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Contiguously Substituted Cyclooctane Polyols. Configurational Assignments via ^{1}H NMR Correlations and Symmetry Considerations

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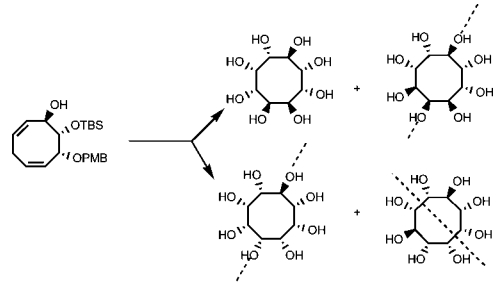


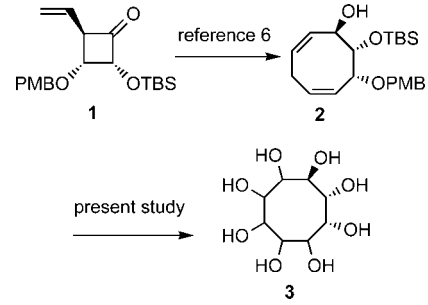
More advanced oxidation of the cyclooctadienol shown, readily available in enantiomerically pure form from D-glucose, has given rise to a series of intermediates whose relative (and ultimately absolute) configuration was assigned on the basis of ^{1}H/^{1}H coupling constant analysis. The selectivities that were deduced in this manner were drawn from the sequential application of CrO_3 oxidation in tandem with Luche reduction, two-step NMO-promoted osmylations bracketed by acetonide formation, and wholesale deprotection. The stereoselectivities of these reactions were traced by ^{1}H NMR spectroscopy, and the stereochemical assignments were confirmed by the presence or absence of symmetry in the final cyclooctane polyols (four shown) generated in this investigation.

Introduction

A program of research initiated in this laboratory several years ago was aimed at developing the zirconocene-mediated ring contraction[1] of enantiopure vinyl pyranosides and furanosides into a synthetically useful protocol.[2] Several complex targets and diverse glycomimetics were initially targeted. Representative successful achievements from the first category include arrival at (−)-neplanocin A,[3] (+)-epiafricanol,[4] and both enantiomers of fomannosin.[5] More extended application has led conveniently to several cyclooctane-1,2,3-triols and 1,2,3,4,5-pentaols.[6]

Presently, we demonstrate that eight-membered ring systems substituted with hydroxyl groups at each of the constituent carbon atoms as in **3** are likewise readily available. These attractive polyols, of potential value for their glycosidase inhibition potential,[7] have been secured by the extensive controlled oxidation of D-glucose-derived **2**[6] (Scheme 1). The specific configurational assignments to each of the isomers of **3** are based upon steric considerations, in tandem with application of the empirical Kishi rule for the OsO_4-promoted dihy-

SCHEME 1. Generic Route for Octacyclitols from Enantiomerically Pure Cyclobutanone 1



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SCHEME 2. Conversion of 4 into the Diastereomers of 8 and 9

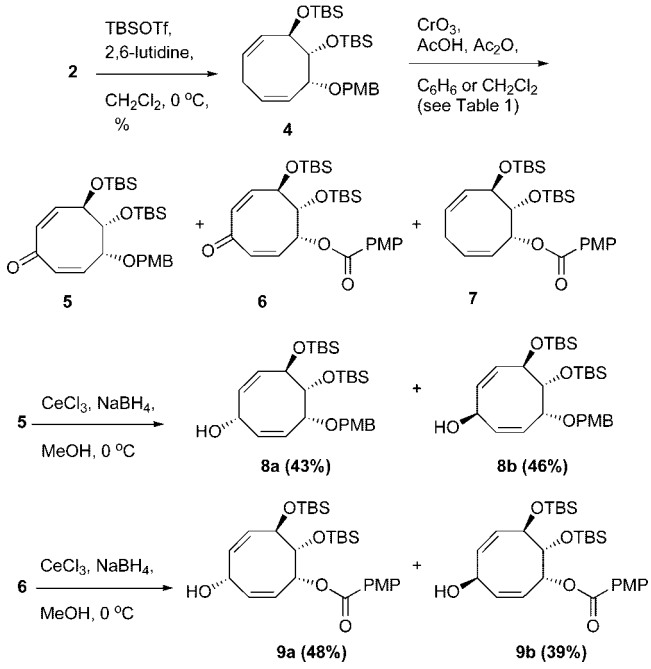

TABLE 1. Oxidation of 4 with CrO_3 and Ac_2O/HOAc

entry	equiv of CrO_3	equiv of AcOH	equiv of Ac_2O	solvent	temperature (°C)	yield (%)	ratio of components[a]
1	5	33	9	benzene	5	68	3:3:1:1
2	5	33	9	benzene	20	63	0:2:1:0
3	5	33	9	benzene	0	55	4:1:1:1
4	5	33	9	benzene	−5	57	10:1:1:1
5	2.5	16	4.5	benzene	−5	59	10:0:0:1
6	10	66	18	benzene	20	53	0:4:1:0
7	20	132	36	benzene	20	43	0:10:1:0
8	5	33	9	CH_2Cl_2	20	65	0:8:1:0
9	2.5	16	4.5	CH_2Cl_2	20	71	0:4:4:0
10	2.5	16	4.5	CH_2Cl_2	−5	68	10:0:0:1

[a] Ratio of **5**:**6**:**7**:**4** after separation/purification by column chromatography.

droxylation of allylic alcohols,[8] and ultimate reliance on the presence or absence of molecular symmetry as determined by NMR spectroscopy.

Results and Discussion

Following the selection of **2** as a suitable reactant, consideration was given to its subsequent conversion to the bissilylated ether **4** in advance of allylic oxidation with chromium trioxide in mixtures of acetic anhydride and acetic acid at or near room temperature.[9,10] In line with precedent, oxidation was observed to occur competitively at the doubly allylic ring position and the activated benzylic site (Scheme 2). Precise adaptation of the Schultz conditions (Table 1, entry 1) gave rise to dienones **5** and **6**, benzoate **7**, and unreacted **4** in a 3:3:1:1 ratio and 68% combined yield. When the reaction temperature was increased from 5 to 20 °C, no **5** was noted and the ratio of **6** to **7** was increased somewhat to 3:1 (entry 2). On the other hand, constant cooling to 0 °C, again in benzene solution, provided predominately **5** (55%, entry 3). A further drop in temperature to −5 °C had the effect of enhancing further the exclusive production of **5** (entry 4). Of the remaining probe experiments, entries 8 and 10 are notable for serving as the best preparative conditions for generating **6** or **5**, respectively.

Next to be examined was the Luche[11] reduction of this pair of cyclooctadienones. Since our aim was to obtain 1:1 mixtures of diastereomers, no attention was accorded to reducing agents that would provide widely imbalanced distributions of dienols. The reaction of **5** with sodium borohydride and cerium trichloride in methanol at 0 °C led to the formation of **8a** and **8b** in 43 and 46% isolated yields, respectively (Scheme 2). Under the same conditions, **6** was transformed into **9a** (48%) and **9b** (39%). Not unexpectedly, NMR analysis of the two sets of diastereomers did not lead to the unequivocal assignment of configuration at the newly generated carbinol center. As outlined in the sequel, however, more advanced functionalization studies ultimately clarified this key issue.

Orthogonal protection of the four different diastereomers followed. To this end, alcohols **8a** and **8b** were esterified with acetic anhydride in pyridine to achieve conversion to acetates **10** and **11** (Scheme 3). The acquisition of **12** and **13**, on the other hand, was realized by treatment of **9a** and **9b** with *tert*-butyldimethylsilyl chloride in the presence of imidazole. All four products were in turn dihydroxylated with catalytic quantities of OsO_4 and NMO in aqueous THF. A salient feature of this set of transformations is its exceptional regioselectivity for attack at the site of the 6,7-double bond. The basis for this assignment was derived from the upfield shifts of H-5 in **10**−**13** which originates as an allylic proton and experiences a status change when progressing to **14a**−**17b** (Table 2). The ratios of the isolated diols **14a/14b** and **16a/16b** are consistent with the operation of good substrate induction during the capture of OsO_4 preferably from the top face. The product distributions realized with **15a/15b** (3.5:1) and **17a/17b** (3:1) were more modest, although again biased in the same facial direction. These data are consistent with the stereoselectivities demonstrated by cyclic allylic alcohols of smaller ring size where control by flanking acyl and siloxy groups does not operate to a significant degree.[12−15] The present situation is further complicated by the more extensive oxygenated patterns resident in these substrates.

Our analysis of the relative stereochemistry of the eight diols generated in Scheme 3 has been derived in part by adaptation of the empirical rule developed by Kishi[8,13] for defining the structures of the major osmylation products of allylic alcohols and their derivatives. His studies revealed a constant pattern in the vicinal H/H coupling patterns for acyclic polyhydroxylated compounds in the same stereochemical series. These patterns serve to unveil relative configuration among a set of contiguous carbon stereocenters. When compound pairs **8a/8b** and **9a/9b** are examined in this manner (Scheme 4), small *J* values are seen to be equivalent to a *syn* relationship between the

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SCHEME 3. Hydroxyl Protection OsO_4-Promoted Dihydroxylation Results

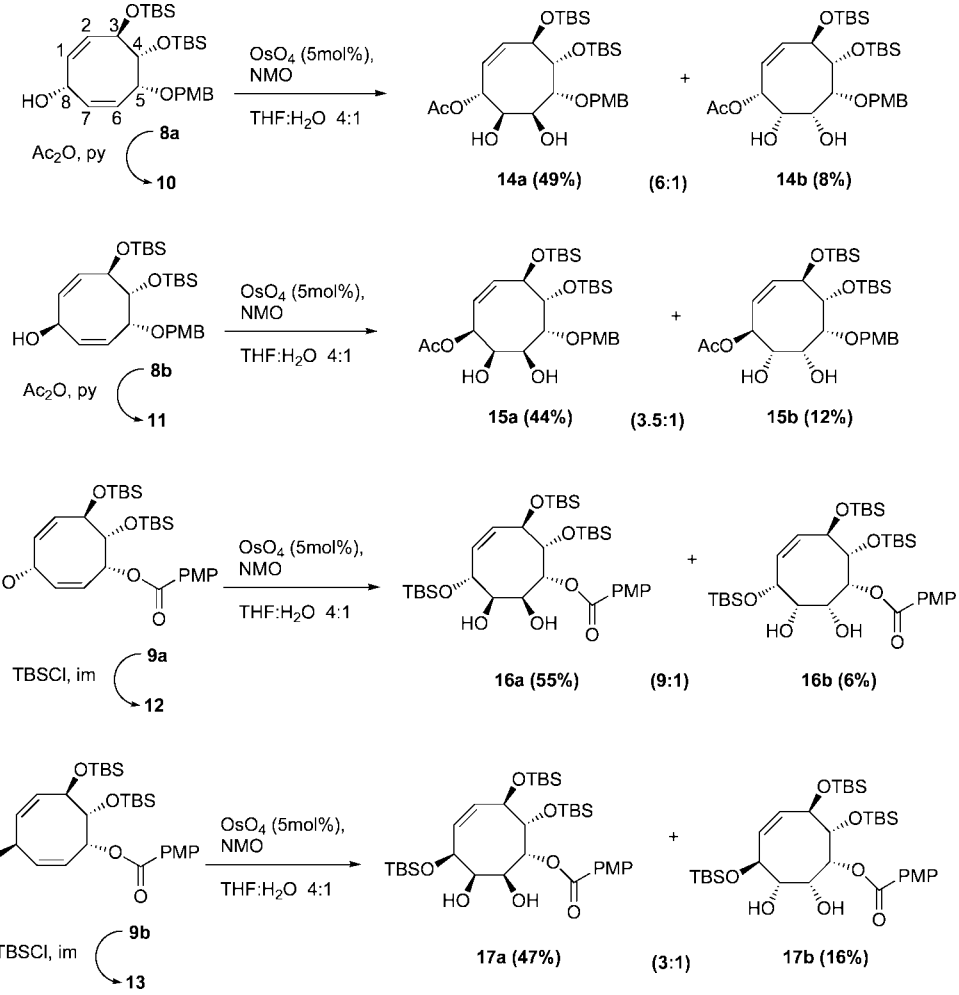


TABLE 2. Chemical Shifts of H-5 in 8a/8b−17a/17b

8a	4.60	**14a**	3.80	**14b**	3.91
8b	4.68	**15a**	3.88	**15b**	3.79
9a	6.33	**16a**	5.63	**16b**	5.62
9b	6.35	**17a**	5.49	**17b**	5.45

stereocenters and large *J* values to reflect an *anti* relationship. More specifically, the fact that stereocenters C-3, C-4, and C-5 in all pairs of diastereomers share in common an *anti*/*syn* relative configuration is now made pictorially evident.

Comparable analysis of diols **14a** and **14b** provided suggestive evidence that the H-5/H-6 and H-7/H-8 relationships in each of the predominant isomers are *anti* (Scheme 5). It follows therefore that **14a** has an *anti*/*syn*/*anti*/*syn*/*anti* arrangement along C-3 to C-8. When depicted analogously, the data for **14b** demonstrate that its configuration is *anti*/*syn*/*syn*/*syn*/*syn* across the same structural span. Thus, the very small *J* values indicative of *syn* configurational arrangements are often seen as broadened singlets in this particular case. Examples **15a** and **15b** exhibit distinctively different patterns (Scheme 5). For **15a**, a *J* coupling distribution is seen that is consistent with an *anti*/*syn*/*anti*/*syn*/*syn* relative stereochemical relationship across the same C-3 to C-8 component of the eight-membered ring. The added number of broad singlets prevailing in the spectrum of **15b** is compatible with the *anti*/*syn*/*syn*/*syn*/*anti* configurational descriptor applied to this diol. The broad singlets for diols **14a**−**15b** were analyzed by extracting the *J* values from the neighboring protons. This analysis will be used for all the future new compounds.

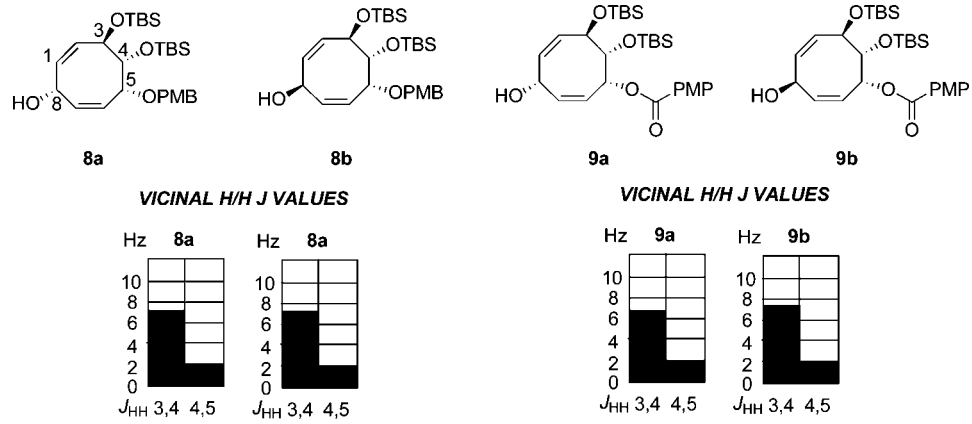
Isomers **16a** and **16b** exhibit quite distinctive patterns (Scheme 6). Instead of many broad singlets arising from numerous *syn* relationships, doublets and small coupling constants (2.5−3.5 Hz) are displayed. Nonetheless, analogous trends were noted that conformed to the *anti*/*syn*/*anti*/*syn*/*anti* relationship for **16a** and the *anti*/*syn*/*syn*/*syn*/*syn* arrangement for **16b**.

Diols **17a** and **17b** exhibit coupling patterns that are consistent with the expected stereochemical outcome of the osmylation reaction. The predominant product **16a** features a spectrum compatible with a *anti*/*syn*/*anti*/*syn*/*anti* setting, while that exhibited by **16b** befits the *anti*/*syn*/*syn*/*syn*/*anti* stereochemical assignment.

Although the Kishi empirical rule deals strictly speaking with relative configurational assignments, the previously established absolute stereochemistry of **4** permits full assignment for all of the functionalized cyclooctanes defined herein. For these formulations to be irrefutable, however, independent proof of the validity of the spectral extrapolations is mandated. This verification was arrived at chemically, and rests on the inherent symmetry or absence thereof in the ultimate polyhydroxylated cyclooctane products.

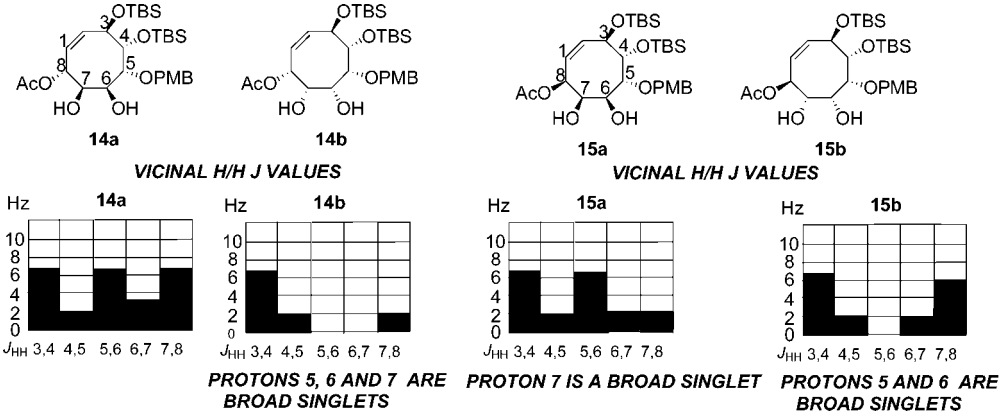
The diol pairs **14a/14b**, **15a/15b**, **16a/16b**, and **17a/17b** were individually transformed into their acetonides by reaction with 2,2-dimethoxypropane in the presence of

SCHEME 4. J_{HH} **Value Analysis for 8a/8b and 9a/9b**[a]



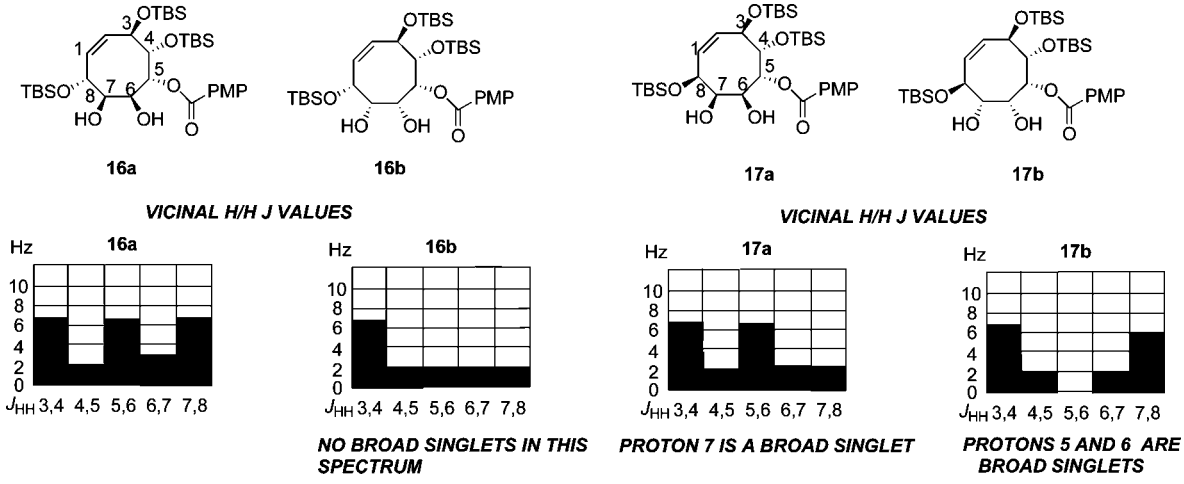
[a] The *x* axis is the carbon number and *y* axis is the vicinal J_{HH} value.

SCHEME 5. J_{HH} **Value Analysis for 14a/14b and 15a/15b**[a]



[a] The *x* axis is the carbon number and *y* axis is the vicinal J_{HH} value.

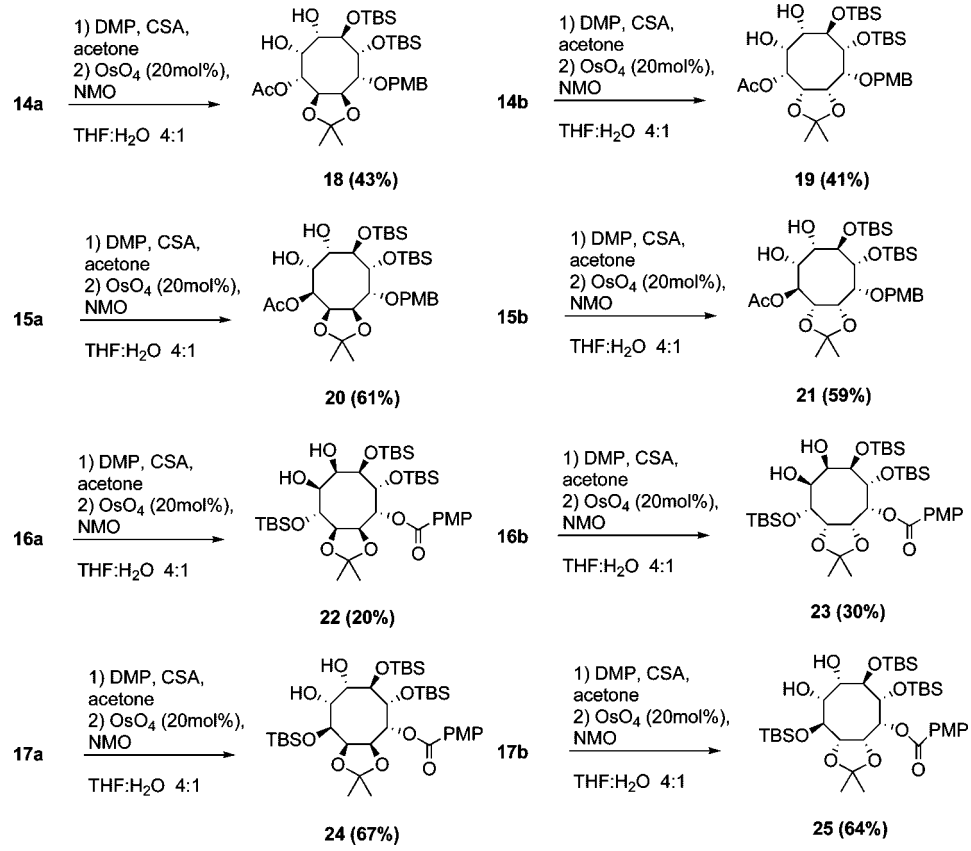
SCHEME 6. J_{HH} **Value Analysis of 16a/16b and 17a/17b**[a]



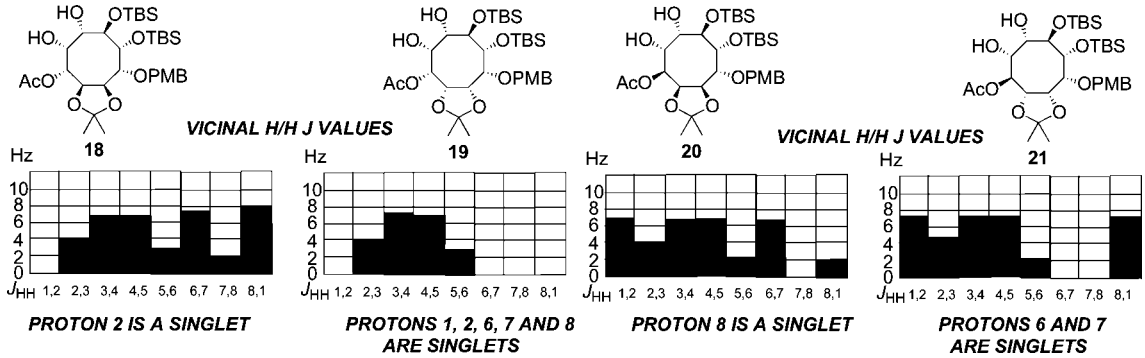
[a] The *x* axis is the carbon number and *y* axis is the vicinal J_{HH} value.

catalytic quantities of CSA. The unpurified products were in turn reacted with catalytic OsO_4 in the presence of NMO to generate the respective diols (Scheme 7). The eight reactions proceeded very slowly, and starting material often remained after 48 h. The yields of products ranged from 20 to 68% under normalized conditions. The stereodisposition of the bulky TBS ether functionality flanking the olefinic reaction center in these medium ring systems clearly controls the rate of conversion to product. The acetonides of diols **15a/15b** and **17a/17b** were transformed into the targeted diols by reaction with OsO_4 from the face opposite to the groups around the double bond (OAc/OTBS for **15a/15b** and OTBS/OTBS for **17a/17b**). The yields were good (61/59 and 67/64%, respectively). In contrast, the acetonides of diols **14a/14b** and **16a/16b** (C-1 has opposite stereochemistry) proceeded to the corresponding diols in lower yields (43/41 and 20/30%, respectively). The underlying reasons for this dropoff in stereoselectivity are presumably complex.

SCHEME 7. Acetonide Protection and OsO_4-Mediated Dihydroxylation Results



SCHEME 8. J_{HH} Value Analysis of 18−21[a]



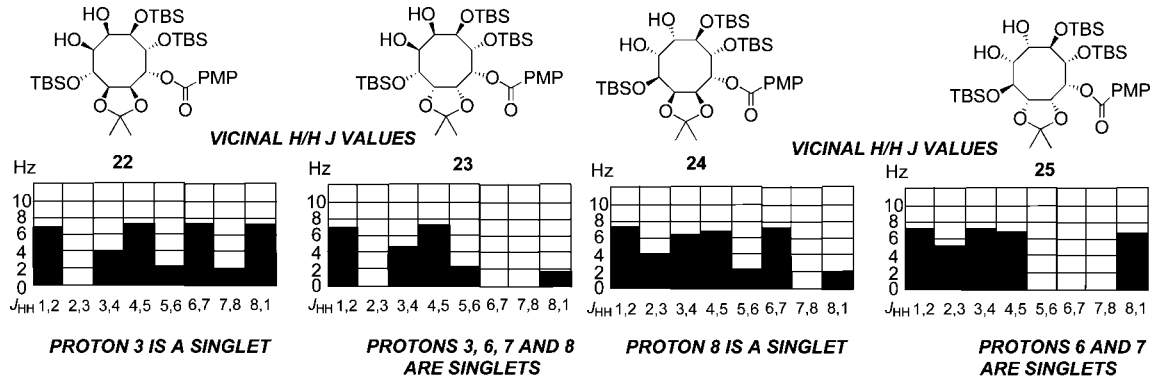
[a] The *x* axis is the carbon number and *y* axis is the vicinal J_{HH} value.

In line with our goals, the vicinal J_{HH} coupling constants for all eight contiguous stereocenters in each of the diols **18**−**25** were measured. The charts for **18**−**21** exhibit a clear pattern of large J_{HH} /small J_{HH} for prevailing *anti*/*syn* relationships (Scheme 8). As expected, those stereocenters that are *syn* to contiguous stereocenters have singlet patterns (C-2 for **18**; C-1, C-2, C-6, C-7, and C-8 for **19**; C-8 for **20**; and C-6 and C-7 for **21**). In line with expectation, the newly introduced hydroxyl-substituted stereocenters (C-1 and C-2) present a recurrent J_{HH} of 4 Hz when they are *syn* to their neighboring peripheral stereocenters. The remaining J_{HH} values proved consistent with the patterns expected on the basis of forecasted stereochemistry.

From the charts for diols **22**−**25**, there emerges again a clear pattern of large J_{HH}/small J_{HH} for *anti*/*syn* relationships (Scheme 9). As above, resonances where a *syn*/*syn* relationship exists among three contiguous stereocenters appear as singlets (e.g., C-3 for **22**; C-3, C-6, C-7, and C-8 for **23**; C-8 for **24**; and C-6 and C-7 for **25**). Like the PMB series, the newly formed hydroxyl-substituted stereocenters (C-1 and C-2) present a recurring J_{HH} of 4−4.5 Hz when they are *syn* to their neighboring stereocenters. Also, the remaining J_{HH} values are consistent with the patterns expected on the basis of their relative stereochemistry.

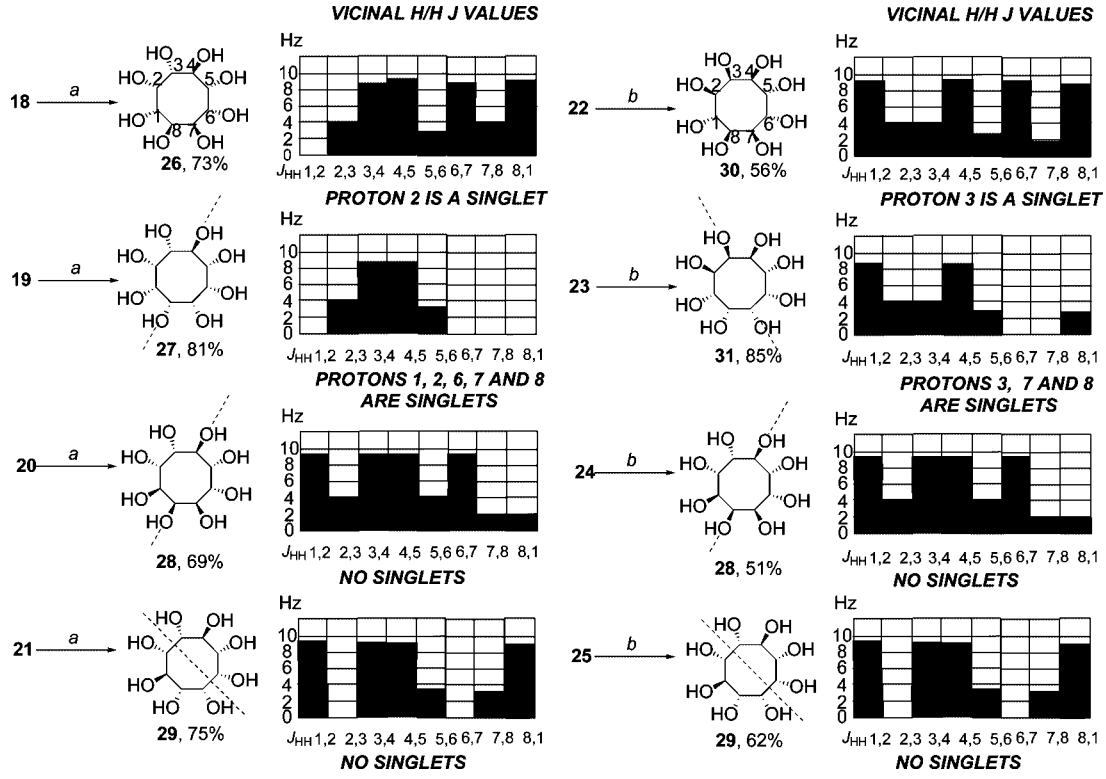
The next goal involved removal of the protecting groups from the series of diols **19**−**21** and **22**−**25**. Substrates **19**−**21** were initially treated individually with DDQ in CH_2Cl_2/H_2O. The crude reaction mixtures were subsequently stirred with 2.5 N HCl in THF followed by K_2CO_3 to provide polyols **26**−**29** in moderate to good yields (73, 81, 69, and 75%, respectively, Scheme 10). Diols **27**, **28**, and **29** each exhibit a symmetric spectrum based on the stereochemical predictions made during the stepwise dihydroxylations. These data were intended to serve as proof of concept for the assignment of relative stereochemistry for contiguous hydroxyl stereocenters in a cyclic molecule

SCHEME 9. J_{HH} **Value Analysis of 22−25**[a]



[a] The *x* axis is the carbon number and *y* axis is the vicinal J_{HH} value.

SCHEME 10. **Global Deprotection and** J_{HH} **Value Analysis of 26−31**



[a] (II) DDQ, CH_2Cl_2/H_2O; (II) 2.5 N HCl in THF; (III) K_2CO_3, MeOH. [b] (I) $LiAlH_4$; (II) 2.5 N HCl in THF.

based on vicinal J_{HH} values. The ^1H NMR of **27**, **28**, and **29** confirmed that these polyols are symmetric, and as a consequence, the assignments of the stereochemical outcomes of the dihydroxylation reactions were properly defined.

When the vicinal J_{HH} values for isomers **26**−**29** were plotted in the same manner as the previously synthesized intermediates (Scheme 10), the plots clearly followed the previous trend (large J_{HH} for *anti* and small J_{HH} for *syn*). This series of compounds showed higher *anti* vicinal J_{HH} values (9−9.5 Hz) than those observed for the previously plotted intermediates. In contrast, the *syn* vicinal J_{HH} values (2−4 Hz) were entirely similar to those of their counterparts.

The final objective involved removal of the protecting groups from the series of diols **22**−**25**. These were treated individually with $LiAlH_4$ in THF to remove the benzoate group. The resulting reaction mixtures were next acidified with 2.5 N HCl in THF and then purified to provide polyols **30**,**31**, **28**, and **29** in good yields (56, 85, 51, and 62%, respectively, Scheme 10). The products of the global deprotection of diols **24** and**25** proved to be identical to those obtained from **28** and **29**. The symmetry found in these compounds also served as further proof of the unequivocal assignment of relative stereochemistry. The product emanating from the global deprotection of **23** provided the previously unknown symmetric polyol **31**. Similarly, the global deprotection of diol **22** provided the new compound **30**. These results established convincingly that this series of diastereomers has the correct assignment of their relative stereochemistries for contiguous hydroxyl stereocenters in a cyclic molecule based on vicinal J_{HH} values.

Also plotted were the vicinal J_{HH} values for the isomers **30**, **31**, **28**, and**29** (Scheme 10). The plots clearly followed the trend found in the previous intermediates. This series of compounds showed higher *anti* vicinal J_{HH} values (9−9.5 Hz) than the

previously plotted intermediates. On the other hand, the *syn* vicinal J_{HH} values (2−4 Hz) were similar to those previously plotted.

Summary

In conclusion, this study has applied the previously developed Zr-mediated ring contraction reaction to the acquisition of a series of diastereomeric cyclooctane polyols. Determination of vicinal J_{HH} coupling patterns associated with each series of intermediates provided the opportunity to predict the relative stereochemistry of the dihydroxylated products of the respective dienols. This analysis was applied with high accuracy to the fully hydroxylated intermediates and ultimately to the polyols. The final proof for this analysis was given by the symmetry resident in compounds **27**, **28**, **29**, and **31**. These results permitted full assignment of the stereochemistry of the five new stereocenters generated in this investigation without further derivatization of the polyols or any of their precursors.

Experimental Section

(2*Z*,4*R*,5*R*,6*R*,7*Z*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)cycloocta-2,7-dienone (5). A 250 mL round-bottomed flask was charged with alcohol **2** (800 mg, 2.13 mmol) and CH_2Cl_2 (30 mL). The resulting solution was placed in an ice bath, and 2,6-lutidine (371 μL, 3.32 mmol) and TBSOTf (590 μL, 2.55 mmol) were added. The resulting mixture was stirred at 0 °C for 3 h and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic fractions were dried and concentrated prior to purification by silica gel flash chromatography (elution with hexanes/ethyl acetate 95:5) to yield **4** as a colorless oil (1.0 g, 93%): $[\alpha]^{20}_D$ −53.1 (*c* 1.2, $CHCl_3$); IR (thin film, cm^{-1}) 3434, 1645, 1248; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 5.66−5.56 (m, 2H), 5.48 (dd, J = 12, 7 Hz, 1H), 5.38 (dd, J = 12, 4 Hz, 1H), 4.68 (d, J = 7 Hz, 1H), 4.51−4.48 (m, 2H), 4.27 (d, J = 11 Hz, 1H), 3.78 (s, 4H), 2.83 (br s, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 134.5, 133.7, 132.4, 130.6, 129.8, 129.6, 128.7, 113.5, 78.1, 74.7, 68.8, 67.8, 55.2, 42.1, 30.2, 26.1, 26.0, 18.5, −3.8, −4.8, −5.1, −5.3. A 100 mL round-bottomed flask was placed in an ice bath and charged with CrO_3 (446 mg, 4.46 mmol) in advance of Ac_2O (875 μL, 8.9 mmol) and AcOH (1.76 mL, 31.7 mmol). The resulting solution was stirred at 0 °C for 10 min, and CH_2Cl_2 (30 mL) was added. The mixture was cooled to −5 °C, and a solution of silyl ether **4** (1.0 g, 1.9 mmol) in dichloromethane (30 mL) was added dropwise. The resulting mixture was stirred for 45 min and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether (2×), and the combined organic fractions were dried and concentrated prior to purification by silica gel flash chromatography (elution with hexanes/ethyl acetate 90:10) to yield **5** (698 g, 68%) as a yellowish oil: $[\alpha]^{20}_D$ +12.1 (*c* 1.6, $CHCl_3$); IR (thin film, cm^{-1}) 1718, 1641, 1607, 1513; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 6.4 Hz, 2H), 6.78 (d, J = 6.6 Hz, 2H), 6.54 (dd, J = 12.4, 7 Hz, 1H), 6.28 (dd, J = 12.4, 1.6 Hz, 1H), 6.24 (dd, J = 10.8, 5.2 Hz, 1H), 6.08 (dt, J = 12.8, 1.2 Hz, 1H), 4.56 (ddd, J = 7.2, 3.2, 1.2 Hz, 1H), 4.50 (t, J = 7.5 Hz, 1H) 4.42 (d, J = 11.6 Hz, 1H), 4.21 (d, J = 11.6 Hz, 1H), 3.92 (dd, J = 7.5, 2.5 Hz, 1H), 3.73 (s, 3H), 0.8 (s, 9H), 0.78 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H), −0.03 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 159.3, 149.6, 148.7, 133.7, 132.7, 129.8, 129.4, 113.7, 79.9, 76.1, 74.9, 71.1, 55.2, 26.1, 25.8, 18.4, 18.1, −3.5, −4.0, −4.1, −4.3; HRMS exact mass calcd for $C_{28}H_{46}O_5Si_2Na^+$ 541.2782, found 541.2791.

(1*R*,2*Z*,5*Z*,7*R*,8*R*)-7,8-Bis(*tert*-butyldimethylsilyloxy)-4-oxocycloocta-2,5-dienyl 4-methoxybenzoate (6). A 100 mL round-bottomed flask was placed in an ice bath and charged with CrO_3 (892 mg, 8.92 mmol) in advance of Ac_2O (1.75 mL, 17.8 mmol) and AcOH (3.52 mL, 63.4 mmol). The resulting solution was stirred at 0 °C for 10 min, and dichloromethane (30 mL) was added. The mixture was allowed to warm to rt, and a solution of **5** (1.0 g, 1.98 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The resulting mixture was stirred for 45 min and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether (2×), and the combined organic fractions were dried and concentrated prior to purification by silica gel flash chromatography (elution with hexanes/ethyl acetate 90:10) to yield **6** (685 g, 65%) as a yellow oil: $[\alpha]^{20}_D$ +28.1 (*c* 1.1, $CHCl_3$); IR (thin film, cm^{-1}) 3533, 1718, 1613, 1249; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 6.4 Hz, 2H), 6.91 (d, J = 6.4 Hz, 2H), 6.62 (dd, J = 12.5, 7.5 Hz, 1H), 6.28 (dd, J = 12.5, 7.5 Hz, 1H), 6.35−6.30 (m, 2H), 6.26 (d, J = 12.5 Hz, 1H), 4.64 (td, J = 7.5, 2 Hz, 1H), 4.22 (dd, J = 7.5, 2.5 Hz, 1H), 3.82 (s, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 165.6, 163.7, 147.8, 143.5, 132.8, 132.7, 132.3, 131.9, 129.8, 122.0, 113.7, 78.4, 76.2, 75.0, 73.0, 55.4, 26.1, 25.9, 18.2, 18.1, −3.1, −3.7, −4.1, −4.6; HRMS exact mass calcd for $C_{28}H_{44}O_6Si_2Na^+$ 555.2574, found 555.2581.

(2*Z*,4*R*,5*R*,6*R*,7*Z*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)cycloocta-2,7-dienol (8a). A 100 mL round-bottomed flask was charged with enone **5** (698 mg, 1.34 mmol) and MeOH (60 mL). The resulting solution was cooled to 0 °C, and $CeCl_3 \cdot 7H_2O$ (499 mg, 1.34 mmol) was added, and the solution was stirred for 5 min. $NaBH_4$ (51 mg, 1.34 mmol) was next added slowly. The resulting solution was stirred for 15 min and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ether (2×), and the combined organic fractions were dried and concentrated, and the crude mixture was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 80:20) to yield the less polar dienol **8a** (300 g, 43%) as a pale yellow oil: $[\alpha]^{20}_D$ −15.1 (*c* 2.6, $CHCl_3$); IR (thin film, cm^{-1}) 3521, 1639, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 6.6 Hz, 2H), 5.80 (dd, J = 11.5, 7 Hz, 1H), 5.77 (dd, J = 9, 2 Hz, 1H), 5.47 (dd, J = 11, 7 Hz, 1H), 5.40 (dd, J = 11.5, 7 Hz, 1H), 5.30 (t, J = 7 Hz, 1H), 4.60 (dd, J = 7, 2 Hz, 1H), 4.50 (d, J = 12 Hz, 1H), 4.32 (d, J = 12 Hz, 1H), 4.22 (t, J = 7 Hz, 1H), 3.92 (dd, J = 7, 2 Hz, 1H), 3.77 (s, 3H), 0.83 (s, 9H), 0.79 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 134.3, 131.3, 130.7, 129.1, 113,6, 75.8, 74.6, 71.0, 70.0, 67.8, 55.2, 25.8, 18.1, 18.0, −4.5, −4.4, −4.9, −5.0; HRMS exact mass calcd for $C_{28}H_{48}O_5Si_2Na^+$ 543.2938, found 543.2903.

(2*Z*,1*R*,4*R*,5*R*,6*R*,7*S*,8*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-7,8-bishydroxycyclooct-2-enyl acetate (14a). A 25 mL round-bottomed flask was charged with acetate **10** (100 mg, 0.178 mmol), THF (2 mL), and H_2O (500 μL). The resulting solution was cooled to 0 °C, NMO (60 mg, 0.51 mmol) was added, and the solution was stirred for 5 min. Then, OsO_4 (9 mg, 0.034 mmol) was introduced. The resulting solution was stirred for 15 min in the cold and at rt for 16 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with ether (2×), and the combined organic fractions were dried and concentrated, and the crude mixture was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 70:30) to yield the less polar isomer **14a** (50 mg, 49%) as a light tan oil: $[\alpha]^{20}_D$ −14.3 (*c* 2.2, $CHCl_3$); IR (thin film, cm^{-1}) 3432, 1721, 1614, 1579, 1445; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.83 (t, J = 11 Hz, 1H), 5.73 (dd, J = 11, 7 Hz, 1H), 5.54 (dd, J = 9, 7.5 Hz, 1H), 4.49−4.46 (m, 2H), 4.23 (d, J = 11.5, 1H), 4.05 (dd, J = 7.5, 2.5 Hz, 1H), 3.94 (dd, J = 7, 2 Hz, 1H), 3.90 (dd, J = 7, 2 Hz, 1H), 3.80 (dd, J = 7.5, 2.5 Hz, 1H), 3.76 (s, 3H), 3.21 (d, J = 10 Hz, 1H), 2.56 (d, J = 11.5 Hz, 1H), 2.10 (s, 3H), 0.85 (s, 9H), 0.82 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.2, 136.0, 130.0, 129.8, 129.7, 126.7,

122.9, 113.8, 83.3, 78.5, 73.7, 72.6, 70.3, 66.5, 55.2, 25.8, 25.6, 22.6, 18.1, 17.7, −4.4, −4.8, −4.9, −5.0; HRMS exact mass calcd for $C_{30}H_{51}O_8Si_2Na^+$ 619.3098, found 619.3073.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*S*,8*R*,9*R*)-5,6-Bis(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-octahydro-7,8-dihydroxy-2,2-dimethylcycloocta[*d*][1,3]dioxol-9-yl acetate (18). A 25 mL round-bottomed flask was charged with diol **14a** (50 mg, 0.08 mmol), acetone (1 mL), 2,2-dimethoxypropane (200 μL), and CSA (2 mg). The resulting solution was stirred for 2 h at rt. The reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic fractions were dried and concentrated. The resulting crude mixture was dissolved in THF (0.5 mL) and H_2O (100 μL) and cooled to 0 °C. NMO (27 mg, 0.23 mmol) was added, and the solution was stirred for 5 min. Then, OsO_4 (4.1 mg, 0.015 mmol) was introduced. The resulting solution was stirred for 15 min in the cold and at rt for 48 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution, the aqueous layer extracted with ether (2×), and the combined organic fractions were dried and concentrated, and the residue was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 1:1) to yield diol **18** (42 mg, 43%) as a light yellow oil: $[\alpha]^{20}_D$ −48.3 (*c* 1.6, $CHCl_3$); IR (thin film, cm^{-1}) 3452, 1714, 1496, 1286; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.69 (d, *J* = 8 Hz, 1H), 4.80 (t, *J* = 7.5, 7 Hz, 1H), 4.43 (s, 2H), 4.36 (dd, *J* = 7.5, 4 Hz, 1H), 4.28 (dd, *J* = 7, 2.5 Hz, 1H), 4.24−4.20 (m, 2H), 4.04 (dd, *J* = 7.5, 2 Hz, 1H), 3.82 (dd, *J* = 7.5, 2.5 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 1H), 3.11 (s, 1H), 2.15 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.2, 130.0, 129.8, 126.7, 113.8, 98.1, 83.3, 80.9, 78.5, 77.2, 76.1, 73.7, 72.6, 70.3, 66.5, 55.2, 25.7, 25.3, 24.1, 23,7, 21.2, 18.1, 17.7, −4.4, −4.8, −4.9, −5.0; HRMS exact mass calcd for $C_{33}H_{58}O_{10}Si_2Na^+$ 693.3458, found 693.3471.

(1*S*,2*S*,3*R*,4*S*,5*S*,6*S*,7*S*,8*R*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (26). A 5 mL round-bottomed flask was charged with diol **18** (43 mg, 0.06 mmol), CH_2Cl_2 (1 mL), H_2O (250 μL), and DDQ (5 mg, 0.12 mmol). The reaction mixture was stirred at rt for 3 h and quenched with saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The residue was filtered trough a small pad of silica gel and concentrated. The residue was mixed in a 5 mL round-bottomed flask with THF (1 mL) and charged with 2.5 N HCl in THF (1 mL). The reaction mixture was stirred at rt for 6 h and quenched with solid sodium bicarbonate. The residue was triturated with MeOH (2 mL) and reacted with K_2CO_3 (10 mg). The resulting mixture was stirred at rt for 2 h, and the solvent was removed under vacuum. The crude mixture was purified by flash chromatography using a reverse phase column (elution with MeOH/$CHCl_3$ 1:3) to yield **26** (11 mg, 73%) as a white solid: mp 268−271 °C; $[\alpha]^{20}_D$ −69.1 (*c* 0.91, MeOH); IR (thin film, cm^{-1}) 3401, 3365, 1421, 1099; ^1H NMR (500 MHz, D_2O) δ 4.26 (dd, *J* = 9, 4 Hz, 2H), 3.91 (dd, *J* = 9, 2.5 Hz, 1H), 3.78 (d, *J* = 9.5 Hz, 2H), 3.60 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.49 (t, *J* = 9.5, 9 Hz, 1H), 3.38 (s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 78.1, 75.9, 74.6, 70.3, 69.7, 64.9, 64.7, 63.2; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0739.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*,7*R*,8*R*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (27). The global deprotection of diol **19** (8 mg, 0.01 mmol) provided **27** (2.3 mg, 81%) as a white solid: mp 272−277 °C; $[\alpha]^{20}_D$ 0 (*c* 0.12, MeOH); IR (thin film, cm^{-1}) 3399, 3187, 1431, 1110; ^1H NMR (500 MHz, D_2O) δ 4.12 (dd, *J* = 9.5, 4 Hz, 2H), 3.96 (s, 2H), 3.76 (s, 2H), 3.71 (s, 1H), 3.51 (t, *J* = 9.5, 9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) 77.1, 75.3, 74.4, 72.2, 70.1, 69.3; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0763.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*S*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (28). The global deprotection of diol **20** (30 mg, 0.05 mmol) provided **28** (7.4 mg, 69%) as a white solid: mp 283−285 °C; $[\alpha]^{20}_D$ 0.0 (*c* 0.35, MeOH); IR (thin film, cm^{-1}) 3487, 3263, 1429; ^1H NMR (500 MHz, D_2O) δ 4.10 (t, *J* = 2.0 Hz, 1H), 3.91 (dd, *J* = 9.5, 4.0 Hz, 2H), 3.83 (dd, *J* = 9.0, 4 Hz, 2H) 3.69 (dd, *J* = 9.5, 2.0 Hz, 2H), 3.43 (t, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 76.2, 72.0, 72.4, 71.2, 70.7, 70.2; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0735.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*S*,7*R*,8*R*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (29). The global deprotection of diol **21** (11 mg, 0.02 mmol) provided **29** (3 mg, 75%) as a white solid: mp 286−289 °C; $[\alpha]^{20}_D$ 0.0 (*c* 0.29, MeOH); IR (thin film, cm^{-1}) 3442, 3220, 1462, 1068; ^1H NMR (500 MHz, D_2O) δ 4.21 (d, *J* = 9.5 Hz, 2H), 4.19 (t, *J* = 9.5, 9 Hz, 2H), 3.90 (d, *J* = 3 Hz, 2H), 3.69 (dd, *J* = 9, 3 Hz, 2H); ^{13}C NMR (125 MHz, D_2O) δ 73.0, 69.3, 69.1, 66.3; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0761.

(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*,7*S*,8*S*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (30). A 5 mL round-bottomed flask was charged $LiAlH_4$ (5 mg, 0.1 mmol) and THF (1 mL) and then cooled to 0 °C. At that temperature, a solution of diol **22** (12 mg, 0.02 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at rt for 3 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The residue was filtered through a small pad of silica gel and concentrated. The residue was mixed in a 5 mL round-bottomed flask with THF (1 mL) and charged with 2.5 N HCl in THF (1 mL). The reaction mixture was stirred at rt for 6 h and quenched with solid sodium bicarbonate. The crude mixture was purified by flash chromatography using a reverse phase column (elution with MeOH/$CHCl_3$ 1:3) to yield **30** (2 mg, 56%) as a white solid: mp 271−275 °C; $[\alpha]^{20}_D$ +3.5 (*c* 0.65, MeOH); IR (thin film, cm^{-1}) 3401, 3221, 1465; ^1H NMR (500 MHz, D_2O) δ 4.51 (dd, *J* = 9.5, 3 Hz, 1H), 4.39 (dd, *J* = 9.0, 3 Hz, 1H), 4.25 (dd, *J* = 9.5, 4 Hz, 1H), 4.12 (dd, *J* = 9, 4 Hz, 1H), 3.92 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.89 (s, 1H), 3.69 (dd, *J* = 9.5, 3 Hz, 1H), 3.52 (t, *J* = 9.5, 9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 78.3, 76.1, 75.3, 72.1, 70.3, 69.4, 65.7, 63.1; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0729.

(1*S*,2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*S*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (31). The global deprotection of diol **23** (3 mg, 0.005 mmol) provided **31** (1 mg, 85%) as a white solid: mp 296−299 °C; $[\alpha]^{20}_D$ 0.0 (*c* 0.14, MeOH); IR (thin film, cm^{-1}) 3429, 3310, 1403, 1093; ^1H NMR (500 MHz, D_2O) δ 4.22 (s, 1H), 3.97 (s, 2H), 3.76 (dd, *J* = 9, 2.5 Hz, 2H), 3.52 (s, 1H), 3.41 (dd, *J* = 9, 4 Hz, 2H); ^{13}C NMR (125 MHz, D_2O) δ 78.1, 76.7, 75.3, 72.4, 70.1; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0757.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*S*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (28). The global deprotection of diol **24** (32 mg, 0.04 mmol) provided **28** (5 mg, 51%) as a white solid: mp 283−285 °C; $[\alpha]^{20}_D$ 0.0 (*c* 0.19, MeOH); IR (thin film, cm^{-1}) 3487, 3259, 1421; ^1H NMR (500 MHz, D_2O) δ 4.10 (t, *J* = 2.0 Hz, 1H), 3.91 (dd, *J* = 9.5, 4.0 Hz, 2H), 3.83 (dd, *J* = 9.0, 4 Hz, 2H) 3.69 (dd, *J* = 9.5, 2.0 Hz, 2H), 3.43 (t, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 76.2, 72.0, 72.4, 71.2, 70.7, 70.2; ^{13}C NMR (125 MHz, D_2O) δ 78.1, 76.1, 74.3, 70.9, 69.6, 65.6, 65.3, 63.5; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0735.

(1*S*,2*S*,3*R*,4*R*,5*S*,6*S*,7*R*,8*R*)-Cyclooctan-1,2,3,4,5,6,7,8-octaol (29). The global deprotection of diol **25** (11 mg, 0.02 mmol) provided **29** (2.5 mg, 62%) as a white solid: mp 286−289 °C; $[\alpha]^{20}_D$ 0.0 (*c* 0.25, MeOH); IR (thin film, cm^{-1}) 3449, 3219, 1465, 1068; ^1H NMR (500 MHz, D_2O) δ 4.21 (d, *J* = 9.5 Hz, 2H), 4.19 (t, *J* = 9.5, 9 Hz, 2H), 3.90 (d, *J* = 3 Hz, 2H) 3.69 (dd, *J* = 9, 3 Hz, 2H); ^{13}C NMR (125 MHz, D_2O) δ 73.0, 69.3, 69.1, 66.3; HRMS exact mass calcd for $C_8H_{16}O_8Na^+$ 263.0743, found 263.0761.

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Supporting Information Available: High-field ^1H and ^{13}C NMR spectra and full characterization for all new compounds are described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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