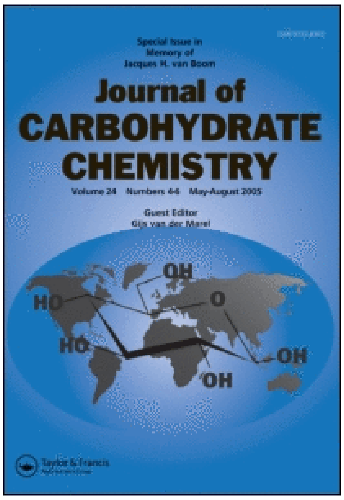

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IMPROVED PREPARATION OF CYCLOHEXYLIDENE DERIVATIVES OF *MYO*-INOSITOL

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ABSTRACT

Condensation of *myo*-inositol with 1,1-dimethoxycyclohexane in the presence of Nafion-H affords directly 1,2-*O*-cyclohexylidene-*myo*-inositol in 45 - 50% yield, along with 1,2:3,4-, 1,2:4,5- and 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositols in lesser amounts.

INTRODUCTION

Traditional methods employed for preparation of mono-, di- and tri-*O*-cyclohexylidene derivatives of *myo*-inositol have involved the direct, acid-catalyzed reaction of cyclohexanone with the cyclitol.[1 - 3] The procedure involves overreaction with cyclohexanone to give a mixture of di- and tri-*O*-cyclohexylidene derivatives, followed by selective hydrolysis to produce 1,2-*O*-cyclohexylidene-*myo*-inositol, a process in our hands which is tedious, giving a product whose purification is complicated by the presence of large amounts of cyclohexanone dimer from unavoidable self-condensation of the ketone. Problems reported with the preparation are documented by the authors.[2]

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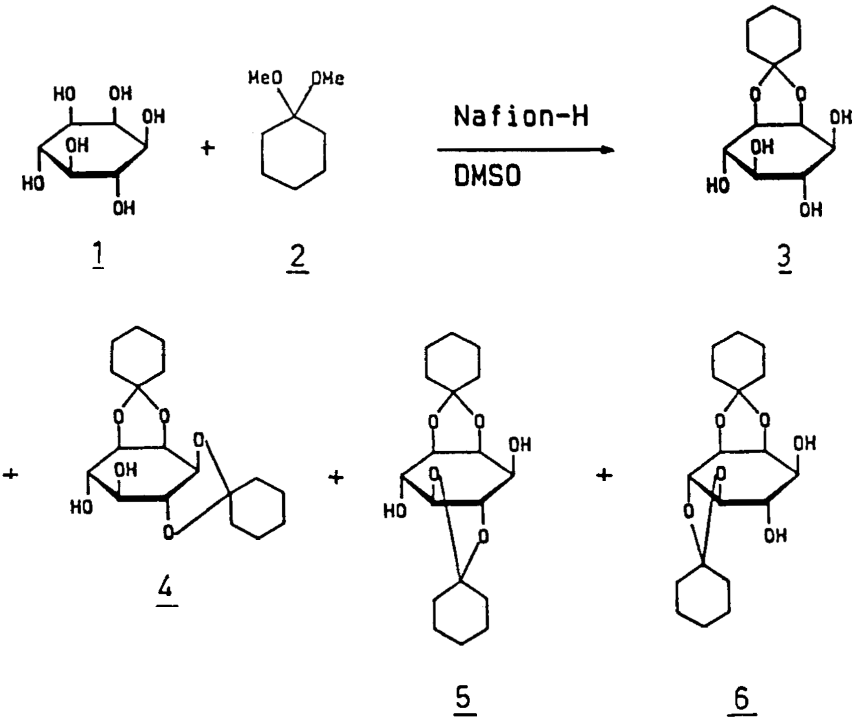
RESULTS AND DISCUSSION

An improved procedure whereby 1,1-dimethoxycyclohexane (2) is employed as the acetalating reagent allows the direct preparation of 1,2-*O*-cyclohexylidene-*myo*-inositol (3) in 45 - 50% yield, along with 1,2:3,4- (4), 1,2:4,5- (5) and 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol (6). The reaction is facilitated by the use of Nafion-H (Dupont),[4] a strongly acidic resin that is easily removed from the reaction mixture. Pyridine is added to the mixture to ensure neutralization of any

SCHEME



acid, and the solvents are evaporated. The mono-O-cyclohexylidene derivative 3 is crystallized directly from the crude reaction mixture, and the di-O-cyclohexylidene derivatives 4 - 6, useful in their own right as synthetic intermediates,[5] are separated by a combination of fractional crystallization and preparative chromatography on silica gel. Alternatively products 4 - 6 can be converted to 3.[2]

EXPERIMENTAL

General. Solvents were evaporated, except where otherwise noted, at aspirator vacuum at ~40 °C. Melting points were determined using a Thomas-Hoover "Unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-sense digital thermometer/8520-55 thermocouple combination that was calibrated with known standards. ^{1}H NMR spectra were determined at 200 MHz using a Nicolet NT-200 instrument. Chemical shifts are reported in δ-units downfield from an internal standard of tetramethylsilane; multiplicities are first-order values (in Hz) and are indicated thusly: d, doublet; s, singlet; t, triplet; m, multiplet; ψt = a "pseudo" triplet, i.e., a dd with equivalent J-values. Solutions were typically ~0.1% for ^{1}H NMR. Thin-layer chromatography (TLC) used 0.2 mm aluminum-backed plates (E. Merck catalog no. 5760). Preparative LC was carried out using a Waters Associates Prep-500A instrument using two Prep-Pak-500/Silica Gel cartridges. Solvents include: A, 5:95 methanol -

chloroform and B, 1.5:98.5 methanol - chloroform. Dimethyl sulfoxide (DMSO) was distilled over calcium hydride under vacuum (ca. 25 torr). Myo-inositol was dried at 80 °C under vacuum (ca. 1 torr) for 12 h. All solvents and reagents were "reagent grade" unless otherwise noted. Cyclohexanone dimethyl acetal (2) was prepared according to the known method:[6] bp = 56 °C/13 torr. ^1H NMR data (chloroform-d): δ 1.40 - 1.63 (10H, CH_2, cyclohexane), 3.17 (6H, s, CH_3O).

Preparation of 1,2-O-Cyclohexylidene-myo-inositol (3), 1,2:3,4-Di-O-cyclohexylidene-myo-inositol (4), 1,2:4,5-Di-O-cyclohexylidene-myo-inositol (5) and 1,2:5,6-Di-O-cyclohexylidene-myo-inositol (6). To 36 g (0.20 mol) of myo-inositol (1) and 8.0 g of Nafion-H™ (32 - 60 mesh ASTM, DuPont) in 130 mL of dry dimethyl sulfoxide was added dropwise 64.8 g (0.45 mol) of 1,1-dimethoxycyclohexane (2)[6] during 0.5 h at room temperature under a dry nitrogen atmosphere. The mixture was stirred at 95 - 100 °C for 12 h, at the end of which time the mixture was cooled to room temperature and the resin was removed by filtration. Ten mL of pyridine was added to the solution, and the dimethyl sulfoxide and pyridine were evaporated at 60 °C under high vacuum (1.0 torr) to provide a golden syrup. Upon addition of 300 mL of methylene chloride to the residue, a white precipitate formed instantly. The precipitate was collected by filtration, washed with 2 x 100 mL of methylene chloride, and dried under vacuum at 40 °C to give 25 g of crude product 3. This crude product was dissolved in 200 mL of 90:10 ethanol - water and crystallized to give 23 g (44.3%) of pure 3: mp 179 - 180 °C (Lit.[1] mp 179 °C); NMR data (chloroform-d): δ 1.40 - 1.84 (10H), 3.24 (1H, ψt, $J_{5,6}$ = $J_{4,5}$ = 9.8 Hz, H-5), 3.52 - 3.68 [2H, m (7 lines), H-1, H-6], 3.85 (1H, dd, $J_{4,5}$ = 9.8 Hz, H-4), 4.05 (1H, dd, $J_{3,4}$ = 7.6 Hz, H-3), 4.46 (1H, ψt, $J_{1,2}$ = $J_{2,3}$ = 4.4 Hz, H-2).

The methylene chloride filtrate was washed with 2 x 150 mL of water, dried over a mixture of potassium carbonate and magnesium sulfate, and evaporated to provide a yellow syrup. This syrup was dissolved in 80 mL of ethyl acetate and 220 mL of petroleum ether under boiling. After cooling at 0 °C for 12 h, 10.1 g of colorless crystals of 5 was deposited. The syrup obtained upon evaporation of the solvent showed three major zones by TLC; R_f 0.42 (5), 0.33 (6), and 0.22 (4) (A), respectively. The mixture was separated by preparative LC on silica gel using solvent B (200 mL/min^{-1} and 225 psi). The fraction which eluted in a zone of retention time of 10 min on the preparative LC was evaporated to give an additional 4.8 g of 5, [total yield of 5 = 14.9 g (21.9%)]: mp 156 - 157 °C (Lit.[1] mp 158 °C); R_f 0.42 (A); NMR data (chloroform-d): δ1.40 - 1.69 (20H), 2.36 - 2.47 (2H, 4 lines, 2-OH, exchangeable with D_2O), 3.31 (1H, dd, $J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = 9.5 Hz, H-5), 3.77 - 4.10 (4H, m, H-1, H-3, H-4, H-6), 4.48 (1H, ψt, $J_{1,2}$ = $J_{5,6}$ = 4.8 Hz, H-2).

The fraction which eluted in a zone of retention time of 14 min was evaporated to give 15.2 g (22.4%) of pure 6: mp 131 - 132 °C (from hexane - ethyl acetate) (Lit.[1] mp 133 °C); R_f 0.33 (A); ^{1}H NMR data (chloroform-d): δ 1.40 - 1.71 (20H), 2.54 - 2.59 (2H, 3 lines, 2-OH, exchangeable with D_2O), 3.40 (1H, dd, $J_{4,5}$ = 10.2 Hz, $J_{5,6}$ = 8.5 Hz, H-5), 3.82 - 4.10 (3H, m, H-3, H-4, H-6), 4.33 (1H, dd, $J_{5,6}$ = 8.0 Hz, H-1), 4.49 (1H, dd, $J_{1,2}$ = 6.3 Hz, $J_{2,3}$ = 4.1 Hz, H-2).

The fraction which eluted in a zone of retention time of 22 min was evaporated to give 7.3 g (10.7%) of 4: mp 174 - 175 °C (from ethyl acetate - hexane) (Lit.[1] mp 174 °C); R_f 0.22 (A); ^{1}H NMR data (chloroform-d): δ 1.25 - 1.81 (20H), 2.8 (2H, bs, 2-OH, D_2O exchangeable), 3.67 - 3.81 (3H, m, H-3, H-5, H-6), 3.98 (1H, ψt, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4), 4.20 (1H, ψt, $J_{1,2}$ = $J_{5,6}$ = 5.4 Hz, H-1), 4.64 (1H, dd, $J_{2,3}$ = 3.0 Hz, H-2).

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