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A stereodivergent approach to 1-deoxynojirimycin, 1-deoxygalactonojirimycin and 1-deoxymannojirimycin derivatives

Charlotte Boucheron, Philippe Compain* and Olivier R. Martin*

Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France

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Abstract—A stereodivergent synthesis of N-alkylated 1-deoxygalactonojirimycin and 1-deoxymannojirimycin derivatives has been achieved from a protected 1-deoxynojirimycin intermediate having two free OH groups tactically positioned at C-2 and C-4. The inversion of configuration of the secondary alcohols was performed by way of a Swern oxidation followed by a highly diastereoselective reduction using $NaBH_4$ or L-Selectride.

Iminosugars are historically known as potent inhibitors of glycosidases.[1] Since the commercialization of the first iminosugar-based drug in 1996 (Glyset™, **1**),[2] the rate of discoveries in the field of sugar mimetics with nitrogen replacing the ring oxygen has increased dramatically (Fig. 1). The scope of their biological activity has been recently extended to the inhibition of a number of enzymes of medicinal interest such as glycosyltransferases,[3] metalloproteinases,[4] a sugar nucleotide mutase,[5] or nucleoside-processing enzymes.[6] Consequently, a number of potential therapeutic applications can be envisioned.[7] Iminosugars constitute promising leads for the development of immunosuppressive,[8] antiviral,[9] antipsoriatic,[4] antidiabetic[10] and antitumour agents.[7] *N*-Butyl 1-deoxynojirimycin (NB-DNJ, Zavesca™, **2**), which has been approved in 2003 for the treatment of Gaucher disease, is currently the only orally administered drug for lysosomal glycosphingolipidoses, a rare group of about 40 inherited diseases.[11]

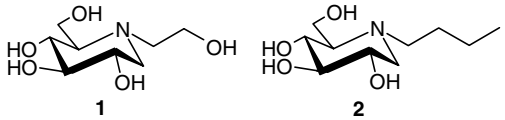

Figure 1.

The scope of action of iminosugars is further expanding towards new unexpected applications: N-alkylated derivatives of 1-deoxynojirimycin have been found recently to reversibly induce infertility in male mice.[12] In view of these recent exciting developments, efficient approaches to iminosugar derivatives are still needed to facilitate and accelerate the finding of new therapeutic agents.[13] We recently described a general access to nojirimycin C-glycosides and analogues.[14] In this letter, we wish to report the extension of this strategy to the synthesis of *N*-alkyl 1-deoxyiminosugars of other configurations (D-*galacto*, D-*manno*). Since a *N*-alkyl chain of at least eight carbon atoms seems to be critical for antiviral activity,[9c,15] we first focussed on the synthesis of *N*-nonyl 1-deoxygalactonojirimycin (NN-DGJ) and *N*-nonyl 1-deoxymannojirimycin (NN-DMJ). Our stereodivergent approach hinges on the 1-deoxynojirimycin derivative **5** having two OH groups tactically positioned at C-2 and C-4.

The synthesis of the key diol **5** began with the nucleophilic substitution of mesylate **3**[14b] using neat nonylamine (Scheme 1). The resulting aminosorbofuranose derivative **4** was directly engaged in the next step without purification. The one-pot sequence of acetal deprotection and intramolecular reductive amination provided the properly protected piperidine **5** with two free OH groups at C-2 and C-4. At this stage, our synthetic strategy required differentiation of the two hydroxyl groups. After various attempts, highly regioselective protection of the less hindered OH group at C-2 was achieved using an excess of TBDMSCl and imidazole.

* Corresponding authors. Tel.: +33 (0) 2 38 49 48 55; fax: +33 (0) 2 38 41 72 81; e-mail addresses: philippe.compain@univ-orleans.fr; olivier.martin@univ-orleans.fr

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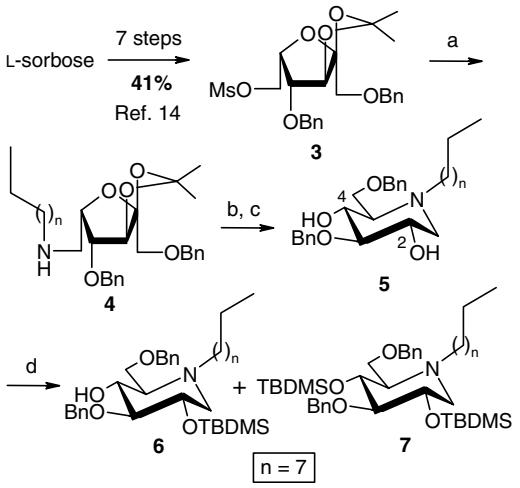
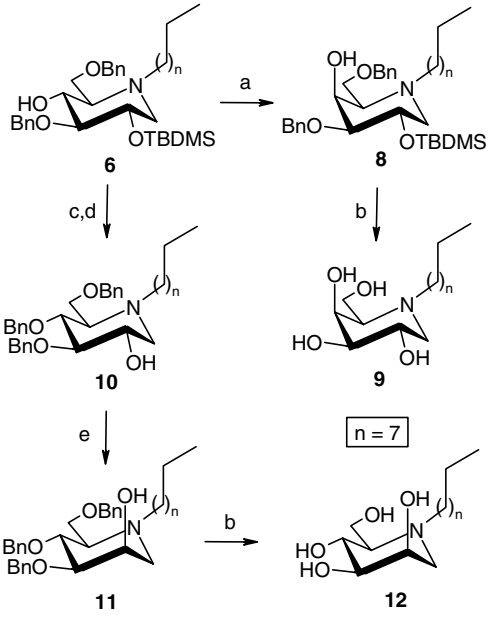


Scheme 1. Reagents and conditions: (a) neat nonylamine, 90 °C, 16 h; (b) TFA/H_2O (9/1), 28 h; (c) $NaBH_3CN$ (5 equiv), AcOH (1 equiv), MeOH, 48 h, 42% (three steps); (d) TBDMSCl (2.5 equiv), imidazole (4 equiv), DMF, 22 h, 76% (**6**), 5% (**7**).



Scheme 2. Reagents and conditions: (a) (i) $(COCl)_2$ (2.5 equiv), DMSO (4.5 equiv), Et_3N (10 equiv), CH_2Cl_2, −78 °C to rt, 2 h; (ii) $NaBH_4$ (10 equiv), MeOH, 0 °C to rt, 16 h, 77%; (b) (i) H_2, Pd/C, MeOH/HCl 5 N (10/1), 48–72 h, quant; (ii) Dowex 1-X2 (OH^- form); (c) BnBr (2 equiv), NaH (3 equiv), *n*-Bu_4NI (0.1 equiv), THF, 0 °C to Δ, 6 h, 94%; (d) *n*-Bu_4NF (3.3 equiv), THF, 7 h, 79%; (e) (i) $(COCl)_2$ (2.5 equiv), DMSO (4.5 equiv), Et_3N (10 equiv), CH_2Cl_2, −78 °C to rt, 2 h, brief aqueous work-up; (ii) L-Selectride (1.5 equiv), THF, −78 °C, 3 h, 64%.

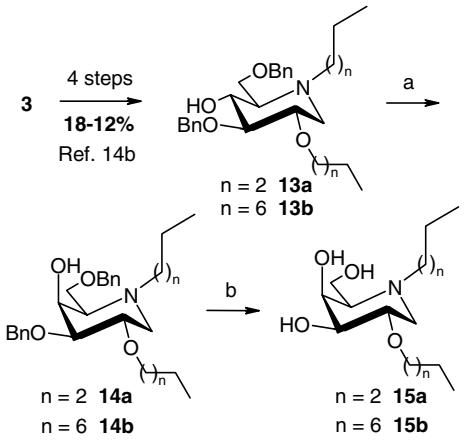
After 1 day, piperidinol **6** and disilylated derivative **7** were isolated in 76% and 5% yield, respectively, after purification on silica gel.

With iminosugar **6** in hand, we first explored the inversion of configuration at C-4. The best strategy found[16] was based on the two-step sequence: oxidation followed by diastereoselective reduction.[17] Under Swern conditions, the tertiary amine function was not affected and oxidation of alcohol **6** afforded the corresponding ketone which was reduced in situ with sodium borohydride (Scheme 2). This highly diastereoselective one-pot procedure[18] provided alcohol **8**[19] in 77% yield from compound **6** (de >98%). The ^1H and ^{13}C NMR parameters established unambiguously the *galacto* configuration of **8**. The one-step removal of the benzyl and silyl protecting groups in **8** was conducted using hydrogen over palladium on carbon in MeOH/HCl 5 N (10/1) to yield NN-DGJ (**9**).[9c,15a,20] The high stereoselectivity of the reduction of the intermediate 4-keto 1-deoxynojirimycin was expected on the basis of precedents in the carbohydrate field. Although small hydride donors are known to reduce simple cyclohexanone derivatives by an axial attack as a result of fine stereoelectronic effects,[21] the reduction of cyclic hexosulosides in which the carbonyl is flanked by two equatorial substituents has generally given predominantly or exclusively the axial alcohol.[22,23] The stereoselectivity appears here to be controlled mainly by steric effects, which favour an equatorial attack. By contrast, the stereoselective reduction of the ketone derived from alcohol **10** required the use of a more hindered hydride donor. After benzylation of the hydroxyl group at C-4 of **6**, the TBDMS group was removed under classical conditions to provide piperidinol **10** in 74% yield for the two steps. Swern oxidation of alcohol **10** followed by reduction using L-Selectride afforded the expected mannonojirimycin derivative **11**[24] in high diastereoselectivity (de >98%) (Scheme 2). These observations are consistent with the fact that electronic factors play a more important role if the ketone carries only one vicinal substituent (as shown, e.g., in the $NaBH_4$ reduction of piperidone derivatives[17]), and that a larger reagent is necessary to achieve high stereoselectivity. Removal of the benzyl groups by hydrogenolysis provided the desired NN-DMJ (**12**).[15a,25]

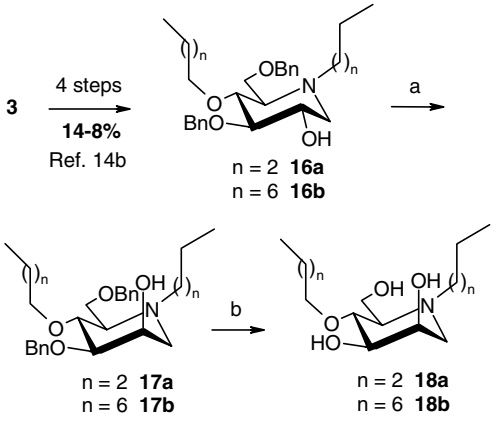
In connection with our recent studies on glycosylceramide synthase inhibitors,[14b] we also applied this strategy to the synthesis of original 'iminoglycolipids' in the D-*galacto* and D-*manno* series. We took advantage of a nonregioselective approach that led to the obtention of di-alkylated iminosugars with a free hydroxyl group at C-2 or C-4 (Schemes 3 and 4).[14b] We were pleased to find that the two-step one-pot conversion of 1-deoxynojirimycin derivatives **13** to their corresponding C-4 epimers **14** proceeded in high yield and high diastereoselectivity (Scheme 3). The benzyl groups were removed by hydrogenolysis over palladium on carbon to afford the 2-O,N-dialkylated 1-deoxygalactonojirimycin derivatives **15** in very good yields after purification on silica gel.

In the series of DMJ derivatives carrying a free 2-OH group, Swern oxidation followed by L-Selectride reduction of the crude ketone provided the expected 1-deoxymannojirimycin derivatives **17** with high diastereoselectivity but in modest yields (42–45%) after purification on silica gel.

It is noteworthy that the use of $NaBH_4$ as a hydride source resulted in a complete loss of stereoselectivity at



Scheme 3. Reagents and conditions: (a) (i) $(COCl)_2$ (2.5 equiv), DMSO (4.5 equiv), Et_3N (10 equiv), CH_2Cl_2, −78 °C to rt, 2 h 30 min; (ii) $NaBH_4$ (10 equiv), MeOH, 0 °C to rt, 2 h, 82% (**14a**), 82% (**14b**); (b) (i) H_2, Pd/C, MeOH/HCl 5N (10/1), 48 h, quant, (**15a**), 87% (**15b**); (ii) Dowex 1-X2 (OH^- form).



Scheme 4. Reagents and conditions: (a) (i) $(COCl)_2$ (2.5 equiv), DMSO (4.5 equiv), Et_3N (10 equiv), CH_2Cl_2, −78 °C to rt, 3 h, brief aqueous work-up; (ii) L-Selectride (2 equiv), THF, −78 °C, 2 h, 45% (**17a**), 42% (**17b**); (b) (i) H_2, Pd/C, MeOH/HCl 5 N (10/1), 48 h, 34% (**18a**), 62% (**18b**); (ii) Dowex 1-X2 (OH^- form).

C-2, the D-*gluco* and D-*manno* products **16** and **17** being obtained as an equimolar mixture after the reaction. In this case, the carbonyl group, which has only one vicinal equatorial substituent, is less hindered than at C-4 and axial attack of $NaBH_4$ is not prevented. Deprotection of **17** by hydrogenolysis under acidic conditions afforded the free 4-O,N-dialkylated 1-deoxymannojirimycin derivatives **18**.

In conclusion, we have described a practical stereodivergent approach for the preparation of iminohexitols related to DNJ of biological interest by way of the highly stereoselective reduction of piperidones. Future work will focus on the extension of this strategy to other series such as D-*allo* or D-*talo* to prepare rare iminosugars. Investigations on the activity of the synthesized glycomimetics as carbohydrate-processing enzyme inhibitors are in progress and will be reported in due course.

Acknowledgements

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18. *Typical experimental procedure*: To a solution of oxalyl chloride (74 μL, 0.85 mmol) in anhydrous dichloromethane (2 mL) was added DMSO (107 μL, 1.5 mmol) under argon. The solution was stirred at −78 °C for 30 min. A solution of alcohol **6** (195 mg, 0.33 mmol) in anhydrous dichloromethane (5 mL) was then added. After 3 h at −78 °C, Et_3N (467 μL, 3.35 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 2 h. A solution of $NaBH_4$ (127 mg, 3.35 mmol) in MeOH (6 mL) was then added at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The crude mixture was evaporated to dryness and then taken into AcOEt (20 mL). The solution was washed with water (20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (petroleum ether/ethyl acetate 6/1) afforded the secondary alcohol **8** as a colourless oil (151 mg, 77%).
19. Selected data for iminoalditol **8**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.09 (s, 6H); 0.90 (m, 12H); 1.14–1.43 (m, 14H); 2.14 (t, 1H, $J = 10.7$ Hz, H-1ax.); 2.44 (m, 2H, H-5, NCH_2); 2.66 (m, 1H, NCH_2); 2.89 (dd, 1H, $J = 5.0$, 11.3 Hz, H-1eq.); 3.12 (dd, 1H, $J = 3.1$, 8.8 Hz, H-3); 3.69 (m, 2H, H-6); 4.00 (m, 2H, H-2, H-4); 4.46 (d, 1H, $J = 11.6$ Hz, OCH_2Ph); 4.53 (d, 1H, $J = 11.9$ Hz, OCH_2Ph); 4.68 (s, 2H, OCH_2Ph); 7.24–7.38 (m, 10H, $2C_6H_5$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −4.7; −4.5; 14.2; 18.1; 22.7; 24.2; 25.9; 27.5; 29.3; 29.6; 29.7; 31.9; 52.9; 57.7; 62.3; 68.9; 70.4; 72.2; 73.5; 83.5; 127.6; 127.7; 127.8; 128.3; 128.4; 137.9; 138.5; $[\alpha]_D^{20}$ +6.5 (*c* 0.6, $CHCl_3$); HRMS (ESI) *m/z* 584.4133 $[M+H]^+$ ($C_{35}H_{58}NO_4Si$ requires 584.4135).
20. Selected data for iminoalditol **9**: ^{1}H NMR (500 MHz, CD_3OD): δ 0.90 (br t, 3H); 1.22–1.36 (m, 12H); 1.49 (m, 2H); 2.11 (t, 1H, $J = 10.5$ Hz, H-1ax.); 2.37 (br t, 1H, H-5); 2.48 (m, 1H, NCH_2); 2.70 (m, 1H, NCH_2); 2.98 (dd, 1H, $J = 5.5$, 10.5 Hz, H-1eq); 3.20 (dd, 1H, $J = 4.0$, 10.0 Hz, H-3); 3.80 (m, 3H, H-6, H-2); 3.97 (m, 1H, H-4); ^{13}C NMR (125 MHz, CD_3OD): δ 14.5; 23.8; 25.1; 28.7; 30.5; 30.7; 30.8; 33.1; 54.1; 58.1; 62.4; 65.3; 69.1; 72.2; 77.3; $[\alpha]_D^{20}$ +5.0 (*c* 0.16, MeOH); HRMS (FAB) *m/z* 290.2328 $[M+H]^+$ ($C_{15}H_{32}NO_4$ requires 290.2331).
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24. Selected data for iminoalditol **11**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (br t, 3H); 1.24–1.41 (m, 14H); 2.37 (br d, 2H, H-1ax., H-5); 2.57 (m, 1H, NCH_2); 2.72 (m, 1H, NCH_2); 2.97 (dd, 1H, $J = 4.4$, 12.2 Hz, H-1eq.); 3.41 (dd, 1H, $J = 3.1$, 8.8 Hz, H-3); 3.62 (dd, 1H, $J = 2.2$, 10.4 Hz, H-6A); 3.68 (dd, 1H, $J = 3.1$, 10.4 Hz, H-6B); 3.81 (t, 1H, $J = 8.8$, H-4); 3.99 (m, 1H, H-2); 4.45 (m, 3H, OCH_2Ph); 4.64 (d, 1H, $J = 11.6$ Hz, OCH_2Ph); 4.73 (d, 1H, $J = 11.9$ Hz, OCH_2Ph); 4.90 (d, 1H, $J = 11.0$ Hz, OCH_2Ph); 7.20–7.37 (m, 15H, 3 C_6H_5); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2; 22.8; 24.8; 27.6; 29.4; 29.6; 29.7; 32.0; 52.7; 55.1; 64.0; 65.4; 66.6; 71.5; 73.3; 75.2; 76.1; 83.7; 127.6; 127.7; 127.8; 128.0; 128.1; 128.4; 128.5; 138.2; 138.4; 138.8; $[\alpha]_D^{20}$ −9.0 (*c* 0.7, $CHCl_3$); HRMS (ESI) *m/z* 560.3740 $[M+H]^+$ ($C_{36}H_{50}NO_4$ requires 560.3740).
25. Selected data for iminoalditol **12**: ^{1}H NMR (500 MHz, CD_3OD): δ 0.89 (br t, 3H); 1.24–1.36 (m, 12H); 1.47 (m, 2H); 2.11 (m, 1H, H-5); 2.48 (dd, 1H, $J = 1.5$, 12.5 Hz, H-1ax); 2.58 (m, 1H, NCH_2); 2.74 (m, 1H, NCH_2); 2.97 (dd, 1H, $J = 4.0$, 12.5 Hz, H-1eq.); 3.29 (dd partly masked by the signal of methanol, 1H, $J = 4.0$ Hz, H-3); 3.65 (t, 1H, $J = 9.5$ Hz, H-4); 3.82 (m, 1H, H-2); 3.87 (m, 2H, H-6); ^{13}C NMR (125 MHz, CD_3OD): δ 14.5; 23.8; 25.3; 28.7; 30.4; 30.74; 30.77; 33.1; 54.0; 56.6; 59.2; 67.0; 69.66; 69.71; 76.7; $[\alpha]_D^{20}$ −40.5 (*c* 0.5, MeOH); HRMS (FAB) *m/z* 290.2333 $[M+H]^+$ ($C_{15}H_{32}NO_4$ requires 290.2331).