JOC Article

From D-Glucose to Enantiomerically Pure Cycloctanoses. The Glycosidase Inhibitory Capacity of Medium-Ring Carbasugars

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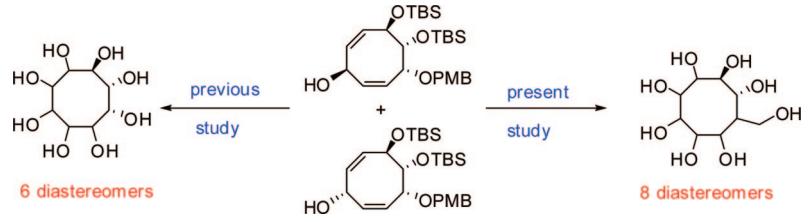
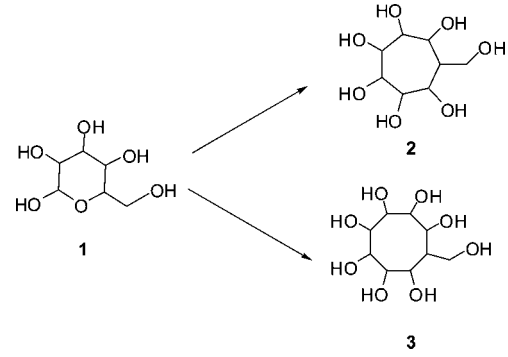


Exhaustive dihydroxylation of the pair of cyclooctadienols consisting of **4** and **5**, which are available in enantiomerically pure form from D-glucose, resulted in the formation of two diastereomeric tetraols in each case. The difference in polarity of the **6/7** and **8/9** pairs facilitated their chromatographic separation. Ensuing acetylation and PMB deprotection allowed for the assignment of relative (and ultimately absolute) stereochemistry to the resulting monohydric alcohols on the basis of J_{HH} analysis of their ^{1}H NMR spectra. The highly functionalized exomethylenecyclooctanes **14**−**17**, which were derived by periodinane oxidation and Wittig olefination, were further elaborated by hydroboration and global deprotection. The eight members of the cyclooctanose family of carbasugars and their precursor intermediates consistently showed patterns of J_{HH} values in line with the contiguous stereochemical relationships. Also assayed was their specific inhibitory behavior toward glycosidases.

Introduction

Interest has recently developed in the acquisition of seven-[1] and eight-membered[2,3] carbasugar homologues to determine if they are capable of mimicking or preferably enhancing the important signaling and recognition capacities of their cyclohexane congeners.[4] The fundamental structural change involves replacement of the core ring oxygen of pyranosides **1** by two or three linear CHOH units as in **2** or **3** (Scheme 1). Inclusion of the contiguous array of hydroxyl substituents is thought to be of likely significance for receptor recognition purposes. The configurational and conformational interrelationships enforced by the vicinal OH groups are also likely to impact other biological properties of interest including enhanced stability toward degradative enzymes.[5]

SCHEME 1. Medium-Ring Carbasugars



As a direct consequence of our past successful efforts directed to the conversion of D-arabinose and D-glucose into enantiopure

(1) (a) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333. (b) Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **1999**, *40*, 4445. (c) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2000**, *65*, 5416. (d) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705. (e) Sisu, E.; Sollogoub, M.; Mallet, G.-M.; Sinay, P. *Tetrahedron Lett.* **2002**, *58*, 10189. (f) Ganesh, N. V.; Gayaraman, N. *J. Org. Chem.* **2007**, *72*, 5500.

(2) Mehta, G.; Singh, V. K. *Chem. Rev.* **1999**, *99*, 881.

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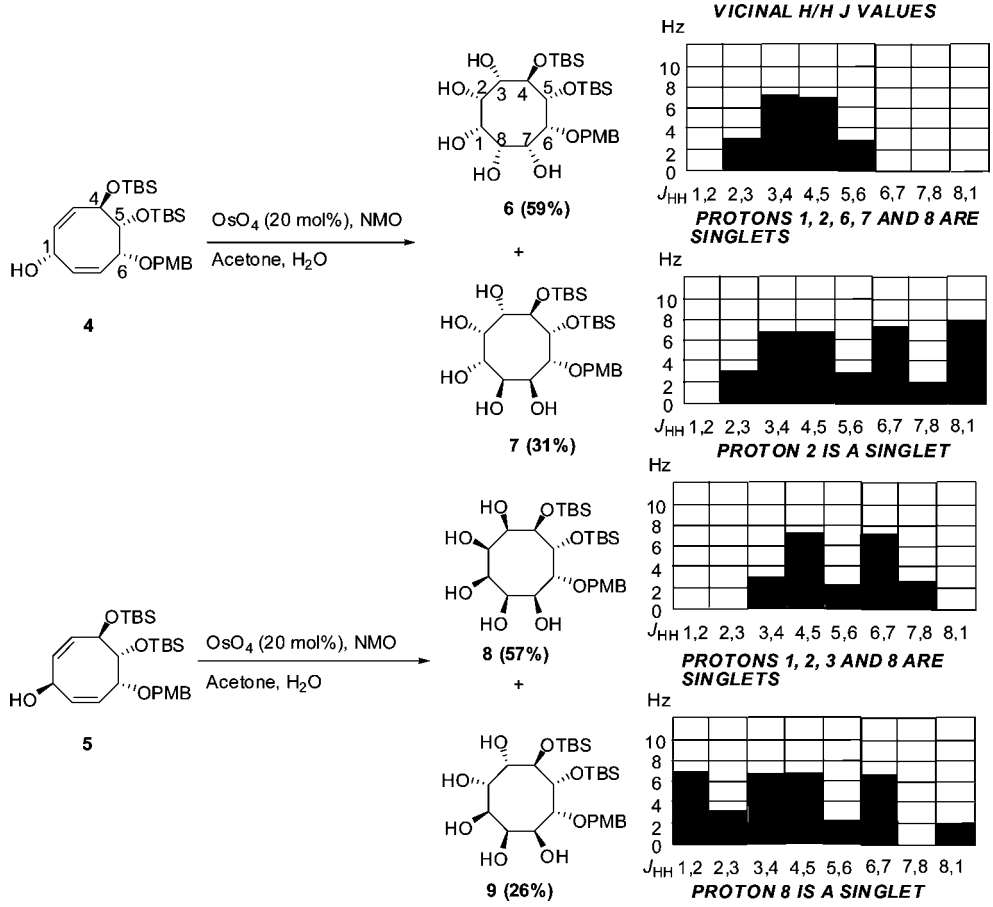
SCHEME 2. Twofold Dihydroxylation of 4 and 5 with J_{HH} Values for 6−9[a]



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

cyclobutanols via zirconocene-mediated ring contraction,[6] subsequent sigmatropic ring enlargement,[7] and ultimate functionalization, a practical route has been developed for the preparation of stereodefined cyclooctane-1,2,3-triols and 1,2,3,4,5-pentaols,[3k] as well as cyclooctane polyols.[31] Presently, we have explored the suitability of this chemistry for the formation of an array of diastereomeric cyclooctanoses, established the relative (and absolute) stereochemistry of these unnatural glycomimetics by J_{HH} vicinal coupling pattern analysis, and evaluated their inhibitory capacity toward a selected group of glycosidases.

Results and Discussion

Synthetic Considerations. The predescribed alcohols **4** and **5**[31] were reacted with 20 mol % of OsO_4 and 2 equiv of NMO to provide two pairs of diastereomers each (Scheme 2). In the case of **4**, the less polar pentaol (59%) was formed at approximately twice the level of the more polar counterpart (31%). Since our expectation was that the major oxidation product would result from doubly directed exhaustive dihydroxylation leading to **6**, the minor polyol was assigned tentatively as **7**, the end roduct of sequential osmylation adjacent to the TBS ether followed by less hindered face attack at the second double bond. In like fashion, alcohol **5** provided a 2:1 mixture of less polar (59%) and more polar diastereomers (26%) tentatively formulated as **8** and **9**, respectively. These configurational assumptions were subsequently confirmed by suitable analysis of the vicinal J_{HH} values as previously defined by Kishi for acyclic diols[8] and Moura-Letts for contiguously substituted cyclooctane polyols.[31]

The plots depicted in Scheme 2 clearly show a pattern of high J_{HH} values for *anti* contiguous stereocenters and low J_{HH} values for *syn* contiguous stereocenters. Singlets are often seen for contiguous *syn* relationships. These relationships are fully consistent with our earlier findings.

Next to be addressed was an orthogonal protection−deprotection sequence suited to the pending one-carbon homologation. To this end, pentaols **6**−**9** were peracetylated with a large excess of acetic anhydride in pyridine. Each of the unpurified reaction mixtures was then exposed to DDQ in wet dichloromethane to deliver the monohydric alcohols **10**−**13** (65−71%, Scheme 3) Vicinal J_{HH} value plots for each exhibited an expectedly clear parallelism to those determined for **6**−**9**. In our view, these data served as further proof of the consistency of this analysis.

(4) Sollogoub, M.; Sinay, P. *Organic Chemistry of Sugars*; CRC Press: Boca Raton, FL, 2006; p 349.

(5) (a) Ogawa, S. In *Carbohydrate Mimics, Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; pp 87−106. (b) Tang, Y.-Q.; Maul, C.; Hofs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (d) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077.

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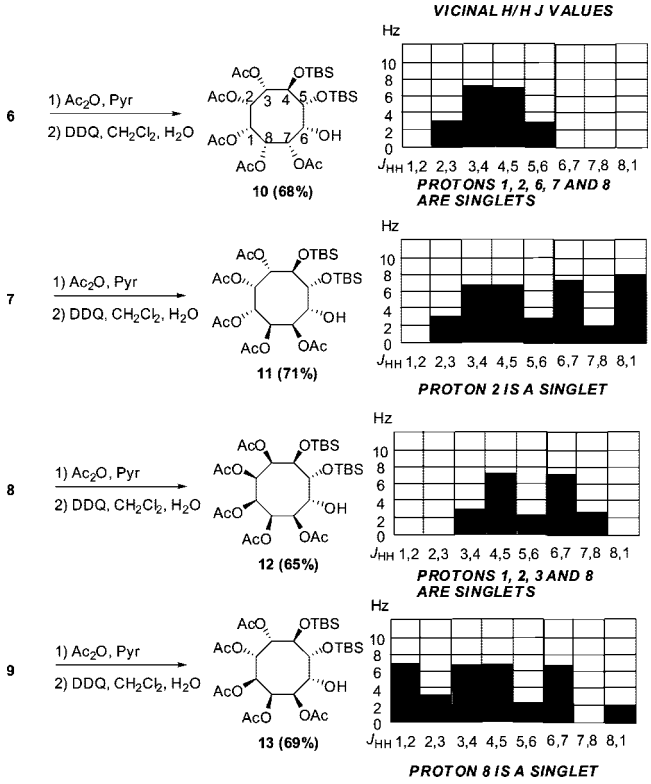
(7) Paquette, L. A.; Kim, I. H.; Cuniere, N. *Org. Lett.* **2003**, *5*, 463.

(8) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (c) Higashibayashi, S.; Czechlitzky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379. (d) Seike, H.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3861.

SCHEME 3. Protection/Deprotection Sequence as Applied to Pentaols 6−9[a]



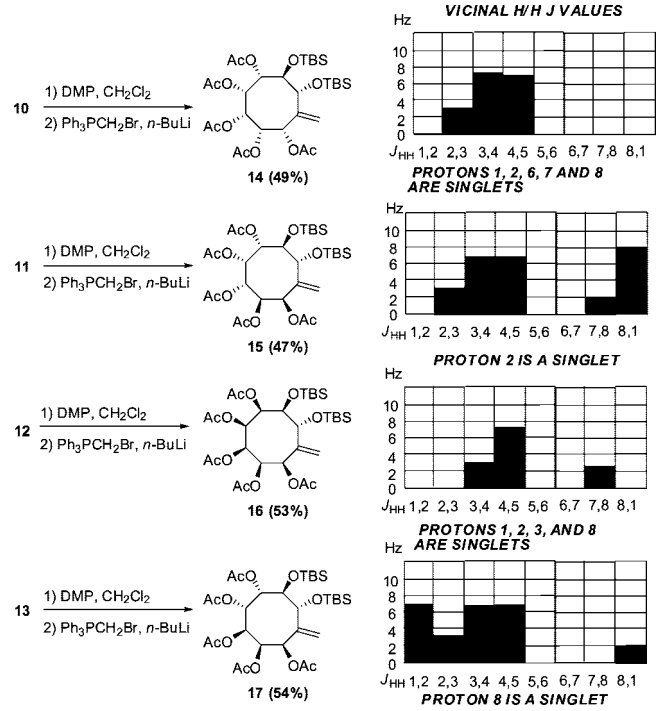
[a] The *x* axis is the carbon number, and *y* axis is the vicinal J_{HH} value.

Advancement to the exomethylene systems **14**−**17** involved initial oxidation with the Dess−Martin reagent (DMP) and ensuing homologation with methylenetriphenylphosphorane. This pair of steps operated smoothly with generation of the exocyclic alkenes **14**−**17** in combined yields ranging from 49 to 54% (Scheme 4). Analysis of the NMR patterns of these four diastereomeric intermediates showed the appropriate downfield shifting of those signals associated with the protons adjacent to the newly introduced olefinic center. In addition, the observed trends were fully consistent with those seen previously.

An assessment of the reactivity of **14**−**17** in the hydroboration reaction followed. Initial probe experiments involving 9-BBN gave evidence of very low reactivity. In contrast, recourse to BH_3·THF gave rise to complete conversion for all of the diastereomers. In all four examples, 1:1 mixtures of diastereomeric primary carbinols were generated (Schemes 5 and 6). Each product exhibited quite distinctive coupling patterns. In the case of **18** and **19**, analysis of the J_{HH} values uncovered a characteristic multiplet (several large J_{HH} coupling constants) and a doublet of doublets (J = 5.5, 4.0 Hz) attributable respectively to H6. These features are in accordance with an *anti*,*anti* relationship for **18** and a *syn*,*syn* relationship for **19**. Moreover, alcohol **18** is less polar than **19**.

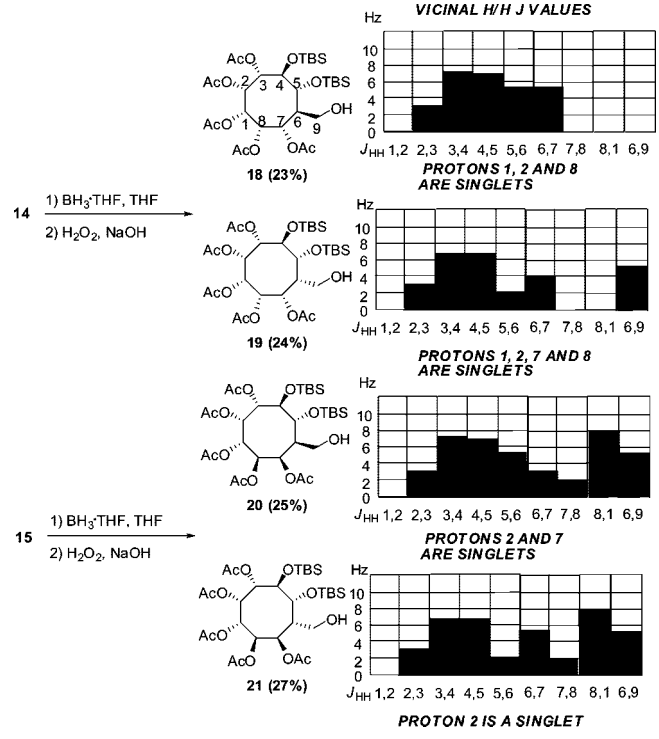
The second pair of carbinols, **20** and **21**, exhibit coupling patterns consisting of a doublet of triplets (J = 5.5, 3.0 Hz) and a triplet (J = 5.5 Hz), respectively. These results identify compound **20** as the *anti*,*syn* isomer and **21** as its *syn*,*anti* counterpart. We have previously encountered *syn* coupling constants on the order of 3−4 Hz for contiguous *syn*,*syn* (C6−C7−C8) relationships in cyclooctane settings as in **20**.[31] The lesser polarity of **20** relative to that of **21** also supports these configurational assignments (Scheme 5).

SCHEME 4. Oxidation/Olefination Steps for Alcohols 10−13[a]



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

SCHEME 5. Hydroboration Products of 14 and 15[a]

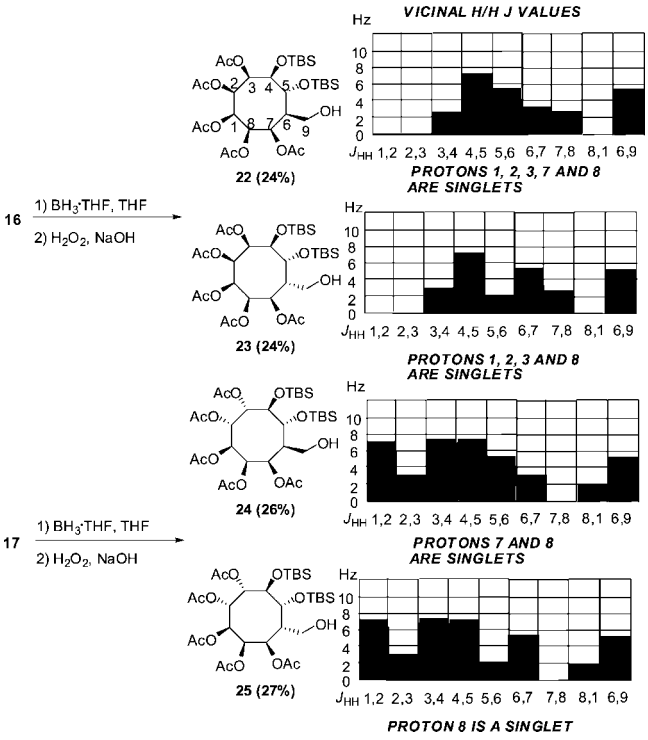


[a] The *x* axis is the carbon number, and *y* axis is the vicinal J_{HH} value.

Compounds **22** and **23** show a doublet of triplets and a triplet, respectively, for H6. These features are in specific agreement with an *anti*,*syn* and *syn*,*anti* relationship for H5/H6/H7, key characteristics which are also found in the spectra of **24/25** (Scheme 6).

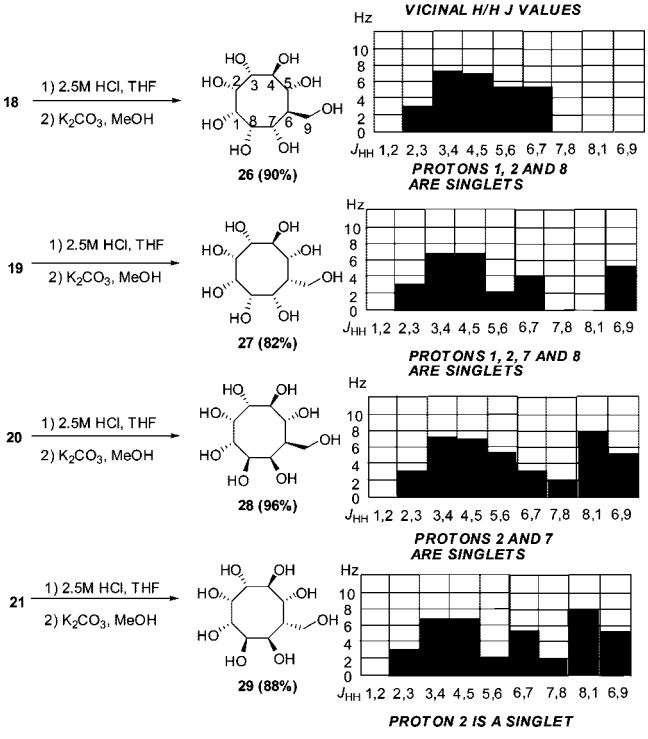
Global deprotection of the above alcohols followed. Solutions of each pure diastereomer in THF were initially stirred with

SCHEME 6. Hydroboration Products of 16 and 17[a]



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

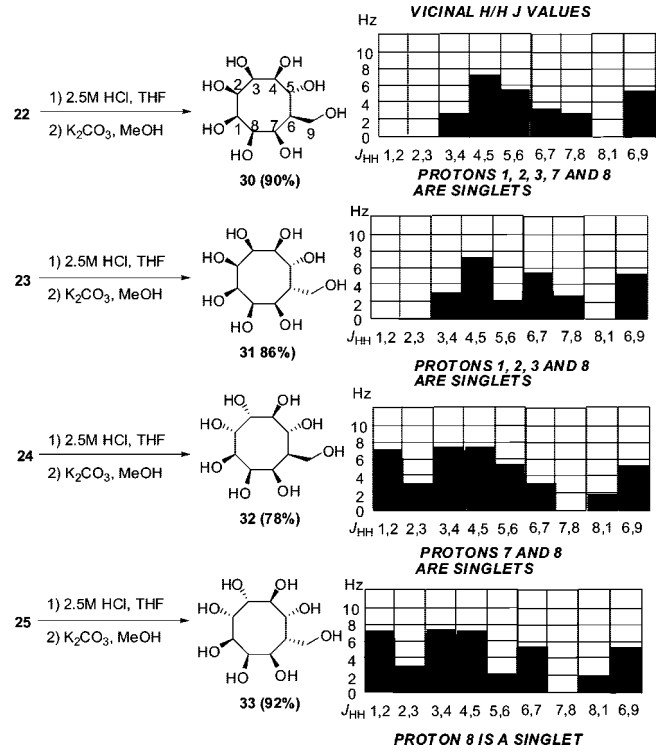
SCHEME 7. Global Deprotection of 18−21[a]



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

2.5 M HCl for 12 h and subsequently deacetylated with K_2CO_3 in methanol to give in each instance a single octaol as a white solid. The yields averaged 88% (Schemes 7 and 8), and the J_{HH} patterns for all the stereocenters were fully congruent with the analysis performed on the starting materials (Schemes 7 and 8).

SCHEME 8. Global Deprotection of 22−25[a]



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

Enzymatic Studies. Use was made of the protocol reported by Saul et al.[9] for assessing glycosidase activity. The experiments measure the extent of formation of *p*-nitrophenol in the reaction involving a specific enzyme and the corresponding *p*-nitrophenyl glycopyranose. The extent of formation of *p*-nitrophenol was measured by recording the OD (optical density) of the reaction mixture. The introduction of an inhibitor that competes positively for the enzyme displays a decrease in the formation of *p*-nitrophenol. Castanospermine was utilized as the standard inhibitor for probing the reproducibility of the experiments. We inferred that cyclooctane polyols **34**−**39** and cyclooctanoses **26**−**33** may be active based on their glycoside-*like* stereochemistry. Accordingly, each was tested against four different enzymes having in common the stereochemical features of β-mannosidase, β-glucosidase, β-galactosidase, and α-glucosidase.

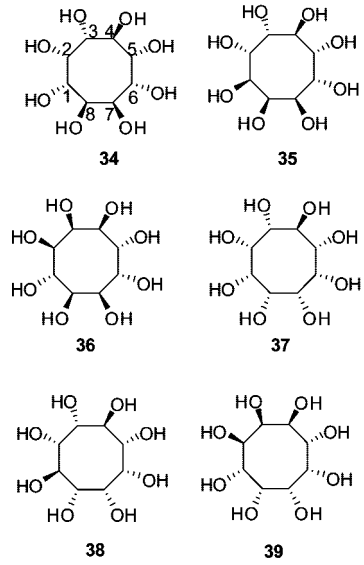
The first goal was to assay the six cyclooctane polyols **34**−**39**[31] against β-mannosidase (Table 1). Diastereomer **36** showed modest activity when tested in this manner. The remaining candidates showed no significant activity.

In the cyclooctanose series, carbasugars **26**, **28**, and **32** were found to exhibit very little activity. Particularly striking was the finding that **30** fully inhibited the formation of *p*-nitrophenol, even at the lowest concentration examined (50 μg/mL). Interestingly, **30** shares with β-D-mannose the same stereochemistry along its C6−C2 backbone. The remaining cyclooctanoses showed no activity (Table 2).

The next goal was to test if this activity is conserved, lost, or expressed with the other cyclooctanoses when β-glucosidase is involved. Compounds **34** and **38** showed modest activity against β-glucosidase. Compounds **35**, **36**, **37**, and **39** exhibited

(9) Saul, R.; Chambers, G. P.; Molynaux, R. G.; Elbin, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593.

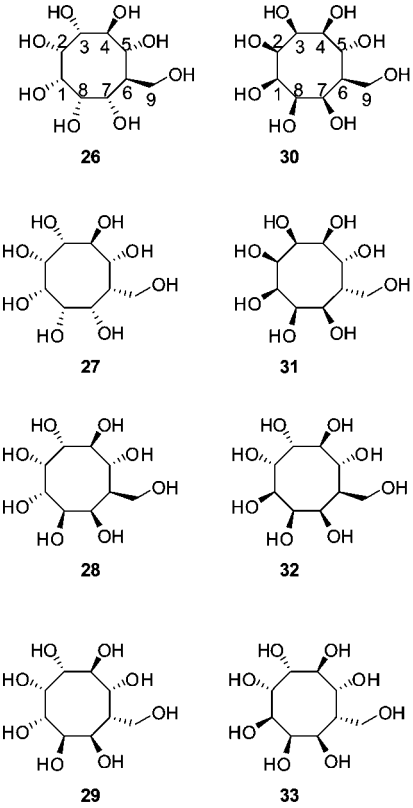
TABLE 1. Inhibitory Activity of Cyclooctane Polyols Against β-Mannosidase



Amount of inhibtor (μg/mL)	inhibitor	OD[a,b]
0	std	0.81
25	std	0.82
50	std	0.83
100	std	0.80
0	**34**	0.79
25	**34**	0.81
50	**34**	0.82
100	**34**	0.87
0	**35**	0.76
25	**35**	0.75
50	**35**	0.76
100	**35**	0.79
0	**36**	0.79
25	**36**	0.69
50	**36**	0.58
100	**36**	0.41
0	**37**	0.79
25	**37**	0.81
50	**37**	0.82
100	**37**	0.81
0	**38**	0.81
25	**38**	0.82
50	**38**	0.80
100	**38**	0.83
0	**39**	0.84
25	**39**	0.83
50	**39**	0.84
100	**39**	0.81

[a] Measured at 410 nm, std = castanospermine, [b] Experiments run against β–mannosidase.

TABLE 2. Inhibitory Activity of Cyclooctanoses against β-Mannosidase



Amount of inhibtor (μg/mL)	inhibitor	OD[a,b]
0	**std**	0.85
25	**std**	0.84
50	**std**	0.87
100	**std**	0.82
0	**26**	0.82
25	**26**	0.79
50	**26**	0.75
100	**26**	0.55
0	**27**	0.82
25	**27**	0.84
50	**27**	0.87
100	**27**	0.86
0	**28**	0.81
25	**28**	0.77
50	**28**	0.72
100	**28**	0.61
0	**29**	0.85
25	**29**	0.86
50	**29**	0.82
100	**29**	0.84
0	**30**	0.84
25	**30**	0.08
50	**30**	0.02
100	**30**	0.02
0	**31**	0.86
25	**31**	0.82
50	**31**	0.84
100	**31**	0.81
0	**32**	0.81
25	**32**	0.70
50	**32**	0.55
100	**32**	0.50
0	**33**	0.82
25	**33**	0.79
50	**33**	0.77
100	**33**	0.80

[a] Measured at 410 nm, std = castanospermine, [b] Experiments run against β-mannosidase.

no inhibitory activity against this enzyme. Moreover, cyclooctanoses **26**, **28**, **30**, and **32** exhibited little activity against the same enzyme (Tables 3 and 4 in the Supporting Information). These four sugar mimics share in common a β-C6 configuration. Moreover, the stereocenters defined as C3, C4, and C5 mirror the absolute stereochemistry present in α-D-glucose.

The *anti*,*anti* relationship between C6, C5, and C4 common to all of our compounds renders them inactive against the β-galactosidase enzyme, given the assumption that activity is dependent upon their glycoside-*like* relative stereochemistry. As a result, both cyclooctane polyols **34**−**39** and cyclooctanoses **26**−**33** exhibit no activity against this enzyme (Tables 5 and 6

in the Supporting Information). Similar results were found when these mimics were tested against α-glucosidase (Tables 7 and 8 in the Supporting Information).

Summary

In conclusion, this study has extended the previously developed synthetic route to obtain optically pure cylcooctanoses. Accordingly, determination of vicinal J_{HH} coupling patterns associated with each series of intermediates allowed us to predict the relative (and absolute) stereochemistry of each cyclooctanose. We were also able to test these cyclooctanoses and the previously synthesized cyclooctane polyols against a battery of glycosidases. The results allowed us to establish that stereochemical similarities along the C2−C6 backbone and the corresponding enzyme are crucial for activity.

Experimental Section

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)cyclooctane-1,2,3,4,5-pentaol (6). A 100 mL round-bottomed flask was charged with alcohol **4** (400 mg, 0.712 mmol), acetone (10 mL), and H_2O (2 mL). The resulting solution was cooled to 0 °C, NMO (420 mg, 4.08 mmol) was added, and stirring maintained for 5 min. OsO_4 (72 mg, 0.286 mmol) was next 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 $CHCl_3$/MeOH 1:1) to yield the less polar isomer **6** (247 mg, 59%) as a light yellow oil: $[\alpha]^{20}_D$ −8.3 (*c* 2.4, $CHCl_3$); IR (thin film, cm^{-1}) 3442, 1606; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.61 (dd, J = 7.5, 2 Hz, 1H), 5.52 (d, J = 11 Hz, 1H), 5.42 (s, 1H), 4.33 (d, J = 11 Hz, 1H), 4.22 (t, J = 7.5 Hz, 1H), 4.18 (s, 1H), 4.03 (s, 1H), 3.94 (dd, J = 7.0, 2.0 Hz, 1H), 3.88 (s, 2H), 3.78 (s, 3H), 3.01 (d, J = 10 Hz, 1H), 2.91 (d, J = 10 Hz, 1H), 2.73 (d, J = 11 Hz, 1H), 2.61 (d, J = 11 Hz, 1H), 2.52 (d, J = 10.5 Hz, 1H), 0.88 (s, 9H), 0.86 (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 165.2, 131.8, 122.6, 113.8, 83.6, 83.2, 81.7, 78.8, 75.5, 74.2, 72.8, 66.1, 55.4, 25.9, 25.8, 18.0, 17.9, −4.2, −4.6, −4.7, −4.9; HRMS exact mass calcd for $C_{28}H_{52}O_9Si_2Na^+$ 611.3042, found 611.3043.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)cyclooctane-1,2,3,4,5-pentaol (7). Alcohol **4** also afforded the more polar isomer **7** (130 mg, 31%) as a light tan oil: $[\alpha]^{20}_D$ +13.5 (*c* 1.8, $CHCl_3$); IR (thin film, cm^{-1}) 3445, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.68 (dd, J = 7, 2 Hz, 1H), 4.59 (s, 1H), 4.50 (d, J = 11 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 4.32 (d, J = 11 Hz, 1H), 4.19 (dd, J = 7, 2.5 Hz, 1H),4.10 (dd, J = 7.5, 2.5 Hz, 2H), 4.02 (dd, J = 7, 2.5 Hz, 1H), 3.89 (dd, J = 7, 2 Hz, 1H), 3.79 (s, 3H), 2.62 (s, 2H), 2.41 (s, 2H), 2.20 (s, 1H), 0.84 (s, 18H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 130.6, 122.4, 112.4, 82.2, 80.8, 79.5, 77.7, 74.5, 69.9, 68.2, 64.6, 63.4, 55.4, 25.8, 25.7, 17.7, 17.6, −4.0, −4.1, −4.4, −4.5; HRMS exact mass calcd for $C_{28}H_{52}O_9Si_2Na^+$ 611.3042, found 611.3037.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)cyclooctane-1,2,3,4,5-pentaol (8). A 100 mL round-bottomed flask was charged with alcohol **5** (400 mg, 0.712 mmol), acetone (10 mL), and H_2O (2 mL). The resulting solution was cooled to 0 °C, NMO (420 mg, 4.08 mmol) was added, and stirring was maintained for 5 min. OsO_4 (72 mg, 0.286 mmol) was next 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 $CHCl_3$/MeOH 1:1) to yield the less polar **8** isomer (239 mg, 57%) as a pale yellow oil: $[\alpha]^{20}_D$ −23.1 (*c* 3.1, $CHCl_3$); IR (thin film, cm^{-1}) 3521, 1639; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.61 (dd, J = 7.5, 4 Hz, 1H), 4.52 (d, J = 11 Hz, 1H), 4.42 (s, 1H), 4.32 (d, J = 11 Hz, 1H), 4.25 (dd, J = 7.5, 2 Hz, 1H), 4.02 (dd, J = 7, 2 Hz, 1H),3.95 (s, 2H), 3.82 (s, 1H), 3.76 (s, 3H), 3.28 (s, 2H), 3.16 (d, J = 10.5 Hz, 1H), 2.99 (d, J = 11 Hz, 1H), 2.91 (d, J = 10.5 Hz, 1H), 0.83 (s, 9H), 0.81 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 131.8, 122.6, 113.8, 83.1, 82.4, 80.9, 79.0, 75.5, 74.2, 72.8, 71.7, 66.1, 55.4, 25.9, 25.8, 25.7, 18.3, 18.2, −4.1, −4.2, −4.3; HRMS exact mass calcd for $C_{28}H_{52}O_9Si_2Na^+$ 611.3042, found 611.3046.

(1*S*,2*S*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)cyclooctane-1,2,3,4,5-pentaol (9). Alcohol **5** also afforded the more polar isomer **9** (109 mg, 26%) as a light yellow oil: $[\alpha]^{20}_D$ −36.3 (*c* 1.9, $CHCl_3$); IR (thin film, cm^{-1}) 3432, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.50 (s, 1H), 4.43 (d, J = 11 Hz, 1H), 4.43 (t, J = 7.5 Hz, 1H), 4.29 (d, J = 11 Hz, 1H), 4.11 (dd, J = 7.5, 2 Hz, 1H), 4.01 (dd, J = 7, 2 Hz, 2H), 3.92 (dd, J = 7.5, 4 Hz, 1H), 3.83 (dd, J = 7, 2 Hz, 1H), 3.79 (s, 3H), 2.83 (d, J = 11 Hz, 1H), 2.53 (s, 1H), 2.41 (d, J = 10.5 Hz, 2H), 2.21 (s, 1H), 0.83 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 130.6, 122.2, 112.9, 79.4, 77.9, 74.2, 73.4, 72.8, 71.4, 68.5, 66.6, 63.4, 55.4, 25.9, 25.8, 25.7, 18.0, 17.9, −4.1, −4.4, −4.5; HRMS exact mass calcd for $C_{28}H_{52}O_9Si_2Na^+$ 611.3042, found 611.3049.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-hydroxycyclooctane-1,2,3,4,5-pentayl pentaacetate (10). A 100 mL round-bottomed flask was charged with pentaol **6** (240 mg, 0.41 mmol), pyridine (10 mL), and acetic anhydride (5 mL). The resulting solution was stirred for 8 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 washed with $CuSO_4$ solution, dried, and concentrated. The resulting crude mixture was dissolved in CH_2Cl_2 (10 mL) and H_2O (2.5 mL), and DDQ (100 mg, 0.82 mmol) was added prior to stirring for 6 h. 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 residue was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 1:1) to yield alcohol **10** (189 mg, 68%) as a light yellow oil: $[\alpha]^{20}_D$ −4.3 (*c* 1.6, $CHCl_3$); IR (thin film, cm^{-1}) 3452, 1726, 1286; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, J = 7, 2 Hz, 1H), 5.79 (s, 2H), 5.64 (s, 1H), 5.59 (s, 1H), 4.61 (s, 1H), 4.23 (t, J = 7.5 Hz, 1H), 3.89 (dd, J = 7.5, 4 Hz, 1H), 2.71 (d, J = 10 Hz, 1H), 2.52 (s, 15H), 0.84 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.5, 160.5, 79.6, 77.4, 75.8, 74.6, 72.2, 70.8, 67.2, 65.3, 25.9, 25.8, 25.7, 21.1, 21.0, 20.9, 18.0, 17.9, −4.5, −4.6, −4.7, −4.8; HRMS exact mass calcd for $C_{30}H_{54}O_{13}Si_2Na^+$ 701.2995, found 701.2991.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-hydroxycyclooctane-1,2,3,4,5-pentaacetate (11). The protection/deprotection sequence applied to pentaol **7** (120 mg, 0.21 mmol) provided alcohol **11** (100 mg, 71%) as a yellow oil: $[\alpha]^{20}_D$ −4.3 (*c* 1.6, $CHCl_3$); IR (thin film, cm^{-1}) 3452, 1714, 1286; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (dd, J = 7, 4.5 Hz, 2H), 5.79 (dd, J = 7, 2.5 Hz, 1H), 5.69 (dd, J = 7.5, 2.5 Hz, 1H), 5.52 (s, 1H), 4.41 (dd, J = 7, 2 Hz, 1H), 4.23 (t, J = 7.5 Hz, 1H), 4.13 (dd, J = 7.5, 2 Hz, 1H), 2.98 (d, J = 10.5 Hz, 1H), 2.51 (s, 15H), 0.86 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 163.2, 162.9, 82.5, 82.0, 81.9, 73.7, 72.6, 70.3, 66.5, 66.2, 25.8, 25.7, 21.4, 21.3, 18.0, 17.6, −4.5,

−4.7, −4.8, −4.9; HRMS exact mass calcd for $C_{30}H_{54}O_{13}Si_2Na^+$ 701.2995, found 701.3001.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-hydroxycyclooctane-1,2,3,4,5-pentaacetate (12). The protection/deprotection sequence applied to pentaol **8** (220 mg, 0.38 mmol) provided alcohol **12** (160 mg, 65%) as a pale tan oil: $[\alpha]^{20}_D$ +31.1 (*c* 2.4, $CHCl_3$); IR (thin film, cm^{-1}) 3443, 1724, 1254; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 2H), 5.81 (dd, J = 7, 2.5 Hz, 2H), 5.72 (s, 1H), 5.50 (s, 1H), 4.22 (dd, J = 7, 2 Hz, 1H), 4.01 (dd, J = 7.5, 2 Hz, 2H), 3.13 (d, J = 11 Hz, 1H), 2.53 (s, 15H), 0.85 (s, 9H), 0.82 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 162.8, 160.5, 82.3, 80.9, 79.0, 74.2, 72.2, 70.8, 69.3, 67.0, 25.8, 25.7, 21.7, 21.6, 18.6, 18.2, −3.9, −4.1, −4.4, −4.6; HRMS exact mass calcd for $C_{30}H_{54}O_{13}Si_2Na^+$ 701.2995, found 701.3003.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-hydroxycyclooctane-1,2,3,4,5-pentaacetate (13). The protection/deprotection sequence applied to pentaol **9** (100 mg, 0.17 mmol) provided alcohol **13** (80 mg, 69%) as a pale tan oil: $[\alpha]^{20}_D$ +15.2 (*c* 2.2, $CHCl_3$); IR (thin film, cm^{-1}) 3461, 1736, 1255; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (dd, J = 7, 2.5 Hz, 1H), 5.79 (dd, J = 7, 2.5 Hz, 1H), 5.55 (dd, J = 7, 2 Hz, 1H), 5.41 (s, 1H), 4.23 (t, J = 7 Hz, 1H), 4.19 (dd, J = 7.5, 2 Hz, 1H), 3.96 (dd, J = 7.5, 2 Hz, 1H), 2.82 (s, 1H), 2.55 (s, 15H), 0.88 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 160.8, 160.6, 160.5, 159.2, 83.5, 82.1, 78.5, 76.1, 73.9, 72.6, 70.3, 66.5, 25.6, 25.5, 25.3, 21.3, 21.2, 21.1, 18.1, 17.8, −4.4, −4.6; HRMS exact mass calcd for $C_{30}H_{54}O_{13}Si_2Na^+$ 701.2995, found 701.3002.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,7*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-methylenecyclooctane-1,2,3,4,5-pentaacetate (14). A 50 mL round-bottomed flask was charged with alcohol **10** (175 mg, 0.26 mmol), CH_2Cl_2 (10 mL), and $NaHCO_3$ (436 mg, 5.2 mmol). To the resulting solution was added Dess−Martin periodinate (166 mg, 0.39 mmol). The solution was stirred for 45 min at rt and then filtered through a pad of Celite. The crude mixture was dissolved in THF (2 mL). A 50 mL round-bottomed flask charged with Ph_3PCH_3Br (371 mg, 1.04 mmol) and THF (6 mL) was treated with *n*-BuLi (1.6 M, 0.78 mmol) at 0 °C for 0.5 h. The solution was warmed to rt and after 0.5 h cooled back to 0 °C. The resulting solution was treated with the crude mixture in THF (2 mL). The solution was stirred for 2 h and then quenched with NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2×), the combined organic fractions were dried and concentrated, and the residue was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 2:1) to yield olefin **14** (86 mg, 49%) as a colorless oil: $[\alpha]^{20}_D$ −23.3 (*c* 1.9, $CHCl_3$); IR (thin film, cm^{-1}) 1736, 1525, 1186; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.92 (d, J = 8.5 Hz, 1H), 5.88 (d, J = 8.5 Hz, 1H), 5.81 (s, 1H), 5.68 (dd, J = 7, 2 Hz, 1H), 5.59 (s, 2H), 4.69 (d, J = 7.5 Hz, 1H), 4.32 (t, J = 7.5 Hz, 1H), 2.51 (s, 15H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.2, 161.8, 159.7, 148.6, 113.8, 83.3, 80.5, 78.9, 73.7, 72.6, 70.3, 66.5, 25.8, 25.7, 25.5, 21.8, 21.7, 21.4, 18.6, 18.5, −4.4, −4.8. −4.9; HRMS exact mass calcd for $C_{31}H_{54}O_{12}Si_2Na^+$ 697.3046, found 697.3051.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-methylenecyclooctane-1,2,3,4,5-pentaacetate (15). The oxidation/olefination sequence applied to alcohol **11** (95 mg, 0.14 mmol) provided olefin **15** (44 mg, 47%) as a pale yellow oil: $[\alpha]^{20}_D$ +1.7 (*c* 2.4, $CHCl_3$); IR (thin film, cm^{-1}) 1722, 1516, 1144; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (s, 1H), 6.03 (s, 1H), 5.95 (d, J = 8.5 Hz, 1H), 5.89 (d, J = 8.5 Hz, 1H), 5.81 (dd, J = 7, 4.5 Hz, 2H), 5.78 (dd, J = 7, 2.5 Hz, 1H), 4.63 (d, J = 7.5 Hz, 1H), 4.23 (t, J = 7.5 Hz, 1H), 2.55 (s, 15H), 0.84 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 165.5, 163.2, 147.8, 113.5, 82.5, 82.3, 74.2, 72.6, 70.5, 68.0, 67.4, 26.0, 25.9, 21.9, 21.7, 21.6, 18.3, 18.2, −3.6, −3.8. −4.0, −4.1; HRMS exact mass calcd for $C_{31}H_{54}O_{12}Si_2Na^+$ 697.3046, found 697.3049.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-methylenecyclooctane-1,2,3,4,5-pentaacetate (16). The oxidation/olefination sequence applied to alcohol **12** (155 mg, 0.23 mmol) provided olefin **16** (82 mg, 53%) as a colorless oil: $[\alpha]^{20}_D$ +9.7 (*c* 1.1, $CHCl_3$); IR (thin film, cm^{-1}) 1712, 1531, 1134; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.93 (s, 1H), 5.84 (d, J = 8.5 Hz, 1H), 5.82 (d, J = 8.5 Hz, 1H), 5.71 (s, 2H), 5.62 (s, 1H), 4.70 (d, J = 7.5 Hz, 1H), 4.24 (dd, J = 7.5, 4 Hz, 1H), 2.59 (s, 15H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.9, 164.9, 163.6, 148.8, 113.8, 80.9, 78.8, 75.5, 74.2, 72.8, 68.8, 68.6, 26.1, 26.0, 25.9, 21.7, 21.6, 21.5, 18.2, 18.1, −4.1, −4.2, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{54}O_{12}Si_2Na^+$ 697.3046, found 697.3052.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-methylenecyclooctane-1,2,3,4,5-pentaacetate (17). The oxidation/olefination sequence applied to alcohol **13** (75 mg, 0.11 mmol) provided olefin **17** (40 mg, 54%) as a colorless oil: $[\alpha]^{20}_D$ −16.8 (*c* 1.6, $CHCl_3$); IR (thin film, cm^{-1}) 1719, 1535, 1162; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.95 (s, 1H), 5.87 (d, J = 8.5 Hz, 1H), 5.81 (d, J = 8.5 Hz, 1H), 5.74 (dd, J = 7.5, 2.5 Hz, 2H), 5.62 (dd, J = 7.5, 2 Hz, 1H), 4.71 (d, J = 7.5 Hz, 1H), 4.32 (t, J = 7.5 Hz, 1H), 2.51 (s, 15H), 0.86 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 162.5, 160.7, 159.5, 148.9, 112.3, 82.5, 81.0, 79.5, 77.4, 70.2, 68.9, 64.6, 26.0, 25.9, 21.9, 21.8, 21.7, 18.2, 18.1, −4.1, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{54}O_{12}Si_2Na^+$ 697.3046, found 697.3050.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,7*R*,8*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (18). A 50 mL round-bottomed flask was charged with olefin **14** (86 mg, 0.12 mmol) and THF (5 mL). To the resulting solution was added BH_3•THF complex (1M, 0.36 mmol) under N_2 at 0 °C. After 10 min, the temperature was raised to rt and stirring was continued for another 2 h. To the resulting solution were added at 0 °C 2 M NaOH (0.3 mL) and H_2O_2 (30%, 0.15 mL). After the evolution of gas ceased, the mixture was quenched with aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2×), the combined organic fractions were dried and concentrated, and the residue was purified by silica gel flash chromatography (elution with hexanes/ethyl acetate 2:1) to yield less polar alcohol **18** (19 mg, 23%) as a colorless oil: $[\alpha]^{20}_D$ −29.1 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3452, 1714, 1224; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (s, 3H), 5.71 (dd, J = 7.5, 4 Hz, 1H), 5.54 (dd, J = 5.5, 2.5 Hz, 1H), 4.21 (t, J = 7.5 Hz, 1H), 4.01 (dd, J = 7.5, 5.5 Hz, 1H), 3.88 (dd, J = 10, 7.5 Hz, 1H), 3.80 (d, J = 10 Hz, 1H), 3.21 (d, J = 9 Hz, 1H), 2.51(s, 15H), 1.69−1.63 (m, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 161.1, 159.2, 158.3, 80.3, 80.1, 74.9, 73.2, 73.0, 71.5, 67.1, 61.9, 47.2, 26.1, 26.0, 25.9, 22.1, 22.0, 21.9, 18.6, 18.5, −4.4, −4.8. −4.9; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3155.

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (19). The hydroboration of olefin **14** also provided a second more polar alcohol **19** (20 mg, 24%) as a pale yellow oil: $[\alpha]^{20}_D$ +3.1 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3448, 1722, 1218; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 3H), 5.73 (dd, J = 7.5, 4 Hz, 1H), 5.44 (s, 1H), 4.21 (t, J = 7.5 Hz, 1H), 4.02 (dd, J = 7.5, 2 Hz, 1H), 3.90−3.85 (m, 2H), 2.53 (d, J = 10 Hz, 1H), 2.51(s, 15H), 1.43 (dd, J = 5.5, 4 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 160.7, 159.8, 158.9, 79.9, 79.7, 75.6, 73.9, 68.9, 68.2, 62.3, 61.6, 47.1, 26.0, 25.9, 21.9, 21.8, 18.2, 18.1, −3.6, −3.8. −4.0, −4.1; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3149.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (20). The hydroboration of olefin **15** (44 mg, 0.07 mmol) provided the less polar alcohol **20** (12 mg, 25%) as a colorless oil: $[\alpha]^{20}_D$ −11.1 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3464, 1736, 1241; ^1H NMR (500

MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.79 (dd, J = 7.5, 2.5 Hz, 1H), 5.68 (s, 1H), 5.59 (dd, J = 7.5, 2.0 Hz, 1H), 5.48 (dd, J = 7.5, 4.0 Hz, 1H), 4.30 (t, J = 7.5 Hz, 1H), 4.22 (dd, J = 7.5, 5.5 Hz, 1H), 4.16 (dd, J = 10, 7.5 Hz, 1H), 3.97 (d, J = 10 Hz, 1H), 2.92 (s, 1H), 2.51 (s, 15H), 1.66 (dt, J = 7.5, 3.5 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 159.9, 159.7, 158.9, 78.7, 78.6, 75.9, 72.4, 71.1, 70.2, 66.2, 63.1, 47.4, 26.0, 25.9, 25.8, 21.6, 21.5, 21.4, 18.2, 18.1, −4.1, −4.2, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3148.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (21). The hydroboration of olefin **15** also provided the more polar alcohol **21** (13 mg, 27%) as a colorless oil: $[\alpha]^{20}_D$ −21.1 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3471, 1722, 1247; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (s, 1H), 5.82 (dd, J = 7.5, 4 Hz, 1H), 5.71 (dd, J = 7.5, 2.5 Hz, 1H), 5.65 (dd, J = 7.5, 2 Hz, 1H), 4.19 (t, J = 7.5 Hz, 1H), 4.06 (dd, J = 7.5, 2 Hz, 1H), 3.95−3.90 (m, 2H), 3.41 (s, 1H), 2.51(s, 15H), 1.57 (t, J = 7.5 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 160.3, 160.2, 81.3, 78.9, 75.8, 73.6, 73.5, 71.9, 63.9, 46.9, 26.0, 25.9, 21.9, 21.8, 21.7, 18.2, 18.1, −4.1, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3151.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*R*,7*R*,8*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (22). The hydroboration of olefin **16** (82 mg, 0.12 mmol) provided the less polar alcohol **22** (20 mg, 24%) as a colorless oil: $[\alpha]^{20}_D$ +9.1 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3460, 1723, 1229; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.73 (s, 1H), 5.62 (s, 1H), 5.45 (s, 2H), 4.32 (dd, J = 7.5, 2 Hz, 1H), 4.26 (dd, J = 7.5, 5.5 Hz, 1H), 3.92 (dd, J = 10, 7.5 Hz, 1H), 3.81 (d, J = 10 Hz, 1H), 2.91 (d, J = 10 Hz, 1H), 2.51 (s, 15H), 1.59 (dt, J = 7.5, 4 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 160.9, 160.8, 159.8, 80.1, 74.9, 74.4, 73.3, 68.8, 65.1, 64.3, 62.1, 47.1, 25.9, 25.8, 25.7, 22.6, 22.5, 22.4, 18.3, 18.2, −4.4, −4.8. −4.9; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3154.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (23). The hydroboration of olefin **16** also provided the more polar alcohol **23** (20 mg, 24%) as a pale yellow oil: $[\alpha]^{20}_D$ +5.3 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3453, 1728, 1239; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.92 (s, 1H), 5.79 (s, 2H), 5.66 (dd, J = 5.5, 2.5 Hz, 1H), 4.30 (dd, J = 7.5, 5.5 Hz, 1H), 4.21 (dd, J = 7.5, 2 Hz, 1H), 3.92−3.88 (m, 2H), 2.78 (d, J = 10 Hz, 1H), 2.51 (s, 15H), 1.58 (t, J = 7.5 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 161.0, 160.9, 80.8, 79.0, 75.9, 74.9, 74.7, 74.3, 63.2, 46.9, 26.0, 25.9, 21.7, 21.6, 21.5, 18.3, 18.2, −3.6, −3.8. −4.0, −4.1; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3153.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*R*,8*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (24). The hydroboration of olefin **17** (40 mg, 0.06 mmol) provided the less polar alcohol **24** (11 mg, 26%) as a colorless oil: $[\alpha]^{20}_D$ +34.9 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3449, 1722, 1221; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.91 (dd, J = 7.5, 2 Hz, 1H), 5.79 (s, 1H), 5.66 (dd, J = 7.5, 2.0 Hz, 1H), 5.57 (dd, J = 7.5, 4.0 Hz, 1H), 4.31 (t, J = 7.5 Hz, 1H), 4.19 (dd, J = 7.5, 5.5 Hz, 1H), 3.98 (dd, J = 10, 7.5 Hz, 1H), 3.89 (d, J = 10 Hz, 1H), 2.59 (s, 1H), 2.51 (s, 15H), 1.65 (dt, J = 7.5, 4 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 161.9, 158.3, 158.2, 79.9, 78.8, 74.7, 74.6, 73.7, 71.3, 62.9, 62.5, 47.2, 26.2, 26.1, 26.0, 21.5, 21.4, 21.3, 18.2, 18.1, −4.1, −4.2, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3155.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-8-(hydroxymethyl)cyclooctane-1,2,3,4,5-pentaacetate (25). The hydroboration of olefin **17** also provided the more polar alcohol **25** (11 mg, 27%) as a colorless oil: $[\alpha]^{20}_D$ +10.6 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3455, 1727, 1218; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.76 (dd, J = 7.5, 4 Hz, 1H), 5.68 (dd, J = 7.5, 2.5 Hz, 1H), 5.55 (dd, J = 5.5, 2 Hz, 1H), 5.39 (dd, J = 7.5, 4 Hz, 1H), 4.32 (dd, J = 7.5, 2 Hz, 1H), 4.21 (t, J = 7.5 Hz, 1H), 3.95−3.89 (m, 2H), 2.70 (s, 1H), 2.51(s, 15H), 1.61 (t, J = 7.5 Hz, 1H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 160.0, 159.9, 159.2, 78.3, 78.2, 75.9, 74.6, 69.3, 68.9, 61.3, 61.1, 46.8, 26.3, 26.2, 26.1, 21.4, 21.3, 21.2, 18.3, 18.2, −4.1, −4.3, −4.4; HRMS exact mass calcd for $C_{31}H_{56}O_{13}Si_2Na^+$ 715.3152, found 715.3156.

(1*R*,2*S*,3*R*,4*R*,5*S*,6*S*,7*S*,8*R*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (26). A 10 mL round-bottomed flask was charged with alcohol **18** (19 mg, 0.027 mmol) and THF (2 mL). The mixture was 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 (76 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** (6 mg, 90%) as a white powder: mp 291−293 °C; $[\alpha]^{20}_D$ −1.3 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3487, 3259, 1121; ^{1}H NMR (500 MHz, D_2O) δ 4.32 (dd, J = 7.5, 2.5 Hz, 1H), 4.28 (s, 1H), 4.12 (dd, J = 7.5, 4.5 Hz, 2H), 3.98 (dd, J = 10, 7.5 Hz, 1H), 3.91 (d, J = 10 Hz, 1H), 3.82 (t, J = 7.5 Hz, 1H), 3.72 (s, 1H), 3.70 (s, 1H), 1.70−1.66 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 78.2, 74.8, 73.5, 70.9, 69.9, 65.1, 64.9, 63.5, 47.8; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0897.

(1*R*,2*S*,3*R*,4*R*,5*S*,6*S*,7*S*,8*S*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (27). The global deprotection of alcohol **19** (20 mg, 0.029 mmol) provided **27** (6 mg, 82%) as white solid: mp 294−295 °C; $[\alpha]^{20}_D$ −1.9 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3491, 3256, 1119; ^{1}H NMR (500 MHz, D_2O) δ 4.09 (dd, J = 7.5, 2 Hz, 2H), 3.98 (s, 2H), 3.92 (s, 1H), 3.89 (s, 1H), 3.85−3.79 (m, 2H), 3.71 (t, J = 7.5 Hz, 2H), 1.59 (dd, J = 6, 4 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 76.0, 72.0, 71.2, 70.9, 70.5, 67.9, 61.0, 60.7, 46.2; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0896.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,8*R*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (28). The global deprotection of alcohol **20** (12 mg, 0.017 mmol) provided **28** (4 mg, 88%) as white a solid: mp 294−296 °C; $[\alpha]^{20}_D$ +16.1 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3468, 3245, 1110; ^{1}H NMR (500 MHz, D_2O) δ 4.42 (dd, J = 7.5, 5.5 Hz, 1H), 4.39 (s, 1H), 4.28 (s, 1H), 4.21 (dd, J = 7.5, 2 Hz, 1H), 4.18 (dd, J = 10, 2.5 Hz, 1H), 4.09 (dd, J = 7.5, 4 Hz, 1H), 3.89 (d, J = 10 Hz, 1H), 3.82 (dd, J = 10, 7.5 Hz, 1H), 3.70 (t, J = 7.5 Hz, 1H), 1.57 (dt, J = 7.5, 4 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 76.5, 75.1, 72.8, 72.4, 71.5, 69.9, 67.1, 63.5, 47.5; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0891.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*,7*R*,8*S*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (29). The global deprotection of alcohol **21** (13 mg, 0.017 mmol) provided **29** (4 mg, 88%) as white a solid: mp 289−290 °C; $[\alpha]^{20}_D$ +4.2 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3493, 3245, 1120; ^{1}H NMR (500 MHz, D_2O) δ 4.19 (dd, J = 7.5, 2 Hz, 1H), 4.10 (s, 1H), 3.85 (dd, J = 7.5, 4 Hz, 2H), 3.73 (dd, J = 7.5, 2.5 Hz, 1H), 3.62−3.55 (m, 2H), 3.32 (t, J = 7.5 Hz, 1H), 1.59 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 77.4, 76.1, 73.9, 71.8, 71.1, 69.8, 68.6, 66.4, 45.5; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0898.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*R*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (30). The global deprotection of alcohol **22** (20 mg, 0.029 mmol) provided **30** (6 mg, 90%) as white a solid: mp 292−295 °C; $[\alpha]^{20}_D$ −33.2 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3488, 3258, 1121; ^{1}H NMR (500 MHz, D_2O) δ 4.26 (s, 3H), 4.21 (s, 1H), 4.04(dd, J = 7.5, 2.5 Hz, 1H), 3.98 (s, 1H), 3.90 (d, J = 10 Hz, 1H), 3.82 (dd, J = 10, 8 Hz, 1H), 3.72 (dd, J = 7.5, 5.5 Hz, 1H), 1.60 (dt, J = 7.5, 4 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 75.1, 73.9, 72.5, 71.9, 68.8, 66.9, 64.3, 64.2, 47.1; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0897.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*S*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (31). The global deprotection of alcohol **23** (20 mg, 0.029 mmol) provided **31** (6 mg, 86%) as white a solid: mp 292−294 °C; $[\alpha]^{20}_{D}$ −2.4 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3477, 3269, 1131; ^{1}H NMR (500 MHz, D_2O) δ 4.39 (s, 1H), 4.30 (s, 1H), 4.09 (dd, J = 7.5, 2.5 Hz, 1H), 3.89 (s, 1H), 3.88 (s, 1H), 3.84−3.78 (m, 2H), 3.72 (dd, J = 5.5, 4 Hz, 2H), 1.59 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 77.5, 76.3, 75.1, 73.2, 71.8, 69.3, 68.1, 66.8, 45.9; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0891.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*S*,7*R*,8*R*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (32). The global deprotection of alcohol **24** (11 mg, 0.016 mmol) provided **32** (3 mg, 78%) as white a solid: mp 295−296 °C; $[\alpha]^{20}_{D}$ −21.7 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3482, 3253, 1129; ^{1}H NMR (500 MHz, D_2O) δ 4.18 (s, 1H), 4.10 (s, 1H), 3.88 (dd, J = 7.5, 2.5 Hz, 2H), 3.67 (dd, J = 7.5, 4.5 Hz, 2H), 3.57 (d, J = 10 Hz, 1H), 3.48 (dd, J = 10, 7.5 Hz, 1H), 3.32 (t, J = 7.5 Hz, 1H), 1.58 (dt, J = 7.5, 4 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 72.4, 71.1, 70.5, 67.8, 66.6, 63.9, 61.5, 47.6; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0893.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*S*,7*R*,8*S*)-8-(Hydroxymethyl)cyclooctane-1,2,3,4,5,6,7-heptaol (33). The global deprotection of alcohol **25** (11 mg, 0.016 mmol) provided **33** (4 mg, 92%) as white a solid: mp 292−293 °C; $[\alpha]^{20}_{D}$ −3.5 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3467, 3229, 1116; ^{1}H NMR 4.19 (dd, J = 7.5, 2 Hz, 2H), 4.11 (s, 1H), 3.89 (dd, J = 5.5, 4 Hz, 2H), 3.82−3.74 (m, 2H), 3.69 (dd, J = 7.5, 2.5 Hz, 1H), 3.58 (dd, J = 7.5, 2.5 Hz, 1H), 3.44 (dd, J = 7.5, 4 Hz, 1H), 3.31 (t, J = 7.5 Hz, 1H), 1.62 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 78.5, 77.2, 76.1, 74.3, 72.8, 68.3, 66.7, 63.3, 47.5; HRMS exact mass calcd for $C_9H_{18}O_8Na^+$ 277.0894, found 277.0891.

Enzyme Reaction. Stock solutions of 4-nitrophenyl-β-D-glucopyranoside (5 mg/mL), β-glucosidase (5 mg/mL), and inhibitor (2 mg/mL) were prepared in 25 mM sodium acetate buffer, pH 5.0. In a 2.5 mL capped vial were added β-glucosidase stock solution (80 μL) and inhibitor stock solution (12.5 μL). The resulting mixture was shaken and mixed with 4-nitrophenyl-β-D-glucopyranoside (80 μL) and the volume brought to 0.5 mL with 25 mM sodium acetate buffer, pH 5.0. The mixture was incubated for 30 min at rt, and 1.5 mL of 0.4 M glycine buffer, pH 10.4, was added. The resulting mixture was shaken, and an aliquot was taken to measure the optical density.

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

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