Synthesis of Hydroxylated and Methoxylated Polybrominated Diphenyl Ethers – Natural Products and Potential Polybrominated Diphenyl Ether Metabolites

Göran Marsh,*[a] Roland Stenutz,[b] and Åke Bergman[a]

Keywords: Aromatic substitution / Halogenation / Natural products / Oxidations / Polybrominated diphenyl ethers

Hydroxylated and methoxylated polybrominated diphenyl ethers (OH-PBDEs and MeO-PBDEs) may be natural products or they may be formed as metabolites of polybrominated diphenyl ethers (PBDEs), frequently used as flame retardants. The aim of this work was to synthesize authentic OH- and MeO-PBDE reference standards for analytical and toxicological studies. Brominated phenoxybenzaldehydes were prepared either by coupling of 2,4-dibromophenol with various fluorobenzaldehydes or by coupling of brominated hydroxybenzaldehydes with 2,2′,4,4′-tetrabromodiphenyliodonium chloride. OH-PBDEs were synthesized via the brominated phenoxybenzaldehydes by Baeyer–Villiger oxidation and acid-catalyzed hydrolysis. These OH-PBDEs were *ortho*- and *para*-brominated (relative to the hydroxy group) with benzyltrimethylammonium tribromide and/or *ortho*-brominated with bromine/*tert*-butylamine, and were also brominated with bromine in one case. MeO-PBDEs were obtained by methylation of the prepared OH-PBDEs. MeO-PBDEs were also prepared through the coupling of brominated methoxyphenols with 2,2′,4,4′-tetrabromodiphenyliodonium salts, the corresponding OH-PBDEs being obtained after demethylation. A majority of the OH-/MeO-PBDEs prepared have the hydroxy/methoxy group in the *ortho* position relative to the diphenyl ether bond. All OH-/MeO-PBDEs prepared have 2,4-dibromo substitution patterns (relative to the diphenyl ether bond) in the non-hydroxy-/non-methoxy-containing ring.

Introduction

Hydroxylated polybrominated diphenyl ethers (OH-PBDEs) and methoxylated polybrominated diphenyl ethers (MeO-PBDEs) are known natural products that have been reported to occur in marine species such as sponges,[1−3] ascidians (tunicates),[4,5] and green alga.[6] Recently, these two groups of substances have also been reported in species at higher trophic levels. MeO-PBDEs were found in fish,[7−9] turtles,[10] birds,[11] and marine mammals.[7,10] OH-PBDEs were reported in fish[8] and humans.[12]

OH-PBDEs have also been identified as metabolites of 2,2′,4,4′-tetrabromodiphenyl ether in mice and rats[13] and in fish.[14] 2,2′,4,4′-Tetrabromodiphenyl ether is generally the most abundant PBDE contaminant in humans and wildlife.[15] Another environmentally relevant PBDE congener, 2,2′,4,4′,5-pentabromodiphenyl ether, has also been shown to form hydroxylated metabolites in rats.[16] PBDEs are used as flame retardants in polymers, rubber, and textiles, and several PBDE congeners have been identified as widespread environmental pollutants.[15,17]

The aim of this work was to synthesize authentic OH-PBDEs and MeO-PBDEs for identification of those compounds present in biota, and to make it possible to assess their toxicity. All OH- and MeO-PBDEs were prepared so as to have a 2,4-dibromo substitution pattern (relative to the diphenyl ether bond) in the non-hydroxy-/non-methoxy-containing ring. This substitution pattern is consistent with all OH- and MeO-PBDEs previously found as natural products containing two bromine atoms in the non-hydroxylated/non-methoxylated ring,[1,2] although it should also be mentioned that 2-bromo[18,19] and 4-bromo substitution patterns[20] have also been reported. Moreover, the dominating bromine substitution in manmade PBDEs containing two bromine atoms in one of the phenyl rings is also the 2,4-dibromo-substitution pattern,[15] although 3,4- and 2,5-dibromo-substitution is also known.[21] All known naturally occurring OH- and MeO-PBDEs are hydroxy-/methoxy-substituted *ortho* to the diphenyl ether bond. In contrast, the hydroxy groups in 2,2′,4,4′-tetrabromodiphenyl ether metabolites seem to be situated at any of the *ortho*-, *meta*-, or even *para*-positions.[13]

The synthesis of some MeO-PBDEs and OH-PBDEs have previously been published, the OH-PBDEs having been obtained in these cases by demethylation of the MeO-PBDEs with BBr_3.[22,23] Brominated 2-methoxyphenols have been coupled with halonitrobenzenes to give nitro-MeO-PBDEs. The nitro group was reduced and the re-

[a] Department of Environmental Chemistry, Stockholm University,
10691 Stockholm, Sweden
[b] Department of Organic Chemistry, Stockholm University,
10691 Stockholm, Sweden
Fax: (internat.) + 46-8/163979
E-mail: goran.marsh@mk.su.se

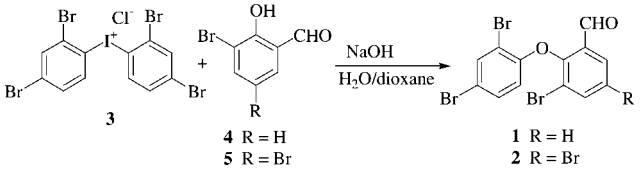
  DOI: 10.1002/ejoc.200300081

sulting amino group was replaced with bromine through diazotization and either Sandmeyer reaction or treatment with copper(II) bromide.[23,24] MeO-PBDEs have also been prepared by the coupling of brominated diphenyliodonium iodides with brominated 2-methoxyphenols.[22]

In this work, a modification of the last method has been used for the synthesis of some OH-PBDEs and MeO-PBDEs. However, the majority of the OH- and MeO-PBDEs were prepared via brominated phenoxybenzaldehydes by conversion of the aldehyde group into a hydroxy group by Baeyer−Villiger oxidation and hydrolysis. The OH-PBDEs obtained were brominated in the *ortho* and *para* positions and/or in the *ortho* position relative to the hydroxy group. Finally MeO-PBDEs were prepared by methylation of the corresponding OH-PBDEs.

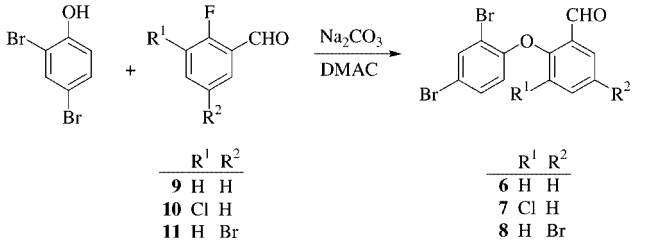
Results and Discussion

Brominated phenoxybenzaldehydes, precursors to the majority of the OH- and MeO-PBDEs with the hydroxy/methoxy group in the *ortho* position to the diphenyl ether bond, were prepared by two different diphenyl ether coupling reactions. In the first coupling, the brominated phenoxybenzaldehydes **1**−**2** were prepared by treatment of 2,2′,4,4′-tetrabromodiphenyliodonium chloride **3** with the brominated 2-hydroxybenzaldehydes **4** and **5**, respectively, in aqueous NaOH/dioxane (Scheme 1). Several halodiphenyliodonium chlorides have previously been coupled with different halogenated 2-methoxyphenols[22,25,26] or phenols[26−29] with water as the only solvent. The use of dioxane as a co-solvent improved solubility and resulted in higher yields. The benzaldehyde **4** was prepared by *ortho*-formylation of phenols as described by Hofsløkken and Skattebøl,[30] whereas the benzaldehyde **5** was commercially available.



Scheme 1. Coupling of 2,2′,4,4′-tetrabromodiphenyliodonium chloride with brominated 2-hydroxybenzaldehydes

In the other diphenyl ether coupling, the brominated phenoxybenzaldehydes **6**−**8** were prepared by substitution of fluorobenzaldehydes **9**−**11** (commercially available) with 2,4-dibromophenol (Scheme 2). This coupling has been reported previously for the synthesis of various monosubstituted phenoxybenzaldehydes, which were converted into hydroxylated diphenyl ethers via Baeyer−Villiger oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA) followed by acid-catalyzed hydrolysis.[31,32]



	R^1	R^2
9	H	H
10	Cl	H
11	H	Br

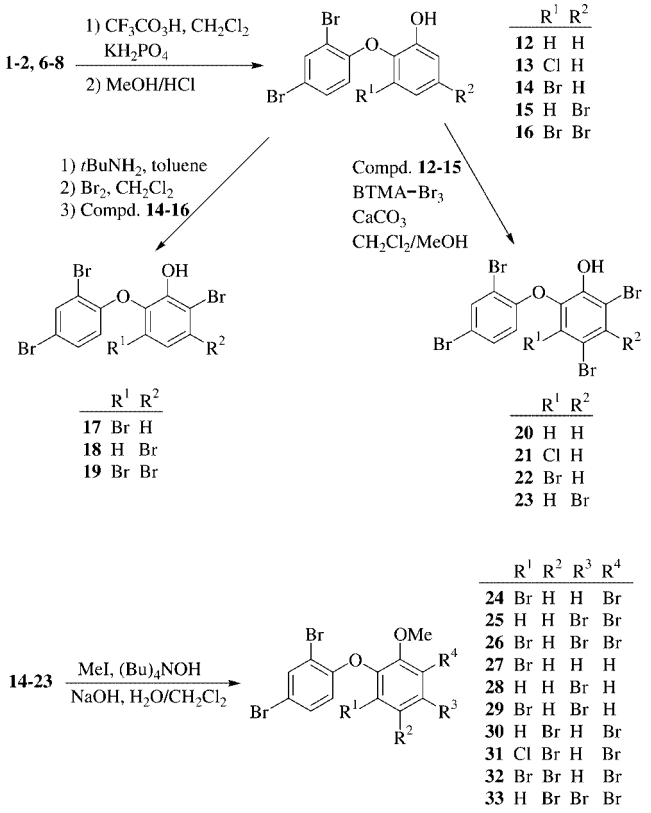
	R^1	R^2
6	H	H
7	Cl	H
8	H	Br

Scheme 2. Coupling of 2,4-dibromophenol with fluorobenzaldehydes; DMAC = *N*,*N*-dimethylacetamide

We also used Baeyer−Villiger oxidation and acid-catalyzed hydrolysis for the preparation of OH-PBDEs **12**−**16**, with the brominated phenoxybenzaldehydes **1**−**2** and **6**−**8** as precursors (Scheme 3). Phenoxybenzaldehyde **6** could be oxidized to the corresponding formate ester with *m*-CPBA (in $CHCl_3$ at 30 °C), whereas phenoxybenzaldehyde **2** was unreactive to this agent. Only 50% of the phenoxybenzaldehyde **8** was converted into the formate after 10 h by *m*-CPBA (in $CHCl_3$ at 30 °C). However, all the brominated phenoxybenzaldehydes were completely oxidized by trifluoroperacetic acid (TFPA), and so this agent was used for all these oxidations in this work, with use of KH_2PO_4 as buffer. In the absence of buffer, side reactions such as ether cleavage and rearrangements were observed. To minimize side-reactions further, the reaction temperature was kept at 0 °C except in the oxidation of phenoxybenzaldehyde **2**, which was carried out at room temperature.

The OH-PBDEs **17**−**19** were prepared from OH-PBDEs **14**−**16** by bromination *ortho* to the hydroxy groups. This was achieved by the method of Pearson et al.[33] by addition of bromine to *tert*-butylamine in toluene at −30 °C, followed by addition of the OH-PBDE in CH_2Cl_2 to the bromine/*tert*-butylamine complex at −70 °C (Scheme 3). The reaction mixture was not allowed to warm up to room temperature in this case, however, but was kept between −60 °C and −65 °C throughout the reaction. The reaction was quenched by addition of water/ethanol (1:9 v/v) simultaneously with passage of a stream of sulfur dioxide through the reaction mixture. Using these conditions the yield of *para*-brominated product never exceeded 1% whereas the *ortho*-*para*-dibrominated product was not formed. These precautions were necessary since the previously described procedure[33] had given not only the desired *ortho*-bromo product but also the *para*-bromo and dibromo products, which decreased the yields and complicated the purification of the desired products. Unchanged starting material was recovered in all these reactions.

Dibrominations *ortho* and *para* to the hydroxy groups of OH-PBDEs **12**−**15** gave the OH-PBDEs **20**−**23** and were carried out in CH_2Cl_2/MeOH solution with use of benzyltrimethylammonium tribromide (BTMA-Br_3)[34,35] (Scheme 3). To avoid ether cleavage of the OH-PBDEs during the bromination, the BTMA-Br_3 had to be added in small portions over several hours and in the presence of calcium carbonate.



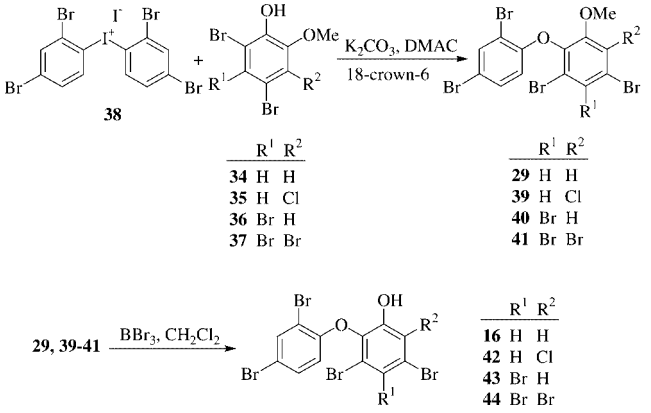
Scheme 3. OH- and MeO-PBDEs prepared by Baeyer−Villiger oxidation and subsequent hydrolysis of brominated 2-phenoxybenzaldehydes, followed by bromination; BTMA-Br_3 = benzyltrimethylammonium tribromide

The MeO-PBDEs **24**−**33** were prepared by use of iodomethane as described previously.[36]

The couplings of the brominated 2-methoxyphenols **34**−**37** with iodonium iodide **38** were carried out in the presence of K_2CO_3 and 18-crown-6 in *N*,*N*-dimethylacetamide (DMAC), giving MeO-PBDEs **29** and **39**−**41** in 49−60% yield (Scheme 4). This route, with the synthesis performed in aqueous NaOH, had been reported earlier[22] for the preparation of **40**−**41** in 52% and 67% yields, respectively, but in our hands this procedure resulted in lower yields (29% and 22%, respectively), despite fewer observed side-reactions. When the 2-methoxyphenols **34** and **36** were used in the coupling with the iodonium chloride **3**, complicated mixtures of products were obtained irrespective of the method applied.

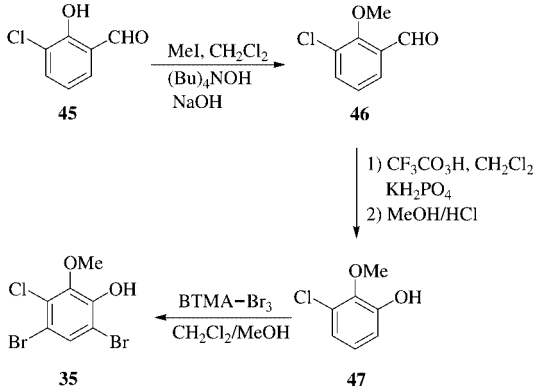
The HO-PBDEs **16** and **42**−**44** were prepared from the corresponding MeO-PBDEs **29** and **39**−**41** by use of BBr_3 in CH_2Cl_2.[22,23] We found that elevated temperatures (50 °C) were necessary in order to achieve acceptable reaction times in the demethylation of MeO-PBDEs.

The synthesis of 2,2′,4,4′-tetrabromodiphenyliodonium chloride **3** was slightly modified from that previously described,[27] and the preparation of the iodide analogue **38** was based on this methodology. Iodonium iodide **38** has been reported previously,[22] but the experimental conditions and chemical characterization of the product were not provided.



Scheme 4. Preparation of OH- and MeO-PBDEs by coupling of 2,2′,4,4′-tetrabromodiphenyliodonium iodide with brominated 2-methoxyphenols; DMAC = *N*,*N*-dimethylacetamide

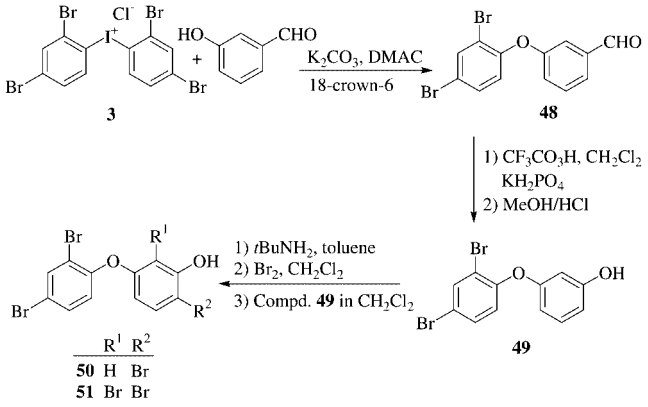
2,3,4-Tribromo-6-methoxyphenol **36** was prepared by treatment of 2-methoxyphenol with an excess of bromine in acetic acid, without any other brominated 2-methoxyphenol congeners being observed. When this reaction was performed with 3 equivalents of bromine as described by Raiford and Silker,[37] dibrominated 2-methoxyphenols (15%, assessed by GC-MS) were obtained besides the desired product **36**. 2-Methoxyphenol in a mixture with $CaCO_3$ has previously been solid-phase perbrominated with bromine, giving 2,3,4,5-tetrabromo-6-methoxyphenol **37** in 97% yield.[22] However, because of difficulties in stirring during the reaction, this procedure gave 30% di- and tribrominated 2-methoxyphenols (as estimated by GC−MS) in our hands. Use of a slight excess of bromine and an ultrasonic bath were more advantageous to us. The pathway for the preparation of 5-chloro-2,4-dibromo-6-methoxyphenol **35** is shown in Scheme 5 and each step for the preparation of hydroxybenzaldehyde **45**, methoxybenzaldehyde **46**, and methoxyphenol **47** includes methods described above.



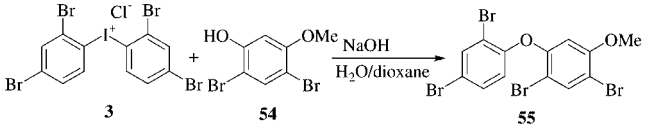
Scheme 5. Preparation of 5-chloro-2,4-dibromo-6-methoxyphenol (**35**), the precursor to MeO-PBDE **39**; BTMA-Br_3 = benzyltrimethylammonium tribromide

OH-PBDEs and the corresponding MeO-PBDEs with the hydroxy/methoxy group in the *meta* position relative to the ether oxygen were prepared as shown in Schemes 6 and

7. The phenoxybenzaldehyde **48** was prepared as for the MeO-PBDEs **29** and **39**−**41** above, but with the iodonium chloride **3** instead of the iodonium iodide **38** (Scheme 6). In aqueous NaOH/dioxane this reaction gave lower yields and more side reactions such as C-arylation [i.e., two compounds (not isolated) with four-bromine isotope patterns and $[M^+] = 558$]. The benzaldehyde **48** was converted into the corresponding OH-PBDE **49** by Baeyer−Villiger oxidation and hydrolysis as described above for the preparation of OH-PBDE **12**−**16**. Dibromination in the two positions *ortho* to the hydroxy group of the OH-PBDE **49** generated two major products (Scheme 6), the tribrominated OH-PBDE **50** being isolated besides the desired product **51**. One additional monobrominated compound and one dibrominated compound were also detected by GC−MS. These side-products were estimated to amount to less than 2% by GC−MS and could be separated from the products on silica. Methylation of OH-PBDEs **50**−**51** gave MeO-PBDEs **52**−**53**. Further OH- and MeO-PBDE compounds with the hydroxy/methoxy groups *meta* to the diphenyl ether bond were prepared by coupling of 2,4-dibromo-5-methoxyphenol **54**[35] with iodonium chloride **3** (Scheme 7) as described above for the brominated phenoxybenzaldehydes **1**−**2**. Demethylation of the obtainedMeO-PBDE **55** gave the corresponding OH-PBDE **56**.

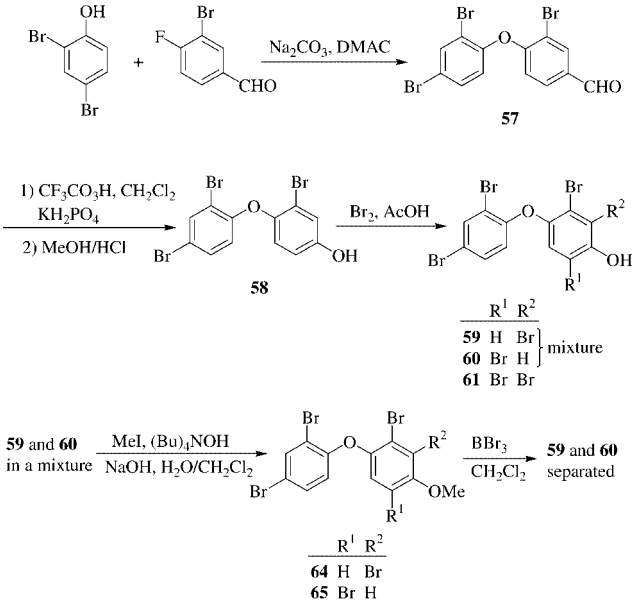


Scheme 6. Pathway for the preparation of OH-PBDEs with the hydroxy group in the *meta*-position to the diphenyl ether bond; DMAC = *N*,*N*-dimethylacetamide



Scheme 7. Pathway for the preparation of a MeO-PBDE with the methoxy group in the *meta*-position to the diphenyl ether bond

The synthesis of OH- and MeO-PBDEs with the hydroxy/methoxy groups *para* to the diphenyl ether bond are shown in Scheme 8. The phenoxybenzaldehyde **57** was prepared by coupling of 3-bromo-4-fluoro-benzaldehyde and 2,4-dibromophenol. Baeyer−Villiger oxidation and hydrolysis converted the aldehyde **57** into the OH-PBDE **58**. Monobromination of OH-PBDE **58**, by use of 1 equiv. bromine in acetic acid, gave the desired tetrabrominated OH-PBDEs **59**−**60** as well as the pentabrominated OH-PBDE **61**, but some unchanged starting material was also recovered. When the bromination was carried out in CH_2Cl_2/MeOH with 1 equiv. BTMA-Br_3, smaller amounts of tetrabrominated OH-PBDEs **59**−**60** were observed, with more OH-PBDE **61** and unchanged OH-PBDE **58**. We were not able to separate the OH-PBDEs **59**−**60** in this step, but they could be separated from OH-PBDEs **58** and **61** on silica gel. These last two compounds were methylated to give the MeO-PBDEs **62** and **63**. The former mixture of OH-PBDE **59** and **60** was methylated, the two MeO-PBDEs **64**−**65** were separated, and each of the pure OH-PBDEs **59** and **60** was recovered after demethylation.



Scheme 8. Pathway for the preparations of OH-PBDEs and MeO-PBDEs with the hydroxy/methoxy group in the *para*-position to the diphenyl ether bond; DMAC = *N*,*N*-dimethylacetamide

Full-scan electron ionization mass spectrometry (EIMS) showed two abundant ions for all OH-PBDEs: the molecule ion $[M]^+$ and the fragment ion $[M - 2\,Br]^+$. OH-PBDEs with a hydroxy group *ortho* to the diphenyl ether bond gave the ion $[C_6H_4Br_2]^+$. The fragment ion showed increasing intensity with number of halogen atoms on the hydroxy-substituted ring. This fragment ion is most probably formed by ether cleavage and hydrogen transfer as previously reported.[20,38] The MeO-PBDEs generated more fragment ions than the OH-PBDEs. All MeO-PBDEs gave the following abundant ions: $[M]^+$, $[M - 2\,Br]^+$, $[M - 2\,BrCH_3]^+$, and $[M - 2\,BrCH_3CO]^+$. The *ortho*-substituted MeO-PBDEs gave a characteristic $[M - BrCH_3]^+$ fragment ion, which was not formed in the cases of the *meta*- and *para*-substituted MeO-PBDEs. The *para*-substituted MeO-PBDEs gave characteristic $[M - CH_3]^+$ fragment ions, which could not be detected for the *ortho*- and *meta*-substituted MeO-PBDEs. This characteristic fragmentation is

consistent with methoxylated polychlorinated diphenyl ethers (MeO-PCDEs)[39,40] as well as methoxylated polychlorinated biphenyls (MeO-PCBs).[41,42]

Conclusion

Twenty OH-PBDEs and their corresponding MeO-PBDEs containing three to six bromine atoms have been synthesized and characterized by EIMS and ^{1}H NMR spectroscopy. Additionally, three OH-PBDEs were prepared as precursors. Three of the OH-PBDEs and two of the MeO-PBDEs prepared contain a chlorine atom. All these compounds are required as authentic reference standards for identification/quantification of the corresponding chemicals in the environment, being natural components in biota or metabolites of PBDEs. Most of the OH-PBDEs were obtained from oxidized and hydrolyzed brominated phenoxybenzaldehydes, which were further brominated, and finally the OH-PBDEs were methylated and isolated as the corresponding MeO-PBDEs. The preparation of certain OH- and MeO-PBDEs by this route is a good alternative to previously described methods.

Experimental Section

General Remarks: Melting points were determined on a Büchi 353 apparatus and were not corrected. ^{1}H NMR spectra (400 MHz) were recorded on a Varian Mercury 400 spectrometer in $CDCl_3$ solution (15 mg/mL) at 25 °C with TMS (δ_H = 0.00 ppm) as internal standard unless stated otherwise. Most of the PBDEs and their derivatives gave easily interpreted ^{1}H NMR spectra with characteristic coupling patterns ($^3J_{H,H} \approx 7-9$ Hz and $^4J_{H,H} \approx 2$ Hz). In some cases in which it was not possible to assign the resonances from their coupling patterns, selective irradiation experiments were performed in order to assign resonances to one of the two aromatic rings. Assignment of the OH resonances in the 2-hydroxybenzaldehydes was confirmed by exchange with D_2O.

Mass spectrometry electron ionization (EIMS) was performed on a quadrupole TSQ 700 Finnigan MAT instrument connected with a Varian 3400 gas chromatograph, with helium as the carrier gas. The electron energy was 70 eV and the ion source temperature was 150 °C.

Except for the iodonium salts, all prepared compounds had a purities of > 98% according to GC−MS. Silica gel column chromatography was carried out on MATREX Silica (60 Å, 35−70 μm, Millipore, Bedford, USA). Except for the two tetrabromodiphenyliodonium salts (**3** and **38**), all organic extracts were dried with anhydrous sodium sulfate. Organic solutions were concentrated in a rotary evaporator under reduced pressure at temperatures not exceeding 35 °C. Solutions containing iodomethane were concentrated in a hood at 30 °C under a stream of nitrogen. Compounds **4**,[30] **34**,[34] **45**,[30] and **54**[35] were prepared by literature procedures without any significant modifications. All other reagents and solvents (including compounds **5** and **9**−**11**) were used as obtained from commercial sources without further purification, except for 2,4-dibromophenol, which was purified by recrystallization (water/ethanol 3:1).

2,2′,4,4′-Tetrabromodiphenyliodonium Chloride (3): A mixture of concd. sulfuric acid (13.0 mL) and fuming sulfuric acid (65%, 6.5 mL) was added dropwise to iodine (5.4 g, 21 mmol). A mixture of concd. sulfuric acid (1.7 mL), fuming sulfuric acid (65%, 0.8 mL), and fuming nitric acid (100%, 3.0 mL) was added dropwise over 30 min, and the reaction mixture was stirred at 75 °C for 2 h, during which time yellow crystals of iodylsulfate precipitated. The reaction mixture was diluted with concd. sulfuric acid (20 mL), and 1,3-dibromobenzene (25 g, 106 mmol) was added over 30 min at 10−15 °C. The mixture was stirred at 40 °C for 12 h. Water (100 mL) was carefully added in small portions, with cooling in a water ice bath, and the formed nitrogen oxides were removed by a stream of nitrogen gas. After standing at 8 °C for 15 h, the clear aqueous solution was decanted off and the crude product was dissolved in MeOH (300 mL). Concd. hydrochloric acid (5 mL) in MeOH (10 mL) was added dropwise, and the crystallized chloride **3** was filtered off and washed with MeOH, toluene, and water. Yield 23.0 g, 87%. Decomposes at 167−168 °C (ref.[27] 164−165 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 7.69 (dd, $^4J_{3\text{-H},5\text{-H}}$ = 2.2, $^3J_{5\text{-H},6\text{-H}}$ = 8.6, 2 H, 5-H), 8.16 (d, 2 H, 3-H), 8.31 (d, 2 H, 6-H) ppm.

2,2′,4,4′-Tetrabromodiphenyliodonium Iodide (38): This compound was prepared as described for **3**, but was crystallized by dropwise addition of potassium iodide (10 g, 60 mmol) in water (10 mL). Yield 25.8 g, 85%. Decomposes at 115−120 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 7.74 (dd, $^4J_{3\text{-H},5\text{-H}}$ = 2.2, $^3J_{5\text{-H},6\text{-H}}$ = 8.6, 2 H, 5-H), 8.21 (d, 2 H, 3-H), 8.36 (d, 2 H, 6-H) ppm.

2,3,4-Tribromo-6-methoxyphenol (36): 2-Methoxyphenol (0.50 g, 4.0 mmol) in acetic acid (4 mL) was treated gradually with bromine (32 mmol, 1.64 mL) in acetic acid (4 mL) over 6 h. After 0.5 h, when approximately one equivalent of bromine had been added, the reaction temperature was raised from room temperature to 35 °C and a gentle stream of nitrogen was allowed to pass through the reaction vessel to remove the hydrobromic acid formed. The reaction mixture was kept at a volume of ≥ 4 mL by addition of acetic acid. After the last addition of bromine the reaction mixture was stirred for an additional hour. The product crystallized when the reaction mixture was cooled to room temperature, and the crude product was dissolved in CH_2Cl_2 (40 mL) and washed with water (40 mL), aqueous $NaHSO_3$ (5%, 2 × 40 mL), and water (2 × 40 mL). The crude product was chromatographed on a silica gel column, eluting with *n*-hexane/ethyl acetate, 2:1. Yield 1.37 g, 95%. M.p. 116−117 °C (ref.[37] 115−116 °C). ^{1}H NMR: δ = 3.91 (s, 3 H, OCH_3), 6.07 (br. s, 1 H, OH), 7.13 (s, 1 H, 5-H) ppm. EIMS: *m*/*z* [ion] (rel. int.%) 360 [M + 2]$^+$ (100), 345 [M − CH_3 + 2]$^+$ (54), 317 [M − CH_3CO + 2]$^+$ (24).

2,3,4,5-Tetrabromo-6-methoxyphenol (37): $CaCO_3$ (2.0 g, 20 mmol) was added in small portions and with careful stirring to 2-methoxyphenol (0.62 g, 5.0 mmol). Bromine (50 mmol, 2.56 mL) was added dropwise, after which the reaction mixture was allowed to stand in an ultrasonic bath for 1 h at room temperature. Excess bromine was removed by use of a stream of nitrogen. The crude product was dissolved in CH_2Cl_2 (30 mL), filtered, and washed with aqueous $NaHSO_3$ (5%, 30 mL) and water (2 × 30 mL). The crude product was chromatographed on a silica gel column, eluted with *n*-hexane/ethyl acetate, 3:1. Yield 1.9 g, 86%. M.p. 162−163 °C (ref.[22] 162−162.5 °C). ^{1}H NMR: δ = 3.92 (s, 3 H, OCH_3), 6.11 (br. s, 1 H, OH) ppm. EIMS: *m*/*z* [ion] (rel. int.%) 440 [M + 4]$^+$ (100), 425 [M − CH_3 + 4]$^+$ (64), 397 [M − CH_3CO + 4]$^+$ (28).

Coupling of 2,2′,4,4′-Tetrabromodiphenyliodonium Salts with 3-Hydroxybenzaldehyde and Brominated 2-Methoxyphenols: 2,2′,4,4′-Tetrabromodiphenyliodonium iodide **38** (2.2 g, 3.0 mmol) was ad-

Table 1. ^{1}H NMR data for the aldehydes

	Aldehyde ring					2′,4′-Dibromo ring				Coupling constants
	2	3	4	5	6	3′	5′	6′	CHO	
1[a]	OAr	Br	7.95[b]	7.33	7.93[b]	7.81	7.26	6.28	10.14	$^3J_{4\text{-H},5\text{-H}}$ = 7.9; $^4J_{4\text{-H},6\text{-H}}$ = 1.6; $^3J_{5\text{-H},6\text{-H}}$ = 7.9; $^5J_{5\text{-H,CHO}}$ = 0.9; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
2	OAr	Br	8.05	Br	8.05	7.81	7.28	6.29	10.06	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.6; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
6	OAr	6.75	7.52	7.22	7.96	7.83	7.45	6.94	10.50	$^3J_{3\text{-H},4\text{-H}}$ = 8.2; $^4J_{3\text{-H},5\text{-H}}$ = 1.1; $^3J_{4\text{-H},5\text{-H}}$ = 7.3; $^4J_{4\text{-H},6\text{-H}}$ = 1.8; $^3J_{5\text{-H},6\text{-H}}$ = 7.7; $^5J_{5\text{-H,CHO}}$ = 0.8; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.2; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
7	OAr	Cl	7.75[b]	7.39	7.91[b]	7.81	7.27	6.31	10.17	$^3J_{4\text{-H},5\text{-H}}$ = 7.8; $^4J_{4\text{-H},6\text{-H}}$ = 1.6; $^3J_{5\text{-H},6\text{-H}}$ = 7.9; $^5J_{5\text{-H,CHO}}$ = 0.7; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
8[a]	OAr	6.62	7.58	Br	8.05	7.83	7.48	6.97	10.49	$^3J_{3\text{-H},4\text{-H}}$ = 8.8; $^4J_{4\text{-H},6\text{-H}}$ = 2.6; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.5; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
48	7.37	OAr	7.25[b]	7.52	7.62[b]	7.81	7.44	6.91	9.97	$^4J_{2\text{-H},4\text{-H}}$ = 1.4; $^4J_{2\text{-H},6\text{-H}}$ = 2.5; $^3J_{4\text{-H},5\text{-H}}$ = 7.5; $^4J_{4\text{-H},6\text{-H}}$ = 1.1; $^3J_{5\text{-H},6\text{-H}}$ = 8.0; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.6
57	8.18	Br	OAr	6.96	7.74	7.84	7.49	6.76	9.90	$^4J_{2\text{-H},6\text{-H}}$ = 1.8; $^3J_{5\text{-H},6\text{-H}}$ = 8.6; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.5

[a] Assignment verified by selective irradiation experiments. [b] Tentative assignment − chemical shifts may be interchanged.

ded to a solution of the brominated 2-methoxyphenols or 3-phenoxybenzaldehyde (2.5 mmol), 18-crown-6 (0.13 g, 0.5 mmol), and suspended K_2CO_3 (0.69 g, 5.0 mmol) in DMAC (30 mL), and the reaction mixture was stirred at 80 °C for 1 h. 2,2′,4,4′-Tetrabromodiphenyliodonium chloride **3** (1.9 g, 3.0 mmol) was used for the preparation of compound **48**. The mixture was diluted with CH_2Cl_2 (30 mL), and water (30 mL) was added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with aqueous $NaHSO_3$ (5%, 50 mL), aqueous NaOH (1 M, 3 × 50 mL), and water (2 × 50 mL). Purification was performed on a silica gel column.

3-(2,4-Dibromophenoxy)benzaldehyde (48): This compound was prepared from 3-hydroxybenzaldehyde (0.31 g, 2.5 mmol). The silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.80 g, 90% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 356 [M + 2]$^+$ (52), 168 [M − 2 BrCO]$^+$ (100). ^{1}H NMR: see Table 1.

3,5-Dibromo-2-(2,4-dibromophenoxy)anisole (29): This compound was prepared from **34**[34] (0.70 g, 2.5 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 0.63 g, 49%. M.p. 115−116 °C (ref.[23] 116.5−117.5 °C). EIMS: *m*/*z* [ion] (rel. int.%) 516 [M + 4]$^+$ (100), 420 [M − $BrCH_3$ + 2]$^+$ (23), 356 [M − 2 Br + 2]$^+$ (28), 341 [M − 2 $BrCH_3$ + 2]$^+$ (7), 313 [M − 2 $BrCH_3CO$ + 2]$^+$ (18). ^{1}H NMR: see Table 3.

3,5-Dibromo-6-chloro-2-(2,4-dibromophenoxy)anisole (39): This compound was prepared from **35** (0.79 g, 2.5 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 4:1. Yield 0.82 g, 60%. M.p. 67−68.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 550 [M + 4]$^+$ (100), 456 [M − $BrCH_3$ + 4]$^+$ (43), 390 [M − 2 Br + 2]$^+$ (45), 375 [M − 2 $BrCH_3$ + 2]$^+$ (7), 347 [M − 2 $BrCH_3CO$ + 2]$^+$ (21). ^{1}H NMR: see Table 3.

3,4,5-Tribromo-2-(2,4-dibromophenoxy)anisole (40): This compound was prepared from **36** (0.90 g, 2.5 mmol). The silica gel eluent was *n*-hexane/$CHCl_3$, 3:1. Yield 0.88 g, 59%. M.p. 155.5−156.5 °C (ref.[22] 158−159 °C). EIMS: *m*/*z* [ion] (rel. int.%) 594 [M + 4]$^+$ (100), 500 [M − $BrCH_3$ + 4]$^+$ (29), 434 [M − 2 Br + 2]$^+$ (41), 419 [M − 2 $BrCH_3$ + 2]$^+$ (11), 391 [M − 2 $BrCH_3CO$ + 2]$^+$ (19). ^{1}H NMR: see Table 3.

3,4,5,6-Tetrabromo-2-(2,4-dibromophenoxy)anisole (41): This compound was prepared from **37** (1.1 g, 2.5 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 6:1. Yield 0.82 g, 49%. M.p. 105.5−106.5 °C (ref.[22] 119−120 °C). EIMS: *m*/*z* [ion] (rel. int.%) 674 [M +6]$^+$ (100), 578 [M − $BrCH_3$ + 4]$^+$ (45), 514 [M − 2 Br + 4]$^+$ (74), 499 [M − 2 $BrCH_3$ + 4]$^+$ (15), 471 [M − 2 $BrCH_3CO$ + 4]$^+$ (22). ^{1}H NMR: see Table 3.

Coupling of 2,2′,4,4′-Tetrabromodiphenyliodonium Chloride with Brominated 2-Hydroxybenzaldehydes and 4,6-Dibromo-3-methoxyphenol: 2,2′,4,4′-Tetrabromodiphenyliodonium chloride **3** (1.9 g, 3.0 mmol) was added to a solution of the brominated hydroxybenzaldehyde or methoxyphenol (2.5 mmol) and NaOH (0.12 g, 3.0 mmol) in water (15 mL) and dioxane (15 mL), and the reaction mixture was stirred at 80 °C for 1−8 h. CH_2Cl_2 (50 mL) and water (40 mL) were added to the reaction mixture. The organic layer was separated and washed with aqueous NaOH (1 M, 3 × 50 mL) and water (3 × 50 mL). The crude product was purified by silica gel chromatography.

3-Bromo-2-(2,4-dibromophenoxy)benzaldehyde (1): This compound was prepared from **4** (0.50 g, 2.5 mmol), with a reaction time of 8 h. The silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 0.87 g, 80%. M.p. 111.5−112.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 434 [M + 2]$^+$ (23), 355 [M − Br + 2]$^+$ (38), 198 [M − $C_6H_4Br_2$]$^+$ (100). ^{1}H NMR: see Table 1.

3,5-Dibromo-2-(2,4-dibromophenoxy)benzaldehyde (2): This compound was prepared from **5** (0.70 g, 2.5 mmol), with a reaction time of 4 h. The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:2. Yield 1.16 g, 90%. M.p. 168−169 °C. EIMS: *m*/*z* [ion] (rel. int.%) 514 [M + 4]$^+$ (21), 433 [M − Br + 2]$^+$ (25), 278 [M − $C_6H_4Br_2$ + 2]$^+$ (100). ^{1}H NMR: see Table 1.

4,6-Dibromo-3-(2,4-dibromophenoy)anisole (55): This compound was prepared from **54**[35] (0.70 g, 2.5 mmol), with a reaction time of 1 h. The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 1.17 g, 91%. M.p. 141.5−142.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 516 [M + 4]$^+$ (76), 356 [M − 2 Br + 2]$^+$ (100), 341 [M − 2 $BrCH_3$ + 2]$^+$ (58), 313 [M − 2 $BrCH_3CO$ + 2]$^+$ (26). ^{1}H NMR: see Table 3.

Coupling of 2,4-Dibromophenol with Fluorobenzaldehydes: 2,4-Dibromophenol (5.0−8.0 mmol, 1 equiv.) and the fluorobenzaldehyde (1 equiv.) were dissolved in DMAC (6−10 mL). Anhydrous Na_2CO_3 (1 equiv.) was added, and the reaction mixture was heated at reflux for 1−3 h. CH_2Cl_2 (30 mL) and water (50 mL) were added to the cooled reaction mixture, and the organic layer was separated and washed with aqueous NaOH (1 M, 2 × 30 mL) and water (2

Table 2. ^{1}H NMR spectroscopic data for the OH-PBDEs

	Phenol ring					2′,4′-Dibromo ring				coupling constants
	2	3	4	5	6	3′	5′	6′	OH	
12	OAr	6.77−6.79 (m, 1 H), 6.82−6.87 (m, 1 H), 7.06−7.08 (m, 2 H)				7.78	7.38	6.84	5.54	$^4J_{3'\text{-H},5'\text{-H}} = 2.2$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
13	OAr	Cl	7.01[a]	7.12	7.00[a]	7.77	7.27	6.45	5.46	$^3J_{4\text{-H},5\text{-H}} = 8.2$; $^4J_{4\text{-H},6\text{-H}} = 1.6$; $^3J_{5\text{-H},6\text{-H}} = 8.2$; $^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
14	OAr	Br	7.18[a]	7.05	7.03[a]	7.78	7.27	6.43	5.42	$^3J_{4\text{-H},5\text{-H}} = 7.7$; $^4J_{4\text{-H},6\text{-H}} = 1.8$; $^3J_{5\text{-H},6\text{-H}} = 8.4$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
15	OAr	6.74	6.96	Br	7.22	7.79	7.40	6.61	5.65	$^3J_{3\text{-H},4\text{-H}} = 8.5$; $^4J_{4\text{-H},6\text{-H}} = 2.5$; $^4J_{3'\text{-H},5'\text{-H}} = 2.2$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
16	OAr	Br	7.33[a]	Br	7.22[a]	7.79	7.29	6.44	5.65	$^4J_{4\text{-H},6\text{-H}} = 2.2$; $^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
17	OAr	Br	7.31[a]	7.11[a]	Br	7.77	7.31	6.41	5.72	$^3J_{4\text{-H},5\text{-H}} = 8.8$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
18[b]	OAr	6.66	7.16	Br	Br	7.79	7.40	6.83	6.02	$^3J_{3\text{-H},4\text{-H}} = 8.8$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
19	OAr	Br	7.55	Br	Br	7.78	7.28	6.42	5.91	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
20	OAr	6.81	Br	7.44	Br	7.82	7.45	6.90	5.31	$^4J_{3\text{-H},5\text{-H}} = 2.1$; $^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
21	OAr	Cl	Br	7.73	Br	7.78	7.29	6.42	5.75	$^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
22	OAr	Br	Br	7.74	Br	7.78	7.28	6.39	5.75	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
23	OAr	7.01	Br	Br	Br	7.81	7.45	6.89	6.04	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
42	OAr	Br	7.53	Br	Cl	7.78	7.28	6.42	5.85	$^4J_{3'\text{-H},5'\text{-H}} = 2.2$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
43	OAr	Br	Br	Br	7.44	7.79	7.30	6.41	5.62	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
44	OAr	Br	Br	Br	Br	7.79	7.29	6.40	5.90	$^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.7$
49	6.44	OAr	6.52[a]	7.18	6.59[a]	7.77	7.38	6.87	4.83	$^4J_{2\text{-H},4\text{-H}} = 2.3$; $^4J_{2\text{-H},6\text{-H}} = 2.3$; $^3J_{4\text{-H},5\text{-H}} = 8.2$; $^4J_{4\text{-H},6\text{-H}} = 0.9$; $^3J_{5\text{-H},6\text{-H}} = 8.2$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
50[b]	6.60	OAr	6.44	7.39	Br	7.78	7.41	6.89	5.54	$^4J_{2\text{-H},4\text{-H}} = 2.7$; $^3J_{4\text{-H},5\text{-H}} = 8.8$; $^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.6$
51	Br	OAr	6.31	7.38	Br	7.79	7.39	6.78	6.05	$^3J_{4\text{-H},5\text{-H}} = 8.9$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.7$
56	6.47[a]	OAr	Br	7.71[a]	Br	7.79	7.41	6.80	5.50	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.7$
58	7.15	Br	OAr	6.90	6.79	7.75	7.29	6.52	4.82	$^4J_{2\text{-H},6\text{-H}} = 2.9$; $^3J_{5\text{-H},6\text{-H}} = 8.8$; $^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
59	Br	Br	OAr	7.03[a]	6.93[a]	7.77	7.31	6.54	5.56	$^3J_{5\text{-H},6\text{-H}} = 8.9$; $^4J_{3'\text{-H},5'\text{-H}} = 2.3$; $^3J_{5'\text{-H},6'\text{-H}} = 8.7$
60	Br	7.33[a]	OAr	Br	7.09[a]	7.77	7.33	6.60	5.42	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$
61	Br	Br	OAr	7.12	Br	7.79	7.36	6.63	5.92	$^4J_{3'\text{-H},5'\text{-H}} = 2.4$; $^3J_{5'\text{-H},6'\text{-H}} = 8.8$

[a] Tentative assignment − chemical shifts may be interchanged. [b] Assignment verified by selective irradiation experiments.

× 30 mL). The crude product was purified by silica gel chromatography.

2-(2,4-Dibromophenoxy)benzaldehyde (6): This compound was prepared from **9** (0.62 g, 5.0 mmol) in DMAC (6 mL), with a reaction time of 3 h. The crude product, an oil, was distilled under reduced pressure at 135 °C and then chromatographed on silica gel with CH_2Cl_2/*n*-hexane, 3:2, as the eluent. Yield 1.16 g, 65%. M.p. 71−72 °C. EIMS: *m*/*z* [ion] (rel. int.%) 356 $[M + 2]^+$ (14), 275 $[M - Br]^+$ (40), 120 $[M - C_6H_4Br_2]^+$ (100). ^{1}H NMR: see Table 1.

3-Chloro-2-(2,4-dibromophenoxy)benzaldehyde (7): This compound was prepared from **10** (0.79 g, 5.0 mmol) in DMAC (6 mL), with a reaction time of 3 h. The silica gel eluent was *n*-hexane/ethyl acetate 7:1. Yield 1.13 g, 58%. M.p. 112−113.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 390 $[M + 2]^+$ (18), 311 $[M - Br + 2]^+$ (27), 154 $[M - C_6H_4Br_2]^+$ (100). ^{1}H NMR: see Table 1.

5-Bromo-2-(2,4-dibromophenoxy)benzaldehyde (8): This compound was prepared from **11** (1.02 g, 5.0 mmol) in DMAC (6 mL), with a reaction time of 1 h. The product was isolated by recrystallization from MeOH/CH_2Cl_2, 3:1, and the residue was purified by silica gel chromatography, eluting with *n*-hexane/ethyl acetate, 7:1. Yield 1.85 g, 85%. M.p. 129−130 °C. EIMS: *m*/*z* [ion] (rel. int.%) 434 $[M + 2]^+$ (22), 355 $[M - Br + 2]^+$ (44), 198 $[M - C_6H_4Br_2]^+$ (100). ^{1}H NMR: see Table 1.

3-Bromo-4-(2,4-dibromophenoxy)benzaldehyde (57): This compound was prepared from 3-bromo-4-fluorobenzaldehyde (1.62 g, 8.0 mmol) in DMAC (10 mL), with a reaction time of 2 h. The silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 2.70 g, 78% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 434 $[M + 2]^+$ (100), 433 $[M - H + 2]^+$ (34), 246 $[M - 2\,BrCO]^+$ (34). ^{1}H NMR: see Table 1.

Preparation of Phenols from Benzaldehydes by Baeyer−Villiger Oxidation and Hydrolysis: KH_2PO_4 (20 equiv.) was added to a solution of the benzaldehyde (1.7−8.0 mmol, 1 equiv.) in CH_2Cl_2 (15−30 mL). The reaction mixture was cooled to 0 °C, a solution of TFPA was added dropwise over 0.5 h, and the mixture was stirred at 0 °C for 0.5−2 h. The TFPA solution was prepared by dropwise addition of trifluoroacetic anhydride (7.5 equiv.) to aqueous hydrogen peroxide (30%, 1.5 equiv.) in CH_2Cl_2 (2 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The reaction mixture

Table 3. ^{1}H NMR spectroscopic data for the MeO-PBDEs

	Anisole ring					2′,4′-Dibromo ring				Coupling constants
	2	3	4	5	6	3′	5′	6′	MeO	
24	OAr	Br	7.37[a]	7.30[a]	Br	7.76	7.30	6.32	3.85	$^3J_{4\text{-H},5\text{-H}}$ = 8.8; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
25[b]	OAr	6.76	7.36	Br	Br	7.78	7.35	6.68	3.91	$^3J_{3\text{-H},4\text{-H}}$ = 8.8;, $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
26	OAr	Br	7.75	Br	Br	7.77	7.26	6.32	3.86	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
27	OAr	Br	7.23	7.11	6.95	7.74	7.21	6.32	3.77	$^3J_{4\text{-H},5\text{-H}}$ = 8.1; $^4J_{4\text{-H},6\text{-H}}$ = 1.5; $^3J_{5\text{-H},6\text{-H}}$ = 8.3; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
28	OAr	6.80	7.06	Br	7.12	7.74	7.29	6.59	3.81	$^3J_{3\text{-H},4\text{-H}}$ = 8.4; $^4J_{4\text{-H},6\text{-H}}$ = 2.2; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
29	OAr	Br	7.41[a]	Br	7.09[a]	7.75	7.23	6.32	3.77	$^3J_{4\text{-H},6\text{-H}}$ = 2.2; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
30	OAr	6.92	Br	7.50	Br	7.79	7.39	6.75	3.90	$^4J_{3\text{-H},5\text{-H}}$ = 2.2; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
31	OAr	Cl	Br	7.79	Br	7.77	7.26	6.33	3.85	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
32	OAr	Br	Br	7.81	Br	7.77	7.26	6.31	3.84	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
33	OAr	7.12	Br	Br	Br	7.80	7.41	6.76	3.92	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.5; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
39	OAr	Br	7.73	Br	Cl	7.77	7.26	6.33	3.86	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.2; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
40	OAr	Br	Br	Br	7.29	7.75	7.23	6.30	3.77	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.2; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
41	OAr	Br	Br	Br	Br	7.78	7.26	6.31	3.85	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
52	6.61	OAr	6.36	7.45	Br	7.78	7.39	6.85	3.86	$^4J_{2\text{-H},4\text{-H}}$ = 2.6; $^3J_{4\text{-H},5\text{-H}}$ = 8.7; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.6
53	Br	OAr	6.52[a]	7.44[a]	Br	7.79	7.38	6.74	3.94	$^3J_{4\text{-H},5\text{-H}}$ = 8.9; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
55	6.48[a]	OAr	Br	7.79[a]	Br	7.79	7.36	6.64	3.79	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7
62	7.17	Br	OAr	6.95	6.85	7.75	7.28	6.51	3.81	$^4J_{2\text{-H},6\text{-H}}$ = 2.9; $^3J_{5\text{-H},6\text{-H}}$ = 9.0; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
63	Br	Br	OAr	7.01	Br	7.80	7.40	6.73	3.89	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.6
64	Br	Br	OAr	6.87[a]	6.97[a]	7.77	7.30	6.53	3.91	$^3J_{5\text{-H},6\text{-H}}$ = 9.1; $^4J_{3'\text{-H},5'\text{-H}}$ = 2.4; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.8
65	Br	7.18[a]	OAr	Br	7.14[a]	7.77	7.33	6.58	3.91	$^4J_{3'\text{-H},5'\text{-H}}$ = 2.3; $^3J_{5'\text{-H},6'\text{-H}}$ = 8.7

[a] Tentative assignment − chemical shifts may be interchanged. [b] Assignment verified by selective irradiation experiments.

was diluted with brine (15−25 mL) and aqueous $NaHSO_3$ (20%, 5−15 mL) at 0 °C. The phases were separated and the aqueous layer was extracted once with an equal volume of CH_2Cl_2. The combined organic layers were washed once with an equal volume of saturated $NaHCO_3$ and water. The crude formate ester was dissolved in MeOH (20−30 mL) containing one drop of concentrated hydrochloric acid. The solution was stirred for 15 h and then concentrated in vacuo. The crude product was purified on a silica gel column.

The preparation of 3,5-dibromo-2-(2,4-dibromophenoxy)phenol **16** was carried out at room temperature with aqueous hydrogen peroxide (30%, 4.0 equiv.), trifluoroacetic anhydride (20.0 equiv.), and KH_2PO_4 (53 equiv.), with a reaction time of 15 h.

3-Chloro-2-methoxyphenol (47): This compound was prepared from **46** (1.36 g, 8.0 mmol) in CH_2Cl_2 (30 mL), with a reaction time of 1 h. The silica gel eluent was CH_2Cl_2/*n*-hexane, 4:1. Yield 1.05 g, 83%. M.p. 34−35.5 °C (ref.[43] 32−33 °C). ^{1}H NMR: δ = 3.93 (s, 3 H, OCH_3), 5.74 (br. s, 1 H, OH), 6.87 (dd, $^3J_{H,H}$ = 7.8, $^4J_{4\text{-H},6\text{-H}}$ = 2.0, 1 H, 4-H or 6-H), 6.89 (dd, $^3J_{H,H}$ = 7.8, 4-H or 6-H), 6.94 (t, 1 H, 5-H) ppm. EIMS: *m*/*z* [ion] (rel. int.%) 158 $[M]^+$ (86), 143 $[M - CH_3]^+$ (100), 115 $[M - CH_3CO]^+$ (32).

2-(2,4-Dibromophenoxy)phenol (12): This compound was prepared from **6** (1.07 g, 3.0 mmol) in CH_2Cl_2 (25 mL), with a reaction time of 1 h. The silica gel eluent was CH_2Cl_2/*n*-hexane, 3:2. Yield 1.01 g, 98% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 344 $[M + 2]^+$ (53), 184 $[M - 2\ Br]^+$ (100). ^{1}H NMR: see Table 2.

3-(2,4-Dibromophenoxy)phenol (49): This compound was prepared from **48** (0.71 g, 2.0 mmol) in CH_2Cl_2 (15 mL), with a reaction time of 2 h. The silica gel eluent was CH_2Cl_2. Yield 0.57 g, 83% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 344 $[M + 2]^+$ (21), 184 $[M - 2\ Br]^+$ (100). ^{1}H NMR: see Table 2.

3-Bromo-2-(2,4-dibromophenoxy)phenol (14): This compound was prepared from **1** (0.74 g, 1.70 mmol) in CH_2Cl_2 (15 mL), with a reaction time of 2 h. The silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.69 g, 96%. M.p. 98.5−99.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 422 $[M + 2]^+$ (83), 262 $[M - 2\ Br]^+$ (100), 236 $[M - C_6H_3BrO_2 + 2]^+$ (11). ^{1}H NMR: see Table 2.

3-Bromo-4-(2,4-dibromophenoxy)phenol (58): This compound was prepared from **57** (2.61 g, 6.0 mmol) in CH_2Cl_2 (30 mL), with a reaction time of 1.5 h. The silica gel eluent was CH_2Cl_2. Yield 2.41 g, 95%. M.p. 88−89 °C. EIMS: *m*/*z* [ion] (rel. int.%) 422 $[M + 2]^+$ (100), 262 $[M - 2\ Br]^+$ (89). ^{1}H NMR: see Table 2.

5-Bromo-2-(2,4-dibromophenoxy)phenol (15): This compound was prepared from **8** (1.74 g, 4.0 mmol) in CH_2Cl_2 (25 mL), with a reaction time of 1.5 h. The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:2. Yield 1.67 g, 99%. M.p. 52−53.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 422 $[M + 2]^+$ (81), 262 $[M - 2\ Br]^+$ (100), 236 $[M - C_6H_3BrO_2 + 2]^+$ (14). ^{1}H NMR: see Table 2.

3-Chloro-2-(2,4-dibromophenoxy)phenol (13): This compound was prepared from **7** (0.98 g, 2.5 mmol) in CH_2Cl_2 (20 mL), with a reaction time of 1.5 h. The silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.74 g, 78%. M.p. 94−95 °C. EIMS: *m*/*z* [ion] (rel. int.%) 378 $[M + 2]^+$ (58), 218 $[M - 2\ Br]^+$ (100). ^{1}H NMR: see Table 2.

3,5-Dibromo-2-(2,4-dibromophenoxy)phenol (16): This compound was prepared from **2** (1.03 g, 2.0 mmol) in CH_2Cl_2 (20 mL). The silica gel eluent was CH_2Cl_2/*n*-hexane, 5:2. Yield 0.76 g, 76%. M.p. 171−172 °C, (ref.[23] 171−173 °C). EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (90), 342 $[M - 2\ Br + 2]^+$ (100), 236 $[M - C_6H_2Br_2O_2 + 2]^+$ (18). ^{1}H NMR: see Table 2.

***ortho*-Bromination of Phenols:** Bromine (1 equiv.) in CH_2Cl_2 (2 mL) was added dropwise at −30 to −35 °C to *tert*-butylamine (2 equiv.) in toluene (25 mL), and the reaction mixture was stirred at this

temperature for 1 h. The phenoxyphenol (1.2−2.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added at −70 °C, and the mixture was stirred at −65 to −60 °C for 4−6 h. Compound **16** was dissolved in CH_2Cl_2 (5 mL) and THF (1 mL). The reaction was quenched at −70 °C by dropwise addition of water (1 mL) in ethanol (9 mL), while a stream of sulfur dioxide was simultaneously passed through the reaction mixture. After the mixture had been stirred at −70 °C for 10 min (during which time the mixture changed from pale yellow to colorless and a white solid) it was allowed to warm to room temperature. CH_2Cl_2 (50 mL) and water (50 mL) were added, and the organic layer was separated and washed with water (2 × 50 mL). The crude product was purified by silica gel chromatography.

2,6-Dibromo-3-(2,4-dibromophenoxy)phenol (51) and 6-Bromo-3-(2,4-dibromophenoxy)phenol (50): These compounds were prepared by the di-*ortho*-bromination of **49** (0.57 g, 1.65 mmol). The reaction time was 6 h and the silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. **51**: Yield 0.41 g, 50%. M.p. 95−96.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (37), 342 $[M - 2\,Br + 2]^+$ (100). ^1H NMR: see Table 3. **50**: Yield 0.20 g, 29% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 422 $[M + 2]^+$ (36), 262 $[M - 2\,Br]^+$ (100). ^1H NMR: see Table 2.

3,6-Dibromo-2-(2,4-dibromophenoxy)phenol (17): This compound was prepared from **14** (0.51 g, 1.2 mmol). The reaction time was 4 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.48 g, 80%. M.p. 93.5−95 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (74), 342 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6H_2Br_2O_2 + 2]^+$ (20). ^1H NMR: see Table 2.

5,6-Dibromo-2-(2,4-dibromophenoxy)phenol (18): This compound was prepared from **15** (0.85 g, 2.0 mmol). The reaction time was 4 h and the silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 0.85 g, 85%. M.p. 108−109.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (88), 342 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6H_2Br_2O_2 + 2]^+$ (24). ^1H NMR: see Table 2.

3,5,6-Tribromo-2-(2,4-dibromophenoxy)phenol (19): This compound was prepared from **16** (0.70 g, 1.4 mmol). The reaction time was 4 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 5:2. Yield 0.60 g, 74%. M.p. 114.5−115.5 °C, (ref.[1] 113−114 °C). EIMS: *m*/*z* [ion] (rel. int.%) 580 $[M + 4]^+$ (78), 420 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_3O_2 + 2]^+$ (36). ^1H NMR: see Table 2.

***ortholpara*-Bromination of Phenols:** BTMA-Br_3 (2.2 equiv.) was added in small portions over time (5 h), at room temperature, to a mixture of the phenol (1.2−3.9 mmol, 1 equiv.) and $CaCO_3$ (3 equiv.) in CH_2Cl_2 (25−50 mL) and MeOH (10−20 mL) (in a ratio of 5:2). After stirring for an additional 1 h, the reaction mixture was filtered and treated with aqueous $NaHSO_3$ (5%, 40 mL) while being stirred. The organic layer was separated and the water phase was extracted with CH_2Cl_2 (30 mL). The combined organic phase was washed with water (2 × 50 mL). The crude product was purified by silica gel chromatography.

2,4-Dibromo-5-chloro-6-methoxyphenol (35): This compound was prepared from **47** (0.48 g, 3.0 mmol). The silica gel eluent was *n*-hexane/ethyl acetate, 3:1. Yield 0.83 g, 87%. M.p. 105−106 °C. ^1H NMR: δ = 3.94 (s, 3 H, OCH_3), 5.95 (br. s, 1 H, OH), 7.56 (s, 1 H, 5-H) ppm. EIMS: *m*/*z* [ion] (rel. int.%) 316 $[M + 2]^+$ (100), 301 $[M - CH_3 + 2]^+$ (65), 273 $[M - CH_3CO + 2]^+$ (27). ^1H NMR: see Table 2.

4,6-Dibromo-2-(2,4-dibromophenoxy)phenol (20): This compound was prepared from **12** (0.96 g, 2.8 mmol). The silica gel eluent was *n*-hexane/ethyl acetate 6:1. Yield 1.31 g, 93%. M.p. 88−89.5 °C (ref.[23] 90−91 °C). EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (62), 342 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6H_2Br_2O_2 + 2]^+$ (20). ^1H NMR: see Table 2.

4,6-Dibromo-3-chloro-2-(2,4-dibromophenoxy)phenol (21): This compound was prepared from **13** (0.61 g, 1.6 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 0.83 g, 97%. M.p. 149−150 °C. EIMS: *m*/*z* [ion] (rel. int.%) 536 $[M + 4]^+$ (77), 375 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_2ClO_2 + 2]^+$ (40). ^1H NMR: see Table 2.

3,4,6-Tribromo-2-(2,4-dibromophenoxy)phenol (22): This compound was prepared from **14** (0.51 g, 1.2 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 0.67 g, 96%. M.p. 126−127 °C. EIMS: *m*/*z* [ion] (rel. int.%) 580 $[M + 4]^+$ (81), 420 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_3O_2 + 2]^+$ (40). ^1H NMR: see Table 2.

4,5,6-Tribromo-2-(2,4-dibromophenoxy)phenol (23): This compound was prepared from **15** (1.65 g, 3.9 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 1:1. Yield 2.20 g, 97%. M.p. 140−141 °C (ref.[20] 138−140 °C). EIMS: *m*/*z* [ion] (rel. int.%) 580 $[M + 4]^+$ (77), 420 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_3O_2 + 2]^+$ (36). ^1H NMR: see Table 2.

Monobromination of 3-Bromo-4-(2,4-dibromophenoxy)phenol: Bromine (5.6 mmol, 0.287 mL) in acetic acid (10 mL) was added dropwise, over 30 min at room temperature, to a solution of **58** (2.37 g, 5.6 mmol) in acetic acid (20 mL). After stirring for an additional 3 h, the reaction mixture was treated with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with aqueous $NaHSO_3$ (5%, 150 mL) and water (2 × 150 mL). Purification of the crude products on a silica gel column, eluting with CH_2Cl_2/*n*-hexane, 2:1, gave the starting compound **58** (0.12 g, 5%), the pentabrominated OH-PBDE **61**, and the two expected tetrabrominated OH-PBDEs as a mixture (2.25 g, 80%). The mixture of **59** and **60** was methylated as described below and separated on a silica gel column, eluted with *n*-hexane/ethyl acetate 6:1.

2,3,6-Tribromo-4-(2,4-dibromophenoxy)phenol (61): Yield 0.33 g, 10%. M.p. 95−96.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 580 $[M + 4]^+$ (68), 420 $[M - 2\,Br + 2]^+$ (100). ^1H NMR: see Table 2.

2,3-Dibromo-4-(2,4-dibromophenoxy)anisole (64): Yield (two steps from **58**) 0.38 g, 13%. M.p. 148−149 °C. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (100), 501 $[M - CH_3 + 4]^+$ (21), 356 $[M - 2\,Br + 2]^+$ (32), 341 $[M - 2\,BrCH_3 + 2]^+$ (21), 313 $[M - 2\,BrCH_3CO + 2]^+$ (20). ^1H NMR: see Table 3.

2,5-Dibromo-4-(2,4-dibromophenoxy)anisole (65): Yield (two steps from **58**) 1.86 g, 64%. M.p. 111−112 °C. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (100), 501 $[M - CH_3 + 4]^+$ (18), 356 $[M - 2\,Br + 2]^+$ (25), 341 $[M - 2\,BrCH_3 + 2]^+$ (22), 313 $[M - 2\,BrCH_3CO + 2]^+$ (22). ^1H NMR: see Table 3.

General Procedure for Methylation of Phenols: Phenol (0.40−8.0 mmol, 1.0 equiv.), NaOH (3.0 equiv.), and tetrabutylammonium hydroxide (2.0 equiv.) were distributed between equal volumes of CH_2Cl_2 (5−30 mL) and water (5−30 mL). Iodomethane (5.0 equiv.) was added, and the reaction mixture was stirred at room temperature for 5 h. The layers were separated and the water phase was extracted once with one volume of CH_2Cl_2. The crude product was purified by silica gel chromatography.

3-Chloro-2-methoxybenzaldehyde (46): This compound was prepared from **45** (1.25 g, 8.0 mmol). The silica gel eluent was CH_2Cl_2/*n*-hexane, 5:1. Yield 1.32 g, 97%. M.p. 29.5−31 °C. ^1H NMR: δ = 7.19 (dd, $^3J_{4\text{-}H,5\text{-}H}$ = 7.9, $^3J_{5\text{-}H,6\text{-}H}$ = 7.7, 1 H, 5-H), 7.64 (dd, $^4J_{4\text{-}H,6\text{-}H}$ = 1.6, 1 H, 4-H), 7.76 (dd, 1 H, 6-H), 10.38 (s, 1 H, CHO) ppm. EIMS: *m*/*z* [ion] (rel. int.%) 170 $[M]^+$ (95), 169 $[M - H]^+$ (35), 155 $[M - CH_3]^+$ (64), 152 $[M - CH_4]^+$ (100).

3-Bromo-2-(2,4-dibromophenoxy)anisole (27): This compound was prepared from **14** (0.34 g, 0.8 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.345 g, 99% as an oil. M.p. ref.[23] 78.5−79.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 436 $[M + 2]^+$ (100), 342 $[M - BrCH_3 + 2]^+$ (48), 276 $[M - 2\,Br]^+$ (36), 261 $[M - 2\,BrCH_3]^+$ (10), 233 $[M - 2\,BrCH_3CO]^+$ (20). ^1H NMR: see Table 3.

3-Bromo-4-(2,4-dibromophenoxy)anisole (62): This compound was prepared from **58** (0.423 g, 1.0 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1.Yield 0.433 g, 99%. M.p. 57−58 °C. EIMS: *m*/*z* [ion] (rel. int.%) 436 $[M + 2]^+$ (100), 421 $[M - CH_3 + 2]^+$ (11), 276 $[M - 2\,Br]^+$ (29), 261 $[M - 2\,BrCH_3]^+$ (17), 233 $[M - 2\,BrCH_3CO]^+$ (18). ^1H NMR: see Table 3.

5-Bromo-2-(2,4-dibromophenoxy)anisole (28): This compound was prepared from **15** (0.423 g, 1.0 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.433 g, 99% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 436 $[M + 2]^+$ (100), 342 $[M - BrCH_3 + 2]^+$ (58), 276 $[M - 2\,Br]^+$ (20), 261 $[M - 2\,BrCH_3]^+$ (8), 233 $[M - 2\,BrCH_3CO]^+$ (16). ^1H NMR: see Table 3.

6-Bromo-3-(2,4-dibromophenoxy)anisole (52): This compound was prepared from **50** (0.101 g, 0.24 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.103 g, 98% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 436 $[M + 2]^+$ (47), 276 $[M - 2\,Br]^+$ (100), 261 $[M - 2\,BrCH_3]^+$ (36), 233 $[M - 2\,BrCH_3CO]^+$ (17). ^1H NMR: see Table 3.

3,5-Dibromo-2-(2,4-dibromophenoxy)anisole (29): This compound was prepared from **16** (0.50 g, 1.0 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 0.505 g, 98%. ^1H NMR: see Table 3. For m.p. and EIMS, see **29** above.

3,6-Dibromo-2-(2,4-dibromophenoxy)anisole (24): This compound was prepared from **17** (0.20 g, 0.40 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 0.20 g, 97%. M.p. 112−113 °C. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (100), 420 $[M - BrCH_3 + 2]^+$ (54), 356 $[M - 2\,Br + 2]^+$ (59), 341 $[M - 2\,BrCH_3 + 2]^+$ (11), 313 $[M - 2\,BrCH_3CO + 2]^+$ (26). ^1H NMR: see Table 3.

4,6-Dibromo-2-(2,4-dibromophenoxy)anisole (30): This compound was prepared from **20** (0.75 g, 1.5 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.74 g, 96% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (100), 420 $[M - BrCH_3 + 2]^+$ (75), 356 $[M - 2\,Br + 2]^+$ (52), 341 $[M - 2\,BrCH_3 + 2]^+$ (11), 313 $[M - 2\,BrCH_3CO + 2]^+$ (25). ^1H NMR: see Table 3.

5,6-Dibromo-2-(2,4-dibromophenoxy)anisole (25): This compound was prepared from **18** (0.50 g, 1.0 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 0.505 g, 98% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (100), 420 $[M - BrCH_3 + 2]^+$ (63), 356 $[M - 2\,Br + 2]^+$ (29), 341 $[M - 2\,BrCH_3 + 2]^+$ (9), 313 $[M - 2\,BrCH_3CO + 2]^+$ (20). ^1H NMR: see Table 3.

2,6-Dibromo-3-(2,4-dibromophenoxy)anisole (53): This compound was prepared from **51** (0.20 g, 0.40 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:2. Yield 0.205 g, 99% as an oil. EIMS: *m*/*z* [ion] (rel. int.%) 516 $[M + 4]^+$ (70), 356 $[M - 2\,Br + 2]^+$ (100), 341 $[M - 2\,BrCH_3 + 2]^+$ (64), 313 $[M - 2\,BrCH_3CO + 2]^+$ (24). ^1H NMR: see Table 3.

4,6-Dibromo-3-chloro-2-(2,4-dibromophenoxy)anisole (31): This compound was prepared from **21** (0.40 g, 0.75 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.405 g, 98%. M.p. 101−102 °C. EIMS: *m*/*z* [ion] (rel. int.%) 550 $[M + 4]^+$ (100), 456 $[M - BrCH_3 + 4]^+$ (65), 434 $[M - BrCl + 2]^+$ (14), 390 $[M - 2\,Br + 2]^+$ (30), 375 $[M - 2\,BrCH_3 + 2]^+$ (11), 347 $[M - 2\,BrCH_3CO + 2]^+$ (19). ^1H NMR: see Table 3.

2,3,6-Tribromo-4-(2,4-dibromophenoxy)anisole (63): This compound was prepared from **61** (0.145 g, 0.25 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 2:1. Yield 0.147 g, 99%. M.p. 104−105 °C. EIMS: *m*/*z* [ion] (rel. int.%) 594 $[M + 4]^+$ (100), 579 $[M - CH_3 + 4]^+$ (39), 434 $[M - 2\,Br + 2]^+$ (24), 419 $[M - 2\,BrCH_3 + 2]^+$ (25), 391 $[M - 2\,BrCH_3CO + 2]^+$ (21). ^1H NMR: see Table 3.

3,4,6-Tribromo-2-(2,4-dibromophenoxy)anisole (32): This compound was prepared from **22** (0.29 g, 0.50 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 0.29 g, 98%. M.p. 78−79.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 594 $[M + 4]^+$ (100), 500 $[M - BrCH_3 + 4]^+$ (60), 434 $[M - 2\,Br + 2]^+$ (63), 419 $[M - 2\,BrCH_3 + 2]^+$ (13), 391 $[M - 2\,BrCH_3CO + 2]^+$ (21). ^1H NMR: see Table 3.

3,5,6-Tribromo-2-(2,4-dibromophenoxy)anisole (26): This compound was prepared from **19** (0.25 g, 0.43 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 4:1.Yield 0.255 g, 100%. M.p. 112−113 °C. EIMS: *m*/*z* [ion] (rel. int.%) 594 $[M + 4]^+$ (100), 500 $[M - BrCH_3 + 4]^+$ (52), 434 $[M - 2\,Br + 2]^+$ (35), 419 $[M - 2\,BrCH_3 + 2]^+$ (6), 391 $[M - 2\,BrCH_3CO + 2]^+$ (16). ^1H NMR: see Table 3.

4,5,6-Tribromo-2-(2,4-dibromophenoxy)anisole (33): This compound was prepared from **23** (1.16 g, 2.0 mmol). The silica gel eluent was *n*-hexane/CH_2Cl_2, 3:1. Yield 1.17 g, 98%. M.p. 87−88 °C. EIMS: *m*/*z* [ion] (rel. int.%) 594 $[M + 4]^+$ (100), 500 $[M - BrCH_3 + 4]^+$ (77), 434 $[M - 2\,Br + 2]^+$ (34), 419 $[M - 2\,BrCH_3 + 2]^+$ (8), 391 $[M - 2\,BrCH_3CO + 2]^+$ (15). ^1H NMR: see Table 3.

General Demethylation Procedure: Boron tribromide (10 equiv.) was added to a solution of the MeO-PBDEs (0.625−1.0 mmol, 1 equiv.) in CH_2Cl_2 (15 mL), and the mixture was heated at 50 °C until all starting material had reacted (5−48 h). Water (15 mL) was carefully added at 0 °C, and the layers were separated and the water phase was extracted once with one volume of CH_2Cl_2. The crude product was purified by silica gel chromatography.

2,3-Dibromo-4-(2,4-dibromophenoxy)phenol (59): This compound was prepared from **64** (0.206 g, 0.40 mmol). The silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1.Yield 0.199 g, 99%. M.p. 82.5−83.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (89), 342 $[M - 2\,Br + 2]^+$ (100). ^1H NMR: see Table 2.

3,5-Dibromo-2-(2,4-dibromophenoxy)phenol (16): This compound was prepared from **29** (0.32 g, 0.625 mmol). The silica gel eluent was CH_2Cl_2/*n*-hexane, 5:2. Yield 0.30 g, 96%. ^1H NMR: see Table 3. For m.p. and EIMS, see **16** above.

4,6-Dibromo-3-(2,4-dibromophenoxy)phenol (56): This compound was prepared from **55** (0.20 g, 0.39 mmol). The reaction time was 5 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 3:2. Yield 0.194 g, 99%. M.p. 82.5−84 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (51), 342 $[M - 2\,Br]^+$ (100). ^1H NMR: see Table 2.

2,5-Dibromo-4-(2,4-dibromophenoxy)phenol (60): This compound was prepared from **65** (1.03 g, 2.0 mmol). The silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1.Yield 0.987 g, 98%. M.p. 90−91 °C. EIMS: *m*/*z* [ion] (rel. int.%) 502 $[M + 4]^+$ (100), 342 $[M - 2\,Br + 2]^+$ (98). ^1H NMR: see Table 2.

3,5-Dibromo-6-chloro-2-(2,4-dibromophenoxy)phenol (42): This compound was prepared from **39** (0.41 g, 0.75 mmol). The reaction time was 36 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.39 mg, 97%. M.p. 97−98.5 °C. EIMS: *m*/*z* [ion] (rel. int.%) 536 $[M + 4]^+$ (72), 375 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_2ClO_2 + 2]^+$ (28). ^1H NMR: see Table 2.

3,4,5-Tribromo-2-(2,4-dibromophenoxy)phenol (43): This compound was prepared from **40** (0.50 g, 0.84 mmol). The reaction time was 36 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 3:1. Yield 0.46 g, 94%. M.p. 193−194.5 °C, (ref.[23] 200−201 °C). EIMS: *m*/*z* [ion] (rel. int.%) 580 $[M + 4]^+$ (80), 420 $[M - 2\,Br + 2]^+$ (100), 236 $[M - C_6HBr_3O_2 + 2]^+$ (36). ^1H NMR: see Table 2.

3,4,5,6-Tetrabromo-2-(2,4-dibromophenoxy)phenol (44): This compound was prepared from **41** (0.42 g, 0.625 mmol). The reaction time was 48 h and the silica gel eluent was CH_2Cl_2/*n*-hexane, 2:1. Yield 0.405 g, 98%. M.p. 159.5−161 °C, (ref.[22] 161−163 °C). EIMS: *m*/*z* [ion] (rel. int.%) 660 $[M + 6]^+$ (63), 500 $[M - 2\,Br + 4]^+$ (100), 236 $[M - C_6Br_4O_2 + 2]^+$ (47). ^1H NMR: see Table 2.

Acknowledgments

We thank Johan Eriksson for valuable discussions on how to quench a bromine/*tert*-butylamine complex at −70 °C and Ioannis Athanasiadis for running the MS. This work was funded by the European Union R&D program 5th framework and the Swedish Foundation for Strategic Environmental Research (MISTRA) through the framework of the NewS program.

[1] B. F. Bowden, L. Towerzey, P. C. Junk, *Aust. J. Chem.* **2000**, *53*, 299−301.
[2] G. M. Cameron, B. L. Stapleton, S. M. Simonsen, D. J. Brecknell, M. J. Garson, *Tetrahedron* **2000**, *56*, 5247−5252.
[3] R. Capon, E. L. Ghisalberti, P. R. Jefferies, B. W. Skelton, A. H. White, *J. Chem. Soc., Perkin I* **1981**, 2464−2467.
[4] R. W. Schumacher, B. S. Davidson, *Tetrahedron* **1995**, *51*, 10125−10130.
[5] X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm, *J. Org. Chem.* **1997**, *62*, 3810−3819.
[6] M. Kuniyoshi, K. Yamada, T. Higa, *Experientia* **1985**, *41*, 523−524.
[7] P. S. Haglund, D. R. Zook, H. R. Buser, J. Hu, *Environ. Sci. Technol.* **1997**, *31*, 3281−3287.
[8] L. Asplund, M. Athanasiadou, A. Sjödin, Å. Bergman, H. Börjeson, *Ambio* **1999**, *28*, 67−76.
[9] A. Kierkegaard, U. Sellström, A. Bignert, M. Olsson, L. Asplund, B. Jansson, C. de Wit, *Organohalogen Compounds* **1999**, *40*, 367−370.
[10] W. Vetter, E. Stoll, M. J. Garson, S. J. Fahey, C. Gaus, J. F. Müller, *Environ. Toxicol. Chem.* **2002**, *21*, 2014−2019.
[11] A. Olsson, K. Ceder, Å. Bergman, B. Helander, *Environ. Sci. Technol.* **2000**, *34*, 2733−2740.
[12] L. Hovander, T. Malmberg, M. Athanasiadou, I. Athanassiadis, S. Rahm, Å. Bergman, E. Klasson Wehler, *Arch. Environ. Contam. Toxicol.* **2002**, *42*, 105−117.
[13] U. Örn, E. Klasson Wehler, *Xenobiotica* **1998**, *28*, 199−211.
[14] A. Kierkegaard, S. Burreau, G. Marsh, E. Klasson Wehler, C. de Wit, L. Asplund, *Organohalogen Compounds* **2001**, *52*, 58−61.
[15] C. de Wit, *Chemosphere* **2002**, *46*, 583−624.
[16] H. Hakk, G. Larsen, E. Klasson Wehler, *Xenobiotica* **2002**, *32*, 369−382.
[17] J. de Boer, K. de Boer, J. P. Boon, *The Handbook of Environmental Chemistry Vol. 3 Part K New types of persistent halogenated compounds* (Ed.: J. Paasivirta), Springer-Verlag, Berlin Heidelberg, **2000**, chapter 3, pp. 61−95.
[18] D. Handayani, R. A. Edrada, P. Proksch, V. Wray, L. Witte, R. W. M. Van Soest, A. Kunzmann, Soedarsono, *J. Nat. Prod.* **1997**, *60*, 1313−1316.
[19] J. Salva, D. J. Faulkner, *J. Nat. Prod.* **1990**, *53*, 757−760.
[20] B. Carté, D. J. Faulkner, *Tetrahedron* **1981**, *37*, 2335−2339.
[21] M. G. Ikonomou, S. Rayne, R. F. Addison, *Environ. Sci. Technol.* **2002**, *36*, 1886−1892.
[22] N. K. Utkina, M. V. Veselova, O. S. Radchenko, *Chem. Nat. Compd. (Engl. Transl.)* **1993**, *29*, 291−293.
[23] K. A. Francesconi, E. L. Ghisalberti, *Aust. J. Chem.* **1985**, *38*, 1271−1277.
[24] G. M. Sharma, B. Vig, *Tetrahedron Lett.* **1972**, *17*, 1715−1718.
[25] T. Humppi, *Synthesis* **1985**, 919−924.
[26] C. A. Nilsson, Å. Norström, M. Hansson, K. Andersson, *Chemosphere* **1977**, *6*, 599−607.
[27] G. Marsh, J. Hu, E. Jakobsson, S. Rahm, Å. Bergman, *Environ. Sci. Technol.* **1999**, *33*, 3033−3037.
[28] T. Nevalainen, J. Koistinen, *Environ. Sci. Technol.* **1994**, *28*, 1341−2347.
[29] A. Garå, K. Andersson, C. A. Nilsson, Å. Norström, *Chemosphere* **1981**, *10*, 365−390.
[30] N. U. Hofsløkken, L. Skattebøl, *Acta Chem. Scand.* **1999**, *53*, 258−262.
[31] G. W. Yeager, D. N. Schissel, *Synthesis* **1995**, 28−30.
[32] G. W. Yeager, D. N. Schissel, *Synthesis* **1991**, 63−68.
[33] D. E. Pearson, R. D. Wysong, C. V. Breder, *J. Org. Chem.* **1967**, *32*, 2358−2360.
[34] S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa, T. Okamoto, *Chemistry Letters* **1987**, 627−630.
[35] S. Kajigaeshi, T. Kakinami, T. Okamoto, H. Nakamura, M. Fujikawa, *Bull. Chem. Soc., Jpn.* **1987**, *60*, 4187−4189.
[36] Å. Bergman, C. A. Wachtmeister, *J. Labelled Comp. Radiopharm.* **1987**, *24*, 925−930.
[37] L. C. Raiford, R. E. Silker, *J. Org. Chem.* **1937**, *2*, 346−355.
[38] M. Deinzer, D. Griffin, T. Miller, R. Skinner, *Biomed. Mass Spectrom.* **1979**, *6*, 301−304.
[39] M. T. M. Tulp, O. Hutzinger, *Biomed. Mass Spectrom.* **1978**, *5*, 224−231.
[40] M. Deinzer, J. Lamberton, D. Griffin, T. Miller, *Biomed. Mass Spectrom.* **1978**, *5*, 566−571.
[41] B. Jansson, G. Sundström, *Biomed. Mass Spectrom.* **1974**, *1*, 386−392.
[42] Å. Bergman, E. Klasson Wehler, H. Kuroki, A. Nilsson, *Chemosphere* **1995**, *30*, 1921−1938.
[43] W. C. Evans, B. S. W. Smith, H. N. Fernley, J. I. Davies, *Biochem. J.* **1971**, *122*, 543−551.

Received February 7, 2003

