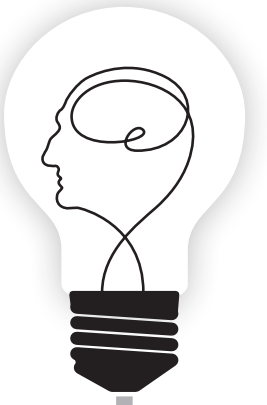
Appendices

I Building blocks for polyfluorinated bis-styrylbenzenes
II Samenvatting
III Dankwoord
IV Curriculum vitae
V Publication list



Synthesis of phosphonate building blocks

General synthetic procedures

All phosphonate building blocks were prepared according to the general synthesis scheme below (**Scheme I.1**) starting from either commercially available dimethylbenzenes, or dimethylbenzenes prepared according to literature procedures.

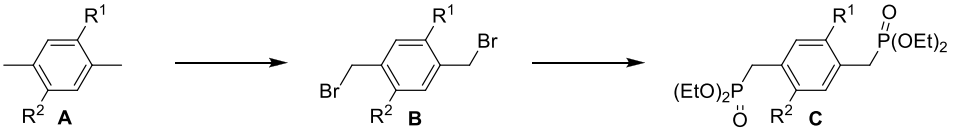
General procedure for bromination (A → B): To a solution of the dimethyl compound (10 mmol) in CCl_4 (22 ml) were added N-Bromosuccinimide (3.92 g, 22 mmol) and benzoyl peroxide (20 mg) and the mixture was heated to reflux for 16 h. After cooling to room temperature, the mixture was filtered over Celite, the filtrate concentrated and the residue applied to column chromatography (0 → 5% EtOAc/light petroleum) to yield the pure product.

General procedure for Arbuzov (B → C): To the dibromide (1 mmol) was added triethyl phosphite (0.42 ml, 2.5 mmol) and the mixture was heated to reflux (150 °C) for 16 h. After cooling to room temperature, the mixture was directly applied to a silica column (50% EtOAc/light petroleum → 10% MeOH/EtOAc) to yield the pure product.

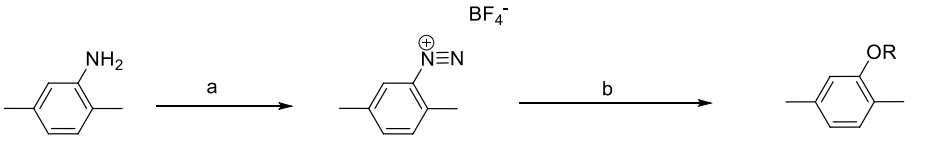
Synthesis of dimethylbenzene precursors

The dimethylbenzene precursors **40 - 42** for phosphonates **29**, **31** – **32** were not commercially available and were prepared from 2,5-dimethylaniline as depicted in **Scheme I.2**.

Diazonium salt **39** was prepared according to literature procedures.[1] To a solution of HBF_4 (50% in H_2O, 25.5 ml, 200 mmol) in water (25.5 ml), 2,5-dimethylaniline (12.5 ml, 100 mmol) was added and the reaction mixture was cooled to 0° C. A solution of $NaNO_2$ (6.9 g, 100 mmol) in water (6 ml) was added dropwise and the reaction mixture warmed to room temperature. The solids were filtered off and washed with 5% aq. HBF_4, EtOH and Et_2O and dried under vacuum. The resulting pinkish powder was dissolved in acetone and precipitated with Et_2O. After filtration, this procedure was repeated two times and after drying under vacuum, the product was



Scheme I.1 General procedure for preparation of phosphonates



40 R = CH_2CF_3
41 R = $CH(CF_3)_2$
42 R = $C(CF_3)_3$

Scheme I.2 Preparation of fluorinated dimethylbenzene precursors

Reagents and conditions: **a**) HBF_4, $NaNO_2$, H_2O, 0°C → rt, 47%. **b**) fluorinated alcohol, reflux, 18 h.

obtained as an off-white powder (10.4 g, 47.4 mmol, 47%). ^{1}H NMR (acetone-d6, 400 MHz): δ 8.54 (s, ^{1}H); 8.03 (d, *J* = 8.2 Hz, ^{1}H); 7.78 (d, *J* = 8.0 Hz, ^{1}H); 2.86 (s, 3H); 2.51 (s, 3H). IR (neat): 2275.8; 1506.6; 1303.6; 1210.7; 1029.3; 847.8; 521.4.

Fluorethers **40 – 42** were synthesized form diazonium salt **39** according to literature procedures.[1] Diazonium salt **39** (2.2 g, 10 mmol) was dissolved in the appropriate fluorous alcohol (25 ml) and the mixture was heated to reflux for 18 h. After cooling to room temperature, 2 N NaOH and Et_2O were added and the layers separated. The organic layer was dried (Na_2SO_4); filtered and concentrated (careful: product is volatile!). The crude product was purified by flash column chromatography (light petroleum) to yield the fluorous ether as a colorless fluid. As the products are volatile, care needs to be taken during evaporation after work-up and column chromatography.

Following the general procedure above, **40** was obtained from reaction of **39** with 2,2,2-trifluoroethanol as a colorless liquid (1.14 g, 5.6 mmol, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03 (d, *J* = 7.5 Hz, ^{1}H); 6.75 (d, *J* = 7.5 Hz, ^{1}H); 6.58 (s, ^{1}H); 4.30 (q, *J* = 8.2 Hz, *J* = 8.2 Hz, 2H); 2.31 (s, 3H); 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5; 136.8; 130.9; 124.9; 124.4; 122.8; 122.1; 112.8; 66.7; 66.3; 66.0; 65.6; 21.2; 15.4. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 3.36 (t, *J* = 8.1 Hz, 3F).

Compound **41** was obtained from reaction of **39** with 1,1,1,3,3,3-hexafluoroisopropanol as a colorless liquid (1.79 g, 6.6 mmol, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, *J* = 7.6 Hz, ^{1}H); 6.85 (d, *J* = 7.6 Hz, ^{1}H); 6.72 (s, ^{1}H); 4.91-4.80 (m, ^{1}H); 2.33 (s, 3H); 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6; 137.3; 131.4; 125.5; 124.7; 122.6; 122.6; 119.8; 114.6; 76.2; 75.9; 75.6; 21.2; 15.3. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 3.90 (d, *J* = 5.7 Hz, 6F). IR (neat): 1511.8; 1368.9; 1250.5; 1218.2; 1192.2; 1155.7; 1134.3; 1104.1; 886.8; 809.9; 686.2.

Following the general procedure above, **42** was obtained from reaction of **39** with nonafluoro-tert-butanol as a colorless liquid (2.22 g, 6.5 mmol, 65%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.00 (s, ^{1}H); 6.94 (d, *J* = 7.7 Hz, ^{1}H); 6.81 (d, *J* = 9.0 Hz, ^{1}H); 2.30 (s, 3H); 2.24 (s, 3H). ^{19}F NMR ($CDCl_3$, 375 MHz): δ 8.23 (s, 9F).

Synthesis of phosphonates 25 – 32

Phosphonate **25** was prepared as described previously.[2] 2,5-dimethylanisole (1.36 g, 10 mmol) was brominated according to the general procedure for bromination. The dibromide was obtained as white solid (1.71 g, 5.8 mmol, 58%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, *J* = 7.7 Hz, ^{1}H); 6.92 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, ^{1}H); 6.89 (s, ^{1}H); 4.52 (s, 2H); 4.44 (s, 2H); 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4; 139.7; 131.0; 126.3; 121.1; 111.5; 55.6; 33.2; 28.3.

The dibromide (1.71 g, 5.8 mmol) was subjected to the Arbuzov reaction according to the general procedure. The pure product was obtained as a yellowish solid (1.55 g, 3.8 mmol, 66%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (dd, *J* = 7.6 Hz, *J* = 2.9 Hz, ^{1}H); 6.86 (s, ^{1}H); 6.83 (d, *J* = 7.6 Hz, ^{1}H); 4.07-3.95 (m, 8H); 3.84 (s, ^{1}H); 3.21 (d, *J* = 21.4 Hz, 2H); 3.13 (d, *J* = 22.2 Hz, 2H); 1.27-1.20 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2; 131.5; 131.1; 121.9; 121.900; 118.85; 112.1; 55.5; 34.4; 33.0; 27.0; 25.6; 16.3. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 27.39 (d, *J* = 9.0 Hz), 26.77 (d, *J* = 9.1 Hz).

To synthesize phosphonate **26** 1,4-bis(chloromethyl)-2,5-dimethoxybenzene (0.24 g, 1 mmol) was added to triethyl phosphite (0.42 ml, 2.5 mmol) and the mixture was heated to reflux for 16 h. After cooling to room temparature, the solids were filtered off, washed with light petroleum

and dried under vacuum, yielding the pure product as a white solid (0.37 g, 0.85 mmol, 85%). ^{1}H NMR (CD_3OD, 400 MHz): δ 6.95 (d, *J* = 1.8 Hz, 2H); 4.03 (m, 8H); 3.82 (s, 6H); 3.24 (s, 2H); 3. 22 (s, 2H); 1.25 (t, *J* = 7.1 Hz, 12H). ^{13}C NMR (CD_3OD, 100 MHz): δ 152.5; 120.5; 115.3; 63.6; 56.6; 27.7; 26.3; 16.7. IR (neat): 1520.1; 1476.4; 1415.0; 1265.3; 1221.0; 1026.7; 963.8; 881.0; 837.8; 819.8; 768.0; 725.8; 700.2; 632.7; 518.4. LC-MS retention time: 6.70 min (10 → 90% MeCN, 13.5 min run). Mass (ESI): *m/z* 439.0 [M + H]+; 876.9 [2M + H]+. Exact mass: Calculated for $[C_{18}H_{33}O_8P_2]$+: 439.16452; $[C_{18}H_{32}O_8P_2]$+: 461.14646. Found: 439.16446 [M + H]+; 461.14583 [M + Na]+.

Phosphonate **27** was prepared as described previously.[2] 2,5-dimethylphenol (6.1 g, 50 mmol) was dissolved in DMF (30 ml), imidazole (3.4 g, 50 mmol) was added and the reaction mixture stirred for 10 min. Subsequently, TBDPS-Cl (15.6 ml, 60 mmol) was added. After stirring for 22 h, the mixture was poured out in water (250 mL) and the aqueous layer extraced three times with DCM. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The resulting yellow oil was purified by column chromatography (0 → 2% EtOAc/ light petroleum) to yield the pure product as a pale yellow oil (16.0 g, 44.3 mmol, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.64 (m, 4H); 7.45-7.33 (m, ^{1}H); 7.01 (d, *J* = 7.6 Hz, ^{1}H); 6.59 (d, *J* = 7.4 Hz, ^{1}H); 6.22 (s, ^{1}H); 2.33 (s, 3H); 1.94 (s, 3H); 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6; 150.2; 135.4; 133.1; 130.4; 129.8; 127.7; 121.4; 119.3; 26.6; 16.7.

The protected phenol (16.0 g, 44.3 mmol) was subjected to the general bromination procedure to yield the pure product as a white solid (9.2 g, 17.8 mmol, 40%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.66 (m, 4H); 7.47-7.35 (m, 6H); 7.29 (d, *J* = 7.8 Hz, ^{1}H); 6.85 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, ^{1}H); 6.39 (d, *J* = 1.7 Hz, ^{1}H); 4.69 (s, 2H); 4.04 (s, 2H); 1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.4; 131.1; 130.1; 130.0; 128.0; 121.7; 119.8; 32.7; 26.5; 26.5.

The dibromide (9.2 g, 17.8 mmol) was converted to the diphosphonate according to the general procedure and the pure product obtained as a viscous yellow oil (6.6 g, 10.4 mmol, 58%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.69 (m, 4H); 7.45-7.30 (m, 7H); 6.82 (d, *J* = 7.8 Hz, ^{1}H); 6.33 (s, ^{1}H); 4.16-3.98 (m, 8H); 3.39 (d, *J* = 21.7 Hz, 2H); 2.74 (d, *J* = 21.5 Hz, 2H); 1.11 (s, 9H); 1.26 (t, *J* = 7.1 Hz, 6H); 1.04 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1; 153.0; 135.3; 132.206; 131.2; 131.0; 129.9; 127.7; 122.4; 120.3; 120.3; 120.2; 120.2; 120.1; 120.0; 120.0; 120.0; 119.9; 61.7; 61.7; 61.7; 33.8; 32.5; 27.4; 26.4; 26.0; 16.4; 16.3; 16.2; 16.2. 31P NMR ($CDCl_3$, 162 MHz): δ 27.24 (d, *J* = 8.5 Hz); 25.77 (d, *J* = 8.5 Hz).

The dibromide precursor of **28** was prepared according to literature procedures.[3] To a solution of $NaBrO_3$ (0.15 g, 1 mmol) in water (0.5 ml), a solution of 4-methyl-3-trifluoromethyl benzyl bromide (0.13 g, 0.5 mmol, in EtOAc (1 ml) was added and the mixture stirred vigorously. A solution of $NaHSO_3$ (0.1 g, 1 mmol) in water (1 ml) was added dropwise and the deep-orange solution was stirred for 77 h. The mixture was poured out in Et_2O and the layers were separated. The aqueous layer was extracted two times with Et_2O and the combined organic layers were washed with 2 M $Na_2S_2O_3$, dried (Na_2SO_4); filtered and concentrated. The resulting brown oil was subjected to column chromatography (0 → 4% EtOAc/light petroleum) and the product was obtained as an off-white solid (0.11 g, 0.33 mmol, 66%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (s, ^{1}H); 7.58 (s, 2H); 4.61 (s, 2H); 4.48 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.5; 136.2; 133.3; 132.8; 126.7; 124.4; 122.3; 31.3; 27.8. IR (neat): 1319.7; 1297.0; 1224.7; 1197.7; 1169.2; 1144.5; 1122.0; 1055.7; 914.3; 908.2; 848.9; 776.2; 746.1; 667.7; 615.4;

583.4. The dibromide (0.96 g, 2.89 mmol) was treated with triethyl phosphite according to the general procedure, yielding diphosphonate **28** as a yellow oil (0.66 g, 1.47 mmol, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (dd, *J* = 7.9 Hz, *J* = 1.4 Hz, ^{1}H); 7.58 (s, ^{1}H); 7.47 (d, *J* = 8.0 Hz, ^{1}H); 4.09-3.98 (m, 8H); 3.35 (d, *J* = 22.6 Hz, 2H); 3.18 (d, *J* = 21.6 Hz, 2H); 1.25 (dd, *J* = 15.6 Hz, *J* = 7.1 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132.8; 132.3; 130.9; 128.8; 127.3; 125.2; 122.4; 62.1; 62.0; 33.7; 32.3; 30.3; 28.9; 16.1.
^{19}F NMR ($CDCl_3$, 375 MHz) δ 18.38 (s, 3F). IR (neat): 1320.6; 1246.7; 1145.4; 1118.5; 1047.3; 1019.5; 958.9; 898.9; 856.8; 819.1; 730.0; 667.8; 641.7; 589.0; 556.2; 522.4. LC-MS retention time: 7.34 min (10 → 90% MeCN, 13.5 min run). Mass (ESI): *m/z* 447.1 [M + H]+; 892.8 [2M + H]+. Exact mass: Calculated for [C17H28F3O6P2]+: 447.13077. Found: 447.13058 [M + H]+.
Following the general procedure for bromination, the dibromide was obtained from 40 (0.85 g, 4.18 mmol) as a yellow solid (0.64 g, 1.76 mmol, 42%).
^{1}H NMR ($CDCl_3$, 400 MHz): 7.35 (d, *J* = 7.7 Hz, ^{1}H); 7.06 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, ^{1}H); 6.88 (s, *J* = 1.2 Hz, ^{1}H); 4.53 (s, 2H); 4.45 (s, 2H); 4.46 (q, *J* = 8.0 Hz, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.1; 140.0; 131.7; 127.4; 124.4; 123.2; 121.7; 113.0; 66.7; 66.3; 66.0; 65.6; 32.5; 27.1. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 3.79 (t, *J* = 8.0 Hz, 3F). IR (neat): 1611.8; 1582.2; 1508.7; 1423.7; 1289.7; 1259.7; 1224.4; 1204.4; 1158.2; 1099.9; 1068.0; 974.4; 855.9; 746.4; 663.3; 556.4; 539.8.
Following the general procedure for the Arbuzov reaction, 29 was obtained from the dibromide (0.64 g, 1.76 mmol) as a yellow oil (0.41 g, 0.86 mmol, 49%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (dd, *J* = 7.8 Hz, *J* = 2.4 Hz, ^{1}H); 6.94 (d, *J* = 7.8 Hz, ^{1}H); 6.88 (s, ^{1}H); 4.41 (q, *J* = 8.2 Hz, *J* = 8.2 Hz, 2H); 4.08-3.96 (m, 8H); 3.23 (d, *J* = 21.0 Hz, 2H); 3.12 (d, *J* = 21.0 Hz, 2H); 1.25 (dt, *J* = 7.1 Hz, *J* = 2.2 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9; 132.0; 132.0; 131.9; 131.9; 131.6; 131.6; 131.6; 131.6; 124.6; 124.0; 124.0; 123.9; 123.9; 121.8; 120.1; 120.1; 120.0; 120.0; 113.9; 113.9; 113.9; 66.9; 66.6; 66.2; 65.9; 62.1; 62.0; 61.8; 61.8; 34.1; 32.7; 26.8; 25.4; 16.3; 16.2; 16.2; 16.1. 31P NMR ($CDCl_3$, 162 MHz): δ 26.58 (d, *J* = 8.7 Hz); 26.27 (d, *J* = 8.3 Hz).
^{19}F NMR ($CDCl_3$, 375 MHz): δ 3.61 (t, *J* = 11.3 Hz, 3F). IR (neat): 1615.8; 1581.8; 1429.8; 1393.3; 1243.0; 1158.0; 1019.8; 957.2; 845.9; 670.0; 624.4; 512.2. LC-MS retention time: 7.38 min (10 → 90% MeCN, 15 min run). Mass (ESI): *m/z* 477.0 [M + H]+; 952.8 [2M + H]+. Exact mass: Calculated for [C18H30F3O7P2]+: 477.14134; [C18H30F3O7P2Na]+: 499.12328. Found: 477.14118 [M + H]+; 499.12261 [M + Na]+.
To obtain compound **30** a chilled (0°C) solution of 2,5-dimethylphenol (1.22 g, 10 mmol) in DMF (50 ml) NaH (60% wt. dispersion in mineral oil, 0.8 g, 20 mmol) was prepared and the mixture was stirred for 10 min. A solution of 1-bromo-4,4,4-trifluorobutane (2.28 g, 12 mmol) in DMF (25 ml) was added and the mixture was stirred at room temperature for 16 h. After cooling to 0°C and quenching with water, the reaction mixture was extracted thrice with EtOAc and the combined organic layers were dried (Na_2SO_4); filtered and concentrated. The resulting yellow oil was subjected to column chromatography (0 → 10% EtOAc/light petroleum) and the pure product was obtained as a yellow fluid (2.13 g, 9.2 mmol, 92%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01 (d, *J* = 7.5 Hz, ^{1}H); 6.68 (d, *J* = 7.5 Hz, ^{1}H); 6.61 (s, ^{1}H); 3.99 (t, *J* = 5.9 Hz, 2H); 2.31 (s, 3H); 2.39-2.25 (m, 2H); 2.17 (s, 3H); 2.10-2.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5; 136.6; 130.4; 128.6; 125.8; 123.5; 121.1; 111.8; 65.8; 31.2; 31.0; 30.7; 30.4; 22.4; 21.3; 15.7. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 11.26 (t, *J* = 10.9 Hz, 3F). IR (neat): 1615.9; 1586.1; 1508.8; 1385.3; 1337.0; 1285.9; 1248.6; 1231.1; 1149.9; 1128.0; 1026.7; 804.7; 661.7; 598.8; 586.4; 553.3.

Following the general procedure for bromination, this dimethyl compound (0.2 g, 0.86 mmol) was converted into the dibromide, which was obtained as a yellow solid (0.26 g, 0.66 mmol, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, *J* = 7.7 Hz, ^{1}H); 6.95 (dd, *J* = 7.7 Hz, *J* = 1.3 Hz, ^{1}H); 6.87 (s, ^{1}H); 4.50 (s, 2H); 4.44 (s, 2H); 4.10 (t, *J* = 5.9 Hz, 2H); 2.48-2.31 (m, 2H); 2.19-2.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5; 139.9; 131.1; 128.5; 126.4; 121.4; 112.1; 66.3; 33.1; 30.9; 30.6; 28.2; 22.2. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 11.4 (t, *J* = 10.6 Hz, 3F). IR (neat): 1685.6; 1607.6; 1496.0; 1450.6; 1383.7; 1337.9; 1249.6; 1230.4; 1149.1; 1025.9; 835.7; 663.2; 626.2; 553.0.

Following the general procedure for the Arbuzov reaction, **30** was obtained from the dibromide (0.26 g, 0.66 mmol) as a yellow oil (0.23 g, 0.45 mmol, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (dd, *J* = 7.5 Hz, *J* = 2.7 Hz, ^{1}H); 6.86 (s, ^{1}H); 6.84 (d, *J* = 9.8 Hz, ^{1}H); 4.08-3.95 (m, 10H); 3.20 (d, *J* = 21.6 Hz, 2H); 3.11 (d, *J* = 21.5 Hz, 2H); 2.44-2.30 (m, 2H); 2.14-2.04 (m, 2H); 1.24 (dd, *J* = 12.8 Hz, *J* = 6.9 Hz, ^{1}H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0; 156.0; 155.9; 155.9; 131.6; 131.6; 131.5; 131.5; 131.1; 131.0; 131.0; 131.0; 128.3; 125.6; 122.1; 122.1; 122.1; 122.0; 118.8; 118.8; 118.7; 118.7; 112.8; 112.8; 112.7; 112.7; 66.1; 61.9; 61.9; 61.7; 61.6; 34.1; 32.8; 30.6; 30.3; 30.0; 29.5; 27.1; 25.7; 22.0; 22.0; 16.2; 16.1; 16.1. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 11.28 (t, *J* = 10.9 Hz, 3F). IR (neat): 1612.1; 1581.7; 1511.6; 1431.2; 1391.5; 1248.9; 1149.2; 1050.8; 1019.6; 954.9; 819.9; 627.5; 518.1. LC-MS retention time: 8.01 min (10 → 90% MeCN, 15 min run). Mass (ESI): *m/z* 505.07 [M + H]+; 1008.87 [2M + H]+. Exact mass: Calculated for $[C_{20}H_{34}F_3O_7P_2]$+: 505.17264; $[C_{20}H_{33}F_3O_7P_2Na]$+: 527.15458. Found: 505.17254 [M + H]+; 527.15411 [M + Na]+.

Compound **31** was prepared as follows. Following the general procedure for bromination, the dibromide was obtained from **41** (1.36 g, 5 mmol) as a yellow solid (0.97 g, 2.25 mmol, 45%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J* = 7.8 Hz, ^{1}H); 7.14 (d, *J* = 7.8 Hz, ^{1}H); 6.99 (s, ^{1}H); 5.11-4.95 (m, ^{1}H); 4.52 (s, 2H); 4.44 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5; 140.3; 132.2; 128.2; 124.9; 122.3; 119.4; 114.0; 75.9; 75.6; 75.2; 75.0; 74.6; 74.2; 73.9; 32.0; 26.0. ^{19}F NMR ($CDCl_3$, 375 MHz): δ 4.47 (d, *J* = 5.6 Hz, 6F). IR (neat): 1616.7; 1578.9; 1507.6; 1425.5; 1368.6; 1256.1; 1193.7; 1147.8; 1103.3; 890.7; 758.3; 686.3; 662.9; 532.8.

Following the general procedure for the Arbuzov reaction, **31** was obtained from the dibromide (0.97 g, 2.25 mmol) as a yellow oil (0.76 g, 1.48 mmol, 66%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, ^{1}H); 7.04 (d, *J* = 7.8 Hz, ^{1}H); 7.00 (s, ^{1}H); 5.13-5.02 (m, ^{1}H); 4.09-3.97 (m, 8H); 3.23 (d, *J* = 20.6 Hz, 2H); 3.14 (d, *J* = 20.5 Hz, 2H); 1.24 (t, *J* = 7.1 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8; 155.8; 155.8; 155.7; 133.8; 133.8; 133.7; 133.7; 133.0; 132.9; 126.5; 126.4; 126.4; 126.4; 124.1; 121.4; 121.3; 121.3; 116.7; 116.6; 75.4; 75.0; 74.7; 63.8; 63.7; 63.6; 63.5; 34.2; 32.8; 27.4; 26.0; 16.7; 16.6; 16.5. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.77 (d, *J* = 1.45 Hz). ^{19}F NMR ($CDCl_3$, 375 MHz): δ 4.25 (d, *J* = 7.5 Hz, 6F).

Phosphonate **32** was obtained similarly. Following the general procedure for bromination, the dibromide was obtained from **42** (0.34 g, 1 mmol) as a yellow solid (0.31 g, 0.62 mmol, 62%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, *J* = 2.4 Hz, ^{1}H); 7.28 (d, *J* = 1.4 Hz, ^{1}H); 6.58 (s, ^{1}H); 4.49 (s, 2H); 4.42 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7; 143.6; 132.2; 130.7; 127.1; 124.1; 121.45; 116.5; 31.7; 25.8.

Following the general procedure for the Arbuzov reaction, **32** was obtained from the dibromide (0.34 g, 0.68 mmol) as a yellow oil (0.10 g, 0.16 mmol, 24%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (dd, *J* = 7.9 Hz, *J* = 1.8 Hz, ^{1}H); 7.22 (s, ^{1}H); 7.15 (d, *J* = 8.0 Hz,

^{1}H); 4.06-3.97 (m, 8H); 3.20 (d, *J* = 20.9 Hz, 2H); 3.12 (d, *J* = 20.6 Hz, 2H); 1.24 (t, *J* = 7.0 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7; 150.7; 150.7; 132.2; 132.1; 132.1; 132.1; 131.7; 127.5; 127.5; 123.6; 123.6; 123.5; 123.5; 121.3; 121.1; 118.2; 61.8; 61.8; 61.7; 61.7; 33.7; 32.3; 27.0; 25.6; 16.0; 15.9; 15.9; 15.8; 15.8. 31P NMR ($CDCl_3$, 162 MHz): δ 25.57 (q, *J* = 7.8 Hz, *J* = 7.8 Hz). ^{19}F NMR ($CDCl_3$, 375 MHz): δ 8.71 (s, 9F). IR (neat): 1506.3; 1425.1; 1393.4; 1250.4; 1135.7; 1022.1; 999.7; 965.7; 849.4; 816.5; 727.5; 629.2; 524.4. LC-MS retention time: 8.85 min (10 → 90% MeCN, 15 min run). Mass (ESI): *m/z* 613.07 [M + H]+; 1224.73 [2M + H]+. Exact mass: Calculated for [$C_{20}H_{28}F_9O_7P_2$]+: 613.11611; [$C_{20}H_{28}F_9O_7P_2Na$]+: 635.09805. Found: 613.11622 [M + H]+; 635.09790 [M + Na]+.

Synthesis of aldehyde building blocks 33 and 34

Aldehyde 33

The silyl-protected aldehyde was prepared according to literature procedures.[4] 4-hydroxybenzaldehyde (1.22 g, 10 mmol) was dissolved in DMF (25 ml), imidazole (0.95 g, 14 mmol) was added and the reaction mixture cooled to 0 □C. A solution of TBDMS-Cl (1.8 g, 12 mmol) in DMF (5 ml) was added dropwise and the reaction stirred at room temperature for 4 h. After removal of the solvent, the residue was taken up in EtOAc and washed with sat. aq. NaHCO3 and sat. aq. NaCl, dried (Na_2SO_4), filtered and concentrated. The crude product was subjected to column chromatography (0 → 5% EtOAc/light petroleum) and obtained as a pale yellow oil (2.12 g, 9.0 mmol, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.89 (s, ^{1}H); 7.79 (d, *J* = 8.6 Hz, 2H); 6.95 (d, *J* = 8.5 Hz, 2H); 1.00 (s, 9H); 0.25 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.8; 161.4; 131.9; 130.3; 120.4; 25.5; 18.2; -4.4.

Aldehyde 34

p-hydroxymethylbenzaldehyde was prepared following literature procedures.[5] Terephtaldicarboxaldehyde (6.71 g, 50 mmol) was dissolved in THF (50 ml). The mixture was cooled to 0°C, $NaBH_4$ (0.66 g, 17.5 mmol) was added and the reaction stirred for 4 h. After concentration of the reaction mixture, the residue was taken up in EtOAc, water was added and the layers separated. The organic layer was washed with water, sat. aq. NaCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (10 → 40% EtOAc/light petroleum) and the pure compound was obtained as an off-white solid (1.88 g, 13.8 mmol, 28%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.99 (s, ^{1}H); 7.87 (d, *J* = 8.1 Hz, 2H); 7.53 (d, *J* = 8.0 Hz, 2H); 4.80 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1; 147.8; 135.6; 129.9; 126.9; 64.5.

p-hydroxymethylbenzaldehyde (1.88 g, 13.8 mmol) was protected with the TBDMS functionality as described for **33**, yielding **34** as a yellow fluid (3.0 g, 12.0 mmol, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.00 (s, ^{1}H); 7.85 (d, *J* = 8.3 Hz, 2H); 7.49 (d, *J* = 8.0 Hz, 2H); 4.82 (s, 2H); 0.96 (s, 9H); 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.0; 148.6; 135.3; 129.8; 126.2; 64.4; 25.9; 18.4; -5.3.

References

1. Canning, PSJ, Maskill, H, McCruddem, K, et al. A product analytical study of the thermal and photolytic decomposition of some arenediazonium salts in solution. Bull Chem Soc Jpn. 2002; 75:789-800.
2. Kumar, P, Zheng, W, McQuarrie, SA, et al. 18F-FESB: Synthesis and automated radiofluorination of a novel 18F-labelled PET tracer for beta-amyloid plaques. J Labelled Comp Radiopharm. 2005;983-996.
3. Kikuchi, D, Sakaguchi, S, and Ishii, Y. An Alternative Method for the Selective Bromination of Alkylbenzenes Using NaBrO(3)/NaHSO(3) Reagent. J Org Chem. 1998; 63:6023-6026.
4. Azuma, H, Miyasaka, K, Yokotani, T, et al. Lipase-catalyzed preparation of optically active 1'-acetoxychavicol acetates and their structure-activity relationships in apoptotic activity against human leukemia HL-60 cells. Bioorg Med Chem. 2006; 14:1811-1818.
5. Mak, CC, Bampos, N, Darling, SL, et al. A strategy for the assembly of multiple porphyrin arrays based on the coordination chemistry of Ru-centered porphyrin pentamers. J Org Chem. 2001; 66:4476-4486.