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Tetrahedron 61 (2005) 4437–4446

Sulfonate protecting groups. Synthesis of O- and C-methylated inositols: D- and L-ononitol, D- and L-laminitol, mytilitol and *scyllo*-inositol methyl ether

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Received 8 December 2004; revised 10 February 2005; accepted 24 February 2005

Available online 23 March 2005

Abstract—Syntheses of D- and L-ononitol, D- and L-laminitol, mytilitol and *scyllo*-inositol methyl ether starting from *myo*-inositol are described. One or two of the *myo*-inositol 1,3,5-orthoformate hydroxyl groups were protected as tosylates. These mono or ditosylates served as key intermediates for the preparation of O- and C-methyl inositols. Racemic 2,4-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate was resolved as its diastereomeric camphanates. Use of sulfonate groups for the protection of inositol hydroxyl groups resulted in substantial improvement in the overall yield of O- and C-methyl inositols.

1. Introduction

Selective protection and deprotection of various functional groups is an indispensable tool for the synthesis of complex organic compounds. Molecules having non-equivalent functional groups of the same kind (polyols, polyamines, polyacids, etc.) pose challenges during their chemical manipulation, as the difference in their reactivity is often subtle. A number of methods have been explored to achieve regioselective protection and deprotection of hydroxyl groups of inositols[1] and these have provided means for the synthesis of phosphoinositols, other natural products and their analogs.[2] *myo*-Inositol orthoesters have been used extensively for the synthesis of phosphoinositols and their derivatives.[1,3] We developed methods for the regiospecific sulfonylation of the three hydroxyl groups of *myo*-inositol 1,3,5-orthoformate and had shown[4] that their sulfonate derivatives can be cleaved with retention of configuration, since *myo*-inositol orthoesters possess the rigid adamantane frame-work. Although hydroxyl groups are seldom protected as their sulfonates due to problems (such as elimination, nucleophilic substitution, etc.) associated with their deprotection, we were able to utilize sulfonate derivatives of *myo*-inositol orthoformate for the efficient preparation of precursors for inositol phosphates[4,5] and *scyllo*-inositol.[6] We herein describe the synthesis of a few naturally occurring O- and C-methylated inositol derivatives (and their unnatural enantiomers) via the protection of

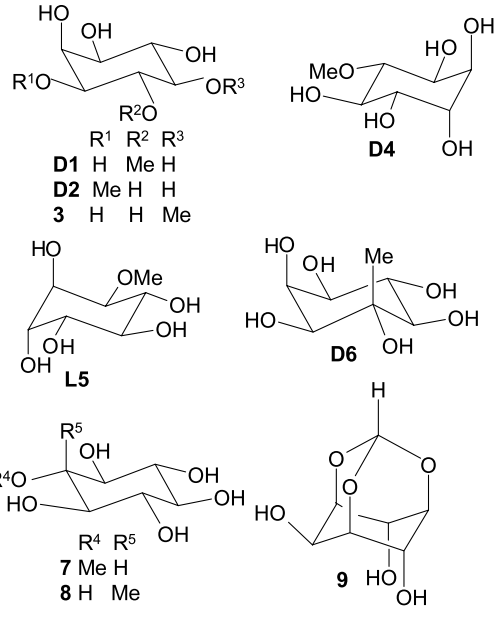

Figure 1.

Keywords: Cyclitol; Inositol; Sulfonate; Protecting group; Orthoester.
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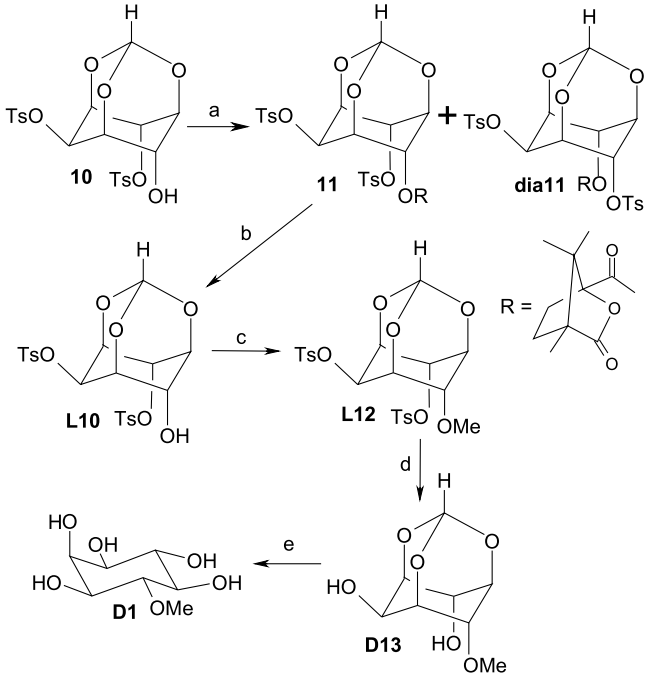
doi:10.1016/j.tet.2005.02.073

myo-inositol orthoformate hydroxyl groups as the corresponding tosylates.

Cyclitols, their derivatives and analogs have continued to attract the attention of chemists and biologists due to their involvement in various biological processes[7] in eukaryotic cells. Although cyclitol derivatives occur in plants as well as animals, their biological role in plants has not been investigated as extensively as in animals. O-methylated inositols (Fig. 1) such as (+)-ononitol (1D-4-*O*-methyl-*myo*-inositol, **D1**), (+)-bornesitol (1D-3-*O*-methyl-*myo*-inositol, **D2**), sequoyitol (5-*O*-methyl-*myo*-inositol, **3**), (+)-pinitol (1D-3-*O*-methyl-*chiro*-inositol, **D4**) and (−)-quebrachitol (1L-2-*O*-methyl-*chiro*-insoitol, **L5**), are present in seeds of many plants, frequently in combination with one another; their glycosylated derivatives are abundant in seeds such as adzuki bean.[8] *O*-methyl-*scyllo*-inositol (**7**) has been isolated from mung beans.[9] C-methyl inositols, (−)-laminitol (**D6**) and mytilitol (**8**), having *myo*- and *scyllo*-type configurations, respectively, occur in marine algae.[10] Galactosyl cyclitols are thought to protect membranes and other cellular structures during seed desiccation or storage in the dry state.[11] Racemic[12] as well as enantiomeric ononitols[13] have been synthesized from *myo*-inositol. Epimerization of pinitol in acetic acid results in the formation of ononitol as one of the products.[14] Posternak[15] established the absolute configuration of laminitol and reported its first synthesis.[16] Racemic and the naturally occurring (−)-laminitol have also been synthesized from *myo*-inositol,[17] toluene[18] and D-glucose.[19]

2. Results and discussion

The racemic ditosylate **10**[4] (Scheme 1) was obtained in high yield by the ditosylation of the triol **9** and resolved as diastereomeric camphanates **11** and **dia11**; their absolute configurations were established by X-ray crystallography (Fig. 2). Aminolysis of the diastereomer **11** gave the enantiomeric ditosylate **L10**. Methylation of **L10** followed by methanolysis of the tosylates (in **L12**) and hydrolysis of the orthoformate (in **D13**[20]) gave the natural ononitol **D1** in 32% overall yield from *myo*-inositol.



Scheme 1. (a) RCl, DMAP, pyr, 80–100 °C, 12 h, **11** (44%), **dia11** (43%); (b) *iso*-$BuNH_2$, MeOH-DCM, reflux, 6 h, 96%; (c) MeI, NaH, DMF, 5 min, 95%; (d) NaOMe, MeOH, reflux, 12 h, 99%; (e) aq. TFA, 1 h, 100%.

Similar sequence of reactions (Scheme 2) on **dia11** provided the unnatural ononitol **L1** in 31% yield. Earlier methods of synthesis[13] gave ononitol (racemic or enantiomeric) in less than 20% yield.

We also attempted to use the ditosylate **10** for the synthesis of laminitol. Oxidation of racemic **10** provided the gem diol **14** (Scheme 3) as the major product (see Section 4 and Supplementary material). The diol **14** did not react with methylmagnesium iodide under the conditions used for the C-methylation of the racemic ketone **18**. Hence, we synthesized enantiomeric laminitols from the dibenzyl ethers **D17** and **L17**. Enantiomeric ethers **D17** and **L17** were prepared from the racemic monotosylate **16** as described previously.[4]

Oxidation of the dibenzyl ether **L17** (Scheme 3) by Swern's method provided the corresponding ketone **L18** as the major product, in contrast to the oxidation of the ditosylate **10**. Grignard reaction of the ketone **L18** with methylmagnesium iodide gave the corresponding C-methyl derivative **L19**. Cleavage of the benzyl groups by hydrogenolysis followed by acid hydrolysis of the orthoformate provided the natural D-laminitol (**D6**) in 30% overall yield from *myo*-inositol. Orthoesters of *myo*-inositol are known to be cleaved by Grignard reagents at higher temperatures;[21] however, we did not observe such cleavage under the conditions (0 °C to ambient temperature) used for the Grignard reaction on **L18**.

An identical reaction sequence from **D17** (Scheme 4) provided the unnatural laminitol (**L6**) in 30% overall yield. Similarly, racemic laminitol was also prepared (overall yield 61%) from the racemic dibenzyl ether **17**. The overall yield in previously reported methods for the synthesis of laminitol (racemic or enantiomeric) did not exceed 15%.[16–19] X-ray crystal structure (Fig. 2) of racemic laminitol orthoformate **20** clearly showed that the *myo*-configuration was retained after the Grignard reaction on **18** (or its enantiomers).

The high yielding (overall yield 48% from *myo*-inositol) synthesis of mytilitol (**8**, Scheme 5) was completed starting from the known ketone **21**.[6] Reaction of **21** with methylmagnesium iodide gave the C-methyl orthoformate **22**. Methanolysis of the tosylates followed by acetylation gave the diacetate **23**, *scyllo*- configuration of which was established by X-ray crystallography (Fig. 2). The triol **24** was isolated as its diacetate **23** as these triols are good metal complexing agents[22] and could bind to metal ions present on silica gel resulting in a reduction in their isolated yield.[6] Aminolysis of the acetates in **23** followed by acid hydrolysis of the orthoformate provided **8**, which was characterized as its hexaacetate (**25**). The previously reported synthesis of **8**

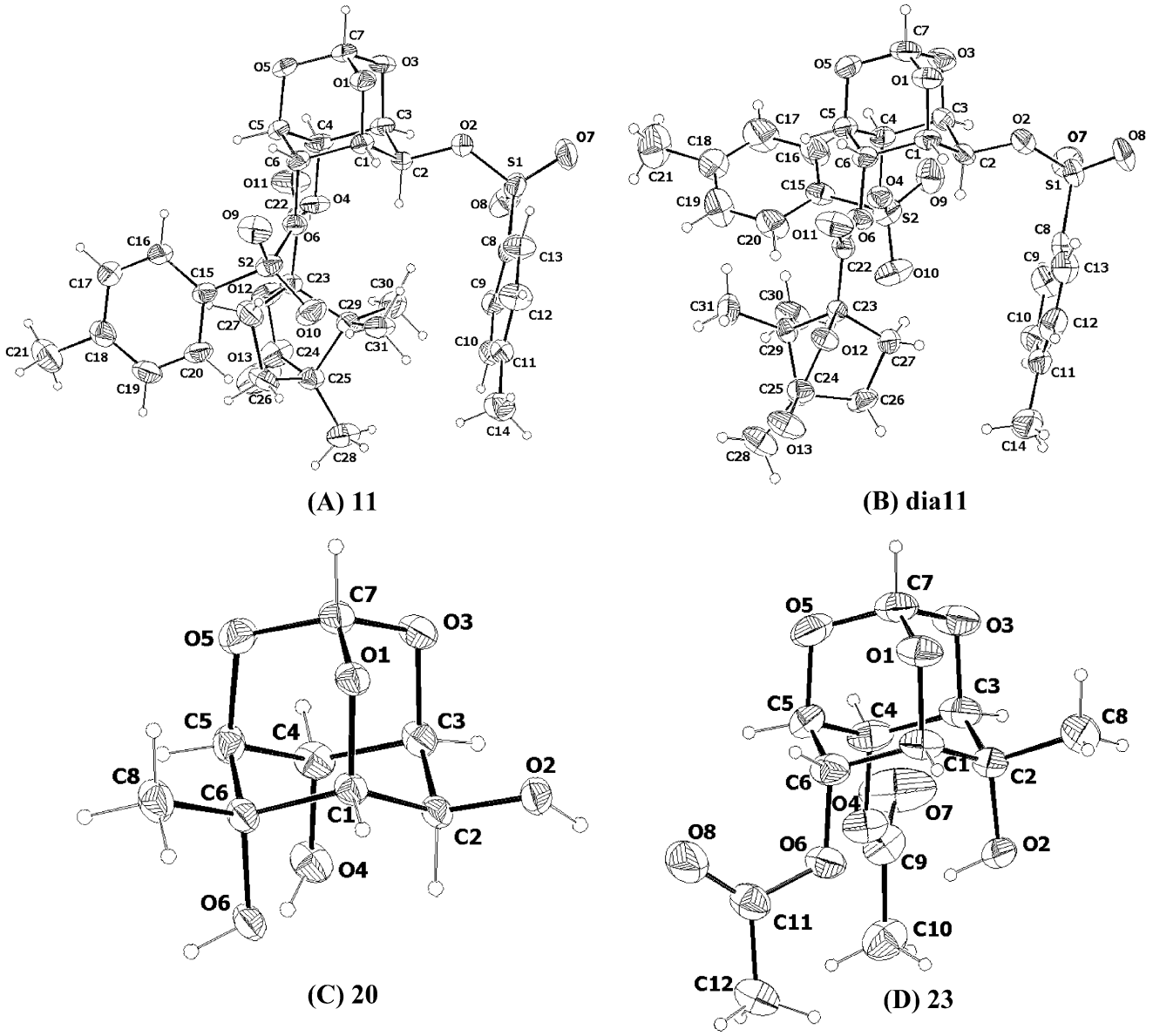
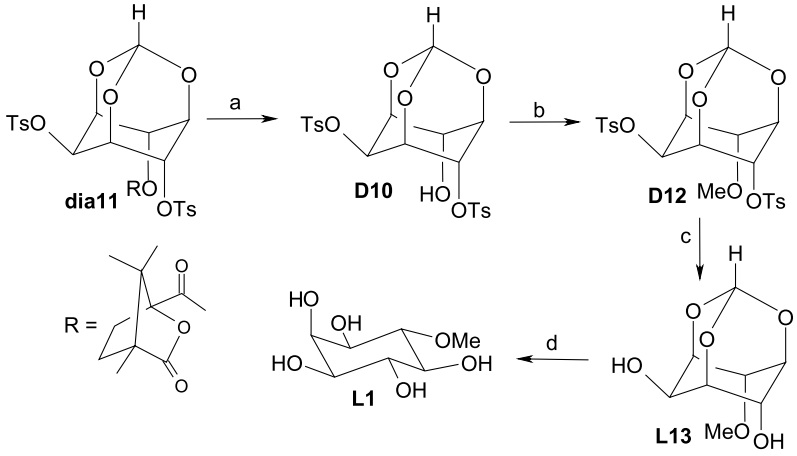
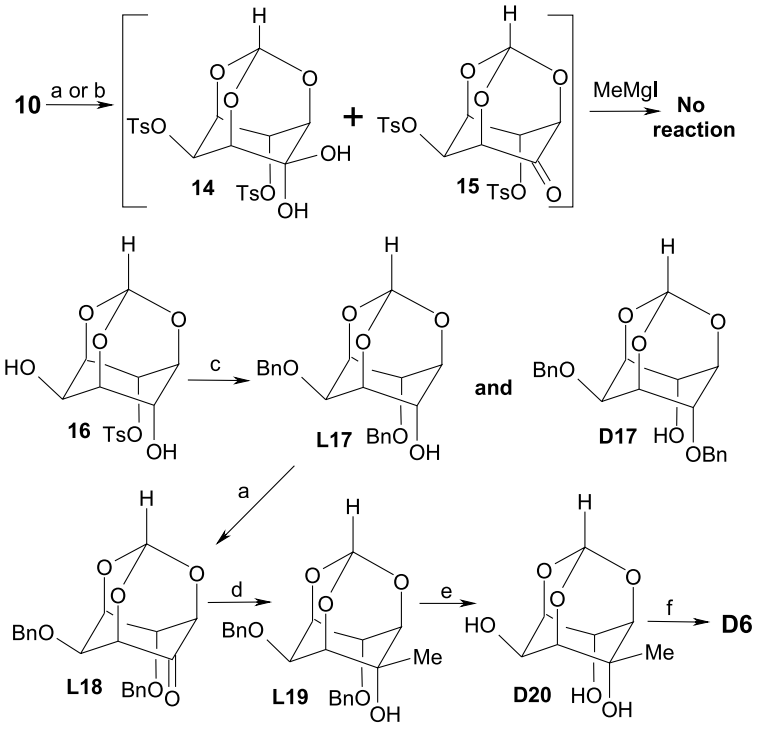


Figure 2. ORTEP view of the compounds **11** (A), **dia11** (B), **20** (C) and **23** (D). Ellipsoids are drawn at 30% probability level.



Scheme 2. (a) *iso*-$BuNH_2$, MeOH-DCM, reflux, 6 h, 97%; (b) MeI, NaH, DMF, 5 min, 95%; (c) NaOMe, MeOH, reflux, 12 h, 99%; (d) aq. TFA, 1 h, 98%.



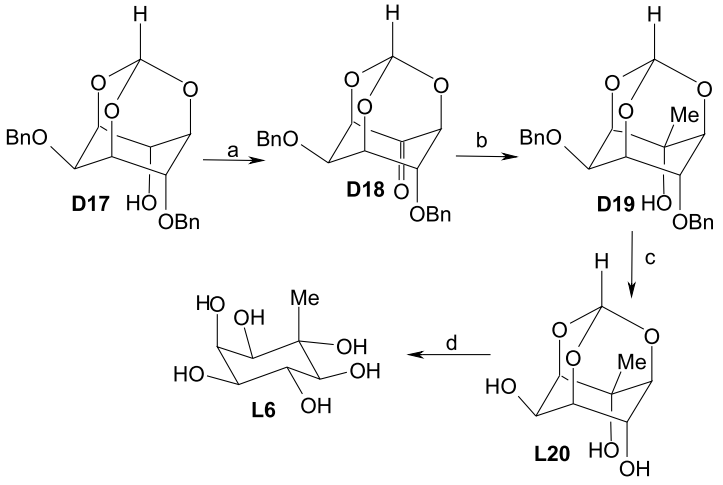
Scheme 3. (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h then Et_3N, rt, 3 h, 82% (for **14**+**15**), 95% for (**L18**); (b) Ac_2O, DMSO, 40 h, 94%; (c) as in Ref. 4; (d) MeMgI, Et_2O, 0 °C–rt, 4 h, 88%; (e) $Pd(OH)_2$, H_2/30 psi, MeOH, 10 h, 98%; (f) aq. TFA, 1 h, 98%.

from glucose gave this C-methyl inositol in 3% overall yield.[19]

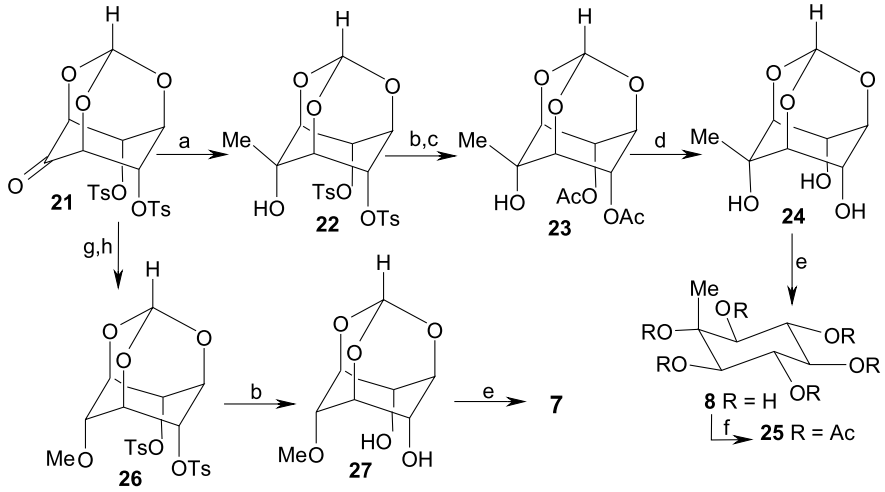
Naturally occurring *scyllo*-inositol methyl ether (**7**) was also obtained from the ketone **21**. Reduction of **21** with sodium borohydride as reported earlier[6] followed by methylation with methyl iodide provided the methyl ether **26**. Removal of the tosylates by methanolysis and acid hydrolysis of the orthoformate gave the natural *scyllo*-inositol methyl ether (**7**) in an overall yield of 60% from *myo*-inositol. It is interesting to note that the ketone **18** and the symmetric ketone **21** were stable while the unsymmetric ketone **15** exists almost completely as the gem diol **14** (see Supporting information). The factors that could control the relative stability of a ketone and its gem diol (or the ease of hydration of a ketone) are electrophilicity of the carbonyl carbon and steric factors that could stabilize the ketone or the gem diol. Further work is necessary to completely understand the relative stability of *myo*-inositol 1,3,5-orthoformate derived ketones[23] **15**, **18** and **21** and the corresponding gem diols resulting by their hydration.

3. Conclusions

We have demonstrated that O- and C-alkylated cyclitol derivatives can be synthesized by the protection of inositol orthoester hydroxyl groups as the corresponding tosylates. It is interesting to note that both O- and C-alkylation could be carried out efficiently in the presence of sulfonate moieties



Scheme 4. (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h then Et_3N, rt, 3 h, 95%; (b) MeMgI, Et_2O, 0 °C–rt, 4 h, 88%; (c) $Pd(OH)_2$, H_2/30 psi, MeOH, 10 h, 98%; (d) aq. TFA, 1 h, 98%.



Scheme 5. (a) MeMgI, Et_2O, THF, 0 °C–rt, 6 h, 74%; (b) NaOMe, MeOH, 12 h, reflux, 94% (for **27**); (c) Ac_2O, pyr, rt, 24 h, 95%; (d) *iso*-$BuNH_2$, MeOH, reflux, 12 h, 96%; (e) aq. TFA, 1 h, 100% (for **8**), 96% (for **7**); (f) Ac_2O, DMAP, pyr, 24 h, 93%; (g) $NaBH_4$, MeOH, THF, 30 min, 99%; (h) MeI, NaH, DMF, 5 min, 92%.

as the adamantane framework does not allow the tosylate groups to function as leaving groups. As evident from the yields of the final products, this unusual protection of hydroxyl groups as their sulfonates resulted in efficient synthesis of inositol derivatives. These synthetic sequences are perhaps among the very few reports in the literature where tosylate groups have been used for the protection of hydroxyl groups and the preparation of enantiomeric end products. Synthesis of complex cyclitol derivatives using this strategy is being pursued presently in our laboratory.

4. Experimental

4.1. General

For details on general experimental conditions see Ref. 4. The orthoformate **9**,[24] racemic ditosylate **10**,[4] benzyl ethers **D17** and **L17**,[4] the ketone **21**,[6] 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate,[25] 4,6-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate[6] and (1*S*)-(−)-camphanoyl chloride[26] were prepared as reported earlier. All the compounds previously reported in the literature were characterized by comparison of their ^{1}H NMR spectra, melting point and/or specific rotation with those of authentic samples. Specific rotations were determined using a Bellingham ADP220 polarimeter (accuracy ±1°) or a JASCO P-1030 polarimeter (accuracy ±0.1°).

4.1.1. D- and L-2,4-Di-*O*-tosyl-6-*O*-[1*S*]-camphanoyl-*myo*-inositol 1,3,5-orthoformate (dia11 and 11). Racemic **10** (1.000 g, 2.008 mmol), DMAP (0.050 g) and freshly prepared (1*S*)-(−)-camphanoyl chloride (0.566 g, 2.614 mmol) were dissolved in dry pyridine (10 mL) and heated at 80 °C for 10 h. The reaction mixture was cooled to ambient temperature, pyridine was evaporated under reduced pressure and the residue was worked-up with dichloromethane. Flash column chromatography of the gum obtained gave **11** (0.600 g, 44%), **dia11** (0.585 g, 43%) and a mixture of **11** and **dia11** (0.135 g, 10%). Data for **11**: white solid, mp 184–185 °C; [found: C, 55.04; H, 5.03. $C_{31}H_{34}O_{13}S_2$ requires C, 54.86; H, 5.05%]; R_f (50% dichloromethane/light petroleum) 0.32; $[\alpha]_D^{25} = -25.4$ (*c* 1, $CHCl_3$); ν_{max} (Nujol) 1788, 1768 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J*=10.0 Hz), 7.78 (2H, d, *J*=10.0 Hz), 7.43 (2H, d, *J*=10.0 Hz), 7.39 (2H, d, *J*=10.0 Hz), 5.50 (1H, s), 5.48–5.45 (1H, m), 5.10–5.05 (1H, m), 4.74 (1H, d, *J*=2.0 Hz), 4.52–4.48 (1H, m), 4.23–4.20 (1H, m), 4.07–4.03 (1H, m), 2.48 (3H, s), 2.45 (3H, s), 2.45–2.40 (1H, m), 2.05–1.90 (2H, m), 1.73–1.65 (1H, m), 1.15 (3H, s), 1.07 (3H, s), 0.95 (3H, s); δ_C (125 MHz, $CDCl_3$) 177.7, 166.1, 146.1, 145.7, 132.5, 131.9, 130.4, 130.3, 128.1, 128.0, 102.6, 90.5, 71.8, 69.5, 68.8, 68.0, 67.7, 66.6, 54.8, 54.4, 30.4, 28.8, 21.7, 21.6, 16.6, 9.7. Data for **dia11**: mp 222–225 °C; [found: C, 54.77; H, 4.84. $C_{31}H_{34}O_{13}S_2$ requires C, 54.86; H, 5.05%]; R_f (50% dichloromethane/light petroleum) 0.29; $[\alpha]_D^{26} = -7.7$ (*c* 1, $CHCl_3$); ν_{max} (Nujol) 1776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J*=10.0 Hz), 7.73 (2H, d, *J*=10.0 Hz), 7.50–7.40 (4H, m), 5.65–5.55 (1H, m), 5.48 (1H, d, *J*=5.0 Hz), 5.00–4.93 (1H, m), 4.90–4.85 (1H, m), 4.40–4.30 (2H, m), 4.15–4.05 (1H, m), 2.48 (6H, s), 2.55–2.40 (1H, m), 2.12–2.05 (1H, m), 2.05–1.90 (1H, m), 1.80–1.70 (1H, m), 1.15 (3H, s), 1.10 (3H, s), 0.98 (3H, s); δ_C (125 MHz, $CDCl_3$) 177.5, 165.9, 146.4, 145.8, 133.0, 131.6, 130.5, 130.3, 128.1, 127.8, 102.6, 90.7, 72.0, 69.5, 67.9, 67.7, 66.5, 54.9, 54.3, 30.5, 29.0, 21.8, 17.0, 16.7, 9.7.

4.1.2. L-2,4-Di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (L10). Isobutylamine (2 mL) and **11** (0.400 g, 0.590 mmol) were dissolved in a mixture of methanol (10 mL) and dichloromethane (10 mL) and refluxed for 6 h. Removal of the solvents under reduced pressure, usual work-up with dichloromethane followed by column chromatography gave **L10** (0.286 g, 96%) as a white solid; mp 112–114 °C; [found: C, 50.37; H, 4.42. $C_{21}H_{22}O_{10}S_2$ requires C, 50.60; H, 4.45%]; $[\alpha]_D^{29} = -9$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3659–3184 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82 (4H, t, *J*=8.8 Hz), 7.41 (2H, d, *J*=8.1 Hz), 7.35 (2H, d, *J*=8.0 Hz), 5.44 (1H, d, *J*=1.4 Hz), 5.10–5.02 (1H, m), 5.02–4.95 (1H, m), 4.60–4.50 (1H, m), 4.40–4.30 (1H, m), 4.25–4.15 (1H, m), 4.10–4.00 (1H, m), 2.65–2.45 (1H, broad, D_2O exchangeable), 2.49 (3H, s), 2.46 (3H, s);

δ_C (50.3 MHz, $CDCl_3$) 146.1, 145.5, 133.0, 131.9, 130.3, 130.1, 128.0, 127.8, 102.3, 72.9, 71.4, 69.6, 68.6, 66.6, 21.6.

4.1.3. L-2,4-Di-*O*-tosyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (L12). To a solution of methyl iodide (0.086 g, 0.606 mmol) and **L10** (0.200 g, 0.402 mmol) in dry DMF (3 mL), was added sodium hydride (0.011 g, 0.458 mmol) and stirred for 5 min. Reaction was quenched with ice, DMF was evaporated under reduced pressure and the reaction mixture was worked-up with dichloromethane to obtain a gum. Purification of the gum by column chromatography gave **L12** (0.195 g, 95%) as a gum; [found: C, 51.79; H, 4.88. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; $[\alpha]_D^{29}=-5$ (*c* 1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.85 (2H, d, $J=8.2$ Hz), 7.78 (2H, d, $J=8.2$ Hz), 7.39 (2H, d, $J=3.5$ Hz), 7.36 (2H, d, $J=3.5$ Hz), 5.44 (1H, d, $J=1.2$ Hz), 5.07–4.95 (1H, m), 4.94–4.85 (1H, m), 4.45–4.37 (1H, m), 4.30–4.20 (1H, m), 4.14–4.03 (1H, m), 4.00–3.90 (1H, m), 3.38 (3H, s), 2.48 (3H, s), 2.47 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 145.7, 145.3, 133.1, 132.2, 130.0, 127.7, 102.4, 74.3, 72.3, 69.6, 69.4, 68.6, 66.6, 57.0, 21.5.

4.1.4. D-4-*O*-Methyl-*myo*-inositol 1,3,5-orthoformate (D13). To a stirred solution of **L12** (0.142 g, 0.277 mmol) in dry methanol (5 mL) was added sodium methoxide (0.151 g, 2.796 mmol) and the mixture refluxed for 12 h. The reaction was quenched with ice, methanol was evaporated under reduced pressure and the product was purified by flash chromatography to obtain **D13** (0.056 g, 99%) as a white solid; mp 102–104 °C; [found: C, 47.15; H, 5.72. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{20}=+3.9$ (*c* 1, EtOH); ν_{max} (nujol) 3523, 3475–3105 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.36 (1H, s), 4.38–4.28 (1H, m), 4.26–4.18 (1H, m), 4.18–4.05 (2H, m), 4.00–3.90 (2H, m), 3.39 (3H, s); δ_C (125 MHz, CD_3OD) 104.3, 77.7, 76.1, 73.6, 69.8, 69.1, 61.2, 57.9.

4.1.5. D-Ononitol (D1). The orthoformate **D13** (0.040 g, 0.196 mmol) was stirred with a mixture of trifluoroacetic acid (0.9 mL) and distilled water (0.3 mL) for 1 h. Evaporation of solvents under reduced pressure followed by co-evaporation with toluene gave D-ononitol **D1** (0.038 g, 100%) as a white solid; mp 167–169 °C; lit.[13] mp 167–169 °C; $[\alpha]_D^{25}=+5.2$ (*c* 2.2, H_2O); lit.[13] $[\alpha]_D=+5.5$ (*c* 2.2, H_2O).

4.1.6. D-2,4-Di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (D10). Reaction of **dia11** (0.450 g, 0.663 mmol) with isobutylamine (3 mL) as in Section 4.1.2 gave **D10** (0.320 g, 97%) as a white solid; mp 112–113 °C; [found: C, 50.66; H, 4.63. $C_{21}H_{22}O_{10}S_2$ requires C, 50.60; H, 4.45%]; $[\alpha]_D^{29}=+9$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3583–3340 cm^{-1}; δ_H and δ_C were similar to that of **L10**.

4.1.7. D-2,4-Di-*O*-tosyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (D12). Methylation of **D10** (0.310 g, 0.622 mmol) with methyl iodide (0.114 g, 0.803 mmol) as in Section 4.1.3 gave **D12** (0.300 g, 95%) as a gum; [found: C, 51.79; H, 4.83. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; $[\alpha]_D^{27}=+5$ (*c* 1, $CHCl_3$); δ_H and δ_C were similar to that of **L12**.

4.1.8. L-4-*O*-Methyl-*myo*-inositol 1,3,5-orthoformate (L13). Methanolysis of **D12** (0.250 g, 0.488 mmol) as in Section 4.1.4 gave **L13** (0.099 g, 99%) as a white solid; mp 102–104 °C; [found: C, 47.00; H, 5.81. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{20}=-3.8$ (*c* 1, EtOH); ν_{max} (nujol) 3523, 3472–3076 cm^{-1}; δ_H and δ_C were similar to that of **D13**.

4.1.9. L-Ononitol (L1). Acid hydrolysis of **L13** (0.060 g, 0.294 mmol) as in Section 4.1.5 gave L-ononitol (**L1**, 0.056 g, 98%) as a white solid; mp 167–169 °C; lit.[13] mp 168–169 °C; $[\alpha]_D^{26}=-5.2$ (*c* 2, H_2O); lit.[13] $[\alpha]_D=-5.7$ (*c* 2, H_2O).

4.1.10. Racemic 4,6-di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (18). To a cooled (−78 °C) solution of oxalyl chloride (0.303 g, 2.405 mmol) in dry dichloromethane (3 mL) was added drop wise, a solution of dry dimethylsulfoxide (0.341 g, 4.372 mmol) in dry dichloromethane (2 mL) and the reaction mixture stirred for 15 min. To this mixture was added (drop wise) a solution of the racemic dibenzyl ether **17** (0.800 g, 2.162 mmol) in dry dichloromethane (5 mL) and stirring was continued for 1 h. Dry triethylamine (1.096 g, 10.851 mmol) was then added and the reaction mixture was allowed to warm to room temperature slowly. The reaction was quenched by the addition of a few drops of water and the organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Purification of the product by column chromatography afforded a mixture of the racemic ketone **18** and the corresponding gem diol (0.730 g, 92%) as a gum; [found: C, 66.73; H, 5.68. $C_{21}H_{20}O_6\cdot 0.5H_2O$ requires C, 66.83; H, 5.61%.]; ν_{max} (neat) 3630–3180, 1765 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.52–7.26 (8H, m), 7.25–7.12 (2H, m), 5.67 (1H, d, $J=1.4$ Hz), 4.69 (2H, q, $J=12.3$, 12.2 Hz), 4.63–4.51 (2H, m), 4.51–4.39 (2H, m), 4.39–4.30 (2H, m), 3.76 (1H, d, $J=1.5$ Hz); δ_C (50.3 MHz, $CDCl_3$) 198.5, 136.1, 135.6, 127.8, 127.6, 127.4, 127.2, 127.1, 102.1, 78.1, 75.9, 75.7, 71.0, 70.9, 70.5, 69.7, 69.6.

4.1.11. Racemic laminitol orthoformate (20). To a stirred cooled (ice bath) solution of racemic **18** (0.150 g, 0.408 mmol) in dry diethyl ether (5 mL), a freshly prepared solution (1.0 M, 2.0 mL) of methylmagnesium iodide in diethylether was added and stirring continued and the reaction mixture was allowed to warm to ambient temperature (3–4 h) while stirring. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with a saturated aqueous solution of ammonium chloride (3 mL). The aqueous layer was extracted with dichloromethane (3×5 mL), the combined organic layer was washed with brine (5 mL) and the solvent removed by evaporation under reduced pressure to obtain a gum. Purification of this gum by column chromatography afforded racemic **19** (0.138 g, 88%) as a gum; ν_{max} ($CHCl_3$) 3595–3338 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.50–7.25 (8H, m), 7.25–7.15 (2H, m), 5.52 (1H, d, $J=1.0$ Hz), 4.73 (2H, q, $J=15.6$, 12.3 Hz), 4.54 (2H, q, $J=10.8$, 4.9 Hz), 4.39 (1H, t, $J=3.9$ Hz), 4.33 (1H, s, D_2O exchangeable), 4.28–4.18 (1H, m), 4.02–3.96 (1H, m), 3.96–3.86 (2H, m), 1.56 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 137.7, 135.9, 128.7, 128.6, 128.4, 127.9, 102.6, 75.9, 74.8, 72.8, 71.9, 71.3, 69.7, 69.3, 67.3, 24.1. Racemic **19** (0.120 g,

0.313 mmol) was subjected to hydrogenolysis (30 psi) in the presence of Pearlmann's catalyst (20% $Pd(OH)_2$ on carbon, 0.044 g) in methanol (5 mL) for 6 h. Removal of the catalyst by filtration followed by removal of the solvent under reduced pressure gave racemic **20** (0.063 g, 98%) as a white solid which was crystallized from methanol. mp 179–181 °C; [found: C, 47.00; H, 6.30. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} (nujol) 3656–3011 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.30 (1H, d, $J=1.5$ Hz), 4.34 (1H, t, $J=3.9$ Hz), 4.10–4.04 (1H, m), 3.98–3.93 (1H, m), 3.77–3.70 (1H, m), 3.63 (1H, dd, $J=2.0$, 1.9 Hz,), 1.44 (3H, s); δ_C (50.3 MHz, CD_3OD) 102.8, 78.7, 74.1, 73.3, 70.2, 68.2, 61.1, 23.7.

4.1.12. Racemic laminitol (6). Racemic **20** (0.030 g, 0.147 mmol) was treated with a mixture of trifluoroacetic acid (0.8 mL) and water (0.2 mL) at room temperature for 1 h. Removal of trifluoroacetic acid and water under reduced pressure gave racemic laminitol (**6**, 0.028 g, 98%) as a white solid; mp 256–258 °C; lit.[17b] mp 262–268 °C; δ_H (200 MHz, D_2O) 4.07–3.93 (1H, m), 3.54–3.41 (3H, m), 3.28–3.13 (1H, m), 1.20 (3H, s).

4.1.13. L-4,6-Di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (L18). Oxidation of **L17** (0.370 g, 1.000 mmol) as in Section 4.1.10 gave **L18** (0.350 g, 95%) containing a small amount of the corresponding gem diol, as a gum; [found: C, 66.43; H, 5.63. $C_{21}H_{20}O_6\cdot 0.6H_2O$ requires C, 66.52; H, 5.64%]; $[\alpha]_D^{26}=-21.0$ (c 1, $CHCl_3$).[27]

4.1.14. D-Laminitol orthoformate (D20). C-methylation of **L18** (0.100 g, 0.272 mmol) as in Section 4.1.11 afforded **L19** (0.093 g, 89%) as a gum; $[\alpha]_D^{26}=-9$ (c 1, $CHCl_3$); ν_{max}, δ_H and δ_C were similar to that of racemic **19**. Hydrogenolysis of **L19** (0.080 g, 0.208 mmol) as in Section 4.1.11 gave **D20** (0.042 g, 98%) as a white solid; mp 179–181 °C; [found: C, 47.25; H, 5.86. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{27}=-3$ (c 1, EtOH); ν_{max}, δ_H and δ_C were similar to that of racemic **20**.

4.1.15. D-Laminitol (D6). Hydrolysis of the orthoformate **D20** (0.030 g, 0.147 mmol) as in Section 4.1.12 gave D-laminitol (**D6**, 0.027 g, 95%); mp 257–259 °C; lit.[10b] mp 260 °C, $[\alpha]_D^{27}=-2.9$ (c 1, H_2O); lit.[18] $[\alpha]_D=-3$ (c 1, H_2O); δ_H: same as in Section 4.1.12.

4.1.16. D-4,6-Di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (D18). Oxidation of **D17** (0.370 g, 1.000 mmol) as in Section 4.1.10 gave **D18** (0.350 g, 95%) containing a small amount of the corresponding gem diol, as a gum; [found: C, 66.37; H, 5.51. $C_{21}H_{20}O_6\cdot 0.6H_2O$ requires C, 66.52; H, 5.64%]; $[\alpha]_D^{26}=+21.2$ (c 1, $CHCl_3$).[27]

4.1.17. L-Laminitol orthoformate (L20). C-methylation of **D18** (0.100 g, 0.272 mmol) as in Section 4.1.11 afforded **D19** (0.092 g, 88%) as a gum; $[\alpha]_D^{26}=+9$ (c 1, $CHCl_3$); ν_{max}, δ_H and δ_C were similar to that of racemic **19**. The dibenzyl ether **D19** (0.080 g, 0.208 mmol) was subjected to hydrogenolysis as in Section 4.1.11 to obtain **L20** (0.041 g, 98%) as a white solid; mp 178–180 °C; [found: C, 47.21; H, 5.86. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%.]; $[\alpha]_D^{25}=+3$ (c 1, EtOH); ν_{max}, δ_H and δ_C were similar to that of racemic **20**.

4.1.18. L-Laminitol (L6). Hydrolysis of **L20** (0.030 g, 0.147 mmol) as in Section 4.1.12 gave L-laminitol (**L6**, 0.028 g, 98%) as a white solid; mp 258–261 °C; $[\alpha]_D^{27}=+3.3$ (c 1, H_2O); δ_H: same as in Section 4.1.12.

4.1.19. 2-*C*-Methyl-4,6-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (22). The ketone **21** (0.750 g, 1.512 mmol) was allowed to react with a freshly prepared diethylether solution of methylmagnesium iodide (1 M, 5.3 mL) in a mixture of dry diethylether (9 mL) and dry THF (3 mL) as in Section 4.1.11 (reaction time 6 h) to obtain **22** (0.572 g, 74%); mp 152–153 °C; [Found: C, 51.94; H, 4.85. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%.]; ν_{max} ($CHCl_3$) 3730–3078 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (4H, d, $J=8.8$ Hz), 7.40 (4H, d, $J=7.8$ Hz), 5.39 (1H, s), 5.17 (2H, t, $J=3.9$ Hz), 4.35–4.25 (1H, m), 3.95–3.80 (2H, m), 3.22 (1H, s, D_2O exchangeable), 2.48 (6H, s), 1.46 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 145.8, 132.4, 130.1, 128.0, 101.8, 72.7, 71.9, 67.2, 24.6, 21.5.

4.1.20. 2-*C*-Methyl-4,6-di-*O*-acetyl-*scyllo*-inositol 1,3,5-orthoformate (23). The ditosylate **22** (0.400 g, 0.781 mmol) was suspended in dry methanol (5 mL) containing sodium methoxide (0.421 g, 7.796 mmol) and refluxed for 9 h. The reaction mixture was quenched with a few drops of 2% hydrochloric acid solution (to pH 5) and the solvent was evaporated under reduced pressure and dried to obtain a solid. The solid obtained was suspended in dry pyridine (5 mL) containing acetic anhydride (3 mL) and the mixture was stirred at room temperature for 24 h. Usual work-up with dichloromethane followed by column chromatography gave the diacetate **23** (0.217 g, 96%); mp 130–132 °C; [found: C, 50.15; H, 5.44. $C_{12}H_{16}O_8$ requires C, 50.00; H, 5.60%.]; ν_{max} ($CHCl_3$) 3560, 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.60 (2H, t, $J=4.0$ Hz), 5.53 (1H, s), 4.53–4.45 (1H, m), 4.10–4.04 (2H, m), 3.59 (1H, d, $J=0.9$ Hz, D_2O exchangeable), 2.13 (6H, s), 1.56 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 168.3, 102.3, 72.4, 68.0, 67.8, 66.1, 24.6, 20.7.

4.1.21. Mytilitol orthoformate (24). Isobutylamine (2 mL) and **23** (0.150 g, 0.521 mmol) were dissolved in methanol (5 mL) and refluxed for 6 h. The solvents were evaporated under reduced pressure to obtain a gum. The gum obtained was washed with hot light petroleum (60–80 °C) several times followed by dichloromethane to obtain **24** as a white solid (0.101 g, 94%); mp 199–201 °C; [found: C, 47.52; H, 5.74. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} (Nujol) 3450–3100 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.24 (1H, s), 4.30 (2H, t, $J=3.9$ Hz), 4.10–4.00 (1H, m), 3.72 (2H, q, $J=2.5$, 1.9 Hz), 1.34 (3H, s); δ_C (50.3 MHz, CD_3OD) 103.3, 76.4, 72.7, 69.4, 26.0.

4.1.22. Mytilitol hexaacetate (25). The orthoformate **24** (0.090 g, 0.441 mmol) was stirred with trifluoroacetic acid (1.6 mL) and distilled water (0.4 mL) for 1 h. Evaporation of the solvents followed by co-evaporation with toluene gave mytilitol (**8**, 0.085 g, 100%) as a white solid; mp 264–266 °C; δ_H (200 MHz, D_2O) 3.23 (5H, s), 0.97 (3H, s). Mytilitol (**8**, 0.030 g, 0.155 mmol), was stirred with acetic anhydride (0.5 mL) and DMAP (0.005 g) in dry pyridine (1 mL) at room temperature for 24 h. Evaporation of the solvents under reduced pressure followed by usual work-up

with dichloromethane gave a gum. Purification of this gum by column chromatography gave the known hexaacetate **25** (0.065 g, 93%) as a white solid; mp 179–180 °C; lit.[19] mp 181 °C.

4.1.23. 2-*O*-Methyl-4,6-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (26). To a solution of 2,4-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate[6] (0.662 g, 1.329 mmol) in dry DMF (4 mL) was added methyl iodide (0.568 g, 4.002 mmol) and the mixture stirred for 5 min. Sodium hydride (0.041 g, 1.708 mmol) was added and stirring continued for additional 5 min. The reaction was quenched by the addition of ice. Evaporation of DMF under reduced pressure followed by work up with dichloromethane by usual procedure gave **26** (0.627 g, 92%) as a white solid; mp 149–150 °C; [found: C, 51.78; H, 4.88. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; δ_H (300 MHz, $CDCl_3$) 7.85 (4H, d, $J=8.3$ Hz), 7.37 (4H, d, $J=8.8$ Hz), 5.45 (1H, s), 5.24–5.06 (2H, m), 4.52–4.43 (2H, m), 4.24–4.15 (1H, m), 4.11–4.03 (1H, m), 3.35 (3H, s), 2.46 (6H, s); δ_C (75 MHz, $CDCl_3$) 145.0, 133.0, 129.8, 127.7, 102.4, 72.9, 69.6, 67.6, 67.2, 56.9, 21.5.

4.1.24. 2-*O*-Methyl-*scyllo*-inositol 1,3,5-orthoformate (27). Sodium methoxide (0.475 g, 8.796 mmol) and **26** (0.461 g, 0.900 mmol) were dissolved in dry methanol (5 mL) and refluxed for 8 h. Evaporation of the solvent and purification of the product by flash chromatography gave **27** (0.172 g, 94%) as a white solid; mp 128–129 °C; [found: C, 47.18; H, 6.23. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} ($CHCl_3$) 3469–3332 cm^{-1}; δ_H (300 MHz, D_2O) 5.64 (1H, s), 4.59–4.53 (2H, m), 4.50–4.44 (2H, m), 4.40–4.33 (1H, m), 4.27–4.22 (1H, m), 3.47 (3H, s); δ_C (125 MHz, D_2O) 101.3, 74.2, 69.9, 68.4, 65.6, 57.1.

4.1.25. *scyllo*-Inositol methyl ether (7). The orthoformate **27** (0.050 g, 0.245 mmol) was stirred with a mixture of trifluoroacetic acid (0.4 mL) and distilled water (0.1 mL) for 1 h. Evaporation of solvents under reduced pressure followed by co-evaporation with toluene gave **7** (0.047 g, 96%) as a white solid; mp 248–249 °C; lit.[9] mp 243 °C; [found: C, 43.39; H, 7.26. $C_7H_{14}O_6$ requires C, 43.30; H, 7.27%]; ν_{max} (Nujol) 3630–3032 cm^{-1}; δ_H (200 MHz, D_2O) 3.85 (3H, s), 3.50–3.20 (4H, m), 3.20–2.95 (2H, m); δ_C (50.3 MHz, D_2O) 45.4, 35.5, 34.9, 21.9.

4.1.26. Oxidation of racemic 2,4-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (10). To a cooled (−78 °C) solution of oxalyl chloride (0.520 g, 4.127 mmol) in dry dichloromethane (4 mL) was added drop wise, a solution of dry dimethyl sulfoxide (0.627 g, 8.038 mmol) in dry dichloromethane (3 mL) and the reaction mixture stirred for 15 min. To this mixture was added (drop wise) a solution of racemic **10** (1.000 g, 2.008 mmol) in dry dichloromethane (8 mL) and stirring was continued for 1 h. Dry triethylamine (1.234 g, 12.218 mmol) was then added and the reaction mixture was allowed to warm to room temperature slowly. The reaction was quenched by adding a few drops of water and the organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography gave a mixture (0.850 g, 82%) of the racemic gem diol **14** and the ketone **15** as a white solid; mp 133–134 °C; ν_{max} and δ_H, see Supplementary data. δ_C (50.3 MHz, $CDCl_3$) 146.1, 145.6, 133.0, 131.9, 130.5,

Table 1. Crystal data for compounds **11**, **dia11**, **20** and **23**

Crystal data	**11**	**dia11**	**20**	**23**
Molecular formula	$C_{31}H_{34}O_{13}S_2$	$C_{31}H_{34}O_{13}S_2$	$C_8H_{12}O_6$	$C_{12}H_{16}O_8$
Molecular mass	678.70	678.70	204.18	288.25
Crystal size (mm)	0.71×0.14×0.08	0.74×0.08×0.07	0.57×0.27×0.22	0.58×0.48×0.37
Temp. (K)	293(2)	293(2)	293(2)	293(2)
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$Pna2_1$	$P2_1/n$
a (Å)	9.057(4)	20.24(4)	11.722(5)	8.019(3)
b (Å)	15.627(7)	17.98(4)	9.029(4)	14.251(5)
c (Å)	22.226(10)	9.14(2)	8.155(4)	11.837(4)
β (°)				106.583(5)
V (Å^3)	3146(2)	3326(12)	863.1(6)	1296.4(8)
Z	4	4	4	4
F(000)	1424	1424	432	608
D calc [g cm^{-3}]	1.433	1.355	1.571	1.477
μ (mm^{-1})	0.237	0.224	0.136	0.126
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
T_{min}	0.8497	0.8517	0.9263	0.9306
T_{max}	0.9824	0.9843	0.9706	0.9548
Reflns. collected	15,869	16,688	3847	11,785
Unique reflns.	5531	5836	1230	2269
Observed reflns.	4589	3666	1211	2219
Index range	$-10\Rightarrow h\Rightarrow 10$, $-18\Rightarrow k\Rightarrow 16$, $-26\Rightarrow l\Rightarrow 24$	$-12\Rightarrow h\Rightarrow 24$, $-21\Rightarrow k\Rightarrow 21$, $-10\Rightarrow l\Rightarrow 10$	$-13\Rightarrow h\Rightarrow 6$, $-10\Rightarrow k\Rightarrow 9$, $-6\Rightarrow l\Rightarrow 9$	$-9\Rightarrow h\Rightarrow 9$, $-16\Rightarrow k\Rightarrow 16$, $-14\Rightarrow l\Rightarrow 14$
R_1 [$I>2\sigma(I)$]	0.0594	0.0743	0.0282	0.0587
wR_2	0.1106	0.1136	0.0734	0.1444
Goodness-of-fit	1.155	1.066	1.073	1.134
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	−0.239, 0.213	−0.161, 0.208	−0.162, 0.154	−0.157, 0.309
CCDC number	255,367	255,368	255,369	255,370

130.3, 130.2, 128.0, 127.8, 102.6, 102.4, 89.2, 75.6, 74.7, 72.7, 71.0, 70.1, 69.8, 69.4, 69.1, 69.0, 21.7.

4.2. X-ray crystallography

Crystals of the compounds **11** and **dia11** were obtained from dichloromethane-light petroleum, those of racemic **20** were obtained from methanol and crystals of **23** were obtained from chloroform-light petroleum. Good quality crystals were selected using Leica Polarizing microscope. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with graphite monochromatized (Mo K_α=0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97[28] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Crystal data and details of data collection, structure solution and refinements for **11**, **dia11**, **20** and **23** are summarized in Table 1 and their ORTEP[29] plots are shown in Figure 2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-255367–CCDC-255370. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

Acknowledgements

The Department of Science and Technology, New Delhi supported this work. MPS and KMS are recipients of Senior Research Fellowships of the Council of Scientific and Industrial Research, New Delhi.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.073.

IR and ^{1}H NMR spectra of oxidation products of **10**, **17** and **21** are available on-line as Supplementary data.

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