Synthesis of 3-hydroxy-5-alkoxyhomophthalates by domino '2 : 1-coupling/intramolecular aldol condensation' reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with tetraalkoxymethanes†

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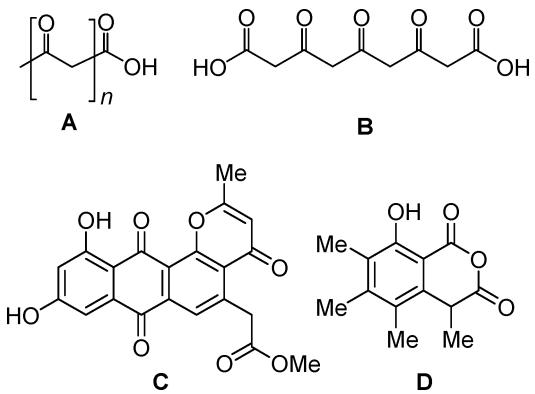
The first domino '2 : 1 condensation/intramolecular aldol' reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadiene with tetraalkoxymethanes provide a convenient approach to 3-hydroxy-5-alkoxyhomophthalates. These products, which contain one free and one protected hydroxyl group, can be functionalized by palladium(0)-catalyzed cross-coupling reactions.

Introduction

A great variety of pharmacologically important natural products are biosynthetically derived from poly(β-oxo)carboxylic acids (polyketides, **A**).[1] This includes a variety of polyhydroxylated arenes, which are biogenetically formed by intramolecular aldol condensation of polyketides. Naturally occurring 3-hydroxyhomophthalic acid derivatives, such as premithramycinon H (**C**)[2] and sclerin (**D**),[3] are biogenetically derived from triketodicarboxylic acids, such as parent hepta-2,4,6-triketo-1,7-dicarboxylic acid **B**, which can be regarded as pentaketides (Scheme 1).



Scheme 1 Polyketides (**A**), hepta-2,4,6-triketo-1,7-dicarboxylic acid (**B**) and polyketide-derived homophthalates (**C**, **D**).

Harris and coworkers reported the biomimetic synthesis of various polyketides based on condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with carboxylic acid derivatives and subsequent spontaneous intramolecular aldol reaction.[4] In this context, Harris and coworkers reported the formation of 3,5-dihydroxyhomophthalic acid in low yield by reaction of the trianion of heptane-2,4,6-trione with carbon dioxide. The reaction proceeds by formation of hepta-2,4,6-triketo-1,7-dicarboxylic acid **B** and subsequent cyclization.[5]

1,3-Bis(silyloxy)-1,3-butadienes can be regarded as equivalents of 1,3-dicarbonyl dianions.[6] Recently, we reported the synthesis of 3,5-dioxoesters by condensation of 1,3-bis(silyloxy)-1,3-butadienes with acid chlorides.[7] In addition, 3,5-dioxopimelic acid diesters, stable 1,3,5,7-tetracarbonyl derivatives, were prepared by reaction of 1,3-bis(silyloxy)-1,3-butadienes with methyl malonyl chloride.[8] Chan and Brownbridge have reported the synthesis of homophthalates by 2 : 1 condensation of 1,3-bis(silyloxy)-1,3-butadienes with trimethyl orthoformate or 1,1,1-trimethoxyethane and subsequent cyclization by intramolecular aldol reaction.[3] We have reported the synthesis of 4-methoxysalicylates by [3 + 3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 3-oxo-orthoesters.[9] Homophthalates have also been prepared by [4 + 2] cycloaddition of 1,3-bis(silyloxy)-1,3-butadienes with dimethyl allene-1,3-dicarboxylate.[10] Herein, we report a convenient approach to 3-hydroxy-5-alkoxyhomophthalates by what are, to the best of our knowledge, the first domino '2 : 1-coupling/intramolecular aldol condensation' reactions of 1,3-bis(silyloxy)-1,3-butadienes with tetraalkoxymethanes.

Results and discussion

The $TiCl_4$-mediated reaction of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**2a**) with tetramethoxymethane (**1a**) afforded the 3-hydroxy-5-methoxyhomophthalate **3a** in 67% yield (Scheme 2). The formation of **3a** can be explained by $TiCl_4$-mediated attack of **2a** to **1a** to give intermediate **E**, attack of a second molecule of **2a** onto **E** to give intermediate **F**, subsequent cyclization to give intermediate **G** and subsequent aromatization (before or during the aqueous work-up). The best yields were obtained when **1a**, **2a** and $TiCl_4$ were employed in a stoichiometric ratio 1 : 2 : 2, when the reaction was carried out in a relatively concentrated solution (5 mL of CH_2Cl_2 per mmol of **1a**) and when hydrochloric acid (10%) was used for the aqueous work up. The use of other Lewis acids, such as Me_3SiOTf, resulted in the formation of complex mixtures. The yield dropped (38%) when **1a**, **2a** and $TiCl_4$ were employed in a stoichiometric ratio 1 : 2 : 1. The yield also dropped (22%) when the reaction was carried out in a more

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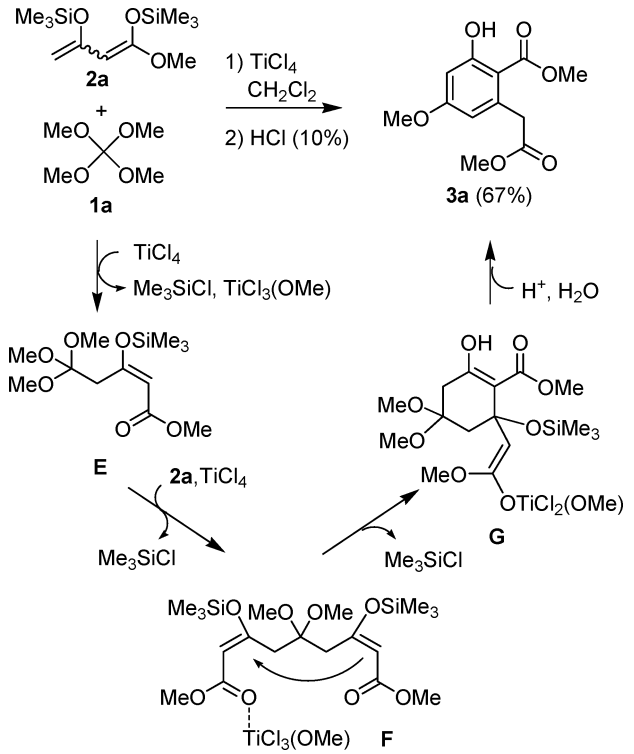
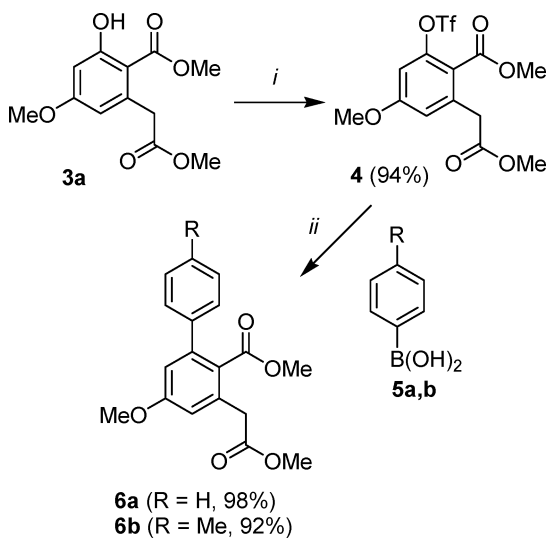


Scheme 2 Possible mechanism of the formation of homophthalate **3a**.

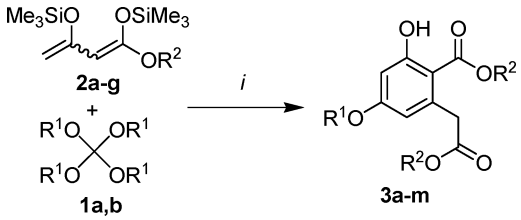
dilute solution (30 mL of CH_2Cl_2 per mmol of **1a**). No product could be isolated when the reaction was carried out at 0 °C instead of −78 °C.

The condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **2a–g** with tetramethoxymethane (**1a**) and tetraethoxymethane (**1b**) afforded the 3-hydroxy-5-alkoxyhomophthalates **3a–m** in 40–67% yield (Scheme 3, Table 1). The reaction of **1a,b** with dienes containing a terminal substituent resulted in the formation of complex mixtures. The employment of 4-alkyl-1,3-bis(silyloxy)-1,3-butadienes resulted in the formation of complex mixtures. The



Scheme 3 Synthesis of **6a,b**. *Conditions*: *i*, Tf_2O, pyridine, CH_2Cl_2, −78 → 20 °C, 4 h; *ii*, **5a,b**, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 4 h.

Table 1 Synthesis of **3a–m**[a]



1	2	3	R^1	R^2	% (3)[b]
a	**a**	**a**	Me	Me	67
a	**b**	**b**	Me	Et	43
a	**c**	**c**	Me	*n*Pr	47
a	**d**	**d**	Me	*i*Pr	47
a	**e**	**e**	Me	*i*Bu	61
a	**f**	**f**	Me	$(CH_2)_2OMe$	63
a	**g**	**g**	Me	Bn	56
b	**b**	**h**	Et	Et	47
b	**c**	**i**	Et	*n*Pr	66
b	**d**	**k**	Et	*i*Pr	47
b	**e**	**l**	Et	*i*Bu	40
b	**f**	**m**	Et	$(CH_2)_2OMe$	41

[a] *Conditions*: *i*, (1) **1** (1.0 equiv.), **2a** (2.0 equiv.), $TiCl_4$ (2.0 equiv.), CH_2Cl_2, −78 → 20 °C, 14 h; (2) HCl (10%). [b] Yields of isolated products.

employment of two different dienes in one reaction again resulted in the formation of complex mixtures.

Homophthalates **3** have some synthetic utility because they contain one free and one protected hydroxyl group. For example, derivative **3a** was transformed into its triflate **4**. The Suzuki reaction of **4** with boronic acids **5a,b** afforded the biaryls **6a,b** in high yields (Scheme 3).

Conclusions

The reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadiene with tetraalkoxymethanes afforded 3-hydroxy-5-alkoxyhomophthalates by the first domino '2 : 1 condensation/intramolecular aldol' reactions. The products, which contain one free and one protected hydroxyl group, could be functionalized by palladium(0)-catalyzed cross-coupling reactions.

Experimental section

General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, 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–g** were prepared according to the literature from the corresponding β-ketoesters in two steps.[11–13]

General procedure for the synthesis of 3a–m

To a CH_2Cl_2 solution (2 mL per mmol of **1a,b**) of **1a,b** (1.0 mmol) was added **2a–g** (2.0 mmol) and, subsequently, $TiCl_4$ (0.23 mL, 2.0 mmol) at −78 °C. The temperature of the solution was allowed

to warm to 20 °C over 12–14 h with stirring. To the solution was added HCl (10%, 10 mL), and the organic and aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (heptane–EtOAc = 20 : 1).

Dimethyl 3-hydroxy-5-methoxy-homophthalate (3a). Starting with **1a** (0.137 g, 1.0 mmol), **2a** (0.521 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3a** was isolated as a colourless solid (0.170 g, 67%); mp = 77–78 °C; R_f 0.70 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 11.64 (s, 1H, OH), 6.46 (d, ^4J = 2.7 Hz, 1H, CH), 6.29 (d, ^4J = 2.7 Hz, 1H, CH), 3.85–3.81 (m, 8H, 2 × OCH_3, $ArCH_2$), 3.68 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 171.0 (C=O), 165.7, 164.1 (C–O), 138.0 (C), 112.8 (CH), 104.9 (C), 100.1 (CH), 55.4, 51.9, 51.7 (OCH_3), 42.7 ($ArCH_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952 (m), 2845 (m), 1726 (s), 1650 (s), 1621 (s), 1585 (s), 1433 (s), 1386 (m), 1333 (s). MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 54), 223 (23), 222 (57), 195 (42), 194 (88), 190 (25), 180 (12), 179 (100), 165 (10). Anal. Calcd for $C_{12}H_{14}O_6$ (254.24): C, 56.69; H, 5.55. Found: C, 56.45; H, 5.62.

Diethyl 3-hydroxy-5-methoxy-homophthalate (3b). Starting with **1a** (0.137 g, 1.0 mmol), **2b** (0.549 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3b** was isolated as a colourless solid (0.119 g, 43%); mp = 64–65 °C; R_f 0.70 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 11.78 (s, 1H, OH), 6.42 (d, ^4J = 2.6 Hz, 1H, CH), 6.28 (d, ^4J = 2.6 Hz, 1H, CH), 4.35 (q, ^3J = 7.2 Hz, 2H, OCH_2), 4.14 (q, ^3J = 7.2 Hz, 2H, OCH_2), 3.86 (s, 2H, $ArCH_2$), 3.81 (s, 3H, OCH_3), 1.36 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 1.24 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 170.8 (C=O), 165.7, 163.9 (C–O), 138.0 (C), 112.7 (CH), 105.3 (C), 100.1 (CH), 61.4, 60.7 (OCH_2), 55.3 (OCH_3), 42.9 ($ArCH_2$), 14.2, 14.0 (CH_2CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985 (m), 2940 (m), 2908 (w), 1724 (s), 1641 (s), 1613 (s), 1588 (s), 1447 (m), 1433 (m), 1366 (s). MS (EI, 70 eV): *m*/*z* (%) = 282 (M^+, 36), 237 (22), 236 (41), 208 (29), 190 (21), 181 (41), 180 (100), 179 (21). Anal. Calcd for $C_{14}H_{18}O_6$ (282.29): C, 59.57; H, 6.43. Found: C, 59.63; H, 6.47.

Di(*n*-propyl) 3-hydroxy-5-methoxy-homophthalate (3c). Starting with **1a** (0.137 g, 1.0 mmol), **2c** (0.578 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3c** was isolated as a colourless oil (0.143 g, 47%); R_f 0.74 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.79 (s, 1H, OH), 6.42 (d, ^4J = 2.6 Hz, 1H, CH), 6.28 (d, ^4J = 2.6 Hz, 1H, CH), 4.25 (t, ^3J = 6.8 Hz, 2H, OCH_2), 4.03 (t, ^3J = 6.8 Hz, 2H, OCH_2), 3.88 (s, 2H, $ArCH_2$), 3.81 (s, 3H, OCH_3), 1.82–1.57 (m, 4H, 2×CH_2CH_3), 0.99 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3), 0.90 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 171.0 (C=O), 165.7, 163.9 (C–O), 138.1 (C), 112.6 (CH), 105.3 (C), 100.1 (CH), 67.2, 66.4 (OCH_2), 55.4 (OCH_3), 42.7 ($ArCH_2$), 21.9, 21.8 (CH_2CH_3), 10.5, 10.3 (CH_2CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967 (m), 2839 (m), 2880 (w), 1734 (s), 1649 (s), 1615 (s), 1576 (s), 1462 (m), 1430 (m), 1397 (m). MS (EI, 70 eV): *m*/*z* (%) = 310 (M^+, 27), 251 (9), 252 (19), 209 (19), 208 (47), 190 (16), 181 (38), 180 (100). Anal. Calcd for $C_{16}H_{22}O_6$ (310.14): C, 61.92; H, 7.15. Found: C, 61.84; H, 7.23.

Diisopropyl 3-hydroxy-5-methoxy-homophthalate (3d). Starting with **1a** (0.137 g, 1.0 mmol), **2d** (0.578 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3d** was isolated as a colourless oil (0.146 g, 47%); R_f 0.73 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 11.90 (s, 1H, OH), 6.41 (d, ^4J = 2.7 Hz, 1H, CH), 6.26 (d, ^4J = 2.7 Hz, 1H, CH), 5.27 (septet, ^3J = 6.3 Hz, 1H, OCH), 4.99 (septet, ^3J = 6.3 Hz, 1H, OCH), 3.86 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 1.36 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 1.23 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.8, 170.5 (C=O), 165.6, 163.7 (C–O), 138.1 (C), 112.4 (CH), 105.7 (C), 100.1 (CH), 69.6, 68.2 (OCH), 55.3 (OCH_3), 42.9 ($ArCH_2$), 21.8, 21.7 ($CH(CH_3)_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980 (m), 2838 (m), 2878 (w), 1730 (s), 1647 (s), 1614 (s), 1577 (s), 1466 (m), 1429 (m), 1374 (s). MS (EI, 70 eV): *m*/*z* (%) = 310 (M^+, 37), 209 (42), 208 (90), 190 (14), 181 (45), 180 (100), 164 (35), 135 (15). Anal. Calcd for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.15. Found: C, 61.95; H, 7.23.

Diisobutyl 3-hydroxy-5-methoxy-homophthalate (3e). Starting with **1a** (0.137 g, 1.0 mmol), **2e** (0.606 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3e** was isolated as a colourless oil (0.205 g, 61%); R_f 0.72 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.78 (s, 1H, OH), 6.42 (d, ^4J = 2.6 Hz, 1H, CH), 6.29 (d, ^4J = 2.6 Hz, 1H, CH), 4.08 (d, ^3J = 7.0 Hz, 2H, OCH_2), 3.91 (s, 2H, $ArCH_2$), 3.84 (d, ^3J = 6.6 Hz, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 2.06 (septet, ^3J = 6.8 Hz, 1H, $CH(CH_3)_2$), 1.90 (septet, ^3J = 6.8 Hz, 1H, $CH(CH_3)_2$), 0.98 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 0.88 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 171.0 (C=O), 165.7, 163.9 (C–O), 138.0 (C), 112.5 (CH), 105.4 (C), 100.1 (CH), 71.8, 70.9 (OCH_2), 55.4 (OCH_3), 42.6 ($ArCH_2$), 27.6, 27.5 ($CH(CH_3)_2$), 19.3, 19.0 ($CH(CH_3)_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (s), 2875 (m), 1735 (s), 1649 (s), 1616 (s), 1577 (s), 1467 (m), 1428 (m), 1371 (s). MS (EI, 70 eV): *m*/*z* (%) = 338 (M^+, 32), 209 (38), 208 (95), 190 (12), 182 (11), 181 (45), 180 (100), 164 (20), 135 (12). HRMS (EI, 70 eV): calcd for $C_{18}H_{26}O_6$ (M^+) 338.17239, found 338.172288.

Di(2-methoxyethyl) 3-hydroxy-5-methoxy-homophthalate (3f). Starting with **1a** (0.137 g, 1.0 mmol), **2f** (0.610 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3f** was isolated as a colourless oil (0.214 g, 63%); R_f 0.23 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.56 (s, 1H, OH), 6.41 (d, ^4J = 2.6 Hz, 1H, CH), 6.29 (d, ^4J = 2.6 Hz, 1H, CH), 4.42 (t, ^3J = 4.8 Hz, 2H, OCH_2), 4.23 (t, ^3J = 4.6 Hz, 2H, OCH_2), 3.94 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 3.67 (t, ^3J = 4.8 Hz, 2H, OCH_2), 3.57 (t, ^3J = 4.6 Hz, 2H, OCH_2), 3.39 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 170.5 (C=O), 165.5, 164.0 (C–O), 138.1 (C), 112.6 (CH), 105.3 (C), 100.1 (CH), 70.3, 69.8, 64.0, 63.8 (OCH_2), 58.8, 58.7, 55.4 (OCH_3), 42.4 ($ArCH_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932 (m), 2889 (m), 1735 (s), 1650 (s), 1616 (s), 1576 (s), 1434 (s), 1368 (m), 1324 (s). MS (EI, 70 eV): *m*/*z* (%) = 342 (M^+, 22), 267 (6), 266 (20), 208 (17), 180 (24), 164 (12), 135 (10), 59 (100). Anal. Calcd for $C_{16}H_{22}O_8$ (342.34): C, 56.13; H, 6.48. Found: C, 56.33; H, 6.34.

Dibenzyl 3-hydroxy-5-methoxy-homophthalate (3g). Starting with **1a** (0.137 g, 1.0 mmol), **2g** (0.674 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3g** was isolated as a colourless solid (0.227 g, 56%); mp = 89–90 °C; R_f 0.48 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.62 (s, 1H, OH), 7.28–7.15 (m, 10H, 2 × Ph), 6.34 (d, ^4J = 2.6 Hz, 1H, CH), 6.19 (d, ^4J = 2.6 Hz, 1H, CH), 5.03 (s, 2H, OCH_2), 4.85 (s, 2H,

OCH_2), 3.78 (s, 2H, ArCH_2CO), 3.71 (s, 3H, OCH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.9, 170.4 (C=O), 165.8, 164.1 (C–O), 137.9, 135.8, 135.1 (C), 128.7, 128.6, 128.5, 128.4, 128.2, 112.8 (CH), 105.1 (C), 100.2 (CH), 66.8, 66.3 (OCH_2), 55.4 (OCH_3), 42.8 (ArCH_2CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3008 (m), 2972 (m), 2847 (w), 1729 (s), 1648 (s), 1614 (s), 1575 (s), 1449 (m), 1432 (m), 1380 (s). MS (EI, 70 eV): *m*/*z* (%) = 406 (M^+, 16), 209 (10), 181 (7), 180 (100), 92 (6), 91 (100). HRMS (EI, 70 eV): calcd for $C_{24}H_{22}O_6$ (M^+) 406.14109, found 406.141134.

Diethyl 5-ethoxy-3-hydroxy-homophthalate (3h). Starting with **1b** (0.193 g, 1.0 mmol), **2b** (0.549 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3h** was isolated as a colourless solid (0.126 g, 47%); mp = 62–63 °C; R_f 0.54 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 11.76 (s, 1H, OH), 6.39 (d, ^4J = 2.5 Hz, 1H, CH), 6.27 (d, ^4J = 2.5 Hz, 1H, CH), 4.34 (q, ^3J = 7.1 Hz, 2H, OCH_2), 4.14 (q, ^3J = 7.1 Hz, 2H, OCH_2), 4.03 (q, ^3J = 7.1 Hz, 2H, OCH_2), 3.84 (s, 2H, $ArCH_2$), 1.43–1.33 (m, 6H, 2 × CH_3), 1.24 (t, ^3J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.4, 170.8 (C=O), 165.6, 163.3 (C–O), 138.0 (C), 113.0 (CH), 105.1 (C), 100.5 (CH), 63.6, 61.4, 60.6 (OCH_2), 42.8 ($ArCH_2$), 14.5, 14.1, 14.0 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983 (m), 2938 (m), 2896 (w), 1731 (s), 1645 (s), 1614 (s), 1575 (s), 1462 (m), 1445 (m), 1368 (s). MS (EI, 70 eV): *m*/*z* (%) = 296 (M^+, 38), 251 (21), 250 (40), 222 (28), 195 (28), 194 (100), 193 (25), 167 (14). Anal. Calcd for $C_{15}H_{20}O_6$ (296.32): C, 60.80; H, 6.80. Found: C, 60.53; H, 6.77.

Di(n-propyl) 5-ethoxy-3-hydroxy-homophthalate (3i). Starting with **1b** (0.193 g, 1.0 mmol), **2c** (0.578 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3i** was isolated as a colourless solid (0.212 g, 66%); mp = 55–56 °C; R_f 0.74 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.78 (s, 1H, OH), 6.40 (d, ^4J = 2.6 Hz, 1H, CH), 6.27 (d, ^4J = 2.6 Hz, 1H, CH), 4.25 (t, ^3J = 6.8 Hz, 2H, OCH_2), 4.07–4.00 (m, 4H, 2×OCH_2), 3.87 (s, 2H, $ArCH_2$), 1.82–1.56 (m, 4H, 2×C$H_2$$CH_3$), 1.40 (t, ^3J = 7.0 Hz, CH_2CH_3), 0.99 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3), 0.90 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 171.0 (C=O), 165.7, 163.3 (C–O), 138.0 (C), 113.0 (CH), 105.1 (C), 100.5 (CH), 67.1, 66.4, 63.7 (OCH_2), 42.7 ($ArCH_2$), 21.9, 21.8 (CH_2CH_3), 14.5, 10.5, 10.3 (CH_2CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967 (m), 2838 (m), 2876 (w), 1730 (s), 1651 (s), 1615 (s), 1576 (s), 1459 (m), 1433 (m), 1406 (m). MS (EI, 70 eV): *m*/*z* (%) = 324 (M^+, 23), 265 (8), 264 (16), 223 (16), 222 (47), 195 (29), 194 (100), 167 (12). Anal. Calcd for $C_{17}H_{24}O_6$ (324.37): C, 62.95; H, 7.46. Found: C, 62.70; H, 7.53.

Diisopropyl 5-ethoxy-3-hydroxy-homophthalate (3k). Starting with **1b** (0.193 g, 1.0 mmol), **2d** (0.578 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3k** was isolated as a colourless oil (0.151 g, 47%); R_f 0.74 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 11.89 (s, 1H, OH), 6.38 (d, ^4J = 2.6 Hz, 1H, CH), 6.25 (d, ^4J = 2.6 Hz, 1H, CH), 5.27 (septet, ^3J = 6.3 Hz, 1H, OCH), 4.99 (septet, ^3J = 6.3 Hz, 1H, OCH), 4.03 (q, ^3J = 7.0 Hz, OCH_2), 3.85 (s, 2H, $ArCH_2$), 1.42–1.34 (m, ^3J = 6.3 Hz, ^3J = 7.0 Hz, 9H, CH_2CH_3, $CH(CH_3)_2$), 1.22 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.8, 170.5 (C=O), 165.6, 163.1 (C–O), 138.1 (C), 112.8 (CH), 105.5 (C), 100.4 (CH), 69.6, 68.2 (OCH), 63.6 (OCH_2), 42.9 ($ArCH_2$), 21.8, 21.7 ($CH(CH_3)_2$), 14.5 (CH_2CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980 (m), 2838 (m), 2878 (w), 1730 (s), 1647 (s), 1614 (s), 1577 (s), 1466 (m), 1429 (m), 1374 (s). MS (EI, 70 eV): *m*/*z* (%) = 324 (M^+, 35), 223 (44), 222 (94), 196 (17), 195 (34), 194 (100), 178 (28), 167 (16). Anal. Calcd for $C_{17}H_{24}O_6$ (323.37): C, 62.95; H, 7.46. Found: C, 63.03; H, 7.61.

Diisobutyl 5-ethoxy-3-hydroxy-homophthalate (3l). Starting with **1b** (0.193 g, 1.0 mmol), **2e** (0.606 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3l** was isolated as a colourless oil (0.139 g, 40%); R_f 0.76 (heptane–EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.77 (s, 1H, OH), 6.40 (d, ^4J = 2.6 Hz, 1H, CH), 6.28 (d, ^4J = 2.6 Hz, 1H, CH), 4.09–4.00 (m, 4H, 2×OCH_2), 3.91 (s, 2H, $ArCH_2$), 3.83 (d, ^3J = 6.8 Hz, 2H, OCH_2), 2.06 (septet, ^3J = 6.8 Hz, 1H, CH(CH_3)$_2$), 1.87 (septet, ^3J = 6.8 Hz, 1H, CH(CH_3)$_2$), 1.40 (t, ^3J = 7.0 Hz, 3H, CH_2CH_3) 0.98 (d, ^3J = 6.8 Hz, 6H, CH(CH_3)$_2$), 0.88 (d, ^3J = 6.8 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 171.0 (C=O), 165.7, 163.9 (C–O), 138.0 (C), 112.9 (CH), 105.2 (C), 100.5 (CH), 71.8, 71.0, 63.7 (OCH_2), 42.6 ($ArCH_2$), 27.6, 27.6 ($CH(CH_3)_2$), 19.3, 19.0, 14.5 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (s), 2875 (m), 1736 (s), 1650 (s), 1617 (s), 1576 (s), 1469 (m), 1422 (m), 1325 (s). MS (EI, 70 eV): *m*/*z* (%) = 352 (M^+, 29), 223 (34), 222 (90), 195 (35), 194 (100), 178 (16), 167 (13). Anal. Calcd for $C_{19}H_{28}O_6$ (352.42): C, 64.75; H, 8.01. Found: C, 64.40; H, 8.18.

Di(2-methoxyethyl) 5-ethoxy-3-hydroxy-homophthalate (3m). Starting with **1b** (0.193 g, 1.0 mmol), **2f** (0.610 g, 2.0 mmol) and $TiCl_4$ (0.23 mL, 2.0 mmol) in CH_2Cl_2 (5 mL), product **3m** was isolated as a colourless oil (0.145 g, 41%); R_f 0.36 (heptane/EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.54 (s, 1H, OH), 6.38 (d, ^4J = 2.6 Hz, 1H, CH), 6.28 (d, ^4J = 2.6 Hz, 1H, CH), 4.42 (t, ^3J = 4.8 Hz, 2H, OC$H_2$$CH_2$), 4.23 (t, ^3J = 4.7 Hz, 2H, OC$H_2$$CH_2$), 4.03 (q, ^3J = 7.1 Hz, 2H, OC$H_2$$CH_3$), 3.93 (s, 2H, $ArCH_2$), 3.67 (t, ^3J = 4.8 Hz, 2H, OC$H_2$$CH_2$), 3.57 (t, ^3J = 4.7 Hz, 2H, OC$H_2$$CH_2$), 3.39 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 1.39 (t, ^3J = 7.1 Hz, 2H, OCH_2CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.4, 170.5 (C=O), 165.5, 163.4 (C–O), 138.0 (C), 113.1 (CH), 105.1 (C), 100.5 (CH), 70.3, 69.8, 63.9, 63.8, 63.7 (OCH_2), 58.8, 58.7 (OCH_3), 42.5 ($ArCH_2$), 14.5 (CH_2CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981 (m), 2931 (m), 2886 (m), 2820 (m), 1736 (s), 1650 (s), 1616 (s), 1575 (s), 1449 (s), 1370 (m), 1323 (s). MS (EI, 70 eV): *m*/*z* (%) = 356 (M^+, 29), 280 (21), 222 (22), 294 (33), 178 (11), 150 (4), 121 (8), 59 (100). Anal. Calcd for $C_{17}H_{24}O_8$ (356.37): C, 57.30; H, 6.79. Found: C, 57.24; H, 6.70.

Dimethyl 5-methoxy-3-trifluormethansulfonyloxy-homophthalate (4). To a stirred dichloromethane solution (30 mL) of **3a** (0.763 g, 3.0 mmol) was added pyridine (0.475 g, 6.0 mmol) at −78 °C and after stirring for 10 min was dropwise added trifluoromethanesulfonic acid anhydride (1.016 g, 3.6 mmol) at the same temperature. The temperature of the mixture was allowed to warm to 0 °C and then stirred for additional 4 h. After direct purification by column chromatography (CH_2Cl_2), product **4** was isolated as a colourless solid (1.086 g, 94%); R_f 0.44 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.83 (d, ^4J = 2.4 Hz, 1H, CH), 6.75 (d, ^4J = 2.7 Hz, 1H, CH), 3.89–3.88 (m, 5H, OCH_3, $ArCH_2$), 3.85 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.6, 164.7 (C=O), 161.7 (C–O), 148.9, 138.0 (C), 118.5 (q, $J_{C,F}$ = 320 Hz, CF_3), 118.4 (C), 117.1, 107.3 (CH), 55.9, 52.4, 52.1

(OCH_3), 39.8 ($ArCH_2$). ^{19}F NMR ($CDCl_3$, 235 MHz): $\delta = -73.6$ (CF_3).

General procedure for the synthesis of 6a,b

A 1,4-dioxane solution (2.5 mL per mmol of **4**) of aryl boronic acid **5a,b** (1.3 mmol), K_3PO_4 (1.6 mmol), $Pd(PPh_3)_4$ (3 mol%) and triflate **4** (1.0 mmol) was stirred at 110 °C for 4 h. After cooling to 20 °C, a saturated aqueous solution of NH_4Cl was added. The organic and aqueous layer were separated and the latter was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (heptane–EtOAc = 10 : 1).

Dimethyl 5-methoxy-3-phenyl-homophthalate (6a). Starting with **4** (0.387 g, 1.0 mmol), **5a** (0.159 g, 1.3 mmol), K_3PO_4 (0.340 g, 1.6 mmol) and $Pd(PPh_3)_4$ (0.035 g, 0.03 mmol) in 1,4-dioxane (2.5 mL), product **6a** was isolated as a light-yellow solid (0.308 g, 98%); mp = 71–72 °C; R_f 0.58 (heptane–EtOAc = 1 : 1). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.30 (m, 5H, Ph), 6.83 (br s, 2H, 2×CH), 3.85–3.81 (m, 5H, OCH_3, $ArCH_2$), 3.69 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 169.6 (C=O), 160.1 (C–O), 143.5, 141.7, 134.7 (C), 128.2, 128.0, 127.4 (CH), 125.2 (C), 115.6, 114.3 (CH), 55.4, 51.9, 51.7 (OCH_3), 42.7 ($ArCH_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2947 (m), 2848 (m), 1731 (s), 1709 (s), 1602 (s), 1574 (m), 1433 (s), 1313 (m), 1286 (s). MS (EI, 70 eV): m/z (%) = 314 (M^+, 40), 283 (28), 282 (28), 255 (58), 254 (93), 240 (17), 239 (100). Anal. Calcd for $C_{18}H_{18}O_5$ (314.33): C, 68.78; H, 5.77. Found: C, 68.82; H, 5.72.

Dimethyl 5-methoxy-3-(4-tolyl)-homophthalate (6b). Starting with **4** (0.271 g, 0.70 mmol), **5b** (0.124 g, 0.91 mmol), K_3PO_4 (0.238 g, 1.6 mmol) and $Pd(PPh_3)_4$ (0.025 g, 0.02 mmol) in 1,4-dioxane (2.0 mL), product **6b** was isolated as a light-yellow solid (0.210 g, 92%); mp = 69–70 °C; R_f 0.60 (heptane–EtOAc = 1 : 1). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.24–7.17 (m, 4H, 4×CH), 6.82–6.80 (m, 2H, 2 × CH), 3.84 (s, 3H, OCH_3), 3.79 (s, 2H, $ArCH_2$), 3.69 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 2.38 (s, 3H, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 169.7 (C=O), 160.1 (C–O), 143.4, 138.3, 137.1, 134.5 (C), 128.9, 127.9 (CH), 125.3 (C), 115.4, 114.3 (CH), 55.4, 52.0, 51.7 (OCH_3), 39.4 ($ArCH_2$), 21.1 ($ArCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948 (m), 2847 (m), 1731 (s), 1708 (s), 1599 (s), 1574 (m), 1430 (s), 1314 (m), 1283 (s). MS (EI, 70 eV): m/z (%) = 328 (M^+, 53), 297 (28), 296 (20), 269 (59), 268 (93), 254 (19), 253 (100). Anal. Calcd for $C_{19}H_{20}O_5$ (328.36): C, 69.50; H, 6.14. Found: C, 69.53; H, 6.21.

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