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7-Functionalized 7-deazapurine β-D and β-L-ribonucleosides related to tubercidin and 7-deazainosine: glycosylation of pyrrolo[2,3-*d*]pyrimidines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D or β-L-ribofuranose

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Abstract—Several 7-functionalized 7-deazapurine ribonucleosides were prepared. Glycosylation of 7-halogenated 6-chloro-7-deazapurines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose gave the protected β-D-nucleosides **8c**–**e** (53–62%) and the β-L-nucleosides **9b**–**e** (57–72%), which were transformed to 7-halogenated 7-deazapurine ribonucleosides related to tubercidin and 7-deazainosine. 7-Alkynyl derivatives (**1f**,**g**) and (**2f**,**g**) were obtained from the 7-iodo nucleosides **1e** and **2e** employing the palladium-catalyzed Sonogashira cross-coupling reaction. Within the series of 7-deazaadenosine (tubercidin) analogues and 7-deazainosine derivatives physical data such as pK_a values, chromatographic mobilities, ^{13}C NMR chemical shifts were determined and correlated to each other.

1. Introduction

Pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) ribonucleosides are naturally occurring. Because of their widespread biological activities they received attention as antiviral and anticancer reagents.[1,2] Among the monomeric molecules are tubercidin (**1a**) and its 7-substituted derivatives, toyocamycin (**1h**) and sangivamycin (**1i**), which were isolated from *Streptomyces* strains (purine numbering is used throughout Section 2) (Fig. 1). 7-Halogenated analogues such as 5′-deoxy-7-iodotubercidin were detected in marine organisms.[3] 7-Deazapurine ribonucleosides were found as constituents of tRNA: queuosine and archaeosine represent 7-substituted 7-deazaguanine ribonucleosides, which are formed by the post-modification of a nucleic acid.[2,4] Other naturally occurring 7-deazapurine nucleoside antibiotics were isolated, including mycalisines A and B,[5] cadeguomycin,[6] the antibiotic AB-116 (kanagawamicin) and dapiramicin.[7–9] 7-Deazainosine has been isolated from the ascidian *Aplidium pantherinum*.[10] As the shape of the 7-deazapurines closely resembles that of purines, they are used as substitutes for the canonical constituents of DNA and RNA.

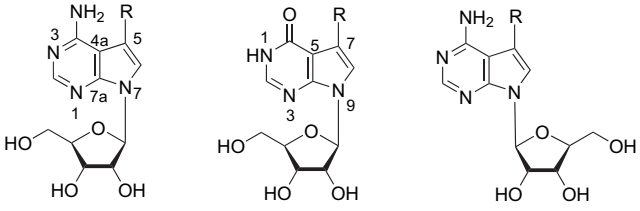

Figure 1. Structures of nucleosides **1**–**3**.

Recent developments in RNA chemistry and biology such as the discovery of the catalytic function of RNA or RNA interference have focused the interest of base modified

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ribonucleosides.[11,12] The frequent occurrence and biological properties of this class of compounds have prompted ample studies toward the synthesis, biological activities, and incorporation in oligonucleotides as well as of chemically designed analogues.[13–21] In many cases these 7-deazapurines are functionalized at the 7-position. Halogen-functionalized derivatives can present biological activity or can be used for further manipulations[22–25] such as cross-coupling chemistry.[26–31]

Earlier work demonstrated that 7-deazapurines resist glycosylation when 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose was employed in the glycosylation reaction.[13,32] Thus, an efficient protocol for the synthesis of 7-deazapurine ribonucleosides is indispensable. Recent work on 7-functionalized 7-deazapurine ribonucleosides focused on the preparation of nucleosides related to guanosine, xanthosine, and purine-2,6-diamine.[33] The present manuscript investigates the synthesis of 7-halogenated 7-deazapurine ribonucleosides related to adenosine and inosine. In particular, the synthesis of 7-deazaadenosines **1c–e**, their β-L-enantiomers **3b–e** as well as 7-deazainosines **2b–e** will be described. The work reports on the further functionalization of the 7-iodo derivatives by the Sonogashira cross-coupling reaction (**1f**,**g** and **2f**,**g**) and studies the influence of the 7-substituents on the physical properties.

2. Results and discussion

2.1. Glycosylation of the 7-deazapurines 4b–e with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (6) or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (7)

Considerable effort has been expended in the development of methods for the synthesis of 7-deazapurine ribonucleosides including tubercidin and 7-deazainosine. Mizuno et al. reported on the 7-deazainosine (**2a**) synthesis using an amino functionalized pyrimidine derivative and a protected sugar aldehyde as starting materials to form a Schiff base as intermediate yielding 7-deazainosine in a multistep procedure.[34] Robins and co-workers synthesized 4-chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine by chlorination of 7-deazainosine which was obtained from the naturally occurring tubercidin by chemical deamination.[35] With this intermediate, halogenated compounds such as **1c–e** and **2d** were prepared in low overall yields.[36] A protocol involving 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose for the glycosylation of a toyocamycin precursor was reported by Townsend, another group employed the fusion reaction which resulted in low yields as well.[37,38] Overall, it was shown that the pyrrole nitrogen is rather inert to glycosylation with the result that the reaction is directed into the pyrimidine moiety,[32] takes place at the more nucleophilic pyrrole carbons[39,40] or results in poor yields.

The development of the stereoselective nucleobase anion glycosylation made 7-deazapurine 2′-deoxyribonucleosides easily accessible.[41–43] Later on, this protocol was applied to 7-deazapurine ribonucleosides' synthesis, using activated ribosugar derivatives (ribofuranosyl halides).[44–52] Unfortunately, *ortho* amides are formed by neighboring group participation when the sugar contains an acyl protecting group at the 2-position with no or little formation of the expected N-9 nucleosides.[45–47] This was circumvented when the nucleobase anion glycosylation of a 7-deazapurine base was performed with a sugar halide protected at the 2′,3′-*cis* diol with benzyl residues or an isopropylidene moiety.[45–52] While benzyl protected sugars lead to anomeric mixture of nucleosides,[17,47] the usage of 1-chloro-2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-D-ribofuranose gives the β-D-anomers exclusively.[45,46,48–52] However, glycosylation of the 7-substituted derivatives did not work satisfactorily.[33] As we wanted to use the commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose as a sugar component for glycosylation, we went back to the silylation of the nucleobase. We and others have already shown that the application of the Wittenburg protocol (silylated base, sugar bromide, and mercuric oxide in benzene or other solvents) results in mixtures of isomeric glycosylation products with very little of the N-7 glycosylated pyrrolo[2,3-*d*]pyrimidine.[32,53] As an alternative the silyl-Hilbert–Johnson reaction[54] was employed. This reaction is usually performed as a two-step protocol (i) silylation of the nucleobase in the presence of ammonium sulfate and (ii) glycosylation with an acylated ribosugar derivative in the presence of a Friedel–Crafts catalyst (Vorbrüggen conditions).[55,56] However, also under these conditions a glycosylation of the pyrrole nitrogen was not observed.[33]

In addition to the above synthetic methods a so called 'one-pot' protocol of the silyl-Hilbert–Johnson reaction was described.[33] This 'one-pot' protocol was used by Wolfe for the synthesis of 2′-*C*-methyl-β-D-ribonucleosides.[57] In this procedure, the nucleobase was silylated with BSA (*N,O*-bis(trimethylsilyl)acetamide) in MeCN and glycosylated with 2′-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose in the presence of $SnCl_4$. Later, Ding employed the same procedure for the synthesis of toyocamycin derivatives and 7-deazainosine derivatives.[58] Here, MeCN was used as a solvent, and TMSOTf (trimethylsilyl trifluoromethanesulfonate) as glycosylation catalyst (Vorbrüggen conditions). The nucleobases were silylated and directly glycosylated in one step. Townsend applied this procedure for the synthesis of toyocamycin.[59]

We used the 'one-pot' method for the synthesis of the 7-deazaadenosine analogues **1c–e**, and the 7-deazainosine nucleosides **2b–e** as well as the β-L-nucleosides **3b–e**. The nucleobases **4b–e**[60,61] were silylated with 1.2 equiv of BSA in anhydrous MeCN at room temperature and then reacted with 1.2 equiv of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**6**) or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**7**) in the presence of TMSOTf (trimethylsilyl trifluoromethanesulfonate) at 80 °C (Scheme 1). This afforded the glycosylated intermediates **8b–e** and **9b–e** in the β-D and the β-L series. It was found that 1.2 equiv of TMSOTf led to completion of the reaction within 1 h resulting in 53–72% yields of the glycosylation products **8b–e** and **9b–e**. This is different from the reaction conditions applied for the more sensitive 7-halogenated 2-amino-6-chloro-7-deazapurines, which required 40–50 °C, with 24 h reaction time.[33] We were not able to perform the glycosylation under the same reaction conditions with the same protected ribofuranoses **6** and **7** using the non-fuctionalized **4a** which is