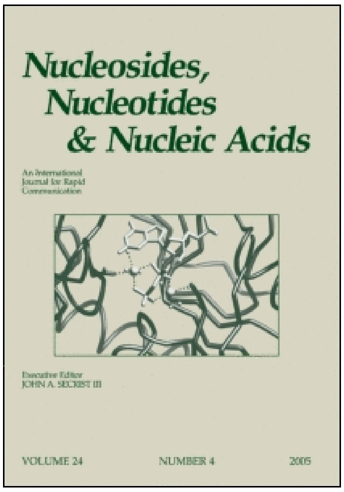

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AN EFFICIENT SYNTHESIS OF 7-FUNCTIONALIZED 7-DEAZAPURINE β-D- OR β-L-RIBONUCLEOSIDES: GLYCOSYLATION OF PYRROLO[2,3-d]PYRIMIDINES WITH 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZOYL-D- OR L-RIBOFURANOSE

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□ *The glycosylation reaction performed with 7-halogenated 7-deazapurines employing commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D- or L-ribofuranoses is described.*

Keywords 7-deazapurines; pyrrolo[2,3-*d*]pyrimidines; glycosylation; functionalization; ribonucleosides; Silyl Hilbert-Johnson reaction

INTRODUCTION

The frequent occurrence and unusual biological properties of 7-deazapurine nucleosides have promoted studies towards the synthesis, biological activity, and incorporation into oligonucleotides of their chemically designed analogs.[1] The 7-position of 7-deazapurine is an ideal site for modifications that can lead to compounds with increased antiviral activity, oligonucleotides labelled with dyes, or a more stable DNA or RNA duplex through the introduction of substituents of moderate size (e.g., alkynyl residues or halogens).[1–3] Earlier, 7-deazapurine ribonucleosides (e.g., **1a**, **2a**, or **3a**; Scheme 1) were prepared by nucleobase anion glycosylation using reactive sugar halides.[4] However, until now no efficient procedure has been reported to synthesize 7-functionalized derivatives related to compounds **1a**, **2a,** or **3a** due to the low nucleophilicity of the pyrrol nitrogen in the pyrrolo[2,3-*d*]pyrimidine system. Here, a convenient method is described for the synthesis of 7-substituted 7-deazapurine

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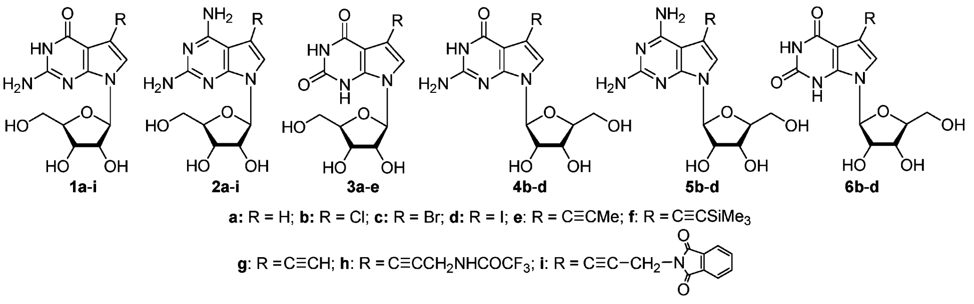
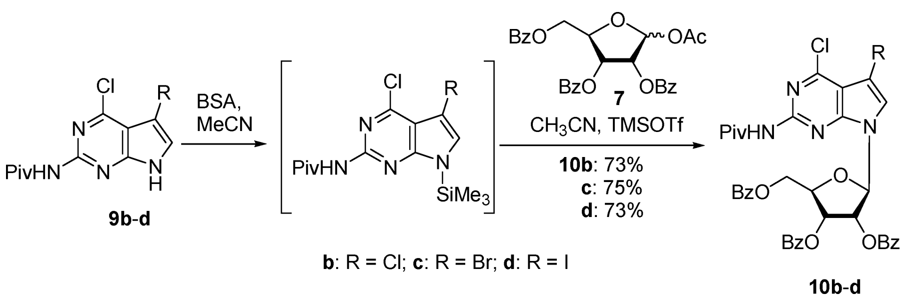


SCHEME 1 Structures of β-D-ribonucleosides **1–3** or β-L-ribonucleosides **4–6**.

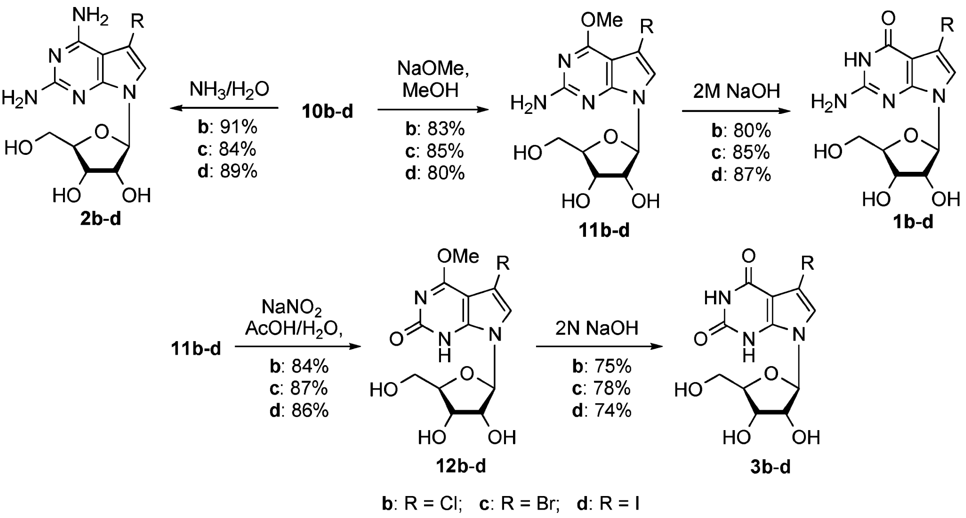
β-D- or β-L-ribonucleosides (**1–3** or **4–6**) using commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D- or L-ribofuranose (**7** or **8**).

RESULTS AND DISCUSSION

The Silyl Hilbert-Johnson glycosylation was employed for the glycosylation of 7-halogenated 2-amino-7-deazapurines with the ribosugar **7**.[5,6] The reaction conditions were changed systematically: (i) different nucleobases and silylation reagents (e.g., HMDS and BSA) were employed; (ii) various solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, $MeNO_2$, and MeCN) were used; (iii) different catalysts ($SnCl_4$ and TMSOTf) were applied; (iv) different reaction temperatures were tested. When all parameters were carefully chosen, a reliable and convenient procedure was developed which, for the first time, makes 7-functionalized 7-deazapurine ribonucleosides easily accessible. The glycosylation of 2-pivaloylamino-6,7-dihalogenated 7-deazapurines **9b–d** with the sugar **7** performed in the one-pot reaction condition (BSA/MeCN/TMSOTf) afforded the β-D-ribonucleosides **10b–d** in 73–75% yield (Scheme 2). The intermediates **10b–d** are useful for further manipulations using nucleophilic displacement reactions or the palladium-catalyzed cross-coupling reaction leading to a series of



SCHEME 2 One-pot glycosylation of the nucleobases **9b–d** with sugar derivative **7**.

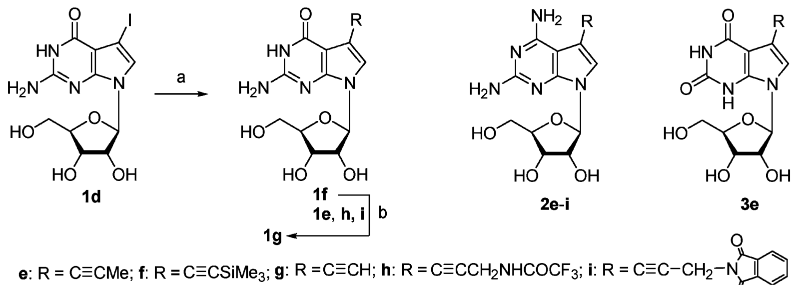


SCHEME 3 Transformation of intermediates **10b–d** to the nucleosides **1b–d**, **2b–d**, and **3b–d**.

7-functionalized 7-deazapurine ribonucleosides. This method was also applied to the synthesis of corresponding β-L-ribonucleosides.[5]

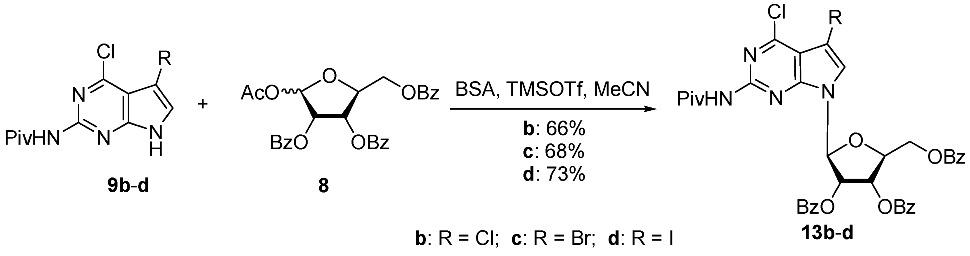
The 2,6-diamino ribonucleosides **2b–d** were prepared from **10b–d** when treated with aq. NH_3 (120°C, 24 h) in an autoclave (Scheme 3). The precursors **10b-d** were also converted to the 4-methoxy derivatives **11b–d** (0.5M NaOMe, reflux). The latter were heated in 2M NaOH giving the guanosine analogs **1b–d**. The deamination of the intermediates**11b–d** with $NaNO_2$/AcOH furnished the nucleosides **12b–d**, which after demethylation with 2N NaOH gave the 7-deazaxanthosine derivatives **3b-d** (74–78% yield).

The iodinated 7-deazapurine ribonucleosides are valuable starting materials for the introduction of alkynyl or aminoalkynyl chains by the Pd-catalyzed cross-coupling reaction.[8] Thus, the 7-iodo compounds **1d**, **2d**, and **3d** were employed in the Sonogashira reaction, yielding a number of



[a] Conditions: (a) HC≡CR, anhydrous DMF, $Pd(0)(PPh_3)_4$, CuI, Et_3N; (b) MeOH, K_2CO_3.

SCHEME 4 Palladium-catalyzed Sonogashira cross-coupling reaction.



SCHEME 5 Glycosylation of **9b–d** with L-ribofuranose **8**.

novel 7-alkynyl- or aminoalkynyl 7-deazapurine ribonucleosides in 50–92% yields (**1e–i**, **2e–i** or **3e**; Scheme 4).

[a] Conditions: (a) HC≡CR, anhydrous DMF, Pd(0)$(PPh_3)_4$, CuI, Et_3N; (b) MeOH, K_2CO_3.

Considering the identical chemical properties of L- and D-nucleosides and their precursors in a nonchiral environment, the protocols developed for the 7-deazapurine D-ribonucleoside synthesis (as described above) can be employed for the preparation of the L-enantiomers. Instead of D-ribofuranose derivative **7**, its L-enantiomer **8** was used as sugar component. The glycosylation of the 2-pivaloylamino-7-deazapurine derivatives **9b–d** with **8** was performed in MeCN/BSA/TMSOTf, affording the β-L-ribonucleosides **13b–d** in 66–73% yield (Scheme 5).[9] Similar to the transformation of **10b–d** into **1–3**, compounds **13b–d** were converted to the 7-functionalized 7-deazapurine β-L-ribonucleosides **4b–d**,**5b–d**, and**6b–d** by nucleophilic displacement reactions (Scheme 1).

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