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A FACILE SYNTHESIS OF NOJIRIMYCIN

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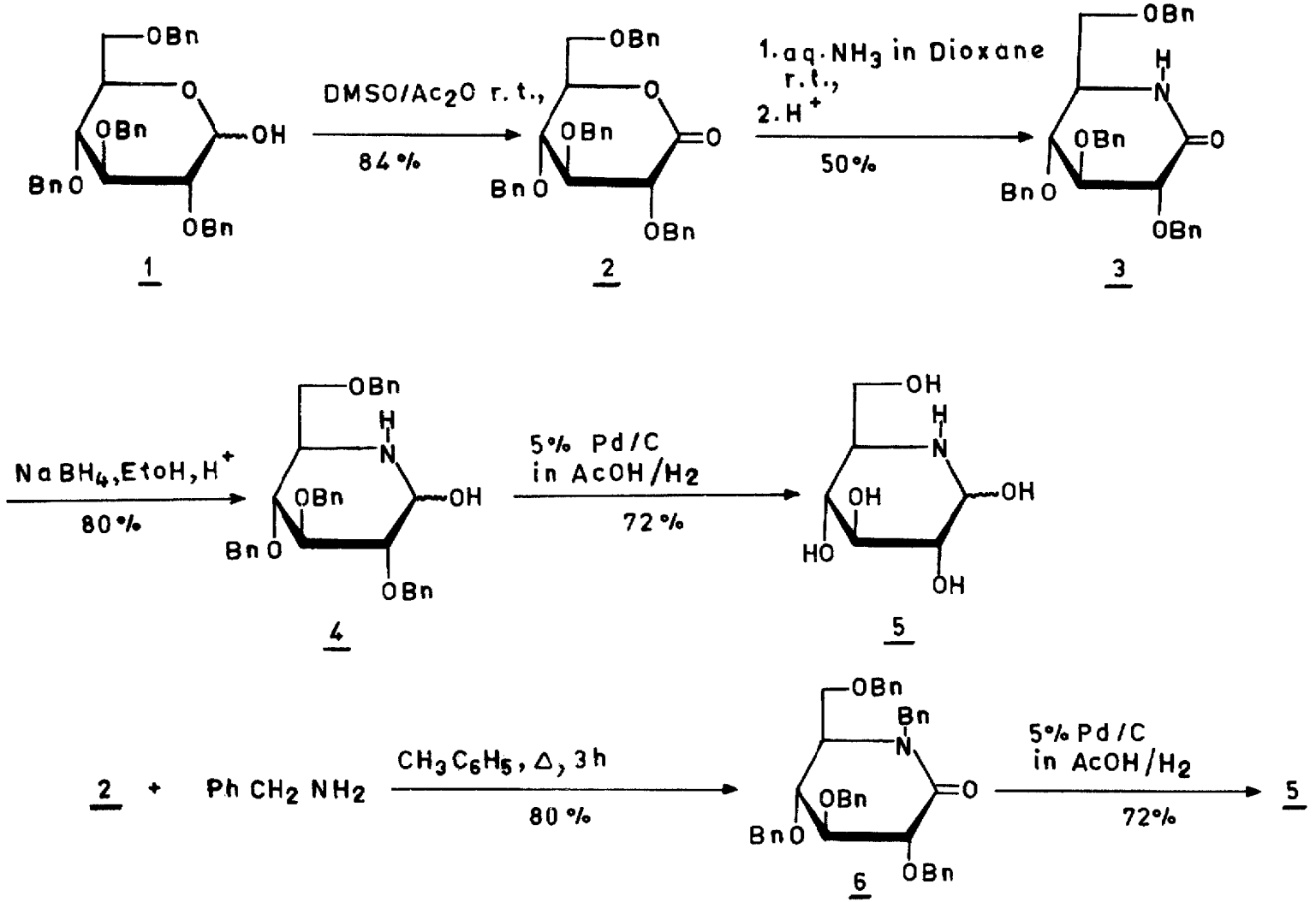
SUMMARY: Expeditious new synthesis of the title compound 5 in high yield from δ-gluconolactone 2 via intermediates 4 and 6 has been described.

Sugar lactones are inexpensive and readily available chiral starting materials for divergent synthesis of polyfunctionalised amino acids[1,2]. Interest continues to grow in several synthetic[3] and naturally[4] occurring 5-deoxy-and 1,5-dideoxy-5-iminohexitol analogues, which have been shown to be potent glycosidase inhibitors since they resemble aza sugars having a basic nitrogen in place of pyranose oxygen[5]. The inhibition of specific intestinal glycosidases by such compounds represents a promising approach to the treatment of carbohydrate-dependent metabolic disorders[6]. Recently, it has been reported that nitrogen analogues of sugars have potent biopesticidal activity[7] and antiviral activity against AIDS[8]. Nojirimycin, first isolated from Streptomyces species[3a)], has been shown to be an inhibitor of several glucosidases[9].

Several methods reported so far for the synthesis of cyclic iminoalditols employ conversion of unsubstituted C-2(OH) or C-5(OH) sugar lactones. For example, replacement of C-2(OH) group in ribonolactone[10] and C-5(OH) group in D-gluconolactone[11] by azide with inversion of configuration would give an iodoazide, a potential precursor for the synthesis of polyhydroxylated D and L amino acids, has been reported. Recently, polyhydroxylated pyrolidines were prepared by cyclisation of dimesylate derivatives of reduced sugar lactones with benzylamine and subsequent hydrogenolysis[12]. In view of the renewed interest and demand for these cyclic iminoalditols, we wish to report here a new synthesis of 5-imino-5-deoxy glucose from δ-gluconolactone having the same relative absolute configuration. Novel feature of this method is the conversion of 2 via sugar lactams 4 and 6 into 5 without inversion of configuration (see scheme).

2,3,4,6-tetra-O-benzyl-α-D-glucopyranose 1 was prepared in 70% overall yield from methyl-α-D-glucopyranoside mp. 151°-152°C, $[\alpha]_D^{25}$+22° (C 1, $CHCl_3$) after some improvements to the procedure of Glaudemans et al.[13] Anomeric oxidation of 1 (3.7 g, 6.8 mmol) at room temperature in DMSO (21 ml, 300 mmol) and acetic anhydride (14 ml, 150 mmol) yielded 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone[14] 2 $[\alpha]_D^{25}$+79° (C 1, $CHCl_3$), 3.1 g, 84%. The syrupy compound 2 showed δ-lactone C=O at 1750 cm^{-1} but no absorption due to OH. Condensation of 2 (2.7 g, 5 mmol) with liq. ammonia[15] (12.5 ml, 25% w/w)


OBn
OBn
OBn
BnO
OH
1
DMSO/Ac2O r.t.,
84%
2
1. aq. NH3 in Dioxane
r.t.,
2. H+
50%
3
NaBH4, EtOH, H+
80%
4
5% Pd/C
in AcOH/H2
72%
5
OH
HO
2 + Ph CH2 NH2
CH3C6H5, Δ, 3h
80%
Bn
6
5% Pd/C
in AcOH/H2
72%
5

Scheme

solution in presence of trace amounts of Amberlite IR 120 H^+ in dioxane (50 ml) at 25°C for 6 h yielded corresponding δ-gluconolactam 3 $[\alpha]_D^{25}$+65° (C 1, $CHCl_3$), 1.30 g, 50%. The syrupy lactam 3 after purification by silica gel column chromatography showed characteristic amide C=O at 1680 cm^{-1} and NH stretching at 3460 cm^{-1}. Reduction of 3 (2.6 g, 5 mmol) with excess $NaBH_4$ in ethanol (25 ml), maintaining pH of the reaction medium[16] at 8-9 by the addition of 2N HCl gave 2,3,4,6-tetra-O-benzyl-5-imino-5-deoxy-glucopyranose 4 mp. 128°-130°C, $[\alpha]_D^{25}$+22° (C 1, $CHCl_3$), 2.2 g, 80%. Compound 4 showed weak NH stretching at 3400 cm^{-1} and disappearance of amide carbonyl. Hydrogenolysis[17] of 4 (1.0 g, 2 mmol) using 5% Pd/C (100 mg) in AcOH (25 ml) followed by purification on ion-exchange column yielded pure 5, mp. 130°C, $[\alpha]_D^{25}$+100° (C 1, H_2O undergoes mutarotation), 260 mg, 72%. Compound 5, thus obtained, was identical with the authentic nojirimycin[3a], on TLC and IR.

Yield of the intermediate 3 can be enhanced by condensing with various primary amines[18]. Condensation of 2 (2.7 g, 5 mmol) with benzylamine (0.5 g, 5 mmol) in refluxing toluene for 3 h in presence of molecular sieves 4 A and catalytic amounts of Amberlite IR 120 H^+, yielded 6[19] mp. 62°-64°C, $[\alpha]_D^{25}$+14° (C 1, $CHCl_3$), 2.5 g, 80%. Compound 6 showed characteristic amide carbonyl at 1650 cm^{-1}. Compound 6 (1.25 g, 2 mmol) was then deprotected to highly pure 5 260 mg, 72% straightaway by rigorous hydrogenolysis using 5% Pd/C in AcOH for 38 h. Thus, compound 6 will serve as an important potential intermediate for the synthesis of 5 in high yields.

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19. Compound (2): Found: C, 75.85; H, 6.50. Calc. for $C_{34}H_{34}O_6$ (538.64): C, 75.81; H, 6.31. IR (neat) cm^{-1}; 1750 (CO). ^{1}H-NMR ($CDCl_3$) δ :5.00-3.60 (m,14H,H-2,H-3,H-4,H-5,H-6 and Ar$\underline{CH_2}$), 7.50-7.40 (br,s,20H,Ar). Compound (3): Found: C, 76.23; H, 6.77; N, 2.59. Calc. for $C_{34}H_{35}O_5N$ (537.0): C, 75.97; H, 6.51; N, 2.60. IR (neat) cm^{-1}: 3320 (NH), 1675 (CO). ^{1}H-NMR δ :4.90-3.50 (m,15H,H-2,H-3,H-4,H-5,H-6, NH and Ar$\underline{CH_2}$), 7.40-7.30 (br,s,20H,Ar). Compound (4): Found: C, 75.69; H, 6.86; N, 2.59. Calc. for $C_{34}H_{37}O_5N$ (539.0): C, 75.69; H, 6.86; N, 2.59. IR (KBr) cm^{-1}: 3400-3360 (OH, NH), 1600 (NH). ^{1}H-NMR δ ;5.00-3.60 (m,16H,H-2,H-3,H-4,H-5,H-6, OH, NH and Ar$\underline{CH_2}$), 5.30 (d,1H,$J_{1,2}$=3.0Hz), 7.50 (br,s,20H,Ar). Compound (5): Found: C, 40.38; H, 7.71; N, 7.75 Calc. for $C_6H_{12}O_5N$ (179.0): C, 40.22; H, 7.26; N, 7.82. IR (Nujol) cm^{-1}; 3360 (OH), 3120 (NH), 1595 (NH). ^{1}H-NMR (DMSO-d_6) δ :3.66-3.40 (m,3H,H-5,H-6 and H-6'), 3.70-3.50 (m,3H,H-2,H-3 and H-4), 4.70 (br,s,5H, OH), 5.20 (d,1H, $J_{1,2}$=3.0Hz). Compound (6): Found: C, 75.58; H, 6.77; N, 2.27. Calc. for $C_{41}H_{41}O_5N$ (627.0); C, 78.46; H, 6.53; N, 2.23. IR (KBr) cm^{-1}: 1650 (CO). ^{1}H-NMR δ :4.90-3.70 (m,16H,H-2,H-3,H-4,H-5,H-6, ArN$\underline{CH_2}$ and Ar$\underline{CH_2}$), 7.50 (m,br, 25H, Ar).
20. The material covered in this communication is the subject of Indian Patent Applications (No.534/DEL/'88; dated 21st June 1988) filed by the CSIR, New Delhi, India.

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