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POLYBROMINATED DIPHENYL ETHERS FROM *DYSIDEA HERBACEA, DYSIDEA CHLOREA* AND *PHYLLOSPONGIA FOLIASCENS*

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Abstract—The marine sponges *Dysidea herbacea, D. chlorea* and *Phyllospongia foliascens* were differentiated with difficulty in the field. *D. herbacea* contained 2-(2',4'-dibromophenoxy)-3,4,5-tribromophenol (**1**), 2-(2',4'-dibromophenoxy)-4,5,6-tribromophenol (**2**) and 2-(2',4'-dibromophenoxy)-3,5-dibromophenol (**6**). *D. chlorea* contained only 2-(2',4'-dibromophenoxy)-4,6-dibromophenol(**3**), a compound previously reported as a metabolite of *D. herbacea*. *Phyllospongia foliascens* contained 2-(3',5'-dibromo-2'-methoxy-phenoxy)-3,5-dibromoanisole (**7**) and a 1:2 mixture of 2-(3',5'-dibromo-2'-hydroxyphenoxy)-3,5,6-tribromophenol (**8**) and 2-(3',5'-dibromo-2'-hydroxyphenoxy)-3,4,5,6-tetrabromophenol (**9**).

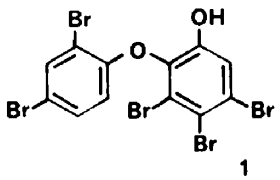
The marine sponge *Dysidea herbacea* Keller is noted for the variety of its secondary metabolites that include chlorinated metabolites derived from amino acids,[1] sesquiterpenes[2] and polybrominated diphenyl ethers.[3] In 1969, Sharma *et al.*[3a] reported the isolation of five polybrominated 2-phenoxyphenol derivatives **1–5** from a sample of *D. herbacea* from the Western Caroline Islands (presumably Palau[4]). These compounds were reported to show anti-microbial activity against Gram negative and Gram positive bacteria. In 1972, Sharma and Vig[3b] reported the structural elucidation of 2-(2',4'-dibromophenoxy)-3,4,5-tribromophenol (**1**) and 2-(4'-bromophenoxy)-3-bromophenol (**5**). The structure **1** was confirmed by synthesis. No details of the structural elucidation of compounds **2–4** have been presented.

We recently collected three sponges that visually resembled *D. herbacea* from Iwayama Bay, Palau. The three grey-green sponges were found adjacent to one another in shallow water and were distinguished by small differences in morphology. The sponges were subsequently identified[5] as *Dysidea herbacea* Keller, *Dysidea chlorea* de Laubenfels and *Phyllospongia foliascens* Pallas.[6] Our sample of *D. herbacea* contained the two pentabrominated 2-phenoxyphenols **1** and **2** and a tetrabrominated 2-phenoxyphenol **6**, isomeric with the reported tetrabrominated 2-phenoxyphenol **3**, and none of the tribrominated and dibrominated 2-phenoxyphenols **4** and **5**. The tetrabrominated 2-phenoxyphenol **3** was identified as the major secondary metabolite of *D. chlorea*. *P. foliascens* contained 2 - (3',5' - dibromo - 2' - methoxyphenoxy) - 3,5 - dibromoanisole (**7**), 2 - (3',5' - dibromo - 2' - hydroxyphenoxy) - 3,5,6 - tribromophenol (**8**) and 2 - (3',5' - dibromo - 2' - hydroxyphenoxy) - 3,4,5,6 - tetrabromophenol (**9**).

The dichloromethane-soluble material from a methanolic extract of *Dysidea herbacea* was chromatographed on silica gel to obtain 2-(2',4'-dibromophenoxy)-3,4,5-tribomophenol (**1**, 1.3% dry weight), 2-(2',4'-dibromophenoxy)-4,5,6-tribromophenol (**2**, 0.07% dry weight) and 2-(2', 4'-dibromophenoxy)-3,5-dibromophenol(**6**, 0.05% dry weight). The phenol **1** was identified from its physical and spectral data that were almost identical to those reported by Sharma and Vig.[3b] The phenol **2**, m.p. 138–140°, had the molecular formula $C_{12}H_5Br_5O_2$, isomeric with phenol **1**. Methylation of the phenol **2** with methyl iodide and potassium carbonate in dry acetone gave a methyl ether **10** that was debrominated by hydrogenation over 10% Pd–C catalyst to obtain 2-phenoxyanisole. The ^{1}H NMR spectrum of **2** contained signals at δ 6.82 (d, 1H, J = 8 Hz), 7.05 (s, 1H), 7.40 (dd, 1H, J = 8,2 Hz) and 7.79 (d, 1H, J = 2 Hz). The signals at δ 6.82, 7.40 and 7.79 were assigned to protons on a 2,4-dibromophenyl ether ring while the signal at 7.05 was assigned to a single proton on the second aromatic ring. The chemical shift of the solitary proton in the corresponding acetate **11** was at δ 7.02 indicating that the proton was meta to the phenolic OH. Comparison of the chemical shift of the proton at C-6' in phenol **2** (δ 6.82) with that in phenol **1** (δ 6.41) indicated a difference in the substitution pattern at C-3 (see below). Thus, phenol **2** was assigned the structure 2-(2',4'-dibromophenoxy)-4,5,6-tribromophenol.

The phenol **6**, m.p. 168–170°, had the molecular formula $C_{12}H_6Br_4O_2$. Methylation followed by hydrogenation again gave 2-phenoxyanisole. The presence of signals at δ 6.43 (d, 1H, J = 8 Hz), 7.26 (dd, 1 H, J = 8,2 Hz) and 7.76 (d, 1H, J = 2 Hz) in the ^{1}H NMR spectrum of phenol **6** indicated the presence of a 2,4-dibromophenoxy ether ring. The two remaining signals at δ 7.19 (d, 1H, J = 2 Hz) and 7.32 (d, 1H, J = 2 Hz) were due to two *meta*-situated aromatic protons. Acetylation of the phenol **6** with acetic anhydride in pyridine gave an acetate **12** having ^{1}H NMR signals for the two *meta*-situated protons at δ 7.30 (d, 1H, J = 2 Hz) and 7.68 (d, 1H, J = 2Hz). These downfield shifts on acetylation were relatively small for protons *ortho* and *para* to phenol although they were considerably larger than those found on acetylation of the alternative isomer **3** (see below). Conversion of the phenol **6** to the corresponding phenolate ion caused large upfield shifts of 1.03 and 1.14 ppm, again implying that the aromatic protons were *ortho* and *para* to the phenolic OH group.[7] We had therefore identified 2-(2',4'-dibromophenoxy)-3,5-dibromophenol (**6**) as a metabolite of *D. herbacea* instead of 2-(2',4'-dibromophenoxy)-4,6-dibromophenol (**3**), the structure identified by Sharma *et al.*[3a]

The dichloromethane extract of a lyophilized sample of *Dysidea chlorea* contained 2-(2,'4'-dibromophenoxy)-4,6-dibromophenol (**3**) (5.6% dry weight) as the major secondary metabolite. The phenol **3**, m.p. 88–90°, had the molecular formula $C_{12}H_6Br_4O_2$ and could also be converted to 2-phenoxyanisole by methylation followed by



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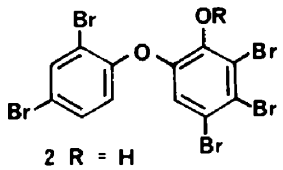
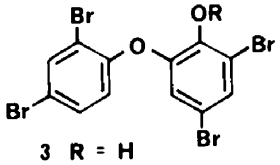


2 R = H
10 R = Me
11 R = Ac



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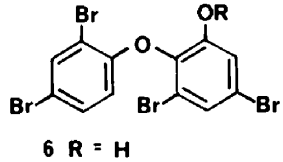

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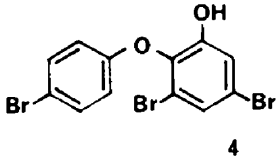
12 R = Ac



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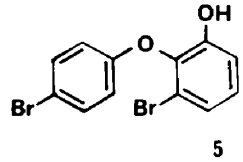

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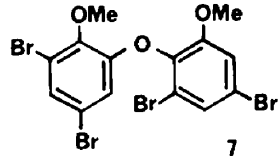

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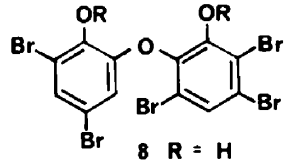

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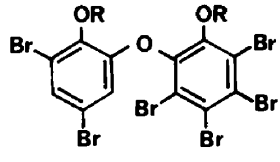
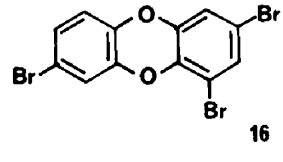
15 R = Me



9 R = H
14 R = Me



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catalytic hydrogenation. The ^{1}H NMR spectrum of phenol **3** contained signals at δ 6.84 (d, 1H, J = 8 Hz), 7.40 (dd, 1H, J = 8,2 Hz) and 7.78 (d, 1H, J = 2 Hz) due to the protons on the 2,4-dibromophenoxy ether ring and at 6.82 (d, 1H, J = 2Hz) and 7.42 (d, 1H, J = 2 Hz) assigned to two *meta* situated aromatic protons on the phenolic ring. Acetylation of the phenol **3** gave the corresponding acetate **13** having a ^{1}H NMR spectrum that was virtually unchanged in the aromatic region. Conversion of the phenol **3** to the corresponding phenolate ion caused upfield shifts of 0.42 and 0.18 ppm for the two aromatic protons that must both be *meta* to the phenolic hydroxyl group. We had therefore shown that *D. chlorea* contained 2-(2',4'-dibromophenoxy)-4,6-dibromophenol (**3**). It is interesting to note that the chemical shift of the C-6' proton was at δ 6.82 and 6.84 in phenols **2** and **3** which have no substituent at C-3 and at δ 6.41 and 6.43 in phenols **1** and **6** which have a bromine at C-3.

Silica gel chromatography of a dichloromethane extract of a lyophilized sample of *Phyllospongia foliascens* gave 2-(3',5'-dibromo-2'-methoxyphenoxy)-3,5-dibromoanisole (**7**) (0.1% dry weight) and an inseparable mixture (2:1, 0.4% dry weight) of 2-(3',5'-dibromo-2-hydroxyphenoxy)3,4,5,6-tetrabromophenol(**9**) and 2-(3', 5'-dibromo-2-hydroxyphenoxy)-3, 5, 6-tribromophenol (**8**). The latter mixture was treated with methyl iodide and potassium carbonate in dry acetone to obtain the corresponding dimethyl ethers **14** and **15** that were separated as required by LC on μ-porasil.

The dimethyl ether **7**, m.p. 86–88°, had the molecular formula $C_{14}H_{10}Br_4O_3$. The ^{1}H NMR spectrum contained two methoxy signals at δ 3.76 (s, 3 H) and 4.00 (s, 3 H) and aromatic proton signals at 6.45 (d, 1 H, J = 2 Hz) coupled to 7.35 (d, 1H, J = 2 Hz) and 7.10 (d, 1H, J = 2 Hz) coupled to 7.42 (d, 1H, J = 2 Hz). Catalytic hydrogenation of the dimethyl ether **7** over 10% Pd–C gave bis-(2-methoxyphenyl) ether identical in all respects to a

sample synthesized[8] from guaicol and 2-bromoanisole. Since the ^{1}H NMR spectrum of the dimethyl ether **7** indicated that each ring contained a different pair of *meta*-situated protons, the compound must be 2-(3',5'-dibromo-2'-methoxyphenoxy)-3,5-dibromoanisole. We assigned the ^{1}H NMR signal at δ 6.45 to the proton *ortho* to the phenoxy oxygen.

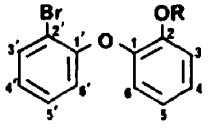
The dimethyl ether **14**, m.p. 160–162°, had the molecular formula $C_{14}H_8Br_6O_3$ and could be converted to bis-(-2-methoxyphenyl) ether by catalytic hydrogenation. The ^{1}H NMR spectrum of dimethyl ether **14** contained two OMe signals at δ 3.82 (s, 3H) and 4.00 (s, 3H) and two *meta*-situated aromatic proton signals at 6.50 (d, 1 H, J = 2 Hz) and 7.41 (d, 1H, J = 2Hz). Thus the dimethyl ether **14** must have been derived from 2-(3',5'-dibromo-2'-hydroxyphenoxy)-3,4,5,6-tetrabromophenol (**9**).

The dimethyl ether **15** had the molecular formula $C_{14}H_9Br_5O_3$ and was also converted to bis-(2-methoxyphenyl) ether on catalytic hydrogenation. The ^{1}H NMR spectrum of dimethyl ether **15** contained two OMe signals at δ 3.81 (s, 3H) and 4.00 (s, 3H), two *meta*-situated aromatic proton signals at 6.50 (d, 1H, J = 2 Hz) and 7.41 (d, 1H, J = 2 Hz) and an aromatic proton signal at 7.73 (s, 1H). The chemical shifts of the *meta*-substituted proton signals were identical to those in dimethyl ether **14** indicating that one of the rings contained 2-methoxy-3,5-dibromophenyl ether substitution pattern and that the other ring contained a Br at the position *ortho* to the ether bridge. Acetylation of the mixture of phenols **8** and **9** gave a mixture of diacetates that contained an aromatic proton signal at δ 7.88 (s). The downfield shift of 0.37 ppm on acetylation suggested that the single proton on the pentasubstituted ring was *ortho* or, more likely, *para* to the phenolic OH group. Comparison of the chemical shift of the single proton (δ 7.51) with calculated values for protons *ortho* (δ 6.91) and *para* (δ 7.26) to the phenolic OH indicated that the diphenol **8** was 2 - (3',5' - dibromo - 2' - hydroxyphenoxy) - 3,5,6 - tribromophenol.

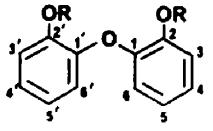
Because of the known severe toxicity of tetrachlorodioxin,[9] we decided to investigate the possibility that polybrominated dioxins could be produced by these sponges. Examination of tlc plates revealed that *D. chlorea* contained at least 10 compounds less polar than the phenol **3**. Dehydrobromination[10] of the phenol **3** gave 3,5,4'-tribromodibenzo-*p*-dioxin (**16**), a compound that we considered to be the most likely polybrominated dioxin present. Comparison of the dioxin **16** with less polar metabolites from *D. chlorea* by thin layer chromatography clearly showed that the dioxin **16** was not present in *D. chlorea*.

Our results differ in many ways from those of the previous study of the polybrominated 2-phenoxyphenol derivatives from *D. herbacea*.[3] Both studies found the pentabromo derivative **1** as the major metabolite of *D. herbacea* and the isomeric compound **2** as a minor metabolite but there the similarities end. We were able to identify two other sponges, *D. chlorea* and *P. foliascens* that could easily have been mistaken for *D. herbacea* in the field. However, we believe that the discovery of so many different metabolites from *D. herbacea* is in some way due to the presence of symbionts, presumably blue-green algae,[11] in the ectosome of the sponge.

Table 1. ^{1}H NMR chemical shift data for selected compounds



1-3, 6, 10-13



7-9, 14, 15

Compound	Solvent	Proton at Carbon Number								R
		3	4	5	6	3'	4'	5'	6'	
1	CCl_4	7.42	Br	Br	Br	7.76	Br	7.26	6.41	H
2	CCl_4	Br	Br	Br	7.05	7.79	Br	7.40	6.82	H
10	CCl_4	Br	Br	Br	7.17	7.77	Br	7.35	6.68	Me
11	CCl_4	Br	Br	Br	7.02	7.79	Br	7.42	6.90	Ac
3	CCl_4	Br	7.42	Br	6.82	7.78	Br	7.40	6.84	H
3	DMSO-d_6	Br	7.56	Br	6.97	7.98	Br	7.58	6.94	H
3	DMSO-d_6	Br	7.14	Br	6.79	7.73	Br	7.34	6.47	Na
13	CCl_4	Br	7.52	Br	6.86	7.79	Br	7.42	6.89	Ac
6	CCl_4	7.19	Br	7.32	Br	7.76	Br	7.26	6.43	H
6	DMSO-d_6	7.18	Br	7.42	Br	7.91	Br	7.43	6.47	H
6	DMSO-d_6	6.15	Br	6.28	Br	7.73	Br	7.33	6.42	Na
12	CCl_4	7.30	Br	7.68	Br	7.73	Br	7.23	6.38	Ac
7	$CDCl_3$	7.10	Br	7.42	Br	Br	7.35	Br	6.45	Me
8	$CDCl_3/CD_3OD$	Br	Br	7.51	Br	Br	7.37	Br	6.50	H
15	$CDCl_3$	Br	Br	7.73	Br	Br	7.41	Br	6.50	Me
9	$CDCl_3/CD_3OD$	Br	Br	Br	Br	Br	7.37	Br	6.50	H
14	$CDCl_3$	Br	Br	Br	Br	Br	7.41	Br	6.50	Me

EXPERIMENTAL

Collection and extraction procedures. All sponges were collected in shallow water (−2 to −4 ft) at Iwayama Bay, Palau. The samples of *Dysidea herbacea and Phyllospongia foliascens* were stored in methanol (1 L) and the sample of *D. chlorea* stored at −20°C for six months. For each of the samples stored in methanol, the solvent was decanted, the bottle refilled with methanol (1 L) and the solvent again decanted. The combined methanol extracts were evaporated to obtain an aqueous suspension that was extracted with dichloromethane (4 × 250 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent evaporated to obtain a green gum. Thus 280 g of *Dysidea herbacea* gave 13 g (4.64% dry weight) of crude extract while 30 g of *P. foliascens* gave 675 mg (2.25% dry weight) of crude extract.

The frozen sample of *Dysidea chlorea* was lyophilized to obtain 23 g of dry sponge. The dried sponge was Soxhlet extracted with dichloromethane (2 L) for 24 hr. Evaporation of the dichloromethane gave a green gum (2.3 g, 10% dry weight).

Chromatography of Dysidea herbacea *extract*: The extract (13 g) was chromatographed on a column (60 × 2.5 cm dia.) of silica gel using eluants of increasing polarity from hexane through ether to ethyl acetate. Fractions eluted with 25% ether in hexane contained a mixture of phenols that were separated by preparative LC on μ-porasil using 10% ether in hexane as eluant to obtain 2-(2',4'-dibromophenoxy)-3,4,5-tribromophenol (**1**, 3.6 g, 1.3% dry weight), 2-(2',4'-dibromophenoxy)-4,5,6-tribromophenol (**2**, 200 mg, 0.07% dry weight) and 2-(2',4'-dibromophenoxy)-3,5-dibromophenol (**6**, 150 mg, 0.05% dry weight).

2-(2',4'-*dibromophenoxy*)-4,5,6-*tribromophenol* (**2**): m.p. 138–140°, UV (MeOH) 307 nm (ϵ 2100), (MeOH + NaOH) 314 nm (ϵ 2200); IR ($CHCl_3$) 3550, 1465, 1375, 1270, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 5.89 (bs, -OH), 6.82 (d, 1H, J = 8Hz), 7.05 (s, 1H), 7.40 (dd, 1H, J = 8,2Hz), 7.79 (d, 1H, J = 2Hz); high-resolution mass measurement, obsd 581.6148, $C_{12}H_5O_2\,^{79}Br_2\,^{81}Br_3$ requires 581.6147.

2-(2',4'-*Dibromophenoxy*)-3,5-*dibromophenol* (**6**): m.p. 168–170°, UV (MeOH) 295 nm (ϵ 1600), (MeOH + NaOH) 305 nm (ϵ 1800); IR ($CHCl_3$) 3600, 1580, 1460, 1225, 1040, 920 cm^{-1}; ^1H NMR (CCl_4) δ5.51 (bs, -OH), 6.43 (d, 1 H, J = 8 Hz), 7.19 (d, 1 H, J = 2 Hz), 7.26 (dd, 1 H, J = 8,2 Hz), 7.32 (d, 1 H, J = 2 Hz), 7.76 (d, 1H, J = 2 Hz); (DMSO-d_6) δ 6.47 (d, 1H, J = 8 Hz), 7.18 (d, 1 H, J = 2 Hz), 7.42 (d, 1 H, J = 2 Hz), 7.43 (dd, 1 H, J = 8,2 Hz), 7.91 (d, 1H, J = 2 Hz); (DMSO-d_6 + NaOD)[7] δ 6.15 (d, 1H, J = 2 Hz), 6.28 (d, 1H, J = 2 Hz), 6.42 (d, 1H, J = 8 Hz), 7.33 (dd, 1H, J = 8,2 Hz), 7.73 (d, 1H, J = 2 Hz); high-resolution mass measurement, obsd 501.7079, $C_{12}H_6O_2\,^{79}Br_2\,^{81}Br_2$ requires 501.7061.

Chromatography of Dysidea chlorea *extract*: The extract (2.3 g) was chromatographed on a column (110 × 2.5 cm dia.) of silica gel using eluants of increasing polarity from hexane through ether to ethyl acetate. Material eluted with 25% ether in hexane was crystallized from ether/hexane to obtain **3** (1.3 g, 5.6% dry weight); m.p. 88–90°; UV (MeOH) 300 nm (ϵ 3650), (MeOH + NaOH) 317 nm (ϵ 4900); IR ($CHCl_3$) 3600, 1600, 1550, 1470, 1410, 1230, 1050, 925 cm^{-1}; ^1H NMR (CCl_4) δ 5.73 (bs, -OH), 6.82 (d, 1 H, J = 2 Hz), 6.84 (d, 1 H, J = 8 Hz), 7.40 (dd, 1 H, J = 8,2 Hz), 7.42 (d, 1 H, J = 2 Hz), 7.78 (d, 1 H, J = 2 Hz); (DMSO-d_6) δ 6.94 (d, 1H, J = 8 Hz), 6.97 (d, 1H, J = 2 Hz), 7.56 (d, 1H, J = 2 Hz), 7.58 (dd, 1 H, J = 8,2 Hz), 7.98 (d, 1 H, J = 2 Hz); (DMSO-d_6 + NaOD) δ 6.47 (d, 1H, J = 8 Hz), 6.79 (d, 1H, J = 2 Hz), 7.14 (d, 1 H, J = 2 Hz), 7.34 (dd, 1 H, J = 8,2 Hz), 7.73 (d, 1H, J = 2 Hz); high resolution mass measurement obsd 501.7069, $C_{12}H_6O_2\,^{79}Br_2\,^{81}Br$ requires 501.7061.

Chromatography of phyllospongia foliascens *extract*: The extract (675 mg) was chromatographed on a column (110 × 2.5 cm dia.) of Sephadex LH-20 using MeOH as eluant. Fractions were screened for antimicrobial activity against *Staphyllococcus aureus*. The combined active fractions were evaporated to a gum (300 mg) that was rechromatographed on a column (60 × 2.5 cm dia.) of silica gel using eluants of increasing polarity from hexane through ether to ethyl acetate. The material eluted with 20% ether in hexane was **7** (30 mg, 0.1% dry weight) while the material eluted with ether contained a 1:2 mixture (120 mg, 0.4% dry weight) of **8** and **9**.

2-(3',5'-*Dibromo*-2'-*methoxyphenoxy*)-3,5-*dibromoanisole* (**7**): m.p. 86–88°; UV (MeOH) 215 nm (ϵ 10,000); IR ($CHCl_3$) 1575, 1470, 1340, 1215, 1040, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.00 (s, 3H), 6.45 (d, 1 H, J = 2 Hz), 7.10 (d, 1 H, J = 2 Hz), 7.35 (d, 1H, J = 2 Hz), 7.42 (d, 1H, J = 2 Hz); high-resolution mass measurement, obsd 545.7343, $C_{14}H_{10}O_3\,^{79}Br_2\,^{81}Br_2$ requires 545.7322.

A soln of the 1:2 mixture of **8** and **9** (60 mg) andMeI (1.0 mL) in dry acetone (10 mL) containing anhyd K_2CO_3 (250 mg) was stirred at 80° for 10 hr. The solvent was evaporated under vacuum and the residue partitioned between water (10 mL) and CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with water (2 × 10 mL), dried over Na_2SO_4 and evaporated to obtain a green oil (70 mg). Chromatography of the oil on a column (20 × 1.0 cm dia.) of silica gel using 10% ether in hexane as eluant gave a 2:1 mixture (55 mg) of **14** and **15** that were separated by LC on μ-porasil using 1% ether in hexane as eluant.

2-(3',5'-*Dibromo*-2'-*methoxyphenoxy*)-3,4,5,6-*tetrabromoanisole* (**14**): m.p. 160–162°; UV (MeOH) 221 nm (ϵ 9000); ^1H NMR ($CDCl_3$) δ 3.82 (s 3 H), 4.00 (s, 3 H) 6.50 (d, 1 H, J = 2 Hz) 7.41 (d, 1 H, J = 2 Hz); high-resolution mass measurement, obsd 703.5507, $C_{14}H_8O_3\,^{79}Br_3\,^{81}Br_3$ requires 703.5512.

2-(3',5'-*Dibromo*-2'-*methoxyphenoxy*)-3,5,6-*tribromoanisole* (**15**): oil; UV (MeOH) 221 nm (ϵ 9000); ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.00 (s, 3H), 6.50 (d, 1H, J = 2 Hz), 7.41 (d, 1H, J = 2 Hz), 7.73 (s, 1H); high-resolution mass measurement, obsd 623.6416, $C_{14}H_9O_3\,^{79}Br_3\,^{81}Br_2$ requires 623.6428.

1:2 *Mixture of phenols* **8** *and* **9**: UV (MeOH) 305 nm, (MeOH + NaOH) 317 nm; IR ($CHCl_3$) 3500–3600, 1515, 1470, 925 cm^{-1}; ^1H NMR ($CDCl_3$–MeOH-d_4) δ 6.50 (m, ~3 H); 7.37 (m, ~3 H), 7.51 (s, 1 H).

Preparation of methyl ethers: A soln of the phenol (~0.1 mmol) and MeI (1 mL) in dry acetone (10 mL) containing anhyds K_2CO_3 (500 mg) was stirred at 80° for 12 hr. The solvent was evaporated and the residue partitioned between water (10 mL) and CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water (2 × 10 mL), dried over $NaSO_4$ and the solvent evaporated to obtain the corresponding methyl ether in ~90% yield.

Hydrogenation of methyl ethers: A soln of the methyl ether (0.02–0.05 mmol) in MeOH (10 mL) containing 10% Pd–C (2 mg) was stirred at 25° under H_2 for 4–6 days. The catalyst was removed by filtration and the solvent evaporated under vacuum to obtain the debrominated product in quantitative yield.

Using the procedures above, phenols **1**,**2**, **3** and **6** were converted into 2-phenoxyanisole; m.p. 76–68°; UV (MeOH) 213 nm (ϵ 9600); ^1H NM,R (CCl_4) δ 3.77 (s, 3H), 6.75–7.25 (m, 9H).

Methyl ethers **7**, **14** and **15** were hydrogenated to obtain bis-(2-methoxyphenyl) ether, m.p. 77–79°, identical in all respects to a sample prepared by the method of Kime and Norymberski.[8]

Preparation of phenyl acetates: A soln of of the phenol (0.02–0.1 mmol) in Ac_2O (0.5 mL) and pyridine (1 mL) was stirred at 25° for 12 hr. Evaporation of the solvents gave the phenyl acetates that could be purified by filtration through a short plug of silica gel in ether.

Acetate **11**: m.p. 139–141°; UV (MeOH) 220 nm; IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (CCl_4) δ 2.30 (s, 3H), 6.90 (d, 1H, J = 8 Hz), 7.02 (s, 1H), 7.42 (dd, 1H, J = 8,2 Hz), 7.79 (d, 1H, J = 2 Hz).

Acetate **12**: m.p. 108–110°; ^1H NMR (CCl_4) δ 2.07 (s, 3H), 6.38 (d, 1H, J = 8 Hz), 7.23 (dd, 1H, J = 8,2 Hz), 7.30 (d, 1H, J = 2 Hz), 7.68 (d, 1 H, J = 2 Hz), 7.73 (d, 1H, J = 2 Hz).

Acetate **13**: m.p. 118–119°C; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 6.86 (d, 1H, J = 2 Hz), 6.89 (d, 1 H, J = 8 Hz), 7.42 (dd, 1 H, J = 8,2 Hz), 7.52 (d, 1H, J = 2 Hz), 7.79 (d, 1H, J = 2 Hz).

3,5,4'-*Tribromodibenzo*-p-*dioxin* (**16**): The phenol **3** (84 mg, 0.17 mmol) was added to NaOMe (10 mg, 0.18 mmol) in dry benzene (10 mL) and the soln was distilled to dryness under N_2. Cuprous chloride (15 mg) and dry pyridine (10 mL) were added and the soln was refluxed under dry N_2 for 12 hr. The product was partitioned between water (50 mL) and ether (3 × 20 mL). The combined ether extracts were washed with 1 N NaOH (20 mL), then water (20 mL), dried over Na_2SO_4 and the solvents evaporated under high vacuum to obtain the *p*-dioxin **16** (56 mg, 80% theoretical): m.p. 163–165°; UV (MeOH) 238 nm (ϵ 9300); IR

($CHCl_3$) 1580, 1480, 1440, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.73 (d, 1H, J = 8 Hz), 6.95 (d, 1H, J = 2 Hz), 7.06 (dd, 1H J = 8,2 Hz), 7.13 (d, 1H, J = 2 Hz), 7.28 (d, 1H, J = 2 Hz).

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