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A Facile Synthesis of 1,2-Anhydroglycofuranose Benzyl Ethers

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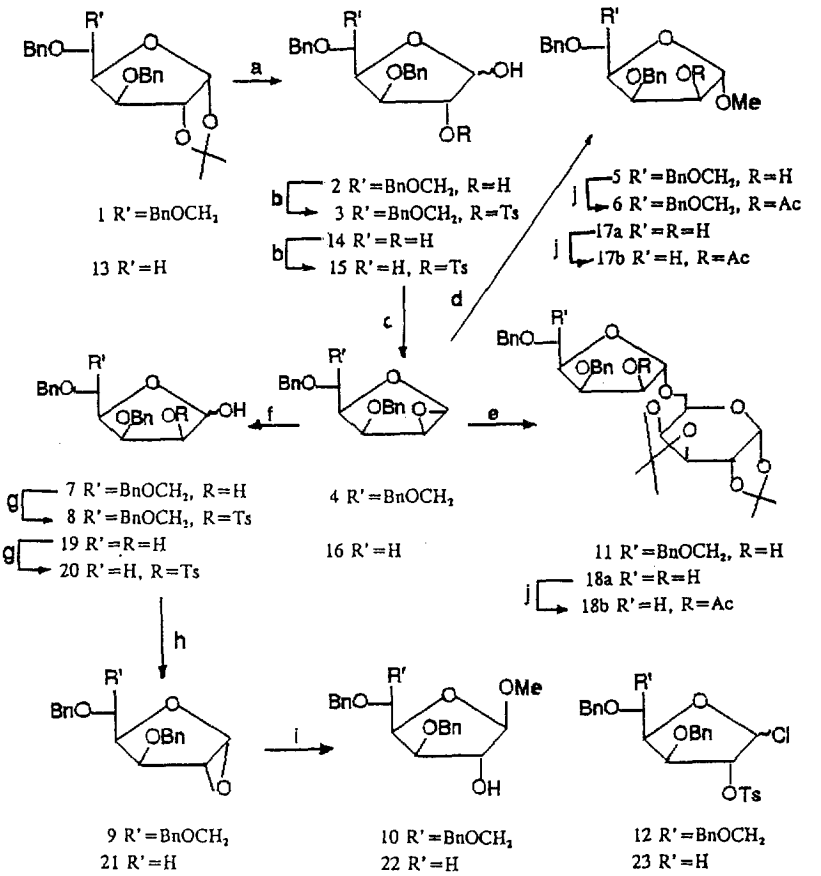
Abstract: The synthesis of 1,2-anhydromanno-, -lyxo-, -gluco-, and -xylofuranose benzyl ethers was successfully achieved *via* intramolecular S_N2 reaction of the corresponding C-1 alkoxide with C-2 bearing tosyloxy group. The key intermediates, furanose 2-sulfonates, were prepared from the corresponding 1,2-diols and tosyl chloride under phase transfer condition in good yields.

1,2-anhydro sugar derivatives are novel monomers for the preparation of the corresponding stereoregular 1-2 linked polysaccharides[1], which are important model compounds for immunological research. Also they are valuable glycosyl donors for the stereospecific synthesis of oligosaccharides[2], and other useful carbohydrate derivatives[3]. Earlier research works in this field were focused on the synthesis of 1,2-anhydropyranose ethers[4]. A recent report[5] showed that some furanans, like ribofuranan and xylofuranan, have high anti-HIV activity and low anticoagulant activity as well as low in *vivo* toxicities, and they are considered to be a potential AIDS drug. The studies into the preparation of 1,2-anhydroribo-, -arabino-, and -galactofuranose derivatives were reported by Danishefsky's group[2,3] using direct epoxidation of the glycals. It seemed, however, that it would be difficult to prepare 1,2-anhydro furanoses having a *cis* arrangement of the 3-hydroxy group and the epoxide ring by this method, and large scale preparation would be inconvenient. In the work described herein, we contribute a facile and general method for preparation of 1,2-anhydro-β-D-manno-, -α-D-gluco-, -β-D-lyxo-, and -α-D-xylo-furanose benzyl ethers. Application of this method for the synthesis of other 1,2-anhydroglycofuranose ethers is in process.

Initial attempts to synthesise the title compounds were focused on an intramolecular S_N2 reaction of C-2 alkoxide with C-1 bearing a halide. For this purpose, a *trans* relationship between the C-2 alkoxide and the C-1 halide was needed. It was found, however, that the furanosyl halides were always obtained as an α and β mixture, and ring closure of the mixture with base gave a product containing the corresponding 1,2-anhydrofuranose and another by-product. Thus our attention turned to "inverse" ring closure, i.e. reaction

Scheme[a]



[a]Reaction conditions: (a) 1M H_2SO_4/H_2O, dioxane, reflux, 3h, 95%(**2**). 50% HOAc/H_2O, HCl, 80°C, 1h, 88%(**14**). (b) TsCl, 5% NaOH/H_2O, TBAHS, CH_2Cl_2, 27°C, 24h, 57%(**3**). 69.6% (**15**). (c) ^{t}BuOK(1.2 equiv.), THF, RT., 20min, 96%(**4**), 97%(**16**). (d) anhyd MeOH, RT, 1h, 100%(**5,17a**). (e) Diacetone glactopyranose, CH_2Cl_2, RT., 2h, 83%(**11**), 85%(**18a**). (f) 0.05N HCl/H_2O, 0°C, 1h, 84%(**7**), 80%(**19**). (g) TsCl, 5% NaOH/H_2O, TBAHS, CH_2Cl_2, 27°C, 24h, 54%(**8**), 65%(**20**). (h) ^{t}BuOK, THF, RT., 20min, 94%(**9**), 95%(**21**). (i) anhyd MeOH, RT., 1h, 100%(**10,22**). (j) Pyr, Ac_2O, 16h, 98%(**6**), 96%(**17b**), 94%(**18b**).

of C-1 alkoxide with C-2 bearing a leaving group. Previously the tosyloxy group proved to be satisfactory for the synthesis of 1,2-anhydropyranose benzyl ethers in this way[4j,4k], and in this work, 3,5,6-tri-*O*-benzyl-2-*O*-tosyl-D-gluco- (**3**) and 3,5-di-*O*-benzyl-2-*O*-tosyl-D-xylofuranose (**15**) were synthesized. When tosylation of **2** or **14** was carried out with tosyl chloride in anhydrous pyridine[4j], only a small amount of **3** or **15** (20%) respectively was obtained. The main product gave a fast moving spot in TLC which was identified by ^{1}H NMR spectrometry as the chloride **12** or **23** (75%) respectively. A similar result was reported for tosylation of the pyranose analogues[4k]. We suppose that the chloride formation was caused by the occurrence of hydrogen chloride produced *in situ* from tosylation of the sugar. We thought that if the tosylation was carried out under phase transfer condition, the hydrogen chloride would be trapped by base immediately. Further the hydroxyl ion would replace C-1 tosyloxy group giving a free hydroxyl group at C-1 if any *O*-tosylation of C-1 occurred. The experimental results confirmed our hypothesis affording a facile method for the preparation of benzylated 2-*O*-tosylate of glycofuranoses with a free hydroxyl group on C-1. The reaction condition was quite mild, and the 2-*O*-tosylate was the sole product. The starting material was recovered and could be reused, and thus the corrected yield was almost quantitative[6]. Compound **3** or **15** was an α and β mixture[7], ring closure of which with potassium *tert*-butoxide in THF gave quantitatively the 1,2-anhydro-3,5,6-tri-*O*-benzyl-β-D-manno- (**4**) or 1,2-anhydro-3,5-di-*O*-benzyl-β-D-lyxofuranose (**16**). **4** or **16** was identified from its ^{1}H NMR spectrum showing an upfield peak of H-2 at δ 3.63 or 3.58 ppm characteristic for the epoxide ring. Methanolysis of **4** or **16** quantitatively gave the corresponding α methyl furanoside **5** or **17a**, confirming the structure of the 1,2-anhydrosugar further. The anhydro sugar **4** or **16** was very reactive, its condensation with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the absence of catalyst yielded an α-linked disaccharide as the sole product in high yield. For the preparation of 1,2-anhydro-3,5,6-tri-*O*-benzyl-α-D-gluco- (**9**) or 1,2-anhydro-3,5-di-*O*-benzyl-α-D-xylofuranose (**21**) analogue, "double inverse" ring closure was conducted as described below. Hydrolysis of **4** or **16** gave the corresponding 1,2-diol **7** or **19**, then tosylation, followed by quantitative ring closure of **8** or **20** gave **9** or **21** respectively. The structure of **9** or **21** was similarly confirmed by the quantitative methanolysis. A typical procedure for the synthesis of 1,2-anhydrofuranose **16** was as follows: To a solution of 3,5-di-*O*-benzyl-D-xylofuranose (**14**) (1.32 g, 4 mmol) in CH_2Cl_2 (30 mL) was added tetrabutylammonium hydrogensulfate (TBAHS) (100 mg, 0.3 mmol), 5% NaOH (7.2 mL, 9 mmol) and tosyl chloride (970 mg, 5.1 mmol). The mixture was stirred for 24 h at room temperature. The 2-sulfonate **15** was obtained (1.35 g, 69.6%), and the starting material **14** (320 mg) was recovered. To the stirred solution of **15** (250 mg, 0.52 mmol) in THF (12 mL) was added potassium *tert*-butoxide (88 mg, 0.78 mmol), and the mixture was stirred at room temperature for 20 min. After concentration of the mixture, the resulting residue was repeatedly extracted with 1:3 EtOAc-petroleum ether. Evaporation of the solvents gave the 1,2-anhydrofuranose **16** as a colourless syrup (156 mg, 97%).

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6. All new compounds were purified and characterized by ^{1}H NMR and elemental analyses. Selected ^{1}H NMR ($CDCl_3$, Me_4Si as internal standard) data are as follows: **3**. α,β mixture(1:6). For β isomer: 7.75(d, 2H, PH-*H* of Ts), 5.07(d, 1H, $J_{H1,OH}$ 11.1 Hz, H-1), 4.79(s, 1H, H-2), 4.30(dd, 1H, H-4), 4.25(d, 1H, H-3), 3.89(m, 1H, H-5), 3.83(dd, 1H, H-6), 3.63(dd, 1H, H-6'), 3.38(d, 1H, $J_{H1,OH}$ 11.1 Hz, O*H*), 2.39(s, 3H, PHCH_3). **4**. 5.11(d, 1H, H-1), 4.50(d, 1H, H-3), 4.40(dd, 1H, H-4), 4.01(m, 1H, H-5), 3.80(dd, 1H, H-6), 3.66(dd, 1H, H-6'), 3.63(d, 1H, H-2). **6**. 5.04(dd, 1H, H-2), 5.01(d, 1H, H-1), 4.40(t, 1H, H-3), 4.28(dd, 1H, H-4), 4.04(m, 1H, H-5), 3.85(dd, 1H, H-6), 3.70(dd, 1H, H-6'), 3.37(s, 3H, OCH_3), 2.0(s, 3H,COCH_3). **10.** 4.78(s, 1H, H-1), 4.39(m, 1H, H-4), 4.17(s, 1H, H-2), 4.07(m, 1H, H-5), 3.96(d, 1H, H-3), 3.88(dd, 1H, H-6), 3.72(dd, 1H, H-6'), 3.36(s, 3H, OCH_3), 1.80(bs, 1H, O*H*). **11**. 5.50(d, 1H, H-1), 4.98(d, 1H, H-1'), 4.57(dd, 1H, H-3), 4.38(dd, 1H, H-3'), 4.32(d, 1H, H-4'), 4.30(dd, 1H, H-2), 4.21(dd, 1H, H-4), 4.10(m, 1H, H-5'), 3.80(dd, 1H, H-6a'), 3.72(dd, 1H, H-6b'), 3.69(dd, 1H, H-2'), 1.55, 1.46, 1.35 and 1.34(4s, 12H, 2C(CH_3)$_2$. **15.** α,β mixture(1:7). For β isomer: 7.76(d, 2H, Ph-*H* of Ts), 5.12(d, 1H, $J_{H1,OH}$ 11.9 Hz, H-1), 4.84(d, 1H, H-2), 4.32(m, 1H, H-4), 4.22(dd, 1H, H-3), 3.90(d, 1H, $J_{H1,OH}$ 11.9 Hz, O*H*), 3.69(dd, 1H, H-5), 3.64(dd, 1H, H-5'), 2.47(s, 3H, PhCH_3). **16.** 5.18(d, 1H, H-1), 4.50(m, 1H, H-4), 4.40(dd, 1H, H-3), 3.83(dd, H-5), 3.68(m, H-5'), 3.58(d, 1H, H-2). **17b.** 5.08(dd, 1H, H-2), 4.95(d, 1H, H-1), 4.40-4.35(m, 2H, H-3,4), 3.72(dd, 1H, H-5), 3.68(dd, 1H, H-5'), 3.38(s, 3H, OCH_3), 2.0(s, 3H, COCH_3). **18b.** 5.51(d, 1H, H-1), 5.18(dd, 1H, H-2'), 5.15(d, 1H, H-1'), 4.58(dd, 1H, H-3), 4.42(m, 1H, H-3'), 4.41(dd, 1H, H-4), 2.01(s, 3H, COCH_3). **22.** 4.75(d, 1H, H-1), 4.36(dd, 1H, H-4), 4.17(dd, 1H, H-2), 3.91(dd, 1H, H-3), 3.71(m, 2H, H-5,5'), 3.40(s, 3H, OCH_3).

7. After acetylation of compound **3** and **15**, the α, β ratios were changed into 1:2 (for **3**) and 1:3 (for **15**).

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