Stereospecific Generation of α- and β-Glycosyl-lithium Reagents from Glycosyl-stannanes: a Stereocontrolled Route to α- and β-*C*-Glycosides

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Treatment of α- and β-D-tri-n-butylstannyl-glucopyranosides with n-butyl-lithium at −78 °C generates configurationally stable α- and β-D-glycosyl-lithium species which accept electrophiles with retention of configuration.

Cleavage of the tin–carbon bond *via* transmetallation is a well established process for preparing organolithium species.[1] Configurationally stable cyclopropyl-lithium[2] and α-alkoxy-organolithium[3] reagents have previously been prepared from the corresponding organostannanes, with retention of configuration. We thus expected that stereoselective anomeric stannylation of carbohydrates would offer, *via* the corresponding glycosyl-lithium derivatives, a stereocontrolled entry to 2,6-disubstituted tetrahydropyrans (*C*-glycopyranosides). We report herein that this is indeed the case.

Hydrochlorination of 3,4,6-tri-*O*-benzyl-D-glucal (**1**) gave the α-hexopyranosyl chloride (**2**),[4] which was treated with tri-n-butylstannyl-lithium[5] [1.5 equiv., tetrahydrofuran (THF), 0 °C, 1 h] to produce selectively the β-D-tri-n-butylstannyl derivative (**3**)† [85% from (**1**)], $[\alpha]_D$ −9°, and a small amount of the α-isomer (**11**)‡ [1% from (**1**)]. The equatorial introduction of tin was shown by ^{1}H n.m.r. spectroscopy: δ 3.63 (1H, dd, $J_{1,2ax}$ 13.2, $J_{1,2eq}$ 1.9 Hz, H-1). Treatment of the organostannane (**3**) with n-butyl-lithium (1.2 equiv., THF, −78 °C, 2 min) and quenching with D_2O (5 equiv., −78 °C, 10 min) *specifically* provided the deuteriated derivative (**5**) (74%), $[\alpha]_D$ +20.5°, most probably *via* the β-D-glucopyranosyl-lithium (**4**). The equatorial introduction of deuterium was confirmed by ^{1}H n.m.r. spectroscopy: δ 3.35 (1H, dd, $J_{1,2ax}$ 12.4, $J_{1,2eq}$ 1.9 Hz, H-1).

Similarly, reaction of (**4**) with benzaldehyde (1.5 equiv., −78 °C, 10 min) and n-hexanal (same conditions) gave the diastereoisomeric mixtures (**7**) (ratio 2:1) (95%) and (**8**) (ratio 1:1) (80%), respectively. In the latter case, compound (**6**)[4] was also isolated (16%). Oxidation (pyridinium chlorochromate, sodium acetate, 4 Å molecular sieve, CH_2Cl_2, room temperature, 1 h) of the mixtures (**7**) and (**8**) gave *single* ketones: (**9**) (72%), $[\alpha]_D$ +7°, ^{1}H n.m.r.: δ 4.58 (1H, dd, $J_{1,2ax}$ 12.4, $J_{1,2eq}$ 1.9 Hz, H-1) and (**10**) (81%), $[\alpha]_D$ +31°, ^{1}H n.m.r.: δ 3.79 (1H, dd, $J_{1,2ax}$ 12.2, $J_{1,2eq}$ 2.3 Hz, H-1). No axial stereoisomers were detected by either high resolution ^{1}H n.m.r. spectroscopy or chromatography. Therefore, the transient and configurationally stable[6] β-D-glycosyl-lithium (**4**) reacts with electrophiles with exclusive formation of an equatorial carbon–carbon bond.

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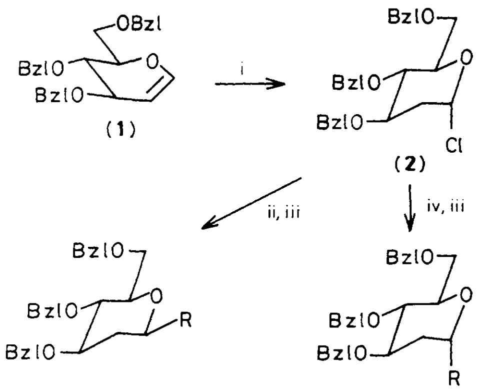
† All new compounds gave satisfactory microanalytical and spectral data. Optical rotations were measured for solutions in chloroform at 20 °C. ^{1}H N.m.r. spectroscopy was performed for $CDCl_3$ solutions at 300 MHz with a Bruker AM-300 WB spectrometer.

‡ The two isomers were easily separated on a silica gel column (ethyl acetate–hexanes, 25:1, v/v).

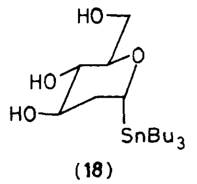


(3) R = $SnBu_3$
(4) R = Li
(5) R = D
(6) R = H
(7) R = CH(OH)Ph
(8) R = $CH(OH)C_5H_{11}$
(9) R = COPh
(10) R = COC_5H_{11}

(11) R = $SnBu_3$
(12) R = Li
(13) R = D
(14) R = CH(OH)Ph
(15) R = $CH(OH)C_5H_{11}$
(16) R = COPh
(17) R = COC_5H_{11}

Scheme 1. Bzl = CH_2Ph. *Reagents:* i, HCl, PhMe, 0 °C; ii, Bu_3SnLi, THF, 0 °C; iii, electrophile; iv, lithium naphthalenide, THF, −78 °C then Bu_3SnCl.

Conversely, the α-D-tri-n-butylstannyl-glycopyranoside (**11**) was prepared by a method recently introduced by us.[4] Reductive lithiation (lithium naphthalenide, 2 equiv., THF, −78 °C, 3 min) of the chloride (**2**) followed by addition of tri-n-butyltin chloride provided selectively the organostannane (**11**) (70%), $[\alpha]_D$ +26°. The anomeric configuration was established by ^1H n.m.r. spectroscopy of the debenzylated derivative (**18**) $[\alpha]_D$ +32.5°; δ 4.52 (1H, dd, $J_{1,2ax}$ 6.1, $J_{1,2eq}$ 1.2 Hz, H-1). Tin–lithium exchange (n-butyl-lithium, 1.2 equiv., THF, −78 °C, 1 min) with the organostannane (**11**) and treatment of the glycosyl-lithium derivative (**12**) which is most probably obtained with D_2O (5 equiv., −78 °C, 5 min) afforded the deuteriated compound (**13**)[4] (70%). Reaction of (**12**) with benzaldehyde (1.5 equiv., −78 °C, 15 min) gave a diastereoisomeric mixture (**14**) (ratio 3 : 1) (64%) which after oxidation (pyridinium chlorochromate) gave a single product (**16**) (69%), $[\alpha]_D$ +63°, ^1H n.m.r.: δ 5.19 (1H, dd, $J_{1,2ax}$ 5.8, $J_{1,2eq}$ 2.1 Hz, H-1). In a similar manner, n-hexanal was converted into the alcohols (**15**) (ratio 1.7 : 1) (60%), then into a single ketone (**17**) (73%), m.p. 67 °C (from ethanol–water), $[\alpha]_D$ +17°, ^1H n.m.r.: δ 4.32 (1H, dd, $J_{1,2ax}$ 5.8, $J_{1,2eq}$ 3.0 Hz, H-1). In accordance with previous observations,[4,7] these latter results demonstrate that a kinetically generated axial§ glycosyl-lithium of type (**12**) is configurationally stable under the conditions used and does not invert to the more stable equatorial epimer.



(18)

In conclusion α- and β-tri-n-butylstannyl glycopyranosides are extremely valuable species for the smooth generation with retention of the anomeric configuration of *configurationally stable lithium reagents* that accept electrophiles again with complete retention. This class of organometallic carbohydrate reagents should find useful application in the stereocontrolled construction of various challenging natural structures regarded as *C*-glycopyranosyl derivatives.

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References

1 E.-I. Negishi in 'Organometallics in Organic Synthesis,' vol. 1, Wiley, New York, 1980, ch. 6, p. 394.

2 E. J. Corey and T. H. Eckrich, *Tetrahedron Lett.*, 1984, **25**, 2415.

3 W. C. Still and C. Szeekumar, *J. Am. Chem. Soc.*, 1980, **102**, 1201.

4 J.-M. Lancelin, L. Morin-Allory, and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1984, 355.

5 Tri-n-butylstannyl-lithium was prepared by the addition of n-butyl-lithium to commercial hexabutylditin in tetrahydrofuran (0 °C, 15 min), according to W. C. Still, *J. Am. Chem. Soc.*, 1977, **99**, 4836; 1978, **100**, 1481.

6 The equatorial organolithium derivative (**4**) is stabilized by a strong stereoelectronic orientational effect, see; J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, 1976, **98**, 7498, and references cited; N. D. Epiotis, R. L. Yates, F. Bernardi, and S. Wolfe, *ibid*, 1976, **98**, 5435.

7 T. Cohen and M.-T. Lin, *J. Am. Chem. Soc.*, 1984, **106**, 1130.

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§ The term 'axial' is used here in contrast with the term 'equatorial' which is used to describe the glycosyl-lithium (**4**). It is probable, although not proven, that the $^4C_1$ conformation depicted for the sake of convenience in Scheme 1 does not describe properly the actual conformation of the lithium reagent (**12**).