A Novel DAST-induced Debenzylative Cycloetherization in D-1,2-*O*-Isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol

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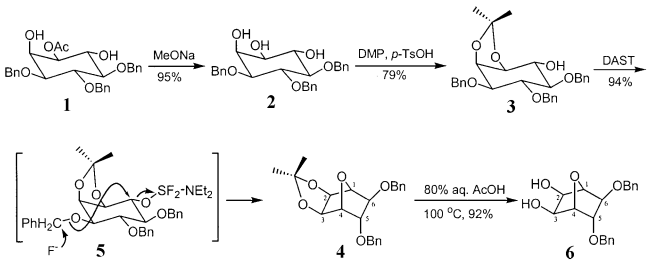
Diethylaminosulfur trifluoride (DAST) has been used extensively for the introduction of fluorine into various types of organic compounds via reactions with alcohols, aldehydes, ketones, and sulfoxides.[1] In particular, DAST has been found to be an excellent reagent for converting ROH to RF. The DAST reaction with alcohols usually occurs with inversion of configuration, although retention of configuration is sometimes observed when the assumed S_N2 process is highly unfavorable for steric reasons or a neighboring group participation is available.[2]

While conducting synthetic studies toward various ring-fluorinated inositol derivatives by employing DAST,[3] we have observed a novel debenzylation with concomitant ring closure, which is the subject of the present report. When D-1,2-*O*-isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol (**3**), prepared from D-1-*O*-acetyl-3,4,5-tri-*O*-benzyl-*myo*-inositol (**1**)[4] in two steps as shown in Scheme 1, was treated with DAST (3.7 mol. equiv.) in dichloromethane at -78 °C to room temperature for 1 hr, an unexpected compound was obtained in 94% yield. The compound contained no fluorine at all, but still retained the isopropylidene and two benzyl groups. The structure was assigned as **4** on the basis of spectral analyses. ^{1}H nmr of **4** showed the isopropylidene methyl groups at δ 1.30 and 1.49 as singlets, the aromatic protons at δ 7.28-7.38, four benzylic protons at δ 4.43-4.57 as multiplets, and six ring protons at δ 3.39 (d, J = 1.7 Hz, H-4), 3.93 (br. d, J = 5.2 Hz, H-5), 4.28 (d, J = 5.7 Hz, H-2), 4.39 (br. s, H-1), 4.44 (d, J = 5.8 Hz, H-6), and 4.77 (d, J = 5.7 Hz, H-3). The ring proton signals were assigned on the basis of ^{1}H-^{1}H COSY, and the ring carbon signals on the basis of Heteronuclear Multiple Quantum Correlation, which clearly showed two sets of benzylic CH_2 protons as well.

In order to confirm the structural assignment of **4**, the experiment was repeated with racemic samples of DL-1,2-*O*-isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol, which was readily derived from *myo*-inositol by the known procedures.[5] When the racemic **3** was treated with DAST under the same conditions, the racemic form of the same cyclic ether was obtained. The product was hydrolyzed with 80% aq. AcOH to give a crystalline diol **6**, whose structure was determined by X-ray diffraction (Figure 1), thus proving the proposed structure of **4** beyond any doubt. Details of the X-ray data collection and structural refinement are presented in Table 1.

A possible mechanistic process for the ether formation is shown in Scheme 1. Treatment of **3** with DAST is expected to give an intermediate **5**. The decomposition of the σ-sulfurane species can generate an incipient cationic species,[6] which is evidently trapped by a conformationally available benzyl ether to give the product **4**. Participation of the benzyl ether to a neighboring cationic site is precedented in the reported transformation of benzyloxy-alcohols to tetrahydrofurans under the Mitsunobu conditions.[7]



Scheme 1

Experimental Section

General methods. All reactions except hydrolyses were performed in oven-dried glassware under inert atmosphere of dry argon or nitrogen. All commercial chemicals were used as obtained without further purification except for solvents, which were purified and dried by standard methods prior to use. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Analytical TLC was carried out on Merck 60 F254 silica gel plate (0.25 mm thickness) and visualization was done with UV light, and/or by spraying with a 5% solution of phosphomolybdic acid followed by charring with a heat gun. Column chromatogra-

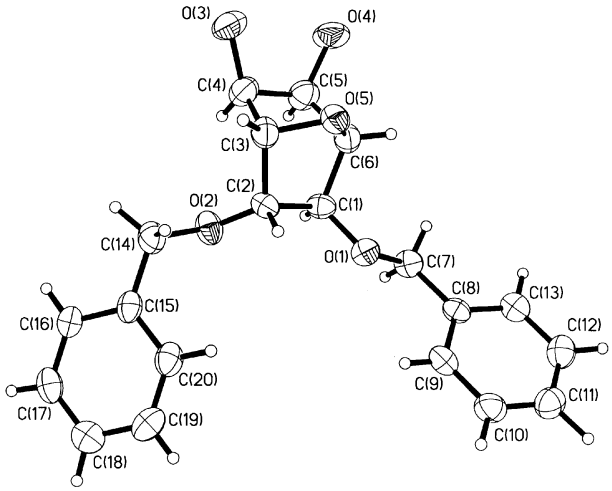


Figure 1. X-ray crystal structure (ORTEP) of compound **6**.

Table 1. Crystal data and structural refinement for **6**

Emperical formula	$C_{20}H_{22}O_5$
Formula weight	342.38
Temp. (K)	188 (2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions (Å)	a = 8.7687 (3) α = 90°
	b = 10.2456 (4) β = 90°
	c = 37.4090 (14) γ = 90°
Volume (Å^3), Z	3360.8 (2), 8
Density (calculated, Mg/m^3)	1.353
Absorption coefficient (mm^{-1})	0.097
F (000)	1456
Crystal size (mm)	0.40×0.40×0.15
θ range for data collection (°)	2.18 to 24.12
Limiting indices	$10 \geq h \geq -9$, $8 \geq h \geq -11$, $42 \geq h \geq -42$
Reflections collected	12439
Independent reflections	2654 (R_{int} = 0.0238)
Completeness to θ = 24.12° (%)	99.3
Absorption correction	None
Max. and min. transmission	0.9856 and 0.9623
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2654 / 0 / 306
Goodness-of-fit on F^2	1.088
Final R indices [I>2σ(I)]	R1 = 0.0670, wR2 = 0.1831
R indices (all data)	R1 = 0.0733, wR2 = 0.1894
Largest diff. Peak and hole (eÅ^{-3})	0.535 and 0.258

phy was performed on Merck 60 silica gel (70-230 mesh or 230-400 mesh). NMR spectra were recorded on a Bruker AM 300 spectrometer. Chemical shifts are reported in ppm, and tetramethylsilane was used as internal standard for ^{1}H NMR. Optical rotations were determined with Jasco DIP-360 polarimeter. Infrared spectra (cm^{-1}) were obtained on a BOMEM model FT-IR M100-C15 spectrometer with liquid film or KBr pellet sample. Mass spectra (EI or FAB) were determined on a KRATOS MS 25 RFA or a micromass PLATFORM II.

D-3,4,5-Tri-*O*-benzyl-*myo*-inositol (2). A solution of **1**[4] (161.6 mg, 0.32 mmol) and sodium methoxide (10 mg) in anhydrous methanol (3 mL) was stirred at rt for 1.5 h. The mixture was poured into sat'd aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and concentrated to give a white solid **2** (140.5 mg, 95%), mp 146-147 °C; $[\alpha]_D^{32}$ -2.7 (c 1.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.51-2.58 (m, 3H, OH), 3.30 (app. t, 1H, J = 9.4 Hz, H-5), 3.38-3.42 (m, 1H, H-1), 3.48 (dd, 1H, J = 2.8, 9.4Hz, H-3), 3.67 (app. t, 1H, J = 9.4 Hz, H-6), 3.93 (app. t, 1H, J = 9.4 Hz, H-4), 4.19 (app. t, 1H, J = 2.6 Hz, H-2), 4.71-4.96 (m, 6H, 3C<u>H</u>$_2$Ph), 7.29-7.32 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 69.21, 71.84, 72.78, 72.84, 75.36, 75.76, 80.19, 81.22, 82.58 (inositol ring carbons and 3<u>C</u>H$_2$Ph), 127.64, 127.82, 127.89, 127.93, 127.98, 128.53, 137.76, 138.57 (3Ph); MS (FAB) m z 473 (M$^+$+Na).

D-1,2-*O*-Isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol (3). A mixture of **2** (85.4 mg, 0.19 mmol), 2,2-dimethoxypropane (2.5 mL) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in acetone (2.5 mL) was stirred at rt. After 20 h, triethylamine (0.5 mL) was added to quench the reaction and the low boiling solvents were evaporated under reduced pressure. The mixture was partitioned between sat'd aq. $NaHSO_3$ and CH_2Cl_2. The organic layer was dried (Na_2SO_4), and concentrated to give a crude mixture. A preparative thin layer chromatography of the mixture afforded compound **3** (73.3 mg, 79%) and D-1,6-*O*-isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol (9 mg, 9.7%). Compound **3**: $[\alpha]_D^{28}$ -25.6 (c 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.34, 1.54 (2s, 6H, C<u>Me</u>$_2$), 2.45 (br. s, 1H, OH), 3.25 (dd, 1H, J = 8.5, 9.8 Hz, H-5), 3.73 (dd, 1H, J = 3.9, 7.8 Hz, H-3), 3.85-3.93 (m, 2H, H-4 and H-6), 3.96 (dd, 1H, J = 5.5, 7.5 Hz, H-1), 4.28 (dd, 1H, J = 3.9, 5.5 Hz, H-2), 4.60-4.92 (m, 6H, 3C<u>H</u>$_2$Ph), 7.27-7.41 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 26.15, 28.28 (C<u>Me</u>$_2$), 73.34, 75.27, 75.48 (3<u>C</u>H$_2$Ph), 74.51, 74.57, 77.74, 78.62, 81.73, 82.27 (inositol ring carbons), 110.13 (<u>C</u>Me$_2$), 127.76, 127.68, 127.94, 127.98, 128.44, 128.55, 138.16, 138.29, 138.35 (3Ph), carbon signals were assigned on the basis of DEPT 135.

Compound 4. A solution of compound **3** (70 mg, 0.14 mmol) in dry CH_2Cl_2 (2 mL) at -78 °C was treated with DAST (0.07 mL, 0.53 mmol). The reation mixture was kept at rt. After 1 h, the reation was quenched by the addition of sat'd aq. $NaHSO_3$. The reation mixture was diluted with CH_2Cl_2 and washed successively with sat'd aq. $NaHSO_3$ and brine. The organic layer was dried (Na_2SO_4), and concentrated to give a crude product. It was purified by prep. TLC to give a compound **4** (50 mg, 94%) as an oil. $[\alpha]_D^{28}$ -31.5 (c 1.8, CH_2Cl_2); IR (film) ν_{max} 2987, 2925, 1370, 1210, 1079, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30, 1.49 (2s, 6H, C<u>Me</u>$_2$), 3.39 (d, 1H, J = 1.7 Hz, H-4), 3.93 (br. d, 1H, J = 5.2 Hz, H-5), 4.28 (d, 1H, J = 5.7 Hz, H-2), 4.39 (br. s, 1H, H-1), 4.44 (d, 1H, J = 5.8 Hz, H-6), 4.43-4.57 (m, 4H, 2C<u>H</u>$_2$Ph), 4.77 (d, 1H, J = 5.7 Hz, H-3), 7.28-7.38 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 25.38, 26.24 (C<u>Me</u>$_2$), 71.56, 73.13 (2<u>C</u>H$_2$Ph), 78.52 (C-3), 79.29 (C-6), 79.88 (C-2), 82.56 (C-4), 83.98 (C-5), 84.05 (C-1), 112.30 (<u>C</u>Me$_2$), 128.21, 128.35, 128.53, 128.92, 128.97, 137.62, 137.81 (2Ph); the signal assignments are made on the basis of ^{1}H-^{1}H and ^{1}H-^{13}C COSY, DEPT 135, ^{1}H-^{13}C HMQC and NOE measurements; MS (EI) m z 382 (M$^+$), 367 (M$^+$-Me), 291 (M$^+$-CH$_2$Ph), 91 (CH$_2$Ph$^+$). The racemic form of compound **4** was similarly prepared from the racemic **3**.[5]

Compound 6. A racemic sample of compound **4** (600 mg, 1.5 mmol) in 80% aq. AcOH (20 mL) was stirred at 100 °C. After 3 h, the reaction mixture was evaporated and chromatographed to give compound **6** (472 mg, 92%), mp 93-95 °C; ^{1}H NMR ($CDCl_3$) δ 3.25 (br. s, 1H, OH), 3.41-3.42 (m, 2H), 3.86-3.88 (m, 2H), 4.34-4.38 (m, 3H), 4.42-4.55 (m, 4H, 2C<u>H</u>$_2$Ph), 7.25-7.38 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 71.53, 73.01 (2<u>C</u>H$_2$Ph), 69.94, 71.82, 82.59, 83.04, 84.00, 87.29 (C-1~C-6), 126.28, 128.23, 128.34, 128.50, 128.91, 128.95, 137.64, 137.78 (2Ph), carbon signals were assigned on the basis of DEPT 135; MS (EI) m z 342 (M$^+$), 251 (M$^+$-CH$_2$Ph).

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