Pergamon

Tetrahedron Letters 42 (2001) 1139–1142

TETRAHEDRON LETTERS

Concise synthesis of 1-deoxy-4-*O*-β-D-galactopyranosyl-D-nojirimycin avoiding a glycosylation step[†,‡]

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Received 5 October 2000; revised 13 November 2000; accepted 22 November 2000

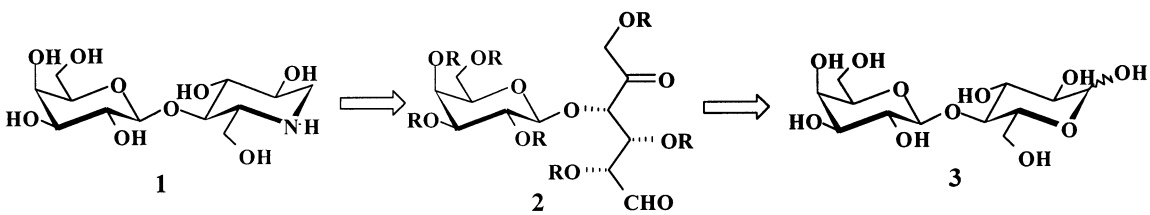
Abstract—2′,6′-Di-*O*-benzyl-2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal was used as starting material for the preparation of the until now unknown 4-*O*-β-D-galactopyranosyl-D-*xylo*-hexos-5-ulose derivatives **7**–**9**, through selective C-5 oxidation of its partially deprotected derivatives **4**–**6**. Hydrolysis of **7**–**9** with aq. CF_3COOH led to deprotected 1,5-dicarbonyl disaccharides **11**–**12**, diastereoselectively transformed without purification into 1-deoxy-4-*O*-β-D-galactopyranosyl-D-nojirimycin derivatives in about 60% yield, through a double reductive amination reaction.

The class of compounds known as iminosugars or azasugars, in which the ring oxygen atom of a sugar is replaced by NH, has proven to include potent inhibitors of glycosidases and glycoprotein-processing enzymes[2] which are intensely investigated for their therapeutic potentiality as antiviral, anti-HIV, antidiabetic, and anticancer agents.[3] 1-Deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol; DNJ) is a powerful inhibitor of α-glucosidases and several of its derivatives have been synthesized and tested for their biological properties.[3]

Some glycosylated DNJ derivatives were isolated from natural products[4,5] or synthesized[6,7] and their effect on various glycosidases has been investigated.[4,7] For instance 4-*O*-α-D-glucopyranosyl-DNJ was shown to have hypoglycemic activity[8] owing to its potent inhibitory activity for sucrase and 2-*O*-α-D-glucopyranosyl-DNJ is more efficient than DNJ against trehalases.[7] Furthermore some sialyl Lewis^x-type analogues containing a DNJ unit have been proposed recently as anti-inflammatory agents because they are recognized by the selectines, receptors involved in leukocyte adhesion and migration processes.[9,10]

We present in this communication an easy and diastereoselective approach to 1-deoxy-4-*O*-β-D-galactopyranosyl-D-nojirimycin (**1**) so far prepared only through enzymatic or chemical glycosylation.[6,10]

The rationale of our synthetic procedure starting from lactose **3** is depicted in Scheme 1 and requires, as the



Scheme 1.

Keywords: 1-deoxy-4-β-D-galactopyranosyl-D-nojirimycin; aminocyclization; β-D-galactopyranosyl-D-*xylo*-hexos-5-uloses; lactose.

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† Dedicated to Prof. Pierre Sinaÿ on the occasion of his 62nd birthday.

‡ Part 13 of the series, 'Rare and Complex Saccharides from D-Galactose and other Milk-derived Carbohydates'; for Part 12, see Ref. 1.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02165-1

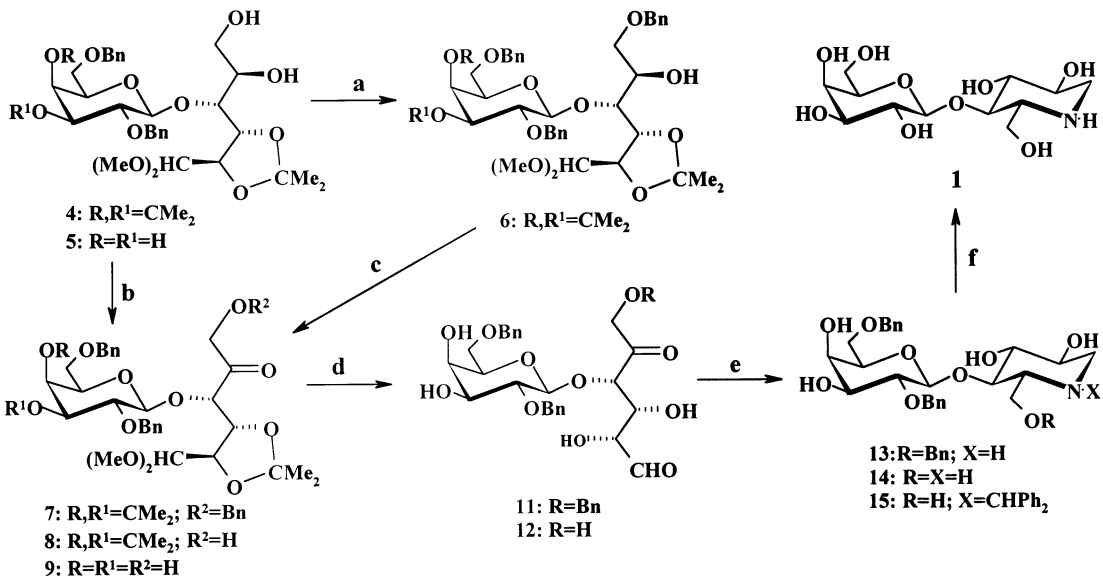
key steps, a double reductive amination of the so far unknown 4-*O*-β-D-galactopyranosyl-D-*xylo*-hexos-5-ulose derivatives, such as **2**.

The starting compounds for our synthesis were the diol **4** and tetraol **5**, readily obtained from lactose (**3**) through a previously described procedure.[11] The selective C-5 oxidation of **4** and **5** was achieved on their *O*-dibutylstannylidene derivatives (Scheme 2) through treatment with dibutyltin oxide (1.05 equiv.) in refluxing toluene and, after a change of the solvent from toluene to chloroform, a direct oxidation with NBS (1.05 equiv.; rt; 1 h). After evaporation of the solvent, flash chromatography of the residue led to the pure uloses **8** (98% yield) and **9** (88% yield). Very interesting and useful is, in the case of tetraol **5**, the high regioselectivity of the oxidation at position 5, only one by-product (~10% yield)[12] derived by oxidation on the D-galacto unit being formed.

The 6-*O*-benzyl ether **7** was obtained from **4** (88% yield) through regiospecific benzylation (BnBr, Bu_4NBr) of the 5,6-stannylidene acetal followed by oxidation of **6** with 4-methylmorpholin-*N*-oxide in the presence of catalytic amounts of tetrapropylammonium perruthenate. In each case, the 5-keto derivatives **7–9** were characterized, and their analytical[13] and NMR data[14] were in agreement with the proposed structures.

The complete removal of the acetal groups of **7–9** was easily achieved with 90% aqueous trifluoroacetic acid, to give the 1,5-dicarbonyl disaccharides **11** and **12** as crude materials complicated by complex mixtures of tautomeric forms. Although the NMR spectra of these 1,5-dicarbonyl disaccharides were not interpreted, their structures were firmly proven by subsequent reactions. The crude products containing **11** and **12** were subjected to a double reductive amination under conditions analogous to those previously reported for the monosaccharide series[15] [$NaBH_3CN$ (2.2 equiv.), NH_4OAc (10 equiv.)/MeOH, 60°C, 2–3 h] giving the corresponding azadisaccharides **13** and **14** in acceptable yields (55–60% based on the uloses **7–9**). The extension of the reaction to a hindered primary amine, i.e. benzhydrylamine, similarly gave pure **15** (54% yield) from **9**. The structures of **13–15** were assigned on the basis of the corresponding analytical[16] and NMR data.[17] The most significant ^1H NMR data were those of the H-1ax and H-1eq protons well characteristic of the DNJ unit located, for example in the case of **15**, at δ 1.95 (dd, $J_{1ax,1eq}=11.2$, $J_{1ax,2}=10.6$ Hz) and at δ 3.07 (dd, $J_{1eq,2}=4.4$ Hz). Finally the 1-deoxy-4-*O*-β-D-galactopyranosyl-D-nojirimycin (**1**) was obtained in nearly quantitative yields by hydrogenolysis of **13–14** over 10% palladium on charcoal (500 mg/mmol) in methanol (20 ml/mmol) under acidic conditions (HCl 1.3 M, 8 ml/mmol). The physico-chemical properties of **1**[18] were identical to those reported.[6]

The complete stereoselectivity of the aminocyclization reaction we have found can be ascribed, as previously suggested,[15] to the hydride attack step on the cyclic iminium ion intermediate, formed after the first amination reaction of the more reactive aldehydic group. An intramolecular hydride transfer from the reducing agent bonded to a free hydroxyl group (OH-4 and/or OH-6) was tentatively proposed as an explanation for the high diastereoselectivity observed with completely[15a] or partially[15b] deprotected D-*xylo*-hexos-5-ulose derivatives. This hypothesis is, however, ruled out by the present findings on the OH-4 and OH-6 protected derivative **11**. An alternative explanation could be based on stereoelectronic[19] and conformational factors providing an axial hydride attack on the more stable (all equatorial) conformer of the cyclic iminium ion intermediate, but a confirmation of this hypothesis requires further studies on appropriately designed derivatives.



Scheme 2. **a:** (1) Bu_2SnO, $PhCH_3$, reflux, 12 h; (2) BnBr, Bu_4NBr, $CHCl_3$, rt, 30 min; **b:** (1) Bu_2SnO, $PhCH_3$, reflux, 12 h; (2) NBS, $CHCl_3$, rt, 1 h; **c**: TPAP (7%)/NMO, CH_2Cl_2, 30 min; **d**: 90% aq. CF_3COOH, rt, 20 min; **e:** X-$NH_3^+AcO^-$, $NaBH_3CN$, MeOH, 60°C, 2 h; **f:** H_2, Pd/C (10%), MeOH–HCl.

In conclusion, our synthetic approach offers a simple method for preparing azadisaccharides avoiding a glycosylation step, in a highly stereoselective way and with acceptable chemical yields. We are now planning to extend this synthetic scheme to other 4-*O*-β-D-galactopyranosyl-D-*xylo*-hexos-5-uloses differently protected in order to examine the stereoselectivity of the aminocyclization reaction and to use our galactosylated DNJ derivatives as starting materials for the synthesis of biologically active complex glycan analogues.

Acknowledgements

Financial support from Università di Pisa and Ministero della Ricerca Scientifica e Tecnologica (MURST, Roma) is gratefully acknowledged.

References

1. Pistarà, V.; Barili, P. L; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett*. **2000**, *41*, 3253–3256.
2. Reviews: (a) Sinnott, M. L. *Chem. Rev*. **1990**, 1171–1202; (b) Legler, G. *Adv. Carbohydr. Chem. Biochem*. **1990**, *48*, 318–384.
3. Reviews: (a) Robinson, K. M.; Rhinehart, B. L.; Ducep, J.-B.; Danzin, C. *Drugs Fut*. **1992**, *17*, 705–720; (b) Hughes, A. B.; Rudge, A. J. *J. Nat. Prod. Rep*. **1994**, 135–162.
4. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res*. **1994**, *259*, 243–255.
5. Asano, N.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res*. **1994**, *253*, 235–245.
6. Kojima, M.; Seto, T.; Kyotani, Y.; Ogawa, H.; Kitazawa, S.; Mori, K.; Maruo, S.; Ohgi, T.; Ezure, Y. *Biosci. Biotech. Biochem*. **1996**, *60*, 694–696.
7. Asano, N.; Oseki, K.; Kaneko, E.; Matsui, K. *Carbohydr. Res*. **1994**, *258*, 255–266.
8. Yoshikuni, Y.; Ezure, Y.; Seto, T.; Mori, K.; Watanabe, M.; Enomoto, H. *Chem. Pharm. Bull*. **1989**, *37*, 106–109.
9. Ogawa, H.; Harada, Y.; Kyotani, Y.; Ueda, T.; Kitazawa, S.; Kandori, K.; Seto, T.; Ishiyama, K.; Kojima, M.; Ohgi, T.; Ezure, Y.; Kise, M. *J. Carbohydr. Chem*. **1998**, *17*, 729–738.
10. Kiso, M.; Katagiri, H.; Furui, H.; Hasegawa, A. *J. Carbohydr. Chem*. **1992**, *11*, 627–644.
11. Catelani, G.; D'Andrea, F.; Puccioni, L. *Carbohydr. Res*. **2000**, *324*, 204–209.
12. Selected ^{13}C NMR data: δ_C ($CDCl_3$, 50 MHz): 67.87 and 68.59 (C-6 and C-6′); 75.85, 76.76, 78.43, 79.17, 81.69, 84.37 (6 pyranosic CH); 101.41 (C-1′); 105.68 (C-1); 201.99 and 210.77 (C-5 and C-4′ or C-3′).
13. Compound **7**. Syrup, (Found: C, 66.95; H, 7.22; $C_{41}H_{52}O_{12}$ requires: C, 66.83; H, 7.11); R_f 0.53 (1:1 hexane/EtOAc); $[\alpha]_D$ −19.9 (*c* 0.95, $CHCl_3$). Compound **8**. Syrup, (Found: C, 62.78; H, 7.21; $C_{34}H_{46}O_{12}$ requires: C, 63.14; H, 7.17); R_f 0.56 (2:8 hexane/EtOAc); $[\alpha]_D$ −17.7 (*c* 1.36, $CHCl_3$). Compound **9**. Solid foam, (found: C, 60.79; H, 6.70; $C_{31}H_{42}O_{12}$ requires: C, 61.37; H, 6.98); R_f 0.45 (1:9 hexane/EtOAc); mp 110–116°C; $[\alpha]_D$ −38.1 (*c* 0.94, $CHCl_3$).
14. The NMR characterization was made directly on **7**–**9** and/or on their peracetylated derivatives. As an example, the NMR data for the tri-*O*-acetyl derivative of **9** are reported: δ_H (CD_3CN, 200 MHz): 1.36 and 1.48 (2 s, each 3 H, $C(CH_3)_2$), 1.88, 2.02 and 2.05 (3 s, each 3 H, 3 x CH_3CO), 3.33 and 3.34 (2 s, each 3 H, 2 x OCH_3), 3.42 (ddd, 1 H, $J_{6'a,6'b}=9.67$ Hz, $J_{5',6'a}=7.26$ Hz, $J_{5',6'b}=5.75$ Hz, H-6′b), 3.56 (dd, 1 H, H-6′a), 3.71 (dd, 1 H, $J_{1',2'}=7.79$ Hz, $J_{2',3'}=10.10$ Hz, H-2′), 3.91 (ddd, 1 H, $J_{4',5'}=1.20$ Hz, H-5′), 4.20 (dd, 1 H, $J_{3,4}=1.78$ Hz, H-3), 4.29 (dd, 1 H, $J_{2,3}=7.06$ Hz, H-2), 4.39 (d, 1 H, $J_{1,2}=5.87$ Hz, H-1), 4.41 (m, 1 H, H-4), 4.39 and 4.51 (AB system, 2 H, $J_{A,B}=11.92$ Hz, benzylic CH_2); 4.46 (d, 1 H, H-1′); 4.69 and 4.89 (AB system, 2 H, $J_{A,B}=11.23$ Hz, benzylic CH_2), 4.82 and 5.22 (AB system, 2 H, $J_{A,B}=18.08$ Hz, H-6a and H-6b), 4.98 (dd, 1 H, $J_{3',4'}=3.60$ Hz, H-3′), 5.32 (dd, 1 H, H-4′); 7.30–7.34 (m, 10 H, phenyl H); δ_C (CD_3CN, 50 MHz) 20.55, 20.79 and 20.92 (3 x CH_3CO), 27.30 and 27.45 ($C(CH_3)_2$); 54.50 and 56.15 (2 x OCH_3); 68.18 (C-6′); 68.95 (C-6); 68.74 (C-4′); 72.57 (C-5′); 73.64 (C-3′); 73.91 and 75.89 (2 benzylic CH_2); 76.39 (C-2); 77.88 (C-2′); 79.48 (C-3); 81.93 (C-4); 102.47 (C-1′); 105.98 (C-1); 111.59 ($C(CH_3)_2$); 128.67–129.30 (phenyl CH); 139.19 (2 phenyl C); 170.15, 170.85 and 170.85 (3 x C=O); 204.78 (C-5).
15. (a) Baxter, E. W.; Reitz, A. B. *J. Org. Chem*. **1994**, *59*, 3175–3185; (b) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem*. **1997**, *62*, 7482–7484; (c) Barili, P. L; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F.; Puccioni, L. *Tetrahedron* **1997**, *53*, 3407–3416.
16. Compound **13**. Solid foam, (Found: C, 66.46; H, 6.59; N, 2.34; $C_{33}H_{41}NO_9$ requires: C, 66.54; H, 6.94; N, 2.35), R_f 0.32 (9:1 $CHCl_3$/MeOH); mp 55–58°C; $[\alpha]_D$ +35.7 (*c* 0.74, $CHCl_3$); Compound **14**. Syrup, (Found: C, 61.81; H, 7.10; N, 2.81; $C_{26}H_{35}NO_9$ requires: C, 61.77; H, 6.98; N, 2.77), R_f 0.33 (8:2 CH_2Cl_2/MeOH); $[\alpha]_D$ +5.9 (*c* 0.64, MeOH); Compound **15**. Solid foam, (Found: C, 69.89; H, 6.95; N, 2.09; $C_{39}H_{45}NO_9$ requires: C, 69.73; H, 6.75; N, 2.08), R_f 0.72 (8:2 $CHCl_3$/MeOH); mp 70–73°C; $[\alpha]_D$ −10.5 (*c* 0.95, $CHCl_3$).
17. Selected NMR data: Compound **13**: δ_H ($CDCl_3$, 200 MHz) 2.52 (dd, 1 H, $J_{1ax,1eq}=12$ Hz, $J_{1ax,2}=10$ Hz, H-1ax), 2.80 (m, 1 H, H-5), 3.16 (dd, 1 H, $J_{1eq,2}=4.6$ Hz, H-1eq); 4.25 (d, 1 H, $J_{1',2'}=7.6$ Hz, H-1′); δ_C ($CDCl_3$, 50 MHz) 48.55 (C-1); 58.90 (C-5); 68.73 (C-4′); 68.93, and 69.35 (C-6, and C-6′); 71.97 (C-2); 73.33 (C-3′); 73.33 (C-5′); 77.47 (C-3); 79.22 (C-2′), 82.39 (C-4); 103.36 (C-1′); Compound **14**: δ_H ($CDCl_3$/CD_3OD, 200 MHz) 2.54 (t broad, 1 H, $J=10.7$ Hz, H-1ax), 2.67 (m, 1 H, H-5), 3.17 (m, 1 H, H-1eq); 4.39 (d, 1 H, $J_{1',2'}=7.2$ Hz, H-1′); δ_C ($CDCl_3$/CD_3OD, 50 MHz) 48.37 (C-1); 60.05 (C-5); 60.28 (C-6); 68.93 (C-6′); 69.06 (C-4′); 71.57 (C-2); 73.23 (C-3′); 73.35 (C-5′); 77.19 (C-3); 79.47 (C-2′), 80.99 (C-4); 103.10 (C-1′). Compound **15**: δ_H ($CDCl_3$, 200 MHz) 1.95 (t broad, 1 H, $J_{1ax,1eq}=11.2$ Hz, $J_{1ax,2}=10.6$ Hz, H-1ax), 2.47 (m, 1 H, H-5), 3.07 (dd, 1 H, $J_{1eq,2}=4.4$ Hz, H-1eq); 4.47 (d, 1 H, $J_{1',2'}=7.4$ Hz, H-1′); δ_C ($CDCl_3$, 50 MHz) 49.97 (C-1); 57.21 (C-6); 62.79, and 63.50 (C-5, and $CHPh_2$); 69.03 (C-6′); 69.03 (C-4′); 70.19 (C-2); 73.20

(C-3′); 73.53 (C-5′); 77.00 (C-3); 79.49 (C-2′), 81.47 (C-4); 103.62 (C-1′).

18. 4-*O*-β-D-Galactopyranosyl-(1->4)-1,5-dideoxy-1,5-imino-D-glucitol (**1**). mp 241–246°C, white crystals from MeOH–H_2O (lit.[6] 247–248°C); $[\alpha]_D$+41.32 (*c* 1.01, H_2O) (lit.[6] $[\alpha]_D$+42.44); ^1H NMR and ^{13}C NMR (Me_2SO) data identical to those previously reported.[6]
19. Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.