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Regioselective synthesis of 6-aryl-5-(chloroethyl)salicylates by domino '[3+3] cyclization/homo-Michael' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-formyl- and 1-acetyl-1-aroyl-cyclopropanes

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ABSTRACT

Functionalized 3-aryl-4-(chloroethyl)phenols are regioselectively prepared by domino '[3+3] cyclization/homo-Michael' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-formyl- and 1-acetyl-1-aroyl-cyclopropanes.

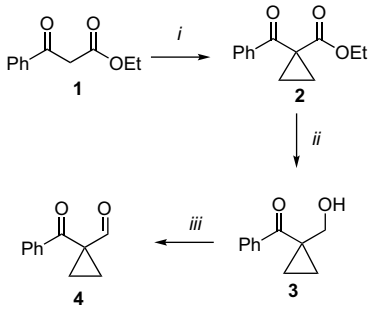
1. Introduction

1,3-Bis(silyloxy)-1,3-butadienes represent electroneutral 1,3-dicarbonyl dianion equivalents (masked dianions).[1] They can react as 1,3-dinucleophiles in formal [3+2],[2] [3+3][3] and [4+3][4,5] cyclocondensations and, like Danishefsky's diene,[6] as electron-rich 1,4-butadienes in [4+2] cycloadditions.[7] Chan and co-workers were the first to report the $TiCl_4$-mediated formal [3+3] cyclizations of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Chan's diene) and related dienes with 3-silyloxy-2-en-1-ones, 1,1,3,3-tetramethoxypropane and other 1,3-dielectrophiles.[8] We developed the $TiCl_4$-mediated domino '[3+3]-cyclization-homo-Michael' reaction of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-diacetylcyclopropane.[9] This cyclization allows an efficient one-pot synthesis of functionalized salicylates containing a chlorinated side-chain. The strategic placement of the halide group in these products makes them to versatile synthetic intermediates. Herein, we report for the first time the application of this methodology to 1-benzoyl-1-formylcyclopropane and to functionalized 1-acetyl-1-aroyl-cyclopropanes. The cyclizations reported allow a convenient and regioselective synthesis of 6-aryl-5-(chloroethyl)salicylates, which are not readily available by other methods.

2. Results and discussion

1-Benzoyl-1-formylcyclopropane (**4**) was prepared following a known procedure.[10] The cyclopropanation of **1** gave the ester **2**, which was reduced to the alcohol **3**. Oxidation (PCC) of **3** afforded **4**. The last step proved to be problematic in our hands and required some optimization. Cyclopropane **4** is rather unstable and has to be used directly after its preparation. Purification is not possible. Therefore, it was important to optimize the reaction time (TLC control) in order to achieve, on the one hand, a complete conversion of **3** into **4** and to avoid, on the other hand, decomposition (Scheme 1).

The $TiCl_4$-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadiene **5a** with 1-benzoyl-1-formylcyclopropane (**4**) afforded the 4-chloroethyl-3-phenylphenol **6a** in 66% yield (Scheme 2). The phenyl group of **6a** is located on the same site as the ester group. The formation of the opposite regioisomer was not observed. The best yields of **6a** were obtained when **4** (1.0 equiv) was reacted with an excess of **5a** (1.7 equiv) and of $TiCl_4$ (2.0 equiv) in a relatively dilute solution of dichloromethane (c(**4**)=0.02 M). To induce a complete aromatization, hydrochloric acid (10%) was used for the aqueous work-up. The formation of **6a** can be explained by $TiCl_4$-mediated regioselective



Scheme 1. Synthesis of **4**. (i) DMSO, **1**, 1,2-dibromoethane (2 equiv), K_2CO_3 (4.0 equiv), 3 d, 20 °C; (ii) ether, $LiAlH_4$, 0 °C, **2**, 2 h reflux; (iii) PCC, CH_2Cl_2, **3**, 1.5 h, 20 °C, filtration (Celite).

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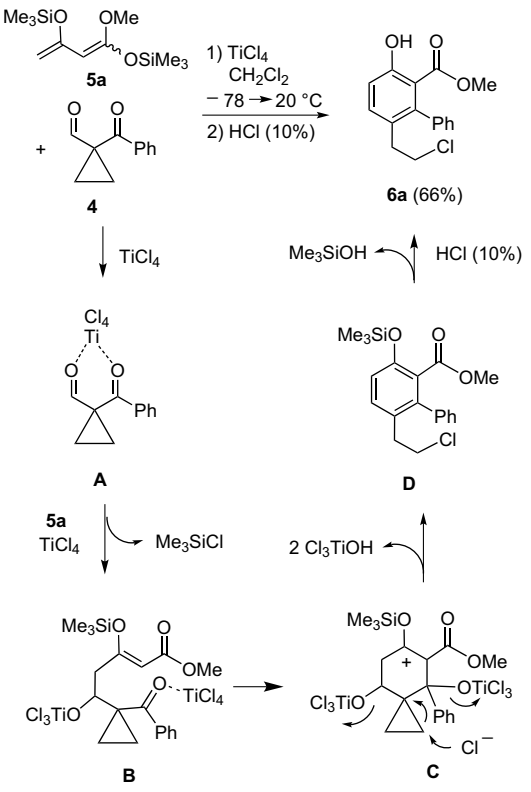
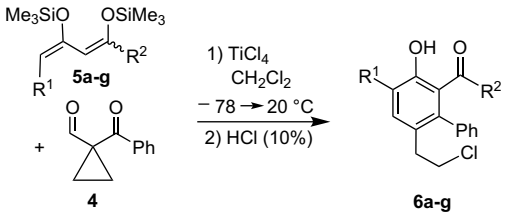
attack of the terminal carbon atom of **5a** onto the aldehyde group (which is more electrophilic than the benzoyl group), cyclization and aromatization (before or during the aqueous work-up).



Scheme 2. Possible mechanism of the formation of **6a**.

The $TiCl_4$-mediated cyclization of **4** with 1,3-bis(silyloxy)-1,3-butadienes **5a**–**g** afforded the 4-chloroethyl-3-phenylphenols **6a**–**g** (Scheme 3, Table 1). Products **6a**–**e** contain an ester group located at carbon atom C-2, while **6f** and **6g** contain an acetyl and a propionyl group, respectively. Phenols **6d**,**e**,**g** contain an additional substituent located at carbon C-6. All products were isolated in moderate to good yields (except for **6e**).



Scheme 3. Synthesis of **6a**–**g**.

Table 1
Synthesis of **6a**–**g**

5, 6	R^1	R^2	% (6)[a]
a	H	OMe	66
b	H	OEt	71
c	H	OCH_2Ph	41
d	Me	OEt	49
e	OMe	OMe	21
f	H	Me	57
g	Me	Et	73

[a] Yields of isolated products.

The structures of all products were established by spectroscopic methods. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[11] In solution and in the solid state an intramolecular hydrogen bond O–H···O is present.

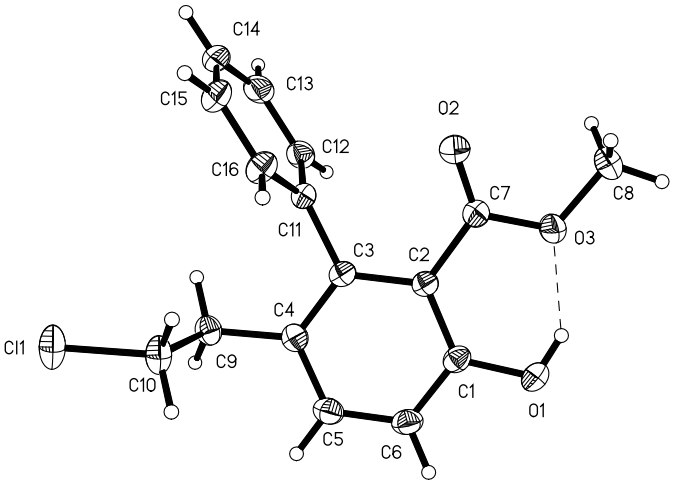
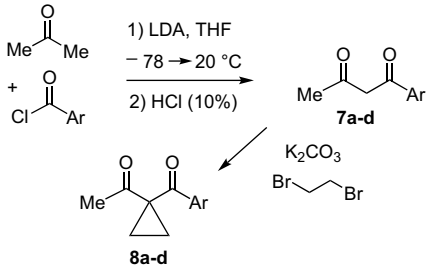
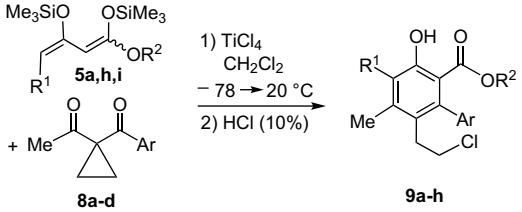


Figure 1. ORTEP plot of **6a** (50% probability level).

The novel 1-acetyl-1-aroyl-cyclopropanes **8a**–**d** were prepared by cyclopropanation of the corresponding 1,3-diketones **7a**–**d** (which are available by LDA-mediated condensation of acetone with the respective aroyl chlorides) (Scheme 4). The $TiCl_4$-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes **5a**,**h**,**i** with **8a**–**d** afforded the 3-aryl-4-chloroethyl-5-methylphenols **9a**–**h** in moderate yields (Scheme 5, Table 2). The cyclizations proved to be possible both for substrates containing electron-poor (**8a**–**d**,**g**) and electron-rich aryl groups (**8e**,**f**). The structures of all products were established by spectroscopic methods.



Scheme 4. Synthesis of **8a**–**d**.



Scheme 5. Synthesis of **9a**–**h**.

The structure of **9a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[11] Similar to **6a**, an intramolecular hydrogen bond O–H···O is present in solution and in the solid state.

Table 2
Synthesis of **9a–h**

5	8	9	R^1	R^2	Ar	% (**9**)[a]
a	**a**	**a**	H	Me	4-FC_6H_4	56
h	**a**	**b**	Me	Me	4-FC_6H_4	59
i	**a**	**c**	Et	Et	4-FC_6H_4	36
a	**b**	**d**	H	Me	2-FC_6H_4	62
a	**c**	**e**	H	Me	3,4,5-$(MeO)_3C_6H_2$	52
h	**c**	**f**	Me	Me	3,4,5-$(MeO)_3C_6H_2$	42
i	**c**	**g**	Et	Et	3,4,5-$(MeO)_3C_6H_2$	40
a	**d**	**h**	H	Me	4-$(O_2N)C_6H_4$	46

[a] Yields of isolated products.

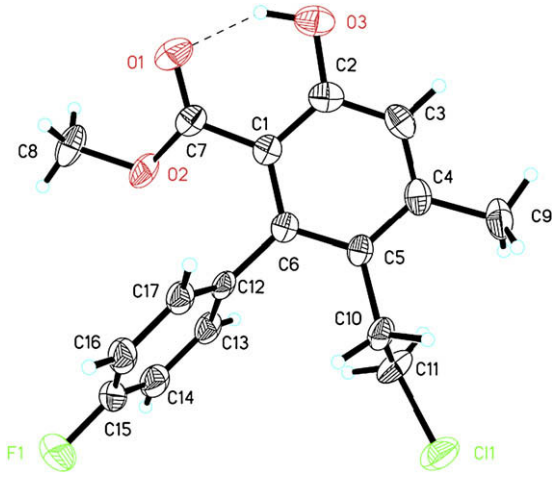


Figure 2. Ortep plot of **9a** (50% probability level).

In conclusion, functionalized 3-aryl-4-(chloroethyl)phenols have been regioselectively prepared by domino '[3+3] cyclization/homo-Michael' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-formyl- and 1-acetyl-1-aroyl-cyclopropanes.

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 ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected. Dienes **5a–i** were prepared according to procedures reported in the literature.[4,8] 1-Benzoyl-1-formylcyclopropane (**4**) was prepared following a known procedure.[10]

3.2. General procedure for the synthesis of 6a–g

To a CH_2Cl_2 solution of 1,3-bis(silyloxy)-1,3-butadiene **5a–g** (1.5–1.7 equiv) and 1-benzoyl-1-(formyl)cyclopropane **4** (1.0 equiv) was dropwise added $TiCl_4$ (2.0 equiv) at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C for 18 h with stirring. To the reaction mixture was added an aqueous solution of HCl (10%). The organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, heptanes/EtOAc) to give the phenols **6**.

3.2.1. 6-(2-Chloroethyl)-3-hydroxy-biphenyl-2-carboxylic acid methyl ester (*6a*)

Starting with **5a** (0.498 g, 1.91 mmol), **4** (0.196 g, 1.125 mmol) and $TiCl_4$ (0.25 mL, 2.25 mmol) in CH_2Cl_2 (50 mL), **6a** was isolated by column chromatography (silica gel, *n*-heptane/EtOAc=50:1) as a yellow solid (0.217 g, 66%), mp=66–70 °C; R_f=0.59 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=2.63 (t, ^3J=7.5 Hz, 2H CH_2), 3.26 (s, 3H, OCH_3), 3.27 (t, ^3J=7.5 Hz, 2H, CH_2), 6.90 (d, ^3J=8.6 Hz, 1H, Ar), 6.96–7.02 (m, 2H, Ar), 7.20–7.31 (m, 4H, Ph/Ar), 10.65 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=36.0, 44.3 (CH_2), 51.8 (OCH_3), 113.0, 128.0, 140.5, 143.5, 160.4 ($C_{Ph,Ar}$), 117.1, 126.9, 136.0 ($CH_{Ph,Ar}$), 127.8, 128.3 (CH_{Ph}), 171.2 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$=3389 (m), 2954 (w), 1724 (s), 1596 (m), 1465 (s), 1443 (s), 1267 (m), 1244 (s), 1180 (s), 1008 (m). MS (EI, 70 eV): *m/z* (%)=290 (M^+, ^{35}Cl, 30), 258 (85), 209 (100), 165 (21), 152 (35). Anal. Calcd for $C_{16}H_{15}ClO_3$ (290.74): C, 66.10; H, 5.20. Found: C, 66.11; H, 5.10.

3.2.2. 6-(2-Chloroethyl)-3-hydroxy-biphenyl-2-carboxylic acid ethyl ester (*6b*)

Starting with **5b** (0.435 g, 1.58 mmol), **4** (0.184 g, 1.06 mmol) and $TiCl_4$ (0.23 mL, 2.11 mmol) in CH_2Cl_2 (50 mL), **6b** was isolated after column chromatography (silica gel, heptanes/EtOAc=30:1) as a yellow solid (0.227 g, 71%), mp=77–79 °C; R_f=0.68 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=0.66 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 2.72 (t, ^3J=7.5 Hz, 2H, CH_2), 3.37 (t, ^3J=7.5 Hz, 2H, CH_2), 3.88 (q, ^3J=7.1 Hz, 2H, CH_2CH_3), 7.00 (d, ^3J=8.7 Hz, 1H, Ar), 7.05–7.14 (m, 2H, Ph), 7.31–7.40 (m, 3H, Ph/Ar), 10.97 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=12.9 (OCH_2CH_3), 36.0, 44.3 (CH_2), 60.9 (OCH_2CH_3), 113.0, 127.9, 140.8, 143.5, 160.6 ($C_{Ph/Ar}$), 117.1, 126.8, 135.9 ($CH_{Ph/Ar}$), 127.8, 128.4 (CH_{Ph}), 170.9 ($COOCH_2CH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$=2973 (w), 2931 (w), 1657 (s), 1589 (m), 1463 (s), 1396 (m), 1320 (s), 1202 (s), 918 (w), 700 (s). MS (EI, 70 eV): *m/z* (%)=304 (M^+, ^{35}Cl, 32), 258 (90), 209 (100), 165 (22), 152 (31). Anal. Calcd for $C_{17}H_{17}ClO_3$ (304.77): C, 67.00; H, 5.62. Found: C, 66.63; H, 5.51.

3.2.3. 6-(2-Chloroethyl)-3-hydroxy-biphenyl-2-carboxylic acid benzyl ester (*6c*)

Starting with **5c** (0.675 g, 2.01 mmol), **4** (0.233 g, 1.34 mmol) and $TiCl_4$ (0.29 mL, 2.68 mmol) in CH_2Cl_2 (50 mL), **6c** was isolated after column chromatography (silica gel, heptanes/EtOAc=30:1) as a yellow solid (0.194 g, 41%), mp=76–78 °C; R_f=0.68 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=2.95 (t, ^3J=7.5 Hz, 2H, CH_2), 3.60 (t, ^3J=7.5 Hz, 2H, CH_2), 5.13 (s, 2H, OCH_2Ph), 7.11–7.18 (m, 2H, Ph), 7.23–7.34 (m, 3H, Ph/Ar), 7.43–7.55 (m, 6H, Ph), 7.62 (d, ^3J=8.6 Hz, 1H, Ar), 11.15 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=36.0, 44.3 (CH_2), 67.3 (OCH_2Ph), 112.8, 128.1, 134.3, 140.3, 143.5, 160.7 ($C_{Ph/Ar}$), 117.2, 126.9, 128.3, 136.1 ($CH_{Ph/Ar}$), 127.7, 128.2, 128.3, 128.8 (CH_{Ph}), 170.7 ($COOCH_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$=2971 (w), 1653 (s), 1594 (m), 1453 (s), 1384 (s), 1222 (s), 1148 (m), 1120 (m), 1093 (m), 987 (w). MS (EI, 70 eV): *m/z* (%)=366 (M^+, ^{35}Cl, 25), 260 (14), 258 (42), 209 (13), 91 (100). HRMS (EI): calcd for $C_{22}H_{19}ClO_3$ (M^+) 366.10172, found 366.10153.

3.2.4. 6-(2-Chloroethyl)-3-hydroxy-4-methylbiphenyl-2-carboxylic acid methyl ester (*6d*)

Starting with **5d** (0.487 g, 1.77 mmol), **4** (0.206 g, 1.18 mmol) and $TiCl_4$ (0.26 mL, 2.37 mmol) in CH_2Cl_2 (50 mL), **6d** was isolated by column chromatography (silica gel, heptanes/EtOAc=20:1) as a yellow solid (0.263 g, 73%), mp=49–51 °C; R_f=0.72 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=2.30 (br s, 3H, CCH_3), 2.72 (t, ^3J=7.6 Hz, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.37 (t, ^3J=7.6 Hz, 2H, CH_2), 7.04–7.11 (m, 2H, Ph), 7.24 (s, 1H, Ar), 7.29–7.40 (m, 3H, Ph), 10.99 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=15.9 (CCH_3), 36.0, 44.3 (CH_2), 51.7 (OCH_3), 112.3, 126.1, 127.1, 140.8, 140.9, 158.7 ($C_{Ph/Ar}$), 126.7, 136.8 ($CH_{Ph/Ar}$), 127.7, 128.5 (CH_{Ph}), 171.7 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$=2997 (w), 1658 (s), 1599 (w), 1493 (w), 1431 (s), 1414 (m), 1323 (s), 1283 (s), 1132 (s), 927 (w). MS (EI, 70 eV): *m/z* (%)=304

(M^+, ^{35}Cl, 32), 272 (100), 223 (83), 209 (35), 165 (32). HRMS (EI): calcd for $C_{17}H_{17}ClO_3$ (M^+) 304.08607, found 304.08620.

*3.2.5. 6-(2-Chloroethyl)-3-hydroxy-4-methoxy-biphenyl-2-carboxylic acid methyl ester (**6e**)*

Starting with **5e** (0.567 g, 1.95 mmol), **4** (0.200 g, 1.15 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol) in CH_2Cl_2 (50 mL), **6e** was isolated by column chromatography (silica gel, heptanes/EtOAc=7:1) as a yellow solid (0.076 g, 21%), mp=88–91 °C; R_f=0.41 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=2.77 (t, ^3J=7.5 Hz, 2H, CH_2), 3.38 (s, 3H, OCH_3), 3.39 (t, ^3J=7.5 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 6.94 (s, 1H, Ar), 7.07–7.12 (m, 2H, Ph), 7.29–7.39 (m, 3H, Ph), 10.05 (s, 1H, OH). ^{13}C NMR (250 MHz, $CDCl_3$): δ=36.4, 44.3 (CH_2), 51.9, 56.2 (OCH_3), 114.8, 127.4, 134.3, 139.9, 147.4, 149.1 ($C_{Ph,Ar}$), 116.4, 126.8 ($CH_{Ph,Ar}$), 127.8, 129.0 (CH_{Ph}), 170.6 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$=2953 (w), 2839 (w), 1660 (s), 1456 (m), 1436 (s), 1354 (s), 1305 (m), 1215 (s), 1150 (m), 1068 (s). MS (EI, 70 eV): *m*/*z* (%)=320 (M^+, ^{35}Cl, 31), 288 (100), 239 (18), 225 (59), 209 (15). Anal. Calcd for $C_{17}H_{17}ClO_4$ (320.77): C, 63.65; H, 5.34. Found: C, 63.65; H, 5.41.

*3.2.6. 1-[6-(2-Chloroethyl)-3-hydroxy-biphenyl-2-yl]-ethanone (**6f**)*

Starting with **5f** (0.396 g, 1.62 mmol), **4** (0.188 g, 1.08 mmol) and $TiCl_4$ (0.24 mL, 2.16 mmol) in CH_2Cl_2 (50 mL), **6f** was isolated by column chromatography (silica gel, heptanes/EtOAc=50:1) as a yellow solid (0.170 g, 57%), mp=38–40 °C; R_f=0.65 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=1.68 (s, 3H, CCH_3), 2.81 (t, ^3J=7.5 Hz, 2H, CH_2), 3.38 (t, ^3J=7.5 Hz, 2H, CH_2), 7.00 (d, ^3J=8.6 Hz, 1H, Ar), 7.21–2.27 (m, 2H, Ph), 7.40 (d, ^3J=8.6 Hz, 1H, Ar), 7.42–7.48 (m, 3H, Ph), 11.80 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=32.0 (CH_3), 35.9, 44.1 (CH_2), 122.0, 127.4, 139.7, 143.0, 160.4 ($C_{Ph/Ar}$), 117.9, 128.4, 136.1 ($CH_{Ph/Ar}$), 128.8, 129.8 (CH_{Ph}), 207.7 (*C*OCH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$=2949 (w), 1616 (s), 1585 (m), 1459 (m), 1441 (m), 1327 (m), 1216 (s), 1145 (m), 1029 (m), 910 (w). MS (EI, 70 eV): *m*/*z* (%)=274 (M^+, ^{35}Cl, 100), 259 (42), 225 (76), 223 (52), 207 (64). HRMS (EI): calcd for $C_{16}H_{15}ClO_2$ (M^+) 274.07551, found 274.07521.

*3.2.7. 1-[6-(2-Chloroethyl)-3-hydroxy-4-methylbiphenyl-2-yl]-propan-1-one (**6g**)*

Starting with **5g** (0.451 g, 1.65 mmol), **4** (0.192 g, 1.10 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol) in CH_2Cl_2 (50 mL), **6g** was isolated by column chromatography (silica gel, heptanes/EtOAc=50:1) as a yellow oil (0.164 g, 49%); R_f=0.72 (heptanes/EtOAc=1:1). ^1H NMR (250 MHz, $CDCl_3$): δ=0.77 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 1.85 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 2.29 (s, 3H, CCH_3), 2.81 (t, ^3J=7.6 Hz, 2H, CH_2), 3.36 (t, ^3J=7.6 Hz, 2H, CH_2), 7.17–7.27 (m, 3H, Ph/Ar), 7.35–7.48 (m, 3H, Ph/Ar), 11.45 (s, 1H, OH). ^{13}C NMR (250 MHz, $CDCl_3$): δ=9.0 (CH_2CH_3), 16.0 (CH_3), 35.9, 44.2 (CH_2), 36.9 (CH_2CH_3), 122.0, 126.6, 126.7, 139.7, 139.9, 157.6 ($C_{Ph/Ar}$), 128.1, 136.3 ($CH_{Ph/Ar}$), 128.7, 130.0 (CH_{Ph}), 211.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$=2974 (w), 2937 (w), 1622 (s), 1413 (m), 1348 (m), 1235 (s), 1153 (w), 1107 (s), 1050 (m), 704 (s). MS (EI, 70 eV): *m*/*z* (%)=302 (M^+, ^{35}Cl, 54), 273 (100), 237 (69), 209 (15), 152 (15). Anal. Calcd for $C_{18}H_{19}ClO_2$ (302.80): C, 71.40; H, 6.32. Found: C, 71.13; H, 6.45.

3.3. Procedure for the synthesis of 7a–d

The novel products **7a–d** were prepared according to a previously reported procedure.[12] The synthesis of **7c** has been previously reported.[12]

*3.3.1. 4-(4-Fluorophenyl)-4-hydroxy-3-buten-2-one (**7a**)*

Starting with LDA (1.5 equiv) in THF (62 mL), acetone (3.7 mL, 50.0 mmol), and 4-fluorobenzoyl chloride (9.51 g, 60.0 mmol), **7a** was isolated as a yellow solid (4.64 g, 43%), mp=48–49 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=2.11 (s, 3H, CH_3), 6.04 (s, 1H, CH), 7.04 (m, 2H, CH), 7.81 (m, 2H, CH), 16.07 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.4 (CH_3), 95.3 (CH), 114 (d, $^2J_{F,C}$=21.8 Hz, $2CH_{Ar}$), 128.4 (d, $^3J_{F,C}$=8.9 Hz, $2CH_{Ar}$), 130.3 (d, $^4J_{F,C}$=2.9 Hz, C), 164.3 (d, ^1J=252.0 Hz, CF), 181.9 (COH), 191.8 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$=1603 (s), 1507 (s), 1297 (m), 1246 (s), 1159 (m), 1095 (m), 1014 (w), 849 (s), 786 (s), 506 (w). MS (EI, 70 eV): *m*/*z* (%)=180 ($[M]^+$, 64), 165 (66), 138 (6), 123 (100), 109 (6), 95 (48), 85 (11), 75 (20), 69 (50), 50 (5), 43 (23). HRMS (EI): Calcd for $C_{10}H_9FO_2$ ($[M]^+$): 180.05811; found: 180.05765.

*3.3.2. 4-(2-Fluorophenyl)-4-hydroxybut-3-en-2-one (**7b**)*

Starting with LDA (1.5 equiv) in THF (62 mL), acetone (3.7 mL, 50.0 mmol), and 2-fluorobenzoyl chloride (9.51 g, 60.0 mmol), **7b** was isolated as a yellowish oil (4.53 g, 42%). ^1H NMR (250 MHz, $CDCl_3$): δ=2.20 (s, 3H, CH_3), 6.28 (s, 1H, CH), 7.07–7.12 (m, 1H, CH_{Ar}), 7.20–7.24 (m, 1H, CH_{Ar}), 7.42–7.46 (m, 1H, CH_{Ar}), 7.93 (ddd, ^3J=7.8 Hz, ^3J=7.8 Hz, ^4J=1.8 Hz, 1H, CH_{Ar}), 16.08 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.0 (CH_3), 101.3 (CH), 116.3 (d, $^2J_{F,C}$=23.1 Hz, CH_{Ar}), 123.1 (d, ^2J=23.4 Hz, CF), 124.4 (d, $^4J_{F,C}$=3.4 Hz, CH_{Ar}), 130.0 (d, $^3J_{F,C}$=9.8 Hz, CH_{Ar}), 133.3 (d, $^3J_{F,C}$=9.2 Hz, CH_{Ar}), 161.0 (d, $^1J_{F,C}$=255.0 Hz, CF), 178.7 (*C*OH), 194.9 (CO).

*3.3.3. 4-Hydroxy-4-(4-nitrophenyl)but-3-en-2-one (**7d**)*

Starting with LDA (1.5 equiv) in THF (62 mL), acetone (3.7 mL, 50.0 mmol), and 4-nitrobenzoyl chloride (11.13 g, 60.0 mmol), **3d** was isolated as a yellow solid (4.405 g, 43%), mp=90–92 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=2.11 (s, 3H, CH_3), 5.74 (s, 1H, CH), 7.95 (d, ^3J=8.7 Hz, 2H, CH_{Ar}), 8.21 (d, ^3J=9.0 Hz, 2H, CH_{Ar}), 15.80 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.0 (CH_3), 98.5 (CH), 124.3 ($2CH_{Ar}$), 128.6 ($2CH_{Ar}$), 140.9, 149.9 (C_{Ar}), 179.8 (COH), 196.6 (C=O). GC–MS (EI 70 eV): *m*/*z* (%)=207 ($[M]^+$, 38), 192 (100), 165 (8), 160 (19), 150 (36), 120 (8), 104 (18), 89 (9), 85 (27), 76 (18), 63 (7), 50 (12), 43 (45). HRMS (EI): Calcd for $C_{10}H_9NO_2$: 207.05261; found: 207.05232.

3.4. General procedure for the synthesis of 8a–d

To a stirred DMSO solution (1 mL/1.0 mmol of **7**) of **7** (10.0 mmol) was added potassium carbonate (40.0 mmol) at room temperature. After the solution was stirred for 30 min, 1,2-dibromoethane (20.0 mmol) was added at 20 °C. After the solution was stirred for 12 h, an excess amount of water was added to remove dimethylsulfoxide and the mixture was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc=30:1→20:1) to give **8a–d**.

*3.4.1. 1-(1-(4-Fluorobenzoyl)cyclopropyl)ethanone (**8a**)*

Starting with DMSO (12 mL), **7a** (2.170 g, 12.0 mmol), K_2CO_3 (6.63 g, 48.0 mmol) and 1,2-dibromoethane (4.524 g, 24.08 mmol), **8a** was isolated as a light yellow oil (1.44 g, 58%). ^1H NMR (250 MHz, $CDCl_3$): δ=1.37 (t, ^3J=6.4 Hz, 2H, CH_2), 1.46 (t, ^3J=6.4 Hz, 2H, CH_2), 1.94 (s, 3H, CH_3), 6.99–7.06 (m, 2H, CH_{Ar}), 7.80–7.86 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.9 (2×CH_2), 27.9 (CH_3), 41.7 (*C*OC*C*O), 116.1 (d, $^2J_{F,C}$=21.7 Hz, $2CH_{Ar}$), 131.4 (d, $^3J_{F,C}$=9.4 Hz, $2CH_{Ar}$), 133.0 (d, $^4J_{F,C}$=2.9 Hz, C_{Ar}), 165.8 (d, $^1J_{F,C}$=256.0 Hz, CF), 194.6, 203.6 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$=3076 (w), 2952 (w), 2923 (w), 2853 (w), 1671 (s), 1596 (s), 1504 (m), 1409 (w), 1359 (m), 1313 (m), 1295 (m), 1227 (m), 1203 (m), 1154 (m), 1134 (m) 1074 (w), 1036 (w), 1003 (m), 951 (w), 848 (m), 781 (w), 688 (w), 625 (w), 592 (m), 595 (w). MS (EI, 70 eV): *m*/*z* (%)=206 ($[M]^+$, 11), 205 (20), 191 (13), 163 (14), 123 (100), 95 (37), 75 (13), 43 (15). HRMS (EI): Calcd for $C_{12}H_{11}FO_2$ ($[M]^+$): 206.07376; found: 206.074435.

*3.4.2. 1-(1-(2-Fluorobenzoyl)cyclopropyl)ethanone (**8b**)*

Starting with DMSO (12 mL), **7b** (2.17 g, 12.0 mmol), K_2CO_3 (6.63 g, 48.0 mmol) and 1,2-dibromoethane (4.524 g, 24.1 mmol), **8b** was isolated as a light yellow oil (1.46 g, 59%). ^1H NMR (250 MHz,

$CDCl_3$): δ=1.47–1.50 (m, 4H, 2×CH_2), 1.95 (s, 3H, CH_3), 6.94–7.02 (m, 1H, CH_{Ar}), 7.09–7.16 (m, 1H, CH_{Ar}), 7.36–7.45 (m, 1H, CH_{Ar}), 7.69 (ddd, ^3J=7.6 Hz, ^3J=7.6 Hz, ^4J=1.8 Hz, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.8 (2×CH_2), 27.0 (CH_3), 44.1 (*C*OC*C*O), 116.4 (d, $^2J_{F,C}$=22.9 Hz, CH_{Ar}), 124.6 (d, $^4J_{F,C}$=3.2 Hz, CH_{Ar}), 125.6 (d, $^2J_{F,C}$=12.4 Hz, CF), 130.7 (d, $^3J_{F,C}$=8.4 Hz, CH_{Ar}), 134.5 (d, $^3J_{F,C}$=8.9 Hz, CH_{Ar}), 161.0 (d, $^1J_{F,C}$=254.0 Hz, CF), 194.1, 203.4 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$=3083 (w), 3013 (w), 2927 (w), 1673 (s), 1608 (s), 1578 (w), 1480 (m), 1452 (m), 1366 (m), 1316 (m), 1300 (m), 1265 (w), 1217 (m), 1199 (m), 1154 (w), 1136 (w), 1103 (m), 1041 (w), 1003 (m), 951 (w), 834 (w), 771 (m), 655 (w), 598 (w), 541 (m). MS (EI, 70 eV): *m*/*z* (%)=206 ([M]$^+$, 8), 205 (15), 191 (17), 187 (17), 163 (10), 123 (100), 95 (28), 75 (13), 43 (19). HRMS (EI): Calcd for $C_{12}H_{11}FO_2$ ([M]$^+$): 206.07376; found: 206.073396.

*3.4.3. 1-(1-(3,4,5-Trimethoxybenzoyl)cyclopropyl)ethanone (**8c**)*

Starting with DMSO (8.5 mL), **7c** (2.23 g, 8.9 mmol), K_2CO_3 (4.89 g, 35.4 mmol) and 1,2-dibromoethane (3.325 g, 17.7 mmol), **8c** was isolated as a light yellowish solid (1.848 g, 75%), mp=102–103 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.41 (t, ^3J=6.2 Hz, 2H, CH_2), 1.49 (t, ^3J=6.0 Hz, 2H, CH_2), 2.03 (s, 3H, CH_3), 3.81 (s, 6H, 2×OCH_3), 3.85 (s, 3H, OCH_3), 7.11 (s, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.7 (2×CH_2), 29.2 (CH_3), 41.7 (*C*OC*C*O), 56.2 (2×OCH_3), 60.9 (OCH_3), 106.2 (2×CH_{Ar}), 131.1, 142.9, 153.2, 153.2 (C_{Ar}), 195.0, 203.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=3008 (w), 2962 (w), 2943 (w), 2840 (w), 1670 (w), 1583 (m), 1501 (w), 1463 (w), 1449 (w), 1413 (m), 1368 (w), 1329 (m), 1237 (m), 1161 (m), 1120 (m), 1064 (m), 996 (m), 939 (w), 860 (w), 775 (w), 729 (m), 595 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=278 ([M$^+$], 75), 196 (11), 195 (100), 43 (11). HRMS (EI): Calcd for $C_{15}H_{18}O_5$ [M$^+$]: 278.11538; found: 278.11567.

*3.4.4. 1-(1-(4-Nitrobenzoyl)cyclopropyl)ethanone (**8d**)*

Starting with DMSO (5 mL), **7d** (1.00 g, 4.8 mmol), K_2CO_3 (2.66 g, 19.3 mmol) and 1,2-dibromoethane (1.81 g, 9.6 mmol), **8d** was isolated as a yellowish oil (0.506 g, 45%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.47 (t, ^3J=6.0 Hz, 2H, CH_2), 1.55 (t, ^3J=6.1 Hz, 2H, CH_2), 1.93 (s, 3H, CH_3), 7.91 (m, 2H, CH_{Ar}), 8.17 (m, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.9 (2×CH_2), 28.0 (CH_3), 42.1 (*C*OC*C*O), 124.1 (2×CH_{Ar}), 1129.6 (2×CH_{Ar}), 141.3, 150.3 (C_{Ar}), 195.0, 203.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=3108 (w), 3079 (w), 3003 (w), 2925 (w), 2851 (w), 1679 (m), 1586 (m), 1523 (s), 1464 (w), 1347 (m), 1291 (m), 1200 (w), 1126 (m), 1004 (m), 922 (w), 853 (m), 790 (w), 709 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=233 ([M$^+$], 8), 232 (16), 218 (34), 216 (30), 186 (12), 174 (12), 150 (100), 144 (15), 120 (25), 115 (9), 92 (17), 76 (30), 75 (11), 50 (13), 43 (65). HRMS (EI): Calcd for $C_{12}H_{11}O_4N$ [M$^+$]: 233.06826; found: 233.068446.

3.5. General procedure for the synthesis of phenols 9a–h

To a dichloromethane solution (75 mL/mmol) of 1,1-diacylcyclopropanes **8a–d** (1.0 equiv) and 1,3-bis(silyl enol ethers) **5** (1.1 equiv) was added $TiCl_4$ (2.0 equiv) at −78 °C. The solution was allowed to warm to ambient temperature within 10 h. To the solution was added a diluted aqueous solution of HCl. The organic and the aqueous layers were separated and the latter was extracted with dichloromethane (three times). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc/heptanes).

*3.5.1. Methyl 6-(2-chloroethyl)-4′-fluoro-3-hydroxy-5-methylbiphenyl-2-carboxylate (**9a**)*

Starting with **8a** (0.206 g, 1.0 mmol), **5a** (0.286 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9a** was isolated as a colourless solid (0.181 g, 56%), mp=84–86 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.27 (s, 3H, CH_3), 2.63 (t, ^3J=7.8 Hz, 2H, *C*$H_2$$CH_2$Cl), 3.13 (t, ^3J=6.3 Hz, 2H, CH_2*C*H_2Cl), 3.26 (s, 3H, OCH_3), 6.77 (s, 1H, CH_{Ar}), 6.93 (m, 2H, CH_{Fph}), 6.97 (m, 2H, CH_{Fph}), 10.74 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.7 (CH_3), 33.1 (*C*$H_2$$CH_2$Cl), 42.3 ($CH_2$*C*$H_2$Cl), 51.8 ($OCH_3$), 111.0 (*C*COOMe), 114.7 (d, ^2J=21.3 Hz, CH_{Fph}), 114.9 (d, ^2J=21.4 Hz, CH_{Fph}), 119.2 (CH_{Ar}), 127.1 (C_{Ar}), 129.8 (d, $^3J_{C,F}$=7.5 Hz, CH_{Fph}), 129.9 (d, $^3J_{C,F}$=7.7 Hz, CH_{Fph}), 136.9 (d, $^4J_{C,F}$=3.8 Hz, CF_{Fph}), 142.9 (C_{Ar}), 144.7 (*C*$CH_2$$CH_2$Cl), 160.2 (*C*OH), 161.8 (d, $^1J_{C,F}$=245 Hz, CF_{Fph}), 171.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$=3044 (w), 3027 (w), 2953 (w), 2923 (w), 2852 (w), 1660 (m), 1599 (w), 1573 (w), 1506 (m), 1460 (w), 1437 (m), 1401 (w), 1336 (m), 1273 (m), 1235 (m), 1218 (s), 1206 (s), 1197 (s), 1146 (m), 1120 (w), 1071 (m), 1013 (w), 954 (w), 869 (w), 833 (m), 794 (m), 752 (w), 708 (m), 650 (w), 629 (m), 588 (w), 570 (m), 529 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=324 ([M$^+$], ^{37}Cl, 10), 322 ([M$^+$], ^{35}Cl, 27), 292 (^{37}Cl, 22), 290 (^{35}Cl, 64), 242 (18), 241 (100), 183 (19), 170 (11), 165 (12). HRMS (EI): Calcd for $C_{17}H_{16}ClO_3F$ ([M]$^+$, ^{35}Cl): 322.07665; found: 322.077009.

*3.5.2. Methyl 6-(2-chloroethyl)-4′-fluoro-3-hydroxy-4,5-dimethylbiphenyl-2-carboxylate (**9b**)*

Starting with **8a** (0.206 g, 1.0 mmol), **5h** (0.301 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9b** was isolated as a yellowish viscous oil (0.196 g, 59%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.71 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.68 (t, ^3J=9 Hz, 2H, *C*$H_2$$CH_2$Cl), 3.17 (t, ^3J=8.25 Hz, 2*H*, CH_2*C*H_2Cl), 3.86 (s, 3H, OCH_3), 6.91 (m, 2H, CH_{Fph}), 6.99 (m, 2H, CH_{Fph}), 10.85 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (CH_3), 18.6 (CH_3), 34.1 (*C*$H_2$$CH_2$Cl), 42.5 ($CH_2$*C*$H_2$Cl), 52.3 ($OCH_3$), 112.9 (*C*COOMe), 114.3 (d, ^2J=21.3 Hz, CH_{Fph}), 115.7 (d, ^2J=21.3 Hz, CH_{Fph}), 123.4, 126.4 (2×C_{Ar}), 129.6 (d, ^3J=8.1 Hz, CH_{Fph}), 135.9 (C_{Ar}), 136.1 (d, ^4J=4.4 Hz, CF_{Fph}), 147.4 (*C*$CH_2$$CH_2$Cl), 158.4 (*C*OH), 162.0 (d, $^1J_{C,F}$=247 Hz, CH_{Fph}), 163 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=1737 (w), 1661 (m), 1605 (w), 1562 (w), 1511 (m), 1439 (w), 1399 (w), 1382 (w), 1319 (w), 1253 (w), 1242 (m), 1220 (m), 1156 (w), 1093 (w), 1015 (w), 911 (w), 837 (w), 739 (w), 581 (w), 531 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=338 ([M$^+$], ^{37}Cl, 8), 336 ([M$^+$], ^{35}Cl, 38), 306 (33), 305 (21), 255 (100), 170 (7), 133 (8), 98 (5). HRMS (EI): Calcd for $C_{18}H_{18}ClO_3F$ ([M]$^+$, ^{35}Cl): 336.09276; found: 336.092553.

*3.5.3. Ethyl 6-(2-chloroethyl)-4-ethyl-4′-fluoro-3-hydroxy-5-methylbiphenyl-2-carboxylate (**9c**)*

Starting with **8a** (0.206 g, 1.0 mmol), **5i** (0.332 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9c** was isolated as a yellowish oil (0.131 g, 36%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.70 (t, ^3J=6.9 Hz, 3H, CH_2*C*H_3), 1.37 (t, ^3J=6.9 Hz, 3H, OCH_2*C*H_3), 2.25 (s, 3H, CH_3), 2.64 (q, ^3J=7.1 Hz, 2H, *C*$H_2$$CH_3$), 3.19 (t, ^3J=8.4 Hz, 2H, *C*$H_2$$CH_2$Cl), 3.91 (t, ^3J=6.9 Hz, 2H, CH_2*C*H_2Cl), 4.39 (q, ^3J=6.6 Hz, 2H, *O*C$H_2$$CH_3$), 6.92 (m, 2H, CH_{Fph}), 6.98 (m, 2H, CH_{Fph}), 10.87 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (OCH_2*C*H_3), 14.2 (CH_2*C*H_3), 20.6 (*C*$H_2$$CH_3$), 20.7 ($CH_3$), 33.1 (*C*$H_2$$CH_2$Cl), 42.3 ($CH_2$*C*$H_2$Cl), 62.0 (O*C*$H_2$$CH_3$), 111.0 (*C*COO$C_2H_5$), 114.7 (d, ^2J=21.3 Hz, CH_{Fph}), 114.8 (d, ^2J=21.4 Hz, CH_{Fph}), 115.7 (d, ^2J=21.5 Hz, CH_{Fph}), 123.5, 126.5 (2×C_{Ar}), 129.6 (d, ^3J=8.0 Hz, CH_{Fph}), 129.9 (d, ^3J=8.1 Hz, CH_{Fph}), 143.0 (C_{Ar}), 144.7 (*C*$CH_2$$CH_2$Cl), 160.5 (*C*OH), 161.9 (d, ^1J=247 Hz, CF_{Fph}), 171.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=3040 (w), 3010 (w), 2952 (w), 2853 (w), 1735 (w), 1660 (m), 1603 (w), 1510 (m), 1440 (w), 1401 (w), 1335 (m), 1270 (m), 1233 (m), 1220 (s), 1200 (s), 1120 (w), 1070 (m), 957 (w), 837 (w), 740 (w), 581 (w), 530 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=366 ([M$^+$], ^{37}Cl, 38), 334 (^{37}Cl, 20), 332 (^{35}Cl, 55), 283 (100), 225 (17), 212 (10), 207 (15), 170 (24), 165 (15), 163 (12). HRMS (EI): Calcd for $C_{20}H_{22}ClO_3F$ ([M]$^+$, ^{35}Cl): 364.1238; found: 364.12372.

*3.5.4. Methyl 6-(2-chloroethyl)-2′-fluoro-3-hydroxy-5-methylbiphenyl-2-carboxylate (**9d**)*

Starting with **8b** (0.206 g, 1.0 mmol), **5a** (0.286 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9d** was isolated as a highly viscous oil (0.198 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.33 (s, 3H, CH_3), 2.70 (t, ^3J=7.0 Hz, 2H, *C*$H_2$$CH_2$Cl), 3.21 (t, ^3J=7.2 Hz, 2H, CH_2*C*H_2Cl), 3.31 (s, 3H, OCH_3), 6.84 (s, 1H, CH_{Ar}), 6.95 (d, ^3J=7.2 Hz, 1*H*, CH_{Fph}), 7.09 (m, 2H, CH_{Fph}), 7.27 (d, ^3J=7.7 Hz, 1H,

CH_{Fph}), 10.92 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.6 (CH_3), 33.5 (CH_2CH_2Cl), 42.0 (CH_2CH_2Cl), 51.9 (OCH_3), 110.9 (*C*COOMe), 115.0 (d, ^2J=21.0 Hz, CH_{Fph}), 119.7 (*C*H_{Ar}), 123.6 (d, ^4J=4.0 Hz, CH_{Fph}), 127.8 (C_{Ar}), 128.5 (d, ^2J=18.5 Hz, C_{Fph}), 129.2 (d, ^3J=7.4 Hz, CH_{Fph}), 130.4 (d, ^3J=6.1 Hz, CH_{Fph}), 137.3 (C_{Ar}), 144.8 (*C*CH_2CH_2Cl), 159.2 (d, ^1J=242 Hz, CF), 160.6 (*C*OH), 170.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=2953 (w), 2955 (w), 2854 (w), 1737 (w), 1665 (s), 1576 (w), 1494 (w), 1442 (m), 1353 (m), 1274 (w), 1239 (m), 1149 (w), 1071 (w), 908 (w), 799 (w), 757 (m), 733 (s), 535 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 416 (M^+, ^{37}Cl, 24), 414 (M^+, ^{35}Cl, 74), 383 (5), 333 (100), 318 (9) 289 (15), 197 (6), 163 (13), 57 (21). HRMS (EI): calcd for $C_{23}H_{20}O_2ClFS$ [M^+, ^{35}Cl]: 414.08518, found 141.08511.

3.5.5. Methyl 2-(2-chloroethyl)-5-hydroxy-3′,4′,5′-trimethoxy-3-methylbiphenyl-4-carboxylate (**9e**)

Starting with **8c** (0.278 g, 1.0 mmol), **5a** (0.286 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9e** was isolated as a yellowish oil (0.205 g, 52%). ^1H NMR (250 MHz, $CDCl_3$): δ=2.25 (s, 3H, CH_3), 2.68 (t, ^3J=8.5 Hz, 2H, CH_2CH_2Cl), 3.22 (t, ^3J=6.8 Hz, 2H, CH_2CH_2Cl), 3.68 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.16 (s, 2H, CH_{Ar}), 6.72 (s, 1H, CH_{Clph}), 10.65 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.7 (CH_3), 33.2 (CH_2CH_2Cl), 43.3 (CH_2CH_2Cl), 52.0 (OMe_{Clph}), 56.3 (2×OMe_{Ar}), 61.0 (OCH_{3Ar}), 106.0 (2×CH_{Ar}), 112.1 (*C*COOMe), 118.9 (CH_{Clph}), 126.9 (*C*CH_2CH_2Cl), 135.7 (C_{Ar}), 136.0 (*C*CH_3), 137.1 (*C*OMe), 148.4 (C_{Clph}), 153.2 (2×*C*OCH_3), 160.0 (*C*OH), 171.2 (CO). IR (Kapillar, cm^{-1}): $\tilde{\nu}$=2998 (w), 2955 (w), 2922 (m), 2850 (w), 1733 (w), 1657 (m), 1585 (m), 1435 (m), 1285 (m), 1236 (s), 1206 (s), 1122 (s), 1009 (m), 727 (w), 545 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=496 ([M^+], ^{37}Cl, 29), 394 ([M^+], ^{35}Cl, 100), 364 (^{37}Cl, 18), 363 (^{37}Cl, 15), 362 (^{35}Cl, 24), 361 (^{35}Cl, 11), 328 (12), 327 (75), 313 (54), 312 (12), 295 (13), 282 (37), 267 (11) 224 (10), 163 (14), 156 (37), 142 (17), 134 (13), 127 (15), 83 (10). HRMS (EI): Calcd for $C_{20}H_{23}ClO_6$ ([M]$^+$, ^{35}Cl): 394.11777.13342; found: 394.118590.

3.5.6. Methyl 2-(2-chloroethyl)-5-hydroxy-3′,4′,5′-trimethoxy-3,6-dimethylbiphenyl-4-carboxylate (**9f**)

Starting with **8c** (0.278 g, 1.0 mmol), **5h** (0301 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9f** was isolated as a yellowish oil (0.171 g, 42%). ^1H NMR (250 MHz, $CDCl_3$): δ=1.78 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.75 (t, ^2J=8.7 Hz, 2*H*, CH_2CH_2Cl), 3.27 (t, ^2J=6.8 Hz, 2*H*, CH_2CH_2Cl), 3.71 (s, 6H, OCH_3), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.17 (s, 2H, CH_{Ar}), 10.86 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (CH_3), 18.7 (CH_3), 34.2 (CH_2CH_2Cl), 43.1 (CH_2CH_2Cl), 52.3 (OMe_{Clph}), 56.2 (2×OMe_{Ar}), 61.0 (OCH_{3Ar}), 105.4 (2×CH_{Ar}), 112.7 (*C*COOMe), 123.2 (*C*CH_3), 126.4 (*C*CH_2CH_2Cl), 135.8 (C_{Ar}), 135.9 (*C*CH_3), 137.0 (*C*OMe), 148.4 (C_{Clph}), 153.3 (2×*C*OCH_3), 158.4 (*C*OH_3), 172.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=2997 (w), 2952 (w), 2923 (m), 2850 (w), 1730 (w), 1656 (m), 1580 (m), 1438 (m), 1284 (m), 1234 (s), 1206 (s), 1123 (s), 1007 (m), 724 (w), 549 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=410 ([M^+], ^{37}Cl, 29), 408 ([M^+], ^{35}Cl, 100), 378 (^{37}Cl, 25), 376 (^{35}Cl, 80), 348 (26), 341 (14), 327 (20), 309 (12), 296 (13), 281 (15), 188 (11), 148 (14), 137 (13), 127 (14), 125 (18), 123 (19), 119 (15), 111 (29), 109 (25), 97 (41), 95 (34), 91 (13), 85 (23), 83 (38), 81 (30), 71 (31), 69 (42), 57 (46), 56 (10), 55 (37), 43 (25), 41 (18). HRMS (EI): Calcd for $C_{21}H_{25}ClO_6$ ([M]$^+$, ^{35}Cl): 408.13342; found: 408.133810.

3.5.7. Ethyl 2-(2-chloroethyl)-6-ethyl-5-hydroxy-3′,4′,5′-trimethoxy-3-methylbiphenyl-4-carboxylate (**9g**)

Starting with **8c** (0.278 g, 1.0 mmol), **5i** (0.322 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9g** was isolated as a viscous oil (0.175 g, 40%). ^1H NMR (250 MHz, $CDCl_3$): δ=0.92 (t, ^3J=5.7 Hz, 3H, CH_2CH_3), 1.08–1.10 (m, 3H, OCH_2CH_3), 2.46 (s, 3H, CH_3), 2.69 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 3.32 (t, ^3J=6.3 Hz, 2H, CH_2CH_2Cl), 3.56 (t, ^3J=6.5 Hz, 2H, CH_2CH_2Cl), 3.76 (s, 6H, 2×OCH_3), 3.86 (s, 3H, O*C*H_3), 4.39 (q, ^3J=7.3 Hz, 2H, O*C*H_2CH_3), 6.25 (s, 2H, CH_{Ar}), 10.88 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.1 (OCH_2CH_3), 14.1 (CH_2CH_3), 18.7 (CH_3), 22.6 (CH_2CH_3), 29.3 (CH_2CH_2Cl), 31.9 (CH_2CH_2Cl), 56.2 (2×OCH_3), 61.0 (*O*CH_3), 61.8 (*OC*H_2CH_3), 105.7 (2CH_{Ar}), 114.1 (*C*COO*C*$_2H_5$), 123.9 (*C*CH_2CH_3), 126.4 (*C*CH_2CH_2Cl), 129.2 (C_{OMeAr}), 135.4 (C_{Ar}), 137.1 (*C*OCH_3), 139.2 (*C*CH_3), 153.2 (2×*C*OCH_3), 158.3 (*C*OH), 171.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$=3004 (w), 2964 (w), 2930 (m), 1735 (m), 1676 (m), 1582 (m), 1461 (m), 1454 (m), 1412 (m), 1237 (s), 1231 (m), 1144 (m), 1122 (s), 990 (m), 772 (m), 588 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=438 ([M^+], ^{37}Cl, 35), 436 ([M^+], ^{35}Cl, 100), 390 (31), 375 (15), 364 (32), 363 (21), 362 (96), 361 (17), 359 (32), 356 (13), 355 (47), 341 (15), 331 (11), 328 (18), 327 (19), 323 (12), 313 (16), 300 (16), 297 (28), 295 (15), 195 (32), 191 (10), 165 (11), 155 (11), 149 (17), 141 (20), 139 (12), 135 (11), 133 (10), 125 (20), 123 (20), 113 (14), 111 (33), 109 (24), 107 (10), 85 (42), 83 (50), 81 (33), 79 (11), 71 (63), 69 (55), 57 (92), 55 (61), 44 (36), 43 (65), 42 (12), 41 (46), 40 (16), 39 (13). HRMS (EI): Calcd for $C_{23}H_{29}ClO_6$ ([M]$^+$, ^{35}Cl): 436.16472; found: 436.164987.

3.5.8. Methyl 2-(2-chloroethyl)-5-hydroxy-3-methyl-4′-nitrobiphenyl-4-carboxylate (**9h**)

Starting with **8d** (0.233 g, 1.0 mmol), **5a** (0.286 g, 1.1 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (75 mL), **9h** was isolated as a highly viscous oil (0.160 g, 46%). ^1H NMR (250 MHz, $CDCl_3$): δ=2.35 (s, 3H, CH_3), 2.46 (t, ^3J=7.8 Hz, 2*H*, CH_2CH_2Cl), 3.30 (s, 3H, OCH_3), 3.41 (t, ^3J=6.2 Hz, 2H, CH_2CH_2Cl), 6.86 (s, 1H, CH_{Ar}), 7.22, 7.28 (m, 2H, CH_{OMeAr}), 8.16, 8.20 (m, 2H, CH_{OCH3Ar}), 10.85 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.9 (CH_3), 30.3 (CH_2CH_2Cl), 49.9 (OCH_3), 59.8 (CH_2CH_2Cl), 113.3 (*C*COOMe), 117.9 (CH_{Ar}), 120.9 (2CH_{NO_2Ar}), 126.0 (*C*CH_2CH_2Cl), 127.7 (2 × CH_{NO_2Ar}), 134 (C_{Ar}), 139.4 (*C*CH_3), 143.6 (C_{NO_2Ar}), 147.2 (*C*NO_2), 158.2 (*C*OH), 168.6 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$=3338 (w), 3107 (w), 2961 (w), 2882 (w), 1722 (w), 1666 (m), 1595 (m), 1514 (s), 1455 (m), 1434 (m), 1345 (s), 1269 (m), 1237 (s), 1198 (m), 1179 (m), 1129 (m), 1076 (m), 1027 (s), 1009 (s), 945 (w), 901 (w), 848 (m), 796 (m), 736 (m), 705 (m), 647 (m), 547 (m). GC–MS (EI, 70 eV): *m*/*z* (%)=349 ([M]$^+$, 5), 331 (27), 300 (35), 299 (28), 269 (16), 268 (100), 222 (55), 194 (12), 165 (25). HRMS (EI): Calcd for $C_{17}H_{16}ClNO_5$ ([M]$^+$): 349.07187; found: 349.071546.

Acknowledgements

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