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A stereospecific synthesis of L-ribose and L-ribosides from D-galactose

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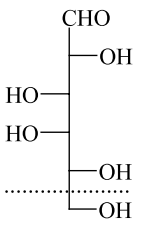
Abstract—An inexpensive D-galactose was converted into L-ribose and its derivatives via mild reaction conditions. The L-ribosyl donor was submitted to a glycosidation according to Vorbrüggen's conditions to give L-ribosides in high yields.

Recently, the use of L-carbohydrates and their corresponding nucleosides in medicinal applications has greatly increased. In particular, several modified nucleosides derived from L-sugars, such as (−)-(2′*R*,5′*S*)-1-(2-hydroxymethyloxathiolan-5-yl)-cytosine (3TC),[1] L-thymidine (L-T),[2] L-3′-thiacytidine (L-3-TC),[3,4] L-5-fluoro-3′-thia-cytidine (L-FTC),[5] L-2′,3′-dideoxycytidine (L - ddC),[6] L - 5 - fluoro - 2′,3′ - dideoxy - cytidine (L - 5-FddC),[7,8] and L-2′-fluoro-5-methylarabinofuranosyl uracil (L-FMAU),[9] have shown great potential as useful antiviral agents. In addition, due to the stereoselectivity of enzymes, L-ribose modified oligoribonucleotides become attractive candidates for diagnostic and therapeutic uses because L-RNA ligands remain uncleaved in biological fluids.[10] For these reasons, L-carbohydrates, modified L-nucleosides, especially L-ribose and its derivatives are of interest. Up to now, several syntheses of L-ribose and L-ribosides from L-arabinose,[11–13] D-glucose,[14] D-ribose,[15] L-xylose[16] have been reported and herein we report a stereospecific synthesis of L-ribose **1** and L-ribosides from D-galactose **2**.



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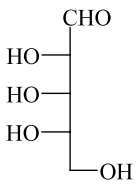

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According to our observations, there exists some useful information of D-galactose **2** in relation to L-ribose **1**, i.e. D-galactose is a hexose while L-ribose is a pentose without C-6 and with configurations at both C-3 and C-4 the same, while C-2 is different. Therefore, the key conversion of D-galactose into L-ribose in our synthetic approach includes oxidation cleavage and reduction at 5,6-diol of galactose and the configuration inversion at 2-hydroxy group of resulting arabinose. The synthetic route to L-ribose is depicted in Scheme 1.

At first, we obtained compound **3**, 1,2,5,6-di-O-isopropylidene-D-galactofuranose from D-galactose as described in the literature.[17] Chemoselective cleavage of the 5,6-*O*-isopropylidene diol of **3** with $NaIO_4/HIO_4$ (1.0 eq./0.5 eq.)-ether in one operation or with 10% AcOH followed by $NaIO_4$ cleavage of the resulting glycol and then reduction of the aldehyde with sodium borohydride in one-pot furnished L-arabinose derivative **4** in 85–92% yield. After some conversions including the protection of 3,5-dihydroxyl groups with benzyl chloride, methanolysis, and methanesulfonylation, a substrate (**7**) for configuration inversion was obtained.

Configuration inversion of the 2-hydroxyl group in compound **7** was attempted by several methods including Mitsunobu method and oxidation/reduction procedure, but all of these were unsuccessful. We therefore reacted **7** with Ac_2O, AcOH and H_2SO_4, this gave only the 1,5-diacetate **8,** but not the 1-acetate, in 89% yield. The inversion of 2-OH configuration and the hydrolysis of the diacetate took place with NaOMe/MeOH for the intramolecular S_N2 reaction of methanesulfonyloxy group with C-1 alkoxide. Then, L-ribose was prepared

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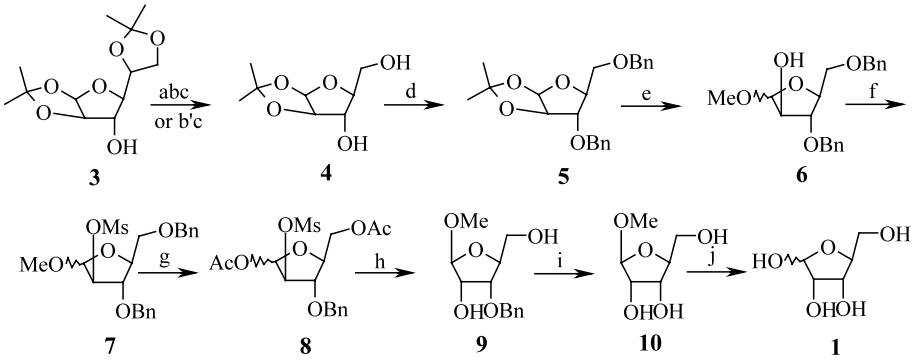
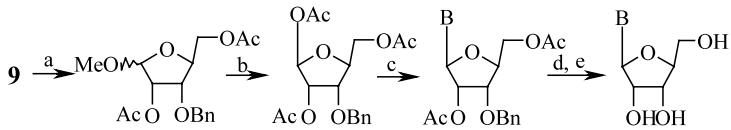


Scheme 1. *Reagents and conditions*: (a) 10% AcOH-H_2O, rt, 24 h; (b) $NaIO_4$, MeOH, H_2O, rt, 1h; (c) $NaBH_4$, MeOH, H_2O, 3 h, three steps in 92% yield; (b′) $NaIO_4/HIO_4$ (1.5 eq.), Et_2O, rt, 4h; (d) KOH, BnCl, 1,4-dioxane, reflux, 2 h, 95%; (e) 10% HCl-MeOH, rt, 3h, 96%; (f) MsCl, Et_3N, rt, overnight, 98%; (g) Ac_2O, AcOH, H_2SO_4, 4°C, overnight, 89%; (h) NaOMe, MeOH, rt, 6 h, 83%; (i) 10% Pd-C, MeOH, H_2, 2 h; (j) Dowex [H^+], H_2O, 50°C, 24 h, two steps in 95% yield.

by debenzylation of **9** with 10% palladium-carbon in methanol followed by hydrolysis of methyl glycoside with ion-exchange resin (H^+ form) in 95% yield. The resulting structure was confirmed by comparison with a commercial sample (Aldrich). In conclusion we have synthesized L-ribose from D-galactose, an inexpensive material, by using cheap reagents under mild reaction conditions.

Scheme 2 shows the syntheses of L-ribosides **14**. Diacetate **11** was prepared by the treatment of **9** with acetic anhydride and pyridine and converted to 1,2,5-tri-*O*-acetyl-3-*O*-benzyl-L-ribofuranoside **12** as an isolable mixture (α:β = 1:11). According to the Vorbrüggen method,[18] the β-*N*-glycosidic bond linkages are made by the L-ribosyl donor **12** and the protected bases. We therefore obtained **13a**, **b**, **c** by treatment of **12** with the protected bases, respectively, in the presence of TMSOTf and BSA (*N*,*O*-bis-trimethylsilylacetamide) in good yields (92%, 88%, 89% for **13a**, **b**, **c**, respectively). The L-ribosides were obtained by deacetylation with NH_3-H_2O/MeOH and then debenzylation using 10% palladium-carbon in methanol in high yield (92%, 91%, 87% for **14a**, **b**, **c**, respectively).[19]

For some bases, sensitive to debenzylation, like purine, 5-iodouracil, N^6-benzoyl-adenine, N^2-O^6-diphenylcarbamoylguanine, we resorted to another synthetic route

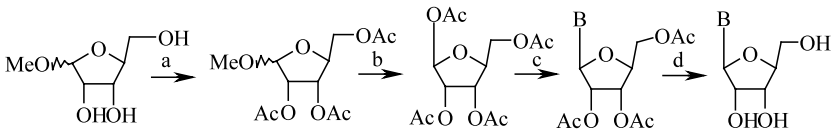


13a: uracil: CH_3CN, 60-65°C, 92% — **14a**: *L*-uridine: 92%

13b: thymine: CH_3CN, 60-65°C, 88% — **14b**: *L*-thymidine: 91%

13c: 5-fluorouracil: CH_3CN, 60-65°C, 89% — **14c**: *L*-5-fluorouridine: 87%

Scheme 2. *Reagents and conditions*: (a) Ac_2O, py, overnight, rt, 92%; (b) AcOH, Ac_2O, H_2SO_4, 4°C, overnight, 83%; (c) Base, TMSOTf, BSA, solvent, overnight; (d) NH_3-H_2O, MeOH, 60°C, overnight; (e) 10% Pd-C, H_2, rt, 3 h



17a: 5-iodouracil: BSA, CH_3CN, 60-65°C, overnight: 94% — **18a**: *L*-iodouridine: 93%

17b: purine: BSA, CH_3CN, 60-65°C, overnight: 83% — **18b**: *L*-puridine: 91%

17c: 6-*N*-benzoyladenine: MFSTA, CH_3CN, 60-65°C, overnight, 81% — **18c**: *L*-adenosine: 94%

17d: 2-*N*-6-*O*-diphenylcarbamoylguanine:[20] BSA, toluene, 3h, 80°C, 86% — **18d**: *L*-guanosine: 91%

Scheme 3. *Reagents and conditions*: (a) Ac_2O, py, overnight, rt, 90%; (b) Ac_2O, AcOH, H_2SO_4, 4°C, overnight, 74%; (c) B, TMSOTf, solvents; (d) NH_3/H_2O, MeOH, 60°C, overnight.

(Scheme 3). Protection of the triol **10** with acetic anhydride and pyridine furnished the triacetate **15** and treatment of **15** with $Ac_2O/AcOH/H_2SO_4$ afforded a separable mixture **16** ($\alpha:\beta=1:7$) of tetra-*O*-acetyl-L-ribose. Using the same procedures for glycosidation, we acquired the L-ribosides (**17a**, **b**, **c**, **d**) in good yield (83–94%) on different bases, selecting BSA (*N*,*O*-bistrimethylsilylacetamide), MFSTA (*N*-methyl-*N*-trimethylsilyl-trifluoroacetamide) and different solvents (acetonitrile or toluene). The deprotected products **18a**, **b**, **c**, **d** were obtained in high yields (91–94%).

Thus we have synthesized L-ribose from the easily available **3** in ten steps and in 57% overall yield. These procedures provide a practical synthesis of L-ribose and its derivatives. The biological activity of the L-ribosides and their derivatives are being assessed.

Acknowledgements

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19. All new compounds gave satisfactory spectral and microanalytical data. Selected data for compound **9**: $[\alpha]_D^{20}=+9.1$(*c* 0.5, MeOH); IR (film, cm^{-1}): 3415, 3032, 1455; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H, Ph), 4.87 (s, 1H, H-1), 4.56 (s, 2H, OBn), 4.23–4.11 (m, 2H, H-3, H-4), 4.04 (d, 1H, $J_{2,3}=4.2$ Hz, H-2), 3.77 (dd, 1H, $J_{4,5a}=2.2$ Hz, $J_{5a,5b}=12.9$ Hz, H-5a), 3.55 (dd, 1H, $J_{4,5b}=3.3$ Hz, $J_{5a,5b}=12.0$ Hz, H-5b), 3.40 (s, 3H, OMe); HRMS (*m*/*z*) calcd. for $C_{13}H_{18}O_5$: 254.1177; found: 254.1154. Compound **1**: $[\alpha]_D^{20}=+19.2$ (*c* 2.0, H_2O); IR (KBr): ν_{max} 3500 (brs) cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 4.93 (d, 0.57H, $J_{1,2}=5.0$ Hz, β-anomer), 4.78 (d, 0.43H, $J_{1,2}=1.5$ Hz, α-anomer), 3.94–3.82 (m, 2H, H-2, H-3), 3.77–3.61 (m, 2H, H-4, H-5a), 3.48 (m, 1H, H-5b); MS (EI): *m*/*z* 151 (M^++1), 133 (M^+–OH); Anal. calcd for $C_5H_{10}O_5\cdot 0.1H_2O$: C, 39.53 H, 6.72; found: C, 39.47, H, 6.79. Compound **13b**: $[\alpha]_D^{20}=-23.4$ (*c* 0.60, MeOH); IR (KBr): ν_{max} 3197 (brs), 1748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H, NH), 7.38–7.30 (m, 5H, Ph), 7.14 (s, 1H, H-6), 5.85 (d, 1H, $J_{1',2'}=3.3$ Hz, H-1′), 5.37 (dd, 1H, $J_{1',2'}=3.3$ Hz, $J_{2',3'}=5.2$ Hz, H-2′), 4.62 (d, 1H, $J=11.3$ Hz, OBn), 4.46 (d, 1H, $J=11.3$ Hz, OBn), 4.31 (dd, 1H, $J_{4'5'}=4.1$ Hz, $J_{5a',5b'}=13.1$ Hz, H-5a′), 4.25–4.19 (m, 2H, H-3′, H-4′), 4.15 (dd, 1H, $J_{4',5b'}=6.3$ Hz, $J_{5a',5b'}=11.8$ Hz, H-5b′), 2.14 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.91 (s, 3H, CH_3); MS (EI): *m*/*z* 307 (M^++1-base); Anal. calcd for $C_{21}H_{24}O_8N_2$: C, 58.33, H, 5.56, N, 6.48; found: C, 58.22, H, 5.56, N, 6,32. Compound **14b**: $[\alpha]_D^{20}=+15.6$ (*c* 1.1, MeOH); ^1H NMR (300 Hz, DMSO-d_6): δ 11.31 (s, 0.25H, NH), 7.74 (s, 1H, H-6), 5.78 (d, 1H, $J_{1',2'}=5.6$Hz, H-1′), 4.03 (t, 1H, $J_{1',2'}=5.5$ Hz, $J_{2',3'}=5.3$ Hz, H-2′), 3.96 (t, 1H, $J_{2',3'}=4.9$ Hz, $J_{3'4'}=3.9$ Hz, H-3′), 3.80 (q, 1H, $J_{3',4'}=3.9$ Hz, $J_{4',5a'}=3.4$ Hz, $J_{4',5a'}=3.4$ Hz, $J_{4',5b'}=3.4$ Hz, H-4′), 3.63 (dd, 1H, $J_{4',5a'}=3.4$ Hz, $J_{5a',5b'}=12.1$ Hz, H-5a′), 3.53 (dd, 1H, $J_{4',5b'}=3.4$ Hz, $J_{5a',5b'}=12.1$ Hz, H-5b′), 1.77 (s, 3H, CH_3); MS (EI): *m*/*z* 258 (M^+); Anal. calcd for $C_{10}H_{14}O_6N_2\cdot 0.25H_2O$: C, 45.71, H, 5.52, N, 10.67; found: C, 45.89, H, 5.44, N, 10.33.
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