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A New Method for Synthesis of Methyl 3-Azido-3-deoxy-2-*O*-mesyl-5-*O*-benzoylxylofuranoside

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Abstract: A new method for synthesis of 3-azido-3-deoxyxylofuranoside was described. D-ribose was methylated, then treated with methanesulfonyl chloride to give II. II was selectively replaced by benzoate at the 5-position to give III. All these processes gave good yields. III was treated with sodium azide to afford IV, whose structure was determined by ^{1}H NMR and ^{13}C NMR.

Keywords: Xylose derivative, nucleoside, synthesis.

Nucleosides with 3-azido-3-deoxy or 3-amino-3-deoxyxylofuranoside sugar moiety have been attracting growing attention because of their various biological activity[1]. There were few reports about preparation of these nucleosides, due to the difficulty of synthesis. If the synthesis was accomplished by action of 2′, 3′-*O*-bismesyl on the nucleosides with sodium azide, much purine or pyrimidine base would be wasted. If use of 3′-azido-3′-deoxy or 3′-azido-2′, 3′-dideoxy-α/β-D-*threo*-pentofuranoside as an intermediate of such kinds of nucleosides, it would be more economic way. Since nucleosides with azido group can be readily reduced to corresponding amino compounds, 3-azido-3-deoxyxylofuranoside became an important intermediate.

The methods for the synthesis of 3-azido-3-deoxy or 3-amino-3-deoxyxylo-furano-side sugar moiety were not so satisfied for long synthetic route and low yields[2,3]. Here we report a novel synthetic method of 3-azido-3-deoxy- xylofuranoside through 4 steps from D-ribose, the yield is higher than others.

The synthetic processes of 3-azido-3-deoxyxylofuranoside were shown in **Scheme 1**. Methylation of D-ribose was accomplished in dry methanol in the presence of HCl to afford a pale-yellow syrup product I. Compound I was reacted with mesyl chloride to give a white solid permesylate II[4]. II was selectively benzoated at the 5-position to give the benzoate III[5]. The reaction time and temperature were the very important factors to the yield, long time and high temperature would give more byproducts. Then III was converted into 3-azido substituted compound IV. This reaction was also effected by temperature, when the temperature was higher than 140°C, more byproducts were formed. ^{1}H NMR of IV showed that the chemical shift of H-3 (δ 4.61 ppm) was at higher field than that of III (δ 5.29 ppm), this confirmed that the azido-group substituted

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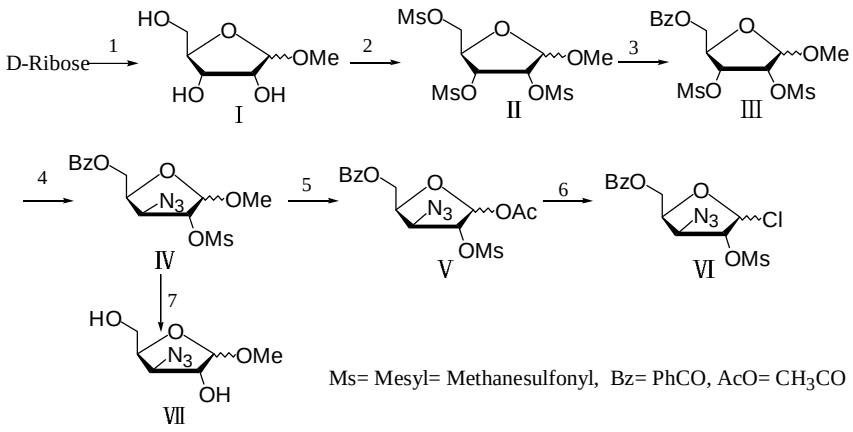
at the 3-position. If the azido substitution was at the 2-position, the difference of the chemical shift of H-3 for IV and III would not be so big. Moreover, the signals of C-4 and C-2 of IV in the ^{13}C NMR are 85.3 and 78.3 ppm respectively, which are similar to the xylofuranoside derivative. IV can be hydrolyzed to corresponding 3-deoxy-3-azido-xylofuranoside VII. Since the resolution of ^{1}H NMR spectrum of IV is poor, we have to convert it to acetate V[6] and chloride VI[7]. The δ value of H-2 was at lower field than H-3 for both compounds, this further demonstrated that the azido group was at the 3-position.

Scheme 1



1. HCl/MeOH, r.t.; 2. MsCl/Et_3N-DMAP, dioxane, 0-5°C; 3. NaOBz/DMF, 120-125°C, 40 min; 4. NaN_3/DMF, 120-125°C, 16 h; 5. Ac_2O-HAc-H_2SO_4; 6. $TiCl_4$/ CH_2Cl_2; 7. Satur. NH_3-CH_3OH.

Experimental

Methyl Ribofuranoside I

Dry HCl was gassed into the solution of D-ribose (3 g, 20 mmol) in 20 mL dry methanol, which was then stirred overnight at room temperature. The solution was neutralized with saturated NH_3 in methanol, the solvent was evaporated under reduced pressure. The residue was dissolved in dry acetone, NH_4Cl was filtered off, the filtrate was evaporated to syrup, which was coevaporated with toluene (10 mL × 3) to give a pale-yellow syrup I, it can be used for the next step reaction without further purification (3.27 g). ^{1}H NMR (acetone-d_6, δ_{ppm}): 4.79 (d, 0.22H, $J_{1,2}$ = 4 Hz, H-1 of α-anomer), 4.73 (s, 0.78H, H-1 of β-anomer), 4.20 (d, 1H, $J_{1,2}$ = 4 Hz, H-2), 4.10 (d, 1H, $J_{4,5}$ = 2.6 Hz, H-3), 3.50 - 4.01 (m, 3H, H-4, H-5, H-5a), 3.34 (s, 3H, OMe) .

Methyl 2, 3, 5-Tri-O-mesylribofuranoside II

Compound I (3.27 g, 20 mmol) was dissolved in dry dioxane (30 mL), NEt_3 (15 mL,

10.8 g, 107 mmol) and DMAP (20 mg, 0.16 mmol) were added. The mixture was cooled in an ice-water bath, methanesulfonyl chloride (6 mL, 8.8 g, 77 mmol) in 10 mL dioxane was slowly dropped in with stirring. After the addition was completed, the reaction mixture was stirred overnight. The reaction mixture was filtered, the filtrate was evaporated to give a syrup residue, which was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution (20 mL × 2), water (20 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was evaporated, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 2/1) to afford 5.8 g colorless solid (mp 130 - 132°C, yield 73%). ^{1}H NMR ($CDCl_3$, δ_{ppm}): 5.28 (dd, 1H, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 7.3 Hz, H-3), 5.10 (s, 1H, H-1), 5.01 (d, 1H, $J_{1,2}$=4.4 Hz, H-2), 4.65(dt, 1H, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 4.0 Hz, H-4), 4.50 (dd, 1H, $J_{4,5}$ = 3.9 Hz, $J_{5,5a}$ = 11.8 Hz, H-5), 4.47 (dd, 1H, $J_{4,5}$ = 4.1 Hz, $J_{5,5a}$ = 11.9 Hz, H-5a), 3.45 (s, 3H, OMe), 3.12, 3.09, 3.05 (s, 9H, OMs). MS: *m/z* (%) 397 (8.3, M^+-1), 367 (13, M^+-OMe), 319 (11), 175 (100).

Methyl 2, 3-Di-O-mesyl-5-O-benzoylribofuranoside III

II (5.5 g, 13.8 mmol) was dissolved in dry DMF (50 mL), then sodium benzoate (2.5 g, 19.5 mmol) was added to the solution. The suspension was refluxed for 40 min at 120-125°C; the hot solution was poured into 50 mL of ice-water, and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with water, dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel column chromatography (petroleum ether / ethyl acetate 4/1) to afford a pale-yellow syrup III (5.4 g, yield 92%). ^{1}H NMR ($CDCl_3$, δ_{ppm}): 7.3 - 8.1 (2m, 5H, Ph), 5.29 (dd, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 7.1 Hz, H-3), 5.08 (s, 1H, H-1), 5.02 (d, 1H, $J_{2,3}$ = 4.5 Hz, H-2), 4.60 (dt, 1H, $J_{3,4}$ = 6.8 Hz, $J_{4,5a}$ = 2.6 Hz, $J_{4,5b}$ = 2.5 Hz, H-4), 4.48 (m, 2H, H-5a, H-5b), 3.32 (s, 3H, OMe), 3.13, 3.10 (s, 6H, OMs). MS: *m/z* (%) 393 (39, M^+-OMe), 315 (33), 285 (11), 253 (13).

Methyl 3-Azido-3-deoxy-2-O-methanesulfonyl-5-O-benzoylxylofuranoside IV

III (5 g, 11.8 mmol) was dissolved in dry DMF (20 mL), then NaN_3 (1.5 g, 23 mmol) was added to the solution. The suspension was refluxed for 16 h at 120-125°C; the hot solution was poured into ice-water (20 mL), and extracted with ethyl acetate (30 mL × 3). The organic layers were washed with water, dried over anhydrous Na_2SO_4, concentration, and purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to give a syrup product (1.84 g, yield 42%). ^{1}H NMR ($CDCl_3$, δ_{ppm}): 7.4 - 8.1 (2m, 5H, Ph), 5.06 (d, 1H, $J_{1,2}$ = 2.5Hz, H-1), 4.4 - 4.8 (m, 5H, H-2~5), 3.43 (s, 3H, OMe), 3.12 (s, 3H, OMs). ^{13}C NMR ($CDCl_3$, δ_{ppm}): 166 (C=O), 133.2, 129.7, 129.6, 129.5, 128.4, 128.4 (6C, Ph), 106 (C-1), 78.2 (C-2), 85.3 (C-4), 64.8 (C-3), 63.6 (C-5), 55.8 (OCH_3), 38.4 (SO_2CH_3). IR (liquid membrane, cm^{-1}): 2114 (N_3), 1722 (Ph-CO). MS: *m/z* (%) 372 (12, M^++1), 340 (100, M^+-OMe), 232 (54), 207 (9.8). Anal. Calcd. for $C_{14}H_{17}N_3O_7S$ (371.37): C, 45.28; H, 4.61; N, 11.32. Found: C, 45.77; H, 4.88; N, 11.38.

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6. ^{1}H NMR ($CDCl_3$, δ_{ppm}) of V: 7.4 - 8.1 (2m, 5H, Ph-H), 6.44 (d, 0.55H, $J_{1,2}$ = 4.4 Hz, H-1 of α-anomer), 6.21 (s, 0.45H, H-1 of β-anomer), 5.14 (dd, 1H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 7.2 Hz, H-2), 4.71 (dt, 1H, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 3.2 Hz, $J_{4,5a}$ = 6.4 Hz, H-4), 4.46 - 4.60 (m, 3H, H-3, H-5, H-5a), 3.1 (s, 3H, OMs), 2.17, 2.08 (s, 3H, OAc).
7. ^{1}H NMR ($CDCl_3$, δ_{ppm}) of IV: 7.4 - 8.1 (2m, 5H, Ph-H), 6.34 (d, 1H, $J_{1,2}$ = 4.3 Hz, H-1 of α-anomer), 5.11 (dd, 1H, $J_{1,2}$ = 4.3 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 4.85 (dd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{4,5}$ = 4.0 Hz, $J_{4,5a}$ = 4.4 Hz, H-4), 4.67 (pseudo t, 1H, $J_{3,4}$ = 8.0 Hz, $J_{2,3}$ = 8.0 Hz, H-3), 4.59 (dd, 1H, $J_{4,5}$ = 3.9 Hz, $J_{5,5a}$ = 12.3 Hz, H-5), 4.46 (dd, 1H, $J_{4,5a}$ = 4.4 Hz, $J_{5,5a}$ = 12.3 Hz, H-5a), 3.18 (s, 3H, OMs)

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