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Use of the *N*-tosyl-activated aziridine 1,2-dideoxy-1,2-iminomannitol as a synthon for 1-deoxymannojirimycin analogues

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Abstract

1-Amino-1-deoxy-D-glucitol was converted into the selectively protected title compound **4**, an *N*-tosyl-activated aziridine that readily underwent ring opening with various nucleophiles. Further deprotection of the 5,6-diol moiety followed by ring closure under Mitsunobu conditions afforded the corresponding 6-substituted analogues of 1-deoxymannojirimycin.

Keywords: aziridines; Mitsunobu reactions; carbohydrates; piperidines.

Azasugars have been recognised as inhibitors of glycosidases for some time,[1] thus representing potential antiviral (including anti-AIDS)[2] and antitumor[3] agents. Consequently, much effort has been devoted to the preparation of both the natural azasugars and their synthetic analogues.[4] We now describe an interesting route for the synthesis of variously substituted polyhydroxypiperidines, which proceeds via the nucleophilic ring opening of an *N*-tosyl-activated aziridine intermediate.

In our previous work, divergent strategies were applied in order to transform 1-aminoglucitol **1**[5] into various analogues of 1-deoxynojirimycin and castanospermine.[6] Thus, the crystalline 3,4;5,6-di-*O*-isopropylidene ammonium salt derivative **2** was isolated and subsequently converted to polyhydroxypiperidines modified at C-2 and C-6. The present work forms an extension of our 'inverse 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.

Our synthetic sequence (Scheme 1) started with protection of the 1-amino group of **2** as the *N*-tosylamide and subsequent activation of 2-OH as the mesylate **3**; this was isolated in 92% yield by using

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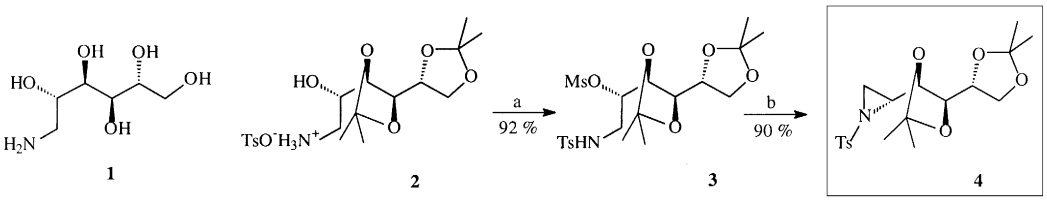
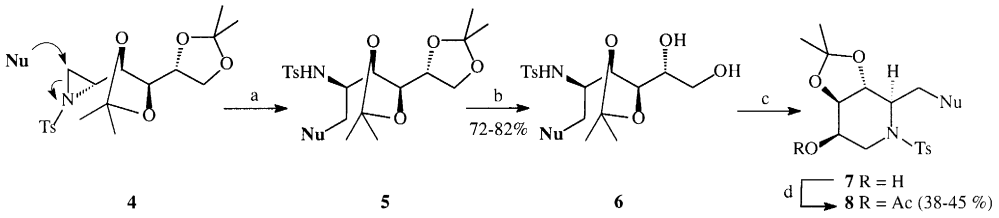
a ‘one-pot procedure’ followed by a single chromatographic purification. Upon treatment with sodium hydride in THF, mesylate **3** was converted to the *N*-tosylaziridine **4** in 90% yield.



Scheme 1. Synthesis of the *N*-tosyl aziridine **4**. (a) 4 equiv. Et_3N, 1.1 equiv. *p*-TsCl, CH_2Cl_2, rt, 30 min; then 1.3 equiv. MsCl, rt, 1 h; (b) 2 equiv. NaH, THF, rt, 1 h

The aziridine structure **4** was confirmed by ^1H and ^{13}C NMR data.[7] In the ^1H NMR spectrum the absorption due to the NH–proton of the tosylamide **3** 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 $^2J \cong 0$ Hz). In the ^{13}C NMR spectrum the values observed for the $^1J_{C–H}$ coupling constants (171 and 179 Hz for C-1 and 171 Hz for C-2) were in agreement with those reported for *N*-methylaziridine.[8]

Compound **4** was shown to be a highly versatile synthon for the construction of imino sugars. This proceeded (Scheme 2) via an initial opening of the aziridine ring using the appropriate nucleophiles; the resulting C-1-substituted 2-aminomannitols in turn could be elaborated into iminosugars of the piperidine type. A similar approach which involved the ring opening of bis(aziridines), was applied by Depezay et al. to prepare analogues of 1-deoxynojirimycin and 1-deoxymannojirimycin.[9]



Scheme 2. Conversion of the aziridine to analogues of 1-deoxymannojirimycin. (a) See Table 1; (b) Dowex, 9:1 MeOH:H_2O, rt, 30–72 h; (c) PPh_3, DEAD, THF, rt, 48–72 h; (d) Py, Ac_2O, rt, 2 h

Table 1 provides an overview of the reaction conditions used for the ring opening of aziridine **4** with various nucleophiles. Except for the reaction with KO*t*Bu, the products **5a**–**h** were isolated in good to excellent yields. One problem encountered when using sodium azide or potassium acetate as the nucleophile was the formation of dimeric products. This side reaction is due to the competitive attack of the *N*-tosylamide anion, i.e. the initial product generated by opening of the aziridine ring, on a second molecule of aziridine. It could be suppressed by using 10 equivalents of the nucleophile. No dimer formation was observed in reactions with the more nucleophilic carbanionic reagents producing **5g** and **5h**, and in those cases where the intermediate *N*-tosylamide anion could abstract an acidic proton, i.e. in the reaction with amines, malonate, and sulfonylacetonitrile. In analogy to the copper(I)-catalyzed ring opening of epoxides by Grignard reagents,[10] the reaction with phenylmagnesium bromide only succeeded after addition of catalytic copper(I)iodide.

The conversion of the 2-aminomannitol derivatives **5** into analogues of 1-deoxymannojirimycin was carried out for representative examples (Nu=N_3, OAc, Ph). In a first step, regioselective deprotection of the terminal isopropylidene group was effected by treatment with an acidic ion exchange resin (Dowex

Table 1
Reaction conditions for the nucleophilic ring opening of aziridine **4**

Product	-Nu	Conditions	Yield
5a	$-N_3$	10 eq. NaN_3, DMF, 90 °C, 6 h	96 %
5b	-NHBn	1.2 eq. $BnNH_2$, DMF, 90 °C, 24 h	67 %
5c	-OAc	10 eq. KOAc, DMF, 90 °C, 18 h	91 %
5d	-O*t*Bu	10 eq. KO*t*Bu, DMF, 90 °C, 24 h	18 %
5e	$-CH(CN)SO_2Ph$ [a]	1.05 eq. $PhSO_2CH_2CN$, 1.2 eq. NaH, THF, rt, 24 h	87 %
5f	$-CH(COOMe)_2$	2 eq. $CH_2(COOMe)_2$, 2.5 eq. NaH, THF, 0 °C; then rt, 48 h	57 % [b]
5g	-Ph	5 eq. PhMgBr, 0.1 eq. CuI, THF, rt, 1 h	95 %
5h		2 eq. 1,3 dithiane, 2 eq. BuLi, THF, 0 °C; 15 min; then rt, 4 h	80 %

[a] Only one stereoisomer detected by ^{1}H-NMR [b] The *N*-tosylpyrrolidinone cyclised product also was isolated (33 %)

50X8-200), affording the 5,6-diols **6** in good yields (azide **6a**, 72%; acetate **6c**, 80%; Ph-compound **6g**, 82%).

Treatment of the 5,6-diols **6** with triphenylphosphine and diethylazodicarboxylate in anhydrous THF (Mitsunobu conditions[11]) produced the piperidine compounds **7**. At room temperature, and even at 40–60°C, the cyclisation reaction was found to proceed very slowly. After 2–3 days, TLC and mass spectrometry confirmed that all starting material had been consumed. However, due to the presence of co-eluting substances originating from the Mitsunobu reagent, isolation of the alcohol products **7** proved to be difficult, and therefore these were converted to the less polar acetates **8**. Compounds **8** were isolated in moderate yields (combined yields for steps c and d: **8a**, 45%; **8c**, 38%; **8g**, 42%) and showed spectroscopic data in accordance with the proposed piperidine structures.[12]

The potential offered by aziridine **4** as a synthon for 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, the application of carbon nucleophiles may pave the way for the introduction of more complex substituents, especially in view of the synthesis of *C*-azadisaccharides.[13] Although deprotection of the *N*-tosyl group (using the sodium–naphthalene procedure[14]) proceeded more readily for the cyclised non-acidic *N*-tosylamides than for the acyclic *NH*-tosylamides, we can now also explore the use of the recently described *N*-*p*-nitrophenylsulfonyl group which can be removed under much milder conditions using the thiophenolate anion as a nucleophilic deprotecting agent.[15]

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7. Selected data for **4**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ=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 tosyl), 2.65 (d, 1H, *J*=7.0 Hz, H-1′), 3.11 (ddd, 1H, *J*=4.0, 4.5, 7.0 Hz, H-2), 3.74 (t, 1H, *J*=7.0 Hz, H-4), 3.88 (dd, 1H, *J*=5.5, 8.5 Hz, H-6), 3.96 (dd, 1H, *J*=4.0, 7.0 Hz, H-3), 3.97 (m, 1H, H-5), 4.08 (dd, 1H, *J*=6.0, 8.5 Hz, H-6′), 7.34 (d, 2H, CH tosyl), 7.83 (d, 2H, CH tosyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=21.6 (Me tosyl), 25.2, 26.5, 26.8, 27.0 (*Me*$_2$C), 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_2*C*), 128.2, 129.7 (CH tosyl), 134.7, 144.7 (C-*ipso* tosyl).
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12. Selected data for **8a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.31 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 2.07 (s, 3H, Me tosyl), 2.43 (s, 3H, MeOOC), 2.97 (dd, 1H, *J*=5.5, 10 Hz, H-3), 3.20 (dd, 1H, *J*=6.5, 15.5 Hz, H-1$_{ax}$), 3.58 (dd, 1H, *J*=3, 12.5 Hz, H-6), 3.82 (dd, 1H, *J*=4.5, 12.5 Hz, H-6′), 3.9 (m, 1H, H-5), 4.01 (dd, 1H, *J*=9, 10 Hz, H-4), 4.3 (m, 1H, H-1$_{eq}$), 5.23 (ddd, 1H, *J*=5.5, 6.5, 8.5 Hz, H-2), 7.37 (m, 2H, CH tosyl), 7.73 (m, 2H, CH tosyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=20.6 (*Me*OOC), 21.4 (Me tosyl), 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_2*C*), 126.9, 130.0 (CH tosyl), 136.0, 144.3 (C-*ipso* tosyl), 169.8 (MeOO*C*).
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