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Convenient synthesis of 2-deoxy-*scyllo*-inosose and 2-deoxy-*scyllo*-inosamine: two key intermediates on the biosynthetic pathway to aminoglycoside antibiotics

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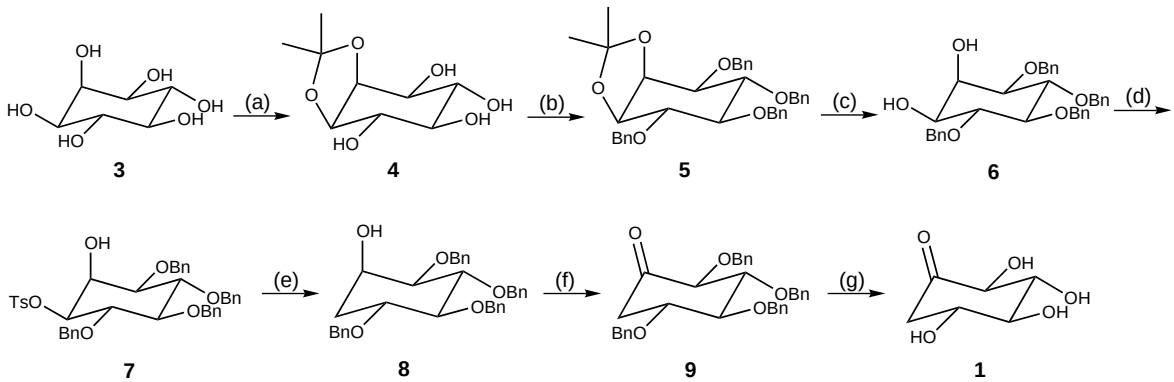
Abstract—2-Deoxy-*scyllo*-inosose **1** and 2-deoxy-*scyllo*-inosamine **2** are two of the key intermediates on the biosynthetic pathway to 2-deoxystreptamine-containing aminoglycoside antibiotics. Convenient syntheses of **1**, **2** and tritium-labelled **2** via stereoselective deoxygenation of *myo*-inositol using LTBH are reported. This should provide the substrates necessary for characterising the enzymes involved on the biosynthetic pathway. © 2001 Elsevier Science Ltd. All rights reserved.

Aminoglycosides containing a 2-deoxystreptamine unit are a large class of clinically important antibiotics. The emergence of multiply resistant bacteria creates the need for new antibiotics. The manipulation of the biosynthetic pathway of the producing organism is an attractive approach to the synthesis of new aminoglycoside antibiotics with potentially greater potency. Towards this goal, the mechanism of each step on the biosynthetic pathway has first to be elucidated. Part of the biosynthetic gene cluster for butirosin, an aminoglycoside which is produced by *Bacillus circulans*, has recently been sequenced.[1] Potentially, this allows the biosynthetic enzymes to be characterised and the complete butirosin pathway to be elucidated. Early work has demonstrated that deoxystreptamine is derived from D-glucose and that 2-deoxy-*scyllo*-inosose may be the first intermediate on the pathway.[2] Subsequent studies with the isolated enzyme proved conclusively that 2-deoxy-*scyllo*-inosose can be formed from D-glucose.[3] However, further investigation into the mechanism by which deoxystreptamine is biosynthesised, and the identification of the other enzymes on the pathway requires the ready availability of all the possible intermediates on the biosynthetic pathway, such as **1** and **2**. The chemical syntheses of **1** from *myo*-inositol and **2** from 6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-gluco-



Scheme 1. *Reagents and conditions*: (a) 2,2-dimethoxypropane, toluene-*p*-sulphonic acid monohydrate, DMSO, 98%; (b) NaOH (powder), BnBr, DMSO, 100°C, 96%; (c) AcOH, H_2O, 100°C, 98%; (d) dibutyltinoxide, tosyl chloride, benzyl triethylammonium chloride, CH_3CN, 92%; (e) LTBH, THF (anhydrous), 79%; (f) PCC, 3 Å MS, DCM, 90%; (g) Pd/C, H_2, MeOH/AcOH, 99%.

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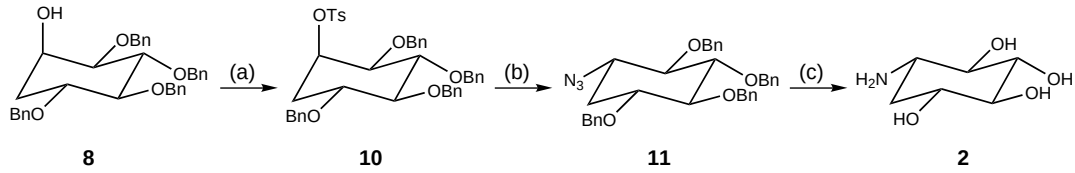
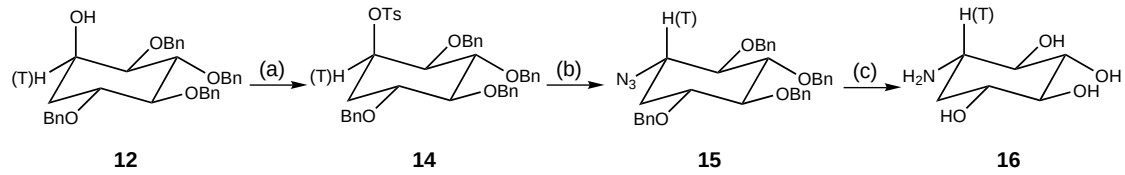


Scheme 2. *Reagents and conditions*: (a) tosyl chloride, pyridine (anhydrous), $CHCl_3$, 0°C, 90%; (b) NaN_3, DMF, 80°C, 95%; (c) Pd/C, H_2, HCl (conc.)/AcOH/MeOH, 99%.



Scheme 3. *Reagents and conditions*: (a) tosyl chloride, pyridine (anhydrous), $CHCl_3$, 0°C, 95%; (b) NaN_3, DMF, 80°C, 92%; (c) Pd/C, H_2, HCl (conc.)/AcOH/MeOH, 98%.

furanose have been reported. However, both synthesis involved many steps and were achieved in low yield.[4,5] In our previous work, we have reported a successful stereoselective deoxygenation reaction using lithium triethylborohydride (LTBH) for the removal of a hydroxyl group from carbocyclic diols.[6] To take advantage of this method, we set out to synthesise both **1** and **2** from *myo*-inositol.

The two *cis*-hydroxyls of *myo*-inositol **3** were protected in the form of 1,2-*O*-isopropylidene-*myo*-inositol **4**. The remaining hydroxyls were reacted with benzyl bromide to give the fully protected *myo*-inositol **5**. Treatment with 2 M HCl leads to the deprotection of the acetal to give *cis*-diol **6**. The equatorial hydroxyl group of the diol **6** was then selectively tosylated using dibutyltin oxide, tosyl chloride and benzyl triethylammonium chloride to give the monotosylate **7**. The monotosylate was subjected to the stereoselective deoxygenation system using LTBH. The displacement of the tosyl group via a proposed 1,2-hydride shift and subsequent reduction of the ketone intermediate by LTBH gave the cyclohexanol **8** in good yield (79%). Compound **8** was oxidised using Jones' reagent to afford **9** and subsequently deprotected to give the required product **1**, in a seven-step synthesis with overall yield of 60% (Scheme 1).

The ready availability of cyclohexanol **8** from this synthetic route offers an obvious route to synthesise compound **2** through displacement of the hydroxyl with an azide moiety followed by hydrogenation. One-pot azidation of **8** by a modified Mitsunobu reaction using either zinc azide/bis-pyridine complex or diphenylphosphoryl azide was attempted with no product isolated.[7,8] Compound **8** was therefore tosylated and reacted with sodium azide to give **11** in 95% yield. Subsequent hydrogenation of **11** gives the final product **2**. This leads to an eight-step synthesis of **2** with overall yield of 52% (Scheme 2).

To establish a sensitive assay for the transformation of 2-deoxy-*scyllo*-inosamine to deoxystreptamine the synthesis was modified to prepare tritium labelled **2**. Compound **9** (0.23 mmol) was reduced with $NaBH_3T$ (100 mCi in 8 ml of EtOH) to give a mixture of tritium labelled cyclohexanol **12** (axial -OH) and **13** (equatorial -OH) from which pure **12** was isolated in 62% yield. **12** was smoothly tosylated to give **14**, which was then subjected to azidation to afford **15**. The tritium labelled azide **15** was then hydrogenated to give the final product **16** (45 mCi per mmol) (Scheme 3).

In summary, an efficient route for the synthesis of two key intermediates on the biosynthetic pathway to deoxystreptamine is established,[9] which has also provided ready access to the radiolabelled version of **2**. Detailed enzymatic studies utilising these compounds are under the way in our laboratory.

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