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Note

Sulfonate protecting groups. Improved synthesis of *scyllo*-inositol and its orthoformate from *myo*-inositol

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Abstract

A convenient high yielding method for the preparation of *scyllo*-inositol and its orthoformate from *myo*-inositol, without involving chromatography is described. *myo*-Inositol 1,3,5-orthoformate was benzoylated to obtain 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate. This diol was tosylated and the benzoyl group removed by aminolysis in a one-pot procedure to obtain 4,6-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate. Swern oxidation of the ditosylate, followed by sodium borohydride reduction and methanolysis of tosylates gave *scyllo*-inositol 1,3,5-orthoformate (isolated as the triacetate). Aminolysis of the acetates followed by acid hydrolysis of the orthoformate moiety with trifluoroacetic acid gave *scyllo*-inositol in an overall yield of 64%. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Cyclitol; Inositol; Inositol phosphate; Orthoesters; Sulfonates; Signal transduction

As a part of an ongoing program on the solid state structure and reactivity of inositol derivatives,[1,2] we required *scyllo*-inositol (**2**) and its orthoformate (**9**). This note describes a convenient method for the conversion of *myo*-inositol to *scyllo*-inositol via its orthoformate. Development of efficient synthetic routes to isomeric inositols is of current interest in view of the role played by phosphoinositols in cellular signal transduction pathways.[3] There are several reports on the conversion of **1** to **2** or its derivatives in overall yields of 10–40%.[4–9] However, none of these methods are useful for the preparation of **9** since the reaction of **2** with triethyl orthoformate does not lead to the formation of **9**.[7,10] The only method so far known[11] for the synthesis of the orthoformate **9** involves chromatographic separations and provides **9** in 28% overall yield from *myo*-inositol. The method described here provides **9** in good yield (69%) and does not require chromatographic purification in any of the steps. The work reported here also illustrates the utility of sulfonate protecting groups for the synthesis of inositol derivatives.[12–14]

myo-Inositol orthoformate (**3**) was benzoylated with sodium hydride and benzoyl chloride to obtain the corresponding 2-benzoate **4**[15] (Scheme 1). Sulfonylation of the diol **4** with tosyl chloride in pyridine followed by aminolysis of the benzoate gave the ditosylate **5**. We had earlier reported[12] a method for the direct sulfonylation of 4- and 6-hydroxyl groups in the triol **3**. However, this procedure (on the larger scale reported here) required chromatography for the isolation of the ditosylate **5**, and hence we preferred to use the indirect method via benzoylation of the orthoformate **3**. The ditosylate **5** on Swern oxidation followed by reduction with sodium borohydride, provided the *scyllo*-ditosylate **7**. Methanolysis of the tosylates in **7** followed by acetylation gave the triacetate **8**. Aminolysis of the acetates in **8** gave *scyllo*-inositol orthoformate **9**, in an overall yield of 69%. The orthoformate **9** on hydrolysis with aqueous acid, provided **2** in 94% yield (overall yield 64% from *myo*-inositol).

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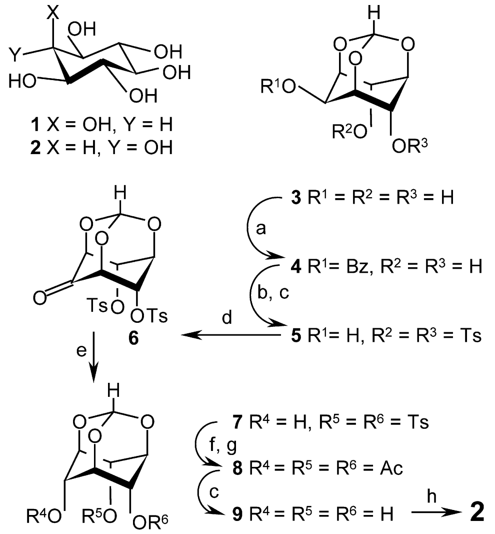
1. Experimental

1.1. General methods

For general experimental conditions, see Ref. 12. The orthoformate **3** was prepared as reported earlier.[16] All the compounds previously reported in the literature were characterized by comparison of their melting point and ^{1}H NMR spectra with those of authentic samples. 'Usual work-up' implies dilution of the reaction mixture with a solvent (EtOAc, $CHCl_3$ or CH_2Cl_2), washing of the organic layer with water, saturated sodium bicarbonate solution followed by brine, drying over anhydrous sodium sulfate and evaporation of the solvent under diminished pressure.

1.2. 2-*O*-Benzoyl-*myo*-inositol 1,3,5-orthoformate (4)

myo-Inositol 1,3,5-orthoformate (**3**, 0.95 g, 5.00 mmol) was dissolved in dry DMF (5 mL) and stirred with sodium hydride (0.30 g, 12.50 mmol) for 5 min. Benzoyl chloride (0.71 g, 5.05 mmol) was then added and the stirring continued for another 5 min. The reaction mixture was worked-up as usual (with EtOAc) and the residue was crystallized from $CHCl_3$–petroleum ether to obtain the known benzoate **4** (1.25 g, 85%); mp 210–212 °C; lit.[17] mp 210–213 °C.



Scheme 1. Reagents and conditions: (a) NaH, BzCl, DMF, rt; (b) *p*-TsCl, pyridine, 80–100 °C; (c) *iso*-butylamine, MeOH, reflux; (d) $(COCl)_2$, Me_2SO, DCM, − 78 °C then Et_3N, rt; (e) $NaBH_4$, MeOH–THF, rt; (f) NaOMe, MeOH, reflux; (g) Ac_2O, pyridine, rt; (h) TFA–water (4:1).

1.3. 4,6-Di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (5)

The 2-benzoate **4** (1.25 g, 4.25 mmol) was dissolved in dry Py (3 mL) and toluene 4-sulfonyl chloride (2.45 g, 12.86 mmol) was added. The reaction mixture was heated at 80–100 °C for 12 h. Pyridine was evaporated under diminished pressure; MeOH (7 mL) and *iso*-butylamine (4 mL) were added to the residue and refluxed for 12 h and concentrated under diminished pressure to a gum. The gum obtained was dissolved in $CHCl_3$ (50 mL) and worked up as usual and the product was crystallized from $CHCl_3$–petroleum ether to obtain the known ditosylate **5** (2.01 g, 95%); mp 182–184 °C; lit.[12] mp 183–185 °C.

1.4. 2,4-Di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (7)

To a cooled (− 78 °C) solution of oxalyl chloride (0.56 g, 4.41 mmol) in dry dichloromethane (5 mL) was added dropwise, a solution of dry Me_2SO (0.63 g, 8.08 mmol) in dry CH_2Cl_2 (5 mL) and the reaction mixture stirred for 15 min. To this mixture was added (dropwise) a solution of the ditosylate **5** (2.00 g, 4.02 mmol) in dry CH_2Cl_2 (15 mL) and stirring was continued for 1 h. Dry Et_3N (2.03 g, 20.10 mmol) was then added and the reaction mixture was allowed to warm to room temperature (rt) slowly. The reaction mixture was quenched by adding a few drops of water and the organic layer was separated, dried over anhyd Na_2SO_4 and the solvent was evaporated under diminished pressure to obtain the ketone **6** as a white solid (1.99 g). A small amount of **6** was purified by column chromatography; mp 142–144 °C. IR ($CHCl_3$): ν 1774, 3490 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.47 (s, 6 H), 4.25–4.35 (m, 2 H), 4.50–4.60 (m, 1 H), 5.35–5.50 (m, 2 H), 5.64 (s, 1 H), 7.30–7.45 (d, 4 H, J 8), 7.80–7.95 (d, 4 H, J 8). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 21.5, 67.7, 71.5, 72.5, 73.4, 76.3, 102.0, 127.8, 130.0, 132.0, 145.8, 195.0. Anal. Calcd for $C_{21}H_{20}O_{10}S_2$: C, 50.80; H, 4.06. Found C, 50.76; H, 4.11. The crude ketone **6** (1.99 g) was dissolved in a mixture of dry THF (10 mL) and dry MeOH (40 mL) and reduced with sodium borohydride (0.45 g, 11.84 mmol) at rt for 30 min. Solvents were evaporated under diminished pressure and the residue was worked up as usual (with CH_2Cl_2) to obtain **7** (1.98 g, 99%); mp 150–151 °C. IR ($CHCl_3$): ν 3587 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.48 (s, 6 H), 2.75–2.85 (d, 1 H, D_2O exchangeable, J 12), 4.20–4.40 (m, 4 H), 5.10–5.20 (m, 2 H), 5.42 (s, 1 H), 7.35–7.45 (d, 4 H, J 9), 7.80–7.90 (d, 4 H, J 9). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 21.6, 65.7, 67.4, 68.7, 70.8, 101.9, 128.0, 130.1, 132.1, 145.8. Anal. Calcd for $C_{21}H_{22}O_{10}S_2$: C, 50.59; H, 4.44. Found C, 50.48; H, 4.12.

1.5. *scyllo*-Inositol 1,3,5-orthoformate (9)

The ditosylate **7** (2.00 g, 4.02 mmol) was refluxed with Me_3ONa (1.30 g, 24.07 mmol) in dry MeOH (20 mL) for 12 h. The solvents were evaporated and the solid obtained was treated with a large excess of Ac_2O (25 mL) in Py (50 mL) at rt for 24 h. The solvents were evaporated under diminished pressure and the residue was worked up as usual (with $CHCl_3$) to obtain the known triacetate **8** as a white solid (1.25 g, 98%); mp 124–126 °C; lit.[11] mp 124–126 °C. The triacetate **8** (1.25 g, 3.96 mmol) was refluxed for 12 h with *iso*-butylamine (4 mL) in MeOH (15 mL). The solvents were evaporated and the gum obtained was washed with CH_2Cl_2–light petroleum mixture (1:3) several times to obtain the known[11] orthoformate **9** as a white solid (0.74 g, 98%); ^1H NMR (200 MHz, D_2O): δ 4.35–4.45 (m, 3 H), 4.45–4.55 (m, 3 H), 5.62 (s, 1 H).

1.6. *scyllo*-Inositol (2)

The orthoformate **9** (0.10 g, 0.53 mmol) was stirred with trifluoroacetic acid (0.75 mL) and distilled water (0.25 mL) at rt for 1 h. The solvents were evaporated under diminished pressure to obtain the known[7,9] **2** as a white solid (0.09 g, 94%); ^1H NMR (200 MHz, D_2O): δ 3.25 (s).

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