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# Expedient Two-Step Synthesis of Phenolic Cyclitols from Benzene

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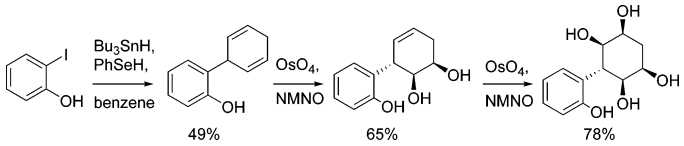


The benzeneselenol-catalyzed, tributyltin hydride-mediated addition of phenolic iodides to benzene gives the 3-(hydroxyaryl)-1,4-cyclohexadienes, predominantly. Under conditions of controlled osmoylation, these are converted to the racemic 1,2-*syn*-2,3-*anti*-3-(hydroxyaryl)-4-cyclohexene-1,2-diols, whereas exhaustive osmoylation gives the 3-(hydroxyaryl)-3,5-dideoxymucoinositols, whose stereochemistry is established by X-ray crystallography.

## Introduction

Polyhydroxylated cyclohexanes and their derivatives are widespread constituents of biologically important compounds, the most obvious instances being the cyclitols,[1] especially the inositols.[2] The carbasugars,[3] carbacyclic analogues of sugars first synthesized by McCasland and co-workers,[4] with their ability to function as glycosidase inhibitors, have potential in many therapeutic areas. Polyhydroxylated cyclohexane rings are also found in the amaryllidaceae family of natural products, most notably pancratistatin, lycoridine, and narciclasine and their relatives.[5] A number of polyhydroxylated cyclohexanes and their arylated analogues have been prepared for use as intermediates in total synthesis by enzymatic oxidative dihydroxylation of arenes and biarenes,[6] as well as by chemical oxidative functionalization of benzene.[7] We report here on a concise alternative approach to the synthesis of a range of aryl-substituted cyclohexenediols and cyclohexanetetraols involving the reductive radical arylation of benzene and subsequent treatment with osmium tetroxide. The method is conceptually related to the work of Landais on the desymmetrization of cyclohexadienylsilanes generated by Birch reduction of arylsilanes, but differs significantly insofar as it employs benzene itself as substrate and incorporates an arylation reaction in the key reduction step.[8,9]

## Results and Discussion

In 1998 we reported the stannane-mediated reductive radical arylation of benzene via rapid addition of aryl radicals to

(1) (a) Posternak, T. *The Cyclitols*; Holden-Day: San Francisco, 1962. (b) Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives: A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993.

(2) (a) *The Inositol Phosphates. Chemical Synthesis and Biological Significance*; Billington, D. C., Ed.; VCH: New York, 1993. (b) *Phosphoinositides: Chemistry, Biochemistry, and Biomedical Applications*; Bruzik, K. S., Ed.; ACS Symposium Series 718; American Chemical Society: Washington, DC, 1999. (c) Thomas, J. R.; Dwek, R. A.; Rademacher, T. W. *Biochemistry* **1990**, *29*, 5413−5422. (d) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933−1972. (e) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477−4503.

(3) (a) Kobayashi, Y. In *Glycosciene: Chemistry and Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; Vol. 3, pp 2595−2661. (b) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155−162. (c) *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: New York, 1998. (d) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831. (e) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Curti, C. In *Bioactive Natural Products (J)*; Atta-ur-Rahman, Ed.; Elsevier Science: New York, 2003; Vol. 29, pp 449−520.

(4) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516−1521.

(5) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, pp 252−376. (b) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, pp 109−148. (c) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, 1998; Vol. 51, pp 323−424. (d) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606−614. (e) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365−405.

(6) (a) Ley, S. V. *Pure Appl. Chem.* **1990**, *62*, 2031−2034. (b) Carless, H. A. *Tetrahedron: Asymmetry.* **1992**, *3*, 795−826. (c) Hudlicky, T.; Thorpe, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1993−2000. (d) Hudlicky, T.; Gonzalez, D.; Gibson, D. *Aldrichimica Acta* **1999**, *32*, 35−62.

(7) Motherwell, W. B.; Williams, A. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 203-213.

(8) (a) Angelaud, R.; Landais, Y. *J. Org. Chem.* **1996**, *61*, 5202−5203. (b) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613−9624.

(9) Reviews on the desymmetrization of cyclohexadienes: (a) Studer, A.; Kim, Y. H. *Synlett* **2005**, 3033−3041. (b) Rahman, N. A.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369−1395.

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**CHART 1**

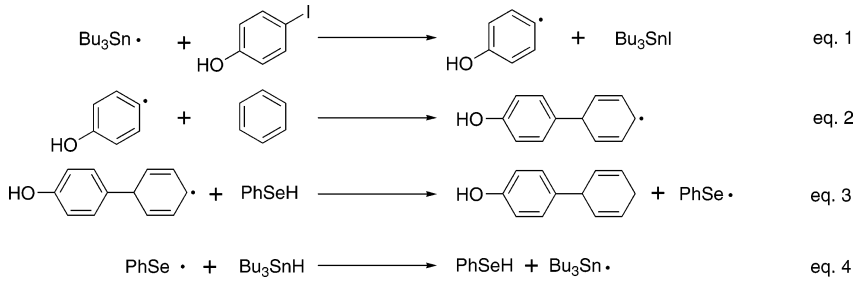
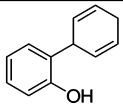
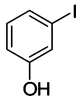
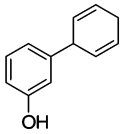
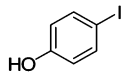
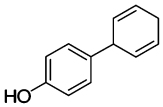
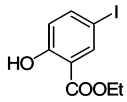
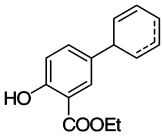
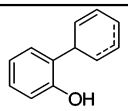
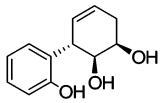
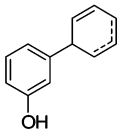
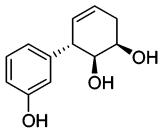
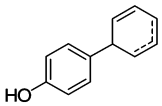
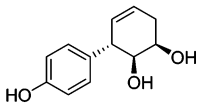
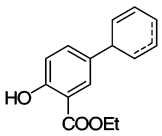
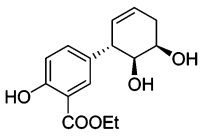



**TABLE 1. Aryl Radical Addition to Benzene**

| Substrate | Product | Yield[a] |
|---|---|---|
|  **1** |  **2** | 52% |
|  **3** |  **4** | 49% |
|  **5** |  **6** | 51% |
|  **7** |  **8** | 62% |

[a] Isolated yields of regiosiomerically pure 1,4-dienes, with the exception of **8**, which was isolated as a 5:1 mixture of 1,4- and 1,3-dienes.

**TABLE 2. Dihydroxylation of Dienes**

| Substrate[a] | Product | Yield |
|---|---|---|
|  **2** |  **9** | 65% |
|  **4** |  **10** | 68% |
|  **6** |  **11** | 63% |
|  **8** |  **12** | 75% |

[a] Reactions were conducted with approximately 5:1 mixtures of the 1,4- and 1,3-dienes.

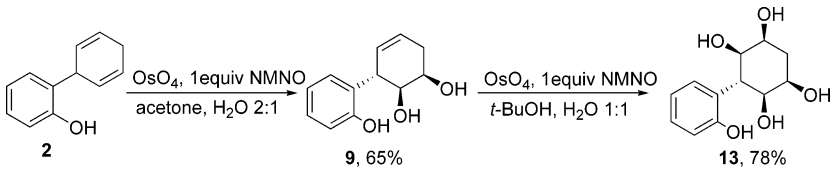
benzene in the presence of a catalytic amount of benzeneselenol.[10] Although it is well-established that aryl radicals will rapidly add to arenes,[11] this reaction had been of limited use synthetically due to the failure of the resulting cyclohexadienyl radical to propagate a radical chain reaction.[12,13] The radical chain chemistry developed in this laboratory makes use of the superior hydrogen atom donating ability of benzeneselenol,[14] generated in situ from diphenyl diselenide and tributyltin hydride,[15] to efficiently trap the adduct cyclohexadienyl radical and propagate the radical chain reaction. Overall, the reaction involves a four-propagation-step radical chain reaction (eqs 1−4; Chart 1) and provides predominantly 3-aryl-1,4-cyclohexadienes, typically containing a minor amount of the regioisomeric 5-aryl-1,3-cyclohexadienes.

The synthetic utility of this reaction has been exploited in the case of aryl iodides bearing a nucleophile at the *o*-position when subsequent electrophilic activation of the cyclohexadiene moiety gives direct access to functionalized tetrahydrocarbazoles and tetrahydrodibenzofurans,[16] as displayed in syntheses of carbazomycin[17] and of a 4,6-substituted dibenzofuran $\beta$-sheet initiator.[18]

We now demonstrate how catalytic osmoylation of the 3-aryl-1,4-cyclohexadienes results in a facile two-step synthesis of *meso*-3-aryl-1,2,4,5-cyclohexanetetraols and, with careful control of stoichiometry, of 3-aryl-4-cyclohexene-1,2-diols. Thus, a

(10) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770.
(11) Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609−3614.
(12) Note that most radical cyclizations onto arenes are oxidative and probably not chain reactions. (a) Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc.* **1989**, *111*, 1830−1835. (b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343−7366. (c) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (d) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98.
(13) Stannane- and silane-mediated intermolecular oxidative radical additions to arenes. (a) Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217−6224. (b) Martínez-Barrasa, V.; Garcia de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933−3935. (c) Crich, D.; Patel, M. *Heterocycles* **2004**, *64*, 499−564.
(14) Newcomb, M.; Choi, S.-Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225−1231.
(15) (a) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84−88. (b) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368−2373.
(16) Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319−3322.
(17) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513−1516.
(18) Crich, D.; Grant, D. *J. Org. Chem.* **2005**, *70*, 2384−2386.

**SCHEME 1. Synthesis of Diol 9 and Tetraol 13**




series of arylated cyclohexadienes were prepared in the standard manner by the dropwise addition of tributyltin hydride and AIBN to a solution of the appropriate iodophenol and a catalytic amount of diphenyl diselenide in benzene at reflux under argon, with the results presented in Table 1.

These dienes were then subjected to dihydroxylation with catalytic osmium tetroxide in the presence of a controlled amount of *N*-methyl morpholine *N*-oxide as the stoichiometric oxidant, under the conditions of van Rheenan and co-workers.[19] As anticipated from the presumed envelope conformation of the cyclohexadienes in which the aromatic ring assumes a pseudoaxial position to minimize allylic strain, the reaction took place exclusively anti to the substituent leading to phenolic diols in good yield (Table 2). The observation of high anti selectivity in these reactions is in agreement with the work of Landais and co-workers on the dihydroxylation of 3-silyl-1,4-cyclohexadienes.[8b] The anti relationship between the phenol and the two hydroxyl groups, which was not readily apparent from the NMR spectra, was confirmed by X-ray crystallographic analysis of **11**, whose structure is presented in the Supporting Information. The X-ray structure of **11** reveals the expected half-chair conformation with the pseudoaxial aryl group, thereby lending weight to the presumed conformation of the starting 3-aryl-1,4-cyclohexadiene and the rationale for stereoselectivity. Application of the Sharpless asymmetric dihydroxylation protocol to **2** gave **9** with yields and diastereoselectivities comparable to those from the van Rheenan protocol (Table 1), but little or no enantioselectivity was obtained. Again, this is comparable to the observations of Landais and co-workers in the 3-silyl-1,4-cyclohexadiene series.[8b] Attempts at phenol-directed syn dihydroxylation of **2** under the Donohoe conditions were similarly unsuccessful, despite the positioning of the phenolic hydroxyl group directly over one face of the cyclohexadiene.[20]

The subjection of 3-aryl cyclohexenediol **9** to a second dihydroxylation under catalytic $OsO_4$/NMNO conditions gave a single phenolic tetraol whose spectra exhibited the simplicity anticipated for the *meso*-isomer, resulting from delivery of the second diol unit anti to the aromatic substituent (Scheme 1).

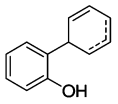
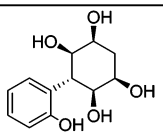
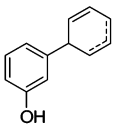
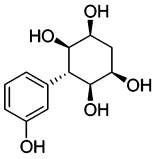
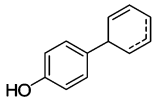
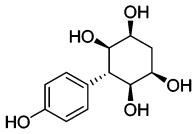
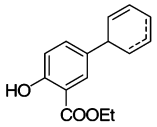
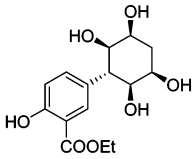
Osmoylation of the diene **2** with 2 equiv of NMNO gave the *meso*-tetraol **13** directly in excellent yield, and a series of tetraols were prepared in this manner (Table 3). The stereochemical assignment of these tetraols, with their pseudoasymmetric C3, as the 3-aryl-3,5-dideoxymucoinositols,[1a] was confirmed unambiguously by X-ray crystallographic analysis of **13**, which exhibits a chair conformation with the phenyl group equatorial.

At least in the crystal, obtained from methanol, the phenolic tetraol **13** exhibits an interesting conformation about the cyclohexyl−aryl bond, which orients the phenolic hydroxyl group in the same direction as the four aliphatic hydroxyl groups.

(19) Van Rheenan, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. No. VI, pp 342−348.

(20) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946−7956.

**TABLE 3. Double Dihydroxylation of Cyclohexadienes**

| Substrate[a] | Product | Yield |
|---|---|---|
|  **2** |  **13** | 65% |
|  **4** |  **14** | 69% |
|  **6** |  **15** | 67% |
|  **8** |  **16** | 78% |

[a] Reactions were conducted with approximately 5:1 mixtures of the 1,4- and 1,3-dienes.

## Experimental Section

**General Procedure for Radical Addition to Benzene.** A dry flask was charged with aryl iodide (2.0 mmol) and diphenyl diselenide (0.4 mmol), fitted with a reflux condenser, and flushed with argon. Dry, degassed benzene (50 mL) was added, and the resulting solution was heated to reflux. A solution of AIBN (0.2 mmol) and tributyltin hydride (3.0 mmol) in dry, degassed benzene (14.0 mL) was added via syringe pump at a rate of 1.0 mL/h. On completion of the addition, the reaction mixture was refluxed 1 h before the solvent was removed in vacuo. Column chromatography over silica gel gave the adducts.

**2-(1,4-Cyclohexadien-3-yl)phenol (2).** The spectral data for this compound match those reported in the literature.[16]

**3-(1,4-Cyclohexadien-3-yl)phenol (4).** Isolated as colorless oil by silica gel chromatography (eluent: 2% EtOAc in hexane). IR $\nu$ 3356 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 2.72−2.77 (m, 2H), 3.89−3.94 (m, 1H), 4.84 (s, 1H), 5.70−5.74 (m, 2H), 5.80−5.84 (m, 2H), 6.67 (dd, $J$ = 7.5, 2.5 Hz, 1H), 6.71 (dd, $J$ = 4.0, 2.5 Hz, 1H), 6.81 (d, 7.5 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 25.8, 41.8, 113.3, 114.9, 120.5, 123.9, 128.3, 129.7, 147.2, 155.8. EI-HRMS calcd for $C_{12}H_{12}O$, 172.0888 $[M]^+$; found, 172.0878.

**4-(1,4-Cyclohexadien-3-yl)phenol (6).** Isolated as colorless oil by silica gel chromatography (eluent: 4% EtOAc in hexanes). IR

$\nu$ 3454 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.71−2.76 (m, 2H), 3.87−3.92 (m, 1H), 4.73 (s, 1H), 5.69−5.72 (m, 2H), 5.78−5.82 (m, 2H), 6.78 (d, $J$ = 9.5 Hz, 2H), 7.10 (d, $J$ = 9.5 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 25.8, 41.1, 115.3, 125.5, 128.8, 129.1, 137.6, 154.0. EI-HRMS calcd for $C_{12}H_{12}O$, 172.0888 [M]$^+$; found, 172.0881.

**Ethyl 5-(1,4-Cyclohexadien-3-yl)salicylate (8).** Isolated as colorless oil by silica gel chromatography (eluent: 1% EtOAc in hexane). IR $\nu$ 3409, 1673 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.42 (t, $J$ = 7.0 Hz, 3H), 2.72−2.80 (m, 2H), 3.89−3.95 (m, 1H), 4.41 (q, $J$ = 7.0 Hz, 2H), 5.66−5.71 (m, 2H), 5.81−5.86 (m, 2H), 6.93 (d, $J$ = 8.5 Hz, 1H), 7.32 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.66 (d, 2.0 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 14.3, 25.8, 41.1, 61.4, 117.8, 124.0, 128.4, 128.6, 135.6, 136.0, 160.3, 170.2. This mixture of isomers was carried forward to the next step without further characterization, owing to the relative instability toward aromatization in air.

**General Procedure for Dihydroxylation of Dienes.** $OsO_4$ (0.002 mmol) was added to a solution of the 1,4-diene containing ~17% of the minor 1,3-isomer (0.10 mmol) in water/acetone (1:1, 1.0 mL) and cooled to 0 °C. NMNO (0.10 mmol) dissolved in water/acetone solution (1/1, 1.0 mL) was added in four portions at 15 min intervals to the reaction mixture while stirring. The reaction mixture was stirred 0.5 h on completion of the NMNO addition and allowed to return to room temperature. $Na_2SO_3$ (1.0 mmol) was added, and the reaction was stirred an additional 1 h before it was diluted with water (20 mL). The product was extracted into EtOAc (3 × 20 mL), and the extracts were washed with brine (20 mL) and dried ($Na_2SO_4$). The solvent was removed in vacuo, and the product was isolated by silica gel chromatography.

**(±)-(1*R**,2*S**,3*S**)-3-(2′-Hydroxyphenyl)-cyclohex-4-ene-1,2-diol (9).** Isolated as a white solid by silica gel chromatography (eluent: 50% EtOAc in hexane). Mp 130−132 °C. IR $\nu$ 3360 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 2.30−2.34 (m, 2H), 3.83−3.88 (m, 2H), 4.00 (s, 1H), 5.52−5.55 (m, 1H), 5.78−5.82 (m, 1H), 6.78 (t, $J$ = 7.5 Hz, 1H), 6.80 (d, $J$ = 7.5 Hz, 1H), 7.04 (t, $J$ = 7.5 Hz, 1H), 7.04 (t, $J$ = 7.5 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 30.2, 41.6, 66.9, 73.7, 114.8, 119.3, 125.0, 126.7, 127.2, 128.6, 128.7, 155.1. EI-HRMS calcd for $C_{12}H_{14}O_3$, 206.0943 [M]$^+$; found, 206.0948.

**(±)-(1*R**,2*S**,3*S**)-3-(3′-Hydroxyphenyl)-cyclohex-4-ene-1,2-diol (10).** Isolated as a white solid by silica gel chromatography (eluent: 50% EtOAc in hexane). Mp 129−130 °C. IR $\nu$ 3361 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 2.27−2.31 (m, 1H), 2.38−2.42 (m, 1H), 3.47−3.48 (m, 1H), 3.73 (dd, $J$ = 6.5, 2.0 Hz, 1H), 3.92 (td, $J$ = 5.0, 2.0 Hz, 1H), 5.53−5.55 (m, 1H), 5.72−5.76 (m, 1H), 6.63 (d, $J$ = 8.0, 1H), 6.69 (s, 1H), 6.72 (d, $J$ = 8.0, 1H), 7.10 (t, $J$ = 8.0, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 31.0, 47.7, 67.0, 74.9, 113.0, 115.2, 119.6, 124.2, 127.4, 128.9, 144.4, 157.1. EI-HRMS calcd for $C_{12}H_{14}O_3$, 206.0943 [M]$^+$; found, 206.0941.

**(±)-(1*R**,2*S**,3*S**)-3-(4′-Hydroxyphenyl)-cyclohex-4-ene-1,2-diol (11).** Isolated as a white solid by silica gel chromatography (eluent: 50% EtOAc in hexane). Mp 178−179 °C. IR $\nu$ 3366 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 2.29−2.31 (m, 1H), 2.37−2.41 (m, 1H), 3.46 (dt, $J$ = 5.0, 2.5 Hz, 1H), 3.68 (dd, $J$ = 6.5, 2.0 Hz, 1H), 3.89−3.97 (m, 1H), 5.52−5.55 (m, 1H), 5.70−5.74 (m, 1H), 6.72 (dd, $J$ = 8.5, 3.0 Hz, 2H), 7.05 (dd, $J$ = 8.5, 3.0 Hz, 2H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 31.0, 47.0, 66.9, 75.2, 114.7, 124.0, 127.8, 129.2, 133.5, 155.7. Anal. Calcd for $C_{12}H_{14}O_3$ (%): C, 69.88; H, 6.84. Found: C, 69.60; H, 6.70.

**(±)-(1*R**,2*S**,3*S**)-3-(Ethyl 5-salicyclyl)-cyclohex-4-ene-1,2-diol (12).** Isolated as a white solid by silica gel chromatography (eluent: 25% hexanes in EtOAc). Mp 116−118 °C. IR $\nu$ 3410, 1674 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.40 (t, $J$ = 7.5 Hz, 3H), 2.25−2.35 (m, 1H), 2.40−2.50 (m, 1H), 3.49−3.55 (m, 1H), 3.64 (d, $J$ = 6.0 Hz, 1H), 3.90−3.93 (m, 1H), 4.40 (q, $J$ = 7.5 Hz, 2H), 5.51−5.54 (m, 1H), 5.74−5.77 (m, 1H), 6.90 (d, $J$ = 8.5 Hz, 1H), 7.38 (dd, $J$ = 8.4, 2.0 Hz, 1H), 7.72 (d, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 13.1, 31.5, 46.2, 61.2, 67.3, 74.9, 112.0, 116.9, 124.6, 127.4, 129.3, 133.9, 135.8, 160.2, 170.1. EI-HRMS calcd for $C_{15}H_{18}O_5$, 278.1142 [M + Na]$^+$; found, 278.1154.

**General Procedure for the Double Dihydroxylation of Dienes.** $OsO_4$ (0.002 mmol) was added to a solution of diene containing ~17% of the minor 1,3-isomer (0.10 mmol) in water/acetone (1:1, 1.0 mL), which was cooled to 0 °C before NMNO (0.25 mmol) was added to the reaction mixture while stirring. The reaction mixture was stirred an additional 0.5 h before being allowed to return to room temperature. $Na_2SO_3$ (1.0 mmol) was added, and the reaction mixture was stirred 1 h before being diluted with water (20 mL) and extracted with hot EtOAc (5 × 20 mL). The organic layer was washed with brine (20 mL), dried ($Na_2SO_4$), concentrated in vacuo, and purified by silica gel chromatography to give the tetraols.

**(1*R*,2*S*,3*r*,4*R*,5*S*)-3-(2′-Hydroxyphenyl)-1,2,4,5-cyclohexanetetraol (13).** Isolated as a white solid by silica gel chromatography (eluent: 75% EtOAc in MeOH). Mp 195−197 °C. IR $\nu$ 3368 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.75 (d, $J$ = 15.0 Hz, 1H), 2.23 (dt, $J$ = 15.0, 3.0 Hz, 1H), 3.40−3.70 (m, 1H), 3.99 (s, 4H), 6.79 (d, $J$ = 8.0 Hz, 1H), 6.83 (t, $J$ = 8.0 Hz, 1H), 7.05 (t, $J$ = 8.0 Hz, 1H), 7.25 (d, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 32.0, 70.7, 72.8, 115.2, 119.4, 126.1, 126.9, 156.4. EI-HRMS calcd for $C_{12}H_{16}O_5$, 263.08915 [M + Na]$^+$; found, 263.08903.

**(1*R*,2*S*,3*r*,4*R*,5*S*)-3(3′-Hydroxyphenyl)-1,2,4,5-cyclohexanetetraol (14).** Isolated as a white solid by silica gel chromatography (eluent: 25% MeOH in EtOAc). Mp 184−186 °C. IR $\nu$ 3366 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.78 (td, $J$ =15.0, 2.5 Hz, 1H), 2.22 (td, $J$ = 15.0, 3.5 Hz, 1H), 3.07 (t, $J$ = 11.0 Hz, 1H), 3.34 (s, 2H), 3.68 (dd, $J$ = 11.0, 3.0 Hz, 2H), 3.98 (d, $J$ = 3.0 Hz, 2H), 6.65 (d, $J$ = 8.0 Hz, 1H), 6.81 (s, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 7.13 (t, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 32.1, 70.6, 74.04, 113.1, 115.8, 120.1, 128.8, 142.0, 156.96. EI-HRMS calcd for $C_{12}H_{16}O_5$, 240.0998 [M]$^+$; found, 240.0982.

**(1*R*,2*S*,3*r*,4*R*,5*S*)-3-(4′-Hydroxyphenyl)-1,2,4,5-cyclohexanetetraol (15).** Isolated as a white solid by silica gel chromatography (eluent: 25% MeOH in EtOAc). Mp 187−189 °C. IR $\nu$ 3366 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.76 (dt, $J$ = 15.0, 2.5 Hz, 1H), 2.11 (dt, $J$ = 15.0, 3.5 Hz, 1H), 3.05 (t, $J$ = 11.0 Hz, 1H), 3.63 (dd, $J$ = 11.0, 2.5 Hz, 2H), 3.97 (d, $J$ = 2.5 Hz, 2H), 6.76 (d, $J$ = 8.5, 2H), 7.17 (d, $J$ = 8.5 Hz, 2H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 32.1, 48.5, 70.7, 74.1, 114.7, 129.7, 131.0, 155.6. EI-HRMS calcd for $C_{12}H_{16}O_5$, 240.0998 [M]$^+$; found, 240.1007.

**(1*R*,2*S*,3*r*,4*R*,5*S*)-3-(Ethyl-5-salicyclyl)-1,2,4,5-cyclohexanetetraol (16).** Isolated as a white solid by silica gel chromatography (eluent: 25% MeOH in EtOAc). Mp 103−105 °C. IR $\nu$ 3359, 1672 cm$^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 1.40 (t, $J$ = 7.0 Hz, 3H), 1.79 (td, $J$ = 15.0, 2.5 Hz, 1H), 2.22 (td, $J$ = 15.0, 3.5 Hz, 1H), 3.12 (t, $J$ = 11.0 Hz, 1H), 3.34 (s, 1H), 3.66 (dd, $J$ = 11.0, 2.5 Hz, 2H), 3.99 (td, $J$ = 5.5, 2.5 Hz, 2H), 4.30 (q, $J$ = 7.0 Hz, 2H), 6.92 (d, $J$ = 8.5 Hz, 1H), 7.50 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.84 (d, $J$ = 2.5 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 13.2, 32.1, 61.1, 70.7, 73.9, 11.9, 116.7, 130.3, 131.4, 135.8, 160.1, 170.2. ESI-HRMS calcd for $C_{15}H_{20}O_7$, 313.1282 [M + H]$^+$; found, 313.1283.

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**Supporting Information Available:** Copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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