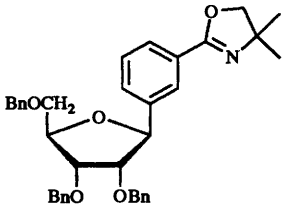
Synthesis of *C*-glycofuranosides by the stereoselective reduction of hemiacetals

Eguzkiñe Calzada, Catherine A. Clarke, Christine Roussin-Bouchard and Richard H. Wightman*
Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK

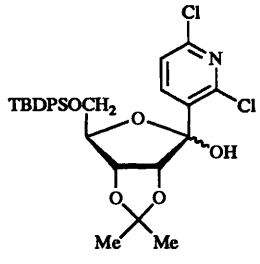
Reaction of protected glycofuranolactones with organolithium reagents and reduction of the resultant hemiacetals with triethylsilane–boron trifluoride gives a stereocontrolled route to *C*-glycofuranosides, with hydride delivery occurring *cis*- to an adjacent oxygen function.

The reaction of glycopyranolactones with organometallic reagents, followed by reduction of the hemiacetal thus formed using a trialkylsilane and a Lewis acid offers a stereoselective route to *C*-glycopyranosides,[1] which has been used, for example, in recent elegant work on the synthesis of *C*-disaccharides.[2] In such reactions the stereochemistry is apparently controlled by electronic effects, with hydride being delivered to the intermediate oxonium ion from an axial direction.

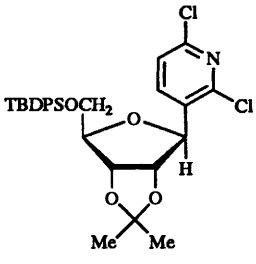
For glycofuranosides the situation is less clear. However, it has recently been reported that the reaction of 2,3,5-tri-*O*-benzyl-D-ribono-1,4-lactone with an aryllithium reagent followed by reduction with triethylsilane and boron trifluoride gives exclusively the β-*C*-glycoside **1**,[3] whilst a report from Benner's laboratory indicates that, under appropriate conditions, reduction of the hemiacetal **2** can give appreciable amounts of the β-product **3**, despite the steric hindrance on the *endo*-face of such systems.[4] Gray and co-workers have described the preponderance of derivatives of 2,5-anhydro-D-mannitol over the analogous anhydro-D-glucitols in reductive cleavage of oligosaccharides containing D-fructofuranosyl units,[5] and it has been reported that reaction of tri-*O*-benzyl-D-arabinono-1,4-lactone **5** with phenyllithium followed by Et_3SiH gives a single *C*-glycoside of undetermined stereochemistry.[6]



1



2



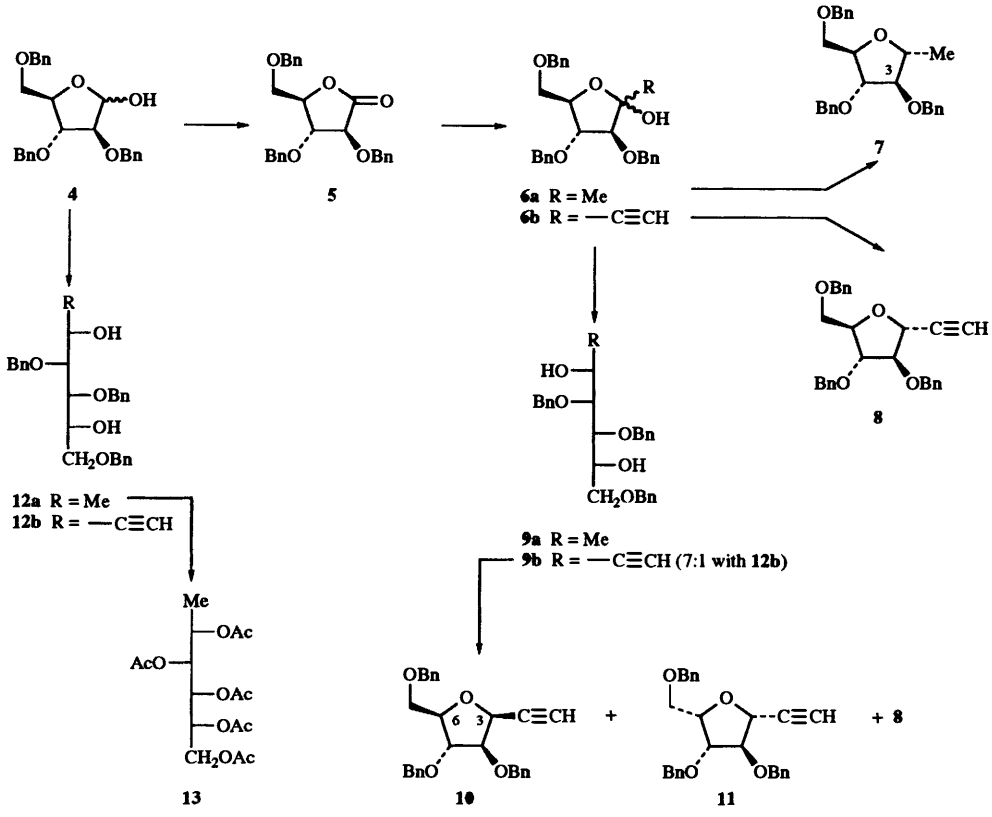
3

We here report further examples of reactions of glycofuranolactones with organometallics, followed by reduction with Et_3SiH, leading with good stereoselectivity to *C*-glycofuranosides in which the major product hydride delivery has occurred *cis*- to an adjacent oxygen substituent, and we suggest that this approach could represent a useful stereodefined method for the synthesis of *C*-glycofuranosides and *C*-nucleosides, and of natural products containing an oxygenated tetrahydrofuran substructure.

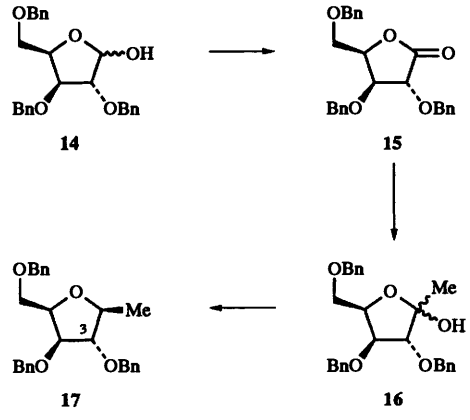
Oxidation of 2,3,5-tri-*O*-benzyl-D-arabinofuranose **4** gave the lactone **5**,[7] which on treatment with MeLi or ethynyllithium[8] in THF gave the hemiacetals **6a**, **b** in good yield (Scheme 1). Treatment of **6a** with Et_3SiH and $BF_3{\cdot}Et_2O$ gave **7** (53%) as a single isomer, $[\alpha]_D$ +9.6 (*c* 1.0, $CHCl_3$), the stereochemistry of which was clearly indicated by strong NOE effects between the CH_3 group and 3-H. Similarly, reduction of **6b** gave **8** (81%) as a 5:1 mixture with its epimer **10**. The stereochemistry of **8** was confirmed by the correlations indicated in Scheme 1, including the synthesis of the epimer **10**. Reduction of **6a** and **6b** with zinc borohydride in ether[9] gave as major products the *erythro*-(*anti*-) isomers **9a** (isomer ratio 6:1) and **9b** (ratio 7:1), respectively. On the other hand, reaction of **4** with the appropriate Grignard reagent in THF gave *threo*-(*syn*-) epimers **12a** (9:1 ratio with **9a**) and **12b** {pure isomer, $[\alpha]_D$ +12.6 (*c* 1.2, $CHCl_3$)}. These stereoselectivities are those predicted from transition states involving α-chelation, and the structure of **12a** was confirmed by its conversion into the crystalline penta-*O*-acetyl compound **13**, mp 104 °C, $[\alpha]_D$ +18.1 (*c* 1.17, MeOH) {lit.,[10] mp 102–104 °C, $[\alpha]_D$ +21.0 (*c* 2.0, MeOH)}. Treatment of **9b** (7:1 with **12b**) with TsCl in pyridine gave as the major product **10**, together with small amounts of an inseparable mixture of **8** and another compound assigned the structure **11**. Product **10** arises from sulfonation of **9b** at the sterically more accessible hydroxy propynyl function, followed by cyclisation, and **8** from the same process on **12b**, whilst **11** is the product of sulfonation of **9b** at the alternative alcohol. The stereostructure of **10** was strongly supported by NOE enhancements observed between 3-H and 6-H.

Similarly (Scheme 2), 2,3,5-tri-*O*-benzyl-D-xylofuranose **14** was oxidised (DMSO, Ac_2O) to lactone **15**, mp 63–64 °C, $[\alpha]_D$ +95.6 (*c* 1.13 in $CHCl_3$), which gave the lactol **16** (81%) with MeLi.† Reduction with Et_3SiH and $BF_3{\cdot}Et_2O$ gave as major product **17** (5:1 with its epimer, 76% combined yield). The stereochemistry of **17** followed from the observation of strong NOE enhancements between the CH_3 group and 3-H, and from the finding that, in the ^{13}C NMR spectrum of a mixture of **17** and its epimer, the minor component showed the signal for the methyl carbon at higher field (δ 14.5) than was observed for the same signal in the major isomer **17** (δ 19.7).[11]

† Reactions of **14** with MeMgI and with ethynylmagnesium bromide, and of **16** and its alkynyl analogue with zinc borohydride, proceeded with the same stereochemical bias as the equivalent reactions in Scheme 1, but with poorer stereoselectivity.



Scheme 1



Scheme 2

Our findings, together with those of others,[3-5] indicate that in reductions of furanoid hemiacetals by Et_3SiH, the incoming hydride approaches the presumed oxonium ion intermediate preferentially from the same face as a vicinal oxygen substituent. The origin of this stereoselectivity must await further studies.

Experimental

3,6-Anhydro-4,5,7-tri-*O*-benzyl-1,1,2,2-tetradehydro-1,2-dideoxy-D-*manno*-heptitol 8 and the D-*gluco*-epimer 10

A solution of the lactol **6b** (0.13 g) in dichloromethane (5 cm^3) at −78 °C was treated with boron trifluoride–diethyl ether (0.24 cm^3) and triethylsilane (0.14 cm^3). After 1 h at −78 °C, the mixture was maintained at −10 °C for 12 h and then partitioned between aqueous sodium hydrogen carbonate (10 cm^3) and dichloromethane (2 × 10 cm^3). The dried organic layers were evaporated and the residue chromatographed on silica gel, with toluene–ether (9:1) as eluent to give a mixture of **8** and **10** (0.10 g, 81%) as an oil; for **8:** δ_H(400 MHz) 2.57 (1 H, d, *J* 2.3,‡ 1-H), 3.62–3.69 (2 H, m, 7-H), 4.04 (1 H, dd, *J* 3.0 and 5.7, 5-H), 4.24 (1 H, t, *J* 3.2, 4-H), 4.27 (1 H, q, *J* 5.25, 6-H), 4.48–4.62 (6 H, m, $PhCH_2$), 4.72 (1 H, m, 3-H) and 7.3 (15 H, m, $PhCH_2$); δ_C(100 MHz) 69.5 (C-7), 71.8, 71.9 (× 2), 73.3, 74.9 (C-2), 81.5, 84.0 and 88.7. For **10**: δ_H(400 MHz) 2.59 (1 H, d, *J* 2.25, 1-H) [Found: $(M^+ - C_7H_7)^+$ 337.1435. $C_{21}H_{21}O_4$ requires *m/z* 337.1440]. Integration of the alkynyl signals in the ^1H NMR spectrum indicated a ratio **8**:**10** of 5:1.

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‡ *J* Values in Hz.