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Synthesis of Bicyclo[2.2.2]octane-2,3,5,6,7,8 hexols (Bishomoinositols) as Glycosidase Inhibitors

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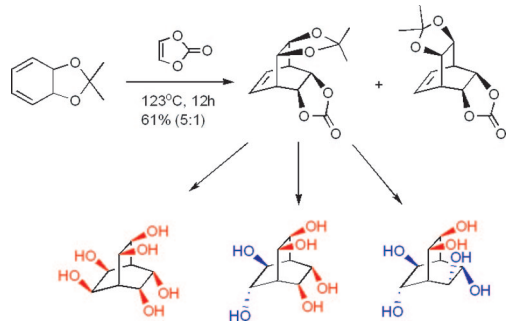

For the construction of the bicyclo[2.2.2]octane skeleton, 2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole was reacted with vinylene carbonate to give two isomeric cycloadditon products having the bicyclo[2.2.2]octane skeleton. Hydrolysis of the ketal ring and the opening of the carbonate functionality, followed by hydroxylation of the remaining double bond resulted in the formation of a symmetrical hexol. Epoxidation of the double bond in the cycloaddition products and the subsequent ring-opening reactions produce two additional hexol derivatives. One of the synthesized molecules exhibited enzyme-specific inhibition against α-glycosidase.

Introduction

Glycosidases and their inhibitors have been the subject of much research in the past decade, much of which has been reviewed. Inhibition of these glycosidases can affect many biological processes.[1] Inhibitors of glycosidases, already used or tested in the treatment of diabetes and HIV infection and as antifungal agents, are expected to arouse increasing interest as therapeutic agents as our understanding of the role of glycosidases in recognition processes improves. Carba-analogues of oligosaccharides (carbasugar) generated by replacing the endocyclic oxygen atom in monosaccharides[2] are thought to be more potent drug candidates than natural sugars, since they are hydrolytically stable.

Recently, several polyhydroxylated bicyclic alkaloids, such as quinolizidine alkaloid **1**, and indolizidine alkaloids castanospermine **2**, and others, have been identified as naturally occurring glycosidase inhibitors in plants and microorganisms.[3] After this discovery, an enormous increase in the synthesis of cyclitol derivatives[4] was observed since these show glycosidase inhibitory properties.[5]

More recently, Buser and Vasella[6] have synthesized a bridged and bicyclic system, the racemic *gluco*-configured norbornane

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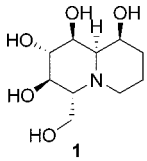

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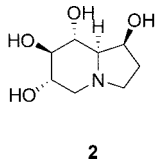

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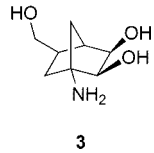
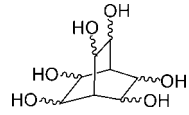


3

3, and tested it as an inhibitor of β-glycosidases. They noticed that the configuration of the hydroxyl group played an important role in inhibitor activity. The different configurated norbornane derivatives show different activity against different glycosidases. In this paper, we were interested in designing a new generation of possible glycosidase inhibitors with the bicyclic structures having the bicyclo[2.2.2]octane skeleton **4**.



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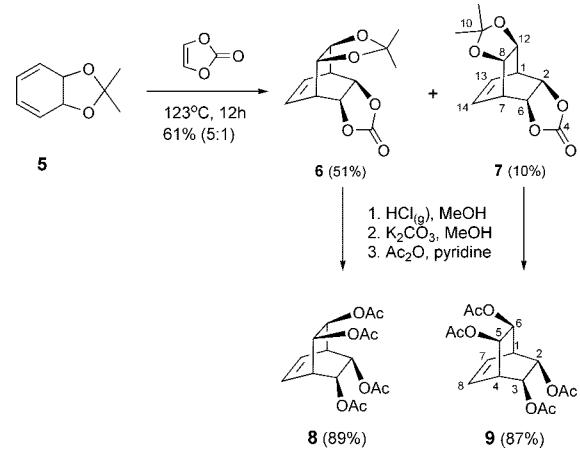
Results and Discussion

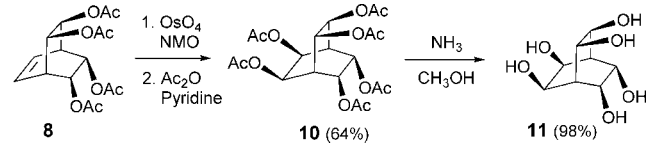
For the construction of the bicyclo[2.2.2]octane skeleton we started from 2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (**5**)[7] and vinylene carbonate. After heating of **5** and vinylene carbonate at 123 °C in a thick-walled sealed tube for 12 h, two cycloaddition products **6** and **7**[8] were isolated in 61% total yield and in a ratio of 5:1 (Scheme 1).[9]

Since the *endo*- and *exo*-faces of the diene **5** are different, the dieonophile can approach the diene unit from alternate sides to form two isomeric cycloaddition products **6** and **7**. The stereochemical course of the cycloadditon may be *syn* or *anti*. The NMR spectroscopic studies did not allow the assignment of the exact configuration of the five-membered rings in **6** and **7**; this was later proven by chemical reactions. Hydrolysis of the ketal ring with HCl and the opening of the carbonate functionality by potassium carbonate in methanol, followed by acetylation in pyridine, resulted in the formation of two isomeric tetraacetates **8** and **9**. These two isomers were easily distinguished by NMR spectral data. The NMR spectrum of **9** was very simple, and consisted of a single methyl signal, whereas

SCHEME 1



SCHEME 2



the isomer **8** displayed two distinct methyl resonances. Furthermore, ^{13}C NMR spectrum of **9** consisted of five carbon resonances. The isomer **8** showed eight resonances. The configurational assignments of **8** and **9** also provided information about the stereochemical course of the cycloaddition reaction. Maleic anhydride approaches mainly the diene unit from the *syn*-face of the diene unit. Gillard and Burnell[10] have studied the cycloaddition of 1,2-substituted cyclohexadienes with *N*-phenylmaleimide and *syn* selectivity was uniformly observed.[11]

In the next step, the double bond in **8** should be hydroxylated to complete the synthesis of the symmetrical hexol **11**. According to the symmetry in the molecule, the hydroxylation reagent can approach **8** from the *endo*- as well as from the *exo*-face. Treatment of **8** with OsO_4/NMO gave only a single isomer that was converted into the hexaacetate **10** (Scheme 2). The ^{1}H NMR spectrum of **10** consisted of three singlets at 5.44, 2.51, and 2.09 arising from the alkoxy, bridgehead, and methyl protons, respectively. The ^{13}C NMR spectrum, having four carbon resonances, also supports the proposed structure. The *anti*-attack to the double bond is favored since acetoxy groups bonded to C2 and C3 are sterically more demanding and block the *syn*-face of the double bond. Removal of the acetate functionalities with ammonia gave the expected hexol **11** in almost quantitative yield (Scheme 2).

The symmetrical cycloaddition product **9** was also submitted to the hydroxylation reaction under the same reaction conditions. No trace of any hydroxylation product such as **13** was isolated since both faces of the double bond in **9** are blocked by the acetoxy groups. In all cases the starting material was recovered unchanged. The attempted epoxidation reaction of **9** with *m*-chloroperbenzoic acid to give **12** also failed (Scheme 3). Since the oxygenation of the double bond in **9** was the major hurdle in the functionalization of the double bond, we decided to brominate the double bond to form the dibromide **14**, followed

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(8) For addition of vinylene carbonatte to cyclohexadiene see: (a) Banwell, M. G.; Coster, M. J.; Edwards, A. J.; Voegtle, M. *Aust. J. Chem.* **2003**, *56*, 577–583. (b) Wright, M. W.; Welker, M. E. *J. Org. Chem.* **1996**, *61*, 133–141.

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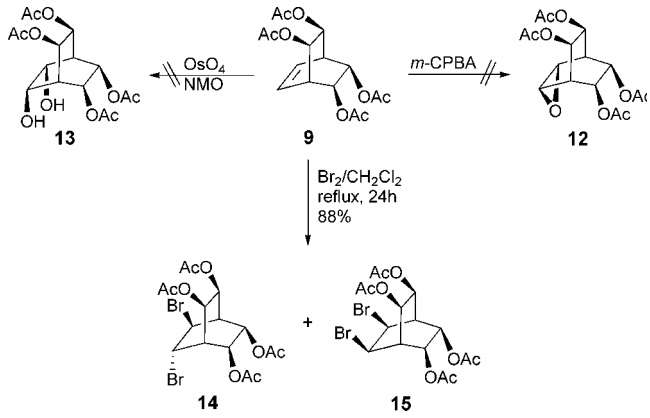
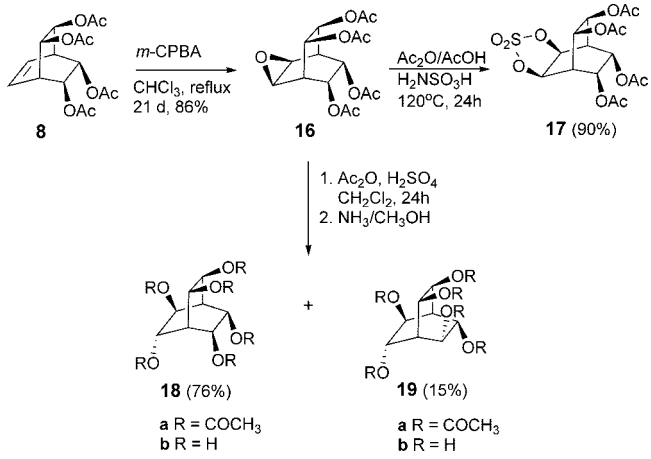
(11) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278.

SCHEME 3



SCHEME 4



by a substitution reaction. Thus, the tetraacetate **9** was treated with bromine in methylene chloride to give a mixture of **14** and **15**. The symmetrical structures were easily distinguished by the NMR spectra. The AB pattern at 5.17 and 4.73 ppm arises from the alkoxy protons and clearly indicates the trans-configuration of the bromine atoms in **14**. The main coupling constant of this AB-system (J = 7.9 Hz) indicates the cis-configuration of the alkoxy protons H_2-H_3 and H_5-H_6. Altough **14** and **15** were readily synthesized, all attempts at converting dibromides to any substitution products were unsuccessful.

For the synthesis of other isomeric hexols with the bicyclo[2.2.2]-octane skeleton, the tetracetate **8** was reacted with *m*-CPBA. The reaction was completed after 21 days by refluxing in chloroform. Only a single isomer **16** was isolated in 86% yield (Scheme 4). The structure was confirmed by NMR-spectral studies. The ring-opening reaction with sulfamic acid[12] in a mixture of acetic acid and acetic anhydride did not form any ring-opening product. Surprisingly, cyclic sulfate **17** was isolated as the single product in 90%.[13] On the other hand, treatment of the epoxide **16** in acidified acetic anhydride resulted in the formation of a mixture of hexaacetates **18a** and **19a**. The structural analyses of these later compounds were nontrivial: extensive NMR experiments such as COSY, HMQC, and HMBC were needed to deduce the structure and the exact configurations of the acetoxy groups. The alkoxy proton

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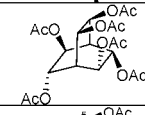
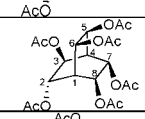
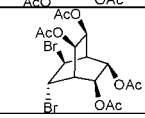
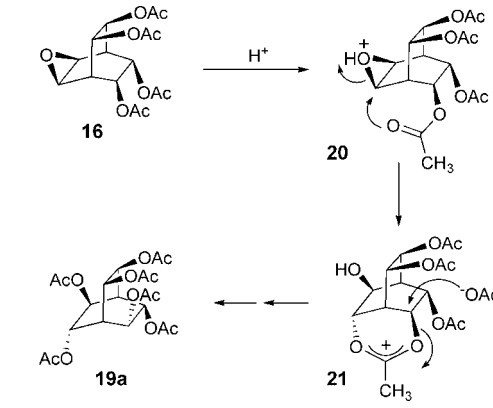
(13) For a similar reaction see: Potekhin, K. A.; Struchkov, Y. T.; Kozmin, A. S.; Zefirov, N. S. *Sulfur Lett.* **1986**, *5*, 51–54.

TABLE 1. The Selected H−H Coupling Constants for Compounds 14, 18a, and 19a

Compound	J_{23}	J_{56}	J_{78}
 **19a**	4.4	8.1	5.6
 **18a**	4.9	8.0	7.8
 **14**	--	7.9	7.9

SCHEME 5



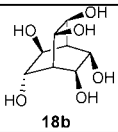
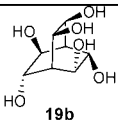
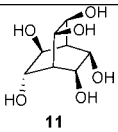
resonances of **18a** and **19a** consist of two distinct AB-systems and one AX-system. The COSY spectra of **18a** and **19a** show the strong correlation between the AB (AX) systems and the bridgehead protons H-1 and H-4, indicating the bicyclo[2.2.2]octane skeleton is preserved during the ring-opening reaction. The main coupling constants (J_{AB} and J_{AX}) in **18a** and **19a** clearly indicate that two pairs of acetoxy groups in **18a** have a cis-configuration and one pair has the trans-configuration. Alternatively in **19a**, two pairs of the acetoxy groups have the trans-configuration (Table 1).

The formation of **18a** is plausible and can be explained by the expected trans-opening of the epoxide ring, whereas the configuration of the other acetates is retained. On the other hand, the configuration of one acetate group in **19a** is changed. The strereocontrolled formation of **19a** can be explained by the neighboring group participation as shown in Scheme 5. The initiaily formed protonated epoxide ring **20** can be attacked by the acetoxy groups attached to the C-7 carbon atom. The formed acetoxonium ion **21** can now undergo a ring-opening reaction through attack by an acetate anion to form the rearranged product **19a**.

In light of these results, we returned to our original plan and submitted these hexaacetates **18a** and **19a** to hydrolysis reaction. Removal of the acetoxy groups by ammonia in methanol resulted in the formation of the target hexols **18b** and **19b**, which were characterized by their NMR spectra.

α-Glycoisdase Inhibition Assay. The inhibitory activities of **11**, **18b**, and **19b** were screened against α-glucosidase. The results are summarized in the Table 2. Only isomer **18b** showed α-glucosidase inhibition and the inhibiton rate was (90 ± 4)% for 10 μM concentration. The other isomers **11** and **19b** did not exhibit inhibition for α-glucosidase. Inhibition assay worked

TABLE 2. Inhibition of α-Glycosidases by 11, 18b, and 19b

Compound	Inhibition [a] (%)	IC_{50} (μM)[d]
 **18b**	90±4[b]	4
 **19b**	NI[c]	—
 **11**	NI[c]	—

[a] Three experiments are performed for all compound and duplicate in each experiment. [b] Inhibition by 10 μM compound. [c] NI: no inhibition. The compound was added in the 5−200 μM range and did not show any inhibition. [d] Concentration required for 50% inhibition of the enzyme activity under the assay conditions.

in 5−200 μM substance concentration also did not show inhibitor activity.

In summary, with relatively little synthetic effort, we have achieved the synthesis of three isomeric bicyclo[2.2.2]octahexols **11**, **18b**, and **19b** using easily available starting materials. One of the synthesized molecules, **18b**, exhibited enzyme-specific inhibition against α-glycosidase.

Experimental Section

Cycloadditon of 1,3-Dioxol-2-one to 2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxole (5). Vinylene carbonate (11.32 g, 131.6 mmol) and isopropylidene-ketal (5.0 g, 32.9 mmol) were mixed in a sealed tube of 50 mL volume having a wall thickness of 3 mm. The sealed tube was heated at a temperature of 123 °C and kept there for 12 h (**Warning**: since the reaction presumably proceeds under pressure, it is desired to put a safety glass to the front of the reaction vessel.) The cycloaddition reaction was carried out in a thick-walled sealed tube presumably under pressure. Unreacted vinylene carbonate was distilled. The residue consisting of a mixture of **6** and **7** was separated on 25 g of silica gel with use of *n*-hexane/EtOAc (2:1) as eluent to give the minor product **7** as the first fraction (R_f 0.71). The major product **6** was isolated as the second fraction (R_f 0.53).

1*R*(*S*),2S(*R*),6*R*(*S*),72*S*(*R*),82*S*(*R*),12*S*(*R*)-10,10-Dimethyl-3,5,9,11-tetraoxabicyclo[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-en-4-one (7). Yield 0.8 g (3.36 mmol, 10%), colorless crystalls from hexane/ethyl acetate (2:1), mp 209−212 °C (lit.[8] mp 205−207 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (quasi-t, 2H), 4.58 (s, 2H), 4.13 (s, 2H), 3.4 (br s, 2H), 1.28 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 128.4, 110.2, 74.5, 74.1, 38.9, 25.1, 24.7; IR (KBr, cm^{-1}) 2988, 2922, 1951, 1835, 1783, 1451, 1432, 1394, 1379, 1370, 1268, 1211, 1165, 1043, 977, 912, 828. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.40; H, 5.85.

1*R*(*S*),2*S*(*R*),6*R*(*S*),72*S*(*R*),8*R*(*S*),12*R*(*S*)-10,10-Dimethyl-3,5,9,11-tetraoxabicyclo[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-en-4-one (6). Yield 4.0 g (16, 8 mmol, 51% (based on isopropylidene-ketal), colorless needless from hexane/ethyl acetate (2:1), mp 169−171 °C (lit. mp 167−169 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (quasi-t, 2H), 5.16 (s, 2H), 4.21 (s, 2H), 3.46 (br s, 2H), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 130.6, 112.3, 74.4, 73.8, 38.6, 25.9, 23.3; IR (KBr, cm^{-1}) 3053, 2968, 2097, 1795, 1458, 1390, 1372, 1308, 1267, 1220, 1176, 1103, 1076, 1052, 969, 875, 836. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H,5.92. Found: C, 60.35; H, 5.99.

1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*),5*R*(*S*),6*S*(*R*)-Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetraacetate (8). A stirred solution of **6** (1.5 g, 6.30 mmol) in 100 mL of methanol was cooled to 0 °C. At the given temperature HCl gas was passed throug the solution over 2 h. The reaction flask was closed with a stoper and stirred at room temperature for an additional hour. After removal of the solvent under reduced pressure (30 °C, 25 mmHg), the residue (without any purification) was dissolved in 100 mL of MeOH:H_2O (20:1) and 1.88 g (12 mmol) of K_2CO_3 was added. The resulting mixture was magnetically stirred at room temperature for 12 h. The mixture was neutralized with AcOH and the solvent was removed. To the residue were added Ac_2O (7.35 g, 72 mmol) and 10 mL pyridine. The mixture was stirred at room temperature for 6 h, then cooled to 0 °C. After addition of 70 mL of 10% HCl solution, the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 × 10 mL) and then dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded tetraacetate **8** (1.9 g, 5.59 mmol, 89%). Recrystallization from hexane−ethyl acetate gave colorless crystalls: mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (quasi-t, 2H), 5.47 (br s, 2H), 4.80 (br s, 2H), 3.10 (br s, 2H), 2.08 (s, 6H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.7, 130.6, 67.2, 64.9, 39.5, 20.6, 20.56, 20.51; IR (KBr, cm^{-1}) 2968, 1737, 1436, 1436, 1390, 1252, 1233, 1196, 1055, 1043, 923, 905. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.29; H, 5.85.

1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*),5*S*(*R*),6*R*(*S*)-Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetraacetate (9). A solution of **7** (1g, 4.20 mmol) in 100 mL of methanol was hydrolyzed and then acetylated as described above. The tetraacetate **9** (1.24 g, 3.64 mmol) was isolated in 87% of yield as colorless crystalls from hexane/ethyl acetate: mp 121−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (quasi-s, 2H), 5.03 (s, 4H), 3.05 (br s, 2H), 1.94 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 129.69, 68.1, 39.4, 20.4; IR (KBr, cm^{-1}) 2965, 1750, 1437, 1376, 1236, 1195, 1087, 1055, 1028, 929, 898, 877. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.25; H, 6.02.

2*S*(*R*),3*R*(*S*),5*R*(*S*),6*S*(*R*),7*S*(*R*),8*R*(*S*)-3,5,6,7,8-Penta(acetyloxy)-[2.2.2]oct-2-yl Acetate (10). To a solution of NMO (0.52 g, 4.48 mmol) in 10 mL of H_2O/acetone (1:1) was added tetraacetate **4** (1,5 g (4.41 mmol) under N_2 atmosphere. To this solution was added 19.0 mg (0.075 mmol) of OsO_4. The resulting mixture was stirred under nitrogen at room temperature for 72 h. The solvent was removed under reduced pressure (25 mmHg, 70 °C). Without further purification, the crude product was submitted to acetylation. For this purpose, pyridine (5 mL) and acetic anhydride (7.5 mL) were added to the residue. The reaction mixture was stirred at room temperature for 24 h and methylene chloride was added (200 mL). The organic phase was extracted with saturated bicarbonate and dried (Na_2SO_4). Removal of the solvent gave hexaacetate **10** as a colorless solid. Recrystallization from hexane/ethyl acetate furnished 1.28 g (2.79 mmol) of hexaacetate in 64% yield as colorless crystalls: mp 171−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (br s, 6H), 2.51 (br s, 2H), 2.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 64.0, 39.8, 20.5; IR (KBr, cm^{-1}) 3005, 2954, 2937, 1748, 1438, 1378, 1367, 1328, 1220, 1112, 1048, 986, 909, 889. Anal. Calcd for $C_{20}H_{16}O_{12}$: C, 52.40; H, 5.72. Found: C, 52.25; H, 5.36.

2*S*(*R*),3*R*(*S*),5*R*(*S*),6*S*(*R*),7*S*(*R*),8*R*(*S*)-Bicyclo[2.2.2]octane-2,3,5,6,7,8-hexol (11). A stirred solution of **10** (1 g, 2.23 mmol) in 20 mL of methanol was cooled to 0 °C. At the given temperature, NH_3 gas was passed through the solution over 3 h. The reaction flask was closed with a stopper and stirred at room temperature for 2 h. Removal of the solvent and acetamide, under reduced pressure (30 °C, 25 mmHg), gave (0.44 g, 2.13 mmol) hexol **11** in 98% yield as colorless crystals: mp 250−253 °C; ^{1}H NMR (400 MHz, D_2O) δ 4.70 (br s, 6H), 4.23 (br s, 6H)

2.25 (br s, 2H); ^{13}C NMR (100 MHz, D_2O) δ 63.4, 45.8; IR (KBr, cm^{-1}) 3468, 3305, 2922, 1651, 1405, 1283, 1094, 1082, 1048, 981, 881. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.33; H, 6.60.

Bromination of the Tetraacetate 9. To a solution of the symmetrical tetraacetate **9** (0.75 g, 2.21 mmol) in 75 mL of dry dichloromethane was added dropwise a solution of bromine (0.5 g, 2.78 mmol) in 50 mL of dry dichloromethane (50 mL) at room temperature over a period of 1 h. After bromine addition was completed, the mixture was refluxed under stirring for 24 h. Evoparation of the solvent under reduced pressure gave a mixture of the dibromides **14** and **15** (1.10 g, quantitative). The residue was chromatographed over silica gel hexane/ethyl acetate. As the first fraction, the trans-addition product **14** was isolated (770 mg, 70%) followed by the cis-addition product **15** (153 mg, 14%).

2*S*(*R*),3*R*(*S*),5*S*(*R*),6*R*(*S*),7*S*(*R*),8*S*(*R*)3,5,6-Tris(acetyloxy)-7,8-dibromobicyclo[2.2.2]oct-2-yl Acetate (14). Mp 214−216 °C from dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (dd, A-part of AB-system, J = 7.9 and 4.2 Hz, 2H, H_3 and H_6), 4.73 (dd, B-part of AB-system, J = 7.9 and 1.5 Hz, 2H, H_2 and H_5), 4.61 (s, 2H, H_7 and H_8), 2.83 (br d, J = 2.9 Hz, 2H, H_1 and H_4), 2.04 (s, 6H, $-CH_3$), 2.03 (s, 6H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.53, 169.50, 67.2, 65.1, 47.0, 43.3, 21.0, 20.2; IR (KBr, cm^{-1}) 2972, 2945, 1748, 1434, 1378, 1295, 1237, 1098, 1070, 1041, 987, 933, 899, 819, 669. Anal. Calcd for $C_{16}H_{20}O_8Br_2$: C, 38.42; H, 4.03. Found: C, 38.08; H, 3.80.

2*S*(*R*),3*R*(*S*),5*S*(*R*),6*R*(*S*),7*S*(*R*),8*R*(*S*)3,5,6-Tris(acetyloxy)-7,8-dibromobicyclo[2.2.2]oct-2-yl Acetate (15). Mp 216−218 °C from hexane/ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (br s, 2H), 5.05 (br s, 2H), 4.85 (br s, 2H), 2.83 (br s, 2H, H_1 and H_4), 2.13 (s, 6H, $-CH_3$), 2.09 (s, 6H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.3, 67.01, 64.8, 42.3, 41.8, 21.1, 20.7; IR (KBr, cm^{-1}) 3044, 3002, 1759, 1435, 1376, 1231, 1192,1043, 907, 842. Anal. Calcd: C, 38.42; H, 4.03. Found: C, 38.50; H, 4.02.

2*S*(*R*),4*R*(*S*),6*R*(*S*),7*S*(*R*),8*S*(*R*),9*R*(*S*)-7,8,9-Tris(acetyloxy)-3-oxatricyclo[3.2.2.0^{2,4}]non-6-yl Acetate (16). Tetraacetate **8** (1.0 g, 2.94 mmol) was dissolved in 100 mL of chloroform and *m*-CPBA (1.50 g, 6 mmol, 70%) was added then the reaction was stirred at reflux temperature for 3 weeks (every 2−3 days, small portions (100 mg) of *m*-CPBA were added). The progress of the reaction was monitored by thin layer chromotography. After completion of the reaction, 50 mL of 20% $NaHSO_3$ was added, and the reaction mixture was stirred for 10 min. After addition of 50 mL of water, the aqueous solution was extracted with chloroform. The organic phase was extracted with aqueous $NaCO_3$ and then with water and dried ($MgSO_4$). Evaporation of solvent under reduced pressure and recrystallization of product from ethyl acetate gave epoxide **16** (0.9 g, 2.64 mmol) in 86% yield as colorless crystals: mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (br s, 2H), 5.06 (br s, 2H), 3.47 (m, 2H), 2.85 (br s, 2H, H_2), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.3, 65.8, 65.5, 47.5, 37.8, 20.5; IR (KBr, cm^{-1}) 3004, 1753, 1431, 1375, 1252, 1200, 1227, 1186, 1043, 982, 905. Anal. Calcd for $C_{16}H_{16}O_9$: C, 53.93; H, 5.66. Found: C, 53.74; H, 5.60.

The Synthesis of Cyclic Sulfate 17. To a stirred suspension of epoxide (0.8 g, 2.25 mmol) in Ac_2O/AcOH (3/3 mL) was added 230 g (2.37 mmol) of sulfamic acid at room temperature. The mixture was warmed to 120 °C and stirred for 24 h. The mixture was poured into water (100 mL) and dichloromethane (100 mL) was added. The organic phase was washed with water (2 × 100 mL) and saturated $NaHCO_3$ (2 × 50 mL). The dichloromethane layer was dried ($MgSO_4$). Evaporation of the dried extract gave solid sulfolene **17** (0.88 g, 90%): mp 210−213 °C from ethyl acetate/hexane (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (br s, 1H, H_1), 5.41 (br s, 1H), 5.29 (br s, 1H), 2.87 (br s, 1H), 2.10 (s, $-CH_3$, 6H), 2.09 (s, $-CH_3$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.99, 168.95, 74.8, 63.0, 62.5, 38.4, 20.4, 20.3; IR (KBr, cm^{-1}) 3009, 1751, 11649, 1393, 1322, 1210, 1118, 1048, 987, 925, 908, 867, 836, 717. Anal. Calcd for $C_{16}H_{20}SO_{12}$: C, 44.04; H, 4.62; S, 7.35. Found: C,44.30; H,4.83; S, 7.41.

Ring-Opening Reaction of the Epoxide 16. Epoxide **16** (1.0 g, 2.81 mmol) was dissolved in 50 mL of dichloromethane. After addition of 3 mL of Ac_2O and two drops of H_2SO_4, the reaction was stirred at room temperature for 24 h. Then the mixture was washed with aqueous Na_2CO_3 solution. The organic phase was dried ($MgSO_4$) and solvent was evaporated. The residue was submitted to silica gel (30 g) column chromatography eluting with hexane/ethyl acetate (3:1). As the first fraction, the hexaacetate **18a** was isolated in 76% yield (980 mg, 2.14 mmol). Recrystallization from hexane/ethyl acetate gave colorless crystals: mp 139−142 °C.

2*S*(*R*),3*S*(*R*),5*S*(*R*),6*R*(*S*),7*S*(*R*),8*R*(*S*)-3,5,6,7,8-Penta(acetyloxy)-[2.2.2]oct-2-yl Acetate (18a). ^{1}H NMR (400 MHz, benzene-*d*6) δ 5.81 (dd, J = 4.9 and 2.5 Hz, A-part of AX-system, H-3), 5.80 (dd, A-part of AB-system, J = 7.8 and 3.2 Hz, H-7), 5.72 (dd, B-part of AB-system, J = 7.8 and 2.4 Hz, H-8), 5.51 (dd, A-part of AB-system, J = 8.0 and 2.3 Hz, H-5), 5.43 (dd, B-part of AB-system, J = 8.0 and 4.2 Hz, H-6), 5.80 (br d, X-part of AX-system, J = 4.9 Hz, H-3), 3.00 (m, H-1), 2.65 (m, H-4), 1.84 (s, $-CH_3$), 1.80 (s, $-CH_3$), 1.74 (s, $-CH_3$), 1.73 (s, $-CH_3$), 1.67 (s, $-CH_3$), 1.62 (s, $-CH_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 169.4, 169.3 169.0, 168.9, 168.7, 168.6, 72.1 (C-2), 69.8 (C-3), 65.8 (C-6), 64.8 (C-8), 64.4 (C-7), 63.8 (C-5), 41.3 (C-4), 39.4 (C-1), 20.2, 20.1 (2C), 19.8, 19.6, 19.4; IR (KBr, cm^{-1}) 3001, 1746, 1434, 1371, 1227, 1031, 971, 913, 652,593. Anal. Calcd for $C_{20}H_{26}O_{12}$: C, 52.40; H, 5.72. Found: C, 52.25; H, 5.56.

The second fraction was characterized as **2*S*(*R*),3*S*(*R*),5*S*(*R*),6*R*(*S*),7*R*(*S*),8*R*(*S*)-3,5,6,7,8-penta(acetyloxy)[2.2.2]oct-2-yl acetate** (**19a**): 0.2 g (0.44 mmol, 15%) from hexane/ethyl acetate, mp 153−156 °C; ^{1}H NMR (400 MHz, benzene-d_6) δ 5.39 (dd, A-part of AB-system, J = 5.6 and 2.2 Hz, H-8), 5.25 (bd, J = 5.6 Hz, B-part of AB-system, H-7), 5.19 (dd, A-part of AX-system, J = 4.4 and 2.4 Hz, H-3), 5.14 (bdd, A-part of AB-system, J = 8.1 and 3.6 Hz, H-6), 5.508 (dd, B-part of AB-system, J = 8.1 and 1.8 Hz, H-5), 4.83 (dd, X-part of AX-system, J = 4.4 and 2.2 Hz, H-2), 2.61 (m, H-1), 2.26 (m, H-4), 2.06 (s, $-CH_3$), 2.057 (s, 2 × $-CH_3$), 2.01 (s, $-CH_3$), 2.00 (s, $-CH_3$), 1.96 (s, $-CH_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 170.2, 169.9 (2C), 169.86, 169.8, 169.4, 71.7 (C-2), 70.3 (C-7), 69.8 (C-8), 69.75 (C-3), 65.0 (C-6), 64.5 (C-5), 42.2 (C-4), 2.61 (C-1), 21.0, 20.9, 20.98, 20.0, 20.7, 20.4. 3001, 1748, 1435, 1371, 1246, 1099, 1031, 970, 912, 865, 698. Anal. Calcd for $C_{20}H_{26}O_{12}$: C, 52.40; H, 5.72. Found: C, 52.02; H, 5.55.

2*S*(*R*),3*S*(*R*),5*S*(*R*),6*R*(*S*),7*S*(*R*),8*R*(*S*)-Bicyclo[2.2.2]octane-2,3,5,6,7,8-hexol (18b). A stirred solution of **18a** (1 g, 2.23 mmol) in 20 mL of methanol was cooled to 0 °C. At the given temperature, NH_3 gas was passed through the solution over 3 h. The reaction flask was closed with a stopper and stirred at room temperature for 2 h. Removal of the solvent and acetamide, under reduced pressure (30 °C, 25 mmHg), gave (0.44 g, 2.13 mmol) hexol **18b** in 98% yield as colorless crystalls: mp ≥300 °C; ^{1}H NMR (400 MHz, D_2O) δ 4.30 (m, 1H), 4.21 (br d, J = 7.4 Hz, 1H), 4.12 (br d, J = 3.2 Hz, 1H), 4.02 (br s, 2H), 3.50 (br d, J = 4.7 Hz, 1H), 2.44 (br s, 1H, 1.95 (br s, 1H); ^{13}C NMR (100 MHz, D_2O) 74.8, 70.6, 65.7, 64.7, 62.9, 62.8, 48.2, 45.3; IR (KBr, cm^{-1}) 3468, 3305, 2922, 1651, 1405, 1283, 1094, 1082, 1048, 981, 881. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.33; H, 7.12.

2*S*(*R*),3*S*(*R*),5*S*(*R*),6*R*(*S*),7*RS*(*S*),8*R*(*S*)-Bicyclo[2.2.2]octane-2,3,5,6,7,8-hexol (19b). Hydrolysis of **19a** (0.8 g, 1.75 mmol) was carried out as described above to give 0.36 g (quantitative) of **19b** as colorless crystals: mp 276−279 °C; ^{1}H NMR (400 MHz, D_2O) δ 4.7 (br s, −OH), 4.22 (m, 2H), 4.05 (br d, J = 7.5 Hz, 1H), 3.87 (m, 2H), 3.53 (d, J = 4.2 Hz, 1H), 2.20 (m, 1H), 1.91 (br s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 72.8, 72.5, 70.7, 70.3, 66.4, 63.2, 49.8, 47.8; IR (KBr, cm^{-1}) 3348, 2939, 2480, 1412, 1348, 1262,

1201, 1103, 910, 861, 711. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84; O, 46.56. Found: C, 46.82; H, 6.61.

α-Glucosidase Inhibition Assay. Enzyme assay was performed for three compounds **11**, **18b**, and **19b**. The reaction mixture containing 0.85 mM PNPG (*p*-nitrophenyl α-D-glycopyranoside), phosphate buffer (pH 6.8), and 10 μM of the corresponding isomers was incubated at 37 °C for 5 min then 0.075 unit of α-glucosidase (Sigma) was added and the resulting mixture was incubated at 37 °C for 30 min, then and reaction was stopped with 2 mL of 100 mM Na_2CO_3 and the absorbance at 400 nm of the liberated *p*-nitrophenol was measured.

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

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