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Synthesis of 2-amino-2,4-*anhydro*-3-*O*-(2-tetrahydropyranyl)-psicofuranose: a versatile intermediate for *S*-type locked nucleosides

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Abstract—2-Amino-2,4-*anhydro*-psicofuranose derivative was synthesized starting from D-fructose.

The furanose ring in natural nucleosides exists in a dynamic equilibrium between northern (N-type, 2′-*exo*/3′-*endo*) and southern (S-type, 2′-*endo*/3′-*exo*) pucker conformations.[1] These conformations are recognized by cellular enzymes in a selective manner.[2] Whereas, in the case of locked nucleosides, furanose ring adopts a fixed conformation and may lead to a higher affinity to the enzymes compared to the unlocked furanose moiety. Hence the synthesis of nucleosides with a rigid conformation gained momentum in recent years.[3] The bicyclic nucleosides with N-type conformation are found to be particularly interesting and found to have greater potency and less toxicity than the corresponding nucleosides with normal furanose ring systems.[4]

Modified nucleosides with S-type conformation have not been studied thoroughly for their biological activities[5] although they have been incorporated into DNA and RNA duplexes to study the stability of their respective oligonucleotides.[6] Our continued interest in the synthesis of modified[7] and conformationally locked[8] nucleosides led us to further our research in this area. To date, surprisingly, synthesis of only one rigid nucleoside wherein the 1, 3 positions in furanose ring are locked is reported.[9] In this letter, we delineate the synthesis of 2-amino-2,4-*anhydro*-psicofuranose derivative **24** as a versatile intermediate to construct such locked nucleosides with natural and unnatural bases.

The desired azido bicyclic sugar **14** (Scheme 2) was envisaged to be obtained from the key intermediate **11** (Scheme 1). The synthesis of methyl glycoside **11** was accomplished as shown in Scheme 1. Thus, di-acetonide **1** was synthesized from D-fructose in high yield following a literature procedure.[10] Alcohol **1** was protected as its benzyl ether **2** under standard conditions. Di-acetonide **2** was selectively opened at glycosidic site under acidic conditions to generate predominantly the desired methyl glycoside **3**.[10] The free hydroxyl in **3** was derivatized as its tosylate **4**, which was then deisopropylenated to obtain the corresponding diol **5**. Exposure of **5** to hydrogen in the presence of 10% Pd/C generated the triol **6**, which was then selectively protected as the di-silyl derivative **7** using Markiewicz's reagent.[11] The secondary hydroxyl in **7** was protected as its tetrahydropyranyl (THP) ether **8** under standard conditions. The reaction of silyl ether **8** with tetrabutylammonium fluoride (TBAF) generated diol **9** for the formation of important bicyclic intermediate **10**. It is gratifying to note that transformation of diol **9** to the bicyclic derivative **10** went smoothly in the presence of excess NaOMe in MeOH under reflux conditions. The primary hydroxyl **10** was then esterified to the corresponding benzoate **11**.

Several of our attempts to convert glycoside **11** to the corresponding di-acetate **12** (Scheme 2) under a variety of conditions had failed. The di-acetate **12** may be used for the synthesis of bicyclic nucleosides with natural bases in oligonucleotides. Furthermore, a direct attempt to couple thymine base with glycoside **11** under Vorbrüggen's[12] conditions also failed to give the desired product **13**. Therefore, we thought to convert glycoside **11** to crucial bicyclic amino alcohol **24** via the corresponding azido derivative **14**. Repeated attempts to

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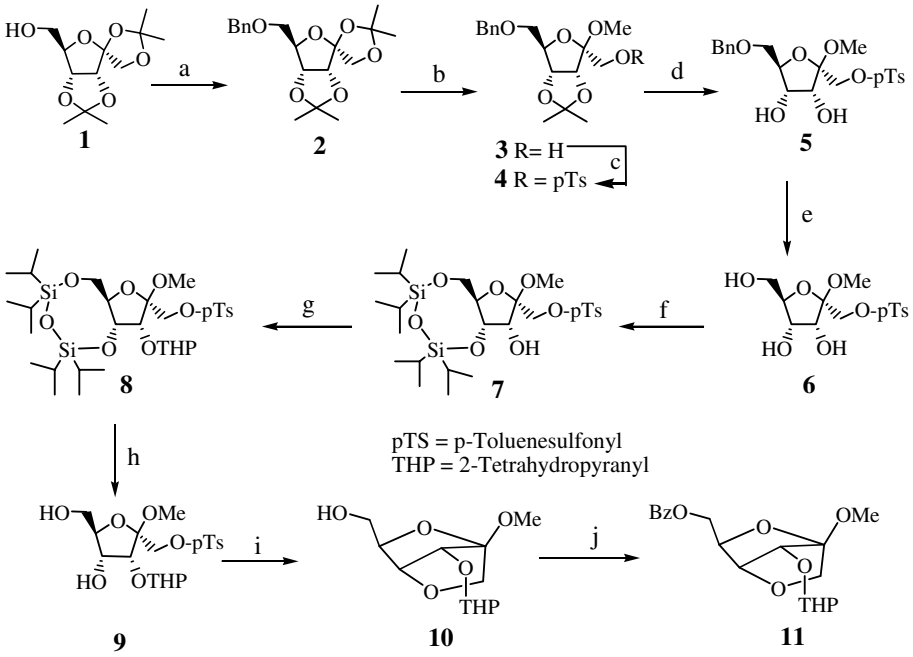
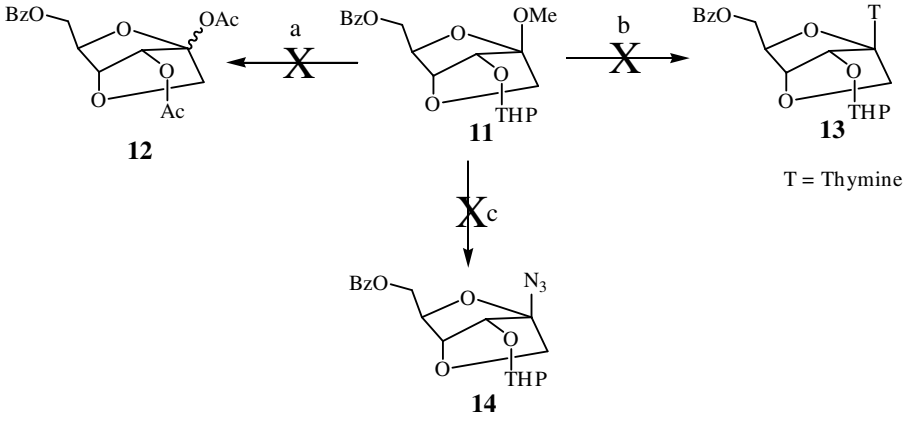


Scheme 1. Reagents and conditions: (a) NaH (1.2 equiv), BnCl (1.25 equiv), DMF, rt, 16 h, quant.; (b) MeOH, concd H_2SO_4, rt, 16 h, 59%; (c) p-TsCl (2.5 equiv), Py, 16 h, rt, 97%; (d) Concd H_2SO_4, MeOH, H_2O (1.3 equiv), rt, 16 h, 95% (based on recovered starting material); (e) 10% Pd/C (25% wt/wt), H_2 (50 psi), rt, 16 h, 91%; (f) TiPSCl (1.25 equiv), Py, rt, 16 h, 74%; (g) DHP (7 equiv), PpTS (1.5 equiv), CH_2Cl_2, 45 °C, 4 h, quant.; (h) TBAF·$3H_2O$ (3 equiv), Py–H_2O (3:2), THF, rt, 16 h, 89%; (i) NaOMe, MeOH, reflux, 16 h, 55%; (j) BzCl, Py, rt, 16 h, quant.

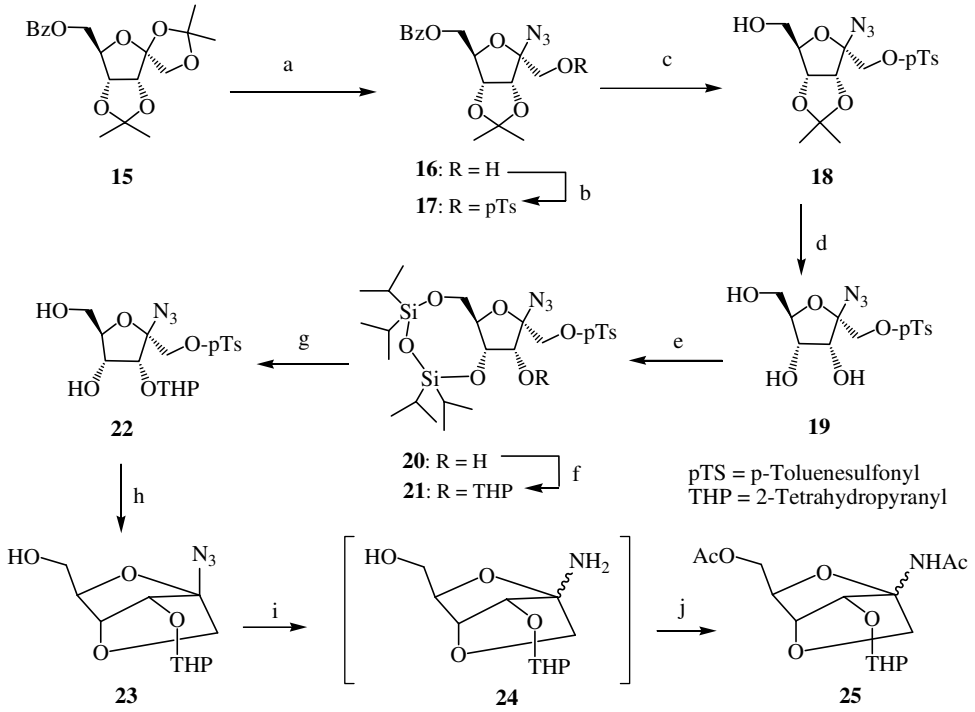


Scheme 2. Reagents and conditions: (a) H_2SO_4, acetic anhydride, acetic acid, 0–4 °C, 16 h; (b) (i) Thymine, HMDS, $(NH_4)_2SO_4$, reflux, 5 h; (ii) $SnCl_4$, 1,2-dichloroethane, 0 °C to rt; (c) TMS–N_3 (2 equiv), TMS–triflate (0.3 equiv), CH_3CN, 0 °C to rt, 1 h.

convert **11** into **14** also failed. Only furanose ring opened products were observed.

However, altering the sequence of reactions afforded the desired 2-amino-*anhydro*-psicofuranose derivative **24** as shown in Scheme 3. Thus, di-acetonide **15**, obtained from alcohol **1** by treating with benzoyl chloride in pyridine, was selectively opened with TMS-azide[10] in the presence of TMS-triflate to obtain azido-alcohol **16**. The alcohol was derivatized as its tosylate **17** under standard conditions. Benzoate **17** was hydrolyzed to alcohol **18**, which was then deisopropylenated to give triol **19**. The 4 and 6 positions in **19** were protected as di-silyl ether **20** by using Markiewicz's reagent. Then, the secondary alcohol in **20** was protected as the corresponding THP ether **21**. This allowed us to selectively deprotect 4 and 6 hydroxyls by exposing disilylether **21** to TBAF which afforded the diol **22**. Conversion of diol **22** to bicyclic sugar **23** was successful with NaOMe in refluxing MeOH. No products were formed involving primary hydroxyl group on C6 since it is in anti position to the leaving tosylate on C1. Hydrogenation of azido compound **23** in the presence of 10% Pd/C afforded the desired amino alcohol **24** which was derivatized further for ease of characterization to the corresponding acetamide **25** by treating it with acetic anhydride in pyridine.

In summary, we have synthesized 2-amino-2,4-*anhydro*-psicofuranose derivative **24**. Further studies involving the synthesis of locked nucleosides using intermediate



Scheme 3. Reagents and conditions: (a) TMS–N_3 (2 equiv), TMS–triflate (0.3 equiv), CH_3CN, 0 °C to rt, 1 h, 86%; (b) p-TsCl (2.5 equiv), Py, 16 h, rt, quant.; (c) methanolic ammonia, rt, 16 h, 91%; (d) Dowex-50 H^+, MeOH–H_2O (2:1), 50 °C, 16 h, quant.; (e) TiPSCl (1.25 equiv), Py, rt, 16 h, 74%; (f) DHP (7 equiv), PpTS (1.5 equiv), CH_2Cl_2, 45 °C, 4 h, quant.; (g) TBAF·$3H_2O$ (3 equiv), Py–H_2O (3:2), THF, rt, 16 h, 89%; (h) NaOMe, MeOH, reflux, 16 h, 63%, (i) 10% Pd/C (10% wt/wt), H_2 (30 psi), rt, 2 h, 98%; (j) Ac_2O (2 equiv), Py, rt, 6 h, quant.

24 are currently underway. These synthetic efforts along with the biological activity of the locked nucleosides produced will be published in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.072.

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