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1,6-Anhydro-β-L-hexopyranoses as valuable building blocks toward the synthesis of L-gulosamine and L-altrose derivatives

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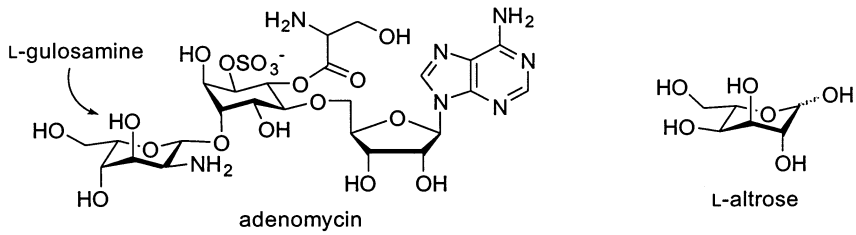
Abstract—1,6-Anhydro-β-L-hexopyranoses as valuable building blocks toward the synthesis of L-gulosamine and L-altrose derivatives via the regioselective triflation and benzoylation of 1,6-anhydro-β-L-idopyranose followed by S_N2 substitution with various nucleophiles as key steps is described here. © 2001 Elsevier Science Ltd. All rights reserved.

As part of our progress in the synthesis of biologically potent L-hexoses,[1] we have interest in L-gulosamine and L-altrose. Adenomycin, a nucleoside antibiotic with significant anti-bacterial activity,[2] contains L-gulosamine as a key component (Scheme 1). L-Altrose[3] is a potent constituent of extracellular polysaccharides from *Butyrivibrio fibrisolvens* strain CF3.[4] Given the importance of L-hexoses in the field of glycobiology and the study of L-gulosamine is unknown, there is a constant need to develop efficient methodologies for their synthesis.

1,6-Anhydro-hexopyranoses are valuable synthons for carbohydrate-based syntheses of oligosaccharides and natural products.[5] Their [3.2.1]bicyclic skeletons ensure that not only a high degree of steric-approach control occurs in their reactions, but also fewer protecting groups at C1 and C6 are needed than their corresponding pyranoses. After the cleavage of internal acetal, further functional group transformation and glycosylation at C6 and C1, respectively, could be carried out. 1,6-Anhydro-β-L-hexopyranoses, which are known as rare L-form sugars, are laborious to prepare. We have explored herein a convenient route to synthesize the 1,6-anhydro-β-L-ido, -gulo, and -altropyranosyl sugars and their applications in the preparation of L-gulosamine and L-altrose derivatives.

A practical synthesis of 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranose **1** from diacetone α-D-glucose in three steps in 57% overall yield was recently developed by us.[1a] The results of compound **1**'s hydrolysis in acidic media at various temperatures followed by per-acetylation are shown in Table 1. In entries 2 and 3, treatment of **1** with 0.2N $H_2SO_{4(aq)}$ at 60 or 80°C often afforded a mixture of L-idose and 1,6-anhydro-β-L-idopyranose **5**. When the hydrolyzed temperature was 35°C only L-idose was obtained (entry 1). Since it was unstable and slowly rearranged to L-sorbose,[6] per-acetylation with acetic anhydride and pyridine gave L-idopyranosyl pentaacetate **2**[7] and L-idofuranosyl pentaacetate **3** in 70 and 26% yields, respectively. Hydrolysis of **1** in 0.2N $H_2SO_{4(aq)}$ or $HCl_{(ethanol)}$ at refluxing temperature (entries 4 and 5) provided **5** (88%) as a single adduct, which was per-acetylated to afford the triacetate **4** in



Scheme 1.

Keywords: carbohydrates; adenomycin; L-gulosamine; L-altrose.

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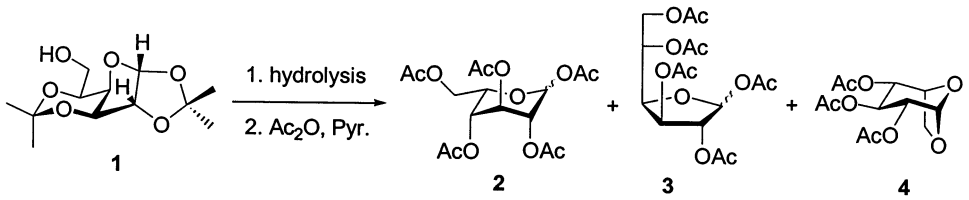
Table 1. The results of compound **1**'s hydrolysis in acidic media followed by per-acetylation



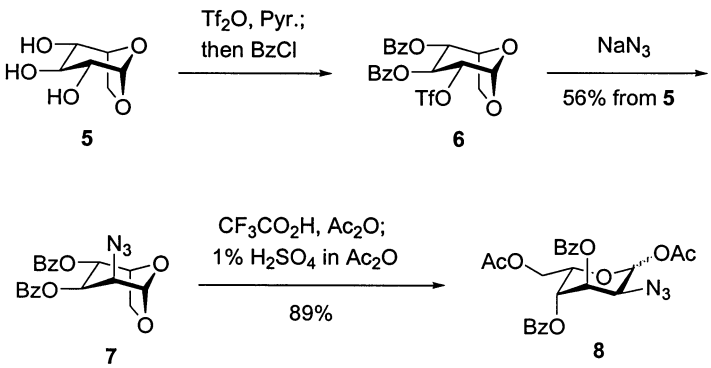
Entry	Acidic media	*t* (°C)	Time (h)	Yield (%)		
				2	**3**	**4**
1	0.2N H_2SO_4 in H_2O	35	44	70	26	–
2	0.2N H_2SO_4 in H_2O	60	12	74	11	7
3	0.2N H_2SO_4 in H_2O	80	12	22	20	48
4	0.2N H_2SO_4 in H_2O	Reflux	12	–	–	90
5	0.2N HCl in EtOH	Reflux	8	–	–	88
6	Acidic resin in EtOH	Reflux	8	–	–	32

excellent yields. When the Amberlite-120 acidic resin was used as the catalyst, the desired product was isolated in low yield (entry 6).

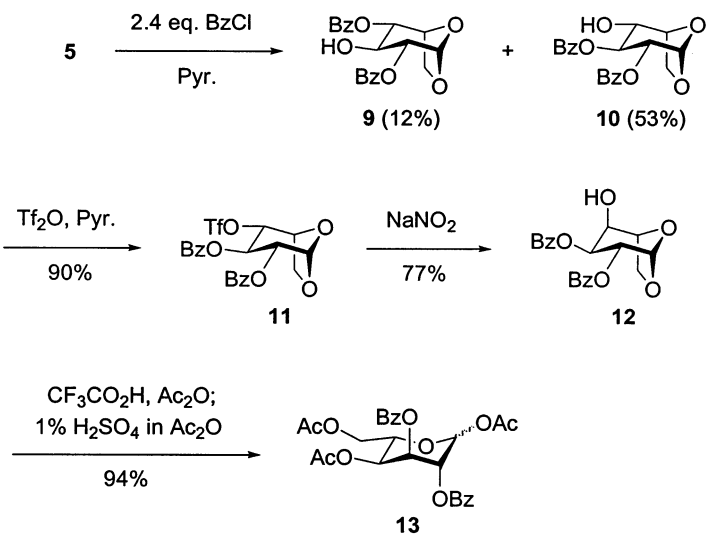
With the key synthon **5** in hand, the distinction of three free equatorial hydroxyls at C2, C3 and C4 was studied and the synthesis of fully protected L-gulosamine in only three steps was carried out (Scheme 2). Due to the inductive effect of two oxygen atoms at C1, the proton of 2-OH is more acidic than the 3- or 4-OH. Regioselective triflation of **5** with one equivalent of trifluoromethanesulfonic anhydride in pyridine provided the 2-OTf derivative as a single isomer. This result allowed the one-pot synthesis of **6** (triflation and benzoylation), which was subjected to nucleophilic substitution with sodium azide to give 2-azido-2-deoxy-3,4-di-*O*-benzoyl-β-L-gulopyranose **7**[8] in 56% overall yield. The absolute structure was firmly secured through the X-ray single crystal analysis.[9] Typical acetolysis of **7** with trifluoroacetic acid and acetic anhydride only recovered the starting material without isolation of any desired ring-opening product **8**. It is noted that extra addition of 1% solution of conc. H_2SO_4 in Ac_2O into the reaction mixture afforded the fully protected L-gulosamine **8** in 89% yield, which is believed to be a potential precursor in the synthesis of adenomycin.

Application of **5** toward the synthesis of L-*altro* sugars is summarized in Scheme 3. Regioselective benzoylation of **5** with 1.2 equiv. of benzoyl chloride in pyridine led to the corresponding 2-OBz compound in 63% yield. When 2.4 equiv. of BzCl was used, the dibenzoates **9** and **10**[8] were isolated in 12 and 53% yields, respectively. Triflation of **10** provided **11** (90%), the absolute configuration of which was determined by X-ray single crystal analysis.[10] Nucleophilic substitution of **11** with sodium nitrite furnished the C4-epimerized product **12**[8] in 77% yield. Typical acetolysis only gave the 4-OAc derivative and the 1,6-anhydro ring could be opened by extra addition of 1% solution of conc. H_2SO_4 in Ac_2O to afford the fully protected L-altropyranosyl sugar **13** in 94% yield.

In conclusion, we have successfully developed a convenient route to prepare the 1,6-anhydro-β-L-*ido*, -*gulo*, and -*altro* sugars and carried out an efficient synthesis of fully protected L-gulosamine **8** and L-altrose **13**, respectively.



Scheme 2.



Scheme 3.

Acknowledgements

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7. Paulsen, H.; Trautwein, W.-P.; Espinosa, F. G.; Heyns, K. *Chem. Ber*. **1967**, *100*, 2822.
8. The selected physical data of key compounds is listed. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H, BzH), 7.99 (m, 2H, BzH), 7.56 (m, 2H, BzH), 7.44 (m, 4H, BzH), 5.77 (dd, J=9.6, 5.3 Hz, 1H, H-3), 5.66 (ddd, J=9.6, 4.2, 0.8 Hz, 1H, H-4), 5.57 (d, J=2.2 Hz, 1H, H-1), 4.86 (t, J=4.2 Hz, 1H, H-5), 4.29 (d, J=8.2 Hz, 1H, H-6b), 4.19 (dd, J=5.3, 2.2 Hz, 1H, H-2), 3.82 (ddd, J=8.2, 4.2, 0.8 Hz, 1H, H-6a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59 (C), 165.30 (C), 133.67 (CH), 130.00 (CH), 129.79 (CH), 128.83 (C), 128.55 (CH), 100.58 (CH), 72.59 (CH), 69.69 (CH), 69.44 (CH), 64.84 (CH_2), 61.92 (CH). Compound **10**: IR ($CHCl_3$) 3067, 2974, 2906, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.97 (m, 4H, BzH), 7.62–7.36 (m, 6H, BzH), 5.60 (d, J=1.5 Hz, 1H, H-1), 5.35–5.28 (m, 2H, H-2, H-3), 4.63 (t, J=4.8 Hz, 1H, H-5), 4.39 (d, J=8.0 Hz, 1H, H-6b), 4.15 (dd, J=7.1, 4.8 Hz, 1H, H-4), 3.85 (dd, J=8.0, 4.8 Hz, 1H, H-6a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.63 (C), 165.81 (C), 133.87 (CH), 133.72 (CH), 133.49 (CH), 130.19 (CH), 130.07 (CH), 129.92 (CH), 129.30 (C), 129.05 (C), 128.62 (CH), 128.57 (CH), 128.45 (CH), 99.07 (CH), 77.02 (CH), 75.37 (CH), 73.86 (CH), 71.16 (CH), 65.53 (CH_2). Anal. calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.92; H, 4.87. Compound **11**: mp 148–149°C, $[\alpha]_D^{30}$ +130 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1732, 1603, 1583 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.95 (m, 4H, BzH), 7.55–7.51 (m, 2H, BzH), 7.41–7.37 (m, 4H, BzH), 5.97 (t, J=8.8 Hz, 1H, H-3), 5.69 (d, J=2.0 Hz, 1H, H-1), 5.19–5.15 (m, 2H, H-2, H-4), 4.87 (t, J=4.8 Hz, 1H, H-5), 4.39 (d, J=8.4 Hz, 1H, H-6b), 3.98 (dd, J=8.4, 4.8 Hz, 1H, H-6a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.58 (C), 165.10 (C), 133.68 (CH), 130.01 (CH), 129.84 (CH), 128.51 (CH), 116.77 (q, J=318 Hz), 99.43 (CH), 81.75 (CH), 74.95 (CH), 73.38 (CH), 69.33 (CH), 65.57 (CH_2); HRMS (FAB, MH$^+$) calcd for $C_{21}H_{18}F_3O_9S$ 503.0624, found: 503.0638. Anal. calcd for $C_{21}H_{17}F_3O_9S$: C, 50.20; H, 3.41. Found: C, 50.29; H, 3.50. Compound **12**: mp 122–123°C, $[\alpha]_D^{30}$ +266 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.99 (m, 4H, BzH), 7.53–7.49 (m, 2H, BzH) 7.40–7.24 (m, 4H, BzH), 5.66 (d, J=1.6 Hz, 1H, H-1), 5.50–5.43 (m, 2H, H-2, H-3), 5.47 (dd, J=5.2, 2.4 Hz, 1H, H-5), 4.32 (ddd, J=9.6, 6.0, 3.6 Hz, 1H, H-4), 4.03 (dd, J=8.4 Hz, 1H, H-6a), 3.92 (dd, J=8.4, 5.6 Hz, 1H, H-6b), 2.33 (d, J=6.0 Hz, 1H, OH-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.91 (C), 165.75 (C), 133.48 (CH), 133.41 (CH), 129.90 (CH), 129.84 (CH), 129.11 (C), 128.48 (CH), 128.41 (CH), 99.48 (CH), 76.85 (CH), 72.44 (CH), 70.64 (CH), 68.99 (CH), 65.72 (CH_2); HRMS (FAB, MH$^+$) calcd for $C_{20}H_{19}O_7$: 371.1131, found: 371.1154. Anal. calcd for $C_{20}H_{18}O_7$: C, 64.80; H, 4.90. Found: C, 64.59; H, 4.77.
9. Crystal structure analysis of **7**: colorless crystals from chloroform/hexane, $C_{20}H_{17}N_3O_6$, fw=395.37, crystal dimensions: 0.41×0.31×0.19 mm^3, crystal system: orthorhombic, space group: $P2_1$, unit-cell dimensions:

$a=10.773(3)$, $b=7.283(4)$, $c=11.9371(12)$ Å, $V=931.0(6)$ Å^3, $Z=2$, $\rho_{calcd}=1.410$ g cm^{-3}, wavelength = 0.7107 Å, $F(000)=411.93$, mu = 0.11 mm^{-1}, $2\theta(max)=50.0$. The deposit number at the Cambridge Crystallographic Data Centre is CCDC 152187.

10. Crystal structure analysis of **11**: colorless crystals from chloroform/hexane, $C_{21}H_{17}F_3O_9S$, fw = 502.42, crystal dimensions: 0.49×0.41×0.38 mm^3, crystal system: orthorhombic, space group: $P2_1$, unit-cell dimensions: $a=5.7578(6)$, $b=16.016(3)$, $c=11.9800(15)$ Å, $V=1100.9(3)$ Å^3, $Z=2$, $\rho_{calcd}=1.516$ g cm^{-3}, wavelength = 0.7093 Å, $F(000)=515.95$, mu = 0.22 mm^{-1}, $2\theta(max)=50.0$. The deposit number at the Cambridge Crystallographic Data Centre is CCDC 152186.