Supplementary Information

Deuterium-Isotope Study on the Reductive Ring Opening of Benzylidene Acetals

I-Chi Lee, Medel Manuel L. Zulueta, Chi-Rung Shie, Susan D. Arco, and Shang-Cheng Hung*

Genomics Research Center, Academia Sinica, 128, Section 2, Academia Road, Taipei 115, Taiwan, Institute of Chemistry, University of the Philippines, Diliman, Quezon City 1101, Philippines, and Department of Applied Chemistry, National Chiao Tung University, 1001, Ta-Hsueh Road, Hsinchu 300, Taiwan

Table of Contents

A. General Procedures ........................................................................................................ 2
B. Synthesis of the Reference Compounds ......................................................................... 2
C. Representative Procedures for Benzylidene Ring Opening ........................................... 6
D. NMR spectra (¹H and ¹³C) ............................................................................................. 8
A. General Procedures

CH₂Cl₂ was purified and dried from a safe purification system filled with anhydrous Al₂O₃. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25 mm, E. Merck); detection was executed by spraying with a solution of Ce(NH₄)₂(NO₃)₆, (NH₄)₆Mo₇O₂₄, and H₂SO₄ in water and subsequent heating on a hot plate. The specific rotations are reported in 10⁻¹ deg cm² g⁻¹. ¹H and ¹³C NMR spectra were recorded using 400 MHz and 600 MHz spectrometers. Chemical shifts are in ppm from Me₄Si calibrated using the resonance of the residual proton and carbon of CDCl₃ (solvent). Proton peak assignments were performed using 2D NMR techniques (¹H-¹H COSY, HMQC and NOESY) and/or guided by the assignment of known undeuterated derivatives; the hydrogen multiplicity of carbon peaks were determined using DEPT experiments.

B. Synthesis of the Reference Compounds

Methyl 4-O-(R)-benzyl-α-d₁-2,3-di-O-benzyl-6-O-tert-butyldiphenylsilyl-α-D-glucopyranoside (10). A mixture of methyl 2,3-di-O-benzyl-6-O-tert-butyldiphenylsilyl-α-D-glucopyranoside 7 (120 mg, 0.196 mmol) and (S)-benzyl-α-d₁-4-methylbenzenesulfonate (6, 32.1 mg, 0.122 mmol) was stirred in N,N-dimethylformamide (DMF, 1 mL) and CH₂Cl₂ (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 10 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to obtain the product 10 (79 mg, 64%). [α]D²⁷ +10.0 (c 0.3 in CHCl₃); IR (CHCl₃) ν 3031, 2930, 1454, 1159, 1105, 822, 738, 700 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.67–7.64 (4 H, m, Ar-H), 7.40–7.26 (16 H, m, Ar-H), 7.23–7.22 (3 H, m, Ar-H), 7.12–7.10 (2 H, m, Ar-H), 4.95, 4.81, (2 H, ABq, J = 10.7 Hz, PhCH₂), 4.80, 4.69.
(2 H, ABq, J = 12.0 Hz, PhCH₂), 4.64 (1 H, d, J = 3.5 Hz, 1-H), 4.55 (1 H, s, PhCHĐ), 3.98 (1 H, t, J = 9.5 Hz, 3-H), 3.86–3.81 (2 H, m, 6-Ha, 6-Hb), 3.69–3.66 (1 H, m, 5-H), 3.58 (1 H, t, J = 9.5 Hz, 4-H), 3.53 (1 H, dd, J = 9.5, 3.5 Hz, 2-H), 3.35 (3 H, s, OCH₃), 1.01 (9 H, s, t-Bu); ¹³C NMR (150 MHz, CDCl₃) δ 138.7 (C), 138.3 (C), 138.2 (C), 135.8 (CH), 135.6 (CH), 133.6 (C), 133.3 (C), 129.6 (CH), 129.5 (C), 128.4 (CH), 128.35 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 97.8 (CH), 82.3 (CH), 80.2 (CH), 77.8 (CH), 75.9 (CH₂), 74.9/74.7/74.6 (CHD), 73.3 (CH₂), 71.4 (CH), 62.9 (CH₂), 54.8 (CH₃), 26.8, (CH₃) 19.3 (C); HRMS [ESI, MNa⁺] calcd for C₄₄H₄₉DO₆SiNa 726.3337, found 726.3329.

Methyl 6-O-(R)-benzyl-α-d₁,2,3-di-O-benzyl-4-O-(2-naphthylmethyl)-α-d-glucopyranoside (11). A mixture of methyl 2,3-di-O-benzyl-4-O-(2-naphthylmethyl)-α-d-glucopyranoside (8, 307 mg, 0.60 mmol) and tosylate 6 (188 mg, 0.72 mmol) was stirred in DMF (1 mL) and CH₂Cl₂ (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 48 mg, 1.19 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 2 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to afford the product 11 (275 mg, 78%). [α]D²⁶ +11.2 (c 1.1 in CHCl₃); IR (CHCl₃) ν 3030, 2923, 1453, 1274, 1160, 1049, 737, 698 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.80–7.71 (22 H, m, Ar-H), 4.99, 4.83 (2 H, ABq, J = 10.8 Hz, ArCH₂), 4.95, 4.61 (2 H, ABq, J = 10.8 Hz, ArCH₂), 4.79, 4.66 (2 H, ABq, J = 12.0 Hz, ArCH₂), 4.63 (1 H, d, J = 3.6 Hz, 1-H), 4.41 (1 H, s, PhCHĐ), 4.00 (1 H, t, J = 9.3 Hz, 3-H), 3.77–3.71 (2 H, m, 5-H, 6-Ha), 3.68 (1 H, t, J = 9.3 Hz, 4-H), 3.64 (1 H, d, J = 9.0 Hz, 6-Hb), 3.58–3.55 (1 H, m, 2-H), 3.37 (3 H, s, OCH₃); ¹³C NMR (150 MHz, CDCl₃) δ 138.8 (C), 138.1 (C), 137.8 (C), 135.7 (C), 133.2 (C), 132.9 (C), 128.4 (CH), 128.38 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.88 (CH), 127.7 (CH), 127.6 (CH), 127.56 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 98.2 (CH), 82.2 (CH),
79.8 (CH), 77.6 (CH), 75.7 (CH₂), 75.0 (CH₂), 73.4 (CH₂), 73.3/73.1/73.0 (CHD), 70.1 (CH), 68.4 (CH₂), 55.2 (CH₃); HRMS [ESI, MNa⁺] calcd for C₃₉H₃₉DO₆Na 628.2785, found 628.2779.

\[
\begin{align*}
\text{p-Methylphenyl 3-O-(R)-benzyl-α-d-1,4,6-O-benzylidene-2-O-(4-methoxybenzyl)-1-thio-α-d-mannopyranoside (12)}.
\end{align*}
\]

A mixture of p-methylphenyl 4,6-O-benzylidene-2-O-(4-methoxybenzyl)-1-thio-α-d-mannopyranoside (9, 138 mg, 0.279 mmol) and tosylate 6 (73.2 mg, 0.279 mmol) was stirred in DMF (1 mL) and CH₂Cl₂ (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 22.3 mg, 0.558 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 3 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to get the product 12 (141 mg, 86%). \([\alpha]_D^{27} +85.1 (c 0.5 \text{ in CHCl}_3)\); IR (CHCl₃) ν 3032, 2900, 1612, 1514, 1454, 1249, 1100, 811, 698 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) δ 7.51–7.49 (2 H, m, Ar-H), 7.38–7.23 (12 H, m, Ar-H), 7.09–7.08 (2 H, m, Ar-H), 6.84–6.82 (2 H, m, Ar-H), 5.62 (1 H, s, PhCH), 5.36 (1 H, s, 1-H), 4.63 (2 H, s, CH₂PhOMe), 4.60 (1 H, s, PhCHD), 4.27–4.25 (3 H, m, 5-H, 6-H₆), 4.21–4.19 (1 H, m, 4-H), 4.00 (1 H, s, 2-H), 3.94 (1 H, dd, \( J = 9.6, 3.4 \) Hz, 3-H), 3.86 (1 H, m, 6-H₆), 3.79 (3 H, s, OCH₃), 2.32 (3 H, s, CH₃); \(^{13}\)C NMR (150 MHz, CDCl₃) δ 159.4 (C), 138.3 (C), 137.9 (C), 137.6 (C), 132.3 (CH), 129.9 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.58 (CH), 126.1 (CH), 113.8 (CH), 101.5 (CH), 87.5 (CH), 79.1 (CH), 77.4 (CH), 76.1 (CH), 72.8/72.7/72.5 (CHD), 72.6 (CH₂), 68.5 (CH₂), 65.4 (CH), 55.2 (CH₃), 21.1 (CH₃); HRMS [ESI, MNa⁺] calcd for C₃₅H₃₅DO₆SNa 608.2193, found 608.2199.
Methyl 4-O-(R)-benzyl-α-d1-2,3-di-O-benzyl-α-D-glucopyranoside (13R).

Compound 10 (61 mg, 86.7 μmol) was stirred in tetrahydrofuran (THF, 1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, and a 1 M solution of tetra-n-butylammonium fluoride (TBAF) in THF (2 mL, 2 mmol) was added to the mixture. After stirring for 16 hours, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to acquire the 6-alcohol 13R (38.3 mg, 95%). [α]D27 +26.9 (c 1.2 in CHCl3); IR (CHCl3) ν 3467, 3031, 2926, 1453, 1356, 1091, 740, 698 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.35–7.25 (15 H, m, Ar-H), 4.97 (1 H, d, J = 11.0 Hz, PhCH2), 4.81 (1 H, d, J = 11.1 Hz, PhCH2), 4.78 (1 H, d, J = 12.1 Hz, PhCH2), 4.64 (1 H, d, J = 12.1 Hz, PhCH2), 4.60 (1 H, s, PhCHD), 4.56 (1 H, d, J = 3.6 Hz, 1-H), 3.99 (1 H, t, J = 9.4 Hz, 3-H), 3.75 (1 H, ddd, J = 11.6, 5.4, 2.7 Hz, 6-Ha), 3.70–3.61 (2 H, m, 6-Hb, 5-H), 3.50 (1 H, dd, J = 9.6, 9.4 Hz, 4-H), 3.48 (1 H, dd, J = 9.4, 3.6 Hz, 2-H), 3.35 (3 H, s, OCH3); HRMS [ESI, MNa+] calcd for C28H31DO6Na 488.2159, found 488.2163.

Methyl 6-O-(R)-benzyl-α-d1-2,3-di-O-benzyl-α-D-glucopyranoside (14R).

Compound 11 (256 mg, 0.433 mmol) was stirred in CH2Cl2 (9 mL) and water (0.5 mL) at room temperature. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 294 mg, 1.30 mmol) was added to the mixture three times, one equivalent at a time, in half-hour intervals. After 4 hours, the mixture was filtered, and ethyl acetate and saturated NaHCO3(aq) was added. The organic layer was collected and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to afford the 4-alcohol 14R (191 mg, 95%). [α]D29 +26.3 (c 1.1 in CHCl3); IR (CHCl3) ν 3467, 3031, 2920, 1496, 1452, 1276, 1055, 738, 698 cm−1; 1H NMR (600 MHz, CDCl3) δ 7.35–7.25 (15 H, m, Ar-H), 4.99, 4.72 (2 H, ABq, J = 11.4 Hz, PhCH2), 4.76, 4.65 (2 H, ABq, J = 12.1 Hz, PhCH2), 4.62 (1 H, d, J = 3.2 Hz, 1-H), 4.51 (1 H, td, J = 9.3, 2.0 Hz, 4-H), 3.77 (1 H, t, J = 9.3 Hz, 3-H), 3.70–3.65 (3 H, m, 5-H, 6-Ha, 6-Hb), 3.59 (1 H, dd, J = 9.3, 3.3 Hz, 2-H), 3.37 (3 H, s, OCH3), 2.30 (1 H, d, J = 2.0 Hz, 4-OH); HRMS [ESI, MNa+] calcd for C28H31DO6Na 488.2159, found 488.2162.
**p-Methylphenyl 3-O-(R)-benzyl-α-d1-4,6-O-benzylidene-1-thio-α-d-manno-pyranoside (15R).** Compound 12 (76.2 mg, 0.13 mmol) was stirred in CH2Cl2 (2.74 mL) and water (0.15 mL) at room temperature. DDQ (60 mg, 0.26 mmol) was added to the mixture twice, one equivalent at a time, in half-hour interval. After 4 hours, the mixture was filtered, and ethyl acetate and saturated NaHCO3(aq) was added. The organic layer was collected and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/3, v/v) to get the 2-alcohol 15R (56 mg, 93%). [α]D27 +209.9 (c 1.2 in CHCl3); IR (CHCl3) ν 3459, 3033, 2899, 1493, 1453, 1210, 1099, 1018, 749, 698 cm–1; 1H NMR (600 MHz, CDCl3) δ 7.53–7.49 (2 H, m, Ar-H), 7.40–7.30 (10 H, m, Ar-H), 7.11 (2 H, d, J = 8.0 Hz, Ar-H), 5.61 (1 H, s, PhCH), 5.51 (1 H, s, 1-H), 4.72 (1 H, s, PhCHD), 4.34 (1 H, td, J = 9.6, 4.9 Hz, 5-H), 4.27 (1 H, dd, J = 3.4, 1.0 Hz, 2-H), 4.20 (1 H, dd, J = 10.3, 4.9 Hz, 6-Hα), 4.16 (1 H, t, J = 9.6 Hz, 4-H), 3.95 (1 H, dd, J = 9.6, 3.4 Hz, 3-H), 3.84 (1 H, m, 6-Hβ), 2.84 (1 H, br s, 2-OH), 2.32 (3 H, s, CH3); HRMS [ESI, MNa+] calcd for C27H27DO5SNa 488.1618, found 488.1613.

**C. Representative Procedures for Benzylidene Ring Opening**

**6-O-Ring opening by AlD3.** AlCl3 (14.4 mg, 0.108 mmol) and LiAlD4 (13.7 mg, 0.325 mmol) were mixed in ice-cold Et2O (1 mL). A solution of compound 1 (50 mg, 0.108 mmol) in CH2Cl2 (1 mL) was added 5 minutes later and the reaction was allowed to warm up to room temperature. After 90 minutes of reaction, ethyl acetate (1 mL) was added followed by a few drops of water. The mixture was diluted with ethyl acetate, washed with water, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/2, v/v) to obtain the target 6-alcohol(s) (44 mg, 88%).

**6-O-Ring opening by BD3•THF.** BF3•Et2O (292 μL, 2.3 mmol) was added to a suspension of NaBD4 (72 mg, 1.72 mmol) in THF (0.7 mL) at room temperature. After overnight stirring, compound 1 (106 mg, 0.23 mmol) and copper(II) trifluoromethanesulfonate (Cu(OTf)2, 4.2 mg, 12 μmol) were sequentially added. The reaction was allowed to proceed for 7 hours and, then, quenched with methanol and Et3N.
The resulting mixture was filtered through Celite, concentrated under reduced pressure, and purified by flash column chromatography (ethyl acetate/hexanes = 1/2, v/v) to get the target 6-alcohol(s) (65.5 mg, 62%).

4-O-Ring opening by Et3SiD. Et3SiD (37 μL, 0.234 mmol) was added to a solution of compound 1 (54.1 mg, 0.117 mmol) in CH3CN (0.5 mL) at room temperature under nitrogen atmosphere. The reaction flask was immersed in an ice-bath, Cu(OTf)2 (0.4 mg, 1 μmol) was added to the mixture, and the resulting solution was gradually warmed up to room temperature. After stirring for 30 minutes, the mixture was diluted with ethyl acetate and, after 1 hour of stirring, the resulting mixture was washed by saturated NaHCO3(aq), dried over anhydrous MgSO4, and concentrated in vacuo. Purification of the residue via flash column chromatography (ethyl acetate/hexanes = 1/2) provided the target 4-alcohol(s) (35.4 mg, 65%).

2-O-Ring opening by AlD3. AlCl3 (17.5 mg, 0.131 mmol) and LiAlD4 (15 mg, 0.394 mmol) were mixed in Et2O (4 mL) at 0 °C. After 15 minutes, this mixture was added to an ice-cooled stirring solution of compound 16 (243 mg, 0.525 mmol) in CH2Cl2/Et2O (2/1, 12 mL). The ice-water bath was removed and the reaction was allowed to warm up to room temperature. Ethyl acetate (10 mL) was added 5 hours later and the solution was washed with water, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to obtain the target 2-alcohol(s) (179 mg, 73%).