Synthesis of a Trihydroxylated Aminoazepane from D-Glucitol by an Intramolecular Aziridine Ring Opening

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Abstract: Transformation of d-glucitol into its 1,6-diazido derivative allowed its conversion into the polyhydroxylated aminoazepane ring in a one-pot reaction using Ph3P and H2O.

Key words: azepanes, 1-deoxynojirimycin, iminosugars, aziridine

Polyhydroxylated piperidine derivatives are very interesting synthetic targets due to their potent and diverse biological activities, related to their inhibition of glycosidases.1 These compounds are considered to be iminosugars because they have the capacity to mimic carbohydrate structures and have thus found applications in the treatment of diabetes and other metabolic diseases,2 in obstructing microbial infection,3 and as antiviral agents, in particular against the human immunodeficiency virus (HIV).4 1-Deoxynojirimycin (DNJ, 1, Figure 1), a potent naturally occurring glycosidase inhibitor, is an example of this class of compounds. Another class of nitrogen heterocycles having similar biological activities are the polyhydroxylated azepanes, some of these being superior homologues of DNJ.5 Because of their highly substituted peculiar seven-membered ring and interesting biological properties, various strategies for azepane syntheses have been described over the last years.5

Figure 1 Polyhydroxylated nitrogen heterocycles

We present herein our efforts to prepare the trihydroxylated aminoazepane 3 via intramolecular aziridine opening of an intermediate 4 obtained stereospecifically from D-glucitol (Scheme 1). The latter is an interesting starting material because it is accessible commercially, is inexpensive, and has the correct configuration at the asymmetric centers required for our synthetic objectives. The literature relates the use of ZnCl2 in acetone to form the desired acetonide 5 but in only 31% yield.5 We have optimized the conditions to produce 5 as the major product of a mixture of acetonides using 2,2-dimethoxypropane in DMF in the presence of TsOH as catalyst (Scheme 2). Theoretical studies using Spartan 4.1 indicate that 5 is the acetonide with the lowest energy (291.3 kcal/mol) when compared to 6 and 7 (difference of 0.4 and 14.3 kcal/mol with respect to 5, respectively).8 Tosylation of the primary hydroxyl group of 5 was carried out using TsCl and Et3N in CH2Cl2 to produce 8 in quantitative yield (Scheme 2). Protection of the remaining free hydroxyl group was obtained by treatment of 8 with NaH and benzyl bromide in the presence of Bu4NI in THF affording 9 in a satisfactory yield (65%). For the selective deprotection of the acetonide in the C5–C6 positions, we applied two methodologies: TsOH/MeOH and I2/MeOH (Table 1). Using the first method, compound 10 was obtained in low yields (entries 1 and 2). Using the I2/MeOH method, decomposition of 9 was observed after 24 hours of reaction at room temperature (entry 3) while 27% of 10 could be obtained by reducing reaction time to 20 hours (entry 4). Increasing the reaction temperature to 35 °C or 40 °C while simultaneously diminishing reactions times to 3 hours or 4 hours afforded acceptable yields of 10 (43% and 45%, respectively, entries 5 and 6). When the temperature was raised to 60 °C however, a drastic decrease of the yield (45% to 19%) was observed despite a very short reaction time (0.5 h, entry 7). In general, the starting material could be recovered.

Diol 10 was then treated with TsCl and Et3N in CH2Cl2 to furnish the ditosylated compound 11 in 86% yield (Scheme 3). Both tosyl groups of 11 were replaced by azido groups using NaN3 in DMF to give 12 (quant).

Alternatively, we could also access the diazide 12 from 9 with NaN3 in DMF and afforded 13 in quantitative yield (Scheme 3). Diacetonide 13 was treated with I2/MeOH affording the monoacetonide 14 in 48% yield which was se-

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lectively tosylated at C6 to give 15 in 54% yield (65% based on the recovery of 14). The desired product 12 could be isolated in quantitative yield when 15 was treated with NaN₃ in DMF.

Conversion of 12 into the azepane 16 was performed using four-step sequence encompassing: (i) reduction of the both azide groups to the corresponding iminophosphorane 12a, (ii) formation of aziridine 12b, (iii) hydrolysis of the second iminophosphorane to the amine 4, and (iv) intramolecular attack of the aziridine at C6. These consecutive steps were performed using Ph₃P in MeCN at 50 °C followed by addition of water to produce the desired azepane 16, isolated as the major product in 29% yield (Scheme 4). There was no evidence of the product arising from attack of the amine at C5.

In conclusion, a new partially protected trihydroxy aminoazepane 16 was synthesized from D-glucitol in seven steps (5% overall yield) having as the key step the one-pot transformation of diazide 12 to azepane 16. Compound 16 was unequivocally characterized by ¹H NMR and NOE analysis (Figure 2).⁹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%) of 10</th>
<th>Recovery (%) of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH/MeOH</td>
<td>0</td>
<td>6</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>TsOH/MeOH</td>
<td>0</td>
<td>9</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>I₂/MeOH</td>
<td>r.t.</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>I₂/MeOH</td>
<td>r.t.</td>
<td>20</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>I₂/MeOH</td>
<td>35</td>
<td>3</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>I₂/MeOH</td>
<td>40</td>
<td>4</td>
<td>45 (54)</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>I₂/MeOH</td>
<td>60</td>
<td>0.5</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

*Yield calculated on the basis of recovered starting material.

Table 1  Selective Deprotection of 9 by TsOH/MeOH and I₂/MeOH

Scheme 2  Preparation of diacetone 9

Scheme 3  Synthesis of diazide intermediate 12
Acknowledgment

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References and Notes

2. (a) Simmott, M. L. Molec. Pharmacol. 1997, 51, 71 (21), 84 (26), 91 (100), 98 (49), 110 (8), 126 (34), 141 (7), 149 (10), 167 (14), 184 (27), 201 (23), 227 (3), 277 (10), 292 (2). 1H NMR (500 MHz, CDCl3): δ = 1.43. 1.44 [6 H, 2 s, C(CH3)2]. 2.13–2.18 (3 H, br s, NH aliphatic and cyclic).