Alkylation and Acylation of Phenylthio 2,3-Dideoxyhex-2-enopyranosides at the Anomeric Centre by Polarity Inversion

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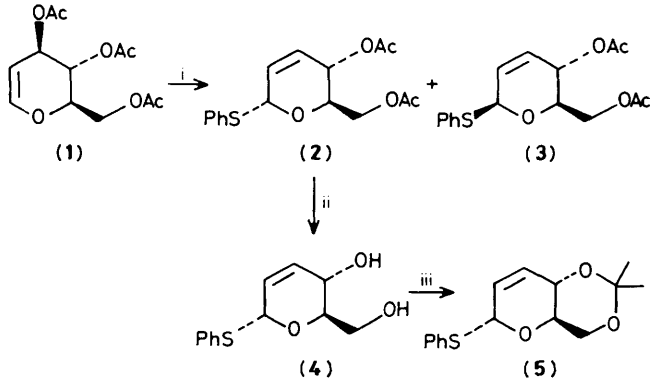
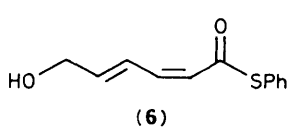
Alkylation and acylation of phenylthio 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside derivatives at the anomeric centre by polarity inversion give C-1 alkylated or acylated phenylthio 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides.

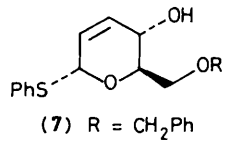
In connection with our project on the synthesis of higher carbon sugars[1] we have now carried out alkylation and acylation reactions at the anomeric carbon by polarity inversion starting from phenylthio 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside derivatives. These reactions open a new way for the synthesis of biologically important compounds such as sialic acids[2] or spiro acetalic compounds like the avermectins[3]. Alkylation and acylation reactions at the anomeric carbon of 2-deoxy-D-glucopyranosyl sulphones by polarity inversion have been published.[4] The work reported in this communication is a further synthetic improvement, since the C-1 alkylated or acylated thioglycosides obtained here allow the introduction of different functionalities with different stereochemistry at carbons C-2 and C-3 by manipulation of the olefinic bond, and have the additional advantage of avoiding the oxidation step of the phenylthio group to the corresponding sulphone.

Treatment[5] of tri-*O*-acetyl-D-glucal (**1**) with thiophenol in the presence of $BF_3 \cdot Et_2O$ gave an 8 : 1 mixture (74% overall yield) of 4,6-di-*O*-acetyl-2,3-dideoxy-α- and β-D-*erythro*-2-

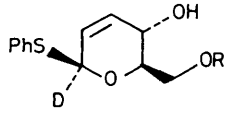


Scheme 1. *Reagents and conditions:* i, PhSH, $BF_3 \cdot Et_2O$, PhH; ii, K_2CO_3, MeOH; iii, $MeOCH_2C{=}CH_2$, *p*-$MeC_6H_4SO_2OH$, CH_2Cl_2, 0 °C.

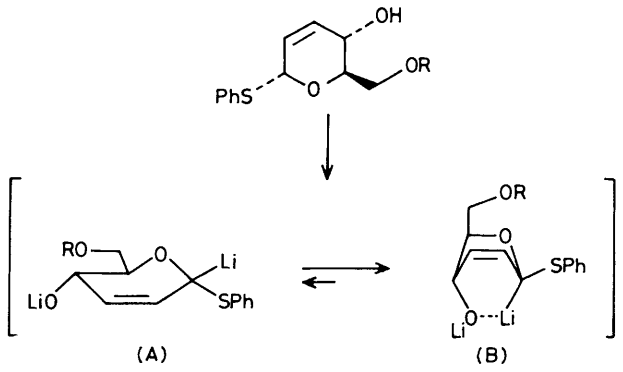




(7) R = CH_2Ph
(9) R = Bu^tMe_2Si
(11) R = Ph_3C



(8) R = CH_2Ph
(10) R = Bu^tMe_2Si
(12) R = Ph_3C



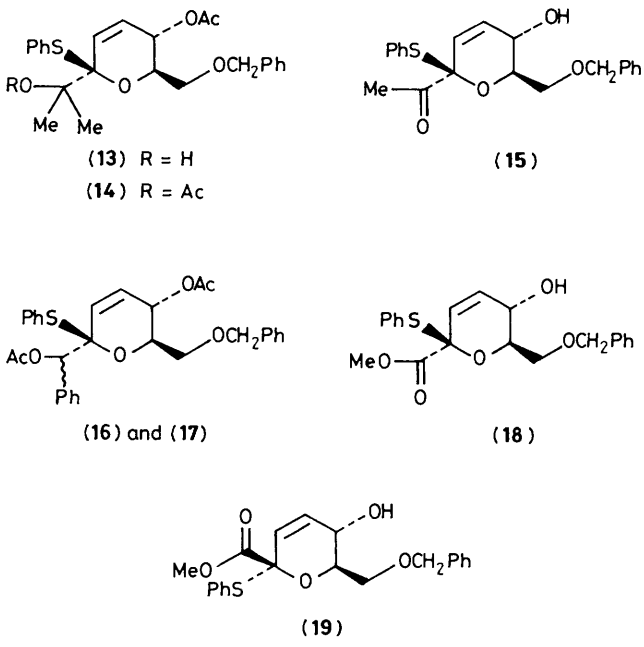
Scheme 2

enopyranosides (**2**) and (**3**) respectively.† The anomeric configurations were assigned according to the well-documented course of the Ferrier rearrangement.[5,6] Compound (**2**) was conventionally converted into (**5**) (Scheme 1) which upon metallation either with BuLi or lithium di-isopropylamide afforded the undesired product of elimination and electrocyclic ring opening, (**6**). Regioselective benzylation of (**4**) *via* stannylation[7] afforded the 6-*O*-benzyl derivative (**7**) (78% yield), which was metallated with BuLi and the reaction mixture subsequently quenched with D_2O to give the β-deuteriated glycoside (**8**) (70% yield of isolated product) with high stereoselectivity.‡ When the same reaction sequence was carried out on the 6-*O*-t-butyldimethylsilyl derivative (**9**), conventionally prepared[8] from (**4**), the β-deuteriated compound (**10**) was obtained in 60% yield as determined by n.m.r. spectroscopy. Treatment of the 6-*O*-triphenylmethyl derivative (**11**), prepared[9] from (**4**), under the same conditions, gave the corresponding β-deuteriated glycoside in low yield (<10% as determined by n.m.r. spectroscopy). In all cases deuteriation was accompanied by configurational inversion at C-1.

The olefinic protons of both the α- and β-glycosides, appear, in all three cases, as singlets and their chemical shifts are characteristic of the α- or β-series. In addition the α- and β-glycosides can be separated by t.l.c. Consequently the assignment of the configuration of the deuteriated derivatives was straightforward using both criteria.

The above results may be explained by assuming that the reaction takes place through intermediate (B) (Scheme 2) in which the 4-HO group interacts with lithium at C-1 and the substituent at C-6 occupies a pseudo-axial orientation.

Alkylation and acylation at C-1 of compound (**7**) by metallation and subsequent reaction with various electrophiles were then investigated. As expected, better yields corresponded to the stronger electrophile. When acetone was used, a product was obtained which upon acetylation afforded compounds (**13**) and (**14**) in 60% overall yield. The reaction with ethyl acetate allowed the isolation of compound (**15**) in 56% yield and that with benzaldehyde gave, after acetylation, a 5:1 mixture of epimers (**16**) and (**17**) in 63% overall yield. Similarly, compounds (**18**) and (**19**), were obtained in a 4:1 ratio in 51% yield when dimethylcarbonate was used as electrophile.§ These compounds show the potential of these reactions in the synthesis of the biologically important derivatives of sialic acid thioglycosides.[10]



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† All new compounds gave satisfactory combustion analysis and spectroscopic data in agreement with the proposed structures.

‡ In this and the following deuteriation experiments the anomeric configuration was determined by n.m.r. spectroscopy by comparison of the chemical shifts of the olefinic protons of the deuteriated compounds with those of the corresponding non-deuteriated phenylthio α- and β-glycosides.

§ The anomeric configuration of compounds (**14**)—(**19**) could not be determined by spectroscopic methods and was tentatively assigned on the basis of the above deuteriation results.