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Synthesis of ethyl 3-(hydroxyphenoxy)benzyl butylphosphonates as potential antigen 85C inhibitors

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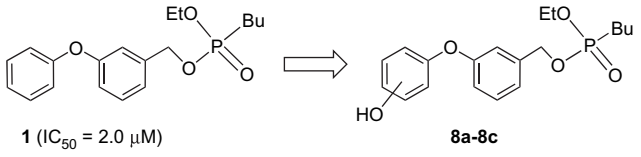
Abstract—All three isomers of ethyl 3-(hydroxyphenoxy)benzyl butylphosphonates as potential antigen 85C inhibitors were synthesized from 3-bromobenzoic acid using Ullman diaryl ether synthesis combined with benzyl- and trityl protection strategy for the phenol hydroxyl groups.

1. Introduction

Recently, we described the design, synthesis and potential antituberculosis activity of the first phosphonate[1] and sulfonate inhibitors[2] of antigen 85C, a major protein component of the mycobacterial cell wall.[3] These novel inhibitors of the mycolyltransferase activity of antigen 85C were designed as simple tetrahedral transition-state analogues of the mycolyltransferase reaction catalyzed by antigen 85C in which the mycolic acid covalently attached to antigen 85C is transferred to trehalose monomycolate (TMM) to form trehalose dimycolate (TDM). The importance of TDM to the stability of the mycobacterial cell wall provides an interesting basis for the development of novel antitubercular drugs.[4]



1 (IC_{50} = 2.0 μM) **8a-8c**

Ethyl 3-phenoxybenzyl butylphosphonate (**1**) inhibited the mycolyltransferase activity of antigen 85C with an IC_{50} value of 2.0 μM and showed substantial inhibition of growth of *Mycobacterium avium* in vitro.[2] The reported inhibitors of antigen 85C comprise three essential parts: an alkyl chain of various lengths mimicking the mycolic acid side chain, a phosphonate group and 3-phenoxybenzyl ether moiety as a simple surrogate of TMM trehalose. We hypothesized that introduction of hydroxyl group(s) on the terminal phenyl ring of the 3-phenoxybenzyl moiety of **1** could strengthen the interaction of the trehalose surrogate with the trehalose binding pocket of the enzyme. In this paper we describe the synthesis of the *ortho*-, *meta*- and *para*-hydroxy analogues **8a–8c** from 3-bromobenzoic acid, applying a strategy of Ullmann diaryl ether synthesis coupled with a combination of benzyl- and trityl protection of the phenol hydroxyl groups.

2. Results and discussion

The synthetic strategy devised for the synthesis of hydroxylic analogues **8a–8c** of antigen 85C inhibitor **1** is outlined in Scheme 1. We anticipated that, starting from appropriate monoprotected phenol derivatives **2** and methyl 3-bromobenzoate, Ullmann diaryl ether synthesis[5] would provide diaryl ethers **3**. These, upon reduction and coupling of the resulting benzyl alcohols **4** with ethyl hydrogen butylphosphonate[6] would afford protected phosphonates **7**, which after deprotection would afford the target compounds **8a–8c**. Protection of the phenol group was inevitable since, in a test reaction, benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP)[7] promoted coupling of 3-(3-(hydroxymethyl)phenoxy)phenol (**9**) with ethyl hydrogen butylphosphonate gave ethyl 3-(3-(hydroxymethyl)-phenoxy)phenyl butylphosphonate (**10**) (Scheme 2), indicating that the reactivity of the phenol group was higher than that of the aliphatic hydroxyl group.

Initially, monomethyl ether protection of catechol, resorcinol, hydroquinone and pyrogallol was applied. 3-Methoxyphenol (**2ab**) and 4-methoxyphenol (**2ac**) were obtained from the respective benzenediols using dimethylsulfate as methylating agent[8] (Scheme 3). These compounds, as well

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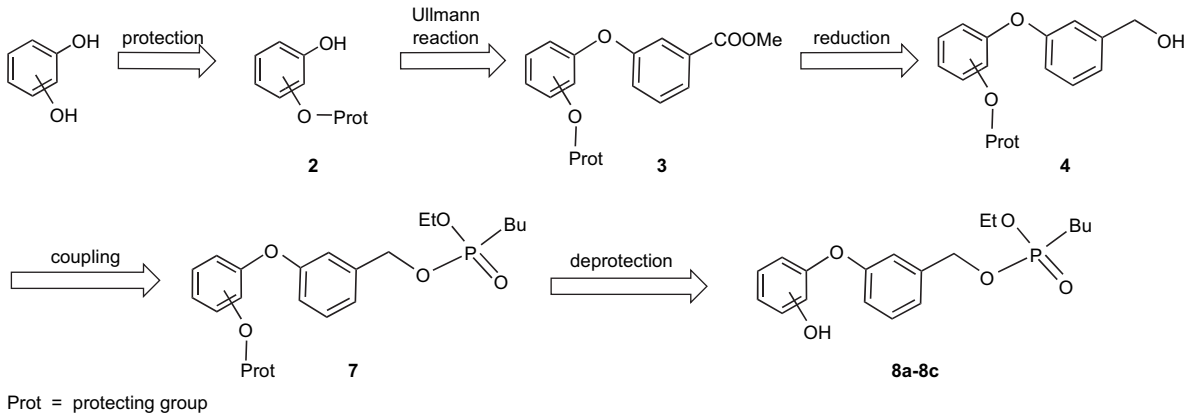
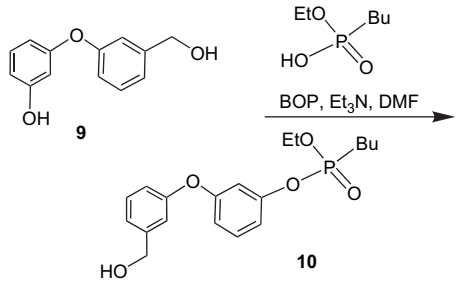


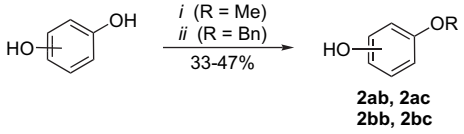
Scheme 1. Strategy for the synthesis of hydroxyl analogues **8a-8c** of antigen 85C inhibitor **1**.

as commercial 2-methoxyphenol and 3,4,5-trimethoxyphenol, were transformed, under conditions of Ullmann diaryl ether synthesis, into *O*-protected ethers **3aa–3ad** (Scheme 4). Reduction of the ester group with borane dimethylsulfide complex[9] afforded *O*-protected benzyl alcohols **4aa–4ad**, which could later also be obtained with better overall yields by Ullmann diaryl ether coupling of unprotected 3-bromobenzyl alcohol and the corresponding methoxyphenols **2aa–2ad**. Coupling of alcohols **4aa–4ad** with ethyl hydrogen butylphosphonate,[6] using BOP as coupling agent,[7] afforded methyl ether protected phosphonates **7aa–7ad,** which, however, decomposed during attempted cleavage of the protecting group with hydrobromic acid[10] or boron tribromide.[11] This required a change in the protection strategy and benzyl protection of the starting diphenols was subsequently tested.

Monobenzyl ethers **2bb** and **2bc** were prepared by alkylating resorcinol and hydroquinone with benzyl bromide in the presence of potassium carbonate in acetone (Scheme 3). Starting from **2ba–2bc**, the reaction sequence described above involving Ullmann diaryl ether synthesis and reduction of the ester group with borane dimethylsulfide complex afforded 3-(benzyloxyphenoxy)benzyl alcohols **4ba–4bc**, which could also be obtained in moderate yield in one step from monobenzyl ethers **2ba–2bc** and methyl 3-



Scheme 2. Coupling of 3-(3-(hydroxymethyl)phenoxy)phenol with ethyl hydrogen butylphosphonate.



Scheme 3. Reagents and conditions: (i) Me_2SO_4, 10% NaOH, reflux; (ii) BnBr, K_2CO_3, acetone, reflux.

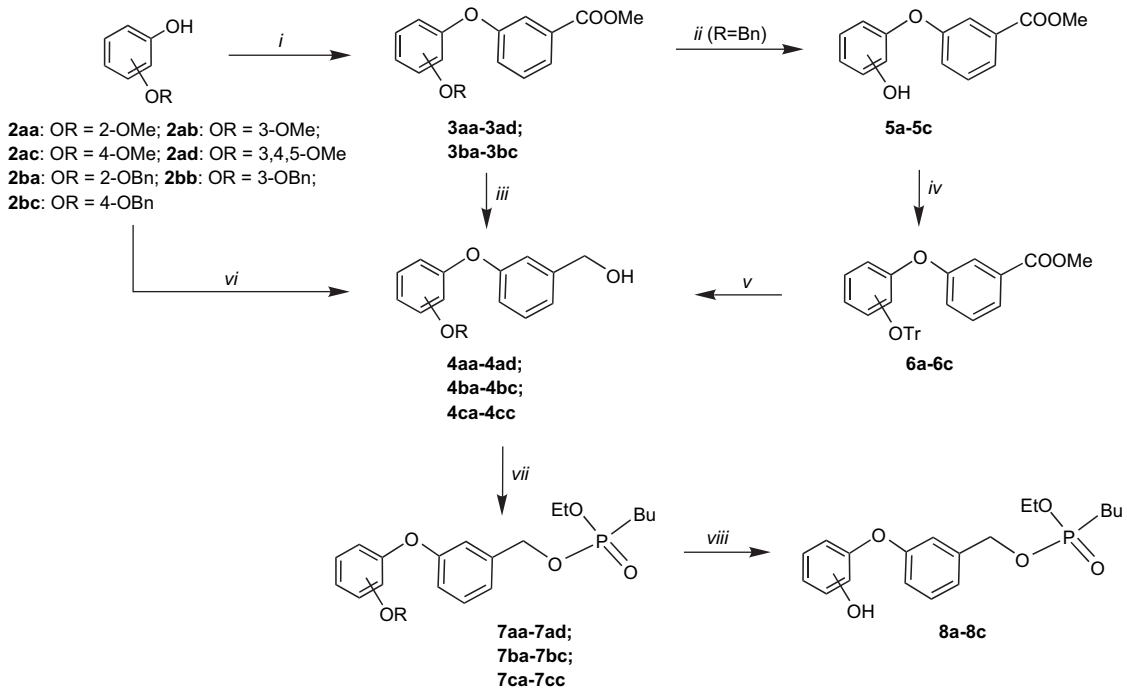
bromobenzoate. Compound **4bc** was condensed with ethyl hydrogen butylphosphonate using BOP coupling strategy to give benzyl protected phosphonate **7bc**. In a test reaction under a variety of reaction conditions, the phenol benzyl ether group of **7bc** could not be selectively cleaved in the presence of the benzyl phosphonate moiety, which was preferentially cleaved giving 3-(4-benzyloxyphenoxy)toluene as the main product. This unsuccessful application of the methyl- and benzyl ether protection strategy prompted us to attempt the synthesis with trityl protection of the phenol hydroxyl group. Since initial test experiments showed that monotrityl ethers of the starting dihydroxybenzenes could not withstand the conditions of the Ullmann diaryl ether coupling reaction, trityl protection was introduced at a later stage. Thus, deprotection of benzyloxy derivatives **3ba–3bc** by catalytic hydrogenation over Pd/charcoal gave methyl 3-(hydroxyphenoxy)benzoates **5a–5c**, which were then protected at the phenol hydroxyl group with trityl chloride to give methyl 3-(trityloxyphenoxy)benzoates **6a–6c**. These could not be reduced with borane dimethylsulfide complex, which had been applied for reduction of the corresponding methyl- and benzyl analogues **3aa–3bc** since, under the applied reaction conditions, the trityl protecting group was cleaved. Trityl protection was later found to be stable towards lithium aluminium hydride, which was then successfully applied for the reduction of **6a–6c** to give 3-(trityloxyphenoxy)benzyl alcohols **4ca–4cc**. These intermediates were coupled with ethyl hydrogen butylphosphonate to give trityl protected phosphonates **7ca–7cc**, which were smoothly detritylated on heating in acetic acid to give the three target hydroxy isomers **8a–8c** (Scheme 4).

In conclusion, the potential antigen 85C inhibitors **8a–8c** were synthesized from catechol, resorcinol and hydroquinone, using Ullmann diaryl ether coupling and BOP-catalyzed formation of the phosphonate ester bond combined with benzyl- and trityl protection of the phenol group. Their biological activity is under investigation.

3. Experimental

3.1. General

2-Methoxyphenol (**2aa**), 3,4,5-trimethoxyphenol (**2ad**) and 2-benzyloxyphenol (**2ba**) were obtained from Acros and



Scheme 4. Reagents and conditions: (i) methyl 3-bromobenzoate, NaH, CuCl, DMF, 160 °C, 6 h; (ii) H_2, Pd/C, MeOH, rt, overnight; (iii) $H_3B \cdot S(CH_3)_2$, THF, reflux, overnight; (iv) TrCl, Et_3N, CH_2Cl_2; (v) $LiAlH_4$, THF, rt, 2H; (vi) 3-bromobenzyl alcohol, NaH, CuCl, DMF, 160 °C, 6 h; (vii) BuPO(OEt)OH, BOP, Et_3N, DMF, rt, overnight; (viii) AcOH, 60 °C, 7.5 h.

used without further purification. Solvents were used without purification or drying, unless otherwise stated. Anhydrous triethylamine, dimethylformamide, dichloromethane and 1,4-dioxane were prepared according to the literature procedures.[6] Reactions were monitored using analytical TLC plates (Merck, silica gel 60 F_{254}) and aluminium oxide (Kemika, F_{254} type T) with UV detection. Column chromatography was carried out on silica gel (Merck, particle size 240–400 mesh) and aluminium oxide (Merck, particle size 70–280 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. NMR spectra were obtained on a Bruker Avance DPX 300 instrument. ^{1}H NMR spectra were recorded at 300 MHz and ^{31}P NMR spectra at 121 MHz using tetramethylsilane and H_3PO_4 as reference compounds. Mass spectra were obtained with a VG-Analytical Autospec Q mass spectrometer using EI, FAB or ES ionization (MS Centre, Jožef Stefan Institute, Ljubljana). IR spectra were recorded on a Perkin–Elmer FTIR 1600 spectrometer. Elemental analyses were performed by the Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, Ljubljana, on a Perkin–Elmer elemental analyzer 240 C.

3.2. Diethyl butylphosphonate

A solution of 1-bromobutane (25.3 g, 185 mmol) in triethyl phosphite (76.9 g, 463 mmol) was heated at 160 °C overnight. The solution was purified by vacuum distillation (bp 43 °C, 0.7 Torr) to give a colourless liquid (33.3 g, 93%). Lit[12]: bp 72 °C/1 Torr. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 0.87 (t, 3H, J=7.4 Hz, $CH_3CH_2CH_2$), 1.15–1.28 (m, 8H, 2×CH_3CH_2O, $CH_3CH_2CH_2$), 1.30–1.53 (m, 2H, $CH_3CH_2CH_2$), 1.60–1.77 (m, 2H, CH_2CH_2P), 3.88–4.10 (m, 4H, 2×CH_3CH_2O); IR (NaCl, film): 3442, 2951, 1244, 1027, 962 cm^{-1}; MS (EI): 194 (M^+, 6), 179 (71), 167 (40), 152 (45), 139 (100), 125 (90), 121 (49), 111 (70), 97 (70), 82 (47), 65 (45), 55 (51).

3.3. Ethyl hydrogen butylphosphonate

Sodium azide (10.36 g, 154.5 mmol) was added to a stirred solution of diethyl butylphosphonate (4.00 g, 20.6 mmol) in *N*,*N*-dimethylformamide. The mixture was heated at 100 °C overnight. Water (100 mL) was added and the resulting solution was washed with ethyl acetate (3×50 mL). The aqueous phase was acidified to pH 1 with 4 M HCl and extracted with ethyl acetate (5×30 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated in vacuo to give a viscous oil (2.9 g, 85%). Lit[6]: bp 147–149 °C/1 Torr. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.85 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.25 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.30–1.42 (m, 2H, $CH_2CH_2CH_2P$), 1.45–1.75 (m, 4H, $CH_2CH_2CH_2P$, CH_2CH_2P), 3.90–4.10 (m, 2H, CH_3CH_2O); IR (NaCl, film): 2951, 1191, 1044, 982 cm^{-1}; MS (EI): 166 (M^+, 4), 152 (7), 139 (4), 111 (65), 97 (34), 93 (35), 37 (100), 55 (46).

3.4. General procedure for the synthesis of methoxyphenols 2ab–2ac

Resorcinol or hydroquinone (5.51 g, 50 mmol) was dissolved in 2.5 M NaOH (25 mL, 62.5 mmol) and dimethylsulfate (6.31 g, 50 mmol) was added dropwise during stirring under an inert atmosphere while the temperature was kept below 40 °C. The solution was heated for 30 min under reflux, whereupon 2.5 M NaOH was added to pH 14. The solution was washed with diethyl ether (3×25 mL), acidified to pH 1 with 1 M aqueous HCl and extracted with diethyl ether (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and evaporated in vacuo.

3.4.1. 3-Methoxyphenol (2ab). The product was synthesized by the procedure described above from resorcinol (6.00 g, 54.41 mmol), 2.5 M NaOH solution (27.2 mL, 68.01 mmol) and dimethylsulfate (6.86 g, 54.41 mmol). The crude product was purified with column chromatography on silica gel using hexane/ethyl acetate (6/1) as eluant to give a viscous red liquid (3.16 g, 47%). Lit[13]: bp 114 °C/5 Torr. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H, CH_3), 4.90 (br s, 1H, OH), 6.42–6.47 (m, 2H, $2H_{Ar}$), 6.49–6.55 (m, 1H, H_{Ar}), 7.11–7.89 (dd, 1H, $J_{5,4}\approx J_{5,6}\approx 8.5$ Hz, 5-H); IR (NaCl, film): 3391, 2960, 2838, 1599, 1494, 1460, 1286, 1286, 1198, 1149, 1041, 944, 764 cm^{-1}; MS (EI): 124 (M^+, 100), 94 (41), 81 (17).

3.4.2. 4-Methoxyphenol (2ac). The procedure described above was used to synthesize **2ac** from hydroquinone (6.00 g, 54.41 mmol), 2.5 M NaOH solution (27.2 mL, 68.01 mmol) and dimethylsulfate (6.86 g, 54.41 mmol). The crude product was triturated with hot petroleum ether (15×15 mL) and the combined organic fractions evaporated under vacuo to give white crystals (2.18 g, 32%), mp 53–55 °C, Lit[14]: mp 50–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.75 (s, 3H, CH_3), 4.58 (s, 1H, OH), 6.68–6.83 (AB system,[†] 4H, H_{Ar}); IR (NaCl, film): 3401, 2834, 2057, 1861, 1608, 1513, 1374, 123, 1102, 1032, 824, 733 cm^{-1}; MS (EI): 124 (M^+, 100), 109 (99), 81 (43), 57 (22).

3.5. General procedure for the synthesis of benzyloxyphenols 2bb and 2bc

Benzyl bromide (4.70 g, 27.5 mmol) was added dropwise to a stirred suspension of the corresponding benzenediol (55.0 mmol) and K_2CO_3 (3.80 g, 27.5 mmol) in acetone (50 mL) under argon atmosphere. The mixture was heated under reflux overnight, filtered and washed with water (2×15 mL). The organic solution was dried over Na_2SO_4, evaporated to dryness under reduced pressure and the crude product purified by column chromatography on silica gel.

3.5.1. 3-Benzyloxyphenol (2bb). Compound **2bb** was synthesized, using the general procedure described above, from resorcinol (6.05 g, 55.0 mmol) and benzyl bromide (4.70 g, 27.5 mmol) in the presence of K_2CO_3 (3.80 g, 27.5 mmol) in acetone (50 mL). The crude product was purified by column chromatography on silica gel using dichloromethane as eluant to give a viscous oil (4.27 g, 77%). Lit[15]: mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.72 (s, 1H, OH), 5.06 (s, 2H, ArCH_2), 6.43–6.48 (ddd, 1H, $J_{4/6,5}$=7.9 Hz, $J_{4,6}$=2.3 Hz, 4/6-H_{Ar}), 6.49–6.52 (dd, 1H, J=2.3 Hz, 2-H_{Ar}), 6.56–6.62 (ddd, 1H, $J_{4/6,5}$= 8.3 Hz, $J_{4,6}$=2.3 Hz, $J_{4/6,2}$=2.8 Hz, 4/6-H_{Ar}), 7.12–7.20 (dd, 1H, $J_{5,4/6}$=7.9 Hz, $J_{5,6/4}$=8.3 Hz, 5-H_{Ar}), 7.32–7.48 (m, 5H, CH_2Ph); IR (NaCl, film): 3388, 1596, 1491, 1285, 1148, 1026, 738 cm^{-1}; MS (FAB): 201 (MH^+, 15), 154 (100), 136 (83), 91 (52), 71 (82), 55 (93).

3.5.2. 4-Benzyloxyphenol (2bc). Compound **2bc** was synthesized, using the general procedure described above, from hydroquinone (6.05 g, 55.0 mmol) and benzyl bromide (4.70 g, 27.5 mmol) in the presence of K_2CO_3 (3.80 g, 27.5 mmol) in acetone (50 mL). The crude product was purified by column chromatography using hexane/diethyl ether as eluant to give white crystals (3.60 g, 65%), mp 118–122 °C (Lit.[16]: mp 119–120 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.42 (s, 1H, O*H*), 5.03 (s, 2H, ArCH_2), 6.78 (d, 2H, J_{AB}=9.1 Hz, 2×H_{Ar}), 6.88 (d, 2H, J_{AB}=9.1 Hz, 2×H_{Ar}), 7.30–7.47 (m, 5H, CH_2Ph); IR (NaCl, film): 3392, 2902, 1605, 1512, 1454, 1368, 1242, 1103, 1016, 820, 697 cm^{-1}; MS (EI): 200 (M^+, 34), 91 (100), 56 (31).

3.6. General procedure for the synthesis of methyl 3-(methoxyphenoxy)benzoates 3aa–3ad and methyl 3-(benzyloxyphenoxy)benzoates 3ba–3bc

To a stirred suspension of NaH (240 mg, 10 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL) the corresponding phenol **2aa**–**2bc** (10.0 mmol) was added. After 10 min methyl 3-bromobenzoate (1.075 g, 5.0 mmol) and CuCl (495 mg, 5.0 mmol) were added and the mixture heated at 160 °C for 6 h under argon atmosphere. The reaction mixture was cooled, ethyl acetate (100 mL) was added and the mixture washed with 1 M NaOH (3×50 mL), 5% aqueous citric acid (2×30 mL) and saturated NaCl solution (2×25 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel.

3.6.1. Methyl 3-(2-methoxyphenoxy)benzoate (3aa). Compound **3aa** was synthesized by the procedure described above from methyl 3-bromobenzoate (1.73 g, 8.05 mmol) and 2-methoxyphenol (**2aa**) (2.00 g, 16.11 mmol) in the presence of NaH (387 mg, 16.11 mmol) and CuCl (797 mg, 8.05 mmol) in anhydrous DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluant to give a colourless liquid (702 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.84 (s, 3H, CH_3OAr), 3.90 (s, 3H, COOCH_3), 6.86–7.06 (m, 3H, H_{Ar}), 7.14–7.22 (m, 2H, H_{Ar}), 7.34–7.41 (dd, 1H, J=7.9 Hz, H_{Ar}), 7.57–7.61 (dd, 1H, $J_{2,4}\approx J_{2,6}\approx 1.9$ Hz, 2-H), 7.71–7.76 (ddd, 1H, $J_{4/6,5}$=7.2 Hz, $J_{4,6}$=1.3 Hz, 4/6-H_{Ar}); IR (NaCl, film): 2952, 2837, 1721, 1581, 1500, 1445, 1276, 1219, 1113, 1025, 903, 752 cm^{-1}; MS (EI): 258 (M^+, 64), 227 (54), 95 (33), 83 (45), 73 (50), 69 (72), 57 (100). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.92; H, 5.56.

3.6.2. Methyl 3-(3-methoxyphenoxy)benzoate (3ab). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (1.17 mg, 5.46 mmol) and 3-methoxyphenol (**2ab**) (1.36 g, 10.92 mmol) in the presence of NaH (262 mg, 10.92 mmol) and CuCl (541 mg, 5.46 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) to give a yellow liquid (135 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.83 (s, 3H, CH_3OAr), 3.92 (s, 3H, COOCH_3), 6.57–6.63 (m, 2H, H_{Ar}), 6.67–6.74 (m, 1H, H_{Ar}), 7.20–7.30 (m, 2H, H_{Ar}), 7.38–7.46 (t, 1H, $J_{5,4}$=$J_{5,6}$=7.9 Hz, 5-H), 7.67–7.71 (dd, 1H, $J_{2,6}\approx J_{2,4}$=2.1 Hz, 2-H), 7.78–7.83 (ddd, 1H, $J_{4/6,5}$=7.9 Hz, $J_{4,6}$=2.6 Hz, 4/6-H); IR (NaCl, film): 2953, 1725, 1584, 1467, 1444, 1284, 1213, 1139, 993, 758 cm^{-1}; MS (EI): 258 (M^+, 100), 227 (36), 183 (25), 77 (57). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.65; H, 5.21.

[†] The outer lines of doublets are not seen.

3.6.3. Methyl 3-(4-methoxyphenoxy)benzoate (3ac). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (430 mg, 2.00 mmol) and 4-methoxyphenol (**2ac**) (496 mg, 4.00 mmol) in the presence of NaH (96 mg, 4 mmol) and CuCl (198 mg, 2.00 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluant to give a yellow liquid (130 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.83 (s, 3H, CH_3OAr), 3.90 (s, 3H, COOCH_3), 6.89–6.95 (d, 2H, J=9.4 Hz, H_{Ar}), 6.97–7.03 (d, 2H, J=9.1 Hz, H_{Ar}), 7.13–7.19 (ddd, 1H, $J_{4/6,5}$=7.9 Hz, $J_{4/6,2}\approx J_{4,6}$=2.1 Hz, 4/6-H), 7.35–7.41 (t, 1H, $J_{4/6,5}$=7.9 Hz, 5-H), 7.59–7.62 (dd, 1H, $J_{2,6}\approx J_{2,4}$=2.1 Hz, 2-H), 7.72–7.76 (m, 1H, 4/6-H); IR (NaCl, film): 3466, 2958, 1505, 1242, 1210, 1029, 835 cm^{-1}; MS (EI): 258 (M$^+$, 100), 243 (20), 227 (20), 215 (10). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.98; H, 5.40.

3.6.4. Methyl 3-(3,4,5-trimethoxyphenoxy)benzoate (3ad). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (1.84 g, 8.56 mmol) and 3,4,5-trimethoxyphenol (**2ad**) (3.15 g, 17.12 mmol) in the presence of NaH (410 mg, 17.12 mmol) and CuCl (847 mg, 8.56 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) to give white crystals (700 mg, 26%), mp=91–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.82 (s, 6H, 2×OCH_3), 3.87 (s, 3H, OCH_3), 3.93 (s, 3H, COOCH_3), 6.29 (s, 2H, 2′-H and 6′-H), 7.17–7.25 (dd, 1H, $J_{4/6,5}$=7.9 Hz, $J_{4/6,2}$=$J_{4,6}$=2.1 Hz, 4/6-H), 7.38–7.46 (t, 1H, $J_{4,5}$=$J_{5,6}$=7.9 Hz, 5-H), 7.63–7.70 (dd, 1H, $J_{2,4}$=$J_{2,6}$=2.1 Hz, 1H, 2-H), 7.75–7.83 (d, 1H, $J_{4/6,5}$=7.9 Hz, 4/6-H); IR (KBr): 3416, 2948, 1726, 1610, 1283, 1214, 1130 cm^{-1}; MS (FAB): 319 [(M+1)$^+$, 100], 154 (37), 136 (44), 91 (31), 81 (31), 73 (47), 69 (53), 55 (82). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.23; H, 5.80.

3.6.5. Methyl 3-(2-benzyloxyphenoxy)benzoate (3ba). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (1.50 g, 6.98 mmol) and 2-benzyloxyphenol (**2ba**) (2.79 g, 13.96 mmol) in the presence of NaH (335 mg, 13.96 mmol) and CuCl (691 mg, 6.98 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluant to give a viscous oil (313 mg, 13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.90 (s, 3H, COOCH_3), 5.08 (s, 2H, $ArCH_2$), 6.98–7.06 (dt, 1H, J=8.1, 1.9 Hz, H_{Ar}), 7.06–7.11 (dd, 1H, J=5.5, 1.9 Hz, H_{Ar}), 7.11–7.21 (m, 4H, H_{Ar}), 7.24–7.30 (m, 3H, H_{Ar}), 7.33–7.41 (t, 1H, J=7.9 Hz, H_{Ar}), 7.41–7.47 (m, 1H, H_{Ar}), 7.58–7.62 (dd, 1H, J=2.6, 1.5 Hz, 2-H), 7.71–7.77 (ddd, 1H, J=7.9, 1.3, 1.1 Hz, H_{Ar}); IR (NaCl, film): 2950, 1722, 1581, 1500, 1448, 1276, 1214, 1112, 903, 752 cm^{-1}; MS (EI): 334 (M$^+$, 100), 303 (45), 211 (36), 184 (53), 155 (13), 128 (27). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.60; H, 5.18.

3.6.6. Methyl 3-(3-benzyloxyphenoxy)benzoate (3bb). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (1.70 g, 7.91 mmol), 3-benzyloxyphenol (**2bb**) (3.17 g, 15.82 mmol), NaH (379 mg, 15.82 mmol) and CuCl (783 mg, 7.91 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluant to give a viscous oil (510 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.92 (s, 3H, $COOCH_3$), 5.05 (s, 2H, $ArCH_2$), 6.60–6.68 (m, 2H, H_{Ar}), 6.75–6.81 (dd, 1H, J=8.29, 2.3 Hz, H_{Ar}), 7.20–7.47 (m, 8H, H_{Ar}), 7.65–7.72 (m, 1H, H_{Ar}), 7.75–7.82 (m, 1H, H_{Ar}); IR (NaCl, film): 3033, 2951, 1724, 1584, 1485, 1444, 1285, 1211, 1138 cm^{-1}; MS (EI): 334 (M$^+$, 35), 303 (12), 128 (5), 91 (100), 65 (13). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.20; H, 5.20.

3.6.7. Methyl 3-(4-benzyloxyphenoxy)benzoate (3bc). The product was synthesized by the procedure described above from methyl 3-bromobenzoate (2.71 g, 12.6 mmol), 4-benzyloxyphenol (**2bc**) (5.05 g, 25.2 mmol), NaH (605 mg, 25.2 mmol) and CuCl (1.25 g, 12.6 mmol) in DMF (30 mL). The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluant to give white crystals (1.10 g, 26%), mp 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.91 (s, 3H, $COOCH_3$), 5.08 (s, 2H, $ArCH_2$), 7.00 (s, 4H, H_{Ar}), 7.14–7.21 (ddd, 1H, J=8.1, 2.6, 0.8 Hz, H_{Ar}), 7.32–7.51 (m, 6H, H_{Ar}), 7.59–7.64 (dd, 1H, J=1.9 Hz, H_{Ar}), 7.71–7.78 (ddd, 1H, J=7.5, 1.1 Hz, H_{Ar}); MS (EI): 334 (M$^+$, 53), 303 (10), 243 (12), 91 (100), 76 (13), 65 (11); IR (NaCl, film): 3478, 1637, 589 cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.68; H, 5.43.

3.7. General procedure for the synthesis of (3-(methoxyphenoxy)phenyl)methanols 4aa–4ad and [3-(4-benzyloxyphenoxy)phenyl]methanol (4ba)

Procedure A. To a solution of the corresponding methyl 3-(methoxyphenoxy)benzoate **3aa**–**3ad** (2.58 g, 10 mmol) in anhydrous tetrahydrofuran (5 mL), borane dimethylsulfide complex (1.52 g, 20 mL, 1 M solution in THF, 20 mmol) was added and the mixture heated overnight under reflux protected from ambient moisture. Saturated aqueous K_2CO_3 solution was added dropwise until CO_2 evolution was finished, when the mixture was heated for another 30 min under reflux. Ethyl acetate (100 mL) was added, the solution was washed with water (2×25 mL), dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo.

3.7.1. [3-(2-Methoxyphenoxy)phenyl]methanol (4aa). The product was synthesized by the general procedure described above from methyl 3-(2-methoxyphenoxy)benzoate (**3aa**) (1.00 g, 3.87 mmol) and borane dimethylsulfide complex (3.9 mL, 2 M solution in tetrahydrofuran, 7.80 mmol) in anhydrous tetrahydrofuran (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to produce a colourless liquid (759 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.68 (t, 1H, J=6.0 Hz, CH_2OH), 3.85 (s, 3H, OCH_3), 4.63–4.70 (d, 2H, J=5.7 Hz, $ArCH_2$), 6.85–6.91 (dd, 1H, $J_{3',4'}$ or $J_{5',6'}$=7.7 Hz, $J_{3',6'}$ or $J_{4',6'}$=2.6 Hz, 6′/3′-H), 6.94–7.06 (m, 4H, H_{Ar}), 7.06–7.09 (m, 1H, 2-H), 7.13–7.20 (ddd, 1H, $^3J\approx$8.0 Hz, $J_{6',4'}$ or $J_{3',5'}$=1.9 Hz, 1H, 5′/4′-H), 7.25–7.33 (t, 1H, $J_{4,5}$=$J_{5,6}$=7.9 Hz, 1H, 5-H); IR (NaCl, film): 3358, 2940, 1582, 1500, 1455, 1264, 1210, 1113, 1025, 933, 764 cm^{-1}; MS (EI): 230 (M$^+$, 100), 185 (18), 121 (46), 77 (39); HRMS: Calcd for $C_{14}H_{14}O_3$: 230.0943, Found: 230.0945. Anal. Calcd for $C_{14}H_{14}O_3\cdot 0.1H_2O$:[18] C, 72.46; H, 6.17. Found: C, 72.18; H, 6.06.

3.7.2. [3-(3-Methoxyphenoxy)phenyl]methanol (4ab). The product was synthesized by the procedure described above from methyl 3-(3-methoxyphenoxy)benzoate (**3ab**) (1.00 g, 3.87 mmol) and borane dimethylsulfide complex (3.9 mL, 2 M solution in tetrahydrofuran, 7.80 mmol) in anhydrous tetrahydrofuran (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to produce a colourless liquid (724 mg, 81.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.69 (t, 1H, J=5.6 Hz, CH_2OH), 3.82 (s, 3H, OCH_3), 4.50–4.70 (d, 2H, J=5.3 Hz, $ArCH_2$), 6.59–6.64 (m, 2H, 4′/6′-H, 2′-H), 6.66–6.72 (m, 1H, 4′/6′-H), 6.94–6.99 (dd, 1H, $J_{4/6,5}$=7.7 Hz, $J_{4,6}$=2.4 Hz, 4/6-H), 7.06 (s, 1H, 2-H), 7.10–7.16 (d, 1H, J=7.9 Hz, 4/6-H), 7.20–7.30 (dd, 1H, $J_{5',4'} \approx J_{5',6'}$=8.5 Hz, 5′-H), 7.30–7.38 (t, 1H, $J_{5,4} \approx J_{5,6}$= 7.7 Hz, 5-H); IR (NaCl, film): 3361, 2934, 1591, 1471, 1259, 1153, 1034 cm^{-1}; MS (EI): 230 (M^+, 100), 213 (15), 92 (63), 77 (25), 63 (14); MS (FAB): 231 (MH^+, 100), 213 (89), 201 (25), 149 (36), 69 (30), 57 (54). HRMS: Calcd for $C_{14}H_{14}O_3$: 230.0943. Found: 230.0950.

3.7.3. [3-(4-Methoxyphenoxy)phenyl]methanol (4ac). The product was synthesized by the procedure described above from methyl 3-(4-methoxyphenoxy)benzoate (**3ac**) (467 mg, 1.81 mmol) and borane dimethylsulfide complex (1.8 mL, 2 M solution in tetrahydrofuran, 3.6 mmol) in anhydrous tetrahydrofuran (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a colourless liquid (364 mg, 87.4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.72 (br s, 1H, CH_2OH), 3.83 (s, 3H, OCH_3), 4.67 (s, 2H, $ArCH_2$), 6.85–6.94 (m, 3H, H_{Ar}), 6.96–7.02 (m, 3H, H_{Ar}), 7.03–7.08 (d, 1H, $J_{4/6,5}$=7.9 Hz, 4/6-H), 7.26–7.34 (t, 1H, $J_{4,5} \approx J_{5,6} \approx$7.9 Hz, 5-H); IR (NaCl, film): 3354, 2940, 1584, 1487, 1446, 1264, 1151, 1041 cm^{-1}; MS (EI): 230 (M^+, 100), 215 (13), 89 (24), 77 (21); HRMS: Calcd for $C_{14}H_{14}O_3$: 230.0943. Found: 230.0950. Anal. Calcd for $C_{14}H_{14}O_3 \cdot 0.2H_2O$:[18] C, 71.90; H, 6.21. Found: C, 72.03; H, 6.36.

3.7.4. [3-(3,4,5-Trimethoxyphenoxy)phenyl]methanol (4ad). The product was synthesized by the procedure described above from methyl 3-(3,4,5-trimethoxy)phenoxy benzoate (**3ad**) (544 mg, 1.71 mmol) and borane dimethylsulfide complex (1.71 mL, 2 M solution in tetrahydrofuran, 3.42 mmol) in anhydrous tetrahydrofuran (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (7/3) as eluant to give white crystals (400 mg, 81%), mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.60 (s, 1H, OH), 3.81 (s, 6H, 2×CH_3O), 3.86 (s, 3H, CH_3O), 4.71 (s, 2H, CH_2OH), 6.30 (s, 2H, 2′-H, 6′-H), 6.91–6.97 (dd, 1H, $J_{4/6,5}$=7.7 Hz, $J_{4,6}$=2.5 Hz, 4/6-H), 7.01–7.06 (s, 1H, 2-H), 7.08–7.13 (d, 1H, $J_{4/6,5}$= 7.7 Hz, 4/6-H), 7.29–7.38 (t, 1H, J=7.7 Hz, 5-H); IR (KBr): 3340, 1595, 1506, 1448, 1226, 1135, 999 cm^{-1}; MS (FAB): 291 (M+1, 100), 275 (19), 55 (19), 154 (12), 136 (10), 77 (7), 71 (12). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.29; H, 6.31.

3.7.5. [3-(4-Benzyloxyphenoxy)phenyl]methanol (4bc). The product was synthesized by the procedure described above from methyl 3-(4-benzyloxyphenoxy)benzoate (**3bc**) (548 mg, 1.64 mmol) and borane dimethylsulfide complex (1.65 mL, 2 M solution in tetrahydrofuran, 3.3 mmol) in anhydrous tetrahydrofuran (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a colourless liquid (250 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.64 (t, 1H, J=6.0 Hz, OH), 4.68 (d, 2H, J=6.0 Hz, CH_2OH), 5.08 (s, 2H, $ArCH_2OAr$), 6.87–6.93 (dd, 1H, J=7.7, 2.1 Hz, H_{Ar}), 6.99 (s, 4H, H_{Ar}), 7.04–7.09 (d, 1H, J=6.8 Hz, H_{Ar}), 7.29–7.50 (m, 7H, H_{Ar}); IR (KBr): 3415, 1719, 1617, 1504, 1241, 1104, 1012, 837, 741, 696 cm^{-1}; MS (EI): 306 (M^+, 61), 215 (35), 91 (100), 77 (19); HRMS: Calcd for $C_{20}H_{18}O_3$: 306.1256, Found: 306.1260.

3.8. General procedure for the synthesis of (3-(methoxyphenoxy)phenyl)methanols 4aa–4ad by coupling of methoxyphenols 2aa–2ad with 3-bromobenzyl alcohol

Procedure B. To a stirred suspension of NaH (240 mg, 10 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL) the corresponding phenol **2aa**–**2ad** (10.0 mmol) was added. After 10 min 3-bromobenzyl alcohol (935 mg, 5.0 mmol) and CuCl (495 mg, 5.0 mmol) were added and the mixture heated at 160 °C for 6 h under argon atmosphere. The reaction mixture was cooled, ethyl acetate (100 mL) was added and the mixture was washed with 1 M NaOH (3×50 mL), 5% aqueous citric acid (2×30 mL) and saturated NaCl solution (2×25 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel.

3.8.1. [3-(2-Methoxyphenoxy)phenyl]methanol (4aa). Compound **4aa** was synthesized using Procedure B from 3-bromobenzyl alcohol (754 mg, 4.03 mmol), guaiacol (**2aa**) (1.00 g, 8.06 mmol), NaH (193 mg, 8.06 mmol) and CuCl (399 mg, 4.03 mmol) in *N*,*N*-dimethylformamide (20 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (1/1) as eluant to give a colourless liquid (379 mg, 41%), which was identical by ^{1}H NMR and IR to **4aa** obtained by Procedure A.

3.8.2. [3-(3-Methoxyphenoxy)phenyl]methanol (4ab). Compound **4ab** was synthesized using Procedure B from 3-bromobenzyl alcohol (1.60 g, 8.55 mmol), 3-methoxyphenol (**2ab**) (2.12 g, 17.10 mmol), NaH (410 mg, 17.10 mmol) and CuCl (846 mg, 8.55 mmol) in DMF (30 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (1/1) as eluant to give a colourless liquid (693 mg, 35%), which was in all respects (^{1}H NMR, IR) identical to **4ab** obtained by Procedure A.

3.8.3. [3-(4-Methoxyphenoxy)phenyl]methanol (4ac). Compound **4ac** was synthesized using Procedure B from 3-bromobenzyl alcohol (1.00 g, 5.35 mmol), 4-methoxyphenol (**2ac**) (1.33 g, 10.70 mmol), NaH (257 mg, 10.70 mmol) and CuCl (530 mg, 5.35 mmol) in *N*,*N*-dimethylformamide (20 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (1/1) as eluant to give colourless liquid (464 mg, 37.7%), which was identical by ^{1}H NMR and IR to **4ac** obtained by Procedure A.

3.8.4. [3-(3,4,5-Trimethoxyphenoxy)phenyl]methanol (4ad). Compound **4ad** was synthesized using Procedure B from 3-bromobenzyl alcohol (500 mg, 2.67 mmol), 3,4,5-

trimethoxyphenol (**2ad**) (984 mg, 5.34 mmol), NaH (128 mg, 5.34 mmol) and CuCl (264 mg, 2.67 mmol) in DMF (10 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3/7) as eluant to give a colourless liquid (347 mg, 45%), which was identical by ^{1}H NMR and IR to **4ad** obtained by Procedure A.

3.9. General procedure for the synthesis of 3-(trityloxyphenoxy)phenyl methanols 4ca–4cc

A solution of methyl 3-(trityloxyphenoxy)benzoate **6a–6c** (486 mg, 1 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (40 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature. The mixture was stirred for 2 h whereupon water (25 mL) was added and the mixture was filtered. The solution was extracted with ethyl acetate (2×25 mL), the combined organic solutions were washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered and evaporated in vacuo.

3.9.1. 3-(2-Trityloxyphenoxy)phenylmethanol (4ca). The product was synthesized using the general procedure described above from methyl 3-(2-trityloxyphenoxy)benzoate (**6a**) (340 mg, 0.70 mmol) and $LiAlH_4$ (27 mg, 0.70 mmol) in anhydrous tetrahydrofuran (10 mL). The crude product was purified by column chromatography on basic aluminium oxide using ethyl acetate/hexane (1/1) as eluant to give a viscous liquid (176 mg, 55%), which was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.58 (t, 1H, J=6.0 Hz, CH_2OH), 4.64 (d, 2H, J=6.0 Hz, CH_2OH), 6.64–6.68 (dd, 1H, J=8.3 Hz, J=1.9 Hz, H_{Ar}), 6.70–6.88 (m, 4H, H_{Ar}), 6.94–6.98 (dd, 1H, J=7.9, 1.70 Hz, H_{Ar}), 7.01–7.06 (br d, 1H, J=8.2 Hz, H_{Ar}), 7.15–7.36 (m, 16H, H_{Ar}); IR (NaCl, film): 3418, 3055, 1615, 1489, 1446, 1260, 1108, 697 cm^{-1}; MS (EI): 243 [$(CPh_3)^+$, 100], 228 (11), 198 (14), 165 (50), 115 (7), 89 (6), 77 (8). Anal. Calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.72. Found: C, 83.89; H, 5.79.

3.9.2. 3-(3-Trityloxyphenoxy)phenylmethanol (4cb). The product was synthesized with the procedure described above from methyl 3-(3-trityloxyphenoxy)benzoate (**6b**) (1000 mg, 2.06 mmol) and $LiAlH_4$ (78 mg, 2.06 mmol) in anhydrous tetrahydrofuran (25 mL). The crude product was purified by column chromatography on basic aluminium oxide using ethyl acetate/hexane (1/1) as eluant to give a viscous liquid (700 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.60 (br s, 1H, OH), 4.63 (s, 2H, CH_2OH), 6.34–6.39 (t, 1H, J=2.2 Hz, H_{Ar}), 6.47–6.58 (m, 2H, H_{Ar}), 6.61–6.68 (dd, 1H, J=7.9, 1.9 Hz, H_{Ar}), 6.83 (br s, 1H, H_{Ar}), 6.94–7.02 (t, 1H, J=8.1 Hz, H_{Ar}), 7.04–7.10 (d, 1H, J=8.3 Hz, H_{Ar}), 7.19–7.35 (m, 10H, H_{Ar}), 7.42–7.52 (m, 6H, H_{Ar}); IR (NaCl, film): 3345, 3059, 2873, 1706, 1584, 1480, 1448, 1262, 1148, 1008, 758, 634 cm^{-1}; MS (EI): 458 (0.25, M^+), 306 (1), 243 (100), 228 (9), 215 (6), 165 (42). Anal. Calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.72. Found: C, 83.73; H, 5.88.

3.9.3. 3-(4-Trityloxyphenoxy)phenylmethanol (4cc). The product was synthesized using the procedure described above from methyl 3-(4-trityloxyphenoxy)benzoate (**6c**) (350 mg, 0.72 mmol) and $LiAlH_4$ (27 mg, 0.72 mmol) in anhydrous tetrahydrofuran (7 mL). The crude product was purified by column chromatography on basic aluminium oxide using ethyl acetate/hexane (1/1) as eluant to give white crystals (267 mg, 81%), mp 113–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 (s, 1H, OH), 4.64 (s, 2H, $-CH_2$OH), 6.66 (s, 4H, H_{Ar}), 6.74–6.80 (dd, 1H, J=8.1, 2.1 Hz, H_{Ar}), 6.84 (br s, 1H, H_{Ar}), 7.00–7.07 (d, 1H, J=7.5 Hz, H_{Ar}), 7.21–7.35 (m, 10H, H_{Ar}), 7.44–7.52 (m, 6H, H_{Ar}); IR (KBr): 3576, 3417, 3059, 1588, 1495, 1443, 1255, 1200, 1012, 963, 742, 694, 634 cm^{-1}; MS (EI): 458 (M^+, 0.25), 379 (0.20), 243 (100), 228 (10), 216 (15), 165 (35). Anal. Calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.72. Found: C, 83.53; H, 5.72.

3.10. General procedure for preparation of methyl 3-(hydroxyphenoxy)benzoates (5a–5c) by catalytic hydrogenation of methyl 3-(benzyloxyphenoxy)benzoates 3ba–3bc

A solution of the corresponding methyl 3-(benzyloxyphenoxy)benzoate **3ba–3bc** (1.67 g, 5 mmol) in methanol (40 mL) was hydrogenated over 10% Pd/C (167 mg) overnight. The solution was filtered and evaporated in vacuo.

3.10.1. Methyl 3-(2-hydroxyphenoxy)benzoate (5a). Following the general procedure described above, compound **5a** was synthesized from methyl 3-(2-benzyloxyphenoxy)-benzoate (**3ba**) (198 mg, 0.59 mmol) and 10% Pd/C (20 mg) in methanol (5 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give white crystals (130 mg, 90%), mp=107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.93 (s, 3H, OCH_3), 5.54 (s, 1H, OH), 6.84–6.95 (m, 2H, H_{Ar}), 7.04–7.12 (m, 2H, H_{Ar}), 7.20–7.27 (ddd, 1H, $J_{3',4'}$/$J_{5',6'}$=8.3 Hz, $J_{3',5'}$/$J_{4',6'}$=2.6 Hz, $J_{3',6'}$=1.1 Hz, 3′/6′-H), 7.38–7.50 (dd, 1H, J=7.9 Hz, H_{Ar}), 7.65–7.68 (dd, 1H, $J_{2,4}$=2.5 Hz, $J_{2,5}$=1.5 Hz, 2-H), 7.77–7.86 (md, 1H, J=7.9 Hz, H_{Ar}); IR (KBr): 3362, 1702, 1498, 1309, 1215, 1106, 756 cm^{-1}; MS (EI): 244 (M^+, 73), 212 (100), 184 (42), 128 (25), 76 (16). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.94; H, 5.09.

3.10.2. Methyl 3-(3-hydroxyphenoxy)benzoate (5b). Following the general procedure described above, compound **5b** was synthesized from methyl 3-(3-benzyloxyphenoxy)-benzoate (**3bb**) (1.12 g, 3.34 mmol) and 10% Pd/C (112 mg) in methanol (25 mL) to give a yellow viscous oil (751 mg, 92%), which required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.92 (s, 3H, OCH_3), 4.9 (br s, 1H, OH), 6.49–6.53 (m, 1H, H_{Ar}), 6.57–6.65 (m, 2H, H_{Ar}), 7.18–7.27 (m, 2H, H_{Ar}), 7.39–7.46 (t, 1H, J=7.9 Hz, H-5/5′), 7.68–7.72 (m, 1H, H_{Ar}), 7.78–7.84 (m, 1H, H_{Ar}); IR (NaCl, film): 3399, 1702, 1586, 1483, 1445, 1282, 1215, 1137 cm^{-1}; MS (EI): 244 (M^+, 100), 213 (90), 185 (42), 157 (43), 149 (72), 128 (42), 76 (24). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.71; H, 4.99.

3.10.3. Methyl 3-(4-hydroxyphenoxy)benzoate (5c). Following the general procedure described above, compound **5c** was synthesized from methyl 3-(4-benzyloxyphenoxy)-benzoate (**3bc**) (1.47 g, 4.40 mmol) and 10% Pd/C (147 mg) in methanol (20 mL). The procedure gave a pure

product as white crystals (729 mg, 68%), mp 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.91 (s, 3H, OCH_3), 4.85 (br s, 1H, OH), 6.82–6.99 (AB system, 4H, J_{AB}=9.1 Hz, H-2′,3′,5′,6′), 7.14–7.21 (dd, 1H, $J_{4,5}/J_{5,6}$=7.9 Hz, $J_{4,6}\approx J_{2,4}\approx J_{2,6}$=2.6 Hz, H-4/6), 7.34–7.43 (t, 1H, J=7.9 Hz, H-5), 7.57–7.63 (m, 1H, 2-H), 7.71–7.77 (d, 1H, J=7.9 Hz, H-4/6); IR (KBr): 3367, 1698, 1583, 1507, 1440, 1311, 1215, 1098, 754 cm^{-1}; MS (EI): 244 (M^+, 100), 213 (48), 185 (15), 157 (29), 128 (16), 109 (17), 76 (21). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.82; H, 4.95.

3.11. General procedure for the synthesis of methyl 3-(trityloxyphenoxy)benzoates 6a–6c by tritylation of methyl 3-(hydroxyphenoxy)benzoates 5a–5c

A solution of 3-(hydroxyphenoxy)benzoate **6a**–**6c** (244 mg, 1 mmol), trityl chloride (279 mg, 1 mmol) and triethylamine (202 mg, 2 mmol) in dichloromethane (10 mL) was stirred for 1 h at room temperature. The reaction mixture was diluted with dichloromethane (40 mL), washed successively with water (2×25 mL) and saturated NaCl solution (25 mL), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude product was passed through a short basic aluminium oxide column and used immediately in the next step without further purification.

3.11.1. Methyl 3-(2-trityloxyphenoxy)benzoate (6a). Compound **6a** was prepared from methyl 3-(2-hydroxyphenoxy)benzoate (**5a**) (325 mg, 1.33 mmol), trityl chloride (371 mg, 1.33 mmol) and triethylamine (269 mg, 2.66 mmol) in dichloromethane (12 mL) using the general procedure described above. The crude product was purified by column chromatography on basic aluminium oxide using hexane/ethyl acetate (6/1) as eluant to give a viscous oil (610 mg, 94%), which was used immediately without purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.93 (s, 3H, OCH_3), 6.63–6.70 (dd, 1H, J=8.2, 1.6 Hz, H_{Ar}), 6.72–6.80 (dt, 1H, J=7.8, 1.9 Hz, H_{Ar}), 6.80–6.89 (dt, 1H, J=7.6, 1.6 Hz, H_{Ar}), 6.94–7.00 (dd, 1H, J=7.9, 1.9 Hz, H_{Ar}), 7.03–7.10 (ddd, 1H, J=8.1, 2.6, 0.9 Hz, H_{Ar}), 7.16–7.24 (m, 9H, H_{Ar}), 7.25–7.40 (m, 6H, H_{Ar}), 7.40–7.49 (m, 1H, H_{Ar}), 7.49–7.53 (dd, 1H, J=2.5, 1.7 Hz, H_{Ar}), 7.70–7.76 (td, 1H, J=7.8, 1.1 Hz, H_{Ar}); IR (NaCl, film): 3452, 3060, 1716, 1603, 1491, 1445, 1272, 1097, 994, 757 cm^{-1}; MS (EI): 243 [(M-CPh_3, CPh_3)$^+$, 100], 212 (12), 183 (17), 165 (41), 110 (69), 92 (10), 77 (19), 64 (27).

3.11.2. Methyl 3-(3-trityloxyphenoxy)benzoate (6b). Compound **6b** was prepared from methyl 3-(3-hydroxyphenoxy)benzoate (**5b**) (732 mg, 3.00 mmol), trityl chloride (837 mg, 3.00 mmol) and triethylamine (606 mg, 6.00 mmol) in dichloromethane (30 mL) using the procedure described above. The crude product was purified by column chromatography on basic aluminium oxide using hexane/dichloromethane (1/1) as eluant to give a viscous oil (940 mg, 64%), which was used immediately without purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.93 (s, 3H, OCH_3), 6.27–6.33 (m, 1H, H-2/H-2′), 6.46–6.52 (ddd, 1H, J=8.2, 2.4, 0.9 Hz, H_{Ar}), 6.52–6.58 (ddd, 1H, J=8.3, 2.4, 0.9 Hz, H_{Ar}), 6.86–6.92 (ddd, 1H, J=8.2, 2.5, 1.0 Hz, H_{Ar}), 6.94–7.02 (t, 1H, J=8.1 Hz, H_{Ar}), 7.16–7.35 (m, 10H, H_{Ar}), 7.39–7.46 (m, 6H, Ar-H), 7.47–7.50 (dd, 1H, J_1=2.4 Hz, J_2=1.7 Hz, H_{Ar}), 7.71–7.77 (m, 1H, H_{Ar}); IR (NaCl, film): 3059, 2950, 1720, 1583, 1479, 1444, 1278, 1208, 1132, 1006, 757, 704 cm^{-1}; MS (EI): 486 (M^+, 0.2), 455 (0.2), 409 (1.5), 391 (2.5), 259 (2), 243 (100), 165 (12), 154 (5).

3.11.3. Methyl 3-(4-trityloxyphenoxy)benzoate (6c). Compound **6c** was prepared from methyl 3-(4-hydroxyphenoxy)benzoate (**5c**) (669 mg, 2.74 mmol), trityl chloride (764 mg, 2.74 mmol) and triethylamine (553 mg, 5.48 mmol) in dichloromethane (25 mL) using the procedure described above. The crude product was purified by column chromatography on basic aluminium oxide using hexane/ethyl acetate (10/1) as eluant to give white crystals (1.04 g, 78%), mp= 39–42 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.91 (s, 3H, OCH_3), 6.66 (s, 4H, H_{Ar}), 7.02–7.07 (ddd, 1H, J=8.2, 2.6, 1.0 Hz, H_{Ar}), 7.21–7.38 (m, 10H, H_{Ar}), 7.44–7.52 (m, 7H, H_{Ar}), 7.68–7.73 (td, 1H, J=7.7, 1.2 Hz, H_{Ar}); IR (KBr): 3414, 1720, 1581, 1498, 1300, 1215, 1076, 991, 706 cm^{-1}; MS (EI): 486 (M^+, 20), 368 (24), 149 (21), 101 (27), 86 (100), 69 (61), 57 (94). Anal. Calcd for $C_{33}H_{26}O_4\cdot 0.33H_2O$: C, 80.47; H, 5.46. Found: C, 80.37; H, 5.74.

3.12. General procedure for the synthesis of *O*-protected phosphonates 7aa–7cc and compound 10

A solution of (3-phenoxy)phenylmethanol **4aa**–**4cc** (1.0 mmol), ethyl hydrogen butylphosphonate (249 mg, 1.5 mmol), BOP (473 mg, 1.07 mmol) and triethylamine (404 mg, 4 mmol) in anhydrous *N*,*N*-dimethylformamide (2 mL) was stirred at room temperature overnight. Ethyl acetate (100 mL) was added and the obtained solution washed with 10% citric acid (3×25 mL), saturated $NaHCO_3$ solution (2×25 mL) and saturated NaCl solution (2×25 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was purified by column chromatography.

3.12.1. Ethyl 3-(2-methoxyphenoxy)benzyl butylphosphonate (7aa). The product was synthesized using the general procedure described above from methyl 3-(2-methoxyphenoxy)phenylmethanol (**4aa**) (156 mg, 0.68 mmol), ethyl hydrogen butylphosphonate (169 mg, 1.02 mmol), BOP (323 mg, 0.73 mmol) and triethylamine (275 mg, 2.72 mmol) in DMF (2 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (7/3) as eluant to give a viscous orange liquid (200 mg, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.84 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.19 (t, 3H, J=6.9 Hz, CH_3CH_2O), 1.26–1.46 (m, 4H, $CH_3CH_2CH_2$), 1.63–1.78 (m, 2H, CH_2CH_2P), 3.73 (s, 3H, CH_3O), 3.85–4.00 (m, 2H, CH_3CH_2O), 4.90 (d, 1H, J_{AB}=13.0 Hz, $ArCH_AO$), 4.98 (d, 1H, J_{AB}=13.0 Hz, $ArCH_BO$), 6.77–6.82 (d, 1H, J=7.5 Hz, H_{Ar}), 6.82–6.86 (s, 1H, 2-H), 6.94–7.01 (m, 3H, H_{Ar}), 7.15–7.27 (m, 2H, H_{Ar}), 7.29–7.35 (t, 1H, $J_{5,4}$=$J_{5,6}$=7.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5, 16.4 (d, $^3J_{PC}$=6.0 Hz), 23.6 (d, $^3J_{PC}$=17.3 Hz), 24.4 (d, $^2J_{PC}$=5.3 Hz), 25.5 (d, $^1J_{PC}$= 139.4 Hz), 55.9, 61.5 (d, $^2J_{PC}$=6.6 Hz), 66.4 (d, $^2J_{PC}$=6.1 Hz), 112.9, 116.0, 116.7, 121.1, 121.3, 121.4, 125.1, 129.6, 138.4 (d, $^3J_{PC}$=6.1 Hz), 144.7, 151.5, 158.3; ^{31}P NMR (121 MHz, DMSO-d_6) δ (ppm): 33.8 (s); IR (NaCl, film): 2958, 1582, 1500, 1457, 1265, 1210, 1025, 942, 746 cm^{-1}; MS (FAB): 379 (MH^+, 75), 213 (100), 154

(25), 71 (30), 57 (34). Anal. Calcd for $C_{20}H_{27}O_5P$: C, 63.48; H, 7.19. Found: C, 63.31; H, 7.44.

3.12.2. Ethyl 3-(3-methoxyphenoxy)benzyl butylphosphonate (7ab). The product was synthesized using the general procedure described above from methyl 3-(3-methoxyphenoxy)phenylmethanol (**4ab**) (331 mg, 1.44 mmol), ethyl hydrogen butylphosphonate (358 mg, 2.16 mmol), BOP (681 mg, 1.54 mmol) and triethylamine (582 mg, 5.76 mmol) in DMF (3 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (7/3) as eluant to give a viscous orange liquid (330 mg, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.84 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.18 (t, 3H, J=7.0 Hz, CH_3CH_2O), 1.27–1.50 (m, 4H, $CH_3CH_2CH_2$), 1.64–1.80 (m, 2H, CH_2CH_2P), 3.76 (s, 3H, CH_3O), 3.95–4.15 (m, 2H, CH_3CH_2O), 4.90 (d, 1H, J_{AB}=13.0 Hz, ArCH_AO), 4.97 (d, 1H, J_{AB}=13.0 Hz, ArCH_BO), 6.57–6.62 (m, 2H, 4′/6′-H_{Ar}, 2′-H_{Ar}), 6.95–7.10 (m, 3H, H_{Ar}), 7.15–7.28 (m, 2H, H_{Ar}), 7.32 (t, 1H, J=7.7 Hz, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5, 16.4 (d, $^3J_{PC}$=5.9 Hz), 23.6 (d, $^3J_{PC}$=17.4 Hz), 24.3 (d, $^2J_{PC}$=5.3 Hz), 25.5 (d, $^1J_{PC}$=139.4 Hz), 55.3, 61.5 (d, $^2J_{PC}$=6.7 Hz), 66.3 (d, $^2J_{PC}$=6.2 Hz), 105.1, 109.1, 111.1, 117.9, 118.6, 122.3, 129.9, 130.1, 138.7 (d, $^3J_{PC}$=6.2 Hz), 157.3, 158.1, 161.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.5 (s); IR (NaCl, film): 3460, 2959, 1585, 1488, 1448, 1251, 1154, 1044, 981 cm^{-1}; MS (EI): 378 (M$^+$, 100), 229 (33), 213 (83), 197 (32), 165 (33), 108 (50); HRMS: Calcd for $C_{20}H_{27}O_5P$: 378.1596. Found: 378.1592. Anal. Calcd for $C_{20}H_{27}O_5P\cdot0.5H_2O$:[18] C, 62.01; H, 7.28. Found: C, 62.03; H, 7.39.

3.12.3. Ethyl 3-(4-methoxyphenoxy)benzyl butylphosphonate (7ac). The product was synthesized using general procedure described above from methyl 3-(4-methoxy)phenoxy benzyl alcohol (**4ac**) (282 mg, 1.22 mmol), ethyl hydrogen butylphosphonate (304 mg, 1.83 mmol), BOP (579 mg, 1.31 mmol) and triethylamine (493 mg, 4.88 mmol) in DMF (3 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (7/3) to give a viscous orange liquid (303 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.85 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.17 (t, 3H, J=7.0 Hz, CH_3CH_2O), 1.27–1.50 (m, 4H, $CH_3CH_2CH_2$), 1.64–1.80 (m, 2H, CH_2CH_2P), 3.76 (s, 3H, CH_3O), 3.85–4.01 (m, 2H, CH_3CH_2O), 4.92 (d, 1H, J_{AB}=13.9 Hz, ArCH_AO), 4.98 (d, 1H, J_{AB}=13.9 Hz, ArCH_BO), 6.86–7.05 (m, 6H, H_{Ar}), 7.06–7.11 (d, 1H, $J_{4/6,5}$=7.9 Hz, 4/6-H_{Ar}), 7.32–7.39 (t, 1H, $J_{5,4}\approx J_{5,6}$=7.9 Hz, 5-H_{Ar}); ^{31}P NMR (121 MHz, DMSO-d_6) δ (ppm): 33.85 (s); IR (NaCl, film): 3466, 2958, 1505, 1242, 1210, 1029 cm^{-1}; MS (EI): 378 (M$^+$, 94), 213 (45), 167 (100), 139 (76), 103 (55), 87 (74), 74 (50), 61 (44), 55 (55); HRMS: Calcd for $C_{20}H_{27}O_5P$: 378.1596. Found: 378.1599. Anal. Calcd for $C_{20}H_{27}O_5P\times0.5H_2O$:[18] C, 62.01; H, 7.28. Found: C, 61.54; H, 7.36.

3.12.4. Ethyl 3-(3,4,5-trimethoxyphenoxy)benzyl butylphosphonate (7ad). The product was synthesized by the procedure described above from methyl 3-(3,4,5-trimethoxy)phenoxy benzyl alcohol (**4ad**) (302 mg, 1.04 mmol), ethyl hydrogen butylphosphonate (259 mg, 1.56 mmol), BOP (491 mg, 1.11 mmol) and triethylamine (420 mg, 4.16 mmol) in DMF (2 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (7/3) as eluant to give a viscous yellow liquid (344 mg, 75%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.84 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.18 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.28–1.52 (m, 4H, $CH_3CH_2CH_2$), 1.65–1.80 (m, 2H, CH_2CH_2P), 3.65 (s, 3H, CH_3O), 3.72 (s, 6H, 2×CH_3O), 3.90–4.02 (m, 2H, CH_3CH_2O), 4.94 (d, 1H, J_{AB}=13.0 Hz, ArCH_AO), 5.02 (d, 1H, J_{AB}=13.0 Hz, ArCH_BO), 6.38 (s, 2H, 2′-H, 6′-H), 6.94–6.99 (dd, 1H, $J_{4/6,5}\approx$7.6 Hz, $J_{2,4}=J_{2,6}$=1.9 Hz, 4/6-H), 7.00–7.04 (t, 1H, $J_{2,4}=J_{2,6}$=1.9 Hz, 2-H), 7.09–7.16 (d, 1H, J=7.5 Hz, 4/6-H), 7.34–7.42 (t, 1H, $J_{5,4}=J_{5,6}\approx$7.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.4 (d, $^4J_{PC}$=1.1 Hz), 16.3 (d, $^3J_{PC}$=6.0 Hz), 23.6 (d, $^3J_{PC}$=17.3 Hz), 24.3 (d, $^2J_{PC}$=5.3 Hz), 25.4 (d, $^1J_{PC}$=139.4 Hz), 56.0, 60.9, 61.5 (d, $^2J_{PC}$=6.5 Hz), 66.2 (d, $^2J_{PC}$=6.0 Hz), 97.1, 117.0, 117.7, 121.9, 129.8, 134.4, 138.6 (d, $^3J_{PC}$=6.2 Hz), 152.6, 153.8, 157.8; ^{31}P NMR (121 MHz, DMSO) δ (ppm): 33.9 (s); IR (NaCl, film): 2958, 1600, 1501, 1447, 1234, 1128, 1008, 784 cm^{-1}; MS (EI): 438 (M$^+$, 100), 273 (85), 149 (24), 69 (20), 55 (30); HRMS: Calcd for $C_{22}H_{31}O_7P$: 438.1807. Found: 438.1819. Anal. Calcd for $C_{22}H_{31}O_7P\times0.5H_2O$:[18] C, 59.05; H, 7.21. Found: C, 58.71; H, 7.38.

3.12.5. Ethyl 3-(4-benzyloxyphenoxy)benzyl butylphosphonate (7bc). The product was synthesized by the procedure described above from 3-(4-benzyloxy)phenoxy benzyl alcohol (**4bc**) (210 mg, 0.69 mmol), ethyl hydrogen butylphosphonate (172 mg, 1.03 mmol), BOP (328 mg, 0.74 mmol) and triethylamine (279 mg, 2.76 mmol) in DMF (2 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give viscous yellow liquid (249 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.89 (t, 3H, J=7.4 Hz, $CH_3CH_2CH_2$), 1.28 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.34–1.46 (m, 2H, $CH_3CH_2CH_2$), 1.49–1.65 (m, 2H, $CH_3CH_2CH_2$), 1.67–1.80 (m, 2H, CH_2CH_2P), 3.94–4.17 (m, 2H, CH_3CH_2O), 4.99–5.12 (2×AB system,[†] 4H, Ar-CH_2), 6.89–6.95 (dd, 1H, J=8.1, 1.5 Hz, H_{Ar}), 6.98 (s, 5H, CH_2Ph), 7.04–7.10 (d, 1H, J=7.5 Hz, H_{Ar}), 7.29–7.49 (m, 6H, H_{Ar}); ^{31}P NMR (121 MHz, DMSO-d_6) δ (ppm): 33.9 (s); IR (NaCl, film): 3412, 2958, 1503, 1242, 1206, 1021, 838 cm^{-1}; MS (FAB): 455 (MH$^+$, 24), 363 (30), 288 (40), 198 (13), 91 (100). Anal. Calcd for $C_{26}H_{31}O_5P\times1.25H_2O$:[18] C, 65.47; H, 7.08. Found: C, 65.13; H, 6.98.

3.12.6. Ethyl 3-(2-trityloxyphenoxy)benzyl butylphosphonate (7ca). The product was synthesized using the general procedure described above from 3-(2-trityloxy)phenoxy benzyl alcohol (**4ca**) (150 mg, 0.33 mmol), ethyl hydrogen butylphosphonate (823 mg, 0.49 mmol), BOP (155 mg, 0.35 mmol) and triethylamine (133 mg, 1.32 mmol) in DMF (1 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a viscous yellow liquid (142 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, J=7.4 Hz, $CH_3CH_2CH_2$), 1.27 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.31–1.47 (m, 2H, $CH_3CH_2CH_2$), 1.49–1.65 (m, 2H, $CH_3CH_2CH_2$), 1.67–1.82 (m, 2H, CH_2CH_2P), 3.94–4.17 (m, 2H, CH_3CH_2O), 4.98–5.06 (AB system,[†] 2H, Ar-CH_2), 6.63–6.69 (dd, 1H, J=8.1, 1.7 Hz, H_{Ar}), 6.70–6.75 (dd, 1H, J=7.4, 1.7 Hz, H_{Ar}), 6.75–6.88 (m, 3H, H_{Ar}), 6.90–6.96 (dd, 1H, J=7.7, 1.7 Hz, H_{Ar}), 7.03–7.10 (br d, 1H,

J=7.9 Hz, H_{Ar}), 7.16–7.34 (m, 16H, H_{Ar}); IR (NaCl, film): 2958, 1721, 1582, 1491, 1449, 1262, 1198, 1027, 704 cm^{-1}; MS (FAB): 605 [$(M-H)^+$, 0.3], 529 (2), 243 (100), 165 (12). Anal. Calcd for $C_{38}H_{39}O_5P$: C, 75.23; H, 6.48. Found: C, 75.05; H, 6.82.

3.12.7. Ethyl 3-(3-trityloxyphenoxy)benzyl butylphosphonate (7cb). The product was synthesized with the procedure described above from 3-(3-trityloxy)phenoxy benzyl alcohol (**4cb**) (320 mg, 0.70 mmol), ethyl hydrogen butylphosphonate (174 mg, 1.05 mmol), BOP (332 mg, 0.75 mmol) and triethylamine (283 mg, 2.8 mmol) in DMF (2 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a viscous yellow liquid (281 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.28 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.31–1.48 (m, 2H, $CH_3CH_2CH_2$), 1.50–1.67 (m, 2H, $CH_3CH_2CH_2$), 1.68–1.84 (m, 2H, CH_2CH_2P), 3.95–4.20 (m, 2H, CH_3CH_2O), 4.92–5.03 (AB system,† 2H, Ar-CH_2), 6.31–6.33 (t, 1H, J=2.3 Hz, H_{Ar}), 6.43–6.52 (m, 2H, H_{Ar}), 6.58–6.63 (dd, 1H, J=8.5, 2.1 Hz, H_{Ar}), 6.83 (br s, 1H, H_{Ar}), 6.90–7.08 (t, 1H, J=7.9 Hz, H_{Ar}), 7.03–7.11 (d, 1H, J=7.9 Hz, H_{Ar}), 7.15–7.31 (m, 10H, H_{Ar}), 7.38–7.43 (m, 6H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5, 16.4 (d, $^3J_{PC}$=6.0 Hz), 23.6 (d, $^3J_{PC}$=17.3 Hz), 24.4 (d, $^2J_{PC}$=5.3 Hz), 25.5 (d, $^1J_{PC}$=139.4 Hz), 61.5 (d, $^2J_{PC}$=6.7 Hz), 66.4 (d, $^2J_{PC}$=6.2 Hz), 91.1, 116.7, 117.3, 119.6, 121.5, 123.0, 127.2, 127.6, 129.1, 129.7, 138.4 (d, $^3J_{PC}$=6.1 Hz), 144.1, 150.7, 152.6, 158.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.47 (s); IR (NaCl, film): 3060, 2958, 2872, 1584, 1481, 1449, 1256, 1152, 1008, 105 cm^{-1}; MS (FAB): 605 [$(M-H)^+$, 0.5], 529 (2), 364 (2), 259 (2), 243 (100), 165 (15). Anal. Calcd for $C_{38}H_{39}O_5P$: C, 75.23; H, 6.48. Found: C, 74.98; H, 6.65.

3.12.8. Ethyl 3-(4-trityloxyphenoxy)benzyl butylphosphonate (7cc). The product was synthesized by the procedure described above from 3-(4-trityloxy)phenoxy benzyl alcohol (**4cc**) (350 mg, 0.76 mmol), ethyl hydrogen butylphosphonate (190 mg, 1.14 mmol), BOP (358 mg, 0.81 mmol) and triethylamine (307 mg, 3.04 mmol) in DMF (2 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a viscous yellow liquid (319 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.37 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.33–1.44 (m, 2H, $CH_3CH_2CH_2$), 1.50–1.62 (m, 2H, $CH_3CH_2CH_2$), 1.65–1.82 (m, 2H, CH_2CH_2P), 3.95–4.19 (m, 2H, CH_3CH_2O), 4.93 (d, 1H, J_{AB}=12.4 Hz, Ar-CH_2), 5.02 (d, 1H, J_{AB}=12.4 Hz, Ar-CH_2), 6.62 (s, 4H, H_{Ar}), 6.72–6.78 (dd, 1H, J=7.7, 2.1 Hz, H_{Ar}), 6.85 (br s, 1H, H_{Ar}), 7.00–7.04 (d, 1H, J=7.9 Hz, H_{Ar}), 7.19–7.32 (m, 10H, H_{Ar}), 7.42–7.48 (m, 6H, H_{Ar}); ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.45 (s); IR (NaCl, film): 3058, 2958, 2872, 1588, 1497, 1448, 1256, 1203, 1027, 960, 703 cm^{-1}; MS (FAB): 605 [$(M-H)^+$, 0.3], 529 (1), 441 (1), 364 (2), 259 (1), 243 (100), 165 (18). Anal. Calcd for $C_{38}H_{39}O_5P$: C, 75.23; H, 6.48. Found: C, 75.23; H, 6.56.

3.12.9. Ethyl 3-(3-(hydroxymethyl)phenoxy)phenyl butylphosphonate (10). The product was synthesized using the general procedure described above from 3-(3-(hydroxymethyl)phenoxy)phenol[17] (**9**) (367 mg, 1.70 mmol), ethyl hydrogen butylphosphonate (424 mg, 2.55 mmol), BOP (805 mg, 1.82 mmol) and triethylamine (687 mg, 6.8 mmol) in DMF (4 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1/1) as eluant to give a viscous orange liquid (386 mg, 62%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.84 (t, 3H, J=7.2 Hz, $CH_3CH_2CH_2$), 1.18 (t, 3H, J=7.0 Hz, CH_3CH_2O), 1.25–1.45 (m, 2H, $CH_3CH_2CH_2$), 1.45–1.60 (m, 2H, $CH_3CH_2CH_2$), 1.82–1.98 (m, 2H, CH_2CH_2P), 3.98–4.25 (m, 2H, CH_3CH_2O), 4.45–4.55 (d, 2H, J=5.6 Hz, CH_2OH), 5.23 (t, 1H, J=5.6 Hz, CH_2OH), 6.79–6.86 (m, 2H, H_{Ar}), 6.88–6.98 (m, 2H, H_{Ar}), 6.90–7.03 (br s, 1H, H_{Ar}), 7.10–7.15 (d, 1H, J=7.5 Hz, H_{Ar}), 7.32–7.42 (m, 2H, H_{Ar}); ^{31}P NMR (121 MHz, DMSO-d_6) δ (ppm): 33.9 (s); IR (NaCl, film): 2958, 1585, 1488, 1447, 1253, 1215, 1023, 691 cm^{-1}; MS (FAB): 365 [$(M+1)^+$, 20], 347 (100), 319 (40), 199 (20), 149 (35), 57 (34). Anal. Calcd for $C_{19}H_{25}O_5P$: C, 62.63; H, 6.92. Found: C, 62.40; H, 6.61.

3.13. General procedure for the synthesis of ethyl 3-(hydroxyphenoxy)benzyl butylphosphonates 8a–8c by deprotection of ethyl 3-(trityloxyphenoxy)benzyl butylphosphonates 7ca–7cc

A solution of the corresponding ethyl 3-(trityloxyphenoxy)-benzyl butylphosphonate **7ca–7cc** (606 mg, 1 mmol) in glacial acetic (20 mL) acid was heated at 56 °C for 7.5 h. The solution was evaporated and the crude product was purified by column chromatography on silica gel.

3.13.1. Ethyl 3-(2-hydroxyphenoxy)benzyl butylphosphonate (8a). Compound **8a** was obtained using the general procedure described above from ethyl 3-(2-trityloxyphenoxy) benzyl butylphosphonate (**7ca**) (100 mg, 0.165 mmol) in glacial acetic acid (5 mL). The crude product was purified by column chromatography using ethyl acetate as eluant to give a colourless liquid (49 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.89 (t, 3H, J=7.3 Hz, $CH_3CH_2CH_2$), 1.27 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.34–1.46 (m, 2H, $CH_3CH_2CH_2$), 1.48–1.65 (m, 2H, $CH_3CH_2CH_2$), 1.66–1.82 (m, 2H, CH_2CH_2P), 3.94–4.17 (m, 2H, CH_3CH_2O), 4.98 (d, 1H, J_{AB}=12.4 Hz, P–O–CH_2), 5.06 (d, 1H, J_{AB}=12.4 Hz, P–O–CH_2), 6.13 (br s, 1H, Ar-OH), 6.81–6.94 (m, 2H, H_{Ar}), 6.94–7.01 (dd, 1H, J=7.7, 2.1 Hz, H_{Ar}), 7.02–7.14 (m, 4H, H_{Ar}), 7.29–7.37 (t, 1H, J=7.9 Hz, H_{Ar}); ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.58 (s); IR (NaCl, film): 3164, 2959, 1585, 1460, 1241, 1024, 745 cm^{-1}; MS (FAB): 365 [$(M+1)^+$, 25], 199 (60), 147 (60), 69 (75), 57 (100); HRMS: Calcd for $C_{19}H_{26}O_5P$: 365.1518. Found: 365.1529.

3.13.2. Ethyl 3-(3-hydroxyphenoxy)benzyl butylphosphonate (8b). Compound **8b** was synthesized by the general procedure described above from ethyl 3-(3-trityloxyphenoxy)-benzyl butylphosphonate (**7cb**) (250 mg, 0.412 mmol) in glacial acetic acid (10 mL). The crude product was purified by column chromatography using ethyl acetate as eluant to give a colourless liquid (123 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.87 (t, 3H, J=7.3 Hz, $CH_3CH_2CH_2$), 1.26 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.33–1.41 (m, 2H, $CH_3CH_2CH_2$), 1.45–1.62 (m, 2H, $CH_3CH_2CH_2$), 1.65–1.81 (m, 2H, CH_2CH_2P), 3.90–4.16

(m, 2H, CH_3CH_2O), 4.92–5.01 (AB system,[†] 2H, Ar-CH_2), 6.50–6.56 (ddd, 1H, J=8.3, 2.3, 0.8 Hz, H_{Ar}), 6.55–6.59 (t, 1H, J=2.3 Hz, H_{Ar}), 6.62–6.67 (ddd, 1H, J=8.1, 2.3, 0.9 Hz, H_{Ar}), 6.96–7.08 (m, 3H, H_{Ar}), 7.11–7.18 (t, 1H, J=7.9 Hz, H_{Ar}), 7.27–7.32 (t, 1H, J=7.7 Hz, H_{Ar}), 8.07 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.4, 16.3 (d, $^3J_{PC}$=6.0 Hz), 23.6 (d, $^3J_{PC}$=17.4 Hz), 24.2 (d, $^2J_{PC}$=5.3 Hz), 25.3 (d, $^1J_{PC}$=139.5 Hz), 61.9 (d, $^2J_{PC}$=6.7 Hz), 66.7 (d, $^2J_{PC}$=6.3 Hz), 106.5, 110.3, 110.9, 117.9, 118.8, 122.1, 129.8, 130.1, 138.2 (d, $^3J_{PC}$=5.9 Hz), 157.5, 157.9, 158.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.54 (s); IR (NaCl, film): 3180, 2960, 1588, 1484, 1449, 1258, 1170, 1023, 970 cm^{-1}; MS (FAB): 365 [(M+1)$^+$, 41], 199 (100), 69 (24), 57 (41), 49 (29); HRMS: Calcd for $C_{19}H_{26}O_5P$: 365.1518. Found: 365.1510.

3.13.3. Ethyl 3-(4-hydroxyphenoxy)benzyl butylphosphonate (8c). Compound **8c** was synthesized by the general procedure described above from ethyl 3-(4-trityloxyphenoxy)benzyl butylphosphonate (**7cc**) (150 mg, 0.247 mmol) in glacial acetic acid (5 mL). The crude product was purified by column chromatography using ethyl acetate as eluant to obtain colourless liquid (65 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (t, 3H, J=7.4 Hz, $CH_3CH_2CH_2$), 1.30 (t, 3H, J=7.2 Hz, CH_3CH_2O), 1.34–1.47 (m, 2H, $CH_3CH_2CH_2$), 1.52–1.64 (m, 2H, $CH_3CH_2CH_2$), 1.69–1.84 (m, 2H, CH_2CH_2P), 3.95–4.17 (m, 2H, CH_3CH_2O), 4.99 (d, 1H, J_{AB}=12.4 Hz, P–O–CH_2), 5.06 (d, 1H, J_{AB}=12.4 Hz, P–O–CH_2), 6.79–6.94 (m, 6H, H_{Ar}, OH), 6.94–6.98 (br s, 1H, H_{Ar}), 7.02–7.08 (d, 1H, J=7.5 Hz, H_{Ar}), 7.24–7.34 (t, 1H, J=7.9 Hz, H_{Ar}); ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 34.67 (s); IR (NaCl, film): 3188, 2960, 2873, 1725, 1588, 1508, 1449, 1205, 1024, 841 cm^{-1}; MS (FAB): 365 [(M+1)$^+$, 30], 199 (85), 167 (15), 149 (49), 121 (15), 109 (24), 95 (43), 81 (45), 69 (73), 57 (100); HRMS: Calcd for $C_{19}H_{26}O_5P$: 365.1518. Found: 365.1510.

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