Simple Generation of a Reactive Glycosyl-lithium Derivative

Jean-Marc Lancelin, Luc Morin-Allory, and Pierre Sinaÿ*

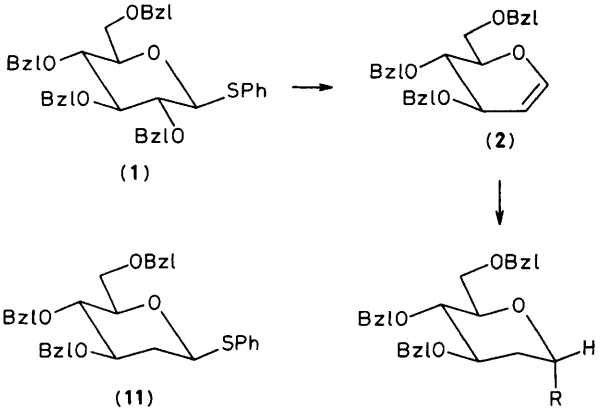
Laboratoire de Biochimie Structurale, E.R.A. 739, U.E.R. de Sciences Fondamentales et Appliquées, 45046 Orléans Cédex, France.

Two-step hydrolithiation of 3,4,6-tri-*O*-benzyl-D-glucal (hydrochlorination and lithium naphthalenide reductive lithiation) gives a reactive glycosyl-lithium derivative which is shown to be a precursor of *C*-glycosides.

A number of natural products regarded as *C*-glycopyranosyl derivatives have, because of their challenging structures,[1] caused intense interest in the field of carbohydrate chemistry. Most of the syntheses of *C*-glycosides developed so far[2] rely on the electrophilic character of the anomeric centre of a carbohydrate. Less conventional recent approaches derive either from the generation and trapping of a glucosyl radical[3] or from the use of 1-deoxy-1-nitro sugars[4] where the nitro group acts as an anion stabilizing substituent for the generation of a reactive anomeric anion in mild conditions.[5] We report herein on the generation and reactivity of 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl-lithium (**4**), the first example to-date of a *C*-glycopyranosyl-lithium reagent.

Treatment of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**)[6] with 2 equiv. of lithium naphthalenide (LN) [tetrahydrofuran (THF), −78 °C, 15 min] resulted in quantitative formation of 3,4,6-tri-*O*-benzyl-D-glucal (**2**).[7] This result indicates that highly selective reductive lithiation[8] occurred at the anomeric centre of (**1**), followed by a fast β-elimination.[9]

Hydrochlorination of (**2**) (toluene, HCl gas, 0 °C, 10 min) gave a quantitative yield of 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl chloride (**3**) which, upon reductive lithiation (2 equiv. LN, THF, −78 °C, 3 min) and quenching with D$_2$O at −78 °C, provided selectively the deuteriated derivative (**6**)† [80% from (**2**)], $[\alpha]_D$ +19°, most probably from the glycopyranosyl lithium (**4**).[10] The axial addition of deuterium was shown by ^{1}H n.m.r. spectroscopy (90 MHz, CDCl$_3$): δ 3.92 (1 H, dd, $J_{1,2ax}$ 5.0, $J_{1,2eq}$ 2 Hz, 1-H*eq*).



(**1**)

(**2**)

(**11**)

(**3**) R = Cl

(**4**) R = Li

(**5**) R = H

(**6**) R = D

(**7**) R = $p\text{-MeOC}_6\text{H}_4\overset{\text{OH}}{\text{CH}}$—

(**8**) R = p-MeOC$_6$H$_4$CO—

(**9**) R = Ph$_2$COH—

(**10**) R = SPh

Bzl = CH$_2$Ph

Treatment of (**4**) with *p*-anisaldehyde gave a 3 : 1 diastereoisomeric mixture (**7**) (65%), from which the two pure diastereoisomers were separated on silica gel (toluene–ethyl acetate, 85 : 15 v/v): major product, $[\alpha]_D$ +16°; minor product, m.p. 65 °C (from diethyl ether–hexane), $[\alpha]_D$ +9°. Oxidation (pyridinium chlorochromate, CH$_2$Cl$_2$, room temperature, 5 h) of the mixture (**7**) gave a single product (**8**) (75%), m.p. 74—75 °C (from hexane), $[\alpha]_D$ +89°, ^{1}H n.m.r. (CDCl$_3$): δ 5.10 (1 H, dd, $J_{1,2ax}$ 6, $J_{1,2eq}$ 2 Hz, 1-H). Treatment of (**4**)‡ with benzophenone gave (**9**) (30%), $[\alpha]_D$ +15°, ^{1}H n.m.r. (CDCl$_3$): δ 1.68 (1 H, m, $J_{1,2}$ 4, $J_{2,3}$ 11, $J_{2eq,2ax}$ 13.5 Hz, 2-H*ax*). In this case, a large amount (30%) of (**5**) was also isolated. Similar results were obtained when phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-1-thio-α-D-*arabino*-hexopyranoside (**10**),§ m.p. 59—60 °C, $[\alpha]_D$ +188°, or its β anomer (**11**),§ $[\alpha]_D$ −36°, were reductively lithiated[11] (2 equiv. LN, THF, −78 °C, 45 min). Therefore the reductively generated glycosyl-lithium (**4**) appears to couple at −78 °C so that electrophiles are introduced in the axial position.

In conclusion, the two-step hydrolithiation of tri-*O*-benzyl-D-glucal reverses the characteristic electrophilicity of the

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† All new compounds gave satisfactory microanalytical and spectral data. Optical rotations were measured for solutions in chloroform at 20 °C. The yields of the reactions have not been optimized.

‡ Reaction of (**4**) with chlorotrimethylsilane gave a single Si-glycoside (36%), $[\alpha]_D$ +15°, whose anomerism has not been ascertained.

§ (**10**) and (**11**) were prepared in four steps from (**3**) [(a) acetone–H$_2$O, Ag$_2$CO$_3$; (b) Ac$_2$O–pyridine; (c) PhSH, BF$_3$·Et$_2$O, CH$_2$Cl$_2$, room temperature, 15 min; (d) silica gel column (CH$_2$Cl$_2$–hexane, 7 : 3, v/v)].

anomeric centre and thus forms a novel route to *C*-glycosides which complements existing procedures. The use of a phenyl thioglycoside as an excellent precursor to a glycal should also find useful applications.

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