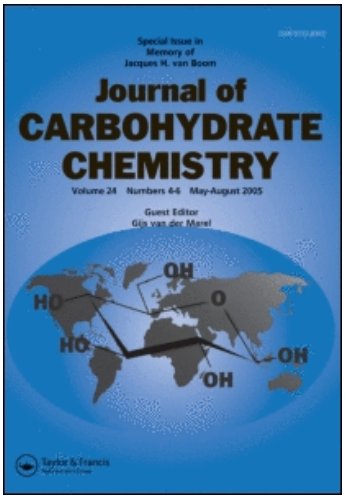

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Synthesis of Different 3,5-Diazidofuranoses: A New and General Synthesis Pathway

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Diamino- and diazidofuranoses represent useful precursors, for example, for the synthesis of substituted nucleosides and metal complexes, respectively. Known procedures for their synthesis lack the availability of cheap starting materials, adequate yields, and the access to all possible diastereomeres. Therefore, 3,5-diazido-3,5-dideoxy- and -2,3,5-trideoxyfuranoses both with *ribo*- and *xylo*-configuration were prepared using different approaches.

Keywords Furanoses, Diazides, Nucleophilic substitution

INTRODUCTION

The synthesis of azido-, amino-, and acetamido-substituted sugars and nucleosides received attention since their derivatives often display biological activity. Amino sugars are structural components of macrolide antibiotics.[1] Azido nucleosides such as AZT have been used as antiviral agents.[2] The coordination of biologically and catalytically active metal ions by selectively modified amino carbohydrates has also gained much attention. For example, the synthesis of cisplatin analogs,[3] radiotracers,[4] and antifungal agents[5] has been reported. Metal complexes of functionalized amino carbohydrates have been synthesized[6] and successfully used as catalysts.[7–9] Nucleosides

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bearing amino groups at the sugar moiety have been applied as ligands for the coordination of metal ions.[10–12]

Their synthesis starting from naturally occurring nucleosides by insertion of amino groups often displays major problems due to the influence of the nucleobase and is strongly limited by the availability of the starting materials. On the other hand, the creation of artificial nucleosides by coupling of sugar derivatives to nucleobases and other heterocyclic systems is well explored.[13] On this background we report an advanced synthesis of 3,5-diazido-3,5-dideoxy- and -2,3,5-trideoxy-furanose derivatives (**1**–**4**, Fig. 1) as useful building blocks for the design of new 3′,5′-diazido-nucleosides and chiral metal complexes thereof.

RESULTS AND DISCUSSION

For both the biological activity and the formation of metal complexes, the absolute configuration is crucial. It is determined by the most demanding step, the nucleophilic substitution with azide anions. The synthesis of the different 3,5-diazido-derivatives **1**, **2**, and **4** has been described earlier, but with low yields or less practical synthetic effort. Derivative **3** has not been prepared yet. **1** was obtained in 61% yield by Brimacombe et al., but starting from rather expensive 1,2-*O*-isopropylidene-α-D-allofuranose.[14] Ozols et al. showed the synthesis for 3,5-diazido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose **2**, but the desired compound could be obtained only in low yields. The corresponding elimination compound was formed as a byproduct in the same amount and the structural characterization was not sufficient.[15] Moravcova et al. tried to optimize the synthesis of **2** by using Mitsunobu reaction conditions, but with less success.[16] The 3,5-diazido-2,3,5-trideoxy-D-ribofuranoside **4** was obtained by Graef et al. in a four-step reaction sequence, but starting from a rarely available derivative.[17] Other furanoside diazides bearing the substituents at different positions and configurations have been synthesized by Unger et al. starting from a 2,3-anhydro-α-D-lyxofuranoside using nucleophilic ring opening reactions.[18] Obviously, the known procedures for the synthesis of 3,5-diazidofuranoses are less efficient, lengthy, and complicated.

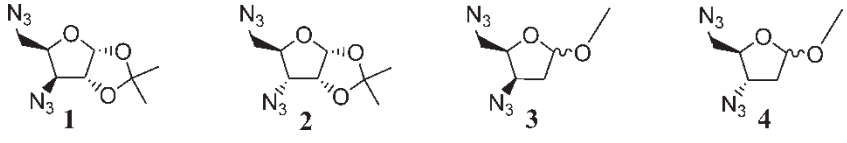


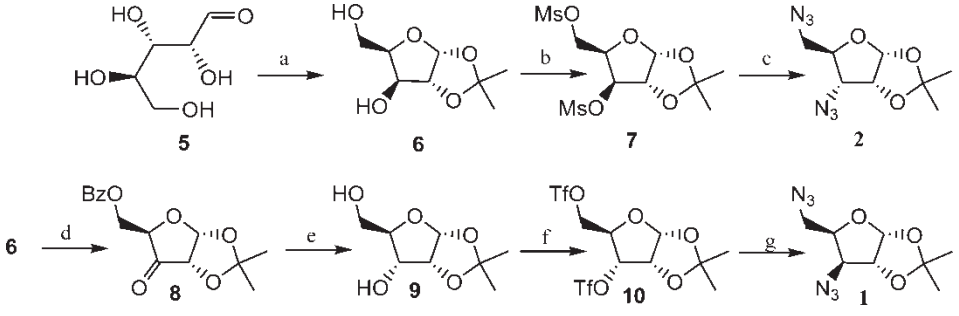
Figure 1: Target structures of 3,5-diazidofuranoses.

The treatment of readily available D-xylose with acetone in the presence of sulfuric acid and anhydrous copper(II) sulfate results in the 1,2-*O*-isopropylidene-furanoside in good yields (Sch. 1).

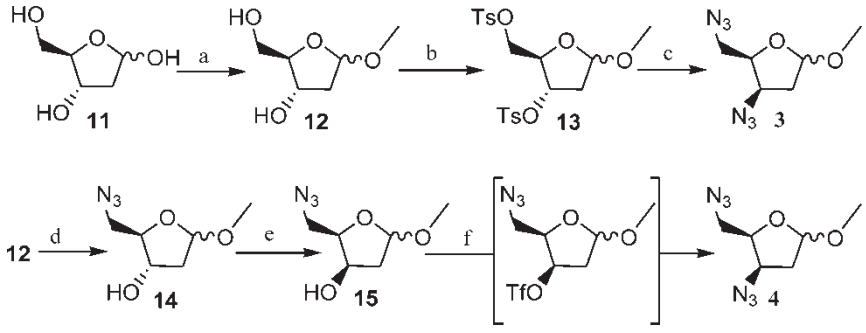
Mesylation of the free hydroxy groups leads to the methanesulfonyl ester **7**, which is the precursor for the target compound **2**. In contrast to the known procedure, we used lithium azide as nucleophil and *N*-methylpyrrolidone as solvent and obtained the diazide **2** in 68% yield. Having done so, the formation of the elimination product can be avoided. This byproduct is formed in all other known pathways in nearly the same amount as the title compound and is difficult to separate from it. The synthesis of the diazide **1** was described earlier, but starting from an uncommon allofuranose derivative.[14] The problems in the synthesis of **1** occur because of the difficult accessibility of the 1,2-*O*-isopropylidene-*ribo*-furanoside **9**. The benzoylation of the primary hydroxy group in **6** followed by oxidation and subsequent reduction at C-3 leads to an inversion of the absolute configuration. After the saponification, the ribofuranoside **9** could be obtained in an overall yield of 70%.

Standard methods for the conversion of **9** to the corresponding diazide **1** led to a mixture of various products. Therefore, different leaving groups, nucleophiles, and solvents were tested. Only the use of triflate as the leaving group and phase transfer conditions led to the desired product **1** in 60% overall yield.

There is only one report for the synthesis of the deoxy derivative **4** from methyl-5-iodo-2,5-dideoxy-xylofuranoside as starting material.[17] Starting from 2-deoxy-D-ribose **11** stirred in dry methanol in the presence of catalytical amounts of acid, the methyl glycoside **12** could be formed. Its conversion to the 5-*O*-tosyl-intermediate **13** followed by the reaction with lithium azide in DMF



Scheme 1: Synthesis of the 3,5-diazido-3,5-dideoxy-furanoses in *ribo*- (**1**) and *xylo*-configuration (**2**): a) 1: $(CH_3)_2CO$, $CuSO_4$, H_2SO_4; 2: 0.1% HCl, 85%; b) MsCl, pyridine, 0°C, 88%; c) LiN_3, NMP, 68%; d) 1: BzCl, Et_3N, CH_2Cl_2, 0°C; 2: Ac_2O, CH_2Cl_2, PDC, reflux, 78%; e) 1: EtOH, $NaBH_4$, 0°C; 2: NaOMe, MeOH, reflux, 90%; f) Tf_2O, pyridine, CH_2Cl_2, −25°C, 79%; g) $(CH_2Cl)_2$, H_2O, NaN_3, 18-crown-6, 15-crown-5, But_4NBF_4, reflux, 76%.



Scheme 2: Synthesis of the 3,5-diazido-2,3,5-trideoxy-furanoses in *ribo*- (**3**) and *xylo*-configuration (**4**): a) MeOH, HCl, 0°C, 74%; b) TsCl, pyridine, −5°C, 70%; c) NaN_3, DMF, 90°C, 52%; d) 1: TsCl, CH_2Cl_2, pyridine, −5°C; 2: LiN_3, DMF, 65°C, 62%; e) 1: Tf_2O, CH_2Cl_2, pyridine, −15°C; 2: DMF, H_2O, 15-crown-5, $NaNO_2$, 71%; f) 1: Tf_2O, CH_2Cl_2, pyridine, −15°C; 2: LiN_3, DMF, 40°C, 68%.

(Sch. 2) gave the 5-azido-derivative **14**. According to the synthesis used, the 2-deoxy-derivatives could only be obtained as an anomeric mixture.

The inversion of the configuration at C-3 could be carried out by preparing the 3-*O*-triflate-derivative and in situ reaction with sodium nitrite in DMF in the presence of water and crown ether to yield 71% of **15**. Applying the standard procedure by forming the sulfonester with triflic anhydride and its subsequent nucleophilic substitution with lithium azide, the methyl-3,5-diazido-2,3,5-trideoxy-D-ribofuranoside **4** could be formed. In contrast to this, the novel *xylo*-diazide **3** could be prepared in a straightforward synthesis from **12** by tosylation and reaction with sodium azide in DMF in 40% overall yield. Compound **4** could be obtained as colorless low viscous oil.

CONCLUSION

In summary, we prepared four different 3,5-diazido-3,5-dideoxy-and -2,3,5-trideoxyfuranoses, both with *ribo*- and *xylo*-configurations.

Although there are a few papers reporting the synthesis of the target compounds, this is the first time a synthesis for all isomers is described. All reactions start from readily available D-xylose and 2-deoxy-D-ribose and can be performed in relatively high yields.

Though in a few papers synthetic studies have been reported to reach these compounds, herewith the first report was given for the synthesis of all isomeres applying new methods. This opens up new possibilities for the synthesis of still unknown artificial nucleosides and chiral metal complexes. For their application it is not necessary to separate the anomeres of the deoxy-derivatives.

EXPERIMENTAL

General Methods

Electronic spectra were recorded with a Varian Cary 1 or Cary 5E spectrophotometer at rt. IR spectra were measured on a Perkin-Elmer 2000 spectrometer and NMR spectra on a Bruker AC-200; mass spectra were carried out on a Finnigan MAT SSQ 710 or a Finnigan MAT 95XL TRAP, and elemental analyses on a Leco CHNS 932.

3,5-Diazido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (1)

Dissolved was 0.47 g of **10** (1.0 mmol) in 10 mL dichloroethane and after that 5 mL water, 510 mg sodium azide (7.85 mmol), 50 mg 18-crown-6 as well as 15-crown-5, and 100 mg tetrabutylammonium tetrafluoroborate were added and the resulting mixture was heated under reflux with vigorous stirring. After 10 h the TLC indicated the complete conversion. The layers were separated, the aqueous layer was extracted twice with chloroform, and the combined organic layers were evaporated. The obtained crude product purified by filtration over Celite gave 190 mg of **1** (yield 76%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.85 (d, 1H, H-1), 4.63 (d, 1H, H-2), 4.26 (dt, 1H, H-4), 3.94 (d, 1H, H-3), 3.56, 3.44 (2dd, 2H, H-5, H-5′), 1.45, 1.27 (2s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 112.5 (**C**$(CH_3)_2$), 104.7 (C1), 83.3 (C2), 77.6 (C4), 66.1 (C3), 49.5 (C5), 26.6, 26.2 (C(**C**$H_3)_2$); MS (EI) m/z 225 $[M\text{-}15]^+$; IR: 2991, 2939, 2096, 1378, 1083, 1019 cm^{-1}; Anal. Calcd for $C_8H_{12}N_6O_3$: C, 40.00; H, 5.04; N, 34.98; Found: C, 41.43; H, 5.08; N, 33.75; ESI-HRMS m/z 225.07288 $[M\text{-}15]^+$, $C_7H_9N_6O_3$ calc. 225.07361307.

3,5-Diazido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (2)

To a solution of 1.24 g of **7** (3.58 mmol) in 20 mL *N*-methylpyrrolidone, 1 g lithium azide (20 mmol) was added. The resulting solution was heated for 8 h at 140°C until the TLC indicated the complete conversion of **7**. The solvent was removed under reduced pressure and the dark brown precipitate was extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered off, and evaporated. The resulting slight yellow oil was purified by flash column chromatography. Yield 585 mg of **2** (68%). ^{1}H NMR ($CDCl_3$) δ 5.84 (d, 1H, H-1) 4.76 (m, 1H, H-2), 4.20 (m, 1H, H-4), 3.74 (dd, 1H, H-5), 3.49 (m, 1H, H-3), 3.36 (dd, 1H, H-5′), 1.57 and 1.37 (2s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 113.4 (**C**$(CH_3)_2$), 104.1 (C1), 80.0 (C2), 76.7 (C4), 60.8 (C3), 50.3 (C5), 26.4 (C(**C**$H_3)_2$); MS (EI) m/z 225 $[M\text{-}15]^+$; IR: 2992, 2940, 2102, 1727,

1670, 1375, 1155, 1043 cm^{-1}; Anal. Calcd for $C_8H_{12}N_6O_3$: C, 40.00; H, 5.04; N 34.98; Found: C, 40.10; H, 5.05; N, 34.86; ESI-HRMS m/z 225.07206 [M-15], $C_7H_9N_6O_3$ calc. 225,07361307.

Methyl-3,5-diazido-2,3,5-trideoxy-D-xylofuranoside (3)

Dissolved was 8.3 g of the ditosylate **15** (18 mmol) in 100 mL dried DMF; 8.82 g lithium azide (180 mmol) was added and the reaction mixture was heated at 90°C for 6 h. After evaporation the resulting mixture was extracted with ethyl acetate, dried with sodium sulfate, filtered off, and evaporated to give 2.8 g of **3** as light yellow oil (yield 78%). The crude product was purified by flash column chromatography (yield 52%). ^{1}H NMR ($CDCl_3$) δ 5.12 (dd, 1H, H-1), 4.21–4.10 (m, 1H, H-4), 3.71–3.34 (m, 6H, H-3, H-5, H-5′, -OCH_3), 2.31–2.16 (m, 2H, H-2, H-2′); ^{13}C NMR ($CDCl_3$) δ 103.9 (C1), 77.9 (C4), 61.6 (C3), 55.4 (C5), 50.4 (-OCH_3), 39.2 (C-2); IR (ATR) 2935, 2839, 2095, 1445, 1266, 1106, 1044, 983 cm^{-1}; Anal. Calcd for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.41; Found: C, 38.48; H, 5.27; N, 39.94; ESI-HRMS m/z 221.07498 [M + Na], $C_6H_{10}N_6O_2Na$ calc. 221.076293.

Methyl-3,5-diazido-2,3,5-trideoxy-D-ribofuranoside (4)

Dissolved was 200 mg of **15** (1.1 mmol) in dried methylene chloride, which was then treated with 0.191 mL pyridine. Added was 100 μL triflic acid anhydride (30 mmol) portionwise with vigorous stirring at –15°C. After the addition had been completed, the reaction mixture was stirred for 30 min, washed with ice water and sodium chloride solution, dried with calcium chloride, filtered off, and evaporated at 30°C. The formed product was quite unstable and had to be handled with care. All steps had to be done as fast as possible. Otherwise, the product decomposed by elimination. It had been used immediately for the next reaction step. Dissolved was 141 mg of the formed methyl-5-azido-2,5-dideoxy-3-*O*-trifluormethanesulfonyl-D-xylofuranoside (0.065 mmol) in 10 mL DMF. After addition of 225 mg lithium azide (4.6 mmol), the reaction mixture was slightly heated until the TLC indicated the complete conversion. After the removal of the solvent extraction with ethyl acetate and evaporation, 77 mg of **4** could be obtained (yield 68%). The crude product was purified by flash column chromatography (yield 41%). ^{1}H NMR (MeOD) 5.15–5.02 (m, 1H, H-1) 4.21–4.11 (m, 1H, H-4), 3.66–3.35 (m, 6H, H-3, H-5, H-5′, -OCH_3), 2.31–2.16 (m, 2H, H-2, H-2′); ^{13}C NMR ($CDCl_3$) δ 105.16, 104.63 (C1), 80.29, 78.36 (C4), 68.56, 68.54 (C3), 55.10, 54.10 (C5), 51.83, 50.06 (-OCH_3), 39.20, 38.80 (C-2); MS (EI) m/z 198 [M +]. Anal. Calcd for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.41; Found: C, 39.00; H, 5.31; N, 36.76; ESI-HRMS m/z 221.07568 [M + Na], $C_6H_{10}N_6O_2Na$ calc. 221.076293.

1,2-*O*-Isopropylidene-α-D-xylofuranose (6)

To 42 g D-xylose (280 mmol) and 70 g of anhydrous copper(II) sulfate (439 mmol) suspended in 800 mL dried acetone, 4 mL concentrated sulfuric acid was added. The reaction mixture was stirred overnight, neutralized with sodium hydrogen carbonate, and filtered off, and the filter cake was washed thoroughly with acetone. The combined organic layers were evaporated and dried in vacuo. The formed 1,2,3,5-di-*O*-isopropylidene-α-D-xylofuranose was dissolved in 250 mL of a 0.2% aqueous hydrochloric acid and stirred at rt until the TLC (R_f 0.5 in ethyl acetate) indicated the complete conversion to the desired mono-isopropylidene derivative. After neutralization the reaction mixture was concentrated to a small volume and extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered off, and evaporated to yield 45 g of **6** (85%). ^{1}H NMR (DMSO-D_6) δ 5.91 (d, 1H, H-1), 5.15 (d, 1H, H-2), 4.65 (dd, 1H, H-4), 4.37 (d, 1H, H-3), 3.95 (s, 2H, -OH), 3.36 (m, 2H, H-5 and H-5′), 1.38, 1.23 (2s, 6H, -CH_3); ^{13}C NMR (DMSO-D_6) δ 110.2 (**C**$(CH_3)_2$), 104.2 (C1), 85.0 (C2), 81.7 (C4), 73.4 (C3), 58.0 (C5), 26.6, 26.4 (2s, 6H, CH_3). MS (EI) m/z 191 [M + 1].

1,2-*O*-Isopropylidene-3,5-di-*O*-methanesulfonyl-α-D-xylofuranose (7)

Dissolved was 10 g of **6** (52 mmol) in 50 mL dried pyridine. After dropwise addition of 13.3 g methanesulfonyl chloride (115 mmol), the reaction mixture was stirred for 3 h, and then 20 mL methanol was added and the mixture stirred again for 30 min. After evaporation and extraction with ethyl acetate, the combined organic layers were dried with sodium sulfate, filtered off, evaporated, and dried in vacuo to yield 15.8 g of **7** as a white solid (88%). ^{1}H NMR ($CDCl_3$) δ 5.93 (d, 1H, H-1), 5.00 (d, 1H, H-2), 4.77 (d, 1H, H-3), 4.51 (m, 1H, H-4), 4.36 (dd, 2H, H-5, H-5′), 3.10, 3.00 (s, 6H, $-SO_2CH_3$), 1.45, 1.18 (2s, 6H, -CCH_3); ^{13}C NMR (DMSO-D_6) δ 113.0 (**C**$(CH_3)_2$), 104.9 (C1), 85.0 (C2), 80.4 (C4) 76.2 (C3), 65.2 (C5), 38.4, 37.6 ($-SO_2$**C**H_3), 26.6, 26.2 (C(**C**$H_3)_2$).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-oxo-α-D-xylofuranose (8)

To 20 g of **6** (105 mmol) dissolved in 50 mL dried methylene chloride, 10.6 g triethylamine (105 mmol) was added. After cooling down to 0°C, 16.2 g benzoyl chloride (116 mmol) dissolved in 50 mL methylene chloride was slowly added. After 3 h the TLC indicated the complete conversion of **6**. The reaction mixture was washed twice with water, dried with sodium sulfate, filtered off, and evaporated to yield 30.6 g of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose as a white solid (99%). ^{1}H NMR ($CDCl_3$) δ 7.99, 7.50, 7.39 (3d, 5H, CH_{aryl}), 5.89 (d, 1H, H-1), 4.52 (d, 1H, H-2), 4.33–4.31 (m, 2H, H-3, H-4), 4.13 (m, 2H, H-5, H-5′), 1.44, 1.24 (2s, 6H, C$(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ

167.4 (C═O), 133.6, 130.1, 129.9, 129.2, 128.6, 128.5 (C_{aryl}), 111.9 ($\mathbf{C}(CH_3)_2$), 105.2 (C1), 85.0 (C2), 78.5 (C4), 74.4 (C3), 61.3 (C5), 26.8, 26.1 ($C(\mathbf{C}H_3)_2$); MS (DEI) m/z 295 $[M+1]^+$; IR(ATR) 3426, 2991, 2949, 1715, 1450, 1379, 1270, 1089, 1070, 1009, 707 cm^{-1}; Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16; Found: C, 61.18; H, 6.14.

Dissolved was 1 g of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (3.4 mmol) in 20 mL methylene chloride. To the stirred solution 1 g acetic acid anhydride (10.2 mmol) and 0.8 g PDC (2.2 mmol) were added. The reaction mixture was heated under reflux for 2 h, filtered through Celite, evaporated, dissolved in chloroform, washed with aqueous sodium hydrogen carbonate solution, dried with calcium chloride, filtered off, and evaporated. The crude product was dissolved in boiling heptane, filtered through Celite, and evaporated to yield 0.8 g of **8** as a white solid (79%). ^{1}H NMR ($CDCl_3$) δ 7.89, 7.47, 7.38 (3d, 5H, CH_{aryl}), 6.07 (d, 1H, H-1), 4.62 (m, 2H, H-5, H-5′), 4.36 (d, 1H, H-2), 1.44, 1.36 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 207.6 (C3), 165.7 (C═O), 133.4, 130.1, 129.9, 129.5, 129.3, 128.5 (C_{aryl}), 114.4 ($C(CH_3)_2$), 103.0 (C1), 77.5 (C2), 76.1 (C4), 63.4 (C5), 27.4 and 27.0 ($C(\mathbf{C}H_3)_2$). MS (DEI) m/z 293 $[M+1]^+$; IR(ATR) 2996, 2926, 1771, 1724, 1451, 1376, 1089, 1070, 1009, 707 cm^{-1}; Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52; Found: C, 61.89; H, 6.09.

1,2-*O*-Isopropylidene-α-D-ribofuranose (9)

In 30 mL ethanol, 4.5 g of **8** (15.4 mmol) was dissolved and cooled down to 0°C. Added dropwise was 0.6 g $NaBH_4$ (15.9 mmol) dissolved in 20 mL water over 2 h with vigorous stirring. After complete addition the reaction mixture was allowed to warm up to rt, stirred overnight, and neutralized with acetic acid. After evaporation the formed 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose was dissolved in methanol and 0.5 mL sodium methanolate solution was added and the resulting mixture was heated for 1 h. After neutralization with ammonium chloride, the reaction mixture was evaporated and redissolved in ethyl acetate and filtered off. The crude product was purified by flash column chromatography using ethyl acetate/methanol 1:1, yielding 2.64 g of compound **9** (90%). ^{1}H NMR (MeOD) δ 5.64 (d, 1H, H-1), 4.46 (m, 1H, H-2), 3.78 (m, 2H, H-5, H-5′), 3.71 (s, 1H, H-4), 3.53 (d, 1H, H-3), 1.44, 1.24 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (MeOD) δ 113.7 ($C(CH_3)_2$), 105.3 (C1), 81.7 (C2), 80.8 (C4), 72.1 (C3), 61.7 (C5), 27.0, 26.7 ($C(CH_3)_2$); MS (EI) m/z 191 $[M+1]^+$; Anal. Calcd for: $C_8H_{14}O_5$: C, 50.52; H, 7.42; Found: C, 51.31; H, 7.04.

1,2-*O*-Isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (10)

To a solution of 0.5 g of **9** (2.6 mmol) in 20 mL methylene chloride, 0.5 g pyridine (6.3 mmol) was added and the solution was cooled down to −25°C.

After addition of 2.3 g triflic acid anhydride (7.9 mmol) dissolved in 10 mL methylene chloride, the reaction mixture was stirred for 30 min, allowed to warm up to rt, and stirred for 30 minutes. The organic layer was washed with sodium hydrogen carbonate solution and twice with water, evaporated, and dried in vacuo to yield 0.94 g (79%) of **10**. The obtained white powder could be stored under argon atmosphere in the refrigerator. ^{1}H NMR ($CDCl_3$) δ 5.81 (d, 1H, H-1), 4.36 (m, 1H, H-2), 4.09 (m, 1H, H-4), 4.01 (d, 1H, H-3), 3.68 (m, 2H, H-5, H-5′), 1.35, 1.19 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 112.7 ($C(CH_3)_2$), 106.3 (C1), 86.9 (C2), 82.4 (C4), 75.8 (C3); 61.0 (C5), 27.1, 26.4 ($C(CH_3)_2$).

Methyl-2-deoxy-D-ribofuranoside (12)

Dissolved was 10 g of 2-deoxy-D-ribose (74.55 mmol) in 80 mL of dried methanol, which was then cooled down to 0°C; 0.5 mL concentrated sulfuric acid was added and the reaction mixture was stirred for 24 h. After neutralization with ion exchange resin Amberlite IRA 420 (OH^- coated), filtration, and evaporation, the crude product was purified by flash column chromatography to yield 8.13 g (74%) of **12** as anomeric mixture. ^{1}H NMR (DMSO-D_6) δ 5.07 (m, 1H, H-1 major anomer), 4.74 (m, 0.2H, H-1 minor anomer), 4.47–3.55 (m, 4H, H-3, H-4, H-5, H-5′), 3.36, 3.34 (2s, 3H, -OCH_3), 2.28–2.14 (m, 2H, H-2, H-2′); ^{13}C NMR (DMSO-D_6) δ 105.4, 105.3 (C1), 87.1, 86.9 (C4), 72.4, 71.8 (C3), 63.5, 62.7 (C5), 55.5, 54.8 (-OCH_3), 42.0, 41.3 (C2). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16, Found: C, 48.59; H, 8.37.

Methyl-2-deoxy-3,5-di-*O*-tosyl-D-ribofuranoside (13)

To 4 g of **12** (27 mmol) dissolved in pyridine, 11.3 g p-toluenesulfonyl chloride (60 mmol) was added portionwise with vigorous stirring at −5°C. After 10 h the TLC indicated the complete conversion of the starting material. The reaction mixture was evaporated and extracted with ethyl acetate to give the product in 70% yield as anomeric mixture. ^{1}H NMR (DMSO-D_6) δ 7.77 (d, 2H, CH_{aryl}), 7.5 (dd, 4H, CH_{aryl}), 7.1 (d, 2H, CH_{aryl}), 5.04 (m, 1H, H-1), 4.60 (m, 1H, H-3), 4.10–3.80 (m, 3H, H-4, H-5, H-5′), 3.26, 3.02 (2s, 3H, -OCH_3), 2.40, 2.27 (2s, 6H, $(-CH_3)_{tosyl}$), 2.12–1.97 (m, 2H, H-2, H-2′); ^{13}C NMR (DMSO-D_6) δ 145.4, 138.0, 132.7, 131.8, 127.5, 125.4 (C_{aryl}), 104.7 (C1), 80.3 (C4), 69.3 (C3), 68.8 (C5), 54.5 (-OCH_3), 38.1 (C2), 20.0 ($(CH_3)_{tosyl}$). IR (ATR) 1596, 1359, 1171, 1095, 987, 916, 811, 654 cm^{-1}; Anal. Calcd for $C_{20}H_{24}O_8S_2$: C, 52.62; H, 5.30; S, 14.05; Found: C, 52.62; H, 5.32; S, 13.70.

Methyl-5-azido-2,5-dideoxy-D-ribofuranoside (14)

To 4 g of **12** (27 mmol) dissolved in 20 mL methylene chloride and 2.37 g pyridine (30 mmol), 5.7 g p-toluenesulfonyl chloride (30 mmol) was added

portionwise with vigorous stirring at −5°C. After 7 h the TLC indicated the complete formation of the methyl-5-*O*-tosyl-2-deoxy-D-ribofuranoside. The reaction mixture was evaporated, extracted with ethyl acetate, dried with sodium sulfate, filtered off, and evaporated to give 6.35 g of the monotosylate (78% yield) that was used for the next reaction step without further purification. Dissolved was 2.5 g (8.26 mmol) of the monotosylate in dried DMF (40 mL), 4.0 g lithium azide (82 mmol) was added, and the reaction mixture was heated for 5 h at 65°C. After evaporation and extraction, the crude product was purified by flash column chromatography to yield 1.14 g (80%) of **14** as anomeric mixture. ^{1}H NMR ($CDCl_3$) δ 5.27–5.04 (m, 1H, H-1), 4.40–4.07 (m, 2H, H-3, H-4), 3.99–3.35 (m, 5H, (-CH_3), H-5, H-5′), 2.28–2.02 (m, 2H, H-2, H-2′); ^{13}C NMR ($CDCl_3$) δ 105.6, 105.4 (C1), 85.7, 84.6 (C4), 73.4, 73.0 (C3), 55.4, 54.9 (C5), 53.8, 52.7 (-CH_3), 41.6, 41.2 (C2). Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27; Found: C, 41.61; H, 6.23; N, 24.02.

Methyl-5-azido-2,5-dideoxy-D-xylofuranose (15)

Dissolved was 200 mg of **14** (1.15 mmol) in 2 mL dried methylene chloride, and 0.2 mL dried pyridine was added. The reaction mixture was cooled down to −15°C and 357 mg (1.265 mmol) triflic acid anhydride was added slowly. After 20 min the reaction mixture was allowed to warm up to rt, washed with ice water and sodium hydrogen carbonate solution, dried, and evaporated to yield methyl-5-azido-2,5-dideoxy-3-*O*-trifluormethanesulfonyl-D-ribofuranoside. This compound was unstable and was used immediately in the next reaction step without further purification. It was dissolved in 50 mL DMF, and three drops of 15-crown-5, 30 μL water, 154 mg sodium nitrite (12.2 mmol) were added and the reaction mixture was stirred overnight. After evaporation the crude product was purified by flash column chromatography to give 142 mg (71%) of **15** as anomeric mixture. ^{1}H NMR ($CDCl_3$) δ 5.29–5.06 (m, 1H, H-1), 4.50–4.11 (m, 2H, H-3, H-4), 3.53–3.36 (m, 5H, (-CH_3), H-5, H-5′), 2.27–2.06 (m, 2H, H-2, H-2′); ^{13}C NMR ($CDCl_3$) δ 105.1, 104.1 (C1), 83.1, 78.4 (C4), 71.8, 71.5 (C3), 55.3, 55.0 (C5), 52.0, 50.1 (-CH_3), 43.0, 41.4 (C2); Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27; Found: C, 41.60; H, 5.96; N, 24.00.

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