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Synthetic Studies Related to Antibiotics Containing Higher-carbon Sugars

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Abstract—The anion of 6-benzenesulfonyl-3-O-benzyl-6-deoxy-1, 2-O-isopropylidene-α-d-glucofuranose was stable and reacted with carbon electrophiles to give higher-carbon sugars. Reactions of uridine 5′-aldehyde with phosphoranes afforded heptofuranose nucleosides.

Keywords—α-chlorosulfoxide · ezomycins · heptofuranose nucleosides · higher-carbon sugar · 1, 2-hydroxysulfonyl sugar · uridine.

Carbohydrates containing carbon chains composed of more than six carbon atoms are generally called higher-carbon sugars. The synthesis of higher-carbon sugars has been one of the challenging problems in carbohydrate chemistry. Starting from a pentose or hexose, these syntheses require the creation of C—C bonds together with the control of the absolute stereochemistry at each carbon center. Complex higher-carbon sugars are found as components of many important antibiotics, for example, hikizimycin[2], tunicamycin complex[3], sinefungin[4], mildiomycin[5], ezomycin complex[6], and apramycin[7]. If the starting materials were to be a readily available pentose or hexose, then chain-extension reactions would be required. Despite the fact that numerous methods are available for chain-extension of carbohydrates, the construction of some highly complex higher-carbon sugars, for example, the undecose in kikizimycin, remains a formidable task; in the case of the undecose in kikizimycin, the difficulty stems from the ten consecutive chiral centers. One approach to the solution of this problem would be the direct coupling of one sugar to another. In order to achieve coupling of one sugar to another through the C—C bond, there should be stable sugar carbanions or carbanionoids available. In fact, a few carbohydrate anions and carbohydrate ylides have been found to react carbonyl compounds. Thus, a sugar nitronate[8], sugar phophoranes[9,10], and sugar

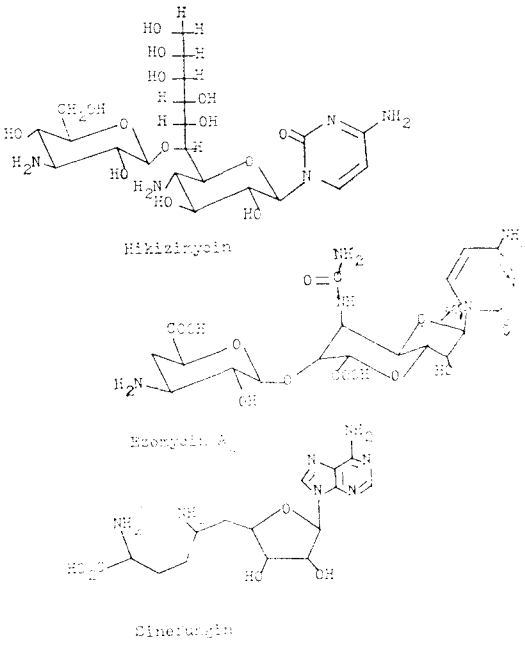

Fig. 1. Antibiotics containing higher-carbon sugars

sulfur ylides[11] have been used for the synthesis of higher-carbon sugars. In this article are described the preparation and the reaction of a new sugar anion. Article also dissusses the synthesis of several heptofuranose nucleosides.

Synthesis of Sugar α-Chlorosulfoxide

Starting from D-galactose, 6-benzenesulfony-6-chloro derivative **4** of galactose was synthesized (Figure 2). The 6-sulfonyl derivative **5** was also prepared from **2** by oxidation with H_2O_2. The synthesis of **5** from **1** by the direct displacement of tosyloxy group with benzenesulfinate salt was not feasible. When the sulfoxide **3** or sulfone **5** was treated with n-BuLi, the anion generated was decomposed. Similary, **4** was decomposed at −78°C. Compound **4** was treated with magnesium in the presence of I_2 hoping that a Grignard type reagent be formed. But this attempt was not successful. The α-chlorosulfoxide and α-chlorosulfone derivatives of D-ribose also did not gave statisfactory results. These results suggested that anions derived from sugar sulfones, sugar sulfoxides, and sugar α-chlorosulfoxides were not stable enough to react with electrophiles.

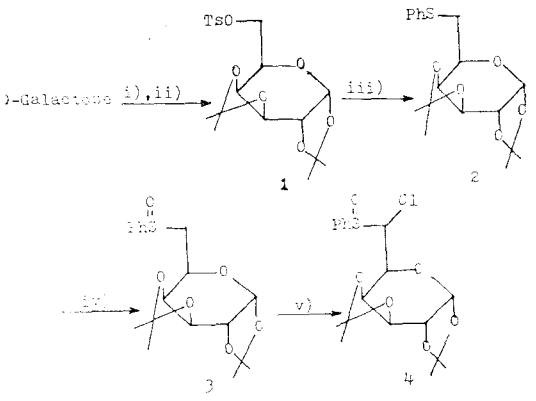

Fig. 2. Synthesis of α-chlorosulfoxide derivative 3 of D-galactose.
(i) $ZnCl_2$, H_2SO_4, acetone; (ii) TsCl, pyridine; (iii) PhSNa, EtOH; (iv) $NaIO_4$, H_2O-MeOH; (v) NCS, pyridine, CH_2Cl_2.

Synthesis and Reaction of 1,2-Hydroxysulfone Derivative of d-Glucose

It was found in the present work, however, that sugar dianion derived from vicinal hydroxy sulfone was stable enough to react with various electrophiles. Compound **8** was synthesized from **7**, which was prepared from D-glucose by 5 step reactions, by substitution with thiophenoxide

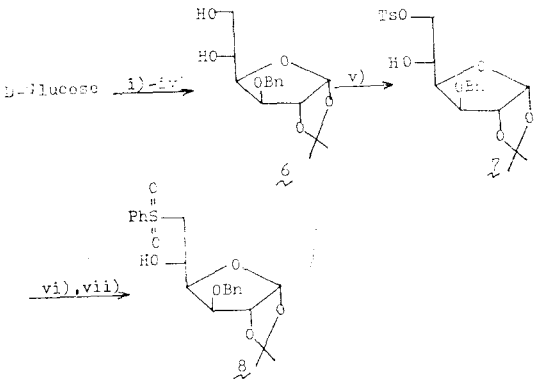

Fig. 3. Synthesis of vicinal hydroxysulfonyl sugar.
(i) acetone, H_2SO_4; (ii) xylene, Na; (iii) $PhCH_2Br$, ether; (iv) 60% aq HOAc; (v) TsCl, pyridine, CH_2Cl_2, 0°C; (vi) PhSNa, EtOH; (vii) 30% H_2O_2, MeOH.

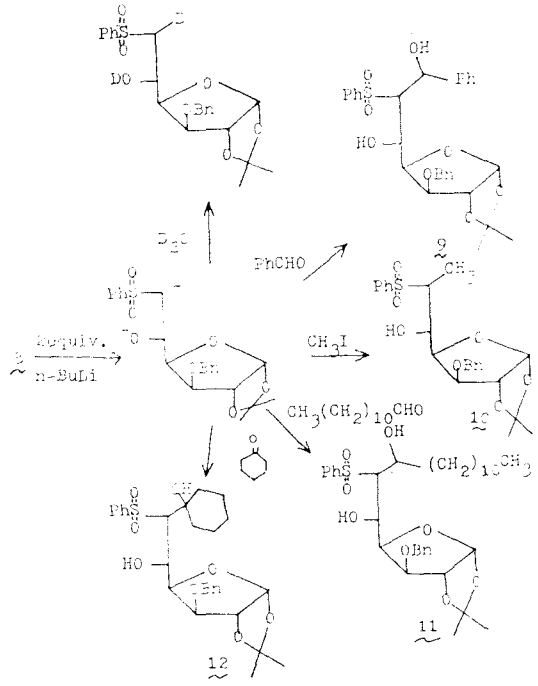

Fig. 4. Reaction of the dianion of **8**.

followed by oxidation with H_2O_2 (Figure 3). The dianion generated from **8** was stable. Thus, **8** was treated with three equivalents of n-BuLi and then with D_2O, the signal attributed to H-6 in ^1H NMR spectrum of the product disappeared. Dianion of **8** nicely reacted with carbon electrophiles such as benzaldehyde, methyliodide, dode canal, and cyclohexanone afforded higher-carbon sugars **9**, **10**, **11**, and **12**, respectively (Figure 4).

Synthesis of Heptofuranose Nucleosides

On the basis of a retrosynthetic analysis for enzomycin complex, it was necessary to prepare octose or heptose nucleosides from ribonucleosides. It was expected that heptofuranose nucleoside **15** would be readily obtained from nuclesodie aldehyde **13** and ylide **14**. Surprisingly, however, Howgate and co-workrs[12] have reported that no reaction occurred between **13** and **14**. The reaction of **13** with **14** was reinvestigated in the present work. Contrary to Howgate's report, compound **15** was readily obtained by Wittig reaction of **13** and **14**. The reason for Howgate's failure to obtain **15** is not clear but it is speculated that Howgate might not detect and, therefore, could not isolate the desired product actually generated in the reaction mixture because we found the R_f values of the starting aldehyde **13** and product **15** were same on the TLC using various eluents. Evidence for the structural assignment of **15** came from many sources. Its UV spectrum, having λ_{max}(EtOH) 256nm, indicated that compound **15** had the intact uracil moiety. The ^1H NMR spectrum of α,β-(**E**)-unsaturated ester **15** clearly exhibited all the expected resonances. Thus, it showed a large trans-ethylenic coupling constant ($J_{5',6'}$=15.8Hz) and a small, long-range coupling constant ($J_{4',6'}$=1.2Hz). The feasibility of two-carbon chain extension of pentofuranose nucleoside by means of Wittig reaction was further examined. Unlike Howgate's report heptofuranose nucleosides **16** and **17** were obtained in high yields.

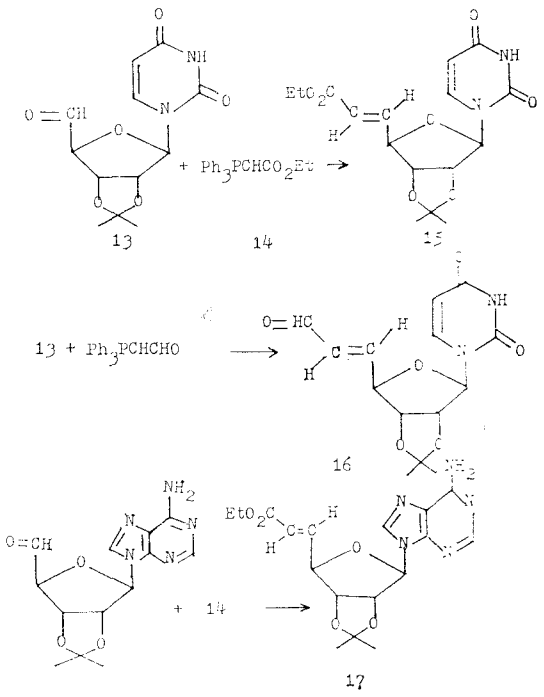

Fig. 5. Synthesis of heptofuranose nucleosides.

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