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Note

Synthesis of 2-amino-1,2-dideoxy-D-galactitol hydrochloride and 5-amino-1,4-anhydro-5,6-dideoxy-L-galactitol hydrochloride

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2-Acetamido-1,2-dideoxy-D-galactitol (**4**) was prepared in connection with our work on the synthesis of carbohydrates using enzymes [1]. It was found that, when **5** was exposed to concentrated hydrochloric acid, it selectively dehydrates to give 5-amino-1,4-anhydro-5,6-dideoxy-L-galactitol hydrochloride (**7**). Compound 5 was previously reported by Dills and Covey [2] as an intermediate in the synthesis of 1-deoxy-D-tagatose starting from 2-amino-2-deoxy-D-galactose hydrochloride (**1**). The compound was not, however, isolated in pure form, and the only physical data given for it were R_F values. Since our aim was to purify each intermediate in the synthesis of **5**, fully protected derivatives were used rather than the procedure of Dills and Covey [2]. Several amino-protecting groups were tested, but only the acetamido group was stable enough to survive the Raney nickel reduction. Two syntheses of 2-acetamido-3,4,5,6-tetra-O-acetyl-2-deoxy-D-galactose diethyl dithioacetal (**2**) have been reported [3,4]. However, we found that in one of these syntheses [3] the compound described as **2** is, instead, a side product, ethyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio-β-D-galactopyranoside (**3**). Reduction of **2** with Raney nickel gave, as expected, 2-acetamido-3,4,5,6-tetra-O-acetyl-1,2-dideoxy-D-galactitol (**4**). Compound **4** could be deprotected quantitatively with dilute hydrochloric acid to give the desired 2-amino-1,2-dideoxy-D-galactitol hydrochloride (**5**). If **4** was deprotected by refluxing with concentrated hydrochloric acid the intermediate **5** was dehydrated to give 5-amino-1,4-anhydro-5,6-dideoxy-L-galactitol hydrochloride (**7**). Compound **7** could be obtained from **5** in quantitative yield by prolonged heating.

Compound **5** was tested as a substrate for galactose oxidase (D-galactose : oxygen oxidoreductase, EC 1.1.3.9), since oxidation at C-6 of **5** would give easy access to

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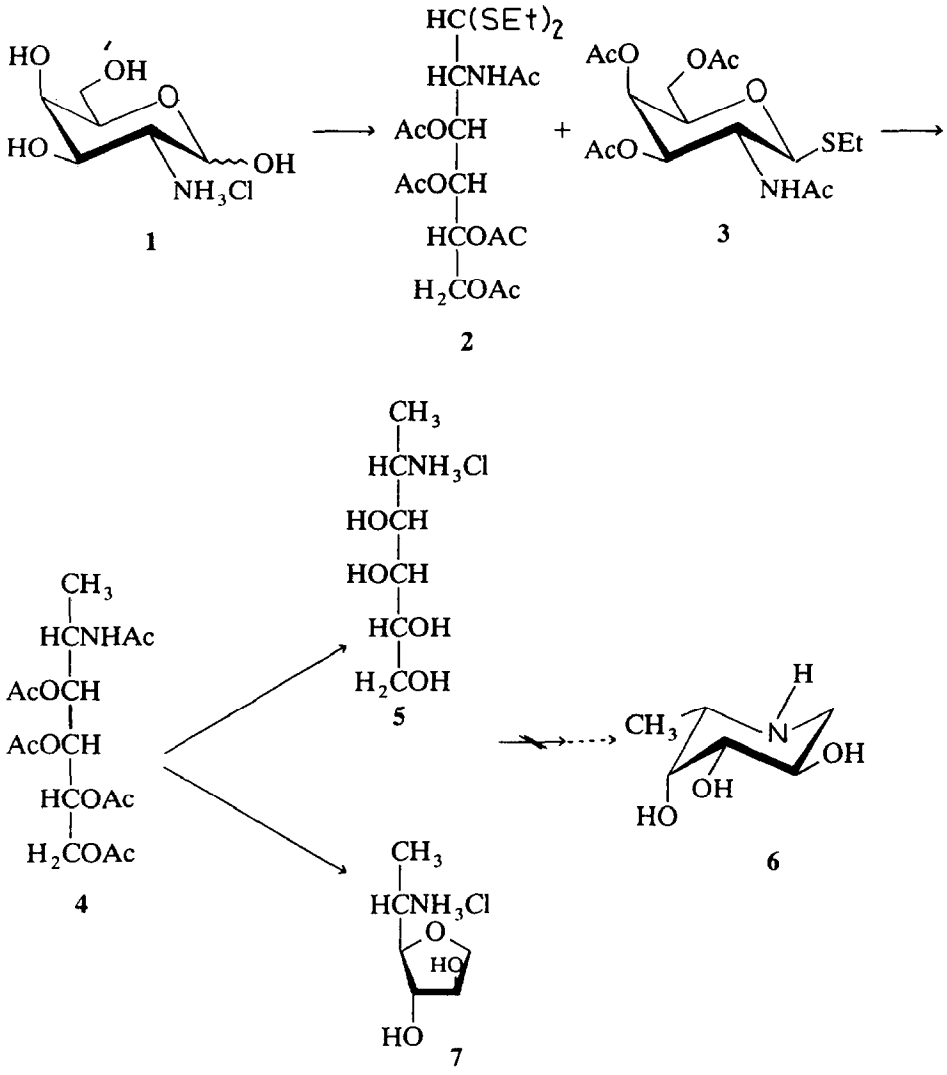

the know α-L-fucosidase inhibitor *, 1,5-dideoxy-1,5-imino-L-fucitol [5,6] (**6**). No conversion of **5** to the corresponding aldehyde could be detected after three days; under similar conditions, complete oxidation of methyl β-D-galactopyranoside to methyl β-D-*galacto*-hexodialdo-1,5-pyranoside was observed within eight hours. Protecting the amino group of **5** as the *N-tert*-butoxycarbonyl derivative did not improve its suitability as a substrate for the enzyme.

* 1,5-Dideoxy-1,5-iminoalditols and their related 5-amino-5-deoxyaldoses and lactams are potentially useful as antiviral agents [7–9] and antineoplastic agents [10,11].

EXPERIMENTAL

General methods.—2-Amino-2-deoxy-D-galactose hydrochloride and Raney nickel were purchased from Aldrich, galactose oxidase was purchased from US Biochemical Co. and catalase from Sigma Chemical Co. ^{1}H-NMR spectra were recorded at 400 MHz; ^{1}H shifts in $CDCl_3$ are referenced to internal Me_4Si (δ 0.00); and ^{1}H shifts in D_2O to the signal of HDO (δ 4.75). ^{13}C-NMR spectra were recorded at 100 MHz (Bruker AM-400); ^{13}C shifts in $CDCl_3$ are referenced to the center of the $CDCl_3$ peaks (δ 77.0); ^{13}C shifts in D_2O are referenced to an external dioxane (δ 67.4). TLC plates (EM Science) were coated with Silica Gel F_{254} (Merck; 0.2 mm). For column chromatography Silica Gel 60 (0.040–0.064 mm, 230–400 mesh ASTM, EM Science) was used.

2-Acetamido-3,4,5,6-tetra-O-acetyl-2-deoxy-D-galactose diethyl dithioacetal (**2**).—2-Amino-2-deoxy-D-galactose (**1**, 2.0 g, 9.3 mmol) was mixed with ethanethiol (10 mL) and concd HCl (17 mL), and stirred for 2 days at room temperature. The mixture was diluted with water and the acid neutralized with $2PbCO_3 \cdot Pb(OH)_2$. The precipitate was separated by filtration and the filtrate concentrated. The resulting solid was suspended in hot EtOH and filtered. The filtrate was concentrated and the remaining solvent coevaporated with pyridine twice. The residue was acetylated with acetic anhydride (25 mL) in pyridine (40 mL) by stirring overnight at room temperature. The solution was poured onto ice and extracted with CH_2Cl_2. The organic phase was successively washed with 4 M HCl and satd $NaHCO_3$ solution, dried ($MgSO_4$), concentrated, and purified on a silica gel column with 1:1 → 1:10 EtOAc–hexane as eluant to give **2** (2.64 g, 73%) as a solid; it could be recrystallized from EtOAc–petroleum ether; mp 133°, $[\alpha]_D$ −5.6° (*c* 1.0, $CHCl_3$); lit. [10] mp 137–139°, $[\alpha]_D$ −17°; ^{1}H-NMR ($CDCl_3$): δ 5.89 (d, 1 H, $J_{NH,2}$ 10.3 Hz, NH), 5.84 (dd, 1 H, $J_{2,3}$ 1.5, $J_{3,4}$ 9.1 Hz, H-3), 5.20 (ddd, 1 H, $J_{4,5}$ 2.2, $J_{5,6}$ 4.7, 7.2 Hz, H-5), 5.16 (dd, 1 H, $J_{3,4}$ 9.1, $J_{4,5}$ 2.2 Hz, H-4), 4.58 (ddd, 1 H, $J_{1,2}$ 5.8, $J_{2,3}$ 1.6, $J_{2,NH}$ 10.2 Hz, H-2), 4.33 (dd, 1 H, $J_{5,6a}$ 4.7 Hz, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.83 (d, 1 H, $J_{1,2}$ 5.8 Hz, H-1), 3.35 (dd, 1 H, $J_{5,6}$ 7.3, $J_{6a,6b}$ 11.9 Hz, H-6b), 2.69–2.61 (m, 4 H, 2 $-SCH_2-$), 1.26 (t, 3 H, *J* 7.3 Hz, CH_3), and 1.24 (t, 3 H, *J* 7.4 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 170.5, 170.4, 169.8, 169.7, 169.2 (5 C=O), 68.8 (C-3), 68.2, 67.4 (C-4,5), 62.5 (C-6), 53.8 (C-1), 50.0 (C-2), 26.0, 25.9 (2 $-SCH_2-$), 23.2, 21.3, 20.8, 20.7, (4 CH_3CO), and 14.4, 14.2 (2 CH_3).

Anal. Calcd for $C_{20}H_{33}NO_9S_2$: C, 48.47; H, 6.71; S, 12.94. Found: C, 48.26; H, 6.73; S, 12.99.

Ethyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio-β-D-galactopyranoside (**3**).—This was isolated from the second fraction of the chromatography and crystallized from EtOAc; mp 182°, $[\alpha]_D$ −35° (*c* 1.2, $CHCl_3$), lit. [3] mp 184°, $[\alpha]_D$ −22°; ^{1}H-NMR ($CDCl_3$): δ 5.46 (bd, 1 H, $J_{NH,2}$ 9.5 Hz, NH), 5.39 (dd, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ 0.9 Hz, H-4), 5.16 (dd, 1 H, $J_{2,3}$ 10.9, $J_{3,4}$ 3.3 Hz, H-3), 4.65 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 4.24 (br q, 1 H, $J_{1,2}$, $J_{2,3}$, $J_{2,NH}$ 10 Hz, H-2), 4.17 (dd, 1 H, $J_{5,6a}$ 6.6, $J_{6a,6b}$ 11.5 Hz, H-6a), 4.11 (dd, 1 H, $J_{5,6b}$ 6.5, $J_{6a,6b}$ 11.3 Hz, H-6b), 3.93 (dt, 1 H, $J_{4,5}$ 0.9, $J_{5,6a}$

6.6 Hz, H-5), 2.82–2.64 (m, 4 H, 2 $-SCH_2-$), 2.17, 2.05, 2.01, 1.98 (s, 12 H, 4 CH_3CO), and 1.28 (t, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 84.9 (C-1), 74.4, 71.2 (C-5,4), 66.9 (C-3), 61.6 (C-6), 49.7 (C-2), 24.4 ($-SCH_2-$), 23.4, 20.7, 20.7 (3 CH_3CO-), and 14.8 (CH_3).

Anal. Calcd for $C_{16}H_{25}NO_8S$: C, 49.10; H, 6.44; S, 8.19. Found: C, 49.18; H, 6.49; S, 8.40.

*2-Acetamido-3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-*D*-galactitol* (**4**).—The dithioacetal **2** (550 mg, 1.1 mmol) was added to a suspension of carefully washed, activated Raney Ni in EtOH (50 mL), and heated at reflux for 20 h. The catalyst was removed by filtration and washed with hot pyridine and EtOH. The combined filtrate was concentrated and the residue stirred overnight with acetic anhydride (10 mL) in pyridine (20 mL). The acetylation was done as a precaution, because deacetylation was sometimes observed during the reduction (the catalyst may be basic). The mixture was poured onto ice and extracted with CH_2Cl_2, and the organic solution was successively washed with 4 M HCl and satd $NaHCO_3$, then dried ($MgSO_4$), and concentrated. Although the product showed only one spot in TLC, it was passed through a silica gel column (10 cm) and eluted with EtOAc to give **4** (230 mg, 55%); ^{1}H-NMR ($CDCl_3$): δ 5.74 (d, 1 H, $J_{NH,2}$ 10.0 Hz, NH), 5.28 (br dd, 1 H, $J_{5,6a}$ 8 Hz, 5 Hz, H-5), 5.20 (s, 2 H, H-3,4), 4.43 (d br q, 1 H, $J_{1,2}$ 6.8, $J_{2,NH}$ 10.7 Hz, H-2), 4.34 (dd, 1 H, $J_{5,6b}$ 4.1, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.81 (dd, 1 H, $J_{5,6b}$ 7.9 Hz, $J_{6a,6b}$ 11.9 Hz, H-6), 2.16, 2.12, 2.10, 2.02, 1.97 (s, 15 H, 5 CH_3CO), and 1.05 (d, 3 H, $J_{1,2}$ 6.8 Hz, H-1): ^{13}C-NMR ($CDCl_3$): δ 170.4, 170.3, 169.7, 169.5, 169.4, (5 C=O), 71.3 (C-3), 68.2, 67.8 C-4, C-5), 62.6 (C-6), 43.1 (C-2), 23.1, 20.6, 20.5, 20.5, 20.5 (5 CH_3CO), and 18.1 (C-1); FABMS: m/z 376.1614 (calc. 376.1608) (M^+).

*2-Amino-1,2-dideoxy-*D*-galactitol hydrochloride* (**5**).—Compound **4** (350 mg, 1.0 mmol) was suspended in M HCl (30 mL) and heated at 80° for 16 h. The mixture was then concentrated and the product passed through a Sephadex G-10 column with water as eluant to give **5** (176 mg, 96%) as a syrup; ^{1}H-NMR (D_2O, pD 2.5): δ 3.83 (dt, 1 H, $J_{4,5}$ 2.0, $J_{5,6a}$ 6.3 Hz, H-5), 3.73 (dd, 1 H, $J_{2,3}$ 2.8, $J_{3,4}$ 7.9 Hz, H-3), 3.66 (dq, 1 H, $J_{1,2}$ 7.0, $J_{2,3}$ 2.8 Hz, H-2), 3.63 (dd, 1 H, $J_{3,4}$ 7.8, $J_{4,5}$ 2.0 Hz, H-4), 3.61 (d, 2 H, $J_{5,6}$ 6.3 Hz, H-6a), and 1.31 (d, 3 H, $J_{1,2}$ 7.0 Hz, H-1); ^{13}C-NMR (D_2O, pD 2.5): δ 71.5, 71.2, 70.9 (C-3,4,5), 63.7 (C-6), 49.6 (C-2), 16.0 (C-1); FABMS: m/z 166.1083 (calc. 166.1079) ($[M - Cl]^+$).

*5-Amino-1,4-anhydro-5,6-dideoxy-*L*-galactitol hydrochloride* (**7**).—Compound **4** (230 mg, 0.6 mmol) was suspended in concd HCl (20 mL) and heated at reflux for 2 days. The mixture was concentrated and passed through a Sephadex G-10 column with water as eluant to give **7** (110 mg, 98%) as a crystalline solid that was recrystallized from EtOH; mp 213–214°; ^{1}H-NMR (D_2O, pD 3) δ 4.22 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 2.0 Hz, H-2), 4.07 (br s, 1 H, H-3), 4.00 (dd, 1 H, $J_{1a,1b}$ 10.2, $J_{1a,2}$ 4.0 Hz, H-1a), 3.89 (br d, 1 H, $J_{1a,1b}$ 10.2 Hz, H-1b), 3.70 (dd, 1 H, $J_{3,4}$ 2.5, $J_{4,5}$ 8.9 Hz, H-4), 3.50 (br dq, 1 H, $J_{4,5}$ 9, $J_{5,6a}$ 7 Hz, H-5), and 1.32 (d, 3 H, $J_{5,6}$ 7 Hz, H-6);

^{13}C-NMR (D_2O, pD 3) δ 87.0 (C-4), 79.7 (C-3), 77.6 (C-2), 74.3 (C-1), 50.1 (C-2), and 15.6 (C-6); FABMS *m/z* 148.0972 (calcd 148.0974) $[M - Cl]^+$.

Enzymic assay.—Compound **5** (45 mg) was dissolved in 0.05 M phosphate buffer (1 mL, pH 7.00). Catalase (9900 units) and galactose oxidase (50 units) were added, and the mixture was vigorously stirred for 3 days under a flow of O_2. ^{1}H-NMR and ^{13}C-NMR spectroscopy of the lyophilized mixture showed only starting material.

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