Design and Synthesis of Substituted Dihydrofuranochromans as New Serotonergic Molecular Probes

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ABSTRACT

Two chemical probes (**4, 5**) for the agonist binding sites of serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors were designed as rigid analogs of the methoxylated hallucinogenic phenylalkylamines. These drugs, hybrids of previously constructed heterocycles, include 5- and 6-membered oxygen-containing rings that restrict the conformational freedom of the alkoxy ring substituents. Various strategies were explored in an attempt to synthesize the new compounds. Specifically, one method involving a reduction/diazotization/substitution sequence and two alternate phenol alkylation methods were employed. Although target molecules **4** and **5** have not yet been prepared, significant progress has been made toward their synthesis with the construction of a key tricyclic intermediate (**6**) *via* a unique ether-cleavage reaction, and our efforts are reported here. Ultimately, pharmacological testing of **4** and **5** will provide more detailed information about the three-dimensional structure and topography of the agonist binding sites in serotonin 5-HT$_2$ receptors.

INTRODUCTION

Previous investigations into the topography of the agonist binding sites of the 5-HT$_{2A}$ and 5-HT$_{2C}$ serotonin receptor subtypes have used molecular probes of general structure **1**.[1,2] These hallucinogenic phenylalkylamines contain the essential structural features required for high-affinity binding to 5-HT$_{2A}$ and 5-HT$_{2C}$ agonist sites.[1,2] However, the directionality of the oxygen lone-pair electrons involved in putative hydrogen-bonding interactions at the receptor sites could not be confirmed due to free rotation about the arene-oxygen bonds in these compounds. Structure–activity relationship (SAR) studies of a series of heterocyclic, conformationally-restricted analogs of **1** ultimately revealed that molecular probe **2** possessed the optimum orientation of the arene oxygen lone-pair electrons.[3] In that work, rat behavioral and in vitro radioligand binding assays clearly showed that **2** is a potent and selective sero-


1

R = H, CH$_3$
X = Br, I, CH$_3$

2

3
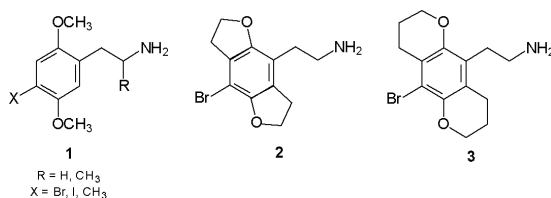
tonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor agonist, suggesting that these receptor sites conform well to the shape of this rigid molecule.[3]

Most recently, the substituted benzodipyran, **3**, was prepared as a bulkier analog of **2**.[4] The affinity of **3** for these same receptor sites was found to be slightly lower than that of **2**, but roughly equipotent to the prototype, DOB (**1**, R = CH$_3$, X = Br).[4] The attenuated potency of **3** must be attributed to the greater steric bulk of one, or both, of the pyranyl groups that flank the arene ring.

The present study sought to address the hypothesis that there may be different-sized binding pockets in the two regions of the receptor that correspond to the alkoxy moieties on either side of the arene ring. In search for the answer to this puzzle, the homologous dihydrofuranochromans **4** and **5** were designed as new probes for the serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor subtypes. These agonists can be viewed as hybrids of molecules **2** and **3**, as each contains one 5- and one 6-membered O-heterocycle, but their respective locations are on alternate sides of the central arene ring.

If one of the proposed dihydrofuranochromans exhibits greater affinity for the serotonin receptors over the other, valuable insight into the relative sizes of the receptor regions involved in binding interactions with agonists will be gained. Additionally, molecules **4** and **5** have the potential to be the first drugs ever synthesized to discriminate between the very similar serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor subtypes.
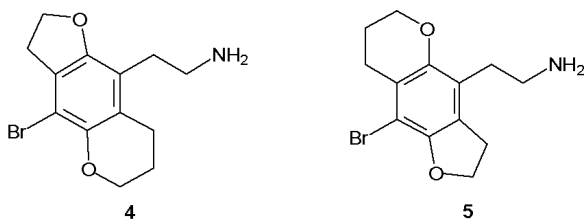
CHEMISTRY

In planning the synthesis of **4** and **5**, it was obvious that a divergent synthesis could be devised in which both of the target compounds, **4** and **5**, could be prepared from the unsubstituted tricyclic intermediate, 2,3-dihydrofurano[2,3-g]chroman (**6**) (Figure 1). The synthesis of this tricyclic intermediate was not as straightforward as the synthesis of the symmetrical analogs **2** and **3** because the asymmetric ring system of **6** warrants independent construction of the two different heterocycles. Several reaction schemes beginning with oxygen-containing starting materials were explored in an attempt to construct **6** and are described here in greater detail.
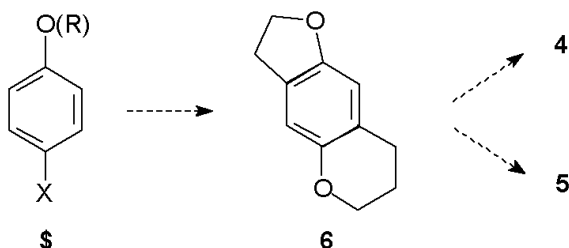

Figure 1. Overall synthetic route to 4 and 5.

One attempted synthesis of intermediate **6** (Scheme 1) began with the alkylation of commercially available 4-nitrophenol **7** with 1,3-dibromopropane. Although this step produced excellent yields of the alkylated nitro compound **8**, major obstacles were encountered in attempting to convert **8** to the desired phenol **11** *via* a reduction/diazotization/hydrolysis sequence. Both catalytic hydrogenation[5] and the use of Sn/HCl[6] were attempted initially in the reductions, yet the free amine **9** proved difficult to isolate and purify. Furthermore, additional safeguards were necessary to prevent the amine group of **9** from undergoing intermolecular attack on the bromine-substituted carbon atom of the alkyl side chain. Attempts to obtain the purified hydrochloride salt of **9** were also unsuccessful.
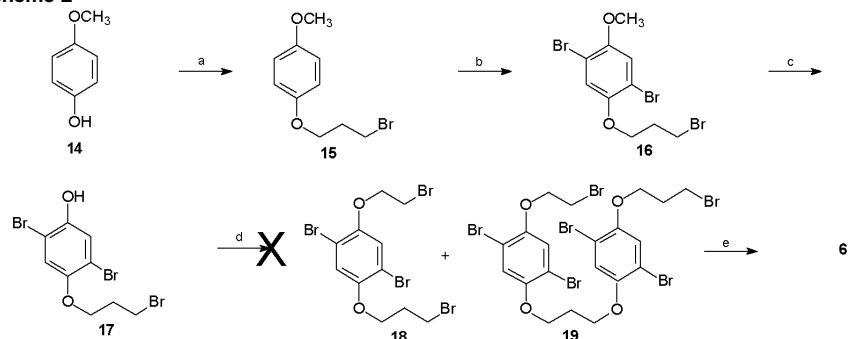
Scheme 1[a]
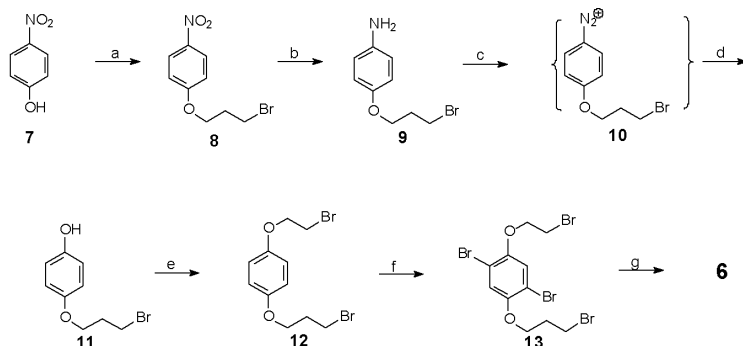
[a](a)Br(CH$_2$)$_3$Br, K$_2$CO$_3$; (b) H$_2$, Pd/C or Sn/HCl; (c) NaNO$_2$, H$_2$O, H$^+$; (d) H$_2$O, Δ or Cu^{2+}, Cu$_2$O or Cu^{2+}, sodium citrate, ascorbic acid; (e) BrCH$_2$CH$_2$Br, K$_2$CO$_3$; (f) Br$_2$; (g) *n*-BuLi, THF

Facing these challenges and acting upon synthetic ideas presented in several literature references, a one-pot transformation of **8** to **11** was attempted.[7-9] Instead of trying to isolate **9** after the reduction phase, attempts were made to reduce the nitro group of **8** and form the phenol **11** (via diazotization/hydrolysis) in a single reaction vessel. The reduction reaction was initially carried out using SnCl$_2$•2H$_2$O and 12 M HCl, followed by a diazotization/hydrolysis procedure utilizing sodium nitrite, HCl, water, and heat.[7] After several failed attempts to isolate **11**, chloride ion (originating from the hydrochloric acid) was suspected to be competing with water for replacement of the diazo group present in intermediate **10**.

With this observation, a new one-pot transformation, substituting sulfuric acid for HCl, was devised to eliminate the presence of chloride ion. This transformation employed a catalytic hydrogenation for the reduction phase, followed by the combination of sulfuric acid, aqueous sodium nitrite, and heat in the diazotization/hydrolysis process.[5,8] Even in the absence of competing chloride ion, the phenolic compound **11** was never isolated using this modified procedure. Heat applied in the hydrolysis was identified as inducing an undesirable side reaction, resulting in the formation of a bright red-colored byproduct. Less rigorous conditions were employed after the diazotization stage to correct this problem, but holding the temperature at 50 °C also failed to produce the desired product **11**.

To avoid the complications of heat-induced substitutions, a more recent procedure in the literature outlined the use of cupric ion in the hydrolysis steps following diazotization.[10, 11] Such substitutions proceed *via* a free-radical mechanism instead of an aryl cation intermediate as in traditional heat-based hydrolyses. Two methods based on the use of cupric ion in the hydrolysis phase were attempted, but both failed to give the desired phenol **11**.
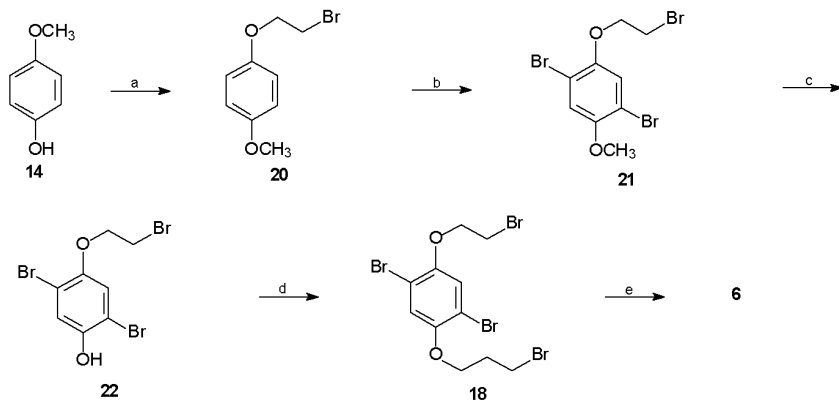
Scheme 2[a]

[a](a) Br(CH$_2$)$_3$Br, K$_2$CO$_3$; (b) Br$_2$, Fe; (c) *B*-bromo-9-BBN; (d) BrCH$_2$CH$_2$Br, K$_2$CO$_3$; (e) *n*-BuLi, THF

With the difficulties encountered in Scheme 1, the focus of constructing the tricyclic intermediate **6** shifted to the route illustrated in Scheme 2. This route began with the alkylation of commercially available 4-methoxyphenol (**14**) with 1,3-dibromopropane and potassium carbonate in acetone. The alkylated product **15** was isolated as a colorless oil (84%) after vacuum distillation, and subsequent bromination of **15** in CH$_2$Cl$_2$ produced transparent crystals of **16** in excellent yield.

To convert **16** to the desired phenol **17**, an ether-cleavage reaction was devised using *B*-bromo-9-BBN.[12,13] This mild demethylating agent was preferred to more rigorous reagents, such as BBr$_3$ and BCl$_3$, that were found to cleave both alkyl chains of the diether. We also discovered that 2 equivalents of *B*-bromo-9-BBN were necessary to facilitate the selective demethylation of **16**, and the desired phenol **17** was isolated in 84% yield after purification by flash-column chromatography.

Following the selective ether-cleavage of **16**, addition of the phenol **17** to a mixture of 1,2-dibromoethane and potassium carbonate in acetone primarily gave the dimeric byproduct **19** and not the desired alkylated product **18**. The dimer was formed by intermolecular attack of the phenolic oxygen atom of one molecule of **17** on the primary alkyl bromide of another molecule of **17**. Nucleophilic substitution was hypothesized to occur preferentially at these terminal carbon atoms than at the more sterically inaccessible carbons of 1,2-dibromoethane.

Scheme 3[a]

[a](a) BrCH$_2$CH$_2$Br, K$_2$CO$_3$; (b) Br$_2$, Fe; (c) *B*-bromo-9-BBN, Δ; (d) Br(CH$_2$)$_3$Br, K$_2$CO$_3$; (e) *n*-BuLi, THF

To correct this problem, the ordering of the alkylation steps was reversed, and the synthetic approach outlined in Scheme 3 was adopted. Thus, initial alkylation of 4-methoxyphenol (**14**) was first carried out with 1,2-dibromoethane and potassium carbonate in acetone. A 10% CH$_2$Cl$_2$-90% hexanes solution was found to precipitate most of the dimeric byproduct while solubilizing the desired monomer. Following removal of the dimer by filtration, sheet-like crystals of the alkylated product **20** were obtained upon recrystallization from ethyl acetate-hexanes. The diether **20** was brominated with the addition of 2 equivalents of Br$_2$ to a solution of **20** dissolved in CH$_2$Cl$_2$, and needle-like crystals of the desired product **21** were isolated in 92% yield following recrystallization.

While only 2 equivalents of *B*-bromo-9-BBN were previously necessary to cleave the methyl carbon-oxygen bond of **16**, we found that both 3 equivalents of the reagent and strong heating were required to facilitate the selective demethylation of **21**. Ethanolamine was used to precipitate the excess *B*-bromo-9-BBN from the reaction mixture, **12** and the desired phenol **22** was isolated by basic extraction and flash-column chromatography.

Alkylation of the phenol **22** in a dilute mixture of 1,3-dibromopropane, potassium carbonate, and acetone at reflux produced spar-like crystals of **18** (50%), and cyclization of the alkylated product **18** with *n*-butyllithium gave the desired tricyclic intermediate **6** upon recrystallization from ethyl acetate-hexanes. The relative locations of the observed peaks in the ^{1}H-NMR spectrum of **6** were consistent with those reported for molecules **2** and **3**. Three peaks assigned to the pyranyl protons of **6** were observed at δ 1.97, 2.72, and 4.10, while resonances due to the protons of the furanyl ring appeared at δ 3.12 and 4.48.

With the construction of intermediate **6**, the remaining route to molecular probes **4** and **5** could follow a well-established literature precedent (Scheme 4).[3,4] The greatest challenge was originally thought to lie in the separation of the two aldehydes (**23a** and **23b**) obtained from the initial formylation step. Because the formyl group can add to either of the two free arene positions of **6**, the formation of two compounds with very similar physical and chromatographic properties was expected. However, preliminary laboratory results have indicated that the two regioisomers can be separated by simple recrystallization. After combining the key

tricyclic intermediate **6** with $SnCl_4$ and Cl_2CHOCH_3 at 0 °C, a mixture of **23a** and **23b** was isolated following extraction into CH_2Cl_2 and subsequent solvent removal. The ¹H-NMR spectrum of this crude product revealed two chemical shift signals just beyond δ 10.0, consistent with the expected two-component mixture obtained from the reaction. Upon recrystallization from ethyl acetate-hexanes, the formylated isomer **23a** was found to preferentially precipitate first from solution. The ¹H-NMR spectrum of the isolated yellow crystals revealed an aldehydic proton resonance at δ 10.36, and IR spectral analysis of **23a** showed an absorption band at 2700 cm⁻¹ corresponding to C-H stretching within the aldehyde group. Once the remainder of isomer **23a** is collected, the other regioisomer **23b** can be isolated from the mixture, and the two aldehydes will then be condensed with nitromethane, reduced, and brominated to yield the desired targets, **4** and **5**.

RESULTS AND DISCUSSION

Upon completion of the synthesis of **4** and **5**, rat behavioral assay and radioligand competition studies of these target molecules will be performed to determine their affinity for $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ serotonin receptors. If one of the probes exhibits greater affinity at the receptor sites relative to the other, more detailed information will be unveiled regarding the three-dimensional topography of these sites. Specifically, the precise locations of binding pockets more tolerant of the bulkier pyran ring may be uncovered, providing insight into the relative size of receptor regions involved in binding interactions with the alkoxy substituents.

Scheme 4a
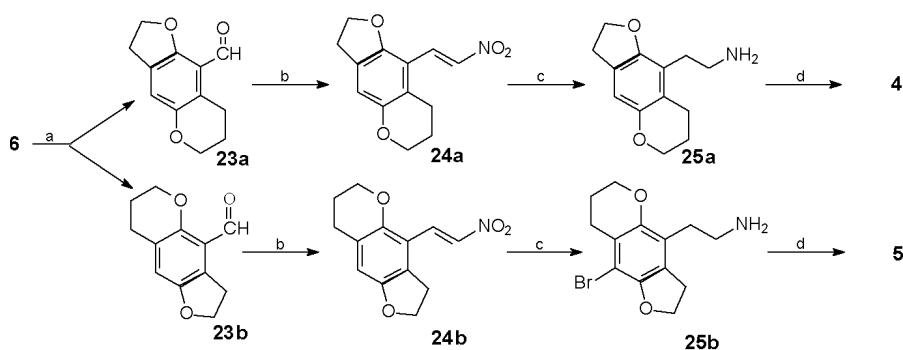
ᵃ(a) Cl_2CHOCH_3, $SnCl_4$, CH_2Cl_2; (b) CH_3NO_2, NH_4OAc, Δ; (c) $LiAlH_4$, THF, reflux; (d) Br_2, HOAc

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ¹H-NMR spectra were obtained using a 300 MHz Bruker AC 300 NMR spectrometer with TMS as the internal standard. Abbreviations used in NMR analyses are as

follows: s = singlet, d = doublet, t = triplet, p = pentet, m = multiplet, Ar = aromatic. Infrared spectra were recorded on a Midac Prospect FT-IR spectrometer. Thin-layer chromatography (TLC) was performed using Baker-flex silica gel plastic-backed plates with fluorescent indicator, developing with CH_2Cl_2, and visualizing with UV light. All solvents (acetone, diethyl ether, CH_2Cl_2, THF, ethyl acetate, hexanes) were obtained from Fisher Scientific and used as received. Most inorganic reagents, along with 4-nitrophenol, 4-methoxyphenol, 1,3-dibromopropane, 1,2-dibromoethane, 10.0 M n-butyllithium in hexanes, dichloromethyl methyl ether, and 1.0 M B-bromo-9-BBN in CH_2Cl_2 were used as received from Aldrich.

3-Bromo-1-(4-nitrophenoxy)propane (8). To a mixture of 73 mL (0.72 mol) of 1,3-dibromopropane, 82 g (0.59 mol) of powdered potassium carbonate, and 500 mL of acetone at reflux was added a solution of 20 g (0.14 mol) of 4-nitrophenol (**7**) in 100 mL of acetone over a 3 h period. The reaction mixture was held at reflux with vigorous stirring for an additional hour before the mixture was cooled to room temperature, and the potassium carbonate was removed by filtration through Celite. After the acetone was removed in vacuo, the remaining residue was taken up in CH_2Cl_2, washed with 2.5 M NaOH (3 x 50 mL), 3 M HCl (3 x 50 mL), and 50 mL of saturated NaCl, and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite. Volatiles were removed under reduced pressure, and the remaining liquid was purified by Kügelrohr distillation. The distillate collected at 190-200 °C spontaneously crystallized upon standing. The solid material was recrystallized from ethyl acetate-hexanes to yield 27 g (73%) of **8** as needle-like crystals: mp 58-60 °C; ^{1}H NMR (CDCl$_3$) δ 2.35 (p, 2, ArOCH$_2$CH_2CH$_2$Br), 3.60 (t, 2, ArOCH$_2$CH$_2$CH_2Br), 4.20 (t, 2, ArOCH_2CH$_2$CH$_2$Br), 6.95 (d, 2, ArH), 8.20 (d, 2, ArH)

1-(4-Aminophenoxy)-3-bromopropane (9) (a). To a suspension of 30 mg of 30% Pd-C catalyst in 100 mL of glacial acetic acid in a Parr hydrogenation bottle was added 0.500 g (1.93 mmol) of **8**. The mixture was shaken under 40 psi of H$_2$ for 5 h. The catalyst was removed by filtration through Celite, and the violet-colored filtrate was placed on the rotatory evaporator to remove most of the acetic acid. The remaining residue was combined with diethyl ether, washed with 2.5 M NaOH (3 x 25 mL) and 25 mL of brine, dried (MgSO$_4$), and filtered through Celite. The resulting oil was unable to be purified before forming an intractable dark sludge.

(b) The alkylated nitro compound **8** (0.739 g, 2.84 mmol) and 3.7 mL of 12 M HCl were stirred and warmed to 80 °C, and tin granules (2.79 g, 23.5 mmol) were slowly added to the suspension. The resulting mixture was stirred and heated for an additional hour. Excess tin was filtered from the reaction mixture (using hot HCl as a rinse), and a white solid settled out of the filtrate. The filtrate was combined with water and washed twice with CH_2Cl_2. The aqueous phase was cooled over an ice bath, placed under a stream of N$_2$, and basified with 5 M NaOH. Additional solid settled out of the milky liquid, and this material was extracted into CH_2Cl_2 (3 x 25 mL). Remaining insoluble material was removed by filtration through Celite. The cloudy filtrate was washed with 50 mL of saturated NaCl, dried over MgSO$_4$, and filtered through Celite. Several attempts to purify the remaining yellow residue by recrystallization failed.

1-(4-Aminophenoxy)-3-bromopropane hydrochloride (9•HCl). To a solution of 1.05 g (4.03 mmol) of **8** and 5 mL of 12 M HCl was slowly added 3.84 g (0.0324 mol) of tin granules with stirring. The mixture was cautiously warmed to 60 °C (to prevent excessive foaming) and heated for 3 h. Excess tin was filtered from the cloudy mixture through Celite, rinsing with hot HCl and water. The acidic mixture was transferred to a separatory funnel and

washed with 3 x 25 mL of CH_2Cl_2 to remove organic contaminants. The aqueous layer was basified with 5 M NaOH and extracted into CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, washed with 50 mL of saturated NaCl, and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite, and the solvent was removed under reduced pressure. The remaining pale yellow residue was treated with 1 M HCl in anhydrous ethanol. Addition of diethyl ether to the solution failed to precipitate any of the desired amine salt.

3-Bromo-1-(4-hydroxyphenoxy)propane (11). (a) A solution of 1.31 g (5.81 mmol) of $SnCl_2 \cdot 2H_2O$, 2 mL of 12 M HCl, and 0.502 g (1.93 mmol) of **8** was stirred and heated at 60ºC for 4 h. The clear solution obtained was cooled slowly over an ice-salt bath whereupon a generous amount of white solid precipitated. The solid was collected by filtration and combined with 30 mL of 12 M HCl. This mixture was cooled to 0 °C before a solution of 0.146 g (2.12 mmol) of $NaNO_2$ in 30 mL of cold water was slowly added below the liquid surface over a 15 min period. The reaction contents were stirred for an additional hour at 0 °C, and a tan-colored precipitate was collected by filtration and added to 50 mL of boiling water. The resulting yellow solution was heated for 30 min with stirring and made strongly basic with 5 M NaOH. The basic solution was washed with CH_2Cl_2 (3 x 25 mL), acidified with 3 M HCl, and extracted once again with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined and washed with 25 mL of saturated NaCl, dried with anhydrous $MgSO_4$, and filtered through Celite. Volatiles were removed *in vacuo*, leaving behind only a trace of organic residue.

(b) Glacial acetic acid (25 mL) and 0.510 g (1.95 mmol) of **8** were placed into a Parr bottle with 30 mg of 30% Pd-C. Once the organic material dissolved in the acidic solvent, the bottle was attached to the hydrogenation apparatus, saturated with H_2, and shaken at 40 psi for 5 h. The catalyst was removed by filtration through Celite, and concentrated H_2SO_4 (3 mL) was added to the violet-colored filtrate. The solution was cooled to 0 ºC, and 0.145 g (2.10 mmol) of $NaNO_2$ dissolved in 30 mL of cold water was slowly added to the reaction vessel (below the surface of the liquid) with stirring. The solution was stirred at 0 ºC for another 30 min, and small portions of urea (0.1 g) in water (5 mL) were added to decompose excess HNO_2. The cold diazonium solution was added dropwise to a boiling solution of 50 mL of water and 10 mL of concentrated H_2SO_4 over a 20 min period. (Care was taken not to allow the diazonium solution to come into contact with the warm sides of the reaction vessel.) The solution was refluxed for an additional 30 min, basified with 5 M NaOH and washed with 3 x 25 mL CH_2Cl_2. The basic solution was acidified with 6 M HCl and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, washed with 25 mL of brine, and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite, and droplets of a reddish-brown residue (0.054 g, 12%) remained after solvent removal under reduced pressure.

(c) A solution of 25 mL of glacial acetic acid and 0.497 g (1.91 mmol) of **8** were placed in a Parr bottle, and 30 mg of 30% Pd-C was added to the vessel. The Parr bottle was shaken under 40 psi of H_2 for 5 h. The catalyst was removed by filtration through Celite, and the violet-colored filtrate was cooled over an ice bath under a stream of N_2 before being basified with NaOH pellets and extracted into diethyl ether. The organic material was subsequently extracted with 50% H_2SO_4, and this acidic extract was cooled to 0 °C. A solution of 0.145 g (2.10 mmol) of $NaNO_2$ and 30 mL of cold water was slowly added to the reaction vessel below the liquid level. The reaction contents were stirred at 0 °C for 30 min and then heated to reflux. The red solution was held at reflux for an additional 12 h, basified with NaOH pel-

lets, and washed three times with CH_2Cl_2. The basic aqueous phase was acidified with 6 M HCl and extracted into CH_2Cl_2 (3 x 25 mL). The organic extract was washed with 25 mL of saturated NaCl and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite. The solvent was removed on the rotatory evaporator, and the crude product was dried under high vacuum, leaving 0.027 g (6.1%) of an orange-red residue.

(d) Glacial acetic acid (25 mL), 3 mL of concentrated H_2SO_4, and 0.502 g (1.93 mmol) of **8** were combined in a Parr bottle. A small portion (30 mg) of 30% Pd-C was added to the vessel once the organic material had dissolved. The Parr bottle was attached to a hydrogenation apparatus and shaken under 40 psi of H_2 for 5 h. The catalyst was removed by filtration through Celite, and the tan-colored filtrate was combined with an additional 5 mL of concentrated H_2SO_4. The solution was cooled to 0 °C, and 0.136 g (1.97 mmol) of $NaNO_2$ in 30 mL of cold water was slowly added to the reaction vessel below the liquid surface. The blue-colored solution was stirred at 0 °C for an additional 45 min, after which a few crystals of urea were added to decompose excess HNO_2. The contents of the reaction vessel were allowed to warm to room temperature and stirred at 50 °C for 24 h. The solution was cooled over an ice bath and made strongly basic with NaOH pellets. A violet-colored precipitate was collected by filtration, and the remaining orange filtrate was washed with 3 x 25 mL of CH_2Cl_2. The basic aqueous solution was acidified with 6 M HCl and extracted into 3 x 25 mL of CH_2Cl_2. The organic extracts were combined and washed with 25 mL of brine and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite. Volatiles were removed *in vacuo*, leaving behind only a trace of orange residue.

(e) A solution of 25 mL of glacial acetic acid and 0.501 g (1.93 mmol) of **8** was reduced with H_2 as in **c**. The catalyst was removed by filtration through Celite, and the violet-colored filtrate was combined with 3 mL of concentrated H_2SO_4. The solution was cooled to 0 ºC and 0.139 g (2.01 mmol) of $NaNO_2$ dissolved in 30 mL of cold water was slowly added to the solution below the liquid level. The contents of the reaction vessel were stirred at 0 °C for an additional 30 min before a few crystals of urea were added to decompose the excess HNO_2. To the 0 °C reaction mixture was added a solution of 7.06 g (0.0303 mol) of $Cu(NO_3)_2 \cdot 2.5H_2O$ in 50 mL of water. Cuprous oxide (0.277 g, 1.94 mmol) was then introduced into the reaction vessel with stirring. The green-colored solution was allowed to warm to room temperature and extracted with 2.5 M NaOH (4 x 25 mL). The basic aqueous layer was acidified with 6 M HCl and extracted into diethyl ether (3 x 25 mL). The ether extracts were combined and washed with 25 mL of saturated NaCl, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under vacuum, and 0.736 g of a yellow oil remained. Solid material appeared to be suspended within the oil after several days of cooling, but ^{1}H-NMR analysis of the crude product revealed the desired phenol was not isolated.

(f) The alkylated nitro compound **8** (0.501 g, 1.93 mmol) was dissolved in 25 mL of glacial acetic acid, placed in a Parr bottle, and reduced as in **c**. The catalyst was removed by filtration through Celite, and the violet-colored filtrate was combined with 3 mL of concentrated H_2SO_4 and 5 mL of water. This solution was cooled to 0 °C before 0.292 g (4.23 mmol) of $NaNO_2$ dissolved in 15 mL of cold water was slowly added to the reaction vessel below the level of the liquid. The solution was stirred at 0 °C for an additional 15 min, and urea (0.1 g) was added to destroy excess HNO_2. A small portion (2 mL) of this cold, golden brown solution was added to a 2-phase mixture consisting of 15 mL of ethyl acetate and 0.265 g (1.06 mmol) of $CuSO_4 \cdot 5H_2O$ and trisodium citrate dihydrate (0.618 g, 2.10 mmol)

dissolved in 15 mL of water. The reaction was initiated by the addition of a solution of 0.054 g of ascorbic acid in 5 mL of water. The remaining diazonium solution was then slowly added with vigorous stirring. The resulting solution turned green before becoming orange in color. The two-phase mixture was stirred for an additional 15 min, transferred to a separatory funnel, and partitioned. The aqueous layer was washed with additional ethyl acetate, and the combined red-orange organic layers were extracted with 2.5 M NaOH (3 x 25 mL). The basic aqueous material was acidified with concentrated HCl and extracted into 3 x 25 mL of diethyl ether. The ether extracts were combined, washed with 25 mL of brine, and dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration through Celite. The gold-colored filtrate was placed under high vacuum, leaving behind 3.59 g of an oily residue containing suspended solids. Spectral analysis of the crude product indicated the desired phenol was not obtained.

   1-Bromo-3-(4-methoxyphenoxy)propane (15). To a mixture of 24.5 mL (0.241 mol) of 1,3-dibromopropane, 33 g (0.22 mol) of finely powdered anhydrous potassium carbonate, and 300 mL of acetone at reflux was added a solution of 10.0 g (0.0806 mol) of 4-methoxyphenol dissolved in 100 mL of acetone over a 12 h period. The reaction mixture was held at reflux with vigorous stirring for an additional 20 h before the mixture was cooled to room temperature, and the potassium carbonate was removed by filtration through Celite. After the acetone was removed *in vacuo*, the remaining residue was taken up in CH_2Cl_2, washed with 2.5 M NaOH (3 x 25 mL), 1 M HCl (3 x 25 mL), and 50 mL of saturated NaCl. The organics were dried over anhydrous $MgSO_4$ before being filtered through Celite. Volatiles were removed from the filtrate *in vacuo*, and the desired product was isolated as a colorless oil (17 g, 84%) upon Kügelrohr distillation.

   1-Bromo-3-(2,5-dibromo-4-methoxyphenoxy)propane (16). Bromine (2.23 mL, 0.0433 mol) dissolved in 30 mL of CH_2Cl_2 was incrementally added to a stirred mixture of the diether **15** (5.05 g, 0.0206 mol), 25 mL of CH_2Cl_2, and a few iron filings over a 1 h period. The red-colored mixture was stirred at ambient temperature overnight, and subsequent washing with 2.5 M NaOH (4 x 25 mL) removed most of the intense color of the mixture. The organic material was further washed with 3 x 25 mL of 1 M HCl and saturated NaCl (1 x 50 mL) and dried over anhydrous $MgSO_4$. After filtration through Celite, the yellow-colored filtrate was placed on the rotatory evaporator for solvent removal, and the remaining oil crystallized spontaneously upon standing. The solid was recrystallized from ethyl acetate-hexanes to yield 7.1 g (85%) of transparent needle-like crystals: mp 61-62 ºC, ^{1}H NMR ($CDCl_3$) δ 2.35 (p, 2, ArOCH$_2$C*H*$_2$CH$_2$Br), 3.65 (t, 2, ArOCH$_2$CH$_2$C*H*$_2$Br), 3.82 (s, 3, ArOC*H*$_3$), 4.10, (t, 2, ArOC*H*$_2$CH$_2$CH$_2$Br), 7.09 (s, 1, Ar*H*), 7.15 (s, 1, Ar*H*)

   2,5-Dibromo-4-(3-bromopropoxy)phenol (17). A solution of 2.0 g (0.0050 mol) of the brominated diether **16**, dissolved in 35 mL of CH_2Cl_2, was placed in a round-bottom flask under a N_2 atmosphere. A solution of 1.0 M *B*-bromo-9-BBN in CH_2Cl_2 (10 mL, 0.010 mol) was introduced to the stirred solution with a syringe over a 2 min period. The mixture was stirred for an additional 24 h before the CH_2Cl_2 was removed *in vacuo*. The remaining residue was combined with 50 mL of diethyl ether and cooled to 0 ºC before ethanolamine (1 mL, 0.02 mol) was slowly added to the cold solution. A white *B*-bromo-9-BBN adduct precipitated from the yellow-colored solution and was removed by filtration through Celite. The filtrate was washed with 3 M HCl (3 x 25 mL) and extracted with 2.5 M NaOH. (Washing of the organics with NaOH produced three distinct layers within the separatory funnel as the deprotonated form of **17** is not very soluble in basic solution.) The bottom two layers from each base extraction were combined and acidified with 6 M HCl, and the aqueous phase was

extracted with Et$_2$O (3 x 25 mL). The ether extracts were further washed with saturated NaCl (50 mL), dried over anhydrous MgSO$_4$, and filtered through Celite. After solvent removal *in vacuo*, the remaining gold-colored residue was dissolved in a minimal amount of CH$_2$Cl$_2$ and introduced onto a silica gel column. The column was eluted with CH$_2$Cl$_2$ and N$_2$ pressure, and the flash-column chromatographic separation was monitored by TLC. The fractions containing the desired product **17** were combined and placed under reduced pressure for solvent removal, yielding 1.63 g (84%) of a fluffy white solid: ^{1}H NMR (CDCl$_3$) δ 2.35 (p, 2, ArOCH$_2$C*H*$_2$CH$_2$Br), 3.62 (t, 2, ArOCH$_2$CH$_2$C*H*$_2$Br), 4.10, (t, 2, ArOC*H*$_2$CH$_2$CH$_2$Br), 5.22 (s, 1, ArO*H*), 7.01 (s, 1, Ar*H*), 7.22 (s, 1, Ar*H*)

1-Bromo-2-(4-methoxyphenoxy)ethane (20).[14] A solution of 10 g (0.089 mol) of 4-methoxyphenol dissolved in 100 mL of acetone was added over a 12 h period to a mixture of 35 mL (0.41 mol) of 1,2-dibromoethane, 35 g (0.25 mol) of finely powdered anhydrous potassium carbonate, and 300 mL of acetone at reflux. The reaction mixture was held at reflux for an additional 125 h, and the potassium carbonate was removed by filtration through Celite. After the acetone was removed *in vacuo*, the remaining residue was combined with CH$_2$Cl$_2$, washed with 2.5 M NaOH (3 x 25 mL), 1 M HCl (3 x 25 mL), and 50 mL of saturated NaCl, and dried over anhydrous MgSO$_4$. The drying agent was removed by filtration through Celite, and evaporation of the volatiles yielded an orange-colored solid. The solid was treated with 100 mL of a 10% CH$_2$Cl$_2$-90% hexanes solution to precipitate dimeric material present. Following filtration through a bed of Celite, the solvent was evaporated *in vacuo* until crystallization occurred. Recrystallization from ethyl acetate-hexanes yielded 8.4 g (45%) of translucent sheet-like crystals (mp 50-51 ºC) with a ^{1}H-NMR spectrum identical to that reported in ref 14.

1-Bromo-2-(2,5-dibromo-4-methoxyphenoxy)ethane (21). A solution of 1.4 mL (0.027 mol, 2.1 equiv) of bromine in 50 mL of CH$_2$Cl$_2$ was dripped into a stirred mixture of 3.08 g (0.0133 mol) of the diether 100 mL of CH$_2$Cl$_2$, and a few iron filings over a 2 h period. The red-colored mixture was stirred overnight, and subsequent washing with 2.5 M NaOH (4 x 25 mL) removed the red color of the solution. The organic phase was further washed with 3 x 25 mL of 1 M HCl and saturated NaCl (1 x 40 mL), and dried over anhydrous MgSO$_4$. Following filtration through Celite, the filtrate was placed on the rotatory evaporator to remove the volatiles. The remaining solid was recrystallized from ethyl acetate-hexanes to yield 4.6 g (92%) of colorless crystals: mp 65-66 °C, ^{1}H NMR (CDCl$_3$) δ 3.62 (t, 2, ArOCH$_2$C*H*$_2$Br), 3.82 (s, 3, ArOC*H*$_3$), 4.27 (t, 2, ArOC*H*$_2$CH$_2$Br), 7.10 (s, 1, Ar*H*), 7.17 (s, 1, Ar*H*)

2,5-Dibromo-4-(2-bromoethoxy)phenol (22). The brominated diether **21** (13 g, 0.033 mol) was dissolved in CH$_2$Cl$_2$ (75 mL) and placed under a N$_2$ atmosphere. A solution of 1.0 M *B*-bromo-9-BBN in CH$_2$Cl$_2$ (100 mL, 0.10 mol) was slowly added to the stirred solution, and the resulting mixture was refluxed for 110 h. After removal of the solvent on the rotatory evaporator, the gold-colored residue was combined with ether and chilled over ice. Dropwise addition of 6.2 mL (0.10 mol) of 2-aminoethanol precipitated a white *B*-bromo-9-BBN adduct which was removed by filtration through Celite. The remaining yellow filtrate was washed with 6 M HCl (3 x 30 mL) and extracted with 3 x 25 mL of 2.5 M NaOH. The basic layers were combined, acidified with 6 M HCl, and extracted with diethyl ether (3 x 25 mL). The organic extracts were combined and washed with saturated NaCl (1 x 50 mL), dried (MgSO$_4$), and filtered through Celite. Following solvent removal *in vacuo*, purification of the gold-colored residue was carried out using flash-column chromatography with a silica gel

stationary phase and eluting with CH_2Cl_2. The colorless fractions containing the desired product (as revealed by TLC) were combined, and CH_2Cl_2 removal gave 11.4 g (91%) of the demethylated phenol as a fluffy white solid: ^1H NMR ($CDCl_3$) δ 3.64 (t, 2, ArOCH_2CH_2Br), 4.25 (t, 2, ArOCH_2CH$_2$Br), 5.26 (s, 1, ArOH), 7.04 (s, 1, ArH), 7.25 (s, 1, ArH)

1-Bromo-3-(2,5-dibromo-4-(2-bromoethoxy)phenoxy)propane (18). The demethylated phenol **22** (9.6 g, 0.026 mol) was dissolved in acetone (175 mL) and incrementally added over an 18 h period to a dilute mixture of acetone (500 mL), finely ground anhydrous potassium carbonate (11 g, 0.082 mol), and 16 mL (0.16 mol) of 1,3-dibromopropane at reflux. The mixture was held at reflux for an additional 4 h before being cooled to room temperature, and the potassium carbonate was removed by filtration through Celite. Acetone removal was carried out on the rotatory evaporator, and the remaining yellow residue was taken up in CH_2Cl_2 and washed with 3 x 25 mL of 2.5 M NaOH, 3 M HCl (3 x 25 mL), and saturated NaCl (1 x 50 mL). The organics were dried ($MgSO_4$), filtered though Celite to remove the drying agent, and placed under vacuum for solvent removal. The remaining solid was recrystallized from ethyl acetate-hexanes to yield 6.4 g (50%) of **18** as a white solid: mp 63-64°C, ^1H NMR ($CDCl_3$) δ 2.33 (p, 2, ArOCH$_2$CH_2CH$_2$Br), 3.65 (pair of nearly superimposed triplets, 4, ArOCH$_2$CH_2Br, ArOCH$_2$CH$_2$CH_2Br), 4.10 (t, 2, ArOCH_2CH$_2$CH$_2$Br), 4.27 (t, 2, ArOCH_2CH$_2$Br), 7.12 (pair of nearly superimposed singlets, 2, ArH)

2,3-Dihydrofurano[2,3-g]chroman (6). A solution of 4.0 g (8.1 mmol) of **18** in 35 mL of anhydrous THF was placed in a N_2 atmosphere and cooled to –78 °C. A solution of 10.0 M n-butyllithium in hexanes (3.2 mL, 0.033 mol) was added slowly *via* syringe to the stirred solution. The yellow reaction mixture was stirred for an additional 4 h before being quenched with 10 mL of distilled water. After the solvent was removed *in vacuo*, the organic residue was partitioned between Et_2O and water. The organic phase was washed with saturated NaCl (50 mL), dried ($MgSO_4$), and filtered. The volatiles were evaporated in vacuo until crystallization occurred. The solid was recrystallized from ethyl acetate-hexanes to yield 0.43 g (30%) of **6** as a white solid: mp 74-75 °C, ^1H NMR ($CDCl_3$) δ 1.97 (p, 2, ArOCH$_2$CH_2CH$_2$), 2.72 (t, 2, ArOCH$_2$CH$_2$CH_2), 3.12 (t, 2, ArOCH$_2$CH_2), 4.10 (t, 2, ArOCH_2CH$_2$CH$_2$), 4.48 (t, 2, ArOCH_2CH$_2$), 6.45 (s, 1, ArH), 6.64 (s, 1, ArH)

Formylated product (23a). A solution of 0.366 g (2.08 mmol) of the tricyclic intermediate **6** in CH_2Cl_2 was stirred under N_2 and cooled over an ice bath. Tin (IV) chloride (0.30 mL, 2.6 mmol) was added to the solution *via* a syringe, and the gold-colored solution was stirred for 10 min. Dichloromethyl methyl ether (0.181 mL, 1.99 mmol) was then introduced into the mixture dropwise over a 2 min period. The resulting red solution was stirred for an additional 50 min before the reaction was quenched with 25 mL of cold water. The two-layer mixture was separated, and the aqueous phase was re-extracted with 3 x 25 mL of CH_2Cl_2 . The combined organic extracts were washed with 1 M HCl (3 x 25 mL) and 50 mL of saturated NaCl, then dried over anhydrous $MgSO_4$. After filtration through Celite, the yellow organic phase was placed under vacuum for solvent removal. Recrystallization of the remaining solid (mixture of **23a** and **23b**) from ethyl acetate-hexanes first afforded yellow crystals (0.12 g, 30%) of **23a**: mp 64-66 °C, ^1H NMR ($CDCl_3$) δ 1.94 (p, 2, ArOCH$_2$CH_2CH$_2$), 3.12 (pair of superimposed triplets, 4, ArOCH$_2$CH$_2$CH_2, ArOCH$_2$CH_2), 4.08 (t, 2, ArOCH_2CH$_2$CH$_2$), 4.62 (t, 2, ArOCH_2CH$_2$), 6.90 (s, 1, ArH), 10.36 (s, 1, ArCHO)

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