Chelation-Assisted C−O Bond Cleavage of Ortho Esters. A Convenient Synthesis of *myo*-Inositol Derivatives Having Free Hydroxy Group(s) at Specific Position(s)

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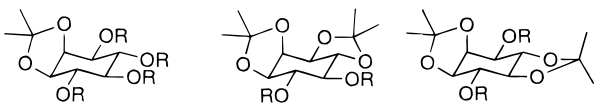
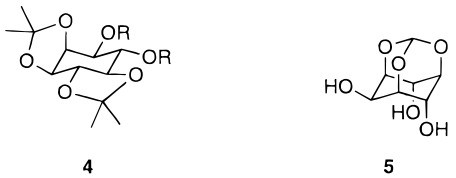
Reactions of ortho esters of *myo*-inositol **8** or **10** with 1−2 equiv of Grignard reagents in benzene−ether yield regio- and stereoselectively the corresponding ring opening products having a free hydroxy group at C-1. The regioselectivity is rationalized owing to the presence of the 2-methoxy group which will serve as an auxiliary to form a chelation complex **12** with magnesium. Inositol derivatives having two free hydroxy group at C-1 and C-3 positions can be achieved from reactions of **6** or **8** with excess Grignard reagents or under more drastic conditions. The reaction of **8b** with excess $LiAlH_4/AlCl_3$, on the other hand, yields the corresponding 1,5-diol **19**.

Inositol derivatives are important biologically.[1] Tremendous efforts have been endeavored in synthesizing partially protected inositols having the free hydroxy group(s) at specific position(s). Acetal functionalities are most commonly used to protect vicinal hydroxy groups in inositols.[1,2] To illustrate this, acetals **1** to **4** have widely been employed as the starting materials for the synthesis of various derivatives of *myo*-inositols.[3,4] However, multistep synthesis and tedious separation of regioisomers are frequently required to access **2**−**4**. More recently, Kishi and several other groups have employed orthoformate of *myo*-inositol **5** for the preparation of certain inositol derivatives having one to three free hydroxy groups.[3]



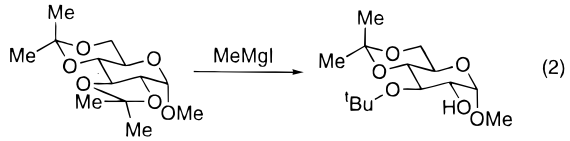
1 **2** **3**



4 **5**

It is well documented that nucleophiles can react with acetals to give the corresponding alkoxy alcohols.[4] Reaction of **6** with Me_3Al has been shown to afford **7** selectively (eq 1).[3e,f] We recently uncovered a chelation-assisted regioselective ring opening of acetals with Grignard reagents (eq 2).[4d,e] We felt that this reaction can be extended to the ortho esters of inositols to selectively give inositol derivatives having one or two free hydroxy groups at certain specific position(s).

6 **7** (1)



(2)

Inositol derivative **8a** was treated with MeMgI (2 equiv) in refluxing benzene−ether (10:3) for 16 h to give the corresponding ring opening derivative **9a** in 83% yield.[5] Similar reactions with EtMgBr and PhMgBr gave **9b** and **9c** in 68% yield each (eq 3).[5] When more reactive **8b** was employed, the reaction was carried out at room temperature in the same medium to afford **9d** in 57% yield.[5] The stereochemistry was determined by 2D NOESY experiments and by the X-ray structure of **9d**.[8] The nucleophile apparently attacks from the opposite site to the C−O bond being cleaved. Presumably, due to the rigidity of the skeleton of **6** or **8**, cleavage of the C−O bond with inversion of configuration was observed.

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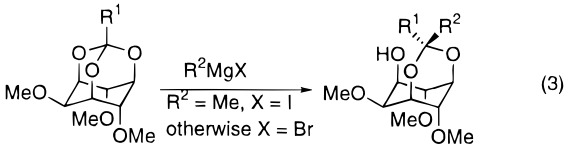
(4) For reviews, see: (a) Trofimov, B. A.; Korostova, S. E. *Russ. Chem. Rev.* **1975**, *44*, 41. (b) Mukaiyama T.; Murakami, M. *Synthesis* **1987**, 1043. (c) Alexakis A.; Mangeney, P. *Tetrahedron*: *Asymmetry* **1990**, *1*, 477. (d) Luh, T.-Y. *Pure Appl. Chem.* **1996**, *68*, 635. (e) Luh, T.-Y. *Synlett* **1996**, 201.

(5) These products were obtained as racemic mixture.

S0022-3263(97)00606-3 CCC: $14.00

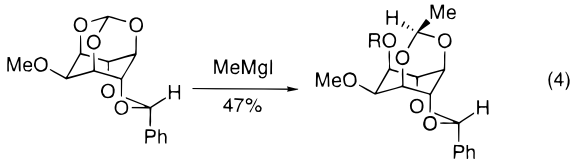


(3)

8a R^1 = H
8b R^1 = Ph

9a R^1 = H, R^2 = Me 83%
9b R^1 = H, R^2 = Et 68%
9c R^1 = H, R^2 = Ph 68%
9d R^1 = Ph, R^2 = Me 57%

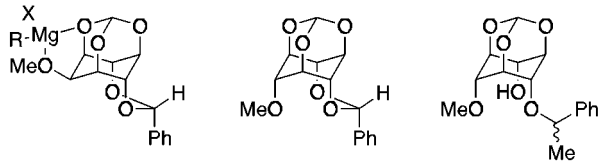
Treatment of **10** with MeMgI under the same conditions gave racemic **11a** as the sole product (eq 4). The benzylic acetal moiety in **10** remained intact under these conditions. The structure of **11a** was proved by the X-ray crystallography of the corresponding ether **11b**.[5]



(4)

10 **11a** R = H
11b R = Me

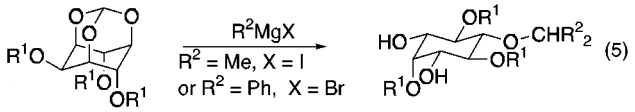
It is noteworthy that the reaction is both regio- and diastereoselective. The regioselectivity of this reaction is understandable owing to the presence of the 2-methoxy group which will serve as an auxiliary to form a chelation complex **12** with magnesium such that selective ring opening is expected. We have tested this viewpoint by investigating the related reaction of *scyllo*-inositol derivative **13** with MeMgI at room temperature. A diastereomeric mixture of **14** (2:1) was obtained in 56% yield. No C−O bond cleavage at the ortho ester moiety in **13** was observed. The methoxy group in **13** apparently directs



12 **13** **14**

the selectivity of the ring opening reaction at the benzylidene moiety. Interestingly, the reaction is nonstereoselective and is compatible with our earlier work on the alkylative ring opening of acetals with the methyl Grignard reagent.[6]

Acetal functionality are known to undergo chelation-assisted regioselective ring opening reactions with Grignard reagents.[4d,e,6] The products shown in eqs 3 and 4 contain such acetal group. We felt that a one-pot process may be developed such that a convenient synthesis of inositol derivatives having two free hydroxy group at C-1 and C-3 positions can be achieved from **6** or **8**. Accordingly, treatments of **6** with 3 equiv of MeMgI and with an excess amount of PhMgBr at refluxing benzene temperature yielded the corresponding diols **15a** and **15b** in 69% and 72% yields, respectively. Compound **8a** behaved similarly to give **15c** in 60% yield (eq 5). ^{13}C NMR data (8 signals for **15a** and 7 signals for **15b**,**c** due to the absorptions of sp^3 carbons) for **15** are consistent with a C_s symmetry.

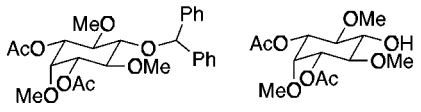


(5)

6 R^1 = Bn
8a R^1 = Me

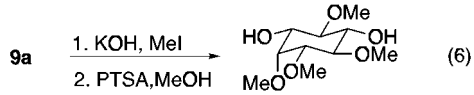
15a R^1 = Bn, R^2 = Me
b R^1 = Bn, R^2 = Ph
c R^1 = Me, R^2 = Ph

Compounds **15** appeared to be important intermediates to furnish various inositol derivatives having one to three free hydroxy group at different positions. For example, diacetate **16** was transformed upon hydrogenolysis into **17** in 86% yield.



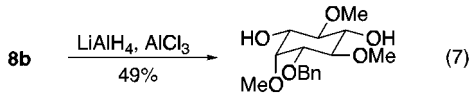
16 **17**

Although the 1,5-dihydroxy derivative can be obtained from **9** by protection of the hydroxy group followed by hydrolysis of the acetal moiety (e.g. **9a** to **18**, eq 6), a more direct synthesis would be desirable. The strategy was based on our previous work using $LiAlH_4/AlCl_3$ to effect regioselective ring opening of acetals.[7] Thus, reaction of **8b** with an excess of $LiAlH_4/AlCl_3$ for 16 h afforded **19** in 49% yield (eq 7). The ^{13}C NMR spectrum of **19** exhibited 10 signals due to absorptions of sp^3 carbons which is consistent with the structure with free hydroxy groups at C_1 and C_5. The discrepancy in regioselectivity between the Grignard reagent and the aluminum hydride reagent in these ring opening reactions, however, remains unclear.



(6)

18



(7)

19

In summary, we have demonstrated a useful method for the selective ring opening of ortho esters of *myo*-inositol derivatives. The procedure described here can serve as a convenient route for the synthesis of *myo*-inositol derivatives having one hydroxy group at C-1 or C-5, and two hydroxy groups at C-1,3 and at C-1,5. Other derivatives could easily be accessed from these intermediates.

Experimental Section

***exo*-3,5-*O*-Ethylidene-2,4,6-tri-*O*-methyl-*myo*-inositol (9a).** Compound **8a** (3.58 g, 15.4 mmol) in benzene (50 mL) was treated with MeMgI (15 mL in 2.05 M ether solution, 30.8 mmol). The mixture was heated at ca. 60 °C for 16 h, cooled,

(6) Yuan, T.-M.; Yeh, S.-M.; Hsieh, Y.-T.; Luh, T.-Y. *J. Org. Chem.* **1994**, *59*, 8192.

(7) Yuan, T.-M.; Hsieh, Y.-T.; Yeh, S.-M.; Shyue, J.-J.; Luh, T.-Y. *Synlett* **1996**, 53.

(8) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

diluted with ether, and washed with saturated NH_4Cl. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to give the residue which was chromatographed (silica gel, 30% EtOAc/hexane) to afford racemic **9a** as an oil (3.15 g, 83%): IR (neat) ν 3503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 4.8 Hz, 3 H), 3.14 (d, J = 5.6 Hz, 1 H), 3.33 (s, 3 H), 3.47 (s, 3 H), 3.49 (s, 3 H), 3.48−4.50 (m, 1 H), 3.73 (dt, J = 1.2, 4.4 Hz, 1 H), 3.79 (dd, J = 6.4, 7.8 Hz, 1 H), 4.15−4.20 (m, 2 H), 4.41 (ddd, J = 2.0, 4.4, 6.4 Hz, 1 H), 5.22 (q, J = 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 56.8, 58.0, 58.6, 67.7, 67.9, 71.2, 73.8, 74.9, 84.5, 90.7; HRMS Calcd for $C_{11}H_{20}O_6$: 248.1260. Found: 248.1263.

***exo*-3,5-*O*-Propylidene-2,4,6-tri-*O*-methyl-*myo*-inositol (9b).** In a manner similar to that described above, **8a** (0.49 g, 2.11 mmol) in benzene (20 mL) was treated with EtMgBr (2.2 mL in 2.5 M ether solution, 5.50 mmol) at 65 °C for 16 h to afford racemic **9b** as an oil (0.38 g, 68%): IR (neat) ν 3511 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3 H), 1.51 (dq, J =5.0, 7.5 Hz, 2 H), 3.05 (br s, 1 H), 3.34 (s, 3 H), 3.71 (dt, J = 1.0, 4.2 Hz, 1 H), 3.82 (dd, J = 6.5, 7.7 Hz, 1 H), 4.14−4.22 (m, 2 H), 4.45 (ddd, J = 1.8, 4.2, 6.5 Hz, 1 H), 4.97 (t, J = 5.0 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.0, 27.9, 56.8, 58.0, 58.5, 67.5, 68.1, 71.4, 73.9, 75.1, 84.5, 94.3; HRMS Calcd for $C_{10}H_{17}O_6$ (M − 43): 233.1025. Found: 233.1028.

***exo*-3,5-*O*-Benzylidene-2,4,6-tri-*O*-methyl-*myo*-inositol (9c).** In a manner similar to that described above, **8a** (1.51 g, 6.51 mmol) in benzene (30 mL) was treated with PhMgBr (4.0 mL in 2.1 M ether solution, 8.4 mmol) at 65 °C for 16 h to afford racemic **9c** as an oil (1.32 g, 68%): IR (neat) ν 3526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (d, J = 6.4 Hz, 1 H), 3.40 (s, 3 H), 3.53 (s, 3 H), 3.69 (d, J = 6.4 Hz, 1 H), 3.90−4.01 (m, 2 H), 4.26−4.31 (m, 1 H), 4.35−4.42 (m, 1 H), 4.62 (ddd, J = 1.8, 4.4, 6.4 Hz, 1 H), 6.07 (s, 1 H), 7.31−7.38 (m, 3 H), 7.43−7.47 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.0, 58.1, 58.6, 68.1, 68.2, 71.9, 73.9, 75.0, 84.4, 93.3, 126.2, 128.3, 129.0, 138.1; HRMS Calcd for $C_{16}H_{22}O_6$: 310.1416. Found: 310.1421.

***exo*-1′-Phenyl-3,5-*O*-ethylidene-2,4,6-tri-*O*-methyl-*myo*-inositol (9d).** In a manner similar to that described above, **8b** (0.47 g, 1.52 mmol) in benzene (15 mL) was treated with MeMgI (8.8 mL in 2 M ether solution, 9.6 mmol) at 15 °C for 16 h to afford racemic **9d** (0.28 g, 57%): mp 102−104 °C; IR (neat) ν 3561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3 H), 2.84 (d, J = 9.0 Hz, 1 H), 3.43 (s, 3 H), 3.45 (s, 6 H), 3.66−3.71 (m, 1 H), 3.81 (dd, J = 1.5, 5.9 Hz, 1 H), 4.07 (ddd, J = 2.7, 5.9, 9.0 Hz, 1 H), 4.45−4.52 (m, 1 H), 4.56−4.65 (m, 1 H), 4.73 (br d, J = 5.6 Hz, 1 H), 7.19−7.32 (m, 3 H), 7.47−7.51 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.6, 56.8, 57.6, 58.7, 68.1, 68.9, 70.7, 72.6, 74.9, 86.0, 98.9, 124.2, 127.7, 128.1, 146.0; Anal. Calcd C, 62.95%; H, 7.46%. Found: C, 62.59%; H, 7.18%.

***endo*-4,6-*O*-Benzylidene-*exo*-3,5-ethylidene-2-*O*-methyl-*myo*-inositol (11a).** In a manner similar to that described above, **10** (0.40 g, 1.37 mmol) in benzene (23 mL) was treated with MeMgI (2.8 mL in 2 M ether solution, 5.6 mmol) at 55 °C for 16 h to afford racemic **11a** (0.20 g, 47%): IR (neat) ν 3457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J = 4.7 Hz, 3H), 2.99 (br, 1 H), 3.54 (s, 3 H), 4.16 (dd, J = 4.9, 7.4 Hz, 1 H), 4.44 (d, J = 7.4 Hz, 1 H), 4.52−4.59 (m, 2 H), 4.63 (dt, J = 1.7, 5.2 Hz, 1 H), 4.81−4.90 (m, 1 H), 5.69 (q, J = 4.7 Hz, 1 H), 6.04 (s, 1 H), 7.34−7.41 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 57.4, 64.2, 67.2, 67.7, 68.8, 72.9, 74.2, 90.9, 92.8, 126.2, 128.5, 129.4, 137.4.

***endo*-4,6-*O*-Benzylidene-*exo*-3,5-ethylidene-1,2-di-*O*-methyl-*myo*-inositol (11b).** To a mixture of **11a** (0.19 g, 0.62 mmol) and solid KOH (0.14 g, 2.50 mmol) in DMSO (5 mL) was added MeI (0.08 mL, 1.3 mmol) dropwise and the mixture was stirred at rt overnight, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried ($MgSO_4$). The solvent was removed in vacuo to give the residue which was chromatographed (silica gel, 20−30% EtOAc/hexane) to give racemic **11b** (0.19 g, 94%): mp 118−119 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 4.9 Hz, 3 H), 3.51 (s, 3 H), 3.58 (s, 3 H), 3.91 (d, J = 7.5 Hz, 1 H), 4.25 (dd, J = 4.7, 7.4 Hz, 1 H), 4.49 (t, J = 4.7 Hz, 1 H), 4.52−4.59 (m, 1 H), 4.61 (td, J = 2.0, 5.0 Hz, 1 H), 4.90 (br t, J = 5.0 Hz, 1 H), 5.85 (q, J = 4.9 Hz, 1 H), 6.08 (s, 1 H), 7.34−7.39 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 57.5, 59.4, 63.9, 67.3, 69.4, 72.1, 73.0, 78.6, 90.6, 92.5, 126.1, 128.5, 129.5, 137.4; HRMS Calcd for $C_{17}H_{22}O_6$: 322.1416. Found: 322.1414. Anal. Calcd C, 63.33%; H, 6.88%. Found: C, 63.22%; H, 6.85%.

3-*O*-Methyl-5-*O*-(1′-phenylethyl)-2,4,6-*O*-methylidyne-*scyllo*-inositol (14). In a manner similar to that described in **9a**, **13** (51.7 mg, 0.18 mmol) in benzene (2 mL) was treated with MeMgI (0.5 mL in 2 M ether solution, 1.0 mmol) at rt for 16 h to afford a mixture of inseparable diasteromers **14** (34.0 mg, 56%, dr = 2:1). The major isomer exhibited ^1H NMR (300 MHz, $CDCl_3$) at δ 1.42 (d, J = 6.4 Hz, 3 H), 3.52 (s, 3 H), 4.07−4.57 (m, 6 H), 4.67 (q, J = 6.4 Hz, 1 H), 5.40 (s, 1 H), 7.25−7.38 (m, 5 H). The minor isomer showed characteristic ^1H NMR absorptions at δ 1.43 (d, J = 6.4 Hz, 3H) and 3.47 (s, 3 H).

5-*O*-Isopropyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (15a). In a manner similar to that described in **9a**, **6** (0.14 g, 0.30 mmol) in benzene (3 mL) was treated with MeMgI (0.45 mL in 2 M ether solution, 0.90 mmol) under reflux for 16 h to afford **15a** (0.11 g, 69%): IR (neat) ν 3455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.0 Hz, 6 H), 2.25 (d, J = 5.4 Hz, 2 H), 3.36 (t, J = 9.6 Hz, 1 H), 3.50 (ddd, J = 2.4, 5.6, 9.6 Hz, 2 H), 3.68 (t, J = 9.6 Hz, 2 H), 3.96 (t, J = 2.4 Hz, 1 H), 4.10 (sept, J = 9.6 Hz, 1 H), 4.74 (d, J = 11.2 Hz, 2 H), 4.77 (s, 2 H), 4.93 (d, J = 11.2 Hz, 2 H), 7.28−7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 72.6, 73.1, 75.2, 75.8, 78.8, 79.6, 82.3, 127.7, 127.8, 128.0, 128.4, 128.5, 138.5, 138.6; HRMS Calcd for $C_{30}H_{36}O_6$: 492.2512. Found: 492.2510.

5-*O*-Benzhydryl-2,4,6-tri-*O*-benzyl-*myo*-inositol (15b). In a manner similar to that described in **9a**, **6** (0.32 g, 0.70 mmol) in benzene (7 mL) was treated with PhMgBr (1.7 mL in 2 M ether solution, 3.40 mmol) and was refluxed for 16 h to yield **15b** (0.32 g, 72%): mp 115−117 °C; IR (neat) ν 3558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (d, J = 5.3 Hz, 2 H), 3.48 (ddd, J = 2.8, 5.3, 9.2 Hz, 2 H), 3.58 (t, J = 9.2 Hz, 1 H), 3.83 (t, J = 9.2 Hz, 2 H), 3.94 (t, J = 2.8 Hz, 1 H), 4.73 (s, 4 H), 4.76 (s, 2 H), 6.13 (s, 1 H), 7.18−7.39 (m, 25 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.6, 75.2, 75.5, 78.3, 78.7, 82.4, 83.5, 127.3, 127.4, 127.8, 128.0, 128.1, 128.2, 128.5, 138.4, 142.6; HRMS Calcd for $C_{40}H_{42}O_6$: 618.2981. Found: 525.2232 (M^+ − 93). Anal. Calcd C, 77.63%; H, 6.85%. Found: C, 77.54%, H, 6.51%.

5-*O*-Benzhydryl-2,4,6-tri-*O*-methyl-*myo*-inositol (15c). In a manner similar to that described in **9a**, **8a** (0.36 g, 1.53 mmol) in benzene (15 mL) was treated with PhMgBr (3.1 mL in 2.0 M ether solution, 6.2 mmol) under reflux for 16 h to give **15c** (0.24 g, 60%): mp 89−90 °C; IR (neat) ν 3420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (d, J = 5.1 Hz, 2 H), 3.29−2.52 (m, 5 H), 3.48 (s, 6 H), 3.63 (s, 3 H), 3.67 (t, J = 2.5 Hz, 1 H), 5.95 (s, 1 H), 7.18−7.39 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.3, 61.7, 72.6, 78.4, 80.4, 83.8, 84.0, 127.3, 127.4, 128.1, 142.7; HRMS Calcd for $C_{22}H_{28}O_6$: 388.1886. Found: 388.1885. Anal. Calcd C, 68.01%; H, 7.27%. Found: C, 67.74%; H, 7.15%.

1,3-*O*-Diacetyl-5-*O*-benzhydryl-2,4,6-tri-*O*-methyl-*myo*-inositol (16). A benzene solution (10 mL) of **15c** (0.97 g, 2.49 mmol), Ac_2O (0.58 mL), and pyridine (0.5 mL) was refluxed for 5 h. The mixture was cooled, diluted with ether, and washed with 10% HCl and saturated NaCl. The organic solution was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (silica gel, 30% EtOAc/hexane) to afford **16** (0.84 g, 71%): mp 135−137 °C; IR (neat) ν 1751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 6H), 3.35 (s, 6 H), 3.42 (t, J = 9.0 Hz, 1 H), 3.47 (s, 3 H), 3.64 (dd, J = 9.1, 10.1 Hz, 2 H), 3.71 (t, J = 2.5 Hz, 1 H), 4.67 (dd, J = 2.5, 10.1 Hz, 2 H), 5.94 (s, 1 H), 7.17−7.39 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 60.9, 61.3, 73.5, 78.0, 78.8, 81.1, 84.4, 127.2, 127.3, 128.0, 142.7, 169.9; HRMS Calcd for $C_{26}H_{32}O_8$: 472.2097. Found: 472.2109. Anal. Calcd C, 66.09%; H, 6.83%. Found: C, 66.06%; H, 6.83%.

1,3-*O*-Diacetyl-2,4,6-tri-*O*-methyl-*myo*-inositol (17). A methanolic solution (100 mL) of **16** (0.42 g, 0.89 mmol) in the presence of Pd/C (5%, 83 mg) was treated with H_2 at 1 atm for 4 h. The mixture was filtered on Celite, and the filtrate was evaporated in vacuo to give the residue which was chromatographed (silica gel, 50% EtOAc/hexane) to afford **17**

(0.23 g, 86%): mp 113−114 °C; IR (neat) ν 3561, 1746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 6 H), 2.65 (d, J = 2.4 Hz, 1 H), 3.40−3.56 (m, 4 H), 3.47 (s, 3 H), 3.54 (s, 3 H), 3.76 (t, J = 2.8 Hz, 1 H), 4.75 (dd, J = 2.4, 9.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 60.8, 61.6, 73.3, 74.2, 78.4, 80.2, 169.9; HRMS Calcd for $C_{13}H_{22}O_8$: 306.1315. Found: 306.1317. Anal. Calcd C, 50.96%; H, 7.24%. Found: C, 51.15%; H, 7.30%.

2,3,4,6-Tetra-*O*-methyl-*myo*-inositol (18). To a mixture of **9a** (1.09 g, 4.40 mmol) and solid KOH (1.01 g, 18.0 mmol) in DMSO (20 mL) was added MeI (0.7 mL, 11.2 mmol) dropwise, and the mixture was stirred at rt overnight, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried ($MgSO_4$). The solvent was removed in vacuo to give the residue which was chromatographed (silica gel, 50% EtOAc/hexane) to give the corresponding ether as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 4.8 Hz, 3 H), 3.35 (s, 3 H), 3.47 (s, 6 H), 3.49 (s, 3 H), 3.57 (d, J = 6.9 Hz, 1 H), 3.70−3.74 (m, 1 H), 3.82 (t, J = 7.5 Hz, 1 H), 3.93 (dd, J = 6.9, 7.5 Hz, 1 H), 4.16 (dd, J = 1.8, 3.5 Hz, 1 H), 4.46 (ddd, J = 1.8, 4.0, 6.3 Hz, 1 H), 5.19 (q, J = 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 56.9, 57.8, 58.1, 58.6, 67.8, 71.9, 72.2, 75.0, 76.6, 82.5, 90.7; HRMS Calcd for $C_{12}H_{22}O_6$: 262.1416. Found: 262.1410.

A mixture of the ether (0.32 g, 1.23 mmol) and TsOH (58 mg, 0.20 mmol) in MeOH (10 mL) was stirred at rt for 6 h and then treated with solid K_2CO_3. After filtration, the filtrate was concentrated, and the racemic **18** was crystallized from the filtrate (0.24 g, 76%): mp 144−146 °C; IR (neat) ν 3451 cm^{-1}; ^1H NMR (400 MHz, D_2O + DMSO-d_6) δ 2.95−3.11 (m, 4 H), 3.20−3.23 (dd, J = 2.4, 9.6 Hz, 1 H), 3.29 (s, 3 H), 3.37 (s, 3 H), 3.40 (s, 3 H), 3.59 (t, J = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 57.9, 59.8, 59.9, 70.9, 73.9, 79.4, 81.4, 82.9, 83.5; HRMS Calcd for $C_{10}H_{20}O_6$: 236.1260. Found: 236.1264.

3-*O*-Benzyl-2,4,6-tri-*O*-methyl-*myo*-inositol (19). Compound **8b** (1.14 g, 3.70 mmol) in CH_2Cl_2 (10 mL) was treated with $LiAlH_4$ (0.17 g) in the presence of a catalytic amount of $AlCl_3$ (ca. 50 mg) in Et_2O (30 mL). The mixture was refluxed for 16 h, diluted with ether, washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (silica gel, 30−50% EtOAc/hexane) to afford racemic **19** (0.57 g, 49%): mp 124−125 °C; IR (neat) ν 3428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (d, J = 6.0 Hz, 1 H), 2.67 (br, 1 H), 3.26−3.39 (m, 4 H), 3.44−3.51 (m, 1 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 3.73 (t, J = 2.3 Hz, 1 H), 4.67 (s, 2 H), 7.27−7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.8, 61.4, 61.5, 72.1, 72.6, 74.6, 79.2, 80.7, 82.6, 82.8, 127.6, 127.8, 128.4, 138.0; HRMS Calcd for $C_{16}H_{24}O_6$: 312.1573. Found: 312.1578. Anal. Calcd C, 61.52%; H, 7.74%. Found: C, 61.27%; H, 7.74%.

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Supporting Information Available: NMR spectra for **9a**−**d**, **11a**, **11b**, **15a**−**c**, and **16**−**19** and ORTEP of **9d** and **11b** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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