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Synthesis of the first example of a nucleoside analogue bearing a 5′-deoxy-β-D-*allo*-septanose as a seven-membered ring sugar moiety ☆

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ABSTRACT

The first example of a nucleoside analogue bearing a 5′-deoxy-β-D-*allo*-septanose as a seven-membered ring sugar moiety, namely 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine, is reported. This compound was synthesized in 14 steps from the commercially available D-*glycero*-D-*gulo*-1,4-lactone. When evaluated in cell culture experiments against a broad range of viruses, it did not exhibit any significant antiviral effect or cytotoxicity.

1. Introduction

To date, septanoses (seven-membered ring sugars)[2–7] have not been extensively studied compared to the pyranose and furanose systems. However, a few papers showing growing interest in the biological studies of septanose derivatives have been published these last years. The first observations were published by Kuszmann and co-workers,[8,9] who studied the antithrombotic activity of a series of 4-substituted phenyl 1,6-dithio-hexoseptanosides, all the compounds tested possessing good activity. More recently, Peczuh and co-workers[10] investigated the ability of the jack bean lectin concanavalin A (ConA) to bind septanose monosaccharides. A series of methyl α- and β-septanosides–ConA complexes were measured, showing that the lectin ConA selectively binds β-septanosides. This was the first direct evidence of unnatural septanose sugars being bound to a natural protein. Nucleoside analogues bearing a five-membered sugar ring or acyclic derivatives[11] have been approved as antiviral drugs. Only few reports have appeared on derivatives with four- and six-membered sugar rings.[12]

On the other hand, and to the best of our knowledge, only six examples of nucleosides with a seven-membered carbohydrate moiety (called oxepane nucleosides according to Sabatino and Damha)[13] have been described in the literature (Chart 1). The first one is a nucleoside containing a dihydro-oxepine ring as the sugar moiety, which was unexpectedly obtained following an unusual ring-expansion reaction in an attempt to synthesize 4′-α-ethenyl ribonucleoside analogues via Wittig reaction of 4′-α-formyl ribonucleoside derivatives.[14]

The second example comprises septanosyl-1,2,3-triazoles, which were synthesized as potential glycosidase inhibitors.[15] The last four oxepane nucleoside examples were synthesized with the goal either to be used as monomeric units of modified oligonucleotides,[13,16] or to impart some degree of conformational restriction to the natural nucleosides.[16,17]

As part of an ongoing project aiming at designing new nucleoside analogues with potential antiviral activity, we embarked upon the synthesis and study of novel series of oxepane nucleosides.[18] Here, we report on the first example of a 5′-deoxy-β-D-*allo*-septanose nucleoside analogue.[1] The title compound, namely 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine (**14**), was synthesized in 14 steps from the commercially available D-*glycero*-D-*gulo*-1,4-lactone. It was evaluated as a potential inhibitor of the replication of several classes of viruses.

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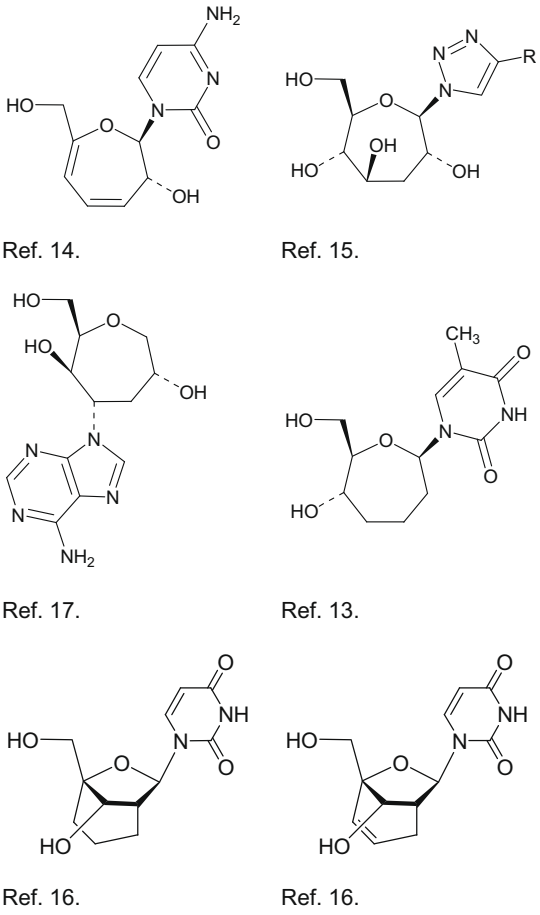

Chart 1. Previously described nucleoside analogues containing a seven-membered ring sugar.

2. Results and discussion

2.1. Synthesis

Our synthetic strategy to obtain the hitherto unknown nucleoside analogue **14** was based on the synthesis of a suitably protected septanose derivative **9**, which was activated as its trichloroacetimidate and reacted with 6-chloropurine.

Septanose derivative **9** (Scheme 1) was obtained from the commercial D-*glycero*-D-*gulo*-1,4-lactone through the known[19] bis(ethylidene)-protected *talo* derivative **1**. Deoxygenation at C-5 was achieved using the Barton–McCombie reaction;[20] the free hydroxyl group of **1** was activated for radical reduction with 1,1′-thiocarbonyldiimidazole. Reduction was performed using azobisisobutyronitrile (AIBN) and tris(trimethylsilyl)silane as the reducing agent, providing the deoxylactone **2**.

Complete reduction of **2** with sodium borohydride in methanol afforded the polyol 5-deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptan-1-itol (**3**), which was treated as a crude with dimethoxytrityl chloride (DMTrCl) to provide the protected compound **4**. In this case, only the primary alcohol group reacted due to the steric hindrance of the hydroxyl group at C4. Compound **5** was obtained after successively treating **4** with NaH and with 4-chlorobenzyl chloride. The primary alcohol of **5** was then selectively deprotected using formic acid, and the free hydroxyl group was oxidized using the convenient Dess–Martin periodinane reagent to afford the heptose **7**. Deprotection was achieved using formic acid in ether to yield the cyclic sugar **8**. The driving force of this reaction at the terminal acetal position is the easy cyclisation that occurs readily afterwards. The primary hydroxyl function of **8** was selectively protected by treatment with imidazole and *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the suitably protected septanose derivative **9**.

The synthesis of the nucleoside analogue **14** from the septanose derivative **9** is summarized in Scheme 2. To achieve the condensation of a carbohydrate with a base, a good leaving group is needed at the anomeric position. In this context, we prepared the trichloroacetimidate derivative of **9**. Indeed, trichloroacetimidate activation is currently one of the most frequently used alternative strategies for glycoside bond formation.[21–23] Treatment of **9** with trichloroacetonitrile in the presence of catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[24] afforded the corresponding trichloroacetimidate derivative **10**.

Trichloroacetimidate sugar **10** was then allowed to react with the N-silylated derivative of 6-chloropurine in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in toluene at reflux to give nucleoside **11** in 15% isolated yield after purification by silica gel chromatography. The structure of compound **11** was confirmed by nuclear Overhauser effect (NOE), which showed that only the β anomer was obtained. Upon irradiation of the doublet at δ 6.58 (H-1′), a reversible NOE was observed with the multiplet at 4.40 (H-6′) (Fig. 1).

Performing the aminolysis at 100 °C provided **12** from **11**. Nucleoside **12** was then treated with BCl_3 to remove the chlorobenzyl-protecting group. Under the used conditions, cleavage of the silyl-protecting group and partial deacetalization also occurred. Thus, reaction of **12** with BCl_3 concomitantly afforded the partially protected nucleoside derivative **13** and the desired nucleoside **14.**

2.2. Antiviral evaluations

9-(5-Deoxy-β-D-*allo*-septanosyl)-adenine **14** was evaluated in cell-based assays (following methods described in Ref. 25) against viruses representative of three genera of the ssRNA$^+$ *Flaviviridae* family: *Pestivirus* (Bovine Virus Diarrhoea Virus), *Flavivirus* (Yellow Fever, Dengue and West Nile Viruses) and *Hepacivirus* (Hepatitis C Virus, HCV), and against one genus of the ssRNA$^+$ *Picornaviridae* family, *Enterovirus* (Coxsackie Virus B2 and Poliovirus Sabin-1). It was also tested against a virus of the ssRNA family, *Retroviridae* (Human Immunodeficiency Virus, HIV-1), against two representatives of a ssRNA$^-$ family, *Paramyxoviridae*: *Pneumovirus* (Respiratory Syncytial Virus) and *Morbillivirus* (Measles Virus) and against a virus representative of a dsDNA virus family, *Poxviridae* (Vaccinia Virus). Unfortunately, against all these viruses, the new nucleoside analogue **14** showed neither antiviral activity nor cytotoxicity at the highest concentration tested (generally 75 μM).

3. Summary and conclusion

The hitherto unknown 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine **14** was synthesized as the first example of a nucleoside analogue bearing a seven-membered 5′-deoxy-β-D-*allo*-septanose sugar moiety. Unfortunately, when evaluated in cell culture experiments against a broad range of viruses, this compound exhibited no significant antiviral effect or cytotoxicity. Several factors could be responsible for the inactivity of 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine **14**, such as its inability to enter cells or to serve as a substrate for intracellular enzymes catalyzing phosphorylation, or perhaps a lack of inhibition of the viral polymerases by its triphosphate.[12,26] Further research would be needed to support these hypotheses, and other results on new kinds of oxepane nucleoside analogues will be reported in due course.