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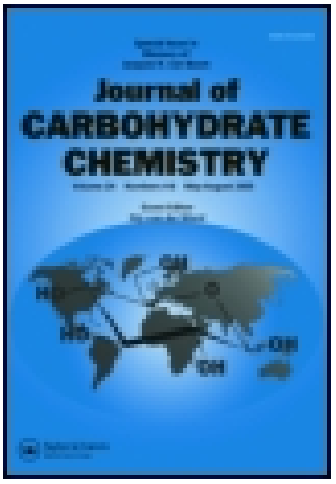

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A Facile Synthesis of 1,2-Anhydro-6-O-acetyl-3,4-di-O-benzyl-d-glycopyranoses and 1,2-Anhydro-5-O-acetyl-3-O-benzyl-D-glycofuranoses

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COMMUNICATION

A FACILE SYNTHESIS OF 1,2-ANHYDRO-6-*O*-ACETYL-3,4-DI-*O*-BENZYL-D-GLYCOPYRANOSES AND 1,2-ANHYDRO-5-*O*-ACETYL-3-*O*-BENZYL-D-GLYCOFURANOSES

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The ability to couple carbohydrate entities to produce glycosides or higher oligomers is an important goal of synthetic organic chemistry.[1] For the past several decades, methods to construct glycosidic linkages have improved as a result of the development of glycosidation procedures.[2] However, owing to their structural complexity, synthesis of oligosaccharides is still a laborious task compared with the synthesis of oligopeptides and oligonucleotides. Many additional sugar derivatives which can improve and simplify synthetic procedures of oligosaccharides are needed.

1,2-Anhydrosugar derivatives, as intermediates for the synthesis of oligosaccharides, have received considerable attention recently because of their excellent reactivity and stereoselectivity,[3,4] and many natural and unusual oligosaccharides have been synthesized from them.[3,4] Studies concerned with the preparation of 1,2-anhydrosugars were reported by Danishefsky's group[3] using direct epoxidation of the glycals. It is, however, difficult to prepare 1,2-anhydrosugars having a *cis* arrangement of the 3-hydroxy group and the epoxide ring by this method, and large scale preparations are inconvenient. Another approach to synthesis of 1,2-anhydro sugars is intramolecular S_N2 reaction, as

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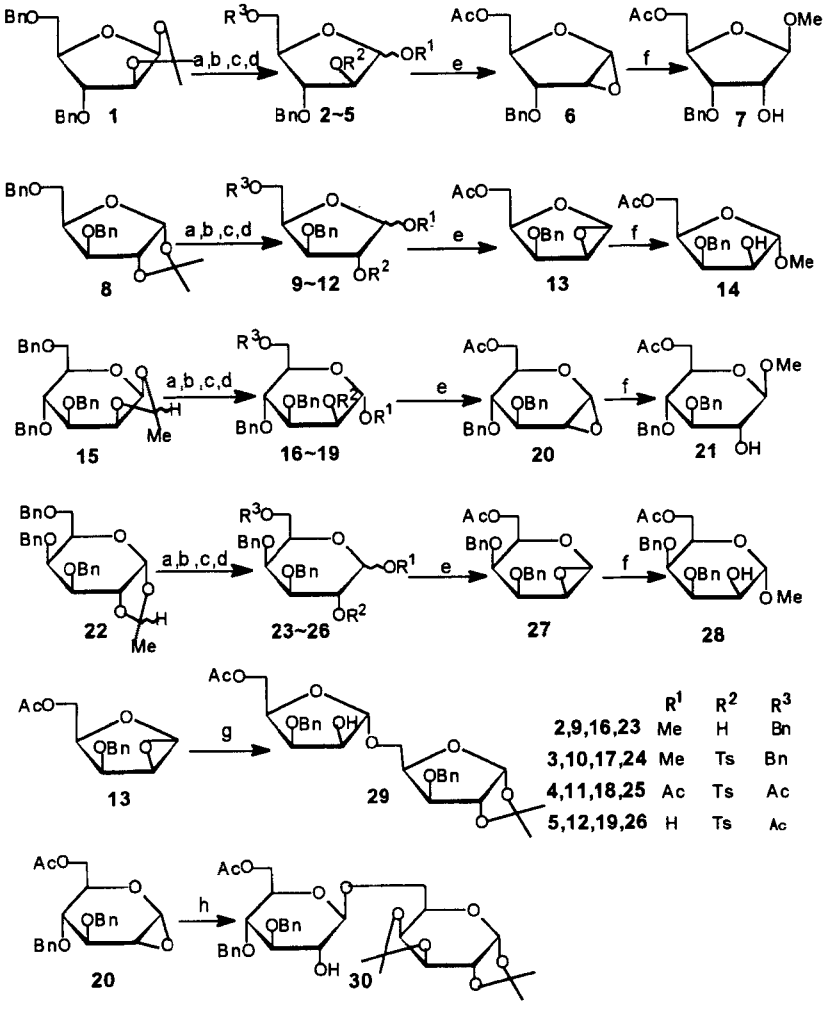

Scheme: (a) catalytic amount of H_2SO_4, CH_3OH, reflux, 3 h, 98% (**2**), 97% (**9**), 98% (**16**), 98% (**23**). (b) TsCl, pyridine, 50° C, 20 h, 98% (**3**), 98% (**10**), 97% (**17**), 98% (**24**). (c) $HOAc/Ac_2O/H_2SO_4$=7/1/0.6 (v), rt, 16 h, 97% (**4**), 96% (**11**), 96% (**18**), 96% (**25**). (d) anhydrous ether saturated with dry ammonia, rt, 24 h, 97% (**5**), 97% (**12**), 96% (**19**), 97% (**26**). (e) NaH (1.1equiv.), THF, rt, 20 min, 95% (**6**), 94% (**13**), 92% (**20**), 94% (**27**). (f) anhydrous MeOH, rt, 1 h, 100% (**7**, **14**, **21**, **28**). (g) 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose, CH_2Cl_2, $ZnCl_2$, rt, 4 h, 84% (**29**). (h) diacetone galactopyranose, CH_2Cl_2, $ZnCl_2$, rt, 4 h, 83% (**30**).

initiated by Schuerch's group.[5] As part of a continuous effort dedicated to the synthesis of 1,2-anhydro sugars by this latter method, a number of 1,2-anhydrosugar benzyl ethers have been synthesized in our laboratory.[4] However, in the stepwise synthesis of oligosaccharides, the preparation of sugar derivatives containing both persistent and temporary blocking groups is required. In the work described herein, we contribute a facile and general method for the synthesis of 1,2-anhydro-6-*O*-acetyl-3,4-di-*O*-benzylglycopyranoses and 1,2-anhydro-5-*O*-acetyl-3-*O*-benzylglycofuranoses being capable of building 2,6- (and 2,5-) homo- or hetero- substituted oligasaccharides.

The synthetic route is depicted in the Scheme. Tosylation of **2**, **9**, **16**, and **23**, which were obtained by methanolysis of **1**, **8**, **15**, and **22**, respectively, afforded the corresponding methyl-2-sulfonate glycosides **3**, **10**, **17**, and **24**. Selective acetolysis of **3**, **10**, **17**, and **24** using $HOAc/Ac_2O/H_2SO_4$ gave the corresponding diacetates **4**, **11**, **18**, and **25**. It was found that selective removal of the 1-*O*-acetyl group of the diacetates by known methods such as using $SnCl_4$[6] or $N_2H_4 \cdot HOAc$[7] suffered from low yields and tedious separation. However the 1-*O*-acetyl group was very successfully removed under the conditions designated for selective removal of 2-*O*-trichloroacetyl[8] of 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride. Thus the key intermediates **5**, **12**, **19**, and **26** were quantitatively obtained from treatment of the corresponding **4**, **11**, **18**, and **25** in anhydrous ether saturated with dry ammonia.[8] Since all of the above applied reactions gave very high yields, the intermediates involved in the procedure could be subjected to the next reaction without chromatographic separation. We were gratified to find that ring closure of **5**, **12**, **19**, and **26** with NaH in THF gave the 1,2-anhydro-6-*O*-acetyl-di-*O*-benzyl-α-D-glucopyranose (**20**), 1,2-anhydro-6-*O*-acetyl-di-*O*-benzyl-β-D-talopyranose (**27**), 1,2-anhydro-5-*O*-acetyl-3-*O*-benzyl-α-D-ribofuranose (**6**), and 1,2-anhydro-5-*O*-acetyl-3-*O*-benzyl-β-D-lyxofuranose (**13**), respectively, in almost quantitative yields. Acetyl groups were not affected under the designated alkaline conditions. The anhydro sugars **6**, **13**, **20**, and **27** were identified from their ^1H NMR spectra showing upfield peaks from H-2 at δ 3.57, 3.60, 3.06, and 3.50 ppm, respectively, a salient feature of the epoxide ring. Methanolysis of **6**, **13**, **20**, and **27** quantitatively gave the corresponding 1,2-*trans* methyl glycosides **7**, **14**, **21**, and **28**, confirming the anhydrosugar structures. Condensation of **13** with 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose using $ZnCl_2$ as the catalyst in

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CH_2Cl_2 yielded an α-linked disaccharide **29** (1,2-*trans*) as the sole product in a high yield, while condensation of **20** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose afforded a β-linked disaccharide **30** (1,2-*trans*) as the sole product in a satisfactory yield. It is noted that 6-*O*-acetyl in **20** did not influence the stereoselectivity of the ring opening coupling of **20** although it is known that replacement of 6-*O*-benzyl with 6-*O*-acetyl altered the stereoselectivity of the coupling reaction of benzylated galactopyranosyl phosphite from 1,2-*trans* to predominant 1,2-*cis*.[9] Compounds **29** or **30** having a free 2-OH group and a potential 5-OH or 6-OH group[10] can be used for further selective functionalization or glycosylation at the C-2 and C-5 or C-6 positions.

In summary, we have successfully developed a highly efficient procedure for the synthesis of 6-*O*-acetyl-1,2-anhydro-3,4-di-*O*-benzylglycopyranoses and 5-*O*-acetyl-1,2-anhydro-3-*O*-benzylglycofuranoses which are important intermediates for the construction of complex carbohydrates.

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10. All new compounds were purified and characterized by ^{1}H NMR, elemental analysis, and optical rotation. Selected ^{1}H NMR ($CDCl_3$, Me_4Si as internal standard) data are as follows: **11**. α, β mixture (2:1): 7.80 (d, 2H, Ph-*H* of Ts), (d, 0.67H, H-1 of α anomer), 5.99 (s, 0.33H, H-1 of β anomer), 5.01(d, 0.33H, H-2 of β anomer), 4.95 (t, 0.67H, H-2 of α anomer), 4.70-4.10 (m, 4H, H-3, 4, 5, 5'), 2.45 (s, 3 × 0.33H, PhCH_3 of β anomer), 2.42 (s, 3 × 0.67H, PhCH_3 of α anomer), 2.03- 2.00 (m, 6H, 2COCH_3). **12**. α, β mixture (1:3): 7.82 (d, 2 × 0.25H, Ph-*H* of Ts of α anomer), 7.80 (d, 2 × 0.75H, Ph-*H* of Ts of β anomer), 5.46 (d, 0.25H, H-1 of α anomer), 5.15 (s, 0.75H, H-1 of β anomer), 4.80 (s, 0.75H, H-2 of β anomer), 4.71 (t, 0.25H, H-2 of α anomer), 4.40-4.15 (m, 4H, H-3, 4, 5, 5'), 2.46 (s, 3 × 0.75H, PhCH_3 of β anomer), 2.42 (s, 3 × 0.25H, PhCH_3 of α anomer), 2.03(s, 3 × 0.75H, COCH_3 of β anomer), 2.00 (s, 3 × 0.25H, COCH_3 of α anomer). **13**. 5.16 (d, 1H, H-1), 4.58-4.35 (m, 3H, H-3, 5, 5'), 4.10 (m, 1H, H-4), 3.60 (t, H-2), 2.08 (s, 3H, COCH_3). **14**. 4.90 (s, 1H, H-1), 4.48-4.30 (m, 3H, H-3, 5, 5'), 4.19 (m, 1H, H-4), 4.07 (d, 1H, H-2), 3.36 (s, 3H, OCH_3), 2.04 (s, 3H, COCH_3). **18**. Only α isomer: 7.85 (d, 2H, Ph-*H* of Ts), 6.04 (d, 1H, H-1), 4.84 (t, 1H, H-2), 4.30 (dd, 1H, H-6), 4.21 (dd, 1H, H-6'), 3.96-3.72 (m, 3H, H-3, 4, 5), 2.40 (s, 3H, PhCH_3), 2.05, 2.02 (2s, 6H, 2COCH_3). **19**. Only α isomer: 7.83 (d, 2H, Ph-*H* of Ts), 5.34 (d, 1H, H-1), 4.81 (t, 1H, H-2), 4.37 (dd, 1H, H-3), 4.14 (dd, 1H, H-6), 3.98 (dd, 1H, H-6'), 3.97 (m, 1H, H-5), 3.72 (t, 1H, H-1), 2.90 (ds, 1H, O*H*), 2.38 (s, 3H, PhCH_3), 2.04 (s, 3H, COCH_3). **20**. 4.95 (d, 1H, H-1), 4.33 (dd, 1H, H-6). 4.24 (dd, 1H, H-6'), 4.01 (dd, 1H, H-3), 3.81 (ddd, 1H, H-5), 3.51 (dd, 1H, H-4), 3.06 (dd, 1H, H-2), 2.03 (s, 3H, COCH_3). **21**. 4.99 (t, 1H, H-2), 4.36 (dd, 1H, H-6), 4.23 (dd, 1H, H-6'), 4.29 (d, 1H, H-1), 3.71-3.50 (m, 3H, H-3, 4, 5), 3.47 (s, 3H, OCH_3), 2.05, 1.98 (2s, 6H, 2COCH_3). **29**. 5.91 (d, 1H, H-1), 4.98 (s, 1H, H-1'), 4.38-4.26 (m, 4H, H-3', 4, 5a, 5b), 4.17 (m, 1H, H-4'), 4.06 (d, 1H, H-2'), 3.94-3.68 (m, 3H, H-3, 5'a, 5'b), 2.64 (bs, 1H, O*H*), 2.05 (s, 3H, COCH_3), 1.52, 1.31 (2s, 6H, 2CCH_3). **30**. 5.50 (d, 1H, H-1), 4.61 (dd, 1H, H-3), 4.33 (dd, 1H, H-2), 4.25 (d, 1H, H-1'), 4.22 (dd, 1H, H-4), 4.07 (dd, 1H, H-2'), 4.01 (m, 1H, H-5), 3.74 (dd, 1H, H-3'), 3.65 (m, 1H, H-5'), 3.60 (dd, 1H, H-4'), 2.02 (s, 3H, COCH_3).

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