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Note

Synthesis of DL-1-deoxy-1-fluoro-6-*O*-methyl-*chiro*-inositol: confirmation of a structural-DAST fluorination correlation

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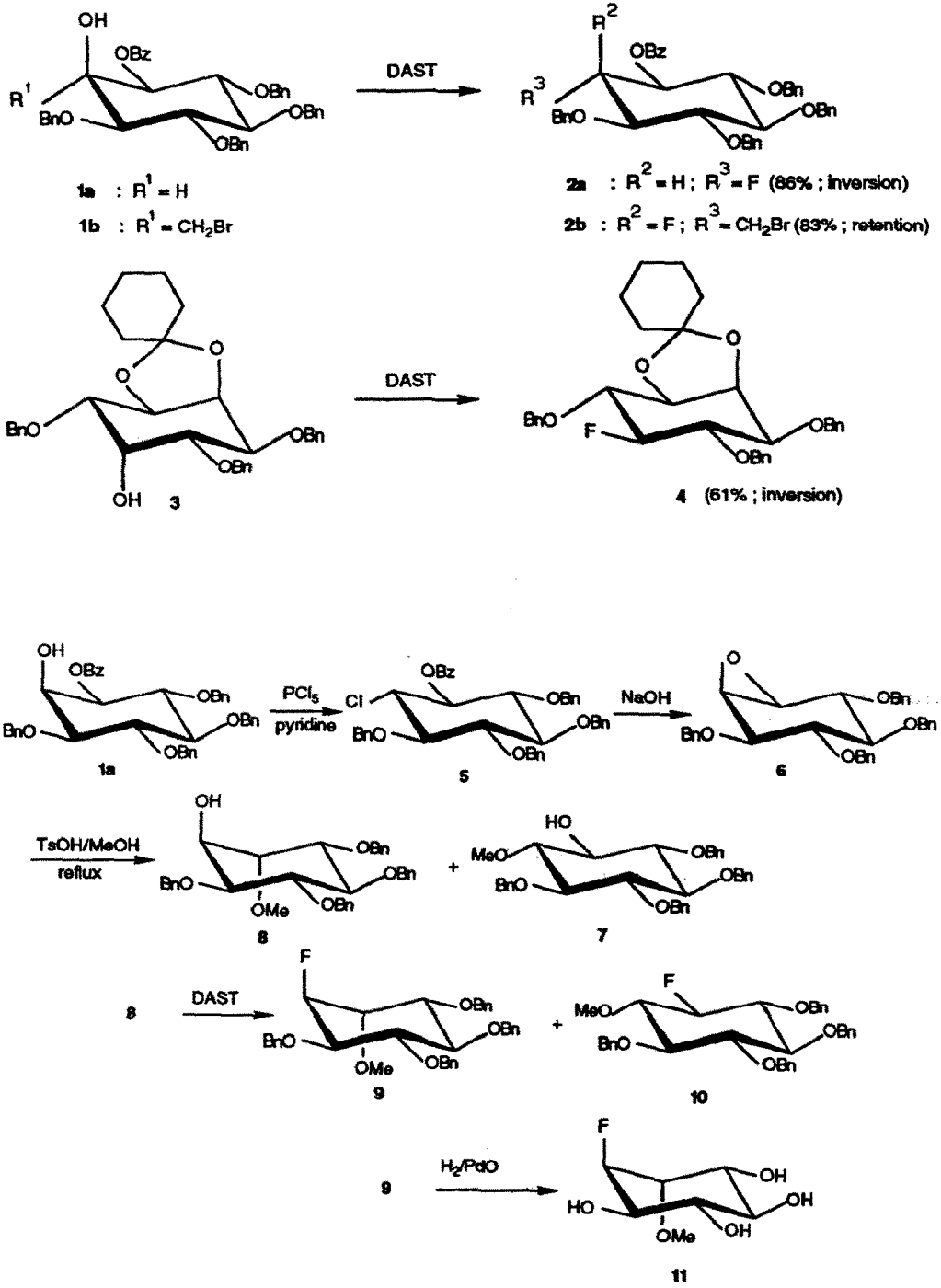
Among many fluorination methods discussed in a recent excellent review on fluorinated carbohydrates by Tsuchiya [1], diethylaminosulfur trifluoride [2] (DAST) appears to be the most convenient and powerful reagent for deoxyfluorination. Although it has been utilized for preparation of fluoro sugars, the correlation of its successful application with sugar structure remains to be explored. Inositols are ideal molecules for establishing this correlation since suitable protection isolates a single axial or a single equatorial hydroxyl function. Our preliminary observations are consistent with axial-OH inositols serving as excellent starting materials for clean and high-yield fluorination by DAST. For example, DAST fluorination of **1a** (ref 3) and **3** (ref 4) gave **2a** and **4** with inversion of configuration in 86 and 61% yields, respectively, while that of **1b** (ref 5) afforded **2b** in 83% yield with retention of configuration, possibly due to anchimeric assistance by vicinal bromine. On the other hand, DAST fluorination of equatorial alcohols seems to result * in additional, nonfluorination side-reactions [6] and gives lower yields of fluoro inositols [6,7]. The structural feature common to **1a**, **1b**, and **3** is the axially situated OH group (secondary or tertiary). To further substantiate this apparent correlation, we decided to synthesize the *chiro*-inositol analogue **8** as a substrate and examine its reaction with DAST. Consequently we report the synthesis of DL-1-deoxy-1-fluoro-6-*O*-methyl-*chiro*-inositol (**11**) from DL-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol [8,9] (**1a**) (Scheme 1; for convenience, D-*myo*-inositol configurations were used to denote DL-*myo*-inositol) and the results of its fluorination with DAST.

The inositol **1a** in pyridine was treated with PCl_5 in the cold to give a 39% yield of DL-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-2-deoxy-2-chloro-*scyllo*-inositol (**5**). Hy-

* DAST fluorination of DL-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-*scyllo*-inositol gave 30% dehydroxybenzylation product, 36% of two transesterification–epimerization products and 30% of three fluoroinositol analogues.


DAST
1a : R1 = H
1b : R1 = CH2Br
2a : R2 = H; R3 = F (86%; inversion)
2b : R2 = F; R3 = CH2Br (83%; retention)
3
4 (61%; inversion)
PCl5
pyridine
NaOH
5
6
TsOH/MeOH
reflux
7
8
9
10
11
H2/PdO

Scheme 1.

drolysis of **5** with 2.5 M NaOH in THF–MeOH afforded DL-1,2-anhydro-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**6**) in 87% yield (Watanabe et al.[10] reported oxidation of the alkene analogue by *m*-chloroperoxybenzoic acid to **7**). Refluxing **6** in MeOH in the presence of *p*-toluenesulfonic acid monohydrate yielded DL-2,3,4,5-tetra-*O*-benzyl-1-*O*-methyl-*chiro*-inositol (**8**) and 81% yield along with DL-3,4,5,6-tetra-*O*-benzyl-1-*O*-methyl-*scyllo*-inositol (**7**, 13%). Heating **8** in toluene with DAST for 10–15 min at 70–75°C gave DL-2,3,4,5-tetra-*O*-benzyl-1-deoxy-1-fluoro-6-*O*-methyl-*chiro*-inositol (**9**, 64%) and DL-3,4,5,6-tetra-*O*-benzyl-1-deoxy-1-fluoro-2-*O*-methyl-*scyllo*-inositol (**10**, 22%). The introduction of fluorine in **9** was confirmed by the mass spectrum and elemental analysis. Although the 400-MHz ^{1}H NMR spectrum of **9** is too complex to assign the ring methine protons, its NMR spectrum is identical with that of an authentic sample * of **9** (ref 11). Hydrogenolysis of **9** with prereduced palladium oxide in 85% aq. ethanol gave DL-1-deoxy-1-fluoro-6-*O*-methyl-*chiro*-inositol (**11**) in quantitative yield.

The structural assignment of **11** was based on analysis of its ^{1}H 400-MHz NMR spectrum and mass-spectral data. That fluorination at C-1 resulted in retention of configuration was readily shown by the coupling constants of vicinal protons at C-2 and C-6. The axial H-2 proton is observed at δ 3.75 ppm (ddm) with a vicinial diaxial F–H coupling constant of 32.2 Hz and diaxial H–H coupling (7.5 Hz). The equatorial H-6 proton centered at 3.86 ppm showed three identical coupling constants of 3.5 Hz for H*e*–H*e*, H*e*–H*a*, and H*e*–F*a* couplings. The C-1 proton (5.03 ppm, ddd) was concluded to be equatorial (and hence F to be axial) in accord with two vicinial H*e*–H*e* and H*e*–H*a* coupling constants of 3.6 and 2.6 Hz as well as geminal F–H coupling (47.5 Hz). With the structure **11** assigned, it is apparent that **9** was obtained from DAST fluorination of **8** with retention of configuration (because of methoxy-group anchimeric assistance) in good yield. The minor product **10** was obtained as a consequence of OMe migration from ring opening of the same intermediate at position 6. This result is in agreement with the correlation that axial OH groups are more suitable than equatorial OH groups from DAST fluorination. Most recently Carless and Busia [12] reported DAST fluorination of (±)-1,4-di-*O*-benzyl-2,3,5-tri-*O*-(2-methoxyethoxymethyl)-*chiro*-inositol to (±)-1,4-di-*O*-benzyl-6-deoxy-6-fluoro-2,3,5-tri-*O*-(2-methoxyethoxymethyl)-*chiro*-inositol in 75% yield with retention of configuration, a result in agreement with our structural-DAST fluorination correlation.

EXPERIMENTAL

General methods.—Melting points were determined with a Thomas–Hoover Uni-Melt apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 or 400 MHz with a Varian XL-200 or a Varian XL-400 NMR spectrometer with

* An authentic sample of **9** was prepared by methylation of DL-1-deoxy-1-fluoro-2,3,4,5-tetra-*O*-benzyl-*chiro*-inositol in 20% yield.

Me_4Si as an internal standard. Only ring protons and selected others are reported. Mass spectra were determined on an LKB-9000 spectrometer.

DL-*1-O-Benzoyl-3,4,5,6-tetra*-O-*benzyl-2-deoxy-2-chloro*-scyllo-*inositol* (**5**).—To a stirred solution of **1a** (4.83 g, 7.49 mmol) in pyridine (60 mL) at 0–5°C was added PCl_5 (3.0 g, 14.4 mmol) in 3 portions during 15 min. After stirring for 1 h at 0–5°C and for 3 h at 22°C, the mixture was poured onto ice–water (100 g) containing $NaHCO_3$ (6 g). The mixture was allowed to stir overnight and then extracted with CH_2Cl_2 (60 mL × 2). The organic layer was washed successively with 5% aq $NaHCO_3$, water, brine, and then dried (Na_2SO_4). Solvent was removed in vacuo to leave a residue which was triturated with ether–hexane to give the crude product. Recrystallization of the product from ethanol–hexane gave **5**; yield 1.92 g (39%); mp 149–151°C; ^1H NMR ($CDCl_3$): δ 3.61 (t, 1 H, H-5), 3.63 (t, 1 H, H-4), 3.68 (t, 1 H, H-6), 3.72 (t, 1 H, H-3), 4.01 (t, 1 H, H-2) and 5.48 (dd, 1 H, H-1); mass spectrum *m/z* 662. Anal. Calcd for $C_{41}H_{39}ClO_6$: C, 74.25; H, 5.93; Cl, 5.35. Found: C, 74.09; H, 5.90; Cl, 5.33.

DL-*1,2-Anhydro-3,4,5,6-tetra*-O-*benzyl*-myo-*inositol* (**6**).—To a stirred solution of **5** (11.6 g, 17.49 mmol) in THF (400 mL) and MeOH (200 mL) was added 2.5 ± M NaOH (60 mL) dropwise during 15 min. After keeping for 3 h at 35–50°C, the solid was filtered off and the filtrate was concentrated in vacuo at 35–50°C to ~ 70 mL. The mixture was then stirred in an ice-bath for 0.5 h. The solid product was collected and recrystallized from CH_2Cl_2–hexane to give **6**; yield 7.95 g (87%); mp 115–116.5°C; ^1H NMR ($CDCl_3$): δ 3.19 (d, 1 H, H-1), 3.32 (dd, 1 H, H-2), 3.47 (dd, 1 H, H-5), 3.62 (dd, 1 H, H-4), 3.98 and 4.01 (two dd, 2 H, H-3 and H-6); mass spectrum *m/z* 522. The analytical sample was recrystallized from EtOH–hexane: mp 116–117°C. Anal. Calcd for $C_{34}H_{34}O_5$: C, 78, 13; H, 6.56. Found: C, 77.93; H, 6.51.

DL-*2,3,4,5-Tetra*-O-*benzyl-1*-O-*methyl*-chiro-*inositol* (**8**).—To a stirred refluxing solution of $TsOH \cdot H_2O$ (100 mg) in MeOH (50 mL) was added **6** (1.0 g, 1.91 mmol) in portions during 10 min. After the dissolution of the solid, excess MeOH (40 mL) was distilled off. The concentrated reaction solution was refluxed for another 2–3 h until complete disappearance of the starting material. Separation of the mixture by preparative TLC on 4 silica gel plates (20 × 20 cm, 2000 μm) developed with 1.6% MeOH in CH_2Cl_2 afforded **8** as an oil (R_f 0.34; 25% EtOAc in hexane): yield 830 mg (81%); ^1H NMR ($CDCl_3$): δ 3.42 (s, 3 H, OMe), 3.67 (d, 1 H, H-1), 3.75 (t, 2 H, H-3 and H-5), 3.86 (t, 2 H, H-4 and H-6), 4.06 (dd, 1 H, H-6); mass spectrum *m/z* 554. Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.90. Found: C, 75.65; H, 6.75.

Also isolated from the preparative plates was DL-3,4,5,6-tetra-*O*-benzyl-1-*O*-methyl-*scyllo*-inositol (**7**): yield 140 mg (13%) (R_f 0.26; 25% EtOAc in hexane); mp 101–103°C; ^1H NMR ($CDCl_3$): δ 3.14 (t, 1 H, H-1), 3.3–3.7 (m, 5 H, all other ring protons), 3.67 (s, 3 H, OMe).

DL-2,3,4,5-*Tetra*-O-*benzyl-1-deoxy-1-fluoro-6*-O-*methyl*-chiro-*inositol* (**9**).—To a stirred solution of **8** (280 mg, 0.50 mmol) in toluene (20 mL) at 70–75°C was added

DAST (200 μL, or 266 mg, 2.0 mmol) dropwise during 5 min and the mixture was stirred for a further 10 min. The mixture was cooled to room temperature and poured onto ice–water (20 g) containing $NaHCO_3$ (1.2 g). The toluene layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified on 3 silica gel plates (1500 μm) developed with 17% EtOAc in hexanes to give **9** (R_f 0.56, 25% EtOAc in hexane) which solidified on prolonged standing at 22°C; yield 180 mg (64%); mp 55–58°C; ^1H NMR ($CDCl_3$): δ 3.38 (s, 3 H, OMe); mass spectrum *m/z* 556. Anal. Calcd for $C_{35}H_{37}FO_5 \cdot 0.5H_2O$: C, 74.34; H, 6.77; F, 3.36. Found: C, 74.68; H, 6.64; F, 3.40.

A minor product, DL-3,4,5,6-tetra-*O*-benzyl-1-deoxy-1-fluoro-2-*O*-methyl-*scyllo*-inositol (**10**), was isolated as an oil: yield 65 mg (22%) (R_f 0.69; 25% EtOAc in hexane); ^1H NMR ($CDCl_3$): δ 3.66 (s, 3 H, OMe), 3.3–3.7 (m, 5 H, all ring protons except H-1), 4.47 (dt, 1 H, $J_{H,F}$ 51 Hz, $J_{H,H}$ 8.5 Hz, H-1).

DL-*1-Deoxy-1-fluoro-6-O-methyl*-chiro-*inositol* (**11**).—A stirred solution of **9** (127.4 mg, 0.229 mmol) in 85% aq EtOH (23 mL) was reduced catalytically with prereduced palladium oxide (125 mg) and H_2 at atmospheric pressure and 22°C for 19 h. The mixture was filtered and the catalyst was washed with 85% aq EtOH. The combined filtrate and washings were evaporated under diminished pressure. The residue was treated with abs EtOH and evaporated 3 times to afford **11** as an oil (46.2 mg, 100% yield) which crystallized slowly on prolonged standing at 22°C; ^1H NMR (D_2O): δ 3.49 (s, 3 H, OMe), 3.53 (m, 2 H, H-3 and H-4), 3.71–3.76 (m, 1 H, H-5), 3.75 (ddm, 1 H, H-2), 3.86 (q, 1 H, H-6), 5.03 (ddd, 1 H, H-1); Mass (FAB) *m/z* 219 $(M + Na)^+$, 415 $(2\ M + Na)^+$. High-resolution mass spectrum: calcd for $C_7H_{13}FO_5 \cdot H_2O$: 178.0641. Found: 178.0659.

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REFERENCES

1 T. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 48 (1990) 91–277.
2 W.J. Middleton, *J. Org. Chem.*, 40 (1975) 574–578.
3 S.S. Yang, T.R. Beattie, and T.Y. Shen, *Tetrahedron Lett.*, 23 (1982) 5517–5520.
4 C. Jiang, D.J.A. Schedler, P.E. Morris, Jr., A.-H.A. Zayed, and D.C. Baker, *Carbohydr. Res.*, 207 (1990) 277–285.
5 S.S. Yang, T.R. Beattie, and T.Y. Shen, *Synth. Commun.*, 16 (1986) 131–138.
6 S.S. Yang, unpublished results.
7 C. Jiang, J.D. Moyer, and D.C. Baker, *J. Carbohydr. Chem.*, 6 (1987) 319–355.
8 D.E. Kiely, G.D. Abruscato, and V. Baburao, *Carbohydr. Res.*, 34 (1974) 307–313.
9 V.P. Schevchnko, T.Yu. Lazurkina, Yu.G. Molotkovsky, and L.D. Bergelson, *Bioorg. Khim.*, 3 (1977) 252–255.
10 Y. Watanabe, M. Mitani, and S. Ozai, *Chem. Lett.* (Japan), (1987) 123–126.
11 S.S. Yang, unpublished results.
12 H.A.J. Carless and K. Busia, *Carbohydr. Res.*, 234 (1992) 207–215.