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Note

Convenient synthesis of 4,6-di-*O*-benzyl-*myo*-inositol and *myo*-inositol 1,3,5-orthoesters

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Abstract

Convenient high yielding methods for the preparation of 4,6-di-*O*-benzyl-*myo*-inositol, *myo*-inositol 1,3,5-orthoformate and *myo*-inositol 1,3,5-orthoacetate, without involving chromatography are described. *Myo*-inositol was converted to racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate by successive treatment with triethyl orthoformate and benzoyl chloride. The dibenzoate obtained on benzylation with benzyl bromide and silver(I) oxide gave 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate. Deprotection of the benzoate and the orthoformate with isobutylamine and aqueous trifluoroacetic acid, respectively gave 4,6-di-*O*-benzyl-*myo*-inositol in an overall yield of 67%. *Myo*-inositol orthoformate and orthoacetate were prepared and isolated as their tribenzoates. The free orthoesters were regenerated by deprotection of the benzoates by aminolysis with isobutylamine.

Keywords: Cyclitol; Inositol; Orthoesters; Signal transduction

Symmetric 4,6-di-*O*-substituted *myo*-inositol derivatives **1** and **2** are important intermediates for the preparation of optically active *O*-protected derivatives of *myo*-inositol, since they can be enantioselectively acylated at the C-1 hydroxyl group in the presence of lipase from *Pseudomonas*.[1,2] This method of asymmetrization of *myo*-inositol was used for the synthesis of its mono- as well as polyphosphates. However, published procedures[1–3] for the preparation of **1** and **2** require the use of chromatographic methods of separation and the maximum yield does not exceed 45% (from *myo*-inositol). We now describe convenient, a high yielding procedure (67% from *myo*-inositol) for the preparation of **1** without the use of chromatography, which is an improvement over our earlier report.[4] We also describe convenient procedures for the preparation of *myo*-inositol orthoesters **8** and **9**, which are important intermediates for the preparation of several biologically important phosphoinositols,[5–12] glycosyl inositols,[13] a deoxyinositol,[14] novel cyclitol based metal complexing agents[15,16] as well as **1** and **2** (Scheme 1).

Most known methods for the preparation of the orthoformate **8** involve chromatography[3] or lyophilization of its aqueous solution.[17] Recently Angyal[15] has reported a modification of the earlier procedure[2] wherein the orthoformate **8** was isolated directly by crystallization. We have isolated the orthoesters of *myo*-inositol as the correspond-

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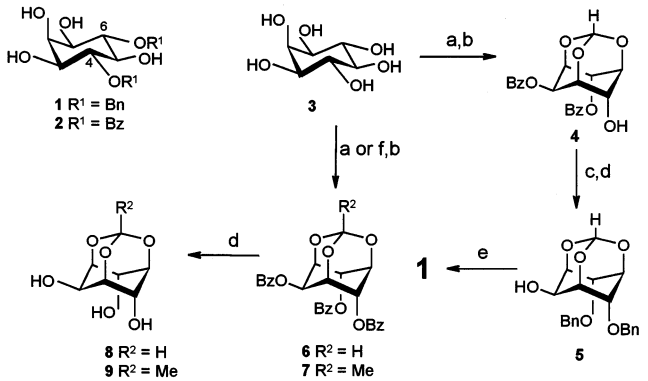

Scheme 1. Reagents and conditions: (a) DMF, $HC(OEt)_3$, pTsA; (b) pyridine, benzoyl chloride; (c) DMF, Ag_2O, BnBr; (d) MeOH, isobutylamine, reflux; (e) trifluoroacetic acid–water; (f) DMF, $MeC(OEt)_3$, pTsA.

ing tribenzoates (**6** and **7**) and regenerated the orthoesters by aminolysis with isobutylamine. The benzamide generated in the process could be easily separated by extraction with diethyl ether, in which the triols **8** and **9** are insoluble. The yield obtained by the procedures described below for **8** is comparable to and for **9** better than the procedures available in the literature.

1. Experimental

General methods.—For general methods see Ref. 18. All the compounds previously known in the literature were characterized by comparison of their melting points and ^1H NMR spectra with those of authentic samples. Silver(I) oxide was prepared by mixing warm (80–90 °C) solutions of silver nitrate (9 g in 150 mL) and NaOH (3.2 g in 100 mL) in deionized water with vigorous stirring. The precipitated solid was washed with deionized water (until the washings were neutral) followed by dry acetone. Silver(I) oxide so obtained was dried at 80 °C under vacuum (yield: 5.8 g).

*Racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate* (**4**).—*Myo*-inositol (10.80 g, 60 mmol), triethyl orthoformate (15 mL) and anhyd toluene–*p*-sulfonic acid (1 g) were taken in a round bottom flask and heated at 100 °C for 1 h. The reaction mixture was cooled to rt and Et_3N (4 mL) was added and low boiling solvents were removed by co-evaporation with benzene (2 × 10 mL) under reduced pressure. The resulting mixture was concentrated under reduced pressure at 70 °C to obtain a syrupy liquid. It was dissolved in pyridine (60 mL), the resulting solution was cooled to 0 °C and freshly distilled benzoyl chloride (18.8 g, 133 mmol) was added dropwise over a period of 1 h with stirring. The reaction mixture was allowed to warm to rt and stirring continued for 18 h. Pyridine was removed from the reaction mixture under reduced pressure and the resulting pasty mass was dissolved in $CHCl_3$ (200 mL), washed with dilute HCl, dilute $NaHCO_3$ solution and brine. The $CHCl_3$ solution was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The solid obtained was crystallized from $CHCl_3$–light petroleum mixture to obtain **4** (19.1 g, 80%); mp 164–165 °C, lit.[19] 163–165 °C.

*4,6-di-*O*-Benzyl-*myo*-inositol* (**1**).—The dibenzoate **4** (2.50 g, 6.28 mmol) was dissolved in DMF (20 mL) and freshly prepared silver(I) oxide (5.83 g, 25.12 mmol) and BnBr (8.59 g, 50.24 mmol) were added. The reaction mixture was stirred at rt for 4 days. It was then diluted with $CHCl_3$ (40 mL) and filtered through Celite. The $CHCl_3$ solution was washed several times with water and then with brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent evaporated under reduced pressure to obtain a gum. The gum was washed several times with light petroleum and dissolved in a mixture of dry MeOH (24 mL) and isobutylamine (6 mL) and refluxed overnight. The clear solution was concentrated under reduced pressure to a paste, which was washed with light petroleum and dissolved in a minimum volume of $CHCl_3$. To this solution, light petroleum was added until the solution turned turbid and then heated on a water bath to obtain a clear solution which was left at rt overnight to obtain crystals of **5** (2.02 g, 87%); mp 124–125 °C, lit.[20] 124–125 °C. The dibenzyl ether **5** (1.00 g, 2.70 mmol) was suspended in a mixture of trifluoroacetic acid (1 mL) and water (0.5 mL) and stirred at rt for 18 h. The reaction mixture was evaporated under reduced pressure to obtain **1** as a white solid. It was crystallized from $CHCl_3$–light petroleum ether (0.94 g, 97%); mp 138–139 °C, lit.[1] mp 138.5–139 °C.

Myo-*inositol 1,3,5-orthoformate* (**8**).—*Myo*-inositol orthoformate was prepared and benzoylated using an excess of benzoyl chloride (24 mL) as in the preparation of **4**. The gummy residue obtained after benzoylation (overnight) was triturated with MeOH (~ 350 mL) and cooled in ice. The precipitated white solid was filtered and washed with MeOH to obtain the tribenzoate **6** (28.31 g, 94%); mp 216–218 °C, lit.[18] mp 216–218 °C. The tribenzoate **6** was suspended in a solution of isobutylamine in dry MeOH (20%, 100 mL) and refluxed for 24 h. The solvents were evaporated to obtain a gummy residue which, on extraction with Et_2O, gave the triol **8** as a colorless precipitate. It was separated by filtration (10.28 g, 90% for three steps); mp 300–301°C, lit.[20] mp 300–302 °C.

Myo-*inositol 1,3,5-orthoacetate* (**9**).—The preparation of **9** was carried out as in the case of **8** using triethyl orthoacetate (16.4 mL) instead of triethyl orthoformate and heating for 8 h. Data for the tribenzoate **7** (29.42 g, 95%); mp 154–155 °C. IR (Nujol): 1726 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64 (s, 3 H, Me), 4.60–4.80 (m, 2 H, H-1, H-3), 4.95 (m, 1 H, H-5), 5.67 (m, 1 H, H-2), 5.84–5.94 (m, 2 H, H-4, H-6), 7.06–7.34 (m, 4 H, aromatic), 7.39–7.73 (m, 5 H, aromatic) 7.75–8.00 (m, 4 H, aromatic), 8.09–8.35 (m, 2 H, aromatic). ^{13}C NMR ($CDCl_3$): δ 24.03, 62.92, 66.97, 68.36, 69.94, 109.35, 128.24, 128.57, 129.38, 129.71, 133.31, 165.03, 166.06. Yield of **9** was 88% (for three steps); mp 186–187 °C, lit.[9] mp 185–187 °C.

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