Stereoselective Transformations on D-Glucose Derived Eight-Membered Ring Carbocycles

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Experimental

Dichloromethane (Baker, p.a.), 1,2-dichlorobenzene (Acros, p.a.), tetrahydrofuran (THF, Baker, HPLC grade), dimethylsulfoxide (DMSO, Baker, p.a.) and ethylacetate (Baker, p.a.) were stored over molecular sieves (4 Å). Methanol (Baker, p.a.) was stored over molecular sieves (3 Å). Ethanol (absolute) was used as received. Toluene was boiled under reflux with P_2O_5 for 3 h, destilled and stored over molecular sieves (4 Å). Sodium borohydride (Acros), cerium(III)chloride heptahydrate (Fluka), palladium 5 wt. % on activated carbon (Aldrich) were used as received. Reactions were run at ambient temperature unless stated otherwise. Drying of organic layers after work-up was effected by addition of $MgSO_4$. TLC-analysis was conducted on DC-Fertigfolien (Schleicher & Schuell, F1500, LS254) or HPTLC aluminium sheets (Merck, silica gel 60, F254) with detection by UV-absorption (254 nm) and charring with 20% H_2SO_4 in ethanol. Column chromatography was performed either on Baker silica gel (0.063-0.200 mm) or Merck silica gel 60 (0.040-0.063 mm). Solvents used for column chromatography were of technical grade and destilled before use. ^{1}H- and ^{13}C-spectra were recorded on a Jeol JNM-FX-200 (200 MHz and 50.1 MHz, respectively) or a Bruker DPX-300 (300 MHz and 75.1 MHz, respectively). NMR shifts are reported in ppm (δ) relative to tetramethylsilane. Mass spectrometry was performed on a PE/SCIEX API 165 equipped with an electrospray interface. Optical rotation values were measured on a Propol Automatic Polarimeter at 589 nm.

(3*R*, 4*R*, 5*S*)-3,4,5-Tri(benzyloxy)-2-methoxy-cyclooct-1-ene-6-one (3)

A solution of crude methyl (4,5,6-tri-*O*-benzyl-1,2,8-trideoxy)-α-D-*xylo*-oct-1,7-dieno-3-ulopyranoside (262 mg, 0.56 mmol) in 1,2-dichlorobenzene (5 mL) was heated to reflux for 2 h, when TLC analysis (20% EtOAc/light petroleum) revealed complete conversion of the starting material. The mixture was allowed to cool to room temperature and was concentrated. Purification of the residue by silica gel chromatography (15% EtOAc/light petroleum) afforded **3** as a white solid (257 mg, 0.54 mmol, 98%); ^{1}H-NMR ($CDCl_3$): δ 7.17-7.36 (m, 15H, CH_{arom}), 4.84 (m, 1H, H-1), 4.27, 4.34, 4.42, 4.59, 4.72 and 4.85 (6d, each 1H, *J* 11.7 Hz, CH_2 Bn), 4.20 (d, 1H, *J* 9.5 Hz, H-5), 4.00 (d, 1H, *J* 3.7 Hz, H-3), 3.82 (dd, 1H, *J* 3.7 and 9.5 Hz, H-4), 3.46 (s, 3H, CH_3), 2.91-2.98 (m, 1H, H-7a), 2.11-

2.35 (m, 3H, H-7b,8a,8b); ^{13}C-NMR ($CDCl_3$): δ 212.7 (C-6), 153.5 (C-2), 137.4, 137.9 and 138.4 (3 C_q, Bn), 126.4-132.3 (CH_{arom}), 99.4 (C-1), 76.6, 77.2 and 85.3 (C-3,4,5), 71.0, 72.1 and 73.9 (3 CH_2 Bn), 54.5 (CH_3), 43.9 (C-7), 21.8 (C-8); MS (ESI): calc. for $C_{30}H_{32}O_5$ 472.2, found m/z 495.5 $[M+Na]^+$.

(*Z*)-(*R*)-7-Benzyloxy-5-*tert*-butyldimethylsilyloxy-8-oxo-oct-6-enoic acid methyl ester (10)

To a solution of lactone **8** (192 mg, 0.33 mmol) in anhydrous methanol (3 mL) and a few droplets of anhydrous dichloromethane was added a catalytic amount of sodium methoxide. After stirring for 2 h, TLC analysis (15% EtOAc/light petroleum) indicated a completed ring-opening. The mixture was neutralised by addition of Dowex H^+-resin, filtered and concentrated. Silica gel chromatography (10% EtOAc/light petroleum) yielded **10** as a colorless syrup (103 mg, 0.25 mmol, 78%); ^{1}H-NMR ($CDCl_3$): δ 9.25 (s, 1H, H-8), 7.26-7.34 (m, 5H, CH_{arom}), 5.87 (d, 1H, *J* 8.0 Hz, H-6), 5.11 (s, 2H, CH_2 Bn), 4.61 (m, 1H, H-5). 3.65 (s, 3H, CH_3), 2.25 (m, 2H, H-2a,2b), 1.26-1.57 (m, 4H, H-3a,3b,4a,4b), 0.85 (s, 9H, CH_3 *t*-Bu), -0.06 and 0.00 (2s, each 3H, Si-CH_3); ^{13}C-NMR ($CDCl_3$): δ 188.9 (C-8), 173.5 (C-1), 151.0 (C-7), 142.4 (C-6), 136.2 (C_q Bn), 128.0-128.2 (CH_{arom}), 72.3 (CH_2 Bn), 66.8 (C-5), 51.2 (*C*H_3), 36.2 (C-4), 33.5 (C-2), 25.5 (CH_3 *t*-Bu), 20.3 (C-3), 17.8 (C_q *t*-Bu), -5.3 and -4.8 (Si-CH_3); MS (ESI): calc. for $C_{22}H_{34}O_5Si$ 406.2, found m/z 429.4 $[M+Na]^+$.

(3*R*, 4*S*, 5*R*, 6*R*, 7*S*)-4,5,6-Tri(benzyloxy)-7-*tert*-butyldimethylsilyloxy-3-hydroxy-cyclooct-1-ene (12)

To a chilled solution of α,β-unsaturated ketone **11** (240 mg, 0.42 mmol) in anhydrous methanol (8 mL) under argon atmosphere was added cerium(III)chloride heptahydrate (315 mg, 0.85 mmol) and the mixture was stirred for 30 minutes. Successively added was sodium borohydride (104 mg, 2.75 mmol) in three portions. After stirring for 4 h at 0 ºC HPTLC analysis (5% EtOAc/toluene) revealed a completed reduction. Therefore, the mixture was partitioned between Et_2O and 1 N HCl. The organic layer was extracted with Brine, dried, filtered and concentrated. Purification by silica gel chromatography gave allylic alcohol **12** as a colorless syrup (135 mg, 0.24 mmol, 56%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.20-7.41 (m, 15H, CH_{arom}), 5.77-5.86 (m, 1H, H-1), 5.69 (dd, 1H, *J* 5.5 and 11.0 Hz, H-2), 4.56, 4.61, 4.64, 4.96, 5.02 and 5.12 (6d, each 1H, *J* 10.9 and 11.3 Hz, CH_2 Bn), 4.36 (m, 1H, H-3), 3.81 (m, 1H, H-7), 3.58 (dd, 1H, *J* 6.6 and 8.6 Hz, H-5), 3.53 (dd, 1H, *J* 6.6 and 8.1 Hz, H-6), 3.35 (t, 1H, *J* 8.8 Hz, H-4), 3.18 (bs, 1H, OH), 2.24-2.38 (m, 2H, H-8a,8b), 0.94 (s, 9H, CH_3 *t*-Bu), 0.05 and 0.15 (2s, each 3H, Si-CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.0 and 138.4 (C_q Bn), 131.2 (C-1), 127.0-128.5 (C-2 and CH_{arom}), 80.7, 82.3 and 85.6 (C-4,5,6), 75.0, 75.3 and 76.3 (CH_2 Bn), 70.5 and 73.1 (C-3,7), 32.5 (C-8), 25.7 (CH_3 *t*-Bu), 17.9 (C_q *t*-Bu), -4.7 (Si-CH_3); MS (ESI): calc. for $C_{35}H_{46}O_5Si$ 574.3, found m/z 597.5 $[M+Na]^+$.

(3*S*, 4*R*, 5*R*, 6*S*, 8*R*)-3,4,5-Tri(benzyloxy)-6-*tert*-butyldimethylsilyloxy-8-trichloroacetamido-cyclooct-1-ene (14)

To a solution of trichloroacetimidate **13** (10 mg, 14 μmol) in 1,2-dichlorobenzene (1 mL) was added K_2CO_3 (1 mg). The mixture was heated to reflux for 2 h when TLC analysis

(15% EtOAc/light petroleum) showed a complete Overman rearrangement. The mixture was allowed to cool to room temperature and was purified by silica gel chromatography (10% EtOAc/light petroleum) to give **14** as a colorless film (8 mg, 11 μmol, 80%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.23-7.38 (m, 15H, CH_{arom}), 6.00 (ddd, 1H, *J* 1.1, 6.9 and 11.8 Hz, H-1), 5.69 (dd, 1H, *J* 7.7 and 11.8 Hz, H-2), 4.94 (t, 1H, *J* 7.8 Hz, H-3), 4.34, 4.53, 4.55, 4.64, 4.66 and 4.76 (6d, each 1H, *J* 11.1, 11.8 and 11.9 Hz, CH_2 Bn), 4.67 (m, 1H, H-8), 4.31 (m, 1H, H-6), 3.76 (dd, 1H, *J* 3.5 and 8.1 Hz, H-5), 3.74 (dd, 1H, *J* 3.5 and 9.8 Hz, H-4), 2.44 (m, 1H, H-7a), 2.11 (m, 1H, H-7b), 0.87 (s, 9H, CH_3 *t*-Bu), -0.04 and 0.00 (2s, each 3H, Si-CH_3); ^{13}C-NMR ($CDCl_3$): δ 160.9 (C=O), 138.2 and 138.5 (C_q Bn), 132.3 (C-1), 131.3 (C-2), 127.2-128.6 (CH_{arom}), 88.7 (CCl_3), 83.7 (C-5), 81.1 (C-4), 78.1 (C-3), 73.0 (C-6) 71.3, 72.6 and 74.5 (CH_2 Bn), 49.4 (C-8), 29.6 (C-7), 26.1 (CH_3 *t*-Bu), 17.0 (C_q *t*-Bu), -4.7 (Si-CH_3); MS (ESI): calc. for $C_{37}H_{46}Cl_3NO_5Si$ 717.2, found m/z 740.2 $[M+Na]^+$.

(3a*R*, 6*S*, 7*R*, 8*S*, 9a*R*)-7,8,9-Tri(benzyloxy)-6-*tert*-butyldimethylsilyloxy-octahydro-cyclooctaoxazol-2-one (16)

A mixture of **15** (48 mg, 66 μmol) and IBX (74 mg, 0.27 mmol) in anhydrous THF (2.6 mL) and DMSO (0.26 mL) in a sealed tube was heated to 90 °C for 6 h. Subsequently added was a second batch of IBX (74 mg, 0.27 mmol) and the mixture was stirred for 16 h at the same temperature, when HPTLC analysis (5% EtOAc/toluene) showed complete disappearance of the starting material. The mixture was allowed to cool to room temperature, diluted with EtOAc and washed with sat. $NaHCO_3$. The organic layer was extracted with Brine, dried, filtered and concentrated. The product was purified by silica gel chromatography (5% EtOAc/toluene) to give **16** as a colorless syrup (20 mg, 28 μmol, 42%); ^{1}H-NMR (300 MHz, C_6D_6): δ 7.03-7.49 (m, 15H, CH_{arom}), 6.81-6.84 (m, 2H, CH_{arom} MP), 6.67-6.70 (m, 2H, CH_{arom} MP), 5.12 (dd, 1H, *J* 6.9 and 9.0 Hz, H-10), 4.69 (t, 1H, *J* 9.0 Hz, H-9), 4.23, 4.69, 4.70 and 4.83 (4d, 6H, CH_2 Bn), 4.20-4.36 (m, 2H, H-7,8), 3.66-3.72 (m, 2H, H-3,6), 3.23 (s, 3H, CH_3), 1.85 (m, 1H, H-4b), 1.30-1.48 (m, 3H, H-4a,5a,5b), 0.82 (m, 9H, CH_3 *t*-Bu), -0.12 and -0.19 (2s, each 3H, Si-CH_3); ^{13}C-NMR ($CDCl_3$): δ 205.7 (C-1), 137.9 and 138.4 (C_q Bn), 127.3-129.1 (CH_{arom}), 114.4, 114.6, 124.7 and 124.9 (CH_{arom} MP), 74.0, 74.5 and 75.7 (CH_2 Bn), 71.6, 78.4, 82.3, 84.4 and 86.5 (C-6,7,8,910), 60.9 (C-3), 55.5 (CH_3), 29.7 (C-4,5), 25.8 (CH_3 *t*-Bu); MS (ESI): calc. for $C_{43}H_{53}NO_7Si$ 723.4, found m/z 746.5 $[M+Na]^+$.

(1*S*, 2*R*, 3*S*, 4*R*, 5*S*)-1,2,3,4-tetrahydroxy-9-aza-bicyclo[3.3.1]nonane (19)

To a solution of azasugar **18** (130 mg, 0.28 mmol) in EtOAc (1 mL), ethanol (2 mL) and 1 N HCl (2 mL) was added palladium on activated carbon (100 mg). The mixture was degassed three times and hydrogen gas was introduced for 48 h when TLC analysis (EtOAc/MeOH/H_2O 7/2/1 v/v/v) showed complete deprotection. The mixture was filtered over Hyflo, concentrated and purified by HW-40 gel filtration and lyophilised to obtain **19** as a white powder (50 mg, 0.22 mmol, 78%); ^{1}H-NMR (300 MHz, MeOD): δ 4.04 (bt, 1H, *J* 5.5 Hz, H-5), 3.87 (t, 1H, *J* 9.0 Hz, H-3), 3.74 (dd, 1H, *J* 6.3 and 9.0 Hz, H-4), 3.36 (dd, 1H, *J* 1.3 and 9.0 Hz, H-2), 2.18 (m, 1H, H-7b), 1.88 (m, 1H, H-6a), 1.55-1.73 (m, 3H, H-6b,8a,8b), 1.35 (m, 1H, H-7a); ^{13}C-NMR (75 MHz, MeOD): δ 97.5

(C-1), 79.9 (C-2), 74.8 and 76.4 (C-3,4), 75.2 (C-5), 30.2 (C-8), 22.2 (C-6), 19.9 (C-7); MS (ESI): calc. for $C_8H_{15}NO_4$ 189.1, found m/z 401.4 $[M+M+Na]^+$.