Dihydroxylation of Polyenes Using Narasaka's Modification of the Upjohn Procedure

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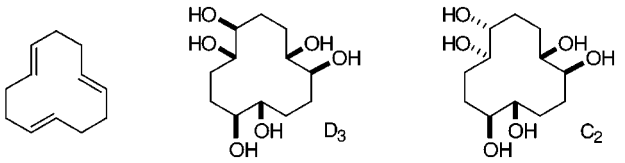
Dihydroxylation of a variety of commercially available polyenes has been investigated using phenylboronic acid, *N*-methylmorpholine *N*-oxide (NMO), and osmium tetroxide in anhydrous solvent. The diastereoselectivity of multiple oxidation steps is in some cases affected by the in situ protection of the intermediate ene−diols as phenyboronic esters, affording polyols not available from the standard Upjohn dihydroxylation procedure. A convenient oxidative deprotection of the phenylboronic esters is also described.

As combinatorial chemistry gains momentum in the chemical community,[1] osmium-catalyzed dihydroxylation of olefins retains its status as the most reliable method for the preparation of vicinal diols.[2−8] The power of this transformation is enhanced by the enormous variety of applicable substrates, enabling quick entry into highly functionalized molecules from commercial sources. However, for various reasons the use of polyenes as substrates for dihydroxylation is a relatively undeveloped area.

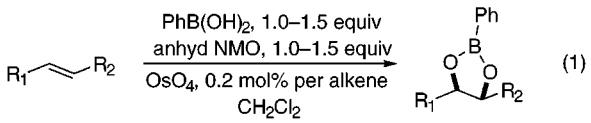
This research stemmed from our continued interest in the D_3-symmetric hexaol **2**, which we planned to use as



1 **2** **3**

a template for building C_3-symmetric ligands. Previous attempts at the synthesis of **2** using the asymmetric dihydroxylation (AD) reaction with *trans*,*trans*,*trans*-cyclododecatriene (**1**) met with limited success[6]—two separate oxidation steps were necessary, isolation and purification was tedious due to the water-solubility of the product, and the yield was low due to the predominant formation of the C_2-symmetric hexaol **3**. Interestingly, this intrinsic preference for the formation of **3** could be decreased by protection of the intermediate diols as acetonides or carbonates. For the cases tested, however, the preference was never completely overcome.

We decided to try the very interesting catalytic osmylation process discovered by Narasaka et al.[9,10] wherein phenylboronic acid replaces water as the agent which "strips" the diolate from the osmium in the NMO/OsO_4 dihydroxylation system. This procedure nicely achieves in situ protection of the product diols as cyclic boronate esters (eq 1). These boronate esters are highly soluble



(1)

in organic solvents, eliminating the solubility problems associated with the corresponding unprotected polyhydroxylated compounds.[6,11,12] Further advantages of this method versus the standard Upjohn dihydroxylation procedure[13] include faster reaction times (down to <1 h from 24 h with certain substrates) even at much lower osmium catalyst loadings[14] and fewer byproducts from overoxidation, which can be a problem when the newly emplaced hydroxyl group(s) is easily oxidized to the carbonyl stage. Additionally, we hoped that the boronate

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(1) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(2) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

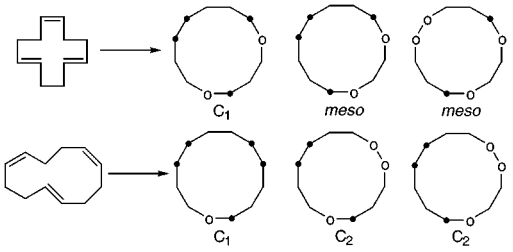
(3) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

(4) Vanhessche, K. P. M.; Sharpless, K. B. *Chem. Eur. J.* **1997**, *3*, 517.

(5) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(6) (a) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345. (b) Unlike the piecemeal sequence required for the earlier perdihydroxylation (ref 12), the Narasaka method allows for perdihydroxylation of squalene in a single step: Gypser, A.; Sharpless, K. B. Unpublished results.

(7) *In our previous paper (see ref 6a) we incorrectly reported the number of possible stereoisomers from exhaustive suprafacial dihydroxylation of the* trans,trans,cis *and* trans,cis,cis *isomers of 1,5,9-cyclododecatriene.* Both the trans,trans,trans and the trans,cis,cis isomers can result in three and not four different diastereomeric products (see scheme below).



(8) Hugger, U.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, *36*, 6603.

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(10) Sakurai, H.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2585.

(11) Tschamber, T.; Backenstrass, F.; Fritz, H.; Streith, J. *Helv. Chim. Acta* **1992**, *75*, 1052.

(12) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993**, *259*, 64.

(13) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, p 342.

(14) Narasaka reported the use of 2 mol % osmium, so the extraordinary activity present in his system went largely unnoticed.

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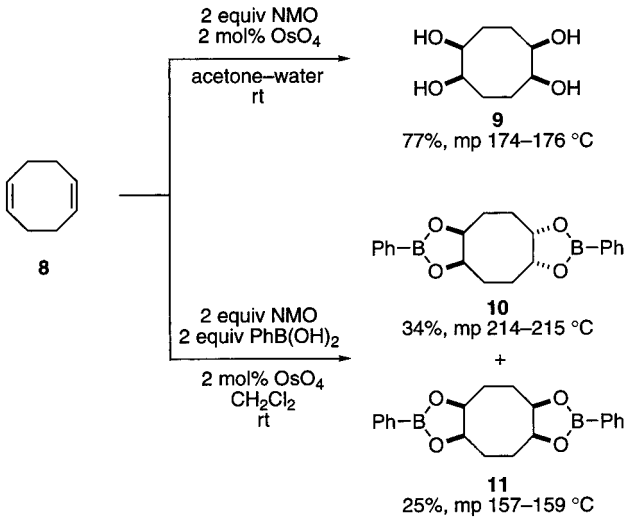
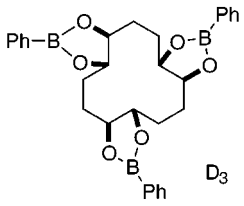
Scheme 1



esters would affect the diastereoselectivity of further dihydroxylation events with polyene substrates, as had acetonides and carbonates in the AD system.[6,8]

Results and Discussion

Reaction of triene **1** under standard Upjohn dihydroxylation conditions[13] gave a 5:95 mixture of the D_3 and C_2 diastereomers *rac*-**2** and *rac*-**3**, respectively.[15] This strong intrinsic preference for the C_2 isomer disappeared using the Narasaka conditions, which provided a high yield of the tris(phenylboronic esters) *rac*-**4** (D_3) and *rac*-**5** (C_2)



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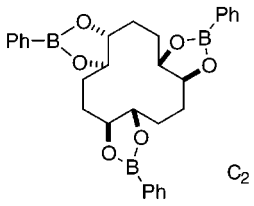

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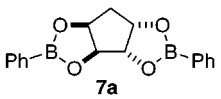
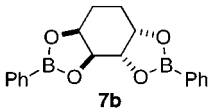
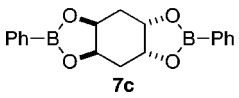
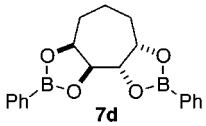
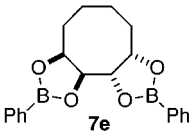
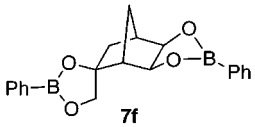
in a 1:1 ratio. Trituration of this D_3/C_2 mixture with acetone provided the pure D_3 isomer *rac*-**4** in 35% yield. It should be noted that the Narasaka conditions require solid ("anhydrous") NMO, whereas for the Upjohn procedure the much less expensive aqueous solution of NMO is preferred.

Compared to the Upjohn process, the Narasaka boronate-capture method allows for a wider range of reaction conditions. For example, due to the absence of water in the solvent mixture, the reaction could be run at low temperatures. Formation of the D_3 isomer was significantly enhanced at −25 °C in CH_2Cl_2 (i.e. D_3:C_2 = 70:30 at −25 °C, cf. ca. 1:1 at 25 °C).

The diastereoselectivity was also examined in several other reaction solvents at room temperature. No change occurred with polar solvents such as tetrahydrofuran or acetonitrile, but the ratio improved to 70:30 in favor of the D_3 isomer in toluene. However, the low solubility of phenylboronic acid in toluene required higher dilution and therefore longer reaction times than in the other solvents. Small- to medium-sized cyclic dienes (**6a**−**f**) were also examined in these modified Narasaka-style boronate-capture osmylations.

Table 1. Bisdihydroxylation of Dienes Using Narasaka's Boronate-Capture Strategy[a]

Substrate	Product	mp	Yield[b]
 **6a**	 **7a**	140–142 °C	68%
 **6b**	 **7b**	161–163 °C	81%
 **6c**	 **7c**	185–188 °C	81%
 **6d**	 **7d**	128–131 °C	75%
 **6e**	 **7e**	112–113 °C	85%
 **6f**	 **7f**	120–121 °C	74%

[a] Reactions performed on an 18 mmol scale minimum; mole ratios for diene/$PhB(OH)_2$/NMO/OsO_4 = 1/2.2/2.2/0.004; CH_2Cl_2, rt, 2−5 h. [b] Isolated yields.

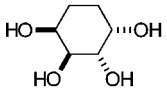
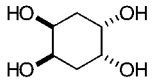
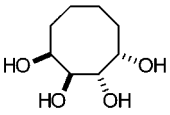
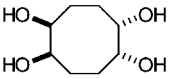
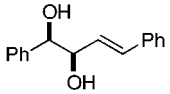
The bis(cyclic boronates) in Table 1 (**7a**−**f**) were all obtained in good yields as single diastereomers. The high anti-selectivity observed for the dienes in entries **6a**−**e** parallels that seen in the corresponding *anti*-tetrols produced in the standard Upjohn process from these same cyclic dienes.[11,16] However, a change in selectivity is observed for 1,5-cyclooctadiene (**8**, Scheme 1). Standard Upjohn oxidation of diene **8** provides the *syn*-tetrol **9** as the sole product, whereas the use of phenylboronic acid as the in situ diol-capture/protecting agent gave an ca. 1:1 mixture of the syn and anti boronate-protected tetrols *anti-meso*-**10** and *syn-meso*-**11**, respectively. A single recrystallization of the mixture provided pure *syn-meso*-**10** in 34% yield; the isomer *anti-meso*-**11** was isolated by column chromatography of the mother liquor. Structural assignments are based on a chemical proof.[17]

We were also interested in achieving monodihydroxylation of conjugated dienes using the phenylboronic acid method. Previous studies with *trans,trans*-1,4-diphenyl-1,3-butadiene using the Upjohn process revealed that the oxidation could not be stopped at the ene−diol stage, since the second oxidation step (giving the tetrol) proceeds at a much faster rate than the first.[2,18] Protection of the diol reduced the rate of the second oxidation, so in theory the in situ protection of the diol as the boronate ester could have a similar effect on the rate. Indeed,

(15) Diastereomer ratio determined by GC analysis of the corresponding hexaacetate derivatives.

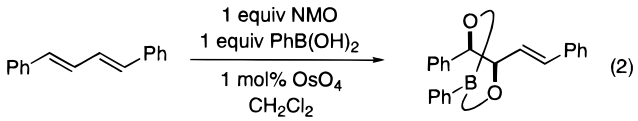
(16) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195.

Table 2. Oxidative Deprotection of Phenylboronic Esters[a,b]

Substrate	Product	mp	Yield [c]
4	*rac*-**2**	270 °C	75%
anti-rac-**7b**	 **14**	210–212 °C	90%
anti-meso-**7c**	 **15**	240–242 °C	89%
anti-rac-**7d**	 **16**	103–104 °C	81%
anti-meso-**10**	 **17**	111–112 °C	86%
rac-**12**	 **18**	165–166 °C	83%

[a] Reference 21. [b] 1.5 equiv of 30% H_2O_2, 1:1 EtOAc−acetone, rt, 4 h. [c] Isolated yields.

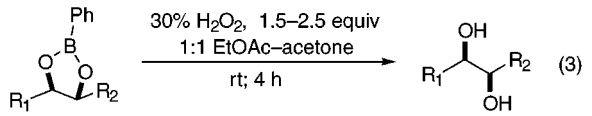
reaction of **12** with 1 equiv each of NMO and phenylboronic acid provided the monooxidation product *rac*-**13** in 42% yield (eq 2). The remainder was starting material and protected tetrol in a 3:1 ratio.



12 **13** (2)

42%, mp 111–112 °C

Several methods for the deprotection of boronates are known,[19−21] including a recently reported method for simultaneously achieving regioselective alkylation of one of the oxygens.[22] In our hands, oxidative cleavage with aqueous hydrogen peroxide proved to be the most reliable method (eq 3).[21]



(3)

In some cases (entries 2 and 3, Table 2) the product polyols were insoluble in the ethyl acetate−acetone solvent mixture and were isolated by simple filtration. In the remaining cases the polyol product was separated from the phenol and boric acid byproducts by column chromatography. With this oxidative cleavage method, however, it is imperative that the starting phenylboronic esters be free from traces of osmium (a single recrystallization usually suffices) in order to avoid osmium-catalyzed overoxidation of the liberated diols.

In summary, we have found that Narasaka's in situ boronate-capture modification of the Upjohn catalytic dihydroxylation process is extremely effective for the exhaustive perhydroxylation of a wide variety of cyclic polyenes. In several cases the Narasaka procedure gave access to a diastereomer not produced under the standard Upjohn conditions.

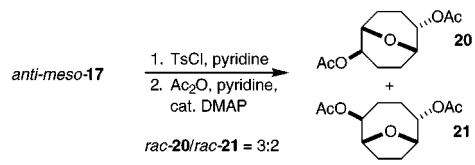
Experimental Section

General Methods. NMO was used either as a solid (97%) or as a 50% aqueous solution, both of which were purchased from Aldrich. Karl Fischer titration showed the solid form to contain 1.4% water. All other reagents were obtained from commercial sources and were used without further purification. Melting points were measured on a capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 250 MHz and 100 or 62.5 MHz, respectively. Multidimensional ^{1}H NMR and NOE experiments were recorded at 600 MHz. Chemical shifts are reported in ppm using the residual protic solvent (^{1}H NMR) or solvent (^{13}C NMR) resonances as internal references. Elemental analyses were performed by Midwest Microlab (Indianapolis, IN). High-resolution mass spectrometry was performed by Dr. Gary Suizdak (The Scripps Research Institute).

(1*R,2*R**,5*R**,6*R**,9*S**,10*S**)-Cyclododecane-1,2,5,6,9,10-hexaol (*rac*-3).** To a mixture of triene **1** (5.6 g, 32 mmol) and 50% aqueous NMO (25 mL, 43 mmol) in acetone (20 mL) and deionized water (30 mL) was added osmium tetroxide (245 mg, 0.96 mmol, 3 mol %). The resulting mixture was stirred at room temperature for 15 h, at which point the white precipitate was collected by filtration. A single trituration with acetone yielded 6.6 g (72%) of analytically pure C_2-hexaol *rac*-**3**: mp 250 °C (MeOH); ^{1}H NMR (D_2O) δ 1.51−2.22 (m, 12 H), 3.61−3.74 (m, 4 H), 3.76−3.81 (m, 2 H), 4.65 (br s, 6 H); ^{13}C NMR (D_2O) δ 28.6, 30.0, 31.9, 74.0, 75.4, 77.3. Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.31; H, 9.22. A smaller scale reaction was run similarly; however the entire reaction mixture (solid and solution) was concentrated in vacuo. The crude residue was peracetylated (Ac_2O, pyridine, catalytic DMAP). GC analysis of the peracetates showed the D_3/C_2 ratio to be 5:95.

(1*R,2*S**,5*R**,6*S**)-Cyclooctane-1,2,5,6-tetrol (*syn-meso*-9).** To a mixture of diene **8** (10 g, 92 mmol) and 50% aqueous NMO (40 mL, 193 mmol) in acetone (50 mL) was added osmium tetroxide (490 mg, 1.93 mmol, 2 mol %). The resulting mixture was stirred at room temperature for 7 h, at which point the white precipitate was collected by filtration. A single recrystallization from 2:1 methanol−acetone gave 12 g (77%) of analytically pure tetrol *syn-meso*-**9**: mp 171−173 °C (lit.[23] mp 174−176 °C); ^{1}H NMR (DMSO-d_6) δ 1.29−1.47 (m, 4 H),

(17) The structures were assigned by exploiting the anti stereochemistry of one of the tetrols. The monotosylate of each tetrol was prepared, and the compound which cyclized to the bicyclic ethers **20** and **21** revealed its anti stereochemistry. See Experimental Section for details.



(18) Park, C. Y. Ph.D. Thesis, Massachusetts Institute of Technology, 1991.
(19) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31.
(20) Bullen, N. P.; Hodge, P.; Thorpe, F. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1863.
(21) Evans, D. A.; Polniaszek, R. P. *Tetrahedron Lett.* **1986**, *27*, 5683.
(22) Oshima, K.; Kitazono, E.-i.; Aoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 5001.

1.76−1.97 (m, 4 H), 3.50−3.66 (m, 4 H), 4.12−4.27 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 26.5, 71.6. Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.59; H, 9.20.

General Procedure A for Direct Single, Double, or Triple Dihydroxylation/Phenylboronic Ester Formation. In a round-bottomed flask under a nitrogen atmosphere, phenylboronic acid (1.0−1.1 equiv per alkene linkage), solid NMO (1.0−1.1 equiv per alkene linkage), and osmium tetroxide (0.0020−0.0025 equiv per alkene linkage) were dissolved in CH_2Cl_2. (Alternatively, osmium tetroxide may be added as a stock solution in CH_2Cl_2.) The flask was immersed in a water bath at room temperature, and the polyene (1.0 equiv) was added as a solution in CH_2Cl_2 over a period of 10−15 min. The final concentration of polyene in CH_2Cl_2 was generally 0.05−0.25 M depending on the scale of the reaction. The reaction was monitored by TLC and was typically complete in 2−5 h. At reaction completion, a 10% aqueous solution of sodium bisulfite (or sodium sulfite) was added, and the mixture was vigorously stirred for 2 h. The two phases were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo, affording a solid which was recrystallized from a 10:1 mixture of hexane−EtOAc unless otherwise noted. The first case below is a representative example of this procedure.

(1*R,2*R**,5*R**,6*R**,9*R**,10*R**)-Cyclododecane-1,2,5,6,9,-10-hexayl-1,2:5,6:9,10-tris(phenylboronate) (*rac*-4).** Phenylboronic acid (11.9 g, 97.7 mmol), solid NMO (11.4 g, 97.7 mmol), and CH_2Cl_2 (75 mL) were added to a 500 mL round-bottomed flask under a nitrogen atmosphere. After dissolution of the solids, osmium tetroxide (47 mg, 0.186 mmol, 0.6 mol %) was added as a solid. The flask was immersed in a water bath at room temperature, and the triene **1** (5.0 g, 31.0 mmol) in CH_2Cl_2 (75 mL) was added over a period of 15 min. After 5 h, the reaction was complete (TLC, 4:1 hexane−EtOAc). A 10% aqueous solution of sodium sulfite (75 mL) was added, and the two-phase mixture was stirred for an additional 2 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were washed with 2 N HCl (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude ratio of diastereomers was determined to be ca. 1:1 by ^{1}H NMR. For purification, acetone (100 mL) was added to the crude residue, and the resulting slurry was refluxed with stirring for 5 min. The mixture was cooled, and the white precipitate was collected by filtration. This trituration procedure was then repeated on the resulting solid product and gave 5.6 g (35%) of the pure D_3-isomer *rac*-**4**: mp 226 °C; ^{1}H NMR ($CDCl_3$) δ 1.75−1.87 (m, 6 H), 2.15−2.25 (m, 6 H), 4.25 (br s, 6 H), 7.37−7.43 (m, 6 H), 7.47−7.52 (m, 3 H), 7.80−7.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 30.7, 83.1, 127.8, 131.6, 134.8; HRMS (FAB$^+$/NBA) calcd for $C_{30}H_{33}B_3O_6$ (MNa^+) *m/e* 545.2454, found *m/e* 545.2469.

(1*R,2*R**,3*R**,4*R**)-Cyclopentane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-7a).** Procedure A was followed using freshly distilled cyclopentadiene (**6a**) (2.4 g, 36 mmol), phenylboronic acid (9.2 g, 76 mmol), and solid NMO (8.9 g, 76 mmol). The usual workup and recrystallization gave 7.5 g (68%) of the bis(boronate) *anti-rac*-**7a**: mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (t, J = 5.6 Hz, 2 H), 5.03 (d, J = 6.3 Hz, 2 H), 5.17 (q, J = 5.8 Hz, 2 H), 7.36−7.43 (m, 4 H), 7.50 (m, 2 H), 7.79−7.84 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 42.3, 81.1, 87.5, 127.9, 131.8, 134.9. Anal. Calcd for $C_{17}H_{16}B_2O_4$: C, 66.74; H, 5.27. Found: C, 66.67; H, 5.37.

(1*R,2*R**,3*R**,4*R**)-Cyclohexane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-7b).** Procedure A was followed using 1,3-cyclohexadiene (**6b**) (4.0 g, 50 mmol), phenylboronic acid (12.7 g, 105 mmol), and solid NMO (12.3 g, 105 mmol). The usual workup and recrystallization gave 13.0 g (81%) of the bis(boronate) *anti-rac*-**7b**: mp 161−163 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (br s, 4 H), 4.87−4.99 (m, 2 H), 4.97−5.03 (m, 2 H), 7.38−7.48 (m, 4 H), 7.48−7.58 (m, 2 H), 7.84−7.90 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 73.8, 74.9, 127.9, 131.8, 135.0; Anal. Calcd for $C_{18}H_{18}B_2O_4$: C, 67.57; H, 5.67. Found: C, 67.55; H, 5.68.

(1*R,2*R**,4*R**,5*R**)-Cyclohexane-1,2,4,5-tetrayl-1,2:4,5-bis(phenylboronate) (*anti-meso*-7c).** Procedure A was followed using 1,4-cyclohexadiene (**6c**) (1.48 g, 18 mmol), phenylboronic acid (4.8 g, 40 mmol), and solid NMO (4.7 g, 40 mmol). The usual workup and recrystallization gave 4.8 g (81%) of the bis(boronate) *anti-meso*-**7c**: mp 185−188 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (m, 4 H), 4.87 (m, 4 H), 7.38−7.46 (m, 4 H), 7.52 (m, 2 H), 7.80−7.88 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.0, 73.1, 127.8, 131.6, 134.8. Anal. Calcd for $C_{18}H_{18}B_2O_4$: C, 67.57; H, 5.67. Found: C, 67.56; H, 5.69.

(1*R,2*R**,3*R**,4*R**)-Cycloheptane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-7d).** Procedure A was followed using 1,3-cycloheptadiene (**6d**) (1.7 g, 18 mmol), phenylboronic acid (4.8 g, 40 mmol), and solid NMO (4.7 g, 40 mmol). The usual workup and recrystallization gave 4.6 g (75%) of the bis(boronate) *anti-rac*-**7d**: mp 128−131 °C; ^{1}H NMR ($CDCl_3$) δ 1.44−1.82 (m, 4 H), 2.16−2.28 (m, 2 H), 4.57−4.70 (m, 4 H), 7.36−7.44 (m, 4 H), 7.50 (m, 2 H), 7.88−7.94 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 18.4, 28.6, 77.5, 81.3, 127.7, 131.5, 135.0. Anal. Calcd for $C_{19}H_{20}B_2O_4$: C, 68.33; H, 6.04. Found: C, 67.93; H, 5.96.

(1*R,2*R**,3*R**,4*R**)-Cyclooctane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-7e).** Procedure A was followed using 1,3-cyclooctadiene (**6e**) (2.0 g, 18 mmol), phenylboronic acid (4.7 g, 40 mmol), and solid NMO (4.8 g, 40 mmol). The usual workup and recrystallization gave 5.8 g (85%) of the bis(boronate) *anti-rac*-**7e**: mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−1.75 (m, 4 H), 1.77−1.94 (m, 2 H), 2.15−2.32 (m, 2 H), 4.61−4.75 (m, 4 H), 7.36−7.45 (m, 4 H), 7.50 (m, 2 H), 7.88−7.95 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 29.7, 79.6, 80.1, 127.8, 131.6, 135.0; Anal. Calcd for $C_{20}H_{22}B_2O_4$: C, 69.03; H, 6.37. Found: C, 69.14; H, 6.44.

(2*R,3*S**,5*S**,8*R**)-2-Methylbicyclo[2.2.1]heptane-2,3,5,8-tetrayl-2,3:5,8-bis(phenylboronate) (*rac*-7f).** Procedure A was followed using 5-methylene-2-norbornene (**6f**) (1.9 g, 18 mmol), phenylboronic acid (4.5 g, 37 mmol), and solid NMO (4.5 g, 38 mmol). The usual workup and recrystallization gave 4.6 g (74%) of the bis(boronate) *rac*-**7f**: mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (dd, J = 14.2, 2.5 Hz, 1 H), 1.79−1.83 (m, 1 H), 2.09−2.14 (m, 2 H), 2.52 (s, 1 H), 2.57 (d, J = 5.3 Hz, 1 H), 4.16 (d, J = 9.3 Hz, 1 H), 4.46−4.52 (m, 3 H), 7.36−7.42 (m, 4 H), 7.47−7.51 (m, 2 H), 7.79−7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 30.1, 41.7, 42.6, 52.6, 72.6, 79.1, 83.3, 85.6, 127.8, 131.5, 131.6, 134.8, 135.0. Anal. Calcd for $C_{20}H_{20}B_2O_4$: C, 69.43; H, 5.83. Found: C, 69.51; H, 5.90.

(1*R,2*S**,5*S**,6*R**)-Cyclooctane-1,2,5,6-tetrayl-1,2:5,6-bis(phenylboronate) (*anti-meso*-10) and (1*R**,2*S**,5*R**,6*S**)-Cyclooctane-1,2,5,6-tetrayl-1,2:5,6-bis(phenylboronate) (*syn-meso*-11).** Procedure A was followed using 1,5-cyclooctadiene (**8**) (2.08 g, 19.2 mmol), phenylboronic acid (5.16 g, 42.3 mmol), and solid NMO (4.96 g, 42.3 mmol). The usual workup gave a solid which showed a ca. 1:1 ratio of isomers by ^{1}H NMR. Recrystallization of the crude mixture from hexanes−EtOAc (250 mL, 4:1) gave 2.25 g (34%) of the bis(boronate) *anti-meso*-**10**: mp 214−215 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−1.65 (m, 4 H), 2.18−2.26 (m, 4 H), 4.65−4.76 (m, 4 H), 7.34−7.43 (m, 4 H), 7.49 (m, 2 H), 7.76−7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 25.4, 80.0, 127.8, 131.5, 134.8. Anal. Calcd for $C_{20}H_{22}B_2O_4$: C, 69.03; H, 6.37. Found: C, 68.98; H, 6.49. The other isomer *syn-meso*-**11** was obtained by column chromatography of the mother liquor (1:1 hexanes−Et_2O) followed by recrystallization (10:1 hexanes−EtOAc), giving 1.67 g (25%) of *syn-meso*-**11**: mp 157−159 °C; ^{1}H NMR ($CDCl_3$) δ 1.75−1.92 (m, 4 H), 2.02−2.20 (m, 4 H), 4.66−4.74 (m, 4 H), 7.32−7.40 (m, 4 H), 7.46 (m, 2 H), 7.75−7.81 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 79.0, 127.8, 131.5, 134.8. Anal. Calcd for $C_{20}H_{22}B_2O_4$: C, 69.03; H, 6.37. Found: C, 69.04; H, 6.47.

Authentic *syn-meso*-**11** was also prepared by refluxing a mixture of phenylboronic acid (2.42 g, 20 mmol) and (1*R**, 2*S**,5*R**,6*S**)-cyclooctane-1,2,5,6-tetrol (*syn-meso*-**9**) (1.76 g, 10

(23) Powell, K. A.; Hughes, H.; Katchian, J. F.; Jerauld, J. F.; Sable, H. Z. *Tetrahedron* **1972**, *28*, 2019. The syn/anti stereochemistry issue for the tetrol was not resolved. According to our results, they prepared the syn isomer, (1*R**,2*S**,5*R**,6*S**)-cyclooctane-1,2,5,6-tetrol.

mmol) in 25 mL of toluene for 30 min. Evaporation of the solvent afforded a white solid which was recrystallized from a 10:1 mixture of hexanes−EtOAc, giving *syn-meso*-**11** as white needles (85%).

(1*R,2*R**)-(3*E*)-1,4-Diphenyl-3-butene-1,2-diyl-1:2-phenylboronate (*rac*-13).** Procedure A was followed using *trans,trans*-1,4-diphenyl-1,3-butadiene (**25**) (2.1 g, 10 mmol), phenylboronic acid (1.2 g, 10 mmol), and solid NMO (1.2 g, 10 mmol). The usual workup gave a black solid containing starting material, desired product, and boronate-protected tetrol in a 3:6:1 ratio (^{1}H NMR). Silica gel chromatography (10:1 hexanes−Et_2O) gave 1.3 g (42%) of the boronate *rac*-**13**: mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 4.94 (td, J = 7.4, 0.7 Hz, 1 H), 5.32 (d, J = 7.6 Hz, 1 H), 6.42 (dd, J = 15.8, 7.3 Hz, 1 H), 6.71 (d, J = 15.8 Hz, 1 H), 7.30−7.50 (m, 12 H), 7.55 (m, 1 H), 7.95−8.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 84.5, 86.3, 125.4, 125.6, 126.7, 127.1, 127.9, 128.2, 128.7, 131.8, 133.5, 134.1, 135.1, 136.0, 140.1; HRMS (FAB$^+$/NBA) calcd for $C_{22}H_{19}BO_2$ (MNa^+) *m/e* 349.1376, found *m/e* 349.1368.

General Procedure B for the Deprotection of Phenylboronic Esters. The protected polyol (1.0 equiv) was dissolved in a 1:1 mixture of EtOAc−acetone (minimum quantity, usually 40 mL/g of boronate). A minimum quantity of solvent was used in order to promote the precipitation of the product from the reaction mixture. A 30% aqueous solution of hydrogen peroxide (1.5−2.5 equiv per phenylboronate moiety) was added, and the reaction was stirred at room temperature for 4 h. For the cases in which the product precipitated from the reaction mixture, the product was isolated by simple filtration. For the remaining cases, silica gel (ca. 2.5× the weight of the starting material) was added directly to the reaction mixture, and the volatiles in the reaction mixture were removed in vacuo. (Due to possible excess H_2O_2, the product−silica gel matrix must not be completely dried or else decomposition of the polyol can occur. Specifically, removal of solvent under reduced pressure is not problematic, but drying under high vacuum causes decomposition.) The products were then isolated by column chromatography of the crude product−silica gel matrix. The procedure for the preparation of *anti-rac*-**14** is a representative example.

(1*R,2*R**,5*R**,6*R**,9*R**,10*R**)-Cyclododecane-1,2,5,6,9,-10-hexaol (*rac*-2).** Procedure B was followed using (1*R**,2*R**,5*R**,6*R**,9*R**,10*R**)-cyclododecane-1,2,5,6,9,10-hexayl-1,2:5,6:9,10-tris(phenylboronate) (*rac*-**4**). After reaction completion, silica gel was added, and the mixture was concentrated in vacuo. Column chromatography (methanol) followed by recrystallization from methanol provided pure racemic D_3-hexaol *rac*-**2** (75%): mp 270 °C; ^{1}H NMR (D_2O) δ 1.21−1.83 (m, 12 H), 3.45 (br s, 6 H), 4.65 (br s, 6 H); ^{13}C NMR (D_2O) δ 25.4, 32.0, 76.0, 80.4; HRMS (FAB$^+$/NBA) calcd for $C_{12}H_{24}O_6$ (MNa^+) *m/e* 287.1471, found *m/e* 287.1477.

(1*R,2*R**,3*R**,4*R**)-Cyclohexane-1,2,3,4-tetrol (*anti-rac*-14).** In a 150 mL round-bottomed flask, (1*R**,2*R**,3*R**,4*R**)-cyclohexane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-**7b**) (2.0 g, 6.3 mmol) was dissolved in 1:1 EtOAc−acetone (100 mL). To this solution was added 30% aqueous hydrogen peroxide (2.2 g, 19.4 mmol) in one portion. Within 15 min a white precipitate appeared. After 3 h, the precipitate was collected by filtration (glass frit), affording 0.84 g of tetrol *anti-rac*-**14** (90%). This crude material was pure by ^{1}H NMR. An analytical sample was obtained by recrystallization from methanol: mp 210−212 °C (lit.[11] mp 214−215 °C); ^{1}H NMR (DMSO-d_6) δ 1.43−1.53 (m, 4 H), 3.53 (br s, 2 H), 3.67 (br s, 2 H), 4.17 (d, J = 4.9, 2 H), 4.34 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 26.1, 67.8, 72.2.

(1*R,2*R**,4*R**,5*R**)-Cyclohexane-1,2,4,5-tetrol (*anti-meso*-15).** Procedure B was followed using (1*R**,2*R**,4*R**,5*R**)-cyclohexane-1,2,4,5-tetrayl-1,2:4,5-bis(phenylboronate) (*anti-meso*-**7c**) (1.0 g, 3.1 mmol) and 30% aqueous hydrogen peroxide (1.1 g, 9.8 mmol). A precipitate formed and was collected by filtration, affording 0.41 g of tetrol *anti-meso*-**15** (89%). This crude material was pure by ^{1}H NMR. An analytical sample was obtained by recrystallization from methanol: mp 240−242 °C (lit.[11] mp 246 °C); ^{1}H NMR (DMSO-d_6) δ 1.60 (m, 4 H), 3.68 (m, 4 H), 4.17 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 34.0, 67.5.

(1*R,2*R**,3*R**,4*R**)-Cyclooctane-1,2,3,4-tetrol (*anti-rac*-16).** Procedure B was followed using (1*R**,2*R**,3*R**,4*R**)-cyclooctane-1,2,3,4-tetrayl-1,2:3,4-bis(phenylboronate) (*anti-rac*-**7d**) (1.0 g, 3 mmol) and 30% aqueous hydrogen peroxide (1.1 g, 10 mmol). After reaction completion, silica gel was added, and the mixture was concentrated in vacuo. Column chromatography (EtOAc) followed by recrystallization from EtOAc provided tetrol *anti-rac*-**16** (81%): mp 103−104 °C; ^{1}H NMR (acetone-d_6) δ 1.44−1.80 (m, 8 H), 2.95 (br s, 2 H), 3.90−4.07 (m, 4 H), 4.50 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 19.6, 31.2, 68.4, 75.8; HRMS (FAB$^+$/NBA) calcd for $C_8H_{16}O_4$ (MNa^+) *m/e* 199.0946, found *m/e* 199.0952.

(1*R,2*S**,5*S**,6*R**)-Cyclooctane-1,2,5,6-tetrol (*anti-meso*-17).** Procedure B was followed using (1*R**,2*S**,5*S**,6*R**)-cyclooctane-1,2,5,6-tetrayl-1,2:5,6-bis(phenylboronate) (*anti-meso*-**10**) (520 mg, 1.5 mmol) and 30% aqueous hydrogen peroxide (860 mg, 7.6 mmol). After reaction completion, silica gel was added, and the mixture was concentrated in vacuo. Column chromatography (methanol−EtOAc) provided 191 mg of tetrol *anti-meso*-**17** (86%): mp 111−112 °C; ^{1}H NMR (DMSO-d_6) δ 1.50−1.70 (m, 8 H), 3.62 (br s, 4 H), 4.18 (d, J = 4 Hz); ^{13}C NMR (DMSO-d_6) δ 26.5, 72.6. Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H 9.15. Found: C, 54.41; H, 9.20.

(1*R,2*R**)-(3*E*)-1,4-Diphenyl-3-butene-1,2-diol (*rac*-18).** (1*R**,2*R**)-(3*E*)-1,4-diphenyl-3-butene-1,2-diyl-1:2-phenylboronate (*rac*-**13**) (0.5 g, 1.5 mmol) and 30% aqueous hydrogen peroxide (0.1 g, 3 mmol) were added to EtOAc (20 mL) and water (10 mL). This mixture was stirred vigorously for 4 h, at which point the phases were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with 1 M NaOH (3 × 20 mL) and water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, providing 0.3 g of diol *rac*-**18** (78%). The crude residue was pure by ^{1}H NMR; an analytical sample was obtained by recrystallization from 10:1 hexanes−EtOAc: mp 83−84 °C (lit.[18] mp 74−76 °C); ^{1}H NMR ($CDCl_3$) δ 2.64−3.04 (m, 2 H), 4.32−4.44 (m, 1 H), 4.53−4.62 (m, 1 H), 6.04 (dd, J = 16.0, 5.8 Hz, 1 H), 6.54 (d, J = 16.0 Hz, 1 H), 7.17−7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 76.8, 77.8, 126.5, 126.9, 127.4, 127.7, 128.1, 128.4, 128.5, 132.1, 136.4, 140.1; HRMS (FAB$^+$/NBA) calcd for $C_{16}H_{16}O_2$ (MNa^+) *m/e* 263.1048, found *m/e* 263.1044.

(2*R,6*S**)-2,6-Diacetoxy-9-oxabicyclo[3.3.1]nonane (*rac*-20) and (2*R**,5*R**)-2,5-Diacetoxy-9-oxabicyclo[4.2.1]nonane (*rac*-21).** Tetrol *anti-meso*-**17** (0.15 g, 0.85 mmol) was added to pyridine (6 mL) with stirring. Once dissolution was complete, *p*-toluenesulfonyl chloride (0.162 g, 0.85 mmol) was added. After the solution was stirred overnight, all volatiles were removed by rotary evaporation; to the residue was added acetic anhydride (2 mL), pyridine (2 mL), and a catalytic amount of DMAP. The reaction was stirred for 3 h, at which point the volatiles were removed by rotary evaporation. Column chromatography (EtOAc−hexane) provided 0.102 g (50%) of a 3:2 mixture of *rac*-**20** and *rac*-**21**. Data for the mixture are as follows. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.70; H, 7.70. HRMS (FAB/NBA): calcd for $C_{12}H_{18}O_5$ (MH^+), *m/e* 243.1232; found, *m/e* 243.1224. Preparative TLC (EtOAc−hexane) allowed for the separation of the two isomers for NMR peak identification. *rac*-**20**: ^{1}H NMR ($CDCl_3$) δ 1.68−1.89 (m, 4 H), 2.01−2.11 (m, 4 H), 2.04 (s, 3 H), 2.09 (s, 3 H), 3.86 (d, J = 5.9 Hz, 1 H), 3.99 (t, J = 5.4 Hz, 1 H), 4.74−4.76 (m, 1 H), 5.05−5.11 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.9, 21.2, 21.4, 23.7, 23.9, 25.4, 66.6, 69.4, 70.1, 70.5, 170.1, 170.7. *rac*-**21**: ^{1}H NMR ($CDCl_3$) δ 1.42−1.48 (m, 1 H), 1.65−1.81(m, 2 H), 1.84−2.00 (m, 4 H), 2.02 (s, 3 H), 2.05 (s, 3 H), 2.18−2.30 (m, 1 H), 4.31−4.35 (m, 1 H), 4.45−4.49 (m, 1 H), 4.68−4.72 (m, 1 H), 4.93−4.98 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.2, 23.9, 24.4, 24.6, 29.9, 73.6, 78.7, 78.8, 82.0, 170.0, 170.7.

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Supporting Information Available: A table of HMQC and NOE data for compound *rac*-**7f**, and a COSY spectrum of compound *rac*-**21** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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