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Total synthesis of rodgersinol: a survey of the Cu(II)-mediated coupling of *ortho*-substituted phenols

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ABSTRACT

Full details of studies directed toward the total synthesis of both enantiomers of rodgersinol are described. The key parts of our synthetic route to rodgersinol included the Cu(II)-mediated coupling of an arylboronic acid with an *ortho*-alkyl substituted phenol and regio- and stereoselective construction of the hydroxypropyl substituent, which avoided tedious protection/deprotection sequence.

1. Introduction

While 2-arylpropionic acids are well known as an important class of non-steroidal anti-inflammatory drugs (NSAIDs), 2-arylpropanols, such as rodgersinol (**1**) are unusual and rarely identified in nature. Rodgersinol (**1**) is a 2-arylpropanol natural product, isolated from the aerial parts of *Rodgersia podophylla*, which is found in East Asia and has traditionally been used for the treatment of inflammatory diseases. It exhibits significant inhibitory effects on *i*NOS and COX-2 expression in LPS-activated macrophages with IC_{50} values of 2 and 3 μM, respectively.[1] The main structural feature of rodgersinol includes an unique diaryl ether bearing a *p*-hydroquinone, appended with a (*E*)-propenyl moiety at C-1 and a chiral hydroxylpropanyl unit at C-3 position as shown in Figure 1.

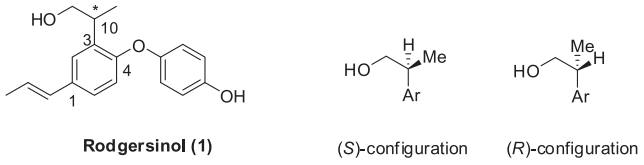

Figure 1. Structure of rodgersinol (**1**).

Considering the unique structural features as well as its excellent biological activities, rodgersinol (**1**) is unarguably a fascinating target for both synthetic chemists and medicinal chemists. In an attempt to design a viable route to the both enantiomers of rodgersinol, we aimed to develop a highly convergent synthetic route employing facile chiral switching at late stage. In this connection, the first total synthesis of (*S*)-(−)-rodgersinol was recently reported by us.[2] Furthermore, comparing both synthetic enantiomers with natural rodgersinol, the absolute stereochemistry at the C-10 position was also elucidated.[2]

On the course of our synthetic studies, we encountered inevitable difficulties in ordering synthetic sequences to couple two parts of the rodgersinol skeleton. This was due to the lack of the related precedents although excellent original papers discussed conditions and mechanism of the diaryl ether coupling. To the best of our knowledge, there are few reports presenting diaryl ether synthesis utilizing various *ortho*-alkyl substituted phenols, which is likely due to the limitation by stereoelectronic effects.[3,4] Herein, we disclosed a full account of the total synthesis of rodgersinol (**1**) and the subsequent structural determination as well as our endeavors for Ulmann-type coupling of a series of *ortho*-substituted phenols to the corresponding diaryl ethers.

2. Result and discussion

Our retrosynthetic analysis of rodgersinol (**1**) is shown in Scheme 1. We hoped to develop a concise and stereo-controlled route from the three synthetic points of view. First, all issues of carbon–carbon and carbon–oxygen bond formation could be achieved by metal-mediated processes, which are virtually void of protecting group manipulations due to their remarkable chemoselectivities. Second, based on our preliminary studies, it is important to introduce the three substituents of the western aromatic ring in an efficient order (A ring in Scheme 1). Indeed, the introduction of the C-3 substituent would be more favorable to proceed between diaryl ether formation and propenyl group installation. Otherwise, we found that such a densely substituted

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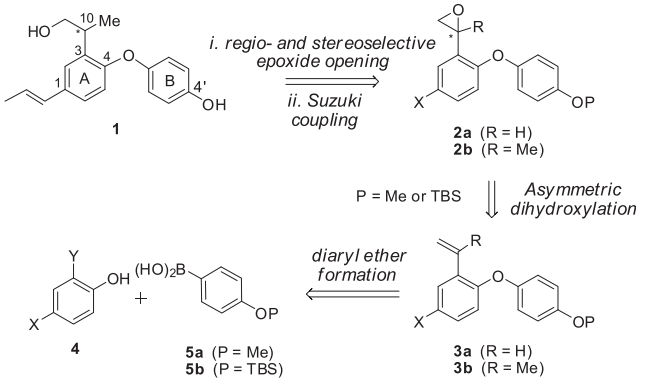


Scheme 1. Retrosynthetic analysis of both (*S*)- and (*R*)-rodgersinol.

aromatic ring unnecessarily required protecting groups and additional transformations. Third, both (*S*)- and (*R*)-enantiomers of rodgersinol could be addressed from the same intermediate at late stage in a regio- and stereoselective manner to achieve maximum efficiency.

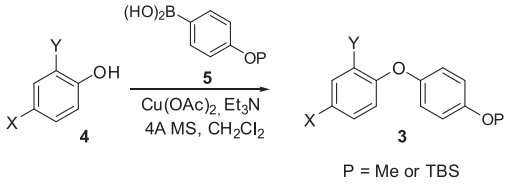
Thus, chiral epoxide **2a** or **2b** was considered to be the optimal intermediate, which could be conveniently transformed into both enantiomers of **1**. These procedures involve Suzuki cross-coupling[5] for the installation of (*E*)-propenyl group and stereoselective methyl addition to aryl oxirane **2a** or hydride addition to 1-methyl-1-aryl oxirane **2b**, respectively. The chiral epoxides **2a** and **2b** would be efficiently introduced via Sharpless asymmetric dihydroxylation[6] of the vinyl- or isopropenyl substituent of the diaryl ethers **3a** and **3b**, which could be obtained from the properly functionalized phenols **4** by coupling with the appropriate boronic acids **5**.[7]

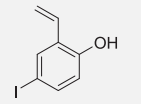
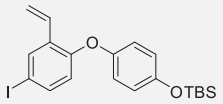
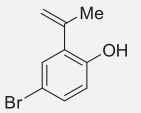
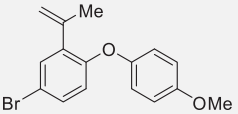
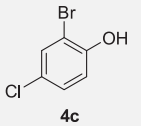
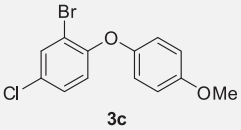
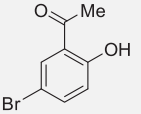
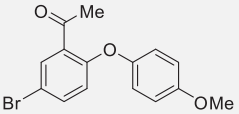
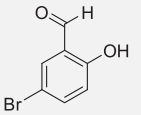
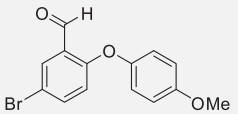
Our synthesis commenced with the preparation of the requisite diaryl ethers **3**. Diaryl ethers have conventionally been prepared by the classical Ullmann-type diaryl ether synthesis or its variations. Development of new methods for the preparation of diaryl ethers has received much attention and there has also been remarkable recent progresses.[3] After considering several effective methods for diaryl ether formation, we selected the $Cu(OAc)_2$ mediated coupling reaction developed by Evans group,[7a,b] because of its mild reaction condition compared to that of other reaction (room temperature versus elevated temperature, >80 °C). However, only a few examples using *ortho*-alkyl substituted phenol (**4**, Y=alkyl group) were found in the literature. On the other hand, it was well-known that the reaction of *ortho*-heteroatom substituted phenols (Y=halogen) proceed smoothly to give the desired O-arylation products. Thus, a number of sterically and electronically diverse substrate **4a**–**e** were initially prepared and evaluated as shown Table 1.

The diaryl ether formation of various phenols **4** with the boronic acids **5** was carried out according to standard procedure.[8] As expected, the *ortho*-heteroatom substituted phenol **4c** underwent facile coupling reaction to afford **3c** in good yield (Table 1, entry 3). Next, we explored the diaryl ether formation with the *ortho*-alkyl substituted **4a** and **4b**.[9] To our delight, treatment of **4a** and **4b** with $Cu(OAc)_2$ in the presence of Et_3N and molecular sieve at room temperature, afforded the desired diaryl ether **3a** and **3b** in 67% and 43% yield (91% and 92% based on recovered starting materials), respectively (entry 1 and 2). The relatively moderate yield seems to arise from the steric factor of *ortho*-substituted alkyl group; however, coupling reaction with the unprecedented *ortho*-alkyl substituted phenols is truly remarkable. It should be also noted that the electron-poor phenols **4d** and **4e** failed to provide the desired coupling products **3d** and **3e** (entry 4 and 5).

With mutigram quantities of the resulting diaryl ethers **3a**–**c** in hand, the remaining challenges of the synthesis were to establish

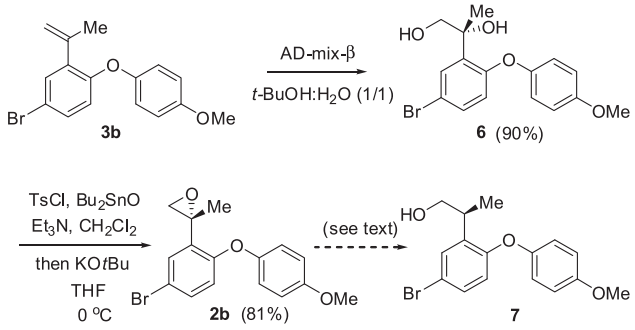
Table 1
Cu(II)-mediated coupling with *ortho*-functional phenols[a]



Entry	Phenol **4**	Diaryl ether **3**	Yield[b] (%)
1	 **4a**	 **3a**	67 (91)[c]
2	 **4b**	 **3b**	43 (92)[c]
3	 **4c**	 **3c**	80
4	 **4d**	 **3d**	NR[d]
5	 **4e**	 **3e**	NR[d]

[a] Reaction condition: 3 equiv of boronic acid **5**, 1 equiv of $Cu(OAc)_2$, 5 equiv of Et_3N, 4 Å MS, CH_2Cl_2, room temperature, 24 h.
[b] Isolated yields after chromatographic purification.
[c] Yield based on recovered starting material.
[d] No reaction.

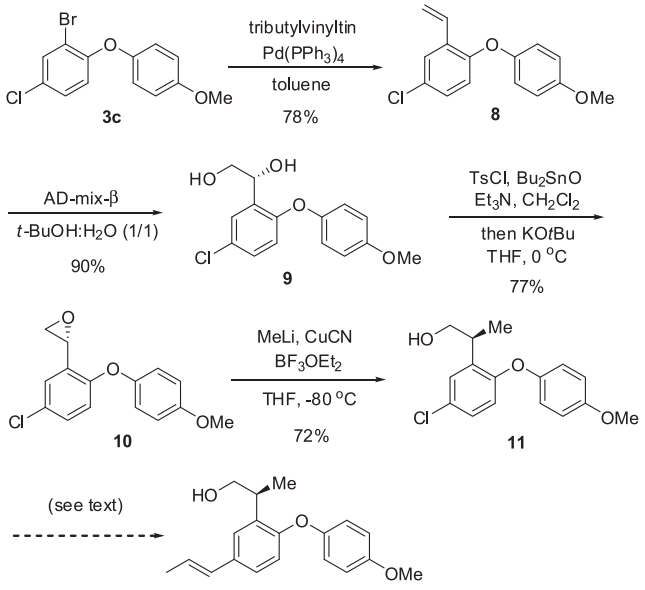
the absolute stereochemistry at C-10 and introduce the propenyl group at C-1. To this end, we initially attempted the synthesis of chiral 2-methyl-2-aryl oxirane **7**, starting from **3b** (Scheme 2). Sharpless asymmetric dihydroxylation of **3b** using AD-mix-β provided the requisite diol **6**, which was transformed into the chiral epoxide **2b** by regioselective tosylation of the primary alcohol using dibutyltin oxide[10] followed by basic treatment (KO*t*-Bu, THF, 0 °C) of the resulting tosylate. With the requisite epoxide **2b** in hand, we



Scheme 2. Initial synthetic approach.

explored a variety of reduction conditions for the epoxide-opening reaction. However, despite extensive efforts involving the use of Raney Nickel and catalytic hydrogenolysis with $Pd(OH)_2$, all attempts to obtain the desired 2-arylpropanol **7** were unsuccessful.[11,12]

Due to the difficulties encountered in epoxide opening together with the significantly low yield of the diaryl ether formation, we attempted an alternative route that employs methyl addition to the epoxide instead of reductive ring-opening (Scheme 3). We performed the conversion of diaryl ether **3c**, which was obtained in highest chemical yield (80%, Table 1, entry 3), to the 2-vinyl-substituted diaryl ether **8** by Stille coupling (Scheme 3) in 78% yield. We transformed the 2-vinyl-substituted product **8** into the epoxide **10** according to the same sequence shown in Scheme 2 and the epoxide **10** could be converted to the 2-arylpropanol **11** upon methyl cuprate treatment in the presence of BF_3. However, the final step of coupling aryl chloride **11** with the propenyl group was unsuccessful, despite using a variety of cross-coupling reaction conditions including the remarkable catalysts, such as $Pd(t\text{-}Bu)_3$ and Verkade's proazaphosphatrane.[13] Unfortunately, only starting material was recovered.

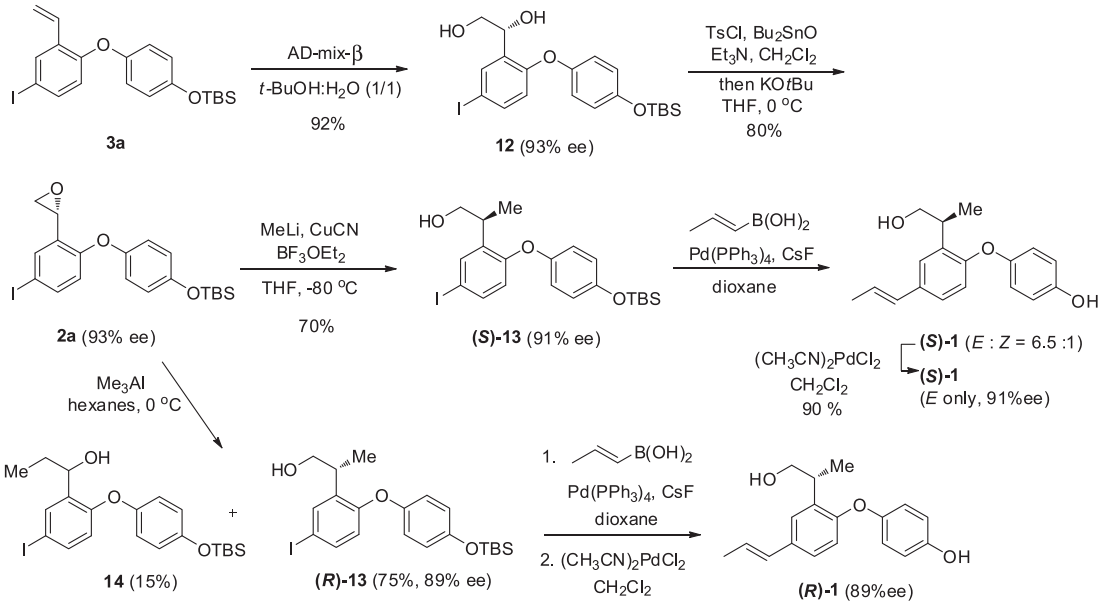


Scheme 3. Revised synthetic approach.

Consideration of the synthetic barrier associated with the poor reactivity of aryl chloride (i.e., **11**) toward the projected Suzuki coupling led us to select 2-vinyl-4-iodo-substitued diaryl ether **3a** as an optimal substrate. Thus, we synthesized the requisite epoxide **2a** through three-step sequence (asymmetric dihydroxylation, selective tosylation, and epoxide formation with base) as shown Scheme 4. Introduction of methyl group at C-10 could be accessed to provide each enantiomer from the same intermediate (i.e., **2a**) by employing two different types of protocols.[14] Upon treatment of (*R*)-epoxide **2a** with methyl cuprate, (*S*)-2-arylpropanol (***S***)-**13** was obtained with stereochemical inversion in 70% yield and 91% ee[14a] In contrast, reaction of the (*R*)-epoxide **2a** with methyl aluminum provided the (*R*)-2-arylpropanol (***R***)-**13** as a major product with retention of configuration in 75% yield and 89% ee,[14b] along with a small amount of regioisomer **14** (15%). The inversion of the stereochemistry could be understood by the intermolecular backside attack of the methyl cuprate promoted by BF_3 while the retention could be explained by an intramolecular methyl migration via aluminum complexed aryl oxirane. Fukumasa et al. proposed an intermediary carbenium ion for the rationalization of retention evidenced by an MO calculation.[14b] Our transformation employing these facile chiral switching protocols proved highly effective by HPLC analysis.[2]

Completion of the total synthesis of both (*S*)- and (*R*)-rodgersinols could be accomplished by the final Suzuki cross-coupling[5,15] from (***S***)-**13** and (***R***)-**13**, respectively. For the Suzuki reaction of (***S***)-**13**, the commercially available (*E*)-propenyl boronic acid, $Pd(PPh_3)_4$ as catalyst and CsF as base were used, effecting simultaneous removal of the TBS group to afford (*S*)-rodgersinol ((***S***)-**1**). As the resulting product was elucidated to be a mixture of *E*/*Z* olefins as a 6.5:1 ratio on the basis of ^1H NMR spectroscopy, $(CH_3CN)_2PdCl_2$-induced olefin isomerization of the mixture afforded (*S*)-rodgersinol ((***S***)-**1**) as an exclusive (*E*)-isomer.[16] In the same manner as the synthesis of (***S***)-**1**, (***R***)-**1** could also be obtained from (***R***)-**13**.

The 2-arylpropanoic acid moiety[17] is a well-known class of non-steroidal anti-inflammatory agents, such as ibuprofen, naproxen,



Scheme 4. Completion of total synthesis of both (*S*)- and (*R*)-rodgersinols.

and ketoprofen.[18] Furthermore, it was representatively revealed that (*S*)-(+)-ibuprofen (dexibuprofen) is the active enantiomer both in vitro and in vivo. Therefore, rodgersinol might be easily comparable with 2-arylpropanoic acids due to the structural and biological similarity. As evidenced by the higher anti-inflammatory activity of 2-arylpropanoic acid with (*S*)-configuration at the chiral center, we also anticipated that the stereochemistry of C-10 stereogenic center would be (*S*)-configuration. As expected, comparing the optical rotation [synthetic (***S***)-**1**, $[\alpha]_D^{20}$ −12.7 (*c* 0.17, MeOH); synthetic (***R***)-**1**, $[\alpha]_D^{20}$ +12.3 (*c* 0.05, MeOH); natural **1**, $[\alpha]_D^{20}$ −14.6 (*c* 0.04, MeOH)] as well as chiral HPLC analysis, the absolute configuration of C-10 stereogenic center was finally determined as (*S*)-configuration.[2]

3. The conclusions

In conclusion, the concise syntheses of both enantiomers of rodgersinol have been achieved from 4-iodo-2-vinylphenol **4a** in high yields. The key features of the synthesis involved efficient diaryl ether formation together with the stereoselective methyl additions to a chiral 2-aryl oxirane for the asymmetric synthesis of the requisite 2-arylpropanol skeleton. In particular, some of the previously unreported scope and limitation in diaryl etherification that could be easily encountered in practical synthesis was elucidated. Our efficient synthetic strategy enabled us to determine the absolute configuration at C-10 of rodgersinol as well as to expand the preparation of other enantiomer and its analogs, which would provide further studies for structure/activity relationship of rodgersinol.

4. Experimental

4.1. General

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Optical rotations were measured with JASCO DIP-1000 digital polarimeter at ambient temperature using 100 mm cell of 2 mL capacity. Infrared spectra were recorded on a Perkin/Elmer 1710 FT-IR spectrometer. Mass spectra were obtained with VG Trio-2 GC–MS instrument. High-resolution mass spectra were obtained with JEOL JMS-AX 505WA instrument. ^{1}H and ^{13}C NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonances), number of protons, and coupling constant in hertz (Hz).[19]

*4.1.1. 4-Bromo-2-isopropenylbenzenol (**4b**).* To a solution of methyltriphenylphosphonium bromide (1.443 g, 4.04 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (2.53 mL of 1.6 M solution in hexane, 4.04 mmol). After stirring for 1 h, a solution of 1-(5-bromo-2-hydroxyphenyl)ethanone (430 mg, 2.02 mmol) in THF (3 mL) was added to this mixture at 0 °C. The reaction mixture was slowly warmed to ambient temperature and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and then diluted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes=1: 6) afforded 375 mg (88%) of **4b** as a colorless oil: FT-IR (thin film, neat) ν_{max} 3503, 1483, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19–7.16 (m, 2H), 6.75 (d, 1H, *J*=9.2 Hz), 5.57 (s, 1H), 5.35 (m, 1H), 5.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0, 150.0, 131.3, 130.8, 130.4, 117.4, 116.7, 112.2, 24.0; LR-MS (FAB) *m*/*z* 213 $(M+H)^+$; HR-MS (FAB) calcd for C_9H_9BrO $(M+H)^+$ 212.9915; found 212.9910.

*4.1.2. 4-Bromo-2-isopropenyl-1-(4-methoxyphenoxy) benzene (**3b**).* To a solution of phenol **4b** (300 mg, 1.41 mmol), boronic acid **5a** (640 mg, 4.23 mmol), and copper acetate (50 mg, 2.82 mmol) in the presence of 4 Å molecular sieves in CH_2Cl_2 (28 mL), was added triethylamine (0.98 mL, 7.05 mmol). The reaction mixture was vigorously stirred for 24 h at ambient temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified via flash column chromatography on silica gel (EtOAc/hexanes=1: 20) to afford 193 mg (43%, 92% borsm) of **3b** as a colorless oil and 160 mg of the starting phenol **4b** (EtOAc/hexane=1: 5): FT-IR (thin film, neat) ν_{max} 2953, 1504, 1226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, 1H, *J*=2.4 Hz), 7.26 (dd, 1H, *J*=8.6, 2.4 Hz), 6.90–6.82 (m, 4H), 6.66 (d, 1H, *J*=8.6 Hz), 5.16–5.12 (m, 2H), 3.77 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 150.6, 142.0, 136.8, 132.4, 131.0, 120.0, 119.9, 119.6, 116.6, 115.4, 114.9, 55.7, 23.0; LR-MS (FAB) *m*/*z* 318 (M^+).

*4.1.3. 2-[5-Bromo-2-(4-methoxyphenoxy)phenyl]-1,2-propanediol (**6**).* To a solution of diaryl ether **3b** (150 mg, 0.47 mmol) in *t*-BuOH/H_2O (5 ml, 1:1) at 0 °C was added the commercially available AD-mix-β (628 mg). After stirring for 5 h, sodium sulfite was slowly added and the suspension was warmed to ambient temperature with vigorous stirring. The mixture was diluted with EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes=1: 1) afforded 146 mg (88%) of **6** as a colorless oil: FT-IR (thin film, neat) ν_{max} 3465, 2979, 1757, 1482, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, *J*=2.5 Hz), 7.21 (dd, 1H, *J*=8.6, 2.4 Hz), 6.88–6.81 (m, 4H), 6.54 (d, 1H, *J*=8.7 Hz), 4.02 (d, 1H, *J*=11.0 Hz), 3.79 (s, 3H), 3.72 (d, 1H, *J*=11.0 Hz), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 154.6, 149.2, 136.1, 131.4, 130.9, 120.8, 119.2, 115.6, 115.2, 74.8, 69.0, 55.7, 24.4; LR-MS (FAB) *m*/*z* 352 (M^+).

*4.1.4. 2-[5-Bromo-2-(4-methoxyphenoxy)phenyl]-2-methyloxirane (**2b**).* To a solution of diol **6** (57 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C were added dibutyltin oxide (0.8 mg, 3.24 μmol), *p*-toluenesulfonyl chloride (34 mg, 0.18 mmol), and triethylamine (27 μL, 0.19 mmol). After stirring for 5 h at ambient temperature, the reaction mixture was concentrated in vacuo. Purification of the residue via flash chromatography on silica gel (EtOAc/hexanes=1: 3) afforded 75 mg (92%) of the mono-tosylate compound as a colorless oil: FT-IR (thin film, neat) ν_{max} 3521, 2923, 1505, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69–7.64 (m, 3H), 7.28–7.23 (m, 3H), 6.90–6.82 (m, 4H), 6.50 (d, 1H, *J*=8.6 Hz), 4.47 (d, 1H, *J*=9.7 Hz), 4.37 (d, 1H, *J*=9.7 Hz), 3.81 (s, 3H), 3.25 (s, 1H), 2.42 (s, 3H), 1.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 154.5, 148.5, 144.9, 134.0, 132.6, 131.8, 130.8, 129.8, 127.9, 121.1, 118.4, 115.4, 115.1, 75.1, 73.0, 55.7, 24.2, 21.6; LR-MS (FAB) *m*/*z* 506 (M^+); HR-MS (FAB) calcd for $C_{23}H_{23}BrO_6S$ (M^+) 506.0399; found 506.0396.

To a solution of mono-tosylate (46 mg, 0.09 mmol) in THF (1 mL) at 0 °C was added potassium *tert*-butoxide (1 mL of 1.0 M solution in THF, 0.10 mmol). After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then diluted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue

via flash column chromatography on silica gel (EtOAc/hexanes=1:5) afforded 27 mg (89%) of the epoxide **2b** as a colorless oil: FT-IR (thin film, neat) ν_{max} 2928, 1501, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, 1H, J=2.6 Hz), 7.30 (dd, 1H, J=2.6, 8.8 Hz), 6.95–6.87 (m, 4H), 6.63 (d, 1H, J=8.8 Hz), 3.81 (s, 3H), 2.92 (d, 1H, J=5.3 Hz), 2.79 (m, 1H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 154.8, 149.8, 134.0, 131.6, 130.6, 120.3, 118.7, 115.2, 115.0, 56.0, 55.7, 55.2, 23.0; LR-MS (FAB) m/z 334 (M^+); HR-MS (FAB) calcd for $C_{16}H_{15}BrO_3$ (M^+) 334.0205; found 334.0209.

*4.1.5. 2-Bromo-4-chloro-1-(4-methoxyphenoxy)benzene (**3c**).* By the same procedure as for the synthesis of diaryl ether **3b**, except with 2-bromo-4-chloro-phenol **4c** in place of phenol **4b**, diaryl ether **3c** was obtained in 80% yield as colorless oil. (EtOAc/hexanes=1:20): FT-IR (thin film, neat) ν_{max} 2952, 1503, 1468, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, 1H, J=2.6 Hz), 7.19 (dd, 1H, J=2.4, 8.8 Hz), 6.97–6.84 (m, 4H), 6.76 (d, 1H, J=8.8 Hz), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 153.9, 149.6, 133.1, 128.5, 128.3, 120.3, 119.2, 115.0, 114.1, 55.7; LR-MS (FAB) m/z 312 (M^+); HR-MS (FAB) calcd for $C_{13}H_{10}BrClO_2$ (M^+) 311.9553; found 311.9540.

*4.1.6. 4-Chloro-1-(4-methoxyphenoxy)-2-vinylbenzene (**8**).* To a solution of diaryl ether **3c** (310 mg, 0.99 mmol) and tributyl(vinyl)tin (97%, 320 mg, 0.99 mmol) in toluene (7 ml), tetrakis(triphenylphosphine)palladium (0) (60 mg, 0.05 mmol) was added. The reaction mixture was stirred for 1 h and heated to reflux for 24 h. The mixture was cooled and filtered through short pad of silica gel. The filtrate was concentrated in vacuo. Purification of the residue via flash chromatography on silica gel (EtOAc/hexanes=1:20) afforded 234 mg (91%) of the styrene **8** as a colorless oil. FT-IR (thin film, neat) ν_{max} 2952, 1504, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, 1H, J=2.4 Hz), 7.12 (dd, 1H, J=2.6, 8.8 Hz), 7.03 (dd, 1H, J=11.0, 17.7 Hz), 6.91–6.83 (m, 4H) 6.73 (d, 1H, J=8.7 Hz), 5.82 (d, 1H, J=17.7 Hz), 5.34 (d, 1H, J=11.4 Hz), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 153.5, 150.5, 130.3, 130.0, 128.5, 128.2, 126.2, 119.7, 119.4, 116.3, 114.9, 55.5; LR-MS (FAB) m/z 260 (M^+); HR-MS (FAB) calcd for $C_{15}H_{13}ClO_2$ (M^+) 260.0604; found 260.0599.

*4.1.7. 1-[5-Chloro-2-(4-methoxyphenoxy)phenyl]-1,2-ethanediol (**9**).* By the same procedure as for the synthesis of diol **6**, except with styrene **8** in place of diaryl ether **3b**, diol **9** was obtained in 90% yield as a white solid: FT-IR (thin film, neat) ν_{max} 3395, 2930, 1505, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, 1H, J=2.6 Hz), 7.08 (d, 1H, J=8.7 Hz), 7.08–6.80 (m, 4H), 6.61 (d, 1H, J=8.7 Hz), 5.15 (dd, 1H, J=2.9, 7.9 Hz), 3.84 (m, 1H), 3.75 (s, 3H), 3.62 (m, 1H), 3.35–3.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 153.5, 149.5, 132.1, 128.4, 127.9, 127.4, 120.4, 117.8, 115.0, 69.6, 66.5, 55.6; LR-MS (FAB) m/z 294 (M^+); HR-MS (FAB) calcd for $C_{15}H_{15}ClO_4$ (M^+) 294.0659; found 294.0669.

*4.1.8. 2-[5-Chloro-2-(4-methoxyphenoxy)phenyl]oxirane (**10**).* By the same procedure as for the synthesis of phenyloxirane **2b**, except with diol **9** in place of diol **6**, phenyloxirane **10** was obtained in 77% yield (two steps) as a colorless oil: FT-IR (thin film, neat) ν_{max} 2925, 1504, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.18 (d, 1H, J=2.4 Hz), 7.13 (dd, 1H, J=2.6, 8.7 Hz) 6.93–6.85 (m, 4H), 6.70 (d, 1H, J=8.7 Hz), 4.19 (m, 1H), 3.79 (s, 3H), 3.13 (m, 1H), 2.71 (dd, 1H, J=2.5, 5.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 155.2, 150.2, 130.2, 128.7, 128.5, 125.4, 120.0, 118.5, 115.1, 55.7, 50.9, 48.0; LR-MS (FAB) m/z 276 (M^+); HR-MS (FAB) calcd for $C_{15}H_{13}ClO_3$ (M^+) 276.0553; found 276.0547.

*4.1.9. 2-[5-Chloro-2-(4-methoxyphenoxy)phenyl]-1-propanol (**11**).* To a solution of copper cyanide (222 mg, 2.44 mmol) in THF (2 mL) was added methyl lithium (1.52 mL of 1.60 M solution in THF, 2.44 mmol) at −40 °C. The reaction mixture was stirred for 30 min and $BF_3 \cdot OEt_2$ (0.48 mL, 2.44 mmol) and a solution of the phenyloxirane **10** (135 mg, 0.49 mmol) was added dropwise at −80 °C. The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl and NH_4OH, and then diluted with Et_2O. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes=1:1) afforded 97 mg (68%) of the 2-arylpropanol **11** as a colorless oil: FT-IR (thin film, neat) ν_{max} 3366, 2961, 1504, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, 1H, J=2.8 Hz), 7.11 (dd, 1H, J=2.6, 8.6 Hz) 6.92–6.83 (m, 4H), 6.72 (d, 1H, J=8.6 Hz), 3.82–3.70 (m, 2H), 3.80 (s, 3H), 3.49 (m, 1H), 1.30 (d, 1H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 154.5, 150.5, 136.0, 128.2, 128.0, 127.4, 119.8, 119.1, 115.0, 67.5, 55.7, 35.5, 16.7; LR-MS (FAB) m/z 292 (M^+); HR-MS (FAB) calcd for $C_{16}H_{17}ClO_3$ (M^+) 292.0866; found 292.0864.

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Supplementary data

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