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Note

(±)-1,2:5,6-Di-*O*-isopropylidene-*myo*-inositol and (±)-6-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol: a practical preparation of key intermediates for *myo*-inositol phosphates

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Abstract

A simple and practical synthetic procedure for the versatile intermediates, (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol and (±)-6-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, is described.

Keywords: Cyclitol; Inositol phosphate intermediate; Debenzoylation

Several *myo*-inositol phosphates are widely recognized for their biological roles as second messengers in intracellular signaling.[1] The discovery of novel inositol phosphates and their functions in living systems is still ongoing.[2] The preparation of properly protected inositol intermediates is a key step in the synthesis of inositol phosphates as well as other related products such as conduritols and pseudosugars. In this paper, we report a simple and practical synthesis of (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol and (±)-6-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, which are versatile intermediates (Scheme 1).

Acetal derivatives are one of the most popular classes of inositol phosphate intermediates; (±)-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**6**) and (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**5**) are two examples of these derivatives. When *myo*-inositol is treated with acetone (or its ketal derivatives) in the presence of an acid catalyst, a mixture of compounds **5**, **6**, and (±)-1,2-*O*-isopropylidene-*myo*-inositol is formed along with other minor isomers. Separation of compounds **5** and **6** requires column chromatography, which may not be appropriate for large-scale synthesis.[3] In situ benzoylation of the mixture, a procedure developed by Gigg et al., greatly facilitates the separation of 3,6-dibenzoate isomer **3** due to its highly crystalline nature (26% yield).[4] However, unlike the case of isomer **3**, further purification of 3,4-dibenzoate **2** from the filtrate is neither efficient (13% yield from inositol) nor straightforward.[5] One of the problems in purification is the presence of a significant amount of (±)-3,4:5,6-tetra-*O*-benzoyl-1,2-*O*-isopropylidene-*myo*-inositol (**4**) (28%) in the filtrate, which competitively crystallizes along with the desirable compound **2**.[5] An alternative approach was introduced for an easy purification of **2** and **3**, but the procedure involves a two-step reaction from *myo*-inositol, using (±)-1,2-*O*-isopropylidene-*myo*-inositol as an intermediate.[6]

To simplify the purification of compound **2**, we attempted to modify the original procedure of Gigg et al.[4] by reducing the formation of tetrabenzoate **4**. A mixture of *myo*-inositol, 2,2-dimethoxypropane, *p*-toluenesulfonic acid in DMF was stirred at 120 °C for 3 h. The reaction mixture was further benzoylated by addition of

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benzoyl chloride and pyridine at 0 °C. After the filtration of compound **3**, HPLC–MS (High-Performance Liquid Chromatography-Mass Spectrometry) was used to monitor the product ratio of compound **2** versus tetrabenzoate **4**. An increased amount of 2,2-dimethoxypropane (up to 16 equiv) in the first step did not significantly reduce the amount of tetrabenzoate **4** (nearly equimolar amount with **2**). The only result was an increased amount of brown oil. Similarly, the addition of molecular sieves to the reaction mixture did not decrease the amount of tetraol.

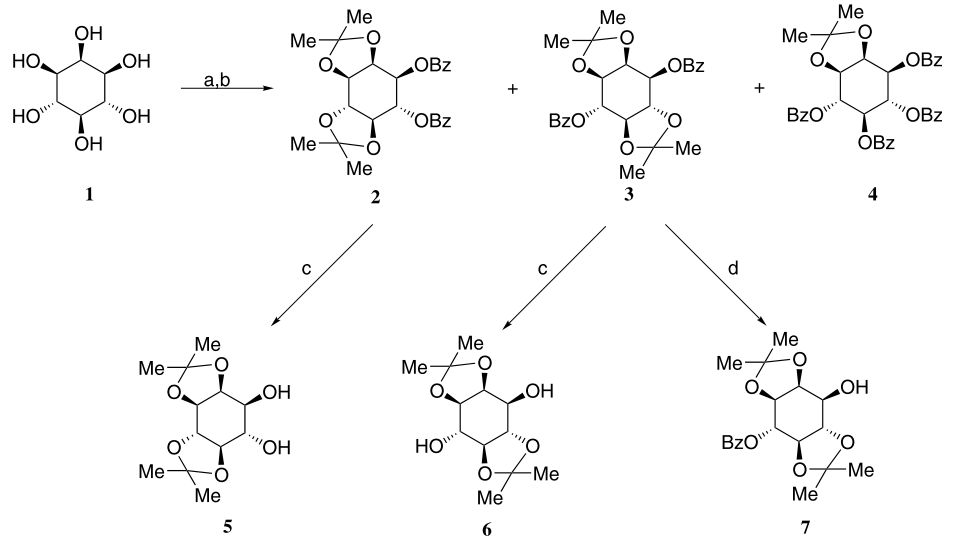
Finally, we undertook a second approach—to remove any existing (±)-1,2-*O*-isopropylidene-*myo*-inositol from the reaction mixture. After 3 h of stirring at 120 °C, the reaction mixture was concentrated by vacuum distillation and filtered through a plug of silica gel. The plug was washed with ethyl acetate to elute a mixture of diols leaving most of the (±)-1,2-*O*-isopropylidene-*myo*-inositol behind. After benzoylation of the diols, compound **3** was isolated by filtration in 26% yield. HPLC–MS examination of the filtrate indicated less than a 4% of tetrabenzoate **4** contamination of compound **2**. The filtrate was stirred with an excess amount of water to give a crude solid material. The solid was then easily recrystallized from acetone to give pure compound **2** in 22% yield.

A previously reported procedure for the hydrolysis of **2** and **3** with NaOH in MeOH requires a mild neutralization of the reaction mixture with solid carbon dioxide to suppress acetal migration or hydrolysis, followed by an extraction.[4,5] This neutralization procedure is usually time consuming due to vigorous gas generation and hypercooling. In order to obtain a high recovery of the product, the extraction step requires a large excess of organic solvent. To simplify this procedure, we used sodium methoxide, combined with a silica gel filtration step in place of neutralization–extraction. Base-catalyzed transacylation of the benzoyl groups in compound **2** or **3** was performed using NaOMe in MeOH. The crude reaction mixture, after dilution with dichloromethane, was filtered through a plug of silica and evaporated to dryness. Washing the solid with ethyl acetate–hexane solvent mixture to remove the byproduct, methyl benzoate, afforded pure diol products **5** or **6** in 91 and 94% yields, respectively.

Finally, we developed regioselective hydrolysis reaction conditions of **3** to synthesize (±)-6-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**7**). Treatment of **3** with sodium hydroxide in a dichloromethane–methanol solvent mixture generated the major component **7**, along with its isomer (±)-3-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**8**), and diol **6** as minor components. GC–MS was used to monitor relative amounts of **3**, **7**, **8**, and **6** (t_R 26.59, 22.03, 21.55, and 15.88 min, respectively). The optimum conditions to maximize the amount of compound **7** were established after a series of screening of solvents, catalysts, reaction times, and temperatures. The reaction mixture was purified by column chromatography to give pure compound **7** in 49% yield. It is noteworthy that the selective benzoylation of diol **6** gives the 3-benzoate **8** as a major product.[7] Thus, this selective debenzoylation is a complementary method to synthesize novel isomer **7**, which otherwise has to be prepared by multiple protection–deprotection procedures.

1. Experimental

General methods.—All reagents were commercially available from Aldrich or Acros and used without



Scheme 1. Reagents: (a) 2,2-dimethoxypropane, *p*-TSA, DMF; (b) BzCl, pyridine; (c) $NaOCH_3$, MeOH; (d) 0.4 equiv NaOH, MeOH, CH_2Cl_2, H_2O.

further purification. NMR spectra were recorded on a Gemini 300 MHz spectrometer. GC–MS data were obtained on a Hewlett–Packard HP5971 GC–MS spectrometer (HP–5MS ultra low bleed 5%-diphenyl–95%-dimethylsiloxane copolymer column, oven temperature range 80–310 °C). HPLC–MS data were obtained on a Hewlett–Packard HP1100 spectrometer equipped with a C18 column (20 × 4 mm, 3 μm) using 5–95% MeCN (over water) gradient. The identities of the compounds were confirmed by electrospray-ionization mass spectra (ESIMS), and the relative quantities were measured by UV absorption at 230 nm. Silica filtrations were performed on Sorbent Technologies, 60 Å silica gel (63–200 mesh). TLC was done on SAI F_{254} precoated silica gel plates (250-μm layer thickness).

Preparation of (±)-3,6-di-O-*benzoyl-1,2:4,5-di*-O-*isopropylidene*-myo-*inositol* (**3**).—A mixture of *myo*-inositol (25 g, 139 mmol), 2,2-dimethoxypropane (75 mL, 600 mmol), and *p*-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) in DMF (100 mL) was heated to 120 °C for 3 h until no more solid remained. The reaction mixture was concentrated by vacuum distillation (50 °C at 20 barr), and Et_3N (0.36 mL) was added to the residual oil. The oil was diluted with 100 mL of EtOAc and vacuum evaporated together with silica (40 g) to complete dryness. The resulting powder was loaded on top of a plug of silica (5.5 cm in height, 8.5 cm in diameter, 120 g) and washed thoroughly with EtOAc (700 mL). After the solvent was removed in vacuo, pyridine (70 mL) and PhCOCl (50 mL, 0.42 mol) were added to the residual oil at 0 °C. The reaction mixture was then allowed to stir at rt for 2 h. The precipitate was collected (the initial filtrate was set aside for further use) and washed with pyridine, water, Me_2CO, and Et_2O to give **3** as a white solid in 26% yield (16.9 g). ^{1}H NMR data were in agreement with those reported in the literature.[5] ESIMS: $[M+H]^+$ Calcd, 469.2; Found, 469.0.

Preparation of (±)-3,4-di-O-*benzoyl-1,2:5,6-di*-O-*isopropylidene*-myo-*inositol* (**2**).—The initial pyridine filtrate from the preparation of **3** was diluted with an excess of water (1 L) and stirred at rt for 48 h. The precipitate was collected, thoroughly washed with water, and recrystallized from acetone to give **2** as a white solid in 22% yield (14.2 g). ^{1}H NMR data were in agreement with those reported in the literature.[5] ESIMS: $[M+H]^+$ Calcd, 469.2; Found, 469.0.

Preparation of (±)-1,2:5,6-di-O-*isopropylidene*-myo-*inositol* (**5**).—Compound **2** (10 g, 21.4 mmol) was dissolved in MeOH (150 mL) and treated with NaOMe (1.38 g, 25.6 mmol). The reaction mixture was allowed to stir at reflux for 1.5 h, cooled down to rt, and diluted with CH_2Cl_2 (750 mL). The solution was then filtered through a plug of silica (4 cm in height, 7 cm in diameter, 50 g). The silica was washed with EtOAc (150 mL), and the solvents were removed in vacuo. The off-white solid was thoroughly washed with 1:5 EtOAc–hexanes solvent mixture to remove methyl benzoate. The white solid **5** was obtained in 91% yield (5.03 g). ^{1}H NMR data were in agreement with those reported in the literature.[5] ESIMS: $[M+H]^+$ Calcd, 261.1; Found, 261.1.

Preparation of (±)-1,2:4,5-di-O-*isopropylidene*-myo-*inositol* (**6**).—Compound **3** (10 g, 21.4 mmol) was suspended in 300 mL of MeOH and treated with NaOMe (1.38 g, 25.6 mmol). The reaction mixture was allowed to stir at reflux until all starting material had reacted (solution turned clear). After an additional 30 min of stirring under reflux, the reaction mixture was cooled to rt and diluted with CH_2Cl_2 (1500 mL). The solution was then filtered through a plug of silica (4 cm in height, 7 cm in diameter, 50 g). The silica was washed with 150 mL of EtOAc, and the solvents were evaporated in vacuo. The off-white solid was thoroughly washed with 1:5 EtOAc–hexanes solvent mixture to remove methyl benzoate. The white solid **6** was obtained in 94% yield (5.2 g). ^{1}H NMR data were in agreement with those reported in the literature.[5] ESIMS: $[M+H]^+$ Calcd, 261.1; Found, 261.1.

Preparation of (±)-6-O-*benzoyl-1,2:4,5-di*-O-*isopropylidene*-myo-*inositol* (**7**).—Compound **3** (5 g, 10.7 mmol) was completely dissolved in CH_2Cl_2 (350 mL) and MeOH (200 mL). NaOH (0.17 g, 4.27 mmol) in water (50 mL) was diluted with MeOH (100 mL) and added to the reaction mixture over 20 min. The reaction mixture was stirred overnight at rt, and the solvents were removed in vacuo. The solid was dissolved in EtOAc and vacuum evaporated together with silica (10 g) to complete dryness. The resulting powder was loaded on top of a plug of silica (4 cm in height, 7 cm in diameter, 50 g) and washed with 5:1 hexanes–EtOAc to elute methyl benzoate and starting material **3**. The silica gel was further washed with 1:1:1 solvent mixture of hexanes–EtOAc–CH_2Cl_2 to elute **7**, that, after evaporation of solvents, was obtained in 49% yield (1.9 g). No trace of **8** was detected by GC–MS analysis. ^{1}H NMR ($CDCl_3$): δ 1.31, 1.38, 1.43, 1.59 (4s, each 3 H, 2 CMe_2), 2.47 (d, 1 H, J 8.5 Hz, 3-OH), 3.51 (dd, 1 H, $J_{5,4}$ 9.0 Hz, H-5), 3.98 (dd, 1 H, $J_{4,3}$ 10.0, H-4), 4.08 (ddd, 1 H, $J_{3,2}$ 4.5 Hz, H-3), 4.29 (dd, 1 H, $J_{1,6}$ 6.7 Hz, H-1), 4.48 (dd, 1 H, $J_{2,1}$ 4.8 Hz, H-2), 5.47 (dd, 1 H, $J_{6,5}$ 11.0 Hz, H-6), 6.37 (dd, 2 H, Ph), 7.51 (dd, 1 H, Ph), 8.03 (d, 2 H, Ph); ESIMS: $[M+H]^+$ Calcd, 365.2; Found, 365.0; Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.48; H, 6.73.

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