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Stereoselective Synthesis of Bishomo-inositols as Glycosidase Inhibitors

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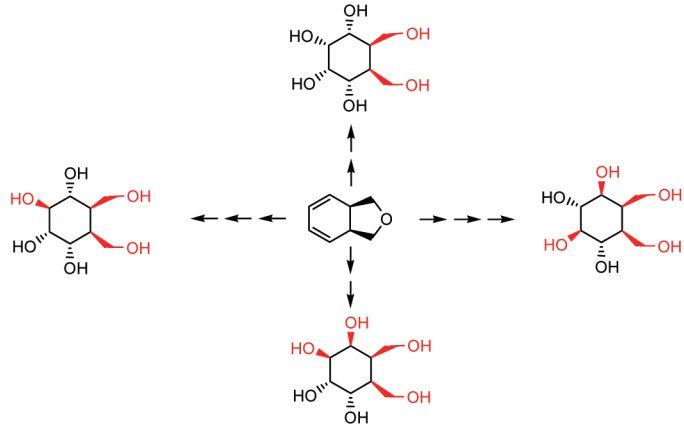
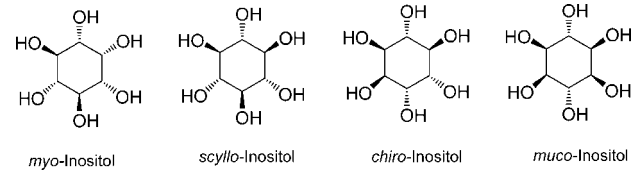


For the synthesis of various bishomo-inositol derivatives, 1,3,3a,7a-tetrahydro-2-benzofuran was used as the key compound. For further functionalization of the diene unit, the diene was subjected to photooxygenation, epoxidation, and *cis*-hydroxylation reactions. The endoperoxide linkage was cleaved by thiourea. The remaining double bond was subjected to epoxidation and *cis*-hydroxylation reactions. The epoxide rings and tetrahydrofuran rings formed were opened by acid-catalyzed reaction with sulfamic acid. The combination of these reactions resulted in the formation of various new inositol derivatives such as bishomo-*chiro*-inositol, bishomo-*myo*-inositol, and two isomeric bishomo-*allo*-inositols.

Introduction

Inositols (cyclohexanehexols) are sugar-like molecules. There are nine stereoisomers, all of which may be referred to as inositol.[1] The most prominent naturally occurring form is *myo*-inositol, *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol, and it is actively involved in cellular events and processes. Other naturally occurring isomers are *scyllo*-, *chiro*-, *muco*-, and *neo*-inositol. It is assumed that these isomers may be made from *myo*-inositol by inversion of the configuration (epimerization) of one or two hydroxyl groups.[5] Inositol 1,4,5-trisphosphate is a second messenger molecule used in signal transduction in biological cells. Since the discovery that *myo*-inositol 1,4,5-triphosphate acts as a Ca^{2+}-mobilizing intracellular second messenger, many other inositol phosphates have been discovered, although it is only in recent years that their physiological functions have begun to be understood.[2−4]



New synthetic methodologies for various inositols and their derivatives have been developed.[6] Motivated by the medical value of certain cyclitol derivatives, we formulated a general

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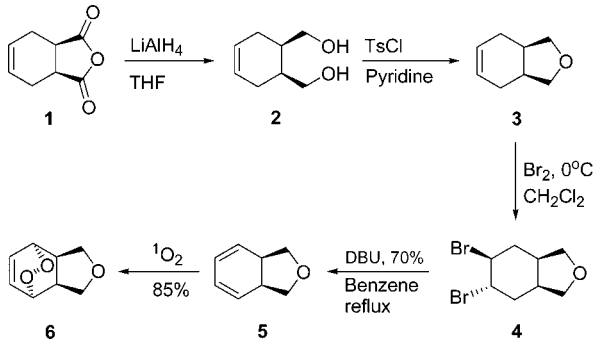
SCHEME 1



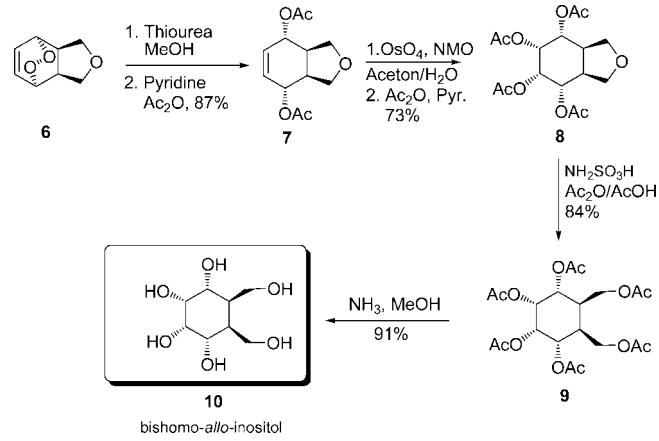
strategy of synthesis based on the photooxygenation of the appropriate dienes.[7] Our aim in the present work was to design a synthesis of an analogue of this molecule, bishomo-inositols, using simple starting materials.

Results and Discussion

The synthesis of the key compound **5**[8] used in the synthesis of bishomo-inositols began with readily available anhydride **1** and was followed by the sequence of steps outlined in Scheme 1. Treatment of the anhydride **1**,[9] obtained by the addition of maleic anhydride to in situ generated butadiene, with $LiAlH_4$ yielded the diol **2**.[10] The diol **2** was successfully converted to the desired tetrahydrofuran derivative **3** by treatment of **2** with tosyl chloride in pyridine.[11] The resulting compound **3** was brominated at low temperature to give only the *trans*-dibromo compound **4** in high yield. Hydrogen bromide elimination with 1,8-biazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at 0 °C gave the diene **5**.

Photooxygenation of **5** in methylene chloride (500 W, projection lamp) at room temperature using tetraphenylporphyrin as the sensitizer afforded the bicyclic endoperoxide **6** in a yield of 85%. The ^1H and ^{13}C NMR spectra reveal the formation of only one isomer. The four-line ^{13}C NMR spectrum is in good agreement with the structure **6**, which possesses a symmetry element. The diene unit in **5** is dissymmetric[12] and can be attacked from both sides of the diene. It is well established that

SCHEME 2



the substituents play an important role in determining the direction of the addition. We assume that the repulsive interaction[13] between the nonbonded electron pairs on the heteroatoms present in the tetrahydrofuran ring and on the singlet oxygen molecule is responsible for the exclusively *anti* addition.[14]

After successful isolation and characterization of the endoperoxide **6**, we turned our attention to the reduction of the peroxide linkage in **6**. Selective reduction of the peroxide linkage with thiourea under very mild conditions followed by acetylation in pyridine afforded the diacetate **7** in 87% yield. Since only the oxygen−oxygen bond breaks in this reaction, it preserves the configuration at all carbon atoms. For further functionalization of the double bond, diacetate **7** was submitted to a *cis*-hydroxylation reaction with OsO_4−NMO[15] followed by acetylation to give the tetraacetate **8**. The spectral data confirmed the formation of a single isomer. The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to the tetrahydrofuran ring. NMR spectroscopic studies did not allow the assignment of the configuration of the acetate groups. The exact configuration of this tetraacetate **8** was later proven by comparison of the spectral data of the tetraacetate **8** with those obtained by *cis*-hydroxylation of the diene **5** with OsO_4 (see Scheme 4). We assume that the molecule **7** prefers mainly the boat conformation in which the acetate groups are located in the pseudoequatorial positions. *syn*-Face attack of OsO_4 is hindered by axial hydrogens as well as by the tetrahydrofuran ring. Similar results have been observed recently by our research group.[16]

Sulfamic acid[17] was used as an efficient catalyst in acetic anhydride to promote the acetolysis reaction of the tetrahydrofuran ring in **8** to produce the hexaacetate **9** in 84% yield (Scheme 2). In particular, the ^{13}C NMR spectrum consisting of 10 resonance signals was in agreement with the proposed

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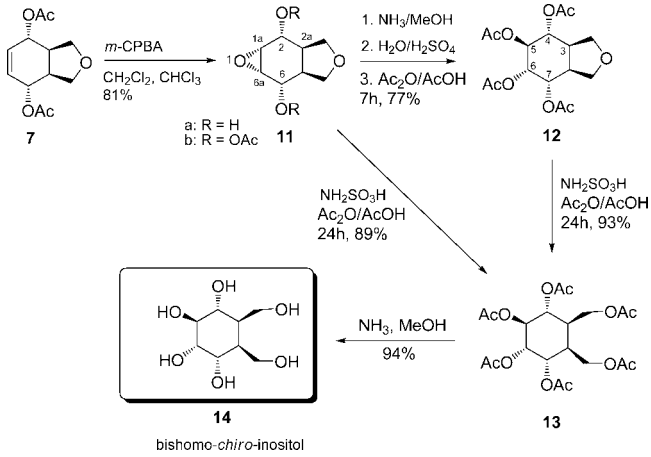
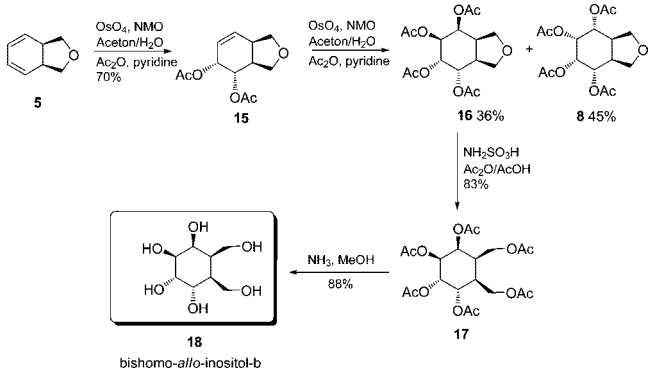
SCHEME 3



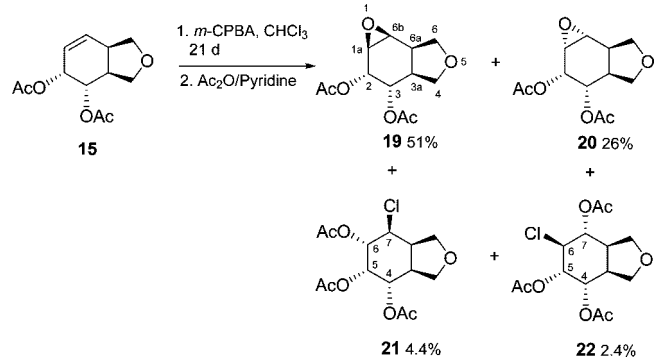
SCHEME 4



structure. Deacetylation of **9** with ammonia was carried out in methanol to give the free hexol, bishomo-*allo*-inositol **10**, in 91% yield.

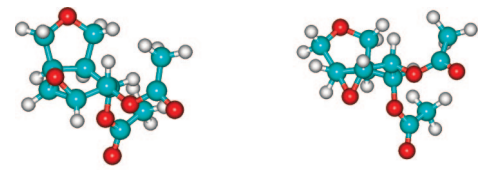
For the synthesis of other isomeric bishomo-inositol derivatives, the diacetate **7** was reacted with *m*-CPBA to give **11b** as the sole isomer (Scheme 3). The exact configuration of the epoxide was confirmed by ^{1}H NMR spectroscopy. The most conspicuous feature in the ^{1}H NMR spectrum is the sharp singlet arising from the epoxide proton-resonances at 3.43 ppm. Geometry optimization calculations (AM1) for the *syn*- and *anti*-epoxides with respect to the tetrahydrofuran ring show dihedral angles of 128° and 82° for $H_{1a}-H_2$. The 82° angle in **11b** is consistent with our assignments. Furthermore, a similar result (*anti*hydroxylation) was obtained by OsO_4 reaction (Scheme 2). Epoxy diacetate **11b** was subjected to an acid-catalyzed ring-opening reaction in the presence of acetic anhydride. Treatment of **11b** with sulfuric acid for 7 h followed by acetylation gave only the tetraacetate **12**. However, the sulfamic acid catalyzed reaction of **11b** in acetic acid in the presence of acetic anhydride for 24 h resulted in the opening of the epoxide ring as well as the tetrahydrofuran ring to afford **13**. To determine the exact configuration of **12**, first we made full assignments for the acetoxy protons with the help of the COSY spectrum. The acetoxy proton H_4 in **12** resonates as a triplet with a coupling constant of $J = 9.8$ Hz, clearly indicating that the neighboring protons H_3 and H_5 are in *trans* positions. The fact that the proton H_5 appears as a doublet of doublets with coupling constants of $J = 9.8$ and 9.3 Hz also support the *trans* relation of the protons H_5 and H_6. The resonance signal of H_6 appears as a doublet of doublets with coupling constants of $J = 9.3$ and 3.2 Hz, which clearly supports the *cis* relation of the protons H_6 and H_7. On

SCHEME 5



the basis of these findings we assigned a *trans-trans-cis* relation to the acetate groups in **12**. These configurational assignments show that the epoxide ring in **11b** undergoes a normal *trans* ring-opening reaction. It is surprising to note that the neighboring acetoxy groups are not involved (no anchimeric assistance) in the ring-opening reaction. This can be attributed to the *cis* configuration of the acetoxy groups with respect to the epoxide ring. To support these observations chemically, acetate groups were removed by treatment of **11b** with ammonia in methanol to give **11a**. Acid-catalyzed ring opening of **11a** followed by acetylation afforded **12** that was identical to the compound obtained from the ring-opening reaction of epoxy diacetate **11b** described above. Noninvolvement of the acetates in the ring-opening reaction was further proven. Deacetylation of **13** with ammonia gave hexol, bishomo-*chiro*-inositol **14**, in 94%. The asymmetry in the molecule was in complete in agreement with the spectroscopic data.

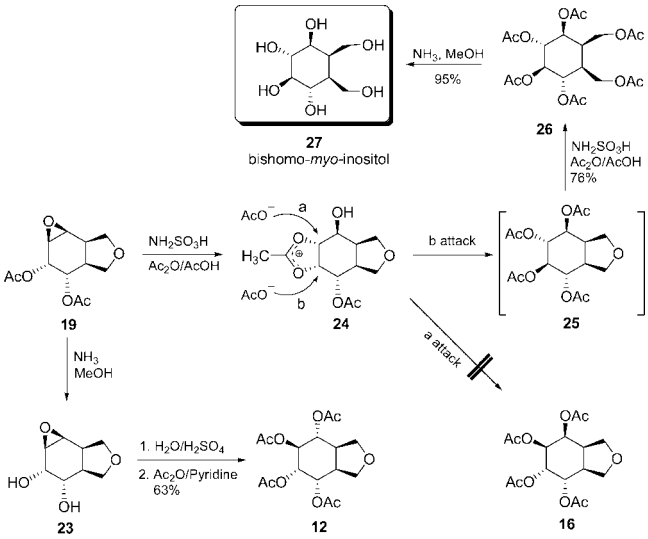
The diene **5** is an ideal substrate for the synthesis of further bishomo-inositol derivatives. For that reason, one of the double bonds of diene **5** was *cis*-hydroxylated with OsO_4-NMO oxidation (Scheme 4). After acetylation of the reaction mixture, only a single isomer **15** was isolated in 70% yield. The NMR spectroscopic studies did not reveal the exact configuration of the acetate groups in **15**, which was later proven by chemical reactions (see Scheme 6). Further reaction of diacetate **15** with an additional 1 mol of OsO_4 followed by acetylation with acetic anhydride in pyridine resulted in the formation of two easily separable tetraacetates (one with symmetrical configuration and the other unsymmetrical configuration) **8** and **16**. The spectral data of the symmetrical tetraacetate was in complete agreement with **8**, which was obtained by *cis*-hydroxylation of **7** followed by acetylation (see Scheme 2). The formation of the tetraacetate **8** from this reaction also establishes the exact configuration of **15**. For the formation of this symmetrical tetraacetate **8**, where all acetoxy groups are in *cis*-position, the acetate groups in **15** must be in *anti* position with respect to the tetrahydrofuran ring. Thus, the formed tetraacetate **16** was converted to the hexaacetate **17**. Hexol **18** itself was readily and almost quantitatively obtained by ammonolysis of the hexaacetate **17** in methanol.



19 **20**

FIGURE 1. AM1 optimized geometries for isomers **19** and **20**.

SCHEME 6

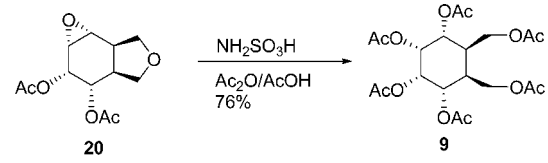


For the synthesis of further bishomo-inositols, the diacetate **15** was reacted with *m*-CPBA to give two isomers **19** and **20** in 51% and 26% yields in addition to the epoxide-opening products **21** and **22**. The structures of **19** and **20** were assigned on the basis of ^{1}H NMR spectra. The most conspicuous features in the ^{1}H NMR spectra of these epoxides **19** and **20** are the epoxide proton resonances. The epoxide protons (H_{1a} and H_{6b}) of **19** resonating at δ 3.39 (J = 3.6 Hz) and 3.26 (J = 3.6 Hz) as triplets show further splitting with adjacent protons. However, the epoxide protons of **20** appear at δ 3.44 (J = 3.6 Hz) and 3.16 (d, J = 3.6) as a triplet and a doublet, respectively. There is no coupling between the epoxide protons H_{6b} and H_{6a} in **20**. Geometry optimization calculations (AM1) on the molecules **19** and **20** show a dihedral angle of 15° for $H_{6b}-H_{6a}$ in **19** and 78° for $H_{6b}-H_{6a}$ in **20**, which are consistent with our assignments.

The positions of chlorine atoms in **21** and **22** were determined with the help of the COSY spectra. The exact configuration of the substituents was established by measuring the corresponding coupling constants between the relevant protons. The acetoxy proton H-5 in **21** resonates as a triplet with a coupling constant of J = 2.6 Hz, indicating the *cis* configuration of the neighboring protons H-4 and H-6. Furthermore, the large coupling between the protons H-6 and H-7 ($J_{6,7}$ = 11.2 Hz) shows the *trans* relation between those protons. On the other hand, the triplet resonance of the proton H-6 in **22** with a large coupling constant ($J_{5,6} = J_{6,7}$ = 10.7 Hz) indicates the *trans* configuration of the neighboring protons. After correct assignment of the configurations to the chlorine compounds **21** and **22** we assume that these compounds are formed by HCl-catalyzed ring-opening reaction of the isomer **20.**

Next we studied the epoxide-opening reaction of **19**. To prevent any neighboring group participation by the acetate we decided to remove the acetates before the ring-opening. For that reason, the *syn*-epoxide **19** was subjected to hydrolysis with ammonia in methanol to provide the epoxy-diol **23** (Scheme 6). The diol **23** was submitted to a ring-opening reaction with sulfuric acid followed by acetylation with acetic anhydride in pyridine. The formed tetraacetate **12** was identical to those obtained from the ring-opening reaction of the epoxide **11**. We assume that the acetate anion prefers to attack the protonated epoxide ring from the less crowded side to produce **12** as a single isomer. However, when the epoxy-diacetate **19** was

SCHEME 7



subjected to a hydrolysis reaction with sulfamic acid the tetraacetate **12** and its further hydrolysis product **13** were not formed; instead, the isomeric tetraacetate **25** was probably formed as the intermediate, which underwent a further ring-opening reaction of the tetrahydrofuran ring to give **26**. It is likely that there is neighboring group participation controlling the mode of the reaction. Probably, the initially protonated epoxide ring undergoes an attack by the adjacent acetoxy group to form cyclic oxolonium ion **24**, which can undergo ring opening through attack by acetate ions. Two possible products **16** and **25** can be formed. We were not able to detect any trace of the isomeric tetraacetate **16** (attack a), which was formed by the *cis*-hydroxylation reaction of the diene **5** (see Scheme 4). The sole formation of **25** can be attributed to the attack from the less hindered site in **24**. Hydrolysis of **25** with ammonia in MeOH resulted in the formation of the bishomo-*myo*-inositol **26** in 95% yield.

Finally, the epoxy diacetate **20** was submitted to a sulfamic acid catalyzed ring-opening reaction in the presence of acetic anhydride (Scheme 7). The epoxide as well as the tetrahydrofuran ring underwent a ring-opening reaction to give the tetraacetate **9** that was identical to the compound obtained by the hydrolysis of **8** (Scheme 2). The exclusive formation of this isomer can be explained by the neighboring group participation of the acetate group as discussed above.

Kinetic Resolution of 15. To test the inhibitory activities of the individual enantiomers in assay, the racemic diacetate **15** was resolved. First, for the resolution of the racemic mixture **(±)-15**, PLE was used. Unfortunately, we were not able to obtain satisfactory results. After this, we turned our attention to the enantioselective esterification of the diol **(±)-28**, which was synthesized by hydrolysis of the diacetate **(±)-15** with ammonia in methanol (Scheme 8). Lipases are able to catalyze asymmetric hydrolysis[18] as well as esterification.[19] Among the lipases studied, *Candida antarctia* (Novozyme) proved to be suitable for the enantioselective esterification of substrate **(±)-28**. To a stirred solution of **(±)-28** in vinyl acetate was added *C. antarctia* lipase in one portion, and reaction mixture was shaken at 30 °C. The conversion was monitored by TLC. After 24 h, about 50% conversiton was observed. The residue was purified on silica gel to give **(+)-28** in a 45% yield and a mixture of the monoacetates **29** and **30**, which were converted into the diacetate **(−)-15** in high yield. The diol **(+)-28** was also converted in the corresponding diacetate **(+)-15**. The analysis of the separated enantiomers showed that the enantiomer **(+)-15** was formed with 89% ee, whereas the enantiomer **(−)-15** with 80% ee, respectively. After the successful synthesis of those enatomeri-

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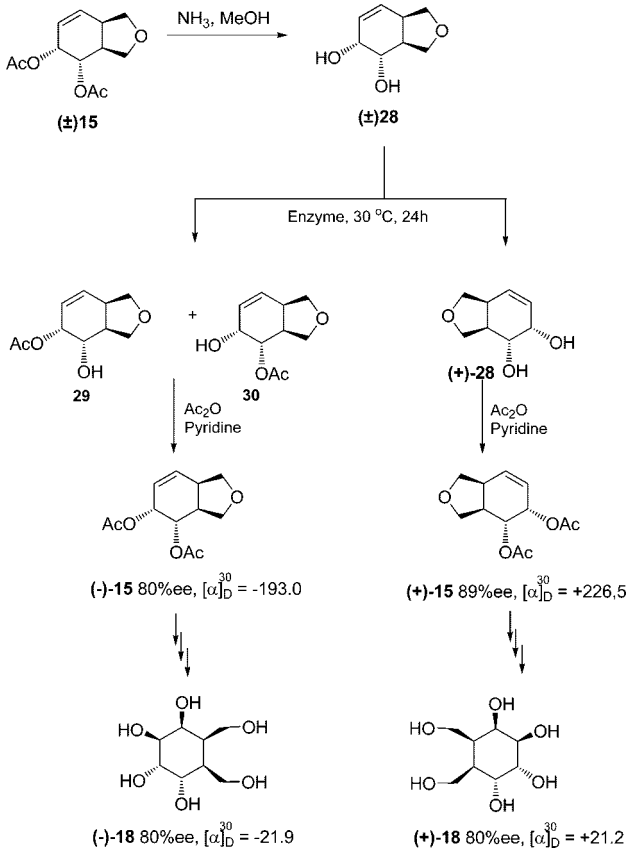
SCHEME 8



cally enriched diacetates, they were converted into the corresponding hexols (+)**-18** and (−)**-18** as described above (Scheme 8).

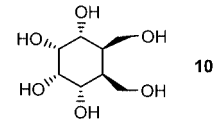
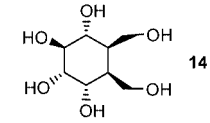
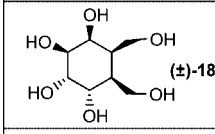
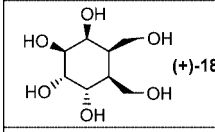
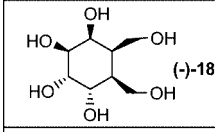
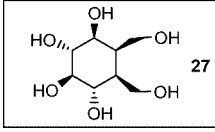
α-Glycosidase Inhibition Assay. The inhibitory activities of **10**, **14**, (±)**-18**, (+)**-18**, (−)**-18**, and **27** were screened against α-glycosidase. The results are summarized in Table 1. Bishomo-*chiro*-inositol **14** did not show inhibition for α-glycosidase even for higher than 200 μM concentration. The other compounds showed α-glycosidase inhibitions and inhibition rates were 57 ± 0.96% for 10 μM, 13 ± 4% for 20 μM, and 26 ± 5.5% for 5 μM concentration for the compounds **10**, **18**, and **24**, respectively. The racemic hexol **18** was resolved, and individual enantiomers were tested in the assay. We noticed that the α-glycosidase inhibitions of the individual enantiyomers (+)**-18** and (−)**-18** were increased compared with the racemic mixture (±)**-18** (Table 1).

In summary, with relatively little synthetic effort, we achieved the stereoselective synthesis of four isomeric bishomo-inositol derivatives **10**, **14**, **18**, and **27** starting from the diene **5** and introduced the complex stereochemistry in a very simple way, by combination of photooxygenation, epoxidation, and *cis*-hydroxylation reactions. Some of the synthesized isomers showed α-glycosidase inhibitions. In the case of **18**, the individual enantiomers showed increased inhibitions. Further studies of the chemistry of the double bonds in **5** directed toward the synthesis of bishomo-aminoinositols are currently in progress.

Experimental Section

1*R*(*S*),3*S*(*R*)-1,3,3a,4,7,7a-Hexahydro-2-benzofuran (3). Hexahydrobenzofuran derivative **3** was prepared according to same procedure as described in the literature.[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 2H), 3.89 (dd, A-part of AB-system, J = 7.5 and 6.4 Hz, 2H), 3.54 (dd, B-part of AB-system, J = 7.5 and 5.6 Hz, 2H), 2.36 (m, 2H), 2.26−2.22 (m, 2H), 1.95 (dd, J = 16.0 and 3.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.9, 73.1, 35.3, 24.1; IR (KBr, cm^{-1}) 3025, 2927, 2857, 1485, 1437, 1377, 1309, 1209, 1189, 1175, 1120, 1088, 1055, 1019, 968, 951, 899. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.4; H, 9.7.

TABLE 1. Inhibition of α-Glycosidases by 10, 14, (±)-18, (+)-18, (−)-18, and 27

Compound	Inhibition [a] (%)	IC_{50} (μM)[d]
 **10**	57±0.96 [a,d]	8
 **14**	NI[a,b]	—
 **(±)-18**	13±4[a,c]	NT[g]
 **(+)-18**	32±1,7[c]	NT[g]
 **(-)-18**	22±1.4[c]	NT[g]
 **27**	26±5.5 [a,e]	8

[a] Four experiments are performed for all compounds and in duplicate in each experiment. [b] NI = no inhibition (the compound was added in the 5−200 μM range and did not show any inhibition). [c] Inhibition by 20 μM compound. [d] Inhibition by 10 μM compound. [e] Inhibition by 5 μM compound. [f] Concentration required for 50% inhibition of the enzyme activity under the assay conditions. [g] NT = not tested

3a*R*(*S*),5*R*(*S*),6*S*(*R*),7a*S*(*R*)-5,6-Dibromooctahydro-2-benzofuran (4). To a magnetically stirred solution of **4** (10.0 g, 80,65 mmol) in 300 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of bromine (13.0 g, 81.2 mmol) in 200 mL of CH_2Cl_2 over a period of 1 h. The reaction mixture was stirred for an additional 2 h at room temperature. The solvent was evaporated. Crystallization of the residue from ether at 0 °C gave 17.87 g of pure **4** (78% after crystallization) as white crystals. Mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42−4.37 (m, 1H), 4.29−4.24 (m, 1H), 3.92−3.81 (m, 3H), 3.69−3.65 (m, 1H), 2.61−2.46 (m, 3H), 2.42−2.36 (m, 1H), 2.25−2.15 (m, 1H), 2.12−2.05 (m, 1H); ^{13}C NMR (100 Mhz, $CDCl_3$) δ 72.4, 70.2, 53.2 (2x), 38.3, 37.2, 34.5, 33.2; IR (KBr, cm^{-1}) 2926, 2871, 1306, 1286, 1246, 1169, 1158, 1118, 1069, 1041, 1029, 1013, 980, 942, 934, 903. Anal. Calcd for $C_8H_{12}Br_2O$: C, 33.83; H, 4.26. Found: C, 34.00; H, 4.23.

3a*R*(*S*),7a*S*(*R*)-1,3,3a,7a-Tetrahydro-2-benzofuran (5). To a solution of dibromide **4** (15.0 g, 52.82 mmol) in 400 mL of dry benzene was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (36.0 g, 236 mmol) in 400 mL of dry benzene at room temperature. The reaction mixture was refluxed for 6 h and then

cooled to room temperature. The solid was filtered off. The benzene phase was poured into water (1000 mL) and extracted with ether (3 × 500 mL). The combined organic phase was washed with saturated aqueous sodium bicarbonate (3 × 500 mL), dried (Na_2SO_4), and evaporated in vacuum to give 4.51 g of **5** (70%) as a colorless liquid.[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86−5.80 (m, 2H), 5.62−5.59 (m 2H), 4.16−4.12 (m, 2H), 3.60−3.57 (m, 2H), 2.96 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$). 126.2, 122.3, 75.0, 37.8.

1*R*(*S*),2*R*(*S*),6*S*(*R*),7*S*(*R*)-4,10,11-Trioxa-tricyclo[5.2.2.0^{2,6}]undec-8-ene (6). A stirred solution of cyclohexadiene derivative **5** (10.0 g, 81.9 mmol) and 200 mg of tetraphenylporphyrine (TPP) in 250 mL of CH_2Cl_2 was irradiated with a projection lamp (500 W) while oxygen was passed through the solution The reaction was completed after 12 h. Evaporation of solvent (30 °C, 20 mmHg) and crystallization of the residue from ether gave 10.7 g of pure endoperoxide (85%) as colorless crystals. Mp 123−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (quasi t, A-part of AA′XX′-system, 2H), 4.71 (m, X-part of AA′XX′-system, 2H), 3.73 (m, 2H), 3.50 (dd, $J_{3,3'(5,5')}$ = 9.3 and 2.6 Hz, 2H), 3.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 72.4, 70.0, 39.9; IR (KBr, cm^{-1}) 3079, 2958, 2923, 2861, 1475, 1465, 1377, 1277, 1198, 1129, 1075, 1040, 1029, 965, 950. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.03; H, 6.59.

3a*S*(*R*),4*R*(*S*),7*S*(*R*),7a*R*(*S*)-7-(Acetyloxy)-1,3,3a,4,7,7a-hexahydro-2-benzofuran-4-yl Acetate (7). To a magnetically stirred slurry of 2.96 g (39 mmol) of thiourea in 50 mL of methanol was added a solution of 5.0 g (32.47 mmol) of endoperoxide **6** in 50 mL of methanol at room temperature. After completion of the addition (ca. 30 min), the mixture was stirred for 3 h at room temperature. The solids were removed by filtration. Pyridine (10 mL) and Ac_2O (15 mL) were added to the formed viscose liquid residue followed by stirring for 12 h at room temperature. Then the residue was quenched with 2 × 30 mL of ice-cold HCl, after stirring for 5 min, and the mixture was extracted with ether (3 × 100 mL). The combined organic extracts were washed with $NaHCO_3$ solution and water and then dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from EtOAc/*n*-hexane (1:3) gave 6.8 g (87%) of diacetate **7** as colorless crystals. Mp 54−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 2H,) 5.14 (d, J_{3a4} = 4.2 Hz, 2H), 3.95 (dd, $J_{1,1'(3,3')}$ = 8.6 and $J_{3,3a(1,7a)}$ = 4.2 Hz, 2H), 3.68 (dd, $J_{1,1'(3,3')}$ = 8.6 and $J_{3',3a(1',7a)}$ = 5.2 Hz, 2H), 2.52 (m, 2H), 2.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.4, 128.6, 70.8, 67.4, 41.0, 21.0; IR (KBr, cm^{-1}) 2968, 1758, 1671, 1665, 1436, 1366, 1345, 1285, 1204, 1124, 1076, 1042, 948, 923, 889. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.62; H, 6.75.

3a*S*(*R*),4*S*(*R*),5*S*(*R*),6*R*(*S*),7*R*(*S*),7a*R*(*S*),-4,6,7-Tris(acetyloxy) octahydro-2-benzofuran-5-yl Acetate (8). A General Procedure for *cis*-Hydroxylation. To a stirred solution of 2.0 g (8.33 mmol) of diacetate **7** in 10 mL of acetone/H_2O (1:1) were added 1.0 g (8.7 mmol) of NMO and 12.0 mg (0.048 mmol) of OsO_4 at 0 °C. The resulting mixture was stirred vigorously under nitrogen at room temperature for 24 h. The reaction was stopped, and the pH of the solution was adjusted to 2 with HCl. After evaporation of solvent, pyridine (5 mL) and Ac_2O (8 mL) were added to the residue, followed by stirring for 25 h at room temperature. The product was hydrolyzed with aqueous ice-cooled HCl (100 mL, 20%), neutralized with aqueous $NaHCO_3$, dried (Na_2SO_4), and filtered. Evaporation of solvent gave **8** (2.18 g, 73%) as pure white crystals from EtOAc. Mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (bs, 1H), 5.12 (bs, 1H), 3.92 (dd, A-part of AB-system, $J_{1,1'(3,3')}$ = 8.9 and $J_{3,3a(1,7a)}$ = 6.6 Hz, 1H), 3.71 (dd, B-part of AB-system, J = 8.9 and $J_{3',3a(1',7a)}$ = 5.1 Hz, 1H), 2.75−2.69 (m, 2H), 2.07 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.7, 69.0, 67.4, 67.3 40.1, 20.7, 20.6; IR (KBr, cm^{-1}) 2967, 2940, 2864, 1751, 1440, 1373, 1228, 1174, 1156, 1108, 1042, 978, 954. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.58; H, 5.97.

3a*S*(*R*),4*S*(*R*),5*S*(*R*),6*R*(*S*),7*R*(*S*),7a*R*(*S*)2,3,4-Tris(acetyloxy)-5,6-bis[(acetyloxy)-methyl]cyclohexyl Acetate (9). General Procedure for Sulfamic Acid Catalyzed Hydrolysis. To a stirred solution of 2.0 g (5.62 mmol) of tetraacetate **8** in Ac_2O/AcOH (15 mL 1:1) was added a catalytic amount of 100 mg (1.0 mmol) of sulfamic acid at room temperature, followed by refluxing for 24 h. The mixture was poured into water (100 mL), acidified with HCl (2−3 drops), and extracted with dichloromethane. The organic phase was washed with water (2 × 100 mL) and saturated $NaHCO_3$ (2 × 50 mL) and dried ($MgSO_4$). Crystallization from EtOAc/hexane (1:2) gave 2.17 g (84%) of **9** as colorless crystals, mp 154−156 °C. ^{1}H NMR (400 MHz, in $CDCl_3$) δ 5.38 (bs, 1H), 5.31 (bd, J = 3.7 Hz, 2H), 4.27 (dd, A-part of AB-system, J = 11.9 and 6.0 Hz, 2H), 4.19 (dd, B-part of AB-system, J = 11.9 and 4.8 HZ, 2H), 2.67 (bs, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0, 169.9, 68.5, 67.9, 61.8, 34.2, 21.00, 20.9, 20.8; IR (KBr, cm^{-1}) 2970, 1734, 1469, 1433, 1373, 1233, 1174, 1128, 1035, 983, 965, 954. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13; O. Found: C, 52.12; H, 6.08.

Synthesis of *cis*-5,6-Bis(hydroxymethyl)cyclohexane 1,2,3,4-Tetraol (10). Tetraacetate **9** (1.0 g, 2.17 mmol) was dissolved in 75 mL of absolute methanol. While dry $NH_{3(g)}$ was passed through solution, the mixture was stirred for 5 h. Evaporation of solvent and formed acetamide gave hexol **10**, which was crystallized from EtOH to give colorless powder (0.37 g, 91%). Mp 142−144 °C; ^{1}H NMR (400 MHz, in D_2O at 60 °C) δ 4.71 (s, 6H, -OH), 4.39−4.27 (m, 4H), 4.22−4.1 (m, 4H), 2.8−2.7 (m, 2H)); ^{13}C NMR (100 MHz, in D_2O at 60 °C) δ 70.2, 70.1 59.6, 38.9; IR (KBr, cm^{-1}) 3332, 2926, 2890, 2430, 1450, 1391, 1323, 1236, 1147, 1109, 1080, 1046, 982, 882. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.82; H, 8.01.

1a*R*(*S*),2*S*(*R*),2a*S*(*R*),5a*R*(*S*),6*R*(*S*),6a*S*(*R*)-6-(Acetyloxy)octahydrooxireno[2,3-*f*][2]benzofuran-2-yl Acetate (11b). General Procedure for Epoxidation. To 2.0 g (8.32 mmol) of diacetate **7** in 150 mL of $CHCl_3$ was added 4.01 g (16.3 mmol, 70%) pf *m*-chloroperbenzoic acid. The resulting mixture was refluxed for 3 weeks, then 15 mL 50% $NaHSO_3$ solution was added, and the mixture was stirred for 15 min. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated to give 1.72 g (6.75 mmol, 81%) f epoxide **11b**, which was crystallized from EtOAc. Colorless crystals, mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (quasi d, J = 7.8 Hz, 2H) 3.81 (dd, A-part of AB-system, J = 9.2 and 6.7 Hz, 2H), 3.61 (dd, B-part of AB-system, J = 9.2 and 4.3 Hz, 2H), 3.43 (s, 2H), 2.54 (ddd, J = 9.2 and 6.6 and 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 71.9, 71.7, 53.4, 39.4, 20.9; IR (KBr, cm^{-1}) 2995, 2961, 2870, 1722, 1480, 1430, 1369, 1349, 1309, 1245, 1159, 1108, 1079, 1033, 987, 930, 881. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.24; H, 6.58.

1a*R*(*S*),2*S*(*R*),2a*S*(*R*),5a*R*(*S*),6*R*(*S*),6a*S*(*R*)-Octahydrooxireno[2,3-*f*][2]benzofuran-2,6-diol (11a). Epoxy diacetate **11b** (1.0 g, 3.91 mmol) was hydrolyzed with ammonia in MeOH as described above for the synthesis of **10**. **11a**: colorless crystals (645 mg, 96%) from MeOH, mp 184−186 °C. ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.79 (bs, 2H, -OH), 3.85−3.80 (m, 4H), 3.70 (dd, B-part of AB-system, J = 8.8 and 3.4 Hz, 2H), 3.30 (s, 2H), 2.35−2.26 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 73.7, 70.8, 57.4, 43.5; IR (KBr, cm^{-1}) 3400, 2931, 2904, 1447, 1382, 1343, 1324, 1256, 1239, 1214, 1196, 1134. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 56.08; H, 7.23.

3*R*(*S*),4*R*(*S*)5*S*(*R*),6*S*(*R*),7*S*(*R*),8*S*(*R*)-4,6,7-Tris(acetyloxy)octahydro-2-benzofuran-5-yl Acetate (12). One gram (3.91 mmol) of epoxy diacetate **11b** was hydrolyzed with ammonia in MeOH as described above. Without any purification, the residue **11a** was dissolved in water (5 mL), and sulfuric acid (1 mL) was added. The mixture was refluxed for 6 h. Evaporation of the solution gave viscous residue. Pyridine (5 mL) and acetic anhydride (7 mL) were added to the mixture, which was stirred at room temperature for 10 h. The mixture was acidified with cold HCl and washed with water (2 × 100 mL) and saturated $NaHCO_3$ (2 × 50 mL), respectively. The organic phase was dried ($NaSO_4$), and evaporation

of the solvent gave tetraacetate **12**. Crystallization from hexane/EtOAc 4:1 gave tetraacetate (**12**) (1,38 g, 77%). Pure white crystals, mp 128−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39−5.35 (m, 2H), 5.16−5.11 (m, 2H), 4.01 (t, A-part of AB-system, J = 9.1 Hz, 1H), 3.80 (d, A-part of AB-system, J = 9.0 Hz, 1H), 3.72, (dd, B-part of AB-system, J = 9.1 and 5.2 Hz, 1H), 3.70 (t, B-part of AB-system, J = 9.0 Hz, 1H), 2.74−2.66 (m, 1H), 2.61−2.55 (m, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (2C), 169.9, 169.7, 71.2, 71.0, 70.97, 69.6, 68.0, 67.9, 42.1, 41.8, 20,9, 20.7, 20.6, 20.55.

^{1}H NMR (400 MHz, benzene-d_6) δ 5.76 (dd, J = 9.8 and 9.3 Hz, 1H), 5.54 (t, J = 3.2 Hz, 1H), 5.44 (t, J = 9.8 Hz, 1H), 5.37 (dd, J = 9.3, J = 3.2 Hz), 3.88 (d, A-part of AB-system, J = 8.8 Hz, 1H) 3.57 (t, A-part of AB-system, J = 9.1 Hz, 1H), 3.45 (m, B-parts of AB-systems) 2H), 2.40−2.34 (m, 1H), 2.30−2.22 (m, 1H), 1.83 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, benzene-d_6) δ 169.4, 169.3, 169.1 (2C), 71.5, 71.2, 70.7, 70.0, 68.1, 67.6, 42.14, 42.06. 20.11, 20.07, 20.00 (2C); IR (KBr, cm^{-1}) 3014, 2943, 1753, 1442, 1375, 1232, 1043, 906. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.58; H, 5.97.

1*R*(*S*),2*R*(*S*)3*S*(*R*),4*S*(*R*),5*R*(*S*),6*S*(*R*)-2,3,4-(Acetyloxy)-5,6-bis[(acetyloxy)methyl]cyclohexyl Acetate (13). To a stirred solution of 2.0 g (7.81 mmol) of epoxydiacetate (**11b**) in AcOH/AcOH (15 mL 1:1) was added 0.15 g (1.55 mmol) sulfamic acid at room temperature, and then the mixture was refluxed for 24 h. The reaction mixture was worked up as described above to give **13** as colorless liquid, (3.19 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (t, J = 2.7 Hz, 1H), 5.32 (t, J = 10.6 Hz, 1H), 5.24 (dd, J = 10.6 and 10.1 Hz, 1H), 5.13 (dd, J = 10.1 and 3.0 Hz, 1H), 4.27−4.17 (m, 3H), 3.93 (dd, J = 11.7 and 3.8 Hz, 1H), 2.58−2.51 (m, 1H), 2.40−2.36 (m, 1H), 2.08 (s, 6H), 1.96 (s, 6H), 1.94 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100-MHz, $CDCl_3$) δ 170.36, 170.23, 170.03, 169.88, 169.79 169.6, 71.6, 70.1, 69.8, 69.6, 61.5, 61.1, 39.3, 36.8, 20.9, 20.8, 20.6, 20.58, 20.5 (2C); IR (KBr, cm^{-1}) 2964, 1746, 1433, 1369, 1230, 1040, 952. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13; Found: C, 51.84; H, 6.09.

1*R*(*S*),2*R*(*S*)3*S*(*R*),4*S*(*R*),5*R*(*S*),6*S*(*R*)-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetrol (14). One gram (2.17 mmol) of hexaacetate **13** was dissolved in methanol (75 mL), $NH_{3(g)}$ was passed through the solution for 5 h, and the solvent concentrated in vacuo to give 429 mg (2.04 mmol, 94%) white solid from EtOH, mp 175−177 °C. ^{1}H NMR (400 MHz, DMSO) δ 4.55 (bs, 1H), 4.43 (bs, 2H), 4.34 (bs, 1H), 4.27 (bs, 2H), 3.88 (bs, 1H), 3.703.67 (m, 1H), 3.53−3.50 (m, 1H), 3.46−3.43 (m, 1H), 3.37 (bs, 1H), 3.3 (bd, J = 7.9 Hz, 1H), 3.27−3.17 (m, 2H), 2.01−1.94 (m, 2H). ^{13}C NMR (100 MHz, DMSO) 75.4, 71.9, 71.4, 70.2, 60.9, 58.6, 43.3, 40.1; IR (KBr, cm^{-1}) 3400, 2931, 2904, 1447, 1382, 1343, 1324, 1256, 1239, 1214, 1196. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.52; H, 7.49.

3a*S*(*R*),4*S*(*R*),5*S*(*R*),7a*R*(*S*)-4-(Acetyloxy)-1,3,3a,4,5,7a-hexahydro-2-benzofuran-5-yl Acetate (15). The diene **5** (8.0 g, 65.6 mmol), NMO (8.91 g, 77.5 mmol), and OsO_4 (ca. 20 mg) in 30 mL of H_2O and acetone (1:1) were reacted as described above. The residue was dissolved in pyridine (10 mL) and Ac_2O (15 mL) and stirred for 25 h at room temperature. The product was hydrolyzed with aqueous ice-cooled HCl (100 mL, 20%), neutralized with aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated to give colorless liquid (12.43 g). After filtration of over silica gel (150 g) with EtOAc, evaporation of solvent and crystallization from EtOAc/hexane (1:2) gave 11.02 g (70%) of colorless crystals, mp 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, A-part of AB-system, J = 9.8 and 3.8 Hz, 1H), 5.83 (ddd, B-part of AB-system, J = 9.8, 5.4 and 1.6 Hz, 1H), 5.46 (dd, J = 3.8 and 3.3 Hz), 5.01 (dd, J = 10.7 and 3.3 Hz, 1H), 4.03 (t, J = 8.5 Hz, 1H), 3.91 (dd, A-part of AB-system, J = 9.3 and 6.5 Hz, 1H), 3.74 (dd, B-part of AB-system, J = 9.3 and 2.8 Hz, 1H), 3.48 (t, J = 8.5 Hz, 1H), 3.09−3.04 (m, 1H), 2.79−2.72 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 132.1, 123.7, 71.8, 70.6, 70.1, 64.9, 40.4, 37.8, 20.9, 20.8; IR (KBr, cm^{-1}) 3041, 2961, 2866, 1739, 1440, 1376, 1244, 1049. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.87; H, 6.92.

***cis*-Hydroxylation of 5. 3a*S*(*R*),4*S*(*R*),5*S*(*R*),6*R*(*S*),7*R*(*S*),7a*R*(*S*),-4,6,7-Tris(acetyloxy)octahydro-2-benzofuran-5-yl Acetate (8) and 3a*S*(*R*),4*S*(*R*),5*S*(*R*),6*S*(*S*),7*S*(*S*),7a*R*(*S*),-4,6,7-Tris(acetyloxy)octahydro-2-benzofuran-5-yl Acetate (16).** An 8.5 g (35.4 mmol) portion of diacetate **15** was submitted to *cis*-hydroxylation reaction as described above. Acetylation of the residue gave a crude mixture consisting of **8** and **16** (10.63 g), which was separated by silica gel chromatography eluting with EtOAc/hexane (1:1). The first fraction was the symmetrical diacetate **8** (5.7 g, 45%). The second fraction was identified as **16** (4.6 g, 36%). Colorless crystals from EtOAc/hexane (1:2), mp 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, J = 5.2 and 3.7 Hz, 1H), 5.34 (dd, J = 6.8 and 2.8 Hz, 1H), 5.26 (m, 2H), 3.90 (dd, J = 8.6 and 6.3 Hz, 1H) 3.83−3.80 (m, 2H), 3.46 (dd, J = 8.3 and 5.6 Hz, 1H), 2.82−2.75 (m, 1H), 2.58−2.52 (m, 1H), 2.01 (s, 9H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170.0, 169.6 (2C), 69.9, 69.3, 68.9, 68.4, 68.1, 67.6, 41.0, 39.5, 20.81 (2C), 20.7, 20.7; IR (KBr, cm^{-1}) 2968, 2876, 1752, 1437, 1371, 1340, 1211, 1100, 1061. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.68; H, 6.51.

1*R*(*S*),2*R*(*S*)3*R*(*S*),4*R*(*S*),5*R*(*S*),6*S*(*R*)-2,3,4-(Acetyloxy)-5,6-bis[(acetyloxy)methyl]-cyclohexyl Acetate (19). The tetraacetate **16** (2.0 g, 5.58 mmol) was reacted with sulfamic acid as described above to give **17**: 2.14 g (83%), colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (bd, 2H); 5.31 (dd, A-part of AB-system, J = 10.7 and 2.8 Hz, 1H), 5.25 (dd, B-part of AB-system, J = 10.7 and 3.0 Hz, 1H), 4.36 (dd, J = 11.8 and 5.1 Hz, 1H), 4.19 (t, J = 10.7 Hz, 1H), 4.16−4.01 (m, 2H), 2.63−2.61 (m, 1H), 2.38−2.34 (m, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.01(s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.0, 169.9, 169.7, 169.6, 69.1, 68.4, 66.7, 61.6, 60.9, 60.3, 39.9, 35.4, 20.9, 20.8, 20.7 (2C), 20.65, 20.60; IR (KBr, cm^{-1}) 2970, 1736, 1373, 1234, 1174, 1094, 1036. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13. Found: C, 52.02; H, 6.05.

(1*R*(*S*),2*R*(*S*),3*R*(*S*),3*R*(*S*),5*R*(*S*),6*S*(*R*)-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetrol (18). One gram (2.17 mmol) pof hexaacetate **17** was hydrolyzed with ammonia as described above to give the free hexol **18**. The residue was crystallized from EtOH to give 0.4 g (88%) of **18** as a colorless powder, mp 156−158 °C. ^{1}H NMR (400 MHz, D_2O) δ 4.7 (bs, 6H, -OH), 4.04 (bs, 1H), 3.92 (bs, 1H), 3.74 (dd, J = 10.0 Hz, 1H), 3.67−3.42 (m, 5H), 2.07 (m, 1H), 2.03 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 71.0 (2C), 69.3, 68.8, 60.1, 59.4, 44.1, 38.6; IR (KBr, cm^{-1}) 3458, 2940, 2868, 1482, 1433, 1372, 1238, 1186, 1044. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.53; H, 7.94.

Reaction of Diacetate 15 with *m*-Chloroperbenzoic Acid. Diacetate **15** (1.5 g, 6.25 mmol) was dissolved in 200 mL of chloroform, *m*-CPBA (3.0 g, 12 mmol, 70%) was added, and then the reaction was stirred at reflux temperature for 3 weeks (every 2−3 days, small portions (200 mg) of *m*-CPBA were added). The reaction mixture was worked up as described in the general procedure. Evaporation of solvent under reduced pressure gave a oily residue (1.5 g), which was treated with 0.5 mL of pyridine and 1 mL of acetic anhydride. The resulting solution was stirred at room temperature for 5 h. The mixture consisting of **19**, **20**, **21**, and **22** was chromatographed on a silica gel column (50 g) eluting with hexane/EtOAc 3:1. Four compounds were isolates in the following order: **21** (92 mg, 4.4%), **22** (50 mg, 2.4%), **19** (816 mg, 51%), **20** (416, 26%).

Data for 4,6-Bis(acetyloxy)-7-chlorooctahydro-2-benzofuran-5-yl Acetate (21). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (t, J = 2.6 Hz, 1H), 5.24 (dd, J = 11.0 and 2.6 Hz, 1H), 4.96 (dd, J = 11.0 and 2.2 Hz, 1H), 4.51 (dd, J = 11.2 and 6.4 Hz, 1H), 4.09 (t, J = 9.2 Hz, 1H), 3.80−3.88 (m, 3H), 3.25−3.12 (m, 1H), 2.60−2.53 (m, 1H), 2.14 (s, 3H), 2.06 (s, 3H), 2.01(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170.0, 169.7, 71.6, 70.6, 70.2, 68.7, 68.3, 55.6, 43.8, 41.0, 21.0, 20.9, 20.8; IR (KBr, cm^{-1}) 2957, 2877, 1738,

1436, 1369, 1214, 1142, 1124, 1073, 1053. Anal. Calcd for $C_{14}H_{19}ClO_7$: C, 50.23; H, 5.72. Found: C, 50.64; H, 5.86.

Data for 3a*S*(*R*),4*S*(*R*),5*R*(*S*),6*R*(*S*),7*R*(*S*),7a*R*(*S*)rel-4,7-Bis-(acetyloxy)-6-chlorooctahydro-2-benzofuran-5-yl Acetate (22). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (t, J = 2.9 Hz, 1H), 5.18 (t, J = 10.3 Hz, 1H), 5.12 (dd, J = 10.6 and 3.3 Hz, 1H), 4.22 (t, J = 10.7 Hz, 1H), 4.03 (dd, J = 9.5 and 9.2 Hz, 1H), 3.85 (d, J = 9.2 Hz, 1H), 3.70 (dd, J = 9.2 and 7.0 Hz, 1H), 3.69 (d, J = 9.5 Hz, 1H), 2.72−2.65 (m, 1H), 2.52−2.47 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.9, 169.8, 73.0, 71.3, 71.1, 67.8, 67.6, 59.0, 43.1, 42.9, 21.1, 21.0, 20.8; IR (KBr, cm^{-1}) 2951, 2838, 1743, 1519, 1451, 1371, 1224, 1038, 924, 894. Anal. Calcd for $C_{14}H_{19}ClO_7$: C, 50.23; H, 5.72. Found: C; 50.46; H, 5.94.

Data for 1a*S*(*R*),2*R*(*S*),3*S*(*R*),3a*S*(*R*),6a*R*(*S*),6b*S*(*R*)2-(Acetyloxy)octahydrooxireno[2,3-*e*][2]benzofuran-3-yl Acetate (19). Colorless crystals from ethylacetate/*n*-hexane, mp 108−110 °C.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (dd, J = 3.6 and 2.8 Hz, 1H), 4.96 (dd, J = 11.2 and 2.8 Hz, 1H), 4.09 (t, J = 8.6, 1H), 3.84 (dd, J = 9.2 and 6.6 Hz, 1H), 3.75 (t, J = 8.6 Hz, 1H), 3.5 (dd, J = 9.2 and 3.9 Hz, 1H), 3.39 (t, J = 3.6 Hz, 1H), 3.26 (t, J = 3.6 Hz, 1H), 2.87 (dq, J = 8.6 and 3.6 Hz, 1H), 2.52−2.44 (m, 1H), 2.17 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.01, 169.96, 71.4, 70.2, 69.8, 66.6, 53.5, 51.1, 37.7, 36.7, 20.8 (2C); IR (KBr, cm^{-1}) 3016, 2980, 2857, 1737, 1441, 1376, 1246, 1093. Anal. Cald for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.26; H, 6.12.

Data for 1a*R*(*S*),2*R*(*S*),3*S*(*R*),3a*S*(*R*),6a*R*(*S*),6b*R*(*S*)2-(Acetyloxy)octahydrooxireno[2,3-*e*][2]benzofuran-3-yl Acetate (20). Colorless crystals from ethylacetate/*n*-hexane, mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (t, J = 4.2 Hz, 1H), 4.92 (dd, J = 8.4 and 4.2 Hz, 1H), 4.05 (t, J = 8.7 Hz, 1H), 3.84−3.77 (m, 1H), 3.72 (dd, J = 9.3 and 3.6 Hz, 1H), 3.44 (t, J = 3.6 Hz, 1H), 3.16 (d, J = 3.6, 1H), 3.02 (q, J = 7.7), 2.59−2.53 (m, 1H), 2.14 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 70.1, 69.8, 67.6, 66.1, 53.2, 51.8, 37.9, 37.7, 20.9, 20.6; IR (KBr, cm^{-1}) 2993, 2939, 2874, 1742, 1429, 1374, 1246, 1174, 1122, 1070, 1050, 972, 950, 916, 891. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.07; H, 5.97.

1a*S*(*R*),2*R*(*S*),3*S*(*R*),3a*S*(*R*),6a*R*(*S*),6b*S*(*R*)-Octahydrooxireno[2,3-*e*][2]benzofuran-2,3-diol (23). One gram (3.91 mmol) of epoxy diacetate **19** was hydrolyzed with ammonia in MeOH as described above for the synthesis of **10** to give **23** as colorless crystals (598 mg, 89%) from MeOH, mp 173−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (bs, 1H), 4.04 (t, J = 8.6 Hz, 1H), 3.83 (d, J = 4.5 Hz, 2H), 3.75 (t, J = 8.2 Hz, 1H), 3.6 (dd, J = 10.8 and 2.6 Hz, 1H), 3.9−3.3 (m, 2H, -OH), 3.44 (t, J = 3.2 Hz, 1H), 3.25 (T, J = 3.7 Hz, 1H), 2.81 (dq, J = 8.9 and 3.9 Hz, 1H), 2.30−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.4, 69.7, 68.7, 67.3, 56.2, 51.6, 38.6, 37.5; IR (KBr, cm^{-1}) 3400, 2931, 2904, 1447, 1382, 1343, 1324, 1256, 1239, 1214, 1196, 1134. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.45; H, 6.78.

3*R*(*S*),4*R*(*S*)5*S*(*R*),6*S*(*R*),7*R*(*S*),8*S*(*R*)-4,6,7-Tris(acetyloxy)octahydro-2-benzofuran-5-yl Acetate (12). Epoxydiol **23** (0.75 g, 4.36 mmol) was dissolved in a mixture of water (5 mL) and H_2SO_4 (three drops). The solution was stirred for 24 h at room temperature, and then the water was evaporated. Without any purification, the remaining residue was treated with pyridine (4 mL) and Ac_2O (7 mL). This solution was then stirred for 12 h at room temperature. EtOAc (100 mL) was added to the reaction mixture, and the product was hydrolyzed with aqueous ice-cooled HCl (100 mL, 5%), neutralized with aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated. After crystallization from hexane/EtOAc 3:1, tetraacetate (**12**) (0.98 g, 63%) was obtained.

1*S*(*R*),2*R*(*S*),3*R*(*S*),4*S*(*R*),5*S*(*R*),6*S*(*R*)-2,3,4-(Acetyloxy)-5,6-bis[(acetyloxy)methyl]cyclohexyl Acetate (26). The epoxide **19** (0.8 g, 3.13 mmol) was hydrolyzed with Ac_2O/AcOH (1/1) and sulfamic acid as described above to give **26** (1.10 g, 76%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.5 (bs, 1H), 5.32 (dd, A-part of AB system, J = 10.7 and 2.8 Hz, 1H), 5.27 (dd, J = 10.1 and 2.8 Hz, 1H), 5.24 (dd, B-part of AB system, J = 10.8 and 3.6 Hz, 1H), 4.24 (b, A-part of AB-system, J = 11.8 Hz, 2H), 4.15 (bd, B-part of AB system, J = 11.8 Hz, 2H), 4.1−4.05 (m, 2H), 2.65−2.58 (m, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H), 1.94 (s, 6H); ^{3}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.9, 169.7, 169.5, 69.7, 69.2, 68.2, 67.3, 61.7, 59.4, 36.5, 35.9, 21.0, 20.8, 20.7, 20.65, 20.58 (2C); IR (KBr, cm^{-1}) 2938, 2870, 1740, 1443, 1368, 1243, 1108, 1066, 965. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13 Found: C, 52.08; H, 6.23.

Bishomo-myoinositol 27. A 0.7 g (1.52 mmol) portion of hexaacetate **26** was hydrolyzed with ammonia in MeOH as described above to give the free hexol **27** (0.30 g, 95%) as a viscous liquid. ^{1}H NMR (400 MHz, D_2O) δ 4.7 (bs, 6H, -OH), 3.99−3.73 (m, 8H), 2.28 (m, 1H), 2.14 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 70.6, 68.7 (2C), 60.9, 57.0 (2C), 40.8 (2C); IR (KBr, cm^{-1}) 3342, 1661, 1397, 1032, 845. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.87; H, 7.53.

Ring-Opening Reaction of the Epoxide 20. The epoxide **20** (0.7 g, 1.96 mmol) was submitted to hydrolysis reaction with sulfamic acid in acetic acid (5 mL) and acetic anhydride (5 mL) at room temperature as described above. The residue was chromatographed of over silica gel (55 g) eluting with EtOAc/hexane (1:2). Evaporation of solvent and crystallization from EtOAc/hexane (1:2) gave 0.955 g (76%) of **9** as colorless crystals, which was identical with that compound obtained by ring-opening reaction of **8**.

(3a*S*,4*S*,5*R*,7a*R*)-1,3,3a,4,5,7a-Hexahydro-2-benzofuran-4,5-diol (28). Diacetate **15** (2.0 g, 8.33 mmol) was dissolved in 100 mL of absolute methanol. While dry $NH_{3(g)}$ was passed through solution, the mixture was stirred for 3 h. Evaporation of solvent and formed acetamide gave diol **28** in quantitative yield (1.36 g). Crystallization from EtOH gave colorless powder, mp 123−128 °C. ^{1}H NMR (400 MHz, in $CDCl_3$) δ 5.85 (bs, 2H), 4.01 (bs, 1H, 3.99 (t, J = 8.8 Hz, 1H), 3.96−3.89 (m, 2H), 3.70 (bd, J = 7.6 Hz, 1H), 3.43 (t, J = 8.0 Hz, 1H), 3.27 (bs, 2H), 2.97−2.93 (m, 1H), 2.53−2.49 (m, 1H); ^{13}C NMR (100 MHz, in $CDCl_3$) δ 130.3, 127.3, 72.16, 70.74, 69.21, 65.3, 40.58, 39.94; IR (KBr, cm^{-1}) 3468, 3025, 2928, 2858, 1437, 1176, 1055, 655. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.45; H, 7.96.

Kinetic Resolution of (±)-15. A solution of racemic diol (±)-**15** (350m g, 2.24 mmol) in vinyl acetate (17.9 mL of solvent as acyl donor) containing lipase from *Candida antarctica* (Novozyme 435) (161.5 mg) was stirred on a water bath shaker at 30 °C until appropriate conversion (55%) of the starting material (24 h). Afterward, the mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent to give the enantiomerically enriched monoacetates **29** and **30** in a 55% yield and diol **28** in a 45% yield. The enantiomeric purity of the products **29** and **30** as well as the diol **28** were determined by HPLC analysis after conversion to diacetate **15** (OD-H, hexane/iPrOH 1:99, flow rate = 0.5 mL min^{-1}, λ = 254 nm), t_R = 9.2 min, t_R = 11.3. (+)-**15** as a white solid; $[\alpha]^{30}_D$ = +226.5 (*c* 4.6, CH_2Cl_2) for 89% ee. (−)-**15** $[\alpha]^{30}_D$ = −193.0 (*c* 3.7, CH_2Cl_2) for 80% ee.

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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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