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Polybrominated diphenyl ethers (BDEs); preparation of reference standards and fluorinated internal analytical standards

Huiling Liu,[a] Monica Bernhardsen[a] and Anne Fiksdahl[b,*]

[a]*Chiron AS, Stiklestadveien 1, NO-7041 Trondheim, Norway*
[b]*Department of Chemistry, Norwegian University of Science and Technology, Sem Sælands v. 8, NTNU, NO-7491 Trondheim, Norway*

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Abstract—Four new difluorinated tetra- and pentabromo BDE internal standards for GC–MS/GC–ECD analysis, **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119**, have been prepared in 98–99.0% purity, mainly by coupling of the new tribromodifluorophenols (**19**–**21**) and symmetrical bromodiphenyliodonium salts (**8**, **22**). The four difluorinated BDEs showed promising properties as internal standards for quantitative BDE analysis. Tetra-, penta-, hexa- and hepta-brominated BDE reference standards, **BDE 75**, **BDE 85**, **BDE 138** and **BDE 183**, were also prepared in 98.4–99.8% purity and characterised.

1. Introduction

Polybrominated diphenyl ethers (BDEs)[1–8] are industrial chemicals used as flame-retardants in electronics, plastics, furnishing foam, textiles, automobile components etc. Three crude technical mixtures of penta-, octa- and deca-brominated BDEs, respectively, are commercially available. They are released into the environment at industrial sites or from household trash. The presence of BDEs in air and biological samples even from remote areas indicates a world-wide pollution problem.

The structurally similarity of BDEs and PCBs has given rise to environmental concern. Like PCBs, BDEs resist degradation in the environment and are thus persistent organic pollutants that remain in the environment for years. BDEs appear to share some toxicological properties with PCBs. In particular, the less brominated isomers such as the tetra-, penta- and hexa-BDEs are potential toxins and accumulate in the bodies of animals and humans due to their high affinity for lipids. Octa- and deca-brominated congeners have lower bioaccumulative and biological activity, but a potential degradation of these BDEs into the less brominated and more toxic BDEs has been suggested. Compared with PCBs, the effects of human exposure to BDEs are not well known and little information is available of human toxicity, carcinogenicity and behavioural effects. The effect of these widespread pollutants on human health and the environment is still under investigation. There are 209 theoretically possible congeners divided into 10 congener groups from mono- to deca-BDE. They are numbered according to IUPAC's PCB based system.[9,10]

Methods for detection and quantification of BDEs are mostly based on extraction and clean-up followed by GC–MS or GC–ECD analysis. However, individual BDEs are not commercially readily available. Due to the lack of pure reference standards for most BDE congeners, quantitative analyses have been carried out using technical BDE product mixtures as standards.

Internal standards are used for quantitative analysis. Some ^{13}C incorporated compounds have been used as internal standard for quantification of BDEs. The preparation of ^{13}C products[11] is, however, inconvenient and laborious since the carbon skeleton of these compounds have to be built up from small ^{13}C isotope labelled building blocks. A small change in the physical and chemical properties of a compound is, however, obtained by the introduction of a fluoro substituent. The slightly more volatile character of such fluoro derivatives make them as suitable internal standards for GC–MS (-ECD). Monofluorinated PAHs have been used as standards for environmental analysis due to their suitable chemical and physical properties. We wanted to prepare fluorinated BDE analogues (F-BDE) and investigate whether these derivatives correspondingly would have suitable physical and chemical properties to be used as internal standards in BDE analysis. Different *o*, *m* and *p* mono- or difluoro isomers were expected to give different degree of chromatographic resolution relative to the parent compounds. This will be discussed.

Keywords: Polybrominated diphenyl ethers; BDE; Flame retardants; Fluorinated BDE; 2F-BDE; Internal standard; Analytical standard; Synthesis.
* Corresponding author. Tel.: +47 73594094; fax: +47 73594256; e-mail: anne.fiksdahl@chem.ntnu.no

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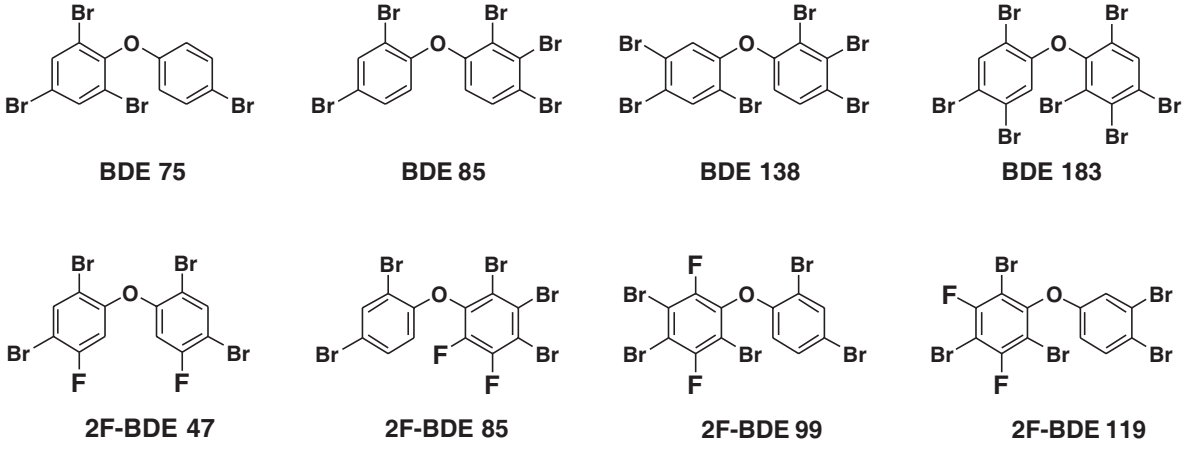
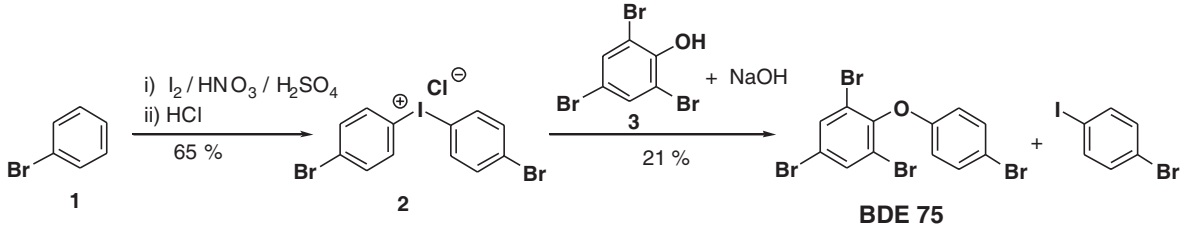


Scheme 1.

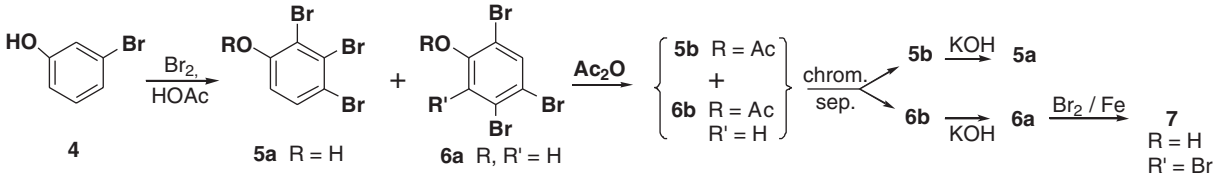
Since there is a need for analytical BDE standards for qualitative and quantitative BDE analysis, we hereby present the synthesis of high purity reference standards and fluorinated internal standards. The four new internal standards **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** (see Scheme 1) and their respective tribromodifluorophenolic precursors (**19**–**21**) have not previously been prepared, while the four reference standards **BDE 75**, **BDE 85**, **BDE 138** and **BDE 183** have not been spectroscopically fully characterised earlier.

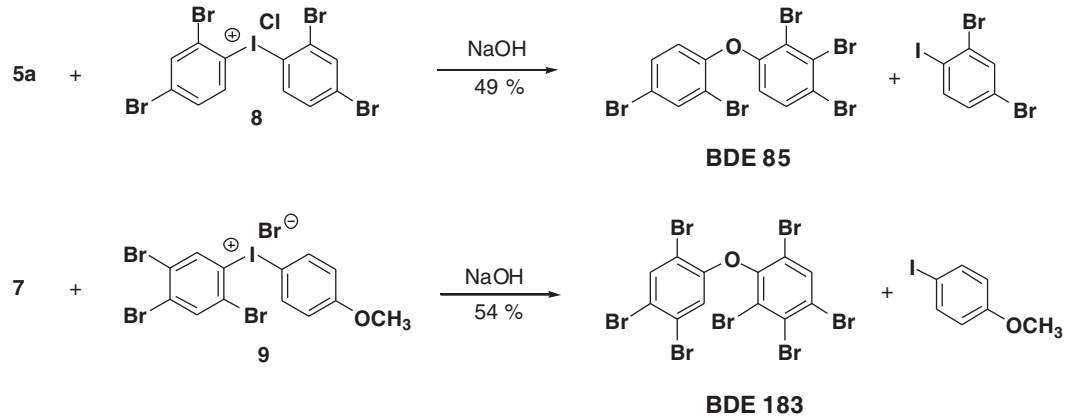
2. Results and discussion

The BDE analytical standards were prepared as described below (Schemes 2–6), mainly from the appropriate

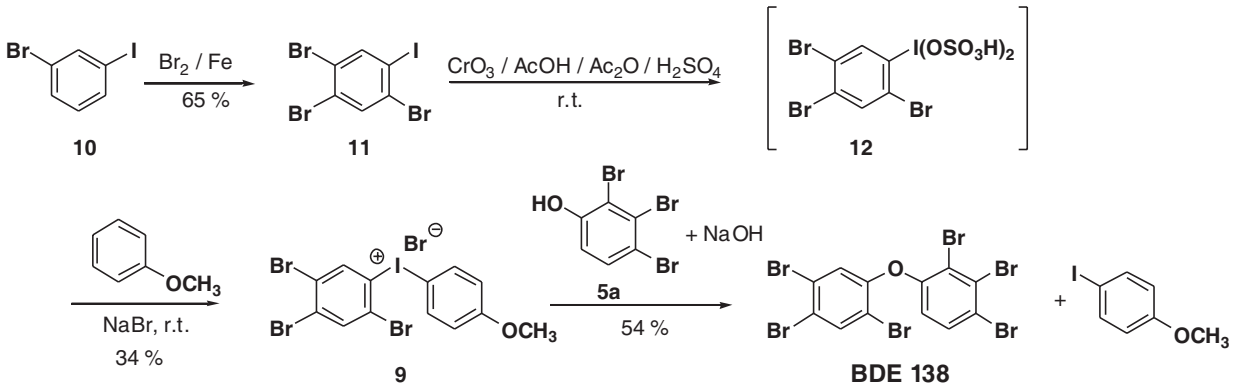


Scheme 2.

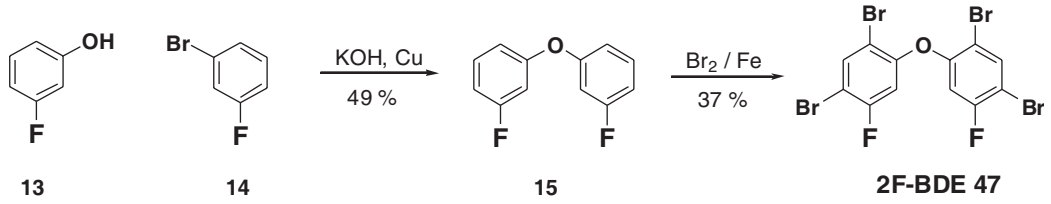




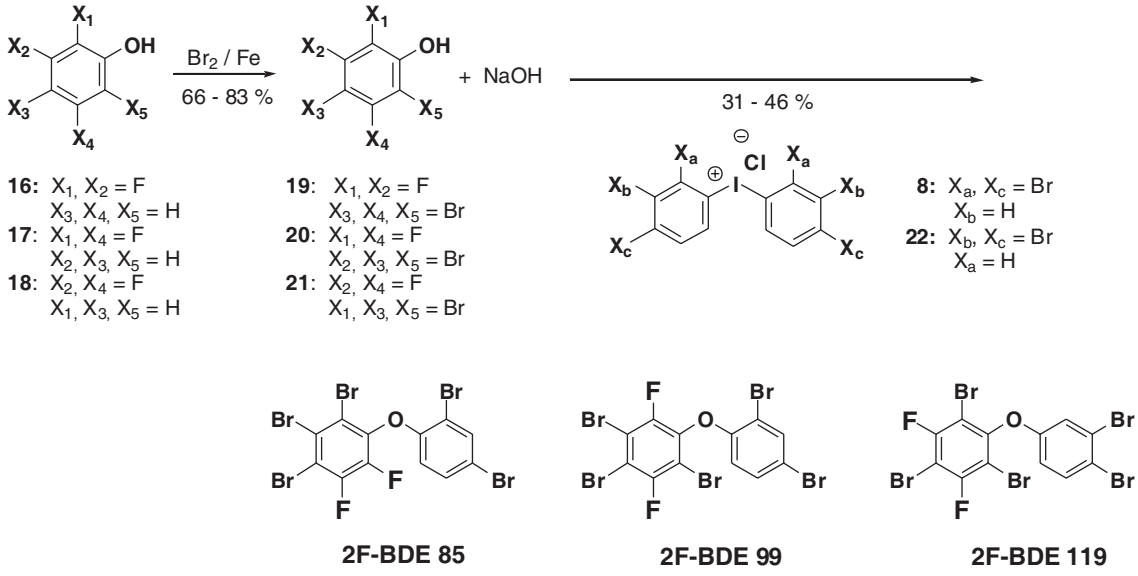
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

brominated diphenyliodonium salts and bromo(fluoro) phenols. Since the purpose of the work was the preparation of reference compounds and internal standards, we focused more on the purity of the products and intermediates than the respective yields.

2.1. Reference standards

Compound **BDE 75**[12,16] was prepared in 98.4% purity from bromobenzene (**1**) and 2,4,6-tribromophenol (**3**) via 4,4′-dibromodiphenyliodium chloride (**2**) as shown in Scheme 2.[13–15] The diphenyliodonium salt (**2**)[16] was prepared by $(IO_2)SO_4$ oxidation of bromobenzene (**1**) followed by coupling with **1** by electrophilic aromatic substitution.[17–20] The coupling is reported always to give only the *para* product, due to steric reasons. Compound **2** was precipitated as the hydrochloride salt by the addition of HCl. Nucleophilic substitution by phenol **3** afforded **BDE 75**. The 4-bromoiodobenzene leaving group was removed by chromatography.

Compounds **BDE 85**[21] (99.0% purity) and **BDE 183**[22] (99.4% purity) were prepared as shown in Scheme 3 from the tri- and tetrabromophenols (**5a**, **7**) and 2,2′,4,4′-tetrabromodiphenyliodonium chloride (**8**) and 4-methoxyphenyl-2′,4′,5′-tribromophenyliodonium bromide (**9**), respectively.[23] The bromophenol nucleophiles **5a** and **7** were prepared by bromination of **4**. As expected, the activated 3-bromophenol

4 gave a mixture of the two *ortho* and *para* substituted product isomers (**5a**, **6a**), with the less sterically hindered **6a** as the dominating isomer. The isomers could not be separated and the bromination product mixture **5a/6a** was therefore acetylated directly to give a mixture of the acetates **5b/6b**. Chromatographic separation of **5b** and **6b** and individual hydrolysis of the respective isomers afforded the pure phenols **5a** and **6a** in 98.2 and 99.4% purity. Due to a modified preparation method, much higher yields of the acetates (**5b**/9% and **6b**/24%) and phenols (**5a**/82% and **6a**/98%) were obtained compared to previous reports (**5b**/1% and **6b**/3%; **5a**/33% and **6a**/88%).[23] Compound **7** was obtained in 98% purity and 71% yield after a final *ortho* bromination[16] of the major isomer **6a**. The symmetrical tetrabrominated diphenyliodonium chloride **8** was prepared from 1,3-dibromobenzene as described in Scheme 2 for the preparation of **2**. The unsymmetrical diphenyliodonium bromide **9** was prepared from 3-bromoiodobenzene (**10**) as shown in Scheme 4 for the preparation of **BDE 138**. As a consequence of the geometry of the transition state, it has been shown that nucleophiles preferentially attack unsymmetrical diphenyliodonium salts, such as **9**, at the aryl group with a large *ortho* substituent.[24] Nucleophilic substitution by tetrabromophenol **7** therefore afforded the coupling product **BDE 183**[25] by nucleophilic attack on the tribromophenyl group of **9**.

Compound **BDE 138**[21] was prepared in 99.8% purity from 3-bromoiodobenzene (**10**) and 2,3,4-tribromophenol (**5a**) as shown in Scheme 4. Bromination[16] of **10** afforded the *ortho* and *para* brominated product **11** in 98% purity after recrystallization. Compound **9** has previously been prepared via the dihydrogensulfate **12** by H_2O_2 oxidation of **11**.[25] However, we obtained a higher yield by CrO_3 oxidation[26] of **11** to **12**, which was not isolated before the *para* coupling with anisole to afford the unsymmetrical appropriately brominated diphenyliodonium bromide (**9**). The tribromophenol **5** was obtained as discussed above for the preparation of **BDE 85** (Scheme 3).

2.2. Internal standards

Internal standards for chromatography are supposed to elute close together with the parent compounds with baseline resolution. There are indications[27] that the *ortho* monofluorinated F-BDEs give larger chromatographic separation from the parent compounds than the corresponding *meta* substituted isomers, while the *para* monofluorinated BDEs give hardly any separation. As expected, difluorinated 2F-BDEs give a larger separation than mono F-BDEs. Based on this experience the four *m*,*m*- and *o*,*m*-difluorinated 2F-BDEs discussed below were supposed to be promising as internal standards and hence they were selected for synthesis.

Compound **2F-BDE 47** was prepared in 98.0% purity by bromination of bis(*m*-fluorophenyl) ether (**15**). Intermediate **15** was synthesised[21] in 98.8% purity from 3-fluorophenol (**13**) and 3-bromofluorobenzene (**14**), see Scheme 5. As expected, the desired and less sterically hindered *ortho* and *para* tetrabrominated isomer was formed on bromination of **15**. The identity of the product was established by ^{1}H and ^{13}C NMR studies. Only two proton signals were observed by ^{1}H NMR, indicating the symmetry of the molecule. Both signals were doublets, and the coupling constants were as expected from *o* or *m* F–H coupling (J_{FH}=7.1, 8.7 Hz). The particular low frequency (*d* 6.68) of the H6 and H6′ signal is caused by the characteristic shielding effect of the fluoro substituent. The ^{13}C NMR data also supported the structure of **2F-BDE47**, and the most characteristic observations were the large C–F coupling constants, $^1J_{CF}$= 250 Hz (J_{F-C1}) and $^2J_{CF}$=26.6 Hz (J_{F-C6}), and the high frequency of the C5 signal at *d* 158.7.

Compounds **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** were obtained in 99.0, 98.8 and 99.0% purity, respectively, by coupling of the appropriate tribromodifluorophenols (**19–21**) and the iodonium salts **8** and **22** as shown in Scheme 6. The nucleophilic substitution reactions were corresponding to the reactions discussed above for the preparation of the external standards in Schemes 2–4. The new phenols (**19–21**) were prepared in 98.4–99.2% purity by complete bromination of the difluorophenol substrates (**16–18**). Bromination in tetrachloromethane as solvent was unsuccessful since a series of chloro-substituted products were isolated. However, the fully brominated phenolic precursors (**19–21**) were obtained in good yields using 1,2-dibromoethane as a solvent. ^{1}H, ^{13}C, and ^{19}F NMR spectra of the new phenols (**19–21**) and the fluorinated **2F-BDE** products showed the characteristic features of fluorinated aryl compounds. Only one single phenolic signal was observed in ^{1}H NMR for the fully substituted phenols (**19–21**) while the 2F-BDEs had the expected ^{1}H NMR coupling patterns to be assigned with the various dibromophenyl groups, similar to **8** and **22**. ^{13}C NMR confirmed the expected tribromodifluoro phenolic and 2F-BDE structures, especially based on the large C–F coupling constants ($^1J_{CF}$ approx.=245–260 Hz, $^2J_{CF}$ approx.=20–26 Hz) and the high frequency of the fluoro connected carbons (approx. d_{C-F} 140–160). The number of signals, the shift values and the coupling patterns in the respective ^{19}F NMR spectra supported the proposed tribromodifluorophenolic (**19–21**) and **2F-BDE** structures.

2.3. GC–MS analysis

All the four internal fluorinated standards prepared in this work separated from the non-fluorinated analogues by GC–MS. The analyses showed that a higher resolution was obtained in the **BDE 47/2F-BDE 47** system and the **2F-BDE 85/BDE 85** system (see Fig. 1) compared to the **2F-BDE 99/BDE 99** and **2F-BDE 119/BDE 119** systems, correspondingly. Since we have experienced[27] that *ortho* fluorinated F-BDEs give larger chromatographic separation from the parent compounds than the corresponding *meta* substituted isomers, the higher net dipole effect obtained by the introduction of two neighbouring *o*-/*m*- fluoro substituents in **2F-BDE 85** could explain the greater separation compared to the *m*-/*m*- difluoro compound **2F-BDE 119**. In **2F-BDE 99** the fluoro substituents are *para* to each other and this may neutralize the effect of the introduction of two fluorines.

All the analytical standards are now available from Chiron AS, Norway, and further work on the syntheses of (2F-)BDEs and the development of analytical methods based on BDE analytical standards are in progress.

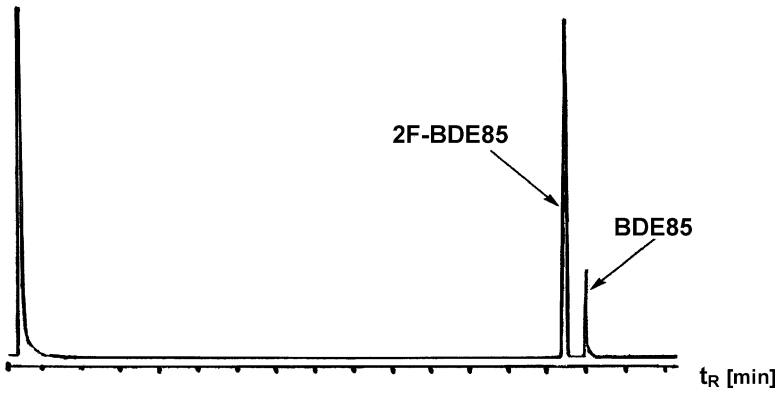


Figure 1. GLC of **2F-BDE 85** and **BDE 85**.

3. Conclusion

Four new difluorinated tetra- and pentabromo BDE internal standards for GC–MS/GC–ECD analysis, **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119**, have been prepared in 98–99.0% purity. **2F-BDE 47** was prepared by bromination of the bis(fluorophenyl) ether (**15**). **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** were synthesised by coupling of the new tribromodifluorophenols (**19–21**) and the symmetrical iodonium salt (**22**, **23**) precursors. All four difluorinated BDEs showed promising properties as internal standards for quantitative BDE analysis. Four tetra-, penta-, hexa- and hepta-brominated reference standards of BDE (**BDE 75**, **BDE 85**, **BDE 138**, **BDE 183**) were prepared in 98.4–99.8% purity from the appropriate brominated diphenyliodonium salts (**2**, **8**, **9**) and phenols (**3**, **5a**, **7**) and characterised.

4. Experimental

4.1. General

Chemicals. Compounds **1**, **3**, **4**, **10**, **13**, **14**, **16**, **17** and **18** were purchased from Acros. Solvents. Analytical quality. $^{1}H/^{13}C$ NMR. Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. Hexafluorobenzene was used as reference for ^{19}F NMR. MS: Finnigan MAT 95 XL Mass Spectrometer (EI/70 eV). All the multiple MS molecular ions for polybrominated compounds, due to the presence of the $^{79}Br/^{81}Br$ isotopes, are assigned as M. IR. Thermo Nicolet Nexus FT-IR spectrophotometer. All melting points are uncorrected, measured by Sanyo Gallenkamp apparatus. Flash chromatography. Silica (sds, 60 A, 40–63 μm).

Method A. General method[13–16] for the preparation of symmetrical diphenyliodonium chlorides (**2**, **8**, **22**). To a mixture of sulfuric acid (concd, 1.9 ml) and fuming sulfuric acid (30%, 3.75 ml) was added I_2 (1.62 g, 6.37 mmol) with stirring. An additional mixture of sulfuric acid (concd, 0.5 ml), fuming sulfuric acid (65%, 0.25 ml) and fuming HNO_3 (100, 0.8 ml) was added slowly. Yellow crystals precipitated after stirring at 75 °C for 1.5 h. The reaction mixture was cooled to 0 °C and the appropriate bromobenzene substrate (32 mmol) was added slowly. After stirring at 45 °C for 2 h and cooling to 0 °C, water (15 ml) was slowly added and nitrogen oxides were removed by N_2 flushing while stirring for 1 h. Water was removed and the brown oily product was dissolved in methanol (150 ml). White crystalline product was obtained by addition of hydrochloric acid (concd, 60 ml), filtering and washing by methanol.

Method B. General method[16–20] for the coupling of diphenyliodonium salts and phenols for the preparation of **BDE 75**, **BDE 85**, **BDE 138**, **BDE 183**, **2F-BDE 85**, **2F-BDE 99**, **2F-BDE 119**. A solution of the phenol (1 equiv) in aqueous NaOH (approx. 1.1 equiv) was refluxed before the addition of the diphenyliodonium chloride (1 equiv). A brown oily product was obtained after 2 h reflux. If necessary, the pH was adjusted by the addition of aqueous NaOH before the crude product was isolated by extraction at pH 11 and dried. The pure diphenyl ether was obtained by flash chromatography (10% dichloromethane in hexane). The product was recrystallised from methanol.

Method C. General method[16] for the Br_2/Fe bromination for the preparation of **7**, **11**, **19**, **20**, **21**. A solution of the substituted phenol or benzene substrate (1 equiv) and Fe powder (0.5–1 equiv) in dichloromethane or 1,2-dibromoethane was refluxed and a solution of bromine (1–6 equiv) in dichloromethane or dibromoethane was added dropwise. (The amount of Fe and Br_2 depended on the number of bromo substituents to be introduced and is given specifically for each experiment below). After 2–5 h reflux $NaHSO_3$ (5%) was added and the product was extracted, dried and recrystallized from hexane.

4.1.1. 4,4′-Dibromodiphenyliodonium chloride (2).[16,17] The title compound was prepared from bromobenzene (**1**) by Method A; 65% yield, pure by ^{1}H NMR (lit.[16] 23%); mp 211–212 °C (lit.[17] 212 °C).

4.1.2. 2,3,4-Tribromophenyl acetate (5b) and 2,4,5-tribromophenyl acetate (6b). The title compound was prepared from 3-bromophenol (**4**).[23] 3-Bromophenol (**4**) (1 equiv) in acetic acid (80 ml) was added dropwise to bromine (2.2 equiv) in acetic acid (125 ml) and stirred at room temperature for 1.5 h. The reaction mixture was added to $NaHSO_3$ (5%, 100 ml) and the 3,4-dibromophenol intermediate was extracted, dried and purified by flash chromatography (CH_2Cl_2/hexane; 3:2). Bromination was

repeated as described above, using 3,4 dibromophenol (1 equiv) in acetic acid (40 ml) and bromine (1 equiv) in acetic acid (18 ml). The product mixture (45% yield) of 2,3,4 tribromophenol (**5a**) and 2,4,5 tribromophenol (**6a**) (1 equiv), pyridine (1 equiv) and acetic acid anhydride (3 equiv) in dichloromethane (100 ml) was stirred vigorously at room temperature for 2 h. The individual acetate products (**5b**) and (**6b**) were isolated by flash chromatography (CH_2Cl_2/hexane; 1:1).

4.1.3. 2,3,4-Tribromophenyl acetate (5b). White crystals; 8.81% yield; 96.9% purity (GLC); mp 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J=8.7 Hz, 1H, H5), 7.00 (d, J=8.7 Hz, 1H, H6), 2.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5 (carbonyl), 148.8 (C1), 132.8 (C5), 129.2 (C3), 123.6 (C6), 123.4 (C4), 121.8 (C2), 21.2 (CH_3); MS: *m*/*z* 376 (M, 2%), 374 (M, 6), 372 (M, 6), 370 (M, 2), 334 (28), 332 88 (100), 330 (99), 328 (28). IR (KBr) ν_{max}: 3070 (w), 1758 (s), 1561 (w), 1458 (w), 1432 (s), 1369 (s), 1353 (s), 1239 (m), 1202 (s), 1052 (m), 1013 (m), 946 (w), 923 (s), 861 (m), 807 (m), 732 (m) cm^{-1}.

4.1.4. 2,4,5-Tribromophenyl acetate (6b).[28] White crystals; 24.2% yield; 99.0% purity (GLC); mp 98.5–99.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H, H3), 7.43 (s, 1H, H6), 2.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9 (s, 1C, carbonyl), 147.8 (C1), 136.8 (C3), 128.4 (C6), 123.9 (C5 or C4), 122.5 (C4 or C5), 115.9 (C2), 20.7 (CH_3); MS: *m*/*z* 376 (M, 3%), 374 (M, 8), 372 (M, 8), 370 (M, 3), 334 (28), 332 (100), 330 (99), 328 (30). IR (KBr) ν_{max}: 3501 (w, br), 3080 (m), 1762 (s), 1452 (m), 1363 (m), 1331 (m), 1244 (w), 1221 (m), 1198 (s), 1108 (m), 1052 (s), 1009 (w), 928 (m), 887 (m) cm^{-1}.

4.1.5. 2,3,4-Tribromophenol (5a).[25,29] The title compound was prepared from **5b**; 2,3,4-tribromophenyl acetate (**5b**) (5.94 g, 15.28 mmol) and KOH (2 M, 10 ml) in methanol (100 ml) were refluxed for 24 h. Methanol was distilled off and the remaining oil was extracted at pH 2–3 after addition of HCl (10%). The product was recrystallised from hexane to give white crystals; 81.7% yield; 98.2% purity (GLC); mp 93–94 °C (lit.[25] 95 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=8.8 Hz, 1H, H5), 6.90 (d, J=8.8 Hz, 1H, H6), 5.63 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6 (C1), 132.9 (C5), 126.8 (C3), 115.9 (C4), 115.8 (C6), 114.6 (C2); MS: *m*/*z* 334 (M, 30%), 332 (M, 98), 330 (M, 100), 328 (M, 32), 252 (12$^+$), 250 (22), 248 (11), 143 (17), 141 (17); IR (KBr) ν_{max}: 3478 (m, br), 3060 (w), 2360 (w), 1886 (w), 1701 (w), 1635 (w), 1575 (m), 1557 (m), 1439 (s), 1381 (m), 1279 (s), 1197 (s), 1181 (m), 1157 (m), 1129 (w), 881 (m), 816 (s) cm^{-1}.

4.1.6. 2,4,5-Tribromophenol (6a).[25,29] The title compound was prepared by hydrolysis of **6b** as described for **5a** above, to give white crystals; 98.4% yield; 99.4% purity (GLC); mp 85–86 °C (lit.[25] 87 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (s, 1H, H3), 7.31 (s, 1H, H6), 5.48 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 152.5 (C1), 135.6 (C3), 125.1 (C5), 121.2 (C6), 116.0 (C4), 110.0 (C2); MS: *m*/*z* 334 (M, 29%), 332 (M, 99), 330 (M, 100), 328 (M, 30),143 (17), 141 (7), 63 (5), 62 (8), 61 (5) IR (KBr) ν_{max}: 3363 (m, br), 3074 (w), 1726 (w), 1574 (w), 1552 (m), 1465 (m), 1446 (s), 1383 (w), 1362 (m), 1281 (m), 1246 (w), 1195 (m), 1106 (w), 1044 (m), 874 (s) cm^{-1}.

4.1.7. 2,3,4,6-Tetrabromophenol (7).[25,30] The title compound was prepared from **6a** by Method C (Fe 1.0 equiv; Br_2 1.1 equiv). The crude product was recrystallised from hexane to give 70.7% yield; 98.0% purity (GLC); mp 113–114 °C (lit.[25] 112 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H, H5), 6.03 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9 (C1), 134.9 (C5), 127.0 (C3), 116.0 (C4), 114.3 (C2), 108.7 (C6); MS: *m*/*z* 414 (M, 13%), 412 (M, 60), 410 (M, 100), 408 (M, 64), 406 (M, 3), 330 (9), 328 (9), 221 (11); IR (KBr) ν_{max}: 3418 (m, br), 3057 (w), 1708 (w), 1540 (w), 1465 (w), 1429 (s), 1348 (s), 1294 (m), 1274 (w), 1251 (w), 1178 (m), 1150 (m), 1076 (m), 895 (w), 868 (m) cm^{-1}.

4.1.8. 2,2′,4,4′-Tetrabromodiphenyliodonium chloride (8).[12,16,25] The title compound was prepared from **5a** by Method A and characterised according to literature.[12]

4.1.9. 2,4,5-Tribromoiodobenzene (11).[25] The title compound was prepared from 3-bromoiodobenzene **10** by Method C (Fe 0.9 equiv; Br_2 2 equiv). The product was recrystallised from hexane to give beige crystals; 64.9% yield; 97.7% purity (GLC); mp 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, H6), 7.84 (s, 1H, H3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C6), 136.2 (C3), 129.3 (C2), 125.5 (C4), 124.3 (C5), 100.0 (C1); MS: *m*/*z* 444 (M, 27%), 442 (M, 99), 440 (M, 100), 438 (M, 28), 317 (6$^+$), 315 (19), 313 (19), 310 (8), 236 (7), 234 (14), 232 (7), 74 (28). IR (KBr) ν_{max}: 3062 (w), 1737 (w), 1458 (w), 1438 (m), 1414 (m), 1288 (m), 1110 (m), 1100 (m), 1037 (w), 1010 (s), 878 (s) cm^{-1}.

4.1.10. 4-Methoxyphenyl-2′,4′,5′-tribromophenyliodonium bromide (9).[16,25] The title compound was prepared[26] from **11**; CrO_3 (1.5 g, 15 mmol) was dissolved in acetic acid (600 ml) and acetic acid anhydride (275 ml), cooled to 0 °C and added **11** (4.5 g, 11.4 mmol). Sulfuric acid (concd 1.9 ml, 34.9 mmol) was added drop-wise to keep the temperature below 25 °C and the reaction was left stirring for 22 h. Anisole (1.365 ml, 12.5 mmol) was added slowly at 0 °C before stirring at room temperature for 96 h. The reaction mixture was poured over an aqueous methanol solution (30%, 1200 ml), stirred for 1 h. and filtered. Aqueous NaBr (2.5 g, 24.3 mmol in 30 ml H_2O) was added slowly and the solution was stirred for 3 h. The beige crystals were filtered off, washed with water and acetone and dried; 34.1% yield; mp 179–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (s, 1H, H6′), 8.34 (s, 1H, H3′), 8.10 (d, 2H, H3, H5), 7.07 (d, 2H, H2, H6), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$: δ 162.3 (C4), 141.8 (C6′), 137.6 (C3′), 137.5 (C2, C6), 129.8 (C2′, C4′, C5′), 129.2 (C2′, C4′, C5′), 127.0 (C2′, C4′, C5′), 125.9 (C1′), 118.1 (C3, C5), 110.7 (C1), 56.5 (OCH_3).

4.1.11. Bis(*m*-fluorophenyl) ether (15).[31] The title compound was prepared from 3-fluorophenol (**13**) and 3-bromofluorophenol (**14**);[21] **13** (3.11 g, 27.8 mmol) and KOH (1.56 g, 27.8 mmol) was stirred at 50 °C for 30 min before the addition of **14** (5.0 g, 28.7 mmol) and Cu powder (1.72 g, 27.1 mmol). The reaction was heated to 170 °C for 2 h. The product was isolated as an oil by flash

chromatography (10% CH_2Cl_2 in hexane). 49.1% yield; 98.8% purity (GLC); ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.29 (dd, J=8.3, 1.6 Hz, 2H, H5 and H5′), 6.83 (ddt, J=8.3, 2–7, 0.8 Hz, 2H, H6, H6′), 6.81 (dd, J=8.3, 2.2 Hz, 2H, H4, H4′), 6.73 (dt, J=10.0, 2.3 Hz, 2H, H2, H2′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (d, $^1J_{CF}$=247.1 Hz, C3, C3′), 158.3 (d, $^3J_{CF}$=11.0 Hz, C1, C1′) 131.1 (d, $^3J_{CF}$=9.4 Hz, C5, C5′), 115.0 (d, $^4J_{CF}$=2.8 Hz, C6, C6′), 111.1 (d, $^2J_{CF}$=21.0 Hz, C4, C4′), 107.2 (d, $^2J_{CF}$=24.3 Hz, C2, C2′); MS: *m/z* 206 (M, 100%), 178 (40), 177 (57), 112 (38), 95 (28); IR (KBr) ν_{max}: 3076 (m), 1606 (s), 1480 (s), 1450 (s), 1309 (s), 1276 (s), 1164 (s), 1135 (s), 1071 (m), 975 (s), 853 (s), 773 (s), 679 (s) cm^{-1}.

4.1.12. 2,3,4-Tribromo-5,6-difluorophenol (19). The title compound was prepared from 2,3-difluorophenol (**16**) by Method C (Fe 0.6 equiv, Br_2 5.8 equiv) to afford beige crystals; 78.8% yield; 99.2% purity (GLC); mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4 (dd, $^1J_{CF}$=249.9 Hz, $^2J_{CF}$=13 Hz, C5), 142.8 (dd, $^2J_{CF}$=11.0 Hz, $^3J_{CF}$=3.3 Hz, C1), 139.1 (dd, $^1J_{CF}$=252.6 Hz, $^2J_{CF}$=16.5 Hz, C6), 121.9 (d, $^3J_{CF}$=4.8 Hz, C3), 109.8 (dd, $^3J_{CF}$=3.7 Hz, $^4J_{CF}$=1.1 Hz, C2), 104.9 (d, $^2J_{CF}$=20.5 Hz, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −120.4 (d, J=21.1 Hz, F5), −153.4 (d, J=21.1 Hz, F6); MS: *m/z* 370 (M, 29%), 368 (M, 100), 366 (M, 100), 364 (M, 30), 288 (6), 286 (11), 284 (5), 259 (8), 257 (8), 179 (12), 177 (12). IR (KBr ν_{max}): 3673 (w), 3528 (m, br), 1605 (m), 1575 (m), 1480 (s), 1405 (m), 1332 (w), 1299 (m), 1240 (m), 1199 (m), 1072 (m), 926 (m), 804 (s) cm^{-1}. HRMS calcd for $C_6Br_3F_2HO$ (M^+): 363.7546. Found: 363.7545.

4.1.13. 2,4,5-Tribromo-3,6-difluorophenol (20). The title compound was prepared from 3,6-difluorophenol (**17**) by Method C (Fe 0.5 equiv; Br_2 5.5 equiv) to afford beige crystals; 66.3% yield; 99.0% purity (GLC); mp 78–79.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1 (dd, $^1J_{CF}$=244.3 Hz, $^4J_{CF}$=3.9 Hz, C3), 145.4 (dd, $^1J_{CF}$=242.6 Hz, $^4J_{CF}$=4.5 Hz, C6), 142.1 (dd, $^2J_{CF}$=17.1 Hz, $^3J_{CF}$=3.8 Hz, C1), 112.6 (dd, $^2J_{CF}$=21.5 Hz, $^3J_{CF}$=1.6 Hz, C5), 103.6 (d, $^2J_{CF}$=26.0 Hz, C4), 98.6 (dd, $^2J_{CF}$=27.1 Hz, $^3J_{CF}$=2.4 Hz, C2); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −96.5 (d, J=9.8 Hz, F3), −125.2 (d/J=9.8 Hz, F6), MS: *m/z* 370 (M, 28%), 368 (M, 99), 366 (M, 100), 364 (M, 29), 98 (15); IR (KBr) ν_{max}: 3506 (m, br), 3403 (w, br), 3126 (m, br), 1583 (w), 1439 (s), 1350 (m), 1325 (m), 1247 (w), 1175 (w), 1078 (m), 1070 (m), 912 (m), 838 (s) cm^{-1}. Anal. Calcd for $C_6Br_3F_2HO$: C, 19.65; H, 0.27. Found: C, 19.45; H, 0.18.

4.1.14. 2,4,6-Tribromo-3,5-difluorophenol (21). The title compound was prepared from 3,5-difluorophenol (**18**) by Method C (Fe 0.5 equiv; Br_2 5 equiv) to afford beige crystals; 83.0% yield; 98.4% purity (GLC); mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4 (dd, $^1J_{CF}$=246.5 Hz, $^3J_{CF}$=5.8 Hz, C3,C5), 150.9 (t, $^3J_{CF}$=4.8 Hz, C1), 94.1 (dd, $^2J_{CF}$=26.5 Hz, $^4J_{CF}$=4.4 Hz, 2C, C2, C6), 90.2 (t, $^2J_{CF}$=27.0 Hz, 1C, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −96.7 (s, 2F); MS: *m/z* 370 (M, 33%), 368 (M, 97), 366 (M, 100), 364 (M, 35), 290 (6), 288 (12), 286 (10). IR (KBr) ν_{max}: 3482 (m, br), 1762 (w), 1685 (w), 1591 (m), 1578 (m), 1451 (s), 1428 (s), 1346 (w), 1297 (m), 1214 (m), 1113 (w), 1078 (m), 1060 (m), 710 (s), 701 (s), 684 (s) cm^{-1}. Anal. Calcd for $C_6HOBr_3F_2$ C: C, 19.65; H, 0.27. Found: C, 19.50; H, 0.26.

4.1.15. 3,3′,4,4′-Tetrabromodiphenyliodonium chloride (22).[12,16,25] The title compound was prepared from 1,2-dibromobenzene by Method A and characterised according to literature.[25]

4.1.16. 2,4,4′,6-Tetrabromodiphenyl ether (BDE 75).[12,16] The title compound was prepared from (**2**) and 2,4,6-tribromophenol (**3**) by Method B; 21% yield, 98.4% purity (GLC) (lit.[16] 23% yield); mp 149–150 °C (lit.[16] 134–135 °C); ^{1}H and ^{13}C NMR was in accordance with literature data;[16] MS: *m/z* 490 (M, 14%), 488 (M, 61), 486 (M, 100), 484 (M, 64), 482 (M,15), 328 (34) 326 (75), 324 (34); IR (KBr) ν_{max}: 2063 (w), 1879 (w), 1730 (w), 1580 (w), 1547 (m), 1483 (s), 1440 (s), 1399 (w), 1372 (m), 1354 (w), 1282 (m), 1253 (s), 1202 (s), 1163 (m), 1070 (m), 1006 (m), 860 (s), 822 (s), 809 (m), 748 (m), 739 (m) cm^{-1}.

4.1.17. 2,2′,3,4,4′-Pentabromodiphenyl ether (BDE 85).[21,25] The title compound was prepared from **5a** and **8** by Method B to give white crystals; 49.2% yield; 99.3% purity (GLC); mp 123–124 °C; ^{1}H NMR were in accordance with literature data;[21] ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8 (C1), 152.3 (C1′), 136.8 (C3′), 132.8 (C5), 132.3 (C5′), 129.9 (C3), 121.5 (C6′, C6 or C4), 120.7 (C6′, C6 or C4), 119.3 (C6′, C6′ or C4), 118.5 (C4′or C2), 118.1 (C4′ or C2), 115.9 (C2′); MS: *m/z* 570 (M, 9%), 568 (M, 46), 566 (M, 95), 564 (M, 100), 562 (M, 49), 560 (M, 10), 408 (26), 406 (81), 404 (83), 402 (27), 203 (19), 202 (19). IR (KBr) ν_{max}: ca 3100 (w), 1573 (w), 1556 (m), 1463 (s), 1427 (s), 1374 (m), 1356 (m), 1256 (s), 1247 (s), 1215 (m), 1076 (w), 1049 (m), 953 (w), 906 (m), 842 (m), 803 (m), 721 (m) cm^{-1}.

4.1.18. 2,2′,3,4,4′,5′-Hexabromodiphenyl ether (BDE 138).[21] The title compound was prepared from **5a** and **9** by Method B; white crystals; 54.0% yield; 99.8% purity (GLC); mp 135–136 °C; (lit.[21] 134.2 °C); ^{1}H NMR were in accordance with literature data;[21] ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7 (C1 or C1′), 152.4 (C1 or C1′), 137.5 (C3′), 132.7 (C5), 129.8 (C3), 124.3 (C5′), 123.4 (C6′), 121.2 (C4 or C4′) 120.3 (C4 or C4′), 119.4 (C6), 119.0 (C2), 113.4 (C2′); MS: *m/z* 649 (M, 4%), 647 (M, 25), 645 (M, 70), 643 (M, 100), 641 (M, 74), 639 (M, 28), 637 (M, 5), 488 (14), 486 (63), 484 (100), 482 (64), 480 (15), 242 (19), 74 (23). IR (KBr) ν_{max}: 3076 (w), 1572 (w), 1552 (m), 1454 (m), 1426 (s), 1358 (w), 1332 (m), 1265 (m), 1248 (m), 1208 (w), 1107 (m), 1049 (m), 931 (m), 884 (m), 842 (w), 798 (m) cm^{-1}.

4.1.19. 2,2′,3,4,4′,5′,6-Heptabromodiphenyl ether (BDE 183).[22,25] The title compound was prepared from **9** and **7** by Method B to afford white crystals; 54.0% yield; 99.4% purity (GLC); mp 174–174.5 °C; ^{1}H NMR were in accordance with literature data;[25] ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7 (s, C1), 148.6 (s, C1′) 137.5 (s, C3′), 136.1 (s, C3), 128.8 (s, C5), 124.0 (s, C5′), 123.6 (s, C4), 123.0 (s, C6′), 118.7 (s, C4′or C2) 118.4 (s, C4′ or C2), 117.0 (s, C6), 111.4 (s, C2′); MS: *m/z* 729 (M, 3%), 727 (M, 17), 725 (M, 55), 723 (M, 98), 721 (M, 100), 719 (M, 58), 717 (M, 18), 715 (M, 3), 567 (8), 565 (40), 563 (91), 561 (92), 559 (43),

557 (9), 281 (18), 74 (15). IR (KBr) ν_{max}: 3078 (w), 1716 (w), 1568 (m), 1530 (w), 1456 (s), 1435 (m), 1405 (s), 1328 (s), 1250 (m), 1236 (m), 1208 (m), 1151 (m), 1115 (m), 1079 (m), 1048 (s), 921 (m), 874 (m), 864 (m), 842 (w), 762 (m), 755 (m), 719 (m) cm^{-1}.

4.1.20. 2,2′,4,4′-Tetrabromo-5,5′-difluorodiphenyl ether (2F-BDE 47). The title compound was prepared from bis(*m*-fluorophenyl) ether (**15**). To refluxing **15** (0.3 g, 1.46 mmol) in CCl_4 (9 ml) was slowly added Br_2 (1.28 g, 0.41 ml, 8.0 mmol, 6.5 equiv) in CCl_4 (5 ml). After 24 h reflux, $NaHSO_3$ (5%, 25 ml) was added and the product isolated by extraction. The crude product was recrystallised twice to obtain 282 mg white crystals; 37.3% yield; 98.0% purity (GLC); mp 137.5–138.5 °C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.85 (d, J_{FH}=7.1 Hz, 2H, H3, H3′), 6.68 (d, J_{FH}=8.7 Hz, 2H, H6, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7 (d, $^1J_{CF}$=250 Hz, C5, C5′), 152.5 (d, $^3J_{CF}$=8.7 Hz, C1, C1′) 137.2 (d, $^3J_{CF}$=1.6 Hz, C3, C3′), 109.3 (d, $^4J_{CF}$=4.4 Hz, C2, C2′), 108.1 (d, $^2J_{CF}$=26.6 Hz, C6, C6′), 105.0 (d, $^2J_{CF}$=22.1 Hz, C4, C4′); MS: *m/z* 526 (M, 13%), 524 (M, 60), 522 (M, 100), 520 (M, 64), 518 (M, 14), 364 (39), 362 (88), 360 (39); IR (KBr) ν_{max}: 3026 (w), 1720 (w), 1680 (w), 1579 (m), 1460 (s), 1376 (s), 1280 (m), 1263 (m), 1163 (s), 1142 (m), 1070 (m), 1007 (m), 881 (m), 843 (m).

4.1.21. 2,2′,3,4,4′-Pentabromo-5,6-difluorodiphenyl ether (2F-BDE 85). The title compound was prepared from **19** and **8** by Method B; to afford white crystals; 45.7% yield; 99.0% purity (GLC); mp 129.5–130.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=2.3 Hz, 1H, H3′), 7.31 (dd, J=8.7, 2.3 Hz, 1H, H5′), 6.45 (dd, J=8.8, 1.1 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3 (s, C1′), 148.5 (dd, $^1J_{CF}$=253.2 Hz, $^2J_{CF}$=12.7 Hz, C5), 143.7 (dd, $^1J_{CF}$=260.3 Hz, $^2J_{CF}$=16.0 Hz, C6), 141.3 (dd, $^2J_{CF}$=11.0 Hz, $^3J_{CF}$=2.2 Hz, C1), 136.4 (s, C3′), 131.4 (s, C5′), 123.8 (d, $^3J_{CF}$=5.0 Hz, C3), 117.1 (d, $^3J_{CF}$=4.4 Hz, C2), 116.5 (s, C4′), 115.8 (s, C6′), 112.8 (s, C2′), 111.9 (d, $^2J_{CF}$=20.0 Hz, C4);^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −118.1 (d, J=21.1 Hz, F5), −144.8 (dd, J=21.1, 1.0 Hz, F6); MS: *m/z* 605 (M, 8%), 603 (M, 45), 601 (M, 98), 599 (M, 100), 597 (M, 47), 595 (M, 9), 444 (25), 442 (82), 440 (83), 438 (26), 333 (9), 221 (18), 220 (15). IR (KBr) ν_{max}: 3442 (w), 3072 (w), 1733 (w), 1571 (m), 1461 (s), 1396 (s), 1380 (m), 1281 (w), 1259 (w), 1221 (m), 1147 (w), 1069 (m), 1041 (m), 940 (w), 868 (m), 846 (m), 808 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.65; H, 0.39.

4.1.22. 2,2′,4,4′,5-Pentabromo-3,6-difluorodiphenyl ether (2F-BDE 99). The title compound was prepared from **20** and **8** by Method B to afford white crystals; 36.70% yield; 98.8% purity (GLC); mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=2.3 Hz, 1H, H3′), 7.31 (dd, J=8.8, 2.3 Hz, 1H, H5′), 6.46 (dd, J=8.7, 1.1 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153. 7 (dd, $^1J_{CF}$=246.8 Hz, $^4J_{CF}$=3.9 Hz, C3), 152.4 (s, C1′), 149.9 (dd, $^1J_{CF}$=252.6 Hz, $^4J_{CF}$=4.4 Hz, C6), 140.6 (dd, $^2J_{CF}$=16.0 Hz, $^3J_{CF}$=3.4 Hz, C1), 136.4 (s, C3′), 131.4 (s, C5′), 116.5 (s, C4′), 116.11 (s, C6′), 113.8 (dd, $^2J_{CF}$=22.2 Hz, $^3J_{CF}$=1.1 Hz, C5), 112.9 (s, C2′), 110.8 (d, $^2J_{CF}$=25.9 Hz, C4), 105.8 (dd, $^2J_{CF}$=26.1 Hz, $^3J_{CF}$=1.6 Hz, C2); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −93.9 (d, J=10.9 Hz, F3), −115.6 (dd, J=10.1, 1.0 Hz, F6); MS: *m/z* 605 (M, 8%), 603 (M, 44), 601 (M, 94), 599 (M, 100), 597 (M, 46), 595 (M, 9), 444 (22), 442 (74), 440 (76), 438 (23), 333 (9), 221 (16), 220 (13); IR (KBr) ν_{max}: 3069 (w), 1741 (w), 1630 (w), 1569 (m), 1467 (s), 1434 (s), 1408 (s), 1377 (m), 1260 (m), 1224 (m), 1066 (m), 1039 (m), 923 (m), 872 (m), 840 (m), 802 (m), 759 (m), 720 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.68; H, 0.52.

4.1.23. 2,3′,4,4′,6-Pentabromo-3,5-difluorodiphenyl ether (2F-BDE 119). The title compound was prepared from **21** and **22** by Method B to afford white crystals; 30, 7% yield; 99, 0% purity (GLC); mp 136.5–137.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J=8.8 Hz, 1H, H5′), 7.11 (d, J=3.0 Hz, 1H, H2′), 6.67 (dd, J=8.9, 3.0 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0 (dd, $^1J_{CF}$=248.8 Hz, $^4J_{CF}$=5.5 Hz, C3,C5), 155.5 (s, C1′), 149.6 (t, $^3J_{CF}$=3.8 Hz, C1), 134.7 (s, C5′), 126.0 (s, C3′), 120.9 (s, C2′), 119.0 (s, C4′), 116.0 (s, C6′), 102.8 (dd, $^2J_{CF}$=24.8 Hz, $^4J_{CF}$=4.4 Hz, C2, C6), 97.4 (t, $^2J_{CF}$=27.1 Hz, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −94.2 (s); MS: *m/z* 605 (M, 8%), 603 (M, 36), 601 (M, 77), 599 (M, 78), 597 (M, 39), 595 (M, 8), 444 (31), 442 (99), 440 (100), 438 (33), 333 (12), 221 (23), 220 (22); IR (KBr) n_{max}: 3447 (w), 3094 (w), 1570 (m), 1455 (m), 1421 (s), 1369 (m), 1270 (w), 1254 (m), 1200 (m), 1099 (m), 1066 (m), 1010 (w), 864 (w), 857 (m), 798 (m), 757 (w), 703 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.84; H, 0.43.

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