Pergamon

Tetrahedron Letters 41 (2000) 77–80

TETRAHEDRON LETTERS

Novel synthesis of 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside and its derivatives at C6

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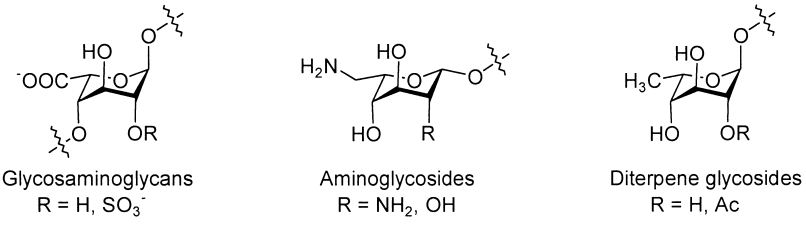
Received 17 September 1999; revised 13 October 1999; accepted 18 October 1999

Abstract

An efficient synthesis of 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside and its derivatives at C6 from diacetone α-D-glucose employing the stereoselective hydroboration and hydrogenation as key steps is described here.

Keywords: hydroboration; hydrogenation; carbohydrates; L-idoses.

L-Idopyranosyl units are important structural elements of several naturally biological oligosaccharides. Glycosaminoglycans, e.g. heparin, heparan sulfate, and dermatan sulfate, containing L-idopyranosyluronate (Scheme 1) as a typical component play significant roles in diverse biological processes, including blood coagulation, cell growth control, inflammation, wound healing, virus infection, tumor metastasis, and diseases of the nervous system.[1] The first chemical synthesis and structural modification of an antithrombin-binding pentasaccharide has been carried out by Sinaÿ[2] and others.[3] Aminoglycoside antibiotics having specific binding to the A-site of prokaryotic 16S *r*RNA interfere with *m*RNA translation and ultimately lead to bacterial cell death.[4] The structurally related aminoglycosides, neomycin B, paromomycin, and lividomycin A, contain 2,6-diamino-2,6-dideoxy-L-idopyranoside as the D-ring. Elegant work in the modification of this D-ring as 6-amino-6-deoxy-L-idopyranoside for



Scheme 1.

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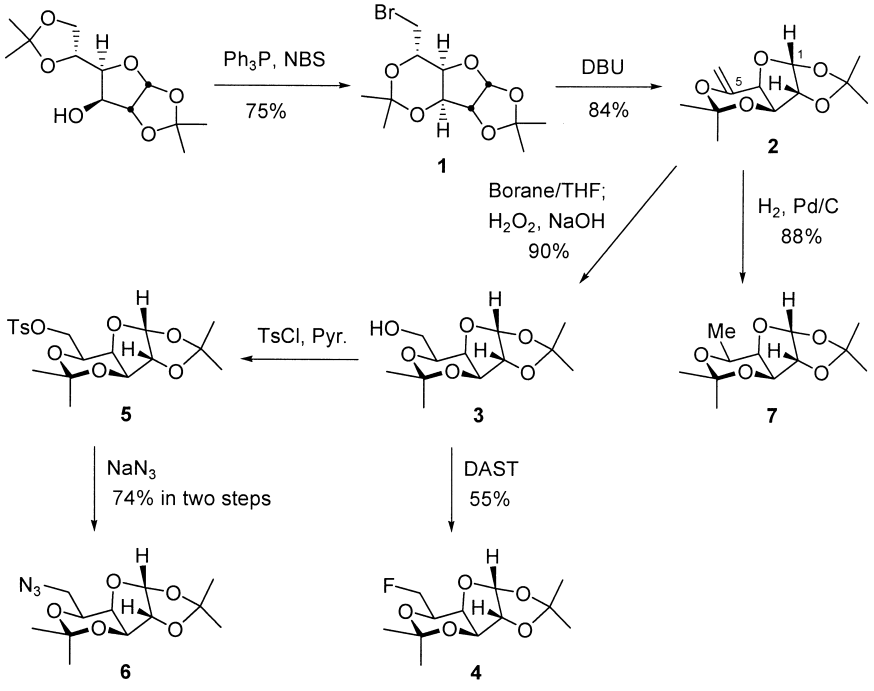
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02004-3

the study of the structure–activity relationship between carbohydrates and RNA presents remarkable antibacterial activity, as reported by Wong and co-workers.[5] Some diterpene glycosides isolated from *Aster spathulifolius* Maxim. also contain unusual 6-deoxy-L-idopyranosides.[6] However, their biological activity remains unclear.

Most synthetic methodologies of L-*ido* sugars begin with D-*gluco* compounds and involve the selective inversion of configuration at C5. Several approaches had been done, including the nucleophilic displacements of a 5-sulfonate or mesylate group in D-glucofuranoside[7] or D-glucofuranuronic acid derivatives;[8] diastereoselective hydroboration of 6-*exo*-glucal derivatives;[5,9] radical reduction of acetylated 5-bromouronates;[10] and others.[11] These methodologies may, however, afford two diastereoisomers needed to be separated or require too many steps to accomplish the inversion at C5. The route we have explored herein is based on the model of isopropylidene fixation on 3,5-dihydroxyl groups of 1,2-*O*-isopropylidene-α-D-glucofuranoside to form a *cis–anti–cis*-tricyclic fused compound **2**. It is predicted to induce higher diastereoselectivity of L-*ido* configuration from the less-hindered side in the hydroboration or hydrogenation of 5-*exo*-double bond.

An efficient synthesis of L-*ido* sugars from diacetone α-D-glucose is indicated in Scheme 2. Treatment of diacetone α-D-glucose with triphenylphosphine and NBS afforded 6-bromo-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranoside **1**[12] (75%) in one pot via a combination of isopropylidene rearrangement and regio-selective bromination. Elimination of HBr with DBU furnished the enol ether **2**[13] in 84% yield. Hydroboration followed by oxidative work-up provided 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside **3**[14] (90%) as a single adduct. The L-form configuration was determined by the X-ray single crystal structural analysis of 6-tosyl-1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside **5** (Fig. 1).[15] The stereo ORTEP drawing illustrates the C4–O4 and C3–C2 bonds are at the axial- and equatorial-positions, respectively. Due to the steric effect, the addition of borane with 5-exo double bond occurs from the α-face, forming the substituted group (CH_2OH) at the equatorial position of C5 (L-form).



Scheme 2.

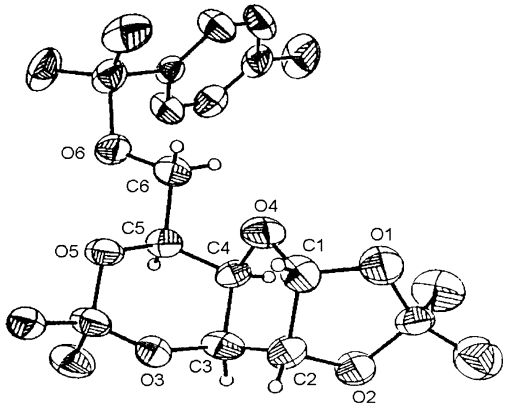


Figure 1. The stereo ORTEP drawing of **5**

Functional group transformation of **3** with DAST and TsCl followed by NaN_3 gave **4**[13] (55%) and **6**[13] (74% in two steps), respectively. Hydrogenation of **2** in the presence of Pd/C led to 6-deoxy-1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside **7**[13] as a single diastereoisomer in 88% yield. Super hydride reduction of **5** furnished the same adduct **7**. It indicates that the methyl group of **7** is at the equatorial-position. The high stereoselectivity is perhaps induced by the steric hindrance in β-face.

In conclusion, a short synthesis of 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside and its derivatives at C6 is successfully developed here. The application of these carbohydrates for the synthesis of biologically important oligosaccharides is currently under investigation.

Acknowledgements

We thank Prof. Sunney I. Chan for his helpful discussion, Dr. Kuan-Jiuh Lin for X-ray single crystal structural analysis, and the National Science Council for financial support.

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13. The selected physical data of new compounds is listed. Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, *J*=3.7 Hz, 1H, H-1), 4.76 (d, *J*=0.8 Hz, 1H, H-6), 4.69 (d, *J*=0.8 Hz, 1H, H-6), 4.56 (d, *J*=3.7 Hz, 1H, H-2), 4.37 (d, *J*=2.3 Hz, 1H, H-3), 4.34 (d, *J*=2.3 Hz, 1H, H-4), 1.52 (s, 3H, methyl), 1.47 (s, 3H, methyl), 1.40 (s, 3H, methyl), 1.33 (s, 3H, methyl); HRMS (FAB, M^+) calcd for $C_{12}H_{18}O_5$: 242.1154; found: 242.1152. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (d, *J*=3.6 Hz, 1H, H-1), 4.66 (ddd, *J*=48.2, 9.8, 4.2 Hz, 1H, H-6), 4.55 (ddd, *J*=48.2, 7.0, 4.2 Hz, 1H, H-6), 4.50 (d, *J*=3.6 Hz, 1H, H-2), 4.37–4.30 (m, 2H, H-3, H-5), 3.96 (t, *J*=2.0 Hz, 1H, H-4), 1.45 (s, 3H, methyl), 1.44 (s, 3H, methyl), 1.39 (s, 3H, methyl), 1.29 (s, 3H, methyl); anal. calcd for $C_{12}H_{20}O_5F$: C, 54.96; H, 7.25; found: C, 54.89; H, 7.36. Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, *J*=3.6 Hz, 1H, H-1), 4.49 (d, *J*=3.6 Hz, 1H, H-2), 4.31 (d, *J*=2.2 Hz, 1H, H-3), 4.14 (ddd, *J*=8.1, 4.5, 2.2, Hz, 1H, H-5), 3.92 (t, *J*=2.2 Hz, 1H, H-4), 3.58 (dd, *J*=12.8, 8.1 Hz, 1H, H-6), 3.36 (dd, *J*=12.8, 4.5 Hz, 1H, H-6), 1.48 (s, 3H, methyl), 1.45 (s, 3H, methyl), 1.40 (s, 3H, methyl), 1.31 (s, 3H, methyl); HRMS (FAB, MH^+) calcd for $C_{12}H_{20}O_5N_3$: 286.1402; found: 286.1405. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J*=3.6 Hz, 1H, H-1), 4.43 (d, *J*=3.6 Hz, 1H, H-2), 4.12 (d, *J*=1.5 Hz, 1H, H-3), 4.07 (dq, *J*=6.5, 1.5, Hz, 1H, H-5), 3.78 (t, *J*=1.5 Hz, 1H, H-4), 1.42 (s, 3H, methyl), 1.37 (s, 3H, methyl), 1.32 (s, 3H, methyl), 1.27 (d, *J*=6.5 Hz, 3H, methyl), 1.25 (s, 3H, methyl); HRMS (FAB, MH^+) calcd for $C_{12}H_{21}O_5$: 245.1388; found: 245.1381.
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15. The deposited number at the Cambridge Crystallographic Data Centre is CCDC 133558.