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Supporting Information

69451 Weinheim, Germany

Three groups good, four groups bad? Atropisomerism in *ortho*-substituted diaryl ethers

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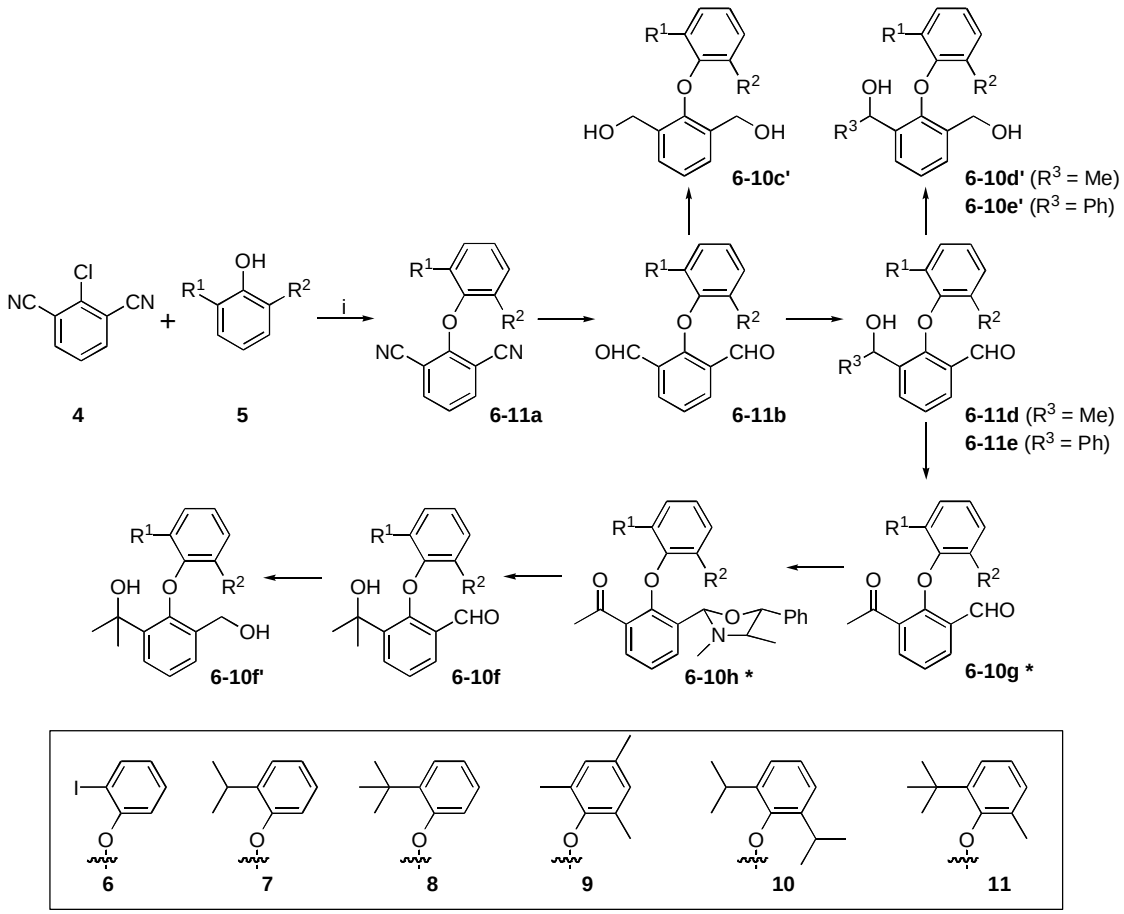
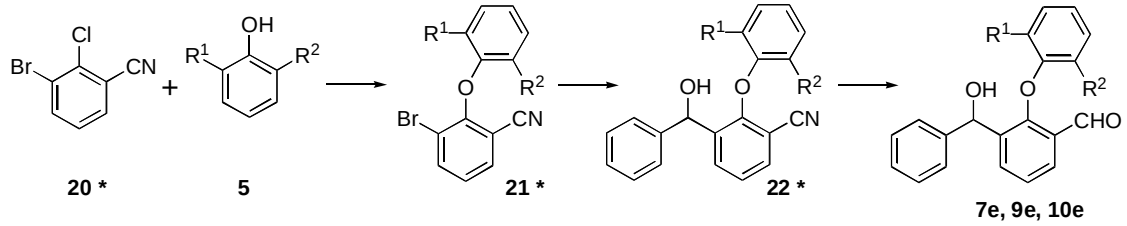
Compound numbering below follows the paper itself, with the addition of some groups of compounds which are not depicted in the paper, indicated by an asterisk (*) in the following schemes. Scheme S1 shows in full compounds made while implementing the route outlined in "Scheme 1" of the paper.



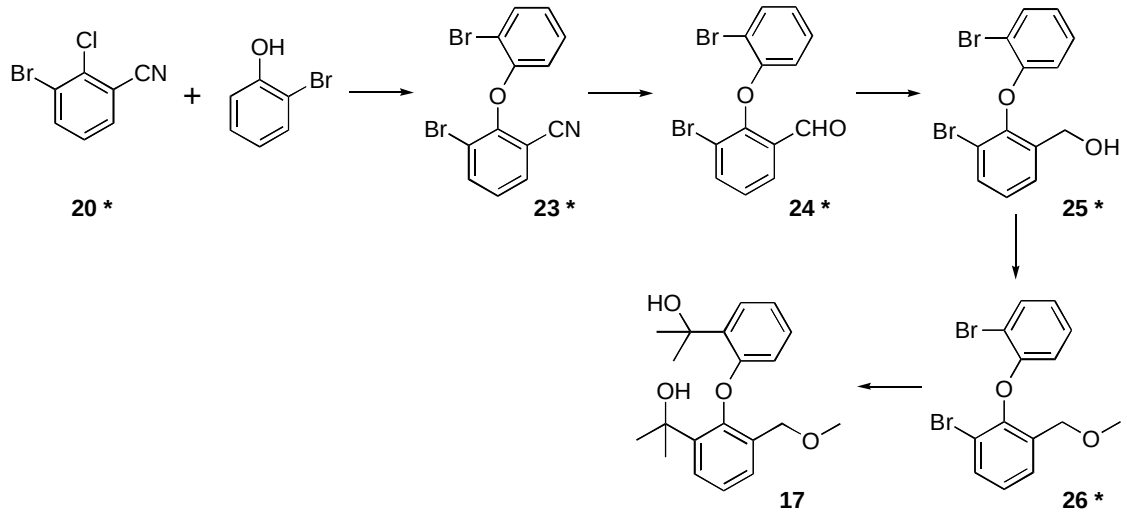
Scheme S1: Compounds used in synthesis by the method of Scheme 1.

Samples of **7e**, **9e** and **10e** were additionally prepared as shown in Scheme S2.



*Scheme S2: Alternative route to **7-10e***

Compound **17** was made the modification of this route shown in Scheme S3



*Scheme S3: Route to **17***

Compounds **16** were made by the route outlined in Scheme 2 of the paper and published in a preliminary communication;[3] full experimental details for **13-16** are given below.

1. Experimental procedures

Standard laboratory procedures and details of spectrometers etc. have been reported previously.[1]

General Procedure A. *Phenoxide substitution reaction.*

The phenol **5** (1 equiv.), potassium hydroxide (1 equiv.), and toluene were charged to a flask and heated under reflux using Dean-Stark conditions for 2 hours, cooled to RT and solvent removed under reduced pressure, to yield the product that was used without purification. 2-chloro-isophthalonitrile (1 equiv.) and dry DMF were added and heated to 150 $^{\circ}$C under N_2. The reaction mixture was allowed to stir at this temperature for 16 hours, and the excess DMF was removed by vacuum distillation. The resultant brown oil was dissolved in portions of EtOAc (x 3) and the combined organics washed with water (x 3), brine, dried (sodium sulphate), and solvent removed under reduced pressure.

General Procedure B. *Reduction of nitriles.*

DIBAL (1M solution in solvent) (2.5 equiv.) was added slowly to a stirring solution of dinitrile **6-11a** (1 equiv.) in dry solvent under nitrogen at –78^{o}C. The mixture was allowed warm to RT over a period of 16 hours, HCl (cooled to 5^{o}C) was added to the mixture and allowed to stir for a further hour. The layers were separated and the organic fraction washed with water (x 3), brine, dried (sodium sulphate), and the solvent removed under reduced pressure.

General Procedure C. *Desymmetrisation of dialdehydes.*

MeLi/PhLi (1 equiv.) was added dropwise to a stirred solution of dialdehyde **6-11b** (1 equiv.) in anhydrous ether at –78^{o}C under N_2, stirred for 16 hours and quenched by addition of saturated ammonium chloride solution. The mixture was warmed to RT and layers separated, the organic fraction was washed with water, brine, dried (sodium sulphate), and solvent removed under reduced pressure.

General Procedure D. *Swern oxidation.*

DMSO was added to stirred solution of oxalyl chloride dissolved in anhydrous DCM at –78oC under N_2 and stirred for 20 min. The alcohol, dissolved in DCM, was added and mixture stirred for a further 20 min, triethylamine added and mixture stirred for 20 min. The mixture was warmed to RT and quenched by addition of saturated ammonium chloride solution, layers separated and organic fraction washed with water (x 2), brine, dried (sodium sulphate) and solvent removed under reduced pressure.

General Procedure E. *Aldehyde protection as oxazolidine.*

The aldehyde and (–)-ephedrine were dissolved in toluene and heated under reflux using Dean-Stark conditions for 16 hours, cooled to RT and solvent removed under reduced pressure.

General Procedure F. *Grignard addition.*

MeMgI/PhMgBr (1.1 equiv.) was added dropwise to a stirred solution of aldehyde (1 equiv.) in anhydrous THF at 0^oC under N_2, stirred for 1 hour, warmed to RT and stirred for a further specified number of hours. HCl was added and the mixture stirred for 1 min, diluted using EtOAc and layers separated, the organic fraction was washed with water, brine, dried (sodium sulphate), and solvent removed under reduced pressure.

General Procedure G. *Aldehyde reduction.*

The aldehyde was dissolved in THF was added to a stirring suspension of sodium borohydride in THF under N_2 and stirred for 16 hours. NaOH solution was added and the mixture stirred for 1 min, diluted using EtOAc and layers separated, the organic fraction was washed with water, brine, dried (sodium sulphate), and solvent removed under reduced pressure.

General Procedure H. *Aryl bromide as nucleophile.*

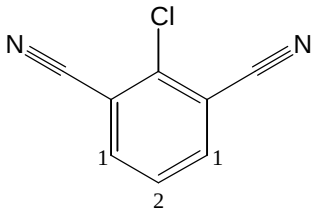
n-BuLi (1.6 M solution in hexane, 1 equiv.) was added dropwise to a stirred solution of aryl bromide (1 equiv.) in anhydrous THF at $–78^oC$ under N_2 and stirred for the specified time. The electrophile was added and the mixture stirred for 16 hours with warming to

RT. Quenched by addition of saturated ammonium chloride solution and diluted using EtOAc. Layers separated and the organic fraction was washed with water, brine, dried (sodium sulphate), and solvent removed under reduced pressure.

General Procedure I. *Methyl ether formation.*

The alcohol (1 equiv.) was dissolved in anhydrous THF and added to a stirred suspension of NaH (1.5 equiv.) in THF under N_2 and stirred for 30 min. MeI was added and the mixture stirred for 16 hours, and quenched by addition of water. Organics were extracted using EtOAc, the organics were washed with water, brine, dried (sodium sulphate), and solvent removed under reduced pressure.

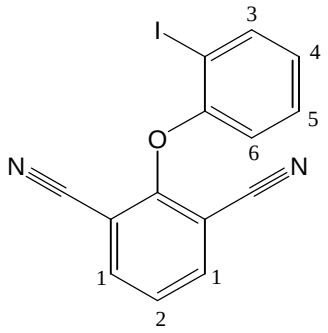
2-Chloroisophthalonitrile **4**



Using a modification of the method described by Krizan,[2] a solution of isophthalonitrile (5 g, 39.02 mmol, 1 equiv.) in anhydrous THF (100 cm^3) was added dropwise to a stirring solution of in LDA (46.82 mmol, 1.2 equiv.) in anhydrous THF (150 cm^3) at –95 ^oC and allowed to stir for approximately 1 hr. Hexachloroethane (14.8 g, 62.44 mmol, 1.6 equiv.) dissolved in anhydrous THF (150 cm^3) was added to the reaction mixture at this temperature and the mixture allowed to stir for 1 hr and warmed to RT over a period of 16 hrs. The mixture was quenched by addition of saturated ammonium chloride solution and organics extracted using EtOAc. The organics were washed with water, brine, dried (sodium sulphate) and solvent removed under reduced pressure. The product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow solid (5.63 g, 88%). δH (300 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8, H-1), and 7.57 (1H, t, *J* 8, H-2). Analyses matched the reported data.[2]

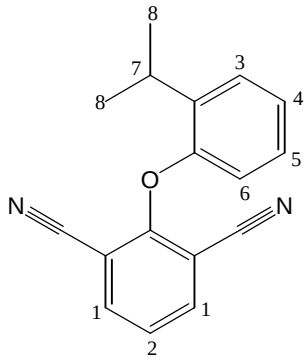
LDA: *n*-BuLi (2.5M in Hexanes) (23 cm^3, 28.09 mmol, 1 equiv.) was added dropwise to a stirred solution of anhydrous diisopropylamine (6.6 cm^3, 28.09 mmol, 1 equiv.) dissolved in anhydrous THF (100 cm^3) at 0^oC under N_2 and allowed to stir for 30 min at this temperature.

2-(2-Iodophenoxy)isophthalonitrile **6a**



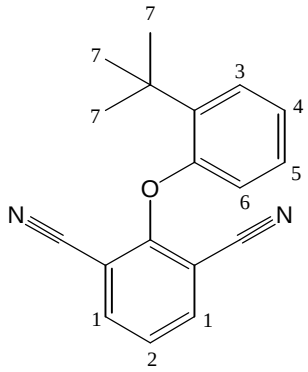
2-Iodophenol (2.6 g, 9.7 mmol, 1 equiv.), potassium hydroxide (0.5 g, 9.7 mmol, 1 equiv.), and toluene were treated as described in general procedure A. 2-Chloroisophthalonitrile (1.6 g, 9.7 mmol, 1 equiv.), 2-iodophenoxide (3 g, 9.7 mmol, 1 equiv.), and dry DMF (50 cm^3) were treated as outlined in General Procedure A. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the product as an orange powder (2.73 g, 81%), m.p. 156 - 159^oC. Rf = 0.07 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2241 (CN); δH (300 MHz; $CDCl_3$) 7.96 (1H, dd, *J* 6.5 and 1.5, H-3), 7.95 (2H, d, *J* 8, H-1), 7.44 (1H, t, *J* 8, H-2), 7.39 (1H, m, H-4), 7.05 (1H, dt, *J* 7.5 and 1.5, H-5) and 6.82 (1H, dd, *J* 8 and 1.5, H-6).; δC (75 MHz; $CDCl_3$) 159.3, 155.8, 140.7, 138.9, 130.1, 127.4, 125.4, 118.1, 113.7, 107.6 and 88.1.; CI *m/z* 364 (M + NH_4^+); (Found: M, 345.9606. $C_{14}H_7N_2OI$ requires *M*, 345.9598).

2-(2-Isopropylphenoxy)isophthalonitrile **7a**



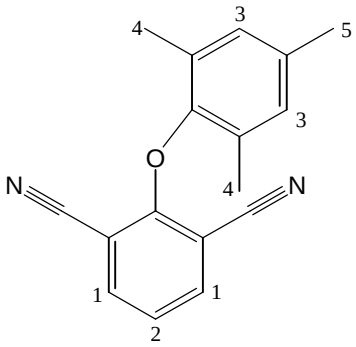
2-Isopropylphenol (1.57 g, 11.5 mmol, 1 equiv.), potassium hydroxide (0.65 g, 11.5 mmol, 1 equiv.), and toluene were treated as described in General Procedure A. 2-Chloroisophthalonitrile (1.8 g, 11.5 mmol, 1 equiv.), 2isopropylphenoxide (2.0 g, 11.5 mmol, 1 equiv.), and dry DMF (50 cm^3) reacted as outlined in General Procedure A. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the product as a light yellow powder (2.15 g, 71%), m.p. 92 - 94^oC. Rf = 0.35 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2238 (CN); δH (300 MHz; $CDCl_3$) 7.93 (2H, d, *J* 8, H-1), 7.44 (1H, dd, *J* 8 and 2, H-3), 7.40 (1H, t, *J* 8, H-2), 7.24 (1H, td, *J* 8 and 2, H-4), 7.17 (1H, td, *J* 8 and 2, H-5), 6.60 (1H, dd, *J* 8 and 1.5, H-6), 3.48 (1H, sept, *J* 7, H-7) and 1.39 (6H, d, *J* 7, H-8).; δC (75 MHz; $CDCl_3$) 160.0, 154.3, 139.1, 138.9, 127.9, 127.2, 125.7, 124.9, 115.9, 113.9, 108.0, 27.7 and 22.9.; EI *m/z* 262 (M); CI *m/z* 280 (M + NH_4^+); (Found: M, 262.1100. $C_{17}H_{14}N_2O$ requires *M*, 262.1101).

2-(2-tert-Butylphenoxy)isophthalonitrile **8a**



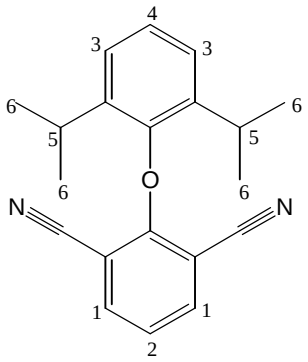
2-*t*-Butylphenol (5.42 cm^3, 35 mmol, 1.2 equiv.), potassium hydroxide (1.96 g, 35 mmol, 1.2 equiv.) were treated as described in general procedure A. 2-Chloroisophthalonitrile (4.7 g, 29.17 mmol, 1 equiv.), 2-*t*-butyl-phenoxide (6.6 g, 35 mmol, 1.2 equiv.), and anhydrous DMF (150 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (4:1 petrol : EtOAc) to yield the product as an light brown powder (5.57 g, 69%), m.p. 117 - 119^oC. Rf = 0.31 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2238 (CN); δH (300 MHz; $CDCl_3$) 7.94 (2H, d, *J* 8, H-1), 7.52 (1H, m, H-3), 7.40 (1H, t, *J* 8, H-2), 7.21 (2H, CH ABXY m, H-4 and H-5), 6.61 (1H, m, H-6) and 1.54 (9H, s, H-7).; δC (75 MHz; $CDCl_3$) 159.6, 155.7, 140.1, 139.0, 128.3, 127.6, 125.3, 124.8, 116.7, 114.1, 107.8, 35.2 and 30.4.; EI *m/z* 276 (M); CI *m/z* 294 (M + NH_4^+); (Found: M, 276.1247. $C_{18}H_{16}N_20$ requires *M*, 276.1257).

2-(2,4,6-Trimethylphenoxy)isophthalonitrile **9a**



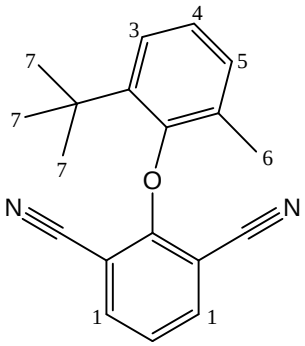
2,4,6-Trimethylphenol (1.64 g, 12.05 mmol, 1.2 equiv.), potassium hydroxide (0.68 g, 12.05 mmol, 1.2 equiv.), and toluene were treated as described in General Procedure A. 2-Chloroisophthalonitrile (1.7 g, 10.04 mmol, 1 equiv.), 2,4,5-trimethylphenoxide (2.1 g, 12.05 mmol, 1.2 equiv.), and dry DMF (60 cm^3) were treated as outlined in General Procedure A. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as light yellow blocks (2.07 g, 78%), m.p. 149-153^{o}C. Rf = 0.62 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2235 (CN); δH (300 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8, H-1), 7.21 (1H, t, *J* 8, H-2), 6.95 (2H, s, H-3), 2.36 (3H, s, H-5) and 2.18 (6H, s, H-4).; δC (75 MHz; $CDCl_3$) 160.9, 149.0, 139.6, 137.3, 130.7, 129.9, 122.6, 113.9, 103.2, 21.2 and 16.6.; CI *m/z* 280 (M + NH_4^+), EI *m/z* 262 (M); (Found: M, 262.1101. $C_{17}H_{14}N_2O$ requires *M*, 262.1101).

2-(2,6-Diisopropylphenoxy)isophthalonitrile **10a**



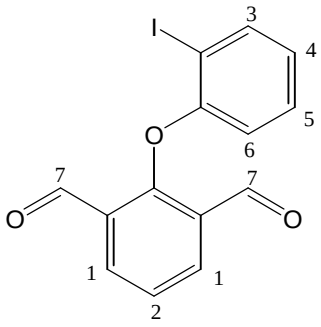
2,6-Di-*iso*-propylphenol (1.16 cm^3, 6.24 mmol, 1.2 equiv.), potassium hydroxide (0.35 g, 6.24 mmol, 1.2 equiv.), and toluene were treated as described in General Procedure A. 2-Chloroisophthalonitrile (0.85 g, 5.2 mmol, 1 equiv.), 2,6-di-*iso*-propyl-phenoxide (1.36 g, 6.24 mmol, 1.2 equiv.), and dry DMF (70 cm^3) were treated as described in General Procedure A. The crude product was purified by flash column chromatography (20:1 petrol : EtOAc) to yield the product as a light orange solid (742 mg, 47%), m.p. 88 - 90^oC. Rf = 0.36 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2235 (CN); δH (300 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8, H-1), 7.41 (1H, t, *J* 8 , H-2), 7.25 (2H, d, *J* 7.5, H-3), 7.21 (1H, t, *J* 7.5, H-4), 2.95 (2H, sept, *J* 7, H-5) and 1.26 (12H, d, *J* 7, H-6).; δC (75 MHz; $CDCl_3$) 161.0, 148.5, 141.6, 139.8, 128.5, 124.7, 122.4, 113.9, 102.6, 28.0 and 23.4.; EI *m/z* 304 (M); CI *m/z* 322 (M + NH_4^+); (Found: M, 304.1563. $C_{20}H_{20}N_2O$ requires *M*, 304.1570).

2-(2-tert-Butyl-6-methylphenoxy)benzene-1,3-dinitrile **11a**



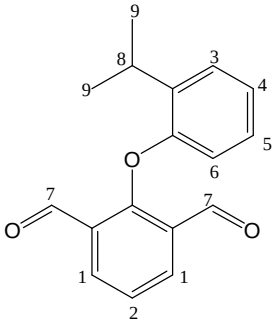
2-*tert*-Butyl-6-methylphenol (1.39 g, 8.46 mmol, 1 equiv.), potassium hydroxide (0.48 g, 8.46 mmol, 1 equiv.) were treated as described in general procedure A. 2-Chloroisophthalonitrile (1.25 g, 7.69 mmol, 1 equiv.), 2-*tert*-butyl-6-methylphenoxide (1.7 g, 8.46 mmol, 1.1 equiv.), and anhydrous DMF (70 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a yellow solid (0.91 g, 40%), m.p. 65 – 68^oC. Rf = 0.36 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2253 (CN); δH (300 MHz; $CDCl_3$) 7.85 (2H, d, *J* 8, H-1), 7.38 (1H, dd, *J* 8 and 1.5, H-3), 7.30 (1H, t, *J* 8, H-4), 7.22 (1H, t, *J* 8, H-2), 7.15 (1H, ddd, *J* 8, 2 and 1, H-5), 2.05 (3H, s, H-6) and 1.44 (9H, s, H-7).; δC (75 MHz; $CDCl_3$) 160.7, 151.1, 143.3, 139.6, 130.8, 129.8, 127.6, 126.0, 122.4, 114.0, 103.2, 35.3, 30.8 and 17.2.; EI *m/z* 290 (M); CI *m/z* 308 (M + NH_4^+); (Found: M + NH_4^+, 308.1765. $C_{19}H_{22}N_30$ requires *M*, 308.1757).

2-(2-Iodophenoxy)benzene-1,3-dicarbaldehyde **6b**



DIBAL (1M solution in toluene) (7.2 cm^3, 7.2 mmol, 2.5 equiv.), nitrile **6a** (1 g, 2.89 mmol, 1 equiv.) and dry toluene (50 cm^3) were treated as described in general procedure B. The crude product was purified by flash column chromatography (8:1 Petrol : EtOAc) to yield dialdehyde **6b** as light yellow blocks (0.98 g, 96%), m.p. 82 - 84°C. Rf = 0.33 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1706, 1682 (CHO); δH (300 MHz; $CDCl_3$) 10.22 (2H, s, H-7), 8.30 (2H, d, *J* 8, H-1), 7.96 (1H, dd, *J* 8 and 1.5, H-3), 7.61 (1H, tt, *J* 7.5 and 0.5, H-2), 7.25 (1H, ddd, *J* 9, 8.5 and 1.5, H-4), 6.90 (1H, td, *J* 7.5 and 1.5, H-5) and 6.43 (1H, dd, *J* 8.5 and 1.5, H-6).; δC (75 MHz, $CDCl_3$) 187.8, 159.5, 159.1, 140.8, 135.1, 130.3, 130.1, 127.0, 125.4, 114.6 and 84.8.; EI *m/z* 352 (M); CI *m/z* 370 (M + NH_4^+); (Found: C 48.01%, H 2.59% and I 36.34%. $C_{14}H_9O_3I$ requires C 47.75%, H 2.58%, I 36.04%).

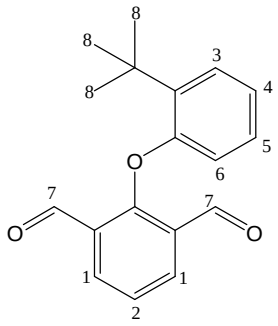
2-(2-Isopropylphenoxy)benzene-1,2-dicarbaldehyde **7b**



DIBAL (1M solution in toluene) (9.5 cm^3, 9.5 mmol, 2.5 equiv.), nitrile **7a** (1 g, 3.8 mmol, 1 equiv.) and toluene (50 cm^3) were treated as described in General Procedure B. The crude product was purified by flash column chromatography (5:1 Petrol : EtOAc) to yield the product **7b** as a yellow solid (0.7 g, 68%), m.p. 63 - 65°C. Rf = 0.69 (5:1

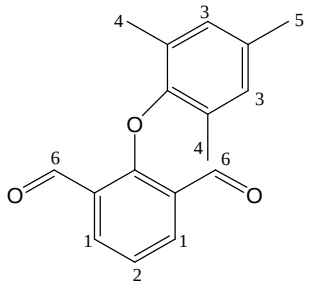
petrol:EtOAc); ν_{max}(film/cm^{-1}) 1708, 1684 (CHO); δH (300 MHz; $CDCl_3$) 10.22 (2H, s, H-7), 8.30 (2H, d, *J* 7.5, H-1), 7.57 (1H, tt, *J* 7.5 and 0.5, H-2), 7.42 (1H, m, H-3), 7.09 (2H, m, H-4 and H-5), 6.37 (1H, m, H-6), 3.64 (1H, sept, *J* 7, H-8) and 1.41 (6H, d, *J* 7, H-9).; δC (75MHZ; $CDCl_3$) 187.9, 1159.8, 158.5, 136.4, 135.1, 130.4, 127.9, 127.5, 126.3, 123.7, 113.7, 27.6 and 23.0.; EI *m/z* 268 (M); CI *m/z* 286 (M + NH_4^+); (Found: M + NH_4^+, 286.1445. $C_{17}H_{16}O_3$ requires *M*, 286.1438).

2-(2-t-Butylphenoxy)benzene-1,2-dicarbaldehyde **8b**



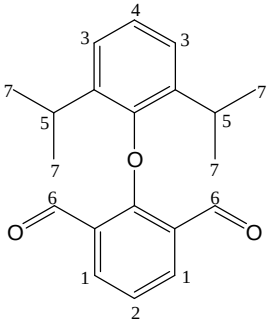
DIBAL (1M solution in toluene) (50 cm^3, 50.34 mmol, 2.5 equiv.), nitrile **8a** (5.57 g, 20.14 mmol, 1 equiv.) and anhydrous toluene (300 cm^3) were treated as described in general procedure B. The crude was purified by flash column chromatography (15:1 Petrol : EtOAc) to yield dialdehyde **8b** as a light yellow solid (3.84 g, 68%), m.p. 81 - 84^{o}C. Rf = 0.41 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1708 and 1684 (CHO); δH (300 MHz; $CDCl_3$) 10.21 (2H, s, H-7), 8.31 (2H, d, *J* 8, H-1), 7.57 (1H, tt, *J* 8 and 0.5, H-2), 7.49 (1H, m, H-3), 7.09 (2H, CH ABXY m, H-4 and H-5), 6.38 (1H, m, H-6) and 2.62 (9H, s, H-8).; δC (75 MHz; $CDCl_3$) 188.0, 160.1, 159.3, 137.3, 135.2, 130.5, 128.3, 128.1, 136.3, 123.5, 114.6, 35.3 and 30.0.; EI *m/z* 282 (M); CI *m/z* 300 (M + NH_4^+); (Found: M, 282.1245. $C_{18}H_{18}O_3$ requires *M*, 282.1250).

2-(2,4,6-Trimethylphenoxy)benzene-1,2-dicarbaldehyde **9b**



DIBAL (1M solution in toluene) (10.5 cm^3, 10.5 mmol, 2.5 equiv.), nitrile **9a** (1.1 g, 4.2 mmol, 1 equiv.) and dry toluene (50 cm^3) were treated as described in General Procedure B. The crude product was purified by flash column chromatography (15:1 Petrol : EtOAc) to yield dialdehyde **9b** as light yellow blocks (0.82 g, 73%), m.p. 159 - 164^oC. Rf = 0.17 (15:1 petrol:EtOAC). ν_{max}(film/cm^{-1}) 1681, 1670 (CHO); δH (300 MHz; $CDCl_3$) 10.14 (2H, s, H-6), 8.08 (2H, d, *J* 8, H-1), 7.28 (1H, t, *J* 8, H-2), 6.92 (2H, s, H-3), 2.32 (3H, s, H-5) and 2.16 (6H, s, H-4).; δC (75 MHz; $CDCl_3$) 188.3, 162.0, 153.9, 135.7, 135.2, 131.1, 128.3, 127.8, 123.1, 20.9 and 17.2.; EI *m/z* 268 (M); CI *m/z* 286 (M + NH_4^+); (Found: M, 268.1087. $C_{17}H_{16}O_3$ requires *M*, 268.1094).

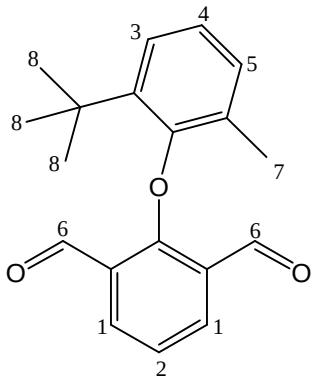
2-(2,6-Diisopropyl-phenoxy)-benzene-1,3-dicarbaldehyde **10b**



DIBAL (1M solution in toluene) (14.5 cm^3, 14.54 mmol, 2.5 equiv.), nitrile **10a** (1.77 g, 5.81 mmol, 1 equiv.) and dry toluene (150 cm^3) were treated as described in General Procedure B. The crude product was purified by flash column chromatography (25:1 Petrol : EtOAc) to yield the product **10b** as a light yellow solid (1.17 g, 65%), m.p. 40 - 42^oC. Rf = 0.73 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1678 (CHO); δH (300 MHz; $CDCl_3$) 93.98 (2H, s, H-6), 8.09 (2H, d, *J* 7.5, H-1), 7.28 (4H, m, H-2, H-3 and H-4), 3.13 (2H, sept, *J* 7, H-5) and 1.19 (12H, d, *J* 7, H-7).; δC (75 MHz; $CDCl_3$) 188.3, 162.1, 153.0,

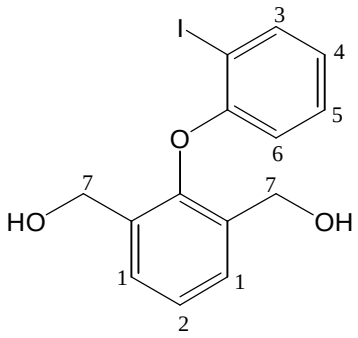
139.5, 135.5, 127.4, 127.2, 125.9, 122.6, 27.9 and 23.3.; EI *m/z* 310 (M); CI *m/z* 328 (M + NH_4^+); (Found: M + NH_4^+, 328.1912. $C_{20}H_{26}O_3N$ requires *M*, 328.1907).

2-(2-tert-Butyl-6-methylphenoxy)benzene-1,3-dialdehyde **11b**



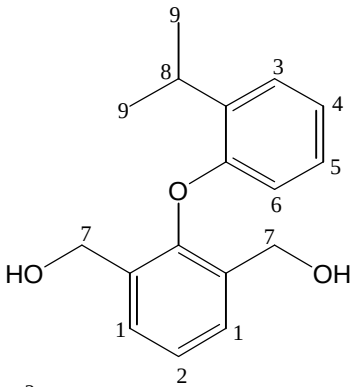
DIBAL (1M solution in toluene) (9 cm^3, 10 mmol, 2.5 eq), nitrile **11a** (839 mg, 2.89 mmol, 1 equiv.) and anhydrous toluene (50 cm^3) were treated as described in general procedure B. The crude was purified by flash column chromatography (20:1 Petrol : EtOAc) to yield dialdehyde **11b** as a yellow solid (664 mg, 77%), m.p. 75 - 79C. Rf = 0.78 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1679 (CHO); δH (300 MHz; $CDCl_3$) 10.01 (2H, s, H-6), 8.12 (2H, d, *J* 7.5, H-1), 7.38 (1H, dd, *J* 8 and 1.5, H-3), 7.27 (1H, tt, *J* 8 and 1.5, 1, H-4), 7.17 (1H, t, *J* 7.5, H-2), 7.10 (1H, ddd, *J* 8, 2 and 1, H-5), 1.96 (3H, s, H-7) and 1.49 (9H, s, H-8).; δC (75MHz; $CDCl_3$) 188.1, 161.3, 156.0, 141.0, 135.5, 131.7, 127.8, 127.3, 126.6, 126.3, 122.9, 35.5, 30.6 and 18.0.; EI *m/z* 296 (M); CI *m/z* 314 (M + NH_4^+), 297 (M + H); (Found: M + NH_4^+, 314.1752. $C_{19}H_{24}NO_3$ requires *M*, 314.1751).

[3-Hydroxymethyl-2-(2-iodophenoxy)phenyl]methanol **6c'**



DIBAL (1 M solution in DCM) (0.85 cm^3, 0.85 mmol, 3 equiv.), dialdehyde **6b** (100 mg, 0.28 mmol, 1 equiv.) and anhydrous DCM (10 cm^3) were treated as described in General Procedure B. The crude product was purified by flash column chromatography (4:1 increasing to 3:1 petrol : EtOAc) to yield the product as a white solid (61 mg, 61%). m.p. 156 - 158^oC; Rf = 0.07 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3320 (OH); δH (300 MHz; $CDCl_3$) 7.89 (1H, dd, *J* 8 and 1.5, H-3), 7.55 (2H, dd, *J* 7.5 and 0.5, H-1), 7.38 (1H, t, *J* 7, H-2), 7.20 (1H, ddd, *J* 8, 7.5 and 0.5, H-4), 6.82 (1H, ddd, *J* 8, 7.5 and 1.5, H-5), 6.40 (1H, dd, *J* 8 and 1.5, H-6) and 4.71 – 4.48 (4H, CH AB m, *J* 13 and 12, H-7); δC (75 MHz; DMSO) 156.8, 147.9, 140.2, 135.4, 130.6, 127.1, 126.4, 124.6, 113.8, 85.9 and 58.2.; CI *m/z* 374 ($M + NH_4^+$); (Found: $M + NH_4^+$, 374.0239. $C_{14}H_{17}O_3NI$ requires *M*, 374.0248). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-7 coalescence observed at 120^oC.

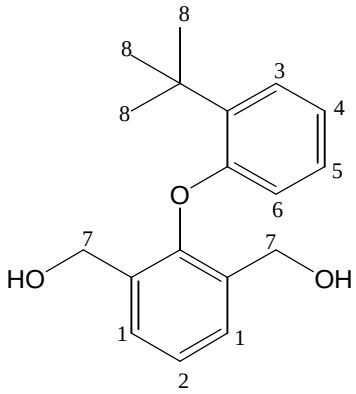
[3-Hydroxymethyl-2-(2-isopropyl-phenoxy)-phenyl]-methanol **7c'**



DIBAL (1 M in DCM) (1.7 cm^3, 1.68 mmol, 3 equiv.), dialdehyde **7b** (150 mg, 0.56 mmol, 1 equiv.) and anhydrous DCM (10 cm^3) were treated as described in General Procedure B, to yield diol **7c**, with no purification, as a white powder (145 mg, 95%).

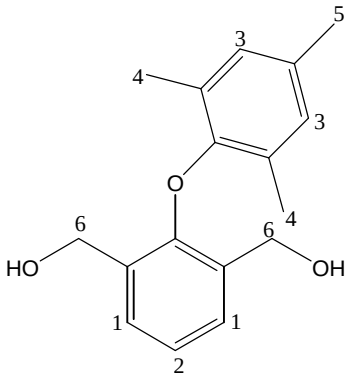
m.p. 106 - 108°C; Rf = 0.12 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3258 (OH).; δH (300 MHz; $CDCl_3$) 7.55 (2H, d, *J* 7.5, H-1), 7.36 (2H, m, H-2 and H-3), 7.02 (2H, m, H-4 and H-5), 6.29 (1H, m, H-6), 4.68 – 4.52 (4H, CH ABXY m, *J* 13, H-7), 3.56 (1H, sept, *J* 7, H-8) and 1.39 (6H, d, *J* 7, H-9).; δC (75 MHz; d_6-DMSO) 155.2, 147.7, 135.9, 135.7, 127.5, 127.3, 127.0, 125.9, 122.3, 112.0, 58.2, 27.4 and 23.3.; CI *m/z* 290 (M + NH_4^+); (Found: M + NH_4^+, 290.1742. $C_{17}H_{24}O_3N$ requires *M*, 290.1751). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 coalescence observed at 125°C.

[2-(2-tert-Butylphenoxy)-3-hydroxymethyl]phenylmethanol **8c'**



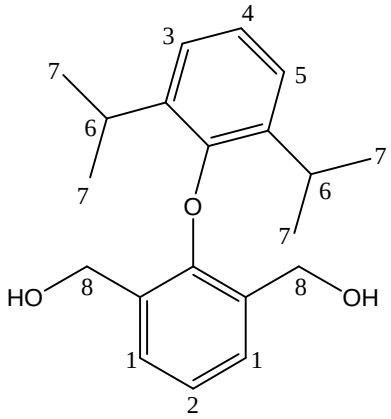
Dialdehyde **8b** (100 mg, 0.35 mmol, 1 equiv.), sodium borohydride (134 mg, 3.55 mmol, 10 equiv.) and anhydrous THF (15 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (5:1 petrol : EtOAc) to yield the product as a white solid (83 mg, 83%). m.p. 102 - 105°C; Rf = 0.08 (7:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3305 (OH).; δH (300 MHz; $CDCl_3$) 7.58 (2H, d, *J* 8, H-1), 7.43 (1H, dd, *J* 7.5 and 2, H-3), 7.38 (1H, t, *J* 8, H-2), 7.01 (2H, CH ABXY m, H-4 and H-5), 6.31 (1H, dd, *J* 7.5 and 2, H6), 4.68 – 4.56 (4H, CH ABXY m, *J* 13.5, H-7) and 1.57 (9H, s, H-8).; δC (75 MHz; d_6-DMSO) 156.5, 147.1, 136.8, 135.6, 128.0, 127.8, 127.1, 126.0, 122.1, 112.3, 58.4, 35.3 and 30.3.; EI *m/z* 286 (M); CI *m/z* 304 (M + NH_4^+); (Found: M, 286.1558, Number. $C_{18}H_{22}O_3$ requires *M*, 286.1563). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 no coalescence observed at 150°C, slight broadening above 125°C.

[3-Hydroxymethyl-2-(2,4,6-trimethylphenoxy)phenyl]methanol **9c'**



DIBAL (1M solution in DCM) (0.93 cm^3, 0.93 mmol, 2.5 equiv.), dialdehyde **9b** (100 mg, 0.37 mmol, 1 equiv.) and DCM (10 cm^3) were treated as described in General Procedure B. The crude product was purified by flash column chromatography (7:1 petrol : EtOAc) to yield the product as a white powder (33 mg, 33%). m.p. 142 - 146 ^oC; Rf = 0.09 (7:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3330 (OH); δH (300 MHz; $CDCl_3$) 7.41 (2H, d, *J* 7.5, H-1), 7.16 (1H, t, *J* 7.5, H-2), 6.88 (2H, s, H-3), 4.54 (4H, s, H-6), 2.31 (3H, s, H-5) and 2.11 (6H, s, H-4).; δC (75 MHz; CD_3OD) 152.1, 151.7, 132.7, 131.3, 129.8, 127.9, 126.8, 122.7, 59.2, 19.5 and 16.2.; EI *m/z* 272 (M); CI *m/z* 272 (M); (Found: M + NH_4^+, 290.1745. $C_{17}H_{24}O_3N$ requires *M*, 290.1751). *VT NMR*; In CD_3OD run from RT to –90^oC, modelling H-6 no de-coalescence observed at –90^oC.

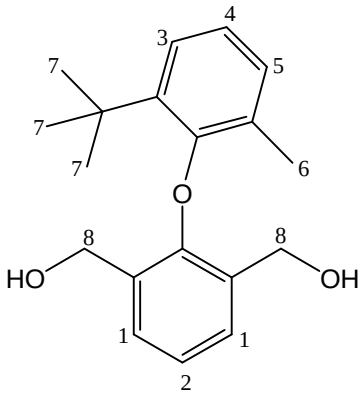
2-[2-(2,6-Diisopropylphenoxy)-3-hydroxymethylphenyl]propan-2-ol **10c'**



Dialdehyde **10b** (50 mg, 0.16 mmol, 1 equiv.), sodium borohydride (61 mg, 1.61 mmol, 10 equiv.) and THF (5 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (8:1 petrol : EtOAc) to yield the product as a white solid (27 mg, 54%). m.p. 110 - 112^oC. Rf = 0.46 (4:1 petrol:EtOAc);

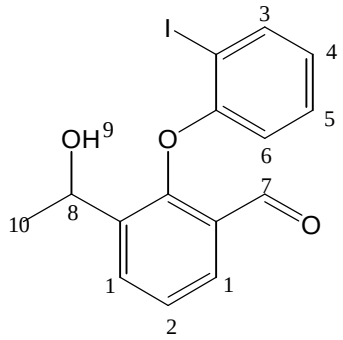
ν_{max}(film/cm^{-1}) 3274 (OH); δH (300 MHz, $CDCl_3$) 7.41 (2H, d, *J* 7.5, H-1), 7.21 (3H, m, H-2, H-3 and H-5), 7.13 (1H, t, *J* 7.5, H-4), 4.50 (4H, s, H-8), 3.16 (2H, sept, *J* 7, H-6) and 1.18 (12H, d, *J* 7, H-7).; δC (75 MHz, CD_3OD) 152.1, 152.0, 139.9, 130.1, 126.8, 124.7, 124.1, 122.1, 59.2, 27.2 and 22.5.; CI *m/z* 332 (M + NH_4^+), 314 (M); (Found: M + NH_4^+, 332.2212. $C_{20}H_{30}O_3N$ requires *M*, 332.2220). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-8 no de-coalescence observed at –90°C.

[2-(2-tert-Butyl-6-methylphenoxy)-3-hydroxymethylphenyl]methanol **11c'**



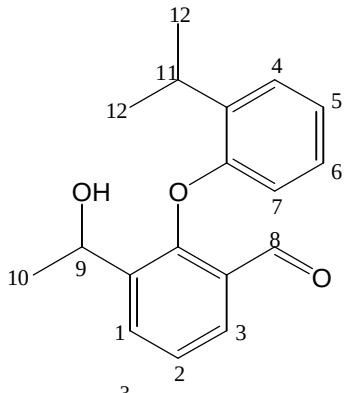
Dialdehyde **11b** (104 mg, 0.3 mmol, 1 equiv.), sodium borohydride (113 mg, 2.98 mmol, 10 equiv.) and anhydrous THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (7:1 petrol : EtOAc) to yield the product as a white solid (75 mg, 83%). m.p. 103 - 108°C; Rf = 0.32 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3323 (OH).; δH (300 MHz; $CDCl_3$) 7.45 (2H, d, *J* 8, H-1), 7.32 (1H, dd, *J* 7.5 and 2, H-3), 7.16 (1H, t, *J* 7.5, H-4), 7.07 (1H, t, *J* 8, H-2), 7.00 (1H, ddd, *J* 7.5, 2 and 0.5, H-5), 4.57 – 4.44 (4H, CHABXY m, *J* 13.5, H-6), 1.84 (3H, s, H-6) and 1.48 (9H, s, H-7).; δC (75 MHz; $CDCl_3$) 155.0, 151.8, 140.4, 130.6, 130.1, 129.0, 128.1, 125.9, 124.3, 123.3, 61.1, 35.6, 30.7 and 18.1.; EI *m/z* 300 (M); CI *m/z* 318 (M + NH_4^+), 300 (M), 283 (M – OH); (Found: M + NH_4^+, 318.2064. $C_{19}H_{28}O_3N$ requires *M*, 318.2064). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 no coalescence observed at 150°C, broadening above 120°C.

2-(2-Iodophenoxy)-3-(1-hydroxyethyl)benzaldehyde **6d**



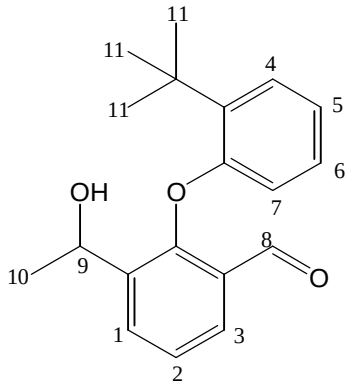
MeLi (1.5M solution in ether) (0.74 cm^3, 1.11 mmol, 1 equiv.), dialdehyde **6b** (392 mg, 1.11 mmol, 1 equiv.) and ether (400 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield alcohol **6d** as a white solid (276 mg, 68%), m.p. 78 - 80^oC. Rf = 0.23 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3437 (OH), 1691 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:4; 10.08 (2H, s, H-$7^{maj+min}$), 8.03 (1H, br d, *J* 8, H-3^{minor}), 7.96 (1H, br d, *J* 8, H-3^{major}), 7.92 (4H, dd, *J* 8 and 1.5, H-$1^{maj+min}$), 7.50 (2H, t, *J* 7.5, H-$2^{maj+min}$), 7.20 (2H, td, *J* 8 and 1.5, H-$4^{maj+min}$), 6.84 (2H, td, *J* 7.5 and 1.5, H-$5^{maj+min}$), 6.41 (1H, br d, *J* 8, H-6^{major}), 6.35 (1H, br d, *J* 8, H-6^{minor}), 5.18 (1H, br, H-8^{minor}), 4.98 (1H, br, H-8^{major}), 1.61 (1H, br d, *J* 6, H-10^{major}) and 1.38 (1H, br d, *J* 6, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 189.2, 158.8, 158.3, 140.5, 134.1, 133.4, 130.1, 129.2, 128.5, 128.2, 127.0, 124.7, 114.1, 113.7, 84.7, 64.9, 63.9, 25.5 and 23.5.; EI *m/z* 368 (M); CI *m/z* 386 (M + NH_4^+); (Found: M + NH_4^+, 386.0246. $C_{15}H_{13}O_3I$ requires *M*, 386.0248). *VT NMR*; In $CDCl_3$ run from –30 to 60^oC, modelling H-8 coalescence observed at 60^oC.

2-(2-Isopropylphenoxy)-3-(1-hydroxyethyl)benzaldehyde **7d**



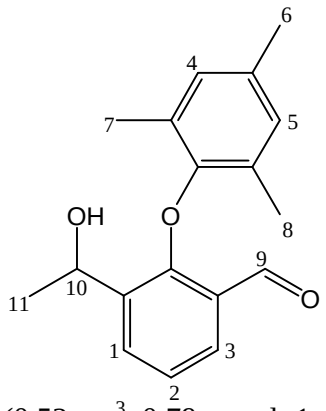
MeLi (1.4 M solution in ether) (3.9 cm^3, 4.29 mmol, 1 equiv.), dialdehyde **7b** (1.15 g, 4.29 mmol, 1 equiv.) and ether (400 cm^3) were treated as described in General Procedure C. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) as the eluant to yield the product **7d** as a light yellow oil (652 mg, 53%). ν_{max}(film/cm^{-1}) 3431 (OH), 1692 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:4. 10.11 (2H, s, H-8$^{maj+min}$), 7.94 (4H, dd, *J* 8 and 1.5, H-1$^{maj+min}$ and H-3$^{maj+min}$), 7.46 (2H, t, *J* 7.5, H-2$^{maj+min}$), 7.39 (2H, m, H-4$^{maj+min}$), 7.03 (4H, m, H-5$^{maj+min}$ and H-6$^{maj+min}$), 6.32 (2H, br, H-7$^{maj+min}$), 5.20 (1H, br, H-9^{minor}), 5.04 (1H, br, H-9^{major}), 3.61 (2H, sep, *J* 7, H-11), 1.54 (6H, br, H-10$^{maj+min}$) and 1.40 (12H, d, *J* 7, H-12).; δC (75 MHz; $CDCl_3$) 189.4, 157.0, 153.7, 140.8, 136.2, 133.8, 133.4, 129.6, 128.1, 127.5, 127.2, 126.4, 123.0, 113.3, 112.8, 64.5, 63.9, 27.4, 25.1 and 23.1.; EI *m/z* 284 (M); CI *m/z* 302 ($M + NH_4^+$); (Found: M, 284.1397. $C_{18}H_{20}O_3$ requires *M*, 284.1407). *VT NMR*; In $CDCl_3$ run from –30 to 55°C, modelling H-9 coalescence observed at 45°C.

2-(2-t-Butylphenoxy)-3-(1-hydroxyethyl)benzaldehyde **8d**



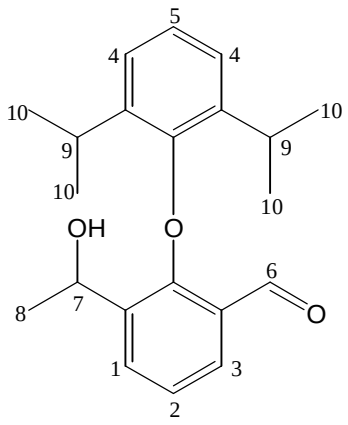
MeLi (1.45M solution in ether) (0.81 cm^3, 1.17 mmol, 1 equiv.), dialdehyde **8b** (330 mg, 1.17 mmol, 1 equiv.) and ether (300 cm^3) were treated as described in General Procedure C. The crude product was purified by flash column chromatography (8:1 petrol : EtOAc) to yield alcohol **8d** as a white solid (236 mg, 68%), m.p. 101 - 102°C. Rf = 0.39 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3386 (OH), 1691 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:4. 10.13 (1H, s, H-8^{major}), 10.09 (1H, s, H-8^{minor}), 8.03 (2H, dd, *J* 7.5 and 2, H-$3^{maj+min}$), 7.99 (2H, ddd, *J* 9.5, 8 and 2, H-$1^{maj+min}$), 7.47 (4H, m, H-$4^{maj+min}$ and H-$2^{maj+min}$), 7.03 (4H, m, H-$5^{maj+min}$ and H-$6^{maj+min}$), 6.35 (1H, m, H-7^{major}), 6.28 (1H, m, H-7^{minor}), 5.27 (1H, q, *J* 6.5, H-9^{minor}), 5.09 (1H, q, *J* 6.5, H-9^{major}), 1.59 (9H, s, H-11^{minor}), 1.58 (9H, s, H-11^{major}), 1.54 (3H, d, *J* 6.5, H-10^{major}) and 1.38 (3H, d, *J* 6.5, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 189.5, 189.4, 159.4, 158.9, 153.7, 153.2, 140.9, 140.5, 137.1, 137.1, 133.9, 133.7, 129.5, 129.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 126.5, 126.4, 122.7, 122.6, 114.2, 113.7, 64.1, 63.9, 35.2, 35.2, 30.1, 30.0, 25.4 and 24.2.; EI *m/z* 298 (M); CI *m/z* 316 (M + NH_4^+); (Found: M, 298.1563. $C_{19}H_{22}O_3$ requires *M*, 298.1563). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 nearing coalescence at 150°C.

2-(2,4,6-Trimethylphenoxy)-3-(1-hydroxyethyl)benzaldehyde **9d**



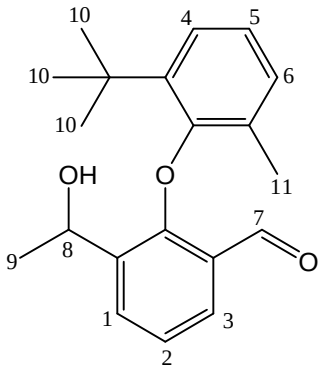
MeLi (1.5 M solution in ether) (0.52 cm^3, 0.79 mmol, 1 equiv.), dialdehyde **9b** (212 mg, 0.79 mmol, 1 equiv.) and anhydrous ether (300 cm^3) were treated as described in General Procedure C. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product **9d** as a white powder (174 mg, 77%), m.p. 91 – 96^oC. Rf = 0.32 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3433 (OH), 1680 (CHO); δH (300 MHz; $CDCl_3$) 9.73 (1H, s, H-9), 7.81 (1H, dd, *J* 7.5 and 2, H-3), 7.71 (1H, dd, *J* 7.5 and 2, H-1), 7.21 (1H, t, *J* 8, H-2), 6.89 (1H, br s, H-4), 6.86 (1H, br s, H-5), 5.32 (1H, q, *J* 6.5, H-10), 2.29 (3H, s, H-6), 2.15 (3H, s, H-7), 2.06 (3H, s, H-8) and 1.57 (3H, d, J 6.5, H-11).; δC (75 MHz; $CDCl_3$) 189.0, 156.9, 154.0, 137.1, 134.6, 132.7, 131.1, 130.9, 128.4, 128.2, 127.7, 127.0, 123.3, 65.3, 24.1, 20.9, 17.4 and 17.2.; EI *m/z* 284 (M); CI *m/z* 302 (M + NH_4^+); Found: M, 284.1409. $C_{18}H_{20}O_3$ requires *M*, 284.1407. *VT NMR*; In CD_3OD run from RT to –90^oC, modelling H-10 no de-coalescence at –90^oC.

2-(2,6-Diisopropylphenoxy)-3-(1-hydroxyethyl)benzaldehyde **10d**



MeLi (1.5M solution in ether) (0.69 cm^3, 1.03 mmol, 1 equiv.), dialdehyde **10b** (320 mg, 1.03 mmol, 1 equiv.) and ether (400 cm^3) were treated as described in General Procedure C. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product **10d** as a white solid (276 mg, 82%), m.p. 50 - 52^oC; Rf = 0.82 (5:1 petrol:EtOAc);. ν_{max}(film/cm^{-1}) 3436 (OH), 1679 (CHO); δH (300 MHz; $CDCl_3$) 9.38 (1H, s, H-10), 7.83 (1H, dd, *J* 7.5 and 2, H-3), 7.69 (1H, dd, *J* 7.5 and 2, H-1), 7.21 (4H, m, H-2, H-4 and H-5), 5.39 (1H, q, *J* 6.5, H-7), 3.10 (2H, sept, *J* 7, H-9), 1.61 (3H, d, *J* 6.5, H-8), 1.24 (3H, d, *J* 7, H-10), 1.23 (3H, d, *J* 7, H-10), 1.15 (3H, d, *J* 7, H-10) and 1.09 (3H, d, *J* 7, H-10).; δC (75 MHz; $CDCl_3$) 188.9, 157.2, 153.2, 139.5, 13.9.3, 136.1, 132.4, 129.0, 126.6, 126.1, 125.8, 125.6, 122.7, 65.7, 27.7, 27.6, 24.6, 24.5, 24.0, 22.4 and 22.3.; EI *m/z* 326 (M); CI *m/z* 344 (M + NH_4^+); (Found: M + NH_4^+, 344.2226. $C_{21}H_{30}O_3N$ requires *M*, 344.2220). *VT NMR*; In CD_3OD run from RT to –90^oC, modelling H-10 no de-coalescence at –90^oC.

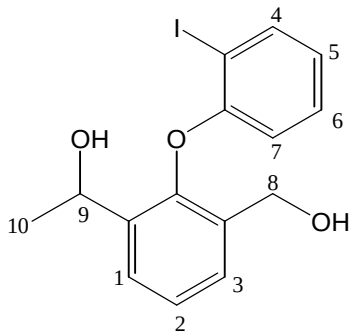
2-(2-t-Butyl-6-methylphenoxy)-3-(1-hydroxyethyl)benzaldehyde **11d**



MeLi (1.5M in ether) (1.05 cm^3, 1.47 mmol, 1 equiv.), dialdehyde **11b** (438 mg, 1.47 mmol, 1 equiv.) and ether (300 cm^3) were treated as described in General Procedure C. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the first diastereoisomer of alcohol **11d** as a light yellow oil (242 mg, 53%). Rf = 0.71 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3424 (OH), 1678 (CHO); δH (300 MHz; $CDCl_3$) 9.52 (1H, s, H-7), 7.85 (1H, ddd, *J* 7.5, 2 and 0.5, H-3), 7.74 (1H, dd, *J* 8 and 2, H-1), 7.35 (1H, dd, *J* 8 and 2, H-4), 7.20 (1H, t, *J* 8, H-2), 7.12 (1H, t, *J* 7.5, H-5), 7.05 (1H, ddd, J 7.5, 2 and 0.5, H-6), 5.38 (1H, q, *J* 6.5, H-8), 1.87 (3H, s, H-11), 1.56 (3H, d, *J* 6.5, H-9) and 1.50 (9H, s, H-10); δC (75 MHz; $CDCl_3$) 188.8, 156.3, 156.2, 140.7, 136.2, 133.1, 131.6, 128.8, 127.5, 126.4, 125.4, 123.1, 65.0, 35.5, 30.7, 23.6 and 18.1.; EI *m/z* 313 (M + H); CI *m/z* 330 (M + NH_4^+), 312 (M), 295 (M – OH); (Found: M + NH_4^+, 330.2069. $C_{20}H_{28}O_3N$ requires *M*, 330.2064).

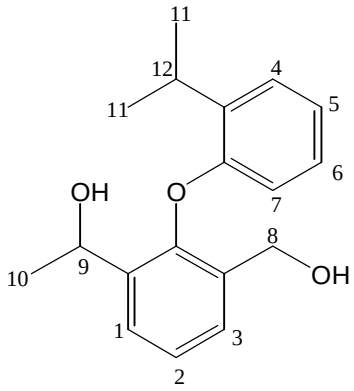
Also obtained was a second diastereoisomer of **11d** as a white solid (133 mg, 30%), m.p. 45 – 48°C. Rf = 0.58 (5:1 petrol:EtOAc); δH (300 MHz; $CDCl_3$) 9.45 (1H, s, H-7), 7.90 (1H, ddt, *J* 8, 2 and 0.5, H-3), 7.75 (1H, dd, *J* 8 and 2, H-1), 7.34 (1H, dd, *J* 7.5 and 2, H-4), 7.21 (1H, td, *J* 8 and 0.5, H-2), 7.10 (1H, t, *J* 7.5, H-5), 7.03 (1H, m, H-6), 5.51 (1H, q, *J* 6.5, H-8), 1.85 (3H, s, H-11), 1.63 (3H, d, *J* 6.5, H-9) and 1.49 (9H, s, H-10).; δC (75 MHz; $CDCl_3$) 188.7, 156.8, 156.0, 140.4, 137.2, 132.6, 131.7, 128.6, 127.4, 126.4, 126.3, 125.2, 123.2, 64.7, 35.5, 30.4, 24.9 and 18.1.; EI *m/z* 312 (M); CI *m/z* 330 (M + NH_4^+), 312 (M), 295 (M – OH); (Found: M + NH_4^+, 330.2070. $C_{20}H_{28}O_3N$ requires *M*, 330.2064).

1-[3-Hydroxymethyl-2-(2-iodophenoxy)phenyl]ethanol **6d'**



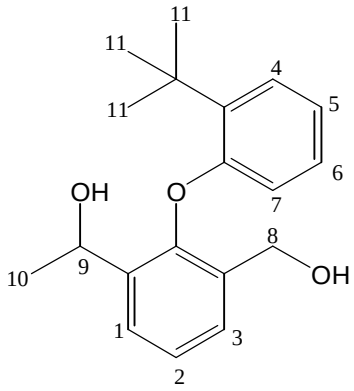
Alcohol **6d** (158 mg, 0.43 mmol, 1 equiv.), sodium borohydride (130 mg, 3.44 mmol, 8 equiv.) and THF (15 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (5:1 petrol:EtOAc) to yield the product as a white gum (136 mg, 85%). Rf = 0.12 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3368 (OH); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 5:4. 7.88 (2H, dd, *J* 8 and 1.5, H-$1^{maj+min}$), 7.65 (1H, dd, *J* 7.5 and 1.5, H-4^{major}), 7.58 (1H, dd, *J* 7.5 and 1.5, H-4^{minor}), 7.51 (2H, ddd, *J* 7.5, ? and 1.5, H-$3^{maj+min}$), 7.38 (2H, td, *J* 7.5 and 1, H-$2^{maj+min}$), 7.18 (2H, td, *J* 7.5 and 1.5, H-$5^{maj+min}$), 6.81 (2H, tt, *J* 7.5 and 1.5, H-$6^{maj+min}$), 6.41 (1H, *J* 8 and 1.5, H-7^{major}), 6.34 (1H, dd, *J* 8 and 1.5, H-7^{minor}), 5.05 (1H, q, *J* 6.5, H-9^{major}), 4.89 (1H, q, *J* 6.5, H-9^{minor}), 4.66 – 4.41 (4H, CH ABXY m, *J* 13.5, 2.5 and 0.5, H-$8^{maj+min}$), 1.54 (1H, d, *J* 6.5, H-10^{major}) and 1.37 (1H, d, *J* 6.5, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 157.4, 156.7, 149.4, 147.0, 140.6, 140.3, 140.1, 135.5, 135.4, 130.5, 130.4, 127.0, 126.6, 126.5, 125.6, 124.5, 114.1, 113.4, 85.9, 85.8, 63.7, 62.8, 58.3, 58.2, 26.4 and 25.7.; CI *m/z* 388 (M + NH_4^+), 370 (M); (Found: M + NH_4^+, 388.0411. $C_{15}H_{19}O_3NI$ requires *M*, 388.0404). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 coalescence observed at 120°C.

1-[3-Hydroxymethyl-2-(2-isopropylphenoxy)phenyl]ethanol **7d'**



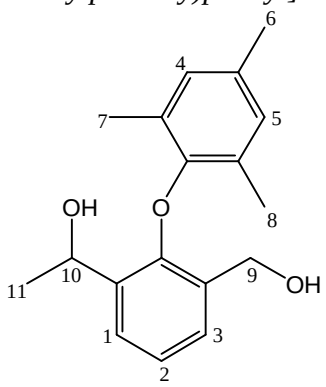
Alcohol **7d** (140 mg, 0.52 mmol, 1 equiv.), sodium borohydride (157 mg, 4.16 mmol, 8 equiv.) and THF (15 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (4:1 petrol:EtOAc) to yield the product as a colourless gum (122 mg, 82%). Rf = 0.04 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3338 (OH); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:4. 7.61 (1H, dd, *J* 7.5 and 1.5, H-4^{major}), 7.55 (1H, dd, *J* 7.5 and 1.5, H-4^{minor}), 7.48 (2H, br d, *J* 7.5, H-$1^{maj+min}$), 7.34 (4H, m, H-$3^{maj+min}$ and H-$2^{maj+min}$), 6.99 (4H, m, H-$5^{maj+min}$ and H-$6^{maj+min}$), 6.32 (1H, m, H-7^{major}), 6.23 (1H, m, H-7^{minor}), 5.07 (1H, q, *J* 6.5, H-9^{minor}), 4.92 (1H, q, *J* 6.5, H-9^{major}), 4.52 (2H, CH ABXY m, *J* 13.5, H-8^{major}), 4.48 (2H, CH ABXY m, *J* 13.5, H-8^{minor}), 3.56 (2H, m, H-$12^{maj+min}$), 1.46 (3H, d, *J* 6.5, H-10^{major}), 1.38 (3H, d, *J* 7, H-11^{major}), 1.37 (3H, d, *J* 7, H-11^{minor}) and 1.31 (3H, d, *J* 6.5, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 155.8, 155.5, 148.7, 148.1, 139.6, 139.0, 136.3, 136.2, 134.5, 134.4, 128.3, 128.1, 127.2, 127.1, 126.9, 136.5, 126.3, 126.1, 122.4, 112.5, 112.0, 65.0, 64.3, 60.5, 60.4, 27.4, 25.0, 23.4, 23.1, and 23.0.; EI *m/z* 286 (M); CI *m/z* 304 (M + NH_4^+); (Found: M + NH_4^+, 304.1908. $C_{18}H_{26}O_3N$ requires *M*, 304.1907). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 coalescence observed at 90°C.

1-[3-Hydroxymethyl-2-(2-t-butylphenoxy)phenyl]ethanol **8d'**



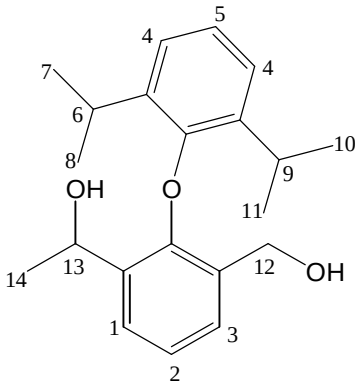
Alcohol **8d** (50 mg, 0.17 mmol, 1 equiv.), sodium borohydride (51 mg, 1.36 mmol, 8 equiv.) and THF (8 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (6:1 petrol:EtOAc) to yield the product as a colourless oil (29 mg, 57%). m.p. 46 - 48 ^oC; Rf = 0.68 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3338 (OH); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:5. 7.66 (1H, dd, *J* 7.5 and 1.5, H-4^{major}), 7.63 (1H, dd, *J* 7.5 and 1.5, H-4^{minor}), 7.54 (2H, m, H-$1^{maj+min}$), 7.43 (2H, dd, *J* 7.5 and 2.5, H-$3^{maj+min}$), 7.38 (2H, td, *J* 7.5 and 1.5, H-$2^{maj+min}$), 7.02 (4H, m, H-$5^{maj+min}$, and H-$6^{maj+min}$), 6.33 (1H, dd, *J* 7.5 and 2, H-7^{major}), 6.25 (1H, dd, *J* 7.5 and 2, H-7^{minor}), 5.13 (1H, q, *J* 6.5, H-9^{minor}), 4.98 (1H, q, *J* 6.5, H-9^{major}), 4.53 (2H, CH ABXY m, *J* 13.5, H-8^{major}), 4.52 (2H, CH ABXY m, *J* 13.5, H-8^{minor}), 1.58 (9H, s, H-11^{minor}), 1.56 (9H, s, H-11^{major}), 1.48 (3H, d, *J* 6.5, H-10^{major}) and 1.33 (3H, d, *J* 6.5, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 157.6, 157.4, 14.2, 147.7, 139.7, 139.2, 137.3, 137.2, 134.4, 134.3, 128.6, 128.5, 127.9, 127.8, 127.6, 127.4, 126.7, 126.5, 126.5, 126.4, 122.1, 122.0, 113.2, 112.7, 64.6, 64.3, 60.6, 60.5, 35.3, 35.2, 30.2, 30.1, 25.2 and 23.8.; CI *m/z* 318 (M + NH_4^+), 300 (M); (Found: M, 300.1718. $C_{19}H_{24}O_3$ requires *M*, 300.1720). *HPLC*; Separation using Inertsil OD-3 column running 0.6 ml/min with 98.2 : 1.8 hexane:IPA, retention times 16.1 and 17.7 min.

1-[3-Hydroxymethyl-2-(2,4,6-trimethylphenoxy)phenyl]ethanol **9d'**



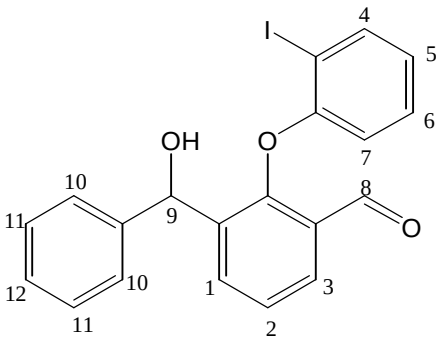
Alcohol **9d** (60 mg, 0.21 mmol, 1 equiv.), sodium borohydride (64 mg, 1.68 mmol, 8 equiv.) and THF (8 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (9:1 petrol:EtOAc) to yield the product as white blocks (42 mg, 70%). m.p. 116 - 120^{o}C; Rf = 0.18 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3349 (OH); δH (300 MHz; $CDCl_3$) 7.47 (1H, m, H-1), 7.34 (1H, m, H-3), 7.16 (1H, t, *J* 8, H-2), 6.86 (1H, br s, H-4), 6.83 (1H, br s, H-4), 5.19 (1H, q, *J* 6.5, H-10), 4.34 (2H, s, H-9), 2.29 (3H, s, H-6), 2.10 (3H, s, H-7), 2.04 (3H, br s, H-8) and 1.48 (3H, d, *J* 6.5, H-10).; δC (75 MHz; $CDCl_3$) 152.3, 136.2, 133.4, 130.6, 130.5, 128.8, 128.3, 128.1, 127.8, 126.3, 123.7, 65.5, 61.2, 23.8, 20.8, 17.6 and 17.5.; EI *m/z* 286 (M); CI *m/z* 304 (M + NH_4^+); (Found: M + NH_4^+, 304.1913. $C_{18}H_{26}O_3N$ requires *M*, 304.1907). *VT NMR*; In CD_3OD run from RT to –90^{o}C, modelling H-10 no de-coalescence observed at –90^{o}C.

2-(2,6-Diisopropyl-phenoxy)-3-hydroxymethyl-phenyl]-ethanol **10d'**



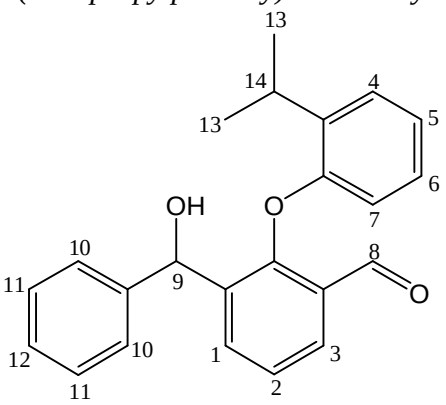
Alcohol **10d** (110 mg, 0.34 mmol, 1 equiv.), sodium borohydride (103 mg, 2.72 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (5:1 petrol:EtOAc) to yield the product as a white solid (90 mg, 81%). m.p. 110 - 112^oC; Rf = 0.45 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3349 (OH); δH (300 MHz; $CDCl_3$) 7.53 (1H, dd, *J* 8 and 2, H-1), 7.35 (1H, dd, *J* 8 and 2, H-3), 7.20 (3H, m, H-4 and H-5), 7.14 (1H, t, *J* 8, H-2), 5.25 (1H, q, *J* 6.5, H-13), 4.25 (2H, s, H-12), 3.20 (1H, sept, *J* 7, H-6), 3.12 (1H, sept, *J* 7, H-9), 1.52 (3H, d, *J* 6.5, H-14), 1.19 (3H, d, *J* 7, H-7), 1.18 (3H, d, *J* 7, H-10), 1.17 (3H, d, *J* 7, H-8) and 1.11 (3H, d, *J* 7, H-11).; δC (75 MHz; $CDCl_3$) 152.9, 152.0, 140.1, 139.8, 135.4, 129.6, 129.2, 126.6, 125.4, 124.9, 124.7, 123.2, 65.6, 61.3, 27.5, 27.3, 24.6, 24.4, 23.9, 22.8 and 22.7.; EI *m/z* 328 (M); CI *m/z* 346 (M + NH_4^+), 328 (M); (Found: M + NH_4^+, 346.2374. $C_{21}H_{32}O_3N$ requires *M*, 346.2377). *VT NMR*; In CD_3OD run from RT to –90^oC, modelling H-10 no de-coalescence observed at –90^oC.

3-(Hydroxyphenylmethyl)-2-(2-iodophenoxy)benzaldehyde **6e**



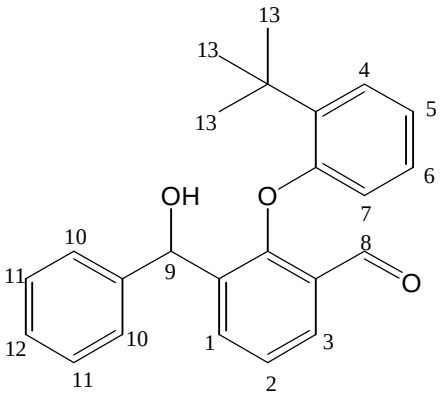
PhLi (1.6 M in ether) (1.3 cm^3, 1.99 mmol, 1 equiv.), dialdehdye **6b** (700 mg, 1.99 mmol, 1 equiv.) and ether (400 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield alcohol **6e** as a white foam (192 mg, 22%), m.p. 42 - 45^oC. Rf = 0.23 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3446 (OH), 1690 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 6:4. 10.00 (1H, s, H-8^{major}), 9.97 (1H, s, H-8^{minor}), 8.38 (2H, br t, *J* 7.5, H-3$^{maj+min}$), 7.90 (1H, br d, *J* 7.5, H-4^{major}), 7.81 (1H, br d, *J* 7.5, H-4^{minor}), 7.47 (4H, m, H-1$^{maj+min}$ and H-2$^{maj+min}$), 7.38 (4H, m, H-10$^{maj+min}$), 7.15 (6H, m, H11$^{maj+min}$ and H-12$^{maj+min}$), 6.82 (3H, H-5$^{maj+min}$ and H-6^{major}), 6.67 (1H, br t, *J* 7.5, H-6^{minor}), 6.40 (1H, br d, *J* 8, H-7^{major}), 6.13 (1H, s, H-9^{minor}), 5.93 (1H, s, H-9^{major}) and 5.84 (1H, br d, *J* 8, H-7^{minor}).; δC (75 MHz; $CDCl_3$) 189.0, 158.3, 154.0, 153.6, 142.9, 140.5, 140.0, 138.7, 134.5, 130.1, 129.6, 129.2, 128.9, 128.6, 128.1, 127.3, 127.0, 126.8, 126.6, 124.7, 124.3, 113.9, 84.6 and 70.5.; EI *m/z* 430 (M); (Found: M + NH_4^+, 448.0407. $C_{20}H_{19}O_3NI$ requires *M*, 448.0404). *VT NMR*; In $CDCl_3$ run from –45 to 65^oC, modelling H-9 coalescence observed at 60^oC.

3-(Hydroxyphenylmethyl)-2-(2-isopropylphenoxy)benzaldehyde **7e**



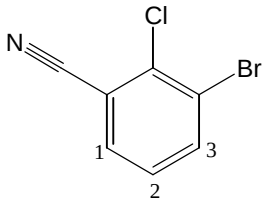
PhLi (1.65 M in ether) (0.68 cm^3, 1.12 mmol, 1 equiv.), dialdehyde **7b** (300 mg, 1.12 mmol, 1 equiv.) and ether (400 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (12:1 petrol : EtOAc) to yield alcohol **7e** as a colourless oil (102 mg, 26%). Rf = 0.49 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3445 (OH), 1691 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 3:2. 10.08 (2H, br s, H-8), 8.06 (1H, br d, *J* 7.5, H-3^{major}), 7.88 (1H, br, H-3^{minor}), 7.47 – 7.22 (14H, br m, H-$1^{maj+min}$, H-$2^{maj+min}$, H-$10^{maj+min}$, H-$11^{maj+min}$ and H-$12^{maj+min}$), 7.21 (2H, br, H-$4^{maj+min}$), 7.06 (2H, br, H-$5^{maj+min}$), 6.95 (1H, br, H-6^{major}), 6.81 (1H, br, H-6^{minor}), 6.42 (1H, br, H-7^{major}), 6.14 (1H, br, H-7^{minor}), 5.97 (2H, br, H-$9^{maj+min}$), 3.61 (1H, br, H-14^{minor}), 3.42 (1H, br, H-14^{major}) and 1.43 – 1.27 (12H, br, H-$13^{maj+min}$).; δC (75 MHz; $CDCl_3$) 189.2, 157.3 br, 156.8 br, 142.9 br, 138.7, 135.0 br, 134.5 br, 129.6, 128.8 br, 128.6 br, 128.1 br, 127.3 br, 126.9 br, 126.7 br, 126.3 br, 123.1 br, 122.8 br, 113.4 br, 113.0 br, 70.2, 27.5 br, 26.8 br, 23.5 br and 22.9 br.; EI *m/z* 346 (M); CI *m/z* 364 (M + NH_4^+); (Found: M + NH_4^+, 364.1917. $C_{23}H_{26}O_3N$ requires *M*, 364.1907). *VT NMR*; In d_8-toluene run from –80 to 100°C, modelling H-9 coalescence observed at 50°C.

2-(2-tert-Butylphenoxy)-3-(hydroxyphenylmethyl)benzaldehyde **8e**



PhLi (1.7 M in ether) (0.2 cm^3, 0.35 mmol, 1 equiv.), dialdehyde **8b** (100 mg, 0.35 mmol, 1 equiv.) and ether (200 cm^3) were treated as described in general procedure C. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield alcohol **8e** as a colourless oil (90 mg, 71%). Rf = 0.27 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3423 (OH), 1690 (CHO); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 10:9. 10.12 (1H, s, H-8^{minor}), 10.06 (1H, s, H-8^{major}), 8.00 (1H, dd, *J* 7.5 and 2, H-3^{major}), 7.97 (1H, dd, *J* 7.5 and 2, H-1^{major}), 7.92 (1H, dd, *J* 7.5 and 2, H-3^{minor}), 7.87 (1H, dd, *J* 7.5 and 2, H-3^{minor}), 7.47 – 7.31 (14H, m, H-$2^{maj+min}$, H-$4^{maj+min}$ and H10 – $12^{maj+min}$), 7.07 (2H, m, H-$5^{maj+min}$), 6.93 (1H, td, *J* 8 and 1.5, H-6^{major}), 6.82 (1H, td, *J* 8 and 1.5, H-6^{minor}), 6.44 (1H, dd, *J* 8 and 1.5, H-7^{major}), 6.18 (1H, br d, *J* 3, H-9^{major}), 6.12 (1H, br d, *J* 3.5, H-9^{minor}), 5.98 (1H, dd, *J* 8 and 1.5, H-7^{minor}), 1.62 (9H, s, $H13^{major}$) and 1.48 (9H, s, H-13^{minor}).; δC (75 MHz; $CDCl_3$) 189.4, 489.3, 159.2, 159.1, 154.5, 154.3, 142.7, 12.1, 138.8, 138.7, 137.3, 136.8, 135.9, 135.2, 129.6, 128.9, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.7, 127.5, 127.0, 126.7, 126.4, 126.2, 122.9, 122.5, 114.6, 114.2, 70.07, 69.3, 35.3, 35.2, 30.2 and 30.1.; CI *m/z* 378 (M + NH_4^+); (Found: M + NH_4^+, 378.2066. $C_{24}H_{28}O_3N$ requires *M*, 378.2064). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-8 coalescence observed at 150°C.

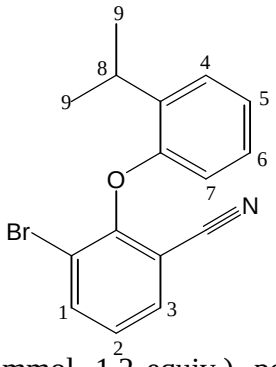
3-Bromo-2-chlorobenzonitrile **20**



A solution of 3-bromobenzonitrile (5 g, 27.47 mmol, 1 equiv.), in anhydrous THF (100 cm^3) and cooled to –95°C, was added dropwise to a stirring solution of LDA (32.96 mmol, 1.2 equiv.) in THF (50 cm^3) at –95°C and allowed to stir for 1 hr. Hexachloroethane (10.4 g, 43.94 mmol, 1.6 equiv.), dissolved in anhydrous THF (150 cm^3) and cooled to –95°C, was added to the reaction mixture at this temperature and the mixture allowed to stir for 1 hr and warmed to RT over a period of 16 hrs. The mixture was quenched by addition of saturated ammonium chloride solution and organics extracted using EtOAc. The organics were washed with water, brine, dried (sodium sulphate) and evaporated to dryness. The product was purified by flash column chromatography (80:1 increasing to 60:1 petrol : EtOAc) to yield the product as light yellow needles (3.85 g, 86%), m.p. 62 - 64°C. Rf = 0.64 (19:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2227 (CN); δH (300 MHz; $CDCl_3$) 7.89 (1H, dd, *J* 8 and 1.5, H-1), 7.68 (1H, dd, *J* 8 and 1.5, H-3), 7.29 (1H, t, *J* 8, H-2).; δC (75 MHz; $CDCl_3$) 138.3, 133.2, 128.3, 124.5, 115.8 and 115.4 (No CN peak observed).

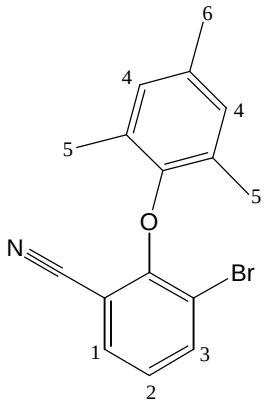
LDA: *n*-BuLi (1.4M in Hexanes) (23.5 cm^3, 32.96 mmol, 1 equiv.) was added dropwise to a stirred solution of anhydrous diisopropylamine (4.6 cm^3, 32.96 mmol, 1 equiv.) dissolved in anhydrous THF (50 cm^3) at 0°C under N_2 and allowed to stir for 30 min.

3-Bromo-2-(2-isopropylphenoxy)benzonitrile **21a**



2-Isopropylphenol (1.81 g, 13.3 mmol, 1.2 equiv.), potassium hydroxide (0.75 g, 13.3 mmol, 1.2 equiv.) and toluene (80 cm^3) were treated as described in General Procedure A. 2-Chloro-3-bromobenzonitrile **20** (2.4 g, 11.09 mmol, 1 equiv.), 2-isopropyl-phenoxide (2.32 g, 13.3 mmol, 1.2 equiv.), and dry DMF (80 cm^3) reacted as outlined in General Procedure A. The crude product was purified by flash column chromatography (40:1 petrol : EtOAc) to yield the product as a yellow solid (2.6 g, 74%), m.p. 59 - 61^oC. Rf = 0.61 (19:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2233 (CN); δH (300 MHz; $CDCl_3$) 7.93 (1H, dd, *J* 8 and 1.5, H-1), 7.70 (1H, dd, *J* 8 and 2, H-3), 7.39 (1H, dd, *J* 7 and 2.5, H-4), 7.26 (1H, t, *J* 8, H-2), 7.09 (2H, m, H-5 and H-6), 6.32 (1H, dd, *J* 7 and 2, H-7), 3.61 (1H, sept, *J* 7, H-8) and 1.41 (6H, d, *J* 7, H-8).; δC (75 MHz $CDCl_3$) 154.6, 154.5, 138.9, 137.4, 133.5, 127.5, 126.8, 126.5, 123.7, 118.9, 113.1, 109.9, 27.5 and 22.9.; EI *m/z* 315 (M); CI *m/z* 333 (M + NH_4^+); (Found: M + NH_4^+, 333.0598. $C_{16}H_{18}ON_2Br$ requires *M*, 333.0597).

3-Bromo-2-(2,4,6-trimethylphenoxy)benzonitrile **21b**



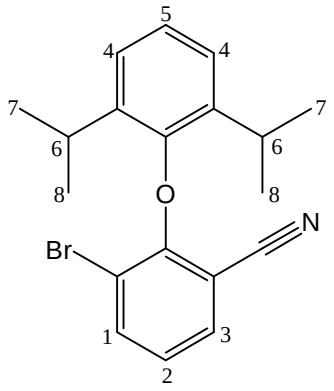
2,4,6-Trimethylphenoxide

2,4,6trimethylphenol (1.81 g, 13.3 mmol, 1.2 equiv.), potassium hydroxide (746 mg, 13.3 mmol, 1.2 equiv.) and toluene (80 cm^3) were treated as described in general procedure A.

3-Bromo-2-(2,4,6-trimethylphenoxy)benzonitrile

2-Chloro-3-bromobenzonitrile (2.4 g, 11.09 mmol, 1 equiv.), 2-*t*-butyl-phenoxide (2.32 g, 13.3 mmol, 1.2 equiv.) and anhydrous DMF (150 cm^3) were treated as described in general procedure A. The crude product was purified by flash column chromatography (45:1 petrol : EtOAc) and recrystallised from ethanol to yield the product **21b** as a light yellow powder (1.31 g, 37%). m.p. 91 - 93^oC; Rf = 0.35 (19:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2224 (CN); δH (300 MHz; $CDCl_3$) 7.87 (1H, dd, *J* 8 and 2, H-1), 7.50 (1H, dd, *J* 8 and 2, H-3), 6.99 (1H, t, *J* 8, H-2), 2.35 (3H, s, H-6) and 2.15 (6H, s, H-5).; δC (75 MHz, $CDCl_3$) 156.1, 150.1, 138.8, 136.1, 134.8, 130.4, 129.9, 123.1, 114.6, 114.2, 101.9, 21.1 and 16.8.; EI *m/z* 315 (M); CI *m/z* 333 (M + NH_4^+); (Found: M + NH_4^+, 333.0600. $C_{16}H_{18}N_20Br$ requires *M*, 333.0597).

2-(2,6-Diisopropylphenoxy)-3-bromobenzonitrile **21c**



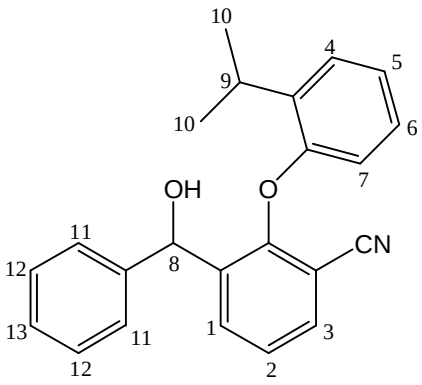
2,6-Diisopropylphenoxide

2,6-diisopropylphenol (1.51 cm^3, 8.15 mmol, 1.2 equiv.), potassium hydroxide (457 mg, 8.15 mmol, 1.2 equiv.), and toluene (80 cm^3) were treated as described in General Procedure A.

2-(2,6-Diisopropylphenoxy)-3-bromobenzonitrile

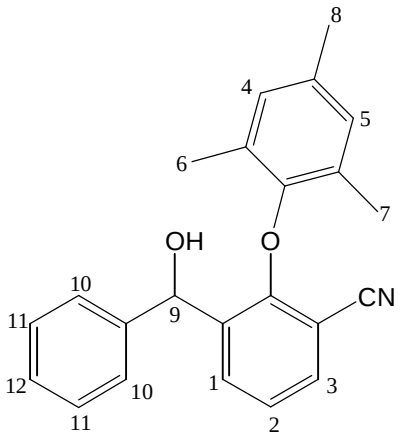
2-Chloro-3-bromobenzonitrile (1.47 g, 6.79 mmol, 1 equiv.), 2-isopropyl-phenoxide (1.77 g, 8.15 mmol, 1.2 equiv.), and dry DMF (80 cm^3) reacted as outlined in General Procedure A. The crude product was purified by flash column chromatography (60:1 petrol : EtOAc) to yield the product **21c** as a yellow solid (1.38 g, 57%), m.p. 30 - 32^oC. Rf = 0.59 (19:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2222 (CN); δH (300 MHz; $CDCl_3$) 7.89 (1H, dd, *J* 8 and 2, H-1), 7.48 (1H, dd, *J* 8 and 2, H-3), 7.37 (1H, m, H-2), 7.24 (2H, d, *J* 8, H-4), 6.80 (1H, t, *J* 8, H-5), 2.96 (2H, sept, *J* 7, H-6), 1.27 (6H, d, *J* 7, H-7) and 1.41 (6H, d, *J* 7, H-8).; δC (75 MHz $CDCl_3$) 156.2, 149.1, 141.6, 138.9, 135.2, 127.8, 124.5, 122.8, 114.0, 114.0, 100.4, 28.0, 24.5 and 22.5.; EI *m/z* 357 (M); CI *m/z* 375 (M + NH_4^+); (Found: M, 357.0716. $C_{19}H_{20}ONBr$ requires *M*, 357.0723).

2-(2-Isopropylphenoxy)-3-(hydroxy(phenyl)methyl)benzonitrile **22a**



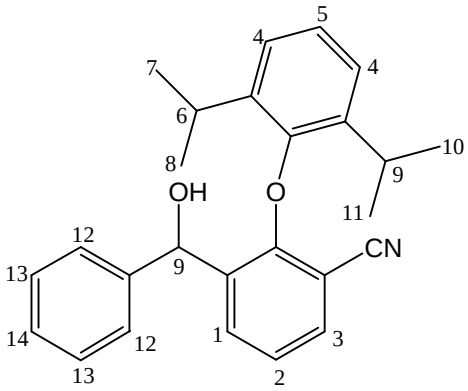
Bromide **21a** (330 mg, 1.05 mmol, 1 equiv.), nBuLi (2.3 M in hexanes) (0.46 cm^3, 1.05 mmol, 1 equiv.), benzaldehyde (0.13 cm^3, 1.26 mmol, 1.2 equiv.) and THF (20 cm^3) were treated as described in General Procedure H. The crude product was purified by flash column chromatography (9:1 petrol : EtOAc) to yield the product as a light yellow oil (233 mg, 65%). Rf = 0.25 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3413 (OH), 2233 (CN); δH (300 MHz; $CDCl_3$) Mixture of two diastereoisomers in the ratio of 3:2. 8.04 – 7.94 (2H, br m, H-$1^{maj+min}$), 6.62 (2H, br d, *J* 7.5, H-$3^{maj+min}$), 7.41 – 7.23 (16H, br m, H-$2^{maj+min}$, H-$4^{maj+min}$, H-$5^{maj+min}$, H-$11^{maj+min}$, H-$12^{maj+min}$ and H-$13^{maj+min}$), 7.09 (2H, br, H-$6^{maj+min}$), 6.87 (1H, br, H-7^{minor}), 6.44 (1H, br, H-7^{major}), 6.11 (1H, br, H-8^{minor}), 5.96 (1H, br, H-8^{major}), 3.57 (1H, br, H-9^{minor}), 3.41 (1H, br, H-9^{major}) and 1.36 (12H, br, H-$10^{maj+min}$).; δC (75 MHz; $CDCl_3$) 154.9 (br), 141.0, 139.1, 137.6 (br), 133.7 (br), 133.3, 132. 8 (br), 132.5, 129.0, 128.8, 128.5, 128.2, 127.9, 127.3, 127.2 (br), 126.8 (br), 125.7 (br), 123.6, 115.6, 114.1 (br), 113.3 (br), 70.5 (br), 27.5 (br), 27.0 (br), 23.2 and 22.9.; EI *m/z* 343 (M); CI *m/z* 361 (M + NH_4^+), 343 (M); (Found: M + NH_4^+, 361.1912. $C_{23}H_{25}O_2N_2$ requires *M*, 361.1911). *VT NMR*; In CD_3OD run from –90 to 60°C, modelling H-8 coalescence observed at 30°C.

3-(Hydroxyphenylmethyl)-2-(2,4,6-trimethylphenoxy)benzonitrile **22b**



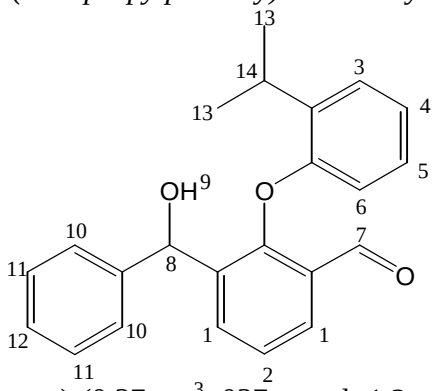
Bromide **21b** (1.51 g, 4.18 mmol, 1 equiv.), nBuLi (2.4 M in hexanes) (1.7 cm^3, 4.18 mmol, 1 equiv.), benzaldehyde (0.51 cm^3, 5.02 mmol, 1.2 equiv.) and THF (30 cm^3) were treated as described in General Procedure H, stirring for 1 min before quench. The crude product was purified by flash column chromatography (25:1 increasing to 10:1 petrol : EtOAc) to yield the product as an orange oil (655 mg, 46%). Rf = 0.31 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3424 (OH), 2222 (CN); δH (300 MHz; $CDCl_3$) 7.95 (1H, ddd, *J* 8, 2 and 1, H-1), 7.44 – 7.29 (6H, m, H-3, H-10, H-11 and H-12), 7.13 (1H, t, *J* 7.5, H-2), 6.88 (1H, s, H-4), 6.82 (1H, s, H-5), 6.24 (1H, s, H-9), 2.31 (3H, s, H-6), 2.05 (3H, s, H-7) and 1.66 (3H, s, H-8).; δC (75 MHz; $CDCl_3$) 155.7, 148.9, 142.6, 136.4, 134.9, 134.3, 132.1, 131.2, 130.7, 129.6, 129.6, 128.8, 128.2, 127.3, 127.2, 122.1, 114.9, 98.5, 71.8, 21.1, 16.5 and 16.0.; EI *m/z* 343 (M); CI *m/z* 361 ($M + NH_4^+$), 326 (M – OH); (Found: $M + NH_4^+$, 361.1916. $C_{23}H_{25}O_2N_2$ requires *M*, 361.1911).

2-(2,6-Diisopropylphenoxy)-3-(hydroxy(phenyl)methyl)benzonitrile **22c**



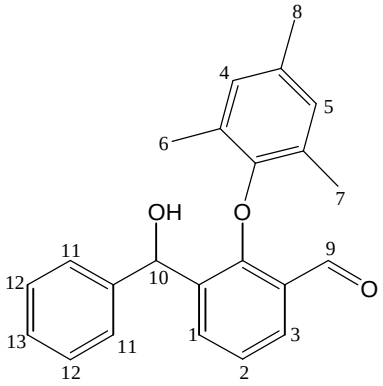
Bromide **21c** (848 mg, 2.37 mmol, 1 equiv.), *n*-BuLi (2.3 M in hexanes) (1.03 cm^3, 2.37 mmol, 1 equiv.), benzaldehyde (0.26 cm^3, 2.6 mmol, 1.1 equiv.) and THF (20 cm^3) were treated as described in General Procedure H. Purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product as a yellow solid (427 mg, 47%), m.p. 143 - 145^{o}C. Rf = 0.36 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3436 (OH), 2221 (CN); δH (300 MHz; $CDCl_3$) 7.95 (1H, ddd, *J* 7.5, 2 and 0.5, H-1), 7.47 – 7.31 (7H, m, H-2, H-3, H-12, H-13 and H-14), 7.21 – 7.12 (3H, m, H-4 and H-5), 6.27 (1H, s, H-9), 2.90 (1H, sept, *J* 7, H-6), 2.34 (1H, sept, *J* 7, H-9), 1.22 (3H, d, *J* 7, H-7), 1.20 (3H, d, *J* 7, H-10), 1.01 (3H, d, *J* 7, H-8) and 0.81 (3H, d, *J* 7, H-11).; δC (75 MHz; $CDCl_3$) 156.3, 148.2, 142.7, 142.3, 141.8, 135.3, 133.8, 132.2, 128.9, 128.4, 127.8, 127.3, 127.2, 124.5, 124.4, 121.9, 114.8, 72.1, 27.7, 27.0, 24.9, 24.5, 22.6 and 22.4.; EI *m/z* 385 (M); CI *m/z* 403 (M + NH_4^+); (Found: M + NH_4^+, 403.2381. $C_{26}H_{31}O_2N_2$ requires *M*, 403.2380).

3-(Hydroxyphenylmethyl)-2-(2-isopropylphenoxy)benzaldehyde **7e**



DIBAL (1M solution in toluene) (0.37 cm^3, 037 mmol, 1.2 equiv.), nitrile **22a** (107 mg, 0.31 mmol, 1 equiv.) and anhydrous toluene (10 cm^3) were treated as described in General Procedure B, at RT. The crude product was purified by flash column chromatography (10:1 petrol : EtOAc) to yield alcohol **7e** as a light yellow oil (37 mg, 34%). Analysis matched that described above.

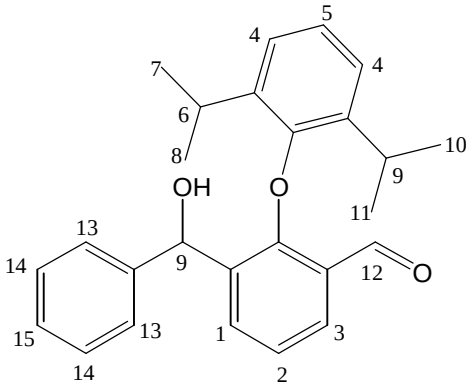
3-(Hydroxyphenylmethyl)-2-(2,4,6-trimethylphenoxy)benzaldehyde **9e**



DIBAL (1M solution in toluene) (0.45 cm^3, 0.45 mmol, 1.2 equiv.), nitrile **22b** (129 g, 0.38 mmol, 1 equiv.) and anhydrous toluene (10 cm^3) were treated as described in General Procedure B at 0 °C. The crude was purified by flash column chromatography (12:1 Petrol : EtOAc) to yield aldehyde **9e** as a colourless oil (52 mg, 40%). Rf = 0.41 (9:1 petrol:EtOAC). ν_{max}(film/cm^{-1}) 3425 (OH), 1680 (CHO); δH (300 MHz; $CDCl_3$) 9.56 (1H, s, H-9), 7.88 (1H, ddd, *J* 7.5, 2 and 1, H-1), 7.69 (1H, dd, *J* 8 and 2, H-3), 7.41 – 7.28 (5H, m, H-11, H-12 and H-13,), 7.19 (1H, t, *J* 7.5, H-2), 6.84 (1H, s, H-4), 6.80 (1H, s, H-5), 6.22 (1H, s, H-10), 6.27 (3H, s, H-6), 2.03 (3H, s, H-7) and 1.77 (3H, s, H-8).; δC (75 MHz; $CDCl_3$) 188.7, 156.8, 153.6, 142.9, 134.9, 134.7, 133.5, 130.8, 130.7,

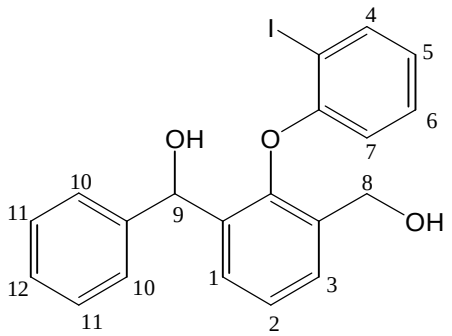
128.7, 128.4, 128.0, 127.9, 127.1, 126.8, 122.9, 71.6, 20.8, 17.1 and 16.6.; EI *m/z* 346 (M); CI *m/z* 364 (M + NH_4^+), 347 (M + H), 329 (M – OH); (Found: M + NH_4^+, 364.1905. $C_{23}H_{26}O_3N$ requires *M*, 364.1907). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-9 no de-coalescence observed at –90°C.

2-(2,6-Diisopropylphenoxy)-3-(hydroxyphenylmethyl)benzaldehyde **10e**



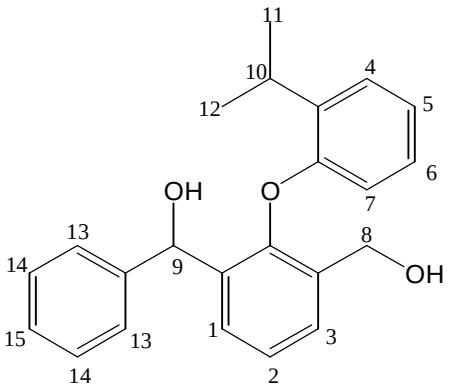
DIBAL (1M solution in toluene) (0.9 cm^3, 0.9 mmol, 1.2 equiv.), nitrile **22c** (290 mg, 0.75 mmol, 1 equiv.) and anhydrous toluene (20 cm^3) were treated as described in General Procedure B, at 0°C. The crude product was purified by flash column chromatography (12:1 petrol : EtOAc) to yield alcohol **10e** as a light yellow oil (80 mg, 27%). Rf = 0.41 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3444 (OH), 1675 (CHO); δH (300 MHz; $CDCl_3$) 9.18 (1H, s, H-12), 7.96 (1H, ddd, *J* 7.5, 2.5 and 0.5, H-1), 7.71 (1H, dd, *J* 8 and 2, H-3), 7.43 – 7.13 (9H, m, H-2, H-4, H-5, H-13, H-14 and H-15), 6.27 (1H, s, H-9), 3.03 (1H, sept, *J* 7, H-6), 2.58 (1H, sept, *J* 7, H-9), 1.21 (3H, d, *J* 7, H-7), 1.09 (3H, d, *J* 7, H-10), 0.94 (3H, d, *J* 7, H-8) and 0.84 (3H, d, *J* 7, H-11).; δC (75 MHz; $CDCl_3$) 188.8, 157.3, 152.8, 143.1, 139.7, 139.5, 133.8, 133.4, 129.3, 128.9, 128.2, 127.2, 126.8, 126.1, 125.7, 125.6, 122.3, 72.2, 27.7, 27.1, 24.8, 24.3, 22.3 and 22.3.; EI *m/z* 388 (M); CI *m/z* 406 (M + NH_4^+); (Found: M + NH_4^+, 406.2364. $C_{26}H_{32}O_3N$ requires *M*, 406.2377). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-9 no de-coalescence observed at –90°C.

3-(Hydroxyphenylmethyl)-2-(2-iodo-phenoxy)-methanol **6e'**



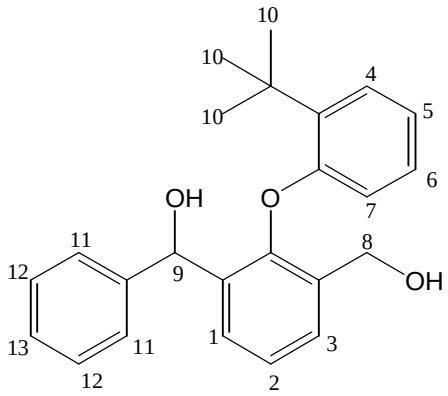
Alcohol **6e** (80 mg, 0.19 mmol, 1 equiv.), sodium borohydride (56 mg, 1.49 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (7:1 petrol:EtOAc) to yield the product as a white solid (53 mg, 65%). m.p. 124 - 126^oC; Rf = 0.12 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3336 (OH); δH (300 MHz; $CDCl_3$) Mixture of two diastereoisomers in ratio of 5:4. 7.86 (1H, dd, *J* 8, and 1.5, H-4^{major}), 7.79 (1H, dd, *J* 8, and 1.5, H-4^{minor}), 7.68 (1H, dd, *J* 7.5, and 1.5, H-1^{major}), 7.57 (1H, dd, *J* 7.5, and 1.5, H-1^{minor}), 7.50 – 7.42 (2H, m, H-$3^{maj+min}$), 7.39 – 7.12 (12H, m, H-$10^{maj+min}$, H-$11^{maj+min}$, H-$12^{maj+min}$ and H-$2^{maj+min}$), 6.82 (3H, m, H-5 $^{maj+min}$ and H-6^{major}), 6.66 (1H, td, *J* 7.5 and 1.5, H-6^{minor}), 6.38 (1H, dd, *J* 8 and 1.5, H-7^{major}), 6.03 (1H, s, H-9^{minor}), 5.91 (1H, dd, *J* 8 and 1.5, H-7^{minor}), 5.86 (1H, s, H-9^{major}) and 4.59 – 4.33 (4H, CH ABXY m, *J* 13.5, H-8).; δC (75 MHz; $CDCl_3$) 156.7, 156.6, 147.8, 147.1, 145.6, 144.3, 140.3, 139.8, 139.1, 138.4, 135.6, 135.5, 130.6, 129.8, 128.8, 129.4, 127.5, 127.4, 127.3, 126.9, 126.7, 126.4, 124.7, 124.1, 114.0, 113.7, 85.7, 85.6, 96.6, 69.1 and 58.2.; EI *m/z* 432 (M); CI *m/z* 450 (M + NH_4^+); (Found: M + NH_4^+, 450.0563. $C_{12}H_{21}O_3NI$ requires *M*, 450.0561). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-1 no coalescence observed at 150^oC, broadening observed above 90^oC, modelling H-8 no coalescence observed at 150^oC, broadening observed above 80^oC.

[3-Hydroxymethyl-2-(2-isopropylphenoxy)phenyl]phenylmethanol **7e'**



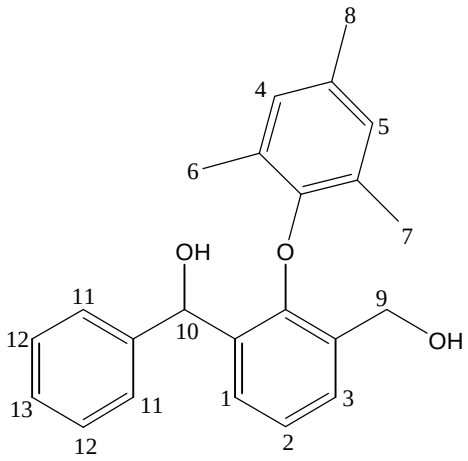
Alcohol **7e** (110 mg, 0.39 mmol, 1 equiv.), sodium borohydride (118 g, 3.12 mmol, 8 equiv.) and THF (15 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (5:1 petrol:EtOAc) to yield the product as a white solid (67 mg, 49%). m.p. 107 - 109^oC; Rf = 0.30 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3337 (OH); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of 5:4. 7.70 (1H, dd, *J* 8 and 1.5, H-1^{minor}), 7.53 (1H, dd, *J* 8 and 1.5, H-1^{major}), 7.45 – 7.27 (17H, m, H-$2^{maj+min}$, H-$3^{maj+min}$, H-$4^{maj+min}$, H-5^{minor}, H-$13^{maj+min}$, H-$14^{maj+min}$ and $15^{maj+min}$), 7.04 (2H, m, H-5^{major} and H-7^{minor}), 6.95 (1H, td, *J* 7.5 and 1, H-6^{major}), 6.84 (1H, td, *J* 7.5 and 1, H-6^{minor}), 6.40 (1H, m, H-7^{major}), 6.05 (1H, s, H-9^{minor}), 5.91 (1H, s, H-9^{major}), 4.63 – 4.46 (4H, CH ABXY m, *J* 13.5, 2.5 and 1.5, $H8^{maj+min}$), 3.57 (1H, sept, *J* 7, H-10^{minor}), 3.44 (1H, sept, *J* 7, H-10^{major}), 1.42 (3H, d, *J* 7, H-11^{minor}), 1.39 (3H, d, *J* 7, H-12^{minor}), 1.33 (3H, d, *J* 7, H-11^{major}) and 1.30 (3H, d, *J* 7, H-12^{major}).; δC (75 MHz; $CDCl_3$) 155.5, 155.2, 149.5, 148.8, 143.5, 142.2, 137.7, 137.6, 136.5, 136.1, 134.6, 134.5, 128.9, 128.7, 128.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.2, 127.1, 127.1, 127.0, 126.8, 126.7, 126.3, 126.1, 122.5, 122.3, 112.7, 112.2, 70.8, 70.7, 60.6, 27.4, 26.8, 23.6, 23.2, 23.1 and 22.9.; EI *m/z* 348 (M); CI *m/z* 366 (M + NH_4^+); (Found: M + NH_4^+, 366.2063. $C_{23}H_{28}O_3N$ requires *M*, 366.2064). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-10 coalescence observed at 110^oC, modelling H-8 coalescence observed between 130 and 140^oC.

[2-(2-tert-Butylphenoxy)-3-hydroxyphenylmethyl]phenylmethanol **8e'**



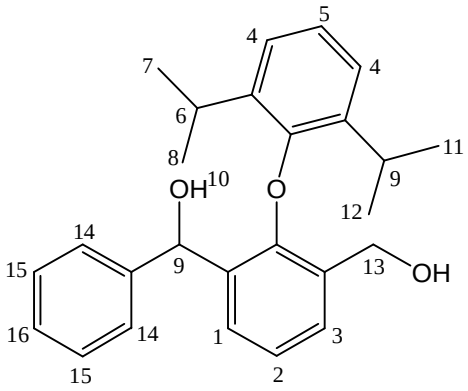
Alcohol **8e** (67 mg, 0.19 mmol, 1 equiv.), sodium borohydride (56 mg, 1.49 mmol, 8 equiv.) and THF (8 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (7:1 petrol:EtOAc) to yield the product as a light yellow oil (47 mg, 68%). Rf = 0.38 (4:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3339 (OH); δH (300 MHz; $CDCl_3$) Mixture of two diastereoisomers in the ratio of 8:7. 7.60 (1H, dd, *J* 7.5 and 2, H-1^{minor}), 7.58 (1H, dd, *J* 7.5 and 2, H-1^{major}), 7.50 (1H, dd, *J* 7.5 and 2, H-3^{minor}), 7.48 (1H, dd, *J* 7.5 and 2, H-3^{major}), 7.41 (2H, m, H-$2^{min+maj}$), 7.35 (4H, m, H-$11^{min+maj}$), 7.30 (6H, m, H-$12^{min+maj}$ and H-$13^{min+maj}$), 7.09 (1H, dd, *J* 7.5 and 2, H-4^{major}), 7.04 (1H, dd, *J* 7.5 and 2, H-4^{minor}), 6.96 (1H, dd, *J* 7 and 1.5, H-5^{minor}), 6.93 (1H, *J* 7 and 1.5, H-5^{major}), 6.88 (1H, dd, *J* 7.5 and 2, H-6^{major}), 6.83 (1H, dd, *J* 7.5 and 2, H-6^{minor}), 6.43 (1H, dd, *J* 7.5 and 1.5, H-7^{major}), 6.08 (1H, s, H-9major), 6.07 (1H, dd, *J* 7.5 and 1.5, H-7^{minor}), 6.05 (1H, s, H-9^{minor}), 4.66 – 4.52 (4H, CH ABXY m, *J* 13.5, H-$8^{maj+min}$), 1.61 (9H, s, H-10^{major}) and 1.49 (9H, s, H-10^{minor}).; δC (75 MHz; $CDCl_3$) 157.5, 157.1, 148.8, 148.6, 143.1, 142.3, 137.5, 137.4, 137.3, 136.9, 134.5, 134.3, 128.9, 128.8, 128.7, 128.4, 128.3, 127.9, 127.5, 127.1, 126.9, 126.8, 126.7, 126.6, 126.3, 126.1, 122.1, 121.8, 113.4, 113.0, 70.3, 69.6, 60.5, 60.4, 35.2, 35.1, 30.2 and 30.1.; CI *m/z* 362 (M); (Found: M, 362.1876. $C_{24}H_{26}O_3$ requires *M*, 362.1876). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-7 no coalescence observed at 150°C.

[3-Hydroxymethyl-2-(2,4,6-trimethylphenoxy)phenyl]phenylmethanol **9e'**



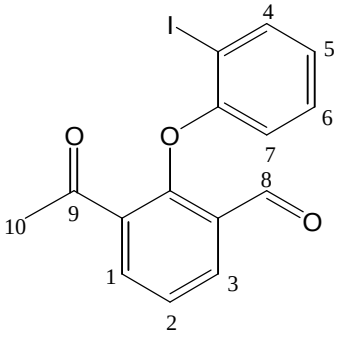
Alcohol **9e** (100 mg, 0.29 mmol, 1 equiv.), sodium borohydride (87 mg, 2.31 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (8:1 petrol : EtOAc) to yield the product as a white solid (80 mg, 79%). m.p. 98 - 102°C. Rf = 0.56 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3349 (OH); δH (500 MHz; $CDCl_3$) 7.33 (1H, dd, *J* 7.5 and 1.5, H-1), 7.23 – 7.11 (6H, m, H-3, H-11, H-12 and H-13), 6.98 (1H, t, *J* 7.5, H-2), 6.67 (1H, s, H-4), 6.64 (1H, s, H-5), 6.00 (1H, s, H-10), 4.10 (2H, s, H-9), 2.12 (3H, s, H-6), 1.85 (3H, s, H-7) and 1.74 (3H, s, H-8).; δC (75 MHz; $CDCl_3$) 152.4, 152.0, 143.3, 134.3, 133.5, 130.5, 130.4, 130.3, 129.3, 128.5, 128.0, 127.7, 127.6, 127.0, 123.4, 71.7, 61.2, 20.8, 17.5 and 17.1.; EI *m/z* 348 (M); CI *m/z* 366 (M + NH_4^+), 348 (M), 331 (M – OH); (Found: M + NH_4^+, 366.2067. $C_{23}H_{28}O_3N$ requires *M*, 366.2064). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-10 no de-coalescence observed at –90°C.

2-(2,6-Diisopropylphenoxy)-3-(hydroxyphenylmethyl)methanol **10e'**



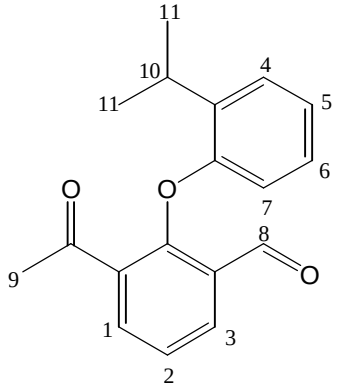
Alcohol **10e** (100 mg, 0.26 mmol, 1 equiv.), sodium borohydride (79 mg, 2.08 mmol, 8 equiv.) and THF (10 cm^3) were reacted in accordance with General Procedure G. The crude product was purified by flash column chromatography (10:1 increasing to 5:1 petrol : EtOAc) to yield alcohol **10e'** as a white solid (79 mg, 78%), m.p. 96 - 98°C; Rf = 0.51 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3368 (OH); δH (300 MHz; $CDCl_3$) 7.53 (1H, dd, *J* 7.5 and 2, H-1), 7.41 – 7.29 (6H, m, H-3, H-14, H-15 and H-16), 7.21 – 7.11 (4H, m, H-2, H4 and H-5), 6.22 (1H, d, *J* 4, H-9), 4.15 (2H, d, *J* 5.5, H-13), 3.10 (1H, sept, *J* 7, H-6), 2.93 (1H, sept, *J* 7, H-9), 2.52 (1H, d, *J* 4, H-10), 1.17 (3H, d, *J* 7, H-7), 1.11 (3H, d, *J* 7, H-11), 1.08 (3H, d, *J* 7, H-8) and 0.94 (3H, d, *J* 7, H-12).; δC (75 MHz; $CDCl_3$) 153.1, 151.8, 143.5, 140.5, 140.0, 133.5, 130.1, 128.8, 128.7, 128.0, 127.8, 127.1, 125.6, 124.7, 124.6, 122.9, 72.02, 61.1, 27.4, 27.3, 24.8, 24.4 and 22.5.; EI *m/z* 390 (M); CI *m/z* 408 (M + NH_4^+), 390 (M); (Found: M + NH_4^+, 408.2531. $C_{26}H_{34}O_3N$ requires *M*, 408.2533). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-10 no de-coalescence observed at –90°C.

3-Acetyl-2-(2-Iodophenoxy)benzaldehyde **6g**



DMSO (0.23 cm^3, 3.23 mmol, 3 equiv.), oxalyl chloride (0.14 cm^3, 1.62 mmol, 1.5 equiv.), alcohol **6d** (397 mg, 1.08 mmol, 1 equiv.), triethylamine (0.9 cm^3, 6.47 mmol, 6 equiv.) and DCM (20 cm^3) were treated as described in General Procedure D. The crude product was purified by flash column chromatography (15:1 Petrol:EtOAc) to yield the product as light yellow blocks (327 mg, 83%). m.p. 100 - 101 ^oC; Rf = 0.51 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1690 ($CH_3COBenz$), 1590, 1571 (CHO); δH (300 MHz; $CDCl_3$) 10.13 (1H, s, H-8), 8.19 (1H, dd, *J* 9 and 2, H-3), 8.16 (1H, dd, *J* 8 and 2, H-1), 7.93 (1H, dd, *J* 8 and 1.5, H-4), 7.55 (1H, td, *J* 7.5 and 1, H-2), 7.21 (1H, ddd, *J* 9, 7.5 and 1.5, H-5), 6.86 (1H, td, *J* 7.5 and 1.5, H-6), 6.33 (1H, dd, *J* 8.5 and 1.5, H-7) and 2.60 (3H, s, H-10).; δC (75 MHz; $CDCl_3$) 197.6, 188.2, 158.6, 155.4, 140.8, 136.8, 134.3, 133.4, 130.3, 129.9, 126.8, 125.1, 113.9, 84.8 and 31.3.; EI *m/z* 366 (M); CI *m/z* 366 (M); (Found: M + NH_4^+, 384.0091. $C_{15}H_{15}O_3NI$ requires *M*, 384.0091).

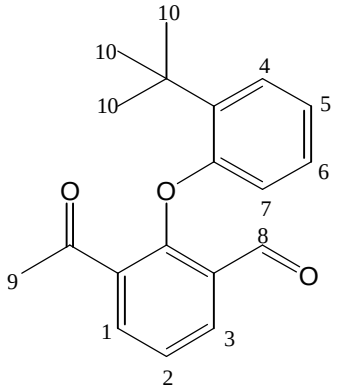
3-Acetyl-2-(2-isopropylphenoxy)benzaldehyde **7g**



DMSO (0.37 cm^3, 5.19 mmol, 3 equiv.), oxalyl chloride (0.23 cm^3, 2.6 mmol, 1.5 equiv.), alcohol **7d** (492 mg, 1.73 mmol, 1 equiv.), triethylamine (1.45 cm^3, 10.38 mmol, 6 equiv.) and anhydrous DCM (30 cm^3) were treated as outlined in General Procedure D.

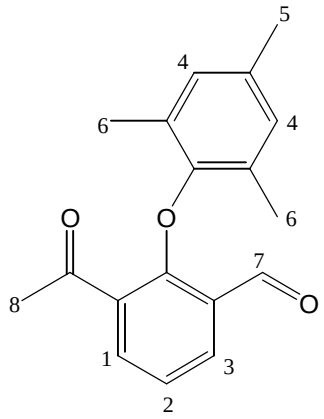
The crude product was purified by flash column chromatography (12:1 Petrol:EtOAc) to yield the product as white solid (420 mg, 86%). m.p. 66 - 69°C; Rf = 0.59 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1691 ($CH_3COBenz$), 1587 (CHO); δH (300 MHz; $CDCl_3$) 10.15 (1H, s, H-8), 8.18 (1H, dd, *J* 7.5 and 2, H-3), 8.13 (1H, dd, *J* 7.5 and 2, H-1), 7.50 (1H, td, *J* 7.5 and 0.5, H-2), 7.42 (1H, m, H-4), 7.07 (2H, m, H-5 and H-6), 6.32 (1H, m, H-7), 3.66 (1H, sept, *J* 7, H-10), 2.55 (3H, s, H-9) and 1.41 (6H, d, *J* 7, H-11).; δC (75 MHz; $CDCl_3$) 197.9, 188.3, 157.2, 156.3, 136.7, 136.6, 134.6, 133.3, 130.2, 127.7, 127.5, 126.1, 123.5, 113.4, 31.0, 26.9 and 23.3.; EI *m/z* 282 (M); CI *m/z* 300 (M + NH_4^+); (Found: C 76.94% and H 6.59%. $C_{18}H_{18}O_3$ requires C 76.57% and H 6.43%).

3-Acetyl-2-(2-t-Butylphenoxy)benzaldehyde **8g**



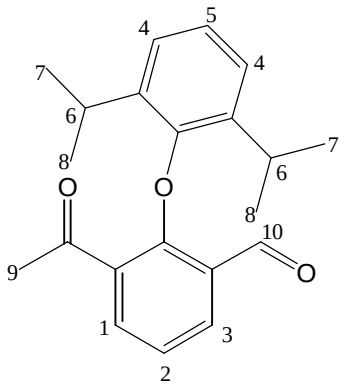
DMSO (0.17 cm^3, 2.37 mmol, 3 equiv.), oxalyl chloride (0.1 cm^3, 1.19 mmol, 1.5 equiv.), alcohol **8d** (236 mg, 0.79 mmol, 1 equiv.), triethylamine (0.66 cm^3, 4.75 mmol, 6 equiv.) and anhydrous DCM (20 cm^3) were treated as described in General Procedure D. The crude product was purified by flash column chromatography (9:1 Petrol:EtOAc) to yield the product as white solid (192 mg, 82%). m.p. 62 - 64 °C; Rf = 0.49 (5:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1691 ($CH_3COBenz$), 1587, 1575 (CHO); δH (300 MHz; $CDCl_3$) 10.08 (1H, s, H-8), 8.17 (1H, dd, *J* 7.5 and 2, H-3), 8.05 (1H, dd, *J* 7.5 and 2, H-1), 7.48 (2H, m, H-2 and H-4), 7.08 (2H, m, H-5 and H-6), 6.44 (1H, dd, *J* 7.5 and 2, H-7), 2.55 (3H, s, H-9) and 1.54 (9H, s, H-10); δC (75 MHz; $CDCl_3$) 198.5, 188.5, 159.4, 155.5, 137.2, 136.3, 135.4, 133.1, 130.0, 128.5, 128.0. 125.9, 123.3, 114.9, 35.3, 31.2 and 30.3.; CI *m/z* 314 (M + NH_4^+); (Found: M + NH_4^+, 314.1750. $C_{19}H_{24}O_3N$ requires *M*, 314.1751).

3-Acetyl-2-(2,4,6-Trimethtylphenoxy)benzaldehyde **9g**



DMSO (0.2 cm^3, 2.87 mmol, 3 equiv.), oxalyl chloride (0.12 cm^3, 1.43 mmol, 1.5 equiv.), Alcohol **9d** (272 mg, 0.96 mmol, 1 equiv.), triethylamine (0.8 cm^3, 5.74 mmol, 6 equiv.) and anhydrous DCM (20 cm^3) were treated as outlined in General Procedure D. The crude product was purified by flash column chromatography (9:1 Petrol:EtOAc) to yield the product as white solid (244 mg, 90%). m.p. 97 - 100^oC; Rf = 0.17 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1688 ($CH_3COBenz$), 1583 (CHO); δH (300 MHz; $CDCl_3$) 10.05 (1H, s, H-7), 7.94 (1H, dd, *J* 8 and 2, H-1), 7.76 (1H, dd, *J* 8 and 2, H-3), 7.22 (1H, td, *J* 8 and 1, H-2), 6.88 (2H, s, H-4), 2.43 (3H, s, H-8), 2.31 (3H, s, H-5) and 2.11 (6H, s, H-6).; δC (75 MHz; $CDCl_3$) 199.6, 188.4, 158.5, 152.9, 135.3, 135.0, 132.5, 132.2, 130.8, 128.8. 127.6, 122.8, 31.3, 20.9 and 17.3.; EI *m/z* 282 (M); CI *m/z* 283 (M + H); (Found: M + H, 283.1337. $C_{18}H_{19}O_3$ requires *M*, 283.1329).

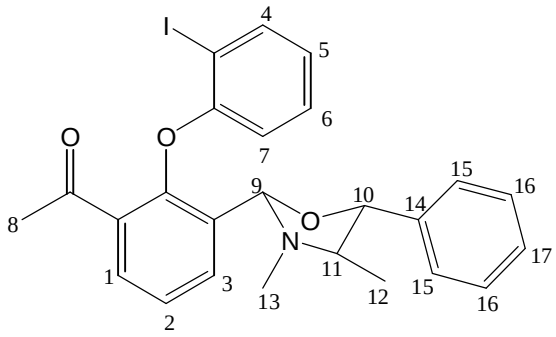
3-Acetyl-2-(2,6-diisopropylphenoxy)benzaldehyde **10g**



DMSO (0.31 cm^3, 4.43 mmol, 3 equiv.), oxalyl chloride (0.19 cm^3, 2.22 mmol, 1.5 equiv.), alcohol **10d** (482 mg, 1.48 mmol, 1 equiv.), triethylamine (1.24 cm^3, 8.87 mmol,

6 equiv.) and anhydrous DCM (40 cm^3) were treated as outlined in General Procedure D. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a white solid (417 mg, 87%). m.p. 70 - 72°C; Rf = 0.33 (9:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 1684 ($CH_3COBenz$), 1584 (CHO); δH (300 MHz; $CDCl_3$) 9.67 (1H, s, H-10), 7.91 (1H, dd, *J* 8 and 2, H-3), 7.80 (1H, dd, *J* 7.5 and 2, H-1), 7.31 – 7.17 (4H, m, H-2, H-4 and H-5), 3.09 (2H, sept, *J* 6.5, H-6), 2.52 (3H, s, H-9), 1.22 (6H, d, *J* 7, H-7) and 1.13 (6H, d, *J* 7, H-8).; δC (75 MHz; $CDCl_3$) 199.8, 188.3. 171.4, 158.7, 152.4, 139.9, 135.4, 132.9, 131.9, 127.0, 125.5, 122.5, 31.6, 27.8, 23.9 and 22.8.; EI *m/z* 324 (M); CI *m/z* 325 (M + H); (Found: M + H, 325.1797. $C_{21}H_{25}O_3$ requires *M*, 325.1798).

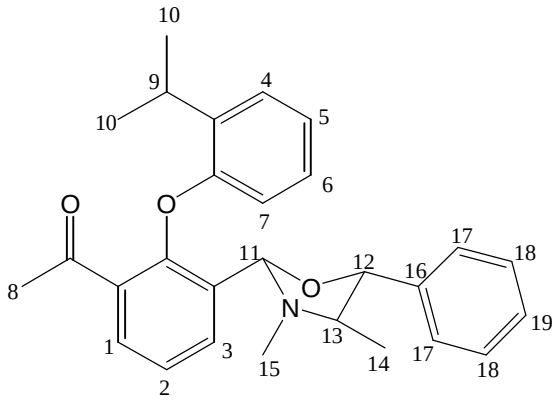
1-[2-(2-Iodophenoxy)-3-(2'S,4'S,5'R)-(3',4'-dimethyl-5'-phenyloxazolidin-2-yl)-phenyl]-ethanone **6h**



Aldehyde **6g** (165 mg, 0.45 mmol, 1 equiv.), (–)-ephedrine (112 mg, 0.68 mmol, 1.5 equiv.) and toluene (40 cm^3) were treated as detailed in experimental procedure D. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a white foam (165 mg, 71%). m.p. 47 - 50°C; Rf = 0.35 & 0.21 (9:1 petrol:EtOAc); $[\alpha]_D^{23}$ = –75.9 (*c* 1.07 in acetone); ν_{max} (film/cm^{-1}) 1687 ($CH_3COBenz$); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of . 8.31 (1H, br dd, *J* 7.5 and 1, H-1^{major}), 8.28 (1H, br m, H-1minor), 7.82 (1H, br dd, *J* 8 and 1.5, H-3^{major}), 7.75 (1H, br d, J 8, H.3^{minor}), 7.64 (1H, br m, H-4^{minor}), 7.58 (1H, br d, *J* 8, H-4^{major}), 7.29 (4H, br d, *J* 7.5, H-$15^{maj+min}$), 7.19 – 7.05 (8H, m, H-$2^{maj+min}$, H-$16^{maj+min}$ and H-$17^{maj+min}$), 6.58 (2H, br m, H-$5^{maj+min}$), 6.25 (3H, br m, H-$6^{maj+min}$ and H-7^{major}), 6.13 (1H, br d, *J* 8, H-7^{minor}), 5.09 (1H, br s, H-9^{major}), 4.97 (2H, br m, H-9^{minor} and H-10^{minor}), 4.57 (1H, br d, *J* 9, H-10^{major}), 2.47 (1H, br m, H-$11^{maj+min}$), 2.32 (3H, br s, H-$8^{maj+min}$), 2.15 (3H, br s, H-

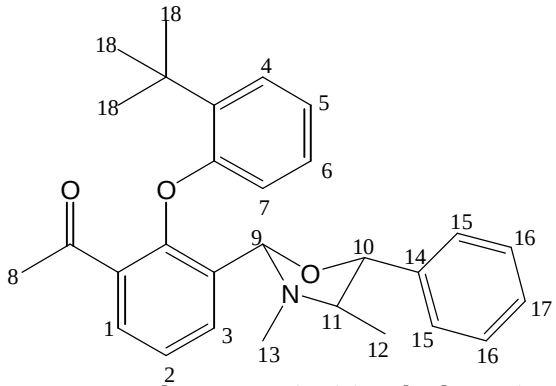
13$^{maj+min}$) and 0.57 (3H, br d, *J* 6.5, H-12$^{maj+min}$).; δC (75 MHz; C_6D_6) 196.7, 158.2, 152.3, 140.2, 139.9, br 134.1, 131.6, 130.0, 128.4 – 127.6 (C 14-17), 126.5, 126.4, 124.0, 114.4, 110.0, 91.5, 82.5, 63.7, 36.0, 30.5 and 15.2.; CI *m/z* 514 (M + H); (Found: M + H, 514.0868. $C_{25}H_{25}O_3NI$ requires *M*, 514.0874).

1-[2-(2-Isopropylphenoxy)-3-(2'S,4'S,5'R)-(3',4'-dimethyl-5'-phenyloxazolidin-2-yl)-phenyl]-ethanone **7h**



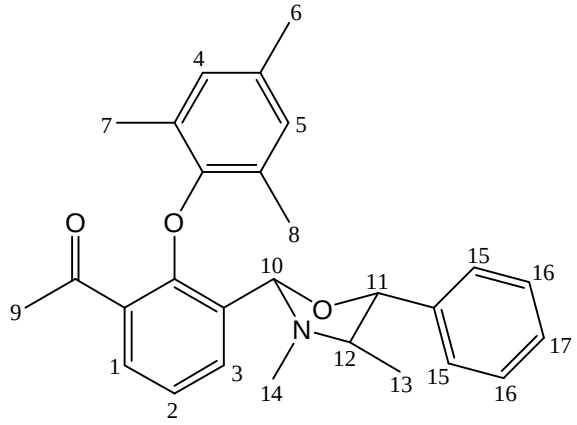
Aldehyde **7g** (387 mg, 1.37 mmol, 1 equiv.), (–)-ephedrine (272 mg, 1.64 mmol, 1.2 equiv.) and toluene (40 cm^3) were treated as detailed in experimental procedure D. The crude product was purified by flash column chromatography (15:1 Petrol:EtOAc) to yield the product as a colourless oil (495 mg, 84%). Rf = 0.55 & 0.41 (9:1 petrol:EtOAc); $[\alpha]_D^{23}$ = –72.2 (*c* 0.98 in acetone); ν_{max} (film/cm^{-1}) 1686 ($CH_3COBenz$); δH (300 MHz; $CDCl_3$) Mixture of diastereoisomers in the ratio of approximately 2:1. 8.32 (2H, br m, H-1$^{maj+min}$), 7.84 (2H, br m, H-3$^{maj+min}$), 7.33 (2H, br d, *J* 7, H-17$^{maj+min}$), 7.22 – 7.07 (10H, br m, H-2$^{maj+min}$, H-4$^{maj+min}$, H-18$^{maj+min}$ and H-19$^{maj+min}$), 6.83 (2H, br m, H-5$^{maj+min}$), 6.73 (1H, br m, H-6$^{maj+min}$), 6.43 (1H, br m, H-7^{minor}), 6.25 (1H, br m, H-7^{major}), 5.14 (1H, br m, H-11^{minor}), 4.95 (2H, br m, H-11^{major} and H-12^{major}), 4.63 (1H, br m, H-12^{minor}), 3.79 (2H, br sept, J 7, H-9$^{maj+min}$), 2.56 (2H, br m, H-13$^{maj+min}$), 2.22 (6H, br s, H-8$^{maj+min}$), 1.38 (18H, br m, H-10$^{maj+min}$ and H-15$^{maj+min}$) and 0.60 (6H, d, *J* 6.5, H-14).; δC (75 MHz; C_6D_6) 197.1, 156.5, 154.6, 140.2, 133.8, 133.6, 131.4, 131.1, 128.4 – 127.6 (C 16-19), 127.1, 126.3, 125.8, 122.6, br 113.0, br 91.8, br 82.5, br 63.7, 35.6, 30.2, br 26.8, br 22.9 and 15.2.; CI *m/z* 430 (M + H); (Found: M + H, 430.2375. $C_{28}H_{32}O_3N$ requires *M*, 430.2377).

1-[2-(2-tert-Butyl-phenoxy)-3-(2'S,4'S,5'R)-(3',4'-dimethyl-5'-phenyloxazolidin-2-yl)-phenyl]-ethanone **8h**



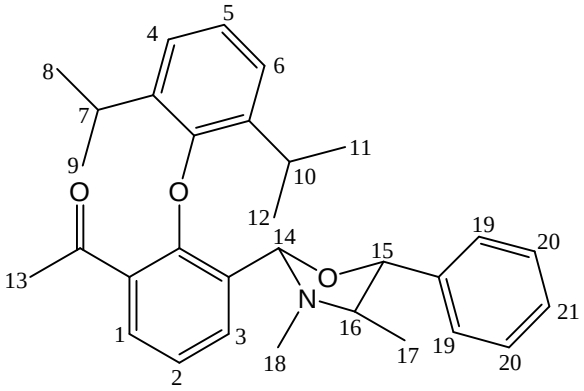
Aldehyde **8g** (175 mg, 0.59 mmol, 1 equiv.), (–)-ephedrine (146 mg, 0.89 mmol, 1.5 equiv.) and toluene (40 cm^3) were treated as detailed in experimental procedure D. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a colourless foam (242 mg, 95%). m.p. 35 - 39^oC; Rf = 0.28 & 0.22 (9:1 petrol:EtOAc); $[\alpha]_D^{23}$ = –58.8 (*c* 0.64 in acetone); ν_{max} (film/cm^{-1}) 1690 ($CH_3COBenz$); δH (300 MHz; C_6D_6) Mixture of diastereoisomers in the ratio of 2:1. 8.34 (1H, dd, *J* 7.5 and 2, H-1^{minor}), 8.32 (1H, dd, *J* 7.5 and 2, H-1^{major}), 7.72 (1H, dd, *J* 7.5 and 2, H-3^{major}), 7.49 (1H, dd, J 7.5 and 2, H-3^{minor}), 7.34 (1H, dd, *J* 7.5 and 2, H-4^{major}), 7.30 (5H, m, H-$2^{maj+min}$, H-4^{minor} and H-$15^{maj+min}$), 7.18 – 7.06 (6H, m, H-$16^{maj+min}$ and H-$17^{maj+min}$), 6.79 (4H, m, H-$5^{maj+min}$ and H-$6^{maj+min}$), 6.58 (1H, m, H-7^{minor}), 6.30 (1H, dd, *J* 8 and 1.5, H-7^{major}), 5.17 (1H, s, H-9^{minor}), 4.92 (1H, d, *J* 8.5, H-10^{major}), 4.84 (1H, s, H-9^{major}), 4.55 (1H, d, *J* 8.5, H-10^{minor}), 2.47 (1H, m, H-11^{minor}), 2.39 (1H, m, H-11^{major}), 2.22 (3H, s, H-8^{major}), 2.11 (3H, s, H-8^{minor}), 1.68 (3H, s, H-13^{minor}), 1.64 (9H, s, H-18^{minor}), 1.62 (9H, s, H-$18^{maj+min}$), 1.55 (3H, s, H-13^{major}) and 0.58 (6H, d, *J* 6.5, H-$12^{maj+min}$).; δC (75 MHz; C_6D_6) 198.0, 197.4, 158.4, 152.8, 151.8, 140.2, 140.1, 137.3, 136.4, 135.6, 133.4, 133.8, 133.7, 132.9, 131.3, 130.7, 127.7, 127.3, 126.2, 126.0, 123.6, 122.2, 122.1, 115.1, 114.1, 91.7, 91.2, 82.5, 82.2, 63.8, 63.6, 35.6, 35.5, 30.5, 30.3 and 15.3.; EI *m/z* 443 (M); CI *m/z* 444 (M + H); (Found: M + H, 444.2537. $C_{29}H_{34}O_3N$ requires *M*, 444.2533).

1-[2-(2,4,6-Trimethylphenoxy)-3-(2'S,4'S,5'R)-(3',4'-dimethyl-5'-phenyl-oxazolidin-2-yl)-phenyl]-ethanone **9h**



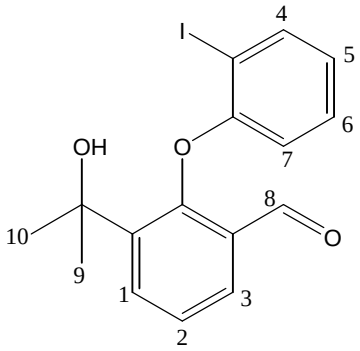
Aldehyde **9g** (194 mg, 0.69 mmol, 1 equiv.), (–)-ephedrine (170 mg, 1.03 mmol, 1.5 equiv.) and toluene (40 cm^3) were treated as detailed in experimental procedure D. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a colourless oil (89 mg, 30%). Rf = 0.50 & 0.44 (9:1 petrol:EtOAc); $[\alpha]_D^{23}$ = –185.5 (*c* 1.02 in acetone); ν_{max} (film/cm^{-1}) 1697 ($CH_3COBenz$); δH (300 MHz; C_6D_6) 8.21 (1H, dd, *J* 7.5 and 2, H-1), 7.37 (2H, br m, H-15), 7.20 – 7.16 (2H, m, H-16), 7.09 (2H, m, H-3 and H-2), 6.92 (1H, t, *J* 7.5, H-17), 6.67 (1H, br s, H-4), 6.54 (1H, br s, H-5), 5.41 (1H, s, H-10), 4.93 (1H, d, *J* 8, H-11), 2.60 (1H, m, H-12), 2.27 (3H, s, H-9), 2.06 (3H, s, H-14), 2.05 (3H, s, H-6), 2.01 (3H, s, H-7), 1.85 (3H, s, H-8) and 0.63 (3H, d, *J* 6.5, H-13).; δC (75 MHz; C_6D_6) 198.9, 155.4, 152.3, 140.5, 133.3, 133.1, 131.5, 130.5, 130.1, 129.9, 128.9, 128.8, 128.3 - 127.6 (C 15 – 17), 122.6, 91.9, 82.6, 63.8, 35.8, 29.6, 20.5, 17.6, 17.4 and 15.3.; CI *m/z* 430 (M + H); (Found: M + H, 430.2375. $C_{28}H_{32}O_3N$ requires *M*, 430.2377).

1-[2-(2,6-Diisopropylphenoxy)-3-(2'S,4'S,5'R)-(3,4-dimethyl-5-phenyloxazolidin-2-yl)-phenyl]-ethanone **10h**



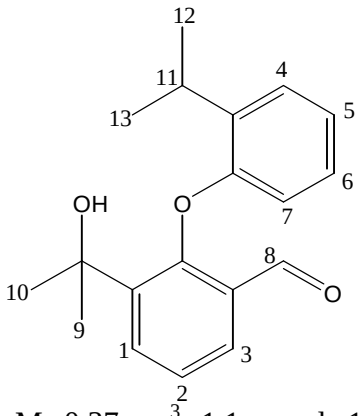
Aldehyde **10g** (131 mg, 0.4 mmol, 1 equiv.), (–)-ephedrine (100 mg, 0.6 mmol, 1.5 equiv.) and toluene (40 cm^3) were treated as detailed in experimental procedure D. The crude product was purified by flash column chromatography (20:1 Petrol:EtOAc) to yield the product as a colourless oil (190 mg, 98%). Rf = 0.77 & 0.63 (10:1 petrol:EtOAc); $[\alpha]_D^{23}$ = –44.2 (*c* 1.1 in acetone); ν_{max} (film/cm^{-1}) 1700 ($CH_3COBenz$); δH (300 MHz; C_6D_6) 8.23 (1H, dd, *J* 8 and 2, H-1), 7.35 (2H, br m, H-19), 7.22 – 7.12 (3H, m, H-3 and H-20), 7.04 (4H, m, H-4, H-5, H-6 and H-21), 6.89 (1H, t, *J* 8, H-2), 5.24 (1H, s, H-14), 4.88 (1H, d, *J* 8, H-15), 3.40 (2H, m, H-7 and H-10), 2.56 (1H, m, H-16), 2.01 (3H, s, H-13), 1.96 (3H, s, H-18), 1.28 (3H, d, *J* 7, H-8), 1.17 (3H, d, *J* 7, H-11), 1.15 (3H, *J* 7, H-9), 1.01 (3H, d, *J* 7, H-12) and 0.64 (3H, d, *J* 6.5, H-17).; δC (75 MHz; C_6D_6) 199.2, 156.0, 152.0, 141.2, 141.0, 140.3, 132.8, 131.9, 129.3, 129.0, 128.2 – 127.2 (C 19-21), 125.6, 124.7, 124.0, 122.4, 91.8, 82.6, 63.8, 35.8, 30.2, 27.7, 27.4, 24.0, 23.8, 22.8, 22.6 and 15.2.; CI *m/z* 472 (M + H); (Found: M + H, 472.2844. $C_{31}H_{38}O_3N$ requires *M*, 472.2846).

3-(1-Hydroxy-1-methylethyl)-2-(2-iodophenoxy)benzaldehyde **6f**



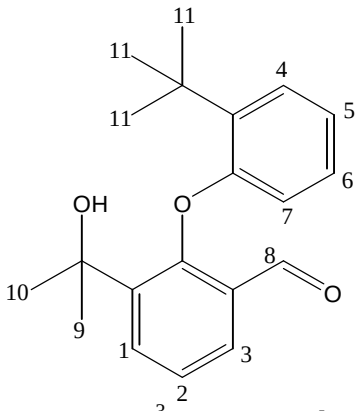
Methyl magnesium iodide (3 M, 0.12 cm^3, 0.37 mmol, 1.2 equiv.), **6h** (160 mg, 0.31 mmol, 1 equiv.) and THF (15 cm^3) at 0^oC were treated as described in General Procedure F and stirred 14 hours. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product **6f** as a white solid (65 mg, 55%). m.p. 99 - 102^oC. Rf = 0. 16 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3448 (OH), 1690 (CHO); δH (300 MHz, $CDCl_3$) 9.91 (1H, s, H-8), 8.03 (1H, dd, *J* 8 and 2, H-4), 7.90 (2H, dd, *J* 8 and 2, H-1 and H-3), 7.42 (1H, td, *J* 8 and 1, H-2), 7.19 (1H, ddd, *J* 8.5, 7.5 and 1.5, H-5), 6.83 (1H, td, *J* 7.5 and 1.5, H-6), 6.38 (1H, dd, *J* 8 and 1.5, H-7), 1.75 (3H, s, H-9) and 1.59 (3H, s, H-10).; δC (75 MHz; $CDCl_3$) 188.9, 159.8, 154.1, 142.6, 140.5, 133.7, 130.2, 129.4, 128.7, 126.4, 124.7, 114.7, 84.8, 72.4, 31.3, and 30.7.; EI *m/z* 382 (M); CI *m/z* 400 (M + NH_4^+); (Found: M, 382.0064 (M). $C_{15}H_{13}O_3I$ requires *M*, 382.0060). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-9 and H-10 coalescence observed at 120^oC.

3-(1-Hydroxy-1-methylethyl)-2-(2-isopropylphenoxy)benzaldehyde **7f**



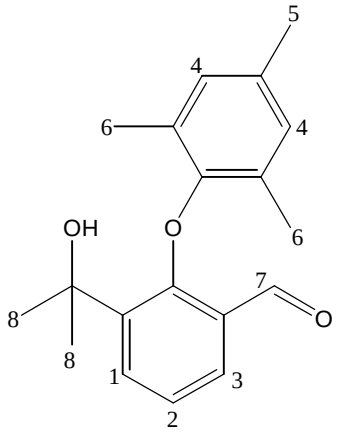
Methyl magnesium iodide (3 M, 0.37 cm^3, 1.1 mmol, 1.2 equiv.), **7h** (396 mg, 0.92 mmol, 1 equiv.) and THF (30 cm^3) at 0^oC were treated as described in General Procedure F and stirred for 16 hours. The crude product was purified by flash column chromatography (12:1 petrol : EtOAc) to yield the product **7f** as a yellow oil (47 mg, 17%). Rf = 0.24 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3459 (OH), 1690 (CHO); δH (300 MHz, $CDCl_3$) 9.97 (1H, s, H-8), 8.03 (1H, dd, *J* 8 and 2, H-3), 7.90 (1H, dd, *J* 8 and 2, H-1), 7.37 (2H, m, H-2 and H-4), 7.02 (2H, m, H-5 and H-6), 6.34 (1H, m, H-7), 3.64 (1H, sept, *J* 7, H-11), 1.71 (3H, s, H-9), 1.59 (3H, s, H-10), 1.41 (3H, d, *J* 7, H-12) and 1.38 (3H, d, *J* 7, H-13).; δC (75 MHz, $CDCl_3$) 189.0, 158.4, 154.9, 142.8, 136.2, 133.4, 129.6, 128.6, 127.5, 127.4, 125.7, 123.2, 114.3, 73.5, 31.1, 30.6, 27.0, 23.6 and 22.9.; EI *m/z* 298 (M); CI *m/z* 316 (M + NH_4^+); (Found: M + NH_4^+, 316.1906. $C_{19}H_{26}O_3N$ requires *M*, 316.1907). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-9 and H-10 coalescence observed at 140^oC.

2-(2-tert-Butylphenoxy)-3-(1-hydroxy-1-methylethyl)benzaldehyde **8f**



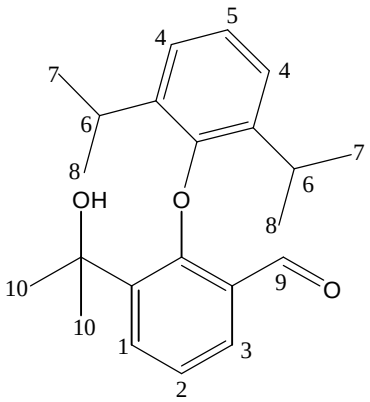
Methylmagnesium iodide (3 M, 0.19 cm^3, 0.57 mmol, 1.1 equiv.), **8h** (224 mg, 0.52 mmol, 1 equiv.) and THF (20 cm^3) at 0^{o}C were treated as described in General Procedure F and stirred for 16 hours. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product **8f** as a colourless oil (63 mg, 39%). Rf = 0.27 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3453 (OH), 1689 (CHO); δH (300 MHz, $CDCl_3$) 9.97 (1H, s, H-8), 8.04 (1H, dd, *J* 8 and 2, H-3), 7.92 (1H, dd, *J* 8 and 2, H-1), 7.46 (1H, dd, *J* 7 and 2, H-4), 7.37 (1H, td, *J* 7 and 1, H-2), 7.03 (2H, CH ABXY m, H-5 and H-6), 6.39 (1H, dd, *J* 8 and 2, H-7), 1.73 (3H, s, H-9), 1.67 (3H, s, H-10), and 1.60 (9H, s, H-11).; δC (75 MHz; $CDCl_3$) 189.4, 160.6, 155.1, 142.8, 137.0, 133.4, 129.5, 128.9, 128.3, 128.0, 125.6, 123.1, 116.6, 72.6, 35.2, 31.4, 30.6, and 30.5.; EI *m/z* 312 (M); CI *m/z* 330 (M + NH_4^+); (Found: M + NH_4^+, 330.2064. $C_{20}H_{28}O_3N$ requires *M*, 330.2064). *VT NMR*; In d_6-DMSO run from RT to 150^{o}C, modelling H-9 and H-10 no coalescence at 150^{o}C.

3-(1-Hydroxy-1-methylethyl)-2-(2,4,6-trimethylphenoxy)benzaldehyde **9f**



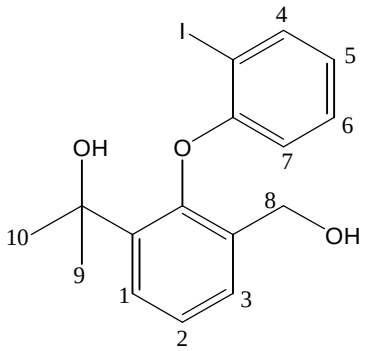
Methylmagnesium iodide (3 M, 0.07 cm^3, 0.22 mmol, 1.2 equiv.), **9h** (78 mg, 0.18 mmol, 1 equiv.) and THF (8 cm^3) at 0°C were treated as described in General Procedure F and stirred for 16 hours. The crude product was purified by flash column chromatography (20:1 petrol : EtOAc) to yield the product **9f** as a light yellow solid (10 mg, 19%). m.p. 71 - 73°C. Rf = 0.48 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3445 (OH), 1681 (CHO); δH (300 MHz, $CDCl_3$) 9.54 (1H, s, H-7), 7.78 (1H, dd, *J* 8 and 2, H-1), 7.63 (1H, dd, *J* 8 and 2, H-3), 7.16 (1H, td, *J* 8 and 1, H-2), 6.89 (2H, s, H-4), 2.29 (3H, s, H-5), 2.12 (6H, s, H-6) and 1.79 (6H, s, H-8).; δC (75 MHz; $CDCl_3$) 188.3, 157.6, 153.4, 138.2, 135.0, 132.3, 121.2, 128.6, 127.8, 127.5, 122.9, 73.0, 30.4, 20.9 and 17.4.; CI *m/z* 316 (M + NH_4^+); (Found: M + NH_4^+, 316.1903. $C_{19}H_{22}O_3$ requires M, 316.1907). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-8 no de-coalescence at –90°C.

2-(2,6-Diisopropylphenoxy)-3-(1-hydroxy-1-methylethyl)benzaldehyde **10f**



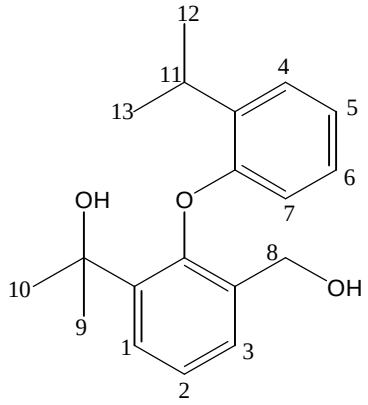
Methylmagnesium iodide (3 M, 0.17 cm^3, 0.48 mmol, 1.2 equiv.), **10h** (190 mg, 0.4 mmol, 1 equiv.) and THF (15 cm^3) at 0^{o}C were treated as described in General Procedure F and stirred for 16 hours. The crude product was purified by flash column chromatography (25:1 petrol : EtOAc) to yield the product **10f** as a light yellow solid (42 mg, 31%). m.p. 108 - 110^{o}C. Rf = 0.27 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3438 (OH), 1680 (CHO); δH (300 MHz; $CDCl_3$) 9.36 (1H, s, H-9), 7.83 (1H, dd, *J* 8 and 2, H-3), 7.64 (1H, dd, *J* 8 and 2, H-1), 7.30 – 7.12 (4H, m, H-2, H-4 and H-5), 3.13 (2H, sept, *J* 7, H-6), 1.81 (6H, s, H-10), 1.22 (6H, d, *J* 7, H-7) and 1.10 (6H, d, *J* 7, H-8).; δC (75 MHz; $CDCl_3$) 188.6, 158.3, 153.1, 139.2, 137.7, 132.3, 129.2, 126.8, 126.0, 122.7, 73.1, 30.2, 27.5, 25.1 and 22.0.; CI *m/z* 358 (M + NH_4^+); (Found: M + NH_4^+, 358.2374 . $C_{22}H_{32}O_3N$ requires *M*, 358.2377). *VT NMR*; In CD_3OD run from RT to –90^{o}C, modelling H-10 no de-coalescence at –90^{o}C.

2-[3-Hydroxymethyl-2-(2-iodophenoxy)phenyl]propan-2-ol **6f'**



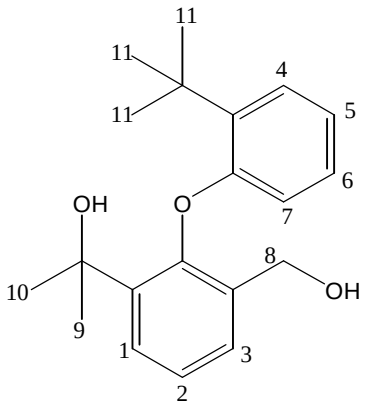
Tertiary alcohol **6f** (65 mg, 0.17 mmol, 1 equiv.), sodium borohydride (51 mg, 1.36 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (5:1 petrol : EtOAc) to yield the product **6f'** as a white solid (25 mg, 38%). m.p. 130 - 133^oC. Rf = 0. 18 (5:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3368 (OH); δH (300 MHz; $CDCl_3$) 7.89 (1H, dd, *J* 8 and 1.5, H-4), 7.64 (1H, dd, *J* 8 and 1.5, H-1), 7.52 (1H, dd, *J* 7.5 and 1.5, H-3), 7.33 (1H, t, *J* 7.5, H-2), 7.20 (1H, ddd, *J* 8.5, 7.5 and 1.5, H-5), 6.82 (1H, td, *J* 8 and 1.5, H-6), 6.40 (1H, dd, *J* 8.5 and 1.5 H-7), 4.55 – 4.24 (2H, CH ABXY m, *J* 13.5, H-8), 1.65 (3H, s, H-9) and 1.58 (3H, s, H-10).; δC (75 MHz; $CDCl_3$) 157.2, 148.8, 141.5, 140.2, 134.6, 129.8, 128.5, 126.6, 126.3, 124.3, 114.2, 85.1, 72.6, 60.8, 31.4, and 30.7.; EI *m/z* 384 (M); CI *m/z* 402 (M + NH_4^+); (Found: M + NH_4^+, 402.0565. $C_{16}H_{21}O_3NI$ requires *M*, 402.0561). *VT NMR*; In d_6-DMSO run from RT to 150^oC, modelling H-8 no coalescence observed at 150^oC, slight broadening above 130^oC.

2-[3-Hydroxymethyl-2-(2-isopropylphenoxy)phenyl]propan-2-ol **7f'**



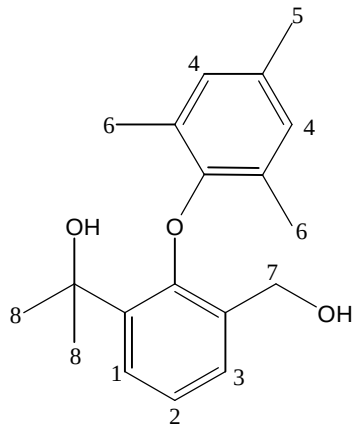
Tertiary alcohol **7f** (81 mg, 0.27 mmol, 1 equiv.), sodium borohydride (82 g, 2.16 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (8:1 petrol : EtOAc) to yield the product **7f'** as a white solid (18 mg, 22%). m.p. 126 - 128°C. Rf = 0.35 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3352 (OH); δH (300 MHz; $CDCl_3$) 7.63 (1H, dd, *J* 8 and 1.5, H-1), 7.53 (1H, m, H-3), 7.37 (1H, m, H-4), 7.31 (1H, t, *J* 8, H-2), 7.04 (2H, m, H-5 and H-6), 6.36 (2H, m, H-7), 4.52 – 4.30 (2H, CH AB m, *J* 13.5, H-8), 3.60 (1H, sept, *J* 7, H-11), 1.63 (3H, s, H-9), 1.59 (3H, s, H-10), 1.40 (3H, d, *J* 7, H-12) and 1.37 (3H, d, *J* 7, H-13).; δC (125 MHz; $CDCl_3$) 155.7, 149.5, 141.7, 136.6, 134.8, 128.7, 127.4, 127.1, 126.5, 125.8, 122.9, 113.8, 73.0, 60.7, 31.4, 30.7, 27.0, 23.8 and 23.1.; EI *m/z* 300 (M); CI *m/z* 318 (M + NH_4^+); (Found: M + NH_4^+, 318.2072. $C_{19}H_{28}O_3N$ requires *M*, 318.2064). *VT NMR*; In d_6-DMSO run from RT to 150°C, modelling H-8 no coalescence observed at 150°C, slight broadening above 100°C.

2-[2-(2-tert-Butyl-phenoxy)-3-hydroxymethylphenyl]propan-2-ol **8f'**



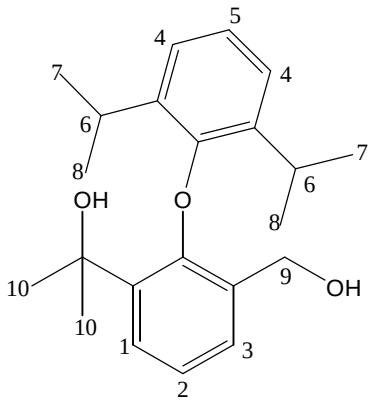
Tertiary alcohol **8f** (57 mg, 0.18 mmol, 1 equiv.), sodium borohydride (54 mg, 1.44 mmol, 8 equiv.) and THF (10 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product **8f'** as a white solid (36 mg, 64%). m.p. 143 - 145^oC. Rf = 0. 38 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3340 (OH); δH (300 MHz; $CDCl_3$) 7.65 (1H, dd, *J* 8 and 2, H-1), 7.56 (1H, dd, *J* 8 and 2, H-3), 7.46 (1H, dd, *J* 7.5 and 2, H-4), 7.31 (1H, t, *J* 8, H-2), 7.02 (2H, m, H-5 and H-6), 6.39 (1H, dd, *J* 8 and 2, H-7), 4.51 – 4.31 (2H, CH ABXY m, *J* 13.5, H-8), 1.65 (3H, s, H-9), 1.63 (3H, s, H-10) and 1.58 (9H, s, H-11).; δC (75 MHz; $CDCl_3$) 157.9, 149.3, 141.7, 137.3, 134.5, 129.1, 128.1, 127.5, 126.5, 125.7, 122.6, 115.4, 72.8, 60.4, 35.2, 31.3, 30.8 and 30.7.; EI *m/z* 314 (M); CI *m/z* 332 (M + NH_4^+); (Found: M + NH_4^+, 332.2224. $C_{20}H_{30}O_3N$ requires *M*, 332.2220). *HPLC*; Separation using β-Gem column running 98 : 2 hexane:IPA, retention times 31.9 and 33.6 min.

2-[3-Hydroxymethyl-2-(2,4,6-trimethylphenoxy)phenyl]propan-2-ol **9f'**



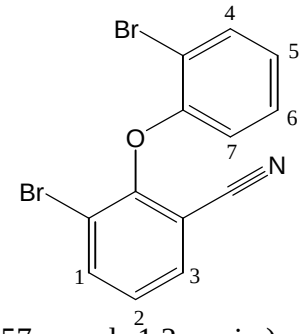
Tertiary alcohol **9f** (10 mg, 0.03 mmol, 1 equiv.), sodium borohydride (10 mg, 0.27 mmol, 8 equiv.) and THF (5 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (6:1 petrol : EtOAc) to yield the product **9f'** as a white solid (3 mg, 30%). m.p. 115 - 118°C. Rf = 0.60 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3369 (OH); δH (300 MHz; $CDCl_3$) 7.47 (1H, br dd, *J* 7.5 and 1.5, H-1), 7.37 (1H, d, *J* 7.5, H-3), 7.14 (1H, t, *J* 7.5, H-3), 6.88 (2H, s, H-4), 4.14 (2H, s, H-7), 2.31 (3H, s, H-5), 2.12 (6H, s, H-6) and 1.75 (6H, s, H-8).; δC (75 MHz; $CDCl_3$) 152.9, 151.3, 137.7, 133.7, 130.7, 130.6, 128.9, 128.0, 126.3, 123.4, 73.3, 61.0, 30.6, 20.8 and 17.8.; EI *m/z* 300 (M); CI *m/z* 318 ($M + NH_4^+$), 283 (M – OH); (Found: $M + NH_4^+$, 318.2064. $C_{19}H_{28}O_3N$ requires *M*, 318.2064). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-7 no de-coalescence observed at –90°C.

2-[2-(2,6-Diisopropylphenoxy)-3-hydroxymethylphenyl]propan-2-ol **10f'**



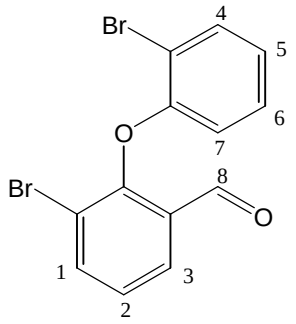
Tertiary alcohol **10f** (55 mg, 0.16 mmol, 1 equiv.), sodium borohydride (48 mg, 1.28 mmol, 8 equiv.) and THF (10 cm^3) were treated as decribed in General Procedure G. The crude product was purified by flash column chromatography (15:1 petrol : EtOAc) to yield the product **10f'** as a white solid (27 mg, 49%). m.p. 124 - 127°C. Rf = 0.60 (4:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 3413 (OH); δH (300 MHz; $CDCl_3$) 7.50 (1H, dd, *J* 8 and 2, H-1), 7.37 (1H, dd, *J* 8 and 2, H-3), 7.20 (3H, m, H-4 and H-5), 7.11 (1H, t, *J* 8, H-2), 4.05 (2H, s, H-9), 3.20 (2H, sept, *J* 7, H-6), 1.77 (6H, s, H-10), 1.18 (6H, d, *J* 7, H-7) and 1.11 (6H, s, H-8).; δC (75 MHz; $CDCl_3$) 153.9, 151.1, 139.9, 137.1, 129.8, 129.1, 126.4, 125.6, 125.1, 123.1, 73.3, 61.0, 30.4, 27.2, 25.4 and 22.2.; EI *m/z* 342 (M); CI *m/z* 360 (M + NH_4^+); (Found: M + NH_4^+, 360.2544. $C_{22}H_{34}O_3N$ requires *M*, 360.2533). *VT NMR*; In CD_3OD run from RT to –90°C, modelling H-9 no de-coalescence observed at –90°C.

3-Bromo-2-(2-bromophenoxy)benzonitrile **23**



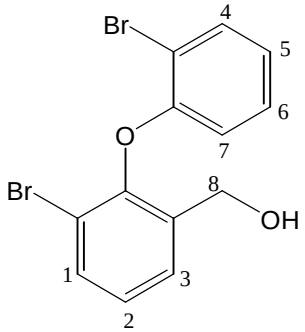
2-Bromophenol (2.4 cm^3, 20.57 mmol, 1.2 equiv.), potassium hydroxide (1.15 g, 2.57 mmol, 1.2 equiv.), and toluene (70 cm^3) were treated as described in general procedure A. 2-Chloro-3-bromobenzonitrile **20** (3.71 g, 17.14 mmol, 1 equiv.), 2-bromophenoxide (4.34 g, 20.57 mmol, 1.2 equiv.), and dry DMF (160 cm^3) were treated as described in General Procedure A. The crude product was purified by flash column chromatography (20:1 petrol : EtOAc) to yield the product as a yellow solid (1.99 g, 32%), m.p. 85 - 87^oC. Rf = 0.25 (9:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 2234 (CN); δH (400 MHz; $CDCl_3$) 7.92 (1H, dd, *J* 8 and 1.5, H-1), 7.70 (1H, dd, *J* 8 and 1.5, H-3), 7.68 (1H, dd, *J* 7.5 and 1.5, H-4), 7.29 (1H, m, H-2), 7.21 (1H, ddd, *J* 8, 7.5 and 1.5, H-5), 7.02 (1H, td, *J* 8 and 1.5, H-6) and 6.48 (1H, dd, *J* 8 and 1.5, H-7).; δC (100 MHz; $CDCl_3$) 153.8, 153.3, 138.8, 134.2, 133.2, 128.4, 126.8, 124.7, 118.1, 115.2, 114.2, 112.4 and 109.5.; CI *m/z* 371 (2 x ^{81}Br M + NH_4^+); (Found: M + NH_4^+, 368.9235. $C_{13}H_{11}N_2OBr_2$ requires *M*, 368.9233).

3-Bromo-2-(2-bromophenoxy)benzaldehyde **24**



DIBAL (1M solution in toluene) (5.1 cm^3, 5.1 mmol, 1.2 equiv.), nitrile **23** (1.49 g, 4.22 mmol, 1 equiv.) and dry toluene (80 cm^3) were treated as described in general procedure B. The crude product was purified by flash column chromatography (50:1 Petrol : EtOAc) to yield the product as a white solid (1.36 g, 91%), m.p. 119 - 122^oC. Rf = 0.34 (19:1 petrol:EtOAc); ν_{max}(film/cm^{-1}) 1707, 1686 (CHO); δH (400 MHz; $CDCl_3$) 10.12 (1H, s, H-8), 7.92 (1H, dd, *J* 11 and 2, H-3), 7.90 (1H, dd, *J* 11 and 1.5, H-1), 7.64 (1H, dd, *J* 8 and 1.5, H-4), 7.29 (1H, td, *J* 8 and 1, H-2), 7.13 (1H, ddd, *J* 10, 8 and 1.5, H-5), 6.94 (1H, td, *J* 8 and 1.5, H-6) and 6.37 (1H, dd, *J* 8 and 1.5, H-7).; δC (100 MHz; $CDCl_3$) 187.2, 153.5, 153.0, 138.8, 133.1, 130.1, 127.6, 126.9, 126.3, 123.1, 117.3, 113.8 and 110.4.; CI *m/z* 374 (2 x ^{81}Br M + NH_4^+), 357 (2 x ^{81}Br M + H); (Found: M, 353.8874. $C_{13}H_8O_2Br_2$ requires *M*, 353.8886).

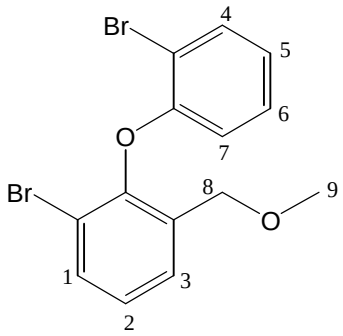
[3-Bromo-2-(2-bromophenoxy)phenyl]methanol **25**



Aldehyde **24** (1.36 g, 3.82 mmol, 1 equiv.), sodium borohydride (1.3 g, 34.38 mmol, 9 equiv.) and anhydrous THF (100 cm^3) were treated as described in General Procedure G. The crude product was purified by flash column chromatography (8:1 petrol : EtOAc) to yield the product as a colourless oil (1.1 g, 80%). Rf = 0.14 (8:1 petrol:EtOAc); ν_{max}

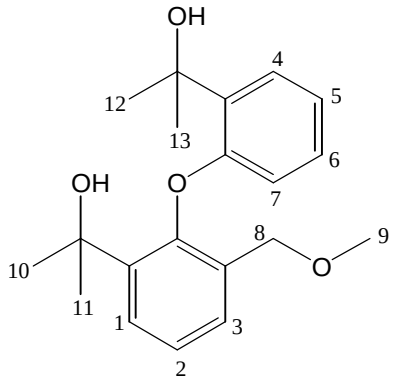
(film/cm^{-1}) 3331 (OH); δH (400 MHz; $CDCl_3$) 7.64 (1H, dd, *J* 8 and 1.5, H-3), 7.61 (1H, dd, *J* 8 and 1.5, H-1), 7.51 (1H, m, H-4), 7.20 (1H, t, *J* 8, H-2), 7.41 (1H, ddd, *J* 8.5, 7.5 and 1.5, H-5), 6.93 (1H, td, *J* 7.5 and 1.5, H-6), 6.41 (1H, dd, *J* 8.5 and 1.5, H-7) and 4.74 – 4.50 (2H, CH ABXY m, *J* 13.5, 7.5 and 5, H-8).; δC (100 MHz; $CDCl_3$) 151.8, 147.3, 134.8, 132.3, 131.6, 126.9, 126.7, 125.7, 122.0, 115.9, 112.7, 109.8 and 59.2.; EI *m/z* 358 (2 x ^{81}Br M); CI *m/z* 376 (2 x ^{81}Br M + NH_4^+); (Found: M, 355.9031. $C_{13}H_{10}O_2Br_2$ requires *M*, 355.9042).

[3-Bromo-2-(2-bromophenoxy)phenyl]methylether **26**



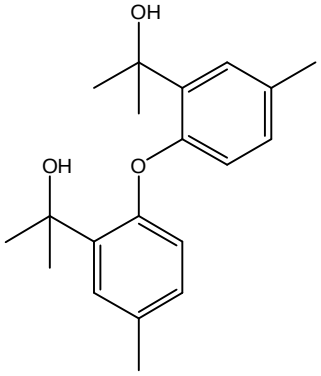
Alcohol **25** (1.01 g, 2.79 mmol, 1 equiv.), sodium hydride (60 wt % dispersion in mineral oil) (168 mg, 4.19 mmol, 1.5 equiv.), iodomethane (0.26 cm^3, 4.19 mmol, 1.5 equiv.) and THF (70 cm^3) were treated as described in General Procedure I. The crude product was purified by flash column chromatography (19:1 petrol : EtOAc) to yield the product as a colourless oil (1.01 g, 97%). Rf = 0.37 (19:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 2926 (CH).; δH (400 MHz; $CDCl_3$) 7.64 (1H, dd, *J* 8 and 1.5, H-3), 7.59 (1H, dd, *J* 8 and 1.5, H-1), 7.51 (1H, m, H-4), 7.19 (1H, t, *J* 8, H-2), 7.13 (1H, ddd, *J* 8.5, 7.5 and 1.5, H-5), 6.92 (1H, td, *J* 7.5 and 1.5, H-6), 6.39 (1H, dd, *J* 8.5 and 1.5, H-7), 4.48 – 4.34 (2H, CH ABXY m, *J* 13, H-8) and 3.33 (3H, s, H-9).; δC (100 MHz; $CDCl_3$) 151.6, 146.8, 132.3, 131.8, 131.0, 126.4, 126.3, 125.1, 121.3, 115.3, 112.4, 109.2, 67.1 and 56.7.; EI *m/z* 371 (1 x ^{81}Br M); CI *m/z* 390 (2 x ^{81}Br M + NH_4^+); (Found: M + NH_4^+, 387.9542. $C_{14}H_{16}NO_2Br_2$ requires *M*, 387.9542).

2-{2-[2-(1-Hydroxy-1-methylethyl)phenoxy]-3-methoxymethylphenyl}propan-2-ol **17**



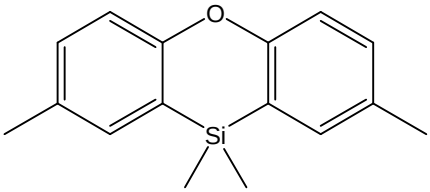
Dibromide **26** (100 g, 0.27 mmol, 1 equiv.), *n*-BuLi (1.4 M in hexanes) (0.39 cm^3, 0.54 mmol, 2 equiv.), acetone (0.05 cm^3, 0.7 mmol, 2.6 equiv.) and THF (10 cm^3) were treated as described in General Procedure H, stirring for 90 secs before quench. The crude product was purified by flash column chromatography (40:1 petrol : EtOAc) to yield the product as a light yellow solid (71 mg, 80%), m.p. 98 - 103°C. Rf = 0.37 (19:1 petrol:EtOAc); ν_{max} (film/cm^{-1}) 3410 (OH).; δH (400 MHz; $CDCl_3$) 7.55 (1H, dd, *J* 8 and 1.5, H-3), 7.45 (2H, m, H-1 and H-4), 7.27 (1H, t, *J* 7.5, H-2), 7.07 (1H, td, *J* 8 and 1.5, H-5), 6.98 (1H, td, *J* 7.5 and 1, H-6), 6.39 (1H, dd, *J* 8 and 1, H-7), 4.30 – 4.07 (2H, CH ABXY m, *J* 12.5, H-8), 3.22 (3H, s, H-9), 1.79 (3H, s, H-12), 1.78 (3H, s, H-13), 1.61 (3H, s, H-10) and 1.49 (3H, s, H-11).; δC (100 MHz; $CDCl_3$) 156.3, 149.0, 141.6, 134.9, 132.4, 128.2, 128.5, 126.9, 126.8, 125.7, 122.1, 114.3, 72.5, 72.3, 69.8, 58.6, 31.2, 31.0, 30.8 and 30.0.; EI *m/z* 330 (M); CI *m/z* 348 ($M + NH_4^+$), 330 (M); (Found: $M + NH_4^+$, 348.2163. $C_{20}H_{30}O_4N$ requires *M*, 348.2169). *HPLC*; Separation using Chiralcel OT+ column running 1 ml/min with 98 : 2 hexane:IPA, retention times 11.3 and 12.7 min with $[\alpha]_D^{23}$ = +11.3 (*c* 0.92 in acetone) and $[\alpha]_D^{23}$ = –13.5 (*c* 0.74 in acetone) respectively.

2-{2-[2-(1-Hydroxy-1-methylethyl)-4-methylphenoxy]-5-methylphenyl}propan-2-ol **16a**.[3]



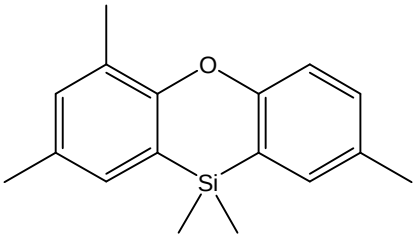
Para-tolyl ether (5.0 g, 25.2 mmol) was dissolved in dry TMEDA (50 mL) and cooled to 0 °C under a nitrogen atmosphere. *n*-BuLi (2.5 M solution in hexanes, 30.3 mL, 75.7 mmol) was added dropwise and the solution stirred at 0 °C for a further 0.5 h before the ice bath was removed and the mixture stirred for a further 24 h. After this time the mixture was cooled back to 0 °C and dry acetone (10 mL) was added which resulted in the mixture changing colour from dark orange to yellow. Water was added and solvents removed under reduced pressure. EtOAc (50 mL) was added and the layers separated. The aqueous was extracted with EtOAc (3 × 20 mL) and the combined organic fractions washed with water (2 × 25 mL), brine (25 mL), dried ($NaSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, petrol:EtOAc, 9:1→6:4) to give the *mono alcohol* (45%) and the *di-alcohol* (23%) as colourless oils; R_f 0.05 (petrol:EtOAc 9:1); ν_{max} (film)/cm^{-1} 3427 (OH), 2971 (CH), 2928 (CH), 1479 (aromatic; δ_H (300 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 1.5, MeCCHCCMe$_2$OH), 7.02 (2H, dd, *J* 8.5 and 1.5, MeCC*H*CH), 6.74 (2 H, d, *J* 8.5, OCCH), 3.20 (2 H, bs, 2 × OH), 2.38 (6 H, s, 2 × ArMe) and 1.72 (12 H, s, 2 × CMe$_2$); δ_C (75 MHz; $CDCl_3$) 152.7, 138.7, 129.0, 127.2, 119.6, 72.4, 30.6 and 21.2; *m/z* (CI) 314 (40%, M^+) and 279 [100%, MH–(2 × H_2O)]. (Found 332.2223. $C_{20}H_{26}O_3NH_4$ requires 332.2220).

2,8,10,10-Tetramethyl-10H-phenoxasiline **13**.[3]



para-Tolyl ether (5.0 g, 25.2 mmol) was dissolved in dry TMEDA (50 mL) and cooled to 0 °C under a nitrogen atmosphere. *n*-BuLi (30.3 mL, 75.7 mmol) (2.5 M solution in hexane, 30.3 mL, 75.7 mmol) was added and the mixture stirred for 20 min at 0 °C before the ice bath was removed and the mixture stirred for 12 h, after which time the solution had turned dark orange. The mixture was cooled to 0 °C and dimethyldichlorosilane (4.60 mL, 37.9 mmol) added dropwise which resulted in an exothermic reaction. The mixture was stirred for a further 2 h at 0 °C and saturated aqueous ammonium chloride solution (50 mL) added, followed by EtOAc (50 mL). The layers were separated and the aqueous layer washed with EtOAc (3 × 30 mL) and the combined organic fractions were washed with aqueous hydrochloric acid (3 M, 30 mL), water (30 mL), brine (30 mL), dried ($MgSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, petrol) to give the *phenoxisiline* as a viscous colourless oil (2.47 g, 9.71 mmol, 39%) which crystallized on standing (plates, mpt. 47-49.5 °C); R_f 0.50 (petrol); n_{max}(film)/cm^{-1}; d_H (300 MHz; $CDCl_3$) 7.40-7.36 (2 H, m, SiCCH), 7.32-7.26 (2 H, m, MeCC*H*), 7.16 (2 H, d, *J* 8.4, OCCH), 2.46 (6 H, s, Ph*Me*), and 0.54 (6 H, s, $SiMe_2$); d_C (75 MHz; $CDCl_3$) 158.0, 134.1, 132.2, 131.7, 119.0, 118.0, 21.0 and –0.0; *m/z* (EI) 254 (50%, *M*) and 239 (100%, M–CH_3) (Found 254.1129. $C_{16}H_{18}OSi$ requires 254.1121).

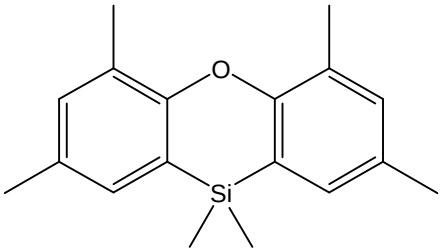
2,4,8,10,10-Pentamethyl-10H-phenoxasiline **13a**.[3]



The phenoxasiline **13** (500 mg, 1.965 mmol) was dissolved in dry Et_2O (10 mL) and dry TMEDA (0.44 mL, 2.95 mmol) and cooled to –78 °C under a nitrogen atmosphere. *s*-BuLi (1.1 M solution in cylohexane, 2.68 mL, 2.95 mmol) was added and after 10 miin

and dry ice bath was replaced with an ice bath. The orange solution was stirred for 2 h and iodomethane (0.18 mL, 2.95 mmol) added. The mixture was stirred for 14 h with gradual warming to room temperature. Saturated aqueous ammonium chloride solution 5 mL) was added and the layers separated. The aqueous layer was washed with Et_2O (3 × 5 mL) and the combined organic fractions were washed with water (2 × 5 mL), brine (5 mL), dried (MgSO4) and solvents removed under reduced pressure. The residue was purified by flash chromatography (silica, petrol) to give the *ether* as a colourless oil (400 mg, 1.49 mmol, 76%); R_f 0.67 (petrol); n_{max}(film)/cm^{-1} 2951 (CH), 2920 (CH), 1604 (aromatic and 1586 (aromatic); d_H (300 MHz; $CDCl_3$) 7.39 (2 H, s, ArH), 7.32-7.14 (4 H, m, 4 × ArH), 2.50 (3 H, s, Ar*Me*$_A$), 2.45 (3 H, s, Ar*Me*$_B$), 2.42 (3 H, s, Ar*Me*$_C$) and 0.54 (6 H, s, $SiMe_2$); d_C (75 MHz; $CDCl_3$) 158.2, 156.2 (O-C), 134.0, 133.6, 132.1, 131.7, 131.5, 126.9, 126.7, 119.2, 118.6, 118.0 (aromatics), 21.0, 20.9, 17.2 (ArMe) and –0.06 ($SiMe_2$); m/*z* (EI) 268 (50% M^+) and 253 (100%, M-Me) (Found 286.1622. $C_{17}H_{20}OSi$ requires 286.1622).

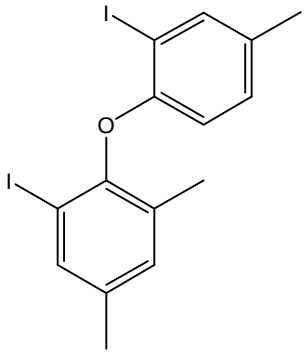
2,4,6,8,10,10-Hexamethyl-10H-phenoxasiline **13b**.[3]



The phenoxasiline **13** (2.10 g, 8.255 mmol) was dissolved in dry ether (30 mL) and dry TMEDA (4.36 mL, 28.9 mmol) and cooled to –78 °C under nitrogen. *s*-BuLi (1.3 M solution in cylohexane, 22.2 mL, 28.89 mmol) was added and after 10 min the dry ice bath was replaced with an ice bath. The orange solution was stirred for 12 h and iodomethane (4.1 mL, 28.9 mmol) added. The mixture was stirred for 3 h with gradual warming to room temperature. Saturated aqueous ammonium chloride solution (20 mL) was added and the layers separated. The aqueous layer was washed with Et_2O (3 × 25 mL) and the combined organic fractions were washed with water (2 × 25 mL), brine (25 mL), dried ($MgSO_4$) and solvents removed under reduced pressure. The residue was purified by flash chromatography (silica, petrol) to give the *ether* as a colourless oil

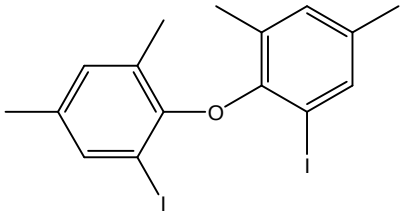
which solidified to a white solid on standing (1.04 g, 3.87 mmol, 47%); R_f 0.41 (petrol); n_{max}(film)/cm^{-1} 2952 (CH), 2919 (CH) and 1458 (aromatic); d_H (300 MHz; $CDCl_3$) 7.18 (2 H, s, 2 × ArH), 7.14 (2 H, s, 2 × ArH), 2.48 (6 H, s, 2 × Ar*Me*$_A$), 2.38 (6 H, s, 2 × Ar*Me*$_B$) and 0.50 (6 H, s, $SiMe_2$); d_C (75 MHz; $CDCl_3$) 156.1, 133.6, 131.5, 131.3, 126.9, 118.5 (aromatics), 20.9, 17.5 (Ar*Me*)and 0.0 ($SiMe_2$); m/z (EI) 282 (65%, M^+) 267 (100%, M–Me) (Found 282.1433. $C_{18}H_{22}OSi$ requires 282.1440).

1-(2-Iodo-4,6-dimethylphenoxy)-2-iodo-4-methylbenzene **14**.[3]



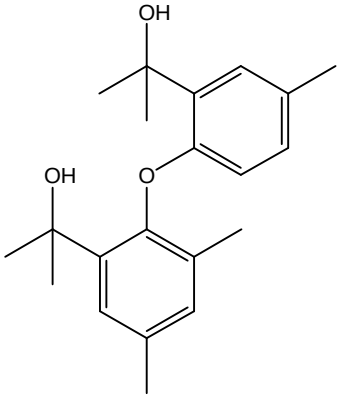
The phenoxasilin **13a** (890 mg, 3.317 mmol) was dissolved in dry DCM (20 mL) under a nitrogen atmosphere and cooled to 0 °C. Iodine monochloride (1.0 M in DCM, 6.97 mL, 6.97 mmol) was added and the mixture stirred for 30 min after which time the ice bath was removed. And stirred for a further 12 h. Saturated aqueous sodium thiosulfate solution (25 mL) was added and the layers separated. The aqueous layer was washed with DCM (3 × 25 mL) and the combined organic fractions were washed with water (2 × 25 mL), brine (25 mL), dried ($MgSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, petrol) to give the *ether* (859 mg, 1.85 mmol, 55%) as a crystalline solid (plates) mpt. 122.5-124.2 °C (hexane:EtOAc); R_f 0.55 (petrol); n_{max}(film)/cm^{-1}3019 (CH), 2919 (CH), 1602 (aromatic) and 1481 (aromatic); d_H (300 MHz; $CDCl_3$) 7.74 (1 H, d, *J* 2.0, (ICCH)$_A$), 7.58 (1 H, s, (ICCH)$_B$), 7.08 (1 H, s, MeCC*H*CMe), 6.98 (1 H, dd, *J* 8.5 and 2.0, OCCHC*H*), 6.20 (1 H, d, *J* 8.5, OCCH), 2.36 (3 H, s, $ArMe_A$), 2.31 (3 H, s, $ArMe_B$) and 2.16 (3 H, s, $ArMe_C$); d_C (75 MHz; $CDCl_3$) 153.8, 151.1, 140.5, 138.3, 138.0, 137.3, 133.4, 132.7, 133.4, 132.7, 132.6, 130.1, 113.1, 92.0 (C-I), 85.4 (C-I), 20.7, 20.4 and 17.6; *m/z* (EI) 464 (15%, MH^+) and 210 (100%, M–I_2) (Found 463.9127. $C_{15}H_{14}OI_2$ requires 463.9129).

2-(2-Iodo-4,6-dimethylphenoxy)-1-iodo-3,5-dimethylbenzene **15**.[3]



The phenoxasiline **13b** (1.57 g, 5.56 mmol) was dissolved in dry DCM (35 mL) under a nitrogen atmosphere and cooled to 0 °C. Iodine monochloride (1.0 M in DCM, 12.8 mL, 12.79 mmol) was added and the mixture stirred for 30 min after which time the ice bath was removed. And stirred for a further 12 h. Saturated aqueous sodium thiosulfate solution (25 mL) was added and the layers separated. The aqueous layer was washed with DCM (3 × 25 mL) and the combined organic fractions were washed with water (2 × 25 mL), brine (25 mL), dried ($MgSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, petrol) to give the *ether* (1.70 g, 3.56 mmol, 64%) as a crystalline solid (plates) mpt. 134.5-135.8 °C (hexane:EtOAc); R_f 0.55 (petrol); n_{max}(film)/cm^{-1} 2958 (CH), 1919 (CH) and 1466 (aromatic) d_H (300 MHz; $CDCl_3$) 7.53 (2 H, s, 2 × CHCI), 6.90 (2 H, s, 2 × CHCMe), 2.28 (6 H, s, 2 × ArMe) and 1.96 (6 H, s, 2 × CHCMe); d_C (75 MHz; $CDCl_3$) 152.1 (C-O) 138.3 (C-H), 134.7 (*C*-Me), 133.1 (C-H), 129.0 (*C*-Me), 89.8 (C-I), 20.3 and 18.6 (alkyl); *m/z* (EI) 478 (10%, M^+) 224 [85%, M–(2 × I)] (Found 477.9294. $C_{16}H_{16}OI_2$ requires 477.9285).

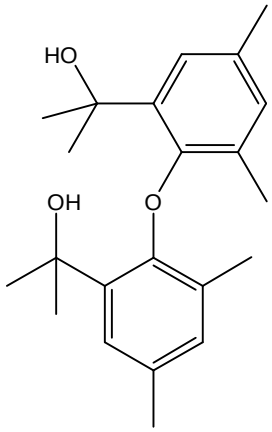
2-{2-[2-(1-Hydroxy-1-methyl-ethyl)-4-methyl-phenoxy]-3,5-dimethyl-phenyl}-propan-2-ol **16b**.[3]



The diaryl ether **14** (200 mg, 0.431 mmol) was dissolved in dry THF (10 mL) and cooled to –78 °C under nitrogen. *n*-BuLi (2.3M solution in hexanes, 0.43 mL, 0.991 mmol) was added (no colour change was observed) and the mixture stirred for 2 min before acetone

(freshly distilled from 4 Å MS, 5 mL) was added . The mixture was stirred for 14 h and then saturated aqueous ammonium chloride solution (5 mL) added and the layers separated. The aqueous layer was washed with Et_2O (3 × 5 mL) and the combined organic fractions were washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$) and solvents removed under reduced pressure. The residue was purified by flash chromatography (silica, petrol:EtOAc, 9:1) to give the *alcohol* as a colourless oil (73.6 mg, 0224 mmol, 52%); R_f 0.08 (petrol:EtOAc, 9:1); n_{max}(film)/cm^{-1} 3400 (OH), 2975 (CH), 2926 (CH), 1609 (aromatic) and 1493 (aromatic) d_H (300 MHz; $CDCl_3$) 7.28-7.24 (2 H, m, 2 × ArH), 7.00 (1 H, s, ArH), 6.88 (1 H, dd, *J* 8.5 and 2.0, OCCHC*H*), 6.34 (1 H, d, *J* 8.5 OCC*H*), 2.39 (3 H, s, Ar*Me*$_A$), 2.32 (3 H, s, Ar*Me*$_B$), 2.02 (3 H, s, Ar*Me*$_C$), 1.80 (3 H, s, (C*Me*$_A$Me$_B$)$_A$), 1.78 (3 H, s, (C*Me*$_A$Me$_B$)$_B$), 1.62 (3 H, s, (CMe$_A$*Me*$_B$)$_A$) and 1.52 (3 H, s, (CMe$_A$*Me*$_B$)$_B$); d_C (75 MHz; $CDCl_3$) 153.7, 147.6, 141.0, 134.7, 134.5, 131.9, 131.8, 130.9, 128.6, 127.5, 125.5, 114.2, 72.6, 72.5, 31.3, 31.0, 30.8, 30.1, 21.3, 21.1 and 17.6; *m/z* (CI) 328 (20%, M^+) (Found 328.2031. $C_{21}H_{28}O_3$ requires 328.2033).

2-{2-[2-(1-Hydroxy-1-methyl-ethyl)-4,6-dimethyl-phenoxy]-3,5-dimethyl-phenyl}-propan-2-ol **16c**.[3]



The diaryl ether **15** (50 mg) was dissolved in dry THF and cooled to –78 °C under a nitrogen atmosphere. *t*-BuLi (1.5 M, 0.31 mL, 0.462 mmol) was added which resulted in the solution turning yellow. The mixture was stirred for 5 min and then dry acetone (0.2 mL) added and the mixture stirred at –78 °C for 1 h and then room temperature for 1 h. Saturated aqueous ammonium chloride solution (3 mL) was added and the layers separated. The aqueous layer was washed with Et_2O (3 × 3 mL) and the combined organic fractions were washed with water (2 × 3 mL), brine (3 mL), dried ($MgSO_4$) and

solvents removed under reduced pressure. The residue was purified by flash chromatography (silica, petrol:EtOAc, 9:1→8:2) to give the *alcohol* as a colourless oil (20.5 mg, 0.0599 mmol, 57%); R_f 0.08 (9:1 petrol:EtOAc); n_{max}(film)/cm^{-1} 3393 (OH), 2976 (CH), 2925 (CH) and 1466 (aromatic); d_H (300 MHz; $CDCl_3$) 7.40 (2 H, d, *J* 2.0, 2 × ArH), 6.82 (2 H, d, *J* 2.0 2 × ArH), 3.70 (2 H, broad s, 2 × OH), 2.32 (6 H, s, 2 × Ar*Me*$_A$), 1.80 (6 H, s, 2 × Ar*Me*$_B$), 1.75 (6 H, s, 2 × C(OH)*Me*$_A$Me$_B$) and 1.72 (6 H, s, 2 × C(OH)Me$_A$*Me*$_B$); d_C (75 MHz; $CDCl_3$) 150.3, 137.4, 132.4, 132.2, 127.4, 125.6 (aromatics) 72.8 (Ar*C*OH), 31.4, 30.1, 21.1 and 18.4; *m/z* (EI) 342 (2%, M^+), 251 (30%) and 149 (50%); (Found 342.2181. $C_{22}H_{30}O_3$ requires 342.2195).

References;

1. Clayden, J.; Vallverdú, L.; Helliwell, M. *Org. Biomol. Chem.* **2006**, in press
2. Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681.
3. Betson, M. S.; Clayden, J. *Synlett* **2006**, 745

2. Determination of kinetic parameters

^{1}H NMR spectra were acquired at temperatures close to (above and below) the coalescence temperature for significant diastereotopic (for interconverting enantiomers) or diastereoisomeric (for interconverting diastereoisomers, which were generally present in a ratio close to 1:1) signals. Lineshapes at a range of temperatures were modelled using gNMR, and rates of exchange *k* between stereoisomers obtained for a range of temperatures (generally 30-40 K). Figure S1 illustrates a typical example (compound **16a**)

Eyring plots (ln [*k*/T] vs. 1/T) of the data points gave straight lines of the form $y = -mx + b$, where

$m = -\Delta H^{\ddagger} / R$

$b = \ln (k_B/h) + \Delta S^{\ddagger} / R$

$\Delta G^{\ddagger}$ was calculated at 25 °C (using $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$).

For the diastereoisomeric subsets **d** and **e** of **6, 6', 7, 7', 8** and **8'**, these values have no physical meaning because the barrier to epimerisation depends on the direction of approach, and only a half-life for the equilibration (see below) is quoted in the paper.

For compounds which showed no decoalescence even at the lowest temperatures obtainable in readily available solvents, we inferred rapid interconversion between two stereoisomers which, at the slow exchange limit, would presumably display at least one pair of signals with a peak separation of >0.1 ppm. We therefore assigned as a minimum rate of stereoisomeric interconversion at –90 °C to these compounds (subsets **c, d** and **f** of **9** and **10**) that which would give coalescence of two peaks with $\Delta\delta$ = 30 Hz (at 300 MHz).

In all cases, the Eyring equation was used to convert $\Delta G^{\ddagger}$ at 25 °C to a half-life for approach to equilibrium, bearing in mind that the rate of interconversion of two enantiomers (ie 1R becomes 1S) is half the rate of racemisation (ie 2R becomes 1R + 1S).

For isomers which were separable, we used HPLC (or on occasion flash chromatography) to obtain small stereoisomerically enriched samples. Figure 2 and 3 below show the HPLC traces of **16b** and **16c**. We then allowed the separated samples to equilibrate at fixed temperature, following their equilibration by HPLC. First order decay was observed, for which line-fitting yielded a rate constant, and hence a half-life and for racemisations, a rotational barrier. For **17** we determined rates at 60 and at 80 °C, and used an Eyring plot to extrapolate a half-life and barrier at 25 °C. For **8d', 8f', 11e, 11f, 16b,** and **17** a rate was determined at only one temperature, and the half-life at 25 °C was estimated assuming $\Delta S^{\ddagger}$ to be close to 0.

*Figure S1: Observed (above) and calculated (below) line broadening of the diastereotopic Me groups of **16b**.*

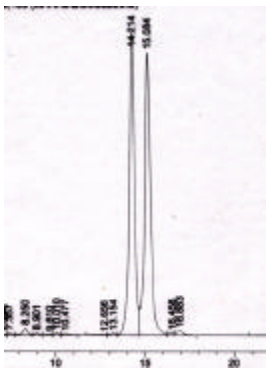


Figure S2:
*HPLC trace obtained for **16b***
(b-GEM column)

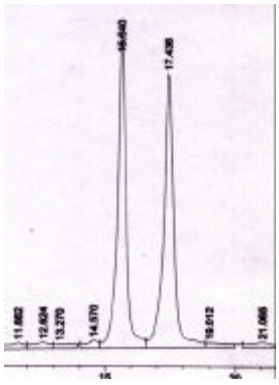


Figure S3:
*HPLC trace obtained for **16c***
(b-GEM column)