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Synthesis of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose from D-ribose

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Abstract

A practical route towards the synthesis of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose from D-ribose is described. The key steps include deoxygenation of methyl 2,3-*O*-isopropylidene-5-*O*-sulfonyloxy-β-D-ribofuranoside by reductive displacement employing hydride reagents. Subsequent total hydrolysis followed by acetylation led to the title compound in 56% overall yield from D-ribose. The sequence is simple, inexpensive, high yielding and clearly suitable for multi-gram preparations.

Keywords: 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose; Lithium tri-*t*-butoxyaluminum hydride (LTTBA); Sodium bis-(methoxyethoxy) aluminium hydride (SMEAH)

1. Introduction

5-Deoxy-D-ribose is key constituent of several nucleosides, which exhibit a variety of biological functions. For example 5′-deoxy-iodotubercidin (**1**)[1] is a nucleoside derivative of 5-deoxy-D-ribose. Compound **1** is a good inhibitor of adenosine kinase, which provides basis for the design of new therapeutic agents for the treatment of inflammatory disease. The prodrug strategy involving tumor-selective delivery of 5-fluorouracil by sequential conversion of a fluoropyrimidine carbamate, capecitabine (**2**)[2] also requires the tri-*O*-acetyl derivative of 5-deoxy-D-ribose, namely 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose, for its synthesis. Our involvement with this latter compound as a starting material, in a linear synthetic route, required examination and modification of existing chemistry to enable a practical bulk synthesis of this compound (Fig. 1).

2. Results and discussion

There are two major synthetic routes available in literature for the synthesis of this intermediate. The first one focuses on preparing a methyl 2,3-*O*-isopropylidene-5-halo-β-D-ribofuranoside[3–5] from methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside,[6] followed by reductive dehalogenation employing either palladium-on-charcoal, or Adams platinum catalyst, yielding 5-deoxy-D-ribose.[4,7] The other route follows the direct deoxygenation of a methyl 2,3-*O*-isopropylidene-5-*O*-sulfonyloxy-β-D-ribofuranoside,[8–10] by reductive displacement using a hydride reagent to give 5-deoxy-D-ribose.[11] Other modification of this general

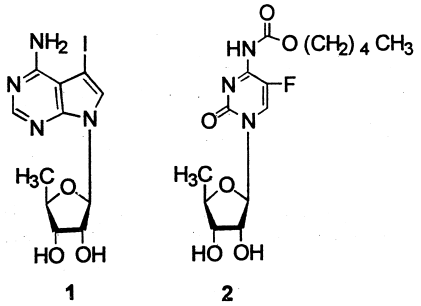

Fig. 1.

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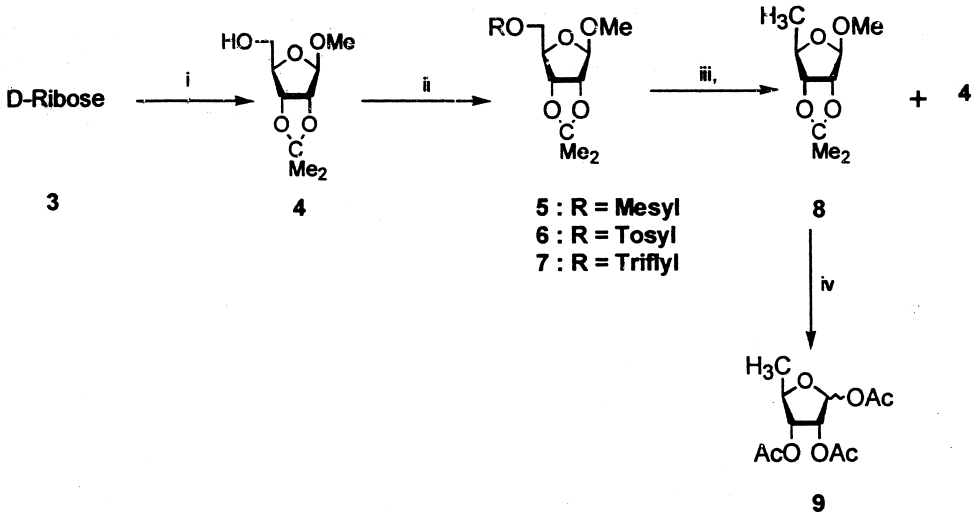

Scheme 1. Reagents: (i) $SnCl_2{\cdot}2H_2O$, Conc.H_2SO_4, acetone, MeOH; (ii) Mesyl chloride, pyridine, CH_2Cl_2 (Compound **5**); **OR** tosyl chloride, pyridine, CH_2Cl_2 (Compound **6**); **OR** triflic anhydirde, pyridine, CH_2Cl_2 (Compound **7**); (iii) $NaBH_4$, Me_2SO (compound **5**,**6**,**7**); **OR** SMEAH, THF (compound **5**,**6**,**7**); **OR** LTTBA, THF (compound **5**,**6**,**7**); (iv) 0.04N H_2SO_4; Ac_2O, pyridine.

Table 1
Percentage yields of isolated products (**4** and **8**) obtained by reaction of compounds **5**, **6**, and **7** with hydride reagents

Hydride reagent	Compound (**5**)		Compound (**6**)		Compound (**7**)	
	4	**8**	**4**	**8**	**4**	**8**
$NaBH_4$	–	80	–	89	70	20
SMEAH	70	–	45	50	30	50
LTTBA	75	–	70	20	–	95

approach required additional steps, which render them unattractive candidates for a large-scale process.[12,13]

Opting the later method, in the present article, we report a comparative study of deoxygenation of three different sulfonyloxy-activated sugar derivatives using three different hydride reagents, two of which are being employed for the first time for such a conversion. Commercially available D-ribose (**3**) is converted into methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**) by a known method.[6] The hydroxyl group at C-5 carbon of compound **4** was activated using three different sufonyl protecting agents *viz*, methanesulfonyl chloride,[8] p-toluenesulfonyl chloride,[9] and trifluoromethanesulfonic anhydride[10] to give compounds **5**, **6**, and **7**. Compounds **5**, **6**, and **7** were independently reduced by three different hydride reagents, namely, sodium borohydride ($NaBH_4$),[11] lithium tri-*t*-butoxyaluminum hydride (LTTBA), and sodium bis(-methoxyethoxy) aluminium hydride (SMEAH), to yield methyl 2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranoside (**8**). Further simplification of reported procedures[4,5] adopted for total hydrolysis and subsequent acetylation yielded the desired intermediate 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (**9**) in 56% overall yield from D-ribose (Scheme 1). The best yield reported[14] earlier for the synthesis of title compound was 52%, and involved hazardous operations like bromination and catalytic hydrogenation.

The main drawback of displacement of sulfonyloxy activated sugar hydroxyl groups by hydride reagents is that they often undergo O–S cleavage[15] to give back the starting compounds. The results of reduction by different hydride reagents of compounds **5**, **6**, and **7** yielded either the 5-deoxy sugar derivative **8** or the product of O–S cleavage, namely the 5-hydroxy sugar derivative **4**, and are summarized in Table 1.

3. Conclusion

We have successfully developed an efficient four-step process for the synthesis of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose. The reaction conditions are operationally simple, robust, and amenable to multi-gram scale. The most favored method of activating the protected ribose **4** would be *p*-toluenesulfonyl chloride to give **6**, as two other sulfonylating reagents gave either lower yields or were labile and difficult to handle.

Subsequent deoxygenation of the activated sugar derivative **6** was best achieved by using $NaBH_4$ which yields compound **8** in high yields in simple and cost-effective way. Total hydrolysis of **8** followed by acetylation yields the title compound.

4. Experimental

4.1. General methods

Melting points were determined with a Büchi 535 apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer 1650 FTIR. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were taken with a Varian Gemini FT-NMR instrument in $CDCl_3$ and Me_2SO-d_6 using Me_4Si as internal standard. Mass spectra were recorded on a, Hewlett-Packard model-5989 instrument with a direct insertion probe at 20 eV. Gas chromatograms were taken with a Shimadzu GC 17A instrument. TLC was performed on Silica Gel 60 F_{254} 230 mesh (E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, as well as H_2SO_4 in water and subsequent heating on a hot plate.

4.2. Preparation of Methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (4)

A mixture of D-ribose (**3**, 250 g, 1.66 mol) and $SnCl_2{\cdot}2H_2O$ (375 g, 1.66 mol) were suspended in acetone (5 L) and methanol (1.3 L) with catalytic amount of conc.H_2SO_4 (18.7 g, 186 mmol) and heated at 40–45 °C for 20 h. The mixture was filtered, and the filtrate was neutralized (pH 6–7) with $NaHCO_3$ solution. The resulting solution was once again filtered through a Celite bed and evaporated to remove acetone and MeOH. The aqueous solution thus obtained was extracted with EtOAc, washed with brine, dried (Na_2SO_4) and evaporated in vacuo to yield **4** (300 g, 88% yield). ^{1}H NMR data were in agreement with those reported in the literature.[6]

4.3. Preparation of methyl-2,3-*O*-isopropylidene-5-*O*-mesyl-β-D-ribofuranoside (5)

Compound **4** (2 g, 9 mmol) in CH_2Cl_2 (20 mL) and pyridine (6 mL, 73 mmol) was added to methanesulfonyl chloride (2 mL, 25 mmol) and stirred at 0–5 °C for 16 h. The reaction mixture was successively washed with 1N HCl, water, $NaHCO_3$, brine. The organic layer was dried (Na_2SO_4) and concentrated to yield a syrupy mass, which was further crystallized from Et_2O to give **5** (1.8 g, 65% yield) as a white solid. ^{1}H NMR data was in agreement with those reported in the literature.[8]

4.4. Preparation of methyl-2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranoside (6)

Compound **4** (350 g, 1.71 mol) dissolved in CH_2Cl_2 and pyridine on reaction with *p*-toluenesulfonyl chloride (630 g, 3.3 mol) yielded **6** (546 g, 89% yield) as a white solid. ^{1}H NMR data were in agreement with those reported in the literature.[9]

4.5. Preparation of methyl-2,3-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-β-D-ribofuranoside (7)

Following the procedure just mentioned, compound **4** (1 g, 4 mmol) in CH_2Cl_2 (10 mL) containing pyridine (0.7 mL, 9 mmol) on reaction with trifluoromethanesulfonic anhydride (1.2 mL, 73 mmol) at 0 °C for 4 h yielded **7** (0.8 g, 50%) as an colourless oil. Due to thermal decomposition at room temperature, no spectral evidence could be obtained.[10]

4.6. Preparation of methyl-2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranoside (8)

Compound **5** (10.0 g, 35 mmol) in Me_2SO (50 mL), was reacted with $NaBH_4$ (6.1 g, 175 mmol) for 12 h at 80–85 °C. The mixture was cooled and 5% aqueous AcOH (100 mL) was added. The mixture was extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated, and purified by column chromatography (10% EtOAc in petroleum ether) to yield **8** (5.3 g, 80%). The NMR data were in agreement with those reported in the literature;[13] $[\alpha]_D^{23}$ −110° (*c* 2, EtOH) [lit[5] $[\alpha]_D^{23}$ −109° (*c* 2, EtOH)]; IR (neat): 2985, 2938, 1210, 1101, 1057, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3 H, $J_{5,4}$ 7, H-5), 1.45 and 1.29 (2s, each 3 H, CMe_2), 3.31 (s, 3 H, OMe), 4.32 (q, 1 H, $J_{4,5}$ 7, H-4), 4.49 (d, 1 H, $J_{2,1}$ 6, H-2), 4.61 (d, 1 H, $J_{3,2}$ 6, H-3), 4.92 (s, 1 H, H-1); ^{13}C NMR($CDCl_3$, 50 MHz): 110 (C-1), 108 (C, CMe_2), 84 (C-2), 83 (C-3), 81 (C-4), 52 (CH_3, OCH_3), 25 and 23 (Me_2, CMe_2), 19 (C-5); mass spectrum: m/z 173 ($M^+ - CH_3$). The structure was also established by the absence of methylene carbon in DEPT. Similarly, **5** (5.0 g, 17 mmol) in THF (50 mL), was treated with SMEAH (70% solution in toluene; 26 mL, 85 mmol) and refluxed for 12 h. The mixture was extracted with CH_2Cl_2 and worked up using 1N HCl to give exclusively compound **4** (2.5 g, 70%). Compound **5** in THF (50 mL) reacted with LTTBA (30% solution in THF, 50 mL, 9 h) and processed as just described also yielded compound **4** (0.54 g, 75%) exclusively.

Compound **6** (300.0 g, 0.83 mol) in Me_2SO (2.2 L) was allowed to react with $NaBH_4$ (127 g, 3.4 mol; 80–85 °C; 3 h). Work up with 5% aqueous AcOH, yielded compound **8** (140 g, 89% yield) upon distillation (bp 65–70 °C, 0.2 mmHg). Similarly **6** (5.0 g, 13 mmol) in THF (50 mL) on reaction with SMEAH (70% solu-

tion in toluene, 20 mL, 69 mmol, 12 h, reflux) followed by column chromatography (10% EtOAc–petroleum ether) gave **8** (1.3 g, 50%) and **4** (1.3 g, 45%). However compound **6** (5.0 g, 13 mmol) in THF (100 mL) when treated with LTTBA (30% solution in THF, 55 mL, 65 mmol, reflux, 16 h) and work up using procedures mentioned earlier provided **8** (0.5 g, 20%) and **4** (2.0 g, 70%).

Compound **7** (1.0 g, 2.9 mmol) in Me_2SO (10 mL) was treated with $NaBH_4$ (0.6 g, 14 mmol, rt, 2 h). Work up with 5% aq. AcOH yielded **8** (0.1g, 20% yield) and **4** (0.42 g, 70%). Similarly **7** (10.0 g, 30 mmol) in THF (100 mL) on reaction with SMEAH (70% solution in toluene, 50 mL, 148 mmol, -40 °C; 1 h) provided **8** (2.8 g, 50%) and **4** (1.8 g, 30%). Furthermore **7** (10.0 g, 30 mmol) in THF (100 mL), when treated with LTTBA (30% solution in THF, 125 mL, 147 mmol; 0 °C 1 h) using similar work up procedures mentioned earlier for LTTBA reactions, yielded **8** (5.35 g, 95%) exclusively.

4.7. Preparation of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (9)

Compound **8** (50 g, 0.26 mol) in 0.04N H_2SO_4 (500 mL) was heated to 80–90 °C for 3 h. The mixture was cooled to rt, neutralized with solid Na_2CO_3, and evaporated to dryness. The residue was dissolved in pyridine (800 mL), treated with Ac_2O (210 mL, 2.2 mol), and stirred at rt for 16 h. Saturated $NaHCO_3$ (5 L) was poured into the reaction mixture, and extracted with CH_2Cl_2 (1×3 L, 2×2 L). The combined organic phase was washed with water (2×1 L), dried (Na_2SO_4), and concentrated in vacuo to 600 mL. To this solution silica gel (65 g) and activated charcoal (6.5 g), were added and the solution was stirred for 1 h at rt. The solution was then filtered, and the filtrate evaporated in vacuo to provide a mixture of the two anomers of the title compound **9** (56 g, 81%) as a syrupy mass. The anomeric mixture (1.0 g) partially crystallized from hexane to yield the crude β anomer, which was further crystallized from Et_2O–hexane to yield the pure β anomer (0.6 g) as white solid, mp: 63–64 °C [lit[4] 64–65 °C]; $[\alpha]_D^{23}$ $-27.0°$ (*c*, 2 in $CHCl_3$) [lit[4] $[\alpha]_D^{23}$ $-26.9°$ (*c*, 2 in $CHCl_3$)].

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