Preparation of 2,8-Dihydroxy-5,6,11,12-Tetrahydro-5,11-epoxydibenzo[*a*,*e*]cyclooctene, an Analogue of Kagan's Ether

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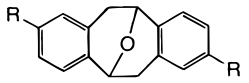
As part of our work with Kagan's ether **1** we came to need an analogue of **1** which could be used to prepare a variety of ligands for the purpose of constructing chiral catalysts and/or large molecular architectures, such as molecular squares or other large ring systems.[1−3] We decided to pursue the synthesis of the simple dihydroxy compound **2**. This report describes the synthesis of racemic and both enantiomerically enriched (*R*,*R*) and (*S*,*S*)-**2**.

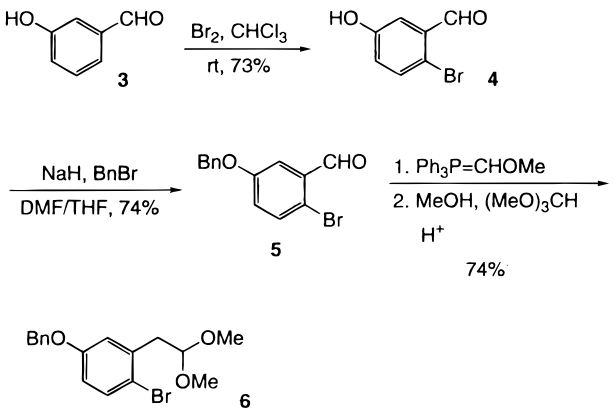


1: R = H
2: R = OH

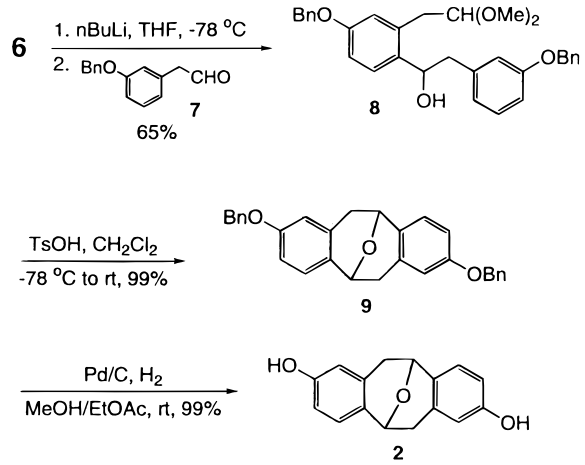
The initial target in our synthesis was the acetal **6**. This was prepared as previously reported (Scheme 1).[1d] Commercially available *m*-hydroxybenzaldehyde was treated with bromine in chloroform to afford 2-bromo-5-hydroxybenzaldehyde **4** in 73% yield.[4] This was treated with NaH in DMF/THF followed by benzyl bromide to give the benzyl ether **5** in 74% yield.[5] Wittig homologation of this aldehyde and formation of an acetal with acidic methanol and trimethyl orthoformate afforded **6** in 74% yield.

With **6** in hand, we proceeded with an alkylation involving halogen−metal exchange and reaction with *m*-(benzyloxy)phenylacetaldehyde.[6] This gave alcohol **8** in 65% yield. For **8**, ^{1}H NMR showed the presence of 18 aromatic protons and two diastereotopic methoxy groups at 3.31 and 3.27 ppm, indicating the presence of a stereogenic center in the molecule.

Scheme 1



Scheme 2



The most interesting aspect of this synthesis involved the next step. Treatment of **8** with tosic acid in dichloromethane resulted in both cyclic acetal formation and intramolecular Friedel−Crafts alkylation to afford **9** in virtually quantitative yield. This is not typical in these systems and presumably results from the presence of an electron-rich aromatic ring, capable of undergoing alkylation under relatively mild conditions. Hydrogenolysis of **9** afforded the target compound **2** as a racemate in 99% yield.

rac-**2** was characterized by standard spectroscopic means as well as by X-ray analysis. The important features of this and all other Kagan's ether analogues are that they are chiral and rigid. In general, the angle between the least squares planes of the benzene rings is around 90°. In the case of **2**, it is 92.4°.

To access enantiomerically enriched versions of **2**, two approaches were taken. In the first, alcohol **8** was oxidized using the Swern procedure to afford ketone **10** in 94% yield (Scheme 3).[7] Reduction with oxazaborolidine **11** gave the alcohol **8** in enantiomerically enriched form.[8] Analysis of the crude reaction mixture using a Chiracel OJ column eluted with pure ethanol (1 mL/min) showed

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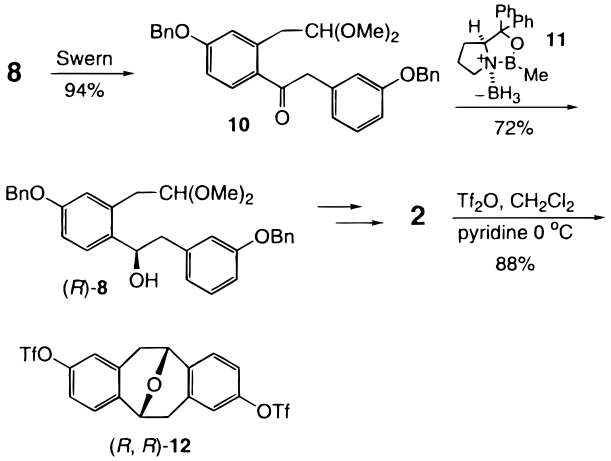
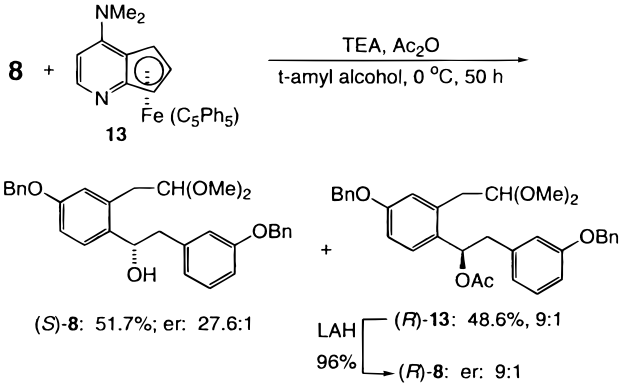
Scheme 3



Scheme 4



two peaks at 17.6 and 21.3 min, respectively. The latter corresponded to the major isomer. The enantiomeric ratio was 87.5 to 12.5 (7:1). Attempted improvement of this ratio using various reaction conditions failed. However, it was found that treatment of the diol with triflic anhydride afforded the ditriflate **12**. This could be recrystallized to high enantiomeric purity, according to HPLC analysis.

Another approach to scalemic **8** involved Fu's kinetic resolution procedure (Scheme 4).[9] Thus, treatment of **8** with acetic anhydride in *tert*-amyl alcohol in the presence of 0.76 mol % of catalyst **13** at 0 °C afforded (*S*)-**8** and the acetate **14** in 51.7% and 43.6% yields, respectively. Acetate **14** was reduced to the alcohol (*R*)-**8** with LAH in 96% yield. The er of the alcohols was determined using HPLC and was found to be 27.6:1 for (*S*)-**8** and 9:1 for (*R*)-**8**.[10] The stereochemical assignments were based on Fu's work and the results obtained from the oxazaborolidine reduction. These alcohols could be taken through the sequence described above to prepare both (*S*,*S*)-and (*R*,*R*)-**2**.

In summary, we have developed a synthesis for racemic **2** and both of its enantiomers. Application of these molecules to the synthesis of a chiral molecular square has been accomplished and other applications are in progress.[11] Results will be reported in due course.

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Experimental Section

2-Bromo-5-hydroxybenzaldehyde (4). To a 500 mL flame-dried, three-necked flask equipped with a magnetic stir bar, a nitrogen inlet, an addition funnel, and two glass stoppers were added *m*-hydroxybenzaldehyde (30.0 g, 0.24 mol) and dry $CHCl_3$ (245 mL). The addition funnel was charged with bromine (12.36 mL, 0.24 mol) which was allowed to add into the flask dropwise over 40−45 min (**CAUTION:** This reaction should be conducted in a good fume-hood). When the addition of bromine was complete, the mixture was stirred at room temperature for about 3 h. Aqueous (10%) glacial acetic acid (100 mL) was added. The resulting black residue was treated with charcoal and filtered through some Celite. The filtrate was then extracted with ether (3 × 100 mL), washed with water and brine, and dried over Na_2SO_4. The extracts were filtered through Celite. The solvent was removed on a rotary evaporator to give a brown solid which was recrystallized from hexane and ether to give light brown crystals (36.22 g, 73%). mp 130 °C, lit.[4] mp 134 °C.

2-Bromo-5-(benzyloxy)benzaldehyde (5). To a 250 mL flame-dried, three-necked flask equipped with a magnetic stir bar, a nitrogen balloon, an addition funnel and two septa was added NaH (2.06 g, 0.051 mol, 60% dispersion in mineral oil) and then rinsed with dry hexanes. A 5:1 mixture of dry THF: DMF (120 mL) was added into the flask. The flask was cooled to 0 °C in an ice bath. One of the septa was replaced with a powder funnel, and solid 2-bromo-5-hydroxybenzaldehyde (10 g, 0.49 mol) was added slowly over a 10 min period. The addition funnel was then charged with benzyl bromide (8.74 mL, 0.073 mol) that was added into the flask dropwise over 20−25 min. When the addition of benzyl bromide was complete, the mixture was allowed to stir at room-temperature overnight. The reaction was quenched with the addition of brine solution (50 mL). The mixture was rinsed into a separatory funnel and extracted with ether (3 × 50 mL), and the organic extracts were washed with water (3 × 50 mL) and brine (1 × 20 mL) and dried over Na_2SO_4. The solvent was removed on a rotary evaporator to give an off-white solid which was recrystallized from hexane and ether to give white crystals (10.7 g, 74%). mp 51−52 °C, lit. 53−54 °C.[5]

2-Bromo-5-(benzyloxy)phenylacetaldehyde Dimethylacetal (6). To a 1 L flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum were added freshly distilled diisopropylamine (15.5 mL, 0.11 mol) and dry THF (741 mL). The flask was cooled to 0 °C in an ice bath. To this flask, was added *n*-BuLi (46.25 mL, 0.11 mol, 2.4 M in hexane) dropwise via a syringe. Powdered (methoxymethyl)-triphenylphosphonium chloride (38.21 g, 0.11 mol) was added as a solid, resulting in a blood-red-colored solution. The mixture was allowed to stir at room temperature for 1−2 h. To this solution was then added a solution of 2-bromo-5-(benzyloxy)-benzaldehyde (21.7 g, 0.074 mol) in 50 mL of dry THF via a syringe over 15−20 min. The reaction mixture was stirred at room temperature for about 8 h. The reaction was quenched with the addition of brine solution (100 mL) and then rinsed into a separatory funnel. The mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with water (3 × 100 mL) and brine (1 × 100 mL) and dried over Na_2SO_4 Removal of solvent afforded a residue which was evacuated at about 0.2 mmHg for 1 h. Dry methanol (743 mL), trimethyl orthoformate (163 mL, 1.48 mol), and 11.5 mL of concentrated sulfuric acid were added, and the mixture was allowed to reflux for 4 h. After cooling, the flask was placed on a rotary evaporator to remove about 2/3 of the methanol. The resulting residue was then rinsed into a separatory funnel and diluted with ethyl acetate (200 mL). It was washed with water (3 × 100 mL) and brine (1 × 100 mL) and was dried over Na_2SO_4 and filtered. After removal of solvent, the residue was purified by flash chromatography (20% ethyl acetate in hexanes in the presence of 1% triethylamine) to give the product as a white solid. An analytical sample was obtained by recrystallization from hexane and ethyl acetate to give white crystals (19.35 g, 74%). mp 64−65 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42−7.30 (m, 6H), 6.94 (d, 1H, J = 3.0 Hz), 6.72 (dd, 1H, J = 3.0 Hz, J = 8.8 Hz), 5.02 (s, 2H), 4.57 (t, 1H, J = 5.6 Hz), 3.33 (s, 6H), 3.00 (d, 2H, J = 5.6 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.9, 137.4, 136.6, 133.0, 128.6, 128.0, 127.4, 118.4, 115.5, 115.0, 103.9, 70.1, 53.8, 40.0. IR

(KBr) 1241 (s), 1125 (s), 1116 (s), 1086 (s), 1019 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{19}BrO$: C, 58.13; H, 5.45. Found: C, 57.88; H, 5.42.3.

(±)-1-[2-(2,2-Dimethoxyethyl)-4-(benzyloxy)phenyl]-2-[3-(benzyloxy)phenyl]ethan-1-ol (8). To a 100 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum were added bromoacetal **6** (2.85 g, 12 mmol) and freshly distilled THF (62 mL). The flask was cooled to −78 °C in an IPA/dry ice bath. *n*-BuLi (5.5 mL, 13 mmol, 2.4 M solution in hexane) was added via a syringe over 5 min, and the mixture was allowed to stir at −78 °C for 1 h. To the resulting yellow solution was added the aldehyde **7** (3.14 g, 13 mmol) as a solution in dry THF (5 mL). The reaction was stirred at −78 °C for 1 h. The mixture warmed to the room temperature and stirred for 1 h. The reaction was quenched by addition of water and rinsed into a separatory funnel. The mixture was extracted with ethyl acetate (3 × 25 mL), and the organic extracts were washed with water (3 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and filtered. Removal of solvent afforded a residue which was purified by flash chromatography (20% ethyl acetate in hexanes in the presence of 1% triethylamine) to give the product as a clear oil (4.3 g, 65%). An analytical sample was obtained by taking a middle fraction from the flash chromatography. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.28 (m, 11H), 7.20 (t, 1H, J = 7.7 Hz), 6.92−6.81 (m, 5H), 5.11 (ddd, 1H, J = 2.2 Hz, J = 5.3 Hz, J = 7.7 Hz), 5.05 (s, 2H), 5.01 (2H), 4.40 (t, 1H, J = 5.10 Hz), 3.31 (s, 3H), 3.27 (s, 3H), 3.07−3.02 (m, 2H), 2.95 (d, 1H, J = 6.0 Hz), 2.91 (d, 1H, J = 5.0 Hz), 2.72 (d, 1H, J = 2.3 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.8, 157.8, 140.5, 137.0, 136.9, 135.8, 135.0, 129.4, 128.5, 128.0, 127.6, 127.4, 122.0, 116.8, 115.9, 133.2, 112.76, 106.9, 70.8, 69.9, 69.8, 54.3, 53.5, 44.0, 36.2. IR (Neat) 1595 (s), 1510 (s), 1458 (s), 1386 (s), 1249 (s) cm^{-1}. Anal. Calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 77.29; H, 7.08.

1-[2-(2,2-Dimethoxyethyl)-4-(benzyloxy)phenyl]-2-[3-(benzyloxy)phenyl]ethanone (10). To a 25 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, an addition funnel, and a septum were added oxalyl chloride (0.196 mL, 2.25 mmol) and freshly distilled CH_2Cl_2 (9 mL). The flask was cooled to −78 °C in an IPA/dry ice bath. To the flask, DMSO (0.32 mL, 4.5 mmol) was added through the addition funnel over 5 min as a solution in 5 mL of CH_2Cl_2, and the reaction was allowed to stir at −78 °C for 10 min. The alcohol **8** (0.90 g, 1.80 mmol) was then added as a solution in dry CH_2Cl_2 (5 mL). The reaction was allowed to stir at −78 °C for 30 min. Freshly distilled TEA (1.25 mL, 9.0 mmol) was added dropwise via syringe, and the mixture was allowed to stir at −78 °C for 1 h. TLC showed the completion of the reaction. The reaction was quenched by addition of water (10 mL) and rinsed into a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were washed with water (3 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and filtered. Solvent removal afforded a residue which was purified by flash chromatography (10% ethyl acetate in hexanes in the presence of 1% triethylamine) to give the product as clear oil (0.83 g, 94%). An analytical sample was obtained by taking a middle fraction from the flash chromatagraphy. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 8.7 Hz), 7.42−7.31 (m, 11H), 6.92−6.82 (m, 5H), 5.08 (s, 2H), 5.01 (s, 2H), 4.44 (t, 1H, J = 5.4 Hz), 4.14 (s, 2H), 3.26 (s, 6H), 3.14 (d, 2H, J = 5.4 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 199.5, 160.8, 159.0, 140.6, 136.9, 136.5, 136.5, 136.3, 131.5, 130.4, 129.6, 128.6, 128.5, 128.1, 127.9, 127.4, 122.1, 119.4, 116.0, 113.1, 112.3, 105.3, 69.9, 69.9, 54.0, 48.1, 38.4. IR (neat) 1605 (s), 1572 (s), 1503 (s), 1241 (s), 1161 (s) cm^{-1}. Anal. Calcd for $C_{32}H_{32}O_5$: C, 77.40; H, 6.50. Found: C, 77.70; H, 6.70.

Asymmetric Reduction of 10. (*R*)-(−)-1-[2-(2,2-Dimethoxyethyl)-4-(benzyloxy)phenyl]-2-[3-(benzyloxy)phenyl]ethan-1-ol (8). To a 10 mL flame-dried recovery flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum was added the oxazaborolidine **11** (0.38 g, 1.3 mmol) under nitrogen in a glovebag. Freshly distilled methylene chloride (2.6 mL) was added to give ca. 0.5 M solution. The flask was cooled to −20 °C in methanol/ice/salt bath. To the solution of the oxazaborolidine, the ketone **10** (0.65 g, 1.3 mmol) was added as a solution in 1 mL of dry methylene chloride over 10−15 min. After the addition of all of the ketone, the mixture was allowed to stir at −20 °C for 1 h. The reaction was quenched by the addition of methanol (5 mL) and stirred at −20 °C for 25 min. The mixture was rinsed into a separatory funnel and extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (3 × 25 mL) and brine (1 × 25 mL) and dried over Na_2SO_4 and filtered. Removal of solvent afforded a residue which was purified by flash chromatography (20% ethyl acetate in hexanes in the presence of 1% triethylamine) to give the product as a clear oil (0.42 g, 72%). The analysis of the crude reaction mixture by a Chiracel OJ column revealed the enantiomer ratio to be 7:1. The column was eluted with 100% EtOH at a flow rate of 1 mL/min. The retention time of (*R*)-isomer was 21.3 min and (*S*)-isomer was 17.6 min.

Kinetic Resolution of *rac*-8. (*S*)-(+)-1-[2-(2,2-Dimethoxyethyl)-4-(benzyloxy)phenyl-2-[3-(benyloxy)phenyl]ethan-1-ol (8). To a 25 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum were added *rac*-**8** (1.29 g, 2.58 mmol) and the catalyst **13** (13 mg, 0.76 mol %) and dissolved in freshly distilled *tert*-amyl alcohol (17 mL) to give ca. 0.15 M solution. The flask was gently heated with a hot gun to dissolve the catalyst. The flask was then placed in a precooled bath at 0 °C. Freshly distilled TEA (0.27 mL, 1.93 mmol) was added in one portion and stirred for 5 min. To this well-stirred solution, the freshly distilled Ac_2O (0.18 mL, 1.93 mmol) was added via a syringe dropwise over 10 min. This solution was allowed to stir at 0 °C for 50 h. TLC showed the partial completion of the reaction. The reaction mixture was filtered through a small plug of silica gel to remove the catalyst. The filtrate was concentrated on a rotary evaporator. The residue was then purified by flash chromatography (20% ethyl acetate in hexanes in the presence of 1% triethylamine to give acetate (*R*)-**14** (0.61 g, 43.6%) and alcohol (*S*)-**8** (0.68 g, 52.7%). The analysis of the alcohol with a Chiracel OJ column eluted with 100% EtOH revealed that the enantiomer ratio to be 27.6:1, $[\alpha]^{24}_D$ = 10.6 (1.0, CH Cl). The acetate was reduced to the alcohol with $LiAlH_4$ in 96% yield and analyzed under the same conditions. The enantiomeric ratio was measured to be 9:1, $[\alpha]^{24}_D$ = −9.52 (1.05, CH_2Cl_2).

2,8-Bis(benzyloxy)-5,6,11,12-tetrahydro-5,11-epoxydibenzo[*a*,*e*]cyclooctene (9). To a 100 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum were added alcohol **8** (1.72 g, 3.4 mmol) and freshly distilled CH_2Cl_2 (69 mL). The flask was then cooled to −78 °C in an IPA/dry ice bath. To this solution was added *p*-toluenesulfonic acid (59 mg, 0.31 mmol, 0.09 equiv) as a solid in one portion, and the bath was removed. The solution was allowed to come to room temperature and stirred for 6−8 h. To the mixture was added solid K_2CO_3 and stirring was continued for 10 min. The K_2CO_3 was removed by filtration. After removal of the solvent, the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give the product as a white solid (1.49 g, 99%). An analytical sample was obtained by recrystallization from hexane and ethyl acetate. mp 130−131 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.21 (m, 10H), 6.94 (d, 2H, J = 8.5 Hz), 6.73 (dd, 2H, J = 2.5 Hz, J = 8.4 Hz), 6.56 (d, 2H, J = 2.3 Hz), 5.20 (d, 2H, J = 5.6 Hz), 4.87 (s, 4H), 3.46 (dd, 2H, J = 5.9 Hz, J = 16.2 Hz), 2.65 (d, 2H, J = 16.2 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.5, 137.0, 133.0, 130.2, 128.4, 127.8, 127.4, 126.1, 114.4, 113.1, 69.8, 68.9, 36.5. IR (CH_2Cl_2) 1615 (s), 1506 (s), 1245 (s), 1030 (s) cm^{-1}. Anal. Calcd for $C_{30}H_{26}O_3$: C, 82.92; H, 6.03. Found: C, 83.00; H, 6.29.

2,8-Dihydroxy-5,6,11,12-tetrahydro-5,11-epoxydibenzo-[*a*,*e*]cyclooctene (2). In an oven-dried pressure tube equipped with a magnetic stir bar was dissolved dibenzyl ether **9** (1.32 g, 3.0 mmol) in 15 mL of a 1:1 mixture of methanol and ethyl acetate to give ca. 0.2 M solution. To the pressure tube, Pd/C (0.31 mg, 0.3 mmol, 10 mol %) was added in one portion, and the vessel was purged with H_2 several times. The tube was pressurized to about 45 psi. This mixture was carefully allowed to stir behind a safety shield for 6 h. The excess H_2 was released, and the mixture was filtered through Celite to remove the catalyst. The filtrate was concentrated on a rotary evaporator. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to give the product as a white solid (0.766 g, 99%). An analytical sample was obtained by recrystallization from acetone and toluene to give white crystals. mp 285−286 °C. (*S*,*S*)-**2**: $[\alpha]^{25}_D$ = −16.24 (1.01, acetone), (*R*,*R*)-**2**: $[\alpha]^{25}_D$ =

14.19 (1.17, acetone). ^{1}H NMR (250 MHz, acetone-d_6) δ 8.00((s, 2H), 6.96 (d, 2H, J = 8.3 Hz), 6.60 (dd, 2H, J = 2.3 Hz, J = 8.2 Hz), 6.45 (d, 2H, J = 2.0 Hz), 5.12 (d, 2H, J = 5.7 Hz), 3.33 (dd, 2H, J = 5.8 Hz, J = 16.2= Hz), 2.63 (d, 2H, J = 16.2 Hz). ^{13}C NMR (62.9 MHz, acetone-d_6) δ 156.8, 134.1, 130.1, 127.1, 115.8, 114.2, 69.6, 37.3. IR (KBr) 3447 (s), 1614 (s), 1513 (s), 1455 (s), 1372 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.47; H, 5.36.

2,8-Bis(trifluoromethanesulfonyl)-5,6,11,12-tetrahydro-5,11-epoxydibenzo[*a*,*e*]cyclooctene (12). To a 25 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, and a septum were added diol **2** (0.156 g, 0.6 mmol) and freshly distilled CH_2Cl_2 (12 mL). The flask was cooled to 0 °C in an ice bath. To this solution was added pyridine (0.122 mL, 1.5 mmol) via a syringe, and stirring was continued for 5 min. Triflic anhydride (0.25 mL, 1.5 mmol) was added via a syringe over a few min, and the mixture was allowed to stir at 0 °C for 30 min. The mixture was diluted with CH_2Cl_2 and rinsed into a separatory funnel. The mixture was washed with water (2 × 25 mL) and brine (1 × 25 mL) and dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give the product as a white solid (0.278, 88%). An analytical sample was obtained by recrystallization from hexane and ether. mp 160−161 °C. (*S*,*S*)-**12**: $[\alpha]^{25}_D$ = −3.80 (1.0, CH Cl), (*R*,*R*)-**12**: $[\alpha]^{25}_D$ = 3.20 (0.5, CH_2Cl_2) ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19−7.16 (m, 2H), 7.08 (dd, 2H, J = 2.1 Hz, J = 8.5 Hz), 6.94 (m, 2H), 5.32 (d, 2H, J = 6.0 Hz), 3.52 (dd, 2H, J = 6.1 Hz, J = 16.6 Hz), 2.77 (d, 2H, J = 16.6 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 148.2, 137.5, 134.0, 127.1, 121.7, 119.4, 118.6 (q, J_{F-C} = 320 Hz), 68.4, 35.9. IR (KBr) 1493 (s), 1420 (s), 1208 (s), 1132 (s), 1104 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{12}F_6O_7S_2$: C, 41.71; H, 2.33. Found: C, 41.73; H, 2.20.

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Supporting Information Available: X-ray data for *rac*-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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