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New synthesis of 1,4-dideoxy-1,4-imino-D-galactitol from D-glucose propane-1,3-diyl dithioacetal

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Abstract—The treatment of 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose propane-1,3-diyl dithioacetal (derived from D-glucose) with mercuric chloride and mercuric oxide in aqueous acetone afforded 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose. Acid-catalyzed deprotection of the azido derivative, followed by catalytic hydrogenation and concomitant intramolecular reductive amination in the presence of 10% palladium on carbon, gave 1,4-dideoxy-1,4-imino-D-galactitol in good yield.

An important group of tight-binding glycosidase and glycotransferase inhibitors includes both natural and unnatural polyhydroxylated pyrrolidines and piperidines (azasugars).[1] Many azasugars that inhibit glycosidases or glycotransferases have been found to be potential chemotherapeutic agents for treatment of diseases such as diabetes and cancer, inflammation and viral infections, including HIV.[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 synthesis,[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 the previous synthetic approaches.

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.[5] Acetonation 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[6] 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, which was separated by column chromatography in yields of 66 and 25%, respectively. Esterification of the free hydroxyl group at the 4-position of **3** with tosyl chloride in pyridine at room temperature resulted in almost complete formation of the expected fully substituted dithioacetal, which was subsequently transformed into 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose propane-1,3-diyl dithioacetal (**4**) by treatment with sodium azide in DMF at 95°C (Scheme 1). A higher yield (70%) was obtained when small amounts of urea and tetra-*n*-butylamonium bromide were added. 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, which was separated by column chromatography in 14% overall yield.

Deprotection of the dithioacetal moiety in **4**, using mercuric chloride and mercuric oxide in boiling methanol, gave 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose dimethylacetal (**5**) in 94% yield.[7,8] Hydrogenation of the azido group of **5** 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 (**6**). Acid-catalyzed removal of the acetal protecting groups in **6** and subsequent ring closure via

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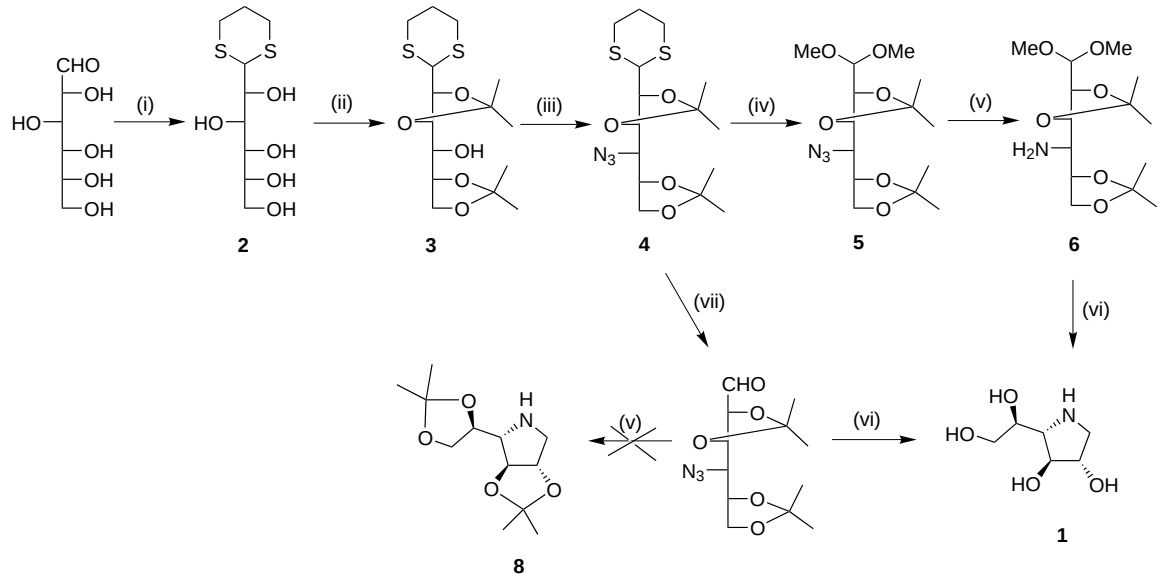

Scheme 1. (i) $HS(CH_2)_3SH$, HCl; (ii) $Me_2C(OMe)_2$, TsOH, DME; (iii) TsCl, pyridine, rt, 2 days; then NaN_3, DMF, 95°C; (iv) $HgCl_2$, HgO, MeOH; (v) 10% Pd/C, H_2, EtOH; (vi) 6 M HCl, EtOH, 45°C; then 10% Pd/C, H_2; (vii) $HgCl_2$, HgO, acetone.

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 in 90% yield. Pyrrolidine **1** was also prepared by a one-pot synthesis from azido dimethylacetal **5** in 91% overall yield.[9] The ^1H and ^{13}C NMR data of compound **1** prepared in this way are in good agreement with those reported in the literature.

When azido dithioacetal **4** was treated with mercuric chloride and mercuric oxide in aqueous acetone, 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-galactose (**7**) was isolated as a colorless syrup in 90% yield. ^1H NMR (9.80 ppm, singlet, 1H, CHO) and ^{13}C NMR spectra (200.3 ppm, CHO) of freshly prepared sample of **7** all indicated that the desired aldehyde had been formed in non-hydrated form;[10] however the compound proved to be unstable upon storage. An attempt to convert **7** into pyrrolidine **8** by Pd-catalyzed reductive amination[11] in ethanol was unsuccessful, but a mixture of unidentified products was obtained. Presumably, the amino group formed by hydrogenation of the azido group in **7** immediately reacted with the free aldehydo group affording polymeric materials. No ring closure via intramolecular attack of the amino group on the aldehydo group was observed, probably because the two reactive centers are too widely separated from each other due to steric restriction effected by the 2,3-*O*-isopropylidene group. In order to overcome this steric restriction, azido derivative **7** was treated with 6 M HCl solution to give the corresponding free aldehyde, whose catalytic hydrogenation and concomitant intramolecular reductive amination provided pyrrolidine **1** (identical with that prepared by the previous route).

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 36% overall yield from D-glucose and compares favorably with the previous synthetic routes.

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7. In Paulsen's work,[4c] azido sugar **5** was prepared in 10% yield by treatment of 2,3:5,6-di-*O*-isopropylidene-4-*O*-tosyl-D-glucose dimethylacetal with sodium azide.

8. Compound **5**: ^{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).
9. To a solution of azido dimethylacetal **5** (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). 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, and the filtrate was concentrated to give a syrup, to which ethanol (20 ml) was added and again evaporated. This was repeated twice more with ethanol to give pyrrolidine hydrochloride of **1**. Free base **1** (73 mg; 91%) was obtained by passing an aqueous solution of the hydrochloride salt of **1** through a column of Amberlite IRA-400 (OH^-).
10. Compound **7**: ^{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, $_{5,6a}=6.7$ 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×CMe_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).
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