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Synthesis of Bishomoinositols and an Entry for Construction of a Substituted 3-Oxabicyclo[3.3.1]nonane Skeleton

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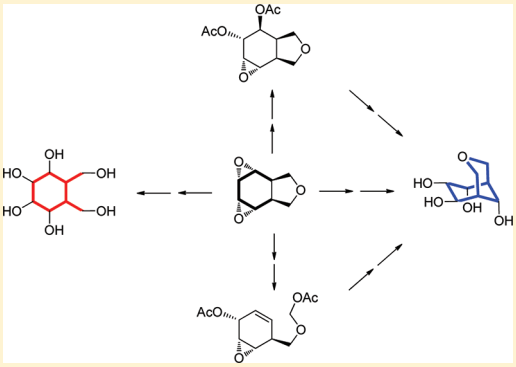
Supporting Information

ABSTRACT: 1,3,3a,7a-Tetrahydro-2-benzofuran was used as key compound for the synthesis of various bishomoinositol derivatives. The diene was subjected to an epoxidation reaction for further functionalization of the diene unit. The bisepoxide obtained was submitted to a ring-opening reaction with acid in the presence of water. Various bishomoinositols were synthesized. However, when the reaction was carried out in the presence of acetic anhydride, a substituted 3-oxabicyclo[3.3.1]nonane skeleton was formed. The mechanism of the formation of the products is discussed.



INTRODUCTION

Cyclitols are sugar-like molecules. They have for the past few decades attracted interest because of their significant biological properties and diverse synthetic intermediates.[1] Among the cyclitols, chemists have extensively studied inositols because of their remarkable, comprehensive, and important biological functions.[2] The most prominent naturally occurring form is *myo*-inositol, *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol (**1**) (Figure 1),

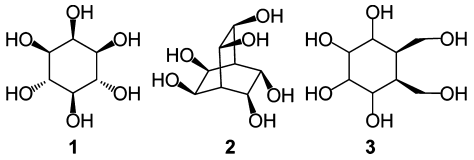


Figure 1. Representative cyclitols.

which is actively involved in cellular events and processes. In recent years, inositol phosphates in particular have been studied and new derivatives have been discovered that possess vital biological and physiological functions in cellular signaling events. Numerous synthetic approaches for inositol derivatives have been developed including the use of naturally occurring inositols,[3] sugars,[4] aromatic compounds,[5] chiral acids,[6] tetrahydrobenzoquinone,[7] and cyclohexene and its derivatives.[8] Moreover, an increasing number of reports also describe the synthesis of analogues of various inositol derivatives with novel architectures.[9]

Recently, we have prepared bicyclic bishomoinositol derivative **2** and other isomeric derivatives, which are locked in rigid conformations with six hydroxyl groups.[10] Furthermore, we reported the synthesis of various isomeric inositol derivatives with skeleton of **3**, starting from the diene **7** (Figure 1).[11] Motivated by the important biological activities of inositol derivatives, we formulated a new strategy of synthesis for new bishomoinositols based on the photooxygenation of diene **7** followed by transformation of the bicyclic endoperoxide formed.

RESULTS AND DISCUSSION

The previously known diene **7**[11] was prepared in five steps starting with the addition of maleic anhydride to in situ generated butadiene. The reduction of the anhydride functionality in **4** followed by tosylation of diol **5** afforded the desired tetrahydrofuran derivative **6**. Bromination of the resulting tetrahydrofuran, and 1,8-biazabicyclo[5.4.0]undec-7-ene (DBU) induced elimination furnished diene **7**. Addition of singlet oxygen[12] to the diene moiety in **7** afforded bicyclic endoperoxide **8** as the sole product (Scheme 1).

Unsaturated bicyclic endoperoxides can be conveniently converted into the corresponding diepoxides with *syn*-configuration by treatment with cobalt(II) tetraphenylporphyrin (CoTPP).[12,13] The reaction of the endoperoxide **8** with CoTPP at 0 °C resulted in the formation of bisepoxide **9** in 84% yield. The symmetrical structure was confirmed by the ^{13}C NMR spectrum consisting of four carbon resonances. Bisepoxide **9** was subjected to an acid-catalyzed ring-opening reaction in the presence of water (to avoid any neighboring

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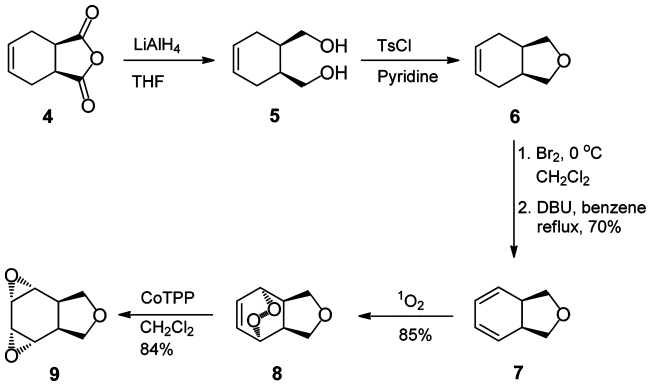
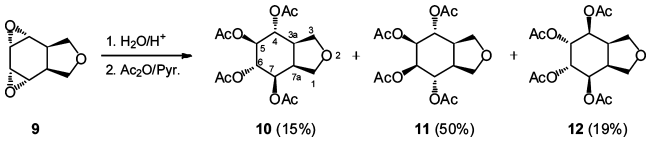
Scheme 1. Preparation of Bisepoxide 9 from Anhydride 4



group participation) followed by acetylation with acetic anhydride in pyridine resulting in the formation of three separable tetraacetates **10**–**12** (two of them with symmetrical structures) in 15, 50, and 19% yields, respectively (Scheme 2). The spectral

Scheme 2. Reaction of Bisepoxide 9 with H_2SO_4 in Water



data of the symmetrical tetraacetates were in complete agreement with the proposed structures **11** and **12**, which are formed by symmetrical *trans*-opening of the epoxide rings in **9**. The ^{13}C NMR spectra of **11** and **12** having eight carbon resonances also support the proposed structures. However, we were not able to make a clear-cut differentiation between those isomers on the basis of NMR data alone. Finally, the structure **12** was further confirmed by single crystal X-ray analysis (Figure 2).

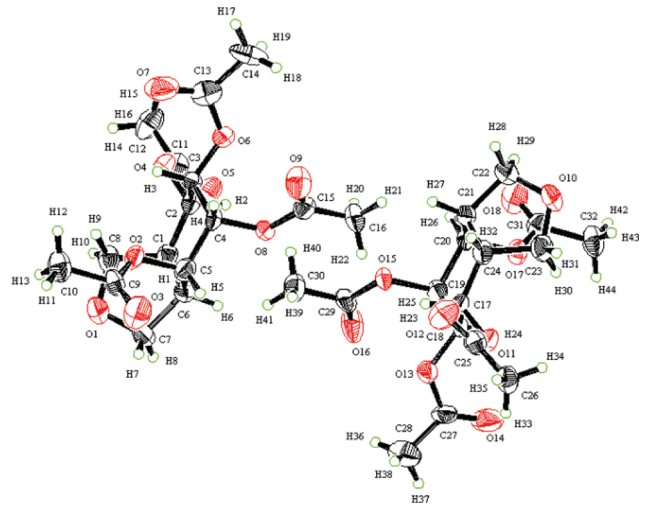


Figure 2. Crystal structures of **12**.

The structure of **10** was found to be in a *trans*–*trans*–*trans* configuration based on the analysis of NMR spectroscopic data (COSY, HSQC, HMBC). The resonance signal of H-5 appears as a doublet of doublets at 5.27 ppm with coupling constants of J = 9.5 and 9.1 Hz, which clearly supports the *trans* relation of the protons H-5–H-4 as well as the protons H-5–H-6. The acetoxy proton H-6 also resonates as a doublet of doublets with coupling constants of J = 9.1 and 10.0 Hz, clearly indicating the *trans* relation of the protons H-6–H-7. On the basis of these findings we assigned a *trans*–*trans*–*trans* relationship to the acetate groups in **10**.

After complete structural characterization of three tetraacetates **10**–**12**, we turned our attention to the opening of the tetrahydrofuran ring and removal of the acetate groups. Sulfamic acid[14] was used as an efficient catalyst in acetic anhydride to promote the acetolysis reaction of the tetrahydrofuran ring. Reaction of sulfamic acid with tetraacetate **10** at reflux temperature of a mixture of acetic acid and acetic anhydride (1:1) afforded the desired hexaacetate **13**, which was characterized by spectral data (Scheme 3). The structure and stereochemistry of this tetraacetate were rigorously established by inspection of NMR spectra. Furthermore, the spectral data of **13** were identical with those synthesized by ring-opening reaction of the dihydroxy epoxide **15**.[10]

The configuration at the carbon atom C-4 in **13** compared with the configuration in **10** was inversed. The exclusive formation of **13** can be explained by neighboring group participation,[15] which controls the mode of the reaction. Probably, initially protonated dihydrofuran ring **16** undergoes an attack by the adjacent acetoxy group to form cyclic oxolonium ion **17**, which can undergo ring-opening through attack by the acetate ion, causing ring-opening and configuration isomerization (Scheme 4). Deacetylation of tetraacetate **13** with ammonia was carried out in methanol to give the free hexol, bishomo-*chiro*-inositol **14** (Scheme 3).

Next, the ring-opening reaction of **11** was studied. The tetraacetate **11** was treated with sulfamic acid in a mixture of acetic acid and acetic anhydride to give the hexaacetate **18** as the sole product in 74% yield. Hydrolysis of **18** with ammonia in MeOH resulted in the formation of bishomo-*muco*-inositol **19** in 92% yield (Scheme 5). Studies of the NMR spectra did not reveal any configuration change in the product. In particular, C-13 NMR of **19** showing only 4 carbon resonances clearly indicates that the original configuration of the tetraacetate **11** was preserved in the product. The geometry optimized structure of the tetraacetate **11** shows that the acetate groups attached to C-4 and C-7 carbon atoms are remote from the methylene groups and can not approach from the back of the methylene carbon atom.

Finally, the tetraacetate **12** was submitted to a sulfamic acid catalyzed ring-opening reaction in the presence of acetic anhydride. Two diastereoisomers **20** and **21** were isolated after column chromatography on silica gel (Scheme 6). The ^1H NMR spectral data of **21** showed that the configuration of acetate groups in **12** was not changed during the ring-opening reaction. The ^1H NMR and ^{13}C NMR spectra of **21** supported the symmetrical structure in the molecule. However, the configuration at C-4 carbon atom in **20** was changed. The 20-line ^{13}C NMR spectrum clearly indicated the presence of an unsymmetrical structure. This outcome was expected. As discussed in the case of **10**, the acetate group attached to C-4 carbon atom is responsible for this configuration isomerization. Hydrolysis of **20** and **21** with ammonia in methanol afforded the corresponding hexols **22** and **23** with *neo*-inositol and *allo*-inositol configuration in high yield.

We then turned our attention to the acid-catalyzed ring-opening reaction of **9** in acetic anhydride instead of water. The attempted analogous epoxide opening with H_2SO_4 in acetic anhydride, however, resulted in the formation of a rearranged product **24** (Scheme 7). First we determined the constitution

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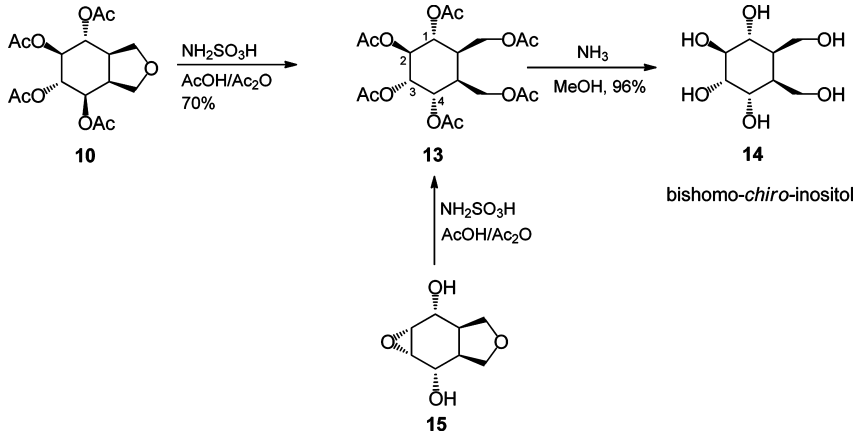
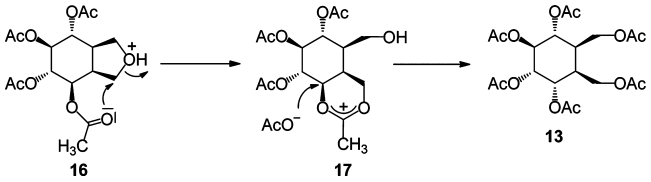
Scheme 3. Synthesis of Bishomo-*chiro*-inositol 14



Scheme 4. Mechanism of Formation of 13



of **24** by using NMR spectroscopic data (COSY, HSQC, HMBC). The COSY spectrum of **24** showed correlation between the high field acetoxy proton H-9 resonance appearing at 4.96 ppm as a broad triplet (J = 2.7 Hz) with two bridgehead protons H-1 and H-5, indicating clearly that this acetoxy proton is located between two bridgehead protons. To confirm this finding and to determine the exact configuration of the acetate groups, an X-ray diffraction study of **24** was undertaken (Figure 3). The results of this study showed that **24** is rearranged and the relations of the acetate groups attached to C-6, C-7, and C-8 carbons are *cis* and *trans*. To gain insight into the mechanism of formation of this product, we ran the reaction in the presence of lower acid concentration eventually to isolate any intermediate formed during the reaction. During the conversion of **9** to **24**, there are two successive reactions: the opening of one of the epoxide rings and the opening of the second epoxide-ring followed by migration of the alkyl group. For this purpose, the bisepoxide **9** was submitted to ring-opening reaction with a catalytic amount of H_2SO_4 in the presence of acetic anhydride. After consumption of the starting material, a mixture of two compounds **26** and **27** was formed in yields of 48% and 39%, respectively. The structures of these compounds were determined unambiguously. To demonstrate the feasibility of converting these products to **24**, they were separately submitted to an acid-catalyzed reaction as applied in case of conversion of **9** to **24**. Analysis of the reaction mixture clearly indicated that both products were converted to tetrahydropyran derivative **24** in high yields.

At this stage, we suggest the following mechanism for the formation of the products **26** and **27**. We assume that the acetate anion prefers first to attack the protonated epoxide ring in **28** from the back (solid arrows in Scheme 8) to form **26**. On the other hand, the acetate anion can also attack the methylene carbon atom followed by cleavage of the carbon−oxygen bond and subsequent formation of the double bond in **29** (broken arrows in Scheme 8).

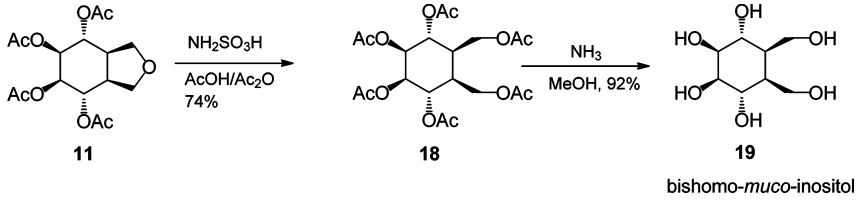
For the formation of **24** from **27**, the following mechanism is suggested. Removal of the acetate group attached to the methylene carbon atom will form a primary carbocation **30** which will be stabilized by the neighboring oxygen atom. The formed oxonium ion can be attacked by double bond electrons to complete the cyclization reaction (Scheme 9). The formed carbocation will be then captured by the acetate anion from the less crowded side to furnish pyrane derivative **24**.[16] The fact that the reaction of **9** with acid in the presence of acetic anhydride forms the rearranged product **24** can be attributed to the weak nucleophilicity of acetic anhydride compared to water.

Attempts were made to cleave the pyran ring in **24** with sulfamic acid under drastic conditions. However, in all cases the starting material was isolated. Finally, deacetylation of **24** with ammonia gave tetrol **25** with a pyran skeleton in the molecule.

■ CONCLUSION

In conclusion, the methodology detailed herein resulted in the convenient conversion of the diene **7** into various bishomoinositol derivatives. The oxygen functionalities were introduced by an epoxide-ring-opening reaction in the presence of water or acetic anhydride. This methodology opens up also an entry to the synthesis of bishomoaminoinositol derivatives. Furthermore, it has been shown in this paper that the bisepoxide **9** can be used for the construction of a bicyclic pyran skeleton. Further work to generate

Scheme 5. Synthesis of Bishomo-*muco*-inositol 19



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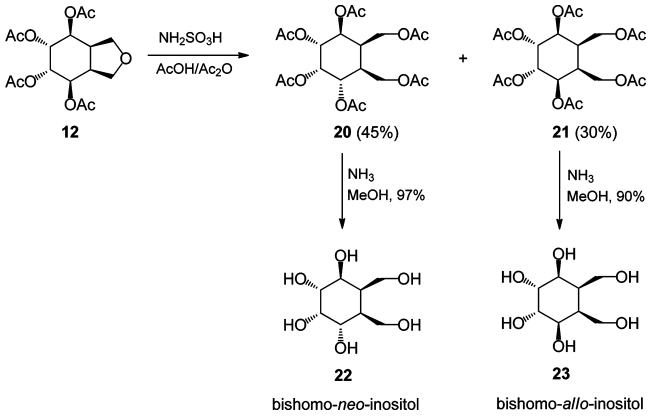
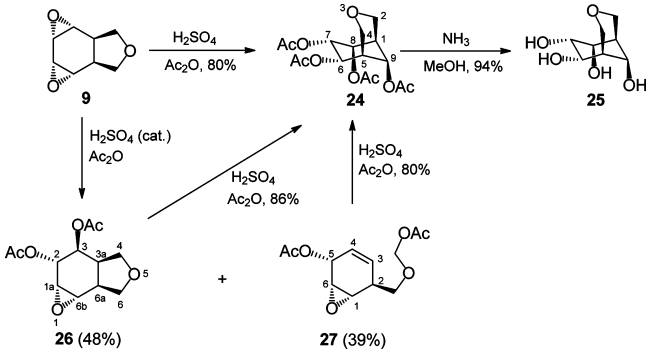
Scheme 6. Synthesis of Bishomo-*neo*-inositol 22 and Bishomo-*allo*-inositol 23



Scheme 7. Reaction of Bisepoxide 9 with H_2SO_4 in Acetic Anhydride



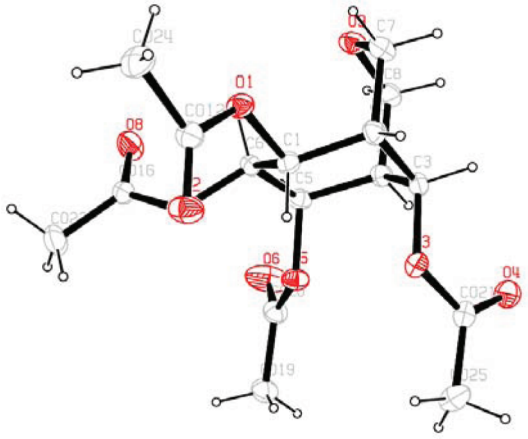


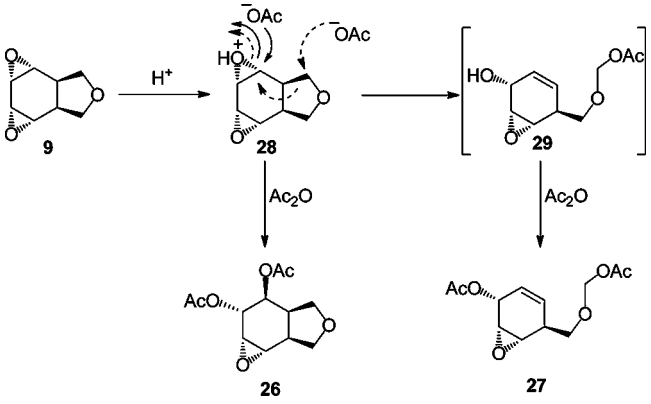
Figure 3. Crystal structures of **24**.

a pyran skeleton with various substituents is currently under investigation by our group.

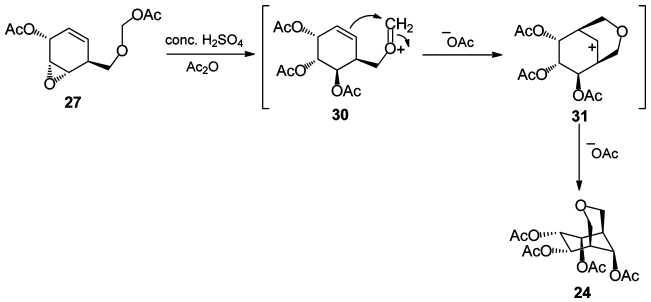
EXPERIMENTAL SECTION

***rel*-(1a*R*,1b*S*,2a*S*,2b*S*,5a*R*,5b*R*)-Octahydrobis(oxireno)[2,3-*e*:2′,3′-*g*]isobenzofuran (9).** To a magnetically stirred solution of bicyclic endoperoxide **8** (2.0 g, 13 mmol) in 40 mL of CH_2Cl_2 was added a solution of cobalt *meso*-tetraphenylporphyrin (60 mg) in 10 mL of CH_2Cl_2 at 0 °C. After complete addition (10 min), the mixture was stirred for 2 h at room temperature. Removal of solvent and chromatography of the residue on 50 g of silica gel eluting with

Scheme 8. Mechanism of Formation of 26 and 27



Scheme 9. Mechanism of Formation of 24 from 27



hexane/EtOAc (2:3) gave diepoxide **9** (1.68 g, 84%), which was crystallized from chloroform: colorless crystals; mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (br t, A-part of AB-system, J = 7.6 Hz, 2H), 3.62 (dd, B-part of AB-system, J = 8.4 and 4.5 Hz, 2H), 3.41 (d, J = 1.3 Hz, 2H), 2.87 (br d, J = 1.3 Hz, 2H) 2.64−2.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 50.4, 47.6, 36.8; IR (KBr, cm^{-1}) 3003, 2956, 2879, 1423, 1365, 1267, 1195, 1070.49, 1049, 1033, 952, 929, 894. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.36; H, 6.65.

Reaction of Bisepoxide with H_2SO_4 in Water. To a slurry of bisepoxide **9** (4.0 g, 26.0 mmol) in 20 mL of water was added H_2SO_4 (4 mL), and the resulting mixture was stirred at room temperature for 24 h. For neutralization of acid $NaHCO_3$ (8.0 g) was added. After evaporation of water, the residue was treated with MeOH and the solid was filtered. MeOH was evaporated, and the residue, without any purification, was treated with pyridine (7 mL) and Ac_2O (10 mL). The resulting mixture was stirred at room temperature for 24 h. EtOAc (300 mL) was added to the mixture and stirred for 5 min, then aqueous ice-cooled HCl (30 mL 5−7%) was added, and the mixture was stirred for a while at room temperature. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and water (3 × 200 mL), dried (Na_2SO_4), and concentrated to give 9.0 g of a mixture of isomeric tetraacetates **10**−**12**. The mixture of isomers was chromatographed on a silica gel column (150 g) eluting with EtOAc/hexane (1:3). Three compounds were isolated in the following order:

***rel*-(3a*R*,4*R*,5*S*,6*S*,7*R*,7a*S*)-Octahydroisobenzofuran-4,5,6,7-tetrayl tetraacetate (10):** 1.39 g, 15% as colorless crystals from hexane/EtOAc (1:4); mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (dd, A-part of AB-system, J_{45} = 9.5 Hz, J_{56} = 9.1 Hz, 1H, H-5), 5.22 (dd, B-part of AB-system, J_{45} = 9.5 Hz, J_{43a} = 6.3 Hz, 1H, H-4), 5.12 (t, J_{77a} = J_{76} = 10.0 Hz, 1H, H-7), 5.4 (dd, J_{67} = 10.0 Hz, J_{56} = 9.1 Hz, 1H, H-6) 3.83 (d, $J_{33'}$ = 9.7 Hz, 2H, H-3, H-3′) 3.75 (d, A part of AB system, $J_{11'}$ = 8.9 Hz, 1H, H-1), 3.69 (dd, B part of AB system, J_{17a} = 4.4 Hz, $J_{11'}$ = 8.9 Hz, 1H, H-1′), 2.98 (tt, J = 9.5 and 6.3 Hz, 1H, H-3a), 2.35 (ddd, J = 10.0, 6.3, and 4.5 Hz, 1H, H-7a), 1.97 (s, 6H, CH_3), 1.94 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.8, 169.7, 169.6, 72.8, 71.1, 70.93, 70.3, 70.0, 67.4, 42.2, 40.5, 20.70, 20.68, 20.57, 20.53; IR (ATR) 2944, 2918, 2882,

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1745, 1734, 1456, 1367, 1265, 1215, 1114, 1053, 1033, 975, 940, 923, 894. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.50; H, 5.94.

^{1}H NMR (400 MHz, benzene-d_6) δ 5.49 (t, J = 9.3 Hz, 1H, H-5), 5.33 (t, J = 10.1 Hz, 1H, H-7), 5.25 (dd, J = 9.3 and 6.6 Hz, H-4), 5.22 (t, J = 9.3 Hz, H-6), 3.72 (dd, J = 8.7 and 1.1 Hz, 1H, CH_2), 3.61−3.53 (m, 2H, CH_2), 3.31 (dd, J = 8.7 and 4.5 Hz, 1H, CH_2), 2.42 (tt, J = 9.76 and 6.6 Hz, H-3a), 1.89−1.63 (m, 1H, H-7a), 1.67 (s, CH_3), 1.66 (s, CH_3), 1.62 (s, CH_3), 1.51 (s, CH_3).

***rel*-(3a*R*,4*R*,5*S*,6*R*,7*S*,7a*S*)-Octahydroisobenzofuran-4,5,6,7-tetrayl tetraacetate (11):** (4.65 g, 50%) colorless crystals from hexane/EtOAc; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33−5.22 (m, 4H, H-4, H-5, H-6, H-7), 3.92−3.88 (m, 4H, H-1, H-3), 2.62−2.57 (m, 2H, H-3a, H-7a), 2.10 (s, 6H, 2 × CH_3), 2.06 (s, 6H, 2 × CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 170.0, 169.9, 70.2, 69.6, 68.1, 42.9, 21.2, 21.0; IR (KBr, cm^{-1}) 3002, 2890, 1739, 1367, 1251, 1213, 1060, 1041, 1028, 933, 906. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.58; H, 6.31.

***rel*-(3a*R*,4*S*,5*R*,6*S*,7*R*,7a*S*)-Octahydroisobenzofuran-4,5,6,7-tetrayl tetraacetate (12):** colorless crystals (1.77 g, 19%) from hexane/EtOAc; mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (br s, 4H, H-4, H-5, H-6, H-7), 3.89 (d, J = 6.4 Hz, 4H, CH_2), 2.94 (br s, 2H, H-3a, H-7a), 2.11 (s, 6H, 2 × CH_3), 2.08 (s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 170.0, 69.5, 69,2, 68.7, 40.1, 21,2, 21.0; IR (KBr, cm^{-1}) 3000, 2955, 1745, 1732, 1369, 1255, 1222, 1213, 1093, 1074, 1031, 885. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.59; H, 6.37.

General Procedure for Ring-Opening of Tetrahydrofuran Derivatives (10−12). To a stirred solution of 1.0 g (2.80 mmol) of tetraacetate in Ac_2O/AcOH (10 mL 1:1) was added sulfamic acid (40 mg) at room temperature, followed by heating at reflux temperature for 24 h. After the mixture was cooled to room temperature, HCl was added (50 mL, 5%) and extracted with ethyl acetate (300 mL). The organic phase was washed with water (2 × 100 mL) and saturated $NaHCO_3$ (2 × 50 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure the residue was crystallized from EtOAc/*n*-hexane (1:4) to give the corresponding hexaacetate.

***rel*-(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Bis(acetoxymethyl)cyclohexane-1,2,3,4-tetrayl Tetraacetate (13).** Tetraacetate **10** (1.0 g, 2.79 mmol) was reacted with sulfamic acid as described above to give hexaacetate **13** as colorless crystals (0.90 g, 70%): mp 105−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (t, J_{34} = J_{34} = 3.2 Hz, 1H, H-4), 5.38 (dd, A part of AB system, J_{12} = 9.4, J_{23} = 10.1 Hz, 1H, H-2), 5.29 (dd, B part of AB system, J_{16} = 11.4 Hz, J_{12} = 9.4 Hz, 1H, H-1) 5.18 (dd, J_{23} = 10.1 Hz, J_{34} = 3.2 Hz, 1H, H-3), 4.29−4.22 (m, 3H), 3.98 (dd, 1H, J = 11.8 and 4.1 Hz, 1H), 2.66−2.56 (m, 1H, H-6), 2.47−2.36 (m, 1H, H-7), 2.14 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.6, 170.4, 170.2, 170.1, 170.0, 71.8, 70.3, 70.0, 69.8, 61.7, 61.4, 39.6, 37.0, 21.2, 21.1, 21.0, 20.9, 20.9; IR (KBr, cm^{-1}) 2964, 1747, 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.

General Procedure for Hydrolysis of Hexaacetates 10−12. Synthesis of Bishomoinositols. Hexaacetate (1.0 mmol) was dissolved in 60 mL of absolute methanol. While dry NH_3(g) was passed through solution, the mixture was stirred for 5 h at room temperature. Evaporation of the solvent and formed acetamide gave hexol.

***rel*-(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetraol (14).** Hexaacetate **13** (1.0 g, 2.17 mmol) was hydrolyzed as described above to give hexol **14**: 0.43 g, 96%, colorless viscous oil; ^{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), 3.70−3.67 (m, 1H), 3.53−3.50 (m, 1H), 3.46−3.43 (m, 1H), 3.37 (bs, 1H), 3.30 (bd, J = 7.9 Hz, 1H), 3.27−3.17 (m, 2H), 2.01−1.94 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 75.4, 71.9, 72.4, 70.2, 60.9, 58.6, 43.2, 40.1; IR (KBr, cm^{-1}) 3400, 2931, 2904, 1447, 1382, 1343, 1324, 1256, 1239, 1214, 1196, 1150, 1134, 1110. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.52; H, 7.49.

***rel*-(1*R*,2*S*,3*R*,4*S*,5*S*,6*R*)-5,6-Bis(acetoxymethyl)cyclohexane-1,2,3,4-tetrayl Tetraacetate (18).** Tetraacetate **11** (0.5 g, 1.40 mmol) was hydrolyzed with sulfamic acid as described above: colorless crystals (0.47 g, 74%) from EtOAc/*n*-hexane (1:4); mp 117−119 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.30 (br s, 4H, H-1, H-2, H-3, H-4); 4,35 (dd, A part of AB System, J = 11.2 and 6.7 Hz, 2H, CH_2), 4.17 (dd, B part of AB System, J = 11.2 and 6.0 Hz, 2H, CH_2), 2.57−2.53 (m, 2H, H-5, H-6), 2.09 (s, 2 × CH_3), 2.07 (s, 2 × CH_3), 2,06 (s, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 170.8, 169.8, 169.7, 70.3, 68.0, 61.7, 38.8, 21.1, 21.0, 20.9 ppm; IR (KBr, cm^{-1}) 1735, 1435, 1367, 1219, 1205, 1180, 1105, 1082, 1031, 989, 945. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13. Found; C, 52.19; H, 6.25.

***rel*-(1*R*,2*S*,3*R*,4*S*,5*S*,6*R*)-5,6-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetraol (19).** The hexaacetate **18** (1.0 g, 2.17.mmol) was hydrolyzed with NH_3(g) as described above to give hexol **19** (0.41 g, 92%) as a colorless viscous oil: ^{1}H NMR (300 MHz, CD_3OD) δ 4.88 (bs, 6H, OH), 3.89−3.83 (m, 4H, CH), 3.79−3.73 (m, 4H, CH_2), 2.18−2.13 (m, 2H, CH); ^{13}C NMR (75 MHz, CD_3OD) δ 73.3, 71.6, 61.2, 43.2; IR (KBr, cm^{-1}) 3294, 2922, 1402, 1039, 999, 769, 632. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C; 46.01, H, 7.78.

Reaction of Tetraacetate 12 with Sulfamic Acid. Tetraacetate **12** (1.0 g, 2.8 mmol) was hydrolyzed with sulfamic acid as desribed above. The mixture was separated by silica gel chromatography eluting with EtOAc/hexane (1:3). The first fraction was the hexaacetate **20**. The second fraction was identified as the symmetrical hexaacetate **21**.

***rel*-(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-5,6-Bis(acetoxymethyl)cyclohexane-1,2,3,4-tetrayl tetraacetate (20):** 0.58 g (45%); colorless crystals from EtOAc/*n*-hexane (1:2); mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (br s, 1H, CH), 5.37 (dd, A part of AB system, J = 10.8, 3.2 Hz, 1H, CH), 5.36−5.30 (m, 1H, CH), 5.31 (dd, B part of AB system, J = 10.6, 5.3 Hz, 1H, CH), 4.31 (dd, 1H, A part of AB system, J = 12.0, 2.4 Hz, 1H, CH_2), 4.21 (dd, B part of AB system, J = 12.0, 3.2 Hz, 1H, CH_2), 4.15 (d, J = 5.5 Hz, 2H, CH_2), 2.72−2.64 (m, 2H, CH), 2.16 (s, CH_3), 2.15 (s, CH_3), 2.10 (s, CH_3), 2.04 (s, CH_3), 2.03 (s, CH_3), 2.01 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.5, 170.4, 170.2, 169.9, 169.8, 69.9, 69.5, 68.3, 67.5, 61.9, 59.6, 36.6, 36.0, 21.3, 21.1, 21.0, 20.9, 20.86 (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.

***rel*-(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-5,6-Bis(acetoxymethyl)cyclohexane-1,2,3,4-tetrayl tetraacetate (21):** 0.39 g (30%); colorless crystals from EtOAc/*n*-hexane (1:2); mp 106−109 °C; NMR (300 MHz, $CDCl_3$) δ 5.30 (br d, 2H, J = 6.8 Hz, 2H, CH), 5.15 (bs, 2H, CH), 4.24 (bs, 4H, CH_2), 2.66 (bs, 2H, CH), 2.11 (s, 2 × CH_3), 2.05 (s, 2 × CH_3), 2.03 (s, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.8, 169.7, 69.5, 67.6, 61.4, 37.3, 21.1, 21.1, 21.0; IR (KBr, cm^{-1}) 1732, 1367, 1230, 1209, 1188, 1064, 1043, 1024, 904. Anal. Calcd for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13. Found: C; 52.36, H, 6.27.

***rel*-(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-5,6-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetraol (22).** Hexaacetate **20** (0.8 g, 1.74 mmol) was hydrolyzed with NH_3(g) as described above to give hexol **22** (0.35 g, 97%) as a colorless viscous oil: ^{1}H NMR (300 MHz, D_2O) δ 4.7 (bs, 6H, OH), 3.99 (bd, J = 2.2 Hz, 1H, CH), 3.94−3.91 (m, 1H, CH), 3.88−3.65 (m, 8H, CH and CH_2), 2.32−2.24 (m, 1H, CH), 2.18−2.10 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O at 60 °C) 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.

***rel*-(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-5,6-Bis(hydroxymethyl)cyclohexane-1,2,3,4-tetraol (23).** Hexaacetate **21** (0.6 g, 1.30 mmol) was hydrolyzed with NH_3(g) as described above to give hexol **23** (0.24 g, 90%) as a colorless viscous oil: ^{1}H NMR (300 MHz, CD_3OD) δ 4.89 (bs, 6H, OH), 3.95−3.62 (m, 8H, CH and CH_2) 2.27 (bs, 2H, CH); ^{13}C NMR (75 MHz, CD_3OD at 80 °C) δ 70.9, 69.9, 58.2, 40.2. IR (KBr, cm^{-1}) 3332, 2926, 1450, 1402, 1039, 999, 769, 632. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.82; H, 7.37.

Ring-Opening Reaction of the Bisepoxide 9 with H_2SO_4 in Acetic Anhydride 9. To a stirred solution of bisepoxide **9** (4.0 g, 26.0 mmol) in 10 mL of acetic anhydride was added dropwise H_2SO_4 (1.5 mL) and then the mixture was stirred for 12 h at room temperature. After completion of the reaction, dichloromethane (500 mL) was added. The resulting solution was extracted first with saturated $NaHCO_3$ solution then with water and dried over $MgSO_4$. Solvent was evaporated and the residue was chromatographed on a silica gel

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column (70 g) eluting with hexane/EtOAc (4:1). The rearranged product **24** was isolated (7.43 g, 80%). Crystallization from hexane/EtOAc (1:4) gave *rel*-(1*R*,5*S*,6*R*,7*R*,8*R*,9*S*)-3-oxabicyclo[3.3.1]nonane-6,7,8,9-tetrayl tetraacetate **24** as colorless crystals, mp 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, J_{78} = 10.3 Hz, J_{76} = 5.4 Hz, 1H, H-7), 5.56 (dd, J_{87} = 10.3 Hz, J_{81} = 4.6 Hz, 1H, H-8), 5.50 (ddd, J_{67} = 5.4 Hz, J_{65} = 2.3 Hz, J_{69} = 0.9 Hz, 1H, H-6), 4.96 (bt, J = 2.7 Hz, 1H, H-9), 4.14 (bd, A-part of AB system, $J_{22'}$ = 11.4 Hz, 1H, H-2), 3.94 (d, A-part of AB system, $J_{44'}$ = 12.1 Hz, 1H, H-4), 3.62 (dd, B-part of AB system, $J_{44'}$ = 12.1 Hz, $J_{4'5}$ = 2.2 Hz, 1H, H-4′), 3.54 (d, B-part of AB system, $J_{22'}$ = 11.4 Hz, 1H, H-2′), 2.43 (m, 1H, H-5), 2.29 (m, 1H, H-1), 2.08 (s, 6H, 2 × CH_3), 2.01 (s, 3H, CH_3), 1.92 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 169.9, 169.87, 72.8, 71.6, 70.0, 69.5, 68.4, 66.5, 39.6, 38.7, 21.2, 21.0, 20.9, 20.7; IR (ATR) 2978, 2856, 1735, 1369, 1216, 1171, 1132, 1114, 1035, 975, 948, 909, 862. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.80; H, 6.43.

rel-(1*R*,5*S*,6*R*,7*R*,8*R*,9*S*)-3-Oxabicyclo[3.3.1]nonane-6,7,8,9-tetraol (25). Tetraacetate **24** (100 mg, 0.28 mmol) was dissolved in 10 mL of methanol. The solution was stirred at room temperature for 24 h while passing $NH_{3(g)}$ through the solution. After evaporation of the solvent and the removal of the acetamide which was formed during the reaction, tetrol **25** was obtained as colorles oil (499 mg, 94%): ^{1}H NMR (400 MHz, CD_3OD) δ 4.95 (bs, 4H, OH), 4.27−4.15 (m, 5H, H-2, H-6, H-7, H-8, H-9), 3.86 (d, A-part of AB system, $J_{44'}$ = 11.8 Hz, 1H, H-4) 3.63 (dd, B-part of AB system, $J_{44'}$ = 11.8 Hz, J_{45} = 2.2 Hz, 1H, H-4), 3.49 (bd, B-part of AB system, $J_{22'}$ = 11.6 Hz, 1H, H-2′), 2.29 (bs, 1H, H-5), 2.16 (bs, 1H, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ 76.6, 74.8, 74.0, 70.6, 69.6, 66.9, 46.5, 43.2; IR (ATR) 3264, 3356, 2921, 2856, 1659, 1394, 1259, 1142, 1127, 1101, 1059, 970. Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.14; H, 7.34.

Ring-Opening Reaction of the Bisepoxide 9 in Acetic Anhydride with Catalytic Amount of H_2SO_4. To a stirred solution of bisepoxide **9** (2.0 g, 13 mmol) in 10 mL of acetic anhydride was added 4−5 drops of H_2SO_4, and then the mixture was stirred for 12 h at room temperature. The reaction mixture was worked up as described above. The residue was chromatographed on a silica gel column eluting with hexane/EtOAc (3:1). The first fraction was the rearranged product **27** (1.39 g, 39%). The second fraction was identified as the epoxide ring-opening product **26** (1.60 g, 48%).

***rel*-(((1*S*,2*S*,5*R*,6*S*)-5-Acetoxy-7-oxabicyclo[4.1.0]hept-3-en-2-yl)methoxy)methyl acetate (27):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (dt, J_{56} = 4.5 Hz, J_{54} = J_{53} = 2.1 Hz, 1H, H-5), 5.53 (ddt, A- part of AB-system, J_{34} = 10.4 Hz, J_{31} = J_{35} = 2.1 Hz, and J_{32} = 4.7 Hz, 1H, H-3), 5.46 (ddt, J_{43} = 10.4 Hz, J_{45} = 2.1 Hz, and J_{42} = J_{46} = 1.6 Hz, 1H, H-4), 5.20 (d, A-part of AB-system, J_{92} = 6.3 Hz, 1H, H-9), 5.16 (d, B-part of AB-system, $J_{9'2}$ = 6.3 Hz, 1H, H-9′), 3.71 (dd, B-part of AB-system, $J_{77'}$ = 9.8 Hz and J_{72} = 9.8 Hz, 1H, H-7′), 3.52 (dd, B-part of AB-system, $J_{77'}$ = 9.8 Hz and J_{72} = 6.7 Hz, 1H, H-7), 3.47 (ddd, J_{65} = 4.2 Hz, J_{65} = 4.5 Hz, J_{62} = 2.2 Hz, 1H, H-6), 3.36 (dt, J_{16} = 4.2 Hz, J_{13} = $J_{1.2}$ = 2.1 Hz, 1H, H-1), 2.88 (m, 1H, H-2), 2.08 (s, 3H, CH_3), 2.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 126.3, 124.1, 89.1, 70.5, 67.7, 53.1, 52.4, 36.4, 21.0, 20.96; IR (ATR) 2922, 1730, 1433, 1369, 1225, 1155, 1123, 1011, 939, 899, 866, 808, 772, 733. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.27; H, 6.40.

***rel*-(1a*S*,2*R*,3*S*,3a*R*,6a*S*,6b*S*)-Octahydrooxireno[2,3-*e*]isobenzofuran-2,3-diyl diacetate (26):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (dd, A-part of AB system, J_{23} = 9.6 and J_{21a} = 1.3 Hz, 1H, H-2), 5.37 (dd, B-part of AB system J_{32} = 9.6 and J_{33a} = 5.0 Hz, 1H, H-3), 3.90 (dd, A-part of AB system, $J_{44'}$ = 9.7 and J_{43a} = 6.7 Hz, 1H, H-4 or H-4′), 3.85 (d, J_{66a} = 4.7 Hz, 2H, H-6), 3.70 (dd, B-part of AB system $J_{44'}$ = 9.7 and $J_{4'3a}$ = 8.3 Hz, 1H, H-4 or H-4′), 3.39 (dt, J_{1a6b} = 4.1 and J_{1a2} = 1.3 Hz, 1H, H-1a), 3.13 (bd, J_{1a6b} = 4.1 Hz, 1H, H-6b), 2.92 (dt, J_{6a3a} = 8.3 and J_{6a6} = $J_{6a6'}$ = 4.7 Hz, 1H, H-6a), 2.75−2.85 (m, 1H, H-3a), 2.07, (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.2, 71.8, 69.3, 69.2, 68.5, 56.9, 54.8, 41.0, 38.6, 21.13, 21.1; IR (ATR) 2958, 2883, 2856, 1735, 1479, 1440, 1367, 1226, 1097, 1064, 1039, 1020, 985, 921, 910, 893, 831, 798. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 55.92; H, 6.35.

Reaction of the Monoepoxide 26 with H_2SO_4 in Acetic Anhydride. To a stirred solution of monoepoxide **26** (1.0 g, 3.9 mmol) in 10 mL of acetic anhydride was added H_2SO_4 (1.5 mL), and then the mixture was stirred for 12 h at room temperature. The reaction mixture was worked up as described above. Chromatography of the residue on silica gel (40 g) column eluting with hexane/EtOAc (4:1) gave 1.2 g (86%) tetraactate **24**.

Reaction of 27 with H_2SO_4 in Acetic Anhydride. To a stirred solution of **27** (1.0 g, 3.9 mmol) in 10 mL of acetic anhydride was added H_2SO_4 (1.5 mL), and then the mixture was stirred for 12 h at room temperature. The reaction mixture was worked up as described above. Chromatography of the residue on silica gel (40 g) column eluting with hexane/EtOAc (4:1) gave 1.1 g (86%) tetraacetate **24**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^{1}H and ^{13}C) for all new compounds and X-ray structures and CIFs of **12** and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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