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Novel Pyranoid Glycals Derived from D-Fructose

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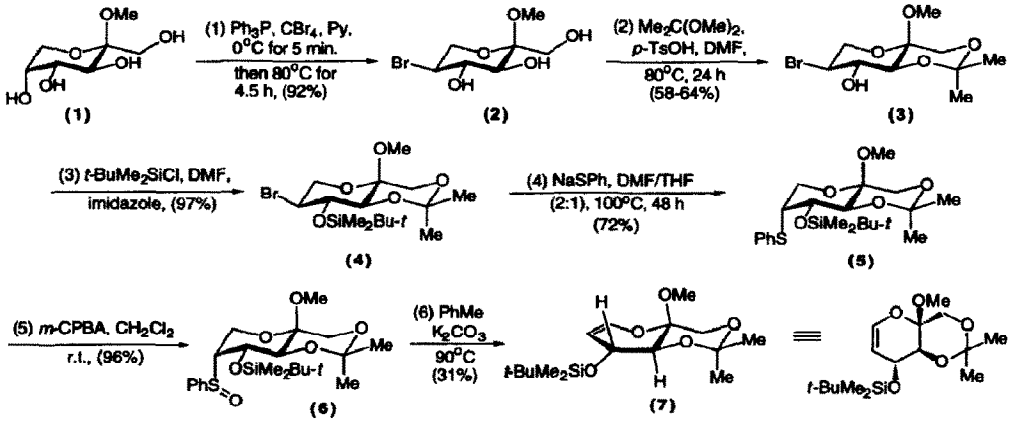
Abstract: A range of 5,6-glycals have been prepared from methyl β-D-fructopyranoside and their chemistry investigated.

Despite the fact that aldose-derived pyranoid glycals have proven useful chiral starting materials for the asymmetric synthesis of natural products,[1] comparatively few attempts have been made to exploit the chemistry of their ketose counterparts, primarily because of their relative synthetic inaccessibility.[1b,2] In this letter, we report on methodology that now allows the efficient construction of several pyranoid 5,6-glycal building blocks from readily available methyl-β-D-fructopyranoside **1**.

Treatment of methyl β-D-fructopyranoside **1**[3] with triphenylphosphine (3.6 equiv) and carbon tetrabromide (3.8 equiv) in pyridine (*ca* 0.19 M) at 80°C for 4.5 h afforded methyl 5-bromo-5-deoxy-α-L-sorbopyranoside **2** {$[\alpha]_D$ -70.6° (*c* 1, CH_2Cl_2)} in 92% yield after chromatography (Scheme 1). Acetalation of **2** with dimethoxypropane and a catalytic quantity of *p*-toluenesulfonic acid in DMF at 80°C, regioselectively blocked the C(1) and C(3)-hydroxyls to produce crystalline 1,3-*O*-isopropylidene derivative **3** {m.p. 78.5-81°C, $[\alpha]_D$ -26°

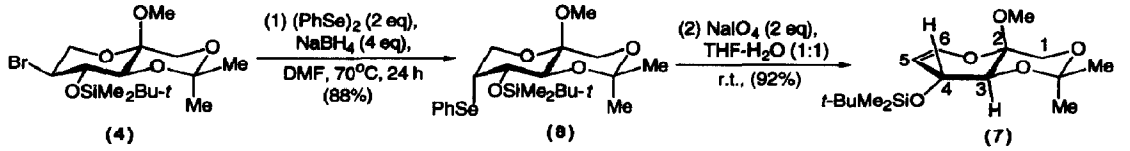
Scheme 1



(*c* 1, CH_2Cl_2)} in 58-64% yield. The structure of **3** was apparent from its 100 MHz ^{13}C NMR spectrum, since the newly installed isopropylidene acetal carbon resonated at δ 100.6, and the methyl carbon signals appeared at δ 28.9 and 18.7, as would be expected for a 1,3-dioxane ring system, according to the rules proposed by Buchanan *et al.*[4] Silylation of **3** proceeded readily with *t*-butyldimethylsilyl chloride and imidazole in DMF at room temperature and led to bromide **4** {$[\alpha]_D$ -12.5° (*c* 0.8, CH_2Cl_2)} in 97% yield. When bromide **4** was treated with sodium thiophenoxide in 2:1 DMF/THF at 100°C it underwent nucleophilic displacement to give

phenylsulfide **5** in 72% yield. Phenylsulfide **5** afforded a 1.6:1 mixture of diastereomeric phenylsulfoxides **6** in 96% yield when oxidised with *m*-CPBA in CH_2Cl_2. Their thermal *syn* elimination reaction proceeded slowly in toluene at 90°C and generally gave **7** in low yield (*ca.* 31%); use of higher temperatures brought about extensive decomposition. It was therefore decided to carry out the displacement of bromide **4** with sodium phenylselenide, convert the resulting product **8** to the selenoxide, and then attempt *syn* elimination.[5] Fortunately, this tactic

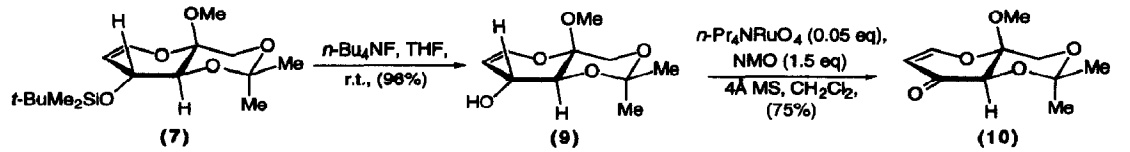
Scheme 2



proved very efficient (Scheme 2), installing the alkene at the C-5 and C-6 positions of the pyranoid ring in 81% overall yield for the two steps. The positional integrity of the alkene in **7** was confirmed by the large $J_{3,4}$ coupling (8.1 Hz) observed between H-3 and H-4.

In view of the ready availability of glycal **7**, we considered it worthwhile to explore ways of manipulating it into other synthetically useful ketose 5,6-glycals. One of the target molecules selected for study was dihydropyrone **10** (Scheme 3). When compound **7** was reacted with tetra-*n*-butylammonium fluoride in THF it was rapidly transformed into a slower-moving product **9** on t.l.c which was isolated in 96% yield. The IR spectrum of **9** contained a broad OH stretching absorption at 3460 cm^{-1}, and a C=C stretching absorption at 1645 cm^{-1} which indicated that the enol ether had remained intact. Alcohol **9** was then oxidised to enone **10** { $[\alpha]_D$ -137.7° (*c* 1, CH_2Cl_2)} using the Ley-Griffith reagent, tetra-*n*-propyl perruthenate in CH_2Cl_2,[6] or with PDC in

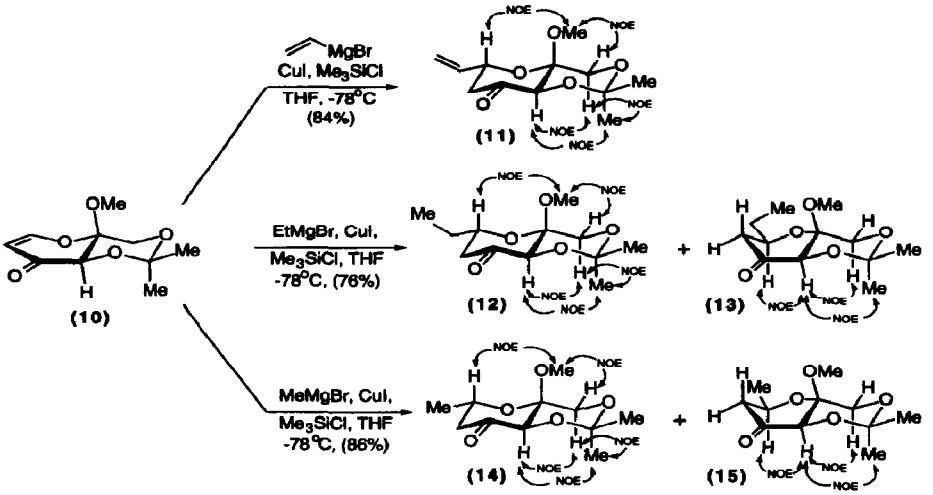
Scheme 3



DMF (77%). The 400 MHz ^1H NMR spectrum of **10** in $CDCl_3$ was highly diagnostic, it containing only eight signals. Both olefinic protons resonated as low field doublets (J = 6.2 Hz) at δ 6.98 and 5.42, while H-3 appeared as a singlet at δ 4.76. The H-1_{ax} and H-1_{eq} resonances formed an AB-quartet at *ca.* δ 4.0, while the methoxy and methyl groups resonated as singlets at δ 3.35, 1.53 and 1.52 respectively. Further confirmation of the structure of **10** came from its IR spectrum which displayed two strong absorptions at 1696 and 1598 cm^{-1}, attributable to the C=O and C=C stretching vibrations of a vinylogous lactone.

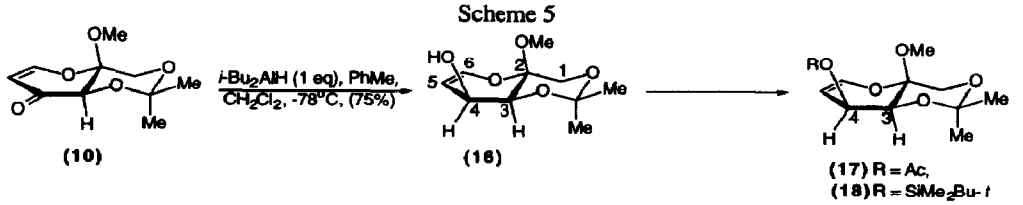
Whilst the synthetic potential of dihydropyrone **10** has not been investigated extensively, preliminary studies indicate that it undergoes a series of markedly stereoselective conjugate addition reactions with organocuprate reagents in the presence of trimethylsilyl chloride (Scheme 4).[7] For example, when a solution of **10** in THF was added to a solution of vinyl magnesium bromide (2 eq, Aldrich 1M in THF), cuprous iodide (1 eq), and trimethylsilyl chloride (5 eq) in THF at -78°C, a single 1,4-addition product **11** was formed, which was isolated from the reaction mixture in 84% yield. The stereochemistry of the newly created asymmetric centre was assigned after examination of the 400 MHz ^1H NOESY spectrum of **11** in $CDCl_3$. This showed a significant cross peak between the H-6 multiplet at δ 4.52 and the methoxy resonance at δ 3.32, which suggested that both these groups were *syn*-related, and that H-6 was therefore axial. Other strong NOE cross peaks observed in the spectrum of

Scheme 4



11 were between the H-3 signal at δ 4.52 and the H-1_{ax} doublet at δ 3.80, and between the methoxy resonance and the H-1_{eq} doublet at δ 4.02. Intriguingly, when dihydropyrone **10** was reacted with ethyl magnesium bromide (Aldrich, 3.0 M in Et_2O), cuprous iodide, and trimethylsilyl chloride in THF at -78°C, a 3:1 mixture of 1,4-adducts **12** and **13** arose, the major isomer possessing the (*6S*)-configuration. However, when methyl magnesium bromide (Aldrich, 1.0 M in *n*-Bu_2O), cuprous iodide, and trimethylsilyl chloride were used at -78°C, a 5:1 mixture of 1,4-addition products **14** and **15** was isolated in 86% yield, the major component again having the (*6S*)-configuration. As previously, the observation of a significant NOE cross peak between the H-6 multiplet at δ 4.20 and the methoxy resonance at δ 3.28 in the 400 MHz ^{1}H NOESY spectrum of **14** led to this stereochemical assignment for the major epimer. The stereoselectivity of these cuprate additions is best understood after inspection of a Drieding molecular model of **10**. This clearly reveals that the methoxy group of the glycoside can adopt an orientation where it shields the top face of the vinylogous lactone system and thus impedes attack of the cuprate reagent from that direction.

Scheme 5



Not surprisingly, underside attack on **10** was also favoured by the bulky hydride reducing agent DIBAL-H (1 eq, Aldrich, 1.5 M in PhMe) in CH_2Cl_2 at -78°C (Scheme 5). This reaction furnished alcohol **16** {$[\alpha]_D$ +31.8° (*c* 1, CH_2Cl_2)} as the sole product in 75% yield. It readily underwent acetylation with acetic anhydride and pyridine. The 400 MHz ^{1}H NMR spectrum of the derived *O*-acetyl derivative **17** in $CDCl_3$ indicated that it contained a single *O*-acetyl group (δ 2.11), and that H-3 and H-4 had a *gauche* relationship since the $J_{3,4}$ value was quite small (5.6 Hz). Alcohol **16** could also be readily silylated (77% yield) with *t*-butyldimethylsilyl chloride (1 eq) and imidazole (1 eq) in DMF at room temperature. The ^{1}H NMR of the derived product **18** revealed an even smaller $J_{3,4}$ value (4.8 Hz), which was indicative of distortion of the pyranoside ring towards a

$^2HC_0$ conformation. Significantly, molecular models of glycal **18** indicate that its top face is quite hindered, and so we fully expect it to undergo electrophilic attack almost exclusively from its underside.

In summary, we have prepared a range of novel pyranoid 5,6-glycals from methyl β-D-fructopyranoside. We believe that they will be useful not only as chiral building blocks for asymmetric synthesis, but will also serve as versatile intermediates for functionalising the C(5) and C(6)-positions of ketoses. Further synthetic studies on these molecules will be reported in due course.

References and Notes

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8. All new compounds reported in this paper gave satisfactory IR, 400 MHz ^1H and 100 MHz ^{13}C NMR spectra as well as HRMS and/or C and H microanalyses. Selected physical data: **(7)** colourless oil, $[\alpha]_D$ -131° (*c* 1, CH_2Cl_2); IR (neat film): 1645 (m), 400 MHz ^1H NMR ($CDCl_3$): δ 6.03 (dd, *J* = 1.7, 6.3 Hz, H-6), 4.73 (dd, *J* = 2.0, 6.2 Hz, H-5), 4.37 (ddd, H-4), 3.95 (d, *J* = 12.5 Hz, H-1a), 3.87 (d, *J* = 8.1 Hz, H-3), 3.62 (d, *J* = 12.5 Hz, H-1b), 3.29 (s, 3H, OMe), 1.46 (s, 3H, Me), 1.43 (s, 3H, Me), 0.85 (s, 9H, Bu-*t*), 0.06 (s, 3H, Me), 0.05 (s, 3H, Me); FAB HRMS Calcd. for $C_{16}H_{30}O_5SiNa$ $(M+Na)^+$ 353.1760; Found: 353.1752; **(11)** m.p. 137-139°C; $[\alpha]_D$ -42.1° (*c* 1, CH_2Cl_2); IR (KBr): 2988 (m), 2900 (m), 1740 (s), 1262 (m), 1195 (s), 1148 (s), 1137 (s), 1116 (s), 1063 (s), 1050 (m), 1034 (s), 1000 (w), 944 (s), 888 (m), 849 (s); 400 MHz ^1H NMR ($CDCl_3$): δ 5.87 (m, H-7), 5.30 (d, *J* = 18.3 Hz, H-8a), 5.22 (d, *J* = 10.4 Hz, H-8b), 4.52 (d, *J* = 0.9 Hz, H-3), 4.52 (m, H-6), 4.02 (d, *J* = 12.6 Hz, $H\text{-}1_{eq}$), 3.80 (d, *J* = 12.6 Hz, $H\text{-}1_{ax}$), 3.32 (s, 3H, OMe), 2.56 (dd, *J* = 4.0, 14.5 Hz, H-5), 2.50 (ddd, *J* = 1.2, 10.5, 14.5 Hz, H-5), 1.53 (s, 3H, Me), 1.50 (s, 3H, Me); Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%. Found: C, 59.19; H, 7.54%; FAB HRMS Calcd. for $C_{12}H_{19}O_5$ $(M+H)^+$ 243.1232. Found: 243.1230; **(16)** m.p. 91-96.5°C; $[\alpha]_D$ +31.8° (*c* 1, CH_2Cl_2); IR (KBr): 3542 (m), 1642 (s), 1384 (s), 1135 (s), 949 (s), 895 (s), 850 (m), 787 (m), 765 (s); 100 MHz ^{13}C NMR ($CDCl_3$): δ 139.8, 106.1, 100.2, 94.1, 70.8, 61.2, 60.3, 49.2, 28.9, 18.6; Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%. Found: C, 55.47; H, 7.64%; **(17)** m.p. 111.5-112.5; $[\alpha]_D$ +107.6° (*c* 0.75, CH_2Cl_2); IR (KBr): 2995 (m), 2940 (m), 1732 (s), 1642 (m), 1464 (w), 1368 (m), 1241 (s), 1107 (s), 1048 (s), 1006 (m), 862 (w); 400 MHz ^1H NMR ($CDCl_3$): δ 6.28 (dd, *J* = 0.9, 6.2 Hz, H-6), 5.27 (dd, *J* = 5.4, 5.1 Hz, H-4), 5.09 (dd, *J* = 5.7, 5.5 Hz, H-5), 4.17 (d, *J* = 5.6 Hz, H-3), 4.10 (d, *J* = 12.6 Hz, H-1a), 3.69 (d, *J* = 12.6 Hz, H-1b), 3.36 (s, 3H, OMe), 2.11 (s, 3H, OAc), 1.51 (s, 3H, Me), 1.48 (s, 3H, Me) **(18)** m.p. 45-46°C; $[\alpha]_D$ +10° (*c* 0.14, CH_2Cl_2); IR (KBr): 1644 (s); 400 MHz ^1H NMR ($CDCl_3$): δ 6.17 (d, *J* = 6.2 Hz, H-6), 4.95 (dd, *J* = 5.8, 5.8 Hz, H-5), 4.13 (dd, *J* = 5.1, 5.1 Hz, H-4), 4.04 (d, *J* = 12.3 Hz, H-1a), 3.88 (d, *J* = 4.8 Hz, H-3), 3.63 (d, *J* = 12.3 Hz, H-1b), 3.32 (s, 3H, OMe), 1.48 (s, 3H, Me), 1.46 (s, 3H, Me), 0.88 (s, 9H, *t*-Bu), 0.06 (s, 3H, Me), 0.04 (s, 3H, Me); FAB HRMS Calcd. for $C_{16}H_{30}O_5SiNa$ $(M+Na)^+$ 353.1760; Found: 353.1764.

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