon atom of **2a** onto **A** afforded intermediate **B**. The elimination of ethoxytrimethylsilane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide (before or during the aqueous work-up) and aromatization resulted in the formation of product **3a**.

1,3-Bis(silyloxy)-1,3-butadienes **2a**–**k** were prepared in analogy to the procedure previously reported.[7] The $TiCl_4$-mediated formal [3+3] cyclization of **1a**,**b** with **2a**–**k** afforded the 6-(dichloromethyl)salicylates **3a**–**p** in moderate yields (Scheme 3, Table 1). The yields mainly depend on the quality of each individual starting material. The yields of the products derived from **1a** are generally higher than those derived from **1b**. The reaction of **3a**–**d** and **3f**–**j** with NaOMe/MeOH and subsequent addition of hydrochloric acid afforded the 6-formylsalicylates **4a**–**i** in good yields.



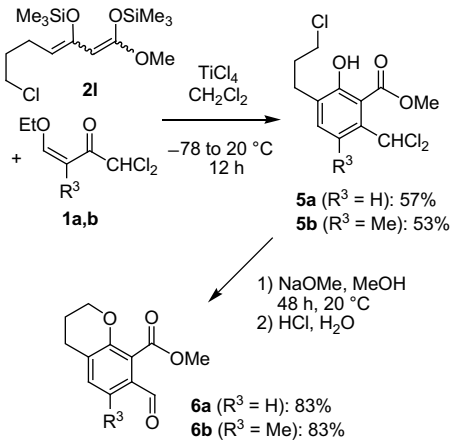
Scheme 3. Synthesis of **3a**–**p** and **4a**–**i**.

The cyclization of **1a** and **1b** with 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **2l**, containing a chlorinated side-chain,[15] afforded the 6-(dichloromethyl)salicylates **5a** and **5b**, respectively (Scheme 4). The reaction of the latter with NaOMe/MeOH and

Table 1
Synthesis of **3a**–**p** and **4a**–**i**

1	2	3	4	R^1	R^2	R^3	% (**3**)[a]	% (**4**)[a]
a	**a**	**a**	**a**	Et	H	H	52	70
a	**b**	**b**	**b**	Me	Me	H	56	85
a	**c**	**c**	**c**	Me	*i*-Pr	H	40	67
a	**d**	**d**	**d**	Me	*n*-Bu	H	48	81
a	**e**	**e**		Et	*n*-Bu	H	25	—[b]
a	**f**	**f**	**e**	Me	*n*-Pent	H	49	78
a	**g**	**g**	**f**	Me	*n*-Hex	H	51	69
a	**h**	**h**	**g**	Me	*n*-Oct	H	45	73
a	**i**	**i**	**h**	Et	*n*-Oct	H	54	76
a	**j**	**j**	**i**	Me	Allyl	H	46	81
b	**a**	**k**		Et	H	Me	30	—[b]
b	**b**	**l**		Me	Me	Me	30	—[b]
b	**c**	**m**		Me	*i*-Pr	Me	30	—[b]
b	**f**	**n**		Me	*n*-Pent	Me	35	—[b]
b	**j**	**o**		Me	Allyl	Me	25	—[b]
b	**k**	**p**		Me	$Ph(CH_2)_3$	Me	42	—[b]

[a] Yields of isolated products.
[b] Experiment was not carried out.



Scheme 4. Synthesis of **6a**,**b**.

subsequent addition of hydrochloric acid afforded the 7-formyl-8-(methoxycarbonyl)chromanes **6a**,**b**. The formation of the latter can be explained by hydrolysis of the dichloromethyl group and base-mediated intramolecular Williamson reaction.

The structures of all products were established by spectroscopic methods. The structure of **4a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[16]

In conclusion, we have reported a convenient synthesis of a variety of 6-formylsalicylates by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones and subsequent transformation of the dichloromethyl into a formyl group.

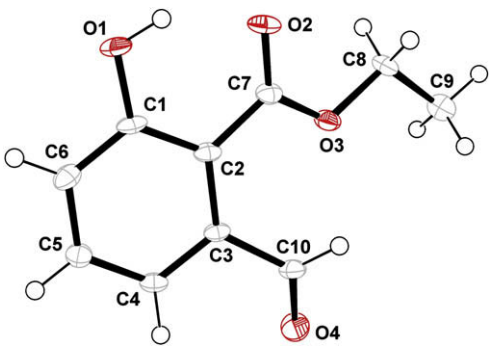


Figure 1. Crystal structure of **4a** (50% probability level).

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H 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, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

3.2. General procedure for the synthesis of 6-(dichloromethyl)salicylates 3a–p and 5a,b

To a CH_2Cl_2 solution (4.0 mL) of **1** (2.0 mmol) and 1,3-bis(silyl enol ether) **2** (4.0 mmol) was added $TiCl_4$ (2.0 mmol) at −78 °C under argon atmosphere. The temperature of the solution was allowed to rise to 20 °C during 20 h. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3×30 mL) with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc=15:1).

3.2.1. Ethyl 2-dichloromethyl-6-hydroxy-benzoate (**3a**)

Starting with **1a** (0.366 g, 2.0 mmol), **2a** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3a** was obtained as a yellow viscous oil (0.259 g, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.49 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3), 4.52 (q, ^3J=7.1 Hz, 2H, OCH_2CH_3), 7.04 (dd, ^3J=8.3 Hz, ^4J=1.3 Hz, 1H, CH_{Ar}), 7.5 (t, ^3J=8.2 Hz, 1H, CH_{Ar}), 7.64 (dd, ^3J=7.9 Hz, ^4J=1.3 Hz, 1H, CH_{Ar}), 7.75 (s, 1H, $CHCl_2$), 11.09 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (OCH_2CH_3), 62.9 (OCH_2CH_3), 69.0 ($CHCl_2$), 109.2 (C_{Ar}), 119.7, 120.3, 134.7 (CH_{Ar}), 141.4, 161.8 (C_{Ar}), 169.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924(s), 2854 (m), 1750 (w), 1713 (w), 1670 (m), 1607 (w), 1437 (m), 1417 (m), 1297 (m), 1255 (s), 1232 (s), 1195 (m), 1143 (s), 1005 (w), 984 (w), 836 (w), 802 (w), 768 (s), 745 (s), 714 (s), 642 (w), 583 (w). MS (GC, 70 eV): *m*/*z* (%)=248 (M^+, 27), 204 (65), 202 (100), 167 (16), 149 (51), 139 (35), 111 (8), 93 (6), 75 (16). HRMS (EI): calcd for $C_{10}H_{10}O_3Cl_2$ (M^+) 248.00015, found 247.999670.

3.2.2. Methyl 6-dichloromethyl-2-hydroxy-3-methyl-benzoate (**3b**)

Starting with **1a** (0.366 g, 2.0 mmol), **2b** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3b** was obtained as a colourless oil (0.293 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): 2.27 (s, 3H, $C_{Ar}CH_3$), 4.04 (s, 3H, OCH_3), 7.38 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.55 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.68 (s, 1H, $CHCl_2$), 11.28 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.2 ($C_{Ar}CH_3$), 53.0 (OCH_3), 69.4 ($CHCl_2$), 108.2 (C_{Ar}), 119.6 (CH_{Ar}), 129.2 (C_{Ar}), 135.5 (CH_{Ar}), 138.8, 160.0, (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034(w), 2954 (w), 2899 (w), 1725 (w), 1671 (m), 1608 (w), 1593 (w), 1438 (w), 1411 (m), 1380 (w), 1326 (w), 1293 (m), 1251 (s), 1221 (w), 1195 (m), 1145 (s), 1051 (w), 1033 (w), 1008 (m), 951 (w), 833 (s), 794 (br s), 767 (s), 732 (br s), 704 (s), 677 (s), 637 (m), 611 (w). MS (GC, 70 eV): *m*/*z* (%)=248 (M^+, 42), 216 (100), 180 (67), 153 (41), 125 (18), 89 (33), 63 (14). HRMS (EI): calcd for $C_{10}H_{10}O_3Cl_2$ (M^+) 248.00015, found 247.999629.

3.2.3. Methyl 6-dichloromethyl-2-hydroxy-3-isopropyl-benzoate (**3c**)

Starting with **1a** (0.366 g, 2.0 mmol), **2c** (1.210 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3c** was obtained as a yellow oil (0.222 g, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.23 (d, ^3J=6.9 Hz, 6H, $CH(CH_3)_2$), 3.37 (m, 1H, $CH(CH_3)_2$), 4.04 (s, 3H, OCH_3), 7.45 (d, ^3J=8.2 Hz, 1H, CH_{Ar}), 7.61 (d, ^3J=8.2 Hz, 1H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 11.33 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=22.1 ($CH(CH_3)_2$), 26.9 ($CH(CH_3)_2$), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.4 (C_{Ar}), 119.9 (CH_{Ar}), 131.3 (CH_{Ar}), 138.4, 139.1, 159.2 (C_{Ar}), 170.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3038(w), 2926 (w), 1771 (m), 1667 (s), 1620 (w), 1608 (w), 1588 (w), 1434 (m), 1415 (s), 1322 (m), 1300 (m), 1254 (s), 1228 (m), 1195 (m), 1139 (s), 1012 (w), 986 (m), 911 (m), 854 (w), 812 (m), 753 (m), 738 (br s), 709 (s), 633 (w), 585 (m). MS (GC, 70 eV): *m*/*z* (%)=276 (M^+, 29), 241 (22), 208 (100), 193 (12), 180 (12), 145 (15), 115 (10), 91 (10), 77 (13). HRMS (EI): calcd for $C_{12}H_{14}O_3Cl_2$ (M^+) 276.03145, found 276.031157.

3.2.4. Methyl 3-butyl-6-dichloromethyl-2-hydroxy-benzoate (**3d**)

Starting with **1a** (0.366 g, 2.0 mmol), **2d** (1.267 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3d** was obtained as colourless oil (0.279 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (t, ^3J=7.3 Hz, 3H, CH_2CH_3), 1.36 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.66 (t, ^3J=7.5 Hz, 2H, CH_2C_{Ar}), 4.04 (s, 3H, OCH_3), 7.38 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.57 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.68 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.9 (CH_2CH_3), 22.6, 29.8, 31.2 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.4 (C_{Ar}), 119.7 (CH_{Ar}), 133.6 (C_{Ar}), 134.7 (CH_{Ar}), 138.7, 159.7 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925(s), 2856 (m), 1749 (w), 1710 (w), 1665 (m), 1636 (m), 1610 (w), 1432 (m), 1417 (m), 1321 (m), 1271 (s), 1232 (s), 1196 (m), 1144 (s), 1021 (w), 984 (w), 844 (w), 806 (w), 771 (s), 746 (s), 716 (s), 647 (w), 581 (w). MS (GC, 70 eV): *m*/*z* (%)=290 (M^+, 30), 255 (26), 222 (100), 180 (75), 159 (11), 89 (22), 77 (11). HRMS (EI): calcd for $C_{13}H_{16}O_3Cl_2$ (M^+) 290.04710, found 290.047046.

3.2.5. Ethyl 3-butyl-6-dichloromethyl-2-hydroxy-benzoate (**3e**)

Starting **1a** (0.366 g, 2.0 mmol), **2e** (1.320 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3e** was obtained as yellow viscous oil (0.153 g, 25%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.93 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 1.39 (m, 2H, CH_2), 1.49 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 1.55 (m, 2H, CH_2), 2.65 (t, ^3J=7.6 Hz, 2H, CH_2C_{Ar}), 4.52 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 7.36 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.71 (s, 1H, $CHCl_2$), 11.34 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.9, 14.0 (CH_2CH_3, OCH_2CH_3), 22.6, 29.8, 31.2 (CH_2), 62.8 (OCH_2CH_3), 69.4 ($CHCl_2$), 108.6 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.7, 159.8 (C_{Ar}), 170.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926(s), 2855 (m), 1751 (w), 1714 (w), 1660 (m), 1600 (w), 1430 (m), 1416 (m), 1321 (m), 1268 (s), 1232 (s), 1196 (m), 1155 (s), 1024 (w), 984 (w), 846 (w), 816 (w), 789 (s), 744 (s), 716 (s), 648 (w), 580 (w). MS (EI, 70 eV): *m*/*z* (%)=304 (M^+, 49), 258 (18), 241 (11), 222 (23), 205 (66), 180 (91), 159 (9), 89 (15), 77 (10). HRMS (EI): calcd for $C_{14}H_{18}O_3Cl_2$ (M^+) 304.06275, found 304.062748.

3.2.6. Methyl 6-dichloromethyl-3-pentyl-2-hydroxy-benzoate (**3f**)

Starting with **1a** (0.366 g, 2.0 mmol), **2f** (1.267 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3f** was obtained as yellow oil (0.298 g, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, ^3J=6.6 Hz, 3H, CH_2CH_3), 1.33–1.38 (m, 4H, $CH_3(CH_2)_2CH_2CH_2$), 1.61 (m, 2H, $CH_2CH_2C_{Ar}$), 2.67 (t, ^3J=7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.05 (s, 3H, OCH_3), 7.38 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.57 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.69 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 22.5, 28.7, 30.0, 31.7 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.4 (C_{Ar}), 119.7 (CH_{Ar}), 133.6 (C_{Ar}), 134.7 (CH_{Ar}), 138.7, 159.8 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954(m), 2927 (m), 2857 (m), 1746 (w), 1704 (w), 1671 (m), 1648 (m), 1613 (m), 1512 (w), 1436 (m), 1416 (m), 1378 (m), 1297 (m), 1254 (s), 1194 (m), 1146 (s), 1121 (m), 1035 (w), 1021 (w), 986 (w), 840 (s), 812 (m), 802 (m), 767 (m), 748 (m), 725 (m), 642 (w), 628 (w), 553 (w). MS (GC, 70 eV): *m*/*z* (%)=304 (M^+, 25), 269 (21), 236 (100), 215 (17), 180 (69), 161 (9), 89 (20), 77 (10). HRMS (EI): calcd for $C_{14}H_{18}O_3Cl_2$ (M^+) 304.06275, found 304.062836.

*3.2.7. Methyl 6-dichloromethyl-3-hexyl-2-hydroxy-benzoate (**3g**)*

Starting with **1a** (0.366 g, 2.0 mmol), **2g** (1.315 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3g** was obtained as a yellow oil (0.325 g, 51%). ^1H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, ^3J=6.9 Hz, 3H, CH_2CH_3), 1.26–1.38 (m, 6H, $CH_3(CH_2)_3CH_2CH_2C$), 1.60 (m, 2H, $CH_3(CH_2)_3CH_2CH_2C$), 2.65 (t, ^3J=7.7 Hz, 2H, CH_2C_{Ar}), 4.04 (s, 3H, OCH_3), 7.37 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.57 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.68 (s, 1H, $CHCl_2$), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 22.6, 29.0, 29.2, 30.1, 31.7 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.3 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.6, 159.7 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954(w), 2926 (m), 2856 (w), 1934 (w), 1746 (w), 1709 (br w), 1671 (w), 1650 (w), 1620 (w), 1436 (m), 1417 (m), 1378 (w), 1299 (m), 1232 (br s), 1195 (m), 1146 (m), 1030 (w), 907 (w), 841 (s), 804 (w), 768 (m), 724 (w), 629 (w). MS (GC, 70 eV): *m*/*z* (%)=318 (M^+, 30), 255 (26), 222 (100), 180 (75), 159 (11), 89 (22), 77 (11). HRMS (EI): calcd for $C_{15}H_{20}O_3Cl_2$ (M^+) 318.04710, found 318.047046.

*3.2.8. Methyl 6-dichloromethyl-2-hydroxy-3-octyl-benzoate (**3h**)*

Starting with **1a** (0.366 g, 2.0 mmol), **2h** (1.491 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3h** was obtained as yellow viscous oil (0.312 g, 45%). ^1H NMR (250 MHz, $CDCl_3$): δ=0.86 (t, ^3J=6.5 Hz, 3H, CH_2CH_3), 1.24–1.32 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.59 (m, 2H, $CH_2CH_2C_{Ar}$), 2.64 (t, ^3J=7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.03 (s, 3H, OCH_3), 7.36 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 22.6, 27.2, 29.0, 29.2, 29.5, 29.7, 30.1 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.4 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.6, 159.7 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924(s), 2854 (m), 1750 (w), 1713 (w), 1670 (m), 1607 (w), 1437 (m), 1417 (m), 1297 (m), 1255 (s), 1232 (s), 1195 (m), 1143 (s), 1005 (w), 984 (w), 836 (w), 802 (w), 768 (s), 745 (s), 714 (s), 642 (w), 583 (w). MS (GC, 70 eV): *m*/*z* (%)=346 (M^+, 18), 271 (14), 263 (25), 231 (100), 215 (26), 180 (24), 159 (9), 115 (5), 89 (10). HRMS (EI): calcd for $C_{17}H_{24}O_3Cl_2$ (M^+) 346.10970, found 346.109276.

*3.2.9. Ethyl 6-dichloromethyl-2-hydroxy-3-octyl-benzoate (**3i**)*

Starting with **1a** (0.366 g, 2.0 mmol), **2i** (1.547 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3i** was obtained as colourless oil (0.390 g, 54%). ^1H NMR (250 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.4 Hz, 3H, CH_2CH_3), 1.24–1.32 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.49 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 1.58 (m, 2H, $CH_2CH_2C_{Ar}$), 2.64 (t, ^3J=7.7 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.52 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 7.36 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.71 (s, 1H, $CHCl_2$), 11.34 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0, 14.1 (CH_2CH_3, OCH_2CH_3), 22.7, 29.1, 29.3, 29.5, 29.6, 30.1, 31.9 (CH_2), 62.8 (OCH_2CH_3), 69.4 ($CHCl_2$), 108.6 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.5 (CH_{Ar}), 138.7, 159.8 (C_{Ar}), 170.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3031(w), 2929 (s), 2852 (m), 1715 (w), 1672 (m), 1604 (w), 1585 (w), 1438 (m), 1416 (m), 1332 (m), 1297 (m), 1255 (s), 1223 (s), 1195 (m), 1140 (s), 1005 (w), 985 (w), 831 (w), 798 (w), 764 (s), 745 (s), 711 (s), 641 (w), 582 (w). MS (GC, 70 eV): *m*/*z* (%)=360 (M^+, 22), 278 (100), 261 (27), 216 (14) 180 (65), 115 (4), 89 (10). HRMS (EI): calcd for $C_{18}H_{26}O_3Cl_2$ (M^+) 360.12535, found 360.124985.

*3.2.10. Methyl 3-allyl-6-dichloromethyl-2-hydroxy-benzoate (**3j**)*

Starting with **1a** (0.366 g, 2.0 mmol), **2j** (1.200 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3j** was obtained as colourless oil (0.253 g, 46%). ^1H NMR (300 MHz, $CDCl_3$): δ=3.43 (d, ^3J=6.6 Hz, 2H, CH_2C_{Ar}), 4.05 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2CHCH_2), 5.98 (ddt, ^3J=6.6 Hz, $^3J_{cis}$=7.9 Hz, $^3J_{anti}$=9.6 Hz, 1H, CH_2CHCH_2), 7.40 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.59 (d, ^3J=8.1 Hz, 1H, CH_{Ar}), 7.69 (s, 1H, $CHCl_2$), 11.31 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=34.0 (CH_2C_{Ar}), 53.1 (OCH_3), 69.3 ($CHCl_2$), 108.5 (C_{Ar}), 116.5 (CH_2CH), 119.8 (CH_{Ar}), 131.0 (C_{Ar}), 134.7 (CH_{Ar}), 135.4 (CH_2CHCH_2), 139.2, 159.5 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036(w), 2954 (w), 2856 (w), 1667 (s), 1640 (w), 1606 (w), 1588 (w), 1436 (m), 1417 (s), 1332 (m), 1301 (m), 1254 (s), 1225 (m), 1208 (m), 1195 (m), 1139 (s), 1007 (w), 987 (m), 915 (m), 874 (w), 816 (w), 802 (m), 738 (br s), 708 (s), 628 (w), 586 (m). MS (GC, 70 eV): *m*/*z* (%)=274 (M^+, 44), 239 (44), 206 (100), 178 (25), 143 (41), 115 (66), 89 (22), 77 (18). HRMS (EI): calcd for $C_{12}H_{12}O_3Cl_2$ (M^+) 274.01580, found 274.015869.

*3.2.11. Ethyl 2-dichloromethyl-6-hydroxy-3-methyl-benzoate (**3k**)*

Starting with 1,1-dichloro-4-ethoxy-3-methyl-but-3-en-2-one **1b** (0.394 g, 2.0 mmol), **2a** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3k** was obtained as a colourless oil (0.158 g, 30%). ^1H NMR (250 MHz, $CDCl_3$): δ=1.48 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 2.65 (s, 3H, $C_{Ar}CH_3$), 4.49 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 6.95 (d, ^3J=8.6 Hz, 1H, CH_{Ar}), 7.27 (d, ^3J=8.6 Hz, 1H, CH_{Ar}), 7.61 (s, 1H, $CHCl_2$), 9.96 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.9 (OCH_2CH_3), 20.0 ($C_{Ar}CH_3$), 62.9 (OCH_2CH_3), 67.7 ($CHCl_2$), 111.8 (C_{Ar}), 119.2 (CH_{Ar}), 130.8, 136.7 (C_{Ar}), 138.3 (CH_{Ar}), 158.2 (C_{Ar}), 169.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092(w), 2981 (w), 2929 (w), 1718 (w), 1668 (s), 1589 (w), 1467 (s), 1396 (w), 1372 (m), 1315 (m), 1297 (s), 1259 (m), 1201 (s), 1176 (s), 1132 (m), 1040 (m), 1010 (m), 983 (w), 912 (w), 857 (m), 829 (m), 752 (s), 717 (m), 697 (m), 657 (m), 657 (w), 624 (w), 590 (s), 545 (w). MS (GC, 70 eV): *m*/*z* (%)=262 (M^+, 26), 216 (100), 181 (62), 163 (47), 153 (35), 125 (8), 89 (22), 77 (15). HRMS (EI): calcd for $C_{11}H_{12}Cl_2O_3$ (M^+) 262.01580, found 262.015223.

*3.2.12. Methyl 2-dichloromethyl-6-hydroxy-3,5-dimethyl-benzoate (**3l**)*

Starting with **1b** (0.394 g, 2.0 mmol), **2b** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3l** was obtained as a colourless oil (0.149 g, 30%). ^1H NMR (250 MHz, $CDCl_3$): δ=2.23 (s, 3H, $C_{Ar}CH_3$), 2.61 (s, 3H, $C_{Ar}CH_3$), 4.02 (s, 3H, OCH_3), 7.15 (s, 1H, CH_{Ar}), 7.53 (s, 1H, $CHCl_2$), 10.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.0 ($C_{Ar}CH_3$), 19.9 ($C_{Ar}CH_3$), 53.0 (OCH_3), 68.0 ($CHCl_2$), 110.8 (C_{Ar}), 128.7, 129.9, 134.2 (C_{Ar}), 139.2 (CH_{Ar}), 156.5 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091(w), 2954 (w), 2929 (w), 1721 (w), 1670 (s), 1589 (w), 1461 (w), 1436 (s), 1407 (m), 1379 (w), 1331 (m), 1293 (s), 1235 (m), 1217 (m), 1194 (s), 1163 (s), 1077 (w), 1016 (br m), 903 (w), 880 (w), 844 (w), 805 (w), 791 (w), 752 (s), 740 (s), 710 (s), 627 (m), 548 (w). MS (GC, 70 eV): *m*/*z* (%)=262 (M^+, 35), 230 (100), 195 (82), 167 (52), 103 (22), 77 (30). HRMS (EI): calcd for $C_{11}H_{12}Cl_2O_3$ (M^+) 262.01580, found 262.015669.

*3.2.13. Methyl 2-dichloromethyl-6-hydroxy-5-isopropyl-3-methyl-benzoate (**3m**)*

Starting with **1b** (0.394 g, 2.0 mmol), **2c** (1.210 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3m** was obtained as a colourless oil (0.163 g, 30%). ^1H NMR (250 MHz, $CDCl_3$): δ=1.23 (d, ^3J=7.0 Hz, 6H, $CH(CH_3)_2$), 2.64 (s, 3H, $C_{Ar}CH_3$), 3.32 (m, 1H, $CH(CH_3)_2$), 4.02 (s, 3H, OCH_3), 7.18 (s, 1H, CH_{Ar}), 7.49 (s, 1H, $CHCl_2$), 10.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=22.1 ($CH(CH_3)_2$), 26.9 ($CH(CH_3)_2$), 31.2 ($C_{Ar}CH_3$), 53.0 (OCH_3), 68.1 ($CHCl_2$), 111.1, 129.9, 133.9 (C_{Ar}), 135.0 (CH_{Ar}), 138.6, 155.6 (C_{Ar}), 170.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956(w), 2871 (w), 1674 (m), 1588 (w), 1436 (m), 1382 (w), 1330 (br m), 1256 (w), 1251 (m), 1226 (m), 1195 (m), 1172 (s), 1151 (m), 1109 (w), 1048 (br m), 1011 (m), 982 (w), 906 (br w), 837 (s), 807 (m), 756 (s), 727 (s), 677 (br m), 654 (m), 627 (w). MS (GC, 70 eV): *m*/*z* (%)=290 (M^+, 31), 258 (34), 222 (100), 194 (21), 159 (15), 115 (30), 91 (17), 77 (14). HRMS (EI): calcd for $C_{13}H_{16}O_3Cl_2$ (M^+) 290.04710, found 290.046525.

*3.2.14. Methyl 2-dichloromethyl-6-hydroxy-3-methyl-5-pentyl-benzoate (**3n**)*

Starting with **1b** (0.394 g, 2.0 mmol), **2f** (1.322 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3n** was obtained as a colourless oil (0.223 g, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ=0.89 (t,

^3J=6.9 Hz, 3H, CH_2CH_3), 1.31–1.35 (m, 4H, $CCH_2CH_2(CH_2)_2CH_3$), 1.59 (m, 2H, $CCH_2CH_2(CH_2)_2CH_3$), 2.57–2.62 (m, 5H, $C_{Ar}CH_2$, $C_{Ar}CH_3$), 4.02 (s, 3H, OCH_3), 7.13 (s, 1H, CH_{Ar}), 7.50 (s, 1H, $CHCl_2$), 10.06 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (CH_2CH_3), 20.0 ($C_{Ar}CH_3$), 22.5, 28.9, 30.0, 31.7 ($C(CH_2)_4CH_3$), 53.0 (OCH_3), 68.1 ($CHCl_2$), 111.1 (C_{Ar}), 129.8, 133.3, 134.1 (C_{Ar}), 138.4 (CH_{Ar}), 156.2 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954(w), 2927 (w), 2858 (w), 1934 (w), 1764 (w), 1703 (w), 1674 (w), 1650 (w), 1612 (w), 1567 (w), 1636 (m), 1379 (w), 1248 (br s), 1195 (s), 1159 (s), 1028 (w), 988 (w), 961 (w), 841 (br s), 810 (w), 751 (s), 727 (m), 650 (w). MS (GC, 70 eV): *m*/*z* (%)=318 (M^+, 31), 283 (18), 250 (99), 230 (24), 194 (100), 176 (15), 103 (20), 77 (17). HRMS (EI): calcd for $C_{15}H_{20}O_3Cl_2$ (M^+) 318.00813, found 318.007726.

3.2.15. Methyl 3-allyl-6-dichloromethyl-2-hydroxy-5-methyl-benzoate (**3o**)

Starting with **1b** (0.394 g, 2.0 mmol), **2j** (1.200 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3o** was obtained as colourless oil (0.145 g, 25%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.63 (s, $C_{Ar}CH_3$), 3.39 (d, ^3J=6.7 Hz, 2H, CH_2C_{Ar}), 4.02 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2CHCH_2), 5.97 (ddt, ^3J=6.6 Hz, $^3J_{cis}$=8.0 Hz, $^3J_{anti}$=9.6 Hz, 1H, CH_2CHCH_2), 7.15 (s, 1H, CH_{Ar}), 7.52 (s, 1H, $CHCl_2$), 10.11 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=20.0 (CH_3C_{Ar}), 34.0 (CH_2C_{Ar}), 53.0 (OCH_3), 67.9 ($CHCl_2$), 111.3 (C_{Ar}), 116.5 (CH_2CH), 130.1, 130.5, 134.7 (C_{Ar}), 135.5 (CH_{Ar}), 138.4 (CH_2CHCH_2), 155.9 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079(w), 2954 (w), 1934 (w), 1671 (s), 1640 (w), 1587 (w), 1435 (s), 1382 (w), 1333 (br m), 1296 (m), 1194 (s), 1161 (s), 1024 (m), 989 (m), 912 (m), 876 (w), 843 (m), 808 (w), 750 (s), 727 (br s), 631 (m). MS (GC, 70 eV): *m*/*z* (%)=288 (M^+, 42), 256 (44), 22 (100), 193 (24), 185 (35), 157 (30), 128 (36), 115 (33), 91 (19), 77 (18). HRMS (EI): calcd for $C_{13}H_{14}O_3Cl_2$ (M^+) 288.03145, found 288.031106.

3.2.16. Methyl 2-dichloromethyl-6-hydroxy-3-methyl-5-(3-phenylpropyl)-benzoate (**3p**)

Starting with **1b** (0.394 g, 2.0 mmol), **2k** (1.515 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **3p** was obtained as a yellow oil (0.308 g, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.94 (m, 2H, $CH_2CH_2CH_2$), 2.62 (s, 3H, $C_{Ar}CH_3$), 2.68 (m, 4H, $C_{Ar}CH_2$), 4.02 (s, 3H, OCH_3), 7.13–7.31 (m, 6H, CH_{Ar}), 7.52 (s, 1H, $CHCl_2$), 10.10 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=20.0 ($C_{Ar}CH_3$), 29.7, 30.6, 35.7 ($CH_2CH_2CH_2$), 53.0 (OCH_3), 68.0 ($CHCl_2$), 111.1 (C_{Ar}), 125.7, 128.3, 128.4 (CH_{Ar}), 129.9, 132.6, 134.3 (C_{Ar}), 134.4 (CH_{Ar}), 142.1 (C_{Ar}), 156.2 (COH), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084(w), 3061 (w), 2929 (w), 2858 (w), 1933 (w), 1698 (w), 1671 (m), 1603 (w), 1586 (w), 1435 (s), 1382 (w), 1334 (m), 1297 (m), 1245 (br m), 1194 (s), 1165 (s), 1079 (w), 1028 (w), 981 (w), 886 (w), 808 (w), 749 (s), 725 (s), 697 (s), 628 (m), 591 (w). MS (EI, 70 eV): *m*/*z* (%)=366 (M^+, 27), 334 (10), 298 (11), 230 (57), 230 (12), 194 (100), 160 (11), 103 (23), 77 (26). HRMS (EI): calcd for $C_{19}H_{20}O_3Cl_2$ (M^+) 366.00813, found 366.007726.

3.2.17. Methyl 3-(3-chloropropyl)-6-dichloromethyl-2-hydroxy-benzoate (**5a**)

Starting with **1a** (0.366 g, 2.0 mmol), **2l** (1.348 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **5a** was obtained as a yellow oil (0.355 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.09 (m, 2H, $CH_2CH_2CH_2$), 2.83 (t, ^3J=7.4 Hz, 2H, $C_{Ar}CH_2$), 3.54 (t, ^3J=6.5 Hz, 2H, CH_2Cl), 4.05 (s, 3H, OCH_3), 7.41 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.58 (d, ^3J=8.0 Hz, 1H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 11.31 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=27.6, 31.5, 44.5 ($CH_2CH_2CH_2$), 53.1 (OCH_3), 69.3 ($CHCl_2$), 108.6 (C_{Ar}), 119.8 (CH_{Ar}), 131.4 (C_{Ar}), 135.2 (CH_{Ar}), 139.4, 159.8 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955(w), 1934 (w), 1701 (w), 1669 (s), 1607 (w), 1586 (w), 1436 (m), 1416 (s), 1335 (br m), 1289 (br m), 1252 (br s), 1195 (s), 1150 (s), 1134 (m), 1047 (w), 1004 (br w), 961 (w), 837 (s), 801 (s), 767 (s), 740 (s), 708 (s), 640 (br m). MS (EI, 70 eV): *m*/*z* (%)=310 (M^+, 19), 275 (21), 243 (100), 207 (25), 180 (60), 161 (13), 115 (18), 89 (24), 69 (18). HRMS (EI): calcd for $C_{12}H_{13}O_3Cl_3$ (M^+) 309.99248, found 309.991699.

3.2.18. Methyl 3-(3-chloropropyl)-6-dichloromethyl-2-hydroxy-5-methyl-benzoate (**5b**)

Starting with **1b** (0.394 g, 2.0 mmol), **2l** (1.348 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4 mL), **5b** was obtained as a colourless oil (0.345 g, 53%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.07 (m, 2H, $CH_2CH_2CH_2$), 2.62 (s, 3H, $C_{Ar}CH_3$), 2.78 (t, ^3J=7.3 Hz, 2H, $C_{Ar}CH_2$), 3.53 (t, ^3J=6.5 Hz, 2H, CH_2Cl), 4.02 (s, 3H, OCH_3), 7.17 (s, 1H, CH_{Ar}), 7.51 (s, 1H, $CHCl_2$), 10.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=20.0 ($C_{Ar}CH_3$), 27.5, 31.7, 44.5 ($CH_2CH_2CH_2$), 53.1 (OCH_3), 67.9 ($CHCl_2$), 111.3 (C_{Ar}), 130.0, 131.0, 134.8 (C_{Ar}), 138.8 (CH_{Ar}), 156.2 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954(w), 1934 (w), 1673 (m), 1588 (w), 1436 (m), 1382 (w), 1336 (w), 1292 (m), 1249 (m), 1195 (s), 1166 (s), 1079 (w), 1010 (br w), 967 (w), 905 (w), 840 (s), 753 (s), 726 (s), 679 (m), 649 (m). MS (GC, 70 eV): *m*/*z* (%)=326 (M^+, 17), 292 (20), 257 (100), 230 (12), 194 (44), 103 (14), 77 (13). HRMS (EI): calcd for $C_{13}H_{15}O_3Cl_2$ (M^+) 324.00813, found 324.007726.

3.3. General procedure for the synthesis of 6-(formyl)salicylates 4a–i and 6a,b

To a methanol or ethanol solution of sodium methanolate or ethanolate (3.0 mmol) was added **3** (1.0 mmol) under argon atmosphere and the solution was stirred for 24 h at room temperature. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3×) with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc=10:1).

3.3.1. Ethyl 2-formyl-6-hydroxy-benzoate (**4a**)

Starting with **3a** (0.239 g, 1.0 mmol), NaOEt (0.196 g, 2.9 mmol) in dry EtOH (5 mL), **4a** was obtained as a colourless solid (0.130 g, 70%); mp 47–49 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.43 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 4.52 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 7.20 (dd, ^3J=8.4 Hz, ^4J=1.3 Hz, 1H, CH_{Ar}), 7.27 (dd, ^3J=7.5 Hz, ^4J=1.3 Hz, 1H, CH_{Ar}), 7.52 (m, 1H, CH_{Ar}), 10.50 (s, 1H, CHO), 10.94 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.2 (OCH_2CH_3), 62.8 (OCH_2CH_3), 111.6 (C_{Ar}), 120.0, 122.6, 134.8 (CH_{Ar}), 139.1, 161.9 (C_{Ar}), 169.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078(w), 2990 (w), 2991 (w), 2376 (w), 2282 (w), 2046 (w), 1986 (w), 1688 (m), 1664 (s), 1597 (w), 1447 (m), 1349 (m), 1373 (m), 1327 (s), 1288 (m), 1231 (s), 1209 (s), 1162 (s), 1132 (s), 1111 (s), 1066 (m) 1015 (s), 971 (m), 915 (w), 861 (m), 818 (s), 780 (s), 737 (br s), 634 (s), 542 (m). MS (GC, 70 eV): *m*/*z* (%)=194 (M^+, 25), 165 (42), 148 (42), 120 (100), 92 (55), 63 (19). HRMS (EI): calcd for $C_{10}H_{10}O_4$ (M^+) 194.05736, found 194.057014.

3.3.2. Methyl 6-formyl-2-hydroxy-3-methyl-benzoate (**4b**)

Starting with **3b** (0.273 g, 1.0 mmol), NaOMe (0.168 g, 3.1 mmol) in dry MeOH (5 mL), **4b** was obtained as a colourless solid (0.170 g, 85%); mp 63–65 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.31 (s, 3H, $C_{Ar}CH_3$), 4.01 (s, 3H, OCH_3), 7.24 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 7.40 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 10.43 (s, 1H, CHO), 11.13 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=16.2 ($C_{Ar}CH_3$), 53.0 (OCH_3), 110.6 (C_{Ar}), 119.7 (CH_{Ar}), 133.0 (C_{Ar}), 135.3 (CH_{Ar}), 136.6, 160.2, (C_{Ar}), 170.5 (C=O), 192.0 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3047(w), 2960 (w), 2917 (w), 2849 (w), 1666 (s), 1577 (w), 1492 (w), 1440 (m), 1417 (m), 1381 (m), 1340 (s), 1290 (m), 1246 (s), 1196 (m), 1142 (s), 1033 (m), 1010 (w), 981 (w), 960 (m), 952 (m), 870 (m), 841 (m), 813 (m), 775 (s), 731 (s), 714 (s), 689 (m), 587 (m), 575 (m). MS (GC, 70 eV): *m*/*z* (%)=194 (M^+, 47), 179 (15), 166 (25), 148 (26), 134 (100), 106 (76), 77 (41). HRMS (EI): calcd for $C_{10}H_{10}O_4$ (M^+) 194.05736, found 194.057224.

*3.3.3. Methyl 6-formyl-2-hydroxy-3-isopropyl-benzoate (**4c**)*

Starting with **3c** (0.200 g, 0.7 mmol), NaOMe (0.117 g, 2.2 mmol) in dry MeOH (4 mL), **4c** was obtained as a yellow oil (0.107 g, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.23 (d, ^3J=6.9 Hz, 6H, CH(CH_3)$_2$), 3.39 (m, 1H, C*H*(CH_3)$_2$), 4.01 (s, 3H, OCH_3), 7.30 (d, ^3J=7.8 Hz, 1H, CH_{Ar}), 7.47 (d, ^3J=7.8 Hz, 1H, CH_{Ar}), 10.41 (s, 1H, CHO), 11.20 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=22.1 (CH(CH_3)$_2$), 27.2 (*C*H(CH_3)$_2$), 53.0 (OCH_3), 110.7 (C_{Ar}), 119.9, 131.2 (CH_{Ar}), 136.3, 142.8, 159.4 (C_{Ar}), 170.6 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960(w), 2873 (w), 1738 (w), 1669 (br s), 1612 (w), 1576 (w), 1493 (w), 1438 (m), 1418 (m), 1384 (w), 1335 (br m), 1277 (m), 1231 (br s), 1196 (m), 1153 (s), 1132 (s), 1066 (w), 1009 (w), 978 (m), 920 (w), 838 (w), 783 (m), 726 (m), 624 (w). MS (GC, 70 eV): *m*/*z* (%)=222 (M$^+$, 68), 207 (29), 190 (51), 175 (100), 162 (45), 147 (43), 134 (76), 119 (23), 91 (52), 77 (24). HRMS (EI): calcd for $C_{12}H_{14}O_4$ (M$^+$) 222.08866, found 222.088498.

*3.3.4. Methyl 3-butyl-6-formyl-2-hydroxy-benzoate (**4d**)*

Starting with **3d** (0.259 g, 0.9 mmol), NaOMe (0.144 g, 2.7 mmol) in dry MeOH (5 mL), **4d** was obtained as a yellow oil (0.168 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (t, ^3J=7.3 Hz, 3H, CH_2CH_3), 1.37 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 2.69 (t, ^3J=7.6 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 7.26 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.11 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.9 (CH_2CH_3), 22.5, 29.9, 31.2 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7, 134.5 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956(w), 2929 (w), 2860 (w), 1742 (w), 1670 (s), 1514 (w), 1577 (w), 1438 (m), 1421 (s), 1379 (w), 1337 (m), 1290 (m), 1240 (s), 1196 (s), 1141 (s), 981 (br w), 917 (w), 873 (w), 812 (w), 781 (s), 581 (m), 541 (w). MS (GC, 70 eV): *m*/*z* (%)=236 (M$^+$, 31), 221 (20), 207 (22), 175 (22), 162 (100), 148 (22), 134 (55), 105 (28), 77 (34). HRMS (EI): calcd for $C_{13}H_{16}O_4$ (M$^+$) 236.10431, found 236.104421.

*3.3.5. Methyl 6-formyl-2-hydroxy-3-pentyl-benzoate (**4e**)*

Starting with **3f** (0.280 g, 0.9 mmol), NaOMe (0.149 g, 2.8 mmol) in dry MeOH (5 mL), **4e** was obtained as a yellow oil (0.179 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.9 Hz, 3H, CH_2CH_3), 1.30–1.35 (m, 4H, $CH_3(CH_2)_2CH_2CH_2C_{Ar}$), 1.61 (m, 2H, $CH_3(CH_2)_2CH_2CH_2C_{Ar}$), 2.68 (t, ^3J=7.7 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 7.26 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.11 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (CH_2CH_3), 22.5, 28.7, 30.2, 31.6 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7, 134.5 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955(w), 2927 (w), 2859 (w), 1744 (w), 1670 (s), 1578 (w), 1439 (m), 1421 (m), 1240 (s), 1196 (s), 1141 (s), 1095 (w), 986 (w), 929 (w), 869 (w), 835 (w), 813 (w), 781 (s), 759 (m), 581 (w). MS (GC, 70 eV): *m*/*z* (%)=250 (M$^+$, 23), 236 (7), 205 (26), 180 (64), 165 (100), 137 (34), 91 (15), 77 (11). HRMS (EI): calcd for $C_{14}H_{18}O_4$ (M$^+$) 250.13561, found 250.135677.

*3.3.6. Methyl 6-formyl-3-hexyl-2-hydroxy-benzoate (**4f**)*

Starting with **3g** (0.300 g, 0.9 mmol), NaOMe (0.152 g, 2.8 mmol) in dry MeOH (5 mL), **4f** was obtained as a yellow oil (0.170 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.8 Hz, 3H, CH_2CH_3), 1.27–1.37 (m, 6H, $CH_3(CH_2)_3CH_2CH_2C_{Ar}$), 1.61 (m, 2H, $CH_3(CH_2)_3CH_2CH_2C_{Ar}$), 2.69 (t, ^3J=7.7 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 7.27 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.11 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 22.6, 29.0, 29.1, 30.3, 31.7 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7, 134.5 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955(w), 2926 (w), 2856 (w), 1738 (w), 1670 (s), 1614 (w), 1578 (w), 1492 (w), 1439 (m), 1420 (m), 1336 (m), 1288 (m), 1239 (s), 1196 (m), 1141 (s), 1099 (w), 1053 (w), 1011 (w), 982 (w), 875 (w), 812 (w), 781 (m), 747 (m), 582 (w). MS (GC, 70 eV): *m*/*z* (%)=264 (M$^+$, 23), 249 (18), 235 (21), 205 (13), 194 (17), 175 (13), 162 (100), 147 (14), 134 (40), 105 (21), 77 (24). HRMS (EI): calcd for $C_{15}H_{20}O_4$ (M$^+$) 264.13561, found 264.135677.

*3.3.7. Methyl 6-formyl-2-hydroxy-3-octyl-benzoate (**4g**)*

Starting with **3h** (0.290 g, 0.8 mmol), NaOMe (0.135 g, 2.5 mmol) in dry MeOH (4 mL), **4g** was obtained as a colourless solid (0.178 g, 73%); mp 48–50 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.5 Hz, 3H, CH_2CH_3), 1.24–1.35 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.60 (m, 2H, $CH_2CH_2C_{Ar}$), 2.68 (t, ^3J=7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.01 (s, 3H, OCH_3), 7.27 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 22.6, 29.0, 29.2, 29.4, 29.5, 30.3, 31.9 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7 (CH_{Ar}), 134.6 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3037(w), 2950 (w), 1217 (m), 2849 (m), 1745 (w), 1689 (s), 1661 (s), 1575 (w), 1494 (w), 1439 (m), 1419 (m), 1392 (w), 1341 (m), 1292 (m), 1243 (s), 1147 (s), 1121 (w), 1092 (w), 1014 (w), 980 (w), 878 (w), 939 (w), 813 (w), 780 (m), 757 (m), 724 (m), 587 (w), 549 (w). MS (GC, 70 eV): *m*/*z* (%)=292 (M$^+$, 22), 277 (19), 263 (23), 233 (12), 194 (24), 162 (100), 147 (13), 134 (36), 105 (16), 77 (17). HRMS (EI): calcd for $C_{17}H_{24}O_4$ (M$^+$) 292.16691, found 292.166507.

*3.3.8. Ethyl 6-formyl-2-hydroxy-3-octyl-benzoate (**4h**)*

Starting with **3i** (0.370 g, 1.0 mmol), NaOEt (0.208 g, 3.1 mmol) in dry EtOH (5 mL), **4h** was obtained as a yellow oil (0.238 g, 76%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.86 (t, ^3J=6.4 Hz, 3H, CH_2CH_3), 1.24–1.33 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.42 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 1.57 (m, 2H, $CH_2CH_2C_{Ar}$), 2.68 (t, ^3J=7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.49 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 7.24 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 7.38 (d, ^3J=7.7 Hz, 1H, CH_{Ar}), 10.45 (s, 1H, CHO), 11.19 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 14.2 (CH_2CH_3), 14.1, 14.2 (CH_2CH_3, OCH_2CH_3), 22.6, 29.0, 29.2, 29.4, 29.5, 30.2, 31.8 (CH_2), 62.7 (OCH_2CH_3), 111.0 (C_{Ar}), 119.6 (CH_{Ar}), 134.4 (CH_{Ar}), 136.7, 137.3, 160.0 (C_{Ar}), 170.1 (C=O), 192.0 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2934(w), 2854 (m), 1744 (w), 1690 (s), 1666 (s), 1578 (w), 1443 (w), 1422 (m), 1396 (w), 1372 (m), 1324 (m), 1240 (s), 1175 (m), 1142 (s), 1096 (w), 1017 (m), 914 (br w), 860 (w), 836 (w), 814 (w), 781 (m), 750 (m), 722 (m). MS (GC, 70 eV): *m*/*z* (%)=306 (M$^+$, 19), 277 (85), 260 (10), 233 (22), 208 (17), 162 (100), 134 (27), 105 (14), 77 (15). HRMS (EI): Calcd for $C_{18}H_{26}O_4$ (M$^+$) 306.18256, found 306.182417.

*3.3.9. Methyl 3-allyl-6-formyl-2-hydroxy-benzoate (**4i**)*

Starting with **3j** (0.233 g, 0.9 mmol), NaOMe (0.137 g, 2.5 mmol) in dry MeOH (4 mL), **4i** was obtained as yellow oil (0.152 g, 81%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.46 (d, ^3J=6.7 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 5.09 (m, 2H, CH_2CHCH_2), 5.98 (m, 1H, CH_2CHCH_2), 7.28 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 7.42 (d, ^3J=7.6 Hz, 1H, CH_{Ar}), 10.43 (s, 1H, CHO), 11.16 (s, 1H, OH). ^{3}C NMR (62.9 MHz, $CDCl_3$): δ=34.1 (CH_2C_{Ar}), 53.0 (OCH_3), 110.9 (C_{Ar}), 116.8 (CH_2CH), 119.8 (CH_{Ar}), 134.5 (C_{Ar}), 134.6 (CH_{Ar}), 135.0 (CH_2CHCH_2), 137.0, 159.7 (C_{Ar}), 170.4 (C=O), 192.0 (CHO). R (ATR, cm^{-1}): $\tilde{\nu}$ = 3079(w), 2956 (w), 2921 (w), 1669 (s), 1577 (w), 1486 (w), 1437 (m), 1421 (s), 1336 (m), 1303 (br m), 1241 (s), 1196 (s), 1139 (s), 989 (m), 916 (m), 872 (w), 836 (m), 813 (m), 781 (s), 746 (br m), 587 (m). MS (GC, 70 eV): *m*/*z* (%)=220 (M$^+$, 55), 205 (19), 173 (38), 159 (49), 145 (16), 131 (100), 115 (15), 103 (48), 77 (60). HRMS (EI): calcd for $C_{12}H_{12}O_4$ (M$^+$) 220.07301, found 220.072813.

*3.3.10. Methyl 7-dichloromethyl-chroman-8-carboxylate (**6a**)*

Starting with **5a** (0.335 g, 1.1 mmol), NaOMe (0.233 g, 4.3 mmol) in dry MeOH (5 mL), **6a** was obtained as colourless solid (0.198 g, 83%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.04 (m, 2H, CH_2CH_2O), 2.86 (t, ^3J=6.5 Hz, 2H, $C_{Ar}CH_2$), 3.95 (s, 3H, OCH_3), 4.26 (t, ^3J=5.3 Hz, 2H, CH_2O), 7.23 (d, ^3J=7.8 Hz, 1H, CH_{Ar}), 7.33 (d, ^3J=7.8 Hz, 1H, CH_{Ar}), 9.87 (s, 1H, CHO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=21.4, 25.4 ($CH_2CH_2CH_2O$), 52.8 (OCH_3), 67.1 (CH_2O), 122.7 (C_{Ar}), 122.7 (CH_{Ar}), 130.1 (C_{Ar}), 131.0 (CH_{Ar}), 132.5, 152.2 (C_{Ar}), 167.5 (C=O), 190.1 (CHO).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079(w), 2956 (w), 2921 (w), 1669 (s), 1577 (w), 1486 (w), 1437 (m), 1421 (s), 1336 (m), 1303 (br m), 1241 (s), 1196 (s), 1139 (s), 989 (m), 916 (m), 872 (w), 836 (m), 813 (m), 781 (s), 746 (br m), 587 (m). MS (GC, 70 eV): *m*/*z* (%)=220 (M^+, 24), 205 (9), 191 (58), 161 (100), 147 (14), 133 (28), 105 (22), 77 (30). HRMS (EI): calcd for $C_{12}H_{12}O_4$ (M^+) 220.07301, found 220.072913.

3.3.11. *Methyl 7-dichloromethyl-6-methyl-chroman-8-carboxylate (**6b**)*

Starting with **5b** (0.325 g, 1.0 mmol), NaOMe (0.216 g, 4.0 mmol) in dry MeOH (5 mL), **6b** was obtained as colourless solid (0.198 g, 83%); mp 81–82 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.03 (m, 2H, CH_2CH_2O), 2.25 (s, 3H, CH_3C_{Ar}), 2.79 (t, ^3J=6.4 Hz, 2H, $C_{Ar}CH_2$), 3.52 (s, 3H, OCH_3), 4.34 (t, ^3J=5.2 Hz, 2H, CH_2O), 6.15 (CHO), 7.10 (s, 1H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.1 (CH_3C_{Ar}), 21.6, 24.7 ($CH_2CH_2CH_2O$), 55.6 (OCH_3), 67.3 (CH_2O), 101.5 (CHO), 113.4, 124.7, 125.2 (C_{Ar}), 137.9 (CH_{Ar}), 142.6, 152.0 (C_{Ar}), 167.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079(w), 2957 (w), 2924 (w), 1669 (s), 1615 (m), 1576 (w), 1468 (w), 1436 (m), 1422 (s), 1332 (m), 1304 (br m), 1241 (s), 1196 (s), 1140 (s), 987 (m), 918 (m), 871 (w), 834 (m), 813 (m), 781 (s), 748 (br m), 586 (m). MS (GC, 70 eV): *m*/*z* (%)=234 (M^+, 44), 203 (100), 175 (60), 147 (12), 115 (7), 91 (13), 77 (7). HRMS (EI): calcd for $C_{13}H_{14}O_4$ (M^+) 234.08866, found 234.088260.

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16. CCDC-729592 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: (+44)1223 336 033; or deposit@ccdc.cam.ac.uk.