JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 15
1988

A Concise Synthesis of 3-Deoxy-2-*O*-methyl-4,5,7-tri-*O*-benzyl-D-*arabino*-heptulosonic Acid and Related Compounds from 3,4,6-Tri-*O*-benzyl-D-glucal

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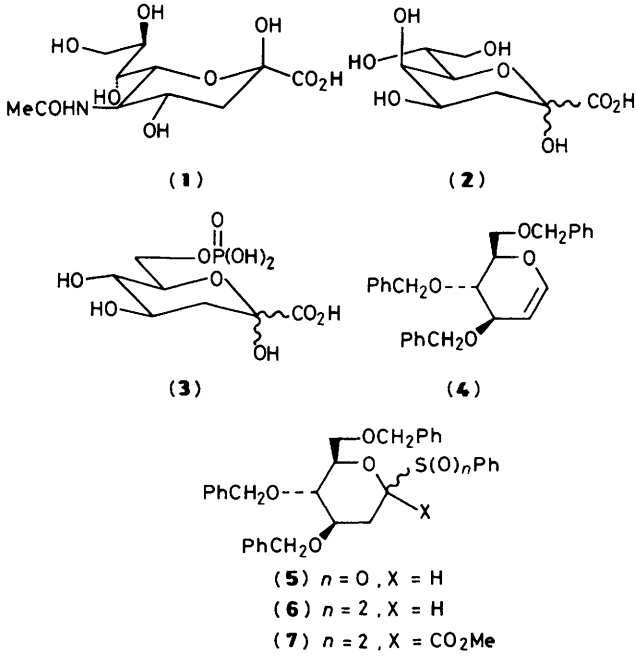
A concise, *de novo* synthesis of the 3-deoxyulosonic acid glycosyl donors (**14**) and (**15**) from trio-*O*-benzyl-D-glucal and their transformation into the corresponding *O*-methyl glycosides is described.

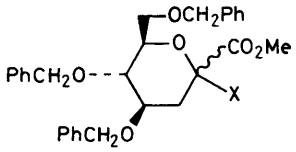
The 3-deoxyulosonic acid function occurs in a variety of important natural products including the well known *N*-acetylneuraminic acid (**1**), 3-deoxy-D-*manno*-octulosonic acid (KDO) (**2**), and 3-deoxy-D-*arabino*-heptulosonic acid-7-phosphate (DAHP) (**3**), an intermediate in the biosynthesis of shikimic acid from D-glucose. We wish to report here a facile transformation of tri-*O*-benzyl-D-glucal into activated derivatives of 3-deoxy-D-*arabino*-heptulosonic acid suitable for use as ulosonic acid glycosyl donors as illustrated by the preparation of the *O*-methyl glycosides.

Thus 3,4,6-tri-*O*-benzyl-D-glucal[1] (**4**) was converted by the method of Sinaÿ,[2,3] *via* the thio glycoside (**5**) and the sulphone (**6**), into the sulphone ester (**7**)† in 51% overall yield. Reductive desulphonylation of (**7**) with 2 equivalents of lithium naphthalenide in tetrahydrofuran (THF) followed by a methanol quench gave a separable 1:2 mixture of the esters (**8**) and (**9**) in 76% combined yield. Deprotonation of (**9**) with LDA in THF at −70 °C and alkylation of the resultant lithium salt with allyl bromide gave the *C*-glycoside (**10**) in 50%, non-optimized, yield as a single stereoisomer. We tentatively assign the stereochemistry of (**10**) as the α-ester in accordance with the studies[4] of Claesson who investigated the quenching of the lithium salt of the closely related esters (**16**) with a range of carbon electrophiles and demonstrated by a combination of chemical correlations and *X*-ray crystallography, that the anion is quenched from the β-face.

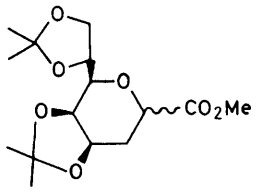
In order to prepare a glycosyl donor the lithium salt of (**9**) was quenched with hexachloroethane followed by warming to room temperature to give the labile glycosyl chloride (**11**) which was treated immediately with methanol in the presence of silver(I) sulphate affording a mixture of the *O*-methyl glycosides (**12**) and (**13**) in 30% overall yield from (**9**). The instability of (**11**) coupled with the desirability of an isolable stable glycosyl donor led us to attempt the preparation of phenylthio glycosides. Thus deprotonation of (**9**) with lithium di-isopropylamide (LDA) and subsequent quenching with diphenyl disulphide gave the stable phenylthio glycosides (**14**) and (**15**) in a combined yield of 30%. In a more expeditious procedure (**7**) was treated with 2 equivalents of lithium naphthalenide in THF followed by diphenyl disulphide to give (**14**) and (**15**) in 62% isolated yield. In this manner a 1.6:1 ratio of the two isomers was obtained; both isomers were stable to silica gel chromatography and the major one was obtained in crystalline form from methanol. The observation of a nuclear Overhauser effect (n.O.e.) between the *ortho*-hydrogens of the phenylthio group and the 3β-hydrogen, coupled with the observations[4] of Claesson, lead us to assign the major isomer as the β-phenylthio glycoside (**15**). Treatment of either (**14**) or (**15**) with mercuric acetate in methanol typically gave the *O*-methyl glycosides (**12**) and (**13**) in greater than 70% yield. Similar results were obtained using *N*-bromosuccinimide as the thio glycoside activating reagent. It is



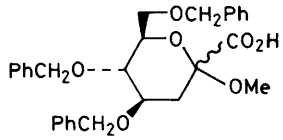
† All new compounds gave satisfactory spectroscopic and microanalytical data.



(**8**) X = α-H (**12**) X = α-OMe
(**9**) X = β-H (**13**) X = β-OMe
(**10**) X = β-$CH_2CH{=}CH_2$ (**14**) X = α-SPh
(**11**) X = Cl (**15**) X = β-SPh



(**16**)



(**17**)

noteworthy that pure samples of (**14**) or (**15**) each gave largely one, but opposite, *O*-methyl glycosides (**12**) or (**13**) suggesting that the glycosylation takes place largely with inversion, although we have not as yet been able to assign anomeric configurations to (**12**) and (**13**) with any certainty. Finally saponification of (**12**) and (**13**) gave the corresponding 3-deoxy-D-*arabino*-heptulosonic acid glycosides (**17**) in 90% isolated yield.

We consider that this route to 3-deoxyulosonic acid glycosides is short and efficient and that given the ready availability of glycals should prove to be general.

We thank the Nuffield Foundation for an equipment grant, the S.E.R.C. for financial support, and Mr. C. J. Cooksey (U.C.L.) for nuclear Overhauser difference spectra.

Received, 29th March 1988; Com. 8/01244E

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