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Synthesis of 3,5-diaryl-4-chlorophthalates by [4+2] cycloaddition of 1-ethoxy-2-chloro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylene dicarboxylate and subsequent site-selective Suzuki–Miyaura reactions

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ABSTRACT

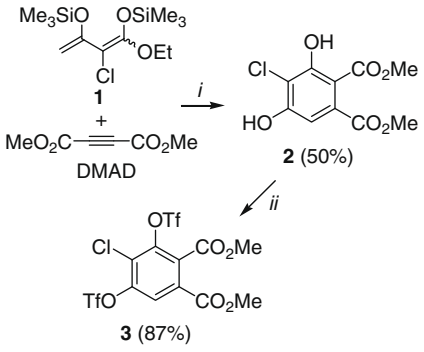
The [4+2] cycloaddition of 1-ethoxy-2-chloro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD) afforded dimethyl 4-chloro-3,5-dihydroxyphthalate. Site-selective Suzuki–Miyaura reactions of its bis(triflate) provide a convenient approach to 3,5-diaryl-4-chlorophthalates containing two different aryl groups.

Aryl chlorides are of pharmacological importance and have been isolated as natural products.[1] In fact, arenes and hetarenes containing a chloride group often show a better pharmacological activity compared to their non-halogenated analogues.[2] In addition, the chloro group can be reacted in palladium(0)-catalyzed cross coupling reactions.[3] However, the synthesis of chlorinated arenes is not straightforward. The direct chlorination of arenes often suffers from several side-reactions, such as low regioselectivity and multiple chlorination. An alternative strategy for the regioselective synthesis of organochlorine compounds relies on the use of appropriate chlorine-containing building blocks in condensation and cyclization reactions. For example, Manzanares and co-workers reported the synthesis of a 4-chlorophenol by [4+2] cycloaddition of a chlorinated thiophene with dimethyl acetylenedicarboxylate.[4]

1,3-Bis(trimethylsilyloxy)-1,3-butadienes (e.g., Chan's diene)[5,6] represent useful synthetic building blocks.[7] Recently, we reported the application of these dienes to the synthesis of chlorinated arenes and hetarenes.[8]

Herein, we report the facile synthesis of dimethyl 4-chloro-3,5-dihydroxyphthalate by [4+2] cycloaddition of 1-ethoxy-2-chloro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD). Suzuki–Miyaura reactions of the bis(triflate) of this product proceed with very good site-selectivity[9] and provide a convenient approach to novel 3,5-diaryl-4-chlorophthalates which are not readily available by other methods.

The [4+2] cycloaddition of 1-ethoxy-2-chloro-1,3-bis(trimethylsilyloxy)-1,3-diene (**1**), readily available from ethyl 2-chloroacetoacetate in two steps, with DMAD afforded dimethyl 4-chloro-3,5-



Scheme 1. Synthesis of **2** and **3**. Reagents and conditions: (i) (1) **1** (1.0 equiv), DMAD (1.5 equiv), −78→20 °C, 20 h; (2) HCl (10%); (ii) (1) and **2** (1.0 equiv), pyridine (4.0 equiv), CH_2Cl_2, −78 °C, 10 min; (2) Tf_2O (2.4 equiv), −78→0 °C, 4 h.

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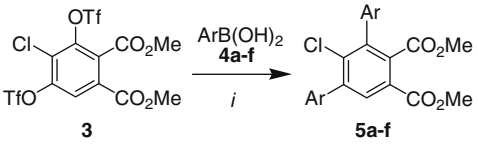
dihydroxyphthalate (**2**) in 50% yield (Scheme 1).[10] The latter was transformed into bis(triflate) **3** in high yield.[11]

The Suzuki reaction of **3** with boronic acids **4a–f** (2.4 equiv) afforded the novel 3,5-diaryl-4-chlorophthalates **5a–f** in good yields (Scheme 2, Table 1). The best yields were obtained when using the arylboronic acid (2.4 equiv), $Pd(PPh_3)_4$ (0.03 equiv) catalyst and K_3PO_4 (3.0 equiv) base in 1,4-dioxane (110 °C, 6 h).[12,13]

The S–M coupling of **3** with arylboronic acids **4a,b,g–j** (1.1 equiv) afforded the 5-aryl-4-chloro-3-(trifluoromethylsulfonyloxy)phthalates **6a–f** in good yields and with very good site-selectivity (Scheme 3, Table 2).[12,14] The formation of the opposite regioisomers was not observed. The site-selectivity can be explained by steric reasons. 3,5-Diaryl-4-chlorophthalates **7a,b**, containing two different aryl groups Ar^1 and Ar^2, were prepared directly from bis(triflate) **3** by the application of a one-pot procedure (Scheme 4, Table 3). The Suzuki reaction of **3** with arylboronic acid **4e** (1.1 equiv, 90 °C) and subsequent addition of arylboronic acids **4a,k** (1.3 equiv, 110 °C) to the in situ formed mono-coupling product afforded products **7a,b** in acceptable yields.[15,16]

The structures of products **5–7** were established by 2D NMR experiments (NOESY, and HMBC). The structures of **5a** and **7a** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[17]

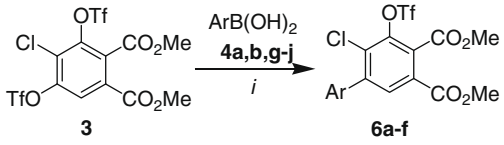


Scheme 2. Synthesis of **5a–f**. Reagents and conditions: (i) **3** (1.0 equiv), **4a–f** (2.4 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 110 °C, 6 h.

Table 1
Synthesis of **5a–f**

4,5	Ar	5[a] (%)
a	4-$(CF_3)C_6H_4$	77
b	C_6H_5	75
c	4-ClC_6H_4	63
d	3-$(CF_3)C_6H_4$	49
e	4-EtC_6H_4	67
f	4-MeC_6H_4	72

[a] Yields of isolated products.

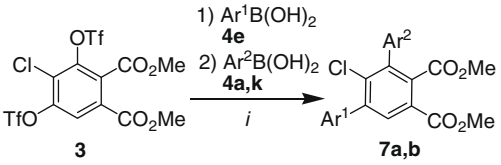


Scheme 3. Synthesis of **6a–f**. Reagents and conditions: (i) **3** (1.0 equiv), **4a**,**b**,**g–j** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 90 °C, 8 h.

Table 2
Synthesis of **6a–f**

4	6	Ar	6[a] (%)
g	**a**	2-$(MeO)C_6H_4$	47
b	**b**	C_6H_5	65
h	**c**	3,4-$(MeO)_2C_6H_3$	47
a	**d**	4-$(CF_3)C_6H_4$	63
i	**e**	3,5-$(Me)_2C_6H_3$	61
j	**f**	2,6-$(MeO)_2C_6H_3$	48

[a] Yields of isolated products.



Scheme 4. One-pot synthesis of **7a**,**b**. Reagents and conditions: (1) **3** (1.0 equiv), **4e** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 90 °C, 8 h; (2) **4a**,**k** (1.3 equiv), K_3PO_4 (1. 5 equiv), 110 °C, 6 h.

Table 3
Synthesis of **7a**,**b**

4	7	Ar^1	Ar^2	7[a] (%)
e, a	**a**	4-EtC_6H_4	4-$(CF_3)C_6H_4$	57
e, k	**b**	4-EtC_6H_4	3-FC_6H_4	53

[a] Yields of isolated products.

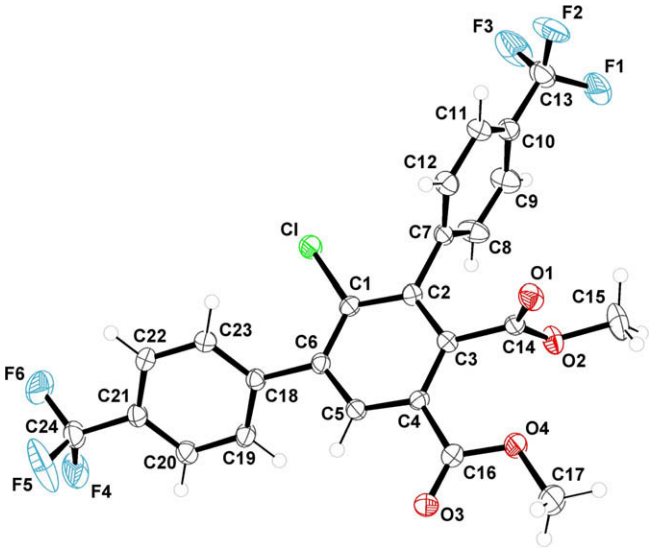


Figure 1. Crystal structure of **5a**.

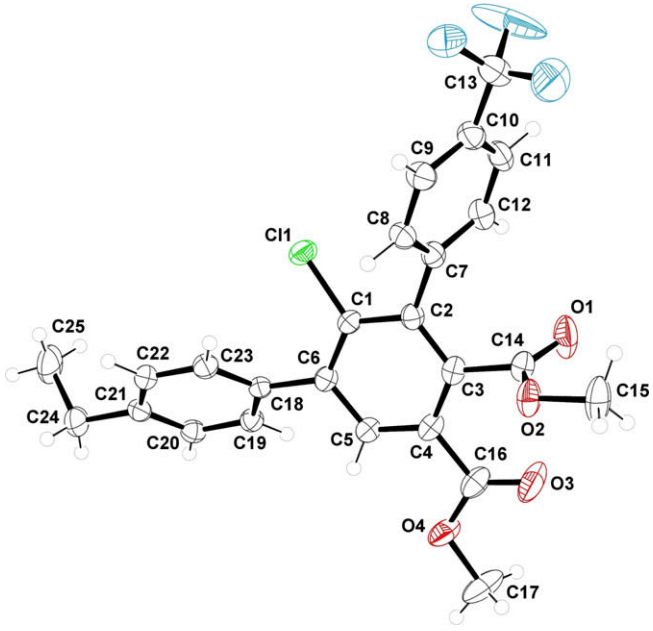


Figure 2. Crystal structure of **7a**.

In conclusion, we reported a convenient approach to dimethyl 4-chloro-3,5-dihydroxyphthalate by [4+2] cycloaddition of 1-ethoxy-2-chloro-1,3-bis(trimethyl-silyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD). The Suzuki–Miyaura coupling of the bis(triflate) of the product proceeds with very good site-selectivity and provides a convenient approach to 3,5-diaryl-4-chlorophthalates containing two different aryl groups. The preparative scope of the methodology is currently being studied.

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9. For a review of site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated substrates, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
10. *Dimethyl 4-chloro-3,5-dihydroxyphthalate* (**2**): Diene **1** (463 mg, 1.5 mmol) was added to DMAD (319 mg, 0.27 mL, 2.25 mmol) at −78 °C. The mixture (neat) was allowed to warm to 20 °C for 20 h with stirring. To the mixture was added hydrochloric acid (10%) and dichloromethane (30 mL each). The organic and the aqueous layers were separated and the latter was extracted 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 to give **2** as a crystalline colourless solid (195 mg, 50%), mp = 127–129 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.57 (s, 1H, OH), 6.57 (s, 1H, ArH), 11.55 (s, 1H, OH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 53.0 (OCH_3), 103.5 (C), 107.5 (CH), 109.3, 135.0 (C), 156.6, 158.7 (C–OH), 168.6, 169.0 (C=O). IR (ATR, cm^{-1}): ν = 2984 (w), 2954 (w), 2905 (w), 2847 (w), 1792 (w), 1722 (s), 1668 (m), 1435 (m), 1328 (m), 1243 (s), 1067 (s), 844 (m). MS (EI, 70 eV): *m/z* (%): 262 (M^+, ^{37}Cl, 9), 260 (M^+, ^{35}Cl, 15), 228 (53), 198 (23), 170 (100), 153 (23), 89 (25). Anal. Calcd for $C_{10}H_9ClO_6$: C 46.08, H 3.48. Found: C 46.21, H 3.31.
11. *Dimethyl 4-chloro-3,5-bis(trifluoromethylsufonyloxy)phthalate* (**3**): To a solution of **2** (1.0 equiv) in CH_2Cl_2 (10 mL/mmol) was added pyridine (4.0 equiv) at −78 °C under an argon atmosphere. After 10 min, Tf_2O (2.4 equiv) was added at −78 °C. The mixture was allowed to warm up to 0 °C and stirred for 4 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The products of the reaction mixture were isolated by rapid column chromatography (flash silica gel, heptanes/EtOAc). Starting with **2** (2.080 g, 8.0 mmol), pyridine (2.6 mL, 32.0 mmol), CH_2Cl_2 and Tf_2O (3.2 mL, 19.2 mmol), **3** was isolated as viscous colourless oil (3.65 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 3.88 (s, 3H, OCH_3), 7.92 (s, 1H, ArH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 52.7 (OCH_3), 117.5 (q, $^1J_{CF}$ = 321 Hz, CF_3), 117.6 (q, $^1J_{CF}$ = 321 Hz, CF_3), 123.0 (CH), 126.5, 128.7, 130.0, 142.4. 145.8 (C), 167.7 (2C, C=O). ^{19}F NMR (282.4 MHz. $CDCl_3$): δ = −71.99 (CF_3), −73.20 (CF_3). IR (ATR, cm^{-1}): ν = 3103 (w), 2960 (w), 2850 (w), 2054 (w), 1980 (w), 1739 (s), 1599 (w), 1567 (w), 1429 (s), 1395 (m), 1305 (m), 1277 (m), 1206 (s), 1129 (s), 1113 (s), 1005 (s), 961 (s), 919 (w), 859 (w), 820 (m), 787 (s), 751 (s), 732 (s), 698 (m), 651 (m), 593 (s), 574 (m). MS (EI, 70 eV): *m/z* (%): 524 (M^+, 30), 493 (100), 460 (13), 429 (39), 391 (4), 365 (36), 299 (42), 271 (6), 238 (11), 199 (12), 171 (9), 143 (3), 84 (8), 69 (38), 59 (13). HRMS (EI) calcd for $C_{12}H_7O_{10}ClF_6S_2$ [M^+]: 523.90679, found 523.907255.
12. *General procedure for Suzuki–Miyaura reactions*: A 1,4-dioxane solution (4 mL per 0.3 mmol of **3**) of **3**, K_3PO_4, $Pd(PPh_3)_4$ and arylboronic acid **4** was stirred at 110 °C or 90 °C for 6 or 8 h. After cooling to 20 °C, a saturated aqueous solution of NH_4Cl was added. The organic and the aqueous layers were separated and the latter was extracted 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.
13. *Dimethyl 4-chloro-3,5-di(4-tolyl)phthalate* (**5f**): Starting with **3** (157 mg, 0.3 mmol), K_3PO_4 (191 mg, 0.9 mmol), $Pd(PPh_3)_4$ (3 mol %), 4-methylphenylboronic acid (98 mg, 0.72 mmol) and 1,4-dioxane (4 mL), **5f** was isolated as a colourless solid (88 mg, 72%); mp = 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 7.10–7.18 (m, 4H, ArH), 7.21–7.29 (m, 4H, ArH), 7.91 (s, 1H, ArH). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.3 ($ArCH_3$), 21.4 ($ArCH_3$), 52.3 (OCH_3), 52.6 (OCH_3), 125.3 (C), 128.7 (2CH), 128.9 (2CH), 129.2 (2CH), 129.4 (2CH), 131.7 (CH), 133.4, 135.7, 136.1, 137.4, 138.0, 138.1, 140.0, 142.2 (C), 165.3 (CO), 168.0 (CO). IR (ATR, cm^{-1}): ν = 3026 (w), 2949 (w), 2922 (w), 2859 (w), 2253 (w), 1906 (w), 1727 (s), 1613 (w), 1584 (w), 1552 (w), 1514 (m), 1434 (m), 1373 (w), 1340 (m), 1259 (s), 1237 (s), 1213 (m), 1145 (m), 1104 (m), 1069 (m), 1021 (m), 969 (m), 909 (m), 890 (m), 814 (m), 783 (m), 730 (m), 720 (m), 634 (m), 554 (m). MS (EI, 70 eV): *m/z* (%): 411 (M+1, ^{37}Cl, 9), 410 (M^+, ^{37}Cl, 36), 409 (M+1, ^{35}Cl, 26), 408 (M^+, ^{35}Cl, 97), 380 (8), 379 (35), 378 (25), 377 (100), 347 (8), 345 (23), 318 (3), 290 (4), 289 (5), 255 (8), 239 (15), 226 (4), 204 (7), 178 (3), 126(9), 91 (2), 59 (1). HRMS (EI) calcd for $C_{24}H_{21}O_4Cl$ [M^+]: 408.11229, found 408.112793.
14. *Dimethyl 4-chloro-3-(2-methoxyphenyl)-5-(trifluoromethylsulfonyl-oxy)phthalate* (**6a**): Starting with **3** (157 mg, 0.3 mmol), K_3PO_4 (95.4 mg, 0.45 mmol), $Pd(PPh_3)_4$ (3 mol %), 2-methoxyphenylboronic acid (50 mg, 0.33 mmol) and 1,4-dioxane (4 mL), **6a** was isolated as a colourless solid (68 mg, 47%), mp = 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.92 (d, J = 8.4 Hz, 1H, ArH), 6.98 (dt, J = 7.4, 1.0 Hz, 1H, ArH), 7.11 (dd, J = 7.5, 1.7 Hz, 1H, ArH), 7.37 (dt, J = 7.8, 1.7 Hz, 1H, ArH), 7.86 (s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 52.0 (OCH_3), 52.3 (OCH_3), 54.9 (OCH_3), 110.0 (CH), 117.5 (q, J = 321 Hz, CF_3), 119.5 (CH), 124.7, 127.0, 128.5, (C), 129.3, 129.8, 131.2 (CH), 131.9, 141.2, 141.3, 155.4 (C), 163.1 (CO), 163.4 (CO). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −71.99 (CF_3). IR (ATR, cm^{-1}): ν = 2955 (w), 2923 (w), 2849 (W), 1738 (s), 1730 (m), 1607 (w), 1582 (w), 1501 (w), 1468 (w), 1429 (w), 1325 (w), 1270 (s), 1242 (m), 1210 (m), 1164 (w), 1135 (m), 1112 (w), 1009 (w), 926 (w), 806 (m), 755 (m), 672 (w), 639 (w), 598 (m), 572 (w), 547 (w), 573 (w). MS (EI, 70 eV): *m/z* (%): 484 (M^+, ^{37}Cl, 40), 482 (M^+, ^{35}Cl, 100), 451 (25), 415 (2), 387 (4), 317 (27), 289 (20), 250 (16), 229 (5), 195 (6), 168 (6), 139 (6), 69 (9), 59 (5). HRMS (EI) calcd for $C_{18}H_{14}O_8ClF_3S$ [M^+]: 482.00445, found 482.005219.
15. *General procedure for the synthesis of* **7a**,**b**: The reaction was carried out in a pressure tube. To a dioxane suspension (4 mL) of **3** (236 mg, 0.45 mmol), $Pd(PPh_3)_4$ (3 mol %) and $Ar^1B(OH)_2$ (0.5 mmol) was added K_3PO_4 (143 mg, 0.67 mmol), and the resultant solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 90 °C under Argon atmosphere for 8 h. The mixture was cooled to 20 °C. $Ar^2B(OH)_2$ (0.6 mmol) and K_3PO_4 (143 mg, 0.67 mmol) were added. The reaction mixtures were heated under an Argon atmosphere for 6 h at 110 °C. They were diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc/heptanes).
16. *Dimethyl 4-chloro-3-(4-ethylphenyl)-5-(4-trifluoromethylphenyl)-phthalate* (**7a**): Starting with **3** (236 mg, 0.45 mmol), K_3PO_4 (143 mg, 0.67 mmol), $Pd(PPh_3)_4$ (3 mol %), 4-ethylphenylboronic acid (75 mg, 0.5 mmol), 1,4-dioxane (4 mL) and 4-trifluoromethylphenylboronic acid (114 mg, 0.6 mmol), **7a** was isolated as colourless crystals (122 mg, 57%), mp = 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, J = 7.8 Hz, 3H, CH_3), 2.65 (q, J = 7.5 Hz, 2H, CH_2), 3.48 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 7.21–7.32 (m, 4H, ArH), 7.35–7.38 (m, 2H, ArH), 7.60–7.63 (m, 2H, ArH), 7.97 (s, 1H, ArH). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 15.3 (CH_3), 28.6 (CH_2), 52.4 (OCH_3), 52.7 (OCH_3), 124.0 (q, J = 272 Hz, CF_3), 125.0 (q, $^3J_{CF}$ = 3.7 Hz, 2CH), 125.7 (C), 127.8 (2CH), 129.2 (2CH), 130.2 (2CH), 130.6 (d, $^2J_{CF}$ = 32.5 Hz, C), 132.4 (CH), 135.4, 135.8, 136.8, 138.5 (C), 140.0 (d, J = 1.4 Hz, C), 142.5, 144.6 (C), 165.1, 167.6 (CO). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −62.7 (CF_3). IR (ATR, cm^{-1}): ν = 3026 (w), 2949 (w), 2922 (w), 2859 (w), 2253 (w), 1906 (w), 1727 (s), 1613 (w), 1584 (w), 1552 (w), 1514 (m), 1434 (m), 1373 (w), 1340 (m), 1259 (s), 1237 (s), 1213 (m), 1145 (m), 1104 (m), 1069 (m), 1021 (m), 969 (m), 909 (m), 890 (m), 814 (m), 783 (m), 730 (m), 720 (m), 634 (m), 554 (m). MS (EI, 70 eV): *m/z* (%): 479 (M+1, ^{37}Cl, 9), 478 (M^+, ^{37}Cl, 36), 477 (M+1, ^{35}Cl, 29), 476 (M^+, ^{35}Cl, 99), 461 (30), 447 (41), 445 (100), 415 (5), 387 (4), 343 (5), 309 (7), 239 (6), 215 (8), 199 (4), 163 (1), 151 (3), 119 (4), 59 (2), 29 (1). HRMS (ESI) calcd for $C_{25}H_{20}O_4ClF_3$ [M]$^+$: 476.1002, calcd for [M+H]$^+$:

477.1075 found 477.10693, and calcd for $C_{25}H_{20}ClF_3NaO_4$ $[M+Na]^+$: 499.08944 found 499.08927.
17. CCDC 754590 and CCDC 754591 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.