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Toward a novel series of furanopyrimidine nucleoside analogues

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Abstract—Based on an unusual furanose ring opening of 1,2-*O*-isopropylidene pentofuranoside derivatives, a preparation scheme of a new series of furanopyrimidine nucleoside analogues has been devised.

For many years, the design of modified nucleosides has been a focal point of research in medicinal chemistry.[1] Nowadays, among a plethora of synthetic analogues, a number of compounds have emerged exhibiting a broad spectrum of biological activities as a result of their interaction with various pathogen specific enzyme systems. In this regard, structure–activity relationship (SAR) studies, led chemists to design a large variety of modifications of nucleosides that affect either their base or their sugar part only or both these moieties as well.[2]

Recently, the group of McGuigan disclosed a new series of deeply modified nucleosides featuring an intriguing unusual bicyclic furanopyrimidine moiety that showed a potent anti-varicella-zoster virus (VSZ) activity (Fig. 1: **1**).[3] To date, it seems that these new bicyclic nucleoside analogues (BCNA), whose mode of action is still under consideration, do not tolerate much modifications within the 2′-deoxyribose core. Thus, a recent report reveals that modifications at position 3′ might abolish the anti-VSZ activity, although they favor a potent inhibition of the replication cycle of another type of virus.[4]

Herein, we envisaged to investigate further this matter by introducing new modifications within the 2′-deoxyri-

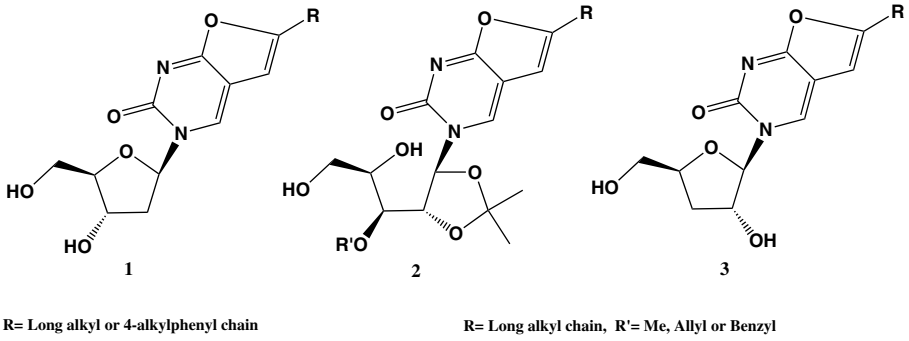

Figure 1. Bicyclic nucleoside analogues (BCNA).

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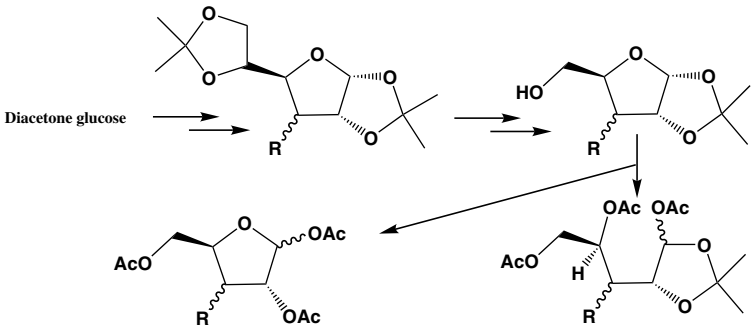


Figure 2. Acetolysis of 1,2-*O*-isopropylidenepentofuranoses.

bose part of these analogues and evaluate their consequences on the anti-viral activity.

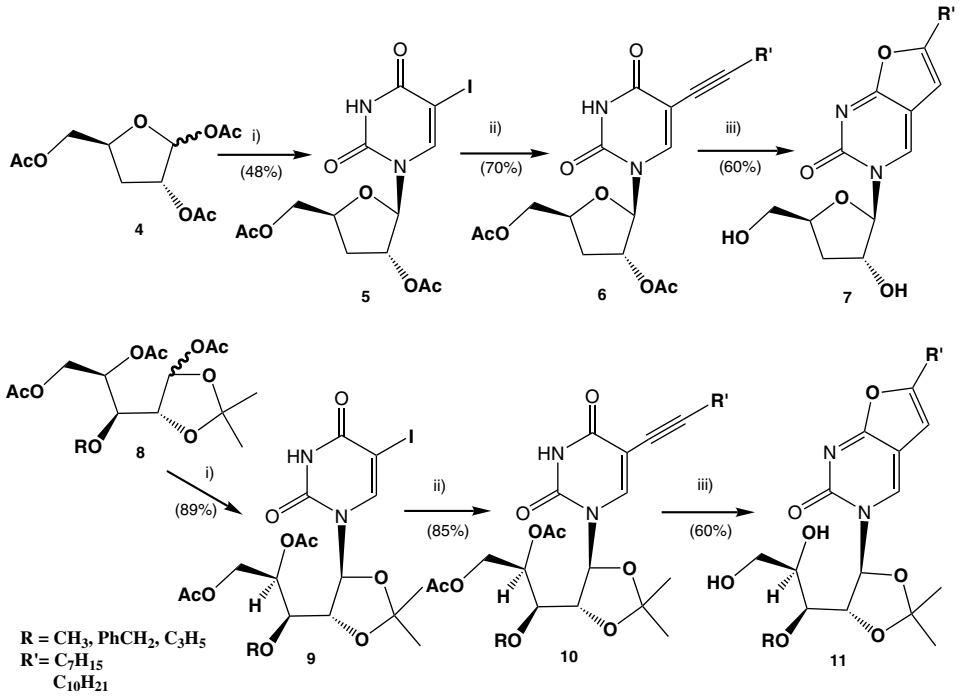
For a long time, diacetone glucose has served for the preparation of a variety of nucleosides having a modified ribose moiety.[5] Indeed, after introducing chemical modifications at the C-3 position, the 5,6-*O*-isopropylidene unit of the hexofuranose can be selectively eliminated to allow a subsequent degradation of the 5,6-bond to provide the corresponding furanose (ribose or xylose) derivative in a satisfactory yield. In general, to continue this sequence, an elimination of the 1,2-*O*-isopropylidene group of the resulting pentose derivative is accomplished. Thus, reaction conditions have been devised, which use a mixture of acetic anhydride and acetic acid containing a definite amount of sulfuric acid (Fig. 2).[6] When such a reaction provides the corresponding 1-*O*-acetylpentofuranoside, this derivative serves as an immediate precursor of a standard nucleoside. Interestingly, the acetolysis course can follow a different route depending on the amount of sulfuric acid and the reaction time. Indeed, using peculiar conditions, the 1,2-*O*-isopropylidene group might be retained giving rise to a 4,4-dimethyl-1,3-dioxolane system, which might be considered as a furanose mimic. Since, to our knowledge, such intermediates never did serve in nucleoside chemistry, we proposed to synthesize novel BCNA structural analogues deriving from this motif (Fig. 1: **2**). Furthermore, it is relevant to note that such new analogues might present a similarity with a number of acyclic nucleosides, which showed remarkable antiviral properties.[2a,7]

As a preliminary step to fulfil this project, we prepared, in a classical manner, the BCNA deriving from 3′-deoxyribose (Fig. 1: **3**) in which the secondary hydroxyl was moved to the vicinal position. Thus, starting from 3-deoxy-1,2-*O*-isopropylidene ribose, as indicated above, a hydrolysis–acetylation step gave rise to the triacetate **4**, suitable for a stereospecific Vorbrüggen reaction with 5-iodouracil to give the expected 3′-deoxy-5-iodouridine analogue **5**. This compound was reacted with nonyne and dodecyne, respectively, in the presence of $Pd[P(Ph)_3]_2Cl_2$ to give the intermediate **6**, which was cyclized in the presence of Cu^+ ions. This step provided directly the BCNA **7** with $R' = C_7H_{15}$ and $C_{10}H_{21}$ (Scheme 1).

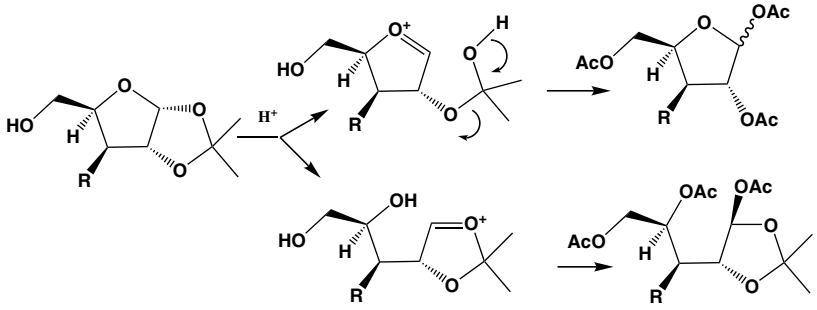
Mastering the know-how to build BCNA nucleosides, we proposed, as a continuation of this work, to prepare the novel BCNA analogues featuring structure **2** (Fig. 1). Thus, starting from a 3-*O*-alkyl-1,2-*O*-isopropylidenexylose (with R = Me, allyl or benzyl),[8] readily obtained from diacetone glucose, we used modified conditions for the hydrolysis–acetylation step. These conditions consist in the treatment of their respective solution in acetic anhydride/acetic acid with fuming sulfuric acid.[9] As a result a selective furanose ring opening was observed giving rise to the corresponding acetylated acyclic carbohydrate **8** (Scheme 1) in 85% yield.

In agreement with the proposed structure, the ^{1}H NMR spectra of compound **8** (R = Me) showed the presence of five *C*-methyl signals (at δ 1.47, 1.48, 2.06, 2.10, and 2.11 ppm). Three of these signals are due to three acetyl groups and the other two to the 1,2-isopropylidene group, which has resisted the acidic conditions. Furthermore, the low field displacement (δ 6.23 ppm) of the anomeric H-1 signal suggested this position to be acetylated. The mechanism of this ring opening reaction is outlined in Scheme 2. In principle, the critical factors that govern the regioselectivity of the cleavage reaction are, among many others, the respective basicity of the *exo*- and *endo*-cyclic oxygen atoms together with the influence of the polar protic solvent.[10] In the present case, we suggest that both acid and water respective concentrations play a critical role in the outcome of the furane versus dioxolane ring opening reaction. Whatever the mechanistic interpretation it is noteworthy that under the proposed acid conditions, a remarkable regiospecificity was observed.

The peracetylated pentose **8** (R = Me), thus obtained, was found suitable to introduce stereoselectively (see below), 5-iodouracil at the anomeric position. The NMR spectrum of the resulting nucleoside analogue **9** (R = Me) showed the disappearance of a methyl acetyl signal and the presence of the H-1′ signal (at δ 6.06 ppm) together with the H-6 singlet (at δ 7.88 ppm). Then, introduction of an alkyne side chain at C-5 was accomplished by means of a Sonogashira reaction to give derivatives **10** (R = Me, $R' = C_7H_{15}$ or $C_{10}H_{21}$). A final cyclization and deacetylation step led to the corresponding bicyclic compounds **11** (R = Me). Thus the structure of the final product **11**



Scheme 1. Reactions and conditions: (i) Bis-*O*-trimethylsilyl-5-iodouracil, trimethylsilyltriflate, DCE, rt, 2–12 h; (ii) Dodecyne (or nonyne), $Pd(PPh_3)_2Cl_2$/CuI, $N(Et)_3$, DMF, rt, 12 h; (iii) MeOH/CuI, $N(Et)_3$, reflux, 3 h.



Scheme 2. Mechanism of the acetolytic cleavage reaction.

($R = Me$, $R' = C_{10}H_{21}$) is in full agreement with its spectral data. In particular, the *trans*-relationship between the substituents in positions 4,5 of the dioxolane was confirmed following a 2D NOESY experiment, which showed correlations of H-1′ and H-2′, each with one of the two isopropylidene group methyls, respectively. Moreover, the methyl which interacts with H-2′ shows a correlation with H-6 of the bicyclic base.

In conclusion, we have prepared a new series of furanopyrimidine nucleoside analogues based on an unusual ring opening of 1,2-*O*-isopropylidene pentofuranoside derivatives under precise acidic conditions. The biological properties of the new derivatives will be reported elsewhere.

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8. For the sake of clarity, we shall discuss the case of R = Me, only. The other benzyl or allyl groups might serve for various chemical manipulations.
9. To a solution of 1,2-*O*-isopropylidene-3-*O*-methylxylofuranose (2.45 mmol) in an acetic anhydride (3.46 mL)/acetic acid (0.42 mL) was added 7 μL of fuming sulfuric acid. After 2 h the solution was cooled (0 °C) and neutralized with a sodium carbonate solution. Usual extraction with ethyl acetate and purification gave **8** (R = Me) in 85% yield.
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