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Facile selective cleavage of a *myo*-inositol *trans*-isopropylidene acetal in the presence of a *cis*-isopropylidene acetal

K. S. Ravikumar and David Farquhar*

Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

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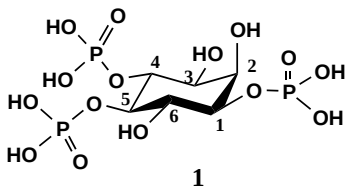
Abstract—1,2:4,5-Di-*O*-isopropylidene *myo*-inositol acetals were selectively deprotected at the 4,5-*trans* position using Amberlite-120 (H^+) resin in $CHCl_3$/MeOH at room temperature over 24–48 h to afford the corresponding *cis*-1,2-*O*-isopropylidene *myo*-inositol acetals in near quantitative yield. © 2002 Elsevier Science Ltd. All rights reserved.

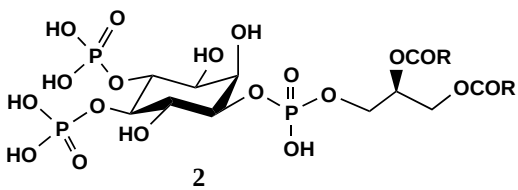
myo-Inositol is the most common inositol isomer in nature. It is the starting material for the biosynthesis of inositol phosphates.[1–3] The 1,4,5-trisphosphate derivative, **1**, possesses second messenger properties[1–3] and plays an important role in the cellular mobilization of calcium.[4] The structurally-related phosphatidylinositols, **2**, play a key role in cell signal transduction pathways and regulate such diverse biologic processes as cell growth, cell cycle progression, apoptosis, differentiation, transformation, mitogenesis, cytoskeletal rearrangement and glucose transport.[5–7]

During the past decade, considerable effort has been directed at the design of analogs of inositol phosphates both as tools to explore cell-signaling pathways and as potential therapeutic agents to control abnormal cell expression.[8–11]

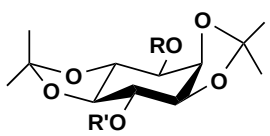
The chemical synthesis of analogs of *myo*-inositol requires the use of alcohol protective groups that can be regioselectively manipulated.[1,2] It is well established[12] that the 1,2- and 4,5-diol positions of *myo*-inositol can be protected as isopropylidene acetals (acetonides) leaving the 3- and 6-hydroxy groups free for further reaction. In studies on the synthesis of analogs of **1** and **2**, we required the selective deprotection of the *trans*-acetonide of 1,2:4,5-diacetonides of the general structure **3**. The most common method for the deprotection of acetonides is acid-catalyzed hydrolysis[13] using protic or Lewis acids. The preferential cleavage of *trans*-acetonides over *cis*-acetonides has been reported using catalytic amounts of acetyl chloride[14,15] in MeOH or *p*-toluenesulfonic acid hydrate (PTSA)[16] in acetone/water (40:1), and is based on the slightly greater acid lability of *trans*-acetonides compared with their *cis*-counterparts. Work up of the



1



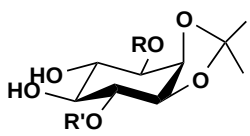
2



3

Amberlite-120 H^+

$CHCl_3$ / MeOH



4

		Yield (%)
a. R = Bn	R' = Bn	93
b. R = Ts	R' = Bn	98
c. R = TBDPSi	R' = Bn	97
d. R = Bz	R' = Bz	94

Keywords: acetal; acetonide; Amberlite-120 resin; inositol; protection, deprotection.

* Corresponding author. Tel.: +(713)792-3629; fax: +(713)792-3628; e-mail: dfarquha@mail.mdanderson.org

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crude reaction mixtures required the addition of triethylamine to neutralize acid, and column chromatography on silica gel to isolate pure product.[17]

To avoid sensitive work up conditions and chromatographic purification procedures, an alternative approach was sought for the selective deprotection of the *trans*-acetonide group of 1,2:4,5-diacetonides. Since the deprotection of acetonides has been reported[18] with aqueous acetic acid, attempts were made to selectively cleave the *trans*-acetonide of **3a** using a weakly acidic ion-exchange resin, Amberlite IRC-50, in $CHCl_3$/MeOH (2:1) solution. No reaction was evident after 24 h at room temperature. However, when a strongly acidic ion-exchange resin, Amberlite 120 H^+, was substituted, smooth cleavage of the *trans*-acetonide occurred and the reaction was complete in 24 h. The product, **4a**, was isolated in near quantitative yield by filtration of the reaction mixture and evaporation of the solvent. No traces of the *cis*-diol, the tetradiol, or the starting material were apparent. In a similar manner, **3b–d** were quantitatively converted over 24–48 h to the corresponding *trans*-diols, **4b–d**. This mild and simple procedure avoids the generation of unwanted by-products in the selective deprotection of the *trans*-acetonide of *myo*-inositol 1,2:4,5-diacetonides and, therefore, precludes the requirement for chromatographic purification procedures. It should be generally useful in the field of *myo*-inositol chemistry.

Selective deprotection of a *myo*-inositol 4,5-*trans*-acetonide in the presence of a 1,2-*cis*-acetonide: Amberlite-120 (H^+) resin was washed successively with 1N H_2SO_4, deionized water, acetone, and air-dried. 3-*O*-Tosyl-6-*O*-benzyl-1,2:4,5-isopropylidene *myo*-inositol, **3b** (0.50 g, 1 mmol) was dissolved in $CHCl_3$/MeOH (2:1, 20 mL) and Amberlite-120 (H^+) resin (0.5 g) was added. The reaction was stirred at room temperature under an inert (argon) atmosphere for 36 h. The mixture was filtered through Celite and the solvent was evaporated in vacuo. The pure diol, 3-*O*-tosyl-6-*O*-benzyl-1,2-isopropylidene *myo*-inositol, was obtained as a white solid (0.455 g, 98%). Mp 153°C. ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.45 (s, 3H), 2.44 (s, 3H), 2.72 (d, $J=2.68$ Hz, 1H), 2.78 (d, $J=2.23$ Hz, 1H), 3.43 (td, $J=7.05$, 2.00 Hz, 1H), 3.49–3.54 (dd, $J=9.40$, 6.68 Hz, 1H), 3.94 (td, $J=9.35$, 2.45 Hz, 1H), 4.15 (t, $J=5.93$ Hz, 1H), 4.33 (t, $J=4.61$ Hz, 1H), 4.64 (d, $J=9.54$ Hz, 1H), 4.66 (d, $J=11.37$ Hz, 1H), 4.89 (d, $J=11.52$ Hz, 1H), 7.28–7.35 (m, 7H), 7.85 (d, $J=8.26$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.66 (q), 25.63 (q), 27.72 (q), 69.97 (t), 72.91 (d), 73.31 (d), 74.26 (d), 78.92 (d), 79.11 (d), 81.05 (d), 110.42 (s), 127.91 (d), 128.01 (d), 128.05 (d), 128.44 (d), 129.74 (d), 133.69 (s), 137.82 (s), 145.05 (s).

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