Organic chemists everywhere join us in honoring Frederick D. Greene II for his wise and far-sighted service for more than a quarter century as Editor-in-Chief of this Journal. As his organic colleagues at the Massachusetts Institute of Technology, we also know and honor him for his thoughtful and generous contributions to our department and particularly for his gifted teaching.

With heartfelt affection and esteem, we wish to dedicate the following papers to Fred on the occasion of his recent retirement from the Editorship.

Glenn A. Berchtold, Stephen L. Buchwald, Rick L. Danheiser, Daniel S. Kemp, Satoru Masamune, and K. Barry Sharpless

Resolution of *trans*-1,2-Dihydroxy-1,2-dihydrobenzene for the Preparation of Optically Pure Benzene Diol Epoxides. Preparation of Bromo- and Chlorobenzene Diol Epoxides†

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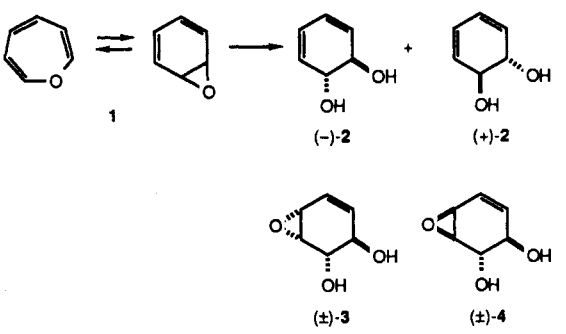
The resolution of (±)-*trans*-1,2-dihydroxy-1,2-dihydrobenzene [(±)-**2**] has been accomplished by esterase-catalyzed hydrolysis of diacetate (±)-**5**. Peracid epoxidation of (+)-**2** and (−)-**2** gave diol epoxides (+)-**3** and (−)-**3**, respectively. The synthesis of diol epoxides of bromobenzene, **17a** and **18a**, and of chlorobenzene, **17b** and **18b**, from **7a** and **7b** is described. Mutagenicity evaluation (*Salmonella typhimurium* forward mutation assay) indicated that (±)-**3**, (+)-**3**, and (−)-**3** were equally mutagenic. The diol epoxides of bromobenzene were somewhat more mutagenic than the corresponding diol epoxides of chlorobenzene. Isomer **18a** was more mutagenic than **17a**, and **18b** was more mutagenic than **17b**.

Although detailed investigations have been reported on the role of diol epoxides as activated metabolites responsible for mutagenic and carcinogenic effects of polycyclic aromatic hydrocarbons,[2] almost no information is available concerning the metabolic formation of diol epoxides and their role in the toxic effects of benzene and benzene derivatives. Benzene metabolism proceeds through initial enzyme-catalyzed oxidation to arene oxide **1** (Scheme I) followed by a variety of multistep enzyme-catalyzed and/or spontaneous transformations.[3] Of the numerous products derived from **1**, enzyme-catalyzed hydration to **2** has been established. In vivo metabolism of benzene in rabbits or in vitro metabolism of **1** with liver microsomes gave (−)-**2** for which the optical purity was estimated to be at least 50%.[4,5] Dihydrodiol (−)-(1*R*,2*R*)-**15b** (optical purity unknown) is an in vivo metabolite of chlorobenzene in rabbits.[4,6] Detailed investigations on the metabolism of bromobenzene have established **15a** as one of numerous metabolic products.[7]

Scheme I



In previous studies, we prepared (±)-**3** and (±)-**4** for comparison of their mutagenic activity with benzene and

† This paper is dedicated to our colleague Professor Frederick D. Greene, II, in appreciation of his years of service as Editor of *The Journal Of Organic Chemistry*.

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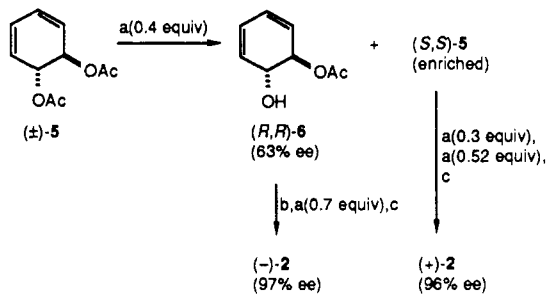
Scheme II[a]



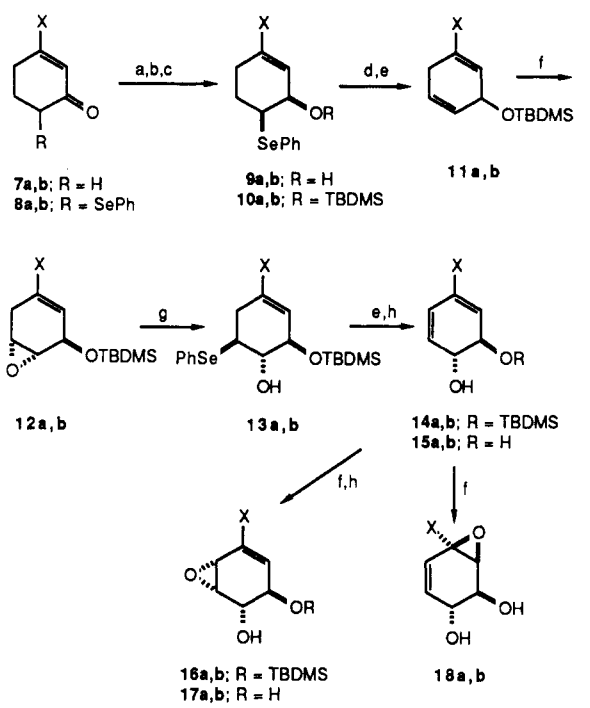
[a] Key: (a) Porcine liver esterase, NaOH, H_2O; (b) AcCl, pyridine, DMAP, CH_2Cl_2; (c) NaOH, H_2O.

(±)-2.[8] Bacterial mutagenesis was measured in the *Salmonella* typhimurium forward mutation assay of Skopek and co-workers.[9] Benzene was not mutagenic at concentrations up to 1000 μg/mL either in the presence or absence of an exogenous metabolizing system (PMS).[10] Dihydrodiol (±)-2 required exogenous metabolism (PMS) for mutagenic activity. Diol epoxide (±)-3 was equally mutagenic in the presence and absence of PMS while diol epoxide (±)-4 was inactive with and without PMS under the conditions of the assay. In the forward mutation assay used, (±)-3 was a weak mutagen compared to (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene or compared to benzo[*a*]pyrene in the presence of PMS. Since the pattern of mutagenicity observed for benzene, (±)-2, and (±)-3 was consistent with the possibility of 3 being a mutagenic benzene metabolite formed via 2, we were interested in comparison of the mutagenic activity of the two enantiomers of 3 and determination of the mutagenic activity of related diol epoxides of bromobenzene and chlorobenzene. Described below are (1) the enzyme-catalyzed resolution of (±)-2, (2) preparation of the pure enantiomers of 3, (3) preparation of diol epoxide isomers of bromo- and chlorobenzene, and (4) evaluation of the mutagenic activity of the substances prepared.

Dihydrodiol (±)-2 was not oxidized under conditions of the Sharpless asymmetric epoxidation.[11] Since (±)-3 is easily prepared by epoxidation of (±)-2 with peracid,[8] enzyme-catalyzed hydrolysis of (±)-5 was selected for preparation of (+)-2 and (-)-2 for oxidation to the pure enantiomers of 3 (Scheme II). Hydrolysis of (±)-5, catalyzed by porcine liver esterase, was carried out at pH 7.8 while the pH and extent of reaction was controlled by addition of NaOH solution from a syringe pump–pH controller unit.[12] Hydrolysis of (±)-5 under these conditions was rapid compared to hydrolysis of 6; and when carried to 40% completion at 0 °C, the reaction provided (*R,R*)-6 (63% ee)[13] and (*S,S*)-5 (ee not determined), which were separated by chromatography. Acetylation of (*R,R*)-6 followed by a second esterase-catalyzed hydrolysis (70% completion) provided (*R,R*)-6 (95% ee), which after base-catalyzed hydrolysis and recrystallization gave (-)-2 (97% ee) in an overall yield of 15% from (±)-5. A second esterase-catalyzed hydrolysis of (*S,S*)-5 isolated from the initial hydrolysis was carried to 30% completion, and unhydrolyzed (*S,S*)-5 was isolated by flash chromatography. Since hydrolysis ($NaOH/H_2O$) of 5 results in substantial aromatization whereas 6 is hydrolyzed to 2 under similar conditions without aromatization, (*S,S*)-5 was subjected to esterase-catalyzed hydrolysis to (*S,S*)-6 followed by addition of NaOH to effect complete hydrolysis to provide (+)-2 (96% ee) in an overall yield of 41% from (±)-5. Epoxidation of (-)-2 and (+)-2 with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave (-)-3 (71% yield) and (+)-3 (67% yield), respectively.

The absolute stereochemistry of (+)-2 and (-)-2 was established by catalytic reduction (H_2, Pd/C, EtOH) to the known (+)- and (-)-*trans*-1,2-dihydroxycyclohexane-,[4,14,15] respectively, in similar fashion to the assignment of

Scheme III[a,b]



[a] For 7a–18a, X = Br; for 7b–18b, X = Cl. [b] Key: (a) LiN($SiMe_3$)$_2$, THF, -78 °C; (b) PhSeCl; (c) $NaBH_4$, $CeCl_3$, C_2H_5OH, 0 °C; (d) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, reflux; (e) *n*-Bu)$_4NIO_4$; (f) *m*-CPBA; (g) $PhSe^-$; (h) (*n*-Bu)$_4$NF, THF.

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(12) Syringe pump: Sage 341A, VWR Scientific. pH controller: Accumet 805MP, Fisher Scientific.

(13) Mosher esters were used to determine enantiomeric excesses of the compounds (see Experimental Section).

absolute stereochemistry of (−)-**2** as the major enantiomer from metabolism of benzene in vivo or hydration of **1** in vitro reported by Jerina and co-workers.[4] The optical rotation observed for (−)-**2** from hydration of **1** by microsomal preparations, $[\alpha]^{25}_D$ −250° (*c* 0.035, EtOH), compared with the value for (−)-**2** prepared herein, $[\alpha]^{25}_D$ −390° (*c* 0.036, EtOH), indicates that (−)-**2** from the enzymatic preparation was ~65% optically pure and is in agreement with the conclusion drawn by Jerina and co-workers.[4]

In view of the biological activity associated with (±)-**3** as described above, we were interested in the preparation of **17a** and **17b**, the corresponding diol epoxides of bromo- and chlorobenzene, respectively. The synthesis of these diol epoxides and regioisomers **18a** and **18b** was accomplished from the known 3-halocyclohex-2-en-1-ones **7a,b**[16,17] (Scheme III). The kinetic enolates of the enones were formed at −78 °C by the slow addition of **7a,b** to a solution of lithium bis(trimethylsilyl)amide (1.1 equiv) in THF and were trapped as the trimethylsilyl enol ethers. Addition of phenylselenenyl chloride to the mixture and warming to room temperature gave the desired selenides **8a,b** (79% and 80% yield). Reduction of enones **8a,b** with $NaBH_4$ in an ethanolic solution containing $CeCl_3 \cdot 7H_2O$, to prevent 1,4-reduction, gave allylic alcohols **9a,b** in 79% and 86% yields as crystalline solids. Attempts to oxidize selenide **9a** and eliminate PhSeOH were unsuccessful, presumably due to intramolecular hydrogen bonding of the cis hydroxyl group with the selenoxide; but protection of the hydroxyl group allowed for facile oxidation–elimination of the selenoxide. Protection of allylic alcohols **9a,b** as the *tert*-butyldimethylsilyl (TBDMS) ethers required rather harsh conditions: 1.3 equiv of trimethylamine and 2.0 equiv of 4-(dimethylamino)pyridine (DMAP) in refluxing CH_2Cl_2 for 48–50 h. Oxidation of selenides **10a,b** and elimination of PhSeOH gave unstable dienes **11a,b** (72% and 66% yield from **9a,b**). Purification of **11a,b** was accomplished by passing a hexane solution of the dienes through a short silica gel plug with short contact time since prolonged exposure to silica gel resulted in extensive aromatization. Alternatively, dienes **11a,b** could be purified by distillation (Kugelrohr) under pressure if the pot temperature was kept below 90 °C to avoid thermal decomposition to the halobenzenes.

Epoxidation of **11a,b** with *m*-CPBA for 43 and 64 h, respectively, provided **12a,b** in 44% and 39% yields after flash chromatography to separate the desired products from other isomeric monoepoxides, isomeric bisepoxides, and unreacted starting material. Addition of $PhSe^-$ to epoxides **12a,b** gave **13a,b** (30% and 80% yields). Oxidation of **13a,b** to the respective selenoxides with $(n\text{-}Bu)_4NIO_4$ and Na_3PO_4 in $CHCl_3$ and selenoxide elimination gave **14a,b** in 67% and 80% yields after purification by chromatography on silica gel. Desilylation with $(n\text{-}Bu)_4NF$ at room temperature gave diols **15a,b** (75% and 89% yields) as stable crystalline materials.[18]

Epoxidation of dienes **14a,b** afforded epoxides **16a,b** (68% and 43% yield) as colorless oils, and desilylation gave diol epoxides **17a,b** (61% and 80% yield) as stable white solids. Peracid epoxidation of diols **15a,b** resulted in selective oxidation at the halogen-bearing double bond to give **18a,b** (62% and 60% yield) as white solids. When the epoxidation reaction was monitored by ^1H NMR, formation of **17a,b** was not observed. Diol epoxides **18a,b** were unstable at room temperature, presumably due to decomposition by the known rearrangement of halogen-substituted epoxides to α-halo ketones.[19]

Table I. Mutagenicity Results

compd	slope[a]	slope (with PMS)[b]
(±)-**3**	0.40 ± 0.09	0.30 ± 0.10
(+)-**3**	0.33 ± 0.06	0.43 ± 0.22
(−)-**3**	0.51 ± 0.10	0.33 ± 0.08
bromobenzene	NS[c]	NS
chlorobenzene	NS	NS
(±)-**15a**	0.20 ± 0.11	NS
(±)-**15b**	NS	NS
(±)-**17a**	0.19 ± 0.04	0.14 ± 0.09
(±)-**17b**	0.13 ± 0.04	0.11 ± 0.09
(±)-**18a**	0.97 ± 0.24	0.33 ± 0.10
(±)-**18b**	0.39 ± 0.08	0.18 ± 0.06
benzo[*a*]pyrene	NS	27 ± 3

[a] Slope in mutant fraction/μg/mL × 10^5. [b] PMS: Rat liver postmitochondrial supernatant (preincuded with Aroclor 1254). [c] NS: Induced mutagenic fraction did not significantly exceed historical control values (99% upper confidence limit).

Mutagenic activity was evaluated by using the *S. typhimurium* forward mutation assay of Skopek and co-workers,[9] and mutagenic activity of each sample was measured as the maximum slope from the dose–response curves. Results are provided in Table I. Within the accuracy of the test system, (±)-**3**, (+)-**3**, and (−)-**3** are equally mutagenic. Bromobenzene, chlorobenzene, and dihydrodiols **15a** and **15b**, like benzene,[8] did not display significant mutagenic activity. With the diol epoxide derivatives, the bromo compounds appear to be more mutagenic than the chloro compounds; and the regioisomers with the halogen substituent on an oxiranyl carbon atom displayed greater mutagenic activity. In view of the instability of these isomers (**18a,b**), mutagenic activity could be due to decomposition products. Since bacterial metabolism may generate additional products, it remains possible that the ultimate mutagens are further metabolites of the diol epoxides. In the forward mutation assay used, the diol epoxides of benzene, bromobenzene, and chlorobenzene that have been investigated are weak mutagens compared to the more potent diol epoxides derived from highly mutagenic polycyclic aromatic hydrocarbons such as benzo[*a*]pyrene.[20]

Experimental Section

General. Unless otherwise noted, ^1H NMR spectra were measured at 250 or 300 MHz in $CDCl_3$, and ^{13}C NMR spectra were measured at 67.9 or 75.4 MHz in $CDCl_3$ with chemical shift values (δ) in parts per million downfield from tetramethylsilane. Melting points are corrected. Flash chromatography refers to the procedure of Still and co-workers.[21] Microanalyses were performed by Robertson Laboratories, Madison, NJ.

(−)-(1*R*,2*R*)-1,2-Dihydroxy-1,2-dihydrobenzene [(−)-2]. A two-phase system of (±)-**5**[22] (7.32 g, 37.3 mmol) and H_2O (200 mL) in a flask equipped with a mechanical stirrer and a pH electrode was cooled to 0 °C with stirring. The pH was adjusted to 7.8 by addition of 0.5 M NaOH, and esterase (Sigma, EC 3.1.1.1, type

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(18) The IR and ^1H NMR spectra of diene **15b** were identical with those of **15b** prepared by the addition of H_2O_2 to 4-chlorobenzene oxide and reduction of the hydroperoxide with $NaBH_4$: Piccolo, D. E.; Berchtold, G. A. Unpublished observations.
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(20) For the benzo[*a*]pyrene diol epoxide (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, slope = 274 in the forward mutation assay used.[8]
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I, from porcine liver; 2500 units) was added. The pH was maintained at 7.8 by the addition of 0.50 M NaOH using a syringe pump–pH controller unit. After 6 h, additional esterase (1500 units) was added, and after 16 h, the desired amount of NaOH solution (30.0 mL, 15.0 mmol, 0.40 equiv) had been introduced. The aqueous phase was saturated with NaCl and extracted with Et_2O (5 × 100 mL). The combined extracts were dried and concentrated with a rotary evaporator. Flash chromatography on silica gel with EtOAc/hexane (1:4) as eluent gave unreacted diacetate **5** (4.46 g, R_f = 0.36) which was enriched in the *S,S* enantiomer. The eluent was changed to EtOAc/hexane (2:3) to give (*R,R*)-**6** (1.92 g, 83%, R_f = 0.34, 63% ee) as an oil: ^1H NMR δ 6.05–5.90 (3 H, m), 5.77 (1 H, m), 5.54 (1 H, m), 4.55 (1 H, d), 2.72 (1 H, br s), 2.13 (3 H, s).

Monoacetate (*R,R*)-**6**, (1.92 g, 12.4 mmol) was added to a mixture of acetyl chloride (1.15 mL, 16.2 mmol, 1.3 equiv) in CH_2Cl_2 (100 mL) containing pyridine (2.0 mL) and DMAP (50 mg). After 1 h at 0 °C followed by 1 h at 25 °C, the solvent was removed with a rotary evaporator. The residue was stirred with Et_2O (3 × 25 mL) and filtered after each extraction. The combined filtrates were concentrated with a rotary evaporator. Flash chromatography on silica gel with EtOAc/hexane (1:3) as eluent gave the diacetate as a clear oil (2.24 g, 92%). By use of the procedure described above for hydrolysis of the racemate, enriched diacetate (*R,R*)-**5** (2.24 g, 11.4 mmol) was hydrolyzed with the esterase (430 units) in H_2O (60 mL) and controlled addition of 1.00 M NaOH. Additional esterase (570 units) was added after 14 h. After 29 h, 8 mL (0.70 equiv) of NaOH solution had been added. The aqueous phase was saturated with NaCl and extracted with Et_2O (6 × 25 mL). The combined extracts were dried and concentrated. Flash chromatography on silica gel with EtOAc/hexane (1:4) as eluent gave unhydrolyzed diacetate (0.74 g), which was discarded. Further elution with EtOAc/hexane (2:3) gave desired monoacetate (*R,R*)-**6** (1.01 g, 82%). The acetate in THF (5.0 mL) was added dropwise to a stirring solution of 1 M NaOH (9.0 mL, 1.4 equiv) at 0 °C. After 15 min, the solution was warmed to room temperature for 30 min. Most of the THF was removed with a rotary evaporator. The solution was saturated with $(NH_4)_2SO_4$ and extracted with Et_2O (4 × 40 mL). The combined extracts were dried and concentrated with a rotary evaporator to give (−)-(*R,R*)-**2** as a solid (0.701 g, 95% ee). Recrystallization from EtOAc/hexane (1:2) gave pure (−)-**2** (0.616 g, 15% based on racemic diacetate, 97% ee): mp 101–105.5 °C; $[\alpha]^{20}_D$ −390° (*c* 0.036, 95% EtOH). The ^1H NMR spectrum of (−)-**2** was identical with the spectrum of (±)-**2**.

(+)-(1*S*,2*S*)-1,2-Dihydroxy-1,2-dihydrobenzene [(+)-2]. Diacetate **5**, enriched in the *S,S* enantiomer, obtained from the initial esterase-catalyzed hydrolysis described in the previous experiment was hydrolyzed by the procedure described above with esterase (1000 units) in H_2O (100 mL) and controlled addition of 0.50 M NaOH. After 27 h, 13.6 mL (0.30 equiv) of NaOH solution had been added. The aqueous phase was saturated with NaCl and extracted with Et_2O (4 × 60 mL). The combined extracts were dried and concentrated. Flash chromatography on silica gel with EtOAc/hexane (1:4) as eluent gave unhydrolyzed diacetate (*S,S*)-**5** (3.03 g, 97%). Since the monoacetate (but not the diacetate) could be cleanly hydrolyzed to the diol without aromatization with NaOH, diacetate (*S,S*)-**5** (3.03 g, 15.4 mmol) was partially hydrolyzed with esterase (1000 units) in H_2O (80 mL) and controlled addition of 1.0 M NaOH at room temperature by the procedure described above for partial hydrolysis of racemic **5**. After 22 h, additional esterase (600 units) was added. After an additional 24-h period, 16 mL (0.52 equiv) of NaOH solution had been added. To the solution was added 1.0 M NaOH (24 mL). After 15 min, the volume of the reaction mixture was reduced to ~20 mL under high vacuum, and the solution was saturated with $(NH_4)_2SO_4$. The solution was extracted with Et_2O (4 × 50 mL), and the combined extracts were dried. Evaporation of solvent with a rotary evaporator gave crude (+)-(*S,S*)-**2** as a white solid: (1.68 g, 97%, 83% ee). Two recrystallizations from EtOAc/hexane (1:2) gave pure (+)-**2** (1.03 g, 25% based on racemic diacetate, 96% ee): mp 100–106 °C; $[\alpha]^{20}_D$ +360° (*c* 0.036, 95% EtOH). The ^1H NMR spectrum of (+)-**2** was identical with the spectrum of (±)-**2**.

Determination of the Optical Purity of (+)-2, (−)-2, and (−)-6. Mosher esters were made from (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA-Cl] by following the general procedure[23] except that EtOAc/hexane (3:7) was used as eluent, and ee's were determined from the ^1H NMR spectrum by integration of the protons attached to the ester-bearing carbon (C-1) at 4.52 and 4.63 ppm of the mono MTPA ester of (−)- and (+)-**2** and integration of the methyl protons at 2.02 and 2.07 ppm of the MTPA ester of (−)- and (+)-**6**. (+)-MTPA-Cl was prepared from (+)-MTPA according to the procedure of Mosher and coworkers.[24]

(+)-(1*S*,2*R*,3*S*,6*R*)-7-Oxabicyclo[4.1.0]hept-4-ene-2,3-diol [(+)-3]. A mixture of (+)-**2** (400 mg, 3.57 mmol), Na_2HPO_4 (1.0 g, 7 mmol), and CH_2Cl_2 (25 mL) was cooled to 0 °C under N_2, and *m*-CPBA (80%, 775 mg, 3.7 mmol, 1 equiv) was added with stirring. The mixture was warmed to room temperature, and stirring was continued for 45 min. The mixture was cooled to −50 °C and filtered. The solid filtrate was washed with cold CH_2Cl_2 (20 mL), and the combined CH_2Cl_2 solutions were concentrated to ~5 mL with a rotary evaporator. Triethylamine (0.80 mL) was added. Flash chromatography on silica gel with EtOAc as eluent gave crude (+)-**3** (R_f = 0.3) as an oil, which was dissolved in CH_2Cl_2 (5.0 mL). Et_2O (5.0 mL) and hexane (3.0 mL) were added, and the solution was cooled to −15 °C overnight. Solid (+)-**3** was separated from the mother liquor via cannula at 15 °C, washed with CH_2Cl_2/hexane (1:1, 2 × 3 mL), and dried. The combined mother liquor and filtrate was concentrated with a rotary evaporator, and the residual oil was flash chromatographed on silica gel with EtOAc as eluent to give a second fraction of (+)-**3**. The two fractions of (+)-**3** were taken up in CH_2Cl_2 (8 mL) and precipitated by the addition of hexane (8 mL) (−15 °C, overnight) to obtain 308 mg (67%) of (+)-**3** as a fluffy, hygroscopic solid: mp 68–70 °C (sealed tube); $[\alpha]^{20}_D$ +42° (*c* 0.37, EtOAc). The ^1H NMR spectrum was identical with that of (±)-**3**.

(−)-(1*R*,2*S*,3*R*,6*S*)-7-Oxabicyclo[4.1.0]hept-4-ene-2,3-diol [(−)-3]. The procedure described above for preparation of (+)-**3** was used to oxidize (−)-**2** to (−)-**3** (325 mg, 71%): mp 68–70 °C (sealed tube); $[\alpha]^{20}_D$ −45° (*c* 0.38, EtOAc).

3-Bromo-6-(phenylseleno)cyclohex-2-en-1-one (8a). To a flame-dried, 1-L three-neck flask equipped with a magnetic stirrer and swept with nitrogen was added anhydrous tetrahydrofuran (600 mL), followed by freshly distilled hexamethyldisilazane (20.8 mL, 98.6 mmol). The resulting solution was cooled with dry ice, and *n*-butyllithium (37.9 mL of a 2.66 M solution in hexanes, 98.6 mmol) was added dropwise. The mixture was stirred for 40 min. The solution was cooled to −78 °C followed by dropwise addition of **7a**[16] (15.00 g, 85.7 mmol). The solution was stirred for 1 h followed by the rapid addition of trimethylchlorosilane (16.43 mL, 0.129 mol). After 30 min, a solution of phenylselenenyl chloride (24.7 g, 0.129 mol) in anhydrous THF (70 mL) was added rapidly. The mixture was stirred for 30 min at −78 °C and warmed to room temperature for an additional 1 h. The reaction was quenched by the slow addition of 2 M KH_2PO_4 (600 mL), and THF was removed under reduced pressure. The aqueous solution was extracted with ethyl ether (4 × 100 mL); and the organic fractions were combined, dried, and concentrated with a rotary evaporator. The residual oil was purified by flash chromatography on silica gel with EtOAc/hexane (1:4) to give 22.4 g (79 %) of **8a** as a light yellow oil: IR (thin film) 1670, 1610 cm^{-1}. UV λ_{max} 243 (ϵ 12050), 203 nm (13200); ^1H NMR δ 7.59 (2 H, m), 7.30 (3 H, m), 6.45 (1 H, s), 3.98 (1 H, t, J = 4.4 Hz), 3.01 (1 H, m), 2.72 (1 H, dt, J = 19, 4.4 Hz), 2.44 (1 H, m), 2.22 (1 H, m); ^{13}C NMR δ 191.7, 148.3, 135.3, 130.7, 129.0, 128.4, 127.0, 45.3, 33.9, 29.0.

3-Chloro-6-(phenylseleno)cyclohex-2-en-1-one (8b). Selenide **8b** was prepared from **7b**[16] (1.00 g, 7.66 mmol) by the same procedure as for the preparation of **8a**. The reaction gave 1.61 g (80%) of **8b** as a light yellow oil: IR (thin film) 1670, 1610 cm^{-1}; ^1H NMR δ 7.60 (2 H, m), 7.31 (3 H, m), 6.20 (1 H, d, J = 2.0 Hz), 3.97 (1 H, t, J = 4.2 Hz), 2.90 (1 H, m), 2.56 (1 H, dt, J = 19, 4.2 Hz), 2.40 (1 H, m), 2.22 (1 H, m); ^{13}C NMR δ 192.6, 156.9, 135.6, 129.2, 128.6, 127.1, 127.0, 45.3, 31.8, 28.5; mass spectrum, m/z (relative intensity) 288, 286, 284 (M^+, 40, 40, 7.9), 184 (55), 183

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(3β,4β)-1-Bromo-3-hydroxy-4-(phenylseleno)cyclohex-1-ene (9a). Sodium borohydride (2.82 g, 74.6 mmol) was added in small portions to a stirred solution of **8a** (22.4 g, 67.8 mmol) in a 0.2 M $CeCl_3 \cdot 7H_2O$ ethanolic solution (425 mL) at 0 °C. The mixture was warmed to room temperature for 1.5 h, quenched with 5% HCl until the pH = 4–5, and diluted with H_2O (500 mL). Ethanol was removed under reduced pressure, and the aqueous solution was extracted with ethyl acetate (5 × 100 mL). The organic fractions were combined, dried, filtered, and concentrated with a rotary evaporator to give a brown solid, which was recrystallized from hexanes to yield 13.7 g of **9a** as a white crystalline solid: mp 66.5–68.5 °C. Recrystallization of the residue from the mother liquor gave an additional 4.08 g of **9a** for a total yield of 79%: IR (KBr) 3500–3100 cm^{-1}; ^1H NMR δ 7.58 (2 H, m), 7.27 (3 H, m), 6.16 (1 H, m), 4.17 (1 H, br d, J = 3.4 Hz), 3.53 (1 H, dt, J = 10.4, 3.4 Hz), 2.70–2.01 (5 H, m); ^{13}C NMR δ 134.3, 130.2, 129.2, 128.4, 127.8, 126.8, 67.0, 48.3, 35.3, 26.8; mass spectrum, m/z (relative intensity) 332, 334 (22, 17), 184 (77), 158 (100), 78 (72), 77 (75). Anal. Calcd for $C_{12}H_{13}BrOSe$: C, 43.40; H, 3.94; Br, 24.06. Found: C, 43.34; H, 4.05; Br, 24.10.

(3β,4β)-1-Chloro-3-hydroxy-4-(phenylseleno)cyclohex-1-ene (9b). Alcohol **9b** was prepared from **8b** (14.0 g, 49.0 mmol) by the same procedure as for the preparation of **9a**. Recrystallization from hexanes gave 10.9 g of **9b** as a white crystalline solid: mp 66.0–67.0 °C. Recrystallization of the residue from the mother liquor gave an additional 1.20 g of **9b** for a total yield of 86%: IR (KBr) 3250–3200, 2900, 1660, 1650, 1580 cm^{-1}; ^1H NMR δ 7.58 (2 H, m), 7.26 (3 H, m), 5.92 (1 H, d, J = 5 Hz), 4.22 (1 H, dm, J = 4 Hz), 3.49 (1 H, dt, J = 11, 3.3 Hz), 2.72 (1 H, d, J = 6 Hz), 2.46 (1 H, m), 2.21 (1 H, m), 2.08 (1 H, m); ^{13}C NMR δ 136.6, 134.5, 129.2, 128.4, 127.9, 125.8, 66.1, 48.5, 33.0, 25.8; mass spectrum, m/z (relative intensity) 290 (21), 288 (48), 286 (24), 284 (8), 186 (17), 185 (15), 184 (100), 183 (34), 182 (50), 181 (32), 180 (23), 160 (15), 158 (92), 157 (24), 156 (45), 155 (25), 154 (21), 133 (7), 131 (22), 115 (11), 113 (24), 104 (27), 95 (27), 78 (43), 77 (73). Anal. Calcd for $C_{12}H_{13}ClOSe$: C, 50.11; H, 4.56. Found: C, 50.24; H, 4.54.

(3β,4β)-1-Bromo-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-(phenylseleno)cyclohex-1-ene (10a). To a stirred solution of **9a** (9.81 g, 29.5 mmol) in methylene chloride (300 mL) were added *tert*-butyldimethylsilyl chloride (8.9 g, 59.1 mmol), DMAP (7.21 g, 59.1 mmol), and triethylamine (5.35 mL, 38.4 mmol). The mixture was heated at gentle reflux for 50 h, washed with aqueous 5% $NaHCO_3$ (2 × 100 mL) and aqueous 5% HCl (2 × 100 mL), dried, filtered, and concentrated with a rotary evaporator to give **10a** as a light yellow oil: IR (thin film) 1640 cm^{-1}; ^1H NMR δ 7.54 (2 H, m), 7.25 (3 H m), 6.05 (1 H, dt, J = 4.8, 1.7 Hz), 4.45 (1 H, t, J = 4.5 Hz), 3.37 (1 H, dt, J = 11.4, 3.5 Hz), 2.61–1.92 (4 H, m), 0.93 (9 H, s), 0.15 (3 H, s), 0.10 (3 H, s); ^{13}C NMR δ 134.0, 130.7, 130.1, 128.9, 127.2, 125.6, 69.2, 46.7, 36.0, 27.3, 25.9, 18.2, −4.0, −4.7; mass spectrum, m/z (relative intensity) 448, 446, 444 (M^+, 1.2, 1.7, 0.6), 391, 389, 387 (56, 71, 32), 233 231 (33), 157 (30), 75 (100). Anal. Calcd for $C_{18}H_{27}BrOSiSe$: C, 48.44; H, 6.10; Br, 17.90. Found: C, 48.40; H, 5.98; Br, 17.60.

(3β,4β)-1-Chloro-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-(phenylseleno)cyclohex-1-ene (10b). The preparation of **10b** from **9b** (15.6 g, 54.2 mmol) was accomplished by the same procedure as for the preparation of **10a**. The reaction gave **10b** as a light yellow oil: IR (thin film) 3080–3050, 1650 cm^{-1}; ^1H NMR δ 7.56 (2 H, m), 7.27 (3 H, m), 5.82 (1 H, m), 4.50 (1 H, m), 3.35 (1 H, dt, J = 10.9, 3.2 Hz), 2.30 (3 H, m), 2.00 (1 H, m), 0.93 (9 H, s), 0.15 (3 H, s), 0.10 (3 H, s); ^{13}C NMR δ 136.0, 134.0, 130.7, 128.9, 127.1, 126.4, 68.5, 47.0, 33.8, 26.7, 26.0, 18.4, −3.8, −4.5; mass spectrum, m/z (relative intensity) 404, 402, 400 (M^+, 1.2, 2.8, 1.2), 347, 345, 343 (38.3, 82.4, 39.9), 217, 215, 213 (13.1, 61.9, 30.8), 189, 187 (19.7, 52.9), 157 (16.9), 75 (100), 73 (80).

1-Bromo-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,4-diene (11a). Crude selenide **10a** was dissolved in chloroform (300 mL), and anhydrous sodium phosphate (8.38 g, 59.1 mmol) and tetrabutylammonium periodate (25.6 g, 59.1 mmol) were added. The mixture was stirred under N_2 for 24 h. The mixture was washed with aqueous 5% $NaHCO_3$ (2 × 75 mL) and brine (75 mL), dried, filtered, and concentrated with a rotary evaporator. Diene **11a** was extracted from the quaternary salts with hexanes (3 × 150 mL), and the mixture was concentrated with a rotary evaporator to give a yellow oil. The oil was passed through a short silica gel plug with hexanes to yield 8.53 g (72% from **9a**) of **11a** as a clear colorless oil. Analytically pure **11a** was obtained by Kugelrohr distillation (85 °C, 1.0 mm): IR (thin film) 3000–2860 cm^{-1}; ^1H NMR δ 6.13 (1 H, s), 5.82 (2 H, s), 4.75 (1 H, m) 3.01 (2 H, m), 0.91 (9 H, s), 0.11 (6 H, s); ^{13}C NMR δ 129.8, 127.2, 125.2, 122.1, 65.7, 35.7, 25.8, 18.2, −4.5; mass spectrum, m/z (relative intensity) 290, 288 (M^+, 1.9, 2.0), 233, 231 (0.9, 1.2), 209 (4), 137 (1.8), 75 (100). Anal. Calcd for $C_{12}H_{21}BrOSi$: C, 49.82; H, 7.32; Br, 27.62. Found: C, 49.59; H, 7.43; Br, 27.36.

1-Chloro-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,4-diene (11b). Diene **11b** was prepared from **10b** (19.6 g, 48.8 mmol) by the same procedure as for the preparation of **11a**. Kugelrohr distillation (70 °C, 0.1 mm) gave 8.76 g (66% from **9b**) of pure **11b** as a light yellow oil: IR (thin film) 1680 cm^{-1}; ^1H NMR δ 5.89 (1 H, m), 5.78 (2 H, m), 4.81 (1 H, m), 2.93, 2.87 (2 H, AB m), 0.93 (9 H, s), 0.12 (6 H, s); ^{13}C NMR δ 132.2, 127.6, 125.7, 124.6, 65.5, 33.6, 25.9, 18.3, −4.4, −4.5.

(1β,2β,6β)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-bromo-7-oxabicyclo[4.1.0]hept-3-ene (12a). A chloroform solution (250 mL) of **11a** (6.11 g, 21.1 mmol), anhydrous sodium phosphate (4.50 g, 31.7 mmol), and *m*-CPBA (80%, 6.83 g, 31.7 mmol) was stirred at room temperature for 43 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in Et_2O (350 mL). The solution was washed with aqueous Na_2SO_3 (2 × 100 mL) and aqueous 5% $NaHCO_3$ (2 × 125 mL), dried, filtered, and concentrated with a rotary evaporator. The oil was chromatographed on silica gel (10:1 hexane/ethyl ether, R_f = 0.38) to yield 2.81 g (44%) of **12a** as a yellow oil: IR (thin film) 1660 cm^{-1}; ^1H NMR δ 5.92 (1 H, m), 4.55 (1 H, m), 3.30 (1 H, m), 3.14 (1 H, m), 2.94 (2 H, d, J = 2 Hz), 0.92 (9 H, s), 0.14 (3 H, s), 0.13 (3 H, s); ^{13}C NMR δ 126.6, 121.1, 65.8, 52.8, 52.1, 34.9, 25.8, 18.3, −4.5, −4.7; mass spectrum, m/z (relative intensity) 306, 304 (M^+, 2.0, 2.4), 249, 247 (18, 18), 231, 229 (14, 14), 153 (14), 75 (100). Anal. Calcd for $C_{12}H_{21}BrO_2Si$: C, 47.21; H, 6.93. Found: C, 47.26; H, 7.03.

(1β,2β,6β)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-chloro-7-oxabicyclo[4.1.0]hept-3-ene (12b). Epoxide **12b** was prepared from **11b** (4.41 g, 18.0 mmol) by the same procedure as for the preparation of **12a**. The oil was chromatographed on silica gel (4:1 hexane/ethyl ether, R_f = 0.50) to yield 1.83 g (39%) of **12b** as a colorless oil: IR (thin film) 1670 cm^{-1}; ^1H NMR δ 5.68 (1 H, m), 4.61 (1 H, m), 3.36 (1 H, m), 3.14 (1 H, m), 2.82 (2 H, m), 0.92 (9 H, s), 0.14 (3 H, s), 0.13 (3 H, s); ^{13}C NMR δ 130.7, 122.5, 65.2, 53.0, 51.6, 32.6, 25.7, 18.2, −4.7; mass spectrum, m/z (relative intensity) 262, 260 (M^+, 0.5, 1.5), 205, 203 (8.3, 22.9), 187, 185 (12.9, 34.1), 95, 93 (9.7, 29.9), 86 (37.1), 84 (56.7), 75 (74.8), 51 (30), 49 (100).

(3β,4α,5β)-1-Bromo-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-5-(phenylseleno)cyclohex-1-ene (13a). Epoxide **12a** (0.350 g, 1.15 mmol) was added to a stirred solution of diphenyl diselenide (0.215 g, 0.69 mmol) in dry CH_3OH (10 mL), which had been decolorized by the addition of $NaBH_4$ at 0 °C. After 12 h, the reaction mixture was decolorized by the addition of a minimal amount of $NaBH_4$. The mixture was stirred for a total of 24 h at room temperature. The solvent was removed with a rotary evaporator, and the residue was dissolved in Et_2O (30 mL), extracted with aqueous 5% HCl (10 mL) and saturated aqueous NH_4Cl (2 × 10 mL), dried, filtered, and concentrated with a rotary evaporator to yield a yellow oil. The oil was purified by flash chromatography on silica gel with hexane/ethyl ether (10:1) as eluent to afford 0.157 g (30%) of **13a** as a colorless oil: IR (thin film) 3510–3490, 1650 cm^{-1}; ^1H NMR δ 7.63 (2 H, m), 7.36 (3 H, m), 5.82 (1 H, t, J = 2.7 Hz), 4.22 (1 H, dt, J = 6.6, 2.0 Hz), 3.48 (1 H, ddd, J = 12, 7.0, 2.0 Hz), 3.35 (1 H, td, J = 11, 5.9 Hz), 2.82, 2.68 (2 H, AB m), 0.94 (9 H, s), 0.16 (3 H, s), 0.15 (3 H, s); ^{13}C NMR δ 136.3, 131.6, 129.2, 128.6, 125.6, 120.7, 74.7, 73.9, 44.8, 42.2, 25.9, 18.3, −4.3, −4.5; mass spectrum, m/z (relative intensity) 462 (M^+, 0.2), 408 (0.7), 406 (1.6), 404 (2.7), 317 (0.4), 317 (1.7), 313 (2.4), 248, 246 (5.6, 5.7), 81 (50.8), 75 (55.3), 69 (100).

(3β,4α,5β)-1-Chloro-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-5-(phenylseleno)cyclohex-1-ene (13b). Selenide **13b** was prepared from **12b** (1.06 g, 4.06 mmol) by the

same procedure as for the preparation of **13a**. The oil was purified by flash chromatography on silica gel with hexane/ethyl ether (7:1) as the eluent to afford 1.36 g (80%) of **13b** as a light yellow oil: IR (thin film) 3520–3490, 3060, 1660, cm^{-1}; ^1H NMR δ 7.61 (2 H, m), 7.32 (3 H, m), 5.58 (1 H, t, J = 2.4 Hz), 4.23 (1 H, m), 3.46 (1 H, ddd, J = 12, 7.2, 1.5 Hz), 3.31 (1 H, td, J = 11, 6.5 Hz), 2.89 (1 H, d, J = 2.3 Hz), 2.63 (2 H, m), 0.91 (9 H, s), 0.14 (3 H, s), 0.12 (3 H, s); ^{13}C NMR δ 136.4, 131.2, 129.3, 128.6, 127.4, 125.6, 74.0, 73.7, 43.9, 39.8, 25.8, 18.1, –4.51, –4.71; mass spectrum, m/z (relative intensity) 262, 260 (0.2, 0.5), 205, 203 (5.0, 13.4), 187, 185 (8.4, 21.5), 95, 93 (11.3, 35.6), 75 (100). Anal. Calcd for $C_{18}H_{27}ClO_2SiSe$: C, 51.73; H, 6.51. Found: C, 51.44; H, 6.27.

(5α,6β)-2-Bromo-5-hydroxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,3-diene (14a). To a stirred solution of **13a** (150 mg, 0.325 mmol) in chloroform (6.0 mL) were added anhydrous sodium phosphate (0.092 g, 0.650 mmol) and tetrabutylammonium periodate (0.282 g, 0.650 mmol). The mixture was stirred under N_2 for 14 h at room temperature. The reaction mixture was diluted with chloroform (30 mL), extracted with aqueous 5% $NaHCO_3$ (3 × 10 mL), dried, filtered, and concentrated with a rotary evaporator to a brown oil. Purification by flash chromatography on silica gel with hexane/ethyl ether (4:1, R_f = 0.33) yielded pure **14a** (0.066 g, 67%) as a colorless oil: IR (thin film) 3450–3380, 1630 cm^{-1}; ^1H NMR δ 6.07 (1 H, s), 5.90 (2 H, s), 4.46 (1 H, s), 4.45 (1 H, s), 2.04 (1 H, s), 0.93 (9 H, s), 0.13 (3 H, s), 0.12 (3 H, s); ^{13}C NMR δ 132.0, 131.5, 128.2, 116.2, 76.3, 73.2, 25.9, 18.2, –4.2, –4.4; mass spectrum, m/z (relative intensity) 306, 304 (M^+, 3.2, 3.2), 249, 247 (2.2, 2.8), 231, 229 (34, 33), 168 (8.6), 115 (4.8), 75 (100).

(5α,6β)-2-Chloro-5-hydroxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,3-diene (14b). Diene **14b** was prepared from **13b** (1.30 g, 3.11 mmol) by the same procedure as for the preparation of **14a**. Purification by flash chromatography on silica gel with hexane/ethyl ether (4:1, R_f = 0.25) yielded pure **14b** (0.651 g, 80%) as a colorless oil: IR (thin film) 3430–3410, 1630, 1590 cm^{-1}; ^1H NMR δ 5.98 (1 H, dd, J = 11, 2.2 Hz), 5.82 (2 H, m), 4.50 (1 H, dd, J = 11, 2.3 Hz), 4.43 (1 H, dm, J = 12 Hz), 2.10 (1 H, br s), 0.92 (9 H, s), 0.12 (3 H, s), 0.11 (3 H, s); ^{13}C NMR δ 132.2, 127.9, 127.0, 126.5, 75.5, 73.3, 25.7, 18.0, –4.4, –4.6.

***trans*-1,2-Dihydroxy-1,2-dihydro-4-bromobenzene (15a).** Diene **14a** (6.1 mg, 0.020 mmol) was dissolved in anhydrous THF (1.0 mL) and treated with tetrabutylammonium fluoride (24 mL of a 1.0 M solution in THF, 0.024 mmol) at room temperature for 60 min. The reaction mixture was concentrated with a rotary evaporator to a brown oil. The crude material was purified by flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.25) to yield 3.0 mg (75%) of **15a** as a white solid: mp 104–105 °C; IR (KBr) 3270–3230, 1630 cm^{-1}; ^1H NMR δ 6.20 (1 H, s), 5.96, 5.92 (2 H, AB m, J = 11 Hz), 4.45 (1 H, s), 4.44 (1 H, s), 2.12 (2 H, s); ^{13}C NMR (acetone-d_6, 75.4 MHz) δ 134.8, 132.6, 127.9, 116.7, 75.5, 72.7; mass spectrum, m/z (relative intensity) 192, 190 (M^+, 19), 174, 172 (9, 10), 163, 161 (13, 14), 146, 144 (35, 33), 111 (11), 93 (21), 65 (100); HRMS calcd for $C_6H_7{}^{79}BrO_2$ 189.9629, found 189.9627.

***trans*-1,2-Dihydroxy-1,2-dihydro-4-chlorobenzene (15b).** Diene **15b** was prepared from **14b** (150 mg, 0.575 mmol) by the same procedure as for the preparation of **15a**. The crude material was purified by flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.28) to yield 75.0 mg (89%) of **15b** as a white solid: mp 106–107 °C; IR (KBr) 3250–2210, 1640, 1590 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 5.99 (1 H, dd, J = 9.7, 3.1 Hz), 5.90 (1 H, t, J = 2.6 Hz), 5.79 (1 H, dt, J = 10, 2.2 Hz), 4.36 (3 H, m), 2.97 (1 H, m); ^{13}C NMR (acetone-d_6, 75.4 MHz) δ 134.9, 128.2, 128.0, 126.1, 74.7, 73.0; mass spectrum, m/z (relative intensity) 148, 146 (M^+, 8.8, 29), 130, 128 (4.5, 15), 119, 117 (8.1, 26), 102, 100 (46, 100), 91, 89 (8.9, 26), 83, 81 (15, 46), 65 (92). Anal. Calcd for $C_6H_7ClO_2$: C, 49.17; H, 4.81; Cl, 24.19. Found: C, 49.12; H, 4.90; Cl, 23.95.

(1β,4β,5α,6β)-2-Bromo-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-7-oxabicyclo[4.1.0]hept-2-ene (16a). A chloroform solution (2.0 mL) of **14a** (66 mg, 0.22 mmol), sodium bicarbonate (0.024 g, 0.29 mmol), and *m*-CPBA (80%, 51 mg, 0.24 mmol) was stirred at room temperature for 3 h. The mixture was concentrated with a rotary evaporator to a white solid. Flash chromatography on silica gel (2:1 hexane/ethyl ether, R_f = 0.38) yielded 0.047 g (68%) of **16a** as a colorless oil: IR (thin film) 3480–3430 cm^{-1}; ^1H NMR δ 6.08 (1 H, t, J = 2.1 Hz), 4.13 (1 H, dd, J = 7.0, 1.9 Hz), 3.87 (1 H, dd, J = 7.4, 1.8 Hz), 3.62 (2 H, m), 2.85–2.45 (1 H, br s), 0.92 (9 H, s), 0.14 (3 H, s), 0.13 (3 H, s); ^{13}C NMR δ 136.1, 115.6, 73.5, 72.6, 56.0, 54.9, 25.7, 18.0, –4.6.

(1β,4β,5α,6β)-2-Chloro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-7-oxabicyclo[4.1.0]hept-2-ene (16b). Epoxide **16b** was prepared from **14b** (116 mg, 0.445 mmol) by the same procedure as for the preparation of **16a**. Purification by flash chromatography on silica gel (2.5:1 hexane/ethyl ether, R_f = 0.24) gave 0.053 g (43%) of **16b** as a colorless oil: IR (thin film): 3480–3430, 1640 cm^{-1}; ^1H NMR δ 5.83 (1 H, t, J = 2.2 Hz), 4.17 (1 H, dd, J = 8.2, 2.3 Hz), 3.85 (1 H, ddd, J = 7.8, 4.8, 1.7 Hz) 3.60 (1 H, dd, J = 4.1, 2.1 Hz), 3.53 (1 H, dd, J = 4.0, 2.7 Hz), 2.34 (1 H, d, J = 5.0 Hz), 0.91 (9 H, s), 0.13 (3 H, s), 0.11 (3 H, s); ^{13}C NMR δ 131.5, 127.0, 73.7, 71.4, 54.4, 25.7, 17.9, –4.6; mass spectrum, m/z (relative intensity) 221, 219 (6.3, 16), 203, 201 (7.4, 22), 186 (4.3), 185 (5.9), 163, 161 (3.9, 9.4), 115 (3.1), 99 (10), 93 (14), 75 (100), 73 (26).

(1β,4β,5α,6β)-2-Bromo-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol (17a). To an anhydrous THF solution (3.0 mL) of **16a** (43 mg, 0.13 mmol) at 0 °C was added tetrabutylammonium fluoride (147 mL of a 1.0 M solution in THF, 0.147 mmol). The mixture was stirred for 90 min at 0 °C and then was concentrated under reduced pressure to a yellow oil. Purification by flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.14) gave 17 mg (61%) of **17a** as a white solid: mp 126–128 °C dec; IR (KBr) 3480–3370, 1630 cm^{-1}; ^1H NMR δ 6.23 (1 H, t, J = 2.7 Hz), 4.16 (1 H, m), 3.89 (1 H, m), 3.68 (1 H, dd, J = 5.0, 1.8 Hz), 3.61 (1 H, dm, J = 3.7 Hz), 2.42 (1 H, br s), 2.35 (1 H, br s); ^{13}C NMR (acetone-d_6, 75.4 MHz) δ 137.6, 116.1, 73.4, 71.9, 56.5, 56.3; mass spectrum, m/z (relative intensity) 208, 206 (M^+, 0.2, 0.2), 191, 189 (0.4, 0.7), 190, 188 (1.3, 1.0), 179, 177 (4.6, 5.4), 127 (58), 109 (20), 81 (64), 69 (100); HMRS calcd for $C_6H_7{}^{79}BrO_3$ 205.9579, found 205.9578.

(1β,4β,5α,6β)-2-Chloro-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol (17b). Diol epoxide **17b** was prepared from **16b** (50 mg, 0.18 mmol) by the same procedure as for the preparation of **17a**. Purification by flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.14) gave 23.6 mg (80%) of **17b** as a white solid: mp 111.5–112.0 °C; IR (KBr) 3470–3370, 164 cm^{-1}; ^1H NMR δ 6.00 (1 H, t, J = 2.6 Hz) 4.23 (1 H, d, J = 7.3 Hz), 3.90 (1 H, d, J = 8.1 Hz), 3.64 (1 H, d, J = 4.3 Hz), 3.59 (1 H, d, J = 4.3 Hz), 2.45 (1 H, br s), 2.36 (1 H, br s); mass spectrum, m/z (relative intensity) 164, 162 (M^+, 0.1, 0.4), 135, 133 (3.3, 9.7), 115 (22.8), 106, 104 (32, 100), 103 (28), 81 (26), 71, 69 (19, 57); HRMS calcd for $C_6H_7{}^{37}ClO_3$ 164.0054, found 164.0054.

(1α,4α,5β,6α)-1-Bromo-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol (18a). To a stirred solution of the diene **15a** (0.015 g, 0.079 mmol) in CH_2Cl_2 (1.0 mL) were added sodium bicarbonate (7.3 mg, 0.087 mmol) and *m*-CPBA (80%, 19 mg, 0.087 mmol) at 0 °C. The mixture was stirred for 90 min. The solution was concentrated with a rotary evaporator to give a white solid, which was purified by flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.27) to afford 10 mg (62%) of **18a** as a white solid: IR (KBr) 3350–3320, 1630 cm^{-1}; ^1H NMR δ 6.14 (1 H, dd, J = 9.5, 3.0 Hz), 5.76 (1 H, dd, J = 10, 1.7 Hz), 4.13 (1 H, m), 3.98 (1 H, m), 3.86 (1 H, s), 2.34 (1 H, m), 2.29 (1 H, m); mass spectrum, m/z (relative intensity) 208, 206 (M^+, 0.2), 161, 159 (13.2, 13.3), 121, 119 (7.5, 7.6), 109 (50.6), 81 (100); HRMS calcd for $C_6H_7{}^{79}BrO_3$ 205.9579, found 205.9579.

(1α,4α,5β,6α)-1-Chloro-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol (18b). Diol epoxide **18b** was prepared from **15b** (8.0 mg, 0.054 mmol) by the same procedure as for the preparation of **18a**. Flash chromatography on silica gel (1:1 hexane/ethyl acetate, R_f = 0.28) gave 5.3 mg (60%) of **18b** as a white solid: IR (KBr) 3340–3320 cm^{-1}; ^1H NMR δ 6.05 (1 H, dd, J = 7.7, 2.2 Hz), 5.89 (1 H, d, J = 7.2 Hz), 4.14 (1 H, m), 3.98 (1 H, t, J = 7.1 Hz), 3.84 (1 H, s), 2.34 (1 H, d, J = 5.6 Hz), 2.29 (1 H, d, J = 4.7 Hz); mass spectrum, m/z (relative intensity) 164, 162 (M^+, 5.9, 17), 146, 144 (7.7, 28), 130, 128 (23, 64), 122, 120 (28, 79), 84 (85), 60 (72), 39 (100); HMRS calcd for $C_6H_7{}^{37}ClO_3$ 164.0054, found 164.0053.

Bacterial Mutagenesis. Mutagenic activity was tested by using the *S. typhimurium* forward mutation assay of Skopek and co-workers.[9] This assay measures the induced 8-azaguanine resistance mutant fraction following a 2-h treatment with test compound at 37 °C. Survival following treatment is measured

so a true mutation fraction can be calculated. Duplicate samples are tested, and triplicate platings are obtained from each sample. Thus a total of six selective plate counts and six bacterial survival counts are available for each sample tested. To mimic animal metabolism, samples are also incubated with Aroclor 1254 induced rat liver postmitochondrial supernatant (PMS). All samples were tested to a concentration of 300 mg/mL or their maximum solubility. There is no single parameter that can describe a complex dose–response relationship between test agent concentration and induced mutant fraction. For simplicity we have chosen to use the maximum slope from dose–response curves as a measure of mutagenic activity of the sample. The 99% confidence limits for each slope were calculated on the basis of the Poisson counting statistics of the data.

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An Efficient One-Pot Method for the Preparation of Polysubstituted Benzothiophenes†

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A one-pot method for the transformation of an aryl bromide, an internal alkyne, and sulfur dichloride into a polysubstituted benzothiophene, in high yield, is described. The method involves the generation and trapping of a zirconocene complex of a substituted benzyne.

Heterocycles are, perhaps, the most frequently used class of compounds in the pharmaceutical industry.[2] Accordingly, a tremendous body of literature on their structure, properties, and synthesis has appeared.[3] While myriad means for the preparation of heterocyclic compounds exist, new methods of higher efficiency and greater generality which utilize readily available precursors are in great demand. We have been concerned with the development of new tactics for the construction of heterocyclic compounds and have recently reported new methods for the preparation of benzisothiazoles,[4a] butenolides,[4b] and pyrroles[4c] using organozirconium-based strategies.[4d] We now report an experimentally simple, general, high-yield synthesis of polysubstituted benzothiophenes.

Benzothiophenes are most frequently constructed via cyclization reactions beginning with thiophenol precursors[5] or by the annulation of an aromatic ring onto a thiophene moiety.[6] While these strategies have merit for the preparation of benzothiophenes of specific substitution patterns, they lack generality and, hence, cannot be used to prepare many polysubstituted variants. In our study of the coupling of nitriles with zirconocene complexes of substituted benzynes,[4a] we observed excellent to complete regioselectivity in metallacycle formation. For the analogous coupling of an unsymmetric alkyne with a zirconium complex of an unsymmetrical benzyne, four regioisomers are possible. Of these possibilities, we felt, based on the above-mentioned work, that only **1a** and/or **1b** (for R^1 larger than R^2) would be produced (Scheme I). In order to induce the formation of a single regioisomer, we sought to differentiate R^3 from R^4 to the greatest extent possible without sacrificing the generality of the transformation. One obvious means to accomplish this would employ a terminal alkyne as the substrate. This possibility, however, is untenable, since, unlike many of the related zirconocene complexes that we have prepared and studied,[4d,7] the benzyne complexes do not undergo clean coupling reactions with terminal alkynes. It was decided, therefore, to employ the trimethylsilyl group as a proton surrogate for two reasons. First, protodesilylation of vinylsilanes is well-precedented.[8] Second, in earlier work on the regiochemical course of the intermolecular cross-coupling of two different alkynes, we observed that, for internal alkynes in which one substituent was a trialkylsilyl group, this trialkylsilyl group always ended up on the 2-carbon in the product zirconacycles.[9] In practice, for cases in which $R^1 = R^2$ or $R^2 = H$, only a single regioisomeric zirconacycle is formed[10] (Scheme II). As we had observed previously, modification of the conditions of Nugent and Fagan[11] allows the clean, high-yield conversion of the intermediate zirconacycles without need for their isolation or purification. Note that in entries 4–15 a commercially available bromoarene and alkyne are converted in a one-pot procedure to the substituted benzothiophene in 60–80% isolated yield as is shown in Table I. In cases 3, 6, 9, 12, and 15, proto-

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