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Note

Synthesis of L-glucose from D-gulono-1,4-lactone

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Abstract

An efficient method for the synthesis of L-glucose from D-gulono-1,4-lactone via 1,2,3,4,5-penta-*O*-benzyl/acetyl/benzoyl-D-gulitol is described in 34–53% overall yield. © 1999 Elsevier Science Ltd. All rights reserved.

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Unnatural carbohydrates have been gaining increasing importance as synthons for the preparation of chiral natural products [1,2] and their analogs [3,4] and as probes in the study of biological processes [5]. One of the most important unnatural monosaccharides is L-glucose (**1**), which has been targeted by many investigators using a variety of chemical and/or enzymatic methods. The initial approaches involved chain elongation of L-arabinose by the cyanohydrin [6] and the nitromethane procedures [7,8]. Other protocols include reduction of L-glucono-6,3-lactone [9], multistep syntheses from D-glucose and L-arabinose [10], an iterative two-carbon extension cycle consisting of asymmetric epoxidation followed by regioselective and stereospecific ring opening [11], asymmetric Diels–Alder reaction [12], and enzymatic syntheses [13].

As part of our program [14] aimed at the development of glycoconjugate vaccines against diseases caused by *Shigella sonnei*, we have reported syntheses of the monosaccharide components of the O-specific polysaccharide of this bacterium, using L-glucose as a key starting material [14a]. The logic of our synthetic plan is that L-glucose is related to D-gulose through inverted oxidation states of their respective C-1 and C-6 carbon atoms. Thus, conversion of C-6 of D-gulose into an aldehydo function and reduction of its C-1 to a hydroxymethyl group should lead to L-glucose. Here we describe how this idea was tested and put into practice.

Commercially available D-gulono-1,4-lactone (**2**) was selected as the starting material. Regioselective protection of O-6 by a trityl group [15] (→**3**) followed by reduction [16] with $NaBH_4$ gave the corresponding gulitol derivative **4**, which was isolated as its acetate **5** in 76% overall yield from **1**. Routine replace-

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ment of the acetyl groups of **5** by benzyls in a two-step sequence [(i) NaOMe–MeOH; (ii) BnBr–NaH] afforded compound **6** from which hydrolytic removal [17] of the trityl group furnished the alcohol **7** in 59% overall yield from **2** (six steps). Next, compound **7** was oxidized by the CrO_3–pyridine complex in the presence of Ac_2O [18] to afford the aldehyde derivative **8**. As the final step in this sequence, catalytic hydrogenolysis of benzyl groups provided **1** in 84% yield. Although the ether-protected intermediates did afford the targeted **1**, the overall yield was moderate (34% from **2**, eight steps). In the hope of higher overall yields, the use of *O*-acyl-protected intermediates were examined next. Thus, **4** was benzoylated (→**9**), then the fully acylated D-*gulo*-derivatives **5** and **9** were detritylated with 7:3 HCO_2H–Et_2O [19] and $BF_3{\cdot}Et_2O$ [20] to give alditols **10** and **11**, respectively. Dess–Martin oxidation [21] of alcohols **10** and **11** proved to be superior to other oxidation methods and afforded the desired aldehydes **12** and **13**, respectively, in clean reactions. On the other hand, attempted oxidation of **11** with either Me_2SO–Ac_2O [22] or pyridine–SO_3 in Me_2SO in the presence of Et_3N [23] was accompanied by rapid elimination [24] of a benzoyl group from the newly formed aldehyde **13**. In the final steps, NaOMe-promoted trans-esterification removed the acyl protecting groups from **12** and **13** to afford **1** in 53 (six steps) and 43% overall yields (eight steps), respectively, from the commercially available precursor **2**.

In conclusion, we have developed a simple protocol for the preparation of the unnatural sugar L-glucose. Our method uses inexpensive reagents and avoids the formation of diastereomeric mixtures that were reported in many previously described approaches. These advantages, combined with high overall yields should make our approach a competitive one to other methods reported previously.

1. Experimental

General.—Organic solutions were concentrated under reduced pressure at 40 °C (bath). Column chromatography was performed on Kieselgel 60 (0.063–0.2 mm, E. Merck). Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (E. Merck) plates. Compounds were visualized by spraying with aq 50% sulfuric acid followed by heating. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at room temperature (rt). ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz nominal frequencies in $CDCl_3$ solutions using Me_4Si as the internal reference, except where indicated otherwise. The mass spectra were recorded in the chemical ionization mode using NH_3 as the ionizing gas.

6-O-*Trityl*-D-*gulono*-1,4-*lactone* (**3**).—A solution of D-gulonic γ-lactone (**2**, 10 g, 56 mmol) and TrCl (18.7 g, 67 mmol) in dry pyridine (80 mL) was stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2, and neutralized with 4 M aq HCl. The mixture was extracted with water. The organic layer was dried ($MgSO_4$) and concentrated. The residue was used directly in the next reaction. Selected ^{13}C NMR: δ 175.98 (C-1), 87.06 (CPh_3), 79.34, 70.74, 70.52, 69.45 (C-2,3,4,5), 63.61 (C-6).

6-O-*Trityl*-D-*gulitol* (**4**).—To a solution of crude **3** in dry MeOH (200 mL) was added $NaBH_4$ (6.4 g, 168 mmol) and NaOMe (0.6 g, 11 mmol) at 0 °C. The mixture was stirred overnight, then the excess of $NaBH_4$ was decomposed with glacial AcOH. The mixture was concentrated. MeOH was added to and evaporated from the residue several times. The residue was used for the next step without further purification. Selected ^{13}C NMR (CD_3OD): δ 87.91 (CPh_3), 74.20, 73.97, 73.00, 70.80 (C-2,3,4,5), 66.20, 64.79 (C-1,6).

1,2,3,4,5-Penta-O-*acetyl*-*6*-O-*trityl*-D-*gulitol* (**5**).—A solution of crude **4** in dry pyridine (150 mL) and Ac_2O (100 mL) was stirred overnight at rt. The reaction mixture was concentrated. Toluene was added to and evaporated from the residue several times. A solution of the residue in CH_2Cl_2 was extracted with water. The organic phase was dried ($MgSO_4$) and concentrated. The residue was used directly in the next reaction. A portion of the crude product was purified by column chromatography (49:1→9:1 CH_2Cl_2–acetone) to give **5**; $[\alpha]_D$ −29.6° (*c* 0.47,

$CHCl_3$); ^1H NMR: δ 7.48–7.18 (m, 15 H, 3 Ph), 5.88 (dd), 5.33 (dd), 5.03 (m) (4 H, H-2,3,4,5), 4.23 (dd, 1 H, H-1_a), 4.06 (dd, 1 H, H-1_b), 3.25 (m, 2 H, H-6_{ab}), 2.10–1.97 (5 s, 15 H, 5 CH_3CO); ^{13}C NMR: δ 170.40, 170.02, 169.73, 169.65, 169.36 (5 C=O), 143.38 (C_{quat}), 128.54–127.12 (3 Ph), 86.75 (CPh_3), 71.30, 68.26 (3C) (C-2,3,4,5), 61.67, 61.42 (C-1,6), 20.77–20.44 (5 CH_3CO); MS *m/z* 652 $[M + NH_4]^+$. Anal. Calcd for $C_{35}H_{38}O_{11}$: C, 66.24; H, 6.03. Found: C, 66.05; H, 6.01.

1,2,3,4,5-Penta-O-*benzyl*-*6*-O-*trityl*-D-*gulitol* (**6**).—To a solution of crude **5** (4 g, approximately 6.3 mmol) in MeOH (100 mL) was added NaOMe (pH ~ 8–9) at rt. The mixture was stirred for 3 h and was then concentrated. To a solution of the residue in DMF (30 mL) were added successively 60% NaH (1.9 g 47.5 mmol) and BnBr (4.5 mL, 37.9 mmol) at 0 °C. The mixture was stirred overnight. The mixture was treated with MeOH and diluted with toluene. The solution was extracted successively with 1 M H_2SO_4 and water, was dried ($MgSO_4$), and concentrated. The residue was used directly in the next reaction. A portion of the residue was purified by column chromatography (49:1 → 19:1 hexane–EtOAc) to give **6**; $[\alpha]_D$ −10.6° (*c* 0.38, $CHCl_3$); ^1H NMR: δ 7.56–7.16 (m, 40 H, 8 Ph), 4.84–4.31 (m, 10 H, 5 $PhCH_2$), 4.15–3.33 (m, 8 H, H-1_{ab},2,3,4,5,6_{ab}); ^{13}C NMR: δ 143.86, 138.60 (C_{quat}), 128.68–126.87 (8 Ph), 8 (CPh_3), 79.60–79.02 (C-2,3,4,5), 74.79, 73.97, 73.17, 72.84, 71.62 (5 $PhCH_2$), 69.65 (C-1), 63.16 (C-6); MS *m/z* 892 $[M + NH_4]^+$. Anal. Calcd for $C_{60}H_{58}O_6$: C, 82.35; H, 6.68. Found: C, 82.55; H, 6.70.

1,2,3,4,5-Penta-O-*benzyl*-D-*gulitol* (**7**).—A solution of crude **6** in 80% aq AcOH (50 mL) was stirred at 60 °C for 2 h. The mixture was cooled and kept at 4 °C overnight. The solids were removed by filtration. The filtrate was diluted with CH_2Cl_2 and the resulting solution was neutralized with K_2CO_3. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. Purification of the residue by column chromatography (4:1 hexane–EtOAc) afforded **7** (2.34 g, 59% for six steps); $[\alpha]_D$ +3.4° (*c* 0.81, $CHCl_3$); ^1H NMR: δ 7.37–7.19 (m, 25 H, 5 Ph), 4.79–4.41 (m, 10 H, 5 $PhCH_2$), 4.00–3.46 (m, 8 H, H-1_{ab},2,3,4,5,6_{ab}), 2.01 (s, 1 H, OH); ^{13}C NMR: δ 138.56–138.21 (C_{quat}), 128.24–127.51 (5 Ph), 79.27 (2C), 78.94, 78.58 (C-2,3,4,5), 74.67, 73.78, 73.27, 72.61, 71.91 (5 $PhCH_2$), 69.57 (C-1), 61.73 (C-6); MS *m/z* 650 $[M + NH_4]^+$. Anal. Calcd for $C_{41}H_{44}O_6$: C, 77.82; H, 7.01. Found: C, 78.01; H, 7.04.

2,3,4,5,6-Penta-O-*benzyl*-aldehydo-L-*glucose* (**8**).—To a stirred mixture of dry CH_2Cl_2 (15 mL) and dry pyridine (1.8 mL, 22.3 mmol) containing powdered 4 Å molecular sieves (0.55 g) was added finely powdered CrO_3 (1.11 g, 11.1 mmol) at 0 °C. The suspension was stirred for 20 min and was then treated, successively, with a solution of **7** (1.76 g, 2.8 mmol) in dry CH_2Cl_2 (10 mL) and Ac_2O (1.05 mL, 11.1 mmol) added dropwise. After 30 min, the mixture was diluted with Et_2O (80 mL), and was filtered through a layer of silica using EtOAc as the eluant. Column chromatographic purification of the residue (4:1 hexane–EtOAc) afforded **8** (1.2 g, 69%); $[\alpha]_D$ −2.9° (*c* 0.42, $CHCl_3$); ^{13}C NMR (90 MHz): δ 200.68 (C-1), 138.43–137.30 (C_{quat}), 129.69–126.65 (5 Ph), 80.77, 79.95, 78.07, 77.14 (C-2,3,4,5), 73.98, 73.59, 73.27, 72.97, 71.68 (5 $PhCH_2$), 68.44 (C-6); MS *m/z* 648 $[M + NH_4]^+$. Anal. Calcd for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71. Found: C, 77.90; H, 6.69.

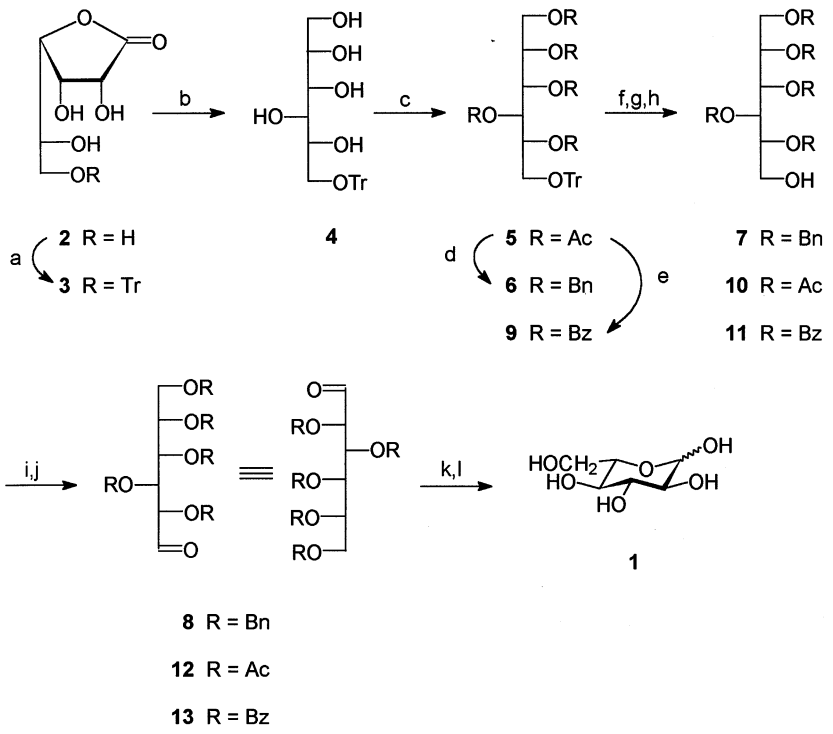
1,2,3,4,5-Penta-O-*benzoyl*-*6*-O-*trityl*-D-*gulitol* (**9**).—To a solution of **5** (4 g, approximately 6.3 mmol) in MeOH (100 mL) was added NaOMe (pH ~ 8–9) at rt. The mixture was stirred for 3 h followed by concentration. To a stirred solution of the residue in dry pyridine (15 mL), BzCl (5.6 mL, 48.2 mmol) was added dropwise at 0 °C. The mixture was stirred overnight then was diluted with CH_2Cl_2. The resulting solution was extracted with water, dried ($MgSO_4$), and concentrated. A portion of the residue was purified by column chromatography (17:3 hexane–EtOAc) to give **9**; $[\alpha]_D$ −27.2° (*c* 0.47, $CHCl_3$); ^{13}C NMR (90 MHz): δ 165.91–164.78 (5 C=O), 143.33 (C_{quat}), 133.56–126.96 (8 Ph), 86.94 (CPh_3), 72.58, 69.33 (3C) (C-2,3,4,5), 62.49, 61.94 (C-1,6); MS *m/z* 962 $[M + NH_4]^+$. Anal. Calcd for $C_{60}H_{48}O_{11}$: C, 76.26; H, 5.12. Found: C, 76.10; H, 5.13.

1,2,3,4,5-Penta-O-*benzoyl*-D-*gulitol* (**11**).—To a solution of crude **9** (1.80 g) in dry

CH_2Cl_2 (80 mL) were added successively $BF_3{\cdot}Et_2O$ (0.25 mL) and dry MeOH (0.8 mL). The mixture was stirred for 2 h and then diluted with CH_2Cl_2. The solution was extracted successively with satd aq $NaHCO_3$ solution and water, was dried ($MgSO_4$), and concentrated. Column chromatographic purification of the residue (7:3 hexane–EtOAc) afforded **11** (0.81 g, 61% for six steps); $[\alpha]_D$ −37.5° (*c* 0.36, $CHCl_3$); ^1H NMR (360 MHz): δ 8.03–7.87 (m, 10 H), 7.50–7.20 (m, 15 H, 5 Ph), 6.23 (m), 5.87 (m), 5.59 (m), 4.84 (dd), 4.56 (dd), 4.09 (dd) (8 H, H-1_{ab},2,3,4,5,6_{ab}), 2.77 (bs, 1 H, OH); ^{13}C NMR (90 MHz): δ 165.91–165.22 (5 C=O), 133.54–128.10 (5 Ph), 73.56, 70.01, 69.64, 69.11 (C-2,3,4,5), 62.48, 60.87 (C-1,6); MS *m*/*z* 720 $[M + NH_4]^+$. Anal. Calcd for $C_{41}H_{34}O_{11}$: C, 70.08; H, 4.88. Found: C, 70.25; H, 4.89.

L-*Glucose* (**1**).—(A) A mixture of **8** (125 mg, 0.2 mmol), 5% Pd–C (200 mg) and EtOH (4 mL) was stirred under H_2 at rt for 12 h, and then filtered through a layer of Celite. Column chromatographic purification of the residue (8:5:1 CH_2Cl_2–MeOH–H_2O) gave **1** (43 mg, 84%); $[\alpha]_D$ −52.2° (*c* 0.44, H_2O, equilibrium), lit. −52.6° [7], −52.0° [8a], −53° [9], −52.9° [10a], −52° [12]; Anal. Calcd for $C_6H_{12}O_6$: C, 40.00; H, 6.71. Found: C, 40.10; H, 6.69.

(B) A solution of **5** (1.27 g, approximately 2.0 mmol) in 7:3 HCOOH–Et_2O (10 mL) was stirred at rt for 20 min and was then diluted with Et_2O. The resulting solution was successively extracted with satd aq $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated (→**10**). The residue was used in the preparation of **12** without further treatment. A solution of **10** (0.90 g, approximately 2.0 mmol) in dry CH_2Cl_2 (12 mL) was added to a stirred solution of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (1.26 g, 3.0 mmol) in dry CH_2Cl_2 (15 mL). After 1 h, the reaction mixture was diluted with Et_2O and poured into satd aq $NaHCO_3$ (60 mL) containing $Na_2S_2O_3$ (12 g). The mixture was stirred until the solids dissolved. The organic layer was extracted with water, dried



Scheme 1. Reagents and conditions: (a) TrCl, pyridine; (b) $NaBH_4$, NaOMe, MeOH; (c) Ac_2O, pyridine, 76% for three steps; (d) 1. NaOMe, MeOH 2. BnBr, NaH; (e) 1. NaOMe, MeOH 2. BzCl, pyridine; (f) **6**, 80% AcOH, 59% for six steps; (g) **5**, 7:3 HCOOH–Et_2O; (h) **9**, MeOH, BF_3Et_2O, CH_2Cl_2, 61% for six steps; (i) **7**, CrO_3, pyridine, Ac_2O, CH_2Cl_2, 69%; (j) **10** or **11**, Dess–Martin periodinane; (k) **8**, 5% Pd–C/H_2, EtOH, 84%; (l) **12** or **13**, NaOMe, MeOH, 70% from **5** or 71% from **11**.

($MgSO_4$), and concentrated to give **12** (0.90 g).

To solutions of **12** (0.9 g) in MeOH (10 mL) was added NaOMe (pH ~ 8–9) at rt. After 3 h, the solution was neutralized with Amberlite IR-120 (H^+) followed by filtration and concentration. Column chromatographic purification of the residue afforded amorphous **1** [191 mg, 53% from **2** (six steps)]. Treatment of a sample by Ac_2O and pyridine afforded 1,2,3,4,6-penta-*O*-acetyl-L-glucopyranose as a 45/55 mixture of the α and β anomers (^1H NMR); $[\alpha]_D$ −44.8° (*c* 0.87, $CHCl_3$), lit. −54.5°, $\alpha/\beta = 4/5$ [10c]; MS *m/z* 408 $[M + NH_4]^+$. Anal. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.35; H, 5.69.

(C) To a stirred solution of Dess–Martin periodinane (0.42 g, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of **11** (0.35 g, 0.50 mmol) in dry CH_2Cl_2 (4 mL) at rt. After 1 h, the reaction mixture was diluted with Et_2O and the resulting solution was poured into satd aq $NaHCO_3$ (20 mL) containing $Na_2S_2O_3$ (4 g). The mixture was processed as described for compound **12** to afford **13** (0.35 g), **13** was then deacetylated as described above (B) and gave amorphous **1** [64 mg, 71% from **11** (two steps)] (Scheme 1).

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