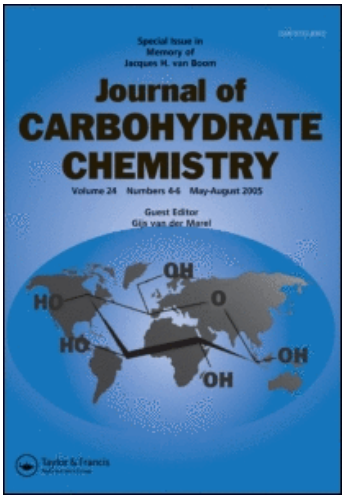

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A Novel Strategy for 2,6-Dideoxy-L-Hexoses: An Application to 3-Amino-2,3,6-Trideoxy-L-Lyxo-Hexopyranose (L-Daunosamine)

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A NOVEL STRATEGY FOR 2,6-DIDEOXY-L-HEXOSES : AN APPLICATION TO 3-AMINO-2,3,6-TRIDEOXY-L-LYXO-HEXOPYRANOSE (L-DAUNOSAMINE)

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ABSTRACT

A synthetic strategy wherein C-1/6 of D-glucose are transformed into C-6/1 of L-daunosamine, circumventing the critical step of epimerisation of the C-5 center is described.

INTRODUCTION

There is a great deal of interest in 3-amino-2,3,6-trideoxy-L-hexoses as they form the sugar components of several biologically active antibiotics.[1] Among various isomers of 3-amino-2,3,6-trideoxyhexoses, perhaps L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose, **1**) has been most widely studied from a synthetic point of view.[2,3] The first synthesis of **1** was developed by Goodman and coworkers[4] starting from L-rhamnose. L-Rhamnose is a logical precursor for **1** due to its L-configuration. However, its high cost prompted others to utilise cheap and easily accessible D-hexoses for this task.[5] In dealing with the synthesis of **1** from D-hexoses, one of the critical steps of the synthesis was the epimerisation at C-5 to achieve the desired L-configuration.[6]

It is noted that in almost all the syntheses of **1**, C-1/6 of the starting precursor are transformed into C-1/6 of L-daunosamine (**1**). However, it appeared[7] to us that if C-1/6 of D-glucose (**2**) are transformed into C-6/1

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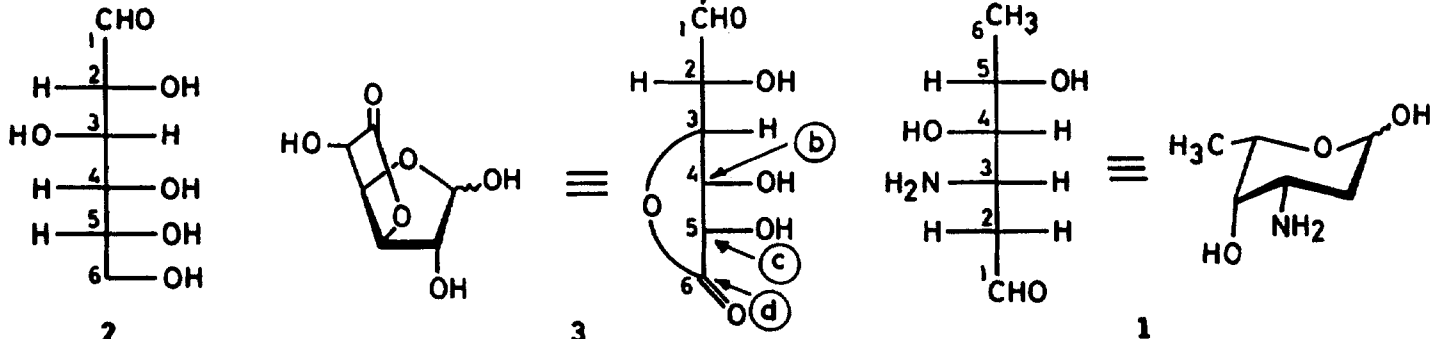


2
D-GLUCOSE

3
D-GLUCURONO-6,3-LACTONE

1
L-DAUNOSAMINE

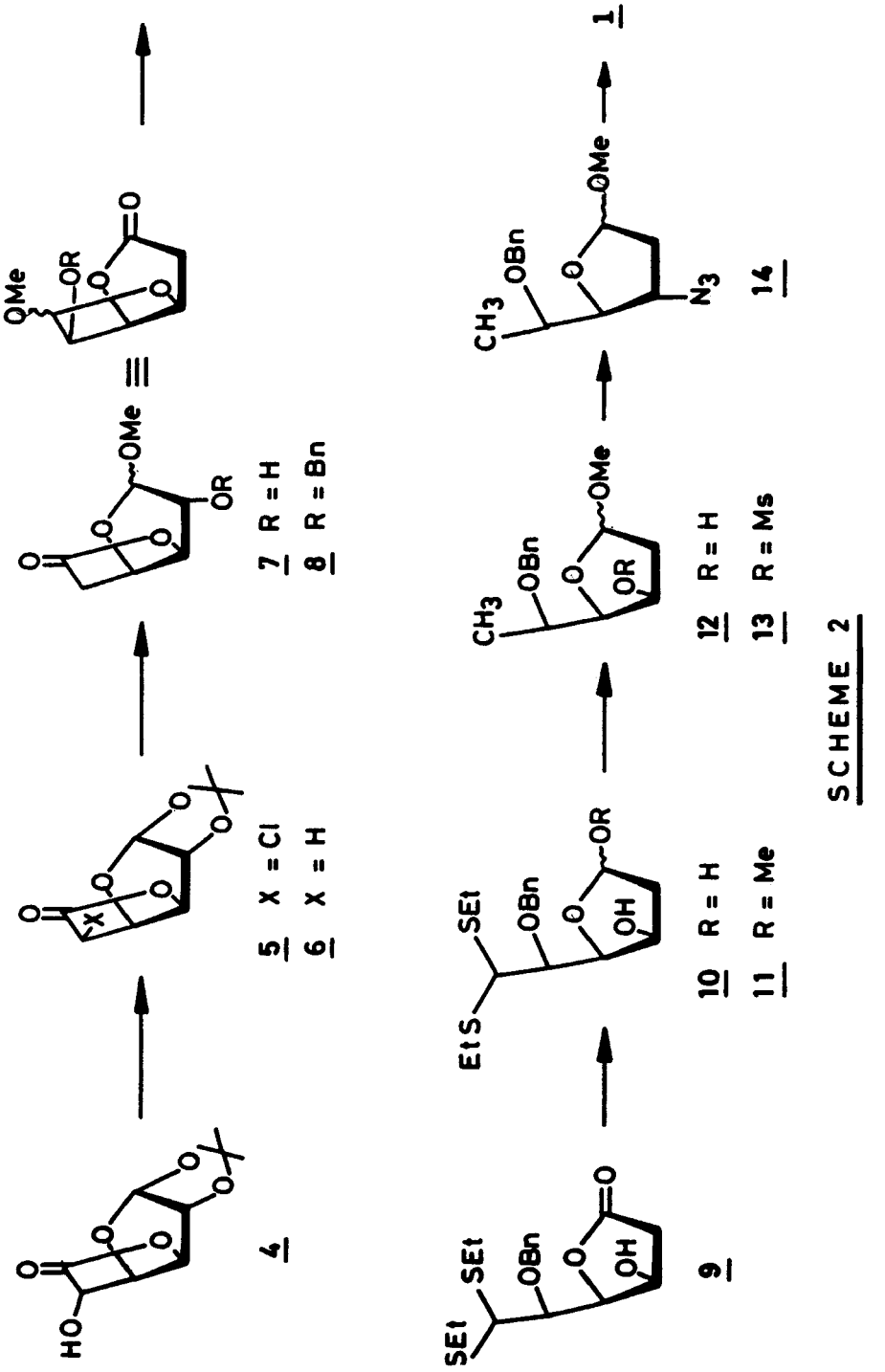
ⓐ CHO ⟶ CH_3

ⓑ OH ⟶ NH_2

ⓒ OH ⟶ H

ⓓ COOR ⟶ CHO

SCHEME 1



SCHEME 2

of 1, then the critical step of epimerisation at C-5 could be curtailed because in this case the stereochemistry at C-2 in 2 would correlate with C-5 in 1 (Scheme 1). With this view in mind, we designed the synthesis of 1 from the commercially available D-glucurono-6,3-lactone (3). The operational viability of this approach would be realised by the successful completion of the four major operations a to d shown in Scheme 1.

RESULTS AND DISCUSSION

The known[8] 1,2-acetonide derivative 4 was treated[9] with a mixture of sulfuryl chloride-pyridine-chloroform to afford the 5-chloro-5-deoxy product 5 (Scheme 2). Reductive dechlorination[10] of 5 with freshly prepared tri-n-butyltin hydride in refluxing toluene containing a catalytic amount α,α'-azobisisobutyronitrile (AIBN) for 8 h gave the 5-deoxy compound[11] 6 in 86% yield. The ^{1}H NMR spectrum of 6 revealed the characteristic multiplet in the upfield region of δ 2.7 for H-5,5'.

Compound 6 and Amberlite IR 120 (H) resin in dry methanol were heated under reflux for 3 h to give a mixture of the α- and β-glycosides 7 in 98% yield. The free hydroxyl group of 7 at C-2 was protected as a benzyl ether by using benzyl bromide-silver oxide in benzene at room temperature to give 8 in 80% yield. The characteristic signals due to benzylic protons were clearly visible in the ^{1}H NMR spectrum of 8.

Treatment of 8 with ethanethiol in concentrated hydrochloric acid at room temperature for 18 h gave the corresponding diethyl dithioacetal derivative 9 whose structure was proved on the basis of its ^{1}H NMR spectrum. Reduction of 9 with DIBAL-H in methylene chloride at -78 °C for 1 h afforded the hemiacetal 10 which subsequently was transformed into methyl (α,β)-glycosides 11 in the presence of Amberlite resin and dry methanol in 35% yield.

The reductive desulfurisation of 11 was effected with freshly prepared W2 Raney nickel in ethanol at room temperature for 48 h to afford 12. In the ^{1}H NMR spectrum of 12, the characteristic signals due to H-6,6',6" were located at δ 1.24. Subsequent mesylation of 12 with methanesulfonyl chloride-pyridine then gave 13 whose ^{1}H NMR spectrum showed the singlet due to mesyl group at δ 3.00. Nucleophilic displacement reaction of 13 with sodium azide in N,N'-dimethylformamide at 120 °C afforded the azido-derivative 14 in 93% yield. The structure of 14 was confirmed by ^{1}H NMR,

IR and MS studies. Since compound **14** had already been converted[12] into **1**, this route constitutes a novel total synthesis of **1** with an overall yield of 1.9% based on **3**.

EXPERIMENTAL

General Procedures. Melting points were determined with a Kofler Hot plate melting point apparatus and are uncorrected. Optical rotations were determined with JASCO DIP 360 polarimeter. ^{1}H NMR spectra were obtained using a Varian FT-80A spectrometer. IR spectra were scanned with a Perkin Elmer 683 spectrometer. Mass spectra were obtained using a Finnigan Mat 1210 operating at 70 eV and employing the direct inlet system. All the evaporations were carried out below 40 °C *in vacuo*. Light petroleum refers to the fraction bp 60-80 °C. Silica gel was purchased from Acme Chemical Company.

5-Deoxy-1,2-O-isopropylidene-α-D- *xylo* -hexofuranurono-6,3-lactone (6). A solution of **5** (7.0 g, 29.85 mmol), AIBN (5 mg) in toluene was heated under reflux in nitrogen atmosphere. Freshly prepared trin-n-butyltin hydride (10 mL) was introduced. After 8 h, the reaction mixture was concentrated and partitioned between acetonitrile and light petroleum. The acetonitrile layer was concentrated and the solid residue was crystallised from ether-light petroleum to afford **6** (5.1 g, 86%); mp 98-99 °C; $[\alpha]_D$ + 98° (c 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.33, 1.49 (2s, 6H, Me_2C), 2.73 (m, 2H, H-5,5'), 4.82 (d, 1H, $J_{3,4}$= 3 Hz, H-3), 4.84 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-2), 5.0 (m, 1H, H-4), 6.00 (d, 1H,H-1).

Anal. Calcd for $C_9H_{12}O_5$: C, 54.0; H, 6.00. Found : C, 54.25; H, 6.03.

Methyl 2-O-Benzyl-5-deoxy-α,β -D- *xylo* -hexofuranosidurono-6,3-lactone (8). Compound **6** (4.0 g, 20 mmol) and Amberlite IR 120 (H^+) resin (2 g) in dry methanol (20 mL) were heated under reflux for 2 h, filtered and concentrated to give **7** (3.4 g, 98%).

To **7** (3.0 g, 17.24 mmol) and silver oxide (8 g) in dry benzene (30 mL) was added benzyl bromide (3 mL) at 0 °C. After stirring at room temperature overnight in the dark, the reaction mixture was filtered through Celite, washed with benzene and concentrated. The residue (3.6 g, 80%) was chromatographed on a silica gel column with ethyl acetate-light petroleum (1:4) to give the pure β-glycoside **8** (0.15 g), $[\alpha]_D$ + 4.3° (c 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.62 (m, 2H, H-5,5'), 3.37 (s, 3H, OMe), 4.12 (s, 1H, H-1), 4.56 (s, 2H, $PhC\underline{H}_2$), 7.31 (s, 5H, Ph).

The major fraction isolated from the column was a mixture of the α- and β-glucosides **8** (3.3 g, 72%).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.1. Found : C, 63.19; H, 6.0.

5-O-Benzyl-2-deoxy-L-*xylo*-furanurono-1,4-lactone-6,6'-diethyl dithioacetal (9). Compound **8** (2.0 g, 7.57 mmol), ethanethiol (4.2 mL) and concentrated hydrochloric acid (6 mL) were stirred at room temperature for 18 h. The reaction mixture was neutralised with sodium carbonate and extracted with chloroform. The chloroform layer was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate-light petroleum (1:3) as eluent to afford **9** (2.0 g, 74%), $[\alpha]_D$ + 43.2° (c 0.9, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.2-1.5 (m, 6H, 2xSCH$_2$C$\underline{H}_3$), 2.43 (bs, 1H, OH), 2.5-2.8 (m, 6H, 2xSC$\underline{H}_2$CH$_3$ + H-2,2'), 7.3 (m, 5H, Ph).

Ana. Calcd for $C_{17}H_{24}O_4S_2$: C, 57.3; H, 6.74. Found : C, 57.86; H, 6.84.

Methyl 5-O-Benzyl-2-deoxy-α,β-L-*xylo*-hexodialdo-1,4-furanoside 6-(diethyl-dithioacetal) (11). A solution of **9** (1.5 g, 4.21 mmol) in dry methylene chloride (15 mL) was cooled to -78 °C. DIBAL-H solution in toluene (21%, 7 mL) was added and the reaction mixture stirred for 1 h at -78 °C. After usual work-up, the crude hemiacetal **10** (0.8 g) was heated under reflux in the presence of dry methanol (20 mL) and Amberlite resin (2 g) for 2 h, filtered and concentrated. The residue was purified by column chromatography on a silica gel column with ethyl acetate-light petroleum (1:4) to give **11** (0.55 g, 35%); ^{1}H NMR ($CDCl_3$) δ 1.2 (m, 6H, 2xSCH$_2$C$\underline{H}_3$), 2.1 (m, 2H, H-2,2'), 2.7 (m, 4H, 2xSC$\underline{H}_2$CH$_3$), 3.25 and 3.27 (2s 3H, α-OMe and β-OMe), 7.3 (m, 5H, Ph).

Anal. Calcd for $C_{18}H_{28}O_4S_2$: C, 58.06; H, 7.52. Found : C, 58.48; H, 7.74.

Methyl 5-O-Benzyl-2,6-dideoxy-3-O-mesyl-α,β-L-*xylo*-hexofuranoside (13). A mixture of **11** (0.5 g, 1.34 mmol), W-2 Raney nickel (3.2 g) in ethanol (10 mL) was vigorously stirred at room temperature for 48 h, filtered and concentrated to give **12** (0.20 g, 59%); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, H-6,6',6''), 2.00 (m, 2H, H-2,2'), 3.31 (bs, 3H, OMe), 7.3 (m, 5H, Ph); MS m/z 251 (M^+ -1), 220 (M^+ -MeOH), 205 (M^+ -MeOH-Me).

Compound **12** (0.12 g, 0.47 mmol) in pyridine (1 mL) at 0 °C was treated with mesyl chloride (0.6 mL) at room temperature for 4 h, followed by work-up and the residue purified by column chromatography on silica gel with ethyl acetate-light petroleum (1:4) to give **13** (0.12 g, 76%); ^{1}H

NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 6 Hz, H-6,6',6"), 3.00 (s, 3H, CH_3SO_2), 3.37 (s, 3H, OMe), 4.68 (ABq, 2H, $PhC\underline{H}_2$), 5.25 (bs, 1H, H-1), 7.3 (m, 5H, Ph).

Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.66. Found : C, 54.3; H, 6.67.

Methyl 3-Azido-5-O-benzyl-2,3,6-trideoxy-α,β-L-lyxo-hexofuranoside (14). Compound **13** (126 mg, 0.38 mmol) and sodium azide (300 mg) in DMF (3 mL) were heated at 120 °C with stirring for 30 min. The reaction mixture was diluted with water, extracted with ethyl acetate, dried and concentrated. The residue was chromatographed on a silica gel column by using ethyl acetate-light petroleum (1:4) to give **14** (98 mg, 93%); IR (Neat) 2100 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 6 Hz, H-6,6',6"), 2.0-2.8 (m, 2H, H-2,2'), 3.37 (s, 3H, OMe), 4.59 (ABq, 2H, $PhC\underline{H}_2$), 5.0 (m, 1H, H-1), 7.31 (s, 5H, Ph); MS m/z 245 (M^+ -MeOH).

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