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Improved synthesis of 1,4-dideoxy-1,4-imino-D-galactitol, an inhibitor of *E. coli K12* UDP-Gal mutase and mycobacterial galactan biosynthesis

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Abstract—The *E. Coli K12* UDP-Gal mutase inhibitor **1** was prepared from D-glucose in 5 steps (42% overall yield). The 4-azido galactose derivative **11**, leading to **1**, was formed by treatment of galactose dithioacetal **7** with mercuric oxide and mercuric chloride in acetone. To obtain **7**, acetal **3** was tosylated or triflated and treated with NaN_3.

1. Introduction

Polyhydroxylated pyrrolidines and piperidines (often referred to as azasugars) are known as specific and competitive inhibitors of glycosidases or glycosyl transferases.[1] These classes of compounds are useful for probing the details of enzyme catalytic mechanisms and have a potential for therapeutic applications, including treatment of diseases such as diabetes, cancer, inflammation, and viral and bacterial infections.[2] 1,4-Dideoxy-1,4-imino-D-galactitol (**1**) is the first known inhibitor of *E. coli K12* UDP-Gal mutase and mycobacterial galactan biosynthesis.[3] Its inhibitory activities are highly specific and may represent a novel therapeutic strategy for the treatment of mycobacterial infections such as leprosy and tuberculosis. In previous syntheses,[3,4] compound **1** was made through complex methods requiring many steps and/or giving low overall yields, which impacted its evaluation for potential use. In this paper, we report a simple synthesis of compound **1** from D-glucose propane-1,3-diyl dithioacetal (**2**) which, we believe, is more than competitive with previous synthetic approaches.[5]

2. Results and discussion

Our synthetic plan relies on the successful Pd-catalyzed reductive amination and concomitant intramolecular cyclization of azide **9**, providing the desired pyrrolidine **1** (Scheme 1). The dithioacetal precursor **2** was easily prepared in 90% yield by treatment of D-glucose with 1,3-propanedithiol in the presence of concentrated hydrochloric acid.[6] Isopropylidenation of **2** with an excess of 2,2-dimethoxypropane and a catalytic amount of toluene-4-sulfonic acid in 1,2-dimethoxyethane under anhydrous conditions[7] gave a mixture of 2,3:5,6-di-*O*-isopropylidene-D-glucose propane-1,3-diyl dithioacetal (**3**) and 3,4:5,6-di-*O*-isopropylidene-D-glucose propane-1,3-diyl dithioacetal (**4**), which were separated by column chromatography to give yields of 66 and 25%, respectively. All attempts to increase the ratio of **3** to **4** by using acetone or 2-methoxypropene instead of 2,2-dimethoxypropane and/or a change of catalyst ($ZnCl_2$) were unsuccessful. However, in some cases, 2,4:5,6-di-*O*-isopropylidene-D-glucose propane-1,3-diyl dithioacetal (**5**) was also isolated.[8]

Esterification of the free hydroxyl group at position 4 of **3** with tosyl chloride in pyridine at room temperature resulted in almost complete formation of the expected fully substituted dithioacetal **6**, which without purification, was subsequently transformed into 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose propane-1,3-diyl dithioacetal (**7**) in 54% overall yield by treatment with sodium azide in DMF at 95°C (Scheme 1). Isolation of the azide **7** indicated that the conversion of tosylated dithioacetal **6** with azido ion proceeded by a single S_N-2 type displacement at C-4. A by-product of the azido replacement was 4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-xylo-hex-3-enose propane-1,3-diyl dithioacetal (**8**), which was formed by elimination of toluene-4-sulfonic acid. Neither replacement of NaN_3 by

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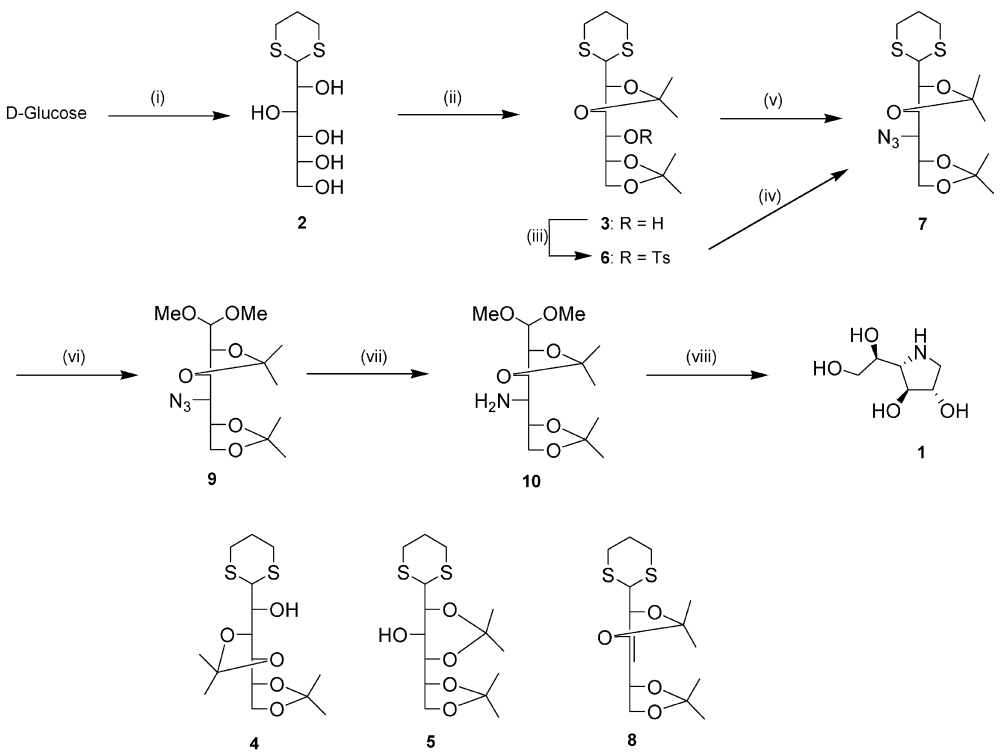
LiN_3 or a change of solvent (DMSO) improved the yields of **7**. However, some changes increased formation of the unsaturated product **8**. A higher yield (70%) of **7** was obtained when small amounts of urea and tetra-*n*-butylamonium bromide were added. When dithioacetal **3** was submitted to mesylation under standard conditions, the reaction gave the desired mesylate derivative quantitatively. However, the substitution reaction of mesylate with sodium azide gave azido derivative **7** in poor yield. The most satisfactory displacement (82%) was achieved, when compound **3** was converted to the corresponding trifluoromethanesulfonate derivative, which was subsequently treated with sodium azide at room temperature

Deprotection of the dithioacetal moiety of **7**, using mercuric chloride and mercuric oxide in boiling methanol, gave 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose dimethylacetal (**9**) in 94% yield.[9] Hydrogenation of the azido group of **9** in the presence of 10% palladium on carbon in ethanol at room temperature afforded an almost quantitative yield of 4-amino-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose dimethylacetal (**10**). A route to pyrrolidine **1** from compound **10** was straightforward and simple to manipulate (Scheme 1). Thus, acid-catalyzed removal of the acetal protecting groups of **10** and subsequent ring closure via attack of the nitrogen upon C-1, followed by hydrogenation of the resulting product in the presence of palladium black gave 1,4-dideoxy-1,4-imino-D-galactitol (**1**) in 90% yield. Pyrrolidine **1** was also prepared by a one-pot synthesis from azido dimethylacetal **9** in 91% overall yield. The identity of compound **1** prepared in this way was confirmed by comparison of its spectroscopic data (^{1}H NMR and ^{13}C NMR) with that in the literature.[4d]

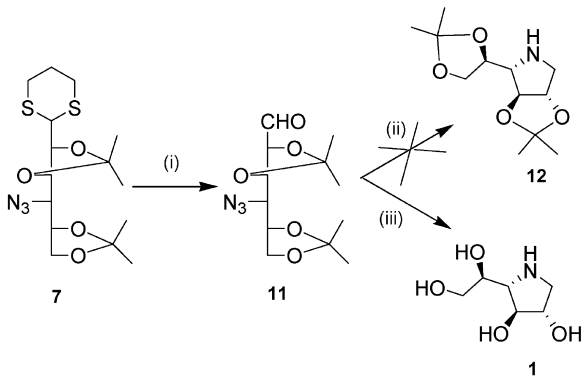
When azido dithioacetal **7** was treated with mercuric chloride and mercuric oxide in aqueous acetone, 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose (**11**) was isolated as a colorless syrup in 90% yield. Both ^{1}H NMR (9.80 ppm, singlet, 1H, CHO) and ^{13}C NMR spectra (200.3 ppm, CHO) of a freshly prepared sample of **11** indicated that the desired aldehyde had been formed in a non-hydrated form; however, the compound proved to be unstable upon storage. Attempts to convert **11** into pyrrolidine **12** by Pd-catalyzed reductive amination[10] in ethanol were unsuccessful; rather a mixture of unidentified products was obtained. No ring closure via intramolecular attack of the amino group on the aldehydo group was observed, probably because the two reactive centers were too widely separated from each other due to steric restriction effected by the 2,3-*O*-isopropylidene group. Presumably, the amino group formed by hydrogenation of the azido group in **11** reacted with the free aldehydo group affording polymeric materials. In order to overcome this steric restriction, azido derivative **11** was treated with 6 M HCl solution to give the corresponding unprotected azido sugar, whose catalytic hydrogenation and concomitant intramolecular reductive amination provided pyrrolidine **1** (identical with that prepared by the previous route) (Scheme 2).

3. Conclusion

In summary, we have described a new simple synthesis of *E. coli K12* UDP-Gal mutase inhibitor **1** from readily available D-glucose propane-1,3-diyl dithioacetal. This five-step approach produces pyrrolidine **1** in 42% overall yield



Scheme 1. (i) $HS(CH_2)_3SH$, HCl; (ii) $Me_2C(OMe)_2$, TsOH, DME; (iii) TsCl, pyridine, rt; (iv) NaN_3, DMF, 95°C; (v) Tf_2O, pyridine, 0°C; then NaN_3, DMF, rt; (vi) $HgCl_2$, HgO, MeOH; (vii) 10% Pd/C, H_2, EtOH; (viii) AcOH, H_2O, 50°C; then 10% Pd/C, H_2.



Scheme 2. (i) $HgCl_2$, HgO, acetone; (ii) Pd/C, H_2, EtOH; (iii) 6 M HCl, 45°C, EtOH; then Pd/C, H_2.

from D-glucose and compares favorably with the previous synthetic routes.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded using a Bruker Spectrometer (300 MHz and 75 MHz, respectively). Chemical shifts are reported in δ values ppm relative to an internal reference of tetramethylsilane (TMS) in $CDCl_3$, except where noted. All reactions were done in oven-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Ascending thin-layer chromatography was performed on plates precoated with silica gel 60 F254 (Merck). Detection was effected by spraying the chromatograms with 10% ethanolic sulfuric acid and charring them on a hot plate. Flash chromatography was carried out using silica gel (Merck 60, 0.04–0.063). All reagents were commercially available and were used without further purification.

4.1.1. D-Glucose propane-1,3-diyl dithioacetal (2). D-Glucose (10 g, 56 mmol) was dissolved at room temperature in concentrated HCl (10 ml). 1,3-Propanedithiol was slowly added, and the solution was stirred vigorously at room temperature overnight. Ethanol (30 ml) was added and the product crystallized from the reaction mixture. Crystals were collected by filtration and washed with cold 85% aqueous ethanol (4×10 ml) to give dithioacetal **2** (14 g, 93%). Compound **2**: ^1H NMR (D_2O, 300 MHz) δ 4.22 (1H, d, $J_{1,2}$=3.5 Hz, H-1); 4.04 (1H, dd, $J_{2,3}$=5.2 Hz, $J_{3,4}$=2.1 Hz, H-3); 3.89 (1H, dd, H-2); 3.75 (1H, dd, $J_{5,6a}$=2.3 Hz, $J_{6a,6b}$=10.8 Hz, H-6a); 3.73–3.64 (2H, H-4, H-5); 3.56 (1H, dd, $J_{5,6b}$=4.9 Hz, H-6b); 2.89–2.81 (4H, m, CH_2–CH_2–CH_2); 2.02 (1H, m, CH_2–CH_2–CH_2); 1.76 (1H, m, CH_2–CH_2–CH_2). ^{13}C NMR δ 73.7, 71.8, 71.3, 69.6 (C-2, C-3, C-4, C-5); 63.0 (C-6); 49.4 (C-1); 29.2, 28.5 (CH_2–CH_2–CH_2); 25.5 (CH_2–CH_2–CH_2).

4.1.2. 2,3:5,6-Di-*O*-isopropylidene-D-glucose propane-1,3-diyl dithioacetal (3) and 3,4:5,6-di-*O*-isopropylidene-D-glucose propane-1,3-diyl dithioacetal (4). A mixture of D-glucose dithioacetal **2** (6 g, 22 mmol), $TsOH.H_2O$ (300 mg) and Drierite (5 g) in DME (100 ml) was stirred at room temperature for 15 min, then 2,2-dimethoxypropane (10 ml) was added. After 24 h stirring at the same temperature, the reaction mixture was neutralized with $NaHCO_3$ (3 g) and filtered. The solids were washed with ethyl acetate (3×10 ml). Concentration of the filtrates afforded a residue, which was subjected to column chromatography with hexanes–ethyl acetate (3:1, v/v) as the eluent to give compounds **3** (5.13 g, 66%) and **4** (1.94 g, 25% yield).

Compound **3**. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.37 (1H, dd, $J_{1,2}$=6.7 Hz, $J_{2,3}$=7.5 Hz, H-2); 4.25 (1H, dd, $J_{3,4}$=1.9 Hz, H-3); 4.05–3.96 (4H, m, H-1, H-4, H-6a, H-6b); 3.68 (1H, m, H-5); 3.00–2.62 (4H, m, CH_2–CH_2–CH_2); 2.08–1.92 (2H, m, CH_2–CH_2–CH_2); 1.43, 1.41, 1.40, 1.32 (4×3H, s, 4×Me). ^{13}C NMR δ 110.1, 109.3 (2×CMe_2); 78.7, 78.0, 76.6, 70.9 (C-2, C-3, C-4, C-5); 66.7 (C-6); 47.6 (C-1); 28.4, 28.2 (CH_2–CH_2–CH_2); 25.5 (CH_2–CH_2–CH_2); 27.1, 26.8, 25.2, 23.6 (4×Me). Anal. calcd for $C_{15}H_{26}O_5S_2$: C, 51.40; H, 7.48; S, 18.30. Found: C, 51.21; H, 7.52; S, 18.42.

Compound **4**. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.41 (1H, dd, $J_{2,3}$=1.6 Hz, $J_{3,4}$=7.2 Hz, H-3); 4.13–4.02 (m, 3H, H-2, H-6a, H-6b); 3.94–3.72 (m, 3H, H-1, H-4, H-5); 2.98–2.75 (m, 4H, CH_2–CH_2–CH_2); 2.06–1.92 (m, 2H, CH_2–CH_2–CH_2); 1.39, 1.37, 1.34, 1.30 (4×3H, s, 4×Me). ^{13}C NMR δ 110.1, 110.0 (2×CMe_2); 79.9, 78.1, 78.0, 70.9 (C-2, C-3, C-4, C-5); 68.1 (C-6); 49.5 (C-1); 27.6, 27.1 (CH_2–CH_2–CH_2); 25.6 (CH_2–CH_2–CH_2); 28.5, 28.0, 27.0, 26.5 (4×Me).

4.1.3. 2,3:5,6-Di-*O*-isopropylidene-4-*O*-(toluene-4-sulfonyl)-D-glucose propane-1,3-diyl dithioacetal (6). Dithioacetal **3** (3.50 g, 10 mmol) was dissolved in pyridine (60 ml) at 0°C and *p*-toluenesulfonyl chloride (3.81 g, 20 mmol) was added. After stirring the mixture overnight at room temperature, the mixture was cooled to 0°C and water (10 ml) was added dropwise. After 15 min, the reaction mixture was poured into aqueous 1 M HCl solution (150 ml), which was extracted with dichloromethane (3×50 ml). The combined organic extracts were washed with 1 M HCl solution (2×50 ml), a saturated solution of $NaHCO_3$ (50 ml) and water (2×100 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated to give the expected fully substituted dithioacetal **6** (5.06 g, 100%), which was used in the next step without purification.

Compound **6**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (2H, d, J=8.5 Hz, H-2′, H-6′); 7.26 (2H, d, H-3′, H-4′); 4.91 (1H, dd, $J_{3,4}$=1.5 Hz, $J_{4,5}$=6.7 Hz, H-4); 4.41 (1H, t, $J_{1,2}$=$J_{2,3}$=7.0 Hz, H-2); 4.30 (1H, dd, H-3); 4.19 (1H, m, H-5); 3.93 (1H, dd, $J_{5,6a}$=5.4 Hz, $J_{6a,6b}$=9.1 Hz, H-6a); 3.92 (1H, dd, $J_{5,6b}$=6.2 Hz, H-6b); 3.82 (1H, d, H-1); 3.09–2.90 (2H, m, CH_2–CH_2–CH_2); 2.67–2.56 (2H, m, CH_2–CH_2–CH_2); 2.36 (3H, s, Me of Ts); 1.98–1.93 (2H, m, CH_2–CH_2–CH_2); 1.32, 1.26, 1.24, 1.20 (4×3H, s, 4×Me). ^{13}C NMR δ 145.0 (C-1′); 133.8 (C-4′); 129.7 (C-2′, C-6′); 127.7 (C-3′, C-5′); 110.6, 109.5 (2×CMe_2); 79.1, 78.6, 77.6, 74.7 (C-2, C-3, C-4, C-5); 66.0 (C-6); 46.7 (C-1); 27.5, 26.6, 26.4, 25.2 (4×Me); 27.3, 27.1 (CH_2–CH_2–CH_2); 25.3 (CH_2–CH_2–CH_2); 21.6 (Me of Ts).

4.1.4. 4-Azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose propane-1,3-diyl dithioacetal (7) and 4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-xylo-hex-3-enose propane-1,3-diyl dithioacetal (8). *From the dithioacetal* **6**.

To a solution of dithioacetal **6** (5.05 g, 10 mmol) in DMF (30 ml) was added sodium azide (2.6 g, 40 mmol), urea (100 mg), tetra-*n*-butylamonium bromide (200 mg) and water (2 ml). The resulting mixture was stirred at 90°C for 3 days. After cooling to room temperature, the reaction mixture was poured into 1 M HCl solution (150 ml), which was extracted with chloroform (3×50 ml). The combined organic extracts were washed with water (3×50 ml), dried (Na_2SO_4) and filtered. The solvent was removed at reduced pressure, and the residue was purified by flash chromatography to afford **7** (2.62 g, 70%) and **8** (465 mg, 14%)

Compound **7**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.30 (1H, dd, $J_{1,2}$=3.5 Hz, $J_{2,3}$=6.3 Hz, H-2); 4.27 (1H, q, H-5); 4.19 (1H, d, H-1); 4.09 (1H, dd, $J_{5,6a}$=6.4 Hz, $J_{6a,6b}$=8.8 Hz, H-6a); 4.06 (1H, dd, $J_{3,4}$=8.3 Hz, H-3); 3.90 (1H, dd, $J_{5,6b}$=6.7 Hz, H-6b); 3.29 (1H, dd, $J_{4,5}$=6.3 Hz, H-4); 3.03–2.95 (2H, m, CH_2–CH_2–CH_2); 2.87–2.68 (2H, m, CH_2–CH_2–CH_2); 2.12–1.93 (2H, m, CH_2–CH_2–CH_2); 1.44, 1.43, 1.38, 1.35 (4×3H, s, 4×Me). ^{13}C NMR δ 111.2, 109.8 (2×CMe_2); 83.9, 77.5, 77.4 (C-2, C-3, C-5); 67.1 (C-6); 65.4 (C-4); 48.1 (C-1); 30.0, 29.4 (CH_2–CH_2–CH_2); 27.5, 26.5, 26.0, 23.9 (4×Me); 25.6 (CH_2–CH_2–CH_2). Anal. calcd for $C_{15}H_{25}N_3O_4S_2$: C, 47.98; H, 6.71; N, 11.19; S, 17.08. Found: C, 47.77; H, 6.68; N, 11.32; S, 17.12.

Compound **8**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.96 (1H, dt, H-5); 4.83 (1H, d, $J_{1,2}$=3.4 Hz, H-2); 4.61 (1H, d, $J_{4,5}$=7.8 Hz, H-4); 4.13 (1H, d, H-1); 4.09 (1H, dd, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=7.9 Hz, H-6a); 3.52 (1H, t, $J_{5,6b}$=7.9 Hz, H-6b); 3.01–2.96 (2H, m, CH_2–CH_2–CH_2); 2.89–2.70 (2H, m, CH_2–CH_2–CH_2); 2.12–1.91 (2H, m, CH_2–CH_2–CH_2); 1.60, 1.43, 1.40, 1.39 (4×3H, s, 4×Me). ^{13}C NMR δ 152.6 (C-3); 112.3, 108.6 (2×CMe_2); 95.2 (C-4); 80.5, 71.5 (C-2, C-5); 69.4 (C-6); 49.2 (C-1); 29.4, 29.2 (CH_2–CH_2–CH_2); 26.8, 26.0, 25.8, 25.4 (4×Me); 25.3 (CH_2–CH_2–CH_2).

From the dithioacetal **3**. Dithioacetal **3** (1.75 g, 5 mmol) was dissolved in dry dichloromethane (30 ml) at 0°C and treated with pyridine (4 ml) and triflic anhydride (0.92 ml, 5.5 mmol). After stirring the mixture for 1 h at 0°C, the reaction was quenched with buffer solution (pH 7) then diluted with dichloromethane and washed with aqueous 1 M HCl solution (50 ml) and water (100 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude triflate was dissolved in DMF (20 ml) and treated with sodium azide (1.3 g, 20 mmol). After 5 h at room temperature, the reaction mixture was poured into 1 M HCl solution (50 ml), which was extracted with chloroform (3×50 ml). The combined organic extracts were washed with water (3×50 ml), dried (Na_2SO_4) and filtered. The solvent was removed at reduced pressure, and the residue was purified by flash chromatography to afford **7** (1.54 g, 82%).

4.1.5. 4-Azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose dimethylacetal (9). To a stirred mixture of azido dithioacetal **7** (1.20 g, 3.2 mmol) and mercuric oxide (3.46 g, 16 mmol) in absolute methanol (100 ml) at refluxing temperature was added dropwise a methanolic solution of mercuric chloride (2.60 g, 9.6 mmol). After refluxing for 10 h and cooling to room temperature, the solids were removed by filtration and washed with abs. methanol (3×20 ml). The combined filtrate and washings were concentrated in the presence of mercuric oxide. The residue was extracted with chloroform (3×50 ml), and the chloroform portions were washed with aqueous 10% KI solution (2×50 ml) and then with water (3×50 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated to give a syrup, which was purified by passing through a short column of silica gel with a mixture of hexanes and ethyl acetate (3:1, v/v) to give **9** (975 mg, 92%).

Compound **9**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.39 (1H, d, $J_{1,2}$=5.2 Hz, H-1); 4.27 (1H, q, H-5); 4.17 (1H, dd, $J_{2,3}$=5.8 Hz, H-2); 4.08 (1H, dd, $J_{3,4}$=6.4 Hz, H-3); 4.05 (1H, dd, $J_{5,6a}$=6.6 Hz, $J_{6a,6b}$=8.3 Hz, H-6a); 3.85 (1H, dd, $J_{5,6b}$=6.6 Hz, H-6b); 3.36 (1H, t, $J_{4,5}$=6.4 Hz, H-4); 3.48, 3.46 (2×3H, s, 2×OMe); 1.49, 1.44, 1.42, 1.38 (4×3H, s, 4×Me). ^{13}C NMR δ 110.6, 109.5 (2×CMe_2); 104.4 (C-1); 78.3, 76.7, 76.0 (C-2, C-3, C-5); 66.5 (C-6); 65.1 (C-4); 56.4, 54.2 (2×OMe); 27.4, 27.2, 26.3, 25.2 (4×Me).

4.1.6. 4-Amino-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose dimethylacetal (10). To a solution of azido dimethylacetal **9** (163 mg, 0.49 mmol) in EtOH (20 ml) was added palladium on carbon (40 mg). A hydrogen stream was introduced into the mixture until no starting material could be detected on TLC (hexanes–ethyl acetate 3:1, v/v). The catalyst was removed by filtration and the filtrate was concentrated to a syrup of amino dimethylacetal **10** (150 mg, 100%).

Compound **10**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.42 (1H, d, $J_{1,2}$=5.3 Hz, H-1); 4.27 (1H, m; H-5); 4.12–3.80 (6H, m, NH_2, H-2, H-3, H-6a, H-6b); 2.99 (1H, t, $J_{3,4}$=$J_{4,5}$=6.6 Hz, H-4); 3.50, 3.48 (2×3H, s, 2×OMe); 1.45, 1.40, 1.37, 1.35 (4×3H, s, 4×Me). ^{13}C NMR δ 109.6, 108.6 (2×CMe_2); 104.4 (C-1); 79.0, 78.0, 75.8 (C-2, C-3, C-5); 66.8 (C-6); 56.5, 55.9 (2×OMe); 54.0 (C-4); 27.0, 26.7, 26.3, 25.0 (4×Me). Anal. calcd for $C_{14}H_{25}O_6N_3$: C, 50.74; H, 7.60; N, 12.68. Found: C, 50.59; H, 7.48; N, 12.78

4.1.7. 4-Azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose (11). A mixture of azido dithioacetal **7** (939 mg, 2.5 mmol), mercuric oxide (2.70 g, 12.5 mmol) and mercuric chloride (2.71 g, 10 mmol) in aqueous acetone (100 ml, acetone–H_2O 4:1, v/v) was refluxed for 10 h. After cooling to room temperature, the solids were removed by filtration and washed with acetone (2×50 ml). The combined filtrate and washings were concentrated in the presence of HgO. The residue was extracted with chloroform (3×50 ml) and the chloroform solution was washed with aqueous 10% KI solution (2×50 ml), and then with water (3×50 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated to give a syrup, which was purified by passing through a short column of silica gel with a mixture of hexanes and ethyl acetate (2:1, v/v), yielding **11** as a colorless syrup (642 mg, 90%).

Compound **11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (1H, s, H-1); 4.55 (1H, d, $J_{2,3}$=6.0 Hz, H-2); 4.22 (1H, dd, $J_{3,4}$=5.5 Hz, H-3); 4.18 (1H, m, H-5); 4.13 (1H, dd, $J_{5,6a}$=6.7 Hz, $J_{6a,6b}$=8.0 Hz, H-6a); 3.91 (1H, dd, $J_{5,6b}$=6.3 Hz, H-6b); 3.58 (1H, t, $J_{4,5}$=5.5 Hz, H-4); 1.54, 1.44, 1.36, 1.35 (4×3H, s, 4×Me). ^{13}C NMR δ 200.3 (C-1);

111.5, 109.8 (2×*C*Me$_2$); 81.8, 76.7, 75.6 (C-2, C-3, C-5); 66.3 (C-6); 64.1 (C-4); 26.3, 26.1, 25.7, 25.1 (4×Me). Anal. calcd for $C_{12}H_{19}O_5N_3$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.59; H, 6.81; N, 14.58.

4.1.8. 1,4-Dideoxy-1,4-imino-D-galactitol (1). *From the azido dimethylacetal* **9**. To a solution of azido dimethylacetal **9** (163 mg, 0.49 mmol) in EtOH (20 ml) was added palladium on carbon (40 mg). A hydrogen stream was introduced into the mixture until no starting material could be detected on TLC (hexanes–ethyl acetate 3:1, v/v). Then 6 M HCl solution (10 ml) was added, and the resulting mixture was heated at 45°C for 6 h. After cooling to room temperature, another portion of palladium on carbon (40 mg) was added. A hydrogen stream was introduced into the mixture for 5 h. The catalyst was removed by filtration through Celite and washed with ethanol. The filtrate was concentrated to a syrup, to which ethanol (20 ml) was added and again evaporated. Evaporation of an ethanol solution was repeated twice more to give the hydrochloride salt of pyrrolidine **1**. Free base **1** (73 mg, 91%) was obtained by passing an aqueous solution of the hydrochloride salt through a column of Amberlite IRA-400 (OH^-). The ^{1}H NMR and ^{13}C NMR data of compound **1** are in good agreement with those reported in the literature. $[\alpha]_D^{20}$=+2.9 (*c*=2.0, H_2O); lit.:[4d] $[\alpha]_D^{20}$=+3.0 (*c*=2.4, H_2O); MS (ESI) *m*/*z* 186 ($M+Na^+$), 164 ($M+H^+$).

From the amino dimethylacetal **10**. A solution of **10** (120 mg, 0.39 mmol) in a mixture of acetic acid (10 ml) and water (1 ml) was heated at 50°C for 3 h. After cooling to room temperature, palladium on carbon (40 mg) was added and a hydrogen stream was introduced into the mixture for 5 h. The catalyst was removed by filtration through Celite and washed with ethanol (2×10 ml). The filtrate and washings were concentrated to a syrup, which was purified by passing through a short column of Amberlite IRA-400 (OH^-) to give free base **1** (59 mg, 92%).

From the azido aldehyde **11**. To a solution of azido aldehyde **11** (149 mg, 0.52 mmol) in EtOH (20 ml) was added aqueous 6 M HCl solution (10 ml). The resulting mixture was heated at 45°C for 6 h. After cooling to room temperature, palladium on carbon (50 mg) was added. A hydrogen stream was introduced into the mixture for 6 h. The catalyst was removed by filtration through Celite and washed with ethanol. The filtrate and washings were concentrated to a syrup, to which ethanol (20 ml) was added and again evaporated. Evaporation of an ethanol solution was repeated twice more to give the hydrochloride salt of pyrrolidine **1**. Free base **1** (76 mg; 90%) was obtained by passing an aqueous solution of the hydrochloride salt through a column of Amberlite IRA-400 (OH^-).

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8. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29 (1H, d, $J_{1,2}$=9.6 Hz, H-1); 4.15 (1H, m, H-5); 3.96 (1H, dd, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=8.6 Hz, H-6a); 3.82 (1H, dd, $J_{2,3}$=1.1 Hz, H-2); 3.78 (1H, t, H-3); 3.74 (1H, dd, $J_{5,6b}$=5.0 Hz, H-6b); 3.54 (1H, dd, $J_{3,4}$=1.2 Hz, $J_{4,5}$=8.1 Hz, H-4); 2.79–2.70 (4H, m, CH_2–CH_2–CH_2); 2.04–1.73 (2H, m, CH_2–CH_2–CH_2); 1.36, 1.34, 1.30, 1.24 (4×3H, s, 4×Me). ^{13}C NMR δ 109.0, 99.9 (2×*C*Me$_2$); 74.1, 73.8, 73.1, 66.7 (C-2, C-3, C-4, C-5); 62.2 (C-6); 46.3 (C-1); 28.9, 28.7 (CH_2–CH_2–CH_2); 25.7 (CH_2–CH_2–CH_2); 29.1, 26.6, 24.9, 18.8 (4×Me).
9. In Paulsen's work,[4c] azido sugar **9** was prepared in 10% yield by treatment of 2,3:5,6-di-*O*-isopropylidene-4-*O*-(toluene-4-sulfonyl)-D-glucose dimethylacetal with sodium azide.
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