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Synthesis of dichloromethyl-substituted salicylates and pyran-4-ones by cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one: control of the C,C- and C,O-regioselectivity by the choice of Lewis acid

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ABSTRACT

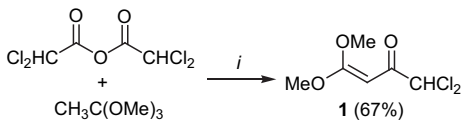
The $TiCl_4$-mediated formal [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one afforded a variety of functionalized 6-dichloromethyl-4-methoxysalicylates with very good regioselectivity. Some of the products were transformed into 6-formyl-4-methoxysalicylates. The employment of Me_3SiOTf instead of $TiCl_4$ resulted in a change of the regioselectivity and in the formation of functionalized 2-(dichloromethyl)pyran-4-ones.

1. Introduction

The dichloromethyl group is of interest as a precursor of aldehydes. Dichloromethyl-substituted arenes are of potential relevance in the field of medicinal chemistry. To date, however, only moderate pharmacological activities have been reported.[1–3] Dichloromethyl-substituted arenes have been previously prepared by chlorination of the corresponding aldehydes using various chlorination agents.[4] Despite its great utility, this approach suffers from the fact that the required starting materials, functionalized aromatic aldehydes, are not always readily available. An alternative synthesis of dichloromethyl-substituted arenes and hetarenes is based on direct nucleophilic substitution reactions of nitroarenes with chloroform.[5] A drawback of this method is the formation of regioisomeric mixtures in some cases. An alternative strategy is based on the application of suitable $CHCl_2$-containing substrates in cyclocondensation reactions ('building block approach'). Such reactions have only scarcely been reported to date. Chan and Stossel reported the synthesis of a 6-dichloromethyl-4-hydroxysalicylate by formal [5+1] cyclization of 1-methoxy-1,3,5-tris(silyloxy)-1,3,5-hexatriene with dichloroacetyl chloride.[6] Recently, we have reported[7] a new approach to 6-(trifluoromethyl)salicylates by formal [3+3] cyclizations[8] of 1,3-bis(silyloxy)-1,3-butadienes[9] with 1-ethoxy-4,4,4-trifluorobut-1-en-3-ones. In addition, it was found that the product distribution of the cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one is influenced by the choice of the Lewis acid.[10] Recently, we have reported the synthesis of 6-formylsalicylates based on the cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-ethoxy-4,4-dichorobut-1-en-3-one.[11] Herein, we report, for the first time, the synthesis of 6-dichloromethyl-4-methoxysalicylates by $TiCl_4$-mediated cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one. The products can be transformed into 6-formyl-4-methoxysalicylates. In addition, we have found that 2-(dichloromethyl)pyran-4-ones were formed when Me_3SiOTf instead of $TiCl_4$ was employed. The products reported herein have not been previously prepared and are not readily available by other methods.

2. Results and discussion

The synthesis of 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one (**1**) has, to the best of our knowledge, not yet been reported.[12] It was prepared, in analogy to the procedure reported for the synthesis of 1,1-diethoxy-4,4,4-trifluorobut-1-en-3-one,[13] by reaction of dichloroacetic anhydride with 1,1,1-trimethoxyethane (Scheme 1).



Scheme 1. Synthesis of **1**. Conditions: *i*, pyridine, CH_2Cl_2, 20 °C, 12 h.

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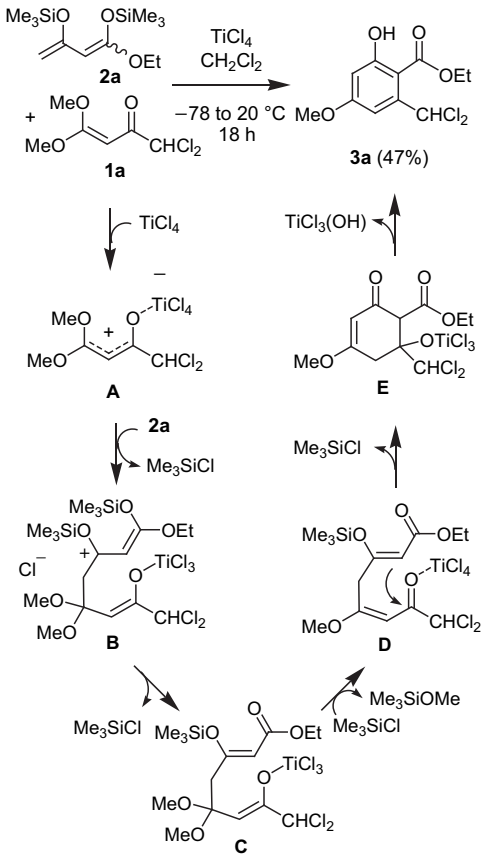
1,3-Bis(silyloxy)-1,3-butadienes **2a–o** were prepared according to the literature from the corresponding β-ketoesters in two steps.[14–16]

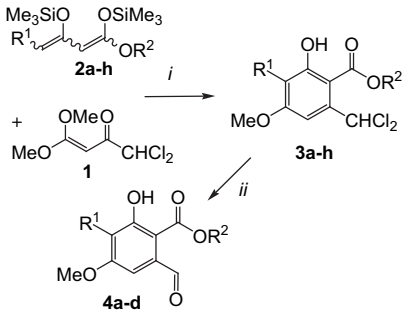
The $TiCl_4$-mediated reaction of **1** with 1,3-bis(silyloxy)-1,3-butadiene **2a** afforded 6-dichloromethyl-4-methoxysalicylate **3a** in 47% yield (Scheme 2). The best yield was obtained when the solution was slowly warmed from −78 °C to 20 °C, when the reaction was carried out in a highly concentrated solution, and when an excess (2.0 equiv) of **2a** was employed.



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

The formation of **3a** can be explained by reaction of **1a** with $TiCl_4$ to give allylic cation **A**. The attack of the terminal carbon atom of **2a** onto **A** afforded intermediate **B** and extrusion of Me_3SiCl gave **C**. The elimination of Me_3SiOMe (intermediate **D**) and subsequent cyclization gave intermediate **E** (Scheme 2). The elimination of $TiCl_3OH$ (before or during the aqueous work-up) and aromatization resulted in the formation of product **3a**. Product **3a**, containing the $CHCl_2$ group located *ortho* to the ester group, was formed with excellent regioselectivity. The formation of the other regioisomer, containing the $CHCl_2$ group located *para* to the ester group, was not observed. The moderate yield can be explained by $TiCl_4$-mediated oxidative dimerization of the diene. This type of process has been previously reported.[17]

The $TiCl_4$-mediated reaction of **1** with 1,3-bis(silyloxy)-1,3-butadienes **2a–h** afforded the 6-dichloromethyl-4-methoxysalicylates **3a–h** in moderate yields (Scheme 3, Table 1). The yields also depend on the type of diene employed. However, no clear trend was observed. The reaction of **3d**,**e**,**g**,**h** with NaOMe–MeOH and subsequent addition of hydrochloric acid afforded the 6-formylsalicylates **4a–d** in good yields. The structures of all products were confirmed by spectroscopic methods. The structures of **3e** and **4b** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[18]



Scheme 3. Synthesis of **3a–h** and **4a–d**. Conditions: *i*, $TiCl_4$, CH_2Cl_2, −78 to 20 °C; *ii*, (1) NaOMe, MeOH, 20 °C, 24 h, (2) HCl, H_2O.

The reaction of **1** with 1,3-bis(silyloxy)-1,3-butadiene **2i**, carried out in the presence of Me_3SiOTf (1.0 equiv) instead of $TiCl_4$, resulted in the formation of 2-(dichloromethyl)pyran-4-one **5a** (Scheme 4).

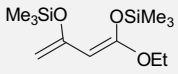
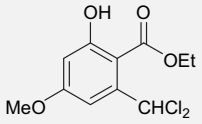
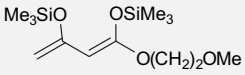
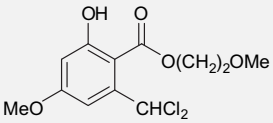
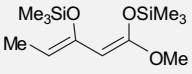
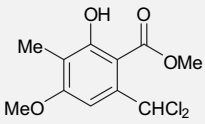
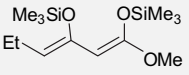
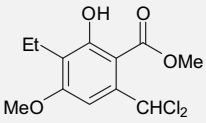
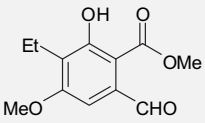
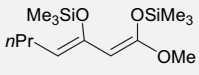
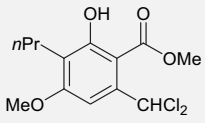
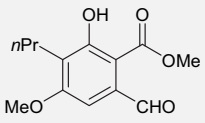
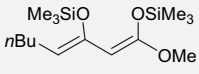
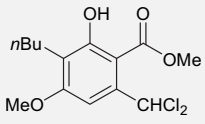
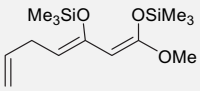
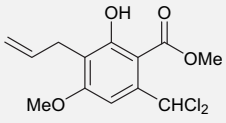
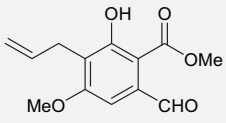
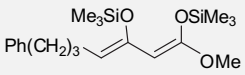
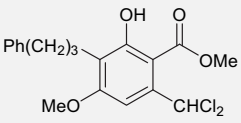
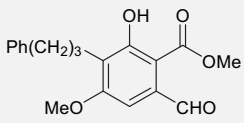
The formation of the corresponding salicylate was *not* observed. The formation of **5a** presumably proceeds by formation of allylic cation **F** (Scheme 4). The attack of the terminal carbon atom of **2i** onto **F** gave intermediate **G**. Now two possible pathways can be discussed. Path A: The direct cyclization of intermediate **G** (via the oxygen atom derived from **1**) afforded intermediate **H**, which was subsequently transformed into **5a** during the aqueous work-up. Alternatively, mechanism path B can be envisaged: the elimination of Me_3SiOTf from **G** gave **I**. The latter underwent elimination of Me_3SiOMe, to give intermediate **J**, and subsequent cyclization by attack of the oxygen atom (derived from **2i**) to give intermediate **K**. The elimination of silanol (before or during the aqueous work-up) resulted in the formation of pyran-4-one **5a**.

The Me_3SiOTf-mediated cyclization of **1** with 1,3-bis(silyloxy)-1,3-butadienes **2a–d** and **2i–o** afforded the functionalized 2-(dichloromethyl)pyran-4-ones **5a–k** (Scheme 5, Table 2). The yields of the esters **5c–k** are higher than the yields of the ketones **5a**,**b**. This can be explained by the higher nucleophilicity of β-ketoester-derived 1,3-bis(silyloxy)-1,3-butadienes compared to those derived from 1,3-diketones. The best yield was obtained for product **5c**, which is derived from the simple diene **2a**. The structures of all products were confirmed by spectroscopic methods. The structures of **5g** and **5i** were independently confirmed by X-ray crystal structure analyses (Figs. 3 and 4).[18]

The change of the regioselectivity depending on the type of Lewis acid employed might be explained based on mechanism path B. The nucleophilicity of the silyl enol ether moiety of intermediate **G** is higher than the nucleophilicity of the titanium enolate moiety of intermediate **B** (due to the high oxophilicity of titanium). Therefore, the elimination of Me_3SiCl from intermediate **B** and formation of **C** is faster than the formation of a pyranone by O-cyclization of the titanium enolate. In contrast, the O-cyclization of the silyl enol ether moiety of intermediate **G** is relatively fast. However, a (reversible) O-cyclization of intermediate **B** cannot be ruled out. Therefore, the regioselective formation of salicylates **3** might be explained also by the assumption that the aromatization of intermediate **E** (by elimination of $TiCl_3OH$) is more rapid than the aromatization of intermediates **H** and **K** (by elimination of Me_3SiOH).

It is important to note that the Me_3SiOTf-mediated formation of $CHCl_2$-substituted pyran-4-ones was generally observed for *all* dienes employed. This result is in contrast to the Me_3SiOTf-mediated synthesis of CF_3-substituted pyran-4-ones, which were formed only for 1,3-bis(trimethylsilyloxy)-1,3-butadienes containing no substituent located at carbon atom C-4.[7] For substituted dienes, the formation of cyclohexenones was observed. This is illustrated by the reactions shown in Scheme 6. The Me_3SiOTf-mediated

Table 1
Synthesis of 6-dichloromethylsalicylates **3a–h** and 6-formylsalicylates **4a–d**

2, 3	4	1,3-Bis(silyloxy)-1,3-butadienes (**2**)	6-Dichloromethylsalicylates (**3**)	%[a] (**3**)	6-Formylsalicylates (**4**)	%[a] (**4**)
a				45		
b				48		
c				32		
d	**a**			48		70
e	**b**			53		77
f				46		
g	**c**			52		81
h	**d**			43		72

[a] Yields of isolated products.

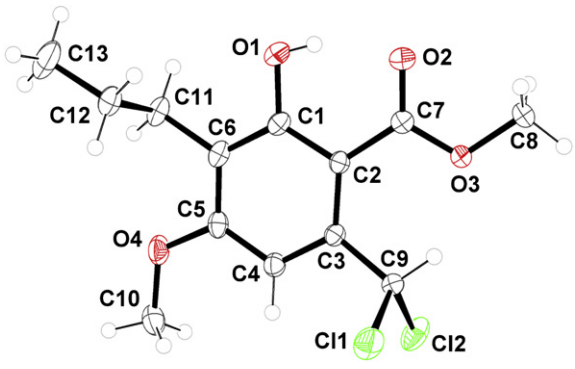


Figure 1. ORTEP plot of **3e** (50% probability level).

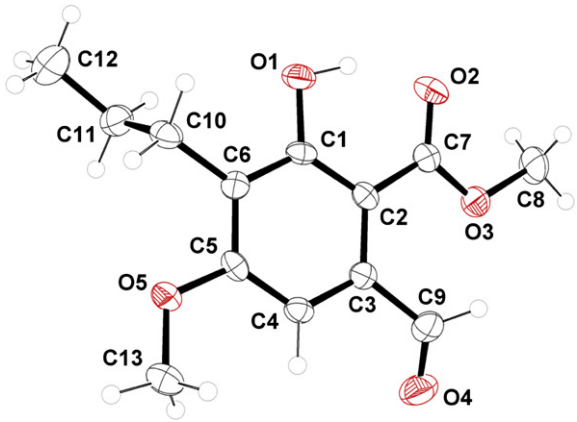
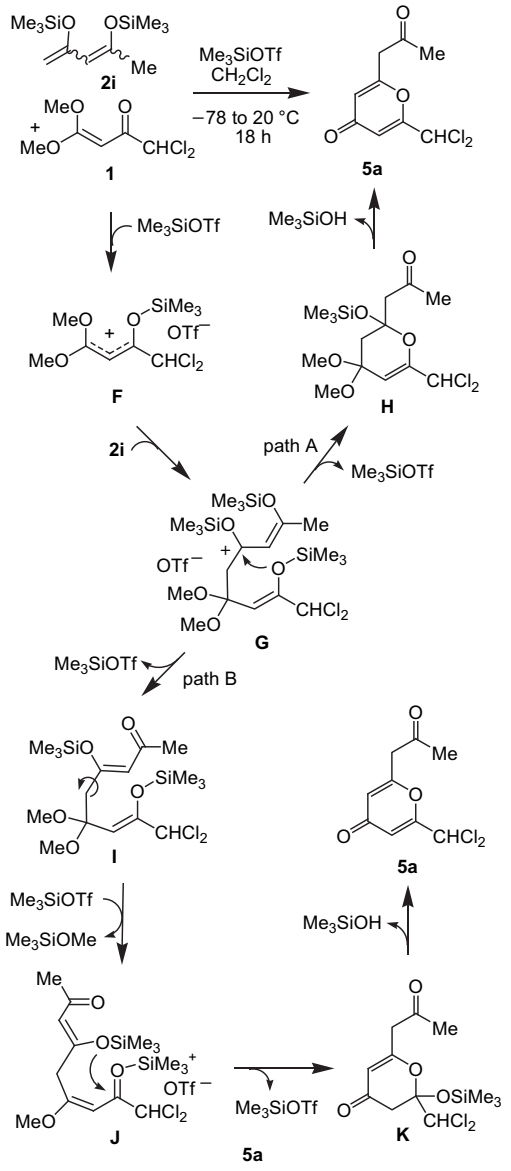
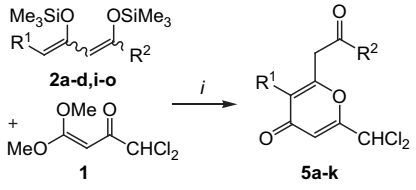


Figure 2. ORTEP plot of **4b** (50% probability level).

cyclization of **2d** with **1** afforded pyran-4-one **5i**, while the cyclization of **2d** with **6** gave under identical conditions the cyclohexanone **7**. The latter did not undergo aromatization under the conditions employed because of the low stability of a cation located next to the CF_3 group. The different regioselectivity of the formation of **5i** and **7** might be explained by the lower nucleophilicity of the CF_3- compared to the $CHCl_2$-substituted silyl enol ether. In addition, the steric influence of the dichloromethyl group (which should be



Scheme 4. Possible mechanisms of the formation of **5a**.



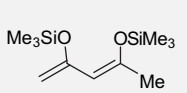
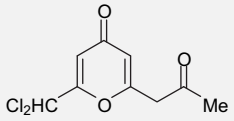
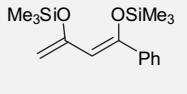
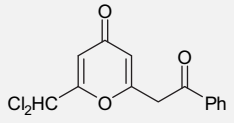
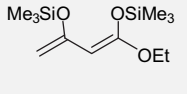
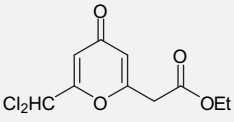
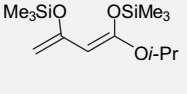
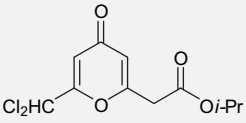
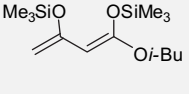
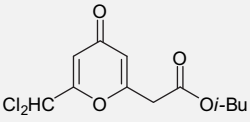
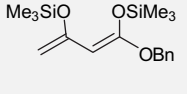
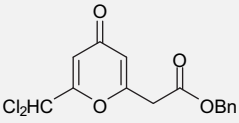
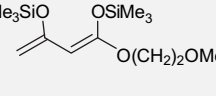
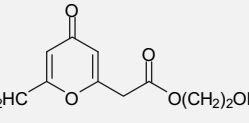
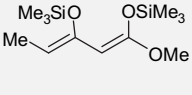
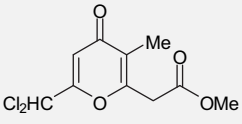
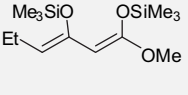
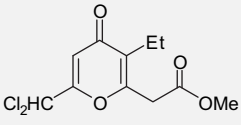
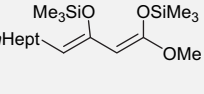
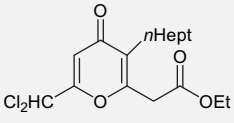
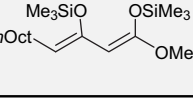
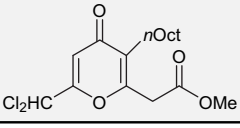
Scheme 5. Synthesis of **5a–k**. Conditions: *i*, Me_3SiOTf, CH_2Cl_2, −78 to 20 °C.

higher than that of the trifluoromethyl group) may play a role (steric interaction with the ester group).

3. Conclusions

In conclusion, we have reported the $TiCl_4$-mediated formal [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one. These reactions allow for convenient synthesis of a variety of functionalized 6-dichloromethyl-4-(methoxy)salicylates with very good regioselectivity. The employment of Me_3SiOTf instead of $TiCl_4$ resulted in a change of the regioselectivity and in the formation of functionalized 2-(dichloromethyl)pyran-4-ones. A different regioselectivity was observed for $CHCl_2$ compared to CF_3-substituted substrates.

Table 2
Synthesis of 2-(dichloromethyl)pyran-4-ones **5a–k**

2	1,3-Bis(silyloxy)-1,3-butadienes (**2**)	5	2-(Dichloromethyl)-pyran-4-ones (**5**)	%[a] (**5**)
i		**a**		21
j		**b**		25
a		**c**		61
k		**d**		47
l		**e**		35
m		**f**		30
b		**g**		35
c		**h**		35
d		**i**		33
n		**j**		30
o		**k**		25

[a] Yields of isolated products.

4. Experimental section

4.1. 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

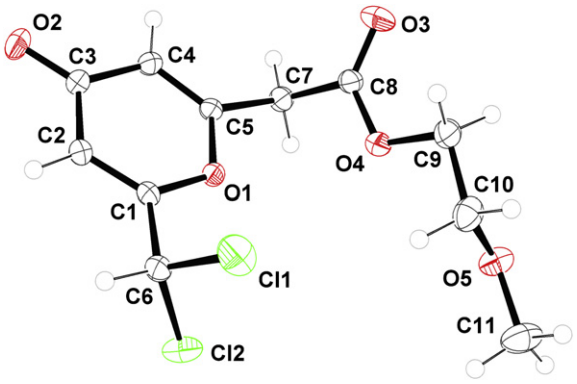


Figure 3. ORTEP plot of **5g** (50% probability level).

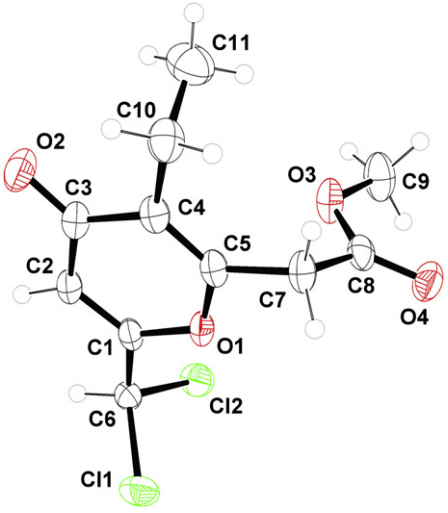
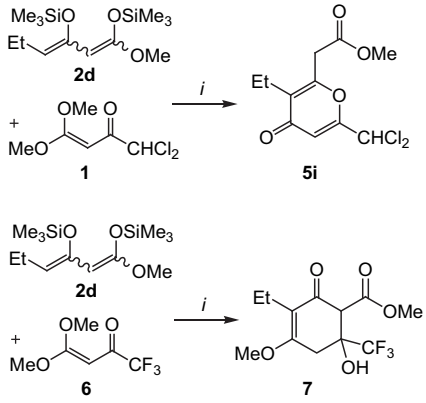


Figure 4. ORTEP plot of **5i** (50% probability level).



Scheme 6. Different regioselectivity of the cyclization of **2d** with **1** and **6**. *Conditions*: *i*, Me_3SiOTf, CH_2Cl_2, −78 to 20 °C.

spectra the deuterated solvents indicated were used. Mass spectrometric (MS) data 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. 1,3-Bis(silyloxy)-1,3-butadienes **2a–o** were prepared according to the literature from the corresponding β-ketoesters in two steps.[14–16]

*4.1.1. 1,1-Dichloro-4,4-dimethoxy-but-3-en-2-one (**1**).* Product **1** was prepared following a known procedure.[13] However, dichloroacetic anhydride instead of dichloroacetic chloride was employed. Starting with methyl orthoacetate (1.202 g, 10.0 mmol), dichloroacetyl anhydride (4.800 g, 20.0 mmol) and dry pyridine (1.820 g, 23.0 mmol) in CH_2Cl_2 (15 mL), **1** was obtained as a colourless solid (1.33 g, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.02 (s, 1H, CCH), 5.89 (s, 1H, $CHCl_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=55.3, 57.3 (OCH_3), 70.8 (*C*HC), 73.1 ($CHCl_2$), 171.2 (CO), 183.8 ($CO(CH_3)_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$=3120 (w), 3002 (w), 1731 (w), 1664 (m), 1531 (s), 1477 (s), 1427 (s), 1306 (s), 1275 (s), 1178 (m), 1137 (m), 1047 (s), 1014 (s), 937 (w), 719 (s). MS (EI, 70 eV): *m*/*z* (%)=198 (M^+, 0.2), 135 (5), 115 (100), 89 (11), 69 (32), 47 (9). HRMS (EI): Calculated for $C_6H_8O_3Cl_2$ (M^+) 197.98450, found 197.98401.

4.2. General procedure for the synthesis of 3a–h

To a CH_2Cl_2 solution (4.0 mL) of **1** (2.0 mmol) and of 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).

*4.2.1. 2-Dichloromethyl-6-hydroxy-4-methoxy-benzoic acid ethyl ester (**3a**).* Starting with **1** (0.400 g, 2.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **2a** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3a** was obtained as a colourless solid (0.251 g, 45%); mp=65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.48 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 4.48 (q, ^3J=7.1 Hz, 2H, OCH_2CH_3), 6.49 (d, ^4J=2.6 Hz, 1H, CH_{Ar}), 7.22 (d, ^4J=2.6 Hz, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.65 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (OCH_2CH_3), 55.6 (OCH_3), 62.4 (OCH_2CH_3), 68.9 ($CHCl_2$), 102.0 (C_{Ar}), 102.2, 109.5 (CH_{Ar}), 143.1, 164.3, 164.9 (C_{Ar}), 169.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3075 (w), 2982 (w), 1656 (s), 1615 (s), 1574 (m), 1463 (w), 1434 (m), 1366 (s), 1327 (m), 1249 (s), 1205 (s), 1160 (s), 1109 (m), 1014 (s), 954 (m), 852 (s), 760 (s), 738 (s), 683 (m). MS (EI, 70 eV): *m*/*z* (%)=278 (M^+, 27), 232 (100), 197 (12), 179 (43), 126 (7), 95 (4). HRMS (EI): Calculated for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.01059.

*4.2.2. 2-Dichloromethyl-6-hydroxy-4-methoxy-benzoic acid 2-methoxy-ethyl ester (**3b**).* Starting with **1** (0.400 g, 2.0 mmol), 1-(2-methoxy-ethoxy)-1,3-bis(trimethylsilyloxy)-buta-1,3-diene **2b** (1.218 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3b** was obtained as a colourless oil (0.277 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.45 (s, 3H, CH_2OCH_3), 3.74 (m, ^3J=4.6 Hz, 2H, CH_2OCH_3), 3.84 (s, 3H, OCH_3), 4.49–4.53 (m, 2H, OCH_2CH_2), 6.47 (d, ^4J=2.6 Hz, 1H, CH_{Ar}), 7.21 (d, ^4J=2.6 Hz, 1H, CH_{Ar}), 7.82 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=55.6 (OCH_3), 59.0 (OCH_3), 64.7 (OCH_2CH_2), 69.0 ($CHCl_2$), 69.7 ($COOCH_2$), 102.1 (C_{Ar}), 102.2, 109.5 (CH_{Ar}), 143.6, 164.3, 164.4 (C_{Ar}), 169.2 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3072 (w), 2893 (w), 1715 (w), 1657 (m), 1615 (s), 1574 (m), 1436 (w), 1368 (m), 1323 (m), 1242 (s), 1200 (s), 1158 (s), 1114 (s), 1045 (s), 954 (m), 842 (w), 726 (s), 621 (m). MS (EI, 70 eV): *m*/*z* (%)=308 (M^+, 15), 232 (100), 198 (10), 169 (21), 135 (8), 59 (31). HRMS (EI): Calculated for $C_{12}H_{14}O_5Cl_2$ (M^+) 308.02128, found 308.02119.

*4.2.3. 6-Dichloromethyl-2-hydroxy-4-methoxy-3-methyl-benzoic acid methyl ester (**3c**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)penta-1,3-diene **2c** (1.096 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3c** was obtained as a colourless solid (0.118 g, 32%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.11 (s,

3H, $C_{Ar}CH_3$), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.54 (s, 1H, OH). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ=52.8 (OCH_3), 55.0 (OCH_3), 69.5 ($CHCl_2$), 102.2 (C_{Ar}), 103.5 (CH_{Ar}), 115.6, 140.3, 161.0, 161.8 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3079 (w), 2954 (w), 1722 (w), 1662 (s), 1574 (m), 1506 (w), 1436 (m), 1402 (m), 1373 (w) 1279 (s), 1226 (m), 1194 (m), 1157 (s), 1125 (br s), 994 (s), 930 (w), 789 (s), 717 (s), 667 (m). MS (EI, 70 eV): *m*/*z* (%)=278 (M^+, 36), 246 (64), 210 (100), 183 (19), 149 (5), 77 (15). HRMS (EI): Calculated for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.01045.

*4.2.4. 6-Dichloromethyl-3-ethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (**3d**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)hexa-1,3-diene **2d** (1.152 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3d** was obtained as a colourless solid (0.281 g, 48%); mp=63–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.08 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 2.68 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.48 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.9 (CH_2CH_3), 16.4 (CH_2CH_3), 52.8 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.4 (C_{Ar}), 103.7 (CH_{Ar}), 121.6, 140.4, 160.8, 161.6 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3083 (w), 2956 (w), 2851 (w), 1659 (s), 1603 (m), 1569 (w), 1437 (m), 1406 (m), 1275 (s), 1218 (s), 1154 (s), 1129 (s), 1001 (s), 943 (w), 849 (w), 724 (s), 587 (m). MS (EI, 70 eV): *m*/*z* (%)=292 (M^+, 23), 260 (20), 224 (100), 206 (10), 161 (16), 125 (2), 77 (7). HRMS (EI): Calculated for $C_{12}H_{14}O_4Cl_2$ (M^+) 292.02637, found 292.02654.

*4.2.5. 6-Dichloromethyl-2-hydroxy-4-methoxy-3-propyl-benzoic acid methyl ester (**3e**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)hepta-1,3-diene **2e** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3e** was obtained as a yellow solid (0.325 g, 53%); mp=68–71 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.94 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.43–1.61 (m, 2H, CH_2CH_3), 2.60–2.66 (m, 2H, $C_{Ar}CH_2$), 3.92 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.20 (s, 1H, CH_{Ar}), 7.75 (s, 1H, $CHCl_2$), 11.49 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.2 (CH_2CH_3), 21.7, 25.0 (CH_2CH_2), 52.8 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.4 (C_{Ar}), 103.7 (CH_{Ar}), 120.2, 140.4, 161.0, 161.8 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3083 (w), 2959 (m), 2899 (w), 1715 (w), 1652 (s), 1602 (m), 1511 (w), 1435 (w), 1270 (s), 1193 (m), 1132 (m), 994 (m), 729 (s), 601 (w). MS (EI, 70 eV): *m*/*z* (%)=306 (M^+, 40), 274 (32), 238 (100), 210 (40), 175 (15), 111 (15), 69 (32). HRMS (EI): Calculated for $C_{13}H_{16}O_4Cl_2$ (M^+) 306.04202, found 306.04150.

*4.2.6. 3-Butyl-6-dichloromethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (**3f**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)octa-1,3-diene **2f** (1.212 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3f** was obtained as a colourless solid (0.294 g, 46%); mp=91–92 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.92 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 1.30–1.39 (m, 2H, CH_2), 1.40–1.52 (m, 2H, CH_2), 2.63–2.68 (m, 2H, $C_{Ar}CH_2$), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.48 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (CH_2CH_3), 22.7, 22.8, 30.7 (CH_2), 52.7 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.3 (C_{Ar}), 103.7 (CH_{Ar}), 120.4, 140.3, 161.0, 161.7 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3080 (w), 2925 (m), 1657 (s), 1605 (m), 1573 (w), 1435 (m), 1404 (m), 1287 (s), 1270 (s), 1190 (m), 1138 (s), 1077 (m), 1004 (s), 991 (s), 851 (m), 725 (s), 644 (m). MS (EI, 70 eV): *m*/*z* (%)=320 (M^+, 35), 277 (22), 245 (65), 210 (100), 179 (12), 145 (5), 89 (8). HRMS (EI): Calculated for $C_{14}H_{18}O_4Cl_2$ (M^+) 320.05767, found 320.05768.

*4.2.7. 3-Allyl-6-dichloromethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (**3g**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)hepta-1,3,6-triene **2g** (1.204 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3g** was obtained as a colourless oil (0.316 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.41–3.44 (m, 2H, $C_{Ar}CH_2$), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.94–5.06 (m, 2H, CH_2CHCH_2), 5.86–5.99 (m, 1H, CH_2CHCH_2), 7.23 (s, 1H, CH_{Ar}), 7.77 (s, 1H, $CHCl_2$), 11.54 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=27.1 ($C_{Ar}CH_2$), 52.8 (OCH_3), 55.8 (OCH_3), 69.4 ($CHCl_2$), 102.5 (C_{Ar}), 103.8 (CH_{Ar}), 114.8 (CH_2CH), 117.2 (C_{Ar}), 135.2 (CH_2CH), 141.0, 160.9, 161.6 (C_{Ar}), 170.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3078 (w), 2955 (w), 1788 (w), 1720 (w), 1659 (s), 1605 (m), 1510 (w), 1403 (m), 1360 (w), 1276 (s), 1195 (s), 1153 (s), 1133 (s), 999 (m), 912 (m), 724 (s), 630 (m). MS (EI, 70 eV): *m*/*z* (%)=304 (M^+, 40), 269 (29), 236 (100), 203 (13), 173 (59), 115 (12), 77 (14). HRMS (EI): Calculated for $C_{13}H_{14}O_4Cl_2$ (M^+) 304.02637, found 304.02625.

*4.2.8. 6-Dichloromethyl-2-hydroxy-4-methoxy-3-(3-phenyl-propyl)-benzoic acid methyl ester (**3h**).* Starting with **1** (0.400 g, 2.0 mmol), (7-methoxy-5,7-bis(trimethylsilyloxy)-hepta-4,6-dienyl)benzene **2h** (1.515 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **3h** was obtained as a colourless oil (0.329 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.89–2.00 (m, 2H, $C_{Ar}CH_2CH_2$), 2.76–2.86 (m, 4H, $C_{Ar}CH_2$), 4.02 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 7.28–7.38 (m, 6H, CH_{Ar}), 7.87 (s, 1H, $CHCl_2$), 11.62 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=22.9, 29.8, 35.9 ($CH_2CH_2CH_2$), 52.7 (OCH_3), 55.7 (OCH_3), 69.5 ($CHCl_2$), 102.4 (C_{Ar}), 103.6 (CH_{Ar}), 119.8 (C_{Ar}), 125.5, 128.1, 128.3 (CH_{Ar}), 140.5, 142.6, 161.0, 161.7 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3025 (w), 2939 (w), 1934 (w), 1804 (w), 1703 (w), 1661 (m), 1605(m), 1496 (w), 1405 (m), 1359 (w), 1280 (s), 1226 (m), 1157 (s), 1116 (s), 1002 (m), 843 (w), 733 (m), 699 (m). MS (EI, 70 eV): *m*/*z* (%)=382 (M^+, 40), 347 (14), 314 (7), 245 (32), 210 (100), 176 (16), 91 (31). HRMS (EI): Calculated for $C_{19}H_{20}O_4Cl_2$ (M^+) 382.07332, found 382.07328.

4.3. General procedure for the synthesis of 4a–d

To a methanol (10 mL) solution of sodium methanolate (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 (3×30 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).

*4.3.1. 3-Ethyl-6-formyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (**4a**).* Starting with **3d** (0.295 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **4a** was obtained as a colourless solid (0.167 g, 70%); mp=57–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.09 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 2.71 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.93 (s, 1H, CH_{Ar}), 10.47 (s, 1H, CHO), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.8 (CH_2CH_3), 16.6 (CH_2CH_3), 52.7 (OCH_3), 55.9 (OCH_3), 103.2 (CH_{Ar}), 105.3, 125.0, 137.5, 161.0, 161.6 (C_{Ar}), 170.4 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$=2961 (w), 2875 (w), 1662 (s), 1596 (m), 1570 (m), 1503 (w), 1437 (m), 1390 (m), 1346 (m), 1276 (s), 1251 (s), 1196 (m), 1155 (s), 1131 (s), 1058 (m), 1003 (m), 957 (m), 944 (m), 806 (m), 729 (m). MS (EI, 70 eV): *m*/*z* (%)=238 (M^+, 65), 209 (41), 191 (26), 179 (100), 150 (63), 135 (31), 107 (16), 77 (29). HRMS (EI): Calculated for $C_{12}H_{14}O_5$ (M^+) 238.08358, found 238.08340.

*4.3.2. 6-Formyl-2-hydroxy-4-methoxy-3-propyl-benzoic acid methyl ester (**4b**).* Starting with **3e** (0.306 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **4b** was obtained as a colourless solid (0.194 g, 77%); mp=72–73 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.93 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.46–1.58 (m, 2H, CH_2CH_3), 2.63–2.68 (m, 2H, $C_{Ar}CH_2$), 3.89 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.92 (s, 1H, CH_{Ar}), 10.47 (s, 1H, CHO), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (CH_2CH_3), 21.6, 25.1 (CH_2CH_2), 52.7 (OCH_3), 55.8 (OCH_3), 103.1 (CH_{Ar}), 105.2, 123.6, 137.6, 161.2, 161.8 (C_{Ar}), 170.4

(C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$=2924 (w), 2867 (w), 1686 (m), 1660 (s), 1570 (m), 1503 (w), 1435 (m), 1386 (m), 1346 (m), 1298 (s), 1285 (s), 1217 (s), 1135 (s), 1077 (m), 1036 (w), 999 (w), 951 (w), 875 (w), 795 (m), 754 (s), 610 (m). MS (EI, 70 eV): *m*/*z* (%)=252 (M^+, 66), 223 (52), 193 (100), 177 (42), 135 (18), 105 (17), 77 (28). HRMS (EI): Calculated for $C_{13}H_{16}O_5$ (M^+) 252.09923, found 252.09915.

*4.3.3. 3-Allyl-6-formyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (**4c**).* Starting with **3g** (0.304 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **4c** was obtained as a colourless solid (0.202 g, 81%); mp=54–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.44–3.47 (m, 2H, $C_{Ar}CH_2$), 3.91 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.95–5.04 (m, 2H, CH_2CHCH_2), 5.85–5.98 (m, 1H, CH_2CH), 6.94 (s, 1H, CH_{Ar}), 10.49 (s, 1H, CHO), 11.32 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=27.2 ($C_{Ar}CH_2$), 52.8 (OCH_3), 56.0 (OCH_3), 103.2 (CH_{Ar}), 105.4 (C_{Ar}), 115.1 (CH_2CH), 120.6 (C_{Ar}), 134.9, (CH_2CH), 138.1, 161.1, 161.7 (C_{Ar}), 170.3 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3077 (w), 2946 (w), 2845 (w), 1661 (s), 1602 (w), 1570 (s), 1504 (w), 1435 (m), 1408 (m), 1344 (m), 1284 (s), 1212 (s), 1158 (s), 1131 (s), 1035 (m), 995 (s), 910 (m), 876 (m), 797 (s), 750 (s), 631 (m). MS (EI, 70 eV): *m*/*z* (%)=250 (M^+, 75), 222 (61), 191 (100), 175 (74), 147 (12), 119 (24), 91 (41). HRMS (EI): Calculated for $C_{13}H_{14}O_5$ (M^+) 250.08358, found 250.08381.

*4.3.4. 6-Formyl-2-hydroxy-4-methoxy-3-(3-phenyl-propyl)-benzoic acid methyl ester (**4d**).* Starting with **3h** (0.153 g, 0.4 mmol), NaOMe (0.083 g, 1.5 mmol) in dry MeOH (5 mL), **4d** was obtained as a colourless solid (0.110 g, 72%); mp=65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.80–1.90 (m, 2H, $C_{Ar}CH_2CH_2$), 2.65–2.79 (m, 4H, $C_{Ar}CH_2$), 3.89 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.93 (s, 1H, CH_{Ar}), 7.15–7.26 (m, 5H, CH_{Ar}), 10.48 (s, 1H, CHO), 11.31 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=23.1, 29.7, 35.9 ($CH_2CH_2CH_2$), 52.7 (OCH_3), 55.8 (OCH_3), 103.1 (CH_{Ar}), 105.2, 123.2 (C_{Ar}), 125.6, 128.1, 128.3 (CH_{Ar}), 137.7, 142.5, 161.2, 161.7 (C_{Ar}), 170.4 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$=2937 (w), 2856 (w), 1746 (w), 1657 (s), 1569 (m), 1494 (w), 1438 (m), 1387 (m), 1341 (m), 1294 (s), 1273 (s), 1255 (s), 1200 (s), 1146 (s), 1107 (s), 1000 (s), 948 (m), 846 (m), 804 (m), 746 (s), 699 (s). MS (EI, 70 eV): *m*/*z* (%)=328 (M^+, 2), 269 (19), 224 (100), 192 (99), 164 (18), 105 (16), 77 (17). HRMS (EI): Calculated for $C_{19}H_{20}O_5$ (M^+) 328.13053, found 328.13059.

4.4. General procedure for the synthesis of 5a–k

To a CH_2Cl_2 solution (10 mL) of **1** (1.0 mmol) was added **2** (2.0 mmol) and, subsequently, Me_3SiOTf (0.244 g, 1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12–14 h with stirring. To the solution was added hydrochloric acid (10%, 10 mL) and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×30 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, heptane–EtOAc=15:1).

*4.4.1. 2-Dichloromethyl-6-(2-oxopropyl)-pyran-4-one (**5a**).* Starting with **1** (0.400 g, 2.0 mmol), 2,4-bis(trimethylsilyloxy)-penta-1,3-diene **2i** (0.978 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5a** was obtained as a brownish viscous oil (0.099 g, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.30 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 6.24 (d, ^4J=2.1 Hz, 1H, CHCO), 6.32 (s, 1H, $CHCl_2$), 6.52 (d, ^4J=2.1 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=30.0 (CH_3), 47.8 (CH_2CO), 65.2 ($CHCl_2$), 112.9, 116.9 (*C*HCO), 161.3, 161.9 (OCCH), 178.7 (CH*C*=O), 200.1 (CH_2CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=3078 (w), 2922 (w), 1725 (m), 1656 (s), 1603 (m), 1394 (m), 1314 (m), 1213 (w), 1156 (s), 975 (w), 928 (s), 873 (m), 761 (s), 741 (s), 655 (m), 621 (w). MS (EI, 70 eV): *m*/*z* (%)=234 (M^+, 1), 192 (100), 157 (27), 128 (7), 109 (8), 69 (17). HRMS (EI): Calculated for $C_9H_8O_3Cl_2$ (M^+) 233.98450, found 233.98491.

*4.4.2. 2-Dichloromethyl-6-(2-oxo-2-phenyl-ethyl)-pyran-4-one (**5b**).* Starting with **1** (0.400 g, 2.0 mmol), (1,3-bis(trimethylsilyloxy)-buta-1,3-dienyl)benzene **2j** (1.224 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5b** was obtained as a colourless solid (0.148 g, 25%); mp=76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.25 (s, 2H, CH_2), 6.29 (d, ^4J=2.2 Hz, 1H, CHCO), 6.31 (s, 1H, $CHCl_2$), 6.53 (d, ^4J=2.2 Hz, 1H, CHCO), 7.49–7.54 (m, 2H, CH_{Ar}), 7.64 (ddd, ^3J=7.4 Hz, ^3J=6.2 Hz, ^4J=2.0 Hz, 1H, CH_{Ar}), 7.97–8.00 (m, 2H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=43.2 (CH_2CO), 65.2 ($CHCl_2$), 113.0, 117.2 (*C*HCO), 128.4, 129.0, 134.2 (CH_{Ar}), 135.5 (C_{Ar}), 161.3, 162.4 (OCCH), 178.6 (C=O), 192.2 ($C_{Ar}CO$). IR (ATR, cm^{-1}): $\tilde{\nu}$=3076 (w), 2979 (m), 2662 (w), 2476 (w), 1668 (s), 1632 (s), 1609 (m), 1449 (w), 1392 (s), 1338 (m), 1299 (m), 1217 (m), 1196 (m), 1149 (m), 1078 (w), 978 (m), 964 (m), 923 (s), 879 (m), 824 (w), 767 (s), 734 (s), 690 (s), 666 (m), 587 (m). MS (EI, 70 eV): *m*/*z* (%)=297 (M^+, 6), 218 (32), 192 (15), 176 (100), 94 (32), 78 (8). HRMS (EI): Calculated for $C_{14}H_{11}O_3Cl_2$ ($(M+H)^+$) 297.00798, found 297.0079.

*4.4.3. (6-Dichloromethyl-4-oxo-4H-pyran-2-yl)-acetic acid ethyl ester (**5c**).* Starting with **1** (0.400 g, 2.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **2a** (1.096 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5c** was obtained as an orange oil (0.321 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 3.59 (s, 2H, CCH_2C), 4.21 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 6.27 (d, ^4J=2.1 Hz, 1H, CHCO), 6.33 (s, 1H, $CHCl_2$), 6.51 (d, ^4J=2.1 Hz, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (OCH_2CH_3), 39.4 (CH_2CO), 62.0 (OCH_2CH_3), 65.1 ($CHCl_2$), 112.9, 116.6 (*C*HCO), 161.2, 161.5 (OCCH), 166.7 (COO), 178.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3078 (w), 2983 (w), 1734 (s), 1659 (s), 1627 (s), 1465 (w), 1393 (s), 1331 (w), 1250 (m), 1162 (m), 1026 (m), 975 (w), 928 (s), 873 (m), 760 (s), 734 (s), 621 (m), 590 (w). MS (EI, 70 eV): *m*/*z* (%)=264 (M^+, 56), 192 (80), 157 (53), 128 (100), 109 (17), 69 (56). HRMS (EI): Calculated for $C_{10}H_{10}O_4Cl_2$ (M^+) 263.99507, found 263.99509.

*4.4.4. (6-Dichloromethyl-4-oxo-4H-pyran-2-yl)-acetic acid isopropyl ester (**5d**).* Starting with **1** (0.400 g, 2.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **2k** (1.114 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5d** was obtained as an orange oil (0.262 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24 (d, ^3J=6.3 Hz, 6H, $OCH(CH_3)_2$), 3.56 (s, 2H, CCH_2C), 5.01–5.10 (m, ^3J=6.3 Hz, 1H, $OCH(CH_3)_2$), 6.26 (d, ^4J=2.2 Hz, 1H, CHCO), 6.33 (s, 1H, $CHCl_2$), 6.51 (d, ^4J=2.2 Hz, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=21.6 ($CH(CH_3)_2$), 39.7 (CH_2CO), 65.1 ($CHCl_2$), 69.9 (COOCH), 112.7, 116.4 (*C*HCO), 161.3, 161.8 (OCCH), 166.2 (COO), 178.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3079 (w), 2982 (w), 1730 (m), 1659 (s), 1627 (m), 1454 (w), 1394 (s), 1321 (m), 1258 (m), 1172 (m), 1101 (s), 996 (m), 928 (s), 873 (m), 761 (m), 680 (w), 621 (m). MS (EI, 70 eV): *m*/*z*=278 (M^+, 11), 219 (14), 192 (27), 163 (11), 128 (12), 69 (15), 43 (100). HRMS (EI): Calculated for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.01083.

*4.4.5. (6-Dichloromethyl-4-oxo-4H-pyran-2-yl)-acetic acid isobutyl ester (**5e**).* Starting with **1** (0.400 g, 2.0 mmol), 1-isobutoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **2l** (1.202 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5e** was obtained as an orange oil (0.205 g, 35%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.85 (d, ^3J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.80–1.96 (m, ^3J=6.8 Hz, 1H, $CH(CH_3)_2$), 3.58 (s, 2H, CCH_2C), 3.88 (d, ^3J=6.7 Hz, 2H, OCH_2CH), 6.25 (d, ^4J=2.2 Hz, 1H, CHCO), 6.36 (s, 1H, $CHCl_2$), 6.48 (d, ^4J=2.2 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=18.8 ($CH(CH_3)_2$), 27.4 ($CH(CH_3)_2$), 39.2 (CH_2CO), 65.0 ($CHCl_2$), 71.8 ($COOCH_2$), 112.7, 116.4 (CHCO), 161.3, 161.7 (OCCH), 166.7 (COO), 178.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3080 (w), 2962 (w), 1736 (m), 1660 (s), 1629 (m), 1469 (w), 1393 (s), 1321 (w), 1246 (br m), 1163 (s), 1104 (w), 1005 (m), 928

(s), 874 (m), 761 (s), 683 (w), 622 (m). MS (EI, 70 eV): m/z=292 (M^+, 41), 237 (77), 192 (55), 163 (15), 128 (30), 99 (11), 69 (28), 57 (100), 41 (60). HRMS (EI): Calculated for $C_{12}H_{14}O_4Cl_2$ (M^+) 292.02637, found 292.02661.

*4.4.6. (6-Dichloromethyl-4-oxo-4H-pyran-2-yl)-acetic acid benzyl ester (**5f**).* Starting with **1** (0.400 g, 2.0 mmol), (1,3-bis(trimethylsilyloxy)buta-1,3-dienyloxymethyl)benzene **2m** (1.344 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5f** was obtained as an orange oil (0.197 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.64 (s, 2H, CCH_2C), 5.19 (s, 2H, OCH_2C), 6.26 (s, 1H, $CHCl_2$), 6.29 (d, ^4J=2.1 Hz, 1H, CHCO), 6.52 (d, ^4J=2.1 Hz, 1H, CHCO), 7.33–7.38 (m, 5H, CH_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=39.3 (CH_2CO), 65.0 ($CHCl_2$), 67.8 ($C_{Ar}CH_2O$), 112.9, 116.9 (*C*HCO), 128.5, 128.7 (CH_{Ar}), 134.1 (C_{Ar}), 161.3, 161.4 (OCCH), 166.5 (COO), 178.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3066 (w), 3004 (w), 1738 (m), 1659 (s), 1605 (br m), 1455 (w), 1395 (m), 1321 (w), 1256 (m), 1210 (m), 1159 (s), 1142 (s), 1000 (m), 929 (m), 874 (m), 730 (s), 696 (s), 646 (w), 620 (m). MS (EI, 70 eV): m/z (%)=326 (M^+, 3), 219 (2), 192 (15), 158 (3), 91 (100), 65 (8). HRMS (EI): Calculated for $C_{15}H_{12}O_4Cl_2$ (M^+) 326.01072, found 326.01085.

*4.4.7. (6-Dichloromethyl-4-oxo-4H-pyran-2-yl)-acetic acid 2-methoxyethyl ester (**5g**).* Starting with **1** (0.400 g, 2.0 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)buta-1,3-diene **2b** (1.216 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5g** was obtained as a colourless solid (0.206 g, 35%); mp=60–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.32 (s, 3H, OCH_3), 3.54–3.57 (m, 2H, CH_2OCH_3), 3.61 (s, 2H, CCH_2C), 4.25–4.28 (m, 2H, $COCH_2$), 6.25 (d, ^4J=2.1 Hz, 1H, CHCO), 6.34 (s, 1H, $CHCl_2$), 6.48 (d, ^4J=2.1 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=39.0 (CH_2CO), 58.8 (OCH_3), 64.7 (OCH_2CH_2), 65.0 ($CHCl_2$), 69.9 ($COOCH_2$), 112.9, 116.5 (*C*HCO), 161.2 (OCCH), 166.7 (COO), 178.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3085 (w), 3006 (w), 2888 (w), 1732 (s), 1653 (s), 1617 (s), 1419 (w), 1400 (s), 1366 (m), 1280 (s), 1229 (m), 1181 (m), 1124 (s), 1098 (m), 1032 (s), 993 (m), 933 (s), 894 (s), 856 (s), 759 (s), 733 (s), 625 (m). MS (EI, 70 eV): m/z=294 (M^+, 12), 228 (59), 192 (51), 158 (30), 128 (34), 99 (12), 69 (33), 45 (100). HRMS (EI): Calculated for $C_{11}H_{12}O_5Cl_2$ (M^+) 294.00563, found 294.05227.

*4.4.8. (6-Dichloromethyl-3-methyl-4-oxo-4H-pyran-2-yl)-acetic acid methyl ester (**5h**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)penta-1,3-diene **2c** (1.096 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5h** was obtained as an orange oil (0.184 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.95 (s, 3H, CCH_3), 3.70 (s, 2H, CCH_2C), 3.74 (s, 3H, OCH_3), 6.33 (s, 1H, $CHCl_2$), 6.54 (s, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=9.8 (CCH_3), 37.3 (CH_2CO), 52.8 (OCH_3), 65.1 ($CHCl_2$), 111.2 (*C*HCO), 124.3 (*C*CH_3), 157.4, 160.6 (OC), 167.5 (COO), 179.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=3084 (w), 3002 (w), 1740 (m), 1656 (s), 1605 (m), 1411 (m), 1381 (m), 1322 (m), 1271 (m), 1204 (m), 1155 (s), 1092 (m), 1044 (w), 1006 (m), 909 (w), 868 (w), 758 (s), 729 (s), 619 (m). MS (EI, 70 eV): m/z (%)=264 (M^+, 92), 233 (25), 196 (100), 155 (86), 142 (58), 83 (4), 69 (34), 53 (27). HRMS (EI): Calculated for $C_{10}H_{10}O_4Cl_2$ (M^+) 263.99507, found 263.99455.

*4.4.9. (6-Dichloromethyl-3-ethyl-4-oxo-4H-pyran-2-yl)-acetic acid methyl ester (**5i**).* Starting with **1** (0.400 g, 2.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)hexa-1,3-diene **2d** (1.152 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5i** was obtained as a colourless solid (0.183 g, 33%); mp=64–65 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.00 (t, ^3J=7.5 Hz, 3H, CH_2CH_3), 2.37 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 3.65 (s, 2H, CCH_2C), 3.70 (s, 3H, OCH_3), 6.32 (s, 1H, $CHCl_2$), 6.47 (s, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=12.6 (CH_2CH_3), 17.9 (CH_2CH_3), 36.8 (CH_2CO), 52.6 (OCH_3), 65.1 ($CHCl_2$), 111.7 (*C*HCO), 129.4 (*C*CH_2CH_3), 157.0, 160.2 (OC), 167.7 (COO), 178.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=2995 (w), 2959 (w), 1739 (s), 1654 (s), 1601 (s), 1461 (w), 1415 (s), 1289 (w), 1263 (s), 1186 (m), 1131 (m), 1108 (m), 1015 (m), 978 (m), 907 (w), 850 (m), 788 (m), 758 (s), 671 (w), 637 (m). MS (EI, 70 eV): m/z (%)=278 (M^+, 21), 242 (99), 210 (100), 184 (21), 169 (51), 143 (21), 101 (11), 69 (24). HRMS (EI): Calculated for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01157, found 278.01148.

*4.4.10. (6-Dichloromethyl-3-heptyl-4-oxo-4H-pyran-2-yl)-acetic acid ethyl ester (**5j**).* Starting with **1** (0.400 g, 2.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)undeca-1,3-diene **2n** (1.492 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5j** was obtained as an orange oil (0.217 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (t, ^3J=6.8 Hz, 3H, CH_2CH_3), 1.27 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3), 1.29–1.46 (m, 10H, $(CH_2)_5CH_3$), 2.36–2.41 (m, 2H, CCH_2CH_2), 3.68 (s, 2H, CCH_2C), 4.21 (q, ^3J=7.1 Hz, 2H, OCH_2CH_3), 6.31 (s, 1H, $CHCl_2$), 6.57 (s, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0, 14.1 (CH_3), 22.6, 24.7, 28.4, 29.1, 29.6, 31.7 ($(CH_2)_6CH_3$), 37.3 (CH_2CO), 62.0 (OCH_2CH_3), 65.2 ($CHCl_2$), 111.6 (*C*HCO), 128.4 (*C*CH_2CH_2), 157.8, 160.4 (OC), 167.3 (COO), 179.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=2926 (w), 2855 (w), 1739 (s), 1645 (s), 1464 (w), 1418 (m), 1267 (m), 1175 (s), 1107 (m), 1025 (m), 867 (w), 763 (s), 676 (m), 637 (w). MS (EI, 70 eV): m/z (%)=362 (M^+, 2), 316 (15), 275 (100), 241 (34), 206 (24), 155 (14), 91 (6). HRMS (EI): Calculated for $C_{17}H_{24}O_4Cl_2$ (M^+) 362.10462, found 362.10426.

*4.4.11. (6-Dichloromethyl-3-octyl-4-oxo-4H-pyran-2-yl)-acetic acid ethyl ester (**5k**).* Starting with **1** (0.400 g, 2.0 mmol), 1-ethoxy-1,3-bis-trimethylsilanyloxy-dodeca-1,3-diene **2o** (1.548 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **5k** was obtained as an orange oil (0.188 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (t, ^3J=6.8 Hz, 3H, CH_2CH_3), 1.27 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 1.28–1.61 (m, 12H, $(CH_2)_6CH_3$), 2.36–2.41 (m, 2H, CCH_2CH_2), 3.67 (s, 2H, CCH_2C), 4.21 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 6.30 (s, 1H, $CHCl_2$), 6.50 (s, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0, 14.1 (CH_3), 22.6, 24.7, 28.4, 29.2, 29.4, 29.7, 31.8 ($(CH_2)_7CH_3$), 37.3 (CH_2CO), 61.9 (OCH_2CH_3), 65.3 ($CHCl_2$), 111.7 (*C*HCO), 128.4 (*C*CH_2CH_2), 157.5, 160.3 (OC), 167.4 (COO), 178.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$=2925 (m), 2854 (w), 1740 (m), 1656 (s), 1602 (m), 1463 (w), 1415 (m), 1323 (w), 1252 (m), 1176 (s), 1107 (m), 1027 (m), 911 (w), 848 (w), 762 (s), 672 (w). MS (EI, 70 eV): m/z (%)=376 (M^+, 5), 330 (19), 289 (100), 278 (33), 255 (18), 206 (23), 177 (12), 155 (12), 69 (20). HRMS (EI): Calculated for $C_{18}H_{26}O_4Cl_2$ (M^+) 376.12027, found 376.12002.

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