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Note

Synthesis of an intermediate fragment of the capsular polysaccharides of *Klebsiella* type 8

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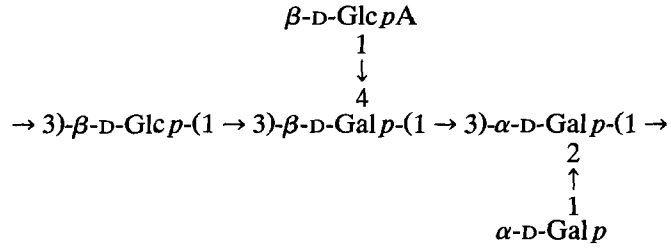
Klebsiella type 8 (K8) is a bacterium[1] of antigenic polysaccharides that possess immunologic activity[2]. The polysaccharides are composed of repeating units having the following structures.



As part of a continuing project on its total chemical synthesis, we have prepared key intermediate fragments and derivatives.

Allyl α-D-galactopyranoside[3] (**1**) was dissolved in acetone in the presence of 4A molecular sieves and *p*-toluenesulfonic acid[4] to give allyl 3,4-*O*-isopropylidene-α-D-galactopyranoside (**2**), which on treatment with benzyl bromide gave allyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**3**). Acid hydrolysis of compound **3** gave allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**4**).

To prepare allyl 2,6-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**5**), we tried several methods[5–7], but the yield of **5** was low. An improved Koenigs–Knorr method, using CaH_2 for the absorption of water, raised the overall yield to 97%. Compound **5** was treated with methyl 2,3,4-tri-*O*-benzyl-1-bromo-1-deoxy-α-D-glucopyranosyluronate (**7**)[8] to give allyl 2,6-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyluronic)-α-D-galactopyranoside (**8**).

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EXPERIMENTAL

General methods.—Melting points were determined with an electrothermal melting-point apparatus and are uncorrected. Optical rotations were measured with a Polaratronic-D automatic polarimeter. Column chromatography was performed on Silica Gel H (Qing Dao Chemical Co.). ^1H and ^{13}C NMR spectra were recorded with a Varian XL300 (300 MHz) spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Mass spectroscopic analyses were performed with a Perkin–Elmer 240c mass spectrometer.

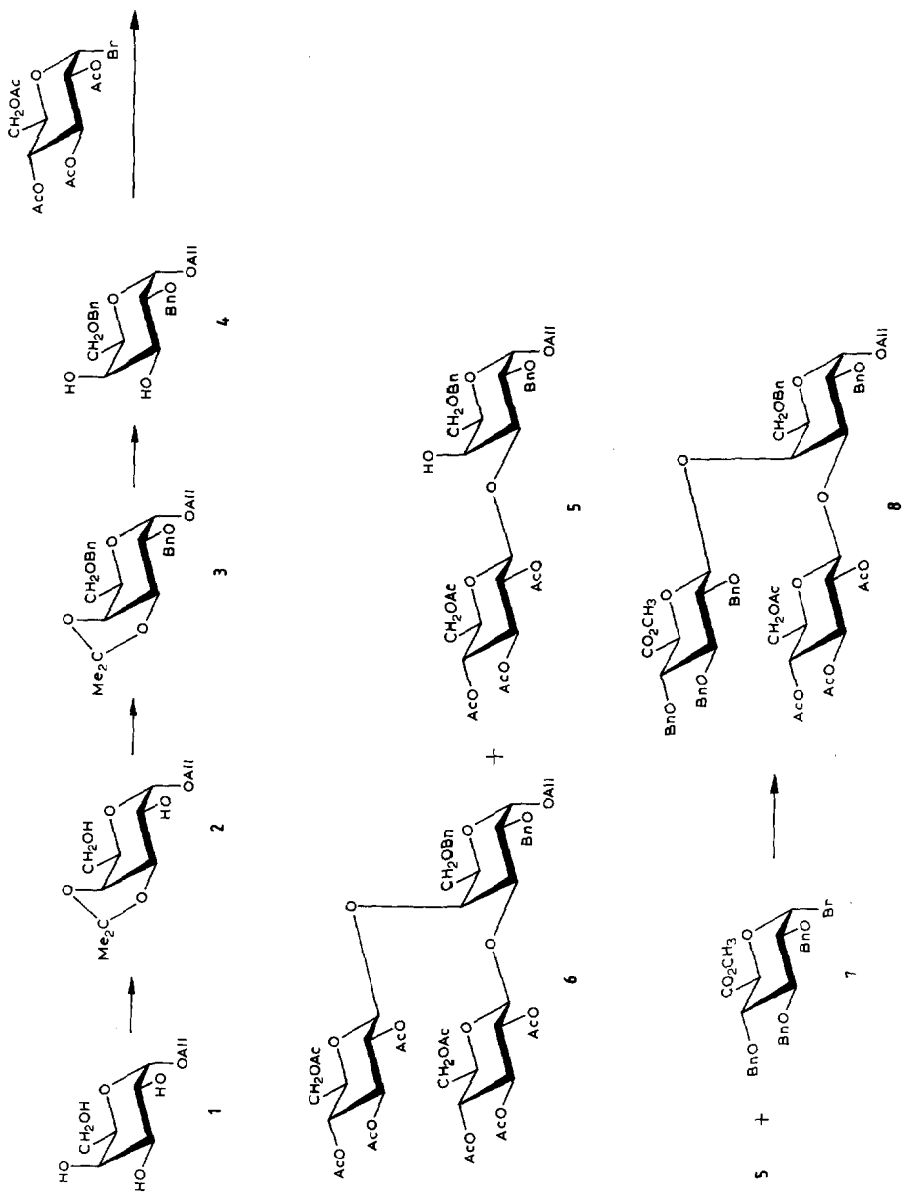
Allyl α-D-galactopyranoside[9] (**1**).—A suspension of D-galactose (40 g, 0.22 mol) and Dowex-50 X-8 (H^+) (30 g, 100–200 mesh) in anhyd allyl alcohol (500 mL) was boiled under reflux for 17.5 h. The resin was filtered off, washed with abs EtOH, the filtrate and washings were combined, and evaporated to a syrup. Crystallization from abs EtOH gave **1** (15 g, 30.7%); mp 146–148°C; $[\alpha]_D^{25}$ +181°C (*c* 1.57, H_2O).

Allyl 3,4-O-isopropylidene-α-D-galactopyranoside (**2**).—Compound **1** (2.5 g, 11.4 mmol) was dissolved in acetone (50 mL) and containing *p*-toluenesulfonic acid (0.2 g) and 4A molecular sieves (5.0 g). The mixture was stirred and boiled under reflux for 1.5 h with exclusion of moisture. When TLC (4:1 cyclohexane-EtOAc) showed the absence of substrate and the presence of product, the mixture was filtered and the filter washed thoroughly with small quantities of acetone (4 × 5 mL). Pyridine (0.2 mL) was added to neutralize the acid and the solvent was evaporated off. Fractionation of the residue on a column of silica gel gave **2** (2.4 g, 81.2%) as a syrup; $[\alpha]_D^{25}$ +131.5° (*c* 1.0, $CHCl_3$); ^1H NMR data: δ 6.18–5.72 (m, 1 H, –CH=), 5.40–5.12 (m, 2 H, $=CH_2$), 4.93 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 4.32–3.80 (m, 8 H, $-OCH_2-$ and sugar-H), 3.59 (2 bs, 2 OH), 1.53 and 1.32 (2s, 6 H, CMe_2).

Allyl 2,6-di-O-benzyl-3,4-O-isopropylidene-α-D-galactopyranoside (**3**).—Compound **2** (2.2 g) was dissolved in DMF (30 mL) and NaH (1.0 g) was added. The mixture was stirred for 30 min, benzyl bromide (5.0 g) was added, and stirring was continued for 3 h to give syrupy **3** (3.6 g, 97%), $[\alpha]_D^{25}$ +112.7° (*c* 0.35, $CHCl_3$); NMR data: δ_H 7.51–7.00 (m, 10 H, Ph-H), 6.18–5.72 (m, 1 H, –CH=), 5.40–5.10 (m, 2 H, $=CH_2$), 4.92 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.52–3.60 (m, 12 H, $-OCH_2-$, $-CH_2Ph$, and sugar-H), 1.50 and 1.32 (2s, 6 H, CMe_2); δ_C 96.3 (C-1). Anal. Calcd for $C_{26}H_{32}O_6$ (440): C, 70.9; H, 7.27. Found: C, 70.7; H, 7.30.

Allyl 2,6-di-O-benzyl-α-D-galactopyranoside (**4**).—Compound **3** (2.5 g) was treated with N HCl (5 mL) in MeOH (30 mL) to give **4** (1.96 g, 86.5%); mp 48–49°C (lit. mp 49–51°C); $[\alpha]_D^{25}$ +104.1° (*c* 1.1, $CHCl_3$).

Allyl 2,6-di-O-benzyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**5**).—Compound **4** (100 mg) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (300 mg) were dissolved in anhyd toluene, and CaH_2 (1.0 g) was added. The mixture was stirred at room temperature for 20 min. Silver carbonate (300 mg) and a small amount of I_2 were added to the mixture, which was stirred for 48 h. The mixture was filtered and the filtrate washed with small quantities of



CH_2Cl_2 (2 × 5 mL), and the solvent was evaporated. Fractionation of the residue by preparative TLC (Silica Gel GF_{254}) using 40:3 CH_2Cl_2–acetone as eluant afforded **5** (95 mg, 52%) as a syrup; $[\alpha]_D^{25}$ +89° (*c* 1.1, $CHCl_3$). NMR data: δ_H 7.50–7.04 (m, 10 H, Ph-H), 6.18–5.72 (m, 1 H, –CH=), 5.40–5.12 (m, 2 H, $=CH_2$), 4.93 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.88 (d, 1 H, $J_{1',2'}$ 7.1 Hz, H-1'), 4.60–3.60 (m, 18 H, $-OCH_2-$, $-CH_2Ph$, and sugar-H), 3.58 (b d, 1 H, OH), 2.15–2.0 (4 × s, $COCH_3$); δ_C 96.8 (C-1), 100.8 (C-1'); *m/z* 730 (M^+). Anal. Calcd for $C_{37}H_{46}O_{11}$ (730): C, 60.8; H, 6.30. Found: C, 60.6; H, 6.27.

*Allyl 2,6-di-*O*-benzyl-3,4-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glycopyranosyl)-α-*D*-galactopyranoside* (**6**).—Compound **4** (100 mg) was dissolved in anhyd toluene (5 mL) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide (500 mg) was added in batches. The procedure used for the synthesis of compound **5** gave **6** (240 mg, 90%) as a syrup; $[\alpha]_D^{25}$ +85.6 (*c* 0.95, $CHCl_3$): NMR data: δ_H 7.55–7.00 (m, 10 H, Ph-H), 6.18–5.70 (m, 1 H, –CH=)), 5.40–5.12 (m, 2 H, $=CH_2$), 4.9–4.7 (m, 3 H, H-1,1',1''), 4.60–3.50 (m, 24 H, $-OCH_2-$, $-CH_2Ph$, and sugar-H), 2.22–2.08 (8 × s, $COCH_3$); δ_C 96.7 (C-1), 101.2 and 101.0 (C-1' and C-1''); *m/z* 1060 (M^+). Anal. Calcd for $C_{51}H_{64}O_{24}$ (1060): C, 57.7; H, 6.04. Found: C, 57.6; H, 6.10.

*Methyl 2,3,4-tri-*O*-benzyl-1-bromo-1-deoxy-*D*-glucopyranuronate* (**7**).—Methyl α-D-glucopyranoside was conveniently transformed into 2,3,4-tri-*O*-benzyl-D-glucopyranuronate[10], which on treatment with PBr_3 gave exclusively compound **7** in 87.5% yield; $[\alpha]_D^{25}$ +96.5° (*c* 1.0, $CHCl_3$).

*Allyl 2,6-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzyl-*D*-glucopyranosyluronic)-α-*D*-galactopyranoside* (**8**).—Compound **5** (100 mg) and compound **7** (200 mg) were dissolved in anhyd toluene (5 mL). The procedure for the synthesis of compound **5** gave **8** (80 mg, 60.4%) as a syrup; $[\alpha]_D^{25}$ +91° (*c* 0.95, $CHCl_3$); NMR data: δ_H 7.40–7.00 (m, 25 H, Ph-H), 6.17–5.70 (m, 1 H, –CH=), 5.40–5.10 (m, 2 H, $=CH_2$), 4.95–4.60 (m, 3 H, H-1,1',1''), 4.58–3.30 (m, 31 H, $-OCH_2-$, $-CH_2Ph$, $-OCH_3$, and sugar-H), 2.20–2.00 (4 × s, $COCH_3$); δ_C 96.8 (C-1), 101.4 and 100.9 (C-1' and C-1''); Mass spectrum: *m/z* 1190 (M^+). Anal. Calcd for $C_{65}H_{74}O_{24}$ (1190): C, 65.6; H, 6.22. Found: C, 65.7; H, 6.17.

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