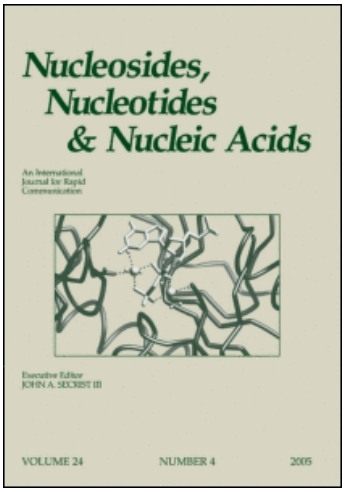

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SYNTHESIS OF L-2′-DEOXYPENTOFURANONUCLEOSIDE DERIVATIVES OF THYMINE FROM D-GLUCOSE

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□ *Convergent synthesis of L-2′-deoxypentofuranonucleoside derivatives of thymine was carried out from D-glucose via 6-O-toluoyl-3-deoxy-1,2-O-isopropylidene-β-L-lyxo-hexofuranose as a key intermediate.*

Keywords L-Deoxynucleosides; thymine; convergent synthesis; L-sugars; D-glucose

INTRODUCTION

L-Nucleoside analogues, the mirror images of the natural D-nucleosides, are extensively investigated and their use in antiviral chemotherapy has greatly increased.[1]Among these, L-2′-fluoro-arabinofuranosyl-5-methyluracil (L-FMAU), L-2′,3′-dideoxy-2′,3′-didehydro-5-fluorocytidine (L-Fd4C), L-thymidine (L-dT), and L-2′-deoxycytidine (L-dC) have shown potent, selective activity against HBV replication, whereas L-3′-thiacytidine (L-3TC), L-2′,3′-dideoxy-5-fluorocytidine (L-FddC) have been found to be active against HIV.[1−2] The main advantage of the L-nucleosides is their lower toxicity profiles in comparison with their D-counterparts. A number of synthetic approaches to different L-nucleosides have been explored from D-carbohydrates such as D-galactose, D-xylose, D-ribitol and D-ribose.[3−6] This report describes the synthesis of L-2′-deoxypentofuranonucleoside derivatives of thymine **12–18** from cheap D-glucose, using a new sequence for preparing intermediate L-2-deoxysugars.

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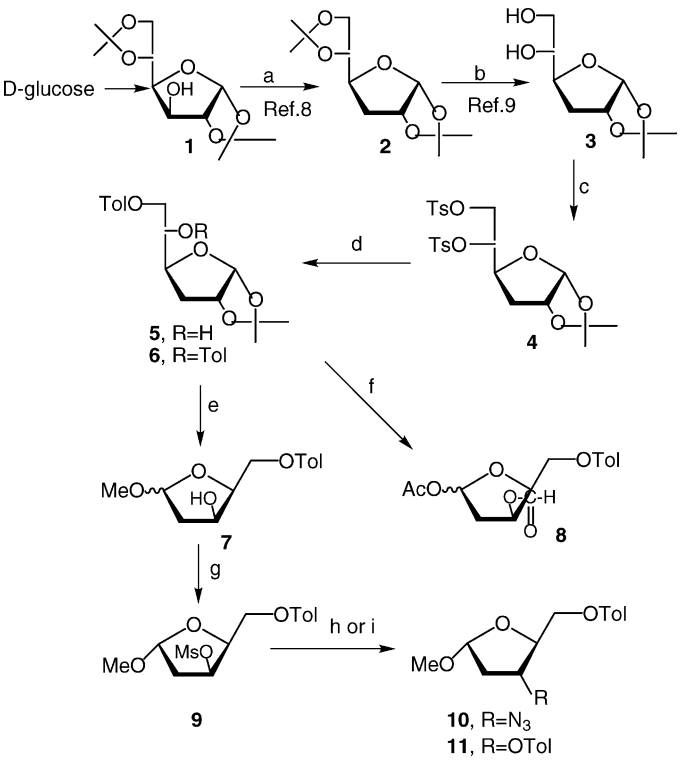
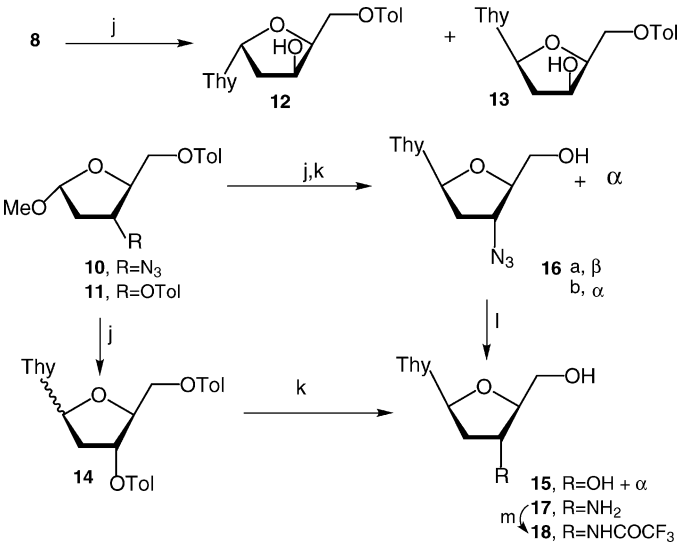
RESULTS AND DISCUSSION

The synthetic route to L-ribose has been reported from D-glucose.[7] From retrosynthetic analysis it was inferred that the synthesis of derivatives of L-2-deoxy-*threo*-pentofuranose is possible from D-glucose via readily available diacetone-D-glucose (**1**). 3-Deoxy-1,2;5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranose (**2**) was synthesized by Barton deoxygenation process of thiocarbonylimidazolide derivative of **1** (Scheme 1).[8] Nucleophilic displacement of the primary and secondary sulphonyloxy groups of ditosyl derivative **4**, prepared in two steps from **2**, by treatment with potassium p-toluate in aqueous *N,N*-dimethylformamide under reflux afforded 6-O-toluoyl- and 5,6-di-O-toluoyl derivatives of 3-deoxy-1,2-O-isopropylidene-β-L-*lyxo*-hexofuranose **5** and **6** which were separated and purified by column chromatography in 57% and 30% yield, respectively. Thus, key crystalline derivative **5** was prepared by inversion configuration at C-5 of 5,6-di-O-tosyl-3-deoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (**4**). Intermediate



SCHEME 1 Reagents and conditions: (a) [i] $(lm)_2C=S/(CH_2Cl)_2$; [ii] Bu_3SnH. toluene, Σ69%; (b) 0.01 N HCl, rt, 82%; (c) TsCl/Py, rt, 70%; (d) TolOK, DMF/H_2O, 150–155°C, (**5**, 57%, **6**, 30%); (e) [i] 90% CF_3COOH, rt. [ii] $NaIO_4$, dioxane/H_2O, rt. [iii] 0.2% HCl/MeOH, rt Σ68%; (f) [i] 90% CF_3COOH, rt [ii] KlO_4, H_2O/EtOH, rt. [iii] Ac_2O, Py, rt, Σ40%, (g) MsCl, Py, O°C, +4°C, 69% (h) NaN_3, DMF, 80–84°C, 60%; (i) TolOK, DMF/H_2O, 100°C, 85%.



SCHEME 2 Reagents and conditions: (j) 2, 4-bis(trimethyl)silylthymine, Me_3SiOTf, CH_3CN, −30°C to rt for **8** (21%, **12**; 9%, **13**,); 60–65°C for **10**; rt for **11** (Σ60%, 2.6/1); (k) NH_3/MeOH, rt, 85%; (l) Ph_3P/Py, rt; NH_4OH, rt, 55%; (m) $(CF_3CO)_2O$/Py/CH_2Cl_2, O°C to rt, MeOH, 57%.

derivative of L-hexofuranose **5** was converted in three steps into methyl 5-O-toluoyl-2-deoxy-L-*threo*-pentofuranoside **7** or peracylated derivative of L-2-deoxy-*threo*-pentofuranose **8** as mixtures of anomers in 68% and 40% overall yields, respectively, after column chromatography on silica gel. Starting from **9**, the synthesis of L-sugars **10** and **11** was carried out by nucleophilic substitution of mesyloxy group by sodium azide and potassium p-toluate, respectively, in DMF (Scheme 1). The condensation of **8** and **11** with silylated thymine in Vorbrüggen conditions yielded L-nucleosides **12-14** (Scheme 2). It should be noted that the formation of mixture nucleosides **12** and **13** (α/β–2.3/1), which was difficult to separate by column chromatography on silica gel, as well as of unseparable mixture of β- and α-nucleosides **14** (2.6/1 according to ^{1}H NMR data, overall 60%) was observed as a result of the coupling reactions of **8** and **11** with silylated thymine in the presence TMSOTf of in acetonitrile. The standard deacylation of **14** yielded the mixture of L-dT (**15**) and its α-anomer after chromatography. The condensation of L-azidosugar (**10**) with thymine (Scheme 2) followed by treatment of anomeric mixture of intermediate protected nucleosides with methanolic ammonia afforded β-L-nucleoside **16**a (27%) and α-L-nucleoside **16**b (16%) which were separated by column chromatography on silica gel. The reduction of azido group of β-L-AZT (**16**a) by consecutive treatment with Ph_3P/Py and aqueous ammonia generated 3′-amino-2′,3′-dideoxy-β-L-thymidine (**17**). Trifluoroacetylation of the latter with trifluoroacetic anhydride in pyridine/methylene

chloride afforded nucleoside **18** (57%). Biological evaluation of 3′-N-trifluoroacetamido-2′,3′-dideoxy-β-L-analogue of thymidine **18** is under investigation.

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