Pergamon

Tetrahedron 57 (2001) 6955–6967

TETRAHEDRON

Synthesis of 1-deoxymannojirimycin analogues using *N*-tosyl and *N*-nosyl activated aziridines derived from 1-amino-1-deoxyglucitol

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Received 30 March 2001; revised 1 June 2001; accepted 19 June 2001

Abstract—3,4;5,6-Diisopropylidene protected 1-amino-1-deoxy-D-glucitol was transformed into *N*-tosyl and *N*-nosyl activated aziridine intermediates, which underwent ring opening by reaction with various nucleophiles. The 5,6-diols resulting from selective hydrolysis of the terminal acetal group were subjected to (2-N→6-OH) cyclisation using two different methods for activation of 6-OH. Final deprotection of the *N*-nosyl and 3,4-acetal group proceeded smoothly to afford 6-substituted analogues of 1-deoxymannojirimycin.

1. Introduction

Many naturally occurring polyhydroxylated piperidines show inhibitory activities towards glycosidases and may have therapeutic value in the treatment of cancer,[1] diabetes,[2] and viral infections[3] (including AIDS).[4] Among these azasugars 1-deoxynojirimycin **1** and 1-deoxymannojirimycin **2**, inhibitors of glucosidases[5] and mannosidases[6] respectively, represent archetypal structures where the ring oxygen of the corresponding pyranosyl carbohydrates has been replaced with a nitrogen atom.

In our previous work, diverging strategies were applied in order to transform 1-aminoglucitol **3** into various analogues of 1-deoxynojirimycin[7] and castanospermine.[8] Thus, the crystalline 3,4;5,6-di-*O*-isopropylidene ammonium salt derivative **4** was isolated and converted to polyhydroxypiperidines modified at C-2 and C-6. We now describe an interesting route for the synthesis of variously substituted polyhydroxypiperidines, which proceeds via nucleophilic ring opening of an *N*-sulfonyl activated aziridine intermediate. The present work forms an extension of our 'inversed chain strategy' concept, which implies that ring closure to form the piperidine derivative occurs between the original carbon C-6 of 1-aminoglucitol (which is to become C-1 of the iminosugar) and an amino group introduced at C-2[9] (Fig. 1).

2. Results and discussion

Our synthetic approach involves conversion of the ammonium salt **4** of 3,4;5,6-di-*O*-isopropylidene-1-deoxy-1-aminoglucitol into an *N*-tosyl or *N*-nosyl-1,2-aziridine inverted at the 2-position (Scheme 1). Subsequent ring opening of the *N*-sulfonyl aziridines is effected by reaction

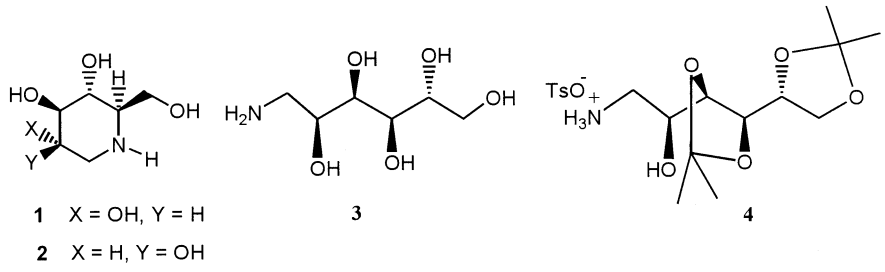

Figure 1.

Keywords: aziridines; Mitsunobu reactions; carbohydrates; piperidines; deoxymannojirimycin.
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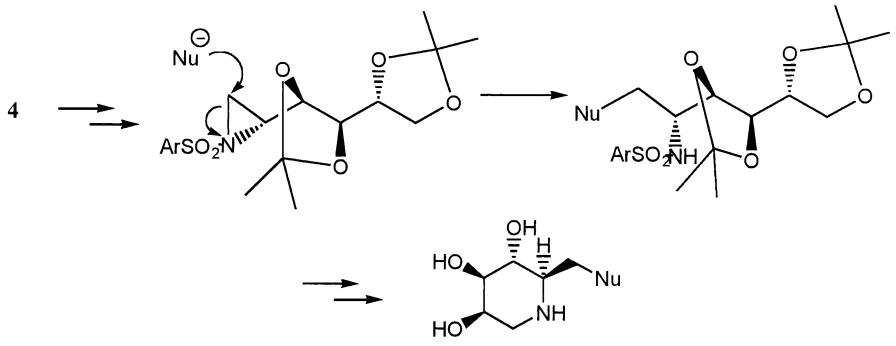
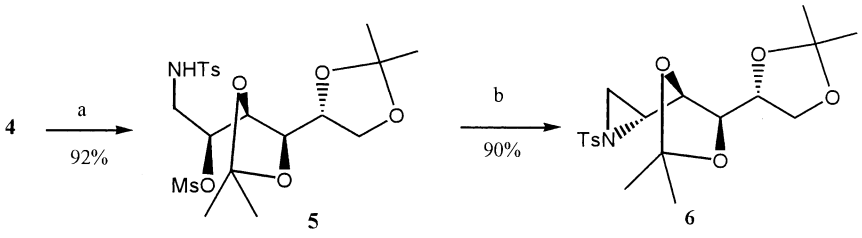


Scheme 1.

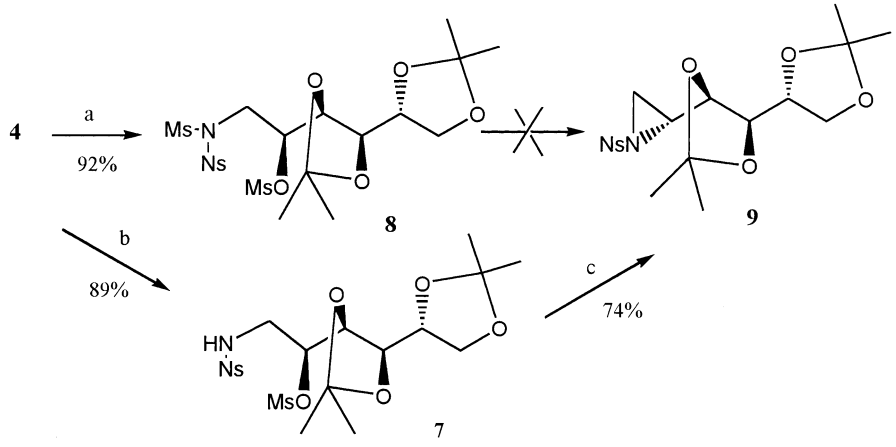
with various nucleophiles to produce the corresponding 2-aminoalditol compounds. Final ring closure proceeds via deprotection of the 5,6-diol and displacement of the activated 6-OH group by the 2-amino nitrogen. A similar strategy which involved the ring opening of bis(aziridines), was applied by Depezay et al. to prepare analogues of 1-deoxynojirimycin and 1-deoxymannojirimycin.[10]

In a first approach (Scheme 2) the ammonium salt **4** was converted to the *N*-tosyl derivative, and the latter was mesylated at the 2-OH position using a 'one-pot procedure' to produce mesylate **5** in 92% overall yield. Upon treatment with sodium hydride in THF, compound **5** was converted to the *N*-tosylaziridine **6** in 90% yield. The aziridine structure **6** was confirmed by ^{1}H- and ^{13}C NMR data. In the ^{1}H NMR spectrum ($CDCl_3$) the absorption due to the NH-proton of the tosylamide **5** had disappeared, while the protons H-1 and H-1′ were differentiated into two doublet signals detected at 2.43 and 2.65 ppm, respectively (geminal coupling value $^{2}J \cong 0$ Hz). In the ^{13}C NMR spectrum the values observed for the $^{1}J_{C-H}$ coupling constants (171 and 179 Hz for C-1 and 171 Hz for C-2) were in agreement with those reported for *N*-methylaziridine.[11]

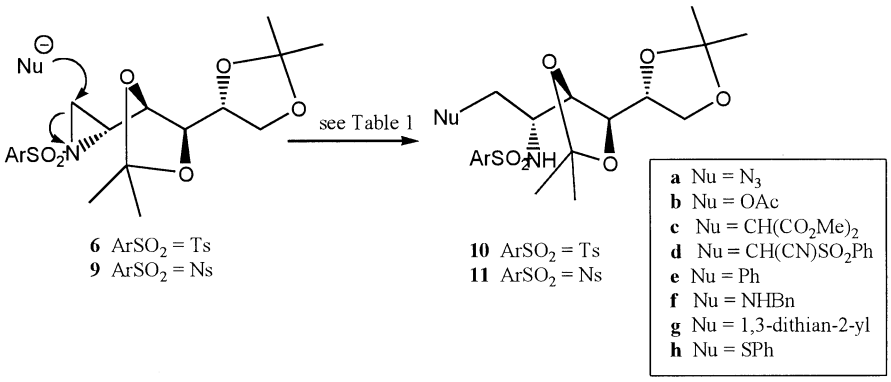
In view of the harsh conditions[12] required for removal of the *N*-tosyl group at a later stage, it was of interest to extend the preceding *N*-tosyl route to provide the corresponding *p*-nitrobenzenesulfonyl (*N*-nosyl) aziridine. Indeed, removal of the *N*-nosyl protecting group proceeds under much milder conditions, i.e. via attack of thiophenolate anion at the sulfonyl *ipso* position.[13] In our initial attempt to prepare 2-*O*-mesylate **7**, we applied a similar one-pot procedure as that described for the *N*-tosyl analogue **5**, using triethylamine as a base for both *N*-nosylation of **4** and subsequent



Scheme 2. *Reagents and conditions*: (a) 4 equiv. Et_3N, 1.5 equiv. *p*-TsCl, CH_2Cl_2, 20°C, 30 min; then 1.3 equiv. MsCl, 20°C, 1 h; (b) 2 equiv. NaH (80%), THF, 20°C, 1 h.



Scheme 3. *Reagents and conditions*: (a) 4 equiv. Et_3N, 1.5 equiv. *p*-NsCl, CH_2Cl_2, 20°C, 30 min; then 1.3 equiv. MsCl, 20°C, 1 h; (b) Na_2CO_3 (aq. sat. solution)/CH_2Cl_2 (1.5:1), 1.5 equiv. *p*-NsCl, 20°C, 30 min; CH_2Cl_2/pyridine (4:1), 1.5 equiv. MsCl, 0–20°C, 4 h; (c) 2 equiv. NaH, THF, 20°C, 4 h.



Scheme 4. *Reagents and conditions*: see Table 1.

2-*O*-mesylation. However, due to the more acidic character of the *N*-nosyl amide, these conditions led to formation of the *N*,*O*-dimesylate **8** instead of 2-*O*-mesylate **7**. The unwanted *N*-mesylation could be avoided by using the weaker base pyridine, but under these conditions a mixture of *N*-nosyl and *N*-tosyl 2-*O*-mesylates was obtained, probably due to formation of a mixed sulfonic anhydride between nosyl chloride and the tosylate counterion of **4**. This problem could be avoided by using an aqueous Na_2CO_3/CH_2Cl_2 two-phase system to remove the tosylate anion from the organic phase. Subsequent 2-*O*-mesylation in CH_2Cl_2-pyridine (89% overall yield from **4**) and final treatment with NaH in THF afforded the required *N*-nosyl aziridine **9** (74%) (Scheme 3).

The *N*-tosyl and *N*-nosyl aziridines **6** and **9** were submitted to reaction with various nucleophiles to produce the corresponding ring opened products **10** and **11** in good to excellent yields (Scheme 4). Reaction conditions and yields are given in Table 1. Due to a better stabilisation of the intermediate *N*-sulfonylamide anion formed by opening of the aziridine ring, this reaction proceeds more readily for the nosyl substrate **9**. One problem encountered when using sodium azide or potassium acetate as the nucleophile to prepare the corresponding 1-azido and 1-acetoxy-*N*-tosyl aziridines **10a**,**b** was the formation of dimeric products. This side reaction results from the competitive attack of the *N*-tosylamide anion (formed after ring opening) on a second molecule of aziridine and could be suppressed by using ten equivalents of the nucleophile. No dimer formation was observed in the reactions with the more nucleophilic carbanionic reagents producing **10e** and **10g**, and in those cases where the intermediate *N*-sulfonylamide anion could abstract an acidic proton, i.e. in the reaction with amine (**10f**), malonate (**10c**), and sulfonylacetonitrile (**10d**). Only one of two possible diastereomers **10d** was detected by ^{1}H- and ^{13}C NMR analysis. Presumably this is due to equilibration occurring at the acidic stereogenic centre C-2 to yield the more stable product. In analogy to the copper(I)-catalysed ring opening of epoxides by Grignard reagents,[14] the reaction with phenylmagnesium bromide only succeeded upon addition of catalytic copper-(I)iodide. However, the latter copper(I) catalysed ring opening reaction using PhMgBr as a nucleophile, did not succeed when applied to the *N*-nosyl aziridine **9**. Interestingly, treatment of **9** with thiophenolate (the reagent that is also used later on for deprotection of the nosylamide function) at room temperature for 1 h led to clean production of 1-phenylthio compound **11h** without any side reaction due to cleavage of the *N*-nosyl protecting group.

Next, representative members of the *N*-tosyl (**10a**) and *N*-nosyl (**11a**,**h**) 2-deoxy-2-aminomannitol derivatives were subjected to a sequence consisting of cleavage of the 5,6-*O*-isopropylidene group and activation of the 6-OH group to form the piperidine ring (Scheme 5). Regioselective deprotection of the terminal acetal group was accomplished by treatment with an acidic ion exchange resin (Dowex 50X8-200) to give the corresponding 5,6-diols **12a** and **13a**,**h** in good yields (72–92%). Both

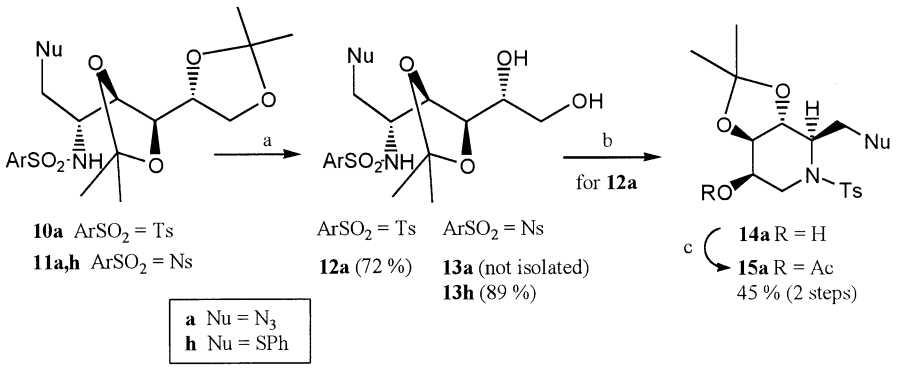
Table 1.

Product	Nu	Conditions	Reaction time (h) (tosyl) **10**	Reaction time (h) (nosyl) **11**	Yield (%) (tosyl) **10**	Yield (%) (nosyl) **11**
10a, **11a**	N_3	a	30	8	96	98
10b, **11b**	OAc	b	18	12	90	83
10c, **11c**	$CH(COOMe)_2$	c	48	4	65	78
10d	$CH(CN)SO_2Ph$	d	24	24	87	mixt.[a]
10e	Ph	e	1	1	75	mixt.[a]
10f	NHBn	f	24	n. tried[b]	67	–
10g	1,3-dithian-2-yl	g	4	n. tried[b]	90	–
11h	SPh	h	n. tried[b]	1	–	89

Reagents and conditions: (a) 10 equiv. NaN_3, DMF 90°C; (b) 10 equiv. KOAc, DMF, 90°C; (c) 2 equiv. $(MeO_2C)_2CH_2$, 2.5 equiv. NaH, THF, 0°C–rt; (d) 1.2 equiv. $PhSO_2CH_2CN$, 1.2 equiv. NaH, THF, 0°C–rt; (e) 5 equiv. PhMgBr, 0.1 equiv. CuI, THF, rt; (f) 1.2 equiv. $BnNH_2$, DMF, 90°C: (g) 2 equiv. 1,3-dithiane, 2 equiv. BuLi, THF, 0°C; 15 min; then rt, 4 h; (h) 3 equiv. PhSH, 3 equiv. K_2CO_3, DMF, rt.

[a] mixt.: Product mixture was not well characterized.

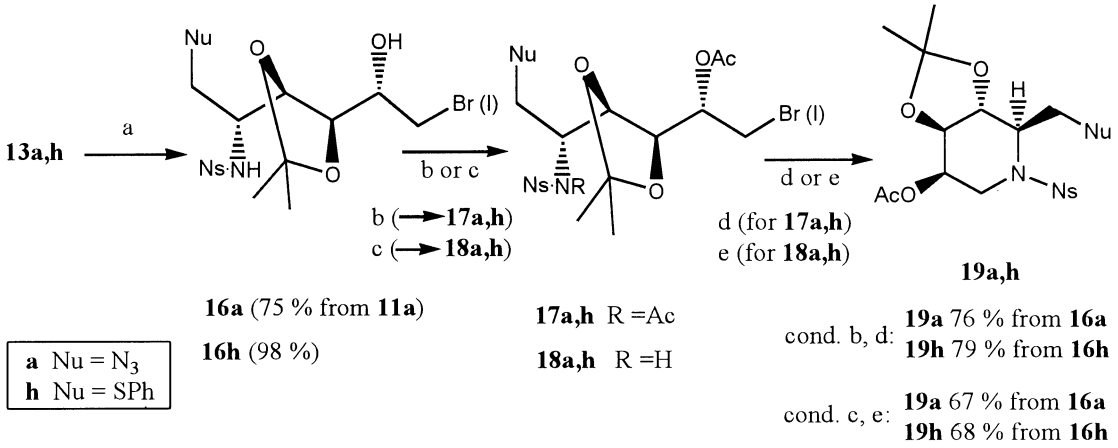
[b] n.tried: Reaction was not tried



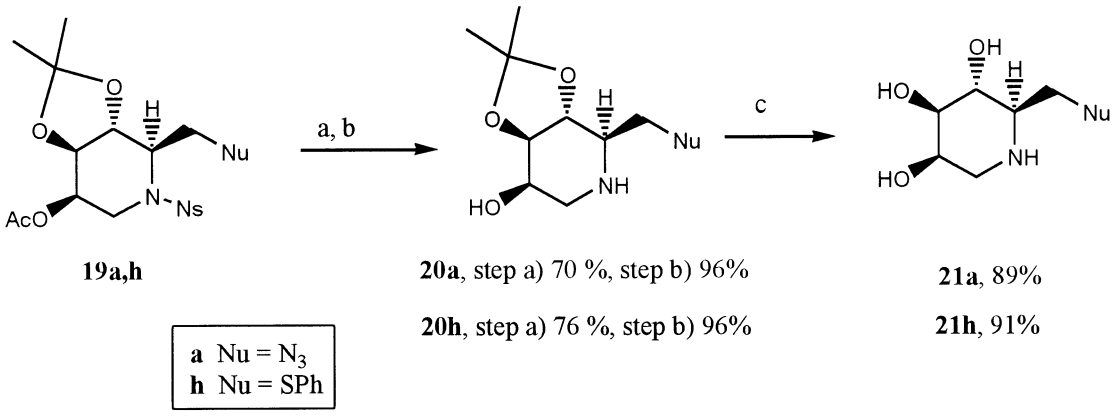
Scheme 5. *Reagents and conditions*: (a) Dowex 50X8-200, 9:1/ MeOH/H_2O, rt, 30 h–7 days; (b) Ph_3P, DEAD, THF, rt, 5 days; (c) pyridine, Ac_2O, rt, 2 h.

Mitsunobu[15] and Appel[16] reaction conditions were applied to achieve selective activation of the 6-OH group and subsequent cyclisation. Treatment of **12a** with triphenylphosphine and diethyl azodicarboxylate in anhydrous THF produced the piperidine compound **14a**. At room temperature, and even at 40–60°C, the cyclisation reaction was found to proceed very slowly. After several days, TLC and mass spectrometric analysis confirmed that all starting material had been consumed. However, due to co-eluting substances originating from the Mitsunobu reagent, isolation of the alcohol product **14a** proved to be difficult, and therefore the latter was converted to the less polar acetate **15a**, which was isolated in moderate yield (combined yield for steps b and c 45%); spectroscopic data were in accordance with the proposed piperidine structure.

In contrast, no cyclisation was observed when diols **13a**,**h** were submitted to the above Mitsunobu reaction conditions. Therefore we resorted to the Appel reaction to introduce a 6-bromo (or 6-iodo) leaving group. Subsequent N-2→C-6 cyclisation was envisioned to proceed either via base-promoted generation of the 5,6-epoxide or via 5-OH protection prior to displacement of the 6-halogen atom by the nosylamide anion. Treatment of the 5,6-diols **13a**,**h** with Ph_3P and CBr_4 in THF at room temperature for 30 min afforded the 6-bromo compounds **16a**,**h** in 75 and 83% overall yield respectively, calculated from diacetonides **11a**,**h**. However, although reaction of **16a**,**h** with NaH in THF gave the expected 5,6-epoxide, the latter failed to cyclise even under more forcing reflux conditions using *t*-BuOK in *i*-PrOH. To explore the alternative route involving protection of the 5-OH group, acetylation of compounds **16a**,**h** was carried out under various conditions. When using Ac_2O, Et_3N, and DMAP in CH_2Cl_2, the *N*,*O*-diacetyl compounds **17a**,**h** were produced. However, selective *O*-acylation to form the mono-acetylated derivatives **18a**,**h** could be accomplished by replacing the Et_3N and DMAP reagents with the less basic pyridine. (For most experiments proceeding through mono-*O*-acetylation the preceding Appel reaction of 5,6-diols **13a**,**h** was carried out using CI_4 instead of CBr_4, resulting in the production of **16a**,**h** and **18a**,**h** as the 6-iodo derivatives.) Subsequent conversion of **18a**,**h** into piperidines **19a**,**h** was achieved in a separate slow cyclisation step using DMAP to effect NH-deprotonation and intramolecular 6-I (6-Br) substitution. Surprisingly, the required piperidines **19a**,**h** could also be prepared by reaction of the *N*,*O*-diacetyl compounds **17a**,**h** with an excess of DMAP. TLC analysis revealed the formation of *N*-deacetylated compounds **18a**,**h** as intermediates, presumably via deprotonation of the *N*-acetyl group and expulsion of ketene to generate the nosylamide anion. Finally, the three-step conversion (**16**→**17**→**18**→**19**) proceeding via *N*,*O*-diacetylation, *N*-deacetylation and cyclisation could be combined in an efficient one-pot procedure by using an excess of DMAP relative to acetic



Scheme 6. *Reagents and conditions*: (a) Ph_3P, CBr_4, THF, rt, 30 min (or Ph_3P, CI_4, THF, rt, 18 h); (b) Et_3N (4 equiv.), DMAP (1 equiv.), Ac_2O (4 equiv.), CH_2Cl_2; (c) CH_2Cl_2/pyridine (4:1), Ac_2O (4 equiv.); (d) see conditions (b), excess of DMAP, 4 days; (e) CH_2Cl_2, excess of DMAP, 4 days.



Scheme 7. *Reagents and conditions*: (a) MeOH, K_2CO_3, 2 h; (b) PhSH, K_2CO_3 MeCN/DMSO (49:1), 50°C, 2 h; (c) sat. HCl/MeOH.

anhydride, to produce **19a** and **19h** in 76 and 79% overall yield, respectively (Scheme 6).

To finalise our synthetic sequence, we had to remove the *N*-sulfonyl and alcohol protecting groups. At this point the route proceeding via cleavage of the *N*-tosyl group was not continued since application of the sodium-naphthalene procedure[12] resulted in poor yields of the free amine. However, deprotection of the *N*-nosyl compounds **19a**,**h** was achieved without difficulty. Following base-catalysed solvolysis of the 2-*O*-acetyl group, the *N*-nosyl group was removed by treatment with thiophenol and K_2CO_3 in acetonitrile/DMSO (49:1) at 50°C to afford free amines **20a**,**h**.[13] Final acid deprotection of the 3,4-*O*-isopropylidene group followed by column chromatography on silica gel furnished the 1-deoxymannojirimycin analogues **21a**,**h** in good yields (Scheme 7).

From the coupling constant values in the ^{1}H NMR spectra it appears that piperidines **20** and **21** with free amino group adopt the expected chair conformation ($J_{3,4}$=$J_{4,5}$=ca. 9 Hz for H-3ax and H-4ax, and $\sum J$=ca. 7 Hz for the coupling of H-2eq with H-1, H-1′, and H-3ax). However, for the *N*-sulfonyl piperidines **15** and **19**, divergent torsional angles for H-1,H-2 were indicated by the coupling values observed for H-2, i.e. $J_{2,1}$=ca. 8 and 6 Hz and $J_{2,3}$=5.2 Hz ($\sum J$= 19 Hz). As reported already for some *N*-Boc analogues,[7a] these values conform to the twist-boat conformer depicted in Fig. 2. Apparently, the chair form of compounds **15** and **19** is disfavoured by the upward orientation imposed on the *N*-sulfonyl substituent by the planar sp^2 ring nitrogen, resulting in a strong repulsive interaction with the nearly coplanar side chain. This repulsion can be minimised by adopting the twist-boat conformer.

3. Conclusion

In this work we used *N*-tosyl and *N*-nosyl activated aziridines for the synthesis of monocyclic iminosugars, i.e. 6-substituted 1,6-dideoxymannojirimycin analogues. The potential offered by *N*-sulfonylaziridines of type **6** and **9** as synthons for the construction of various iminosugars is demonstrated by the varying nature of the nucleophiles utilised for ring opening, i.e. nitrogen-, oxygen-, and carbon-based reagents. In particular, application of carbon nucleophiles may pave the way for the introduction of more complex substituents, especially in view of the synthesis of *C*-azadisaccharides.[17] Although both *N*-tosyl and *N*-nosyl aziridines appear to be attractive intermediates allowing for ready opening of the three-membered ring and subsequent ring closure to form the piperidine ring, the *N*-nosyl derivatives are preferred, as they can easily be removed at the end of the synthetic sequence.

4. Experimental

4.1. General methods

Melting points are uncorrected. The optical rotations were measured on a Propol polarimeter fitted with a 7 cm cell. IR spectra were recorded as thin films between NaCl plates or as KBr pellets on a Perkin–Elmer 297 grating IR spectrophotometer. ^{1}H- and ^{13}C NMR were recorded on Bruker AMX 400 and WM 250 instruments operating at 400 and 250 MHz for ^{1}H and 100 and 62.9 MHz for ^{13}C. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are reported in Hz. EI and CI mass spectra were run on Hewlett–Packard

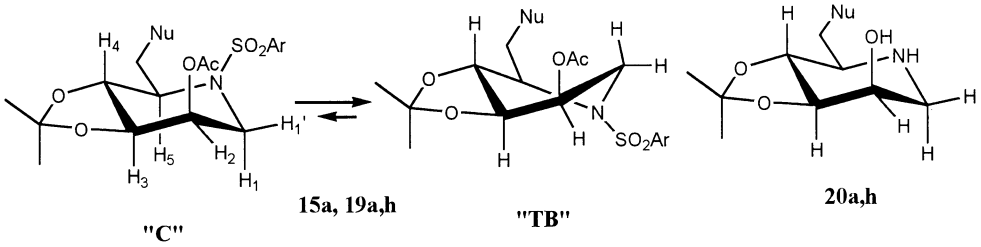


Figure 2.

MS-Engine 5989A or Kratos MS50TC instruments; the ion source temperature was 150–250°C as required. Exact mass measurements were performed at a resolution of 10,000. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224. Column chromatography was done using 70–230 mesh silica gel 60 (E. M. Merck). The purity of compounds was checked by TLC using the solvent systems mentioned for column chromatography. Solutions were dried over $MgSO_4$. All reactions were performed under a nitrogen atmosphere. Dry solvents were freshly distilled before use.

4.1.1. 1-Deoxy-3,4;5,6-di-*O*-isopropylidene-2-*O*-methanesulfonyl-1-(*N*-*p*-toluenesulfonyl)-amino-D-glucitol (5). The ammonium salt **4** (10.00 g, 23.1 mmol) was suspended in dry CH_2Cl_2 (100 mL), and to this suspension was added 13.0 mL, Et_3N (92 mmol) and 4.85 g *p*-TsCl (26 mmol) at 0°C. The mixture was stirred at room temperature for 30 min until TLC showed the disappearance of starting material. After cooling the mixture to 0°C, MsCl (3.60 mL, 30.0 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction was worked up by adding 30 mL NH_4Cl (aq. sat. solution). The mixture was extracted three times with CH_2Cl_2 (3×15 mL) the organic phase was dried with $MgSO_4$ and the product was purified by column chromatography on silica gel (EtOAc/hexanes 50:50). A colourless oily product (**5**) was obtained (10.5 g, 92%); $[\alpha]_D$=+12.9 (*c* 0.42, CH_2Cl_2); IR 3295, 2995, 2940, 1450, 1380, 1345, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 2.43 (s, 3H, Me,Ts), 3.13 (s, 3H, $MeSO_3$), 3.31 (ddd, 1H, *J*=14.0, 6.0, 5.0 Hz, H-1), 3.31(ddd, 1H, *J*=14.0, 8.0, 4.0 Hz, H-1′), 3.88 (dd, 1H, *J*=8.5, 7.0 Hz, H-4), 3.91 (dd, 1H, *J*=8.5, 5.5 Hz, H-6), 4.00 (ddd, 1H, *J*=8.5, 6.0, 5.5 Hz, H-5), 4.05 (dd, 1H, *J*=7.0, 3.5 Hz, H-3), 4.17 (dd, 1H, *J*=8.5, 6.0 Hz, H-6′), 4.80 (ddd, 1H, *J*=6.0, 4.0, 3.5 Hz, H-2), 5.31 (dd, 1H, *J*=8.0, 5.0 Hz, NH), 7.32 (d, 2H, Ts-H), 7.76 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (*Me*,Ts), 25.1, 26.2, 26.4, 27.2 (Me_2C), 39.0 ($MeSO_3$), 45.0 (*C*-1), 67.9 (*C*-6), 77.0, 77.5, 77.6, 80.2 (*C*-2, 3, 4, 5), 110.2, 110.7 (Me_2C), 127.1, 129.8 (*C*H, Ts), 136.7, 143.7 (*C-ipso*, Ts); MS (CI, methane), *m*/*z* (%): 494 (MH^+, 47%), 436 (MH^+−acetone, 46%), 398 (MH^+−MsOH, 36%), 49 (100%); HRMS: calcd for $C_{19}H_{28}O_9NS_2$ (M^+−Me) 478.1206, found 478.1207 (36%).

4.1.2. 1,2-Dideoxy-3,4;5,6-di-*O*-isopropylidene-1,2-(*N*-*p*-toluenesulfonyl)-imino-D-mannitol (6). To an ice-cooled solution of mesylate **5** (2.68 g, 5.44 mmol) in dry THF (50 mL) was added NaH (0.33 g, 10.88 mmol) in small portions, and the mixture was stirred at room temperature for 1 h. When TLC showed the disappearance of starting material, the mixture was cooled to 0°C and worked up by adding 20 mL NH_4Cl (aq. sat. solution). The mixture was extracted three times with CH_2Cl_2 (3×10 mL), the organic phase was dried with $MgSO_4$ and the product was purified by column chromatography on silica gel (EtOAc/hexanes 50:50). The aziridine (**6**) was obtained as white crystals (1.70 g, 79%); mp 96.8–97.5°C; $[\alpha]_D$=+44 ($CHCl_3$, *c* 0.39); IR 2990, 1380, 1320, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm), 1.26 (s, 3H, Me_2C), 1.34 (s, 6H, Me_2C), 1.41 (s, 3H, Me_2C), 2.43 (d, 1H, *J*=4.5 Hz, H-1), 2.44 (s, 3H, Me-Ts), 2.65 (d, 1H, *J*=7.0 Hz, H-1′), 3.11 (ddd, 1H, *J*=7.0, 4.5, 4.0 Hz, H-2), 3.74 (t, 1H, *J*=7.0 Hz, H-4), 3.88 (dd, 1H, *J*=8.5, 5.5 Hz, H-6), 3.96 (dd, 1H, *J*=7.0, 4.0 Hz, H-3), 3.97–4.00 (m, 1H, H-5), 4.08 (dd, 1H, *J*=8.5, 6.0 Hz, H-6′), 7.34 (d, 2H, Ts-H), 7.83 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 (*Me*,Ts), 25.2, 26.5, 26.8, 27.0 (Me_2C), 30.4 (C-1), 40.1 (C-2), 67.1 (C-6), 76.4, 77.6, 79.1 (*C*-3, 4, 5), 109.8, 110.4 (Me_2C), 128.2, 129.7 (*C*H, Ts), 134.7, 144.7 (*C-ipso*, Ts); MS (CI, methane), *m*/*z* (%): 398 (MH^+, 45%), 340 (MH^+−acetone, 100%), 282 (MH^+−2acetone, 28%); HRMS: calcd for $C_{18}H_{24}O_6NS$ (M^+−Me) 382.1324, found 382.1329 (67%).

4.1.3. 1-Deoxy-3,4;5,6-di-*O*-isopropylidene-2-*O*-methanesulfonyl-1-(*N*-*p*-nitrobenzenesulfonyl)-amino-D-glucitol (7). The ammonium salt **4** (13.06 g, 30.2 mmol) was added to a two-phase system consisting of 100 mL CH_2Cl_2 and 150 mL Na_2CO_3 (aq. sat. solution), and the mixture was stirred for 10 min. After adding *p*-NsCl (10.03 g, 45.3 mmol) the reaction mixture was stirred at room temperature until TLC showed the disappearance of starting materials (about 1 h). The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2 (3×20 mL). The organic layers were combined and dried on $MgSO_4$. After evaporation of the solvent, the residue was redissolved in 100 mL, CH_2Cl_2 and the solution was cooled to 0°C. Pyridine (25 mL, 0.30 mol) and MsCl (4.67 mL, 60.4 mmol) were added. After reaction for 1 h the mixture was worked up by adding 30 mL saturated NH_4Cl, and extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel (EtOAc/hexanes 40:60) afforded a colourless oil (**7**) (14.13 g, 89%); $[\alpha]_D$=+45 ($CHCl_3$, *c* 0.22); IR 3290, 2990, 1532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm), 1.34 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 3.13 (s, 3H, $MeSO_3$), 3.38 (ddd, 1H, *J*=14.5, 6.0, 4.7 Hz, H-1), 3.60 (ddd, 1H, *J*=14.5, 7.8, 3.9 Hz, H-1′), 3.86 (dd, 1H, *J*=8.5, 6.9 Hz, H-4), 3.92 (dd, 1H, *J*=8.7, 5.5 Hz, H-6), 4.02 (dt, 1H, *J*=8.5, *ca.* 6.2 Hz, H-5), 4.05 (dd, 1H, *J*=6.9, 3.9 Hz, H-3), 4.17 (dd, 1H, *J*=8.7, 6.2 Hz, H-6′), 4.77 (td, 1H, *J*=ca. 6.5, 3.9 Hz, H-2), 5.83 (dd, 1H, *J*=7.8, 4.7 Hz, NH), 8.08 (d, 2H, *J*=8.9 Hz, Ns-H), 8.36 (d, 2H, *J*=8.9 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 26.1, 27.0, 27.1 (Me_2C), 38.7 (Me-SO_3), 44.9 (*C*-1), 67.8 (*C*-6), 76.9 (*C*-5), 77.7 (*C*-4), 78.0 (*C*-2), 79.9 (*C*-3), 110.2, 110.8 (Me_2C), 124.4, 128.3 (*C*H, Ns), 145.7, 150.1 (*C-ipso*, Ns); MS (CI, methane), *m*/*z* (%): 525 (MH^+, 29%), 467 (MH^+−acetone, 63%), 429 (MH^+−MsOH, 35%), 371 (MH^+−acetone–MsOH, 100%); HRMS: calcd for $C_{18}H_{25}O_{11}N_2S_2$ (M^+−Me) 509.0900, found 509.0895 (7%).

4.1.4. 1,2-Dideoxy-3,4;5,6-di-*O*-isopropylidene-1,2-(*N*-*p*-nitrobenzenesulfonyl)-imino-D-mannitol (9). Compound **7** (9.28 g, 17.6 mmol) was dissolved in dry THF (150 mL) and the solution cooled to 0°C. NaH (1.06 g, 35.2 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. After cooling to 0°C 30 mL saturated NH_4Cl was added, the mixture was extracted three times with CH_2Cl_2 (3×15 mL), and the organic phase dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 30:70) afforded a white crystalline product (**9**) (5.62 g, 74%); mp 111.4–112.0°C; $[\alpha]_D$=+50 ($CHCl_3$, *c* 0.38);

IR, 3449, 2989, 1534, 1350, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm), 1.23 (s, 3H, Me_2C), 1.33 (s, 3H, Me_2C), 1.34 (s, 3H, Me_2C), 1.42 (s, 3H, Me_2C), 2.58 (d, 1H, J=4.6 Hz, H-1), 2.77 (d, 1H, J=7.4 Hz, H-1′), 3.29 (ddd, 1H, J=7.4, 4.6, 3.2 Hz, H-2), 3.70 (t, 1H, J ca. 7.6 Hz, H-4), 3.91 (dd, 1H, J=8.5, 5.4 Hz, H-6), 4.04 (dt, 1H, J=7.9, ca. 5.7 Hz, H-5), 4.07 (dd, 1H, J=7.3, 3.2 Hz, H-3), 4.11 (dd, 1H, J=8.5, 6.2 Hz, H-6′), 8.17 (d, 2H, Ns-H), 8.39 (d, 2H, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.1, 26.5, 26.7, 26.9 (Me_2C), 30.9 (*C*-1), 40.8 (*C*-2), 67.5 (*C*-6), 76.5, 77.2, 79.0 (*C*-3, 4, 5), 109.9, 110.4 (Me_2C), 124.2, 129.5 (*C*H, Ns), 143.7, 150.7 (*C-ipso*, Ns); MS (CI, methane), *m/z* (%): 429 (MH^+, 41%), 371 (MH^+−acetone, 100%), 313 (MH^+−2acetone, 20%); HRMS: calculated for $C_{17}H_{21}N_2O_8S$ (M^+−Me) 413.1019, found 413.1023 (57%).

4.1.5. 1-Azido-1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-toluenesulfonyl)-amino-D-mannitol (10a). To a solution of *N*-tosyl aziridine **6** (3.0 g, 7.6 mmol) in dry DMF (50 mL) was added NaN_3 (4.91 g, 75.5 mmol) and the reaction mixture was stirred at 90°C for 8 h. Saturated aq. NH_4Cl (20 mL) was added, and the mixture was extracted three times with CH_2Cl_2 (3×10 mL). The organic phase was dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 50:50) afforded an oil (**10a**) (3.2 g, 96%); $[\alpha]_D$=−8.2 (CH_2Cl_2, *c* 0.19); IR 3245, 2995, 2940, 2105, 1450, 1380, 1340, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.26 (s, 3H, Me_2C), 1.32 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.54 (s, 3H, Me_2C), 2.44 (Me,Ts), 3.36 (ddt, 1H, J=8.5, 6.0, ca. 3.5 Hz, H-2), 3.47 (dd, 1H, J=12.5, 3.0 Hz, H-1), 3.53 (dd, 1H, J=12.5, 3.5 Hz, H-1′), 3.55 (dd, 1H, J=8.5, 6.5 Hz, H-4), 3.77 (dd, 1H, J=9.0, 6.5 Hz, H-6), 3.94 (dt, 1H, J=8.5, 6.5 Hz, H-5), 3.96 (dd, 1H, J=8.5, 6.5 Hz, H-3), 4.15 (dd, 1H, J=9.0, 6.5 Hz, H-6′), 5.70 (d, 1H, J=6.0 Hz, NH), 7.34 (d, 2H, Ts-H), 7.78 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.4, (*Me*,Ts), 24.9, 26.2, 26.7, 26.9 (Me_2C), 51.2 (*C*-1), 55.7 (*C*-2), 67.8 (*C*-6), 76.6, 78.1 (*C*-3, 5), 79.7 (*C*-4), 110.1, 110.4 (Me_2C), 127.1, 129.6 (*C*H, Ts), 137.0, 143.8 (*C-ipso*, Ts); MS (CI, methane), *m/z* (%): 441 (MH^+, 7%), 383 (MH^+−acetone, 49%), 325 (MH^+−2acetone, 100%); HRMS: calculated for $C_{18}H_{25}N_4O_6S$ (M^+−Me) 425.1495, found 425.1499 (22%).

4.1.6. 1-*O*-Acetyl-2-deoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-toluenesulfonyl)-amino-D-mannitol (10b). To a solution of *N*-tosyl aziridine **6** (2.5 g, 6.3 mmol) in dry THF (50 mL) was added KOAc (6.2 g, 63 mmol). After reaction at 90°C for 18 h, 20 mL sat. aq. NH_4Cl was added and the mixture was extracted three times with CH_2Cl_2 (3×10 mL). The organic phase was dried on MgSO4. Column purification on silica gel (EtOAc/hexanes 50:50) afforded **10b** as white crystals (2.6 g, 90%); mp 100–101°C; $[\alpha]_D$=+3.4 (CH_2Cl_2, *c* 0.13); IR 3265, 2990, 2935, 1745, 1440, 1370, 1335, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.29 (s, 3H, Me_2C), 1.31 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 1.93 (s, 3H, $MeCO_2$), 2.43 (s, 3H, Me,Ts), 3.62 (ddd, 1H, J=7.0, 4.5, 3.0 Hz, H-2), 3.71 (dd, 1H, J=8.5, 6.5 Hz, H-4), 3.83 (dd, 1H, J=8.5, 6.0 Hz, H-6), 3.92–4.01 (m, 2H, H-3, 5), 4.12–4.21 (m, 3H, H-1, 1′, 6′), 5.41 (d, 1H, J=7.0 Hz, NH), 7.30 (d, 2H, Ts-H), 7.77 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 ($MeCO_2$), 21.4 (*Me*,Ts), 25.1, 26.3, 26.7, 27.0 (Me_2C), 54.6 (*C*-2), 62.8 (*C*-1), 67.8 (*C*-6), 76.8, 79.1, 79.3 (*C*-3, 4, 5), 110.1, 110.4 (Me_2C), 127.1, 129.5 (*C*H, Ts), 137.7, 143.6 (*C-ipso*, Ts), 170.6 ($MeCO_2$);); MS (CI, methane), *m/z* (%): 458 (MH^+, 82%), 400 (MH^+−acetone, 100%), 342 (MH^+−2acetone, 38%); HRMS: calculated for $C_{20}H_{28}NO_8S$ (M^+−Me) 442.4536, found 442.4538 (17%).

4.1.7. Methyl 3,4-dideoxy-5,6;7,8-di-*O*-isopropylidene-2-(methoxycarbonyl)-4-(*N*-*p*-toluenesulfonyl)-amino-D-*manno*-octanoate (10c). To an ice-cooled solution of dimethyl malonate (625 μL, 5.46 mmol) in dry THF (12 mL) was added NaH (0.25 g, 9.19 mmol). A solution of *N*-tosyl aziridine **6** (1.09 g, 2.73 mmol) in THF (12 mL) was added dropwise, and the mixture was stirred at room temperature for 48 h. Sat. aq. NH_4Cl (10 mL) was added, the reaction mixture was extracted three times with CH_2Cl_2 (3×10 mL), and the organic phase was dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 40:60) afforded **10c** as a light yellow oil (0.88 g, 65%); IR, 2988, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.20 (s, 3H, Me_2C), 1.27 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 2.02 (ddd, 1H, J=14.5, 9.5, 5.2 Hz, H-3), 2.24 (ddd, 1H, J=14.5, 9.0, 3.8 Hz, H-3′), 2.43 (s, 3H, MeSO3), 3.45 (t, 1H, J=7.9 Hz, H-5), 3.58–3.61 (m, 1H, H-2), 3.60–3.65 (m, 1H, H-4), 3.72–3.76 (m, 8H, MeO_2C+H-7, 8), 4.05–4.12 (m, 2H, H-6, 8′), 5.03 (d, 1H, J=9.0 Hz, NH), 7.28 (d, 2H, Ts-H), 7.77 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (*Me*-Ts), 25.1, 26.3, 26.6, 26.8 (Me_2C), 29.8 (*C*-3), 47.9, 53.4, 77.0, 78.3, 81.6 (*C*H, *C*-2, 4, 5, 6, 7), 52.5, 52.6 (CO_2Me), 67.93 (*C*-8), 109.9, 110.1 (Me_2C), 127.3, 129.6 (*C*H, Ts), 137.8, 149.6 (*C-ipso*,Ts), 169.4, 170.2 (CO_2Me); MS (CI, methane), *m/z* (%): 530 (MH^+, 100%), 498 (MH^+−MeOH, 97%), 472 (MH^+−acetone, 39%), 440 (MH^+−MeOH−acetone, 67%); HRMS: calcd for $C_{24}H_{35}NO_{10}S$ (M^+) 529.1982, found 529.1980 (100%).

4.1.8. 3,4-Dideoxy-5,6;7,8-di-*O*-isopropylidene-2-phenylsulfonyl-4-(*N*-*p*-toluenesulfonyl)amino-D-*manno*-octanonitrile (10d). To an ice-cooled solution of (phenylsulfonyl)acetonitrile (0.9 g, 5.0 mmol) in dry THF (35 mL) was added NaH (0.2 g, 6.0 mmol), and then dropwise a solution of the *N*-tosyl aziridine **6** (2.0 g, 5.0 mmol) in THF (25 mL). After reaction at room temperature for 24 h, 15 mL sat. aq. NH_4Cl was added, the mixture was extracted with CH_2Cl_2 (3×10 mL), and the organic phase dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 50:50) afforded **10d** as a white solid (2.5 g, 87%); mp184–185°C; $[\alpha]_D$=−56 (CH_2Cl_2, *c* 0.43); IR 3280, 2990, 2360, 1445, 1375, 1360, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.22 (s, 3H, Me_2C), 1.23 (s, 3H, Me_2C), 1.34 (s, 3H, Me_2C), 1.49 (s, 3H, Me_2C), 2.29 (ddd, 1H, J=14.0, 12.0, 2.5 Hz, H-3), 2.42 (s, Me,Ts), 2.44 (ddd, 1H, J=14.0, 10.5, 3.5 Hz, H-3′), 3.22 (dd, 1H, J=8.5, 7.0 Hz, H-6), 3.52–3.58 (m, 1H, H-4), 3.61 (dd, 1H, J=7.0, 5.5 Hz, H-5), 3.64–3.69 (m, 1H, H-8), 3.71 (dd, 1H, J=11.5, 6.0 Hz, H-8′), 4.05–4.10 (m, 1H, H-7), 4.47 (dd, 1H, J=12.0, 3.5 Hz, H-2), 5.45 (d, 1H, J=8.0 Hz, NH), 7.31 (d, 2H, Ts-H), 7.65 (d, 2H, Ts-H), 7.78–8.03 (m, 5H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (Me,Ts), 24.7, 26.3, 26.4, 26.7 (Me_2C), 29.2 (*C*-3), 52.7 (*C*-4), 54.8 (*C*-2), 67.9 (*C*-8), 76.6, 78.1, 81.4 (*C*-5, 6, 7), 110.1, 110.5 (Me_2C), 113.9 (*C*-1), 127.5, 129.5,

129.6, 129.9, 135.3 (*C*H Ts, Ph), 135.8, 136.5, 144.3 (*C-ipso*Ts, Ph); MS (CI, methane), *m/z* (%): 579 (MH^+, 51%), 521 (MH^+−acetone, 18%), 57 (100%); HRMS: calculated for $C_{27}H_{34}N_2O_8S_2$ (M^+) 578.1757, found 578.1742 (35%).

4.1.9. 1,2-Dideoxy-3,4;5,6-di-*O*-isopropylidene-1-*C*-phenyl-2-(*N*-*p*-toluenesulfonyl)amino-D-mannitol (10e). To a cooled (0°C) solution of PhBr (2.7 mL, 25 mmol) in dry THF (25 mL) was added Mg wire (0.6 g, 25 mmol) and a crystal of I_2. The mixture was allowed to react first at room temperature and then at reflux until complete consumption of Mg (30–45 min). The mixture was cooled to −78°C, and CuI (0.1 g, 2.5 mmol) was added followed by dropwise addition of a solution of *N*-tosyl aziridine **6** (2.0 g, 5.0 mmol) in THF (30 mL). After reaction at room temperature for 1 h, the mixture was cooled to 0°C and worked up by adding 25 mL sat. aq. NH_4Cl. The mixture was extracted three times with CH_2Cl_2 (3×15 mL), and the organic phase dried on $MgSO_4$. Column chromatography on silica gel (EtOAc/hexanes 30:70) afforded **10e** as white crystals (1.8 g, 75%); mp 101–102°C; $[\alpha]_D$=−1.7 (CH_2Cl_2, *c* 0.26); IR 3280, 2985, 2935, 1455, 1370, 1330, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.33 (s, 3H, Me_2C), 1.34 (s, 6H, Me_2C), 1.44 (s, 3H, Me_2C), 2.39 (s, 3H, Me,Ts), 2.80 (dd, 1H, *J*=14.0, 4.5 Hz, H-1), 2.91 (dd, 1H, *J*=14.0, 7.0 Hz, H-1′), 3.63 (dd, 1H, *J*=8.0, 7.0 Hz, H-4), 3.62–3.69 (m, 1H, H-2), 3.80 (dd, 1H, *J*=8.5, 6.0 Hz, H-6), 3.90–3.96 (m, 2H, H-3, 5), 4.09 (dd, 1H, *J*=8.5, 6.7 Hz, H-6′), 4.98 (d, 1H, *J*=7.0 Hz, NH), 6.96–7.12 (m, 2H, Ph-H), 7.03–7.22 (m, 3H, Ph-H), 7.18 (d, 2H, Ts-H), 7.59 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.3 (*Me*,Ts), 25.0, 26.4, 26.9, (Me_2C), 35.5 (*C*-1), 55.9 (*C*-2), 67.6 (*C*-6), 76.7, 78.9 80.5 (*C*-3, 4, 5), 109.7, 109.8 (Me_2C), 126.3, 127.1, 128.2, 129.3, 129.7 (*C*H Ts, Ph), 136.3, 136.9, 143.1 (*C-ipso*,Ts; Ph); MS (CI, methane), *m/z* (%): 476 (MH^+, 41%), 418 (MH^+−acetone, 100%), 360 (MH^+−2acetone, 29%); HRMS: calculated for $C_{24}H_{30}NO_6S$ (M^+−Me) 460.1794, found 460.1797 (16%).

4.1.10. 1-Benzylamino-1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-toluenesulfonyl)-amino-D-mannitol (10f). To a solution of *N*-tosyl aziridine **6** (1.5 g, 3.8 mmol) in dry DMF (40 mL) was added $BnNH_2$ (0.5 mL, 4.6 mmol). The reaction mixture was stirred at 90°C for 24 h, then cooled to room temperature, and treated with 15 mL sat. aq. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the organic phase dried on $MgSO_4$ and evaporated. Column purification on silica gel (EtOAc/hexanes 50:50) gave **10f** as a light yellow oil (1.3 g, 67%); IR 3265, 2985, 2935, 1455, 1375, 1335, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.26 (s, 3H, Me_2C), 1.30 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 1.42 (s, 3H, Me_2C), 2.40 (s, 3H, Me,Ts), 2.48 (dd, 1H, *J*=12.5, 4.5 Hz, H-1), 2.84 (dd, 1H, *J*=12.5, 4.0 Hz, H-1′), 3.38–3.46 (m, 1H, H-2), 3.58 (d, 1H, *J*=13.5 Hz, CH_2Ph), 3.61 (d, 1H, *J*=13.5 Hz, CH'_2Ph), 3.62 (dd, 1H, *J*=7.0, 6.0 Hz, H-3), 4.04–4.18 (m, 1H, H-6′), 7.23 (m, 5H, Ph-H), 7.30 (d, 2H, Ts-H), 7.72 (d, 2H, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (Me,Ts), 25.2, 26.5, 26.8, 27.0 (Me_2C), 47.5 (CH_2Ph), 53.6 (*C*-1), 54.2 (*C*-2), 67.6 (*C*-6), 76.8, 78.9, 80.7 (*C*-3, 4, 5), 109.9, 110.0 (Me_2C), 127.3, 128.0, 128.4, 129.6 (*C*H Ts, Ph), 137.3, 139.9, 143.4 (*C-ipso*Ts, Ph); MS (CI, methane), *m/z* (%): 505 (MH^+, 100%), 447 (MH^+−acetone, 12%); HRMS: calcd for $C_{25}H_{33}O_6N_2S$ (M^+−Me) 489.2059, found 489.2060 (20%).

4.1.11. 2,3-Dideoxy-4,5;6,7-di-*O*-isopropylidene-3-(*N*-*p*-toluenesulfonyl)-amino-D-*manno*-heptose propane-1,3-diyl-dithioacetal (10g). A mixture of dithiane (1.11 g, 9.27 mmol) and BuLi (1.6 M in THF, 5.8 mL, 9.27 mmol) in dry THF (35 mL) was stirred at 0°C for 30 min. To this mixture was added dropwise a solution of *N*-tosyl aziridine **6** (1.84 g, 4.63 mmol) in dry THF (35 mL) during 20 min. After being stirred at room temperature for 21 h, the mixture was cooled to 0°C, and worked up by adding 15 mL sat. aq. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3×10 mL) and the organic phase was dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 40:60) afforded **10g** as a yellow foam (2.14 g, 90%); $[\alpha]_D$=−6.1 ($CHCl_3$, *c* 0.61); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.24 (s, 3H, Me_2C), 1.28 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 1.81–1.87 (m, 1H, dithiane H-5), 1.95 (dt, 2H, *J*=8.9, 3.7 Hz, H-2), 2.02–2.06 (m, 1H, dithiane H-5′), 2.60 (ddd, 1H, *J*=13.7, 11.0, 2.6 Hz, dithiane H-4), 2.72–2.82 (m, 3H, dithiane H-4′,6,6′), 3.49 (dd, 1H, *J*=7.0, 8.0 Hz, H-7), 3.76–3.85 (m, 4H, H-3, H-4, H-6, H-7′), 4.00 (dd, 1H, *J*=8.9, 5.2 Hz, H-1), 4.10 (dd, 1H, *J*=8.0, 5.8 Hz, H-5), 5.14 (d, 1H, *J*=8.4 Hz, NH), 7.29 (d, 2H, *J*=8.3 Hz, Ts-H), 7.83 (d, 2H, *J*=8.3 Hz, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.45 (*Me*,Ts), 25.11, 26.55, 26.74, 26.83 (Me_2C), 25.73 (*C*-2), 29.26, 29.84 (dithiane *C*-4,6), 36.61 (dithiane *C*-5), 42.80 (*C*-3), 52.36 (*C*-1), 67.70 (*C*-7), 76.86, 78.48, 82.09 (*C*-4, *C*-5, *C*-6), 109.85, 109.98 (Me_2C), 127.43, 129.50 (*C*H, Ts), 137.78, 143.32 (*C-ipso*,Ts); MS (EI), *m/z* (%): 517 (M^+, 5%), 502 (M^+−CH_3, 9%), 444 (502−Me_2CO, 2%), 384 (M^+−$CH_3CH_2(SCH_2)_2CH_2$, 1%), 362 (M^+−Ts, 7%), 230 (362−$CHCH_2(SCH_2)_2CH_2$, 100%), 172 (230−Me_2CO, 26%); HRMS: calcd for $C_{23}H_{35}O_6NS_3$ (M^+) 517.1626, found 517.1627 (7%).

4.1.12. 1-Azido-1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-nitrobenzenesulfonyl)amino-D-mannitol (11a). To a solution of *N*-nosyl aziridine **9** (3.00 g, 7.02 mmol) in dry DMF (50 mL) was added NaN_3 (4.56 g, 70.2 mmol). After reaction at 90°C for 8 h, 25 mL sat. aq. NH_4Cl was added and the mixture extracted with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel (EtOAc/hexanes 30:70) afforded **11a** as a white crystalline product (3.24 g, 98%); mp 98.8–99.3°C; $[\alpha]_D$=+14.3 ($CHCl_3$, *c* 0.38); IR 3263, 2989, 2107, 1532, 1350, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.32 (s, 3H, Me_2C), 1.34 (s, 3H, Me_2C), 1.40 (s, 3H, Me_2C), 1.53 (s, 3H, Me_2C), 3.51–3.55 (m, 3H, H-1, 1′, 2), 3.66 (dd, 1H, *J*=8.6, 6.8 Hz, H-4), 3.85 (dd, 1H, *J*=8.7, 6.2 Hz, H-6), 3.97 (dt, 1H, *J*=8.6, 6.2 Hz, H-5), 4.01 (t, 1H, *J*=6.8 Hz, H-3), 4.20 (dd, 1H, *J*=8.7, 6.2 Hz, H-6′), 5.94 (d, 1H, *J*=4.1 Hz, NH), 8.11 (d, 2H, *J*=7.1 Hz, Ns-H), 8.39 (d, 2H, *J*=7.1 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 26.3, 26.8, 26.9 (Me_2C), 51.2 (*C*-1), 56.0 (*C*-2), 68.0 (*C*-6), 76.7, 78.6, 79.8 (*C*-3, 4, 5), 110.5, 110.7 (Me_2C), 124.3, 128.3 (*C*H, Ns), 146.4, 150.1 (*C-ipso*, Ns); MS (CI, methane), *m/z* (%): 472 (MH^+, 100%), 414 (MH^+−acetone, 84%), 356 (MH^+−2acetone, 20%); HRMS: calcd for $C_{18}H_{25}O_8N_5S$ (M^+) 471.1424, found 471.1434 (65%).

4.1.13. 1-*O*-Acetyl-2-deoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-nitrobenzenesulfonyl)amino-D-mannitol (11b). To a solution of *N*-nosyl aziridine **9** (2.24 g, 5.23 mmol) in dry DMF (45 mL) was added KOAc (5.13 g, 52.3 mmol). After being stirred at 90°C for 18 h, the reaction mixture was diluted with 20 mL sat. aq. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the organic phase was dried on $MgSO_4$. After evaporation, the residue was purified on silica gel (EtOAc/hexanes 30:70) to yield **11b** as a slightly yellow oil (2.12 g, 83%); $[\alpha]_D$=+29.6 ($CHCl_3$, *c* 0.52); IR 3445, 2989, 1740, 1532, 1350, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.31 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 1.92 (s, 3H, $MeCO_2$), 3.75 (dd, 1H, *J*=8.5, 6.8 Hz, H-4), 3.76–3.81 (m, 1H, H-2), 3.88 (dd, 1H, *J*=8.6, 5.8 Hz, H-6), 3.95 (t, 1H, *J*=6.8 Hz, H-3), 3.92–3.98 (m, 1H, H-5), 4.12 (dd, 1H, *J*=11.8, 5.5 Hz, H-1), 4.18 (dd, 1H, *J*=8.6, 6.1 Hz, H-6′), 4.21 (dd, 1H, *J*=11.8, 3.8 Hz, H-1′), 5.68 (d, 1H, *J*=7.2 Hz, NH), 8.09 (d, 2H, *J*=9.2 Hz, Ns-H), 8.36 (d, 2H, *J*=9.2 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 (*Me*CO_2), 25.1, 26.3, 26.8, 26.9 (*Me*$_2$C), 54.9 (*C*-2), 62.5 (*C*-1), 67.9 (*C*-6), 76.9, 79.3, 79.5 (*C*-3, 4, 5), 110.3, 110.6 (Me_2C), 124.2, 128.3 (*C*H, Ns), 146.9, 150.0 (*C-ipso*, Ns); MS (CI, methane), *m*/*z* (%): 489 (MH^+, 33%), 431 (MH^+−acetone, 100%), 373 (MH^+−2acetone, 18%); HRMS: calcd for $C_{20}H_{28}O_{10}N_2S$ (M^+) 488.1465, found 488.1469 (26%).

4.1.14. Methyl 3,4-dideoxy-5,6;7,8-di-*O*-isopropylidene-2-(methoxycarbonyl)-4-(*N*-*p*-nitrobenzenesulfonyl)amino-D-*manno*-octanoate (11c). To an ice-cooled solution of dimethyl malonate (1.08 mL, 9.46 mmol) in dry THF (30 mL) was added NaH (0.43 g, 14.1 mmol), and then dropwise a solution of *N*-nosyl aziridine **9** (2.02 g, 4.73 mmol) in THF (30 mL). The mixture was stirred at room temperature for 4 h. Sat. aq. NH_4Cl (25 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and the organic phase was dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 40:60) afforded **11c** as a slightly yellow oil (2.07 g, 78%); IR 3278, 2989, 1737, 1532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.21 (s, 3H, Me_2C), 1.28 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.49 (s, 3H, Me_2C), 2.10 (ddd, 1H, *J*=14.7, 9.7, 5.2 Hz, H-3), 2.23 (ddd, 1H, *J*=14.7, 9.4, 3.6 Hz, H-3′), 3.58 (t, 1H, *J*=7.5 Hz, H-5), 3.68 (dd, 1H, *J*=9.4, 5.2 Hz, H-2), 3.67–3.70 (m, 1H, H-6), 3.77–3.80 (m, 1H, H-4), 3.76 (s, 6H, MeO_2C), 3.80–3.82 (m, 1H, H-7), 3.83 (dd, 1H, *J*=13.7, 5.4 Hz, H-8), 4.12 (dd, 1H, *J*=13.7, 7.2 Hz, H-8′), 5.61 (d, 1H, *J*=9.0 Hz, NH), 8.11 (d, 2H, *J*=8.9 Hz, Ns-H), 8.36 (d, 2H, *J*=8.9 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.9, 26.2, 26.5, 26.7 (*Me*$_2$C), 29.2 (*C*-3), 47.8 (*C*-2), 52.5, 52.6 (MeO_2C–), 53.7 (*C*-4), 67.7 (*C*-8), 77.0 (*C*-7), 78.2 (*C*-6), 81.8 (*C*-5), 109.9, 110.2 (Me_2C), 124.1, 128.4 (*C*H, Ns), 146.7, 149.9 (*C-ipso*, Ns), 169.0, 169.7 (Me_2O_2C); MS (CI, methane), *m*/*z* (%): 561 (MH^+, 31%), 529 (MH^+−MeOH, 30%), 503 (MH^+−acetone, 76%), 471 (MH^+−acetone−MeOH, 64%), 445 (MH^+−2acetone, 75%); HRMS: calcd for $C_{23}H_{32}O_{12}N_2S$ (M^+) 560.1676, found 560.1669 (28%).

4.1.15. 1,2-Dideoxy-3,4;5,6-di-*O*-isopropylidene-2-(*N*-*p*-nitrobenzenesulfonyl)-amino-1-phenylthio-D-mannitol (11h). To a solution of the *N*-nosyl aziridine **9** (2.54 g, 5.93 mmol) in dry DMF (50 mL) was added K_2CO_3 (2.46 g, 17.8 mmol) and PhSH (0.91 mL, 8.90 mmol). The reaction mixture was stirred at room temperature for 1 h. Sat. aq. NH_4Cl (25 mL) was added, the mixture was extracted with CH_2Cl_2 (3×15 mL) and the organic layer dried on $MgSO_4$. Column purification on silica gel (EtOAc/hexanes 20:80) afforded **11h** as a white crystalline product (2.84 g, 89%); mp 85.0–85.5°C; $[\alpha]_D$=+55 ($CHCl_3$, *c* 0.60); IR 3404, 1354, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.31 (s, 3H, Me_2C), 1.34 (s, 3H, Me_2C), 1.40 (s, 3H, Me_2C), 1.44 (s, 3H, Me_2C), 3.08 (dd, 1H, *J*=14.0, 4.5 Hz, H-1), 3.19 (dd, 1H, *J*=14.0, 5.9 Hz, H-1′), 3.74 (dd, 1H, *J*=8.5, 6.9 Hz, H-4), 3.74–3.79 (m, 1H, H-2), 3.89 (dd, 1H, *J*=8.6, 6.2 Hz, H-6), 4.00 (dt, 1H, *J*=8.5, 6.2 Hz, H-5), 4.17 (dd, 1H, *J*=8.6, 6.2 Hz, H-6′), 4.20 (t, 1H, *J*=6.9 Hz, H-3), 5.67 (d, 1H, *J*=6.5 Hz, NH), 7.10 (m, 5H, SPh-H), 7.97 (s, 2H, Ns-H), 8.17 (d, 2H, *J*=7.0 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 25.2, 26.4, 26.9, 27.7 (*Me*$_2$C), 34.9 (C-1), 54.8 (C-2), 68.0 (C-6), 76.9, 79.2, 80.4 (C-3, 4, 5), 110.2, 110.4 (Me_2C), 124.0, 126.4, 128.4 (*C*H, SPh), 128.9, 129.0 (*C*H, Ns), 135.3 (*C-ipso*, SPh), 146.0, 149.9 (*C-ipso*, Ns); MS (CI, methane), *m*/*z* (%): 539 (MH^+, 37%), 481 (MH^+−acetone, 100%), 423 (MH^+−2acetone, 27%); HRMS: calcd for $C_{23}H_{27}O_8N_2S_2$ (M^+−Me) 523.1209, found 523.1216 (12%).

4.1.16. 2-*O*-Acetyl-6-azido-1,6-dideoxy-3,4-*O*-isopropylidene-(*N*-*p*-toluenesulfonyl)-mannojirimycin (15a). To a solution of compound **10a** (1.01 g, 2.3 mmol) in MeOH/H_2O 9:1 (40 mL) was added Dowex 50X8-200 (1.2 g) and the mixture was allowed to react at room temperature for 30 h. The mixture was filtered and the resin washed thoroughly with MeOH. Following concentration under diminished pressure, the residue was purified by column chromatography on silica gel (EtOAc/hexanes 80:20) to afford diol **12a** (0.65 g, 72%). To an ice-cooled solution of the diol (0.20 g, 0.5 mmol) in dry THF (40 mL) was added Ph_3P (0.20 g, 0.75 mmol) and DEAD (0.13 g, 0.75 mmol). The mixture was allowed to react at room temperature for 5 days. Sat. aq. NH_4Cl was added and the mixture was extracted three times with CH_2Cl_2 (3×10 mL), the organic phase dried on $MgSO_4$ and evaporated. The residue was made to react with pyridine (5 mL) and Ac_2O (1 mL). After reaction at room temperature for 5 h, the mixture was concentrated under diminished pressure and the residue was purified by column chromatography on silica gel (EtOAc/hexanes 50:50) to give **15a** as a slightly yellow oil (0.09 g; 45%); IR 2985, 2935, 2105, 1755, 1450, 1370, 1360, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.31 (s, 1H, Me_2C), 1.37 (s, 3H, Me_2C), 2.07 (s, 3H, Me,Ts), 2.43 (s, 3H, OAc), 2.97 (dd, 1H, *J*=10.0, 5.5 Hz, H-3), 3.20 (dd, 1H, *J*=15.5, 6.5 Hz, H-1), 3.58 (dd, 1H, *J*=12.5, 3.0 Hz, H-6), 3.82 (dd, 1H, *J*=12.5, 4.5 Hz, H-6′), 3.86–3.91 (m, 1H, H-5), 4.01 (dd, 1H, *J*=10.0, 9.0 Hz, H-4), 4.26–4.30 (m, 1H, H-1′), 5.23 (ddd, 1H, *J*=8.5, 6.5, 5.5 Hz, H-2), 7.35 (d, 2H, *J*=7 Hz, Ts-H), 7.73 (d, 2H, *J*=7 Hz, Ts-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 (*Me*CO_2), 21.4 (*Me*,Ts), 26.4, 26.8 (*Me*$_2$C), 46.5 (*C*-1), 53.3 (*C*-6), 58.6, 64.1, 70.8, 75.5 (*C*-2, 3, 4, 5), 113.2 (Me_2C), 126.9, 130.0 (*C*H, Ts), 136.0, 144.3 (*C-ipso*,Ts), 169.8 (Me*C*O_2); MS (CI, methane), *m*/*z* (%): 425 (MH^+, 34%),

367 (MH^+−acetone, 100%); HRMS: calculated for $C_{17}H_{21}NO_6S$ (M^+−Me) 409.1182, found 409.1188 (9%).

4.1.17. 1-Azido-6-bromo-3,4-*O*-isopropylidene-2-(*N*-*p*-nitrobenzenesulfonyl)amino-1,2,6-trideoxy-D-mannitol (16a). To a solution of compound **11a** (0.87 g, 1.85 mmol) in MeOH/H_2O (13.5 mL, 9:1) was added Dowex 50X8-200 (0.73 g) and the reaction mixture was stirred at room temperature for 2 days. The mixture was filtered and the resin washed thoroughly with MeOH. Following evaporation of the solvent, the residue containing diol **13a** was freed from residual water by co-evaporation with toluene. In another flask, the Appel reagent was prepared by reaction of Ph_3P (0.73 g, 2.78 mmol) and CBr_4 (0.86 g, 2.59 mmol) in dry THF (40 mL) at 0°C. When a yellow precipitate had formed, a THF (30 mL) solution of the diol **13a** was added and the mixture was stirred for 30 min at room temperature. Then MeOH (0.3 mL) was added dropwise to destroy the excess of reagent. Following addition of 20 mL sat. aq. NH_4Cl, the organic layer was collected and the aqueous phase was further extracted with CH_2Cl_2 (3× 10 mL). Purification by flash column chromatography on silica gel (EtOAc/hexanes 40:60) afforded **16a** as a slightly yellow oil (0.68 g, 75%); $[\alpha]_D$=+8.1 ($CHCl_3$, *c* 0.92); IR 3498, 2106, 1637, 1534, 1160, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.32 (s, 3H, Me_2C), 1.35 (s, 3H, Me_2C), 3.06 (s, 1H, –OH), 3.42 (dd, 1H, *J*=10.3, 2.5 Hz, H-6), 3.44–3.46 (m, 1H, H-2), 3.48–3.52 (m, 1H, H-4), 3.54 (dd, 1H, *J*=10.3, 6.4 Hz, H-6′), 3.61 (dd, 1H, *J*=12.7, 3.5 Hz, H-1), 3.70–3.73 (m, 1H, H-5), 3.75 (dd, 1H, *J*=12.7, 2.5 Hz, H-1′), 4.10 (dd, 1H, *J*=8.0, 6.4 Hz, H-3), 6.10 (s, 1H, NH), 8.12 (d, 2H, *J*=9.0 Hz, Ns-H), 8.39 (d, 2H, *J*=9.0 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 26.8, 26.9 (*Me*$_2$C), 37.5 (*C*-6), 52.0 (*C*-1), 56.6 (*C*-2), 73.2 (*C*-5), 78.5, 79.3 (*C*-3, 4), 110.1 (Me_2C), 124.4, 128.5 (*C*H, Ns), 146.0, 150.2 (*C-ipso*, Ns); MS (CI, methane), *m*/*z* (%): 496 (MH^+, 2%), 414 (MH^+−HBr, 7%), 356 (MH^+−HBr−acetone, 100%); HRMS: calcd for $C_{14}H_{19}O_7N_5BrS$ (M^+−Me), 478.0032, found 478.0064 (25%).

4.1.18. 1-Phenylthio-6-bromo-3,4-*O*-isopropylidene-2-(*N*-*p*-nitrobenzenesulfonyl)amino-1,2,6-trideoxy-D-mannitol (16h). To a solution of compound **11h** (0.52 g, 0.96 mmol) in MeOH/H_2O (7.05 mL, 9:1) was added Dowex 50X8-200 (0.38 g), and the reaction mixture was stirred at room temperature for 7 days. The mixture was filtered and the resin washed thoroughly with MeOH. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/hexanes 80:20) to give diol **13h** as an oil (0.43 g, 89%). To a solution of the diol (0.42 g, 0.84 mmol) in dry THF (30 mL) was added Ph_3P (0.74 g, 2.84 mmol) and CBr_4 (0.47 g, 1.42 mmol) at 0°C. The reaction mixture was stirred at room temperature for 30 min. Then MeOH (0.2 mL) was added dropwise to destroy the excess of reagent. Sat. aq. NH_4Cl (20 mL) was added and the organic layer was collected. The aqueous layer was further extracted with CH_2Cl_2 (3×10 mL). Flash column chromatography on silica gel (EtOAc/hexanes 40:60) afforded **16h** as a slightly yellow oil (0.46 g, 98%); $[\alpha]_D$=+43 ($CHCl_3$, *c* 0.64); IR 3500, 3280, 2990, 1530, 1350, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.32 (s, 3H, Me_2C), 1.35 (s, 3H, Me_2C), 3.13 (dd, 1H, *J*=14.2, 6.2 Hz, H-1), 3.22 (dd, 1H, *J*=14.2, 4.0 Hz, H-1′), 3.51 (dd, 1H, *J*=11.1, 6.7 Hz, H-6), 3.72–3.80 (m, 4H, H-2, 4, 5, 6′), 4.25 (t, 1H, *J*=6.2 Hz, H-3), 6.00 (d, 1H, *J*=7.2 Hz, NH), 7.10–7.21 (m, 5H, SPh), 7.96 (d, 2H, *J*= 8.9 Hz, Ns-H), 8.19 (d, 2H, *J*=8.9 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 26.9 (*Me*$_2$C), 35.4 (C-1), 37.7 (C-6), 55.6 (C-2), 73.0 (C-5), 78.7, 80.6 (C-3, 4), 110.7 (Me_2C), 124.1, 126.3, 128.4, 128.8, 129.0 (*C*H, Ns; *C*H, SPh), 135.4 (*C-ipso*, SPh), 145.8, 150.0 (*C-ipso*, Ns); MS (CI, methane), *m*/*z* (%): 563 (MH^+, 2%), 481 (MH^+−HBr, 16%), 423 (MH^+− HBr−acetone, 100%); HRMS: calcd for $C_{21}H_{25}O_7N_2BrS_2$ (M^+) 560.0287, found 560.0279 (10%).

4.1.19. 2-*O*-Acetyl-6-azido-1,6-dideoxy-3,4-*O*-isopropylidene-(*N*-*p*-nitrobenzenesulfonyl)-mannojirimycin (19a). *Procedure A*: To an ice-cooled solution of 6-bromo derivative **16a** (2.58 g, 5.8 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (3.2 mL, 23.0 mmol), DMAP (4.21 g, 34.5 mmol) and Ac_2O (2.2 mL, 23.0 mmol). After reaction at room temperature for 4 days, 30 mL sat. aq. solution of Na_2CO_3 was added. The mixture was extracted with CH_2Cl_2 (3× 15 mL). The organic phase was dried on $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes 30:70) to give **19a** as white crystals (2.00 g, 76%); mp 56.3–57.8°C; $[\alpha]_D$=−36 ($CHCl_3$, *c* 0.91); IR 3468, 2990, 2106, 1740, 1534, 1350, 1166, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.37 (s, 3H, Me_2C), 1.41 (s, 3H, Me_2C), 2.09 (s, 3H, OAc), 3.27 (dd, 1H, *J*=9.0, 5.2 Hz, H-3), 3.29 (dd, 1H, *J*=15.5, 6.5 Hz, H-1), 3.62 (dd, 1H, *J*=13.0, 3.3 Hz, H-6), 3.82 (dd, 1H, *J*=13.0, 3.6 Hz, H-6′), 4.00–4.06 (m, 1H, H-5), 4.04 (t, 1H, *J*=9.0 Hz, H-4), 4.22 (dd, 1H, *J*=15.5, 7.8 Hz, H-1′), 5.32 (ddd, 1H, *J*=7.8, 6.5, 5.2 Hz, H-2), 8.06 (d, 2H, *J*=6.9 Hz, Ns-H), 8.40 (d, 2H,*J*=6.9 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 (*C*H_3COO), 26.4, 26.9 (*Me*$_2$C), 47.0 (*C*-1), 52.7 (*C*-6), 59.1 (*C*-5), 64.1 (*C*-2), 70.8 (*C*-4), 75.9 (*C*-3), 113.6 (Me_2C), 124.6, 128.2 (*C*H, Ns), 145.0, 150.2 (*C-ipso*, Ns), 169.8 (*C*H_3*C*OO); MS (CI, methane), *m*/*z* (%): 456 (MH^+, 27%), 428 (MH^+−N_2, 7%), 398 (MH^+−acetone, 100%), 213 (MH^+−Ns, 10%); HRMS: calculated for $C_{16}H_{19}N_5O_8S$ (M^+−Me) 440.0876, found 440.0876 (2.8%).

Procedure B proceeding via 5-O-acetyl-6-iodo derivative **18a**: To a solution of diol **13a** (1.25 g, 2.90 mmol) in dry THF (50 mL) was added Ph_3P (2.28 g, 8.70 mmol) and CI_4 (2.26 g, 4.35 mmol). The reaction mixture was stirred at room temperature for 18 h. MeOH (15 mL) and sat. aq. NH_4Cl (20 mL) were added and the mixture was extracted three times with CH_2Cl_2 (3×20 mL). The organic phase was dried on $MgSO_4$ and evaporated, and the residue was purified on silica gel using EtOAc/Hexane (40:60) to give the 6-iodo analogue of **16a** as an oil (1.10 g, 70%).

The 6-iodo derivative **16a** (1.10 g, 2.03 mmol) was dissolved in CH_2Cl_2 (10 mL). Pyridine (0.98 mL, 12.2 mmol) and Ac_2O (0.77 mL, 8.1 mmol) were added and the mixture was stirred at room temperature for 2 h. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel using EtOAc/Hexane (30:70) yielded the 6-iodo

analogue of **18a** as a slightly yellow oil (1.12 g, 95%); IR 3283, 2107, 1741, 1531, 1350, 1230, 1165, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.36 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 2.22 (s, 3H, OAc), 3.38 (dd, 1H, J=12.0, 5.5 Hz, H-6), 3.40–3.42 (m, 1H, H-1), 3.54–3.56 (m, 2H, H-1′+H-2), 3.58 (dd, 1H, J=12.0, 3.5 Hz, H-6′), 4.00 (dd, 1H, J=7.7, 6.0 Hz, H-4), 4.06 (t, 1H, J=6.0 Hz, H-3), 4.63 (ddd, 1H, J=7.7, 5.5, 3.5 Hz, H-5), 5.48 (d, 1H, J=8.9 Hz, NH), 8.10 (d, 2H, J=7.0 Hz, Ns-H), 8.39 (d, 2H, J=7.0 Hz, H-Ns); ^{13}C NMR (100 MHz, $CDCl_3$) 5.29 (*C*-6), 21.0 (*Me*CO_2), 27.0 (*Me*$_2$C), 27.2 (*Me*$_2$C), 50.8 (*C*-1), 55.7 (*C*-2), 72.7 (*C*-5), 78.6, 79.2 (*C*-3, 4), 111.2 (Me_2C), 124.5, 128.2 (*C*H, Ns), 146.4, 150.2 (*C-ipso*, Ns), 170.0 (Me*C*O_2); MS (CI, methane), *m/z* (%): 556 (MH^+-N_2, 1%), 496 (MH^+-N_2-AcOH, 19%), 456 (MH^+-HI, 29%), 398 (MH^+-HI−acetone, 100%).

The 6-iodo derivative **18a** (0.90 g, 1.54 mmol) was dissolved in CH_2Cl_2 (20 mL), DMAP (1.88 g, 15.4 mmol) was added, and the mixture was stirred at room temperature for 3 days. Sat. aq. NH_4Cl (10 mL) was added, and the mixture extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel using EtOAc/Hexane (30:70) gave **19a** as white crystals (0.49 g, 70%).

4.1.20. 2-*O*-Acetyl-6-phenylthio-1,6-dideoxy-3,4-*O*-isopropylidene-(*N*-*p*-nitrobenzenesulfonyl)-mannojirimycin (19h). *Procedure A*: To an ice-cooled solution of 6-bromo derivative **16h** (0.15 g, 0.27 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.15 mL, 1.1 mmol), DMAP (0.20 g, 1.6 mmol) and Ac_2O (0.10 mL, 1.1 mmol). After reaction at room temperature for 4 days, 10 mL sat. aq. solution of Na_2CO_3 was added. The mixture was extracted three times with CH_2Cl_2 (3×10 mL). The organic phase was dried on $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes 40:60) to give **19h** as a colourless oil (0.11 g, 79%); $[\alpha]_D=-72$ (CH_2Cl_2, *c* 0.45); IR 3454, 2987, 1747, 1532, 1350, 1165, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.28 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), 2.07 (s, 3H, OAc), 3.27 (dd, 1H, J=9.9, 5.2 Hz, H-3), 3.34–3.44 (m, 3H, H-1, 6, 6′), 4.05 (t, 1H, J=9.9 Hz, H-4), 4.18–4.20 (m, 1H, H-5), 4.21 (dd, 1H, J=15.2, 8.0 Hz, H-1′), 5.31 (ddd, 1H, J=8.0, 6.4, 5.2 Hz, H-2), 7.20–7.35 (m, 5H, SPh), 7.98 (d, 2H, J=9.0 Hz, Ns-H), 8.31 (d, 2H, J=9.0 Hz, Ns-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 (*C*H_3COO), 26.2, 26.9 (*Me*$_2$C), 37.3 (*C*-6), 47.2 (*C*-1), 59.6 (*C*-5), 64.4 (*C*-2), 72.4 (*C*-4), 76.0 (*C*-3), 113.3 (Me_2C), 124.5, 126.7, 128.3, 129.1, 129.4 (*C*H, Ns; *C*H, SPh), 135.5 (*C-ipso*, SPh), 145.2, 150.1 (*C-ipso*, Ns), 169.9 (CH_3COO); MS (CI, methane), *m/z* (%): 523 (MH^+, 29%), 465 (MH^+-acetone, 100%); HRMS: calcd for $C_{23}H_{26}O_8N_2S_2$ (M^+) 522.1131, found 522.1141 (22%).

Procedure B proceeding via 5-O-acetyl-6-iodo derivative **18h**: To a solution of diol **13h** (0.62 g, 1.24 mmol) in dry THF (30 mL) was added Ph_3P (0.98 g, 3.73 mmol) and CI_4 (0.97 g, 1.87 mmol). The reaction mixture was stirred at room temperature for 18 h. MeOH (10 mL) and sat. aq. NH_4Cl (20 mL) were added and the mixture was extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated, and the residue was purified on silica gel using EtOAc/Hexane (40:60) to give the 6-iodo analogue of **16h** as an oil (0.54 g, 71%).

The 6-iodo derivative **16h** (0.41 g, 0.68 mmol) was dissolved in CH_2Cl_2 (5 mL). Pyridine (0.33 mL, 4.05 mmol) and Ac_2O (0.26 mL, 2.70 mmol) were added and the mixture was stirred at room temperature for 2 h. Sat. aq. NH_4Cl (5 mL) was added and the mixture extracted three times with CH_2Cl_2 (3×10 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel using EtOAc/Hexane (30:70) yielded the 5-*O*-acetyl-6-iodo derivative **18h** as a slightly yellow oil (0.44 g, 96%); IR 3443, 1740, 1649, 1530, 1348, 1226, 1160, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.32 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 2.10 (s, 3H, OAc), 3.06 (d, 2H, J=6.2 Hz, H-1+H-1′), 3.42 (dd, 1H, J=11.2, 4.8 Hz, H-6), 3.60 (dd, 1H, J=11.2, 3.6 H-6′), 3.67–3.72 (m, 1H, H-2), 4.07 (dd, 1H, J=8.0, 7.0 Hz, H-4), 4.19 (dd, 1H, J=7.0, 4.1 Hz, H-3), 4.53 (ddd, 1H, J=8.0, 4.8, 3.6 Hz, H-5), 5.26 (d, 1H, J=8.3 Hz, NH), 7.12–7.28 (m, 5H, H-SPh), 7.91 (d, 2H, J=8.9 Hz, H-Ns), 8.20 (d, 2H, J=8.9 Hz, H-Ns); ^{13}C NMR (100 MHz, $CDCl_3$) 6.20 (*C*-6), 20.9 (*Me*CO_2), 26.9 (*Me*$_2$C), 27.1 (*Me*$_2$C), 33.8 (*C*-1), 54.9 (*C*-2), 72.6 (*C*-5), 77.9, 80.9 (*C*-3,4), 111.0 (Me_2C), 124.1, 126.8, 128.2, 129.2, 129.3 (*C*H-SPh), 134.6 (*C-ipso*, SPh), 146.2, 150.0 (*C-ipso*, Ns), 169.8 (Me*C*O_2); MS (CI, methane), *m/z* (%): 651 (MH^+, 2%), 591 (MH^+-AcOH, 65%), 533 (MH^+-AcOH−acetone, 45%), 523 (MH^+-HI, 43%), 465 (MH^+-HI−acetone, 100%).

6-Iodo compound **18h** (0.44 g, 0.68 mmol) was dissolved in CH_2Cl_2 (15 mL). DMAP (0.83 g, 6.77 mmol) was added, and the mixture was stirred at room temperature for 3 days. Sat. aq. NH_4Cl (10 mL) was added, and the mixture extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried on $MgSO_4$ and evaporated. Column purification on silica gel using EtOAc/Hexane (30:70) gave **19h** as a colourless oil (0.25 g, 71%).

4.1.21. 6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene mannojirimycin (20a). To an ice-cooled solution of compound **19a** (2.00 g, 4.4 mmol) in MeOH (50 mL) was added K_2CO_3 (0.30 g, 2.2 mmol). After reaction at room temperature for 2 h, 20 mL sat. aq. solution of NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (3×15 mL). The organic phase was dried and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes 40:60) to afford the alcohol product as an oil (1.26 g, 70%). To a solution of the alcohol (1.02 g, 2.5 mmol) in MeCN/DMSO (49:1) (50 mL) was added K_2CO_3 (1.37 g, 9.9 mmol) and PhSH (1.27 mL, 12.4 mmol). After reaction at 50°C for 2 h, 15 mL sat. aq. NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the organic phase was dried and evaporated. The residue was purified by column chromatography on silica gel (CH_3Cl/MeOH 92:8) to afford **20a** as a colouress oil (0.54 g, 96%); $[\alpha]_D=-19$ ($CHCl_3$, c 0.29); IR 3414, 2986, 2910, 2103, 1658, 1230, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.43 (s, 3H, Me_2C), 1.45 (s, 3H, Me_2C), 2.23 (s, 2H, OH+NH), 2.73 (dd, 1H, J=14.6, 1.8 Hz, H-1), 2.85 (ddd, 1H, J=9.4, 5.6, 3.2 Hz, H-5), 3.16 (dd, 1H, J=14.6, 2.3 Hz, H-1′), 3.42 (dd, 1H, J=9.4, 2.4 Hz, H-3), 3.53 (dd, 1H, J=12.5, 5.6 Hz, H-6),

3.61 (dd, 1H, J=12.5, 3.2 Hz, H-6′), 3.65 (t, 1H, J=9.4 Hz, H-4), 4.25 (m, 1H, Σ^3J=6.5 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) 26.6, 26.8 (Me_2C), 49.6 (*C*-1), 52.8 (*C*-6), 58.4 (*C*-5), 67.4 (*C*-2), 72.1 (*C*-4), 80.8 (*C*-3), 109.2 (Me_2C); MS (CI, methane), *m/z* (%): 229 (MH^+, 100%), 171 (MH^+-acetone, 81%), 153 (MH^+-acetone$-H_2O$, 22%); HRMS: calcd for $C_8H_{13}O_3N_4$ (M^+-Me) 213.0988, found 213.0977 (5%).

4.1.22. 6-Phenylthio-1,6-dideoxy-3,4-*O*-isopropylidene mannojirimycin (20h). To an ice-cooled solution of compound **19h** (1.73 g, 3.3 mmol) in MeOH (50 mL) was added K_2CO_3 (0.23 g, 1.7 mmol). After reaction at room temperature for 2 h, 20 mL sat. aq. NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (3×15 mL), and the organic phase was dried and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes 40:60) to give the alcohol product as an oil (1.21 g, 76%). To a solution of the alcohol (0.79 g, 1.6 mmol) in MeCN/DMSO (49:1) (50 mL) was added K_2CO_3 (0.19 g, 6.6 mmol) and PhSH (0.84 mL, 8.2 mmol). After reaction at 50°C for 2 h, 20 mL sat. aq. NH_4Cl was added. The mixture was extracted three times with CH_2Cl_2 (3× 15 mL), and the organic phase was dried and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 92:8) to afford **20h** as a slightly yellow oil (0.46 g, 96%); $[\alpha]_D=-7.6$ ($CHCl_3$, *c* 0.28); IR, 3300, 2983, 2914, 1583, 1090 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.34 (s, 3H, Me_2C), 1.41(s, 3H, Me_2C), 2.28 (2H, NH+OH), 2.73 (dd, 1H, J=14.3, 1.8 Hz, H-1), 2.93 (ddd, 1H, J=9.4, 7.6, 3.1 Hz, H-5), 3.06 (dd, 1H, J= 13.6, 7.6 Hz, H-6), 3.16 (dd, 1H, J=14.3, 2.4 Hz, H-1′), 3.37 (dd, 1H, J=9.4, 2.4 Hz, H-3), 3.39 (dd, 1H, J=13.6, 3.16 Hz, H-6′), 3.60 (t, 1H, J=9.4 Hz, H-4), 4.22 (m, 1H, Σ^3J=6.6 Hz, H-2), 7.17–7.42 (m, 5H, SPh); ^{13}C NMR (100 MHz, $CDCl_3$) 26.4, 26.8 (Me_2C), 36.7 (*C*-6), 49.7 (*C*-1), 58.3 (*C*-5), 67.1 (*C*-2), 74.1 (*C*-4), 80.9 (*C*-3), 109.0 (Me_2C), 126.0, 128.8, 129.3 (*C*H, SPh), 136.2 (*C-ipso*, SPh); MS (CI, methane), *m/z* (%): 296 (MH^+, 100%), 238 (MH^+-acetone, 39%), 220 (MH^+-acetone$-H_2O$, 5%); HRMS: calcd for $C_{15}H_{21}O_3NS$ (M^+) 295.1242, found 295.1245 (28%).

4.1.23. 6-Azido-1,6-dideoxy-mannojirimycin (21a). Compound **20a** (0.52 g, 2.3 mmol) was treated with saturated methanolic HCl (10 mL) for 2 h. The solution was evaporated and the residue was co-evaporated twice with MeOH. Purification by column chromatography on silica gel ($CHCl_3$/MeOH/H_2O/NH_4OH 70:28:1:1) afforded **21a** as an oil (0.38 g, 89%); $[\alpha]_D=-46$ (MeOH, *c* 1.12); IR, 3360, 2094, 1290, 1060 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD), δ (ppm) 2.48 (dt, 1H, J=9.5, 4.2 Hz, H-5), 2.72 (dd, 1H, J=14.0, 1.5 Hz, H-1), 2.98 (dd, 1H, J=14.0, 2.8 Hz, H-1′), 3.38 (dd, 1H, J=9.5, 3.2 Hz, H-3), 3.51 (t, 1H, J= 9.5 Hz, H-4), 3.63 (d, 2H, J=4.2 Hz, H-6); 3.86 (m, 1H, Σ^3J=7.5 Hz, H-2),; ^{13}C NMR (100 MHz, CD_3OD) 50.5 (*C*-1), 53.3 (*C*-6), 61.1 (*C*-5), 70.6 (*C*-2, 4), 76.5 (*C*-3);); MS (CI, methane), *m/z* (%): 189 (MH^+, 100%), 171 (MH^+-H_2O, 14%); HRMS: calcd for $C_5H_{10}O_3N$ ($M^+-CH_2N_3$) 132.0661, found 132.0674 (100%).

4.1.24. 6-Phenylthio-1,6-dideoxy-mannojirimycin (21h). Compound **20h** (0.38 g, 1.3 mmol) was treated with saturated methanolic HCl (10 mL) for 2 h. The solution was evaporated and the residue was co-evaporated twice with MeOH. Purification by column chromatography on silica gel ($CHCl_3$/MeOH/H_2O/NH_4OH 70:28:1:1) afforded **21h** as a slightly yellow oil (0.30 g, 91%); $[\alpha]_D=+35$ (MeOH, *c* 0.50); IR 3350, 2910, 1260, 1090 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD), δ (ppm) 2.55 (ddd, 1H, J=9.3, 7.8, 3.0 Hz, H-5), 2.68 (dd, 1H, J=13.8, 1.6 Hz, H-1), 2.98 (dd, 1H, J=13.8, 2.9 Hz, H-1′), 3.04 (dd, 1H, J=13.5, 7.8 Hz, H-6), 3.34 (dd, 1H, J=9.3, 3.2 Hz, H-3), 3.49 (dd, 1H, J=13.5, 3.0 Hz, H-6′), 3.50 (t, 1H, J=9.3 Hz, H-4), 3.84 (m, 1H, Σ^3J=7.7 Hz, H-2), 7.15–7.42 (m, 5H, SPh); ^{13}C NMR (100 MHz, CD_3OD) 37.1 (*C*-6), 50.6 (*C*-1), 61.2 (*C*-5), 70.5 (*C*-2), 72.9 (*C*-4), 76.6 (*C*-3), 127.1, 130.0, 130.4 (*C*H, SPh), 137.9 (*C-ipso* SPh); MS (CI, methane), *m/z* (%): 256 (MH^+, 100%), 238 (MH^+-H_2O, 12%); HRMS: calcd for $C_{12}H_{17}O_3NS$ (M^+) 255.0929, found 255.0930 (8%).

Acknowledgements

The authors wish to thank the F.W.O. (Fund for Scientific Research—Flanders, Belgium) for financial support. We are also indebted to R. De Boer and Professor S. Toppet for mass and NMR measurements. H. Mao also thanks the K.U. Leuven for a fellowship.

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