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Note

1L-2,3:4,5-Bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*chiro*-inositol: a useful intermediate for the preparation of several novel cyclitols ☆

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Modified inositols have emerged both as important probes of the enzymes of the phosphatidylinositol pathway [2–6] and also as inhibitors of cell growth [7–9]. Furthermore, certain cyclitol epoxides and related compounds have shown significant activity as inhibitors of various hydrolases [10–12]. While conduritol epoxides are widely used examples of potent, irreversible glycosidase inhibitors [10], compounds such as the bromoconduritols and conduritol aziridines are just a few of the more recently developed examples [11,12]. Lately there has been renewed interest in the discovery of novel glycosidase inhibitors as potential antiviral agents [13].

As part of our ongoing studies in the preparation and evaluation of novel cyclitols, we have developed an expedient route to the optically pure intermediate, 1L-2,3:4,5-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*chiro*-inositol (**1**), by utilizing the bifunctional protecting agent 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane $\{[Cl(Me_2CH)_2Si]_2O\}$. The utility of this intermediate was subsequently demonstrated by transforming it into several important derivatives including conduritol B epoxide (**3**), 1L-1,2-dideoxy-1,2-epithio-*myo*-inositol (**5**), and the naturally occurring deoxy cyclitol, (−)-viburnitol (**4**).

The $[Cl(Me_2CH)_2Si]_2O$ reagent was primarily developed for the simultaneous protection of the 3′–5′-hydroxy functions of nucleosides [14], but it has since proven to be quite a versatile blocking group for a large variety of diols [15–17]. Ozaki and co-workers have

☆ For a preliminary report see Ref. [1].

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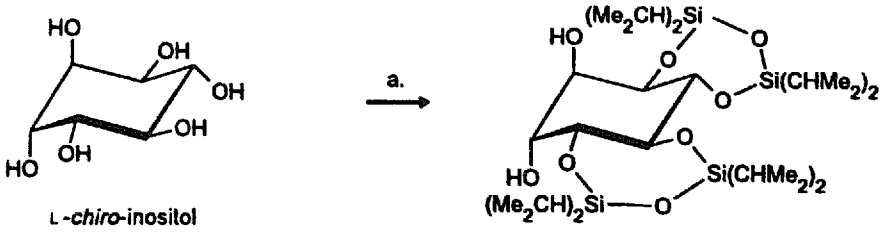


L-*chiro*-inositol

1

Reagents: a. $[Cl(Me_2CH)_2Si]_2O$ / Pyridine.

Scheme 1.

treated *myo*-inositol with this reagent to afford racemic 1,6:3,4-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*myo*-inositol with no appreciable formation of any other isomers [18]. By applying a similar methodology, we have demonstrated the formation of **1** exclusively, in one step, from L-*chiro*-inositol.

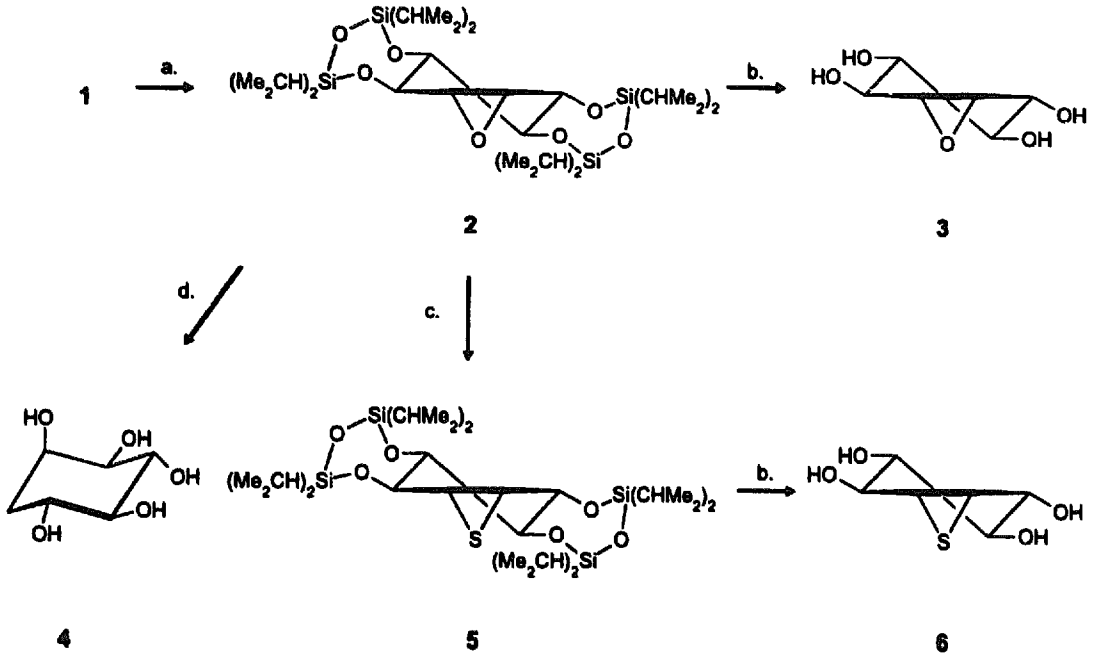
Early studies on the protection of diols using $[Cl(Me_2CH)_2Si]_2O$ established that the reagent initially adds to the most accessible hydroxyl group of a molecule and then proceeds to cyclize to form a seven- or eight-membered ring [19]. It has also been well-established for both *myo*- and *chiro*-inositol that the equatorial hydroxyl groups vicinal to axial substituents are most reactive towards both alkylation and acylation [20,21]. Since Bruzik and Tsai had recently taken advantage of these facts to prepare a number of regiospecifically protected *myo*-inositols [22], we believed that a high degree of specificity could also be achieved in the $[Cl(Me_2CH)_2Si]_2O$ protection of *chiro*-inositol.

Treatment of L-*chiro*-inositol with 2.1 equiv of $[Cl(Me_2CH)_2Si]_2O$ in pyridine for 19 h provided a single product that was identified as 1L-2,3:4,5-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*chiro*-inositol (**1**, Scheme 1). The $[Cl(Me_2CH)_2Si]_2O$ addition therefore appears to take place at either the 2- or 5-positions (which are equivalent), followed by cyclization onto the next most accessible adjacent hydroxyl groups. This affords a *chiro*-inositol derivative with the two axial hydroxyl groups free and all of the equatorial positions blocked. Thus, the use of $[Cl(Me_2CH)_2Si]_2O$ to provide the trans-diaxial diol **1** represents an alternative strategy to the standard inositol acetal protection methodology, which initially affords the equatorial 3,4-diol [18,23,24].

In order to demonstrate the utility of this uniquely protected inositol, we carried out several facile transformations of **1** into three useful inositol derivatives **3**, **4**, and **6** as outlined in Scheme 2.

A precursor to the potent glycosidase inhibitor, conduritol B epoxide (1L-1,2-anhydro-*myo*-inositol, **3**), is formed through an epoxidation of the diaxial diol of intermediate **1**. Treatment of **1** with triphenylphosphine in the presence of diethyl azodicarboxylate (DEAD) in THF afforded the fully protected 1L-1,2-anhydro-3,4:5,6-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*myo*-inositol (**2**) in very good yield. Desilylation of **2** with tetrabutylammonium fluoride provided **3** as a crystalline solid whose identity was confirmed through comparison of its ^1H NMR spectrum and optical rotation with those in the literature [25]. This three-step route constitutes, by far, the most expedient preparation reported for this optically pure glycosidase inhibitor.

The recent discovery that effective glycosidase inhibition can be retained by replacement of the oxirane oxygen of conduritol B epoxide with nitrogen (to form the conduritol aziridine



Reagents: a. PPh_3 / $EtO_2CN{=}NCO_2Et$ / THF; b. Bu_4NF / THF; c. $PPh_3(S)$ / CF_3CO_2H / C_6H_6; d. $LiBHEt_3$ / THF; Bu_4NF / THF.

Scheme 2.

[12]) has led us to investigate the preparation of a sulfur analogue. Treatment of the protected epoxide **2** with triphenylphosphine sulfide in the presence of trifluoroacetic acid afforded the episulfide intermediate, 1L-1,2-dideoxy-1,2-epithio-3,4:5,6-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*myo*-inositol (**5**) in moderate yield. The ^1H and ^{13}C NMR spectra (see Experimental section) resembled those of the bis-protected epoxide **2**. In particular the ^{13}C NMR spectrum showed appropriate upfield shifts for C-1 and C-2 in **5** relative to those in **2**. Desilylation of **5** with tetrabutylammonium fluoride provided 1L-1,2-dideoxy-1,2-epithio-*myo*-inositol (**6**). Compound **6** was further characterized by elemental analysis and will be evaluated shortly for glycosidase activity.

We have recently shown that the naturally occurring deoxy cyclitol, (−)-viburnitol, (1L-1,2,4/3,5-cyclohexanepentol, **4**) can inhibit *myo*-inositol uptake and also act as an inhibitor of the enzyme, phosphatidylinositol synthase [5]. It therefore represents a potentially useful probe for studying the role of the phosphoinositides in signal transduction and possibly in oncogenesis. Although several preparations of (−)-viburnitol have appeared in the literature of late [5,26], many of the previous preparations are often lengthy and require elaborate blocking schemes in order to effect the desired deoxygenation [27–29]. We can now report its facile one-vessel preparation from intermediate **2**. Reduction of the epoxide **2** with lithium triethylborohydride in THF, followed directly by fluoride desilylation, affords (−)-viburnitol (**4**) as a crystalline solid in very good overall yield. The physicochemical data for our synthetic **4** matched those reported [28,30].

In conclusion, a one-step procedure for the simultaneous protection of all four equatorial hydroxyl groups of L-*chiro*-inositol has been developed. The resulting diaxial diol **1** has subsequently been converted into several biologically significant compounds in three

extremely expedient processes. These strategies could, of course, be analogously applied to the D enantiomer of *chiro*-inositol to give access to another set of optically pure derivatives.

1. Experimental

General methods.—^{1}H NMR spectra were recorded at 250 MHz using a Bruker AC 250 spectrometer as solutions that were typically 1–2% (w/v). ^{1}H chemical shifts are reported in δ-units downfield from an internal tetramethylsilane (Me_4Si) standard in chloroform-*d*, while those in deuterium oxide are reported downfield from an external 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) standard, or with an internal acetone reference as indicated. Multiplicities are first-order values in Hz and are indicated as: b, broad; s, singlet; d, doublet; dd, doublet of doublets; m, multiplet; p, pentet; q, quartet; t, triplet; ψt, "pseudo" triplet (i.e., a doublet of doublets having nearly equal *J*-values). Proton-decoupled ^{13}C NMR spectra were recorded at 62.5 MHz using the Bruker AC 250 spectrometer. Chemical shifts are reported in δ-units with respect to the solvent in the case of chloroform-*d* and with respect to the external DSS standard in deuterium oxide. Electron-impact [(+)-EI] and negative-ion fast-atom-bombardment [(−)-FAB] mass spectrometry were carried out on a VG ZAB-EQ (VG Analytical, Manchester, UK) instrument. Optical rotations were measured in the indicated solvent and concentration at the sodium D line in a 1-dm cell at ambient temperatures (20–25°C) with a Perkin–Elmer model 241 spectropolarimeter. Adsorption chromatography was carried out using E. Merck Silica Gel-60 products: (*a*) TLC on 0.2-mm aluminum-backed plates; (*b*) open column chromatography using 38–63 μm silica gel. TLC visualizations were carried out with 2.5% $NaIO_4$ spray followed by 2.5% $KMnO_4$ spray with heating. All solvents and reagents were reagent grade unless noted otherwise. Tetrahydrofuran (THF) was distilled from potassium–benzophenone ketyl at atmospheric pressure. Solvents, unless noted otherwise, were evaporated at ca. 40°C/30 torr on a Büchi Rotovapor. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

2,3:4,5-Bis-O-*(tetraisopropyldisiloxane-1,3-diyl)*-L-chiro-*inositol* (**1**).—A solution of 1L-*chiro*-inositol (821 mg, 4.55 mmol) in pyridine (20 mL) was treated dropwise with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (3.00 g, 9.49 mmol), and the resulting suspension was allowed to stir for 19 h at ambient temperature. Filtration to remove unreacted 1L-*chiro*-inositol and contaminating pyridinium salts, followed by concentration of the filtrate, afforded a glass which, after recrystallization from 1:5 EtOH–toluene, gave **1** (650 mg, 22%; 75% when calculations reflect recovered starting material): R_f 0.16 (1:1 CH_2Cl_2–hexanes); $[\alpha]_D^{21}$ +7.5° (*c* 1.25, CH_2Cl_2); ^{1}H NMR data ($CDCl_3$, 250 MHz): δ 0.88–1.27 [m, 56 H, $(CH_3)_2CHSi$], 2.62 (s, 2 H, 2×OH), 3.87 (dd, 2 H, $J_{4,5}=J_{2,3}=2.4$, $J_{3,4}$ 6.3 Hz, H-3,4), 3.99 (dψt, 2 H, $J_{1,2}=J_{5,6}=2.2$ Hz, H-2,5), 4.06–4.08 (m, 2 H, $J_{1,6}$ 2.2 Hz, H-1,6); ^{13}C NMR data ($CDCl_3$, 62.5 MHz): δ 12.0, 12.1, 12.9, 13.0, 17.2, 17.2, 17.3, 17.4, 17.5, 17.6, 71.9, 75.0, 76.5. Anal. Calcd for $C_{30}H_{64}O_8Si_4 \cdot 0.5H_2O$: C, 53.46; H, 9.72. Found: C, 53.25; H, 9.63.

*1*L-*1,2-Anhydro-3,4:5,6-bis*-O-*(tetraisopropyldisiloxane-1,3-diyl)*-myo-*inositol* (**2**).—To a stirred solution of **1** (410 mg, 0.62 mmol) in THF (10 mL) at ambient temperature

was added Ph_3P (812 mg, 3.09 mmol), followed by the dropwise addition of diethyl azodicarboxylate (0.44 mL, 484 mg, 2.82 mmol). The resulting solution was stirred for 7 h under N_2, at the end of which time the mixture was concentrated to give a colorless glass that was percolated through silica gel, eluting with CH_2Cl_2–hexanes to separate the starting diol **1** (49 mg) from **2** (312 mg, 78%; 89% when calculations reflect recovered starting material), isolated as a colorless glass: R_f 0.49 (1:1 CH_2Cl_2--hexanes); ^1H NMR data ($CDCl_3$, 250 MHz): δ 0.90–1.20 [m, 56 H, $\{Cl(Me_2CH)_2Si\}_2O$, 3.17 (d, 1 H, J 3.6 Hz), 3.35 (bs, 1 H), 3.50–3.67 (m, 2 H), 4.03 (ddd, 2 H, J 12.5, J 6.9, J 1.4 Hz, H-1,2); ^{13}C NMR data ($CDCl_3$, 62.5 MHz): δ 12.1, 12.2, 12.4, 12.6, 12.8, 13.0, 13.1, 17.2, 17.4, 17.6, 56.2 (C-1), 57.5 (C-2), 73.5, 74.6, 75.5, 79.1. Anal. Calcd for $C_{30}H_{62}O_7Si_4$: C, 55.68; H, 9.73. Found C, 55.59; H, 9.66.

1L-1,2-Anhydro-myo-*inositol* (**3**).—A solution of **2** (240 mg, 0.37 mmol) in THF (5 mL) and Bu_4NF (0.18 mL of a M solution in THF, 0.18 mmol) was allowed to stand for 3.5 h at ambient temperature, at which time the solution was treated with ice–water (10 mL). The aq phase was separated and extracted with EtOAc (2×5 mL) to give **3** (27 mg, 61%) after lyophilization of the aq phase; $[\alpha]_D^{25}$ −68° (*c* 1.00, H_2O), lit. $[\alpha]_D$ −70° (*c* 0.6, H_2O) [25]; ^1H NMR data [D_2O (DSS) 250 MHz]: δ 3.02–3.21 (m, 3 H, H-2,3,5), 3.37 (bs, 1 H, H-4), 3.68 (bs, 1 H, H-1), 3.82 (bs, 1 H, H-6).

1L-1,2,4/3,5-Cyclohexanepentol (**4**).—A solution of **2** (175 mg, 0.27 mmol) in THF (5 mL) was treated with a solution of lithium triethylborohydride (0.14 mL of a M solution in THF, 0.14 mmol) and allowed to stir at 45°C under Ar for 12 h. Filtration to remove any insoluble lithium salts, followed by concentration of the filtrate, provided a residue that was treated immediately with Bu_4NF (0.14 mL of a M solution in THF, 0.14 mmol). The resulting solution was allowed to stand for 2 h at room temperature, at which time the mixture was treated with ice–water (10 mL). The aq phase was separated and extracted with EtOAc (2×15 mL) to give **4** (27 mg, 61%) after lyophilization of the resulting aq phase and recrystallization from MeOH–H_2O; mp 178–180°C; lit. 180–181°C [30]; $[\alpha]_D^{26}$ −49.8° (*c* 0.5, H_2O), lit. $[\alpha]_D$ −50° [28]; ^1H NMR data [D_2O (DSS) 250 MHz]: δ 1.54 (ddd, 1 H, J_{gem} 14.0, $J_{3a,4}$ 12.0 Hz, H-3a), 2.09 (dψt, 1 H, $J_{3e,4}$ 4.2 Hz, H-3e), 3.23 (ψt, $J_{5,6}$ 9.0 Hz, H-5), 3.48–3.57 (m, 2 H, H-1,6), 3.75 (ddd, 1 H, $J_{4,5}$ 9.0, H-4), 4.06 (dd, 1 H, $J_{2,3a}$ 3.0, $J_{2,3e}$ 4.2 Hz, H-2).

1L-1,2-Dideoxy-1,2-epithio-3,4:5,6-bis-O-*(tetraisopropyldisiloxane-1,3-diyl)*-myo-*inositol* (**5**).—Trifluoroacetic acid (113.7 μL, 1.78 mmol) in benzene (6 mL) was added to a stirring, 0°C solution of triphenylphosphine sulfide (996.8 mg, 3.39 mmol) and the protected epoxide **2** (871 mg, 1.32 mmol) in benzene (17 mL). The mixture was allowed to warm to ambient temperature and react with stirring for 20 h. The benzene was evaporated, the residue was dissolved in toluene (3×15 mL), and the toluene was repeatedly evaporated. The residue was partitioned between CH_2Cl_2 (25 mL) and water (25 mL). The organic layer was dried ($MgSO_4$) and filtered. Separation over a silica gel column eluted with hexanes afforded a white solid (155.6 mg, 23%); R_f 0.82 (1:20 EtOAc–hexanes); mp 57–58°C; $[\alpha]_D^{20}$ +16.33° (c 1, $CHCl_3$); ^1H NMR data ($CDCl_3$, 250 MHz): δ 3.14 (d, 1 H, $J_{3,4}$ 6.3, H-4), 3.43 (dd, 1 H, $J_{2,3}$ 4.3 Hz, H-3), 3.53 (dd, 1 H, $J_{1,6}$ 9.9, $J_{5,6}$ 7.2 Hz, H-6), 3.71 (dd, 1 H, $J_{1,2}$ 7.8 Hz), 4.28 (d, 1 H, H-5), 4.32 (dd, 1 H, H-2); ^{13}C NMR data ($CDCl_3$, 62.5 MHz): δ 12.0, 12.1, 12.3, 13.0, 17.1, 17.3, 17.3, 17.6, 39.9 (C-1), 42.4 (C-

2), 73.3, 74.7, 76.5, 77.0, 77.3, 77.5, 79.8. Anal. Calcd for $C_{30}H_{62}O_6Si_4$: C, 54.35; H, 9.43; S, 4.84. Found: C, 54.3; H, 9.42; S, 4.83.

1L-1,2-Dideoxy-1,2-epithio-myo-*inositol* (**6**).—Tetrabutylammonium fluoride (1.04 mL of a M solution, 1.04 mmol) was added to a stirred solution of 1L-1,2-dideoxy-1,2-epithio-3,4:5,6-bis-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*myo*-inositol (**5**, 155.6 mg, 0.24 mmol) in THF (1.5 mL), and the reaction was allowed to continue for 1 h at ambient temperature. The solution was evaporated to an oil and partitioned between Et_2O (15 mL) and water (15 mL). The ether layer was then washed with water. After combining the aq layers, the solution was shell frozen and lyophilized under high vacuum. The remaining solid was purified through a silica gel column eluted with 15:85 MeOH–EtOAc to yield a white solid (5.6 mg, 12%); mp 232–233°C; R_f 0.50 (15:85 MeOH–EtOAc); ^{1}H NMR [D_2O (acetone) 250 MHz]: δ 3.13 (d, 1 H, $J_{1,6}$ 6.4 Hz, H-6), 3.24 (dd, 1 H, $J_{4,5}$ 8.1, $J_{3,4}$ 10.5 Hz, H-4), 3.38 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-3), 3.49 (dd, 1 H, $J_{1,2}$ 4.3 Hz, H-1), 4.09 (d, 1 H, H-5), 4.17 (dd, 1 H, H-2); ^{13}C NMR data (D_2O, 90.5 MHz): δ 42.2, 44.1, 73.0, 73.9, 76.2, 78.8; EIHRMS: Calcd for $C_6H_{10}O_4S$: 160.0194. Found: 160.0203.

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