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Synthesis of *anhydro* psicofuranosyl nucleosides

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Abstract—Methyl 1-*O*-mesyl-5-*O*-toluoyl-β-D-psicofuranoside (**5**) was synthesised from the known 1,3;4,5-di-*O*-isopropylidene-β-D-psicofuranose (**1**) as a key carbohydrate precursor for the preparation of *anhydro* psicofuranosyl nucleosides. Transformation of **5** into acetate **7** or bromide **10** followed by (i) coupling with persilylated N^6-benzoyladenine in the presence of $SnCl_4$, and (ii) treatment with MeONa/MeOH gave 1′,3′-*anhydro* nucleoside **9**. Employment of silylated thymine in a similar sequence of reactions afforded the 1′,4′-*anhydro* nucleoside **12**. Reaction of blocked **11** with NH_3/MeOH gave O^2,1′-*anhydro* nucleoside **13**, which was rearranged into **12** upon MeONa/MeOH treatment. Condensation of the 1′,3′-*anhydro* sugar **15** with silylated thymine gave, after deprotection, the 1′,3′-*anhydro* nucleoside **16**.

During recent years, rigid nucleosides have attracted much attention as constituents of oligonucleotides.[1–3] Oligonucleotides containing rigid nucleosides display a number of exciting biological properties, which are of importance for possible biomedical applications.

In the present communication, we describe the synthesis of new rigid nucleosides (**9** and **16**, **12** and **13**), which contain different kinds of *anhydro* bridges. The first part of this approach was to prepare the aforementioned rigid nucleosides by the synthesis of methyl 1-*O*-mesyl-5-*O*-toluoyl-β-D-psicofuranoside (**5**) as a key carbohydrate precursor (Scheme 1). This was obtained in four steps, in high combined yield, by conventional procedures from the known 1,3;4,5-di-*O*-isopropylidene-β-D-psicofuranose (**1**).[4] Acetylation of **5** gave methyl glycoside **6,** which was used in a reaction with persilylated bases, similar to the procedure, reported earlier.[5] It was, however, found that **6** reacts very slowly with persilylated N^6-benzoyladenine in the presence of $SnCl_4$ under reflux for 8 h in 1,2-dicloroethane (DCE) to furnish the protected β-D-nucleoside **8** in 33% yield.

Application of acetate **7** or bromide **10** in a coupling reaction with silylated bases was found to be advantageous over that of **6**. Thus, the reaction of **7** with persilylated N^6-benzoyladenine in the presence of $SnCl_4$ under reflux for 35 min in acetonitrile (MeCN) gave, after standard workup, the desired **8** in 95% yield. Condensation of bromide **10** with the same base resulted in the formation of **8** (95%). Bromide **10**, in turn, was prepared in quantitative yield either from acetate **7**, or directly from methyl glycoside **6**. Treatment of the protected nucleoside **8** with MeONa/MeOH under very mild conditions resulted in deprotection, accompanied by the 1′,3′-*anhydro* ring closure giving rise to nucleoside **9**.[6]

The coupling of bromide **10** with silylated thymine, followed by treatment of intermediate **11** with MeONa/MeOH, afforded the 1′,4′-*anhydro* nucleoside **12** (23%, combined).[7] Under more mild conditions, upon treatment of **11** with methanolic ammonia, we have monitored (RP HPLC) the gradual deacetylation of **11** to tentative **14**, followed by an intramolecular attack of the C2 carbonyl group at the base on the C1′ carbon atom, leading to the O^2,1′-*anhydro* nucleoside **13**[8] in 26% combined yield.[9] The latter rearranged to the 1′,4′-*anhydro* nucleoside **12** upon treatment with MeONa/MeOH.

In order to prepare 1′,3′-*anhydro* thymine nucleoside **16**, an alternative procedure was developed (Scheme 2).

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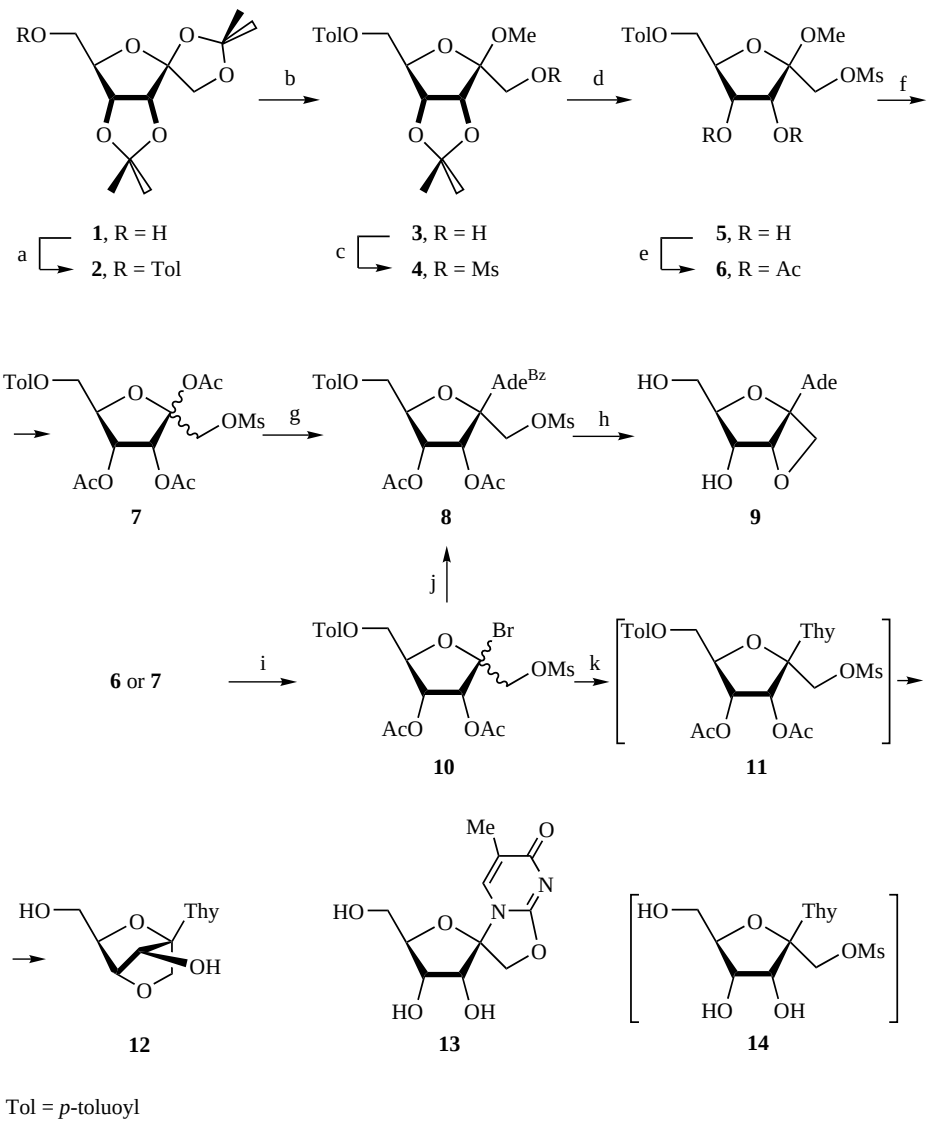

Scheme 1. (a) Tol-Cl/Py/toluene, −78°C, −20°C, 24 h (78–94%); (b) 0.4 M HCl/MeOH, 20°C, 2–3 h (91%); (c) $MsCl/NEt_3$/toluene, 20°C, 18 h (95%); (d) 1.0 M HCl/MeOH, 20°C, 48 h (87% based on the conversion of **4**, 28% of which was recovered); (e) Ac_2O/Py, 20°C, 18 h (73%); (f) (i) CF_3COOH/H_2O (95:5, vol), 20°C, 19–20 h; (ii) Ac_2O/Py, −4°C, 20 h (Σ50%); (g) **7**/persilylated N^6-benzoyladenine/$SnCl_4$ (molar ratio = 1.0:1.5:3.4), MeCN, reflux, 35 min (95%); (h) **8**/MeONa/MeOH, 20°C, 18 h (87%); (i) **6** or **7**/HBr/AcOH, 20°C, 1–3 h; (j) **10**/persilylated N^6-benzoyladenine/$SnCl_4$ (molar ratio = 1.0:1.5:2.0), MeCN, 60°C, 3 h; (k) (i) **10**/persilylated thymine/$SnCl_4$ (molar ratio = 1.0:1.5:2.0), MeCN, 60°C, 1.5 h; (ii) 0.4 M MeONa/MeOH, 50°C, 18 h (**12**, 23% combined)

Glycoside **5** was transformed in two steps to the 1,3-*anhydro* derivative **15** in high yield. Its condensation with silylated thymine, in the presence of $SnCl_4$ under reflux, followed by deprotection resulted in the formation of the desired **16** in 50% overall yield.[10]

In conclusion, we have developed two alternative pathways for the preparation of 1′,3′-*anhydro* psicofuranosyl nucleosides. The synthesis of 1′,4′- and O^2,1-*anhydro* psicofuranosyl thymine nucleosides was also achieved.

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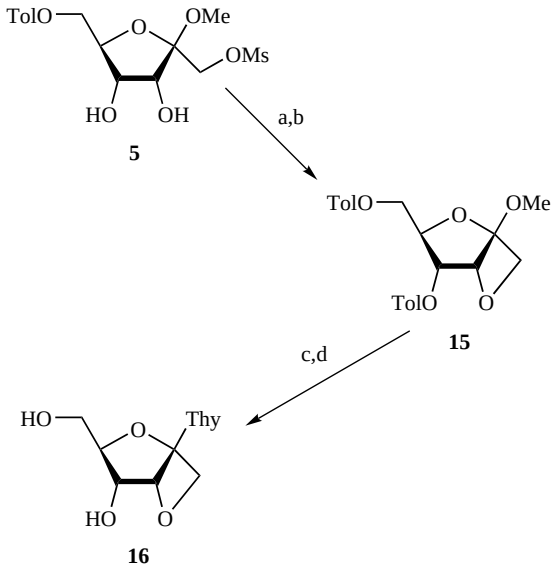

Scheme 2. (a) 0.4 M MeONa/MeOH, 20°C, 24 h; (b) Tol-Cl/NEt_3/toluene, 20°C, 18 h (the yield of **15** from **5** was 72%); (c) **15**/persilylated thymine/$SnCl_4$ (molar ratio = 1.0:1.5:2.0), MeCN, reflux, 18 h (79%); (d) saturated NH_3 in MeOH 20°C, 72 h (the yield of **16** from **15** was 64%).

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6. 9-(1,3-Anhydro-β-D-psicofuranosyl)adenine (**9**): mp 226–230°C (from MeOH); UV (MeOH): λ_{max} nm (ε) 259.0 (13 900), λ_{min} 226.0 nm (1900); CD (MeOH) λ, nm ([Θ]×10^{-3}): 215.0 (−8.8), 254.0 (+5.6), 275.0 (−4.0), 230, 265 and 291.0 (0). HPLC [(column: Waters XTerra RP18, 5 μm, 4.6×150 mm; linear gradient (0→4%) of CH_3CN in water; flow rate of 1.0 mL/min (time of analysis 30 min)]: retention time (t_R) 10.5 min; ^{1}H NMR (CD_3OD), δ_{TMS}, ppm; *J*, Hz: 8.22 and 8.21 (2s, 2H, H-2 and H-8), 5.55 (d, 1H, $J_{1',1''}$ = 8.3, H-1′), 5.09 (d, 1H, H-1″), 5.76 (d, 1H, $J_{3',4'}$ = 4.26, H-3′), 4.46 (dd, 1H, $J_{4',5'}$ = 8.59, H-4′), 4.51 (ddd, 1H, $J_{5',6'}$ = 2.35, $J_{5',6''}$ = 4.99, H-5′), 4.05 (dd, 1H, $J_{6',6''}$ = 12.88, H-6′), 3.85 (dd, 1H, H-6″). ^{13}C NMR (DMSO-d_6), δ_{TMS}, ppm: 158.64 (C-6), 156.02 (C-2), 151.56 (C-4), 142.48 (C-8), 121.57 (C-5), 91.40 (C-3′), 85.84 (C-5′), 82.37 (C-1′), 73.18 (C-4′), 63.13 (C-6′), the low intensity resonance of C-2′ is either overlapped by the resonances of the other pentofuranose carbons, or is absent due to the long relaxation time.
7. 1-(1,4-Anhydro-β-D-psicofuranosyl)thymine (**12**): glassy product; UV (MeOH): λ_{max} nm (ε) 261.0 (10 000), λ_{min} 232.0 nm (2800); CD (MeOH) λ, nm ([Θ]×10^{-3}): 264.0 (−4.8), 293.0 (+2.75), 248 and 278 (0). HPLC [(column: Waters XTerra RP18, 5 μm, 4.6×150 mm; linear gradient (0→4%) of CH_3CN in water; flow rate of 1.0 mL/min (time of analysis 20 min)]: retention time (t_R) 7.5 min; ^{1}H NMR (D_2O), δ_{TMS}, ppm; *J*, Hz: 7.49 (br.s, 1H, H-6), 4.64 (d, 1H, $J_{1',1''}$ = 8.85, H-1′), 4.27 (d, 1H, H-1″), 4.96 (br.s, 1H, $J_{3',4'}$ < 1.0, H-3′), 4.31 (br.s, 1H, $J_{4',5'}$ < 1.0, H-4′), 4.21 (dt, 1H, $J_{5',6'} = J_{5',6''}$ = 5.02, H-5′), 3.62 (d, 2H, H-6′ and H-6″), 1.85 (d, 3H, $J_{CH3,H6}$ = 1.16, 5-C$\underline{H}_3$. ^{13}C NMR (DMSO-d_6), δ_{TMS}, ppm: 167.14 (C-4), 152.82 (C-2), 140.20 (C-6), 113.11 (C-5), 96.51 (C-2′), 83.67 (C-5′), 78.34 (C-4′), 71.39 (C-1′), 71.45 (C-3′), 61.06 (C-6′), 12.33 (5-$\underline{C}$H$_3$).
8. O^2,1′-Anhydro-1-(β-D-psicofuranosyl)thymine (**13**): started to darken at 195°C and melted at 208°C (from EtOH); UV (MeOH): λ_{max} nm (ε) 229.0 (9200) and 254.0 (11 300), λ_{min} 215.5 nm (7180) and 236.5 (8650); CD (MeOH) λ, nm ([Θ]×10^{-3}): 242.0 (−14.45), 265.0 (+10.4), 275.0 (−4.0), 224, 255 and 300 (0). HPLC [(column: Waters XTerra RP18, 5 μm, 4.6×150 mm; linear gradient (0→4%) of CH_3CN in water; flow rate of 1.0 mL/min (time of analysis 20 min)]: retention time (t_R) 6.5 min; ^{1}H NMR (CD_3OD/H_2O), δ_{TMS}, ppm; *J*, Hz: 7.77 (q, 1H, $J_{H6,CH3}$ = 1.16, H-6), 5.14 (d, 1H, $J_{1',1''}$ = 10.64, H-1′), 4.67 (d, 1H, H-1″), 4.72 (d, 1H, $J_{3',4'}$ = 4.73, H-3′), 4.35 (dd, 1H, $J_{4',5'}$ = 2.08, H-4′), 4.17 (m, 1H, $J_{5',6'}$ = 3.48, $J_{5',6''}$ = 4.00, H-5′), 3.78 (dd, 1H, $J_{6',6''}$ = 12.66, H-6′), 3.77 (dd, 1H, H-6″), 1.96 (d, 3H, $J_{CH3,H6}$ = 1.16, 5-C$\underline{H}_3$). ^{13}C NMR (CD_3OD/H_2O), δ_{TMS}, ppm: 178.3 (C-4), 163.61 (C-2), 134.38 (C-6), 121.64 (C-5), 101.84 (C-2′), 88.56 (C-5′), 76.36 (C-4′), 75.25 (C-1′), 73.75 (C-3′), 64.04 (C-6′), 15.92 (5-$\underline{C}$H$_3$).
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10. 1-(1,3-Anhydro-β-D-psicofuranosyl)thymine (**16**): mp 195°C (from EtOH); UV (MeOH): λ_{max} nm (ε) 269 (8300), λ_{min} 233 nm (70); CD (MeOH) λ, nm ([Θ]×10^{-3}): −221 (0), 243 (+2.14), 256 (0), 272 (−3.21) and 295 (0). HPLC [(column: Waters XTerra RP18, 5 μm, 4.6×150 mm; linear gradient (0→4%) of CH_3CN in water; flow rate of 1.0 mL/min (time of analysis 30 min)]: retention time (t_R) 12.0 min; ^{1}H NMR (CD_3OD), δ_{TMS}, ppm; *J*, Hz: 7.58 (q, 1H, $J_{H6,CH3}$ = 1.22, H-6), 4.24 (d, 1H, $J_{1',1''}$ = 14.80, H-1′), 3.91 (d, 1H, H-1″), 3.78 (d, 1H, $J_{3',4'}$ = 4.62, H-3′), 4.15 (dd, 1H, $J_{4',5'}$ = 7.68, H-4′), 4.01 (m, 1H, $J_{5',6'}$ = 3.00, $J_{5',6''}$ = 6.65, H-5′), 3.76 (dd, 1H, $J_{6',6''}$ = 12.07, H-6′), 3.61 (dd, 1H, H-6″), 1.87 (d, 3H, $J_{CH3,H6}$ = 1.22, 5-C$\underline{H}_3$). ^{13}C NMR (CD_3OD), δ_{TMS}, ppm: 166.71 (C-4), 153.63 (C-2), 143.81 (C-6), 110.88 (C-5), 108.98 (C-2′), 85.22 (C-5′), 75.48 (C-3′), 72.69 (C-4′), 64.10 (C-6′), 46.43 (C-1′), 12.30 (5-$\underline{C}$H$_3$).