Convenient Synthesis of *D*-Talose from *D*-Galactose

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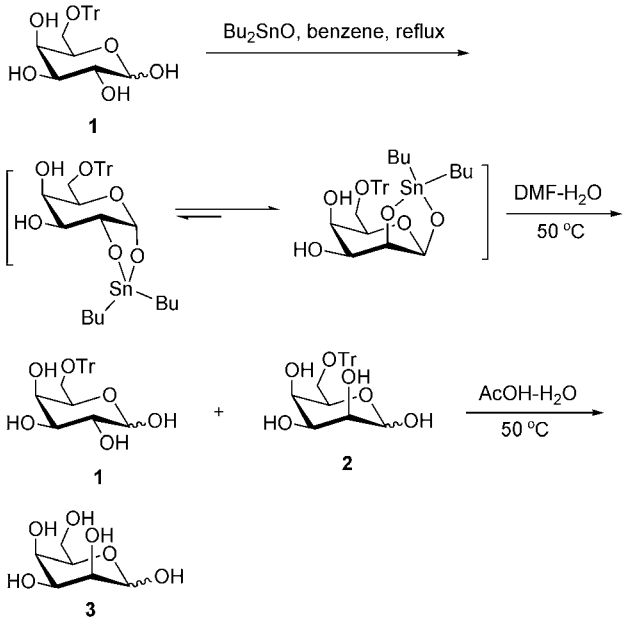
The rare and expensive *D*-talose was conveniently synthesized from readily available *D*-galactose in four steps with an overall yield of 58%. The key step was the inversion of equatorial 2-OH of galactose to the axial one by S_N2 reaction under the modified Lattrell-Dax reaction conditions.

Keywords rare sugar, carbohydrate, *D*-talose, S_N2 reaction, synthesis

Introduction

Rare sugars are defined as a class of monosaccharides and derivatives which exist in nature with a few amount.[1] Over the past few years there has been growing interest in the role of rare sugars for a variety of uses, such as potential inhibitors of various glycosidases,[2] low-calorie carbohydrate sweeteners and bulking agents,[3,4] and improving the clinical effect as an immunosuppressant.[5] In addition, many results have demonstrated that rare sugar structures in many anticancer and antimicrobial natural products provide an important function. For example, rare sugar moieties in some antineoplastic drugs, such as daunorubicin,[6] rebeccamycin,[7] anthracycline antibiotics adriamycin[8] and tallysomycin[9] are critical in forming the anthracycline-DNA binary and anthracycline-DNA-topoisomerase ternary complexes ultimately leading to DNA damage and cell death.[10] The unique disaccharide appendage in glycopeptide antibiotic vancomycin has been shown to be important for promoting dimerization,[11] which appears to be beneficial due to cooperative binding of the target ligands.[12,13] Talose, a rare sugar existing in certain plants and bacteria, its derivatives and talose-containning glycoconjugates have been reported to present some important biological and pharmacological activities, including anti-tumor,[14,15] antimicrobial,[16-18] inhibition of the galactose-binding galectin-4[19] and recrystallization-inhibition (RI) activity.[20] Talose is also a marker of the O-antigens.[21] Therefore, development of mass production method of the expensive sugar for further applications has become very attractive. In the past years, generous chemical methods were used to prepare talose, notably by Masamune and Sharpless,[22] Trautwein,[23] O'Doherty[24,25] and Kovac.[26,27] Among the varies procedures, the synthetic strategy reported by Kovac and co-workers was most efficient (Scheme 1). Starting from 6-*O*-trityl-*D*-galactose, 1,2-*O*-stannylene complex was formed with Bu_2SnO in benzene. The equilibrium shifted largely in favor of talose-1,2-*cis*-*O*-stannylene acetal at reflux temperature, which was subsequently hydrolysized by treatment with 15∶1 (*V*/*V*) DMF-H_2O at 50 ℃ to give 6-*O*-trityl-*D*-talose in yield of 60%—70% along with comparative 6-*O*-trityl-*D*-galactose recovery. The intermediate was detritylated smoothly to afford *D*-talose in 90% yield.

Scheme 1



Due to the impalpable R_f value difference, isolation of 6-*O*-trityl-*D*-talose from 6-*O*-trityl-*D*-galactose was formidable. Moreover, in this procedure large amount of expensive Bu_2SnO was needed and could not be recycled. Therefore it is unsuitable for the mass production. Fortunately, during our synthesis of *N*-glycan octasac-

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charide,[28] we found that the equatorial 2-OH of glucoside could be completely inverted to the axial one by S_N2 reaction and the 2-*O*-acetyl group of penta-*O*-acetyl-*β*-*D*-galactopyranose could be selectively removed in the presence of 90% TFA without destroying other acetyl groups.[29,30] Taking the two points into account, here we would like to report a new route to conveniently prepare *D*-talose from *D*-galactose.

Results and discussion

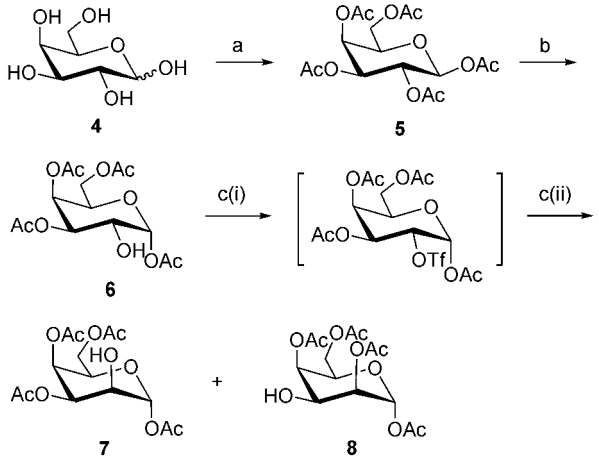
Following our method, *D*-talose would be prepared from *D*-galactose in four steps, as outlined in Scheme 2. *D*-galactose was firstly converted to known 1,2,3,4,6-penta-*O*-acetyl-*β*-*D*-galacotose **5**[31] in 94% yield. Then selective cleavage of 2-*O*-acetyl group of **5** with 90% TFA prepared the key intermediate 1,3,4,6-tetra-*O*-acetyl-*β*-*D*-galactopyranose **6** in yield of 40%—50% (Lit.[29] in 70% yield) and by-product 2,3,4,6-tetra-*O*-acetyl-*β*-*D*-galactopyranose. We observed that the ratio of the by-product increased during the working up when the reaction mixture was concentrated at high temperature to remove the TFA. We presumed that part of **6** was converted to the by-product under the conditions. Therefore in order to inhibit the transformation, we improved the working up by washing out the TFA with water and saturated aqueous Na_2CO_3. As a result, the key **6** was obtained in a good yield of 66% through recrystallization and the by-product was reduced greatly as expected. Subsequent estification of the 2-OH of tetra-*O*-acetate **6** was carried out by treatment with trifluoromethanesulfonic anhydride to provide 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-*β*-*D*-galactopyranose, without separation purification, followed by treatment with 10∶1 (*V*/*V*) DMF-H_2O at 70 ℃ to afford a mixture of 1,3,4,6-tetra-*O*-acetyl-*α*-*D*-talose (**7**) and 1,2,4,6-tetra-*O*-acetyl-*α*-*D*-talose (**8**) in 94% yield in a 1∶0.7 ratio. Compound **7** (54%) and **8** (40%) could be separated by column chromatography on silical gel. The relative configurations of **7** and **8** were determined by examining relevant coupling constants and NOEs from ^{1}H NMR, and ^{1}H,^{1}H-COSY experiments.

The structures of **7** and **8** were further confirmed by acteylation with Ac_2O in pyridine, both giving compound **9** with the same NMR data. Zemplén deacetylation of **7** and **8** afforded *D*-talose as a mixture of anomers (*α*,*β*-pyranoses and *α*,*β*-furanoses) in quantitive yield (Scheme 3). The observed ^{13}C NMR spectral data were in agreement with standard substance of talose.

Conclusion

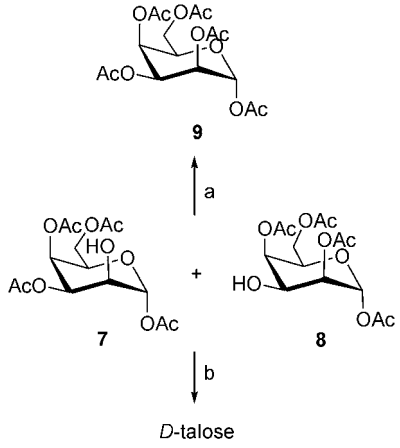
In summary, we developed a simple and efficient method for the synthesis of *D*-talose from cheap and readily available *D*-galactose (58% overall yield) in four steps. This route also provided a method for the preparation of two intermediate compounds tetra-*O*-acetyl-*D*-taloses **5** and **6** which could be converted to talose or as a raw material for the synthesis of various chiral compounds. It also has an important guiding significance for the synthesis of other rare sugar compounds.

Scheme 2



Reagents and conditions: (a) NaOAc, Ac_2O, 120 ℃, 94%; (b) 90%TFA, 66%; (c) (i) Tf_2O, pyr, CH_2Cl_2; (ii) H_2O/DMF, 70 ℃, **7** (54%), **8** (40%).

Scheme 3



Reagents and conditions: (a) Ac_2O, pyr, quantitive; (b) CH_3ONa, CH_3OH, quantitive.

Experimental protocols

General methods

Solvents were purified in a conventional manner. Thin layer chromatography (TLC) was performed on pre-coated E. Merck silica gel 60 F254 plates. Flash column chromatography was performed on silica gel (200—300 mesh). Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a Q-TOF Global mass spectrometer.

Synthesis

1,3,4,6-Tetra-*O*-acetyl-*α*-*D*-galacotose (6) A so-

lution of 1,2,3,4,6-penta-*O*-acetyl-*β*-*D*-galacotose (**5**)[31] (7.8 g, 20 mmol) in 90% trifluoroacetic acid aqueous solution (50 mL) was stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with H_2O (100 mL×2), saturated aqueous $NaHCO_3$ (100 mL×2), brine (100 mL×2), dried (Na_2SO_4) and concentrated. Isopropyl ether was added to the residue and a white precipitate formed, the resultant solid was collected by filtration and recrystallized with EtOAc/petroleum ether to give **3** (4.6 g, 66.0%) as a white solid. $[\alpha]_D^{25}$ +116.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 6.31 (d, *J*=3.7 Hz, 1H, H-1), 5.46 (t-like, *J*=1.8 Hz, 1H, H-4), 5.18 (dd, *J*=10.5, 3.2 Hz, 1H, H-3), 4.29—4.27 (m, 1H, H-5), 4.18 (dd, *J*=10.6, 4.1 Hz, 1H, H-2), 4.12—4.06 (m, 2H, H-6a, H-6b), 2.19, 2.15, 2.07, 2.04 (s, 3H each, CH_3CO). HRESIMS calcd for $C_{14}H_{20}O_{10}Na$ 371.0954, found 371.0961.

1,3,4,6-Tetra-*O*-acetyl-*α*-*D*-talose (7) and 1,2,4,6-tetra-*O*-acetyl-*α*-*D*-talose (8) To a solution of 1,3,4,6-tetra-*O*-acetyl-*α*-*D*-galacotose (**6**) (3.5 g, 10 mmol) in distilled CH_2Cl_2 (60 mL) was added pyridine (1.7 mL, 20 mmol). The reaction was cooled to −15 ℃. Tf_2O (1.8 mL, 11 mmol) was then added dropwise over a 2 min period, and the reaction mixture was stirred for 10 min. The reaction was concentrated under high vacuum. The crude mixture was dissolved in 20 mL of DMF, then 2 mL of H_2O was added, and the reaction mixture was stirred for 24 h at 70 ℃. Then the reaction mixture was concentrated under high vacuum and purified by silica gel column chromatography (4∶1, *V*∶*V*, petroleum ether-EtOAc) to give **7** (1.9 g, 54.3%) and **8** (1.4 g, 40.0%) as white solid.

7: $[\alpha]_D^{25}$ +43.1 (*c* 0.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6) *δ*: 5.90 (d, *J*=2.2 Hz, 1H, H-1), 5.25 (d, *J*=5.5 Hz, 1H, 2-OH), 5.23 (s, 1H, H-4), 5.02 (t, *J*=3.8 Hz, 1H, H-3), 4.29 (td, *J*=6.1, 1.1 Hz, 1H, H-5), 4.05 (dd, *J*=6.6, 2.8 Hz, 2H, H-6a, H-6b), 3.76—3.75 (m, 1H, H-2), 2.10, 2.04, 1.99, 1.98 (s, 3H each, CH_3CO×4); ^{13}C NMR (DMSO-d_6) *δ*: 170.6, 170.5, 170.1, 169.3 (CH_3CO×4), 94.3 (C-1), 69.2 (C-5), 67.7 (C-3), 66.4 (C-4), 65.7 (C-2), 62.0 (C-6), 21.4, 21.2, 21.1, 21.1 (CH_3CO×4). $J_{H(1),C(1)}$=175.6 Hz. HRESIMS calcd for $C_{14}H_{20}O_{10}Na$ 371.0954, found 371.0965.

8: $[\alpha]_D^{25}$ +28.9 (*c* 0.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6) *δ*: 5.91 (s, 1H, H-1), 5.35 (d, *J*=7.7 Hz, 1H, 3-OH), 5.17 (d, *J*=1.1 Hz, 1H, H-4), 4.85 (d, *J*=2.2 Hz, 1H, H-2), 4.24 (t, *J*=6.0 Hz, 1H, H-5), 4.06—3.97 (m, 3H, H-3, H-6a, H-6b), 2.10, 2.08, 2.06, 1.98 (s, 3H each, CH_3CO×4); ^{13}C NMR (DMSO-d_6) *δ*: 170.7, 170.5, 170.5, 169.0 (CH_3CO×4), 91.7(C-1), 69.7 (C-5), 68.7 (C-2), 68.5 (C-4), 63.4 (C-3), 62.4 (C-6), 21.4, 21.2, 21.1 (CH_3CO × 4). $J_{H(1),C(1)}$ = 175.6 Hz. HRESIMS calcd for $C_{14}H_{20}O_{10}Na$ 371.0954, found 371.0960.

1,2,3,4,6-Penta-*O*-acetyl-*α*-*D*-talose (9) To a solution of 1,3,4,6-tetra-*O*-acetyl-1-thio-*α*-*D*-talose (**7**) (300 mg, 0.86 mmol) in dry CH_2Cl_2 (10 mL) was added pyridine (0.5 mL), Ac_2O (0.5 mL) and DMAP (20 mg) at 0 ℃, the solution was stirred for 15 min at 0 ℃ and 1 h at room temperature (r.t.). The solution was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (20 mL×3), brine (20 mL×3), dried (Na_2SO_4), and evaporated to give a residue, which was purified by silica gel column chromatography (3∶2, *V*∶*V*, petroleum ether-EtOAc) to give **6** (330 mg, 100%) as a light yellow solid.

Starting from 1,2,4,6-tetra-*O*-acetyl-1-thio-*α*-*D*-talose (**8**) (300 mg, 0.86 mmol) and using the same procedure as described above, compound **9** was also prepared (330 mg, 100%). R_f=0.38 [*V*(petroleum ether)∶*V*(acetic ether)=3∶2]; $[\alpha]_D^{25}$ +32.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ*: 6.16 (d, *J*=1.9 Hz, 1H, H-1), 5.36 (t-like, *J*=1.9, 1.8 Hz, 1H, H-4), 5.32 (t-like, *J*=3.7 Hz, 1H, H-3), 5.10 (t-like, *J*=1.9 Hz, 1H, H-2), 4.34—4.31 (m, 1H, H-5), 4.19 (dd, *J*=11.8, 6.9 Hz, 1H, H-6a), 4.16 (dd, *J*=11.5, 6.9 Hz, 1H, H-6b), 2.16 (s, 6H, CH_3CO), 2.15, 2.05, 2.01 (s, 3H each, CH_3CO); ^{13}C NMR ($CDCl_3$) *δ*: 170.5, 169.8, 168.2, 91.5, 68.8, 66.4, 65.3, 65.2, 61.5, 21.0, 20.9, 20.7. HRESIMS calcd for $C_{16}H_{22}O_{11}K$ 429.0799, found 429.0778.

***D*-Talose**

To a solution of 1,3,4,6-tetra-*O*-acetyl-*α*-*D*-talose (**7**) and 1,2,4,6-tetra-*O*-acetyl-*α*-*D*-talose (**8**) (300 mg, 0.86 mmol) in DCM-MeOH (*V*∶*V*=1∶3, 40 mL) was added a catalytic amount of NaOMe (20 mg), the reaction mixture was stirred at room temperature for 30 min, then neutralized cautiously with Dowex 50×8 (H^+) resin until pH=7, filtered and concentrated under vacuum to give *D*-talose (158 mg, 100%). Crystallization from EtOH gave material (a mixture of anomers) melting at 123—124 ℃ (Lit.[26] mp. 126—127 ℃). ^{13}C NMR (D_2O) *δ*: 103.4, 99.2, 97.4, 96.8, 85.2, 84.5, 78.4, 77.8, 74.5, 74.2, 73.9, 73.7, 73.5, 73.4, 73.3, 73.3, 72.3, 71.4, 71.1, 67.8, 65.4, 64.2, 63.9.

Sample of *D*-talose ^{13}C NMR (D_2O) *δ*: 103.6, 99.2, 97.3, 96.8, 85.2, 84.6, 78.4, 77.9, 74.5, 74.2, 73.9, 73.7, 73.5, 73.4, 73.3, 73.3, 72.3, 71.4, 71.1, 67.8, 65.6, 65.4, 64.2, 63.9.

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