Halogenation of Phenols and Phenyl Ethers with Potassium Halides in the Presence of 18-Crown-6 on Oxidation with *m*-Chloroperbenzoic Acid

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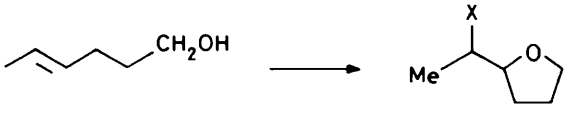
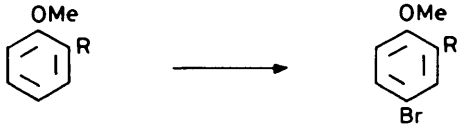
Several types of phenyl ethers have been monobrominated in the ring in good yields with potassium bromide in the presence of 18-crown-6 on oxidation with *m*-chloroperbenzoic acid. Monoiodination takes place with both phenyl ethers and free phenols when potassium iodide is employed.

We recently reported [1] that oxidation of halogen salts (sodium or potassium chlorides, bromides, or iodides) with *m*-chloroperbenzoic acid (MCPBA) in the presence of both 18-crown-6 and suitable hydroxy or carboxy alkenes led, in high yield, to production of cyclic halogeno ethers or halogeno lactones. We assumed that the halide anion was oxidized by the peroxy acid to afford a positive halogen species (possibly forming an acyl hypohalite) which attacked the double bond leading to a halonium ion; anticyclization led to cyclic ethers or lactones. We suggested that the ready formation of a positive halogen species could make possible the introduction of various new synthetic methodologies.



X = Br, I, Cl

We report now that the same reagent system may be used to prepare monohalogenated phenyl ethers as well as monoiodophenols.[2a] This reaction represents a laboratory equivalent to the biological halogenation of phenolic compounds which takes place by oxidation of halide ions by peroxidases in the presence of hydrogen peroxide, followed by halogenation by the newly formed halogen species.[2b]

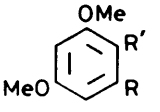


(1) R = H (2) R = H
(3) R = Ac (4) R = Ac

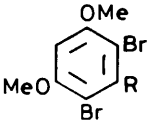
Simple phenol ethers undergo monobromination under the convenient standard conditions of the reaction with potassium bromide–18-crown-6–MCPBA (see Experimental section). Anisole (**1**) gave 4-bromoanisole (**2**) in 87% yield; 2′-methoxyacetophenone (**3**) produced 5′-bromo-2′-methoxyacetophenone (**4**) in 80% yield (Table 1).

The next group of compounds we investigated was the resorcinol dialkyl ethers. Resorcinol dimethyl ether (**5**) gave essentially one compound, 1-bromo-2,4-dimethoxybenzene (**6**) in 80% yield. By comparison, standard bromination of compound (**5**) with bromine (1 equiv.) in carbon tetrachloride led to the bromide (**6**) in 60% yield, in addition to a considerable amount of starting material. Excess of bromine (1.5 equiv.) in carbon tetrachloride gave bromide (**6**) in only 30%; 1,5-dibromo-2,4-dimethoxybenzene (**19**) was obtained in 54% yield.

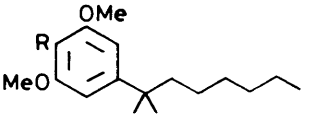
Olivetol dimethyl ether (**9**) presented a similar picture. Our reagent produced 2-bromo-1,5-dimethoxy-3-pentylbenzene (**10**) in 82% yield with traces of the 2,4-dibromo compound (**20**). Comparative bromination with bromine in carbon tetrachloride gave a mixture of the mono- and di-bromo derivatives (in the ratio 1:2). The bromination of 1-(1,1-dimethylheptyl)-3,5-dimethoxybenzene (**13**) presented a different picture. While the



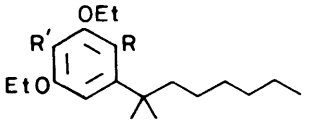
(5) R = R′ = H
(6) R = H, R′ = Br
(7) R = Me, R′ = H
(8) R = Me, R′ = Br
(9) R = C_5H_{11}, R′ = H
(10) R = C_5H_{11}, R′ = Br
(11) R = Ac, R′ = H
(12) R = Ac, R′ = Br
(13) R = DMH, R′ = H
(14) R = DMH, R′ = Br
(15) R = H, R′ = Cl
(16) R = H, R′ = I
(17) R = Me, R′ = I
(18) R = C_5H_{11}, R′ = I



(19) R = H
(20) R = C_5H_{11}



(21) R = Br
(22) R = I



(23) R = R′ = H
(24) R = Br, R′ = H
(25) R = H, R′ = Br

DMH = $-CMe_2C_6H_{13}$

potassium bromide–18-crown-6–MCPBA reagent gave the expected 2-bromo derivative (**14**), bromination with bromine led to the 4-bromo derivative (**21**). The same observation was made with 1-(1,1-dimethylheptyl)-3,5-diethoxybenzene (**23**). Our reagent produced the 2-bromo product (**24**) exclusively; bromine gave the 4-bromo product (**25**). Additional bromination examples are presented in Table 1. A comparison between the two types of bromination is given in Table 2.

The potassium bromide–18-crown-6–MCPBA reaction with free phenols is not practical under our conditions. Low yields and complicated mixtures were obtained. In only one case were we able to obtain satisfactory results: cannabidiol (**26**), a hashish constituent, gave monobromocannabidiol (**27**) in 45% yield.

Table 1. Halogenation of phenyl ethers with potassium halide–18-crown-6–MCPBA[a]

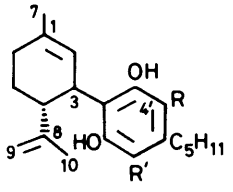
Starting material	Salt used	Product (% yield)	Ref. to product (% yield)
(1)	KBr	(2) (87%)	*, 4
(3)	KBr	(4) (80%)	5 (34%)
(5)	KBr	(6) (80%)	6 (see also text)
(7)	KBr	(8) (78%)	7
(9)	KBr	(10) (82%)	8 (see also text)
(11)	KBr	(12) (65%)[b]	
(13)	KBr	(14) (75%)[c]	
(5)	KCl	(15) (65%)[c]	*, 9
(5)	KI	(16) (80%)[d]	10 (46% before crystallization)
(7)	KI	(17) (70%)[d]	11 (72%)
(9)	KI	(18) (85%)[d]	12 (67%, together with 16% di-iodo derivative)
(13)	KI	(22) (80%)[d]	
(23)	KBr	(24) (84%)	

* Indicates commercially available material. [a] Standard halogenation conditions (see Experimental section except where otherwise indicated). [b] MCPBA (1.5 equiv.) used. [c] At room temperature, slow addition of MCPBA. [d] $CuCl_2$ (1 equiv.) and MCPBA (2.5 equiv.) used.

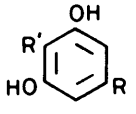
Table 2. Comparison of brominations: Br_2 in CCl_4 *versus* KBr–18-crown-6–MCPBA

Starting material	Reaction with Br_2–CCl_4[a] product(s) (% yield)	Reaction with KBr–18-crown-6–MCPBA product(s) (% yield)
(5)	(6) (60%) (5) (30% recovery)	(6) (80%)
(5)	[Reaction with Br_2 (1.5 equiv.)] (19) (54%) and (16) (30%)	
(9)	(10) (20%) (20) (40%)	(10) (82%)
(13)	(21) (85%)	(14) (75%)
(23)	(25) (85%)	(24) (84%)

[a] (1 equiv.) except when otherwise indicated.



(26) R = R′ = H
(27) R = Br, R′ = H
(34) R = I, R′ = H
(35) R = R′ = I



(28) R = Me, R′ = H
(29) R = Me, R′ = I
(30) R = C_5H_{11}, R′ = H
(31) R = C_5H_{11}, R′ = I
(32) R = DMH, R′ = H
(33) R = DMH, R′ = I

Few reagents are available for the monoiodination of phenols or alkyl phenols.[2] Hence we investigated this reaction using potassium iodide–18-crown-6–MCPBA. The reaction proved to be sluggish. However, addition of $CuCl_2$ increased the rate. Contrary to the bromination reaction which is synthetically practicable with phenyl ethers, but not with free phenols, the iodination reaction takes place with both types of compounds (Tables 1 and 3). With phenyl ethers the yields are generally

Table 3. Halogenation of phenols with potassium halide–18-crown-6–MCPBA

Starting material	Salt used	Product (% yield)
(28)	KI	(29) (55%)
(30)	KI	(31) (82%)
(32)	KI	(33) (87%)
(26)	KI	(34) (55%)
(26)	KI	(35) (75%)[a]
(26)	KBr	(27) (45%)

[a] Triethylamine (2 equiv.) added before addition of MCPBA

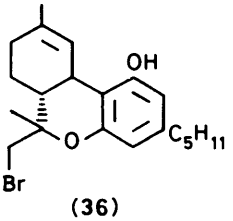
excellent (*ca.* 80%); with free phenols the yields are lower (50–80%). The regiospecificity observed on bromination of phenyl ethers (see above) is not strictly followed on iodination. While iodination of the resorcinol dialkyl ethers (**5**), (**7**), and (**9**) gave the expected 2-iodo derivatives (**16**), (**17**), and (**18**) respectively, the bulky dimethylheptyl substituent in compound (**13**) apparently made iodination on C-2 too difficult; instead, iodination of compound (**13**) proceeded exclusively at C-4 to give the iodide (**22**).

The number of examples of iodination of *free* phenols investigated by us is not extensive enough to allow us to make a generalization as regards regiospecificity. It is obvious that it differs from the iodination of resorcinol ethers where iodination at C-4 was observed in most cases examined (see above). With free resorcinols [*e.g.* (**28**), (**30**), and (**32**)] iodination took place at C-2 exclusively [forming compounds (**29**), (**31**), and (**33**)] (Table 3).

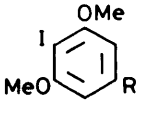
Under the standard conditions employed by us only monoiodination was noted. Thus cannabidiol (**26**) gave only monoiodocannabidiol (**34**). However, when we added triethylamine (2 equiv.) to the reaction mixture before the oxidation with MCPBA, the di-iodo compound (**35**) was obtained.

We have, so far, investigated only one case of chlorination with potassium chloride–18-crown-6-MCPBA. Resorcinol dimethyl ether (**5**) gave the 4-chloro derivatives (**15**) albeit in a lower yield (65%) than that observed in the bromination and iodination reactions (75 and 80% respectively) (Table 1).

Cannabidiol (**26**) is a compound in which halogenation with the potassium halide–18-crown-6–MCPBA reagents can *a priori* lead to either halogenocyclic ethers [for example (**36**)] or to aromatic halides. We observed the latter reaction only (see above). Apparently attack on the aromatic ring is preferred to one on olefins (at least for the two types of olefins present in cannabidiol). The aromatic ring is also preferentially halogenated, as compared with benzylic groups [*cf.* substrates (**7**), (**9**)], allylic groups [*cf.* cannabidiol (**26**)] or acetyl groups [*cf.* substrates (**3**), (**11**)].



(36)



(37) R = Me
(38) R = C_5H_{11}

The structure of the reaction products, many of which have previously been reported (see Experimental section), was established on the basis of their mass and n.m.r. spectra. In the resorcinol series halogenation at C-2 gives compounds with two magnetically equivalent protons; halogenation at C-4 leads to compounds with two non-equivalent protons. In some cases

simple derivatives were prepared in order to give support to the proposed structures. Thus the iodoresorcinols (**29**) and (**31**) were converted into the iodo dimethyl ethers (**37**) and (**38**). The n.m.r. spectra (equivalent methyl groups and aromatic protons) established the position of the iodine atom.

We have made some observations which throw additional light on the pathway through which the new reagent reacts, although the mechanism of the reaction is not yet established. Thus one can assume that on oxidation of bromide, a Br^+ species is formed which, with the excess of bromide in the reaction mixture, may give molecular bromine. Crown ethers are known to form complexes with molecular bromine.[3] We have now treated ethers (**13**) and (**23**) with bromine–18-crown-6 in methylene dichloride. Bromination took place exclusively at C-2 (resorcinol numbering) leading to compounds (**21**) and (**25**); as mentioned above the parallel reaction with potassium bromide–18-crown-6–MCPBA led to C-4 (resorcinol numbering) bromination [compounds (**14**) and (**24**)]. We conclude that molecular bromine–18-crown-6 is not the reactive species.

In summary, we have described a new halogenation reagent which is easy to handle and which has certain advantages over the existing ones used in halogenation of phenyl ethers and iodination of free phenols, in particular as regards monohalogenation, regiospecificity and, in most cases, yields.

Experimental

Unless otherwise stated the following apply. Mass spectra were recorded on a LKB 2091 Gas Chromatograph–Mass Spectrometer at 70 eV. I.r. spectra were recorded as thin films (for oils) and in Nujol mulls or in KBr discs (for solids) on a Perkin-Elmer grating infrared spectrophotometer, model 457. U.v. spectra were taken for solutions in ethanol on a Varian u.v.–vis spectrophotometer, model 635. ^1H N.m.r. spectra were determined at 60 MHz on a Bruker W.P. 60 or at 300 MHz on a Brucker W.H. 300 instrument. M.p.s are uncorrected and were measured in closed capillaries in a Thomas-Hoover instrument. Column chromatography was performed by medium-pressure liquid chromatography (m.p.l.c.) with an FMI pump on Merck Kieselgel 60, 230—400 mesh ASTI, with mixtures of diethyl ether (ether) and light petroleum (b.p. 60—80 °C) in the ratios 2:98 or 5:95.

General Halogenation Procedure.—A suspension prepared from the potassium halide (50 mmol), 18-crown-6 (264 mg, 1 mmol), and the aromatic compound (10 mmol) in methylene dichloride (35 ml) was stirred well at room temperature. It was then cooled to 0 °C and, while being stirred, was treated with a solution of 80% MCPBA (2.59 g, 12 mmol) (Aldrich) in CH_2Cl_2 (20 ml) during 5 min. The reaction mixture was vigorously stirred for an additional 15 min and then ether (70 ml) was added. The solution was washed successively with a 10% aqueous reducing solution [sodium hydrogen sulphite or pyrosulphite ($Na_2S_2O_5$)], saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, and was then dried ($MgSO_4$) and evaporated. The reaction products were chromatographed by m.p.l.c.

Starting Materials.—Anisole(**1**),2′-methoxyacetophenone(**3**), orcinol (**28**), olivetol (**30**), and olivetol dimethyl ether (**9**) were purchased from Fluka. Resorcinol dimethyl ether (**5**), orcinol dimethyl ether (**7**), and 3′,5′-dimethoxyacetophenone (**11**) were prepared by the standard etherification procedure described below for the preparation of 2-iodo-1,3-dimethoxy-5-methylbenzene (**37**). 1-(1,1-Dimethylheptyl)-3,5-dimethoxybenzene (**13**) and 5-(1,1-dimethylheptyl)resorcinol (**32**) were prepared according to a published procedure.[13] Cannabidiol (**26**) was isolated from hashish.[14] N.m.r. assignments of aromatic protons were made by comparison with values calculated according to ref. 15.

4-Bromoanisole (**2**).*[4] $\delta(CDCl_3)$ 3.76 (3 H, s, Me), 6.76 (2 H, d, *J* 9.2 Hz, 2- and 6-H), and 7.37 (2 H, d, *J* 9.2 Hz, 3- and 5-H).

5′-Bromo-2′-methoxyacetophenone (**4**).[5] $\delta(CDCl_3)$ 2.58 (3 H, s, Ac), 3.89 (3 H, s, OMe), 6.84 (1 H, d, *J* 8.8 Hz, 3′-H), 7.52 (1 H, dd, *J* 8.8, 2.6 Hz, 4′-H), and 7.81 (1 H, d, *J* 2.6 Hz, 6′-H); *m/z* 230 (35%), 228 [M^+ (Br^{79}), 35], 215 (90), and 213 (100) [lit.,[5a] $\delta(CCl_4)$ 2.53 (Ac), 3.90 (OMe), 6.82 (3′-H), 7.47 (4′-H), and 7.72 (6′-H)].

1-Bromo-2,4-dimethoxybenzene (**6**).*[6] $\delta(CDCl_3)$ 3.77 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.39 (1 H, dd, *J* 9.0, 3.0 Hz, 5-H), 6.48 (1 H, d, *J* 3.0 Hz, 3-H), and 7.37 (1 H, d, *J* 9.0 Hz, 6-H) [identical with a spectrum of a commercial sample of compound (**6**) published in ref. 16]; *m/z* 218 (100%) and 216 [M^+ (Br^{79}), 100].

2-Bromo-1,5-dimethoxy-3-methylbenzene (**8**).[7] M.p. 55—56 °C; $\delta(CDCl_3)$ 2.36 (3 H, s, ArMe), 3.76 (3 H, s, OMe), 3.82 (3 H, s, OMe), 6.31 (1 H, d, *J* 3.0 Hz, 6-H), and 6.39 (1 H, d, *J* 3.0 Hz, 4-H); *m/z* 232 (100%) and 230 [M^+ (Br^{79}), 100] (lit.,[7] m.p. 53.5—54.5 °C).

2-Bromo-1,5-dimethoxy-3-pentylbenzene (**10**).[8] $\delta(CDCl_3)$ 0.90 (3 H, t, ω-H_3), 2.72 (2 H, t, benzylic H), 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), and 6.36 (2 H, br s, 4- and 6-H); *m/z* 288 (30%), 286 (30), 232 (48), 230 (48), 207 (28), and 151 (100), (lit.,[8] oil, no physical constants).

2′-Bromo-3′,5′-dimethoxyacetophenone (**12**). M.p. 103—104 °C (from ethanol); $\delta(CDCl_3)$ 2.61 (3 H, s, Ac), 3.81 (3 H, s, OMe), 3.88 (3 H, s, OMe), 6.46 (1 H, d, *J* 3.0 Hz, 4′-H), and 6.54 (1 H, d, *J* 3.0 Hz, 6′-H); *m/z* 260 (88%), 258 [M^+ (Br^{79}), 88], 245 (100), and 243 (100) (Found: C, 46.1; H, 4.4; Br, 31.35. $C_{10}H_{11}BrO_3$ requires C, 46.33; H, 4.24; Br, 30.88%).

2-Bromo-1-(1,1-dimethylheptyl)-3,5-dimethoxybenzene (**14**). $\delta(CDCl_3)$ 0.89 (3 H, t, ω-H_3), 1.19 (6 H, s, CMe_2), 3.80 (3 H, s, OMe), 3.87 (3, H, s, OMe) 6.40 (1 H, d, *J* 3.0 Hz, 4-H), and 6.60 (1 H, d, *J* 3.0 Hz, 6-H); *m/z* 344 (87%) and 342 [M^+ (Br^{79}), 87%] (Found: C, 60.0; H, 8.2. $C_{17}H_{27}BrO_2$ requires C, 59.47; H, 7.87%).

1-Chloro-2,4-dimethoxybenzene (**15**).*[9] The preparation of this compound was carried out according to the general procedure described above, except that it was performed at room temperature with addition of MCPBA during 30 min. The reaction mixture was then stirred for 3 h and worked up as described above to give an oil, $\delta(CDCl_3)$ 3.79 (3 H, s, OMe), 3.87 (3, H, s, OMe), 6.39 (1 H, dd, *J* 8.0, 3.0 Hz, 5-H), 6.52 (1 H, d, *J* 3.0 Hz, 3-H), and 7.20 (1 H, d, *J* 8.0 Hz, 6-H); *m/z* 174 (30%) and 172 [M^+ (Cl^{35}), 30].

1-Iodo-2,4-dimethoxybenzene (**16**).[10] The preparation of this compound was carried out according to the general procedure; however, $CuCl_2$ (1 equiv.) was added to the reaction mixture, which was then vigorously stirred for 15 min, and MCPBA (2.5 equiv.) was added. The reaction was then continued and the mixture worked up as before to give the iodide (**16**), m.p. 41 °C; $\delta(CDCl_3)$ 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.26 (1 H, dd, *J* 8.0, 3.0 Hz, 5-H), 6.40 (1 H, d, *J* 3.0 Hz, 3-H), and 7.58 (1 H, d, *J* 8.0 Hz, 6-H); *m/z* 264 (M^+, 100) (lit.,[10] m.p. 40—41 °C).

2-Iodo-1,5-dimethoxy-3-methylbenzene (**17**).[11] Prepared in a similar way to that described for compound (**16**), m.p. 83—85 °C; $\delta(CDCl_3)$ 2.44 (3 H, s, Ar*Me*), 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.26 (1 H, d, *J* 3.0 Hz, 6-H), and 6.45 (1 H, d, *J* 3.0 Hz, 4-H); *m/z* 278 (M^+, 100%) (lit.,[11] m.p. 84—86 °C).

2-Iodo-1,5-dimethoxy-3-pentylbenzene (**18**).[12] Prepared in a similar way to that described for compound (**16**), $\delta(CDCl_3)$ 0.93 (3 H, t, ω-H_3), 2.73 (2 H, t, *J* 6.8 Hz, ArCH_2), 3.80 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.28 (1 H, d, *J* 2.0 Hz, 6-H), and 6.45 (1 H, d, *J*

* Indicates compound is available commercially.

2.0 Hz, 4-H); *m/z* 334 (M^+, 100%) (lit.,[12] identical n.m.r. and mass spectra).

5-(1,1-Dimethylheptyl)-2-iodo-1,3-dimethoxybenzene (**22**). Prepared similarly to compound (**16**). Obtained as an oil, δ($CDCl_3$) 0.89 (3 H, t, *J* 6.0 Hz, ω-H_3), 1.29 (6 H, s, aliphatic Me), 3.88 (6 H, s, 2 OMe), and 6.47 (2 H, s, 4- and 6-H); *m/z* 390 (M^+, 60%), 376 (2), 348 (6), 334 (8), 320 (7), 305 (100), 291 (11), and 277 (9).

2-*Bromo*-1-(1,1-*dimethylheptyl*)-3,5-*diethoxybenzene* (**24**). Under the standard reaction conditions this compound was obtained in 84% yield as crystals, m.p. 62—63 °C (from cold pentane); δ($CDCl_3$) 0.92 (3 H, t, *J* 6.0 Hz, ω-H_3), 1.45 (6 H, s, CMe_2), 1.58 (6 H, t, *J* 7.0 Hz, OCH_2Me), 4.05 (2 H, q, *J* 6.0 Hz, OCH_2), 4.03 (2 H, q, *J* 6.0 Hz, OCH_2), 6.37 (1 H, d, *J* 3.0 Hz, 4-H), and 6.58 (1 H, d, *J* 3.0 Hz, 6-H); *m/z* 372 (10%), 370 [M^+ (Br^{79}), 10], and 208 (100) (Found: C, 62.0; H, 8.6. $C_{19}H_{31}BrO_2$ requires C, 61.45; H, 8.35%).

1,3-*Dihydroxy*-2-*iodo*-5-*methylbenzene* (**29**). M.p. 113—114 °C (from pentane); δ($CDCl_3$) 2.25 (3 H, s, Me), 5.28 (2 H, s, OH), and 6.39 (2 H, s, 4- and 6-H); *m/z* 250 (M^+, 100%), 232 (11), 221 (3), and 123 (8) (Found: C, 33.7; H, 2.8. $C_7H_7IO_2$ requires C, 33.60; H, 2.80%).

1,3-*Dihydroxy*-2-*iodo*-5-*pentylbenzene* (**31**). M.p. 68—69 °C (from cold pentane); δ($CDCl_3$) 0.88 (3 H, t, *J* 6.2 Hz, ω-H_3), 2.50 (2 H, t, ArCH_2), 5.28 (2 H, s, OH), and 6.42 (2 H, s, 4- and 6-H); *m/z* 306 (M^+, 31%), 263 (13), and 249 (100) (Found: C, 43.2: H, 4.9. $C_{11}H_{15}IO_2$ requires C, 43.13; H, 4.90%).

5-(1,1-*Dimethylheptyl*)-1,3-*dihydroxy*-2-*iodobenzene* (**33**). δ($CDCl_3$) 0.87 (3 H, t, 5.0 Hz, ω-H_3), 1.21 (6 H, s, CMe_2), 5.37 (2 H, s, OH), and 6.55 (2 H, s, 4- and 6-H); *m/z* 362 (M^+, 29%), 350 (11), 306 (11), 292 (16), 273 (95), 272 (100), 263 (16), 249 (19), and 150 (39) (Found: C, 50.4; H, 6.7; I, 34.9. $C_{15}H_{23}IO_2$ requires C, 49.72; H, 6.35; I, 35.08%).

Methylation of compound (**33**), following the procedure described for the preparation of compound (**37**) (see below), gave compound (**22**) in 92% yield. Compound (**22**) thus prepared was identical (t.l.c., i.r., n.m.r.) with a sample prepared by iodination of compound (**13**) (see above).

4′-Iodocannabidiol (**34**). δ($CDCl_3$) 0.90 (3 H, t, *J* 6.0 Hz, ω-H_3), 1.67 (3 H, s, 7- or 10-H_3), 1.78 (3 H, s, 10- or 7-H_3), 2.60 (2 H, t, *J* 7.0 Hz, ArCH_2), 3.95 (1 H, m, 3-H), 4.43 (1 H, br s, 9-H), 4.56 (1 H, br s, 9-H), 5.52 (1 H, br s, 2-H), and 6.36 (1 H, s, 6′-H); *m/z* 439 ($M^+ - 1$, 19%), 424 (2), 371 (21), and 356 (100).

Acetylation of compound (**34**) with an excess of acetic anhydride in pyridine (ratio 1:10) at room temperature overnight gave the diacetate of compound (**34**) in quantitative yield, $[\alpha]_D$ −83°; $\lambda_{max.}$ 272sh nm (ε 802); δ($CDCl_3$) 0.90 (3 H, t, *J* 5.1 Hz, ω-H_3), 1.59 (3 H, s, 7- or 10-H_3), 1.66 (3 H, s, 10- or 7-H_3), 2.20 (6 H, s, OAc), 2.71 (2 H, t, *J* 8.0 Hz, ArCH_2), 3.48 (1 H, m, 3-H), 4.46 (1 H, br s, 9-H), 4.55 (1 H, br s, 9-H), 5.17 (1 H, br s, 2-H), and 7.05 (1 H, s, 6′-H); *m/z* 522 ($M^+ - 2$, 50%), 480 (36), 479 (64), 438 (21), 413 (57), 371 (32), and 356 (100).

4′,6′-Di-iodocannabidiol (**35**). This compound was prepared according to the general procedure described above; however, triethylamine (2 equiv.) was added to the reaction mixture before the addition of MCPBA (2 equiv.). Compound (**35**) was obtained as an oil, δ($CDCl_3$) 0.94 (3 H, t, *J* 4.4 Hz, ω-H_3), 1.47 (3 H, s, 7- or 10-H_3), 1.78 (3 H, s, 10- or 7-H_3), 3.03 (2 H, t, *J* 7.0 Hz, ArCH_2), 4.07 (1 H, m, 3-H), 4.39 (1 H, d, 9-H), 4.53 (1 H, m, 9-H), and 5.49 (1 H, br s, 2-H); *m/z* 565 ($M^+ - 1$, 28%), 513 (3), 498 (22), and 483 (100).

4′-*Bromocannabidiol* (**27**). δ($CDCl_3$) 0.89 (3 H, t, *J* 5.1 Hz, ω-H_3), 1.69 (3 H, s, 7- or 10-H_3), 1.79 (3 H, s, 10- or 7-H_3), 2.61 (2 H, t, *J* 7.0 Hz, ArCH_2), 3.97 (1 H, m, 3-H), 4.42 (1 H, br s, 9-H), 4.53 (1 H, m, 9-H), 5.54 (1 H, br s, 2-H), and 6.33 (1 H, s, 6′-H); *m/z* 394 (12%), 392 [M^+ (Br^{79}), 12], 326 (20), 324 (20), 311 (100), and 309 (100) (Found: C, 63.7; H, 7.5. $C_{21}H_{29}BrO_2$ requires C, 64.12; H, 7.38%).

Acetylation of compound (**27**) with an excess of acetic anhydride in pyridine (ratio 1:10) at room temperature overnight gave the diacetate of compound (**26**) in quantitative yield, $[\alpha]_D$ −84°; $\lambda_{max.}$ 268 (ε 400) and 273sh nm (300); $\nu_{max.}$ 1 770 cm^{-1}; δ($CDCl_3$) 0.89 (3 H, t, *J* 5.0 Hz, ω-H_3), 1.59 (3 H, s, 7- or 10-H_3), 1.66 (3 H, s, 10- or 7-H_3), 2.21 (3 H, s, OAc), 2.25 (3 H, s, OAc), 2.71 (2 H, t, ArCH_2), 3.46 (1 H, m, 3-H), 4.46 and 4.54 (2 H, m, 9-H_2), 5.15 (1 H, s, 2-H), and 6.81 (1 H, s, 6′-H); *m/z* 478 (20%), 476 [M^+ (Br^{79}), 20], 435 (33), 366 (40), 326 (27), 324 (27), 311 (73), and 309 (100).

Methylation of 1,3-*Dihydroxy*-2-*iodo*-5-*methylbenzene* (**29**).—Compound (**29**) (250 mg, 1 mmol) was dissolved in dimethylformamide (5 ml). Potassium carbonate (250 mg) and methyl iodide (426 mg, 3 mmol) were added. The reaction mixture was stirred under nitrogen for 3 h. Water was added and the organic layer was dried ($MgSO_4$) and evaporated to give 2-iodo-1,3-dimethoxy-5-methylbenzene (**37**) (264 mg, 95%), m.p. 96—97 °C; δ($CDCl_3$) 2.35 (3 H, s, Ar*Me*), 3.87 (6 H, s, OMe), and 6.34 (2 H, s, 4- and 6-H); *m/z* 278 (M^+, 100%) (lit.,[17] m.p. 96—97 °C).

Methylation of 1,3-*Dihydroxy*-2-*iodo*-5-*pentylbenzene* (**31**).—This reaction followed the procedure described for the methylation of compound (**29**) (see above). 2-*Iodo*-1,3-*dimethoxy*-5-*pentylbenzene* (**38**) thus obtained in quantitative yield was an oil, δ($CDCl_3$) 0.89 (3 H, t, *J* 5.0 Hz, ω-H_3), 2.58 (2 H, t, *J* 7.3 Hz, ArCH_2), 3.86 (6 H, s, OMe), and 6.34 (2 H, s, ArH); *m/z* 334 (M^+, 90), 305 (3), 292 (10), 278 (100), 263 (5), and 232 (3) (Found: C, 47.4; H, 5.9; I, 37.2. $C_{13}H_{19}IO_2$ requires C, 46.70: H, 5.68; I, 38.02%).

Brominations in the Absence of 18-*Crown*-6.—For comparison with the reactions described above several brominations in the absence of the crown reagent were undertaken. The general procedure was as follows. The substrate (1 mmol) was dissolved in CCl_4 (10 ml). The solution was stirred and a solution of bromine (1 mmol, or as indicated) in CCl_4 (2 ml) was slowly added. After 5 min the reaction mixture was worked up and the residue was chromatographed as described in the general halogenation procedure.

(a) *Bromination of resorcinol dimethyl ether* (**5**). 1-Bromo-2,4-dimethoxybenzene (**6**) (60%) was obtained in addition to starting material (30% recovered).

When excess of bromine (1.5 mmol) was used, bromide (**6**) was obtained in only 30% yield. In addition 1,5-dibromo-2,4-dimethoxybenzene (**19**) (54%) was isolated, m.p. 140—141 °C; δ($CDCl_3$) 3.89 (6 H, s, OMe), 6.48 (1 H, s, 3-H), and 7.64 (1 H, s, 6-H) (lit.,[18] m.p. 141—143 °C).

(b) *Bromination of olivetol dimethyl ether* (**9**). 2-Bromo-1,5-dimethoxy-3-pentylbenzene (**10**) was obtained in 20% yield; 2,4-dibromo-1,5-dimethoxy-3-pentylbenzene (**20**) was obtained in 40% yield, as crystals, m.p. 73—74 °C; δ($CDCl_3$) 3.89 (6 H, s, OMe) and 6.40 (1 H, s, 6-H) (lit.,[8] m.p. 74.5—75.5 °C).

(c) *Bromination of* 1-(1,1-*dimethylheptyl*)-3,5-*dimethoxybenzene* (**13**). Only 2-*bromo*-5-(1,1-*dimethylheptyl*)-1,3-*dimethoxybenzene* (**21**) was identified, and was obtained as an oil (85%), δ($CDCl_3$) 0.92 (3 H, t, *J* 5.0 Hz, ω-H_3), 1.29 (6 H, s, CMe_2), 3.89 (6 H, s, OMe), and 6.54 (2 H, s, 4- and 6-H); *m/z* 344 (40%), 342 [M^+ (Br^{79}), 40], 302 (7), 300 (7), 288 (10), 286 (10), 259 (100), 257 (100), and 180 (79) (Found: C, 60.2; H, 8.3. $C_{17}H_{27}BrO_2$ requires C, 59.47; H, 7.87%).

(d) *Bromination of* 1-(1,1-*dimethylheptyl*)-3,5-*diethoxybenzene* (**23**). Only 2-*bromo*-5-(1,1-*dimethylheptyl*)-1,3-*diethoxybenzene* (**25**) was identified, and was obtained as an oil (85%), δ($CDCl_3$) 0.91 (3 H, t, *J* 4.2 Hz, ω-H_3), 1.26 (6 H, s, CMe_2), 1.45 (6 H, t, *J* 7.0 Hz, OCH_2Me), 4.10 (4 H, q, *J* 7.0 Hz, OCH_2), and 6.52 (2 H, s, 4- and 6-H); *m/z* 372 (36%), 370 [M^+ (Br^{79}), 36], 330 (7), 328

(7), 316 (9), 314 (9), 302 (10), 300 (10), 287 (100), 285 (93), 259 (15), and 257 (15) (Found: C, 61.8; H, 8.1. $C_{19}H_{31}BrO_2$ requires C, 61.45; H, 8.35%).

Bromination of 1-(1,1-*Dimethylheptyl*)-3,5-*dimethoxybenzene* (**13**) *with Bromine–*18-*Crown*-6.—Compound (**13**) (264 mg, 1 mmol) was dissolved in methylene dichloride (10 ml) containing 18-crown-6 (27 mg, 0.1 mmol). Bromine (80 mg, 1 mmol) was added to the vigorously stirred solution. After 15 min the reaction mixture was worked up, and the residue was chromatographed as described in the general halogenation procedure. The 4-substituted product (**21**) (292 mg, 0.98 mmol) was obtained.

Bromination of 1-(1,1-*Dimethylheptyl*)-3,5-*diethoxybenzene* (**23**) *with Bromine–*18-*Crown*-6.—This reaction was performed exactly as the one described above with compound (**13**). The 4-bromo product (**25**) was obtained in 85% yield.

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